Borrowing Hydrogen in the Synthesis of Alcohols and Amines

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Signed..... Date.....

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Abstract

This thesis is concerned with the transformation of carbonyl compounds and allylic alcohols (and some amines) into alcohols *via* the process of transfer hydrogenation. The main work develops the idea of a new hydrogen donor for transfer hydrogenation and then applies it to an impressive one pot reaction. The transformation of amines shows an unexpected reaction and investigation into this reveals a possible mechanism for the reaction.

Chapter 2: 1,4-Butanediol is introduced as a new hydrogen donor. It is used to convert a wide range of carbonyl substrates successfully into their alcohol counterparts after optimisation of conditions. A comparison with other straight chain alkanediols proves that 1,4-butanediol is the most suitable diol to use. The asymmetric aspect of the chemistry is investigated, but the results obtained do not compare to those already published in the literature.[1]

Chapter 3: A one pot reaction of isomerisation and reduction of allylic alcohols is proposed and proven. This is achieved by using 1,4-butanediol as the solvent and hydrogen donor. A wide range of allylic alcohols are converted to their corresponding saturated alcohols. The conditions were not applicable to asymmetric results.[2]

Chapter 4: The reaction of straight chain alkanediols with themselves is discovered and investigated to find they produce cyclic acetals. Results vary depending on the length of the alkyl chain. A series of experiments improved initial results to complete conversion. However isolation of these compounds remains a problem and requires more work.

Chapter 5: During the synthesis of Diphenhydramine, an unexpected rearrangement reaction was discovered. This reaction was found to be specific to a certain structural arrangement on the compound. Investigations using ^{13}C labelling found a plausible mechanism to explain the reaction.[3]

Acknowledgements

First and foremost, my thanks go to Professor Jon Williams for his unrelenting help, support, patience and faith in me over the last few years. In times where I have struggled, he has always brought me back to reality and refocused my attention to where it needed to be. It has not been an easy journey, but I am grateful and relieved to have made it!

To Alex, who has been fantastic over the last three years. I want to thank you for your emotional support and never ending love, no matter what state I get myself into. Not only have you been my best friend, but you have taught me so many things about myself, life and love. Your patience has been infallible and known no bounds, and frankly how you put up with me sometimes I will never know! Thank you for making me a better person and teaching me how to cope with all the evils life throws at you. I love you with all my heart.

To my family, thank you for helping me to achieve my PhD! Thanks must go to both my Mum and my sister, Sarah, for listening to an endless number of whinges about chemistry. Sarah especially deserves extra credit as she describes hearing about chemistry as “another language” because she doesn’t understand any of it. They also deserve thanks for their support, both emotionally and financially! Hopefully one day I can repay my debt.

To John Lowe, Anneke Lubben and Mary Mahon, thanks for your help with NMR, mass spectrometry and X-ray crystallography respectively! John must get a special thank you, for always running my samples with enthusiasm and going above and beyond the call of duty to get the right result for me.

Finally, thanks go to the members of the Williams group, past and present. To Paul, who taught me so much in the early days and is still a fantastic friend today, I owe a great deal of gratitude. Haniti was a wonderful friend and a joy to work with, because she always made you smile no matter how bad things were feeling! Andy, Tracy, Liana, James and Ory all deserve thanks for

making my final year at Bath a much better one than my previous two. Thank you for all the questions you answered, all the times you've made me laugh and all the times you've made me feel happier about chemistry and life in general when I've been down. I would also like to thank the members of the Bull group, past and present over the last three years, particularly Iwan, for their friendship and laughs when we've all felt like not doing work!

Abbreviations

aq.	aqueous
atm	atmospheres
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
cat.	catalyst
cod	cyclooctadiene
conv.	conversion
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
CSA	camphorsulphonic acid
Cy	cyclohexyl
d	day(s)
DCE	dichloroethane
DCM	dichloromethane
DMSO	dimethylsulphoxide
DPEN	1,2-diphenylethylenediamine
DPEphos	Bis[(2-diphenylphosphino)phenyl]ether
dppf	1,1'-*bis*(diphenylphosphino) ferrocene
ee	enantiomeric excess
en	1,2-ethanediamine
equiv.	equivalent
F	Faraday constant, F = 9.648 x 10^4 C
FGI	functional group interconversion
G	Gibbs free energy
H	enthalpy
h	hour(s)
HIV	human immunodeficiency virus
^{i}Pr	*iso*-propyl
K	equilibrium constant
k	rate constant
LDA	lithium diisopropylamide
LiDTBB	lithium 4,4'di-*tert*-butylbiphenyl
LiHMDS	lithium bis(trimethylsilyl)amide

[M]	metal catalyst
mesitylene	1,3,5-trimethylbenzene
min.	minute(s)
MPV	Meerwein-Ponndorf-Verley reduction
MS	molecular sieves
N_A	Avagadro constant, $N_A = 6.023 \times 10^{23}$ mol^{-1}
n-BuLi	normal-butyl lithium
t-BuLi	tert-butyl lithium
n/d	not determined
NMP	*N*-methylpyrrolidone
o/n	overnight
OTC	over-the-counter
[ox]	oxidizing agent
PBT	poly(butylene terephthalate)
PCA	principal component analysis
p-cymene	*para-iso*propyltoluene
Ph	phenyl
PhMe	toluene
p-TsOH	*para*-toluenesulphonic acid
R	gas constant, R = 8.314 J K^{-1} mol^{-1}
rac	racemic
r.t.	room temperature
S	entropy
sec	secondary
T	temperature
^{t}Bu	*tert*-butyl
Tf	triflate
tert	tertiary
THF	tetrahydrofuran
trig	trigonal
Ts	tosyl
TsDPEN	(1*S*,2*S*)-(+)-*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine
Xantphos	4,5-*bis*(diphenyl-phosphino)-9,9-dimethylxanthene

CHAPTER 1 - INTRODUCTION

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1.1 Alcohols

In the chemistry world, alcohols are very useful synthetic intermediates, even though the amount of functional interconversions they can undergo is limited.

Alcohols have two main transformations, alkylations and oxidations (Figure 1.1).

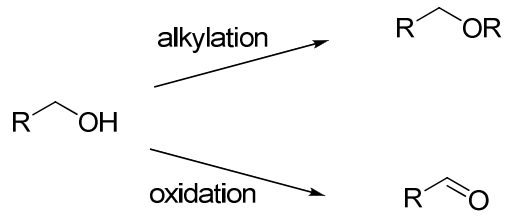
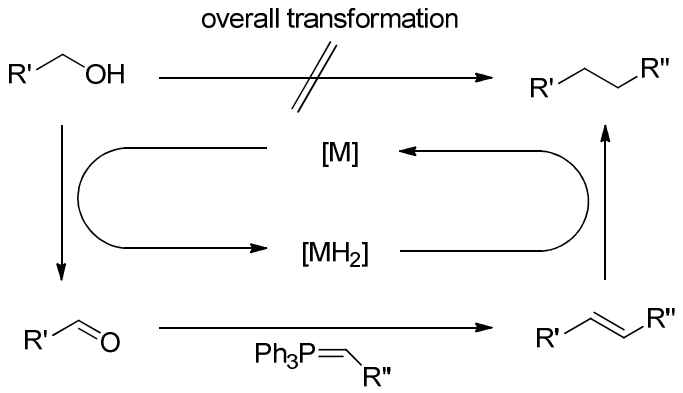


Figure 1.1 – Principal reactions of alcohols

Alkylations usually lead to ethers, or a group which enhances the leaving properties. Oxidation to carbonyl compounds however, provides a larger amount of available reactions. Carbonyl compounds are much more versatile than alcohols, with Aldol reactions, Wittig reactions, McMurry couplings, imine formations and Grignard reactions being just a few of the reactions that could be carried out.

In terms of synthetic chemistry, taking an alcohol, oxidising to a carbonyl compound and then carrying out another reaction is an attractive prospect. This is not a new idea, and has been carried out extensively by the Williams group. For example, alcohols have been transformed into alkanes in one pot *via* oxidation of the alcohol, an *in situ* Wittig reaction and subsequent reduction (Scheme 1.1).[4]



Scheme 1.1 – One pot reaction of an alcohol to an alkane

This reaction oxidises the alcohol by the removal of hydrogen and storage of this hydrogen on the metal catalyst. This hydrogen is stored, or "borrowed" by the metal whilst a different reaction takes place (here the Wittig reaction), and is then returned to furnish the desired alkane product. This "borrowing hydrogen" is a phrase that has been coined by Williams, and has been applied to other types of *in situ* reactions, such as imine formation[5] to form amines. However, in order to understand these one pot reactions properly, we need to understand the principle of transfer hydrogenation, which is the process on which the initial step is reliant.

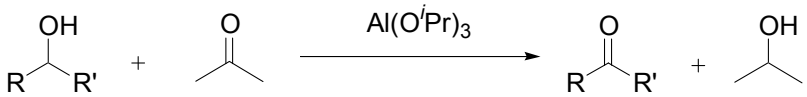
1.2 Transfer Hydrogenation

Transfer hydrogenation is a process in which hydrogen is removed from one compound and delivered to another. The overall net transformation is one oxidation and one reduction. A catalyst is usually essential for this process, otherwise unselective reactions can occur and may require extended time periods. The earliest examples of transfer hydrogenation were reported by Oppenauer, Meerwein, Ponndorf and Verley (see Section ***1.2.1***).

1.2.1 The Oppenauer Oxidation and the Meerwein-Ponndorf-Verley Reduction

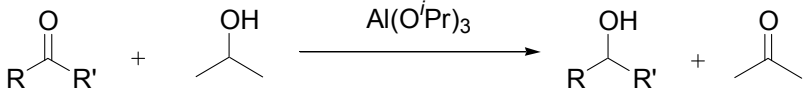
Oxidation and reduction reactions are usually irreversible, but the Oppenauer[6] oxidation and the Meerwein-Ponndorf-Verley (MPV)[6] reduction are both reversible processes.

The Oppenauer oxidation oxidises an alcohol to a carbonyl compound in the presence of an excess of a ketone, which acts as a hydrogen acceptor (Scheme 1.2).



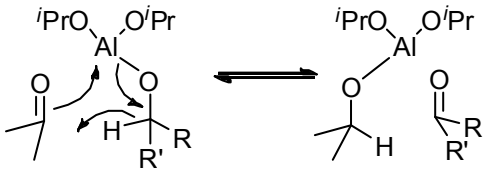
Scheme 1.2 – Oppenauer oxidation

The MPV reduction does the exact opposite – it reduces a carbonyl compound in the presence of an excess of alcohol, which acts as a hydrogen donor (Scheme 1.3).



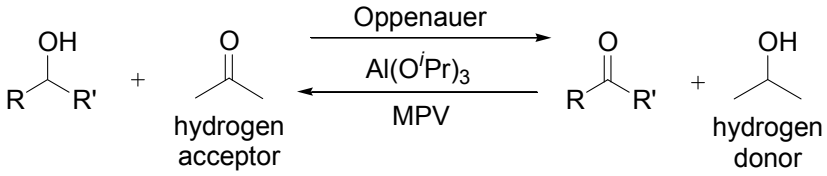
Scheme 1.3 – The Meerwein-Ponndorf-Verley reduction

Both reactions use the same aluminium reagent – Al(O^{i}Pr)$_3$. The reagent could be described as catalytic because the reaction will not proceed without it. However, the amount of reagent required is stoichiometric and the species is not regenerated at the end of the reaction. The aluminium acts by binding to the oxygen of both compounds, which is similar to the action of a normal catalyst. Scheme 1.4 shows the cyclic transition state which the aluminium goes through to transfer hydrogen from one compound to another. The diagram shows the transition state for an Oppenauer oxidation.[6-7] This type of hydrogen transfer is known as “direct H-transfer”[8] because it involves both the donor and acceptor being bound to the metal.



Scheme 1.4 – Cyclic transition state for an Oppenauer oxidation

The Oppenauer oxidation and MPV reduction reactions are known as transfer hydrogenation processes, and generate an equilibrium between the alcohol and carbonyl compound. The position of equilibrium can be determined by examining the oxidation potentials of the two ketones involved. The higher the oxidation potential of a carbonyl compound, the easier it is to be reduced, so the equilibrium will lie towards the side which has the ketone with the lower oxidation potential.



Scheme 1.5 – The Oppenauer oxidation and the MPV reduction in equilibrium

The position of equilibrium is easily calculated from the concentration of the species present in the reaction (Figure 1.2).

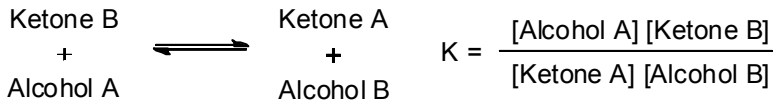


Figure 1.2 – How equilibrium constants are determined

The specific equation for K is as follows:

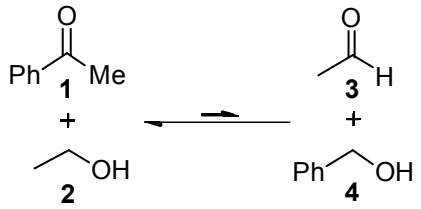
$$K = 10^{((E_1 - E_2) / 29.6)}$$

where E_1 and E_2 are the oxidation potentials of the two ketones (in mV) and 29.6 is RT/N_AF (for mV). The ratio of ketones at equilibrium is given by $\sqrt{K}$:1. For example, in a system with equal amounts of acetophenone **1** (118 mV)

and ethanol **2** (226 mV)[9], the equilibrium is 67:1 in favour of the acetophenone **1** (Scheme 1.6). The rate constant and ratio calculations are as follows:

$K = 10^{((226 - 118) / 29.6)} = 4453$

$\sqrt{K} = 67$, therefore the ratio is 67:1. This illustrates that primary alcohols are therefore a poor choice as a reducing agent.



Scheme 1.6 – Equilibrium between acetophenone **1** and acetaldehyde **3**

1.2.2 Transfer hydrogenation with transition metal catalysts

Transfer hydrogenation is also widely employed with transition metal catalysts. The most popular metals used are ruthenium, iridium and rhodium. These have a different catalytic action to that of aluminium, and can often form a transition metal hydride during the catalytic cycle.[8] This transition metal hydride species can either be mono- or dihydride. Rhodium and iridium usually form the simpler monohydride species, whereas ruthenium can form both (Figure 1.3).

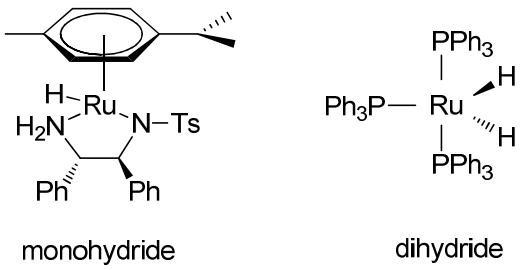


Figure 1.3 - Examples of monohydride and dihydride ruthenium species

This type of hydrogen transfer is known as the “hydridic route”, where the donor and the acceptor interact separately with the metal centre. The hydridic

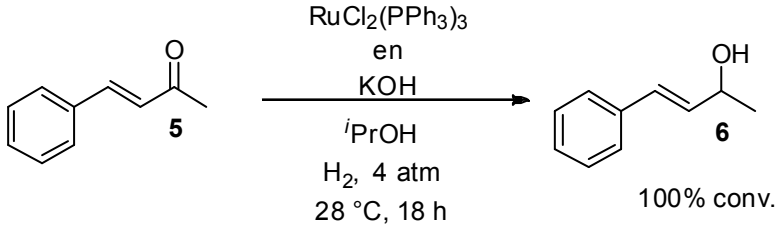
route is followed by transition metals, where as the direct H-transfer (as mentioned above) is followed by non-transition metals.

1.3 Ruthenium as a catalyst

Ruthenium is a very useful metal to use as a catalyst because it can be found in varying oxidation states between -2 (*e.g.* $Ru(CO)_4^{2-}$) to +8 (*e.g.* RuO_4). Within each oxidation state, a variety of geometries can be found. These factors mean that ruthenium can be used for a wide variety of catalytic transformations, for example, hydrogenation (both direct and transfer), oxidation, cyclopropanation, isomerisation, metathesis and carbon – carbon bond forming reactions.

1.3.1 Ruthenium catalysed hydrogenation

Ruthenium can hydrogenate both aldehydes and ketones to give primary and secondary alcohols, as well as converting alkenes into alkanes, and imines into amines. Selectivity can be achieved for one type of bond over another; for example, Noyori *et al.* have reduced carbonyls selectively over alkenes.[10] The following example shows the reduction of the carbonyl bond in *trans*-4-phenyl-3-buten-2-one **5** with the alkene remaining untouched (Scheme 1.7).

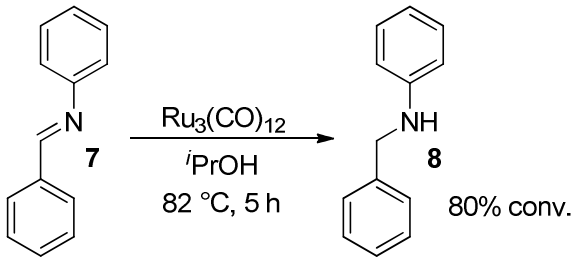


ketone:Ru:diamine:KOH ratio = 10,000:1:1:2

Scheme 1.7 – Selective reduction using ruthenium

This hydrogenation takes place *via* activation of the hydrogen gas by the ruthenium catalyst. This differs to transfer hydrogenation since a donor is required to produce that hydrogen. The most commonly used donors are *iso*-

propanol and formic acid (mixed with triethylamine in a 5:2 ratio). When an alcohol is used as a donor, the hydrogen is removed from it in order to facilitate the reduction. An example of the reduction of an imine *via* transfer hydrogenation is given in Scheme 1.8.[11]

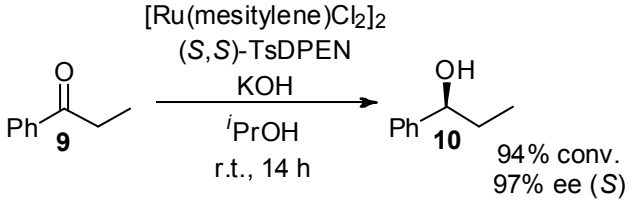


Scheme 1.8 – Reduction of imine **7** using *iso*-propanol *via* transfer hydrogenation

In the case of formic acid, hydrogen (and carbon dioxide) is evolved. This evolved hydrogen is then used by the catalyst to reduce the carbonyl. The exact mechanism involved is not clear, however, it is thought that the hydrogen must at some point be bound to the metal centre in order for it to be transferred.[12]

1.3.2 Asymmetric ruthenium catalysed hydrogenation

When the ruthenium catalyst and hydrogen donor are used in conjunction with a chiral ligand, asymmetric reduction is readily achieved (Scheme 1.9).[13]



Scheme 1.9 – Asymmetric reduction using a chiral ligand

Scheme 1.9 shows the conversion of propiophenone **9** under mild conditions into (*S*)-1-phenyl-1-propanol **10** using *iso*-propanol as the hydrogen donor, and (*S*,*S*)-TsDPEN **11** as the chiral ligand. The structure of (*S*,*S*)-TsDPEN **11** is shown in Figure 1.4.

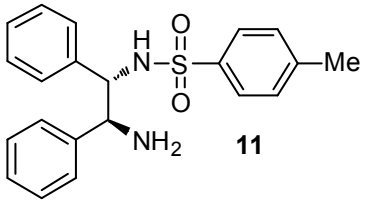


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Figure 1.4 – Structure of (*S*,*S*)-TsDPEN **11**

There are two comprehensive reviews which cover the topic of asymmetric transfer hydrogenation[8,14]. Gladiali's review from 2006 concentrates on the chiral ligands and their applications in asymmetric synthesis and kinetic resolution. It does however mention that Noyori's catalyst (a version of which is shown above in Scheme 1.9) has the "*broadest scope as it provides significant ee's with a large variety of substrates*" (Wills, 2008). A study by Wills *et al.* in 2004[15] showed that TsDPEN **11** is an ideal ligand for the asymmetric transfer hydrogenation of ketones because it has matched stereogenic centres (*i.e.* the chiral centres are both (*S*,*S*), or (*R*,*R*)) and the *trans* nature of the phenyl groups help to provide further stereocontrol.

Wills has developed a series of catalysts which are very similar to Noyori's original catalyst (of a ruthenium arene dichloride dimer and enantiomerically pure diamine). These catalysts are either ruthenium[16] or rhodium[17] based, and contain a "tether" between the diamine and the arene (in the case of ruthenium) or the tetramethylcyclopentadienyl group (in the case of rhodium) (Figure 1.5).

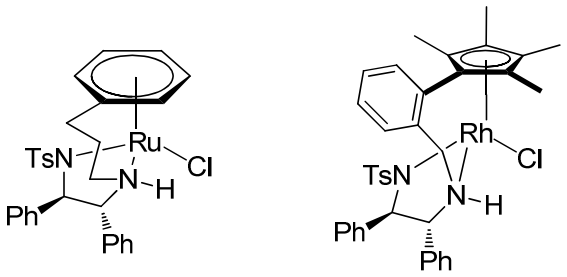
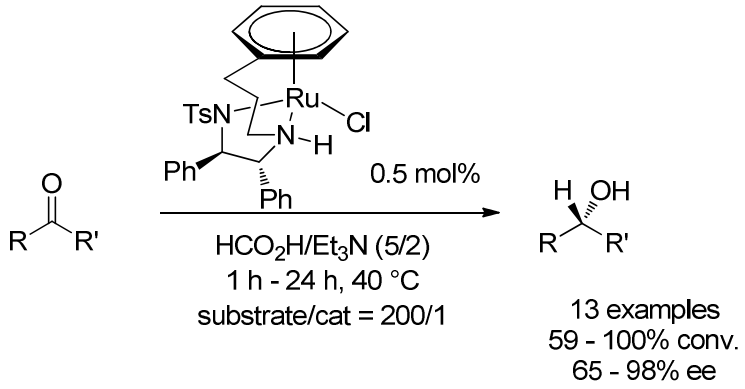


Figure 1.5 – Examples of Wills' tethered ruthenium and rhodium catalysts

These complexes furnish high enantioselectivities when used in a formic acid/triethylamine mixture (ratio 5/2). Their activity however, is much reduced when used in *iso*-propanol, due to the lack of solubility in this solvent.

The ruthenium complex has been shown to reduce a wide range of ketones including substituents such as furan, thiophene, pyridine and an aromatic ortho-methoxy group (Scheme 1.10).[18]



Scheme 1.10 – Ruthenium catalysed reduction of ketones

Studies have been carried out on this catalyst to investigate the effect of the length of the tether,[19] the introduction of a benzylic linker[20] (like the rhodium complex in Figure 1.5) and the introduction of a cyclohexyldiamine ligand[20] instead of the diphenyl substituted diamine.

The rhodium complex has been shown to reduce a wide range of ketones, from those containing aromatic ortho-chloro, -trifluoromethyl and –methoxy substituents to those containing heterocycles such as furans, thiophenes and pyridines. The conversions range from 27 – 100% and ees from 62 – 99%.[21] The same rhodium catalyst has also been used to reduce a similar range of ketones in water with sodium formate,[21] obtaining conversions of 96 – 100% with ees of 51 – 98%. Further to this, the use of the rhodium complex has been extended to reduce imines.[22]

1.4 1,4-Butanediol 12

The majority of this thesis focuses on the use of diols as hydrogen donors in transfer hydrogenation. 1,4-Butanediol **12** is the main focal point of the studies.

1.4.1 Formation of 1,4-Butanediol 12

At the current time, 1,4-butanediol **12** can be produced from several routes. The following process obtains 1,4-butanediol **12** from crude oil. Maleic anhydride **13** (Figure 1.6) is taken from the C4 fraction of crude oil, and *via* a reduction, hydration (to succinic acid **14**) and reduction, 1,4-butanediol **12** can be formed (Scheme 1.11).

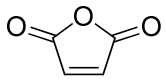


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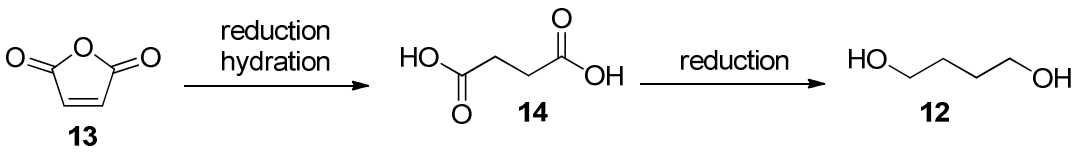
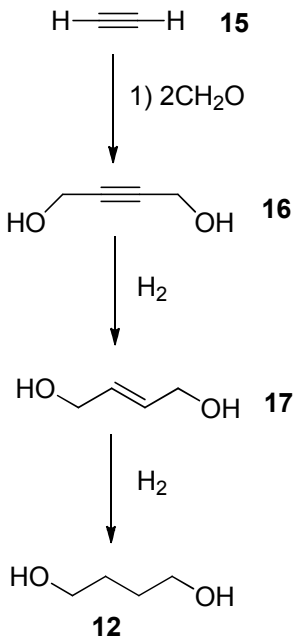
Figure 1.6 – Structure of maleic anhydride **13**



13 **14** **12**

Scheme 1.11 – Conversion of maleic anhydride **13** to 1,4-butanediol **12**

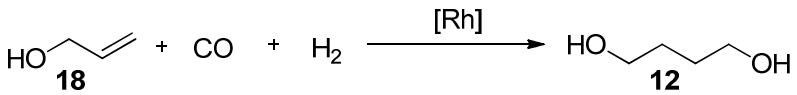
A second route utilises the 'Reppe Process', which was named after a chemist named Walter Reppe. He developed the carbonylation of acetylene **15**. The process uses ruthenium and a rhodium catalyst at a temperature in excess of 300 °C and a pressure of 900 atm.[23] This process has been adapted to carry out hydrocarbonylation, where a reactant with an active hydrogen, *e.g.* alcohols, water, amines, reacts with the olefin/acetylene. 1,4-Butanediol **12** can be produced from acetylene **15** using this hydrocarbonylation (Scheme 1.12).



Scheme 1.12 – Formation of 1,4-butanediol **12** from acetylene **15**

The initial first step is the Reppe process, converting acetylene **15** to 2-butyne-1,4-diol **16**. Then two subsequent hydrogenations give 1,4-butanediol **12**, *via* 2-butene-1,4-diol **17**.

A third route to produce 1,4-butanediol **12** involves the hydroformylation of allyl alcohol **18** (Scheme 1.13).

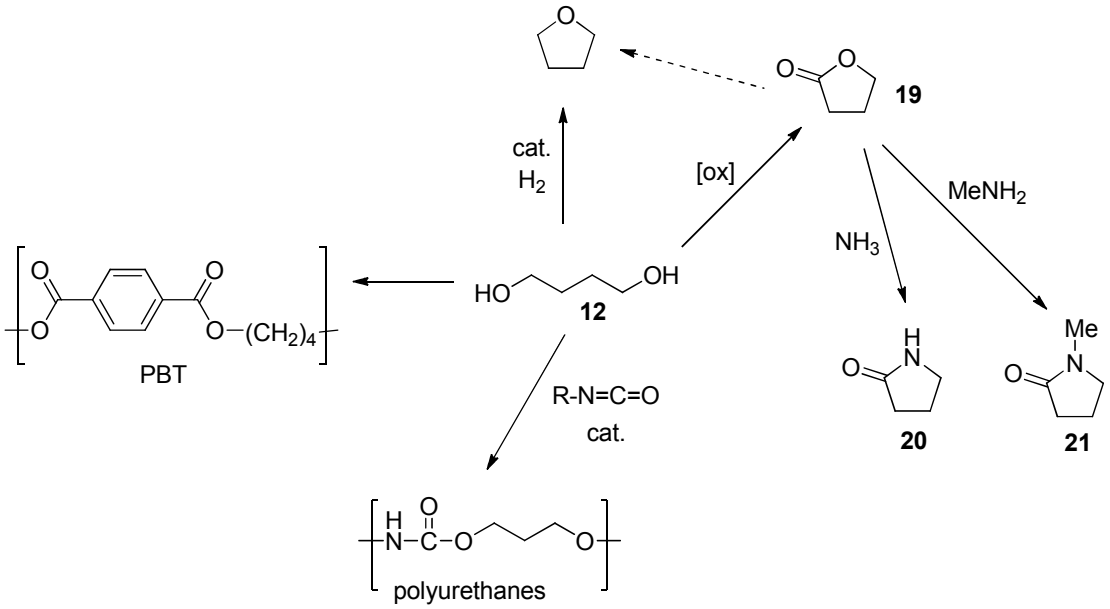


Scheme 1.13 – Hydroformylation of allyl alcohol **18**

1.4.2 Uses of 1,4-butanediol 12

1,4-Butanediol **12** is used mainly as a solvent, but it is more widely used to make other commodity chemicals or polymers. It is easily converted into THF, which itself has uses as a solvent. 1,4-Butanediol **12** is also easily transformed into γ-butyrolactone **19** (and can be by transfer hydrogenation, see Scheme 2.3). γ-Butyrolactone **19** can be further converted into

pyrrolidones, for example, pyrrolidin-2-one **20** and NMP (*N*-methylpyrrolidone) **20** (Scheme 1.14).



Scheme 1.14 - The conversion of 1,4-butanediol **12** into other compounds

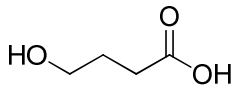
1,4-Butanediol **12** is also used in the manufacture of poly(butylene terephthalate) (PBT). This polymer has a high strength, a good thermal stability and is very durable, thus it is used widely in the electrical and automotive industries. In the area of polyurethanes, 1,4-butanediol **12** is used as a component or a chain extender. The properties which 1,4-butanediol **12** lends to these polymers means that the end products have good mechanical properties over a range of temperatures. It aids crystallinity in certain polymers which can also improve their properties.

1.4.3 1,4-Butanediol 12 from renewable materials

With the increasing demands for green processes and CO_2 neutral resources, biotechnology is receiving a large amount of attention. Several recent publications[24,25] and two patents[26,27] detail how 1,4-butanediol **12** can be produced from renewable feedstocks. An American company named Genomatica filed both of the patents, and their process is to produce 1,4-butanediol **12** directly from sugar. They are expecting this biomanufacture to

reduce greenhouse gas emissions by up to 25% and energy emissions by up to 30% compared with current processes.[28]

The way in which the 1,4-butanediol **12** is produced is by the use of a bioorganism. The bioorganism is not naturally occurring, and has been manipulated by gene disruption in order to couple growth of the organism with the production of 1,4-butanediol **12**. The bioorganism converts a low cost renewable feedstock, such as sugar, into 4-hydroxybutanoic acid **22** (Figure 1.7).



22

Figure 1.7 – Structure of 4-hydroxybutanoic acid **22**

This compound is then subsequently converted into γ-butyrolactone **19** and 1,4-butanediol **12**. All these pathways can be carried out using enzymes or bioorganisms.

In the order of one million metric tonnes of 1,4-butanediol **12** is produced worldwide every year with an estimated 4 – 5% annual growth. The demand for this compound is so high because of all the chemicals it can be used to make (see Section ***1.4.2***). Therefore, a synthesis based on bioorganisms is a very attractive option. This makes 1,4-butanediol **12** an ideal compound to use in chemical synthesis, because it will become a renewable chemical of the future.

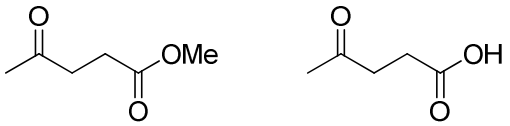
CHAPTER 2 - RESULTS AND DISCUSSION I

CHAPTER 2 - RESULTS AND DISCUSSION I

2.1 Background

The reduction of carbonyl compounds to alcohols is a very common, well used and well researched reaction. The area of ruthenium catalysed hydrogenation has three main ways in which carbonyl compounds can be reduced. These are hydrogenation using hydrogen gas, and two different types of transfer hydrogenation, using a hydrogen donor such as *iso*-propanol, or formic acid. It can be argued that each method has a drawback. Hydrogen gas is extremely flammable and can cause explosions, and sometimes high pressure equipment is required to carry out hydrogenations. The use of a hydrogen donor often means a vast excess of reagent, due to the fact that the reduction reaction is in equilibrium with the respective oxidation reaction (see Oppenauer Oxidation and Meerwein-Ponndorf Verley Reduction, Section ***1.2.1***). The drawback of a large excess of reagent also applies to formic acid. Formic acid is used in conjunction with triethylamine, leaving the reaction mixture basic upon completion. The idea of a new way of reducing carbonyl compounds is therefore attractive.

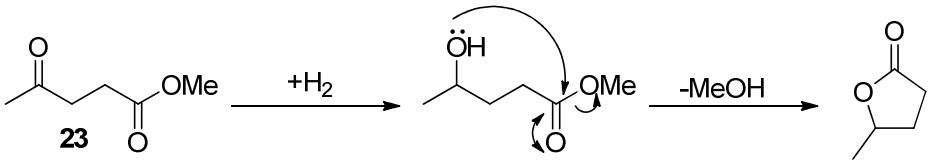
Previous work in the Williams group used a "lactone trap" in order to push the equilibrium of oxidations of secondary alcohols by transfer hydrogenation to completion.[29] A range of alcohols was oxidised to the corresponding ketones, using levulinic acid **24** or one of its esters (Figure 2.1).



Methyl Levulinate **23** Levulinic Acid **24**

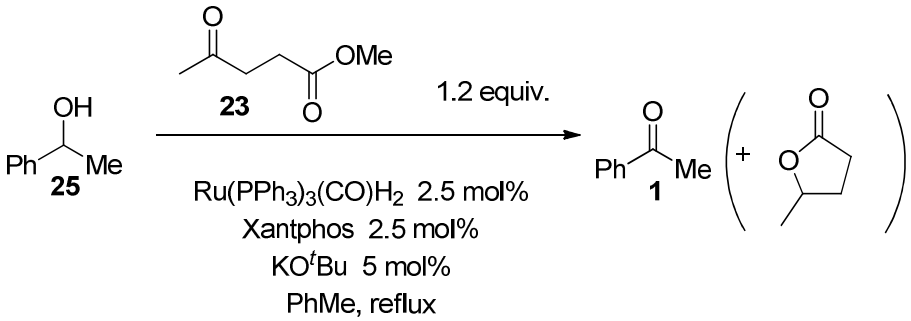
Figure 2.1 – Hydrogen acceptors used in previous work in the Williams group

These hydrogen acceptors are reduced during the reaction, and subsequently undergo an intramolecular cyclisation to form a γ-lactone (Scheme 2.1). This cyclisation renders the oxidation reaction irreversible, thus pushing the equilibrium to one side and achieving reaction completion.



Scheme 2.1 – Formation of the "lactone trap"

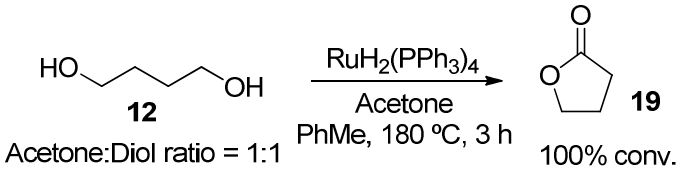
For example, *sec*-phenethyl alcohol **25** can be fully converted into acetophenone **1** in 24 hours using methyl levulinate **23** as the hydrogen acceptor (Scheme 2.2).



Scheme 2.2 – Example of oxidation

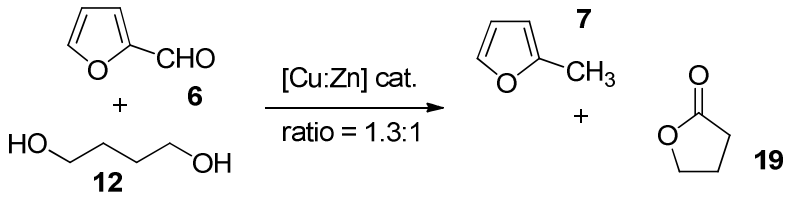
Using the principle of lactone formation, it was theorised that carbonyl reduction could be carried out in a similar fashion. All that would be required is a compound which once oxidised formed a lactone.

In 1981, Murahashi *et al.* showed that 1,4-butanediol **12** could be converted into γ-butyrolactone **19** using a ruthenium catalyst[30] (Scheme 2.3).



Scheme 2.3 – Conversion of 1,4-butanediol **12** into lactone **19**

There is also literature that reports 1,4-butanediol **12** being used as a hydrogen donor. 1,4-Butanediol **12** is used to achieve the reduction of furfural **26** to 2-methylfuran **27**[31] (Scheme 2.4). The reaction is attractive since both products, 2-methylfuran **27** and γ-butyrolactone **19**, are used in other processes, meaning there is little waste from the reaction. 2-Methylfuran **27** is used in the synthesis of insecticides and for intermediates in the perfume industry. γ-Butyrolactone **19** is used to produce *N*-methylpyrrolidone **20** (NMP), other pyrrolidinones and tetrahydrofuran (THF) (see Section ***1.4.2***).



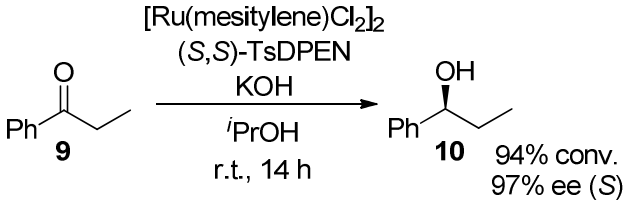
Scheme 2.4 – Reduction of furfural **26**

2.2 Research Goals

The above examples show that 1,4-butanediol **12** has strong potential to reduce carbonyl compounds by being converted into a lactone to force the equilibrium to the side of the alcohol. Therefore, the objective of this research is to investigate the potential of 1,4-butanediol **12** and optimise conditions for the reduction.

The area of asymmetric reduction should also be investigated. There are currently some highly optimised conditions in the literature for asymmetric transfer hydrogenation, such as Noyori's, for both hydrogen donor and formic acid methods,[13,32] Wills',[16-17] as mentioned in section **1.3.2** and Blacker's

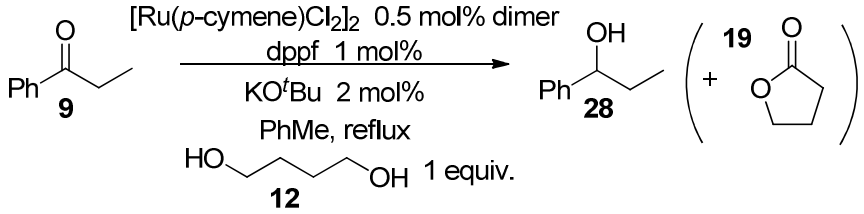
CATHy™ catalyst,[33] which uses *iso*-propanol. Consequently, the further aim of this research is to develop conditions for asymmetric reduction of carbonyl compounds that are competitive with those already published in the literature (for example Scheme 2.5 and see Section ***1.3.2***, Figure 1.4).[13]



Scheme 2.5 – An example of Noyori's asymmetric reduction conditions

2.3 Initial Studies

A simple ketone substrate was chosen and reaction conditions were selected based upon a catalyst system that had success with other reactions in the Williams group[34].



Scheme 2.6 – Initial conditions for reduction

After 14 hours, there was 73% conversion into the alcohol **28**. This result shows that 1,4-butanediol **12** can reduce a carbonyl compound effectively. The assumed mechanism of formation of the lactone **19** is shown in Figure 2.2.

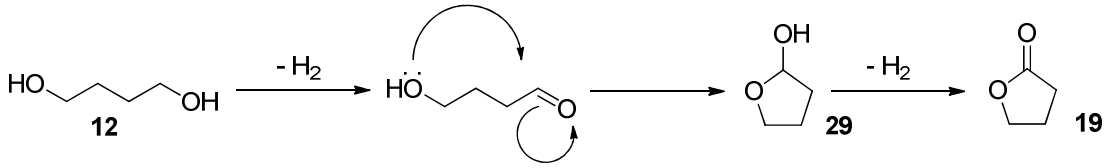
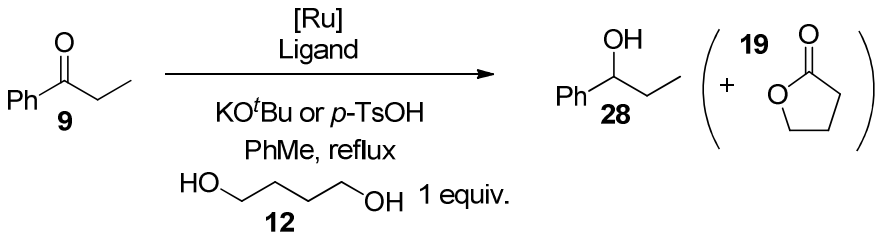


Figure 2.2 – Formation of γ–butyrolactone **19**

The conditions were then optimised to achieve complete conversion. A catalyst screen was carried out using two different ruthenium catalysts, a variety of ligands and either acidic or basic conditions.



Scheme 2.7 – Catalyst screen

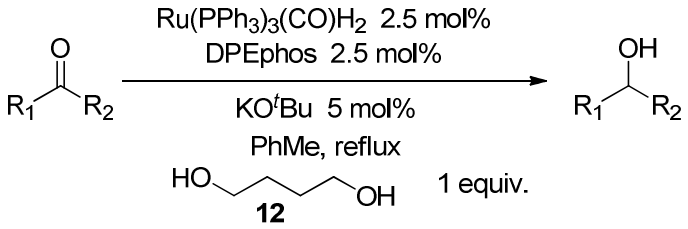
Both [Ru(*p*-cymene)Cl_2]$_2$ and Ru(PPh_3)$_3$(CO)H_2 were chosen for this screen because they are well known to be successful transfer hydrogenation catalysts.[35] Previous work in the Williams group has shown the success of using DPEphos,[29] Xantphos[36] and dppf[34] as ligands for transfer hydrogenation, and DPEN was selected as it is an enantiomerically pure ligand. The base[29] and acid[37] were also chosen because of their use in previous chemistry within the Williams group.

Table 2.1 – Results of catalyst screen[a]

Entry	Catalyst[b]	Ligand[c]	Acid or Base [d]	Conversion after 14 h (%)	Conversion after 24 h (%)
1	$[Ru(p\text{-cymene})Cl_2]_2$	dppf	KO^{t}Bu	73	89
2	$[Ru(p\text{-cymene})Cl_2]_2$	dppf	-	61	64
3	$[Ru(p\text{-cymene})Cl_2]_2$	DPEN	KO^{t}Bu	25	27
4	$[Ru(p\text{-cymene})Cl_2]_2$	Xantphos	KO^{t}Bu	15	19
5	$[Ru(p\text{-cymene})Cl_2]_2$	DPEphos	KO^{t}Bu	72	86
6	$Ru(PPh_3)_3(CO)H_2$	Xantphos	KO^{t}Bu	29	31
7	$Ru(PPh_3)_3(CO)H_2$	Xantphos	*p*-TsOH	69	73
8	$Ru(PPh_3)_3(CO)H_2$	DPEphos	KO^{t}Bu[e]	80	95
9	$Ru(PPh_3)_3(CO)H_2$	dppf	KO^{t}Bu	78	84
10	$Ru(PPh_3)_3(CO)H_2$	DPEN	KO^{t}Bu	96	98

[a] Reactions were carried out on a 1 mmol scale in 1 mL of toluene. Conversions were calculated using ^{1}H NMR and show the amount of alcohol **28**. [b] $[Ru(p\text{-cymene})Cl_2]_2$ and $Ru(PPh_3)_3(CO)H_2$ were used in 0.5 mol% (dimer) and 2.5 mol% amounts respectively in the reactions. [c] Ligands were used in 1 mol% for $[Ru(p\text{-cymene})Cl_2]_2$ and 2.5 mol% for $Ru(PPh_3)_3(CO)H_2$ in the reactions. [d] Base and acid, where required, were used at 2 mol%. [e] This reaction used 5 mol% base.

Table 2.1 shows at least seven good results, with the main conclusion being that $Ru(PPh_3)_3(CO)H_2$ appears to be a better catalyst for this reaction. Entry 10 shows 98% conversion into the alcohol **28** in 24 hours. This indicates that there is promise for asymmetric reduction in later research. Entry 8 uses the exact conditions described for the "lactone trap" oxidation[29] (see above, Section ***2.1***), and shows that the conditions are successful for both oxidation and reduction. These conditions were then used to reduce a variety of carbonyl substrates.



Scheme 2.8 – Substrate screen

Table 2.2 – Substrate screen results[a]

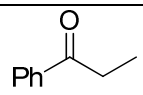
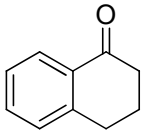
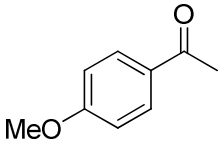
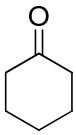
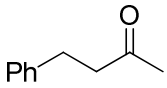
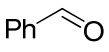
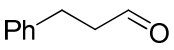
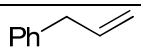
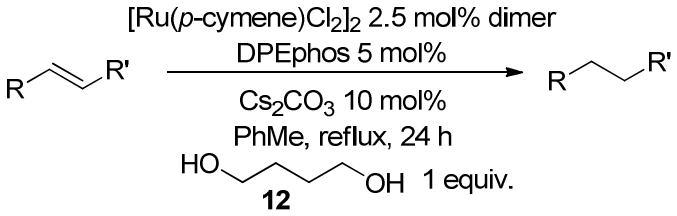
Entry	Carbonyl Compound	Time (h)	Conversion (%)
1	 **9**	24	97
2	 **30**	24	69 (91)[c]
3	 **31**	24	87
4	 **32**	24	100
5	 **33**	24	100
6	 **34**	24	100
7	 **35**	24	100

Table 2.2 cont.

Entry	Carbonyl Compound	Time (h)	Conversion (%)
8[b]	 **36**	24	47[d]

[a] Reactions were carried out on a 1 mmol scale in 1 mL of toluene. Conversions were calculated using ^{1}H NMR and show the amount of alcohol, except for entry 8. [b] This reaction was carried out using allylbenzene **36** to see if the system would reduce alkenes as well as carbonyls. [c] 50 h. [d] The conversion shows the amount of propyl benzene **37** produced, the remaining 53% was the isomerisation product, *trans*-β-methylstyrene **38**.

Table 2.2 demonstrates that various ketones and aldehydes are effectively reduced by this system. Entries 4 – 7 show complete conversion in 24 hours. Even α-tetralone **30**, a notoriously difficult ketone to reduce, due to the low oxidation potential,[9] is reduced in a high conversion after 50 hours. Entry 8 illustrates that the system can also reduce alkenes, although this is not as effective as carbonyl reduction. The system carries out isomerisation of the double bond in slight preference to reduction, so unfortunately it seems that this system would not be tolerant of compounds that contain an alkene (or possibly alkyne) functional group. Recent work in the Williams group has seen the reduction of alkenes using 1,4-butanediol **12** (Scheme 2.9).[2]



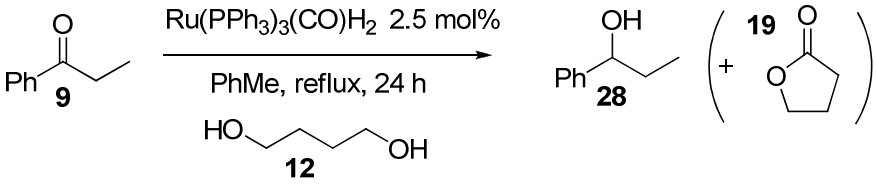
9 examples, 51-85% isolated yield

Scheme 2.9 – Reduction of alkenes using 1,4-butanediol **12**

These slightly different conditions prove that alkenes can be reduced by 1,4-butanediol **12**, so compounds containing alkene groups would not be tolerated under the conditions used in Scheme 2.8.

2.4 Optimisation of Conditions

In order to optimise the current conditions further and generate milder conditions for the reaction, a series of reactions was carried out to vary the presence of ligand, presence of base and amount of 1,4-butanediol **12**.



Scheme 2.10 – Variation of conditions

Table 2.3 – Results of varying conditions[a]

Entry	Ligand[b]	Base[c]	1,4-Butanediol **12** (equiv.)	Conversion (%)
1	DPEphos	-	1.0	86
2	-	KO^{t}Bu	1.0	94
3	-	-	1.0	95
4	DPEphos	KO^{t}Bu	0.5	89
5	-	-	0.6	95
6[d]	-	-	1.0	81

[a] Reactions were carried out on a 1 mmol scale in 1 mL of toluene for 24 hours. Conversions were calculated using ^{1}H NMR. [b] DPEphos, where used, is 2.5 mol%. [c] KO^{t}Bu, where used, is 5 mol%. [d] This reaction was carried out in 0.5 mL of toluene.

The results from these reactions are very encouraging since they suggest that the reaction works well without base (entry 1), without ligand (entry 2), without base and ligand (entry 3) and with a lower equivalent of 1,4-butanediol **12** (entries 4 and 5). It is worth noting however, that increasing the concentration of the reaction mixture does not increase conversion.

1,4-Butanediol **12** was selected as the hydrogen donor not only because it forms a lactone, but because the lactone it does form (γ-butyrolactone **19**) is kinetically favoured by Baldwin's Rules,[38] and this ring formation is faster

(over other sized lactones). Following these rules, γ-butyrolactone **19** is the five membered ring being formed, the bond being broken as the ring forms is the carbonyl (see Figure 2.3) which is outside the ring, making it *exo*, and the carbon that is being attacked is sp^2 hybridised, making it trig. Any cyclisation that is *exo*-trig is favoured according to Baldwin's Rules.

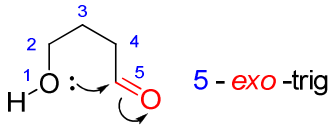
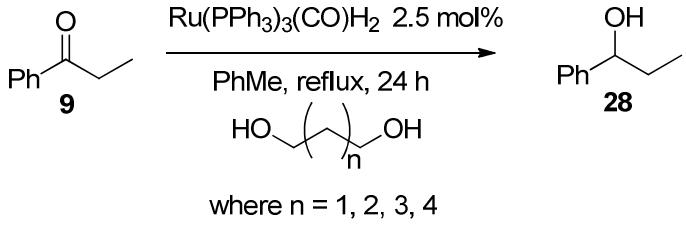


Figure 2.3 - Diagrammatic explanation of Baldwin's Rules favouring the formation of γ-butyrolactone **19**

The formation of other lactones from similar alkanediols is also favoured *via* Baldwin's Rules, however the resultant ring is not as stable as the five membered ring of γ-butyrolactone **19**. The seven membered lactone, ε-caprolactone **39**, which would be formed when using 1,6-hexanediol **40**, is known to polymerise,[39] and it is thought that the four membered lactone (which would be formed from 1,3-propanediol **41**), β-propiolactone **42**, could also do the same. The five and six membered lactones have very similar stability (formed from 1,4-butanediol **12** and 1,5-pentanediol **43** respectively) and so both diols should be good hydrogen donors. Applying the current conditions but substituting 1,4-butanediol **12** with other alkanediols should ascertain if the decision to use 1,4-butanediol **12** was the right one. Note in the following set of reactions that two alcohols were used to give a direct comparison to 1,4-butanediol **12** and show that the presence of a second alcohol group is required for the reaction to take place.



where n = 1, 2, 3, 4

Scheme 2.11 – Variation of hydrogen donor

Table 2.4 – Results of varying the hydrogen donor[a]

Entry	Hydrogen Donor	Conversion (%)
1	1,3-propanediol **41**	9
2	1,4-butanediol **12**	96
3	1,5-pentanediol **43**	50
4	1,6-hexanediol **40**	25
5	*n*-butanol	6
6	*tert*-butanol	0

[a] Reactions were carried out on a 1 mmol scale in 1 mL of toluene, using 1 equivalent of hydrogen donor. Conversions were calculated using ^{1}H NMR.

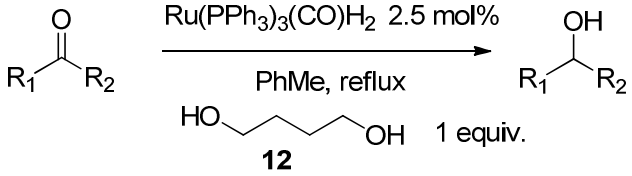
Table 2.4 shows clearly that 1,4-butanediol **12** is the right alkanediol to use. It gives the highest conversion (entry 2). Increasing the chain length on the alkanediol by one has a detrimental effect on the conversion, reducing it by half (entry 3). This result may indicate that the formation of the six-membered ring is slower than that of the five-membered ring. However, this idea cannot be supported by any evidence as the intermediate aldehyde and lactol are not observed in the ^{1}H NMR.

Increasing the chain length by another carbon again decreases the conversion by a further half (entry 4). The use of *n*-butanol, which is structurally similar to 1,4-butanediol **12** apart from the absence of a second hydroxyl group, shows a very small conversion, comparable with that of 1,3-propanediol **41** (entries 5 and 1 respectively). This result is expected because once *n*-butanol is oxidised to butyraldehyde, there is no second hydroxyl group to attack the carbonyl. This means the aldehyde is open to reduction back to *n*-butanol and that the reaction is reversible.

As the results of using 1,3-propanediol **41** (entry 1) and *n*-butanol (entry 5) are similar, it could be argued that 1,3-propanediol **41** does not react in the same way as 1,4-butanediol **12**, *i.e.* forming a lactone. It is possible that the conversion has simply come from oxidation of one hydroxyl group, and no further reaction of the intermediate aldehyde has occurred. Unfortunately,

due to the lack of intermediates in the ^{1}H NMR spectra, this remains unconfirmed.

Due to the success of the reaction with propiophenone **9** in the absence of ligand and base, various substrates were subjected to the same conditions.



Scheme 2.12 – Substrate screen without ligand and base

Table 2.5 – Substrate screen results[a]

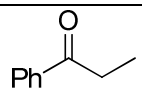
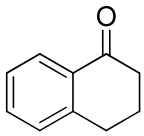
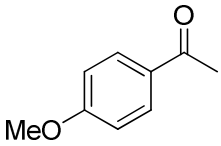
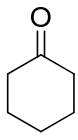
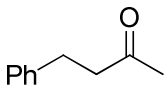
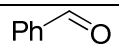
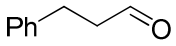
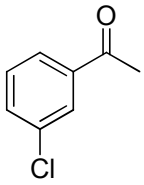
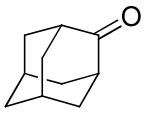
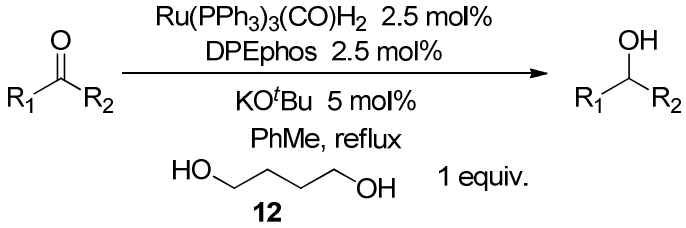
Entry	Carbonyl Compound	Time (h)	Conversion (%)
1	 **9**	24	96
2	 **30**	24	0 (0)[b]
3	 **31**	24	22 (33)[b]
4	 **32**	24	100 (60)[c]
5	 **33**	24	39

Table 2.5 cont.

Entry	Carbonyl Compound	Time (h)	Conversion (%)
6	 **34**	24	79
7	 **35**	24	99 (87)[c]
8	 **44**	24	63 (89)[b]
9	 **45**	24	0

[a] Reactions were carried out on a 1 mmol scale in 1 mL of toluene. Conversions were calculated using ^{1}H NMR. [b] 48 h. [c] Isolated yields are given in parenthesis.

From these results we can conclude that the requirement of ligand and base is substrate dependent. Whilst some results are comparable with the original substrate screen (Table 2.2), for example cyclohexanone **32** (entry 4) and hydrocinnamaldehyde **35** (entry 7), there are substrates which are not reduced at all under these conditions, *e.g.* α-tetralone **30** (entry 2). Therefore it is necessary to carry out further reactions with the inclusion of base and ligand since their presence has not been seen to be detrimental to the conversion.



Scheme 2.13 – Repeat of substrate screen

Table 2.6 – Results of new substrate screen[a]

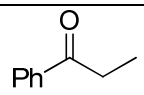
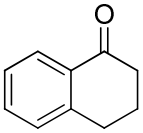
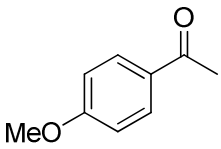
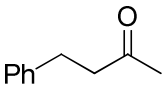
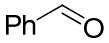
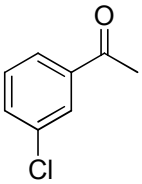
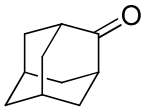
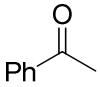
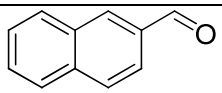
Entry	Carbonyl Compound	Time (h)	Conversion[b] (%)
1	 **9**	48	92 (88)
2	 **30**	48	91
3	 **31**	48	79
4	 **33**	24	95 (91)
5	 **34**	24	98 (81)
6	 **44**	48	98 (79)
7	 **45**	48	100
8	 **1**	48	90 (84)

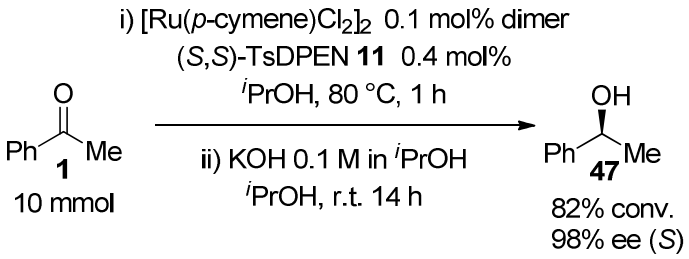
Table 2.6 cont.

Entry	Carbonyl Compound	Time (h)	Conversion (%)[b]
9	 **46**	48	100 (82)

[a] Reactions were carried out on a 1 mmol scale in 1 mL of toluene. Conversions were calculated using ^{1}H NMR. [b] Isolated yields are given in parenthesis.

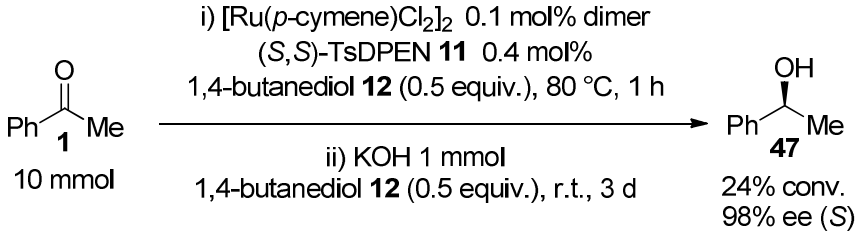
2.5 Asymmetric Optimisation

The best current literature conditions for ruthenium based asymmetric reduction of carbonyl compounds using *iso*-propanol are still those by Noyori.[40-41] Noyori's experimental procedure was consulted and the following results were obtained.



Scheme 2.14 – Noyori's conditions for asymmetric reduction

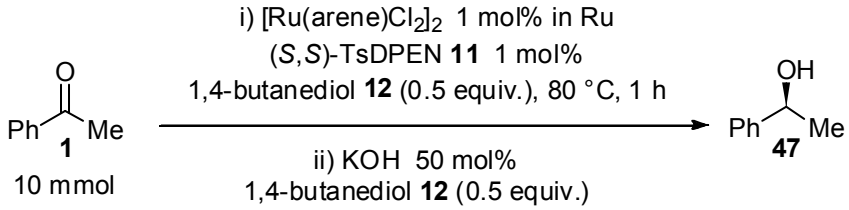
Noyori reports 95% conversion after 15 hours with 97% ee of the (*S*)-enantiomer. These conditions were adapted to incorporate 1,4-butanediol **12**.



Scheme 2.15 – Noyori's conditions but using 1,4-butanediol **12**

This result shows that high ees are possible using 1,4-butanediol **12**, although it is disappointing that the conversion is so low even after 3 days of reaction time. What should be noted is the difference in quantity of solvent/hydrogen donor – Noyori's conditions require a large excess of *iso*-propanol, approximately 100 mL, yet the amount of 1,4-butanediol **12** used is only 1 equivalent, approximately 1.0 mL.

The reaction was repeated using slightly varied conditions.



Scheme 2.16 – Varied conditions

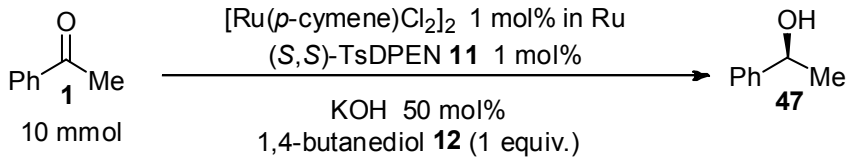
Table 2.7 – Varied conditions results[a]

Entry	Catalyst	Conversion after 17 h (%)	ee after 17 h (% (*S*))	Conversion after 72 h (%)[b]	ee after 72 h(% (*S*))[b]
1	[Ru(*p*-cymene)Cl_2]$_2$	32	99	52	93
2	[Ru(benzene)Cl_2]$_2$	12	94	34	82

[a] Reactions were carried out on a 10 mmol scale using 1,4-butanediol **12** as the solvent and the hydrogen donor. Conversions were calculated using ^{1}H NMR and ees were obtained using a Chiracel OD column with 90:10 hexane:*iso*-propanol at 0.5 mL/min. [b] These results were obtained by stirring the reaction at room temperature for 17 h, then heating to 40 °C for the remaining time period.

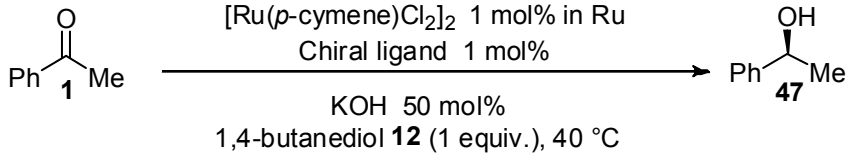
After 17 hours, the conversions for both catalysts were poor, but the ees were high. The reactions were heated to 40 °C, which, while improving conversion, diminished the ees. Previous work in the Williams group has demonstrated that increasing temperature decreases ee[42] and these results certainly fit that trend. However, if the conversion can be increased significantly (by reacting at a higher temperature) whilst still keeping the ee above 90%, the reaction could still prove to be useful.

Up until this point, Noyori's conditions had been followed exactly, just with the substitution of 1,4-butanediol **12**. The pre-forming of the catalyst was removed, and all components were added at once.



Scheme 2.17 – Removing the catalyst preparation step

After 72 hours at room temperature, the conversion of this reaction was 81% and ee was 88% (conversion after 19 hours was 58%). These results are encouraging, with a much higher conversion and only slightly lower ee. This reaction was repeated at an elevated temperature, and a different chiral ligand was employed for comparison purposes (for structure see Figure 2.4). This particular ligand was chosen because of its wide use in asymmetric synthesis.[43]



Scheme 2.18 – Variation of chiral ligand and elevated temperature

Table 2.8 – Variation of chiral ligand results[a]

Entry	Chiral Ligand	Conversion after 24 h (%)	ee after 24 h (% (*S*))	Conversion after 42 h (%)	ee after 42 h (% (*S*))
1	(*S*,*S*)-TsDPEN **11**	70	38[b]	90	87[c]
2	(1*S*, 2*R*)-(-)-1-Aminoindan-2-ol **48**	86	57	91	42

[a] Reactions were carried out on a 10 mmol scale using 1,4-butanediol **12** as the solvent and the hydrogen donor. Conversions were calculated using ^{1}H NMR and ees were obtained using a Chiracel OD column with 90:10 hexane:*iso*-propanol at 0.5 mL/min. [b] This result is significantly lower than expected and does not follow the trend of previous reactions, so it is assumed that this result is spurious. [c] This ee is from the isolated product.

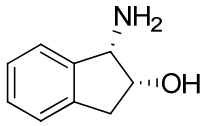
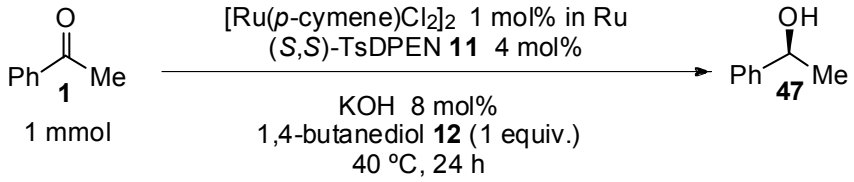


Figure 2.4 – Structure of (1*S*, 2*R*)-(-)-1-Aminoindan-2-ol **48**

Entry 2 shows that while a different ligand has a better initial conversion, the ee is not comparable with that of the Noyori system.

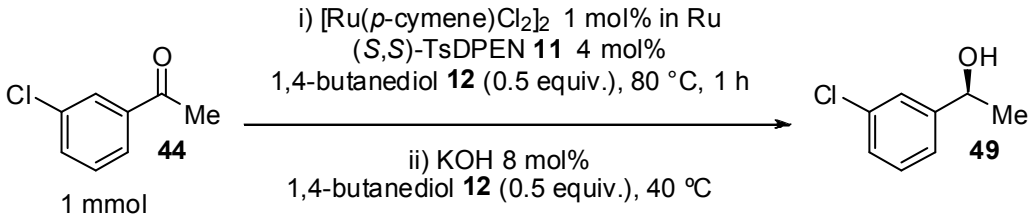
The amount of base used in the reaction is very high. Noyori's original conditions use far less base because a standard solution of KOH in *iso*-propanol is prepared. KOH is sparingly soluble in 1,4-butanediol **12**, so in order to make the active catalyst species, a higher amount of base has been used. This elevated level of base can be detrimental to the reaction since it can promote side reactions.[44] The amount of ligand was also changed in order to mimic Noyori's conditions (see Scheme 2.19).



Scheme 2.19 – Reducing base concentration

This reaction was carried out with two different procedures, one with a pre-forming step of the catalyst, the other with adding all components at once. With a pre-formed catalyst, the result was 88% conversion and 89% ee. With the "all-in" approach, the result was 49% conversion and 78% ee.

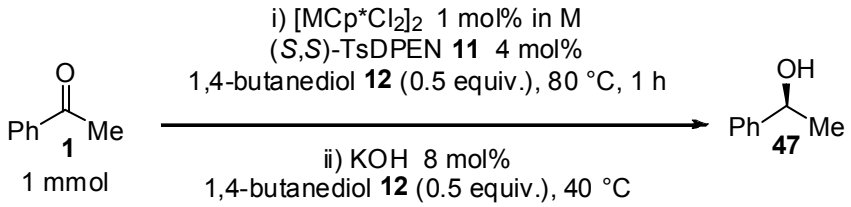
The conditions were tested on a second substrate, which was also demonstrated by Noyori to give good conversions and enantioselectivity[13] – 3-chloroacetophenone **44**.



Scheme 2.20 – Testing of conditions on a different substrate

After 24 hours, the reaction gave 98% conversion and 83% ee. This result merely demonstrates that 3-chloroacetophenone **44** is easier to reduce than acetophenone **1**.

As a last attempt to improve the conversion and enantioselectivity, two other metal catalysts were subjected to the reaction conditions. Both rhodium and iridium were used, in the form $[MCp^*Cl_2]_2$ (which are structurally and electronically related to $[Ru(p\text{-cymene})Cl_2]_2$).



Scheme 2.21 – Utilising different metal catalysts

Table 2.9 – Results of different metal catalysts[a]

Metal (M)	Conversion after 20 h (%)	ee after 20 h (% (*S*))	Conversion after 68 h (%)	ee after 68 h (% (*S*))
Ir	63	93	70	89
Rh	75	90	80	86

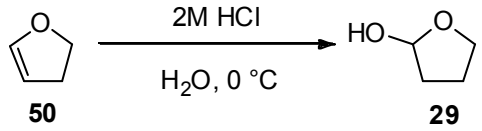
[a] Reactions were carried out on a 10 mmol scale using 1,4-butanediol **12** as the solvent and the hydrogen donor. Conversions were calculated using ^{1}H NMR and ees were obtained using a Chiracel OD column with 90:10 hexane:*iso*-propanol at 0.5 mL/min.

Table 2.9 shows that neither rhodium nor iridium gave better results than ruthenium. Both catalysts have precedent in the literature for good conversions and ees for transfer hydrogenation,[45] meaning the outcome is disappointing. It does however illustrate that ee can diminish with extended reaction time.

2.6 Asymmetric Hydrogenations with Different Hydrogen Donors

Due to the limited success of 1,4-butanediol **12** under asymmetric conditions, other hydrogen donors were considered. The limited success is thought to be due to the initial oxidation of 1,4-butanediol **12** to the aldehyde (see Scheme X) being slow. No intermediates, such as the aldehyde, were seen in the ^{1}H NMR spectra of crude reaction mixtures, suggesting that once the aldehyde is formed, the lactone is then produced rapidly. Therefore, it logically follows that the intermediate lactol could be used as a hydrogen donor and that it should react faster than 1,4-butanediol **12**.

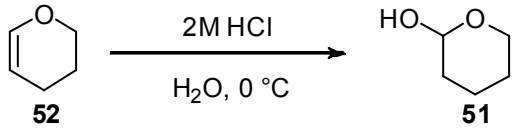
Investigations into the literature showed that the lactol could be prepared by acid catalysed reaction of dihydrofuran **50** with H_2O.[46]



50 **29**

Scheme 2.22 – Reaction of dihydrofuran **50** to produce required lactol **29**

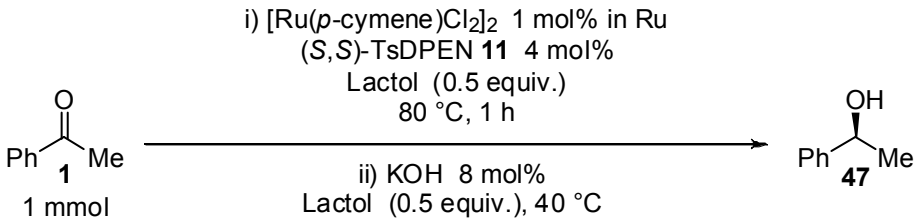
Similarly, the six-membered lactol **51** could be produced in the same manner.[47]



52 **51**

Scheme 2.23 – Reaction of 3,4-dihydro-2*H*-pyran **52** to produce the six-membered lactol **51**

The lactols were used in place of 1,4-butanediol **12**.



Scheme 2.24 – Use of lactols as the hydrogen donors

Table 2.10 – Results using lactols[a]

Entry	Lactol	Solvent	Conversion[b] (%)	ee[c] (% (*S*))
1	2-Hydroxytetrahydrofuran **29**	-	11	n/d
2	2-Hydroxytetrahydrofuran **29**	*t*BuOH	18	n/d
3	Tetrahydro-2*H*-pyran-2-ol **51**	-	0	-
4	Tetrahydro-2*H*-pyran-2-ol **51**	*t*BuOH	0	-

[a] Reactions were carried out on a 1 mmol scale using either the lactol or *tert*-butanol as the solvent. Conversions were calculated using ^{1}H NMR and ees were obtained using a Chiracel OD column with 90:10 hexane:*iso*-propanol at 0.5 mL/min. [b] Reactions with lactol **29** were carried out for 3 days, but reactions with lactol **51** were carried out for 24 hours only. [c] n/d stands for not determined.

Entries 1 and 2 show a small amount of conversion after 3 days. Entries 3 and 4 were only carried out for 24 hours, since there was no conversion observed and the results for the other lactol **29** were so poor there was nothing to be gained from running these reactions for a longer time period. Ees were not determined due to the low conversions. Theoretically these reactions should be fast and simple because the lactones are much more stable than the lactols. One explanation could be that the catalyst is destroying the lactols; there is however no evidence to support this claim. Another explanation could be that the active catalyst is not formed under these conditions.

1,4-Pentanediol **53** (Figure 2.5) was considered as a hydrogen donor because the branched nature of the chain should speed up lactone formation. This is due to the Thorpe-Ingold effect.

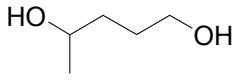


Figure 2.5 – 1,4-Pentanediol **53**

The Thorpe-Ingold effect, or gem-dimethyl effect, explains how the rate or equilibrium constant of a ring forming reaction is increased by the presence of substituents on the ring. The effect was first reported in 1915 when Beesley, Ingold and Thorpe carried out a study on cyclisation reactions.[48]

For example, the formation of succinic anhydride **54** from succinic acid **14** is a ring forming reaction. If the rate constant of ring formation is assumed to be 1, when substituents are added to the carbon chain, the rate is increased markedly (Figure 2.6).[38]

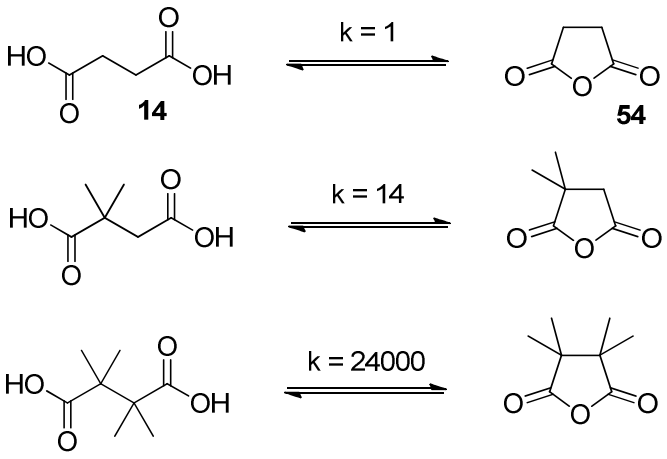


Figure 2.6 – The relative rate constants of the ring formation of succinic anhydride **54** with increasing substitution

There are two main reasons why this occurs. The bond angle of a carbon atom in a chain should be close to 109.5°. Once substituents are added to this carbon atom (for example methyl groups), they will repel the carbons already present in the chain, pushing them closer together, *i.e.* decreasing the bond angle. This decreased angle then means ring formation is faster because the amount of strain the angle has to undergo is less.

The second reason involves entropy and is more applicable to larger ring forming reactions. The reason above is more applicable to small ring forming reactions. When a larger ring is formed, more entropy is lost at the transition state (*i.e.* a more negative value), meaning a less favourable Gibbs Free

Energy, $\Delta G^{\ddagger}$ ($\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$). When a compound is more substituted, it has less entropy, but also the substituents can block rotation to form certain conformations (see Figure 2.7). The brackets indicate that rotation is restricted, therefore fewer conformations are possible. These fewer conformations are closer in energy to the transition state, meaning the move to the transition state results in a smaller loss in entropy (*i.e.* a less negative value). This in turn means the value of $\Delta G^{\ddagger}$ is more negative and the ring will form faster.

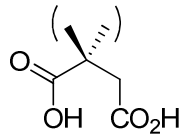
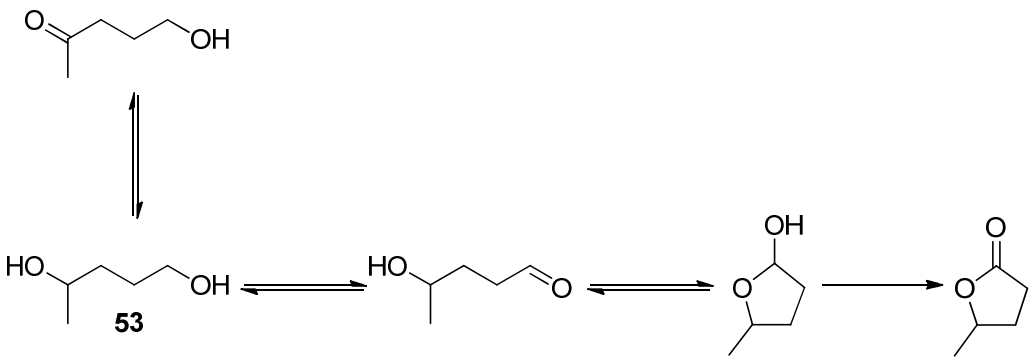
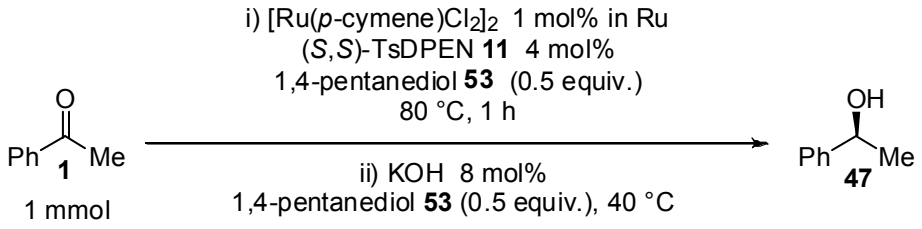


Figure 2.7 – Diagram to show the restricted rotation when the compound is substituted

The premise of using 1,4-pentanediol **53** is the same as before. Although oxidation is preferred at the secondary alcohol, this does not aid lactone formation. The idea was that oxidation at the primary alcohol would be competitive since once the corresponding aldehyde is formed, lactone is produced immediately (Scheme 2.25).



Scheme 2.25 – Reaction of 1,4-pentanediol **53** as the hydrogen donor



Scheme 2.26 – Reaction using 1,4-pentanediol **53** as a hydrogen donor

After 24 hours, 43% conversion and 78% ee were achieved. The idea that the branched chain diol would increase the speed of lactone formation did not succeed. The reaction was not pursued further since extended reaction times would reduce ee.

After a search of the literature, it was found that 1,2-benzenedimethanol **55** (Figure 2.8) had been shown to form its corresponding lactone under transfer hydrogenation conditions using iridium and acetone.[49] It was thought that this lactone formation could provide hydrogen in the same way as 1,4-butanediol **12**.

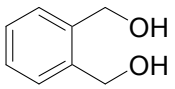
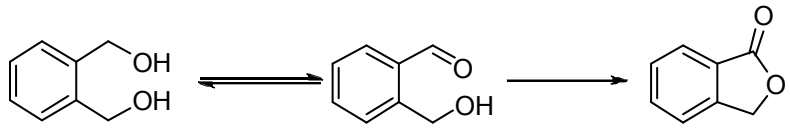


Figure 2.8 – 1,2-benzenedimethanol **55**

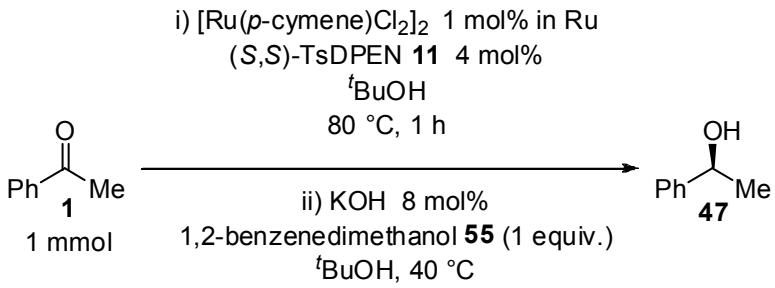
Like the other diols discussed in this chapter, the mechanism of lactone formation is similar (Scheme 2.27). The resultant lactone has conjugation between the aromatic ring and the carbonyl, and it was thought this added stability would aid lactone formation.



XX

Scheme 2.27 – Reaction of 1,2-benzenedimethanol **55** as a hydrogen donor

The reaction was carried out in *tert*-butanol since 1,2-benzenedimethanol **55** is a solid.



Scheme 2.28 – Using 1,2-benzenedimethanol **55** as the hydrogen donor

After 24 hours, a 57% conversion and 83% ee was observed. These results are better than those achieved with 1,4,-pentanediol **53**. However, due to the limited solubility of 1,2-benzenedimethanol **55** in *tert*-butanol, the results have been affected because not all of the hydrogen donor has been able to interact with the catalyst and substrate. If the reaction were run in a larger quantity of solvent, the conversion (and possibly ee) may be improved, because more of the hydrogen donor would be in solution. However, this may not be the case due to the reduced concentration of the reaction mixture.

The idea of using a sugar for a hydrogen donor was considered because their structures are abundant with hydroxy groups. It was hoped that at least one would be oxidised and give up hydrogen to reduce acetophenone **1**. A recent publication has shown the use of glycerol **56** (Figure 2.9) as a solvent and a hydrogen donor in transfer hydrogenation[50] (Scheme 2.29).

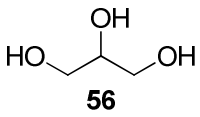
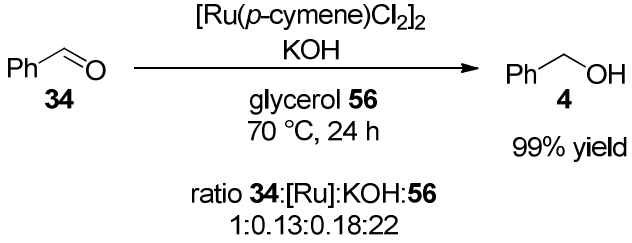


Figure 2.9 – Structure of glycerol **56**



Scheme 2.29 – Transfer hydrogenation using glycerol as solvent and hydrogen donor

The chosen sugar was D-(-)-fructose **57**, and the structure can be see in Figure 2.10.

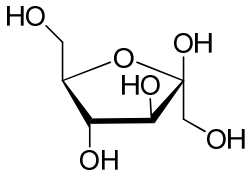
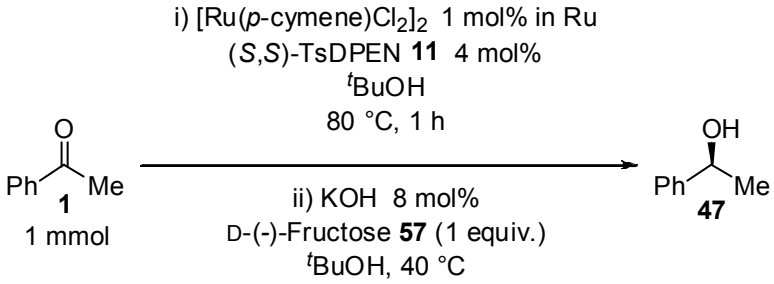


Figure 2.10 - D-(-)-Fructose **57**

The reaction, like that of 1,2-benzenedimethanol **55**, was run in *tert*-butanol.



Scheme 2.30 – Attempted reduction using D-(-)-Fructose **57**

After 24 hours, no conversion was observed. As no results were obtained that match or better the current literature, the work was discontinued.

2.7 Conclusions

A new method of transfer hydrogenation has been developed utilising commercially available reagents. The new conditions have been applied successfully to a range of substrates in high conversions and yields in an achiral manner.[1]

These conditions were then adapted to use a chiral ligand to produce enantioselectivity. The best results obtained were 89% conversion and 84% ee of (*S*)-sec-phenethyl alcohol **47**. Several different hydrogen donors were investigated in an attempt to improve the conversion and ee. None of these

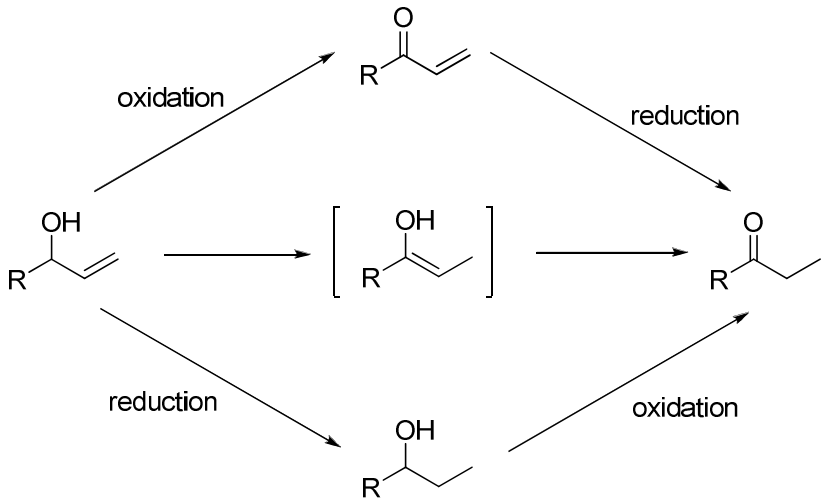
hydrogen donors gave a result comparable with that of 1,4-butanediol **12**. Further work could include investigations into the use of Wills' tethered ruthenium catalyst,[16] in order to see if this provided better conversions and ees.

CHAPTER 3 - RESULTS AND DISCUSSION II

CHAPTER 3 – RESULTS AND DISCUSSION II

3.1 Background

The redox isomerisation of allylic alcohols is a process where the carbon-carbon double bond is moved (isomerised) to the adjacent carbon, forming an enol. This enol then tautomerises to form a ketone, since this is the more stable form of the compound (Scheme 3.1). The process is deemed a redox isomerisation because at first glance, it would appear that both an oxidation and a reduction have taken place.

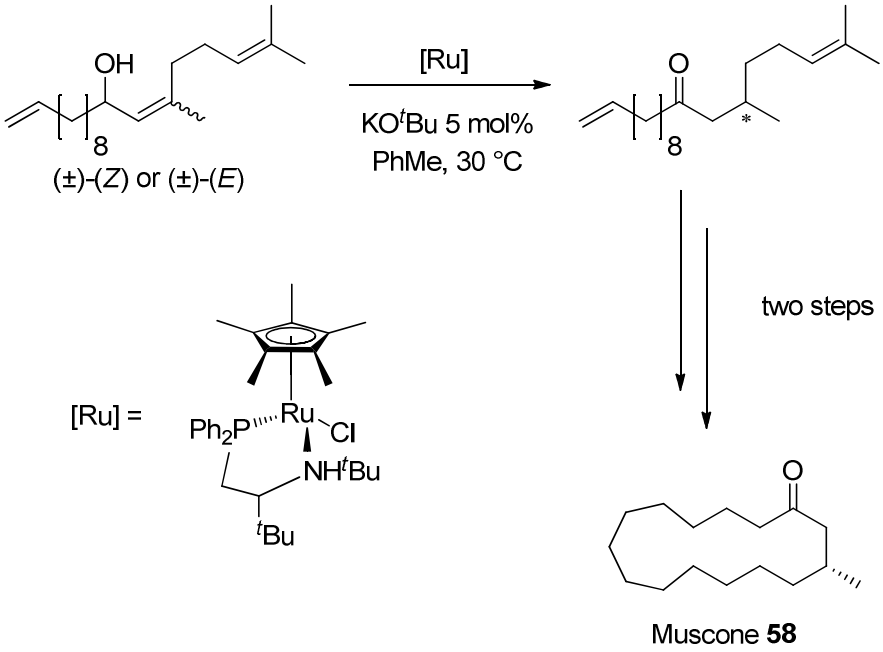


Scheme 3.1 – the principle of redox isomerisation

This type of reaction has been reported heavily in the literature since the 1970s, and there are many examples of the process using various different transition metals: Co, Cr, Fe, Ir Pd, Pt, Rh and Ru.[51] The process can be deemed as green chemistry because there is no overall change in mass of reactant/product. This therefore makes the reaction attractive for use in the industrial sector.

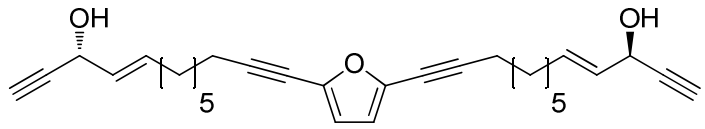
This process has been used to obtain several natural products. One example is the synthesis of muscone (3-methylcyclopentadecanone) **58**, which is a naturally occurring compound found in a gland under the skin of the abdomen

of a male musk deer. In its naturally occurring form, muscone is found as the (-)-enantiomer, but in industry, the synthetically produced material is marketed as a racemate. Ikariya *et al.* have used the isomerisation of an allylic alcohol to a ketone in a short synthesis of muscone (Scheme 3.2).[52]

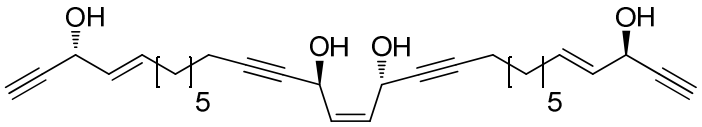


Scheme 3.2 – Synthesis of Muscone **58** using redox isomerisation

A second example involves the synthesis of adociacetylene B **59**. This compound is an oxidation product of petrosynol **60**, which is found in an Okinawan marine sponge, and has high biological activity for treatment of the human immunodeficiency virus (HIV) (Figure 3.3).



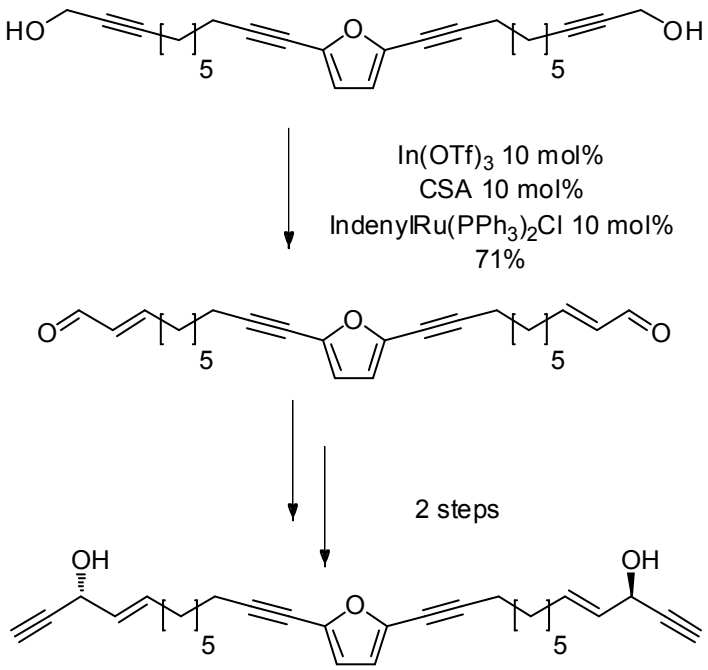
Adociacetylene B **59**



Petrosynol **60**

Figure 3.3 – Structures of Adociacetylene B **59** and Petrosynol **60**

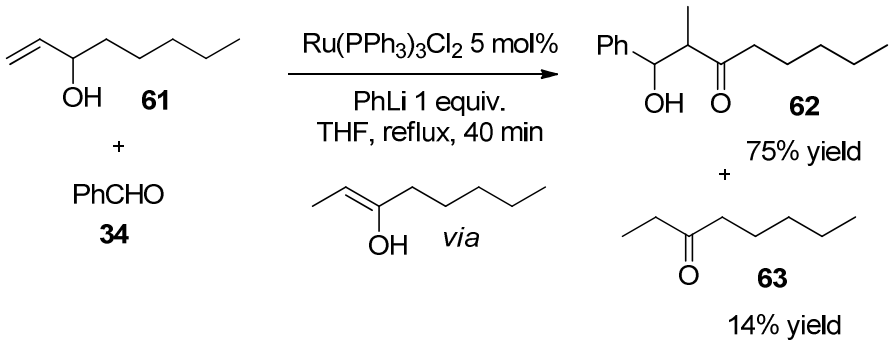
Due to the low yielding isolation of petrosynol **60**, the synthesis of adociacetylene B **59** is attractive. Trost and Weiss have reported a 5-step synthesis of this compound, including a double redox isomerisation (Scheme 3.4).[53]



Scheme 3.4 – Synthesis of adociacetylene B **59**

Trost has demonstrated in the above synthesis that only the alkynes adjacent to the alcohol are isomerised. The other alkynes remain untouched meaning the reaction is selective.

Also present in the literature is the isomerisation of allylic alcohols combined with another process, such as the aldol reaction. Grée *et al.* have shown that various ruthenium and rhodium complexes affect a tandem isomerisation-aldol condensation under mild conditions.[54] The isomerisation is effectively halted at the enol stage, and it is the enol that reacts on to carry out the aldol condensation (Scheme 3.5).



Scheme 3.5 – Isomerisation-aldol condensation reported by Grée

Grée has also reported the same reaction using nickel[55] and iron.[56] The iron reaction uses $Fe(CO)_5$ and requires irradiation. The reaction is not ideal since small quantities of regioisomeric aldol products were formed (Figure 3.1). The nickel reaction however, is completely regioselective and higher yielding. The work also reports a mechanism where the isomerisation is transition metal mediated to the enol, then the enol reacts with an aldehyde to give the required aldol product.

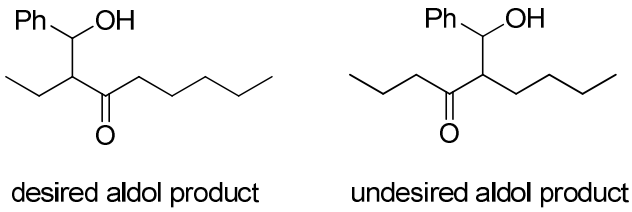
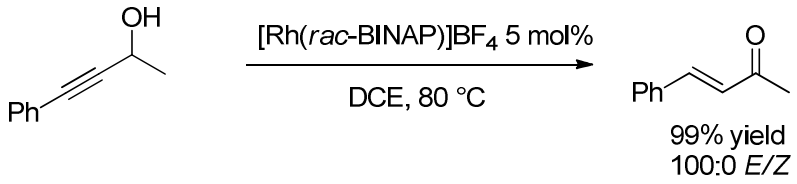


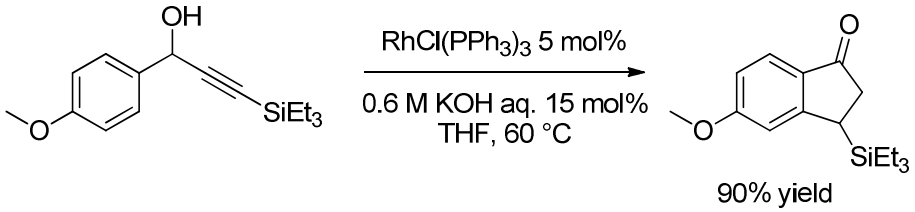
Figure 3.1 – Regioisomeric aldol products produced in the $Fe(CO)_5$ mediated reaction

The scope of the reaction is not limited to just allylic alcohols, propargylic alcohols are also isomerised. For example, Tanaka has reported the isomerisation of various propargylic alcohols using a rhodium catalyst (Scheme 3.6).[57]



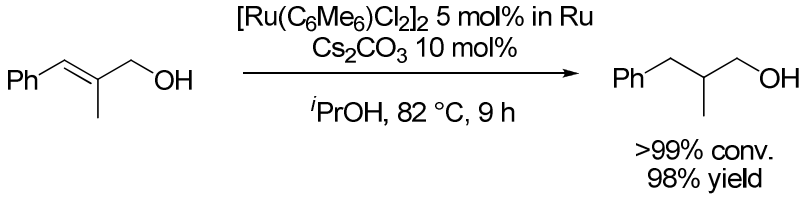
Scheme 3.6 – Isomerisation of propargylic alcohols using rhodium

The isomerisation of propargylic alcohols can also be combined with other processes, such as the formation of indanones. This reaction proceeds smoothly with α-arylpropargyl alcohols containing a triethylsilyl group present (Scheme 3.7).[58]



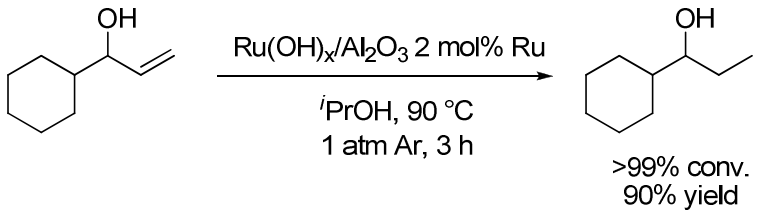
Scheme 3.7 – Isomerisation of propargylic alcohol to indanone

However, the most interesting combination of a reaction with allylic alcohol isomerisation is the subsequent reduction of the carbonyl. The reduction can be carried out *via* transfer hydrogenation, potentially using the same catalyst for reduction as for isomerisation. There are already several examples of such a combination in the literature. Cadierno *et al.* have shown that isomerisation of various allylic alcohols can be taken through to their corresponding saturated alcohols using ruthenium and *iso*-propanol (Scheme 3.8).[59]



Scheme 3.8 – Tandem isomerisation reduction reported by Cadierno *et al.*

In a similar manner, a supported ruthenium catalyst on alumina has been used to isomerise and reduce various allylic alcohols.[60] Scheme 3.9 shows the effectiveness of the catalyst, but the authors also report that the catalyst can be reused (recycled) to give similar conversions in a maximum of three further cycles.

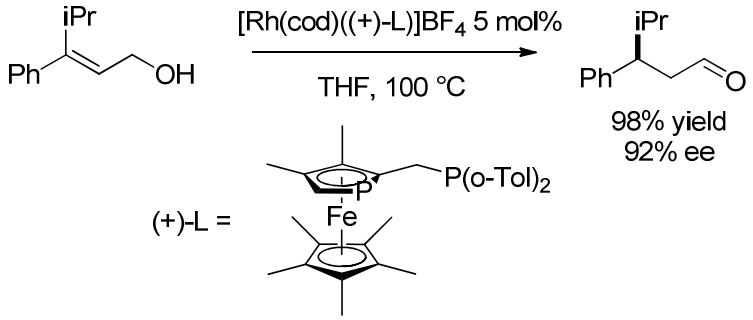


Scheme 3.9 – Tandem isomerisation reduction using a heterogeneous catalyst

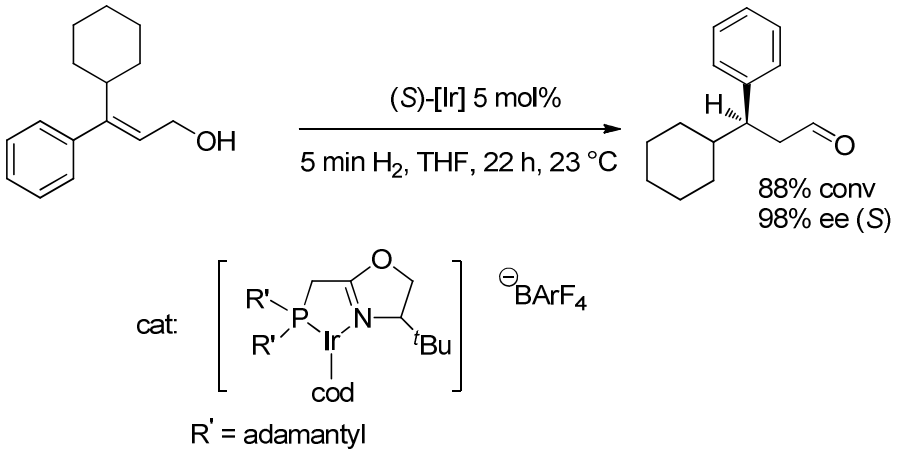
3.2 Research Goals

Having observed the success of using a tandem isomerisation/transfer hydrogenation reduction with *iso*-propanol, we wanted to apply our new found hydrogen donor to this process. As 1,4-butanediol **12** is going to be a renewable material in the very near future, the process could be considered as green chemistry. The atom efficiency would be high, since the overall gain in mass would only be 2 units, plus the 1,4-butanediol **12** would be transformed into γ-butyrolactone **19**, which could further be recycled from the process and used to make other compounds (see Section **1.4.2**).

The ideal result would then be a one-pot process, where the starting material is an allylic alcohol, and the product would be the corresponding saturated alcohol. The transformation would occur with the use of only one catalyst, and not include additions of other reagents (or catalyst) during the process. Once the tandem isomerisation/reduction process is optimised, there is possible scope for making the transformation asymmetric. There is precedent in the literature for asymmetric isomerisation reactions, for example with rhodium (Scheme 3.10)[61,62] and with iridium (Scheme 3.11),[63] but not yet for asymmetric isomerisation/reduction reactions.

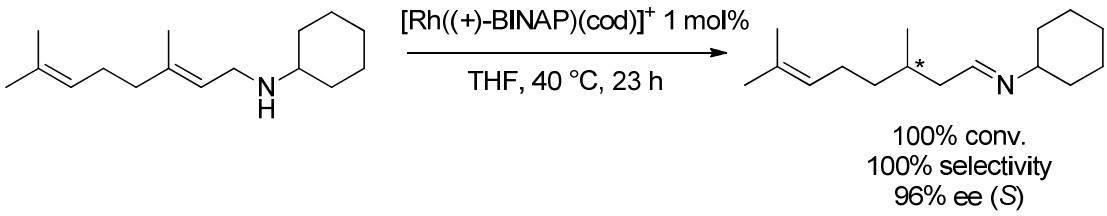


Scheme 3.10 – Enantioselective isomerisation using rhodium



Scheme 3.11 – Enantioselective isomerisation using iridium

This transformation of allylic alcohol to saturated alcohol could potentially be very useful for installing stereocentres in compounds produced in industry. This is proved by the developments of asymmetric isomerisation of allylic amines to enamines.[64]

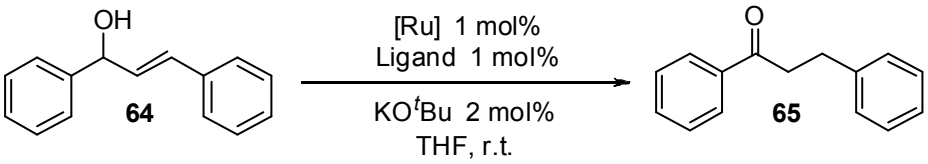


Scheme 3.12 – Example of asymmetric allylic amine isomerisation

3.3 Initial Studies

The isomerisation was investigated first as a single process, since we already know from the results of Chapter 2 that the reduction with 1,4-butanediol **12** is viable and successful.

A simple substrate was chosen, *trans*-1,3-diphenyl-2-propen-1-ol **64**, and an initial catalyst screen was run, using two ruthenium catalysts.



Scheme 3.13 – Initial catalyst screen

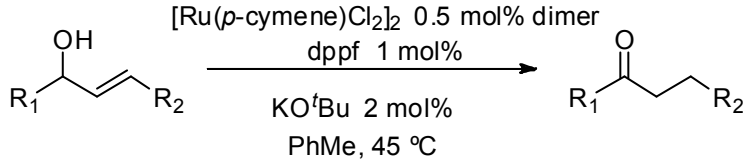
Table 3.1 – Results of using different catalysts and ligands[a]

Entry	Catalyst	Ligand	Conversion (%)
1	[Ru(*p*-cymene)Cl_2]$_2$	Xantphos	6
2	[Ru(*p*-cymene)Cl_2]$_2$	dppf	9
3	[Ru(*p*-cymene)Cl_2]$_2$	PPh_3	4
4	[Ru(*p*-cymene)Cl_2]$_2$	-	7
5	Ru(PPh_3)$_3$(CO)H_2	Xantphos	1
6	Ru(PPh_3)$_3$(CO)H_2	dppf	0
7	Ru(PPh_3)$_3$(CO)H_2	PPh_3	2
8	Ru(PPh_3)$_3$(CO)H_2	-	0
9	-	-	0

[a] Reactions were carried out on a 1 mmol scale in 1 mL of THF for 24 hours at room temperature, then the reactions were heated to reflux for 2 hours. Conversions were calculated using ^{1}H NMR.

These results clearly show that the [Ru(*p*-cymene)Cl_2]$_2$ catalyst is better for the reaction than Ru(PPh_3)$_3$(CO)H_2 under the conditions used above. It is also clear that the reaction does not proceed without a catalyst. As the conversions are very low, the reactions need to be run at a higher

temperature to achieve completion. In order to achieve a higher temperature, toluene was used since it has a boiling point of 110.6 °C (and THF only has a boiling point of 66 °C). The above reaction was repeated using the best conditions (Scheme 3.14), toluene instead of THF, a temperature of 45 °C, and a number of different substrates (Table 3.2).



Scheme 3.14 – Second initial screen using various substrates

Table 3.2 – Results for the substrate screen[a]

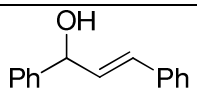
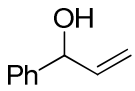
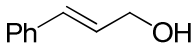
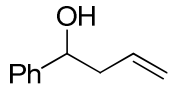
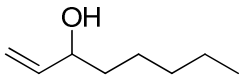
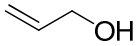
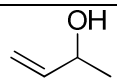
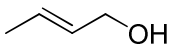
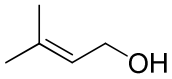
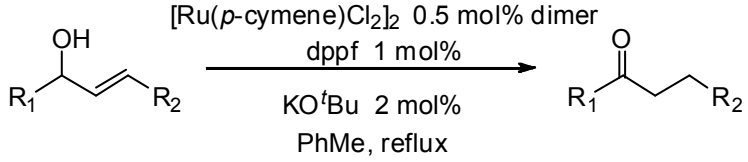
Entry	Allylic Alcohol	Conversion (%)
1	 **64**	2
2	 **66**	26
3	 **67**	12[b]
4[c]	 **68**	0
5	 **61**	22
6	 **18**	0

Table 3.2 cont.

Entry	Allylic Alcohol	Conversion (%)
7	 **69**	0
8	 **70**	0
9	 **71**	0

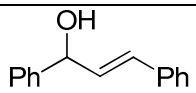
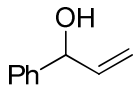
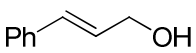
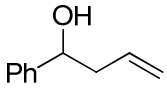
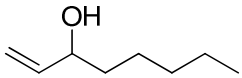
[a] Reactions were carried out on a 1 mmol scale in 1 mL of toluene for 48 hours at 45 °C. Conversions were calculated using ^{1}H NMR. [b] This reaction appears to have produced saturated aldehyde **35** (desired product), unsaturated aldehyde **72** and unsaturated alcohol **73**. [c] This substrate is homoallylic.

Table 3.2 shows the reaction is working for entries 1, 2, 3 and 5, but with low conversions. Entry 4, although no conversion is seen, should work as homoallylic substrates have been seen to isomerise in the literature.[65] 4-Phenyl-1-buten-4-ol **68** obviously requires harsher conditions to react. Entries 6, 7, 8 and 9 are thought to be too volatile to survive either the reaction conditions or the work up. These substrates were therefore abandoned. The other five substrates were repeated using the same conditions but at reflux in toluene (Scheme 3.15).



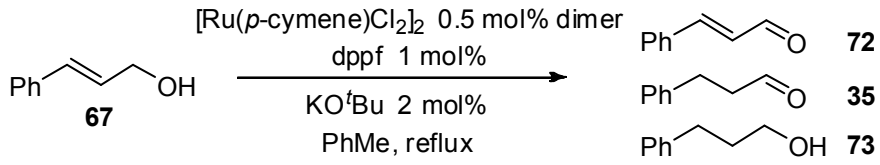
Scheme 3.15 – Substrate screen with higher temperature

Table 3.3 – Results at higher temperature[a]

Entry	R_1	R_2	Time (h)	Conversion (%)
1	 **64**		2	100
2	 **66**		2	100
3	 **67**		24	98[b]
4[c]	 **68**		1	100
5	 **61**		1	100

[a] Reactions were carried out on a 1 mmol scale in 1 mL of toluene at 110 °C. Conversions were calculated using ^{1}H NMR. [b] This conversion was 45% of the saturated aldehyde (desired product) **35**, 24% of the saturated alcohol **73** and 29% of the unsaturated aldehyde **72**. [c] This substrate is homoallylic.

Table 3.3 shows that four of the five substrates have been successfully converted into their corresponding ketones, in as little as one hour (entries 4 and 5). Entry 4 shows that at a higher temperature, complete conversion of the homoallylic alcohol is seen, proving that isomerisation can be achieved with a greater distance between the double bond and the alcohol group. Entry 3 shows interesting results; a 98% conversion is seen, but there is a mixture of products produced (Scheme 3.16).

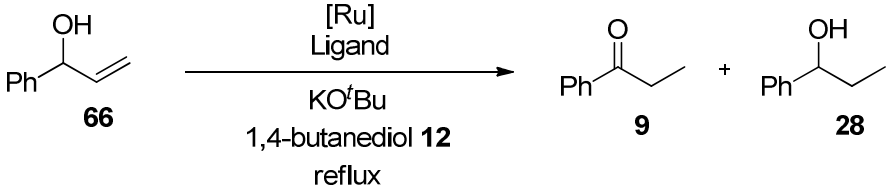


Scheme 3.16 – Mixture of products from Entry 3 Table 3.3

This mixture of products suggests that more than one type of reaction is occurring under these conditions. Looking back at Scheme 3.1, we can propose that oxidation of the starting alcohol **67** is producing the unsaturated aldehyde **72** and reduction of the double bond is producing the saturated alcohol **73**. What is not clear is whether the required saturated aldehyde **35** is being produced by isomerisation, or whether it is being produced by a combination of oxidation and reduction reactions (as described).

3.4 Combining Isomerisation and Reduction: The Introduction of 1,4-Butanediol 12

Having proved that 1,4-butanediol **12** is effective at reducing carbonyl compounds by transfer hydrogenation, it can now be introduced to see if it is possible to combine isomerisation and reduction. Although there is a defined catalyst system above, the initial idea was to try both this catalyst system and the one optimised for the reduction. The number of equivalents of 1,4-butanediol **12** was also varied, in order to see if it had an effect on the reduction (Scheme 3.17 and Table 3.4).



Scheme 3.17 – Catalyst screen using 1,4-butanediol **12**

Table 3.4 – Catalyst screen introducing 1,4-butanediol **12**[a]

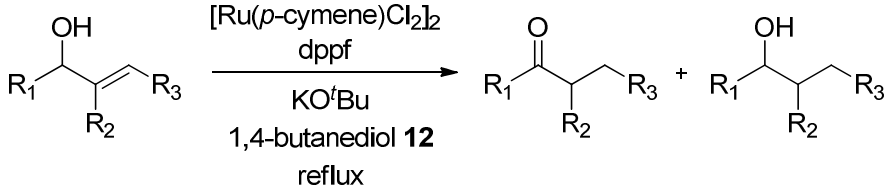
Entry	Catalyst/Ligand[c]	No. Equiv. 1,4-Butanediol **12**	Conversion After 2 h (%)[d] (**9**/**28**)	Conversion After 24 h (%)[d] (**9**/**28**)	Conversion After 3 d (%)[d] (**9**/**28**)
1	[Ru(*p*-cymene)Cl_2]$_2$ / dppf	~ 10	100 (60/40)	100 (16/84)	100 (3/97)
2	[Ru(*p*-cymene)Cl_2]$_2$ / dppf	~ 5	100 (26/74)	100 (3/97)	100 (3/97) (92)[e]
3[b]	[Ru(*p*-cymene)Cl_2]$_2$ / dppf	1	100 (20/80)	100 (11/89)	100 (10/90)
4	Ru(PPh_3)$_3$(CO)H_2 / DPEphos	~ 10	47 (33/14)	100 (3/97)	100 (1/99)
5	Ru(PPh_3)$_3$(CO)H_2 / DPEphos	~ 5	39 (25/14)	100 (57/43)	100 (30/70)
6[b]	Ru(PPh_3)$_3$(CO)H_2 / DPEphos	1	87 (80/7)	91 (16/75)	100 (3/97)

[a] Reactions were carried out on a 1 mmol scale, in neat 1,4-butanediol **12** with KO^{t}Bu and heated to 110 °C. [b] These entries were carried out in 1 mL of toluene. [c] Catalyst loadings for [Ru(*p*-cymene)Cl_2]$_2$ were 1 mol% dimer and for Ru(PPh_3)$_3$(CO)H_2 were 2.5 mol%. Ligand loadings for dppf were 1 mol% and for DPEphos were 2.5 mol%. Base loading for entries 1 - 3 was 2 mol% and for entries 4 – 6 was 5 mol%. [d] Conversions were calculated using ^{1}H NMR and reflect the conversion of α-vinylbenzyl alcohol **66**. The numbers in parenthesis show the ratio of propiophenone **9** to 1-phenyl-1-propanol **28**. [e] The second number in parenthesis is isolated yield.

The first thing to notice about these results is that the [Ru(*p*-cymene)Cl_2]/dppf system gives an initial higher and faster conversion of α-vinylbenzyl alcohol **66** to propiophenone **9** and 1-phenyl-1-propanol **28** than that of Ru(PPh_3)$_3$(CO)H_2/DPEphos. This result is expected since the latter was optimised for the reduction not the isomerisation. However, the proportion of 1-phenyl-1-propanol **28** is higher in entries 1 – 3 after 48 hours than those in

entries 4 – 6. The best result after 24 hours is entry 2, with 97% of the reaction mixture being the required alcohol (1-phenyl-1-propanol **28**).

Therefore, these conditions were used to convert a wide range of allylic alcohols into their corresponding saturated alcohols (Scheme 3.18 and Table 3.5).



Scheme 3.18 – Substrate screen

Table 3.5 – Substrate screen[a]

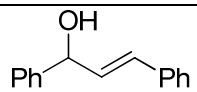
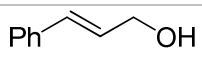
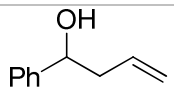
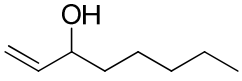
Entry	Substrate	Conversion After 2 h (%)[b]	Conversion After 24 h (%)[b]	Conversion After 48 h (%)[b]	Conversion After 3 d (%)[b]
1	 **64**	41 (27/14) (59 = 24/35, (E)/(Z))	100 (0/100) (52)[d]	-	-
2	 **67**	61 (0/2/59)[c]	100 (0/0/100)[c] (90)[d]	-	-
3	 **68**	65 (46/19)	100 (45/55)	100 (33/67)	100 (30/70) (52)[d]
		100 (19/81)	100 (3/97) (91)[d]	-	-
4	 **61**	100 (59/41)	100 (13/87)	100 (11/89)	100 (9/91) (80)[d]
		100 (15/85)	100 (9/91)	100 (8/92)	100 (3/97)

Table 3.5 cont.

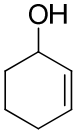
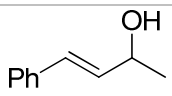
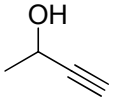
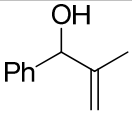
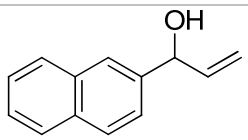
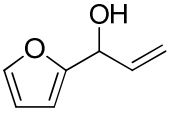
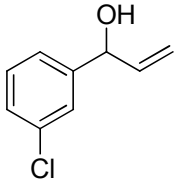
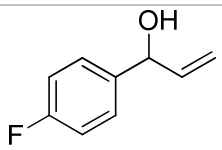
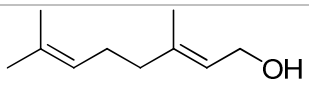
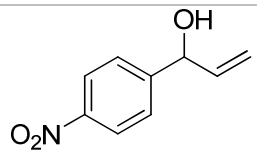
Entry	Substrate	Conversion After 2 h (%)[b]	Conversion After 24 h (%)[b]	Conversion After 48 h (%)[b]	Conversion After 3 d (%)[b]
5	 **74**	64 (25/39)	100 (0/100) (68)[d]	-	-
6	 **6**	52 (27/25) (48 = 22/26, (E)/(Z))	76 (41/35)	90 (47/43)	100 (47/53)
		100 (10/90)	100 (7/93)	100 (6/94)	100 (5/95) (62)[d]
7	 **75**	-	-	-	-
8	 **76**	37 (27/10)	89 (56/33)	100 (62/38)	100 (35/65) (51)[d]
		100 (22/78)	100 (6/94)	100 (1/99) (94)[d]	-
9	 **77**	80 (10/70)	100 (60/40)	100 (44/56)	100 (33/67) (33)[d]
		100 (13/87)	100 (9/91)	100 (5/95) (75)[d]	-
10	 **78**	-	-	-	-

Table 3.5 cont.

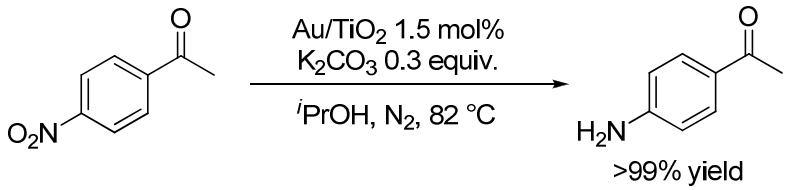
Entry	Substrate	Conversion After 2 h (%)[b]	Conversion After 24 h (%)[b]	Conversion After 48 h (%)[b]	Conversion After 3 d (%)[b]
11	 **79**	100 (32/68)	100 (0/100) (19)[d]	-	-
		100 (0/100) (47)[d]	-	-	-
12	 **80**	100 (47/53)	100 (37/63)	100 (31/69)	100 (29/71) (30)[d]
		100 (14/86)	100 (15/85)	100 (12/88)	100 (6/94) (37)[d]
13	 **81**	51 (0/51)	100 (0/100) (71)[d]	-	-
14	 **82**	n/d	n/d	n/d	(3/8)[e]

[a] Reactions were carried out on a 1 mmol scale, in neat 1,4-butanediol **12** and heated to 110 °C. Reactions were initially run with 0.5 mol% of the ruthenium dimer, 1 mol% dppf and 2 mol% KO^{t}Bu. If the conversions were low, reactions were rerun using 2.5 mol% dimer, 5 mol% dppf and 10 mol% KO^{t}Bu. The upper values reflect the lower loadings, the lower values reflect the higher loadings. [b] Conversions were calculated using ^{1}H NMR and reflect the conversion of the unsaturated alcohol. The numbers in parenthesis show the ratio of ketone/saturated alcohol. [c] The first numbers in parenthesis represent the ratio of saturated aldehyde, unsaturated aldehyde and saturated alcohol. [d] The second numbers in parenthesis show the isolated yield. [e] The numbers in parenthesis represent the ratio of isolated yield of the ketone **83** and saturated alcohol **84**.
n/d stands for not determined.

Table 3.5 shows that a wide range of allylic alcohols can be converted into their respective saturated alcohols in good conversions, and reasonable

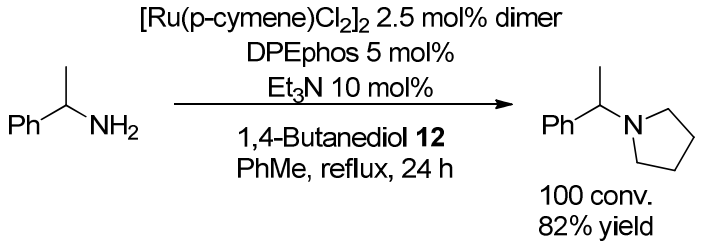
yields in most cases. The optimised system is tolerant of both *meta*- and *para*-substituents (entries 11 and 12) and substitution on the carbon-carbon double bond (entry 8). Aliphatic allylic alcohols were also converted successfully under these conditions (entries 4 and 5). Even a homoallylic system is easily isomerised and then reduced (entry 3). It is also interesting to note that a trisubstituted double bond is left untouched by the catalyst (entry 13), meaning the system is selective for allylic carbon-carbon double bonds. Entry 13 is also interesting since it is a naturally occurring compound – geraniol **81**, and is converted into another naturally occurring compound, β-citronellol **85**. Entry 2 exhibits the same behaviour as seen in Scheme 3.16, with a tiny proportion of the saturated aldehyde **35** being formed, showing that there is some oxidation occurring in addition to the isomerisation. It is important to note however, that because the proportion of this aldehyde **35** is so low, it shows that the isomerisation is a much faster process. This can also be demonstrated by the fact that in most entries above, the isomerisation is complete within two hours. It is then the reduction of the compound which is the lengthier process.

There is one exception in the results above, entry 14. The nitro compound **82** has only produced 3% yield of the corresponding ketone, 1-(4-nitrophenyl)propan-1one **83** and 8% yield of the corresponding saturated alcohol, 1-(4-nitrophenyl)propan-1-ol **84**. The crude reaction mixture was difficult to analyse by ^{1}H NMR, so conversions were not determined. Initially, it was thought that the substrate may undergo a reduction of the nitro group and subsequent reaction with 1,4-butanediol **12**, as well as the isomerisation and reduction. There is some precedence in the literature for the reduction of nitro groups under transfer hydrogenation conditions[66,67,68,69,70,71] (Scheme 3.19).



Scheme 3.19 – Selective reduction of nitro over ketone using a gold supported catalyst

Previous work in the Williams group has seen the reaction of aromatic amines with 1,4-butanediol **12** to form *N*-heterocycles (Scheme 3.20).[3]



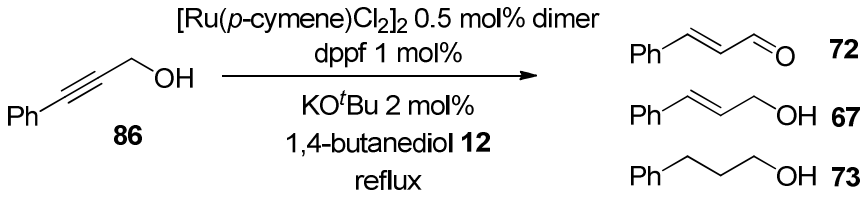
Scheme 3.20 – Example of the formation of an *N*-heterocycles with 1,4-butanediol **12**

However, despite these literature precedences, the conditions used above were not able to reduce the nitro group. Only a small amount of isomerisation and reduction was observed, hence the disappointing yields. This result is most likely due to the electron withdrawing nature of the nitro group.

It remains unclear why the furan based compound, **78**, did not isomerise and reduce. The crude reaction mixture did not show the starting material or the product by ^{1}H NMR, so the conclusion is that the compound is simply not stable under the reaction conditions and degrades.

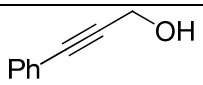
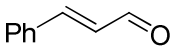
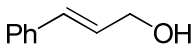
The one propargylic alcohol included in this set of substrates showed no reaction under these conditions. There were no other compounds observed in the crude ^{1}H NMR other than that of the starting material, 3-butyne-2-ol **75**, and that of 1,4-butanediol **12**. This result was surprising as it was expected that propargylic alcohols would react, due to precedence in the literature(see Scheme 3.6).[57] Initially it was thought that products may be too volatile to be

observed in the ^{1}H NMR, but the lack of γ–butyrolactone in the crude spectrum eliminated this possibility (since it has a boiling point of 204 °C and would be present if the reaction had worked in some way). In order to prove that the system would isomerise and reduce propargylic alcohols, a different substrate was chosen, 3-phenyl-2-propyn-1-ol **86** (Scheme 3.21).



Scheme 3.21 – Isomerisation and reduction of 3-phenyl-2-propyn-1-ol **86**

Table 3.6 – Results with 3-phenyl-2-propyn-1-ol **86**[a]

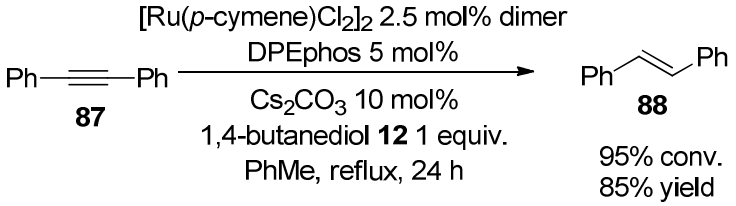
	 **86**	 **72**	 **67**	 **73**
Amount After 2 h (%)[b]	100	0	trace	0
Amount After 24 h (%)[b]	0	5	66	29
Amount After 48 h (%)[b]	0	1	35	64
Amount After 3 d (%)[b]	0	0	24	76

[a] The reactions was carried out on a 1 mmol scale, in neat 1,4-butanediol **12** and heated to 110 °C. [b] Conversions were calculated using ^{1}H NMR and reflect the conversion of the propargylic alcohol **86**.

This reaction does not appear to follow the initial fast isomerisation like many of the entries from Table 3.5 above. However, after 24 hours, the alkyne has been consumed. The results of this reaction show three products, with the unsaturated aldehyde **72** being formed after isomerisation. The aldehyde must then be reduced (to give cinnamyl alcohol **67**) and a second isomerisation will take place (giving 3-phenyl-1-propanol **73**). The conversion

of 3-phenyl-1-propanol **73** after 3 days (76%) is moderate and would most likely be improved with a higher catalyst loading. It does however demonstrate that this system is applicable to propargylic alcohols.

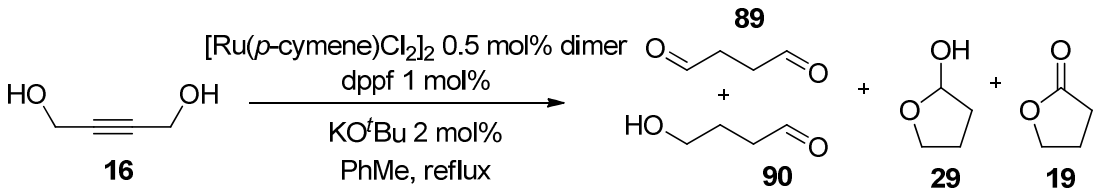
Recent work in the Williams group has demonstrated that diphenylacetylene **87** can be reduced to 1,2-diphenylethene **88** using 1,4-butanediol **12** (Scheme 3.22).[2]



Scheme 3.22 – Reduction of diphenylacetylene **87** using 1,4-butanediol **12**

This reaction provides proof that the alkyne could be reduced before any transfer hydrogenation takes place. What is interesting however is that no reduction of the alkene **88** is observed. This could show that although initial reduction of the alkyne takes place, any remaining alkene (*i.e.* any allylic alcohol formed from the propargylic one) is all isomerised and not reduced.

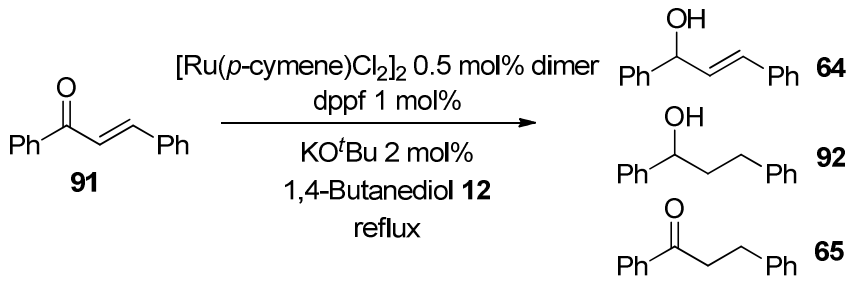
After the success of isomerising a propargylic alcohol, a second substrate was investigated. This particular substrate, 2-butyne-1,4-diol **16**, had the exciting potential to react all the way through to γ–butyrolactone **19**. If 2-butyne-1,4-diol **16** underwent a double isomerisation, it would form dialdehyde **89**. This could then be reduced at one end to form 4-hydroxybutanal **90**, which would then cyclise (see Scheme 3.23) to give lactol **29**, and then be oxidised to give γ–butyrolactone **19**. The reaction was run in toluene as it was thought that the species formed *in situ* would be able to act as hydrogen donors to push the reaction to completion.



Scheme 3.23 – Attempted isomerisation of 2-butyne-1,4-diol **16**

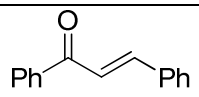
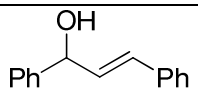
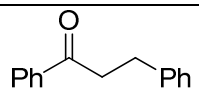
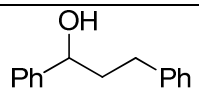
After 3 days at reflux, the reaction had not afforded any products. The crude reaction mixture simply contained the starting material.

Chalcone **91** contains both a carbon-oxygen double bond, and a carbon-carbon double bond. In order for this substrate to undergo redox isomerisation and reduction, an initial reduction is required. Since the system already reduces carbonyls and has an excess of 1,4-butanediol **12**, it did not seem too much to expect that it would carry out this extra reduction. The results of the reaction are shown below (Scheme 3.24 and Table 3.7).



Scheme 3.24 – Isomerisation and reduction of chalcone **91**

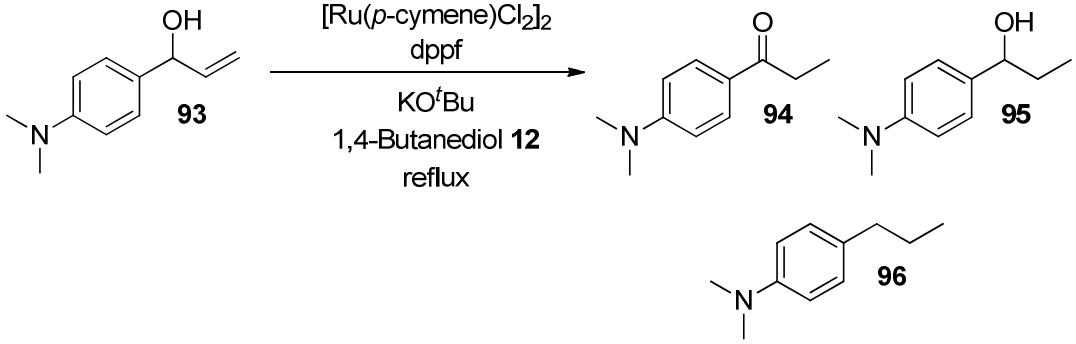
Table 3.7 – Isomerisation reduction of chalcone **91**[a]

	 **91**	 **64**	 **65**	 **92**
Amount After 2 h (%)[b]	0	0	49	51
Amount After 24 h (%)[b]	0	0	0	100 (97)[c]

[a] The reaction was carried out on a 1 mmol scale, in neat 1,4-butanediol **12** and heated to 110 °C. [b] Conversions were calculated using ^{1}H NMR and reflect the conversion of chalcone **91**. [c] The number in parenthesis is isolated yield.

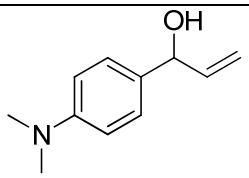
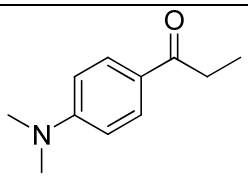
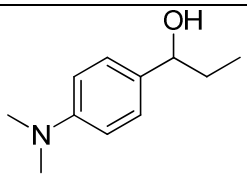
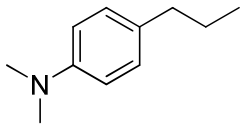
Table 3.7 shows that chalcone **91** was converted quickly into 1,3-diphenyl-propan-1-ol **92**. It is interesting that no *trans*-1,3-diphenyl-2-propen-1-ol **64** was observed in the crude reaction mixture. However, assuming that the reaction is undergoing a reduction of the carbonyl first, once the allylic alcohol **64** is formed, it must be reacting quickly and forming the ketone **65**. This is not unexpected, since it has already been seen that the allylic alcohol **64** undergoes fast isomerisation and a slower reduction (see Tables 3.3 and 3.5).

All of the above substrates have demonstrated predictable or expected behaviour. The following two substrates have furnished slightly different products. The first substrate, 1-(4-dimethylaminophenyl)prop-2-en-1-ol **93** is shown in Scheme 3.25, and the results in Table 3.8.



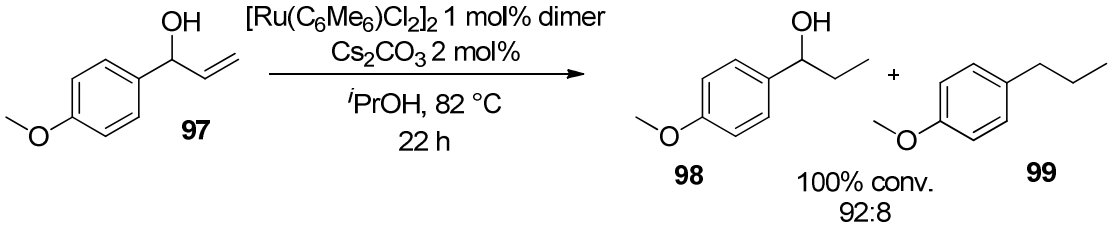
Scheme 3.25 – Isomerisation, reduction and loss of OH from 1-(4-dimethylaminophenyl)prop-2-en-1-ol **93**

Table 3.8 – Results of 1-(4-dimethylaminophenyl)prop-2-en-1-ol **93**[a]

	 **93**	 **94**	 **95**	 **96**
Amount After 2 h (%)[b]	0	63	25	12
	0	50	34	16
Amount After 24 h (%)[b]	0	28	61	11
	0	17	68	15
Amount After 48 h (%)[b]	0	18	64	18
	0	6	68	26
Amount After 3 d (%)[b]	0	14	63	23
	0	11	52	37

[a] Reactions were carried out on a 1 mmol scale, in neat 1,4-butanediol **12** and heated to 110 °C. Reactions were initially run with 0.5 mol% of the ruthenium dimer, 1 mol% dppf and 2 mol% KO^{t}Bu. If the conversions were low, reactions were rerun using 2.5 mol% dimer, 5 mol% dppf and 10 mol% KO^{t}Bu. There are two sets of results per row, the upper reflects the lower catalyst loading, the lower reflects the higher catalyst loading. [b] Conversions were calculated using ^{1}H NMR and reflect the conversion of the allylic alcohol **93**. The numbers in parenthesis show the ratio of ketone **94**/saturated alcohol **95**/propyl compound **96**.

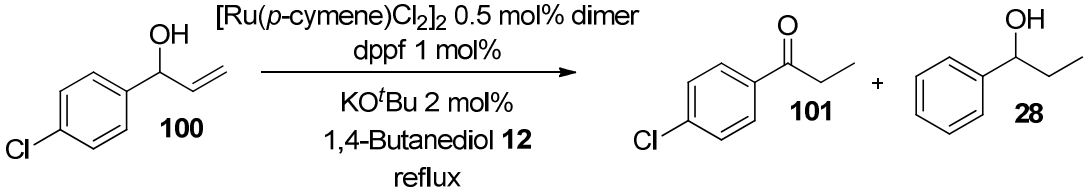
The results show the expected ketone **94** and saturated alcohol **95** formation, but a further reaction is taking place to give *N*,*N*-dimethyl-4-propylaniline **96**. At present there is no proposed mechanism for the reaction, however there is precedence in the literature. Cadierno *et al.* observed the loss of OH from 1-(4-methoxyphenyl)prop-2-en-1-ol **97** under similar conditions, but not to the extent seen above with the dimethylamino **93** compound (Scheme 3.26).[59]



Scheme 3.26 – Reaction observed by Cadierno *et al.*

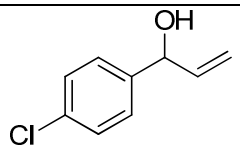
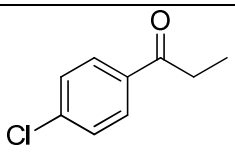
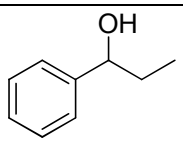
Their results only show 8% of compound **99** with 1 mol% ruthenium. This is minimal compared to the 26% (with 1 mol% ruthenium) and 37% (with 5 mol% ruthenium) seen in Table 3.8. Unfortunately, Cadierno has not offered an explanation for this reaction. The reason for it must be due to the electron donating effect of the substituent. Both methoxy and dimethylamino groups are electron donating to the ring and this makes the OH (of the saturated alcohol) group more labile, either to hydrogenolysis or to dehydration. Neither of these processes has been confirmed, but both seem plausible. This could be further explored by using other electron donating substituted allylic alcohols.

The second substrate to provide interesting results, 1-(4-chlorophenyl)prop-2-en-1-ol **100** is shown below (Scheme 3.27 and Table 3.9).



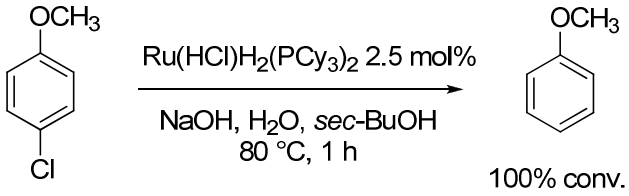
Scheme 3.27 – Dechlorination of 1-(4-chlorophenyl)prop-2-en-1-ol **100**

Table 3.9 – Dechlorination results[a]

	 **100**	 **101**	 **28**
Amount After 2 h (%)[b]	0	47	53
Amount After 24 h (%)[b]	0	4	96
Amount After 48 h (%)[b]	0	3 (trace)[c]	97 (80)[c]

[a] The reaction was carried out on a 1 mmol scale, in neat 1,4-butanediol **12** and heated to 110 °C. [b] Conversions were calculated using ^{1}H NMR and reflect the conversion of the allylic alcohol **100**. [c] The number in parenthesis is isolated yield.

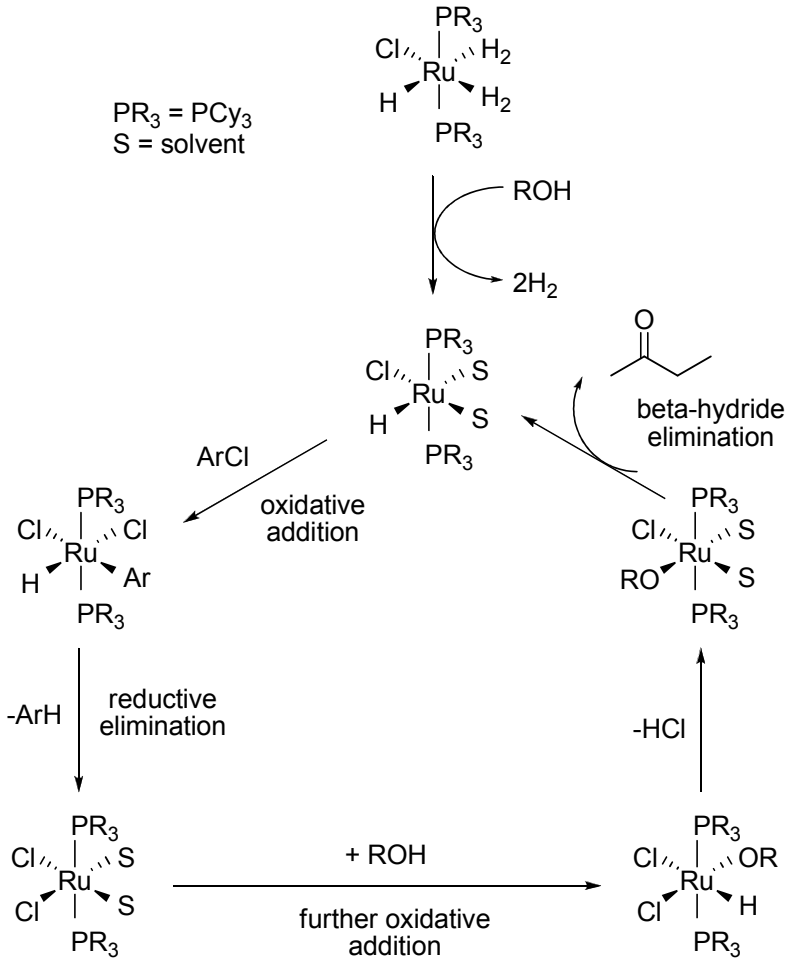
As Table 3.9 shows, the isomerisation occurs as expected, but at the point of reduction, dechlorination takes place also. Dechlorination ONLY occurs on the alcohol **28**, no dechlorination has been observed on the ketone **101**. This has been confirmed by the isolation of a small amount of chlorinated ketone **101**, and the absence of any chlorinated saturated alcohol. Again there is precedence in the literature for dechlorination, Grubbs has reported a system using ruthenium and a diphosphine ligand which fully dechlorinates a range of chloroarene compounds (Scheme 3.28).[72]



Scheme 3.28 – Dechlorination reported by Grubbs

Grubbs' system includes the use of *sec*-butanol, and the mechanistic claim is that a transfer hydrogenation step is part of the reaction. If this is the case, it may help to explain why dechlorination was observed with 1-(4-chlorophenyl)prop-2-en-1-ol **100**. If the role which *sec*-butanol plays in the

reaction could be replicated by 1,4-butanediol **12**, this would explain the above observations. The mechanism proposed by Grubbs is shown below (Scheme 3.29).



Scheme 3.29 – Grubbs proposed mechanism for dechlorination

The mechanism seems plausible for the observed dechlorination, however, Grubbs uses a large amount of strong base (sodium hydroxide) in order to drive the release of hydrogen chloride from the complex (see above). The current conditions only use 2 mol% potassium *tert*-butoxide. If the above mechanism is occurring under the $[Ru(p\text{-cymene})Cl_2]_2$ and dppf reaction conditions, this amount of base is obviously sufficient for the release of HCl. Although the mechanism is plausible, there is no direct evidence that it is occurring, and no explanation why the saturated alcohol dechlorinates yet the ketone does not.

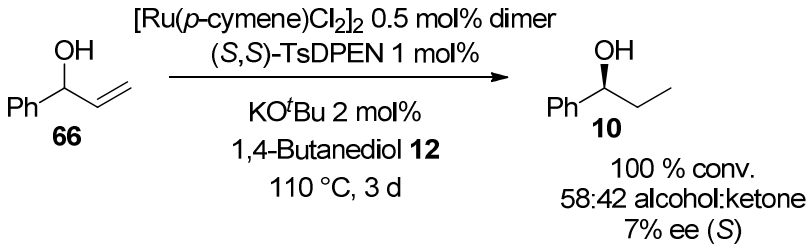
The final substrate subjected to the redox isomerisation reduction conditions was an alkene. The idea was to see if the alkene would be reduced under these conditions. If it was reduced, then it could be argued that the overall process was not strictly isomerisation. Allylbenzene **36** was chosen as the substrate and the below scheme shows the results (Scheme 3.30).

Scheme 3.30 – Isomerisation of allylbenzene **36**

In 2 hours, the allylbenzene **36** was completely converted into *trans*-1-phenyl-1-propene **102**. The reaction was carried out for a further 24 hours, and no reduction of the alkene was seen. The compound was isolated easily but underwent a small amount of geometric isomer interconversion whilst on silica. From this result it can be speculated that the redox isomerisation of allylic alcohols is occurring *via* movement of the carbon-carbon double bond (isomerisation) rather than a combination of oxidation and reduction reactions.

3.5 Asymmetric Isomerisation and Reduction Using 1,4-Butanediol 12

In Section **2.5**, the asymmetric reduction of carbonyls using 1,4-butanediol **12** was reported. These results were not comparable to those already published in the literature; however, the conditions were applied to the isomerisation reduction in order to see if an ee could be achieved (Scheme 3.31).



Scheme 3.31 – Attempted asymmetric isomerisation reduction

The above results show that although there is 100% conversion from the allylic alcohol **66**, there is only 58% conversion to the alcohol, 1-phenyl-1-propanol **28** over 3 days. This means that (*S*,*S*)-TsDPEN is a much poorer ligand for the overall transformation than dppf. The result is also disappointing because the ee is so low that it can be considered to be racemic. The ee is likely to have been affected by the temperature and the extended reaction time.[42] Having studied both the isomerisation process and the reduction process separately, it is likely that a higher ee (and conversion) could be achieved by splitting the one-pot reaction. This would entail carrying out the isomerisation first at a higher temperature in the absence of 1,4-butanediol **12**, then lowering the temperature for the reduction, and then adding the 1,4-butanediol **12**. The disadvantage of this would be the loss of the one-pot nature of the reaction.

3.6 Conclusions

The redox isomerisation of allylic alcohols has been investigated and optimised using a ruthenium diphosphine based catalyst system. This process has been combined with the reduction of the produced carbonyl using 1,4-butanediol **12**. The reaction conditions have been applied to a wide range of substrates with generally good conversions and yields. Several substrates provided unusual results, for example a dehalogenation and a dehydration. The catalyst system has been shown to be selective for allylic carbon-carbon double bonds over simple alkene carbon-carbon bonds. The system has also isomerised and reduced a propargylic alcohol and an α,β-unsaturated ketone.[2] Unfortunately the attempt at gaining a respectable ee was

unsuccessful; however this could be improved with further work. It would also be interesting to test the optimised (achiral) conditions on allylic amines.

CHAPTER 4 - RESULTS AND DISCUSSION III

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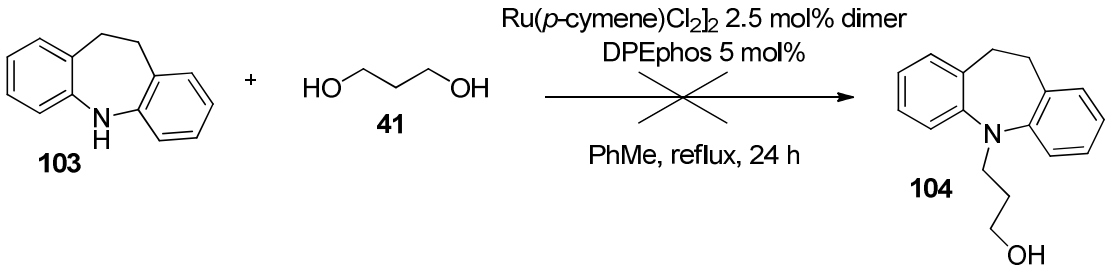
4.1 Background

Diols are very versatile compounds. The number of reactions they can undergo is plentiful, for example they can be used as a protecting group for aldehydes, they can be made into lactones (as seen in Chapters 2 and 3) and they can be used as solvents and in the production of polymers. Asymmetric diols have uses in chiral synthesis as both auxiliaries and ligands.[73] However, the use of diols has been scrutinised, since they are produced from non-renewable feedstocks, such as 1,4-butanediol **12** being produced from succinic acid **14**. Although this may have been the case, recent developments have shown that both 1,3-propanediol **41** and 1,4-butanediol **12** can be produced by the action of an enzyme on a renewable chemical.[24,25,74] If this is the case, then alkanediols could be the fuels of the future.

Additionally, if synthetic building blocks could be accessed *via* alkanediols, then production of certain chemicals could become cheaper and more efficient.

Whilst trying to react 1,3-propanediol **41** with a particularly unreactive amine, iminodibenzyl **103** (Scheme 4.1), it was discovered that the diol was reacting with itself. The original reaction was an attempt to synthesise imipramine **104**, which is one of a group of tricyclic antidepressants.



Scheme 4.1 – Failed attempt at making imipramine **104**

The product the diol formed with itself, 2-(1,3-dioxan-2-yl)ethanol **105**, could be described as the product of oxidative dimerisation (Figure 4.1), since two molecules of 1,3-propanediol **41** are required to make it.

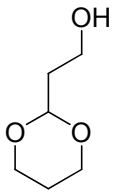


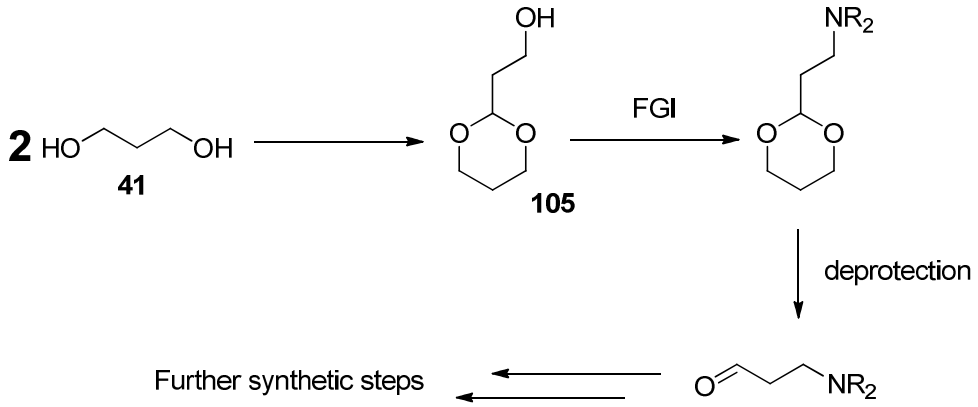
Figure 4.1 – Structure of the dimerised diol, 2-(1,3-dioxan-2-yl)ethanol **105**

The single H signal for the O-(CH)-O is very distinctive, appearing as a triplet at 4.77 ppm. The downfield shift of this signal meant that the proton had to be next to one or more oxygens, and that it was only next to a CH_2 group. The ^{13}C spectrum showed an absence of signals in the carbonyl region and only had 5 signals, all appearing below 110 ppm. From all of these facts the above structure was proposed, and then confirmed by comparison of the corresponding ^{1}H NMR and ^{13}C NMR found in the literature.

Once the structure has been confirmed, an idea was proposed of how this compound could be of interest. With there being a free hydroxyl group at one end of the molecule, there are many potential reactions that could be carried out on this functional group. At the other end of the molecule, there is the acetal ring, which looks very similar to an existing type of protecting group for hydroxy aldehydes.

As protecting groups, acetals are stable to both nucleophiles and any attack by base. Removal is also simple, and can be done by using acid in acetone, or by hydrolysis in wet solvents or aqueous acid.

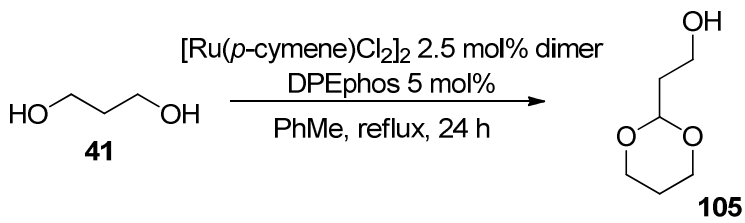
With this versatility of the acetal group, the molecule could be deprotected to leave an aldehyde and this then could be further functionalised (Scheme 4.2). This type of molecule could then be used as a building block in synthesis and could provide an easy initial route to more complex structures.



Scheme 4.2 – Premise of using acetal compounds as building blocks

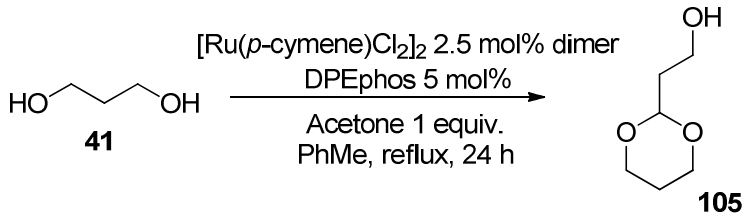
4.2 Initial Studies

Due to the formation of 2-(1,3-dioxan-2-yl)ethanol **105** only being seen in small quantities, as observed in Scheme 4.1, the reaction was attempted without the presence of iminodibenzyl **103** (Scheme 4.3).



Scheme 4.3 – Formation of 2-(1,3-dioxan-2-yl)ethanol **105**

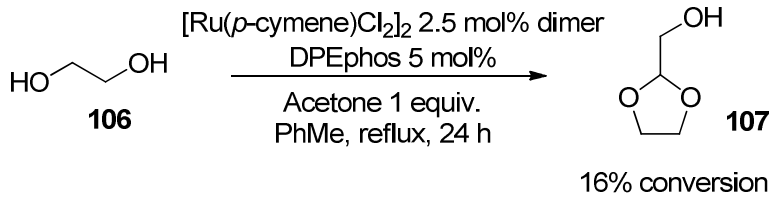
The conversion of this reaction is only 26%, which is disappointing, but much improved from the trace that was observed in the failed imipramine **104** reaction. The reaction was then tried with the presence of a hydrogen acceptor, acetone (Scheme 4.4). The reason for this was because the reaction was assumed to be occurring initially as transfer hydrogenation, *i.e.* oxidation of one of the alcohol groups. With the presence of a hydrogen donor, hopefully it can accept the hydrogen from the diol and help to improve the conversion.



Scheme 4.4 – Reaction involving a hydrogen acceptor, acetone

The addition of acetone increased the conversion from 26% to 77% in 24 hours.

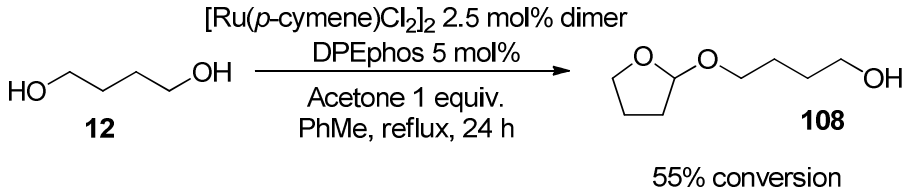
Having shown that this potential building block compound can be formed from 1,3-propanediol **41**, other diols were considered. Ethylene glycol **106** was subjected to the same reaction conditions to afford a similar product (Scheme 4.5). However, the conversion was low in comparison with that found for 1,3-propanediol **41**.



Scheme 4.5 – Reaction of ethylene glycol **106**

Unfortunately this conversion is not very high and suggests that ethylene glycol **106** is not very reactive under these conditions (the crude reaction mixture contains 16% of the product **107** and the rest is remaining starting

material). 1,4-Butanediol **12** was also reacted under these conditions, but this reaction provided a different product (Scheme 4.6).



Scheme 4.6 – Reaction of 1,4-butanediol **12**

The conversion of this reaction is more promising, although the product is different. Initially the expected product was thought to be a seven membered ring (Figure 4.2), but this structure did not correspond to the obtained ^{1}H NMR data. The O-(CH)-O signal that was used before to identify 2-(1,3-dioxan-2-yl)ethanol **105** could not be used with this compound, since the signal is similar for both structures.

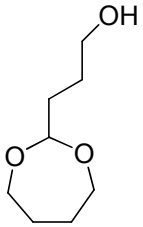


Figure 4.2 – Proposed seven membered ring structure

The seven membered ring structure has a certain amount of symmetry. It has a mirror plane of symmetry through the CH (Figure 4.3).

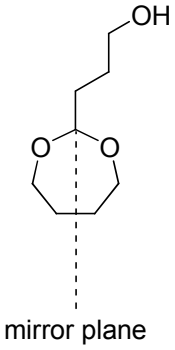
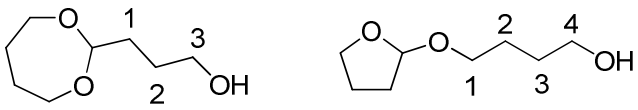


Figure 4.3 – Structure showing the symmetry in the seven membered ring structure

This symmetry means the two sets of CH_2 groups in the ring are similar, and will appear in the same region in the ^1H NMR and at the same place in the ^{13}C NMR. The actual structure of the compound does not contain any symmetry, therefore you would expect there to be more carbon signals in the ^{13}C NMR. Also, because of the nature of the structure, the carbon chain has four carbons, compared with the seven membered ring structure which only has three (Figure 4.4).



3 carbon chain 4 carbon chain

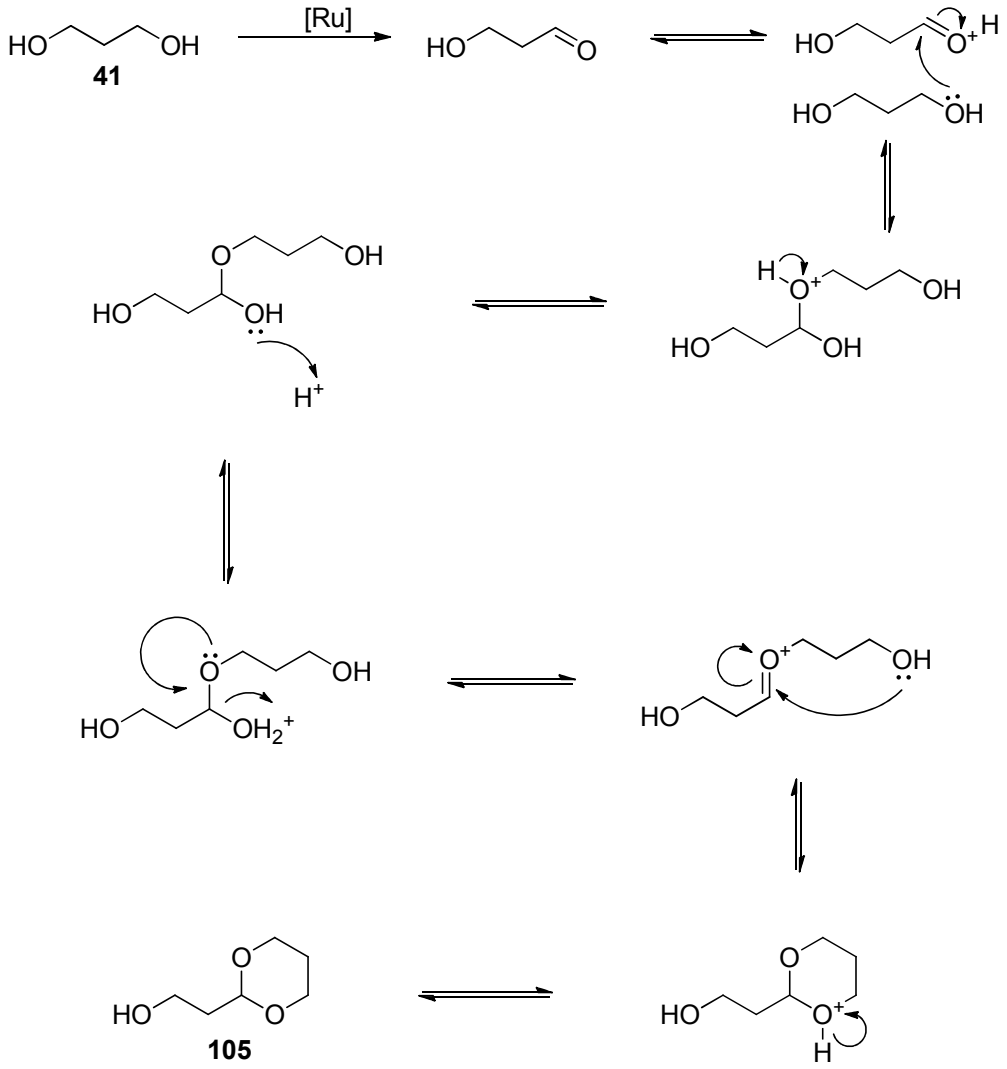
Figure 4.4 - Comparison of the two proposed structures

This means you would expect to see three distinct triplets in the ^1H NMR for the actual structure, one for the O-(CH)-O, and two for the CH_2 next to the ether oxygen and the CH_2 next to the OH. In the seven membered ring structure there would only be two distinct triplets, the O-(CH)-O and the CH_2 next to the oxygen.

The different structure is probably due to the instability of the proposed seven membered ring. However, the obtained structure still adheres to the idea of using the compounds as building blocks, since it is a THF ether. This is also a protecting group, and can be easily removed to leave a diol for further functionalisation.

4.3 Optimisation

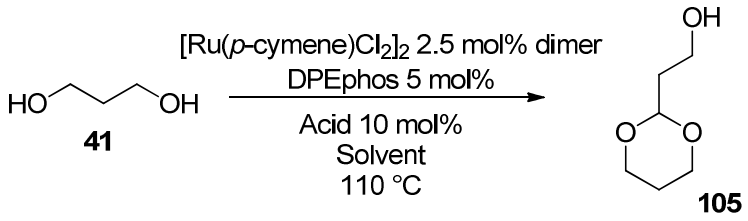
The optimisation of the reaction was investigated in terms of solvent and the addition of acid. As the reaction is forming an acetal, it was hoped that the addition of acid would aid the reaction in terms of speed and conversion. It was assumed that the mechanism of formation follows that of any simple acetal formation (Scheme 4.7).



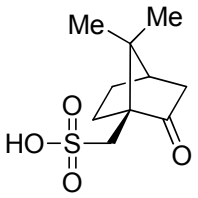
Scheme 4.7 – Mechanism of acetal formation, using 1,3-propanediol **41**

Optimisation was carried out by Principal Component Analysis (PCA, see Appendix A). This was carried out in collaboration with Mark Armitage at GlaxoSmithKline Plc., at their Tonbridge site in Kent. PCA involves selecting a variable you wish to change, and then choosing the property of that variable that is the most important. In this case, the variable chosen was solvent, and the important property was the boiling point. The reaction requires a high temperature (at least 100 °C) as lower temperature reactions failed. A second variable was also introduced, and this was the inclusion of acid. Using the PCA software, a design of experiments was carried out in order to improve the conversion of the reaction. The design of experiments produced 20 reactions to be run, using different combinations of solvents and acids. At this

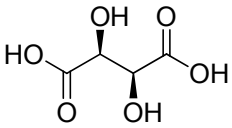
point, the inclusion of acetone has to be considered. Since the introduction of acetone increased the conversion threefold, it seemed necessary to include it in the 20 experiments. However, some of the solvents selected contained alkene or carbonyl functional groups which were deemed to be able to act as hydrogen acceptors, so the inclusion of acetone was not required. The following table displays the results of the 20 experiments. They were carried out using 1,3-propanediol **41** since the initial experiments were carried out on this compound (Scheme 4.8, Figure 4.5 and Table 4.1).



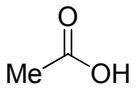
Scheme 4.8 – Variation of solvent and acid



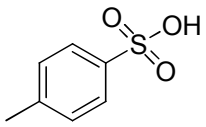
(1*S*)-(+)-10-Camphor sulphonic Acid **109**



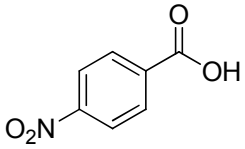
D-Tartaric Acid **110**



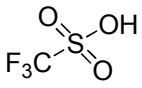
Acetic Acid **111**



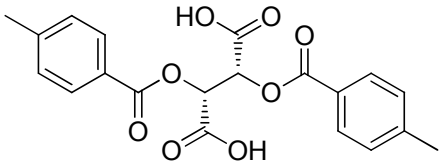
p-Toluene sulphonic Acid **112**



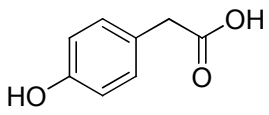
4-Nitrobenzoic Acid **113**



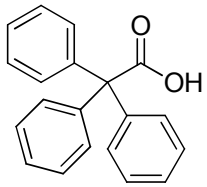
Trifluoromethane sulphonic Acid **114**



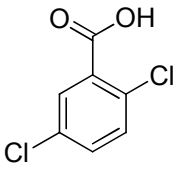
Di-*p*-Toluoyl-L-tartaric Acid **115**



4-Hydroxyphenyl acetic acid **116**



Triphenylacetic Acid **117**



2,5-Dichlorobenzoic Acid **118**

Figure 4.5 – Structures of the acids used in the optimisation work

Table 4.1 – Results of variation of solvent and acid[a]

Entry	Solvent	Acid	Acetone (1 equiv.)	Conversion after 18 h (%)	Conversion after 24 h (%)
1	DMSO-d_6	**109**	Yes	0	-
2	Cyclopentyl methyl ether	**110**	Yes	71	80
3	3-Pentanone	**111**	No	73	74
4	Chlorobenzene	**112**	Yes	33	-
5	Cyclohexanone	**113**	No	0	-
6	NMP	**114**	No	-	-
7	Chlorobenzene	**115**	Yes	83	99
8	Cyclohexanone	**116**	No	38	-

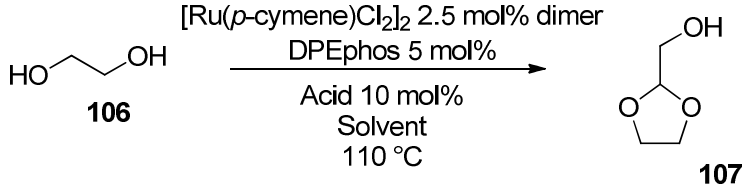
Table 4.1 cont.

Entry	Solvent	Acid	Acetone (1 equiv)	Conversion after 18 h (%)	Conversion after 24 h (%)
9	Methyl cyclohexane	**117**	Yes	73	92
10	*n*-Propyl acetate	**112**	No	0	-
11	*p*-Xylene	**111**	Yes	74	74
12	Cyclopentyl methyl ether	**109**	Yes	0	-
13	DMSO-d_6	**110**	Yes	0	-
14	1,4-Dioxane	**113**	Yes	23	-
15	*p*-Xylene	**118**	Yes	87	98
16	NMP	**117**	No	-	-
17	*n*-Propyl acetate	**115**	No	64	-
18	3-Pentanone	**118**	No	31	-
19	Methyl cyclohexane	**114**	Yes	0	-
20	1,4-Dioxane	**116**	Yes	40	-
21	Toluene	-	Yes	71	77

[a] Reactions were carried out on 1 mmol scale in 1 mL of solvent. Acetone, where used is 0.5 equivalents. Conversions were calculated from analysis of GC-MS and ^{1}H NMR spectra of crude reaction mixtures.

Table 4.1 shows a varied range of results. Certain combinations gave little or no conversion, and so these experiments were terminated after 18 hours (Entries 1, 4, 5, 6, 8, 10, 12, 13, 14, 16, 18, 19 and 20). Entries 1 and 13 were run in deuterated DMSO due to problems removing the solvent in work up. Entries 6 and 16 suffered from a similar problem, and deuterated NMP was deemed too expensive to use as a replacement. There were 6 good results, entries 2, 3, 7, 9, 11 and 15. Entries 3 and 11 provided conversions in a similar area to that of the control reaction, toluene and acetone (Entry 21). Entries 2, 7, 9 and 15 gave much higher conversions. Based on the conversions after 24 hours, the combination of solvents and acids of entries 7,

9 and 15 were used to obtain conversions using ethylene glycol **106** (Scheme 4.9 and Table 4.2) and 1,4-butanediol **12** (Scheme 4.10 and Table 4.3).



Scheme 4.9 – Reaction of ethylene glycol **106** with different solvent and acid combinations

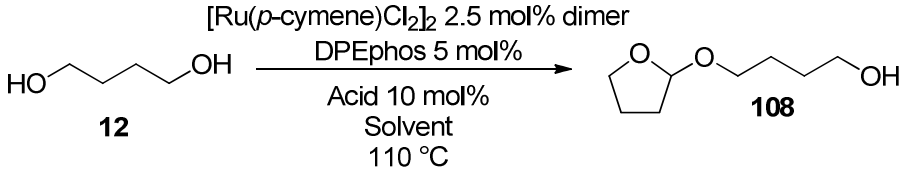
Table 4.2 – Results with ethylene glycol **106**[a]

Entry	Solvent	Acid	Acetone	Conversion after 18 h (%)	Conversion after 24 h (%)
1	Chlorobenzene	**115**	Yes	7	6
2	*p*-Xylene	**118**	Yes	8	3
3	Methyl cyclohexane	**117**	Yes	3	5
4	Toluene	-	Yes	7	16
5	Chlorobenzene	**115**	No	7	11
6	*p*-Xylene	**118**	No	7	7
7	Methyl cyclohexane	**117**	No	9	5
8	Toluene	-	No	8	15

[a] Reactions were carried out on 1 mmol scale in 1 mL of solvent. Acetone, where used is 0.5 equivalents. Conversions were calculated from analysis of GC-MS and ^{1}H NMR spectra of crude reaction mixtures.

The results in Table 4.2 are disappointing. It would appear that regardless of conditions, ethylene glycol **106** is not very reactive in terms of forming an acetal. Interestingly, the reactions run in toluene, with and without acetone, have similar conversions. This would suggest that acetone does not affect the conversion, but as the conversion is so low, it is probably not that

significant. The results do show however, that this is not a viable route for building blocks which only (initially) contain a two carbon chain.



Scheme 4.10 – Reaction of 1,4-butanediol **12** with different solvent and acid combinations

Table 4.3 – Results with 1,4-butanediol **12**[a]

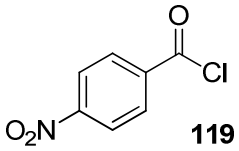
Entry	Solvent	Acid	Acetone	Conversion after 18 h (%)	Conversion after 24 h (%)
1	Chlorobenzene	**115**	Yes	31	64
2	*p*-Xylene	**118**	Yes	55	58
3	Methyl cyclohexane	**117**	Yes	24	50
4	Toluene	-	Yes	19	55
5	Chlorobenzene	**115**	No	77	81
6	*p*-Xylene	**118**	No	30	40
7	Methyl cyclohexane	**117**	No	39	31
8	Toluene	-	No	24	41

[a] Reactions were carried out on 1 mmol scale in 1 mL of solvent. Acetone, where used is 0.5 equivalents. Conversions were calculated from analysis of GC-MS and ^{1}H NMR spectra of crude reaction mixtures.

The results using 1,4-butanediol **12** are more promising, but not as impressive as those with 1,3-propanediol **41**. The above table does show however, that the best conditions for 1,4-butanediol **12** are not the same as the best conditions for 1,3-propanediol **41**. The other interesting point is that the best result was found without the use of acetone. Again, like ethylene glycol **106**, this would suggest that acetone is not required for the formation of the

product. Unfortunately, this means that the solvent acid screen which has been carried out with 1,3-propanediol **41** is substrate specific. This limits the idea of making lots of different building blocks using this method.

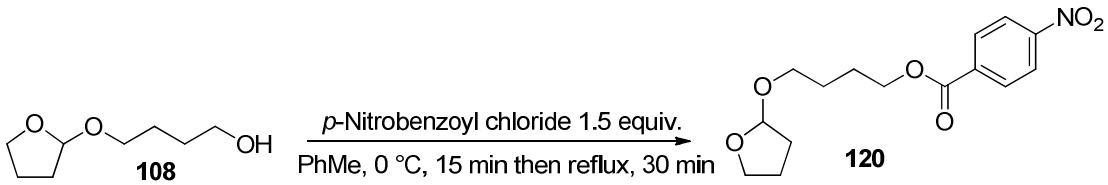
The other issue with this chemistry is isolation. In Table 4.1, entry 7, there is a 99% conversion to 2-(1,3-dioxan-2-yl)ethanol **105**. However, column chromatography only furnishes 25% yield of the product. The only solvent system that appeared to purify the compound was dichloromethane:methanol (95:5). However, the 2-(1,3-dioxan-2-yl)ethanol **105** is not stable in methanol and degrades. Attempts to purify the compound by Kügelrohr also failed. Further isolation problems exist with 4-(tetrahydrofuran-2-yloxy)butan-1-ol **108**. Due to the incomplete conversion of 1,4-butanediol **12**, there is a large amount left over at the end of the reaction which is not able to be removed under vacuum (due to the high boiling point, 230 °C). It was found by column chromatography that the two compounds co-elute and so are difficult to separate. Therefore, the idea of making a derivative was suggested, using *p*-nitrobenzoyl chloride **119** (Figure 4.6).



119

Figure 4.6 – *p*-Nitrobenzoyl chloride

The idea was to form the *p*-nitrobenzoate ester (Scheme 4.11), and then this would be easier to separate and isolate from the starting material because *p*-nitrobenzoate esters are usually crystalline solids with sharp melting points, making them good for characterisation purposes.



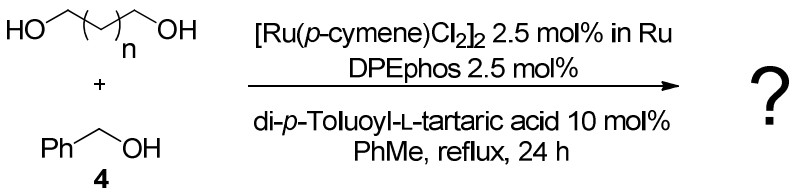
108 **120**

Scheme 4.11 – Formation of *p*-nitrobenzoate ester

The formation of the *p*-nitrobenzoate was a good idea in theory, and the reaction did indeed form the ester **120**. However, the bis ester of the starting 1,4-butanediol **12** was also produced. The separation of this compound from the desired 4-(tetrahydrofuran-2-yloxy)butan-1-ol **108** encountered the same problems as before – column chromatography would not separate the two compounds. This meant that although the premise of the chemistry was excellent, the practicality of the chemistry failed on this occasion.

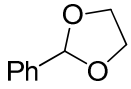
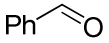
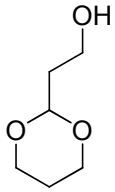
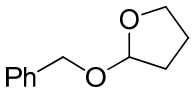
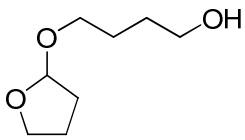
4.4 Further Studies

As the above chemistry was not so successful, the diols were then added to another alcohol in order to see how they reacted. The chosen alcohol was benzyl alcohol **4** (Scheme 4.12 and Table 4.4). The reactions were carried out in toluene with di-*p*-toluoyl-L-tartaric acid as these conditions gave the best results after a few test reactions.



Scheme 4.12 – Reaction of diols with benzyl alcohol **4**

Table 4.4 – Results of reaction of diols with benzyl alcohol **4**[a]

Entry	Diol	Major Product	Minor Product	Overall Conversion (%)	Ratio of Products (major:minor) (%)
1	ethylene glycol **106** (n = 0)	 **121**	 **34**	20	19:1
2	1,3-propanediol **41** (n = 1)	 **105**	-	29	-
3	1,4-butanediol **12** (n = 2)	 **122**	 **108**	49	32:17

[a] Reactions were carried out on 1 mmol scale in 1 mL of solvent. Conversions were calculated from analysis of ^{1}H NMR spectra of crude reaction mixtures.

Table 4.4 confirms that this process is not ideal for forming building blocks for synthesis. Entry 1 shows that ethylene glycol **106** simply forms a protecting group, *i.e.* the benzyl alcohol **4** is oxidised and then reacts to form a dioxolane protecting group **121**. Entry 2 proves that this chemistry is definitely substrate specific. The only product formed from the reaction is 2-(1,3-dioxan-2-yl)ethanol **105** and the crude reaction mixture contains both unreacted benzyl alcohol **4** and 1,4-butanediol **12**. It would appear that the presence of benzyl alcohol **4** is inhibiting the production of 2-(1,3-dioxan-2-yl)ethanol **105**. Entry 3 shows that although 1,4-butanediol **12** reacts with benzyl alcohol **4** to give what would be a useful product for the target of this chemistry, it also reacts largely with itself, forming 4-(tetrahydrofuran-2-yloxy)butan-1-ol **108**. From these results, the decision was made to terminate any further experiments on this topic of chemistry.

4.5 Conclusions

The idea presented at the start of this chapter would be useful in synthesis, and the initial results of the reaction of 1,3-propanediol **41** and the subsequent solvent/acid screen results showed a very promising step towards this goal. However, a number of setbacks have been encountered and in order for the chemistry to be useful, there would be a large amount of work to do. The isolation problems need to be sorted in order for the 1,3-propanediol **41** reaction to be of any use. The other diols did not give high enough conversions for their products to be useful. The further problem of the products not being stable in methanol is also obviously a major drawback. In conclusion, there are, at this point in time, far too many problems with this chemistry. A large amount of work would be required to bring the chemistry to a standard in which it could be reported in the literature. The idea of producing useful synthetic building blocks from diols (which are to become available from renewable sources) is still a valid one, there just needs to be a fresh approach toward it.

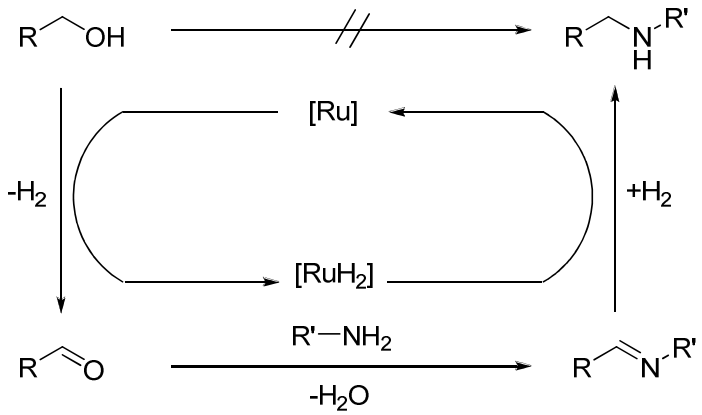
CHAPTER 5 - RESULTS AND DISCUSSION IV

CHAPTER 5 – RESULTS AND DISCUSSION IV

5.1 Background

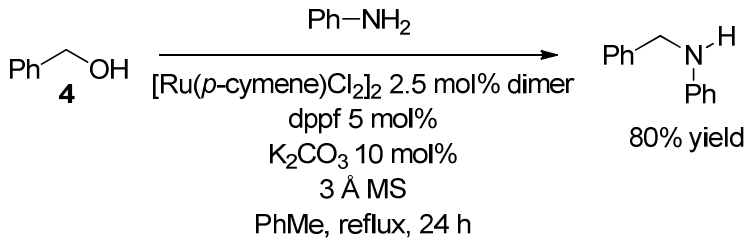
Amines are very important molecules. Their annual production in the world is around 100, 000 tonnes,[75] and this applies to not only bulk chemicals but also to intermediates in organic synthesis and final drug molecules, among others.

Amines are traditionally synthesised by the alkylation of alkyl halides with an amine, or ammonia.[38] This process is not always effective however, since over-alkylation is common, providing mixtures of primary, secondary and tertiary amines, as well as quaternary salts. An alternative method of producing amines involves the borrowing hydrogen approach (Scheme 5.1). The Williams group has investigated ruthenium catalysts for this reaction.[5,34]



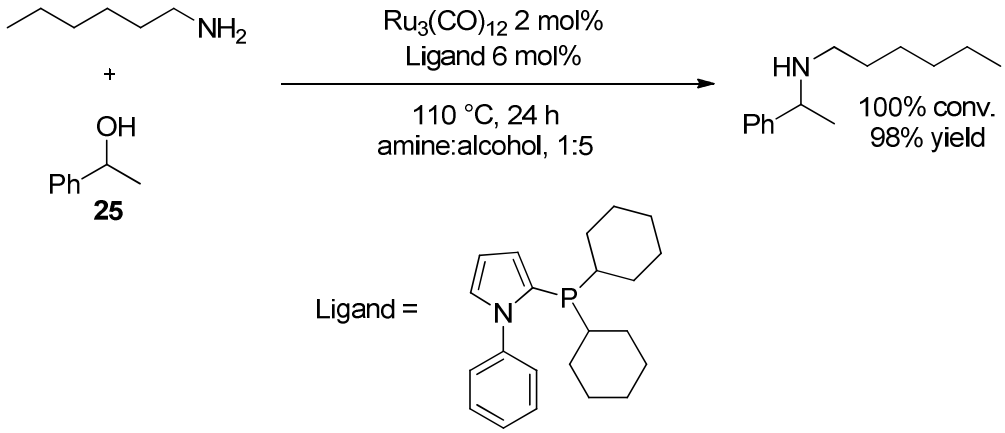
Scheme 5.1 – The borrowing hydrogen approach to form amines from alcohols

The borrowing hydrogen approach (see Section ***1.1***) forms an aldehyde from the starting alcohol, then this aldehyde reacts with an amine to form an imine, then with the addition of hydrogen the desired amine is formed. Below is an example of this method forming secondary amines (Scheme 5.2).



Scheme 5.2 – Example of secondary amine formation *via* borrowing hydrogen

A similar effect to that shown in Scheme 5.2 has been shown by Beller *et al.* to occur with a ruthenium carbonyl cluster catalyst[76,77] (Scheme 5.3).



Scheme 5.3 – Example of Beller *et al.* catalyst system

Drug molecules containing the dimethylamino moiety are very common. Below are several examples of these molecules (Figure 5.1).

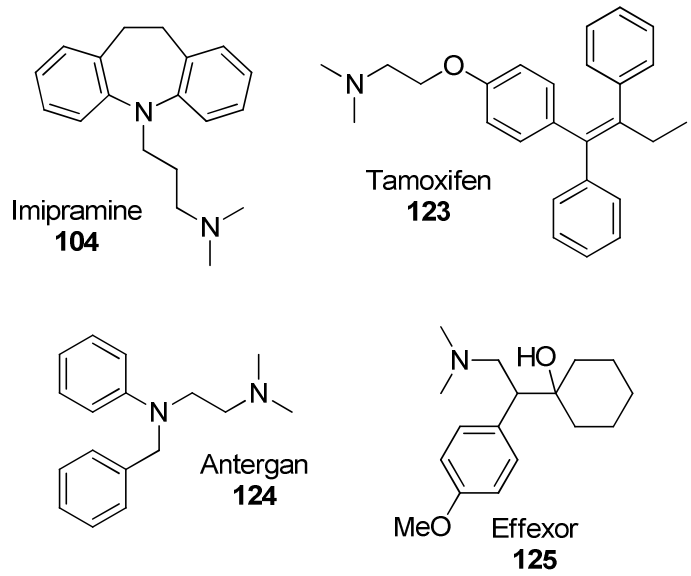
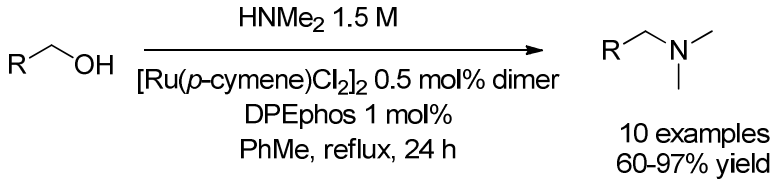


Figure 5.1 – Structures of 4 drug molecules containing a dimethylamino group

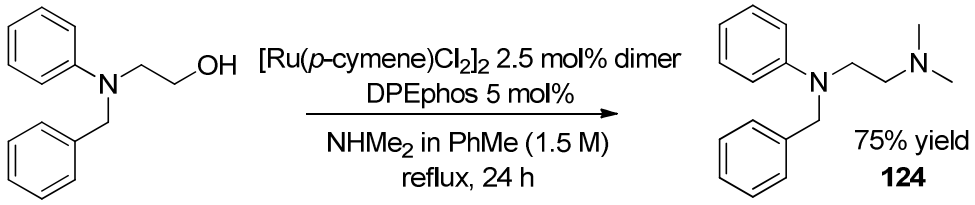
Antergan **124** is an antihistamine, and actually the first to be used in humans in 1942.[78] Effexor **125** (also known as Venlafaxine) is a prescription drug and is used to treat depression and anxiety disorders.[79] Imipramine **104** was also used to treat depression,[80] although it is no longer as widely used as it once was (there are now more effective treatments available). It was the first, in 1952, of a series of tricyclic antidepressants to be developed and provided a comparison for all the newly developed drugs. Tamoxifen **123** is an effective treatment for breast cancer in both men and women. Since the 1970s when it was first developed, it has helped to prolong life in many millions of individuals all over the world.[81]

One of the above mentioned drug molecules has been synthesised by a borrowing hydrogen approach in the Williams group. The conditions described above to *N*-alkylate amines with alcohols were developed in order to alkylate alcohols with dimethylamine (Scheme 5.4)[3].

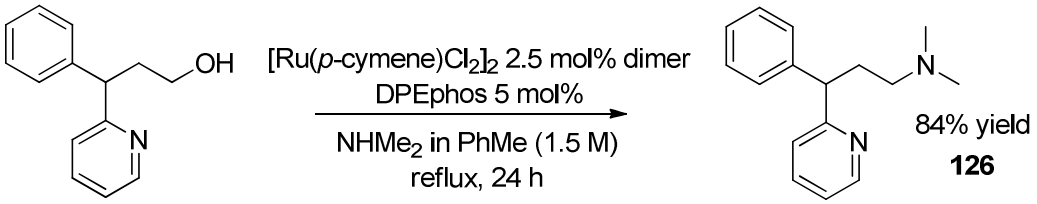


Scheme 5.4 – Conditions to alkylate alcohols with dimethylamine

Thus these conditions were used to make antergan **124** and a structurally similar molecule, pheniramine **126** in good yields (Schemes 5.5 and 5.6).[3]



Scheme 5.5 – Synthesis of antergan **124**



Scheme 5.6 – Synthesis of pheniramine **126**

5.2 Research Goals

Diphenhydramine **127** (Figure 5.2) is also a drug molecule that contains a dimethylamino moiety. The drug is an antihistamine and sold under a trade name of Dimedrol© in the UK and Benadryl© in the USA. It is not just used to treat hayfever and other related allergies, but can be used as a mild sedative and an antiemetic. It is available in tablet form as an over-the-counter (OTC) medicine, and in injectable form as the HCl salt on prescription. The injectable form can be used to treat anaphylactic shock (serious allergic reactions to (pea)nuts, bee stings *etc.*) instead of epinephrine (adrenaline). Due to its mild sedative nature, diphenhydramine **127** can also be found in treatments such as Nytol© and Tylenol©, which help the patient to achieve a good nights' sleep. This does however mean that it cannot be used as widely as some other hayfever treatments since it is not non-drowsy.

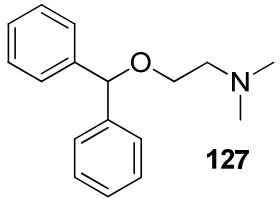


Figure 5.2 – Structure of diphenhydramine

Diphenhydramine **127** which is known as Benadryl© in the USA, is not to be confused with the OTC drug marketed as Benadryl© in the UK. The drug marketed in the UK is also used to treat hayfever and rhinitis but its trade name is actually Acrivastine **128**. The structure is shown below (Figure 5.3).

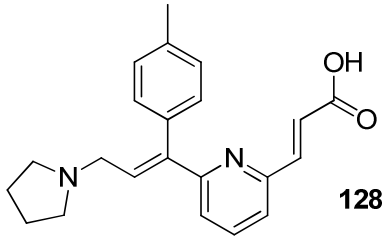
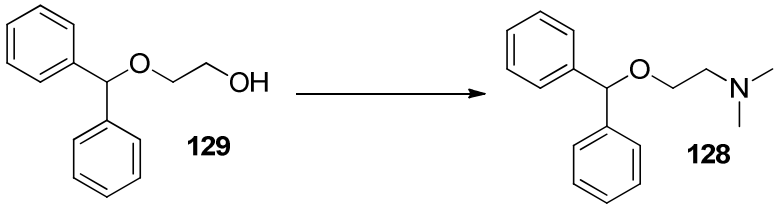


Figure 5.3 – Structure of Acrivastine **128**, the compound sold as Benadryl Allergy Relief in the UK

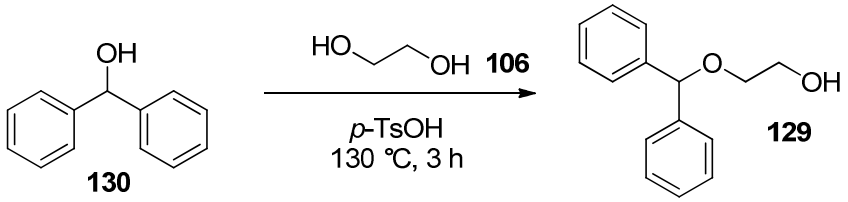
The aim of this chapter is to synthesise diphenhydramine **127** from its precursor alcohol (Scheme 5.7) and investigate similar compounds under the same conditions.



Scheme 5.7 – Proposed synthesis of diphenhydramine **127**

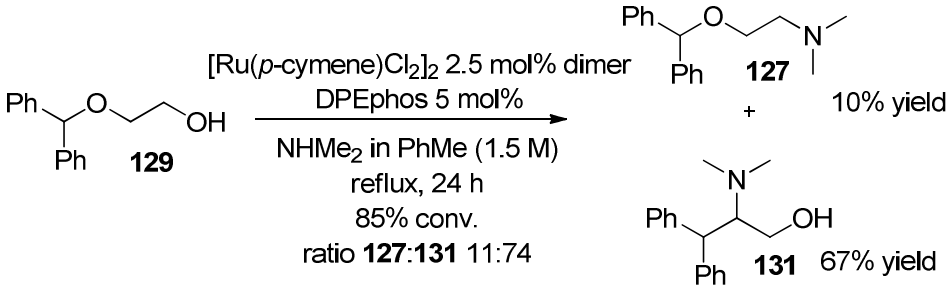
5.3 Initial Studies

In order to synthesise diphenhydramine **127**, the precursor alcohol **129** needed to be prepared. This was in turn synthesised from benzhydrol **130** and ethylene glycol **106** (Scheme 5.8).[82]



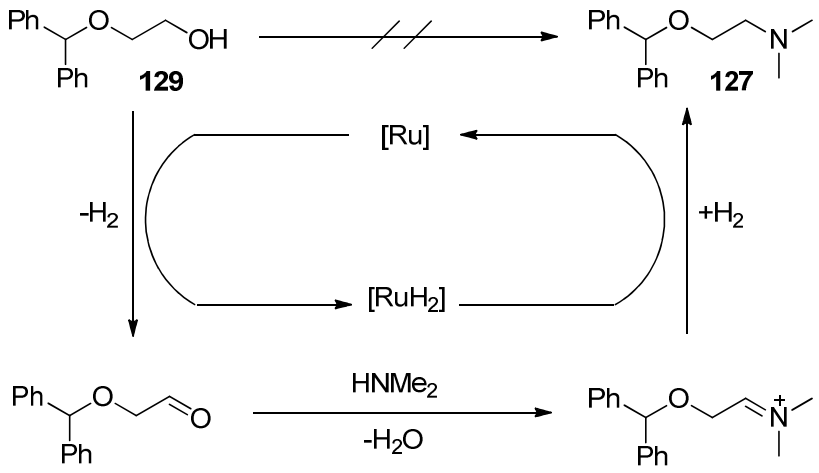
Scheme 5.8 – Preparation of 2-benzhydryloxyethanol **129**

The 2-benzhydryloxyethanol **129** was then subjected to the reaction conditions described above in section 5.1 (Scheme 5.9).



Scheme 5.9 – Reaction of 2-benzhydryloxyethanol **129**

Scheme 5.9 shows that there were two products formed from the reaction, the expected diphenhydramine **127** and a second product, 2-(dimethylamino)-3,3-diphenylpropan-1-ol **131**. The presence of diphenhydramine **127** is easily explained since it follows the expected mechanism proposed by the Williams group[34] (Scheme 5.10).



Scheme 5.10 – Proposed mechanism for the formation of diphenhydramine **127**

The second product is more difficult to explain. When the reaction was first carried out, the product was thought to contain the dimethylamino and hydroxyl groups in the opposite positions (Figure 5.4). This was due to the chemical shift of the –(CH)-OH and –(CH_2)-N(CH_3)$_2$ signals. The proton at C2 appears at 3.70 ppm in the ^{1}H NMR, and the two protons at C3 appear at 3.27 and 3.12 ppm. The proton that is further downfield (3.70 ppm) would be expected to be next to the more electronegative atom which is the oxygen, hence the structure proposed in Figure 5.4.

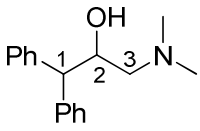


Figure 5.4 – Initial proposed structure of the second product

This structure (Figure 5.4) led to the belief that the molecule was undergoing a rearrangement, or some kind of splitting and recombination process. However, the proposed structure did not correlate with the ^{1}H NMR data. It was fortuitous that a crystal was obtained of the compound and a crystal structure was obtained, since the impure compound was a very viscous liquid and most attempts to purify and crystallise failed. The crystal structure showed that the product was definitely in the opposite regioisomer to the initial proposed structure (Figures 5.5 and 5.6).

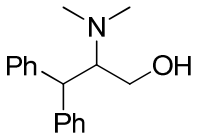


Figure 5.5 – Actual structure of the second product, 2-(dimethylamino)-3,3-diphenylpropan-1-ol **131**

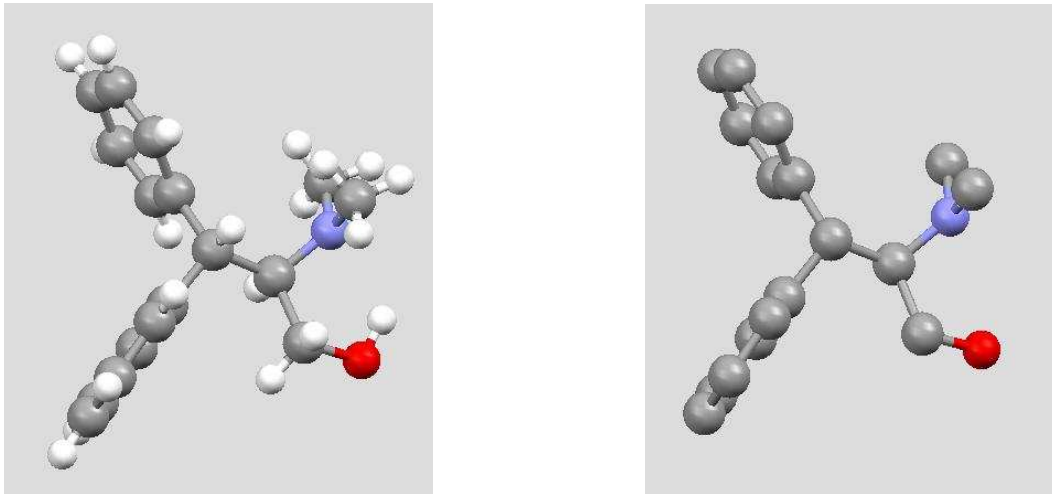
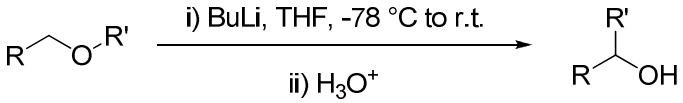


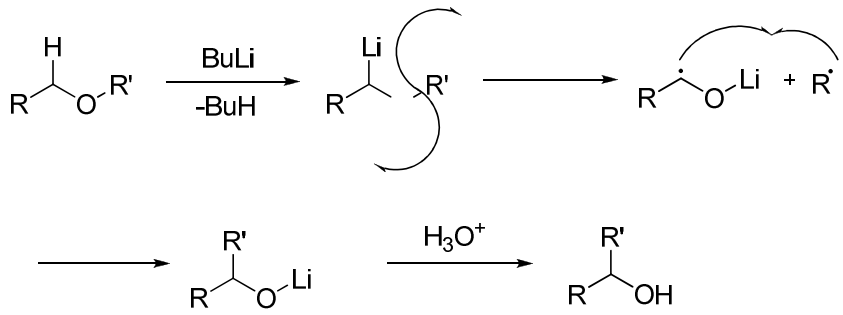
Figure 5.6 – Crystal structure representations of 2(dimethylamino)-3,3-diphenylpropanol-1-ol **131**, with (left) and without (right) hydrogen

With the thought that the molecule was undergoing a rearrangement, types of rearrangements were investigated and it was thought that the compound may be going through [1,2]-Wittig rearrangement. A [1,2]-Wittig rearrangement is a base promoted reaction where ethers become either secondary or tertiary alcohols (Scheme 5.11).



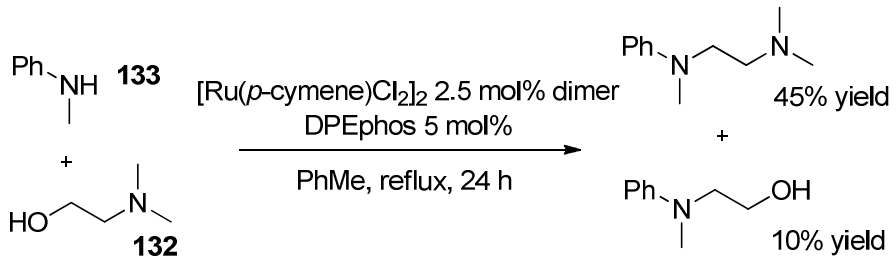
Scheme 5.11 – The [1,2]-Wittig rearrangement

The reaction starts with the deprotonation of the CH_2 next to the oxygen, then a radical dissociation-recombination takes place to give the alcohol (Scheme 5.12).



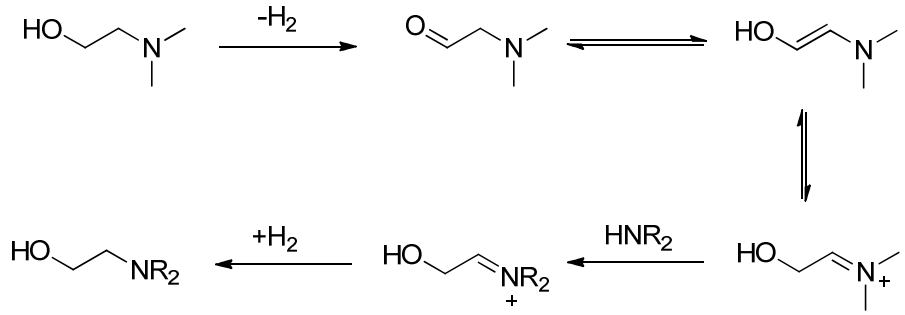
Scheme 5.12 – Mechanism of the [1.2]-Wittig rearrangement

After a search of the literature, it was found that the reaction was only mediated by a strong base (for example *n*-BuLi, *t*-BuLi, LiHMDS, LDA, LiDTBB). This provided the theory with doubts, since the only bases present in the reaction mixture were the dimethylamine and the diphenhydramine. The mechanism that was thus proposed was based on earlier results obtained by the Williams group.[3] The reactivity of *N*,*N*-dimethylethanolamine **132** with *N*-methylaniline **133** under the standard conditions for *N*-alkylation of alcohols produces two products. The expected amine and a small amount of amino alcohol were formed (Scheme 5.13).



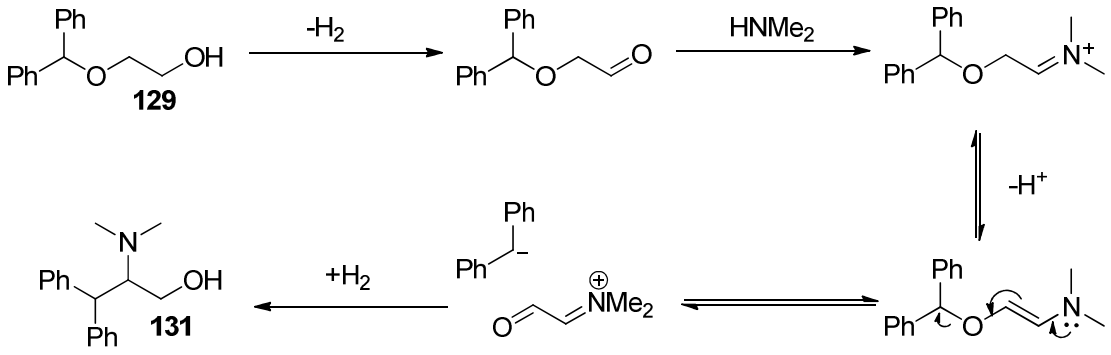
Scheme 5.13 – Reactivity of *N*,*N*-dimethylethanolamine **132**

As there is alcohol present as a product, it was reasoned that some form of isomerisation and displacement was occurring (Scheme 5.14).



Scheme 5.14 – Proposed mechanism of formation of the unexpected alcohol product from **Scheme 5.13**

Therefore it was proposed that the unexpected product **131** was a result of both isomerisation and a dissociation-recombination mechanism (Scheme 5.15).



Scheme 5.15 – Proposed mechanism of formation of the unexpected product **131**

The proposed mechanism involves the usual oxidation of the alcohol and imine formation, but instead of hydrogen being returned to the molecule at this stage, the compound isomerises to give an enamine, and then splits into two fragments. The recombination occurs at the carbon adjacent to the nitrogen to give the unexpected, rearranged product **131**. However, a radical rearrangement cannot be ruled out as the intermediate enamine could fragment into ions or radicals and no experimental work has been carried out to confirm either possibility.

5.4 Reaction of Different Substrates

Once the rearranged product **131** had been observed, it was wondered what effect the number and position of phenyl groups would have on the reaction, *i.e.* is the rearranged product still the major product? Three substrates were chosen to investigate this possibility (Figure 5.7).

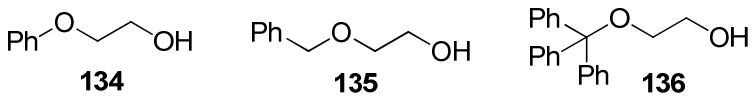
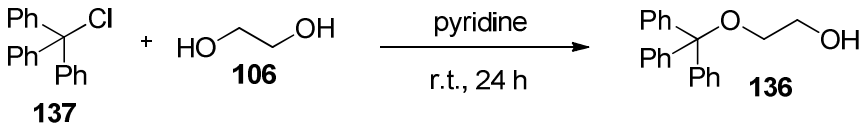


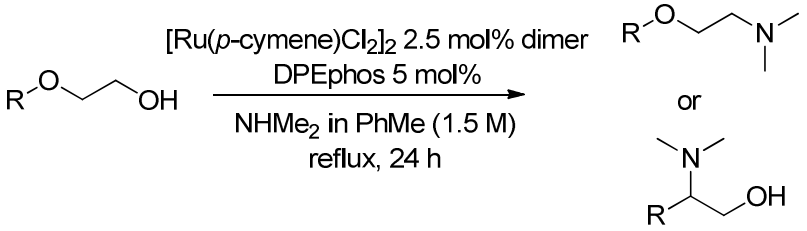
Figure 5.7 – Substrates for investigation

The first two substrates, 2-phenoxyethanol **134** and 2-(benzyloxy)ethanol **135** are commercially available, but the third, 2-(trityloxy)ethanol **136**, needed to be synthesised. This was carried out using trityl chloride **137** and ethylene glycol **106** (Scheme 5.16).[83]



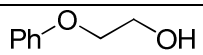
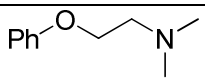
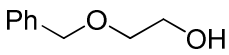
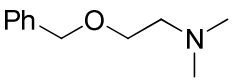
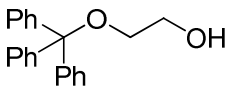
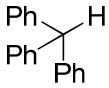
Scheme 5.16 – Preparation of 2-(trityloxy)ethanol **136**

The three substrates were then subjected to the reaction conditions as used in section **5.3** (Scheme 5.17 and Table 5.1).



Scheme 5.17 – Substrate screen

Table 5.1 – Substrate screen results[a]

Entry	Substrate	Product	Conversion[b]
1	 **134**	 **138**	96 (77)
2	 **135**	 **139**	100 (29)
3	 **136**	 **140**	76

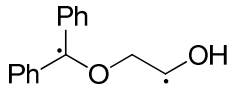
[a] Reactions were carried out on a 1 mmol scale in toluene. The toluene contained 1.5 M dimethylamine, prepared by liquefying dimethylamine gas. [b] Conversions were calculated using ^{1}H NMR and reflect the conversion of each substrate. The numbers in parenthesis are isolated yield.

Table 5.1 shows that the rearranged type product is not observed with any of the three substrates. Entries 1 and 2 show that the expected "addition" products are formed as the sole products in high conversions. However, entry 3 shows that when 3 phenyl groups are present, the product is neither the addition product nor the unexpected product. The presence of triphenylmethane **140** can be attributed to a similar mechanism as proposed above in Scheme 5.15. It is assumed that the oxidation and imine formation occur as expected, but once the molecule splits into two fragments, the recombination does not take place. The suggested reason for this lack of recombination is that the trityl anion is too bulky and is simply protonated instead. When 2-(trityloxy)ethanol **136** was prepared, a large amount of the by-product seen was triphenylmethane **140**, so it seemed obvious that the trityl anion is relatively stable and not very reactive.

5.5 Mechanistic Studies

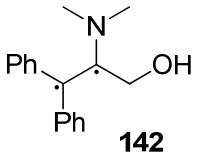
The rearranged product is only produced when 2 phenyl groups are present on the ether. In order to prove the theory of dissociation and recombination, a

^{13}C labelling study was carried out. It was proposed that by synthesising the doubly ^{13}C labelled 2-benzhydryloxyethanol **141** (Figure 5.8), that when the molecule separates and recombines, the 2 carbon labels would end up adjacent to one another (Figure 5.9).



141

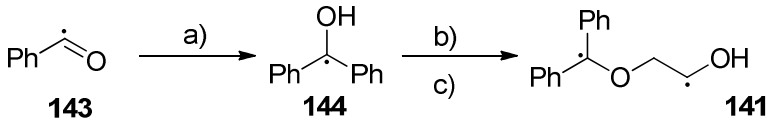
Figure 5.8 – Doubly ^{13}C labelled 2-benzhydryloxyethanol **141**



142

Figure 5.9 – Doubly ^{13}C labelled rearranged product **142**

The ^{13}C doubly labelled 2-benzhydryloxyethanol **141** was prepared in several steps in order in install the two labelled centres (Scheme 5.18).

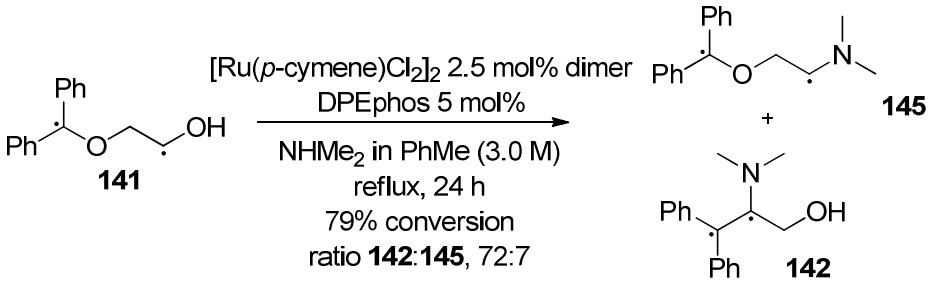


143 **144** **141**

a) PhMgBr (1.5 equiv.), Et_2O, 0 °C - r.t., o/n
b) NaH (1.05 equiv.), ethyl bromoacetate-1-^{13}C (1 equiv.), Et_2O, 0 °C - r.t., o/n
c) $LiAlH_4$ (1.7 equiv.), Et_2O, 0 °C - r.t., 2 h

Scheme 5.18 – Synthesis of 2-benzhydryloxyethanol **141**

This ^{13}C labelled compound **141** was then subjected to the above reaction conditions (Scheme 5.19).



Scheme 5.19 – Reaction of ^{13}C doubly labelled 2-benzhydryloxyethanol **141**

The above results show a similar conversion to the non-labelled experiment (see Scheme 5.9). What is evident is that in the rearranged compound, the 2 ^{13}C labelled centres are now neighbouring one another. The following two diagrams show the non-labelled ^{1}H NMR spectrum and the labelled ^{1}H NMR spectrum (Figures 5.10 and 5.11). The region which involves the CH (H_a and H_b) and CH_2 (H_c and H_d) protons has been expanded to show the clear difference when the ^{13}C centres are present.

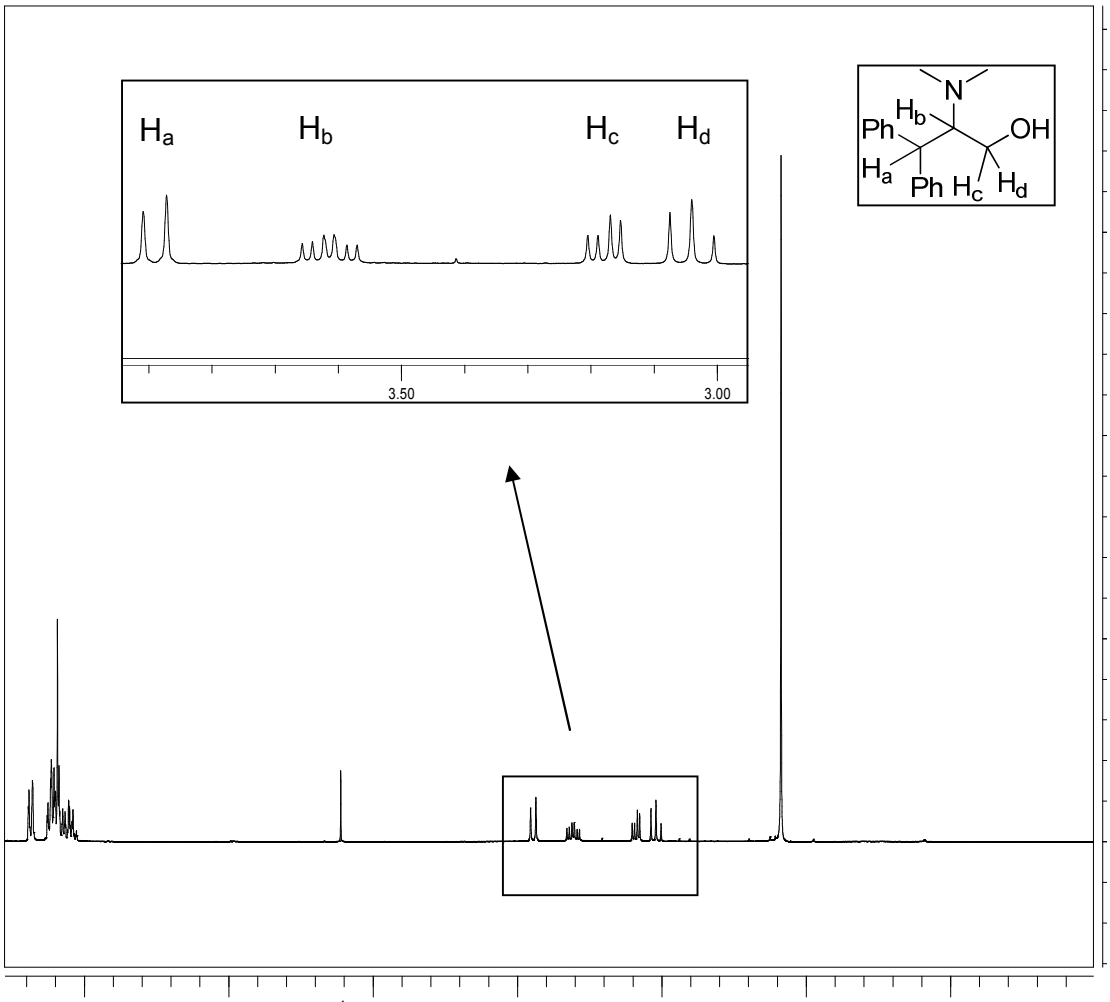


Figure 5.10 - ^{1}H Spectrum of the non-labelled compound **131**

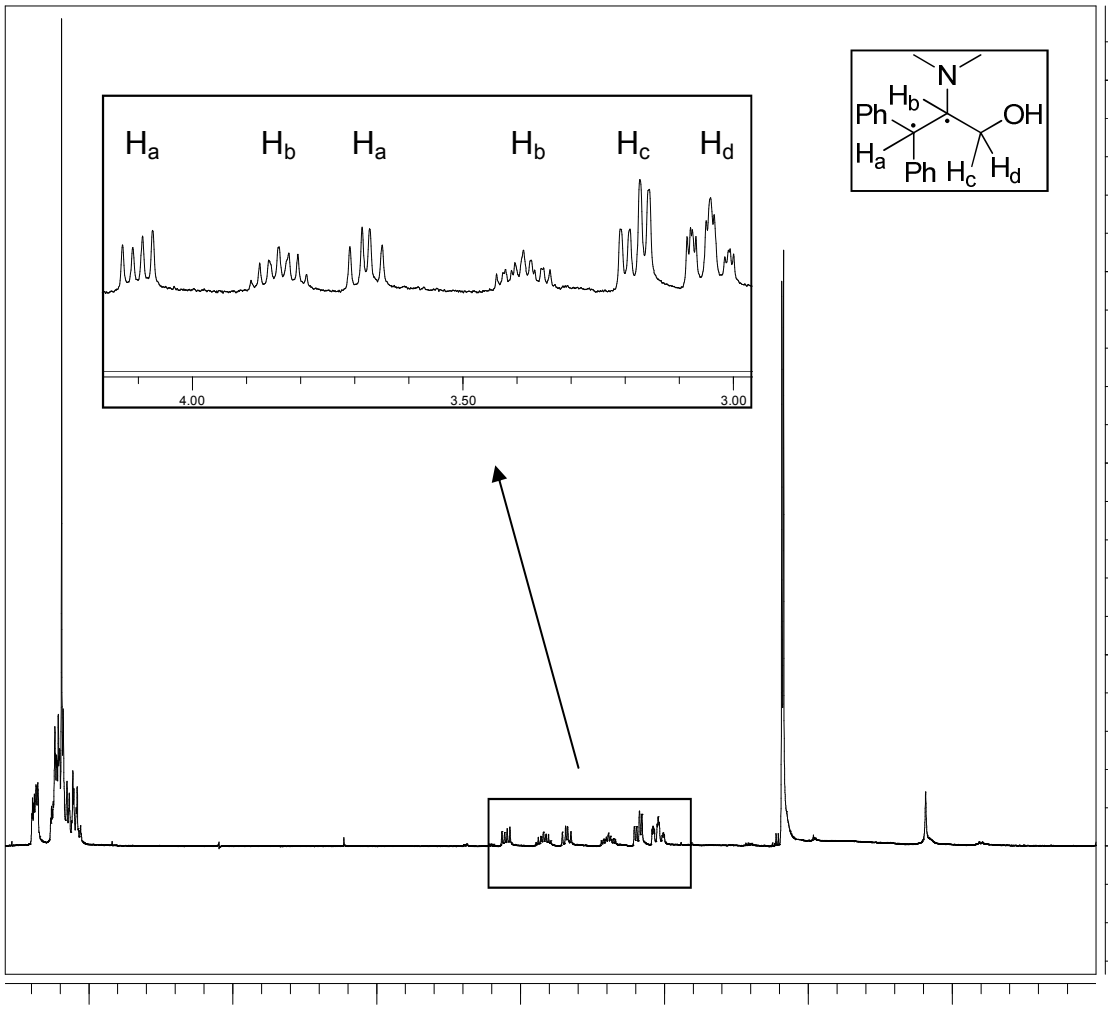


Figure 5.11 - ^{1}H Spectrum of the labelled compound **142**

Figure 5.10 shows that there are four distinct signals for the four (main) protons on the non-labelled compound **131**. The CH_2 group is diastereotopic, hence the separate splitting of each proton (H_c and H_d). In the labelled compound **142**, Figure 5.11 shows that both H_a and H_b are split two further times compared with the original (non-labelled) spectrum. This is further illustrated by Figures 5.12 and 5.13, which show the coupling constants of H_a for both the non-labelled **131** and labelled **142** compounds.

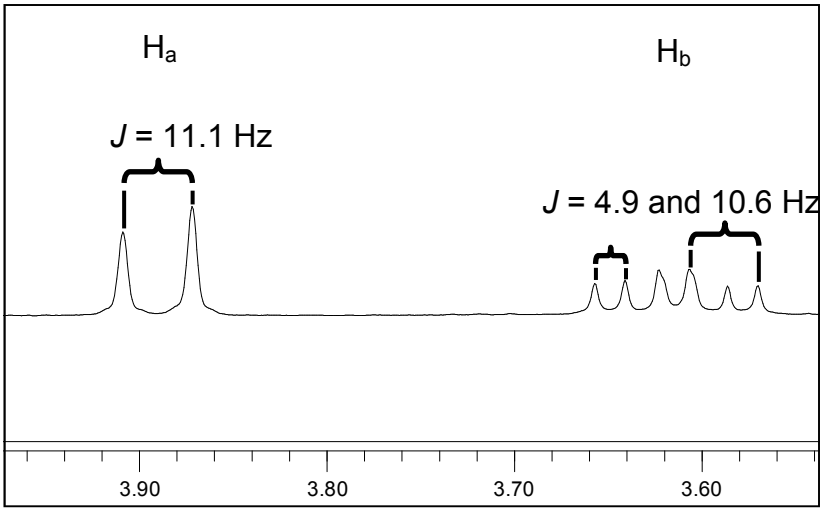


Figure 5.12 - ^{1}H coupling constants for H_a for the non-labelled compound **131**

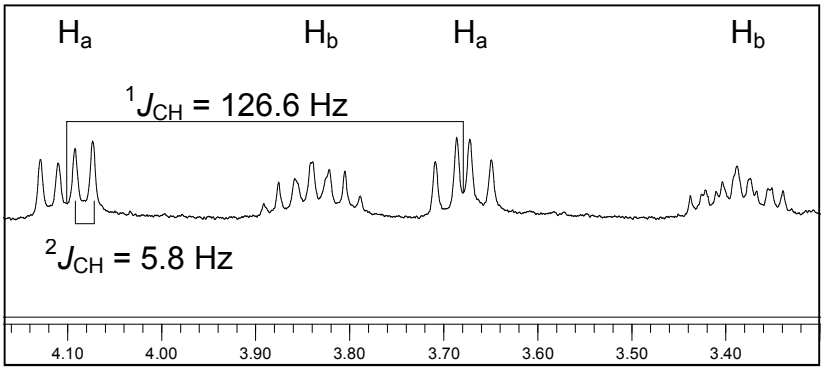


Figure 5.13 - ^{1}H coupling constants for H_a for the labelled compound **142**

The large splitting is caused by being directly attached to a ^{13}C centre (coupling constants, $^{1}J_{CH}$ = 126.6 and 135.0 Hz for H_a and H_b respectively). The smallest splitting is caused by being on a carbon adjacent to a ^{13}C centre (coupling constant illustrated above, $^{2}J_{CH}$ = 5.8 Hz). The third splitting is the same as the non-labelled compound **131** would be, *i.e.* $^{3}J_{HH}$ = 11.1 Hz, as shown in Figure 5.12. The same three splittings apply to H_b.

The dimethylamino group in the labelled compound **142** is also split by the ^{13}C attached to the nitrogen. The signal in the non-labelled compound is a singlet. This fact, combined with the ones explained above confirms that the two ^{13}C labelled centres are adjacent to one another in the labelled compound **142**.

The two protons on the CH_2OH group are inequivalent. In the non-labelled compound **131**, the two protons (H_c and H_d) give two different signals, a doublet of doublets and an apparent triplet. In the labelled compound **142**, the doublet of doublets remains the same (including the coupling constants, see ***6.5.2*** and ***6.5.7***), but the apparent triplet is split by the ^{13}C (compare Figures 5.10 and 5.11). The reason for this is assumed to be due to the conformation of the molecule. As the molecule contains both a nitrogen and an oxygen, it is assumed that the molecule will reside in a position where it can maximise the distance between the two elements. The conformation obviously leads to one proton being affected by the ^{13}C centres, and the other is unaffected by the labelling. This conformation could be explained by intramolecular hydrogen bonding (Figure 5.14), although this has not been confirmed.

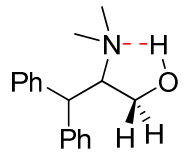


Figure 5.14 - Possible hydrogen bonding to lock the conformation of the structure

Further evidence that the two ^{13}C labels are now adjacent to one another is the splitting in the ^{13}C NMR spectrum. The two carbons which exhibit the ^{13}C label are split into doublets in the ^{13}C NMR spectrum. If these two labels were not adjacent to one another, then the spectrum would not show any splitting. Figures 5.15 and 5.16 show the two doublets present in the ^{13}C spectrum.

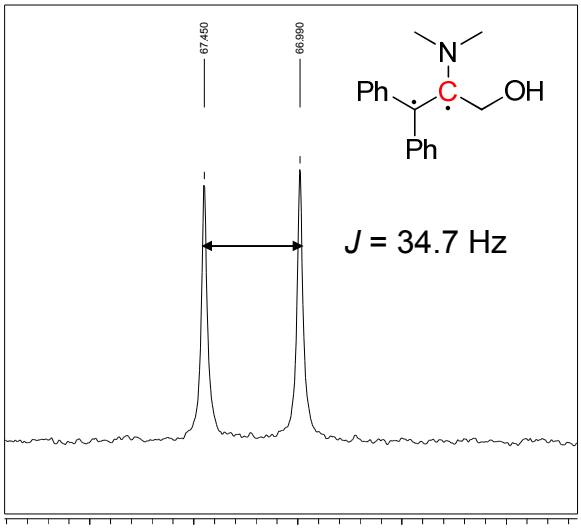


Figure 5.15 – ^{13}C splitting observed in the ^{13}C NMR for one labelled carbon

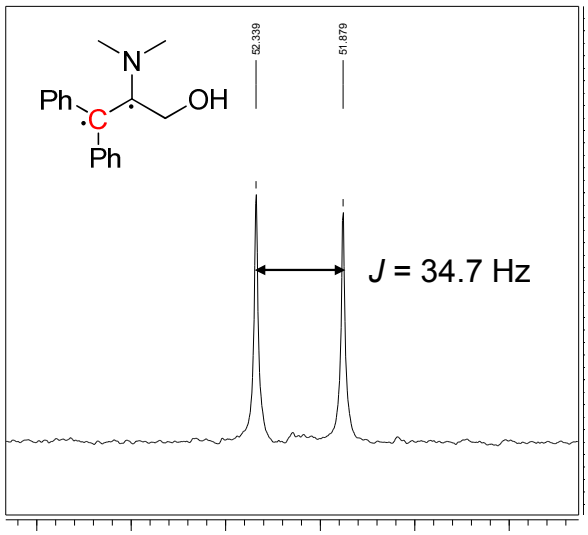


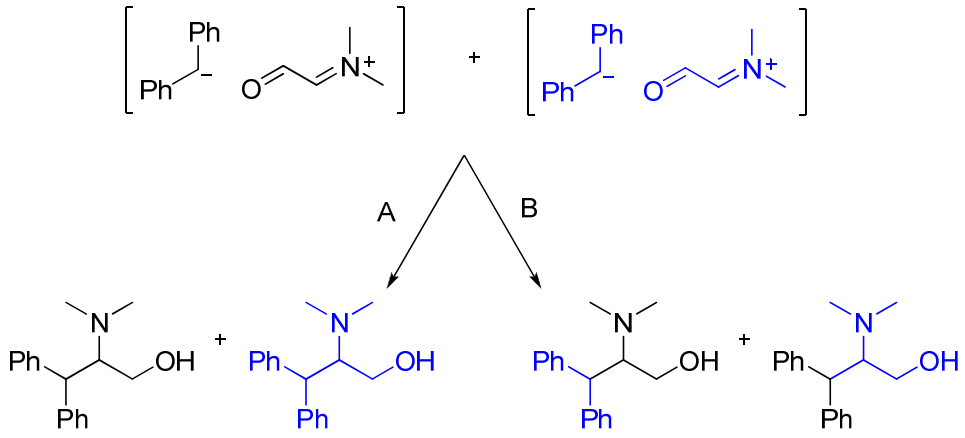
Figure 5.16 – ^{13}C splitting observed in the ^{13}C NMR for the second labelled carbon

The *J* values of both splittings is 34.7 Hz and this is indicative of two ^{13}C centres bonded to one another. From this evidence and the splitting observed in the ^{1}H NMR the theory of dissociation and recombination is confirmed.

5.6 Crossover Studies

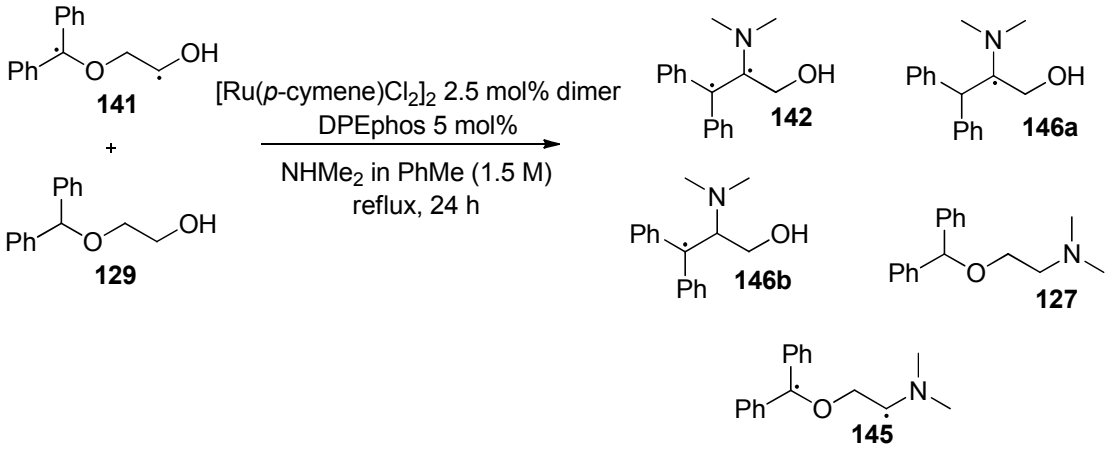
A further thought regarding the mechanism was whether or not there was any crossover behaviour occurring. In terms of this reaction, crossover behaviour (Scheme 5.20) denotes whether or not the same two fragments which split

from one another then recombine with one another (pathway A), or whether they recombine with a different fragment from another ion (or radical) pair (pathway B).



Scheme 5.20 – Diagrammatic explanation of crossover behaviour

By running a reaction which contains both non-labelled 2-benzhydryloxyethanol **129** and labelled 2-benzhydryloxyethanol **141** (Scheme 5.21), it should be evident whether or not crossover behaviour can be observed. If any singly labelled rearranged product is present, then crossover behaviour is taking place.



Scheme 5.21 – Reaction to determine crossover behaviour

After a period of analysis, the ^{1}H NMR spectrum of the crude reaction mixture was shown to contain the presence of both doubly labelled **145** and non-labelled diphenhydramine **127**, doubly labelled rearranged product **142** and

an amount of singly labelled rearranged product **146a** and **146b**. The overall conversion was calculated as 89%, with 5% of this being diphenhydramine (combined labelled and non labelled products), and 84% being rearranged product (combined singly labelled and doubly labelled products). However, in order to calculate the amount of crossover, the ^{13}C NMR spectrum was used because the ^{1}H NMR spectrum was too complicated. The areas of interest in the ^{13}C spectrum were the signals of the carbons which were labelled. After comparison of the ^{13}C spectra of both the non labelled **131** and doubly labelled **142** compounds, the areas of interest are around 52 ppm and 67 ppm. These regions in the ^{13}C spectrum of the crossover reaction mixture show an interesting pattern (Figures 5.17 and 5.18).

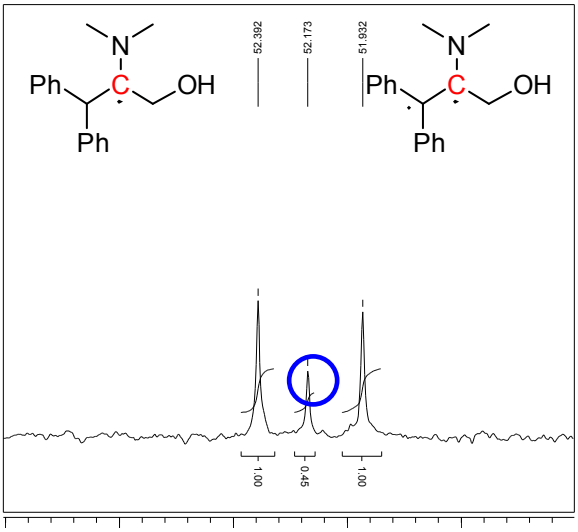


Figure 5.17 – The region of 52 ppm in the ^{13}C spectrum

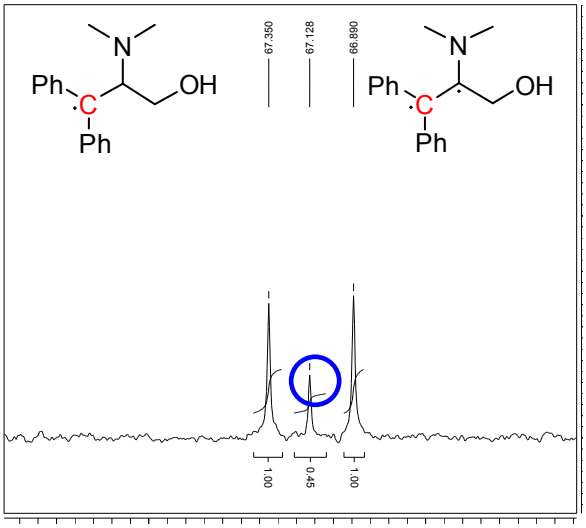


Figure 5.18 – The region of 67 ppm in ^{13}C spectrum

The pattern displayed in Figures 5.17 and 5.18 above appears to be an inverted triplet. However, the signals correspond to two different compounds. The blue circled signals correspond to the singly labelled products (**146a** and **146b**), and the two outer signals are the doublet of the doubly labelled product **142**. In order to calculate the amount of crossover, these signals were integrated. Each doublet integrates to 2.00 (1.00 + 1.00 for each signal), and each singlet integrates to 0.45. The following calculation demonstrates that there is 18% crossover occurring in the reaction.

(0.45 / (2.00 + 0.45)) * 100 = 18%

5.7 Conclusions

A successful synthesis of diphenhydramine **127** has been carried out, although it was in a rather disappointing yield. However, a novel compound, 2-(dimethylamino)-3,3-diphenylpropan-1-ol **131** has been synthesised and characterised. The mechanism of formation of this compound has been investigated and confirmed, and has been shown to involve splitting of the molecule after alcohol oxidation and imine formation. The recombination then gives the rearranged product **131**. The mechanism was realised by synthesising the doubly labelled ^{13}C starting material alcohol **141**. The

reaction was attempted with three other substrates, and none of these substrates exhibited the same behaviour. Therefore it can be concluded that it is only the diphenyl benzyl ether moiety which produces the observed results.[3] It would be an interesting extension to the work to synthesise similar substrates and see if the reaction occurs in the same way.

CHAPTER 6 - EXPERIMENTAL

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6.1 General Experimental Details

Reactions which required the use of anhydrous, inert atmosphere techniques were carried out under an atmosphere of nitrogen or argon. All reactions were carried out in oven dried, nitrogen purged glassware. In most cases, solvents were obtained by passing through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. All other solvents were purchased anhydrous from Sigma Aldrich.

TLC using polythene, aluminium or glass backed plates precoated with Macherey-Nagel Sil G/UV_{254nm} neutral silica were used to monitor reactions where appropriate. Visualisation of these plates was by 254 nm UV light and/or $KMnO_4$, Ninhydrin or Phosphomolybdic Acid (PMA) dip followed by gentle warming. Organic layers were routinely dried with anhydrous $MgSO_4$ or Na_2SO_4 and evaporated using a Büchi rotary evaporator. Where necessary, further drying was facilitated by high vacuum. Flash column chromatography was carried out using Davisil LC 60 Å silica gel (35-70 micron) purchased from Fluorochem. Purification by Kügelrohr distillation refers to the use of Kügelrohr distillation apparatus under high vacuum, at a pressure between 0.3 – 0.1 mmHg, and a temperature between 120 – 200 °C. IR spectra were recorded on a Perkin-Elmer 1600 FT IR spectrometer with only selected absorbances quoted as v in cm^{-1}.

NMR spectra were run in $CDCl_3$ (unless otherwise stated) on either a Bruker Avance 250 (250 MHz), Bruker Avance 300 (300 MHz), Bruker Avance 400 (400 MHz) or Bruker Avance 500 (500 MHz) instrument and recorded at the following frequencies: proton (^1H – 250/300/400/500 MHz), carbon (^{13}C – 62.9/75.4/100.6/125.8 MHz). The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; sex, sextet, app. sex., apparent sextet, app. oct., apparent octet, dd, doublet of doublets, m, multiplet and br., broad. Structural assignments of both protons and carbons were achieved with

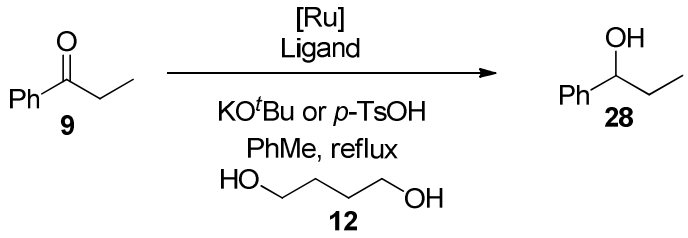
comparisons from analogous literature compounds; references are given in most cases. Protons that have chemical but not magnetic equivalence (AA'BB' systems) as in the case of 1,4-substituted aromatics are treated either as multiplets or as doublets, depending on their appearance in the spectra.

A micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) was used; this was coupled to an Agilent 1200 LC system (Agilent Technologies, Waldbronn, Germany). The LC system was used as an autosampler only. 10 µL of sample was injected into a 30:70 flow of water:acetonitrile at 0.6 mL/min to the mass spectrometer. For each acquisition 10 µL of a calibrant of 5 mM sodium formate was injected after the sample. The observed mass and isotope pattern perfectly matched the corresponding theoretical values as calculated from the expected elemental formula. High Pressure Liquid Chromatography (HPLC) was carried out using a PerkinElmer Series 200 and a Chiracel OD ® column obtained from Fisher Scientific supplies; the solvent and flow rate used are detailed in the relevant experiment. Gas Chromatography (GC) was carried out using an Agilent 6890N and this was coupled to an Agilent 5975B mass spectrometer (MS). The autosampler used was a Gerstel MPS2 with helium as the carrier gas and a run time of around 25 minutes. The compounds were identified by both their retention time and corresponding molecular ion.

Unless preparative details are provided, all reagents were commercially available and purchased from either Acros Organics, Sigma Aldrich, Alfa Aesar, Avocado, Fluka, Lancaster, Maybridge or Strem chemical companies.

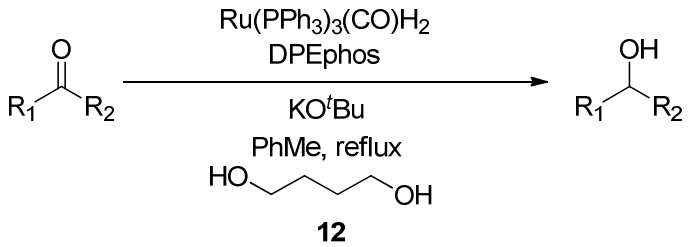
6.2 Experimental Procedures for Chapter 2

6.2.1 Initial Catalyst Screen



To oven dried and nitrogen purged Radley's carousel tubes containing the required ruthenium catalyst (0.005 mmol, 0.005 equiv. for Ru[(*p*-cymene)Cl_2]$_2$ and 0.025 mmol, 0.025 equiv. for Ru(PPh_3)$_3$(CO)H_2), the required ligand (0.01 mmol, 0.01 equiv. when used with Ru[(*p*-cymene)Cl_2]$_2$ and 0.025 mmol, 0.025 equiv. when used with Ru(PPh_3)$_3$(CO)H_2), the required additive (KO^{t}Bu - 0.02 mmol, 0.02 equiv. for all reactions except one at 0.05 mmol, 0.05 equiv. and *p*-TsOH – 0.02 mmol, 0.02 equiv.), was added propiophenone **9** (0.1342 g, 1 mmol, ρ = 1.009 gmL^{-1}, 0.1330 mL, 1 equiv.) and 1,4-butanediol **12** (0.092 g, 1 mmol, = 1.017 gmL^{-1}, 0.089 mL, 1 equiv.) followed by toluene (1 mL). The reactions were then heated to reflux for 14 hours, samples were taken and filtered through Celite and silica, washed through with DCM and concentrated *in vacuo*. The reactions were heated at reflux for a further 10 hours before being filtered through Celite and silica, washed through with DCM and concentrated *in vacuo*. Conversions were calculated from peak integral ratios characteristic of propiophenone **9** and 1-phenyl-1-propanol **28** in the crude ^{1}H NMR.

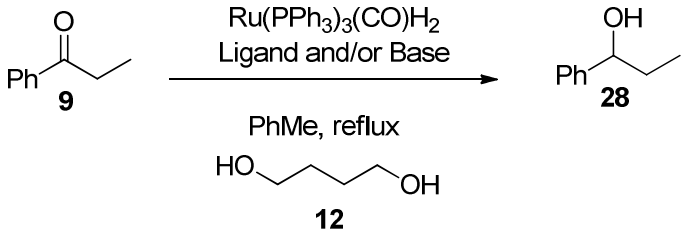
6.2.2 Substrate Screen using Optimised Conditions



To oven dried and nitrogen purged Radley's carousel tubes containing Ru(PPh_3)$_3$(CO)H_2 (22.9 mg, 0.025 mmol, 0.025 equiv.), DPEphos (13.5 mg,

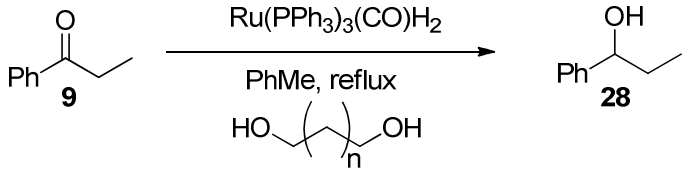
0.025 mmol, 0.025 equiv.), KO^{t}Bu (5.6 mg, 0.05 mmol, 0.05 equiv.), was added the required substrate (1 mmol, 1 equiv.) and 1,4-butanediol **12** (0.092 g, 1 mmol, ρ = 1.017 gmL^{-1}, 0.089 mL, 1 equiv.) followed by toluene (1 mL). The reactions were heated to reflux for 24 hours (except in the case of α-tetralone **30**, this reaction was heated for 50 hours). The reactions were then filtered through Celite and silica, washed through with DCM and concentrated *in vacuo*. Conversions were calculated from peak integral ratios characteristic of the required substrates and their corresponding alcohols (except for allylbenzene **36**, where its isomerisation product and reduced product were used) in the crude ^{1}H NMR.

6.2.3 Variation of conditions



To oven dried and nitrogen purged Radley's carousel tubes containing $Ru(PPh_3)_3(CO)H_2$ - when required (22.9 mg, 0.025 mmol, 0.025 equiv.), DPEphos – when required (13.5 mg, 0.025 mmol, 0.025 equiv.), KO^{t}Bu – when required (5.6 mg, 0.05 mmol, 0.05 equiv.), were added propiophenone **9** (0.1342 g, 1 mmol, ρ = 1.009 gmL^{-1}, 0.1330 mL, 1 equiv.) and the required amount of 1,4-butanediol **12** (either 0.092 g, 1 mmol, ρ = 1.017 gmL^{-1}, 0.089 mL, 1 equiv., 0.045 g, 0.5 mmol, ρ = 1.017 gmL^{-1}, 0.044 mL, 0.054 g, 0.5 equiv or 0.6 mmol, ρ = 1.017 gmL^{-1}, 0.053 mL, 0.6 equiv.) followed by toluene (1 mL). (See Table 2.3 for specific reaction conditions.) The reactions were heated to reflux for 24 hours and were then filtered through Celite and silica, washed through with DCM and concentrated *in vacuo*. Conversions were calculated from peak integral ratios characteristic of propiophenone **9** and 1-phenyl-1-propanol **28** in the crude ^{1}H NMR.

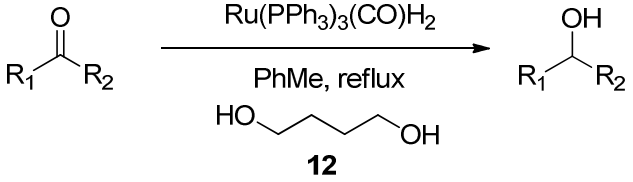
6.2.4 Variation of hydrogen donor



where n = 1, 2, 3, 4

To oven dried and nitrogen purged Radley's carousel tubes containing $Ru(PPh_3)_3(CO)H_2$ (22.9 mg, 0.025 mmol, 0.025 equiv.), was added propiophenone **9** (0.1342 g, 1 mmol, ρ = 1.009 gmL^{-1}, 0.1330 mL, 1 equiv.) and the required hydrogen donor (1 mmol, 1 equiv.) followed by toluene (1 mL). The reactions were heated to reflux for 24 hours and were then filtered through Celite and silica, washed through with DCM and concentrated *in vacuo*. Conversions were calculated from peak integral ratios characteristic of propiophenone **9** and 1-phenyl-1-propanol **28** in the crude ^1H NMR.

6.2.5 Substrate screen without ligand and base

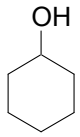


To oven dried and nitrogen purged Radley's carousel tubes containing $Ru(PPh_3)_3(CO)H_2$ (22.9 mg, 0.025 mmol, 0.025 equiv.), was added the required substrate (1 mmol, 1 equiv.) and 1,4-butanediol **12** (0.092 g, 1 mmol, ρ = 1.017 gmL^{-1}, 0.089 mL, 1 equiv.) followed by toluene (1 mL). The reactions were heated to reflux for either 24 or 48 hours (depending on the substrate, see Table X) and were then filtered through Celite and silica, washed through with DCM and concentrated *in vacuo*. Conversions were calculated from peak integral ratios characteristic of the substrates and their corresponding alcohols in the crude ^1H NMR.

*6.2.5.1 Preparation of cyclohexanol **147***

Following procedure ***6.2.5***, using cyclohexanone **32** (0.098 g, 1 mmol, ρ = 0.947 gmL^{-1}, 0.1036 mL, 1 equiv.) the title compound was obtained and

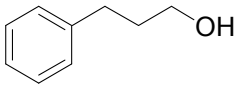
purified by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (1:1), R_f = 0.38 to give a colourless liquid (0.605 g, 60%).
This reaction was also run on a 5 mmol scale, following procedure ***6.2.5*** (scaled up accordingly). Once the crude product had been obtained, it was dissolved in DCM (5 mL) and 2 M NaOH solution (2 mL) was added. The reaction was stirred vigorously for 16 hours. The organic layer was then separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was isolated as a pale brown oil (0.1057 g, 21%).



^{1}H NMR (300 MHz, $CDCl_3$): δ 3.56 – 3.65 (m, 1H, CH), 1.48 – 1.92 (m, 6H, CH), 1.09 – 1.36 (m, 5H, CH/OH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 70.3, 35.5, 25.4, 24.1. ν_{max} /cm^{-1} (neat): 3311, 2929, 2853, 1450, 1066.
These data were consistent with those reported in the literature.[84]

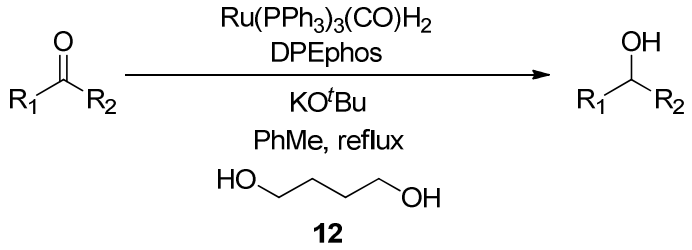
6.2.5.2 Preparation of 3-phenyl-1-propanol ***73***

Following procedure ***6.2.5***, using hydrocinnamaldehyde **35** (0.1342 g, 1 mmol, ρ = 1.019 gmL^{-1}, 0.1317 mL, 1 equiv.) the title compound was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (3:2), R_f = 0.24 to give a pale yellow liquid (0.1213 g, 87%).



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 – 7.34 (m, 5H, Ph), 3.68 (t, 2H, *J* = 6.5 Hz, CH_2), 2.72 (t, 2H, *J* = 7.7 Hz, CH_2), 1.91 (m, 2H, CH_2), 1.56 (s, 1H, OH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 141.8, 128.38, 128.36, 125.8, 62.2, 34.2, 32.1. ν_{max} /cm^{-1} (neat): 3312, 3061, 2934, 2861, 1454.
These data were consistent with those reported in the literature.[85]

6.2.6 Repeat of substrate screen, with ligand and base

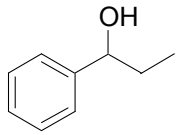


12

To oven dried and nitrogen purged Radley's carousel tubes containing $Ru(PPh_3)_3(CO)H_2$ (22.9 mg, 0.025 mmol, 0.025 equiv.), DPEphos (13.5 mg, 0.025 mmol, 0.025 equiv.), KO^{t}Bu (5.6 mg, 0.05 mmol, 0.05 equiv.), was added the required substrate (1 mmol, 1 equiv.) and 1,4-butanediol **12** (either 0.092 g, 1 mmol, ρ = 1.017 gmL^{-1}, 0.089 mL, 1 equiv.) followed by toluene (1 mL). The reactions were heated to reflux for 24 or 48 hours (see below for specific preparations) and were then filtered through Celite and silica, washed through with DCM and concentrated *in vacuo*. Conversions were calculated from peak integral ratios characteristic of the appropriate carbonyls and corresponding alcohols in the crude ^{1}H NMR.

*6.2.7.1 Preparation of 1-phenyl-1-propanol **28***

Following procedure ***6.2.6***, using propiophenone **9** (0.1342 g, 1 mmol, ρ = 1.009 gmL^{-1}, 0.1330 mL, 1 equiv.) the title compound was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (4:1), R_f = 0.17 to give a pale brown liquid (0.1196 g, 88%).

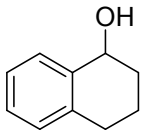


^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 – 7.33 (m, 5H, Ph), 4.59 (t, 1H, *J* = 6.5 Hz, CH), 1.76 (m, 2H, CH_2), 0.91 (t, 3H, *J* = 7.5 Hz, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 143.0, 128.5, 127.3, 75.3, 32.0, 9.6. ν_{max} /cm^{-1} (neat): 3341, 2964, 2934, 2877, 1592, 1491, 1408.

These data were consistent with those reported in the literature.[86]

*6.2.6.2 Preparation of α-tetralol **148***

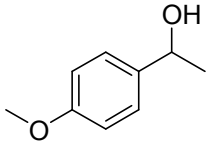
Following procedure ***6.2.6***, using α-tetralone **30** (0.1462 g, 1 mmol, ρ = 1.099 gmL^{-1}, 0.1330 mL, 1 equiv.) the title compound was obtained in 91% conversion after 50 hours. The product was not isolated; conversion was calculated from peak integral ratios characteristic of α-tetralol **148** in the crude ^1H NMR spectrum.



^1H NMR (250 MHz, $CDCl_3$): δ 7.13 – 7.39 (m, 4H, Ar), 4.82 (m, 1H, CH), 2.78 – 2.94 (m, 2H, CH_2), 1.76 - 2.08 (m, 4H, CH_2).
These data were consistent with those reported in the literature.[87]

*6.2.6.3 Preparation of 1-(4-methoxyphenyl)ethanol **149***

Following procedure ***6.2.6***, using *p*-methoxyacetophenone **31** (0.1502 g, 1 mmol, 1 equiv.) the title compound was obtained in 87% conversion after 24 hours. The product was not isolated; conversion was calculated from peak integral ratios characteristic of 1-(4-methoxyphenyl)ethanol **149** in the crude ^1H NMR spectrum.

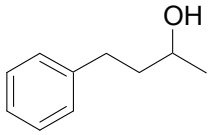


^1H NMR (250 MHz, $CDCl_3$): δ 7.08 (d, 2H, *J* = 7.1 Hz, Ar), 6.78 (d, 2H, *J* = 8.8 Hz, Ph), 4.73 (q, 1H, *J* = 6.4 Hz, CH), 3.69 (s, 3H, CH_3), 1.19 (d, 3H, *J* = 6.4 Hz, CH_3).
These data were consistent with those reported in the literature.[88]

*6.2.6.4 Preparation of 4-phenyl-2-butanol **150***

Following procedure ***6.2.6***, using 4-phenyl-2-butanone **33** (0.1482 g, 1 mmol, ρ = 0.989 gmL^{-1}, 0.1499 mL, 1 equiv.) the title compound was obtained and

purified by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (3:2), R_f = 0.24 to give a pale yellow liquid (0.1213 g, 92%).

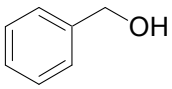


^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 – 7.32 (m, 5H, Ph), 3.84 (app. sex., 1H, *J* = 6.2 Hz, CH), 2.63 – 2.82 (m, 2H, CH_2), 1.74 – 1.82 (m, 2H, CH_2), 1.43 (s, 1H, OH), 1.23 (d, 3H, *J* = 6.3 Hz, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 142.0, 128.4, 125.8, 67.5, 40.8, 32.1, 23.6. ν_{max} /cm^{-1} (neat): 3322, 3027, 2964, 2926, 2860, 1454.

These data were consistent with those reported in the literature.[89]

*6.2.6.5 Preparation of benzyl alcohol **4***

Following procedure ***6.2.6***, using benzaldehyde **34** (0.1061 g, 1 mmol, ρ = 1.044 gmL^{-1}, 0.1016 mL, 1 equiv.) the title compound was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (70:30), R_f = 0.32 to give a pale yellow liquid (0.0878 g, 81%).

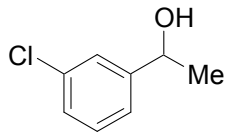


^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 – 7.31 (m, 5H, Ph), 4.59 (s, 2H, CH_2), 1.82 (br. s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.8, 128.5, 127.8, 127.0, 65.8.

These data were consistent with those reported in the literature.[90]

*6.2.6.6 Preparation of 1-(3-chlorophenyl)ethanol **151***

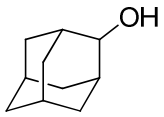
Following procedure ***6.2.6***, using 3-chloroacetophenone **44** (0.1546g, 1 mmol, ρ = 1.191 gmL^{-1}, 0.1230 mL, 1 equiv.) the title compound was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40-60 °C)/diethyl ether (1:1), R_f = 0.32 to give a pale yellow liquid (0.1240 g, 79%).



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 – 7.17 (m, 4H, Ar), 4.77 (q, 1H, J = 3.3, 9.9 Hz, CH), 1.90 (br. s, 1H, OH), 1.38 (d, 3H, *J* = 6.5 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8, 134.3, 129.8, 127.5, 125.6, 123.5, 69.8, 25.2.
These data were consistent with those reported in the literature.[91]

*6.2.6.8 Preparation of 2-adamantanol **152***

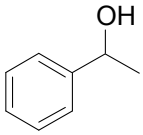
Following procedure ***6.2.6***, using 2-adamantanone **45** (0.1502 g, 1 mmol, 1 equiv.) the title compound was obtained in 100% conversion after 48 hours. The product was not isolated; conversion was calculated from peak integral ratios characteristic of 2-adamantanol **152** in the crude ^{1}H NMR spectrum.



^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88 (s, 1H, CH), 2.07 (m, 2H, CH), 1.64 – 1.94 (m, 11H, CH/OH), 1.53 (m, 2H, CH).
These data were consistent with those reported in the literature.[92]

*6.2.6.9 Preparation of sec-phenethyl alcohol **25***

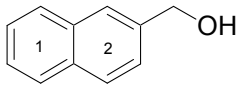
Following procedure ***6.2.6***, using acetophenone **1** (0.1202 g, 1 mmol, ρ = 1.030 gmL^{-1}, 0.1200 mL, 1 equiv.) the title compound was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (7:3), R_f = 0.21 to give a pale yellow liquid (0.1027 g, 84%).



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14 – 7.26 (m, 5H, Ph), 4.79 (q, 1H, *J* = 6.5 Hz, CH), 1.78 (br. s, 1H, OH), 1.40 (d, 3H, *J* = 6.5 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.8, 128.5, 128.2, 127.4, 125.3, 70.4, 25.1.
These data were consistent with those reported in the literature.[93]

*6.2.6.10 Preparation of 2-naphthalenemethanol **153***

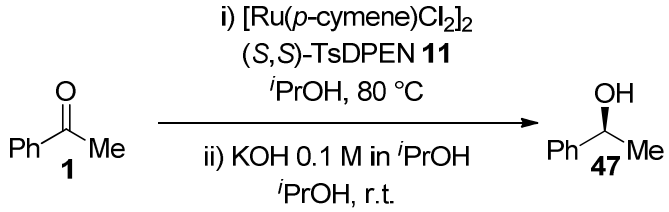
Following procedure ***6.2.6***, using 2-naphthaldehyde **46** (0.1562 g, 1 mmol, 1 equiv.) the title compound was obtained and purified by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (1:1), R_f = 0.41 to give a white solid (0.1293 g, 82%).



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 – 7.87 (m, 4H, Ar_1), 7.47 – 7.52 (m, 3H, Ar_2), 4.85 (d, 2H, *J* = 4.6 Hz, CH_2), 1.85 (br. s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 133.3, 132.9, 128.3, 127.9, 127.7, 126.2, 125.9, 125.4, 125.1, 65.5.

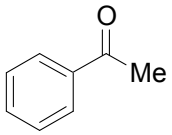
These data were consistent with those reported in the literature.[94]

6.2.7 Noyori's conditions for asymmetric reduction

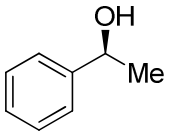


To an oven dried and argon purged 250 mL round bottomed flask containing [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg, 0.01 mmol, 0.001 equiv.) and (*S*,*S*)-TsDPEN **11** (14.7 mg, 0.04 mmol, 0.004 equiv.) was added *iso*-propanol (5 mL). The reaction was heated to 80 °C for 1 hour under an atmosphere of nitrogen. A pale orange solution was obtained. Acetophenone **1** (1.202 g, 10 mmol, ρ = 1.030 gmL^{-1}, 1.1700 mL, 1 equiv.) and *iso*-propanol (94 mL) were degassed separately under argon and then added to the pale orange solution (once it had been allowed to cool to room temperature). A solution of 0.1 M KOH in *iso*-propanol was then prepared (0.056 g KOH in 10 mL *iso*-propanol) and 2 mL of this solution was added to the pale orange solution, upon which a pale pink solution was obtained which turned orange once stirring was restored. The reaction was then stirred at room temperature for 14 hours. After this time, the reaction was quenched with 2M HCl (1 mL) and stirred for a further 30 minutes at room temperature. The reaction mixture was then concentrated

in vacuo, and ethyl acetate was added. The ethyl acetate layer was then washed with saturated brine solution 3 times, dried over $MgSO_4$, filtered and reduced *in vacuo* giving a pale yellow liquid (ee = 98%, Chiracel OD column 90:10 hexane:*iso*-propanol solvent, 0.5 mL/min flow, retention times = 9.7 min (S), 12.3 min (*R*)). Conversion was calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of acetophenone **1** and (*S*)-*sec*-phenethyl alcohol **47**.

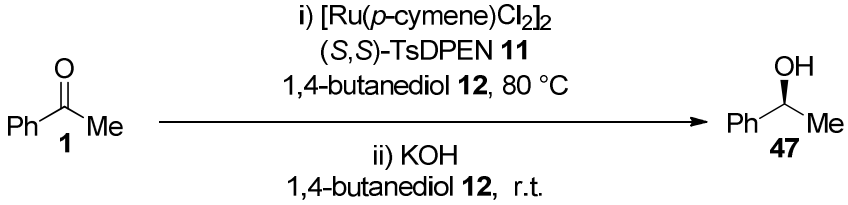


^{1}H NMR of acetophenone **1** corresponds to the data obtained from the supplier.



^{1}H NMR (250 MHz, $CDCl_3$): δ 7.19 – 7.50 (m, 5H, Ph), 4.83 (q, 1H, *J* = 6.5 Hz, CH), 2.03 (br. s, 1H, OH), 1.43 (d, 3H, *J* = 6.5 Hz, CH_3).
These data were consistent with those reported in the literature.[95]

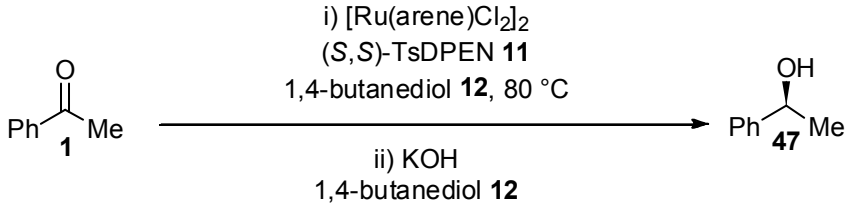
6.2.8 Noyori's conditions for asymmetric reduction, using 1,4-butanediol 12



To an oven dried and argon purged 10 mL round bottomed flask containing $[Ru(p\text{-cymene})Cl_2]_2$ (6.1 mg, 0.01 mmol, 0.001 equiv.) and (*S*,*S*)-TsDPEN **11** (14.7 mg, 0.04 mmol, 0.004 equiv.) was added 1,4-butanediol **12** (0.4506 g, 5 mmol, ρ = 1.017 gmL^{-1}, 0.443 mL, 0.5 equiv.). The reaction mixture was then heated to 80 °C for 1 hour under an atmosphere of nitrogen. Meanwhile, KOH (56.0 mg, 1 mmol, 0.1 equiv.) was dissolved in 1,4-butanediol **12** (0.4506 g, 5 mmol, ρ = 1.017 gmL^{-1}, 0.443 mL, 0.5 equiv.) by stirring at room

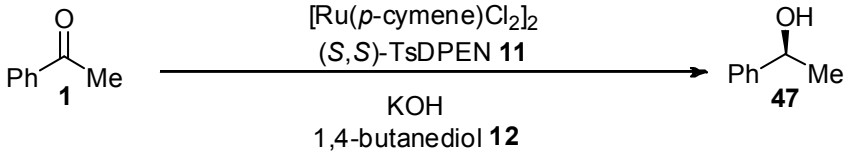
temperature. Once the reaction mixture had cooled to room temperature, the base mixture was added, followed by acetophenone **1** (1.202 g, 10 mmol, ρ = 1.030 gmL^{-1}, 1.1700 mL, 1 equiv.). The reaction was then stirred at room temperature for 17 hours. After this time the reaction was quenched with 2 M HCl and stirred for a further 30 minutes at room temperature. Ethyl acetate was then added, and the organic layer was washed with brine 3 times, dried over $MgSO_4$, filtered and reduced *in vacuo* giving a pale yellow liquid (ee = 98%, Chiracel OD column 90:10 hexane:*iso*-propanol solvent, 0.5 mL/min flow, retention times = 9.7 min (*S*), 12.3 min (*R*)). Conversion was calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of acetophenone **1** and (*S*)-*sec*-phenethyl alcohol **47**.

6.2.9 Asymmetric reduction using different arene catalysts



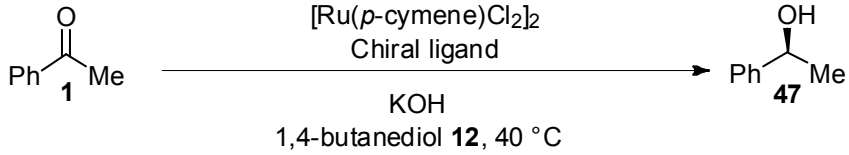
Following procedure ***6.2.8***, using either [Ru(*p*-cymene)Cl_2]$_2$ (30.6 mg, 0.05 mmol, 0.005 equiv.) or [Ru(benzene)Cl_2]$_2$ (25.0 mg, 0.05 mmol, 0.005 equiv.), the reactions were stirred at room temperature for 3 days. After this time the reactions were worked up as described in procedure ***6.2.8*** to give a pale yellow liquid, in both cases (ee = 99% and 94% after 17 hours and 93% and 82% after 3 days for [Ru(*p*-cymene)Cl_2]$_2$ and [Ru(benzene)Cl_2]$_2$ respectively, Chiracel OD column 90:10 hexane:*iso*-propanol solvent, 0.5 mL/min flow, retention times = 9.7 min (*S*), 12.3 min (*R*)). Conversion was calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of acetophenone **1** and (*S*)-*sec*-phenethyl alcohol **47**.

6.2.10 Removing the catalyst preparation step



To an oven dried and argon purged 10 mL round bottomed flask containing $[Ru(p\text{-cymene})Cl_2]_2$ (30.6 mg, 0.05 mmol, 0.005 equiv.), (*S*,*S*)-TsDPEN **11** (73.3 mg, 0.1 mmol, 0.01 equiv.) and KOH (0.2805 g, 0.5 mmol, 0.05 equiv.) was added acetophenone **1** (1.202 g, 10 mmol, ρ = 1.030 gmL^{-1}, 1.1700 mL, 1 equiv.) and 1,4-butanediol **12** (0.9012 g, 10 mmol, ρ = 1.017 gmL^{-1}, 0.900 mL, 1 equiv.). The reaction was stirred at room temperature for 3 days. After this time the reaction was worked up as described in procedure ***6.2.8*** to give a pale yellow liquid (ee = 88%, Chiracel OD column 90:10 hexane:*iso*-propanol solvent, 0.5 mL/min flow, retention times = 9.7 min (*S*), 12.3 min (*R*)). Conversion was calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of acetophenone **1** and (*S*)-*sec*-phenethyl alcohol **47**.

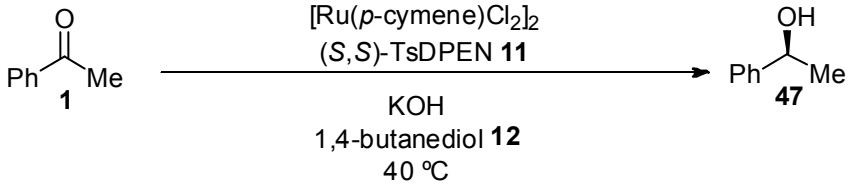
6.2.11 Asymmetric reduction using different chiral ligands



Following procedure ***6.2.10***, two reactions were carried out, one using the same reagents as described in ***6.2.10***, the other using (1*S*,2*R*)-(-)-1-aminoindan-2-ol **48** (29.8 mg, 0.1 mmol, 0.01 equiv.). The reactions were heated to 40 °C for 42 hours (instead of being stirred at room temperature) and worked up as described in ***6.2.10*** to give pale yellow liquids in both cases (ee = 38% and 57% after 24 hours and 87% and 42% after 42 hours for (*S*,*S*)-TsDPEN **11** and (1*S*,2*R*)-(-)-1-aminoindan-2-ol **48** respectively, Chiracel OD column 90:10 hexane:*iso*-propanol solvent, 0.5 mL/min flow, retention times = 9.7 min (*S*), 12.3 min (*R*)). Conversion was calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of acetophenone **1** and (*S*)-*sec*-phenethyl alcohol **47**.

Note: the ee achieved for (*S*,*S*)-TsDPEN **11** after 42 hours was determined from the isolated product. See section **6.2.7** for spectral data.

6.2.12 Lowering the base concentration



6.2.12.1 Reaction Using a Catalyst Preparation Step

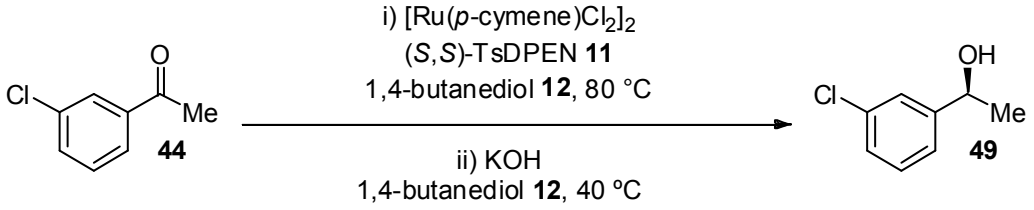
To an oven dried and argon purged Young's Tap NMR tube containing [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg, 0.01 mmol, 0.001 equiv.) and (*S*,*S*)-TsDPEN **11** (14.7 mg, 0.04 mmol, 0.004 equiv.) was added 1,4-butanediol **12** (0.0451 g, 0.5 mmol, ρ = 1.017 gmL^{-1}, 0.045 mL, 0.5 equiv.). The reaction mixture was then heated to 80 °C for 1 hour under an atmosphere of nitrogen (with intermittent shaking as a means of stirring). Meanwhile, KOH (4.5 mg, 0.08 mmol, 0.008 equiv.) was dissolved in 1,4-butanediol **12** (0.0451 g, 0.5 mmol, ρ = 1.030 gmL^{-1}, 0.045 mL, 0.5 equiv.) by stirring at room temperature. Once the reaction mixture had cooled to room temperature, the base mixture was added, followed by acetophenone **1** (0.1202 g, 1 mmol, ρ = 1.030 gmL^{-1}, 0.1200 mL, 1 equiv.). The reaction was then heated to 40 °C for 24 hours (again with intermittent shaking as a means of stirring). After this time the reaction was worked up as described in procedure ***6.2.10*** to give a pale yellow liquid (ee = 84%, Chiracel OD column 90:10 hexane:*iso*-propanol solvent, 0.5 mL/min flow, retention times = 9.7 min (*S*), 12.3 min (*R*)). Conversion was calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of acetophenone **1** and (*S*)-*sec*-phenethyl alcohol **47**.

6.2.12.2 Reaction without a Catalyst Step

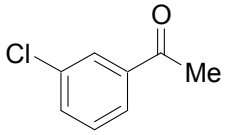
To an oven dried and argon purged Young's Tap NMR tube containing [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg, 0.01 mmol, 0.001 equiv.), (*S*,*S*)-TsDPEN **11** (14.7 mg, 0.04 mmol, 0.004 equiv.) and KOH (4.5 mg, 0.08 mmol, 0.008 equiv.) was added acetophenone **1** (0.1202 g, 1 mmol, ρ = 1.030 gmL^{-1}, 0.1200 mL, 1

equiv.) and 1,4-butanediol **12** (0.0901 g, 1 mmol, ρ = 1.017 gmL^{-1}, 0.090 mL, 1 equiv.). The reaction was heated to 40 °C for 24 hours (with intermittent shaking as a means of stirring). After this time the reaction was worked up as described in procedure ***6.2.10*** to give a pale yellow liquid (ee = 78%, Chiracel OD column 90:10 hexane:*iso*-propanol solvent, 0.5 mL/min flow, retention times = 9.7 min (*S*), 12.3 min (*R*)). Conversion was calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of acetophenone **1** and (*S*)-*sec*-phenethyl alcohol **47**.

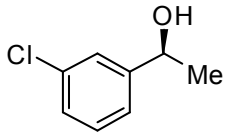
6.2.13 Asymmetric reduction of 3-Chloroacetophenone 44



Following procedure ***6.2.12.2*** using 3-chloroacetophenone **44** (0.1546g, 1 mmol, ρ = 1.191 gmL^{-1}, 0.1230 mL, 1 equiv.), the reaction was heated to 40 °C for 24 hours (with intermittent shaking as a means of stirring). After this time the reaction was worked up as described in procedure ***6.2.10*** to give a pale yellow liquid (ee = 82%, Chiracel OD column 90:10 hexane:*iso*-propanol solvent, 0.5 mL/min flow, retention times = 9.3 min (*S*), 10.8 min (*R*)). Conversion was calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of 3-chloroacetophenone **44** and (*S*)-1-(3-chlorophenyl)ethanol **49**.

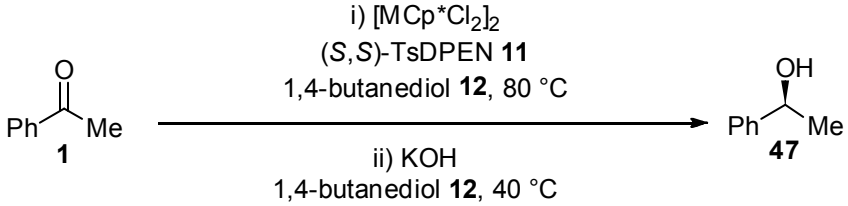


^{1}H NMR of 3-chloroacetophenone **44** corresponds to the data obtained from the supplier.



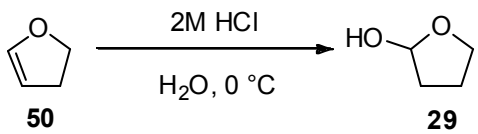
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 – 7.17 (m, 4H, Ar), 4.77 (q, 1H, *J* = 3.3, 9.9 Hz, CH), 1.90 (br. s, 1H, OH), 1.38 (d, 3H, *J* = 6.5 Hz, CH_3).
These data were consistent with those reported in the literature.[91]

6.2.14 Asymmetric reduction using different metal catalysts



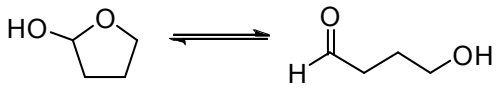
Following procedure ***6.2.8***, using the metal catalysts where M = Ir ($[IrCp^*Cl_2]_2$, 7.7 mg, 0.01 mmol, 0.001 equiv.) and where M = Rh ($[RhCp^*Cl_2]_2$, 6.2 mg, 0.01 mmol, 0.001 equiv.) the reaction mixtures were heated to 40 °C for 3 days (again with intermittent shaking as a means of stirring). After this time the reaction was worked up as described in procedure ***6.2.8*** to give a pale yellow liquid (ee = 93% and 90% after 20 hours, and 89% and 86% after 3 days for Ir and Rh respectively, Chiracel OD column 90:10 hexane:*iso*-propanol solvent, 0.5 mL/min flow, retention times = 9.7 min (*S*), 12.3 min (*R*)). Conversion was calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of acetophenone **1** and (*S*)-*sec*-phenethyl alcohol **47**.

6.2.15 Preparation of 2-hydroxytetrahydrofuran 29[46]



An oven dried 250 mL round bottomed flask containing 2,3-dihydrofuran **50** (7.01 g, 100 mmol, ρ = 0.927 gmL^{-1}, 7.56 mL, 1 equiv.) was stirred under ice for 30 minutes in order to reach 0 °C. An oven dried 10 mL round bottomed flask containing 2 M HCl (20 mmol, 1.7 mL, 0.2 equiv.) was also stirred under ice for 30 minutes to reach 0 °C. The acid was then added to the starting

material and the reaction was stirred under ice for 30 minutes. The reaction was then left to stir to warm to room temperature for an hour. The reaction was neutralised to pH 7 (using saturated $NaHCO_3$ solution) and then DCM (20 mL) was added. The organic layer was collected, dried over $MgSO_4$, filtered and reduced *in vacuo* resulting in a colourless liquid (quantitative yield).

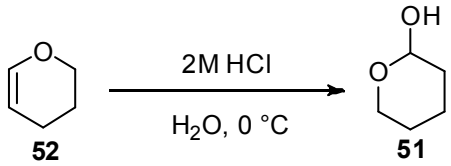


^{1}H NMR (250 MHz, $CDCl_3$): δ 9.74 (t, 1H, *J* = 1.7 Hz, CH), 5.55 (m, 1H, CH), 5.05 – 5.08 (m, 1H, CH), 4.05 (m, 1H, CH), 3.84 (t, 1H, *J* = 6.7 Hz, CH), 3.63 – 3.70 (dt, 2H, *J* = 6.2, 9.7 Hz, CH_2), 3.36 – 3.43 (dt, 2H, *J* = 6.0, 9.7 Hz, CH_2), 2.47 (td, 1H, *J* = 1.7, 9.7 Hz, CH), 1.77 – 2.02 (m, 4H, CH_2). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 202.3, 103.7, 99.9, 67.2, 66.8, 41.0, 32.6, 23.3.

(NOTE: 2-Hydroxytetrahydrofuran **29** exists in equilibrium with its corresponding aldehyde, as shown above.)

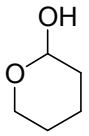
These data were consistent with those reported in the literature.[46]

6.2.16 Preparation of tetrahydro-2H-pyran-2-ol 51[47]



52 **51**

Following procedure ***6.2.15***, using 3,4-dihydro-2*H*-pyran **52**, (8.28 g, 100 mmol, ρ = 0.922 gmL^{-1}, 8.35 mL, 1 equiv.), a colourless liquid was obtained. The crude product was distilled using a Kügelrohr distillation apparatus (at a temperature of 80 °C and pressure of around 5 mmHg) giving the product as a colourless liquid (quantitative yield).

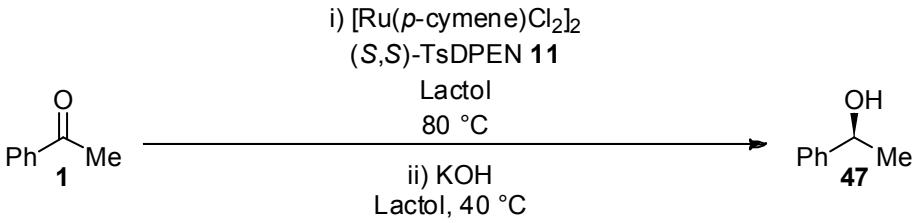


^{1}H NMR (250 MHz, $CDCl_3$): δ 4.87 – 4.90 (m, 1H, CH), 3.96 – 4.05 (m, 1H, CH), 3.72 (br. s, 1H, OH), 3.48 – 3.58 (m, 1H, CH), 1.74 – 1.88 (m, 2H, CH_2),

1.42 – 1.61 (m, 4H, CH_2). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 94.3, 63.8, 31.8, 25.1, 20.2.

These data were consistent with those reported in the literature.[47]

6.2.17 Asymmetric reduction using lactols 29 and 51 as hydrogen donors



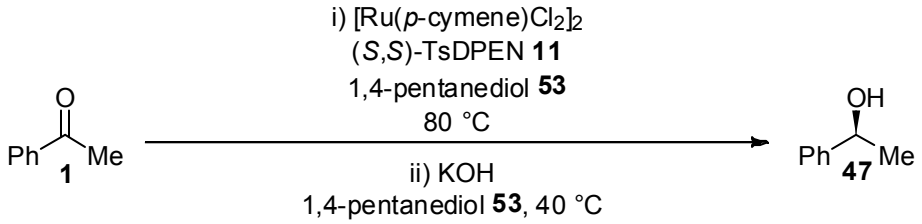
6.2.17.1 Reaction using lactol as the solvent

Following procedure ***6.2.12.1***, the appropriate lactol (either tetrahydro-2*H*-pyran-2-ol **51**, 0.1021 g, 1 mmol, ρ = 1.055, 0.0968 mL, 1 equiv. or 2-hydroxytetrahydrofuran **29**, 0.0881 g, 1 mmol, ρ = 1.102, 0.0780 mL, 1 equiv.) was used as the solvent for both the catalyst preparation and the dissolving of base, in order to prepare (*S*)-*sec*-phenethyl alcohol **47**. Tetrahydro-2*H*-pyran-2-ol **51** did not afford any product after 24 hours. 2-Hydroxytetrahydrofuran **29** afforded 11% of the required alcohol after 3 days.

6.2.17.2 Reaction using lactols but with added solvent

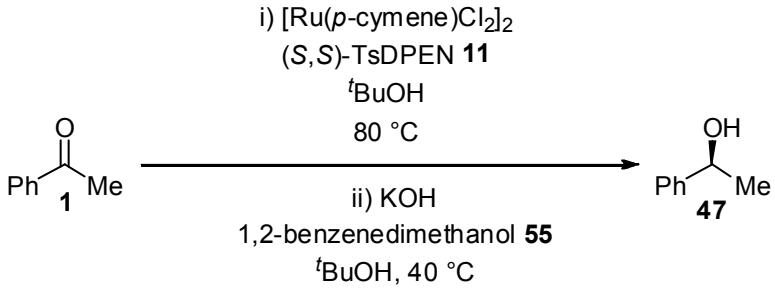
Following procedure ***6.2.12.1***, ^{t}BuOH (0.0741 g, 1 mmol, ρ = 0.775 gmL^{-1}, 0.0956 mL, 1 equiv.) was used as a solvent instead of lactols **29** and **51**. The lactols **29** and **51** were added at the same time as the base and acetophenone **1**, and the rest of the procedure was carried out in the same way. Reaction using tetrahydro-2*H*-pyran-2-ol **51** did not afford any product after 24 hours. Reaction using 2-hydroxytetrahydrofuran **29** afforded 18% of the required alcohol after 3 days.

6.2.18 Asymmetric reduction using 1,4-pentanediol 53 as a hydrogen donor



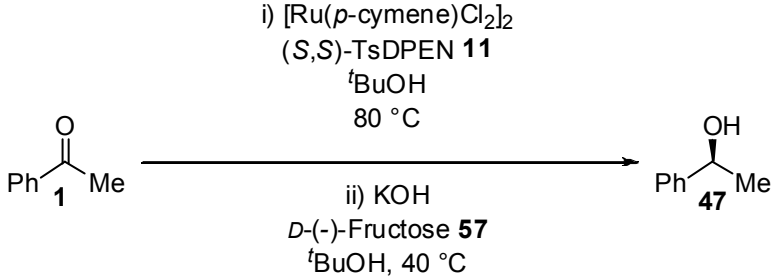
Following procedure ***6.2.12.1***, 1,4-pentanediol **53** (0.1042 g, 1 mmol, ρ = 0.986 gmL^{-1}, 0.1056 mL, 1 equiv.) was used as the solvent for both the catalyst preparation step and the dissolving of the base. 1,4-Pentanediol **53** afforded 48% conversion to (*S*)-*sec*-phenethyl alcohol **47** after 24 hours (ee = 74%, Chiracel OD column 90:10 hexane:*iso*-propanol solvent, 0.5 mL/min flow, retention times = 9.7 min (*S*), 12.3 min (*R*)). Conversion was calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of acetophenone **1** and (*S*)-*sec*-phenethyl alcohol **47**.

6.2.19 Asymmetric reduction using 1,2-benzenedimethanol 55 as a hydrogen donor



Following procedure ***6.2.12.1***, 1,2-benzenedimethanol **55** (0.1382 g, 1 mmol, 1 equiv.) was used as the hydrogen donor. Due to this compound being a solid, solvent was required for the catalyst preparation step, dissolving of the base and 1,2-benzenedimethanol **55**. ^{t}BuOH was used as the solvent. The reaction afforded 57% conversion to (*S*)-*sec*-phenethyl alcohol **47** after 24 hours (ee = 83%, Chiracel OD column 90:10 hexane:*iso*-propanol solvent, 0.5 mL/min flow, retention times = 9.7 min (*S*), 12.3 min (*R*)). Conversion was calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of acetophenone **1** and (*S*)-*sec*-phenethyl alcohol **47**.

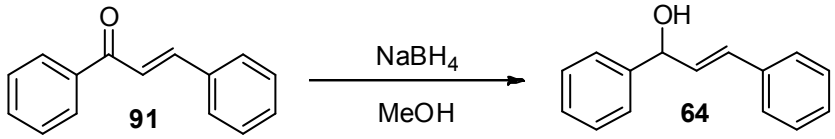
6.2.20 Asymmetric reduction using D-(-)-fructose 57 as a hydrogen donor



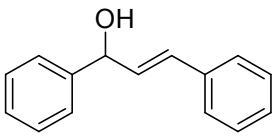
Following procedure ***6.2.19***, *D*-(-)-fructose **57** (0.1802 g, 1 mmol, 1 equiv.) was used as the hydrogen donor. No product was afforded after 3 days.

6.3 Experimental Procedures for Chapter 3

6.3.1 Preparation of trans-1,3-diphenyl-2-propen-1-ol 64[96]



To an oven dried 250 mL round bottomed flask containing chalcone (1,3-diphenyl-2-propenone) **91** (6.25 g, 0.03 mol, 1 equiv.) in methanol (375 mL), was added $NaBH_4$ (2.27 g, 0.06 mol, 1 equiv.) portion-wise over a period of 10 minutes. The reaction was then left to stir for 1 hour. The solvent was then removed under reduced pressure and the resultant sticky, off white solid was taken up in ethyl acetate (150 mL), washed with deionised water (2 x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*, giving a pale yellow liquid. The liquid was then crystallised under high vacuum leaving a pale yellow solid (4.96 g, 79%).

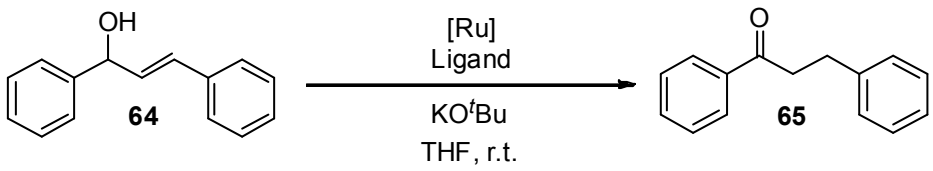


^{1}H NMR (250 MHz, $CDCl_3$): δ 7.24 – 7.50 (m, 10H, Ar), 6.73 (d, 1H, *J* = 15.8 Hz, CH), 6.42 (dd, 1H, *J* = 6.3, 15.8 Hz, CH), 5.43 (d, 1H, *J* = 6.0 Hz, CH),

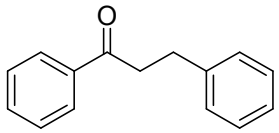
1.61 (br. s, 1H, OH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 142.7, 136.5, 131.5, 130.5, 128.6, 128.5, 127.7, 127.0, 126.6, 126.3, 75.1.

These data were consistent with those reported in the literature.[97]

6.3.2 Initial catalyst screen



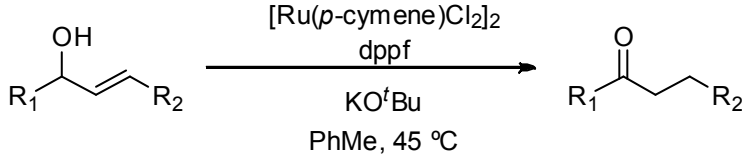
To oven dried and nitrogen purged Radley's carousel tubes containing the required ruthenium catalyst (0.01 mmol, 0.01 equiv.), the required ligand (0.01 mmol, 0.01 equiv.) (see Table 3.1 for specific catalysts and ligands), KO^{t}Bu (2.2 mg, 0.02 mmol, 0.02 equiv.) and *trans*-1,3-diphenyl-2-propen-1-ol **64** (0.2103 g, 1 mmol, 1 equiv.), was added THF (1 mL). The reactions were stirred for 24 hours at room temperature under a pressure of nitrogen, and then heated to reflux for a further 2 hours. After this time, the reactions were filtered through Celite and silica, washed through with DCM and concentrated *in vacuo*. Conversion was calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of *trans*-1,3-diphenyl-2-propen-1-ol **64** and 3-phenylpropiophenone **65**.



^{1}H NMR (250 MHz, $CDCl_3$): δ 7.17 – 7.57 (m, 10H, Ar), 3.30 (t, 2H, *J* = 7.5 Hz, CH_2), 3.06 (t, 2H, *J* = 7.7 Hz, CH_2).

These data were consistent with those reported in the literature.[45]

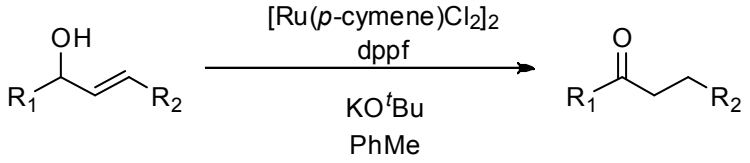
6.3.3 Second initial screen using various substrates



To oven dried and nitrogen purged Radley's carousel tubes containing [Ru(*p*-cymene)Cl_2]$_2$ (3.1 mg, 0.005 mol, 0.005 equiv.), dppf (5.5 mg, 0.01 mol, 0.01

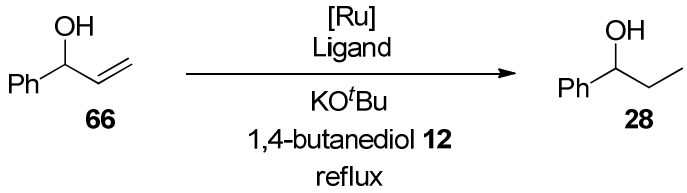
equiv.) and KO^{t}Bu (2.2 mg, 0.02 mol, 0.02 equiv.), were added the required substrates (1 mmol, 1 equiv.) followed by toluene (1 mL). The reactions were then heated to 45 °C for 48 hours. After this time, the reactions were worked up as described in procedure ***6.3.2***. Conversions were calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of the allylic alcohol starting materials and the carbonyl products.

6.3.4 Substrate screen with higher temperature



Following procedure ***6.3.3***, only the first five substrates from Table 3.2 were used, but the reaction temperature was increased to reflux (approximately 110 °C). Conversions were calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of the allylic alcohol starting materials and the carbonyl products.

6.3.5 Catalyst screen involving 1,4-butanediol 12

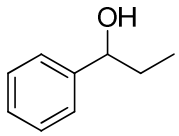


To oven dried and nitrogen purged Schlenk carousel tubes containing the required ruthenium catalyst (0.005 mmol, 0.005 equiv. for Ru[(*p*-cymene)Cl_2]$_2$ and 0.025 mmol, 0.025 equiv. for Ru(PPh_3)$_3$(CO)H_2), the required ligand (0.01 mmol, 0.01 equiv. when used with Ru[(*p*-cymene)Cl_2]$_2$ and 0.025 mmol, 0.025 equiv. when used with Ru(PPh_3)$_3$(CO)H_2)) and KO^{t}Bu (0.02 mmol, 0.02 equiv. when used with Ru[(*p*-cymene)Cl_2]$_2$ and 0.05 mmol, 0.05 equiv. when used with Ru(PPh_3)$_3$(CO)H_2)) was added α-vinylbenzyl alcohol **66** (0.1342 g, 1 mmol, ρ = 1.021 gmL^{-1}, 0.1314 mL, 1 equiv.), 1,4-butanediol **12** (see Table 3.4 for number of equivalents) and toluene (1 mL, if required). The reactions were then heated to 110 °C for up to 3 days. Conversions were calculated by

analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of α-vinylbenzyl alcohol **66**, propiophenone **9**, and 1-phenyl-1-propanol **28**.

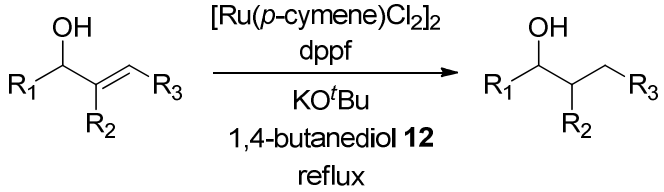
*6.3.5.1 Preparation of 1-phenyl-1-propanol **28***

Following procedure ***6.3.5***, using α-vinylbenzyl alcohol **66** (0.1342 g, 1 mmol, ρ = 1.021 gmL^{-1}, 0.1314 mL, 1 equiv.) the title compound was obtained and isolated by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (4:1), R_f = 0.22 to give a colourless liquid (0.1253 g, 92%).



Spectroscopy data corresponds to that shown in section *6.2.7.1*.

6.3.6 Substrate screen using 1,4-butanediol 12

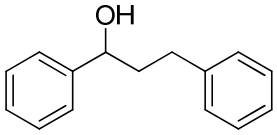


To oven dried and nitrogen purged Schlenk carousel tubes containing Ru[(*p*-cymene)Cl$_2$]$_2$ (0.005 mmol, 0.005 equiv. or 0.025 mmol, 0.025 equiv), dppf (0.01 mmol, 0.01 equiv. or 0.05 mmol, 0.05 equiv.) and KO^{t}Bu (0.02 mmol, 0.02 equiv. or 0.1 mmol, 0.1 equiv.) was added the required substrate (1 mmol, 1 equiv.) and 1,4-butanediol **12** (0.4505 g, 5 mmol, ρ = 1.017 gmL^{-1}, 0.50 mL, ~ 5 equiv.). The reactions were then heated to 110 °C for up to 3 days. Conversions were calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of the allylic alcohols, ketones and saturated alcohols.

*6.3.6.1 Preparation of 1,3-diphenyl-propan-1-ol **92***

Following procedure ***6.3.6***, using *trans*-1,3-diphenyl-2-propen-1-ol **64** (0.2103 g, 1 mmol, 1 equiv.) the title compound was obtained and isolated by column

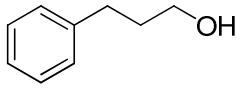
chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (4:1), R_f = 0.17 to give a colourless liquid (0.1105 g, 52%).



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 – 7.36 (m, 10H, Ar), 4.69 (dd, 1H, *J* = 2.4, 5.4 Hz, CH), 2.71 (m, 2H, CH_2), 2.08 (m, 2H, CH_2). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 144.5, 141.7, 128.5, 127.7, 125.9, 73.9, 40.4, 32.0. ν_{max} /cm^{-1} (neat): 3365, 2921, 2861, 1603, 1494, 1453.
These data were consistent with those reported in the literature.[98]

*6.3.6.2 Preparation of 3-phenyl-1-propanol **73***

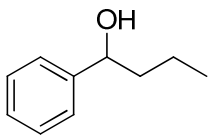
Following procedure ***6.3.6***, using cinnamyl alcohol **67** (0.1342 g, 1 mmol, ρ = 1.044 gmL^{-1}, 0.129 mL, 1 equiv.) the title compound was obtained and isolated by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (3:2), R_f = 0.17 to give a colourless liquid (0.1222 g, 90%).



Spectroscopy data corresponds to that shown in section *6.2.6.2*.

*6.3.6.3 Preparation of 1-phenyl-1-butanol **154***

Following procedure ***6.3.6***, using 4-phenyl-1-buten-4-ol **68** (0.1482 g, 1 mmol, ρ = 0.992 gmL^{-1}, 0.1494 mL, 1 equiv.) the title compound was obtained and isolated by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (3:1), R_f = 0.39 to give a colourless liquid (0.0787 g, 52%).



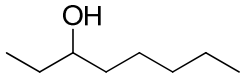
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 – 7.27 (m, 5H, Ph), 4.60 (dd, 1H, *J* = 1.5, 6.0 Hz, CH), 1.59 – 1.66 (m, 2H, CH_2), 1.17 – 1.40 (m, 2H, CH_2), 0.85 (t, 3H, *J* = 7.4 Hz, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 144.9, 128.4, 127.5, 125.9,

74.4, 41.2, 19.0, 13.9. ν_{max} /cm^{-1} (neat): 3321, 3029, 2957, 2930, 2872, 1454, 761, 700.

These data were consistent with those reported in the literature.[99]

*6.3.6.4 Preparation of 3-octanol **155***

Following procedure ***6.3.6***, using 1-octen-3-ol **61** (0.1282 g, 1 mmol, ρ = 0.83 gmL^{-1}, 0.1545 mL 1 equiv.) the title compound was obtained and isolated by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (4:1), R_f = 0.28 to give a colourless liquid (0.1042 g, 80%).

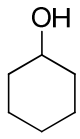


^{1}H NMR (300 MHz, $CDCl_3$): δ 3.46 (m, 1H, CH), 1.15 – 1.54 (m, 12H, CH_2/CH_3/OH), 0.80 – 0.90 (m, 5H, CH_2/CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 73.3, 36.9, 32.0, 30.1, 25.3, 22.6, 14.0, 9.9. ν_{max} /cm^{-1} (neat): 3337, 2959, 2927, 2859, 1459.

These data were consistent with those reported in the literature.[100]

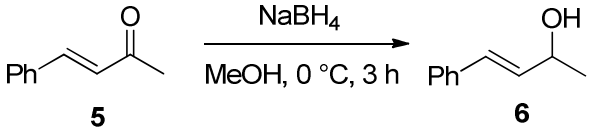
*6.3.6.5 Preparation of cyclohexanol **147***

Following procedure ***6.3.6***, using 2-cyclohexen-1-ol **74** (0.098 g, 1 mmol, ρ = 1.00 gmL^{-1}, 0.098 mL 1 equiv.) the title compound was obtained and isolated by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (1:1), R_f = 0.33 to give a colourless liquid (0.0686 g, 68%).



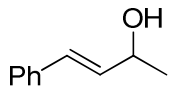
Spectroscopy data corresponds to that shown in section *6.2.6.1*.

6.3.6.6.1 Preparation of (*E*)-4-phenylbut-3-en-2-ol **6**†



5 **6**

To an oven dried and nitrogen purged round bottomed flask containing *trans*-4-phenyl-3-buten-2-one **5** (2.04 g, 13.95 mmol, 1 equiv.) and methanol (5 mL) at 0 °C, was added sodium borohydride (0.56 g, 14.80 mmol, 1.06 equiv.) slowly. The reaction was stirred at 0 °C for 3 hours. Hydrochloric acid was then added until effervescence ceased, and the resultant mixture was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The title compound was obtained and purified by column chromatography eluting with hexane/ethyl acetate (9:1), R_f = 0.24 to give a colourless liquid (0.99 g, 48%).

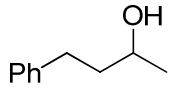


^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 – 7.40 (m, 5H, Ph), 6.57 (d, 1H, *J* = 15.9 Hz, CH), 6.27 (dd, 1H, *J* = 6.3, 16.0 Hz, CH), 4.46 – 4.54 (m, 1H, CH), 1.69 (br. s, 1H, OH), 1.38 (d, 3H, *J* = 6.6 Hz, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 136.6, 133.5, 129.4, 128.6, 127.6, 126.4, 68.9, 23.4. ν_{max} /cm^{-1} (neat): 3339, 3026, 2972, 2927, 2872, 1449, 965.

These data were consistent with those reported in the literature.[101]

*6.3.6.6.2 Preparation of 4-phenylbutan-2-ol **156***

Following procedure ***6.3.6***, using (*E*)-4-phenylbut-3-en-2-ol **6** (0.1482 g, 1 mmol, 1 equiv.) the title compound was obtained and isolated by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (4:1), R_f = 0.05 to give a colourless liquid (0.0933 g, 62%).



Spectroscopy data corresponds to that shown in section *6.2.7.4*.

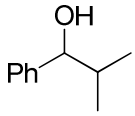
† This work was carried out by James Taylor.

*6.3.6.7 Reaction of 3-butyn-2-ol **75***

Following procedure ***6.3.6***, using 3-butyn-2-ol **75** (0.070 g, 1 mmol, ρ = 0.894 gmL-1, 0.078 mL, 1 equiv.) no reaction was observed after 3 days.

*6.3.6.8 Preparation of 2-methyl-1-phenyl-1-propanol **157***

Following procedure ***6.3.6***, using 2-methyl-1-phenyl-2-propen-1-ol **76** (0.1482 g, 1 mmol, 1 equiv.) the title compound was obtained and isolated by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (4:1), R_f = 0.28 to give a colourless liquid (0.0763 g, 51%).

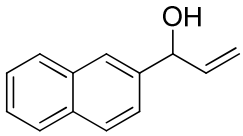


^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 – 7.28 (m, 5H, Ph), 4.28 (d, 1H, *J* = 6.9 Hz, CH), 1.88 (app. octet, 1H, *J* = 6.9 Hz, CH), 1.67 (br. s, 1H, OH), 0.92 (d, 3H, *J* = 6.9 Hz, CH_3), 0.72 (d, 3H, *J* = 6.9 Hz, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 143.6, 128.2, 127.4, 126.5, 80.1, 35.3, 19.0, 18.2. ν_{max} /cm^{-1} (neat): 3373, 3029, 2957, 2871, 1603, 1452, 759, 700.

These data were consistent with those reported in the literature.[99]

*6.3.6.9.1 Preparation of 1-(naphthalene-2-yl)prop-2-en-1-ol **77***

To an oven dried and argon purged flask was added 2-naphthaldehyde **46** (2.00 g, 12.8 mmol, 1.0 equiv.) in THF (10 mL). This was stirred in an ice bath to reach 0 °C. Vinylmagnesium bromide (1.0 M solution in THF) (13.0 mL, 13.0 mmol, ~1.0 equiv.) was then added dropwise over approximately ten minutes. The reaction was stirred at 0 °C for 2 hours. Diethylether (50 mL) was then added to dilute the reaction, followed by saturated ammonium chloride solution (50 mL). The organic layer was then washed with water (2 x 50 mL), dried over sodium sulphate, filtered and concentrated *in vacuo* to obtain a pale yellow liquid (1.7133 g, 73%). The compound was used without further purification.

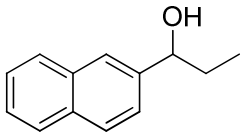


^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 – 7.28 (m, 7H, Ar), 5.94 (ddd, 1H, *J* = 6.3, 10.4, 16.5 Hz, CH), 5.27 (dt, 1H, *J* = 17.1, 1.4 Hz, CH), 5.10 – 5.16 (m, 2H, CH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 141.0, 139.9, 128.7, 128.3, 127.7, 115.6, 74.7. ν_{max} /cm^{-1} (neat): 3321, 3051, 1633, 1601, 1508, 988, 927, 819, 746.

These data were consistent with those reported in the literature.[102]

6.3.6.9.2 Preparation of 1-(naphthalen-2-yl)propan-1-ol ***158***

Following procedure ***6.3.6***, using 1-(naphthalene-2-yl)prop-2-en-1-ol **77** (0.1842 g, 1 mmol, 1 equiv.) the title compound was obtained and isolated by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (4:1), R_f = 0.14 to give a colourless liquid (0.0607 g, 33%).

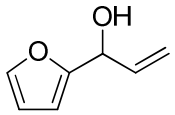


^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 – 7.84 (m, 4H, Ar), 7.44 – 7.49 (m, 3H, Ar), 4.77 (t, 1H, *J* = 6.6 Hz, CH), 1.89 (m, 2H, CH_2), 0.94 (t, 3H, *J* = 7.4 Hz, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 133.0, 130.5, 128.2, 127.9, 127.7, 126.1, 125.8, 124.7, 124.1, 122.7, 76.1, 31.8, 10.1. ν_{max} /cm^{-1} (neat): 3333, 3054, 2963, 2931, 2875, 1601, 1508, 1455, 1375.

These data were consistent with those reported in the literature.[103]

6.3.6.10.1 Preparation of 1-(furan-2-yl)prop-2-en-1-ol ***78***

Following procedure *6.3.6.9.1*, using 2-furaldehyde **159** (2.00 g, 20.8 mmol, ρ = 1.160 gmL^{-1}, 1.7200 mL, 1.0 equiv.) and vinylmagnesium bromide (1.0 M solution in THF) (21.0 mL, 21.0 mmol, ~1.0 equiv.), the title compound was obtained and used as an orange liquid without further purification (1.7993 g, 70%).



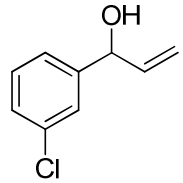
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (dd, 1H, *J* = 0.9, 1.8 Hz, CH), 6.34 (dd, 1H, *J* = 1.7, 3.3 Hz, CH), 6.26 (dt, 1H, *J* = 3.3, 0.8 Hz, CH), 6.13 (ddd, 1H, *J* = 5.7, 10.4, 16.2 Hz, CH), 5.43 (dt, 1H, *J* = 17.1, 1.4 Hz, CH), 5.30 (dt, 1H, *J* = 10.2 1.4 Hz, CH), 5.23 (br. t, 1H, *J* = 4.4 Hz, CH), 2.02 (d, 1H, *J* = 4.8 Hz, OH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 155.4, 142.9, 137.2, 116.9, 110.7, 107.1, 69.0. ν_{max} /cm^{-1} (neat): 3379, 1148, 988, 928, 791, 736.
These data were consistent with those reported in the literature.[104]

*6.3.6.10.2 Reaction of 1-(furan-2-yl)prop-2-en-1-ol **78***

Following procedure **6.3.6**, using 1-(furan-2-yl)prop-2-en-1-ol **78** (0.1241 g, 1 mmol, 1 equiv.) no reaction was observed in 3 days.

*6.3.6.11.1 Preparation of 1-(3-chlorophenyl)prop-2-en-1-ol **79***

Following procedure *6.3.6.9.1*, using 3-chlorobenzaldehyde **160** (2.00 g, 14.2 mmol, ρ = 1.241 gmL^{-1}, 1.610 mL, 1.0 equiv.) and vinylmagnesium bromide (1.0 M solution in THF) (14.4 mL, 14.4 mmol, ~1.0 equiv.), the title compound was obtained and used without further purification (1.7605 g, 73%).

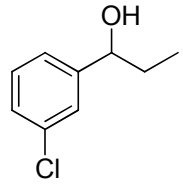


^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 – 7.39 (m, 4H, Ar), 6.00 (ddd, 1H, *J* = 6.2, 10.4, 16.5 Hz, CH), 5.36 (dt, 1H, *J* = 17.1, 1.4 Hz, CH), 5.23 (dt, 1H, *J* = 10.2, 1.3 Hz, CH), 5.18 (br. d, 1H, *J* = 6.0 Hz, CH). ^{13}C NMR (75.4 MHz, $CDCl_3$): 144.5, 139.7, 129.8, 127.8, 126.9, 124.8, 115.8, 74.7. δ ν_{max} /cm^{-1} (neat): 3301, 1596, 1574, 989, 929, 784, 728.
These data were consistent with those reported in the literature.[105]

*6.3.6.11.2 Preparation of 1-(3-chlorophenyl)propan-1-ol **160***

Following procedure ***6.3.6***, using 1-(3-chlorophenyl)prop-2-en-1-ol **79** (0.1686 g, 1 mmol, 1 equiv.) the title compound was obtained and isolated by column

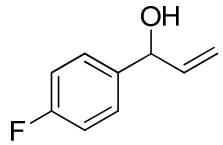
chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (9:1), R_f = 0.18 to give a colourless liquid (0.0810 g, 47%).



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 – 7.36 (m, 4H, Ar), 4.59 (t, 1H, *J* = 6.5 Hz, CH), 1.67 – 1.88 (m, 3H, CH_2/OH), 0.92 (t, 3H, *J* = 7.4 Hz, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 146.6, 134.3, 129.7, 127.6, 126.1, 124.1, 75.3, 31.9, 9.9. ν_{max} /cm^{-1} (neat): 3343, 2966, 2930, 2875, 1462, 1431, 1084, 784.
These data were consistent with those reported in the literature.[106]

*6.3.6.12.1 Preparation of 1-(4-fluorophenyl)prop-2-en-1-ol **80***

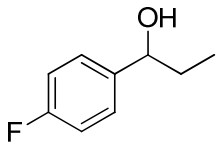
Following procedure *6.3.6.9.1*, using *p*-fluorobenzaldehyde **161** (2.00 g, 16.1 mmol, ρ = 1.176 gmL^{-1}, 1.700 mL, 1.0 equiv.) and vinylmagnesium bromide (1.0 M solution in THF) (16.2 mL, 16.2 mmol, ~1.0 equiv.), the title compound was obtained and used without further purification (2.10 g, 86%).



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 – 7.38 (m, 2H, Ar), 7.06 (m, 2H, Ar), 6.04 (ddd, 1H, *J* = 6.0, 10.3, 16.5 Hz, CH), 5.36 (dt, 1H, *J* = 17.5, 1.3 Hz, CH), 5.19 – 5.23 (m, 2H, CH). ^{13}C NMR (75.4 MHz, $CDCl_3$): 162.3 (d, *J* = 245.5 Hz), 140.1, 138.3 (d, *J* = 3.1 Hz), 128.1 (d, *J* = 8.1 Hz), 115.5, 115.3 (d, *J* = 10.3 Hz), 74.6. δ ν_{max} /cm^{-1} (neat): 3361, 1602, 1221, 989, 927, 834.
These data were consistent with those reported in the literature.[107]

*6.3.6.12.2 Preparation of 1-(4-fluorophenyl)propan-1-ol **162***

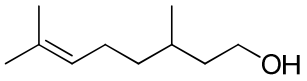
Following procedure ***6.3.6***, using 1-(4-fluorophenyl)prop-2-en-1-ol **80** (0.1522 g, 1 mmol, 1 equiv.) the title compound was obtained and isolated by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (4:1), R_f = 0.18 to give a colourless liquid (0.0578 g, 37%).



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 – 7.34 (m, 2H, Ar), 6.99 – 7.06 (m, 2H, Ar), 4.59 (t, 1H, *J* = 6.6 Hz, CH), 1.65 – 1.88 (m, 3H, CH_2/OH), 0.90 (t, 3H, *J* = 7.5 Hz, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 162.1 (d, *J* = 244.8 Hz), 140.3 (d, *J* = 3.2 Hz), 127.6 (d, *J* = 8.0 Hz), 115.2 (d, *J* = 21.3 Hz), 75.4, 32.0, 10.0. ν_{max} /cm^{-1} (neat): 3343, 2964, 2924, 2876, 1459, 1222, 834.
These data were consistent with those reported in the literature.[108]

6.3.6.13 Preparation of β-citronellol ***85***

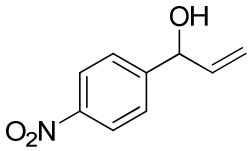
Following procedure ***6.3.6***, using geraniol **81** (0.154 g, 1 mmol, ρ = 1.476 gmL^{-1}, 0.1045 mL, 1 equiv.) the title compound was obtained and isolated by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (4:1), R_f = 0.12 to give a colourless liquid (0.112 g, 71%).



^{1}H NMR (300 MHz, $CDCl_3$): δ 5.07 – 5.13 (m, 1H, CH), 3.62 – 3.75 (m, 2H, CH_2), 1.89 – 2.08 (m, 2H, CH_2), 1.12 – 1.68 (m, 12H, CH/CH_2/CH_3), 0.91 (d, 3H, *J* = 6.6 Hz, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 131.3, 124.7, 61.2, 39.9, 37.2, 29.2, 25.7, 25.4, 19.5, 17.6.
This data corresponds to that of the commercially available compound.

6.3.6.14.1 Preparation of 1-(4-nitrophenyl)prop-2-en-1-ol ***82***

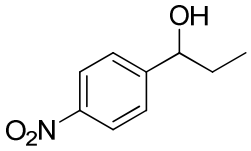
According to representative procedure *6.3.6.9.1*, using *p*-nitrobenzaldehyde **163** (2.00 g, 13.2 mmol, 1.0 equiv.) and vinylmagnesium bromide (1.0 M solution in THF) (13.5 mL, 13.5 mmol, ~1.0 equiv.), the title compound was obtained and used as an orange liquid without further purification (0.5104 g, 24%).



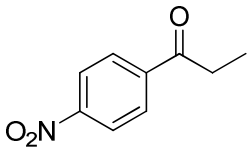
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (m, 2H, Ar), 7.55 (m, 2H, Ar), 5.99 (ddd, 1H, *J* = 6.5, 10.2, 16.8 Hz, CH), 5.40 (dt, 1H, *J* = 17.1, 1.2, Hz, CH), 5.32 (br. d, 1H, *J* = 6.6 Hz, CH), 5.27 (dt, 1H, *J* = 10.5, 1.1 Hz, CH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 149.5, 147.4, 139.2, 126.9, 123.7 116.8, 74.6. ν_{max} /cm^{-1} (neat): 3286, 1511, 989, 931, 852.
These data were consistent with those reported in the literature.[104]

*6.3.6.14.2 Preparation of 1-(4-nitrophenyl)propan-1-ol **84** and 1-(4-nitrophenyl)propan-1-one **83***

Following procedure ***6.3.6***, using 1-(4-nitrophenyl)prop-2-en-1-ol **82** (0.1792 g, 1 mmol, 1 equiv.) the title compounds were obtained and isolated by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (4:1), to give brown liquids, R_f = 0.03 (0.0148 g, 8%) and R_f = 0.35 (0.0057 g, 3%) respectively.



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (m, 2H, Ar), 7.51 (m, 2H, Ar), 4.75 (t, 1H, *J* = 6.3 Hz, CH), 1.74 – 1.84 (m, 3H, CH_2/OH), 0.94 (t, 3H, *J* = 7.5 Hz, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 151.9, 147.3, 126.6, 123.6, 74.8, 32.1, 9.7. ν_{max} /cm^{-1} (neat): 3374, 2965, 2933, 2877, 1514, 1459, 1342, 851, 748.
These data were consistent with those reported in the literature.[106]



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (m, 2H, Ar), 8.11 (m, 2H, Ar), 3.06 (q, 2H, *J* = 7.2 Hz, CH_2), 1.26 (t, 3H, *J* = 7.2 Hz, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 199.1, 158.5, 141.3, 129.0, 123.8, 32.4, 7.9. ν_{max} /cm^{-1} (neat): 3048, 2985, 2920, 2856, 1686, 1519, 1461, 1340, 852, 740.
These data were consistent with those reported in the literature.[109]

6.3.7 Reaction of 3-phenyl-2-propyn-1-ol 86

Following procedure ***6.3.6***, using 3-phenyl-2-propyn-1-ol **86** (0.1322 g, 1 mmol, ρ = 1.06 gmL^{-1}, 0.1247 mL, 1 equiv.) 3-phenyl-1-propanol **73** and cinnamyl alcohol **67** were observed in the crude ^{1}H NMR. Conversions were calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of the 3-phenyl-2-propyn-1-ol **86**, 3-phenyl-1-propanol **73** and cinnamyl alcohol **67**. The products were not isolated due to co-elution on silica gel.

6.3.8 Reaction of 2-butyne-1,4-diol 16

Following procedure ***6.3.6***, using 2-butyne-1,4-diol **16** (0.086 g, 1 mmol, 1 equiv.) and toluene (1 mL) instead of 1,4-butanediol **12**. No products were observed after 3 days at reflux.

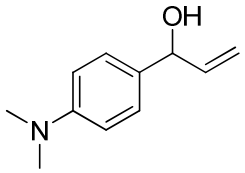
6.3.9 Reaction of chalcone 91

Following procedure ***6.3.6***, using chalcone **91** (0.2083 g, 1 mmol, 1 equiv.) 3-phenyl-1-propanol **73** was obtained and isolated by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (3:2), R_f = 0.17 to give a colourless liquid (0.2070 g, 97%).
Spectroscopy data corresponds to that shown in section *6.3.6.2*.

6.3.10.1 Preparation of 1-(4-(dimethylamino)phenyl)prop-2-en-1-ol 93

Following procedure *6.3.6.9.1*, using *p*-dimethylaminobenzaldehyde **164** (2.00 g, 13.4 mmol, 1.0 equiv.) and vinylmagnesium bromide (1.0 M solution in

THF) (14.0 mL, 14.0 mmol, ~1.0 equiv.), the title compound was obtained and used as an orange liquid without any further purification (1.9429 g, 82%).

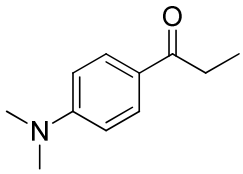


^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, 2H, *J* = 8.7 Hz, Ar), 6.72 (d, 2H, *J* = 8.7 Hz, Ar), 6.07 (ddd, 1H, *J* = 5.7, 10.5, 15.9 Hz, CH), 5.33 (dt, 1H, *J* = 17.1, 1.5 Hz, CH), 5.17 (m, 2H, CH), 2.94 (s, 6H, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 150.4, 140.5, 130.6, 127.4, 114.2, 112.6, 75.0, 40.6. ν_{max} /cm^{-1} (neat): 3364, 3077, 1613, 1520, 987, 920. HRMS(ESI-TOF) calcd for $C_{11}H_{15}NOH^+$: 178.1212. Found: 178.1226. (MH^+). *Anal. Calc.* for $C_{11}H_{15}NO$: C, 75.54 %; H, 8.53 %; N, 7.90 %; Found: C, 74.0 %; H, 8.48 %; N, 7.85 %.

6.3.10.2 Preparation of 1-(4-(dimethylamino)phenyl)propan-1-ol 95, 1-(4-(dimethylamino)phenyl)propan-1-one 94 and N,N-dimethyl-4-propylaniline 96

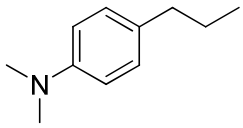
Following procedure ***6.3.6***, using 1-(4-(dimethylamino)phenyl)prop-2-en-1-ol **93** (0.1772 g, 1 mmol, 1 equiv.), 1-(4-(dimethylamino)phenyl)propan-1-ol **95**, 1-(4-(dimethylamino)phenyl)propan-1-one **94** and *N*,*N*-dimethyl-4-propylaniline **96** were observed in the crude ^{1}H NMR. Conversions were calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of 1-(4-(dimethylamino)phenyl)propan-1-ol **95**, 1-(4-(dimethylamino)phenyl)propan-1-one **94** and *N*,*N*-dimethyl-4-propylaniline **96**. 1-(4-(Dimethylamino)phenyl)propan-1-ol **95** was not isolated due to co-elution with γ-butyrolactone **19**.

1-(4-(dimethylamino)phenyl)propan-1-one **94** was isolated by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (4:1), R_f = 0.26 to give a brown liquid (trace).



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, 2H, *J* = 9.0 Hz, Ar), 6.66 (d, 2H, *J* = 9.0 Hz, Ar), 3.06 (s, 6H, CH_3), 2.91 (q, 2H, *J* = 7.3 Hz, CH_2), 1.21 (t, 3H, *J* = 7.4 Hz, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 199.2, 153.3, 130.1, 125.0, 110.6, 40.0, 31.0, 8.8. HRMS(ESI-TOF) calcd for $C_{11}H_{15}NOH^+$: 200.1051. Found: 200.1037. (MNa^+).
These data were consistent with those reported in the literature.[110]

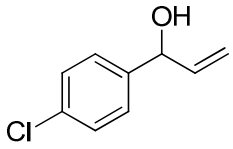
N,*N*-dimethyl-4-propylaniline **96** was isolated by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (4:1), R_f = 0.71 to give a brown liquid (0.0599 g, 37%).



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.05 (d, 2H, *J* = 8.7 Hz, Ar), 6.70 (d, 2H, *J* = 8.4 Hz, Ar), 2.90 (s, 6H, CH_3), 2.49 (t, 2H, *J* = 7.7 Hz, CH_2), 1.59 (sex, 2H, *J* = 7.4 Hz, CH_2), 0.92 (t, 3H, *J* = 7.4 Hz, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 145.5, 132.7, 129.6, 129.0, 113.5, 113.2, 41.1, 37.1, 24.8, 13.9. HRMS(ESI-TOF) calcd for $C_{11}H_{17}NH^+$: 164.1439. Found: 164.1428. (MH^+).
These data were consistent with those reported in the literature.[111]

6.3.11.1 Preparation of 1-(4-chlorophenyl)prop-2-en-1-ol 100

According to representative procedure *6.3.6.9.1*, using *p*-chlorobenzaldehyde **165** (2.00 g, 14.2 mmol, 1.0 equiv.) and vinylmagnesium bromide (1.0 M solution in THF) (15.0 mL, 15.0 mmol, ~1.0 equiv.), the title compound was obtained and used as a pale yellow liquid without further purification (2.001 g, 83%).



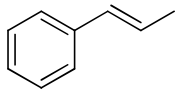
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 – 7.86 (m, 2H, Ar), 7.47 – 7.51 (m, 2H, Ar), 6.13 (ddd, 1H, *J* = 6.0, 10.3, 16.3 Hz, CH), 5.42 (dt, 1H, *J* = 17.1, 1.4 Hz, CH), 5.38 (br. d, 1H, *J* = 5.9 Hz, CH), 5.25 (dt, 1H, *J* = 10.4, 1.4 Hz, CH), 2.07 (br. s, 1H, OH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ. 140.1, 139.9, 133.3, 128.4, 127.7, 115.4, 75.5. ν_{max} /cm^{-1} (neat): 3320, 2883, 987, 926, 820, 728.
These data were consistent with those reported in the literature.[102]

6.3.11.2 Preparation of 1-phenyl-1-propanol 28 via dechlorination

Following procedure ***6.3.6***, using 1-(4-chlorophenyl)prop-2-en-1-ol **100** (0.1686 g, 1 mmol, 1 equiv.) the title compound was obtained and isolated by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (4:1), R_f = 0.20 to give a colourless liquid (0.1096 g, 80%). Spectroscopy data corresponds to that shown in section *6.3.5.1*.

6.3.12 Reaction of allylbenzene 36

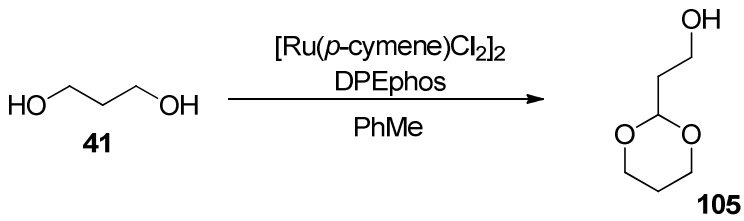
Following procedure ***6.3.6***, using allylbenzene **36** (0.1182 g, 1 mmol, ρ = 0.892 gmL^{-1}, 0.1325 mL, 1 equiv.) *trans*-1-phenyl-1-propene **YY78** was obtained and isolated by column chromatography eluting with petroleum ether (b.p. 40–60 °C)/diethyl ether (4:1) R_f = 0.80, to give a colourless liquid (0.1122 g, 95%).



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 – 7.28 (m, 5H, Ar), 6.33 (dd, 1H, *J* = 1.4, 14.4 Hz, CH), 6.16 (m, 1H, CH), 1.80 (dd, 3H, *J* = 1.5, 6.3 Hz, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 137.9, 131.0, 128.4, 126.7, 125.8, 18.5. ν_{max} /cm^{-1} (neat): 3025, 2962, 2914, 1598, 1578, 1496, 961, 734, 692.
These data were consistent with those reported in the literature.[112]

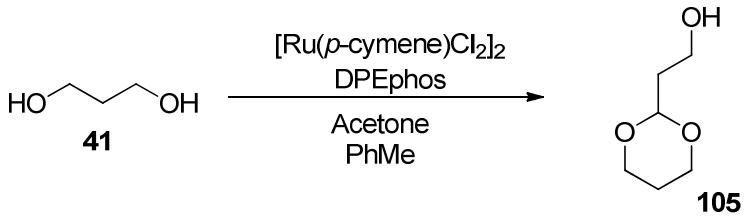
6.4 Experimental Procedures for Chapter 4

6.4.1 Initial reaction of 1,3-propanediol 41

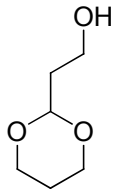


To an oven dried nitrogen purged carousel tube containing [Ru(*p*-cymene)Cl_2]$_2$ (0.0077 g, 0.025 mmol, 0.025 equiv.) and DPEphos (0.0135 g, 0.025 mmol, 0.025 equiv.) were added 1,3-propanediol **41** (0.0761 g, 1 mmol, ρ = 1.053 gmL^{-1}, 0.072 mL, 1 equiv.) and toluene (1 mL). The reaction was then heated to reflux for 24 hours. Once cooled the reaction was concentrated *in vacuo* to give a brown liquid. Conversion (26%) was calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of 1,3-propanediol **41** and 2-(1,3-dioxan-2-yl)ethanol **105**.

6.4.2 Preparation of 2-(1,3-dioxan-2-yl)ethanol 105 via introduction of hydrogen acceptor, acetone

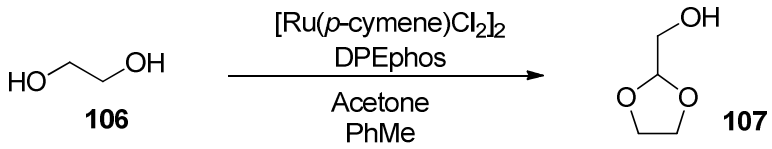


Following procedure ***6.4.1***, adding acetone (0.0291 g, 1 mmol, ρ = 0.079 gmL^{-1}, 0.036 mL, 1 equiv.) at the same time as the solvent, 2-(1,3-dioxan-2-yl)ethanol **105** was produced in a higher conversion, 77%. The title compound was obtained and isolation by column chromatography eluting with dichloromethane/methanol (95:5), R_f = 0.38 to give a green liquid (0.1600 g, 25%).

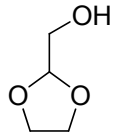


^{1}H NMR (500 MHz, $CDCl_3$): δ 4.77 (t, 1H, *J* = 4.6 Hz, CH), 4.12 (dd, 2H, *J* = 4.9, 10.8 Hz, CH), 3.76 – 3.82 (m, 4H, CH_2/CH), 2.07 – 2.16 (m, 1H, CH), 1.86 – 1.89 (m, 2H, -CH), 1.35 – 1.38 (m, 1H, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 101.9, 66.9, 58.7, 37.0, 25.7. HRMS(ESI-TOF) calcd for $C_6H_{12}O3Na^+$: 155.0684. Found: 155.0687. (MNa^+).
These data were consistent with those reported in the literature.[113]

6.4.3 Reaction of ethylene glycol 106, producing (1,3-dioxolan-2-yl)methanol 107

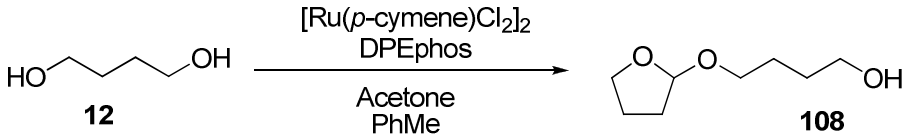


Following procedure ***6.4.1***, using ethylene glycol **106** (0.0621 g, 1 mmol, ρ = 1.113 gmL^{-1}, 0.056 mL, 1 equiv.) and acetone (0.0291 g, 1 mmol, ρ = 0.079 gmL^{-1}, 0.036 mL, 1 equiv.), a conversion of 16% was achieved. The title compound was obtained and isolated by column chromatography eluting with dichloromethane/methanol (92:8), R_f = 0.33 affording a green liquid (trace).



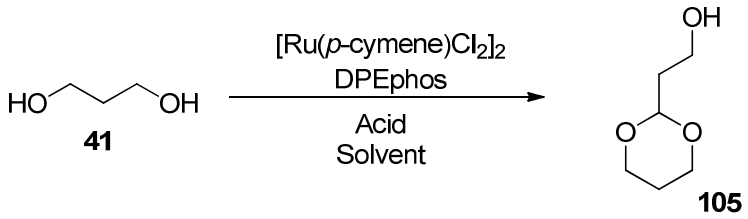
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.01 (t, 1H, *J* = 3.1 Hz, CH), 3.91 – 4.06 (m, 4H, CH_2), 3.69 (d, 2H, *J* = 3.0 Hz, CH_2), 3.57 (br. s, 1H, OH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 103.1, 66.0, 63.0.
These data were consistent with those reported in the literature.[114]

6.4.4 Reaction of 1,4-butanediol 12



Following procedure ***6.4.1***, using 1,4-butanediol **12** (0.0901 g, 1 mmol, ρ = 1.017 gmL^{-1}, 0.089 mL, 1 equiv.) and acetone (0.0291 g, 1 mmol, ρ = 0.079 gmL^{-1}, 0.036 mL, 1 equiv.), a conversion of 55% was achieved. Conversion was calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of 1,4-butanediol **12** and 4-(tetrahydrofuran-2-yloxy)butan-1-ol **108**.

6.4.5 Solvent and acid screen for 1,3-propanediol 41



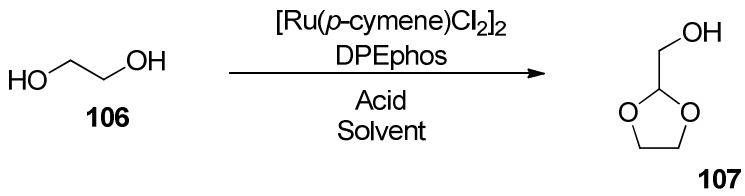
To oven dried nitrogen purged carousel tubes containing [Ru(*p*-cymene)Cl_2]$_2$ (0.0077 g, 0.025 mmol, 0.025 equiv.), DPEphos (0.0135 g, 0.025 mmol, 0.025 equiv.) and acid (0.01 mmol, 0.1 equiv.) were added 1,3-propanediol **41** (0.0761 g, 1 mmol, ρ = 1.053 gmL^{-1}, 0.072 mL, 1 equiv.), acetone (where required) (0.0291 g, 1 mmol, ρ = 0.079 gmL^{-1}, 0.036 mL, 1 equiv.) and solvent (1 mL). The reactions were then heated to reflux for 24 hours. Once cooled the reactions were concentrated *in vacuo* to give brown liquids. Conversions were calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of 1,3-propanediol **41** and 2-(1,3-dioxan-2-yl)ethanol **105** and by analysis of the crude product GC-MS spectrum.

*6.4.5.1 Preparation of 2-(1,3-Dioxan-2-yl)ethanol **105***

Following procedure ***6.4.5*** on a 5 mmol scale, using di-*p*-toluoyl-L-tartaric acid **115** (0.1932 g, 0.01 mmol, 0.1 equiv.) and chlorobenzene (5 mL), the title compound was obtained and isolated by column chromatography eluting with

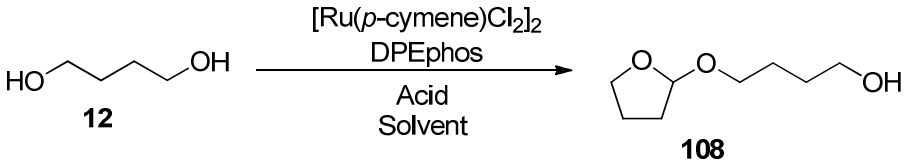
dichloromethane/methanol (95:5), R_f = 0.38 to give a green liquid (0.6608 g, 57%). Spectroscopy data corresponds to that reported in procedure **6.4.2**.

6.4.6 Solvent and acid screen for ethylene glycol 106



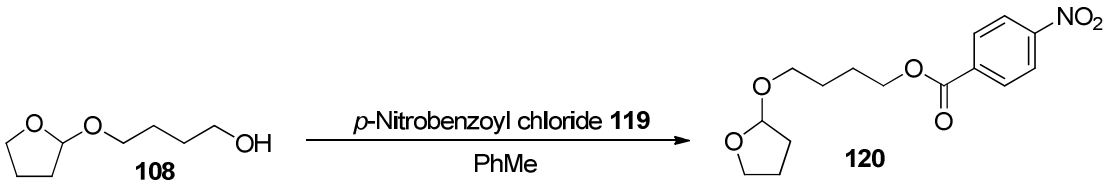
Following procedure **6.4.5**, using ethylene glycol **106** (0.0621 g, 1 mmol, ρ = 1.113 gmL^{-1}, 0.056 mL, 1 equiv.), the conversions were calculated by analysis of the crude product ^1H NMR spectrum using the characteristic peaks of ethylene glycol **106** and (1,3-dioxolan-2-yl)methanol **107** and by analysis of the crude product GC-MS spectrum.

6.4.7 Solvent and acid screen for 1,4-butanediol 12



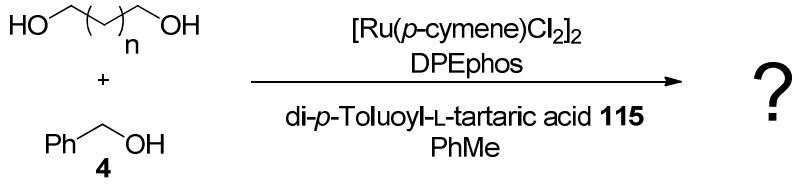
Following procedure **6.4.5**, using 1,4-butanediol **12** (0.0901 g, 1 mmol, ρ = 1.017 gmL^{-1}, 0.089 mL, 1 equiv.), the conversions were calculated by analysis of the crude product ^1H NMR spectrum using the characteristic peaks of 1,4-butanediol **12** and 4-(tetrahydrofuran-2-yloxy)butan-1-ol **108** and by analysis of the crude product GC-MS spectrum.

6.4.8 Formation of p-nitrobenzoate ester



To an oven dried, nitrogen purged 10 mL round bottomed flask containing p-nitrobenzoyl chloride **119** (0.1856 g, 1.5 mmol, 1.5 equiv.) was added toluene (1 mL) and the mixture was stirred in an ice bath to reach 0 °C. The crude reaction mixture containing 4-(tetrahydrofuran-2-yloxy)butan-1-ol **108** and unreacted 1,4-butanediol **12** was dissolved in toluene (1 mL) and added slowly to the cold solution. The reaction was stirred at 0 °C for 15 minutes before being heated to reflux for 30 minutes. The reaction was then cooled and concentrated *in vacuo*. The crude reaction mixture was analysed by ^{1}H NMR, and conversion was deemed to be quantitative. All attempts to separate the products were unsuccessful.

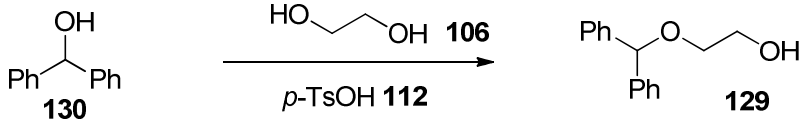
6.4.9 Reaction of diols with benzyl alcohol 4



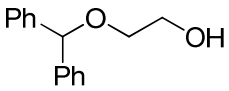
To oven dried nitrogen purged carousel tubes containing [Ru(*p*-cymene)Cl_2]$_2$ (0.0077 g, 0.025 mmol, 0.025 equiv.), DPEphos (0.0135 g, 0.025 mmol, 0.025 equiv.) and di-*p*-toluoyl-L-tartaric acid **115** (0.1932 g, 0.01 mmol, 0.1 equiv.) was added the diol (1 mmol, 1 equiv.) and toluene (1 mL). The reactions were heated to reflux for 24 hours. Once cooled the reactions were concentrated *in vacuo* to give brown liquids. Conversions were calculated by analysis of the crude product ^{1}H NMR spectrum using the characteristic peaks of the diols and the representative products (see Chapter 4, Table 4.4).

6.5 Experimental Procedures for Chapter 5

6.5.1 Preparation of 2-benzhydryloxyethanol 129[82]

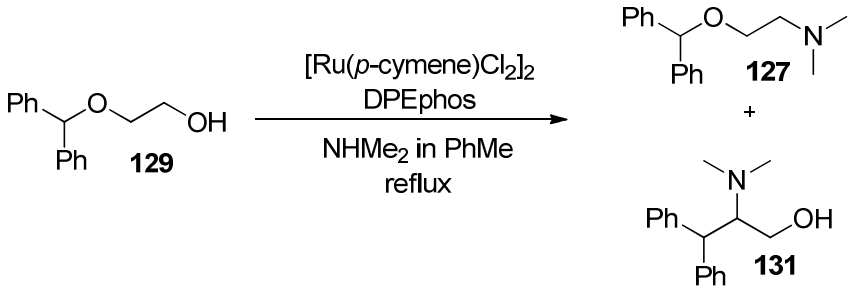


To a 250 mL round bottomed flask containing benzhydrol **130** (11.0400 g, 60 mmol, 1 equiv.) and *para*-toluene sulphonic acid **112** (0.0900 g, 0.48 mmol, 0.008 equiv.) was added ethylene glycol **106** (133.5600 g, 2.2 mol, ρ = 1.113 gmL^{-1}, 120 mL, 36.7 equiv.). The reaction was heated to 130 ºC for 3 hours. Once the reaction had cooled, it was added to water (600 mL) containing sodium hydroxide (2 M) (30 mL). This was then extracted with diethyl ether (2 x 150 mL). The combined organic extracts were then washed with water (2 x 150 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to approximately 60 mL. Petroleum ether was then added to crystallise the product. The product was recrystallised by dissolving in hot diethyl ether and layering with petroleum ether whilst cooling. The supernatant liquid was decanted and the crystals titurated with petroleum ether to give the product as colourless blocks (6.948 g, 55%).

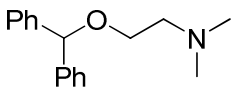


^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 – 7.36 (m, 10H, Ar), 5.41 (s, 1H, CH), 3.79 (m, 2H, CH_2), 3.60 (t, 2H, *J* = 4.6 Hz, CH_2), 2.00 (t, 1H, *J* = 6.3 Hz, OH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 141.9, 128.5, 127.6, 127.0, 84.1, 70.4, 62.1. HRMS(ESI-TOF) calcd for $C_{15}H_{16}O_2H^+$: 229.29. Found: 229.12. (MH^+). These data were consistent with those reported in the literature.[82]

6.5.2 Preparation of diphenhydramine 127 and 2-(dimethylamino)-3,3-diphenylpropan-1-ol 131

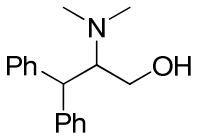


To an oven-dried, nitrogen-purged Schlenk tube containing [Ru(*p*-cymene)Cl_2]$_2$ (7.7 mg, 0.0125 mmol) and DPEphos (13.5 mg, 0.025 mmol) was added 2-benzhydroloxyethanol **129** (1.14 g, 5 mmol), followed by a 1.5 M Me_2NH solution in toluene (1 mL). The reaction mixture was then heated to reflux for 24 h. On completion the reaction was allowed to cool to room temperature, diluted with dichloromethane, and the solvent was removed *in vacuo.* The title compounds were obtained in 11% and 74% conversion respectively. The title compounds were obtained and purified by column chromatography. Diphenhydramine **127** was obtained first eluting with dichloromethane/methanol (9:1), R_f = 0.28 to give a brown liquid (0.10 g, 10%). 2-(Dimethylamino)-3,3-diphenylpropan-1-ol **131** was obtained second eluting with dichloromethane/methanol (93:7), R_f = 0.30 to give a sticky brown liquid which solidified on standing (0.66 g, 67%).



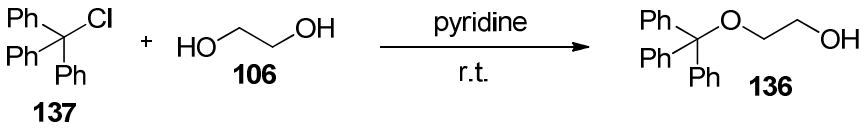
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.97 – 7.14 (m, 10H, Ph), 5.10 (s, 1H, CH), 3.40 (t, 2H, *J* = 5.6 Hz, CH_2), 2.56 (t, 2H, *J* = 5.6 Hz, CH_2), 2.19 (s, 6H, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 142.3, 129.1, 128.8, 128.6, 127.8, 127.7, 127.3, 84.6, 66.7, 58.5, 45.4. HRMS(ESI-TOF) calcd for $C_{17}H_{20}NOH^+$: 256.1700. Found: 256.1701. (MH^+).

These data were consistent with those reported in the literature.[115]

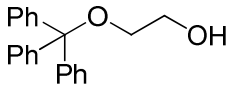


m.p. 53 – 55 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 – 7.47 (m, 10H, Ph), 3.98 (d, 1H, *J* = 11.1 Hz, CH), 3.70 (dt, 1H, *J* = 4.9, 10.6 Hz, CH), 3.27 (dd, 1H, *J* = 5.2, 10.8 Hz, CH), 3.12 (app. t, 1H, *J* = 10.5 Hz, CH), 2.26 (s, 6H, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 142.5 (C, Ph), 129.2 (CH, Ph), 129.0 (CH, Ph), 128.8 (CH, Ph), 128.2 (CH, Ph), 127.1 (CH, Ph), 67.6 (CH, -*C*HNMe$_2$), 60.8 (CH_2, -*C*H$_2$OH), 52.5 (CH, (Ph)$_2$*C*H-), 41.2 (CH_3, -N(*C*H$_3$)$_3$). HRMS(ESI-TOF) calcd for $C_{17}H_{20}NOH^+$: 256.1701. Found: 256.1686. (MH^+). (For crystallographic data, see Appendix B.)

6.5.3 Preparation of 2-(trityloxy)ethanol 136[83]

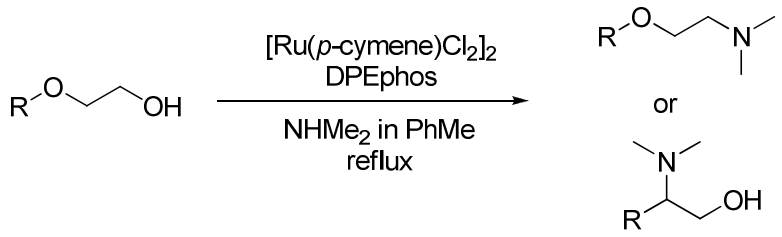


To a round bottomed flask containing trityl chloride **137** (16.7 g, 60 mmol) were added ethylene glycol **106** (5.0 mL, 90 mmol) and pyridine (240 mL). The reaction was stirred at room temperature for 24 hours. Toluene was then added and the pyridine was removed (*via* azeotroping) *in vacuo*. This process (of adding toluene and concentrating *in vacuo*) was repeated several times in order to remove the pyridine. The azeotrope process was then repeated but using ethyl acetate and dichloromethane to remove any residual solvent. From these processes a white solid was obtained. The title compound was obtained and purified by column chromatography. A gradient eluent system was employed. The column was first subjected to neat *iso*-hexane (500 mL) in order to remove any residual pyridine. Then 95:5 *iso*-hexane/ethyl acetate (500 mL) was used, followed by 85:15 *iso*-hexane/ethyl acetate (500 mL) to obtain the title compound as a white solid, R_f = 0.15, (5.02 g, 24%).



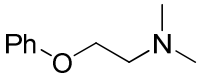
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 – 7.47 (m, 15H, Ar), 3.74 – 3.78 (m, 2H, CH_2), 3.28 (t, 2H, *J* = 4.7 Hz, CH_2), 1.94 (t, 1H, *J* = 6.3 Hz, OH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 144.0, 128.7, 128.0, 127.9, 127.1, 86.7, 64.9, 62.4. HRMS(ESI-TOF) calcd for $(C_{19}H_{15})^+$: 243.1200. Found: 243.1200. [$(Ph_3C)^+$]. These data were consistent with those reported in the literature[83].

6.5.4 Reaction of different substrates



*6.5.4.1 Preparation of N,N-dimethyl-2-phenoxyethanamine **138**[†]*

Following procedure **6.5.3**, using 2-phenoxyethanol **134** (0.1382 g, 1 mmol, ρ = 1.105 gmL^{-1}, 0.1254 mL, 1 equiv.) using 5 mol% Ru, the title compound was obtained and isolated by column chromatography eluting with dichloromethane/methanol (9:1), R_f = 0.27 to give a brown oil (0.13 g, 77%).



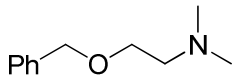
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.32 (m, 2H, Ph), 6.92-6.98 (m, 3H, Ph), 4.09 (t, 2H, *J* = 5.7 Hz, CH_2), 2.77 (t, 2H, *J* = 5.7 Hz, CH_2), 2.37 (s, 6H, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 158.7, 129.4, 120.8, 114.5, 65.7, 58.3, 45.8. HRMS(ESI-TOF) calcd for $C_{10}H_{15}NOH^+$: 166.1231. Found: 166.1226. (MH^+). These data were consistent with those reported in the literature.[116]

*6.5.4.2 Preparation of 2-(benzyloxy)-N,N-dimethylethanamine **139***

Following procedure **6.5.3**, using 2-(benzyloxy)ethanol **135** (0.1522 g, 1 mmol, ρ = 1.071 gmL^{-1}, 0.1421 mL, 1 equiv.) using 5 mol % Ru, the title compound

[†] This work was carried out by Haniti Hamid.

was obtained and isolated by column chromatography eluting with dichloromethane/methanol (9:1), R_f = 0.48 to give a brown liquid (0.05 g, 29%).

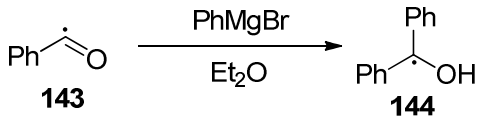


^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 – 7.36 (m, 5H, Ph), 4.55 (s, 2H, CH_2), 3.57 (t, 2H, *J* = 5.9 Hz, CH_2), 2.56 (t, 2H, *J* = 5.9 Hz, CH_2), 2.29 (s, 6H, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 138.3, 128.3, 127.7, 127.6, 73.2, 68.0, 58.8, 45.8. HRMS(ESI-TOF) calcd for $C_{11}H_{17}NOH^+$: 180.1383. Found: 180.1389. (MH^+). These data were consistent with those reported in the literature.[117]

*6.5.4.3 Reaction of 2-(trityloxy)ethanol **136***

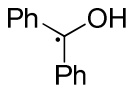
Following procedure **6.5.3**, using 2-(trityloxy)ethanol **136** (0.3042 g, 1 mmol, 1 equiv.), triphenylmethane **140** was obtained in 76% conversion. Conversion was calculated from analysis of the crude product ^{1}H NMR spectrum using the characteristic signals of 2-(trityloxy)ethanol **136** and triphenylmethane **140**. The compound was not isolated.

6.5.5 Preparation of ^{13}C-labelled benzhydrol 144



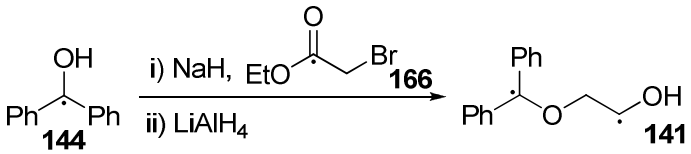
To an oven dried, argon purged tube containing benzaldehyde-α-^{13}C **143** (0.25 g, 2.33 mmol) and diethyl ether (4 mL) at 0 °C, was added phenylmagnesium bromide (3.0 M solution in diethyl ether) (1.17 mL, 3.50 mmol) dropwise over 20 minutes. The reaction was then allowed to warm to room temperature and left to stir overnight. Saturated aqueous NH_4Cl (10 mL) was then added slowly and stirred until the fizzing subsided. Diethyl ether (10 mL) was then added and the layers were separated. The aqueous layer was extracted with diethyl ether (2 x 20 mL) and then the combined organic extracts were washed with water (20 mL) and brine (20 mL), then dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a pale yellow

liquid which solidified on standing. The compound was isolated in quantitative yield and required no further purification before being used in the next step.



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 – 7.42 (m, 10H, Ph), 5.86 (dd, 1H, *J* = 3.5, 143.9, CH), 2.25 (t, 1H, *J* = 2.4, OH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 143.8 (d, *J* = 47.3 Hz), 128.5 (d, *J* = 3.8 Hz), 127.6, 126.5 (d, *J* = 2.9 Hz), 76.3.

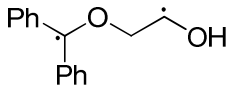
6.5.6 Preparation of doubly ^{13}C labelled 2-(benzhydryloxy)ethanol 141



To an oven-dried, argon purged tube containing sodium hydride (95% dry) (0.06 g, 2.45 mmol) in diethyl ether (10 mL) at 0 °C was added ^{13}C-labelled benzhydrol **144** (0.43 g, 2.33 mmol) in diethyl ether (10 mL) dropwise over 30 minutes. The reaction was then warmed to 30 °C and stirred for 2 hours. After this time, the reaction was cooled to 0 °C and ethyl bromoacetate-1-^{13}C **166** (0.39 g, 2.33 mmol) in diethyl ether (5 mL) was added dropwise over 20 – 25 minutes. The reaction was then warmed to room temperature and left to stir overnight. Water (20 mL) was added slowly until any observed fizzed had stopped. Diethyl ether (20 mL) was added and the layers separated. The aqueous layer was extracted with diethyl ether (2 x 20 mL) and then the combined organic layers were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a pale yellow liquid. By analysis of ^{1}H NMR, the conversion of the reaction was seen to be 47%. The crude reaction mixture was used directly in the next step.

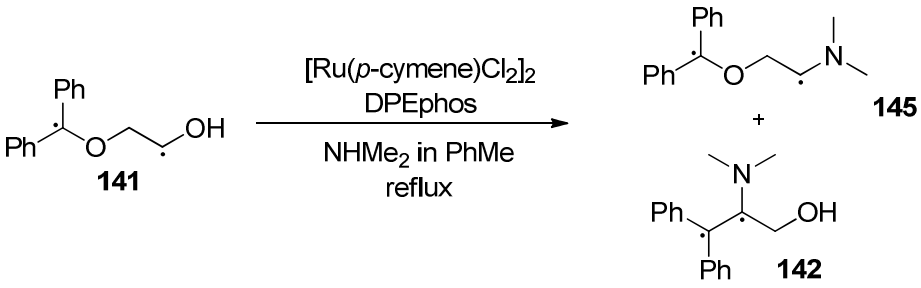
To an oven dried, argon purged tube containing lithium aluminium hydride (0.15 g, 4.00 mmol) in diethyl ether (5 mL) at 0 °C was added the crude reaction mixture in diethyl ether (5 mL) dropwise over 20 minutes. The reaction was then warmed to room temperature for 2 hours. After this time, diethyl ether (10 mL) was added and the reaction was cooled to 0 °C. Water

(0.2 mL) was then added slowly until any observed fizzing had stopped, followed by 15% aqueous NaOH solution (0.2 mL) and water (0.6 mL). A white precipitate was observed on the addition of NaOH. The reaction was warmed to room temperature and stirred for 15 minutes. $MgSO_4$ was added and the reaction was left to stir overnight. The white solids were filtered off and washed through with diethyl ether, then concentrated *in vacuo*. The desired product was isolated and purified by column chromatography eluting with ether (b.p. 40-60 ºC)/ethyl acetate (5:1), R_f = 0.09 to give a colourless liquid which solidified on standing (0.22 g, 42%).



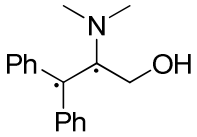
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 – 7.35 (m, 10H, Ph), 5.42 (d, 1H, *J* = 141.5 Hz, CH), 3.80 (dm, 2H, *J* = 141.5 Hz, CH_2), 3.62 (m, 2H, CH_2), 2.01 (dt, 1H, *J* = 3.3, 6.0 Hz, OH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 128.5 (d, *J* = 3.5 Hz), 127.6, 126.9 (d, *J* = 2.6 Hz), 84.1 (d, *J* = 3.6 Hz), 62.1 (d, *J* = 3.7 Hz), 61.5.

6.5.7 Reaction of doubly ^{13}C labelled 2-(benzhydryloxy)ethanol 141



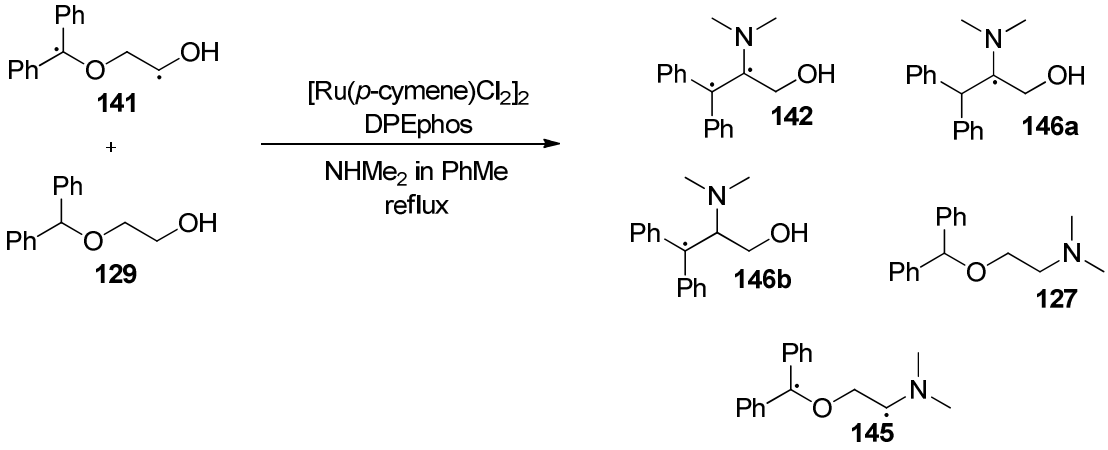
To an oven-dried, nitrogen purged Schlenk carousel tube containing [Ru(*p*-cymene)Cl_2]$_2$ (3.3 mg, 0.025 mmol) and DPEphos (5.9 mg, 0.025 mmol) was added doubly labelled ^{13}C 2-benzhydryloxyethanol **141** (0.1 g, 0.43 mmol) in toluene (0.5 mL) and 3.0 M Me_2NH solution in toluene (0.25 mL). The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 10 minutes and then heated to reflux for 24 hours. On completion the reaction was allowed to cool to room temperature, diluted with dichloromethane, and the solvent removed *in vacuo.* By analysis of the ^{1}H NMR, 79% conversion of the doubly labelled ^{13}C 2-benzhydryloxyethanol **141**

was seen. Of this 79%, 7% was the doubly labelled ^{13}C addition product **145** and 72% was the doubly labelled ^{13}C rearranged product **142**. The doubly labelled ^{13}C rearranged product **142** was obtained and purified by column chromatography eluting with dichloromethane/methanol (9:1), R_f = 0.12, to give a brown solid (3.10 mg, 3%).



^1H NMR (300 MHz, $CDCl_3$): δ 7.12 – 7.47 (m, 10H, Ar), 3.96 (ddd, 1H, *J* = 5.8, 11.1, 126.6, ^{13}CH), 3.69 (dm, 1H, *J* = 135.0 Hz, ^{13}CH), 3.25 (dd, 1H, *J* = 5.4, 10.8 Hz, CH), 3.11 (tdd, 1H, *J* = 1.1, 1.8, 10.4 Hz, CH), 2.25 (d, 6H, *J* = 3.3 Hz, CH_3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 128.8, 127.7, 126.7, 67.2 (d, *J* = 34.7 Hz), 60.4, 52.1 (d, *J* = 34.7 Hz), 41.1.

6.5.8 Crossover Reaction



To an oven-dried, nitrogen purged Schlenk carousel tube containing [Ru(*p*-cymene)Cl_2]$_2$ (6.7 mg, 0.025 mmol), DPEphos (11.7 mg, 0.025 mmol) and non-labelled 2-benzhydryloxyethanol **129** (0.1 g, 0.43 mmol) were added doubly ^{13}C-labelled 2-benzhydryloxyethanol **141** (0.1 g, 0.43 mmol) in toluene (0.5 mL) and 3.0 M Me_2NH solution in toluene (0.45 mL). The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 10 minutes and then heated to reflux for 24 h. On completion the reaction was allowed to cool to room temperature, diluted with dichloromethane, and the

solvent removed *in vacuo.* By analysis and comparison of the ^{1}H and ^{13}C spectra, the amount of crossover was calculated to be 18%. The products were not isolated.

CHAPTER 7 - REFERENCES

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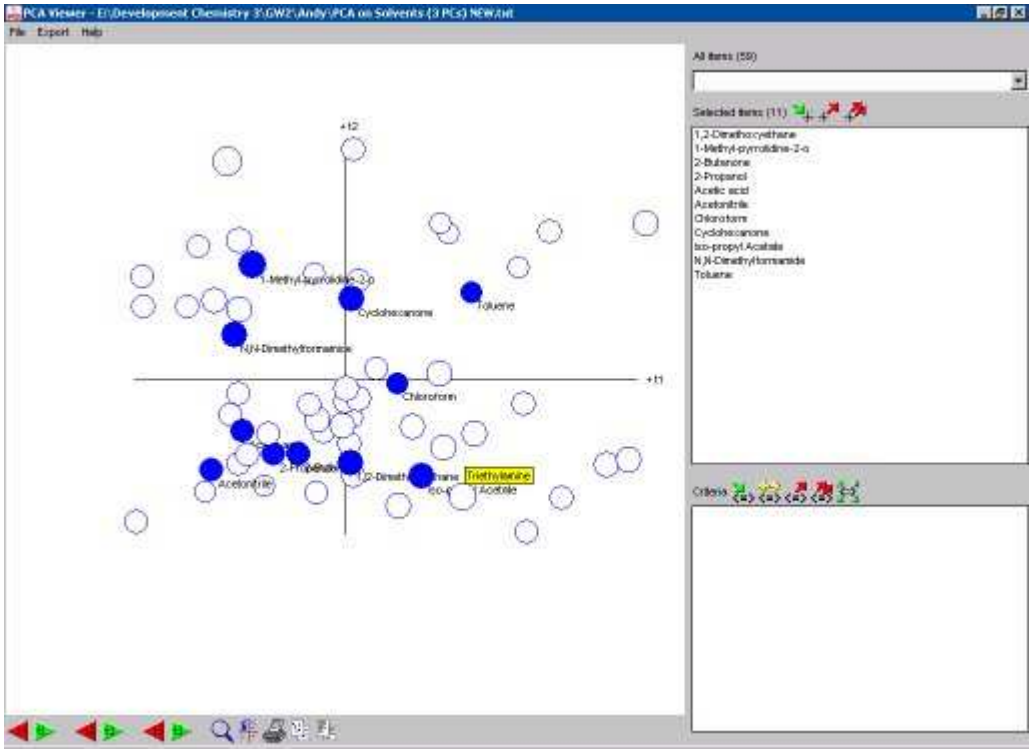
APPENDIX

Appendix A

Principal Component Analysis PCA/Partial Least Squares PLS

PCA is used as a means for selecting reagents for screening studies. A given class of compounds e.g. solvents, can be described by a range of chemical descriptors such as melting point, dipole moment, refractive index, etc… Wide ranges of such descriptors are collected for each compound in a class and compiled in data tables. PCA is used to determine patterns in this data and subsequently reduces the properties down into a series of vectors or principal components. By reducing the output down to three vectors (t1, t2, t3) the positions of the compounds may be visualised in three-dimensional space. An example of a PCA model showing the positions of several solvents is shown in figure 12 below.

Solvents that are expected to behave similarly are close in space (e.g. DMF and NMP below), whereas solvents that are expected to behave entirely differently are diametrically opposed (e.g. cis-decalin and water). When choosing a group of compounds for an initial screen it is common to choose at least one from each octant and also a few compounds at the centre of the model. Choosing solvents or reagents in this way ensures a good spread over the model and reduces the chances of missing the optimum type of reagent. If a solvent or reagent proves to be particularly successful then more are investigated from the same region.



Screen shot of a PCA solvent model

Partial Least Squares (PLS) is a multivariate technique for relating input variables e.g. solvent properties, to a response e.g. yield. PLS is able to model variables taking on any value and so is less reliant on a symmetrical design, unlike Design of Experiments (DoE). The input factors for a PLS model may be the actual values from principal components (PC's) to generate a predictive model linking solvent or reagent properties to a response.

Like DoE it is possible to perform a small number of experiments (e.g. using different combinations of solvents and bases) and use the model to predict responses for the untested combinations. A set of combinations predicted to give desirable results may then be tested to investigate the accuracy of the predictions.

Solvent/Acid Screen

A matrix of 20 solvent/acid combinations was constructed from GSK solvent and acid PCA models. The aim of the study was to ensure diversity of

reaction conditions by selecting both solvents and acids from across the whole PCA space.

Solvent	Base
DMSO	(1S)-(+)-10-Camphor-10-sulphonic
Cyclopentyl methyl ether	D Tartaric
3-Pentanone	Acetic
1,2-Dichlorobenzene	p-Toluenesulphonic acid
cyclohexanone	4-Nitrobenzoic
NMP	Trifluoromethanesulphonic
1,2-Dichlorobenzene	di-p-Toluoyl L tartaric
cyclohexanone	2-Hydroxyphenylacetic
Methyl cyclohexane	Triphenylacetic
n-Propyl acetate	p-Toluenesulphonic acid
Xylene	Acetic
Cyclopentyl methyl ether	(1S)-(+)-10-Camphor-10-sulphonic
DMSO	D Tartaric
1,4-Dioxane	4-Nitrobenzoic
Xylene	2,5-Dichlorobenzoic
NMP	Triphenylacetic
n-Propyl acetate	di-p-Toluoyl L tartaric
3-Pentanone	2,5-Dichlorobenzoic
Methyl cyclohexane	Trifluoromethanesulphonic
1,4-Dioxane	2-Hydroxyphenylacetic

SIMCA PLS Analysis

SIMCA software was used to perform PLS analysis on the data generated from the solvent/acid reaction screen. The response, product at 18hrs, was modelled. The analysis indicated the following

Yield range 0 to 87%

$R^2 = 0.74$, $Q^2 = 0.45$

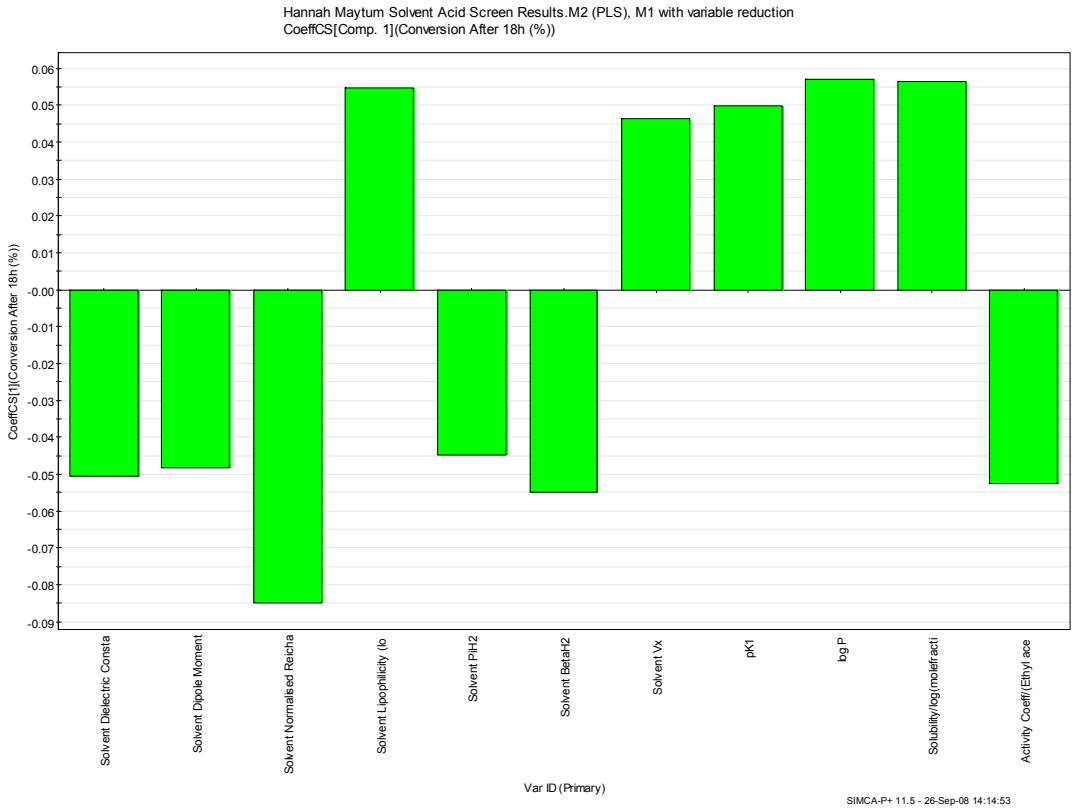
R^2 is a measure of how much the solvent and acid properties can explain the variation in the yield, in this case 74%. Q^2 is a measure of how good the model is at predicting results. In an ideal model both R^2 and Q^2 would equal 1.0, but anything above 0.6 is considered very good. The value of 0.45 for Q^2 is not ideal but a general guideline is as follows:

- Q2 < 0.3 - 0.4: Model bad, use predictions only if in agreement with chemistry knowledge
- 0.4 < Q2 < 0.6: OK
- Q2 > 0.6: Very good

Coefficients Plot

The coefficients plot indicates which solvent and/or acid properties are influencing yield and which direction. The plot below illustrates this, green bars above the line are positively correlated with product and those below are negatively correlated. Thus to obtain high conversion in this reaction we require

- solvents of low dipole moment, dielectric constant, Normalised Reichardt-Dimroth Parameter, PiH2 and beta H2
- solvents of high lipophilicity and Vx
- acids of high pKa, log P, and Solubility/log(molefraction) (Ethyl acetate)
- acids of low Activity Coeff/(Ethyl acetate)



Normalised Reichardt-Dimroth Parameter - A measure of the ionizing power (loosely polarity) of a solvent, based on the maximum wavenumber of the longest wavelength electronic absorption band of Reichardt's dye (2,6-diphenyl-4-(2,4,6-triphenyl-1-pyridinio)phenolate) in a given solvent.

Solvent PiH2 - Polarity/polarizability parameter PiH2, the ability of a solute to stabilise a neighbouring dipole by virtue of its capcity for orientation and induction interactions. Represents solute dipolarity/polarisability due to solute-solvent interactions between bond dipoles and induced dipoles

Solvent BetaH2 - H-Bonding basicity parameter BetaH2, relates to the strength and number of H-bonds formed by the lone pairs in the solute when they interact with donor solvents

Solvent Vx - The McGowan volume

Appendix B

Crystallographic Data for 131

Table 1. Crystal data and structure refinement for 1.

Identification code	k08jmjw7
Empirical formula	C17 H21 N O
Formula weight	255.35
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21/c
Unit cell dimensions	a = 12.0500(4)Å □ = 90°
	b = 8.8860(4)Å □ = 91.914(2)°
	c = 13.4890(5)Å □ = 90°
Volume	1443.55(10) Å^3
Z	4
Density (calculated)	1.175 Mg/m^3
Absorption coefficient	0.072 mm^{-1}
F(000)	552
Crystal size	0.40 x 0.40 x 0.05 mm
Theta range for data collection	3.79 to 25.03°
Index ranges	-14<=h<=14; -10<=k<=10; -16<=l<=16
Reflections collected	23394
Independent reflections	2545 [R(int) = 0.0949]
Reflections observed (>2□)	1743
Data Completeness	0.996
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00 and 0.71
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2545 / 1 / 179
Goodness-of-fit on F^2	1.044
Final R indices [I>2□(I)]	R1 = 0.0993 wR2 = 0.2733
R indices (all data)	R1 = 0.1332 wR2 = 0.3047
Largest diff. peak and hole	0.808 and -0.275 eÅ^{-3}

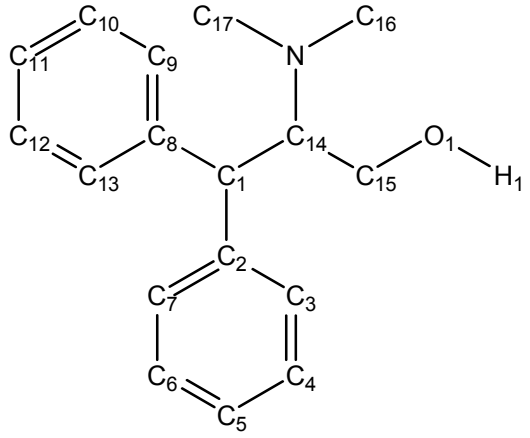
Notes: Crystals presented as very thin plates. Data truncated to 25° to account for fall off in diffracting ability.

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
O1-H1	0.900	2.054	123.46	2.659	N1
O1-H1	0.900	2.239	127.13	2.874	O1 [-x+1, -y, -z+1]

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1.U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
O(1)	4307(3)	1180(4)	5363(3)	78(1)
N(1)	3704(3)	1126(5)	3450(3)	64(1)
C(1)	2754(3)	3681(5)	3524(3)	54(1)
C(2)	1805(3)	3436(5)	2728(3)	49(1)
C(3)	1889(4)	4166(5)	1820(3)	54(1)
C(4)	1043(4)	4087(5)	1108(3)	63(1)
C(5)	97(4)	3244(6)	1283(4)	65(1)
C(6)	22(4)	2498(6)	2170(4)	63(1)
C(7)	867(4)	2608(6)	2882(3)	60(1)
C(8)	2449(3)	4855(5)	4259(3)	49(1)
C(9)	3036(4)	6223(6)	4346(4)	71(1)
C(10)	2789(5)	7274(5)	5083(4)	70(1)
C(11)	1986(4)	6988(6)	5721(4)	66(1)
C(12)	1378(4)	5685(5)	5657(3)	56(1)
C(13)	1612(3)	4639(5)	4938(3)	51(1)
C(14)	3135(3)	2214(5)	4045(3)	56(1)
C(15)	3908(4)	2509(6)	4987(3)	63(1)
C(16)	4640(4)	1704(7)	2907(4)	76(2)
C(17)	3023(5)	163(7)	2846(4)	82(2)



Hydrogens are omitted for clarity.
Hydrogens are numbered with respect to the carbon they are attached to. For example, C_{15} is bonded to H_{15a} and H_{15b}.

Table 3. Bond lengths [Å] and angles [°] for 1.

O(1)-C(15)	1.367(6)	O(1)-H(1)	0.9001(10)
N(1)-C(17)	1.423(6)	N(1)-C(14)	1.445(6)
N(1)-C(16)	1.459(6)	C(1)-C(8)	1.494(6)
C(1)-C(14)	1.543(6)	C(1)-C(2)	1.558(6)
C(1)-H(1A)	1.0000	C(2)-C(7)	1.370(6)
C(2)-C(3)	1.393(6)	C(3)-C(4)	1.378(6)
C(3)-H(3)	0.9500	C(4)-C(5)	1.392(7)
C(4)-H(4)	0.9500	C(5)-C(6)	1.373(7)
C(5)-H(5)	0.9500	C(6)-C(7)	1.381(7)
C(6)-H(6)	0.9500	C(7)-H(7)	0.9500
C(8)-C(13)	1.398(6)	C(8)-C(9)	1.409(6)
C(9)-C(10)	1.403(8)	C(9)-H(9)	0.9500
C(10)-C(11)	1.341(7)	C(10)-H(10)	0.9500
C(11)-C(12)	1.371(7)	C(11)-H(11)	0.9500
C(12)-C(13)	1.379(6)	C(12)-H(12)	0.9500
C(13)-H(13)	0.9500	C(14)-C(15)	1.573(6)
C(14)-H(14)	1.0000	C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900	C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800	C(16)-H(16C)	0.9800
C(17)-H(17A)	0.9800	C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800		
C(15)-O(1)-H(1)	102(4)	C(17)-N(1)-C(14)	116.4(4)
C(17)-N(1)-C(16)	111.4(4)	C(14)-N(1)-C(16)	115.6(4)
C(8)-C(1)-C(14)	111.4(3)	C(8)-C(1)-C(2)	111.3(3)
C(14)-C(1)-C(2)	113.3(4)	C(8)-C(1)-H(1A)	106.8
C(14)-C(1)-H(1A)	106.8	C(2)-C(1)-H(1A)	106.8
C(7)-C(2)-C(3)	117.9(4)	C(7)-C(2)-C(1)	124.1(4)
C(3)-C(2)-C(1)	117.9(4)	C(4)-C(3)-C(2)	121.0(4)
C(4)-C(3)-H(3)	119.5	C(2)-C(3)-H(3)	119.5
C(3)-C(4)-C(5)	120.0(4)	C(3)-C(4)-H(4)	120.0
C(5)-C(4)-H(4)	120.0	C(6)-C(5)-C(4)	119.1(4)
C(6)-C(5)-H(5)	120.5	C(4)-C(5)-H(5)	120.5
C(5)-C(6)-C(7)	120.2(5)	C(5)-C(6)-H(6)	119.9
C(7)-C(6)-H(6)	119.9	C(2)-C(7)-C(6)	121.7(4)
C(2)-C(7)-H(7)	119.1	C(6)-C(7)-H(7)	119.1
C(13)-C(8)-C(9)	115.8(4)	C(13)-C(8)-C(1)	122.5(4)
C(9)-C(8)-C(1)	121.6(4)	C(10)-C(9)-C(8)	121.1(5)
C(10)-C(9)-H(9)	119.5	C(8)-C(9)-H(9)	119.5
C(11)-C(10)-C(9)	120.2(5)	C(11)-C(10)-H(10)	119.9
C(9)-C(10)-H(10)	119.9	C(10)-C(11)-C(12)	121.0(5)
C(10)-C(11)-H(11)	119.5	C(12)-C(11)-H(11)	119.5
C(11)-C(12)-C(13)	119.5(4)	C(11)-C(12)-H(12)	120.3
C(13)-C(12)-H(12)	120.3	C(12)-C(13)-C(8)	122.5(4)
C(12)-C(13)-H(13)	118.8	C(8)-C(13)-H(13)	118.8
N(1)-C(14)-C(1)	116.9(4)	N(1)-C(14)-C(15)	106.4(3)
C(1)-C(14)-C(15)	112.7(4)	N(1)-C(14)-H(14)	106.8
C(1)-C(14)-H(14)	106.8	C(15)-C(14)-H(14)	106.8
O(1)-C(15)-C(14)	110.3(4)	O(1)-C(15)-H(15A)	109.6

C(14)-C(15)-H(15A)	109.6	O(1)-C(15)-H(15B)	109.6
C(14)-C(15)-H(15B)	109.6	H(15A)-C(15)-H(15B)	108.1
N(1)-C(16)-H(16A)	109.5	N(1)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5	N(1)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5	H(16B)-C(16)-H(16C)	109.5
N(1)-C(17)-H(17A)	109.5	N(1)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5	N(1)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5	H(17B)-C(17)-H(17C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for 1. The anisotropic displacement
factor exponent takes the form: -2 gpi^2 [h^2 a^{*2} U11 + ... + 2 h k a* b* U

Atom	U11	U22	U33	U23	U13	U12
O(1)	83(2)	81(3)	71(2)	-9(2)	-10(2)	25(2)
N(1)	67(2)	63(2)	60(2)	-4(2)	5(2)	-6(2)
C(1)	44(2)	58(3)	59(3)	15(2)	1(2)	0(2)
C(2)	53(2)	46(2)	47(2)	6(2)	8(2)	9(2)
C(3)	69(3)	41(2)	51(2)	3(2)	9(2)	6(2)
C(4)	94(4)	51(3)	45(2)	-3(2)	0(2)	16(3)
C(5)	73(3)	63(3)	59(3)	-27(2)	-14(2)	18(3)
C(6)	59(3)	64(3)	68(3)	-11(2)	10(2)	2(2)
C(7)	58(3)	67(3)	54(3)	8(2)	4(2)	1(2)
C(8)	42(2)	46(2)	56(2)	11(2)	-7(2)	-1(2)
C(9)	54(3)	72(3)	86(4)	25(3)	2(2)	-10(2)
C(10)	87(4)	42(3)	81(4)	-2(2)	-8(3)	-11(2)
C(11)	78(3)	55(3)	65(3)	5(2)	-5(2)	0(2)
C(12)	60(3)	53(3)	55(3)	5(2)	-4(2)	5(2)
C(13)	47(2)	49(2)	55(2)	12(2)	-3(2)	-3(2)
C(14)	48(2)	55(3)	66(3)	4(2)	0(2)	0(2)
C(15)	65(3)	70(3)	52(3)	-3(2)	-2(2)	10(2)
C(16)	70(3)	84(4)	77(3)	0(3)	18(3)	7(3)
C(17)	87(4)	81(4)	78(3)	-34(3)	-13(3)	16(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for 1.

Atom	x	y	z	U(eq)
H(1A)	3408	4076	3168	65
H(3)	2539	4726	1689	64
H(4)	1107	4610	498	76
H(5)	-489	3185	796	78
H(6)	-615	1904	2294	76
H(7)	797	2096	3495	72
H(9)	3608	6436	3899	85
H(10)	3193	8191	5130	84
H(11)	1835	7699	6224	79
H(12)	801	5504	6105	67
H(13)	1188	3738	4903	61
H(14)	2451	1709	4282	68
H(15A)	4536	3161	4806	75
H(15B)	3483	3038	5498	75
H(16A)	5086	861	2673	115
H(16B)	5101	2345	3345	115
H(16C)	4363	2295	2337	115
H(17A)	2787	696	2238	123
H(17B)	2367	-132	3210	123
H(17C)	3444	-738	2673	123
H(1)	4440(50)	650(60)	4810(30)	100(20)

Table 6. Dihedral angles [°] for 1.

Atom1 - Atom2 - Atom3 - Atom4	Dihedral
C(8) - C(1) - C(2) - C(7)	-78.7(5)
C(14) - C(1) - C(2) - C(7)	47.8(6)
C(8) - C(1) - C(2) - C(3)	98.0(4)
C(14) - C(1) - C(2) - C(3)	-135.5(4)
C(7) - C(2) - C(3) - C(4)	1.6(6)
C(1) - C(2) - C(3) - C(4)	-175.3(4)
C(2) - C(3) - C(4) - C(5)	-1.4(6)
C(3) - C(4) - C(5) - C(6)	0.0(6)
C(4) - C(5) - C(6) - C(7)	1.1(7)
C(3) - C(2) - C(7) - C(6)	-0.5(7)
C(1) - C(2) - C(7) - C(6)	176.3(4)
C(5) - C(6) - C(7) - C(2)	-0.9(7)
C(14) - C(1) - C(8) - C(13)	-59.3(5)
C(2) - C(1) - C(8) - C(13)	68.2(5)
C(14) - C(1) - C(8) - C(9)	116.9(4)
C(2) - C(1) - C(8) - C(9)	-115.6(4)
C(13) - C(8) - C(9) - C(10)	0.8(6)
C(1) - C(8) - C(9) - C(10)	-175.7(4)
C(8) - C(9) - C(10) - C(11)	0.1(8)
C(9) - C(10) - C(11) - C(12)	-1.2(8)
C(10) - C(11) - C(12) - C(13)	1.3(7)
C(11) - C(12) - C(13) - C(8)	-0.3(6)
C(9) - C(8) - C(13) - C(12)	-0.7(6)
C(1) - C(8) - C(13) - C(12)	175.8(4)
C(17) - N(1) - C(14) - C(1)	-82.0(5)
C(16) - N(1) - C(14) - C(1)	51.7(5)
C(17) - N(1) - C(14) - C(15)	151.1(4)
C(16) - N(1) - C(14) - C(15)	-75.1(5)
C(8) - C(1) - C(14) - N(1)	-165.4(3)
C(2) - C(1) - C(14) - N(1)	68.2(5)
C(8) - C(1) - C(14) - C(15)	-41.7(5)
C(2) - C(1) - C(14) - C(15)	-168.2(3)
N(1) - C(14) - C(15) - O(1)	-44.9(5)
C(1) - C(14) - C(15) - O(1)	-174.2(4)

Symmetry transformations used to generate equivalent atoms: