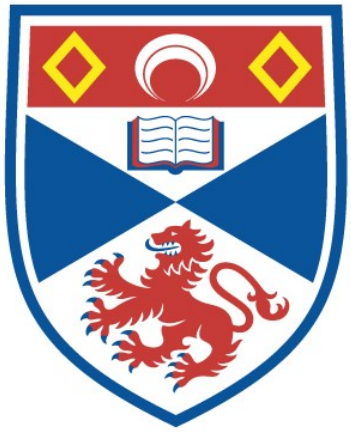
Arylboronic acid-catalysed dehydrative substitution of alcohols

Susana Estopiñá Durán

A thesis submitted for the degree of PhD
at the
University of St Andrews



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Acknowledgements

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Abstract

This thesis is focused on the investigation of new procedures for the activation of alcohols towards dehydrative nucleophilic substitution reaction that release water as the sole by-product using commercially available arylboronic acids as catalysts.

First, in Chapter I, the concept and background of dehydrative nucleophilic substitution reactions using Lewis or Brønsted acid catalysis is detailed. The use of boron-based catalyst for the activation of alcohols towards different reactions is described, with the intention of placing the work of this thesis in the context of the literature.

In Chapter II, the development of a new system for the catalytic activation of benzylic alcohols towards dehydrative substitution using a second alcohol as the nucleophile is described. A commercially available arylboronic acid catalyst in combination with oxalic acid as a ligand can be used for the synthesis of symmetrical, cyclic, and unsymmetrical ethers. Mechanistic control experiments have identified a possible active catalytic species in the reaction media and a plausible reaction mechanism is discussed.

Chapter III focuses on the application of the newly developed catalyst system for the dehydrative substitution of benzylic alcohols using carbon-based nucleophiles. The procedure has been demonstrated for a range of C-C bond forming reactions using either 1,3-diketone derivatives or allyltrimethylsilane as the nucleophile.

Finally, in Chapter IV, a new protocol for the dehydrative Nazarov electrocyclization of allylic alcohols to form substituted furans is investigated. The optimised procedure uses a readily available arylboronic acid catalyst under mild conditions to promote the dehydrative cyclisation. Preliminary control experiments detailing the preparation of the possible active catalytic species are also described.

Contents

Abreviations

Å	Ångstrom(s) (1 x 10^{-10} m)
Ar	Aromatic
Aq	Aqueous
BA	Brønsted acid
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
br	Broad
Bu	Butyl
Conv	Conversion
cat	Catalyst
d	Doublet
dr	Diastereomeric ratio
er	Enantiomeric excess
rr	Regioisomeric ration
Et	Ethyl
equiv.	Equivalent(s)
g	Grams
i-Pr	Isopropyl
IR	Infrared
LA	Lewis acid
M	Molar
m	Multiplet
m	*Meta*
M.S.	Molecular sieves
Me	Methyl
min	Minute(s)
mp	Melting point
NMR	Nuclear magnetic resonance
o	*Ortho*
p	*Para*
Ph	Phenyl
R	Alkyl group
rac	Racemic

rt	Ambient (room) temperature
s	Singlet
Sn1	Nucleophilic substitution (unimoleclar)
Sn2	Nucleophilic substitution (bimolecular)
T	Temperature
t-Bu	*tert*-Butyl
TBD	Triazabicyclodecene
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl

List of publications

This thesis is based on the following peer reviewed publications to date:

I. “Aryl Boronic Acid Catalysed Dehydrative Substitution of Benzylic Alcohols for C–O Bond Formation”
Susana Estopiñá-Durán, Liam J. Donnelly, Euan B. Mclean, Bryony M. Hockin, Alexandra M. Z. Slawin and James E. Taylor*, *Chem. Eur. J.* **2019**, *25*, 3950 – 3956.

Unpublished works:

II. “Dehydrative substitution for C–C Bond Formation Using Arylboronic acid catalysis”; Susana Estopiñá-Durán, Liam J. Donnelly, Euan B. Mclean, Bryony M. Hockin and James E. Taylor*.

III. “Arylboronic Acid-Catalysed Dehydrative Nazarov Cyclisation”; Susana Estopiñá-Durán and James E. Taylor*.

1 Introduction

1.1 Alcohols in organic synthesis

Alcohols are one of the most versatile and common motifs in organic chemistry. The hydroxyl group, connected to a saturated (sp^3) carbon can be synthesised from many different procedures and can be used as a precursor for many common functional groups including ketones, ethers, esters and acids[1] (Figure 1.1). The covalent bonds of an hydroxyl group are polarized with oxygen being the nucleophilic part and the carbon and hydrogen the electrophilic sites.

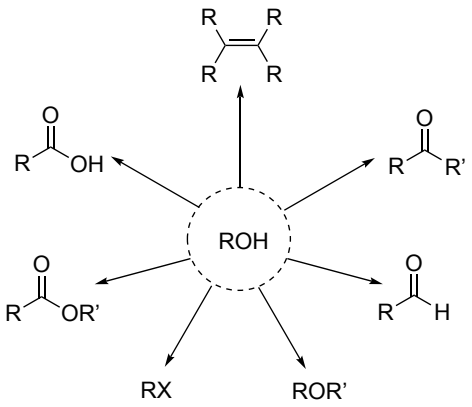
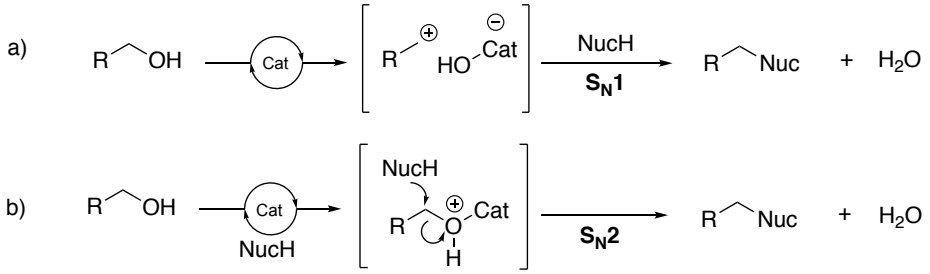


Figure 1.1 Alcohols as precursors to other functional groups

1.2 Nucleophilic substitution reactions

The direct dehydrative substitution of alcohols is one of the most desired reactions for sustainable organic synthesis, releasing water as the only by-product. However, this reaction is challenging due to the hydroxyl group being a poor leaving-group, due to modest charge stabilization. Traditionally, alcohols are activated towards substitution by conversion into a more reactive functional group using stoichiometric reagents. For example, conversion into an alkyl halide or a tosylate is common strategy. Alternative procedures include *in situ* stoichiometric activation, for example in Mitsunobu processes.[2] In each case, these reactions generate stoichiometric by-products that must be removed. Theoretically, a catalyst could activate an alcohol towards substitution by promoting carbocation formation and subsequent

SN1-type substitution (Scheme 1.1a). Alternatively, the hydroxyl group could be activated by a catalyst to afford an SN2-type reaction (Scheme 1.1b).



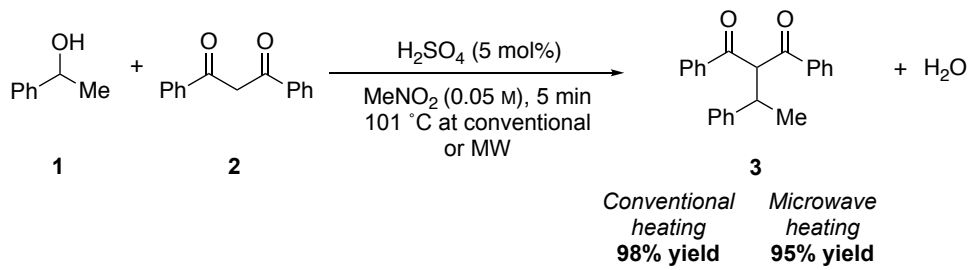
Scheme 1.1 Catalytic activation of alcohols towards substitution reactions

The direct catalytic substitution of alcohols with a range of nucleophiles has received increased attention in recent years with a number of examples reported.[3,4]

1.2.1 Brønsted acid-catalysed dehydrative substitution

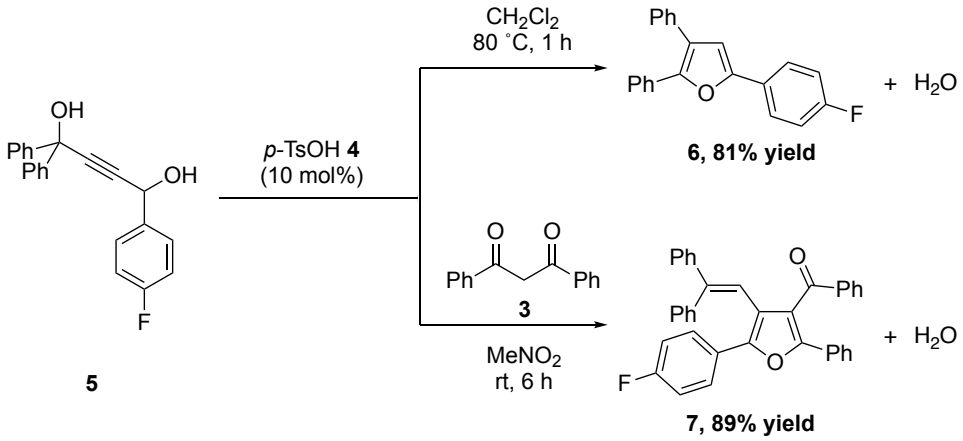
Brønsted acid-catalysis has emerged as an efficient method for promoting a range of dehydrative nucleophilic substitution reactions. Typically, the Brønsted acid protonates the hydroxyl group to promote an SN1 type substitution.[5,6]

For example, the use of sulfuric acid as a Brønsted acid-catalyst for nucleophilic substitution reactions with 1,3-diketone was reported by Liu and co-workers.[7] Different benzylic alcohols were used as electrophiles for reaction with 1,3-diketones to give the substituted products in high yields after 5 min in nitromethane under both conventional heating and microwave conditions. For example, 1-phenyl ethanol **1** react with 1,3-diketone **2** in sulfuric acid (5 mol%) at 101°C to give product **3** in high yields using both conditions (Scheme 1.2).



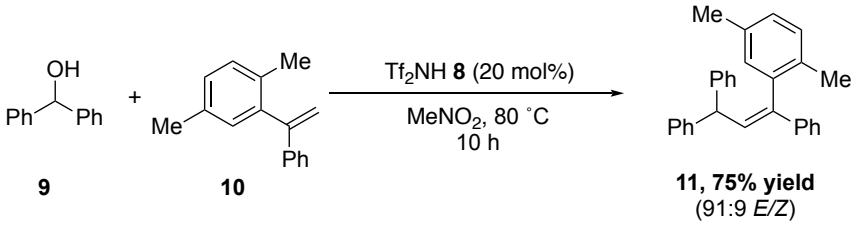
Scheme 1.2 Use of sulfuric acid as Brønsted acid

In 2012, the use of *para*-toluene sulfonic **4** acid as a Brønsted acid catalyst for intramolecular dehydrative substitution was reported by Chan and co-workers.[8] Tri- and tetrasubstituted furans were synthesized from propargylic diols **5** in the presence of 10 mol% *p*-TsOH in (Scheme 1.3). When the reaction was performed using dichloromethane at 80 °C for 1 h, trisubstituted furans such as **6** were formed in good yields. When 1,3-diketone **2** was added using nitromethane as solvent at rt, a tandem alkylation/cycloisomerization of the but-2-yne-1,4-diols was observed to give tetrasubstituted furan **7** in 89% yield.



Scheme 1.3 Substituted furan synthesis with *p*-TsOH 4

Li and co-workers reported in 2015 the use of bis(trifluoromethane)sulfonimide **8** as a catalyst for the synthesis of trisustituted alkenes from 1,1-disubstituted alkenes and benzylic alcohols.[9] A range of Lewis and Brønsted acids was tested, with superior reactivity and *E:Z* selectivity observed when Tf_2NH **8** (20 mol%) was used in nitromethane as solvent. The procedure was studied with different benzylic alcohols and alkenes, obtaining good yields and selectivities. For example, benzhydrol **9** was treated with 1,4-dimethyl-2-(1-phenylvinyl)benzene **10** resulting in product **11** in good 75% yield and high 91:9 (*E*/*Z*) selectivity (Scheme 1.4).

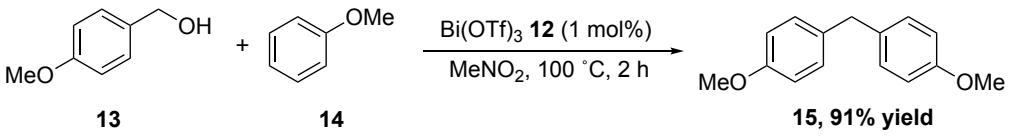


Scheme 1.4 Brønsted acid catalysis for substituted alkene formation

1.2.2 Lewis acid-catalysed dehydrative substitution

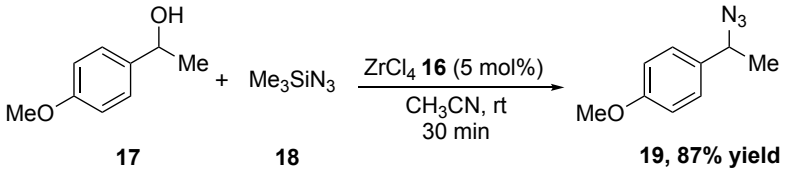
Popular Lewis acid catalysts for dehydrative nucleophilic substitutions are based on p-block metals such as aluminium, silicon, tin or d-block metals such as iron, copper, titanium, zirconium and zinc. Nucleophilic substitution reactions using Lewis acids as catalysts have been extensively investigated with a broad range of applications.[10]

For example, in 2006 Leawsuwan and co-workers reported the use of bismuth triflate (1 mol%) in nitromethane at 100 °C for the Friedel-Crafts benzylation of arenes in good yields.[11] The substrate scope showed the use of electron-rich aryls such as 1,2-xylene, phenol and anisole resulted in the expected products in good yields. Furthermore, the use of heteroaromatics such as thiophene or 3-methylindole was also successful under the optimum conditions. For example, 4-methoxybenzyl alcohol **13** was treated with anisole **14** resulting in product **15** in high 91% yield (Scheme 1.5).



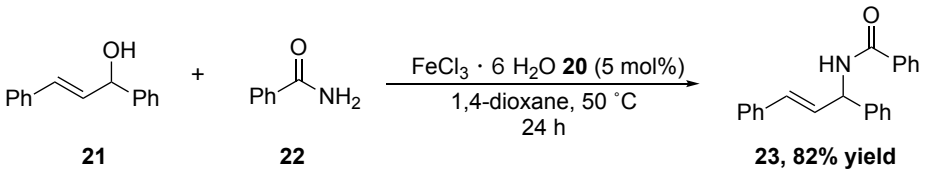
Scheme 1.5 Activation of alcohols using $Bi(OTf)_3$ as Lewis acid catalyst

Metal Lewis acid catalysis can also be used for heteroatom alkylation reactions using alcohols as electrophiles. For example, $ZrCl_4$ **16** (5 mol%) catalyses the formation of aryl azides from benzylic alcohols[12] (Scheme 1.6). A small substrate scope was studied using electron-rich substituents on the secondary carbinol, affording the expected products in good isolated yields.



Scheme 1.6 Use of zirconium tetrachloride for the azidation of benzylic alcohols

Najera and co-workers reported in 2012 the use of 5 mol% $FeCl_3 \cdot 6\ H_2O$ **20** as a Lewis acid catalyst for an allylic amination reaction (Scheme 1.7).[13] A number of different phenyl amines with an electron withdrawing Cl or NO_2 group at *para* position were investigated using allylic alcohols resulting in excellent yields. Also, the reaction of a various allylic alcohols with primary amides or sulfonamides was studied, requiring high temperatures and catalyst loadings to obtain the allylic amidation products in good yields. For example, (*E*)-*N*-(1,3-diphenylallyl)benzamide **23** was obtained from **21** and **22** under the optimum conditions in 82% yield.



Scheme 1.7 Use of 5 mol% $FeCl_3 \cdot 6\ H_2O$ 20 as Lewis acid

1.3 Organoboron catalysts

Boron is a non-metal generally found in nature as BO_3 within minerals. Boron compounds are typically trivalent at an sp^2-hybridised boron atom with an empty *p*-orbital due to their trigonal planar geometry.[14] Boron readily forms covalent bonds with oxygen to form different classes of compounds such as boric acids, boronic acids or esters, borinic acids and boranes. Their applicability and stability differ, with variable reactivity also observed in a number of different reactions (Figure 1.2).

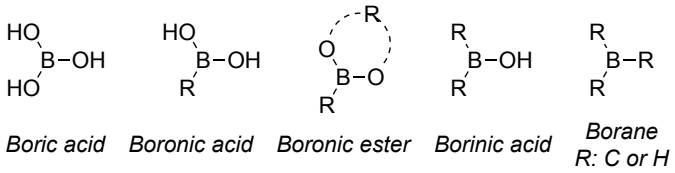


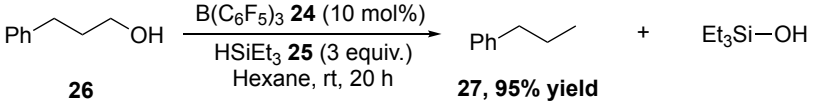
Figure 1.2 Oxygen-containing boron compounds

Boron compounds have been used extensively as either Lewis acid or Brønsted acid catalysts for a range of transformations.[15–17] Of particular relevance to this thesis is their use in the catalytic activation of alcohols. Boronic acids can form covalent bonds with alcohols in a reversible manner, promoting either complete or partial ionization of the C–O bond to form a carbocation intermediate, which can then undergo nucleophilic attack. Compared with strong Brønsted acids, boronic acids often exhibit a wider functional group tolerance due to their mildly Lewis acidic character.[14]

1.3.1 Borane catalysis

Boranes are highly Lewis acidic and have been widely applied as catalysts in a range of reactions. The most commonly used borane is tris(pentafluorophenyl)borane (BCF) **24**, which has been shown to catalyse a range of reactions including borylations, hydrogenations and hydrosilylations.[18–23]

For the catalytic activation of alcohols, Yamamoto and co-workers reported in 2000 the use of BCF **24** (10 mol%) in presence of triethylsilane **25** for the direct reduction of primary alcohols.[24] For example, primary alcohol **26** was reduced to alkane **27** in excellent 95% yield in hexane after 20 h at room temperature (Scheme 1.8).

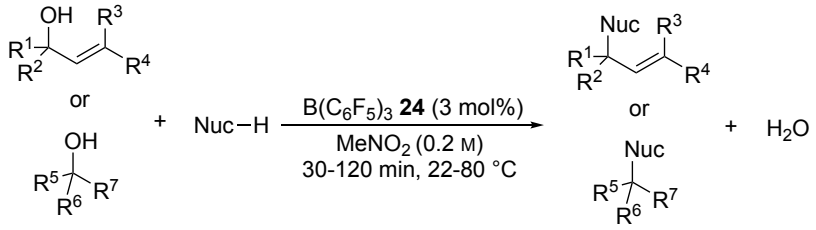


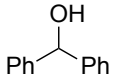
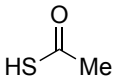
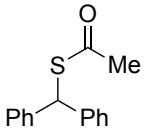
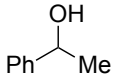
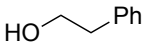
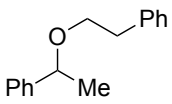
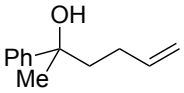
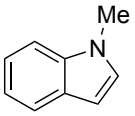
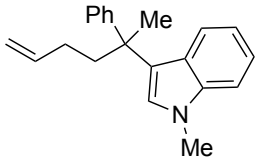
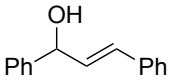
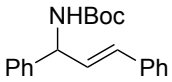
Scheme 1.8 Reduction of alcohols using $B(C_6F_5)_3$ 24 as catalyst

In 2015, Moran and co-workers showed BCF **24** was an efficient catalyst for the intra- and intermolecular substitution of alcohols using various nucleophiles.[25] A number of π-activated and aliphatic alcohols were investigated with different nucleophiles under low catalyst loading (3 mol%) to afford the dehydrative substitution products in good to high yields (Table

1.1). For example, various alcohols were used as electrophiles in reaction with thioacetic acid (entry 1), alcohols (entry 2), amines (entry 3) and indoles (entry 4) as nucleophiles.

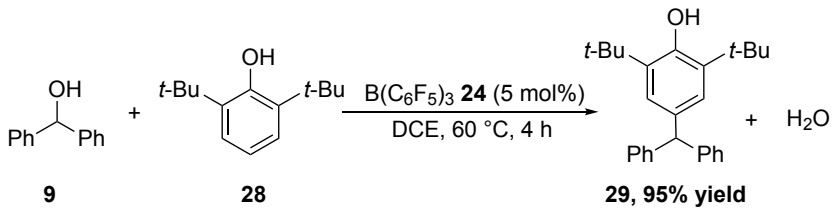
Table 1.1 Use of $B(C_6F_5)_3$ 24 in a nucleophilic substitution reaction



Entry	Alcohol	Nucleophile	Time (min)	Product	Yield (%)
1			120		85
2			60		96
3			60		96
4		NH_2Boc	120		94

In 2018, Chan and co-workers reported a similar procedure using $B(C_6F_5)_3$ **24** (5 mol%) for the catalytic activation of alcohols towards dehydrative substitution (Scheme 1.9).[26] Secondary benzylic alcohols were used as electrophiles for reactions with alcohols and thiols to form ethers and thioethers, respectively. The system could also be used for catalytic dehydrative Friedel-Crafts alkylation reactions. For example, benzhydrol **9** reacts with 2,6-di-*tert*-butylphenol **28** to give triarylmethane **29** in high 95% yield using DCE as a solvent. The

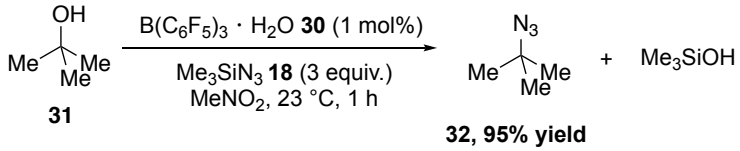
reactions were performed under air, therefore the catalyst was considered as a strong Brønsted acid as water will be coordinated into the borane catalyst.



9 **28** **29, 95% yield**

Scheme 1.9 Triarylmethane synthesis using $B(C_6F_5)_3$ 24 as catalyst

Moran has also reported the azidation of tertiary alcohols **31** with $TMSN_3$ **18** using $B(C_6F_5)_3 \cdot H_2O$ **30** (1 mol%) as a Brønsted acid catalyst.[27] Tertiary azides were obtained in high yields using nitromethane as the solvent. The reaction was also studied using benzene as a suitable solvent, however 50 mol% of a nitroadditive was needed to give good reactivity, showing the importance of the nitro group in this reaction. IR experiments suggests a hydrogen bonding interaction between the hydroxyl on the $B(C_6F_5)_3 \cdot H_2O$ **30** catalyst and nitromethane, which may result in higher order aggregates in solution that may be the active catalytic species in these reactions. For example, tertiary alcohol **31** reacts with $TMSN_3$ **18** (3 equiv.) in the presence of $B(C_6F_5)_3 \cdot H_2O$ **30** (1 mol%) for 1 h to give product **32** in 95% yield (Scheme 1.10).



31 **32, 95% yield**

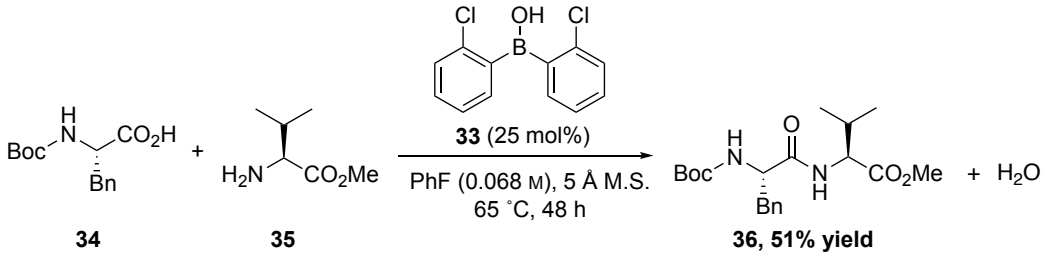
Scheme 1.10 Azidation reaction using $B(C_6F_5)_3 \cdot H_2O$

1.3.2 Borinic acid catalysis

Borinic acids are stronger Lewis acids than boronic acids and have two tuneable arene positions that can vary the Lewis acidity on boron by enhancing the electronic nature using either electron-donating or electron-accepting groups.[28,29] However, the use of borinic acid catalysts is less well explored, possibly due to the lack of commercial availability.

In 2015, Blanchet and co-workers[30] reported the use of a borinic acid as a pre-catalyst for direct peptide synthesis from amino acids. The use of bis(2-chorophenyl)borinic acid **33** in

fluorobenzene at 65 °C was found to be optimal. For example, Boc-L-phenylalanine **34** was efficiently coupled with methyl L-valinate **35** to give dipeptide **36** in good 51% yield, with water being the only formal by-product (Scheme 1.11).



Scheme 1.11 Peptide synthesis using borinic acids

1.3.3 Boronic acid catalysis

Boronic acids are trivalent boron organic compounds with one carbon substituent and two hydroxyl group.[14] With only six valence electrons, the sp^2-hybridized boron atom has a vacant *p*-orbital. This low-energy orbital is orthogonal to the three substituents, which are oriented in a trigonal planar geometry. Boronic acids are not found in nature, but are derived synthetically from primary sources of boron such as boric acid, which is made by the acidification of borax with carbon dioxide.[31] Boronic acids and their derivatives are most commonly used as substrates in Suzuki-Miyaura cross-coupling reactions,[32–34] can also be used in medicinal chemistry as part of drug structures.[35] Boronic acids have also been shown to be suitable catalysts for different transformations[36] and often have good solubility in organic solvents with their polar character obtained from a combination of the Lewis acidity of the boron atom and the hydrogen bond donating capability of their hydroxyl groups. Boronic acids are usually stable in the presence of air, easy to handle and are generally non-toxic.[14,36] The properties of the boron centre as a Lewis acid can be modified by changing the carbon group or through the use of heteroatom ligands coordinated with the boron atom.

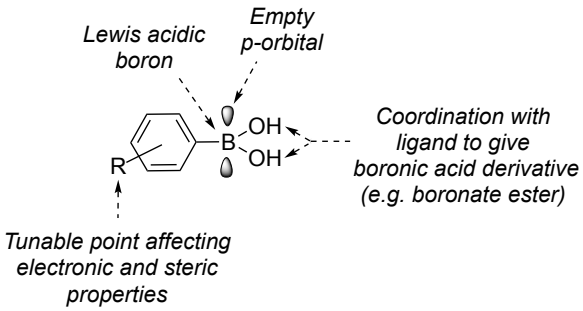
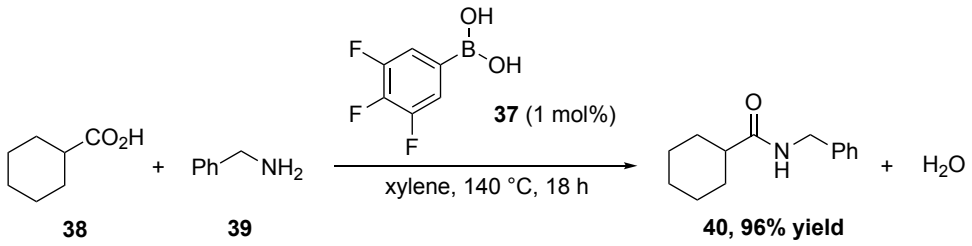


Figure 1.3 Boronic acid structure and tuneable points

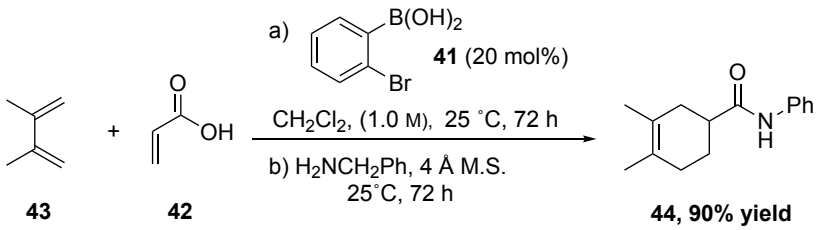
1.3.3.1 Boronic acid: activation of carboxylic acids

An early example of arylboronic acid catalysis was reported in 1996 by Yamamoto and co-workers.[37] Trifluoro-phenylboronic acid **37** (1 mol%) catalyses the direct amidation between carboxylic acids and amines. For example, cyclohexanecarboxylic acid **38** reacts with phenylmethanamine **39** using 1 mol% catalyst **37** at 140 °C for 18 h in xylene to give amide **40** in an excellent 96% yield (Scheme 1.12). Since this initial discovery, many advances in boronic acid-catalysed direct amidation have been reported and the area has been subject of many comprehensive reviews.[38–40]



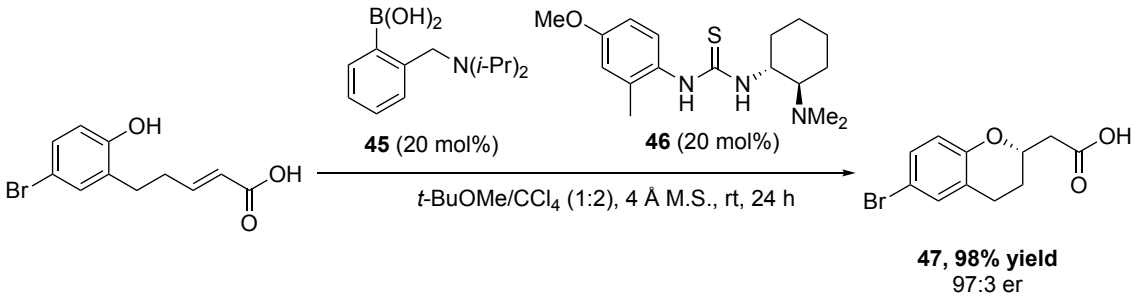
Scheme 1.12 First use of a boronic acid as catalyst

Boronic acids can also activate carboxylic acids towards cycloaddition reactions. Hall and co-workers[41] investigated the use of electron-deficient *o*-bromophenyl boronic acid **41** (20 mol%) to catalyse the reaction of acrylic acid **42** and simple diene **43**, resulting in the [4+2] Diels-Alder cycloaddition product **44** in high yields and selectivity. Furthermore, a one-pot consecutive Diels-Alder cycloaddition/amidation sequence was reported using a single catalyst **41** to give the amide product in good yield (Scheme 1.13).



Scheme 1.13 One-pot cycloaddition/amidation using boronic acid 41

In 2014, Takemoto and co-workers[42] reported a dual catalyst system for enantioselective intramolecular conjugate additions of phenols to tethered α,ß-unsaturated acids (Scheme 1.14). A combination of (2-((diisopropylamino)methyl)phenyl)boronic acid **45** (20 mol%) and chiral aminothiourea 1-((1*R*,2*R*)-2-(dimethylamino)cyclohexyl)-3-(4-methoxy-2-methylphenyl)thiourea **46** (20 mol%) showed reactivity for the enantioselective intramolecular Michael addition to give product **47** in excellent 98% yield and 97:3 er. However, the corresponding asymmetric aza-Michael addition of an aniline resulted in a lower reactivity (25% yield) and only 75:25 er of the product.



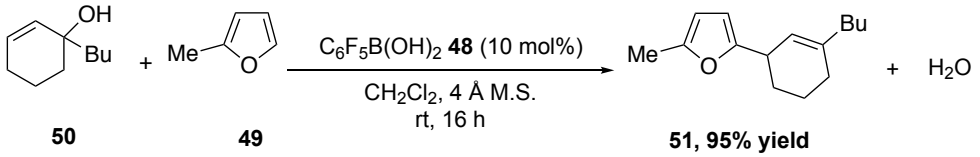
Scheme 1.14 Dual catalyst system for asymmetric Michael addition

1.3.3.2 Boronic acid activation of alcohols

In recent years, boronic acids and boronic esters have been investigated for the catalytic activation of alcohols. This area has recently been extensively reviewed by Hall.[36]

For example, McCubbin and co-workers[43] reported a Friedel-Crafts alkylation catalysed by a highly Lewis acidic pentafluorophenyl boronic acid **48.** Using secondary or tertiary allylic alcohols with electron-rich aromatic compounds including anisoles, indoles, pyrroles and furans the alkylation products were obtained in good yields, releasing water as the only by-product. For example, 2-methylfuran **49** reacts with tertiary allylic alcohol **50** to give Friedel-

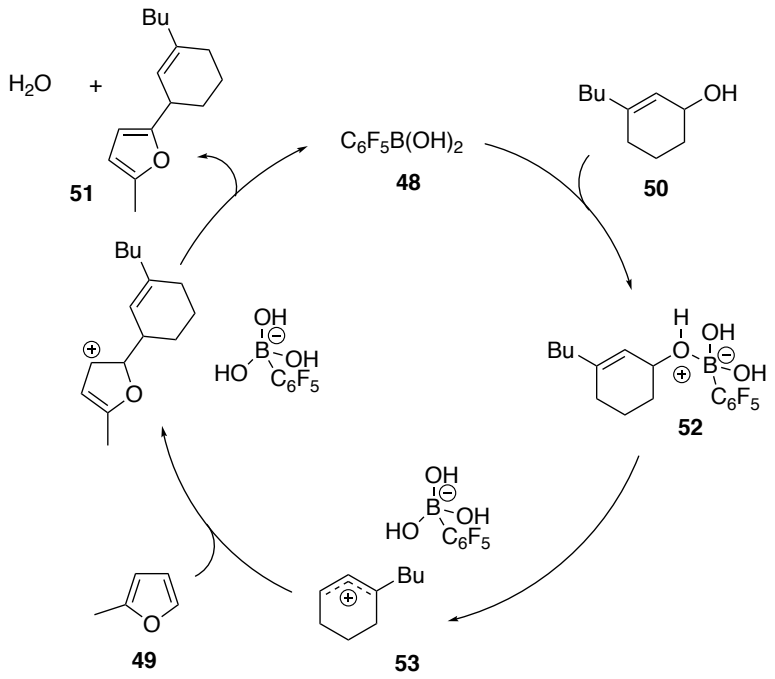
Crafts product **51** as a single regioisomer in 95% yield (Scheme 1.15). The reaction works well for a wide range of cyclic and acyclic tertiary allylic alcohols, giving the furan products in high yields. However, when electron-neutral or halogen substituents were present at the acyclic secondary allylic alcohols, no reactivity was observed. This procedure was also suitable for a range of electron-rich aryl rings as well as other heteroaromatics including pyrroles and indole.



50 **49** **51, 95% yield**

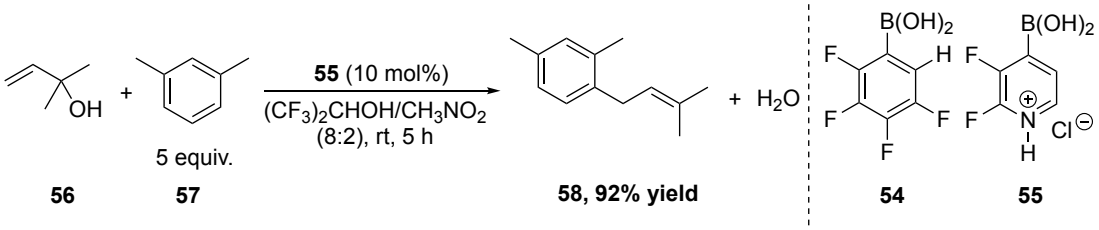
Scheme 1.15 Allylation of 2-methylfuran.

Mechanistically, complexation of arylboronic acid **48** to allylic alcohol **50** results in the formation of boronate **52** (Scheme 1.16). This enhances the leaving group ability of the hydroxyl group, resulting in the formation of resonance-stabilized carbocation **53**. The aromatic nucleophile attacks the carbocation, followed by a deprotonation to afford the product and catalyst turnover. In the same year, McCubbin[44] reported a Friedel-Crafts allylation using benzylic alcohols as electrophiles under similar reaction conditions. For example, benzhydrol **9** underwent Friedel-Crafts alkylation with aromatic substrates in excellent to quantitative yields.



Scheme 1.16 Proposed catalytic cycle

Hall and McCubbin[45] extended this work to the Friedel-Crafts allylation of electron-neutral and electron-rich benzene derivatives using acyclic secondary or tertiary allylic alcohols. In this case, the use of 2,3,4,5-tetrafluorophenyl boronic acid **54** (10 mol%) in a 4:1 mixture of hexafluoroisopropanol and nitromethane at rt was optimum, forming the substitution products in high yields. The use of difluoropyridinium boronic acid **55** (10 mol%) led to similar yields. The reaction tolerates various secondary and tertiary allylic alcohols bearing allyl and aryl substituents. A number of electron-rich benzene derivatives were also suitable nucleophiles, giving the Friedel-Crafts products in good yields with high levels of regioselectivity. For example, tertiary alcohol **56** reacts with 5 equivalents of **57** using boronic acid catalyst **55** (10 mol%) at room temperature for 5 h to give product **58** in high 92% yield (Scheme 1.17).



Scheme 1.17 Friedel-Crafts alkylation of *m*-xylene catalysed by boronic acids 54 or 55.

The increased activity of 2,3,4,5-tetrafluorophenylboronic acid **54** compared with pentafluorophenylboronic acid **48** was rationalised by a possible stabilising role of the H in the *ortho* position by hydrogen bonding with the incoming alcohol (Figure 1.4).

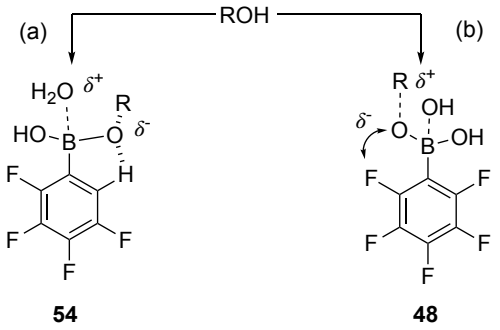
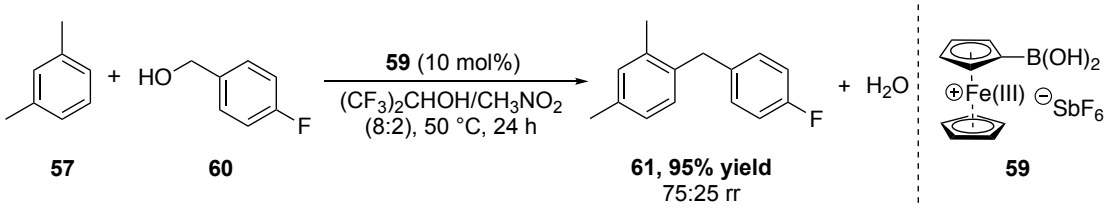


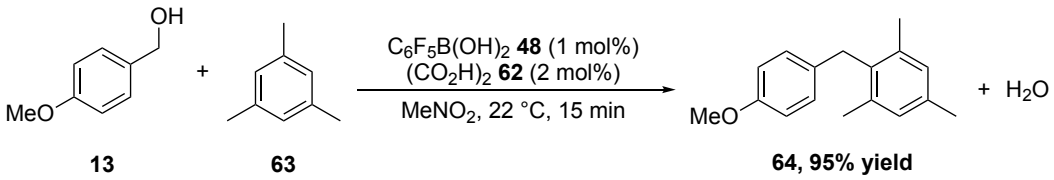
Figure 1.4 Proposed stabilizing (a) and destabilising (b) role of *ortho* substituents

In 2015, Hall and McCubbin[46] reported a Friedel-Crafts alkylation catalysed by ferrocene-based boronic acid **59** (10 mol%), reacting secondary benzylic alcohols with substituted electron-rich benzene derivates. It was proposed that the lifetime of the intermediate carbocations would increase in the presence of charged boronic acids due to an ion exchange process. Ferroceneboronic acid and its oxidized Fe^{III} counterpart was prepared with $AgSbF_6$ in acetone at rt to form the ferrocenium boronic acid salt **59** (Scheme 1.18). The Friedel-Crafts reaction using catalyst **59** (10 mol%) in a mixture of hexafluoroisopropanol and nitromethane (4:1) at a 50 °C was optimal. Benzylic alcohols containing electron-donating or halogen substituents gave Friedel-Crafts products in high yields; however, benzylic alcohols with strongly electron-withdrawing groups such as nitro or cyano gave low yields of the products. The scope of arene nucleophiles was also studied, with benzene, toluene, *o*-xylene, naphthalene and halide-substituted arenes all reacting efficiently at 80 °C. However, deactivated arenes such as dichlorobenzene, methyl benzoate and trifluoromethylbenzene failed to afford the respective products. For example, *m*-xylene **57** reacts with benzylic alcohol **60** using catalyst **59** (10 mol%) at 50 °C for 24 h to give Friedel-Crafts product **61** in excelent 95% yield (Scheme 1.18).



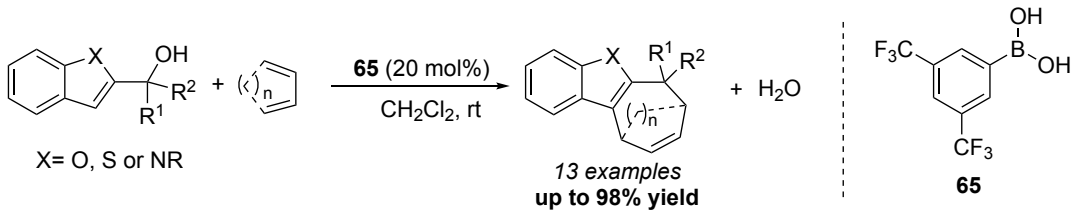
Scheme 1.18 Friedel-Crafts benzylation

In the same year, Moran and co-workers[47] reported a combinatorial strategy for hit identification in catalyst optimization, which was applied to the Friedel-Crafts alkylation of mesytilene **63** with *p*-methoxybenzyl alcohol **13** as the electrophile using boronic acid catalysis (Scheme 1.19). After the rapid screening study, a combination of pentafluorophenyl boronic acid **48** (1 mol%) and oxalic acid **62** (2 mol%) in nitromethane was identified as optimal, forming product **64** in 95% yield. However, the scope of this reaction was not investigated under these conditions.



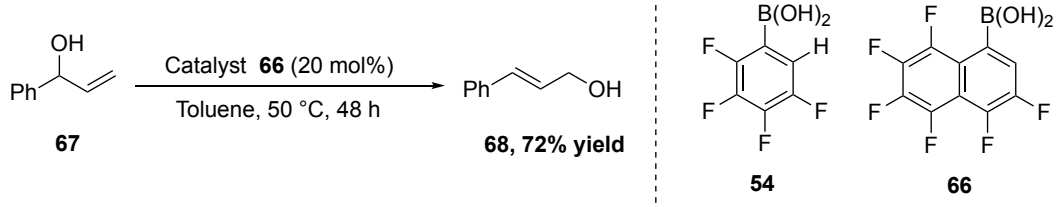
Scheme 1.19 Dehydrative Friedel-Crafts reaction.

Zheng and co-workers have reported the use of boronic acids as catalysts for [4+3] cycloaddition reactions.[48] Cyclohepta[*b*]benzofurans and cyclohepa[*b*]indoles were obtained using (3,5-bis(trifluoromethyl)phenyl)boronic acid **65** (20 mol%) as the catalyst for the reaction of substituted benzofurans with dienes. Benzofuran substrates with both electron-donating or electron-withdrawing substituents on the aryl group were tolerated, giving the products in good yield and high selectivity (Scheme 1.20). Different dienes including cyclopentadiene or acyclic isoprene were also competent in this protocol, giving good reactivity. The proposed mechanism involves activation of the hydroxyl group in the presence of boronic acid **65** to give an allylic cation, which undergoes *via* [4+3] cycloaddition with the diene.



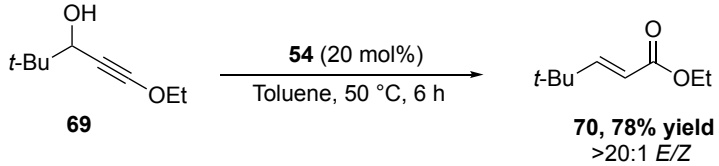
Scheme 1.20 [4+3] cycloaddition using boronic acid 65

In 2011, Hall reported a selective boronic acid-catalysed rearrangement of secondary allylic alcohols into primary allylic alcohols.[49] The reaction works using either boronic acid **54** or **66** (20 mol%) in toluene, with some of the rearrangement reactions requiring heating up to 80 °C. For example, rearrangement of secondary allylic alcohol **67** using **66** (20 mol%) at 50 °C produced cinnamyl alcohol **68** in 72% yield after 48 h (Scheme 1.21). A range of secondary and tertiary allylic alcohols bearing alkyl, aryl or heteroaryl substituents gave the rearrangement products in good yields.



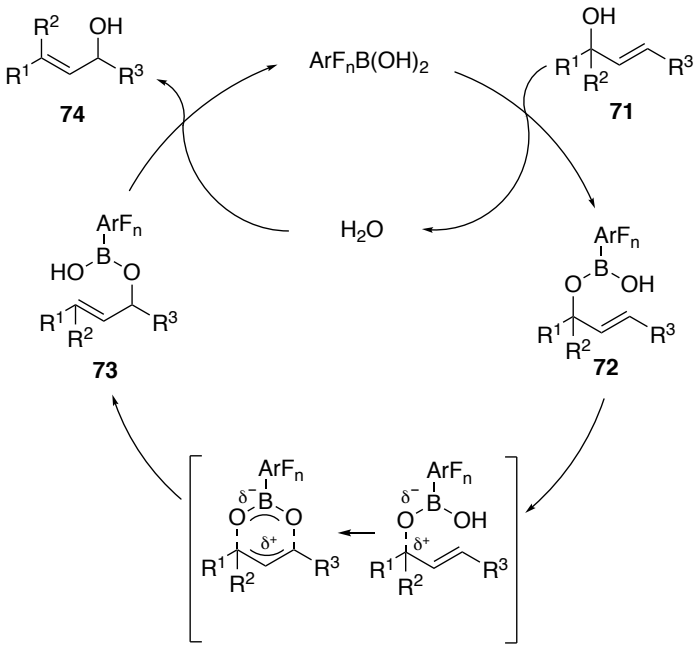
Scheme 1.21 Boronic acid-catalysed rearrangement of allylic alcohols

Boronic acids **54** and **66** also promotes the Meyer-Schuster rearrangement of secondary or tertiary propargylic alcohols under the same conditions. For example, propargylic alcohol **69** reacts with catalyst **54** (20 mol%) to give α,β-unsaturated ester **70** in 78% yield (Scheme 1.22). The reaction works for a number of substituted propargylic alcohols, which rearrange to give α,β-unsaturated aldehydes, ketones, esters, thioesters and amides in good yields.



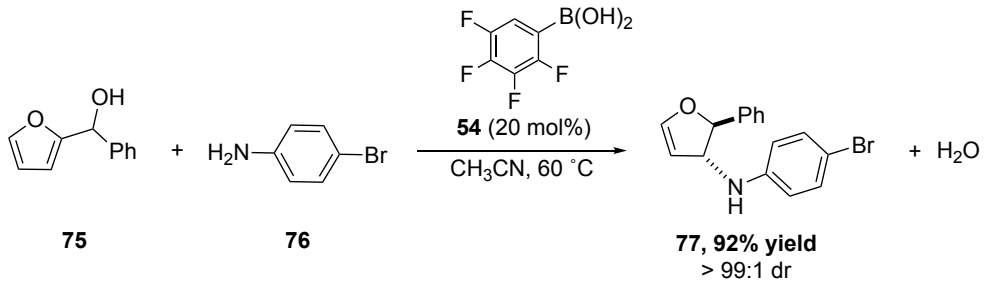
Scheme 1.22 Boronic acid-catalysed Meyer-Schuster rearrangement

The proposed mechanism is a pseudo S_N1 reaction involving partial or full ionization into an allylic or propargylic carbocation (Scheme 1.23). The arylboronic acid is initially attacked by the allylic alcohol **71** to form intermediate **72**, which undergoes either a partial or complete ionization upon rearrangement into intermediate **73**. This intermediate can be hydrolysed to give the rearranged product **74** and release the catalyst.



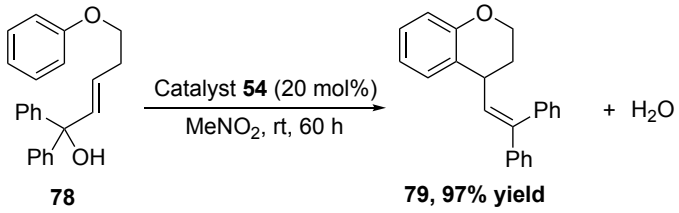
Scheme 1.23 Proposed catalytic cycle for 1,3-transposition of allylic alcohols catalysed by boronic alcohols 54 or 66.

Zheng and co-workers reported the first example of an aza-Piancatelli rearrangement using 2,3,4,5-tetrafluorophenylboronic acid **54** as catalyst (Scheme 1.24).[50] The reaction to form *trans*-4,5-disubstituted cyclopentenones tolerates both electron-withdrawing and donating furylcarbinols alongside a number of primary and secondary amines to give the products as a single diastereoisomer in good to excellent yields. For example, furan-2-yl(phenyl)methanol **75** reacts with aniline **76** using arylboronic acid **54** (20 mol%) in acetonitrile to give product **77** in excellent 92% yield.



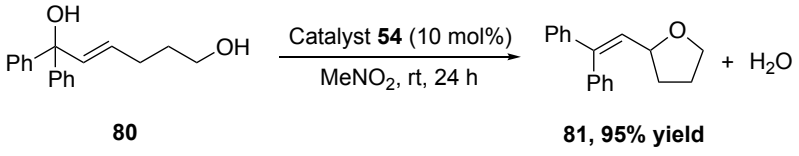
Scheme 1.24 Aza-Piancatelli rearrangement using boronic acid 54

In 2012, Hall and co-workers reported the intramolecular cyclization of carbon, nitrogen and oxygen-based nucleophiles onto substituted allylic alcohols using boronic acid catalysis.[51] For example, the intramolecular Friedel-Crafts cyclization of **78** using boronic acid **54** (20 mol%) in nitromethane gives substituted benzopyran **79** in 97% yield (Scheme 1.25).



Scheme 1.25 Catalytic intramolecular Friedel-Crafts cyclization

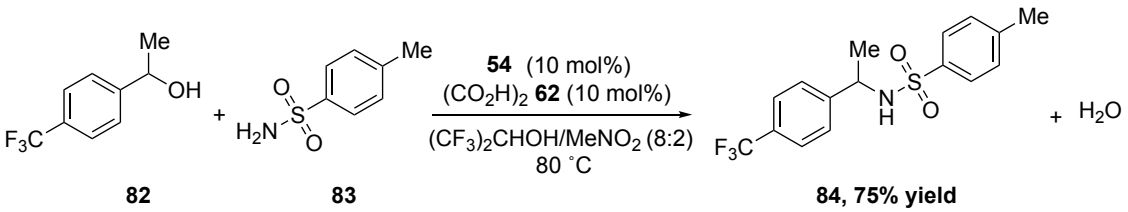
The intramolecular cyclization was extended to the use of pendent heteroatom nucleophiles to form various heterocycles. For example, substituted diol **80** reacts with boronic acid **54** (10 mol%) to give THF **81** in 95% yield (Scheme 1.26). The process works for both oxygen and nitrogen nucleophiles and with different chain lengths to afford substituted THFs, pyrans, oxepans, pyridines and piperidines in high yields.



Scheme 1.26 Intramolecular cyclization to form substituent THF

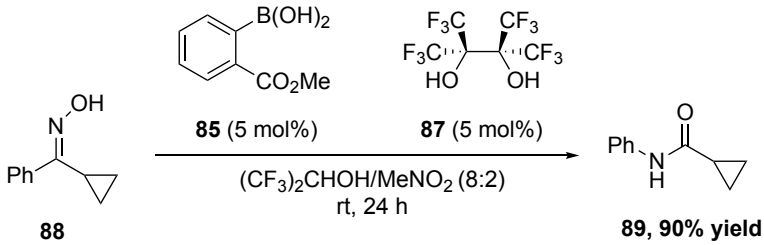
In 2017, Hall and co-workers reported the combination of 2,3,4,5-tetrafluorophenylboronic acid **54** (10 mol%) and oxalic acid **62** (10 mol%) as the active catalyst for the alkylation of sulfonamides using benzylic alcohols.[52] The substrate scope was studied with a range of secondary benzylic alcohols bearing a number of different electronic substituents. For

example, electron-deficient alcohol **82** reacts with sulfonamide **83** to give protected amine **84** in 75% yield (Scheme 1.27). A number of different substituted sulfonamides also displayed good reactivity under the optimal reaction conditions.



Scheme 1.27 Sulfonamidation of benzylic alcohols

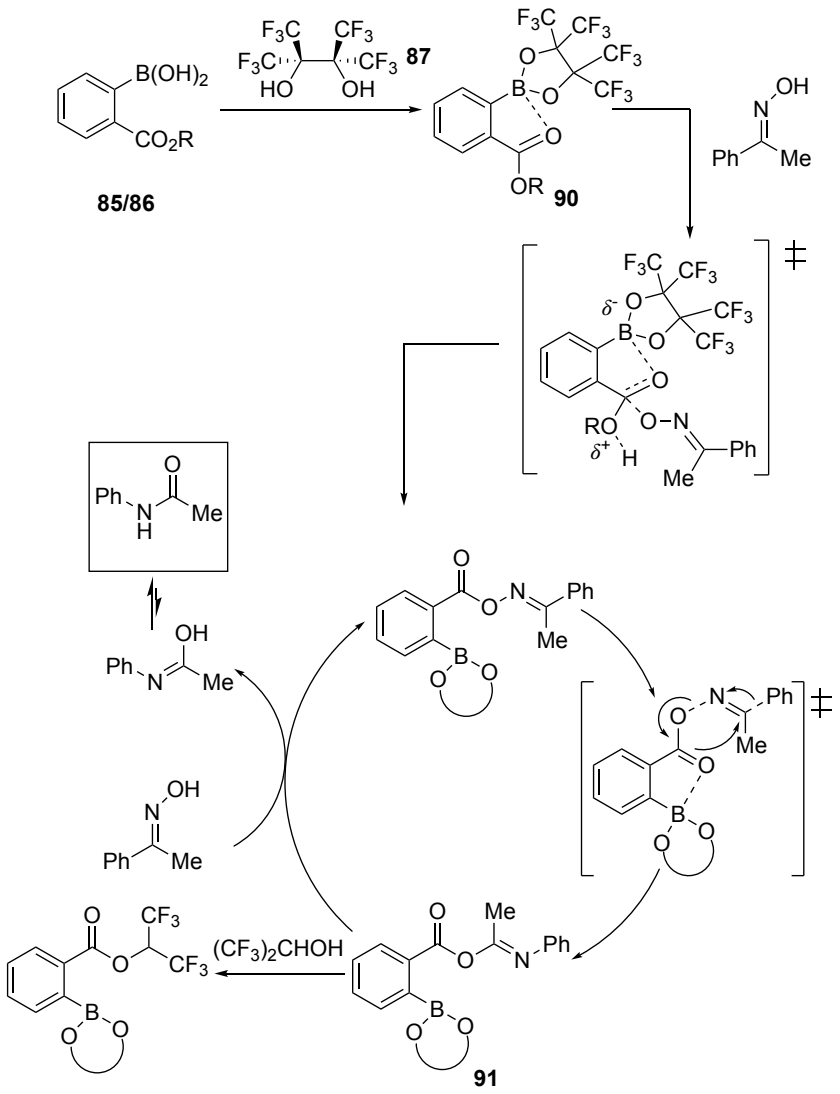
In 2018, Hall and co-workers discovered that 2(methoxycarbonyl)phenylboronic acid **85** or 2(phenoxycarbonyl)phenylboronic acid **86** in combination with perfluoropinacol **87** catalyzes the Beckman rearrangement of oximes (Scheme 1.28).[53] The substrate scope shows the reaction tolerates various functional groups including halides, alcohols, amides and nitrile groups, giving the amide products in good yields. Substrates containing acid sensitive protecting groups suc as Boc or Ts in the oxime also reacted efficiently. For example, (*E*)-cyclopropyl(phenyl)methanone oxime **88** reacts using boronic acid **85** (5 mol%) and perfluoropinacol **87** (5 mol%) in a mixture of hexafluoroisopropanol and nitromethane (4:1) to give amide **89** in 90% yield.



Scheme 1.28 Beckman rearrangement using boronic acids 85 as catalysts.

Mechanistic studies suggested a novel organocatalytic pathway initiated by a boron promoted transesterification of the phenyl ester from the boronic acid with the oxime substrate, followed by unimolecular Beckman rearrangement (Scheme 1.29). Transesterification of rearranged intermediate with either a second oxime substrate or HFIP releases the amide product. Perfluoropinacol **87** is thought to condense with the boronic acid

to form boronate ester **90**, which is more Lewis acidic to stabilize both the transesterification and rearrangements steps.



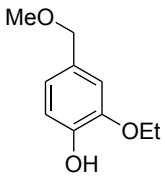
Scheme 1.29 Proposed mechanism for Beckman rearrangement using boronic acids 85 or 86

2 Dehydrative Substitution of Benzylic Alcohols for C-O Bond Formation.

2.1 Introduction

Ethers are one of the most extensively used functional groups in organic chemistry that have applications in both industry and academia. For example, glycerol ethers made from ethylene oxide E-series glycerol are typically used in inks, paints and cleaners with a global market value of $1.64 billion in 2015,[54] which is expected to increase over the coming years.

The fragrance industry also extensively uses ether molecules. For example, methyl diantilis **92** (Figure 2.1) contains both a methyl and an ethyl ether. “Spicy, carnation, sweet and vanilla” are its olfactive features and it is used in shampoos and fragrances with a large commercial success.[55]



92
Methyl diantilis

Figure 2.1 Structure at Methyl diantilis

A number of natural products and biologically active molecules also contains ether linkages (Figure 2.2). For example, Miconazole **93** has a dibenzyl ether and is used as an antifungal drug.[56] Etofenprox **94** also contains a benzylic ether and has been tested as an insecticide.[57] A range of secondary diaryl ethers with similar structures have different biological applications. Carbinoxamine **95** has displayed antihistamine activity,[58] while Tofenacin **96** has been used as an antidepressant drug since the 1970’s.[59] Structurally related Orphenadrine **97** is used as a drug to help with motor control in Parkinson’s disease.[60]

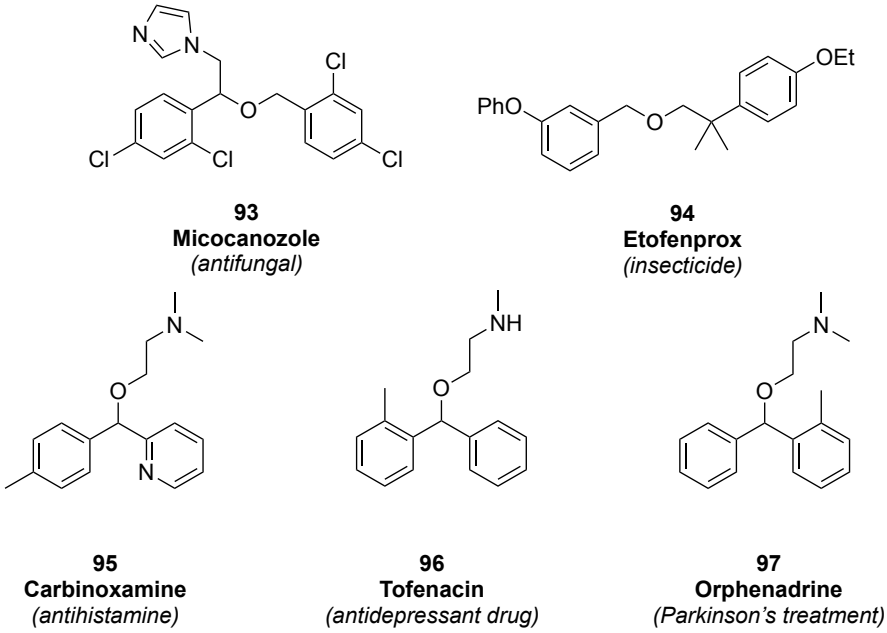
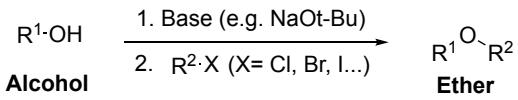


Figure 2.2 Natural products and biologically active molecules containing ethers.

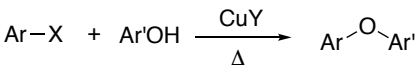
2.1.1 Synthesis of ethers

One of the most traditional etherification methods was first reported in the mid 19th century by Williamson (Scheme 2.1).[61] The reaction involves treating an alcohol with an inorganic base (e.g. NaO*t*-Bu) leading to deprotonation into an intermediate alkoxide. This can be reacted with an appropriate electrophile, such as alkyl halide, *via* an SN2 reaction to get the ether product. This method has been extensively used on both an industrial and a laboratory scale to form both symmetrical and unsymmetrical ethers.



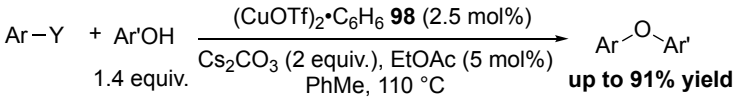
Scheme 2.1 Williamson ether synthesis

Another common method for etherification is the copper-promoted Ullmann-type reaction involving aryl halides and suitable alcohol nucleophiles (Scheme 2.2).[62]



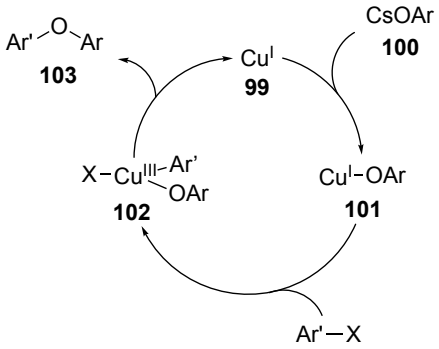
Scheme 2.2 General Ullman-type ether formation

The first examples of Ullmann-type etherification used stoichiometric amounts of copper and usually harsh reaction conditions.[63] In 1997, Buchwald reported the use of copper triflate **98** (2.5 mol%) as a catalyst in the reaction between aryl halides and phenols, but the process requires super-stoichiometric caesium carbonate.[64] This reaction resulted in a variety of substituted unsymmetrical aryl ethers in high yields (Scheme 2.3).



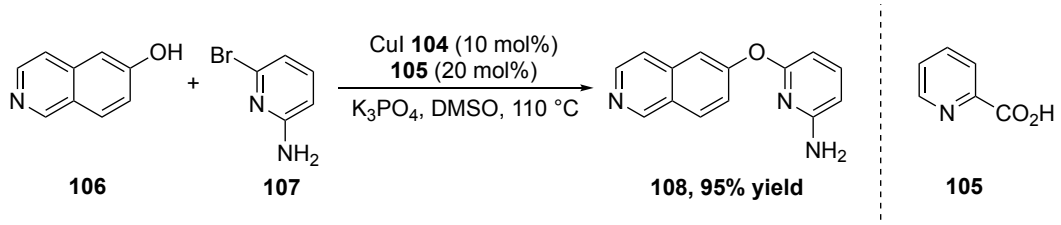
Scheme 2.3 Buchwald's catalytic Ullmann-type coupling

In the proposed mechanism, Cu(I) **99** is first attacked by aryl alkoxide **100** to form intermediate **101**. Oxidative addition into the aryl halide gives Cu (III) intermediate **102**, with reductive elimination giving the new ether linkage **103** and releasing the catalyst (Scheme 2.4).



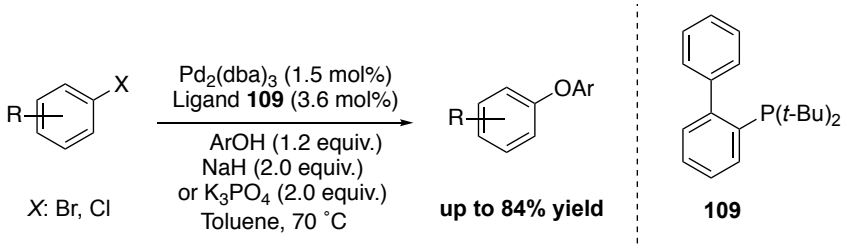
Scheme 2.4 Proposed mechanism of the Cu-catalysed Ullmann reaction

Since Buchwald's first report, different Cu(I) ligand systems have been developed for the synthesis of challenging diaryl ethers. In 2010 the same author reported the use of CuI **104** (10 mol%) and picolinic acid **105** (20 mol%) as a ligand combined with K_3PO_4 as base in DMSO to form sterically demanding *ortho*-substituted diaryl ethers as well as substituted heteroaryl ethers in high yields.[65] For example, using CuI **104** (10 mol%) and picolinic acid **105** (20 mol%) in the presence of a base reacts **106** and **107** at 110 °C to give diaryl ether **108** in 95% yield (Scheme 2.5).



Scheme 2.5 Challenging CuI-catalysed heteroaryl ether synthesis

An alternative to the Ullmann ether synthesis is the palladium-catalysed Buchwald-Hartwig coupling to obtain both aryl ethers and diaryl ethers. Buchwald first reported palladium-catalysed aromatic C-O intramolecular bond formation between an aryl halide with a tethered alcohol to form heterocycles in moderate to good yields, with the use of tertiary alcohols and certain secondary alcohols as a limitation.[66] One year later, Buchwald reported a Pd-catalysed system in presence of bulky phospine **109** for the intermolecular coupling of alcohols and aryl bromides to form aryl ethers as a product (Scheme 2.6).[67]

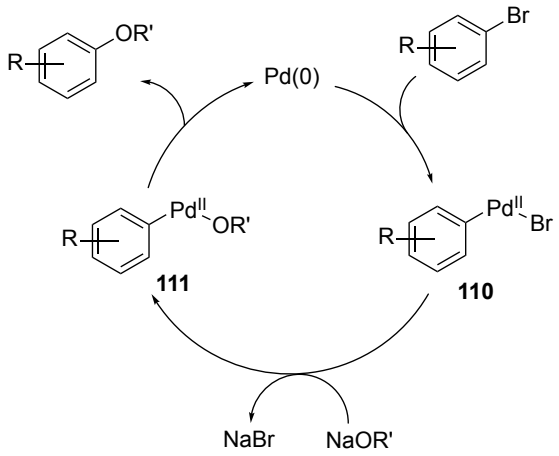


Scheme 2.6 Pd catalysed etherification reaction

Aryl bromides with electron-withdrawing groups coupled effectively with a range of alcohols such as 2-propanol, 3-pentanol or benzyl alcohol in 24 h using $Pd_2(dba)_3$ (1.5 mol%) and tol-BINAP (3.6 mol%) at 70 °C in toluene, with yields up to 84%. The use of electron-rich and neutral aryl bromides also affords the desired coupling products in good yields, although this is limited to alkoxides from either tertiary alcohols or substituted phenols.

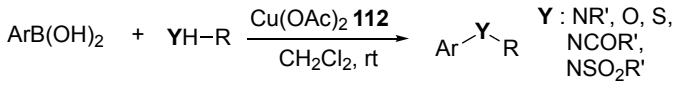
The proposed mechanism starts with an oxidative addition of Pd(0) to the aryl bromide to form **110** (Scheme 2.7). Substitution of the bromide with the alkoxide gives intermediate **11**, with reductive elimination affording the desired aryl ether with regeneration of the catalyst. Reductive elimination is favoured over a competitive ß-hydride elimination pathway due to

ligands effects. Sterically demanding and less electron-donating ligands were found to promote the desired reductive elimination pathway.



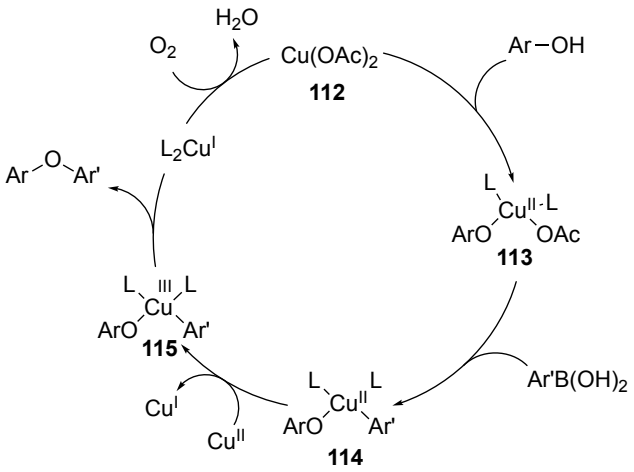
Scheme 2.7 Proposed catalytic cycle for Buchwald aryl etherifications

Another procedure for ether synthesis is the Chan-Evans-Lam coupling, which often avoids the use of high temperatures and anhydrous conditions (Scheme 2.8).[68–70] The reaction uses a copper(II) catalyst **112** for oxidative coupling of boronic acids with heteroatom nucleophiles such us phenols, amides, amines, anilines, imides, ureas, carbamates and sulfonamides.



Scheme 2.8 Chan-Evans-Lam coupling reaction

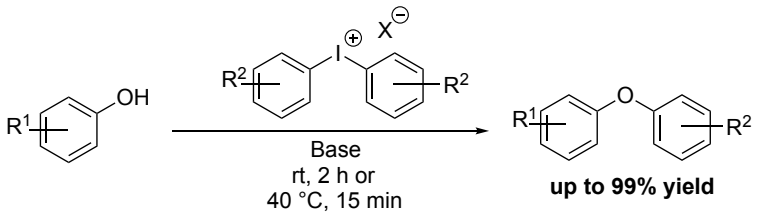
The proposed mechanism for ether synthesis is shown in Scheme 2.9. Initially, a ligand exchange with phenol results in compound **113**. Transmetallation with the arylboronic acid gives intermediate **114,** which is oxidised using a second Cu(II) species to get Cu(III) intermediate **115**. Finally, reductive elimination from **115** forms the ether product and the resulting Cu(I) species is re-oxidised using O_2.



Scheme 2.9 Chan-Evans-Lam coupling proposed mechanism

While the majority of transition metal-catalysed ether formations employ either copper or palladium-based catalysts, there are many other reports using different metals to catalyse C—O bond formations including iron, cobalt and rhodium amongst others.[71]

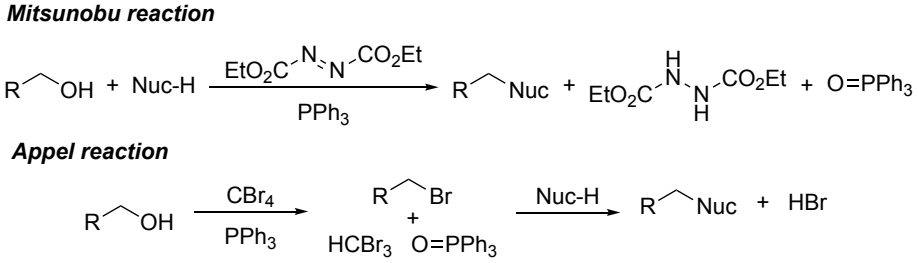
A number of transition metal-free ether syntheses have also been developed. One example was reported by Silva and Ishikawa using phenols and diaryliodonium salts to synthesise diaryl ethers (Scheme 2.10).[72] The reaction requires a base such as sodium hydroxide or potassium *t*-butoxide to deprotonate the phenol and uses the diaryliodonium salt as an arylating agent. The etherification reactions were complete after 15 min at 40 °C or after 2 h at rt. The ether products were obtained in mostly excellent yields using phenols containing electron-withdrawing, electron-donating, *ortho* aryl substituents and carbonyl substituents.



Scheme 2.10 Transition metal-free synthesis of diaryl ethers

2.1.2 Catalytic activation of alcohols for etherification

The alkylation of heteroatoms is usually performed using an alkyl halide as the electrophile, or alternatively uses stoichiometric amounts of pre-activated alcohols, such as tosylates, with appropriate nucleophiles. Alcohols can also be activated *in situ* using super-stoichiometric amounts of reagents, such as in the Mitsunobu reaction (Scheme 2.11).[2,73] The Appel reaction[74,75] can be used to form alkyl halides from alcohols, which can react with various nucleophiles. In both cases, these reactions produce multiple stoichiometric by-products that must be separated from the desired product.

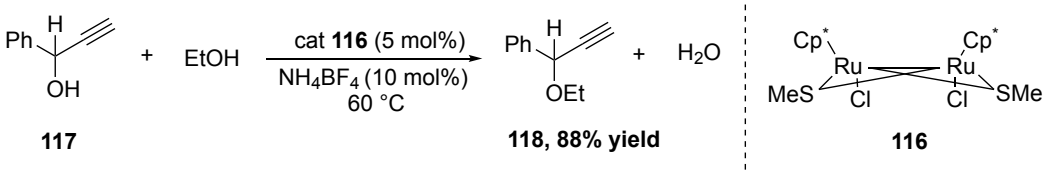


Scheme 2.11 Mitsunobu and Apple reactions

The area of catalytic alcohol activation as electrophiles in substitution reactions with different nucleophiles has increased in interest in recent years, with a number of examples reported. However, the need for further developments and milder conditions in new methods has again been highlighted last year by the ACS Green Chemistry Institute Roundtable as a top research priority.[76,77] In theory, an alcohol may be activated using a mild Lewis or Brønsted acid catalyst to increase its leaving group capacity. Once the electrophilic alcohol is activated, a nucleophilic substitution reaction using a second alcohol as the nucleophile can then follow *via* an S_N1 or S_N2-type mechanism, affording the desired ether product and having water as the only by-product.

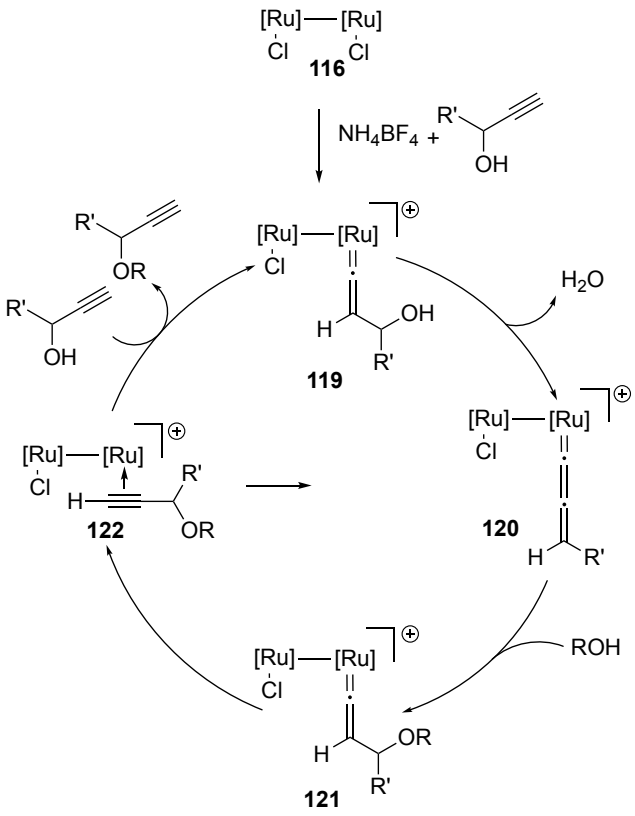
Hidai and co-workers reported a catalytic reaction of propargylic alcohols with simple alkyl alcohols (e.g. methanol, ethanol or isopropanol) using diruthenium-based catalyst **116**.[78] Propargylic substitution reactions of 1-monoalkyl and 1,1-dialkyl–substituted propargylic alcohols occurred rapidly, giving the corresponding ether in up to 88% yield. However, 1,1-diaryl propargylic alcohols reacted slowly and required longer times to form the ether products in moderate yields. When the reaction was performed using enantiomerically pure

primary alcohols, a 1:1 mixture of two diastereoisomers was formed in moderate to high yields. For example, propargylic alcohol **117** reacts with ethanol in presence of catalyst **116** (5 mol%) and ammonium tetrafluoroborate (10 mol%) at 60 °C to give ether **118** in 88% yield (Scheme 2.12).



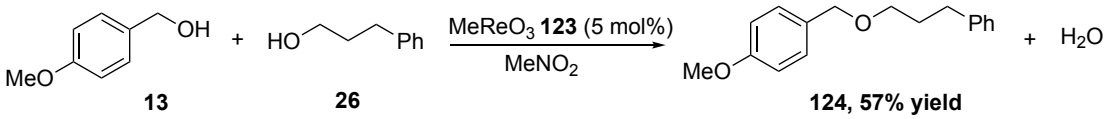
Scheme 2.12 Propargylic substitution reaction catalysed by di-ruthenium based catalyst 116

The proposed mechanism includes initial formation of vinylidene complex **119** from the propargylic alcohol (Scheme 2.13). Loss of water gives allenylidene complex **120** and subsequent nucleophilic attack of the primary alcohol on intermediate **120** forms complex **121**. Tautomerization into coordinated propargylic ether **122** occurs, which releases the ether product upon reaction with a new propargylic alcohol to regenerate **119**.



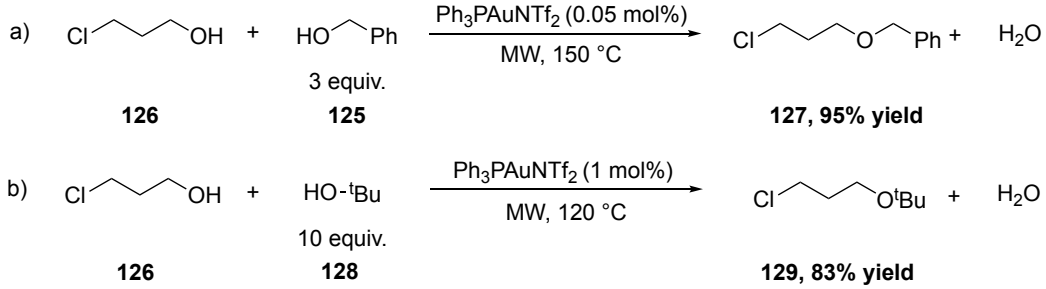
Scheme 2.13 Proposed catalytic cycle

Samec and co-workers reported another example of catalytic dehydrative substitution in which different metal catalysts were used depending on the nature of the nucleophile.[79] The activation of reactive benzylic, allylic and propargylic alcohols using different Lewis aci catalysts using oxygen, nitrogen and sulphur-based nucleophiles was investigated. For catalytic nucleophilic substitution by O-centred nucleophiles, the use of $MeReO_3$ **123** (5 mol%) was the most effective. For example, reacting *p*-methoxybenzyl alcohol **13** with alcohol **26** using the Re(VII) **123** catalyst in nitromethane at room temperature formed ether **123** in 57% yield (Scheme 2.14).



Scheme 2.14 Etherification using rhenium (VII) 123 as catalyst

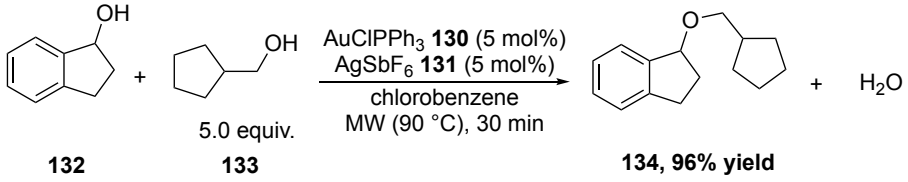
In 2015, Cheng and co-workers reported a gold-catalysed reaction between benzylic alcohols and alkyl alcohols using microwave irradiation to obtain unsymmetrical ethers under solvent-free conditions.[80] The method was applied to benzylic alcohol **125** with simple alkyl alcohols such as **126** (Scheme 2.15a), giving ether **127** in 95% yield after microwave irradiation at 150 °C. The process was also studied using *tert*-butyl alcohol **128** with alcohol **125** (Scheme 2.15b), which afforded the corresponding ether **129** in 83% yield. The procedure was reported to work for a range of primary alcohols and substituted aliphatic alcohols, giving excellent yields of the ether products.



Scheme 2.15 Gold(I)-catalysed benzyl ether 127 and *t*-butyl ether 129 formation reaction

In the same year, Wenzel and co-workers reported a similar reaction using $AuClPPh_3$ **130** (5 mol%) as the catalyst with $AgSbF_6$ **131** (5 mol%) as an activator.[81] For example, the reaction of

indanol **132** with primary alcohol **133** was performed under microwave irradiation at 90 °C in chlorobenzene to give ether **134** in 96% yield (Scheme 2.16).



Scheme 2.16 Gold-catalysed ether synthesis under MW conditions

In 2005, Uenishi reported the use of a palladium catalyst for the stereospecific cyclisation of an hydroxyl group onto an allylic alcohol to give tetrahydropyran rings used in the synthesis of the natural product (–)-Laulimalide **135** (Figure 2.3).[82]

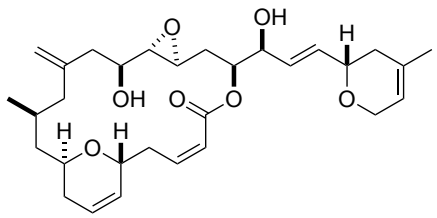
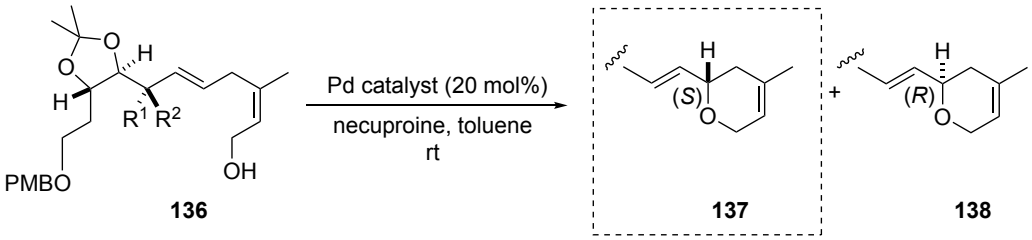


Figure 2.3 (–)-Laulimalide 135

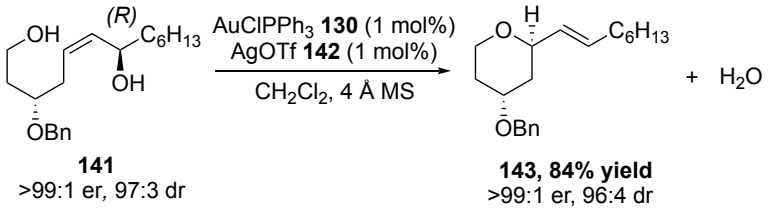
The palladium-catalysed allylic substitution to form the key tetrahydropyran intermediate **137** was shown to be stereospecific (Table 2.1). For example, reacting allylic carbonate **136a** with $Pd_2(dba)_3$ **139** (20 mol%) gave pyran **137** in 59% yield. However, reacting diastereomeric carbonate **136b** under the same conditions formed the opposite diastereoisomer of pyran **138** in 43% yield. The reaction could also be performed on the un-protected allylic alcohols using $PdCl_2(MeCN)_2$ **140** as the catalyst. The reaction was again stereospecific with opposite diastereoisomers of the allylic alcohol giving two different diastereoisomers of the product. The observed product configuration suggests that the reaction occurs *via* double-inversion pathway, with overall retention of stereochemistry.

Table 2.1 Pd-catalysed intramolecular O-allylation



Entry	Compound	R^1	R^2	Catalyst	137	138	Yield (%)
1	136a	OCOOMe	H	$Pd_2(dba)_3$ **139**	100	0	59
2	136b	H	OCOOMe	$Pd_2(dba)_3$ **139**	0	100	43
3	136c	OH	H	$PdCl_2(MeCN)_2$ **140**	100	0	89
4	136d	H	OH	$PdCl_2(MeCN)_2$ **140**	0	100	77

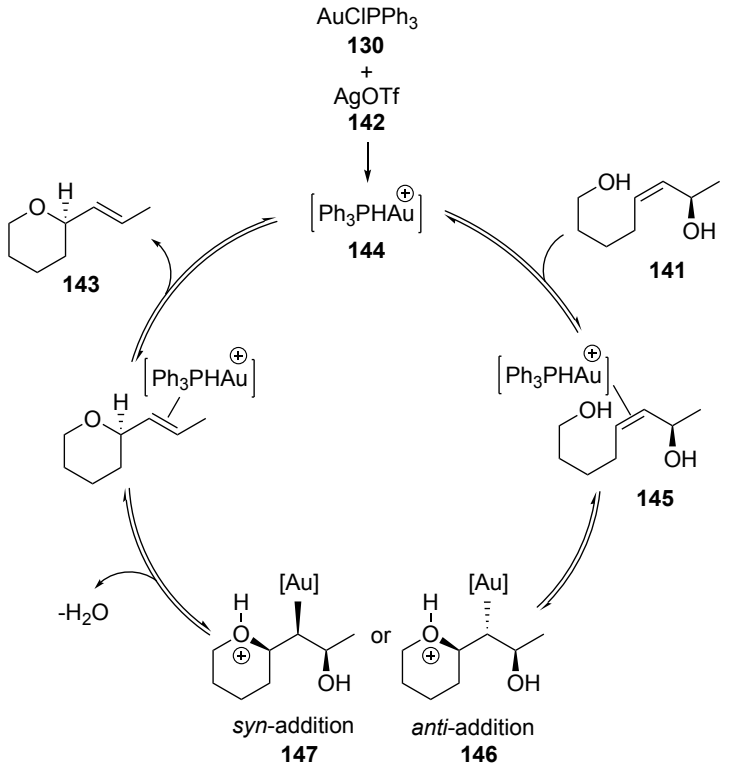
A similar reaction can be performed using a gold catalyst to obtain an intramolecular cyclization of a primary alcohol onto an allylic alcohol. Aponick and Biannic reported the use of gold(I) to catalyse the stereospecific cyclization of primary alcohols onto allylic alcohols to form pyrans.[83] The use of enantiomerically pure allylic alcohols afforded excellent chirality transfer, with the configuration of the new stereocentre dependent on the geometry of the alkene and the configuration of the starting material. For example, reaction of **141** with $Au(PPh_3)Cl$ **130** (1 mol%) and AgOTf **142** (1 mol%) formed pyran **143** with high enantiopurity (Scheme 2.17).



Scheme 2.17 Alkene dependent chirality transfer

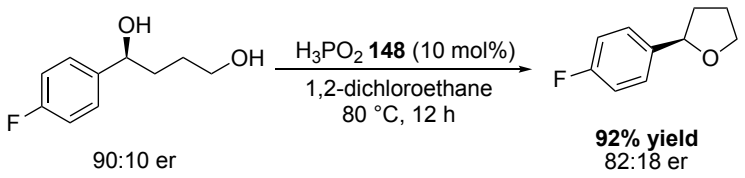
Mechanistically, the cationic Au(I) complex **144** is formed from the catalyst precursors with loss of AgCl (Scheme 2.18). Coordination to the π-bond of the allylic alcohol forms **145**, with nucleophilic addition of the pendent alcohol followed by elimination of water forming the

tetrahydropyran ring. The diastereoselectivity of the addition/elimination step is unknown, with *anti*-addition via **146** followed by a*nti*-elimination and *syn*-addition *via* **147** followed by *syn*-elimination both affording the observed product configuration. However, the authors favoured the *anti*/*anti* pathway based upon other gold-catalysed reactions.



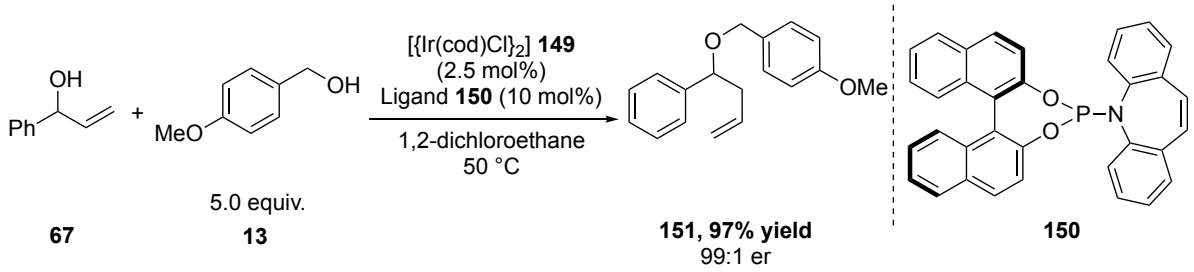
Scheme 2.18 Proposed catalytic cycle

Samec and co-workers reported a stereospecific intramolecular dehydrative cyclization to form substituted tetrahydrofurans using a phosphinic acid as a Brønsted acid catalyst (Scheme 2.19).[84] The reaction used 10 mol% phosphinic acid **148** in 1,2-dichloroethane at 80 °C to generate the products in high yields with good chirality transfer. The reaction of benzylic alcohols bearing electron-withdrawing aryl substituents gave higher levels of chirality transfer, whereas the presence of electron-donating groups led to lower enantiopurity. The intramolecular cyclization also worked for allylic, propargylic and secondary aliphatic alcohols to afford the substituted tetrahydrofurans in high yields and good selectivity. It was suggested that the phosphinic acid promotes the intramolecular substitution *via* bifunctional Brønsted acid/Brønsted base catalysis to activate both the nucleophile and the leaving group in the cyclization reaction.



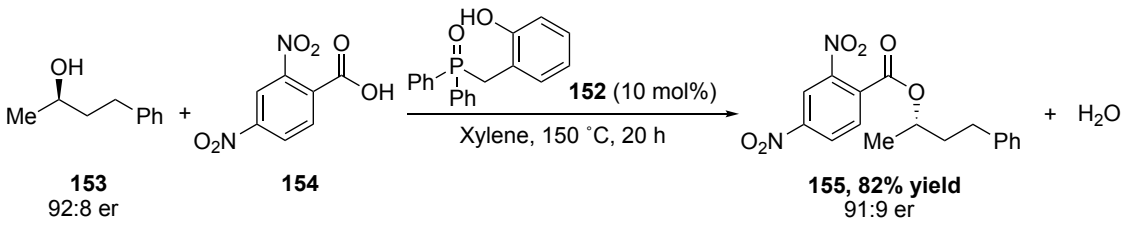
Scheme 2.19 Phosphinic acid-catalysed intramolecular substitution of benzylic alcohols.

Carreira and co-workers reported an enantioselective crossed etherification reaction using an Ir-catalyst **149** with a chiral phosphoramidite ligand (Scheme 2.20).[85] The reaction uses allylic alcohols as the electrophile that are activated by the iridium and phosphoroamidate ligand **150**. For example, reacting allylic alcohol **67** with *p*-methoxybenzyl alcohol **13** forms ether **151** in excellent 97% yield and 99:1 er. The process tolerates primary and secondary aliphatic alcohols as the nucleophile, while electron-deficient and heteroaromatic-substituted allylic alcohols are suitable electrophiles.



Scheme 2.20 Ir-catalysed allylic etherification

In 2019, Denton and co-workers reported the use of (2-hydroxybenzyl)diphenylphosphine oxide **152** (10 mol%) as a redox-neutral catalyst for the mitsunobu substitution of primary and secondary alcohols, producing water as the sole by-product.[86] The reaction tolerates a range of sensitive functional groups, forming the products in mostly high yields with excellent selectivity. For example, (*R*)-4-phenylbutan-2-ol **153** reacts with 2,4-dinitrobenzoic acid **154** using 10 mol% **152** in xylenes to give ester **155** in 82% yield with complete inversion of stereochemistry (Scheme 2.21).

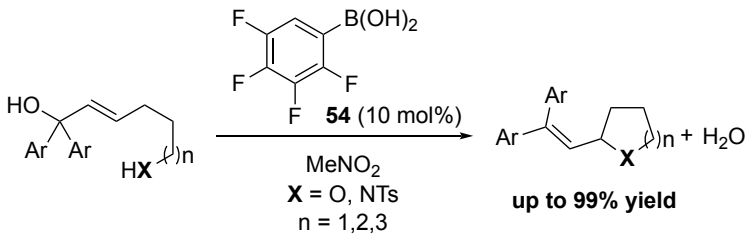


Scheme 2.21 Redox-free catalytic Mitsunobu reaction

Despite the recent advances in dehydrative substitution, the development of readily available catalysts that can activate alcohols under milder conditions is desirable. This project focuses on the use of simple aryl boronic acids as catalysts for etherification reactions using alcohols as both the nucleophile and the electrophile.

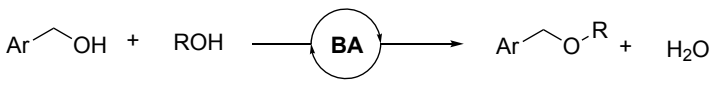
2.1.3 Uses of boron for C-O bond formation

Previous reports using boronic acids for the activation of alcohols have been discussed in Chapter I. However, there is only one report by Hall and co-workers using an aryl boronic acid to afford an intramolecular heterocyclisation of pendent oxygen and nitrogen nucleophiles onto tertiary allylic alcohols (Scheme 2.22).[51]



Scheme 2.22 Boronic acid-catalysed intramolecular heterocyclisation.

With no previous reports using aryl boronic acids as catalysts for intermolecular dehydrative substitution, our initial investigation was focused into the use of readily available benzylic alcohols as the electrophilic component in combination with a second alcohol as the nucleophile in a dehydrative substitution reaction (Scheme 2.23).



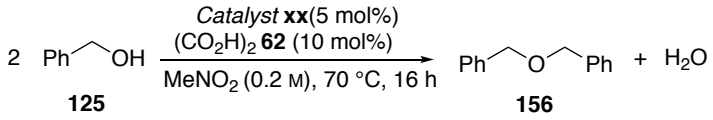
Scheme 2.23 Dehydrative substitution reaction for ether synthesis

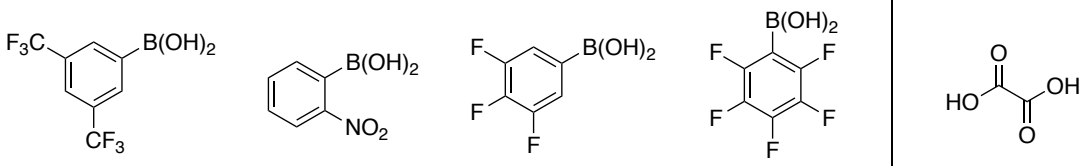
2.2 Symmetrical ether formation

2.2.1 Reaction optimisation

Initially, catalytic dehydrative substitution using a single benzylic alcohol substrate as both the electrophile and the nucleophile was investigated. Inspired by the work of Moran on dehydrative Friedel-Crafts alkylation reactions,[47] the first tests used a small range of electron-deficient arylboronic acids (5 mol%) in combination with oxalic acid **62** at 70 °C in nitromethane for the reaction of benzyl alcohol **125** to form dibenzyl ether **156** (Table 2.2). While the use of catalysts **65, 157** and **37** gave little or no reactivity, the use of commercially available pentafluorophenylboronic acid **48** gave dibenzyl ether **156** in a promising 67% yield.

Table 2.2 Catalyst optimisation





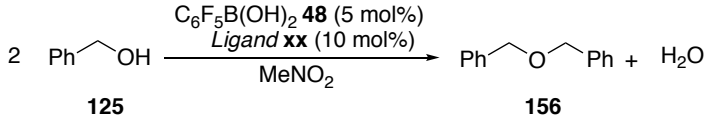
Catalysts Ligand

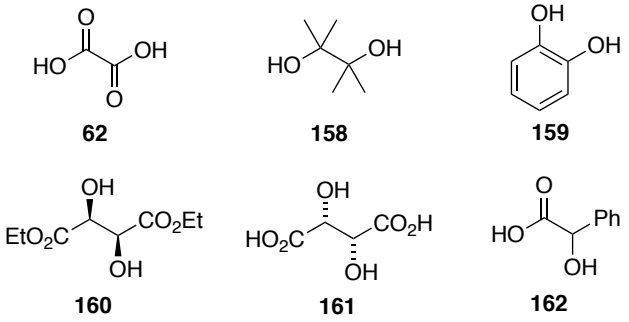
Entry	Boronic acid	yield **156** (%)
1	3,5-bis(trifluoromethyl)phenylboronic acid **65**	0
2	2-nitrophenylboronic acid **157**	0
3	3,4,5-trifluorophenylboronic acid **37**	10
4	pentafluorophenylboronic acid **48**	67

Different ligands (10 mol%) for boron were then screened in combination with pentafluorophenylboronic acid **48** (5 mol%) and nitromethane as solvent (Table 2.3). When pinacol **158** (entry 2), catechol **159** (entry 3) and (*S,S*)-diethyl tartrate **160** (entry 4) were used with arylboronic acid **48** (5 mol%) for 16 h at 70 °C in nitromethane, no reaction was observed.

However, tartaric acid **161** (entry 5) led to a 38% yield of ether **156**. Using mandelic acid **162** (entries 7 and 8) at 90 °C for 96 h gave quantitative conversion into product **156**, allowing it to be isolated in 65% yield. The yield obtained using mandelic acid **162** was comparable with the yield obtained using oxalic acid **62** but required heating at 90 °C and longer reaction times. Oxalic acid **62** enhanced the reactivity with 67% yield of ether **156** obtained after only 3 h (entry 10) and therefore this was chosen as optimal ligand. Control experiments in the absence of either boronic acid **48** or oxalic acid **62** under the otherwise optimal reaction conditions resulted in no product formation (Table 2.3, entries 1 and 11).

Table 2.3 Ligands screening





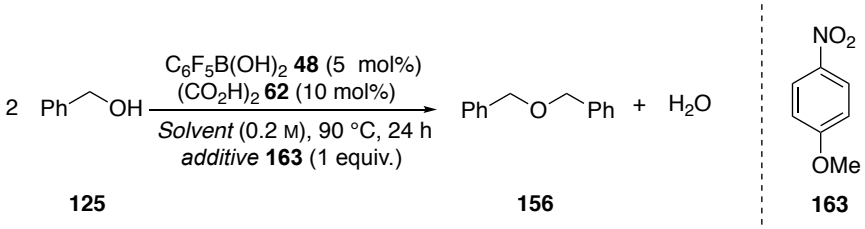
Entry	Ligand (mol%)	T(°C)	t(h)	Yield **156**(%)
1	—	70/90	16/3	0/0
2	pinacol **158** (10)	70	16	0
3	catechol **159** (10)	70	16	0
4	(*S,S*)-diethyl tartrate **160** (10)	70	16	0
5	tartaric acid **161** (10)	70	16	38
6	oxalic acid **62** (10)	70	16	67
7	mandelic acid **162** (10)	70	16	23
8	mandelic acid **162** (10)	90	96	65
9	oxalic acid **62** (5)	90	16	55
10	oxalic acid **62** (10)	90	3	67
11[(a)]	oxalic acid **62** (10)	90	3	0

[(a)]No boronic acid **48** was used

Similarly, the use of other solvents such as toluene, THF, acetonitrile or dichloromethane, including various mixtures with nitromethane led to no reactivity, limiting the possibility of using a solvent other than nitromethane in the procedure (Table 2.4). Moran and co-workers

have previously reported that nitromethane could be replaced as a solvent if nitroanisole **163** was used as an additive in either toluene or benzene.[27] However, the use of this additive gave no reactivity in this system (entries 7 and 8).

Table 2.4 Screening of the solvents

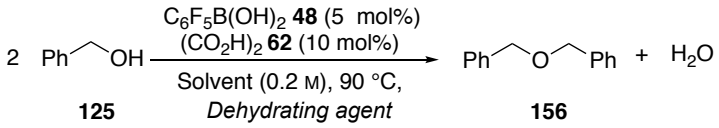


Entry	Solvent	Ratio	Additive mmol	Conv **156**(%)[a]
1	$MeNO_2$[b]	100	–	(67)[c]
2	$MeNO_2$:Toluene	100	–	7
3	$MeNO_2$:THF	100	–	2
4	$MeNO_2$:CH_3CN	50:50	–	0
5	$MeNO_2$:Toluene	50:50	–	0
6	CH_2Cl_2	100	–	0
7[d]	Toluene	–	0.2	0
8[d]	Benzene	–	0.2	2

[a]Determined by ^{1}H NMR spectroscopic analysis [b]Reaction performed for 3 h [c]Isolated yield [d]Reaction time 72 h

Next, in an attempt to further improve the yield, the possibility of removing the water formed during the reaction was investigated (Table 2.5). However, performing the reaction in the presence of various sizes of molecular sieves or magnesium sulphate gave a complete loss in reactivity, with no conversion into ether **156** obtained.

Table 2.5 Reaction optimization with dehydrating agents or an additive



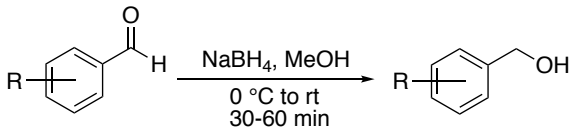
Entry	Dehydrating agent	Solvent	Conversion **156**(%)
1	3 Å MS	$MeNO_2$	0
2	4 Å MS	$MeNO_2$	0
3	5 Å MS	$MeNO_2$	0
4	$MgSO_4$	$MeNO_2$	0
5	–	$MeNO_2$	67[(a)]

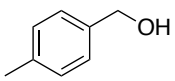
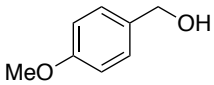
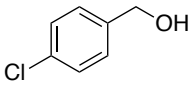
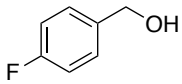
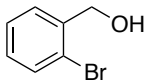
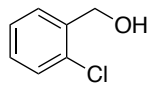
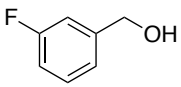
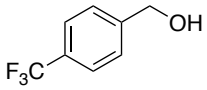
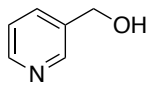
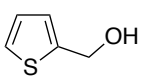
[(a)]Isolated yield after column chromatography

2.2.2 Synthesis of starting materials

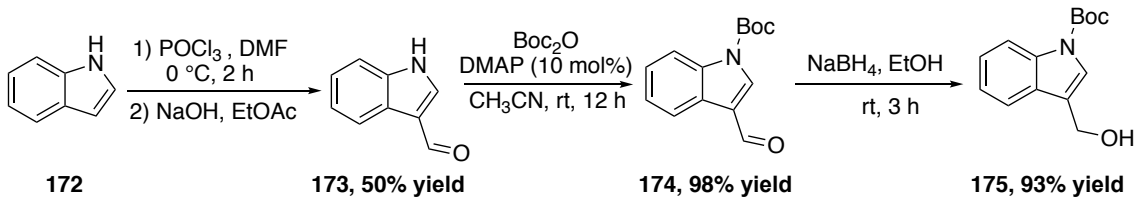
In order to access the required starting materials for the substrate scope, a range of benzylic alcohols was easily prepared in a one-step synthesis from the corresponding aldehydes by reduction using sodium borohydride in methanol.[87] This reduction method has been used for the synthesis of a range of substituted benzyl alcohols as well as heterocyclic alcohols, generally in high yields (Table 2.6).

Table 2.6 Starting materials synthesis



				
164, 96% yield	**13, 97% yield**	**165, 80% yield**	**60, 87% yield**	**166, 98% yield**
				
167, 87% yield	**168, 98% yield**	**169, 93% yield**	**170, 25% yield**	**171, 97% yield**

Heterocyclic indole-containing alcohol **175** was also prepared. First, indole **172** was treated under Vilsmeier-Haack formylation conditions to form **173** in 50% yield (Scheme 2.24).[88] The N–H was then protected using Boc-anhydride to form indole **174** in 98% yield.[89] The aldehyde was reduced into the corresponding alcohol **175** in an excellent 93% yield.



172 **173, 50% yield** **174, 98% yield** **175, 93% yield**

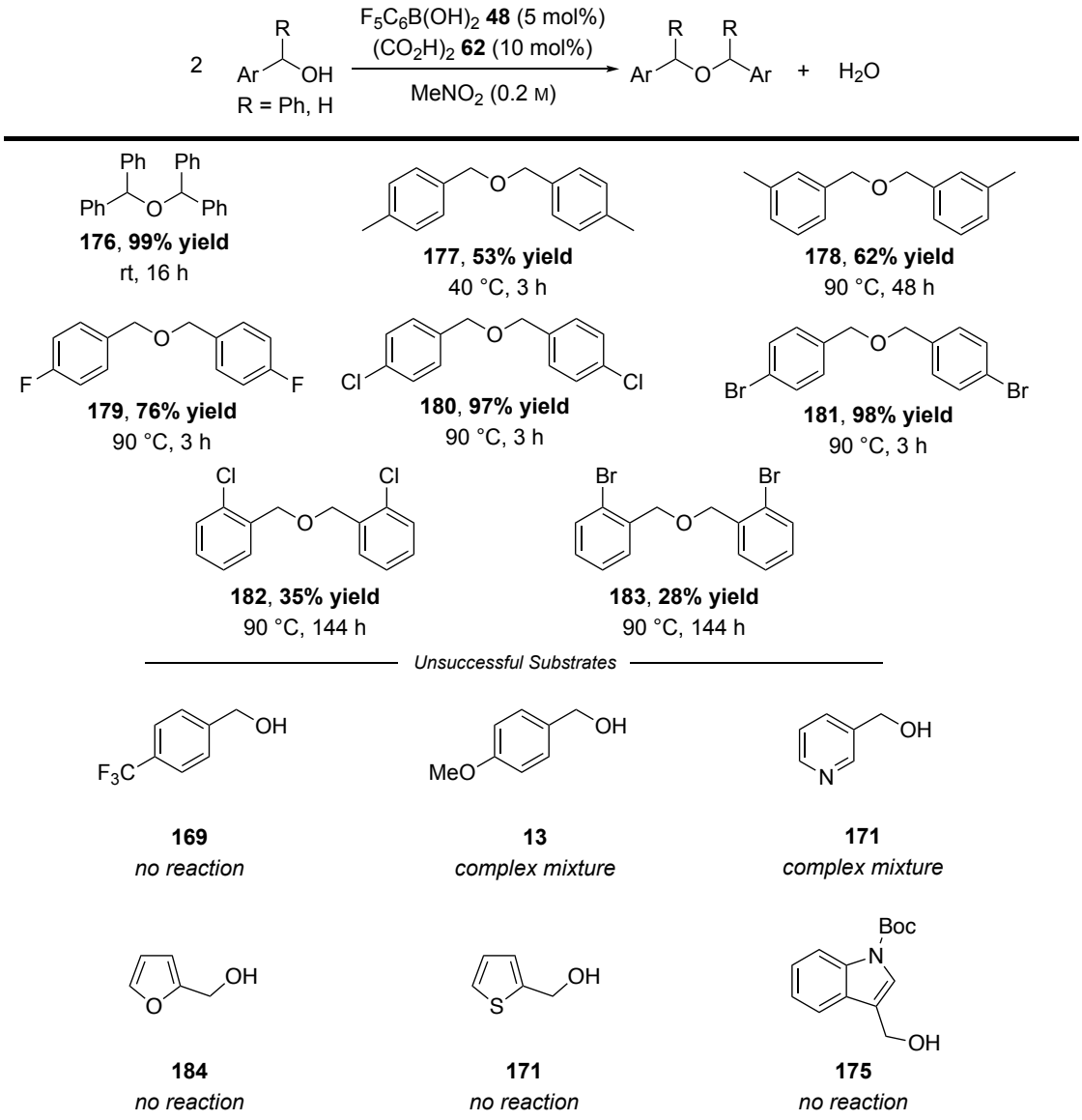
Scheme 2.24 Indole alcohol synthesis

2.2.3 Substrate scope

The scope of the aryl boronic acid-catalysed intermolecular dehydrative etherification was then investigated using the different substituted benzylic alcohols under the previously optimized reaction conditions (Table 2.7). Benzhydrol **9** was highly reactive and led to ether **176** in excellent 99% yield at room temperature. The reaction using *p*-tolyl alcohol **164** under the previously optimised conditions at 90 °C gave different undesired side products, including those from Friedel-Crafts alkylations. However, lowering the reaction temperature to 40 °C gave **177** in 53% yield after purification by column chromatography. In contrast, reaction with 3-methylbenzyl alcohol needed heating at 90 °C for an extended time (48 h) to afford symmetrical ether **178** in 62% yield. Halogen-substituted benzyl alcohols were especially well tolerated, with 4-fluoro, 4-chloro- and 4-bromobenzyl alcohols giving the corresponding ethers **179**-**181** in excellent yields. However, the use of more sterically demanding 2-chloro- and 2-bromobenzyl alcohol gave reduced reactivity, with increased reaction times required to afford ethers **182** and **183** in low 35% and 28% yield, respectively. Limitations of this methodology include the presence of highly electron-withdrawing aryl substituents. For example, 4-trifluoromethylbenzyl alcohol **169** returned only starting material even after extended reaction times. In contrast, electron-rich 4-methoxybenzyl alcohol **13** was highly reactive, resulting in a complex mixture of products including those from undesired Friedel-Crafts alkylation processes.[90] Lowering the temperature to either rt or –10 °C did not improve the selectivity of the reaction with **13**, with only minimal amounts of ether formation

observed. The use of heterocyclic alcohols, including 3-pyridylcarbinol **171**, also resulted in a complex mixture under the standard reaction conditions and other heterocycle containing furyl **184**, thiophenyl **171** or indol alcohol **175** substituents were also unsuccessful.

Table 2.7 Intermolecular dehydrative etherification of benzylic alcohols



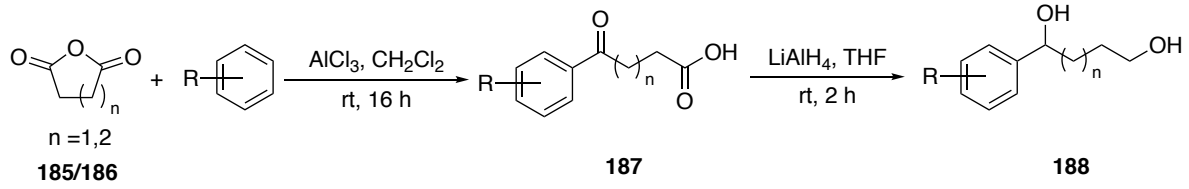
2.3 Intramolecular dehydrative etherification.

Next, the intramolecular dehydrative substitution of secondary benzylic alcohols with a tethered primary alcohol to synthesise saturated oxygen heterocycles was investigated.

2.3.1 Starting materials synthesis

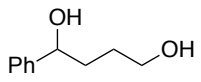
A range of starting materials was made in two steps from the corresponding substituted benzenes (Table 2.8). First, an aluminium trichloride-promoted Friedel-Crafts acylation using either succinic anhydride **185** or glutaric anhydride **186** formed a substituted keto-acid **187**, which was reduced into the corresponding diol **188** using lithium aluminium hydride at room temperature. The reaction worked well for a range of substituted benzenes, giving the desired diols in high yields over the two steps after purification by column chromatography.

Table 2.8 Starting materials synthesis for THF and THP products

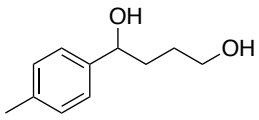


185/186 **187** **188**

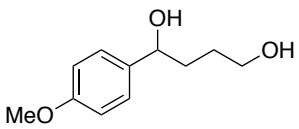
n=1



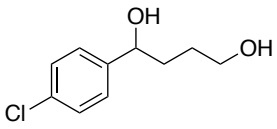
189, 59% yield



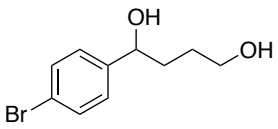
190, 82% yield



191, 87% yield

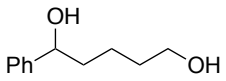


192, 84% yield

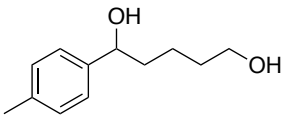


193, 86% yield

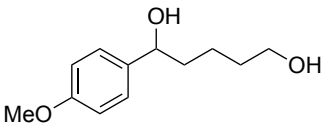
n=2



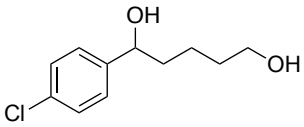
194, 61% yield



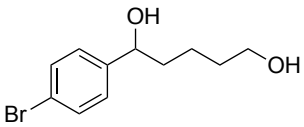
195, 98% yield



196, 75% yield



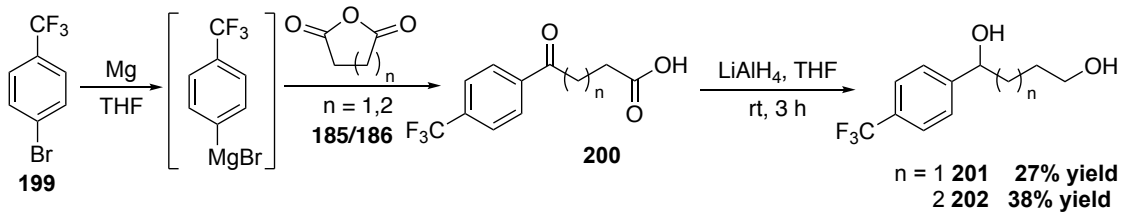
197, 64% yield



198, 73% yield

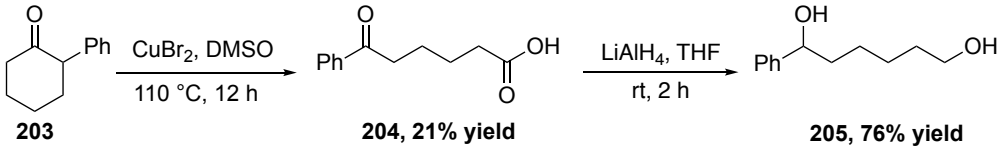
The synthesis of diols bearing a trifluoromethyl substituent started from bromobenzotrifluoride **199**. The corresponding Grignard was made *in situ*, which was added

to a solution of either succinic anhydride **185** or glutaric anhydride **186** to afford substituted keto-acid **200**. Subsequent reduction into the desired diol **201** or **202** again used lithium aluminium hydride at room temperature.



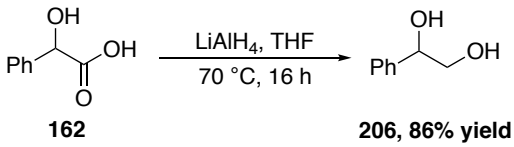
Scheme 2.25 Synthesis of 1-(4-(trifluoromethyl)phenyl)butane-1,4-diol 201 and 1-(4-(trifluoromethyl)phenyl)pentane-1,5-diol 202

The synthesis of chain extended 1-phenylhexane-1,6-diol **205** was performed by reacting 2-phenylcyclohexanone **203** with copper dibromide in DMSO to give crude oxo-acid **204,** which was reduced into the corresponding diol **205** using lithium aluminium hydride (Scheme 2.26).



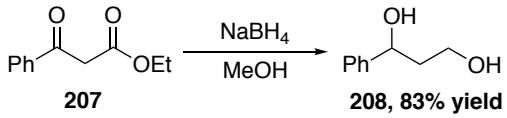
Scheme 2.26 Synthesis of 1-phenylhexane-1,6-diol 205

For the investigation into the formation of three-membered epoxide rings, 1,2-diol **206** was prepared directly in high yield from mandelic acid **162** through reduction using lithium aluminium hydride (Scheme 2.27).



Scheme 2.27 Synthesis of 1,2-diol 206

Finally, the cyclisation to form a four-membered oxetane was studied using 1-phenylpropane-1,3-diol **208**, which was easily synthesized from ethyl benzoylacetate **207** through reduction using sodium borohydride in high 83% yield.



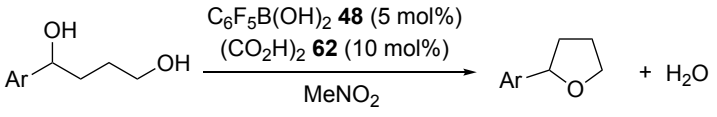
207 **208, 83% yield**

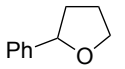
Scheme 2.28 1-Phenylpropane-1,3-diol 208 synthesis

2.3.2 Substituted THF synthesis

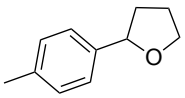
The intramolecular dehydrative substitution of secondary benzylic alcohols bearing a pendant primary alcohol substituent was first tested for the preparation of THF derivatives (Table 2.9). Under the previously optimised conditions using pentafluorophenylboronic acid **48** (5 mol%) and oxalic acid **62** (10 mol%), the intramolecular cyclisation of 1-phenylbutane-1,4-diol **189** proceeded smoothly at 40 °C, forming THF **209** in 92% yield with no products from competing intermolecular processes observed. When the starting material contained a mildly electron-donating 4-methyl substituent, THF **210** was obtained in high 86% yield. In contrast with the intermolecular substitution, reaction with a strongly electron-donating 4-methoxy aryl substituent was tolerated in the intramolecular substitution to give **211** in good yield. Notably, cyclisation in the presence of an electron-withdrawing 4-trifluoromethyl substituent was also possible, with THF **212** isolated in 54% yield after an extended 48 h reaction time. This is again in contrast to the intermolecular reaction, where the use of CF_3 electron-withdrawing group gave no reactivity. Halogen substituents were also well tolerated, with products **213** and **214** obtained in good yields after reaction at 90 °C.

Table 2.9 Intramolecular dehydrative THF formation

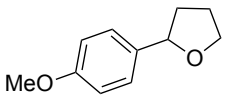




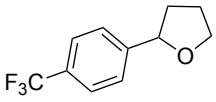
209, **92% yield**
40 °C, 6 h



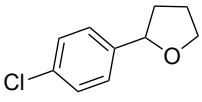
210, **86% yield**
40 °C, 6 h



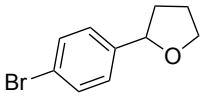
211, **60% yield**
40 °C, 6 h



212, **54% yield**
40 °C, 48 h

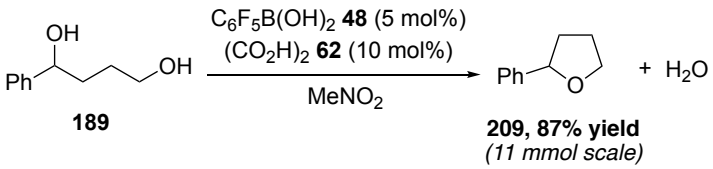


213, **67% yield**
90 °C, 6 h



214, **86% yield**
90 °C, 6 h

This reaction was also performed on a preparative 11 mmol scale, giving 1.4 g of THF **209** in 87% yield (Scheme 2.29).

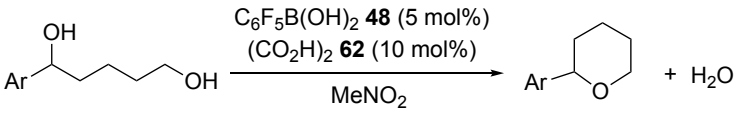


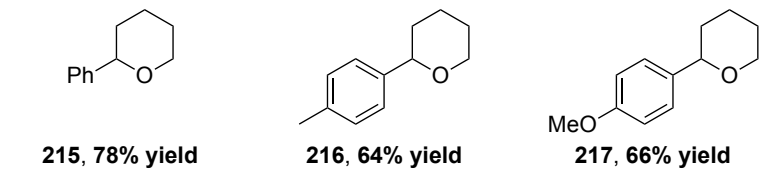
Scheme 2.29 Reaction performed on an 11 mmol scale

2.3.3 Substituted THP synthesis

Next, the synthesis of 2-aryl substituted THP derivatives from 1,5-diols was investigated under the standard reaction conditions (Table 2.10). Similar reactivity trends to the THF formation were observed, with neutral and electron-rich aryl substituents reacting well to give products **215, 216** and **217** in good yields. In this case, incorporation of an electron-withdrawing 4-trifluoromethyl substituent resulted in lower reactivity, with THP **218** obtained in only 29% yield after 48 h at 90 °C. As previously, 4-chloro and 4-bromo-aryl substitution was well tolerated, with THP products **219** and **220** isolated in 87% and 62% yield, respectively.

Table 2.10 THP intramolecular dehydrative synthetic etherification

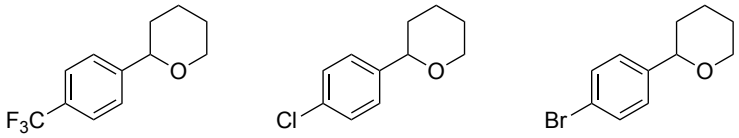




215, **78% yield** 90 °C, 6 h

216, **64% yield** 40 °C, 6 h

217, **66% yield** 40 °C, 6 h



218, **29% yield** 90 °C, 48 h

219, **87% yield** 40 °C, 6 h

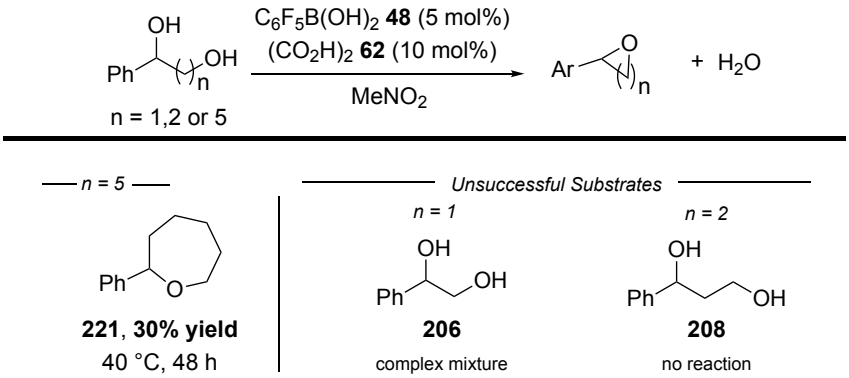
220, **62% yield** 40 °C, 6 h

2.3.4 Other ring sizes

While the intramolecular dehydrative cyclisations to form THF and THP rings were mostly successful, the preparation of alternative ring sizes proved to be more challenging (Table

2.11). Catalytic intramolecular etherification for the synthesis of larger 2-phenyloxepane **221** from the corresponding 1,6-diol **205** was only moderately successful, giving 30% yield after 48 h at 40 °C. Attempts to increase the yield at higher temperatures resulted in product decomposition. The formation of smaller ring sizes was unsuccessful under the standard reaction conditions, with 1,2-diol substrate **206** giving a complex mixture,[91] while efforts to form oxetanes from 1,3-diol **208** returned only the starting material.

Table 2.11 Limitations for intramolecular dehydrative etherification



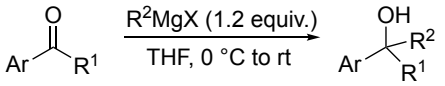
2.4 Intermolecular dehydrative crossed etherification

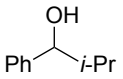
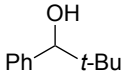
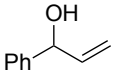
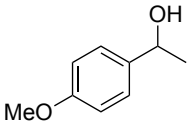
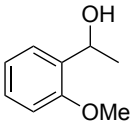
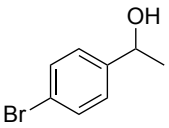
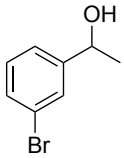
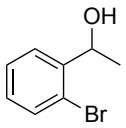
The use of two different alcohols in an intermolecular crossed etherification process *via* selective catalytic dehydrative substitution was then investigated.

2.4.1 Starting materials synthesis

The required secondary benzylic alcohol starting materials were easily prepared in a one-step synthesis from the corresponding aldehydes by Grignard addition (commercially available or freshly made Grignards). This method has been used for the synthesis of a range of substituted benzylic alcohols, giving the products in generally good yields (Table 2.12).

Table 2.12 Synthesis of secondary benzylic alcohols

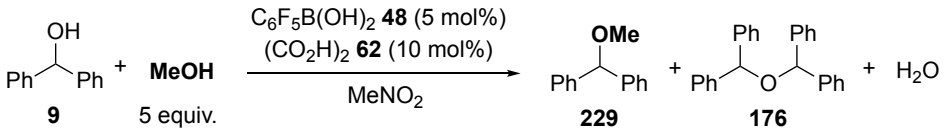


				
1, **99% yield**	**222, 47% yield**	**223, 22% yield**	**67, 99% yield**	**224, 61% yield**
				
17, 35% yield	**225, 89% yield**	**226, 99% yield**	**227, 98% yield**	**228, 99% yield**

2.4.2 Reaction optimisation

Initially, benzhydrol **9** was used as the electrophile in combination with an excess of methanol (5 equiv.) as the nucleophile using pentafluorophenylboronic acid **48** (5 mol%) and oxalic acid **62** (10 mol%) in $MeNO_2$ at room temperature (Table 2.13). Complete conversion of benzhydrol **9** was observed giving a 70:30 mixture of the desired crossed ether product **229** and the benzhydrol derived symmetrical ether **176** as determined by ^1H NMR spectroscopic analysis. A brief investigation was undertaken to improve the selectivity for the desired crossed ether product **229**. Lowering the reaction concentration to 0.05 M (entry 3), gave a ratio of 90:10 **229**:**176** after 16 h. However, no additional improvement was observed by further lowering the concentration. (Table 2.13, entry 4). Similarly, using 10 equivalents of MeOH led to no better product ratio (Table 2.13, entry 5).

Table 2.13 Reaction optimization



Entry	[M]	Conv (%)[(a)]	229:176
1	0.2	97	70:30
2	0.1	>98	75:25
3	0.05	>98	90:10
4	0.03	>98	88:12
5[(b)]	0.05	>98	90:10

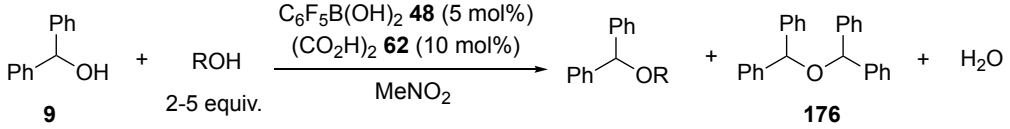
[(a)]Determined by ^{1}H NMR [(b)]Reaction using 10 equiv. of MeOH

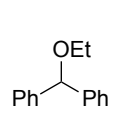
2.4.3 Substrate scope

2.4.3.1 Variation of the nucleophile

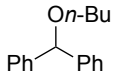
The scope of the intermolecular crossed etherification method was investigated through variation of the alkyl alcohol component in combination with benzhydrol **9** (Table 2.14). Various alkyl-substituted alcohols were applicable under the previously optimised conditions, with complete conversion of benzhydrol **9** observed in all cases. Crossed ethers **230**-**234** were all obtained as the major product as a mixture with a minor amount of symmetric ether **176** derived from benzhydrol **9**. The use of trifluoroethanol as a nucleophile was less well tolerated, forming a 63:37 mixture of ether **235** to **176**. Satisfyingly, the use of hex-5-en-1-ol as the nucleophile resulted in selective crossed dehydrative substitution, with ether **236** isolated as the only product in high 84% yield after purification by column chromatography. Alkynyl substitution was also well tolerated, with ether **237** obtained in an excellent 97% yield. Importantly, substrates bearing pendant functional groups including esters and allyl ethers were also tolerated, forming ethers **238** and **239** in good yields.

Table 2.14 Nucleophilic component variation

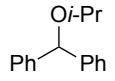




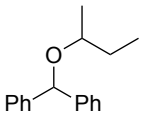
230, **71% yield**
rt, 16 h
(97:3[(a)] **230/176**)



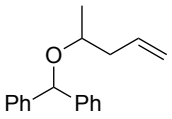
231, **98% yield**
rt, 16 h
(97:3[(a)] **231/176**)



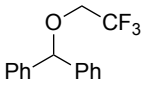
232, **99% yield**
rt, 16 h
(94:6[(a)] **232/176**)



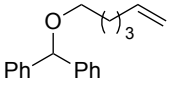
233, **86% yield**
rt, 16 h
(95:5[(a)] **233/176**)



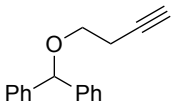
234, **92% yield**
rt, 16 h
(97:3[(a)] **234/176**)



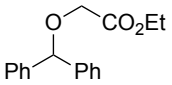
235, **87% yield**
rt, 16 h
(63:37[(a)] **235/176**)



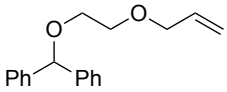
236, **84% yield**
rt, 16 h



237, **97% yield** (2.5 g)
rt, 16 h



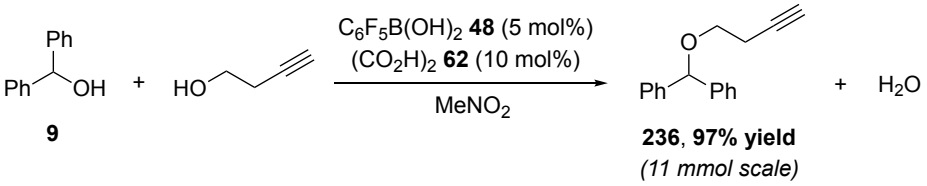
238, **59% yield**
rt, 16 h



239, **83% yield**
rt, 16 h

[(a)]Obtained ratio after column chromatography

The synthetic utility of this procedure was further demonstrated by performing this reaction on an 11 mmol scale, allowing the isolation of 2.52 g of ether **236** (Scheme 2.30).



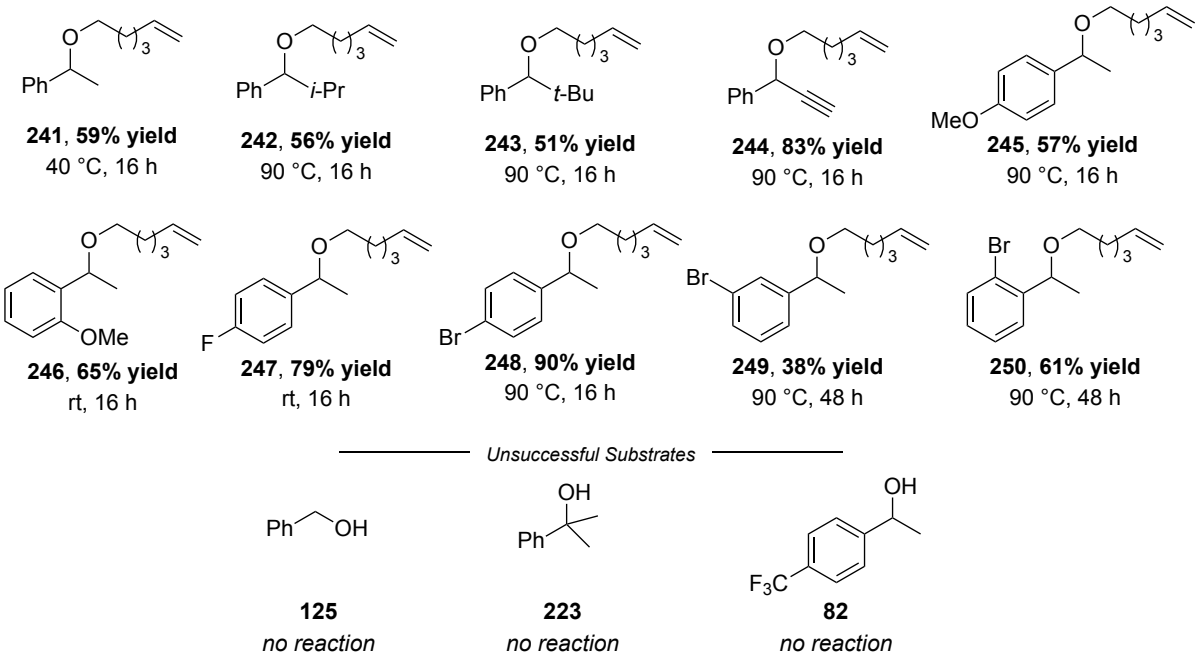
Scheme 2.30 Reaction performed on an 11 mmol scale

2.4.3.2 Variation of the electrophile

Next, the benzylic alcohol component was varied using hex-5-en-1-ol **240** as the standard nucleophile (Table 2.15). Alkyl-substituted secondary benzylic alcohols reacted to form ethers **241**-**244** in good yields. Remarkably, the reaction was completely selective for the crossed-intermolecular substitution process, with no symmetrical ether formation or unwanted elimination to form styrene derivatives observed. The presence of an alkynyl substituent on the secondary carbinol centre did not affect the reactivity, with ether **244** isolated in 83% yield after reaction at 90 °C. Substitution on the aryl ring was also possible, with electron-

donating or halogen-substituted 4-methoxy-, 2-methoxy- 4-fluoro- and 4-bromophenyl ethanol well tolerated to afford ethers **245**-**248** in high yields. The use of more sterically demanding 3-bromo- and 2-bromophenyl ethanol as electrophiles gave ethers **249** and **250** in 38% and 61% yield, respectively after 48 h at 90 °C. However, the presence of an electron-withdrawing 4-trifluoromethyl substituent or tertiary alcohol gave no reactivity and returned only starting materials. The reaction of primary benzyl alcohol **125** with alkyl alcohols such as methanol or hex-5-en-1-ol **240** was also investigated under the standard conditions, but returned only unreacted starting material.

Table 2.15 Electrophilic component variation

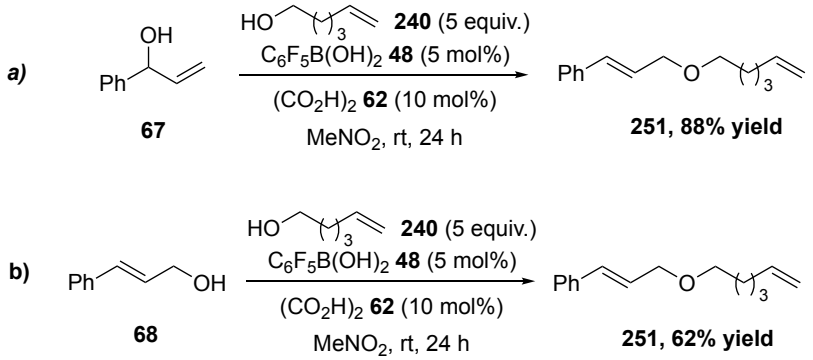


2.5 Proposed reaction mechanism

2.5.1 Control experiments

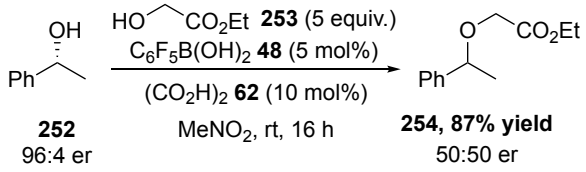
A number of control experiments was then performed to investigate the mechanistic pathway and to probe the nature of any catalytic species formed between pentafluorophenylboronic

acid **48** and oxalic acid **62**. First, the intermolecular crossed-dehydrative substitution using hex-5-en-1-ol **240** was performed under the standard reaction conditions using both α-vinylbenzyl alcohol **67** and isomeric cinnamyl alcohol **68** as the electrophile (Scheme 2.31). In both cases, linear ether product **251** was formed as a single regioisomer in good yield. This is consistent with the formation of a common reaction intermediate from both substrates.



Scheme 2.31 Control experiments

Next, the dehydrative substitution was performed using enantiomerically enriched (*R*)-1-phenylethan-1-ol **252** (96:4 er) and ethyl glycolate **253** under the standard conditions (Scheme 2.32). Ether product **254** was formed in 87% yield, but as a racemic mixture. This suggests the formation of a planar intermediate with loss of stereochemical information. These experiments are consistent with a catalytic S_N1-type substitution pathway proceeding via a planar carbocation intermediate and is in line with the proposed mechanisms previously reported for aryl boronic acid-catalysed Friedel-Crafts alkylation processes.

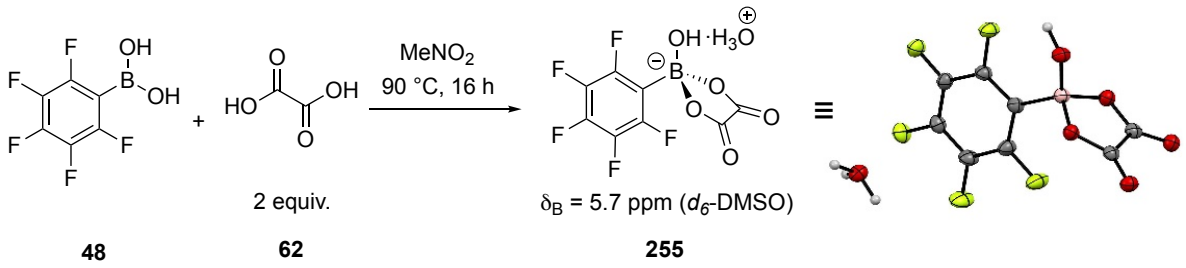


Scheme 2.32 Reaction studying the er of the etherification reaction

2.5.2 Pre-catalyst synthesis

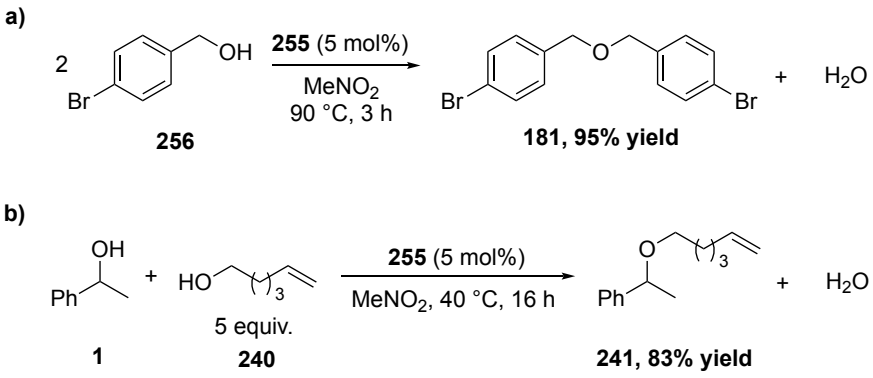
While the use of pentafluorophenylboronic acid **48** in combination with oxalic acid **62** had been previously reported for dehydrative Friedel-Crafts reactions,[27] the nature of any intermediate catalytic species formed *in situ* has not been investigated. A preparative

experiment reacting pentafluorophenylboronic acid **48** with oxalic acid **62** (2 equiv.) in $MeNO_2$ at 90 °C followed by removal of the solvent afforded a white powder, from which small crystals could be obtained. X-Ray crystallographic analysis (performed by Prof. Alexandra Slawin, University of St Andrews) showed the formation of hydrated boronate ester **255** (Scheme 2.33),[92] with ^{11}B, ^{19}F and $^{13}C\{^{1}H,^{19}F\}$ NMR spectroscopic analysis in d_6-DMSO consistent with this structure.



Scheme 2.33 Synthesis of active catalyst species 255

Testing its catalytic activity, boronate ester complex **255** is a competent pre-catalyst for both the intermolecular etherification of benzylic alcohols (Scheme 2.34a) and crossed-etherification (Scheme 2.34b), leading to products **181** and **241** in comparable yields to the *in situ* catalyst formation procedure.



Scheme 2.34 Test reaction using synthesised active boron catalyst 255

However, boronate ester **255** cannot be unequivocally identified as the active catalytic species in solution, as NMR analysis in d_3-$MeNO_2$ shows the formation of a dynamic equilibrium between at least three species. In d_3-$MeNO_2$ the three boron-containing species are present in an approximate 7:7:1 ratio at equilibrium, as determined by $^{19}F\{^{1}H\}$ NMR spectroscopic analysis (Figure 2.4). The addition of water, which is formed during the

etherification process, does not affect the position of equilibrium. The same equilibrium is established between a mixture of pentafluorophenylboronic acid **48** and oxalic acid **62** (1:2 **48**/**62**) in *d*$_3$-$MeNO_2$ (Figure 2.5), which includes the non-coordinated arylboronic acid **48** (δ_B = 26.8 ppm) and two tetrahedral sp^3-hybridised boron species (δ_B = 7.4 and 5.4 ppm).

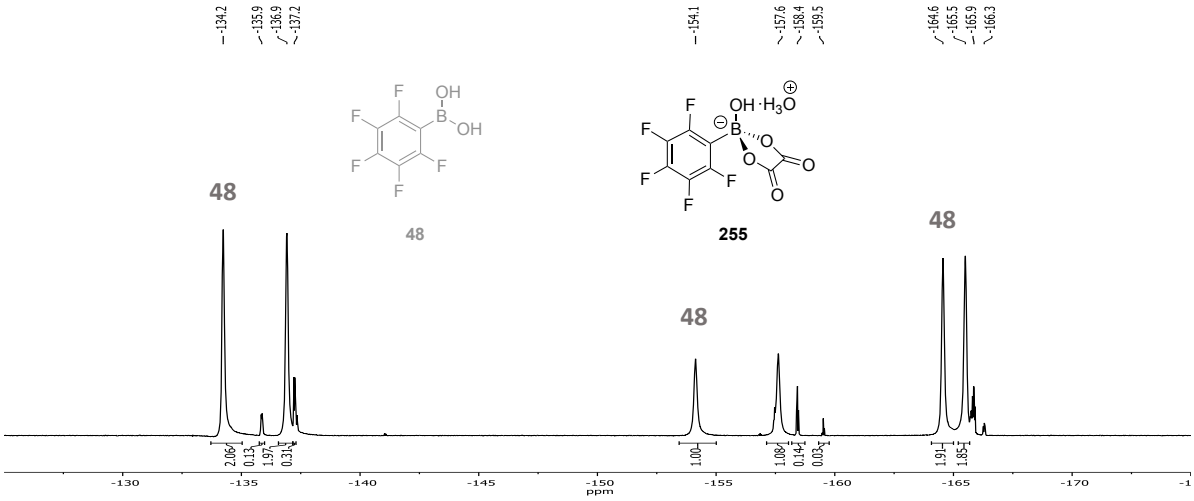


Figure 2.4 $^{19}F\{^1H\}$ NMR (470 MHz, d_3-$MeNO_2$) of 255

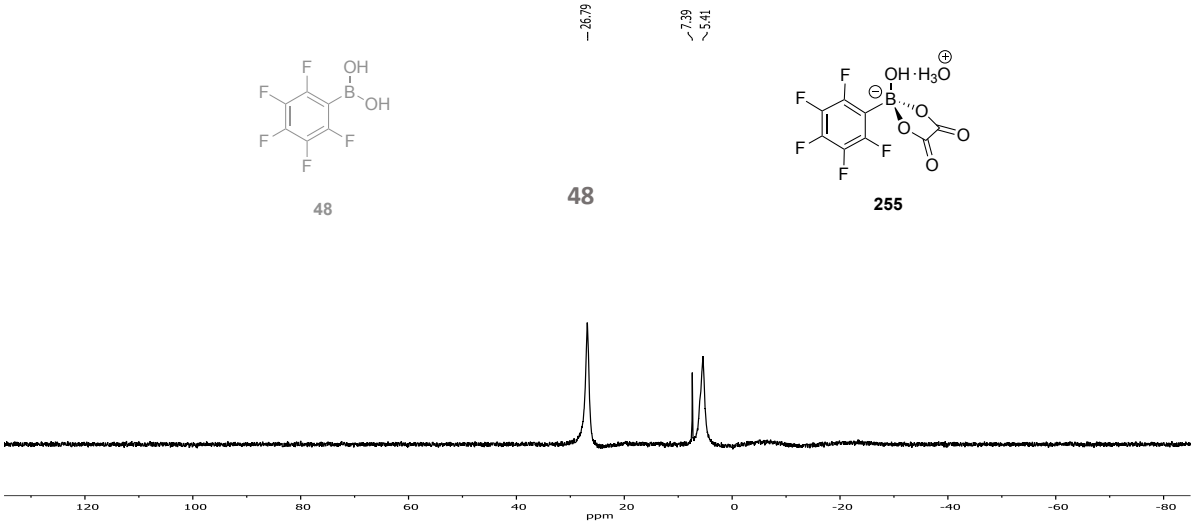


Figure 2.5 ^{11}B NMR (160 MHz, d_3-$MeNO_2$) of 255

The signal at 5.4 ppm is consistent with structure **255** (analogous to the signal observed for **255** in *d*$_6$-DMSO), with the increased Lewis acidity of the boron atom upon complexation with

oxalic acid **62** resulting in a greater affinity for the solvent. A NMR study of **48** and **62** using *d*$_6$-DMSO as a solvent was also performed, finding a mixture of starting material **48** and active catalytic species **255** by $^{19}F\{^1H\}$ (Figure 2.6), ^{11}B (Figure 2.7) and $^{13}C\{^1H,^{19}F\}$ (Figure 2.8) NMR analysis.

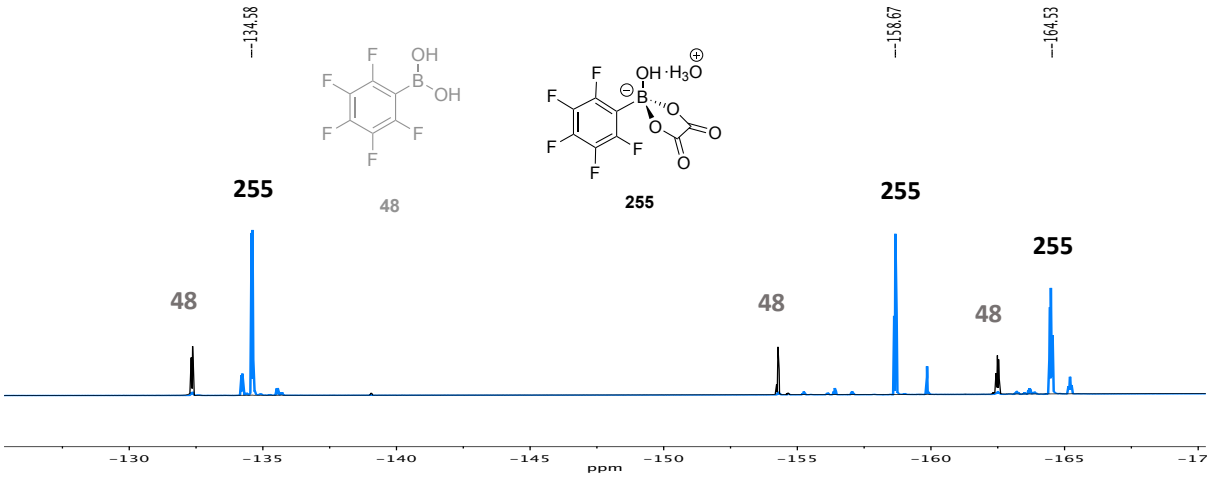


Figure 2.6 $^{19}F\{^1H\}$ NMR (470 MHz, d_6-DMSO) of 255

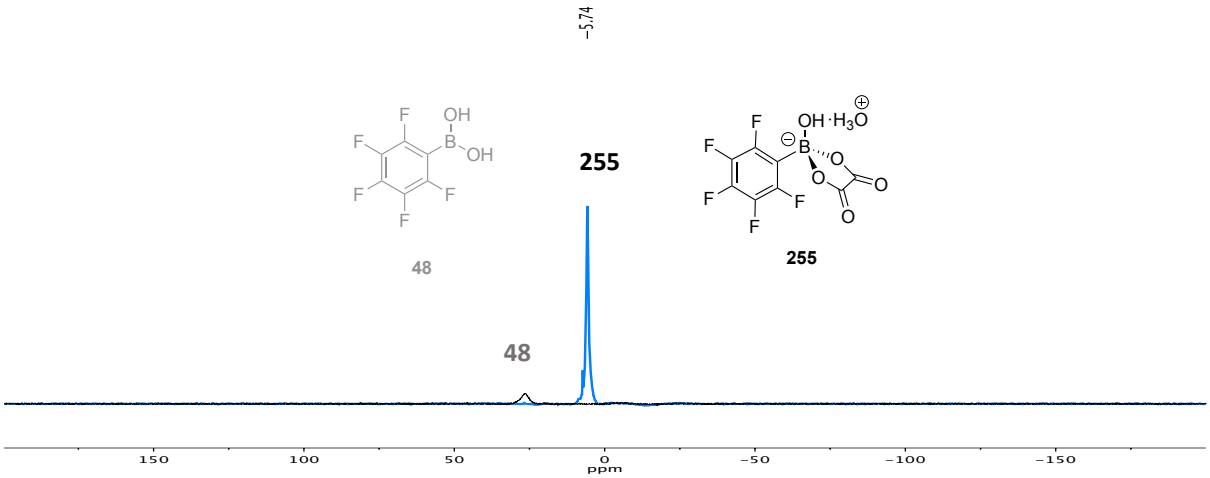


Figure 2.7 ^{11}B NMR (160 MHz, d_6-DMSO) of 255

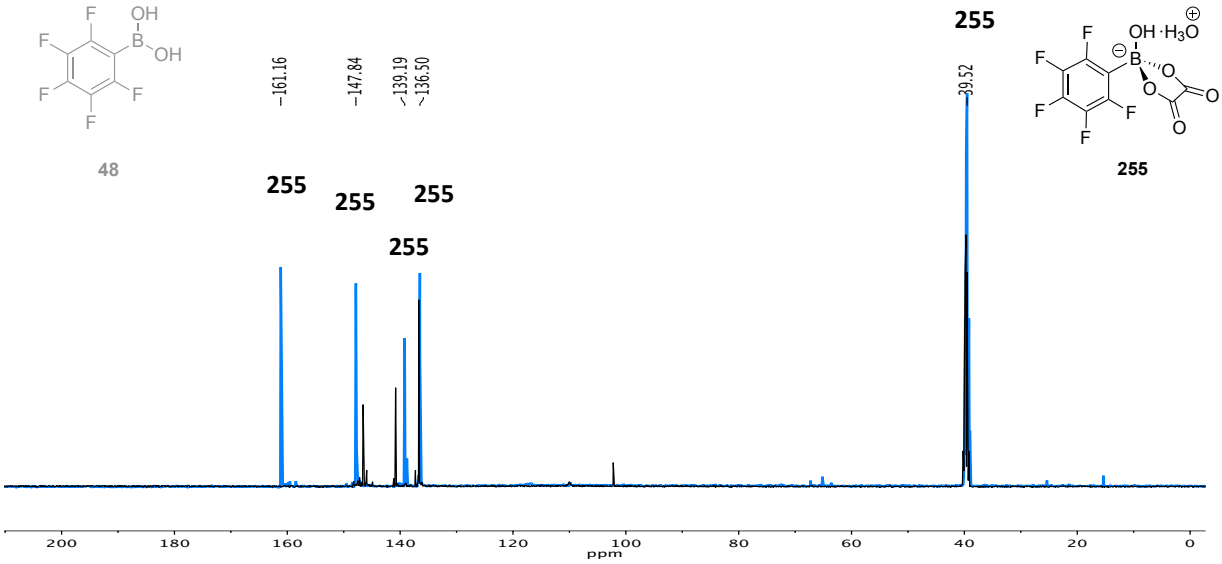
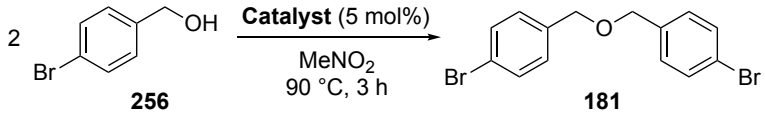


Figure 2.8 $^{13}C\{^{1}H,^{19}F\}$ NMR (126 MHz, d_6-DMSO) of 255

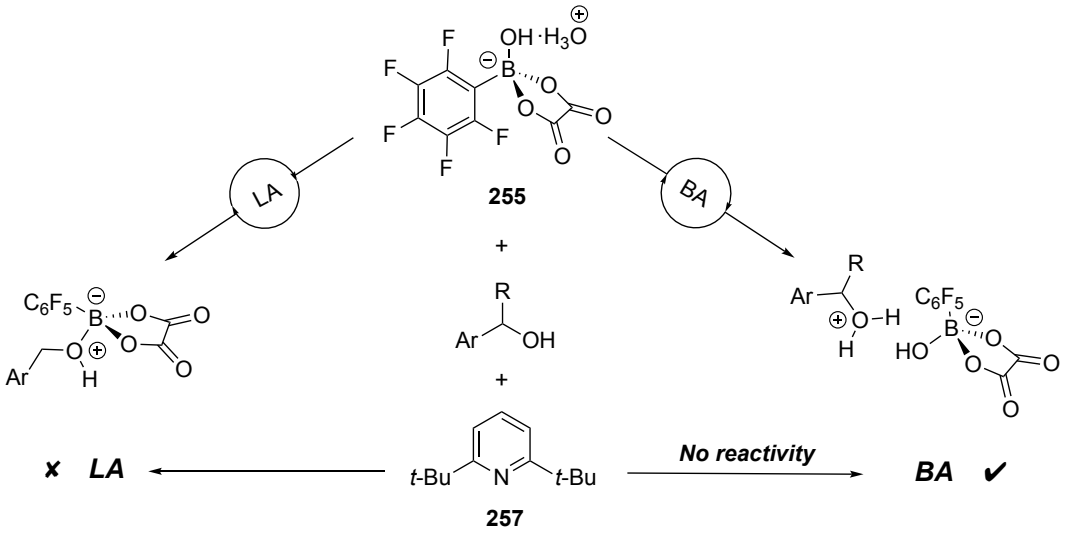
Further control experiments were performed to probe whether the active boron species in solution acts as either a Lewis acid or Brønsted acid catalyst. Isolated complex **255** was a competent pre-catalyst for the intermolecular etherification of benzylic alcohol **256**, forming ether **181** in 95% yield after 3 h (Table 2.16, entry 1). The use of alternative strong Brønsted acids as catalysts resulted in low product formation. For example, trifluoroacetic acid (TFA) gave a complex mixture of products after 3 h (Table 2.16, entry 2), while (+)-camphorsulfonic acid ((+)-CSA) gave no reactivity (Table 2.16, entry 3). However, the use of 4-toluenesulfonic acid (*p*-TsOH·H_2O) did show some reactivity, giving 36% conversion into ether **181** (Table 2.16, entry 4).

Table 2.16 Brønsted acid catalysis control experiments



Entry	Catalyst (mol%)	Additive (mol%)	Conv (%)
1	255 (5)	–	>98(95)
2	TFA (5)	–	Complex mixture
3	(+)–CSA (5)	–	0
4	*p*-TsOH·H_2O (5)	–	36
5	$C_6F_5B(OH)_2$ **48** (5), $(CO_2H)_2$ **62** (10)	2,6-(*t*-Bu_2)C_5H_3N **257** (5)	0

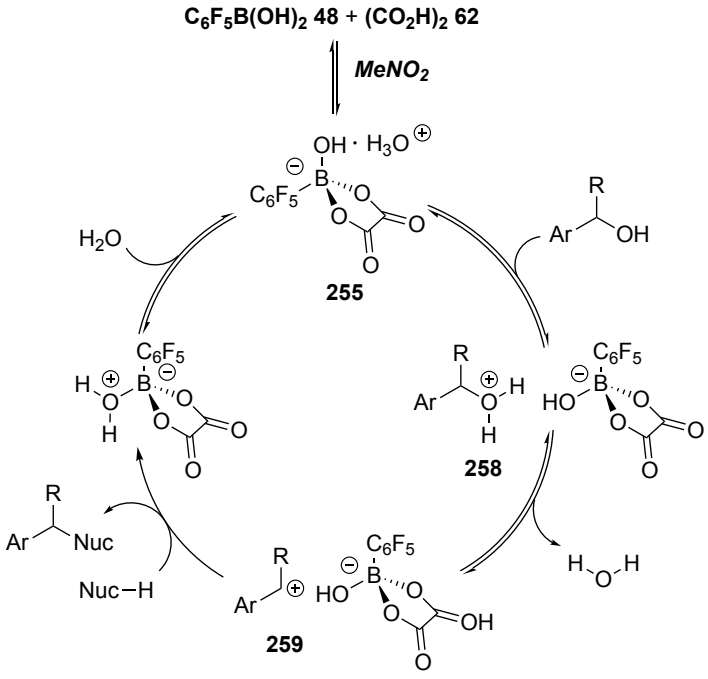
While alternative Brønsted acid catalysts showed some reactivity, the aryl boronic acid catalyst system provides both increased reactivity and selectivity. Performing the reaction under the standard conditions in the presence of sterically demanding Lewis base 2,6-di-*tert*-butyl pyridine **257** (5 mol%) results in complete reaction inhibition, which suggests that the active aryl boron species formed in solution acts as a Brønsted acid catalyst (Scheme 2.35).[93]



Scheme 2.35 Test reaction using 2,6-di-*tert*-butyl pyridine 257

2.5.3 Proposed reaction mechanism

Using the evidence obtained, a possible reaction mechanism for dehydrative nucleophilic substitution using aryl boronic acid catalysis is suggested in Scheme 2.36. A dynamic equilibrium between pentafluorophenylboronic acid **48** and oxalic acid **62** in solution may result in the formation of complex **255**, which is expected to act as a strong Brønsted acid catalyst. Protonation of the benzylic alcohol forms ion pair **258**, which is sufficiently activated to dissociate into ion pair **259**. Reaction of carbocation **259** with a suitable alcohol nucleophile gives the substitution product, with the released boronate species **255** likely to be in equilibrium with other hydrated forms in the presence of water. Reversible protonation of the different alcohols rationalises the selectivity in the crossed-etherification processes, with only benzylic alcohols capable of forming a stabilised carbocation for onwards reaction. Although the proposed mechanism is consistent with the observed reaction scope and control experiments, alternative mechanisms involving different boronate intermediates and/or Brønsted acid catalysis cannot be ruled-out at this stage.



Scheme 2.36 Suggested reaction mechanism

The reaction optimisation showed that the use of nitromethane as solvent is essential for reactivity. This is also the case for other boronic acid-catalysed alcohol activation procedures

reported in the literature;[45,47] however, the role of nitromethane in these reactions is largely unknown. Nitromethane is known to be a weak hydrogen-bond acceptor and could therefore assist in the dissociation/stabilization of the alcohol substrates to form the intermediate carbocations in solution. Moran and co-workers have also suggested nitromethane or other nitro additives can form higher-order aggregates of catalysts in solution. [27] However, further mechanistic investigations are required to fully understand the exact role of nitromethane in these etherification reactions.

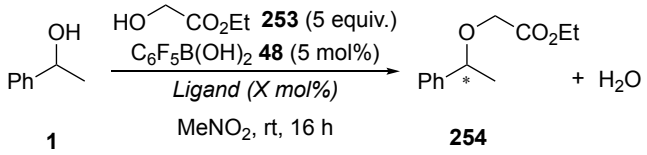
2.6 Enantioselective dehydrative substitution

2.6.1 Asymmetric Counterion-Directed catalysis

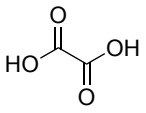
After all the positive results for the different dehydrative substitution processes, the possibility of an enantioselective reaction was investigated. As the reaction is thought to proceed *via* a catalytic SN1 process, a chiral boronate counterion within ion-pair **48** may be able to influence the selectivity of nucleophilic addition.

The possibility of using chiral ligands for the arylboronic acid was investigated for the reaction of 1-phenylethan-1-ol **1** and ethyl glycolate **253** to form ether **254** (Table 2.17). Treating **1** and **253** with pentafluorophenylboronic acid **48** (5 mol%) and (*R*)-BINOL **260** (5 mol%) as a ligand gave some reactivity, resulting in 50% of ether **254**. However, HPLC analysis using a chiral stationary phase showed that the product was racemic. The use of (*S,S*)-diethyl tartrate **160** (5 mol%) gave ether **254** in 71% yield, but again was racemic. (entry 4). This process is also highly sensitive to the ratio of catalyst to ligand as using a 10 mol% of either ligand **260** or **160** returned only starting material (entries 3 and 5).

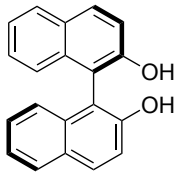
Table 2.17 Enantioselective intermolecular dehydrative crossed etherification reaction



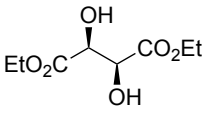
1 **254**



62



260



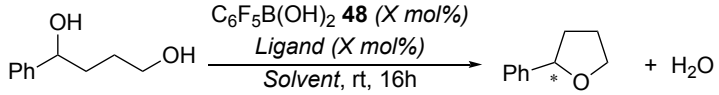
160

Entry	Ligand	Yield **254** (%)[a]	er[c]
1[b]	Oxalic acid **62** (10 mol%)	87	50:50
2	(*R*)-BINOL **260** (5 mol%)	50	50:50
3	(*R*)-BINOL **260** (10 mol%)	0	–
4	(*S,S*)-DET **160** (5 mol%)	71	50:50
5	(*S,S*)-DET **160** (10 mol%)	0	–

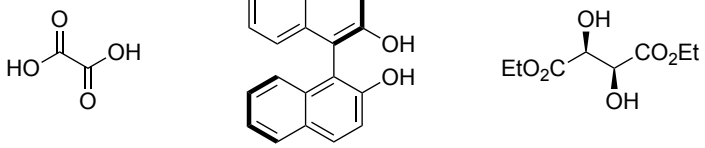
[a]Yield after column chromatography [b]Using (*R*)-1-phenylethan-1-ol **252** as starting material [c]Determined by chiral HPLC

The use of a chiral ligands was also tested for intramolecular dehydrative substitution of **189** to form THF **209** (Table 2.18). The reaction was again sensitive to the amount of ligand used, with no reaction observed when a 1:1 ratio with the arylboronic acid was used (entries 2 and 3). Using 15 mol% **48** with 10 mol% (*R*)-BINOL **260** at (0.05 M) in nitromethane did give some reactivity, with THF **209** obtained in 60% yield. However, HPLC analysis showed that a racemic mixture was formed. Under the same conditions, (*S,S*)-diethyl tartrate **160** gave no reactivity. The reaction with (*R*)-BINOL **260** was then tested in different solvents. The use of either HFIP or acetone led to THF **209** in 78% and 11% yield, respectively, but both products were racemic.

Table 2.18 Enantioselective intramolecular dehydrative etherification reaction



189 **209**



62 **260** **160**

Entry	Boron catalyst (mmol%)	Ligand (mmol%)	M	Solvent	Yield **209**(%)	er[(c)]
1[(a)]	5	Oxalic acid **62** (10)	0.2	$MeNO_2$	92	–
2	15	(*R*)-BINOL **260** (15)	0.2	$MeNO_2$	0	–
3	15	(*R*)-BINOL **260** (15)	0.05	$MeNO_2$	0	–
4	15	(*R*)-BINOL **260** (10)	0.05	$MeNO_2$	60	50:50
5	15	(*S,S*)-DET **160** (15)	0.05	$MeNO_2$	0	–
6[(b)]	15	(*R*)-BINOL **260** (10)	0.05	HFIP	78	50:50
7[(b)]	15	(*R*)-BINOL **260** (10)	0.05	Acetone	11	50:50

[(a)]Reaction performed at 40 °C for 6h [(b)]Reaction performed for 48h [(c)]Determined by chiral HPLC.

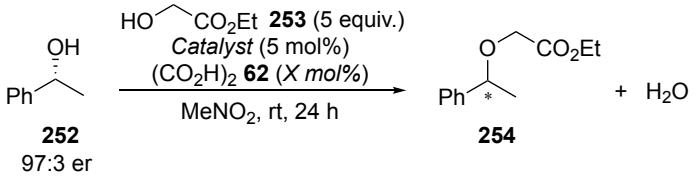
2.6.2 Catalytic SN2 dehydrative substitution

As initial attempts to influence enantioselectivity with asymmetric counterion-directed catalysis were unsuccessful, the possibility of developing a dehydrative SN2 substitution was investigated.

The reaction of (*R*)-1-phenylethan-1-ol **252** (97:3 er) with ethyl glycolate **253** was investigated with alternative boron species (Table 2.19). The use of trialkyl borates (5 mol%) or borinic acids (5 mol%) with oxalic acid **62** (10 mol%) in nitromethane gave the desired reaction, with the ether **254** formed in up to 70% yield. However, in each case, HPLC analysis showed the

product was racemic. The reaction in the absence of oxalic acid resulted in lower reactivity and the product was again racemic.

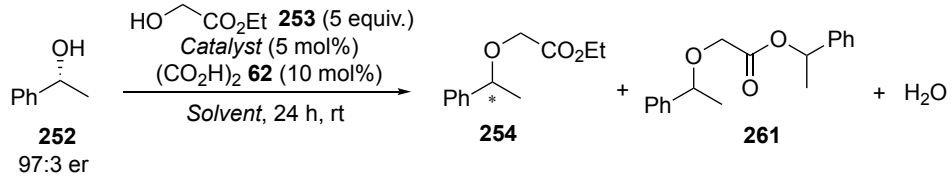
Table 2.19 Boron screening for the SN2 dehydrative substitution



Entry	Catalyst	Oxalic acid **62** (mmol%)	Conv(%)	Yield **254** (%)	er
1	$B(OMe)_3$	0	37	–	–
2	$B(OMe)_3$	10	100	35	50:50
3	$B(O\textit{t}\text{-}Bu)_3$	0	11	–	–
4	$B(O\textit{t}\text{-}Bu)_3$	10	100	70	50:50
5	$B(OEt)_3$	0	37	–	–
6	$B(OEt)_3$	10	100	45	50:50
7	$B(O\textit{i}\text{-}Pr)_3$	0	50	–	–
8	$B(O\textit{i}\text{-}Pr)_3$	10	100	28	50:50
9	$(4\text{-}FC_6H_4)_2BOH$	0	40	–	–
10	$(4\text{-}FC_6H_4)_2BOH$	10	100	35	50:50
11	$(C_6H_5)_2BOH$	0	0	–	–
12	$(C_6H_5)_2BOH$	10	100	33	50:50

The process was then trialled in different solvents. The use of either acetonitrile or THF resulted in much lower reactivity to give ether **254** in low yields as a racemic mixture. These solvents also gave different amounts of unexpected product **261**, resulting from transesterification of either ethyl glycolate **253** or ether **254** with alcohol **252** (Table 2.20).

Table 2.20 Solvent screening SN2 dehydrative substitution

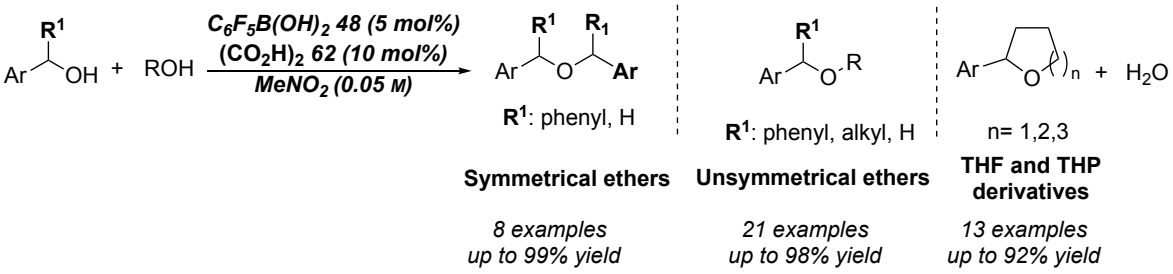


Entry	Boron compound	Solvent	Conv (%)	Yield (%)	254:261	er
1	$B(OMe)_3$	Acetonitrile	23	22	1:2	–
2	$B(O\textit{t}\text{-}Bu)_3$	THF	32	25	0:1	–
3	$B(O\textit{t}\text{-}Bu)_3$	Acetonitrile	23	20	1:2	–
4	$B(OEt)_3$	Acetonitrile	17	6	1:0	50:50
5	$B(O\textit{i}\text{-}Pr)_3$	Acetonitrile	32	12	1:2	–
6	$(4\text{-}FC_6H_4)_2BOH$	Acetonitrile	38	5	1:4	–

As the initial attempts at the both counterion-directed catalysis and promoting an SN2 process were unsuccessful, this line of investigation was stopped to focus on alternative applications of dehydrative substitution.

2.7 Conclusion

In conclusion, a procedure was found for the dehydrative substitution of alcohols to synthesise symmetrical, non-symmetrical and cyclic ethers with water as the only by-product. The use of pentafluorophenylboronic acid **48** (5 mol%) and oxalic acid **62** (10 mol%) in nitromethane were the optimised conditions for this new procedure. Broad substrate scope was found in the presence of electron-rich and electron-poor groups with yields up to 99% (Scheme 2.37).



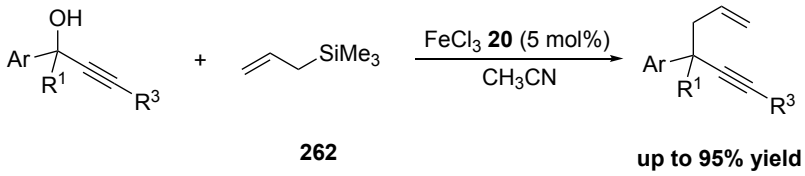
Scheme 2.37 Catalytic dehydrative substitution reaction

3 Dehydrative Substitution of Benzylic Alcohols for C-C Bond Formation

Having demonstrated that arylboronic acids catalyse dehydrative C-O bond formation, the investigation was next focused on the formation of C-C bonds *via* dehydrative substitution reaction.

3.1 Introduction

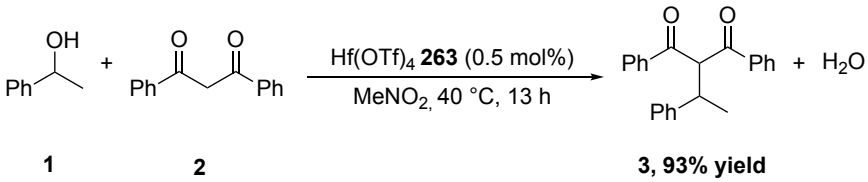
Dehydrative substitution of benzylic alcohols for C-C bond formation has previously been investigated using different methods. For example, in 2006 Zhan and co-workers reported the use of iron as a catalyst for the nucleophilic substitution of propargylic alcohols (Scheme 3.1).[94] Cheap and commercially available iron trichloride **20** was a suitable catalyst for substitution with carbon-centred nucleophiles such as allyl trimethylsilane **262** to give the propargylic products in high yields with complete regioselectivity. Both electron-rich and electron-poor aromatic substrates were well tolerated for the allylation reaction, while variation of the alkyne substituent using alkyl, aryl or trimethylsilyl groups afforded the products in high 86-95% yield.



262 **up to 95% yield**

Scheme 3.1 Nucleophilic allylation of propargylic alcohols

In 2007, Ishii and co-workers investigated the use of different metal triflate catalysts for the benzylation of 1,3-diketones.[95] Rare earth metal triflates have similar chemical properties, but different Lewis acidities. Therefore, La, Yb, Sc and Hf triflates were screened as catalysts in the reaction of **1** with **2** with the least Lewis acidic $Hf(OTf)_4$ **263** resulting in 93% yield of **3** (Scheme 3.2).

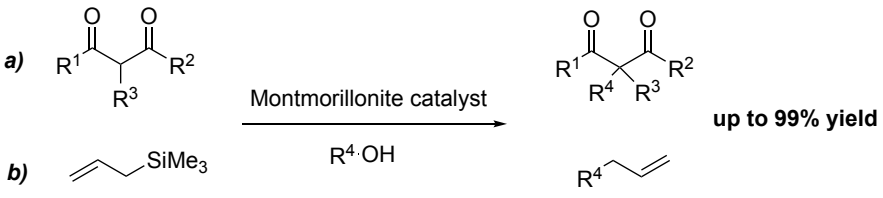


Scheme 3.2 Benzylation of 1,3-dicarbonyl compounds using metal triflates

The use of triflic acid (5 mol%) acting as a Brønsted acid catalyst was reported by Rodriguez and co-workers for the direct nucleophilic substitution of benzylic alcohols with active 1,3-dicarbonyl compounds (Scheme 3.3).[96] High yields were obtained using different substituents on both components, for example electron-donating groups and halogens, after reaction at reflux in nitromethane.

Scheme 3.3 Use of triflic acid as a catalyst

Nucleophilic substitution of alcohols using heterogeneous montmorillonite as a Brønsted acid catalyst has been reported by Kaneda and co-workers (Scheme 3.4).[97] 1,3-Dicarbonyl compounds and allylsilanes were investigated as nucleophiles with a range of primary and secondary allylic, benzylic and aliphatic alcohols. Good yields were obtained across a range of reactions and the catalyst could be reused at least three times without loss of either activity or selectivity.

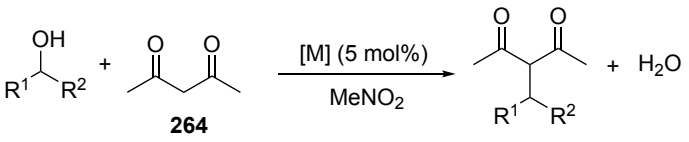


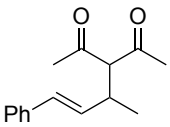
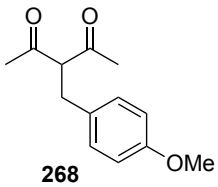
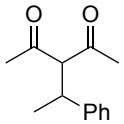
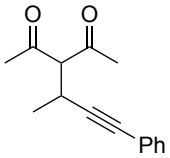
Scheme 3.4 Nucleophilic substitution reactions using montmorillonite catalysts

In 2013, Samec and co-workers trialled different Lewis and Brønsted acid catalysts in catalytic dehydrative substitution using carbon nucleophiles (Table 3.1).[79] Iron, bismuth, palladium and HCl were used, amongst others, in the reaction of 1,3-diketone **264** with primary or

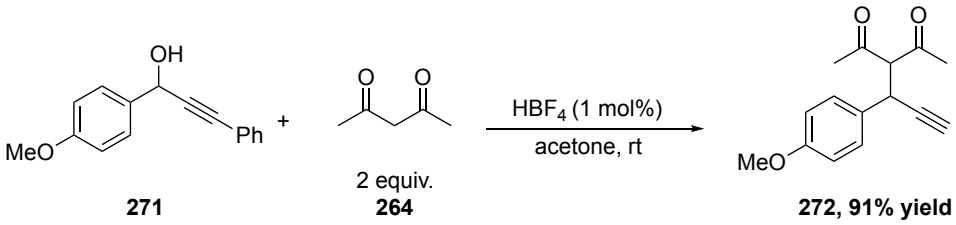
secondary alcohols. Allylic substrate showed high reactivity using the different catalysts, with product **266** obtained in high yield. Primary benzylic alcohols gave lower efficiency than the allylic substrate, with $BiBr_3$ the most effective catalyst. The use of secondary benzylic alcohols required the use of higher temperatures (60 °C) and showed excellent yields when Fe^{III} **20**, Bi^{III} **265** and Pd^{II} **267** based catalysts were used. A propargylic alcohol was the least effective electrophile for the nucleophilic substitution, resulting in low reactivity for all the catalysts even at high temperatures. Overall, the Bi^{III} **265** and Fe^{III} **20** Lewis acids resulted in higher yields across the range of substrates compared with redox metal or hydrochloric acid.

Table 3.1 Use of different catalysts for a C-C bond formation



Catalysts	 **266**	 **268**	 **269**	 **270**
$FeCl_3$ **20**	87%	30%	99%	38%
$BiBr_3$ **265**	88%	65%	92%	38%
$[PdCl_2(MeCN)_2]$**267** **140**	74%	63%	98%	0%
HCl	49%	29%	12%	0%

In 2015, Sheppard and co-workers reported the use of HBF_4 (1 mol%) for a carbon nucleophilic substitution reaction with propargylic alcohols.[98] Good to excellent yields were obtained in the presence of a range of substituted propargylic alcohols, and different carbon nucleophiles, including phenols and 1,3-diketones. For example, 4-methoxyphenyl propargylic alcohol **271** reacts with pentane-2,4-dione **264** in the presence of HBF_4 (1 mol%) at rt in acetone, resulting in an excellent 91% yield of **272** (Scheme 3.5).

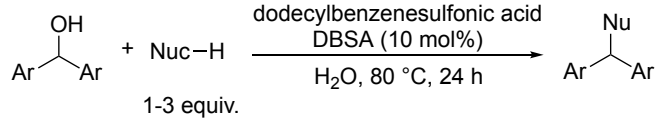


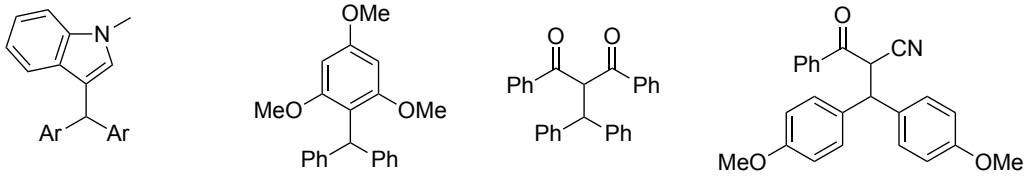
271 **264** **272, 91% yield**

Scheme 3.5 Nucleophilic substitution of propargylic alcohols

In 2017, Herrera and co-workers reported the use of dodecylbenzenesulfonic acid (10 mol%) under aqueous conditions to obtain a C-C bond between a benzylic alcohol and different carbon nucleophiles (Table 3.2).[99] Substituted diphenyl methanols were used as the electrophile with a range of nucleophiles giving the products in very good yields. For example, using 1-methylindole **273** led to Friedel-Crafts alkylation products **276-278** in high yields using a different substituents on the aromatic ring. Other nucleophiles including 1,3,5-trimethoxybenzene **274**, 1,3-diketone **1**, or 3-oxo-3-phenylpropanenitrile **275** were also successful, giving the corresponding products **279, 280** and **281** with 89%, 82% and 93% yield, respectively.

Table 3.2 Dehydrative substitution using DBSA





Ar: **276,** Ph **85% yield**
277, 4-$OMeC_6H_4$ **92% yield**
278, 4-FC_6H_4 **92% yield**

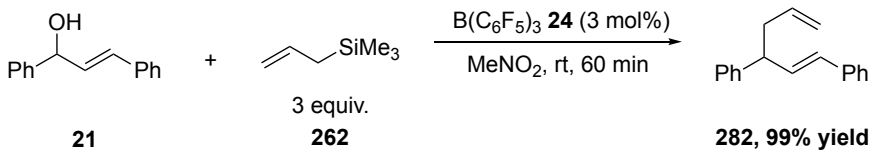
279, 89% yield **280, 82% yield** **281, 93% yield**

3.1.1 Uses of boron catalysts for C-C bond formation

Previous examples using arylboronic acid-based catalysts for C-C bond formation using alcohols have been reported, most notably Friedel-Crafts alkylation (see Chapter I).

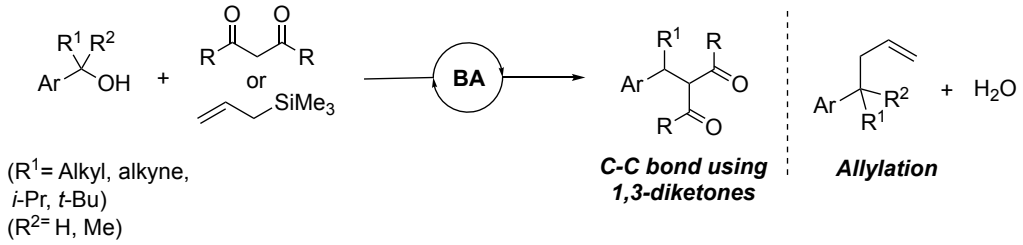
Moran and co-workers have shown that $B(C_6F_5)_3$ **24** (3 mol%) is an efficient catalyst for intermolecular alcohol substitution with different N, O and C-centred nucleophiles (Scheme

3.6).[25] For example, allylation of allylic alcohol **21** was tested using allyltrimethylsilane **262** as the nucleophile, affording the corresponding product **282** in excellent yield at room temperature in nitromethane. The use of different Lewis and Brønsted acid catalysts was tested with TFA and *p*-TsOH leading to product formation, but with lower yields.



Scheme 3.6 Allylation using $B(C_6F_5)_3$ 24 as catalyst

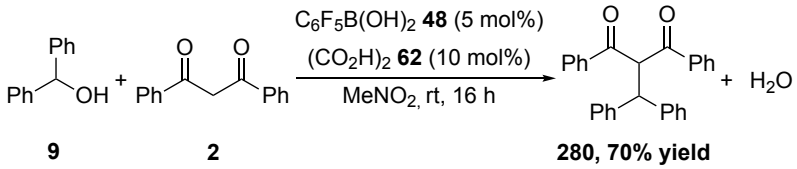
There are currently no previous reported examples using arylboronic acids as catalysts for dehydrative C-C bond formation other than Friedel-Crafts. Due to our previous results for the dehydrative substitution reaction of benzylic alcohol for C-O bond formation, a range of different C-centred nucleophiles was tested in reactions with benzylic alcohols (Scheme 3.7).



Scheme 3.7 Dehydrative substitution of benzylic alcohols for C-C bond formation

3.2 Initial investigations

An initial test reaction was performed using 1,3-diphenylpropane-1,3-dione **2** with benzhydrol **9** under the previously optimized conditions of pentafluorophenylboronic acid **48** (5 mol%) and oxalic acid **62** (10 mol%) in nitromethane (0.05 M) at room temperature. The reaction worked well, affording the desired product **280** in 70% yield after 16 h (Scheme 3.8). As the previously optimized conditions for C-O bond formation were also suitable for C-C bond formation, the substrate scope was investigated.



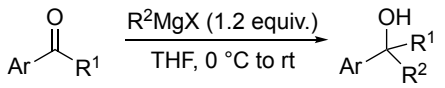
9 **2** **280, 70% yield**

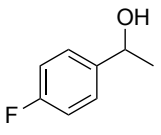
Scheme 3.8 Initial investigations for C-C bond

3.3 Starting materials synthesis

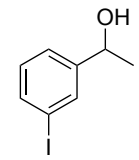
In addition to the secondary benzylic alcohols previously synthesised (see page 46), some additional substrates were prepared (Table 3.3). Addition of the required Grignard reagent (commercially available or freshly made) into an aldehyde or ketone gave a range of substituted secondary alcohols in good yields.

Table 3.3 Synthesis of starting materials

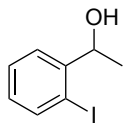




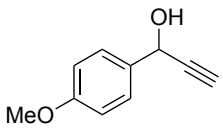
283, 84% yield



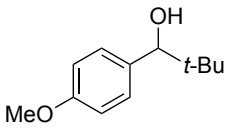
284, 96% yield



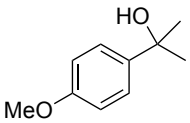
285, 95% yield



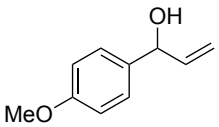
286, 76% yield



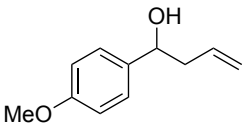
287, 81% yield



288, 90% yield

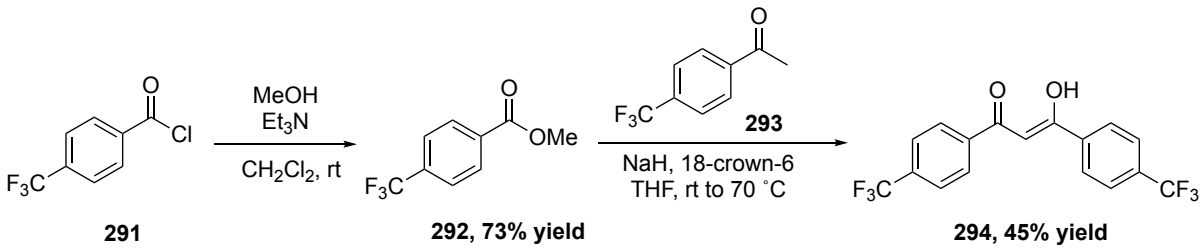


289, 89% yield



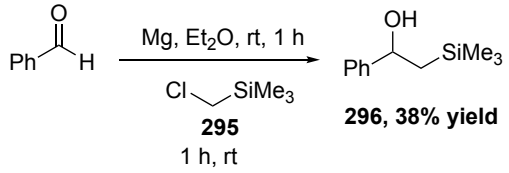
290, 96% yield

The synthesis of 1,3-bis(4-(trifluoromethyl)phenyl)propane-1,3-dione **294** performed using a two step procedure from 4-(trifluoromethyl)benzoyl chloride **291** in dichloromethane with addition of a solution of a methanolic solution of Et_3N. Methyl 4-(trifluoromethyl)benzoate **292** was obtained in good 75% yield and then treated with sodium hydride and a solution of 1-(4-(trifluoromethyl)phenyl)ethan-1-one **293** to give the desired product **294** in 45% yield after purification by column chromatography (Scheme 3.9).



Scheme 3.9 Synthesis of 1,3-diketone 294

Synthesis of 1-phenyl-2-(trimethylsilyl)ethan-1-ol **296** was performed through a Grignard reaction using benzaldehyde and chloromethyltrimethylsilane **295**.[100] The crude material was purified by column chromatography to give the desired product **296** in 38% yield (Scheme 3.10).

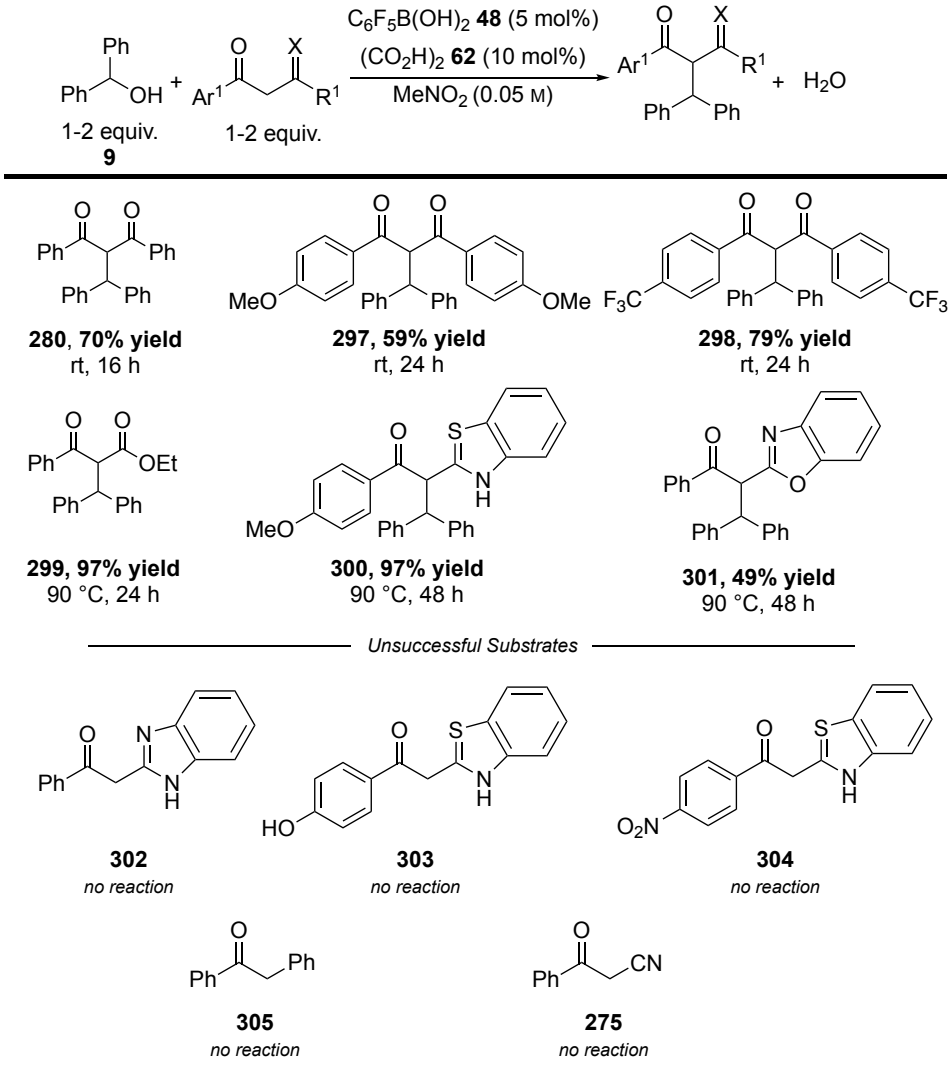


Scheme 3.10 Synthesis of 1-phenyl-2-(trimethylsilyl)ethan-1-ol 296

3.4 Substrate scope with 1,3-diketone derivatives

First, the reaction scope was explored using different 1,3-diketones, benzothiazoles, benzoxazoles or benzimidazoles with benzhydrol **9** as the standard benzylic alcohol (Table 3.4). In general, good reactivity was obtained using both electron donating or electron withdrawing substituents on the aromatic substituent of the 1,3-diketones, giving **297** and **298** in 59% and 79% yield, respectively. The use of ethyl 3-oxo-3-phenylpropanoate **207** gave an excellent yield of **299** after 24 h at 90 °C. Next, a substituted benzothiazole was tested as the nucleophile. The reaction was successful after heating at 90 °C for 48 h, with the electron-rich substrate giving **300** in 97% yield. The use of a benzoxazole resulted in decreased reactivity, with **301** obtained in 49% yield. Despite the identified reactivity, some limitations were also found. For example, benzoimidazole **302** and benzothiazoles **303** and **304** returned only starting materials at all temperatures tested (rt, 40 °C and 90 °C). The reactions using α-aryl ketone **305** and α-cyano ketone **275** were also unsuccessful.

Table 3.4 Use of different nucleophiles for C-C bond formation

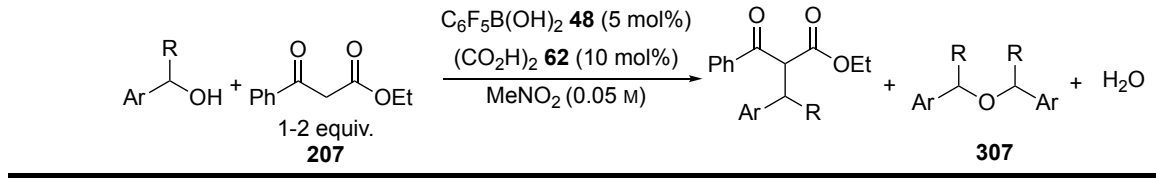


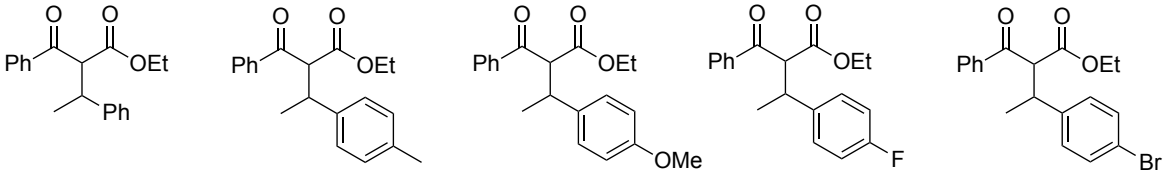
3.4.1 Use of ethyl ß-ketoesters with benzylic alcohols

As ß-ketoester substrate **207** reacted with benzhydrol **9** to give **299** in an excellent 97% yield, it was chosen as the standard nucleophile for further investigations with different benzylic alcohols (Table 3.5). As expected, the reactions gave mixtures of diastereoisomers, which could not be separated by column chromatography. The use of electron-rich aryl substituents was well tolerated giving **308** and **309** in high yields. Halogen substituents were also tolerated, although the yields were lower. A number of limitations to the scope were also observed. Iodo-substituted alcohol **284** and **285** gave symmetric ethers **312** and **313** as the main product at 90 °C, while no reaction was observed at room temperature. Electron-rich propargylic alcohol **286** and sterically demanding alcohols **224** and **222** were also unreactive at all

temperatures. Silyl-substituted alcohol **296** was also not suitable and underwent decomposition under the reaction conditions.

Table 3.5 Substrate scope using ethyl 3-oxo-3-phenylpropanoate 299 as nucleophile





306, **98% yield**
90 °C, 16 h
57:43 dr
(rt-40 °C, 16 h
307 98%
60:40 dr)

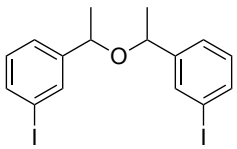
308, **85% yield**
90 °C, 24 h
54:46 dr

309, **80% yield**
40 °C, 7 h
57:43 dr

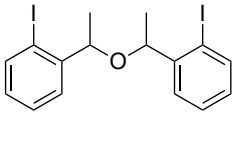
310, **10% yield**
90 °C, 24 h
58:42 dr

311, **53% yield**
90 °C, 24 h
52:48 dr

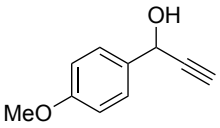
Unsuccessful Substrates



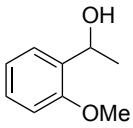
312, 57% yield
90 °C, 48 h
60:40 dr



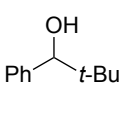
313, 47% yield
90 °C, 48 h
60:40 dr



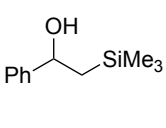
286
90 °C, 24 h
SM+dec



224
90 °C, 48 h
SM+P/90%:10%



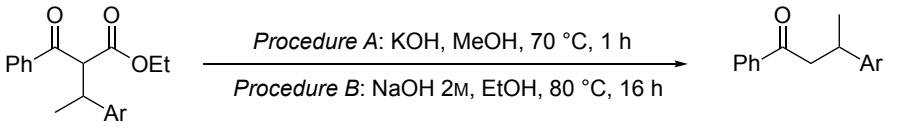
222
90 °C, 24 h
SM+dec

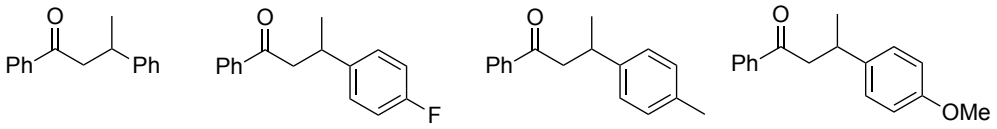


296
rt, 16 h
dec

A selection of the products were then derivatized through decarboxylation to the corresponding 1,3-diphenylbutan-1-ones (Table 3.6). Different reactivity was encountered in this procedure depending on the substituent present on the aryl group. Two different procedures using either potassium hydroxide[101] or sodium hydroxide[102] were tested to obtain the desired products in good yields. Potassium hydroxide was favourable when no substituent or an electron-withdrawing fluoro substituent was present on the aromatic ring, forming products **314** and **315** in 49 and 43% yield, respectively. Electron-donating substituents, methyl and methoxy, favoured sodium hydroxide giving **316** and **317** in 98% and 65% yield, respectively.

Table 3.6 Decarboxylative derivatizations



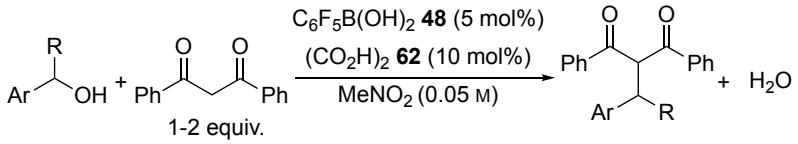


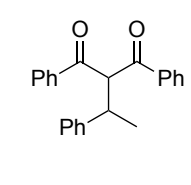
314	**315**	**316**	**317**
A **49% yield** *B* **29% yield**	*A* **43% yield** *B* **22% yield**	*A* **60% yield** *B* **98% yield**	*A* **10% yield** *B* **65% yield**

3.4.2 Use of 1,3-diketones with different benzylic alcohols

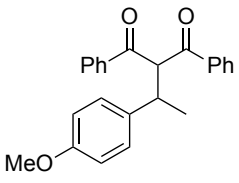
Next, a range of benzylic alcohols was tested in combination with 1,3-diphenylpropane-1,3-dione **2** as the nucleophile (Table 3.7). The reactions were performed under the standard conditions and were highly selective with no presence of symmetrical ether side products observed. Substitution on the aryl ring was investigated, with electron-donating or halogen-substituents giving the desired products **318**-**323** in high yields. The use of 3-bromo and 2-bromophenyl ethanol as the electrophile resulted in reduced 38% and 51% yield, respectively, after 24 h at 90 °C. Alkynyl substitution on the secondary benzylic alcohol was well tolerated, giving product **324** in an excellent 98% yield. Some limitations of the methodology were also observed. Surprisingly, allylic alcohol **67** gave no reactivity either at rt or 90 °C. The presence of a sterically demanding *tert*-butyl group also gave no reactivity, returning only starting material **243**. Attempts to increase reactivity by introducing an electron-donating aryl substituent **287** were unsuccessful. Tertiary benzylic alcohols **223** and **288** were also unsuitable, returning starting materials only. In each case, no undesired symmetrical ether formation was observed.

Table 3.7 Different electrophiles used for C-C bond formation

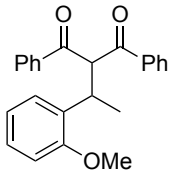




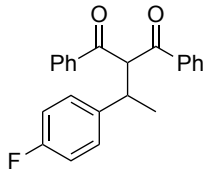
3, 88% yield
90 °C, 24 h



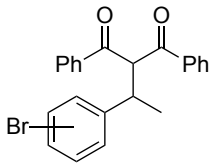
318, **70% yield**
90 °C, 24 h



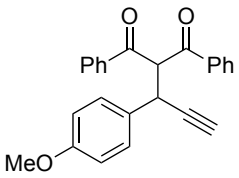
319, **95% yield**
40 °C, 16 h



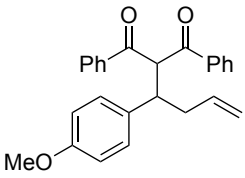
320, **90% yield**
90 °C, 24 h



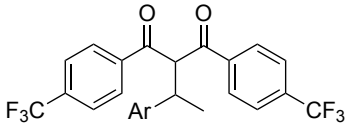
4-Br 321, **71% yield**
3-Br 322, **38% yield**
2-Br 323, **51% yield**
90 °C, 24 h



324, **98% yield**
rt, 16 h

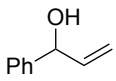


325, **34% yield**
90 °C, 24 h

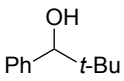


326, **20% yield**
rt, 24 h
(Ar: 4-MeOC$_6$H$_4$)

Unsuccessful Substrates

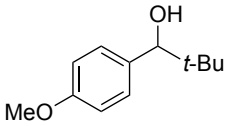


67
no reaction

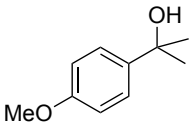


243
no reaction

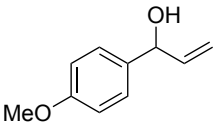
223
no reaction



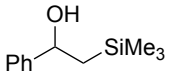
287
no reaction



288
no reaction



289
90 °C, decomposition

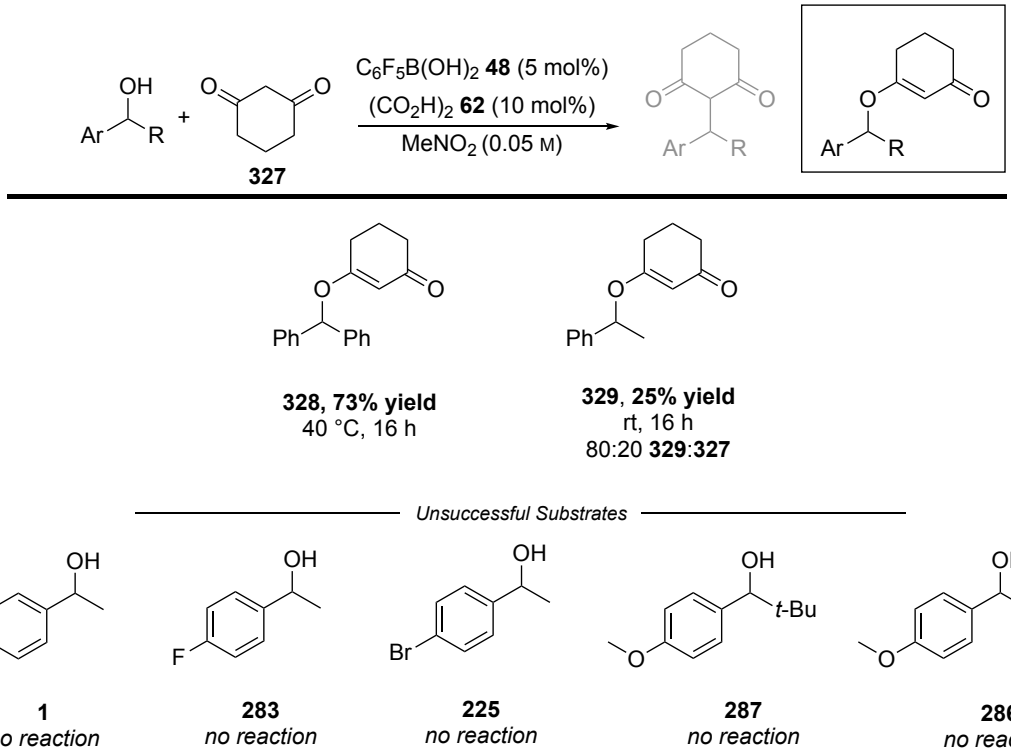


296
decomposition

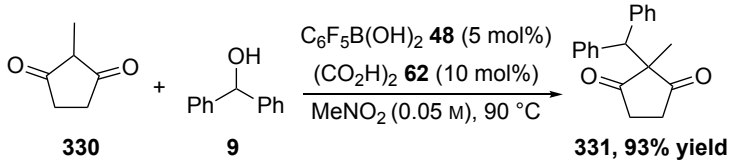
3.4.3 Cyclic 1,3-diketones

The reaction of 1,3-cyclohexanedione **327** with benzhydrol **9** under the standard conditions did not give the expected C-C bond formation, but instead gave selective O-alkylation.[103] Product **328** was obtained in 73% yield after purification by column chromatography. However, this process was not reproducible, with a range of alternative secondary benzylic alcohols giving either very low or no reactivity (Table 3.8).

Table 3.8 Substrate scope using 1,3-cyclohexanedione 327



The reaction of benzhydrol **9** with 2-methyl-1,3-cyclopentanedione **330** was carried out at 90 °C due to the poor solubility at lower temperatures. Initial reaction was more promising with the desired C-C product **331** obtained in an excellent 93% yield after purification by column chromatography. However, once again the process was not general and the use of different benzylic alcohols did not result in the desired C-C bond formation and returned either the symmetrical ether by-product or starting materials (Scheme 3.11).

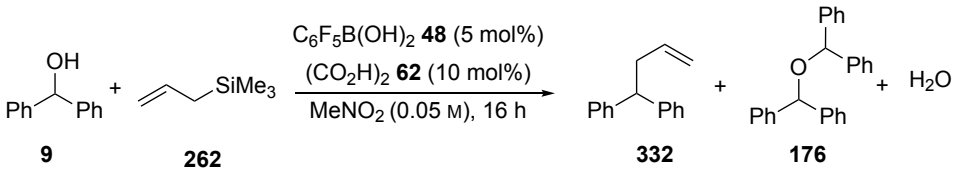


Scheme 3.11 Reaction using 2-methyl-1,3-cyclopentanedione 330

3.5 Dehydrative allylation

Allyltrimethylsilane is a widely used nucleophile for allylation reactions, so was tested in our method using benzylic alcohols as the electrophile (Table 3.9). The reaction using allyltrimethylsilane **262** (2 equiv.) and benzhydrol **9** with pentafluorophenylboronic acid **48** (5 mol%) and oxalic acid **62** (10 mol%) in nitromethane was first investigated. Symmetrical ether **176** was obtained as the sole product (entry 1) after 16 h at rt. Increasing the equivalents of **262** and performing the reaction at 40 °C gave no improvement, with the ether **176** formed in high conversion. However, when the reaction was performed at 90 °C the ether formation was avoided, and the desired allylation product **332** was obtained in excellent 96% yield after 16 h.

Table 3.9 Initial investigations using allyltrimethylsilane as the nucleophile



9 **262** **332** **176**

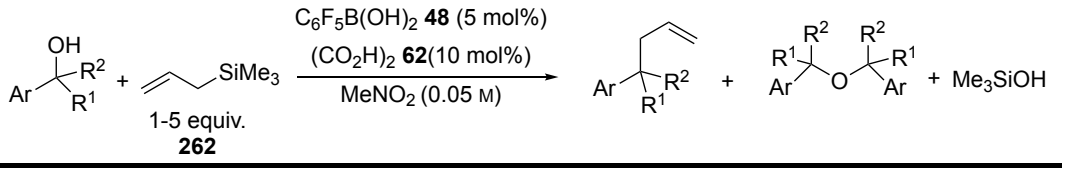
Entry	Allyltrimethylsilane	T (°C)	**332** (yield %)	**176** (%)[a]
1	2 equiv.	rt	0	98
2	5 equiv.	rt	0	98
3	2 equiv.	40	0	93
4	2 equiv.	90	96	0

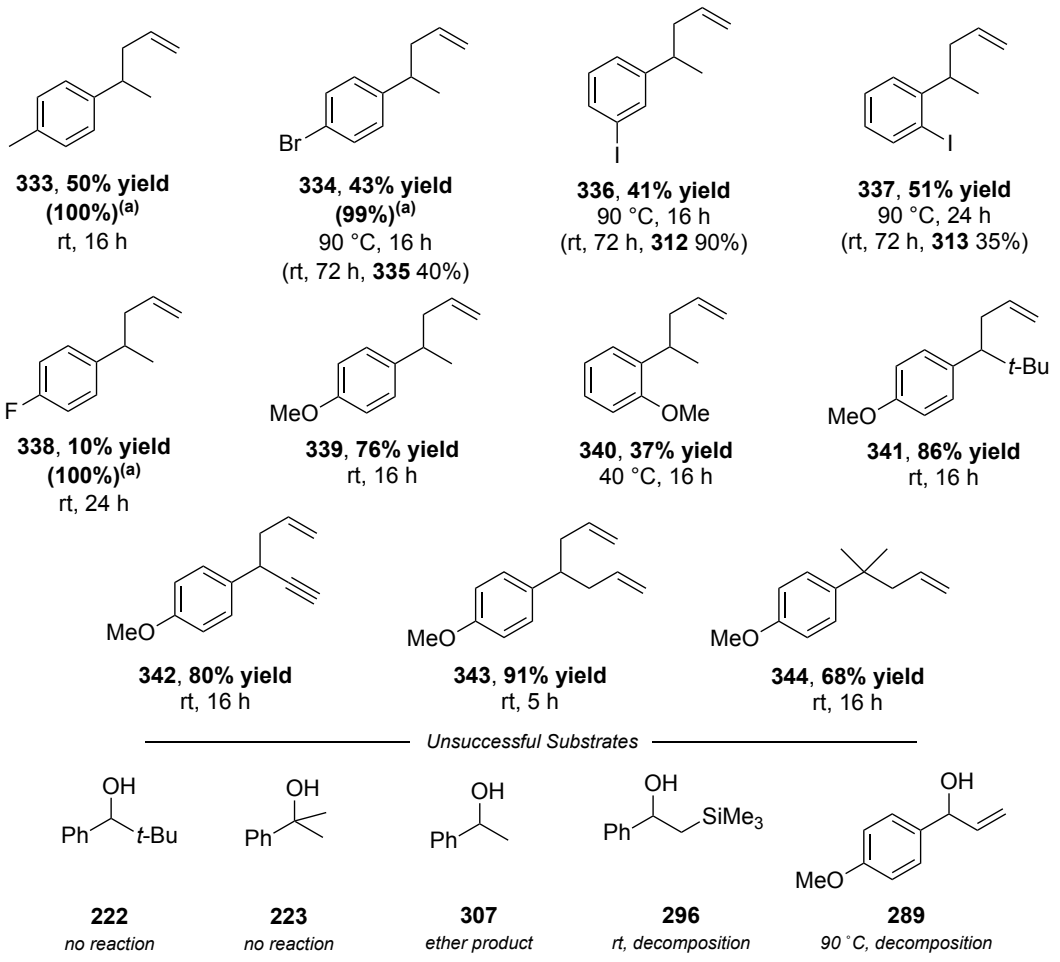
[a)]Conversion determined by ^{1}H NMR

Having demonstrated the desired reactivity using allyltrimethylsilane **262** as the nucleophile, the use of different benzylic alcohols was then investigated (Table 3.10). Surprisingly, 1-phenyl ethanol **1** did not give the allylation product at either rt, 40 °C or 90 °C, with the corresponding symmetric ether **307** formed as a 1:1 mixture of diastereoisomers in each case. In contrast, the presence of an electron-donating methyl substituent gave selective allylation at rt, allowing product **333** to be isolated in 50% yield. Halogen-substituted electrophiles such

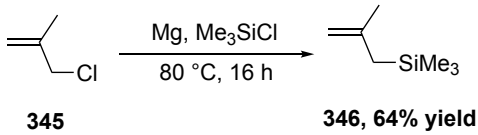
as 4-bromo, 3-iodo and 2-iodophenyl ethanol required heating at 90 °C to give the desired products **334**, **336** and **337** in 43%, 41% and 51% yield, respectively. The reaction with 4-fluoro ethanol gave excellent 99% conversion at room temperature, but product **338** was not easily purified by column chromatography and was obtained in a low 10% yield. The presence of an electron-donating methoxy substituent was beneficial for the reactivity. For example, while phenyl substituted alcohol **222** bearing a bulky *tert*-butyl group was unreactive, the corresponding 4-methoxy derivatives gave products **341** and **342** in 86% and 80% yield, respectively, after reaction at room temperature. A range of other methoxy substituted alcohols was also well tolerated, giving products **340** and **344** in generally high yield. In contrast to previous nucleophiles investigated, a tertiary alcohol could be used to give product **344** containing an all-carbon quaternary centre in 68% yield. However, unsubstituted tertiary alcohol **223** remained unreactive under the standard conditions.

Table 3.10 Substrate scope of allylation reaction



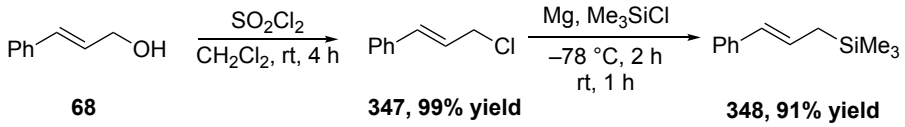


Next, a couple of substituted allylsilanes were prepared and tested in the dehydrative C-C bond formation. First, trimethyl(2-methylallyl)silane **346** was synthesised via a Grignard reaction using 3-chloro-2-methylprop-1-ene **345,** giving 64% yield after purification by distillation (Scheme 3.12).[104]



Scheme 3.12 Grignard reaction to synthesize trimethyl(2-methylallyl)silane 346

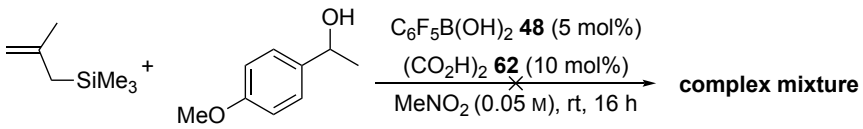
Cinnamyl trimethylsilane **348** was prepared in two steps from cinnamyl alcohol **68.** Treatment with thionyl chloride gave cinnamyl chloride **347** in quantitative yield, with a subsequent Grignard reaction giving cinnamyl trimethylsilane **348** in excellent 91% yield (Scheme 3.13).[105]



68 **347, 99% yield** **348, 91% yield**

Scheme 3.13 Synthetic procedure for cinnamyl trimethylsilane 348

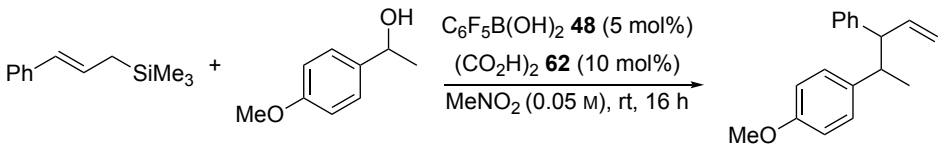
The reaction between of trimethyl(2-methylallyl)silane **346** and 4-methoxyphenyl ethanol **17** under the standard catalytic conditions was unsuccessful, with a complex mixture obtained after 16 h at room temperature, with no evidence of a product formation (Scheme 3.14).



346 **17**

Scheme 3.14 Reaction using trimethyl(2-methylallyl)silane 346 as the nucleophile

The reaction with cinnamyl trimethylsilane **348** was more successful, giving product **349** as a 64:36 mixture of diastereoisomers in 77% yield (Scheme 3.15). The reaction was completely selective, with no presence of other undesired side-products in the crude ^{1}H NMR.



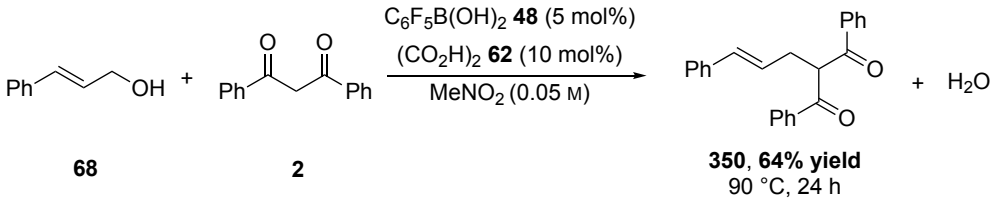
348 **17** **349, 77% yield**
64:36 dr

Scheme 3.15 Use of cinnamyl trimethylsilane 348 as the nucleophile

3.6 Mechanistic control experiments

Different control experiments were performed to study the mechanistic pathway of the dehydrative C-C bond formation. First, the regioselectivity of C-C bond formation was investigated under the standard reaction conditions using cinnamyl alcohol **68** and 1,3-diphenylpropane-1,3-dione **2**. The reaction gave 2-cinnamyl-1,3-diphenylpropane-1,3-dione

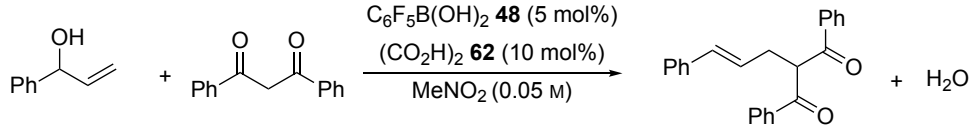
350 as the only product in 64% yield after purification by column chromatography (Scheme 3.16).



68 **2** **350**, **64% yield**
90 °C, 24 h

Scheme 3.16 Reaction of cinnamyl alcohol 68 with 1,3-diphenylpropane-1,3-dione 2

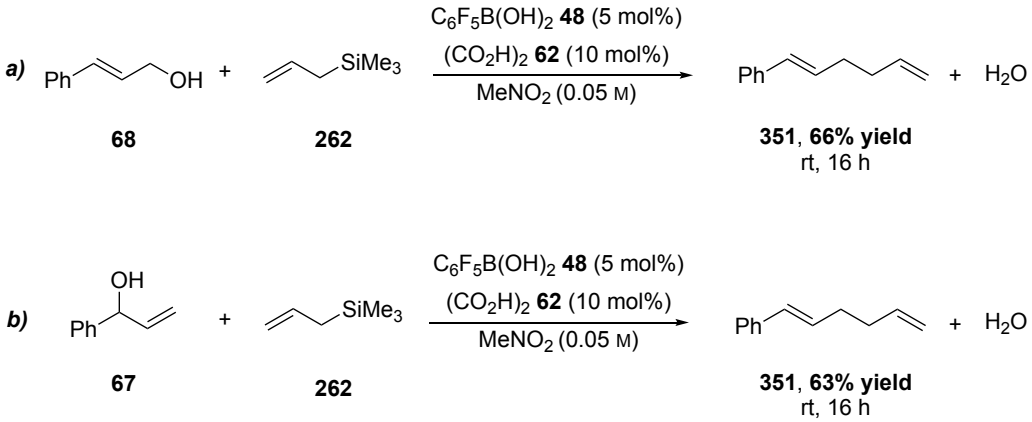
Next, the reaction was performed under the same conditions but starting from 1-phenylprop-2-en-1-ol **67** as the electrophile (Scheme 3.17). The same regioisomer of product **350** was obtained in a comparable 66% yield. This is consistent with the results for C-O bond formation and suggests the reaction proceeds *via* a common intermediate from both substrates.



67 **2** **350**, **66% yield**
90 °C, 24 h

Scheme 3.17 Reaction of 1-phenylpropenol 67 with 1,3-diphenylpropane-1,3-dione 2

The same control experiment was then performed using allyltrimethylsilane **262** as the nucleophile. As previously, cinnamyl alcohol **68** and vinyl alcohol **67** react to give the linear allylation product **351** in comparable yields (Scheme 3.18).

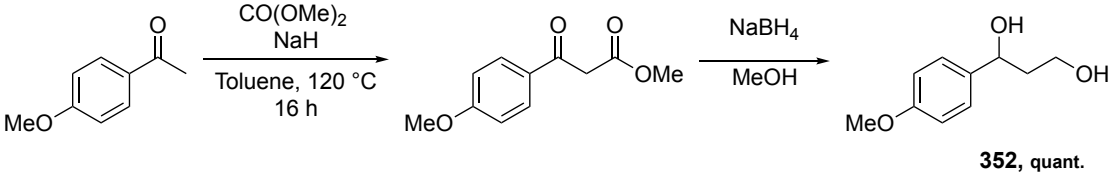


68 **262** **351**, **66% yield**
rt, 16 h

67 **262** **351**, **63% yield**
rt, 16 h

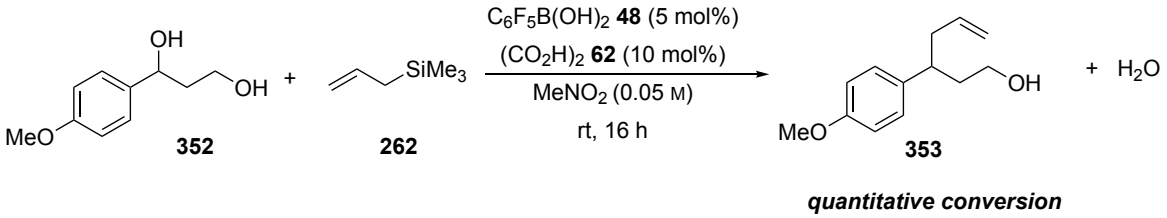
Scheme 3.18 Reaction of cinnamyl alcohol 68 and 1-phenylpropenol 67 with allyltrimethylsilane 262

Substituted diol **352** has been synthesised in two step process. Dimethyl carbonate reacts with 4-methoxyacetophenone in presence of sodium hydride to give methyl 3-(4-methoxyphenyl)-3-oxopropanoate. Diol **352** was obtained after reduction using sodium borohydride in quantitative yield (Scheme 3.19).



Scheme 3.19 Synthesis of diol 352

The chemoselectivity of C-C bond formation was tested by reacting 1,4-diol **352** with allyltrimethylsilane **262** (Scheme 3.20). The reaction formed **353** as the only product in quantitative conversion by NMR analysis, showing complete selectivity for the substitution of the secondary benzylic alcohol over the primary alcohol. This supports a catalytic SN1 substitution proceeding *via* a stabilised benzylic carbocation intermediate.

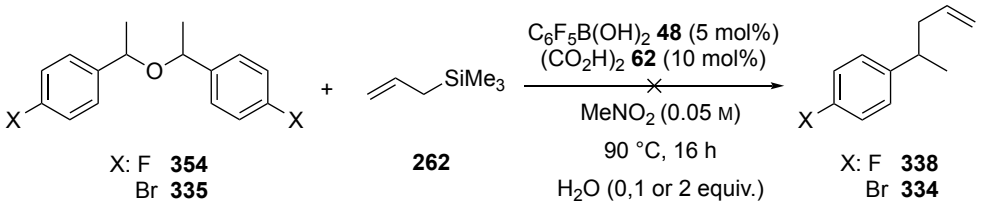


Scheme 3.20 Control reaction from diol 352 and allyltrimethylsilane 262

An interesting observation for some of the allylation reactions was the formation of ether side-products at low temperature, but selective C-C bond formation for the same substrates at higher temperatures. One hypothesis is that symmetrical ether formation is reversible, and the ether is an intermediate at higher temperatures. This is consistent with the observations of Hall for arylboronic acid-catalysed dehydrative Friedel-Crafts alkylations.[106] To test the reversibility or ether formation, 4,4'-(oxybis(ethane-1,1-diyl))bis(fluorobenzene) **354** (1:1 dr) was reacted with allyltrimethylsilane **262** under the standard conditions for 16 h. However, no reaction was observed and the starting materials were returned. Next, symmetric ether **335** (2:1 dr) was investigated in the presence of either 0, 1 or 2 equivalents of water, which would be released during the dehydrative substitution. In the absence of water, no reaction

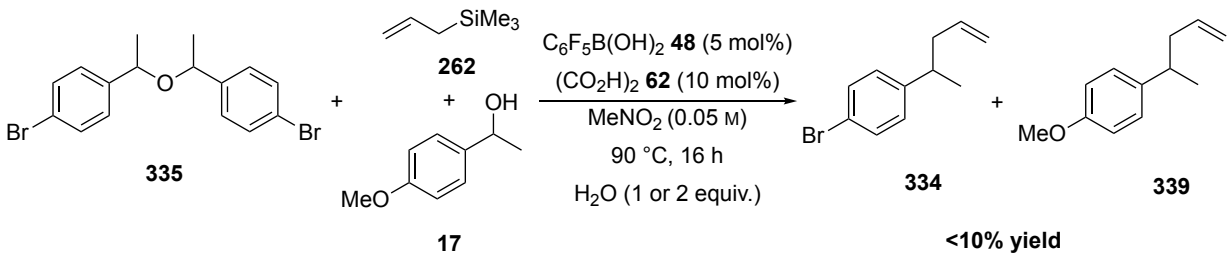
was observed and the ether was stable. However, the presence of either 1 or 2 equivalents led to complete conversion into a complex mixture that could not be easily identified by ^{1}H NMR analysis of the crude material. While this experiment does not provide evidence of the ether being an intermediate in the allylation process, it does show that the ether is unstable to the reaction conditions at high temperature (90 °C) in the presence of water(Table 3.11).

Table 3.11 Control reaction starting from symmetrical ether 354/335



Entry	X	H_2O equiv.	Product
1	F **354** (1:1 dr)	0	—
2	Br **335** (2:1 dr)	0	—
3	Br **335** (2:1 dr)	1	Complex mixture
4	Br **335** (2:1 dr)	2	Complex mixture

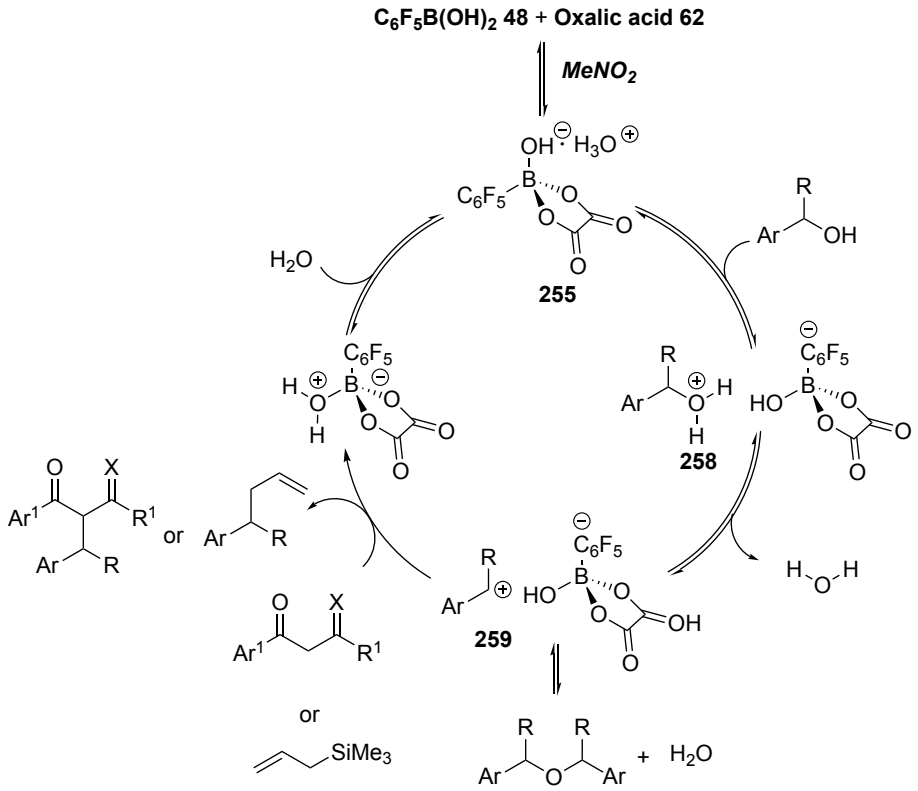
Next, a crossover experiment was performed to investigate the reversibility of the reaction (Scheme 3.21). Symmetrical ether **335** was mixed in a reaction with allyltrimethylsilane **262** and 4-methoxyphenyl ethanol **17** under standard conditions in presence of 0, 1 or 2 equivalents of water. A mixture of allylated compounds **334** and **339** with an unreacted started material was encountered in the reaction when 1 or 2 equivalents of water was present at the reaction media. Although the conversion was low (<10% by ^{1}H NMR analysis), this results again suggests that the symmetrical ether could be a possible intermediate in our reaction.



Scheme 3.21 Crossover experiment

3.7 Proposed reaction mechanism

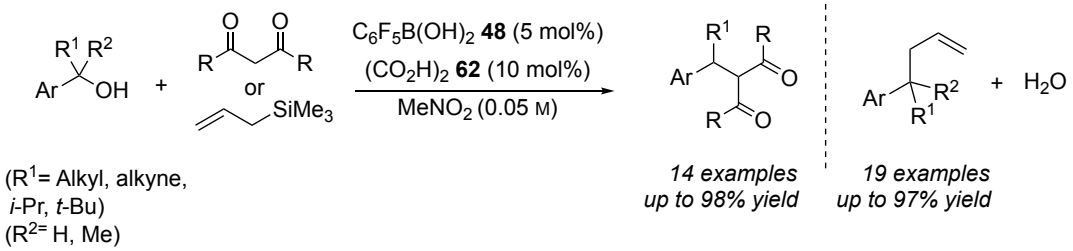
The evidence obtained suggests a similar mechanism as for C-O bond formation (Scheme 3.22). An initial equilibrium between pentafluorophenylboronic acid **48** and oxalic acid **62** in nitromethane may result in the formation of complex **255**, which is likely to act as a strong Brønsted acid catalyst. Protonation of an electrophilic benzyl alcohol gives ion pair **258**, which can dissociate into ion pair **259**. Reaction of carbocation **259** with an enolized 1,3-diketone equivalent or allyltrimethylsilane **262** affords the substitution product, with the released boronate species in equilibrium with other hydrated forms in the presence of water. The reaction of ion pair **259** with a second molecule of alcohol to form a symmetrical ether by-product is sometimes observed, but may be reversible at high temperatures. Therefore, in some cases, ether formation may be the kinetic product, but C-C bond formation is thermodynamically favourable.



Scheme 3.22 Proposed reaction mechanism

3.8 Conclusion

In conclusion, a procedure was found for the dehydrative substitution of alcohols to C-C bond using a range of 1,3-diketones and allyltrimethylsilane with water as the sole by-product (Scheme 3.23). Previous standard conditions were used, pentafluorophenylboronic acid **48** (5 mol%) and oxalic acid **62** (10 mol%) in nitromethane for this new protocol. Broad substrate scope was found in the presence of electron-rich and electron-poor groups with yields up to 98% yield.



Scheme 3.23 Dehydrative substitution reaction for C-C bond formation using arylboronic acid 48

4 Arylboronic Acid-Catalysed Dehydrative Nazarov Cyclisation

4.1 Introduction

Furan is a five-membered heterocycle consisting of four carbons and one oxygen atom. Furans are very important motifs in organic chemistry and have wide applicability in areas such as the synthesis of natural products, medicinal chemistry,[107] polymer chemistry,[108,109] and food chemistry[110]. For example, furan is the core moiety in Roseophilin **355,** which has displayed antitumoral activity (Figure 4.1).[111] Nifuroxazide **356** has been tested to treat colitis and diarrhoea,[112] hydroxymethyl furfural **357** has been used as a food additive[113] and lapatinib **358** is used as a treatment for breast cancer.[114]

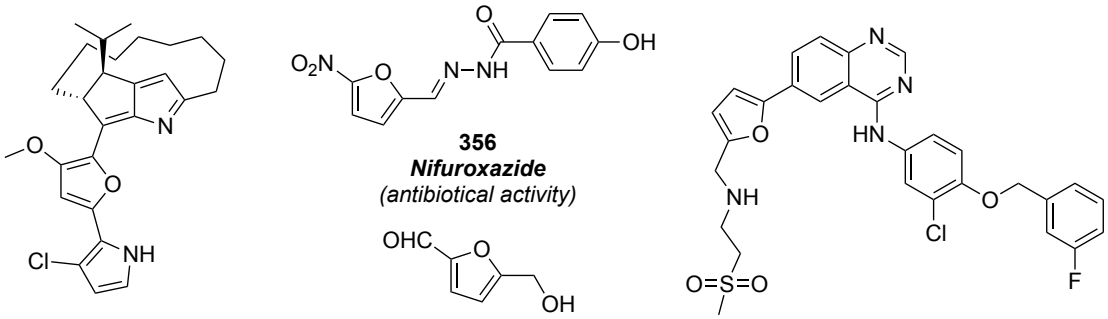
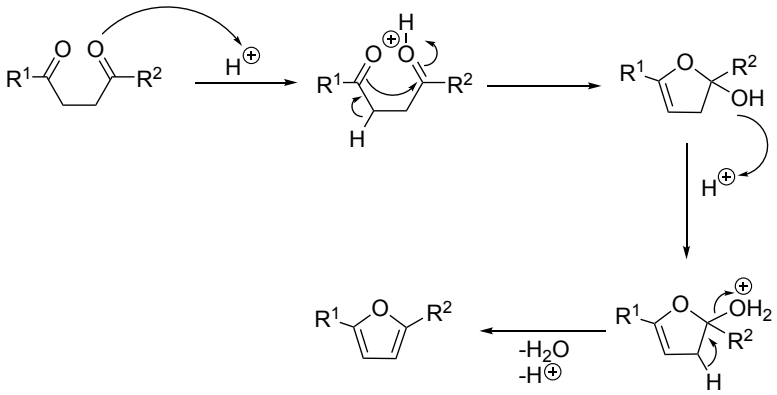


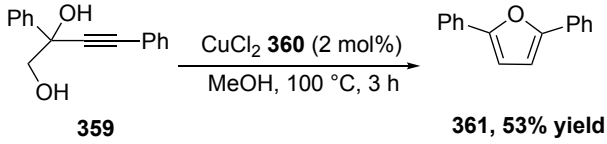
Figure 4.1 Furan containing compounds

The most classic method for furan synthesis is the Paal-Knorr reaction from 1,4-diketones.[115] An acid catalyses the furan synthesis by protonation of one carbonyl followed by intermolecular cyclisation through the end tautomer of the second carbonyl (Scheme 4.1). The furan is formed after dehydration of the resulting hemiacetal. One of the challenges with the Paal-Knorr reaction is often the synthesis of the 1,4-diketone starting materials and therefore many other methods for furan synthesis have been investigated.[116]



Scheme 4.1 Paal-Knorr furan synthesis

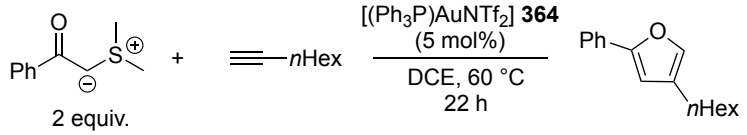
Some selected recent examples include the work of Gabrielle and co-workers in 2010, who investigated the use of a straightforward and cheap method for a furan synthesis from 3-yne-1,2-diols.[117] Only four examples were reported using $CuCl_2$ **360** (2 mol%) as a catalyst for the 5-endo-dig heterocyclodehydration reaction in reasonable yields. For example, propargylic alcohol **359** reacts in the presence of $CuCl_2$ **360** (2 mol%) in MeOH at 100 °C to give furan **361** in 53% yield (Scheme 4.2). Starting from the same 3-yne-1,2-diols, the use of $AuBr_3$ and $AuCl_3$ has also been reported in good yields, but with limited reaction scope.[118,119]



359 **361, 53% yield**

Scheme 4.2 Furan synthesis using $CuCl_2$ 360

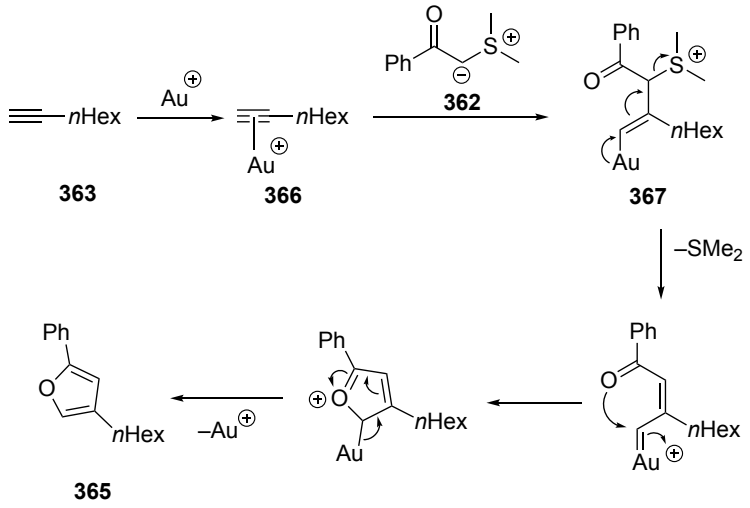
Alternative gold-catalysed process has also been reported for furan synthesis. For example, in 2012 Skrydstrup and co-workers showed that sulfur ylide **362** reacts with terminal alkyne **363** in the presence of an Au(I) **364** catalyst to form furan **365** (Scheme 4.3).[120]



362 **363** **365, 63% yield**

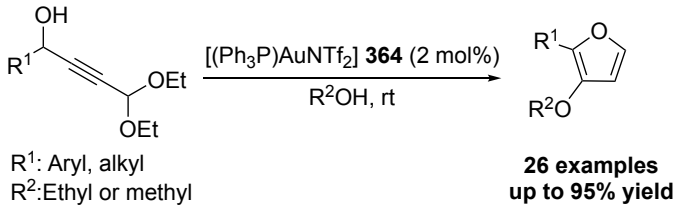
Scheme 4.3 Gold-catalysed furan synthesis

Regioselective addition of the ylide **362** across the activated alkyne **366** followed by elimination of dimethyl sulphide **367** and subsequent intramolecular trapping of the gold carbene gives 2,4-disubstituted furan **365** in good yields (Scheme 4.4).



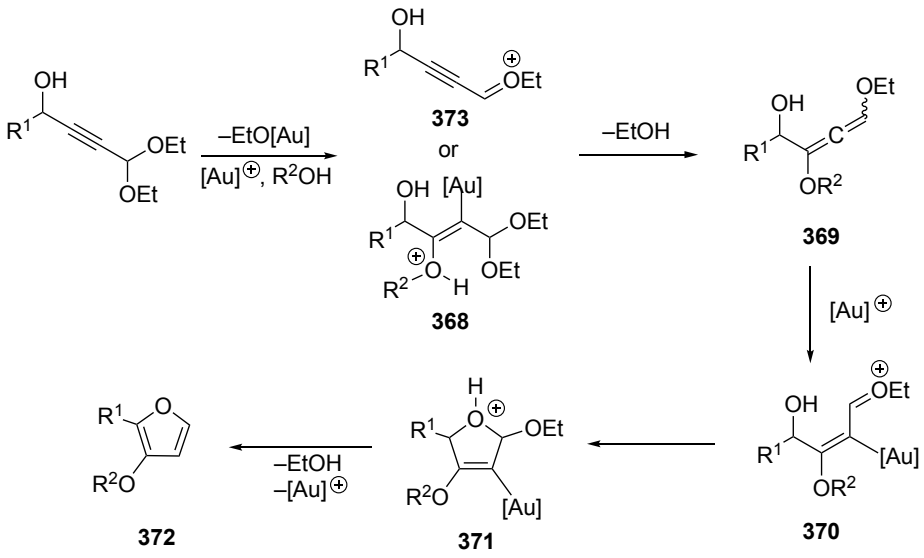
Scheme 4.4 Proposed mechanism for the Au-catalysed furan synthesis

In 2014, Sheppard and co-workers reported the use of acetal-containing propargylic alcohols with gold catalyst **364** and a second alcohol leading to 3-alkoxyfurans products (Scheme 4.5).[121] A number of examples was reported in high yields and good tolerance of electron-deficient, electron-rich or sterically hindered groups at the 2-position.



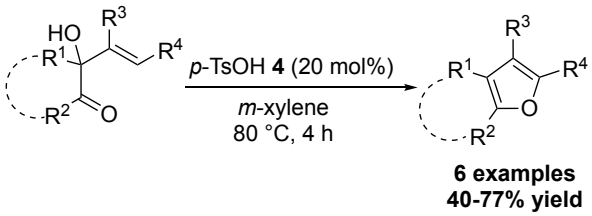
Scheme 4.5 Synthesis of 3-alkoxyfurans products

The proposed mechanism starts with regioselective gold-catalysed addition of the alcohol into the alkyne, obtaining vinyl gold intermediate **368** (Scheme 4.6). Loss of ethanol generates allenyl ether **369**, with subsequent gold activation to generate oxonium **370**. Dihydrofuran intermediate **371** was obtained by intramolecular cyclisation followed by loss of gold and ethanol to obtain furan **372**. A different initial pathway was also suggested, proceeding by Lewis-acid activation to generate **373** followed by conjugate addition of the alcohol to obtain **369**.



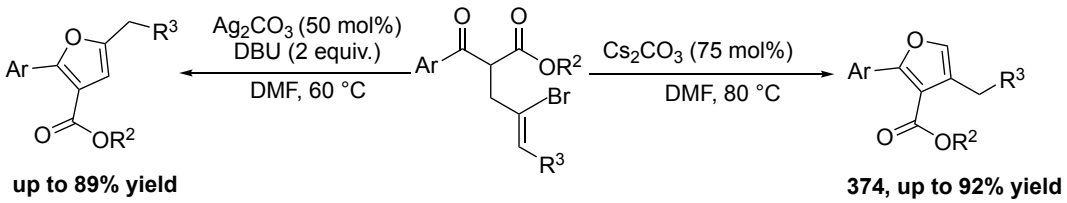
Scheme 4.6 Suggested mechanism for the gold-catalysed synthesis of 3-alkoxyfurans

In the same year, a Brønsted acid-catalysed furan synthesis from ß,γ-unsaturated α-hydroxyketones was investigated by Krische and co-workers.[122] Protonation at the tertiary alcohol using *para*-toluensulfonic acid **4** (20 mol%) at 80 °C resulted in a cyclodehydrative process to form tetrasubstituted furans in good yields (Scheme 4.7).



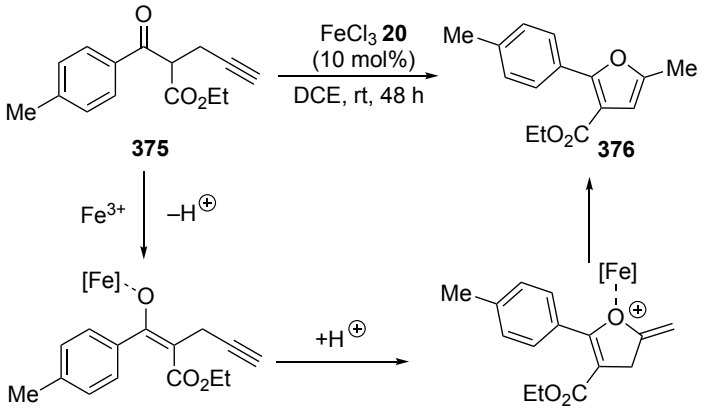
Scheme 4.7 Furan synthesis from ß,γ-unsaturated α-hydroxyketones as starting materials

In 2015, Chang and co-workers reported the use of silver salt Ag_2CO_3 and DBU for the synthesis of 2,5-disubstituted furan-3-carboxylates in good yields.[123] When caesium carbonate was used as a base without the presence of Ag_2CO_3; regioisomeric furan-3-carboxylates **374** were obtained as the major product (Scheme 4.8). In general, substrates having electron-donating groups on the aryl ring resulted in higher yields compared with those having electron-withdrawing groups. Substrates containing naphthyl and other heterocycles also proceeded efficiently, giving good yields of the furan products.



Scheme 4.8 Furan synthesis in presence of silver salt or with caesium carbonate base

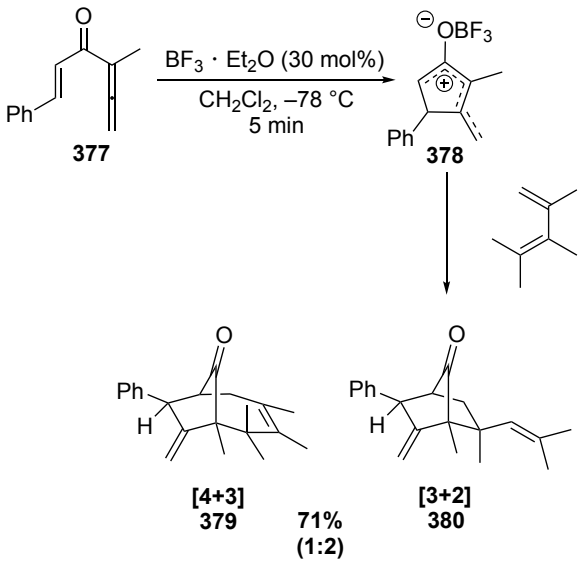
In 2017, iron trichloride **20** (10 mol%) was reported as a mild Lewis acid catalyst for furan synthesis by Schindler and co-workers.[124] The reaction involves 5-exo-dig cycloisomerization of substrates such as **375** to give furan **376** in 92% yield (Scheme 4.9). The procedure tolerates electron-poor and electron-rich aryl ketone substrates affording the desired heterocycles in good to high yields.



Scheme 4.9 Furan synthesis using mild and efficient $FeCl_3$ 20 as catalyst

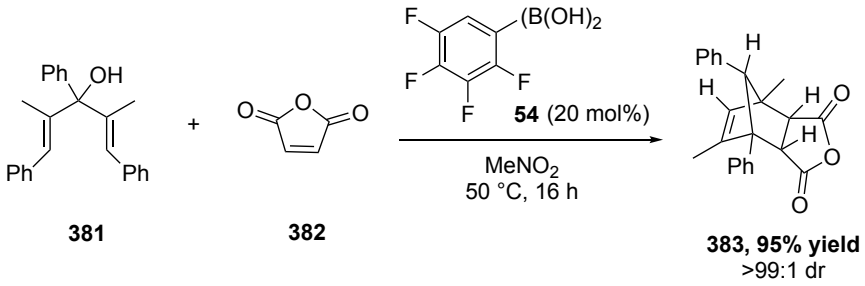
4.1.1 Boron-catalysed Nazarov cyclisations

The use of boron compounds as catalysts for the Nazarov cyclisation has not been extensively studied. In 2010, Burnell and co-workers developed a cascade reaction using $BF_3{\cdot}Et_2O$ as a Lewis acid catalyst for Nazarov cyclisation formation of allenes **377**, with the resulting oxalyl cation **378** reacting with different dienes to obtain a mixture of [4+3] **379** and [3+2] **380** cycloaddition products (Scheme 4.10).[125]



Scheme 4.10 Nazarov cyclisation using $BF_3 \cdot Et_2O$

Hall and co-workers reported the use of tetrafluorophenylboronic acid **54** as a catalyst for a dehydrative Nazarov cyclisation from tertiary allylic alcohols (Scheme 4.11).[126] The process forms a cyclopentadiene product, which was further reacted in one-pot with dienophiles to undergo [4+2]-cycloadditions. For example, dehydrative Nazarov cyclisation of **381** followed by reaction with maleic anhydride **382** gives bicyclic product **383** in an excellent 95% yield as a single diastereoisomer.

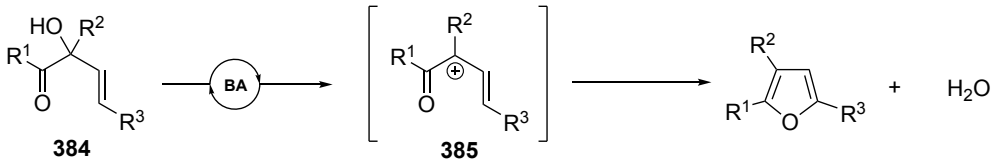


Scheme 4.11 Sequential Nazarov cyclisation/Diels-Alder reaction

4.1.2 Arylboronic acid-catalysed furan synthesis

To the best of our knowledge, there are no previous reports of furan ring synthesis using boronic acid catalysis *via* alcohol activation for homo-Nazarov cyclisation reactions. Our investigation was focused on the use of ß,γ-unsaturated α-hydroxyketones **384** in combination with aryl boronic acid catalysis for the synthesis of substituted furans. It was envisaged that catalytic dehydration of **384** would give an allylic cation **385**, which would

undergo electrocyclization followed by deprotonation to form the desired furans (Scheme 4.12).

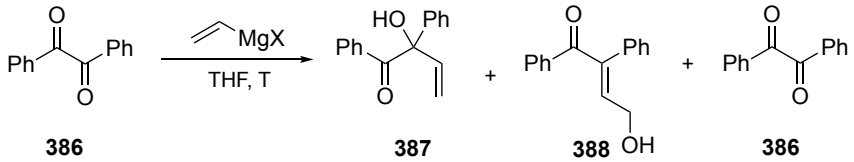


Scheme 4.12 General scheme for furan synthesis

4.2 Initial investigations

First, the reaction of ß,γ-unsaturated α-hydroxyketone **387** was investigated. The substrate synthesis was first attempted by reacting 1,2-diketone **386** with commercially available vinylmagnesium chloride **389** at rt for 4 h. The reaction gave 25% yield of desired product **387** after purification by column chromatography, along with 29% of isomeric product **388** and 30% of the staring material (Table 4.1,entry 1). In an attempt to avoid isomerization into **387** the reaction temperature was lowered to −78 °C. The conversion to ß,γ-unsaturated α-hydroxyketone **387** was improved, but after purification resulted in very low 16% yield alongside 23% of isomer **388** (Table 4.1, entry 2). When the reaction was performed for longer times (16 h) no better conversion to the desired product was obtained. Decreasing the concentration was detrimental for reactivity, forming only 18% of desired product **387**. The reaction was also investigated using vinylmagnesium bromide **390** (2 equiv.), which increased the reactivity, however, after purification product **387** was obtained in low 18% yield as previously (Table 4.1, entry 6). While the yields of **387** were low, sufficient amount of material was obtained to perform initial test reactions.

Table 4.1 ß,γ-unsaturated α-hydroxyketone 387 synthesis



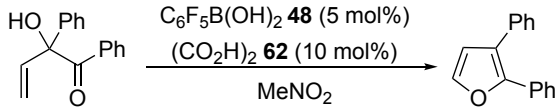
386 **387** **388** **386**

Entry	X (equiv.)	T (°C)	Time	[M]	**387** (%)[(a)]	**388** (%)[(a)]	386 (%)
1	Cl (1.2) **389**	rt	4 h	0.25	37(25)	33(29)	30
2	Cl (1.2) **389**	−78	20 min	0.25	55(16)	28(23)	16
3	Cl (1.2) **389**	−78	16 h	0.25	45(18)	29(27)	26
4	Cl (1.2) **389**	−78	30 min	0.06	18(15)	12(10)	69
5	Br (1.2) **390**	−78	20 min	0.25	46(18)	26(25)	18
6	Br (2.0) **390**	−78	30 min	0.25	58(18)	15(14)	27

[(a)]Conversion determined by ^{1}H NMR of crude reaction mixture; isolated yield in parenthesis

First, ß,γ-unsaturated α-hydroxyketone **387** was reacted under the standard conditions used for the previous dehydrative substitution reactions (Table 4.2). Reacting pentafluorophenylboronic acid **48** (5 mol%) and oxalic acid **62** (10 mol%) with **387** in nitromethane at room temperature gave no reactivity, with the starting material returned. Heating the reaction to 60 °C for either 2 or 6 h, gave the desired product **391** in 8 and 20% conversion, respectively, as determined by ^{1}H NMR analysis (entries 2 and 3). Increasing the reaction time to 16 h did not improve the yield, with complete decomposition of the furan product observed in the ^{1}H NMR of the crude mixture (entry 4). Increasing the temperature to 80 °C for 2 h also led to complete decomposition (entry 5).

Table 4.2 Initial furan synthesis reaction



387 **391**

Entry	T (°C)	Time (h)	Conversion **391** (%)[(a)]
1	rt	16	SM
2	60	2	8
3	60	6	20
4	60	16	Decomposition
5	80	2	Decomposition

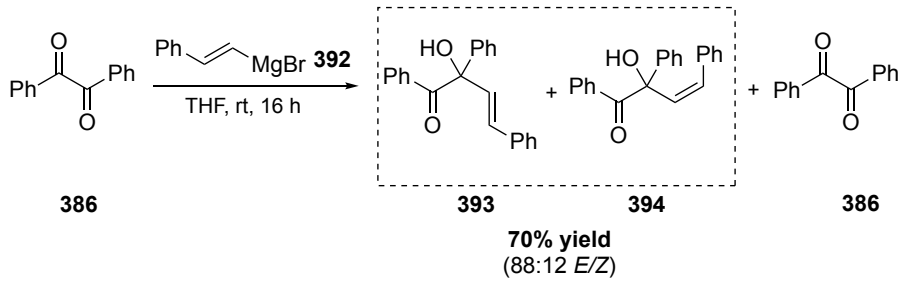
[(a)]Conversion determined by ^{1}H NMR analysis

Further investigations were carried out with the aim to avoid product decomposition; therefore, different boronic acids, ligands, equivalents, molarity and dehydrating agents were tested. However, no improvement was observed and decomposition remained a significant problem. The use of the isolated isomer **388** was also tested in the reaction under standard conditions with no reactivity obtained after 16 h at rt.

The use of vinyl substrate **387** would lead to furan **391** that is unsubstituted at the C(5) position. This could make the product susceptible to undesired Friedel-Crafts alkylation processes and/or polymerisation reactions. Therefore, a different substrate that would lead to a 2,5-substituted furan product was investigated. The product should be more stable and would make reaction development simpler.

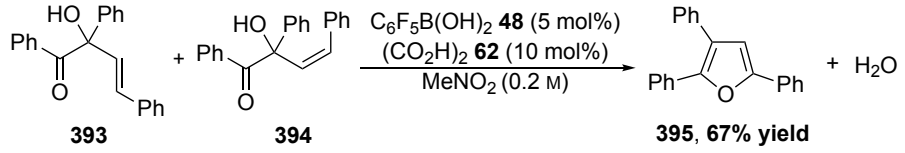
4.3 Reactions of ß,γ-unsaturated α-hydroxyketones

ß,γ-Unsaturated α-hydroxyketones **393** and **394** were synthesized by adding freshly prepared vinylic magnesium bromide **392** into diketone **386** at room temperature. The desired product was obtained as an inseparable 88:12 mixture of *cis-trans* isomers in 70% yield after purification by column chromatography (Scheme 4.13).



Scheme 4.13 Synthesis of ß,γ-unsaturated α-hydroxyketone 393/394

Reacting α-hydroxyketone **393/394** with pentafluorophenylboronic acid **48** (5 mol%) and oxalic acid **62** (10 mol%) in nitromethane at rt gave complete conversion within 6 h. The desired furan product **395** was obtained in a promising 67% yield after purification with no evidence of any side products or product decomposition (Scheme 4.14).

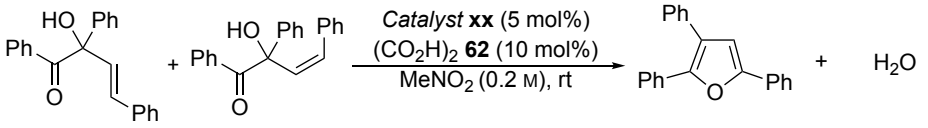


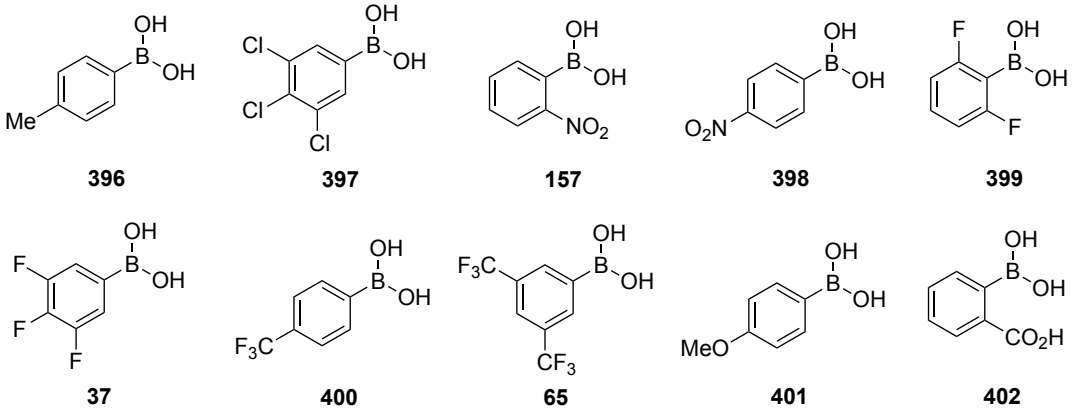
Scheme 4.14 Homo-Nazarov dehydrative cyclisation using ß,γ-unsaturated α-hydroxyketone 393/394

4.4 Reaction optimization

Initially, dehydrative cyclisation using different arylboronic acids (5 mol%) was investigated. In general, the reaction showed very good reactivity, leading to the desired furan product **395** in moderate to good yields (Table 4.3). For example, the use of 4-methylphenylboronic acid **396** (Table 4.3, entry 1) and 3,4,5-trichlorophenylboronic acid **397** (Table 4.3, entry 2) resulted in 61 and 66% yield of cyclic product **395** after 6 h at rt. Boronic acids having different numbers of electron withdrawing groups including nitro, fluorine or trifluoromethyl also gave furan product **395** in good yields (entries 5,6,7 and 11). Also, when electron donating methoxy boronic acid **401** was used, 58% of product **395** was formed. The best reactivity was encountered when 2-carboxyphenylboronic acid **402** and was used as the catalyst, giving the desired product **395** in 86% yield after just one hour (Table 4.3, entry 11). Finally, a control reaction in the absence of an arylboronic acid catalyst was performed, giving furan product **395** in only 20% conversion after 24 h. This shows that oxalic acid can itself promote the reaction, but the rate is significantly improved using an arylboronic acid.

Table 4.3 Catalyst optimization



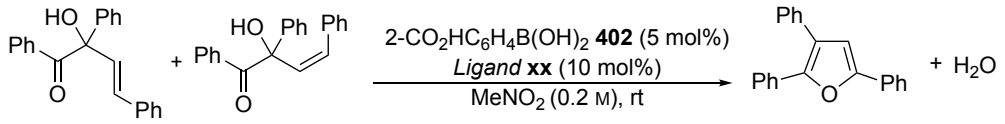


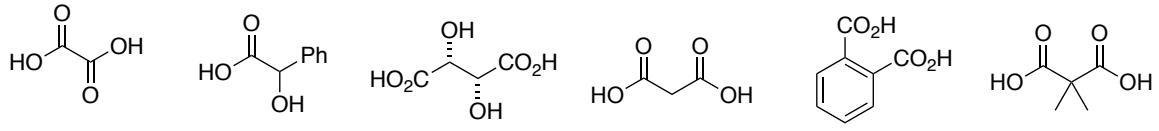
Entry	Boronic acid	Time (h)	Yield **395** (%)[a]
1	4-methylphenylboronic acid **396**	6	61
2	3,4,5-trichlorophenylboronic acid **397**	6	66
3	2-nitrophenylboronic acid **157**	16	40[b]
4	4-nitrophenylboronic acid **398**	16	47[b]
5	2,6-difluorophenylboronic acid **399**	1	57
6	3,4,5-trifluorophenylboronic acid **37**	16	61[b]
7	4 (trifluoromethyl)phenylboronic acid **400**	16	46[b]
8	3,5-bis(trifluoromethyl)phenylboronic acid **65**	16	67[b]
9	4-methoxyphenylboronic acid **401**	16	58[b]
10	Pentafluorophenylboronic acid **48**	6	67
11	2-carboxyphenylboronic acid **402**	1	86
12	None	24	20[c]

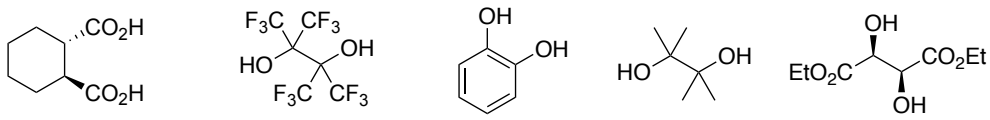
[a]% yield after column chromatography [b]After 6 h, 95% conversion of starting material [c]Conversion determined by ^{1}H NMR of crude reaction mixture

Using 2-carboxyphenylboronic acid **402** (5 mol%) as the optimal catalyst, different ligands (10 mol%) were screened in nitromethane at room temperature (Table 4.4). The use of mandelic acid **162** (entry 2) and tartaric acid **160** (entry 3) gave furan **395** with moderate conversion after 16 h reaction. Next, malonic acid **403** (entry 4), phthalic acid **404** (entry 5) and dimethylmalonic acid **405** (entry 6) were tested, resulting in very low reactivity giving only 10% of furan **395**. When *trans*-1,2-cyclohexanedicarboxylic acid **406** (entry 7) was tested, no reactivity was found. Using oxalic acid **62** (entry 1) and perfluoropinacol **87** (entry 8), quantitative conversion into furan product **395** was observed, with isolated yields of 86% and 82%, respectively. The yield using perfluoropinacol **87** was comparable with that obtained using oxalic acid **62**, but requires longer reaction times and therefore oxalic acid was chosen as the optimal ligand. When catechol **159** (entry 9) or pinacol **158** (entry 10) were used in the presence of phenylboronic acid **402** for 16 h at rt in nitromethane, no reaction was observed. (*S,*S)-Diethyl tartrate **161** (entry 11) was also tested, resulting in low reactivity to give only 10% of **395**. A control experiment in the absence of ligand resulted in no product formation (entry 12).

Table 4.4 Ligands screening







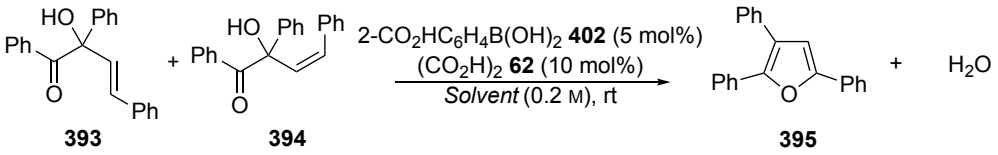
Entry	Ligand	Time (h)	Conv **395** (%)[a]
1	Oxalic acid **62**	1	100 (86)[b]
2	Mandelic acid **162**	16	44
3	Tartaric acid **160**	16	50
4	Malonic acid **403**	16	10
5	Phthalic acid **404**	16	11
6	Dimethylmalonic acid **405**	16	13
7	*trans*-1,2-Cyclohexanedicarboxylic acid **406**	12	0
8	Perfluoropinacol **87**	16	100 (82)[b]
9	Catechol **159**	16	0
10	Pinacol **158**	16	0
11	(*S,S*)-Diethyl tartrate **161**	16	10
12	None	24	0

[a]Conversion determined by ^{1}H NMR of crude reaction mixture [b]% yield after column chromatography

Next, the use of different solvents was investigated (Table 4.5). The use of *n*-butanol (entry 2) and tetrahydrofuran (entry 8) in combination with 2-carboxyphenylboronic acid **402** (5 mol%) and oxalic acid **62** (10 mol%) gave poor or no reactivity after 24 h. Acetone (entry 3),

toluene (entry 5) and dichloromethane (entry 6) resulted in 40%, 80% and 60% yield, respectively, of desired product **395** after 24 h reaction. When chloroform (entry 7) was used for 24 h, **395** was obtained in high 90% yield. Shorter times were required to obtain 100% conversion after 1 or 2 hours using trifluoroethanol (entry 8), hexafluoroisopropanol (entry 9) or acetonitrile (entry 10) as a solvent. Overall, the reaction using acetonitrile was most efficient, resulting in 90% yield of product **395**.

Table 4.5 Solvent screening

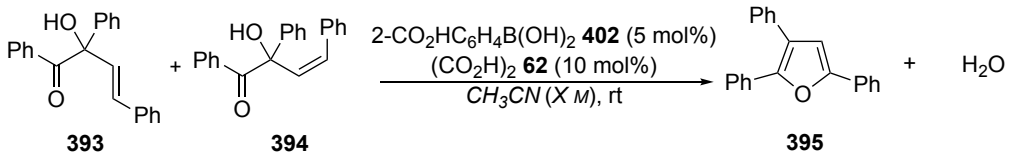


Entry	Solvent	Time (h)	Yield **395** (%)[(a)]
1	Nitromethane	1	86
2	*n*-Butanol	24	8
3	Tetrahydrofuran	24	0
4	Acetone	24	40
5	Toluene	24	80
6	Dichloromethane	24	60
7	Chloroform	24	90
8	Trifluoroethanol	1	69
9	Hexafluoroisopropanol	1	39
10	Acetonitrile	2	90

[(a)]% yield after column chromatography

The reaction concentration was then varied (Table 4.6). In general, the results were similar, with more and less concentrated reactions requiring longer times for completion. Increased concentration gave a drop in yield to 71% (entry 1), but lowering the concentration to 0.05 M had negligible effect on the yield.

Table 4.6 Molarity screening

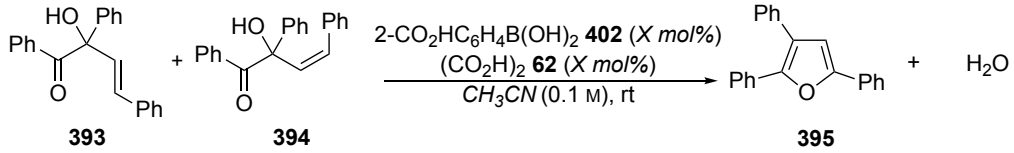


Entry	Molarity [M]	Time (h)	**395** (%)[(a)]
1	0.5	2	71
2	0.2	2	90
3	0.1	1.5	91
4	0.05	2	88

[(a)]% yield after column chromatography

Finally, the catalyst loading and ratio with the ligand was investigated (Table 4.7). The catalyst loading could be reduced to 3 mol% without affecting the yield (entry 2), but with the use of 1 mol% **402** gave much lower conversion. The 1:2 ratio of catalyst/ligand was also not necessary under these conditions. Using either 2 mol% or 3 mol% of both boronic acid **402** and oxalic acid **62** gave furan product **395** in excellent yield (entries 4 and 5). Final control experiments in the absence of boronic acid **402**, oxalic acid **62**, or both were performed under the otherwise optimal conditions, resulting in no reactivity or low conversion after 16 h at room temperature (entries 6-8).

Table 4.7 Investigation of the catalyst:ligand ratio



Entry	**402** (mol%)	**62** (mol%)	Time (h)	Conv **395** (%)[a]
1	5	10	2	(90)[b]
2	3	6	2	90
3	1	2	2	20
4	2	2	2	100 (93)[b]
5	3	3	2	100 (92)[b]
6	0	2	16	0
7	2	0	16	26
8	0	0	16	0

[a]Conversion determined by ^{1}H NMR of crude reaction mixture [b]% yield after column chromatography

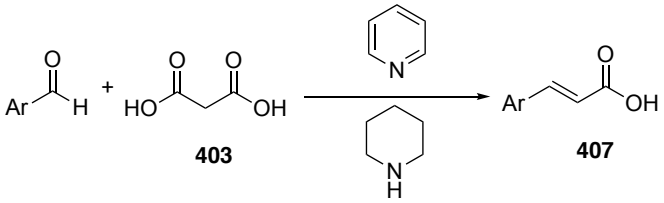
Overall, the use of 2-carboxyphenylboronic acid **402** (2 mol%) and oxalic acid **62** (2 mol%) in acetonitrile (0.1 M) at room temperature for 2 h proved optimal, forming dehydrative Nazarov cyclisation product **396** in excellent 93% yield after purification.

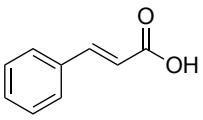
4.5 Substrate scope

4.5.1 Synthesis of ß,γ-unsaturated α-hydroxyketones.

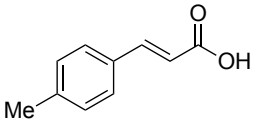
To get the different substituted ß,γ-unsaturated α-hydroxyketones at the R^4 position, a range of styrene bromides was prepared in two steps from commercially available aldehydes. First, reaction with malonic acid **403** *via* the Doebner modification of the Knoevenagel condensation gave cinnamic acids in high yields after recrystallization procedure from aqueous ethanol (Table 4.8).

Table 4.8 Cinnamic acids synthesis

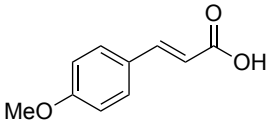




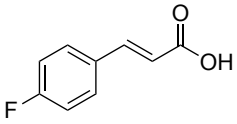
408, **88% yield**



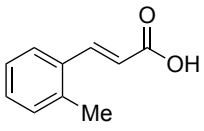
409, **93% yield**



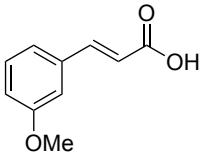
410, **85% yield**



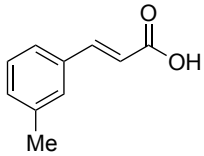
411, **91% yield**



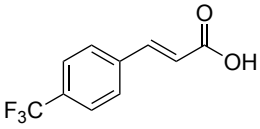
412, **83% yield**



413, **89% yield**



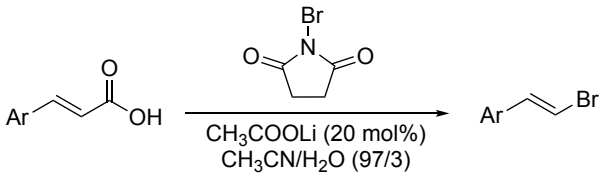
414, **91% yield**

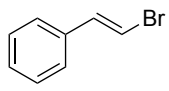


415, **78% yield**

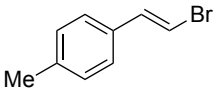
Next, the acids were reacted with lithium acetate (20 mol%) and *N*-bromosuccinimide in a mixture of acetonitrile and water solution to give the desired styrene bromides in mostly high yields (Table 4.9).

Table 4.9 Styrene bromide synthesis

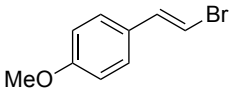




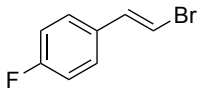
416, **54% yield**



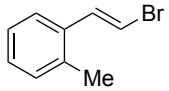
417, **99% yield**



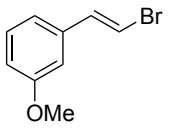
418, **99% yield**



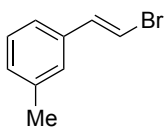
419, **21% yield**



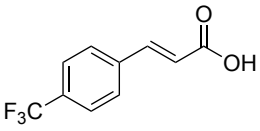
420, **36% yield**



421, **55% yield**



422, **30% yield**

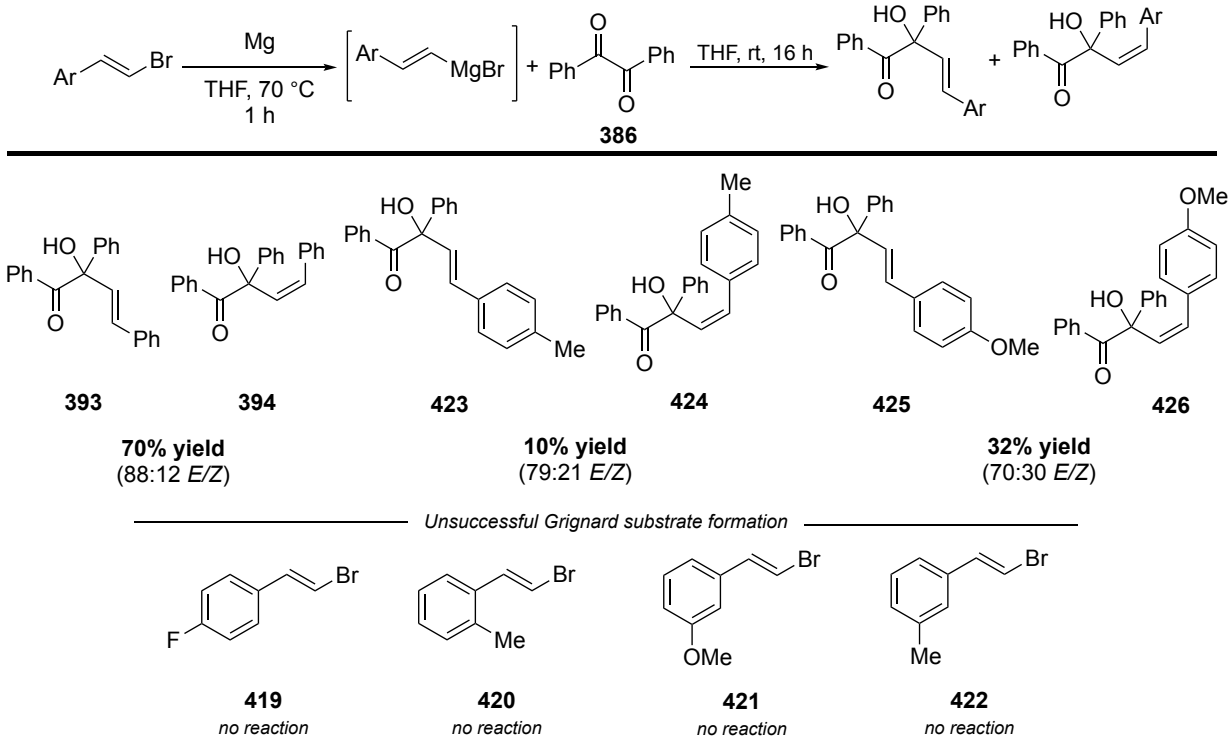


415, **Decomposed**

For the synthesis of substituted ß,γ-unsaturated α-hydroxyketones, the styrene bromides were reacted with magnesium to form the Grignard reagents. After titration of the freshly

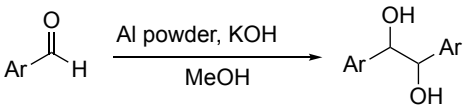
synthesised Grignards were then added directly into 1,2-diketone **386** (Table 4.10). Unfortunately, this procedure resulted in an inseparable mixture of *cis-trans* isomers for **423/424** and **425/426** in only 10% and 32% yield, respectively. The reaction with styrenes **419**-**422** was also unsuccessful as the Grignard formation did not occur in these cases, despite multiple attempts.

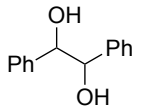
Table 4.10 Synthesis of different ß,γ-unsaturated α-hydroxyketones



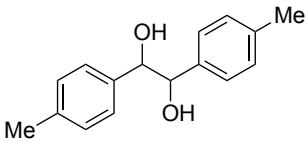
Next, the symmetrical diketone was varied to give different substituted ß,γ-unsaturated α-hydroxyketones (Table 4.11). First, a range of substituted benzaldehydes underwent pinacol coupling using aluminium powder in the presence of KOH and methanol for 16 h. This procedure worked well, giving a range of symmetric diols in good yields after purification by column chromatography.

Table 4.11 Symmetrical diol synthesis

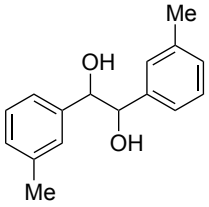




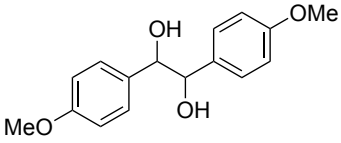
427, **96% yield**



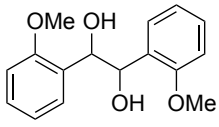
428, **49% yield**



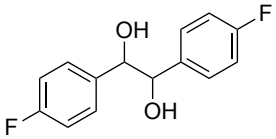
429, **70% yield**



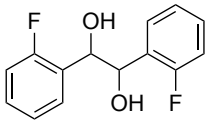
430, **78% yield**



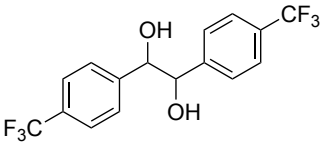
431, **57% yield**



432, **73% yield**



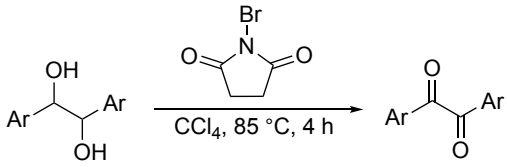
433, **33% yield**

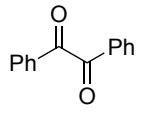


434, **57% yield**

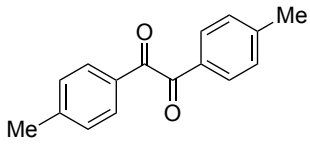
The diols were oxidised into the corresponding 1,2-diketones using NBS in CCl_4 at 85 °C, giving the products in good to high yields (Table 4.12).

Table 4.12 Synthesis of symmetrical 1,2-diketones

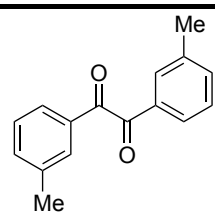




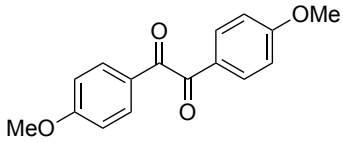
386, **99% yield**



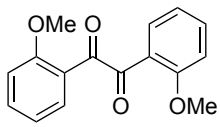
435, **82% yield**



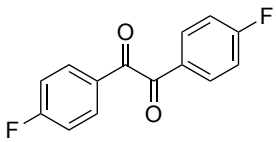
436, **81% yield**



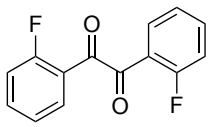
437, **62% yield**



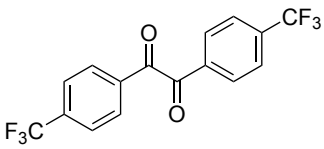
438, **81% yield**



439, **89% yield**



440, **51% yield**

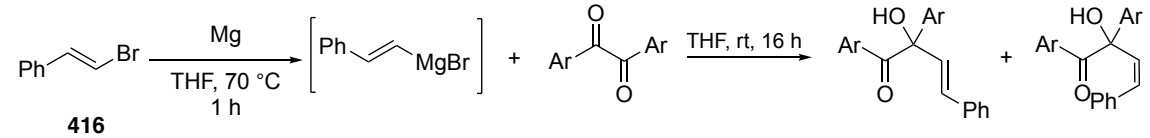


441, **56% yield**

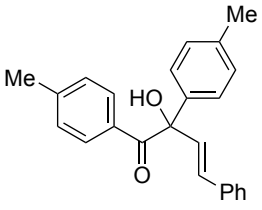
Addition of freshly prepared styrylmagnesium bromide **416** after titration with 2-hydroxybenzaldehyde phenylhydrazone into the 1,2-diketones was again challenging.

Analysis of the crude products by ^{1}H NMR showed a mixture of product *E:Z* isomers, which were purified by column chromatography. The mixtures were obtained also in moderate to low yields (Table 4.13).

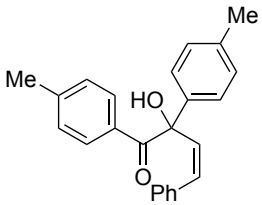
Table 4.13 Synthesis of R^1=R^2 ß,γ-unsaturated α-hydroxyketones



416

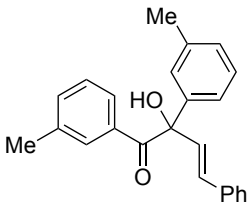


442

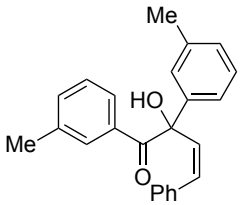


443

23% yield
(89:11 *E/Z*)

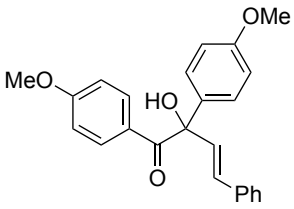


444

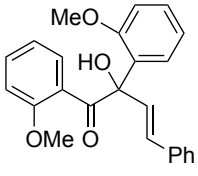


445

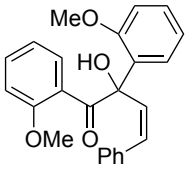
63% yield
(81:19 *E/Z*)



446
32% yield

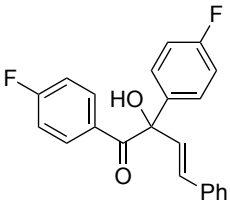


447

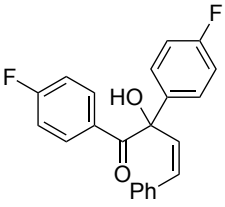


448

16% yield
(89:11 *E/Z*)

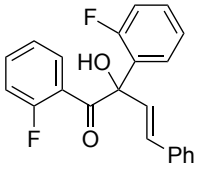


449

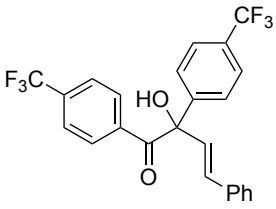


450

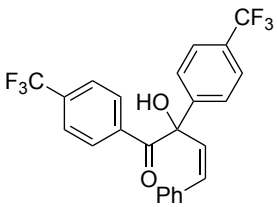
34% yield
(75:25 *E/Z*)



451
22% yield



452

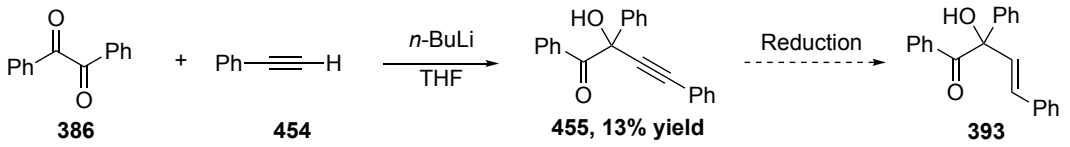


453

35% yield
(75:25 *E/Z*)

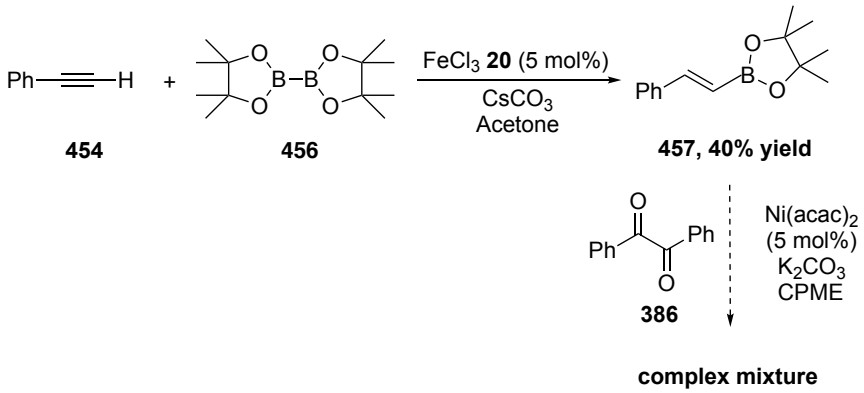
As low yields were encountered for the styryl Grignard addition into 1,2-diketones for the synthesis of different ß,γ-unsaturated α-hydroxyketones, various procedures were tried to obtain the products in higher yields. One idea was to reduce the corresponding propargylic alcohol **455** into the desired allylic alcohol **393** (Scheme 4.15). However, reacting phenylacetylene **454** with *n*-BuLi followed by addition to diketone **386** gave a complex

mixture, giving the desired product in only 13% yield after column chromatography. As the first step was very low yielding, this procedure was not studied further.



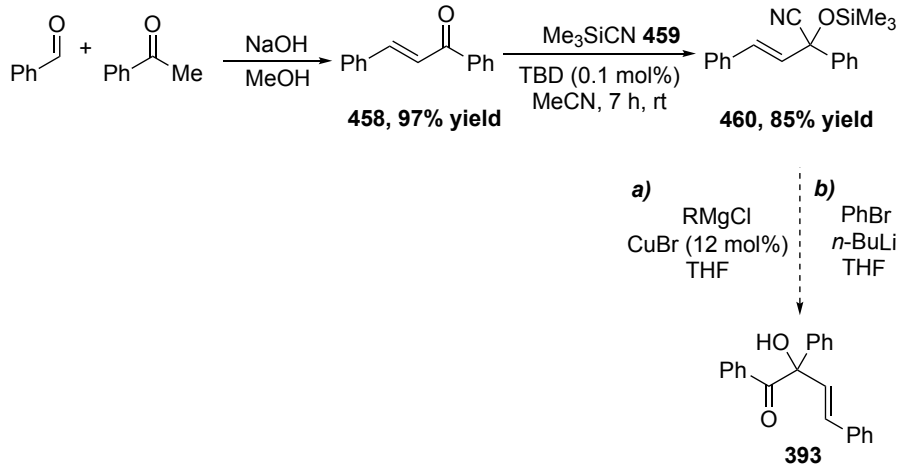
Scheme 4.15 Synthesis of propargylic alcohol 455

Next, the catalytic addition of vinylboronate esters into 1,2-diketones was investigated. Hydroboration of phenylacetylene **454** with bis(pinacolato)diboron **456** using catalytic $FeCl_3$ **20** (5 mol%) gave vinylboronate **457** in moderate 40% yield after purification by column chromatography.[127] However, the nickel-catalysed addition of **457** into 1,2-diketone **386** was unsuccessful, with a complex mixture produced and no presence of the desired ß,γ-unsaturated α-hydroxyketone product (Scheme 4.16).



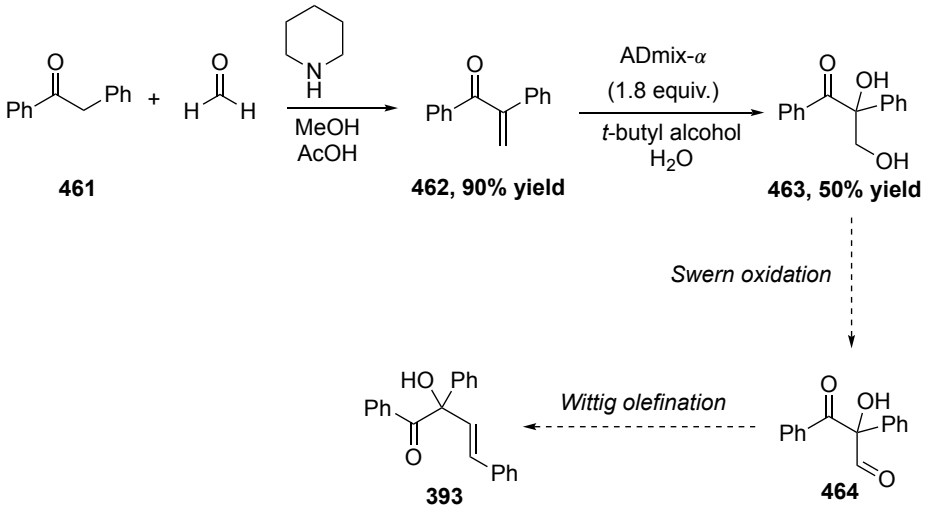
Scheme 4.16 Styrene boronate pinacol ester 457 addition into diketone 386

Berger and co-workers reported that α-hydroxy ketones could be obtained by adding Grignard reagents into secondary cyanohydrin derivatives.[128] Therefore, this procedure was tested for the synthesis of tertiary α-hydroxyketones. First, trimethylsilyl cyanide **459** was added to chalcone **458** catalysed by TBD (0.1 mol%) to give cyanohydrin **460** in very good 85% yield.[129] The reaction of **460** with either PhMgBr or MeMgBr was unsuccessful, with no reactivity observed at different temperatures and reaction times. Treatment of **460** with phenyl lithium was also unsuccessful, giving decomposition of the starting material with no evidence of the desired product (Scheme 4.17).



Scheme 4.17 Synthesis of ß,γ-unsaturated α-hydroxyketone 393 through cyanide 460 compound

Finally, a four-step procedure to the desired ß,γ-unsaturated α-hydroxyketone is under investigation (Scheme 4.18). Reacting 2-phenylacetophenone **461** with formaldehyde in the presence of piperidine affords 1,2-diphenylprop-2-en-1-one **462** in 90% yield.[130] Dihydroxylation of **462** using ADmix-α gave diol[131] **463** in 50% yield after purification by column chromatography. The next step is oxidation of the primary alcohol into the corresponding aldehyde **464**, followed by Wittig olefination to give the product **363**. However, due to time constraints this method has not been optimised and requires further investigation.

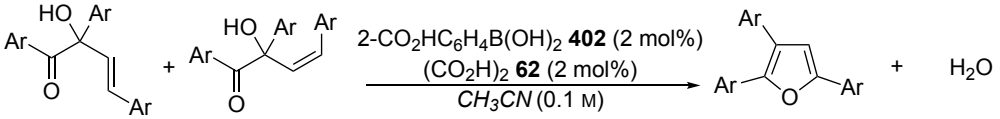


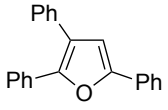
Scheme 4.18 Route for the synthesis of desired ß,γ-unsaturated α-hydroxyketone 393

4.5.2 Dehydrative Nazarov-scope

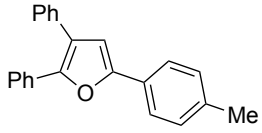
The substrate scope of the dehydrative Nazarov cyclisation was investigated using the ß,γ-unsaturated α-hydroxyketones obtained *via* Grignard addition, even though some starting materials were used as a mixture of isomers. The reactions were performed under the previously optimised conditions using 2-carboxyphenylboronic acid **402** (2 mol%) and oxalic acid **62** (2 mol%) in acetonitrile (Table 4.14). Electron-donating aryl substituents at C(5) were well tolerated, giving furans **465** and **466** in 72% and 88% yield, respectively. Next, the reactions to form furans with different C(2) and C(3) substituents were tested. The reaction of para-tolyl substituted **442/443** worked well at 50 °C, giving **467** in 99% yield, while meta-methyl substitution gave **468** in 54% yield after reaction at 90 °C. The presence of strong electron-donating methoxy group in either the *para* or the *ortho* position gave low 20% yields of **469** and **470**. The presence of fluoro substituents afforded 60% and 56% yield for *para* and *ortho* substituted products **471** and **472**, respectively. The use of a very strong electron-withdrawing CF_3 substituents resulted in low reactivity, giving **473** in only 16% yield after 48 hours at room temperature.

Table 4.14 Substrate scope for furan synthesis

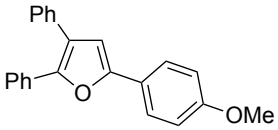




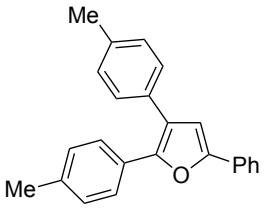
395, **93% yield**
rt, 2 h



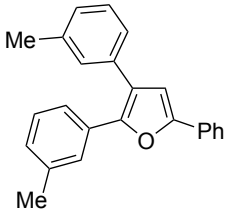
465, **72% yield**
rt, 2 h



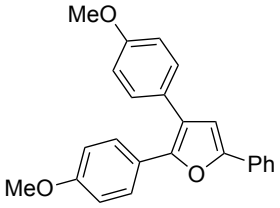
466, **88% yield**
rt, 2 h



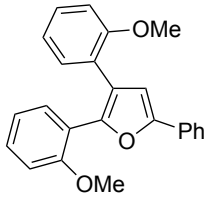
467, **99% yield**
50 °C, 6 h



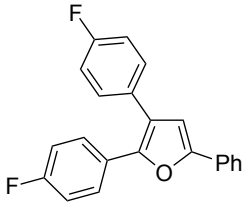
468, **54% yield**
90 °C, 6 h



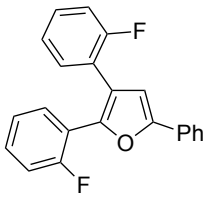
469, **20% yield**
90 °C, 24 h



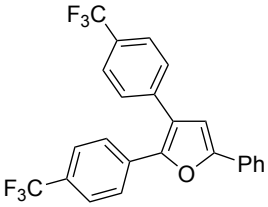
470, **20% yield**
90 °C, 24 h



471, **60% yield**
50 °C, 6 h



472, **56% yield**
90 °C, 24 h

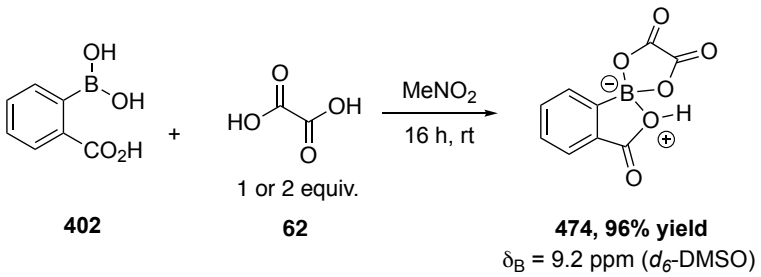


473, **16% yield**
rt, 48 h

4.6 Control reactions

Investigation of the nature of the possible catalytic species was then performed. A preparative experiment reacting 2-carboxyphenylboronic acid **402** with either 1 or 2 equivalents of oxalic acid **62** at rt in $MeNO_2$ for 16 h followed by removal of the solvent afforded a white powder (Scheme 4.19). Spectroscopic analysis by IR, ^{11}B, ^{1}H and ^{13}C NMR in DMSO-d_6 is consistent with structure **474**. IR analysis showed stretches at 1787 and 1678 cm^{-1} which can be assigned to the oxalic acid-derived carbonyls and is in accordance with the observed signals in the ^{13}C NMR analysis at 161.1 and 160.0 ppm (Figure 4.2). ^{11}B NMR analysis gave a broad single at 9.25 ppm, suggesting the presence of a tetracoordinate boron atom (Figure 4.4). This suggests coordination to the boron, either from the carboxylic acid at

the 2-position or from water. Unfortunately, no suitable crystals of **474** have been grown for X-ray analysis.



Scheme 4.19 Catalyst 474 synthesis

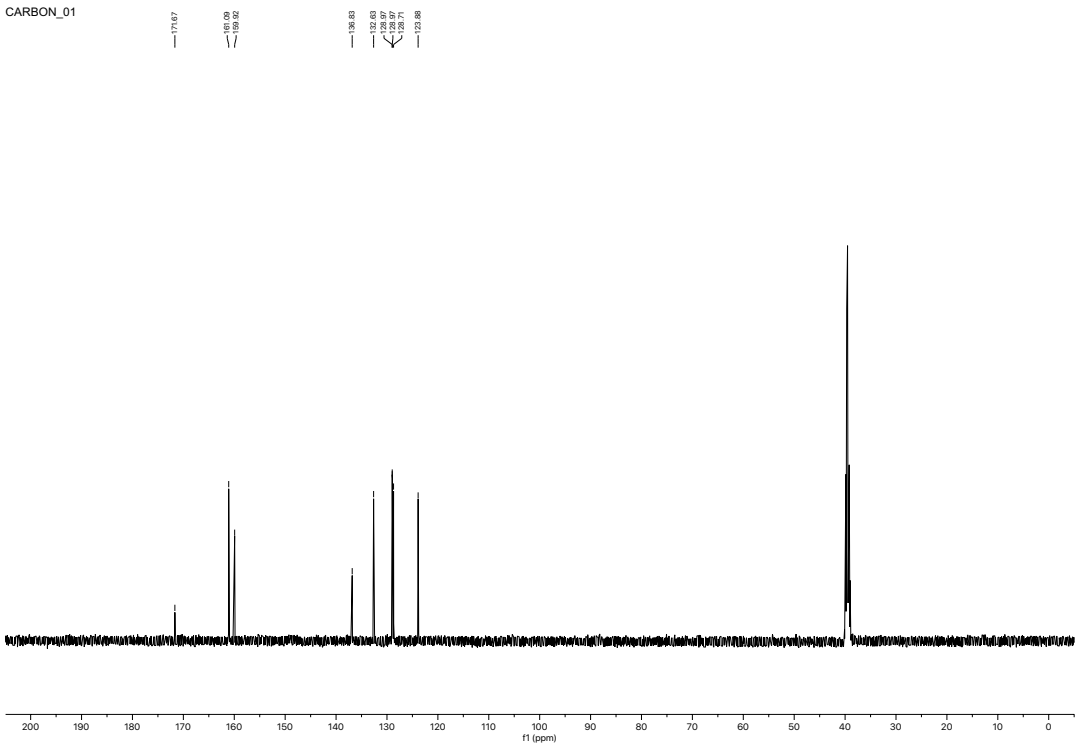


Figure 4.2 $^{13}C\{^{1}H\}$ NMR (126 MHz, d_6-DMSO) of 474

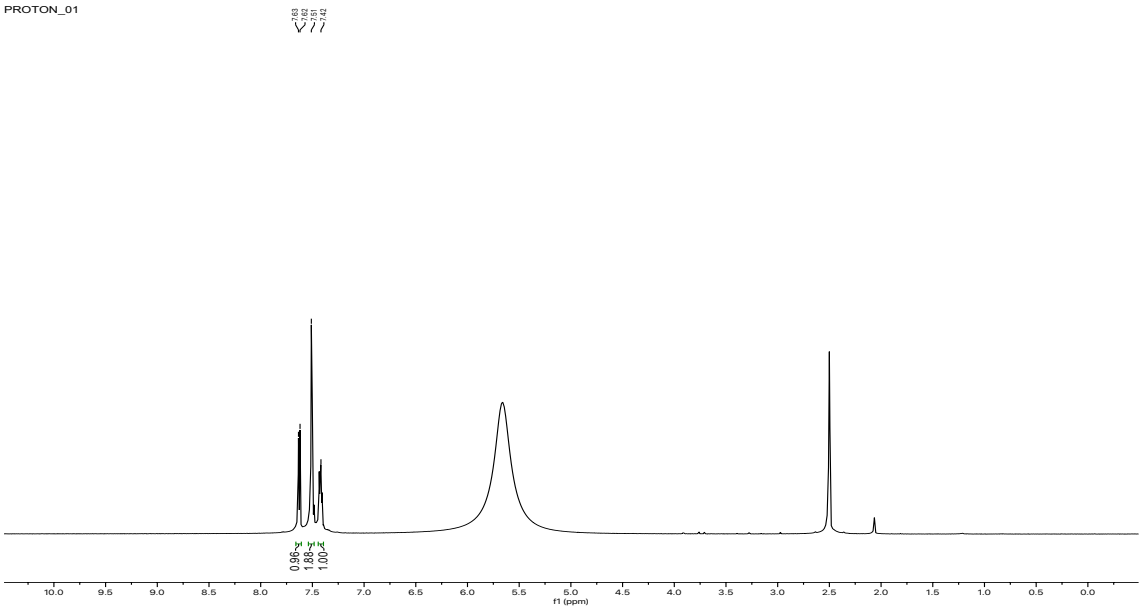


Figure 4.3 ^{1}H NMR (500 MHz, d_6-DMSO) of 474

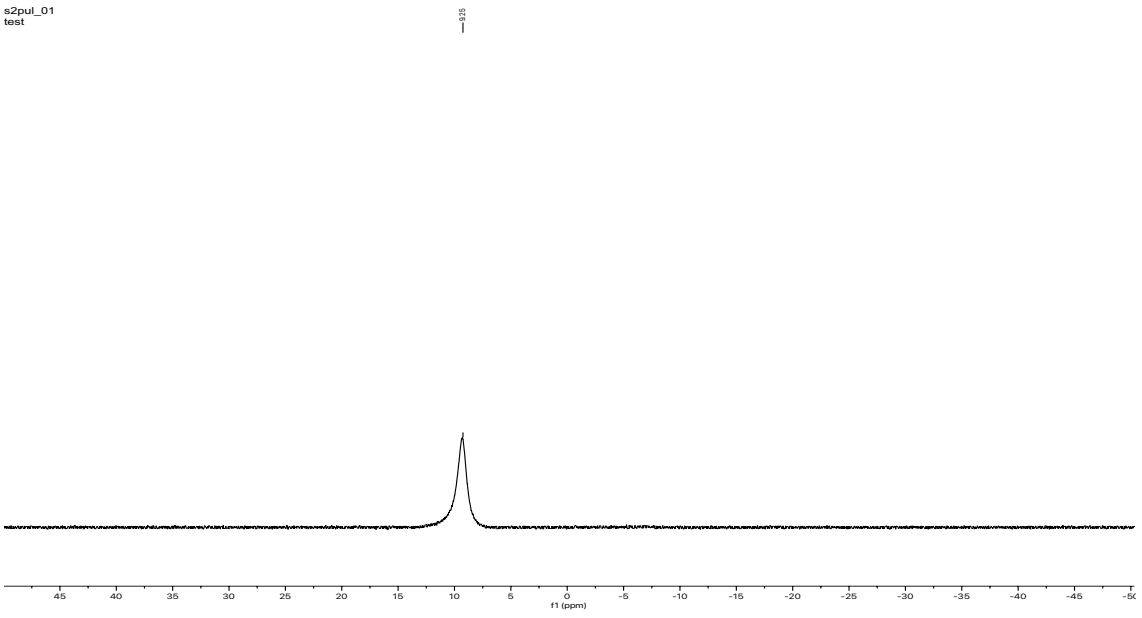
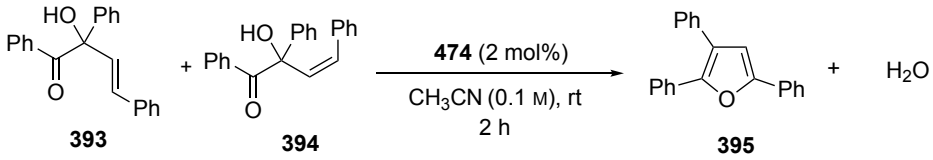


Figure 4.4 ^{11}B NMR (160 MHz, d_6-DMSO) of 474

The catalytic activity of the species formed from the stoichiometric reaction was tested for the formation of furan **395** from **393/394** (Table 4.15). The reaction using the 1:1 adduct as an active precatalyst, formed furan **395** in 94% yield. This is comparable to the optimised *in*

situ procedure. The 1:2 adduct was also a successful precatalyst, although **395** was obtained in lower 65% yield after purification.

Table 4.15 Catalyst control reaction

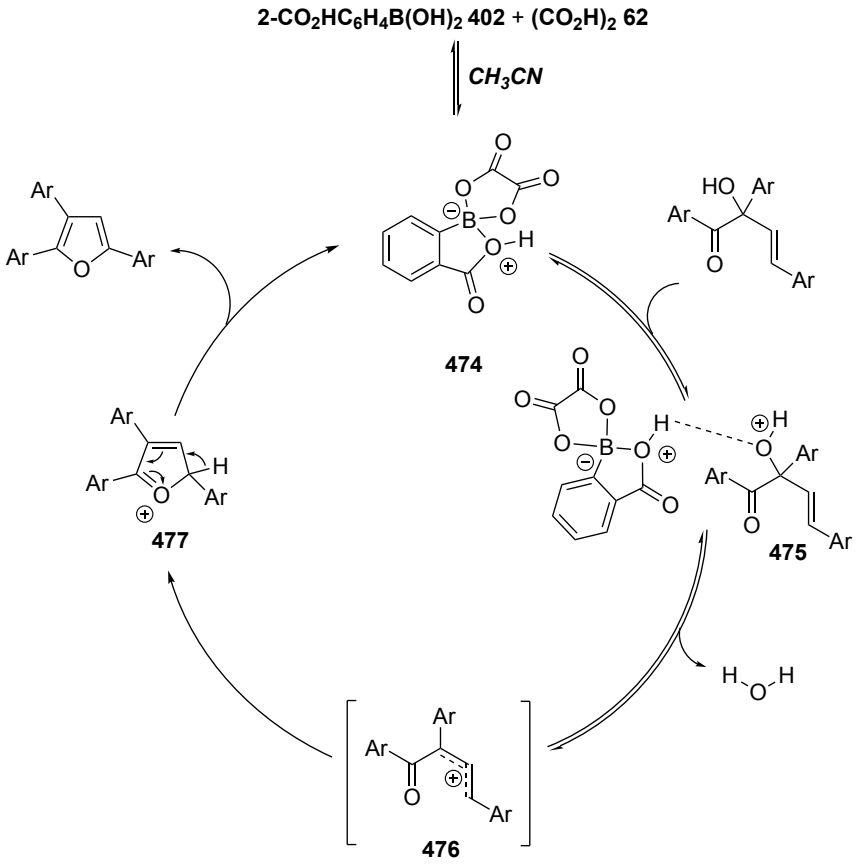


Entry	Catalyst	Conversion	Yield **395** (%)
1	**474** (1:1 equiv.)	100	94
2	**474** (1:2 equiv.)	100	65

4.7 Proposed reaction mechanism

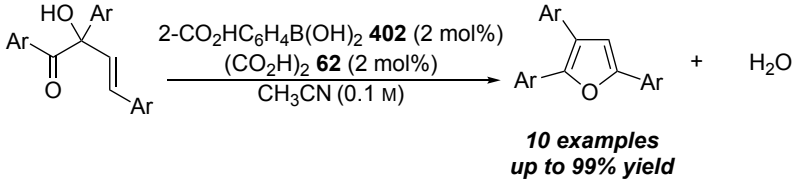
In 2011, Mattson and co-workers reported 2-carboxypinacolborate as a Lewis acid-assisted Brønsted acid catalysis for conjugate addition reactions.[132] In the mechanism, it was suggested a Lewis acidic coordination between the carboxylic acid and the boron made the proton more acidic, enhancing the catalytic activity. The idea of boronate ester-assisted Brønsted acid catalysis was extended by Maruoka and co-workers in 2015,[133] using a chiral diol to bind to boron for enantioselective aza-Michael additions.

Using this literature precedence, a plausible mechanism for our furan synthesis is shown in Scheme 4.20. Reaction between 2-carboxyphenylboronic acid **402** and oxalic acid **62** in acetonitrile may give complex **474**, which is expected to act as a Lewis-acid assisted Brønsted-acid catalysis system due to the interaction from the carbonyl with boron increasing the Brønsted-acidity and improving its catalytic activity. Protonation of an α-hydroxyketone forms **475**, which releases water to give allylic cation **476**. A thermally allowed 4π electrocyclic ring closure gives intermediate **477**, which can be deprotonated to give aromatic furan.



Scheme 4.20 Proposed dehydrative cyclisation mechanism

In conclusion, a new procedure for a furan synthesis *via* dehydrative Nazarov cyclisation was investigated starting from ß,γ-unsaturated α-hydroxyketones (Scheme 4.21). The use of mild and cheap 2-carboxyphenylboronic acid **402** (2 mol%) and oxalic acid **62** (2 mol%) in acetonitrile were the optimised conditions for this new procedure (Scheme 4.21). The substrate scope with different electron-donating and electron-accepting groups was tested, giving yields up to 99%. Future work will be focused on the investigation of new procedures for the starting material synthesis to enhance the scope and efficiency of the overall process.

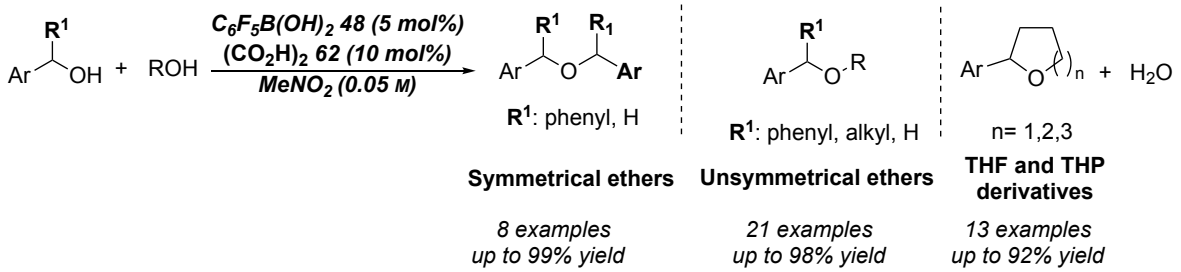


Scheme 4.21 Furan synthesis using boronic acid

5 Conclusions

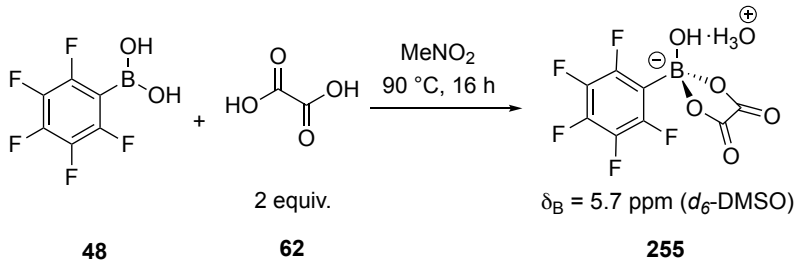
In conclusion, the work described in this thesis shows that arylboronic acids are suitable catalysts for a range of dehydrative reactions of benzylic and allylic alcohols. These catalytic procedures avoid the need for stoichiometric activation of the alcohol substrates and release water as the only by-product. The new process aligns with many of the principles of green chemistry including waste prevention, improving atom economy, providing less hazardous synthesis, reducing derivatives, and use of catalysis. However, the replacement of potentially hazardous nitromethane as the solvent would be desirable for further developments of this new process.

Initial investigations found that a combination of pentafluorophenylboronic acid **48** (5 mol%) and oxalic acid **62** (10 mol%) is an effective catalyst for the activation of primary and secondary benzylic alcohols towards nucleophilic substitution using a second alcohol as the nucleophile, releasing water as the only by-product. These reactions can be performed in both an inter- and intramolecular fashion to form a range of symmetrical and unsymmetrical ethers. The protocol tolerates a range of non-participating function groups, forming the ether products in generally good yields.



Scheme 5.1Dehydrative substitution reaction for C-O bond formation

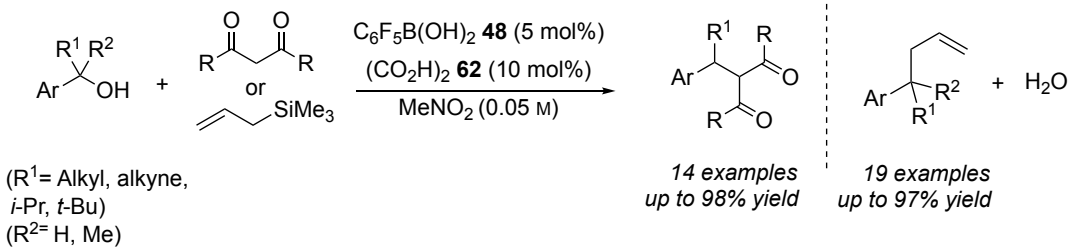
Control experiments suggest that boronic acid **48** and oxalic acid **62** condense t to form a strong Brønsted acid-catalyst in solution, which promotes a catalytic SN1 substitution using benzylic alcohols as the electrophile.



48 **62** **255**

Scheme 5.2 Brønsted acid catalyst synthesis

The same catalysts system is also effective for catalytic C-C bond formation using either 1,3-diketone derivatives or allyltrimethylsilane as the nucleophile. The protocol works using various secondary benzylic alcohols as the electrophile, forming the desired products in high yields. Limitations of this system include the use of primary or tertiary benzylic alcohols as the electrophile, and the use of cyclic 1,3-diketones or other electron-deficient ketones as the nucleophile. The use of ß-keto esters leads to a mixture of diastereoisomers with unsymmetrical secondary benzylic alcohols, but the products can undergo decarboxylation to yield substituted ketone derivatives in reasonable yields.



(R^1= Alkyl, alkyne, *i*-Pr, *t*-Bu)
($R^{2=}$ H, Me)

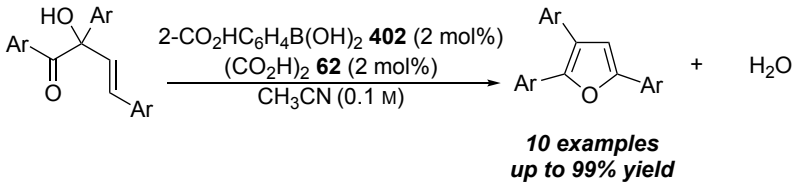
14 examples
up to 98% yield

19 examples
up to 97% yield

Scheme 5.3 Dehydrative substitution reaction for C-C bond formation

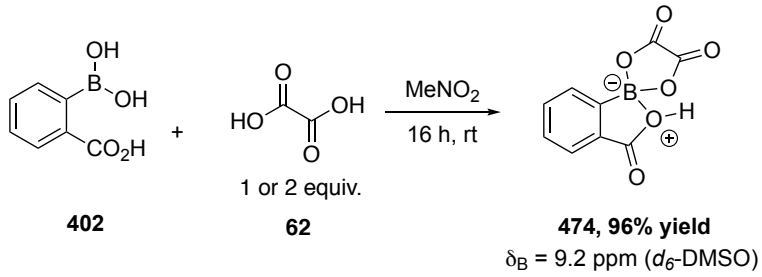
Finally, a combination of 2-carboxyphenylboronic acid **402** (2 mol%) and oxalic acid **62** (2 mol%) can promote the dehydrative Nazarov electrocyclisation of allylic alcohols in acetonitrile to form highly substituted furans. The required ß,γ-unsaturated α-

hydroxyketones starting materials can be prepared through the addition of vinyl Grignard reagents to symmetrical 1,2-diketones, although the yields of this protocol can be low. The dehydrative electrocyclization procedure is generally efficient for the range of substrates investigated to date, forming the trisubstituted furan products in good yields.



Scheme 5.4 Furan synthesis using 2-carboxyphenylboronic acid 402

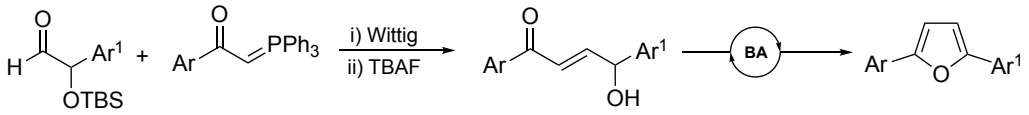
Control experiments suggest boronate ester **474** is obtained from condensation of oxalic acid **62** with boronic acid **402**. The formation of the boronate ester increases the acidity of the carboxylic acid as an internal Lewis acid assisted Brønsted acid catalysis. In contrast with boron catalyst **255**, the ^{11}B NMR of **474** shows a single broad signal at 9.25 ppm, which suggests the presence of a single tetracoordinate boron species. In this case, it was not possible to determine the presence of any residual water associated with the pre-synthesised catalyst.



Scheme 5.5 Synthesis of precatalyst 474

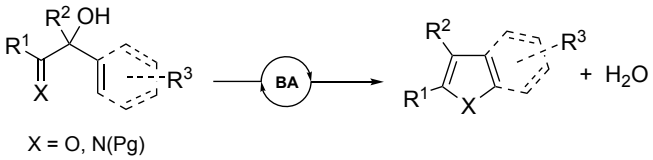
6 Future work

While the boronic acid-catalysed dehydrative Nazarov cyclisation to from trisubstituted furan derivatives gives good yields, the synthesis of the required ß,γ-unsaturated α-hydroxyketone starting materials was a significant challenge. The low yields of the current procedure and the difficulties in varying the substituents means that a new route towards suitable starting materials is required to make the catalytic procedure more general. One possibility is to start from isomeric α,ß-unsaturated γ-hydroxyketones, as these would ionise to give the same allylic carbocation intermediates as previously. These substrates could be prepared through a Wittig reaction between α-ketophosphonates and α-hydroxyaldehydes, which should provide a versatile route to substrates with different substituents (Scheme 6.1).



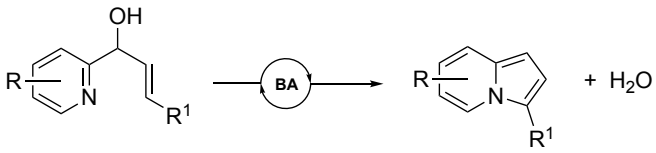
Scheme 6.1 Synthesis of α,ß-unsaturated γ-hydroxyketones as possible starting materials for dehydrative Nazarov cyclisation

The general strategy of activating substituted allylic alcohols towards electrocyclization using dehydrative boronic acid catalysis may be extended to the synthesis of other valuable heterocycles. For example, the catalytic procedure will be trialled for the synthesis of substituted benzofurans, pyrroles, and indoles from the corresponding alcohol substrates (Scheme 6.2).



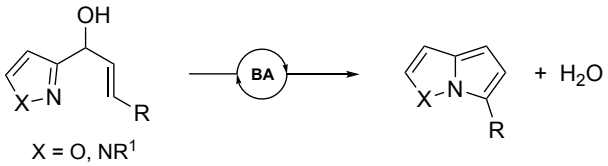
Scheme 6.2 Synthesis of tetrasubstituted furans

The methodology could then be extended to substrates containing heteroaromatics to prepare different classes of heterocyclic product after electrocyclization. For example, indolizines may be prepared from substituted pyridine derivatives (Scheme 6.3). The presence of the pyridine nitrogen atom may be challenging for the boron-based Brønsted acid catalysts, so this procedure is likely require further optimisation.



Scheme 6.3 Synthesis of indolizine rings

The principle could then be further extended to the preparation of heterocycles containg two heteroatoms, such as pyrrolo pyrazoles or pyrrolo isoxazoles (Scheme 6.4). The use of electron-rich five membered ring heterocycles in the starting materials will again present a challenge, with competing Friedel-Crafts alkylation a potential problem. However, developing a mild catalytic procedure for the synthesis of these challenging heterocycles would be valuable due to the interest of such structures in the preparation of biologically active molecules.



Scheme 6.4 Synthesis of pyrrolo pyrazole or isoxazole product

7 Experimental

7.1 General information

Reactions involving moisture sensitive reagents were carried out in flame-dried glassware under an inert atmosphere (N_2 or Ar) using standard vacuum line techniques. Anhydrous solvents (Et_2O, CH_2Cl_2, and THF) were obtained after passing through an alumina column (Mbraun SPS-800). Petrol is defined as petroleum ether 40–60 °C. All other solvents and commercial reagents were used as received without further purification unless otherwise stated.

Room temperature (rt) refers to 20–25 °C. Temperatures of 0 °C were obtained using an ice/water. Reaction involving heating were performed using DrySyn blocks and a contact thermocouple.

Commercialy available starting materials were used without purification.

Boron compound used in chapter II, bis(4-fluorophenyl)(hydroxy)borane was synthesised by *Dr Stefania F. Musolino*.

Starting materials used in chapter III, 2-(benzo[*d*]thiazol-2-yl)-1-(4-methoxyphenyl)ethan-1-one, 2-(benzo[*d*]oxazol-2-yl)-1-phenylethan-1-one, 2-(1*H*-benzo[*d*]imidazol-2-yl)-1-phenylethan-1-one **302** , 2-(3*H*-1λ^3-benzo[*d*]thiazol-2-yl)-1-(4-hydroxyphenyl)ethan-1-one **303** and 2-(3*H*-1λ^3-benzo[*d*]thiazol-2-yl)-1-(4-nitrophenyl)ethan-1-one **304** compounds, have been synthesised by *Dr Mark Greenhalgh*.

"Experiments run, and data acquired at the University of St Andrews"

Under reduced pressure refers to the use of either a Büchi Rotavapor R-200 with a Büchi V-491 heating bath and Büchi V-800 vacuum controller, a Büchi Rotavapor R-210 with a Büchi V-491 heating bath and Büchi V-850 vacuum controller, a Heidolph Laborota 4001 with vacuum controller, an IKA RV10 rotary evaporator with a IKA HB10 heating bath and ILMVAC

vacuum controller, or an IKA RV10 rotary evaporator with a IKA HB10 heating bath and Vacuubrand CVC3000 vacuum controller. Rotary evaporator condensers are fitted to Julabo FL601 Recirculating Coolers filled with ethylene glycol and set to –5 °C.

Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F254 silica) and visualisation was achieved using ultraviolet light (254 nm) and/or staining with ethanolic phosphomolybdic acid followed by heating. Manual column chromatography was performed in glass columns fitted with porosity 3 sintered discs over Kieselgel 60 silica using the solvent system stated.

Melting points were recorded on an Electrothermal 9100 melting point apparatus, (dec) refers to decomposition.

GC analyses were obtained on a Shimadzu GC consisting of a Shimadzu AOC-20i auto injector and a Shimadzu GC-2025 gas chromatograph. Analysis was performed using Shimadzu GCsolution v2.41 software and separation was achieved using the column DB-5.

^{1}H and ^{13}C{^{1}H} NMR spectra were acquired on either a Bruker AV300 with a BBFO probe (^{1}H 300 MHz; ^{13}C{^{1}H} 75 MHz), a Bruker AV400 with a BBFO probe (^{1}H 400 MHz; ^{13}C{^{1}H} 101 MHz), or a Bruker AVII 400 with a BBFO probe (^{1}H 400 MHz; ^{13}C{^{1}H} 101 MHz) in the deuterated solvent stated. All chemical shifts are quoted in parts per million (ppm) relative to the residual solvent peak. All coupling constants, J, are quoted in Hz. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and multiples thereof. The abbreviation Ar denotes aromatic, Ph to denote phenyl, Bn to denote benzyl and app denotes apparent. NMR peak assignments were confirmed using 2D ^{1}H correlated spectroscopy (COSY), 2D ^{1}H nuclear Overhauser effect spectroscopy (NOESY), 2D ^{1}H–^{13}C heteronuclear multiple-bond correlation spectroscopy (HMBC), and 2D ^{1}H–^{13}C heteronuclear single quantum coherence (HSQC) where necessary.

“Experiments run, and data acquired at the University of Bath”

Data for allylation reactions, formation of ß-keto esters, decarboxylative derivatization and furan project

NMR Spectroscopy: ^{1}H and ^{13}C NMR spectra (unless otherwise specified) on Agilent ProPulse 500 MHz or Bruker Advanced 250, 300, 400 or 500 MHz instruments at 298 K.

Infrared Spectroscopy: IR spectra were recorded on a Perkin-Elmer PerkinElmer Spectrum 100 ATR-FTIR spectrometer with only selected absorbances quoted as v in cm^{-1}.

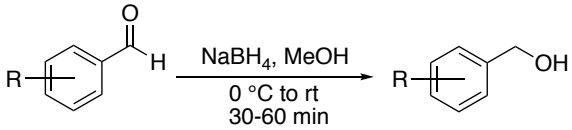
Mass Spectrometry: A microTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) was used. Data are reported in the form of m/z (intensity relative to the base peak = 100). The observed mass and isotope pattern matched the corresponding theoretical values as calculated from the expected elemental formula.

Melting Points: Melting points (mp) were determined on an Stanford Research Systems OptiMelt automated capillary melting point apparatus in open capillary tubes and are uncorrected.

X-Ray Crystallography: X-Ray crystallography was recorded on a Nonius Kappa CCD diffractometer with Mo- Kα radiation (λ=0.71074 Å). All structures were solved by direct methods and refined on all F2 data using SHELX-97 suite of programs.

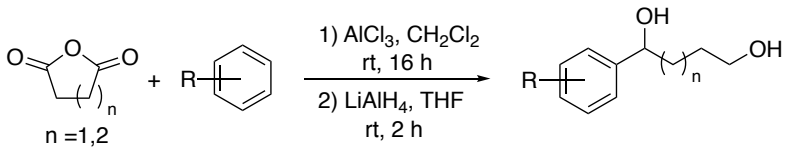
7.2 General Synthetic Procedures

General Procedure A: *Reduction of benzaldehydes*



Sodium borohydride (2.0 equiv.) was added to a solution of the required benzaldehyde (1.0 equiv.) dissolved in methanol (0.4 M) at 0 °C. The mixture was stirred at 0 °C until complete by TLC analysis. The mixture was concentrated under reduced pressure before being diluted with CH_2Cl_2, washed with water and dried over Na_2SO_4 to afford the product that did not require further purification.

General Procedure B: *Friedel-Crafts acylation and reduction*

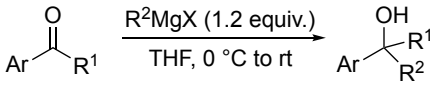


Succinic anhydride (n=1) or glutaric anhydride (n=2, 1.0 equiv.) and the corresponding arene (1.1 equiv.) were dissolved in anhydrous CH_2Cl_2 (0.3 M) under an N_2 atmosphere. $AlCl_3$ (2.2 equiv.) was added portion-wise at rt over 5 min and the reaction was stirred at rt until complete by TLC analysis. The reaction was cooled to 0 °C and quenched carefully by addition of water followed by 2 M KOH. The suspension was stirred at rt for 1 h before aq. $NaHCO_3$ was added and the layers separated. The aqueous was acidified to pH 1–2 with aq. 2 M HCl and extracted with CH_2Cl_2 (3×10 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure and the crude material was used directly in the next step.

The crude oxo-acid (1 equiv.) was dissolved in anhydrous THF (0.2 M) and cooled to 0 °C under an N_2 atmosphere. A solution of $LiAlH_4$ (2.4 M in THF, 3.7 equiv.) was added dropwise at 0 °C before the reaction was warmed to rt and stirred for 1 h. The reaction was cooled to 0 °C before being carefully quenched with water and aq. 2 M KOH. The resulting precipitate was dissolved through addition of aq. 1 M HCl and the reaction mixture was warmed to rt and

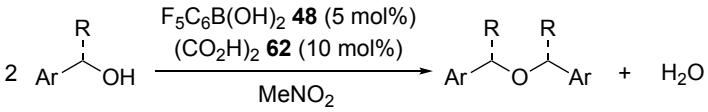
stirred for 1 h. The solution was extracted with EtOAc (3×10 mL) and the combined organics dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography as required.

General Procedure C: *Grignard addition to aldehydes or ketones*



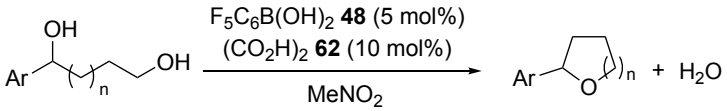
The required Grignard reagent (1.2 equiv.) was added dropwise to a solution of ketone or aldehyde (1.0 equiv.) in anhydrous THF (0.35 M) at 0 °C under an atmosphere of N_2. The resulting mixture was stirred at 0 °C for 30 min and then at rt for 6 h. The reaction was quenched with aq. NH_4Cl and the organic layer was separated. The aqueous layer was extracted with EtOAc (10×3 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residual oil was either purified by silica-gel column chromatography (petrol/EtOAc) or used without further purification.

General Procedure D: *Catalytic intermolecular dehydrative substitution to form symmetrical ethers*



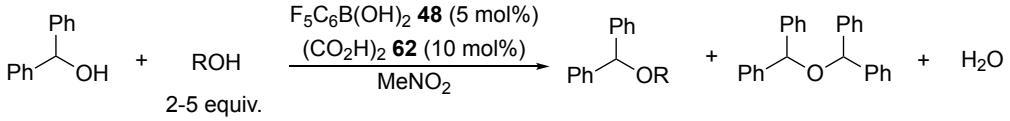
Pentafluorophenylboronic acid **48** (5 mol%) and oxalic acid **62** (10 mol%) were dissolved in $MeNO_2$ (0.2 M) in a Wheaton vial and the solution was stirred at rt for 5 min. Once the catalyst mixture is completely dissolved, the required benzylic alcohol (2.0 equiv.) was added. The reaction was stirred at the stated temperature until complete by TLC analysis. The reaction was cooled to rt, diluted with toluene and concentrated under reduced pressure to give the crude product, which was further purified by silica-gel column chromatography.

General Procedure E: *Catalytic intramolecular dehydrative substitution*



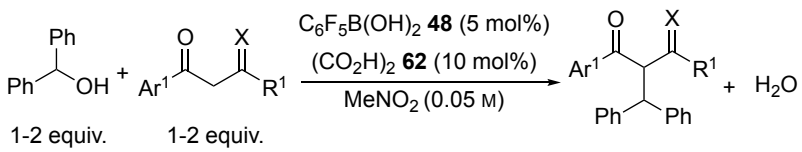
Pentafluorophenylboronic acid **48** (5 mol%) and oxalic acid **62**(10 mol%) were dissolved in $MeNO_2$ (0.2 M) in a Wheaton vial and the solution was stirred at rt for 5 min. Once the catalyst mixture is completely dissolved, the required diol (1.0 equiv.) was added. The reaction was stirred at the stated temperature until complete by TLC analysis. The reaction was cooled to rt, diluted with toluene and concentrated under reduced pressure to give the crude product, which was further purified by silica-gel column chromatography.

General Procedure F: *Catalytic intermolecular dehydrative substitution to form unsymmetrical ethers*



The required nucleophilic alcohol (2.0–5.0 equiv.) was added to a solution of pentafluorophenylboronic acid **48** (5 mol%) and oxalic acid **62** (10 mol%) in $MeNO_2$ (0.05 M) and was stirred at rt for 5 mins. The required benzylic alcohol (1.0 equiv.) was added and the reaction stirred at the stated temperature until complete by TLC analysis. The reaction was cooled to rt, diluted with toluene and concentrated under reduced pressure to give the crude product, which was further purified by silica-gel column chromatography.

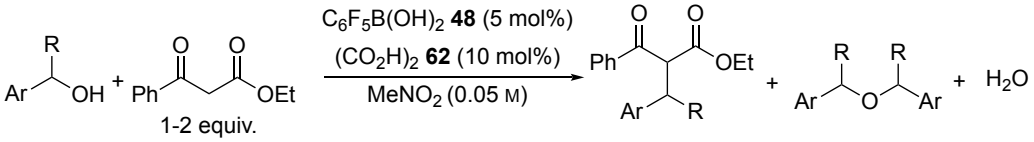
General Procedure G : *Catalytic intermolecular dehydrative C-C bond formation*



The required nucleophile (2.0–5.0 equiv.) was added to a solution of pentafluorophenylboronic acid **48** (5 mol%) and oxalic acid **62** (10 mol%) in $MeNO_2$ (0.05 M) and was stirred at rt for 5 mins. Benzylic alcohol (1.0 equiv.) was added and the reaction stirred at the stated temperature until complete by TLC analysis. The reaction was cooled to

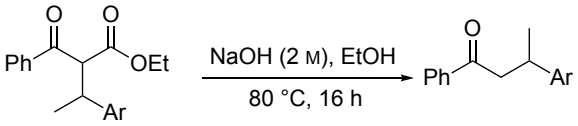
rt, diluted with toluene and concentrated under reduced pressure to give the crude product, which was further purified by silica-gel column chromatography.

General Procedure H: *Catalytic intermolecular dehydrative C-C bond formation*



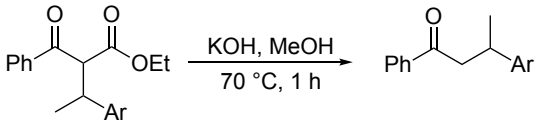
Ethylbenzoylacetate (1.0–2.0 equiv.) was added to a solution of pentafluorophenylboronic acid **48** (5 mol%) and oxalic acid **62** (10 mol%) in $MeNO_2$ (0.05 M) and was stirred at rt for 5 mins. Benzylic alcohol (1.0 equiv.) was added and the reaction stirred at the stated temperature until complete by TLC analysis. The reaction was cooled to rt, diluted with toluene and concentrated under reduced pressure to give the crude product, which was further purified by silica-gel column chromatography.

General Procedure I: *Decarboxylation*[102]



To a solution of Ethyl 3-aryl-2-benzoylbutanoate (1.0 equiv.) in EtOH (0.75 M) was added NaOH (2 M) and was stirred at 80 °C for 16 h. After complete reaction studied by TLC analysis, cool to rt. HCl (2 M) was added until pH=4 and was extracted with Et_2O (3x20 mL), washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (Petrol/EtOAc) to give the pure product.

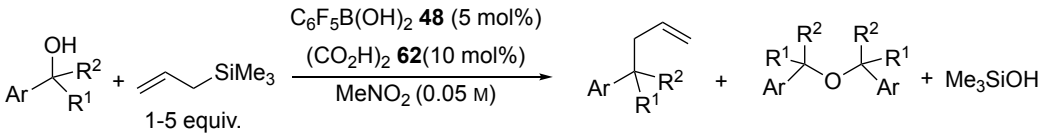
General Procedure J: *Decarboxylation*[101]



To a solution of Ethyl 3-aryl-2-benzoylbutanoate (1.0 equiv.) in MeOH (0.5 M) was added KOH (10 equiv. in H_2O 4.4 M) and was stirred at 70 °C. After complete reaction studied by TLC analysis (1 h), cool to rt. Dissolve in CH_2Cl_2 (20 mL), wash with water, brine, dry over $MgSO_4$,

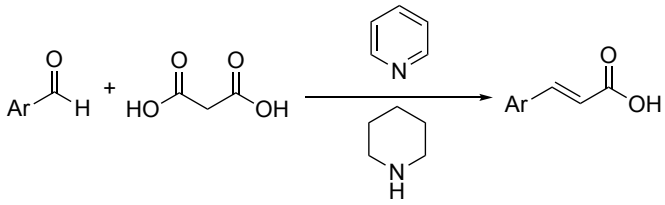
and concentrate under reduced pressure. The crude product was purified by silica-gel column chromatography (Petrol/EtOAc) to give the pure product.

General Procedure K: *Catalytic intermolecular dehydrative allylation C-C bond formation*



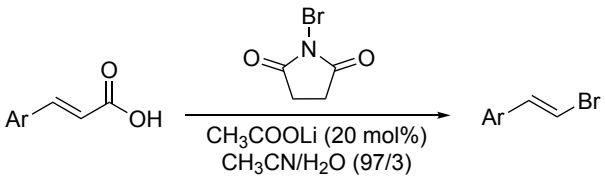
Allyltrimethylsilane (1.0–5.0 equiv.) was added to a solution of pentafluorophenylboronic acid **48** (5 mol%) and oxalic acid **62** (10 mol%) in $MeNO_2$ (0.05 M) and was stirred at rt for 5 mins. Benzylic alcohol (1.0 equiv.) was added and the reaction stirred at the stated temperature until complete by TLC analysis. The reaction was cooled to rt, diluted with toluene and concentrated under reduced pressure to give the crude product, which was further purified by silica-gel column chromatography.

General Procedure L: *Cinnamic acid synthesis via Doebner-modification*



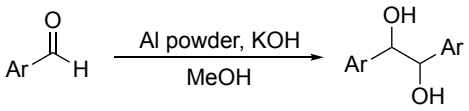
To a mixture of benzaldehyde (1 equiv.) in malonic acid **403** (1.1 equiv.) dissolved in pyridine (3 equiv.) was added piperidine (10 mol%). The mixture was refluxed until complete by TLC analysis between 30 min and 12 h. The reaction was quenched with 2M HCl at 0 ^{o}C. The solid precipitated was collected by filtration, washed with cold water and dried to afford the crude α,ß-unsaturated carboxylic acids. If necessary, recrystallization from aqueous ethanol gave pure cinnamic acids.

General Procedure M: *Synthesis of styryl bromides*[134]



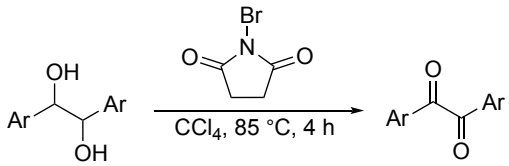
Cinnamic acid (1 equiv.) was added into a solution of lithium acetate (20 mol%, 0.04 M) in a mixture of $CH_3CN–H_2O$ (97:3 v/v). Mixture was stirred for 5 minutes at room temperature. N-bromosuccinimide was added (1.1 equiv.) and reaction was monitored by TLC until completion. The reaction was extracted with EtOAc (3×20 mL), the combined organic layers were washed with $Na_2S_2O_5$, water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residual solid was either purified by silica-gel column chromatography (petrol) or used without further purification.

General Procedure N: *Pinacol coupling for diol synthesis*[135]



Aluminium powder (2 equiv.) was added into a solution of aldehyde (1 equiv.) in methanol (1 M) at 0 °C. At the same temperature, KOH was added (9 equiv.) under vigorous stirring for 16 h allowing the reaction to warm until room temperature. After this time, the resulting slurry was filtrated and washed with methanol. The filtrate was quenched with 1 M HCl and extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (petrol/EtOAc) to give the pure diols.

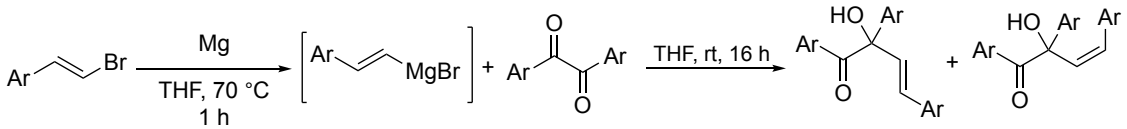
General Procedure O: *Diketone synthesis using CCl_4*[136]



A mixture of diol (1 equiv.) and N-bromosuccinimide (3 equiv.) and pyridine (2 equiv.) (for aliphatic 1,2-diols) in CCl_4 was refluxed for 3 h. After reaction was monitored by TLC until

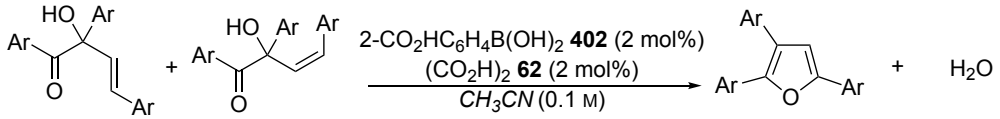
completion was quenched with water (3x30 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3x20 mL). Combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product. Pure diketones were obtained after purification by silica-gel column chromatography (petrol/EtOAc).

General Procedure P: *Synthesis of ß,γ-unsaturated α-hydroxyketone*



A freshly Grignard reagent was synthesized in-situ using Mg (1.2 equiv.) in dry THF (1.5 M), 1 or 2 drops of styrene bromide in anhydrous THF solution (1 equiv, 3 M) and a tiny amount of iodine at high temperature until complete discoloration was shown. After magnesium was activated, the rest of styrene bromide was added dropwise, and reaction was refluxed at 70 °C for 1 h. Freshly Grignard reagent was titrated under N_2 using 0.2 mmol of 2-hydroxybenzaldehyde phenylhydrazone in 1 mL of dry THF. Freshly synthesised Grignard was added dropwise until change of colour was observed from yellow to orange solution. 1,2-diketone (1 equiv.) was dissolved into dry THF (0.15 M) at rt and then, the freshly synthesised Grignard (1.2 equiv.) was added dropwise at 0 °C under an atmosphere of N_2. The resulting mixture was stirred at rt for 16 h. The reaction was quenched with aq. NH_4Cl and the organic layer was separated. The aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (3×10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residual sticky oil was purified by silica-gel column chromatography (petrol/EtOAc).

General Procedure Q: *Nazarov cyclisation*



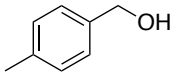
2-carboxyphenylboronic acid **402** (2 mol%) and oxalic acid **62** (2 mol%) were dissolved in CH_3CN (0.1 M) in a Wheaton vial and the solution was stirred at rt for 5 min. Once the catalyst mixture is completely dissolved, the required ß,γ-unsaturated α-hydroxyketone (1.0 equiv.)

was added. The reaction was stirred at the stated temperature until complete by TLC analysis. The reaction was cooled to room temperature, diluted with CH_3CN and concentrated under reduced pressure to give the crude product, which was further purified by silica-gel column chromatography.

7.3 Chapter II

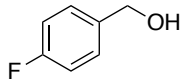
7.3.1 Primary Benzylic Alcohols

4-Methylbenzyl alcohol, 164



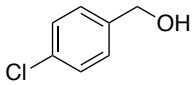
Following **General Procedure A**, *p*-tolualdehyde (1.20 g, 10 mmol) and sodium borohydride (0.76 g, 20 mmol) in MeOH (50 mL) gave title compound **164** (1.17 g, 96%) without further purification as yellow oil, with spectroscopic data in accordance with the literature.[137] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.36 (3H, s, C*H*$_3$), 4.64 (2H, s, C*H*$_2$OH), 7.17 (2H, d, *J* 7.9, ArC(3,5)*H*), 7.22–7.37 (2H, m, ArC(2,6)*H*).

4-Fluorobenzyl alcohol, 60



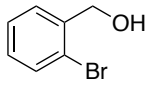
Following **General Procedure A**, 4-fluorobenzaldehyde (1.24 g, 10 mmol) and sodium borohydride (0.76 g, 20 mmol) in MeOH (50 mL) gave title compound **60** (1.10 g, 87%) without further purification as a colorless oil, with spectroscopic data in accordance with the literature.[137] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.66 (2H, s, C*H*$_2$OH), 5.30 (1H, s, O*H*), 6.97–7.12 (2H, m, ArC(3,5)*H*), 7.28–7.40 (2H, m, ArC(2,6)*H*).

4-Chlorobenzyl alcohol, 165



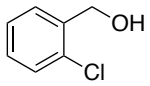
Following **General Procedure A**, 4-chlorobenzaldehyde (1.41 g, 10 mmol) and sodium borohydride (0.76 g, 20 mmol) in MeOH (50 mL) gave title compound **165** (1.14 g, 80%) without further purification as a colorless oil, with spectroscopic data in accordance with the literature.[137] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.66 (2H, s, C*H*$_2$OH), 7.21–7.38 (4H, m, ArC*H*).

2-Bromobenzyl alcohol, 166



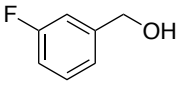
Following **General Procedure A**, 2-bromobenzaldehyde (1.85 g, 10 mmol) and sodium borohydride (0.76 g, 20 mmol) in MeOH (50 mL) gave title compound **166** (1.82 g, 98%) without further purification as a colourless oil, with spectroscopic data in accordance with the literature.[137] mp 77–81 °C {Lit.[137] 75–80 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.76 (2H, d, *J* 6.2, C*H*$_2$OH), 7.17 (1H, t, *J* 7.7, ArC*H*), 7.34 (1H, t, *J* 7.7, ArC*H*), 7.49 (1H, t, *J* 7.7, ArC*H*), 7.55 (1H, d, *J* 8.0, ArC*H*).

2-Chlorobenzyl alcohol, 167



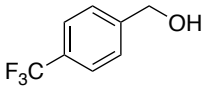
Following **General Procedure A**, 2-chlorobenzaldehyde (1.41 g, 10 mmol) and sodium borohydride (0.76 g, 20 mmol) in MeOH (50 mL) gave title compound **167** (1.24 g, 87%) without further purification as a white solid, with spectroscopic data in accordance with the literature.[137] mp 69–71 °C {Lit.[137] 70–72 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.79 (2H, d, *J* 6.0, C*H*$_2$OH), 7.18–7.34 (2H, m, ArC*H*), 7.36 (1H, dd, *J* 7.4, 1.7, ArC*H*), 7.48 (1H, dd, *J* 7.1, 2.1, ArC*H*).

3-Fluorobenzyl alcohol, 168



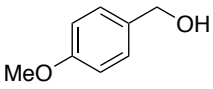
Following **General Procedure A**, 3-fluorobenzaldehyde (1.24 g, 10 mmol) and sodium borohydride (0.76 g, 20 mmol) in MeOH (50 mL) gave title compound **168** (1.24 g, 98%) without further purification as a colourless oil, with spectroscopic data in accordance with the literature. [137] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.70 (2H, d, *J* 5.6, C*H*$_2$OH), 6.93–7.03 (1H, m, ArC*H*), 7.04–7.19 (1H, m, ArC*H*), 7.28–7.39 (1H, m, ArC*H*).

4-Trifluoromethylbenzyl alcohol, 169



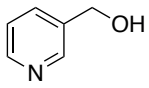
Following **General Procedure A**, 4-trifluoromethylbenzaldehyde (1.74 g, 10 mmol) and sodium borohydride (0.76 g, 20 mmol) in MeOH (50 mL) gave title compound **169** (1.64 g, 93%) without further purification as a colorless oil, with spectroscopic data in accordance with the literature.[138] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.77 (2H, s, C*H*$_2$OH), 7.48 (2H, d, *J* 8.1, ArC(2,6)*H*), 7.62 (2H, d, *J* 8.1, ArC(3,5)*H*).

4-Methoxybenzyl alcohol, 13



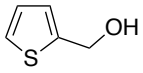
Following **General Procedure A**, *p*-anisaldehyde (1.36 g, 10 mmol) and sodium borohydride (0.76 g, 20 mmol) in MeOH (50 mL) gave title compound **13** (1.35 g, 97%) without further purification as colorless oil, with spectroscopic data in accordance with the literature.[137] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.81 (3H, s, OC*H*$_3$), 4.62 (2H, d, *J* 4.8, C*H*$_2$OH), 5.30 (1H, s, O*H*), 6.80–6.95 (2H ,m, ArC(3,5)*H*), 7.27–7.33 (2H, m, ArC(2,6)*H*).

3-Pyridine carbinol, 170



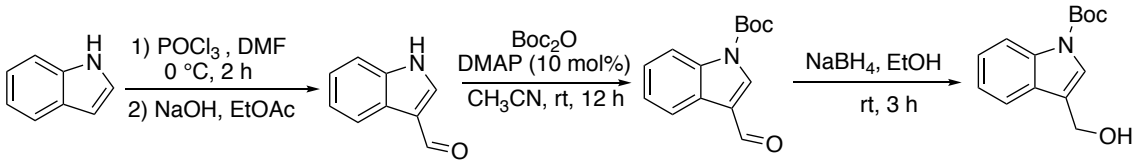
Following **General Procedure A**, 3-pyridinecarboxaldehyde (2.50 g, 23.6 mmol) and sodium borohydride (0.88 g, 23.6 mmol) in MeOH (50 mL) gave title compound **170** (0.62 g, 25%) without further purification as a yellow oil, with spectroscopic data in accordance with the literature.[139] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.82 (2H, s, C*H*$_2$OH), 7.51 (1H, dd, *J* 7.9, 5.7, ArC*H*), 7.96 (1H, d, *J* 7.9, ArC*H*), 8.53 (1H, d, *J* 5.8, ArC*H*), 8.61 (1H, s, ArC(2)*H*).

Thiophene-3-methanol, 171



Following **General Procedure A**, thiophene-3-carboxaldehyde (1.12 g, 10 mmol) and sodium borohydride (0.76 g, 20 mmol) in MeOH (50 mL) gave the title compound **171** without further purification (1.10 g, 97%) as brown oil, with spectroscopic data in accordance with the literature.[137] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.70 (2H, s, CH_2), 7.08–7.14 (1H, m, ArCH), 7.21–7.25 (1H, m, ArCH), 7.30-7.35 (1H, m, ArCH).

tert-Butyl 3-(hydroxymethyl)-1H-indole-1-carboxylate, 175



A solution of indole 121 (4.10 g, 35 mmol) in DMF (40 mL) was added to a stirred solution of $POCl_3$ (20 mL, 0.22 mmol) in DMF (40 mL) at 0 °C. After 2 h, the reaction mixture was poured into 300 mL ice water and NaOH pellets were added until pH= 9. The mixture was filtered and extracted with EtOAc (3×50 mL). The combined organics were dried over NaOH before being concentrated under reduced pressure to afford **173** (2.07 g, 50%) without any further purification as orange-brown solid, with spectroscopic data in accordance with the literature.[140] mp 193–197 °C {Lit.[140] 193.9–196.9 °C}; ^{1}H NMR (300 MHz, d_6-DMSO) δH: 7.17–7.28 (2H, m, ArCH), 7.45–7.57 (1H, m, ArCH), 8.00–8.14 (1H, m, NCHC), 8.28 (1H, s, ArCH), 9.92 (1H, s, CHO), 12.12 (1H, s, NH).

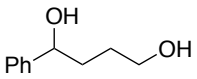
1H-Indole-3-carbaldehyde **173** (1.16 g, 8 mmol) was dissolved in MeCN (20 mL) before di-*tert*-butyldicarbonate (1.75 g, 9.6 mmol) and DMAP (100 mg, 0.8 mmol) were added. The reaction was stirred 16 h at rt until complete by TLC analysis. The solvent was removed under reduced pressure and the residue was dissolved in Et_2O (20 mL) and washed with 1 M HCl (2×10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the title compound **174** (2.53 g, 98%) without any further purification as a brown solid, with spectroscopic data in accordance with the literature.[140] mp 118–120

°C{Lit.[140] 123.4–124.8 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.73 (9H, s, $C(CH_3)_3$), 7.36–7.48 (2H, m, ArCH), 8.14–8.21 (1H, m, ArCH), 8.26 (1H, s, NCHC), 8.28–8.35 (1H, m, ArCH), 10.12 (1H, s, CHO).

To a solution of **174** (1.53 g, 6 mmol) in EtOH (25 mL) was added $NaBH_4$ (0.59 g, 15.6 mmol) at 0 °C. The reaction was stirred at rt for 3 h before the reaction was filtered and concentrated under reduced pressure. The crude material was extracted with EtOAc (3×10 mL) and washed with H_2O (2×10 mL). The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine before being dried over Na_2SO_4. The solution was concentrated under reduced pressure to afford the title compound **175** (1.37 g, 93%) without any further purification as an brown oil, with spectroscopic data in accordance with the literature.[140] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.67 (9H, s, $C(CH_3)_3$), 4.85 (2H, d, *J* 3.0, CH_2OH), 7.27–7.39 (2H, m, ArCH), 7.59 (1H, s, NCHC), 7.63–7.67 (1H, m, ArCH), 8.14 (1H, d, *J* 8.2, ArCH).

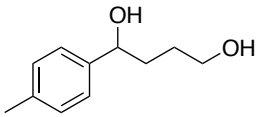
7.3.2 Diols

1-Phenylbutane-1,4-diol, 189



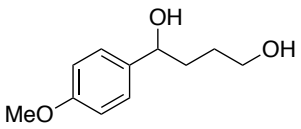
Following **General Procedure B**, succinic anhydride (2.00 g, 20 mmol), benzene (1.9 mL, 22 mmol) and $AlCl_3$ (5.87 g, 44 mmol) were reacted in anhydrous CH_2Cl_2 (67 mL) to give the oxo-acid (3.39 g, 95%), which was sufficiently pure to use directly. The oxo-acid (1.00 g, 5.62 mmol) and $LiAlH_4$ (2 M in THF, 10.7 mL, 20.8 mmol) were reacted in THF (27 mL) and. The crude was purified by silica-gel column chromatography (Petrol/EtOAc, 90:10, R_f: 0.33) to give title compound **189** (1.26 g, 63%) as a white solid, with spectroscopic data in accordance with the literature.[141] mp 65–67 °C {Lit.[141] 65–67 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.74–1.90 (1H, m, CH^AH^BCH_2OH), 1.94–2.10 (2H, m, CH_2CH), 2.23–2.42 (1H, m, CH^A$H^B$$CH_2OH$), 3.87–4.01 (1H, m, C$H^A$H^{B}OH), 4.09–4.13 (1H, m, CH^AH^BOH), 4.90 (1H, t, *J* 7.2, C*H*OH), 7.17–7.29 (2H, m, ArC(2,6)*H*), 7.31–7.37 (3H, m, ArC(3,4,5)*H*).

1-(*p*-Tolyl)butane-1,4-diol, 190



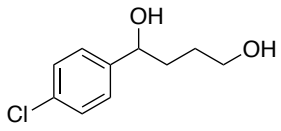
Following **General Procedure B**, succinic anhydride (2.00 g, 20 mmol), toluene (2.55 mL, 24 mmol) and $AlCl_3$ (4.00 g, 30 mmol) were reacted in anhydrous CH_2Cl_2 (67 mL) to give the oxo-acid (3.77 g, 98%), which was sufficiently pure to use directly. The oxo-acid (1.15 g, 6.0 mmol) and $LiAlH_4$ (2M in THF, 11.1 mL, 22.2 mmol) were reacted in THF (30 mL). The reaction did not require further purification to give title compound **190** (0.90 g, 83%) as a white solid, with spectroscopic data in accordance with the literature.[141] mp 56–59 °C {Lit.[141] 58–60 °C};[1]H NMR (300 MHz, $CDCl_3$) δ_H: 1.61–1.75 (2H, m, C*H*$_2$CH$_2$OH), 1.79–1.92 (2H, m, C*H*$_2$CH), 2.34 (3H, s, C*H*$_3$), 3.61–3.75 (2H, m, C*H*$_2$OH), 4.69 (1H, t, *J* 6.3, C*H*OH), 7.15 (2H, d, *J* 8.1, ArC(3,5)*H*), 7.19–7.30 (2H, m, ArC(2,6)*H*).

1-(4-Methoxyphenyl)butane-1,4-diol, 191



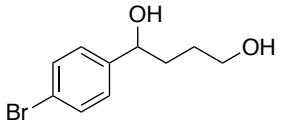
Following **General Procedure B**, succinic anhydride (2.0 g, 20 mmol), anisole (261 mL, 24 mmol) and $AlCl_3$ (4.00 g, 30 mmol) were reacted in anhydrous CH_2Cl_2 (67 mL) to give the oxo-acid (4.00 g, 96%), which was sufficiently pure to use directly. The oxo-acid (1.04 g, 5.0 mmol) and $LiAlH_4$ (2M in THF, 9.3 mL, 18.5 mmol) were reacted in THF (25 mL). The reaction did not require further purification to give title compound **191** (0.81 g, 83%) as a yellow oil, with spectroscopic data in accordance with the literature.[141] [1]H NMR (300 MHz, $CDCl_3$) δ_H: 1.76–1.86 (1H, m, C*H*^{A}H^{B}CH$_2$OH), 1.96–2.08 (2H, m, C*H*$_2$CH), 2.20–2.37 (1H, m, CH^A*H*^{B}CH$_2$OH), 3.80 (3H, s, OC*H*$_3$), 3.88–3.97 (1H, m, C*H*^{A}H^{B}OH), 4.06–4.15 (1H, m, CH^A*H*^{B}OH), 4.73–4.88 (1H, m, C*H*OH), 6.81–6.92 (2H, m, ArC(3,5)*H*), 7.22–7.32 (2H, m, ArC(2,6)*H*).

1-(4-Chlorophenyl)butane-1,4-diol, 192



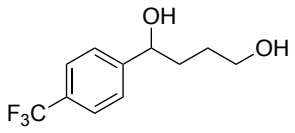
Following **General Procedure B**, succinic anhydride (2.00 g, 20 mmol), chlorobenzene (3 mL, 24 mmol) and $AlCl_3$ (4.00 g, 30 mmol) were reacted in anhydrous CH_2Cl_2 (67 mL) to the oxo-acid (4.10 g, 96%), which was sufficiently pure to use directly. The oxo-acid (1.1 g, 5.0 mmol) and $LiAlH_4$ (2M in THF, 9.5 mL, 18.5 mmol) were reacted in THF (25 mL). The reaction did not require further purification to give title compound **192** (0.95 g, 91%) as a white solid, with spectroscopic data in accordance with the literature.[142] mp 84–86 °C {Lit.[142] 83–84 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.63–1.77 (2H, m, C*H*$_2$CH$_2$OH), 1.84 (2H, q, *J* 6.7, C*H*$_2$CH), 3.65–3.80 (2H, m, C*H*$_2$OH), 4.73 (1H, t, *J* 6.2, C*H*OH), 7.28–7.35 (4H, m, ArC*H*).

1-(4-Bromophenyl)butane-1,4-diol, 193



Following **General Procedure B**, succinic anhydride (2.00 g, 20 mmol), bromobenzene (2.52 g, 24 mmol) and $AlCl_3$ (4.00 g, 30 mmol) were reacted in anhydrous CH_2Cl_2 (67 mL) to give the oxo-acid (4.41 g, 90%), which was sufficiently pure to use directly. The oxo-acid (1.23 g, 5.0 mmol) and $LiAlH_4$ (2M in THF, 9.3 mL, 18.5 mmol) were reacted in THF (25 mL). The reaction did not require further purification to give title compound **193** (1.08 g, 88%) as a white solid, with spectroscopic data in accordance with the literature.[143] mp 77–79 °C {Lit.[143] 77–78 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.58–1.74 (2H, m, C*H*$_2$CH$_2$OH), 1.76–1.92 (2H, m, C*H*$_2$CH), 3.60–3.77 (2H, m, C*H*$_2$OH), 4.64–4.78 (1H, m, C*H*OH), 7.17–7.29 (2H, m, ArC(2,6)*H*), 7.42–7.53 (2H, m, ArC(3,5)*H*).

1-(4-(Trifluoromethyl)phenyl)butane-1,4-diol, 201



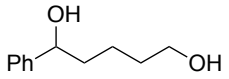
Mg turnings (20 mmol) and a small amount of the bromobenzotrifluoride were suspended in anhydrous THF (40 mL) under an N_2 atmosphere. A few crystals of iodine were added and the suspension heated to reflux. Upon initiation the solution turned colourless at which point the rest of the bromobenzotrifluoride (2.31 g, 10.25 mmol) in THF (10 mL) was added dropwise. The resulting mixture was heated at reflux for 1 h before being cooled to rt and used immediately.

The freshly prepared Grignard reagent was added dropwise to a solution of succinic anhydride (1.03 g, 10.25 mmol) in anhydrous THF (30 mL) under an N_2 atmosphere at rt. The reaction was stirred at rt for 30 min before being quenched with cold water (10 mL) and aq. 2 M KOH (10 mL). The suspension was stirred at rt for 1 h before aq. $NaHCO_3$ was added and the layers separated. The aqueous was acidified to pH 1–2 with aq. 2 M HCl and extracted with CH_2Cl_2 (3×30 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure and the crude material was used directly in the next step.

The crude oxo-acid (0.55 g, 1.8 mmol) was dissolved in anhydrous THF (27 mL) and cooled to 0 °C under an N_2 atmosphere. A solution of $LiAlH_4$ (2.4 M in THF, 3.0 mL, 7.20 mmol) was added dropwise at 0 °C before the reaction was warmed to rt and stirred for 1 h. The reaction was cooled to 0 °C before being carefully quenched with water and aq. 2 M KOH. The resulting precipitate was dissolved through addition of aq. 1 M HCl and the reaction mixture was warmed to rt and stirred for 1 h. The solution was extracted with EtOAc (3×50 mL) and the combined organics dried over $MgSO_4$ and concentrated under reduced pressure. mL) and the combined organics dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 80:20 to 10:90, R_f: 0.23) to give title compound **201** (0.15 g, 27%) as a yellow oil. ν_{max} (film) 3307 (C-OH), 2943 (C-H), 1620 (C-C Ar), 840 (C-H Ar); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.61–1.74 (2H, m, C*H*$_2$CH$_2$OH), 1.77–1.94 (2H, m, CHOHC*H*$_2$), 3.62–3.77 (CH$_2$C*H*$_2$OH), 4.74–4.86 (1H, m, ArC*H*OHCH$_2$), 7.40–

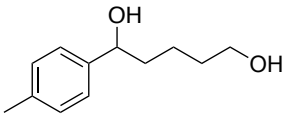
7.52 (2H, m, Ar(2,6)*H*), 7.55–7.65 (2H, m, Ar(3,5)*H*). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 29.2 (*C*H_2CH_2OH), 36.8 (OHCH*C*H_2), 62.9 (*C*H_2OH), 73.7 (OH*C*HCH_2), 123.2 (*C*F_3), 125.5 (Ar*C*(3,5)H), 126.2 (Ar*C*(2,6)H), 129.3 (Ar*C*(4)), 148.8 (Ar*C*(1)), $^{19}F\{^{1}H\}$ NMR (471 MHz, $CDCl_3$) δ_F: –62.4, HRMS (NSI^-) $C_{11}H_{12}F_3O_2$ $[M–H]^-$ found 233.0796, requires 233.0795 (+0.5 ppm).

1-Phenylpentane-1,5-diol, 194



5-Oxo-5-phenylpentanoic acid (1.00 g, 5.20 mmol) was dissolved in anhydrous THF (67 mL) and cooled to 0 °C under an N_2 atmosphere. A solution of $LiAlH_4$ (2.0 M in THF, 10 mL, 20 mmol) was added dropwise at 0 °C before the reaction was warmed to rt and stirred for 1 h. The reaction was cooled to 0 °C before being carefully quenched with water (10 mL) and aq. 2 M KOH (10 mL). The resulting precipitate was dissolved through addition of aq. 1 M HCl (10 mL) and the reaction mixture was warmed to rt and stirred for 1 h. The solution was extracted with EtOAc (5×40 mL) and the combined organics dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was recrystallised (EtOAc/hexane) to give title compound **194** (0.63 g, 63%) as a white solid, with spectroscopic data in accordance with the literature.[144] mp 55–58 °C {Lit.[144] 53–55 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.38–1.47 (2H, m, CHCH_2CH_2) 1.51–1.60 (2H, m, CH_2CH_2OH), 1.60–1.67 (2H, m, CHCH_2), 3.63 (2H, t, *J* 6.4, CH_2OH), 4.69 (1H, dd, *J* 7.6, 5.6, C*H*OH), 7.26–7.39 (5H, m, ArC*H*).

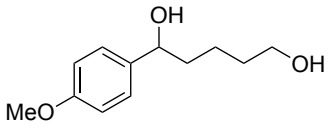
1-(*p*-Tolyl)pentane-1,5-diol, 195



Following **General Procedure B**, step glutaric anhydride (2.28 g, 20 mmol), toluene (2.11 g, 24 mmol) and $AlCl_3$ (5.87 g, 44 mmol) were reacted in anhydrous CH_2Cl_2 (67 mL) to give the oxo-acid (1.76 g, 44%), which was sufficiently pure to use directly. The oxo-acid (1.03 g, 5.0 mmol) and $LiAlH_4$ (2 M in THF, 9.3 mL, 18.5 mmol) were reacted in THF (25 mL). The reaction did not require further purification to give title compound **195** (0.97 g, 99%) as a colorless oil, with spectroscopic data in accordance with the literature.[144] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.33–

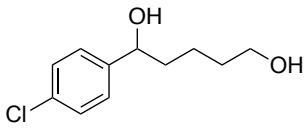
1.56 (2H, m, C*H*$_2$CH$_2$CH$_2$OH), 1.57–1.66 (2H, m, CH$_2$C*H*$_2$CH$_2$OH), 1.70–1.93 (2H, m, CHC*H*$_2$) 3.65 (2H, t, *J* 6.5, C*H*$_2$OH), 4.73 (1H, m , C*H*OH), 7.14–7.22 (2H, m, ArC(3,5)*H*), 7.23–7.29 (2H, m, ArC(2,6)*H*).

1-(4-Methoxyphenyl)pentane-1,5-diol, 196



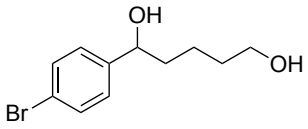
Following **General Procedure B**, glutaric anhydride (2.28 g, 20 mmol), anisole (2.60 g, 24 mmol) and $AlCl_3$ (5.87 g, 44 mmol) were reacted in anhydrous CH_2Cl_2 (67 mL) to give the oxo-acid (1.84 g, 41%), which was sufficiently pure to use directly. The oxo-acid (1.11 g, 5.0 mmol) and $LiAlH_4$ (2 M in THF, 9.3 mL, 18.5 mmol) were reacted in THF (25 mL). The reaction did not require further purification to give title compound **196** (0.80 g, 76%) as a colorless oil, with spectroscopic data in accordance with the literature.[144] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.53–1.73 (4H, m, C*H*$_2$C*H*$_2$CH$_2$OH), 1.74–1.99 (2H, m, CHC*H*$_2$), 3.55–3.68 (2H, m, C*H*$_2$OH), 3.79 (3H, s, OMe), 4.22–4.32 (1H, m, C*H*OH), 6.80–6.92 (2H, m, ArC(3,5)*H*), 7.22–7.33 (2H, m, ArC(2,6)*H*).

1-(4-Chlorophenyl)pentane-1,5-diol, 197



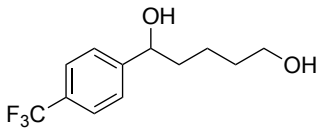
Following **General Procedure B**, glutaric anhydride (2.28 g, 20 mmol), chlorobenzene (2.52 g, 24 mmol) and $AlCl_3$ (4.00 g, 30 mmol) were reacted in anhydrous CH_2Cl_2 (67 mL) to give the oxo-acid (1.47 g, 23%), which was sufficiently pure to use directly. The oxo-acid (1.13 g, 5.0 mmol) and $LiAlH_4$ (2 M in THF, 9.3 mL, 18.5 mmol) were reacted in THF (25 mL). The reaction did not require further purification to give title compound **197** (0.93 g, 72%) as a colorless oil, with spectroscopic data in accordance with the literature.[144] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.30–1.54 (2H, m, CHCH$_2$C*H*$_2$), 1.54–1.64 (2H, m, C*H*$_2$CH$_2$OH) 1.64–1.83 (2H, m, CHC*H*$_2$), 3.58–3.70 (2H, m, C*H*$_2$OH), 4.63–4.69 (1H, m, C*H*OH), 7.16–7.33 (2H, m, ArC(2,6)*H*), 7.36–7.43 (2H, m, ArC(3,5)*H*).

1-(4-Bromophenyl)pentane-1,5-diol, 198



Following **General Procedure B**, glutaric anhydride (2.28 g, 20 mmol), bromobenzene (3.77 g, 24 mmol) and $AlCl_3$ (5.87 g, 44 mmol) were reacted in anhydrous CH_2Cl_2 (67 mL) to give the crude oxo-acid (1.67 g, 31%), which was sufficiently pure to use directly. The oxo-acid (1.36 g, 5.0 mmol) and $LiAlH_4$ (2 M in THF, 9.3 mL, 18.5 mmol) were reacted in THF (25 mL The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 80:20 to 20:80, R_f: 0.22) to give title compound **198** (0.78 g, 75%) as a yellow oil. ν_{max} (film) 3309(C-OH), 2935 (C-H), 1718 (C-C Ar), 821 (C-H Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.31–1.41 (1H, m, CH^AH^BCH_2CH_2OH), 1.42–1.53 (1H, m, CH^A$H^B$$CH_2CH_2OH$), 1.54–1.51 (2H, m C*H*OH), 1.65–1.72 (2H, m, CH^AH^{B}CHOH+OH), 3.55–3.66 (2H, m, CH_2OH), 4.64–4.72 (1H, m, C*H*OH), 7.16–7.23 (2H, m, ArC(2,6)*H*), 7.42–7.49 (2H, m, ArC(3,5)*H*). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 22.0 ($CH_2CH_2CH_2OH$), 32.4 (CH_2CH_2OH), 38.8 (OHCHCH_2), 62.7 (CH_2OH), 73.9 (OH$CHCH_2$), 121.4 (Ar*C*(4)), 127.7 (Ar*C*(2,6)H), 131.7 (Ar*C*(3,5)H), 143.9 (Ar*C*(1)), HRMS (NSI$^-$) $C_{11}H_{15}BrO_2$ $[M–H]^-$ found 257.0186, requires 257.0186 (+1.3 ppm).

1-(4-(Trifluoromethyl)phenyl)pentane-1,5-diol, 202



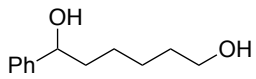
Mg turnings (20 mmol) and a small amount of the bromobenzotrifluoride were suspended in anhydrous THF (40 mL) under an N_2 atmosphere. A crystal of iodine was added and the suspension heated to reflux. Upon initiation the solution turned colourless at which point the rest of the bromobenzotrifluoride (2.31 g, 10.25 mmol) in THF (10 mL) was added dropwise. The resulting mixture was heated at reflux for 1 h before being cooled to rt and used immediately.

The freshly prepared Grignard reagent was added dropwise to a solution of glutaric anhydride (2.29 g, 20 mmol) in anhydrous THF (30 mL) under an N_2 atmosphere at rt. The reaction was

stirred at rt for 3 h before being quenched with cold water (10 mL) and aq. 2 M KOH (10 mL). The suspension was stirred at rt for 1 h before aq. $NaHCO_3$ (30 mL) was added and the layers separated. The aqueous was acidified to pH 1–2 with aq. 2 M HCl and extracted with CH_2Cl_2 (3×30 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure and the crude material was used directly in the next step.

The crude oxo-acid (1.00 g, 3.1 mmol) was dissolved in anhydrous THF (27 mL) and cooled to 0 °C under an N_2 atmosphere. A solution of $LiAlH_4$ (2.4 M in THF, 5.0 mL, 11.5 mmol) was added dropwise at 0 °C before the reaction was warmed to rt and stirred for 3 h. The reaction was cooled to 0 °C before being carefully quenched with water and aq. 2 M KOH. The resulting precipitate was dissolved through addition of aq. 1 M HCl and the reaction mixture was warmed to rt and stirred for 1 h. The solution was extracted with EtOAc (3×50 mL) and the combined organics dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 80:20 to 10:90, R_f: 0.18) to give title compound **202** (0.37 g, 38%) as a yellow oil. ν_{max} (film) 3315(C-OH), 2939 (C-H), 1613 (C-C Ar), 843 (C-H Ar); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.34–1.50 (2H, m, C*H*$_2$CH$_2$OH), 1.57–1.68 (2H, m, C*H*$_2$C*H*$_2$C*H*$_2$OH), 1.71–1.93 (2H, m, C*H*$_2$C*H*$_2$C*H*$_2$OH), 3.67 (2H, t, *J* 6.3, C*H*$_2$OH), 4.80 (1H, t , *J* 6.6, C*H*OH), 7.46–7.51 (2H, m, ArC(2,6)*H*), 7.60–7.66 (2H, m, ArC(3,5)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 22.0 (*C*H$_2$CH$_2$CH$_2$OH), 32.4 (*C*H$_2$CH$_2$OH), 39.0 (OHCH*C*H$_2$), 62.7 (*C*H$_2$OH), 73.9 (OH*C*HCH$_2$), 123.2 (q, $^1J_{C\text{-}F}$ 273, CF_3), 125.5 (q, $^3J_{C\text{-}F}$ 3.5, Ar*C*(3,5)H), 126.2 (Ar*C*(2,6)H), 129.7 (q, $^2J_{C\text{-}F}$ 32.4, Ar*C*(4)), 148.9 (Ar*C*(1)), ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F: –62.4, HRMS (NSI$^-$) $C_{12}H_{14}F_3O_2$ $[M–H]^-$ found 247.0953, requires 247.0951 (+0.7 ppm).

1-Phenylhexane-1,6-diol, 205

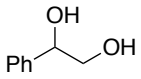


$CuBr_2$ (22 mg, 0.10 mmol) in DMSO (4 mL) and 2-phenylcyclohexanone (1.7 g, 10 mmol) was added and left at 110 °C for 12 h. The resulting solution was dissolved through addition of DCM (5 mL) and the reaction mixture was warmed to rt. The solution was washed with water (6x30 mL), extracted with DCM (3×5 mL) and the combined organics dried over $MgSO_4$ and

concentrated under reduced pressure. The reaction did not require further purification to give crude oxo-acid.

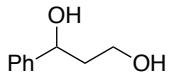
The crude oxo-acid (0.38 g, 2 mmol) was dissolved in anhydrous THF (5 mL) and cooled to 0 °C under an N_2 atmosphere. A solution of $LiAlH_4$ (2.4 M in THF, 3.1 mL, 7.4 mmol) was added dropwise at 0 °C before the reaction was warmed to rt and stirred for 3 h. The reaction was cooled to 0 °C before being carefully quenched with water and aq. 2 M KOH. The resulting precipitate was dissolved through addition of aq. 1 M HCl and the reaction mixture was warmed to rt and stirred for 1 h. The solution was extracted with EtOAc (3×50 mL) and the combined organics dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 80:20 , R_f: 0.23) to give the title compound **205** (0.27 g, 76%) as a colorless oil, with spectroscopic data in accordance with the literature.[145] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.31–1.45 (4H, m, C*H*$_2$C*H*$_2$C*H*$_2$OH), 1.50–1.62 (2H, m, CHC*H*$_2$), 1.67–1.88 (2H, m, C*H*$_2$C*H*$_2$CH$_2$OH), 3.63 (2H, *t*, *J* 6.5, C*H*$_2$OH), 4.64–4.71 (1H, m, C*H*OH), 7.27–7.31 (1H, m, ArC(4)*H*), 7.32–7.40 (4H, m, ArC(2,3,5,6)*H*).

1-Phenylethane-1,2-diol 206



Mandelic acid **162** (1.00 g, 6.3 mmol) was suspended in anhydrous THF (20 mL) and 2 M $LiAlH_4$ (20 mL, 36 mmol) was added dropwise. The reaction was heated to reflux and stirred for 16 h. The solution was then cooled to 0 °C before being quenched through the dropwise addition of H_2O (5 mL) and then 2 M KOH. The resulting precipitate was dissolved by adding 1 M HCl, the aqueous layer extracted with EtOAc (3×20 mL) and dried over $MgSO_4$. The title compound **206** (0.86 g, 86%) was obtained without further purification as a pale pink solid, with spectroscopic data in accordance with the literature.[146] mp 67–69 °C {Lit.[146] 66–67 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.62–3.74 (1H, m, C*H*^{A}H^{B}OH), 3.75–3.83 (1H, m, CH^A*H*^{B}OH), 4.83 (1H, dd, *J* 8.1, 3.6, C*H*OH), 7.28–7.52 (5H, m, ArC*H*).

1-Phenylpropane-1,3-diol, 208



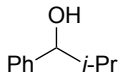
Ethyl benzoyl acetate (0.96 g, 5.0 mmol) was dissolved in MeOH (10 mL) before $NaBH_4$ (0.57 g, 15 mmol) was added portion-wise. The reaction was stirred for 15 min at rt until complete by TLC analysis. The solution was concentrated under reduced pressure before EtOAc (50 mL) was added. The solution was washed with brine (30 mL) and the aqueous further extracted with EtOAc (3×50 mL). The combined organics were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica column chromatography (petrol/EtOAc 80:20 to 50:50, R_f: 0.23) to give the title compound **208** (0.80 g, 83%) as a colourless oil, with spectroscopic data in accordance with the literature.[147] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.87–2.16 (2H, m,CH_2CH), 3.85–3.95 (2H, m, CH_2OH), 4.98 (1H, dd, *J* 8.6, 3.9, C*H*OH), 7.27–7.32 (1H, m, ArC*H*), 7.32–7.40 (4H, m, ArC*H*).

7.3.3 Secondary Benzylic Alcohols

1-Phenylethan-1-ol, 1

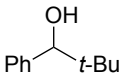
Following **General Procedure C**, benzaldehyde (1.04 g, 9.8 mmol) and MeMgBr (3.0 M in THF, 4.0 mL, 11.8 mmol) were reacted in THF (24 mL). The reaction did not require further purification to give title compound **1** (1.20 g, 99%) as an orange oil, with spectroscopic data in accordance with the literature.[148] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.50 (3H, d, *J* 6.5, CHCH_3), 2.04 (1H, s, O*H*), 4.90 (1H, q, *J* 6.5, OC*H*), 7.25–7.34 (2H, m, ArC(2,6)*H*), 7.35–7.46 (3H, m, ArC(3,4,5)*H*).

2-Methyl-1-phenylpropan-1-ol, 222



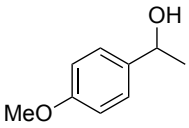
Following **General Procedure C**, benzaldehyde (1.1 mL, 9.8 mmol) and *i*-PrMgBr (1.0 M in THF, 12 mL, 11.8 mmol) were reacted in THF (15 mL). The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 9:1 to 7:3, R_f: 0.45) to give title compound **222** (0.68 g, 47%) as a colourless oil, with spectroscopic data in accordance with the literature.[149] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.80 (3H, d, *J* 6.8, CH(C*H*$_3$)$_2$), 1.00 (3H, d, *J* 6.8, 3H, CH(C*H*$_3$)$_2$), 1.96 (1H, m, C*H*(CH$_3$)$_2$), 4.36 (1H, d, *J* 6.9, HOC*H*), 7.24–7.41 (5H, m, ArC*H*).

2,2-Dimethyl-1-phenylpropan-1-ol, 223



Following **General Procedure C**, benzaldehyde (1.1 mL, 9.8 mmol) and *t*-BuMgCl (1.0 M in THF, 12 mL, 11.8 mmol) were reacted in THF (15 mL). The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 9.5:0.5 to 90:10, R_f: 0.51) to give title compound **223** (0.36 g, 22%) as a yellow oil, with spectroscopic data in accordance with the literature.[150] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.94 (9H, s, CH(C*H*$_3$)$_3$), 2.09 (1H, s, O*H*), 4.38 (1H, s, PhC*H*), 7.22–7.34 (5H, m, ArC*H*).

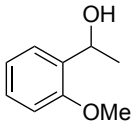
1-(4-Methoxyphenyl)ethan-1-ol ,17



Following **General Procedure C**, 4-methoxybenzaldehyde (1.33 g, 9.8 mmol) and MeMgBr (3.0 M in THF, 4.0 mL, 11.8 mmol) were reacted in THF (24 mL). The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 9:1 to 7:3, R_f: 0.39 (8:2)) to give title compound **17** (0.52 g, 35%) as colourless oil, with spectroscopic data in accordance with the literature.[148] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.47 (3H, d, *J* 6.4, CHC*H*$_3$), 1.83 (1H, s, O*H*), 3.80

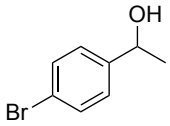
(3H, s, OC*H*$_3$), 4.85 (1H, q, *J* 6.4, C*H*CH$_3$), 6.82–6.93 (2H, m, ArC(3,5)*H*), 7.22–7.35 (2H, m, ArC(2,6)*H*).

1-(2-Methoxyphenyl)ethan-1-ol, 225



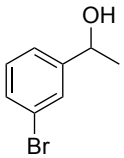
Following **General Procedure C**, 2-methoxybenzaldehyde (0.50 g, 3.7 mmol) and MeMgBr (3.0 M in Et$_2$O, 1.50 mL, 4.41 mmol) were reacted in Et$_2$O (15 mL). The reaction did not require further purification to give title compound **225** (0.51 g, 89%) as an orange oil, with spectroscopic data in accordance with the literature.[148] ^{1}H NMR (400 MHz, CDCl$_3$) δ_H: 1.54 (3H, d, *J* 6.6, CHC*H*$_3$), 2.66 (1H, s, O*H*), 3.90 (1H, s, OC*H*$_3$), 5.07–5.17 (1H, m, C*H*CH$_3$), 6.87–6.95 (1H, m, ArC*H*), 6.95–7.04 (1H, m, ArC*H*), 7.25–7.32 (1H, m, ArC*H*), 7.34–7.40 (1H, m, ArC*H*).

1-(4-Bromophenyl)ethan-1-ol, 226



Following **General Procedure C**, 4-bromobenzaldehyde (1.81 g, 9.8 mmol) and MeMgBr (3.0 M in THF, 4.0 mL, 11.8 mmol) were reacted in THF (24 mL). The reaction did not require further purification to give title compound **226** (1.95 g, 99%) as an orange oil, with spectroscopic data in accordance with the literature.[148] ^{1}H NMR (400 MHz, CDCl$_3$) δ_H: 1.45–1.53 (3H, m, CHC*H*$_3$), 1.98 (1H, s, O*H*), 4.86 (1H, q, *J* 6.5, C*H*CH$_3$), 7.21–7.33 (2H, m, ArC(2,6)*H*), 7.42–7.52 (2H, m, ArC(3,5)*H*).

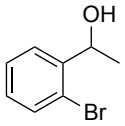
1-(3-Bromophenyl)ethan-1-ol 227



Following **General Procedure C**, 3-bromobenzaldehyde (1.81 g, 9.8 mmol) and MeMgBr (3.0 M in THF, 4.0 mL, 11.8 mmol) were reacted in THF (24 mL). The reaction did not require further

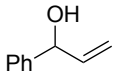
purification to give title compound **227** (1.92 g, 98%) as an orange oil, with spectroscopic data in accordance with the literature.[148] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.46 (3H, d, *J* 6.5, CHC*H*$_3$), 2.15 (1H, s, O*H*), 4.84 (1H, q, *J* 6.5, C*H*CH$_3$), 7.13–7.23 (1H, m, ArC*H*), 7.23–7.31 (1H, m, ArC*H*), 7.34–7.43 (1H, m, ArC*H*), 7.47–7.57 (1H, m, ArC*H*).

1-(2-Bromophenyl)ethan-1-ol, 228



Following **General Procedure C**, 2-bromobenzaldehyde (1.81 g, 9.8 mmol) and MeMgBr (3.0 M in THF, 4.0 mL, 11.8 mmol) were reacted in THF (24 mL). The reaction did not require further purification to give title compound **228** (1.94 g, 99%) as an orange oil, with spectroscopic data in accordance with the literature.[151] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.49 (3H, d, *J* 6.6, CHC*H*$_3$), 2.17 (1H, s, O*H*), 5.15–5.33 (1H, m, C*H*CH$_3$), 7.05–7.20 (1H, m, ArC*H*), 7.31–7.39 (1H, m, ArC*H*), 7.49–7.52 (1H, m, ArC*H*), 7.57–7.63 (1H, m, ArC*H*).

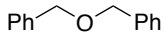
1-Phenylprop-2-en-1-ol, 67



Following **General Procedure C**, benzaldehyde (1.1 mL, 9.8 mmol) and vinyl magnesium bromide (0.7 M in THF, 17.0 mL, 11.8 mmol) were reacted in THF (10 mL). The reaction did not require further purification to give title compound **67** (1.31 g, 99%) as an orange oil, with spectroscopic data in accordance with the literature.[152] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.02 (1H, s), 5.15–5.21 (1H, m, CH^{A}C*H*^{B}), 5.24 (1H, m, HOC*H*), 5.39 (1H, dt, *J* 16.9, 1.4, CH^{A}C*H*^{B}), 6.00–6.11 (1H, m, C*H*CH$_2$), 7.26–7.33 (m, 1H, ArC*H*), 7.33–7.41 (m, 4H, ArC*H*).

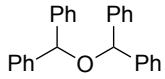
7.3.4 Intermolecular Dehydrative Substitution to form Symmetrical Ethers

Dibenzyl ether, 156



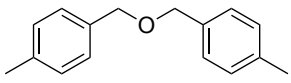
Following **General Procedure D**, benzyl alcohol **125** (43 mg, 0.4 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (2.0 mL) were reacted at 90 °C for 3 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 80:20, R_f: 0.27) to give title compound **156** (27 mg, 68%) as a colourless oil, with spectroscopic data in accordance with the literature.[153] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.57 (4H, s, C*H*$_2$OC*H*$_2$), 7.27–7.33 (2H, m, ArC*H*), 7.33–7.39 (8H, m, ArC*H*).

Bis(diphenylmethyl) ether, 176



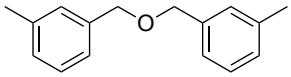
Following **General Procedure D**, benzhydrol **9** (37 mg, 0.2 mmol), pentafluorophenylboronic acid **48** (2 mg, 10 µmol) and oxalic acid **62** (1 mg, 20 µmol) in $MeNO_2$ (1.0 mL) were reacted at rt for 16 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 80:20, R_f: 0.21) to give title compound **176** (34 mg, 98%) as a colourless oil, with spectroscopic data in accordance with the literature.[154] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 5.40 (2H, s, Ph$_2$C*H*O), 7.25–7.39 (20 H, m, ArC*H*).

4,4'-(Oxybis(methylene))bis(methylbenzene), 177



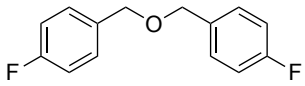
Following **General Procedure D**, 4-methylbenzyl alcohol **164** (73 mg, 0.6 mmol), pentafluorophenylboronic acid **48** (6 mg, 30 µmol) and oxalic acid **62** (4 mg, 60 µmol) in $MeNO_2$ (3.0 mL) were reacted at 40 °C for 3 h. The crude was purified by silica-gel column chromatography (petrol/PhMe, 50:50, R_f: 0.27) to give title compound **177** (38 mg, 52%) as a colourless oil, with spectroscopic data in accordance with the literature.[153] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.35 (6H, s, C*H*$_3$), 4.50 (4H, s, C*H*$_2$OC*H*$_2$), 7.06–7.44 (8H, m, ArC*H*).

3,3'-(Oxybis(methylene))bis(methylbenzene), 178



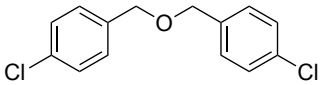
Following **General Procedure D**, 3-methylbenzyl alcohol (50 mg, 0.4 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (2.0 mL) were reacted at 90 °C for 72 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 90:10, R_f: 0.25) to give title compound **178** (28 mg, 62%) as a colourless oil, with spectroscopic data in accordance with the literature.[155] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.52 (4H, s, CH_2OCH_2), 6.82–7.01 (2H, m, ArC*H*), 7.03–7.25 (6H, m, ArC*H*).

4,4'-(Oxybis(methylene))bis(fluorobenzene), 179



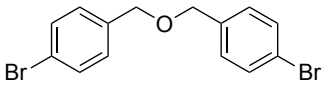
Following **General Procedure D**, 4-fluorobenzyl alcohol **60** (50 mg, 0.4 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (2.0 mL) were reacted at 90 °C for 3 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 90:10, R_f: 0.31) to give title compound **179** (38 mg, 76%) as a colourless oil, with spectroscopic data in accordance with the literature.[153] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.51 (4H, s, CH_2OCH_2), 6.99–7.11 (4H, m, ArC(3,5)*H*), 7.30–7.36 (4H, m, ArC(2,6)*H*).

4,4'-(Oxybis(methylene))bis(chlorobenzene), 180



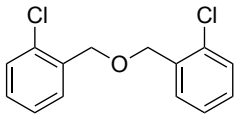
Following **General Procedure D**, 4-chlorobenzyl alcohol **165** (57 mg, 0.4 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (2.0 mL) were reacted at 90 °C for 3 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 90:10, R_f: 0.33) to give title compound **180** (55 mg, 98%) as a colourless oil, with spectroscopic data in accordance with the literature.[153] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.51 (4H, s, CH_2OCH_2), 7.27–7.37 (8H, m, ArC*H*).

4,4'-(Oxybis(methylene))bis(bromobenzene), 181



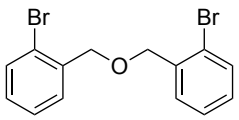
Following **General Procedure D**, 4-bromobenzyl alcohol (37 mg, 0.2 mmol), pentafluorophenylboronic acid **48** (2 mg, 10 µmol) and oxalic acid **62** (1 mg, 20 µmol) in $MeNO_2$ (1.0 mL) were reacted at 90 °C for 3 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 90:10, R_f: 0.33) to give title compound **181** (37 mg, 98%) as a colourless oil, with spectroscopic data in accordance with the literature.[153] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.49 (4H, s, C*H*$_2$OC*H*$_2$), 7.20–7.25 (4H, m, ArC(2,6)*H*), 7.44–7.53 (4H, m, ArC(3,5)*H*).

2,2'-(Oxybis(methylene))bis(chlorobenzene), 182



Following **General Procedure D**, 2-chlorobenzyl alcohol **167** (57 mg, 0.4 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (2.0 mL) were reacted at 90 °C for 72 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 50:50, R_f: 0.29) to give title compound **182** (20 mg, 35%) as a yellow oil, with spectroscopic data in accordance with the literature.[153] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.75 (4H, s, C*H*$_2$OC*H*$_2$), 7.21–7.33 (4H, m, ArC*H*), 7.37–7.41 (2H, m, ArC*H*), 7.57–7.62 (2H, m, ArC*H*).

2,2'-(Oxybis(methylene))bis(bromobenzene), 183

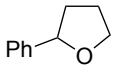


Following **General Procedure D**, 2-bromobenzyl alcohol **166** (75 mg, 0.4 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (2.0 mL) were reacted at 90 °C for 144 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 80:20, R_f: 0.22) to give title compound **183** (20 mg, 28%) as a

colourless oil, with spectroscopic data in accordance with the literature.[156] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.54 (4H, s, CH_2OCH_2), 6.96–7.02 (2H, m, ArC*H*), 7.08–7.20 (2H, m, ArC*H*), 7.25–7.38 (2H, m, ArC*H*), 7.53–7.60 (2H, m, ArC*H*).

7.3.5 Intramolecular Dehydrative Substitution

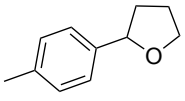
2-Phenyltetrahydrofuran, 209



Following **General Procedure E**, 1-phenylbutane-1,4-diol 1**89** (100 mg, 0.6 mmol), pentafluorophenylboronic acid **48** (7 mg, 30 µmol) and oxalic acid **62** (6 mg, 60 µmol) in $MeNO_2$ (3.0 mL) were reacted at 40 °C for 6 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 90:10, R_f: 0.27) to give title compound **209** (93 mg, 92%) as a colourless oil, with spectroscopic data in accordance with the literature.[157] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.72–1.90 (1H, m $CH_2CH_2CH_2$), 1.98–2.12 (2H, m, CH_2CH), 2.31–2.40 (1H, m, CH_2CHO), 3.93–4.01 (1H, m, OCH^AH^B), 4.09–4.16 (1H, m, OCH^AH^B), 4.90 (1H, t, *J* 7.2, $CHCH_2$), 7.26–7.39 (5H, m, ArC*H*).

Gram-Scale: Following **General Procedure E**, 1-phenylbutane-1,4-diol **189** (1.80 g, 10.85 mmol), pentafluorophenylboronic acid **48** (114 mg, 54 mmol) and oxalic acid **62** (98 mg, 1.1 mmol) in $MeNO_2$ (55 mL) were reacted at 40 °C for 6 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 90:10, R_f: 0.27) to give title compound **209** (1.40 g, 87%) as a colourless oil, with spectroscopic data as above.

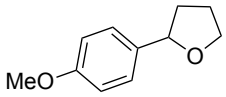
2-(*p*-Tolyl)tetrahydrofuran, 210



Following **General Procedure E**, 1-(*p*-tolyl)butane-1,4-diol **190** (109 mg, 0.6 mmol), pentafluorophenylboronic acid **48** (7 mg, 30 µmol) and oxalic acid **62** (6 mg, 60 µmol) in $MeNO_2$ (3.0 mL) were reacted at 40 °C for 6 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 90:10, R_f: 0.21) to give title compound **210** (97 mg, 86%) as a

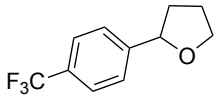
colourless oil, with spectroscopic data in accordance with the literature.[157] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.68–1.87 (1H, m, $CH_2CH^AH^BCH_2$), 1.92–2.08 (2H, m, CH_2CH), 2.22–2.39 (1H, m, $CH_2CH^AH^BCH_2$), 2.34 (3H, s, CH_3), 3.85–3.98 (1H, m, OCH^AH^B), 4.02–4.20 (1H, m, OCH^AH^B), 4.86 (1H, t, *J* 7.1, OC*H*), 7.14 (2H, d, *J* 7.8, ArC(3,5)*H*), 7.19–7.25 (2H, m, ArC(2,6)*H*).

2-(4-Methoxyphenyl)tetrahydrofuran, 211



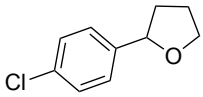
Following **General Procedure E**, 1-(4-methoxyphenyl)butane-1,4-diol **191** (39 mg, 0.2 mmol), pentafluorophenylboronic acid **48** (2 mg, 10 µmol) and oxalic acid **62** (1 mg, 20 µmol) in $MeNO_2$ (1.0 mL) were reacted at 40 °C for 6 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 90:10, R_f: 0.25) to give title compound **211** (23 mg, 60%) as a colourless oil, with spectroscopic data in accordance with the literature.[157] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.70–1.88 (1H, m, $CH_2CH^AH^BCH_2$), 1.88–2.13 (2H, m, CH_2CH), 2.21–2.41 (1H, m, $CH_2CH^AH^BCH_2$), 3.80 (3H, s, $ArOCH_3$), 3.87–3.98 (1H, m, OCH^AH^B), 4.03–4.16 (1H, m, OCH^AH^B), 4.83 (1H, t, *J* 7.1, OC*H*C), 6.86–6.95 (2H, m, ArC(3,5)*H*), 7.22–7.34 (2H, m, ArC(2,6)*H*).

2-(4-(Trifluoromethyl)phenyl)tetrahydrofuran, 212



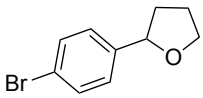
Following **General Procedure E**, 1-(4-(trifluoromethyl)phenyl)butane-1,4-diol **201** (60 mg, 0.2 mmol), pentafluorophenylboronic acid **48** (2 mg, 10 µmol) and oxalic acid **62** (1 mg, 20 µmol) in $MeNO_2$ (1.0 mL) were reacted at 90 °C for 48 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 9.5:0.5, R_f: 0.33) to give title compound **212** (30 mg, 54%) as a colourless oil, with spectroscopic data in accordance with the literature.[158] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.72–1.87 (1H, m, $CH_2CH^AH^BCH_2$), 1.97–2.09 (2H, m, CH_2CH), 2.34–2.46 (1H, m, $CH_2CH^AH^BCH_2$), 3.93–4.04 (1H, m, OCH^AH^B), 4.07–4.17 (1H, m, OCH^AH^B), 4.91–5.03 (1H, t, *J* 7.2, OC*H*C), 7.41–7.53 (2H, m, ArC(2,6)*H*), 7.54–7.64 (2H, m, ArC(3,5)*H*).

2-(4-Chlorophenyl)tetrahydrofuran, 213



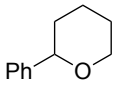
Following **General Procedure E**, 1-(4-chlorophenyl)butane-1,4-diol **192** (120 mg, 0.6 mmol), pentafluorophenylboronic acid **48** (7 mg, 30 µmol) and oxalic acid **62** (6 mg, 60 µmol) in $MeNO_2$ (3.0 mL) were reacted at 90 °C for 6 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 90:10, R_f: 0.25) to give title compound **213** (78 mg, 65%) as a colourless oil, with spectroscopic data in accordance with the literature.[157] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.63–1.84 (1H, m, $CH_2CH^AH^BCH_2$), 1.97–2.09 (2H, m, CH_2CH), 2.24–2.44 (1H, m, $CH_2CH^AH^BCH_2$), 3.9–4.01 (1H, m, OCH^AH^B), 4.06–4.16 (1H, m, OCH^AH^B), 4.86 (1H, t, *J* 7.1, OC*H*), 7.21–7.35 (4H, m, ArC*H*).

2-(4-Bromophenyl)tetrahydrofuran, 214



Following **General Procedure E**, 1-(4-bromophenyl)butane-1,4-diol **193** (49 mg, 0.2 mmol), pentafluorophenylboronic acid **48** (2 mg, 10 µmol) and oxalic acid **62** (1 mg, 20 µmol) in $MeNO_2$ (1.0 mL) were reacted at 90 °C for 6 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 90:10, R_f: 0.25) to give title compound **214** (49 mg, 85%) as a colourless oil, with spectroscopic data in accordance with the literature.[143] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.65–1.86 (1H, m, $CH_2CH^AH^BCH_2$), 1.90–2.11 (2H, m, CH_2CH), 2.23–2.46 (1H, m, $CH_2CH^AH^BCH_2$), 3.91–4.01 (1H, m, OCH^AH^B), 4.06–4.16 (1H, m, OCH^AH^B), 4.85 (1H, t, *J* 7.1, OC*H*C), 7.18–7.25 (2H, m, ArC(2,6)*H*), 7.44–7.51 (2H, m, ArC(3,5)*H*).

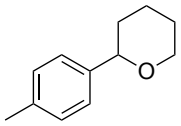
2-Phenyltetrahydro-2*H*-pyran, 215



Following **General Procedure E**, 1-phenylpentane-1,5-diol **194** (36 mg, 0.2 mmol), pentafluorophenylboronic acid **48** (2 mg, 10 µmol) and oxalic acid **62** (1 mg, 20 µmol) in

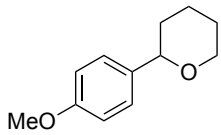
$MeNO_2$ (1.0 mL) were reacted at 90 °C for 6 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 90:10, R_f: 0.25) to give title compound **215** (28 mg, 78%) as a colourless oil, with spectroscopic data in accordance with the literature.[157] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.55–1.75 (4H, m, OCH_2CH_2 and $CHCH_2CH_2$), 1.79–1.89 (1H, m, CH^AH^BCH), 1.95–2.02 (1H, m, CH^AH^BCH), 3.60–3.70 (1H, m, CH^AH^BO), 4.15–4.21 (1H, m, CH^AH^BO), 4.29–4.37 (1H, m, $CHCH_2$), 7.26–7.32 (1H, m, ArC*H*), 7.31–7.39 (4H, m, ArC*H*).

2-(*p*-Tolyl)tetrahydro-2*H*-pyran, 216



Following **General Procedure E**, 1-(*p*-tolyl)pentane-1,5-diol **195** (39 mg, 0.2 mmol), pentafluorophenylboronic acid **48** (2 mg, 10 µmol) and oxalic acid **62** (1 mg, 20 µmol) in $MeNO_2$ (1.0 mL) were reacted at 40 °C for 6 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 93:7, R_f: 0.30) to give title compound **216** (23 mg, 64%) as a colourless oil, with spectroscopic data in accordance with the literature.[159] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.54–1.72 (4H, s, OCH_2CH_2 and $CHCH_2CH_2$), 1.77–1.83 (1H, m, CH^AH^BCH), 1.90–1.96 (1H, m, CH^AH^BCH), 2.33 (3H, s, CH_3), 3.55–3.66 (1H, m, CH^AH^BO), 4.08–4.18 (1H, m, CH^AH^BO), 4.24–4.32 (1H, m, $CHCH_2$), 7.07–7.18 (2H, m, ArC(3,5)*H*), 7.22–7.25 (2H, m, Ar(2,6)*H*).

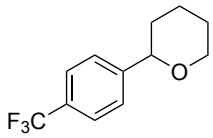
2-(4-Methoxyphenyl)tetrahydro-2*H*-pyran, 217



Following **General Procedure E**, 1-(4-methoxyphenyl)pentane-1,5-diol **196** (126 mg, 0.6 mmol), pentafluorophenylboronic acid **48** (7 mg, 30 µmol) and oxalic acid **62** (6 mg, 60 µmol) in $MeNO_2$ (3.0 mL) were reacted at 40 °C for 6 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 93:7, R_f: 0.15) to give title compound **217** (76 mg, 66%) as a colourless oil, with spectroscopic data in accordance with the literature.[157] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.56–1.76 (4H, m, OCH_2CH_2 and $CHCH_2CH_2$), 1.77–1.86 (1H, m, CH^AH^BCH), 1.91–2.02 (1H, m, CH^AH^BCH), 3.56–3.66 (1H, m, CH^AH^BO), 3.79 (3H, s, OMe), 4.10–4.19 (1H, m,

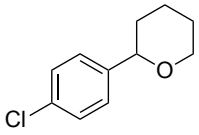
$CH^{A}H^{B}O$), 4.25–4.33 (1H, m, C*H*CH_2), 6.84–6.93 (2H, m, ArC(3,5)*H*), 7.25–7.34 (2H, m, ArC(2,6)*H*).

2-(4-(Trifluoromethyl)phenyl)tetrahydro-2*H*-pyran, 218



Following **General Procedure E**, 1-(4-(trifluoromethyl)phenyl)pentane-1,5-diol **202** (62 mg, 0.2 mmol), pentafluorophenylboronic acid **48** (2 mg, 10 µmol) and oxalic acid **62** (1 mg, 20 µmol) in $MeNO_2$ (1.0 mL) were reacted at 90 °C for 48 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 95:5 to 80:20, R_f: 0.30) to give title compound **218** (17 mg, 29%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.48–1.64 (2H, m, OCH_2CH_2), 1.65–1.76 (2H, m, $CHCH_2CH_2$), 1.80–1.90 (1H, m, $CH^{A}H^{B}CH$), 1.90–2.00 (1H, m,z $CH^{A}H^{B}CH$), 3.56–3.68 (1H, m, $CH^{A}H^{B}O$), 4.11–4.19 (1H, m, $CH^{A}H^{B}O$), 4.33–4.42 (1H, m, C*H*CH_2), 7.41–7.49 (2H, m, ArC(2,6)*H*), 7.55–7.63 (2H, m, ArC(3,5)*H*), ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 24.0 (*C*$H_2CH_2CH_2OH$), 25.9 (*C*H_2CH_2OH), 34.3 ($OCHCH_2$), 69.1 (*C*H_2O), 79.5 ($OCHCH_2$), 123.3 (q, $^1J_{C\text{-}F}$ 272, CF_3), 125.3 (q, $^3J_{C\text{-}F}$ 3.5, ArC(3,5)H), 126.1 (ArC(2,6)H), 129.5 (q, $^2J_{C\text{-}F}$ 33, ArC(4)), 147.5 (Ar*C*(1)), ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: –62.4, HRMS (ASAP$^-$) $C_{12}H_{13}F_3O$ $[M–H]^-$ found 229.0839, requires 229.0840 (–0.4 ppm).

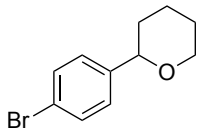
2-(4-Chlorophenyl)tetrahydro-2*H*-pyran, 219



Following **General Procedure E**, 1-(4-chlorophenyl)pentane-1,5-diol **197** (49 mg, 0.2 mmol), pentafluorophenylboronic acid **48** (2 mg, 10 µmol) and oxalic acid **62** (1 mg, 20 µmol) in $MeNO_2$ (1.0 mL) were reacted at 40 °C for 6 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 93:7, R_f: 0.15) to give title compound **219** (42 mg, 87%) as a colourless oil, with spectroscopic data in accordance with the literature.[157] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.51–1.74 (4H, m, OCH_2CH_2 and $CHCH_2CH_2$), 1.78–1.88 (1H, m, $CH^{A}H^{B}CH$), 1.91–

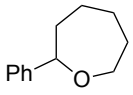
2.02 (1H, m, CH^A*H*^{B}CH), 3.57–3.69 (1H, m, C*H*^{A}H^{B}O), 4.11–4.20 (1H, m, CH^A*H*^{B}O), 4.30 (1H, dd, *J* 2.3, 11.0 Hz, C*H*CH$_2$), 7.26–7.35 (4H, m, ArC*H*).

2-(4-Bromophenyl)tetrahydro-2*H*-pyran, 220



Following **General Procedure E**, 1-(4-bromophenyl)pentane-1,5-diol **198** (155 mg, 0.6 mmol), pentafluorophenylboronic acid **48** (7 mg, 30 µmol) and oxalic acid **62** (6 mg, 60 µmol) in $MeNO_2$ (3.0 mL) were reacted at 40 °C for 6 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 93:7, R_f: 0.50) to give title compound **220** (89 mg, 62%) as a colourless oil, with spectroscopic data in accordance with the literature.[160] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.48–1.73 (4H, m, OCH$_2$C*H*$_2$ and CHCH$_2$C*H*$_2$), 1.74–1.87 (1H, m, C*H*^{A}H^{B}CH), 1.88–1.99 (1H, m, CH^A*H*^{B}CH), 3.53–3.67 (1H, m, C*H*^{A}H^{B}O), 4.08–4.18 (1H, m, CH^A*H*^{B}O), 4.24–4.32 (1H, m, C*H*CH$_2$), 7.18–7.26 (2H, m, ArC(2,6)*H*), 7.42–7.48 (2H, m, ArC(3,5)*H*).

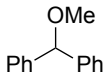
2-Phenyloxepane, 221



Following **General Procedure E**, 1-phenylhexane-1,6-diol **205** (71 mg, 0.4 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (2.0 mL) were reacted at 40 °C for 24 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 95:5, R_f: 0.30) to give title compound **221** (21 mg, 30%) as a colourless oil, with spectroscopic data in accordance with the literature.[161] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.65–1.92 (6H, m, OCH$_2$(C*H*$_2$)$_3$), 1.83–1.93 (1H, m, C*H*^{A}H^{B}CH), 1.96–2.19 (1H, m, CH^A*H*^{B}CH), 3.69–3.82 (1H, m, C*H*^{A}H^{B}O), 4.92–4.06 (1H, m, CH^A*H*^{B}O), 4.56–4.65 (1H, m, C*H*CH$_2$), 7.22–7.28 (1H, m, ArC*H*), 7.31–7.40 (4H, m, ArC*H*).

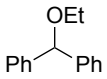
7.3.6 Intermolecular Dehydrative Substitution to form Unsymmetrical Ethers

(Methoxymethylene)dibenzene, 229



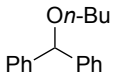
Following **General Procedure F**, benzhydrol **9** (74 mg, 0.4 mmol), MeOH (82 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at rt for 16 h. The crude was purified by silica-gel column chromatography (petrol/THF, 95:5, R_f: 0.30) to give a 90:10 mixture **229**/**176** (56 mg, **229**: 45 mg, 0.23 mmol, 58%; **176** 11 mg, 0.03 mmol, 13%), with spectroscopic data in accordance with the literature.[162] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.39 (3H, s, OCH_3), 5.25 (1H, s, PhC*H*), 7.23–7.28 (2H, m, ArC*H*), 7.30–7.38 (8H, m, ArC*H*).

(Ethoxymethylene)dibenzene, 230



Following **General Procedure F**, benzhydrol **9** (74 mg, 0.4 mmol), EtOH (117 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at rt for 16 h. The crude was purified by silica-gel column chromatography (petrol/THF, 95:5, R_f: 0.3) to give a 97:3 mixture **230**/**176** (60 mg, **230**: 57 mg, 0.27 mmol, 67%; **176**: 3 mg, 0.008 mmol, 4%), with spectroscopic data in accordance with the literature.[163] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.27 (3H, t, *J* 7.4 OCH_2CH_3), 3.53 (2H, q, *J* 7, OCH_2CH_3), 5.36 (1H, s, PhC*H*), 7.21–7.26 (2H, m, ArC*H*), 7.28–7.40 (8H, m, ArC*H*).

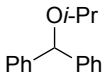
(Butoxymethylene)dibenzene, 231



Following **General Procedure F**, benzhydrol **9** (74 mg, 0.4 mmol), butanol (183 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at rt for 16 h. The crude was purified by silica-gel column chromatography (petrol/THF, 95:5, R_f: 0.30) to give a 97:3 mixture **231**/**176** (93 mg, **231**:

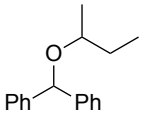
89 mg, 0.37 mmol, 93%; **176**: 4 mg, 0.01 mmol, 6%), with spectroscopic data in accordance with the literature.[164] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.91 (3H, t, *J* 7.4 $CH_2CH_2CH_3$) 1.36–1.40 (2H, m, $CH_2CH_2CH_3$) 1.58–1.70 (2H, m, $CH_2CH_2CH_2$), 3.45 (2H, t, *J* 6.5, OCH_2CH_2), 5.33 (1H, s, PhC*H*), 7.21–7.26 (2H, m, ArC*H*), 7.27–7.40 (8H, m, ArC*H*).

(Isopropoxymethylene)dibenzene, 232



Following **General Procedure F**, benzhydrol **9** (74 mg, 0.4 mmol), isopropanol (153 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at rt for 16 h. The crude was purified by silica-gel column chromatography (petrol/THF, 95:5, R_f: 0.30) to a 94:6 mixture **232**/**176** (86 mg, **232**: 79 mg, 0.35 mmol, 89%; **176**: 7 mg, 0.02 mmol, 11%), with spectroscopic data in accordance with the literature.[165] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.22 (6H, d, *J* 6.1, $OCH(CH_3)_2$), 3.59–3.73 (1H, m, $OCH(CH_3)_2$), 5.49 (1H, s, PhC*H*OPh), 7.21–7.27 (2H, m, Ar*H*), 7.29–7.37 (8H, m, Ar*H*).

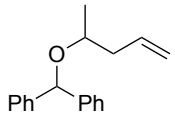
(*sec*-Butoxymethylene)dibenzene, 233



Following **General Procedure F**, benzhydrol **9** (74 mg, 0.4 mmol), 2-butanol (183 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at rt for 16 h. The crude was purified by silica-gel column chromatography (petrol/THF, 95:5, R_f: 0.30) to give a 95:5 mixture **233**/**176** (82 mg, **233**: 75 mg, 0.31 mmol, 78%; **176**: 7 mg, 0.02 mmol, 8%). ν_{max} (film) 3062 (C-H Ar), 2966 (C-H alkane), 1558 (C-C Ar), 1056 (C-O ether), 752 (C-H Ar); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.90 (3H, t, *J* 7.5, CH_2CH_3), 1.17 (3H, d, *J* 6.1, $OCHCH_3$), 1.44–1.53 (1H, m, $CH^AH^BCH_3$), 1.59–1.70 (1H, m, $CH^AH^BCH_3$), 3.40–3.50 (1H, m, $OCHCH_3$), 5.49 (1H, s, PhC*H*), 7.19–7.25 (2H, m, ArC*H*), 7.27–7.33 (8H, m, ArC*H*). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 10.0 (CH_2CH_3), 19.4 ($CHCH_3$), 29.5 (CH_2CH_3), 74.1 ($CHCH_3$), 80.6 (PhCH), 127.1 (ArC(4)H), 127.3 (ArC(2,6)H), 128.4 (ArC(3,5)H),

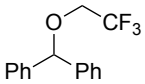
142.3 (Ar*C*(1)), 143.4 (Ar*C*(1)); HRMS (EI$^+$) $C_{17}H_{24}ON$ $[M+NH_4]^+$ found 258.1852, requires 258.1852 (–0.2 ppm).

((Pent-4-en-2-yloxy)methylene)dibenzene, 234



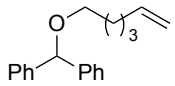
Following **General Procedure F**, benzhydrol **9** (74 mg, 0.4 mmol), pent-4-en-2-ol (410 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at rt for 16 h. The crude was purified by silica-gel column chromatography (petrol/THF, 95:5, R_f: 0.30) to give a 97:3 mixture **234**/**176** (80 mg, **234**: 78 mg, 0.31 mmol, 78%; **176**: 2 mg, 0.02 mmol, 8%). ν_{max} (film) 3063 (C-H Ar), 3026(C-H alkene), 2927 (C-H alkane), 1641 (C-C Alkene), 1599 (C-C Ar), 1070 (C-O ether), 750 (C-H Ar); H NMR (400 MHz, $CDCl_3$) δ_H: 1.18 (3H, d, *J* 6.4, OC*H*CH_3), 2.21–2.32 (1H, m, CHC$H^A$$CH^B$), 2.34–2.44 (1H, m, $CHCH^AC$$H^B$), 3.53–3.63 (1H, m, OC*H*CH_3), 5.00–5.09 (2H, m, CHC$H^A$$H^B$), 5.51 (1H, s, PhC*H*), 5.75–5.83 (1H, m, *CH*CH_2), 7.20–7.25 (2H, m, ArC*H*), 7.27–7.39 (8H, m, ArC*H*). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 19.7 ($CHCH_3$), 41.2 (CH_2CH), 72.5 ($CHCH_3$), 80.7 (Ph*C*H), 117.0 ($CHCH_2$), 127.1 (ArC(4)H), 127.4 (Ar*C*(2,6)H), 128.4 (Ar*C*(3,5)H), 135.3 (*CH*CH_2), 142.8 (Ar*C*(1)),143.2 (Ar*C*(1)),; HRMS (EI$^+$) $C_{18}H_{20}O_1$ $[M]^+$ found 252.1511, requires 252.1509 (+0.9 ppm).

((2,2,2-Trifluoroethoxy)methylene)dibenzene, 235



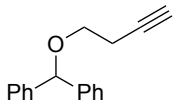
Following **General Procedure F**, benzhydrol **9** (74 mg, 0.4 mmol), 2,2,2-trifluoroethan-1-ol (150 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at rt for 16 h. The crude was purified by silica-gel column chromatography (petrol/THF, 95:5, R_f: 0.30) to give a 78:22 mixture **235**/**176** (88 mg, **235**: 64 mg, 0.24 mmol, 61%; **176**: 24 mg, 0.06 mmol, 34%), with spectroscopic data in accordance with the literature.[166] ^1H NMR (300 MHz, $CDCl_3$) δ_H: 3.82 (2H, q, *J* 8.7 OCH_2CF_3), 5.54 (1H, s, PhC*H*), 7.22–7.38 (16H, m, ArC*H*).

((Hex-5-en-1-yloxy)methylene)dibenzene, 236



Following **General Procedure F**, benzhydrol **9** (74 mg, 0.4 mmol), 5-hexen-1-ol **240**(240 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at rt for 16 h. The crude product was purified by flash column chromatography (petrol/Et_2O, 99:1, R_f: 0.52) to give title compound **236** (89 mg, 84%) as a colourless oil, with spectroscopic data in accordance with the literature.[167] ^1H NMR (400 MHz, $CDCl_3$) δ_H : 1.47–1.64 (2H, m, C*H*$_2$CH$_2$CH), 1.64–1.75 (2H, m, OCH$_2$C*H*$_2$), 2.04–2.14 (2H, m, CH$_2$C*H*$_2$*CH*), 3.48 (2H, t, *J* 6.7, OC*H*$_2$), 4.91–5.06 (2H, m, CHC*H*$_2$), 5.35 (1H, s, PhC*H*), 5.34–5.36 (1H, m, *CH*CH$_2$), 7.24–7.29 (2H, m, ArC*H*), 7.31–7.41 (8H, m, ArC*H*).

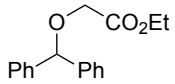
((But-3-yn-1-yloxy)methylene)dibenzene, 237



Following **General Procedure F**, benzhydrol **9** (74 mg, 0.4 mmol) and 3-butyn-1-ol (151 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at rt for 16 h. The crude product was purified by flash column chromatography (Petrol/EtOAc, 100:0 to 95:5, R_f: 0.30) to give title compound **237** (91 mg, 97%) as a colourless oil, with spectroscopic data in accordance with the literature.[168] ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.99 (1H, t, *J* 2.7, CH$_2$CC*H*), 2.57 (2H, td, *J* 7.0, 2.7, C*H*$_2$CCH), 3.49 (2H, q, *J* 7.0, OC*H*$_2$CH$_2$), 5.44(1H, s, PhC*H*), 7.24–7.31 (2H, m, ArC*H*), 7.31–7.44 (8H, m, ArC*H*).

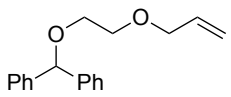
Gram-Scale: Following **General Procedure F**, benzhydrol **9** (2.02 g, 11 mmol) and 3-butyn-1-ol (4.20 mL, 55 mmol), pentafluorophenylboronic acid **48** (117 mg, 0.55 mmol) and oxalic acid **62** (100 mg, 1.1 mmol,) in $MeNO_2$ (65 mL) were reacted at rt for 16 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 100:0 to 95:5, R_f: 0.30) to give title compound **237** (2.53 g, 97%) as a colourless oil, with spectroscopic data as above.

Ethyl 2-(benzhydryloxy)acetate, 238



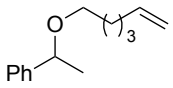
Following **General Procedure F**, benzhydrol **9** (74 mg, 0.4 mmol) and ethyl glycolate **253** (189 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at rt for 16 h. The crude product was purified by silica-gel column chromatography (petrol/Et_2O, 95:5 to 85:15, R_f: 0.10) to give title compound **238** (64 mg, 59%) as a colourless oil, with spectroscopic data in accordance with the literature.[169] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.22–1.33 (3H, m, CH_2CH_3), 4.10 (2H, s, OC*H*$_2$), 4.22 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 5.59 (1H, s, PhC*H*), 7.24–7.30 (2H, m, ArC(4)*H*), 7.30–7.41 (8H, m, ArC*H*).

((2-(Allyloxy)ethoxy)methylene)dibenzene, 239



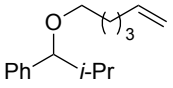
Following **General Procedure F**, benzhydrol **9** (74 mg, 0.4 mmol) and 2-(allyloxy)ethan-1-ol (214 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at rt for 16 h. The crude product was purified by silica-gel column chromatography (petrol/Et_2O, 99:1, R_f: 0.16) to give title compound **239** (89 mg, 83%) as a colourless oil. ν_{max} (film) 3028 (C-H alkene), 2860 (C-H alkane), 1091 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.62–3.74 (4H, m, OC*H*$_2$C*H*$_2$O), 4.10 (2H, dt, *J* 5.6, 1.5, OC*H*$_2$*CH*), 5.15–5.24 (1H, m, CHC*H*^{A}H^B), 5.26–5.36 (1H, m, CHCH^A*H*^{B}), 5.46 (1H, s, PhC*H*OPh), 5.90–6.02 (1H, m, C*H*CH^{A}H^B), 7.23–7.29 (2H, m, ArC(4)*H*), 7.31–7.36 (4H, m, ArC(2,6)*H*), 7.37–7.42 (4H, m, ArC(3,5)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 68.3 (OCH$_2$*C*H$_2$O), 69.4 (O*C*H$_2$CH$_2$O), 72.0 (CH$_2$O*C*H$_2$), 83.8 (Ph*C*H), 116.7 (CH*C*H$_2$), 126.9 (ArC(4)H), 127.3 (Ar*C*(2,6)H), 128.2 (Ar*C*(3,5)H), 134.7 (*CH*CH$_2$), 142.0 (Ar*C*(1)); HRMS (APCI$^+$) $C_{18}H_{19}O_2$ $[M–H]^+$ found 267.1380, requires 267.1380 (+0.2 ppm).

(1-(Hex-5-en-1-yloxy)ethyl)benzene, 241



Following **General Procedure F**, 1-phenylethan-1-ol **1** (49 mg, 0.4 mmol) and 5-hexen-1-ol **240** (240 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 16 h. The crude product was purified by silica-gel column chromatography (petrol/Et_2O, 95:5 to 85:15, R_f: 0.10) to give title compound **241** (48 mg, 59%) as a colourless oil. ν_{max} (film) 2976 (C-H alkene), 2858 (C-H alkane), 1639 (C=C), 1101 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.38–1.46 (5H, m, C$H_2$$CH_2$CH and CHC$H_3$), 1.50–1.62 (2H, m, OCH_2CH_2), 1.97–2.07 (2H, m, CH_2CH_2CH), 3.29 (2H, t, *J* 6.6, OCH_2), 4.38 (1H, q, *J* 6.5, PhC*H*OCH_3), 4.90–4.94 (1H, m, CHCH^AH^B), 4.94–5.01 (1H, m, CHCH^AH^B), 5.72–5.85 (1H, m, *CH*CH_2), 7.23–7.29 (1H, m, ArC*H*), 7.29–7.37 (4H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 24.4 ($OCHCH_3$), 25.6 ($O(CH_2)_2CH_2$), 29.5 (OCH_2CH_2), 33.7 ($CH_2(CHCH_2)$), 68.6 (OCH_2), 78.0 (Ar*C*HOCH_3), 114.6 ($CHCH_2$), 126.2 (Ar*C*(2,6)H), 127.4 (Ar*C*(4)H), 128.5 (Ar*C*(3,5)H), 138.9 (H*C*=CH_2), 144.4 (Ar*C*(1)H)HRMS (ASAP$^+$) $C_{14}H_{19}$ [M–H_2O+H]$^+$ found 187.1491, requires 187.1487 (+0.8 ppm).

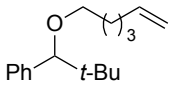
(1-(Hex-5-en-1-yloxy)-2-methylpropyl)benzene, 242



Following **General Procedure F**, 2-methyl-1-phenylpropan-1-ol **222** (49 mg, 0.4 mmol) and 5-hexen-1-ol **240** (240 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 16 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 100:0 to 90:10, R_f: 0.34) to give title compound **242** (52 mg, 90%) as a colourless oil. ν_{max} (film) 3010 (C-H alkene), 2955 (C-H alkane), 1641 (C=C Alkene), 1580 (C-C Ar), 1070 (C-O ether), 754 (C-H Ar); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.72 (3H, d, *J* 6.8 CH(CH_3)), 1.00 (3H, d, *J* 6.6, CH(CH_3)), 1.39–1.49 (2H, m, C$H_2$$CH_2$CH), 1.50–1.60 (2H, m, OCH_2CH_2) 1.83–1.95 (1H, m, (OCHC*H*$(CH_3)_2$), 1.98–2.08 (2H, m, CH_2CH_2CH), 3.15–3.24 (1H, m, OCH^AH^B), 3.25–3.34 (1H, m, OCH^AH^B), 3.81 (1H, d, *J* 7.4, PhC*H*OPh), 4.90–4.95 (1H, m, CHCH^AH^B), 4.95–5.01 (1H, m, CHCH^AH^B), 5.72–5.88 (1H, m,

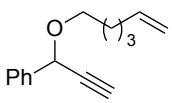
CHCH_2), 7.22–7.27 (3H, m, ArC*H*), 7.29–7.35 (2H, m, ArC*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 19.2 (CH(*C*H_3)$_2$), 25.7 ($OCH_2CH_2CH_2$), 29.5 (OCH_2CH_2), 33.7 (*C*H_2(CHCH_2), 35.0 *C*(CH_3), 69.0 (O*C*H_2), 88.1 (Ar*C*HOCH_3), 114.5 (CH*C*H_2), 127.3 (Ar*C*(4)H), 127.5 (Ar*C*(3,5)H), 128.9 (Ar*C*(2,6)H), 139.1 (*CH*CH_2), 142.1 (Ar*C*(1)); HRMS (ASAP$^+$) $C_{16}H_{23}$ $[M–H_2O+H]^+$ found 215.1797, requires 215.1800 (–1.4 ppm).

(1-(Hex-5-en-1-yloxy)-2,2-dimethylpropyl)benzene, 243



Following **General Procedure F**, 2,2-dimethyl-1-phenylpropan-1-ol **223** (66 mg, 0.4 mmol) and 5-hexen-1-ol **240** (240 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 16 h. The crude product was purified by silica-gel column chromatography (petrol/Et_2O, 100:0 to 98:2, R_f: 0.46) to give title compound **243** (102 mg, 90%) as a colourless oil. ν_{max} (film) 2951 (C-H alkene), 2864 (C-H alkane), 1641 (C=C alkene), 1101 (C-O ether) ; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 0.90(9H, s, C(C*H*$_3$)$_3$), 1.43–1.51 (2H, m, C*H*$_2$CH$_2$CH), 1.54–1.60 (2H, m, OCH$_2$C*H*$_2$), 1.99–2.13 (m, 2H, CH$_2$C*H*$_2$*CH*), 3.12–3.20 (1H, m, OC*H*^{A}H^B), 3.24–3.36 (1H, m, OCH^A*H*^{B}), 3.85 (1H, s, PhC*H*), 4.92–4.97 (1H, m, CHC*H*^{A}H^B), 4.97–5.03 (1H, m, CHCH^A*H*^{B}), 5.75–5.88 (1H, m, *CH*CH_2), 7.23–7.28 (3H, m, ArC*H*), 7.28–7.33 (2H, m, ArC*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 25.8 ($OCH_2CH_2CH_2$), 26.4 C(*C*H_3), 29.5 (OCH_2CH_2), 33.7 (*C*H_2(CHCH_2), 35.7 *C*(CH_3), 69.2 (O*C*H_2), 90.1 (Ar*C*HOCH_3), 114.5 (CH*C*H_2), 127.1 (Ar*C*(4)H), 127.5 (Ar*C*(3,5)H), 128.6 (Ar*C*(2,6)H), 139.2 (*CH*CH_2), 140.5 (Ar*C*(1)); HRMS (APCI$^+$) $C_{17}H_{25}O$ $[M–H]^+$ found 245.1900, requires 245.1900 (+0.0 ppm).

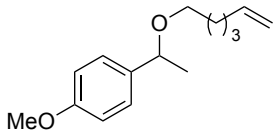
(1-(Hex-5-en-1-yloxy)prop-2-yn-1-yl)benzene, 244



Following **General Procedure F**, 1-phenyl-propyn-2-ol (49 µL, 0.4 mmol) and 5-hexen-1-ol **240** (240 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 16 h. The crude product was

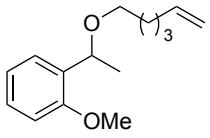
purified by silica-gel column chromatography (petrol/Et_2O, 98:2 to 95:5, R_f: 0.67) to give title compound **244** (71 mg, 83%) as a colourless oil. ν_{max} (film) 3292 (C-H alkyne), 2935 (C-H alkene), 2860 (C-H alkane), 1639 (C=C), 1038 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.44–1.54 (2H, m, CH_2CH$_2$CH), 1.61–1.72 (2H, m, OCH$_2$CH_2), 2.01–2.13 (m, 2H, CH$_2$CH_2CH), 2.65 (1H, d, *J* 2.2, CHCC*H*), 3.45–3.57 (1H, m, OCH^AH^B), 3.64–3.73 (1H, m, OCH^AH^B), 4.94–4.99 (1H, m, CHCH^AH^B), 4.99–5.05 (1H, m, CHCH^AH^B), 5.17 (1H, d, *J* 2.2, PhC*H*), 5.75–5.89 (1H, m, *C*HCH$_2$), 7.32–7.37 (1H, m, ArC*H*), 7.37–7.42 (2H, m, ArC*H*), 7.51–7.56 (2H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 25.6 (O(CH$_2$)$_2$*C*H$_2$), 29.2 (OCH$_2$*C*H$_2$), 33.6 (*C*H$_2$(CHCH$_2$), 68.4 (O*C*H$_2$), 71.4 (OCHC*C*H), 75.5 (Ar*C*H), 82.0 (OCH*C*CH), 114.7 (CH*C*H$_2$), 127.4 (Ar*C*(2,6)H), 128.5 (Ar*C*(4)H), 128.5 (Ar*C*(3,5)H), 138.5 (Ar*C*(1)), 138.8 (*C*HCH$_2$); HRMS (APCI$^+$) $C_{15}H_{22}ON$ $[M+NH_4]^+$ found 232.2696, requires 232.2696 (0.0 ppm).

1-(1-(Hex-5-en-1-yloxy)ethyl)-4-methoxybenzene, 245



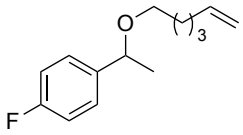
Following **General Procedure F**, 1-(4-methoxyphenyl)ethan-1-ol **17** (61 mg, 0.4 mmol) and 5-hexen-1-ol **240** (240 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 16 h. The crude product was purified by silica-gel column chromatography (petrol/Et_2O, 99:1 to 95:5, R_f: 0.34) to give title compound **245** (52 mg, 57%) as a colourless oil. ν_{max} (film) 2974 (C-H), 2837 (C-H), 1097 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.34–1.49 (5H, m, CH_2CH$_2$CH and CHCH_3), 1.50–1.62 (2H, m, OCH$_2$CH_2), 1.97–2.07 (2H, m, CH$_2$CH_2CH), 3.27 (2H, t, *J* 6.5, OCH_2), 3.81 (3H, s, OCH_3), 4.34 (1H, q, *J* 6.5, PhC*H*), 4.90–4.95 (1H, m, CHCH^AH^B), 4.95–5.01 (1H, m, CHCH^AH^B), 5.72–5.85 (1H, m, *C*HCH$_2$), 6.83–6.93 (2H, m, ArC(3,5)*H*), 7.19–7.26 (2H, m, ArC(2,6)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 24.3 (OCH*C*H$_3$), 25.6 (O(CH$_2$)$_2$*C*H$_2$), 29.5 (OCH$_2$*C*H$_2$), 33.7 (*C*H$_2$CHCH$_2$), 55.4 (O*C*H$_3$), 68.4 (O*C*H$_2$), 77.5 (Ar*C*HOCH$_3$), 113.8 (Ar*C*(3,5)H), 114.6 (CH*C*H$_2$), 127.4 (Ar*C*(2,6)H), 136.4 (Ar*C*(1)H), 139.0 (*C*HCH$_2$), 159.0 (Ar*C*(4)H); HRMS (APCI$^+$) $C_{15}H_{21}O_2$ $[M–H]^+$ found 233.1536, requires 233.1536 (0.0 ppm).

1-(1-(Hex-5-en-1-yloxy)ethyl)-2-methoxybenzene, 246



Following **General Procedure F**, 1-(2-methoxyphenyl)ethan-1-ol **225** (61 mg, 0.4 mmol) and 5-hexen-1-ol **240** (240 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at rt for 16 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 95:5 to 80:20, R_f: 0.40) to give title compound **246** (61 mg, 65%) as a colourless oil. ν_{max} (film) 2932 (C-H), 2858 (C-H), 1680 (C=C), 1587 (C-C Ar), 1089 (C-O), 804 (C-H Ar); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.37 (3H, d, *J* 6.4, CHC*H*$_3$), 1.40–1.50 (2H, m, OCH$_2$C*H*$_2$), 1.56–1.66 (2H, m, C*H*$_2$CH$_2$CH), 1.98–2.09 (2H, m, CH$_2$C*H*$_2$CH*),* 3.27–3.33 (2H, m, OC*H*$_2$), 3.82 (3H, s, OC*H*$_3$), 4.82 (1H, q, *J* 6.4, PhC*H*), 4.89–4.95 (1H, m, CHC*H*^{A}H^B), 4.95–5.03 (1H, m, CHCH^A*H*^{B}), 5.74–5.85 (1H, m, *CH*CH$_2$), 6.82–6.89 (1H, m, ArC*H*), 6.93–7.02 (1H, m, ArC*H*), 7.18–7.25 (1H, m, ArC*H*), 7.37–7.45 (1H, m, ArC*H*), ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 23.0 (OCH*C*H$_3$), 25.7 (O(CH$_2$)$_2$*C*H$_2$), 29.6 (OCH$_2$*C*H$_2$), 33.8 (*C*H$_2$(CHCH$_2$), 55.4 (OCH$_3$) 68.8 (O*C*H$_2$), 71.6 (Ar*C*HOCH$_3$), 110.3 (Ar*C*(5)H), 114.5 (CH*C*H$_2$), 120.9 (Ar*C*(3)), 126.1 (Ar*C*(6)H), 126.5 (Ar*C*(1)H), 127.9 (Ar*C*(4)H), 132.8 (Ar*C*(3)H), 139.0 (*CH*CH$_2$), 156.7 (Ar*C*(2)OMe); HRMS (NSI$^+$) $C_{15}H_{23}O_2$ $[M+H]^+$ found 235.1695, requires 235.1693 (+1.0 ppm).

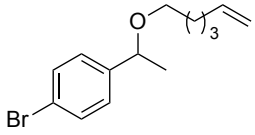
1-Fluoro-4-(1-(hex-5-en-1-yloxy)ethyl)benzene, 247



Following **General Procedure F**, 1-(4-fluorophenyl)ethan-1-ol **283** (51 µL, 0.4 mmol) and 5-hexen-1-ol **240** (240 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 16 h. The crude product was purified by silica-gel column chromatography (petrol/Et_2O, 100:0 to 95:5, R_f: 0.56) to give title compound **247** (70 mg, 79%) as a colourless oil. ν_{max} (film) 2976 (C-H alkene), 2860 (C-H alkane), 1641 (C=C), 1220 (C-F), 1101 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.39–

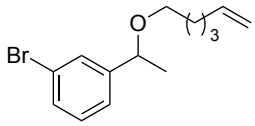
1.47 (5H, m, C*H*$_2$CH$_2$CH and CHC*H*$_3$), 1.53–1.63 (2H, m, OCH$_2$C*H*$_2$), 1.98–2.09 (2H, m, CH$_2$C*H*$_2$C*H*), 3.21–3.35 (2H, m, OC*H*$_2$), 4.36 (1H, q, *J* 6.5, PhC*H*), 4.91–4.96 (1H, m, CHC*H*^{A}H^B), 4.96–5.01 (1H, m, CHCH^A*H*^{B}), 5.73–5.85 (1H, m, *CH*CH$_2$), 6.99–7.07 (2H, m, ArC(3,5)*H*), 7.23–7.32 (2H, m, ArC(2,6)*H*); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ_C: 24.3 (OCH*C*H$_3$), 25.6 (O(CH$_2$)$_2$*C*H$_2$), 29.5 (OCH$_2$*C*H$_2$), 33.7 (*C*H$_2$(CHCH$_2$), 68.6 (O*C*H$_2$), 77.4 (Ar*C*HOCH$_3$), 114.6 (CH*C*H$_2$), 115.3 (d, $^2J_{C\text{-}F}$ 21.3, ArC(3,5)H), 127.8 (d, $^3J_{C\text{-}F}$ 8.2, ArC(2,6)H), 138.9 (CHCH$_2$), 140.1 (d, $^4J_{C\text{-}F}$ 3.1, ArC(1)), 162.2 (d, $^1J_{C\text{-}F}$ 244.8, ArC(4)H); ^{19}F{^{1}H} NMR (377 MHz, CDCl$_3$) δ_F: –115.7; HRMS (ESI$^+$) C$_{14}$H$_{18}$OF [M–H]$^+$ found 221.1330, requires 221.1336 (–2.8 ppm).

1-Bromo-4-(1-(hex-5-en-1-yloxy)ethyl)benzene, 248



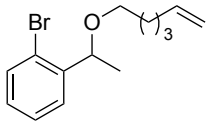
Following **General Procedure F**, 1-(4-bromophenyl)ethan-1-ol **226** (80 mg, 0.4 mmol) and 5-hexen-1-ol **240** (240 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in MeNO$_2$ (8.0 mL) were reacted at 90 °C for 16 h. The crude product was purified by silica-gel column chromatography (petrol/Et$_2$O, 98:2, R$_f$: 0.64) to give title compound **248** (102 mg, 90%) as a colourless oil. ν_{max} (film) 2976 (C-H), 2858 (C-H), 1099 (C-O); ^{1}H NMR (500 MHz, CDCl$_3$) δ_H: 1.38–1.48 (5H, m, C*H*$_2$CH$_2$CH and CHC*H*$_3$), 1.52–1.61 (2H, m, OCH$_2$C*H*$_2$), 1.98–2.08 (2H, m, CH$_2$C*H*$_2$C*H*), 3.21–3.35 (2H, m, OC*H*$_2$), 4.34 (1H, q, *J* 6.5, PhC*H*OCH$_3$), 4.91–4.96 (1H, m, CHC*H*^{A}H^B), 4.96–5.02 (1H, m, CHCH^A*H*^{B}), 5.72–5.87 (1H, m, *CH*CH$_2$), 7.14–7.22 (2H, m, ArC(2,6)*H*), 7.42–7.51 (2H, m, ArC(3,5)*H*); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ_C: 24.2 (OCH*C*H$_3$), 25.6 (O(CH$_2$)$_2$*C*H$_2$), 29.5 (OCH$_2$*C*H$_2$), 33.7 (*C*H$_2$(CHCH$_2$), 68.7 (O*C*H$_2$), 77.4 (Ar*C*HOCH$_3$), 114.6 (CH*C*H$_2$), 121.1 (Ar*C*(4)H), 128.0 (Ar*C*(2,6)H), 131.6 (Ar*C*(3,5)H), 138.8 (*C*HCH$_2$), 143.5 (Ar*C*(1)H); HRMS (ASAP$^+$) C$_{14}$H$_{19}$BrO [M+H]$^+$ found 283.0695, requires 283.0695 (-1.1 ppm).

1-Bromo-3-(1-(hex-5-en-1-yloxy)ethyl)benzene, 249



Following **General Procedure F**, 1-(3-bromophenyl)ethan-1-ol **227** (80 mg, 0.4 mmol) and 5-hexen-1-ol **240** (240 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 48 h. The crude product was purified by silica-gel column chromatography (petrol/Et_2O, 100:0 to 95:5, R_f: 0.50) to give title compound **249** (43 mg, 38%) as a colourless oil. ν_{max} (film) 3030 (C-H Ar), 2976 (C-H), 2930 (C-H), 1639 (C=C), 1570 (C-C Ar), 1075 (C-O ether), 750 (C-H Ar); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.34–1.49 (5H, m, CHC*H*$_3$ *and* C*H*$_2$CH$_2$CH), 1.52–1.64 (2H, m, OCH$_2$C*H*$_2$), 1.98–2.09 (2H, m, CH$_2$C*H*$_2$*CH*), 3.22–3.34 (2H, m, OC*H*$_2$), 4.33 (1H, q, *J* 6.5, PhC*H*OCH$_3$), 4.91–4.96 (1H, m, CHC*H*^{A}H^B), 4.96–5.04 (1H, m, CHCH^A*H*^{B}), 5.71–5.86 (1H, m, *CH*CH$_2$), 7.17–7.25 (2H, m, ArC*H*), 7.36–7.42 (1H, m, ArC*H*), 7.42–7.48 (1H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 24.3 (OCH*C*H$_3$), 25.6 (O(CH$_2$)$_2$*C*H$_2$), 29.5 (OCH$_2$*C*H$_2$), 33.7 (*C*H$_2$(CHCH$_2$), 68.9 (O*C*H$_2$), 77.4 (Ar*C*HOCH$_3$), 114.7 (CH*C*H$_2$), 122.7 (Ar*C*(3)), 124.9 (Ar*C*(6)H), 129.4 (Ar*C*(5)H), 130.2 (Ar*C*(4)H), 130.5 (Ar*C*(2)H), 138.9 (*C*HCH$_2$), 147.0 (Ar*C*(1)H); HRMS (APCI$^+$) $C_{14}H_{18}OBr$ $[M–H]^+$ found 281.0537, requires 281.0536 (0.5 ppm).

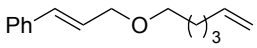
1-Bromo-2-(1-(hex-5-en-1-yloxy)ethyl)benzene, 250



Following **General Procedure F**, 1-(2-bromophenyl)ethan-1-ol **228** (80 mg, 0.4 mmol) and 5-hexen-1-ol **240** (240 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 16 h. The crude product was purified by silica-gel column chromatography (petrol/Et_2O, 100:0 to 99:1, R_f: 0.70) to give title compound **250** (69 mg, 61%) as a colourless oil. ν_{max} (film) 2951 (C-H), 2860 (C-H), 1103 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.36–1.51 (5H, m, C*H*$_2$CH$_2$CH and CHC*H*$_3$), 1.53–1.66 (2H, m, OCH$_2$C*H*$_2$), 2.00–2.09 (2H, m, CH$_2$C*H*$_2$*CH*), 3.25–3.30 (2H, m, OC*H*$_2$), 4.79

(1H, q, *J* 6.4, PhC*H*OCH$_3$), 4.90–4.96 (1H, m, CHC*H*^{A}H^B), 4.96–5.03 (1H, m, CHCH^A*H*^{B}), 5.74–5.88 (1H, m, *CH*CH$_2$), 7.07–7.17 (1H, m, ArC*H*), 7.29–7.38 (1H, m, ArC*H*), 7.46–7.53 (2H, m, ArC*H*), ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ_C: 22.9 (OCH*C*H$_3$), 25.6 (O(CH$_2$)$_2$*C*H$_2$), 29.5 (OCH$_2$*C*H$_2$), 33.7 (*C*H$_2$(CHCH$_2$), 69.0 (O*C*H$_2$), 76.6 (Ar*C*HOCH$_3$), 114.6 (CH*C*H$_2$), 122.7 (Ar*C*(2)), 127.2 (Ar*C*(6)H), 128.0 (Ar*C*(5)H), 128.7 (Ar*C*(4)H), 132.7 (Ar*C*(3)H), 138.9 (*CH*CH$_2$), 143.4 (Ar*C*(1)H); HRMS (ASAP$^+$) $C_{14}H_{20}OBr$ $[M+H]^+$ found 283.0699, requires 283.0698 (0.1 ppm)

(*E*)-(3-(Hex-5-en-1-yloxy)prop-1-en-1-yl)benzene, 251

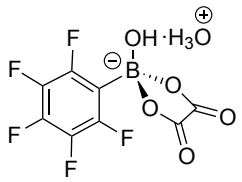


*From 1-Phenylprop-2-en-1-ol **67**:* Following **General Procedure F**, 1-phenylprop-2-en-1-ol **67** (54 mg, 0.4 mmol) and 5-hexen-1-ol **240** (240 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 40 °C for 16 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 100:0 to 95:5, R_f: 0.42) to give title compound **251** (76 mg, 88%) as a colourless oil. ν_{max} (film) 3010 (C-H Ar), 2933 (C-H), 2860 (C-H), 1680 (C=C), 1639 (C-C Ar), 1099 (C-O), 654 (C-H Ar); ^{1}H NMR (500 MHz, CDCl$_3$) δ_H: 1.44–1.53 (2H, m, C*H*$_2$CH$_2$CH), 1.60–1.68 (2H, m, OCH$_2$C*H*$_2$), 2.05–2.12 (2H, m, CH$_2$C*H*$_2$*CH*), 3.49 (2H, t, *J* 6.6, OC*H*$_2$), 4.07–4.22 (2H, m, CHC*H*$_2$O) 4.93–4.98 (1H, m, CHC*H*^{A}H^B), 4.98–5.06 (1H, m, CHCH^A*H*^{B}), 5.77–5.88 (1H, m, *CH*CH$_2$), 6.25–6.36 (1H, m, CH*CH*CH$_2$), 6.57–6.65 (1H, m, Ph*CH*CH), 7.21–7.26 (1H, m, ArC*H*), 7.29–7.34 (2H, m, ArC*H*), 7.38–7.42 (2H, m, ArC*H*), ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ_C: 25.6 (OCH$_2$CH$_2$*C*H$_2$), 29.4 (OCH$_2$*C*H$_2$), 33.7 (*C*H$_2$(CHCH$_2$), 70.4 (O*C*H$_2$), 71.6 (Ar*C*HOCH$_3$), 114.7 (CH*C*H$_2$), 126.5 (ArCH*C*H), 126.6(Ar*C*HCH), 127.7 (Ar*C*(4)H), 128.7 (Ar*C*(3,5)H), 132.3 (Ar*C*(2,6)H), 136.9 (Ar*C*(1)H), 138.9 (*C*HCH$_2$); HRMS (APCl$^+$) $C_{15}H_{21}O$ $[M+H]^+$ found 217.1586, requires 217.1587 (–0.4 ppm).

*From (E)-3-phenylprop-2-en-1-ol **68**:* Following **General Procedure F**, (*E*)-3-phenylprop-2-en-1-ol **68** (54 mg, 0.4 mmol) and 5-hexen-1-ol **240** (240 µL, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 40 °C for 16 h. The crude product was purified by silica-gel

column chromatography (petrol/EtOAc, 100:0 to 95:5, R_f: 0.42) to give title compound **251** (54 mg, 62%) as a colourless oil, with spectroscopic data as above.

2-hydroxy-4,5-dioxo-2-(perfluorophenyl)-1,3,2-dioxaborolanide, 255



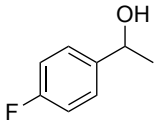
255

Pentafluorophenylboronic acid **48** (0.50 g, 2.36 mmol) and oxalic acid **62** (0.42 g, 4.7 mmol) were dissolved in $MeNO_2$ (12 mL) and the reaction heated at 90 °C for 16 h. The reaction was cooled to rt and concentrated under reduced pressure to give boronate ester complex **255** (0.69 g, 97%) as a white powder. Analysis by NMR showed one predominant species in *d*$_6$-DMSO, while multiple species in equilibria were observed in *d*$_3$-$MeNO_2$ (vide infra). mp 147–148 °C and 180–182 °C; ν_{max} (film) 1772, 1697, 1411, 1261, 962; $^{19}F\{^1H\}$ NMR (470 MHz, *d*$_6$-DMSO) δ_F: –164.6– –164.4 (m, ArC(4)F), –158.7 (t, $^3J_{FF}$ 21.0, ArC(3,5)F), –134.6– –134.5 (m, ArC(2,6)F); $^{11}B\{^1H\}$ NMR (160 MHz, *d*$_6$-DMSO) δ_B: 5.7; $^{13}C\{^1H\}\{^{19}F\}$ NMR (126 MHz, *d*$_6$-DMSO) δ_C: 136.5 (ArC(3,5)F), 139.2 (ArC(4)F), 147.8 (ArC(2,6)F), 161.0 (O_2CCO_2), 161.2 (O_2CCO_2), ArC(1)B not observed. Crystals for X-ray analysis were obtained directly from the powder.

7.4 Chapter III

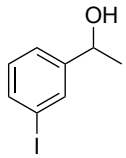
7.4.1 Secondary Benzylic Alcohols

1-(4-Fluorophenyl)ethan-1-ol, 283



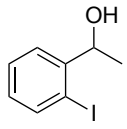
Following **General Procedure C**, 1-(4-fluorophenyl)ethan-1-one (2.0 mL, 16.5 mmol) and $NaBH_4$ (1.25 g, 33 mmol) were reacted in MeOH (83 mL). The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 80:20 to 70/30, R_f: 0.31) to give title compound **283** (1.94 g, 84%) as a colourless oil, with spectroscopic data in accordance with the literature.[148] H NMR (300 MHz, $CDCl_3$) δ_H: 1.48 (3H, d, *J* 6.5, CHC*H*$_3$), 4.89 (1H, q, *J* 6.4, C*H*CH_3), 6.97–7.10 (2H, m, ArC(3,5)*H*), 7.28–7.41 (2H, m, Ar(2,6)*H*).

1-(3-Iodophenyl)ethan-1-ol, 284



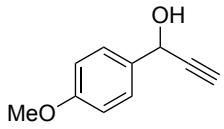
Following **General Procedure C**, 1-(3-iodophenyl)ethan-1-one (1.5 mL, 10 mmoL) and $NaBH_4$ (0.76 g, 20 mmol) were reacted in MeOH (50 mL). The reaction did not require further purification to give title compound **284** (2.36 g, 96%) as a colourless oil, with spectroscopic data in accordance with the literature.[170] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.46 (3H, d, *J* 6.4, CHC*H*$_3$), 5.07 (1H, q, *J* 6.4, C*H*CH_3), 6.97 (1H, td, *J* 1.8, 7.5, ArC*H*), 7.31–7.44 (1H,m, ArC*H*), 7.53–7.61 (1H, m, ArC*H*), 7.76–7.83 (1H, m, ArC*H*).

1-(2-Iodophenyl)ethan-1-ol, 285



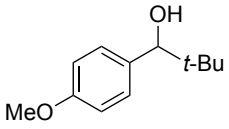
Following **General Procedure C**, 1-(2-iodophenyl)ethan-1-one (1.5 mL, 10 mmol) and $NaBH_4$ (0.76 g, 20 mmol) were reacted in MeOH (50 mL). The reaction did not require further purification to give title compound **285** (2.35 g, 95%) as a colourless oil, with spectroscopic data in accordance with the literature.[171] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.48 (3H, d, *J* 6.5, CHC*H*$_3$), 4.85 (1H, q, *J* 6.4, C*H*CH$_3$), 7.08 (1H, t, *J* 7.8, ArC*H*), 7.30–7.41 (1H, m, ArC*H*), 7.52–7.60 (1H, m, ArC*H*), 7.71–7.77 (1H, m, ArC*H*).

1-(4-Methoxyphenyl)prop-2-yn-1-ol, 286



Following **General Procedure C**, 4-methoxybenzaldehyde (1.2 mL, 9.8 mmol) and ethynylMgCl (0.5 M in THF/Toluene, 24 mL, 11.8 mmol) were reacted in THF (24 mL). The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 90:10 to 70:30, R_f: 0.33) to give title compound **286** (1.21 g, 76%) as yellow oil, with spectroscopic data in accordance with the literature.[98] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.67 (1H, d, *J* 2.3, CC*H*), 3.82 (3H, s, OC*H*$_3$), 5.43 (1H, q, *J* 6.2, ArC*H*OH), 6.82–6.99 (2H, m, ArC(3,5)*H*), 7.42–7.58 (2H, m, ArC(2,6)*H*).

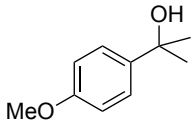
1-(4-Methoxyphenyl)-2,2-dimethylpropan-1-ol, 287



Following **General Procedure C**, 4-methoxybenzaldehyde (1.2 mL, 9.8 mmol) and *tert*-butylMgCl (1.7 M in THF, 7 mL, 11.8 mmol) were reacted in THF (24 mL). The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 95:5 to 85:15, R_f: 0.39) to

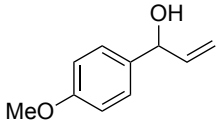
give title compound **287** (1.54 g, 81%) as yellow oil, with spectroscopic data in accordance with the literature.[172] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.91 (9H, s, (C*H*$_3$)$_3$), 3.81 (3H, s, OC*H*$_3$), 4.36 (1H, s, ArC*H*OH), 6.83–6.88 (2H, m, ArC(3, 5)*H*), 7.21–7.25 (2H, m, ArC(2, 6)*H*).

2-(4-Methoxyphenyl)propan-2-ol, 288



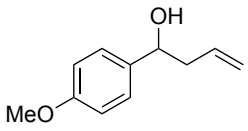
Following **General Procedure C**, 1-(4-methoxyphenyl)ethan-1-one (1.2 mL, 9.8 mmol) and MeMgCl (3 M in Et_2O, 4 mL, 11.8 mmol) were reacted in Et_2O (24 mL). The reaction did not require further purification to give title compound **288** (1.45 g, 90%) as a colourless oil, with spectroscopic data in accordance with the literature.[173] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.57 (6H, s, (C*H*$_3$)$_2$), 3.81 (3H, s, OC*H*$_3$), 6.81–6.93 (2H, m, ArC(3, 5)*H*), 7.38–7.47 (2H, m, ArC(2, 6)*H*).

1-(4-Methoxyphenyl)prop-2-en-1-ol, 289



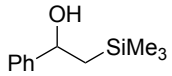
Following **General Procedure C**, 4-methoxybenzaldehyde (1.2 mL, 9.8 mmol) and vinylMgBr (1 M in THF, 12 mL, 11.8 mmol) were reacted in THF (24 mL). The reaction did not require further purification to give title compound **289** (1.43 g, 89%) as a colourless oil, with spectroscopic data in accordance with the literature.[174] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.82 (3H, s, OC*H*$_3$), 5.13–5.19 (1H, m, ArC*H*OH), 5.20–5.22 (1H, m, CHC*H*$_2$), 5.29–5.40 (1H, m, CHC*H*$_2$), 5.97–6.13 (1H, m, C*H*CH$_2$), 6.83–6.94 (2H, m, ArC(3,5)*H*), 7.28–7.36 (2H, m, ArC(2,6)*H*).

1-(4-Methoxyphenyl)but-3-en-1-ol, 290



Following **General Procedure C**, 4-methoxybenzaldehyde (1.2 mL, 9.8 mmol) and allylMgBr (1 M in THF, 12 mL, 11.8 mmol) were reacted in THF (24 mL). The reaction did not require further purification to give title compound 290 (1.68 g, 96%) as a yellow oil, with spectroscopic data in accordance with the literature.[175] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.46–2.54 (2H, m, CHC*H*$_2$), 3.81 (3H, s, OC*H*$_3$), 4.69 (1H, t, *J* 6.5, ArC*H*OH), 5.07–5.23 (2H, m, CHC*H*$_2$), 5.78–5.88 (1H, m, *CH*CH_2), 6.81–6.99 (2H, m, ArC(3,5)*H*), 7.27–7.34 (2H, m, ArC(2,6)*H*).

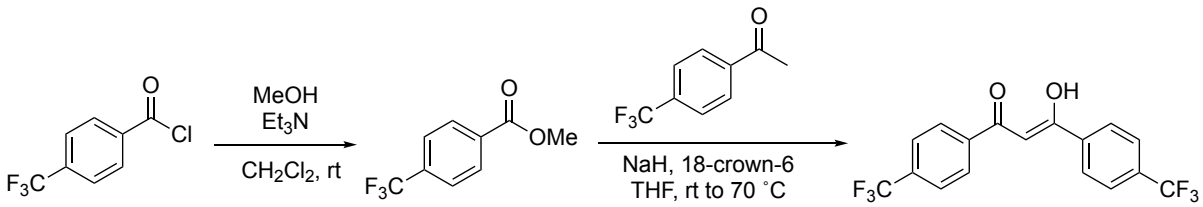
1-Phenyl-2-(trimethylsilyl)ethan-1-ol, 296



Mg (0.37 g, 15 mmol) was suspended in anhydrous Et_2O (2 mL), before 1 or 2 drops of chloromethyltrimethylsilane in anhydrous THF solution (1.5 g, 12 mmol, 1.7 mL) and a crystal of iodine were heated with a heat gun until complete discoloration was shown. After the Mg was activated, the rest of the chloromethyltrimethylsilane solution was added dropwise and stirred for 1 h at rt. To the freshly prepared Grignard was added benzaldehyde (1.0 mL, 10 mmol) at 0 °C and reaction was then stirred for 1 h at rt. The reaction was quenched with NH_4Cl and extracted with EtOAc (3×20 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (Petrol/EtOAc, 95:5 to 80:20 R_f: 0.31) to give title compound **296** (0.73 g, 38%) as a colourless oil, with spectroscopic data in accordance with the literature.[100] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: –0.08 (9H, s, Si(C*H*$_3$)$_3$), 1.12–1.33 (2H, m, C*H*$_2$Si), 4.80–4.90 (1H, m, C*H*COH), 7.27–7.40 (5H, m, ArC*H*).

7.4.2 1,3-Diketone Nucleophiles

1,3-Bis(4-(trifluoromethyl)phenyl)propane-1,3-dione, 294

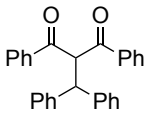


4-(Trifluoromethyl)benzoyl chloride **291** (2.5 g, 12 mmol) was added slowly to a solution of MeOH (0.5 mL, 12.0 mmol) and Et_3N (3.5 mL, 24 mmol) were dissolved in anhydrous CH_2Cl_2 (36 mL) under a N_2 atmosphere. The reaction was stirred at rt for 19 h before being quenched with aq. 1 M HCl (10 mL). The layers were separated and the aqueous extracted with CH_2Cl_2 (3×50 mL). The combined organics were washed successively with aq. $NaHCO_3$, aq. $CuSO_4$, and brine before being dried over $MgSO_4$, filtered and concentrated at reduced pressure to give methyl 4-(trifluoromethyl)benzoate **292** (1.79 g, 73%) as a yellow oil, with spectroscopic data in accordance with the literature.[176] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.96 (3H, s, OC*H*$_3$), 7.71 (2H, d, *J* 8.2, ArC(2,6)*H*), 8.16 (2H, d, *J* 8.0, ArC(3,5)*H*).

Methyl 4-(trifluoromethyl)benzoate **292** (1.22 g, 6.0 mmol) was dissolved in anhydrous THF (2 mL) under an Ar atmosphere before NaH was (0.24 g, 6.0 mmol) was added. Absolute ethanol (2 drops) was added followed by a solution of 1-(4-(trifluoromethyl)phenyl)ethan-1-one **293** (0.57 g, 3 mmol) in anhydrous THF (2 mL) and then a solution of 18-crown-6 (16 mg, 0.06 mmol) in anhydrous THF (2 mL). The reaction was stirred at rt for 30 min before being heated at reflux for 6 h. The solvent was removed under reduced pressure and the crude purified by silica-gel column chromatography (petrol/PhMe, 50:50, R_f: 0.68) to give title compound **294** (0.45 g, 45%) as an orange solid, with spectroscopic data in accordance with the literature.[177] mp 124-126 °C {Lit.[177] 130°C}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.88 (1H, s, C*H*), 7.77 (4H, d, *J* 8.2, ArC(2,6)*H*), 8.10 (4H, d, *J* 8.1, ArC(3,5)*H*).

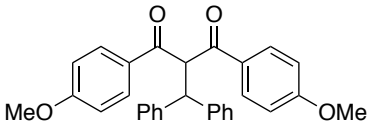
7.4.3 Intermolecular Dehydrative C-C Bond Formation

2-Benzhydryl-1,3-diphenylpropane-1,3-dione, 280



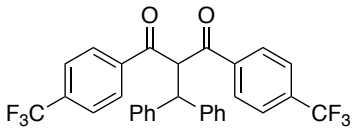
Following **General Procedure G,** benzhydrol **9** (74 mg, 0.4 mmol), 1,3-diphenylpropane-1,3-dione **2**(0.45 g, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$/MeCN (1:1, 8.0 mL) were reacted at rt for 26 h. The crude was purified by trituration with cold Et_2O to give title compound **280** (0.17 g, 70%) as a white solid, with spectroscopic data in accordance with the literature.[178] mp 226 °C {Lit.[178] 227-229 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.35 (1H, d, *J* 11.6, PhCC*H*), 6.38 (1H, d, *J* 11.6, OCC*H*), 7.04–7.11 (2H, m, ArC*H*), 7.17 (4H, t, *J* 7.7, ArC*H*), 7.27 (4H, d, *J* 7.2, ArC*H*), 7.32–7.40 (4H, m, ArC*H*), 7.45–7.55 (2H, m, ArC*H*), 7.82–7.91 (4H, m, ArC*H*).

2-Benzhydryl-1,3-bis(4-methoxyphenyl)propane-1,3-dione, 297



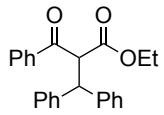
Following **General Procedure G,** benzhydrol **9** (74 mg, 0.4 mmol), 1,3-bis(4-methoxyphenyl)propane-1,3-dione (0.57 g, 2.0 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at rt for 24 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 95:5, R_f: 0.13) to give title compound **297** (0.11 g, 59%) as a yellow solid, with spectroscopic data in accordance with the literature.[178] mp 182 °C {Lit.[178] 182-183.5 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.83 (6H, s, OCH_3), 5.35 (1H, d, *J* 11.7, PhCHC*H*), 6.24 (1H, d, *J* 11.7, ArCOC*H*), 6.80–6.87 (4H, m, ArC*H*), 7.05–7.10 (2H, m, ArC*H*), 7.13 (4H, m, ArC*H*), 7.24–7.30 (4H, m, ArC*H*), 7.85–7.93 (4H, m, ArC*H*).

2-Benzhydryl-1,3-bis(4-(trifluoromethyl)phenyl)propane-1,3-dione, 298



Following **General Procedure G,** benzhydrol **9** (0.15 g, 0.8 mmol), 1,3-bis(4-(trifluoromethyl)phenyl)propane-1,3-dione **294** (0.15 g, 0.4 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at rt for 24 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 95:5, R_f: 0.27) to give title compound **298** (0.17 g, 79%) as a white solid. mp 206-209 °C; ν_{max} (solid) 3061 (C-H), 1699 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 5.30 (1H, d, *J* 11.7, PhCHC*H*), 6.29 (1H, d, *J* 11.7, ArCOC*H*), 7.04–7.11 (2H, m, ArC*H*), 7.17 (4H, t, *J* 7.6, ArC*H*), 7.20–7.25 (4H, m, ArC*H*), 7.62 (4H, d, *J* 8.1, ArC*H*), 7.91 (4H, d, *J* 8.1 ArC*H*); ^{13}C{^{1}H} NMR δ_C: (126 MHz, $CDCl_3$) 52.6 (ArC*C*H), 63.5 (ArCO*C*H), 123.5 (q, $^1J_{C\text{-}F}$ 273, Ar*C*F_3*)*, 125.9 (q, $^3J_{C\text{-}F}$ 3.5, Ar*C*CF_3), 127.2 (Ar*C*CH×2), 128.2 (Ar*C*CH×8), 128.9 (q, $^3J_{C\text{-}F}$ 4.7, Ar*C*CF_3), 134.8 (2C, q, $^2J_{C\text{-}F}$ 32.9, Ar*C(4)*CF_3), 139.5 (Ar*C*CO×2), 141.1 (Ph*C*CH×2), 193.3 (ArC*C*O×2); ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: –63.26 ; HRMS (APCI$^+$) $C_{30}H_{24}F_6O_2N$ $[M+NH_4]^+$ found 544.1710, requires 544.1711 (–0.1 ppm).

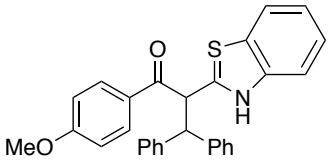
Ethyl 2-benzhydryl-3-oxo-3-phenylpropanoate, 299



Following **General Procedure G,** benzhydrol **9** (0.15 g, 0.8 mmol), ethyl benzoyl acetate **207** (0.8 g, 0.4 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 24 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 99:1 to 90:10, R_f:0.30) to give title compound **299** (0.14 g, 97%) as a white solid, with spectroscopic data in accordance with the literature.[178] mp 133-135 °C {Lit.[178] 138-140 °C}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.94 (3H, t, *J* 7.1, CH_2CH_3), 3.90–3.95 (2H, m, CH_2CH_3), 5.10 (1H, d, *J* 11.8, ArCHC*H*), 5.43 (1H, d, *J* 11.8,

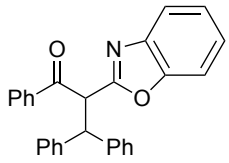
ArCOC*H*), 7.04–7.09 (1H, m, ArC*H*), 7.13–7.22 (3H, m, ArC*H*), 7.23–7.32 (4H, m, ArC*H*), 7.37–7.47 (4H, m, ArC*H* and ArCO), 7.53–7.59 (1H, m, ArCO), 8.01–8.05 (2H, m, ArCO).

2-(Benzo[*d*]thiazol-2-yl)-1-(4-methoxyphenyl)-3,3-diphenylpropan-1-one, 300



Following **General Procedure G,** benzhydrol **9** (74 mg, 0.4 mmol), 2-(benzo[*d*]thiazol-2-yl)-1-(4-methoxyphenyl)ethan-1-one (0.23 g, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 48 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 90:10 to 70:30, R_f: 0.23) to give title compound **300** (0.15 g, 98%) as a pale brown solid, mp 182-184 °C; ν_{max} (solid) 3022 (C-H), 1686 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.81 (3H, s, OCH_3), 5.23 (1H, d, *J* 11.9, ArCHC*H*), 6.30 (1H, d, *J* 11.9, ArCOC*H*), 6.89 (2H, d, *J* 8.7, ArC(3,5)*H*), 7.01–7.06 (1H, m, ArC(4)*H*), 7.07–7.12 (1H, m, ArC(4)*H*), 7.15 (2H, t, *J* 7.6, ArC(2,6)*H*), 7.20 (2H, t, *J* 7.6, Ar(2,6)*H*), 7.24–7.31 (1H, m, HetArNC(3)*H*), 7.33–7.44 (5H, m, HetArNC(4)*H*+ArC(3,5)*H*×2), 7.74 (1H, d, *J* 8.0, HetArNC(5)*H*), 7.92 (1H, d, *J* 8.1, HetArNC(2)*H*), 8.10 (2H, d, *J* 8.7, ArC(2,6)*H*); ^{13}C{^{1}H} NMR δ_C: (126 MHz, $CDCl_3$) 54.9 (ArCH*C*H), 55.6 (O*C*H_3), 56.8 (ArCHOC*C*H), 114.0 (ArC(3,5)*H*), 121.7 ((HetArN*C*H), 123.0 (HetArN*C*H), 125.1 (HetArN*C*H), 125.9 (HetArN*C*H), 126.4 (Ar*C*H), 126.8 (Ar*C*H), 127.8 (Ar*C*H×2), 128.6 (Ar*C*H), 128.8 (Ar*C*H), 129.6 (ArCH), 131.4 (Ar*C*H), 135.7 (HetArN*C*), 141.3 (Ar*C*H), 142.3 (Ar*C*H), 152.2 (HetArN*C*), 164.0 (Ar*C*(4)), 167.9(SAr*C*N), 194.6(ArC*C*O); HRMS (APCI$^+$) $C_{29}H_{24}NO_2S$ $[M+H]^+$ found 450.1521, requires 450.1522 (–0.3 ppm).

2-(Benzo[*d*]oxazol-2-yl)-1,3,3-triphenylpropan-1-one, 301

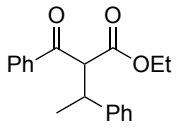


Following **General Procedure G**, benzhydrol **9** (74 mg, 0.4 mmol), 2-(benzo[*d*]oxazol-2-yl)-1-phenylethan-1-one (0.19 g, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and

oxalic acid **62** (3.6 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 48 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 90:10 to 70:30, R_f: 0.23) to give title compound **301** (79 mg, 49%) as a white solid. mp 215.4-218.1 °C {Lit.[38] 122-124 °C}; ν_{max} (film) 3059(C-H Ar), 3030 (C-H alkane), 1700 (C=O ketone), 1540 (C=C Ar), 1069 (C-N), 937 (C=C Ar); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 5.40 (1 H, d, *J* 12, ArC*H*), 6.07 (1 H, d, *J* 12, ArCOC*H*), 6.98–7.07 (1H, m, ArC(4)*H*), 7.09–7.14 (3H, m, ArC*(4)H* and ArC*(3,5)H*), 7.20–7.27 (4H, m, ArC*(3,5)H* and HetNArC*(4,3)H*), 7.30–7.34 (2H, m, ArC(2,6)*H*), 7.34–7.38 (2H, m, ArC(2,6)*H*), 7.41–7.47 (3H, m, ArC(3,5)*HCO and* HetOArC*(2)H*), 7.52–7.56 (1H, m, ArC(4)*HCO),* 7.58–7.62 (1H HetOArC*(5)H*), 7.98–8.13 (2H, m, ArC(2,6)*H*CO); ^{13}C{^{1}H} NMR δ_C: (126 MHz, $CDCl_3$) 51.8 (ArCH*C*H) 52.6 (ArCO*C*H), 110.6 (HetOAr*C*(2)H), 120.0 (HetOAr*C*(5)H), 124.3 (HetOAr*C*(3)H), 125.0 (HetOAr*C*(4)H), 126.8 (Ar*C*(4)H×2), 127.8 (Ar*C*(2,6)H), 128.0 (Ar*C*(2,6)H), 128.6 (Ar*C*(3,5)H), 128.7 (Ar*C(3,5)*H, 128.8 (Ar*C*(3,5)HCO), 128.8 (Ar*C*(2,6)HCO), 133.7 (Ar*C*(4)*HC*O), 136.3 (Ar*C*(1)*C*O), 140.9 (HetOArC(1)), 141.2 (Ar*C(1)*), 141.6 (Ar*C(1)*), 150.9 (HetNAr*C(6)*), 161.7(OAr*C*N), 193.2 (ArC*C*O); HRMS (NSI$^+$) $C_{28}H_{22}O_2N$ $[M+H]^+$ found 404.1645, requires 404.1645 (+0.0 ppm).

7.4.4 Use of ethylbenzoylacetates

Ethyl 2-benzoyl-3-phenylbutanoate, 306a/306b



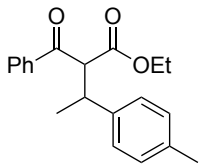
Following **General Procedure H,** 1-phenylethan-1-ol **1** (0.10 g, 0.8 mmol), ethylbenzoylacetate **207** (77 mg, 0.4 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 16 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 98:2 to 90:10 R_f: 0.19) to give combined **306a** and **306b** diastereoisomers (57:43 dr) (0.21 g, 98%) as a colourless oil, with spectroscopic data in accordance with the literature.[95]

Data for major diastereoisomer **306a** : ^{1}H NMR (300 MHz, $CDCl_3$) (*selected)* δ_H: 0.88 (3H, t, *J* 7.1, OCH_2CH_3), 1.25–1.32 (3H, m, CH_3CH), 3.75–3.89 (2H, m, CH_2CH_3), 4.14–4.26 (1H, m,

C*H*CH_3), 4.64 (1H, d, *J* 10.6, ArCC*H*CO), 7.06–7.24 (2H, m, ArC*H*), 7.28–7.41 (3H, m, ArC*H*), 7.44–7.55 (2H, m, ArC*H*), 7.57–7.64 (1H, m, ArC*H*), 8.07–8.14 (2H, m, ArC*H*).

Data for minor diastereoisomer **306b** : ^{1}H NMR (300 MHz, $CDCl_3$) (*selected)* δ_H: 1.19–1.24 (3H, m, OCH_2CH_3), 3.75–3.89 (2H, m, CH_2CH_3), 4.14–4.26 (1H, m, C*H*CH_3), 4.69 (1H, d, *J* 10.6, COC*H*CO), 7.06–7.24 (2H, m, ArC*H*), 7.28–7.41 (3H, m, ArC*H*), 7.57–7.64 (1H, m, ArC*H*), 7.80–7.89 (2H, m, ArC*H*), 7.92–8.01 (2H, m, ArC*H*).

Ethyl 2-benzoyl-3-(*p*-tolyl)butanoate, 308a/308b



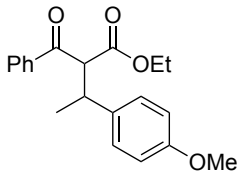
Following **General Procedure H,** 1-(*p*-tolyl)ethan-1-ol (0.87 g, 6.4 mmol), ethylbenzoylacetate **207** (0.62 g, 3.2 mmol), pentafluorophenylboronic acid **48** (34 mg, 0.16 mmol) and oxalic acid **62** (29 mg, 0.32 mmol) in $MeNO_2$ (64 mL) were reacted at 90 °C for 24 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 98:2 to 90:10 R_f: 0.22) to give combined **308a** and **308b** diastereoisomers (54:46 dr) (0.97 g, 97%) as a colourless oil. ν_{max} 2973 (C–H), 1733 (C=C), 1685 (C=C), 1515 (C=C);

Data for major diastereoisomer **308a**: ^{1}H NMR (300 MHz, $CDCl_3$) (*selected)* δ_H: 0.93 (3H, t, *J* 7.1, C*H*$_3$), 1.24–1.29 (3H, m, C*H*$_3$CH), 2.34 (3H, ArC*H*$_3$), 3.77–3.91 (2H, m, C*H*$_2$CH$_3$), 4.18–4.32 (1H, m, C*H*CH_3), 4.64 (1H, d, *J* 10.7, ArCOC*H*CO), 6.98–7.03 (2H, m, ArC*H*), 7.10–7.16 (2H, m, ArC*H*), 7.49–7.55 (2H, m, ArC*H*), 7.60–7.66 (1H, m, ArC*H*), 8.10–8.15 (2H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 13.8 (CH_2CH_3), 20.5 ($CHCH_3$), 21.1 (CH_3), 39.4 ($CHCH_3$), 46.2 (CH_2CH_3), 61.3 (ArCOCHCO), 127.4 (Ar*C*(2,6)H), 128.6 (Ph*C*H), 128.9 (Ph*C*H), 129.2 (Ar*C*(3,5)H), 133.8 (Ph*C*H), 136.1 (Ph*C(1)*), 136.9 (Ar*C*(4)Me), 140.6 (Ar*C*), 168.2 (*C*OOEt), 193.8 (Ph*C*O); HRMS (ESI$^+$) $C_{20}H_{22}O_3Na$ $[M+Na]^+$ found 333.1468, requires 333.1558 (+0.95 ppm).

Data for minor diastereoisomer **308b**: ^{1}H NMR (300 MHz, $CDCl_3$) (*selected)* δ_H: 1.19–1.24 (3H, m, C*H*$_3$), 2.24 (3H, ArC*H*$_3$), 3.77–3.91 (2H, m, C*H*$_2$CH$_3$), 4.18–4.32 (1H, m, C*H*CH_3), 4.69 (1H, d, *J* 10.5, ArCOC*H*CO), 7.10–7.16 (2H, m, ArC*H*), 7.20–7.25 (3H, m, ArC*H*), 7.49–7.55 (2H, m,

ArC*H*), 7.60–7.66 (1H, m, ArC*H*), 7.86–7.90 (2H, m, ArC*H*); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) (*selected)* δ_C: 14.2 ($CH_2\mathit{C}H_3$), 20.9 ($CH\mathit{C}H_3$), 21.2 ($\mathit{C}H_3$), 40.0 ($\mathit{C}HCH_3$), 46.2 ($\mathit{C}H_2CH_3$), 61.6 (ArCO*C*HCO), 127.7 (Ar*C*(2,6)H), 133.9 (Ar*C*H), 136.4 (Ar*C*(1)), 137.1 (Ar*C*(4)Me), 141 (Ar*C*), 168.9 (*C*OOEt), 194.1 (Ar*C*O).

Ethyl 2-benzoyl-3-(4-methoxyphenyl)butanoate, 309a/309b

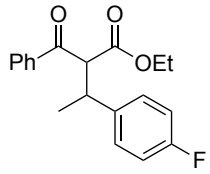


Following **General Procedure H,** 1-(4-methoxyphenyl)ethan-1-ol **17** (61 mg, 0.4 mmol), ethylbenzoylacetate **207** (0.15 g, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 40 °C for 24 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 95:5 to 85:15 R_f: 0.25) to give combined **309a** and **309b** diastereoisomers (54:46 dr) (0.11 g, 80%) as a colourless oil, with spectroscopic data in accordance with the literature.[95]

Data for major diastereoisomer **309a**: ^{1}H NMR (300 MHz, $CDCl_3$) (*selected)* δ_H: 0.93 (3H, t, *J* 7.1, CH_3), 1.24–1.29 (3H, m, CH_3CH), 3.73–3.90 (5H, m, CH_2CH$_3$+OCH_3), 4.06–4.24 (1H, m, CHCH$_3$), 4.58 (1H, d, *J* 10.7, ArCOCHCO), 6.81–6.89 (2H, m, ArC*H*), 7.20–7.26 (2H, m, ArC*H*), 7.33–7.42 (1H, m, ArC*H*), 7.45–7.54 (2H, m, ArC*H*), 8.06–8.15 (2H, m, ArC*H*).

Data for minor diastereoisomer **309a**: ^{1}H NMR (300 MHz, $CDCl_3$) (*selected)* δ_H: 1.15–1.30 (3H, m, CH_3), 3.70 (3H, s, OCH_3) 3.73–3.90 (2H, m, CH_2CH$_3$), 4.06–4.24 (1H, m, CHCH$_3$), 4.63 (1H, d, *J* 10.5, ArCOCHCO), 6.67–6.65 (2H, m, ArC*H*), 7.09–7.18 (2H, m, ArC*H*), 7.45–7.54 (2H, m, ArC*H*), 7.60–7.66 (1H, m, ArC*H*), 7.81–7.89 (2H, m, ArC*H*).

Ethyl 2-benzoyl-3-(4-fluorophenyl)butanoate, 310a/310b

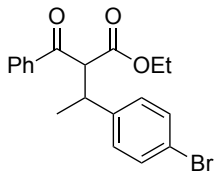


Following **General Procedure H,** 1-(4-fluorophenyl)ethan-1-ol **283** (56 mg, 0.4 mmol), ethylbenzoylacetate **207** (0.16 g, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 μmol) and oxalic acid **62** (3 mg, 40 μmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 24 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 97:3 to 95:5 R_f: 0.25), combined **310a** and **310b** diastereoisomers (58:42 dr) (13 mg, 10%) as a colourless oil. ν_{max} 2970 (C–H), 1734 (C=C), 1685 (C=C), 1508 (C=C);

Data for major diastereoisomer **310a**: ^{1}H NMR (300 MHz, $CDCl_3$) (*selected)* δ_H: 0.91 (3H, t, *J* 7.1, C*H*$_3$), 1.27–1.29 (3H, m, C*H*$_3$CH), 3.75–3.90 (3H, m, C*H*$_2$CH$_3$), 4.13–4.26 (1H, m, C*H*CH$_3$), 4.58 (1H, d, *J* 10.8, ArCOC*H*CO), 6.94–7.04 (2H, m, ArC*H*), 7.27–7.25 (2H, m, ArC*H*), 7.33–7.42 (1H, m, ArC*H*), 7.46–7.54 (2H, m, ArC*H*), 8.06–8.15 (2H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 13.9 (CH$_2$*C*H$_3$), 20.4 (CH*C*H$_3$), 39.2 (*C*HCH$_3$), 41.9 (*C*H$_2$CH$_3$), 61.4 (ArCO*C*HCO), 115.3 (d, $^{2}J_{C\text{-}F}$ 22.0, Ar*C*(3,5)H), 127.7 (Ar*C*H), 128.5 (Ar*C*H), 129.1 (d, $^{3}J_{C\text{-}F}$ 7.4, Ar*C*(3,5)H), 133.5 (Ar*C*H), 136.8 (Ar*C(1)*), 147.1 (d, $^{4}J_{C\text{-}F}$ 3.3, ArC(1)), 162.2 (d, $^{1}J_{C\text{-}F}$ 246.7, ArC(4)H), 162.8 (*C*OOEt), 193.8 (Ar*C*O); ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: –116.1; HRMS (ESI$^-$) $C_{18}H_{19}FO_3$ [M–H]$^-$ found 313.1316, requires 313.1318 (–0.81 ppm).

Data for minor diastereoisomer **310b**: ^{1}H NMR (300 MHz, $CDCl_3$) (*selected)* δ_H: 1.17–1.27 (3H, m, C*H*$_3$), 3.75–3.90 (2H, m, C*H*$_2$CH$_3$), 4.13–4.26 (1H, m, C*H*CH$_3$), 4.62 (1H, d, *J* 10.7, ArCOC*H*CO), 6.94–7.04 (2H, m, ArC*H*), 7.14–7.23 (2H, m, ArC*H*), 7.46–7.54 (2H, m, ArC*H*), 7.57–7.66 (1H, m, ArC*H*), 7.81–7.87 (2H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) (*selected)* δ_C: 14.2 (CH$_2$*C*H$_3$), 20.9 (CH*C*H$_3$), 39.7 (*C*HCH$_3$), 41.9 (*C*H$_2$CH$_3$), 61.8 (CO*C*HCO), 115.7 (d, $^{2}J_{C\text{-}F}$ 22.0, Ar*C*(3,5)H), 128.7 (Ar*C*H), 129.4 (d, $^{3}J_{C\text{-}F}$ 7.4, Ar*C*(3,5)H), 133.9 (Ar*C*), 137.0 (d, $^{4}J_{C\text{-}F}$ 3.2, ArC(1)), 168.1 (*C*OOEt); ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: –116.4.

Ethyl 2-benzoyl-3-(4-bromophenyl)butanoate, 311a/311b



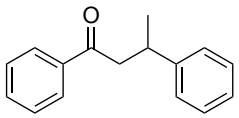
Following **General Procedure H,** 1-(4-bromophenyl)ethan-1-ol **226** (80 mg, 0.4 mmol), ethylbenzoylacetate **207** (0.16 g, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 μmol) and oxalic acid **62** (3 mg, 40 μmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 24 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 95:5 to 85:15 R_f: 0.19), combined **311a** and **311b** diastereoisomers (52:48 dr) (91 mg, 61%) as a colourless oil. ν_{max} 2979 (C–H), 1742 (C=C), 1695 (C=C), 1523 (C=C);

Data for major diastereoisomer **311a**: ^{1}H NMR (300 MHz, $CDCl_3$) (*selected)* δ_H: 0.92 (3H, t, *J* 7.1, C*H*$_3$), 1.18–1.30 (3H, m, C*H*$_3$CH), 3.75–3.90 (3H, m, C*H*$_2$CH$_3$), 4.13–4.30 (1H, m, C*H*CH$_3$), 4.58 (1H, d, *J* 10.8, ArCOC*H*CO), 7.16–7.23 (2H, m, ArC*H*), 7.28–7.34 (2H, m, ArC*H*), 7.36–7.46 (1H, m, ArC*H*), 7.46–7.54 (2H, m, ArC*H*), 8.05–8.14 (2H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 13.9 (CH$_2$*C*H$_3$), 20.3 (CH*C*H$_3$), 39.3 (*C*HCH$_3$), 46.2 (*C*H$_2$CH$_3$), 61.4 (ArCO*C*HCO), 120.4 (Ar*C*(4)Br), 128.7 (Ar*C*H), 128.9 (Ar*C*H), 129.4 (Ar*C*(2,6)H), 133.6 (Ar*C*(3,5)H), 133.9 (Ar*C(4)*H), 136.2 (PAr*C(1)*), 142.7 (Ar*C(1)*), 168.0 (*C*OOEt), 193.4 (Ar*C*O); HRMS (ESI$^-$) $C_{18}H_{19}BrO_3$ $[M–H]^-$ found 373.0518, requires 373.0518 (+0.19 ppm).

Data for minor diastereoisomer **311b**: ^{1}H NMR (300 MHz, $CDCl_3$) (*selected)* δ_H: 1.18–1.30 (3H, m, C*H*$_3$), 3.75–3.90 (3H, m, C*H*$_2$CH$_3$), 4.13–4.30 (1H, m, C*H*CH$_3$), 4.62 (1H, d, *J* 10.7, ArCOC*H*CO), 7.06–7.14 (2H, m, ArC*H*), 7.36–7.46 (2H, m, ArC*H*), 7.47–7.54 (2H, m, ArC*H*), 7.57–7.66 (1H, m, ArC*H*), 7.82–7.89 (2H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) (*selected)* δ_C: 14.2 (CH$_2$*C*H$_3$), 20.7 (CH*C*H$_3$), 39.4 (*C*HCH$_3$), 61.6 (ArCO*C*HCO), 120.7 (Ar*C*(4)Br), 128.8 (Ar*C*H), 129.0 (Ar*C*H), 129.6 (Ar*C*(2,6)H), 133.9 (Ar*C*(3,5)H), 136.9 (Ar*C(1)*), 143.1 (Ar*C(1)*), 168.5 (*C*OOEt), 193.6 (Ar*C*O).

7.4.5 Decarboxylation products

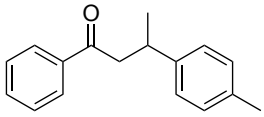
1,3-Diphenylbutan-1-one, 314



Following **General Procedure I**, ethyl 2-benzoyl-3-phenylbutanoate **306** (50 mg, 0.17 mmol), NaOH (4 mL) in EtOH (4 mL) was heated at reflux for 16 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 98:2 to 95:5 R_f: 0.28) to give title compound **314** (11 mg, 29%) as a pale yellow solid, with spectroscopic data in accordance with the literature.[179] mp 67-69 °C {Lit.[179] 68-69 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.34 (3H, d, *J* 6.9, C*H*$_3$), 3.19 (1H, dd, *J* 16.5, 8.3 C*H*^{A}H^B), 3.31 (1H, dd, *J* 16.5, 5.7 C*H*^{A}H^B),3.43–3.57 (1H, m, C*H*CH$_3$), 7.15–7.23 (1H, m, ArC*H*), 7.26–7.36 (4H, m, ArC*H*), 7.39–7.49 (2H, m, ArC*H*), 7.49–7.61 (1H, m, ArC*H*), 7.87–7.99 (2H, m, ArC*H*).

Following **General Procedure J**, ethyl 2-benzoyl-3-phenylbutanoate **306** (50 mg, 0.17 mmol) in MeOH (0.5 mL), was added KOH (0.10 g, 1.7 mmol in 0.5 mL of H_2O) and was heated at reflux for 1 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 98:2 to 90:10 R_f: 0.31) to give title compound **314** (19 mg, 49%) as a colourless oil, with spectroscopic data in as above.

1-Phenyl-3-(*p*-tolyl)butan-1-one, 316

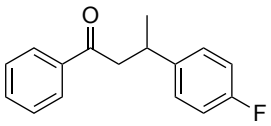


Following **General Procedure I**, ethyl 2-benzoyl-3-(*p*-tolyl)butanoate **308** (0.27 g, 0.85 mmol), NaOH (4 mL) in EtOH (4 mL) was heated at reflux for 16 h. Crude product was purified by silica-gel column chromatography (petrol/EtOAc, 98:2 to 95:5 in presence of Et_3N (1%), R_f: 0.27) to give title compound **316** (0.2 g, 98%) as a viscous yellow oil, with spectroscopic data in accordance with the literature.[179] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.32 (3H, d, *J* 6.9, C*H*$_3$), 2.32 (3H, s, ArC*H*$_3$), 3.17 (1H, dd, *J 16.5,* 8.3 C*H*^{A}H^B), 3.28 (1H, dd, *J* 16.5, 5.7 CH^A*H*^{B}), 3.40–

3.54 (1H, m, C*H*CH_3), 7.07–7.21 (4H, m, ArC*H*), 7.40–7.49 (2H, m, ArC*H*), 7.51–7.61 (1H, m, ArC*H*), 7.89–7.97 (2H, m, ArC*H*).

Following **General Procedure J**, ethyl 2-benzoyl-3-(*p*-tolyl)butanoate **308** (0.27 g, 0.85 mmol) in MeOH (1.7 mL), was added KOH (0.48 g, 8.5 mmol in 2 mL of H_2O) and was heated at reflux for 1 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 97:3 to 95:5 R_f: 0.25) to give title compound **316** (0.12 g, 60%) as a viscous yellow oil, with spectroscopic as above.

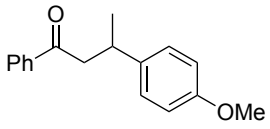
3-(4-Fluorophenyl)-1-phenylbutan-1-one, 315



Following **General Procedure I**, ethyl 2-benzoyl-3-(4-fluorophenyl)butanoate **310** (0.27 g, 0.85 mmol), NaOH (4 mL) in 4 mL of EtOH was heated at reflux for 16 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 98:2 to 95:5 in presence of Et_3N (1%), R_f: 0.23) to give title compound **315** (45 mg, 22%) as a viscous colourless oil, with spectroscopic data in accordance with the literature.[179] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.32 (3H, d, *J* 6.9, C*H*$_3$), 3.17 (1H, dd, *J* 16.6*,* 7.8, C*H*^{A}H^B), 3.27 (1H, dd, *J* 16.6, 6.2CH^A*H*^{B}), 3.4–3.59 (1H, m, C*H*CH_3), 6.92–7.03 (2H, m, ArC(3,5)*H*), 7.19–7.26 (2H, m, ArC(2,6)*H*), 7.39–7.51 (2H, m, ArC*HCO*), 7.52–7.60 (1H, m, ArC*HCO*), 7.88–7.95 (2H, m, ArC*HCO*).

Following **General Procedure J**, ethyl 2-benzoyl-3-(4-fluorophenyl)butanoate **310** (0.18 g, 0.56 mmol) in MeOH (1.2 mL), was added KOH (0.31 g, 5.6 mmol in 1.3 mL of H_2O) and was heated at reflux for 1 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 98:2 to 95:5 R_f: 0.28) to give title compound **315** (58 mg, 43%) as a white solid, with spectroscopic data as above.

3-(4-Methoxyphenyl)-1-phenylbutan-1-one, 317

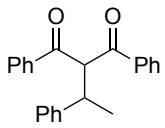


Following **General Procedure I**, ethyl 2-benzoyl-3-(4-methoxy)butanoate **309** (0.20 g, 0.60 mmol), NaOH (4 mL) in EtOH (4 mL) was heated at reflux for 16 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 98:2 to 95:5 R_f: 0.23) to give title compound **317** (0.10 g, 65%) as a white powder, with spectroscopic data in accordance with the literature.[179] mp 66-68 °C {Lit.[179] 64-66 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.31 (3H, d, *J* 6.9, C*H*$_3$), 3.15 (1H, dd, *J* 16.4, 8.1, C*H*^{A}H^B), 3.27 (1H, dd, *J* 16.4, 6.8, CH^A*H*^{B}), 3.38–3.53 (1H, m, C*H*CH$_3$), 3.79 (3H, s, OC*H*$_3$), 6.78–6.91 (2H, m, ArC(3,5)*H*), 7.13–7.24 (2H, m, ArC(2,6)*H*), 7.40–7.50 (2H, m, ArC*H*), 7.51–7.62 (1H, m, ArC*H*), 7.88–7.98 (2H, m, ArC*H*).

Following **General Procedure J**, ethyl 2-benzoyl-3-(4-methoxy)butanoate **309** (0.20 g, 0.60 mmol) in MeOH (0.4 mL), was added KOH (0.38 g, 6 mmol in 1.4 mL of H_2O) and was heated at reflux for 1 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 98:2 to 95:5 R_f: 0.23) to give title compound **317** (15 mg, 10%) as a white solid, with spectroscopic data in accordance as previously reported.

7.4.6 Intermolecular Dehydrative C-C Bond Formation Using a Range of Electrophiles

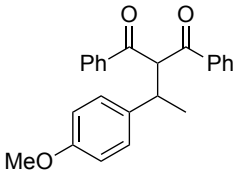
1,3-Diphenyl-2-(1-phenylethyl)propane-1,3-dione, 3



Following **General Procedure G**, 1-phenylethan-1-ol **1** (52 mg, 0.4 mmol), 1,3-diphenylpropane-1,3-dione **2** (0.18 g, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 24 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 93:7 R_f:0.30) to give title compound **3** (0.12 g, 88%) as a white solid, with spectroscopic data in accordance with the literature.[95] mp 120-122 °C {Lit.[95] 128-129 °C}; ^{1}H NMR (400 MHz, $CDCl_3$)

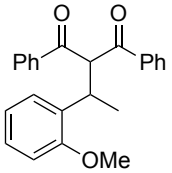
δ_H: 1.37 (3H, d, *J* 7.0, CHC*H*$_3$), 4.04–4.17 (1H, m, ArC*H*), 5.63 (1H, d, *J* 10.1, ArCOC*H*), 7.07–7.15 (1H, m, ArC*H*), 7.17–7.23 (2H, m, ArC*H*), 7.27–7.34 (4H, m, ArC*H* and ArC*H*CO), 7.42–7.50 (1H, m, ArC*H*CO), 7.56–7.62 (1H, m, ArC*H*CO), 7.74–7.79 (2H, m, ArC*H*CO), 8.02–8.13 (2 H, m, ArC*H*CO).

2-(1-(4-Methoxyphenyl)ethyl)-1,3-diphenylpropane-1,3-dione, 318



Following **General Procedure G**, 1-(4-methoxyphenyl)ethan-1-ol **17** (61 mg, 0.4 mmol), 1,3-diphenylpropane-1,3-dione **2** (0.18 g, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 24 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 93:7 R_f:0.26) to give title compound **318** (0.10 g, 70%) as an off-white crystalline solid, with spectroscopic data in accordance with the literature.[95] mp 106–108 °C{Lit.[95] 109–113 °C}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.32 (3H, d, *J* 7.0, CHC*H*$_3$), 3.70 (3H, s, OC*H*$_3$), 4.04 (1H, dq, *J* 10.1, 7.0, ArC*H*), 5.55 (1H, d, *J* 10.1, ArCOC*H*), 6.65–6.80 (2H, m, ArC(3,5)*H*), 7.12–7.21 (2H, m, ArC(2,6)*H*), 7.23–7.32 (2H, m, ArC*HCO*), 7.37–7.49 (3H, m, Ar*CHCO*), 7.50–7.61 (1H, m, ArC*HCO*), 7.69–7.79 (2H, m, ArC*HCO*), 7.95–8.14 (2H, m, Ar*CHCO*).

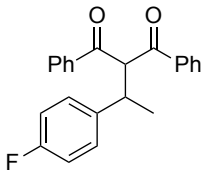
2-(1-(2-Methoxyphenyl)ethyl)-1,3-diphenylpropane-1,3-dione, 319



Following **General Procedure G**, 1-(2-methoxyphenyl)ethan-1-ol **225** (61 mg, 0.4 mmol), 1,3-diphenylpropane-1,3-dione **2** (0.18 g, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 40 °C for 48 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 100:0 to 85:15 R_f: 0.35) to give title compound **319** (0.14 g, 95%) as colorless oil. ν_{max} (film) 3062 (C-

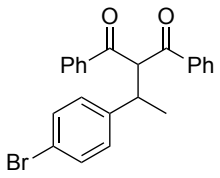
H Ar), 2962 (C-H alkane), 1693 (C=O Ketone), 1662 (C=C Ar), 1250 (C-O ether), 810 (C-H Ar); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.37 (3H, d, *J* 7.1, CHC*H*$_3$), 3.86 (3H, s, OC*H*$_3$), 4.14–4.31 (1H, m, ArCC*H*), 5.99 (1H, d, *J* 8.8, ArCOC*H*), 6.72–6.78 (1H, m, ArC*H*), 6.78–6.86 (1H, m, ArC*H*), 7.07–7.15 (1H, m, ArC*H*), 7.20–7.25 (1H, m, ArC*H*), 7.31–7.38 (2H, m, ArC*H*), 7.41–7.52 (3H, m PhC*H*), 7.52–7.61 (3H, m ArC*H*), 7.81–7.92 (2H, m, ArC*H*), 7.95–8.07 (2H, m, ArC*H*).^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 17.9 (*C*HCH$_3$), 37.03 (CH*C*H$_3$), 55.2(O*C*H$_3$), 61.1 (OC*C*H), 110.8 (Ar*C*(5*)H)*, 120.8 (Ar*C*(3)*H*), 127.8 (Ar*C*(4,6)*H*), 128.6 (Ar*C(3,5)*H×2), 128.8 (Ar*C(2,6)*H×2), 131.7 (ArC(1)), 133.0 (Ar*C(4)*H), 133.3 (Ar*C*(4)H), 137.0 (Ar*C*(1)), 137.6 (Ar*C*(1)) 157.2 (*C*(2)OCH$_3$), 195.5 (*C*O), 196.0 (*C*O); HRMS (APCI$^+$) $C_{24}H_{21}O_3$ $[M+H]^+$ found 357.1486, requires 357.1485 (+0.2 ppm).

2-(1-(4-Fluorophenyl)ethyl)-1,3-diphenylpropane-1,3-dione, 320



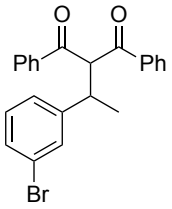
Following **General Procedure G**, 1-(4-fluorophenyl)ethan-1-ol **283** (56 mg, 0.4 mmol), 1,3-diphenylpropane-1,3-dione **2** (0.18 g, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 24 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 100:0 to 85:15 R_f:0.21) to give title compound **320** (0.13 g, 90%) as a white solid, with spectroscopic data in accordance with the literature.[180] mp 109-110 °C {Lit.[180] 110-112 °C}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.35 (3H, d, *J* 7.0, CHC*H*$_3$), 4.07–4.16 (1H, m, ArC*H*), 5.54 (1H, d, *J* 10.2, ArCOC*H*), 6.82–6.90 (2H, m, ArC(3,5)*H*), 7.18–7.25 (2H, m, ArC(2,6)*H*), 7.27–7.35 (2H, m ArC*HCO*), 7.40–7.50 (3H, m, ArC*HCO*), 7.53–7.61 (1H, m ArC*HCO*), 7.71–7.77 (2H, m, ArCHCO), 8.00–8.06 (2H, m, ArC*HCO*).

2-(1-(4-Bromophenyl)ethyl)-1,3-diphenylpropane-1,3-dione, 321



Following **General Procedure G**, 1-(4-bromophenyl)ethan-1-ol **226** (81 mg, 0.4 mmol), 1,3-diphenylpropane-1,3-dione **2** (0.18 g, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 24 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 100:0 to 85:15 R_f:0.21) to give title compound **321** (80 mg, 71%) as a white solid, with spectroscopic data in accordance with the literature.[181] mp 83-85 °C {Lit.[181] 82-84 °C}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.38 (3H, d, *J* 7.0, CHC*H*$_3$), 4.00–4.15 (1H, m, ArCC*H*), 5.55 (1H, d, *J* 10.2, ArCOC*H*), 7.11–7.21 (2H, m, ArC(2,6)*H*), 7.27–7.40 (4H, m, ArC*H*), 7.43–7.56 (2H, m ArC*H*), 7.56–7.67 (2H, m ArC*H*), 7.74–7.84 (2H, m, ArC(3,5)*H*), 8.01–8.11 (2H, m, ArC*H*).

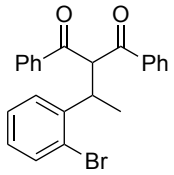
2-(1-(3-Bromophenyl)ethyl)-1,3-diphenylpropane-1,3-dione, 322



Following **General Procedure G**, 1-(3-bromophenyl)ethan-1-ol **227** (81 mg, 0.4 mmol), 1,3-diphenylpropane-1,3-dione **2** (0.18 mg, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 24 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 100:0 to 85:15 R_f:0.21) to give title compound **322** (43 mg, 38%) as a white powder; mp 111-113 °C; ν_{max} (film) 3061 (C-H Ar), 2962 (C-H), 1705 (C=O), 1595 (C=C Ar), 783 (C-H Ar), 758 (C-Br); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.34 (3H, d, *J* 6.9, CHC*H*$_3$), 4.08–4.21 (1H, m, ArCC*H*), 5,59 (1H, d, *J* 10.1, ArCOC*H*), 7.01–7.08 (2H, m, ArC*H*), 7.16–7.24 (2H, m, ArC*H*), 7.40–7.56 (4H, m, ArC*H*), 7.52–7.63 (2H, m ArC*H*), 7.74–7.86 (2H, m ArC*H*), 8.01–8.12 (2H, m, ArC*H*); ^{13}C{^{1}H} NMR δ_C: (126 MHz, $CDCl_3$) 20.2 (*C*HCH$_3$), 40.9 (CH*C*H$_3$), 64.4 (ArCO*C*H), 122.5 (Ar*C*(3)Br), 126.8

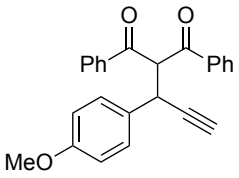
(Ar*C(6)H)*, 128.6 (Ar*C(3,5)H*), 128.7 (Ar*C(3,5)H*), 128.9 (Ar*C*(2,6)H), 129.0 (Ar*C*(2,6)H), 129.9 (Ar*C*(4)H), 130.1(Ar*C*(5)H), 130.8 (Ar*C(2)H*), 133.4 (Ar*C*(4)H), 133.8 (Ar*C*(4)H), 136.7 (Ar*C*(1)), 136.7 (Ar*C*(1)), 146.3 (Ar*C*(1)), 194.4 (CO), 194.7 (CO); HRMS (APCI$^+$) $C_{23}H_{20}BrO_2$ $[M+H]^+$ found 407.0639, requires 407.0641 (–0.5 ppm).

2-(1-(2-Bromophenyl)ethyl)-1,3-diphenylpropane-1,3-dione, 323



Following **General Procedure G**, 1-(2-bromophenyl)ethan-1-ol **228** (89 mg, 0.4 mmol), 1,3-diphenylpropane-1,3-dione **2** (0.18 g, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 48 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 100:0 to 85:15 R_f:0.35) to give title compound **323** (83 mg, 51%) as a white solid, with spectroscopic data in accordance with the literature.[96] mp 121-123 °C {Lit.[96] 122-124 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.35 (3H, d, *J* 7.1, CHC*H*$_3$), 4.43–4.57 (1H, m, ArCC*H*), 5,59 (1H, d, *J* 10.1, ArCOC*H*), 6.97–7.04 (1H, m, ArC*H*), 7.10–7.16 (1H, m, ArC*H*), 7.18–7.23 (1H, m, ArC*H*), 7.33–7.40 (2H, m, ArC*H*), 7.40–7.48 (2H, m, ArC*H*), 7.48–7.61 (3H, m ArC*H*), 7.86–7.93 (2H, m, ArC*H*). 7.93–8.01 (2H, m, ArC*H*).

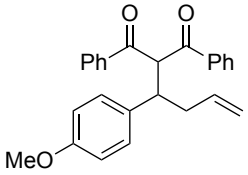
2-(1-(4-Methoxyphenyl)prop-2-yn-1-yl)-1,3-diphenylpropane-1,3-dione, 324



Following **General Procedure G**, 1-(4-methoxyphenyl)prop-2-yn-1-ol **286** (32 mg, 0.2 mmol), 1,3-diphenylpropane-1,3-dione **2** (90 mg, 0.4 mmol), pentafluorophenylboronic acid **48** (2 mg, 10 µmol) and oxalic acid **62** (1 mg, 20 µmol) in $MeNO_2$ (4.0 mL) were reacted at rt for 16 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 100:0 to 80:20 R_f:0.22) to give title compound **324** (72 mg, 98%) as a white solid. mp 106-112 °C;

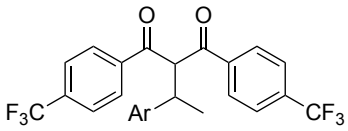
ν_{max} 3030 (C–H), 2916 (C–H), 1716 (C=O), 1597 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.18 (1H, d, *J* 2.5, CH–C–C*H*), 3.71 (3H, s, OC*H*$_3$), 4.92 (1H, dd, *J* 10.2, 2.5, C*H*–C–CH), 5.79 (1H, d, *J* 10.2, ArCOC*H*), 6.71–6.79 (2H, m, ArC(3,5)*H*), 7.27–7.39 (2H, m, ArC(2,6)*H*), 7.41–7.49 (3H, m, ArC*HCO*), 7.53–7.61 (3H, m, ArC*HCO*), 7.69–7.74 (2H, m, ArC*HCO*), 7.98–8.06 (2H, m, ArC*HCO*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 37.5 (*C*HC), 55.4 (O*C*H$_3$), 63.8 (CO*C*HCO), 72.7 (C*C*H), 84.3 (*C*CH), 114.2 (Ar*C*(3,5)H), 128.7 (Ar*C*H), 128.8 (Ar*C*H), 128.8 (Ar*C*H), 128.8 (Ar*C*H), 129.7 (Ar*C*(2,6)H), 130.4 (Ar*C*(1)), 133.5 (Ar*C*(4)H), 133.7 (Ar*C*(4)H), 159 (Ar*C*(4)OMe), 192.9 (*C*O), 193.3 (*C*O); HRMS (ESI$^-$) $C_{24}H_{22}O_4$ $[M–H]^-$ found 374.1500, requires 374.1518 (–4.8 ppm).

2-(1-(4-Methoxyphenyl)but-3-en-1-yl)-1,3-diphenylpropane-1,3-dione, 325



Following **General Procedure G**, 1-(4-methoxyphenyl)but-3-en-1-ol **290** (36 mg, 0.2 mmol), 1,3-diphenylpropane-1,3-dione **2** (90 mg, 0.4 mmol), pentafluorophenylboronic acid **48** (2 mg, 10 µmol) and oxalic acid **62** (1 mg, 20 µmol) in $MeNO_2$ (4.0 mL) were reacted at 90 °C for 24 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 95:5 to 90:10 R_f: 0.20) to give title compound **325** (26 mg, 34%) as a sticky yellow solid. ν_{max} 3060 (C–H), 2931 (C–H), 1685 (C=O), 1511 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.34–2.53 (2H, m, CHC*H*$_2$CH), 3.70 (3H, s, OC*H*$_3$), 4.04-4.14 (1H, m, ArC*H*), 4.80–4.93 (2H, m, CHC*H*$_2$), 5.64 (1H, d, *J* 10.3, ArCOC*H*), 6.64–6.73 (2H, m, ArC(3,5)*H*), 7.06–7.16 (2H, m, ArC(2,6)*H*), 7.27–7.34 (2H, m, ArC*HCO*), 7.36–7.50 (3H, m, ArC*HCO*), 7.50–7.61 (1H, m, ArC*HCO*), 7.69–7.78 (2H, m, ArC*HCO*), 8.01–8.09 (2H, m, ArC*HCO*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 20.6 (ArC*C*H), 38.6 (CH*C*H$_2$), 55.3 (O*C*H$_3$), 64.4 (CO*C*HCO), 113.9 (Ar*C*(3,5)H), 117 (CH*C*H$_2$), 128.6 (Ar*C*(2,6)H), 128.7 (Ar*C*H), 128.8 (Ar*C*H), 129.0 (Ar*C*H), 129.8 (Ar*C*H), 130.1 (Ar*C*H), 133.6 (Ar*C*(4)), 133.7 (Ar*C*(4)), 135.8 (*C*HCH$_2$), 137.2 (Ar*C*(1)), 137.4 (Ar*C*(1)), 158.3 (Ar*C*(4)OMe), 194.7 (*C*O), 195.1 (*C*O); HRMS (ESI$^-$) $C_{26}H_{24}O_3$ $[M–H]^-$ found 384.1712, requires 384.1725 (–3.38 ppm).

2-(1-(4-Methoxyphenyl)ethyl)-1,3-bis(4-(trifluoromethyl)phenyl)propane-1,3-dione, 326

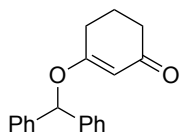


Ar: 4-$MeOC_6H_4$

Following **General Procedure G**, 1-(4-methoxyphenyl)but-3-en-1-ol **17** (36 mg, 0.2 mmol), 1,3-diphenylpropane-1,3-dione **2** (90 mg, 0.4 mmol), pentafluorophenylboronic acid **48** (2 mg, 10 µmol) and oxalic acid **62** (1 mg, 20 µmol) in $MeNO_2$ (4.0 mL) were reacted at 90 °C for 24 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 95:5 to 90:10 R_f: 0.26) to give title compound **326** (20 mg, 20%) as a white solid; mp 86-87 °C; ν_{max} 3028 (C–H), 2923 (C–H), 1727 (C=O), 1537 (C=C), 1321 (C–F); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.34 (3H, d, *J* 7.0, C*H*$_3$), 3.70 (3H, s, OC*H*$_3$), 3.97–4.08 (1H, m, ArC*H*CH_3), 5.47 (1H, d, *J* 10.1, ArCOC*H*), 6.64–6.75 (2H, m, Ar*CH*), 7.07–7.14 (2H, m, Ar*CH*), 7.52–7.60 (2H, m, Ar*CH*), 7.67–7.86 (m, 2H, Ar*CH*), 8.05–8.15 (4H, m, Ar*CH*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 20.4 (*C*H_3), 40.2 (*C*HCH_3), 55.3 (O*C*H_3), 66.6 (CO*C*HCO), 114.1 (Ar*C*(3,5)OMe), 123.5 (q, $^1J_{C\text{-}F}$ 272, CF_3), 125.8 (q, $^3J_{C\text{-}F}$ 4, Ar*C*(3,5)CF_3), 128.8 (q, $^4J_{C\text{-}F}$ 1, Ar*C*(2,6)CF_3), 134.9 (q, $^2J_{C\text{-}F}$ 31.8, Ar*C*(4)CF_3), 139.6 (Ar*C*(1)CF_3), 142.8 (ArC(1)OMe), 160.4 (ArC(4)OMe), 193.9 (*C*O); ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: –64.26 ; HRMS (ESI$^-$) $C_{26}H_{20}F_6O_3$ $[M–H]^-$ found 494.1313, requires 494.1317 (–0.74 ppm).

7.4.7 Use of cyclic 1,3-diketones

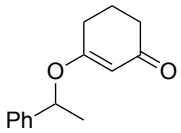
3-(benzhydryloxy)cyclohex-2-en-1-one, 328



Following **General Procedure G**, cyclohexane-1,3-dione **327** (43 mg, 0.4 mmol), benzhydrol **9** (0.15 g, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 40 °C for 16 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 90:10 to 40:60 R_f: 0.12) to give title compound **328** (81 mg, 73%) as a yellow oil. ν_{max} 3029 (C–H), 2934 (C–H), 1646 (C=C),

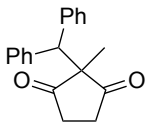
1610 (C=C), 1582 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.91–2.09 (2H, m, *C*H$_2$C*H$_2$C*H$_2$), 2.31 (2H, dd, *J* 7.3, 5.9, *C*H$_2$CH$_2$*CH$_2$*COCH), 2.55 (2H, t, *J* 6.2, CO*CH$_2$*CH$_2$*C*H$_2$), 5.37 (1H, s, C*H*), 6.11 (1H, s, OC*H*), 7.28–7.39 (10H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 20.7 (CH$_2$*C*H$_2$CH$_2$), 29.4 (CO*C*H$_2$), 36.8 (CO*C*H$_2$), 76.4 (Ar*C*HAr), 105.5 (CO*C*HCO), 126.8 (Ar*CH*), 127.4 (ArCH), 127.6 (Ar*CH*), 127.7 (Ar*CH*), 128.4 (ArCH), 128.6 (ArCH), 128.7 (ArCH), 128.9 (ArCH), (139.8 (ArC(1)), 144.0 (Ar*C*(1)), 176.6 (COCH*C*O), 199.9 (*C*O); HRMS (ESI$^-$) $C_{18}H_{18}O_2$ [M–H]$^-$ found 377.1202, requires 377.1207 (–1.82 ppm).

3-(1-Phenylethoxy)cyclohex-2-en-1-one, 329



Following **General Procedure G**, cyclohexane-1,3-dione **327** (87 mg, 0.8 mmol), 1-phenyl ethanol **1** (49 mg, 0.4 mmol, 50 µL), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at rt for 16 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 80:10 to 60:40 R_f: 0.19) to give title compound **329** (21 mg, 25%) as a yellow oil with spectroscopic data in accordance with the literature.[103] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.58 (1H, d, *J* 6.4, C*H$_3$*), 1.90–2.03 (2H, m, *C*H$_2$C*H$_2$*C*H$_2$), 2.25–2.34 (2H, m, *C*H$_2$CH$_2$*CH$_2$*COCH), 2.45–2.50 (2H, m, CO*CH$_2$*CH$_2$*C*H$_2$), 5.20 (1H, q, *J* 6.4, OC*H*), 5.28 (1H, s, C*H*), 7.21–7.31 (2H, m, ArC*H*), 7.31–7.42 (3H, m, ArC*H*).

2-Benzhydryl-2-methylcyclopentane-1,3-dione, 331

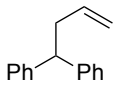


Following **General Procedure G**, 2-methylcyclopentane-1,3-dione **330** (90 mg, 0.8 mmol), benzhydrol **9** (74 mg, 0.4 mmol, 50 µL), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 16 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 95:5 to 80:20 R_f: 0.23) to give title compound **331** (0.11 g, 93%) as a light yellow solid. mp 132-133 °C; ν_{max}

3030 (C–H), 2917 (C–H), 1716 (C=C), 1598 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.11 (3H, s, C*H*$_3$), 1.95–2.16 (2H, m, *C*H$_2$C*H*$_2$), 2.43–2.72 (2H, m, CH$_2$*CH*$_2$), 4.36 (1H, s, C*H*), 7.16–7.26 (4H, m, ArC*H*), 7.27–7.33 (2H, m, ArC*H*), 7.41–7.47 (4H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 20.2 (C*C*H$_3$), 36.1 (*C*H$_2$*C*H$_2$), 58.5 (Ar*C*HAr), 60.5 (*C*CH$_3$), 127.3 (ArCH), 128.7 (ArCH), 129.7 (ArCH), 139.7 (ArC(1)), 217.8 (*C*O); HRMS (ESI$^+$) $C_{19}H_{18}O_2Na$ [M+Na]$^+$ found 301,1220 requires 301.1222 (+4.85 ppm).

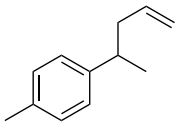
7.4.8 Intermolecular Dehydrative Allylation

But-3-ene-1,1-diyldibenzene, 332



Following **General Procedure K,** benzhydrol **9** (74 mg, 0.4 mmol), allyltrimethylsilane **262** (320 µL, 2 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 16 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 95:5 R_f: 0.33) to give title compound **332** (80 mg, 96%) as a colourless oil, with spectroscopic data in accordance with the literature.[182] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.79–2.90 (2H, m, C*H*$_2$CH), 4.04 (1H, t, *J* 7.9, ArC*H*Ar), 4.94–5.12 (2H, m, CH$_2$CHC*H*$_2$), 5.66–5.84 (1H, m, CH$_2$C*H*CH$_2$), 7.15–7.36 (10H, m, ArC*H*×2).

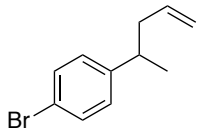
1-Methyl-4-(pent-4-en-2-yl)benzene, 333



Following **General Procedure K**, 1-(*p*-tolyl)ethan-1-ol (54 mg, 0.4 mmol), allyltrimethylsilane **262** (130 µL, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at rt for 16 h. ^{1}H NMR catalysis of the crude reaction mixture showed 100% conversion. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 98:2 R_f: 0.31) to give title compound **333** (37 mg, 40%) as a colourless oil, with spectroscopic data in accordance with the literature.[183] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.23 (3H, d, *J* 6.9, C*H*$_3$), 2.08–2.52 (5H, m, C*H*$_2$CH+C*H*$_3$), 2.67–2.84 (1H,

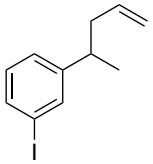
m, CH_2CH), 4.91–5.04 (2H, m, CH_2CHCH_2), 5.60–5.82 (1H, m, CH_2CHCH_2), 7.03–7.16 (4H, m, ArC*H*).

1-Bromo-4-(pent-4-en-2-yl)benzene, 334



Following **General Procedure K**, 1-(4-bromophenyl)ethan-1-ol **226** (80 mg, 0.4 mmol), allyltrimethylsilane **262** (130 µL, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at rt for 16 h. ^{1}H NMR catalysis of the crude reaction mixture showed 100% conversion. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 90:10 R_f: 0.36) to give title compound **334** (51 mg, 43%) as a colourless oil, with spectroscopic data in accordance with the literature.[183] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.22 (3H, d, *J* 7.0, C*H*$_3$), 2.16–2.40 (2H, m, C*H*$_2$CH), 2.67–2.84 (1H, m, CH_2CH), 4.90–5.04 (2H, m, CH_2CHCH_2), 5.60–5.80 (1H, m, CH_2CHCH_2), 6.96–7.14 (2H, m, ArC(2,6)*H*), 7.32–7.49 (2H, m, ArC(3,5)*H*).

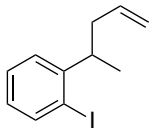
1-Iodo-3-(pent-4-en-2-yl)benzene, 336



Following **General Procedure K**, 1-(3-iodophenyl)ethan-1-ol **284** (100 mg, 0.4 mmol), allyltrimethylsilane **262** (130 µL, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 16 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 95:5 R_f: 0.33) to give title compound **336** (45 mg, 41%) as a colourless oil. ν_{max} 3074 (C–H), 2961 (C–H), 1639 (C=C), 1561 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.22 (3H, d, *J* 6.9, C*H*$_3$), 2.17–2.43 (2H, m, C*H*$_2$CH), 2.63–2.79 (1H, m, CH_2CH), 4.91–5.05 (2H, m, CH_2CHCH_2), 5.58–5.77 (1H, m, CH_2CHCH_2), 6.97–7.07 (1H, m, ArC*H*), 7.12–7.19 (1H, m, ArC*H*), 7.48–7.56 (2H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.2 ($CHCH_3$), 39.6 ($CHCH_3$), 42.6 ($CHCH_2CH$), 94.6 (ArC(3)I),

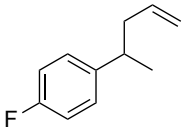
116.5 (CH*C*H$_2$), 126.5 (Ar*C*(6)I), 130.2 (Ar*C*(5)I), 135.2 (Ar*C*(4)I), 136.3 (*C*HCH$_2$), 136.7 (Ar*C*(2)I), 149.7 (Ar*C*(1)I); HRMS (ESI$^-$) $C_{10}H_{13}I$ [M–H]$^-$ found 271.0052, requires 271.0062 (–3.65 ppm).

1-Iodo-2-(pent-4-en-2-yl)benzene, 337



Following **General Procedure K**, 1-(2-iodophenyl)ethan-1-ol **285** (100 mg, 0.4 mmol), allyltrimethylsilane **262** (130 µl, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at 90 °C for 16 h. Crude product was purified by silica-gel column chromatography (petrol/EtOAc, 95:5 R_f: 0.34) to give title compound **337** (59 mg, 54%) as a colourless oil. ν_{max} 3084 (C–H), 2943 (C–H), 1628 (C=C), 1542 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.21 (3H, d, *J* 6.9, C*H*$_3$), 2.13–2.29 (1H, m, C*H*^{A}*C*H^{B}CH), 2.33–2.47 (1H, m, CH^A*CH*^{B}CH), 3.07–3.23 (1H, m, CH$_2$*CH*), 4.93–5.07 (2H, m, CH$_2$CHC*H*$_2$), 5.64–5.85 (1H, m, CH$_2$C*H*CH$_2$), 6.83–6.94 (1H, m, ArC*H*), 7.14–7.21 (1H, m, ArC*H*), 7.26–7.35 (1H, m, ArC*H*), 7.78–7.86 (1H, m, ArC*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 20.6 (CH*C*H$_3$), 41.7 (CH*C*H$_2$CH), 43.1 (*C*HCH$_3$), 101.7 (Ar*C*(1)I), 116.5 (CH*C*H$_2$), 126.8 (Ar*C*(5)H), 127.9 (Ar*C*(4)H), 128.6 (Ar*C*(6)H), 136.6 (*C*HCH$_2$), 139.7 (Ar*C*(3)H), 148.8 (Ar*C*(1)H); HRMS (ESI$^-$) $C_{10}H_{13}I$ [M–H]$^-$ found 271.0042, requires 271.0052 (–3.65 ppm).

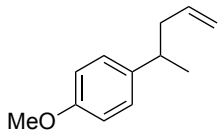
1-Fluoro-4-(pent-4-en-2-yl)benzene, 338



Following **General Procedure K**, 1-(4-fluorophenyl)ethan-1-ol **283** (56 mg, 0.4 mmol), allyltrimethylsilane **262** (130 µl, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at rt for 16 h. ^{1}H NMR catalysis of the crude reaction mixture showed 100% conversion. The crude product was either extracted with EtOAc (3×10 mL), washed with $NaHCO_3$, brine and dried over anhydrous $MgSO_4$ or purified by silica-gel column chromatography (petrol/EtOAc, 98:2 to 95:5 R_f: 0.42)

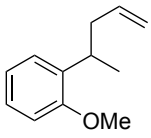
to give title compound **338** (35 mg, 55%) as a colourless oil, with spectroscopic data in accordance with the literature.[183] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.24 (3H, d, *J* 6.9, C*H*$_3$), 2.21–2.45 (5H, m, C*H*$_2$CH+C*H*$_3$), 2.66–2.83 (1H, m, CH$_2$C*H*), 4.88–5.08 (2H, m, CH$_2$CHC*H*$_2$), 5.62–5.81 (1H, m, CH$_2$C*H*CH$_2$), 7.05–7.16 (4H, m, ArC*H*).

1-Methoxy-4-(pent-4-en-2-yl)benzene, 339



Following **General Procedure K**, 1-(4-methoxyphenyl)ethan-1-ol **17** (61 mg, 0.4 mmol), allyltrimethylsilane **262** (130 µL, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were reacted at rt for 16 h. ^{1}H NMR catalysis of the crude reaction mixture showed 100% conversion. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 98:2 R_f: 0.38) to give title compound **339** (54 mg, 76%) as a colourless oil, with spectroscopic data in accordance with the literature.[183] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.23 (3H, d, *J* 7.0, C*H*$_3$), 2.15–2.42 (2H, m, C*H*$_2$CH), 2.67–2.84 (1H, m, CH$_2$C*H*), 3.79 (3H, s, OC*H*$_3$), 4.89–5.06 (2H, m, CH$_2$CHC*H*$_2$), 5.60–5.80 (1H, m, CH$_2$C*H*CH$_2$), 6.77–6.90 (2H, m, ArC(3,5)*H*), 7.05–7.17 (2H, m, ArC(2,6)*H*).

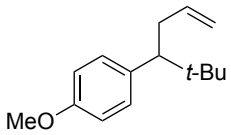
1-Methoxy-2-(pent-4-en-2-yl)benzene, 240



Following **General Procedure K**, 1-(2-methoxyphenyl)ethan-1-ol **225** (31 mg, 0.2 mmol), allyltrimethylsilane **262** (64 µL, 0.4 mmol), pentafluorophenylboronic acid **48** (2 mg, 10 µmol) and oxalic acid **62** (1 mg, 20 µmol) in $MeNO_2$ (4.0 mL) were reacted at 90 °C for 16 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 95:5 to 90:10 R_f: 0.37) to give title compound **340** (13 mg, 37%) as a colourless oil, with spectroscopic data in accordance with the literature.[184] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.21 (3H, d, *J* 6.9, C*H*$_3$), 2.17–2.32 (1H, m, C*H*^{A}C*H*^{B}CH), 2.35–2.48 (1H, m, CH^A*CH*^{B}CH), 3.16–3.34 (1H, m, CH$_2$C*H*), 3,83

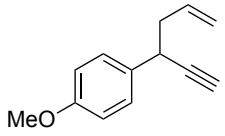
(3H, s, OC*H*$_3$), 4.88–5.07 (2H, m, CH_2CHCH_2), 5.66–5.86 (1H, m, CH_2CHCH_2), 6.72–6.93 (1H, m, ArC*H*), 6.97–7.12 (1H, m, ArC*H*), 7.13–7.21 (2H, m, ArC*H*).

1-(2,2-Dimethylhex-5-en-3-yl)-4-methoxybenzene, 341



Following **General Procedure K**, 1-(4-methoxyphenyl)-2,2-dimethylpropan-1-ol **287** (40 mg, 0.2 mmol), allyltrimethylsilane **262** (64 µL, 0.4 mmol), pentafluorophenylboronic acid **48** (2 mg, 10 µmol) and oxalic acid **62** (1 mg, 20 µmol) in $MeNO_2$ (4.0 mL) were reacted at rt for 16 h. ^{1}H NMR catalysis of the crude reaction mixture showed 100% conversion. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 95:5 to 90:10 R_f: 0.31) to give title compound **341** (38 mg, 86%) as a colourless oil. ν_{max} 3030 (C–H), 2931 (C–H), 1698 (C=C), 1581 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.87 (9H, s, C(C*H*$_3$)$_3$), 2.30–2.59 (3H, m, C*H*$_2$CH+CH$_2$C*H*), 3.79 (3H, s, OC*H*$_3$), 4.74–4.97 (2H, m, CH_2CHCH_2), 5.42–5.58 (1H, m, CH_2CHCH_2), 6.75–6.87 (2H, m, ArC(3,5)*H*), 6.98–7.08 (2H, m, ArC(2,6)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 28.3 (C(*C*H$_3$)$_3$), 34.1 (CH*C*H$_2$CH), 34.2 (*C*(CH$_3$)$_3$), 55.3 (O*C*H$_3$), 56.0 (*C*HC(CH$_3$)$_3$), 113.0 (Ar*C*(3,5)H), 115.1 (CH*C*H$_2$), 130.6 (Ar*C*(2,6)H), 134.5 (Ar*C*(1)), 138.7 (*C*HCH$_2$), 157.9 (Ar*C*(4)OMe); HRMS (ESI$^-$) $C_{17}H_{25}O_3$ [M+CH_3COO^-] found 277.1840, requires 277.1839 (+0.05 ppm).

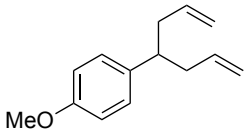
1-(Hex-5-en-1-yn-3-yl)-4-methoxybenzene, 342



Following **General Procedure K**, 1-(4-methoxyphenyl)prop-2-yn-1-ol **286** (40 mg, 0.2 mmol), allyltrimethylsilane **262** (64 µL, 0.4 mmol), pentafluorophenylboronic acid **48** (2 mg, 10 µmol) and oxalic acid **62** (1 mg, 20 µmol) in $MeNO_2$ (4.0 mL) were reacted at rt for 16 h. ^{1}H NMR catalysis of the crude reaction mixture showed 100% conversion. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 95:5 to 90:10 R_f: 0.31) to give title compound **342** (38 mg, 86%) as a colourless oil, with spectroscopic data in accordance

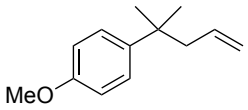
with the literature.[185] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.29 (1H, d, *J* 2.5, CC*H*), 2.44–2.54 (2H, m, C*H*$_2$CH), 3.60–3.71 (1H, m, CH$_2$C*H*), 3.80 (3H, s, OC*H*$_3$), 4.99–5.15 (2H, m, CH$_2$CHC*H*$_2$), 5.75–5.94 (1H, m, CH$_2$C*H*CH$_2$), 6.82–6.92 (2H, m, ArC(3,5)*H*), 7.24–7.30 (2H, m, ArC(2,6)*H*).

1-(Hepta-1,6-dien-4-yl)-4-methoxybenzene, 343



Following **General Procedure K**, 1-(4-methoxyphenyl)but-3-en-1-ol **290** (36 mg, 0.2 mmol), allyltrimethylsilane **262** (64 µL, 0.4 mmol), pentafluorophenylboronic acid **48** (2 mg, 10 µmol) and oxalic acid **62** (1 mg, 20 µmol) in $MeNO_2$ (4.0 mL) were reacted at rt for 5 h. ^{1}H NMR catalysis of the crude reaction mixture showed 100% conversion. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 95:5 R_f: 0.38) to give title compound **343** (37 mg, 91%) as a colourless oil, with spectroscopic data in accordance with the literature.[186] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.20–2.45 (4H, m, C*H*$_2$CH+ C*H*$_2$CH), 2.58–2.63 (1H, m, CH$_2$C*H*), 3.78 (3H, s, OC*H*$_3$), 4.80–5.11 (4H, m, CH$_2$CHC*H*$_2$), 5.53–5.74 (2H, m, CH$_2$C*H*CH$_2$), 6.75–6.89 (2H, m, ArC(3,5)*H*), 6.97–7.12 (2H, m, ArC(2,6)*H*).

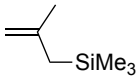
1-Methoxy-4-(2-methylpent-4-en-2-yl)benzene, 344



Following **General Procedure K**, 2-(4-methoxyphenyl)propan-2-ol **288** (33 mg, 0.2 mmol), allyltrimethylsilane **262** (64 µL, 0.4 mmol), pentafluorophenylboronic acid **48** (2 mg, 10 µmol) and oxalic acid **62** (1 mg, 20 µmol) in $MeNO_2$ (4.0 mL) were reacted at rt for 16 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 95:5 R_f: 0.29) to give title compound **344** (26 mg, 68%) as a colourless oil, with spectroscopic data in accordance with the literature.[187] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.28 (6H, s, C(C*H*$_3$)$_2$), 2.33 (2H, t, *J* 7.3, C*H*$_2$CH), 3.80 (3H, s, OC*H*$_3$), 4.86–5.04 (2H, m, CH$_2$CHC*H*$_2$), 5.46–5.64 (1H, m, CH$_2$C*H*CH$_2$), 6.81–6.88 (2H, m, ArC(3,5)*H*), 7.22–7.30 (2H, m, ArC(2,6)*H*).

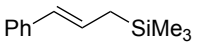
7.4.9 Silanes

Trimethyl(2-methylallyl)silane, 346



Mg (0.54 g, 22 mmol) was suspended in anhydrous THF (2 mL), before 1 or 2 drops of 3-chloro-2-methylpropene in anhydrous THF solution (1.5 g, 16.5 mmol, 1.6 mL) and a crystal of iodine were heated with a heat gun until complete discoloration was shown. After the Mg was activated, the rest of the 3-chloro-2-methylpropene solution was added dropwise followed by addition of TMSCl (1.2 g, 11 mmol, 1.4 mL) and the reaction heated at reflux for 16 h. The reaction cool to rt, quench with NH_4Cl and extracted with EtOAc (3×20 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by distillation (110–112 °C) affording the title compound **346** (1.35 g, 64%) as a colourless oil, with spectroscopic data in accordance with the literature.[188] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.11 (9H, s, Si(C*H*$_3$)$_3$), 1.52 (2H, s, C*H*$_2$Si), 1.74 (3H, s, C*H*$_3$), 4.67–4.65 (2H, m, C*H*$_2$C).

Cinnamyltrimethylsilane, 348

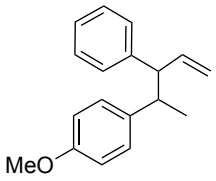


Mg (0.23 g, 9.20 mmol) was suspended in anhydrous THF (2 mL) before 1 or 2 drops of cinnamyl chloride in anhydrous THF solution (0.70 g, 4.60 mmol, 0.6 mL) and a crystal of iodine were heated with a heat gun until complete discoloration was shown. After the Mg was activated, the reaction was cooled to –78 °C and the rest of the cinnamyl chloride solution was added dropwise followed by addition of TMSCl (2.4 mL, 18.4 mmol) and the reaction was stirred at –78 °C for 2 h followed by 30 min at rt. The reaction was quenched with cold water and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The reaction did not require further purification to give title compound **348** (0.80 g, 91%) as a colourless oil, with spectroscopic data in accordance with the literature.[105] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.05

(9H, s, Si(C*H*$_3$)$_3$), 1.63–1.71 (2H, m, CHC*H*$_2$), 6.22–6.26 (2H, m, C*H*C*H*), 7.12–7.20 (1H, m, ArC(4)*H*), 7.27–7.35 (4H, m, ArC*H*).

7.4.10 Control reactions

1-Methoxy-4-(3-phenylpent-4-en-2-yl)benzene, 349a/349b



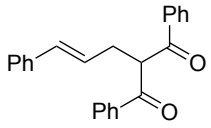
Cinnamyltrimethylsilane **348** (76 mg, 0.4 mmol) was added to a solution of pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in $MeNO_2$ (8.0 mL) were stirred at rt for 5 mins. 1-(4-Methoxyphenyl)ethan-1-ol **17** (30 mg, 0.2 mmol) was added and the reaction reacted at rt for 16 h. Reaction was diluted with toluene and concentrated under reduced pressure to give the crude product, which was further purified by silica-gel column chromatography (Petrol/EtOAc, 99:1 to 95:5 R_f:0.23) to give a combined **349a** and **349b** diastereoisomers (64:36 dr) (73 mg, 77%) as a colourless oil. ν_{max} 3093 (C–H), 2968 (C–H), 1629 (C=C), 1537 (C=C);

Data for major diastereoisomer **349a**: **^{1}H** NMR (300 MHz, $CDCl_3$) (*selected)* δ_H: 1.30 (3H, d, *J* 7.0, C*H*$_3$), 2.94–3.09 (1H, m, ArC*H*CH$_3$), 3.30–3.41 (1H, m, PhC*H*CH), 3.72 (3H, s, OC*H*$_3$*)*, 5.02–5.15 (2H, m, CHC*H*$_2$), 5.99–6.08 (1H, m, C*H*CH$_2$), 6.88–6.95 (2H, m, ArC*H*), 6.96–7.03 (2H, m, ArC*H*), 7.03–7.25 (4H, m, ArC*H*), 7.27–7.38 (1H, m, ArC*H*). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 20.5 (CH*C*H$_3$), 44.2 (*C*HCH$_3$), 55.2 (*C*HCH$_2$CH), 57.7 (O*C*H$_3$), 113.4 (Ar*C*(3,5)H), 115.5 (CH*C*H$_2$), 125.9 (Ar*C*H), 126.4 (Ar*C*(2,6)H), 128.2 (Ar*C*H×2), 137.5 (Ar*C*H), 140.8 (*C*HCH$_2$), 143.6 (Ar*C*(1)), 157.7 (Ar*C*(4)OMe); HRMS (ESI$^-$) $C_{20}H_{23}O_3$ [M+CH$_3$COO$^-$] found 311.1814, requires 311.1686 (+4.22 ppm).

Data for minor diastereoisomer **349b**: **^{1}H** NMR (300 MHz, $CDCl_3$) (*selected)* δ_H: 1.06 (3H, d, *J* 6.9, C*H*$_3$), 2.94–3.09 (1H, m, ArC*H*CH$_3$), 3.30–3.41 (1H, m, ArC*H*CH), 3.80 (3H, s, OC *H*$_3$*)*, 4.68–4.90 (2H, m, CHC*H*$_2$), 5.77–5.92 (1H, m, C*H*CH$_2$), 6.64–6.72 (2H, m, ArC*H*), 6.80–6.87 (2H, m, ArC*H*), 7.03–7.25 (4H, m, ArC*H*), 7.27–7.38 (1H, m, ArC*H*). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C:

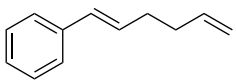
21.0 (CH*C*H$_3$), 44.7 (*C*HCH$_3$), 55.3 (*C*HCH$_2$CH), 58.5 (O*C*H$_3$), 113.6 (Ar*C*(3,5)H), 115.6 (CH*C*H$_2$), 126.8 (Ar*C*(2,6)H), 128.8 (Ar*C*H×2), 158.0 (Ar*C*(4)OMe);

1,3-Diphenyl-2-(1-phenylallyl)propane-1,3-dione, 350



Following **General Procedure G,** cinnamyl alcohol **68** (54 mg, 0.4 mmol) or vinylbenzyl alcohol **67** (54 mg, 0.4 mmol), 1,3-diphenylpropane-1,3-dione **2** (0.18 g, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in MeNO$_2$ (8.0 mL) were reacted at 90 °C for 24 h. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 95.5:0.5 to 85:15 R_f: 0.21) to give title compound **350** (87 mg, 64% from cinnamaldehyde, 66% from vinylbenzyl alcohol) as a yellow solid, with spectroscopic data in accordance with the literature.[95] mp 73-75°C {Lit.[95] 74-76 °C}; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H: 3.02 (2H, td, *J* 7.0, 1.3, CHC*H*$_2$CH), 5.35 (1H, t, *J* 7.0, CHCH$_2$C*H*), 6.20–6.29 (1H, m, CHC*H*CH$_2$), 6.47 (1H, d, *J* 1.3, C*H*CHCH$_2$), 7.15–7.22 (1H, m, CHArC*H*), 7.25–7.27 (4H, m, CHArC*H*), 7.41–7.49 (4H, m, ArC*H*CO), 7.54–7.60 (2H, m, ArC*H*CO), 7.95–8.00 (4H, m, ArCC*H*OC).

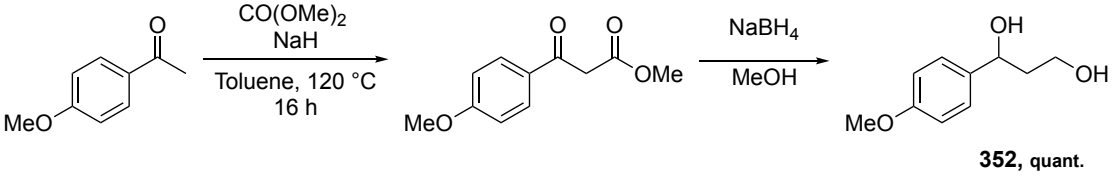
(*E*)-hexa-1,5-dien-1-ylbenzene, 351



Following **General Procedure K**, 1-phenylprop-2-en-1-ol **67** (54 mg, 0.4 mmol) or cinnamyl alcohol **68** (54 mg, 0.4 mmol), allyltrimethylsilane **262** (130 µl, 0.8 mmol), pentafluorophenylboronic acid **48** (4 mg, 20 µmol) and oxalic acid **62** (3 mg, 40 µmol) in MeNO$_2$ (8.0 mL) were reacted at rt for 16 h. ^{1}H NMR catalysis of the crude reaction mixture showed 100% conversion. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 100:0 to 90:10 R_f: 0.36) to give title compound **351** (57 mg, 63%) as a colourless oil, with spectroscopic data in accordance with the literature.[189] ^{1}H NMR (300 MHz, CDCl$_3$) δ_H: 2.18–2.38 (4H, m, C*H*$_2$C*H*$_2$CH), 4.95–5.13 (2H, m, CH$_2$CHC*H*$_2$), 5.78–5.96

(1H, m, CH_2CHCH_2), 6.15–6.31 (1H, m, ArCHC*H*CH_2), 6.35–6.47 (1H, m, ArC*H*CHCH_2), 7.12–7.24 (1H, m, ArC(4)*H*), 7.28–7.38 (4H, m, ArC*H*).

1-(4-Methoxyphenyl)propane-1,3-diol, 352

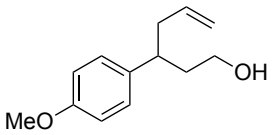


352, quant.

Dimethyl carbonate (1.1 mL, 13.3 mmol) and NaH (0.49 g, 18.65 mmol) were dissolved in toluene (7 mL) and was heated at reflux for 30 min. 4-Methoxyacetophenone was added dropwise over 30 min and the reaction was heated at 120 °C for 16 h. Before cool to rt, add glacial acetic acid until pH=4. The solid obtained was filtered, dissolved in hot water and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The reaction did not require further purification to give methyl 3-(4-methoxyphenyl)-3-oxopropanoate (2.1 g, quant.) as a sticky yellow oil, with spectroscopic data in accordance with the literature.[174] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.75 (3H, s, OC*H*$_3$), 3.88 (3H, s, ArOC*H*$_3$), 3.97 (2H, s, ArCOC*H*$_2$CO), 6.89–7.03 (2H, m, ArC(3,5)*H*), 7.87–8.00 (2H, m, ArC(2,6)*H*).

Following **General Procedure K**, methyl 3-(4-methoxyphenyl)-3-oxopropanoate (2.0 g, 9.61 mmol) and $NaBH_4$ (2.93 g, 77 mmol) were reacted in MeOH (20 mL). The reaction did not require further purification to give title compound **352** (1.68 g, 96%) as a brown oil, with spectroscopic data in accordance with the literature.[190] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.77–1.89 (1H, m, C*H*^{A}H^B), 1.99–2.11 (1H, m, CH^A*H*^{B}), 3.73–3.84 (5H, m, OC*H*$_2$+OC*H*$_3$), 4.44 (1H, dd, *J* 9.0, 4.1, ArC*H*OH), 6.84–6.93 (2H, m, ArC(3,5)*H*), 7.19–7.25 (2H, m, ArC(2,6)*H*).

3-(4-Methoxyphenyl)hex-5-en-1-ol, 353

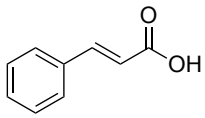


Following **General Procedure K**, 1-(4-methoxyphenyl)propane-1,3-diol **352** (40 mg, 0.2 mmol), allyltrimethylsilane **262** (64 µL, 0.4 mmol), pentafluorophenylboronic acid **48** (2 mg, 10 µmol) and oxalic acid **62** (1 mg, 20 µmol) in $MeNO_2$ (5.0 mL) were reacted at rt for 16 h. ^{1}H NMR catalysis of the crude reaction mixture showed 100% conversion. The crude product gave the title compound **353** (41 mg, quantitative conversion) as a colourless oil. ν_{max} 3233,(OH), 3037 (C–H), 2943 (C–H), 1628 (C=C), 1542 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.15–2.30 (1H, m, ArCHC*H*$_2$), 2.30–2.41 (2H, m, CHC*H*$_2$), 2.63–2.82 (1H, m, C*H*^{A}*C*H^{B}CH), 3.57–3.66 (1H, m, CH^A*CH*^{B}CH), 3.67–3.72 (1H, m, ArC*H*), 3.77 (3H, s, OC*H*$_3$), 4.86–5.21 (2H, m, CH_2CHC*H*$_2$), 5.56–5.93 (1H, m, CH_2C*H*CH_2), 6.76–6.90 (2H, m, ArC(3,5)*H*), 7.04–7.19 (2H, m, ArC(2,6)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 38.7 (CH*C*H_2), 41.6 (CH*C*H_2), 45.8 (C*H**C*H$_2$), 55.4 (O*C*H_3), 61.4 (*C*H_2OH), 114.0 (Ar*C*(3,5)H), 116.2 (CH*C*H$_2$), 128.6 (Ar*C*(2,6)H), 136.2 (Ar*C*(1)), 137.1 (*C*HCH$_2$), 158.1 (Ar*C*(4)OMe);HRMS (ESI$^-$) $C_{13}H_{17}O_2$ [M–H] found 205.1234, requires 205.1207 (–0.58 ppm).

7.5 Chapter IV

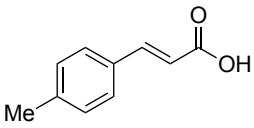
7.5.1 Cinnamic acids

Cinnamic acid, 408



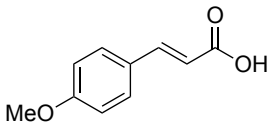
Following **General Procedure L**, malonic acid **403** (10.87 g, 104.5 mmol), pyridine (23 mL, 285 mmol), benzaldehyde (9.70 mL, 95 mmol) and piperidine (0.95 mL, 9.5 mmol) were heated at reflux for 30 min. The crude was purified by recrystallisation from aqueous ethanol to give title compound **407** (12.41 g, 88%) as a white solid, with spectroscopic data in accordance with the literature.[191] mp 132–135 °C {Lit[191] 134–136 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.46 (1H, d, *J* 16.0, C*H*COOH), 7.37–7.45 (3H, m, ArC*(3,4,5)H),* 7.52–7.60 (2H, m, ArC*(2,6) H*), 7.80 (1H, d, *J* 16.0, ArC*H*CH).

(*E*)-3-(*p*-Tolyl)acrylic acid, 409



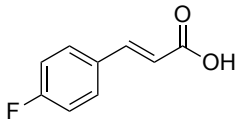
Following **General Procedure L**, malonic acid **403** (10.87 g, 104.5 mmol), pyridine (23 mL, 285 mmol), 4-methylbenzaldehyde (11.20 mL, 95 mmol) and piperidine (0.95 mL, 9.5 mmol) were heated at reflux for 6 h. The crude was purified by recrystallisation from aqueous ethanol to give title compound **409** (14.41 g, 93%) as a white solid, with spectroscopic data in accordance with the literature.[192] mp 199–200 °C {Lit[192] 190–192 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.39 (3H, s, CH_3), 6.42 (1H, d, *J* 16.0, C*H*COOH), 7.19–7.25 (2H, m, ArC(3,5)*H),* 7.43–7.49 (2H, m, ArC(2,6)*H*), 7.78 (1H, d, *J* 16.0, ArC*H*CH).

(*E*)-3-(4-Methoxyphenyl)acrylic acid, 410



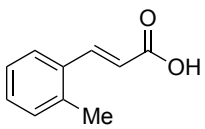
Following **General Procedure L**, malonic acid **403** (10.87 g, 104.5 mmol), pyridine (23 mL, 285 mmol), 4-methoxybenzaldehyde (11.60 mL, 95 mmol) and piperidine (0.95 mL, 9.5 mmol) were heated at reflux for 7 h. The crude was purified by recrystallisation from aqueous ethanol to give title compound **410** (14.35 g, 85%) as a white solid, with spectroscopic data in accordance with the literature.[191] mp 173–178 °C {Lit[191] 175–176 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.85 (3H, s, OC*H*$_3$), 6.33 (1H, d, *J* 15.9, C*H*COOH), 6.86–6.99 (2H, m, ArC(3,5)*H*), 7.47–7.57 (2H, m, ArC(2,6)*H*), 7.75 (1H, d, *J* 15.9, ArC*H*CH).

(*E*)-3-(4-Fluorophenyl)acrylic acid, 411



Following **General Procedure L**, malonic acid **403** (7.41 g, 71.25 mmol), pyridine (11.50 mL, 142.5 mmol), 4-fluorobenzaldehyde (5.0 mL, 47.5 mmol) and piperidine (0.50 mL, 4.8 mmol) were heated at 110 °C for 12 h. The crude was purified by recrystallisation from aqueous ethanol to give title compound **411** (7.20 g, 91%) as a white solid, with spectroscopic data in accordance with the literature.[191] mp 207–209 °C {Lit[191] 205–207 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.37 (1H, d, *J* 16.0, C*H*COOH), 7.05–7.18 (2H, m, ArC(3,5)*H*), 7.49–7.59 (2H, m, ArC(2,6)*H*), 7.74 (1H, d, *J* 16.0, ArC*H*CH).

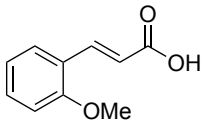
(E)-3-(o-Tolyl)acrylic acid, 412



Following **General Procedure L**, malonic acid **403** (9.34 g, 89.8 mmol), pyridine (20 mL, 244.8 mmol), 2-methylbenzaldehyde (10.0 mL, 81.6 mmol) and piperidine (0.80 mL, 8.2 mmol) were

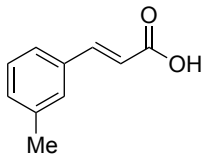
heated at 110 °C for 12 h. The crude was purified by recrystallisation from aqueous methanol to give title compound **412** (10.93 g, 83%) as a white solid, with spectroscopic data in accordance with the literature.[191] mp 176–178 °C {Lit[191] 175–176 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.47 (3H, s, C*H*$_3$), 6.39 (1H, d, *J* 15.8, C*H*COOH), 7.20–7.25 (2H, m, ArC(3,4)*H*), 7.28–7.35 (1H, m, ArC(5)*H*), 7.57–7.64 (1H, m, ArC(6)*H*), 8.10 (1H, d, *J* 15.8, ArC*H*CH).

(E)-3-(2-Methoxyphenyl)acrylic acid,413



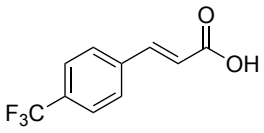
Following **General Procedure L**, malonic acid **403** (9.41 g, 90.5 mmol), pyridine (20 mL, 246.9mmol), 2-methoxybenzaldehyde (10.0 mL, 82.3 mmol) and piperidine (0.80 mL, 8.2 mmol) were heated at 110 °C for 12 h. The crude was purified by recrystallisation from aqueous methanol to give title compound **413** (13.07 g, 89%) as a white solid, with spectroscopic data in accordance with the literature.[192] mp 185–187 °C {Lit[192] 182–184 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.91 (3H, s, OC*H*$_3$), 6.56 (1H, d, *J* 16.1, C*H*COOH), 6.89–7.04 (2H, m, ArC(3,5)*H*), 7.33–7.43 (1H, m, ArC(4)*H*), 7.51–7.58 (1H, m, ArC(6)*H*), 8.10 (1H, d, *J* 16.2, ArC*H*CH).

(E)-3-(*m*-Tolyl)acrylic acid, 414



Following **General Procedure L**, malonic acid **403** (9.73 g, 93.5 mmol), pyridine (20.50 mL, 255 mmol), 3-methylbenzaldehyde (10.0 mL, 85 mmol) and piperidine (0.90 mL, 8.5 mmol) were heated at 110 °C for 12 h. The crude was purified by recrystallisation from aqueous methanol to give title compound **414** (13.07 g, 89%) as a white solid, with spectroscopic data in accordance with the literature.[191] mp 113–116 °C {Lit[191] 116–118 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.38 (3H, s, C*H*$_3$), 6.45 (1H, d, *J* 16.0, C*H*COOH), 7.19–7.26 (1H, m, ArC(4)*H*), 7.29–7.34 (1H, m, ArC(5)*H*), 7.34–7.40 (2H, m, ArC(2,6)*H*), 7.77 (1H, d, *J* 16.0, ArC*H*CH).

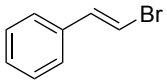
(*E*)-3-(4-(Trifluoromethyl)phenyl)acrylic acid, 415



Following **General Procedure L**, malonic acid **403** (10.7 g, 102.81 mmol), pyridine (22.6 mL, 280.41 mmol), 4-trifluoromethylbenzaldehyde (10.0 mL, 93.5 mmol) and piperidine (0.90 mL, 9.35 mmol) were heated at 110 °C for 12 h. The crude was purified by recrystallisation from aqueous ethanol to give title compound **415** (7.20 g, 78%) as a white solid, with spectroscopic data in accordance with the literature.[191] mp 230–233 °C {Lit[191] 206–208 °C}; ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ_H: 6.54 (1H, d, *J* 16.0, C*H*COOH), 7.63–7.71 (4H, m, ArC*H*), 7.79 (1H, d, *J* 16.0, ArC*H*CH).

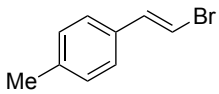
7.5.2 Styrene bromides

(*E*)-(2-Bromovinyl)benzene, 416



Following **General Procedure M**, cinnamic acid **408** (2.0 g, 13.5 mmol), lithium acetate (0.18 g, 2.7 mmol) and NBS (2.64 g, 14.85 mmol) in a mixture of CH_3CN/H_2O (33/1 mL) were stirred at rt for 16 h. The crude was purified by silica-gel column chromatography (Petrol 100, R_f*:* 0.41) to give title compound **416** (1.33 g, 54%) as a colourless oil, with spectroscopic data in accordance with the literature.[193] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.78 (1H, d, *J* 14.0, C*H*CBr), 7.11 (1H, d, *J* 14.0, ArC*H*CH). 7.28–7.35 (5H, m, ArC*H*).

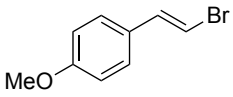
(*E*)-1-(2-Bromovinyl)-4-methylbenzene, 417



Following **General Procedure M**, (E)-3-(4-p-tolyl)acrylic acid, **409** (1.0 g, 6.6 mmol), lithium acetate (90 mg, 1.32 mmol) and NBS (1.29 g, 7.24 mmol) in a mixture of CH_3CN/H_2O (32/1 mL) were stirred at rt for 5.5 h. The crude was purified by silica-gel column chromatography

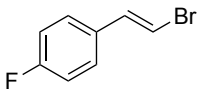
(Petrol/EtOAc 100:0 to 96:4, R_f: 0.44) to give title compound **417** (1.28 g, 99%) as a yellow solid, with spectroscopic data in accordance with the literature.[193] mp 44–46 °C {Lit[193] 45–46 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.33 (3H, s, C*H*$_3$), 6.71 (1H, d, *J* 14.0, C*H*CBr), 7.07 (1H, d, *J* 14.0, ArC*H*CH). 7.11–7.17 (2H, m, ArC(3,5)*H*), 7.17–7.24 (2H, m, ArC(2,6)*H*).

(*E*)-1-(2-Bromovinyl)-4-methoxybenzene, 418



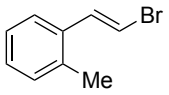
Following **General Procedure M**, (*E*)-3-(4-methoxyphenyl)acrylic acid, **410** (1.0 g, 5.6 mmol), lithium acetate (74 mg, 1.22 mmol) and NBS (1.1 g, 6.18 mmol) in a mixture of CH_3CN/H_2O (27/0.90 mL) were stirred at rt for 5.5 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 100:0 to 98:2, R_f: 0.39) to give title compound **418** (1.18 g, 99%) as a white solid, with spectroscopic data in accordance with the literature.[193] mp 52–55 °C {Lit[193] 53–54 °C} ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.81 (3H, s, OC*H*$_3$), 6.61 (1H, d, *J* 14.0, C*H*CBr), 6.80–6.90 (2H, m, ArC(3,5)*H)*, 7.04 (1H, d, *J* 14.0, ArC*H*CH). 7.19–7.29 (2H, m, ArC(2,6)*H*).

(*E*)-1-(2-Bromovinyl)-4-fluorobenzene, 419



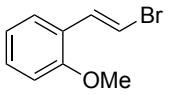
Following **General Procedure M**, (*E*)-3-(4-fluorophenyl)acrylic acid **411** (1.0 g, 6.02 mmol), lithium acetate (79 mg, 1.20 mmol) and NBS (1.1 g, 6.18 mmol) in a mixture of CH_3CN/H_2O (29/0.90 mL) were stirred at rt for 5.5 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 100:0 to 98:2, R_f: 0.39) to give title compound **419** (1.18 g, 99%) as a colourless oil, with spectroscopic data in accordance with the literature.[194] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.70 (1H, d, *J* 14.0, C*H*CBr), 6.98–7.11 (3H, m, ArC*(3,5)H and* ArC*H*CH), 7.24–7.32 (2H, m, ArC(2,6)*H*).

(*E*)-1-(2-Bromovinyl)-2-methylbenzene, 420



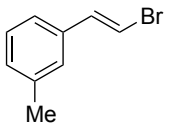
Following **General Procedure M**, (*E*)-3-(*o*-tolyl)acrylic acid **412** (1.0 g, 6.2 mmol), lithium acetate (81 mg, 1.24 mmol) and NBS (1.21 g, 6.78 mmol) in a mixture of CH_3CN/H_2O (30/1.0 mL) were stirred at rt for 6.5 h. The crude was purified by silica-gel column chromatography (Petrol 100, R_f: 0.37) to give title compound **420** (0.44 g, 36%) as a colourless oil, with spectroscopic data in accordance with the literature.[195] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.34 (3H, s, C*H*$_3$), 6.64 (1H, d, *J* 13.8, C*H*CBr), 7.13–7.25 (3H, m, ArC(3,4)*H and* ArC*H*CH), 7.28–7.36 (2H, m, ArC(5,6)*H*).

(*E*)-1-(2-Bromovinyl)-2-methoxybenzene, 421



Following **General Procedure M**, (*E*)-3-(2-methoxyphenyl)acrylic acid **413** (1.0 g, 5.61 mmol), lithium acetate (74 mg, 1.12 mmol) and NBS (1.1 g, 6.17 mmol) in a mixture of CH_3CN/H_2O (27/1.0 mL) were stirred at rt for 8 h. The crude was purified by silica-gel column chromatography (Petrol 100, R_f: 0.37) to give title compound **421** (0.66 g, 55%) as a colourless oil, with spectroscopic data in accordance with the literature.[196] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.86 (3H, s, OC*H*$_3$), 6.86–6.96 (3H, m, ArC*(3,5)H and* C*H*CBr), 7.23–7.35 (3H, m, ArC*(4,6)H and* ArC*H*CH).

(*E*)-1-(2-Bromovinyl)-3-methylbenzene, 422

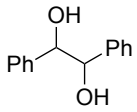


Following **General Procedure M**, (*E*)-3-(*m*-tolyl)acrylic acid **414** (1.0 g, 6.2 mmol), lithium acetate (81 mg, 1.24 mmol) and NBS (1.21 g, 6.78 mmol) in a mixture of CH_3CN/H_2O (30/1.0 mL) were stirred at rt for 6.5 h. The crude was purified by silica-gel column chromatography (Petrol 100, R_f: 0.40) to give title compound **422** (0.44 g, 36%) as a colourless oil, with

spectroscopic data in accordance with the literature.[197] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.35 (3H, s, CH_3), 6.75 (1H, d, *J* 14.0, C*H*CBr), 7.03–7.17 (4H, m, ArC*(2,4,5)H and* ArC*H*CH), 7.18–7.25 (1H, m, ArC(6)*H*).

7.5.3 Diols

1,2-Diphenylethane-1,2-diol, 427a/427b

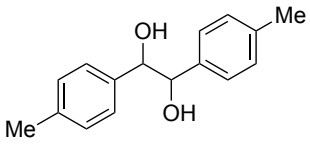


Following **General Procedure N**, benzaldehyde (240 µL, 1.4 mmol), Aluminium powder (20 mg, 2.7 mmol) and potassium hydroxide (0.68 g, 12.15 mmol) in MeOH (2 mL) was stirred for 16 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 80:20 to 60:40, R_f*:* 0.39) to give combined **427a** and **427b** diastereoisomers (53:47 dr) (0,24 g, 96%) as a white solid, with spectroscopic data in accordance with the literature.[198] mp 102–103 °C {Lit[198] 104–105 °C};

*Data for major diastereoisomer **427a***: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.61 (2H, s, *Ar*C*H*C*HAr*), 7.02–7.23 (10H, m, ArC*H*)

*Data for minor diastereoisomer **427b***: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H:4.74 (2H, s, *Ar*C*H*C*HAr*), 7.02–7.23 (10H, m, ArC*H*)

1,2-di-*p*-Tolylethane-1,2-diol, 428a/428b



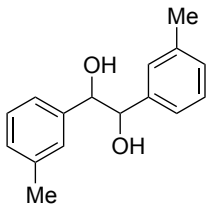
Following **General Procedure N**, 4-methylbenzaldehyde (1.0 mL, 8.34 mmol), Aluminium powder (0.45 g, 16.6 mmol) and potassium hydroxide (4.2 g, 75 mmol) in MeOH (10 mL) was stirred for 16 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 80:20 to 50:50, R_f*:* 0.14) to give combined **428a** and **428b** diastereoisomers (58:42 dr)

(0.49 g, 49%) as a white solid, with spectroscopic data in accordance with the literature.[198] mp 148–153 °C {Lit[198] 150–152 °C};

Data for major diastereoisomer ***428a***: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.30 (6H, s, CH_3×2), 4.69 (2H, s, *Ar*C*H*C*HAr*), 7.00–7.10 (8H, m, ArC*H*).

Data for minor diastereoisomer ***428b***: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.34 (6H, s, CH_3×2), 4.75 (2H, s, *Ar*C*H*C*HAr*), 7.1–7.24 (8H, m, ArC*H*)

1,2-di-*m*-Tolylethane-1,2-diol, 429a/429b

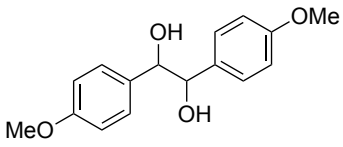


Following **General Procedure N**, 3-methylbenzaldehyde (1.0 mL, 8.34 mmol), Aluminium powder (0.45 g, 16.6 mmol) and potassium hydroxide (4.2 g, 75 mmol) in MeOH (10 mL) was stirred for 16 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 80:20 to 60:40, R_f*:* 0.24) to give combined **429a** and **429b** diastereoisomers (50:50 dr) (0.68 g, 70%) as a white solid, with spectroscopic data in accordance with the literature.[199] mp 124–130 °C {Lit[199] 124–126 °C};

Data for major diastereoisomer ***429a*** ^{1}H NMR (300 MHz, $CDCl_3$) (*selected*) δ_H: 2.30 (6H, s, CH_3×2), 4.69 (2H, s, *Ar*C*H*C*HAr*), 6.89–6.93 (1H, m, ArC*H*), 6.99–7.08 (2H, m, ArC*H*), 7.09–7.18 (4H, m, ArC*H*), 7.21–7.28 (1H, m, ArC*H*).

Data for minor diastereoisomer ***429b***: ^{1}H NMR (300 MHz, $CDCl_3$) (*selected*) δ_H: 2.35 (6H, s, CH_3×2), 4.72 (2H, s, *Ar*C*H*C*HAr*), 6.94–6.98 (1H, m, ArC*H*), 6.99–7.08 (2H, m, ArC*H*), 7.09–7.18 (4H, m, ArC*H*), 7.21–7.28 (1H, m, ArC*H*).

1,2-bis(4-Methoxyphenyl)ethane-1,2-diol, 430a/430b

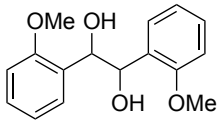


Following **General Procedure N**, 4-methoxybenzaldehyde (450 µL, 3.28 mmol), Aluminium powder (0.18 g, 6.55 mmol) and potassium hydroxide (1.65 g, 29.52 mmol) in MeOH (5 mL) was stirred for 16 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 80:20 to 30:70, R_f: 0.24) to give combined **430a** and **430b** diastereoisomers (55:45 dr) (0,39 g, 78%) as a white solid, with spectroscopic data in accordance with the literature.[200] mp 158–161 °C {Lit[200] 164–168 °C};

*Data for major diastereoisomer **430a***: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.77 (6H, s, OCH_3×2), 4.64 (2H, s, *ArCHCHAr*), 6.72–6.82 (4H, m, ArC(3,5)*H*), 7.01–7.09 (4H, m, ArC(2,6)*H*).

*Data for minor diastereoisomer **430b***: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.81 (6H, s, OCH_3×2), 4.74 (2H, s, *ArCHCHAr*), 6.83–6.91 (4H, m, ArC(3,5)*H*), 7.18–7.25 (4H, m, ArC(2,6)*H*).

1,2-bis(2-Methoxyphenyl)ethane-1,2-diol, 431a/431b

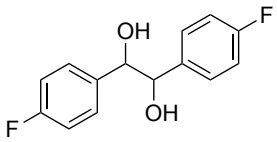


Following **General Procedure N**, 2-methoxybenzaldehyde (450 µL, 3.28 mmol), Aluminium powder (0.18 g, 6.55 mmol) and potassium hydroxide (1.65 g, 29.52 mmol) in MeOH (10 mL) was stirred for 16 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 80:20 to 50:50, R_f: 0.18) to give combined **431a** and **431b** diastereoisomers (50:50 dr) (0,64 g, 57%) as a white solid, with spectroscopic data in accordance with the literature.[201] mp 152–155 °C {Lit[201] 156–158 °C};

*Data for major diastereoisomer **431a***: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.65 (6H, s, OCH_3×2), 5.04 (2H, s, *ArCHCHAr*), 6.72–6.93 (4H, m, ArC(3,4)*H*), 7.12–7.26 (4H, m, ArC(5,6)*H*).

*Data for minor diastereoisomer **431b***: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.69 (6H, s, OCH_3×2), 5.25 (2H, s, *ArCHCHAr*), 6.72–6.93 (4H, m, ArC(3,4)*H*), 7.12–7.26 (4H, m, ArC(5,6)*H*).

1,2-bis(4-Fluorophenyl)ethane-1,2-diol, 432a/432b

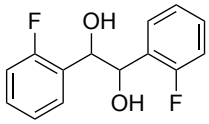


Following **General Procedure N**, 4-fluorobenzaldehyde (1.0 mL, 9.35 mmol), Aluminium powder (0.51 g, 18.7 mmol) and potassium hydroxide (4.7 g, 84.2 mmol) in MeOH (10 mL) was stirred for 16 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 80:20 to 50:50, R_f*:* 0.20) to give combined **432a** and **432b** diastereoisomers (52:48 dr) (0,85 g, 73%) as a white solid, with spectroscopic data in accordance with the literature.[135] mp 148–151 °C {Lit[135] 150–156 °C}.

*Data for major diastereoisomer **432a***: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.64 (2H, s, *ArCHCHAr*), 8.86–7.02 (4H, m, ArC(3,5)*H*), 7.03–7.21 (4H, m, ArC(2,6)*H*).

*Data for minor diastereoisomer **432b***: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.84 (2H, s, *ArCHCHAr*), 8.86–7.02 (4H, m, ArC(3,5)*H*), 7.03–7.21 (4H, m, ArC(2,6)*H*).

1,2-bis(2-Fluorophenyl)ethane-1,2-diol, 433a/433b

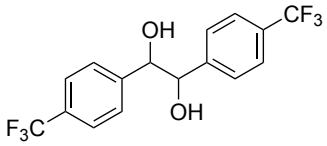


Following **General Procedure N**, 2-fluorobenzaldehyde (1.0 mL, 9.35 mmol), Aluminium powder (0.51 g, 18.7 mmol) and potassium hydroxide (4.7 g, 84.2 mmol) in MeOH (10 mL) was stirred for 16 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 90/10 to 70/30, R_f: 0.26) to give combined **433a** and **433b** diastereoisomers (54:46 dr) (0,38 g, 33%) as a white solid, with spectroscopic data in accordance with the literature.[202] mp 154–156 °C {Lit[202] 156–158 °C}.

*Data for major diastereoisomer **433a***: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.99 (2H, s, *ArCHCHAr*), 6.89–6.98 (2H, m, ArC*(5)H*), 7.13–7.27 (4H, m, ArC*(3,6)H*), 7.31–7.41 (2H, m, ArC*(4)H*).

*Data for minor diastereoisomer **433b***: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 5.20 (2H, s, *ArCHCHAr*), 7.05–7.12 (2H, m, ArC(5)*H*), 7.13–7.27 (4H, m, ArC(3,6)*H*), 7.58–7.69 (2H, m, ArC(4)*H*).

1,2-bis(4-(Trifluoromethyl)phenyl)ethane-1,2-diol, 434a/434b



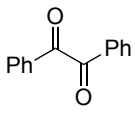
Following **General Procedure N**, 4-fluorobenzaldehyde (1.0 mL, 7.06 mmol), Aluminium powder (0.38 g, 14.12 mmol) and potassium hydroxide (3.6 g, 63.6 mmol) in MeOH (8 mL) was stirred for 16 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 80:20 to 50:50, R_f: 0.20) to give combined **434a** and **434b** diastereoisomers (57:43 dr) (0.70 g, 57%) as a yellow sticky solid, with spectroscopic data in accordance with the literature.[135] mp 138–142 °C {Lit[135] 128–130 °C};

*Data for major diastereoisomer **434a***: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.77 (2H, s, *ArCHCHAr*), 7.22–7.35 (4H, m, ArC(2,6)*H*), 7.48–7.60 (4H, m, ArC(3,5)*H*).

*Data for minor diastereoisomer **434b***: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.98 (2H, s, *ArCHCHAr*), 7.22–7.35 (4H, m, ArC(2,6)*H*), 7.48–7.60 (4H, m, ArC(3,5)*H*).

7.5.4 1,2-Diketones

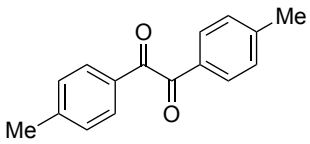
Benzil, 386



Following **General Procedure O**, 1,2-diphenylethane-1,2-diol **427a/427b** (0.25 g, 1.17 mmol) and NBS (0.63 g, 3.51 mmol) in CCl_4 (12 mL) were heated at 80–85 °C for 3 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 95:5 to 90:10, R_f: 0.39) to give title compound **386** (0.24 g, 99%) as a yellow solid, with spectroscopic data in accordance

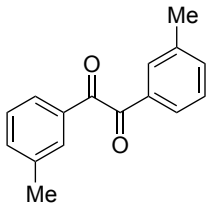
with the literature.[136] mp 94–96 °C {Lit[136] 95–96 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.46–7.58 (4H, m, ArC(3,5)*H*), 7.63–7.71 (2H, m, ArC(4)*H*), 7.94–8.02 (4H, m, ArC(2,6)*H*)**.**

1,2-di-*p*-Tolylethane-1,2-dione, 435



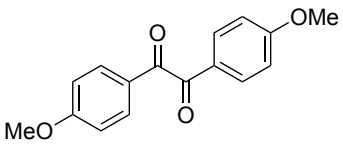
Following **General Procedure O**, 1,2-di-*p*-tolylethane-1,2-diol, **428a/428b** (0.86 g, 3.54 mmol), NBS (1.89 g, 10.6 mmol) and pyridine (290 µL, 3.54 mmol) in CCl_4 (35 mL) were heated at 80–85 °C for 3 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 95:5 to 90:10, R_f*:* 0.42) to give title compound **435** (0.69 g, 82%) as a yellow solid, with spectroscopic data in accordance with the literature.[136] mp 96–98 °C {Lit[136] 100–102 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.44 (6H, s, C*H*$_3$×2), 7.26–7.36 (4H, m, ArC(3,5)*H*), 7.78–7.92 (4H, m, ArC(2,6)*H*)**.**

1,2-di-*m*-Tolylethane-1,2-dione, 436



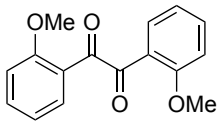
Following **General Procedure O**, 1,2-di-*m*-tolylethane-1,2-diol, **429a/429b** (0.5 g, 2.06 mmol), NBS (1.1 g, 6.2 mmol) and pyridine (810 µL, 10 mmol) in CCl_4 (21 mL) were heated at 80–85 °C for 3 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 95:5 to 90:10, R_f*:* 0.34) to give title compound **436** (0.39 g, 81%) as a yellow solid, with spectroscopic data in accordance with the literature.[203] mp 95–98 °C {Lit[203] 97–99 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.40 (6H, s, C*H*$_3$×2), 7.35–7.51 (4H, m, ArC(3,5)*H*), 7.72–7.84 (4H, m, ArC(2,6)*H*)**.**

1,2-bis(4-Methoxyphenyl)ethane-1,2-dione, 437



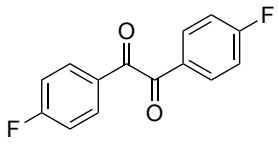
Following **General Procedure O**, 1,2-bis(4-methoxyphenyl)ethane-1,2-diol, **430a/430b** (0.5 g, 1.82 mmol), NBS (1.0 g, 5.8 mmol) and pyridine (300 µL, 3.64 mmol) in CCl_4 (18 mL) were heated at 80–85 °C for 3 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 95:5 to 80:20, R_f*:* 0.25) to give title compound **437** (0.30 g, 62%) as a yellow solid, with spectroscopic data in accordance with the literature.[203] mp 122–125 °C {Lit[203] 121–122 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.89 (6H, s, OCH_3×2), 6.92–7.04 (4H, m, ArC(3,5)*H*), 7.88–8.02 (4H, m, ArC(2,6)*H*)**.**

1,2-bis(2-Methoxyphenyl)ethane-1,2-dione, 438



Following **General Procedure O**, 1,2-bis(2-methoxyphenyl)ethane-1,2-diol, **431a/431b** (0.5 g, 1.82 mmol), NBS (1.0 g, 5.8 mmol) and pyridine (730 µL, 9.1 mmol) in CCl_4 (18 mL) were heated at 80–85 °C for 3 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 95:5 to 85:15, R_f*:* 0.31) to give title compound **438** (0.40 g, 81%) as a yellow solid, with spectroscopic data in accordance with the literature.[203] mp 132–135 °C {Lit[203] 130–131 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.73 (6H, s, OCH_3×2), 6.84–7.11 (2H, m, ArC(3)*H*), 7.19–7.48 (6H, m, ArC(4,5,6)*H*)**.**

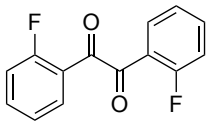
1,2-bis(4-Fluorophenyl)ethane-1,2-dione, 439



Following **General Procedure O**, 1,2-bis(4-fluorophenyl)ethane-1,2-diol, **432a/432b** (0.50 g, 2.03 mmol) and NBS (1.1 g, 6.09 mmol) in CCl_4 (20 mL) were heated at 80–85 °C for 3 h. The

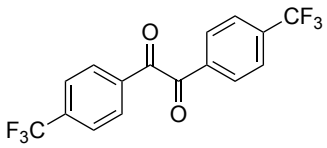
crude was purified by silica-gel column chromatography (Petrol/EtOAc 95:5 to 90:10, R_f: 0.40) to give title compound **439** (0.44 g, 89%) as a yellow solid, with spectroscopic data in accordance with the literature.[203] mp 115–116 °C {Lit[203] 118–119 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.15–7.25 (4H, m, ArC(3,5)*H*), 7.98–8.02 (4H, m, ArC(2,6)*H*)**.**

1,2-bis(2-Fluorophenyl)ethane-1,2-dione, 440



Following **General Procedure O**, 1,2-bis(2-fluorophenyl)ethane-1,2-diol, **433a/433b** (0.50 g, 2.03 mmol) and NBS (1.1 g, 6.09 mmol) in CCl_4 (20 mL) were heated at 80–85 °C for 3 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 95:5 to 80:20, R_f: 0.27) to give title compound **440** (0.25 g, 51%) as a yellow solid, with spectroscopic data in accordance with the literature.[204] mp 116–118 °C {Lit[204] 118–119 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.09–7.21 (2H, m, ArC(5)*H*), 7.31–7.43 (2H, m, ArC(3)*H*), 7.60–7.75 (2H, m, ArC(4)*H*), 8.00–8.17 (2H, m, ArC(6)*H*).

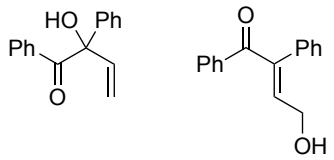
1,2-bis(4-(Trifluoromethyl)phenyl)ethane-1,2-dione, 441



Following **General Procedure O**, 1,2-bis(4-(Trifluoromethyl)phenyl)ethane-1,2-diol, **434a/434b** (0.50 g, 1.43 mmol) and NBS (0.76 g, 4.28 mmol) in CCl_4 (15 mL) were heated at 80–85 °C for 3 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 95:5 to 80:20, R_f: 0.37) to give title compound **441** (0.38 g, 77%) as a yellow solid, with spectroscopic data in accordance with the literature.[205] mp 125–128 °C {Lit[205] 132–136 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.76–7.86 (4H, m, ArC(2,6)*H*), 8.08–8.15 (4H, m, ArC(3,5)*H*)**.**

7.5.5 ß,γ-unsaturated α-hydroxyketones

2-hydroxy-1,2-diphenylbut-3-en-1-one, 387 or (*E*)-4-hydroxy-1,2-diphenylbut-2-en-1-one, 388



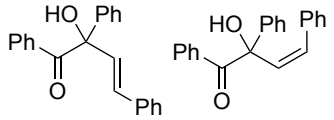
387 **388**

Following **General Procedure P**, vinylmagnesium bromide **390** (1.6 M in THF, 1.2 mL) was added dropwise to a solution of benzil (0.32 g, 1.5 mmol) in anhydrous THF (6 mL). The reaction was stirred at rt for 16 h resulting crude product (61:39 **387**:**388**) that was purified by flash silica chromatography (CH_2Cl_2/Petrol 90:10 to 70:30, R_f: 0.32 and 0.29) to give:

387 (67 mg, 28%) as a yellow sticky solid, with spectroscopic data in accordance with the literature.[206] ν_{max} 3429 (OH), 3027 (C-H), 1662 (C=O), 1597 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 5.07 (1H, s, O*H*), 5.45 (1H, dd, *J* 10.5,1.5 C*H*^{A}CH^{B}CH), 5.83 (1H, dd, *J* 16.8,1.5 C*H*^{A}CH^{B}CH), 6.58 (1H, dd, *J* 16.8, 10.5, CH_2C*H*), 7.27–7.35 (2H, m, ArC*H*), 7.33–7.40 (5H, m, ArC*H*), 7.43–7.52 (1H, m, ArC*H*), 7.67–7.74 (2H, m, ArC*H*).

388, (48 mg, 20%) as a yellow sticky solid, with spectroscopic data in accordance with the literature.[207] ν_{max} 3429 (OH), 3027 (C-H), 1662 (C=O), 1597 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.17 (1H, dd, *J* 6.8, 2.1 C*H*^{A}CH^{B}OH), 4.34 (1H, dd, *J* 14.3, 2.1 C*H*^{A}CH^{B}CH), 6.08 (1H, s, O*H*), 6.57 (1H, dd, *J* 14.3, 6.8, CH_2C*H*), 7.33–7.45 (2H, m, ArC*H*), 7.49–7.61 (5H, m, ArC*H*), 7.65–7.73 (1H, m, ArC*H*), 7.96–8.05 (2H, m, ArC*H*).

(*E*)-2-Hydroxy-1,2,4-triphenylbut-3-en-1-one, 393/394



393 **394**

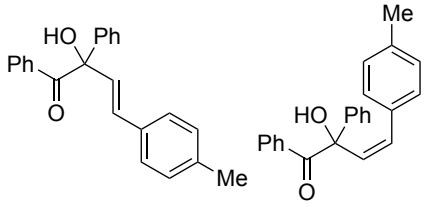
Following **General Procedure P**, freshly prepared Grignard from (*E*)-(2-bromovinyl)benzene **416** was synthesized (0.45 M, 6 mL) and added dropwise to a solution of benzil (0.70 g,

3.33 mmol) in anhydrous THF (20 mL). The reaction was stirred at rt for 16 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 70:30 to 30:70, R_f: 0.29) to yield the combined *E* and *Z* isomers (78:22) (0.66 g, 70%) as a yellow solid, with spectroscopic data in accordance with the literature.[208] mp 98–103 °C {Lit[208] 87–90 °C};

Data for major isomer trans-**393**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.86 (1H, d, *J* 15.6, CHC*H*Ar), 7.15 (1H, d, *J* 15.6, ArC*H*CHAr), 7.19–7.25 (1H, m, ArC*H*), 7.27–7.46 (10H, m, ArC*H*), 7.46–7.56 (2H, m, ArC*H*), 7.73–7.79 (2H, m, ArC*H*);

Data for minor isomer cis-**394**: ^{1}H NMR (300 MHz, $CDCl_3$) *(selected)* δ_H: 6.48 (1H, d, *J* 12.5, CHC*H*Ar), 6.84 (1H, d, *J* 12.5, ArC*H*CHAr), 7.63–7.69 (2H, m, ArC*H*), 7.71–7.73 (1H, m, ArC*H*), 7.96–8.01 (1H, m, ArC*H*), 8.05–8.11 (2H, m, ArC*H*).

(*E*)-2-Hydroxy-1,2-diphenyl-4-(*p*-tolyl)but-3-en-1-one, 423/424



423 **424**

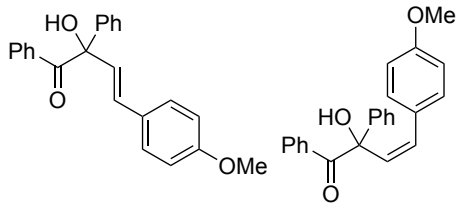
Following **General Procedure P**, freshly prepared Grignard from (*E*)-1-(2-bromovinyl)-4-methylbenzene **417** was synthesized (0.27 M, 8 mL) and added dropwise to a solution of benzil (0.63 g, 3 mmol) in anhydrous THF (20 mL). The reaction was stirred at rt for 16 h resulting crude product (79:21 *E*:*Z*) that was purified by flash silica chromatography (Petrol/CH_2Cl_2 70:30 to 30:70, R_f: 0.22 and 0.19) to give:

Trans-**423** (108 mg, 11%) as a yellow sticky solid; ν_{max} 3429 (OH), 3027 (C-H), 1662 (C=O), 1597 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.33 (3H, s, CH_3), 5.27 (1H, s, O*H*), 6.80 (1H, d, *J* 15.6, CHC*H*Ar), 7.06–7.15 (3H, m, ArC*H*×2 and ArC*H*CHAr), 7.27–7.46 (8H, m, ArC*H*), 7.46–7.54 (1H, m, ArC*H*, 7.70–7.80 (2H, m, ArC*H*)**;** ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.6 (*C*H_3), 82.6 (ArOH*C*CH), 127.3 (*C*HCHAr), 128.5 (Ar*C*H), 128.6 (Ar*C*H), 128.9 (Ar*C*H), 129.3 (Ar*C*H), 129.8 (CH*C*HAr), 130.2 (Ar*C*(4)), 130.9 (Ar*C*H), 133.4 (Ar*C(4))*, 136.7 (Ar*C(1)*), 133.8 (Ar*C(1)*), 134.9

(Ar*C(4)CH₃*), 142.7 (Ar*C(1)*), 199.4 (Ar*C*OPhOH); HRMS (ESI⁺) $C_{23}H_{20}O_2Na$ $[M+Na]^+$ found 351.1365, requires 351.1364 (+0.32 ppm).

Cis-**424**, (49 mg, 5%) as a yellow sticky solid; ν_{max} 3429 (OH), 3027 (C-H), 1662 (C=O), 1597 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.29 (3H, s, C*H*$_3$), 4.92 (1H, s, O*H*), 6.41 (1H, d, *J* 12.5, CHC*H*Ar), 6.80 (1H, d, *J* 12.5, ArC*H*CHAr), 6.97–7.05 (2H, m, ArC*H*), 7.12–7.19 (2H, m, ArC*H*, 7.27–7.40 (4H, m, ArC*H*), 7.41–7.48 (2H, m, ArC*H*), 7.50–7.56 (2H, m, ArC*H*), 7.72–7.77 (2H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.6 (*C*H$_3$), 82.6 (ArOH*C*CH), 127.3 (*C*HCHAr), 128.5 (Ar*C*), 128.6 (Ar*C*H), 128.9 (Ar*C*H), 129.3 (Ar*C*H), 129.8 (CH*C*HAr), 130.2 (Ar*C*(4)), 130.9 (Ar*C*H), 133.4 (Ar*C(4)*), 136.7 (Ar*C(1)*), 133.8 (Ar*C(1)*), 134.9 (Ar*C(4)CH₃*), 142.7 (Ar*C(1)*), 199.4 (Ar*C*OPhOH); HRMS (ESI⁺) $C_{23}H_{20}O_2Na$ $[M+Na]^+$ found 351.1355, requires 351.1364 (+4.65 ppm).

(*E*)-2-Hydroxy-4-(4-methoxyphenyl)-1,2-diphenylbut-3-en-1-one, 425/426



425 **426**

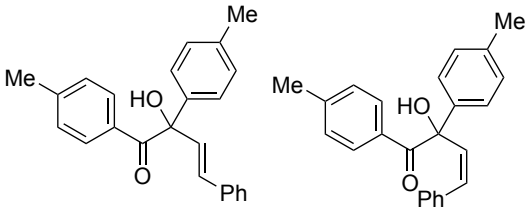
Following **General Procedure P**, freshly prepared Grignard from (*E*)-1-(2-bromovinyl)-4-methoxybenzene **418** was synthesized (0.40 M, 8 mL) and added dropwise to a solution of benzil (0.70 g, 3.33 mmol) in anhydrous THF (20 mL). The reaction was stirred at rt for 16 h. The crude was purified by silica-gel column chromatography (Hexane/ CH_2Cl_2 70:30 to 30:70, R_f: 0.20 and 0.16) to give the combined *E* and *Z* isomers (70:30) (325 mg, 29%) as a sticky yellow solid. ν_{max} 3425 (OH), 3058 (C-H), 1671 (C=O), 1597 (C=O);

Data for major isomer trans-**425**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.77 (3H, s, C*H*$_3$), 5.06 (1H, s, O*H*), 6.71 (1H, d, *J* 15.6, CHC*H*Ar), 6.80–6.87 (2H, m, ArC*H*), 7.08 (1H, d, *J* 15.6, ArC*H*CHPh), 7.27–7.46 (8H, m, ArC*H*), 7.46–7.57 (2H, m, ArC*H*), 7.73–7.79 (2H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 55.5 (O*C*H$_3$), 81.2 (ArOH*C*CH), 114.2 (Ar*C*(3,5)H), 125.4 (*C*HCHAr), 126.2 (Ar*C*H), 126.33 (Ar*C(4)*), 127.4 (Ar*C*H), 128.2 (Ar*C*(1)), 128.6 (Ar*C*H), 129.0 (Ar*C*H), 130.6 (CH*C*HAr), 130.8 (Ar*C*(2,6)H), 131.3 (Ar*C*(4)), 133.5 (Ar*C*(1)*CO)*, 134.5 (Ar*C*(1)), 164.7

(Ar*C*(4)OCH_3), 182.5 Ar); HRMS (ESI^-) $C_{23}H_{19}O_2$ $[M–H]^-$ found 343.1343, requires 343.1312 (+0.21 ppm).

Data for minor isomer cis-**426**: ^{1}H NMR (300 MHz, $CDCl_3$) *(selected)* δ_H: 3.80 (3H, s, CH_3), 5.30 (1H, s, O*H*), 6.34 (1H, d, *J* 12.5, CHC*H*Ph), 6.73 (1H, d, *J* 12.5, ArC*H*CHPh), 7.27–7.29 (1H, m, ArC*H*).

(*E*)-2-Hydroxy-4-phenyl-1,2-di-*p*-tolylbut-3-en-1-one, 442/443



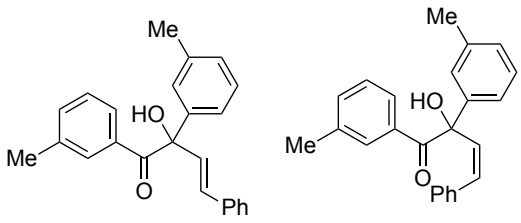
442 **443**

Following **General Procedure P**, freshly prepared Grignard from styrene bromide **416** was synthesized (0.29 M, 8 mL) and added dropwise to a solution of 1,2-di-*p*-tolylethane-1,2-dione, **435** (0.25 g, 1.0 mmol) in anhydrous THF (20 mL). The reaction was stirred at rt for 16 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 95:5 to 85:15, R_f*:* 0.31) to give the combined *E* and *Z* isomers (89:11) (84 mg, 24%) as a sticky yellow solid. ν_{max} 3395 (OH), 3027 (C-H), 1660 (C=O), 1605 (C=O), 1512 (C=C);

Data for major isomer trans-**442**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.35 (6H, s, CH_3×2), 5.32 (1H, s, O*H*), 6.86 (1H, d, *J* 15.6, CHC*H*Ph), 7.07–7.21 (5H, m, ArC*H and* ArC*H*CHPh), 7.23–7.35 (5H, m, ArC*H*), 7.36–7.46 (2H, m, ArC*H*), 7.66–7.72 (2H, m, ArC*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) 21.3 (*C*H_3), 21.7 (*C*H_3), 82.3 (PhOH*C*CH), 127.0 (Ar*C*H), 127.1 (*C*HCHAr), 128.1 (Ar*C*(4)), 128.7 (Ar*C*H), 129.1 (CH*C*HAr), 129.3 (Ar*C*H), 129.8 (Ar*C*H), 131.0 (Ar*C*H), 132.7 (Ar*C(1))*, 136.6 (Ar*C(1)*), 138.3 (Ar*C(1)*), 140.1 (Ar*C(4)*CH_3), 144.0 (Ar*C(4)*CH_3), 199.4 (Ph*C*OPhOH); HRMS (ESI^-) $C_{24}H_{23}O_4$ $[M+HCOO]^-$ found 387.1639, requires 387.1720 (+4.35 ppm).

Data for minor isomer cis-**443**: ^{1}H NMR (300 MHz, $CDCl_3$) *(selected)* δ_H: 2.32 (3H, s, CH_3), 2.33 (3H, s, CH_3), 6.45 (1H, d, *J* 12.5, CHC*H*Ph), 6.98–7.05 (1H, m, ArC*H*), 7.84–7.95 (2H, m, ArC*H*).

(*E*)-2-Hydroxy-4-phenyl-1,2-di-*m*-tolylbut-3-en-1-one, 444/445



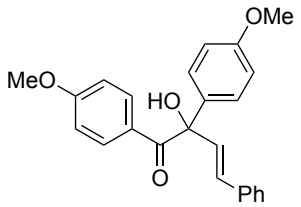
444 **445**

Following **General Procedure P**, freshly prepared Grignard from styrene bromide **416** was synthesized (0.28 M, 8 mL) and added dropwise to a solution of 1,2-di-*m*-tolylethane-1,2-dione, **436** (0.25 g, 1.0 mmol) in anhydrous THF (20 mL). The reaction was stirred at rt for 16 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 95:5 to 85:15, R_f: 0.31) to give the combined *E* and *Z* isomers (81:19) (270 mg, 63%) as a sticky yellow oil; ν_{max} 3395 (OH), 2921 (C-H), 1660 (C=O), 1605 (C=C);

Data for major isomer trans-**444**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.33 (6H, s, C*H*$_3$×2), 5.28 (1H, s, O*H*), 6.85 (1H, d, *J* 15.6, CHC*H*Ph), 6.89–7.25 (8H, m, ArC*H and* ArC*H*CHPh), 7.27–7.34 (2H, m, ArC*H*), 7.36–7.49 (2H, m, ArC*H*), 7.66–7.71 (2H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.3 (*C*H$_3$), 21.7 (*C*H$_3$), 82.3 (ArOH*C*CH), 124.3 (Ar*C*H), 125.2 (Ar*C*H), 127.8 (*C*HCHAr), 128.1 (Ar*C*H), 128.3 (Ar*C*H), 128.7 (Ar*C*H), 128.8 (Ar*C*H), 129.1 (Ar*C*H), 129.4 (CH*C*HAr), 131.1 (Ar*C*H), 132.7 (Ar*C*H), 134.3 (Ar*C*H), 136.6 (Ar*C(1))*, 138.5 (Ar*C(1)*), 139.0 (Ar*C(1)*), 142.8 (Ar*C(3)CH*$_3$), 143.0 (Ar*C(3)CH*$_3$), 199.3 (Ar*C*OPhOH); HRMS (ESI$^-$) $C_{24}H_{22}O_2Na$ $[M+Na]^+$ found 365.1511, requires 365.1520 (–0.82 ppm).

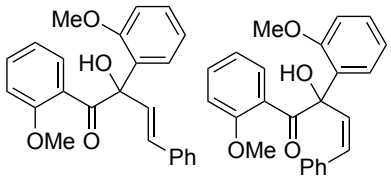
Data for minor isomer cis-**445**: ^{1}H NMR (300 MHz, $CDCl_3$) *(selected)* δ_H: 2.32 (6H, s, C*H*$_3$×2), 6.44 (1H, d, *J* 12.5, CHC*H*Ph), 6.82 (1H, d, *J* 12.5, ArC*H*CHPh), 7.93–7.99 (1H, m, ArC*H*).

(*E*)-2-Hydroxy-1,2-bis(4-methoxyphenyl)-4-phenylbut-3-en-1-one, 446



Following **General Procedure P**, freshly prepared Grignard from styrene bromide **416** was synthesized (0.25 M, 8 mL) and added dropwise to a solution of 1,2-bis(4-methoxyphenyl)ethane-1,2-diol, **437** (0.25 g, 1 mmol) in anhydrous THF (20 mL). The reaction was stirred at rt for 16 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 85:15 to 70:30, R_f: 0.28) to give title compound **446** (119 mg, 32%) as a sticky yellow solid. ν_{max} 3396 (OH), 2933 (C-H), 1667 (C=O), 1597 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.74 (3H, s, OC*H*$_3$), 3.77 (3H, s, OC*H*$_3$), 6.02 (1H, s, O*H*), 6.63 (1H, d, *J* 15.6, CHC*H*Ph), 6.81–7.10 (9H, m, ArC*H* and ArC*H*CHPh), 7.41–7.47 (2H, m, ArC*H*), 7.51–7.57 (2H, m, ArC*H*), 7.91–7.98 (1H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 55.2 (O*C*H$_3$), 55.4 (O*C*H$_3$), 83.4 (PhOH*C*CH), 113.5 (Ar*C*(3,5)H), 113.7 (Ar*C*(3,5)H), 126.2 (*C*HCHAr), 127.6 (ArCH), 127.8 (Ar*C*(4)), 127.9 (ArCH), 128.2 (ArC(1)), 128.7 (Ar*C*H), 129.0 (CH*C*HAr), 130.2 (Ar*C*(1)), 131.0 (Ar*C*(2,6)H), 138.5 (Ar*C*(1)), 163.9 (Ar*C*(4)OCH$_3$), 169.1 (Ar*C*(4)OCH$_3$), 194.5 (Ph*C*OPhOH); HRMS (ESI$^-$) $C_{25}H_{25}O_6$ [M+CH$_3$COO]$^-$ found 433.1676, requires 433.1818 (–2.84 ppm).

(*E*)-2-Hydroxy-1,2-bis(2-methoxyphenyl)-4-phenylbut-3-en-1-one, 447/448



447 **448**

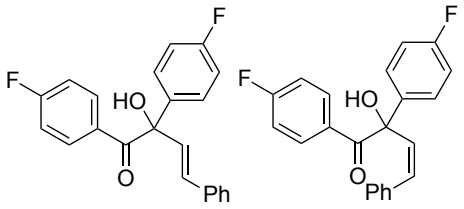
Following **General Procedure P**, freshly prepared Grignard from styrene bromide **416** was synthesized (0.25 M, 8 mL) and added dropwise to a solution of 1,2-bis(2-methoxyphenyl)ethane-1,2-diol, **438** (0.25 g, 1 mmol) in anhydrous THF (20 mL). The reaction was stirred at rt for 16 h. The crude was purified by silica-gel column chromatography

(Petrol/EtOAc 90:10 to 75:25, R_f: 0.31) to give the combined *E* and *Z* isomers (56:44) (58 mg, 16%) as a sticky yellow oil. ν_{max} 3549 (OH), 2929 (C-H), 1734 (C=O), 1596 (C=C);

Data for major isomer trans-**447**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.73 (3H, s, OC*H*$_3$), 3.77 (3H, s, OC*H*$_3$), 5.25 (1H, s, O*H*), 6.55 (1H, d, *J* 15.6, CHC*H*Ph), 6.76–7.10 (9H, m, ArC*H* and ArC*H*CHPh), 7.41–7.50 (5H, m, ArC*H*). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 55.4 (O*C*H$_3$), 83.4 (ArOH*C*CH), 113.1 (Ar*C*H), 114.8 (Ar*C(1)OMe*), 123.3 (Ar*C*H), 127.0 (ArCH), 127.4 (ArCH), 128.2 (ArCH), 128.8 (Ar*C*H), 129.6 (CH*C*HAr), 130.31 (ArCH), 133.0 (Ar*C*H), 141.0 (Ar*C*H), 150.0 (Ar*C(1)*), 159.9 (Ar*C(2)*OCH$_3$), 160.3 (Ar*C(2)*OCH$_3$), 195.3 (Ar*C*OPhOH); HRMS (ESI$^-$) $C_{25}H_{25}O_6$ [M+CH$_3$COO]$^-$ found 433.1676, requires 433.1818 (–2.84 ppm).

Data for minor isomer cis-**448**: ^{1}H NMR (300 MHz, $CDCl_3$) *(selected)* δ_H: 3.82 (6H, s, C*H*$_3$), 6.44 (1H, d, *J* 12.5, CHC*H*Ph), 6.82 (1H, d, *J* 12.5, ArC*H*CHPh), 7.93–7.99 (1H, m, ArC*H*).

(*E*)-1,2-bis(4-Fluorophenyl)-2-hydroxy-4-phenylbut-3-en-1-one, 449/450



449 **450**

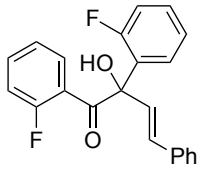
Following **General Procedure P**, freshly prepared Grignard from styrene bromide **416** was synthesized (0.30 M, 8 mL) and added dropwise to a solution of 1,2-bis(4-fluorophenyl)ethane-1,2-diol, **439** (0.25 g, 1.0 mmol) in anhydrous THF (20 mL). The reaction was stirred at rt for 16 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 95:5 to 85:15, R_f: 0.19) to give the combined *E* and *Z* isomers *(*75:25) (119 mg, 34%) as a sticky yellow solid. ν_{max} 3423 (OH), 3067 (C-H), 1669 (C=O), 1596 (C=C);

Data for major isomer trans-**449**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 5.19 (1H, s, O*H*), 6.78 (1H, d, *J* 15.5, CHC*H*Ph), 6.98–7.13 (5H, m, ArC*H and* ArC*H*CHPh), 7.28–7.37 (2H, m, ArC*H*), 7.38–7.43 (4H, m, ArC*H*), 7.75–7.87 (2H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 81.9 (PhOH*C*CH), 115.9 (d, $^2J_{C\text{-}F}$ 21.9, Ar*C*(3,5)H), 116.2 (d, $^2J_{C\text{-}F}$ 21.6, Ar*C*(3,5)H), 126.9 (*C*HCHAr), 127.7 (Ar*C*(4)), 127.9 (Ar*C*H), 128.0 (Ar*C*H), 128.3 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (Ar*C*H), 128.7 (Ar*C*H), 129 (d,

$^{3}J_{C\text{-}F}$ 8.3, Ar*C*(3,5)H), 129.3 (CH*C*HAr), 133.2 (d, $^{4}J_{C\text{-}F}$ 2, Ar*C*(1)), 133.5 (d, $^{3}J_{C\text{-}F}$ 9.5, Ar*C*(3,5)H), 136.1 (Ar*C(1)*), 138.5 (d, $^{4}J_{C\text{-}F}$ 2, Ar*C*(1)), 162.8 (d, $^{1}J_{C\text{-}F}$ 257*, C*F), 165.7 (d, $^{1}J_{C\text{-}F}$ 257*, C*F), 197.1 (Ph*C*OPhOH). $^{19}F\{^{1}H\}$ NMR (471 MHz, $CDCl_3$) δ_F: –112.7, –103.2; HRMS (ESI^-) $C_{23}H_{17}F_2O_4$ $[M+HCOO]^-$ found 395.1100, requires 395.1218 (–3.36 ppm).

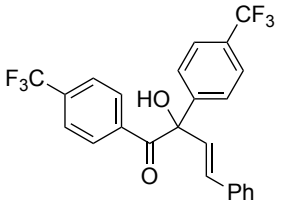
*Data for minor isomer cis-***450**: ^{1}H NMR (300 MHz, $CDCl_3$) *(selected)* δ_H: 6.44 (1H, d, *J* 12.5, CHC*H*Ph), 7.45–7.51 (2H, m, ArC*H*), 7.58–7.66 (2H, m, ArC*H*), 8.06–8.17 (2H, m, ArC*H*); ^{13}C NMR (126 MHz, $CDCl_3$) *(selected)* δ_C: 81.5 (PhOH*C*CH), 115.4 (d, $^{2}J_{C\text{-}F}$ 21.9, Ar*C*(3,5)H), 133.2 (d, $^{4}J_{C\text{-}F}$ 2, Ar*C*(1)), 134.9 (Ar*C(1)*), 198.0 (Ph*C*OPhOH); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: –113.6, –104.0.

(*E*)-1,2-bis(2-Fluorophenyl)-2-hydroxy-4-phenylbut-3-en-1-one, 451

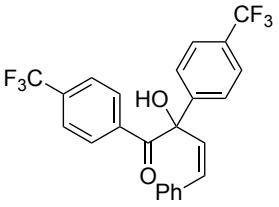


Following **General Procedure P**, freshly prepared Grignard from styrene bromide **416** was synthesized (0.25 M, 8 mL) and added dropwise to a solution of 1,2-bis(2-fluorophenyl)ethane-1,2-diol, **440** (0.25 g, 1.0 mmol) in anhydrous THF (20 mL). The reaction was stirred at rt for 16 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 95:5 to 85:15, R_f*:* 0.18) to give the *E* product **451** (76 mg, 22%) as a sticky yellow oil; ν_{max} 3434 (OH), 2933 (C-H), 1610 (C=O), 1597 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 5.00 (1H, s, O*H*), 6.75 (1H, d, *J* 15.6, CHC*H*Ph), 6.90–7.23 (7H, m, ArC*H and* ArC*H*CHPh), 7.27–7.39 (3H, m, ArC*H*), 7.41–7.53 (2H, m, ArC*H*), 7.54–7.69 (2H, m, ArC*H);* $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 81.4 (PhOH*C*CH), 116.3 (d, $^{2}J_{C\text{-}F}$ 21.8 , Ar*C*H), 117.1 (2C, d, $^{2}J_{C\text{-}F}$ 21.7, Ar*C*H), 124.3 (d, $^{4}J_{C\text{-}F}$ 2.7, Ar*C*), 124.5 (d, $^{4}J_{C\text{-}F}$ 3.5, Ar*C*), 126.3 (*C*HCHAr), 127.0 (Ar*C*H), 128.4 (Ar*C*H), 128.5 (Ar*C*H), 128.3 (Ar*C*H), 128.8 (Ar*C*H), 130.6 (d, $^{3}J_{C\text{-}F}$ 8.5, Ar*C*H), 131.2 (CH*C*HAr), 132.0 (Ar*C*H), 133.9 (Ar*C*H), 134.8 (d, $^{3}J_{C\text{-}F}$ 9.5, Ar*C*), 136.4 (Ar*C(1)*), 164.4 (1C, d, $^{1}J_{C\text{-}F}$ 248*, C*F), 197.1 (Ph*C*OPhOH). ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: –112.4, –106.1; HRMS (ESI^-) $C_{22}H_{15}F_2O_2$ $[M–H]^-$ found 349.1039, requires 349.1018 (–0.22 ppm).

(*E*)-2-Hydroxy-4-phenyl-1,2-bis(4-(trifluoromethyl)phenyl)but-3-en-1-one, 452/453



452



453

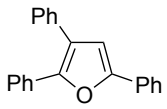
Following **General Procedure P**, freshly prepared Grignard from styrene bromide **416** was synthesized (0.30 M, 8 mL) and added dropwise to a solution of 1,2-bis(4-trifluorophenyl)ethane-1,2-diol, **441** (0.25 g, 0.7 mmol) in anhydrous THF (20 mL). The reaction was stirred at rt for 16 h. The crude was purified by silica-gel column chromatography (Petrol/EtOAc 98:2 to 90:10, R_f: 0.23) to give the combined *E* and *Z* isomers (75:25) (114 mg, 35%) as a yellow oil. ν_{max} 3422 (OH), 3064 (C-H), 1688 (C=O), 1598 (C=C);

Data for major isomer trans-**452**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.96 (1H, s, O*H*), 6.80 (1H, d, *J* 15.6, ArC*H*CHPh), 7.12 (1H, d, *J* 15.6, CHC*H*Ph), 7.29–7.44 (5H, m, ArC*H*), 7.51–7.60 (3H, m, ArC*H*), 7.62–7.71 (3H, m, ArC*H*), 7.81–7.89 (2H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 82.6 (Ar*C*OHCH), 124.3 (q, $^1J_{C\text{-}F}$ 269, *CF*$_3$), 125.8 (q, $^3J_{C\text{-}F}$ 4, Ar*C*H), 126.4 (q, $^3J_{C\text{-}F}$ 4, Ar*C*H), 127.0 (*C*HCHAr), 127.1 (Ar*C*H), 128.1 (ArCH), 128.8 (Ar*C*H), 128.9 (Ar*C*H), 130.1 (Ar*C*H), 130.9 (*C*HCHAr), 131.3 (q, $^2J_{C\text{-}F}$ 30, Ar*C*H), 136.1 (q, $^2J_{C\text{-}F}$ 31.8, Ar*C*H), 135.8 (ArC(1)), 139.5 (Ar*C*(1)), 197.7 (Ph*C*OPhOH). ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: –112.7, –103.2; HRMS (ESI^-) $C_{24}H_{15}F_6O_2$ $[M–H]^-$ found 449.0980, requires 449.1054 (–0.39 ppm).

Data for minor isomer cis-**453**: ^{1}H NMR (300 MHz, $CDCl_3$) *(selected)* δ_H: 4.52 (1H, s, O*H*), 6.49 (1H, d, *J* 12.3, CHC*H*Ph), 6.90 (1H, d, *J* 12.3, ArC*H*CHPh), 7.17–7.24 (2H, m, ArC*H*), 7.44–7.49 (2H, m, ArC*H*), 7.76–7.80 (1H, m, ArC*H*), 8.14–8.20 (1H, m, ArC*H*).

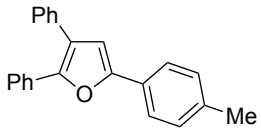
7.5.6 Furan products

2,3,5-Triphenylfuran, 395



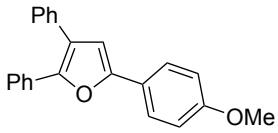
Following **General Procedure Q**, (*E*)-2-hydroxy-1,2,4-triphenylbut-3-en-1-one, **393/394** (31 mg, 0.1 mmol), 2-carboxyphenylboronic acid **402** (0.3 mg, 2 µmol) and oxalic acid **62** (0.2 mg, 2 µmol) in CH_3CN (1.0 mL) were reacted at rt for 2 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 95:5, R_f*:* 0.33) to give title compound **395** (28 mg, 93%) as a yellow solid, with spectroscopic data in accordance with the literature.[209] mp 90–93 °C {Lit[209] 91–93 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.83 (1H, s, C*H*), 7.24–7.38 (5H, m, ArC*H*), 7.39–7.44 (4H, m, ArC*H*), 7.46–7.48 (2H, m, ArC*H*), 7.58–7.66 (2H, m, ArC*H*), 7.74–7.81 (2H, m, ArC*H*).

2,3-Diphenyl-5-(*p*-tolyl)furan, 465



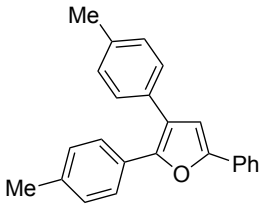
Following **General Procedure Q**, (*E*)-2-hydroxy-1,2-diphenyl-4-(*p*-tolyl)but-3-en-1-one **423/424** (33 mg, 0.1 mmol), 2-carboxyphenylboronic acid **402** (0.3 mg, 2 µmol) and oxalic acid **62** (0.2 mg, 2 µmol) in CH_3CN (1.0 mL) were reacted at rt for 2 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 95:5, R_f*:* 0.28) to give title compound **465** (22 mg, 72%) as a yellow solid, with spectroscopic data in accordance with the literature.[210] mp 90–94 °C {Lit[210] 99–100 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.39 (3H, s, CH_3), 6.77 (1H, s, C*H*), 7.19–7.42 (8H, m, ArC*H*), 7.45–7.51 (2H, m, ArC*H*), 7.57–7.73 (4H, m, ArC*H*).

5-(4-Methoxyphenyl)-2,3-diphenylfuran, 466



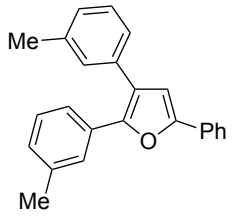
Following **General Procedure Q**, (*E*)-2-hydroxy-4-(4-methoxyphenyl)-1,2-diphenylbut-3-en-1-one, **425/426** (34 mg, 0.1 mmol), 2-carboxyphenylboronic acid **402** (0.3 mg, 2 µmol) and oxalic acid **62** (0.2 mg, 2 µmol) in CH_3CN (1.0 mL) were reacted at rt for 2 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 95:5 to 93:7, R_f: 0.23) to give title compound **466** (29 mg, 88%) as a yellow solid, with spectroscopic data in accordance with the literature.[211] mp 91–94 °C {Lit[212] 96–97 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.86 (3H, s, OC*H*$_3$), 6.69 (1H, s, C*H*), 6.91–7.403 (2H, m, ArC*H*), 7.19–7.41 (6H, m, ArC*H*), 7.43–7.51 (2H, m, ArC*H*), 7.56–7.64 (2H, m, ArC*H*), 7.65–7.76 (2H, m, ArC*H*).

5-Phenyl-2,3-di-*p*-tolylfuran, 467



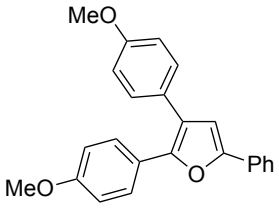
Following **General Procedure Q**, (*E*)-2-hydroxy-4-phenyl-1,2-di-*p*-tolylbut-3-en-1-one **442/443** (34 mg, 0.1 mmol), 2-carboxyphenylboronic acid **402** (0.3 mg, 2 µmol) and oxalic acid **62** (0.2 mg, 2 µmol) in CH_3CN (1.0 mL) were reacted at 50 °C for 6 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 98:2 to 96:4, R_f: 0.20) to give title compound **467** (32 mg, 99%) as a sticky yellow solid, with spectroscopic data in accordance with the literature.[212] mp 91–95 °C {Lit.[212] 96–98 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.36 (3H, s, C*H*$_3$), 2.40 (3H, s, C*H*$_3$), 6.80 (1H, s, C*H*), 7.09–7.16 (2H, m, ArC*H*), 7.17–7.22 (2H, m, ArC*H*), 7.27–7.32 (1H, m, ArC*H*), 7.35–7.46 (4H, m, ArC*H*), 7.50–7.58 (2H, m, ArC*H*), 7.70–7.82 (2H, m, ArC*H*).

5-Phenyl-2,3-di-*m*-tolylfuran, 468



Following **General Procedure Q**, (*E*)-2-hydroxy-4-phenyl-1,2-di-*m*-tolylbut-3-en-1-one, **444/445** (34 mg, 0.1 mmol), 2-carboxyphenylboronic acid **402** (0.3 mg, 2 µmol) and oxalic acid **62** (0.2 mg, 2 µmol) in CH_3CN (1.0 mL) were reacted at 90 °C for 6 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 98:2 to 96:4, R_f: 0.29) to give title compound **468** (17 mg, 54%) as a sticky yellow solid. ν_{max} 3033, 2919 (C-H), 1604 (C=C), 1225 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.33 (3H, s, C*H*$_3$), 2.37 (3H, s, C*H*$_3$), 6.1 (1H, s, C*H*), 7.04–7.10 (1H, m, ArC*H*), 7.12–7.22 (2H, m, ArC*H*), 7.27–7.33 (3H, m, ArC*H*), 7.34–7.46 (4H, m, ArC*H*), 7.50–7.58 (1H, m, ArC*H*), 7.72–7.81 (2H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.6 (*C*H$_3$), 21.7 (*C*H$_3$), 109.6 (Furan*C*H), 123.5 (Furan*C(1)*Ar4*Me*), 123.9 (Ar*C*(6)H), 124.6 (Ar*C*(6)H), 125.9 (Ar*C*Ph), 126.8 (Ar*C*(2)H), 127.6 (Ar*C*H), 128.1 (Ar*C*H), 128.4 (ArC(4,5)H), 128.6 (ArC(4,5)H), 129.5 (Ar*C*H), 130.8 (Ar*C*(1)), 131.2 (Ar*C*(2)H), 138.1 (Ar*C*(1)), 138.4 (Ar*C(4)H*), 148.1 (Furan*C*Ph), 152.5 (Furan*C*Ar4-OMe); HRMS (ESI$^-$) $C_{24}H_{19}O$ $[M–H]^-$ found 323.1421, requires 323.1514 (–1.21 ppm).

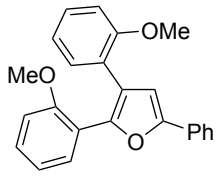
2,3-bis(4-Methoxyphenyl)-5-phenylfuran, 469



Following **General Procedure Q**, (*E*)-2-hydroxy-1,2-bis(4-methoxyphenyl)-4-phenylbut-3-en-1-one, **446** (37 mg, 0.1 mmol), 2-carboxyphenylboronic acid **402** (0.3 mg, 2 µmol) and oxalic acid **62** (0.2 mg, 2 µmol) in CH_3CN (1.0 mL) were reacted at 90 °C for 24 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 98:2 to 96:4, R_f: 0.27) to give title compound **469** (7 mg, 20%) as a yellow solid, with spectroscopic data in accordance with the

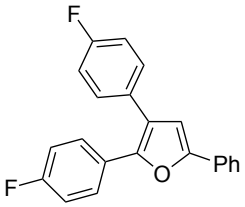
literature.[212] mp 90–94 °C {Lit.[212] 98–102 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.82 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 6.77 (1H, s, C*H*), 6.82–6.88 (2H, m, ArC*H*), 6.90–6.95 (2H, m, ArC*H*), 7.27–7.32 (1H, m, ArC*H*), 7.34–7.45 (4H, m, ArC*H*), 7.50–7.59 (2H, m, ArC*H*), 7.71–7.78 (2H, m, ArC*H*).

2,3-bis(2-Methoxyphenyl)-5-phenylfuran, 470



Following **General Procedure Q**, (*E*)-2-hydroxy-1,2-bis(2-methoxyphenyl)-4-phenylbut-3-en-1-one, **447/448** (38 mg, 0.1 mmol), 2-carboxyphenylboronic acid **402** (0.30 mg, 2 µmol) and oxalic acid **62** (0.2 mg, 2 µmol) in CH_3CN (1.0 mL) were reacted at 90 °C for 24 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 98:2 to 96:4, R_f*:* 0.24) to give title compound **470** (7 mg, 20%) as a sticky yellow solid. ν_{max} 3017, 2924 (C-H), 1671 (C=C), 1440 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.72 (3H, s, OC*H*$_3$), 3.79 (3H, s, OC*H*$_3$), 6.79–6.83 (2H, m, ArC*H and* C*H*), 6.85–6.93 (1H, m, ArC*H),* 6.99–7.09 (2H, m, ArC*H*), 7.14–7.19 (1H, m, ArC*H*), 7.20–7.25 (2H, m, ArC*H*), 7.27–7.36 (2H, m, ArC*H*), 7.37–7.48 (2H, m, ArC*H*), 7.72–7.80 (2H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 47.0 (O*C*H$_3$), 111.4 (Furan *C*H), 114.3 (Ar*C*(3,5)H), 118.8 (Furan*C*Ar4-*OMe*), 124.0 (Ar*C*H), 127.7 (ArC(4)H), 128.6 (Ar*C(1)*), 128.9 (Ar*C(1)*), 129.6 (ArCH), 130.2 (ArC(1)), 148.6 (Furan*C*Ph), 155.6 (Furan*C*Ar4-OMe), 166.6 (Ar*C(4)*H); HRMS (ESI$^+$) $C_{24}H_{20}O_3Na$ $[M+Na]^+$ found 373.1413, requires 373.1418 (+0.70 ppm).

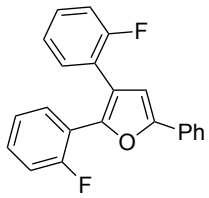
2,3-bis(4-fluorophenyl)-5-phenylfuran, 471



Following **General Procedure Q**, (*E*)-1,2-bis(4-fluorophenyl)-2-hydroxy-4-phenylbut-3-en-1-one, **449/450** (35 mg, 0.1 mmol), 2-carboxyphenylboronic acid **402** (0.3 mg, 2 µmol) and oxalic acid **62** (0.2 mg, 2 µmol) in CH_3CN (1.0 mL) were reacted at 50 °C for 6 h. The crude was

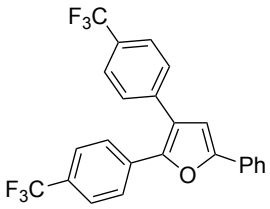
purified by silica-gel column chromatography (petrol/EtOAc, 98:2 to 96:4, R_f: 0.29) to give title compound **471** (20 mg, 60%) as a sticky yellow solid, with spectroscopic data in accordance with the literature.[212] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.78 (1H, s, C*H*), 6.97–7.04 (2H, m, ArC*H*), 7.06–7.14 (2H, m, ArC*H*), 7.29–7.35 (1H, m, ArC*H*), 7.36–7.48 (4H, m, ArC*H*), 7.50–7.60 (2H, m, ArC*H*), 7.71–7.79 (2H, m, ArC*H*).

2,3-bis(2-Fluorophenyl)-5-phenylfuran, 472



Following **General Procedure Q**, (*E*)-1,2-bis(2-fluorophenyl)-2-hydroxy-4-phenylbut-3-en-1-one, **451** (35 mg, 0.1 mmol), 2-carboxyphenylboronic acid **402** (0.3 mg, 2 µmol) and oxalic acid **62** (0.2 mg, 2 µmol) in CH_3CN (1.0 mL) were reacted at 50 °C for 6 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 98:2 to 96:4, R_f: 0.29) to give title compound **472** (20 mg, 60%) as a sticky yellow solid. ν_{max} 3043, 2937 (C-H), 1668 (C=C), 1228 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.96 (1H, s, C*H*), 7.02–7.20 (4H, m, ArC*H*), 7.26–7.35 (4H, m, ArC*H*), 7.39–7.47 (2H, m, ArC*H*), 7.54–7.63 (1H, m, ArC*H*), 7.73–7.82 (2H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 109.1 (Furan *C*H), 116.0 (d, $^2J_{C\text{-}F}$ 22.0, Ar*C*(3)H), 116.3 (d, $^2J_{C\text{-}F}$ 21.3, Ar*C*(3)H), 120.6 (Furan*C*Ar2-F), 124.1 (d, $^4J_{C\text{-}F}$ 3.8, Ar*C*(5)H), 124.2 (d, $^4J_{C\text{-}F}$ 3.7, Ar*C*(5)H), 128.9 (Ar*C*Ph), 130.0 (d, $^3J_{C\text{-}F}$ 8.2, ArC(4)H×2), 130.2 (Ar*C*(1*)*Ph), 130.5 (d, $^3J_{C\text{-}F}$ 8.8, ArC(6)H×2), 153.6 (d, $^1J_{C\text{-}F}$ 268, Ar*C*(2)CF×2), 171.3 (Furan*C*Ph), 172.7 (Furan*C*Ar2-F); ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: –114.2, –111.6; HRMS (ESI$^+$) $C_{22}H_{17}F_2O$ $[M+H]^+$ found 333.1083, requires 332.1113 (–0.54 ppm).

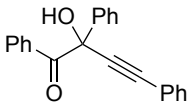
5-Phenyl-2,3-bis(4-(trifluoromethyl)phenyl)furan, 473



Following **General Procedure Q**, (*E*)-2-hydroxy-4-phenyl-1,2-bis(4-(trifluoromethyl)phenyl)but-3-en-1-one, **452/453** (45 mg, 0.1 mmol), 2-carboxyphenylboronic acid **402** (0.3 mg, 2 μmol) and oxalic acid **62** (0.2 mg, 2 μmol) in CH_3CN (1.0 mL) were reacted at rt for 48 h. The crude was purified by silica-gel column chromatography (petrol/EtOAc, 98:2 to 96:4, R_f*:* 0.31) to give title compound **473** (8.5 mg, 19%) as a sticky yellow solid, with spectroscopic data in accordance with the literature.[212] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.84 (1H, s, C*H*), 7.42–7.49 (2H, m, ArC*H*), 7.55–7.62 (2H, m, ArC*H*), 7.65–7.74 (4H, m, ArC*H*), 7.74–7.86 (4H, m, ArC*H*), 8.09–8.16 (1H, m, ArC*H*).

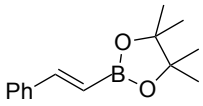
7.5.7 Different synthesis

2-Hydroxy-1,2,4-triphenylbut-3-yn-1-one, 455



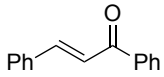
To a solution of benzil **386** (2.11 g, 10 mmol) in anhydrous Et_2O (36 mL) under nitrogen atmosphere at –10 °C was added dropwise solution of (phenylethynyl) lithium (15 mL in THF, 1.1 equiv., 11 mmol freshly prepared from phenyl acetylene **454** (1.0 mL, 9.11 mmol) and ^{n}BuLi (1.6 M in hexane, 6 mL)). The reaction was stirred for 6 h at rt before being quenched with cold water (10 mL). The suspension was extracted with Et_2O (3×30 mL). The combined organics were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was was purified by silica-gel column chromatography (petrol/EtOAc, 80:20 to 50:50, R_f*:* 0.18) to give title compound **455** (0.38 g, 13%) as a colourless oil, with spectroscopic data in accordance with the literature.[213] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 5.58 (1H, s O*H*), 7.30–7.40 (8H, m, ArC*H*), 7.42–7.50 (3H, m, ArC*H*), 7.63–7.69 (2H, m, ArC*H*), 8.05–8.12 (2H, m, ArC*H*).

(*E*)-Prop-1-en-1-ylbenzene-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 457



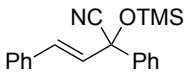
Phenyl acetylene **454** (300 μL, 2.72 mmol), bis(pinacolato)diboron **456** (0.83 g, 3.27 mmol), Cs_2CO_3 (1.78 g, 3.27 mmol) and $FeCl_3$ **20** (22 mg, 0.12 mmol) in acetone (14 mL) were mixed and heated at 60 °C for 12 h. After completion of the reaction, EtOAc (10 mL) was added the organic layer was filtered to remove the catalyst. The organic layer was washed with water (10 mL). The aqueous layer was extracted with EtOAc (3x10 mL) and combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 80:20, R_f: 0.38) to give title compound **457** (0.17 g, 40%) as a pale yellow oil, with spectroscopic data in accordance with the literature.[127] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.21 (12H, s C*H*$_3$), 6.17 (1H, d, *J 18.9,* C*H*B), 7.23–7.30 (3H, m, ArC*H*), 7.35–7.45 (3H, m, ArC*H* and C*H*CHB).

(*E*)-Chalcone, 458



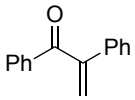
Benzaldehyde (1 mL, 9.8 mmol) and acetophenone (1.3 mL, 10.78 mmol) were dissolved in EtOH (28 mL) and aqueous solution of NaOH (0.6 M) was added using a dropping funnel at 0 °C. The reaction was left to warm to rt for 16 h before refrigerating the mixture for 1 h. The resulting solid was filtrated under vacuum and washed three times with cold ethanol and water. The crude product was sufficiently pure to use directly in the next step. The title compound **458** (1.99 g, 97%) was obtained as a pale yellow solid, with spectroscopic data in accordance with the literature.[214] mp 55-56 °C {Lit[214] 55–57 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 7.39–7.47 (3H, m, ArC*H*), 7.48–7.55 (2H, m, ArC*H*), 7.58–7.61 (2H, m, ArC*H*), 7.62–7.70 (2H, m, ArC*H* and CHC*H*CO), 7.83 (1H, d, *J 15.7,* C*H*CHCO), 8.00–8.08 (2H, m, ArC*H*).

(*E*)-2,4-Diphenyl-2-((trimethylsilyl)oxy)but-3-enenitrile, 460



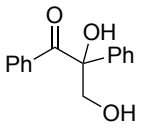
To a solution of chalcone **458** (0.5 g, 2.4 mmol) and TMSCN **459** (330 µL, 2.64 mmol) in CH_3CN (2.5 mL) was added 1 mM solution of TBD (3.5 mg, 24 µmol), in CH_3CN at rt. After reaction was stirring for 7 h, the solution was extracted with EtOAc (3x10 mL) and the combined organic layers washed with water, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica-gel column chromatography (petrol/EtOAc, 97:3 to 90:10, R_f*:* 0.38) to give title compound **460** (0.37 g, 85%) as a pale yellow oil, with spectroscopic data in accordance with the literature.[129] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.24 (9H, s (C*H*$_3$)$_3$), 6.19 (1H, d, *J 15.9,* PhCHC*H*), 7.01 (1H, d, *J 15.9,* PhC*H*CH), 7.30–7.48 (8H, m, ArC*H*), 7.51–7.63 (2H, m, ArC*H*).

1,2-Diphenylprop-2-en-1-one, 462



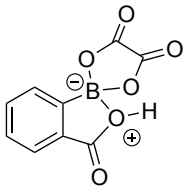
To a stirred solution of deoxybenzoin **461** (1.0 g, 5.1 mmol) in MeOH (13 mL), was added formaldehyde (37% aq. solution, 1.9 mL), piperidine (65 µL, 0.66 mmol) and acetic acid (64 µL, 0.22 mmol). The reaction was heated at reflux for 3 h. The reaction was cooled to rt and concentrated. Crude mixture was washed with water and extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were washed with water, brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was sufficiently pure to use directly in the next step. The title compound **462** (0.96 g, 90%) was obtained as a colourless oil, with spectroscopic data in accordance with the literature.[215] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 5.65 (1H, s, C*H*^{A}H^B), 6.08 (1H, s, CH^A*H*^{B}), 7.31–7.40 (3H, m, ArC*H*), 7.40–7.48 (4H, m, ArC*H*), 7.51–7.65 (1H, m, ArC*H*), 7.80–8.05 (2H, m, ArC*H*).

2,3-Dihydroxy-1,2-diphenylpropan-1-one, 463



Tert-butyl alcohol (5 mL), water (5 mL) and AD-mix-ß (1.35 g, 1.73 mmol) were stirred at rt for 30 min. After, 1,2-diphenylprop-2-en-1-one **462** (0.20 g, 0.96 mmol) was added and the heterogeneous slurry was stirred vigorously at rt for 20 h. Sodium sulphite was added and stirred for 1 h before extractions with EtOAc (3x10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was sufficiently pure to use directly in the next step. The title compound **463** (0.96 g, 90%) was obtained as a sticky orange solid, with spectroscopic data in accordance with the literature.[216] ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.38 (1H, d, *J* 12.7 C*H*^{A}H^B), 4.50 (1H, d, *J* 12.7 CH^A*H*^{B}), 4.64 (1H, s, OH), 7.30–7.38 (2H, m, ArC*H*), 7.39–7.47 (2H, m, ArC*H*), 7.48–7.57 (2H, m, ArC*H*), 7.86–7.98 (4H, m, ArC*H*).

3-hydroxy-spiro[benzo[*c*][1,2]oxaborole-1,2'-[1,3,2]dioxaborolane]-4',5'-dione, 474



2-Carboxyphenylboronic acid **402** (0.15 g, 0.90 mmol) and oxalic acid **62** (81 mg, 0.90 mmol) were dissolved in $MeNO_2$ (10 mL) and the reaction was stirred at rt for 16 h. The reaction was concentrated under reduced pressure to give boronate ester complex **474** (0.22 g, 96%) as a white powder. Analysis by NMR showed **474** in d_6-DMSO: mp 267–273 °C; ν_{max} (film) 3417, 1787, 1678, 1454, 1334, 936; ^{1}H NMR (300 MHz, d_6-DMSO) δ_H: 7.40–7.46 (1H, m, ArC*H*), 7.48–7.54 (2H, m, ArC*H*), 7.61–7.65 (1H, m, ArC*H*); ^{11}B{^{1}H} NMR (160 MHz, d_6-DMSO) δ_B: 9.25; ^{13}C{^{1}H}NMR (126 MHz, d_6-DMSO) δ_C: 123.9 (ArC(5)H), 128.7 (ArC(4)H), 129.0 (ArC(3)H), 129.1 (ArC(6)H), 132.6 (ArC(2)), 136.8 (ArC(1)B), 160.0 (O_2CCO_2), 161.1 (O_2CCO_2), 171.7 (*C*O).

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