Applications of Tethered Asymmetric Hydrogenation Catalysts

By

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Abbreviations

$[M+X]^+$	Mass spectrometry ion adduct
$[\alpha]_D^T$	Specific rotation
3Å MS	3 angstrom molecular sieves
4Å MS	4 angstrom molecular sieves
Å	Angstrom
ACE	Angiotensin converting enzyme
AH	Asymmetric Hydrogenation
API	Active Pharmaceutical Ingredient
Ar	Aromatic Group, generic indicator (NOT argon)
ATH	Asymmetric Transfer Hydrogenation
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
br.	broad peak
CAM	Cerium ammonium molybdate
CAT	Catalyst
CBS	Corey-Bakshi-Shibata
cc-pVTZ	Correlation consistent basis set as described by Dunning.[1]
CH	Catalytic Hydrogenation
CIP	Cahn-Ingold-Prelog
conv	Conversion
Cp*	pentamethylcyclopentadienyl
d	doublet
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DCM	Dichloromethane
dd	doublet of doublets
DFADH	*Pseudomonas fluorescens* Alcohol Dehydrogenase
DFT	Density Functional Theory
DiPAMP	Ethane-1,2-diylbis[(2-methoxyphenyl)phenylphosphine]
DKR	Dynamic Kinetic Resolution
DMAPEN	N1,N1-dimethyl-2-phenylethane-1,2-diamine
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
DPEN	1,2-diphenylethane-1,2-diamine
dq	doublet of quartets
dt	doublet of triplets
ee	Enantiomeric Excess
eq	Equivalent
er	Enantiomeric ratio
ESI	Electrospray Ionisation
Et	Ethyl
EWG	Electron withdrawing group
FA/TEA	Formic Acid/Triethylamine (5:2 azeotrope)
GC	Gas Chromatography
GC	Gas Chromatography
GDH	Glucose Dehydrogenase

HF	Hartree-Fock
HMB	Hexamethylbenzene
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HMQC	Heteronuclear multiple quantum coherence
HPLC	High performance liquid chromatography
HSQC	Heteronuclear single quantum coherence
HWE	Horner-Wadsworth-Emmons
IL	Ionic Liquid
IPA	Isopropanol
Ips	*para*-iodosulfonyl
KIE	Kinetic Isotope Effect
KR	Kinetic Resolution
LCMS	Liquid chromatography-mass spectrometry
maug-	Minimally augmented basis set as described by Truhlar[2]
MCM-41	Mobil Composition of Matter No. 41
Mp	melting point
MPN	N^{th} Order Møller–Plesset perturbation theory
MPV	Meerwein-Ponndorf-Verley
MPW1B95	DFT method as described by Zhao and Truhlar.[3]
MS	Mass Spectrometry
MS	Mass spectrometry
NAD+	Nicotinamide adenine dinucleotide, oxidised form
NMR	Nuclear Magnetic Resonance
NSAID	Non-steroidal anti-inflammatory drug
o-	Ortho-substituted
p-	Para-substituted
PEG	Polyethylene glycol
Pet ether	40-60°C petroleum ether
Ph	phenyl
q	quartet
R	Any hydrocarbon group
R/S	Cahn-Ingold-Prelog notation for enantiomers
RBF	Round bottom flask
ROMP	Ring Opening Metathesis Polymerisation
rt	Room temperature
s	singlet
S/C	Substrate : Catalyst ratio
t	Time
T	Temperature
t	triplet
TBAF	Tetra-n-butylammonium fluoride
*t*Bu	tert-butyl
td	triplet of doublets
TH	Transfer Hydrogenation
THF	Tetrahydrofuran
TLC	Thin layer chromatography

TMS	Trimethylsilyl (group)or Tetramethylsilane (substance)
ToF	Time of flight
TON	Turnover Number
Ts	tosyl
TsDPEN	N-(2-amino-1,2-diphenylethyl)-4-methylbenzenesulfonamide
TsDPEN	N-Tosyl 1,2-Diphenyl-1,2-ethylenediamine
X	Any halide
δ_C	Carbon chemical shift
ΔG	Gibbs free energy change
δ_H	Proton chemical shift
ΔH	Enthalpy change
λ	Wavelength
ν_{max}	maximum intensity infrared absorption

Acknowledgements

Firstly I would like to thank Prof Martin Wills, for the funding and support, many hours of discussion and debate and for giving me the opportunity to undertake this project.

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Finally to my family for supporting me at every step, and to Emma, without whom I probably would have given up a long time ago.

Declaration

The work described in this thesis is solely that of the author unless otherwise specified. The research was carried out at the Department of Chemistry, University of Warwick between October 2013 and March 2017. It has not previously been submitted for a degree.

Some of this work has been published previously in the following scientific journals:

1 R. Soni, T. H. Hall, B. P. Mitchell, M. R. Owen and M. Wills, *J. Org. Chem.*, 2015, **80**, 6784–6793.

2 R. Soni, K. E. Jolley, S. Gosiewska, G. J. Clarkson, Z. Fang, T. H. Hall, B. N. Treloar, R. C. Knighton and M. Wills, *Organometallics*, 2018, **37**, 48–64.

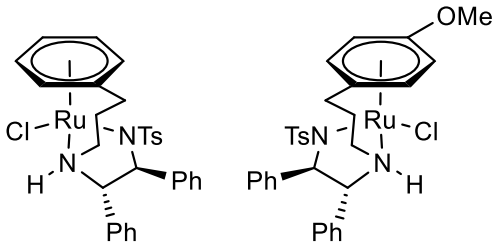
The work presented (including data generated and data analysis) was carried out by the author except in the cases outlined below:

1 Section 2.3.7: Nitrogen Substituted Compounds:
The experimental work was carried out by a MChem student, Ben Mitchell. I contributed practical guidance and supervision in the lab, as well as some analysis of spectra.

Abstract

Attempts have been made to prepare new polymer supported and maleimide functionalised ruthenium catalysts for asymmetric transfer hydrogenation. Synthetic approaches were found to be challenging but did lead to the development of a series of complexes containing the para-Iodobenzenesulfonyl group, which may potentially serve as a handle for future functionalisation.

The arene exchange route to tethered complexes as previously published by Wills et. al. has been refined in an attempt to improve reliability. The practical challenges of carrying out the reaction and especially purifying the resulting complexes are discussed and the use of molecular sieves as a trap for free hydrogen chloride gas is recommended.



Known tethered complexes reported by Wills have been applied to the reduction of electron rich ketones, containing oxygen or nitrogen substituents on their aromatic rings. Such ketones are relatively unreactive and require higher temperatures and extended reaction times, however in most cases the chiral alcohols could still be obtained with good yield and enantioselectivity. The choice of solvent/hydrogen donor is shown to be important and substrate dependant.

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Finally, reduction of β-chloropropiophenone to the dehalogenated chiral alcohol prompted an investigation into the reductions of enones with tethered catalysts. Selectivity between 1,4- and 1,2- reduction products is shown to be strongly substrate dependant but can also be influenced by the choice of catalyst, with the recently developed methoxy tethered catalyst demonstrating an increased preference for 1,4- reduction in all cases.

1 Introduction

1.1 Chirality and Asymmetric Synthesis

A chiral object is one that cannot be superimposed upon its own mirror image, such as a human hand. An achiral object has at least one plane of symmetry such that its mirror images are superimposable. Indeed chiral objects are often referred to as right or left handed to distinguish the otherwise identical mirror images.

The most common form of chirality in organic chemistry is a chiral centre, an atom bound to four different atoms or functional groups. One chiral centre gives rise to two possible mirror-image isomers, known as enantiomers. These may be identified using the Cahn-Ingold-Prelog (CIP) notation which is based on the relative priority of functional groups arranged around the chiral centre, as illustrated in Figure 1.[4,5]

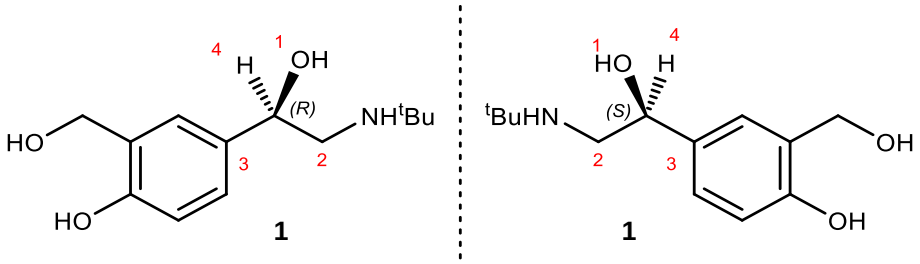
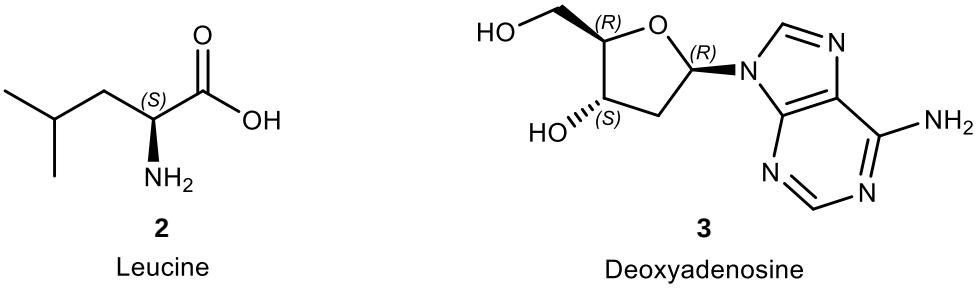


Figure 1: (*R*) and (*S*) enantiomers of salbutamol, a common asthma drug. CIP numbering shown.

1.1.1 Chirality in Nature

Chiral molecules are ubiquitous in nature; proteins, carbohydrates and DNA are all constructed from chiral building blocks such as those shown in Figure 2. Naturally occurring amino acids such as **2** exist in the L-configuration, and this means that the enzymes and receptors they form are all also chiral and of a single handedness in themselves. The chiral 5 membered sugar in nucleosides such as **3** contributes to the highly organised overall structure of DNA.

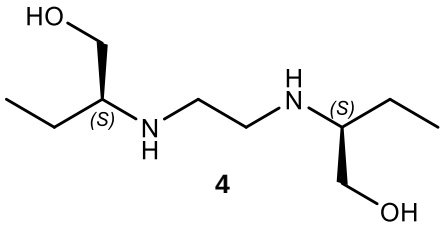


2
Leucine

3
Deoxyadenosine

Figure 2: Chemical structures of chiral natural building blocks L-Leucine and Deoxyadenosine.*

Binding sites in natural macromolecular structures formed from such chiral building blocks will interact optimally only with the correct configuration of substrate, in the same way that a left hand fits well only in a left handed glove. As a result pharmaceutical and agricultural chemicals generally need to be produced as one specific enantiomer. For example, (*S,S*)-ethambutol **4** is an inexpensive drug for tuberculosis included on the World Health Organisation's list of essential medicines, while its enantiomer (*R,R*)-**4** is both 200 times less active and may cause blindness.[6,7]



4

Figure 3: Structure of (*S,S*)-ethambutol

1.1.2 Distinguishing Enantiomers

Enantiomers consist of exactly the same set of atoms with identical connectivity, and as such have identical physical and chemical properties. However they can be distinguished by their interaction with plane polarised light traveling through a solution, which can be measured using a polarimeter. For each pair of enantiomeric molecules, one enantiomer will rotate the plane of polarisation clockwise (+), while the other will rotate the plane by the same amount anticlockwise (-). Equation 1 shows the equation for the calculation of specific rotation.

* D and L-configuration is an antiquated notation still in common use for saccharides and amino acids that refers to a compounds relative stereochemistry compared to L-Glyceraldehyde.[4]

$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{lc}$$

Equation 1: Calculation of specific rotation from measured optical rotation. α = optical rotation, l= path length in dm, c=concentration in g cm^{-3}. T = temperature in °C, λ = wavelength of plane polarised light.

A molecule with n chiral centres may have up to $2^{(n-1)}$ distinguishable pairs of enantiomers, in which the relative configurations of chiral centres differ between each of these pairs. These pairs of stereoisomers are known as diastereomers and owing to their varied structures these may differ in their chemical and physical properties in much the same way as regioisomers.

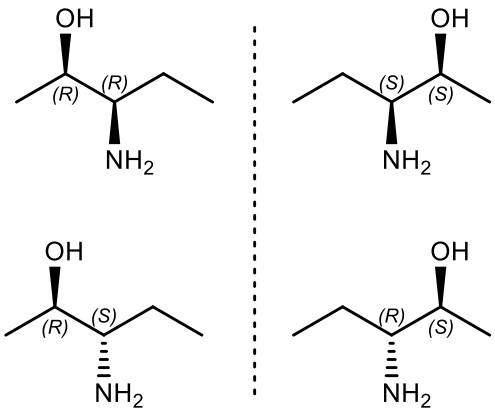
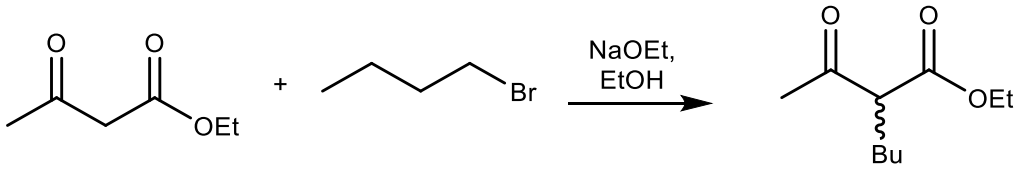


Figure 4: An example set of two diastereomeric pairs of enantiomers.

1.1.3 Mixtures of Enantiomers

While many compounds originating from biological sources are isolated as single enantiomers, it is more common for synthetic production of chemicals to produce a mixture. A racemic mixture contains a 1:1 ratio of enantiomers and induces no optical rotation; effectively the rotation due to each enantiomer is cancelled out by the other. Common reactions such as alkylation or reduction of achiral starting materials, whilst creating new chiral centres, will produce racemic products such as **7** when there is no chiral controlling influence in the reaction (Scheme 1).



5 **6** **7**

Scheme 1: Chemical reactions commonly create a chiral centre but in racemic form

A scalemic mixture is any mixture of enantiomers not in a 1:1 ratio. Most practical syntheses of chiral molecules produce a scalemic mixture rather than a pure enantiomer, and as such the ratio of enantiomers should be measured and reported. Historically this was done by measurement of the optical purity, which is the percentage ratio of specific optical rotation of the scalemic mixture with that of an enantiomerically pure sample. An optical purity of 80% theoretically implies that 20% of the sample is racemic and 80% is a single enantiomer, i.e. there is an 80% enantiomeric excess (ee), or a 9:1 enantiomeric ratio (er). However optical purity is not a reliable measure of ee, as the specific optical rotations measured are highly sensitive to sample purity and often non-linear in their response to changes in concentration.[8] Reference values reported in the literature often vary over a wide range for similar reasons.

$$Optical\ Purity = 100 \times \frac{[\alpha]_{sample}}{[a]_{single\ enantiomer}}$$

Equation 2: Definition of Optical Purity. α = measurement of optical rotation.

In the scientific literature, asymmetric preparations of compounds are often compared by the ee of the products produced. Expressed as a percentage, ee can be calculated from the mole fractions of major and minor enantiomers (Equation 3), which are directly measured by chiral chromatography or other analytical methods.

$$ee = 100\ \times \frac{x_{major} - x_{minor}}{x_{major} + x_{minor}}$$

Equation 3: Calculation of enantiomeric excess from mole fractions of enantiomers.

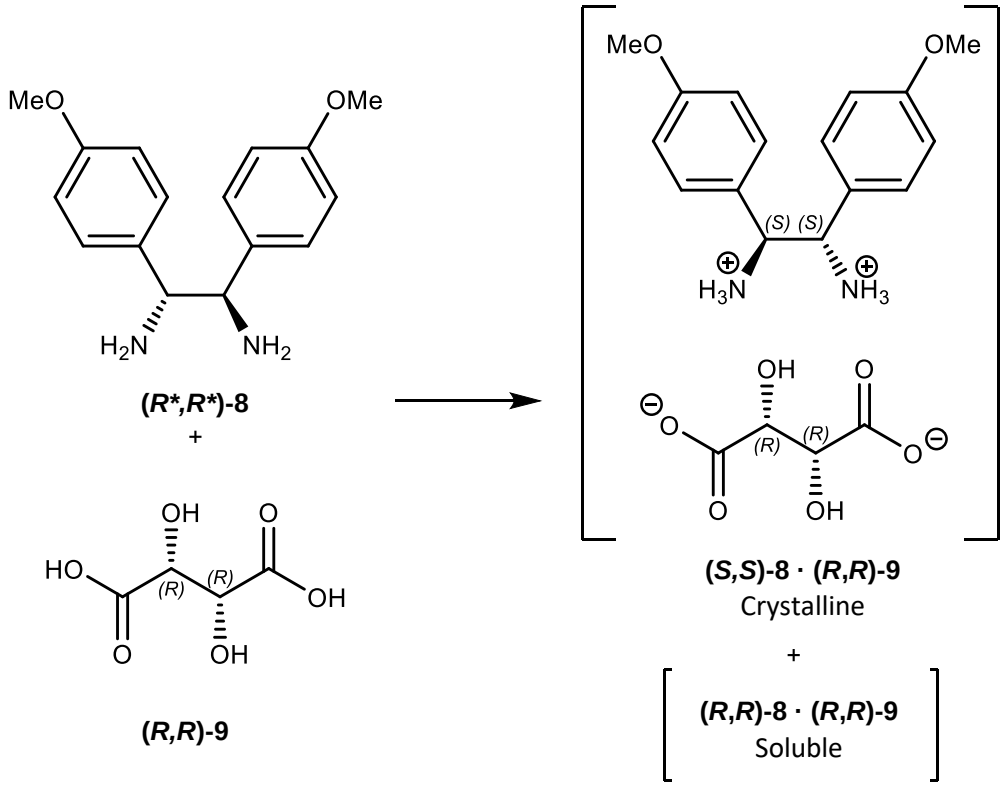
1.1.4 Separation of Enantiomers

1.1.4.1 Resolution

Single enantiomers may simply be isolated from their racemic mixture by resolution. Classically this is achieved by forming a pair of diastereomeric salts between the substrate

enantiomers and a stereochemically pure resolving agent. These salts are separated by crystallization, taking advantage of the differing solubility of the diastereomeric pairs.

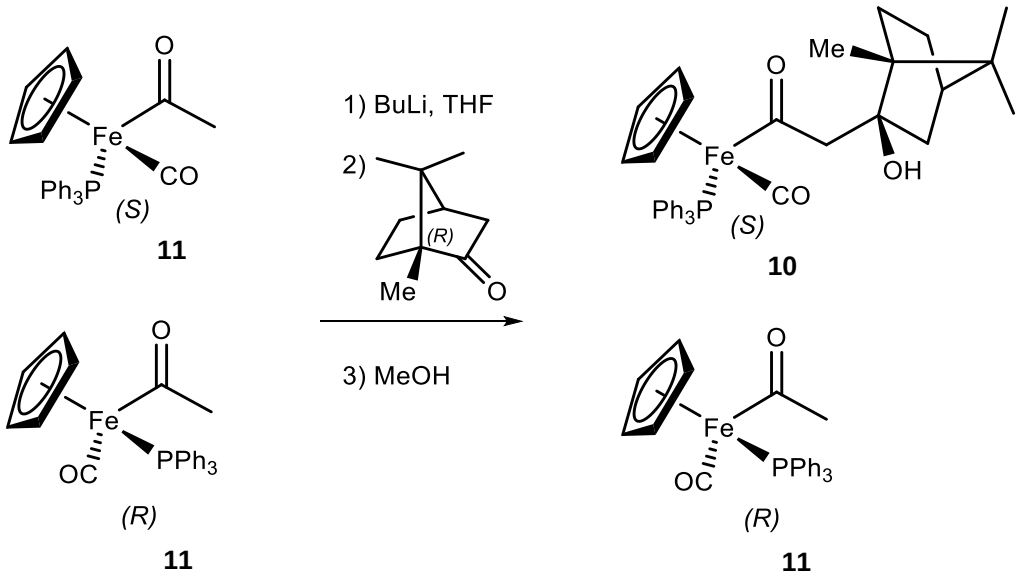
Scheme 2 illustrates the resolution of racemic *trans*-diamine ligand **8**, which was prepared by diastereoselective reductive amination of a benzil derivative. The desired (*S,S*) enantiomer was isolated by classical resolution using (*R,R*)-tartaric acid **9**.[9]



Scheme 2: Optical resolution of enantiomers of racemic *trans*-diamine **8**

Classical resolution may allow the use of cheap achiral reagents in the synthesis, but introduces up to three additional steps; reaction with the resolving agent, separation, and removal of the resolving agent. It also requires the substrate to have suitable acidic or basic functionality, or be modified in order to be able to react with the resolving agent.

Kinetic resolution is a related method in which the difference between rates of reaction of enantiomers with a chiral reagent is exploited. One enantiomer of a mixture will react faster with the resolving agent, while under optimal reaction conditions and timing the other enantiomer will remain unchanged. Separation of the two enantiomers therefore becomes a question of separating two distinct compounds and can be done by any conventional method such as chromatography, crystallization, extraction etc.



Scheme 3: Kinetic resolution of Davies iron acyl complexes with Camphor

Scheme 3 illustrates an example. A racemic mixture of Davies iron acyl complex [FeAc(CO)Cp(PPh_3)] **11** can be kinetically resolved by reaction with naturally occurring (*R*)-camphor, yielding the (*S*)-camphor adduct **10** by aldol reaction and unreacted (*R*)-**11**.[10] Pure (*S*)-**11** can then be obtained by a reverse aldol reaction, allowing access to both enantiomers. Kinetic resolution is useful when diastereomeric salts cannot easily be formed due to a lack of acidic or basic functionality in the starting material.

1.1.4.2 Chiral Chromatography

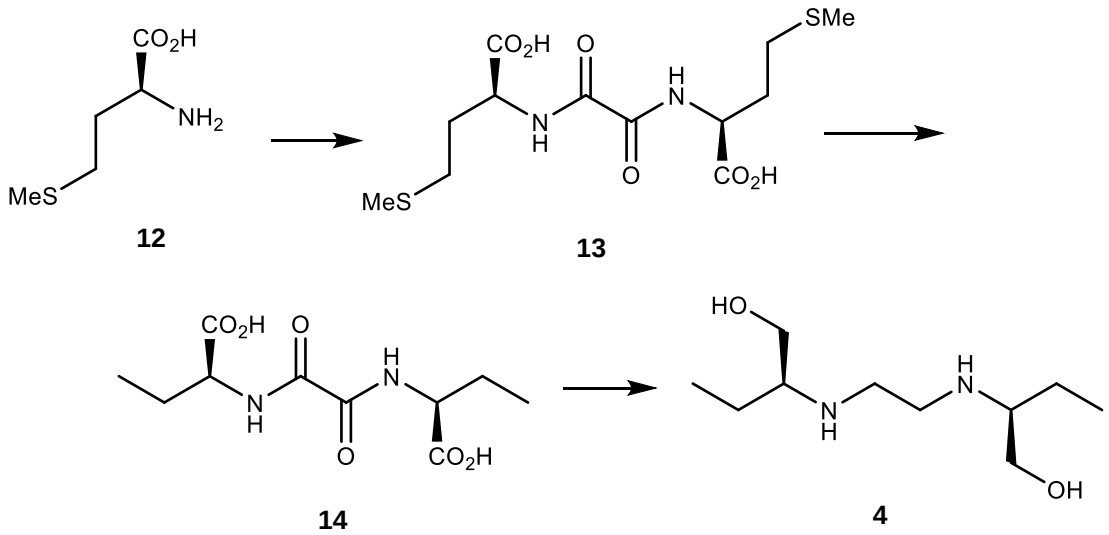
An alternative to classical resolution on small scales is chiral chromatography. Here the stationary phase is coated with or covalently bonded to a chiral agent, commonly a carbohydrate derivative. As the mixture of enantiomers passes through the column, each will have a different interaction with the chiral stationary phase and hence their retention time on the column will differ. This approach is extremely common for analytical purposes, in order to quantify the ratio of enantiomers in an asymmetric mixture. However the chiral stationary phase is costly, and at large scale preparative chromatography requires very efficient solvent recycling processes to be economical.[11]

Both resolution and chromatography are wasteful, at most half of a racemic mixture can be recovered as the desired enantiomer. However if both enantiomers are required in their pure form then separation becomes a very attractive option.

1.1.5 Preparation of single Enantiomers

1.1.5.1 Chiral Pool method

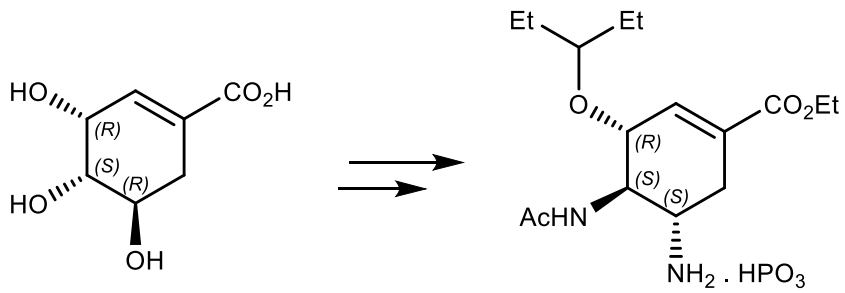
An obvious alternative to racemic synthesis and separation is to directly prepare the desired product as a single enantiomer. This is often achieved by starting from a commonly available natural product that already has the correct stereochemistry present. Assuming the reaction conditions do not lead to racemisation this can be an extremely effective route and is often the first considered option for scale up synthesis. However the primary disadvantage is that the natural product starting material is frequently only available as a single enantiomer, meaning that only one enantiomer of final product may be accessible. For example the (*S,S*) configuration of ethambutol **4** described earlier can be prepared in four steps from naturally occurring amino acid L-methionine **12**.[12]



Scheme 4: Chiral pool synthesis of (*S,S*)-ethambutol with retention of chiral centres

1.1.5.2 Stereoselective reactions.

An initial chiral centre need not remain unchanged throughout a synthesis. In a stereoselective reaction, one chiral centre in a substrate controls the creation of one or more additional chiral centres in the reaction product. For example, in the Hoffman-La Roche industrial synthesis of oseltamivir **16**, two of the three chiral centres in naturally occurring (*R,S,R*)-shikimic acid **15** are inverted in an absolute sense, giving the (*R,S,S*) configuration of **16** selectively.[13]

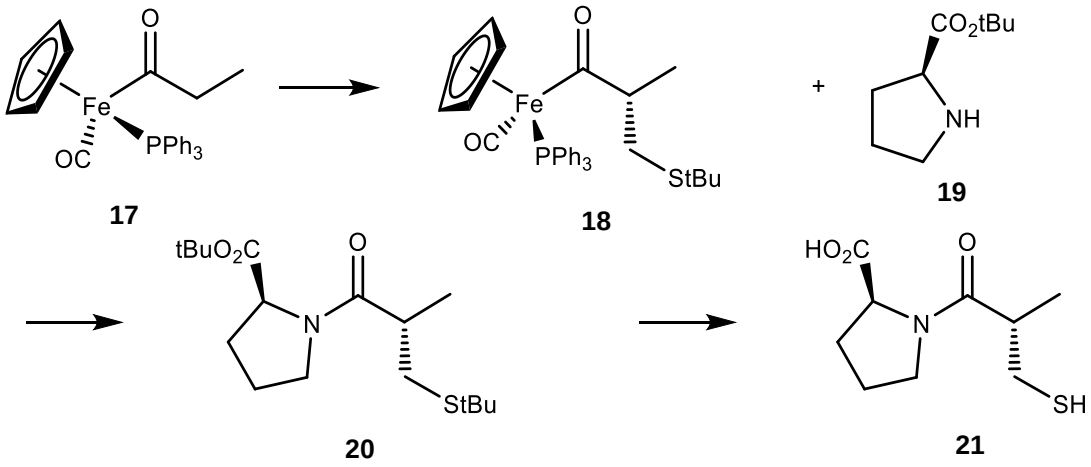


15 **16**

Scheme 5: Stereoselective chiral pool synthesis of oseltamivir (Tamiflu) from shikimic acid.

1.1.5.3 Chiral auxiliaries

Stereoselective synthesis can also be performed when there is no suitable chiral centre in the required starting substrate. Chiral auxiliaries are single enantiomers with a reactive functional group that allows addition to a substrate. The auxiliary-substrate complex undergoes a stereoselective transformation before the auxiliary is removed. Scheme 6 demonstrates how a homologue of iron complex **11** described earlier can be used to control the synthesis of ACE inhibitor captopril **21**.[14] Auxiliary **17** controls an enolate alkylation to intermediate **18**, after which it acts as a leaving group for amidation with proline derived ester **19**. Amide **20** is then simply deprotected to yield **21**.

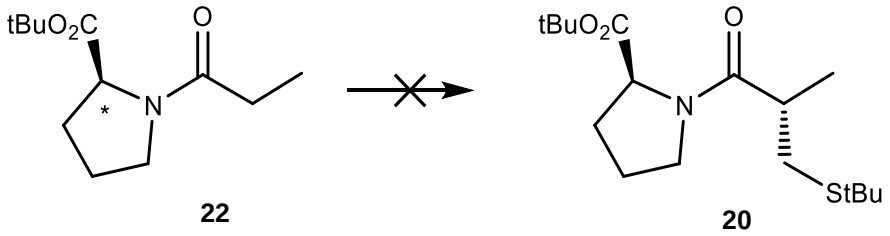


17 **18** **19** **20** **21**

Scheme 6: Synthesis of Captopril using a chiral auxiliary approach.

A theoretical alternative route to protected intermediate **20** via a stereoselective alkylation of amide **22** is explored in Scheme 7. While this route would bypass the need for a chiral auxiliary, it is not guaranteed to be effective. In practice the presence of a chiral centre of correct configuration is necessary but not sufficient for a stereoselective reaction. Conformational rigidity and size of substituents both strongly affect the ability of one chiral

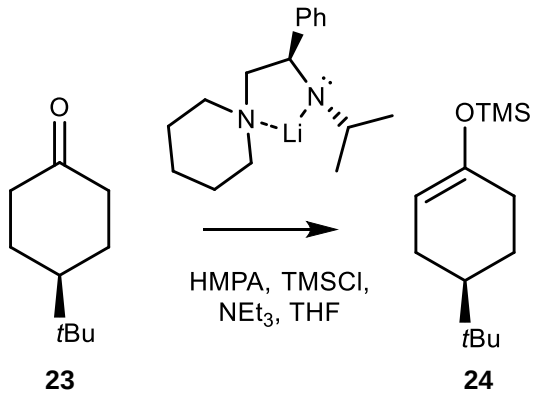
centre to influence another; a chiral centre with small or flexible groups will not enforce a significant energy difference between diastereomeric transition states of reaction. This requirement for effective "transfer" of chirality requires careful design of chiral auxiliaries and limits the scope of stereoselective reactions.



Scheme 7: Ineffective diastereoselective alkylation of intermediate amide.

1.1.5.4 Chiral reagents.

In some cases it is possible to use a chiral reagent, which performs a stereoselective reaction without its own chiral centre(s) being incorporated into the reaction product. Scheme 8 illustrates an example of stereoselective deprotonation of prochiral cyclohexanone **23** with a chiral lithium amide base.[15] The (*R*)-enolate formed is isolated immediately as the trimethylsilyl enol ether **24** to prevent racemisation.



Scheme 8: Example of a chiral lithium amide mediated enolate formation

1.1.6 Summary

Preparation of stereochemically pure compounds and measurement of mixtures of stereoisomers are crucially important in organic chemistry, especially in the production of fine chemicals in the pharmaceutical and agrochemical industries. Several methods for

separation of enantiomers or production of single enantiomers via chiral pool and chiral auxiliary approaches exist, each of which may be appropriate in different circumstances. However, most research in asymmetric synthesis in recent times has been directed towards developing asymmetric catalysts, which have the advantage of being able to produce many equivalents of chiral product for each chiral precursor used.

1.2 Asymmetric Catalysis

IUPAC defines a catalyst as a substance that accelerates the rate of a chemical reaction without changing the overall standard Gibbs free energy change of the reaction.[4] In principle the catalyst is both a product and reactant, and is not itself permanently changed during the course of the reaction. While this is not a fundamental part of the definition of a catalyst, frequently a single mole of catalyst is able to promote the reaction of many moles of reagents. The number of conversions achieved is defined as the Turnover Number (TON). Such catalysts are used at lower stoichiometry, with the catalyst loading being defined by the substrate : catalyst ratio (S/C).

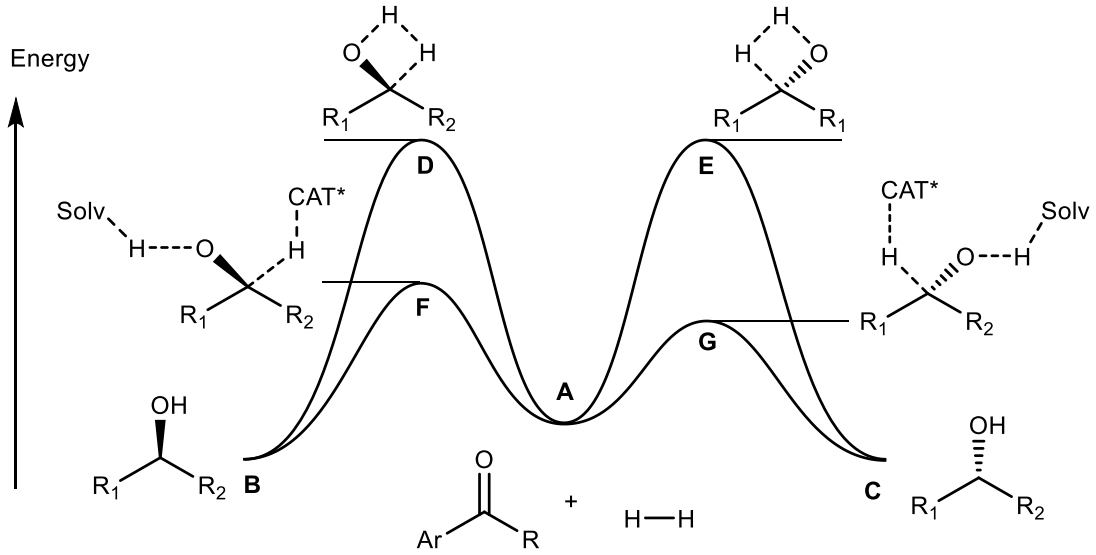


Figure 5: Example simplified free energy plot for uncatalysed and asymmetric hydrogenation of ketones. The energy difference between catalysed and uncatalysed barrier heights is not drawn to scale and would be much larger in reality.

An asymmetric catalyst is enantiomerically pure, and when controlling a reaction between achiral substrates this leads to diastereomeric transition state complexes (**F**/**G**, Figure 5) that differ in energy for each of the possible product enantiomers (**B**/**C**). This results in a lower activation energy for formation of **G** and the difference in transition state free energies can be used to calculate the product distribution according to Equation 4. Crucially the free

energies of final products **B** and **C** are equal, therefore an asymmetric catalyst operates by kinetic rather than thermodynamic control.

$$\Delta G_{\ddagger} = RT \ln(K)$$

Equation 4: Relationship between free energy ($\Delta G_{\ddagger}$) and ratio of reaction rates (K) for diastereomeric transition states.

It can be seen that while small absolute energy differences will introduce moderate asymmetric induction, to increase the product ee close to 100% requires an exponential increase in the energy difference between the two transition states (Table 1).

Table 1: Free energies and enantiomeric excesses for given ratios of enantiomers.

er	ee	$\Delta G_{\ddagger}$ / kJ mol^{-1}
1 : 1	0	0.00
1 : 3	50	2.72
1 : 9	80	5.45
1 : 49	96	9.65
1 : 199	99	13.12

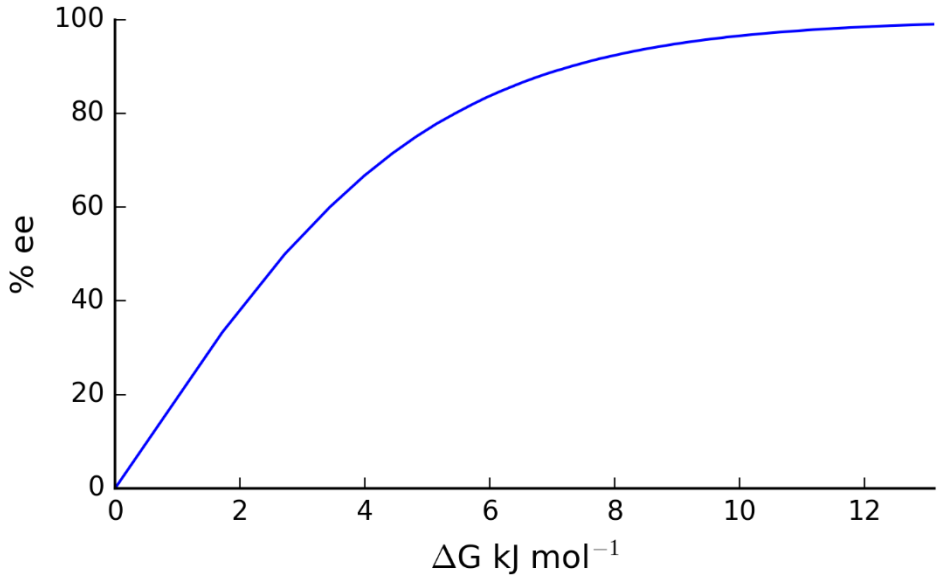


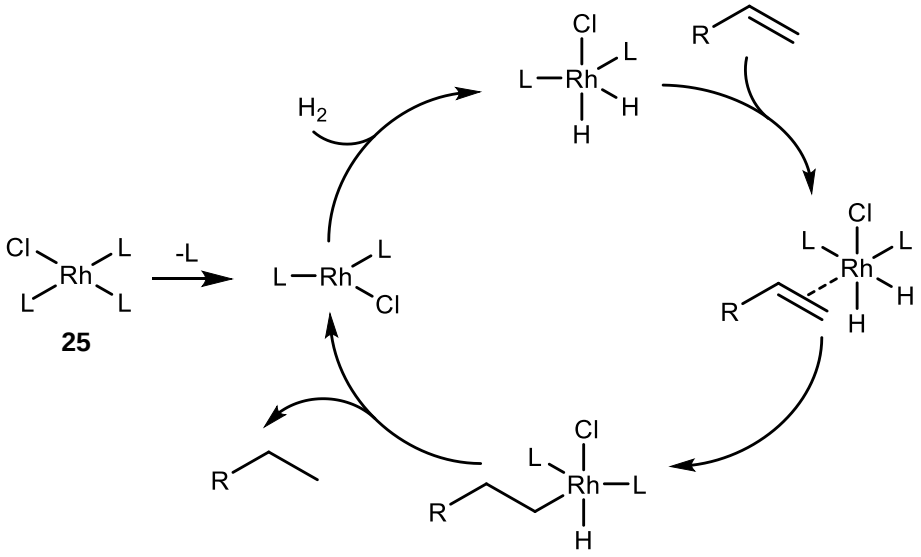
Figure 6: Relationship between ee and ΔG

1.2.1 Features of a Good Asymmetric Catalyst.

Asymmetric catalysts at laboratory scale are primarily compared by the extent of asymmetric induction they produce; as measured by the ee or er of the final product. However other factors to be considered include cost, activity (often compared by the S/C ratio or TON at larger scale, and the reaction rate), selectivity (ability to discriminate between reactive sites in the substrate and react with the preferred site) and robustness (how sensitive the catalyst is to changes in reaction conditions, impurities, or contaminants such as air or water). These factors can become much more important when working on a large scale and result in the selection of a catalyst with lower asymmetric induction but otherwise superior properties, on the basis that the enantiopurity of the final product can often be upgraded through crystallization.

1.2.2 Catalytic Hydrogenation.

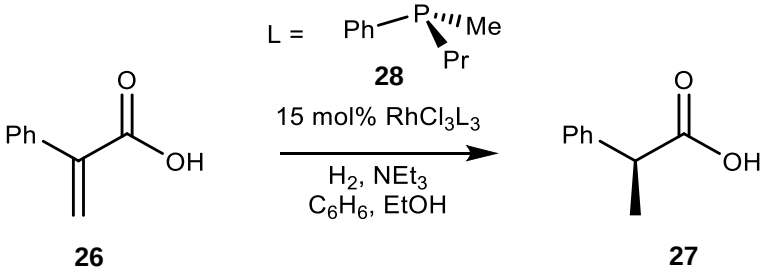
Heterogeneous racemic hydrogenation of organic compounds over metal catalysts has been known since the end of the 19th century, when Paul Sabatier discovered the catalytic properties of finely divided nickel.[16] This was the first direct hydrogenation method and since then a wide variety of metals including nickel, iron, platinum, palladium and more have been used.[17] However, the chirality required for an asymmetric hydrogenation (AH) is hard to incorporate into a heterogeneous catalyst. It would take until the mid-20th century for the first effective homogenous catalysts to be developed,[18] such as Wilkinson's rhodium complex **25** which was effective for alkene reduction (Scheme 9).[19] Loss of a labile PPh_3 ligand is followed by oxidative addition of the Rh(I) complex into dihydrogen. Coordination to the alkene substrate forms a coordinatively saturated octahedral complex, and migratory insertion across the alkene double bond followed by reductive elimination recycles the catalyst and yields the reduced alkane.



Scheme 9: Catalytic cycle for alkene hydrogenation with Wilkinson's catalyst. L = PPh_3

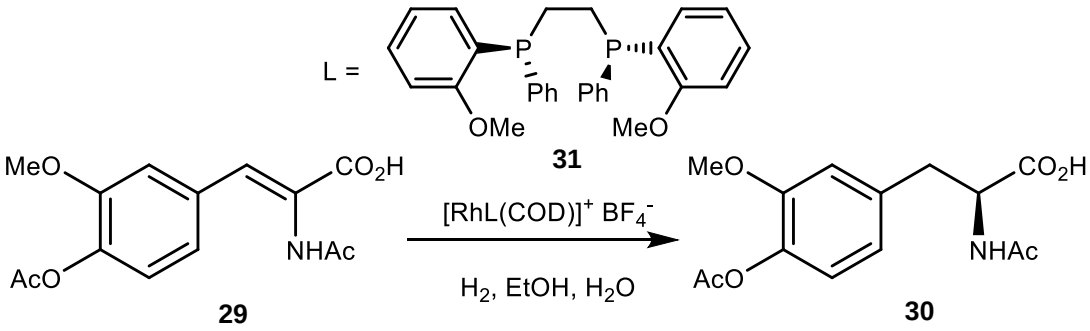
1.2.3 Asymmetric Hydrogenation

A simple logical step in the design of an asymmetric reaction was to replace the achiral PPh_3 ligands in **25** with chiral phosphines. Scheme 10 illustrates an early example from Knowles utilising methylpropylphenylphosphine **28** was capable of a slight asymmetric induction in the reduction of 2-phenylacrylic acid **26**.[20]



Scheme 10: Asymmetric reduction with a chiral phosphine, product ee is 15%

This served as proof of principle and gave rise to one of the key concepts in AH; the importance of matching chiral ligand and substrate to create significant asymmetric induction. A wide range of chiral phosphine ligands were developed shortly afterwards, leading to the discovery of the bidentate DiPAMP ligand **31** and its application to the Monsanto industrial synthesis of L-DOPA (Scheme 11).[21,22]

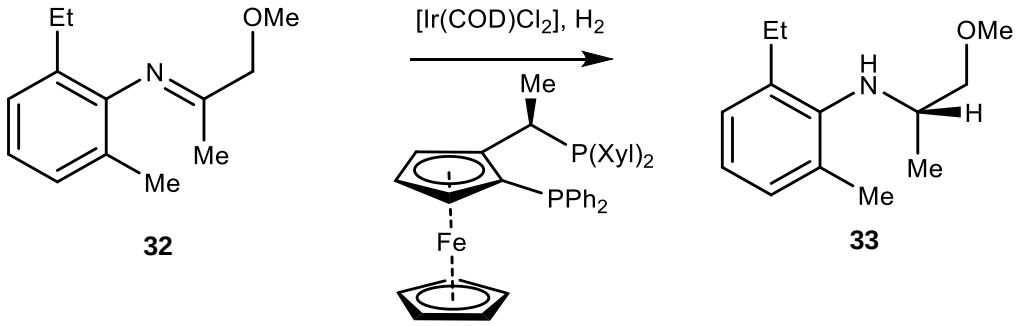


Scheme 11: Key AH step in an industrial process for L-DOPA, used for treatment of Parkinson's disease. S/C ratios up to 20,000:1. Global deprotection yields L-DOPA.

Chelate ligands such as **31** have two key advantages for asymmetric catalysis. Their multi point attachment makes complexation more entropically favourable, making them less likely to dissociate. Secondly, they are much less conformationally flexible, being unable to rotate about their metal-ligand bonds, and this creates a well-defined chiral environment that increases the likelihood of a strong transfer of chirality from the ligand to the substrate in the transition state.

1.2.3.1 AH: a Modern Example

Asymmetric hydrogenation has been one of the most successful applications of asymmetric catalysis. A wide variety of unsaturated substrates including alkenes, ketones, imines etc. can be reduced selectively to give one enantiomer, and as AH can be optimised to perform at extremely high S/C ratios it can be suitable for large scale industrial processes.



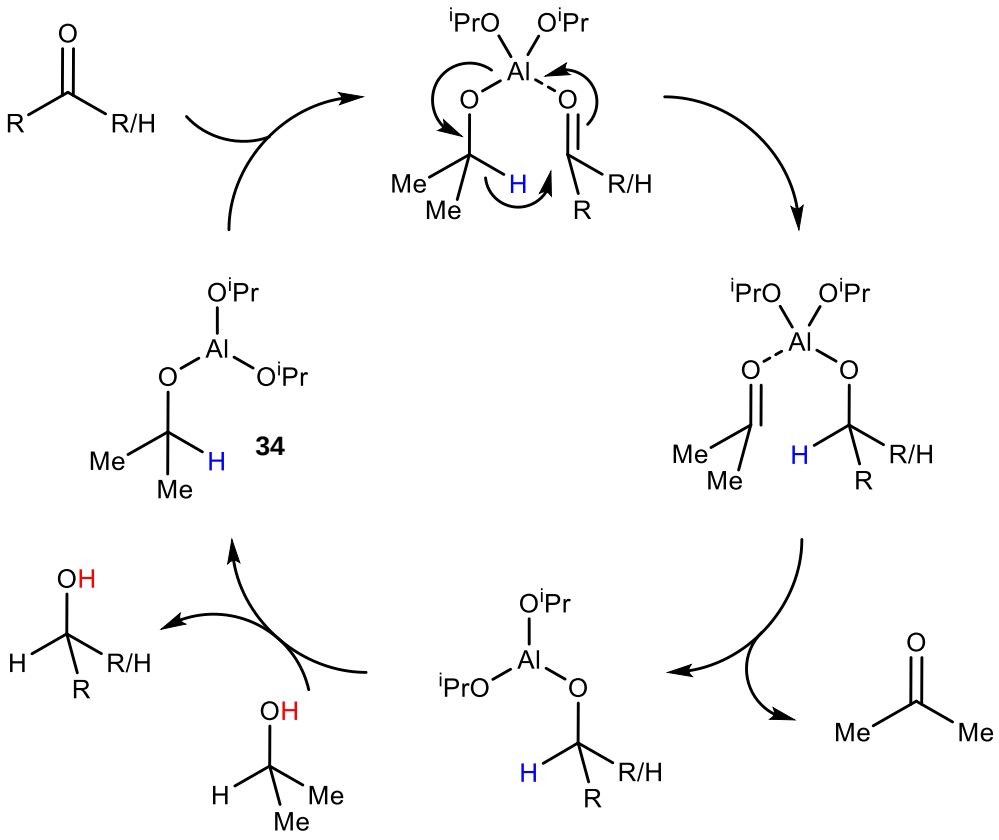
Scheme 12: Efficient asymmetric hydrogenation of imine **32** at 200,000:1 S/C

One example from towards the end of the 20th century comes from the application of an iridium bis-phosphine catalyst to AH of imine **32** (Scheme 12).[23] This process produces a key

intermediate **33** in the production of (*S*)-Metolachlor at very low catalyst loading, such that 0.05 mol of Ir is used to produce 10,000 mol of amine.

1.2.4 Transfer Hydrogenation.

Catalytic hydrogenation (CH) processes traditionally utilise pressurised hydrogen gas directly as the source of hydrogen for reduction. Greater pressures of H_2 generally lead to faster reductions and allow lower catalyst loadings but require specialised equipment. In transfer hydrogenation (TH), use of a liquid or solid phase hydrogen donor in place of hydrogen gas can circumvent this problem. As with CH, a catalyst is required to remove hydrogen from the donor and transfer it to the substrate at reasonable rate, while the oxidised by-product from the donor must be easily separable and non-reactive.

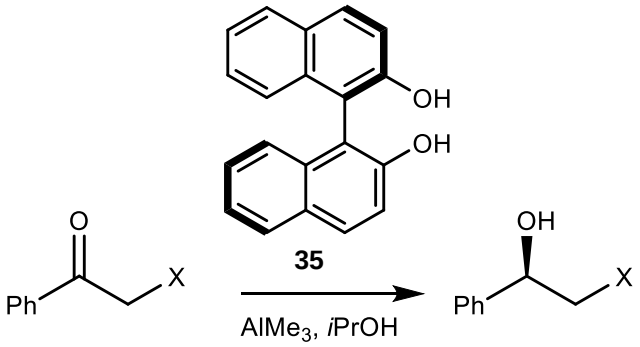


Scheme 13: Mechanism of the Meerwein-Ponndorf-Verley, the first example of a transfer hydrogenation reaction.

In 1925 the first such TH was developed in the form of the Meerwein-Ponndorf-Verley (MPV) reaction, which utilised an aluminium isopropoxide catalyst **34** to transfer hydrogen from

isopropanol (IPA) to ketones or aldehydes.[24] The key step in the proposed catalytic cycle is hydride transfer from alcohol to ketone via a six membered cyclic transition state (Scheme 13).

A more recent asymmetric example of the MPV reduction replaces **34** with $AlMe_3$ and a chiral bidentate BINOL ligand **35** (Scheme 14). This system achieves reasonable enantioselectivity in reduction of alpha-chloroacetophenone but is sensitive to the nature of the alpha functional group; acetophenone itself is reduced in only 30% ee.[25]



Scheme 14: Asymmetric MPV reduction. X= Cl: 99% yield, 80% ee. X= H: 54% yield, 30% ee.

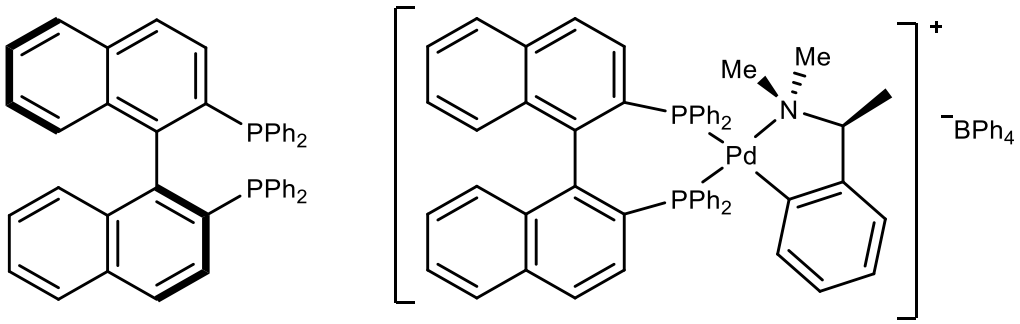
MPV reduction was largely replaced in the mid-20th century by the development of the commonly used metal hydride reagents $NaBH_4$ and $LiAlH_4$. Though not catalytic, these reagents provide a simple and convenient method for racemic reduction of a wide variety of carbonyl and other unsaturated compounds.[26] However they are not without their own disadvantages; often a large excess of hydride reagent must be used, the resulting salts (especially for aluminium hydrides) can cause difficulties during work-up, and crucially these reagents do not easily lend themselves to use in asymmetric reductions.

1.2.5 Summary

Hydrogenation has been one of the first and most successful applications of catalysis and many important advances were made in this area in the 20th century. The development of homogenous rhodium complexes allowed the first practical AH catalysts to be designed by ligand optimisation. Following this work, the discovery of several catalytically active Ru(II) complexes by Noyori had a significant further impact on the field.[27]

1.3 Ru(II) Catalysis of AH and ATH

Several of the following AH catalysts described in the next section are based on the axially chiral BINAP ligand (**36**) which was first synthesised in 1980. Preparation of a specific enantiomer would be challenging but both enantiomers of **36** are useful, so the original procedure was based on resolution by complexation with a chiral palladium complex.[28]



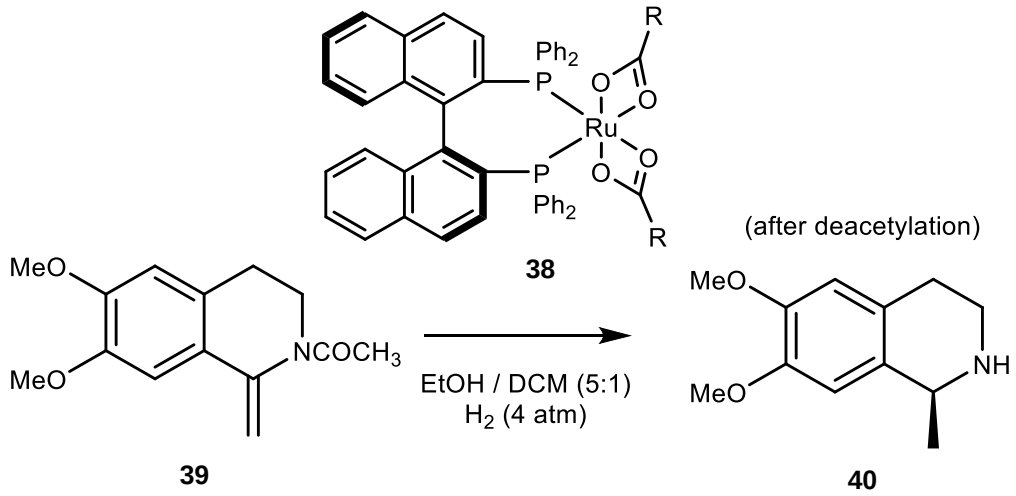
36 **37**

Figure 7: Left: (*S*)-BINAP. Right the Pd complex used to resolve racemic BINAP.

1.3.1 Asymmetric Hydrogenation with Ruthenium Catalysts

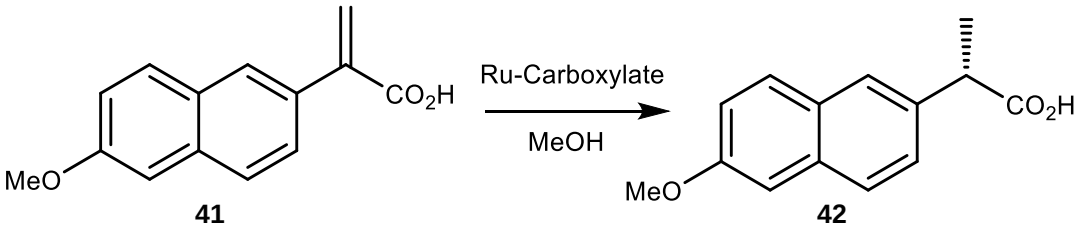
1.3.1.1 Alkene Hydrogenation with [Ru(BINAP)Carboxylate]

In 1986 Noyori *et*. *al*. reported the ruthenium carboxylate complex **38** was effective for AH of N-acyl-1-alkylidinetetrahydro-isoquinolines.[29] For example (*S*)-salsolidine **40** could be prepared from enamide **39** by hydrogenation and deprotection (Scheme 15).



Scheme 15: ATH of tetrahydroisoquinolines with Λ-(*S*)-**38**, ee 96% for **40**.

Shortly afterwards, complex **38** was found to be capable of AH of various functionalised olefins, such as allylic and homoallylic alcohols,[30] and unsaturated carboxylic acids.[31] In the latter case this was applied to the direct preparation of (*S*)-naproxen **42** from the alkene precursor **41** (Scheme 16).

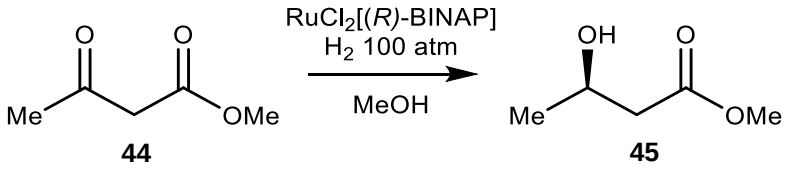


41 **42**

Scheme 16: Synthesis of (*S*)-naproxen by AH with Λ-(*S*)-**38**. 92% yield, 97% ee.

1.3.1.2 Activated Ketone Hydrogenation with [Ru(BINAP)X_2]

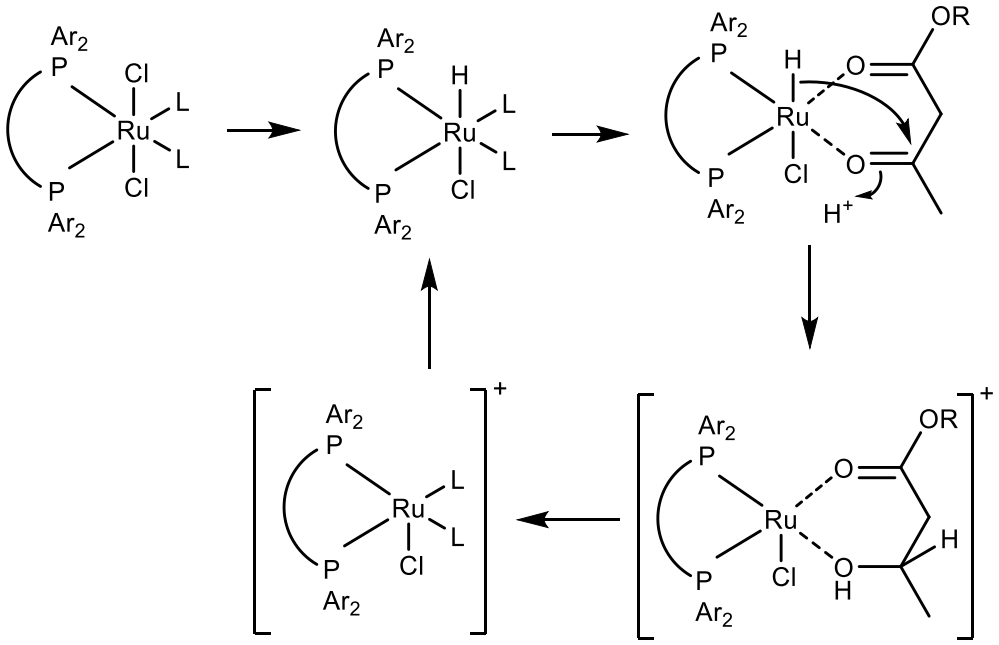
In an attempt to extend this AH methodology to reduction of ketones, Noyori et. al. screened a variety of Ru complexes in the reduction of methyl-3-oxobutanoate.[32] Carboxylate complex **38** was ineffective, however replacing the carboxylate ligands with halides by reaction with HCl gave a poorly defined catalyst with the empirical formula [Ru(BINAP)Cl_2] **43**. This catalyst was found to be generally effective in AH of β-keto esters. Methyl 3-oxobutanoate **44** was reduced to the corresponding 3-hydroxybutanoate **45** in 99% ee with an S/C ratio of 2000 (Scheme 17).



44 **45**

Scheme 17: β-keto ester hydrogenation

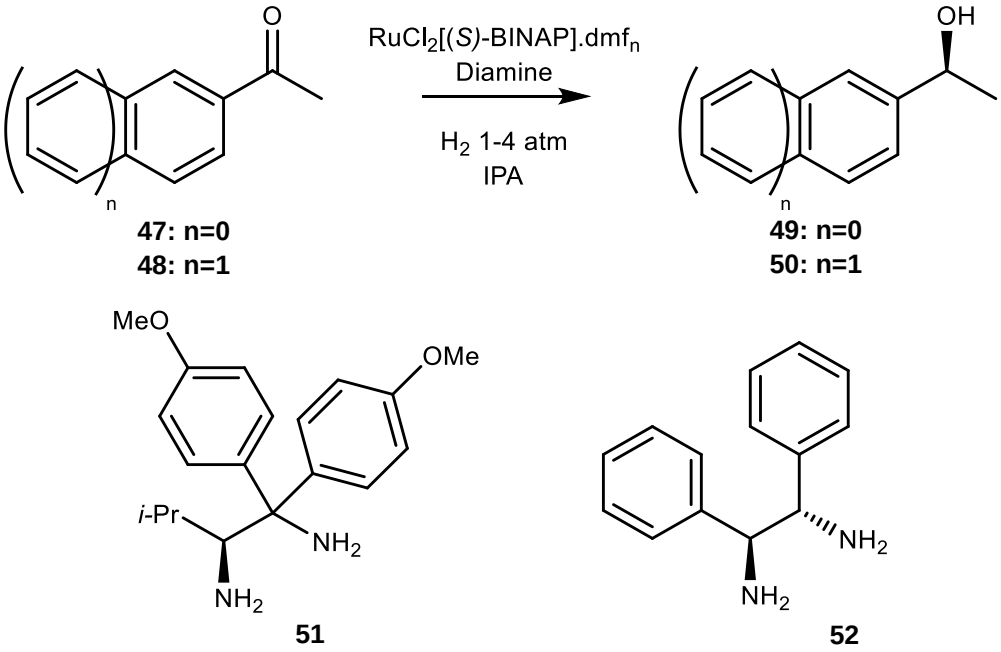
Both ketone and ester functionalities in **44** are required to bind to the catalyst before hydrogen transfer can take place.[33] Enantioselectivity is controlled by delivery of hydride to one face of one of the possible diastereomers formed by substrate chelation. The mechanism is described in Scheme 18, assuming a monomeric catalyst formed by coordination of solvent molecules or similar.



Scheme 18: Mechanism of AH of β-keto esters by Ru(BINAP)carboxylate complex **38**. L = unspecified solvent ligand. Atoms on the diphosphine ligand backbone have been omitted for clarity.

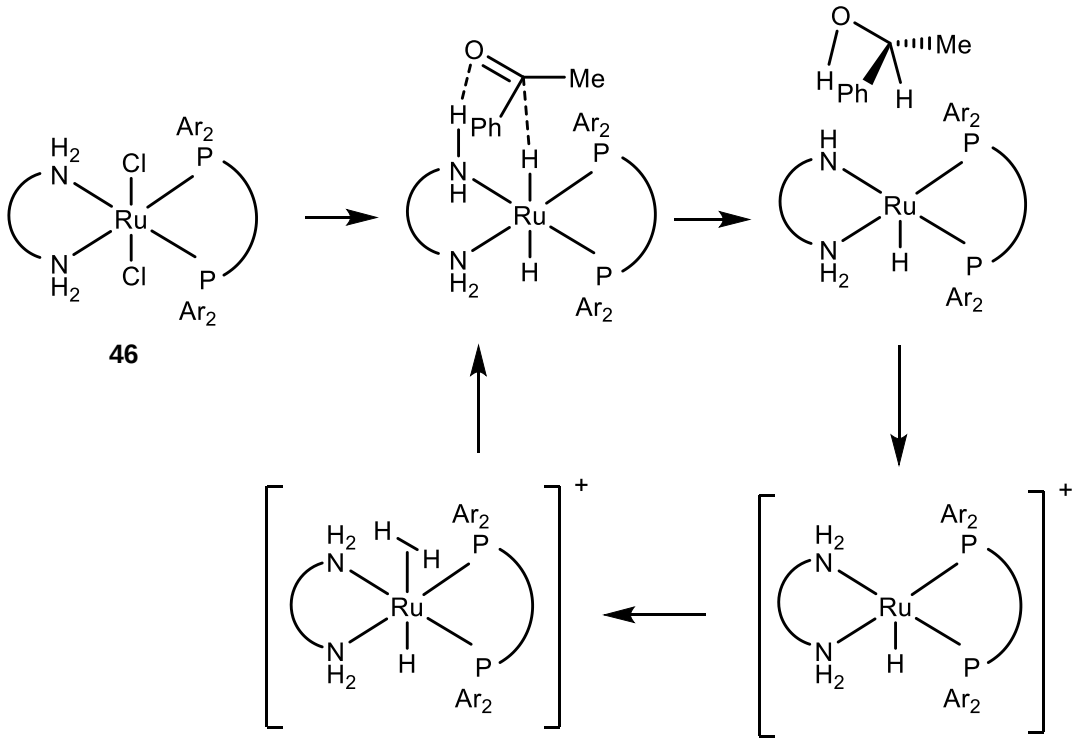
1.3.1.3 Simple Ketone Hydrogenation with [Ru(BINAP)(Diamine)X_2]

Catalysts **38** and **43** were still ineffective for reduction of simple ketones, such as acetophenone **47**, which lack an additional directing group. However combining the monomeric DMF complex of catalyst **43** with chiral diamines gave a new class of catalyst [$RuCl_2$(BINAP)(diamine)] (**46**) capable of reducing 2-acetonapthone **48** in 95% ee and acetophenone **47** in 87% (Scheme 19).[34] These transformations took place in basic isopropanol, although deuterium labelling experiments verified that H_2 was the hydrogen source and not isopropanol. A variety of diamine ligands were effective, including (*S*)-DAIPEN **51** and the C_2 symmetric ligand (*S,S*)-DPEN **52**



Scheme 19: Above: Reduction of simple aromatic ketones with Ru-BINAP-Diamine complex **46**. Below: Diamine ligands for Ru-BINAP-Diamine hydrogenation.

The diamine ligand is crucial to the reactivity of this system. Scheme 20 shows the proposed mechanism for ketone reduction with catalyst **46**.[35] A nitrogen transfers a proton to the ketone oxygen atom, whilst the ruthenium transfers H^- to the carbonyl carbon, all within a single concerted process. In contrast with the dihalide catalyst **43**, hydrogenation takes place in acidic alcohol solvent generated during the catalyst activation stage. H^+ is continually replenished in the system by heterolytic fission of H_2 during catalyst regeneration. Importantly, the ketone substrate is never required to co-ordinate directly to ruthenium in this catalytic cycle. Instead hydrogen is transferred directly from the metal centre and the ligand amine group to a loosely associated substrate molecule. This "outer-sphere" mechanism allows the BINAP/diamine catalyst to reduce simple ketones without directing groups.



Scheme 20: Catalytic cycle for ketone reduction by Ru-BINAP-Diamine complex **46**. Atoms on the diphosphine and diamine ligand backbones omitted for clarity.

Stereochemical control is dependent on the orientation of the ketone as it approaches the catalyst.[36] The carbonyl carbon approaches directly above the ruthenium centre in line with the hydride. The oxygen then aligns above the amine group with an axial hydrogen aligned with the ruthenium hydride (e.g. Figure 8, red pair of hydrogens), thereby discriminating between the two amines and setting the orientation of the C=O bond. Finally selection between the two pro-chiral faces of the ketones is determined by steric repulsion between the substrate aromatic group and the diphosphine ligand backbone.

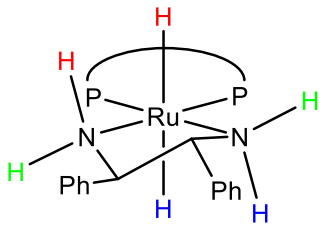
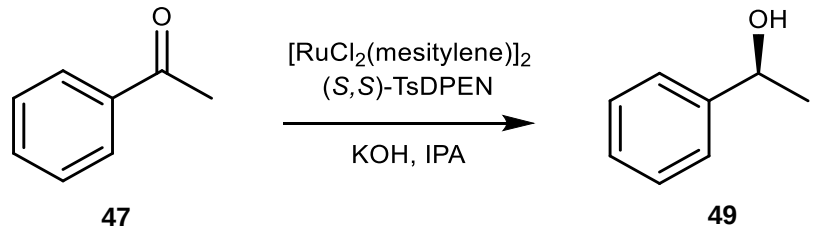


Figure 8: C_2 symmetry of hydrogen atoms in bifunctional catalyst **46**

1.3.2 Application to Asymmetric Transfer Hydrogenation.

1.3.2.1 N-Tosylated Diamine and Amino-Alcohol Ligands

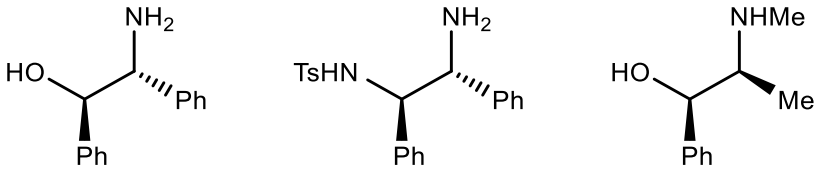
The major breakthrough in the field of ATH came in 1995, when a new N-tosyl-1,2-diaminodiphenylethane (TsDPEN, Figure 9) ligand **55** was combined with a dimeric ruthenium arene complex $[Ru(C_6H_3Me_3Cl_2]_2$ (**53**).[37] Use of (*S,S*) ligand lead to the production of (*S*)-1-phenylethanol **49** in 97% ee after 15 hours reaction in isopropanol (Scheme 21).



47 **49**

Scheme 21: Asymmetric transfer hydrogenation of acetophenone with Ru complex. Results: Yield 95%, ee 97%.

Other ligands that proved effective with this ruthenium arene precursor were chiral β-amino alcohols such as ephedrine **56** and 2-amino-1,2-diphenylethanol **54** (Figure 9).[38] Both classes of ligand contain a neutral amine donor and a relatively acidic heteroatom (-OH or -NHTs) that is deprotonated on coordination to ruthenium, and it was demonstrated that tertiary amines without a free NH are ineffective ligands for the ATH reaction, indicating that the NH bond is directly involved in the reduction.



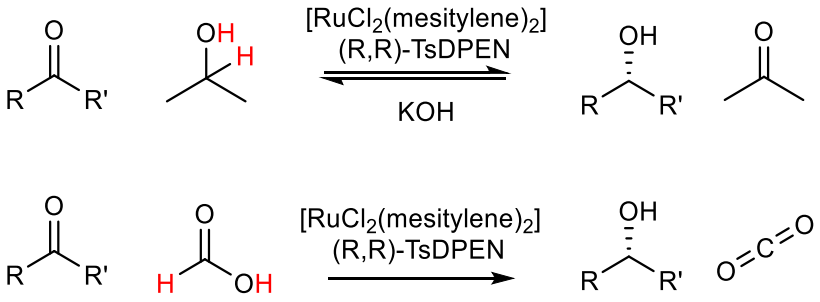
54 **55** **56**

Figure 9: New ligands used with arene/Ru complexes to create highly selective ATH catalysts.

1.3.2.2 Formic Acid as Hydrogen Source.

Most early work in the field used isopropanol as hydrogen source due to its low cost and ability to dissolve a wide range of compounds.[39,40] The acetone by-product is also volatile and unreactive, making it simple to remove from the reduction products.

Further development revealed that for catalysts such as **58**[*], a 5:2 azeotrope of formic acid and triethylamine (FA/TEA) was also effective as a hydrogen donor. [41] The highly thermodynamically favourable decomposition of formic acid to carbon dioxide is assisted by the escape of gaseous CO_2 from the reaction solution. This alleviates the requirement for large molar excess of hydrogen donor, allowing higher reaction concentrations of up to 2M to be used. By comparison reductions in isopropanol are commonly performed at substrate concentrations of ~0.1M.



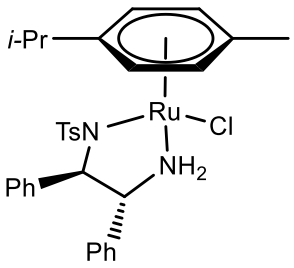
Scheme 22: Comparison of formic acid and isopropanol as hydrogen donors

1.3.3 Catalyst Mechanism and Structure

1.3.3.1 Structures of Active Species

In 1997, Noyori obtained X-ray crystal structures for the active catalytic species and intermediate, derived from a monomeric ruthenium chloride precatalyst **58** isolated from reaction of $[RuCl_2(p\text{-cymene})]_2$ **57** and TsDPEN **55** (Figure 10).[42] This complex has distorted octahedral coordination around the metal, and the diamine ligand and metal form a chiral 5 membered ring. Because complex **58** is formed as a single diastereomer, the ligand stereochemistry determines the configuration at the metal centre, with (*R,R*)-**55** forming (*R*)-**58**. The ruthenium to nitrogen bond lengths are very similar for both the amine and amido portions of the ligand, 2.12 and 2.14 Å respectively.

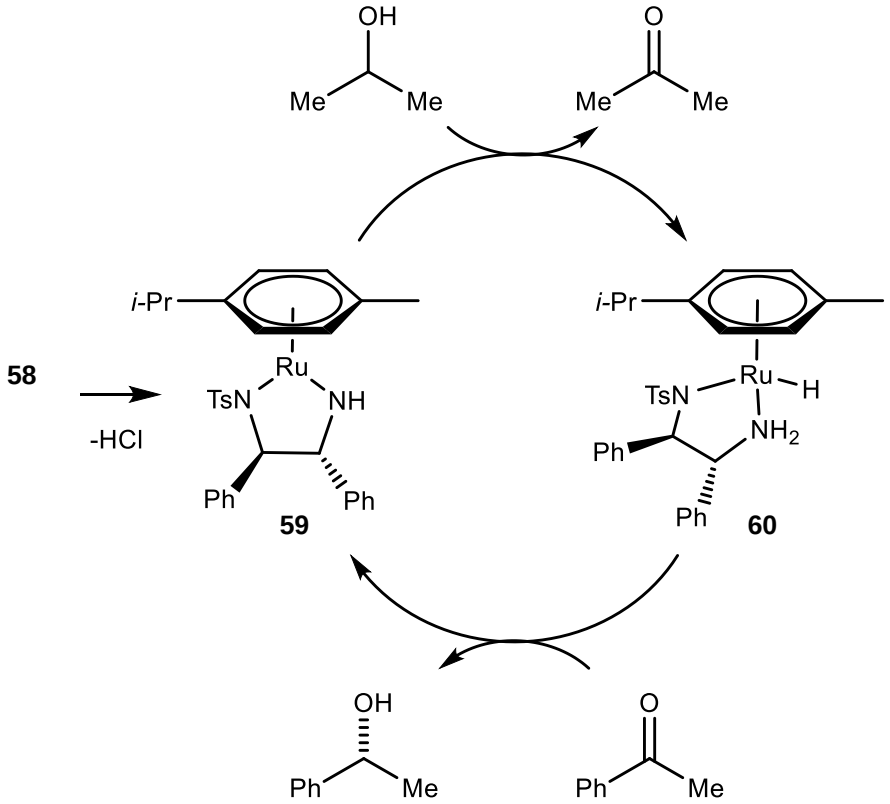
[*] Catalysts containing amino alcohol ligands such as **54** and **56** are unsuitable for use with FA/TEA.[190]



58

Figure 10: [RuCl(arene)TsDPEN] precatalyst, commonly known as the Noyori catalyst.

The active species is proposed to be a 16e planar intermediate **59** derived from the precatalyst **58** by elimination of HCl under basic conditions (Scheme 23). Complex **59** shows some double bond character between the amine and ruthenium, with the bond length shortened to 1.90 Å. This bond can be saturated by a hydrogen donor to form an 18e ruthenium hydride species **60**, similar in geometry to **58**. Both **59** and **60** have been shown to be active for the reduction of acetophenone in isopropanol in neutral conditions, implying that the KOH needed for use of **58** in ATH with IPA is simply required for catalyst activation.



Scheme 23: Catalytic cycle for ATH of ketones with precatalyst **58** via intermediates **59** and **60**.

The catalytic cycle therefore consists of catalyst activation in base, followed by dehydrogenation of the hydrogen source. Hydrogen transfer via an outer-sphere* mechanism to the substrate completes the cycle with the catalyst shuttling back and forth between 16 and 18 electron species **59** and **60** until the reaction reaches equilibrium or full conversion is achieved.

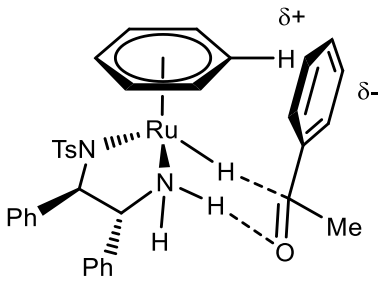


Figure 11: Favoured transition state for enantioselective reduction of **47**

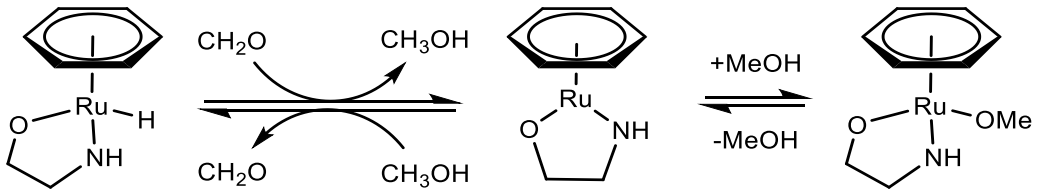
Product enantioselectivity is proposed to arise from the interaction of the ketone substrate with **60**. Electrostatic edge to face interactions between the η^6-arene ligand on ruthenium, and the electron-rich π cloud on the ketone aryl group, lead to a preferred transition state for hydrogen transfer that gives the (*R*) product in acetophenone reduction when using the (*R,R*) ligand (Scheme 23).[40]

As both steps in the cycle are reversible, the reaction is driven by the equilibrium between hydrogen donor and substrate. It could be predicted that the same catalyst would be capable of oxidation, and indeed the 16e complex **59** can be formed and used for kinetic resolution of alcohols by selective oxidation of one enantiomer in the presence of acetone as hydrogen acceptor.[39,43]

1.3.3.2 Synchronous Hydrogen Transfer

Computational modelling soon provided further support for a catalytic cycle based on outer-sphere hydrogen exchange with **59** and **60** as intermediates.[44,45] Using a simplified catalyst with benzene and ethanolamine as ligands, the authors modelled the gas phase hydrogen transfer from **61** to formaldehyde and acetone (Scheme 24).

* There is no direct coordination of the substrate to the metal centre.



61 **62** **63**

Scheme 24: Model ATH system for reduction of formaldehyde (reduction of acetone not included for clarity).

The results support Noyori's hypothesis of a two-step catalytic cycle between 16 and 18 electron intermediates. Substrate binding to the metal centre in **61** is not required for hydrogen transfer. However alcohol to metal coordination is observed in the model as an unproductive equilibrium between species **62** and **63**.

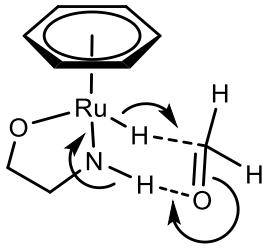
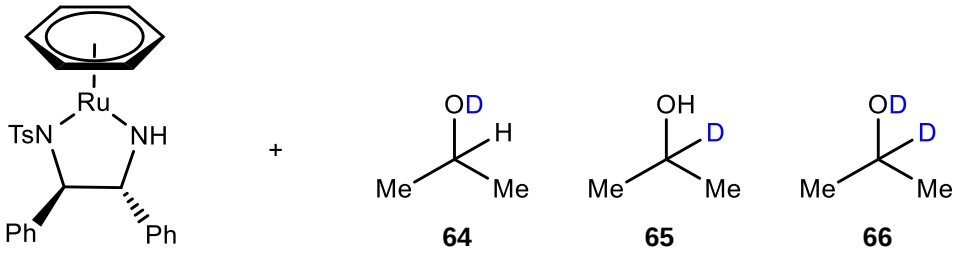


Figure 12: Concerted mechanism for hydrogen transfer from **61** to formaldehyde

The models also indicate that hydrogen transfer occurs synchronously via a 6 membered cyclic transition state (Figure 12). This compares favourably to a high energy β-elimination-insertion route, which would require partial dissociation of the η^6 arene ring in order to create additional coordination sites for both ketone and hydride.

Evidence for the synchronous mechanism was reinforced by studies on the kinetic isotope effect (KIE) for stoichiometric hydrogen transfer from isopropanol and its deuterated derivatives **64**, **65** and **66** to 16 electron complex **59**.[46] The KIE for bis-deuterated alcohol **66** is approximately the product of the KIEs for each of the mono-deuterated alcohols. The authors argue that this can only be explained if hydrogen transfer occurs as a single step.

Table 2: Measurement of KIEs in hydrogen transfer to **59**, relative to its reaction with isopropanol..



Alcohol	K_H/K_D
64	1.79
65	2.86
66	4.88

1.3.3.3 Asynchronous Hydrogen Transfer: Solution effects

Detailed computational modelling by Dub and Ikariya explicitly includes the effect of isopropanol as solvent and a complete ligand structure.[47] This appears to support a non-concerted transition state for reduction of acetophenone by the mesitylene analogue of **60**. Hydride transfer takes place first leading to a short lived ion-pair intermediate **67** (Figure 13). Solvent contributions assist protonation of the chiral alkoxide to generate the expected alcohol and 16e complex of type **59**.*

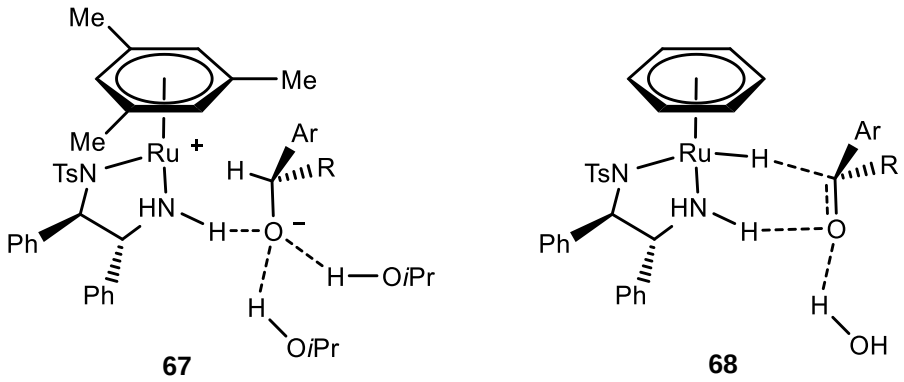


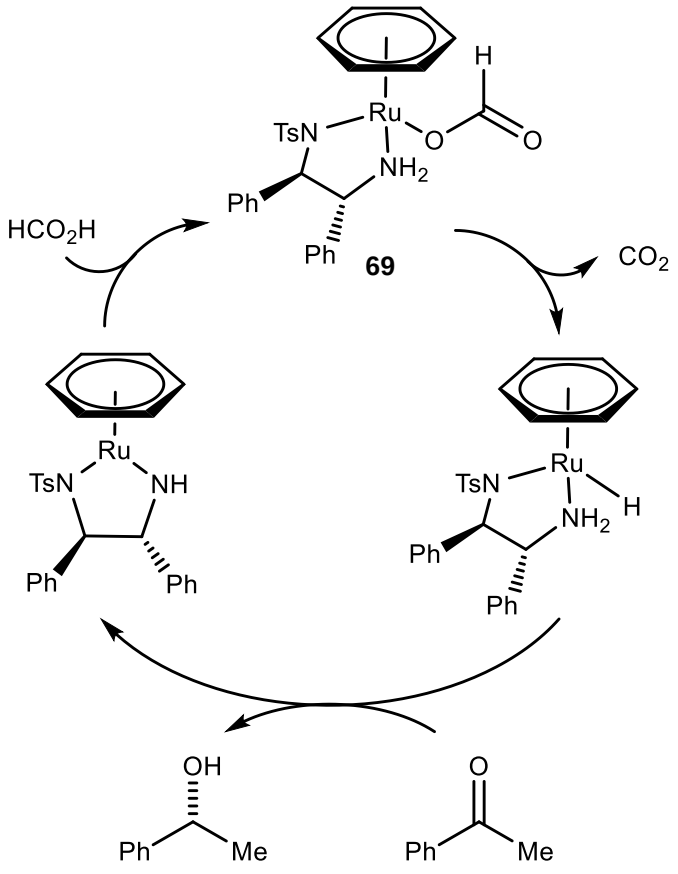
Figure 13: Proposed asynchronous transition states in isopropanol and aqueous reductions

* Very recent and extensive computational work by Dub and Gordon suggests that proton transfer takes place primarily from the solvent to the substrate, with the ligand N-H solely assisting through hydrogen bonding[191,192]

These results diverge from earlier kinetic evidence for a concerted reaction. The authors suggest this is due to the relatively slow ^{1}H NMR timescale, and as they are able to probe much shorter timescales with their calculations they can present a rapid asynchronous mechanism which fits the experimental data. This expands upon computational work by Wu *et*. *al*., which suggested a water molecule may participate in transition state **68** for aqueous reductions using sodium formate.[48]

1.3.3.4 Formate complexes: reversible CO2 formation.

Ikariya has investigated the mechanism of hydrogen transfer from donor source to catalyst during ATH with formic acid.[49] NMR experiments revealed that hydrogen transfer to 16e ruthenium species **59** was not taking place in a one step process as occurs for isopropanol, but instead occurs via ruthenium formate complex **69** (Scheme 25).

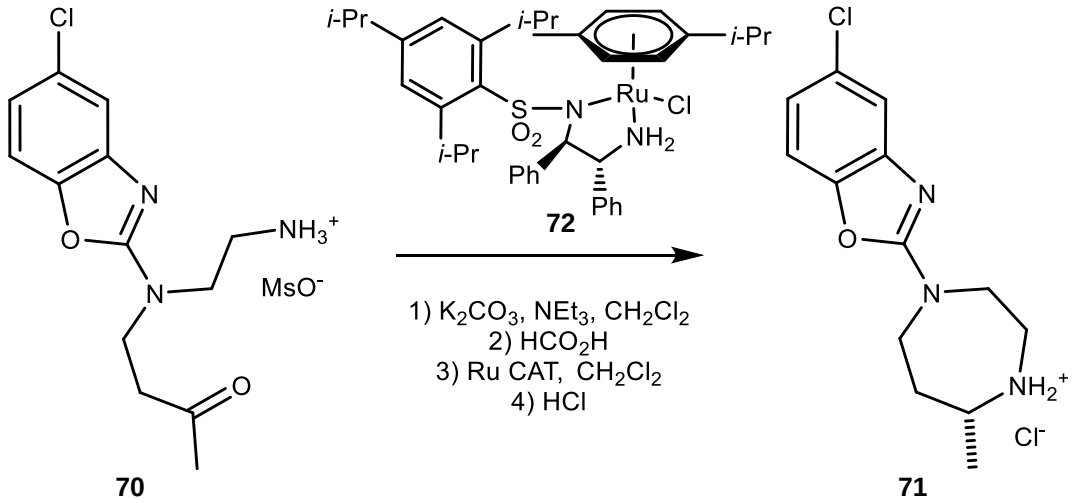


Scheme 25: Catalytic cycle including ruthenium formate intermediate **69**

Another important observation made from this work is that this reaction is partially reversible; CO_2 is able to insert into ruthenium hydride **60** to generate **69**. This has

implications for reactions performed on scale using formic acid as hydrogen source, as it implies that if CO_2 is not effectively removed from the reaction mixture it could inhibit catalysis.

During the course of a detailed mechanistic study into the Ru catalysed reductive amination of dialkyl ketone **70**, further evidence confirmed Ikariya's results regarding CO_2 inhibition (Scheme 26).[50] Deliberate addition of CO_2 reduced the reaction rate by an order of magnitude, subsequently purging with nitrogen gas throughout the reaction lead to a 60% increase in reaction rate.



Scheme 26: Asymmetric reductive amination of a dialkyl ketone. The reaction rate is highly dependent on [CO_2].

1.3.4 Tethered Ru ATH Catalysts.

In 2004-2005 Wills *et al.* introduced a new series of 'tethered' complexes (Figure 14) that contained a covalent linker between the arene and bidentate ligands.[51] The goal was to create a complex that was more stable to ligand dissociation, as the chelate effect ensures that each of the ligand components is effectively bound more strongly.

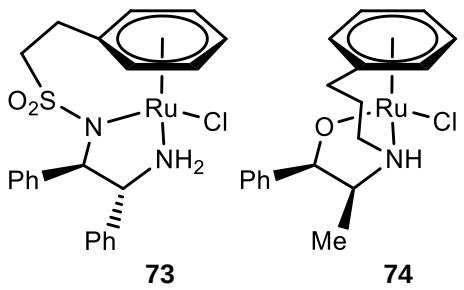
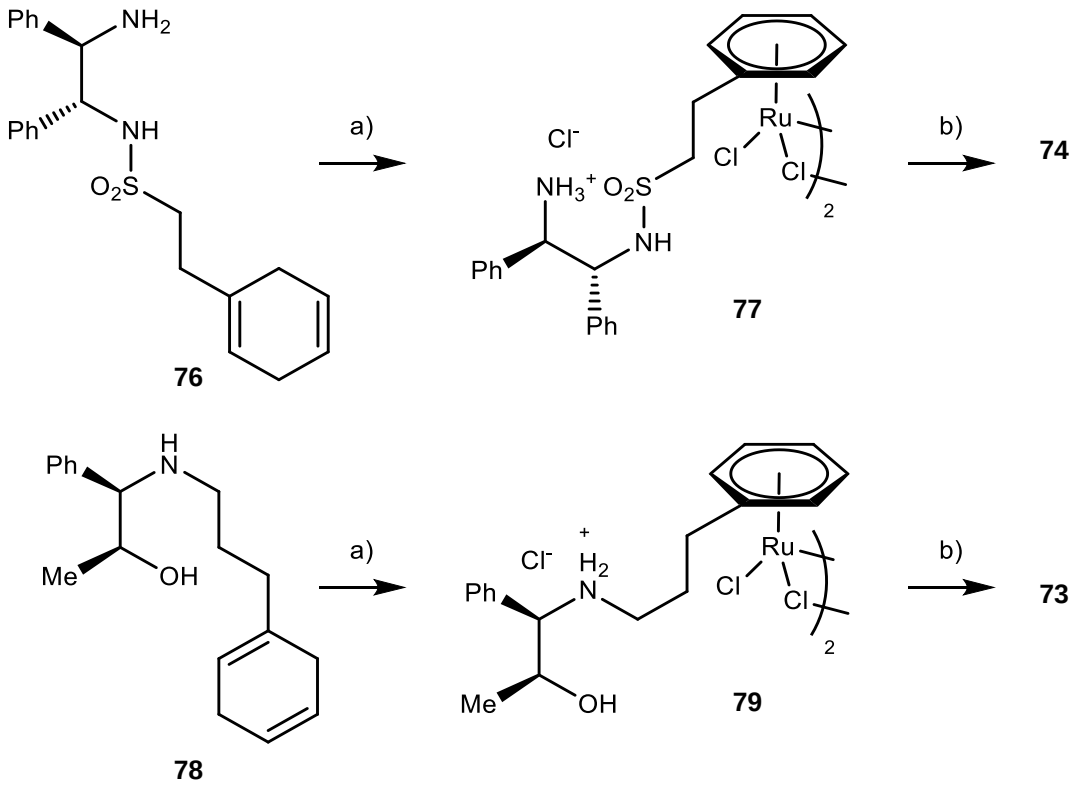


Figure 14: Early tethered complexes for ATH, based on the Noyori catalyst.

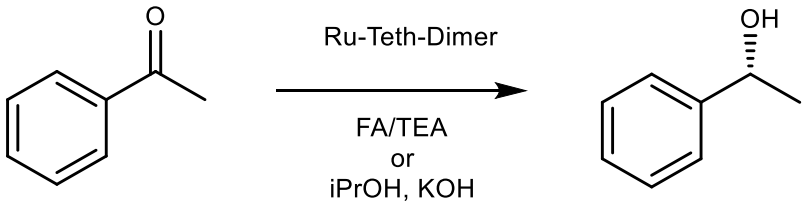
The first developed complexes **73** and **74** contained a saturated alkyl chain linking an amino alcohol or sulfonylated diamine respectively to a phenyl ligand. Their synthesis first requires preparation of ligand precursors **76**/**78** containing a cyclohexadiene ring, which can then be dehydrogenated by the common ruthenium source [$RuCl_3 .xH_2O$] **75** to form substituted ruthenium arene chloride dimers **77**/**79** (Scheme 27). The dimers are isolated as hydrochloride salts, preventing decomposition by premature coordination of the free amine to ruthenium. Cyclisation in basic conditions splits the ruthenium dimer and forms the monomeric chloride complex.



Scheme 27: Synthesis of first generation tethered complexes **73** and **74**. a) i) HCl, Et_2O, ii) **75**, EtOH, reflux. b) NEt_3, IPA, reflux

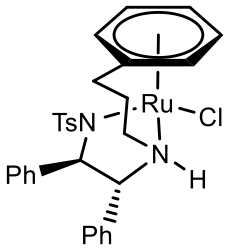
Dimer **79** was used directly for ATH of ketones in IPA/KOH, where it gave marginal improvements in ee relative to the analogous untethered [$RuCl(C_6H_6)$ephedrine] complex. It could also be used at a reduced S/C ratio of 1000:1. As found previously with complexes containing amino alcohol ligands, FA/TEA was not suitable as a hydrogen source.

Table 3: Reduction of acetophenone with first generation tethered catalyst dimers **77** and **79**



Entry	Catalyst	S/C	H-source	% Yield	% ee
1	**79**	100	*i*PrOH	96	66
2	**79**	1000	*i*PrOH	83	67
3	**77**	100	FA/TEA	99	96
4	**77**	1000	FA/TEA	99	93

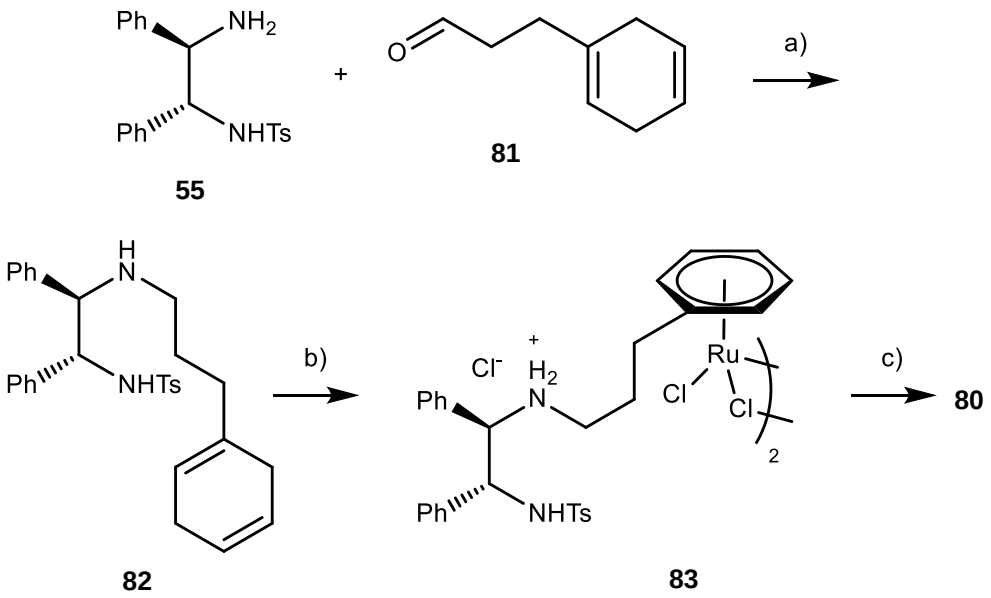
Sulfonamide tethered dimer **77** was more effective, reducing acetophenone **47** in 96% ee at 28 °C. It was also effective at S/C ratio of 1000:1 and was used in an extended reaction trial, whereby after a complete reduction of **47** in FA/TEA over 24hr, further portions of ketone and solvent were added and fully consumed after 3 and 7 days. This indicates the catalyst remains active for a long period of time.



3C-teth (80)

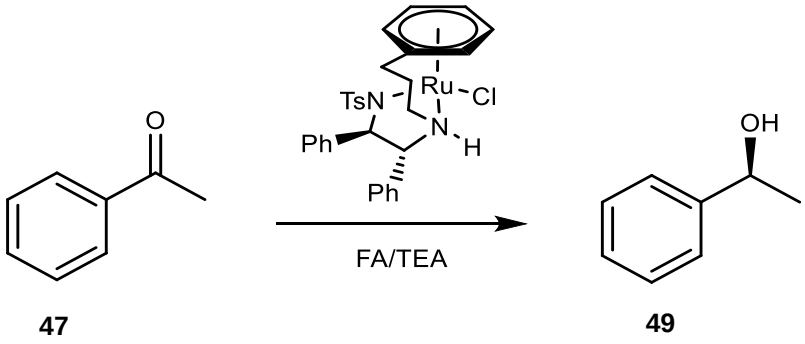
Figure 15: 3C-tethered catalyst with improved activity.

In 2005 a new tethered diamine variant **80** was reported, in which the alkyl chain is attached to the free amine as in **74** rather than through the sulfonyl group.[52] The synthetic route was similar to that for **74**, with reductive amination used to link the cyclohexadiene-aldehyde **81** with TsDPEN before dimerization to **83**. Again basic conditions lead to formation of the monomeric species **80**.



Scheme 28: Synthetic approach to 2nd generation tethered catalyst **80**.Conditions: a) i) 4Å MS, DCM; ii) $LiAlH_4$, THF; b) i) HCl, Et_2O, ii) **75**, EtOH, reflux; c) NEt_3, IPA, reflux

This complex was significantly more active than **73** and **74**, giving complete reduction of acetophenone **47** in 96% ee in only 3 hrs rather than the overnight reaction required for untethered complex **58**. The increased activity allowed the use of the catalyst at loadings as low as 10,000:1, where **47** is reduced in 98% conv over three days.



Scheme 29: ATH of acetophenone with **3C-teth (80)**. Results: at S/C 200:1, Conv 100%, ee 96% in 3 hours; at S/C 10000:1, Conv 98%, ee 96% in 79 hours.

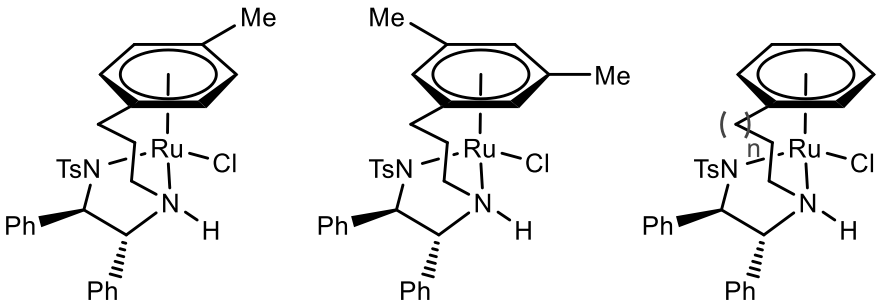
Catalyst **80** has proven useful in several academic and industrial applications, and both enantiomers have been commercially produced by Johnson Matthey.[53*]

Further references and patents available from *Impact case study REF3b*, 2014 : https://impact.ref.ac.uk/CaseStudies/CaseStudy.aspx?Id=7263

1.3.5 Further Tethered Ru ATH Catalysts

1.3.5.1 Tether Length and Arene Substitution

Wills *et*. *al*. have applied the same synthetic route to prepare a series of tethered complexes with varying tether length and substitution pattern on the aromatic ring.[54]

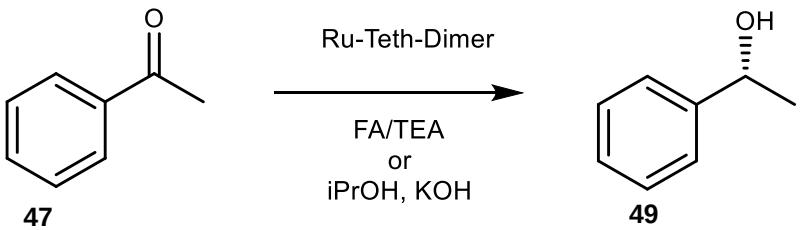


84 **85** **86: n= 0**
87: n= 2
88: n= 3

Scheme 30: Structural variants of 3C-teth catalyst **80**, with methyl substitution and differing tether length.

The optimum tether length appears to be limited to 3 or 4 carbon atoms. The 5C complex **88** forms very slowly from its corresponding dimer and cannot be isolated in large quantities. When tested in ATH of acetophenone in FA/TEA, catalyst **88** gives only 38% conversion, and the highly restricted 2C-complex **86** was even less active. However both catalysts maintain good enantioselectivity. The 4C-complex **87** is actually more active than the originally reported **3C-teth (80)** complex, achieving full acetophenone reduction in 75 mins at 40 °C compared to 2 hr for **80** (Table 4).

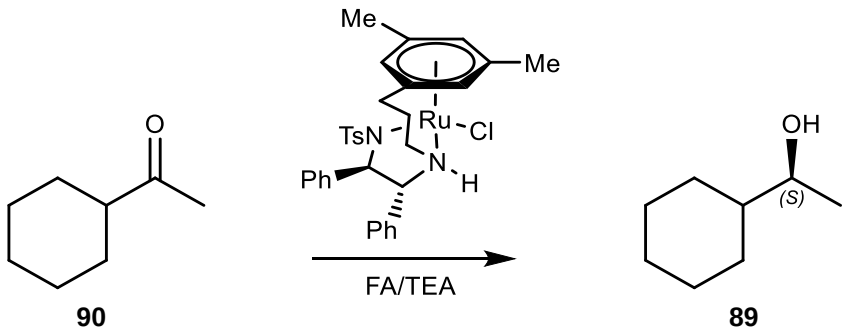
Table 4: Reduction of acetophenone with tethered catalysts **80** and **84**-**88**



47 **49**

Entry	Catalyst	Tether	Arene Substituent	t /hr	% conv	% ee
1	**86**	2C	H	15	19	92
2	**80**	3C	H	2	100	96
3	**87**	4C	H	1.25	100	96
4	**88**	5C	H	6	38	94
5	**84**	3C	Me	4	100	96
6	**85**	3C	Me_2	5	100	93

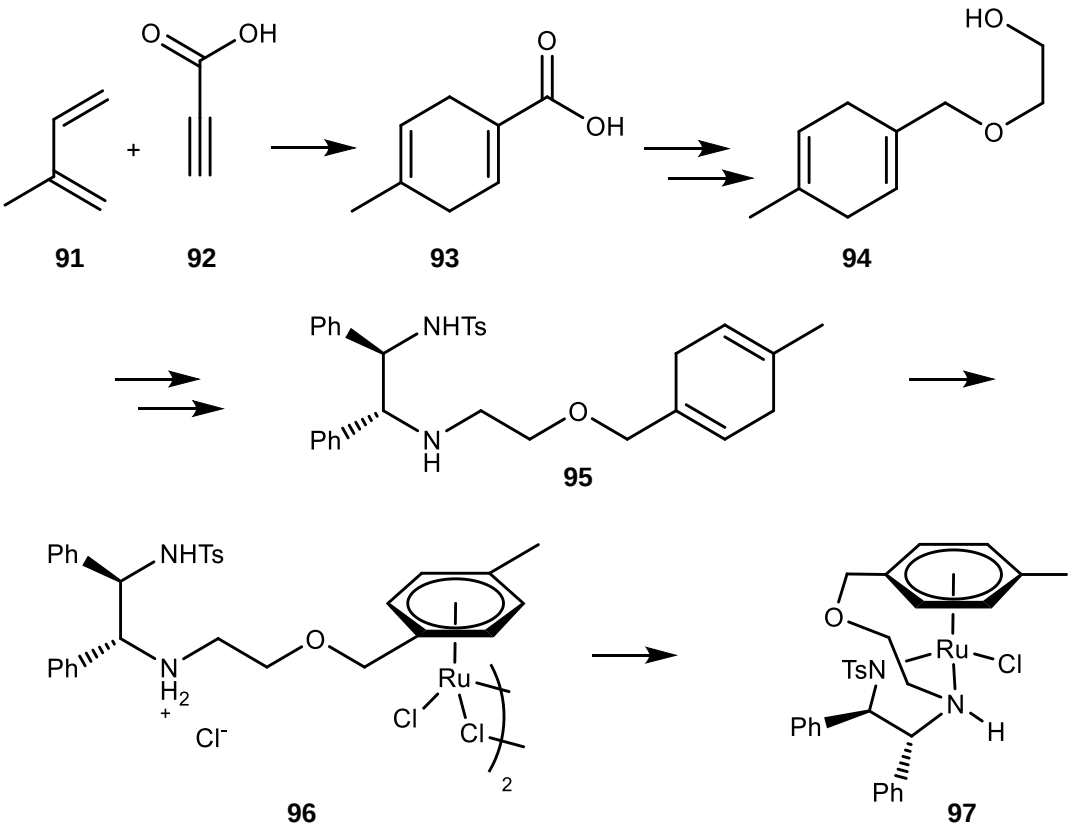
For the substituted 3C tethered catalysts, additional substitution on the arene ligand decreases the reaction rate. Complex **84** achieves complete acetophenone conversion in 4 hours with good enantioselectivity (96%). Dimethyl complex **85** is marginally slower and the arene substitution results in a slight decrease in enantioselectivity (93%). However **85** showed good enantioselectivity (90%) in the reduction of an alkyl-alkyl ketone, which is not suitable for reduction with the **3C-teth (80)** complex (Scheme 31).



Scheme 31: Reduction of alkyl-alkyl ketone with tethered catalyst **85**. 100% Conv, 90% ee.

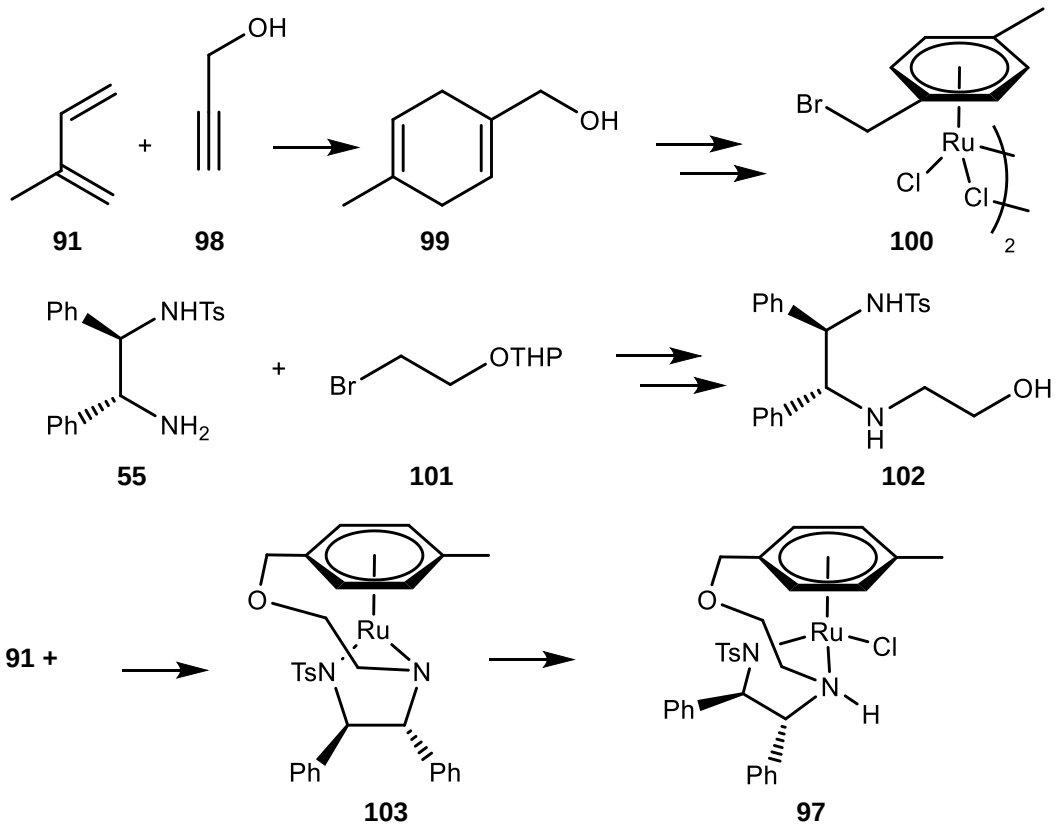
1.3.5.2 Ether-Tethered Catalysts; Cycloaddition Approach

In an attempt to improve upon the synthetic route to tethered complexes, Wills and Ikariya independently reported the oxo-tethered catalyst DENEB **97** in 2011-2012.[55,56] Both groups adopted a similar synthetic strategy which bypassed the troublesome Birch reduction by starting with a 4+2 cycloaddition to isoprene **91** to prepare the cyclohexadiene component (Scheme 32 and Scheme 33)



Scheme 32: Wills' synthesis of DENEB **97**

Wills' approach is linear on the ligand, whereby the cycloaddition product **93** is reduced and chain extended to an ethylene glycol **94**, linked with TsDPEN by oxidation-reductive amination to form **95** and then converted to the complex **97** by dimerization and cyclisation as for the standard tethered complex synthesis.



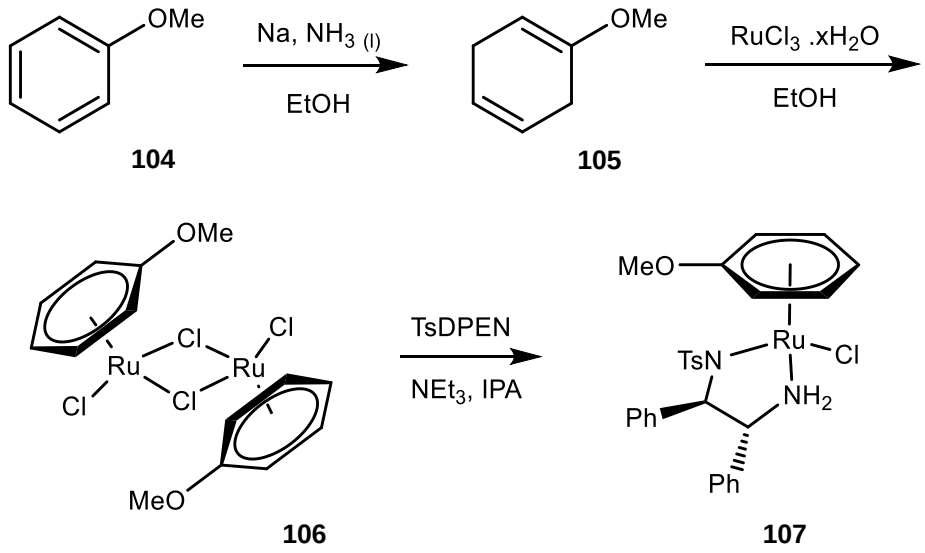
Scheme 33: Ikariya's synthesis of DENEB **97**

Ikariya's approach is more convergent. The cycloaddition takes place with propargyl alcohol **98** to form the alcohol cycloaddition product directly. Dehydrogenation with **75** and bromination forms the required ruthenium dimer **100**. The alkoxy substituted ligand **102** is prepared by alkylation and deprotection of TsDPEN **55**. Finally the ligand and dimer undergo substitution and cyclisation in one step to form the 16e complex **103**, which can be converted to DENEB **97** by reaction with HCl.

1.3.5.3 Methoxy Substituted tethered Catalysts

The methods described thus far for tethered catalyst synthesis have only dealt with alkyl substitutions on the ruthenium arene. In order to prepare a tethered methoxy functionalised complex a different approach has been taken.

Scheme 34 first illustrates a potential synthesis of a non-tethered OMe-functionalised complex **107** and its simple precursor dimer **106**. While the Birch reduction works well for anisole, the dehydrogenation reaction of cyclohexadiene **105** with ruthenium trichloride **75** is challenging and requires a 6-fold excess of diene.[57]

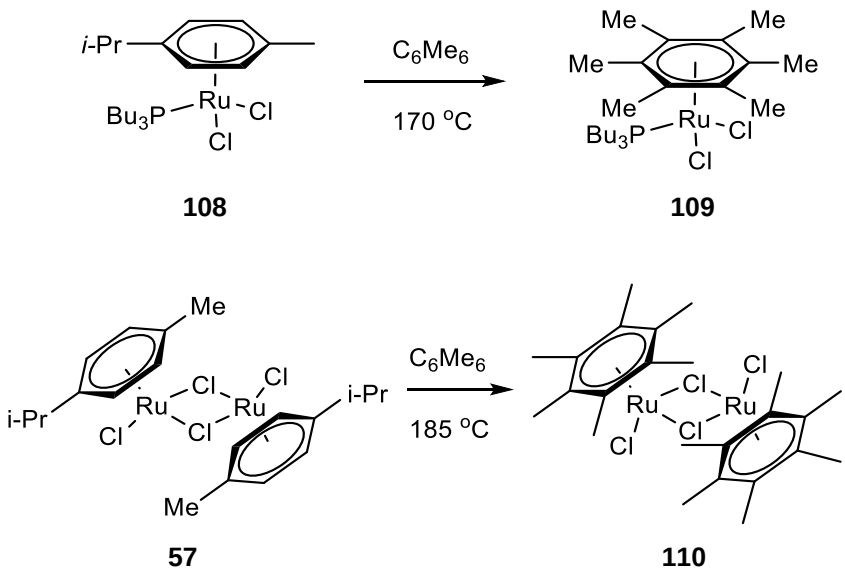


Scheme 34: Theoretical synthetic route for preparation of methoxy functionalised non-tethered catalyst.

However this would be an unacceptable route to tethered complexes as the required diamine-functionalised diene is complex and requires at least a two-step synthesis in its own right from expensive chiral starting materials, therefore using it in 6-fold excess is unlikely to be practical.

1.3.5.4 Arene exchange as a Synthetic Route to Tethered Catalysts

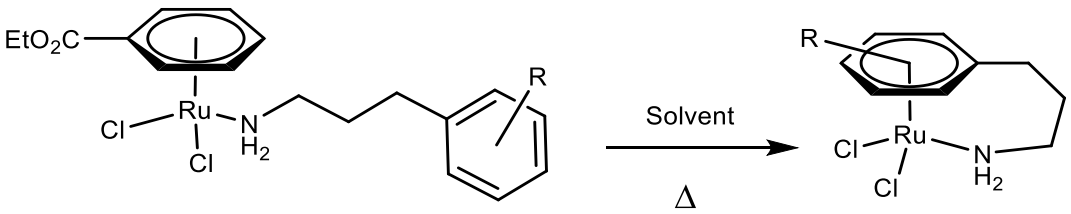
An alternative route to a tethered form of complex **107** would be the direct exchange of a ligand aromatic group with a more easily prepared ruthenium dimer such as **57** (Scheme 35). Such arene exchange has been known for some time in the literature for simple half sandwich complexes such as [$RuCl_2$(p-Cymene)PBu_3] **108**, and typically takes place by heating the precursor complex in an aromatic solvent.[58]



Scheme 35: Preparation of hexamethylbenzene ruthenium complexes by arene exchange.

It was found that electron poor solvents will not displace ruthenium arene complexes, while electron rich ones will. For example, the hexamethylbenzene (HMB) complex **109** can be prepared in 21% yield by heating **108** with HMB at 170 °C. The low yield represents an improvement on the Birch reduction approach, which is intractable for hexamethylbenzene. Bennett has also prepared the corresponding dimer complex **110** in 80% yield in a similar fashion.[59]

Table 5: Successful examples of arene exchange with simple monodentate amine ligands.

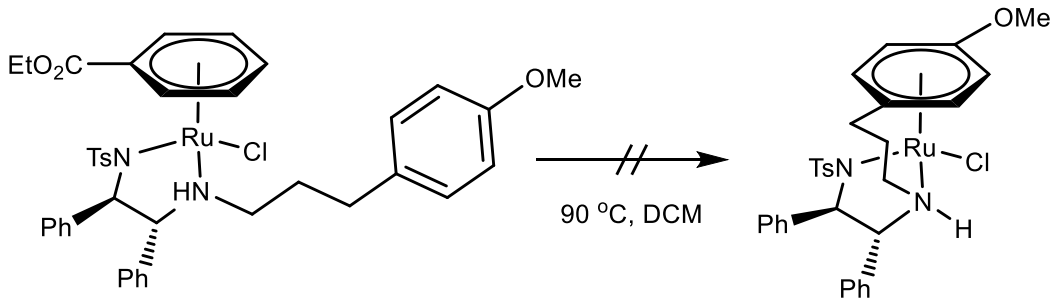


Complex	R=	Solvent	t /hr	T /°C	% Yield
111	H	DCE, THF	90	85	42
112	Me x5	Chlorobenzene	2	140	32

Sadler has demonstrated a successful example of intramolecular arene exchange using simple monodentate amine and chloride ligands (Table 5).[60] Complex **111** is prepared by heating in DCE, and a small quantity of THF was added in an attempt to accelerate the

reaction.* Ikariya has also published a similar example with a pentamethylated arene ligand, in which the exchange occurs at a higher temperature in chlorobenzene.[61] Ethyl benzoate ($C_6H_5CO_2Et$: **113**) was used in both cases as the aromatic ligand due to its electron poor nature.

Wills *et*. *al*. attempted to prepare **OMe-teth (115)** via arene exchange from the half sandwich precursor **114** (Scheme 36).[62] Complex **114** was resistant to arene exchange however, yielding only 15% of the desired product and extensive decomposition of the starting materials.

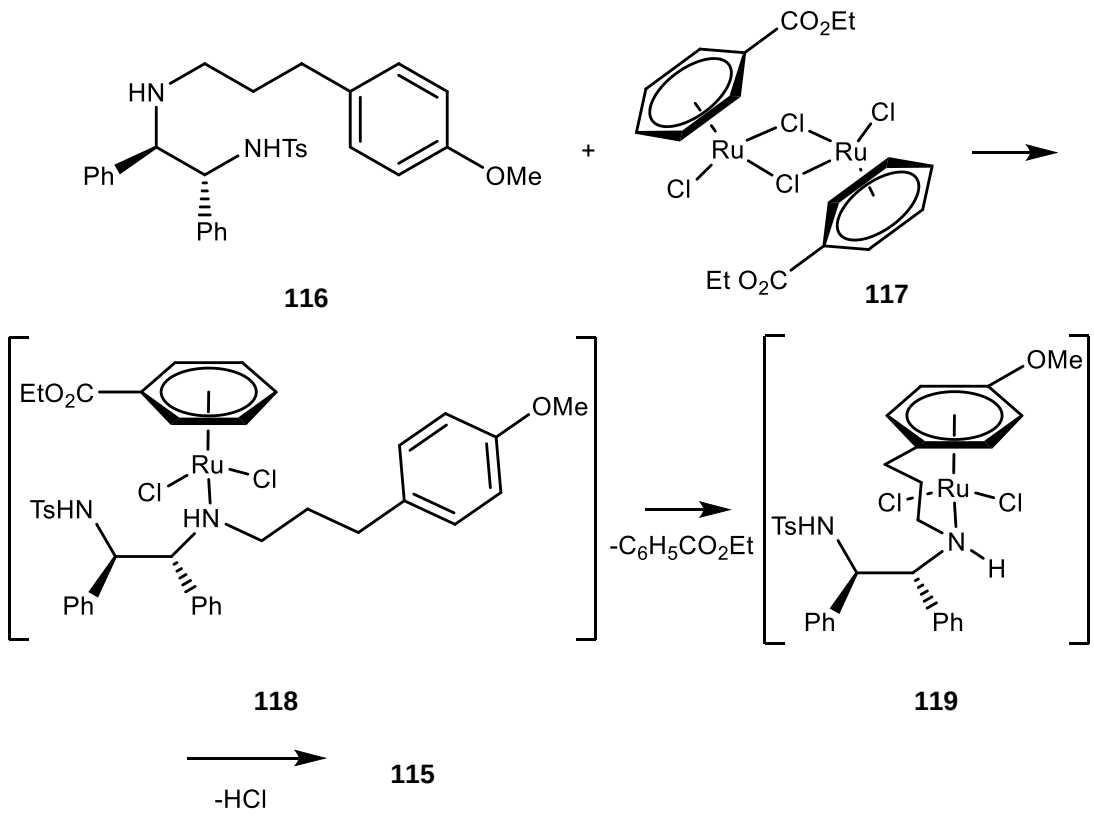


114 **OMe-teth (115)**

Scheme 36: Unsuccessful arene exchange reaction for diamine co-ordinated ruthenium complex. Conversion < 15%

This problem was resolved by an adjustment of reaction conditions (Scheme 37). A methoxyphenyl substituted diamine ligand **116** was reacted with $[RuCl_2(C_6H_5CO_2Et)]_2$ **117** at high temperature and in the absence of base. The proposed mechanism involves initial complexation between ruthenium and the free amine on the ligand gives monomeric intermediate **118**. The monodentate amine and chlorine ligands on ruthenium resemble the structure of **Error! Reference source not found.**, and the conditions encourage rapid arene exchange to intermediate **119**. Finally the tosylated amine bonds to ruthenium with loss of HCl.

* Based on work by Bennet *et*. *al*. on monophosphine tethered complexes.[193]



Scheme 37: Arene exchange synthetic route to tethered complex **115**

Catalyst **115** proved to be highly active in ATH of a variety of ketones, some of which will be detailed further in section 1.4.

1.3.6 Summary

Ru(II) half sandwich compounds such as **58** have proven themselves as highly efficient ATH catalysts for ketone reduction. The development of tethered versions of these complexes such as **80**, **97** and **115** has further improved the catalytic activity and selectivity available. However these tethered complexes introduce extra complexity into the synthesis, especially the Birch reduction in the synthesis of complex **80** which is particularly challenging on scale. Complexes **97** and **115** offer an alternative to this particular step but still have difficulties in their own synthesis. DENEB **97** requires seven steps, while **115** takes five but the final complexation is practically challenging and yields are limited. For these catalysts to compete with **58**, which is available in one high yielding step from TsDPEN and commercially available ruthenium dimer, their synthesis must be optimised. In particular the final arene exchange step to form **115** represents an area for possible improvement and efforts to this end will be described in the results section 2.2.

1.4 Substrates for ATH

While original AH catalysts were first developed for olefin reduction, the most common substrate class for ATH with Ru(II) catalysts are the aryl-alkyl ketones, such as acetophenone **47**.[39] This is due to the effective enantioface discrimination provided by the stabilising edge to face interaction between catalyst and substrate aromatic rings (Figure 16).

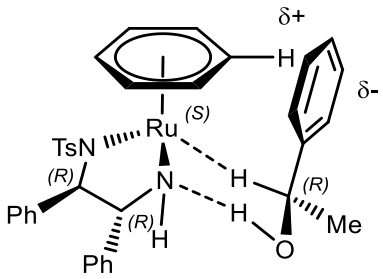
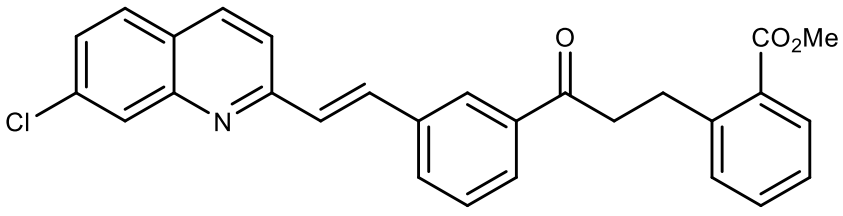


Figure 16: Stereochemistry in transition state for acetophenone reduction.

New catalysts are often compared by their performance in the reduction of acetophenone, the simplest alkyl-aryl ketone. New catalysts strive for the highest possible ee and full conversion at moderate temperature, short reaction times and high concentrations.

Ru(II)Arene ATH catalysts are also particularly selective for ketone reduction, and hence tolerant of many other functionalities in more complex substrates, including halides, alcohols, amines, esters, amides, alkenes and alkynes, heterocycles, and nitriles. For example, the ketone functionality in **120** can be reduced selectively by the Noyori catalyst **58** without affecting the halide, quinolone, alkene or ester functionalities.[41]



120

Figure 17: Multifunctional ketone substrate. The corresponding alcohol is formed in 68% yield, 92% ee.

However the scope of ATH is not simply limited to acetophenones. Other directing groups capable of engaging in the stabilising edge to face interaction with the η^6-arene ring protons of the catalyst have been used in the reduction of ketones, such as alkynes (Figure 18).[63]

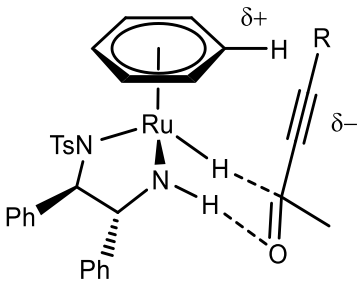


Figure 18: Proposed transition state for asymmetric alkyne reduction

Alternatively, aryl-aryl ketones can also be reduced asymmetrically based on a difference in electron density on the aromatic rings; the electron rich ring will have a stronger edge to face interaction with the positive aromatic hydrogen of the catalyst.[41] For example 4-(4-methoxybenzoyl)benzonitrile is reduced with moderate enantioselectivity (~70%) by a mesitylene analogue of complex **60**, although this is still impressive for a substrate with such similar functional groups to discriminate between (Figure 19).

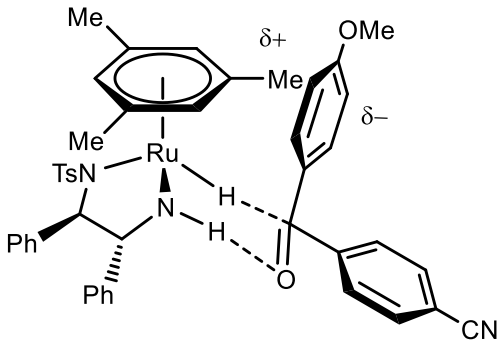
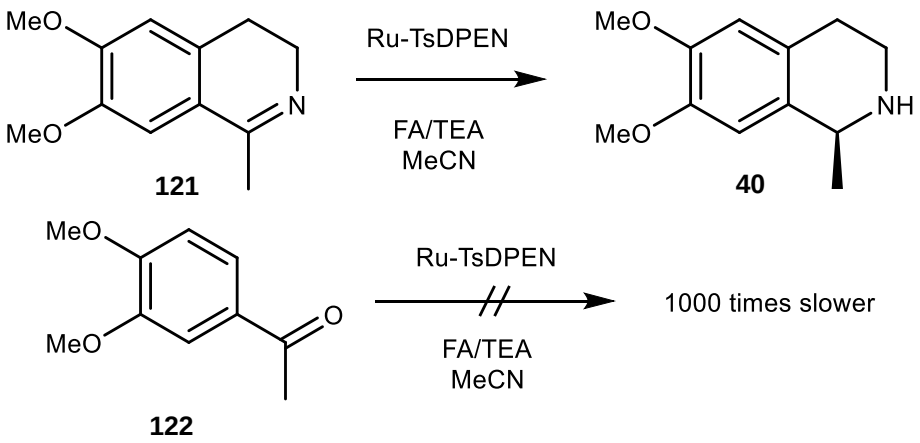


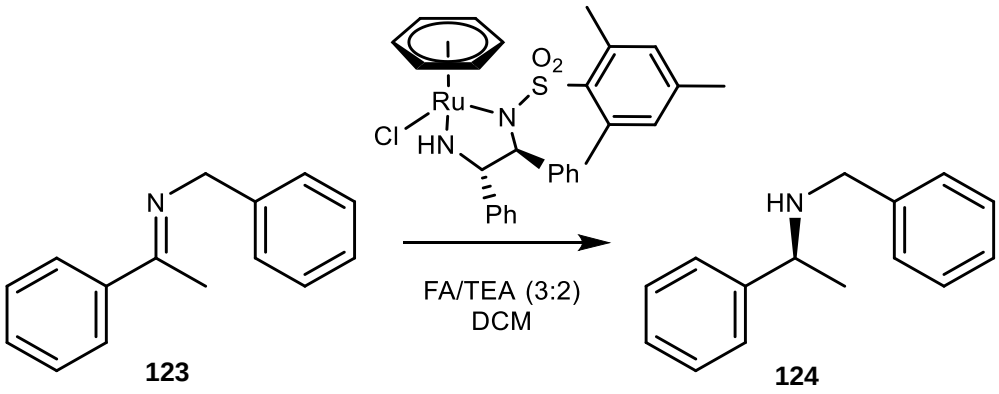
Figure 19: Proposed transition state for asymmetric benzophenone reduction

Imines have also been reduced.[64] For example, salsolidine **40** was prepared in 95% ee by ATH of imine **121** with catalyst **58**. It was also found that the imine is much more reactive in a competition reaction than a structurally related ketone **122**. Section 1.4.1 discusses the difficulties inherent in reduction of such electron rich ketones in more detail.



Scheme 38: Reduction of salsolidine and its ketone analogue with Noyori catalyst **58**. Imine reduction: Yield 99%, ee 95%.

Cyclic imines are more suited to these reduction conditions, as the imine is more stable and less likely to hydrolyse before reduction. The reduction of acyclic imine **123** with a related catalyst derivative containing the bulkier mesitylene sulfonyl group and a benzene ligand on ruthenium delivers the chiral amine **124** in only 77% ee and 77% yield. The reduced enantioselectivity in this instance may also be due to competition between the benzyl and phenyl groups to direct the asymmetric reduction.

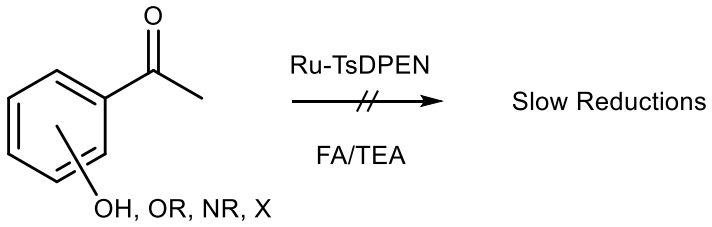


Scheme 39: Reduction of acyclic imine with Noyori catalyst **58**. Yield 72%, ee 77%.

Some examples of ATH of alkenes conjugated to strongly electron-withdrawing groups have been reported and are described in more detail in section 1.4.2

1.4.1 Electron Rich Ketones

Ketones with electron donating substituents bonded to the aromatic ring are more challenging substrates for ATH. Reductions tend to be sluggish and require more forceful conditions, which leads to reduced enantioselectivity.



Scheme 40: Electron-rich substrates with slow reaction time

The reason for the lack of reactivity is clear when considering the resonance structures for such ketones. Electron donation into the ring is encouraged in a push-pull effect up into the ketone, leading to a resonance structure with substantial single bond character for the carbon-oxygen bond and an increase in electron density at the carbonyl carbon. Oxygen is a less powerful electron donor than nitrogen and asymmetric reduction of oxygen-substituted ketones has been more thoroughly explored in the literature.

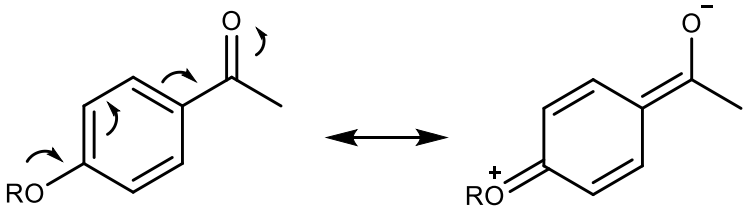
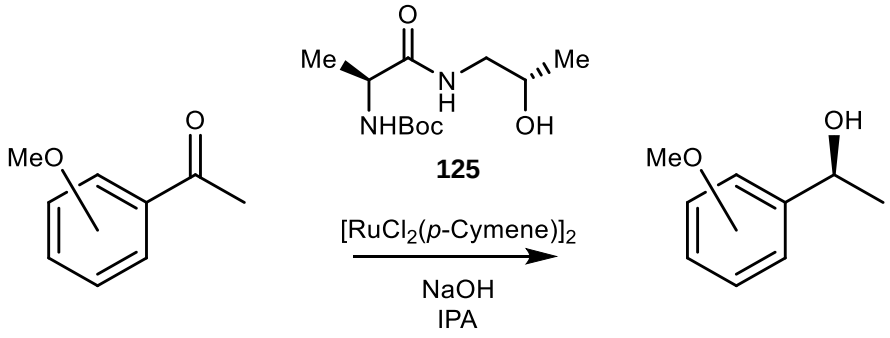


Figure 20: Ketone stabilising resonance structure for para-substituted ketones

1.4.1.1 Effect of Oxygen Substitution Position on ATH

Indeed the stabilising effect of oxygen is most pronounced for 2' and 4' substituted ketones, as has been shown in the reduction of isomers of methoxy-acetophenone (**126**, **127**, **128**) by a Ru(II) half-sandwich catalyst formed in situ with an amino acid derived ligand **125** (Table 6).[65] Reduction of the **2'** and **4'** isomers in isopropanol was low yielding but selective (94% ee), while the **3'** isomer was more reactive.

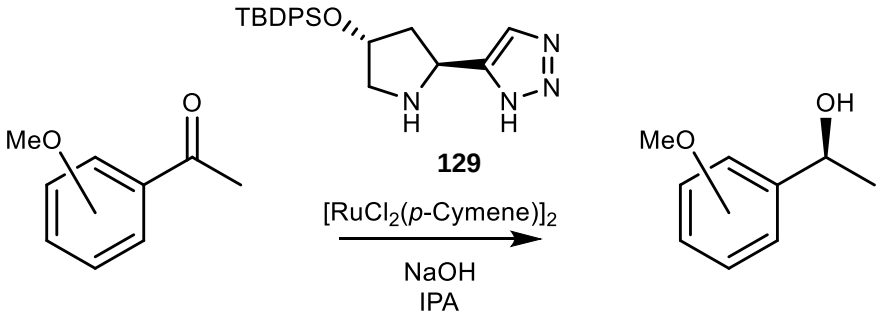
Table 6: Reduction of isomers of methoxyacetophenone.



Substrate	Isomer	% Conv	% ee
126	2’	49	94
127	3’	85	97
128	4’	59	94

The relative effect of substituent position will depend on the catalyst. Another amino acid ligand **129** derived from proline was again most effective at reducing **127** in isopropanol, in 85% conversion and 75% ee (Table 7).[66] However reduction of **126** suffered from low ee (34%) and **128** from poor conversion (24%).

Table 7: ATH of isomers of methoxyacetophenone.



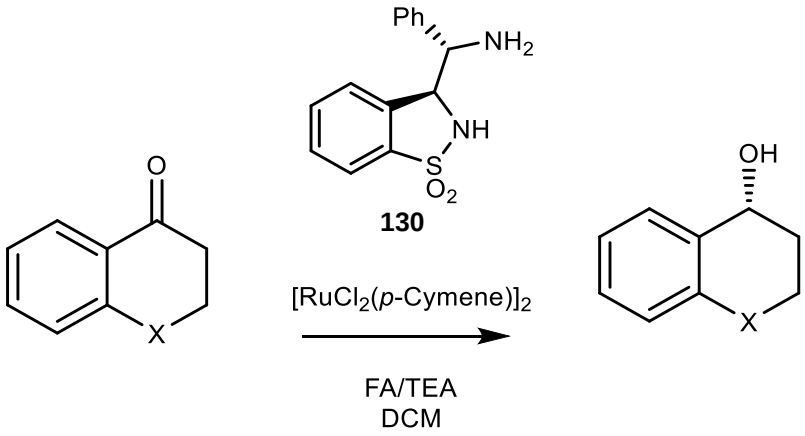
Substrate	Isomer	% Conv	% ee
126	2’	94	34
127	3’	85	75
128	4’	24	71

1.4.1.2 ATH: Further Examples of Ru(II) Catalysis

Other reports include the Ru(II) catalysed ATH of 4-chromanone **132** in FA/TEA in 100% conv and 99% ee (Table 8).[67] The γ-sultam ligand **130** appears to be primarily suited to reduction

of cyclic ketones, as it gives similar results for the reduction of tetralone **131** but is less effective for reduction of acetophenone **47**.

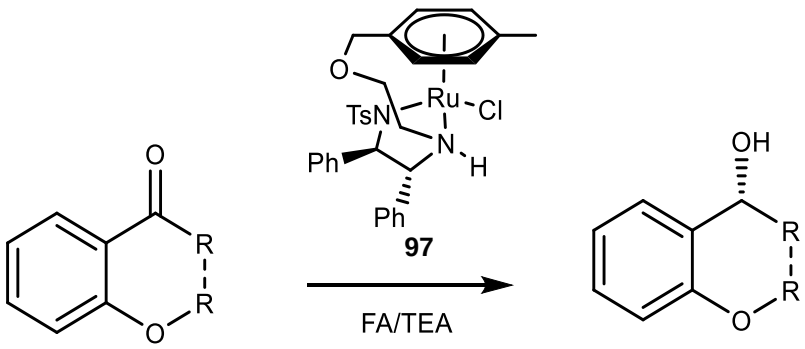
Table 8: ATH of cyclic ketones with Ru- γ-sultam system.



Substrate	X=	% Conv	% ee
131	CH2	99	99
132	O	100	99
Acetophenone **47**		100	85

Ikariya has applied the DENEB catalyst (**97**) described in section 1.3.5 to the reduction of **126** and **132**, giving complete conversions and 93 and 99% ee respectively (Table 9).[55] These reductions take place at an impressively low catalyst loading of 1000:1 S/C.

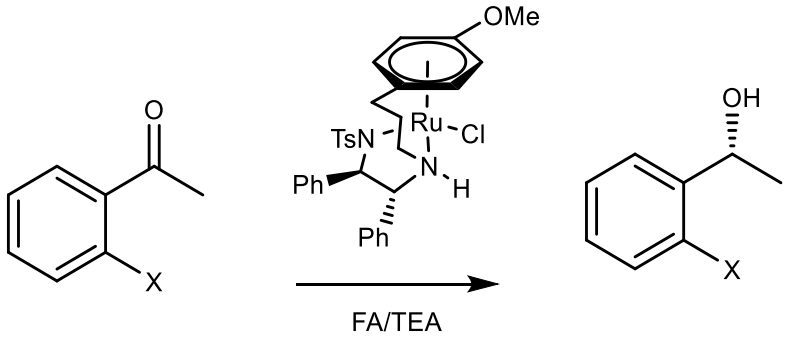
Table 9: Reduction of electron rich ketones with oxo-tethered catalyst **97**



Substrate	R	% Conv	% ee
126	Me	99	99
132	(CH_2CH_2)	100	99

Finally Wills *et*. *al*. have applied catalyst **115** to the ATH of *ortho*-methoxy and *ortho*-hydroxy acetophenone. Both substrates are reduced effectively at low catalyst loading (Table 10)

Table 10: ATH of *ortho*-substituted ketones with **115**



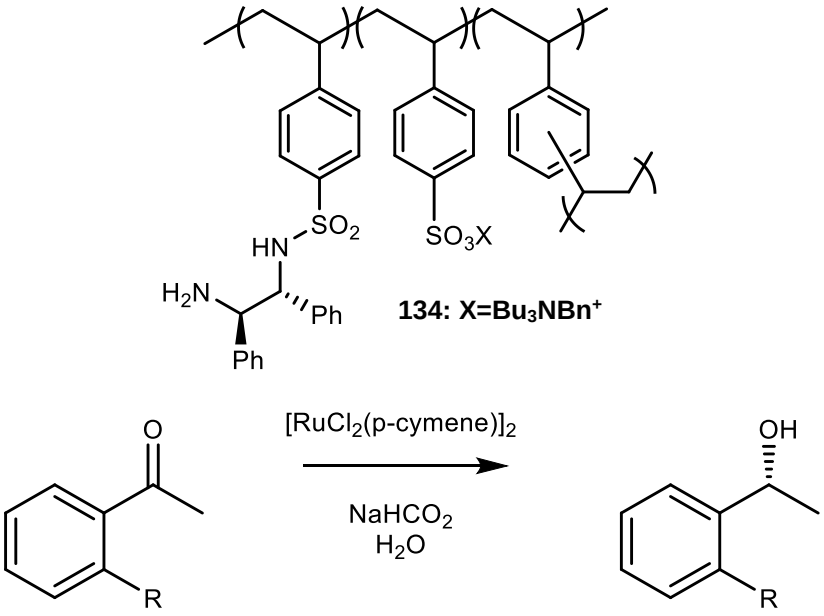
Substrate	X =	% Conv	% ee
126	OMe	100	96
133	OH	100	99

Conditions: S/C 1000:1, 60°C.

1.4.1.3 ATH: Supported Ru Catalysts

Two examples of ATH of methoxyacetophenones are from reports of immobilised catalysts under aqueous conditions (more examples of polymer supported catalysts are discussed in section 1.5.1). Itsuno uses a polystyrene sulfonate support in the reduction of **126**, and although conversion is reduced relative to acetophenone **47**, the ee remains reasonably high at 91% (Table 11).[68] The results of reduction with catalyst **134** also appear to be better than those obtained for the unsupported monomeric catalyst **58** (85% conv, 95% ee), although the latter reaction was only run for 0.5 hours and may have been stopped before complete conversion was achieved.

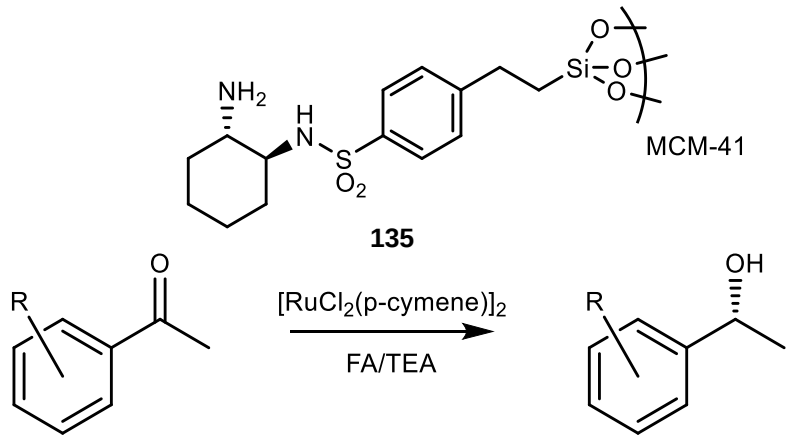
Table 11: ATH of **47** and **126** with polymer supported catalyst.



Substrate	R	% Conv	% ee
47	H	100	98
126	OMe	79	91

Rahman *et*. *al*. employ a silica-immobilised supported catalyst for reduction of both **126** and **127** (Table 12).[69] Surprisingly they found no significant difference in reactivity or selectivity between the two isomers and actually achieved better conversion in both cases than in ATH of acetophenone.

Table 12: ATH with MCM-41 silica supported catalyst **135**

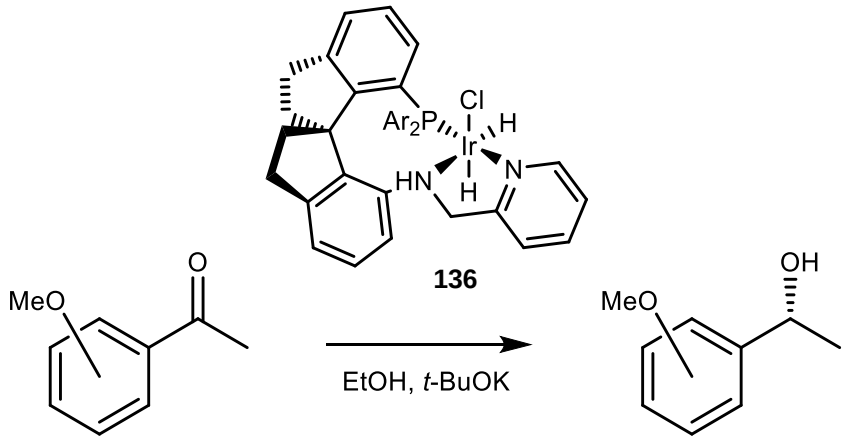


Substrate	Isomer	R	% Yield	% ee
47		H	85	86
126	2’	OMe	93	83
127	3’	OMe	94	85

1.4.1.4 ATH: Other Metal Catalysts

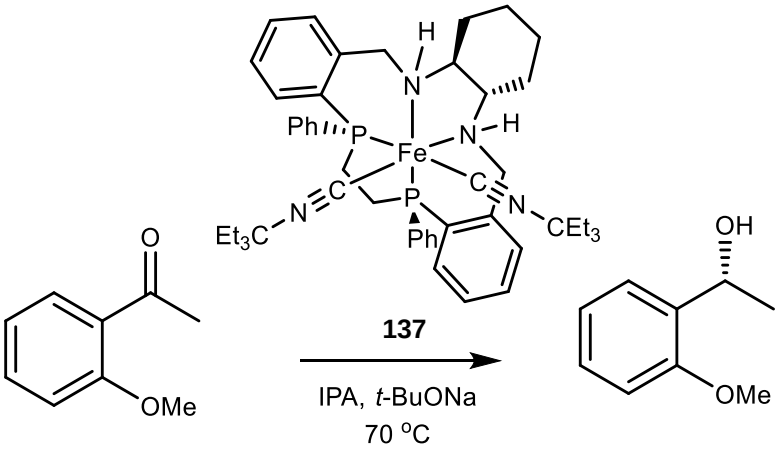
An Ir catalyst **136** containing a tridentate spiro-amino-phosphine ligand has been shown to be effective for the reduction of substituted acetophenones in EtOH/*t*BuOK, including **126** and **128** (Table 13).[70] This catalyst system shows little variation in performance across the range of halide, alkyl and alkoxy substituents tested.

Table 13: Example reduction of electron rich ketones with Ir catalyst **136**



Substrate	Isomer	% Yield	% ee
126	2’	99	96
128	4’	93	95

Iron catalysts are much sought after as an inexpensive alternative to platinum group metals.[71] Recently an Iron macrocyclic complex **137** was applied to a simple series of ketones for reduction in isopropanol, including **126**, giving the product in 99% ee (cf. 96% ee for reduction of **47**).[72] Complex **137** does require handling under strict inert conditions, but has been demonstrated to be practical at a reasonable scale of 100 mmol and the selectivity and yield of this reduction are impressive.



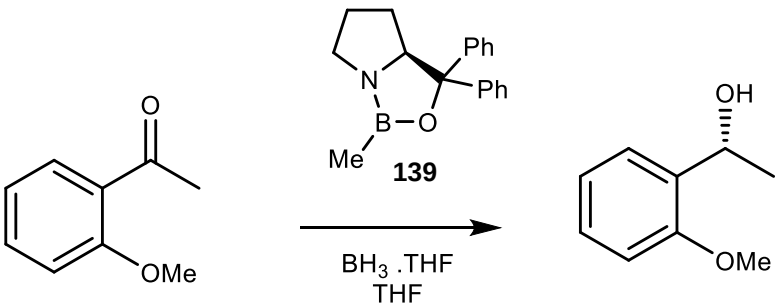
Scheme 41: ATH of **126** using an Iron macrocyclic complex. Yield 99%, ee 99%.

Aside from ATH, CBS reduction, AH and enzymatic reduction have all been applied in the reduction of oxygen substituted acetophenones. Some relevant literature examples are described below.

1.4.1.5 CBS reduction

CBS reduction uses a chiral oxazaborolidine catalyst to promote the borane reduction of ketones.[73] The method was developed in the late 1980s and has found broad application across a range of substrates.[74] Typical conditions involve a catalyst loading of 10% and use of anhydrous THF as solvent.

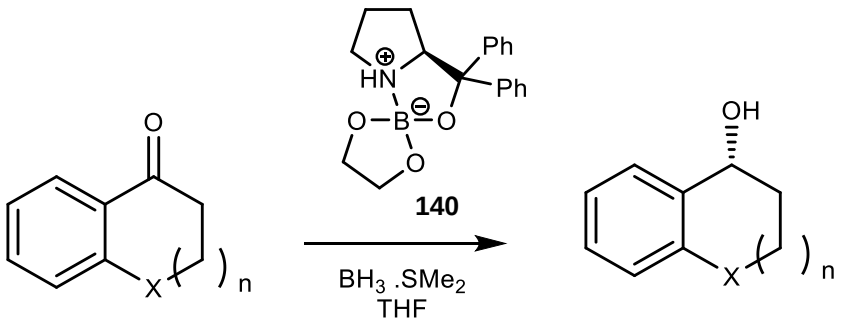
CBS conditions using **139** have been effectively applied at 100 mmol scale to the reduction of **126**.[75] The chiral alcohol was obtained in good yield and 96% ee, although a very high catalyst loading was required (Scheme 42).



Scheme 42: CBS reduction of **126**. 40 mol% catalyst, Yield 99%, ee 96%

A related bench stable spiroborate ester **140** has been applied to reduction of a variety of substrates, including chroman-4-one **132** with 10% catalyst loading.[76] The smaller ring in **141** results in a slightly higher yielding but less selective reaction, while sulfur in substrate **142** has less of a detrimental effect on reaction rate, giving a good yield of alcohol at lower catalyst loading.

Table 14: CBS Reduction of electron rich ketones and heterocycles with spiroborate **140**

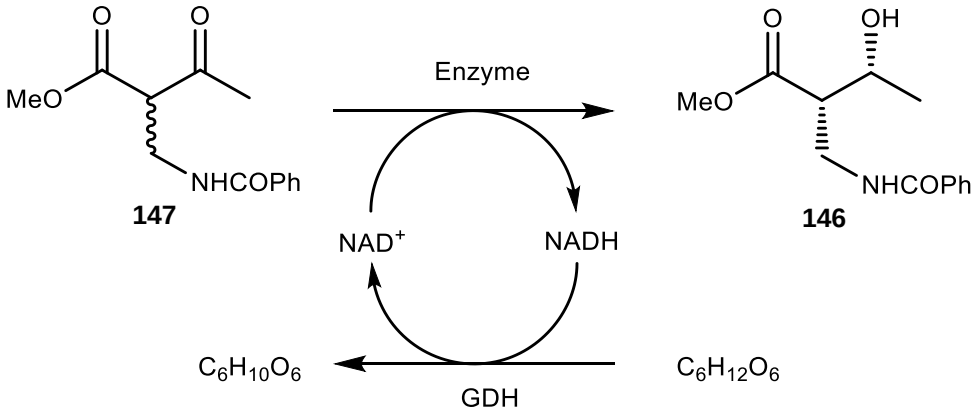


Substrate	X=	n=	S/C	% yield	% ee
132	O	1	10	82	99
141	O	0	10	86	92
142	S	1	100	92	99

1.4.1.6 Enzymatic reduction

Enzymatic reduction can be an extremely efficient alternative to ATH in certain cases. Enzymes are extremely specific in their reactivity and are often only suitable for a narrow range of substrates. However they can be very efficient, with high TON under mild conditions.

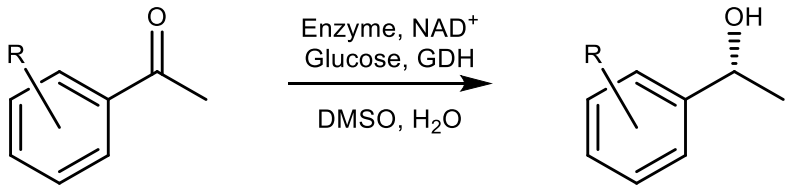
For example, Zheng compares a set of 3 recombinant alcohol dehydrogenase enzymes (*Bg*ADH1 (**143**), *Bg*ADH2 (**144**), *Bg*ADH5, (**145**)) derived from the *Burkholderia gladioli* bacteria strain and expressed in *Lactobacillus brevis*.[77] This system was designed for the selective DKR of an α-alkylamino-β-keto ester **147** to the (2S, 3R) product (Scheme 43). The reduction uses NAD^+ as co-enzyme, which is regenerated in situ using glucose dehydrogenase (GDH) and glucose as the overall hydrogen source.



Scheme 43: Enzymatic DKR and co-catalyst regeneration

Enzymes **143**-**145** were applied to the reduction of a range of simple ketones to observe the substrate specificity (Scheme 44). Reduction of the hindered *ortho*-substituted **126** was less selective than reduction of acetophenone but could still be prepared with 90-95% ee. Interestingly the para-isomer **128** was reduced with higher ee than **126** for each of the 3 enzymes. Activity was reduced in both cases. Reduction of the 3,5-dimethoxy substrate **148** gives intermediate activities but results in a complete reversal of selectivity for just one of the enzymes tested, an unexpected result.

Scheme 44: Enzymatic reduction of ketones



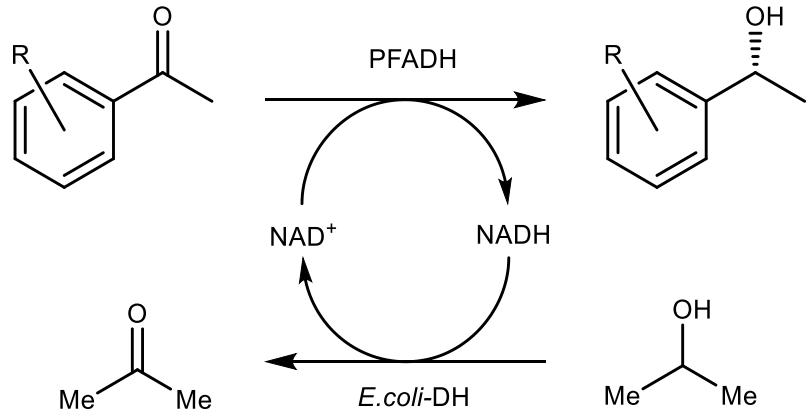
Substrate	**R=**	***Bg*ADH1** 143		***Bg*ADH2** 144		***Bg*ADH5** 145	
		Activity / U mg^{-1}	% ee	Activity / U mg^{-1}	% ee	Activity / U mg^{-1}	% ee
47	H	6.13	99	6.35	99	4.51	90
126	2'-OMe	4.18	93	4.83	95	3.64	90
128	4'-OMe	6.29	99	6.57	99	4.63	95
148	3',5'-OMe	5.11	99	5.19	99 (S)	4.03	99

All alcohols (*R*) configuration except where noted.

A recombinant alcohol dehydrogenase (PFADH) derived from *Pseudomonas fluorescens* was expressed in *Escherichia coli* by Bornscheuer.[78] With NAD^+ as cofactor and isopropanol as

hydrogen source the catalytic system was applied to a small set of substituted acetophenones (Table 15). Unexpectedly electron rich **126** is the most selective substrate, being reduced in 99% ee compared to **47** (92% ee), however the conversion is much worse so reduced reactivity is still an issue for this system. The 3' and 4' isomers are also reduced and a similar pattern of reactivity is displayed as found by Adolfsson[65], with **127** being reduced efficiently while **128** is both unreactive and unselective.

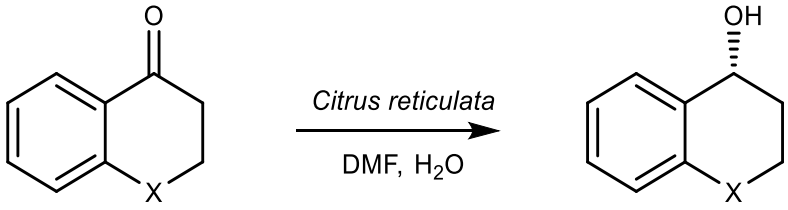
Table 15: Enzymatic reduction of ketones with PFADH



Substrate	R=	t /hr	% Conv	% ee
47	H	21	95	92
126	2'-OMe	21	31	99
127	3'-OMe	19	89	92
128	4'-OMe	20	38	45

An unusual example of whole cell biocatalysis using clementine (C*itrus reticulata*) as source of both enzyme and reducing sugar has been reported.[79] The fruit is heated in water at 30 °C for 20 mins before the ketone is added as a DMF solution, then after the reaction filtration, extraction into organic solvent and purification by chromatography gave the asymmetric alcohols. Acetophenone **47** was not reactive under these conditions, while the cyclic ketone tetralone **131** was reduced to the (*R*) alcohol in 99% ee. Oxygen substituted chroman-4-one **132** was less selective, forming the (*S*) alcohol in only 31% ee. Yields were low in both successful cases, indicating that this is not a reliable method for preparation of such alcohols.

Table 16: Whole cell enzymatic reduction of ketones with *Citrus reticulata*

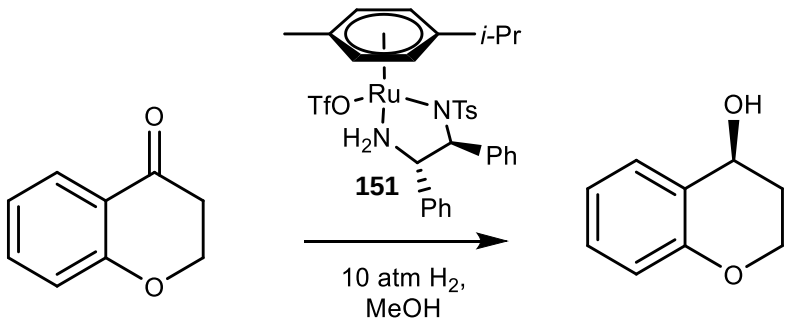


Substrate	X=	% Yield	% ee
149	CH2	30	99
150	O	35	31
Acetophenone **47**	-	-	-

The authors do perform a comparison with aqueous ATH by Ru catalysis with a series of amino-amide ligands, for which the optimal ligand in each case was superior to the biocatalytic method: (82% yield, 94% ee for **131**, 90% yield, 98% ee for **132**). However the ruthenium loading was 5 mol%, which is unusually high.

1.4.1.7 Asymmetric Hydrogenation

The triflate complex **151** derived from reaction of 16 e complex **59** with triflic acid (CF_3SO_3H), is easily ionisable in methanol solution and can be used for AH. Catalyst **151** was first applied in the reduction of **132**, as before this point no effective conditions existed for AH of this substrate.[80] The hydrogenation was carried out in neutral conditions with methanol as solvent at up to 2.4 kg scale and yielded the (*S*) alcohol in excellent yield and ee.



Scheme 45: AH of **132** with triflate complex. 99% yield, 98% ee.

The **OMe-teth (115)** catalyst is capable of AH without exchange of the chloride ligand. Wills *et*. *al*. also achieve a similar result in reduction of substrate **132**. (98% Conv, 99% ee).[62]

1.4.1.8 Summary

A range of methods for reduction of oxygen substituted ketones have been explored. Ortho-substituted compounds such as **126** and **132** have been focused on especially as they provide a double challenge of electron donation and steric hindrance about the ketone, although the later factor may increase the reduction potential of such ketones.[72]

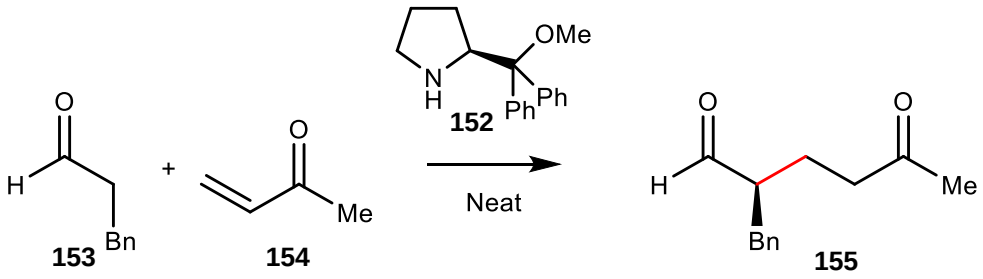
Of the 8 ATH and 6 alternative methods explored, the best results came from ATH with the Ir and Fe catalysts **137** and **136**. In general the results came from substrate screening on a range of ketones, and so the effect of further ring substitution or larger substituents on oxygen have not been systematically explored.

Tethered catalyst **115** has similarly been tested before in the reduction of simple substrates **126** and **133** but have not been systematically applied to a wider range of electron rich substrates. This will be explored in results section 2.1.

1.4.2 α,β-Unsaturated Ketones

1.4.2.1 Conjugate Addition

While alkenes are normally unreactive under ATH conditions, α,β-Unsaturated ketones (enones) are an important exception. The conjugated electron withdrawing group polarises the alkene π system and nucleophilic reagents are able to attack both the carbonyl and β carbons. The latter results in an enolate, which after protonation will usually revert to the more stable ketone form. Scheme 46 illustrates an example of an organocatalyzed conjugate addition of an aldehyde **153** to enone **154**.[81]

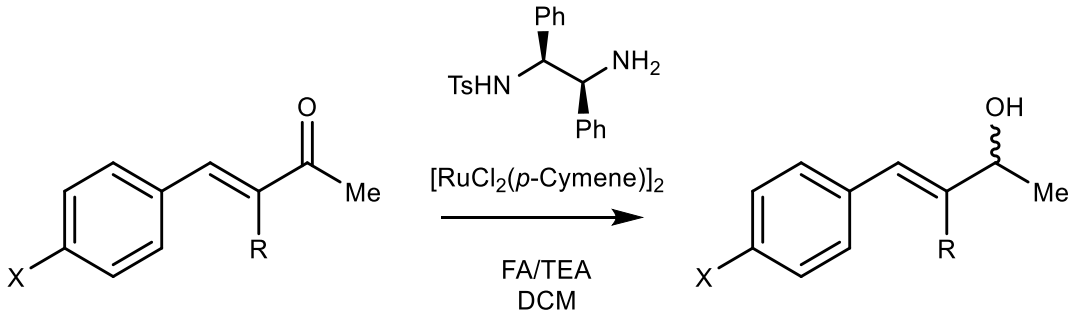


Scheme 46: Organocatalysed 1,4- addition

Deng has undertaken a detailed study of TH and ATH of various α,β-unsaturated ketones.[82] Methyl ketones **156**-**159** are reduced with the Noyori catalyst system **58** to the corresponding allylic alcohols in high yield (>90%, Table 17). Enantioselectivity is mixed,

ranging from 30-70% depending on exact substitution pattern on the alkene, though it is not expected to be high for reduction of a non-aromatic ketone. Ketone **156** is also reduced under TH conditions using the achiral TsEN ligand, and the conversion and reaction time are very similar.

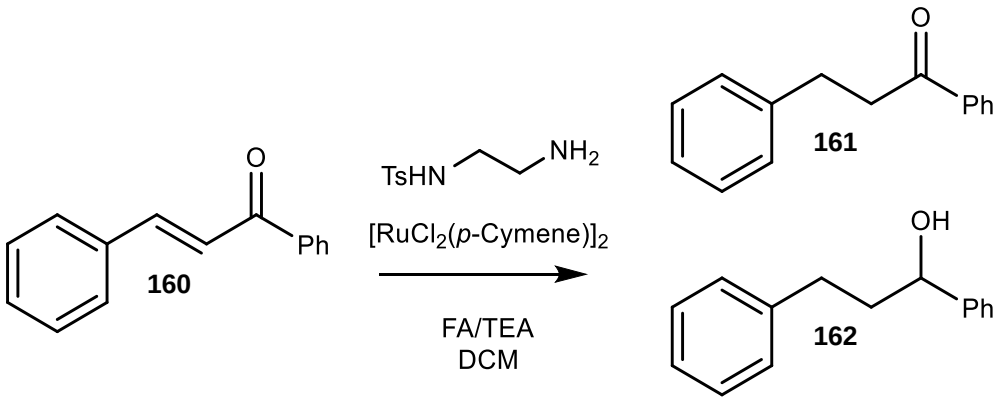
Table 17: 1,2-reduction of para-substituted benzylideneacetone derivatives



Substrate	R=	X=	% Yield	% ee
156	H	H	89	39
157	Me	H	85	76
158	Me	NO_2	98	38
159	Me	OMe	61	69
156[a]	H	H	90	0

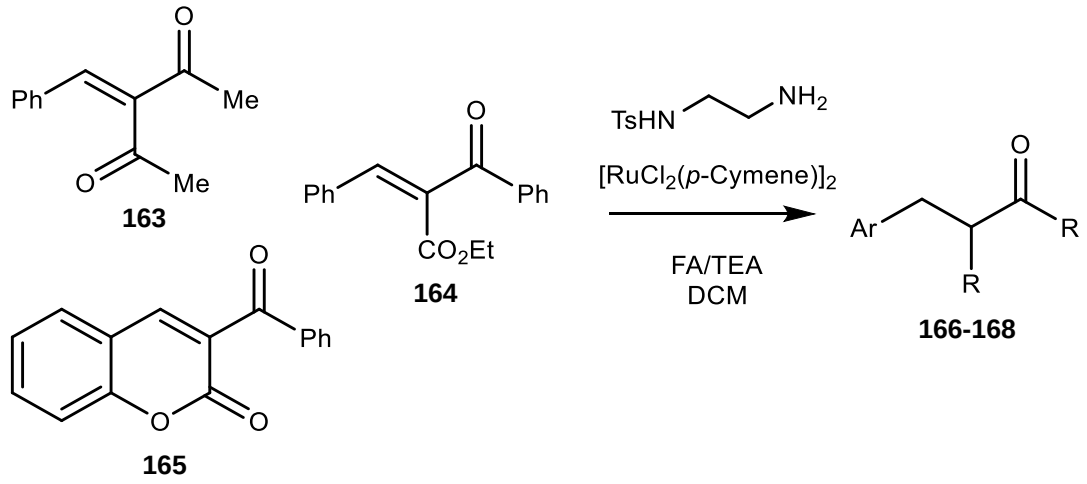
a) Reduced using $NH_2CH_2CH_2NHTs$ as ligand instead of TsDPEN

However when subjecting the bis-aromatic compound chalcone **160** to TH conditions with an achiral ligand, they find the reduction product to be an approximately 3:1 mixture of saturated ketone **161** and the saturated alcohol **162**.



Scheme 47: 1,4-reduction of chalcone. Results: **161** Yield: 75%; **162** Yield: 23%, ee 93%. Overall Yield 98%.

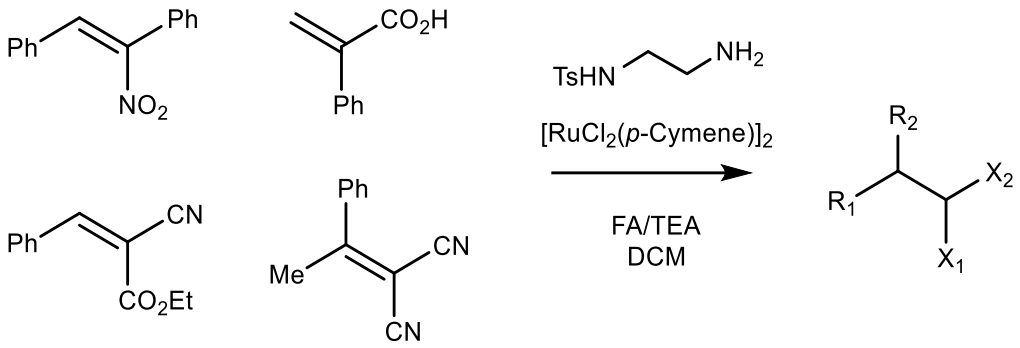
This TH of the alkene functionality can be promoted further by incorporating an additional electron withdrawing group at the α position. For these substrates the achiral TsEN catalyst is highly selective for C=C reduction and over 90% of the saturated ketone product can be isolated (Scheme 48). Notably this occurs even for the bis-methyl ketone **163** where the methyl group promotes carbonyl reduction relative to the stabilising phenyl group in **164** and **165**.



Scheme 48: α-EWG substituted enones that undergo alkene reduction exclusively under TH conditions. Yield from **163**: 90%. Yield from **164**: 94%. Yield from **165**: 91%.

Further substrate scope investigation shows that the effect is generic for alkenes with conjugated electron withdrawing substituents such as nitro, ester, nitrile and carboxylic acid functionalities (Table 18). Compounds **169**-**172** were all reduced to the corresponding alkanes conditional on the other alkene substituents being H or Aromatic. When an additional alkene stabilising β-methyl substituent was included on the double bond, only the malonitrile derivative **172** was reactive. From these results it seems apparent that polarisation of the double bond through conjugation is crucial to its reactivity.

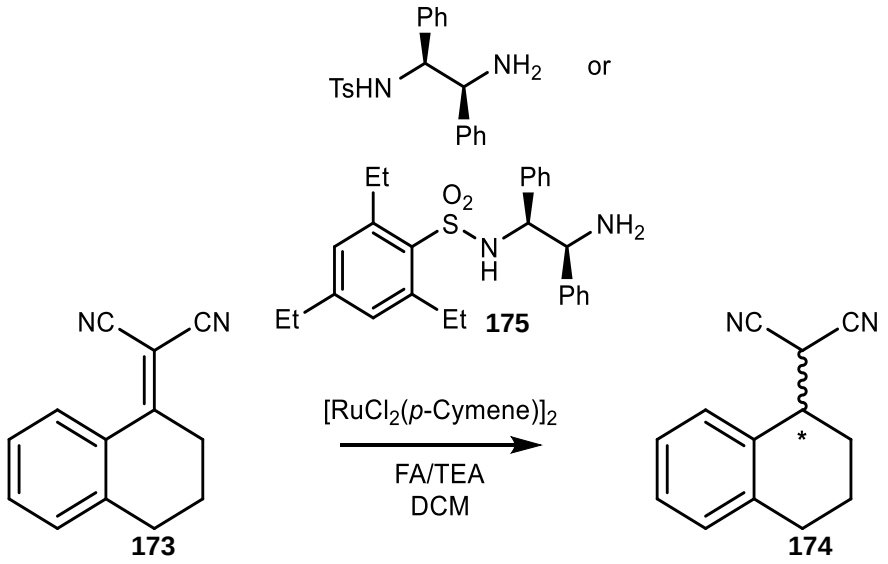
Table 18: Conjugated substrates with non-ketone EWGs tested in ATH of alkenes.



Substrate	R_1	R_2	X_1	X_2	% Yield
169	Ph	H	NO_2	Ph	89
170	H	H	CO_2H	Ph	99
171	Ph	H	CN	CO_2Et	97
172	Me	Ph	CN	CN	93

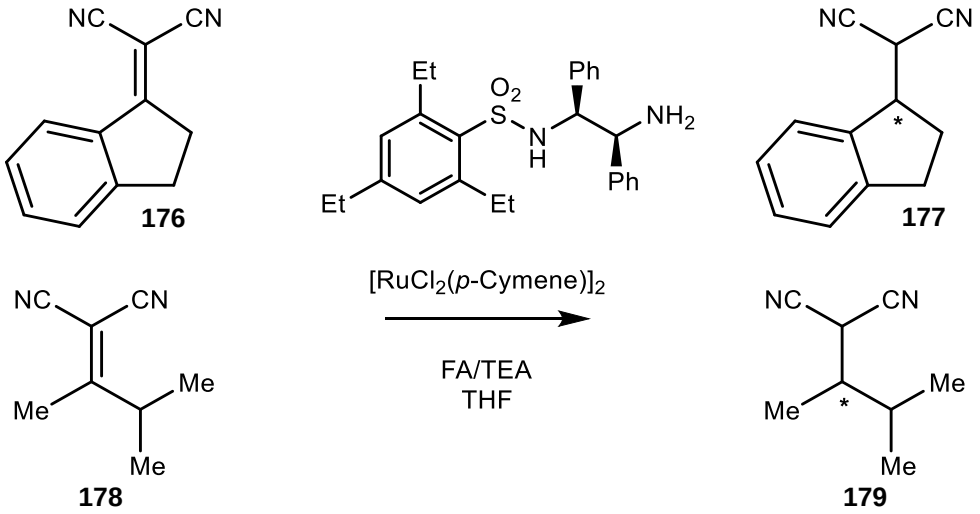
In an attempt to produce the sp^3 centres asymmetrically, the asymmetric Noyori catalyst **58** gives very low or zero enantioselectivities for alkene reduction on these substrates, with the exception the malonitrile derivative **172** which is reduced in 49% ee.

A marginal improvement was found in reduction of the related cyclic substrate **173**, which was reduced in 54% ee (Scheme 49). Further optimisation on this substrate increased the ee for alkene reduction of **173** to 85%, by use of THF as co-solvent and a bulky triethylbenzenesulfonic acid derivative **175** as ligand.



Scheme 49: ATH of malonitrile derivative **173**, preferred substrate for asymmetric alkene reduction. With ligand **55**: Yield= 98%, ee=54%. With ligand **175**: Yield = 98%, ee=85%.

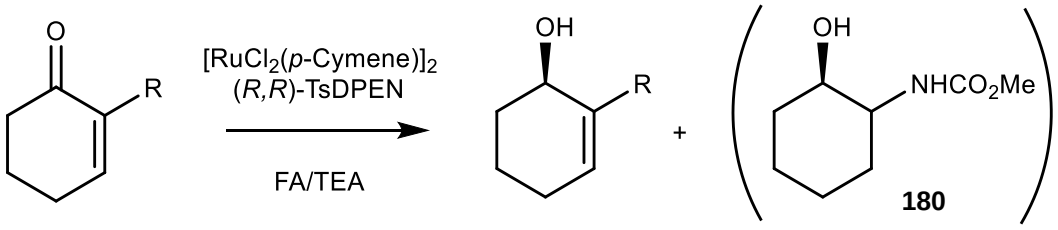
However the fused 6 membered ring structure is essential, malonitrile derivatives **176** and **178** formed from 1-indanone or acyclic ketones were more challenging and reduced to the corresponding alkanes in lower ee (Table 19).



Scheme 50: Less effective indanone/acyclic ketone derived substrates for alkene ATH. Results: From **176**, Yield: 37%, ee=58%. From **178**, Yield: 95%, ee=27%.

Wills *et*. *al*. have also investigated the ATH of enones with ruthenium catalysts.[83] A series of α-substituted cyclic α,β-unsaturated ketones are reduced selectively with the Noyori complex **58** to the corresponding cycloalkenols in the case of **181** and **182**, while carbamate substituted **183** also yields a small amount of the 1,4- reduction product **180**.

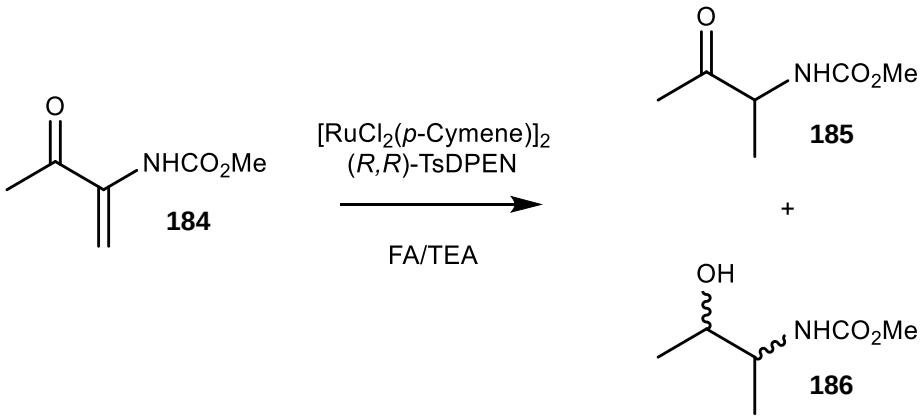
Table 19: 1,2- reduction of cyclic enones



Substrate	R=	% Yield	% ee
181	Ph	47	72
182	OBn	78	99
183	$NHCO_2Me$	54[a]	99

a) 20% of the by-product **180** observed in crude product mixture before purification.

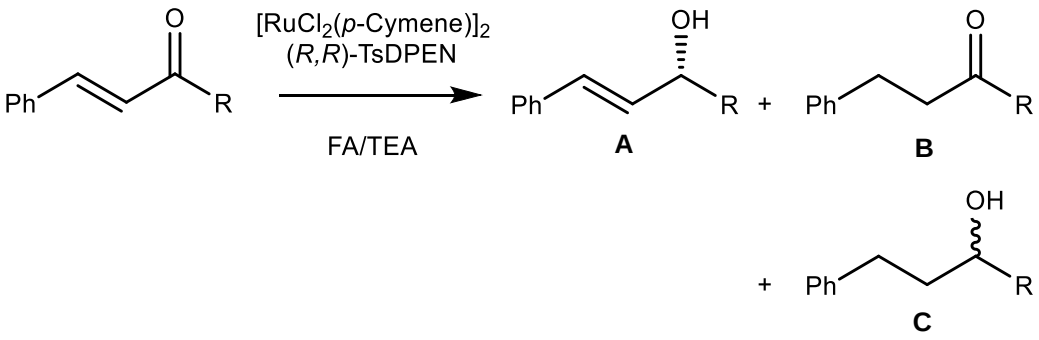
Amino-alkenone **184** was prepared as an acyclic analogue of **183** and reduced under the same conditions. Complete 1,4-alkene reduction was observed, yielding a mixture of saturated ketone **185** and alcohol **186**.



Scheme 51: 1,4- reduction of **184**. Results: Saturated Ketone **185** conv: 33%. Saturated Alcohol **186** conv: 67%. Overall conv: 100%

While Deng found primarily 1,2 selectivity for reduction of benzylideneacetone derivatives with an achiral catalyst, Wills *et*. *al*. demonstrated that increasing the steric bulk of the alkyl substituent on benzylideneacetone **156** through the series ethyl, isopropyl and *tert*-butyl had a complicated effect on the reduction selectivity with the chiral catalyst **58** (Table 20):

Table 20: Variation between 1,2- and 1,4- reduction of alkyl-benzylideneacetone derivatives



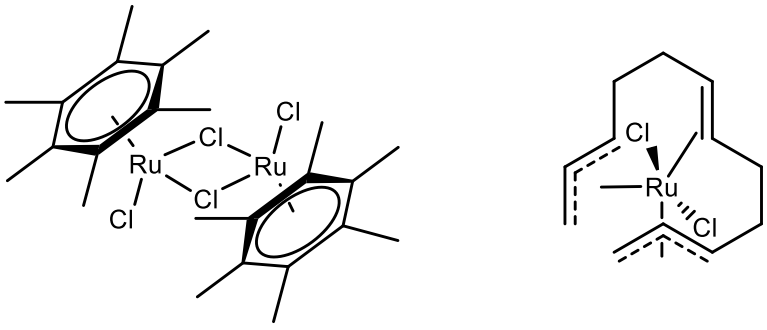
Substrate	R=	% Total Conv	% A	% B	% C	% ee
156	Me	100	75	0	25	30
187	Et	100	90	4	6	6
188	*i*-Pr	94	48	30	16	28
189	*t*-Bu	87	13	71	3	57

The ethyl substituent in **187** leads to increased 1,2 selectivity with 100% conversion. The larger isopropyl group in **188** results in slightly decreased overall conversion and gives equal proportions of 1,2- and 1,4- reduction products. The *tert*-butyl substituent strongly disfavours all ketone reduction, leading primarily to the saturated ketone product **B** and reducing the overall conversion to 87%

These results show that the product selectivity in ATH of enones is highly substrate dependant, with a balance of factors tipping selectivity towards 1,2- or 1,4- reduction. The later can sometimes be stopped after addition of hydrogen to the alkene only to give a saturated ketone as the end product. The next sections contain some further literature examples of TH and ATH of these substrates.

1.4.2.2 Racemic Transfer Hydrogenation of C=C double bonds

Cadierno and Gimeno report a ruthenium catalysed transfer hydrogenation of allylic alcohols into the corresponding saturated alcohols using $[RuCl_2(HMB)]_2$ **110** or a bisallylruthenium chloride monomer **190** as catalyst (Table 21).[84] The reduction takes place at high temperatures in isopropanol or water/sodium formate, however unlike the previous examples the reduction occurs via isomerisation to the corresponding carbonyl compound, followed by TH of the aldehyde/ketone.

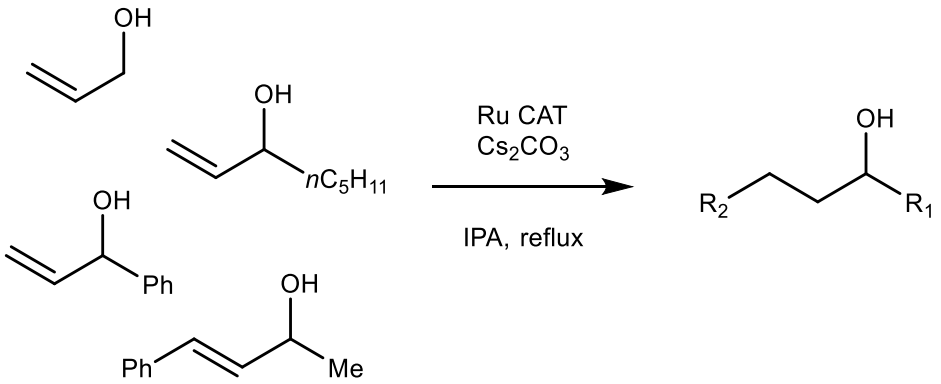


110 **190**

Figure 21: Catalysts for allylic alcohol isomerisation

Reduction is found to be the rate limiting step for all substrates, hence primary allylic alcohols such as **191** are particularly well suited to this process as the aldehyde intermediates are highly reactive and easier to reduce. However the reaction works well with a range of secondary alcohol substrates, although large alkyl groups such as *n*-pentyl in substrate **192** hinder reduction of the ketone intermediate and result in a low yield of desired alcohol, with the remainder of converted material remaining as ketone.

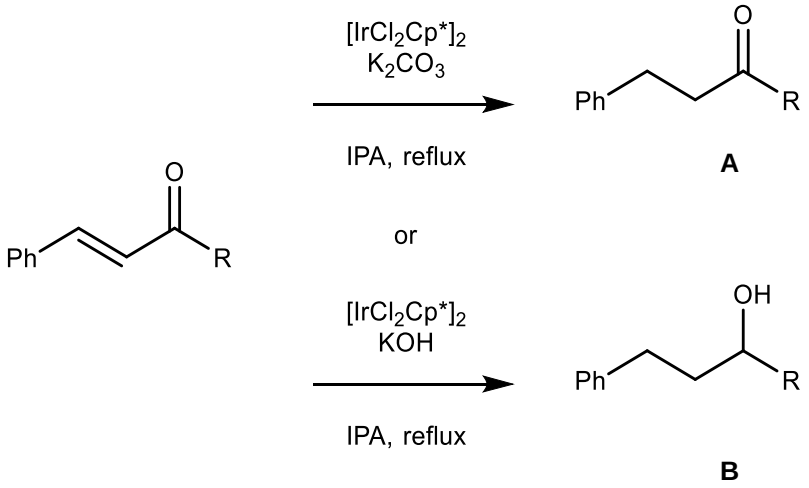
Table 21: Example substrates for Ru-catalysed one-pot isomerisation-transfer hydrogenation



Substrate	R_1	R_2	Catalyst: 110		Catalyst: 190	
			% Conv	% Yield	% Conv	% Yield
191	H	H	99	99	99	99
192	*n*-C_5H_{11}	H	99	79	99	82
193	Ph	H	99	23	99	67
194	Me	Ph	93	93	99	98

Recently Cai reported a simple iridium dimer catalyst $[IrCl_2(Cp^*)]_2$ that was capable of a controllable 1,4 reduction of enones to either the saturated ketone or to the alcohol, by use of K_2CO_3 or KOH as base respectively.[85] Chalcone **160**, as well as a variety of enones including the 1,2 favouring methyl-ketone **156** are all reduced at the alkene (Table 22). Electron donating para-methoxy (**196**) and para-methyl (**195**) substituents on the ketone side slow down the reduction and require increased catalyst loading from 1 to 2 mol%, while the electron withdrawing *p*-chloro (**197**) substrate is very reactive and the yield of saturated alcohol **197B** is high.

Table 22: Switchable 1,4 reduction of enones to ketones or alcohols with Ir catalysed TH.

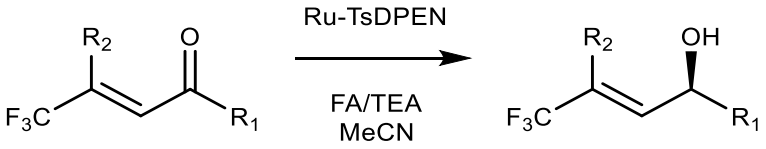


Substrate	Base	S/C	A	B
			% Conv	% Conv
156	Me	100 : 1	95	92
160	Ph	100 : 1	97	88
195	*p*-MeC_6H_4	50 : 1	90	83
196	*p*-$OMeC_6H_4$	50 : 1	85	78
197	*p*-ClC_6H_4	100 : 1	98	91

1.4.2.3 Asymmetric Transfer Hydrogenation of Conjugated Ketones

The Noyori catalyst has been applied to ATH of β-alkyl β-trifluoromethyl α,β-unsaturated ketones.[86] These substrates are very hindered at the β carbon and the electron withdrawing CF_3 group will partly counteract the polarisation caused by the ketone. Indeed all of the substrates tested were selectively reduced 1,2 in the ATH reaction.

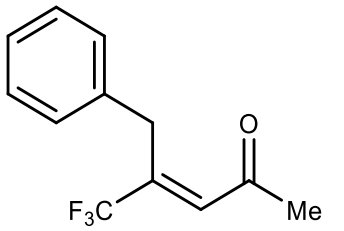
Table 23: Selective 1,2- reduction of β-trifluoromethyl enones



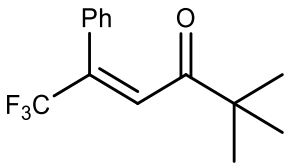
Substrate	R_1=	R_2=	% Yield	% ee
198	Ph	Ph	97	97
199	Ph	*p*-BrC_6H_4	93	97
200	Me	Ph	93	24
201	Me	Benzyl	67	99
202	*t*-Bu	Ph	75	99

The aryl-ketone substrates **198** and **199** are reduced in high ee as expected, while methyl ketone **200** gives poor enantioselectivity (Table 23). Interestingly the authors also successfully reduce β alkyl methyl ketone **201** and *tert*-butyl ketone **202**, in very good ee, albeit with moderate yields (67-75%).

The previously described literature results would have suggested **201** to have poor enantioselectivity as a methyl-alkenyl ketone, and **202** to be hindered in ketone reduction by the large *tert*-butyl group. It is clear that although the trifluoromethyl group is a large distance from the ketone it has a significant effect on the balance of ketone and alkene reactivity in the conjugated system.



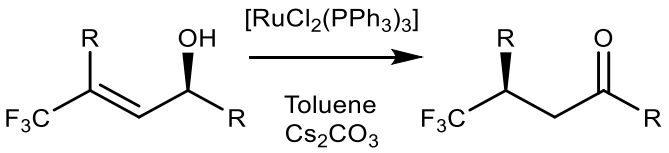
201



202

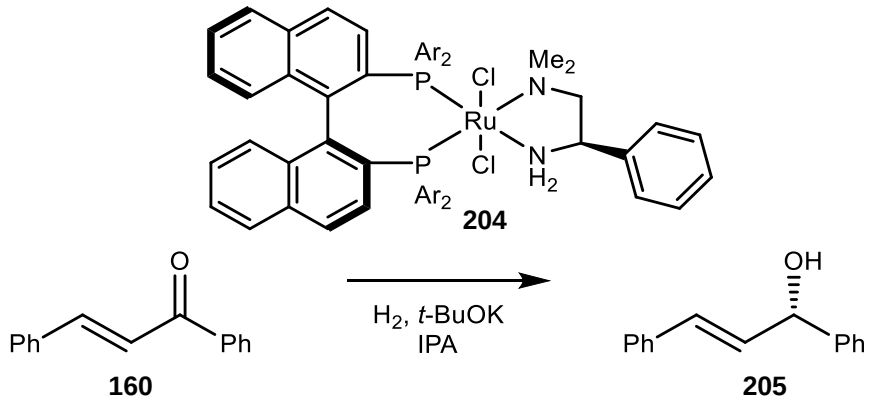
Scheme 52: Unusual substrates for 1,2 reduction

The asymmetric alcohols obtained were then isomerised stereospecifically by another ruthenium catalyst, $[RuCl_2(PPh_3)_3]$ (**203**) to produce chiral β-trifluoromethylated ketones (Scheme 53).



Scheme 53: Stereospecific isomerisation of chiral allylic alcohols to β-trifluoromethyl ketones

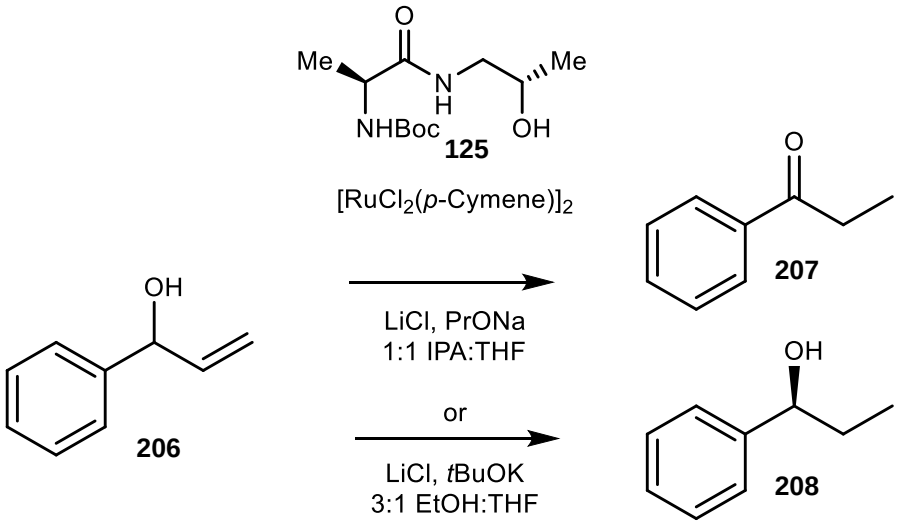
Asymmetric hydrogenation with a variant on the Noyori hydrogenation catalyst [$RuCl_2${(*S*)-tol-BINAP}{(*R*)-DMAPEN}] (**204**) is found to be an effective way to perform selective 1,2-reduction with good enantioselectivity without relying on substrate control.[87] Chalcone is hydrogenated to the corresponding allylic alcohol **205** in 97% ee. Hydrogenations were performed on ice, raising the temperature to 30 °C lead to increased quantities of saturated ketone **161** and saturated alcohol **162** as by-products.



Scheme 54: 1,2-selective AH of chalcone with Ru(II) catalyst at 0°C. Yield: 99%, ee: 97%. At 30°C: Yield 82%, ee 96%.

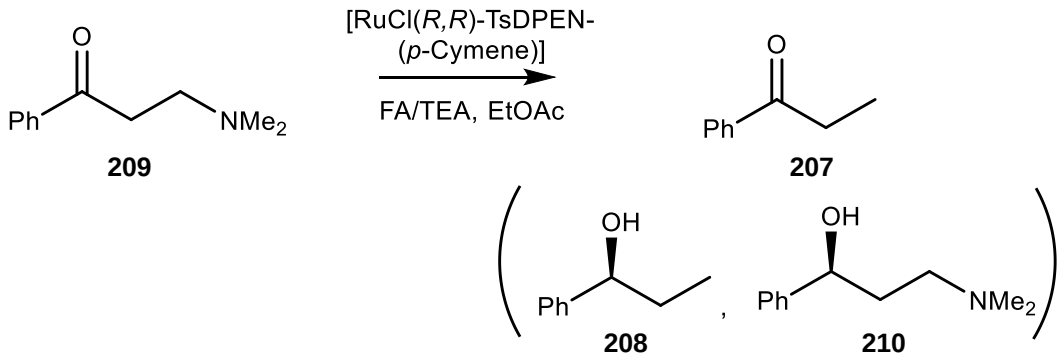
1.4.2.4 In-Situ Enone reduction

In some cases an enone can be formed in situ and directly reduced. For example, Adolfsson's α-amino acid hydroxyamide **125** ligand has been applied to ATH of allylic alcohols by oxidation to the corresponding enone, followed by complete reduction of alkene and carbonyl functionalities.[88] Initially the conditions lead only to ketone **207**, however use of the stronger base potassium *tert*-butoxide allowed ketone reduction to take place, giving the asymmetric alcohol **208**. Control experiments performed without the ligand showed that the isomerisation step will still occur but no ketone reduction takes place.



Scheme 55: Isomerisation and reduction of benzyl-vinyl alcohol. Optimised conditions give saturated alcohol **208** in 99% conv, 85% yield, 93% ee.

Kosmalski applied the standard Noyori catalyst **58** to the reduction of β-dimethylamino-acetophenone **209** but found the main product was the partially reduced elimination product **207**.[89] Elimination of the usually stable NMe_2 group is surprising, presumably this occurs through a protonated intermediate but no mechanistic investigation is given.



Scheme 56: In-situ elimination and partial reduction of a β-(dimethylamino)ketone. Yield: 71% ketone **207**, 16% alcohol **210** (95% ee), 13 % alcohol **208** (95% ee)

1.4.2.5 Summary

The balance between 1,4 -and 1,2- reduction is affected by both substrate and catalyst control. For example, AH with catalyst **204** has been shown to be highly selective for 1,2-reduction even on substrates that favour 1,4- reduction such as **160**, while ATH with catalyst **58** is highly selective for 1,2- reduction when applied to trifluoromethylated enones such as **198**. Cyclic ketones such as **181** favour 1,2- reduction under similar conditions, as do alkyl-

alkenyl ketones such as **156**, but varying substituents can lead both to favour 1,4- reduction. Furthermore, other electron withdrawing groups such as CN (as in **172**) can activate the normally unreactive alkene group towards TH/ATH.

Therefore while there is a reasonable body of literature on the topic, there is still scope for increased understanding of the subtle effects of substrate structure on the regioselectivity of enone reduction. Furthermore, tethered catalysts such as **80** and **115** have not been systematically studied in the reduction of enones and they may display a different pattern of reactivity. This will be explored further in results section 2.4.

1.5 Improving on Ru(II) Catalysis

Homogenous Ru(II) catalysts for ATH reaction therefore enjoy simple and relatively safe reaction conditions, low catalyst loadings, excellent chemoselectivity within their substrate scope and high enantioselectivity in reductions. However they suffer from some disadvantages that limit their application.

Firstly use of transition metal catalysts results in strict regulations for product purity in order to prevent metal contamination in active pharmaceutical ingredients (API). If the ATH step occurs late in the synthesis it is not unusual for traces of ruthenium to be carried through into the final product, requiring a lengthier and expensive purification process that will inevitably reduce the final yield.

Additionally materials for the catalyst are expensive, both the ruthenium source itself and the chiral ligand which generally requires a multi-step synthesis. In a conventional ATH reaction the catalyst is removed by filtration through silica and is not recoverable. The catalyst therefore represents a significant portion of the cost of performing an ATH process at scale.

1.5.1 Polymer-Supported Catalysts

Both of these issues can in theory be ameliorated by finding a way to recycle the catalyst, reducing the environmental impact of reactions and potentially increasing the economy. A common approach is to anchor a ligand to a solid support, followed by complexation with ruthenium. The catalyst is then easily removed from the reaction medium by a simple physical process such as filtration, and may be recycled.

1.5.1.1 Literature examples of polymer supported catalysts

Several examples exist in the literature of potential polymer supported catalysts where a monomer has been co-polymerised with a functionalised ligand.

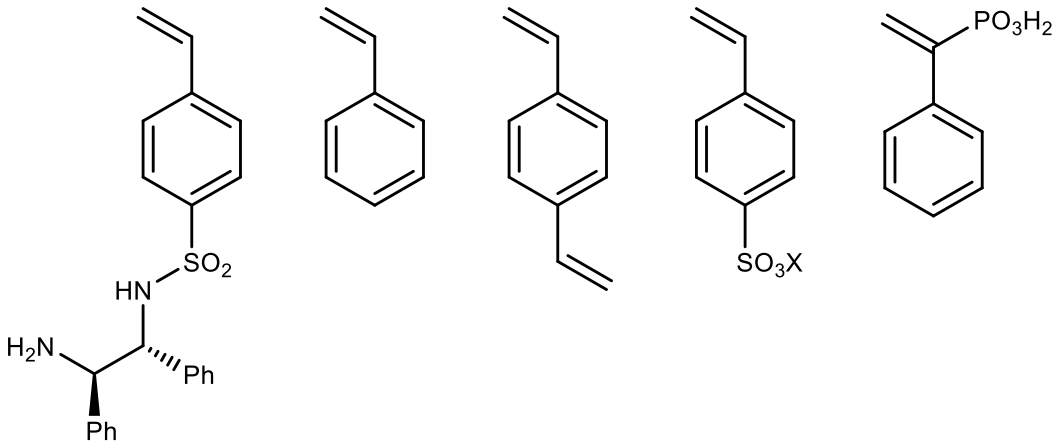
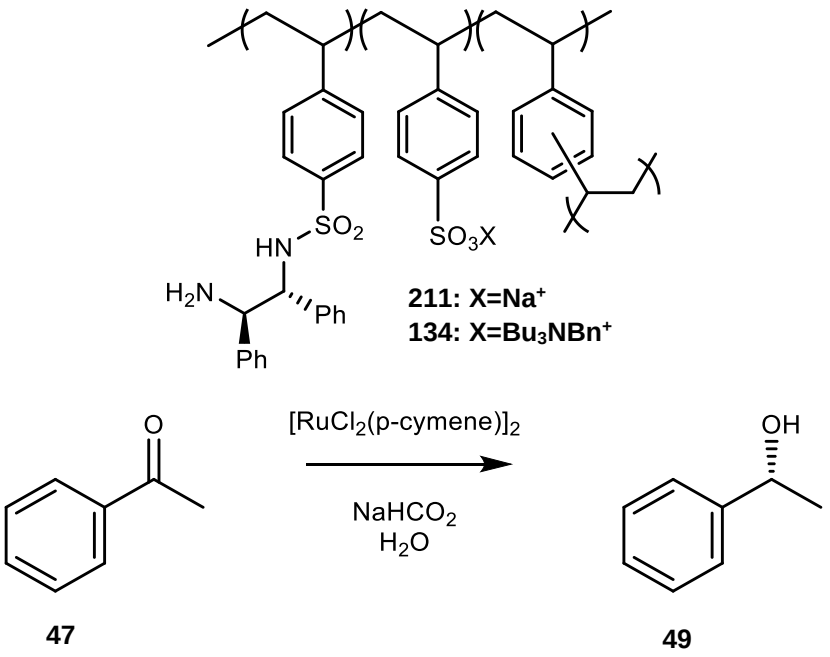


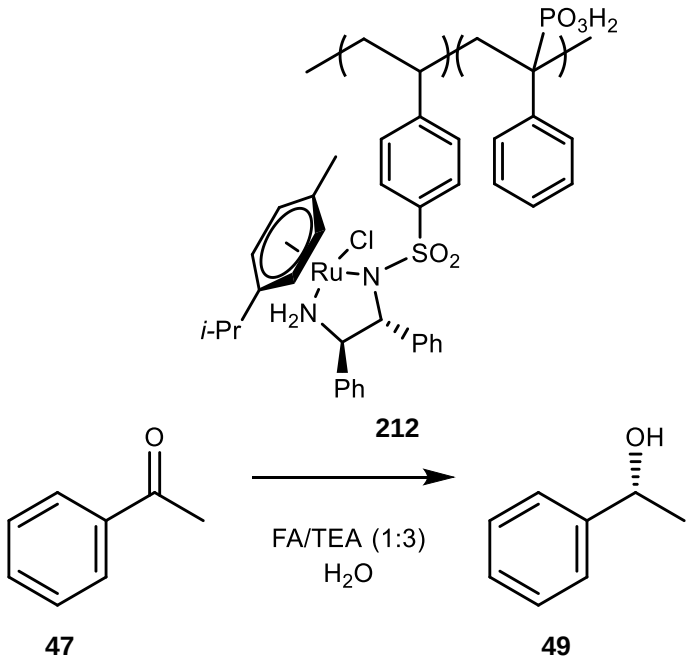
Figure 22: Vinyl-substituted ligand and selection of co-monomers for incorporation into a polymeric ligand support.

Itsuno reported polystyrene sulfonate supported ligands **211** and **134** for application to ATH of ketones in water.[90] Reaction of ketones such as acetophenone **47** with a combination of the ligand and $[RuCl_2(p\text{-Cymene})]_2$ **57** as metal source gave the chiral alcohol **49** in good ee (91-98%) when crosslinked polymer supports were used (Scheme 57). The larger organic tributylbenzylammonium anion in **134** promoted better polymer swelling in aqueous solution and lead to higher conversions and enantioselectivity.



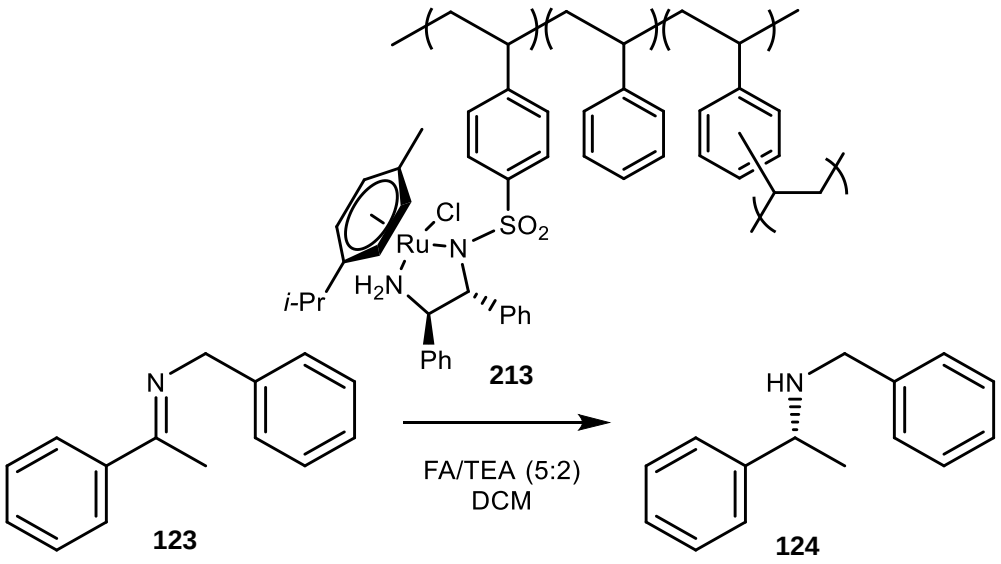
Scheme 57: Reduction of acetophenone with hydrophilic polymer supported ligands.

Ma and Peng report another hydrophilic polymer suitable for ATH in water by using a phosphonate substituted polymer backbone (Scheme 58).[91] The catalyst was isolated in solid form by reaction of the polymer with **57**, and extensively characterised by a range of spectroscopic techniques. ATH of acetophenone **47** is performed at relatively low catalyst loadings (660:1 S/C), where the loading is determined by the wt. % of ruthenium in the isolated polymer (~1.5%). The reduction is sensitive to pH and can be tuned by varying the ratio of formic acid and trimethylamine used, with the optimum being a 1:3 ratio.



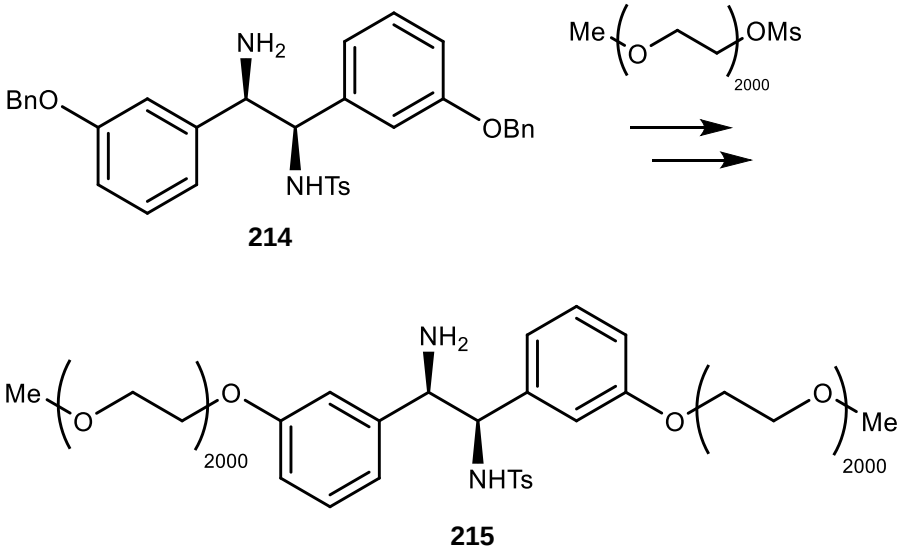
Scheme 58: Aqueous phase reduction of acetophenone with phosphonated hydrophilic polymer **212**

Itsuno has also reported hydrophobic polystyrene based catalyst **213**.[92] It was applied to ATH of a range of imines including acyclic substrate **123** in FA/TEA and organic solvents, as illustrated in Scheme 59. The result represents a marginal improvement on the unsupported reaction discussed earlier in section 1.4 with the equivalent unsupported Noyori catalyst **58**, which gave the product in 77% ee.



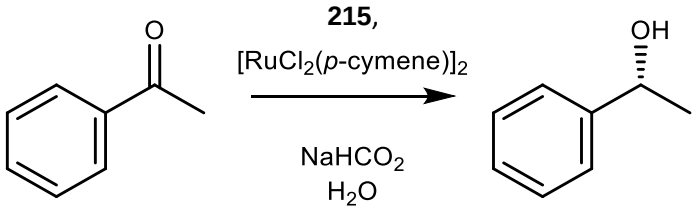
Scheme 59: Reduction of acyclic imine with polymer supported catalyst. Conversion 95%, ee 84%.

Alternatively the polymer may be pre-formed and simply reacted directly with the functionalised ligand. One of the first reported examples features a ligand derived from *meta*-benzyloxy TsDPEN derivative **214** and a monomesylated PEG chain (Scheme 60).[93] One advantage of this approach is that the PEG polymer is soluble in polar solvents required for reduction and precipitates in non-polar solvents that can extract the low molecular weight products.



Scheme 60: Synthesis of PEGylated ligand **215**. Steps include Boc protection of the free amine, deprotection of the OBn groups by hydrogenolysis, ether formation and amine deprotection.

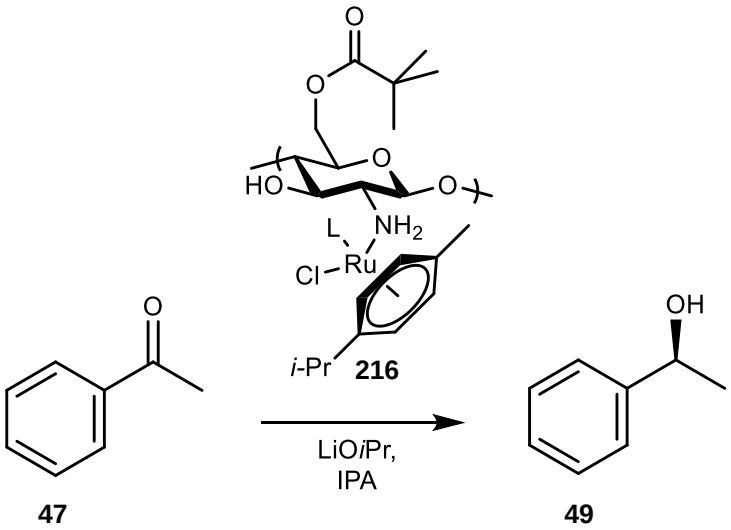
The hydrophilic PEG groups mean ligand **215** can be used for ATH of acetophenone in water.[94] The catalyst is very active and has reasonable enantioselectivity, close to that of the homogeneous Noyori catalyst **58**.



Scheme 61: ATH of acetophenone in water with PEG supported catalyst. 99% conv, 98% yield, 92% ee.

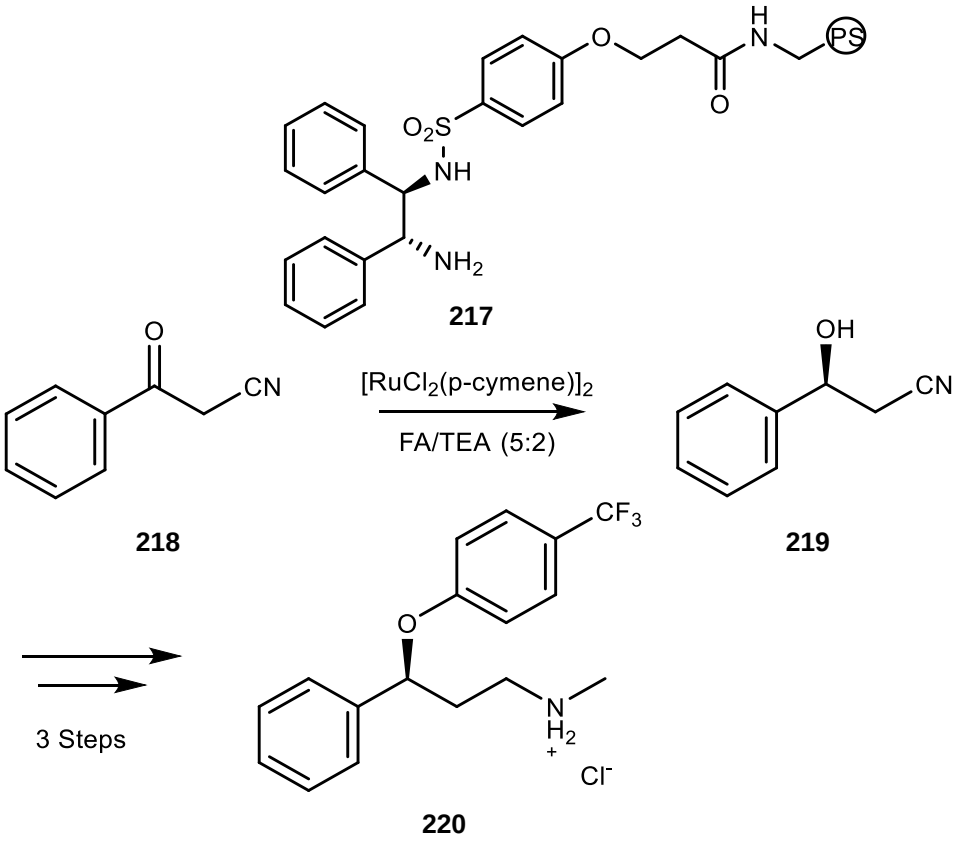
Naturally occurring polymers have been used in place of synthetic ones. An interesting example uses a modified polysaccharide biopolymer (chitosan), which acts both as support

and chiral ligand (Scheme 62).[95] However in this case the monodentate ligand is not as active or selective for ketone reduction as the TsDPEN complexes in common usage.



Scheme 62: Reduction of acetophenone with chiral biopolymer ligand **216**. Yield 70%, ee 63%,

Wang has described a polystyrene supported ligand prepared from DPEN **52**.[96] The ligand is bound to aminomethylated polystyrene via a DCC amide coupling to give polymer supported ligand **217**, which is combined with Ru source **57** in situ for ketone reduction.



Scheme 63: Synthesis of (*S*)-Fluoxetine with polymer supported ATH as key step.

217 is applied in the reduction of alpha-EWG substituted ketones such as **218** that serve as intermediates to the synthesis of Fluoxetine (Prozac, **220**). However the synthesis of **217** is very linear and requires several protecting group transformations, making it less cost effective as a ligand.

1.5.1.2 Recycling experiments

Many of the above polymer supported ligands/catalysts were tested in recycling experiments, whereby the catalyst was separated by a physical process such as filtration (for catalysts bound to macroscopic polymer solids) or precipitation (for catalysts bound to soluble polymers). Washing, followed by addition of a fresh charge of solvent, hydrogen donor and substrate allows the re-use of the same catalyst for further reduction. Some of these results are summarised in Table 24.

Table 24: Summary of catalyst recycling results for reduction of acetophenone.

Catalyst		First Cycle		Nth Cycle	
	No uses	% Conv	% ee	% Conv	% ee
134	5	100	98	*	97
212	5	99	98	90	97
215	14	99	92	87	92
217	3	98	97	81	93

* Data on conversion after 2nd recycle is not provided in the paper.

Frustratingly not all of the literature reviewed includes data on catalyst recycling experiments, even though it is universally described as a key potential benefit in the introductory sections of papers describing polymer supported catalysts.

1.5.1.3 Disadvantages of polymer supported catalysts

However these approaches have not yet overcome enough practical limitations to become superior to the classical homogenous reduction yet. As each approach requires a custom, often complex ligand synthesis catalyst itself is made much more expensive. Loading of ruthenium is variable and difficult to monitor. Frequently analysis by methods such as (ICP-OES) is used to determine a ruthenium loading per gram of support, but it is difficult to know how much of this ruthenium is actively bound into the desired chiral ligand sites, and how much is adsorbed non-specifically onto the substrate. Variation between batches of supported catalysts will therefore be higher, reducing process robustness. Metal leaching is frequently observed, with some ruthenium escaping into the reaction solvent, and a small mechanical loss of the support during filtration and washing in each cycle results in a reduced catalyst loading and loss of activity.[*] Therefore improved supported catalysts will aim to minimise activity decay, minimise metal leaching and mechanical losses, and have a simple cost effective ligand synthesis.

1.5.2 Non-Organic Solvents

A high proportion of the costs and hazards associated with fine chemical processes are often related to the solvents used.[97] Formic acid/triethylamine and isopropanol are convenient organic solvents for use on a lab scale and easier to handle than pressurised hydrogen gas

[*] McGowen *et. al.* report a physical loss of 40% of their resin after 26 decantation cycles. [194]

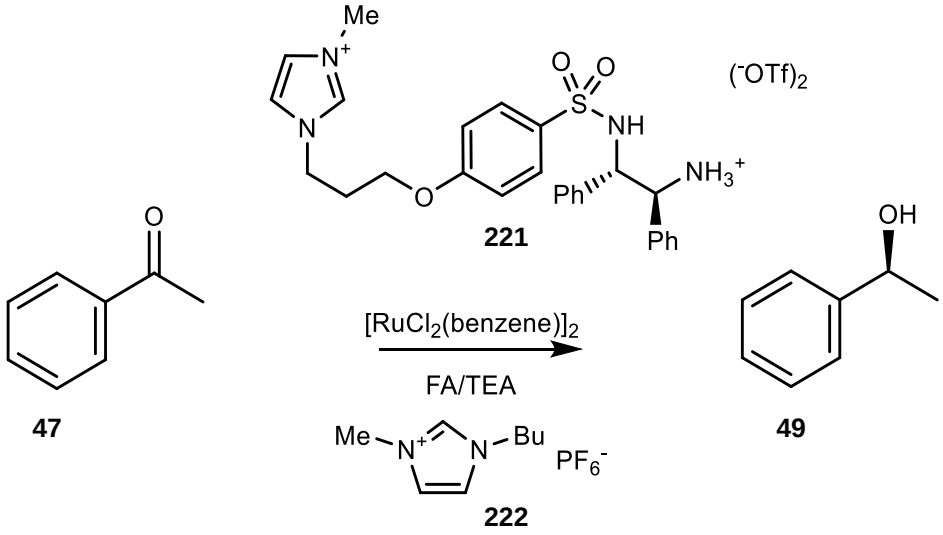
and methanol, however if the quantity of organic solvent required for ATH could be reduced the process might be made safer and more environmentally friendly.

1.5.2.1 Ionic Liquids

Room temperature ionic liquids (ILs) have been explored as a potential alternative solvent. Due to their high boiling points, exposure to vapours is less of an issue for workers. If an ion-functionalised catalyst is used it may be immobilised in the ionic liquid. Extraction with organic solvents allows the product and remaining substrate to be removed while in principle the catalyst remains bound in the IL phase.

1.5.2.2 Literature examples of IL supported catalysts.

Ohta describes an imidazolium functionalised ligand **221** that can be used with a ruthenium source for the ATH of acetophenone in IL solvent **222**.[98] FA/TEA is used as hydrogen source and the catalyst can be recycled up to 5 times, though after the third cycle performance is substantially poorer.

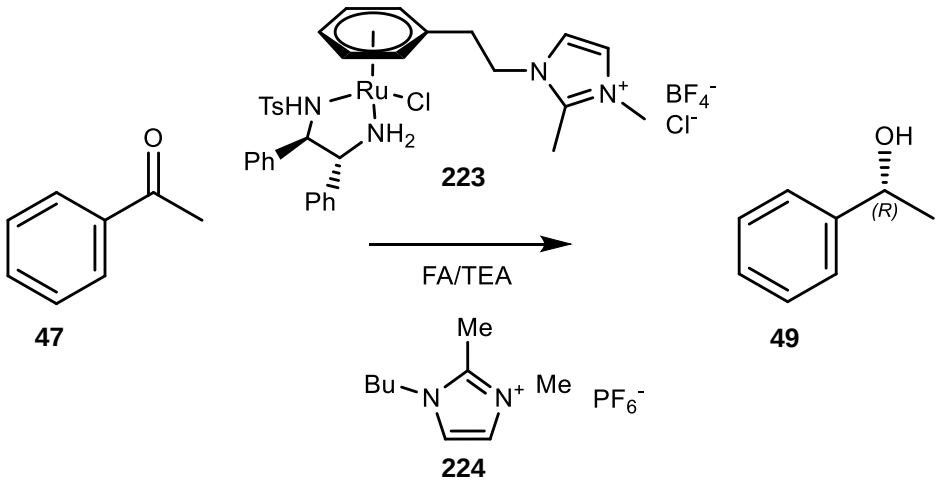


Scheme 64: ATH of acetophenone in ionic liquid solvent. Results: conv 96%, ee 93%. Activity on 5th cycle: conv 75%, ee 90%

Interestingly the authors also describe the recycling of a conventional Noyori-type catalyst [RuCl(benzene)TsDPEN], which is also soluble in the ionic liquid and can be recycled effectively 3 times.

Dyson has also prepared an imidazolium functionalised catalyst **223**, in this case with the additional group attached through the ruthenium arene rather than the diamine ligand

(Scheme 65). They isolate the ruthenium complex and use this directly in ATH of acetophenone in IL **224**. Recycling is performed by extraction of product into hexane or ether, and then spent hydrogen donor is washed out with water. However **223** is too hydrophilic and is washed out of the ionic liquid phase after the second cycle.



Scheme 65: ATH of acetophenone in IL with cationic Ru complex **223**.
Results: conv 99%, ee 99%. After 2nd cycle: conv 68%, ee 99%.

Again the authors also perform recycling on the conventional Noyori catalyst **58** which in this case outperforms the modified complex **223**. Catalyst **58** is usable over 4 cycles, and although the activity remains high in this case it is the selectivity that degrades, down to 45% ee on the 4th cycle.

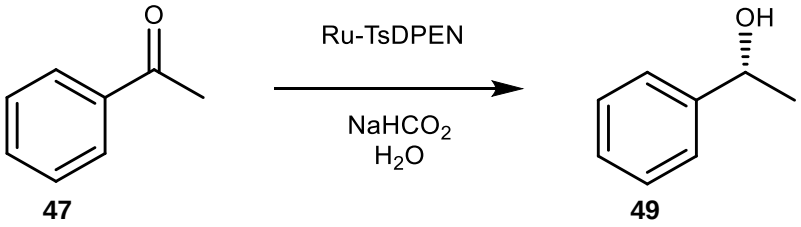
1.5.2.3 Disadvantages of IL supported catalysts.

There are some significant disadvantages to use of IL solvents for ATH. The IL solvents themselves are generally based on the imidazolium structure, which has some safety concerns as a potential carcinogen. IL solvents are extremely hydrophilic and require extensive drying to remove water, which is energy intensive. Finally, organic solvent is generally required for extraction and the volume of this is far greater than the reaction volume, meaning that only a small portion of the total organic solvent usage is being replaced by the IL.

1.5.2.4 ATH in water.

Water has also been explored as an alternative solvent. There are several examples in the literature of reactions that are accelerated in aqueous media compared to their conventional

solvent based protocols, most famously the Diels Alder reaction.[99] The theory is that reagents are forced into dense highly concentrated pockets due to their hydrophobic repulsion from the bulk water phase. This effect has been extensively explored for ATH catalysts by Wu et. al., who originally reported a very fast reduction of acetophenone with the Noyori catalyst **58** in 2004.[100]

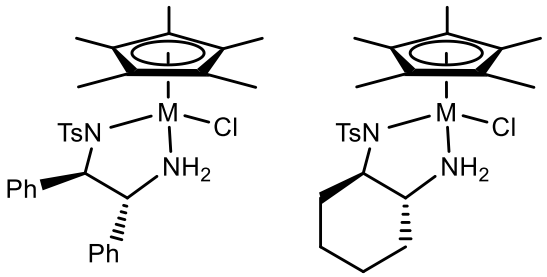


Scheme 66: Accelerated ATH of acetophenone in water. Reaction time: 30 mins, 76% conv, 95% ee.

Wu has published several papers in this area including detailed investigations on the effects of pH, and mechanistic investigations into rate acceleration effect which as described previously propose a solvent assisted protonation of the substrate.[48,101]

1.5.3 Rh and Ir Cp Complexes*

Another option to improve the performance of transition metal catalysts is changing the metal source. Between 1998 and 1999 several research groups independently reported the use of [Cp*MCl(diamine)] complexes for ATH of ketones and imines, where M = Rh or Ir.[102–104] These group 9 transition metal complexes are isoelectronic with the Noyori complex **58**.



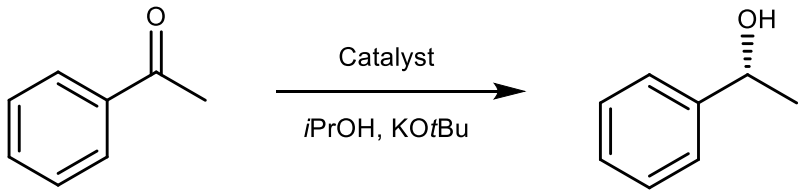
225: M = Rh **226: M = Rh**
227: M = Ir

Figure 23: Early rhodium and iridium Cp* complexes for ATH

Comparison of their performance in acetophenone reduction showed that Rh was more reactive than Ir, and that the mono-tosylated cyclohexyldiamine ligand gave better reactivity

than TsDPEN (Table 25). In comparison to the Noyori catalyst **58**, Cp* complex **226** was less active but slightly more enantioselective, giving the chiral alcohol product in 97 % ee compared to 94% for the ruthenium catalyst.

Table 25: Comparison of simple Ru, Rh and Ir catalysts in ATH of acetophenone

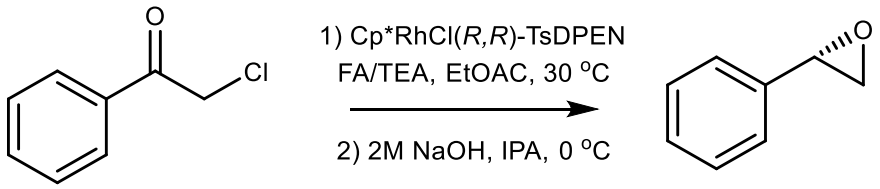


47 **49**

Catalyst	M	Arene	Ligand	% Conv	% ee
58	Ru	*p*-Cymene	TsDPEN	92	94
225	Rh	Cp*	TsDPEN	14	90
226	Rh	Cp*	TsCYDEN*	85	97
227	Ir	Cp*	TsCYDEN	36	96

Conditions: 12hr reaction time, 30 °C, 200:1 S/C.

In certain cases the Rh complexes are able to achieve significantly better results than their Ru counterparts. For example, complex **225** has found application in the reduction of 2-chloroacetophenones where it can be used in a two-step, one pot reaction to prepare the corresponding chiral styrene oxides very efficiently (Scheme 67).[105]

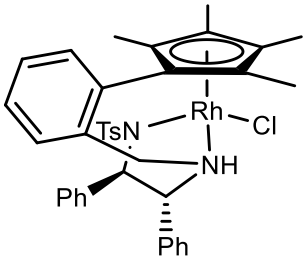


228 **229**

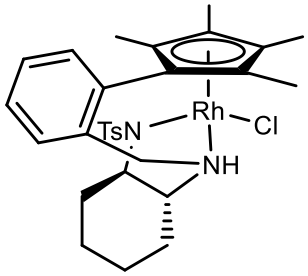
Scheme 67: ATH and cyclisation of 2-chloroacetophenone with Rh catalyst **225** at S/C: 1000/1. Yield 83%, ee 97%.

* Also referred to in later literature as TsDAC: *N*-tosyl-1,2-diaminocyclohexane

1.5.3.1 Tethered Rh Cp* complexes



230

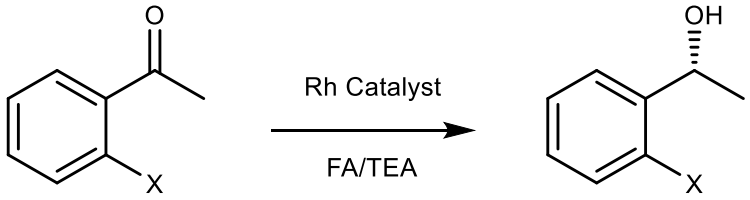


231

Figure 24: Tethered Rh Cp* catalysts for ATH of ketones.

Wills et al have prepared tethered forms of the Rh Cp* catalysts.[106,107] Both TsDPEN and TsDPEN were used as chiral diamines, but mirroring the results found in the literature for non-tethered catalysts the diaminocyclohexane complex **231** was found to be more active, reducing acetophenone in 100% conversion in 2 hours compared to 10 for TsDPEN complex **230** (Table 26). This result is comparable to that achieved by the **3C-teth (80)** complex, which reduces acetophenone in 3 hours under similar conditions.

Table 26: Reduction of acetophenones with tethered Rh Cp* Catalysts

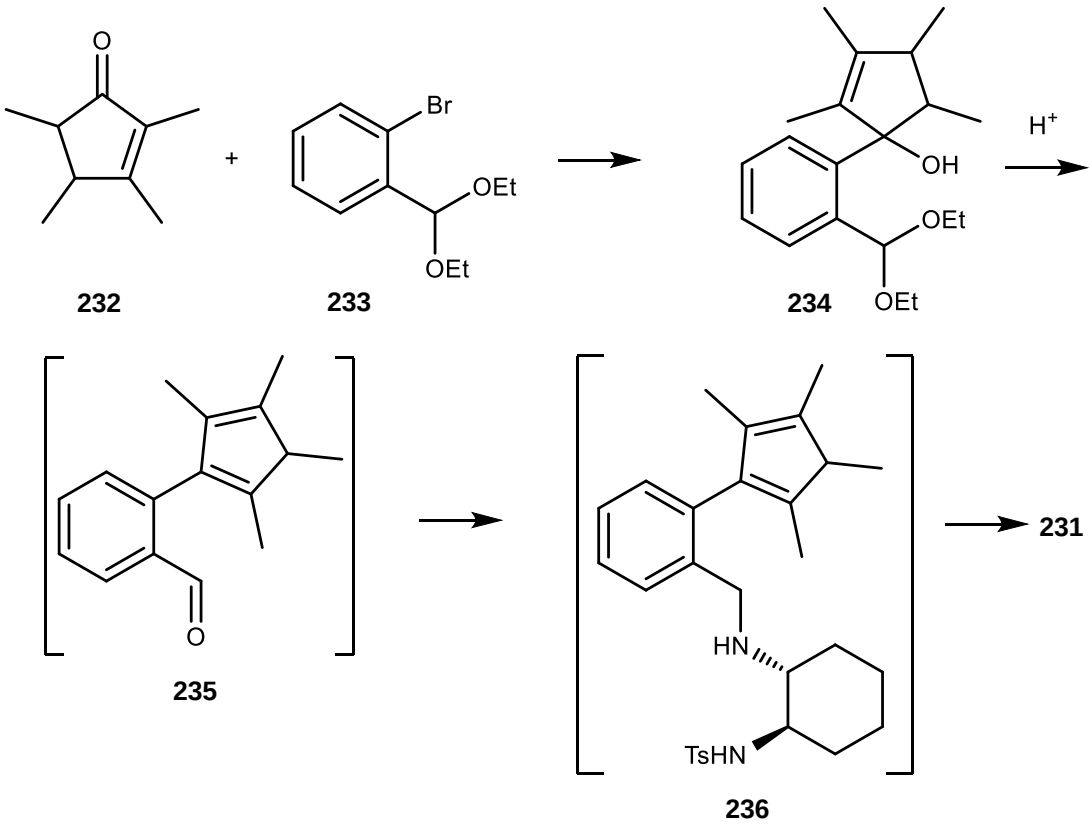


Catalyst	X=	Temp /°C	Time /hr	% Conv	% ee
80	H	28	3	100	96
230	H	25	10	100	98
231	H	28	2	100	96
230	Cl	25	28	100	77
231	Cl	28	8	100	85
230	OMe	25	48	93	90
231	OMe	28	22	100	94

Conditions: S/C 200:1, [Substrate] = 2M in FA/TEA

The synthesis of these benzyl tethered complexes is somewhat more challenging than that required for **3C-teth (80)** and is illustrated for the TsCYDEN complex in Scheme 68. Ortho-Lithiation and addition of **233** to cyclopentenone **232** gave a tertiary alcohol **234**, which could

be eliminated under acidic conditions to produce a mixture of cyclopentadiene isomers. Reductive amination of the resulting aldehyde with a chiral diamine followed by reaction with rhodium trichloride gave the tethered Rh catalyst **231**.



Scheme 68: Synthetic approach to tethered Rh Cp* catalyst **231**

Rh Cp* catalysts therefore provide an alternative to the Ru (II) catalysts for ATH of ketones. In certain cases they may provide superior activity or selectivity, and according to a review by Xiao *et. al.* they are also less air sensitive during reductions in aqueous conditions.[108]

A primary disadvantage of Rh complexes is the cost of the metal itself; at the time of writing Rh metal is 10 times more expensive than Ru.* This means that successful application of a Rh complex requires that it be several times more efficient, either due to increased activity or selectivity that cannot be achieved with the Ru complex.

1.6 Summary

Air stable, highly selective and versatile Ru(II) catalysts for ATH and AH have been developed over the last 30 years. The original Noyori type catalyst for ATH still finds widespread

* As determined by the JM price chart at http://www.platinum.matthey.com/prices/price-charts

applications in the literature, but has been improved upon by the development of tethered variants with increased activity.

The synchronous, two step mechanism for ATH was originally described with some certainty and detail shortly after the discovery of the Noyori catalyst **58**, but gradually more evidence has accumulated to question this original proposal. The development of computational methods capable of including solvation effects have played a major part in this reinterpretation of the original mechanism.

The substrate scope for such catalysts is broadly limited to alkyl-aryl ketones, but in certain cases and with modification of the ligand steric effects more challenging substrates can be reduced. Electron rich ketones and α,β-unsaturated ketones present a particular challenge of reactivity and selectivity respectively.

While there is a reasonable body of literature showing examples of both substrate classes, this tends to be in the form of substrate screens presenting a fairly broad array of products, generally to showcase the versatility of new catalysts or ligands. Some interpretation is required for those substrates not investigated in such publications, which may simply have not been tested, or may have performed poorly and not been included.

Polymer catalysts can greatly simplify product separation during ATH reactions, as well as offering a potential advantage of reusability over a small number of reaction cycles. However degradation or leaching of the catalyst is a frequent issue. Additionally there are serious practical difficulties of lengthy multi-step syntheses of polymer supported ligands that will reduce the uptake of such catalysts among other research groups. While it is relatively quick to test commercially available metal sources and ligands in new applications, custom synthesis of catalyst components is a much slower process.

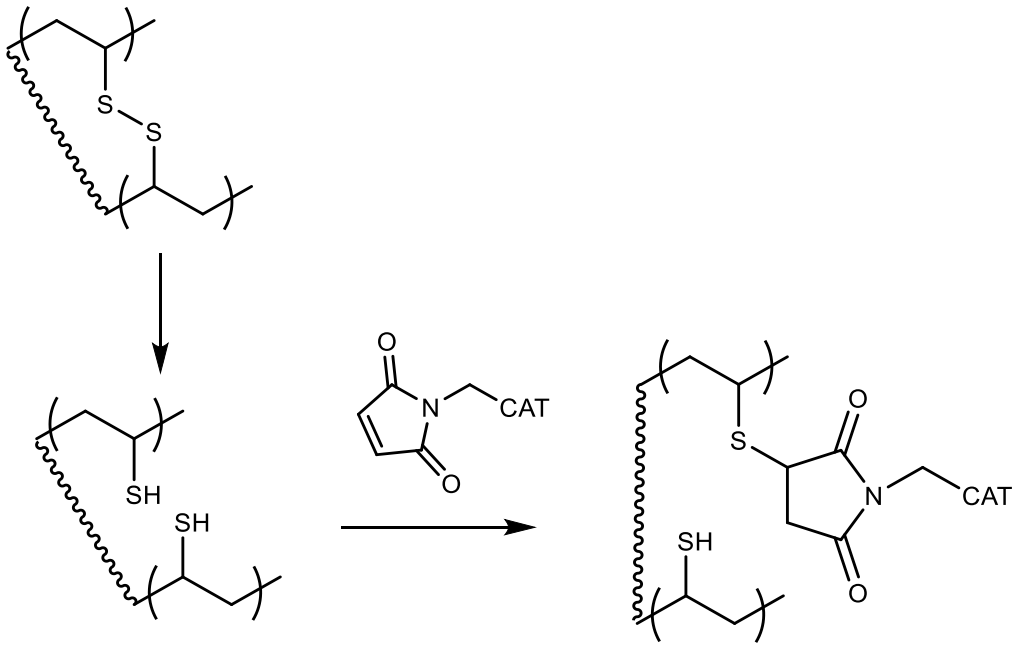
2 Results and Discussion

An initial goal of the project was the development of new polymer supported catalysts, as the majority of literature reports so far have not yet conclusively demonstrated a decisive advantage over their homogenous parent compounds.

2.1 Synthetic Approaches to Supported or Functionalised Catalysts

2.1.1 Maleimide Catalyst.

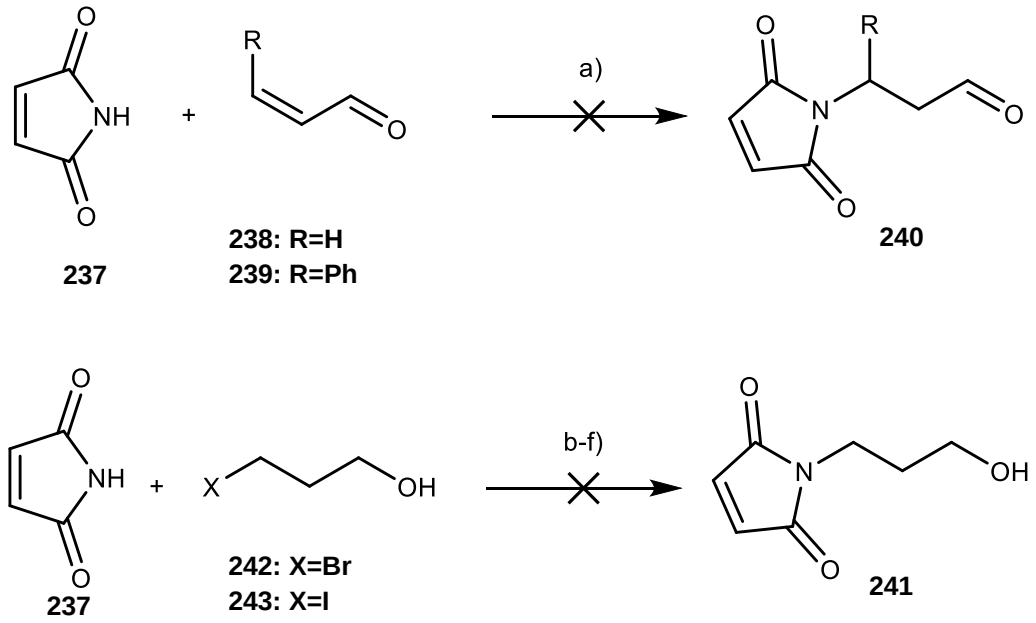
Incorporating a maleimide functional group was an early objective in the project. This would in principle allow easy attachment of a ligand or preformed ruthenium catalyst onto a protein scaffold. Either an existing free cysteine residue is required, or a disulphide bond can be reduced to produce two available sites. The resulting free thiol would then react rapidly with maleimide in a Michael addition.[109–111]



Scheme 69: Theoretical procedure for protein conjugation of maleimide functionalised catalysts.

Initial attempts to prepare a non-tethered functionalised catalyst were made using commercially available maleimide **237**. Two approaches were tried; alkylation of the

maleimide with hydroxy-propyl halides **242/243**, or direct conjugate addition with acrolein **238** or cinnamaldehyde **239**

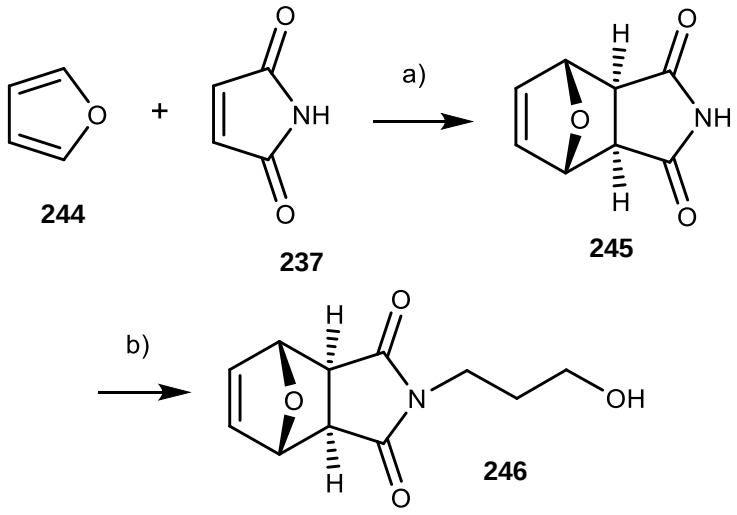


Scheme 70: Attempted Michael reaction and alkylation of maleimide.
a) MeONa, MeOH, rt, 2.5 hr. b) **242**, KOH, DMF, rt to 90°C, 24 hr. c) **243**, KOH, DMF, 4Å MS, rt to 80°C, 24 hr. d) **243**, K_2CO_3, THF, 65°C, 24hr. e) **243**, K_2CO_3, Acetone, rt, 24hr. f) **243**, K_2CO_3, MeCN, rt, 24hr.

All attempts to functionalise **237** in this way were unsuccessful, either failing to react or causing decomposition of the starting material.

2.1.1.1 Furan protection and synthesis

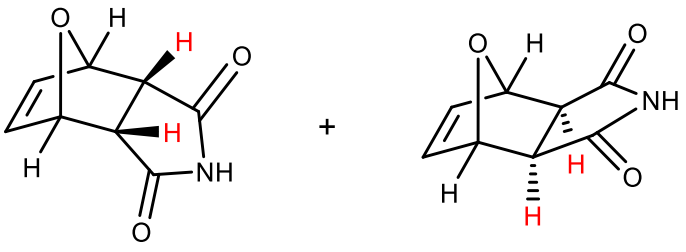
A protecting group approach to the alkylated product **241** was adopted based on the Diels-Alder cycloaddition between furan **244** and imide **237**, which was easily carried out following a literature procedure.[112] With the reactive double bond protected, room temperature alkylation then becomes possible under mild conditions, giving good yields of the alcohol **246** over two steps.



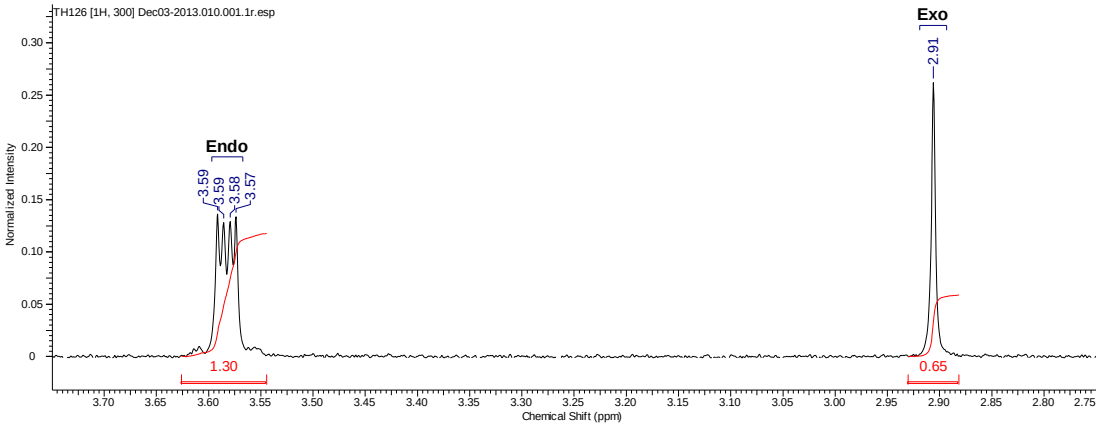
Scheme 71: Protection and N-alkylation of **237**.
a) Et_2O, 100°C sealed tube, 20 hr, 50-82%. b) **242**, K_2CO_3, Acetone, rt, 4 days, 90-99%.

Performing the Diels-Alder reaction at room temperature yields a mixture of exo and endo isomers of **245**, which can be distinguished by ^1H NMR. However by using a pressure vessel and increasing the reaction temperature to 90 °C, the thermodynamically favoured exo isomer could be formed selectively.

Table 27: Structure of endo/exo isomers of the maleimide-furan adduct **245** and NMR data (2:1 mixture shown in diagram)

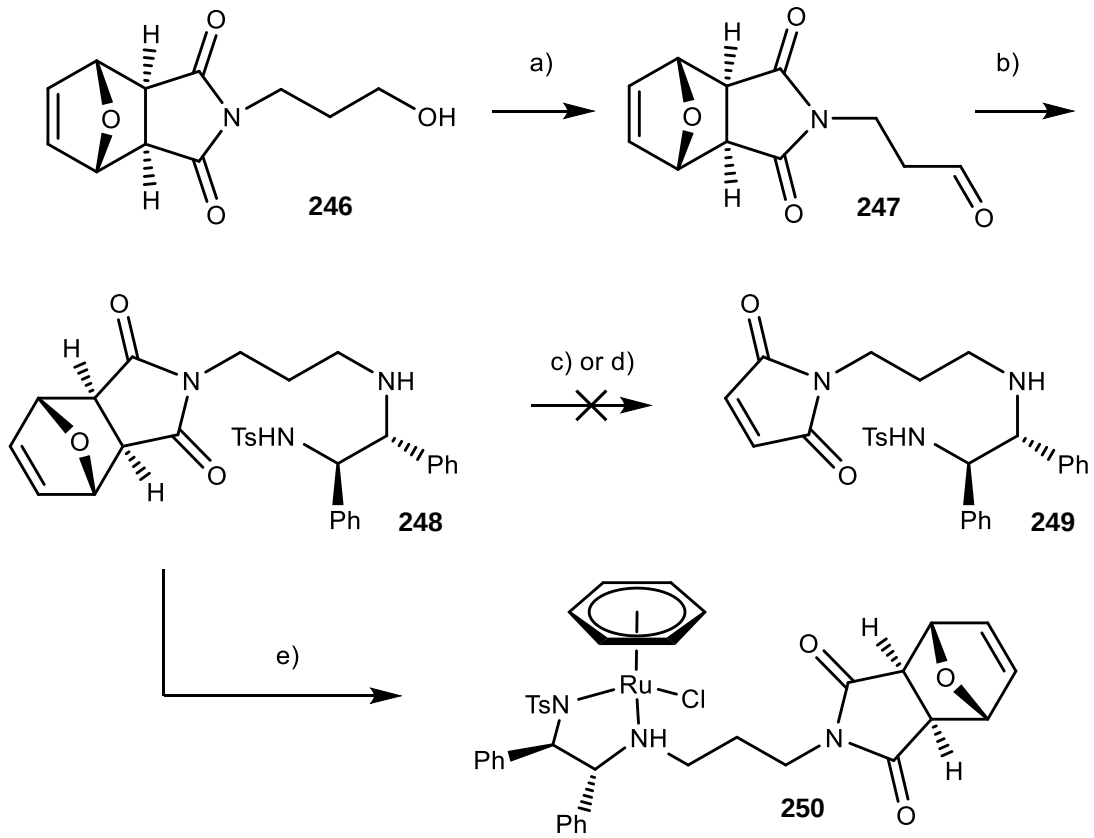


Endo-245 **Exo-245**



Entry	T /°C	Time	NMR Integral for Alpha Protons		Endo : Exo
			(dd, J=1.7, 3.5Hz)	(s)	
1	25	4 days	1.30	0.65	2:1
2	90	12 hours	0.02	2.00	1:100

Coupling with TsDPEN **55** was performed in a two-step process. Swern oxidation to aldehyde **247** followed by reductive amination gives the desired ligand **248** cleanly. Over the four steps only one chromatographic purification was required (Scheme 72).



Scheme 72: Synthetic approach to maleimide functionalised non-tethered complex. a) $C_2O_2Cl_2$, DMSO, NEt_3, DCM, -78 °C to rt, 10-57%. b) (*R,R*)-TsDPEN **55**, AcOH, 4Å MS, MeOH, rt, 3 hr then $NaBH_3CN$, rt 45 hr, 79-97%. c) Toluene, 110 °C, 3 hr. d) Xylene, 150 °C, 15 min. e) $[RuCl_2(C_6H_6)]_2$, NEt_3, IPA, 80 °C, 24% (impure).

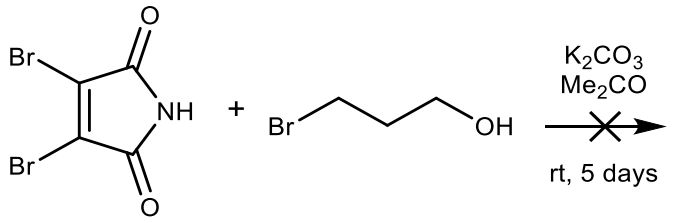
Attempts to deprotect ligand **248** by thermal decomposition in refluxing toluene or xylene appeared to yield a complex mixture of structurally related products. A possibility is that the amines are interfering with the maleimide group at the high temperatures required for deprotection.

A crude sample of complex **250** was prepared by reaction of **248** with benzeneruthenium chloride dimer. Although NMR and LCMS evidenced the formation of the desired orange complex, even after chromatography the product obtained was contaminated with several

unknown impurities and the mass recovery was poor. No further experiments were performed using this material.

2.1.1.2 Dibromomaleimide

Dibromomaleimides can be utilised without protection,[113,114] and have a different pattern of reactivity in their reaction with thiols, giving substitution instead of addition products. However, attempting to alkylate **251** did not yield the desired product (Scheme 73).



251 **242**

Scheme 73: Attempted alkylation of dibromomaleimide. a) K_2CO_3, Acetone, rt, 6 days.

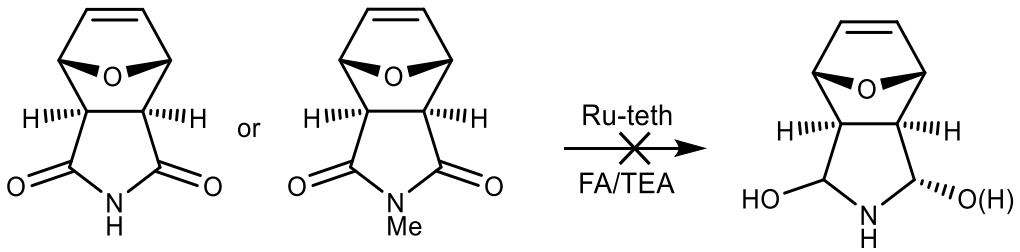
On the basis that this synthetic approach only leads to non-tethered catalysts, and owing to the practical difficulties encountered, the project did not continue further in this direction.

2.1.2 Ring-Opening Metathesis Polymerisation

The maleimide-furan cycloadduct **245** had been prepared earlier as an intermediate in the attempts to access a maleimide functionalised ruthenium complex. Although thermal deprotection to reveal the maleimide group had not been successful, a new approach was considered utilising the cycloadduct as a strained cycloalkane substrate for ring opening metathesis polymerisation (ROMP). The polymerisation occurs under mild and neutral conditions and may offer a way to incorporate a preformed Ru complex into a polymeric network.

2.1.2.1 Monomer Validation

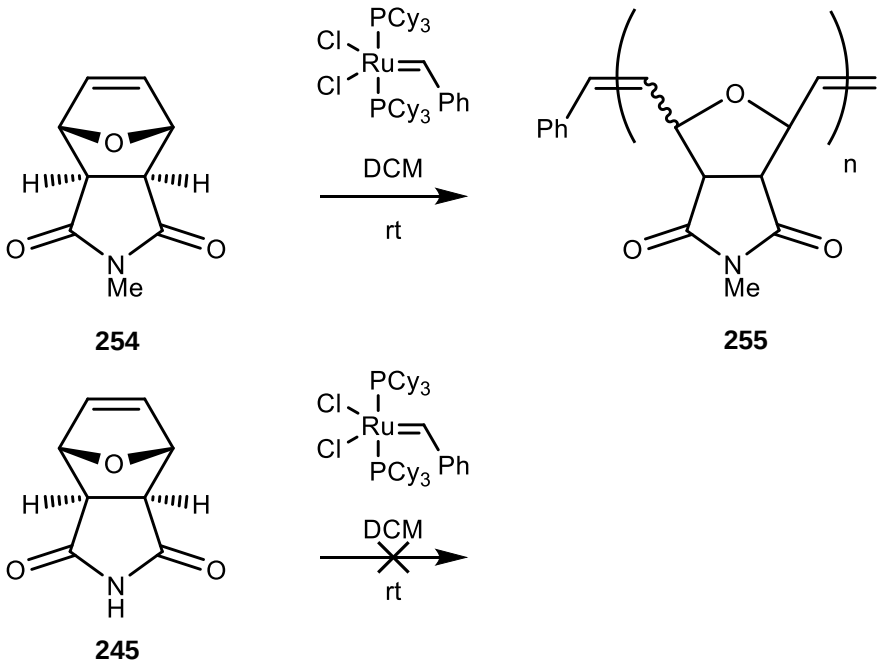
The monomers **245** and **254** (prepared from N-methylmaleimide and furan as for **245**) were subjected to transfer hydrogenation with (*S,S*)-**80** (Scheme 74). The imide carbonyls in these substrates were found to be inert in FA/TEA at 40 °C, an important prerequisite to the use of this structure as a polymeric catalyst support.



Scheme 74: ATH of monomers **245** and **254** with catalyst **80**. Conditions: (*S,S*)-**80** (1%), FA/TEA, 40 °C, 22 hr. No reaction observed.

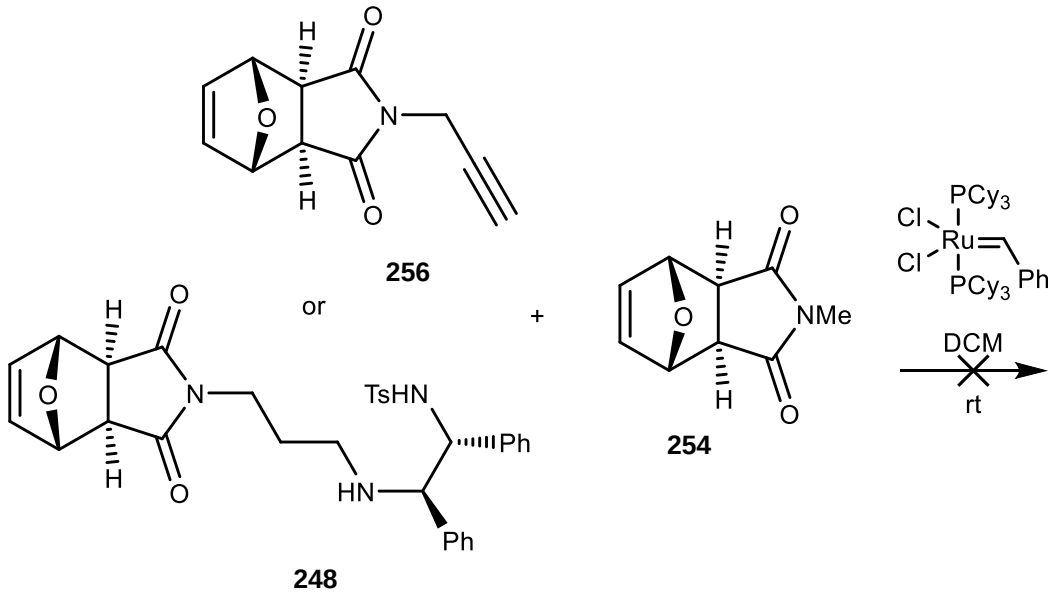
2.1.2.2 Polymerisation

ROMP was investigated using the Generation I Grubbs catalyst. The NH containing monomer **245** is unreactive, but the N-methyl variant **254** polymerises successfully to give the polyoxanorbornene **255** with a mixture of *cis* and *trans* double bonds (Scheme 75). The polymer was sufficiently soluble for NMR analysis and showed the expected peak broadening, however analysis of MW etc. was not performed at this stage as this reaction was simply for proof of concept.



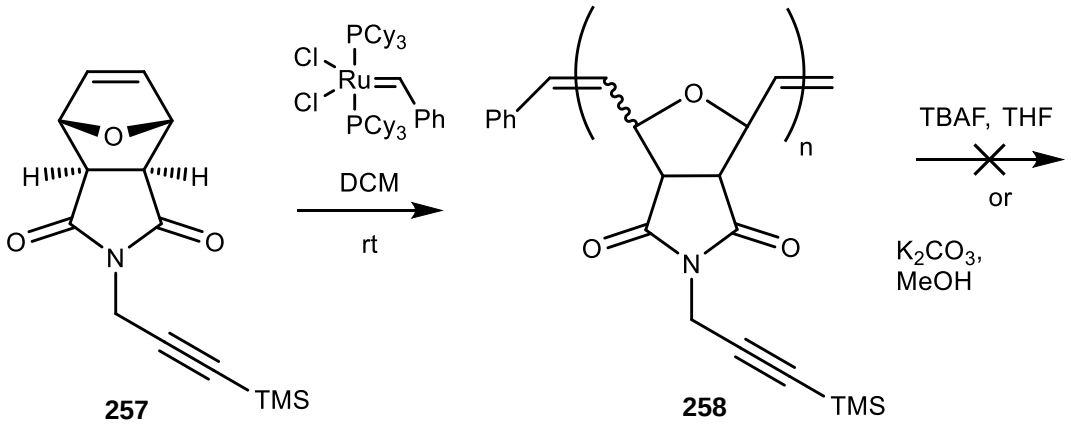
Scheme 75: ROMP of maleimide-furan Diels Alder products **245** and **254**. Mass recovery of **255**: 122%**.**

The more usefully functionalised N-propargyl **256** and TsDPEN **248** substituted monomers did not co-polymerise with **254** under the same conditions, and only starting materials were recovered (Scheme 76).



Scheme 76: Attempted co-polymerisations of functionalised monomers with **254**.

The TMS protected substrate **257** could be easily prepared by alkylation of **245** with $(CH_3)_3SiCCCH_2Br$ and successfully polymerised (Scheme 77).



Scheme 77: Polymerisation and attempted deprotection of TMS protected monomer.

Deprotection of **258** with TBAF or K_2CO_3/MeOH was attempted, however on work up the polymer violently exothermically degraded, forming a highly insoluble brown material formed which defied further analysis. It is possible that some traces of ruthenium catalyst remained trapped within **258** after the polymerisation, and once the free alkyne groups were revealed these reacted immediately. At this point in the project it was decided not to pursue the maleimide strategy any further.

2.1.3 Cross-Coupling Strategy

Instead a new synthetic approach to functionalise complexes via Pd catalysed cross-coupling was considered. The synthesis simply requires incorporating an aryl iodide functionality in place of the usual tosylate methyl group of TsDPEN **55**. This functional group is in a remote position that does not preclude the possibility of tethering the amine and arene ligands (Figure 25).

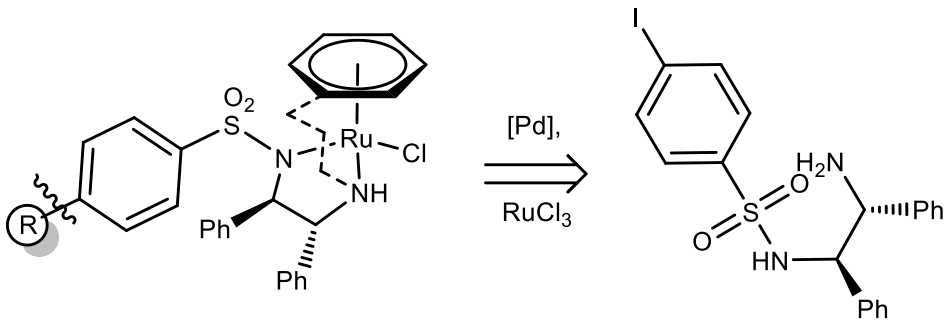
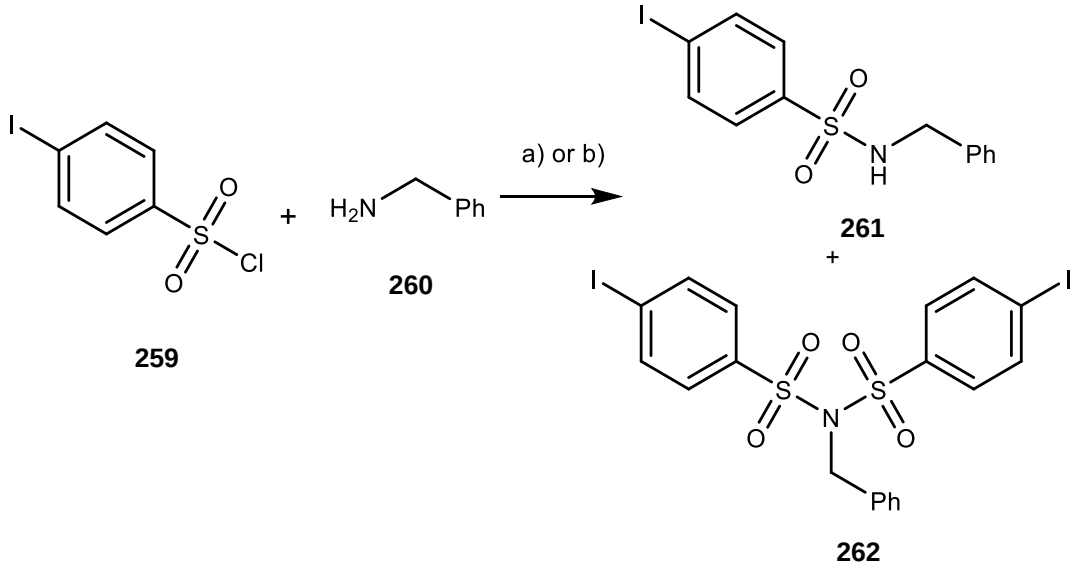


Figure 25: Proposed cross-coupling strategy for introducing new functional groups in tethered or non-tethered Ru catalysts.

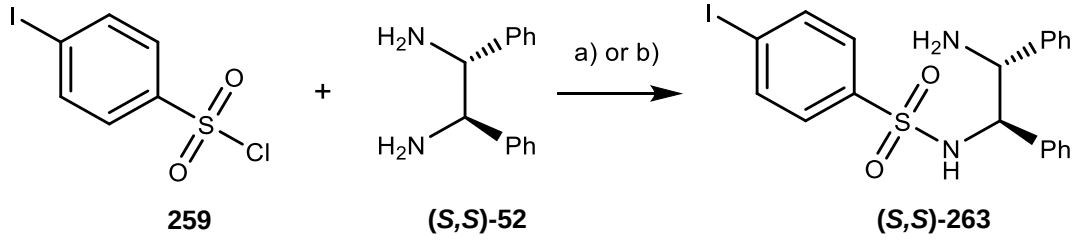
2.1.3.1 Synthesis of *para*-Iodo Substituted Ligands

To test conditions for preparation of required ligand **263** a model reaction was performed. Commercially available *para*-iodosulfonyl chloride **259** (IpsCl) was reacted with benzylamine **260** in DCM using either triethylamine or aqueous sodium hydroxide as base (Scheme 78). Triethylamine could be removed by washing with HCl, however this approach would not be compatible with the free amino group in DPEN derived ligand **263**.



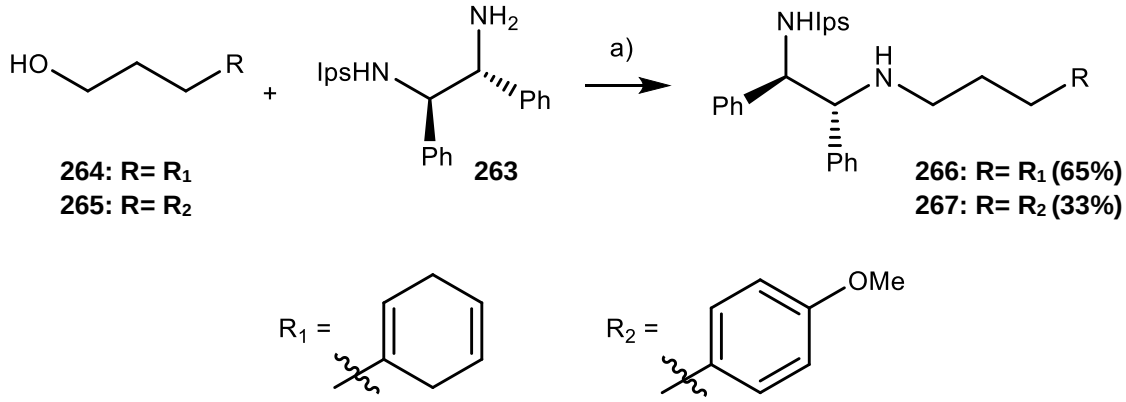
Scheme 78: Model reaction for sulfonylation.
a) NEt_3, DCM, 0 °C to rt, 42 hr. b) 2M NaOH, DCM, 0 °C to rt, 42 hr, 54%.

The Schotten-Baumann biphasic conditions gave a slightly higher proportion of di sulfonylated side product **262** in the crude product mixture, however the base was much more easily removed during workup. Recrystallization from diisopropyl ether effectively separated the desired mono sulfonylated product **261**. Application of these conditions to **259** and (*S*,*S*)-**52** gave the desired monosulfonylated ligand **263**.



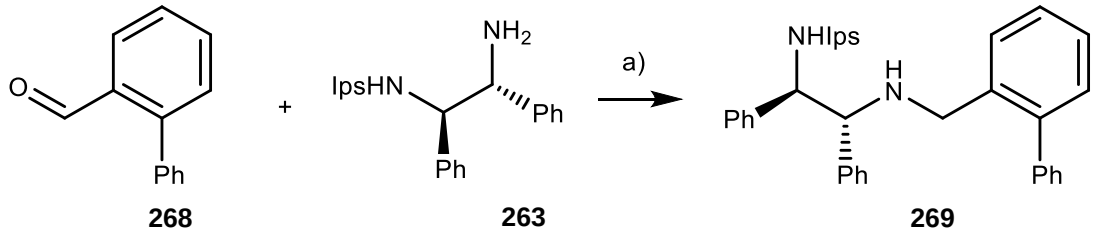
Scheme 79: Synthesis of aryl iodide containing sulfonamide ligand.
a) 2M NaOH, DCM, 0 °C to rt, 45 hr, 52%; b) K_2CO_3, DCM, 0 °C to rt, 4 days, 84%

As the reaction was scaled up in further experiments replacing NaOH with K_2CO_3 and extending the reaction time improved the reliability of the sulfonylation process. Recrystallization from toluene allowed efficient preparation of **263** on 2g scale (Scheme 79). In order to prepare Ips containing ligands for tethered complex synthesis, two approaches were used. Alcohols **264** and **265** underwent a one pot triflation/substitution reaction with diamine **263** to produce ligands **266** and **267**. (Scheme 80).



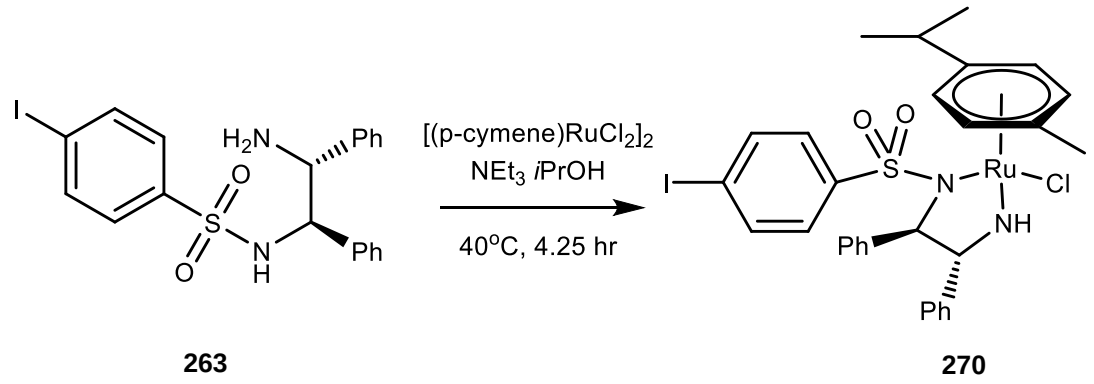
Scheme 80: Preparation of Ips- (*p*-$IC_6H_4SO_2$-) substituted ligands. a) 1) Alcohol, Tf_2O, 2,6-lutidine, DCM, 0°C, rt. 2) **263** , NEt_3, DCM, 0°C to rt, 24hr.

Ligand **269**.could be prepared more easily by reductive amination of aldehyde **268** with diamine **263**.



Scheme 81: Preparation of Ips substituted benzyl bridged ligand. a) AcOH, 4Å MS, MeOH, rt, 6 hr then $NaBH_3CN$, rt, 3 days. 82% Yield.

2.1.3.2 Synthesis of *para*-Iodo Substituted Complexes



Scheme 82: Preparation of untethered Iodine containing complex **270**. Yield 70%

Ligand **263** has been used to prepare the untethered complex **270**. This reaction is usually performed at 80°C in the literature, however it was found that the complexation occurs cleanly at 40°C and pure **270** is isolated easily by filtration.

The X-ray structure of **270** confirms that the (*R,R*)-ligand imparts (*R*) geometry at ruthenium, and that the bond angles and distances around the ruthenium centre are comparable with those reported by Noyori for [RuCl(*p*-cymene)TsDPEN].[42]

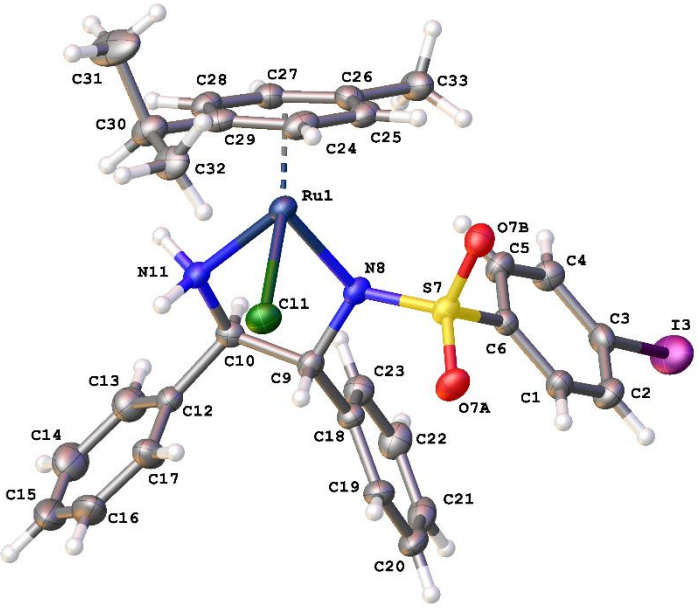
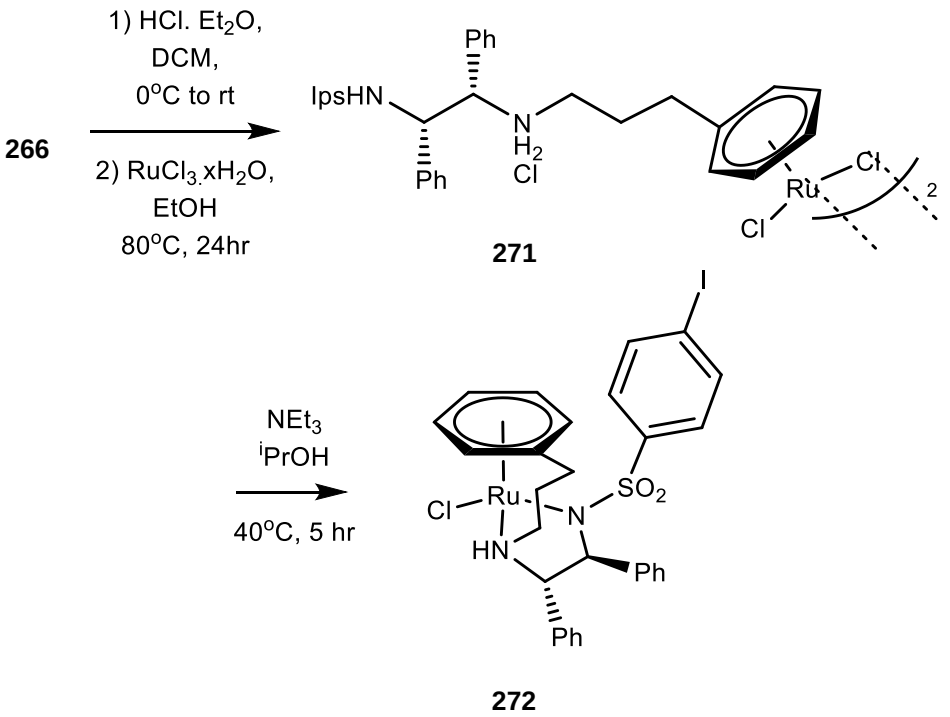


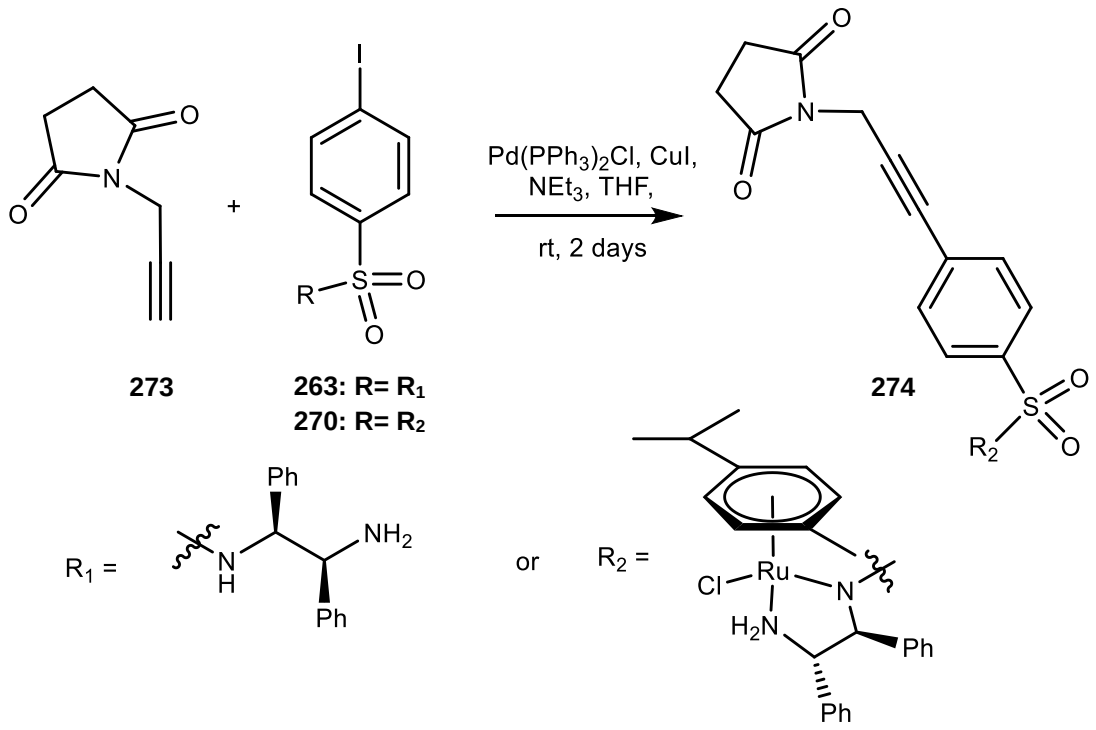
Figure 26: X-ray crystal structure of [RuCl(IpsDPEN)(p-cymene)]

The cyclohexadiene ligand **266** could be converted to tethered complex **272** via dimer **271**, in a synthesis that is analogous to that used for **3C-teth (80)**, however only test arene exchange reactions were performed with the other ligands **267** and **269** and fully characterised samples of their respective complexes have not been obtained.



Scheme 83: Synthesis of tethered Ips functionalised catalyst. 12% Yield over two steps.

The objective of preparing these complexes was to utilise the aryl iodide group as a site for further functionalization of either ligands or complexes. An initial attempt to perform a Sonogashira coupling on both **263** and **270** with a test alkyne **273** gave mixed results. The free amino group in **263** appeared to inhibit coupling, with no trace of reaction visible by NMR or mass spectrometry, possibly due to coordination of basic amine to the palladium or copper catalysts. However **270** appears to have reacted completely by mass spectrometry, as inferred by a shift in the $[M\text{-}Cl]^+$ peak in the product from 713 to 722, consistent with replacing -I for $-C_7H_6NO_2$. However, the resulting product was impure even after column chromatography and no other data was obtained to prove that the product is complex **274**.



Scheme 84: Attempted coupling of alkyne with para-iodo compounds. No reaction with R = DPEN. Possible reaction with R = [RuCl(DPEN)(*p*-cymene)]. a) $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, THF, rt, 2 days.

From practical experience it appears to be a general rule that purification of monomeric ruthenium complexes is low yielding and difficult*, normally requiring either crystallization, purification on silica or both. Therefore, coupling to form another monomeric compound is likely to be inefficient, and the coupling strategy will only be of value if used to attach the complex to a new group that allows for simple purification. For example, coupling to a solid support allows purification by washing and filtration.

2.1.4 Chapter Summary

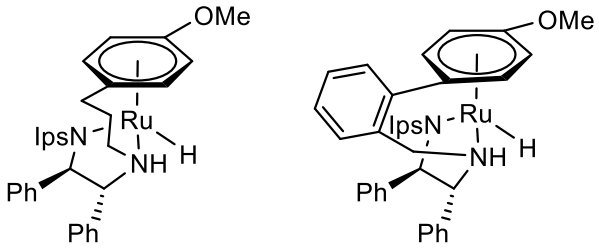
At this point in the project there was no clear indication of success. Preparation of the maleimide functionalised ligand **248** was achieved, as well as an impure sample of complex **250**, however the issue of deprotection or polymerisation of the maleimide group to incorporate it into a support has not been successfully addressed.

Iodine substituted complexes were prepared that may provide more promise for future consideration. The cross coupling reaction between untethered complex **270** has shown

* See Chapter 2.2 for a more detailed discussion with relation to purification of tethered complexes formed by arene exchange

some potential, although clearly much more work is required to prove formation of pure, coupled monomeric complex and apply this methodology to coupling to any polymeric support.

The synthesis of IpsDPEN **263** and several complexes derived from it, resulting from continued work by members of the Wills group in this area, have now been published.[115] These include complex **275** derived from ligand **267**, and benzyl-bridged complex **276** that is derived from a methoxy analogue of ligand **269**. (Figure 27)



275 **276**

Figure 27: New Ips functionalised complexes developed in further work. Results for reduction of acetophenone (100 : 1 S/C, FA/TEA, 40 °C). **275**: 99% Conv, 97% ee in 24 hr. **276**: 99% Conv, 97% ee in 7 hr.

These results demonstrate that the iodine substitution does not appear to affect the activity/selectivity of these complexes in ATH of ketones. This is encouraging as it indicates that cross coupling to support through this site is unlikely to interfere with the active part of the catalyst. However at the time of the project, with mixed indications of future success, it was decided to change the direction of the research project towards the use of known catalysts with new substrates.

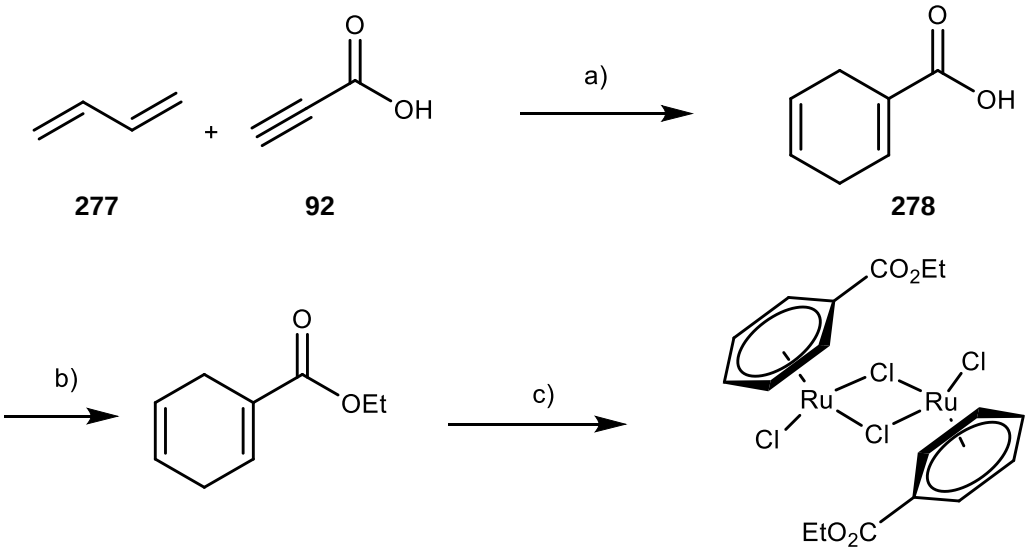
2.2 Optimisation of Arene Exchange Methods

During this project it became necessary to prepare further quantities of **OMe-teth (115)** for use in substrate reductions. As discussed in introduction section 1.3.6 , the arene exchange reaction used for preparation of **115** is particularly challenging and not yet optimised. Some efforts at better understanding the practical aspects of this reaction and to improve its robustness are described in this section.

2.2.1 Synthetic Preparation of Ligand and Metal Source

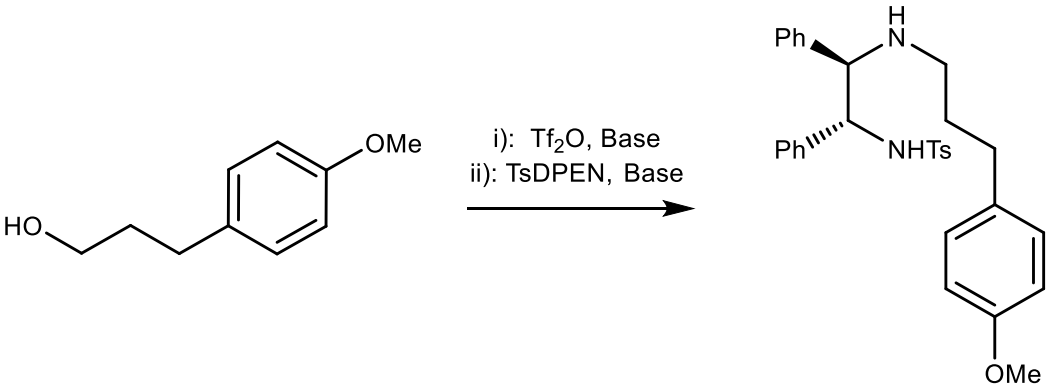
The approach used previously within the group for preparation of ruthenium dimer **117** was followed without modification.[116] High pressure Diels-Alder cycloaddition of butadiene and

propiolic acid gave the cyclic acid **278**, which decomposes within a few days at room temperature and must be stored in the freezer. Esterification with sulfuric acid and ethanol gave the stable ethyl ester **279**. Dehydrogenation with ruthenium trichloride was carried out by refluxing in ethanol. Dimer **117** could be easily isolated by filtration and no purification was required. The overall yield for the process was 57% for 0.9 g of dimer.



Scheme 85: Preparation of ruthenium dimer **117**. Conditions: a) neat, -78°C to 110°C, 110 mbar, 78%; b) H_2SO_4, EtOH, 80°C, 79%; c) **75**, EtOH, 80°C, 93%.

Ligand **116** was prepared using a published procedure from within the group.[62] One pot triflation of commercially available alcohol **280**, followed by S_N2 amination with TsDPEN gave the desired ligand on 5g scale in 66% yield. The aqueous workup was simplified by solvent switching from DCM to EtOAc, and product isolation achieved by recrystallization of the crude amine from ethanol, rather than by chromatography. While the resulting yield was somewhat lower than the literature reports (66 vs 89%),[62] this reaction was carried out at 10 times the scale of the reported procedure, and the crystallization process represents a more attractive option for future scale up.

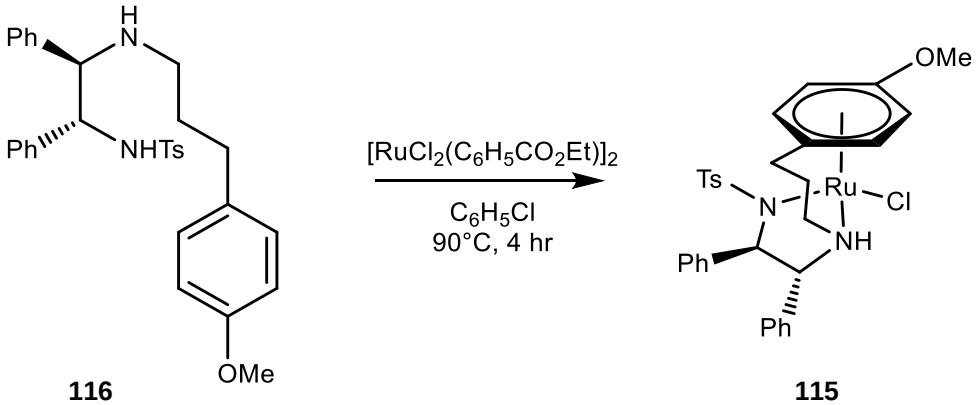


280 **116**

Scheme 86: Preparation of Ts-DPEN-3C-OMe ligand.
Conditons: i) Tf_2O, 2,6 lutidine, DCM, 0°C to rt, 2hr; ii) (*R,R*)-TsDPEN, NEt_3, DCM, 0°C to rt, 24hr. Yield 66%

2.2.2 Arene Exchange Reaction

With both ligand and metal source in hand, the arene exchange reaction was attempted. In the initial test reaction at 0.2 mmol scale. Initial mass recovery after concentration of the reaction mixture was 135% of theoretical. ^{1}H NMR showed a characteristic doublet at ~8.02 ppm that is characteristic of ethylbenzoate.



116 **115**

Scheme 87: Initial attempt at arene exchange reaction to form **OMe-teth (115)**. Mass recovery of crude product: 135%. Mass recovery of impure product after chromatography: 62%.

Test chromatography on ~20% of the crude material with DCM/MeOH as eluent successfully separated three components; ethylbenzoate **113** in the solvent front, unreacted ligand **116,** and the target complex. However both ligand and complex fractions are contaminated with an unidentified brown material, which streaks extensively during chromatography. Dark coloured impurities resulting from the arene exchange reaction are known from the previous

work and observation of their presence during TLC was used as a proxy for gauging impurity formation during reaction optimisation (the original diagram illustrating this is reproduced in Figure 28).

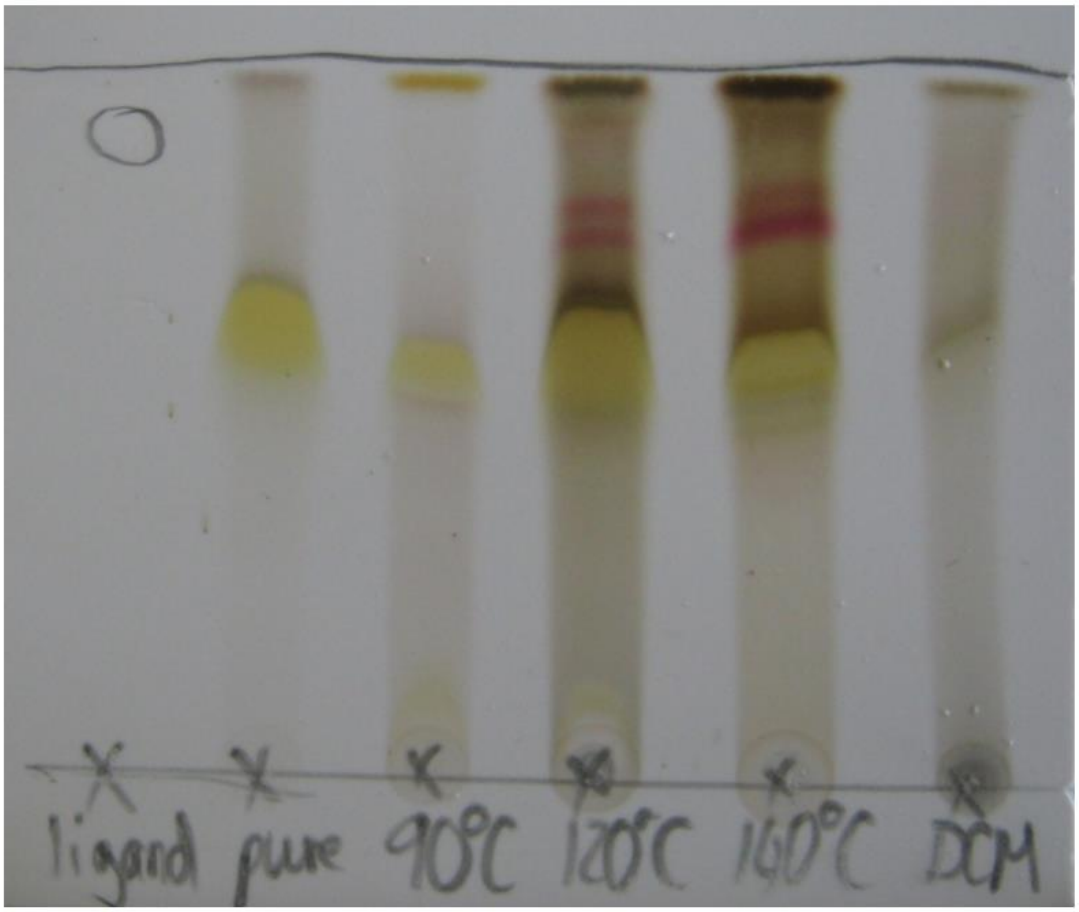


Figure 28: TLC visualisation of dark coloured impurity. Image taken from Wills *et*. *al*.[62]

The remaining crude was treated with diethyl ether to form a red precipitate, which was recovered by filtration. The NMR of the precipitate contained the desired peaks, and the mass recovery of the process was ~50%. NMR analysis of the filtrate showed the presence of ethylbenzoate (as expected), as well as peaks characteristic of the target complex, and diethyl ether. Both sets of spectra were again significantly broadened and distorted

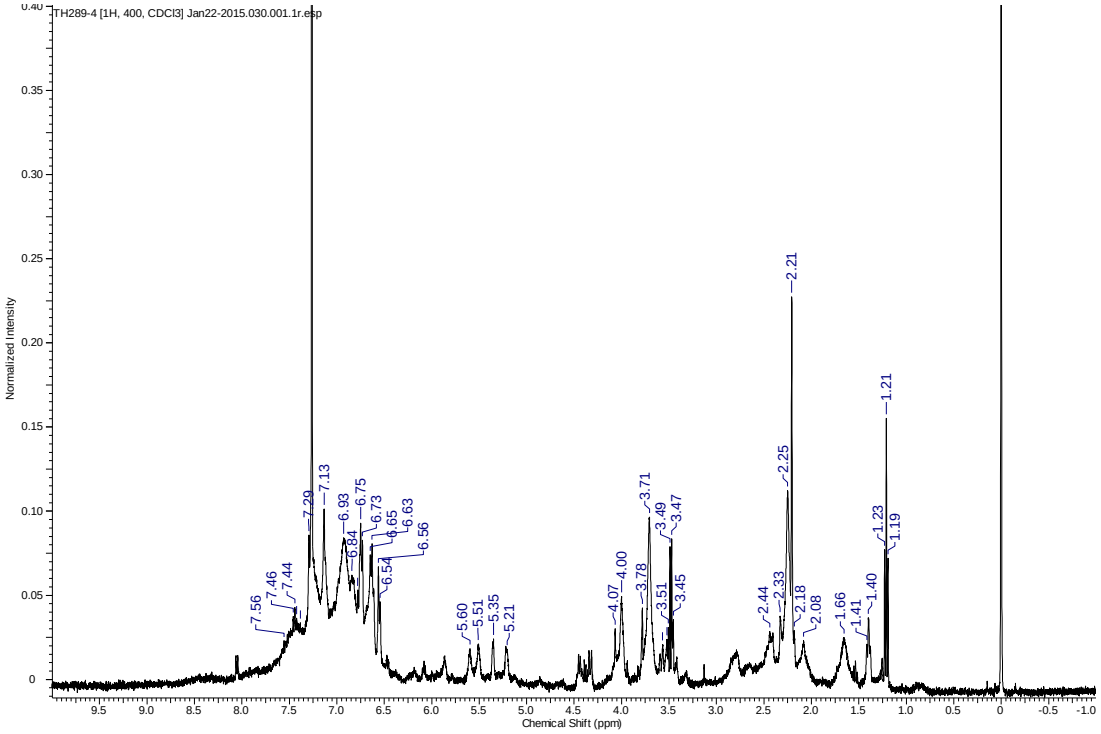


Figure 29: Poor quality ^{1}H NMR spectrum of **115**.

None of the material obtained in this first reaction was of sufficient quality to be characterised fully or used in ATH reactions. The brown impurity was of particular concern on the basis of its known attributes (NMR distortion, no assignable peaks in ^{1}H or ^{13}C NMR, streaking during chromatography, dark colour and staining). These may well indicate the presence of a metallic impurity which would impede accurate assessment of the catalytic properties of **115**. Therefore further method optimisation was required.

2.2.2.1 Varying Dimer to Ligand Ratio

The ligand to metal ratio was varied in small scale tests, with 0.1 mmol dimer and between 0.1 and 0.4 mmol of ligand in a fixed solvent volume of 5 ml chlorobenzene. The reactions were carried out under N_2 in a parallel synthesis kit rather than the usual pressure tube apparatus that had been used before, in order to allow reaction sampling over time. The reaction was followed by LC-MS as described previously by the group.[62,116] Once complete, the crude was concentrated and precipitated from diethyl ether before being passed through a short silica plug with a mixture of ethyl acetate and ethanol (3:1).

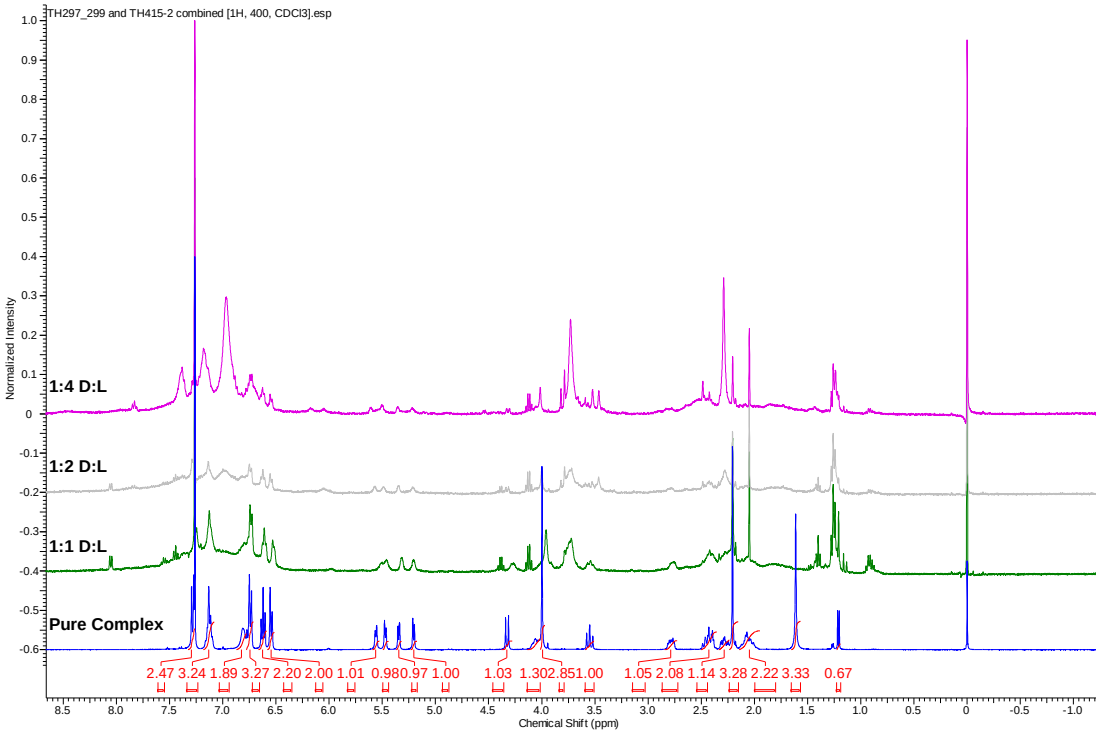
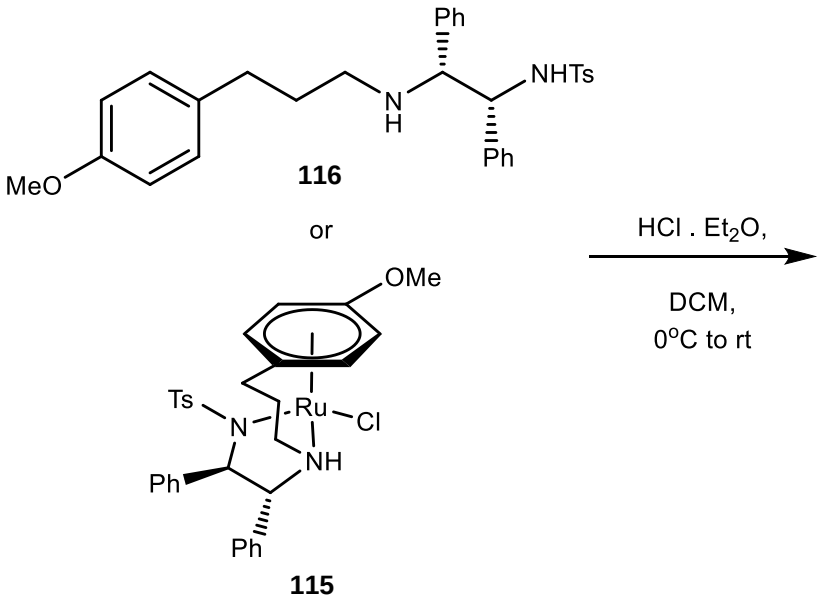


Figure 30: Comparison of ^{1}H NMR spectra for crude products of arene exchange reactions at varying ratios. D = dimer, L = Ligand.

^{1}H NMR analysis of these crude products showed that in all three cases the spectra of the crude products are of poor quality. The characteristic 4H ruthenium arene system from complex **115** is visible between 5.1-5.6 ppm in all cases, though peak positions are slightly variable and coupling constants are not visible. Despite the workup which involved precipitation from diethyl ether, the ethylbenzoate peak at ~8.1 ppm is clearly visible in the 1:1 and 1:2 ratio reactions. Interestingly the reaction with excess ligand does not show any trace of ethylbenzoate **113**. Despite a slightly cleaner NMR spectrum in the 1:1 case, there was not enough clear evidence of improvement to justify the inefficient stoichiometry, which would waste one atom of ruthenium metal per molecule of complex formed.

2.2.2.2 HCl Gas as a Potential Contaminant.

During reaction monitoring white fumes were observed when the hot reaction mixture was disturbed by a syringe for withdrawing aliquots. As the reaction is performed in the absence of base and elimination of HCl is required for ligation of the sulfonamide to ruthenium, it is highly likely that these fumes are gaseous HCl. While this will be partially removed during concentration at the end of the reaction, there is also a possibility that the HCl gas is reacting with the various amine bases and forming hydrochloride salts that are interfering with the purification and spectral analysis.



Scheme 88: Micro-scale (0.02 mmol) reaction of ligand **116** and complex **115** with HCl.

A small experiment was performed to test this hypothesis. Standard samples of pure ligand **116** and complex **115** were prepared in $CDCl_3$ and the ^1H NMR spectra recorded. The samples were then evaporated, dissolved in DCM and stirred with 0.5 eq of ethereal HCl for 3 hours, before being evaporated again (Scheme 88). The full sample was re-dissolved in $CDCl_3$ and the ^1H NMR spectra recorded and compared.

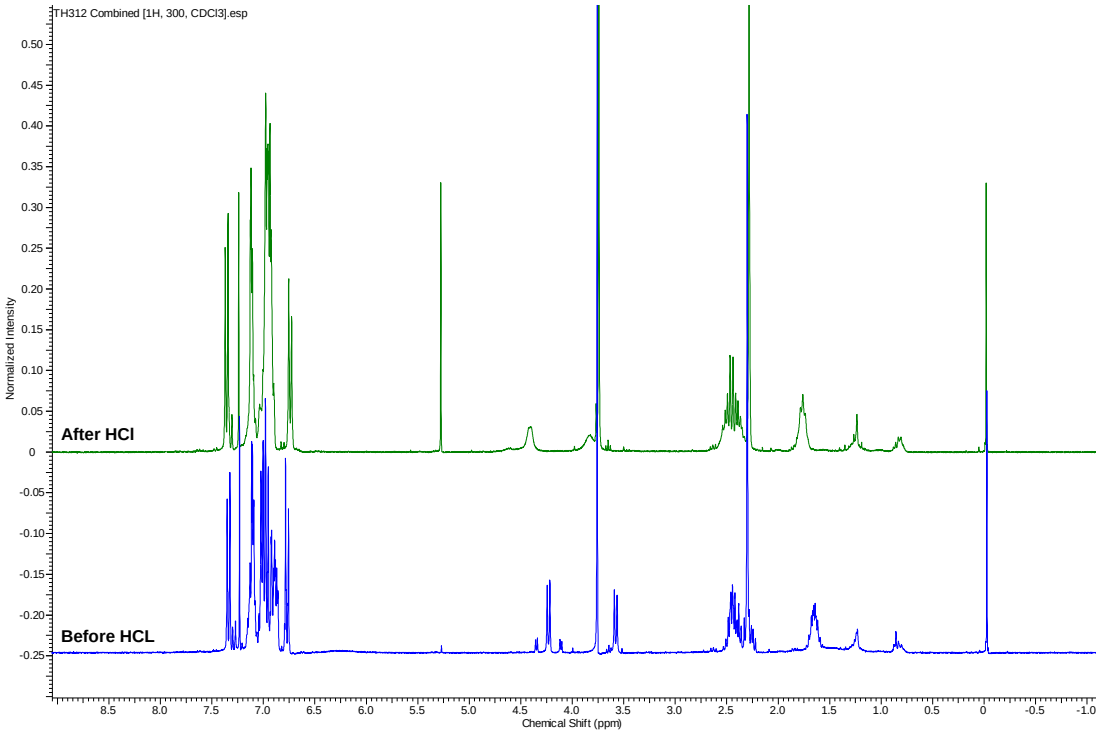


Figure 31: ^{1}H NMR spectra of ligand **116** before (lower) and after (upper) treatment with HCl

In the case of ligand **116**, treatment with HCl had a small effect (Figure 31). The ligand tertiary CH protons at ~4.25 and 3.59 ppm have shifted downfield by 0.17 and 0.24 ppm respectively, and are so broadened that the coupling pattern is no longer visible. The sulphonamide NH peak is no longer visible, and the diastereotopic CH_2 proton at 2.28 ppm is also no longer visible to the right of the large tosyl CH_3 signal at 2.31 ppm. Finally the remaining aromatic and alkyl multiplets are somewhat broadened and couplings are not clearly visible.

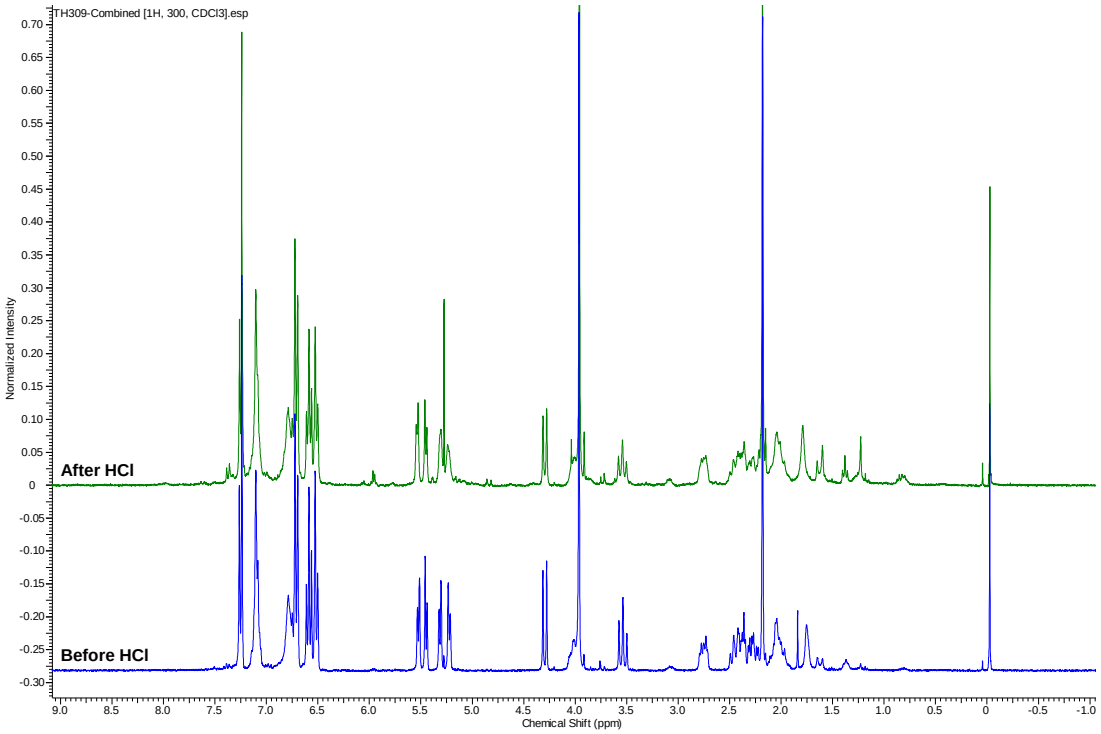


Figure 32: ^{1}H NMR spectra of complex **115** before (lower) and after (upper) treatment with HCl

For complex **115**, HCl treatment was also detrimental (Figure 32). The ruthenium arene protons between 5.5 and 5.2 ppm, which had been clearly visible as doublets or doublets of doublets were now broadened into two indistinct doublets and two broad singlets. Additionally many of the peaks in the alkyl region have partially coalesced. Unlike the spectra of ligand **116**, there were no major shifts in peak position.

While the spectra display some adverse effects as a result of HCl treatment, the peak broadening is not as severe as that observed in crude reaction mixtures. Therefore while it was considered prudent to attempt to remove HCl residues from the reaction mixture in some form before analysis, the severe spectrum degradation is more likely to be a result of contamination with the dark coloured impurities noted previously.

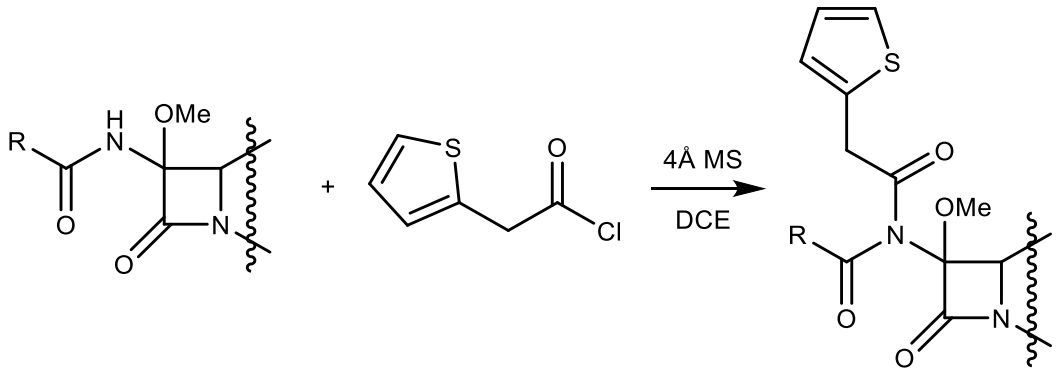
The arene exchange reaction was repeated on test scale, incorporating an aqueous workup with DCM and $NaHCO_3$ in an effort to remove HCl residue from the crude product. Crude filtration through a silica plug* achieved a rough separation between ligand and complex.

* Solvent mixture: 1): 70% petroleum ether, 22.5% ethyl acetate, 7.5% ethanol; 2): 40% petroleum ether, 45% ethyl acetate, 15% ethanol. Solvent mixture choice based on work by Taygerly *et. al.*[195]

Column chromatography with DCM/EtOAc/EtOH then gave a relatively pure sample of complex, however the overall yield for this process was poor (18%).

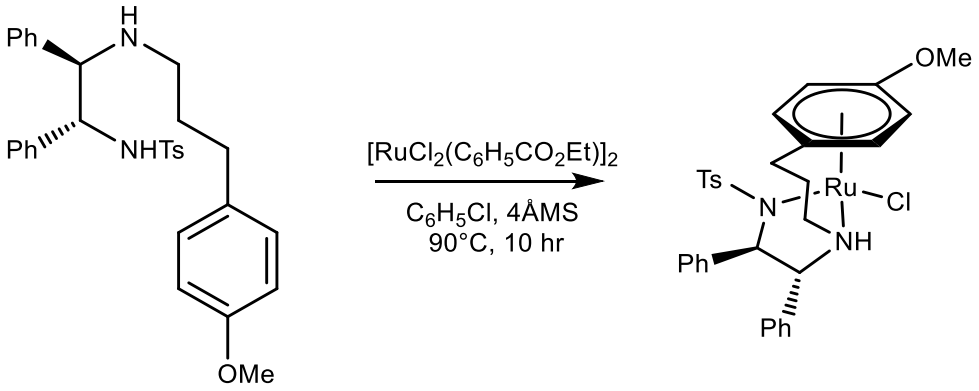
2.2.2.3 Final Reaction Conditions

While at the outset of this project improving on the reported literature yields of 40-50% for arene exchange reactions had been considered a useful goal, experimentation thus far had shown that it would be an achievement to simply replicate the literature results. The final conditions chosen for a 1.5 mmol scale synthesis of **OMe-teth (115)** were a result of the experience acquired thus far.



Scheme 89: Literature conditions for use of molecular sieves as HCl scavenger.[117]

One change made was the incorporation of 4Å Molecular sieves to the reaction mixture as HCl scavenger. This was inspired by a literature reference to a successful amide acylation performed in neutral conditions where amine bases had proven ineffective (Scheme 89).[117] Thus the arene exchange reaction was carried out at 90°C in chlorobenzene, under N_2 and monitored by LCMS (Scheme 90). Crucially, during monitoring no white fumes were observed, indicating that the molecular sieves were fulfilling their role. After an extended reaction time of 10 hours, filtration through a bed of Celite with a thin band of silica in the middle gave the crude complex with some of the brown colouration removed.



116 **115**

Scheme 90: Optimised conditions for arene exchange. 330 mg isolated, 34% yield.

Column chromatography was then used with careful selection of conditions to minimise streaking of impurities. The crude was dry loaded and eluted isocratically with a mixture of petroleum ether, DCM and isopropanol (5:4:1). This finally yielded clean product, with most of the brown colouration removed in an early band (with the ligand) and a trailing band that follows on from the pure catalyst. The ^{1}H NMR spectra of this purified material were now acceptable, with a flat baseline and well defined peaks that matched the reported literature values.

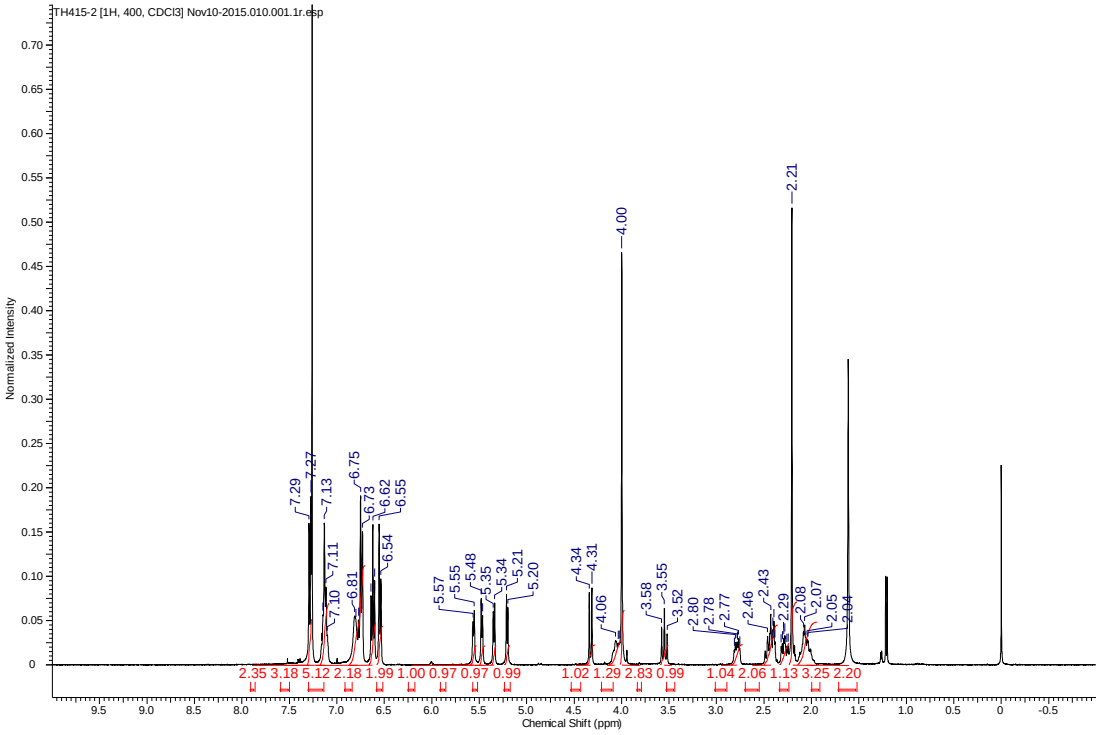


Figure 33: ^{1}H NMR spectrum of pure complex **115**.

2.2.3 Chapter Summary

Some of the complexities of the arene exchange route to tethered complexes have been explored in detail. While the absence of base helps promote the desired arene exchange reaction, this results in the release of free HCl as the condensation between the ligand sulfonamide and ruthenium progresses. This was shown to potentially degrade the quality of the ^{1}H NMR spectra of crude products from the reaction, which makes analysis of conversion more challenging.

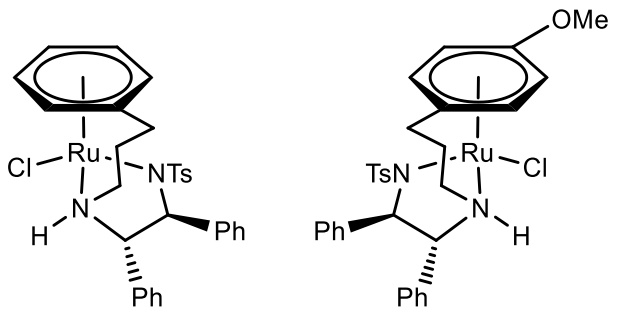
The use of molecular sieves as a HCl trap, while not resulting in an improvement on the reported literature yield, simplified the operation and allowed preparation of a batch of catalyst on sufficient scale to perform several of the reductions in the remainder of this project.

2.3 ATH of Electron Rich Ketones:

As discussed in the introduction, electron rich aromatic ketones are challenging substrates for reduction due to a lack of reactivity.[65,118] This makes them a prime target for exploring the applications of tethered catalysts, which show enhanced activity compared to their non-tethered counterparts.

2.3.1 Initial Substrates for Investigation

Ortho-hydroxy (**133**) and ortho-methoxy (**126**) acetophenones were chosen as simple starting substrates for investigation. Both substrates were reduced with **3C-teth (80)** and **OMe-teth (115)** catalysts under standard (FA/TEA) conditions and slightly elevated temperature (40 °C). All four reactions progressed at a reasonable rate, giving high to complete conversions in ~4 hours (Table 28) Conversion was determined by ^{1}H NMR spectroscopy and the ee's were determined by chiral GC or HPLC as appropriate.

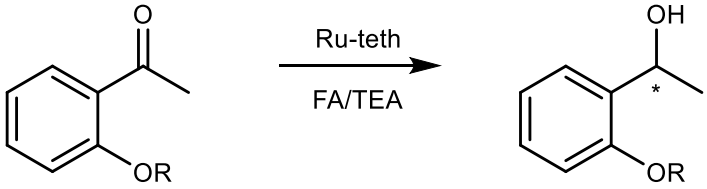


80 **115**

Figure 34: Catalysts (*S,S*)-**80** and (*R,R*)-**115** used for reduction of electron rich ketones.

Racemic standards were obtained by sodium borohydride reduction where possible, or peak positions of enantiomers were confirmed by observing switching of positions in products formed using the pseudo-enantiomeric catalysts (*S,S*)-**80** and (*R,R*)-**115**.

Table 28: Initial reductions of electron-rich ketones



Substrate	Catalyst:	(*R,R*)-115			(*S,S*)-80		
	R =	**t / hr**	**% Conv**	**% ee**	**t / hr**	**% Conv**	**% ee**
133	H	3.5	99	99 (*R*)	4	99	99 (*S*)
126	Me	3.75	98	96 (*R*)	3.75	95	68 (*S*)

Standard conditions: S/C = 100, T = 40 °C. Configuration determined by sign of optical rotation.

Both catalysts are extremely effective in reduction of **133**, giving the product in 99% ee. **115** was also effective in reducing the O-methylated substrate **126**, with a slight drop in ee to 96%, however the 3C-teth catalyst performed unexpectedly poorly, giving the product in 68% ee.

It was considered possible that the different ortho substituents were enforcing a different conformation of the carbonyl group relative to the phenyl ring. Intuitively it was expected that **133** would adopt a simple planar conformation stabilised by hydrogen bonding, while the methoxy group in **126** might be large enough to force the phenyl ring to rotate out of plane and hence disfavour the edge to face interaction expected in the transition state for ATH (Figure 35).

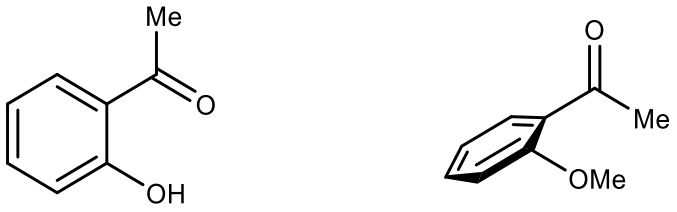


Figure 35: Proposed conformations of ketones **133** and **126**.

2.3.2 Conformational Calculations

Gas phase quantum chemical calculations at the B3LYP/6-31G* level showed that both **133** and **126** appear to prefer planar conformations. Plots of the conformational energy change against dihedral angle for both ketones show two stable conformers with O=C-C-C(OR)

dihedral angles of 0° and 180°, although the lowest energy conformer is different between the two ketones. The barrier to rotation is approximately three times higher for **133** at ~70 kJ mol^{-1}, compared to ~25 kJ mol^{-1} for **126** (Figure 36)

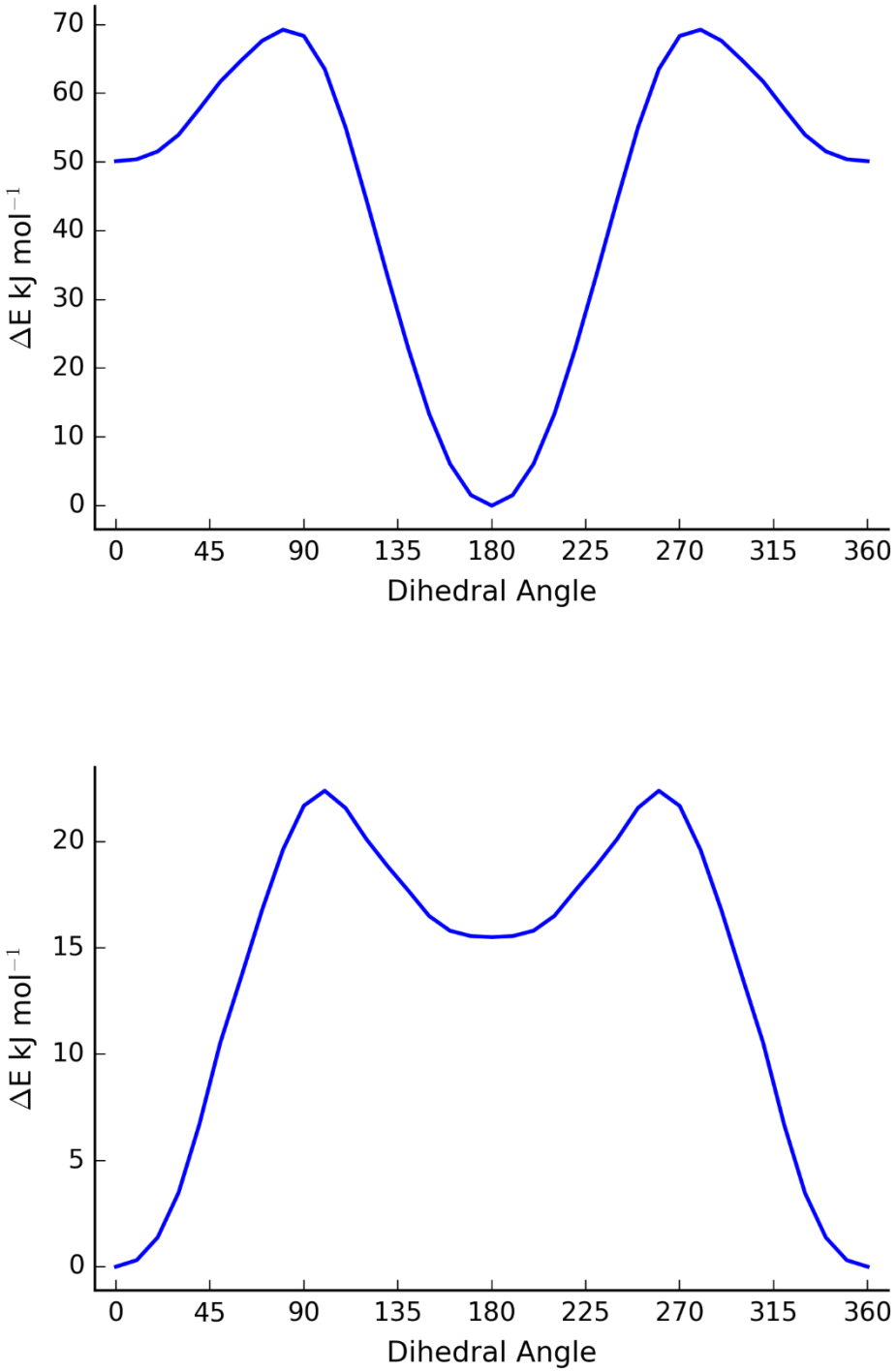


Figure 36: Calculated conformational energy diagram for top: **133**, bottom: **126**

Both minima and the transition state structure for **133** and **126** were re-optimised without constraints at the B3LYP/6-31G* level and the structures verified by frequency calculations. Single point calculations at the MPW1B95/maug-cc-pVTZ level were performed to obtain more accurate energies, which are summarised in Table 29

Table 29: MPW1B95/maug-cc-PVTZ//B3LYP/6-31G* calculated relative energies for conformers of ketones **133** and **126**.

Substrate	R=	Min 1	Min 2	TS
133	OH	0	46.28	61.37
126	OMe	0	13.07	18.03

Min 1 = lowest energy conformer, Min 2 = second lowest energy conformer, TS = transition state

Figure 37 shows the calculated lowest energy minima for both ketones. The expected hydrogen bonded structure can be seen in **133**, while for **126** the ketone-aromatic bond has rotated 180 degrees. Surprisingly the largest deviation from 120° of any bond is the C(OMe)-C-CO angle. At 126.2°, this is a significant bend away from the methyl group. The equivalent C(OH)-C-CO bond angle in **133** is 119.5°.

Therefore in both substrates the aromatic group lies co-planar with the ketone and is able to participate in the usual edge to face interaction with the catalyst.[40] The hydrogen bond in **133** might be expected to activate this substrate towards reduction by increasing polarisation of the carbonyl π bond, and indeed the conversion is slightly higher (99 vs 98-95%) with both catalysts given similar reaction times.

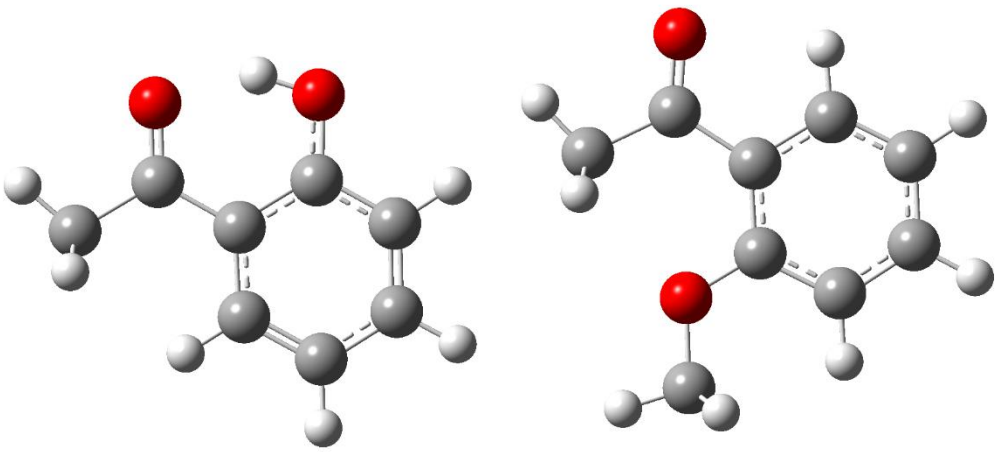


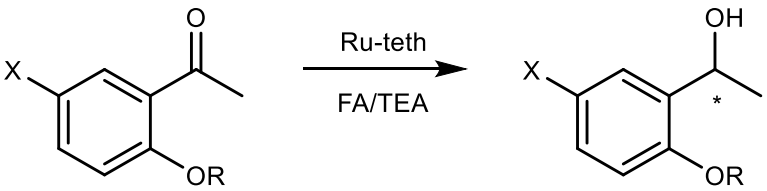
Figure 37: Preferred conformations of ketones **133** and **126**

The difference in selectivity for methylated substrate **126** in ATH with catalysts **80** and **115** may therefore be due to a difference in steric interactions between aromatic rings in the transition state for reduction, but a more conclusive explanation cannot be reached without further investigations that are beyond the scope of this study.

2.3.3 Meta-Substituted Ketones:

An expanded set of commercially available substrates with substituents in the *meta* position was then reduced with both catalysts (Table 30). Peak positions in GC/HPLC were confirmed by the switch in intensity when reduced with different enantiomers of catalyst. The order of elution for *R* or *S* enantiomers was assumed to be consistent for the varying meta-substituted products.

Table 30: ATH of meta-substituted ketones.



Substrate	**Catalyst:**		**(*R,R*)-115**		**(*S,S*)-80**	
	R =	**X =**	**% Conv**	**% ee**	**% Conv**	**% ee**
281	H	Br	98	94 (*R*)	99	91 (*S*)
282	H	Cl	97	93 (*R*)	99	90 (*S*)
133	H	H	99	99 (*R*)	99	99 (*S*)
283	H	Me	100	95 (*R*)	99	94 (*S*)
284	H	OMe	91	92 (*R*)	92	91 (*S*)
126	Me	H	98	96 (*R*)	95	68 (*S*)
285	Me	OMe	99	90 (*R*)	99	69 (*S*)

Standard conditions: S/C = 100, T = 40 °C

All OH-containing compounds were reduced in high ee, with **OMe-teth (115)** generally giving marginally better results than **3C-teth (80)**. The electron donating or withdrawing effects of the *meta*- substituent had very little effect save for a slight drop in conversion for the electron donating 5'-OMe substrate **284**, though all substituents slightly lowered the ee relative to parent compound **133**.

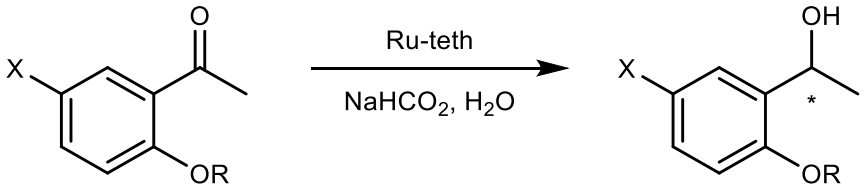
A second O-methylated substrate, 2',5'-dimethoxyacetophenone **285**, showed a similar trend to that observed with the parent compounds **126** and **133** , being reduced in 90% ee

by **115** but only 69% ee by **80**. Conversions in both cases were essentially complete, this result reinforces the earlier finding that catalyst **115** is substantially better at reducing *ortho*-methoxy substituted ketones.

2.3.4 Aqueous Reductions of meta-Substituted Ketones

The same set of 7 ketones was also reduced under aqueous conditions with both catalysts, using sodium formate as the hydrogen source and increasing the temperature to 60 °C as is standard for this type of ATH reaction in the literature (Table 31).[119]

Table 31: ATH of meta-substituted ketones using sodium formate in water.



Substrate	**Catalyst:**		**(*R,R*)-115**		**(*S,S*)-80**	
	R =	**X =**	**% Conv**	**% ee**	**% Conv**	**% ee**
282	H	Cl	10	63 (*R*)	100	24 (*S*)
133	H	H	33	63 (*R*)	99	22 (*S*)
283	H	Me	80	87 (*R*)	15	61 (*S*)
284	H	OMe	35	61 (*R*)	89	38 (*S*)
126	Me	Me	92	96 (*R*)	89	55 (*S*)
285	Me	OMe	52	97 (*R*)	47	70 (*S*)

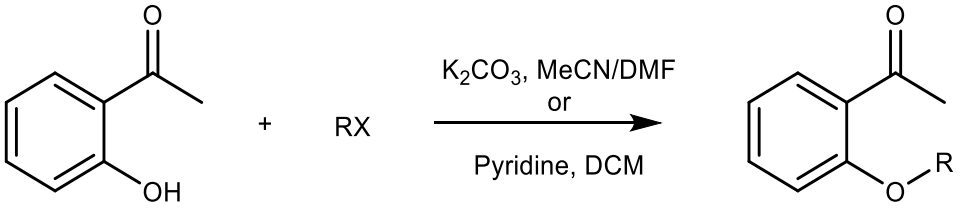
Standard conditions: S/C = 100, T = 60 °C

The results were extremely variable with no consistent trend observed in conversions. Enantioselectivities were moderate to low, and catalyst **80** gave a lower ee in each case than **115**. In general the aqueous conditions appeared to be slower and less robust than reduction in FA/TEA. This may be to do with practical elements of the reaction set up; the aqueous reduction is biphasic and the substrate and catalyst form a concentrated oil on top of the sodium formate solution. Good stirring is needed to mix the phases to bring the catalyst in contact with the hydrogen source but this combined with high temperatures leading to the aqueous phase partially evaporating could leave parts of the organic phase scattered onto the walls of the flask and unable to react further. However for the purposes of this study it was concluded that aqueous conditions would not be effective without further detailed optimisation of mixing and reaction set up.

2.3.5 Increasing ortho-*Substituent Size:*

Next the **OMe-teth (115)** catalyst was applied to a larger scope of substituted hydroxyacetophenones with increasing steric hindrance at the *ortho* position. Ethyl, isopropyl, allyl, benzyl and acetyl substituted ketones were prepared from **133** by alkylation/acylation under standard conditions.

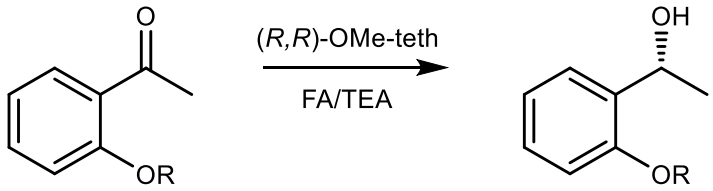
Table 32: Ortho-substituted ketone synthesis by nucleophilic substitution



Product	R=	X=	Base	Solvent	% Yield
286	Et	I	K_2CO_3	MeCN	85
287	*i*Pr	OMs	K_2CO_3	DMF	85
288	Allyl	Br	K_2CO_3	MeCN	96
289	Bn	Br	K_2CO_3	MeCN	89
290	Ac	Cl	Pyridine	DCM	69

The ketones were subjected to ATH conditions using catalyst **115**. Racemic standards were prepared on micro scale (~0.1 mmol) by sodium borohydride reduction and used to confirm peak position in GC/HPLC.

Table 33: ATH of alkoxy acetophenones.



Substrate	R=	t /hr	% Conv	% ee
133	H	3.5	99	99
126	Me	3.75	98	96
286	Et	6	100	99
288	Allyl	4.5	100	98
289	Bn	5	100	95
290	Ac	48	-	-

Standard conditions: S/C = 100, T = 40 °C, (*R,R*)-**115**. All products assumed to be (*R*) configuration by analogy to substrates **133** and **126**.

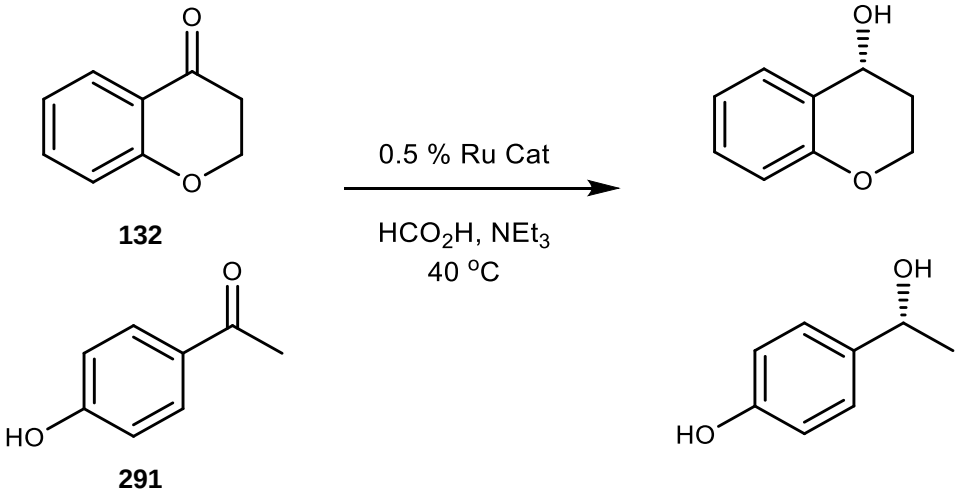
It was expected that a bulky *ortho* substituent would hinder reduction and possibly reduce the ee, but the results do not show such a trend (Table 33). On increasing the substituent size from methyl to ethyl or allyl, the enantioselectivity increased to 99 and 98% respectively. Substrate **289** containing the larger benzyl group was less selective but was still reduced in 95% ee, and there was no indication of hydrogenolysis of the benzyl group.

The acetyl containing substrate **290** appeared to be resistant to conversion by TLC, and when worked up and analysed after two days an impure mixture was obtained. ^{1}H NMR analysis revealed some peaks corresponding to starting material, as well as a phenolic proton that indicates partial hydrolysis of the acetyl group and secondary alcohol protons that indicate some reduction has taken place, but a clear distinction could not be made between components and measurements of conversion or ee were not obtained.

2.3.6 Other O-Substituted Ketones

Commercially available *para*-hydroxy acetophenone and chromanone were also reduced with **OMe-teth (115)** (Table 34).

Table 34: ATH of Chromanone and *p*-hydroxyacetophenone



Substrate	t / hr	% Conv	% ee
132	6	100	99
291	22	100	96

Standard conditions: S/C = 100, T = 40 °C, (*R,R*)-**115**. Configurations determined by optical rotation.

Consistent with literature results, chromanone **132** is an extremely good substrate for ATH and is easily reduced in >99% ee, while para-hydroxy acetophenone **291** is much slower to react than its *ortho*-substituted isomer **133**, requiring 22 hours to reach full conversion and in a reduced ee of 96%.

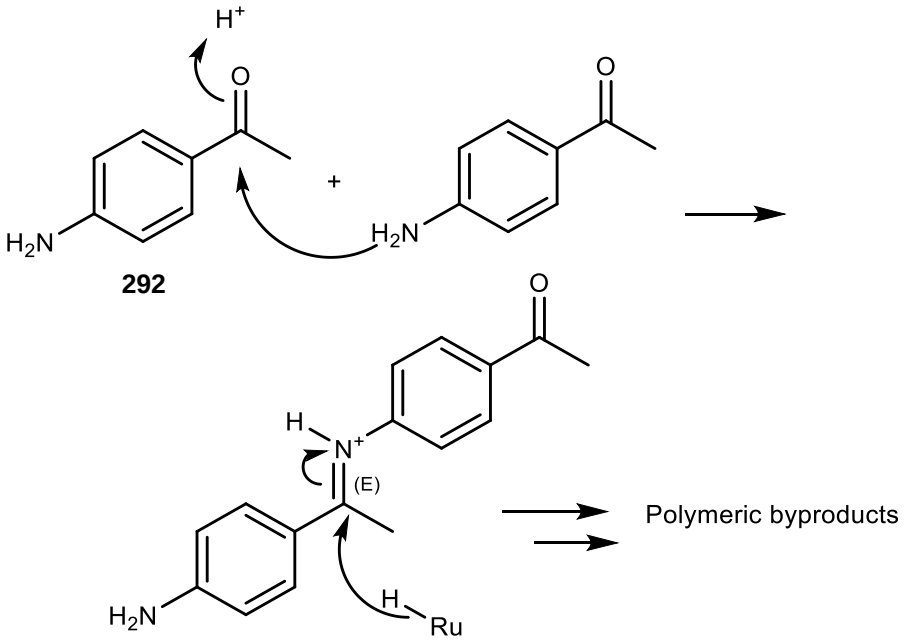
2.3.7 Nitrogen Substituted Compounds

Reductions of nitrogen substituted ketones as described in this section were carried out by final year MChem student Ben Mitchell, supervised in the lab by myself and published in 2015.[119] Experimental details can be found in the literature.

Nitrogen is a superior electron donor to oxygen, due to its lower electronegativity. As a result, para-amino substituted ketones are even more electron rich and will be even less reactive in transfer hydrogenation reactions. In order to scope the limit of applicability of tethered catalysts to the reduction of this class of ketones, several primary, secondary and tertiary amino-ketones were reduced.

As expected, the amino-ketone substrates were unreactive and required harsher conditions to force conversion, typically temperatures of 40-60°C and 5-70 hours reaction time.

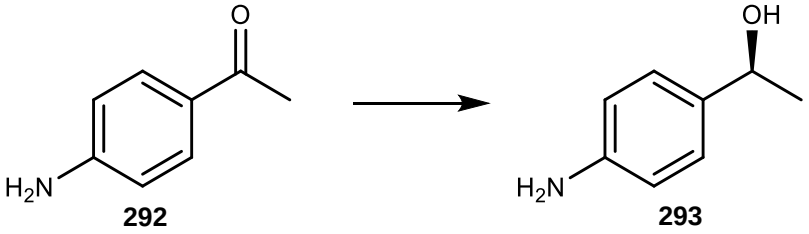
The commercially available para-amino substrate **292** could not be reduced in FA/TEA using **3C-teth (80)**. No conversion to alcohol product was observed and the starting material decomposes to a gummy precipitate. This was not unexpected based on the potential for acid-catalysed intermolecular side reactions between the free amine and ketone, leading to imine intermediates that could then be reduced or react further.



Scheme 91: Para-amino acetophenone dimerization and reduction under FA/TEA ATH conditions

It was anticipated that this side reaction could be prevented by carrying out the reduction in non-acidic conditions. Indeed reduction of **292** in isopropanol gave some clean conversion to the alcohol, however the reaction was extremely sluggish and conversion was poor at only 50% after six days at room temperature. Aqueous conditions gave far superior results. Using a 1:1 water : methanol mix, complete reduction was achieved in 4.5 hours at 60 °C with both **80** and **115** giving good enantioselectivity (Table 35).

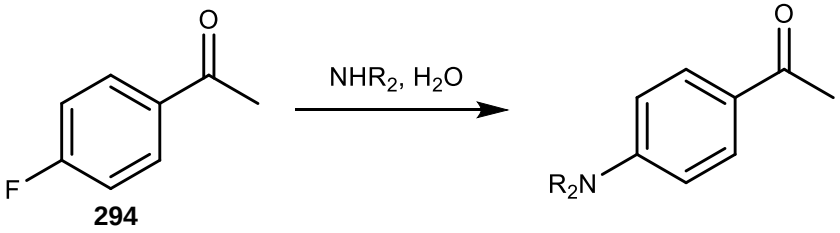
Table 35: ATH of para-amino acetophenone



292 **293**

Entry	Catalyst	Solvent	T /°C	t /hr	% Conv	% ee
1	**80**	FA/TEA	60	24	-	-
2	**80**	*i*PrOH	28	144	50	-
3	**80**	MeOH/H_2O	60	4.5	99	94
4	**115**	MeOH/H_2O	60	4.5	99	94

Owing to the high cost of **292**, substituted aminoketones were prepared by a S_NAr approach from the corresponding secondary amine and readily available p-fluoroacetophenone. Ketone was added to an aqueous solution of amine and the mixture heated in a sealed pressure tube at 150-180 °C. The amine products precipitated as crystalline solids and were easily purified by crystallization

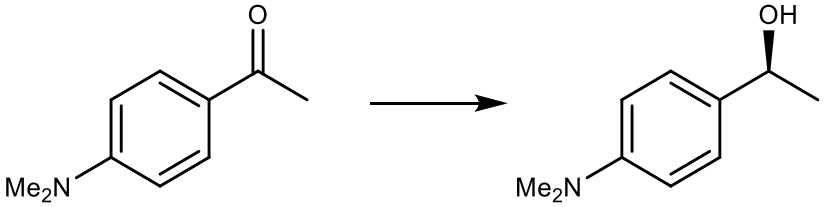


294

Scheme 92: Synthesis of substituted *p*-aminoacetophenones.

p-Dimethylaminoacetophenone **296** was tested next as a simple tertiary aminoketone. The same reaction conditions remained effective, with conversions of 97-99% and ee of 91-92%. However due to the lack of free NH protons, this substrate can also be reduced in FA/TEA, with similar conversion and ee, although the reduction was extremely slow. Reduction in Isopropanol is still too slow to be useful (Table 36).

Table 36: ATH of *para*-dimethylaminoacetophenone

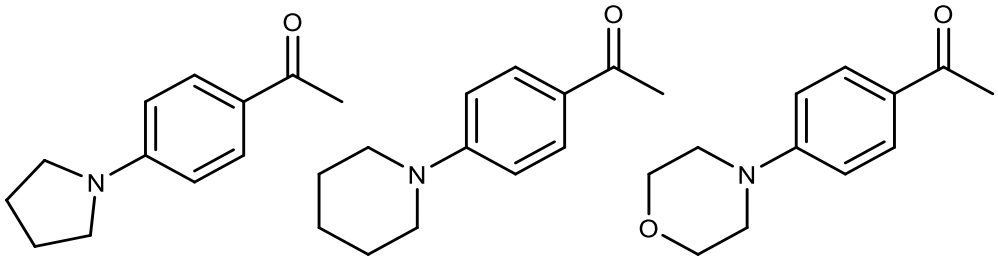


296 **295**

Entry	Catalyst	Solvent	T /°C	t /hr	% Conv	% ee
1	**80**	FA/TEA	40	45	95	93
2	**80**	*i*PrOH	28	26	35	-
3	**80**	MeOH/H_2O	40	5	99	92
4	**115**	MeOH/H_2O	60	4.5	97	91

The scope of tertiary aminoketones was extended to include a few cyclic substituents, including pyrrolidine, piperidine and morpholine. The substituent effect was minimal, with good conversions achieved in both aqueous and FA/TEA solvents, and ee's ranging from 87-95%, although the reaction is somewhat quicker with the piperidyl substrate **298**.

Table 37: ATH of *para*-dimethylamino acetophenone



297 **298** **299**

Substrate	t /hr	% Conv	% ee
297	70	98	89
298	24	99	95
299	45	100	91

Conditions: (*S,S*)-**80**, $NaHCO_2$, MeOH/H_2O, 40 °C

2.3.8 Chapter Summary

The reduction of several oxygen and nitrogen substituted compounds has been studied with tethered ruthenium complexes. As was expected from the previous literature, reduction of oxygen containing ketones was somewhat sluggish, requiring slightly forcing conditions. The effect of the oxygen substituent on reactivity and selectivity was also highly dependent on

whether it was alkylated. o*rtho*-Phenols such as **133** appear to activate their ketone substituent via intramolecular hydrogen bonding, and are reducible in high enantiomeric excess with both **3C-teth (80)** and **OMe-teth (115)**. Methylated derivatives such as **126** adopt the opposite planar conformation and are surprisingly unselective when reduced with **80**, but are reduced in high ee by the methoxy substituted complex **115**. Increasing the size of the alkyl substituent can have a further positive effect on selectivity for this catalyst.

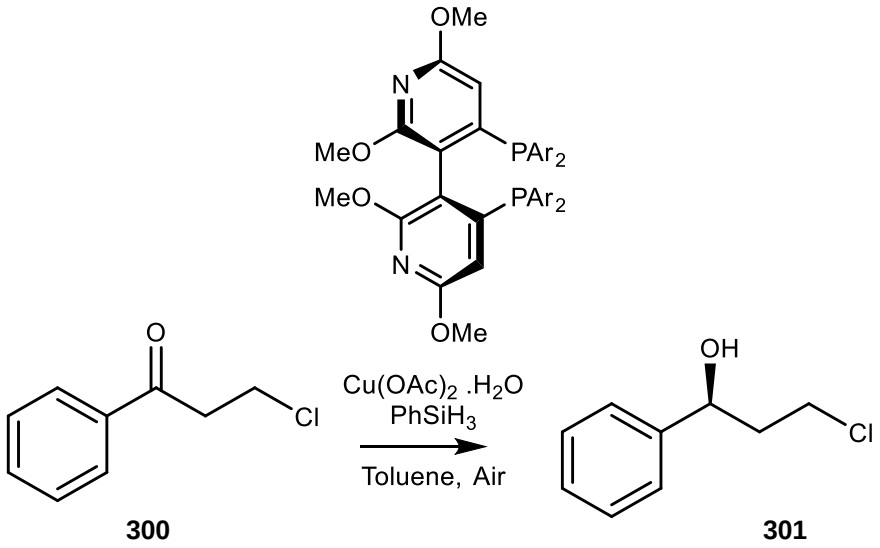
Nitrogen substituted ketones can also be effectively reduced and Ben Mitchell has demonstrated several useful examples of this reaction primarily using **80**.

In summary a useful synthetic method has been developed for the reduction of electron rich ketones with oxygen or nitrogen substituents. This method is complementary to those in the literature and extends current examples by exploring the range of substituents beyond simple monosubstituted amino, hydroxyl and methoxy ketones.

2.4 ATH of α,β-Unsaturated Ketones.

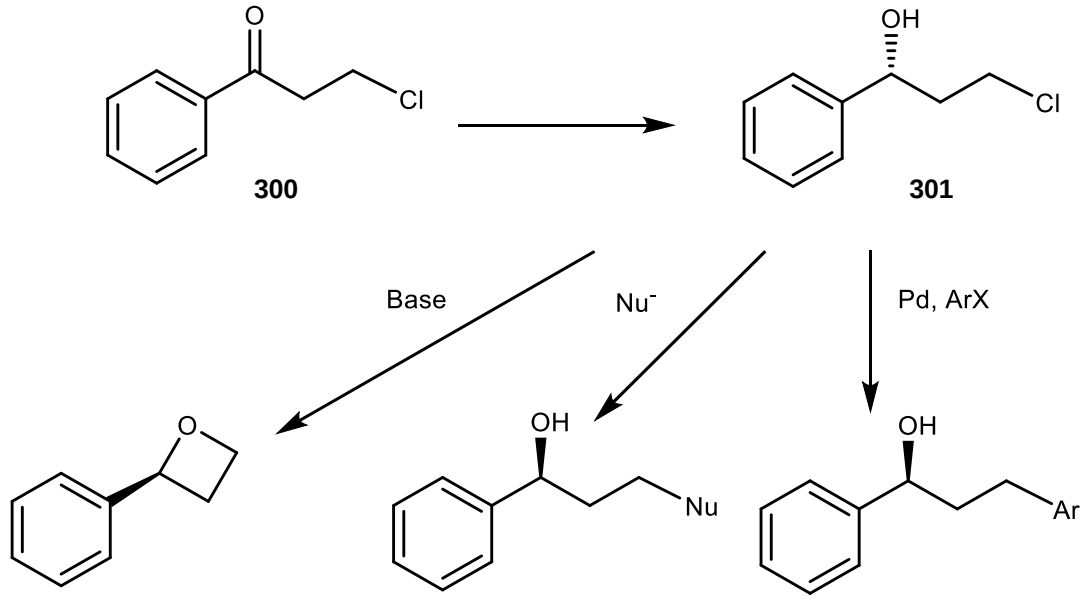
2.4.1 ATH of β-chloro ketones

Initially this section of the project began by attempting the ATH of β-chloroacetophenone **300** as a typical β-halo ketone. There are many published examples of reductions of α-haloacetophenones but for this particular substrate there are very few examples, including a hydrosilylation with a Cu(II) catalyst (Scheme 93).[120]



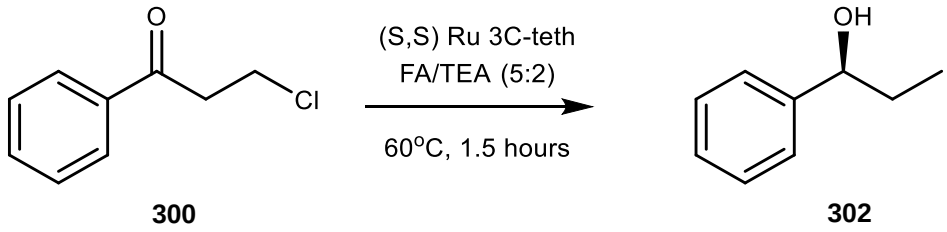
Scheme 93: Literature example of hydrosilylation of β-chloroacetophenone

In principle the chiral halohydrin could be a useful building block for further reactions, such as oxetane formation, substitution or cross coupling. (Scheme 94).



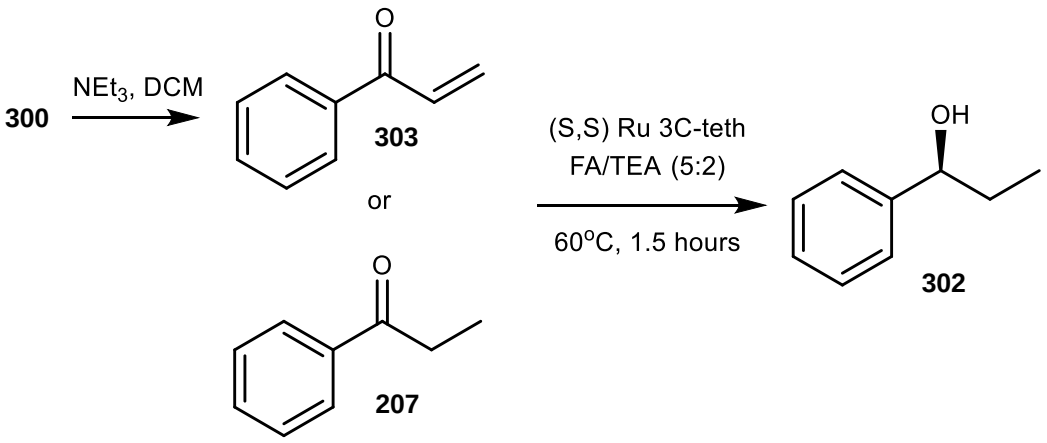
Scheme 94: Potential further applications reactions of chiral beta-chlorohydrin **301**

Initially unexpectedly, reduction of β-chloropropiophenone **300** with **3C-teth (80)** in formic acid/triethylamine at 60 °C gave complete conversion to 1-phenylpropan-1-ol **302**, with high stereoselectivity. The initial hypothesis was that the β relationship between chlorine and the ketone activates this particular substrate to elimination of HCl, promoted by triethylamine (Scheme 95).



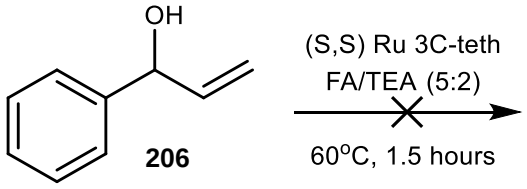
Scheme 95: Reduction of β-chloropropiophenone **300**. Yield of dehalogenated alcohol: 72%, 100% conv and 97% ee

This was confirmed through some simple control experiments. Vinyl ketone **303** could be prepared from the starting substrate by elimination with NEt_3. Subjecting this intermediate to the same ATH conditions also gives the saturated reaction product **302**, with identical enantiomeric excess as measured by chiral GC. This indicates **303** could be the common intermediate in formation of **302**.



Scheme 96: Reduction of dehalogenated intermediates with (*S,S*)-**3C-teth (80)**.

The commercially available vinyl alcohol **206** is inert under the same conditions. This demonstrates that complete elimination of chlorine must occur before ketone reduction occurs, as no trace of **206** is observed in the product mixture in reduction of **300** or **303**.



Scheme 97: Non-reactive potential vinyl alcohol intermediate **206**.

The literature is relatively scarce when searching for asymmetric examples of the transformation from **300** to **302**, spare a few examples of enzymatic reduction in which a mixture of ketone reduction and dehalogenation products are obtained.[121,122] There have however been examples of successful conversion of **300** to the chlorinated product **301** via ATH[123,124], hydrosillyation[120] and borane reduction[125].

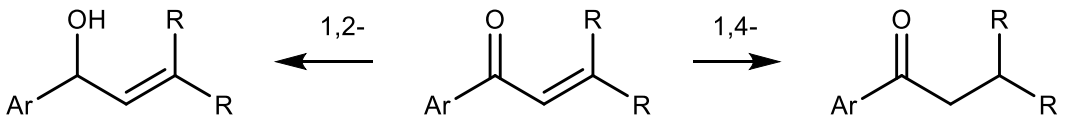


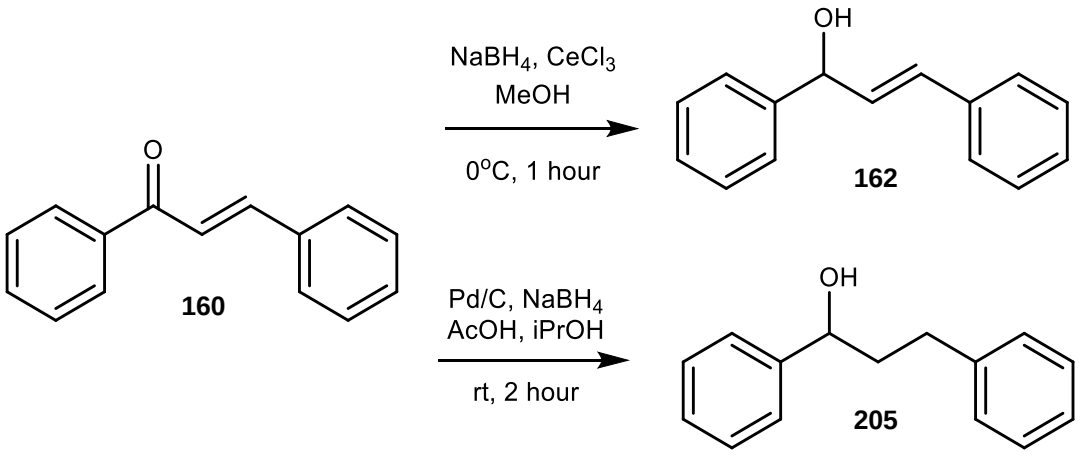
Figure 38: Classification of 1,4 and 1,2 reduction products.

Of the two possible modes of reduction of vinyl ketone **303**, 1,4- reduction is expected to be favourable due to high reactivity of the unhindered mono-substituted vinyl group. As discussed in the introduction previously, there are many examples of both 1,2- and 1,4-

reductions of enones, that the degree of 1,4- selectivity strongly depended on the exact structure of substrates chosen. These results prompted further investigation.

2.4.2 ATH of Chalcone: Optimisation of 1,4- Reduction Conditions

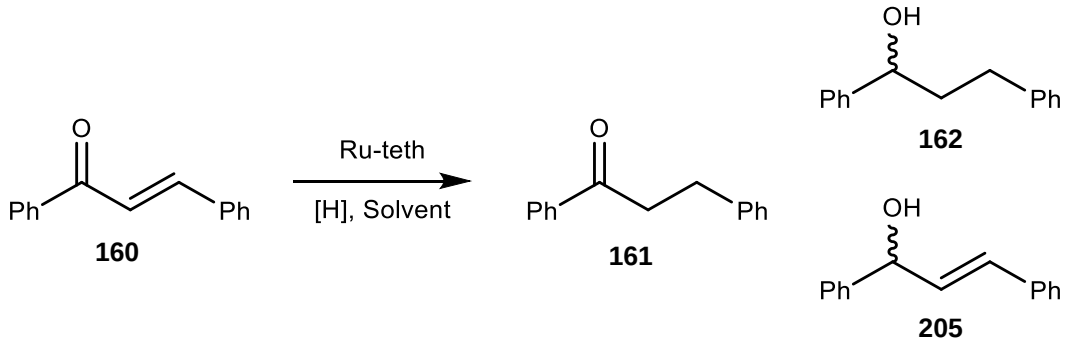
Commercially available *trans*-benzylideneacetophenone (Chalcone, **160**) was used as a simple model substrate. Racemic standards of both possible alcohol products were prepared using sodium borohydride (Scheme 98). Alcohol **205** could be easily prepared by Luche reduction, while **162** was produced by a one pot reduction in the presence of palladium on carbon, acetic acid, isopropanol, and sodium borohydride.[126] HPLC conditions were found that allowed separation of the enantiomers of **162** and **205** simultaneously.



Scheme 98: Preparation of racemic standards of alcohols **162** and **205**

Following this, **160** was reduced with both **3C-teth (80)** and **OMe-teth (115)** catalysts under a variety of conditions. The product ratio was determined by ^{1}H NMR spectroscopy and the results are illustrated in Table 38.

Table 38: ATH of Chalcone and its reduction products.



Entry	Catalyst	t / hr	% Conv	161 : 162 : 205	% ee 162	% ee 205	R/S
1[a]	(*S,S*)-**80**	1.5	100	2.1 : 90.9 : 7.0	96	73	*S*
2[a]	(*R,R*)-**115**	4	100	1.7 : 96.2 : 2.1	98	84	*R*
3[b]	(*S,S*)-**80**	20	100	0.1 : 88.5 : 11.4	95	79	*S*
4[b]	(*R,R*)-**115**	22	100	0 : 96.3 : 3.7	98	85	*R*
5[c]	(*S,S*)-**80**	5.5	100	2.0 : 88.3 : 9.8	95	78	*S*
6[d]	(*R,R*)-**115**	45	100	6.3 : 93.7 : 0	86	-	*R*

Standard conditions: a) 2M in FA/TEA, 100:1 S/C, 40 °C. b) 0.5M in 1:1 FA/TEA : MeOH, 100:1 S/C, 40 °C. c) as a) with $CeCl_3$ additive (0.5 eq). d) 0.5M in 1:1 H_2O/MeOH, $NaHCO_2$, 100:1 S/C, 60 °C.

Initially, standard conditions (2M substrate concentration) were used with both **80** and **115** as the catalyst (Table 38, entries 1 and 2). In both cases complete consumption of starting material was observed, however ~2% of the product mixture was observed to be the saturated ketone intermediate **161**.

1,4-reduction is highly favoured, especially by catalyst **115** which was 98% selective for the saturated products **161** and **162**. Alcohol **162** is produced with consistently good ee, 95-98% in FA/TEA for both catalysts. The unsaturated alcohol **205** is formed with a lower ee (73-85%), which is consistent with the fact that it has two π systems that could compete as directing groups for reduction, one on either side of the ketone. **OMe-teth (115)** delivers higher enantioselectivity than **3C-teth (80)** under the same conditions, especially for allylic alcohol **205**.

During the course of the reaction, ketone **161** is formed rapidly and then slowly converted to saturated alcohol **162**. This could be observed by TLC of the reaction mixture. Therefore although the conversion is 100% in all the entries in Table 38, it is the total conversion to alcohol products **162** and **205** that accurately describes the extent of completion of the

reaction. Where this is less than 100%, 1,4 selectivity can be calculated as the proportion of **161** and **162** in the final product mixture.

Given the well documented effect of cerium trichloride in the Luche reduction[127] it was tested as an additive in reduction with catalyst **80** in order to see if the proportion of **205** could be increased (Table 38, entry 5). Methanol was chosen as co-solvent due to its common usage in Luche reductions. The Ce additive had only a marginal effect, increasing the proportion of **205** from 7 to 10%. However the additional co-solvent was a practically convenient, as substrate **160** was poorly soluble in FA/TEA at the small scales used for screening (0.5-1.0 mmol), there was sometimes difficulty in stirring the reaction mass. Further reactions using equal quantities of FA/TEA and MeOH at lower concentration (0.5 M instead of 2 M) were more reliable to run and had the advantage of ensuring there was sufficient hydrogen donor available for two consecutive reductions. (Table 38, entries 3 and 4).

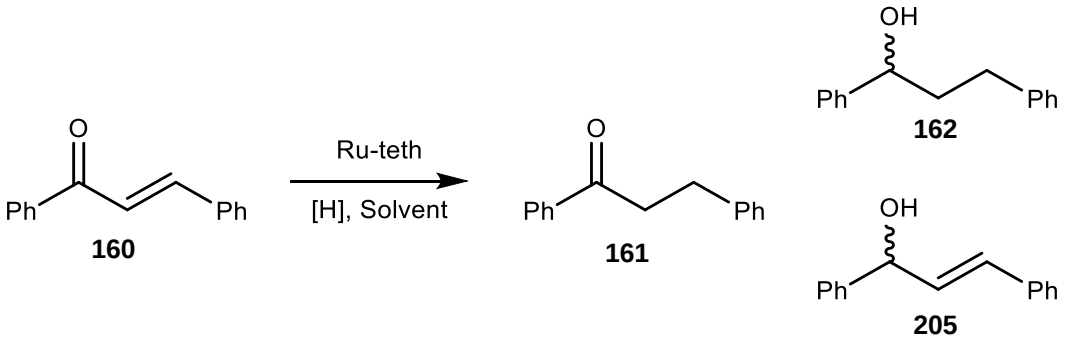
Aqueous conditions were also investigated, using H_2O/MeOH as solvent system and sodium formate as hydrogen donor (Table 38, entry 6). Under these biphasic conditions with **OMe-teth (115)** the reduction was completely 1,4 selective, with no trace of **205** detected by NMR spectroscopy. However the reaction is much slower, with 6% of saturated ketone **161** remaining in the product mixture after two days at 60 °C. The ee of alcohol **162** is reduced to 85%.

As a result of these initial experiments, conditions from entries 3 and 4, Table 38 were taken forwards for use in further reactions.

2.4.2.1 Variation of Conditions

The effect of varying temperature was investigated next (Table 39). As the 1,4-selectivity depends on the relative rate of two competing reaction pathways, temperature is often an effective method for adjusting the product ratio in partially selective reactions. Increasing temperature to 60 °C lowers the ee of both alcohol products and increases the 1,4-selectivity (Table 39, entry 3). Decreasing the reaction temperature to 25 °C has minimal effect on enantioselectivity and slightly increases the proportion of **205**. Total conversion to alcohols is also reduced despite increased reaction time.

Table 39: Effect of temperature variation on chalcone reduction

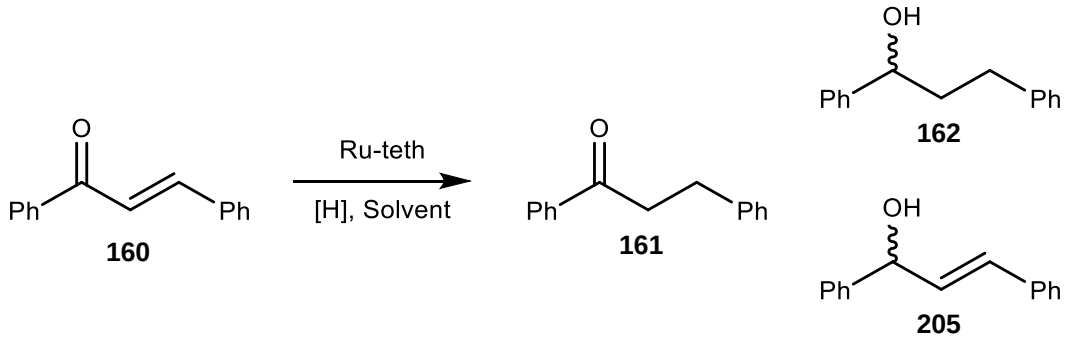


Entry	T / °C	t / hr	% Conv	161 : 162 : 205	% ee 162	% ee 205
1	25	25	100	4.1 : 91.3 : 4.6	98	83
2	40	22	100	0 : 96.3 : 3.7	98	85
3	60	18	100	1.1 : 96.4 : 2.6	96	77

Conditions: 0.5M in 1:1 FA/TEA : MeOH, 100:1 S/C, (*R,R*)-**115**. *R* product produced.

Screening of co-solvents in the reduction of **160** shows some small effects on reaction rate, selectivity and ee, but no major changes (Table 40). All of the aprotic solvents tested perform similarly, giving similar or slightly improved 1,4- selectivity and ee compared to reactions with MeOH as co-solvent. Notably all of these solvents increase the reaction rate by a factor of ~4. Water was also tested as a co-solvent with FA/TEA; unlike the aqueous biphasic reaction in Table 38 entry 6, this reaction occurs in a single phase. However the solubility of **160** in the aqueous FA/TEA mixture is poor, and the enantioselectivity of both products substantially poorer than for the other solvents tested.

Table 40: Effect of co-solvent in ATH of chalcone



Entry	Co-Solvent	t / hr	% Conv	161 : 162 : 205	% ee 162	% ee 205
1	MeOH	22	100	0 : 96.3 : 3.7	98	85
2	EtOAc	4	100	0 : 96.7 : 3.3	96	83
3	THF	4.5	100	0 : 97.8 : 2.2	96	88
4	MeCN	4.5	100	0 : 97.3 : 2.7	96	86
5	Toluene	6.5	100	0 : 97.8 : 2.2	96	87
6	DCM	6.5	100	0 : 96.9 : 3.1	96	87
7	H_2O	23	100	0 : 96.4 : 3.6	92	75
8	AcOH	96	100	27 : 65.9 : 7.1	93	76
9	NEt_3	5.5	100	0 : 99.4 : 0.6	98	92
10[a]	MeCN	6	100	0 : 98.3 : 1.7	94	86
11[a]	Toluene	6	100	0 : 96.3 : 3.7	98	88

Standard conditions: 0.5M in 1:1 FA/TEA : Co-Solvent, 100:1 S/C, (*R,R*)-**115**. *R* product produced. a) $ScOTf_3$ additive, 5 mol %

The effect of pH was crudely investigated by use of acidic and basic co-solvents, AcOH and trimethylamine. (Table 40, entries 8 and 9) AcOH has a more dramatic effect than the other protic co-solvents, leading to incomplete conversion to alcohols even after four days and leading to a slight increase in proportion of **205**. This change in 1,4 selectivity was expected on the basis that acidic conditions could help activate the ketone group in **160**, increasing the nucleophilicity of the carbonyl carbon (Figure 39). The large decrease in reaction rate is presumed to be likely due to acidic inhibition of the catalytic cycle and precludes any practical use of acidic conditions to modify selectivity. The ee of both products is also impaired (93% for **162**, 76% for **205**), giving a similar result to that obtained with water as co-solvent.

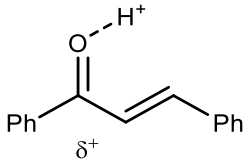


Figure 39: Acidic activation of ketone group of chalcone **160**

The addition of triethylamine conversely leads to highly selective 1,4 reduction in a similar reaction time to the aprotic solvents. It is assumed that the increased 1,4 selectivity in this scenario is due to simply a reduction of the acid promoted effect shown in Figure 39 relative to that occurring in stock 5:2 FA/TEA, rather than a specific involvement of trimethylamine in the reaction mechanism.

Scandium triflate was tested as an additive in acetonitrile and toluene, however the effects on 1,4-selectivity and reaction rate were negligible (Table 40, entries 10 and 11).

2.4.2.2 Selection of Conditions for Further Reactions

Initial investigations with MeOH as co-solvent (See Table 38) were performed to solve practical issues, whereby the volume of solvent was insufficient to stir and cover the poorly soluble starting material. While the rate of reduction was observed to decrease, at the time this was assumed to be simply due to a decrease in substrate concentration. Hence MeOH was used as co-solvent in following reactions. Even after it became apparent that other co-solvents allowed for faster reactions (Table 40), MeOH was still used to allow for comparison to previous results.

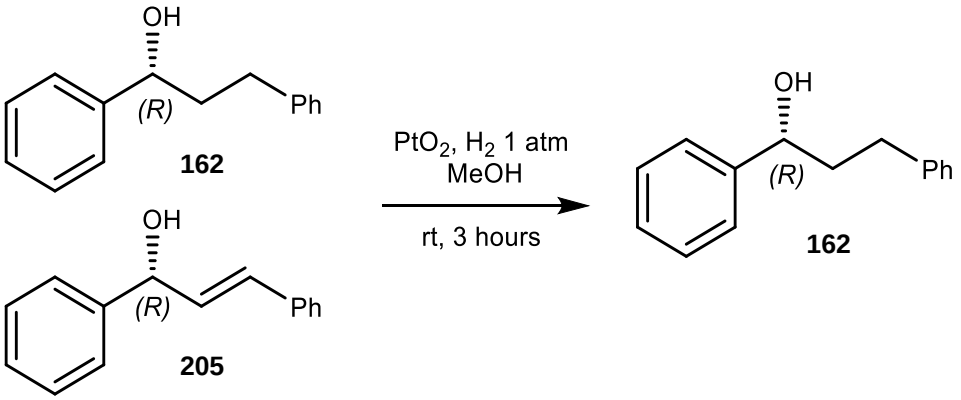
The optimal conditions for 1,4-reduction of chalcone **160** appear to be use **OMe-teth (115)** as catalyst, NEt_3 co-solvent at 40 °C. For 1,2 reduction, **3C-teth (80)** and any of the aprotic solvents at 25 °C or less would give the highest proportion of unsaturated alcohol **205**, though for this substrate it appears that ATH with tethered catalysts is not suitable for selective 1,2 reduction and AH may be a better choice.

2.4.2.3 Enantioselectivity and configuration of reduction.

In general **162** is usually formed with greater enantioselectivity than **205**. The steric hindrance associated with both ketones **160** and **161** are very similar, therefore the difference in enantioselectivity may be a result of the alkene in **205** competing with the phenyl group in C-H π interactions with the catalyst.

Fortunately, **205** is formed in small quantities and can be hydrogenated to **162** with a simple metal catalyst without any effect on the alcohol chiral centre. Therefore reaction conditions that can both minimise formation of **205** and increase its ee are favourable for preparative production of the **162** if followed by alkene hydrogenation, on the condition that the sense of induction of both chiral products is similar (Table 41).

Table 41: Reduction of a product mixture to a single saturated product, ee analysis.

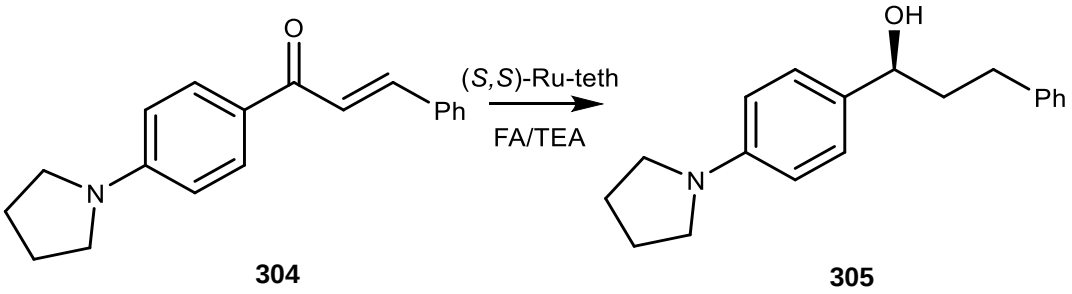


Expected results if configuration:		**Is the same**		**Is Opposite**	
		R	*S*	*R*	*S*
er by HPLC	**162**	98.8	1.2	98.8	1.2
	205	92.3	7.7	7.7	92.3
Normalised ratio:	**162**	95.2	1.1	95.2	1.1
	205	3.5	0.3	0.3	3.5
After PtO_2 reduction:	**162** er	98.6	1.4	95.4	4.6
	162 % ee	97.2		90.9	

This was expected to be the case and was proved by hydrogenating the product mixture from Table 38 entry 4 with Pt_2O. Given the ratio of alcohols **162** and **205**, the predicted ee of **162** after racemic alkene hydrogenation is 97.2% if the configuration of both alcohols is the same, 90.9% if it is different. The experimental measurement of ee after hydrogenation was exactly 97.2%, proving that **162** and **205** have the same configuration. On this basis it has been assumed that both saturated and unsaturated alcohols have the same configuration for all of the aryl-ketone substrates tested.

2.4.3 ATH of Para-*Substituted Chalcones:*

Following these initial results it was expected that the electronic nature of the ketone aromatic ring could influence the 1,4- vs 1,2- selectivity of reduction. Indeed previous work within the group in a different project had already suggested that ATH of **304**, derived from **297** gave only the 1,4- product **305** in what was at the time an unexpected result.

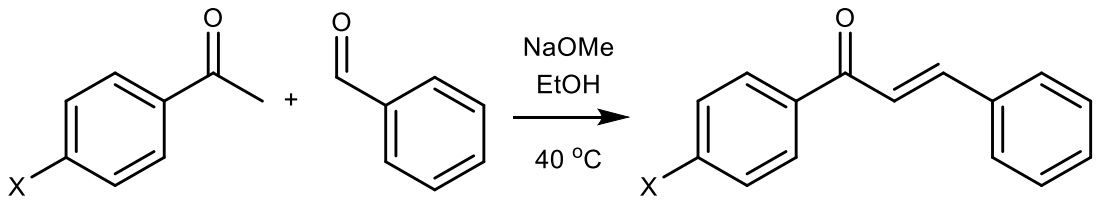


304 **305**

Scheme 99: Reduction of *p*-pyrrolidinyl substituted chalcone to 1,4- product.

A small series of substrates was prepared via Claisen-Schmitt aldol condensation of the appropriate para-substituted acetophenone with benzaldehyde **306** in basic aqueous alcohol, followed by recrystallization. Either NaOH/EtOH or NaOMe/MeOH were suitable for this transformation, and the base could be used in a catalytic quantity (10-50%) (Table 42). As described earlier in Scheme 92, dimethyl amino ketone **296** is itself prepared from p-fluoroacetophenone by a S_NAr substitution.

Table 42: Preparation of *para*-substituted chalcones



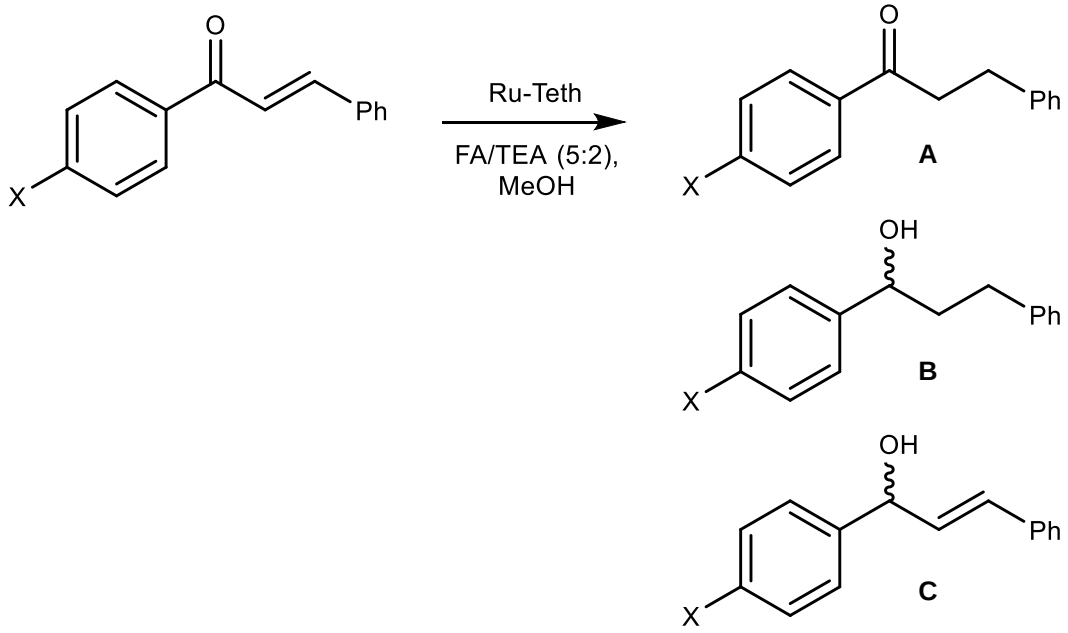
306

Acetophenone:	X =	t / hr	% Yield
307	Cl	24	100
47	H	22	100
128	OMe	22	100
296	NMe_2	24	93

Conditions: 0.1-0.5 eq NaOMe, EtOH, 40°C. Recrystallization from aqueous EtOH

These substrates were reduced with **OMe-teth (115)** using the screening conditions derived for chalcone **160** (Table 43).

Table 43: ATH of para-substituted chalcones



Substrate	X =	t / hr	% Conv	A : B : C	% ee B	% ee C	*R/S*
308	Cl	24	100	0 : 96.4 : 3.6	94	69	*R*
160	H	22	100	0 : 96.3 : 3.7	98	84	*R*
196	OMe	22	100	0 : 98.7 : 1.3	98	n/d	*R*
309	NMe_2	24	100	6.6 : 93.4 : 0	97	n/d	*R*

Standard Conditions: 0.5M in FA/TEA, MeOH (1:1), 100:1 S/C, (*R,R*)-OMe-teth **(115)** catalyst. Assumed *R* product is formed by analogy with chalcone and same order of elution in HPLC.

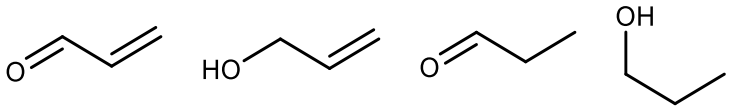
As expected, electron donating substituents increase the 1,4- selectivity. The proportion of 1,2-product **C** was so low for the para-methoxy and para-dimethylamino substrates that the ee was not determined. The strongly electron donating NMe_2 substituent resulted in a sluggish reaction, with 6% of the saturated ketone product **A** remaining in the reaction mixture after 24 hours. A mildly electron withdrawing chloro group had minimal effect on regioselectivity but did lead to lower enantioselectivity in the reduction products.

2.4.4 Computational Calculations

A theoretical study was performed in order to try and better understand the electronic structural effects behind the influence of para-substituents on the reactivity of these chalcones.

2.4.4.1 Benchmarking with a Model System

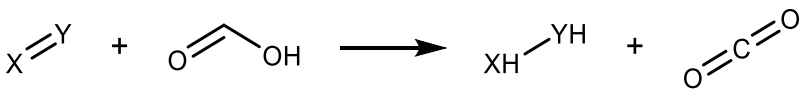
Chalcone does not have useful experimental heats of formation so acrolein **238** and its reduction products (**191**, **310**, **311**) were chosen as a simple representative set of compounds containing similar functionality, for which accurate experimental enthalpies of formation of were available.



238 (SK) **191** (UA) **311** (SK) **310** (SA)

Figure 40: Chemical structures of acrolein and its reduction products for use in test calculations.

In order to balance the chemical equations of hydrogenation, the simplest H source to use would be H_2. However the electronic environment that hydrogen atoms in organic molecules experience is very different to the environment in dihydrogen, and calculations involving species with similar functional groups are expected to benefit from a greater degree of error cancellation. By using HCO_2H and CO_2 to balance the reactions the results are likely to be more accurate and also better reflect the conditions used experimentally.



$$\Delta H_{R1} = (E_{SK} + E_{CO_2}) - (E_{UK} + E_{HCO_2H})$$

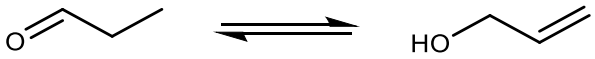
$$\Delta H_{R2} = (E_{UA} + E_{CO_2}) - (E_{UK} + E_{HCO_2H})$$

$$\Delta H_{R3} = (E_{SA} + E_{CO_2}) - (E_{SK} + E_{HCO_2H})$$

$$\Delta H_{R4} = (E_{SA} + E_{CO_2}) - (E_{UA} + E_{HCO_2H})$$

Equation 5: Use of formic acid and carbon dioxide to balance hydrogenation reactions. Two letter abbreviations refer to substrate enone and reduction products, the corresponding structures for acrolein can be found in Figure 40.

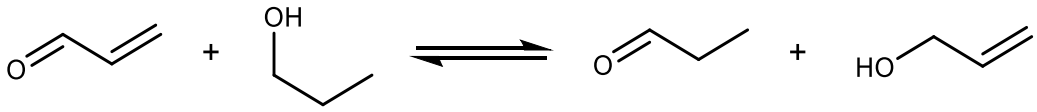
As well as the four enthalpies of reaction calculated from experimental data, two further quantities are defined. ΔH_{R5} Is calculated from the difference in enthalpies of alkene or ketone reduction for **238**, which is simply the enthalpy difference between the two isomeric partially reduced products **191** and **311**



$$\Delta H_{R5} = \Delta H_{R1} - \Delta H_{R2}$$

Equation 6: Definition of isomer enthalpy for an enone and its reduction products

ΔH_{R6} is the difference in enthalpies for alkene reduction of **238** and **191** (or the difference in enthalpy of ketone reduction of **238** and **311**). It gives an indication of the stabilisation provided by conjugation between the double bonds and is equivalent to the enthalpy of partial transfer hydrogenation of **238** with **310**.



$$\Delta H_{R6} = \Delta H_{R4} - \Delta H_{R1} == \Delta H_{R3} - \Delta H_{R2}$$

Equation 7: definition of resonance enthalpy for an enone and its reduction products

Both of these quantities are independent of the choice of hydrogen source used for the reduction reactions. As a result they are expected to better benefit from error cancellation and be even easier to predict computationally. The experimental values for ΔH R1 to R6 are displayed graphically in Figure 41.

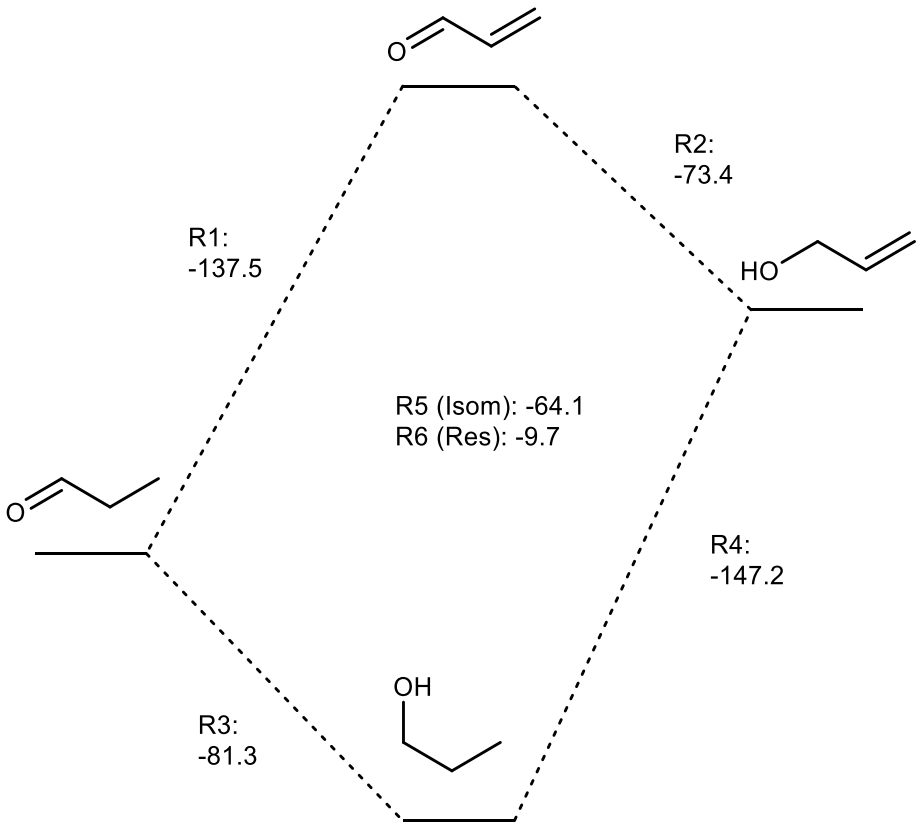


Figure 41: Graphical representation of the experimental enthalpy changes for reduction of **238**

The gas phase geometries of the four possible unsaturated and saturated, ketones and alcohols were optimised at the B3LYP/6-31G* level of theory and frequencies calculated to verify that they were true minima. Conformational scans about the OC-CC bond were carried out at this level in order to find the lowest energy conformers to use for comparison. Thermal corrections to enthalpy at 298K were taken and used to create an enthalpy correction factor for each of R1 to R6.

The values of enthalpy changes R1 to R6 were then calculated from a range of single point calculations using HF, MP2 and DFT methods, with different basis sets. These values were compared to the experimental data and the absolute differences tabulated in Table 44

Table 44: Differences from experimental values for enthalpy changes R1-R6.

	Method	Basis	R1	R2	R3	R4	R5	R6	MUE
1	b3lyp	6-31G(d)	13.73	19.20	13.90	19.03	32.93	5.30	17.35
2	b3lyp	cc-pVTZ	1.90	7.08	5.31	0.13	5.18	1.76	3.56
3	pbe1pbe	cc-pVTZ	6.83	0.68	0.02	6.17	6.15	0.66	3.42
4	mpw1pw91	cc-pVTZ	6.24	0.02	0.32	5.91	6.23	0.33	3.17
5	MPW1B95	cc-pVTZ	5.64	1.02	0.44	4.18	4.61	1.46	2.89
6	HF	cc-pVTZ	4.41	2.92	3.85	3.48	7.33	0.93	3.82
7	MP2	cc-pVTZ	19.73	12.43	14.16	21.46	7.30	1.73	12.80
8	SCS-MP2	cc-pVTZ	15.86	7.69	9.43	17.60	8.16	1.74	10.08
9	MP3	cc-pVTZ	2.16	0.31	0.35	2.82	2.47	0.66	1.46
10	MP4(SDQ)	cc-pVTZ	8.25	1.49	0.72	7.48	6.76	0.77	4.24
11	MPW1B95	cc-pVDZ	12.27	2.79	5.41	9.66	15.06	2.62	7.97
12	MPW1B95	cc-pVQZ	3.92	1.40	0.02	2.55	2.53	1.38	1.97
13	MPW1B95	aug-cc-pVDZ	2.80	3.19	4.43	4.04	0.39	1.25	2.68
14	MPW1B95	may-cc-pVTZ	0.90	0.04	1.04	0.10	0.94	1.00	0.67
15	MPW1B95	jun-cc-pVTZ	0.92	0.17	1.05	0.30	0.75	1.22	0.73
16	MPW1B95	jul-cc-pVTZ	0.82	0.15	1.07	0.39	0.67	1.22	0.72
17	MPW1B95	aug-cc-pVTZ	0.72	0.25	0.99	0.52	0.48	1.24	0.70
18	MPW1B95	apr-cc-pVQZ	2.23	1.17	0.11	0.94	1.05	1.29	1.13
19	MPW1B95	aug-cc-pVQZ	1.90	1.06	0.27	0.57	0.84	1.33	1.00

MUE: Mean Unsigned Error.

On comparing the errors it can be seen that the 6-31G(d) basis used for geometry optimisation is far too small for accurate energies. The performance of B3LYP is poor even at a larger cc-pVTZ basis, though it does better for C=C reduction (Table 44, entries 1 and 2).

Of the *ab-initio* methods HF theory is inadequate, producing consistent large errors (entry 6). MP2 unexpectedly performs even worse, even with the SCS corrected method,[128] while MP3 gives similar results to HF. MP4(SDQ) performs somewhat worse again. All of the *ab-initio* struggle to describe the C=C reductions accurately.

More DFT methods were tested using the pbe1pbe, mpw1pw91 and MPW1B95 functional (entries 3-5). Of the three, MPW1B95 performs best, though all three are particularly good at describing the ketone reductions R2 and R3.

The MPW1B95 functional was then used to explore the effect of varying basis sets. The DZ basis was too small to give reliable results (entry 11), significant improvement to a mean error of less than 3 KJ/mol is found at TZ level (entry 5) and the significantly larger QZ basis set gives a small further improvement (entry 12).

Augmentation with diffuse functions significantly improves the results in general, though full augmentation is not required, with the first set of diffuse functions (may-TZ, apr-QZ) accounting for almost the entire effect at much lower computational cost.[2]

The best DFT results come from use of partially augmented TZ and QZ basis sets and consistently come to within 1 kJ mol^{-1} of the experimental values. This indicates that the system is well described at the level of theory used. MPW1B95/maug-cc-pVTZ was chosen as the method of choice for further calculations due to its combination of high accuracy and moderate computational cost.

2.4.4.2 Application to *para*-Substituted Chalcones

Using the low energy conformations as a starting point, geometries of chalcone and its reduction products were taken through a similar process of optimisation and frequency calculation at the B3LYP/6-31G* level.

The geometries were used for single point calculations at the MPW1B95/maug-cc-pVTZ level of theory. These energies were finally combined with zero point and enthalpy corrections taken from the frequency calculations. The results are summarised in Table 45.

Table 45: Calculated enthalpies of reaction for series of para-substituted chalcones

Substrate	R1	R2	R3	R4	R5	R6
*p*Cl	-117.19	-53.72	-60.90	-124.38	-63.48	-7.19
*p*H	-117.58	-53.12	-61.21	-125.68	-64.47	-8.10
*p*OMe	-117.58	-47.03	-54.67	-125.22	-70.55	-7.65
pNMe_2	-117.71	-40.94	-49.58	-126.35	-76.77	-8.64

It can be seen that for all para substituents, the enthalpy of reduction of the alkene in the starting material is similar, at around -117.5 kJ/mol (Table 45, R1). It is the reactivity of the ketone that varies within a 14 kJ mol^{-1} range, with ketone reduction becoming less favourable for the strongly electron donating methoxy and dimethylamino substituents (Table 45, R2). In all cases, reduction of the second double bond after the first has been saturated is more exothermic by ~7-8 KJ/mol, consistent with the fact that the two double bonds are conjugated and hence stabilised by resonance (Table 45, R4).

The 1,4- reduction preference of catalysts **80** and **115** is therefore well borne out by the thermodynamic preference for alkene reduction. However if thermodynamic control was the only distinguishing factor then no 1,2- product would be expected in any of the cases. This thermodynamic control is therefore tempered by a kinetic preference for carbonyl

reduction. Further conclusions cannot be drawn from this simple analysis, more detailed calculations of possible transition states would be required.

2.4.5 Alkyl Substituted Enones

With the electronic effect on reduction selectivity relatively well understood, more diverse substrates were studied. First the effect of removing aromaticity at either end of the substrate was investigated; in order to keep a similar steric bulk and molecular mass the corresponding cyclohexyl substituted substrates **312** and **313** were prepared (Figure 42).

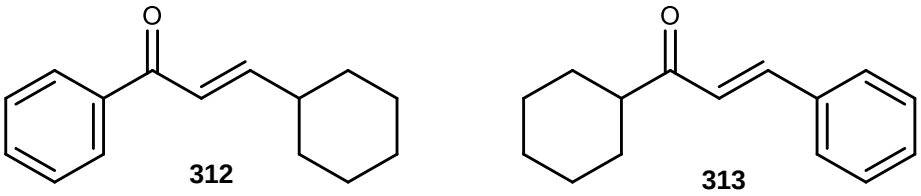
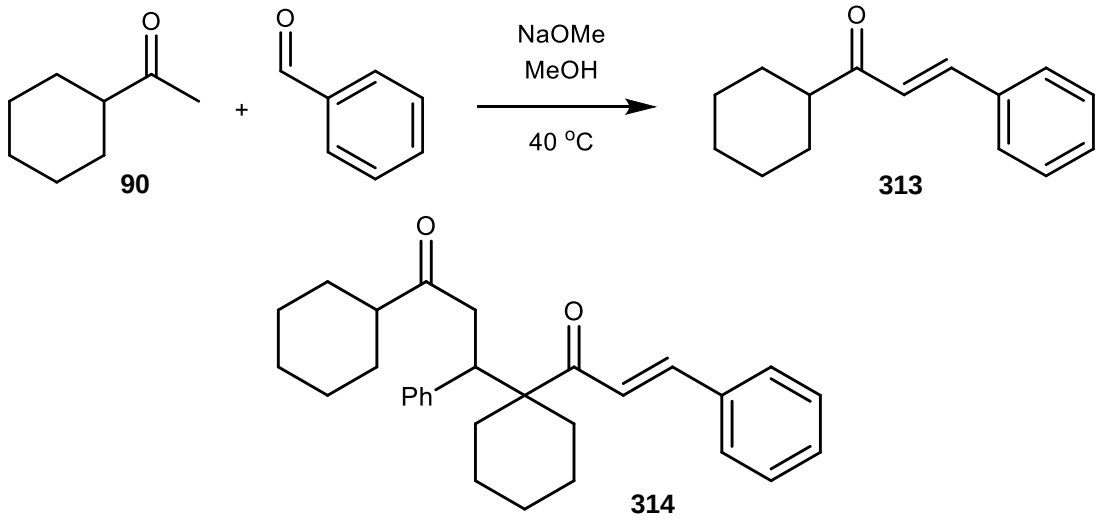


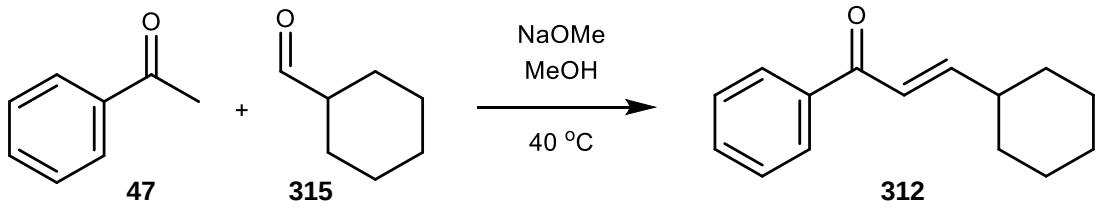
Figure 42: Target cyclohexyl substituted enones

Surprisingly the classic Claisen-Schmidt aldol condensation conditions were effective for preparing **313** from cyclohexyl methyl ketone **90** and benzaldehyde **306**, despite the starting material containing enolizable protons on both sides (Scheme 100). However a by-product **314** was observed by NMR that appears to result from dimerization of the enone product. The by-product was isolated during a second crystallization of the mother liquors from purification of **313**, and was identified by its increased melting point, mass spectroscopy and NMR spectra.



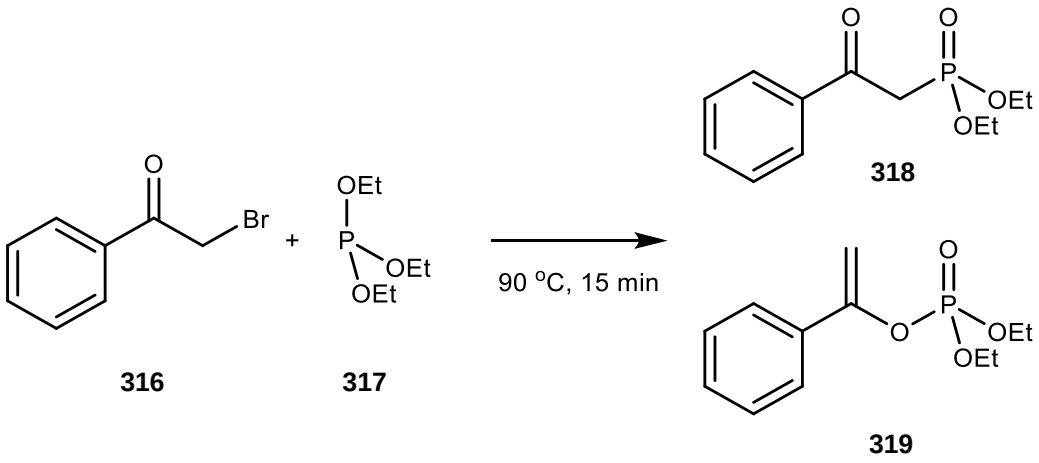
Scheme 100: Synthesis of enone **313** and associated by-product which was isolated.

For the alkene-cyclohexyl isomer **312** the corresponding aldol reaction between acetophenone **47** and aldehyde **315** was not suitable (Scheme 101). Complete decomposition of the reactive aldehyde was observed, while **47** was recovered unreacted.



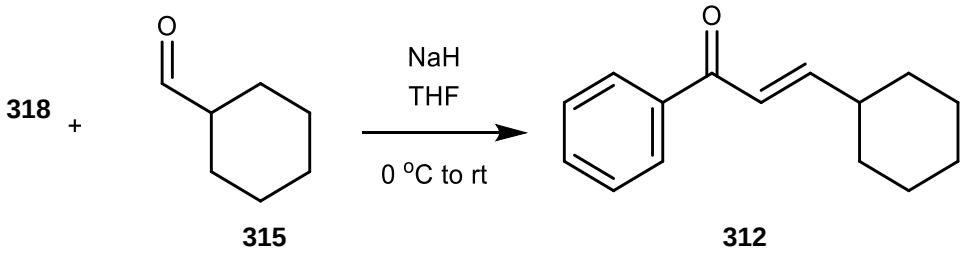
Scheme 101: Failed synthesis of enone **312** by aldol reaction

An alternative two-step route required conversion of commercially available alpha-bromoacetophenone **316** into its di-ethylphosphonate **318** via a Michaelis-Arbuzov reaction (Scheme 102). The enol-phosphate by-product **319** was separated during aqueous workup using a literature procedure; **318** was deprotonated with KOH and taken up as the potassium enolate in the aqueous phase while **319** was washed out in organic solvent.[129] Protonation with HCl gave **318**.



Scheme 102: Preparation of keto-phosphonate **318**. Yield 57%.

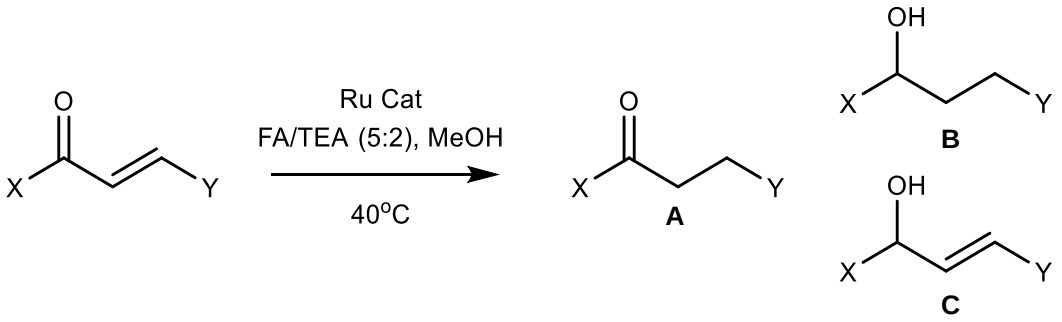
The target enone was then prepared by Horner-Wadsworth-Emmons olefination of **318** with aldehyde **315**. Formation of the E isomer was confirmed by the large *trans* coupling constant (15.6 Hz) for the alpha alkene proton, no signals corresponding to the Z isomer were detected. Purification by low temperature crystallization from methanol gave **312** in acceptable quality for reduction (Scheme 103).



Scheme 103: Synthesis of β-cyclohexyl enone **312** by HWE olefination. Yield 45% (26% over two steps from **316**)

Reduction of substrates **312** and **313** with tethered catalysts **80** and **115** gave very different results (Table 46). Ketone **312** reacted with similar selectivity to chalcone **160**, with a slight increase in 1,4 selectivity that can be attributed to reduced resonance stabilisation of the alkene and hence increased reactivity. The 1,4 product was formed with excellent enantioselectivity, with an ee of 97%.

Table 46: ATH of cyclohexyl substituted enones



Entry	Substrate	X=	Y=	t / hr	% Conv	A : B : C	% ee B	% ee C	R/S
1	**313**	Cy	Ph	2	100	18.9 : 8.0: 73.1	36	59	Nd
2[a]	**313**	Cy	Ph	23	100	0 : 58.6 : 41.4	21	76	Nd
3[b]	**313**	Cy	Ph	19	100	2.2 : 66.6 : 31.2	49	82	Nd
4	**312**	Ph	Cy	3	100	0 : 97.5 : 2.5	97	Nd	*S*

Standard conditions: 0.5M in 1:1 FA/TEA : MeOH, 100:1 S/C, (*S,S*)-**80**, 40 °C. a) With (*R,R*)-**115** as catalyst. b) 0.5M in 1:1 H_2O : MeOH, $NaHCO_2$, 100:1 S/C, (*R,R*)-**115**, 60 °C. Configuration for the product in entry 4 assumed by analogy to substrate **160**.

Reduction of **313** gave very different results to those observed with previous substrates. In general it gave a high product of 1,2- product **C** when reduced with either catalyst in FA/TEA, but **3C-teth (80)** promotes much more 1,2 reduction, leading to 73% of product **B** compared to 41% for **OMe-teth (115)**. Use of the later catalyst under aqueous conditions with sodium formate as hydrogen source further increases the 1,4 selectivity, however unsaturated product **C** still accounted for approximately 1/3 of the product mixture.

The ee of reduction was poor in most cases, though still better than that for purely aliphatic substrates such as cyclohexyl methyl ketone. Interestingly the use of aqueous conditions improved the enantioselectivity for both alcohol products of reduction of **313**. Also the unsaturated product **C** is formed more enantioselectively than the saturated product **B**, which contrasts with the results found for the aryl-ketone **160**. This may indicate that the alkene is acting as a directing group in reduction and since there is no arene to compete with it leads to greater enantioselectivity.

2.4.6 Further Variants

Several enones bearing different structure and functionality around the alkene were then synthesised and subjected to ATH conditions. In many cases the reduction is no longer selective and produces a complex mixture of products, in these cases the product

distribution has been analysed in order to gain an insight into the reaction selectivity, however the products have not always been isolated or fully characterised.

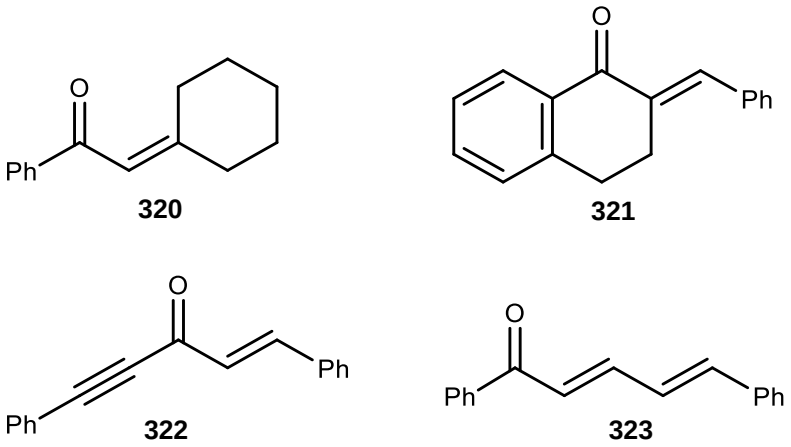
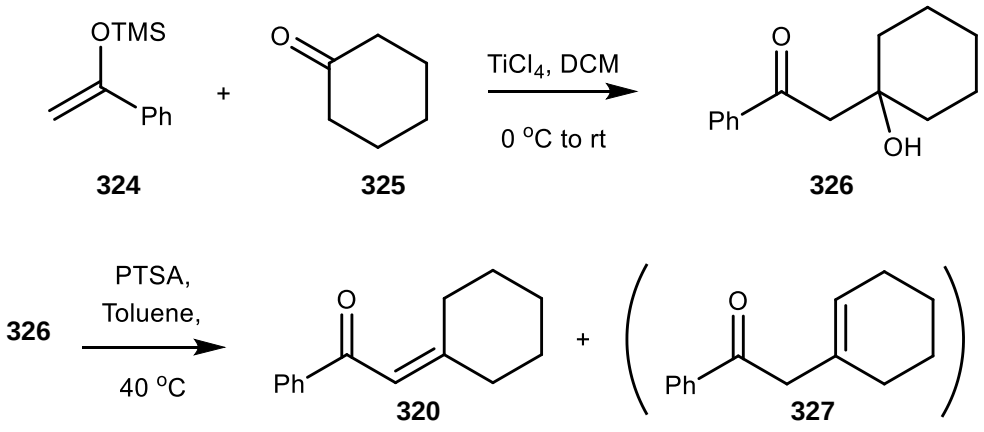


Figure 43: Further varied structures of α,β-unsaturated ketones

2.4.6.1 β,β-Dialkyl Unsaturated Ketone **320**

First the β,β-cyclohexylidene acetophenone derivative **320** was prepared by a two-step synthesis (Scheme 104). Mukaiyama aldol condensation between commercially available silyl enol ether **324** and cyclohexanone **325** gave the crystalline tertiary alcohol **326**. Acid catalysed dehydration yields an inseparable mixture of desired alkene **320** and side product **327**. The isomeric impurity was quantified at ~13% by ^{1}H NMR and the mixture carried forwards.



Scheme 104: Synthesis of **320** by alcohol dehydrogenation. Yield 41% over two steps, product contains 13% isomeric impurity **327**.

The literature indicates that tertiary alkenes such as **327** are sometimes formed instead of the expected conjugated quaternary alkene due to allylic strain.[130,131] In **320** there is significant strain between one arm of the cyclohexyl group and the ketone substituent, which are forced into the same plane by the conjugated system. In **327**, allylic strain between the alkene hydrogen and the more flexible -CH_2COPh group is much reduced.

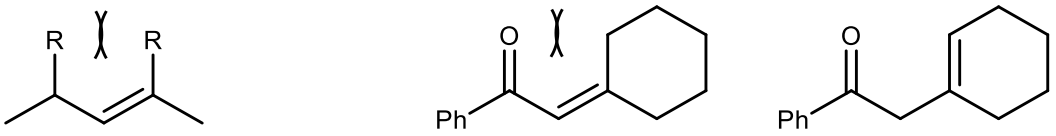
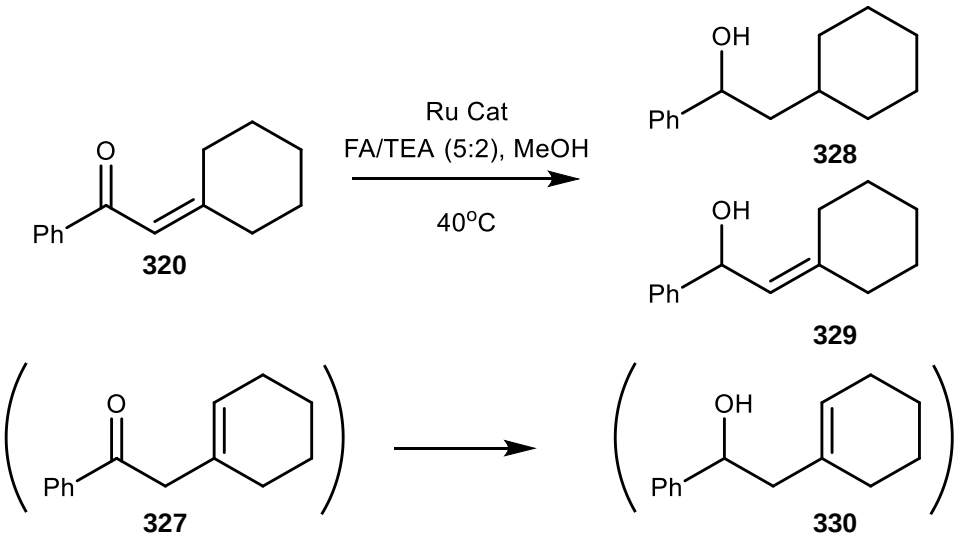


Figure 44: Allylic strain in **320** and its relief in isomer **327**.

ATH of **320**/**327** with tethered catalysts gives results similar to those obtained from chalcone **160** and mono β-alkyl substrate **312** (Table 47). 1,4 Selectivity remains high despite the increased steric hindrance and electron donation around the alkene. The non-conjugated impurity **327** was reduced to alcohol **330** in the product mixture from reduction with **80** with no reduction of the alkene, as expected. However reduction with **115** yields a product mixture with a substantially increased proportion of product **330**. The reason for this increase is not clear, but indicates some specific interaction with the catalyst as the reaction times in both cases are similar.

Table 47: ATH of β,β-cyclohexylidene substrate **320**



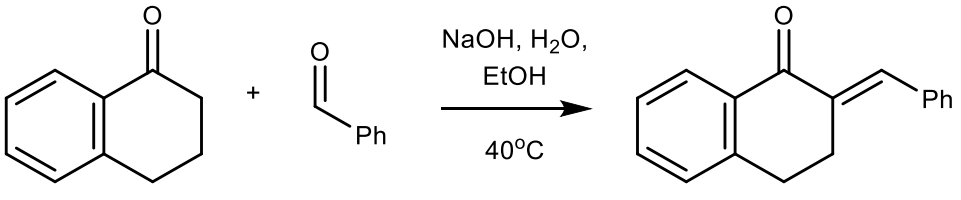
Entry	Catalyst	t / hr	% Conv	328 : 329 : 330	% ee 328	% ee 329
1	(*S*,*S*)-**80**	23	100	80.0 : 7.1 : 13.9	97	Nd
2	(*R*,*R*)-**115**	25	100	74.1 : 3.7 : 22.2	97	Nd

Standard conditions: 0.5M in 1:1 FA/TEA : MeOH, 100:1 S/C, 40 °C. Configuration of products not determined but estimated to be (*S*) for entry 1 and (*R*) for entry 2 by analogy to reduction of **160**.

Alcohol **328** is the primary product and is obtained with high enantioselectivity, while the ee of the minor product **329** was not determined. This was partly due to its low abundance in the reaction mixture, but also the fact that the prepared racemic standard of this material decomposed before suitable conditions for separation in chiral chromatography could be found.

2.4.6.2 Cyclic Exo-Unsaturated Ketone **321**

Next the tetralone derivative **321** was very easily prepared by Claisen-Schmidt condensation of tetralone and benzaldehyde. The product is very crystalline and precipitates out of the reaction mixture, purification by recrystallization provided **321** in 81% yield.



131 **306** **321**

Scheme 105: Synthesis of cyclic α-substituted enone **321**

Reduction of **321** with tethered catalysts introduces additional complication as the α-carbon is pro-chiral, meaning that the 1,4- reduction product could form either *cis* or *trans* diastereomers. In both cases a mixture of all three products was obtained and the ratios determined by ^{1}H NMR and comparison to literature values.[132,133]

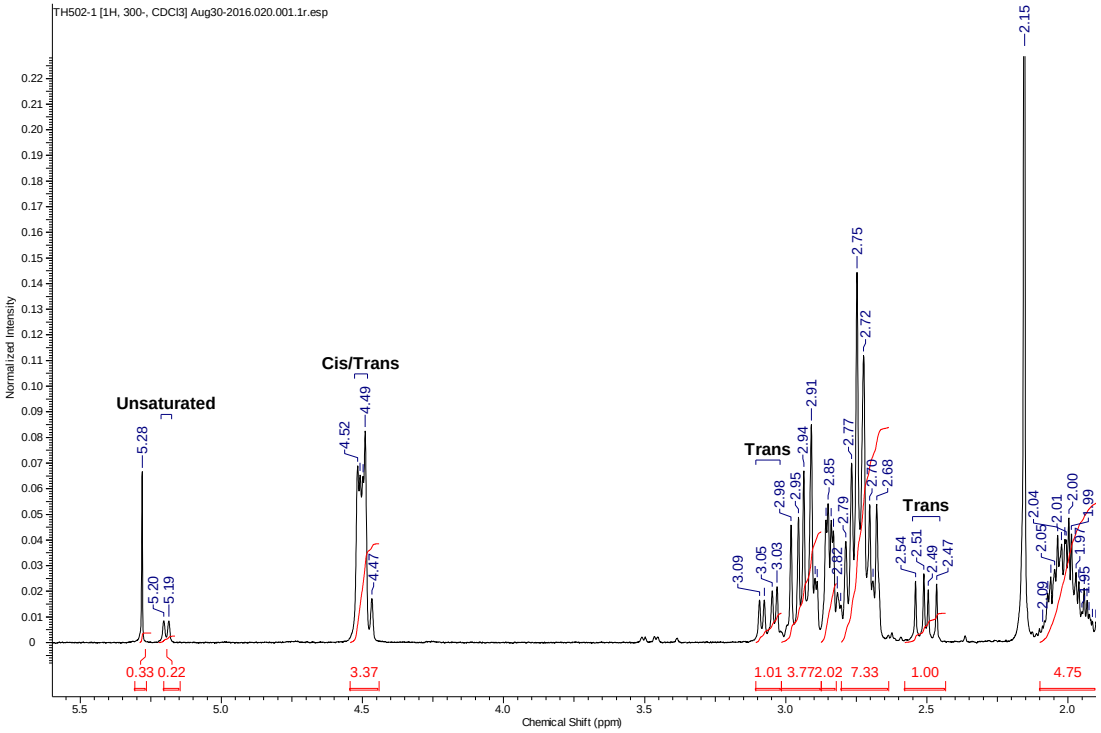
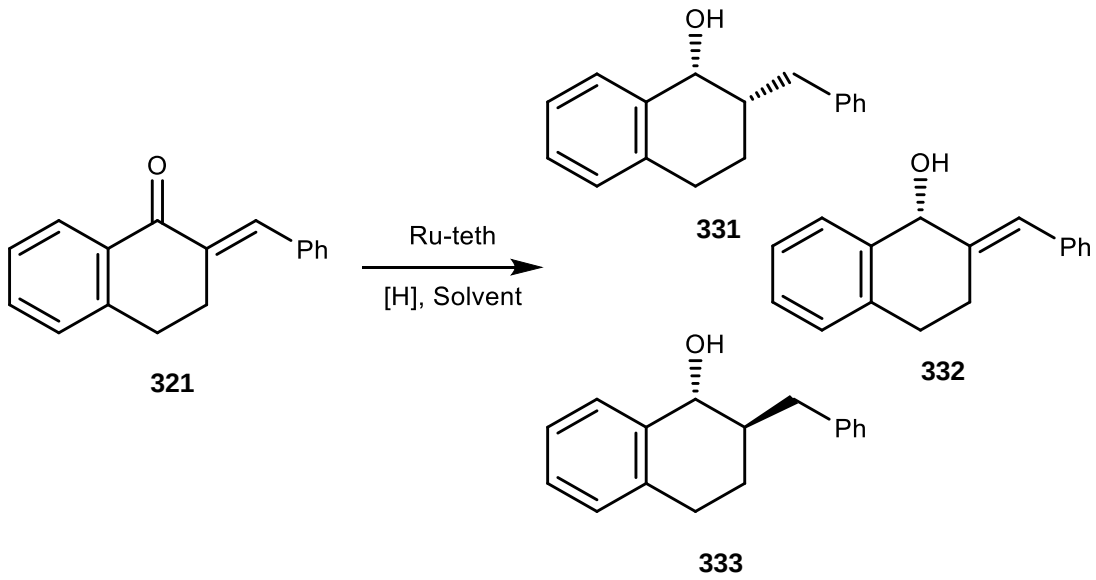


Figure 45: Partial ^{1}H NMR spectrum of product mixture from **321** showing resonances used to calculate product ratios.

ATH using **3C-teth (80)** catalyst gives approximately 75% 1,4- reduction products with the remainder being converted to the unsaturated alcohol **332**, a small but significant reduction in 1,4-selectivity relative to chalcone. The 1.23 : 1 ratio of *cis* (**331**) to *trans* (**333**) products represents quite a low diastereoselectivity in 1,4 reduction. Use of **OMe-teth (115)** catalyst gives an improvement on both counts, with 95% 1,4-selectivity and increasing the dr to 2.35 : 1.

Table 48: ATH of benzylidine-tetralone substrate **321**



321 **331** **332** **333**

Entry	Catalyst	T / °C	t / hr	% Conv	**331** : **333** : **332**
1	(*S,S*)-**80**	40	24	100	43 : 35 : 22
2	(*R,R*)-**115**	40	27	100	66 : 28 : 6

Standard conditions: 0.5M in 1:1 FA/TEA : MeOH, 100:1 S/C, 40 °C. Relative stereochemistry shown, in configuration as might be assumed for reduction with (*S,S*) catalyst, but no evidence collected for assignment.

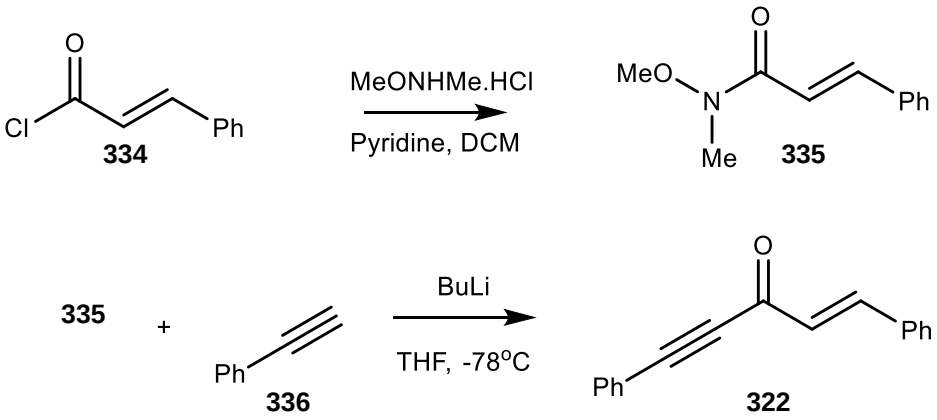
It is not known at this point what factors influence the configuration of the alkane chiral centre. Given that the alkene will likely be reduced first in the ATH reaction, control of configuration at the α position may be due to catalyst control, substrate control, or racemisation of the saturated ketone intermediate. However as the ee of 1,4- products **331** and **333** has not been determined* there is not sufficient evidence to comment on the mechanism of alkene reduction in this case.

2.4.6.3 Ene-yne ketone **322**

It is known in the literature that alkynes are usually unreactive under ATH conditions, and are in fact capable of acting as directing groups when conjugated with ketones.[63,134] To test whether this still applies when also considering conjugation to an alkene, the cross conjugated substrate **322** was synthesised in two steps from cinnamoyl chloride, via the

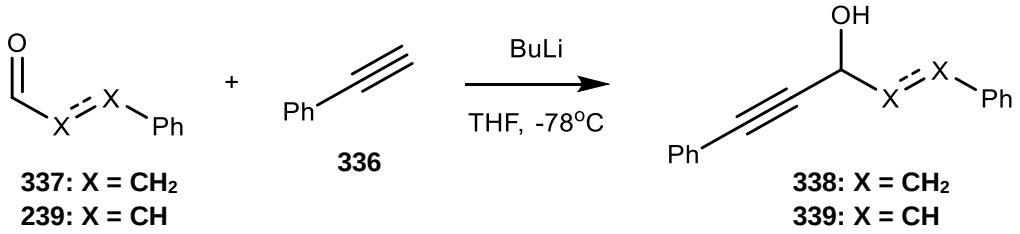
* Due to experimental difficulties in separating the chiral alcohol products by HPLC.

Weinreb amide **335**. The amide substitution was low yielding but was sufficient to supply enough substrate for testing.



Scheme 106: Synthesis of alkyne-alkene cross-conjugated ketone **322**. Step 1: 79% yield, Step 2: 21% yield.

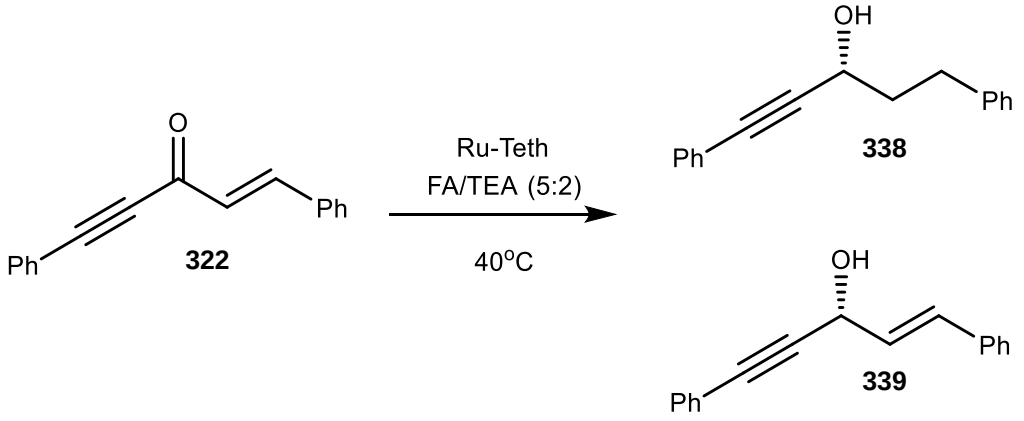
Racemic standards could be efficiently prepared by addition of the same phenylacetylenyl lithium reagent to aldehydes.



Scheme 107: Addition of lithiated **336** to aldehydes for preparation of racemic standards. With $CHO(CH_2)_2Ph$ (**337**): 66% yield. With $CHO(CH)_2Ph$ (**239**): 71% yield.

Reduction of ketone **322** with **OMe-teth (115)** gave primarily the 1,4- product **338**, with no indication of reduction at the alkyne (Table 49). Comparing the result with **322** to reduction of chalcone **160**, the alkyne substituent appears to be less effective at stabilising the ketone, resulting in a decrease in 1,4-selectivity. However the enantioselectivity for both modes of reduction is high, with **338** formed in 98% ee and even the unsaturated alcohol **339** is formed in 89% ee.

Table 49: ATH of cross conjugated substrate **322**

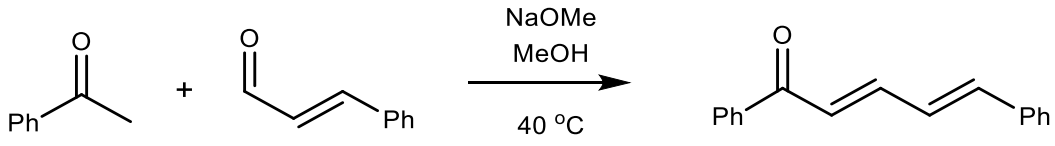


Entry	Catalyst	t / hr	% Conv	338 : 339	% ee 338	% ee 339	R/S
1	(R,R)-**115**	25	100	86.9 : 13.1	98	89	*R*

Standard conditions: 0.5M in 1:1 FA/TEA : MeOH, 100:1 S/C, 40 °C. Configuration of product determined by comparison to literature optical rotation.

2.4.6.4 αβγδ- Unsaturated Ketone **323**

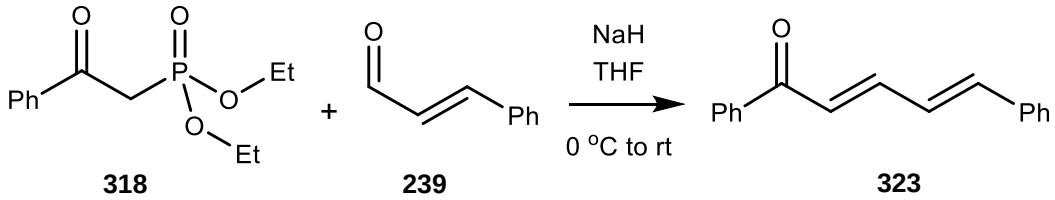
Extended conjugated ketone **323** contains three possible bonds for reduction and was prepared in order to further probe the mechanism of alkene reduction. While following a literature procedure for Claisen-Schmitt aldol condensation between **47** and cinnamaldehyde **239** did yield the desired product, it was very impure as assessed by ^{1}H NMR spectroscopy.[135]



47 **239** **323**

Scheme 108: Preparation of extended conjugated substrate **323** by aldol method. Mass recovery of impure product: 98%

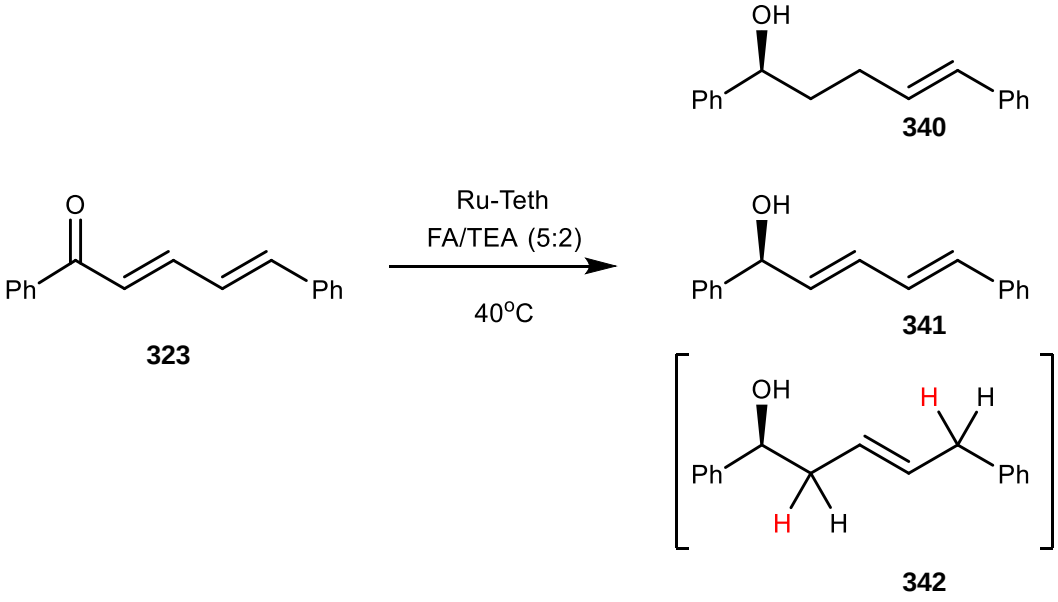
Instead, the keto-phosphonate **318** prepared previously for synthesis of β-alkyl substrate **312** was used in a HWE olefination of aldehyde **239**. The product was isolated in moderate yield and purified by crystallisation.



Scheme 109: HWE-olefination approach to synthesis of **323**. Yield 41%.

Ketone **323** was subjected to ATH with **3C-teth (80)** as catalyst, and an inseparable mixture of alcohol products was obtained. Analysis of the mixture by ^{1}H NMR and comparison with reported literature values allowed determination of the ratio of products (Table 50).[136–138]

Table 50: Product distribution from ATH of conjugated ketone **323**.



Product	Label	Product Ratio by ^{1}H NMR
340	A	62
341	B	25
342	C	13

Configuration of product alcohols assumed by analogy to substrate **160** and usual mode of reactivity of catalyst **80**, however the mixture was not separated by chiral chromatography and therefore no analysis of enantioselectivity can take place.

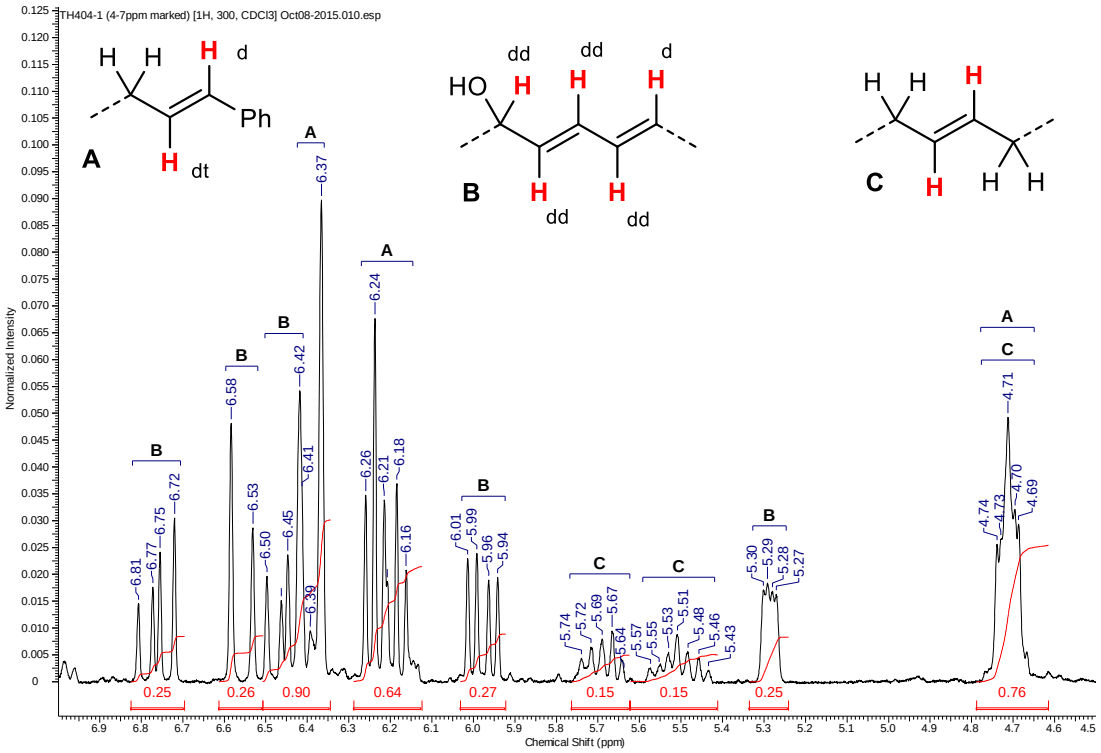
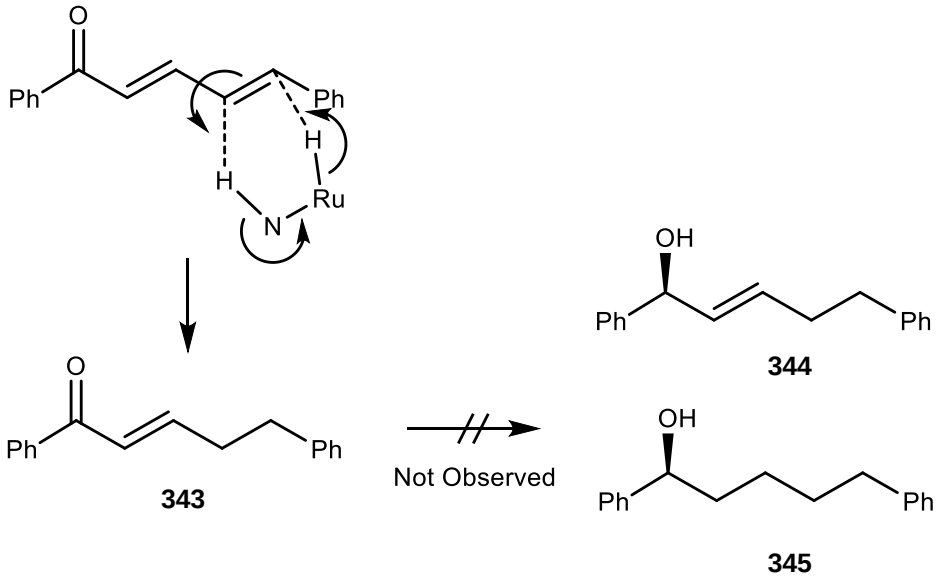


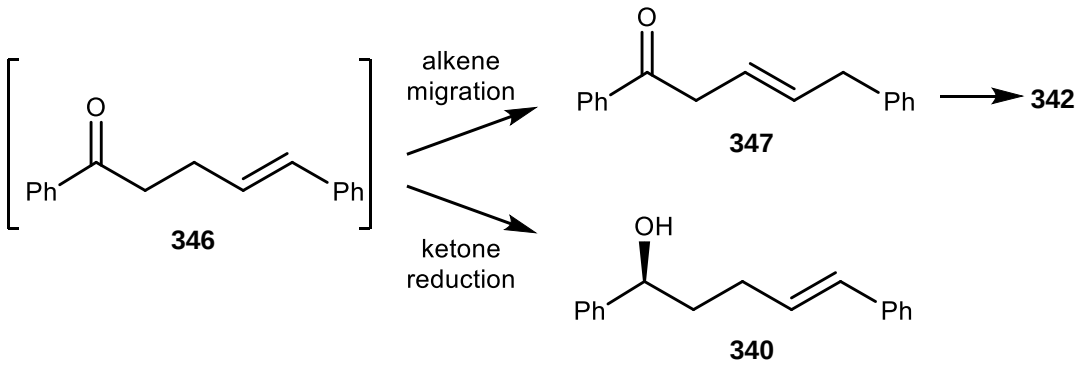
Figure 46: Combined NMR Analysis of product mixture **340**-**342** between 4 and 7 ppm.

Three major products can be observed in the reaction mixture. The majority of substrate **323** has undergone 1,4- reduction followed by further ketone reduction to yield the partially saturated alcohol **340**. The 1,2- reduction product **341** is also observed, as is ~15% of the full 1,6- reduction product **342**. The last of these is very interesting as it provides a useful mechanistic insight into alkene reduction in conjugated systems.



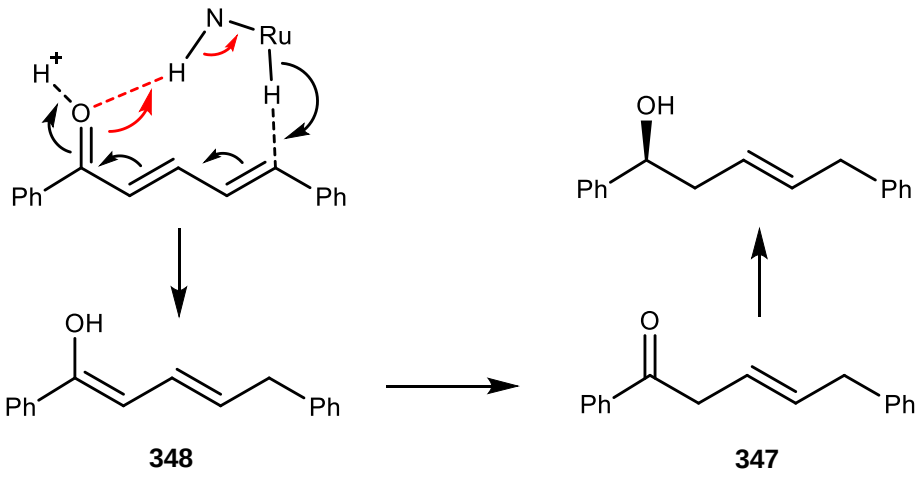
Scheme 110: Theoretical products expected to arise from 5,6-alkene reduction of conjugated substrate **323**.

Scheme 110 elaborates further. If the γ,δ-alkene were to be reduced 5,6- in a cyclic 6-membered transition state as is usually invoked for ketones, the expected product would be the α,β- unsaturated ketone **343**. Based on the behaviour of chalcone and other substrates investigated thus far, this would be expected to be reduced further to yield 1,4- and 1,2-reduction products **344** and **345**. However neither of these are observed in the product mixture. Furthermore formation of product **342** in this scenario requires an alkene migration from partially saturated ketone **346**, followed by ketone reduction of the rearranged β,γ-unsaturated ketone **347**. (Scheme 111).



Scheme 111: Proposed partial alkene migration route to observed products **340** and **342** following 1,4 reduction of substrate **323**. There is little precedent to suggest catalyst **80** would promote the migration of the alkene bond out of conjugation under normal reaction conditions.

The observed product distribution can be more simply explained if a 1,6- reduction mechanism is invoked. Hydride is transferred from the catalyst to the δ carbon of substrate **323** with protonation of the oxygen leading to enol product **348**. Keto-enol tautomerism to **347** followed by ketone reduction gives the observed side product **342** (Scheme 112).



348 **347**

Scheme 112: Explanation of observed product **342** via a 1,6-reduction mechanism.

A question that remains to be answered is where the proton comes from in this 1,6 reduction step. Protonation by solvent (black arrows, Scheme 112) appears more feasible, as concerted proton transfer from the catalyst amine would require a 10-membered cyclic transition state, of which a significant portion is held in a rigid planar conformation by the π-system of the substrate.*

2.4.7 Chapter Summary

A β-Chlorinated ketone was shown to undergo elimination and 1,4- reduction in one pot to form a saturated alcohol intermediate. Further investigation of a range of enone substrates showed that this 1,4- reactivity is common with tethered catalysts, and the majority of aromatic-ketone substrates are reduced to their saturated alcohols with 75-95% 1,4-selectivity. Enantioselectivity was generally high, especially for the 1,4- reduction products. Electron donating para-substituents on the ketone favour 1,4- reduction even more and yield exclusively the saturated alcohol products. Reduction of an alkyl-ketone lead to a mixture of products with low enantioselectivity.

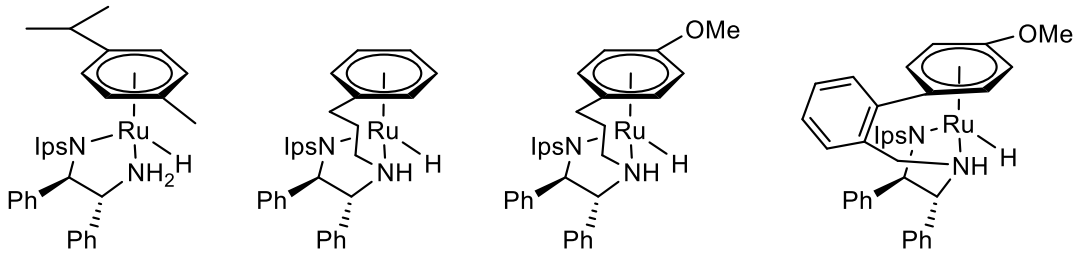
* See Hoveyda *et. al.* for an example of a Cu catalysed 1,6 conjugate addition with a planar substrate in the transition state and for more background on the difficulties of 1,6 addition reactions.[196]

3 Conclusions and Future Work

3.1 Supported and Functionalised Complexes

Attempts at preparing polymer supported catalysts did not yield any useful supported complexes. Various synthetic issues were encountered throughout the routes explored, however ultimately it is also the case that the author did not have the practical experience or knowledge to prepare or manipulate polymers experimentally. However the Iodo-substituted ligands and complexes that were successfully prepared may present an opportunity for future work in preparing functionalised catalysts. Some limited evidence for successful Pd coupling of a monomeric Ips complex and an alkyne was collected that may be worth further investigation.

Attempts at optimising the arene exchange route to catalyst synthesis hints at a possible improvement by absorbing HCl with molecular sieves. However the reaction remains temperamental and apparently depends strongly on the "hands-factor"; great skill and patience are required of the chemist in the workup and purification to obtain a good yield of pure catalyst.



270 **272** **275** **276**

Scheme 113: Ips substituted complexes for further investigation.

Some further work in this area has already occurred, as discussed in section 2.1.4. Specifically complexes **275** and **276** have been prepared and tested in the reduction of acetophenone and other ketones. Although some further testing could be performed with Ips complexes **270** and **272** it appears reasonably clear already that the Iodo functional group does not interfere with the selectivity or activity of the catalysts. Further work could therefore focus on completing the Pd catalysed coupling of monomeric complexes onto solid supports. The preparation of a polymeric support containing a suitable functional group for cross coupling

with an aryl iodide should be achievable and would be a good opportunity for collaboration with a research group with expertise in polymer synthesis.

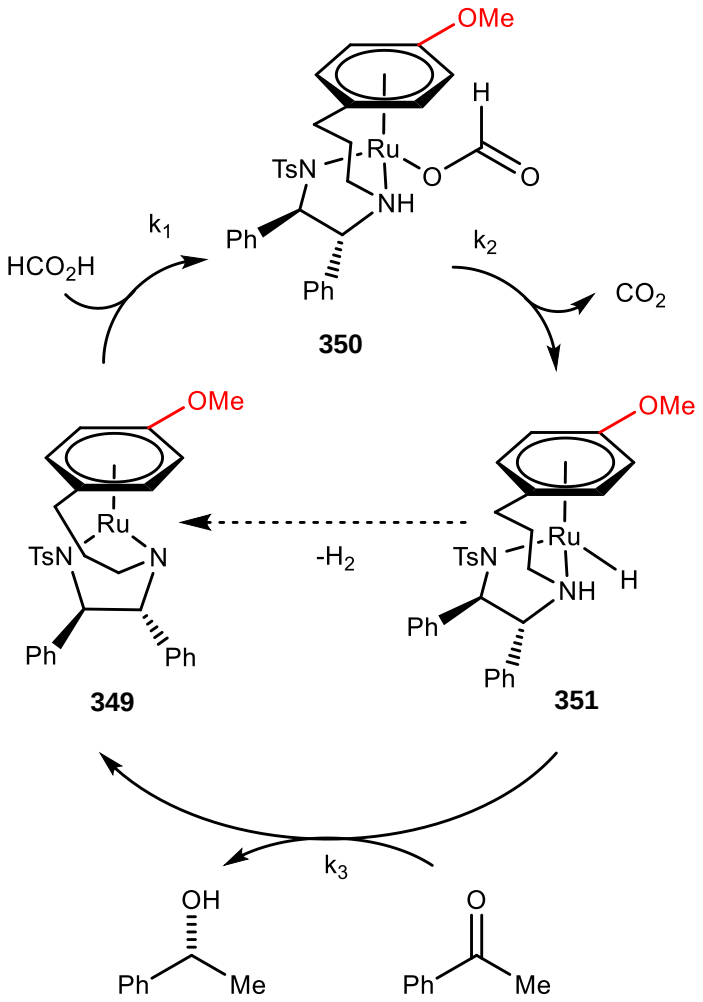
3.2 Applications of Tethered Catalysts

Tethered catalysts **3C-teth (80)** and **OMe-teth (115)** have been used to undertake more detailed investigation of challenging substrates for ATH. These substrates cause issues of reactivity or selectivity. In several cases chiral alcohols could be obtained with good conversions and enantiomeric excesses.

3.2.1 Mechanism of Reduction in FA/TEA

Many of the results found relate to subtle differences in reactivity and selectivity between **80** and **115**. Direct experiments to probe the mechanism of action of these catalysts have not been performed but some attempt can be made to rationalise their differences by considering their structure and the mechanism of ketone reduction in FA/TEA.

Scheme 114 describes a simple three step catalytic cycle. In principle each of these steps are reversible, including loss of CO2 from the formate complex **350**. The insertion of CO_2 into the hydride complex **351** has been demonstrated in the literature by NMR experiments at low temperatures,[41,49] and removal of CO_2 by trapping with an amine or by purging of the reaction mixture has been shown to accelerate the reduction of acetophenone.[50] However, the influence of CO_2 inhibition will be strongly dependant on the scale of the reaction, as the available surface area for loss of gas scales slower than the reaction volume.



Scheme 114: Catalytic cycle for ketone reduction in FA/TEA with tethered catalysts.

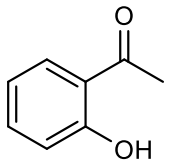
Even without the presence of substrate the cycle above can still progress. Formic acid is decomposed into H_2 and CO_2 by the presence of ATH catalysts, presumably hydrogen elimination from **351**. This can be observed in the laboratory as effervescence on addition of the catalyst to FA/TEA.

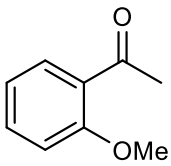
An attempt can now be made to rationalise some of the beneficial effects of electron donating substituents on the ruthenium arene. Increased electron density on the arene, due to the carbon tether or a methoxy substituent could be expected to promote step 3 in the cycle above, where the metal becomes coordinatively unsaturated and the hydride acts as a nucleophile. The same effect may retard step 1, but the addition of formic acid to the 16e complex **349** is known to be rapid and is unlikely to be the rate limiting step, especially as under the catalytic reaction conditions [FA] > [Sub]. Therefore increasing electron density on the aromatic ring could promote the hydrogen transfer step.

3.2.2 Selectivity in Reduction of ortho- *Substituted Ketones*

Significant and unexpected differences in selectivity in the reduction of electron rich *ortho*-oxy-ketones was observed, that appears to be dependent on a specific match between the catalyst structure and the substrates substitution pattern. Both **3C-teth (80)** and **OMe-teth (115)** are excellent catalysts for *ortho*-hydroxyacetophenones such as **133**, producing the chiral diol products in high ee's and conversions. This result is especially pleasing given the potential of such products to act as catalyst inhibitors, and indeed there are few examples of ATH of these compounds in the literature.

Table 51: Summary of results for reduction of ketones **133** and **126**





Catalyst **80**:	99% Conv, 99% ee	95% Conv, 68% ee
Catalyst **115**:	99% Conv, 99% ee	98% Conv, 96% ee

However *ortho*-methoxyacetophenone **126** is reduced selectively only by catalyst **115**, while catalyst **80** is much less selective. Conclusive results to explain this change in selectivity were not obtained, nor was it possible to model the relevant transition states computationally using the equipment available. However at this point some potential explanations can be explored, building on the results obtained in this thesis.

Firstly, computational results in the literature indicate that a destabilising SO_2/π interaction between the ligand sulfonyl group and the aromatic ring of the substrate disfavours the transition state leading to the minor enantiomer and therefore contributes significantly to the selectivity of catalyst **58**.[47]

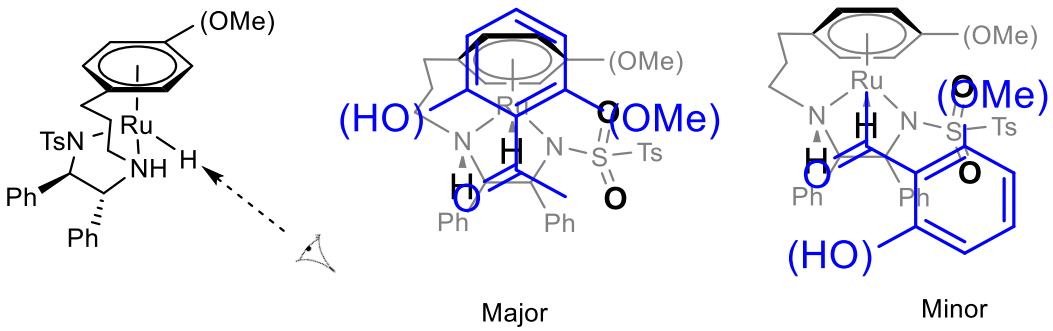


Figure 47: Potential interactions in the transition states for reduction of **133** (OH) and **126** (OMe) with tethered complexes **80** or **115**.

Figure 47 considers some of the possibilities that this effect might have when taking into account the different conformations of substrates **133** and **126**. For comparison both substrates are represented as a single compound with their corresponding *ortho* functional group shown in brackets in the orientation it would exist in in their preferred ground state conformation. Clearly the major transition state for both substrates includes the classic stabilising CH/π interaction between the ruthenium arene and the substrates aromatic ring, while the minor transition state lacks this interaction.

The *ortho* hydroxy group of **133** in both transition states seems unlikely to engage in any specific interaction with the catalyst. However the *ortho* methoxy group of **126** is close in space to the SO_2 group of the catalyst, and therefore it is possible that there are some additional interactions in both major and minor transition states. While it is not possible to quantify these interactions without detailed further investigation, it is plausible that they could account for some of the reduced enantioselectivity in reduction of **126** if the interactions are relatively less favourable in the major transition state. This balance of interactions may also explain why there is not a clear trend in enantioselectivity with substituent size in *ortho*-alkoxy ketones.

As to why **OMe-teth (115)** is more effective in reduction of **126** than **3C-teth (80)** in the reduction of **126**, there is not a clear explanation. The arene methoxy group is relatively close in space to the sulfonyl and substrate methoxy group, and could potentially exert its influence via steric, electronic or solvent mediated hydrogen bonding effects. Much more detailed mechanistic investigation through both experiment and computation would be required to give a definitive answer.

Future work could include reduction of the hindered *ortho*-substituted oxo-ketones prepared in section 2.3.5 with **3C-teth (80)**, to observe whether the low enantioselectivity found in reduction of methoxy substrate **126** is a general trend. Higher level computational

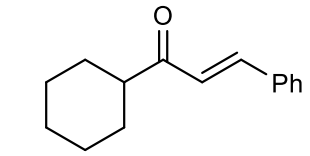
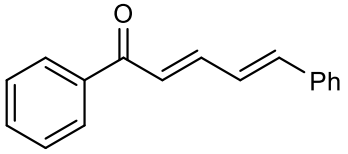
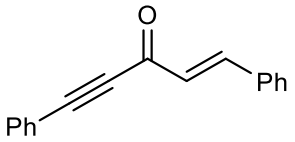
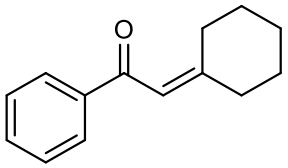
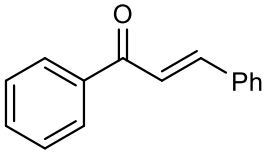
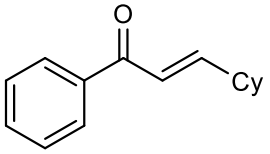
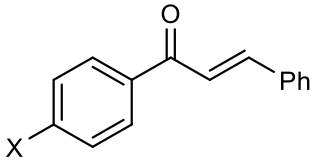
modelling of the transition states may then illuminate some of the specific factors that influence the changes in reactivity and selectivity between catalysts **80** and **115** in reduction of this substrate class.

3.2.3 Selectivity in Reduction of α,β-Unsaturated Ketones

Tethered Ru catalysts were shown to be effective for the 1,4 reduction of α,β-unsaturated ketones. This selectivity appears to rely on a fine balance between the thermodynamic drive for 1,4 reduction and the catalysts own kinetic preference for ketone reduction. For aromatic ketones such as chalcone **160** and its derivatives the **OMe-teth (115)** catalyst is particularly effective.

In order to consider the overall effect of substrate structure on reaction selectivity, several substrates have been ranked by the total proportion of 1,4 reduction products obtained in the reaction mixture during their reduction with **115** (Table 52).

Table 52: Summary of results for reduction of α,β-unsaturated ketones with **OMe-teth (115)**

Substrate	Compound Number	% of 1,4 reduction products in product mixture
	**313**	58.6
	**323**	75
	**322**	86.9
	**320**	95.2
	**160**	97.9
	**312**	97.5*
	**308**,**196**,**309**	96.4-100

* Result from reduction with **3C-teth (80)** as reduction not performed with **115**. The expected proportion of 1,4 products for reduction with **OMe-teth (115)** would be higher.

It can be seen that the type of substituent on the ketone has the biggest impact on reaction selectivity. The two non-aromatic ketones **313** and **322** show a strong tendency towards ketone reduction, which suggests that the aromatic ring in substrates such as **160** stabilises the ketone and hinders direct reduction. Substitution on the alkene is less significant, except in the case of **323** where the additional alkene group leads to further possibilities such as 1,6-reduction, but also appears to promote additional 1,2 reduction. Electron donating groups

on the ketone further hinder ketone reduction, leading to increased 1,4 selectivity at the cost of reactivity.

The exact mechanism of 1,4 reduction has not been investigated, and further study in the area could be illuminating. Specifically computational calculations of transition states for 1,2 and 1,4 reduction could provide additional insight into the effects of catalyst structure, solvent and substrate structure on selectivity of reduction.

4 Experimental

4.1 General Experimental

All reagents and solvents were used as purchased and without further purification, with the exception of cyclohexane carboxaldehyde which was redistilled for storage.

All reactions were carried out under a nitrogen atmosphere unless otherwise specified. Reactions at elevated temperature were maintained by thermostatically controlled oil-baths or aluminium heating blocks. A temperature of 0 °C refers to an ice slush bath, -78 °C to a dry ice acetone bath.

NMR spectra were recorded on a Bruker AV (250 MHz), Bruker DPX (300 or 400MHz), Bruker DRX (500 MHz) or Bruker AV-II. (700 MHz). All chemical shifts are rounded to the nearest 0.01ppm for ^{1}H spectra and the nearest 0.1 ppm for ^{13}C spectra, and are referenced to the solvent chemical shift. Coupling constants are rounded to the nearest 0.1 Hz. Mass spectra were recorded on an Esquire 2000 and high resolution mass spectra were recorded on a Bruker Micro ToF or MaXis. IR spectra were recorded on a PerkinElmer spectrum100 and peaks are reported in wavenumbers. Optical rotations were measured on an Optical Activity Ltd. AA-1000 Polarimeter and are reported in deg cm^2 g^{-1}.

The chiral GC measurements were performed using a Perkin-Elmer 8500 or Hewlett-Packard 1050 instrument linked to a PC running DataApex Clarity software. HPLC measurements were performed out using a Hewlett Packard 1050 Series with a quaternary pump, autosampler and variable wavelength detector linked to a PC running DataApex Clarity software.

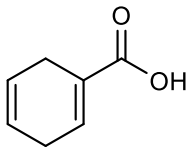
Melting points were determined on a Stuart scientific melting point apparatus and are uncorrected. Flash column chromatography was performed using silica gel of mesh size 230-400, Thin layer chromatography was carried out on aluminium backed silica gel 60(F254) plates, visualised using 254nm UV light, potassium permanganate, iodine stains or cerium ammonium molybdate (CAM) as appropriate.

Column chromatography was performed either by gradient elution (reported as a range, e.g. EtOAc/Petroleum ether (2-12%)), or by isocratic elution. In the later case retention times and mass loadings of silica were often simulated using the spreadsheet provided by Fair and Kormos.[139]

4.2 Preparation of Compounds, Arene Exchange:

4.2.1 OMe-Tethered Complex: Preparation of Materials

Cyclohexa-1,4-diene-1-carboxylic acid



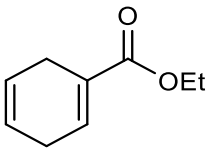
278

This compound is known.[140]

Propiolic acid (8.60 g, 123 mmol, 1 eq) was poured into an open glass insert with stirrer bar, cooled to -78 °C and covered. Butadiene (~11g, 203 mmol, 1.65 eq) was condensed from a gas cylinder into a nitrogen filled sealed RBF cooled to -78 °C, and then poured into the glass insert. The insert was then assembled into a Parr hydrogenator apparatus, which was sealed and allowed to warm to rt with stirring in an aluminium heating block. The temperature of the block was increased by 10 °C every half hour until it reached 110°C, after which it was left overnight. The pressure reached a maximum of 12 bar during heating. After 24 hours reaction time the pressure had decreased to 10 bar, the block was allowed to cool fully to rt and vented. The yellow crystalline solid product was scraped out from the insert and carried directly into the next step (11.83 g, 78%)

Mp 113-121 °C; δ_H (250 MHz, $CDCl_3$): 11.78 (1H, br. s., COOH), 7.17 - 6.94 (1H, m, CC=C*H*), 5.87 - 5.73 (1H, d, *J* = 10.5 Hz, *H*C=CH), 5.73 - 5.59 (1H, d, *J* = 10.5 Hz, HC=C*H*), 2.91 (4H, s, CH_2); δ_C (101 MHz, $CDCl_3$): 172.7 (CO), 139.2 (CH), 127.2 (C), 124.3 (CH), 122.1 (CH), 27.2 (CH_2), 24.7 (CH_2).

Ethyl cyclohexa-1,4-diene-1-carboxylate



279

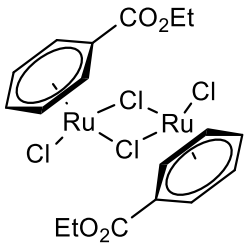
This compound is known.[141]

To a solution of **278** (11.83 g, 95.3 mmol, 1.0 eq) in Ethanol (66 mL) was added conc sulphuric acid (4.4 ml) and the reaction mixture was heated to reflux (80 °C) and stirred for 18 hours.

The dark red solution was cooled to rt and diluted with brine (40 mL) and DCM (40 mL), before neutralising with NaOH (3 g in 25 mL water). The aqueous phase was extracted with DCM (2 x 40 mL) and the combined organic extracts dried over Na_2SO_4 and concentrated to give an orange oil (14.11 g). The crude product was purified by distillation to give a clear oil (12.60 g, 75.0 mmol, 79%).

Bp 74-76°C at 3 mbar; δ_H (400 MHz, $CDCl_3$): 7.07 - 6.80 (1H, m, CC=C*H*), 5.86 - 5.71 (1H, m, *H*C=CH), 5.69 - 5.58 (1H, m, HC=C*H*), 4.27 - 4.11 (2H, m, OCH_2), 3.03 - 2.68 (4H, m, CH_2), 1.35 - 1.17 (3H, m, CH_3); δ_C (101 MHz, $CDCl_3$): 167.0 (CO), 136.1 (CH), 127.8 (C), 124.4 (CH), 122.3 (CH), 60.3 (CH_2), 27.0 (CH_2), 25.1 (CH_2), 14.3 (CH_3).

Dichloro(ethylbenzoate)ruthenium(II) dimer



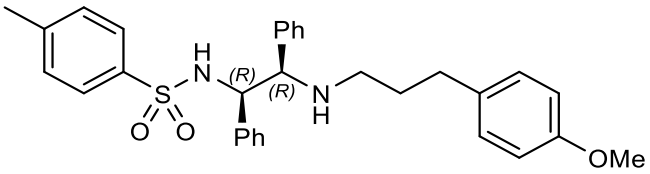
117

This compound is known.[142]

A solution of **279** (2.10 g, 12.5 mmol, 4.2 eq) and $RuCl_3 . xH_2O$ (788 mg, 3 mmol, 1 eq assuming x = 3) in Ethanol was heated to reflux (100 °C). After 27 hours, the brown suspension was filtered and the brick red solid was washed with ethanol and diethyl ether to yield the dimeric product with no purification required (901 mg, 93%).

δ_H (400 MHz, $(CD_3)_2SO$): 6.69 (2H, d, *J* = 5.9 Hz, *o*-ArH), 6.29 (1H, t, *J* = 5.9 Hz, *p*-ArH), 6.04 (2H, t, *J* = 5.9 Hz, *m*-ArH), 4.33 (2H, q, *J* = 7.0 Hz, CH_2), 1.31 (3H, t, *J* = 7.0 Hz, CH_3); δ_C (101 MHz, $CDCl_3$): 163.9 (CO), 92.4 (CH), 91.8 (CH), 85.2 (CH), 82.5 (C), 62.1 (CH_2), 14.2 (CH_3).

*N-((1*R*,2*R*)-2-((3-(4-methoxyphenyl)propyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide*



116

This compound is known.[62]

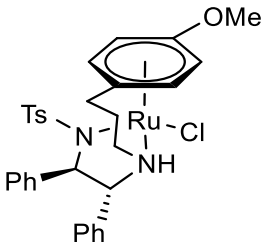
To a stirred solution of 3-(4-methoxyphenyl)-1-propanol (4.11 g, 25 mmol, 1.6 eq) and 2,6-lutidine (3.65 ml, 32 mmol, 2.1 eq) in dry DCM (100 ml) at 0°C was added by a dropping funnel a solution of triflic anhydride in DCM (1M, 25 ml, 25 mmol, 1.7 eq), maintaining the solution temperature below 3 °C as measured by an internal thermometer. The dropping funnel was rinsed in with 10 ml dry DCM and removed. The resulting yellow solution was stirred for 30 mins at 0°C and 1 hour at rt. To the reaction mixture a separate solution of (*R,R*)-TsDPEN (5.45 g, 15 mmol, 1 eq) and triethylamine (5.0 ml, 36 mmol, 2.4 eq) in dry DCM (50 ml) was added dropwise by cannula at 0°C, maintaining the reaction temperature below 3 °C. The flask and cannula were rinsed in with dry DCM (10ml) The reaction was stirred for 22 hours at room temperature, then solvent switched to ethyl acetate by repeated dilution (100, 50, 50 ml) and concentration to ~100 ml volume. The resulting suspension was washed with sat. $NaHCO_3$ solution (2x 100 ml, 2x 50 ml), water (2x 50 ml) and brine (50 ml), dried (Na_2SO_4) and concentrated to give a yellow oil. (10.45 g) that solidifies on standing in the freezer.

The crude product was taken up hot EtOH and concentrated to a saturated solution. No solids formed after standing on ice. Addition of hexanes (~10 ml) and rapid stirring gave a fine slurry. This was left in the freezer overnight, and the resulting crystalline solid collected by filtration and washed with ice cold ethanol to yield the pure product as fine white crystals (5.08 g, 66%).

TLC: 50% EtOAc : Petroleum ether, silica, Rf =0.5, I_2 and UV; Mp 104 °C; δ_H (500 MHz, $CDCl_3$): 7.37 (2H, d, *J* = 8.2 Hz, *ar*-H), 7.15 - 7.10 (3H, m, *ar*-H), 7.09 - 6.97 (7H, m, *ar*-H), 6.96 - 6.92 (2H, m, *ar*-H), 6.91 - 6.87 (2H, m, *ar*-H), 6.82 - 6.77 (2H, m, *ar*-H), 6.26 (1H, br. s., NH), 4.25 (1H, d, *J* = 7.9 Hz, CH), 3.78 (3H, s, OCH_3), 3.59 (1H, d, *J* = 7.8 Hz, CH), 2.55 - 2.38 (3H, m, CH*H* and CH_2), 2.33 (3H, s, $ArCH_3$), 2.28 (1H, dt, *J* = 11.6, 6.8 Hz, C*H*H), 1.75 - 1.59 (2H, m, CH_2-C*H*$_2$-CH_2) 1.51 (1H, br. s., NH); δ_C (126 MHz, $CDCl_3$): 157.8 (C), 142.7 (C), 139.3 (C), 138.4 (C), 137.1 (C), 133.8 (C), 129.2 (2* *ar*-CH), 129.1 (2* *ar*-CH), 128.3 (2* *ar*-CH), 127.9 (2* *ar*-CH), 127.6

(2* *ar*-CH), 127.5 (2* *ar*-CH), 127.4 (*ar*-CH), 127.3 (2* *ar*-CH), 127.1 (*ar*-CH), 113.8 (2* *ar*-CH), 67.8 (CH), 63.1 (CH), 55.3 (OCH_3), 46.4 (NCH_2), 32.4 (CH_2), 31.7 (CH_2), 21.4 (CH_3).

*{N-((1*R*,2*R*)-2-((3-(4-methoxyphenyl)propyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide} ruthenium chloride*



115

This compound is known. [62]

116 (780 mg, 1.52 mmol, 1 eq), **117** (483 mg, 0.75 mmol, 0.5 eq) and 4Å molecular sieves (752 mg, 100 wt% relative to ligand) were dissolved in chlorobenzene (30 ml). The mixture was degassed 3 times with vacuum and nitrogen, then heated to 90 °C with stirring. No HCl fumes were observed. The reaction was monitored by the ratio of Complex to Ligand peaks in LC-MS, which steadily increased up to ~2:1. After 10 hours reaction time, the mixture was cooled to rt and filtered through a short layered pad of Celite (25g), silica (5g) and Celite (25g) with a 10% mixture of isopropanol in chloroform (200 ml), to yield the crude product as a dark brown residue (1.41 g).

This crude was dry loaded onto silica (5 g) and purified by column chromatography (silica, 60g), with 10% isopropanol, 40% DCM and 50% hexane (1 L) as eluent. Fractions were assessed by LC-MS. Contaminated ligand was eluted within the first 50-200 ml of eluent as a dark brown band. Clean fractions of the target complex were obtained between 350 and 500 ml of eluent, concentration under reduced pressure yielded the purified product as a free flowing orange-brown powder (400 mg, 41%).

The product thus obtained appeared clean by NMR and pure enough for use, however an attempt to further purify it and remove non-NMR visible impurities was made. The solid was suspended in hot isopropanol (50 ml) and refluxed for a few minutes. The suspension was cooled and filtered to yield the product as a slightly brighter orange powder (331 mg, 34%).

TLC: 10% MeOH/DCM, silica, Rf, = 0.2, I_2; δ_H (400 MHz, $CDCl_3$): 7.28 (2H, d, *J* = 8.1 Hz, *ar*-H), 7.18 - 7.08 (3H, m, *ar*-H), 6.81 (2H, br. s., *ar*-H), 6.78 - 6.70 (3H, m, *ar*-H), 6.62 (2H, t, *J* = 7.6 Hz, *ar*-H), 6.57 - 6.51 (2H, m, *ar*-H), 5.56 (1H, d, *J* = 5.3 Hz, Ru-ArH), 5.47 (1H, d, *J* = 5.7 Hz, Ru-ArH), 5.34 (1H, d, *J* = 5.1 Hz, Ru-ArH), 5.21 (1H, d, *J* = 6.0 Hz, Ru-ArH), 4.33 (1H, d, *J* = 10.9 Hz,

CHPh), 4.13 - 4.02 (1H, m, NH), 4.00 (3H, s, OCH_3), 3.55 (1H, t, *J* = 11.6 Hz, NHC*H*Ph), 2.85 - 2.73 (1H, m, CH_2), 2.52 - 2.36 (2H, m, CH_2), 2.34 - 2.23 (1H, m, CH_2), 2.21 (3H, s, $ArCH_3$), 2.14 - 1.97 (2H, m, CH_2); δ_C (101 MHz, $CDCl_3$): 143.8 (C), 138.7 (C), 138.4 (C), 136.3 (C), 134.6 (C), 128.7 (CH), 128.6 (CH), 128.3 (CH), 127.7 (CH), 127.0 (CH), 126.8 (CH), 126.0 (CH), 91.1 (C), 84.7 (CH), 81.5 (CH), 78.6 (CH), 72.2 (CH), 68.9 (CH), 65.5 (CH), 56.8 (CH_3), 49.4 (CH_2), 30.2 (CH_2), 27.3 (CH_2), 21.1 (CH_3); *m/z* (ESI): 615.1 ($[M - Cl]^+$), top peak of Ru Isotope pattern.

4.2.2 OMe-Tethered Complex: Arene Exchange Optimisation

NMR Degradation tests

Pure standards of Ligand **116** and Complex **115** (0.02 mmol) were taken up in $CDCl_3$ (0.5 ml) and the NMR spectra obtained. The NMR sample was then concentrated into vial, dissolved in DCM (1 ml) and anhydrous HCl (2M in diethyl ether, 10 µL) was added at 0°C and the mixture stirred for 3 hrs at rt. After this time the DCM had evaporated under the flow of nitrogen, so the remaining solid was taken up in $CDCl_3$ (0.5ml) and re-analysed. Comparisons of spectra are included in the main results on pages 105 and 106.

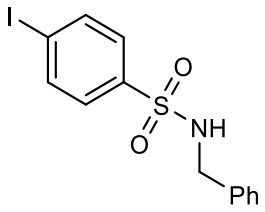
Ligand to Ru Ratio

General procedure: Ligand **116** (0.1, 0.2 or 0.4 mmol) and Dimer **117** (64 mg, 0.1 mmol, 1 eq) were dissolved in chlorobenzene (5 ml) under N_2 in a Radleys parallel synthesis reaction tube (~20 ml volume). The mixture was immediately heated to 90°C and stirred for 24 hours. ~10uL Samples were withdrawn by syringe and diluted in MeOH for analysis by LCMS throughout the reaction. On completion the reaction mixture was concentrated under vacuum to give a dark brown residue, which was triturated with diethyl ether (~5 ml). Excess solvent was removed by pipette. The remaining residue was then filtered through a short silica plug with EtOAc/EtOH (3:1) as eluent and concentrated to give the crude product mixture for analysis.

4.3 Preparation of Compounds, Supported Catalysts:

4.3.1 Untethered Ips Complex

N-benzyl-4-iodobenzenesulfonamide.



261

This compound has been reported but not fully characterised.[143]

Method 1: Benzylamine (218 µL, 2 mmol, 1 eq) was dissolved in DCM (13 ml) and cooled to 0 °C. 4-iodobenzenesulfonyl chloride (604 mg, 2 mmol, 1 eq) in DCM (2 ml) was added dropwise over 10 minutes and the reaction mixture stirred for 42 hours and monitored by TLC. The reaction was neutralised with NH_4Cl (sat., 15 ml) and extracted with DCM (30 ml). The combined organic layers were dried (Na_2SO_4) and concentrated to give the impure product as an off white powder. (728 mg).

^1H NMR signals corresponding to trimethylamine could be removed by suspending this crude product in DCM (~15 ml) and washing with HCl (2M, 2* 10 ml). The organic layer was dried (Na_2SO_4) and concentrated to give the purified product (432 mg, 58%)

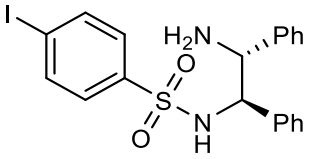
Method 2: Benzylamine (218 µL, 2 mmol, 1 eq) was suspended in a mixture of DCM (8 ml) and NaOH (2M, 5 ml) and cooled to 0 °C. 4-iodobenzenesulfonyl chloride (604 mg, 2 mmol, 1 eq) in DCM (2 ml) was added dropwise over 10 minutes and the resulting suspension stirred for 42 hours and monitored by TLC. The reaction was acidified to pH 2 with HCl (2M) and extracted with DCM (15 ml). The combined organic layers were dried (Na_2SO_4) and concentrated to give the crude product as a white powder (764 mg).

Recrystallization of the crude material from method 2 with hot diisopropyl ether gave the purified product as transparent needles (405 mg, 54%).

TLC: 30% EtOAc/Petroleum ether, silica, R_f = 0.4, I_2 and $KMNO_4$; Mp 130-131 °C; HRMS: found (ESI): $[M + Na]^+$, 395.9521. ($C_{13}H_{12}INNaO_2S$ requires 395.9526); ν_{max}: 3263, 3061, 2856, 1567, 1324, 1156, 729, 523 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.85 (2H, d, *J* = 8.5 Hz, SO_2Ar-H), 7.55 (2H, d, *J* = 8.5 Hz, SO_2Ar-H), 7.32 - 7.25 (3H, m, Ar-H), 7.20 - 7.16 (2H, m, Ar-H), 4.78 (1H, br. s., NH), 4.15 (2H, d, *J* = 6.0 Hz, CH_2); δ_C (75 MHz, $CDCl_3$): 139.1 (C), 137.7 (CH), 135.3 (C), 128.1 (CH),

127.9 (CH), 127.4 (CH), 127.3 (CH), 99.4 (CI), 46.7 (CH_2); *m/z* (ESI): 371.9 ([M - H]$^-$), 395.9 ([M + Na]$^+$).

N-((1S,2S)-2-amino-1,2-diphenylethyl)-4-iodobenzenesulfonamide



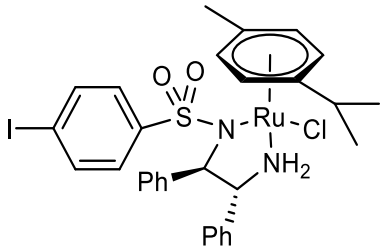
263

This compound is novel.

(*S,S*)-DPEN (1.03 g, 4.85 mmol, 1.0 eq) and potassium carbonate (0.69 g, 5 mmol, 1.0 eq) were suspended in a mixture of DCM (20 mL) and water (12.5 mL) and the mixture was cooled to 0 °C. 4-Iodobenzenesulfonyl chloride (1.51 g, 4.99 mmol, 1.0 eq) in DCM (5 mL) was added dropwise over 15 minutes and the resulting suspension stirred for 4 days at room temperature and monitored by TLC. The reaction was neutralised with NH_4Cl (sat., 12.5 mL) and stirred overnight. The aqueous phase was then extracted with DCM (50 mL portions) until clear. The combined organic layers were dried (Na_2SO_4) and concentrated to give the crude product as a white powder (2.20 g). Recrystallization from boiling toluene gave the product as white flaky crystals (1.91 g, 84%)

TLC details: 30% EtOAc/Petroleum ether, silica, Rf =0.1, I_2; Mp 180-181 °C; $[\alpha]_D^{22}$ -26.1 (*c* 0.435 in $CHCl_3$); HRMS: found (ESI): [M + H]$^+$, 479.0288. ($C_{20}H_{20}IN_2O_2S$ requires 479.0285); ν_{max}: 3335, 3163, 3022, 2853, 1570, 1451, 1318, 1148, 695, 543 cm^{-1}; 7.60 (2H, d, *J* = 8.6 Hz, *o*-I ArH), 7.14 (2H, d, *J* = 8.6 Hz, *o*-SO_2 ArH), 7.12 - 7.05 (5H, m, ArH), 7.03 - 6.96 (3H, m, ArH), 6.96 - 6.90 (2H, m, ArH), 4.32 (1H, d, *J* = 7.2 Hz, SO_2NCH), 4.04 (2H, br. s., NH2), 3.96 (1H, d, *J* = 7.2 Hz, NCH); δ_C (101 MHz, $(CD_3)_2SO$): 142.4 (C_n), 140.8 (C), 139.6 (C), 137.3 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 127.2 (CH), 126.5 (CH), 126.4 (CH), 99.5 (CI), 64.8 (CH), 60.5 (CH); *m/z* (ESI-): 476.9 ([M - H]$^-$); (ESI+): 478.9 ([M + H]$^+$, 100%), 500.9 ([M + Na]$^+$, 27%).

N-((1R,2R)-2-amino-1,2-diphenylethyl)-4-iodobenzenesulfonamide p-cymeneruthenium chloride.

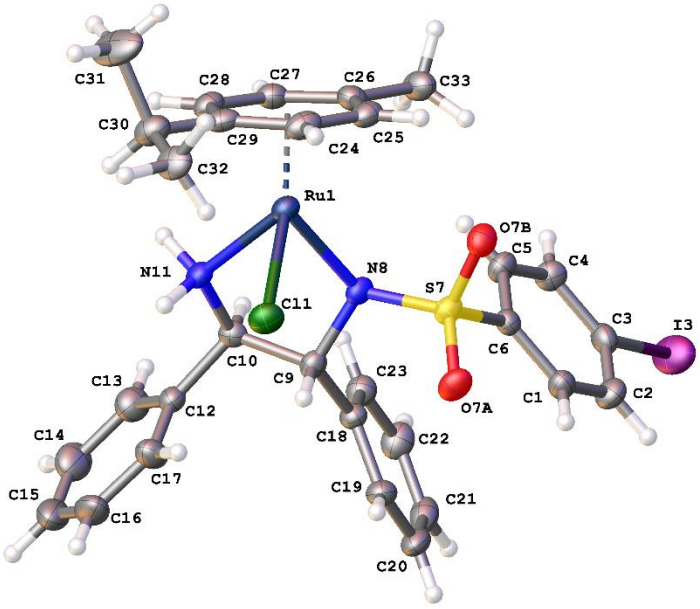


270

This compound is novel.

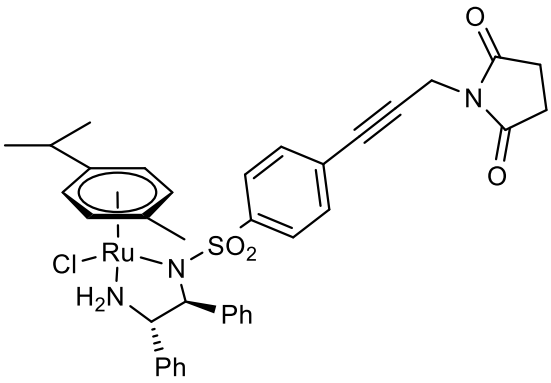
(R,R)-263 (196 mg, 0.41 mmol, 1.0 eq) and p-cymeneruthenium chloride dimer (122 mg, 0.20 mmol, 0.50 eq) were suspended in dry isopropanol (7 ml). Triethylamine (41 mg, 0.80 mmol, 2.0 eq) was added and the reaction mixture was heated to 40°C for 4.25 hours and monitored by TLC and LCMS. The brown precipitate was isolated by vacuum filtration and washed with isopropanol and water. Drying under high vacuum gave the product as an orange powder (210 mg, 70%).

TLC: 100% EtOAc, silica, Rf =0.1, I_2; Mp 230°C, decomposed; $[\alpha]_D^{22}$ -87.0 (*c* 0.022 in $CHCl_3$); HRMS: found (ESI): $[M - Cl]^+$, 713.0276. ($C_{30}H_{32}IN_2O_2{}^{102}RuS$ requires 713.0275); ν_{max}: 3293, 3212, 2954, 1568, 1472, 1382, 1275, 1132, 923, 816, 695 cm^{-1}; δ_H (500 MHz, methanol-d_4): 7.40 (2H, d, *J* = 8.4 Hz, *o*-I ArH), 7.16 - 7.08 (3H, m, Ph), 7.02 (2H, d, *J* = 8.5 Hz, *o*-SO_2 ArH), 6.92 (2H, dd, *J* = 2.7, 6.1 Hz, Ph), 6.86 (1H, t, *J* = 7.5 Hz, Ph), 6.72 (2H, t, *J* = 7.5 Hz, Ph), 6.62 (2H, d, *J* = 7.5 Hz, Ph), 5.73 (2H, s, Ru ArH), 5.66 (2H, s, Ru ArH), 3.94 (1H, d, *J* = 11.0 Hz, SO_2NCH), 3.71 (1H, d, *J* = 11.0 Hz, NHCH), 3.10 (1H, quin, *J* = 7.0 Hz, C*H*$(CH_3)_2$), 2.39 (3H, s, ArMe), 1.42 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_2$), 1.42 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_2$); δ_C (126 MHz, METHANOL-d_4): 145.5 (C), 139.3 (C), 138.2 (C), 136.4 (CH), 129.1 (CH), 128.4 (CH), 128.1 (CH), 127.7 (CH), 126.9 (CH), 126.9 (CH), 126.3 (CH), 104.3 (C), 95.3 (C or CI), 95.2 (C or CI), 85.0 (CH), 81.3 (CH), 81.2 (CH), 79.2 (CH), 71.8 (CH), 68.8 (CH), 30.5 (CH), 22.0 (CH_3), 20.6 (CH_3), 17.7 (CH_3); *m/z* (ESI): 713 ($[M - Cl]^+$), top peak of Ru Isotope pattern.



Crystal Data for $C_{30}H_{34}ClIN_2O_3RuS$ (*M* =766.07 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 6.10796(15) Å, *b* = 19.9093(6) Å, *c* = 25.1125(7) Å, *V* = 3053.80(14) Å^3, *Z* = 4, *T* = 150.01(10) K, μ(MoKα) = 1.714 mm^{-1}, *Dcalc* = 1.666 g/cm^3, 87583 reflections measured (5.222° ≤ 2Θ ≤ 63.088°), 9769 unique (R_{int} = 0.0902, R_{sigma} = 0.0631) which were used in all calculations. The final R_1 was 0.0493 (I > 2σ(I)) and wR_2 was 0.0956 (all data).

N-((1S,2S)-2-amino-1,2-diphenylethyl)-4-(3-(2,5-dioxopyrrolidin-1-yl)prop-1-yn-1-yl)benzenesulfonamide p-cymeneruthenium chloride



274

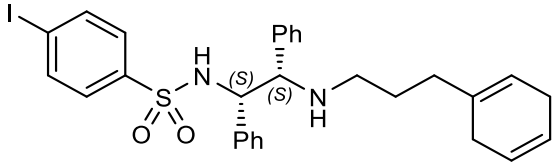
To a degassed suspension of **270** (187 mg, 0.25 mmol, 1.0 eq), $[PdCl_2(PPh_3)_2]$ (8.8 mg, 12.5 μmol, 5%), and CuI (4.8 mg, 25 μmol, 10%) in triethylamine (0.7 ml, 5 mmol, 20 eq) and THF (2.5 ml) was added **273** (103 mg, 0.75 mmol, 3.0 eq) in THF (1.7 ml). The reaction mixture was stirred at room temperature for 2 days, then filtered through Celite with acetonitrile (20

ml). The crude product was precipitated by the addition of diethyl ether and the excess solvent decanted. The remaining residue was dissolved in DCM (15 ml) and washed with water (2 x 15 ml) and $NaHCO_3$ (sat., 15 ml), dried over Na_2SO_4 and concentrated to give the crude product as a red solid (170 mg, 90%)

m/z (ESI): 722.2 ([M - Cl]$^+$), top peak of Ru Isotope pattern.

4.3.2 3C-Tethered Ips Complex

N-((1S,2S)-2-((3-(cyclohexa-1,4-dien-1-yl)propyl)amino)-1,2-diphenylethyl)-4-iodobenzenesulfonamide.



352

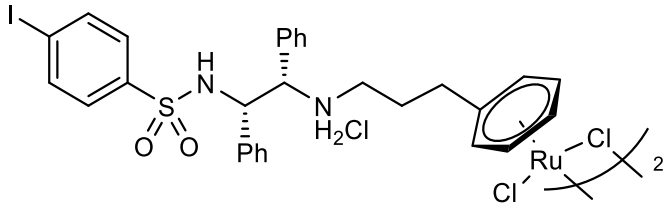
This compound is novel.

To a stirred solution of 3-cyclohexa-1,4-dienylpropan-1-ol (663 mg, 4.8 mmol) and 2,6-lutidine (675 mg, 6.3 mmol) in DCM (30 mL) at 0^{o}C was added dropwise a 1M solution of triflic anhydride in DCM (5.1 mL, 5.1 mmol). The resulting yellow solution was stirred for 30 mins at 0^{o}C and 1 hour at rt. To this a separate solution of **263** (1430 mg, 3.0 mmol) and triethylamine (729 mg, 7.2 mmol) in DCM (15 mL) was added dropwise at 0^{o}C. The reaction was stirred for 21 hours at room temperature, then diluted with EtOAc (30 ml) and concentrated to ~30 ml volume. The organic phase was washed with sat. $NaHCO_3$ solution (4 x 30 ml), water (2 x 30 ml) and brine (30 ml), dried (Na_2SO_4) and concentrated to give a yellow solid (1.81 g). The crude product was taken up in DCM (~10 ml) and hot EtOH, filtered through activated charcoal and concentrated by boiling until saturated. On cooling the product was isolated as white crystals by filtration. (1.16 g, 65%).

TLC: 50% EtOAc : Petroleum ether, silica, Rf =0.55 I_2 and CAM; Mp 141-142 °C; $[\alpha]_D^{25}$ -7.09 (*c* 0.55 in $CHCl_3$); HRMS: found (ESI): [M + H]$^+$, 599.1235. ($C_{29}H_{32}IN_2O_2S$ requires 599.1224); ν_{max}: 3291, 2819, 1568, 1428, 1327, 1160, 1051, 811, 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.57 - 7.50 (2H, app d, *J* = 8.7 Hz, ArH, *o*-I ArH), 7.19 - 7.03 (8H, m, ArH), 7.02 - 6.93 (4H, m, ArH), 6.40 (1H, br. s., SO_2NH), 5.74 - 5.66 (2H, m, HC=CH), 5.30 (1H, br. s., CC=CH), 4.31 (1H, d, *J* = 7.5 Hz, SO_2NCH), 3.65 (1H, d, *J* = 7.3 Hz, CH_2NCH), 2.71 - 2.59 (2H, m, diene CH_2), 2.57 - 2.47 (2H, m, diene CH_2), 2.47 - 2.36 (1H, m, NC*H*H), 2.32 - 2.23 (1H, m, NCH*H*), 1.94 - 1.81 (2H, m, 2H, m, =CCH_2CH_2), 1.62 - 1.39 (2H, m, CH_2); δ_C (126 MHz, $CDCl_3$): 139.8 (C), 139.1 (C), 138.0 (C),

137.6 (CH), 134.2 (C), 128.4 (CH), 128.1 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 124.2 (CH), 124.2 (CH), 118.7 (CH), 99.3 (CI), 67.5 (CH), 63.1 (CH), 46.6 (CH_2), 34.8 (CH_2), 28.8 (CH_2), 27.4 (CH_2), 26.7 (CH_2); m/z (ESI): 599.0 ([M + H]+), 600.0 (M+1, 33%), 601.0 (M+2, 10%).

N-((1S,2S)-1,2-diphenyl-2-((3-phenylpropyl)amino)ethyl)-4-iodobenzenesulfonamide ruthenium(II) chloride dimer



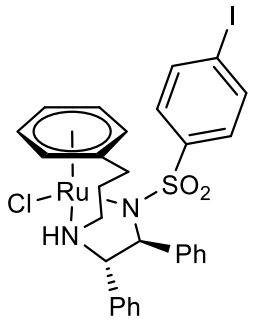
353

This compound is novel.

To an ice-cold degassed solution of **352** (748 mg, 1.25 mmol, 1.25 eq) in DCM (25 mL) was added dry HCl (1M in diethyl ether, 5 mL, 5 mmol, 5 eq). The reaction mixture was allowed to warm to rt and stirred for 30 minutes before being concentrated to dryness. $RuCl_3 . xH_2O$ (261 mg, 1 mmol, 1 eq assuming x = 3) was added and the solids suspended in dry ethanol (30 ml). The reaction mixture was degassed and heated to reflux (80°C) for 19 hours before being concentrated to dryness. The resulting green residue was triturated in diethyl ether and filtered to collect the dimer as a dark green powder (964 mg, 96% from ligand). No further purification was attempted at this stage, the crude dimer was carried forwards directly to the next step.

Mp >200 °C (decomposed, melts at >250 °C); $[\alpha]_D$ Not determined; absorbance too high; ν_{max}: 3062, 2880, 1567, 1457, 1383, 1159, 734, 697, 599, 552 cm^{-1}; δ_H (500 MHz, $(CD_3)_2SO$): 9.73 (1H, br. s., N*H*H), 9.16 (1H, br. s., NH*H*), 9.05 - 8.88 (1H, m, SO_2NH), 7.55 (2H, d, *J* = 8.4 Hz, *o*-I ArH), 7.30 (2H, s, Ph), 7.23 - 7.17 (3H, m, Ph), 7.13 (2H, d, *J* = 8.4 Hz, *o*-SO_2 ArH), 6.92 - 6.87 (1H, m, Ph), 6.86 - 6.78 (4H, m, Ph), 5.99 (2H, q, *J* = 5.7 Hz, Ru ArH), 5.77 (2H, q, *J* = 5.7 Hz, Ru ArH), 5.70 (1H, d, *J* = 5.7 Hz, Ru ArH), 4.85 - 4.75 (1H, m, SO_2NCH), 4.58 (1H, m, CH_2NCH), 2.90 - 2.77 (1H, m, NC*H*H), 2.76 - 2.66 (1H, m, NCHH), 2.45 - 2.34 (1H, m, $ArCH_2$, overlaps with DMSO), 2.12 - 1.93 (2H, m, CH2); δC (126 MHz, $CDCl_3$): 157.7 (C-OMe), 139.8 (C), 139.1 (C), 137.9 (C), 137.6 (CH), 133.9 (C), 129.2 (CH), 128.4 (CH), 128.4 (CH), 128.1 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 113.8 (CH), 99.2 (C-I), 67.5 (CH), 63.1 (CH), 55.2 (OCH_3), 46.3 (CH_2), 32.4 (CH_2), 31.5 (CH_2); m/z (ESI): 627.1 ([1/2M -2H -3Cl]+).

N-((1S,2S)-1,2-diphenyl-2-((3-phenylpropyl)amino)ethyl)-4-iodobenzenesulfonamide ruthenium (II) chloride complex.



354

This compound is novel.

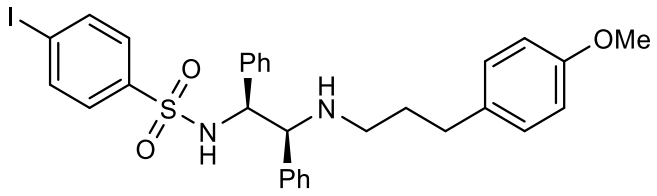
To a suspension of dimer **353** (800 mg, 0.5 mmol, 0.5 eq) in dry isopropanol (25 ml) was added triethylamine (0.42 mL, 3 mmol, 3 eq). The reaction mixture was degassed, heated to 40 °C and stirred for 6 hours before the isopropanol was removed under vacuum. The residue was dissolved in DCM (50 ml) and washed with water (3 x 100 ml), dried over Na_2SO_4 and concentrated. The crude product was partially purified by column chromatography on silica (gradient elution, methanol/DCM, 0-10%) to give a brown/orange residue. This was dissolved in a minimum volume of DCM, diluted with ~4 volumes of ethanol and heated to 60 °C with nitrogen bubbling through the solution for 4 hours. The resulting saturated ethanolic solution was then kept in the fridge for several days and the orange crystalline solid was filtered off to yield the pure product (93 mg, 13%).

TLC: 60% (3:1 EtOAc/EtOH)/Petroluem ether, silica, Rf, = 0.2, I_2; Mp 200 °C (decomposed, slow melt up to 230 °C); $[\alpha]_D^{29}$ 216 (c 0.022 in $CHCl_3$); HRMS: found (ESI): $[M - Cl]^+$, 696.9983. ($C_{29}H_{28}IN_2O_2{}^{102}RuS$ requires 696.9961); $\nu_{max.}$ 3191, 3059, 3027, 2935, 1567, 1453, 1280, 1265, 1131, 1081, 937, 905, 835, 697 cm^{-1}; 7.38 (2H, d, *J* = 8.3 Hz, *o*-I ArH), 7.13 - 7.08 (3H, m, Ph), 7.07 (2H, d, *J* = 8.3 Hz, *o*-SO_2 ArH), 6.87 (1H, t, *J* = 7.4 Hz, Ph), 6.77 (2H, d, *J* = 6.7 Hz, Ph), 6.73 (2H, t, *J* = 7.4 Hz. Ph), 6.59 (2H, d, *J* = 7.4 Hz, Ph), 6.23 (1H, t, *J* = 5.3 Hz, Ru ArH), 6.21 - 6.15 (2H, m, Ru ArH), 5.26 (1H, d, *J* = 4.9 Hz, Ru ArH), 5.06 (1H, d, *J* = 5.2 Hz, Ru ArH), 4.49 - 4.40 (1H, m, NH), 4.05 (1H, d, *J* = 11.3 Hz, SO_2NCH), 3.67 (1H, t, *J* = 11.3 Hz, CH_2NCH), 2.84 (1H, ddd, *J* = 4.1, 9.1, 13.1 Hz, NC*H*H), 2.68 (1H, td, *J* = 6.6, 13.1 Hz, NCH*H*), 2.54 (1H, ddd, *J* = 3.6, 6.9, 13.0 Hz), 2.31 (1H, ddd, *J* = 3.4, 9.1, 13.0 Hz, ArCH*H*), 2.25 - 2.11 (1H, m, C*H*H), 2.03 - 1.93 (1H, CH*H*); δ_C (126 MHz, $CDCl_3$): 144.8 (C), 138.6 (C), 136.4 (CH), 136.3 (C), 129.0 (CH), 129.0 (CH), 128.7 (CH), 128.4 (CH), 127.5 (CH), 127.0 (CH), 126.6 (CH), 99.3 (C), 96.0 (CI), 93.1 (CH),

91.6 (CH), 82.5 (CH), 78.8 (CHN), 78.1 (CH), 73.4 (CH), 69.0 (CHN), 48.6 (CH_2), 29.6 (CH_2), 26.7 (CH_2); m/z (ESI): 697.0 ([M - Cl]+), top peak of Ru Isotope pattern.

4.3.3 OMe-Tethered Ips Complex

4-iodo-N-((1S,2S)-2-((3-(4-methoxyphenyl)propyl)amino)-1,2-diphenylethyl)benzenesulfonamide



355

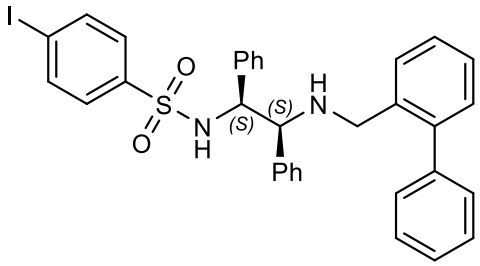
This compound is novel

To a stirred solution of 3-(4-methoxyphenyl)-propan-1-ol (798 mg, 4.8 mmol) and 2,6-lutidine (675 mg, 6.3 mmol) in DCM (30 mL) at 0 °C was added dropwise a 1M solution of triflic anhydride in DCM (5.5 mL, 5.5 mmol). The resulting pink solution was stirred for 30 mins at 0 °C and 1 hour at rt. To this a separate solution of **263** 1430 mg, 3.0 mmol) and triethylamine (729 mg, 7.2 mmol) in DCM (15 mL) was added dropwise at 0°C. The reaction was stirred for 21 hours at room temperature, then diluted with EtOAc (30 mL) and concentrated to ~30 ml volume. The organic phase was washed with sat. $NaHCO_3$ solution (4x 30 mL), water (2x 30 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated to give a yellow solid (1.73 g). The crude product was taken up in DCM (~10 ml) and hot EtOH, filtered through activated charcoal and concentrated by boiling until saturated. On cooling the product was isolated as white crystals by filtration. (625 mg, 33%).

TLC: 50% EtOAc : Petroleum ether, silica, Rf =0.55 I_2 and CAM; Mp 122-124 °C; $[\alpha]_D^{26}$ -4.56 (*c* 0.44 in $CHCl_3$); HRMS: found (ESI): $[M + H]^+$, 627.1176. ($C_{30}H_{32}IN_2O_3S$ requires 627.1173); ν_{max}: 3305 (br), 2926, 1567, 1510, 1242, 1161, 1036, 811, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$):7.54 (2H, d, *J* = 8.5 Hz, *o*-I ArH), 7.20 - 7.04 (8H, m, *o*-SO_2 ArH + Ph), 7.03 - 6.92 (6H, m, *o*-CH_2 ArH + Ph), 6.86 - 6.78 (2H, d, *J* = 8.5 Hz, *o*-OMe ArH), 6.62 - 6.13 (1H, br.s, SO_2NH), 4.33 (1H, d, *J* = 7.3 Hz, SO_2NCH), 3.80 (3H, s, OCH_3), 3.64 (1H, d, *J* = 7.5 Hz, CH_2NCH), 2.56 - 2.40 (3H, m, $ArCH_2$ + NHC*H*H), 2.36 - 2.23 (1H, m, NHCH*H*), 1.76 - 1.59 (2H, m, CH_2); δ_C (126 MHz, $CDCl_3$): 157.7 (C-OMe), 139.8 (C), 139.1 (C), 137.9 (C), 137.6 (CH), 133.9 (C), 129.2 (CH), 128.4 (CH), 128.4 (CH), 128.1 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 113.8 (CH), 99.2 (C-I), 67.5 (CH), 63.1 (CH),

55.2 (OCH_3), 46.3 (CH_2), 32.4 (CH_2), 31.5 (CH_2); *m/z* (ESI): 627.1 ($[M + H]^+$), 628.1 (M+1, 34%), 629.1 (M+2, 10%).

N-((1S,2S)-2-(([1,1'-biphenyl]-2-ylmethyl)amino)-1,2-diphenylethyl)-4-iodobenzenesulfonamide



356

This compound is novel.

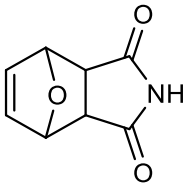
To **263** (475 mg, 0.99 mmol, 1.0 eq) and 4Å molecular sieves (500 mg) was added a solution of biphenyl-2-carboxaldehyde (214 mg, 1.17 mmol, 1.15 eq) in dry methanol (20 ml). Acetic acid (60 mg, 1.00 mmol, 1.0 eq) was added and the reaction mixture stirred at room temperature under nitrogen for 6 hours and monitored by TLC. Then sodium cyanoborohydride (261 mg, 4.15 mmol, 4.15 eq) was added in one portion and the reaction mixture stirred for 3 days. The mixture was filtered through Celite, concentrated and suspended in NaOH (1M, 40 mL) and extracted with DCM (3x 40 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give the crude product as a clear oil. This was suspended in pentane and stirred, decanting off the pentane gave the product as a white solid (526 mg, 82%).

Mp 131-133 °C; $[\alpha]_D^{26}$ +13.5 (c 0.46 in $CHCl_3$); HRMS: found (ESI): $[M + H]^+$, 645.1067. ($C_{33}H_{30}IN_2O_2S$ requires 645.1067); ν_{max}: 3275, 3058, 1570, 1411, 1325, 1162, 1087, 760, 731, 701 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.49 (2H, d, *J* = 8.0 Hz, *o*-I ArH), 7.38 - 7.29 (5H, m, ArH), 7.22 - 7.12 (4H, m, ArH), 7.12 - 7.04 (8H, m, ArH), 6.90 (2H, d, *J* = 7.3 Hz, ArH), 6.77 (2H, d, *J* = 7.3 Hz, ArH), 5.98 (1H, br. s., SO_2NH) 4.21 (1H, d, *J* = 5.8 Hz, SO_2NCH), 3.59 - 3.51 (1H, d, *J* = 5.8 Hz, CH_2NCH, + 1H, d, *J* = 12.5 Hz, CH*H*), 3.29 (1H, d, *J* = 12.5 Hz, C*H*H), 1.38 (1H, br. s. RNH); δ_C (126 MHz, $CDCl_3$): 142.2 (C), 141.1 (C), 139.8 (C), 138.6 (C), 138.1 (C), 137.6 (2* CH), 136.6 (C), 130.3 (CH), 129.7 (CH), 128.8 (2* CH), 128.4 (2* CH), 128.3 (2* CH), 128.2 (2* CH), 127.5 (CH), 127.5 (CH), 127.5 (CH), 127.3 (CH), 127.3 (2* CH), 127.3 (2* CH), 127.0 (CH), 99.3 (C-I),

67.0 (CH), 63.1 (CH), 49.0 (CH_2); *m/z* (ESI): 645.1 ($[M + H]^+$), 646.1 (M+1, 37%), 647.1 (M+2, 11%).

4.3.4 N-TsDPEN furan maleimide adducts

3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione



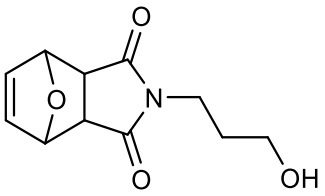
245

This compound is known.[112]

To a solution of maleimide (1.94 g, 20 mmol, 1.0 eq) in dry diethyl ether (15 mL) was added Furan (2.04 g, 30 mmol, 1.5 eq) in a pressure tube under nitrogen flow. The tube was sealed and heated to 100 °C, and stirred for 20 hours. After cooling to room temperature, the white precipitate was collected by filtration, washed with cold diethyl ether and dried to give the product as a white powder (2.72 g, 82%).

TLC: 80% EtOAc/Pet Ether, silica, R_f = 0.45, I_2; Mp 163-164 °C; HRMS: (found (ESI): $[M - H]^-$, 164.0342. $C_8H_6NO_3$ requires 164.0353); ν_{max} 3145, 3062, 1700, 1187, 633cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.93 (1H, br. s., NH), 6.50 (2H, s, HC=CH), 5.30 (2H, s, O-CH), 2.87 (2H, s, COCH); δ_H (300 MHz, D_2O): 6.56 (2H, s, HC=CH), 5.27 (2H, s, O-CH), 3.07 (2H, s, COCH); δ_C (75 MHz, D_2O): 180.6 (C), 136.3 (CH), 80.8 (CH), 48.6 (CH); *m/z* (ESI) 164 ($[M - H]^-$).

2-(3-hydroxypropyl)-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione.



Exact Mass: 223.08

246

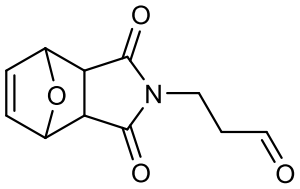
This compound is known.[144]

To a stirred solution of **245** (500 mg, 3.03 mmol, 1 eq) and potassium carbonate (502 mg, 3.63 mmol, 1.2 eq) in acetone (30 ml) was added 3-bromo-1-propanol (504 mg, 3.65 mmol,

1.2 eq) dropwise at room temperature. The reaction mixture was stirred for 5 days under nitrogen and monitored by TLC. The mixture was filtered, concentrated and suspended in pentane (25 ml) and stirred for 45 mins. The pentane was decanted and the remaining solid dried under vacuum to give the product as a white free flowing powder (670 mg, 3.00 mmol, 99%).

TLC: 80% EtOAc/Pet Ether, silica, R_f = 0.20, I_2 and $KMNO_4$; Mp 107-111 °C (melt then decomposed); HRMS found (ESI): $[M + Na]^+$, 246.0735. ($C_{11}H_{13}NNaO_4$ requires 246.0737); ν_{max} 3505 (br), 2946, 1684, 1155, cm^{-1}; δ_H (250 MHz, $CDCl_3$): 6.52 (2H, t, *J* = 1 Hz, HC=CH), 5.27 (2H, t, *J* = 1 Hz, O-CH), 3.65 (2H, t, *J* = 6.5 Hz, NCH2), 3.52 (2H, q, *J* = 6.5 Hz, CH2), 2.87 (2H, s, COCH), 2.47 (1H, t, *J* = 6.5 Hz, OH), 1.77 (2H, m, CH2); δ_C (101 MHz, $CDCl_3$): 177.0 (C=O), 136.5 (CH), 81.0 (CH), 58.6 (CH_2), 47.5 (CH), 35.2 (CH_2), 30.3 (CH_2); *m/z* (ESI): 246 ($[M + Na]^+$).

3-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-epoxyisoindol-2-yl)propanal.



247

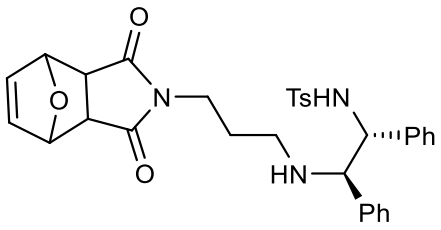
This compound is novel.

To a 2 neck rbf fitted with dropping funnel and septum was added oxalyl chloride (2M in DCM, 2.5 ml, 5 mmol, 2.5 eq). The flask was cooled to -78 °C and DMSO (0.35 ml, 5 mmol, 2.5 eq) in DCM (3 ml) was added dropwise over 5 minutes and the reaction stirred for 15 minutes. Compound **246** (440 mg, 1.97 mmol, 1 eq) in DCM (2 ml) was then added dropwise over 10 minutes and the reaction mixture stirred for 1 hour. Triethylamine (1.65 ml, 12 mmol, 6 eq) was added dropwise over 10 minutes and the reaction mixture was then warmed to room temperature and stirred for 1.25 hours before quenching with water (5 ml). The mixture was extracted with DCM (15 ml), dried (Na_2SO_4) and concentrated to give the crude product as a yellow solid. Flash chromatography on silica gel using ethyl acetate/petroleum ether (60-75%) gave the purified product as a white crystalline solid (251 mg, 1.13 mmol, 57%).

TLC: 100% EtOAc, silica, R_f = 0.4, I_2 and $KMNO_4$; Mp 114-118 °C (melted then decomposed); HRMS found (ESI): $[M + Na]^+$, 244.0583. ($C_{11}H_{11}NNaO_4$ requires 244.0580); ν_{max} 2852, 1716, 1690, 1169, cm^{-1}; δ_H (300 MHz, $CDCl_3$): 9.70 (1H, t, *J* = 1.2 Hz, CHO), 6.48 (2H, s, C=CH), 5.23

(2H, s, O-CH), 3.78 (2H, t, *J* = 7.1 Hz, NCH_2), 2.82 (2H, s, COCH), 2.72 (2H, td, *J* = 7.2, 1.1 Hz, C*H*$_2$CHO); δ_C (75 MHz, $CDCl_3$): 198.5 (CHO), 175.3 (C=O), 135.9 (CH), 80.3 (CH), 46.8 (CH), 40.8 (CH_2), 31.9 (CH_2); *m/z* (ESI) 244 ($[M + Na]^+$).

N-((1R,2R)-2-((3-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-epoxyisoindol-2-yl)propyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide.



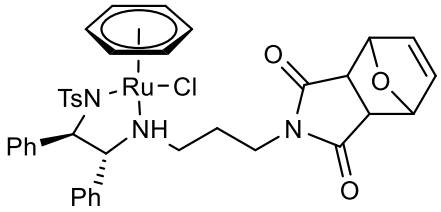
248

This compound is novel.

To (*R,R*) TsDPEN (187 mg, 0.51 mmol, 1 eq) and 4Å molecular sieves (480 mg) was added a solution of **247** (127 mg, 0.575 mmol, 1.15 eq) in dry methanol (10 ml). Acetic acid (0.05 ml, 0.87 mmol, 1.75 eq) was added and the reaction mixture stirred at room temperature under nitrogen for 3 hours and monitored by TLC. Then sodium cyanoborohydride (135 mg, 2.15 mmol, 4 eq) was added in one portion and the reaction mixture stirred for 45 hours and monitored by TLC. The mixture was filtered through Celite, concentrated and partitioned between DCM (20 ml) and NaOH (1M, 10 ml), followed by extraction with DCM (20 ml). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give the crude product as a white solid. This was suspended in pentane and stirred, decanting off the pentane gave the product as a white solid (282 mg, 0.49 mmol, 97%).

TLC: 100% EtOAc, silica, R_f = 0.5, I_2; Mp 135 °C (dec); $[\alpha]_D^{25}$ = -12.5 (*c* 0.51 in $CHCl_3$); HRMS found (ESI): $[M + H]^+$, 572.2212. $C_{32}H_{34}N_3O_4S$ requires 572.2214); ν_{max} 3505 (br), 2946, 1684, 1155 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.44 (2H, d, *J* = 8.5 Hz, ArH), 7.15 - 7.08 (3H, m, ArH), 7.08 - 6.94 (5H, m, ArH), 6.93 - 6.83 (4H, m, ArH), 6.51 (2H, s, HC=CH), 5.25 (1H, s, OCH), 5.20 (1H, s, OCH), 4.24 (1H, d, *J* = 8.5 Hz, NCHPh), 3.65 - 3.39 (3H, m, NCHPh and NCH_2), 2.84 (2H, s, COCH), 2.34 (4H, m, $ArCH_3$ and NHCH*H'*), 2.29 - 2.13 (1H, m, *J* = 8.5 Hz, NHC*H*H'), 1.65 (2H, m, CH_2) ; δ_C (176 MHz, $CDCl_3$): 176.6 (C=O), 176.5 (C=O), 142.7 (C), 139.1 (C), 138.3 (C), 137.2 (C), 136.5 (CH), 129.1 (CH), 128.2 (CH), 127.8 (CH), 127.7 (CH), 127.7 (CH), 127.5 (CH), 127.4 (CH), 127.2 (CH), 81.0 (CH), 80.9 (CH), 68.0 (CH), 63.2 (CH), 47.4 (CH), 47.4 (CH), 43.5 (CH_2), 36.4 (CH_2), 27.5 (CH_2), 21.5 (CH_3); *m/z* (ESI): 572 ($[M + H]^+$).

N-((1R,2R)-2-((3-(1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-epoxyisoindol-2-yl)propyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide benzeneruthenium chloride.



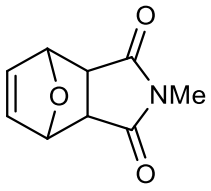
250

This compound is novel.

Compound **248** (117 mg, 0.2 mmol, 1 eq) and benzeneruthenium chloride dimer (51 mg, 0.2 mmol, 0.5 eq) were dissolved in dry isopropanol (7 ml). Triethylamine (41 mg, 0.41 mmol, 2 eq) was added and the reaction mixture was heated to 80 °C for 22 hours and monitored by TLC. The reaction mixture was concentrated to give the crude product as a brown residue. Flash chromatography on silica gel using methanol/ethyl acetate (2-10% gradient) gave an impure product as an orange solid (37 mg). The product was too impure to be fully characterised but evidence for its formation occurs in LCMS and ^{1}H NMR

Selected ^{1}H peaks: δ_H (400 MHz, $CDCl_3$): 7.30 (2H, d, *J* = 8.0 Hz, ArH), 7.15 - 7.09 (4H, m, ArH), 6.84 (3H, d, *J* = 8.0 Hz, ArH), 6.76 (2H, t, *J* = 7.5 Hz, ArH), 6.68 (2H, d, *J* = 6.8 Hz, ArH), 6.58 (2H, d, *J* = 7.5 Hz, ArH), 6.54 - 6.48 (2H, m, HC=CH), 5.88 - 5.84 (6H, s, RuC_6H_6), 5.22 (2H, d, *J* = 6.8 Hz, OCH), 3.98 (1H, d, *J* = 11.0 Hz, NCHPh), 3.85 (1H, t, *J* = 11.0 Hz, NCHPh), 3.56 (2H, t, *J* = 11.0 Hz, CH_2), 2.89 - 2.82 (2H, m, CH_2), 2.23 (3H, s, CH_3); *m/z* (ESI): 750 ($[M - Cl]^+$).

2-methyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione



254

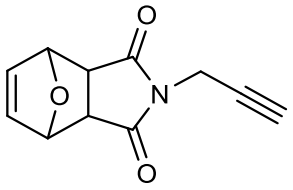
This compound is known.[145]

To a solution of N-methyl maleimide (2.22 g, 20 mmol, 1.0 eq) in dry diethyl ether (15 mL) was added furan (2.04 g, 30 mmol, 1.5 eq) in a pressure tube under nitrogen flow. The tube was sealed and heated to 100 °C, and stirred for 20 hours. After cooling to room

temperature, the white precipitate was collected by filtration, washed with cold diethyl ether and dried to give the product as a white powder (2.72 g, 82%).

Mp 144-145 °C; ν_{max}: 3013, 1759, 1685, 1440, 1378, 1283, 1139, 1017, 877 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 6.52 (2H, s, HC=CH), 5.27 (2H, s, 2x OCH), 2.98 (3H, s, NCH_3), 2.88 - 2.82 (2H, s, 2x COCH); δ_C (75 MHz, $(CD_3)_2SO$): 176.6 (C=O), 136.4 (CH), 80.2 (CH), 47.3 (CH), 24.3 (CH_3).

2-(prop-2-yn-1-yl)-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione



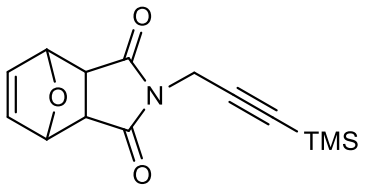
256

This compound is known.[146]

To a stirred solution of **245** (448 mg, 2.71 mmol, 1.0 eq) and potassium carbonate (454 mg, 3.28 mmol, 1.2 eq) in acetone (27 ml) was added propargyl bromide (80 wt. % in toluene) (449 mg, 3.02 mmol, 1.1 eq) dropwise at room temperature. The reaction mixture was stirred for 3 days under nitrogen and monitored by TLC. The mixture was filtered, concentrated, and dried to give the product as an off-white free flowing powder (550 mg, 100%).

TLC: 80% EtOAc/Pet Ether, silica, R_f = 0.55, I_2; Mp 153-154 °C; ν_{max}: 3255, 1775, 1698, 1411, 1335, 1182, 875cm^{-1}; δ_H (250 MHz, $CDCl_3$): 6.53 (2H, t, *J* = 0.9 Hz, C=CH), 5.30 (2H, t, *J* = 0.9 Hz, OCH), 4.24 (2H, d, *J* = 2.6 Hz, CH_2), 2.91 (2H, s, COCH), 2.20 (1H, t, *J* = 2.6 Hz, C≡CH); δ_C (75 MHz, $CDCl_3$): 174.2 (C=O), 136.0 (CH), 80.3 (CH), 75.8 (CH), 70.8 (C), 47.0 (CH), 27.9 (CH_2).

2-(3-(trimethylsilyl)prop-2-yn-1-yl)-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione



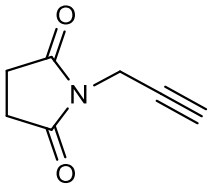
257

This compound is known.[147]

To a stirred solution of **245** (658 mg, 3.99 mmol, 1.0 eq) and potassium carbonate (659 mg, 4.77 mmol, 1.2 eq) in acetone (40 mL) was added 3-bromo-1-(trimethylsilyl)-1-propyne (910 mg, 4.76 mmol, 1.2 eq) dropwise at room temperature. The reaction mixture was stirred for 3 days under nitrogen, then filtered through Celite, concentrated, and dried to give the product as a white crystalline powder (1067 mg, 97%).

δ_H (300 MHz, $CDCl_3$): 6.53 (2H, s, HC=CH), 5.30 (2H, s, 2 x OCH), 4.24 (2H, s, CH_2), 2.91 (2H, s, COCH), 0.14 (9H, s, $Si(CH_3)_3$); δ_C (101 MHz, $CDCl_3$): 174.8 (C=O), 136.6 (CH), 97.7 (C), 88.2 (C), 80.9 (CH), 47.6 (CH), 28.9 (CH_2), -0.3 ($SiCH_3$)

1-(prop-2-yn-1-yl)pyrrolidine-2,5-dione.



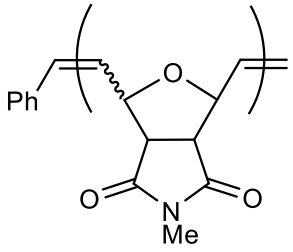
273

This compound is known.[148]

Succinimide (1.00 g, 10.1 mmol, 1.0 eq) and potassium carbonate (1.66 g, 12.0 mmol, 1.2 eq) were suspended in acetone (50 ml) under N_2. Propargyl bromide (80 wt.% in toluene) (1.85 g, 12.0 mmol, 1.2 eq) was added dropwise at room temperature and the reaction mixture was stirred for 3 days. The mixture was filtered through Celite with 100 ml acetone and concentrated to give the crude product as an orange oil (1.00 g, 73%). Combining multiple batches, Kugelrohr distillation at 160-165 ^oC, 1 mbar, gave 2.525 g from 3.022 g of crude (91% assay, final yield 66%)

TLC: 60% EtOAc/Petroleum ether, silica, Rf = 0.35, I_2 and $KMNO_4$; δ_H (300 MHz, $CDCl_3$): 4.25 (2H, d, *J* = 2.5 Hz, NCH_2), 2.74 (4H, s, CH_2CH_2), 2.17 (1H, t, *J* = 2.5 Hz, CH); δ_C (75 MHz, $CDCl_3$): 173.9 (C=O), 74.7 (CH), 69.5 (C), 26.3 (CH_2), 25.8 (CH_2)

Poly(2-methyl-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione)



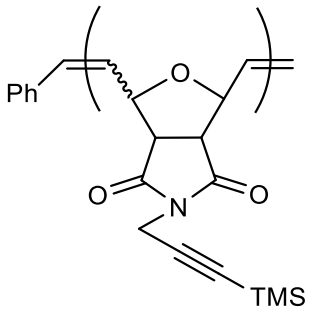
255

This compound is known[145]

To a solution of **254** (90 mg, 0.5 mmol, 100 eq) in DCM (1 ml) was added a solution of Grubbs 1st generation catalyst (4.1 mg, 0.005 mmol, 1.0 eq) in DCM (1 ml). The reaction mixture was stirred under nitrogen for 1.5 hours, then quenched by the addition of ethyl vinyl ether (0.1 ml) and stirred for 3 hours. Hexane (5 ml) was added and the volatiles removed by rotary evaporation to give the polymer as a grey powder (111 mg, 122%). Ratio of *cis*/*trans* double bonds by ^{1}H NMR is 0.25:0.75

δ_H (400 MHz, $(CD_3)_2SO$): 5.96 (1.5H, br. s., *trans*-HC=CH), 5.73 (0.5H, br. s., *cis*-HC=CH), 4.86 (0.5H, br. s., *cis*-OCH), 4.45 (1.5H, br. s., *trans*-OCH), 3.39 (2H, br. s., COCH), 2.83 (3H, br. s., CH_3)

Poly(2-(3-(trimethylsilyl)prop-2-yn-1-yl)-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione)



258

This compound is unknown but related compounds have been prepared.[146]

To a solution of **257** (275 mg, 1 mmol, 200 eq) in DCM (2 ml) was added a solution of Grubbs 1st generation catalyst (4.1 mg, 0.005 mmol, 1.0 eq) in DCM (1 ml). The reaction mixture was stirred under nitrogen for 3 hours, then quenched by the addition of ethyl vinyl ether (0.1

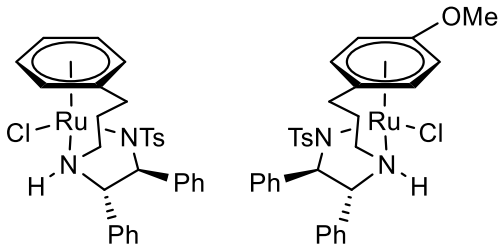
ml) and stirred for 3 hours. Hexane (5 ml) was added and the volatiles removed by rotary evaporation to give the polymer as a grey powder (274 mg, 99%). Ratio of *cis*/*trans* double bonds by ^{1}H NMR is 0.3:0.7.

δ_H (400 MHz, $(CD_3)_2SO$): 5.96 (1.4H, br. s., *trans*-HC=CH), 5.75 (0.6H, br. s., *cis*-HC=CH), 4.83 (0.6H, br. s., *cis*-OCH), 4.42 (1.4H, br. s., *trans*-OCH), 4.19 (2H, br. s., NCH_2), 3.49 (2H, br. s., COCH), 0.12 (9H, br. s., $Si(CH_3)_3$)

4.4 Preparation of Compounds, Electron Rich Ketones:

4.4.1 Formic Acid and Aqueous Reductions

All reductions were carried out with **3C-teth (80)** or **OMe-teth (115)** catalysts.



4.4.1.1 General Method 1: FA/TEA Reductions

Catalyst (5 µmol, 200:1 S/C) was dissolved in FA/TEA (5:2, 0.5 ml) and stirred at 40°C for 30 mins. Substrate (1 mmol, 1.0 eq) was added and the reaction monitored by TLC. On completion the reaction mixture was filtered through a silica plug with 50 % EtOAc in petroleum ether. The organic phase was washed with $NaHCO_3$ (sat.), dried (Na_2SO_4) and concentrated to yield the crude alcohol. Conversion was determined by NMR, ee by chiral GC or HPLC. If required the crude product was purified by flash chromatography.

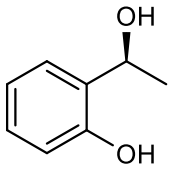
4.4.1.2 General Method 2: Aqueous Reduction

Sodium formate (340 mg, 5.0 mmol, 5.0 eq), catalyst (0.005 µmol, 200:1 S/C) and substrate (1.0 mmol, 1.0 eq) were suspended in water (1 mL), degassed and heated to 60 °C with fast stirring. On completion, the reaction mixture was diluted with water (2 mL) and extracted with ethyl acetate (3 x 2 mL), and the organic extracts dried over Na_2SO_4 and concentrated. The crude was dissolved in diethyl ether and passed through a short silica plug to yield the product. Conversion was determined by NMR, ee by chiral GC or HPLC.

4.4.1.3 General Method 3: Racemic Reductions

To a solution of Ketone (0.1 mmol, 1.0 eq) in methanol (0.5 ml) was added in one portion sodium borohydride (7-14 mg, 2-4 eq). The mixture was stirred in a vial until complete conversion by TLC, or overnight. On completion the mixture was partitioned between ethyl acetate and water. An aliquot of the organic phase filtered through a short silica plug in a pipette and taken directly for analysis by chiral chromatography. The product was not isolated.

(S)-2-(1-hydroxyethyl)phenol



357

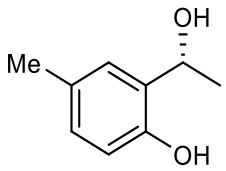
This compound is known[62].

FA/TEA reduction: See general method 1. With (*S*,*S*)-**3C-teth (80)**; 4 hours reaction time, >99% conversion and 99% ee. With (*R*,*R*)-**OMe-teth (115)**; 5.5 hours reaction time, >99% conversion and 99% ee.

Aqueous reduction: See general method 2. With (*S,S*)-**3C-teth (80)**; 4.5 hours reaction time, 99% conversion and 23% ee. With (*R,R*)-**OMe-teth (115)**;4.25 hours reaction time, 33% conversion and 63% ee.

(*S*) Configuration for product from reduction with (*S*,*S*)-**80** assigned by comparison with literature optical rotation. The opposite enantiomer is produced by reduction with (*R*,*R*)-**115**. TLC: 50% EtOAc/Pet Ether, silica, R_f = 0.5, I_2 and $KMNO_4$; $[\alpha]_D^{32}$ -20.9 (*S*), 99% ee (*c* 0.42 in $CHCl_3$); lit $[\alpha]_D^{32}$ +22.3 (*R*), 99% ee (c 0.65 in solvent); δ_H (300 MHz, $CDCl_3$): 7.91 (1H, s, ArOH), 7.21 - 7.12 (1H, m, ArH), 6.97 (1H, dd, *J* = 1.6, 7.4 Hz, ArH), 6.90 - 6.78 (2H, m, ArH), 5.07 (1H, dq, *J* = 4.0, 6.6 Hz, C*H*OH), 2.43 (1H, d, *J* = 4.0 Hz, CHO*H*), 1.58 (3H, d, *J* = 6.6 Hz, CHCH_3); δ_C (101 MHz, $CDCl_3$): 155.3 (C), 128.9 (CH), 128.5 (C), 126.5 (CH), 119.9 (CH), 117.0 (CH), 71.5 (CH), 23.4 (CH_3); Chiral HPLC (Chiralpak IA Column: (0.46 x 25 cm), 1 ml/min, 10% IPA : 90% Hexane; 256 nm UV, 30 °C), retention times: 7.18 (*S*) and 7.42 (*R*) minutes.

(R)-2-(1-Hydroxyethyl)-4-methylphenol.



358

This compound has been reported in racemic form.[144] The optical rotation for the asymmetric form has not been reported.[149]

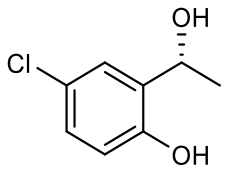
FA/TEA reduction: See general method 1. With (*S*,*S*)-**3C-teth (80)**; 5.5 hours reaction time, 99% conversion and 94% ee. With (*R*,*R*)-**OMe-teth (115)**; 23 hours reaction time, >99% conversion and 95% ee.

Aqueous reduction: See general method 2. With (*S,S*)-**3C-teth (80)**; 6 hours reaction time, 15% conversion and 61% ee. With (*R,R*)-**OMe-teth (115)**; 6 hours reaction time, 80% conversion and 87% ee.

(*R*) Configuration for product from reduction with (*R*,*R*)-**115** assumed by analogy to parent compound **357**. The order of elution of peaks in HPLC is the same. The opposite enantiomer is produced by reduction with (*S*,*S*)-**80**.

TLC: 50% EtOAc/Pet Ether, silica, R_f = 0.5, I_2 and $KMNO_4$; $[\alpha]_D^{32}$ +24.1 (*R*), 95% ee (*c* 0.36 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$): 6.98 (1H, dd, *J* = 1.8, 8.4 Hz, ArH), 6.83 - 6.67 (2H, m, ArH), 5.03 (1H, q, *J* = 6.6 Hz, C*H*OH), 2.42 (1H, br. s., CHO*H*), 2.25 (3H, s, $ArCH_3$), 1.59 (3H, d, *J* = 6.6 Hz, $CHCH_3$); δ_C (75 MHz, $CDCl_3$): 152.5 (C), 128.7 (CH), 128.4 (C), 127.5 (C), 126.4 (CH), 116.3 (CH), 71.1 (CH), 22.9 (CH_3), 19.9 (CH_3); Chiral HPLC (Chiralpak IA Column: (0.46 x 25 cm), 1 ml/min, 10% IPA : 90% Hexane; 256 nm UV, 30 °C), retention times: 7.83 (*S*) and 8.53 (*R*) minutes.

(R)-4-Chloro-2-(1-hydroxyethyl)phenol.



359

This compound has been reported in racemic form.[150] The asymmetric form has not been reported.

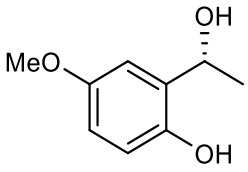
FA/TEA reduction: See general method 1. With (*S,S*)-**3C-teth (80)**; 4.75 hours reaction time, >99% conversion and 90% ee. With *(R,R)*-**OMe-teth (115)**; 23 hours reaction time, 97% conversion and 93% ee.

Aqueous reduction: See general method 2. With (*S,S*)-**3C-teth (80)**; 24 hours reaction time, >99% conversion and 24% ee. With (*R,R*)-**OMe-teth (115)**; 24 hours reaction time, 10% conversion and 63% ee.

(*R*) Configuration for product from reduction with (*R*,*R*)-**115** assumed by analogy to parent compound **357**. The order of elution of peaks in HPLC is the same. The opposite enantiomer is produced by reduction with (*S*,*S*)-**80**

TLC: 50% EtOAc/Pet Ether, silica, R_f = 0.5, I_2 and $KMNO_4$; $[\alpha]_D^{30}$ +18.5 (*R*), 93% ee (*c* 0.46 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$): 7.93 (1H, s, ArOH), 7.10 (1H, dd, *J* = 2.6, 8.7 Hz, ArH), 6.94 (1H, d, *J* = 2.6 Hz, ArH), 6.79 (1H, d, *J* = 8.7 Hz, ArH),5.03 (1H, dq, *J* = 3.5, 6.6 Hz, C*H*OH), 2.42 (1H, d, *J* = 3.5 Hz, CHO*H*), 1.57 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$); δ_C (75 MHz, $CDCl_3$): 153.9 (C), 129.8 (C), 128.7 (CH), 126.3 (CH), 124.6 (C), 118.4 (CH), 71.1 (CH), 23.4 (CH_3); Chiral HPLC (Chiralpak IA Column: (0.46 x 25 cm), 1 ml/min, 10% IPA : 90% Hexane; 256 nm UV, 30 °C), retention times: 7.52 (*S*) and 8.10 (*R*) minutes.

(R)-2-(1-hydroxyethyl)-4-methoxyphenol.



360

This compound has been reported in racemic form.[151] The optical rotation for the asymmetric form has not been reported.

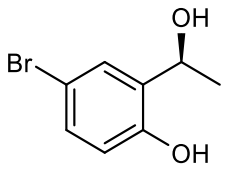
FA/TEA reduction: See general method 1. With (*S,S*)--**3C-teth (80)**; 5.5 hours reaction time, 92% conversion and 91% ee. With *(R,R)*-**OMe-teth (115)**; 6.5 hours reaction time, 91% conversion and 92% ee.

Aqueous reduction: See general method 2. With (*S,S*)-**3C-teth (80)**; 24 hours reaction time, 89% conversion and 38% ee. With (*R,R*)-**OMe-teth (115)**; 24 hours reaction time, 35% conversion and 61% ee.

(*R*) Configuration for product from reduction with (*R*,*R*)-**115** assumed by analogy to parent compound **357**. The order of elution of peaks in HPLC is the same. The opposite enantiomer is produced by reduction with (*S*,*S*)-**80**

TLC: 50% EtOAc/Pet Ether, silica, R_f = 0.4, I_2 and $KMNO_4$; $[\alpha]_D^{30}$ +9.26 (*R*), 92% ee (*c* 0.55 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$): 7.42 (1H, br. s., ArOH), 6.79 (1H, d, *J* = 8.8 Hz, ArH), 6.71 (1H, dd, *J* = 2.8, 8.8 Hz, ArH), 6.54 (1H, d, *J* = 2.8 Hz, ArH), 5.01 (1H, q, *J* = 6.7 Hz, C*H*OH), 3.73 (3H, s, OCH_3), 2.39 (1H, br. s., CHO*H*), 1.57 (3H, d, *J* = 6.7 Hz, CHC*H*$_3$); δ_C (101 MHz, $CDCl_3$): 153.0, (C) 149.2, (C) 129.2, (C) 117.6, (CH) 113.7, (CH) 112.3, (CH) 71.6, (CH) 55.8, (OCH_3) 23.3 (CH_3); Chiral HPLC (Chiralpak IA Column: (0.46 x 25 cm), 1 ml/min, 10% IPA : 90% Hexane; 256 nm UV, 30 °C), retention times: 11.16 (*S*) and 12.16 (*R*) minutes.

(S)-4-bromo-2-(1-hydroxyethyl)phenol



361

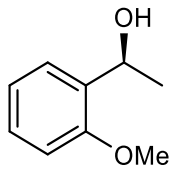
This compound is known in racemic form.[151] The optical rotation for the asymmetric form has not been reported.

FA/TEA reduction: See general method 1. With (*S*,*S*)-**3C-teth (80)**; 4 hours reaction time, 99% conversion and 91% ee. With (*R*,*R*)-**OMe-teth (115)**; 5.5 hours reaction time, 98% conversion and 94% ee.

(*S*) Configuration for product from reduction with (*S*,*S*)-**80** assumed by analogy to parent compound **357**. The order of elution of peaks in HPLC is the same. The opposite enantiomer is produced by reduction with (*R*,*R*)-**115**.

TLC: 50% EtOAc/Pet Ether, silica, R_f = 0.5, I_2 and $KMNO_4$; $[\alpha]_D^{30}$ -23.60 (*S*), 91% ee (*c* 0.68 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$): 7.97 (1H, br. s., ArOH), 7.26 (1H, dd, *J* = 2.4, 8.6 Hz, ArH), 7.10 (1H, d, *J* = 2.4 Hz, ArH), 6.76 (1H, d, *J* = 8.6 Hz, ArH), 5.04 (1H, q, *J* = 6.7 Hz, C*H*OH), 2.45 (1H, br. s., CHO*H*), 1.59 (3H, d, *J* = 6.6 Hz, CHC*H*3); δ_C (101 MHz, $CDCl_3$): 154.6 (C), 131.6 (CH), 130.4 (C), 129.2 (CH), 119.0 (CH), 111.8 (C), 71.1 (CH), 23.4 (CH_3); Chiral HPLC (Chiralpak IA Column: (0.46 x 25 cm), 1 ml/min, 10% IPA : 90% Hexane; 256 nm UV, 30 °C), retention times: 7.95 (*S*) and 8.75 (*R*) minutes.

(S)-1-(2-Methoxyphenyl)ethan-1-ol.



362

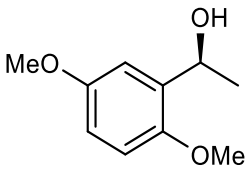
This compound is known.[62]

FA/TEA reduction: See general method 1. With (*S*,*S*)--**3C-teth (80)**; 3.75 hours reaction time, 95% conversion and 68% ee. With *(R,R)*-**OMe-teth (115)**; 3.75 hours reaction time, 98% conversion and 96% ee.

Aqueous reduction: See general method 2. With (*S,S*)-**3C-teth (80)**; 4 hours reaction time, 89% conversion and 55% ee. With (*R,R*)-**OMe-teth (115)**; 3.5 hours reaction time, 92% conversion and 96% ee.

(*S*) Configuration for product from reduction with (*S*,*S*)-**80** assigned by comparison with literature optical rotation. The opposite enantiomer is produced by reduction with (*R*,*R*)-**115**. TLC: 40% EtOAc/Pet Ether, silica, R_f = 0.45, I_2; $[\alpha]_D^{32}$ -13.9 (*S*), 68% ee (*c* 0.39 in $CHCl_3$); lit $[\alpha]_D^{32}$ +26.3 (*R*), 95.5% ee (*c* 1.23 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 7.33 (1H, d, *J* = 7.5 Hz, ArH), 7.28 - 7.20 (1H, m, ArH), 6.95 (1H, t, *J* = 7.4 Hz, ArH), 6.87 (1H, d, *J* = 8.3 Hz, ArH), 5.09 (1H, quin, *J* = 6.0 Hz, C*H*OH), 3.85 (3H, s, OCH_3), 2.74 (1H, d, *J* = 4.3 Hz, OH), 1.50 (3H, d, *J* = 6.5 Hz, CH_3); δ_C (101 MHz, $CDCl_3$): 156.5 (C), 133.5 (C), 128.3 (CH), 126.1 (CH), 120.8 (CH), 110.4 (CH), 66.5 (CH), 55.3 (OCH_3), 22.9 (CH_3); Chiral G.C; (CP-Chirasil-Dex-Cβ, 25m x 0.25mm x 0.25µm column, oven temperature 150 ºC, inj.: split 220 ºC, det.: FID 250 ºC, 18Psi He), retention times: 5.84 (*S*) and 6.30 (*R*) minutes.

(S)-1-(2,5-Dimethoxyphenyl)ethan-1-ol.



363

This compound is known.[152]

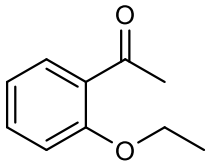
FA/TEA reduction: See general method 1. With (*S,S*)-**3C-teth (80)**; 3.75 hours reaction time, >99% conversion and 69% ee. With *(R,R)*-**OMe-teth (115)**; 3.75 hours reaction time, >99% conversion and 90% ee.

Aqueous reduction: See general method 2. With (*S,S*)-**3C-teth (80)**; 9.25 hours reaction time, 47% conversion and 70% ee. With (*R,R*)-**OMe-teth (115)**; 9.25 hours reaction time, 52% conversion and 97% ee.

(*S*) Configuration for product from reduction with (*S*,*S*)-**80** assigned by comparison with literature optical rotation. The opposite enantiomer is produced by reduction with (*R*,*R*)-**115**. TLC: 40% EtOAc/Pet Ether, silica, R_f = 0.35, I_2; $[\alpha]_D^{32}$ -15.8 (*S*), 69% ee (*c* 0.60 in $CHCl_3$); lit $[\alpha]_D^{27}$ −23.6 (*S*), 76% ee (c 1.4 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$): 6.92 (1H, d, *J* = 2.8 Hz, ArH), 6.79 (1H, d, *J* = 8.9 Hz, ArH), 6.73 (1H, dd, *J* = 2.8, 8.9 Hz, ArH), 5.04 (1H, dq, *J* = 5.5, 6.4 Hz, C*H*OH), 3.81 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 2.60 (1H, d, *J* = 5.5 Hz, CHO*H*), 1.47 (3H, d, *J* = 6.4 Hz, CHCH_3); δ_C (101 MHz, $CDCl_3$): 153.8 (C), 150.6 (C), 134.8 (CH), 112.4 (C), 112.3 (CH), 111.4 (CH), 66.4 (CH), 55.8 (OCH_3), 55.7 (OCH_3), 23.0 (CH_3); Chiral G.C; (CP-Chirasil-Dex-Cβ, 25m x 0.25mm x 0.25µm column, oven temperature 150 ºC, inj.: split 220 ºC, det.: FID 250 ºC, 18Psi He), retention times: 15.72 (*R*) and 16.93 (*S*) minutes.

4.4.2 Ortho-Substituted ketones

1-(2-ethoxyphenyl)ethan-1-one



286

This compound is known.[153,154]

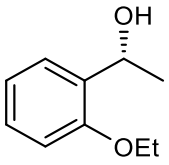
To a stirred suspension of 2'hydroxyacetophenone (831 mg, 6.11 mmol, 1 eq) and potassium carbonate (1609 mg, 11.64 mmol, 1.9 eq) in acetonitrile (30 ml) was added dropwise at room temperature ethyl iodide (1240 mg, 7.97 mmol, 1.3 eq). The resulting suspension was stirred at rt for 5 days, then filtered through Celite and concentrated to yield the crude product in only 50% conversion.

The crude was reacted with a further portion of potassium carbonate (0.8 g), ethyl iodide (0.65 g) in acetonitrile (20 ml) at 60 °C for 20 hours and concentrated to a residue. This was suspended in 5% NaOH solution (30 ml) and extracted with ethyl acetate (40 ml). The organic

layer was dried (Na_2SO_4) and concentrated to yield the product as a yellow solid (848 mg, 85%)

δ_H (300 MHz, $CDCl_3$): 7.74 (1H, d, *J* = 7.6 Hz, Ar*H*), 7.44 (1H, t, *J* = 7.8 Hz, Ar*H*), 7.02 - 6.89 (2H, m, Ar*H*), 4.14 (2H, q, *J* = 6.8 Hz, CH_2), 2.64 (3H, s, COCH_3), 1.48 (3H, t, *J* = 6.8 Hz, CH_3); δ_C (75 MHz, $CDCl_3$): 200.0 (CO), 158.4 (C), 133.6 (C), 130.3 (CH), 128.3 (CH), 120.4 (CH), 112.3 (CH), 64.0 (CH_2), 32.0 (CH_3), 14.7 (CH_3);

(R)-1-(2-ethoxyphenyl)ethan-1-ol



364

This compound is known but not characterised.[155]

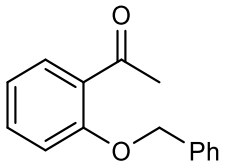
See general method 1. With (*R,R*)-**OMe-teth (115)**; 5.5 hours reaction time, 100% conversion and 99% ee.

(*R*) Configuration for product from reduction with (*R*,*R*)-**115** assumed by analogy to parent compounds **357** and **362**.

$[\alpha]_D^{26}$ +47.8 (*R*), 99% ee (*c* 0.52 in MeOH); HRMS: found (ESI): $[M + Na]^+$, 189.0887. ($C_{10}H_{14}NaO_2$ requires 189.0886); ν_{max}: 3374, 2976, 1600, 1450, 1243, 751 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.39 - 7.31 (1H, m, Ar*H*), 7.30 - 7.19 (1H, m, Ar*H*), 7.02 - 6.93 (1H, m, Ar*H*), 6.92 - 6.85 (1H, m, Ar*H*), 5.11 (1H, quin, *J* = 6.0 Hz, C*H*), 4.12 (2H, q, *J* = 6.9 Hz, CH_2), 2.82 (1H, d, *J* = 5.0 Hz, O*H*), 1.55 (3H, d, *J* = 6.5 Hz, CHCH_3), 1.47 (3H, t, *J* = 6.9 Hz, CH_2CH_3); δ_C (75 MHz, $CDCl_3$): 156.0 (C), 133.4 (C), 128.2 (CH), 126.2 (CH), 120.6 (CH), 111.3 (CH), 66.9 (CH), 63.5 (CH_2), 22.8 (CH_3), 14.9 (CH_3); *m/z* (ESI): 189.4 ($[M + Na]^+$).

Chiral G.C; (CP-Chirasil-Dex-Cβ, 25m x 0.25mm x 0.25µm column, oven temperature 135 ºC, inj.: split 220 ºC, det.: FID 250 ºC, 18Psi H_2), retention times: 5.3 (*S*) and 6.1 (*R*) minutes

1-(2-(benzyloxy)phenyl)ethan-1-one



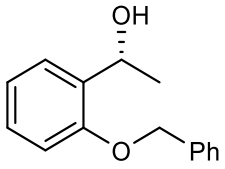
289

This compound is known.[156]

To a stirred suspension of 2'hydroxyacetophenone (530 mg, 3.89 mmol, 1 eq) and potassium carbonate (1090 mg, 7.86 mmol, 2 eq) in acetonitrile (20 ml) was added dropwise at room temperature benzyl bromide (881 mg, 5.15 mmol, 1.3 eq). The resulting suspension was stirred at rt for 2 days, then filtered through Celite and concentrated to yield the crude product. Excess benzyl bromide was removed by addition of triethylamine (202 mg, 2 mmol) and stirring in acetonitrile (2ml) overnight. The mixture was diluted with diethyl ether and washed with water, dried over Na_2SO_4 and concentrated to yield the purified product as a pale yellow oil (810 mg, 89%)

δ_H (300 MHz, $CDCl_3$): 7.76 (1H, d, *J* = 7.6 Hz, Ar*H*), 7.51 - 7.32 (6H, m, Ar*H*), 7.08 - 6.98 (2H, m, Ar*H*), 5.18 (2H, s, CH_2), 2.61 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$): 200.0 (CO), 158.0 (C), 136.2 (C), 133.6 (CH), 130.5 (CH), 128.7 (CH), 128.2 (CH), 127.5 (CH), 120.9 (CH), 112.8 (CH), 70.7 (CH_2), 32.1 (CH_3);

(R)-1-(2-(benzyloxy)phenyl)ethan-1-ol



365

This compound is known.[157,158]

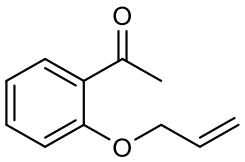
See general method 1. With (*R,R*)-**OMe-teth (115)**; 5.5 hours reaction time, 100% conversion and 95% ee.

(*R*) Configuration for product from reduction with (*R*,*R*)-**115** assigned by comparison with literature optical rotation.

$[\alpha]_D^{26}$ +14.9 (*R*), 95% ee (*c* 0.65 in $CHCl_3$) ; lit[158] $[\alpha]_D^{20}$ +26.1 (*R*), 95% ee (c 1.44 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$): 7.53 - 7.33 (6H, m, Ar*H*), 7.32 - 7.22 (1H, m, Ar*H*), 7.09 - 6.95 (2H, m, Ar*H*),

5.26 - 5.17 (1H, m, C*H*), 5.15 (2H, s, CH_2), 2.64 (1H, br. s., O*H*), 1.56 (3H, d, *J* = 6.4 Hz, CH_3); δ_C (75 MHz, $CDCl_3$): 155.6 (C), 136.7 (C), 133.8 (C), 128.7 (CH), 128.3 (CH), 128.1 (CH), 127.3 (CH), 126.2 (CH), 121.1 (CH), 111.7 (CH), 70.1 (CH), 66.4 (CH_2), 22.9 (CH_3);
Chiral HPLC (Chiralpak IA Column: (0.46 x 25 cm), 1 ml/min, 10% IPA : 90% Hexane; 220 nm UV, 30 °C), retention times: 7.6 (*R*) and 9.5 (*S*) minutes.

1-(2-(allyloxy)phenyl)ethan-1-one

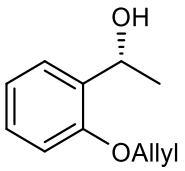


288

This compound is known.[159]

To a stirred suspension of 2'hydroxyacetophenone (542 mg, 3.98 mmol, 1 eq) and potassium carbonate (1118 mg, 8.08 mmol, 2 eq) in acetonitrile (8 ml) was added dropwise at room temperature allyl bromide (748 mg, 6.18 mmol, 1.6 eq) in acetonitrile (2 ml). The resulting suspension was stirred at rt for two days and concentrated to a residue. This was suspended in 5% NaOH solution (20 ml) and extracted with ethyl acetate (25 ml). The organic layer was dried (Na_2SO_4) and concentrated to yield the product as a pale yellow oil (676 mg, 96%)
TLC: 10% EtOAc/Pet ether, silica, Rf = 0.26, UV; δ_H (300 MHz, $CDCl_3$): 7.74 (1H, d, *J* = 7.6 Hz, Ar*H*), 7.44 (1H, t, *J* = 7.7 Hz, Ar*H*), 7.06 - 6.87 (2H, m, Ar*H*), 6.09 (1H, ddt, *J* = 17.3, 10.5, 5.0 Hz, =C*H*CH_2), 5.44 (1H, d, *J* = 17.3 Hz, =C*H*H), 5.33 (1H, d, *J* = 10.5 Hz, =CH*H*), 4.65 (2H, d, *J* = 5.0 Hz, OCH_2), 2.64 (3H, s, CH_3); δ_C (101 MHz, $CDCl_3$): 199.9 (CO), 157.9 (C), 133.5 (CH), 132.6 (CH), 130.4 (CH), 128.6 (C), 120.8 (CH), 118.2 (CH_2), 112.7 (CH), 69.4 (CH_2), 32.0 (CH_3);

(R)-1-(2-(allyloxy)phenyl)ethan-1-ol



366

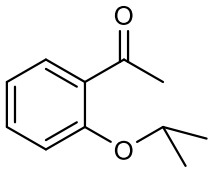
This compound is known in racemic form.[160]

See general method 1. With (*R,R*)-**OMe-teth (115)**; 5.5 hours reaction time, 100% conversion and 98% ee.

(*R*) Configuration for product from reduction with (*R*,*R*)-**115** assumed by analogy to parent compounds **357** and **362**.

$[\alpha]_D^{22}$ = +49.9 (*R*), 98% ee (*c* 0.09 in MeOH); δ_H (400 MHz, $CDCl_3$): 7.37 (1H, dd, *J* = 7.5, 1.3 Hz, Ar*H*), 7.23 (1H, td, *J* = 7.8, 1.6 Hz, Ar*H*), 6.98 (1H, td, *J* = 7.5, 0.6 Hz, Ar*H*), 6.88 (1H, d, *J* = 8.2 Hz, Ar*H*), 6.08 (1H, ddt, *J* = 17.2, 10.6, 5.2 Hz, C*H*=CH_2), 5.44 (1H, dd, *J* = 17.2, 1.5 Hz, =C*H*H), 5.31 (1H, dd, *J* = 10.5, 1.3 Hz, =CH*H*), 5.15 (1H, quin, *J* = 6.2 Hz, C*H*OH), 4.63 - 4.56 (2H, m, OCH_2), 2.67 (1H, d, *J* = 5.3 Hz, O*H*), 1.54 (3H, d, *J* = 6.6 Hz, CH_3); δ_C (101 MHz, $CDCl_3$): 155.5 (C), 133.7 (C), 133.0 (CH), 128.2 (CH), 126.2 (CH), 121.0 (CH), 117.6 (CH_2), 111.6 (CH), 68.7 (CH_2), 66.6 (CH), 22.9 (CH_3); Chiral HPLC (Chiralpak IC Column: (0.46 x 25 cm), 0.5 ml/min, 2% IPA : 98% Hexane; 254 nm UV, 30 °C), retention times: 27.3 (*S*) and 28.9 (*R*) minutes.

1-(2-isopropoxyphenyl)ethan-1-one



287

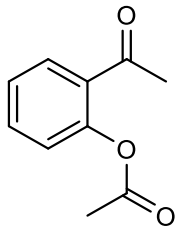
This compound is known.[156]

To a stirred suspension of 2'hydroxyacetophenone (540 mg, 3.9 mmol, 1 eq) and potassium carbonate (1110 mg, 8.0 mmol, 2 eq) in acetonitrile (9 ml) was added dropwise at room temperature isopropyl mesylate (828 mg, 6.0 mmol, 1.5 eq), which was washed in with acetonitrile (1 ml). The resulting suspension was heated to 60°C under a condenser for 18 hours. The dark brown suspension was concentrated to remove excess acetonitrile, taken up in ethyl acetate (30 ml) and washed with NaOH (2M, 20 ml) and brine (sat. 20 ml). The organic extract was dried (Na_2SO_4) and concentrated to yield a mixture of phenol, mesylate and crude product with only 10% conversion.

The crude was reacted with a further portion of potassium carbonate (1.1 g) and isopropyl mesylate (0.65 g) in DMF (10 ml) at 70 °C for 2 days. The reaction was quenched while hot with NaOH (2M, 20 ml) and stirred for 30 mins to encourage hydrolysis of *i*-PrOMs. The aqueous suspension was allowed to cool to room temperature, extracted with ethyl acetate (40 ml, 2x 10 ml) and washed with water (3x 5ml) and $NaHCO_3$ (sat., 3x 15 ml). The organic extracts were dried (Na_2SO_4) and concentrated to yield the product as a brown oil (620 mg, 85%)

δ_H (400 MHz, $CDCl_3$): 7.71 (1H, dd, *J* = 7.9, 1.7 Hz, ArH), 7.47 - 7.35 (1H, m, ArH), 7.00 - 6.88 (2H, m, ArH), 4.69 (1H, dt, *J* = 12.1, 6.1 Hz, C*H*$(CH_3)_2$), 2.62 (3H, s, CH_3), 1.40 (6H, d, *J* = 6.1 Hz, CH(C*H*$_3)_2$); δ_C (101 MHz, $CDCl_3$): 200.4 (C=O), 157.3 (C), 133.4 (CH), 130.5 (CH), 129.3 (C), 120.2 (CH), 113.5 (CH), 70.6 (CH), 32.1 (CH3), 22.3 (CH3), 22.1 (CH3).

2-acetylphenyl acetate



290

This compound is known.[161]

To a solution of 2'hydroxyacetophenone (550 mg, 4.0 mmol, 1 eq) and pyridine (0.64 ml, 8.0 mmol, 2 eq) in dichloromethane (4 ml) was added dropwise at 0°C acetyl chloride (487 mg, 6.2 mmol, 1.6 eq). The resulting suspension was warmed to rt, and stirred for 20 hours. The mixture was diluted with ethyl acetate (15 ml), washed with 1M HCl (10 ml) and sat. $NaHCO_3$ soln (10 ml). The organic layer was dried (Na_2SO_4) and concentrated to yield the product as a yellow residue. This was redissolved in ethyl acetate (6 ml) and hexane (6 ml) and slow concentrated until saturated, then cooled to 0°C. The resulting off-white crystalline solid was isolated by filtration (493 mg, 69%)

δ_H (300 MHz, $CDCl_3$): 7.82 (1H, d, *J* = 7.8 Hz, ArH), 7.60 - 7.50 (1H, m, ArH), 7.39 - 7.29 (1H, m, ArH), 7.13 (1H, d, *J* = 8.1 Hz, ArH), 2.57 (3H, s, ArCOC*H*$_3$), 2.36 (3H, s, OCOC*H*$_3$);

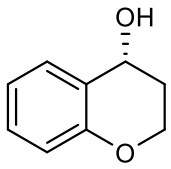
δ_C (101 MHz, $CDCl_3$): 197.6 (CO), 169.5 (CO), 149.0 (C), 133.4 (CH), 130.7 (C), 130.3 (CH), 126.0 (CH), 123.8 (CH), 29.3 (CH_3), 21.2 (CH_3).

4.4.2.1 Attempted reduction of 2-acetylphenyl acetate **290**

See general method 1. With (*R,R*)-**OMe-teth (115)**; 48 hours reaction time. Conversion unknown, mixture of products obtained.

4.4.3 Other Ketones

(R)-chroman-4-ol



367

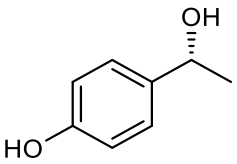
This compound is known.[76]

See general method 1. With (*R,R*)-**OMe-teth (115)**; 6 hours reaction time, 100% conversion and 99% ee.

(*R*) Configuration for product from reduction with (*R*,*R*)-**115** assigned by comparison with literature optical rotation.

$[\alpha]_D^{25}$ +77.7 (*R*), 99%ee (*c* 0.46 in $CHCl_3$) ; lit $[\alpha]_D^{20}$ +61 (*R*), 99% ee (c 0.45 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$): 7.32 (1H, d, *J* = 7.5 Hz, ArH), 7.26 - 7.17 (1H, m, ArH), 6.99 - 6.89 (1H, m, ArH), 6.86 (1H, d, *J* = 8.2 Hz, ArH), 4.85 - 4.75 (1H, m, CH), 4.33 - 4.23 (2H, m, OCH_2), 2.22 - 1.98 (2H, m, CH_2), 1.86 (1H, d, *J* = 4.6 Hz, OH); δ_C (75 MHz, $CDCl_3$): 154.6 (C), 129.7 (CH), 129.6 (C), 124.3 (CH), 120.6 (CH), 117.1 (CH), 63.2 (CH), 61.9 (CH_2), 30.8 (CH_2); Chiral HPLC (CHIRALPAK IB column: (0.46 x 25 cm), 1 ml/min, 7% IPA : 93% Hexane; 254 nm UV, 30 °C): retention times: 10.3 (*S*) and 11.3 (*R*) minutes.

(R)-4-(1-hydroxyethyl)phenol



368

This compound is known.[162]

See general method 1. With (*R,R*)-**OMe-teth (115)**; 22 hours reaction time, 100% conversion and 96% ee.

(*R*) Configuration for product from reduction with (*R*,*R*)-**115** assigned by comparison with literature optical rotation.

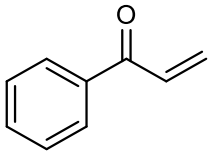
$[\alpha]_D^{26}$ +41.5 (*R*), 96% ee (*c* 0.44 in MeOH); lit $[\alpha]_D^{23}$ -47.6 (*S*), 99% ee (*c* 1.0 in EtOH); δ_H (300 MHz, $(CD_3)_2SO$): 9.16 (1H, s, O*H*), 7.18 - 7.03 (2H, m, Ar*H*), 6.76 - 6.59 (2H, m, Ar*H*), 4.90 (1H,

d, *J* = 3.7 Hz, O*H*), 4.66 - 4.54 (1H, m, C*H*), 1.26 (3H, d, *J* = 6.2 Hz, CH_3); δ_C (75 MHz, $(CD_3)_2SO$): 155.9 (C), 137.7 (C), 126.4 (CH), 114.6 (CH), 67.7 (CH), 25.9 (CH_3); Chiral HPLC (Chiralpak IA Column: (0.46 x 25 cm), 1 ml/min, 7% IPA : 93% Hexane; 220 nm UV, 30 °C), retention times: 25.6 (*R*) and 27.1 (*S*) minutes.

4.5 Preparation of Compounds, α,β-Unsaturated Ketones:

4.5.1 β-Chloro Ketones

1-phenylprop-2-en-1-one.



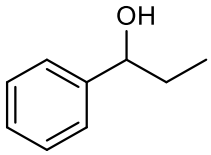
303

This compound is known.[163]

To a solution of 3-chloropropiophenone (844 mg, 5 mmol, 1.0 eq) in chloroform (10 mL) was added triethylamine (1214 mg, 12 mmol, 2.4 eq). The resulting clear solution was stirred at rt for 48 hours, diluted with chloroform (5 mL) and washed with HCl (1M, 2 x 5 mL) and $NaHCO_3$ (sat., 10 mL). The organic layer was dried over Na_2SO_4 and concentrated to give the product as a yellow oil (625 mg, 95%). If desired the coloured impurity could be removed on activated carbon, however the colour returns on standing for ~1 week at 4 °C. The product decomposes within ~3 months at 4 °C.

δ_H (300 MHz, $CDCl_3$): 8.02 - 7.89 (2H, m, Ph), 7.64 - 7.54 (1H, m, *p*-Ph), 7.53 - 7.45 (2H, m, Ph), 7.17 (1H, dd, *J* = 10.5, 17.1 Hz, COCH=C), 6.45 (1H, dd, *J* = 1.7, 17.1 Hz *trans*-CO=C*H*H), 5.94 (1H, dd, *J* = 1.7, 10.5 Hz *cis*-CO=CH*H*).

1-phenylpropan-1-ol



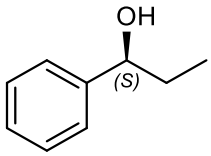
208

This compound is known.[164]

To a solution of propiophenone (66 mg, 0.49 mmol, 1 eq) in methanol (0.9 ml) and water (0.1 ml) was added sodium borohydride (41 mg, 1.08 mmol, 2 eq) as a solid in one portion. The reaction was monitored by TLC. After stirring for 6 hours, the reaction mixture was concentrated under vacuum, the residue suspended in water (1 ml) and extracted with Et_2O (3 ml total). The organic layer was dried (Na_2SO_4) and concentrated to give the product as a clear oil (35 mg, 52 %)

The spectral data were consistent with those observed for the asymmetric product.

(S)-1-phenylpropan-1-ol



302

This compound is known.[164]

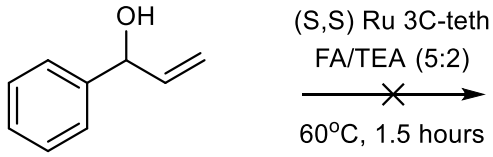
A degassed solution of 3-chloropropiophenone (170 mg, 1.01 mmol, 1.0 eq) and (*S,S*)-**3C-teth (80)** (3.1 mg, 0.005 mmol, 0.5%) in FA/TEA (5:2, 0.5 mL) was stirred at 60 °C for 1.5 hours. The mixture was diluted with ethyl acetate (5 mL) and quenched with $NaHCO_3$ (sat., 5 mL), the aqueous layer is extracted further with ethyl acetate (2 x 5 mL) and the organic extracts dried over Na_2SO_4 and concentrated to give a brown oil. The crude was dissolved in diethyl ether and passed through a silica plug to yield the product as a red oil (123 mg, 72%) in 100% conv and 97% ee as measured by GC.

(*S*) Configuration for product from reduction with (*S*,*S*)-**80** assigned by comparison with literature optical rotation.

$[\alpha]_D^{22}$ -43.5 (*S*), 97% ee (*c* 0.35 in $CHCl_3$); lit[164] $[\alpha]_D^{22}$ -43.6 (*S*) (c 1.0 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$): 7.41 - 7.22 (5H, m, Ph), 4.58 (1H, dt, *J* = 3.2, 6.6 Hz, C*H*OH), 1.99 - 1.89 (1H, m, OH), 1.88 - 1.66 (2H, m, CH_2), 0.91 (3H, t, *J* = 7.4 Hz, CH_3); δ_C (75 MHz, $CDCl_3$): 144.6 (C), 128.4 (CH), 127.5 (CH), 125.9 (CH), 76.0 (CH), 31.8 (CH_2), 10.1 (CH_3); Chiral G.C; (CP-Chirasil-Dex-Cβ, 25m x 0.25mm x 0.25µm column, oven: hold 12 mins at 125 ºC, then ramp 1 °C/min, final temp 145 ºC, inj.: split 220 ºC, det.: FID 250 ºC, 18 Psi He), retention times: 11.2 (*R*) and 11.4 (*S*) minutes.

The compound could also be prepared with 100% conversion and 97 % ee with the same method, starting from **303** (126 mg, 0.95 mmol, 1 eq), (*S,S*)-**3C-teth (80)** (3.5 mg, 0.006 mmol, 0.5%) and FA/TEA (5:2, 0.5 ml). The product was isolated as a clear oil (103 mg, 79%).

4.5.1.1 Attempted reduction of 1-phenylprop-2-en-1-ol



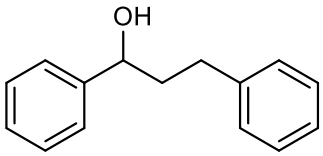
Application of the same method to commercially available α-vinylbenzyl alcohol **206** (134 mg) and (*S,S*)-**3C-teth (80)** (3.3 mg, 5 µmol, 0.5%) in FA/TEA (5:2. 0.5 ml) gave no reaction in 1.5 hr at 60°C.

4.5.2 Chalcones

4.5.2.1 General Method 4: FA/TEA/MeOH Reductions

A degassed suspension of enone (0.5 mmol, 1 eq) and catalyst (5 µmol, 100:1 S/C) in FA/TEA (5:2, 0.5 ml) and methanol (0.5 ml) was stirred at 40°C for 2-24 hours. On completion the reaction mixture is homogenous. The mixture was diluted with diethyl ether (2 ml) and quenched with $NaHCO_3$ (sat., 2 ml), the aqueous layer is extracted further with ether (2x 2 ml) and the organic extracts dried over Na_2SO_4 and passed through a silica plug to yield the product.

1,3-diphenylpropan-1-ol



162

This compound is known.[133,165]

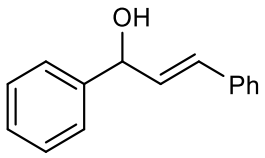
To a suspension of chalcone (212 mg, 1.02 mmol, 1 eq) and Pd/C (5% w/w, 52 mg, 24 µmol, 2.5 % Pd) in isopropanol (5 ml) was added acetic acid (124 mg, 2.06 mmol, 2 eq) followed by sodium borohydride (160 mg, 4.23 mmol, 4 eq), with vigorous effervescence. The reaction mixture was stirred at rt for 2 hours and quenched slowly with HCl (0.2M, 2.5 mL). The resulting suspension was neutralised with NaOH (2M, ~1.5 ml) and filtered through Celite with isopropanol to remove Pd/C. The mixture was concentrated to remove excess isopropanol and then the aqueous layer was extracted with diethyl ether (3 x 20 mL), dried

over Na_2SO_4 and concentrated to give the saturated alcohol as a clear oil that solidifies on standing. (183 mg, 85%)

δ_H (400 MHz, $CDCl_3$): 7.34 (4H, br. s., Ph), 7.30 - 7.23 (3H, m, Ph), 7.22 - 7.14 (3H, m, Ph), 4.67 (1H, br. s., CHOH), 2.82 - 2.55 (2H, m, $PhCH_2$), 2.20 - 1.96 (2H, m, $CHCH_2$), 1.92 (1H, br. s., OH); δ_C (101 MHz, $CDCl_3$): 144.5 (C), 141.7 (C), 128.5 (CH), 128.4 (CH), 128.4 (CH), 127.6 (CH), 125.9 (CH), 125.8 (CH), 73.8 (CH), 40.4 (CH_2), 32.0 (CH_2);

Chiral HPLC (CHIRALPAK IB column: (0.46 x 25 cm), 1 ml/min, 7% IPA : 93% Hexane; 256 nm UV, 30 °C): retention times: 9.4 (*S*) and 10.4 (*R*) minutes

(E)-1,3-diphenylprop-2-en-1-ol



205

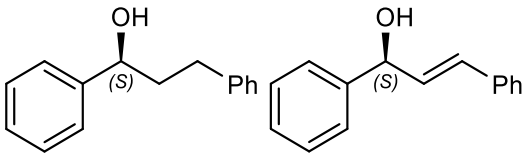
This compound is known. [166,167]

To a suspension of chalcone (625 mg, 3.0 mmol, 1 eq) and cerium trichloride heptahydrate (1120 mg, 3.0 mmol, 1 eq) in methanol (6 mL) was added sodium borohydride (113 mg, 3.0 mmol, 1 eq) at 0 °C. The reaction was stirred for 1 hour, quenched with NH_4Cl (sat., 10 mL) and extracted with diethyl ether (3x 10 mL). The organic layers were dried over Na_2SO_4 and concentrated to give the unsaturated alcohol as a clear oil that solidifies on standing (532 mg, 84%).

δ_H (400 MHz, $CDCl_3$): 7.48 - 7.19 (10H, m, Ph), 6.69 (1H, d, *J* = 15.8 Hz, =CHPh), 6.38 (1H, dd, *J* = 6.4, 15.8 Hz CHC*H*=), 5.39 (1H, d, *J* = 6.4 Hz, C*H*OH), 2.08 (1H, br. s., OH); δ_C (101 MHz, $CDCl_3$): 142.7 (C), 136.4 (C), 131.4 (CH), 130.4 (CH), 128.5 (CH), 128.5 (CH), 127.7 (CH), 126.5 (CH), 126.3 (CH), 74.9 (CH).

Chiral HPLC (CHIRALPAK IB column: (0.46 x 25 cm), 1 ml/min, 7% IPA : 93% Hexane; 256 nm UV, 30 °C): retention times: 13.4 (*S*) and 16.9 (*R*) minutes.

(S)-1,3-diphenylpropan-1-ol and (S,E)-1,3-diphenylprop-2-en-1-ol



162 and **205**

These compounds are known.[165,166]

A degassed suspension of trans-chalcone (208 mg, 1 mmol, 1 eq) and (*S*,*S*)-**3C-teth (80)** (6.2 mg, 0.01 mmol, 1%) in FA/TEA (5:2, 0.5 ml) was stirred at 40°C for 1.5 hours. On completion the reaction mixture is homogenous. The mixture was diluted with diethyl ether (2 ml) and quenched with $NaHCO_3$ (sat., 2 ml), the aqueous layer is extracted further with ether (2x 2 ml) and the organic extracts dried over Na_2SO_4 and passed through a silica plug to yield the product as an off white solid (203 mg, 96%).The product is obtained as a mixture of saturated and unsaturated alcohols, ratio 93:7 by ^{1}H NMR. Total conv 98%, major product ee was 96% as determined by HPLC, minor product ee was 73% as determined by HPLC.

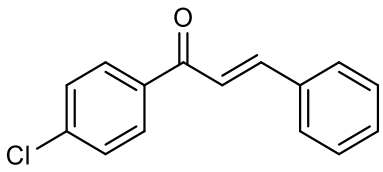
The opposite enantiomer was obtained using (*R,R*)-**OMe-teth (115)** (3.3 mg, 1%), trans-chalcone (104 mg), FA/TEA (0.5 ml) and methanol (0.5 ml), to give a mixture of saturated and unsaturated alcohols (102 mg, 96%), ratio 97:3 by ^{1}H NMR. Total conversion 100%, major product ee was 98% as determined by HPLC, minor product ee was 85% as determined by HPLC.

Spectral data for asymmetric product is consistent with the prepared standards. (*R*) Configuration for major product from reduction with (*R*,*R*)-**115** assigned by comparison with literature optical rotation. (*R*) Configuration for minor product demonstrated by reduction with PtO_2, see Table 41, page 132.

Mp 52 °C; $[\alpha]_D^{27}$ + 29.4 (*R*), 98% ee (c 0.425 in $CHCl_3$); lit[165] $[\alpha]_D^{22}$ +27.3 (*R*), 93% ee (*c* 0.51 in $CHCl_3$); Chiral HPLC (CHIRALPAK IB column: (0.46 x 25 cm), 1 ml/min, 7% IPA : 93% Hexane; 256 nm UV, 30 °C): retention times: 10.0 (*S*)-saturated, 11.0 (*R*)-saturated, 13.4 (*S*)-unsaturated and 16.8 (*R*)-unsaturated minutes.

4.5.3 Para-Substituted Chalcones

(E)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one



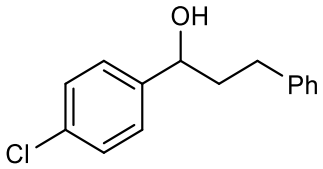
308

This compound is known.[168]

4'-chloroacetophenone (1.54 g, 10.0 mmol, 1 eq) was dissolved in a solution of sodium methoxide (25 wt % in MeOH, 1.11 g, 5.1 mmol, 0.5 eq) and MeOH (20 ml) and cooled to 0 °C. Benzaldehyde (1.59 g, 15.0 mmol, 1.5 eq) in MeOH (5 ml) was added and the suspension was warmed to 40 °C. The resulting solution was stirred for 18 hours, THF (10 ml) was added to dissolve solids and the reaction was then quenched by dropwise addition of HCl (0.25M, 20 ml). The resulting yellow crystalline precipitate was isolated by filtration and purified by recrystallization from hot ethanol and water. The pure product was isolated as an off white crystalline solid (2.08 g, 86%)

Mp 93-96 °C; δ_H (400 MHz, $CDCl_3$): 7.98 (2H, d, *J* = 8.3 Hz, *o*-CO ArH), 7.83 (1H, d, *J* = 15.8 Hz, CH=), 7.71 - 7.61 (2H, m, *J* = 3.8 Hz, Ph), 7.49 (2H, d, *J* = 8.8 Hz, o-Cl ArH), 7.50 (1H, d, *J* = 14.8 Hz, CH=H_n), 7.45 - 7.41 (3H, m, Ph). δ_C (126 MHz, $CDCl_3$): 189.2 (CO), 145.3 (CH), 139.2 (C), 136.5 (C), 134.7 (C), 130.7 (CH), 129.9 (CH), 129.0 (CH), 128.9 (CH), 128.5 (CH), 121.5 (CH)

1-(4-chlorophenyl)-3-phenylpropan-1-ol



369

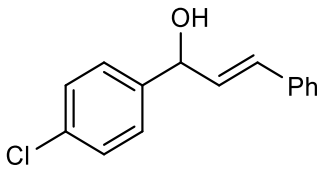
This compound is known.[169]

To a solution of 4-chlorobenzaldehyde (141 mg, 1.0 mmol, 1 eq) in THF (1 ml) at -78 °C was added phenethyl magnesium chloride (1M in THF, 1 ml, 1 eq). The reaction was allowed to warm to rt over 2.5 hours, quenched with sat. NH_4Cl (2 ml) and extracted with Et_2O (2x 2.5 ml). The organic extract was dried over $MgSO_4$ and concentrated to give the product as a

pale yellow oil. Purification by column chromatography (5 g silica, 30% Et2O:Petroleum ether) gave the pure product as a white solid (192 mg, 78%)

δ_H (400 MHz, $CDCl_3$): 7.35 - 7.24 (6H, m, Ph), 7.23 - 7.14 (3H, m, Ph), 4.70 - 4.62 (1H, m, C*H*OH), 2.78 - 2.60 (2H, m, $PhCH_2$), 2.15 - 1.93 (2H, m, CHCH_2), 1.91 - 1.84 (1H, m, OH); δ_C (101 MHz, $CDCl_3$): 143.0 (C), 141.5 (C), 133.2 (C), 128.6 (CH), 128.4 (CH), 128.4 (CH), 127.3 (CH), 125.9 (CH), 73.1 (CH), 40.5 (CH_2), 31.9 (CH_2); Chiral HPLC (CHIRALPAK IB column: (0.46 x 25 cm), 1 ml/min, 7% IPA : 93% Hexane; 210 nm UV, 30 °C): retention times: 9.3 (*S*) and 10.6 (*R*) minutes.

(E)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-ol



370

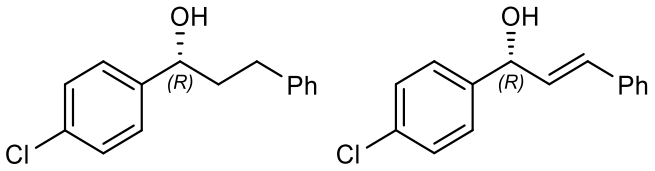
This compound is known.[166,170]

To a suspension of **308** (242 mg, 1.0 mmol, 1 eq) and cerium trichloride heptahydrate (392 mg, 1.1 mmol, 1 eq) in methanol (2 mL) was added sodium borohydride (43 mg, 1.1 mmol, 1 eq) at 0 °C. The reaction was stirred for 1 hour and quenched with NH_4Cl (sat., 5 mL) and extracted with diethyl ether (3x 5 mL) and passed through a plug of activated carbon/Celite. The filtrate was concentrated to give the unsaturated alcohol as a clear oil that solidifies on standing in the freezer for 3 days (239 mg)

Trituration from water gave a sticky white solid that was dried under hi vacuum to yield pure compound as a grey solid. (174 mg, 71%).

δ_H (400 MHz, $CDCl_3$): 7.59 - 7.06 (9H, m, ArH), 6.67 (1H, d, *J* = 15.8 Hz, =CHPh), 6.32 (1H, dd, *J* = 15.9, 6.7 Hz, CHC*H*=), 5.36 (1H, d, *J* = 6.3 Hz, C*H*OH), 2.10 (1H, br. s., OH); δ_C (101 MHz, $CDCl_3$): 141.1 (C), 136.2 (C), 133.5 (C), 131.0 (CH), 131.0 (CH), 128.7 (2* CH), 128.6 (2* CH), 128.0 (CH), 127.7 (2* CH), 126.6 (2* CH), 74.5 (CH); Chiral HPLC (CHIRALPAK IB column: (0.46 x 25 cm), 1 ml/min, 7% IPA : 93% Hexane; 210 nm UV, 30 °C): retention times: 12.5 (*S*) and 17.9 (*R*) minutes.

(R)-1-(4-chlorophenyl)-3-phenylpropan-1-ol and (R,E)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-ol



370 and **369**

The major compound is known in racemic form.[169] The asymmetric form has not been reported. The minor compound is known.[171]

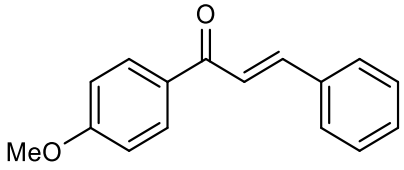
A degassed suspension of **308** (120 mg, 0.49 mmol, 1 eq) and (*R,R*)-**OMe-teth (115)** (3.3 mg, 0.005 mmol, 1%) in FA/TEA (5:2, 0.5 ml) and methanol (0.5 ml) was stirred at 40°C for 22 hours. The mixture was quenched with $NaHCO_3$ (sat., 2 ml), extracted into diethyl ether (2 ml) and dry loaded onto silica (~200 mg). Filtration with 40% Et_2O/Hexane through a silica plug (~200 mg) gave the crude product as a sticky red film (114 mg). Purification by column chromatography (15% EtOAc in petroleum ether) gave the pure mixture of alcohols as a clear oil. (98 mg, 80%)

The product is obtained as a mixture of saturated and unsaturated alcohols, ratio 96:4 by ^1H NMR. Total conv 100%, major product ee was 94% as determined by HPLC, minor product ee was 69% as determined by HPLC.

Spectral data matched those of the racemic compounds. (*R*) Configuration for products from reduction with (*R*,*R*)-**115** assumed by analogy to parent compounds **370** and **369**. The order of elution of peaks in HPLC is the same.

$[\alpha]_D^{27}$ +12.8 (*R*), 96% ee (*c* 0.375 in $CHCl_3$); Chiral HPLC (CHIRALPAK IB column: (0.46 x 25 cm), 1 ml/min, 7% IPA : 93% Hexane; 210 nm UV, 30 °C): retention times: 9.6 (*S*)-saturated, 10.8 (*R*)-saturated, 13.0 (*S*)-unsaturated and 16.1 (*R*)-unsaturated minutes.

(E)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one



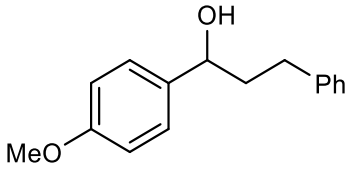
196

This compound is known.[168]

4'-methoxyacetophenone (1.51 g, 10.1 mmol, 1 eq) was dissolved in a solution of sodium methoxide (25 wt % in MeOH, 0.43 g, 2.0 mmol, 0.2 eq) and MeOH (20 ml) and cooled to 0 °C. Benzaldehyde (1.50 g, 14.1 mmol, 1.4 eq) in MeOH (5 ml) was added and the suspension was warmed to 40 °C. The resulting solution was stirred for 48 hours, then quenched by dropwise addition of HCl (0.25M, 20 ml). The resulting white crystalline solid was isolated by filtration (2.20 g, 92%)

δ_H (500 MHz, $CDCl_3$): 8.09 - 8.02 (2H, m, ArH), 7.81 (1H, d, *J* = 15.7 Hz, =CH), 7.65 (2H, dd, *J* = 7.2, 2.1 Hz, ArH), 7.55 (1H, d, *J* = 15.7 Hz, =CH), 7.45 - 7.36 (3H, m, ArH), 7.02 - 6.96 (2H, m, ArH), 3.89 (3H, s, OCH_3); δ_C (126 MHz, $CDCl_3$): 188.7 (C), 163.5 (C), 144.0 (CH), 135.1 (C), 131.1 (C), 130.8 (CH), 130.3 (CH), 128.9 (CH), 128.4 (CH), 121.9 (CH), 113.9 (CH), 55.5 (CH_3).

1-(4-methoxyphenyl)-3-phenylpropan-1-ol



371

This compound is known.[133]

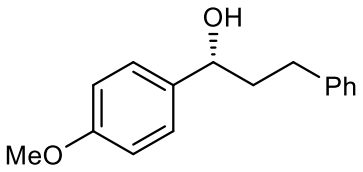
To a suspension of **196** (240 mg, 1.0 mmol, 1 eq) and Pd/C (5% w/w, 54 mg, 25 µmol, 2.5 % Pd) in isopropanol (5 ml)was added acetic acid (120 mg, 2.0 mmol, 2 eq) followed by sodium borohydride (152 mg, 4.0 mmol, 4 eq), with vigorous effervescence. The reaction mixture was stirred at rt for 2.5 hours, then additional sodium borohydride was added (76 mg, 2.0 mmol, 2 eq). The suspension was stirred for another hour, then filtered through Celite with isopropanol (40 ml) and water (10 ml). The filtrate was partially concentrated under vacuum but continued to evolve gas, so was quenched with NH_4Cl (sat. soln, 10 ml) and concentrated at 50°C. The concentrated residue was partitioned between diethyl ether (10 ml) and NaOH (2M soln, 5 ml). The aqueous layer was extracted with further portions of ether (2x 5 ml), and the combined organic layers were dried (Na_2SO_4) and concentrated under vacuum to give the crude product as a clear oil that solidifies into a sticky solid on standing (218 mg)

This material was dissolved in a minimum quantity of methanol and water was added until a white emulsion formed. Concentrating the emulsion gave a the pure product as a white crystalline solid (206 mg, 84%)

Mp 52-53 °C; δ_H (400 MHz, $CDCl_3$): 7.32 - 7.23 (4H, m, Ph), 7.22 - 7.13 (3H, m, Ph), 6.88 (2H, d, *J* = 8.3 Hz, *o*-O Ph), 4.78 - 4.53 (1H, m, C*H*OH), 3.80 (3H, s, OCH_3), 2.79 - 2.58 (2H, m, $PhCH_2$),

2.20 - 1.94 (2H, m, CHCH_2), 1.83 (1H, br. s., OH); δ_C (101 MHz, $CDCl_3$): 159.1 (C), 141.9 (C), 136.7 (C), 128.5 (CH), 128.4 (CH), 127.2 (CH), 125.9 (CH), 113.9 (CH), 73.5 (CH), 55.3 (CH_3), 40.4 (CH_2), 32.2 (CH_2); Chiral HPLC (CHIRALPAK IB column: (0.46 x 25 cm), 1 ml/min, 7% IPA : 93% Hexane; 210 nm UV, 30 ^oC): retention times: 11.9 (*S*) and 13.1 (*R*) minutes.

(R)-1-(4-methoxyphenyl)-3-phenylpropan-1-ol



371

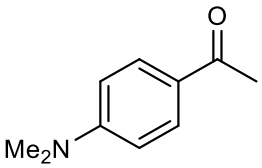
This compound is known.[172]

A degassed suspension of **196** (121 mg, 0.51 mmol, 1 eq) and (*R,R*)-**OMe-teth (115)** (3.3 mg, 0.005 mmol, 1%) in FA/TEA (5:2, 0.5 ml) and methanol (0.5 ml) was stirred at 40^{o}C for 22 hours. The mixture was quenched with $NaHCO_3$ (sat., 2 ml), extracted into diethyl ether (2 ml) and dry loaded onto silica (~200 mg). Filtration with 20% Et2O/Hexane (10 ml) through a silica plug (~0.2 g) gave the pure product as a white solid (110 mg, 89%) in 99% ee.

Spectral data matched those of the racemic compound. (*R*) Configuration for product from reduction with (*R*,*R*)-**115** assigned by comparison to literature optical rotation. The order of elution of peaks in HPLC is the same as for **162**.

$[\alpha]_D^{22}$ +19.4 (*R*), 99% ee (*c* 0.24 in $CHCl_3$); lit[172] $[\alpha]_D^{22}$ +10.3 (*R*), 88% ee (*c* 0.86 in $CHCl_3$); Chiral HPLC (CHIRALPAK IB column: (0.46 x 25 cm), 1 ml/min, 7% IPA : 93% Hexane; 210 nm UV, 30 ^{o}C): retention times: 11.7 (*S*) and 13.1 (*R*) minutes.

1-(4-(dimethylamino)phenyl)ethan-1-one



296

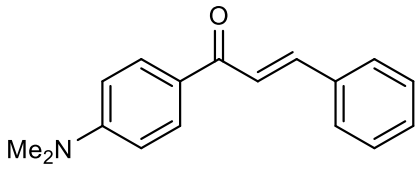
This compound is known.[173]

4'-fluoroacetophenone (691 mg, 5.0 mmol, 1 eq) was placed into a pressure tube and purged with nitrogen through a septum. An aqueous solution of dimethylamine (40% wt/wt, 2.2 ml, 17.5 mmol, 3.5 eq) was added, the reaction vessel was sealed and the clear mixture heated

to 100 °C and stirred for 23 hours. The mixture was cooled over ice and the yellow/green precipitate formed was isolated by filtration, washed with water and dried under vacuum. Recrystallization from 5 ml of hot heptane gives the product as a yellow crystalline solid (609 mg, 75%)

δ_H (400 MHz, $CDCl_3$): 7.90 - 7.84 (2H, m, *J* = 8.5 Hz, *o*-COR ArH), 6.67 - 6.62 (2H, m, *J* = 8.5 Hz, *o*-NMe_2 ArH), 3.06 (6H, s, NMe_2), 2.51 (3H, s, $N(CH_3)_2$); δ_C (101 MHz, $CDCl_3$): 196.5 (CO), 153.4 (CN), 130.5 (CH), 125.3 (C), 110.6 (CH), 40.1 (2* CH_3), 26.0 (CH_3).

(E)-1-(4-(dimethylamino)phenyl)-3-phenylprop-2-en-1-one



309

This compound is known. [168]

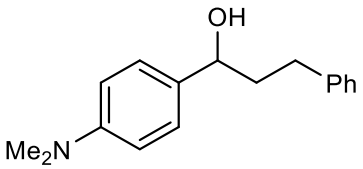
296 (1.63 g, 10 mmol, 1 eq) was dissolved in a solution of sodium methoxide (25 wt % in MeOH, 1.08 g, 5 mmol, 0.5 eq) and MeOH (20 ml) and cooled to 0 °C. Benzaldehyde (1.59 g, 15 mmol, 1.5 eq) in MeOH (5 ml) was added and the suspension was warmed to 40 °C. The resulting yellow solution was stirred for 48 hours, then quenched with HCl (0.25M, 20 ml). The resulting yellow precipitate was filtered and washed with aqueous methanol.

The crude solid was purified by recrystallization from hot ethanol, to give the pure chalcone as a fluffy yellow solid, (884 mg, 35%*)

Mp 168-170 °C; δ_H (500 MHz, $CDCl_3$): 8.02 (2H, d, *J* = 9.0 Hz, *o*-CO ArH), 7.80 (1H, d, *J* = 15.6 Hz, CH=), 7.65 (2H, dd, *J* = 1.3, 7.7 Hz, Ph), 7.60 (1H, d, *J* = 15.6 Hz, CH=), 7.45 - 7.37 (3H, m, Ph), 6.71 (2H, d, *J* = 9.0 Hz, *o*-NMe_2 ArH), 3.09 (6H, s, $N(CH_3)_2$); δ_C (126 MHz, $CDCl_3$): 187.7 (CO), 153.4 (C), 142.5 (CH), 135.5 (C), 130.8 (CH), 129.9 (CH), 128.8 (CH), 128.2 (CH), 125.9 (C), 122.2 (CH), 110.8 (CH), 40.0 (CH_3);

* some material lost to spillage

1-(4-(dimethylamino)phenyl)-3-phenylpropan-1-ol



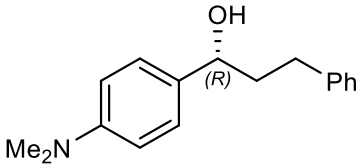
372

This compound is known but not fully characterised.[174]

To a solution of 4-(dimethylamino)benzaldehyde (152 mg, 1.02 mmol, 1 eq) in THF (1 ml) at -78 °C was added phenethyl magnesium chloride (1M in THF, 1 ml, 1 eq). The reaction was allowed to warm to rt over 5.5 hours and quenched with sat. NH_4Cl (1 ml), diluted with water (1 ml) and extracted with Et2O (3x 3 ml). The organic extract was dried over MgSO4 and concentrated to give the product as a white solid (266 mg, 102%). No purification was necessary.

Mp 67-68 °C; HRMS: found (ESI): $[M + H]^+$, 256.1692. ($C_{17}H_{22}NO$ requires 256.1696); δ_H (300 MHz, $CDCl_3$): 7.32 - 7.11 (8H, m, Ph), 6.73 (2H, d, *J* = 7.5 Hz, *o*-N Ph), 4.59 (1H, t, *J* = 6.5 Hz, C*H*OH), 2.95 (6H, s, NMe_2), 2.79 - 2.56 (2H, m, $PhCH_2$), 2.24 - 1.93 (2H, m, $CHCH_2$), 1.69 (1H, br. s., OH); δ_C (75 MHz, $CDCl_3$): 150.3 (C), 142.0 (C), 132.3 (C), 128.5 (CH), 128.3 (CH), 127.0 (CH), 125.7 (CH), 112.5 (CH), 73.7 (CH), 40.6 (CH_3), 40.0 (CH_2), 32.3 (CH_2); m/z (ESI): 256.2 ($[M + H]^+$)); Chiral HPLC (CHIRALPAK IB column: (0.46 x 25 cm), 1 ml/min, 10% IPA : 90% Hexane; 210 nm UV, 30 °C): retention times: 10.6 (*S*) and 11.3 (*R*) minutes.

(R)-1-(4-(dimethylamino)phenyl)-3-phenylpropan-1-ol



372

The asymmetric form of this compound has not been reported.

A degassed suspension of **309** (129 mg, 0.51 mmol, 1 eq) and (*R,R*)-**OMe-teth (115)** (3.3 mg, 0.005 mmol, 1%) in FA/TEA (5:2, 0.5 ml) and methanol (0.5 ml) was stirred at 40°C for 24 hours. The mixture was quenched with $NaHCO_3$ (sat., 2 ml), extracted into diethyl ether (2 ml) and dry loaded onto silica (~200 mg). Filtration with 20% EtOAc/petroleum ether (10 ml) through a silica plug (~0.75 g) gave the crude alcohol containing 7% saturated ketone (121

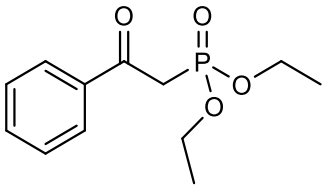
mg). Purification by column chromatography (20% EtOAc in petroleum ether) gave the pure product as a white solid (98 mg, 75%). in 97% ee as determined by HPLC.

Spectral data matched those of the racemic compound. (*R*) Configuration for product from reduction with (*R*,*R*)-**115** assumed by analogy to parent compound **162**. The order of elution of peaks in HPLC is the same.

TLC: 30% EtOAc in petroleum ether, silica, Rf = 0.22 (SM 0.28); $[\alpha]_D^{24}$ +18.8 (*R*), 97% ee (c 0.295 in $CHCl_3$); Chiral HPLC (CHIRALPAK IB column: (0.46 x 25 cm), 1 ml/min, 10% IPA : 90% Hexane; 210 nm UV, 30 °C): retention times: 10.6 (*S*) and 11.2 (*R*) minutes.

4.5.4 Alkyl Substituted Enones

diethyl (2-oxo-2-phenylethyl)phosphonate



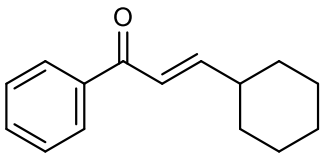
318

This compound is known. The Arbuzov (**318**) and Perkow (**319**) products were separated using a literature procedure.[129]

Triethyl phosphite (1.83 g, 11 mmol, 1.1 eq) was heated to 90°C in an RBF open to air. 2-bromoacetophenone (2.00 g, 10 mmol, 1.0 eq) was added portionwise over 1 minute with rapid bubbling observed. The reaction mixture was stirred for a further 15 minutes, then concentrated under vacuum. The residue was suspended in potassium hydroxide solution (2.0 g in 150 ml), and extracted with 19:1 petroleum ether : DCM (2 x 100 ml). The aqueous layer was acidified with conc HCl and extracted with DCM (2 x 50 ml). The DCM extracts were dried over Na_2SO_4 and concentrated to give the product as an orange oil (1.46 g, 57%).

δ_H (400 MHz, $CDCl_3$): 8.02 (2H, d, *J* = 7.5 Hz, *o*-ArH), 7.60 (1H, t, *J* = 7.5 Hz, p-ArH), 7.49 (2H, t, *J* = 7.5 Hz, *m*-ArH), 4.14 (4H, quin, *J* = 7.4 Hz, OCH_2), 3.64 (2H, d, *J* = 23.1 Hz, PCH_2), 1.28 (6H, t, *J* = 7.3 Hz, CH_3); δ_C (101 MHz, $CDCl_3$): 191.9 (d, *J* = 6.6 Hz), 136.4 (d, *J* = 1.5 Hz), 133.6, 128.9, 128.5, 62.5 (d, *J* = 6.6 Hz), 38.3 (d, *J* = 130 Hz), 16.2 (d, *J* = 6.6 Hz).

(E)-3-cyclohexyl-1-phenylprop-2-en-1-one



312

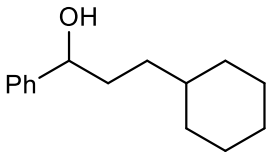
This compound is known.[175]

To a suspension of sodium hydride (60 wt % dispersion in mineral oil, 0.20 g, 5.0 mmol, 1.0 eq) in THF (5 ml) at 0 °C was added dropwise a solution of **318** (1.25 g, 4.9 mmol, 1.0 eq) in THF (5 ml) and the resulting clear solution was stirred for 30 minutes at room temperature. Cyclohexanecarboxaldehyde (0.57 g, 5.1 mmol, 1.0 eq) was added neat and the reaction mixture stirred at room temperature overnight. The reaction was quenched with NH_4Cl (half saturated, 30 ml) and extracted with ethyl acetate (3 x 15 ml), the organic extracts washed with brine (25 ml), dried over Na_2SO_4 and concentrated to give the crude product as a clear oil (1.13 g).

The crude was taken up in methanol (50 ml) and cooled to -72 °C. The resulting white precipitate was filtered and dried to give the pure product as a white solid (492 mg, 45 %)

Mp 46-48 °C; δ_H (400 MHz, $CDCl_3$): 7.92 (2H, d, *J* = 7.5 Hz, *o*-Ph), 7.57 - 7.51 (1H, m, *p*-Ph), 7.49 - 7.42 (2H, m, *m*-Ph), 7.01 (1H, dd, *J* = 7.0, 15.6 Hz, =C*H*CH), 6.83 (1H, d, *J* = 15.6 Hz, COC*H*=), 2.32 - 2.18 (1H, m, Cy), 1.88 - 1.74 (4H, m, Cy), 1.70 (1H, d, *J* = 12.0 Hz, Cy), 1.43 - 1.13 (6H, m, Cy); δ_C (101 MHz, $CDCl_3$): 191.4 (CO), 154.9 (CH), 138.2 (C), 132.6 (CH), 128.5 (CH), 128.5 (CH), 123.4 (CH), 41.1 (CH), 31.9 (CH_2), 26.0 (CH_2), 25.8 (CH_2).

3-cyclohexyl-1-phenylpropan-1-ol



373

This compound is known.[176]

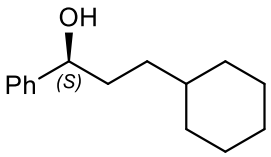
To a suspension of **312** (215 mg, 1.0 mmol, 1 eq) and Pd/C (5% w/w, 55 mg, 26 µmol, 2.5 % Pd) in isopropanol (5 ml) was added acetic acid (121 mg, 2.0 mmol, 2 eq) followed by sodium borohydride (153 mg, 4.0 mmol, 4 eq), with vigorous effervescence. The reaction mixture was stirred at rt for 2.5 hours, then additional sodium borohydride was added (75 mg, 2.0

mmol, 2 eq). The reaction was stirred for an additional 2 hours and then quenched slowly with HCl (0.2M, 2.5 mL). The resulting suspension was neutralised with NaOH (2M, ~1.5 ml) and filtered through Celite with isopropanol to remove Pd/C. The mixture was concentrated to remove excess isopropanol and then the aqueous layer was extracted with diethyl ether (3 x 10 mL), dried over Na_2SO_4 and concentrated to give the product as a white solid (214 mg, 98%)

δ_H (300 MHz, $CDCl_3$): 7.39 - 7.31 (4H, m), 7.31 - 7.26 (1H, m), 4.63 (1H, ddd, *J* = 3.3, 5.9, 7.3 Hz), 1.88 - 1.57 (8H, m), 1.39 - 1.06 (6H, m), 0.94 - 0.77 (2H, m); δ_C (75 MHz, $CDCl_3$): 162.3 (C), 128.4 (CH), 127.5 (CH), 125.9 (CH), 75.1 (CH), 37.7 (CH), 36.5 (CH_2), 33.5 (CH_2), 33.4 (CH_2), 33.3 (CH_2), 26.7 (CH_2), 26.4 (CH_2), (One CH_2 not observed, must overlap. Consistent with literature).

Chiral HPLC (CHIRALPAK IB column: (0.46 x 25 cm), 1 ml/min, 4% IPA : 96% Hexane; 210 nm UV, 30 °C): retention times: 7.4 (*S*) and 7.9 (*R*) minutes.

(S)-3-cyclohexyl-1-phenylpropan-1-ol



373

The asymmetric form of this compound has not been reported.

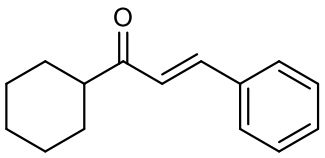
FA/TEA/MEOH reduction: See general method 4.

With **312** (107 mg) and (*S*,*S*)-**3C-teth (80)**; 3 hours reaction time, total conversion 100%. Product obtained as a grey solid (55 mg, 50%) containing a mixture of saturated and unsaturated alcohols, ratio 97.5 : 2.5 by ^{1}H NMR. Major product ee 97%.

Spectral data matched those of the racemic compound. (*S*) Configuration for product from reduction with (*S*,*S*)-**80** assumed by analogy to parent compound **162**. The order of elution of peaks in HPLC is the same.

$[\alpha]_D^{24}$ -10.9 (c 0.245 in $CHCl_3$); Chiral HPLC (CHIRALPAK IB column: (0.46 x 25 cm), 1 ml/min, 4% IPA : 96% Hexane; 210 nm UV, 30 °C): retention times: 7.5 (*S*)-saturated and 7.9 (*R*)-saturated minutes.

(E)-1-cyclohexyl-3-phenylprop-2-en-1-one



313

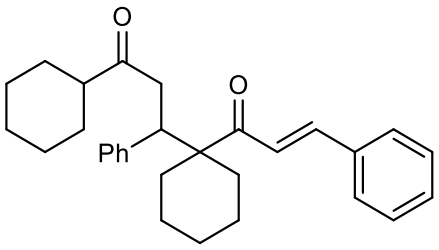
This compound is known.[177]

Sodium methoxide solution (25% w/w, 5.96 g, 27.6 mmol, 1 eq) was diluted to 50 ml with methanol and added to cyclohexylmethyl ketone (3.33 g, 26.4 mmol, 1 eq). The mixture was cooled to 0 °C and a solution of benzaldehyde (2.81 g, 26,5 mmol, 1 eq) in methanol (15 ml) was added. The reaction mixture was warmed to 40 °C and stirred for 3 days. The reaction was quenched with 0.25M HCl (100 ml) and extracted with diethyl ether (4 x 100 ml), the organic layers were dried and concentrated to give the crude product as a yellow oil that solidifies slowly on standing.

The oil was dissolved in ~150 ml of methanol and cooled to -78 °C, the resulting precipitate was filtered and washed once with cold methanol and dried to give the purified product as a white solid (2.78 g, 49%).

Mp 54-58 °C; δ_H (250 MHz, $CDCl_3$): 7.60 (1H, d, *J* = 15.9 Hz, PhCH=), 7.60 - 7.52 (2H, m, *o*-Ph), 7.43 - 7.35 (3H, m, *m,p*-Ph), 6.82 (1H, d, *J* = 15.9 Hz, COCH=), 2.75 - 2.57 (1H, m, CHCO), 2.01 - 1.77 (4H, m), 1.77 - 1.65 (1H, m), 1.55 - 1.14 (5H, m).

(E)-1-(1-(3-cyclohexyl-3-oxo-1-phenylpropyl)cyclohexyl)-3-phenylprop-2-en-1-one



314

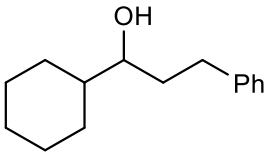
This compound is novel. Some evidence for its proposed structure is presented.

Side product isolated from second crystallization of **313**

δ_H (600 MHz, $CDCl_3$): 7.65 (1H, d, *J* = 15.8 Hz, =CHPh), 7.53 - 7.48 (2H, m, ArH), 7.42 - 7.36 (3H, m, ArH), 7.30 - 7.19 (3H, m, ArH), 7.16 (2H, d, *J* = 7.5 Hz, ArH), 6.93 (1H, d, *J* = 15.0 Hz,

=CHCOR), 3.48 (1H, dd, *J* = 10.5, 3.8 Hz, CHPh), 3.01 (1H, dd, *J* = 17.3, 9.8 Hz, RCOCH*H*), 2.78 (1H, dd, *J* = 17.3, 3.8 Hz, RCOC*H*H), 2.29 (1H, d, *J* = 9.0 Hz, C*H*$(CH_2)_5$), 2.23 - 2.15 (2H, m, Cy), 1.74 - 1.52 (8H, m, Cy), 1.41 - 0.99 (10H, m, Cy)δ_C (151 MHz, $CDCl_3$): 212.1 (C=O), 203.4 (C=O), 142.5 (CH), 140.0 (C), 135.0 (C), 130.3 (CH), 129.8 (CH), 128.8 (CH), 128.4 (CH), 127.8 (CH), 126.8 (CH), 122.3 (CH), 54.3 (C), 51.2 (CH), 47.9 (CH), 41.1 (CH_2), 33.4 (CH_2), 30.7 (CH_2), 28.2 (CH_2), 28.1 (CH_2), 25.8 (CH_2), 25.8 (CH_2), 25.6 (CH_2), 25.5 (CH_2), 23.5 (CH_2), 23.2 (CH_2).

1-cyclohexyl-3-phenylpropan-1-ol



374

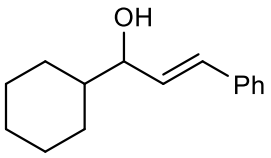
This compound is known.[176]

To a solution of cyclohexane carboxaldehyde (128 mg, 1.14 mmol, 1 eq) in THF (1 ml) was added phenethyl magnesium chloride (1M in THF, 1 ml, 1 mmol, 1 eq) at -78 °C. The reaction was stirred for 2.75 hours while gradually warming to ~0 °C, then quenched with NH_4Cl (sat. soln, 2 ml) and water (1 ml). The suspension was extracted with Et2O (2 x 2.5 ml), the organic layers dried over MgSO4 and concentrated to give the crude product as a white solid.

The crude was purified by column chromatography (10% EtOAc in petroleum ether) to give the pure product as a white powder (110 mg, 50%)

TLC: 10% EtOAc in petroleum ether, silica, Rf 0.16, $KMnO_4$; Mp 68-70 °C; δ_H (300 MHz, $CDCl_3$): 7.33 - 7.26 (2H, m, Ph), 7.24 - 7.14 (3H, m, Ph), 3.39 (1H, dtd, *J* = 3.5, 5.3, 8.9 Hz, C*H*OH), 2.91 - 2.78 (1H, m, CHC*H*H), 2.72 - 2.58 (1H, m, CHCH*H*), 1.89 - 1.60 (7H, m, CH_2 and Cy), 1.37 - 0.97 (7H, m, OH and Cy); δ_C (75 MHz, $CDCl_3$): 142.4 (C), 128.4 (CH), 128.4 (CH), 125.7 (CH), 75.6 (CH), 43.8 (CH), 35.9 (CH_2), 32.4 (CH_2), 29.2 (CH_2), 27.8 (CH_2), 26.5 (CH_2), 26.3 (CH_2), 26.2 (CH_2); Chiral HPLC (CHIRALPAK IB column: (0.46 x 25 cm), 1 ml/min, 4% IPA : 96% Hexane; 210 nm UV, 30 °C): retention times: 8.3 and 13.3 minutes.

(E)-1-cyclohexyl-3-phenylprop-2-en-1-ol

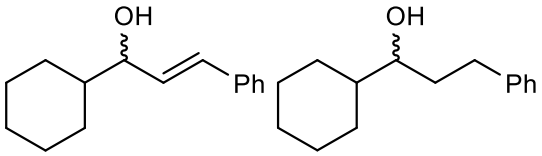


375

This compound is known.[178]

To a suspension of **313** (211 mg, 1.0 mmol, 1 eq) and cerium trichloride heptahydrate (372 mg, 1.0 mmol, 1 eq) in methanol (2 mL) was added sodium borohydride (43 mg, 1.1 mmol, 1 eq) at 0 °C. The reaction was stirred for 1.5 hours, quenched with NH_4Cl (sat., 5 mL), diluted with water (3 ml), and extracted with diethyl ether (3x 5 mL). The organic layers were dried over Na_2SO_4 and concentrated to give the unsaturated alcohol as a white solid (168 mg, 79%). δ_H (400 MHz, $CDCl_3$): 7.43 - 7.36 (2H, m, *o*-Ph), 7.32 (2H, t, *J* = 7.5 Hz, *m*-Ph), 7.27 - 7.19 (1H, m, *p*-Ph), 6.55 (1H, d, *J* = 15.8 Hz, =CHPh), 6.23 (1H, dd, *J* = 7.2, 15.9 Hz, =C*H*CH), 4.02 (1H, br. s., C*H*OH), 1.92 (1H, d, *J* = 12.0 Hz, OH), 1.83 - 1.61 (4H, m, Cy), 1.60 - 1.42 (2H, m, Cy), 1.35 - 0.90 (5H, m, Cy); δ_C (101 MHz, $CDCl_3$): 136.8 (C), 131.2 (CH), 131.1 (CH), 128.6 (CH), 127.6 (CH), 126.5 (CH), 77.6 (CH), 44.0 (CH), 28.9 (CH_2), 28.7 (CH_2), 26.5 (CH_2), 26.1 (CH_2), 26.1 (CH_2); Chiral HPLC (CHIRALPAK IB column: (0.46 x 25 cm), 1 ml/min, 4% IPA : 96% Hexane; 210 nm UV, 30 °C): retention times: 9.9 and 14.4 minutes.

(E)-1-cyclohexyl-3-phenylprop-2-en-1-ol and 1-cyclohexyl-3-phenylpropan-1-ol



374 and **375**

The asymmetric form of this compound has not been reported.

FA/TEA/MEOH reduction: See general method 4.

With **313** (97 mg) and (*S*,*S*)-**3C-teth (80)**; 2.5 hours reaction time, total conversion to alcohols 82%, with the remainder being the saturated ketone intermediate. Product obtained as a clear oil (78 mg, 80%) containing a mixture of saturated and unsaturated alcohols, ratio 9.9 : 90.1 by ^1H NMR. Major (1,2-) product ee 59%, minor (1,4-) product ee 36%.

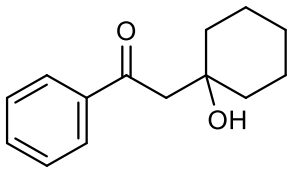
With **313** (108 mg) and (*R*,*R*)-**OMe-teth (115)**; 23 hours reaction time, total conversion 100%. Product obtained as a white solid (111 mg, 100%) containing a mixture of saturated and unsaturated alcohols, ratio 58.6 : 41.4 by ^{1}H NMR. Major product ee 21%, minor product ee 76%.

Aqueous reduction: Sodium formate (170 mg, 2.5 mmol, 5 eq), **313** (110 mg, 1.0 mmol, 1 eq) and (*R*,*R*)-**OMe-teth (115)** (3.3 mg, 5 µmol, 1%) were suspended in water (1 ml) and methanol (0.5 ml) and heated to 60°C. The solids melt and form a brown oil on top of the aqueous phase. The mixture was stirred vigorously for 19 hours before being cooled to rt and diluted with diethyl ether (2 ml). The organic layer was separated, then concentrated directly onto silica. Elution through a short silica plug with 40% diethyl ether in petroleum ether gave the product in 98% conversion as a clear oil (103 mg, 90%) containing a mixture of saturated and unsaturated alcohols, ratio 68.1 : 31.9 by ^{1}H NMR. Major product ee 49%, minor product ee 82% by HPLC.

HPLC peak positions were taken from racemic standards prepared above. Configuration of the product alcohols has not been determined.

4.5.5 Structure variants

2-(1-hydroxycyclohexyl)-1-phenylethan-1-one



326

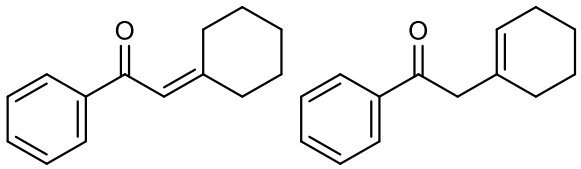
This compound is known.[179]

$TiCl_4$ (1M in DCM, 12 ml, 12 mmol, 1.2 eq) was added dropwise at 0°C to a solution of cyclohexanone (1.23 g, 12.5 mmol, 1.25 eq) in DCM (20 ml) and stirred for 25 mins. To the resulting yellow suspension was added dropwise 1-phenyl-1-(trimethylsiloxy)ethylene (1.94 g, 10 mmol, 1 eq). The resulting orange suspension was allowed to warm to rt and stirred for 24 hours before being quenched with water (35 ml). The mixture was extracted with DCM (2 x 20 ml), washed with brine (10 ml) and filtered through a plug of silica gel (~4 g) with DCM to give the crude product as a thick yellow oil that crystallises on standing (2.69 g).The crude was dissolved in hot methanol, concentrated to a thick oil and then crystallised by addition of hexane (~10 ml) to give the pure product as a white crystalline solid (0.95 g, 43%). A second

crop was isolated by concentration of the mother liquors and addition of hexane to give white plates (0.20 g, 9%). Combined yield (1.15 g, 52%).

TLC: 20% EtOAc in petroleum ether, silica, Rf = 0.2, UV; Mp 78-79 °C; δ_H (400 MHz, $CDCl_3$): 8.00 - 7.91 (2H, m, *o*-Ph), 7.63 - 7.56 (1H, m, *p*-Ph), 7.52 - 7.45 (2H, m, *m*-Ph), 3.98 (1H, s, OH), 3.12 (2H, s, $COCH_2$), 1.83 - 1.65 (5H, m, Cy), 1.58 (1H, dd, *J* = 2.9, 6.2 Hz, Cy), 1.52 - 1.41 (4H, m, Cy), 1.36 - 1.23 (1H, m, Cy); δ_C (101 MHz, $CDCl_3$): 202.0 (CO), 137.5 (C), 133.5 (CH), 128.7 (CH), 128.1 (CH), 71.0 (C), 47.7 (CH_2), 37.8 (CH_2), 25.8 (CH_2), 22.0 (CH_2).

2-cyclohexylidene-1-phenylethan-1-one and 2-(cyclohex-1-en-1-yl)-1-phenylethan-1-one



320 and **327**

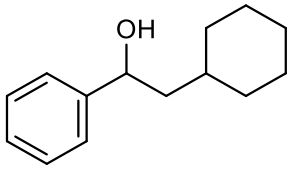
This compound is known.[180]

326 (868 mg, 3.9 mmol, 1 eq) and *p*-toluenesulfonic acid monohydrate (613 mg, 3.2 mmol, 0.8 eq) were suspended in toluene (8 ml) and stirred at 40 °C for 4.5 hours, as monitored by TLC. Na_2SO_4 (~0.5 g) and petroleum ether (5 ml) were added, and the resulting suspension filtered through a silica plug (~1 g) with 10% EtOAc in petroleum ether to give the crude mixture of ketones as a yellow oil.

The crude was purified by column chromatography (6% Et_2O in pentane) to give the pure mixture as a pale yellow oil (616 mg, 77%), 87.1 : 12.9 ratio by ^1H NMR

TLC: 10% EtOAc / Pet ether, silica, Rf 0.38, UV; δ_H (300 MHz, $CDCl_3$): 8.03 - 7.89 (2H, m, *o*-Ph), 7.57 - 7.49 (1H, m, *p*-Ph), 7.48 - 7.40 (2H, m, *m*-Ph), 6.60 (1H, s, =CH), 2.81 - 2.72 (2H, m, Cy), 2.35 - 2.28 (2H, m, Cy), 1.80 - 1.50 (6H, m, Cy); δ_C (75 MHz, $CDCl_3$): 192.4 (C), 162.8 (C), 139.3 (C), 132.3 (CH), 128.4 (CH), 128.3 (CH), 118.8 (CH), 38.4 (CH_2), 30.7 (CH_2), 28.9 (CH_2), 28.0 (CH_2), 26.3 (CH_2).

2-cyclohexyl-1-phenylethan-1-ol



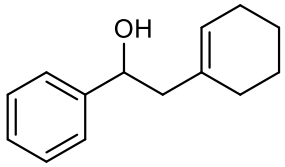
328

This compound is known.[181]

To a suspension of **320** (215 mg, 1.0 mmol, 1 eq) and Pd/C (5% w/w, 55 mg, 26 µmol, 2.5 % Pd) in isopropanol (5 ml) was added acetic acid (121 mg, 2.0 mmol, 2 eq) followed by sodium borohydride (153 mg, 4.0 mmol, 4 eq), with vigorous effervescence. The reaction mixture was stirred at rt for 2.5 hours, then additional sodium borohydride was added (75 mg, 2.0 mmol, 2 eq). The reaction was stirred for an additional 2 hours and then quenched slowly with HCl (0.2M, 2.5 mL). The resulting suspension was neutralised with NaOH (2M, ~1.5 ml) and filtered through Celite with isopropanol to remove Pd/C. The mixture was concentrated to remove excess isopropanol and then the aqueous layer was extracted with diethyl ether (3 x 10 mL), dried over Na_2SO_4 and concentrated to give the product as a white solid (214 mg, 98%)

Mp 57-59 °C; HRMS: found (ESI): $[M + Na]^+$, 227.1406 ($C_{14}H_{20}NaO$ requires 227.1411); ν_{max}: 3240 (OH), 2920 (CH), 2847 (CH), 1446 (C-O), 1003, 697 (monosubstituted Ph) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.38 - 7.31 (4H, m, Ph), 7.31 - 7.24 (1H, m, Ph), 4.79 (1H, ddd, *J* = 8.7, 4.9, 3.7 Hz, C*H*OH), 1.91 - 1.59 (6H, m, C*H*H + Cy), 1.58 - 1.48 (2H, m, OH + CH*H*), 1.48 - 1.36 (1H, m, CH), 1.31 - 1.08 (3H, m), 1.04 - 0.87 (2H, m); δ_C (126 MHz, $CDCl_3$): 145.4 (C), 128.5 (CH), 127.5 (CH), 125.8 (CH), 72.1 (CH), 47.1 (CH_2), 34.2 (CH), 34.0 (CH_2), 32.9 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 26.2 (CH_2); *m/z* (ESI): 227.1 ($[M + Na]^+$); Chiral G.C; (CP-Chirasil-Dex-CB 25m x 0.25mm x 0.25µm column, oven temperature 155 ºC, inj.: split 220 ºC, det.: FID 250 ºC, 100 Pa H_2) retention times 13.1 (*S?*) and 13.8 (*R?*) minutes.

Alkene isomer evidence:

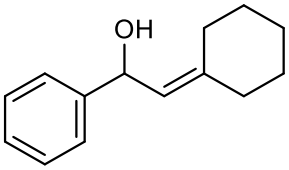


330

Peaks corresponding to isomer **330** were observed in the ^{1}H NMR and chiral GC data obtained for racemic standard **328**, as well as in the asymmetric reduction product mixtures.

Selected data: δ_H (300 MHz, $CDCl_3$): 5.60 (1H, m., =CH), 4.74 (1H, dd, *J* = 4.5, 2.3 Hz, C*H*OH); *m/z* (ESI): 225.1 ([M' + Na]$^+$); Chiral G.C; (CP-Chirasil-Dex-CB 25m x 0.25mm x 0.25µm column, oven temperature 155 ºC, inj.: split 220 ºC, det.: FID 250 ºC, 100 Pa H_2) retention times 12.9 and 13.1 minutes.

2-cyclohexylidene-1-phenylethan-1-ol



329

This compound has been reported as part of a mixture of isomers but has not been fully characterised.[182]

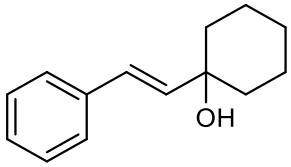
To a suspension of **320** (101 mg, 0.5 mmol, 1 eq) and cerium trichloride heptahydrate (185 mg, 0.5 mmol, 1 eq) in methanol (1 mL) was added sodium borohydride (29 mg, 0.8 mmol, 1.5 eq) at 0 ^{o}C. The reaction was stirred for 2 hours and quenched with NH_4Cl (sat., 0.5 mL), diluted with water (0.5 ml) and extracted with diethyl ether (3x 2 mL). The organic extracts were dried over Na_2SO_4 and concentrated to give the product as a clear oil (103mg).

The crude product was purified by column chromatography on silica gel (2.6 g) with 10% diethyl ether in petroleum ether as eluent, to yield the pure product as a clear oil (65 mg, 64%). The pure product decomposes at room temperature within a few days.

HRMS: found (ESI): [M + H]$^+$, 225.1251. ($C_{14}H_{18}NaO$ requires 225.1250); ν_{max}: 3374 (OH), 2928 (CH), 2854 (CH), 1447 (CO), cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.42 - 7.29 (4H, m, Ph), 7.27 - 7.19 (1H, m, Ph), 5.50 (1H, dd, *J* = 1.5, 8.9 Hz, C*H*OH), 5.33 (1H, d, *J* = 8.8 Hz, =CH), 2.41 - 2.21 (2H, m, Cy), 2.10 (2H, t, *J* = 4.5 Hz, Cy), 1.95 (1H, br. s., OH), 1.69 - 1.44 (6H, m, Cy); δ_C (101 MHz,

$CDCl_3$): 144.4 (C), 143.0 (C), 128.3 (CH), 127.1 (CH), 125.7 (CH), 124.4 (CH), 69.7 (CH), 37.0 (CH_2), 29.3 (CH_2), 28.3 (CH_2), 27.8 (CH_2), 26.6 (CH_2); *m/z* (ESI): 225.1 ([M + Na]$^+$), 185.1 (30%, [M - OH]$^+$).

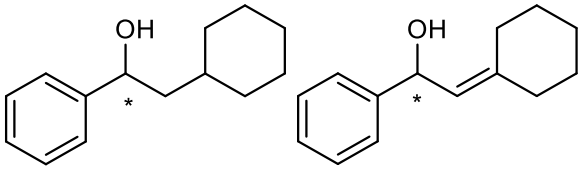
Chiral HPLC/GC not obtained, suitable conditions for separation were not found before the compound decomposed.



Selected ^{1}H NMR peaks for decomposed product, proposed structure.

δ_H (400 MHz, $CDCl_3$): 7.55 - 7.07 (5H+, m, ArH), 6.63 (1H, d, *J* = 16.1 Hz, =CH), 6.34 (1H, d, *J* = 16.1 Hz, =CH), 1.83 - 1.26 (10H+, m, Cy: CH_2).

2-cyclohexyl-1-phenylethan-1-ol and 2-cyclohexylidene-1-phenylethan-1-ol



328 and **329**

This compound is known in racemic form. [181,182]

A suspension of **320** (95 mg, 0.47 mmol, 1 eq) and (*S,S*)-**3C-teth (80)** (3.1 mg, 0.01 mmol, 1%) in FA/TEA (5:2, 0.5 ml) and MeOH (0.5 ml) was stirred at 40°C for 22.5 hours. The mixture was diluted with diethyl ether (2 ml) and quenched with $NaHCO_3$ (sat., 2 ml), the aqueous layer was extracted further with ether (2x 2 ml) and the organic extracts dried over Na_2SO_4 and passed through a silica plug to yield the product as an off white solid (92mg, 96%). The product was obtained in full conversion as a mixture of saturated and unsaturated alcohols, ratio 93:7 by ^{1}H NMR. Major product ee was 97% as calculated by HPLC and GC.

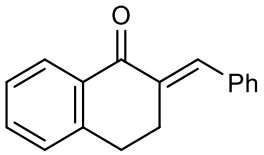
The opposite enantiomer was obtained using (*R,R*)-**OMe-teth (115)** (3.3 mg), **320** (101 mg), FA/TEA (0.5 ml) and methanol (0.5 ml), to give full conversion to a mixture of saturated and unsaturated alcohols (100 mg, 96%), ratio 96:4 by ^{1}H NMR. Major product ee was ~97% as calculated by GC.

Purification by chromatography on silica (8% Et2O / Petroleum ether) separated the unsaturated alcohol and gave the purified product as a white solid (77 mg, 74%).

Spectral data for asymmetric product is consistent with the prepared standards. The configuration was not determined, assuming the sense of reduction is consistent with that for **160** the optical rotation has been reported for the *R* isomer, however further evidence would be required to prove the configuration.

Mp 52 °C; $[\alpha]_D^{26}$ +50.4, (*R?*) (c 0.245 in $CHCl_3$); Chiral G.C; (CP-Chirasil-Dex-CB 25m x 0.25mm x 0.25µm column, oven temperature 155 ºC, inj.: split 220 ºC, det.: FID 250 ºC, 100 Pa H_2) retention times 13.3 (*S?*) and 13.9 (*R?*) minutes.

(E)-2-benzylidene-3,4-dihydronaphthalen-1(2H)-one



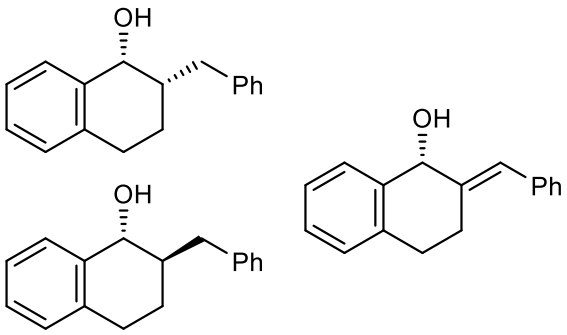
321

This compound is known.[183]

A solution of α-Tetralone (2.98 g, 20.4 mmol, 1 eq) and benzaldehyde (3.20 g, 30.2 mmol, 1.5 eq) in ethanol (5 ml) was cooled to 0°C. Sodium hydroxide solution (1M, 10 ml, 10 mmol, 0.5 eq) was added in one portion and the resulting suspension was stirred for 24 hours. The reaction was quenched by addition of ethanol (5 ml) and HCl (2M, 5 ml). Initially the crude product oiled out but after stirring for 30 mins it precipitated cleanly as a brown solid, which was collected by filtration and stored in a desiccator overnight. (5.01 g).

Recrystallization from hot ethanol (~20 ml, 90 °C) gave the pure product as pale yellow flaky crystals (3.88 g, 81%).TLC: solvent, solid phase, Rf, visualisation method; Mp 105-107 °C; δ_H (500 MHz, $CDCl_3$): 8.14 (1H, dd, *J* = 1.2, 7.9 Hz), 7.88 (1H, s), 7.49 (1H, dt, *J* = 1.5, 7.5 Hz), 7.46 - 7.40 (4H, m), 7.39 - 7.33 (2H, m), 7.25 (1H, dd, *J* = 0.6, 7.6 Hz), 3.14 (2H, dt, *J* = 1.7, 6.6 Hz), 2.95 (2H, t, *J* = 6.6 Hz); δ_C (126 MHz, $CDCl_3$): 187.9 (CO), 143.2 (C), 136.6 (CH), 135.8 (C), 135.4 (C), 133.5 (C), 133.3 (CH), 129.9 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.2 (CH), 127.0 (CH), 28.9 (CH_2), 27.2 (CH_2).

Analysis of ATH products of ***321***



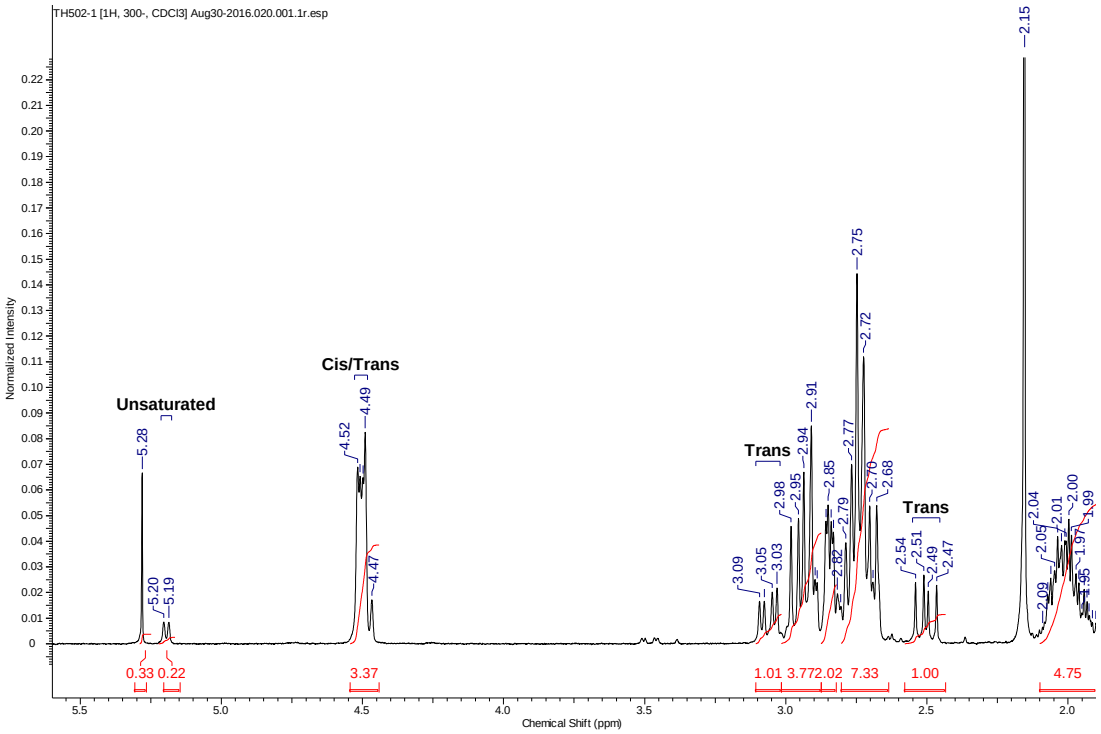
331, **333**, **332**

FA/TEA/MEOH reduction: See general method 4.

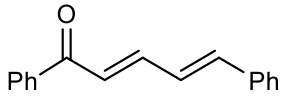
With **321** (115 mg) and (*S*,*S*)-**3C-teth (80)**; 24 hours reaction time, total conversion 100%. Product obtained as a clear oil (87 mg, 74%) containing a mixture of *cis* : *trans* : 1 ,2- products in a 41 : 35 : 22 ratio.

With **321** (117 mg) and (*R*,*R*)-**OMe-teth (115)**; 27 hours reaction time, total conversion 100%. Product obtained as a clear oil (110 mg, 92%) containing a mixture of *cis* : *trans* : 1 ,2- products in a 66 : 28 : 6 ratio.

Ratio of products determined by characteristic ^{1}H NMR shifts in product mixtures and comparison to literature values.[132,133] The 1,2- product could be clearly distinguished by its secondary alcohol proton at 5.19 (1H, d, *J* = 3.3 Hz); lit: 5.16 (s, 1H), while the 1,4 to 1,2 selectivity could by calculated using the equivalent overlapping resonance for cis and trans at 4.58 - 4.41 (1H, m); lit (cis): 4.49 (s, 1H), lit (trans): 4.49 (t, *J* = 7.2 Hz, 1H). Finally there is then a pair of reasonably distinct resonances for the *trans* product that can be integrated at 3.08 (1H, dd, *J* = 13.5, 5.0 Hz); lit: 3.07 (dd, *J* = 13.8, 5.2 Hz, 1H) and 2.50 (1H, dd, *J* = 13.5, 9.1 Hz); lit: 2.51 (dd, J = 13.7, 8.9 Hz, 1H). Integrating these allows approximate calculation of the *cis* : *trans* ratio.



(2E,4E)-1,5-diphenylpenta-2,4-dien-1-one



323

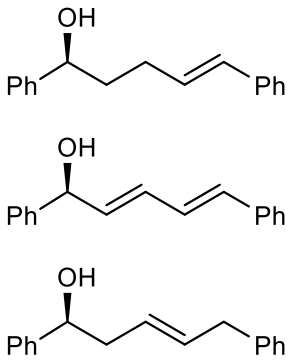
This compound is known.[135]

To a suspension of sodium hydride (60 wt % dispersion in mineral oil, 0.21 g, 5.3 mmol, 1.0 eq) in THF (5 ml) at 0 °C was added dropwise a solution of **318** (1.29 g, 5.0 mmol, 1.0 eq) in THF (5 ml) and the resulting yellow solution was stirred for 30 minutes at room temperature. The mixture was again cooled to 0 °C, cinnamaldehyde (1.05 g, 7.9 mmol, 1.6 eq) was added neat and the reaction mixture stirred at room temperature overnight. The reaction mixture was filtered through paper with diethyl ether and concentrated to yield the crude product contaminated with starting aldehyde as an oily yellow solid (1.57 g).

The crude was taken up in chloroform (25 ml), layered with methanol (25 ml) and left to stand for several days. The resulting green/yellow tinted precipitate was collected by filtration and dried under high vacuum to yield the purified product (478 mg, 41%).

δ_H (300 MHz, $CDCl_3$): 8.01 - 7.95 (2H, m, ArH), 7.67 - 7.54 (2H, m, ArH and =CH), 7.54 - 7.46 (4H, m, ArH), 7.42 - 7.28 (3H, m, ArH), 7.10 (1H, d, *J* = 14.9 Hz, =CH), 7.06 - 7.00 (2H, m, CH=CH).

Analysis of ATH products of ***323***



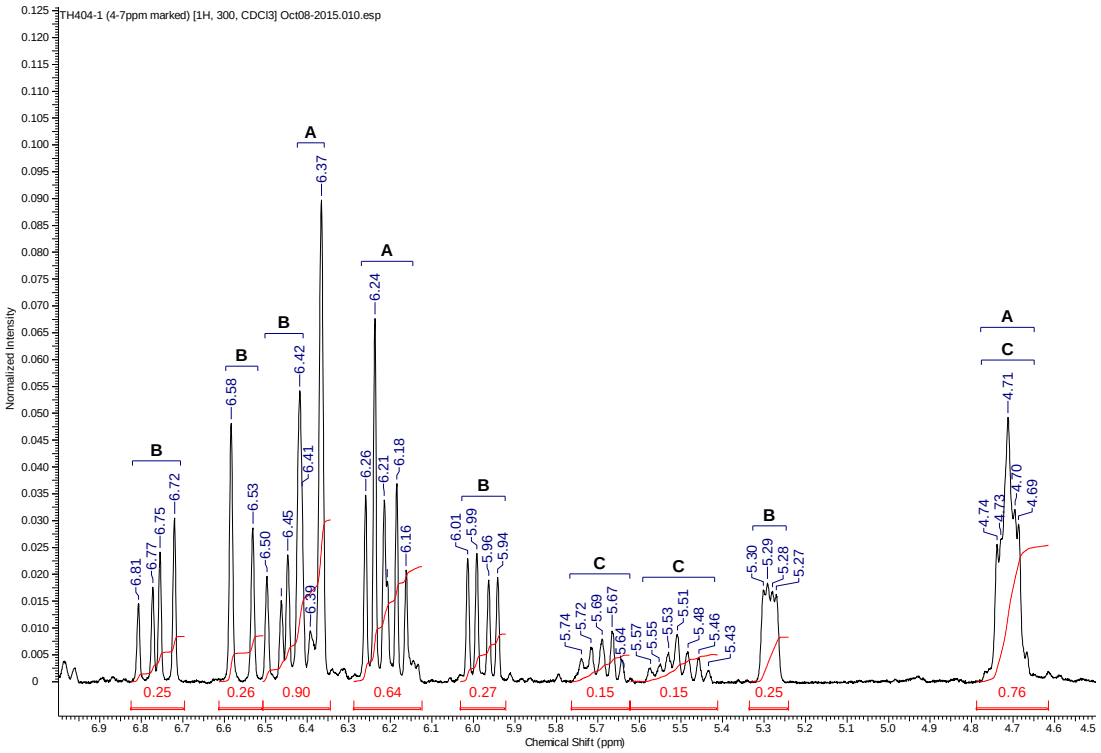
340, **341**, **342**

FA/TEA/MEOH reduction: See general method 4.

With **323** (117 mg) and (*S*,*S*)-**3C-teth (80)**; 5.25 hours reaction time, total conversion 100%. Product obtained as a clear oil (87 mg, 74%) containing a mixture of 1,4- : 1 ,2- : 1,6- products in a 61 : 23 : 15 ratio.

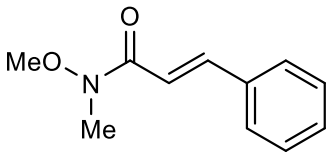
(*S*) Configuration for products from reduction with (*S*,*S*)-**80** assumed by analogy to compound **162**, although the product mixture was not separated by chromatography.

Ratio of products determined by characteristic ^{1}H NMR shifts in product mixtures and comparison to literature values.[136–138] All of the products have reasonably distinct resonances between 4 and 7 ppm corresponding to alkene and secondary alcohol functionalities. Normalising the integrals such that the secondary alcohol resonances at ~5.3 and ~4.7 sum to 1 allows the ratio of products to be determined. All of the alkene shifts can then be assigned, and the observed coupling patterns match those found in the literature and support the proposed structures.



δ_H (300 MHz, $CDCl_3$):	A (1,4-)	B (1,2)-	C (1,6-)
6.76 (1H, dd, *J* = 15.4, 10.3 Hz, PhCH=C*H*),		γ alkene	
6.56 (1H, d, *J* = 15.8 Hz, PhC*H*=CH),		δ alkene	
6.45 (1H, dd, *J* = 15.0, 10.5 Hz, C(OH)CH=C*H*),		β alkene	
6.39 (1H, d, *J* = 15.6 Hz, =CHPh),	γ alkene		
6.21 (1H, dt, J = 16.0, 6.6 =C*H*CH_2),	δ alkene		
5.98 (1H, dd, J = 15.0, 6.6 Hz, CH(OH)C*H*=),		α alkene	
5.76 - 5.63 (1H, m, =CH),			β/γ alkene
5.59 - 5.41 (1H, m, =CH),			β/γ alkene
5.29 (1H, dd, *J* = 6.5, 2.8 Hz, C*H*OH),		*sec*-alcohol	
4.77 - 4.65 (2H, m, 2* C*H*OH)	*sec*-alcohol		*sec*-alcohol
Sum Protons from 4-7ppm	3	5	3

N-methoxy-N-methylcinnamamide



335

This compound is known.[184]

A solution of cinnamoyl chloride (1.96 g, 11.8 mmol, 1 eq) and *N,O*-dimethylhydroxylamine hydrochloride (1.17 g, 12.1 mmol, 1 eq) in DCM (24 ml) was cooled to 0 °C in an ice bath. Pyridine (1.9 ml, 24 mmol, 2 eq) was added dropwise over 5 minutes and the resulting white suspension was allowed to warm to rt and stirred for 18 hours. The reaction was diluted with diethyl ether (40 ml) and washed successively with HCl (1M, 2x 20 ml), water (20 ml) and Sat. $NaHCO_3$ (20 ml). The organic phase was dried (Na_2SO_4) and concentrated to give the crude product as a clear oil (2.02 g)

The product was crystallised from DCM and petroleum ether to give a white crystalline solid (1.77 g, 79%[*]).

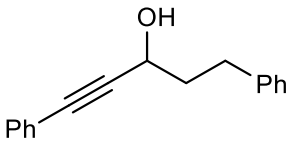
δ_H (300 MHz, $CDCl_3$): 7.74 (1H, d, *J* = 15.9 Hz, =C*H*), 7.61 - 7.52 (2H, m, Ar*H*), 7.44 - 7.31 (3H, m, Ar*H*), 7.04 (1H, d, *J* = 15.9 Hz, =C*H*), 3.76 (3H, s, OCH_3), 3.31 (3H, s, NCH_3); δ_C (75 MHz, $CDCl_3$): 166.9 (CO), 143.4 (CH), 135.1 (C), 129.8 (CH), 128.7 (CH), 128.0 (CH), 115.7 (CH), 61.8 (CH_3), 32.5 (CH_3).

4.5.5.1 Preparation of PhCCLi

To a solution of phenylacetylene (844 mg, 8.3 mmol, 1 eq) in THF (6.5 ml) was added dropwise at -78°C *n*BuLi (2.5M in hexane, 3.5 ml, 8.75 mmol, x1.05 eq). The resulting suspension was stirred for 15 mins, warmed to 0°C and stirred for a further 15 mins. 3 ml portions of the resulting solution were used immediately.

[*] the starting material contained 15% cinnamic acid as an impurity, which was removed during the reaction. Accounting for this gives a 93% yield.

1,5-diphenylpent-1-yn-3-ol



338

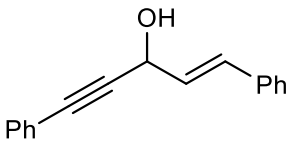
This compound is known.[185]

Lithiated phenylacetylene solution (3 ml, ~2.5 mmol alkyllithium, 1.25 eq) was added dropwise at -78°C to a precooled solution of 3-phenylpropanal (270 mg, 2.0 mmol, 1 eq) in THF (1 ml). The reaction mixture was stirred for 4.5 hours before being warmed to 0°C and quenched with NH_4Cl (sat. soln, 1 ml) and diluted with water (1 ml). The aqueous phase was extracted with diethyl ether (2 ml), and the organic extracts dried (Na_2SO_4) and concentrated under vacuum to give a yellow oil.

Purification by column chromatography on silica (6.6g, 100 ml of 10% ethyl acetate in petroleum ether) gave the pure alcohol as a yellow oil (313 mg, 66%).

δH (400 MHz, $CDCl_3$): 7.49 - 7.40 (2H, m, ArH), 7.36 - 7.17 (9H, m, ArH), 4.60 (1H, q, *J* = 6.4 Hz, C*H*OH), 2.87 (2H, t, *J* = 7.8 Hz, CH_2), 2.21 - 2.07 (2H, m, CH_2), 1.89 (1H, d, *J* = 5.6 Hz, OH); δC (101 MHz, $CDCl_3$): 141.3 (C), 131.7 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 126.0 (CH), 122.6 (C), 89.8 (C), 85.3 (C), 62.3 (CH), 39.3 (CH_2), 31.5 (CH_2); Chiral HPLC (CHIRALPAK IB column: (0.46 x 25 cm), 1 ml/min, 20% IPA : 80% Hexane; 254 nm UV, 30 °C): retention times: 5.9 and 8.5 minutes.

(E)-1,5-diphenylpent-1-en-4-yn-3-ol



339

This compound is known.[186]

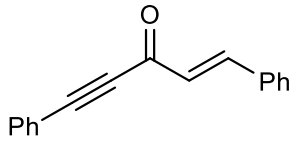
Lithiated phenylacetylene solution (3 ml, ~2.5 mmol alkyllithium, 1.25 eq) was added dropwise at -78°C to a precooled solution of cinnamaldehyde (284 mg, 2.1 mmol, 1 eq) in THF (1 ml). The reaction mixture was stirred for 4.5 hours before being warmed to 0°C and quenched with NH_4Cl (sat. soln, 1 ml) and diluted with water (1 ml). The aqueous phase was

extracted with diethyl ether (2 ml), and the organic extracts dried (Na_2SO_4) and concentrated under vacuum to give a yellow oil.

The crude was taken up in a minimum volume of DCM (~0.5 ml) and layered with hexane (5 ml). The resulting white crystalline solid was collected by filtration to give the pure alcohol (358 mg, 71%).

δH (400 MHz, $CDCl_3$): 7.51 - 7.45 (2H, m, ArH), 7.45 - 7.40 (2H, m, ArH), 7.36 - 7.23 (6H, m, ArH), 6.84 (1H, d, *J* = 15.8 Hz, PhCH=), 6.39 (1H, dd, *J* = 15.8, 6.0 Hz, =CH), 5.28 (1H, t, *J* = 5.4 Hz, C*H*OH), 2.15 (1H, d, *J* = 5.6 Hz, OH); δC (101 MHz, $CDCl_3$): 136.1 (C), 132.1 (CH), 131.8 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 126.9 (CH), 122.4 (C), 87.9 (C), 86.5 (C), 63.5 (CH); Chiral HPLC (CHIRALPAK IB column: (0.46 x 25 cm), 1 ml/min, 20% IPA : 80% Hexane; 254 nm UV, 30 °C): retention times: 6.8 and 14.0 minutes.

(E)-1,5-diphenylpent-1-en-4-yn-3-one



322

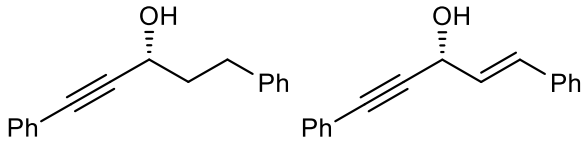
This compound is known.[187]

To a solution of phenylacetylene (520 mg, 5.1 mmol, 1.15 eq) in THF (4 ml) was added dropwise at -78°C *n*BuLi (2.5M in hexane, 1.8 ml, 4.5 mmol, x1.05 eq). The resulting suspension was stirred for 15 mins, warmed to 0°C and stirred for a further 15 mins. This solution was then transferred dropwise by syringe to a precooled (-78°C) solution of **335** (832 mg, 4.4 mmol, 1 eq) in dry THF (2 ml). The resulting yellow homogenous solution was stirred for 4.5 hours before being warmed to 0°C and quenched with NH_4Cl (sat. soln, 4 ml) and diluted with water (2 ml). The aqueous phase was extracted with diethyl ether (2 ml), and the organic extracts dried (Na_2SO_4) and concentrated under vacuum to give a yellow oil.

This oil was taken up in methanol (10 ml), concentrated to 1/3 of its volume and seeded with a sample of pure compound prepared previously. The resulting white crystalline solid was isolated by filtration (214 mg, 21%).

Mp 73-74 °C; δ_H (400 MHz, $CDCl_3$): 7.93 (1H, d, *J* = 16.1 Hz, =CH), 7.67 (2H, d, *J* = 7.2 Hz, ArH), 7.64 - 7.59 (2H, m, ArH), 7.54 - 7.38 (6H, m, ArH), 6.89 (1H, d, *J* = 16.1 Hz, =CH); δ_C (101 MHz, $CDCl_3$): 178.2 (CO), 148.3 (CH), 134.0 (C), 132.9 (CH), 131.1 (CH), 130.6 (CH), 129.1 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 120.2 (C), 91.5 (C), 86.6 (C).

(R)-1,5-diphenylpent-1-yn-3-ol and (R,E)-1,5-diphenylpent-1-en-4-yn-3-ol



338 and **339**

The major product is known.[188]

FA/TEA reduction: See general method 4.

With **322** (116 mg) and (*R,R*)-**OMe-teth (115)**; 25 hours reaction time, total conversion 100%. Product obtained as a yellow oil (104 mg, 89%) containing a mixture of alcohols, ratio 86.9 : 13.1 by ^{1}H NMR. Major product ee 98%, minor product ee 89%.

(*R*) Configuration of major product determined by optical rotation. (*R*) Configuration of minor product assumed by analogy to the major product.

$[\alpha]_D^{30}$ -54.2, (*R*), 98% ee (c 0.365 in $CHCl_3$); lit $[\alpha]_D^{22}$ +37.45, (*S*), 97% ee (*c* 0.5 in $CHCl_3$)

Chiral HPLC (CHIRALPAK IB column: (0.46 x 25 cm), 1 ml/min, 20% IPA : 80% Hexane; 254 nm UV, 30 °C): retention times: 5.9 (*R*)-saturated, 6.8 (*R*)-unsaturated, 8.6 (*S*)-saturated and 13.9 (*S*)-unsaturated minutes.

4.6 Electronic Structure Calculations

Computational calculations were carried out with Gaussian 03 software (revision D.02). Structures were built using GaussView v3.09. Calculations were performed on the Warwick University Cluster of Workstations (COW) or the author's personal laptop. DFT integration grids with 99 radial and 590 angular points (Ultrafine) were used for all DFT calculations.

```
# int=ultra
```

The Minnesota MPW1B95 hybrid-meta GGA method[3] calculations were carried out by use of the mpwb95 method and setting the proportion of DFT and HF exchange to 0.69 and 0.31 respectively.

```
# mpwb95/basis IOp(3/76=0690003100)
```

Partially augmented versions of Dunning's correlation consistent basis sets were implemented using the corresponding cc-pVNZ parent basis set along with extrabasis

keyword.[1,2,189] Basis information for the diffuse functions was taken from the EMSL basis set exchange at https://bse.pnl.gov/bse/portal then specified in a separate file. For example, to carry out a B3LYP/maug-cc-pVTZ calculation on a molecule containing only C,H,O atoms:

```
# b3lyp/cc-pvtz extrabasis …
…
@C_O_ccpvtz_diffusebasis.gbs/N
```

Where the basis set file contains all of the diffuse basis functions for the aug-cc-pVTZ method. The D and F diffuse functions are commented out to leave only the S and P functions for C and O atoms, as required by the specification.[2]

```
C 0
S   1   1.00
      0.0440200              1.0000000
P   1   1.00
      0.0356900              1.0000000
!D   1   1.00
!      0.1000000              1.0000000
!F   1   1.00
!      0.2680000              1.0000000
****
O 0
S   1   1.00
      0.0737600              1.0000000
P   1   1.00
      0.0597400              1.0000000
!D   1   1.00
!      0.2140000              1.0000000
!F   1   1.00
!      0.5000000              1.0000000
****
!cc-pVTZ diffuse functions
```

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