Catalytic Methods for Etherification Reactions

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Ph.D. Thesis

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“We need to remember what's important in life: friends, waffles, and work. Or waffles, friends, work. It doesn't matter. But work is third.”

- Leslie Knope, Parks & Recreation

Declaration of Authenticity

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Abstract

Throughout all chemical sectors, from lubricants to agrochemicals, ether linkages are important motifs in a broad range of chemical entities. Safety issues and environmental concerns associated with common etherification methods render these methodologies undesirable for large scale applications. We have examined the reductive etherification approach, whereby a carbonyl compound is condensed with an alcohol to afford an enol ether intermediate, which is reduced by hydrogen gas and a heterogeneous platinum catalyst to the corresponding ether product in an overall, atom efficient process. In this work, a thorough interrogation of the reductive etherification reaction conditions with regards to the reaction catalyst, solvent, pH and the specific stoichiometries of these components. This investigation resulted in an improved set of mild conditions utilising a commercially available catalyst and readily available additives. The developed methodology allows access to a range of ethers, including aromatic-containing products, whilst addressing safety and environmental considerations related to all components of the reaction system.

A homogeneous iridium catalyst was also investigated for ether bond formation of allylic alcohol substrates. This catalyst, containing an *N*-heterocyclic carbene and bulky phosphine ligand, is shown to mediate the condensation of allylic alcohols with other alcohol nucleophiles to form a wide array of ether substrates. Further study of this reaction was performed through design of experiment statistical analysis to provide an efficient manifold with low catalyst and nucleophile loadings.

Abbreviations

2-MeTHF	2-Methyl tetrahydrofuran
Å	Angstrom (x 10^{-10} m)
Ac	Acetyl
Ad	Adamantyl
AKA	Also known as
Bar	Bar gauge
Bara	Bar absolute
BAr_F	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BBPO	*N*,*N*'-Bis(2-phenylphenyl) oxalamide
Bn	Benzyl
BNMO	*N*,*N*'-Bis(naphthalen-1-ylmethyl)oxalamide
Boc	*tert*-Butyloxycarbonyl
BP	Boiling point
c-Hex	cyclohexane
Cat	Catalyst
Cbz	Benzyloxycarbonyl
COD	1,5-Cyclooctadiene
COSY	Homonuclear correlation spectroscopy
COPD	Chronic obstructive pulmonary disease
CPME	Cyclopentyl methyl ether
Cy	Cyclohexyl
DCE	1,2-Dichloroethane
DCM	Dichloromethane
D*i*PP	1,3-Bis-(2,6-diisopropylphenyl)imidazolinium
DoE	Design of Experiment statistical analysis
DPEO	*N*,*N*'-Diphenethyloxalamide
DNA	Deoxyribonucleic acid
DMF	*N*,*N*-Dimethylformamide

DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
EDG	Electron donating group
ee	Enantiomeric excess
Equiv	Equivalents
Et	Ethyl
EtOAc	Ethyl acetate
g	Gram(s)
GC	Gas chromatography
GP	General procedure
GSK	GlaxoSmithKline plc.
h	Hour(s)
HIE	Hydrogen isotope exchange
HMBC	Heteronuclear multiple bond correlation spectroscopy
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence spectroscopy
IBn	1,3-Dibenzylimidazol-2ylidene
IMes	1,3-Bis(2,4,6-trimethylphenyl)imidazolinium
IPA	*iso*-Propyl alcohol
iPAc	*iso*-Propyl acetate
IPr	1,3-Bis(2,6-di-*iso*-propylphenyl)imidazolylidene
^{i}Pr	*iso*-Propyl
IR	Infrared
JM	Johnson Matthey
Jr	Junior
L	Litres
LC	Liquid chromatography
LCMS	Liquid chromatography mass spectrometry
LG	Leaving group

M	Molar
Me	Methyl
MIBK	4-Methyl-2-pentanone
min	Minute(s)
mol	Moles
mol%	Mole Percent
MS	Molecular sieves
MSA	Methanesulfonic acid
MTSR	Maximum temperature of the synthetic reaction
MW	Molecular weight
*n*BuOAc	*n*-Butyl acetate
NHC	*N*-Heterocyclic Carbene
NMR	Nuclear magnetic resonance spectroscopy
P	Pressure
PCA	Principal component analysis
Piv	Pivaloyl
PMB	*para*-Methoxybenzyl
PMI	Process mass intensity
PPBO	*N*-(2-Phenyl-phenyl)-*N*'-benzyl oxalamide
ppm	Parts per million
PSI	Pounds per square inch
QTC	Quantitative time course
ROESY	Rotating frame nuclear Overhauser effect spectroscopy
rpm	Revolutions per minute
RT	Retention time
sec-	Secondary
S_N2	Bimolecular Nucleophilic Substitution
Sol	Solvent
t	Time
T	Temperature

TAME	2-Methoxy-2-methylbutane
TBME	*tert*-Butyl methyl ether
tert-	Tertiary
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMDS	1,1,3,3-Tetramethyldisiloxane
TON	Turnover number
Ts	*para*-Toluenesulfonyl
UI	User interface
UPLC	Ultra performance liquid chromatography
V	Solvent volumes

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Contents

Declaration of Authenticity I

Abstract III

Abbreviations IV

Acknowledgements and Dedications VIII

Contents X

1 Platinum Catalysed Reductive Etherification 1

1.1 Introduction 1

1.1.1 Classical Methods 2

1.1.2 Palladium Catalysed Etherification Reactions 4

1.1.3 Copper Catalysed Etherification Reactions 9

1.1.4 Reductive Methods for Ether Formation 14

1.1.5 Heterogeneously Catalysed Reductive Etherification Reactions 17

1.2 Current Limitations 23

1.3 Proposed Work 25

1.4 Results and Discussion 29

1.4.1 Investigation of Gooßen Conditions 30

1.4.2 Investigation of Pressure and Temperature 34

1.4.3 Initial Substrate Screen 37

1.4.4 Large Scale Reaction and Mechanistic Investigation 42

1.4.5 Heterogeneous Catalyst Screen 45

1.4.6 Initial Quantitative Time Course Experiment 49

1.4.7 Catalyst pH Screen 52

1.4.8 Acid Screen 54

1.4.9 Relation of Intermediate Formation to Ether Formation 58

1.4.10 Investigation of the Number of Acid Equivalents 59

1.4.11 Investigation of Wet Pt/C Catalysts 62

1.4.12 Large Scale Reaction in AutoMATE 67

1.4.13 Solvent Screen 72

1.4.14 Ester Solvent Screen 76

1.4.15 Investigation of Reproducibility Issues 78

1.4.16 Catalyst Wetting Investigation 82

1.4.17 Design of Experiments Optimisation 86

1.4.18 Quantitative Time Course with Optimised Conditions 91

1.4.19 Saturated Substrate Scope 93

1.4.20 Aromatic Substrate Investigation 98

1.4.21 Aromatic Substrate Scope 100

1.4.22 Ether Substitution with Acetate Work Up 106

1.4.23 Deuterium Labelling Studies 108

1.5 Conclusions 120

1.6 Future Work 129

1.7 Experimental 134

1.7.1 General Procedure 1 for Use of the CAT96 High Pressure Reactor 135

1.7.2 General Procedure 2 for Use of the ChemSCAN II High Pressure Reactor... 136

1.7.3 General Procedure 3 for Use of the ChemSCAN II High Pressure Reactor... 137

1.7.4 General Procedure 4 for Calculation of Solution Yield 137

1.7.5 Investigation of Gooβen Conditions 138

1.7.6 Williamson Ether Synthesis of Cyclopentyl Butyl Ether (**29**) 139

1.7.7 Investigation of Pressure 140

1.7.8 Initial Substrate Scope 141

1.7.9 Neutral Large Scale Reaction 142

1.7.10 Heterogeneous Catalyst Screen 143

1.7.11 Initial Large Scale Quantitative Time Course 145

1.7.12 Catalyst pH Screen 146

1.7.13 Acid Screen 148

1.7.14 Investigation of Number of Acid Equivalents 149

1.7.15 Heterogeneous Catalyst Screen with Acid Additive 152

1.7.16 Large Scale Reaction In AutoMATE 155

1.7.17 Solvent Screening 156

1.7.18 Ester Solvent Screen 158

1.7.19 Reproducibility Screen 160

1.7.20 Catalyst Wetting Investigation 160

1.7.21 Solvent Screening at Lower Solvent Volumes and Catalyst Loadings 162

1.7.22 Design of Experiments Optimisation 164

1.7.23 Large Scale Quantitative Time Course with Optimised Conditions 170

1.7.24 Saturated Substrate Scope 171

1.7.25 Large Scale Quantitative Time Course of Heptan-2-one and *n*-Butanol 175

1.7.26 Large Scale Quantitative Time Course of 4-Phenylbutan-2-one and *n*-Butanol 176

1.7.27 Aromatic Substrate Scope Including Transetherification Reactions 178

1.7.28 C2 Indole Functionalisation 193

1.7.29 4-Hydroxyacetophenone Protection Reactions 194

1.7.30 4-Aminoacetophenone Protection Reactions 197

1.7.31 Deuterium Labelling Studies 199

2 Iridium Catalysed Allylic Alcohol Etherification 211

2.1 Introduction 211

2.1.1 Reductive Methods 211

2.1.2 Etherification of Alcohols 216

2.1.3 Allylic Alcohol Substitution Reactions 218

2.2 Results and Discussion 227

2.2.1 Initial Scoping Reactions 227

2.2.2 Solvent Screening 230

2.2.3 Catalyst Screening 232

2.2.4 Design of Experiment Optimisation 233

2.2.5 Alcohol Nucleophile Screening 239

2.2.6 Reactions with Hydrogen Activation 241

2.3 Conclusion 244

2.4 Future Work 245

2.5 Experimental 251

2.5.1 Catalyst Synthesis 252

2.5.2 3-Phenylcyclohexenol Synthesis 255

2.5.3 Initial Scoping Reactions 257

2.5.4 Solvent Screening 261

2.5.5 Catalyst Screening 262

2.5.6 Design of Experiment 264

2.5.7 Alcohol Nucleophile Evaluation 276

2.5.8 ChemSCAN Validation Reactions 284

2.5.9 Reactions with Hydrogen Activation 286

References 291

1 Platinum Catalysed Reductive Etherification

1.1 Introduction

Ether linkages are among the most prevalent motifs found in molecules throughout all chemical sectors. Ethers are generally unreactive and their properties often allow for effective solubilisation of organic compounds.[1] For this reason, simple ethers such as diethyl ether, cyclopentyl methyl ether (CPME) and *tert*-butyl methyl ether (TBME) have been widely employed as solvents for the synthesis of many organic molecules, such as perfumes, dyes and resins. The vapours of some ethers are even used as insecticides and fumigants in agriculture.[2]

Volatile ethers are widely utilised in the automotive industry as starter fluids for combustion engines.[3] Longer chain ethers have low volatility and low viscosity, both of which are ideal properties for lubricants.[3-4] Other uses for ethers include propellants, plasticisers and refrigerants.[5] More recently, dimethyl ether has become regarded as a green fuel for power generation as well as for heating and cooking, with competitive properties to those of fossil fuels.[6] Etherification reactions of bio derived molecules are very important processes due to their ability to reduce the hygroscopicity of a molecule while simultaneously increasing the energy content and ignition speed; all desirable qualities for biofuels.[7-9]

For over 150 years, the effect of ethers upon the human body has been of interest to medical practitioners. Even very simple ethers such as diethyl ether and methyl ethyl ether show biological activity as anaesthetics, having been widely used in the mid-1800s.[10] Subsequently, ether linkages became a key functionality within pharmaceutical molecules and are present in many top selling drugs (Figure 1).[11-14]

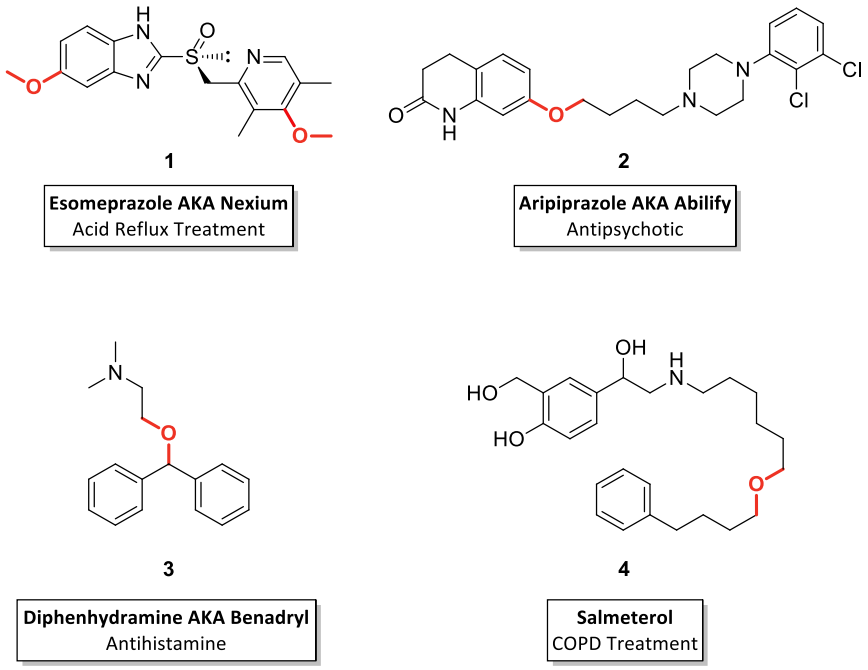
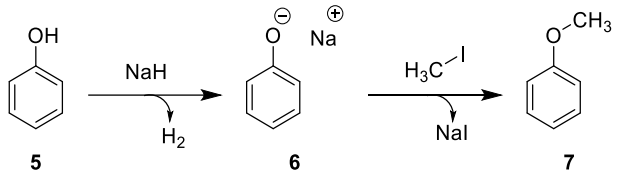


*Figure 1: Chemical structures of esomeprazole (**1**), aripiprazole (**2**), diphenhydramine (**3**) and salmeterol (**4**) with the ether linkage(s) highlighted in red.*

1.1.1 Classical Methods

Ether linkages represent a key disconnection in retrosynthetic analysis and, as such, there are classical methodologies for forming these linkages, including the Williamson ether synthesis (Scheme 1).[5] This synthesis utilises a strong base to deprotonate an alcohol which can then partake in an S_N2 reaction with an alkyl halide.

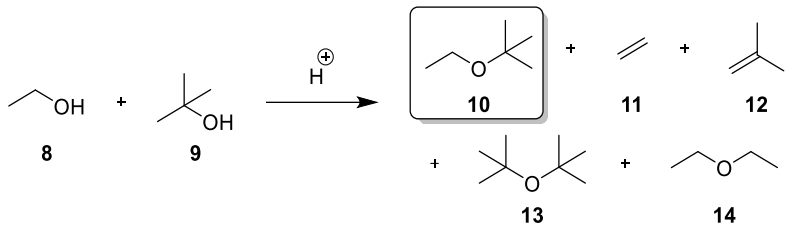


*Scheme 1: Williamson ether synthesis of anisole (**7**) from phenol (**5**).*

This method of synthesising ethers is widely used in chemical laboratories around the globe but poses issues when applied to industrial scale syntheses due to the requirement for

alkylating agents such as methyl iodide. Alkylating agents are hazardous chemicals classed as genotoxins.[15] Genotoxins are able to modify the chemical structure of DNA, potentially resulting in diseases, cancers and cell death. As such, the use of these chemicals for large scale synthesis is disfavoured.[16] When utilising potentially genotoxic reagents in the synthesis of a pharmaceutical, various extra steps must be taken to ensure that residual reagent levels are strictly controlled to parts per million detection levels.[17] Use of sodium hydride as a base represents a significant hazard as, not only does this reagent form hydrogen gas during the reaction, which, if not vented appropriately from the reactor, could easily result in an explosion, but thermal stability of NaH in a number of solvents has been of growing concern to the process chemistry community.[18] The Williamson ether synthesis also results in formation of a stoichiometric amount of waste salt and is therefore not considered an atom economical or environmentally friendly process.

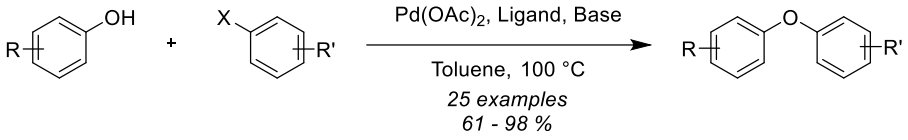
To avoid the wasteful formation of inorganic by-products in the Williamson ether synthesis, it is possible to perform a dehydrative coupling of two alcohols with use of a strong acid, as reported by Bellefon *et al.* (Scheme 2).[19] This results in a much smaller environmental impact than the Williamson method as the only waste product is water. However, this alternative method comes with selectivity issues, as the protonated alcohol can partake in a competing elimination reaction, dehydrating to form one or more alkenes (**11**, **12**). There is also an inherent lack of control in the ether formation, as all possible ethers will be formed in the reaction (symmetrical (**13**, **14**) and the desired unsymmetrical ether (**10**)). The use of strong acid in the dehydrative method also reduces the practicality of the reaction, as it precludes the use of acid-sensitive functionalities.[20]



Scheme 2: Acid-catalysed dehydration reaction between ethanol and tert-butanol to form a mixture of ethers and alkenes.

1.1.2 Palladium Catalysed Etherification Reactions

Catalytic approaches to etherification reactions have been pioneered by Buchwald *et al.* using palladium catalysts and intricately designed phosphine ligands.[21] Building on the extensive research of Buchwald and Hartwig into palladium catalysed C-N bond forming reactions, this knowledge was advanced further to form C-O bonds in diaryl ethers.[22-23] This advancement was aided through the development of electron-rich bulky phosphine ligands within the Buchwald group (Scheme 3).[24]

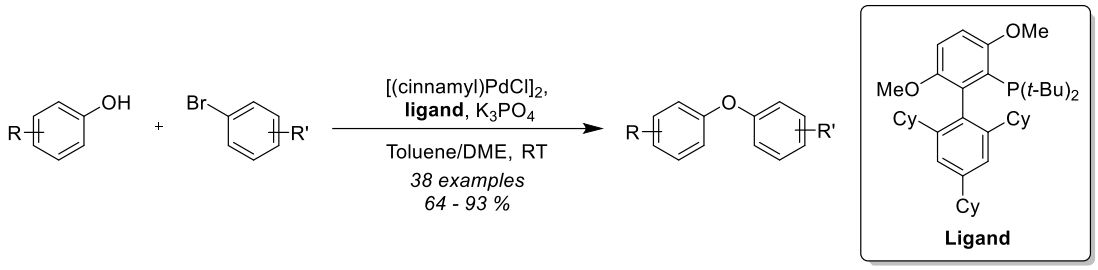


Scheme 3: Palladium catalysed diaryl ether synthesis. X = Cl, Br, OTf.

Within this palladium catalysed diaryl ether formation, a number of different reaction components are used. The base employed for this etherification in most cases is K_3PO_4, however, in some cases NaH is still required. With regards for the ligands required for etherification, six of these are mentioned for use within the publication. While they are all bulky phosphines, they possess very different structures. Although some guidance on ligand selection is given for people wishing to apply this methodology (bulkier ligands for more

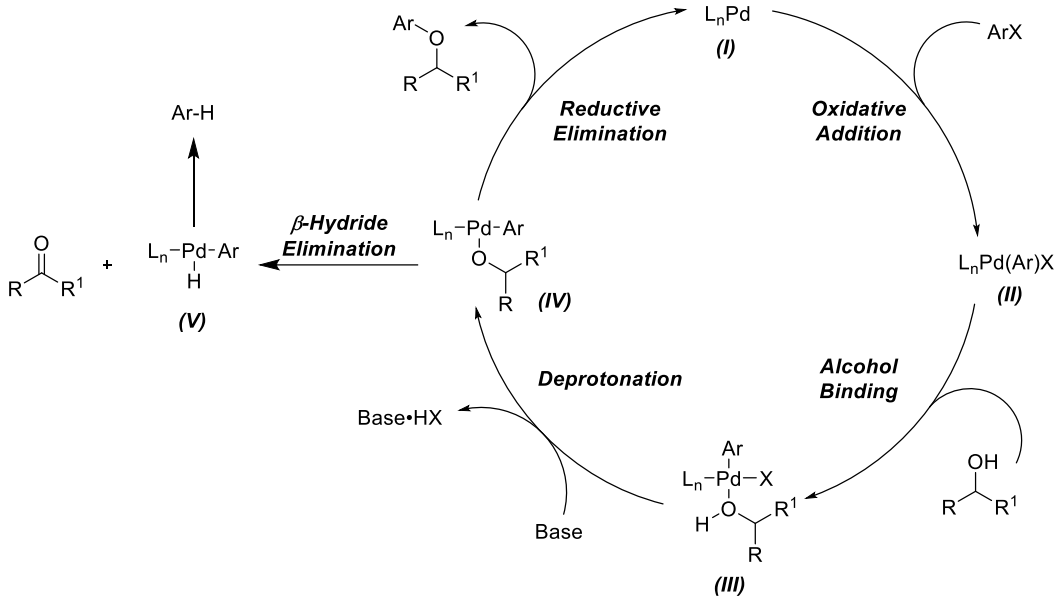
electron rich aryl halides) it appears that multiple reaction mechanisms are ongoing and some catalyst screening would be required when utilising this process.

Through further optimisation of the diaryl etherification reaction, the Buchwald group narrowed this down to one bulky biaryl phosphine catalyst for use within the reaction. Use of this catalyst also removed the need for NaH base within the reaction (Scheme 4).[25]



Scheme 4: Palladium catalysed diaryl ether synthesis from phenols and aryl bromides.

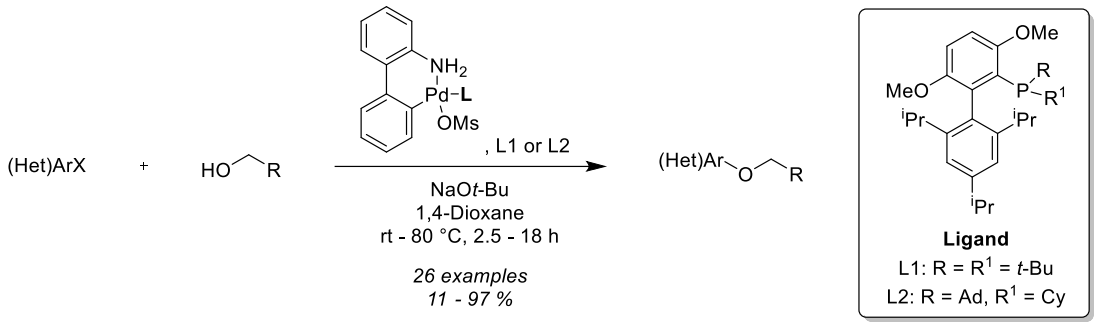
Although diaryl ethers are important functional motifs, a similar method to synthesise alkyl ethers would also be of interest. To address this, further work by Buchwald *et al.* was performed to expand the scope of the palladium catalysed etherification reaction into the realms of primary and secondary aryl ethers. This was also performed in tandem with some mechanistic studied to propose a reaction mechanism (Scheme 5).[26-27]



Scheme 5: General catalytic cycle of palladium catalysed C–O cross-coupling of aryl halides with alcohols. R = alkyl or hydrogen.

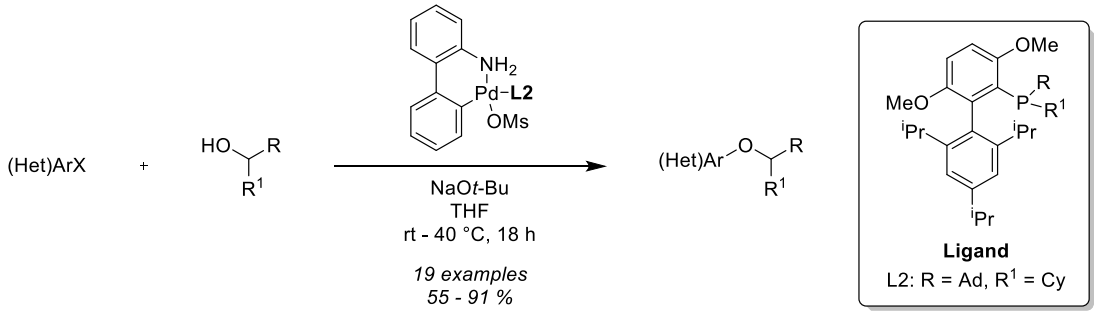
As is known from many other Pd cross coupling reactions, Pd(0) can oxidatively add across an aryl halide (or pseudo halide) bond.[28] The resulting palladium species (**II**) then binds the alcohol etherification partner which is subsequently deprotonated by base. The palladium alkoxy species (**IV**) can then partake in reductive elimination of the desired aryl ether returning the initial catalytic Pd(0) (**I**). Within this mechanism these is a side reaction made possible by β-hydride elimination from the palladium alkoxy complex (**IV**). This side reaction would result in the dehalogenated aryl halide and oxidised alcohol. The fate of this alcohol will be either a ketone or an aldehyde depending on whether a primary or secondary alcohol is selected for use.

Through application of this reaction mechanism, a catalytic method of forming primary aryl ethers was developed. This used a Buchwald palladium pre-catalyst to release Pd(0) within the reaction mixture. The mild conditions also allowed heteroaryl ethers to be synthesised (Scheme 6).[26]



Scheme 6: Palladium catalysed synthesis of alkyl aryl ethers using aryl halides and primary alcohols. X = Cl or Br.

This developed methodology shows a facile way to access primary aryl ethers from commonly available starting materials but still describes two ligands for use in this process. Ligand 1 is more commonly known as *t*-BuBrettPhos and provides a commercially accessible way to perform this reaction however, in all cases where the two catalysts are compared, ligand 2 is shown to outperform ligand 1 by up to 76%. It is advised that for electron deficient (hetero)aryl halides, ligand 1 is used, while ligand 2 is used for electron rich (hetero)aryl halides.



Scheme 7: Palladium catalysed formation of alkyl aryl ethers starting from aryl halides and secondary alcohols. X = Cl or Br.

The superior performance of ligand 2 with respect to the cross coupling of primary alcohols drove the Buchwald group to select this catalyst for use within the cross coupling of secondary alcohols (Scheme 7). This catalyst and ligand once again proved to be ideal for use

within etherification reactions and, as such was commercialised by Buchwald *et al*.[27] The reason for the superior performance of ligand 2 (AKA AdCyBrettPhos) within the etherification reaction is noted to be under investigation but it is hypothesised that its medium size (in comparison to other ligands developed by the Buchwald group) aids stages of the catalytic cycle other than reductive elimination.

While the advancements in etherification developed by Buchwald *et al.* have led to a thoroughly investigated and efficiently working reaction manifold, there are some important considerations that must be addressed when applying reactions to a pilot plant campaign. Palladium is a precious metal and comes with associated costs, financial and environmental. Use of palladium within large scale synthesis would result in a large amount of palladium waste and recovery of palladium from this would be highly beneficial. Recovery of palladium from waste streams is something that has already garnered significant attention from the process chemistry community and studies have already been performed.[29] Much of this research has been concentrated on removal of palladium from drug products to ensure no contamination of pharmaceutical ingredients. Much less attention has been given to the removal of palladium from chemical reactions for the purposes of metal recovery.[30] Many reports disclose palladium recovery to ppm levels but do not make clear where the palladium ends up.[31-33] As the palladium may be present in different oxidation states and ligated in various complexes its distribution across process waste streams is not so simple.

Of course, purchase and recovery of the palladium metal is not the only concern within this methodology. The bulky biaryl phosphine ligands developed by Buchwald *et al.* also represent a significant financial investment. As these catalysts are complex and specially designed and developed for these purposes, they can commonly cost as much, if not more than the metal centre. To purchase 1 g of AdCyBrettPhos, the ligand used within the alkyl

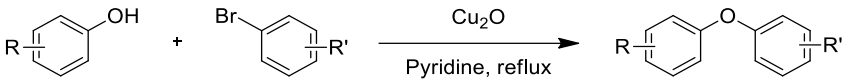
aryl etherification reactions reported previously, would cost £374 (£220k per mole).[*] When applying precious metal catalysis, the cost of the metal is often of concern, however the price of 1 g of palladium acetate (£18.7k per mole) is eclipsed by the price of the ligand for this synthesis.[†] Not only would use of this synthesis require a significant financial investment to be used in large scale synthesis but would also have similar issues relating to the recovery upon rection completion.

1.1.3 Copper Catalysed Etherification Reactions

A further method of synthesising aryl ethers is the Ullmann ether synthesis, which utilises a copper catalyst to couple a phenol and an aryl halide (Scheme 8).[34] Use of a non-precious metal to perform this coupling is economically favourable when compared to the palladium-catalysed couplings, developed by Buchwald and Hartwig.[21] However, this method commonly requires harsh reaction conditions, large excesses of the phenol component and, in some cases, high catalyst loadings which can lead to the production of stoichiometric copper waste. Furthermore, the specifics of the cross-coupling reaction mechanism are still being investigated meaning there are many unknown catalyst deactivation pathways, leading to the aforementioned high catalyst loadings and inconsistent results upon scale up. Reaction rates are also substrate dependent, with electron poor and *ortho*- substituted aryls reacting slowly.[21] These factors limit the utility of the Ullmann synthesis on large scales.[35]

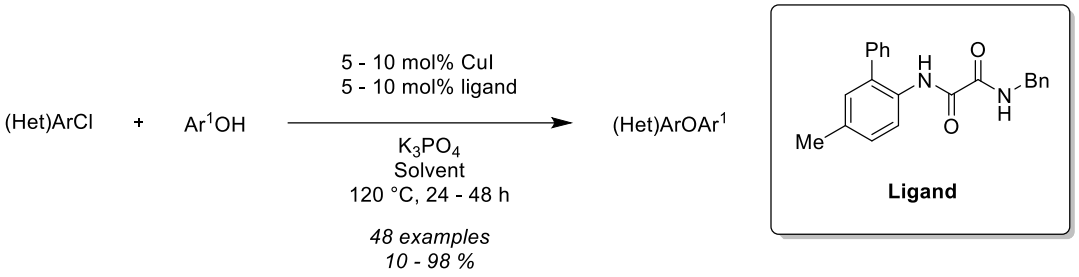
[*] Price correct as of 24/6/21 from Sigma Aldrich website

[†] Price correct as of 18/6/21 from Sigma Aldrich website



Scheme 8: Ullmann synthesis of diaryl ethers.

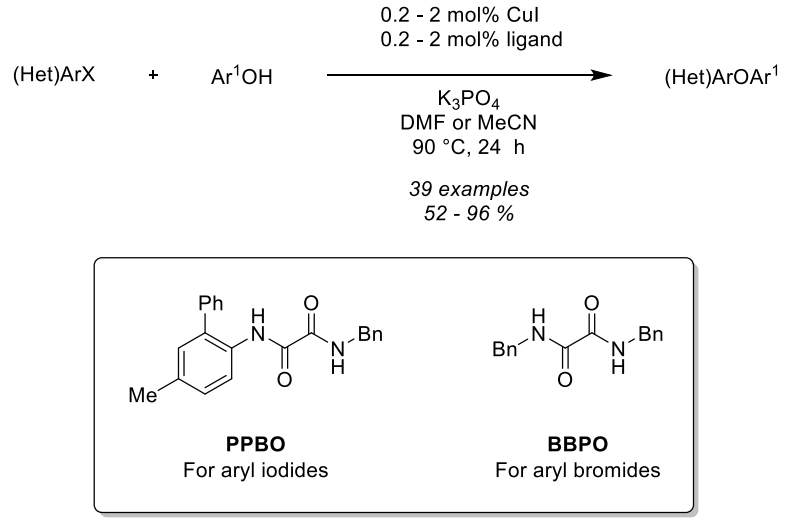
Almost 100 years after publication of the Ullmann reaction, further research was performed by Ma *et al.*[36] This research began by increasing the reaction rate of amination reactions through use of amino acid ligands for the copper catalyst. This was later expanded into etherification reactions through development of oxalamide ligand systems. This advancement allowed diaryl ethers to be synthesised in good to high yields using a copper catalyst in much lower catalyst loadings than the Ullmann process outlined previously (Scheme 9).[37]



Scheme 9: Ullmann-Ma coupling of (hetero)aryl chlorides and phenols catalysed by copper and an oxalamide ligand. Solvent = DMF or DMSO

Although application of these oxalamide ligand systems to the reaction has enabled a much lower loading of copper catalyst to be employed, these oxalamides would require their own synthesis and due to their unsymmetrical nature, this would be multiple reaction steps. Further optimisation of this ligand was performed by Ma *et al.* to include a symmetrical oxalamide ligand (Scheme 10). This expansion of the methodology allowed the catalyst

loadings to be lowered while expanding the aryl halide scope to include bromides and iodides and avoiding the use of DMSO solvent.[38]

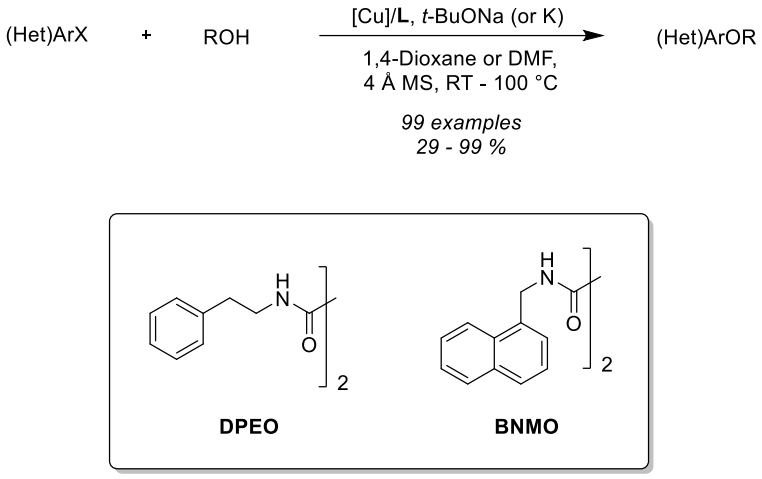


Scheme 10: Ullmann-Ma coupling of (hetero)aryl halides and phenols catalysed by copper at lower catalyst loadings and oxalamide ligands. X = Br or I

Although ligands utilised in this advanced methodology are still not commercially available, inclusion of a symmetrical oxalamide ligand does reduce the complexity of the synthesis. Unfortunately, this symmetrical oxalamide ligand only proved to be superior for use with aryl bromide starting materials. Aryl bromides are readily available starting materials however, a general method for use of aryl halides would be preferable. This would expand the applicability of the reaction and allow cheaper aryl halides to be utilised.

Use of acetonitrile as a solvent within this reaction is much more favourable as this is more volatile than the DMF and DMSO used previously. This would allow removal of the reaction solvent by evaporation under reduced pressure. Unfortunately, this solvent is not used by the Ma group for the majority of examples within the publication with only a select few being performed in acetonitrile.

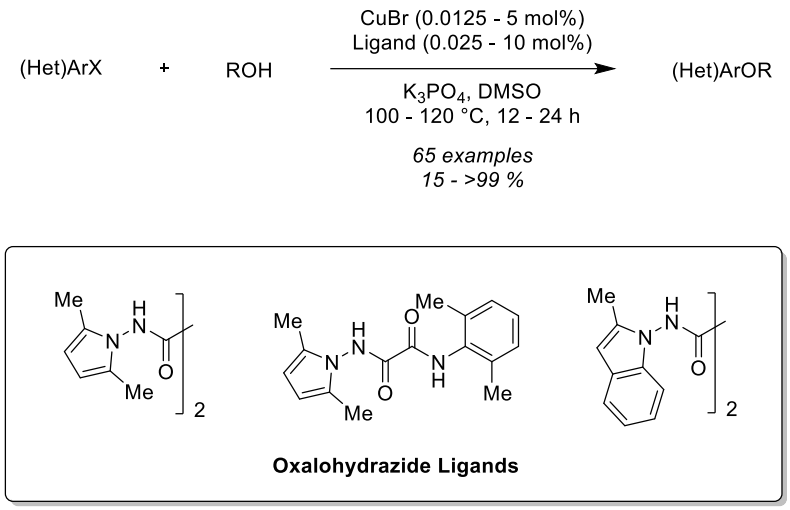
While diaryl ethers are valuable motifs, application of this methodology to formation of aryl alkyl ethers would be desirable. As such, Ma and co-workers developed another set of oxalamide ligand systems to allow this transformation to be performed in an efficient manner with copper catalysis (Scheme 11).[39]



Scheme 11: Ullmann-Ma coupling of (hetero)aryl chlorides and alkyl alcohols catalysed by copper and oxalamide ligands. X = Cl, Br, I

Through further development of the oxalamide ligand systems, Ma *et al.* were not only able to expand the scope of their copper catalysed etherification reaction to include alkyl alcohols but also allow aryl chlorides, bromides and iodides to be used. The synthesis of these ligands is much more favourable due to their symmetrical nature.

By lowering the catalyst loadings even further, efforts were made by Hartwig *et al.* to make the copper catalysed etherification reaction more amenable to large scale synthesis (Scheme 12).[40] Through further investigation of the oxalamide ligand systems, oxalohydrazide ligands were developed and turnover numbers (TONs) were increased by two orders of magnitude from those reported by Ma *et al.*[38]



Scheme 12: Copper catalysed alkyl aryl ether formation using oxalohydrazide ligands.

The copper catalysed etherification reported by Hartwig *et al.* is demonstrated with a substrate scope equivalent to if not slightly expanded upon that reported by Ma. To produce this transformation on such a wide range of molecules utilising such a tiny amount of catalyst and ligand is no doubt of interest to the process chemistry community.[41] As such a small amount of ligand would be required for this process, and the synthesis would be simpler for the symmetrical oxalohydrazides, specialist synthesis of these would be more feasible.

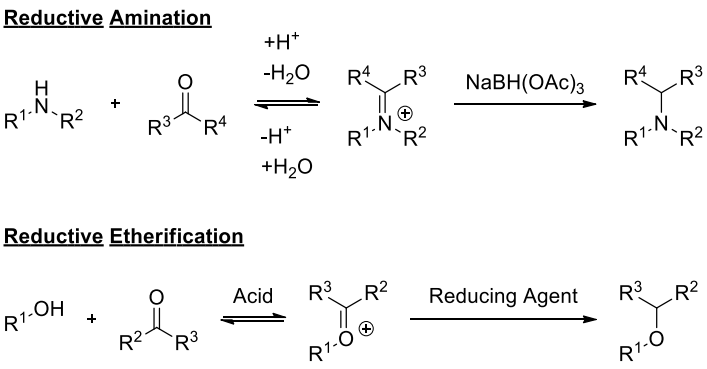
The design and optimisation of the oxalamide ligands performed by Hartwig and Ma have built upon the foundations of the Ullmann coupling reaction to allow a huge array of ethers to be accessed through copper catalysis. These ligands have also improved upon the large catalyst loadings outlined in the Ullmann approach and allowed the copper to be used in very low loadings (0.2 mol%).

As these ligands are not commercially available, additional synthesis would be required. Use of water miscible solvents such as 1,4-dioxane, acetonitrile, DMSO and DMF also adds extra complexity to chemical reactions.[42] Not only will their miscibility with water not allow

purification through solvent separation but, these solvents come with hazardous properties to the user such as low level toxicity, and carcinogenicity.[43-46] Although these solvents are not avoided entirely, use of less hazardous solvents is definitely preferable. The use of molecular sieves within the copper catalysed formation of alkyl aryl ethers is also unfavourable within pilot plant synthesis. Grinding and smashing of these fragile materials upon agitation of the reaction mixture would create an abrasive, insoluble powder. These crushed molecular sieves would cause abrasion upon contact with the vessel walls, damaging the commonly used glass lined reactors. For these reasons, the copper catalysed Ullmann-Ma etherification reaction would not be easily implemented for chemical synthesis within a pharmaceutical pilot plant.

1.1.4 Reductive Methods for Ether Formation

An ideal method to synthesise ethers would be by a catalytic transformation analogous to the reductive amination reaction, used for amine synthesis (Scheme 13).[47] This method should utilise milder reagents than the Williamson method, be more functional group tolerant than the acid-catalysed dehydration, and produce more environmentally friendly by-products than the Ullmann synthesis. Reductive etherification reactions have been investigated in recent years and a variety of different reaction conditions have been employed to achieve etherification with some success.[48]

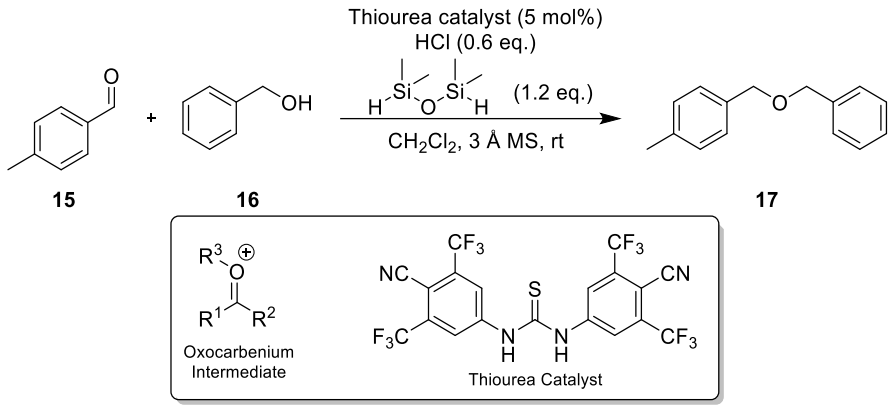


Scheme 13: General scheme for reductive amination and the proposed analogous reductive etherification reaction.

The etherification reaction most similar to the reductive amination approach was reported by Siedel *et al*. (Scheme 14).[49] This method uses hydrochloric acid to form an oxocarbenium intermediate, which is unstable and readily decomposes.[50] As such, a thiourea catalyst has to be included in order to stabilise the intermediate *via* anion binding. This thiourea catalyst is proposed to increase the nucleophilicity of the carbonyl component and aid elimination of water from the resulting ketal intermediate through hydrogen bonding of the two N-H centres.[51] This anion binding effect also increases the reactivity of the intermediate to reduction by the silane, allowing formation of the desired ether product. This reaction manifold was then demonstrated across a number of substrate classes, proving an efficient way to access ethers containing alkenes, alkynes, alkyl bromides, amides, phthalamides and rather impressively, tertiary carbon centres adjacent to the ether linkage. Protecting groups such as NBoc and NCBz were also shown to be tolerated.

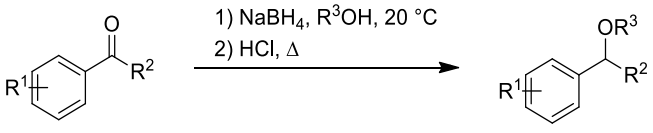
Unfortunately, stoichiometric amounts of silane are required within this protocol. This stoichiometric reagent is a very atom inefficient method of delivering a hydride to the reactive intermediate and will ultimately produce stoichiometric amounts of silicon waste. Additionally, depending on the identity of the silane reductant selected for use in this

reaction, it may come with safety concerns, such as the risk of formation of explosive silane gas, when applied to scale up and plant processes.[52]



Scheme 14: Reductive etherification reported by Siedel et al. which proceeds via an oxocarbenium intermediate.

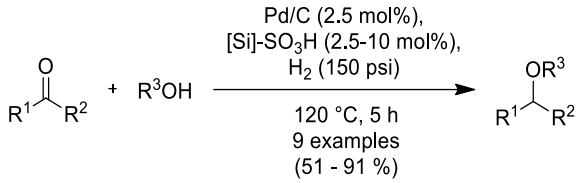
Mochalov *et al.* also reported a reductive etherification reaction in a two-step one-pot protocol (Scheme 15).[53] As this method is split into two clear stages, the reaction pathway is more evident. Firstly, $NaBH_4$ is used to reduce the aryl ketone to the corresponding alcohol. This alcohol is subsequently dehydrated with acid in the presence of an alcoholic solvent, to form the desired ether product. The limitation of this method is that it can only be applied to benzylic carbonyl substrates with electron-donating substituents in the *para*- position of the ring. This suggests that the reaction proceeds through a benzylic carbocation, stabilised by electron donation from the adjacent ring. This significantly limits the scope of the substrates compatible with this reaction, and hence the overall applicability of the protocol.



Scheme 15: Two-step one-pot reductive etherification of benzaldehydes, alkyl aryl ketones and benzophenones.

1.1.5 Heterogeneously Catalysed Reductive Etherification Reactions

Research into another catalytic method for reductive etherification has been described by Bell *et al.* for the purposes of synthesising long chain ethers for use as automotive lubricants (Scheme 16).[3] This procedure utilises a palladium on charcoal catalyst with a solid supported sulfonic acid resin present. As long carbon chains are involved in this method (11<C<32), high temperatures and pressures of hydrogen are employed to overcome the entropic barriers involved.

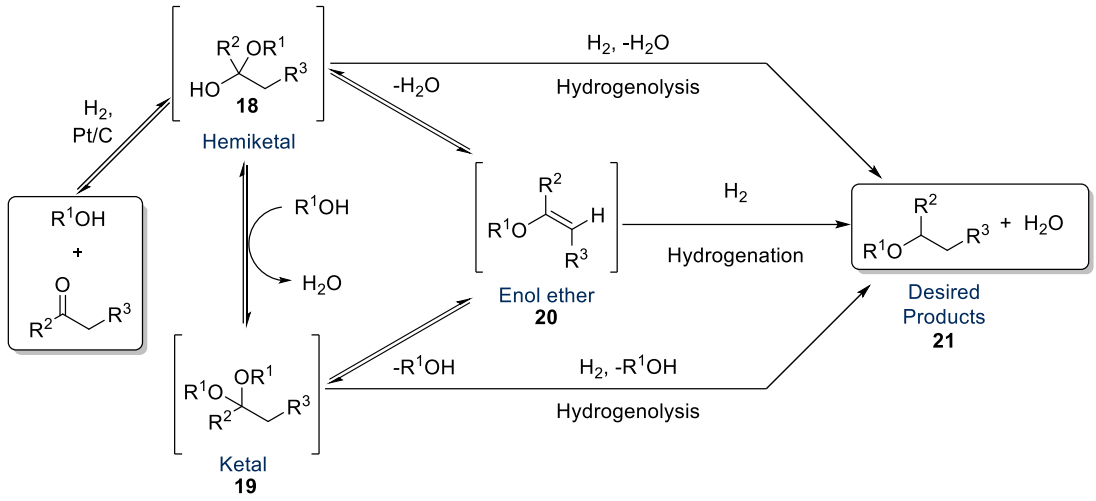


Scheme 16: Catalytic reductive etherification reaction utilising a palladium catalyst and a solid supported sulfonic acid resin, [Si].

The use of this acidic support implies that the reaction mechanism could be similar to that proposed by Siedel and Mochalov; however, a different mechanism was proposed for this reaction by Fujii *et al.* (Scheme 17).[54]

This mechanism is proposed to begin with a condensation of an alcohol and carbonyl to form the hemiketal intermediate, **18**. From this hemiketal intermediate, two further pathways are possible. With C-H bonds adjacent to the hemiketal, an elimination of water from this intermediate can occur to form enol ether, **20**. Alternatively, the hemiketal intermediate, **18**, could undergo a reaction with a second equivalent of alcohol to form the ketal intermediate, **19**. This ketal intermediate could also eliminate an equivalent of alcohol to form the enol ether intermediate, **20**.

Direct hydrogenation of alkene within the enol ether intermediate, **20**, would result in the desired ether product, **21**. Hydrogenolysis of the hemiketal, **18**, or the ketal, **19**, is also known and would result in formation of the desired ether product, **21**.[55]



Scheme 17: Possible reaction mechanism for ether formation by catalytic hydrogenation proposed by Fujii et al.

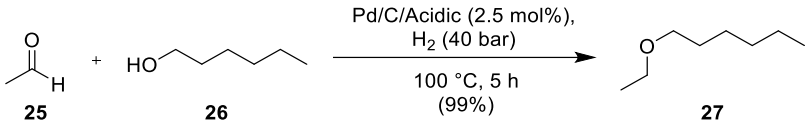
Fujii *et al.* report the isolation of the ketal (**19**) to confirm this reaction mechanism, noting that neutral or acidic type Pd/C catalysts show optimal activity under the examined reaction conditions. Although the enol ether (**20**) was never isolated, it was proven not to be a critical intermediate in the reaction by the reductive etherification of 2,2-dimethylpropionaldehyde, which does not possess any β-hydrogens with which to enolise. Hydrogenolysis of ketals with a palladium catalyst has been known for a number of years, and has also been investigated with ruthenium, platinum and rhodium catalysts.[55]

Within the methodology developed by Fujii *et al.*, numerous features of the reaction are unfavourable for large scale synthesis. Firstly, this reaction utilises the alcohol component as reaction solvent, with the aldehyde (0.22 mol) added dropwise over 8 hours. This slow addition, although maybe possible on a submolar reaction scale, would take up a huge amount of time on a multi-kilo scale. Use of reaction components as solvents is also not

commonly employed in pharmaceutical pilot plant synthesis and this would reduce the applicability of the reaction to those which use liquid alcohols as starting materials.

The most concerning part of the experimental procedure, is the use of hydrogen gas bubbling through the reaction mixture at elevated temperatures (105 - 160 °C). This is reported to helping the water byproduct evaporate from the reaction mixture, becoming condensed back into the Dean-Stark trap. This gaseous bubbling at elevated temperatures would also assist in the evaporation of low-boiling organic compounds within the reaction mixture. A mixture of these volatile organic compounds and hydrogen gas would be highly explosive upon contact with air. This gas mixture would have to be diluted with nitrogen gas to acceptable levels and be vented in a very careful and controlled manner.[56] As such, a safer protocol for this reaction requires development.

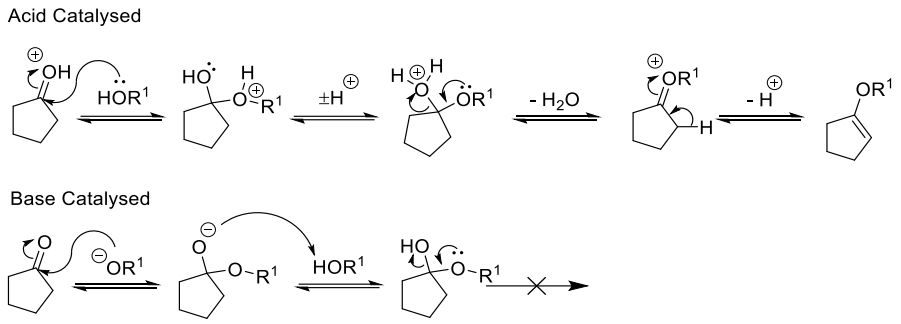
Further studies into acid additives for reductive etherification have been performed by Bethmont *et al.* through use of custom-made catalysts displaying varying acidities.[57-58]



Scheme 18: Catalytic reductive etherification utilising a palladium catalyst on a carbon support, pre-treated with nitric acid.

The Bethmont group have also performed research into palladium catalysed reductive etherification in the presence of hydrogen gas. Use of hydrogen gas at such high pressures (40 bar) is well above the maximum capability of the hydrogenation vessels within the GSK network and would not be possible for direct application to plant synthesis.

Bethmont *et al.* also report that reductive etherification, when performed in the presence of a custom-made acidic catalyst, shows an increase in rate due to the ability of the ketal to eliminate to form the enol ether (Scheme 18). This elimination is a well-known chemical process which would be disfavoured in basic media due to the requirement to eliminate a hydroxide anion (Scheme 19).[59]



Scheme 19: Specific acid and specific base catalysed enol ether formation. Base catalysed enol ether formation does not occur as HO^- is not a good leaving group, meaning only the hemi-acetal is formed.

To prove this, the Bethmont team also attempted a reductive etherification of pivaldehyde. This reductive etherification reaction shows minimal ether formation as well as slow ketal formation. The acidity of the solution is also noted by Van der Waal and co-workers as part of a high throughput catalyst screen for reductive etherification of furfural, stating that the acidity of surface oxides on the support play a crucial role in the mechanism of ether formation.[60]

As the catalyst reported by Bethmont *et al.* is not commercially available and would require specialist equipment to make, use within GSK pilot plant systems would not be favourable. The Bethmont group were kind enough to include directions for its preparation within the publication, however, its synthesis would be particularly hazardous.[57] Not only is use of concentrated nitric acid hazardous but heating of the charcoal support to 1000 °C under

hydrogen atmosphere would be particularly dangerous without previous experience and specialist equipment.

Bethmont *et al.* also report use of one of the reaction components as solvent within the reaction.[57] Solventless reactions can be an environmentally friendly option within many areas of chemistry and, as such, this has garnered a huge amount of attention in recent years.[61] As drug products are usually fairly structurally complex, use of their building blocks as solvents may not be feasible if they are dosed as solids.

Solvent also plays a crucial role with regards to process safety of pharmaceutical pilot plant scale reactions. The boiling point of solvent is a key factor within reaction design and, precise control of this parameter can have a great impact on the hazard potential of the reaction (Figure 2).[62]

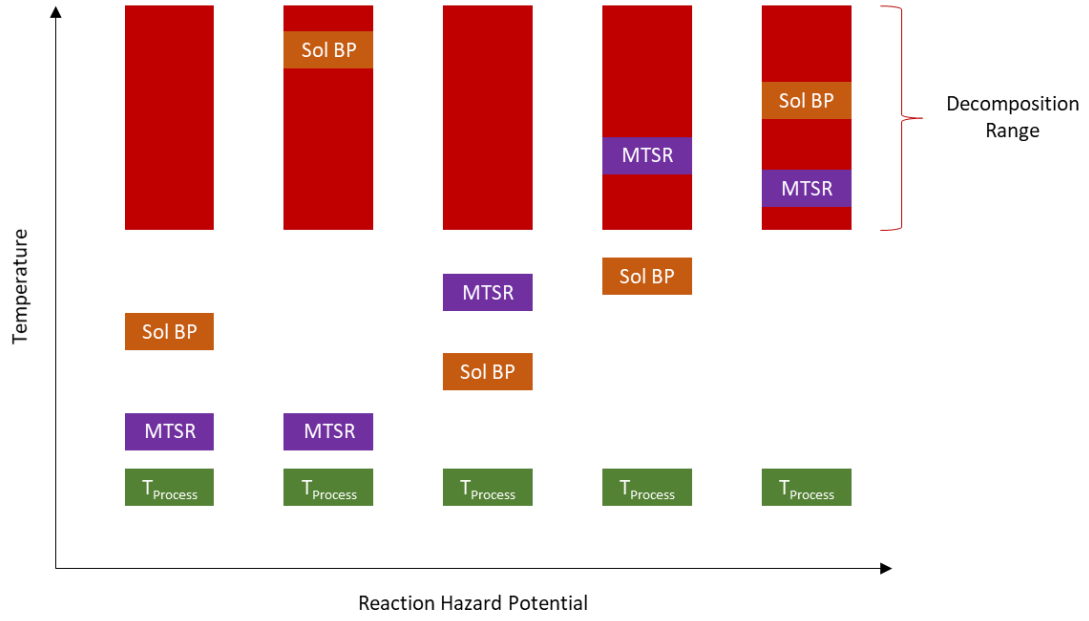


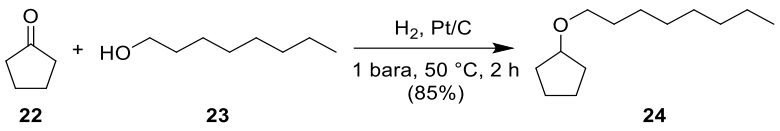
Figure 2: Stoessel diagram of reaction criticality class. MTSR is the maximum temperature of the synthetic reaction.

Within this Stoessel diagram, MTSR is the maximum temperature of the synthetic reaction and represents the maximum exotherm produced by the reaction should no external cooling be applied.[63] In the safest cases, this maximum exotherm should not overlap with the decomposition range of the chemical reaction. Should this be the case and, by some accidental process the MTSR is reached, decomposition of reaction components would be initiated. This may lead to gas evolution, pressurisation of the reactor vessel and the consequences could be catastrophic. To avoid this occurrence, the boiling point of solvent could be used as a barrier. Should the temperature rise be initiated, reflux of the reaction solvent would begin. With efficient condensers fitted to the reaction vessel, a constant reaction temperature would be reached that is below the decomposition range of the reaction components. Within solventless reaction, this extra safety barrier would not be available.

Another catalytic reductive etherification reaction, more amenable to scale up within the pharmaceutical industry due to lower hydrogen pressures, was reported by Gooßen *et al.* in a brief communication. This reductive etherification method reported use of a platinum catalyst at 50 °C and ambient hydrogen pressure (Scheme 20).[64] The milder conditions employed in this method reduce the chance of carbonyl reduction to furnish the alcohol by-product. The authors report a detrimental effect of water on reaction performance; therefore, drying of solvents, catalyst, and an addition of molecular sieves to the reaction mixture have been included in the experimental section of this report.

Interestingly, Gooßen and co-workers report that when aromatic substrates are utilised in this method, they are reduced to the corresponding cyclohexanes. As such, this methodology was only demonstrated on long chain saturated substrates. This observation was not

explored further but is a curious reaction to be observed under such mild conditions and therefore merits further investigation.



Scheme 20: Catalytic reductive etherification reaction utilising a supported platinum catalyst at ambient hydrogen pressure.

Within other similar reactions reported by Bethmont and Fujii, only one example of an aromatic substrate is found. Within the substrate scope investigated by Fujii *et al.*, acetophenone is reacted with *n*-octanol to form product ether in 18% yield. Isolation of an aromatic ether from these reaction conditions is encouraging and low productivity of this reaction is suggested to be due to the resonance stabilisation energy of acetophenone.

Further studies into reductive etherification have been performed but this has mainly been focused in custom catalyst systems to optimise the processes for the biofuels and lubricants industry.[65-67]

1.2 Current Limitations

In a typical pharmaceutical pilot plant setting, hydrogenation reactions are limited by the standard equipment used and high pressures (> 6 bara) and temperatures (> 100 °C) are not feasible. As such, it is desirable to perform reductive etherification at near ambient conditions. For this reason, the literature reductive etherification method most amenable to scale up is that proposed by Gooßen *et al.*[64] This method reports the reductive etherification at ambient hydrogen pressure and 50 °C – mild conditions which would apply well to a typical pharmaceutical pilot plant campaign.

Although being the preferred starting point for the investigation, Gooßen's method comes with a number of associated issues which would require optimisation. The substrate scope outlined in this method would not be applicable to the pharmaceutical industry, as a very high proportion of pharmaceuticals under development contain some degree of unsaturation, with aromatic ring count being a key property in the development of a drug.[68] For this reason, a reductive etherification method which reduces aryl and heteroaryl systems would not be generally useful.

The use of molecular sieves is unfavourable on a pilot plant scale. Molecular sieves are structurally fragile and tend to grind into a fine powder upon stirring. This introduces issues with stirring the reaction mixture, as well as removal at the end of the reaction. Additional measures must be put into place to make sure there are no residual levels of sieves to contaminate the batch of active pharmaceutical ingredient. Also, a problem associated with stirring fine powders is abrasion of the reactor vessel. This will restrict the reaction to being performed solely in metal vessels, as glass vessels will be damaged more easily. Molecular sieves can be purchased relatively cheaply in bulk, however, when used in this reductive etherification reaction, will become contaminated with catalyst. This will result in the spent sieves requiring disposal as contaminated platinum waste, rather than reactivation for reuse or simple landfill disposal. This also limits the chances of recovering and reusing the catalyst for further processes.

Due to the associated health risks, chloroform is an undesirable solvent for scale up of reactions to pilot plant.[69] This solvent is a suspected carcinogen, has been shown to have detrimental effects upon fertility and is also toxic to aquatic life.[70-71] Chloroform has been listed as highly hazardous on the CHEM21 solvent selection review and even been banned for use by chemists at Sanofi.[42] It would be highly desirable to replace this solvent with one

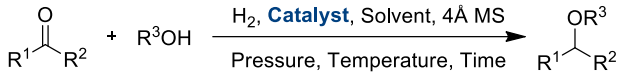
that is more environmentally friendly and is without the associated health hazards, while maintaining its desirable qualities such as solubility.

Degussa, the manufacturer of the catalyst utilised in the Gooßen reductive etherification, has since been acquired by another catalyst supplier, Evonik. Previously reported Degussa catalysts are no longer available, and the exact catalyst reported for the Gooßen reductive etherification is now unobtainable, as has been confirmed through personal correspondence with Evonik. This could prove to be a major issue when replicating the results published by the Gooßen team. Catalyst suppliers hold all the intellectual property associated with their catalysts and are very selective about what information they divulge. The name of the Degussa R-Type F105 R/D 5% platinum on charcoal catalyst describes the catalyst as containing 5% platinum metal on a charcoal support in a dry/reduced form. This is very basic information as it does not describe the distribution of the metal throughout the support (egg shell, intermediate or uniform), the particle size, the surface area, the porosity, the specific carbon support or any other intricate details associated with the preparation of the catalyst or support. For these reasons, the chances of finding a commercially available catalyst equivalent to the Degussa F105 without extensive screening are slim.

1.3 Proposed Work

The aim of the project herein is to develop an environmentally benign, functional group tolerant, easy and safe catalytic method for synthesising ethers from alcohol and carbonyl starting materials. The starting point will be to attempt to reproduce the results reported by Gooßen *et al*. with a view to developing the reaction conditions further to make them more amenable to scale up within the pharmaceutical industry.[64]

As the Degussa catalyst utilised in the original reductive etherification reported by Gooßen *et al*. is no longer commercially available, a catalyst screen will have to be performed (Scheme 21). A selection of wet and dry heterogeneous catalysts will be evaluated to find an appropriate catalyst for performing the reductive etherification.[72] Evonik will be consulted directly for recommendations of catalysts with a similar function.



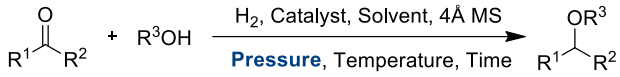
Scheme 21: Proposed catalyst screen to find a commercially available catalyst of equivalent performance to the Degussa F105 R/D 5% platinum on a charcoal support.

The pH of the heterogeneous catalysts in aqueous media are also to be determined as this has been reported to influence the reaction.[54, 57] To address the safety issues associated with handling pyrophoric dry precious metal catalysts, an investigation is to be performed into the potential to use wet pastes of precious metals upon a carbon or other support.

As Gooßen and co-workers reported the reduction of aromatic rings, this will first be reproduced and then the conditions investigated to disfavour this side reaction. As most pharmaceutical ingredients incorporate aromatic rings into their structures, their reduction constitutes an undesired reaction pathway. If the reaction conditions did appear to result in reduction of aromatic rings, a process facilitating this reduction under such mild conditions (50 °C and ambient hydrogen pressure) would no doubt be desirable elsewhere in the synthetic chemistry community.

Although Gooßen reports reductive etherification at ambient hydrogen pressure, the effect of pressure on the reaction is also to be investigated (Scheme 22). This may vary with the catalyst chosen and may alter the rate of the reaction. As the investigation of the reaction is

being performed with a view to application on a large scale, somewhat higher pressures than ambient are acceptable, as the required equipment is available within the GSK network.



Scheme 22: Proposed investigation into the hydrogen pressure upon the reductive etherification reaction.

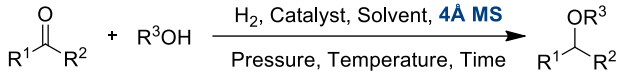
As the reaction mechanism seems split between those which progress *via* dehydrative etherification and those that progress *via* reductive etherification, some investigation should be performed into the mechanism of the Gooßen reaction. In the first instance, the most significant mechanistic consideration to assess is whether the carbonyl reduction occurs as the first step. Consequently, this will allow a direct comparison to be made, as to how analogous these two reaction mechanisms are.

To further probe the mechanism, a series of deuterium labelling studies could be performed. Use of deuterium gas and analysis of the deuteration pattern of the products should be a simple change to the reaction manifold and may possibly give a deeper insight into the inner workings of the reductive etherification reaction. The deuteration pattern of the products could provide valuable information about the reaction intermediates and how these interact with the catalyst and hydrogen gas.

If acidic conditions are shown to be beneficial to the reductive etherification reactions, acidification of the reaction mixture is to be considered. Bethmont *et al.* report use of an acidic catalyst to achieve this low pH, however, their catalyst is custom-made. Synthesis of this catalyst is very energy intensive, requiring temperatures of 500 – 1000 °C and, as such, is particularly unfavourable.[57] As GSK is a pharmaceutical company, custom catalyst production is not a commonplace activity and commercial catalysts are much preferred.

Should no commercial catalyst trialled be shown to be acidic, a screen of suitable organic acids is to be performed. As part of this screen, the amount of acid required for completion of the reaction is to be investigated. As an acid additive is increasing the overall process mass intensity[‡] of the reaction, it would be beneficial to use as little as possible.

The use of molecular sieves is to be investigated as the inclusion of these in a reaction preparation is not desirable within a pilot plant (Scheme 23). Molecular sieves constitute an additional cost to both acquire and dispose of in the overall process, not to mention the additional problems of removal from the reaction mixture. Therefore, it will be highly beneficial to avoid their use in this reaction.



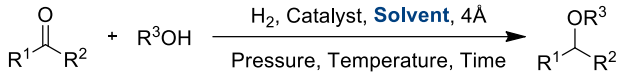
Scheme 23: Evaluation of the molecular sieves within the reductive etherification reaction.

Design of Experiment analysis could be utilised to streamline the optimisation process and more accurately balance the quantities of reaction components to maximise product formation. The reductive etherification manifold has many parameters with which to improve the reaction and DoE statistical analysis will allow all of these to be analysed and optimised within the least amount of reactions possible.

[‡] Process Mass Intensity is defined as the total mass of materials used to produce a specified mass of product. Materials include reactants, reagents, solvents used for reaction and purification, and catalysts.

Once conditions have been optimised, a quantitative time course experiment will be performed in an attempt to elucidate the reaction mechanism through observation of any intermediates. This time course may also identify slow steps of the reaction which could be further developed to decrease the overall reaction time.

It will also be important to find an improved solvent to address the safety concerns associated with chloroform (Scheme 24). The selection of such a solvent will take into account properties such as environmental considerations, hygroscopicity and polarity. The chosen solvents also need to be compatible with the reductive etherification reaction. This would exclude alcoholic solvents and solvents containing an aldehyde or ketone functional group. A diverse array of solvents meeting these criteria will be selected using a principal component analysis (PCA) visualisation developed at GSK.



Scheme 24: Proposed solvent screen to be performed with the aim of replacing chloroform as the reaction solvent.

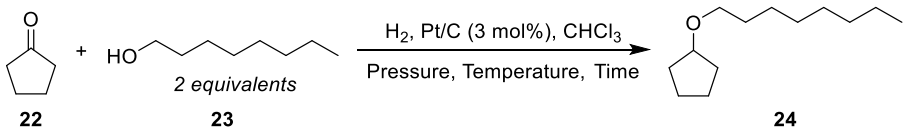
1.4 Results and Discussion

For the initial exploratory studies discussed in the first sections, only qualitative results are reported for Sections 1.4.1-1.4.5. A reference sample of cyclopentyl butyl- and octyl ethers with sufficient purity to be used as a reference standard had not yet been obtained at the time these initial studies were performed. Isolation of this compound was challenging due to the complexities regarding isolation and purification of this volatile model substrate. Other reaction components with sufficient reference samples could also not be quantified, as a GC method which integrated these peak areas for quantitative comparison had not yet been

developed. These issues are addressed throughout the study and quantitative analysis begins in Section 1.4.6.

1.4.1 Investigation of Gooßen Conditions

Cyclopentanone (**22**) and *n*-octanol (**23**) were chosen as the starting materials with which to investigate the reaction parameters (Scheme 25) as this coupling had already been reported by Gooßen *et al*.[64]



Scheme 25: Proposed reductive etherification reaction conditions.

The first step taken was to repeat the reaction in the HEL ChemSCAN II high pressure parallel synthesiser (Figure 3) with two different Pt/C catalysts. The exact catalyst used by Gooßen (5% Degussa R-Type: F 105 R/D) is no longer available following acquisition of Degussa by Evonik.[64]

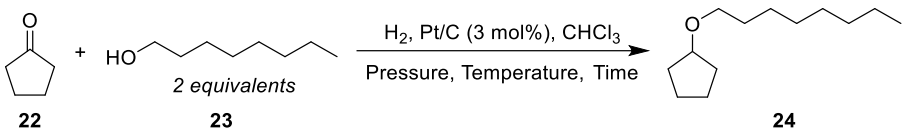
As Degussa was acquired by Evonik, scientists from Evonik were consulted about the function of the F105 catalyst. Although they were unable to supply further information about the catalyst, they reviewed the properties of the F105 catalyst themselves and recommended an Evonik catalyst considered to be most similar. The catalysts advised for testing in reductive etherification were the Evonik Noblyst P2053 5% and Evonik Noblyst P2085 3% platinum on carbon catalysts. These catalysts are dry and thus pose additional hazards when handling; dry carbon-based precious metal catalysts are generally more pyrophoric than their wet

paste counterparts. To make this process safer to work with on a large scale, this safety aspect would require to be addressed.



Figure 3: HEL ChemSCAN II high pressure parallel synthesiser equipped with 8 x 16 mL independently controlled Hastelloy reactors.

These catalysts were assessed in the reductive etherification of **22** with octanol **23** (Table 1). The 5% Pt content catalyst showed greater activity than the 3% catalyst on a mole for mole basis at 50 °C and 1 bar, but neither catalyst provided a complete reaction using the 2-hour reaction period reported. Due to higher conversion of starting materials to products after 6 hours, the 5% catalyst was chosen as the starting point from which to investigate the reductive etherification reaction. The 3% catalyst showed a larger peak corresponding to cyclopentanol suggesting a greater extent of direct carbonyl reduction.



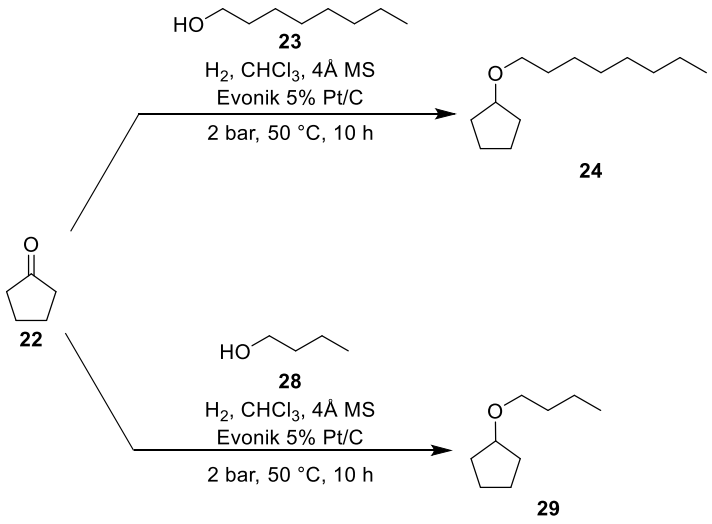
22 23 24

Catalyst	Pressure	Cyclopentanol	Ether Product
Evonik Noblyst P2085 3%	1 bara	Present by GC	Present by GC
Evonik Noblyst P2053 5%	1 bara	Present by GC but in less quantity than 3%	Present by GC
Evonik Noblyst P2053 5%	1 barg (2 bara)	Present by GC but in less quantity than 1 bara	Present by GC

Table 1: Qualitative analysis of initial scoping reactions.

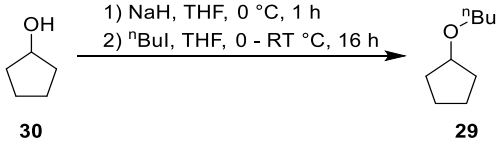
The Gooßen conditions were also evaluated with respect to 1 bar gauge and 1 bar absolute hydrogen pressure, with 1 bar gauge showing better conversion of starting materials to product by GC analysis. Within the GC trace for the reaction at 1 bar gauge, a smaller peak corresponding to cyclopentanone/cyclopentanol was observable and so 1 bar gauge was used in future reactions.

As *n*-octanol is a non-volatile alcohol, separation of the product from the excess alcohol after the reaction proved to be problematic due to the low polarity of both substances. For this reason, replacement of *n*-octanol with *n*-butanol was trialled (Scheme 26). Cyclopentyl butyl ether (**29**) proved to be a volatile product which evaporated readily during isolation. However, it was possible to analyse conversion to cyclopentyl butyl ether by NMR spectroscopic analysis of the crude reaction mixtures after removing chloroform by rotary evaporation.



Scheme 26: Product optimisation to improve ease of isolation.

To verify the results from the crude NMR assays, an authentic sample of cyclopentyl butyl ether (**29**) was required. This was synthesised by the Williamson method, as shown in Scheme 27.



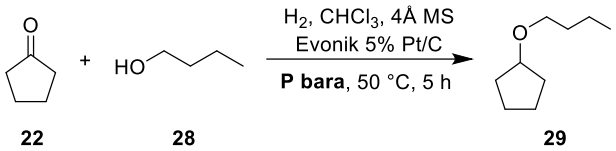
Scheme 27: Williamson ether synthesis of cyclopentyl butyl ether.

Although this method posed similar problems with isolation and characterisation of the desired product, the GC trace and the crude NMR spectrum of the product correlated exactly with those from the reductive etherification method. The difficulties of purification of these compounds on small scale is something noted by numerous others within the field and is attributed to the low volatility and polarity of the product ethers alongside their ability to azeotrope with alcohols during evaporation.[55, 73] Nonetheless, cyclopentanone and *n*-butanol

were chosen as the reaction partners with which to investigate the reductive etherification reaction henceforth.

1.4.2 Investigation of Pressure and Temperature

As 2 bar absolute H_2 pressure had been more productive with respect to reductive etherification than 1 bar absolute, reactions were trialled at 2, 3, 4 and 5 bar absolute H_2 pressure, at both 40 and 50 °C. All reactions showed conversion of starting materials to products but in no case was complete conversion observed after 5 hours. As expected, lower temperatures showed lower conversion, and higher pressures led to reduction of cyclopentanone to cyclopentanol at a greater extent (Figure 4).



22 **28** **29**

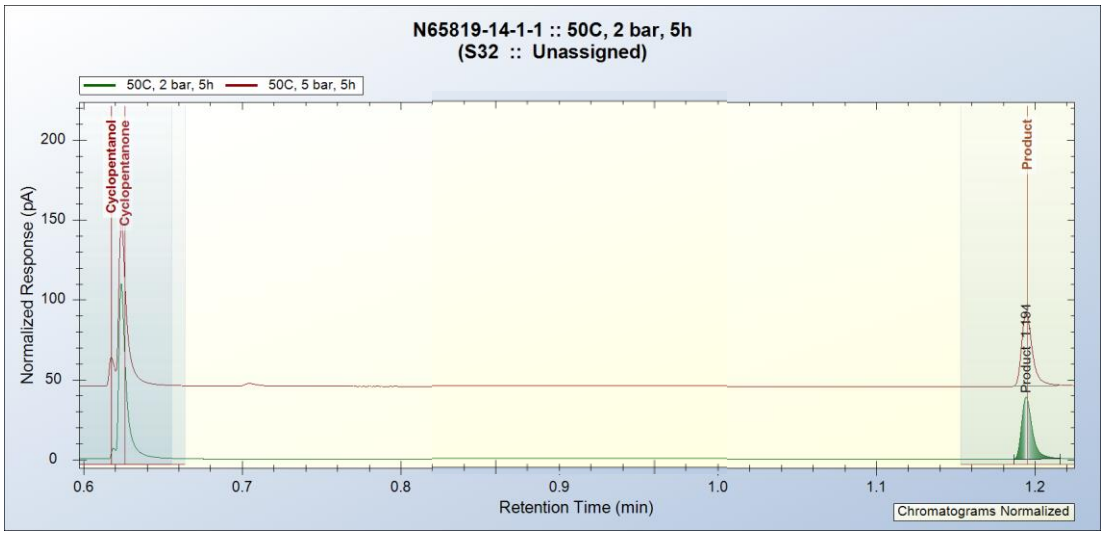
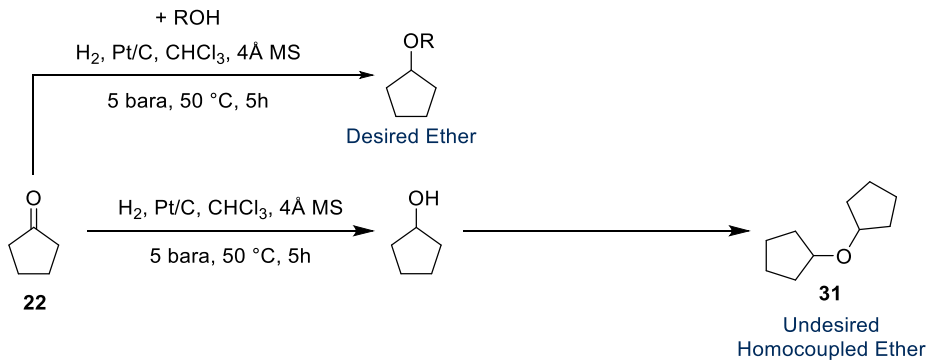


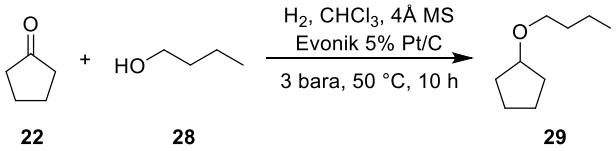
Figure 4: GC overlays of the reductive etherification reaction of cyclopentanone and n-butanol at 50 °C and 2 or 5 bara hydrogen atmosphere. The peak for cyclopentanol can be seen to be increased at 5 bara.

Direct reduction of the carbonyl is an undesirable process in this reaction. Not only does it decrease the amount of carbonyl compound available for reductive etherification, it also increases the number of alcohol species which can participate in reductive etherification, leading to formation of the symmetrical ether (**31**) (Scheme 28). It was found that, once cyclopentanol had been formed, the reductive etherification process halted. This observation suggests that this process does not follow a reaction pathway of reduction followed by dehydrative etherification.



*Scheme 28: Formation of dicyclopentyl ether (**19**) under the reductive etherification reaction conditions.*

As a result of the pressure study, use of 3 bara appears to lead to greater selectivity for reductive etherification over carbonyl reduction and, as such, was chosen as the pressure at which to further investigate the reaction. A short temperature study showed that a temperature of 50 °C gave an increased reaction rate, compared to reactions at 40 °C, although reaction times were longer than those reported by Gooßen *et al.* in their catalyst system.[64] For these reasons, a set of initial reaction conditions were chosen as the baseline from which to optimise issues such as safety, usability, substrate scope and reaction times (Scheme 29).



Scheme 29: Initial reaction conditions for catalytic reductive etherification of cyclopentanone and n-butanol.

Overall, this brief initial study of the reaction parameters reported by Goosen *et al.* resulted in a new set of reaction conditions which are: 3 bara of hydrogen pressure, Evonik P2053 5% Pt/C catalyst, reaction temperature of 50 °C, and an extended reaction time of 10 hours.

1.4.3 Initial Substrate Screen

With the baseline conditions set, they were applied to a range of substrates in a 24-reaction plate in the CAT96 pressure reactor (Figure 5), to determine the applicability of the reaction. Although still qualitative in nature, this investigation was designed with the dual aims of determining any limitations of the reaction manifold, and validation of the incompatibilities reported by Goosen *et al.* regarding aromatic substrates.[64]

This screen reacted four different carbonyl compounds (cyclopentanone **22**, 2-heptanone **32**, acetone **33** and acetophenone **34**) with six different alcohols (methanol **35**, ethanol **8**, propanol **44**, butanol **28**, cyclopentanol **30** and benzyl alcohol **16**), potentially resulting in the formation of up to 24 different products (Table 2). As Gooßen *et al.* had noted that aromatic rings were not tolerated under the reaction conditions, one aromatic carbonyl and one aromatic alcohol were chosen to examine this observation in our own hands. A pressure of 3 bara was previously identified as the optimal reaction pressure, however, the screening reactions in the CAT96 reactor are performed in sealed HPLC vials. These vials have punctures within the septa to allow the reacting gas inside. To ensure the reacting gas penetrates the seal, previous experience within our laboratories has shown that reactions in this equipment are best performed under a minimum of 5 bara hydrogen pressure.

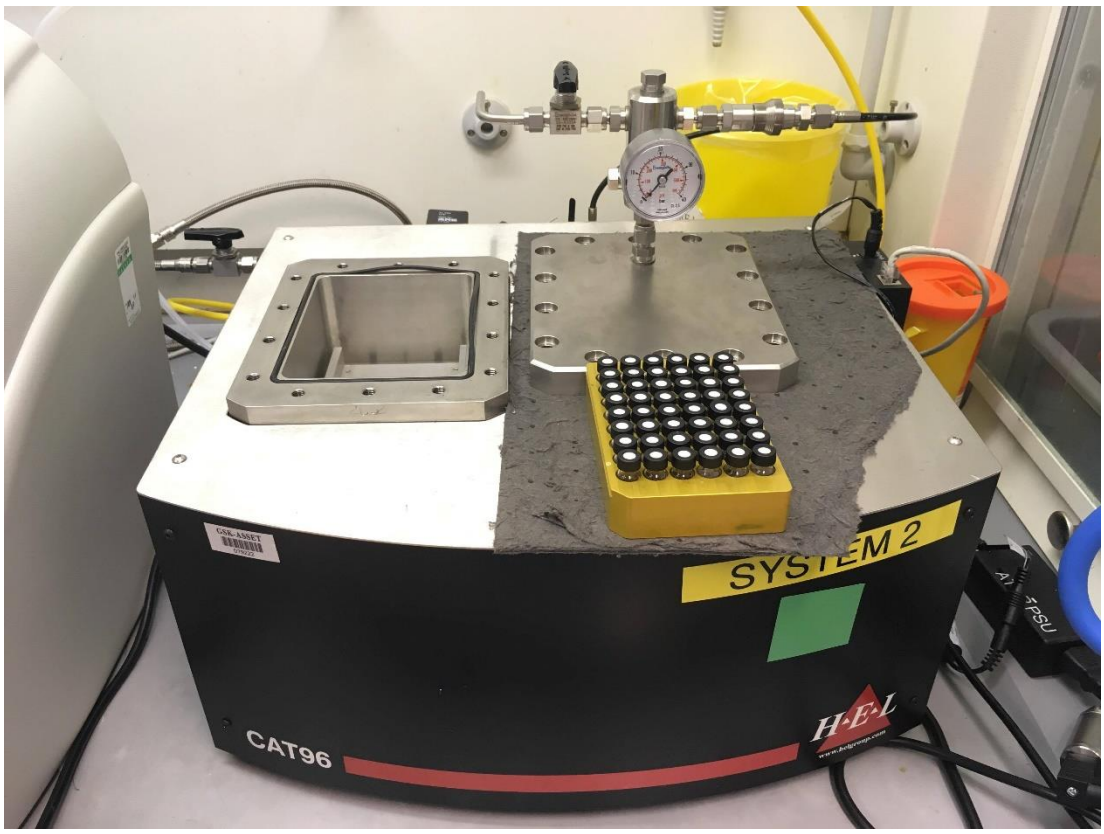


Figure 5: CAT96 pressure reactor showing a 48 well plate of HPLC sized reaction vials and the reaction vessel.

Where possible, products were referenced to known compounds. If this was not possible, product formation was inferred by GC analysis, using the knowledge that GC retention times are proportional to the boiling point of analytes and the boiling point of ethers usually increases with size.[74-75]

The results of this screen are shown in Table 2. CPME (**36**) was referenced to a known sample and is shown in dark green. Other light green substrates are suspected to be formed due to patterns observed by GC analysis. Methyl *iso*-propyl ether and ethyl *iso*-propyl ether are thought to have formed within the reaction mixture but are shown in orange. Due to the size and volatility of these molecules, the retention times are thought to be similar to that of methanol and no product peak was observable by GC analysis. As previously reported by

Gooβen *et al*., none of the reactions incorporating aromatic substrates showed any signs of product formation. Accordingly, these results are displayed in red.

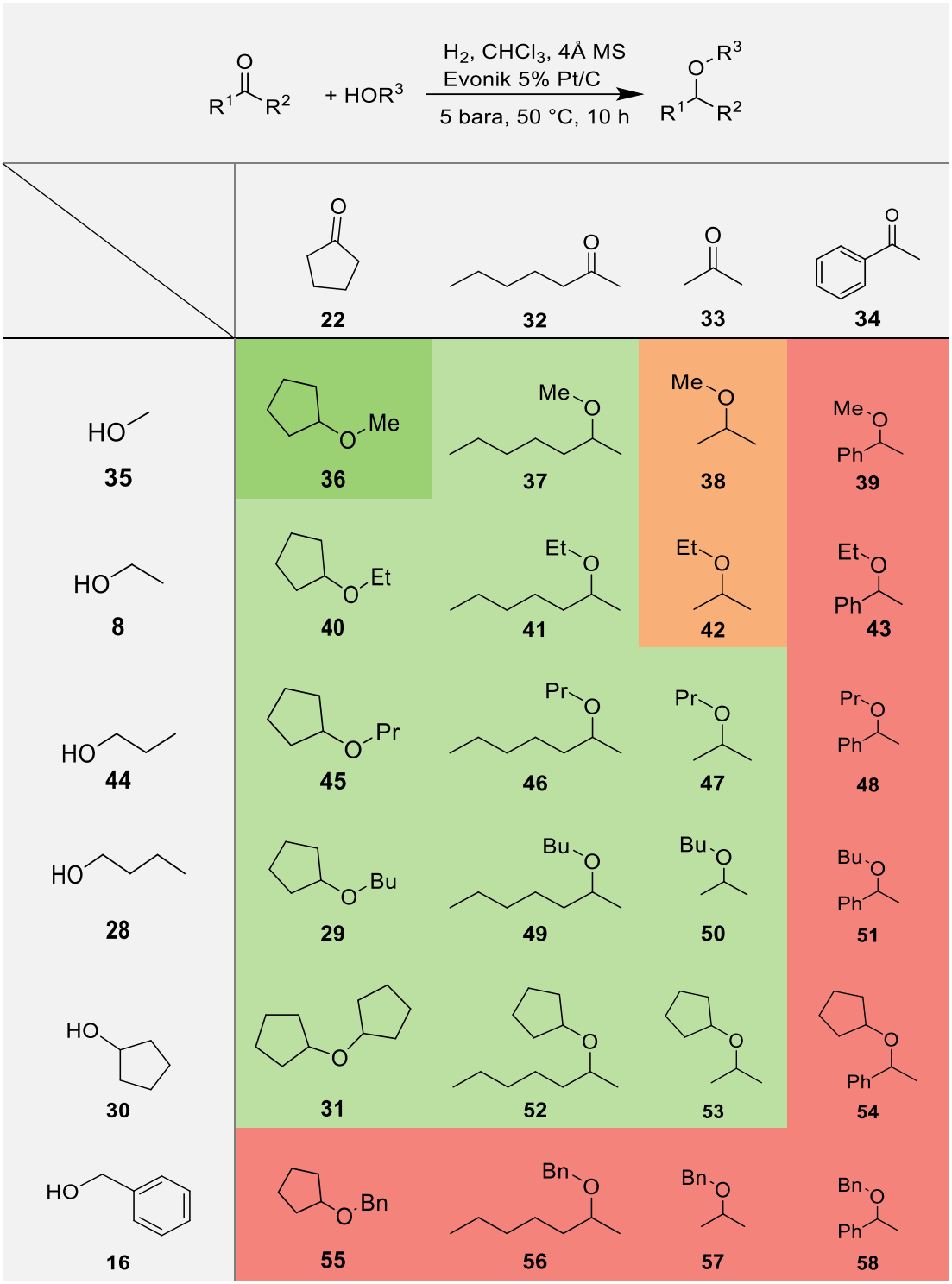
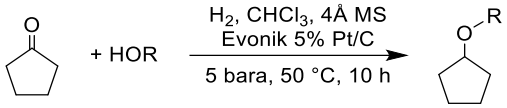


*Table 2: Combinations of alcohols and ketones reacted in first CAT96 screening plate. Green products are suspected to be formed. CPME, (**36**) was confirmed by GC comparison against a reference sample. Products in red indicate no later-running peak by GC consistent with product formation. Products in orange are considered likely to be formed but could not be detected under solvent front.*

Reactions with cyclopentanone worked well (**36, 40, 45, 29** and **31**), with possible products being observed by GC analysis for all proposed ethers other than for the reductive etherification with benzyl alcohol (**56**). As can be seen by the overlaid chromatograms (Figure 6), the reaction to form CPME was referenced against a known sample and then the product peaks migrate to later retention times, as would be expected as the product molecular weight increases.



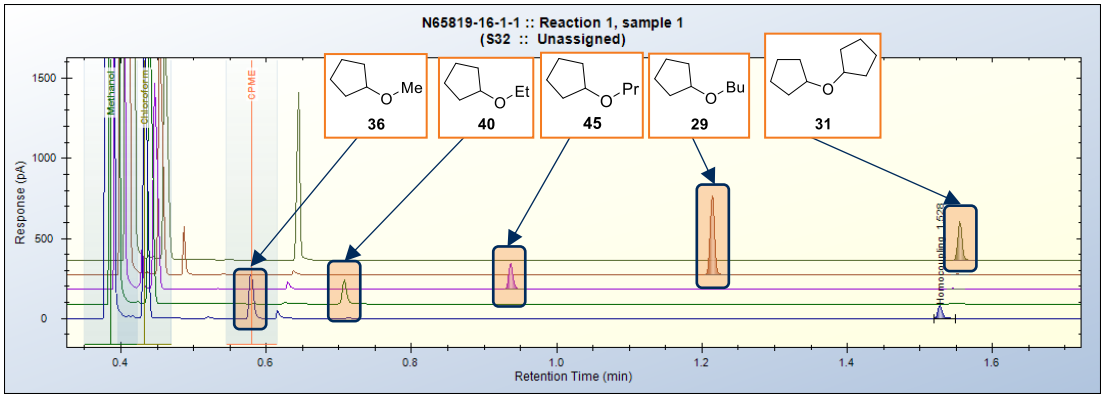
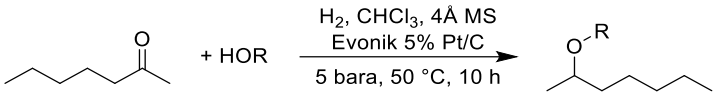


Figure 6: Overlaid reaction chromatograms for reactions of cyclopentanone with methanol, ethanol, propanol, butanol and cyclopentanol.

The same can be said for the reductive etherification between 2-heptanone and all alcohols (**37, 41, 46, 49, 52**) aside from benzyl alcohol (**57**). Once again, as seen by the overlaid chromatograms (Figure 7), the putative product peaks migrate to later retention times as would be expected by products of increasing size. The competing direct reduction of the carbonyl can be observed to a greater extent for this ketone substrate, with a greater peak area being detected with the secondary, cyclopentanol etherification partner.



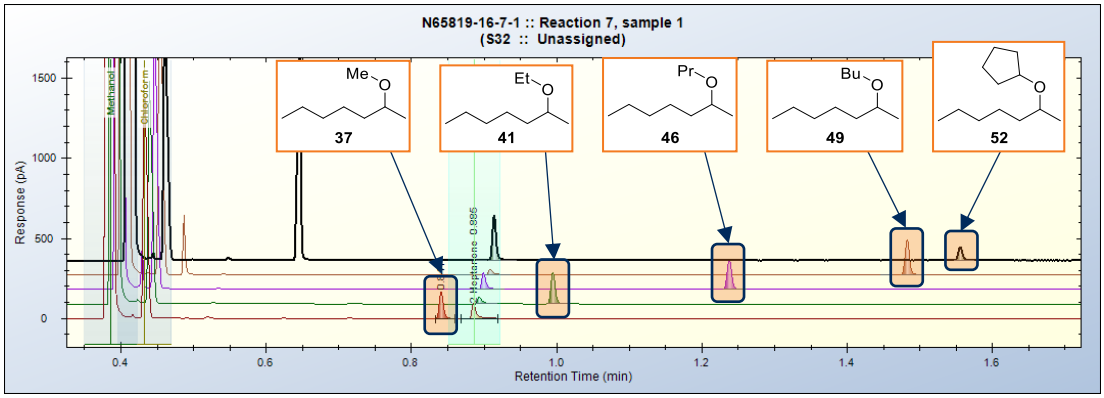
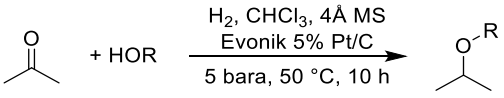


Figure 7: Overlaid reaction chromatograms for reactions of 2-heptanone with methanol, ethanol, propanol, butanol and cyclopentanol.

When using acetone as the ketone, only potential product peaks for the reductive etherification with *n*-propanol (**47**), *n*-butanol (**50**) and cyclopentanol (**53**) were observable (Figure 8). This is hypothesised to be due to the size and volatility of both starting materials and product. Once again, the reaction with benzyl alcohol was unsuccessful (product **58**).



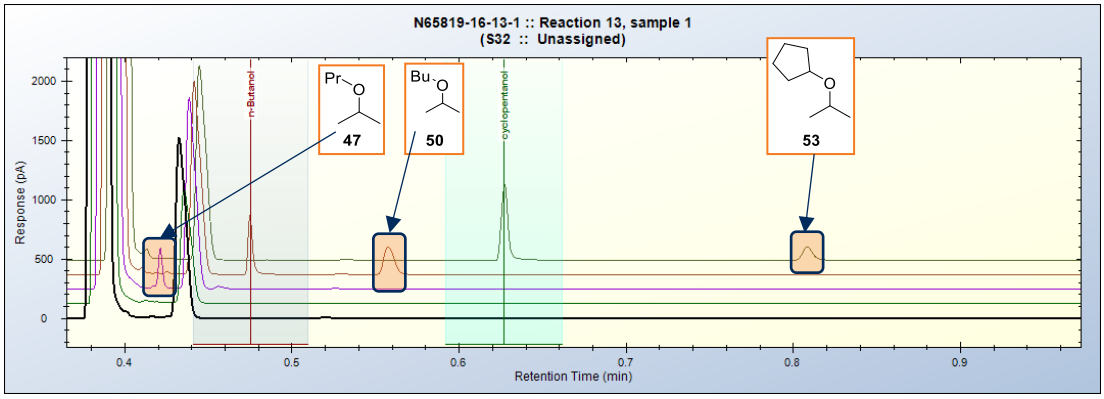
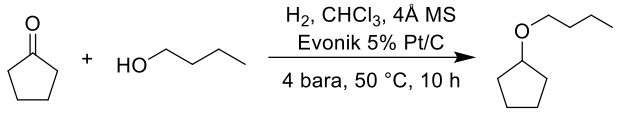


Figure 8: Overlaid reaction chromatograms for reactions of acetone with methanol, ethanol, propanol, butanol and cyclopentanol.

Curiously, for all reactions containing aromatic substrates (**56 – 59, 39, 43, 48, 51** and **54**), no chromophore was detectable after the reaction, and no starting material was observable by GC analysis. This was particularly puzzling for the reactions with benzyl alcohol, as this is present in excess in the reaction mixture, and as such, should still be detectable by GC after the reaction. The reaction between benzyl alcohol and cyclopentanone (**56**) was analysed by NMR spectroscopy after the reaction and no signals were detected in the aromatic region of the spectrum. These observations could indicate reduction of the aromatic ring, as reported by Gooßen *et al*.[64]

1.4.4 Large Scale Reaction and Mechanistic Investigation

To reproduce the results of the pressure and temperature screen, the opportunity was taken to test the reaction on a larger scale of 12.5 mmol cyclopentanone, as opposed to previous reactions at 1 mmol (Scheme 30).



Scheme 30: Initial large scale reaction within the EasyMax pressure vessel.

This reaction was performed at 4 bara and 50 °C, without molecular sieves in an EasyMax high pressure reactor (Figure 9). An EasySampler was employed in monitoring this reaction and the reaction mixture was sampled every 20 minutes.

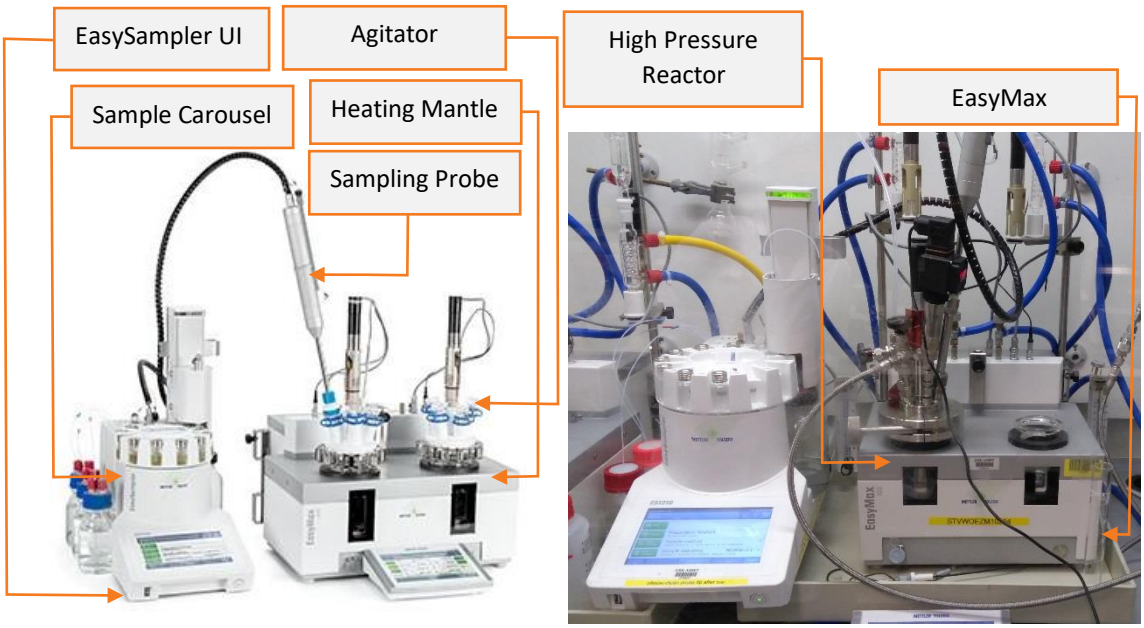
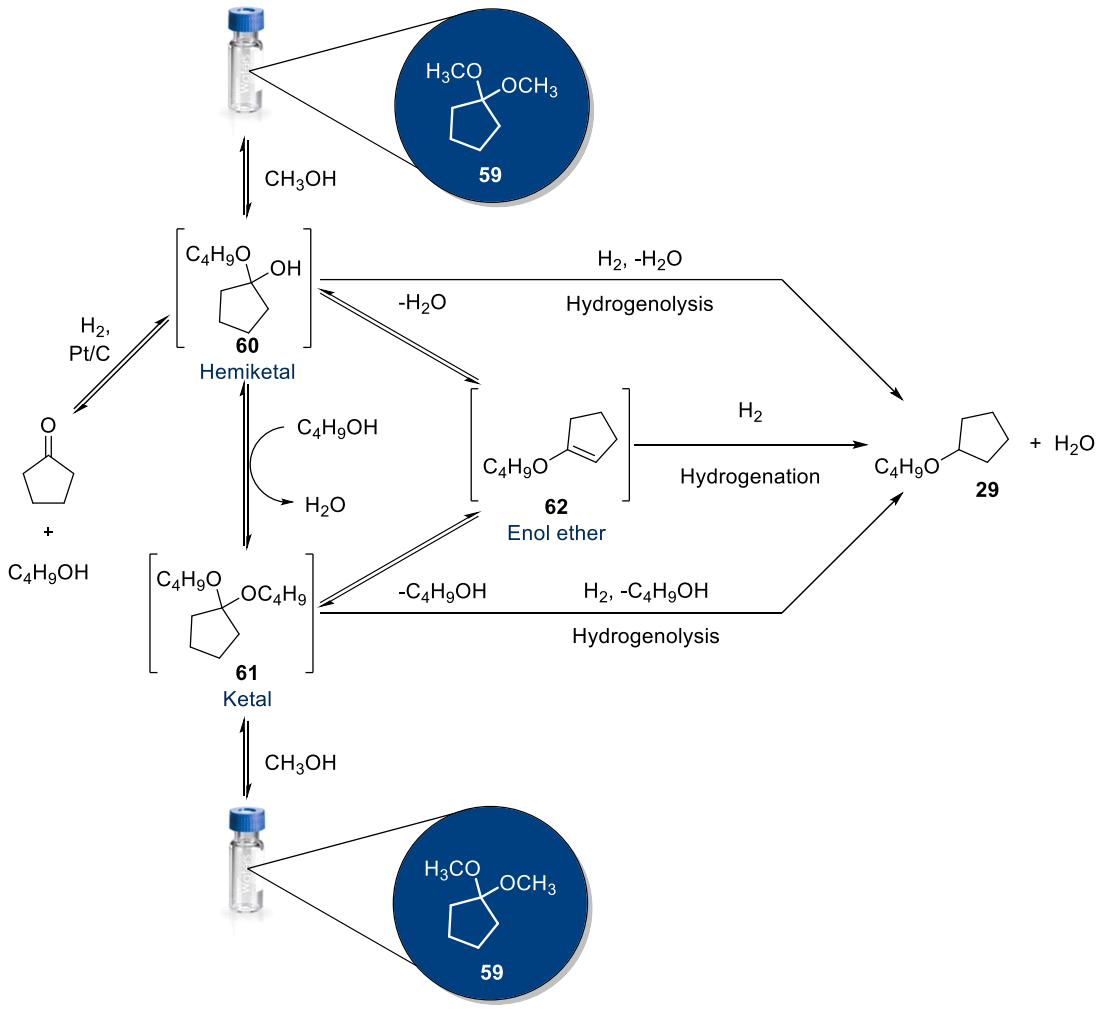


Figure 9: EasyMax high pressure reaction vessel fitted with an EasySampler AutoMATE sampler (left). Reductive etherifications were performed in a Hastelloy reactor (right).

GC analysis of the reaction mixture (Figure 10) showed formation of a previously unobserved intermediate, which was consumed as the reaction progressed. Curiously, the intermediate appeared to be relatively stable, and could still be observed after aging the sample for three weeks. Unfortunately, the identity of this intermediate proved to be difficult to establish due to the issues with isolation of the product. It was hypothesised that the reaction progresses *via* formation of the corresponding ketal, as proposed by Fujii *et al*., as the intermediate formed has a retention time halfway between reactants and products in the GC trace, suggesting a compound with a mass between the two.[54] The intermediate ketal was hypothesised to exchange with the methanol used to dilute the reaction mixture aliquots before analysis, forming the dimethoxy ketal **59**. To support this, a sample of 1,1-dimethoxycyclopentane was purchased and shown to have a GC retention time correlating exactly with this intermediate (Figure 10). Accordingly, in analysis of further reactions using

this method, we take observation of the dimethyl ketal **59** as a proxy for the ketal of the reacting alcohol.



*Scheme 31: Proposed mechanism of the reductive etherification of cyclopentanone and n-butanol showing the origin of the referenced ketal intermediate, 1,1-dimethoxycyclopentane (**59**).*

A commercially available sample of 1,1-dimethoxycyclopentane was used as a surrogate for all three proposed reaction intermediates (**60**-**62**). When the samples of the reaction mixture are diluted in methanol for GC analysis, the ketal, hemiketal and enol ether are believed to exchange and form the dimethyl ketal. This allows approximation of the reaction intermediates by solution yield determination against a tridecane internal standard.

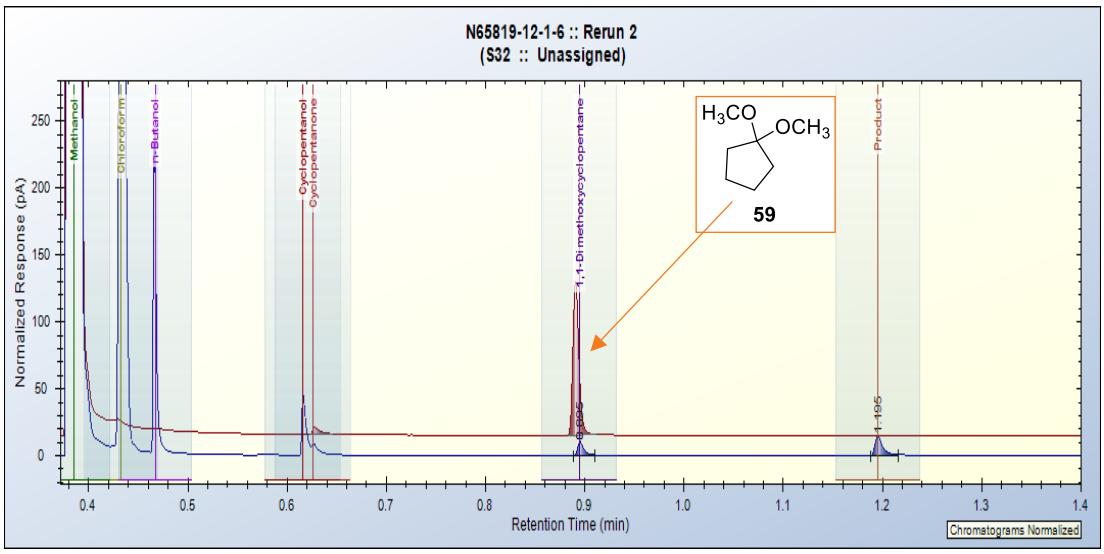


*Figure 10: GC chromatogram of a sample taken from the large scale reaction overlaid with the reference sample of the ketal intermediate (**59**).*

Additionally, the omission of molecular sieves from this reaction did not inhibit product formation but did have a detrimental effect on the reaction, as formal reduction of the carbonyl compound was observed to a greater extent when compared to previous, small-scale, work.

1.4.5 Heterogeneous Catalyst Screen

Evonik 5% Noblyst P2053 platinum on a carbon support was found to be the best dry platinum catalyst for reductive etherification so far. However, literature precedent has shown that other transition metals have been utilised for etherification reactions.[48] Dry catalysts also come with safety hazards due to their pyrophoricity and, as such, wet catalyst pastes are preferred for handling and dispensing, particularly on large scale.[76] Based on this, a variety of wet and dry supported precious metal catalysts were screened in the reductive etherification reaction. A screen of 24 catalysts was performed, using mostly dry pastes (and, where available, the corresponding wet pastes) known to be recommended for

hydrogenolysis reactions. Although substrates with aromatic rings had already been observed to be incompatible with the existing conditions for reductive etherification, each catalyst was screened in the reaction of a saturated (*n*-butanol) and an aromatic (benzyl alcohol) alcohol. The results of the catalyst screen are shown below (Figure 11 for reactions with butanol and Figure 12 for reactions with benzyl alcohol). As an appropriate GC method was still under development, the reaction could not be quantified at this stage. For this reason, only the major product observed in each reaction has been indicated in the following figure.

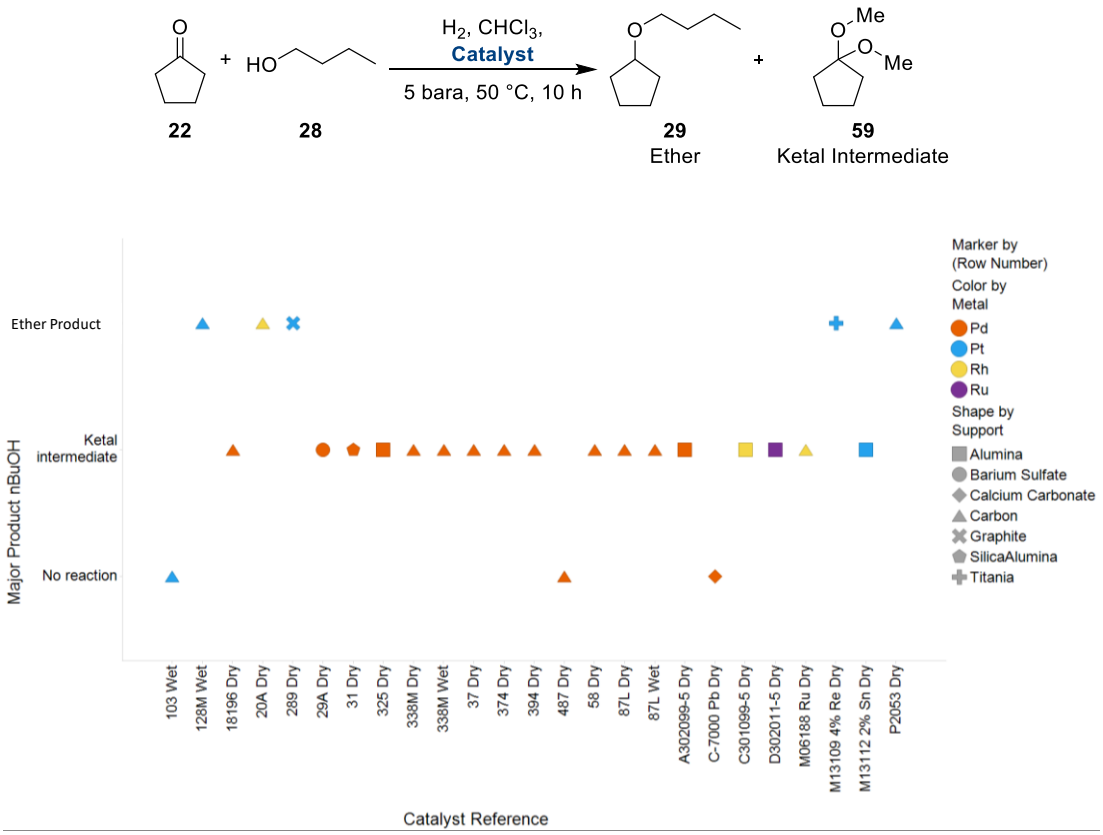


Figure 11: Reductive etherification reactions between cyclopentanone and n-butanol utilising a selection of precious metal catalysts and the major product formed in each case.

When the catalyst screen was performed with respect to the reductive etherification of cyclopentanone and *n*-butanol, mainly the platinum catalysts displayed the desired

reactivity. When palladium and rhodium catalysts were investigated (Figure 11 and Figure 12), these appeared to form the same ketal intermediate (**59**) with the majority not performing the desired reductive etherification reaction to any appreciable extent within the 10-hour reaction time. For the reactions with benzyl alcohol, no product ether was formed with any catalyst.

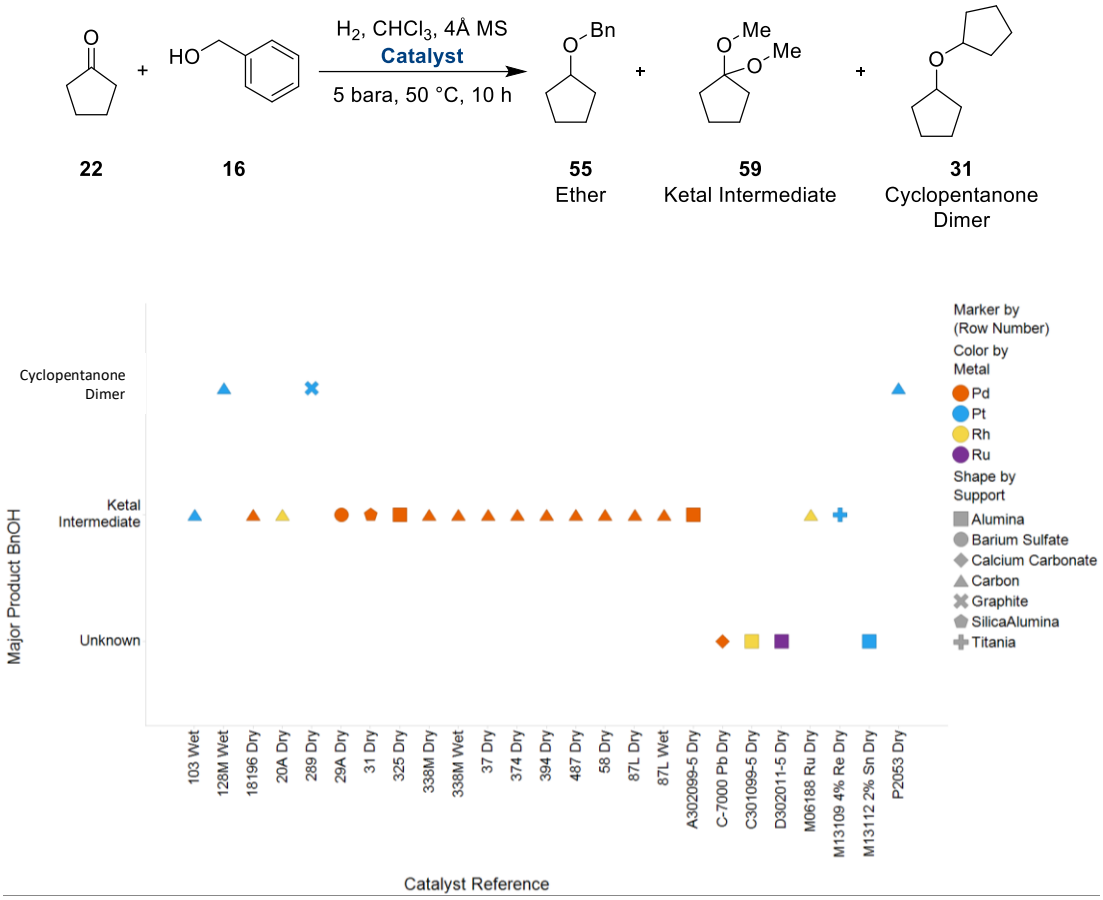
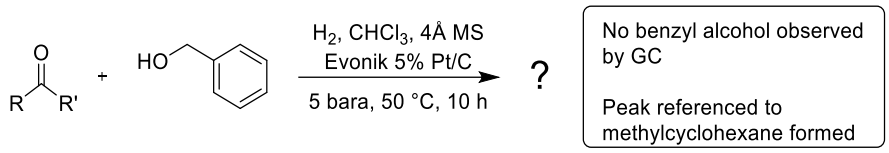


Figure 12: Reductive etherification reactions between cyclopentanone and benzyl alcohol utilising a selection of precious metal catalysts and the major product formed in each case.

Interestingly, in almost all cases, benzyl alcohol was not detected at the end of the reaction. This again shows the incompatibility of aromatic systems to the current reaction conditions (Scheme 32). For comparison, a GC spectrum of cyclohexylmethanol was obtained to verify whether Gooßen was correct in attributing the loss of aromaticity to reduction to the

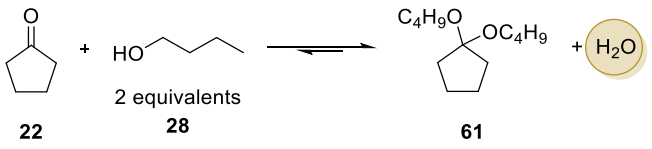
corresponding cyclohexane. When compared to GC analysis of the reaction mixture, no cyclohexylmethanol was observed, however, a peak in the chromatogram could be referenced to methylcyclohexane, suggesting reduction of both the aromatic ring and the alcohol.



Scheme 32: Platinum catalysed reductive etherification reaction with benzyl alcohol.

As can be seen in Figure 11 and Figure 12, the most common product detected within the GC trace was the dimethoxy ketal intermediate **59**. This was verified by correlation of GC retention time with a reference sample of 1,1-dimethoxycyclopentane (**59**).

Correlating with the results of the last catalyst screen, drier reactions, employing dry catalyst, outperformed those containing water for the majority of catalysts trialled. Clearly, the presence of water has a detrimental effect on the desired reaction pathway. This could be because the molecular sieves are removing water from the reaction mixture, driving the formation of the ketal intermediate (Scheme 33). However, one wet paste catalyst (5R128M) was shown to form the ether as the major reaction product. This is a very encouraging result with respect to further development of the reaction to use a wet paste catalyst.



*Scheme 33: Equilibrium between cyclopentanone, n-butanol and the dibutoxy ketal intermediate (**61**) with resulting water being trapped by molecular sieves.*

Additionally, carbon-supported catalysts outperformed alumina or titania supported catalysts. Based on this screen, the optimal catalyst for the reaction remained unchanged from the Evonik 5% Noblyst P2053.

At this point, a modified method was finalised to allow GC analysis of these reaction mixtures. This was a modification of the method used previously in this report with integration parameters tailored to exclude solvent peaks for chloroform and methanol, while integrating all reaction components of interest. The fact that this was the same as the previously utilised method, with increased integration parameters, was very important as this allowed all the reference samples already run on the GC method to be retained for future use.

1.4.6 Initial Quantitative Time Course Experiment

Experiments were performed to calculate the response factor for each component of the reaction on the gas chromatograph. Solutions of known concentrations were prepared for *n*-butanol, cyclopentanol, cyclopentanone, 1,1-dimethoxycyclopentane and cyclopentyl butyl ether (isolated upon completion of this quantitative time course experiment) with an internal standard of tridecane. This allowed response factors to be calculated using Equation 1.

$$K_X = \frac{Peak\ Area_{ISTD} \times Weight_X}{Peak\ Area_X \times Weight_{ISTD}}$$

Equation 1: Equation used to calculate response factor for reaction component, X, with respect to an internal standard.

The samples of known concentration were analysed three times and response factors for the reaction components were calculated. These response factors were then averaged to account for any deviations in the analysis. Calculated K_X values can be found in Table 3.

Reaction Component	Average K_X
n-Butanol	1.44
Cyclopentanol	1.22
Cyclopentanone	1.34
1,1-Dimethoxycyclopentane	1.87
Cyclopentyl butyl ether	1.21

Table 3: Calculated K_X values for reaction components.

These values were then applied to a larger scale reaction utilising the EasySampler in order to sample the reaction at regular intervals. When these samples were analysed by GC, the response factors were used to give a real-time evaluation of the quantities of each component present in the reaction mixture (Figure 13).

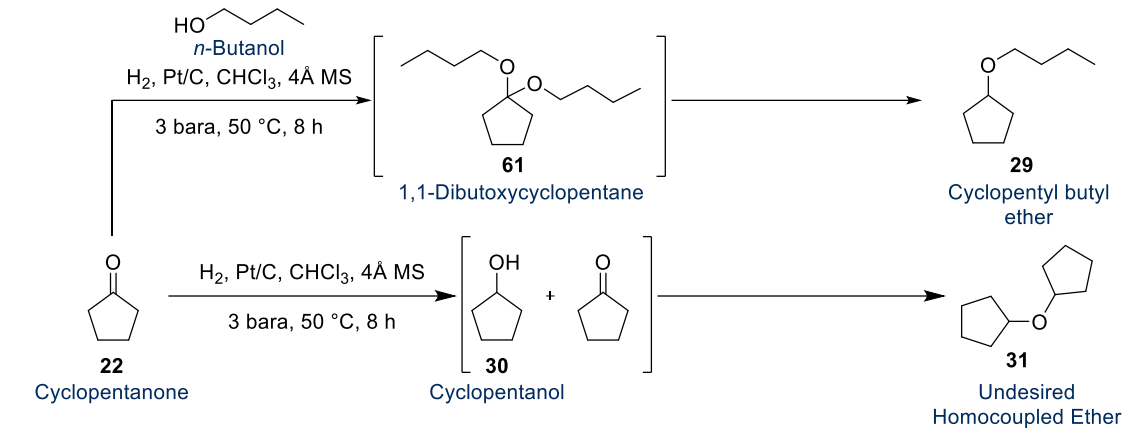




Figure 13: Quantitative time course data for the reductive etherification reaction to form cyclopentyl butyl ether.

The results of this quantitative time course study are very interesting and give significant insight into the inner workings of the reaction. The data show that the ketal intermediate (purple, **61**) is formed almost immediately and in high solution yields (95%). It also shows that the slowest step of the reaction is the hydrogenolysis of this ketal intermediate.

The data also show an equilibrium between cyclopentanone (orange, **22**) and the ketal intermediate (purple, **61**) with an increase of one being mirrored by consumption of the other.

Formation and accumulation of this intermediate within the reaction mixture was something to be addressed with further optimisation of the reaction. This intermediate is formed relatively rapidly (15 minutes) and consumed relatively slowly (8 hours). It was postulated that, if the rate of conversion of this intermediate to the desired products was increased to avoid its accumulation, then the overall rate of reaction would be increased. With the reaction pH seemingly being an important factor within similar etherification reactions, it was clear that this key parameter be investigated in more detailed studies.[54, 57]

1.4.7 Catalyst pH Screen

As it was hypothesised that the pH of the reaction medium would have a dramatic effect upon the reaction yield and overall rate, the pH of the evaluated catalysts was determined. Bethmont *et al.* had achieved catalyst acidity *via* a custom-made species pre-treated with nitric acid (pH 3.9). Therefore, an acidic catalyst which was commercially available would be ideal for this reaction.[57]

The catalysts were slurried in water in the same proportions they would be for reactions on a corresponding scale (3.75 µmol Pt in 0.5 mL water). These mixtures were then stirred at room temperature for 6 hours and the pH was then measured using indicator paper. This method of measuring catalyst pH was outlined by the Bethmont team when determining the pH of their custom-made catalyst, and would thus allow direct comparison.[57]

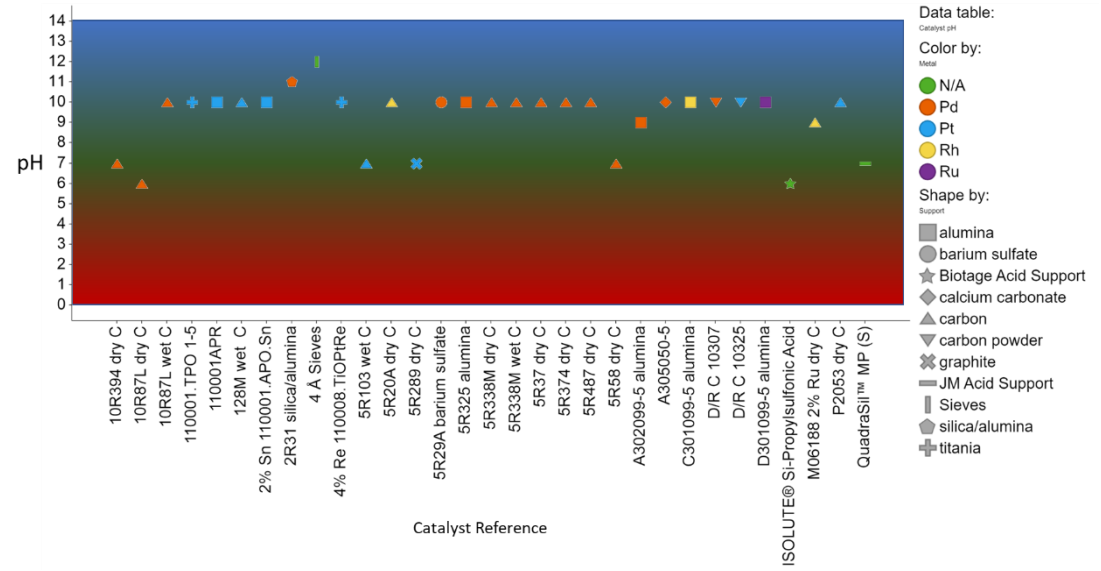


Figure 14: pH values of the previously screened catalysts.

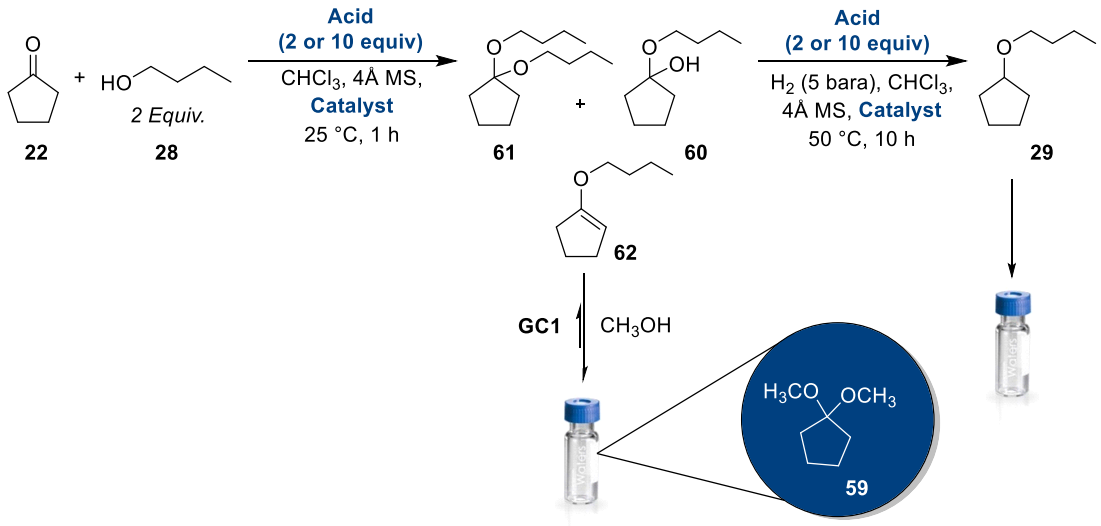
Most catalysts were found to be moderately basic, with the most basic catalyst at pH 11. Only one catalyst fell in the category of mildly acidic (pH 6), and the remaining catalysts fell within the category of mildly basic.

As molecular sieves are currently used in the reductive etherification, the pH of these additives was also measured (60 mg in 0.5 mL water). The molecular sieves were shown to be basic (pH 12), suggesting that even the most acidic catalyst (pH 6), when combined with the molecular sieves (pH 12), would result in a basic reaction mixture. This dominant basicity was proposed to hinder formation of the enol ether intermediate and subsequently decrease the rate of product formation.

As the hydrogenation of the enol ether is proposed to be faster than the hydrogenolysis of the ketal intermediate, this could account for the slow rate observed in the previous quantitative time course (Figure 13). As enol ethers are only formed in acidic conditions, it is important for the reductive etherification reactions to employ an acid additive.[59]

1.4.8 Acid Screen

As no catalyst was found to have a low pH, it was deemed preferable to add an acid additive to the reaction rather than custom-making an acidic catalyst. Four common organic acids, with a range of pK_a values, and compatible with the Hastelloy reactors at GSK, were chosen for an acid screen. These acids were evaluated at high and low concentrations, in 2 and 10 acid equivalents with respect to cyclopentanone, with each of the five catalysts that had been shown to form the ether as the major product in Section 1.4.5. These five catalysts are: Evonik Noblyst P2053 Pt/C, JM Type 5R289 Pt/C, JM Type 5R128M Pt/C, JM Pt/Re on titania support and JM Type 5R20A Rh/C. These five catalysts represent a good mix of wet/dry, active metal, metal content, additional metal doping and support type. For these reactions, GC samples were taken after stirring at room temperature for 1 hour, and then after 10 hours under hydrogen atmosphere. This sampling method allowed comparison between the formation of the dimethoxy ketal intermediate (**60**) before subjection to hydrogenation conditions, and formation of the product ether (**29**) after applying reductive conditions (Scheme 34).



Scheme 34: Proposed reductive etherification reaction scheme intended to investigate the effect of a variety of acids and catalysts.

The four organic acids chosen for this screen had a range of pK_a values to allow a range of acidities to be achieved within the reaction mixtures. Acetic acid (pK_a = 4.76 in water), trifluoroacetic acid (pK_a = -0.25 in water), methanesulfonic acid (pK_a = -2.6 in water) and benzoic acid (pK_a = 4.2 in water) were selected as the acids with which to perform the screen.

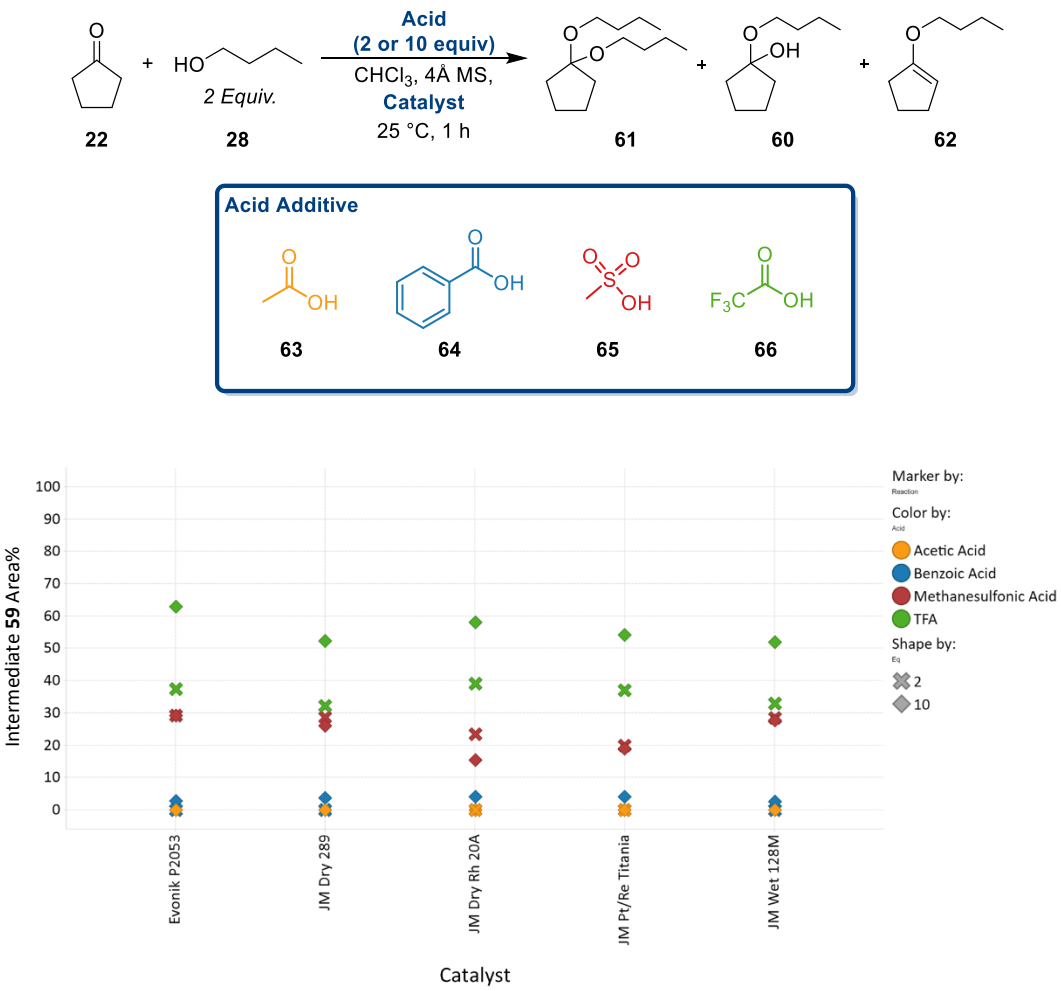


Figure 15: GC area% of ketal intermediate formed for each acid, acid equivalent and catalyst used in the acid screen.

As is illustrated by Figure 15, TFA was found to be the superior acid with regards to forming the ketal intermediate, with 10 equivalents of acid giving a higher conversion after 1 hour than 2 equivalents. Methanesulfonic acid (MSA) was also shown to form moderate amounts

of ketal intermediate, with both equivalent levels of acid performing very similarly. Benzoic acid and acetic acid were both shown to form minimal amounts of ketal. This may be due to the higher pK_a values associated with these acids when compared to TFA and MSA.

To assess the effect of the acid additive upon the hydrogenation/hydrogenolysis reaction, the reaction mixtures were subjected to 5 bara hydrogen atmosphere at 50 °C and sampled after 10 hours (Figure 16).

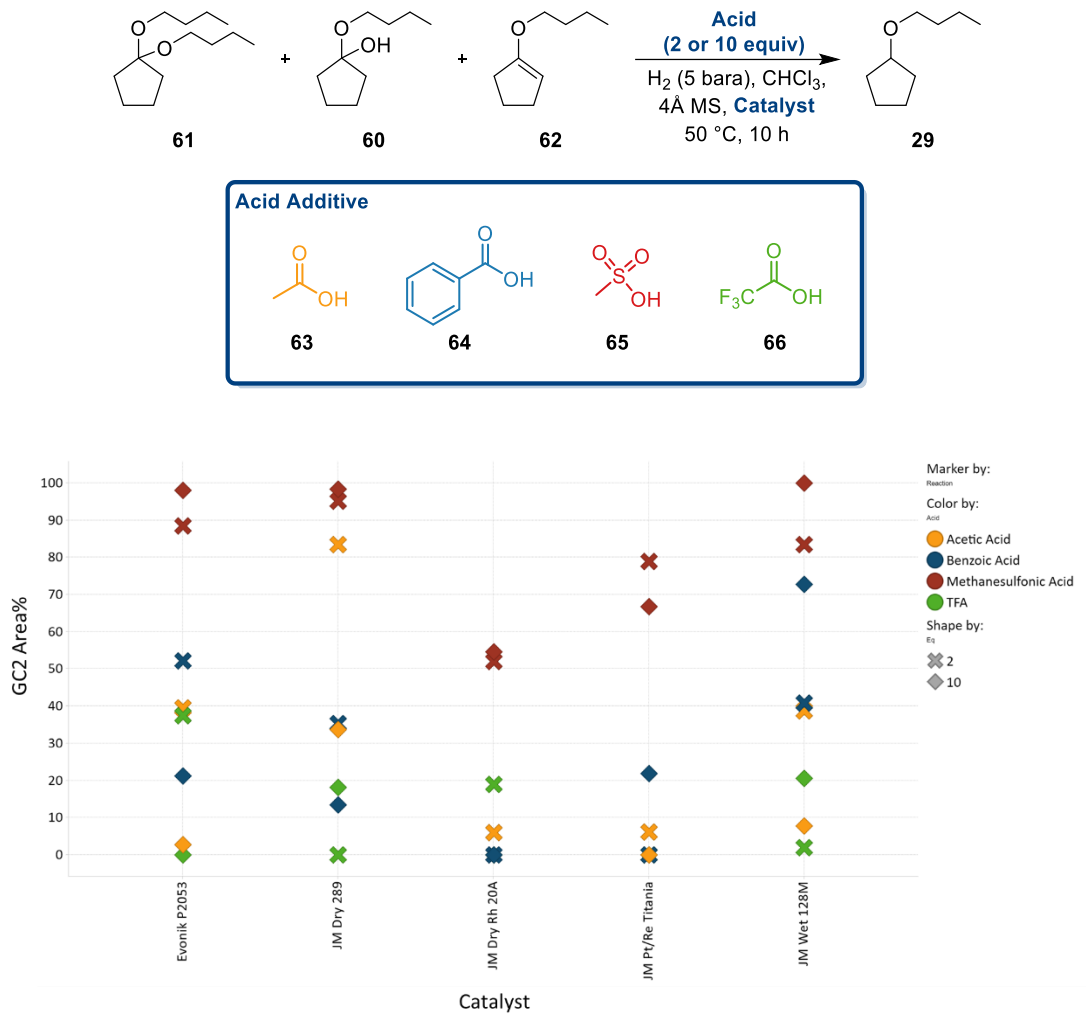


Figure 16: GC area% of cyclopentyl butyl ether formed for each acid, acid equivalent and catalyst used in the acid screen.

Surprisingly, with the acid which was shown to be superior for ketal formation, TFA, little to no conversion to ether product was observed in the hydrogenation/hydrogenolysis reaction. Benzoic acid and acetic acid, although forming little to no ketal intermediate, showed mixed results with respect to ether formation. Acetic acid also appears to inhibit ether formation at higher acid equivalents. Encouragingly, however, methanesulfonic acid was shown to be the highest yielding acid additive for product in all cases, with 2 and 10 equivalents of acid performing very similarly. These are promising results with regards to further optimisation of the reaction and reduction of the acid equivalents.

Another deduction which can be made from Figure 16 is the superiority of the platinum only catalysts over the rhodium and the rhenium doped catalysts. These results support the conclusion made in the earlier catalyst screen, that platinum is the most active metal within the reductive etherification reaction. It is also notable that the wet paste platinum catalyst (JM Wet 5R128M) performs equally as well, if not better, than the dry powder catalysts (JM Dry 5R289 and Evonik P2053).

One further conclusion which can be drawn from the comparison of wet and dry Pt/C catalysts in methanesulfonic acid is that the wet catalyst performs better than the dry at 10 equivalents of acid, and worse than the dry at 2 equivalents. This may represent the requirement of a trade-off between safety, with regards to catalyst pyrophoricity, and safety with regards to the amount of acid used in the reaction. More acid equivalents will also come with the associated cost of materials as well as an increased cost of disposal upon completion of the process. An unnecessary excess of acid would also increase the process mass intensity, and may also lead to complications with vessel compatibility depending upon concentration.[77-78]

1.4.9 Relation of Intermediate Formation to Ether Formation

Previously, it had been hypothesised that an acid additive would facilitate formation of the ketal intermediate in the first step of the reaction. Furthermore, this acid additive would enable the ketal intermediate to convert to the enol ether for rapid hydrogenation. From the data collected from the acid screens, it is possible to plot the percentage area of the ketal intermediate, after 1 hour stirring at room temperature under air, and to the product ether, after 10 hours at 50 °C and 5 bara hydrogen (Figure 17). If this hypothesis is correct then a positive correlation between the formation of the two compounds would be observed with the reactions producing more intermediate in GC1 producing more ether product in GC2.

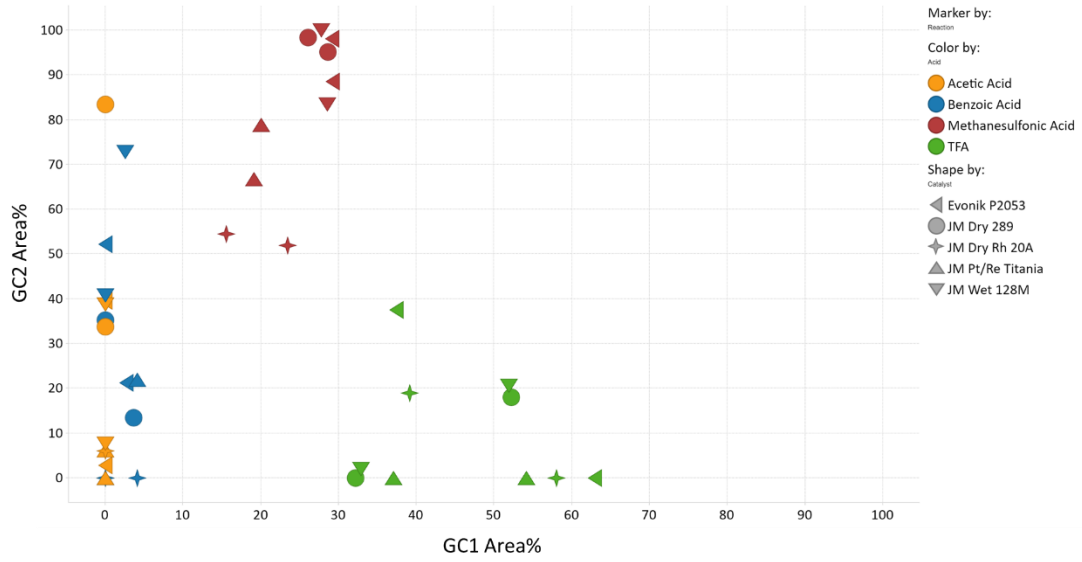


Figure 17: GC area% of the ketal intermediate before the hydrogenation versus product ether formation after the hydrogenation for all catalyst and acid combinations trialled in the screens detailed above in this report.

Interestingly, there seems to be no positive correlation between ketal formation and ether formation. Rather counterintuitively, the reactions which formed most ketal intermediate with TFA formed little to no product. This is in contrast to reactions with methanesulfonic acid, which formed moderate amounts of ketal intermediate but near quantitative yields of

ether after hydrogenation. This suggests that the effect of acid on the reaction is not as simple as first thought, and reaction mixtures capable of forming the most ketal intermediate are not necessarily the ones to produce the most ether product.

1.4.10 Investigation of the Number of Acid Equivalents

In terms of process efficiency, a large excess of the acid additive creates numerous issues. Firstly, the cost of the process will be increased as a larger amount of starting materials will be required. Secondly, the process mass intensity (PMI) of the reaction will increase as there are is a higher mass of materials used for this process with respect to the mass of product. This will reduce the overall environmental sustainability of the process. Finally, a highly acidic reagent will require special handling measures on a large scale to ensure the process is safe. The process will need to be performed in acid-compatible vessels and then the resulting acidic waste will have to be quenched and disposed of safely. As such, it would be desirable to reduce the equivalents of acid as much as possible whilst still maintaining high yields.

In an effort to reduce the equivalents of acid while simultaneously evaluating the role of molecular sieves, methanesulfonic acid was trialled at varying levels (0.5 – 5 equivalents with respect to ketone) with each of the three best catalysts (Evonik Dry P2053, JM Dry 5R289 and JM Wet 5R128M), with and without molecular sieves. This screen of 48 reactions would give insight into the optimal number of equivalents for acid catalysis in the reaction, while also comparing reactions with and without molecular sieves (Figure 18). As the retention times for cyclopentanone and cyclopentanol were very similar by GC (within 0.01 min), the peaks in the chromatogram were not very well resolved. For this reason, the solution yield was calculated from a sum of the peaks using an average response factor value of the two components relative to an internal standard of tridecane.

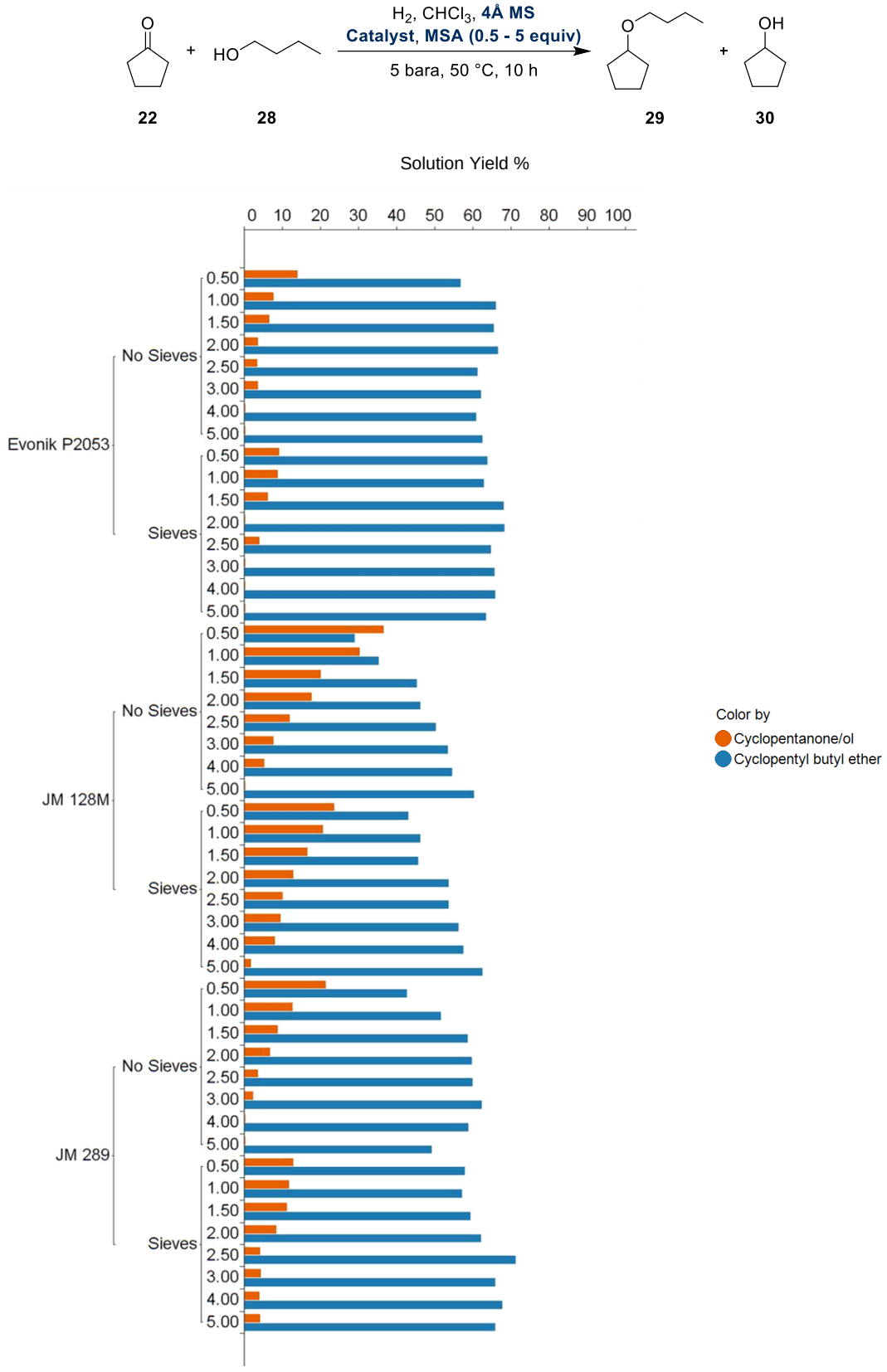


Figure 18: Internal standard yields of cyclopentanone/ol and cyclopentyl butyl ether against an internal standard of tridecane. These reductive etherification reactions were performed with respect to three different catalysts, with or without molecular sieves and at varying equivalents of methanesulfonic acid.

As evidenced by the data collected, a higher number of equivalents of methanesulfonic acid within the reaction mixture results in an increased product solution yield and a decreased side product solution yield. The only catalyst which did not follow this trend was the JM 289 dry catalyst without molecular sieves. The product formation for this reaction peaked at 3 equivalents of methanesulfonic acid. All reactions with 3 equivalents of methanesulfonic acid formed a reasonable amount of product, with very little improvement observed for further excess. Some reactions showed good selectivity for the desired reductive etherification at 1 equivalent of methanesulfonic acid. For this reason, a further Pt/C catalyst screen was planned at both 1 and 3 equivalents of methanesulfonic acid.

All solution yields follow the same pattern of increasing with higher acid equivalents, however, the difference between the reactions with sieves and those without is minimal. Although the reactions without molecular sieves are consistently lower yielding than those with molecular sieves, the minor reduction in yield, when contextualised against the issues associated with their use, is an acceptable outcome which may be improved upon with further optimisation. As a result, it was decided that future reactions would be performed in the absence of molecular sieves.

Evidently, from the solution yields calculated, the total yields of all reaction components do not combine to 100%. There are a few possible reasons for this:

- The K_X value is inaccurate and requires recalculation from a new sample of cyclopentylbutyl ether.

- As peaks in the spectra for cyclopentanone and cyclopentanol are not well resolved, the solution yield is calculated from the integration of both peaks and a K_X value

which is an average of the individual K_X values. As the proportion of cyclopentanol to cyclopentanone varies from 1:1, this value becomes increasingly inaccurate.

- The reference sample of cyclopentyl butyl ether was not run before and after each set of samples to account for any variation in the GC responses.

Efforts were made to address these issues in future reactions where solution yields were determined, but as the response factors will be applied to all reactions within the same study, all solution yields will be relative in comparison to the internal standard. This ensures that the same conclusions will be drawn at the end of each study regardless of the absolute accuracy of the K_X value.

1.4.11 Investigation of Wet Pt/C Catalysts

As a consequence of the results collected in the acid screen regarding the JM 5R128M wet catalyst paste, a screen of wet platinum catalysts on carbon supports was proposed. This screen intended to address the issues with pyrophoricity associated with handling dry precious metal catalysts. Only platinum catalysts were considered, as these were shown to display superior activity in the catalyst screen involving palladium, rhodium and ruthenium.

21 wet paste catalysts were chosen to be screened for activity in the reductive etherification reaction. These were tested alongside the Evonik P2053 Pt/C and JM 5R289 Pt/C dry powder catalysts from the previous acid screen. These 23 catalysts were each reacted in the presence of 1 and 3 equivalents of methanesulfonic acid. One reference sample was included for the Evonik P2053 Pt/C catalyst without the acid additive, to allow direct comparison between the original and optimised conditions. One reaction was performed with the acid additive but in

the absence of catalyst to determine the amount of ketal intermediate formed at elevated temperatures and pressure (Figure 19).

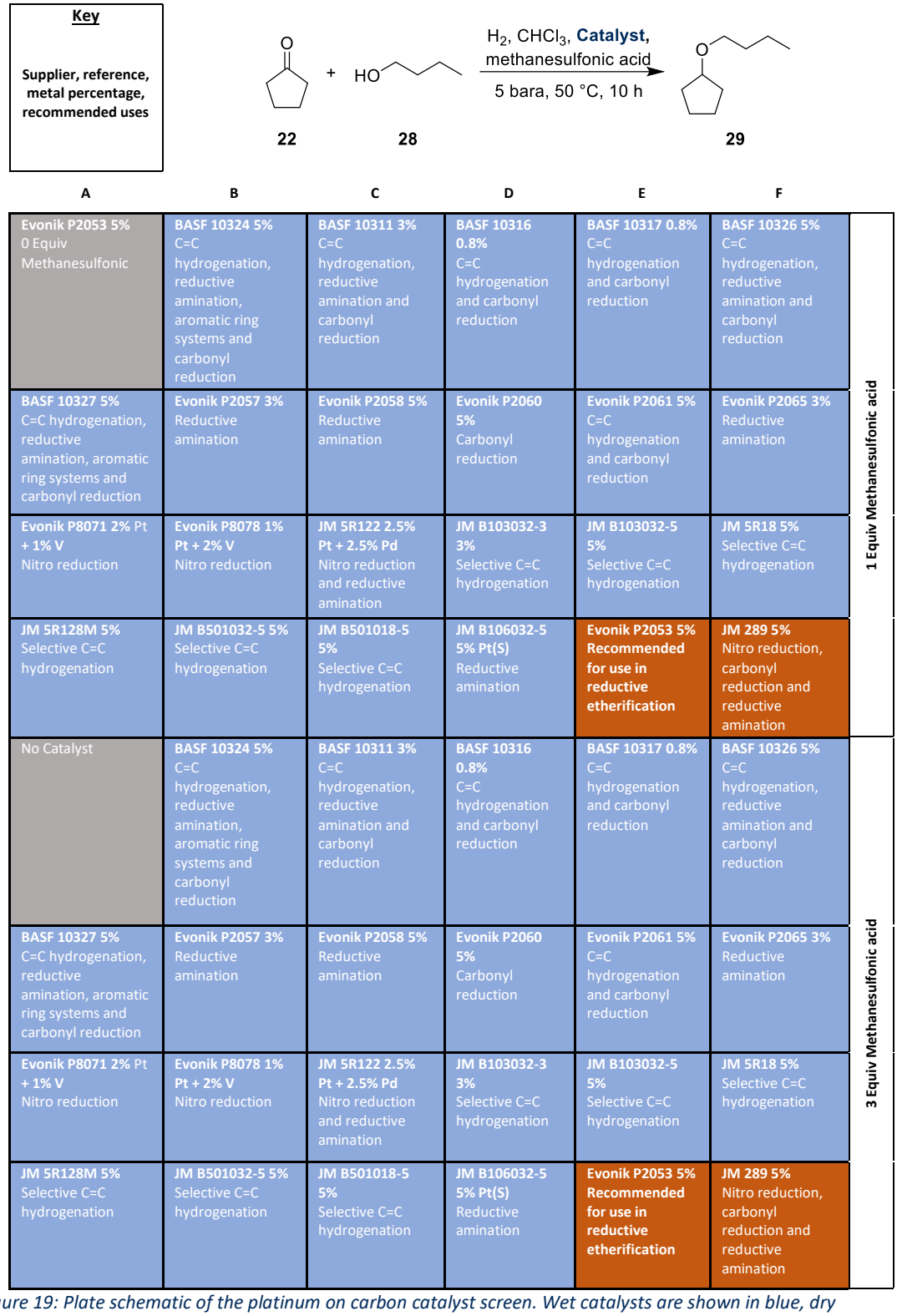


Figure 19: Plate schematic of the platinum on carbon catalyst screen. Wet catalysts are shown in blue, dry catalysts are shown in orange and reference samples without acid or catalyst are shown in grey.

As is evident from the plate schematic (Figure 19), the variety of catalysts selected for the screen is wide ranging. These cover platinum catalysts on a carbon support, doped with various other elements including palladium, sulfur and vanadium, of a range of percentage metal content, all recommended for differing uses in organic synthesis.

These catalysts were employed in the reductive etherification of cyclopentanone and *n*-butanol with methanesulfonic acid (1 or 3 equivalents) in the absence of molecular sieves. These reactions all contained an internal standard of tridecane, allowing solution yields to be calculated *via* the K_X values determined previously. These solution yields were displayed in a heat map of the plate (Figure 20).

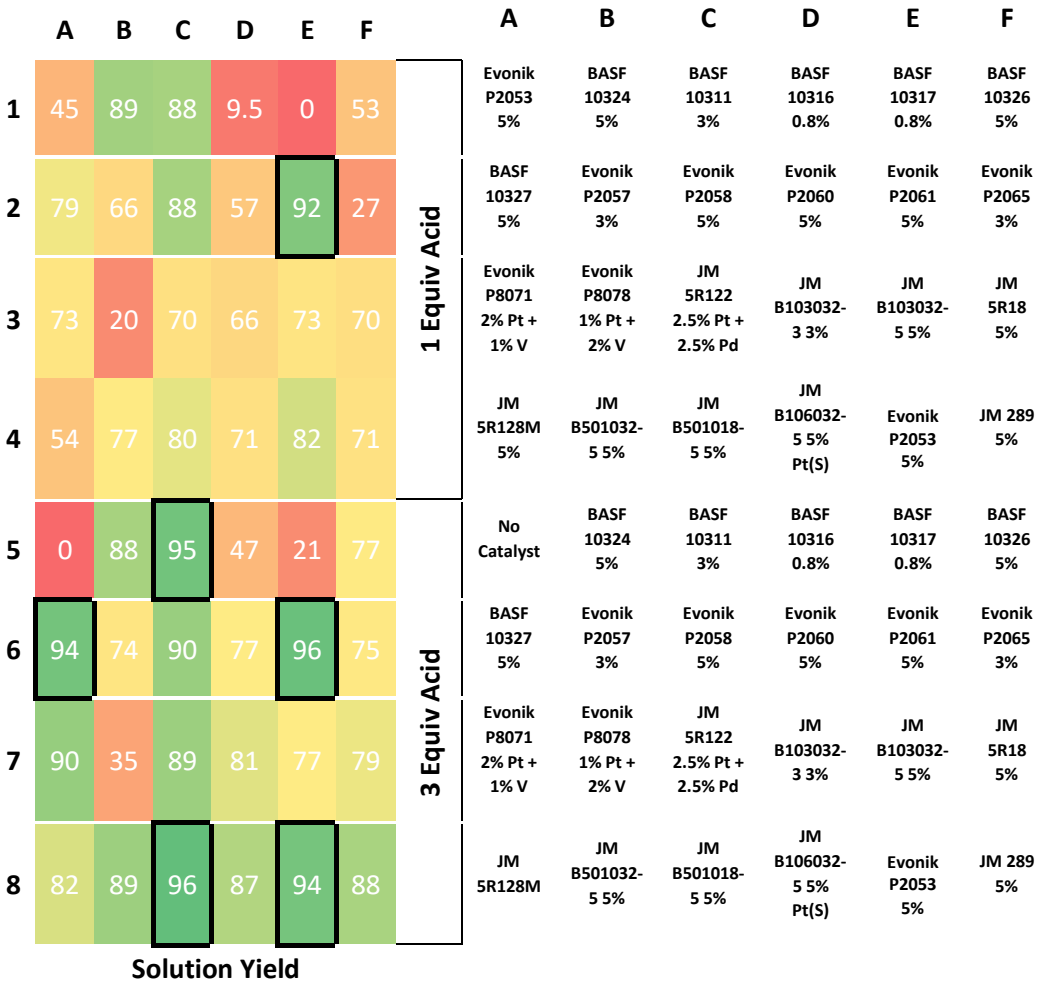


Figure 20: Heat map of solution yields calculated from the screen of platinum catalysts.

Once the solution yields had been calculated, the six highest yielding reactions were chosen for validation on a larger scale. These were reactions **E2** (Evonik P2061 with 1 equiv acid), **C5** (BASF 10311 with 3 equiv acid), **A6** (BASF 10327 with 3 equiv acid), **E6** (Evonik P2061 with 3 equiv acid), **C8** (JM B501018-5 with 3 equiv acid) and **E6** (Evonik P2053 with 3 equiv acid).

A curious observation which was noted after completion of the reactions involving the Evonik P8071 (**A3** and **A7**) and Evonik P8078 (**B3** and **B7**) catalysts was the presence of a small, immiscible green phase on top of the reaction mixture. Interestingly, this was not observed for all catalysts (Figure 21).

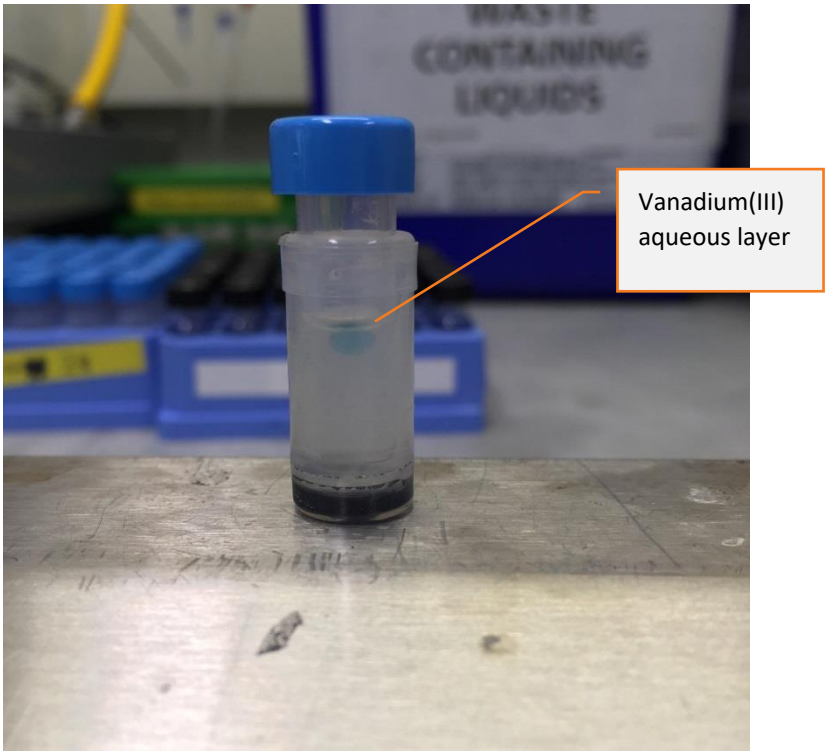


Figure 21: Filtered reaction mixture of the reductive etherification reaction utilising the Evonik P8078 platinum on carbon catalyst doped with vanadium.

Upon inspection of the catalyst composition, the Evonik P8071 and P8078 catalysts are doped with vanadium. It is well known that transition metals, when solubilised, display an elaborate array of colours. Vanadium(III), in aqueous media, is known to display a vibrant green

colour.[79] This observation suggests the presence of water in the reaction mixture as a consequence of ketal formation. This can be related to the absence of molecular sieves in the reaction, which previously would have removed this water layer from the reaction mixture. It is hypothesised that the molecular sieves may be omitted, in this case, as chloroform is not miscible with water. Therefore, the water is effectively excluded from the reaction mixture by formation of a biphasic system. This suggests water miscibility may be a factor to investigate when optimising the reaction solvent.

Pertaining to the screen, of the six highest yielding reactions involved, only one reaction was a dry platinum catalyst on carbon support. The other five wet catalyst pastes proved to be as effective, if not more so, than the dry catalysts. This is an important optimisation of the reaction towards making this process pilot plant friendly and generally safer to operate. To confirm these results, the six reactions were repeated in the ChemSCAN on a larger scale than initially trialled (Figure 22).

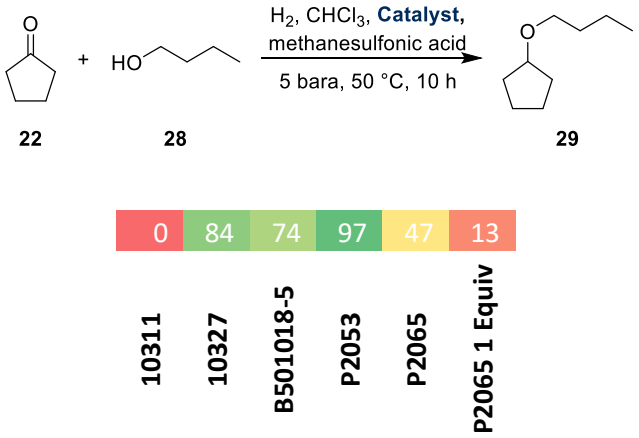


Figure 22: Solution yields of the six highest yielding reactions from the platinum catalyst screen, when applied to a larger scale reaction (4 mL) in the ChemSCAN.

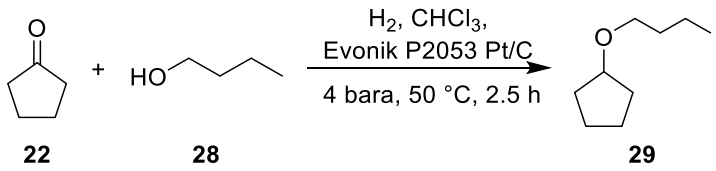
When the screening reactions were scaled up to the ChemSCAN high pressure parallel synthesiser, they were shown not to behave in the same manner as in the smaller scale screen. All reactions underperformed their corresponding reaction on a 0.5 mL scale (all

reactions 92-96%), with the BASF 10311 platinum catalyst on carbon support yielding no ether product whatsoever.

Upon troubleshooting the reactions performed, it was deduced that the Evonik P2065 platinum catalyst on carbon support had been selected for use in this reaction in error and the Evonik P2061 platinum catalyst should have been trialled instead. At this point, no reasoning could explain the variability of the results upon scale up of the reaction mixture, therefore, further investigation was required.

1.4.12 Large Scale Reaction in AutoMATE

To allow direct comparison between the optimised acidic conditions and the original conditions run without the acid additive, a quantitative time course was proposed (Scheme 35). This reaction would be performed on a similar scale to the initial QTC (Section 1.4.6) with samples being taken *via* the EasySampler as per the QTC outlined previously (Figure 13, page 51). As the reaction would contain an internal standard, solution yields of the reaction components would be calculated from the K_X values determined beforehand.



Scheme 35: Proposed reductive etherification reaction to be performed as a quantitative time course experiment.

The reactor selected to perform the reductive etherification reaction on such a scale (50 mL) was the HEL AutoMATE parallel AutoMATE reactor (Figure 23). This reactor has the benefit

of being equipped with fittings for both the EasySampler and ReactIR probes while being a comparable scale to the EasyMax vessel used in the previous QTC.

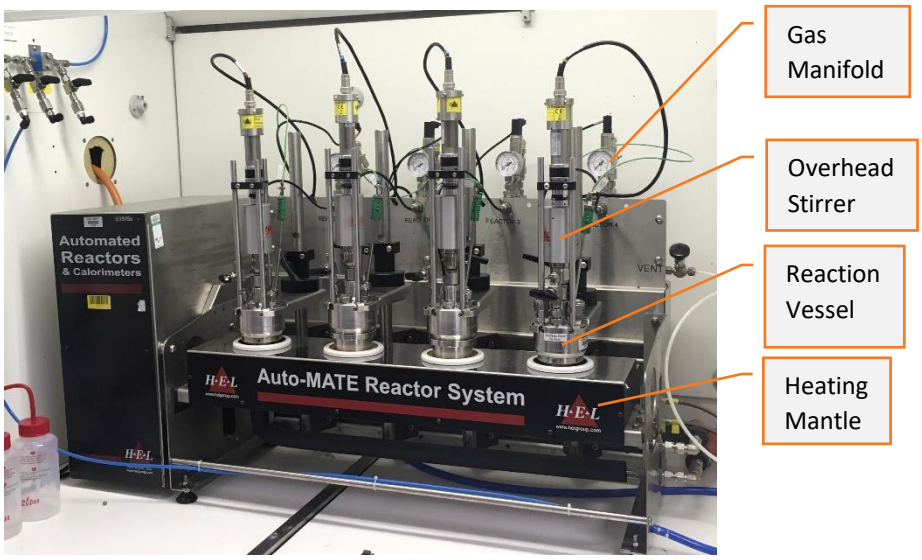


Figure 23: AutoMATE high pressure parallel synthesiser.

The ReactIR probe is an *in situ* probe to monitor the IR absorbance of the reaction mixture and show graphically which IR absorbances in the reaction are decreasing or increasing over time. If certain IR stretches are identified to correspond to product, reactant or intermediate, this will be another way of monitoring the rate of the reductive etherification.

The reaction was prepared on a 50 mL scale and reference samples of the reaction components were analysed by ReactIR. Upon agitation of the reaction mixture, it quickly became apparent from the analytical probes that a problem had occurred. The EasySampler probe became blocked while taking the first sample and the IR absorbance began to weaken when stirring was initiated. The EasySampler probe was suspected to have become blocked by the catalyst, however, the IR absorbance was thought to have changed due to vigorous stirring, leading to a vortex which resulted in the IR probe being open to the headspace above the reaction mixture. As no GC or IR data could be collected from this reaction, the

completion of the reaction was estimated *via* hydrogen uptake measured by the reactor software (Figure 24).

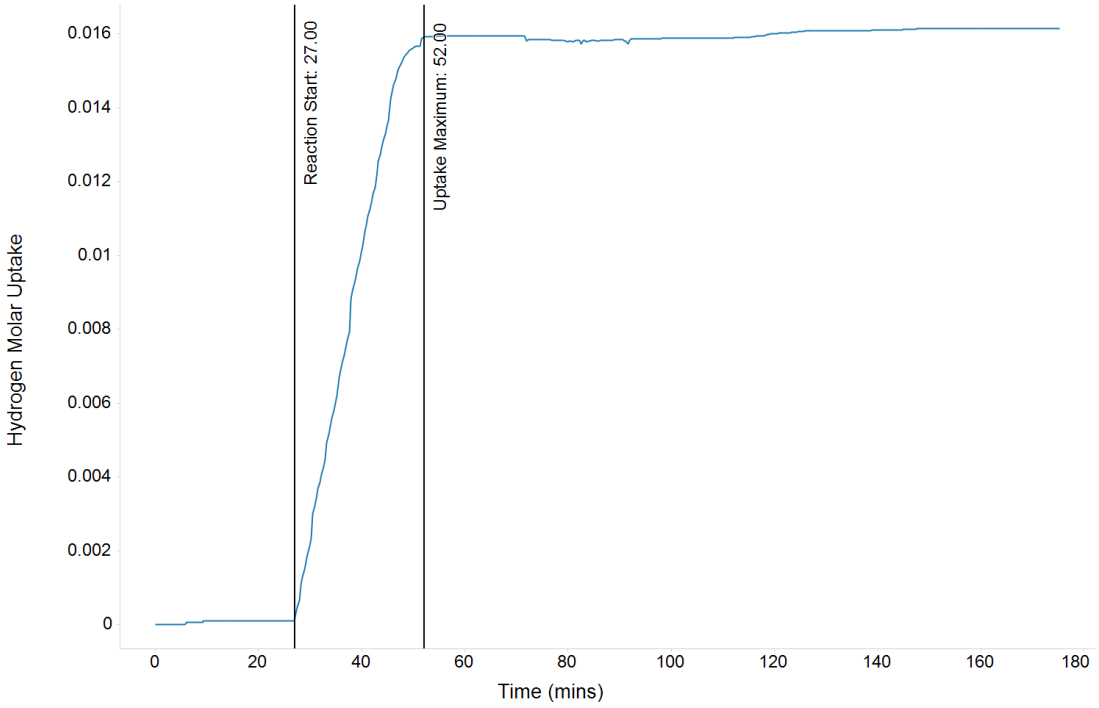


Figure 24: Molar uptake data from the large scale reactor in the AutoMATE. Reaction was initiated at 25 minutes.

The amount of hydrogen uptake is calculated *via* the software controlling the reactor, and is a measure of the amount of hydrogen which is required to keep the reactor vessel at a pre-set constant pressure. As can be seen from the graph, this stopped increasing after 25 minutes, implying that the reaction had used all the hydrogen from the atmosphere needed to complete the chemical reaction. This was a vast improvement upon the 8 hours determined in the previous process.

To be certain that the reaction was complete, the process was left for two more hours before the reaction was halted and a GC sample was taken (Figure 25). From this analysis of the solution, the product ether was calculated to be 62% against an internal standard of tridecane. As can be seen by the spectrum, the reaction progressed very cleanly with only a

few minor peaks observable for cyclopentanol and dicyclopentyl ether (Figure 25). When compared to the end point of the previous QTC (section 1.4.6) an improvement of ketone consumption was observed (20% to 3% remaining after the reaction) in a 75% reduction of the reaction time.

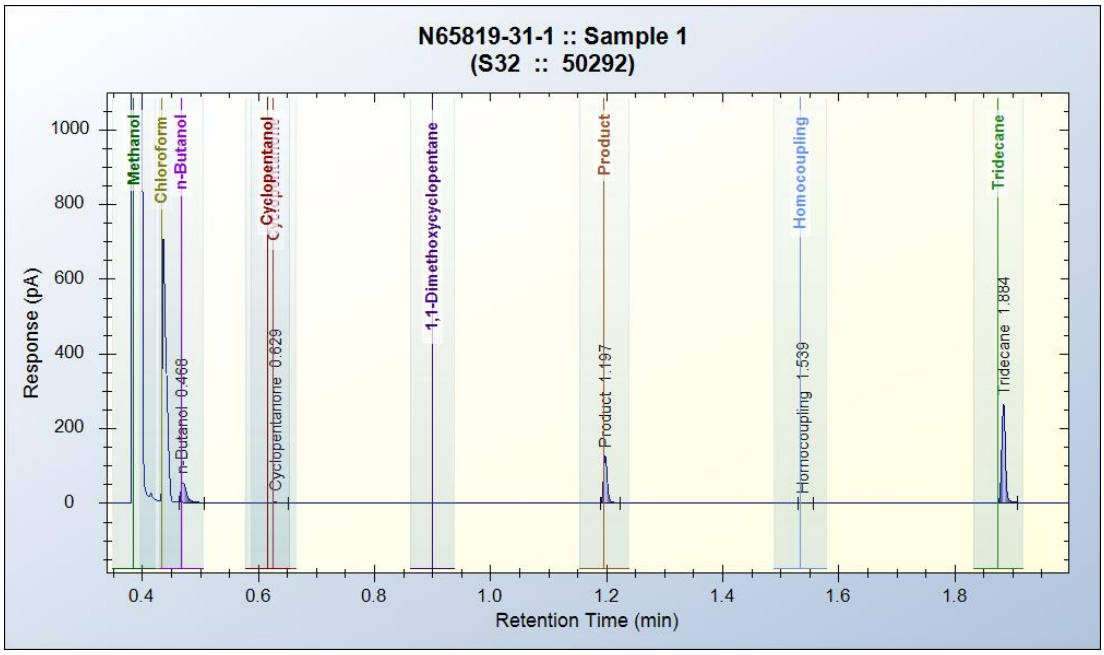


Figure 25: GC spectrum acquired at the end of the QTC reaction in the AutoMATE reactor.

Upon opening the reaction vessel, the problem with the EasySampler and ReactIR became apparent. The catalyst was observed to disfavour formation of a suspension in chloroform, and instead became deposited on the exposed surfaces of the reactor vessel (Figure 26). For this reason, solid catalyst had become lodged into all moving parts of the EasySampler, resulting in a blockage. The ReactIR probe had also become coated in catalyst, shielding the sensor from the reaction mixture.



Figure 26: AutoMATE reactor probes after completion of the large scale reductive etherification reaction was performed.

As the catalyst suspends poorly in chloroform, this could explain the variability of the reaction upon scale up. Upon further inspection, the catalyst had a tendency to coat the reactor walls and agglomerate. Clearly, this reduced the relative surface area for reaction, however, smaller volume vessels exhibit a larger surface area to volume ratio. This surface area to volume ratio will decrease as the volume increases, decreasing the surface area on which the

catalyst can be deposited. This may explain why the results observed in the CAT96 on a 0.5 mL scale were not consistent with reactions in the ChemSCAN at a 4 mL scale.

1.4.13 Solvent Screen

To address the obvious environmental, health and safety issues; the unfavourable catalyst suspension; and the subsequent inconsistency of the reductive etherification reaction upon scale up, a solvent screen was performed. It was hypothesised that a solvent that allowed the catalyst to suspend well in the reaction mixture would improve reproducibility of the reactions as well as consistency on scale up.

As molecular sieves could now be omitted from the reactions, the water miscibility of the solvents selected would be an interesting variable to consider. A noticeable aqueous layer was observable during the catalyst screen due to leaching of the vanadium doped catalysts, forming a vibrant green vanadium(III) aquo complex.[80] As water is immiscible with chloroform, it may be the case that the chloroform was removing water from the reaction mixture, therefore driving the equilibrium. When replacing chloroform in this reaction, it was anticipated that a water-miscible solvent could change the position of equilibrium to disfavour ketal and enol ether formation.

The solvents chosen for use in this reaction were carefully selected based on reactivity, sustainability characteristics and water miscibility, through use of a principal component analysis (PCA) factors model. Principal component analysis is a method of displaying reaction solvents (or any other set of variables), in graphical form, by reducing their measured properties into three principal components that describe the majority of the variability in the data.[81] When these principal components are plotted against each other on a three dimensional graph as a continuum, this forms a "map". The combination of a number of

principal components places each solvent in a unique area of space on the map, surrounded by solvents which, in theory, possess similar combined properties.[81] A range of solvents close to chloroform on the PCA map were selected to encompass functional groups such as ethers, esters and aromatic rings, and avoiding ketones and alcohols (Figure 27).

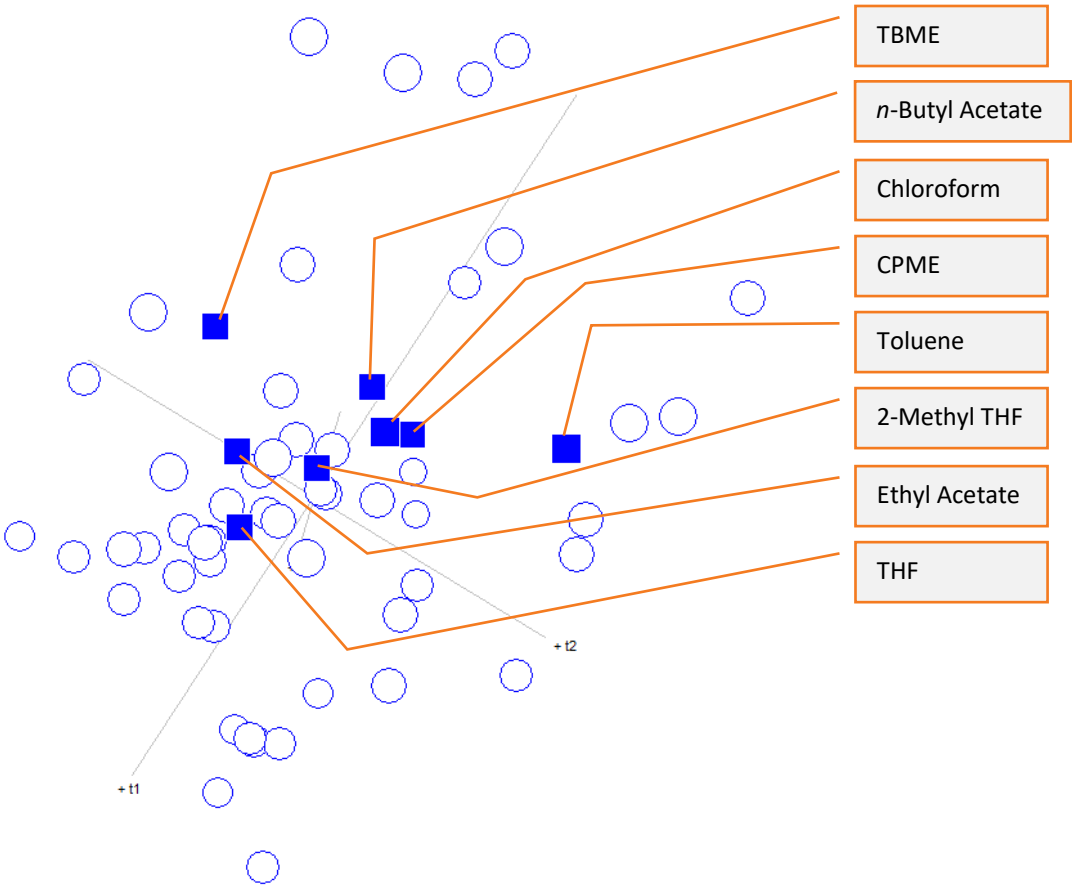
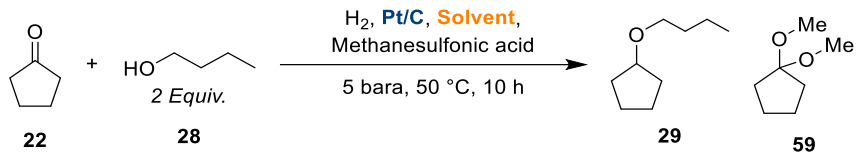


Figure 27: Principal component analysis factors map with the eight solvents selected shown as blue squares.

The solvent screen was performed on a 0.5 mL scale (0.125 mmol cyclopentanone) in the CAT96 high pressure reactor. These reactions were performed in the presence of tridecane as an internal standard and solution yields were calculated after 10 hours at 50 °C and 5 bara. Reactions with chloroform were included as a reference against which other solvent systems could be measured.



22 28 29 59

Product Ether (29) Yield							Ketal Intermediate (59) Yield					
1.4	2.4	3.1	0	91	0	Toluene	74	71	79	0	3	86
0	18	1.4	6.3	3.4	0	THF	52	21	104	37	34	58
0	2.8	3.6	22	0	0	2-MeTHF	83	83	80	0	77	80
0	120	70	1.4	85	0	*n*BuOAc	101	3.9	29	73	20	103
0	0	0	2.9	0	0	EtOAc	70	100	108	0	66	111
0	0	0	0	1.7	0	TBME	99	82	62	62	45	78
0	0	0	2.4	3.2	0	CPME	72	64	81	65	65	86
89	0.7	106	1.9	98	0	Chloroform	0	38	0.3	52	0	96
10311, 3 Equiv MSA	10327, 3 Equiv MSA	B501018-5, 3 Equiv MSA	P2053, 3 Equiv MSA	P2061, 3 Equiv MSA	P2061, 1 Equiv MSA		10311, 3 Equiv MSA	10327, 3 Equiv MSA	B501018-5, 3 Equiv MSA	P2053, 3 Equiv MSA	P2061, 3 Equiv MSA	P2061, 1 Equiv MSA

Figure 28: Heat map of the 48 solvent screening reactions between eight solvents selected via the PCA model and the six best catalysts from the catalyst screen. Solution yields of the product ether and ketal intermediate are calculated versus tridecane.

The product ether solution yields calculated from these reactions (Figure 28) confirm the suitability of chloroform for the reductive etherification reaction (three reactions ≥ 89%). Unfortunately, the majority of alternative solvents chosen for this reaction showed little to no product formation (CPME, TBME, EtOAc, THF and 2-MeTHF). Toluene showed little to no activity with five out of the six chosen catalysts; however, good yields were obtained for toluene in combination with the Evonik P2061 catalyst in the presence of 3 equivalents of methanesulfonic acid (91%). *n*-Butyl acetate showed comparable activity to chloroform in the reductive etherification reaction with three out of six of the reactions showing good to excellent solution yields (≥ 70%).

When comparing water-miscible solvent (THF) with water-immiscible solvents (2-MeTHF, CPME, EtOAc, TBME), no clear pattern is observed. It appears that the water miscibility of the reaction solvent has no clear bearing upon the performance, as all of the solvents performed poorly within the reductive etherification reaction conditions. When comparing ketal intermediate formation after 10 hours under hydrogenation conditions, use of THF can be seen to result in formation of less ketal than other, water-immiscible solvents, with the exception of the reaction with THF in combination with the JM B501018-5 catalyst.

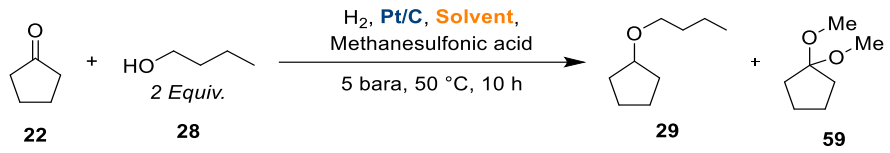
From this screen, it appears that all reactions involving 1 equivalent of methanesulfonic acid resulted in 0% solution yield of the product ether. For this reason, all forthcoming reactions would be performed in the presence of 3 equivalents of methanesulfonic acid.

Upon inspection of the GC traces relating to the reactions with *n*-butyl acetate as solvent, an excess of *n*-butanol is observable. While *n*-butanol is present in the reaction in 2 equivalents, a greater excess than has previously been observed is clear in all reactions involving *n*-butyl acetate. Through calculation of *n*-butanol solution yield against tridecane internal standard, the quantity of *n*-butanol remaining after the reaction can be calculated at 260 mg. This is 168 mg more than should be remaining after completion of the reaction. It is hypothesised the solvent is cleaved under the acidic conditions of the reaction, producing a larger excess of *n*-butanol than expected. This is not an issue for this particular reductive etherification reaction as the alcohol component is *n*-butanol. However, were a different alcohol to be used, hydrolysis of the solvent would result in a butyl ether byproduct being present in the reaction mixture. To tackle this issue, it will be useful to trial more sterically hindered acetate solvents to determine the rates of hydrolysis and suitability for use as a solvent within this reaction.

The hydrolysis reaction observed to be taking place in the *n*-butyl acetate reactions may pose another problem, additional to that of *n*-butanol release. As cleavage of the ester bond would release two components, *n*-butanol and acetic acid, the effect of both components on the reaction mixture must be considered. If the same molar amount of acetic acid is free in the reaction mixture as there is *n*-butanol, this results in 2.3 equivalents of acetic acid. This calculation is an assumption as some acetic acid may react with cyclopentanol in the reaction mixture; however, the amounts of cyclopentanol generated in this side-reaction will be minimal in comparison to the significant excesses calculated here. When compared to the earlier acid screen, acetic acid showed itself to have a detrimental effect upon the reductive etherification reaction with lower yields at higher acid equivalents. For this reason, it is important that the solvent hydrolysis side reaction is avoided.

1.4.14 Ester Solvent Screen

As *n*-butyl acetate proved to be a promising solvent in the solvent screen, but showed incompatibilities relating to hydrolysis of the ester bond, it became important to investigate other acetate solvents. These acetate solvents should have varying degrees of steric hindrance around the ester group to disfavour the hydrolysis reaction. With this in mind, eight liquid esters were chosen with which to perform a solvent screen against the six selected catalysts. These esters were ethyl *iso*-butyrate, benzyl *iso*-butyrate, *iso*-propyl acetate, *sec*-butyl acetate, *tert*-butyl acetate, phenyl acetate, *iso*-amyl acetate and menthyl acetate. Upon opening of the reaction mixture containing *tert*-butyl acetate and the BASF 10327 Pt/C catalyst (black), the HPLC vial shattered and the reaction mixture could not be recovered.



Product Ether (29) Yield							Ketal Intermediate (59) Yield					
0	68	12	13	67	7.1	MenthylAcetate[a]	30	0	28	11	0	34
1.2	0.7	1.1	2	5.1	5.3	*i*AmylAcetate	32	33	22	9.3	3	1.2
8.5	6.9	5.1	0	17	14	PhenylAcetate	27	22	29	24	25	3.4
17		24	9.9	31	4.6	*t*ButylAcetate	38		26	26	21	35
0	0.9	0	0	4	0	*s*ButylAcetate	42	34	40	16	28	58
0	0	0	1.6	0	0	*i*PropylAcetate	39	40	40	0	42	25
0	4.6	0	9.5	0	0	Benzyl*i*Butyrate[a]	48	22	56	37	47	50
0	1.4	0	6.3	2.6	0	Ethyl*i*Butyrate	54	41	50	8.1	16	51
10311, 3 Equiv MSA	10327, 3 Equiv MSA	B501018-5, 3 Equiv MSA	P2065, 3 Equiv MSA	P2061, 3 Equiv MSA	P2061, 1 Equiv MSA		10311, 3 Equiv MSA	10327, 3 Equiv MSA	B501018-5, 3 Equiv MSA	P2065, 3 Equiv MSA	P2061, 3 Equiv MSA	P2061, 1 Equiv MSA

Figure 29: Heat map of the 48 solvent screening reactions between eight acetate solvents and the six catalysts from the catalyst screen. Solution yields of the product ether and ketal intermediate are calculated against tridecane internal standard. [a]Yields quoted are area% by GC due to overlapping solvent and internal standard peaks.

Rather disappointingly, none of the ester solvents screened for use in this reaction performed well. More important than this is the fact that, in all cases, hydrolysis of the ester solvent was observable by GC analysis.

Rather interestingly, the reactions which did not form any product ether were shown to form a reasonable amount of ketal intermediate. The solution yields observed in this screen are greatly reduced compared to previous reactions, suggesting side reactions with the liberated alcohol from the solvent are taking place.

Although no acetate solvent trialled performed better than *n*-butyl acetate in the reductive etherification reaction, the incompatibility of ester solvents within the reductive etherification reaction – even hindered ones – is clear.

1.4.15 Investigation of Reproducibility Issues

When relating the solution yields of comparable reactions on the same, or different, scales some issues with the reproducibility of the reductive etherification reaction becomes evident. All six catalysts selected from the initial catalyst screening displayed solution yields between 92 and 96% (section 1.4.5). Upon repeating these reactions in the solvent screen, half of the catalysts delivered yields of less than 2% (section 1.4.13). The solution yields of all six catalysts showed variability upon scale up (from 0.5 mL to 4 mL) in the ChemSCAN (section 1.4.11) and this continued upon further scale up of the Evonik P2053 in the AutoMATE (50 mL) (section 1.4.12). The stochastic nature of the reductive etherification reaction can be seen by comparing the solution yields of each reaction on each scale, as shown in Figure 30.

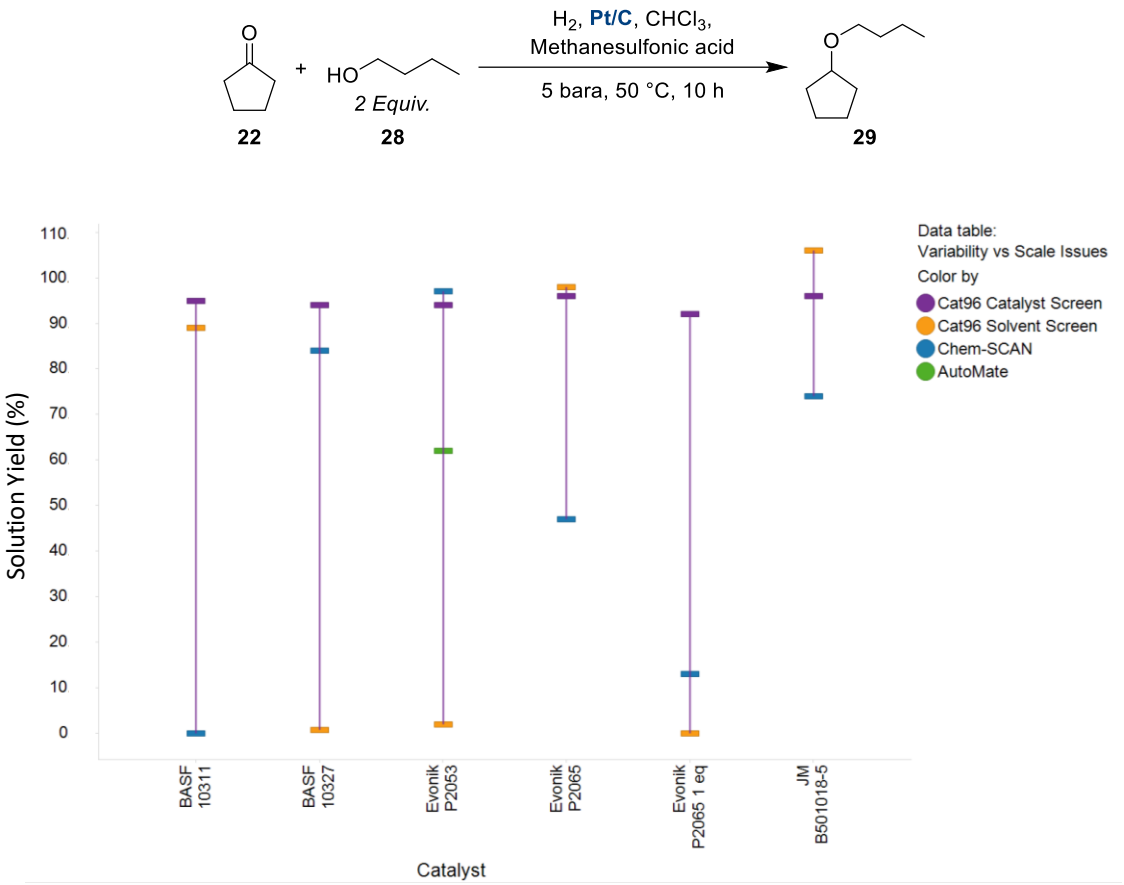


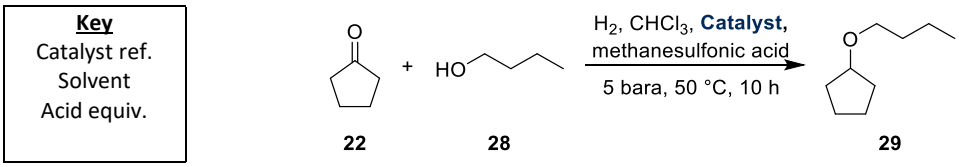
Figure 30: Variability in the solution yield of the 6 chosen catalysts across varying screening reactions of different scales.

The variability of this reaction is thought to be due to the fact that they were all run in chloroform. The dispersion of the catalyst within chloroform is not favourable and, as such, it is proposed that the dispersion is not consistent between the reactions, especially upon scale up.

Another factor which could affect the outcome is the stirring of the reaction mixtures. As with all gas-liquid reactions, stirring of the reaction mixture to incorporate the reacting gas is an extremely important aspect. In both the CAT96 and the ChemSCAN high pressure reactors, the stirring of the reaction mixture is facilitated by magnetic drivers which rotate magnetic stirrer bars within the reaction mixture. Any clumping or coating of the catalyst in

the reaction mixture may decrease the rate of stirring or even halt it completely. Additionally, in the CAT96 reactor, each of the 48 reaction mixtures does not have its own designated magnetic driver. Instead, the individual reactions, each containing their own magnetic stirrer bar, are driven by two magnetic drivers in the base of the reaction chamber. Clearly, this means that the magnetic field experienced by all 48 stirrer bars will not be identical and thus, the mixing occurring as a result of the stirrer bars' rotation in the magnetic field will not be uniform.

To attempt to investigate this variability with respect to the reaction vessel and catalyst dispersion in the solvent used, a plate of reactions was designed for use within the CAT96 high pressure reactor. This screening plate included the six desired catalysts for use in this reaction in chloroform as solvent. These were utilised in the reductive etherification reaction of cyclopentanone and *n*-butanol with tridecane as an internal standard to calculate solution yields. Each reaction was repeated four times in a different part of the plate (Figure 31).



10311 $CHCl_3$ 3 Equiv MSA	10327 $CHCl_3$ 3 Equiv MSA	B501018-5 $CHCl_3$ 3 Equiv MSA	P2065 $CHCl_3$ 3 Equiv MSA	P2061 $CHCl_3$ 3 Equiv MSA	P2061 $CHCl_3$ 1 Equiv MSA
P2061 $CHCl_3$ 1 Equiv MSA	10311 $CHCl_3$ 3 Equiv MSA	10327 $CHCl_3$ 3 Equiv MSA	B501018-5 $CHCl_3$ 3 Equiv MSA	P2065 $CHCl_3$ 3 Equiv MSA	P2061 $CHCl_3$ 3 Equiv MSA
P2061 $CHCl_3$ 3 Equiv MSA	P2061 $CHCl_3$ 1 Equiv MSA	10311 $CHCl_3$ 3 Equiv MSA	10327 $CHCl_3$ 3 Equiv MSA	B501018-5 $CHCl_3$ 3 Equiv MSA	P2065 $CHCl_3$ 3 Equiv MSA
P2065 $CHCl_3$ 3 Equiv MSA	P2061 $CHCl_3$ 3 Equiv MSA	P2061 $CHCl_3$ 1 Equiv MSA	10311 $CHCl_3$ 3 Equiv MSA	10327 $CHCl_3$ 3 Equiv MSA	B501018-5 $CHCl_3$ 3 Equiv MSA

Figure 31: Plate schematic of the reproducibility screen. Reactions utilising the same catalysts are in the same colour.

After subjecting these reaction mixtures to hydrogenation conditions for 10 hours, they were analysed by GC and solution yields were calculated. These were grouped together by catalyst and solvent to show any variability between comparable reactions.

As can be seen for the solution yields (Figure 32), the variability within these reactions was low. Only one of the 24 reactions resulted in a 0% yield. The Evonik P2065 Pt/C catalyst showed most variability of all the catalysts trialled in this screening plate, however, this is the least productive catalyst for reductive etherification of the 6 trialled.

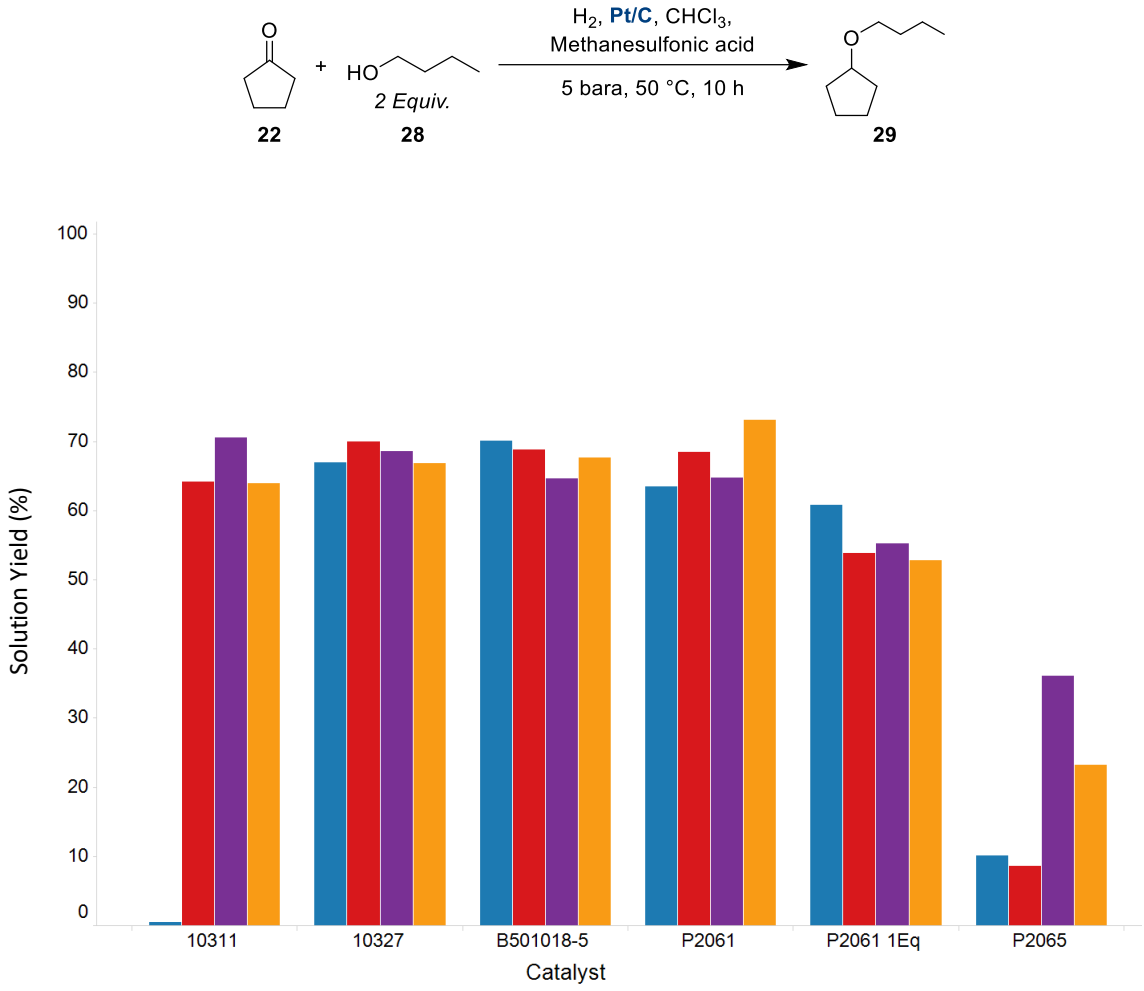


Figure 32: Solution yields of reductive etherifications using chloroform as the reaction medium, grouped together by catalyst used.

The BASF 10327 Pt/C and JM B501018-5 Pt/C catalysts were shown to be fairly consistent throughout the four reactions trialled in this screen, with all yields >60%. These catalysts were chosen for further optimisation studies.

1.4.16 Catalyst Wetting Investigation

As the wettability of the catalyst paste within the reaction mixture was thought to be a crucial parameter relating to the success of the reductive etherification reaction, a visual evaluation of the catalyst wetting properties of each solvent was performed. BASF 10311 and JM B501018-5 were selected as the two catalysts for investigation, based on their results within the reproducibility screening and availability within the GSK catalyst library. Both catalysts were shown to be high yielding, with some degree of variability for BASF 10311 and good consistency of results for JM B501018-5.

A quantity of catalyst corresponding to 3.75 nmol Pt content of BASF 10311 or JM B501018-5 was stirred in a number of different solvents with 24 µL of methanesulfonic acid (3 equivalents) at 50 °C for 10 hours to replicate the reaction conditions. The reaction mixtures were then inspected to determine the extent of catalyst wetting. The ideal solvents would distribute the catalyst uniformly through the reaction mixture when agitated and settle upon standing with the more favourable mixtures settling the slowest. For this reason, solvents that resulted in smearing of the catalyst on the vial would be deemed inappropriate for the optimised reaction. These results are presented in Table 4.

BASF 10311	**Methanol** Good suspension, uniform distribution	**Ethanol** Good suspension, some settling observable	**^{t}Amyl Alcohol** suspension, some settling observed	**^{t}Butanol** Good suspension, some settling observed	**Acetonitrile** Good suspension, uniform distribution	**Chloroform** Catalyst clumped in one corner
	DCM Catalyst coated bottom and lower sides of vial	**TBME** Catalyst has granular consistency and settles very quickly	**CPME** Catalyst has granular consistency and settles very quickly	**2-MeTHF** Good suspension but some settling observed	**THF** Good suspension but some settling observed	**Anisole** Good suspension but some settling observed
	Toluene Catalyst coated bottom of vial	**Acetone** Good suspension, uniform distribution. Polymerisation was observed by GC	**MIBK** Good suspension, some settling observed	**Diethyl Carbonate** Catalyst has granular consistency and settles very quickly	**Propylene Carbonate** Good suspension and uniform distribution but vial is pressurised by solvent decomposition	**NMP** Good suspension but some settling observed
	TamiSolve™ Good suspension, uniform distribution	**TAME** Catalyst clumping observed				
JM B501018-5	**Methanol** Good suspension, uniform distribution	**Ethanol** Good suspension, uniform distribution	**^{t}Amyl Alcohol** Good suspension, some settling observed	**^{t}Butanol** Good suspension, some settling observed	**Acetonitrile** Good suspension, uniform distribution	**Chloroform** Catalyst coated the inside of the vial
	DCM Catalyst coated the inside of the vial	**TBME** Good suspension, uniform distribution	**CPME** Catalyst has granular consistency and is clumped at the bottom	**2-MeTHF** Good suspension, some settling observed	**THF** Good suspension, uniform distribution	**Anisole** Good suspension but some settling observed
	Toluene Catalyst coated the inside of the vial	**Acetone** Good suspension, uniform distribution	**MIBK** Good suspension, some settling observed	**Diethyl Carbonate** Good suspension, some settling observed	**Propylene Carbonate** Good suspension and uniform distribution but vial is pressurised by solvent decomposition	**NMP** Good suspension but some settling observed
	TamiSolve™ Good suspension, uniform distribution	**TAME** Catalyst coated the inside of the vial				

Table 4: Evaluation of catalyst wetting properties for BASF 10311 and JM B501018-5 with methanesulfonic acid additive in a number of different solvents. Green indicates good catalyst wetting and red indicated bad catalyst wetting.

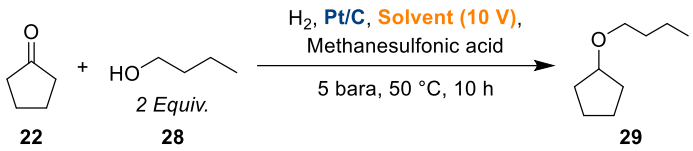
As can be deduced from Table 4, JM B501018-5 formed uniform distributions in more solvents than BASF 10311. It can also be noted that the solvents with the best catalyst wetting properties were those containing a heteroatom capable of forming a hydrogen bond. These solvents were methanol, ethanol, acetonitrile, TBME, THF, acetone and TamiSolve™.

As all solvents within this screen containing an alcohol or a carbonyl moiety showed favourable catalyst wetting properties, these were deemed inappropriate for use within the reductive etherification reaction. Were these to be used as solvents, they would not remain innocent within the reaction mixture and would instead take part in reductive etherification. Should the desired product incorporate the solvent, this may result in an alternative reaction manifold. However, to keep the substrate scope of the reaction as wide as possible, ketone and alcohol solvents were not chosen. It was also apparent upon completion of the experiment that the carbonate solvents had decomposed within the reaction mixture. The sealed reaction vials were shown to have pressurised significantly, with bulging rubber septa at the top. The catalyst wetting properties of these solvents could no longer be deduced, as the favourable dispersion of the catalysts within these solvents was most probably due to the corresponding alcohols formed upon decomposition.

As ketone and alcohol functional groups clearly aided the catalyst wetting properties of the reaction mixture, it was hypothesised that increasing the concentration of the ketone and alcohol starting materials may help disperse the catalyst. The concentration of the reaction mixture had already been identified as a factor for optimisation of the reaction towards large scale synthesis. For this reason, replication of the solvent screen would be performed at 10 solvent volumes instead of the 50 solvent volumes (V) used previously.

Catalyst loading was also a factor identified for further optimisation. Although 3 mol% catalyst loading is already quite low, it had been noted that, due to the Pt metal content of

the catalyst and low molecular weight of the starting materials, the weight of catalyst added to the reaction was similar to or greater than the weight of carbonyl component. It was decided that the solvent screening was to be replicated not only at 10 solvent volumes but also at 0.5 mol% catalyst loading. These solvents were evaluated with the highest 4 yielding catalysts from the reproducibility screening (1.4.15) (Figure 33).



BASF 10311	BASF 10327	JM B501018-5	Evonik P2061	
104	80	61	67	**Chloroform**
11	12	12	13	**EtOAc**
70	58	65	53	***n*BuOAc**
45	37	38	44	**2MeTHF**
51	52	42	41	**THF**
58	62	68	58	**CPME**
3.2	6.6	5.8	12	**TBME**
60	56	9.2	6.6	**Toluene**

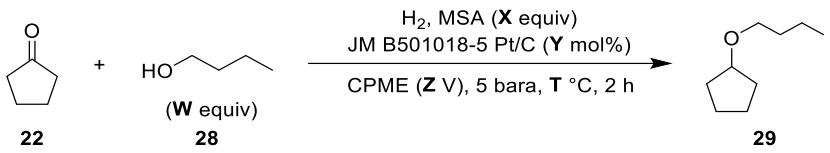
Figure 33: Solution yields of the solvent screening reactions at 10 solvent volumes, 0.5 mol% catalyst loading and 3 equivalents of methanesulfonic acid.

This solvent screen replication at 10 solvent volumes and 0.5 mol% catalyst identified CPME as the most consistent solvent appropriate for use within the reductive etherification reaction, after ruling out chloroform and *n*-butyl acetate. JM B501018-5 was also selected as the best performing catalyst within this screen and the most consistent catalyst from the optimisation reactions thus far.

1.4.17 Design of Experiments Optimisation

With a catalyst and solvent for the reductive etherification reaction in hand, further optimisation of the reaction manifold was performed using Design of Experiment analysis.[82-83] Design of Experiment is a statistical tool that, in this case, was utilised to optimise select reaction parameters in the least number of reactions possible. This optimisation was performed using DX10, a computer program which aided the design of the reactions and the analysis of the results. Entry of the parameters and ranges in which to investigate them allowed a list of reactions to be compiled. These reactions were performed and the solution yields entered into DX10, allowing statistical analysis to be performed. This statistical analysis separates the effects of each parameter individually to show which are important and where the optimal set of conditions lie.

For the initial DoE optimisation, an augmented central composite response surface was designed between these ranges: 1 - 2 equivalents of *n*-butanol, 1 - 3 equivalents of methanesulfonic acid, 0.1 - 0.5 mol% of Pt/C catalyst, 40 - 60 °C and 5 - 15 solvent volumes of CPME (Table 5).



Source	Sum of Squares	df	Mean Square	F Value	p-value
Block	1354.63	1	1354.63		
Model	14859.60	10	1485.96	36.93	< 0.0001
A-Temperature	*544.34*	*1*	*544.34*	*13.53*	*0.0013*
B-Alcohol Equivalents	*20.41*	*1*	*20.41*	*0.51*	*0.4838*
C-Acid Equivalents	*9319.20*	*1*	*9319.20*	*231.63*	*< 0.0001*
D-Catalyst Loading	*2582.64*	*1*	*2582.64*	*64.19*	*< 0.0001*
E-Concentration	*1260.81*	*1*	*1260.81*	*31.34*	*< 0.0001*
AB	*473.23*	*1*	*473.23*	*11.76*	*0.0024*
BD	*155.39*	*1*	*155.39*	*3.86*	*0.0621*
CD	*245.76*	*1*	*245.76*	*6.11*	*0.0217*
C^2	*220.65*	*1*	*220.65*	*5.48*	*0.0286*
D^2	*175.03*	*1*	*175.03*	*4.35*	*0.0488*
Residual	885.13	22	40.23		
Lack of Fit	*715.07*	*16*	*44.69*	*1.58*	*0.2986*
Pure Error	*170.06*	*6*	*28.34*		
Cor Total	17099.37	33			

Table 5: ANOVA for response surface reduced quadratic model.

Through this analysis, factors A (temperature), C (acid equivalents), D (catalyst loading) and E (concentration) were shown to have an F value >10. This shows that within the described model, these factors were statistically significant upon the outcome of the reductive etherification reaction. These factors were not significant in isolation and combinations of AB, CD, C^2 and D^2 were also therefore statistically significant. The model itself was shown to have a p-value <0.0001, showing that there was no significant lack of fit determined for the model. This means that the design of experiment analysis would be able to predict values

within the confines of its model, and there would be a high level of confidence the predictions were valid and not due to noise within the model.

Of all the parameters investigated, the number of equivalents of methanesulfonic acid was shown to have an F value 5 times higher than all other factors. This shows that the equivalents of acid is by far the biggest contributor to the success of the reaction. Optimal conditions would have high acid equivalents, high alcohol equivalents, low temperature, low catalyst loading and low solvent volumes (Figure 34).

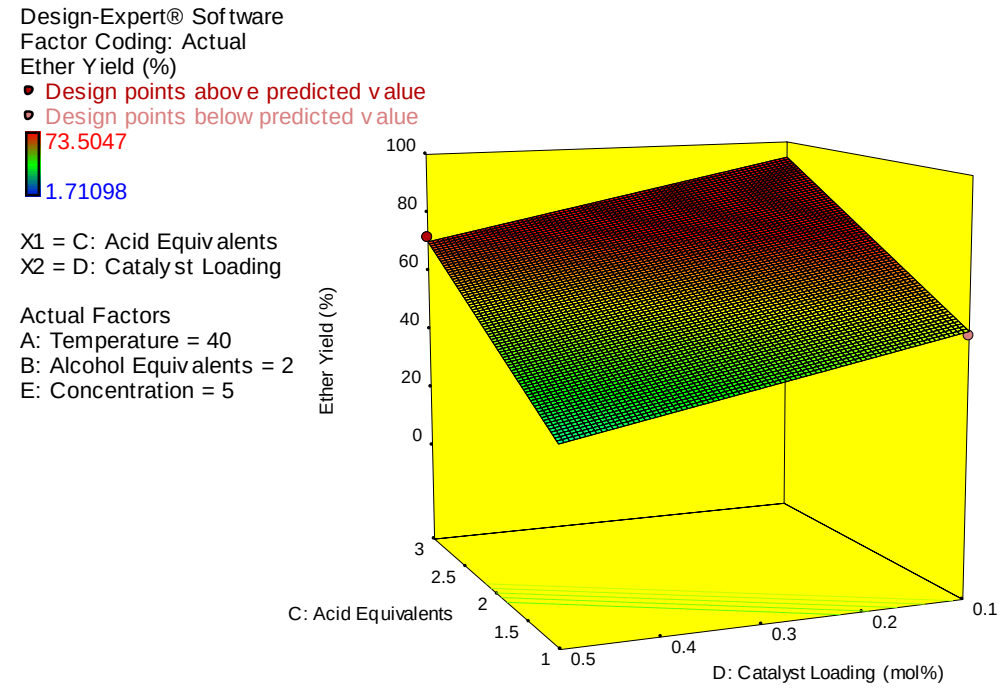


Figure 34: 3D response surface of the initial DoE analysis with ether yield plotted against catalyst loading and acid equivalents as the two most statistically significant factors.

With this initial DoE optimisation suggesting lower temperatures and lower catalyst loadings are beneficial for the reaction, a second response surface study was designed outside of the ranges of the first DoE optimisation. This secondary DoE optimisation was performed

between these ranges: 1 - 2 equivalents of *n*-butanol, 1 - 3 equivalents of methanesulfonic acid, 0.05 - 0.25 mol% of catalyst, 20 - 30 °C and 5 - 15 solvent volumes of CPME.

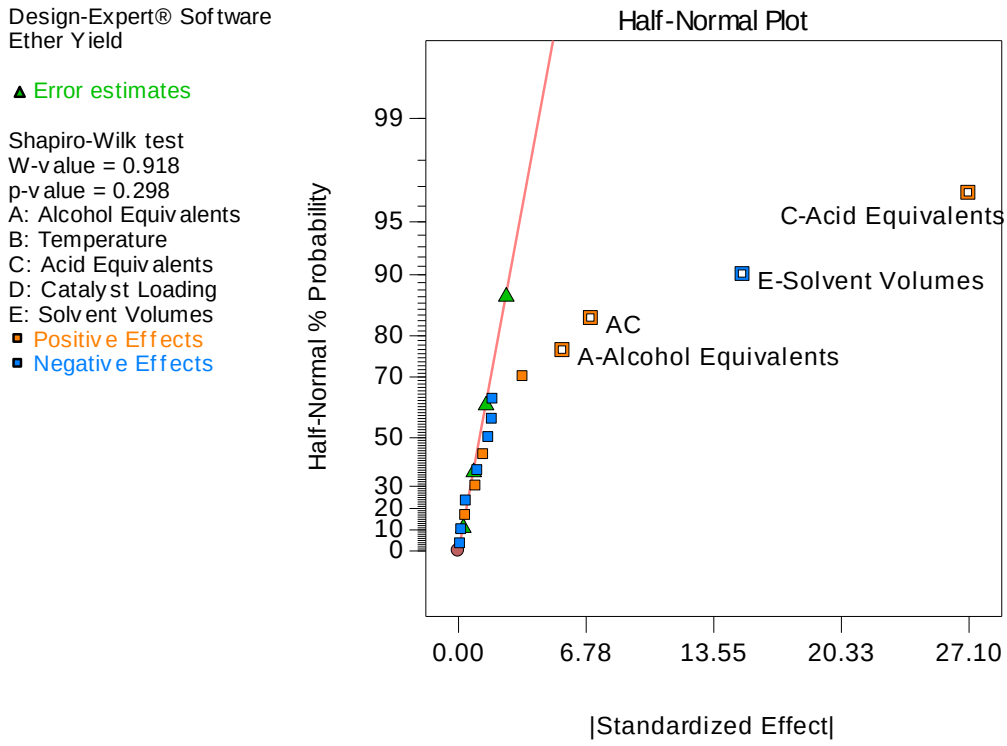


Figure 35: Half normal plot for the revised DoE performed at lower temperatures and catalyst loadings.

Between these adjusted ranges, there was no significant lack of fit within the model and only 2 parameters were deemed statistically significant to the ether yield (Figure 35). High acid equivalents and low solvent volumes were required for maximum ether formation and alcohol equivalents, catalyst loading and temperature all had no statistical significance on the yield of the reductive etherification reaction.

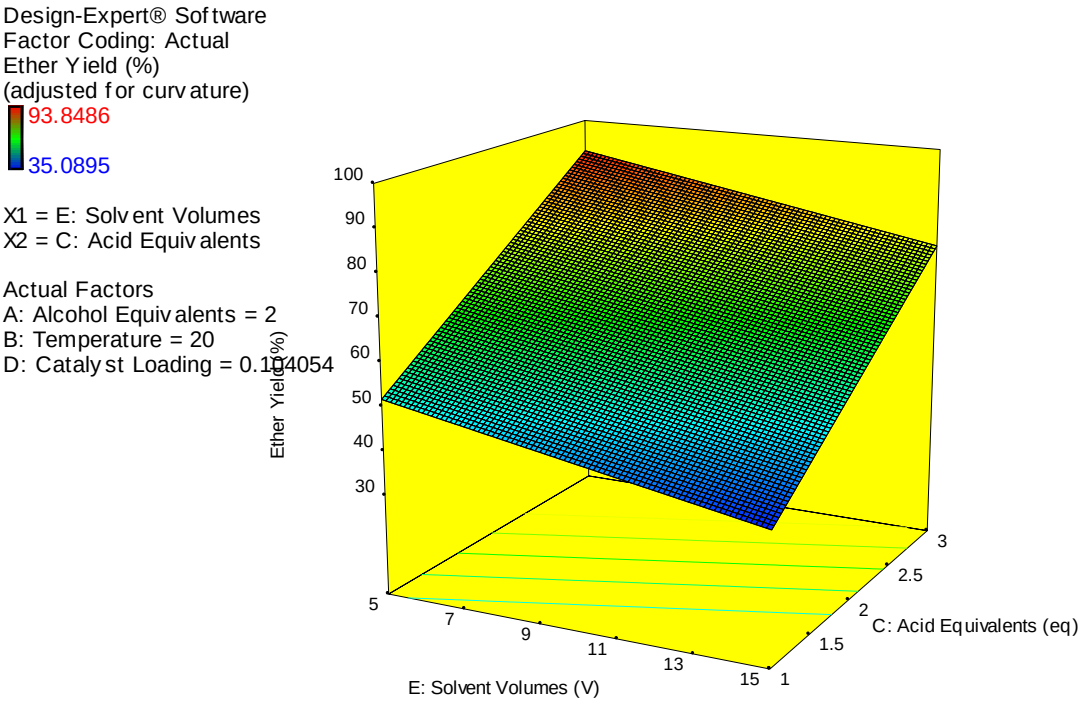
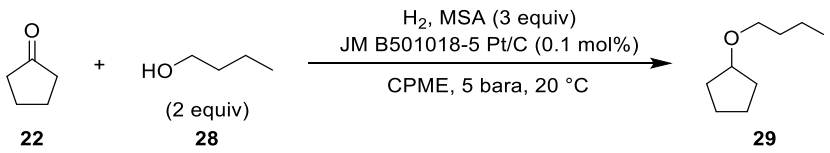


Figure 36: 3D response surface of the revised DoE analysis with ether yield plotted against solvent volumes and acid equivalents as the two most statistically significant factors.

As a result of the DoE optimisation, the chosen optimal reaction conditions were: 3 equivalents of methanesulfonic acid, 2 equivalents of alcohol, 0.1 mol% catalyst loading, 20 °C and 5 solvent volumes of CPME (Figure 36, Scheme 36).



Scheme 36: Optimised reaction conditions from the DoE analysis.

Although alcohol equivalents were not deemed statistically significant in the secondary DoE optimisation, when applying these reaction conditions to different substrates, the electronics

of the carbonyl component and nucleophilicity of the alcohol components will likely vary substantially. It was hypothesised that 2 equivalents of alcohol would promote the reductive etherification of the less reactive starting materials, but successful reactions would be repeated at 1 equivalent alcohol loading.

1.4.18 Quantitative Time Course with Optimised Conditions

With optimised conditions in hand, a quantitative time course was performed to give comparable data to that collected with unoptimised conditions in Section 1.4.4. This data would not only validate the use of an acid additive through rate increase but also test the design of experiment optimisation with comparison of solution yields against an internal standard of tridecane.

A number of factors within the reductive etherification manifold have been improved upon since the first QTC was collected. The design of experiment optimisation gave insight into the relative amounts of the reagents and temperatures required for the reaction and other factors were also improved through removal of molecular sieves, transitioning to a wet paste catalyst, and substitution of chloroform for a non-chlorinated and green solvent, CPME.

This large scale time course was performed on the EasyMAX pressure vessel, fitted with the EasySampler sampling probe, as was used in the first large scale time course (1.4.4)

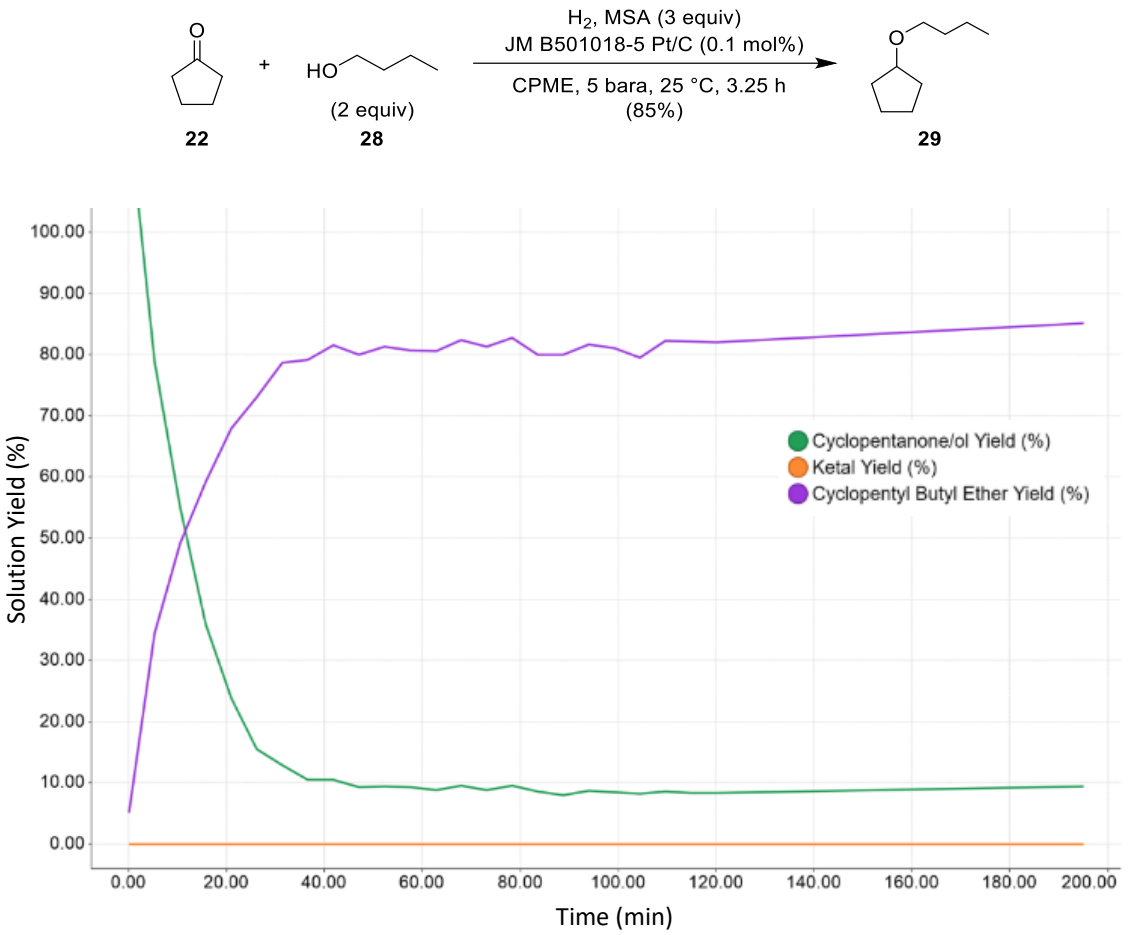


Figure 37: Large scale quantitative time course of the optimised reductive etherification reaction of cyclopentanone and butanol to form cyclopentyl butyl ether.

This quantitative time course not only justifies use of an acid additive by showing a vastly decreased reaction time from 8 hours to 30 minutes, but the final solution yield of ether formed is also increased from 60% to 85% (Figure 37). It is also of note that in this time course, we observe no accumulation of intemediate species under the optimised reaction conditions.

The overall result of these optimisations is a faster, higher yielding reductive etherification reaction at room temperature with decreased catalyst loading and increased concentration.

1.4.19 Saturated Substrate Scope

Following the careful optimisation to arrive at a high-yielding reductive etherification reaction, a small substrate scope of saturated ethers was evaluated. This substrate scope investigated the tolerance of both the carbonyl and alcohol starting materials, at equimolar amounts and with the alcohol in excess. Functional group tolerance of the reaction was also probed, as well as some steric effects from the use of cyclic and linear carbonyl components (Figure 38).

Although the previously studied reductive etherification of cyclopentanone and butanol was shown to be complete in around 30 minutes, the reaction time for the substrate scope was increased to 6 hours. This would allow substrates with more steric hindrance and/or lower reactivity to undergo the reductive etherification to an appreciable degree upon sampling the reaction.

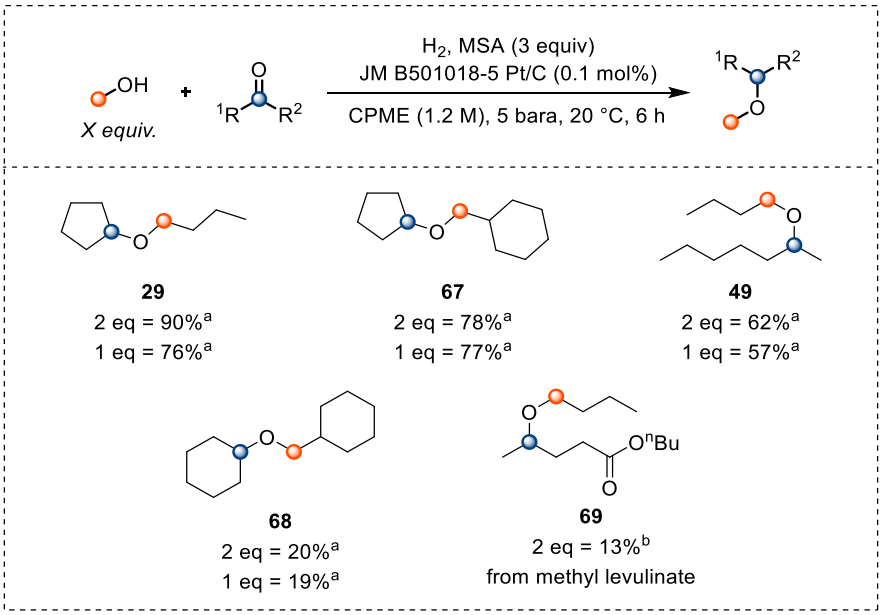


Figure 38: Substrate scope of saturated ethers formed via the optimised reductive etherification reaction. Yields are reported as an average of two runs. [a]Denotes solution yield measured against an internal standard of tridecane. [b]Denotes yields for reactions performed once.

Through this application of the reductive etherification reaction, it was interesting to see that in many cases the solution yields at 1 and 2 equivalents of alcohol were comparable. This was predicted from the DoE optimisation but was now demonstrable across a number of substrates. Also, reactions where cyclopentanone was used as the carbonyl component were shown to perform well (Figure 38, **29** and **67**). This was also unsurprising as the DoE optimisation was performed on cyclopentanone.

When the reductive etherification was applied to 2-heptanone in the presence of butanol, a significantly lower yield was obtained (Figure 38, **49**). This is hypothesised to be due to the linear nature of 2-heptanone, providing a much more sterically accessible carbonyl for direct reduction by H_2 to the corresponding alcohol. In fact, when studied by QTC, 2-heptanol was observed as a major by-product in the reaction.

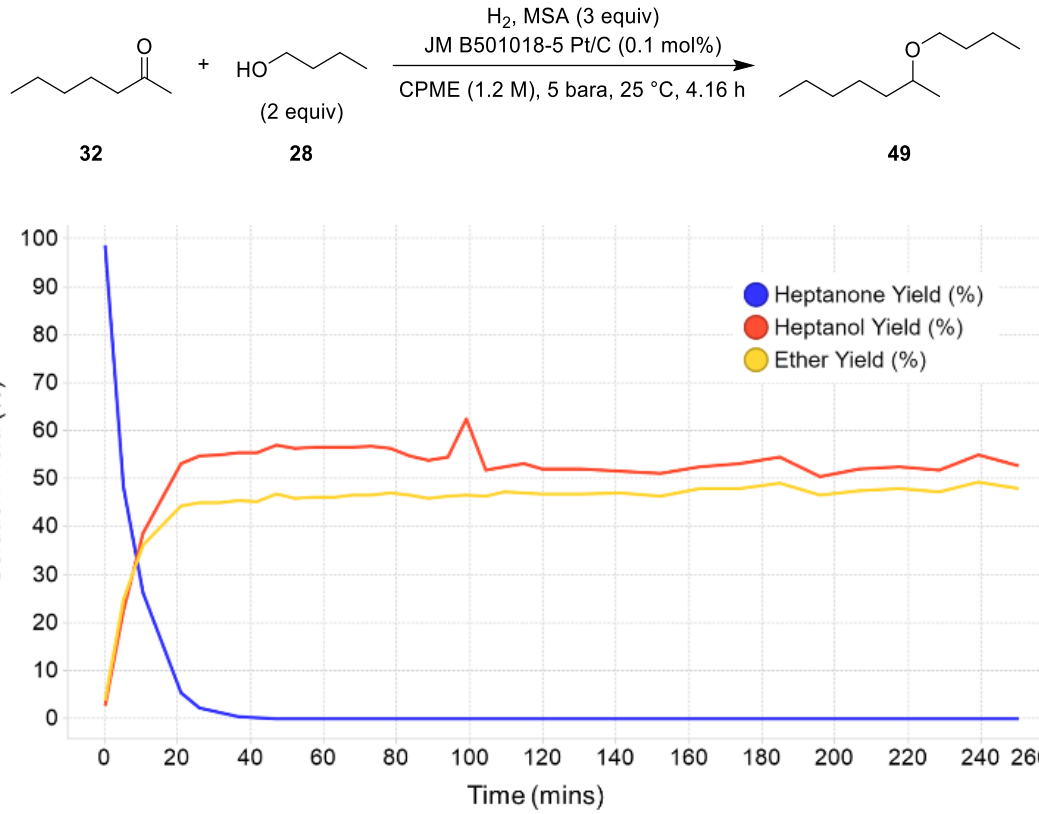


Figure 39: Reductive etherification of 2-heptanone and butanol showing the formation of heptyl butyl ether and 2-heptanol.

The reductive etherifications of cyclohexanone (Figure 38, **68**) were shown to be significantly lower yielding, both at 1 and 2 equivalents of alcohol. This is to be expected, as the ring size is known to play an important role in the reactivity of the carbonyl. Through studies by Newman and Harper Jr., it was shown that the ketal of cyclopentanone was formed slightly slower than that of cyclohexanone.[84] Once formed, however, this cyclopentyl ketal was much more reactive to hydrolysis than the ketal of cyclohexanone. During the reductive etherification, it is hypothesised that the ketal intermediate formed within the reaction is formed faster for reactions of cyclohexanone. The increased stability of this cyclohexyl ketal intermediate may then be slowing down the subsequent elimination/reduction stage of the reaction, resulting in a decreased yield.

Pleasingly, the optimised reaction manifold was tolerant to ester functionality, with butyl 4-butoxypentanoate (Figure 38, **69**) being isolated in 13% yield. This decreased yield was thought to be due to the linear nature of the ketone, promoting direct reduction to the alcohol as well as transesterification. The starting material for this reaction, methyl levulinate, has clearly transesterified to give the butyl ester as the product of the reaction (Figure 40, **69**). This suggests that products of this reaction could reasonably be the carboxylic acid (**74** or **75**), the methyl ester (**72** or **73**) or the butyl ester (**69** or **71**), each of these with the butyl ether or alcohol present through reaction of the carbonyl moiety. Another possible product under the acidic reaction conditions, upon reduction of the ketone, is cyclisation to form the lactone, γ-valerolactone (**76**). This was isolated from the reaction and characterised by ^{1}H NMR spectroscopy against a reference sample.

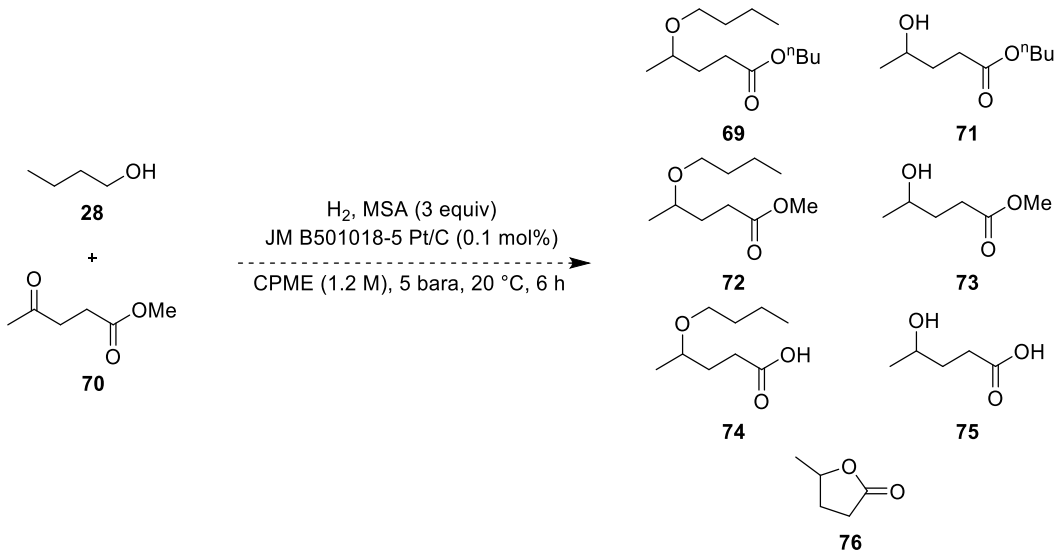
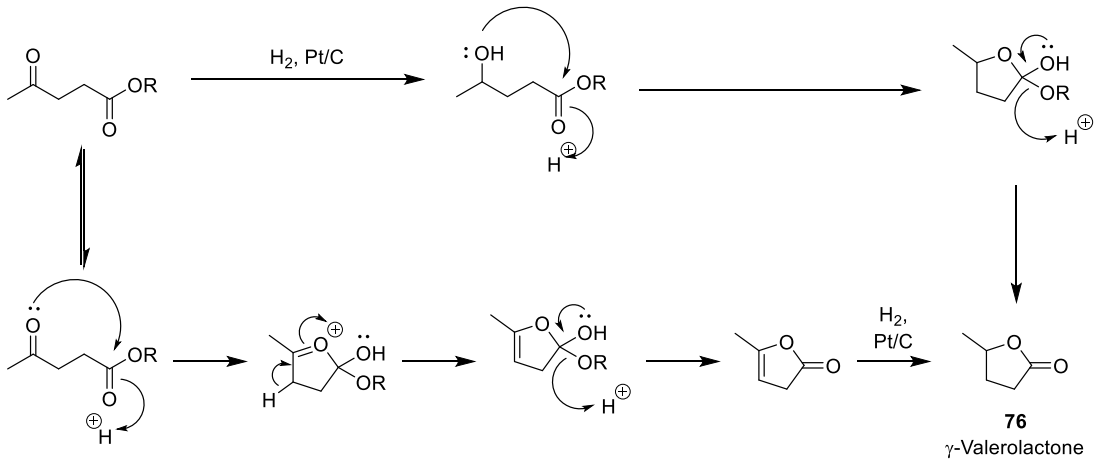


Figure 40: Possible products formed from the reductive etherification reaction of methyl levulinate and butanol.

As cyclisations are often very facile reactions, especially when forming 5 membered rings, this cyclic ester product could be formed through conversion of any of the alcohols formed through direct carbonyl reduction. γ-Valerolactone can also be formed through cyclisation of levulinic acid and subsequent hydrogenation (Scheme 37).[85]



Scheme 37: Possible routes for formation of γ-valerolactone within the reductive etherification reaction of methyl levulinate. R = methyl, n-butyl or H.

Unsuccessful substrates within the optimised conditions were notably those bearing any substituent α to the carbonyl group (Figure 41). This substituent no doubt contributes to the steric hindrance around the carbonyl site, making nucleophilic attack from an incoming alcohol less favourable. The resulting ketal will also have unfavourable interactions with the adjacent groups, leading to a higher energy intermediate, which is more difficult to access. In the case of 2-acetyl cyclopentanone (**78**), a number of products can be formed from direct reduction and/or etherification at either carbonyl, leading to a complex reaction mixture.

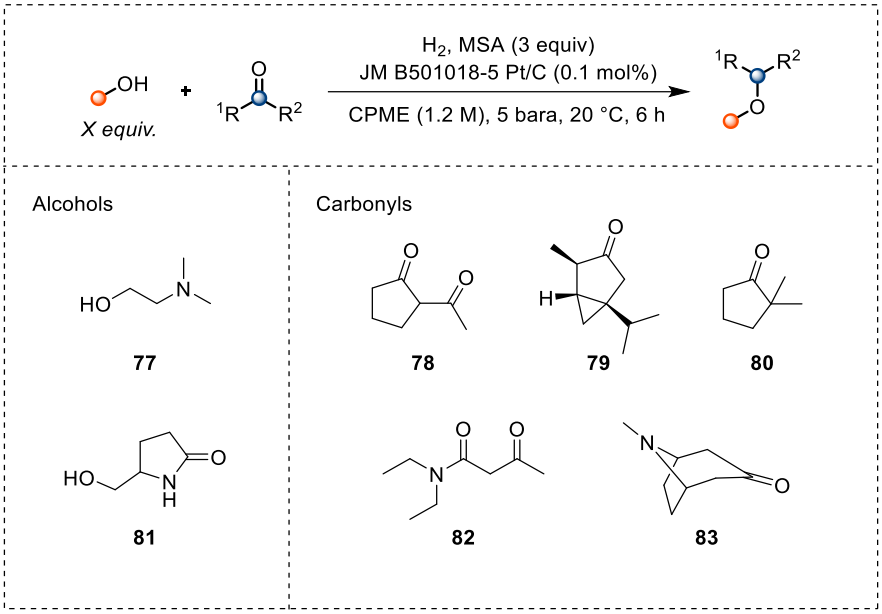


Figure 41: Unsuccessful saturated substrates for reductive etherification

Other substrates which led to an unproductive reductive etherification reaction were those bearing a basic nitrogen centre (Figure 41). Upon inspection of these reaction mixtures, formation of an insoluble precipitate or viscous liquid was evident. It was apparent that, although use of an acid additive was require for a successful reaction system, functional groups featuring a basic nitrogen centre were protonated and rendered unreactive. Use of methanol as a reaction solvent to circumvent this issue was attempted without success.

1.4.20 Aromatic Substrate Investigation

With the optimised reductive etherification reaction being shown to work well for a small range of saturated substrates, the next step was to apply it to substrates containing an aromatic system. Within the platinum catalysed reductive etherification reaction developed by Gooβen, 4-phenylbutan-2-one was specifically mentioned to be unsuitable for use within this methodology.[64] Indeed, aromatic substrates were reported to be reduced to their corresponding cyclohexanes. For this reason, 4-phenylbutan-2-one was chosen as the model substrate on which to explore the platinum catalysed reductive etherification reaction optimised within this research program.

4-Phenylbutan-2-one was subjected to the optimised reaction conditions of 3 equivalents of methanesulfonic acid, 5 bara of hydrogen pressure, 0.1 mol% Pt/C catalyst loading, 2 equivalents of butanol, at 5 solvent volumes of CPME at 25 °C (Figure 42). Solution yields of reaction components were calculated against an internal standard of tridecane and a quantitative time course was plotted.

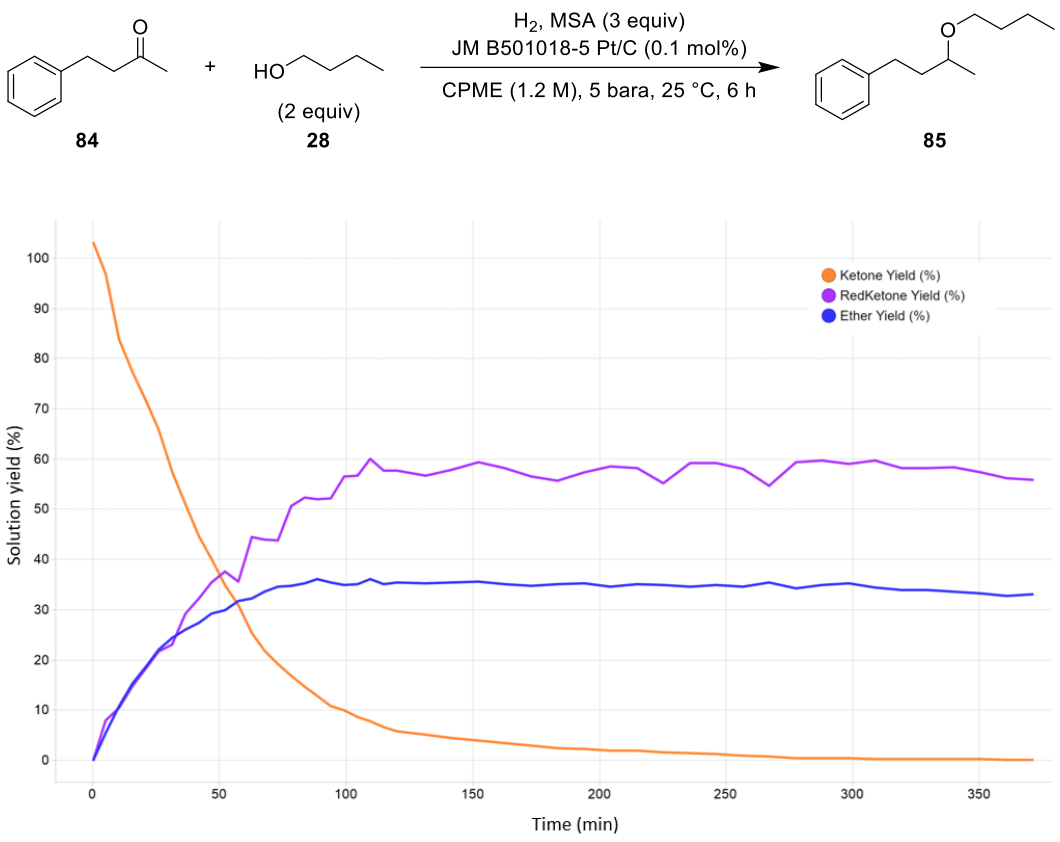


Figure 42: QTC of 4-phenylbutan-2-one and n-butanol under the optimised reaction conditions. The yield of 4-phenylbutan-2-ol has also been plotted as the major side product within this reaction.

Pleasingly, 4-phenylbutan-2-one was shown to be a viable etherification partner within the optimised reductive etherification conditions. This represents a considerable advance compared to the previously reported conditions by Gooβen *et al.* who reported this substrate to be incompatible with their reductive etherification conditions.[64] Although a moderate product yield of 35% was observed, this reaction parallels that of heptan-2-one, where the moderate yield was hypothesised to be due to the linear nature of the carbonyl. The reduced steric hindrance of this linear carbonyl site is thought to promote direct reduction from Pt/C and hydrogen, resulting in a substantial side product of 4-phenylbutan-2-ol.

In contrast to the conclusions drawn by the Gooβen group, the aromatic substrate was shown to be compatible with this optimised methodology, with the aromatic ether and alcohol side

product also being stable to the reaction conditions. Once the solution yields of these products reached their maximum within the QTC, they remained relatively unchanged when held under the reaction conditions for a further 4 hours.

1.4.21 Aromatic Substrate Scope

As aromatic rings were shown to be tolerated by the successful synthesis of (3-butoxybutyl)benzene (**85**) and the aromatic containing entities stable to the optimised conditions, an aromatic substrate scope study was performed (Figure 43).

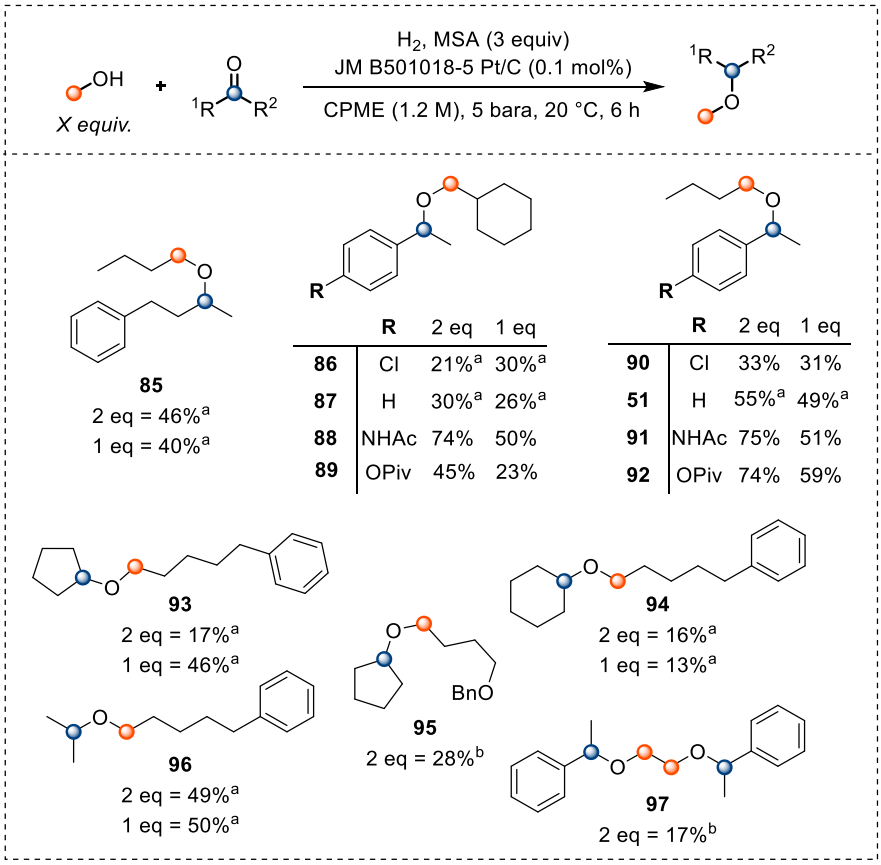


Figure 43: Substrate scope of aromatic ethers formed via the optimised reductive etherification reaction. Yields are reported as an average of two runs. [a]Denotes solution yield measured against an internal standard of tridecane. [b]Denotes yields for reactions performed once.

Benzylic ethers derived from acetophenone (**51**, **87** and **97**) and its derivatives were shown to be accessible in good yields under the optimised conditions. These included substrates bearing *para*-chloro (**86** and **90**), -acetanilide (**88** and **91**) and -pivalate (**89** and **92**) substituents. These functional groups are of great utility in organic synthesis, with opportunities for further reaction of the product ether at these sites. The aryl halide moiety, in particular, is very important within metal catalysed cross coupling reactions, whereas the acetanilide and pivalate groups can easily be deprotected to subsequently react through the free NH_2 or OH centres.

Due to the conjugated nature of the benzylic carbonyl groups, their reactivity is significantly diminished in comparison to the cyclopentanone model substrate. For this reason, the reactions employing 2 equivalents of alcohol perform much better. Presumably, the increased amount of alcohol coupling partner within the reaction mixture aids the formation of the ketal intermediate. This increased concentration of the ketal intermediate is not only required for the success of the reaction, but also protects the carbonyl starting material from direct reduction, providing higher yielding etherification reactions.

5-Phenylpentan-1-ol was shown to be a good etherification partner, forming products in good to excellent yields at both 1 and 2 equivalents, with cyclopentanone (**93**), cyclohexanone (**94**) and acetone (**96**).

Ethylene glycol also showed itself to be a viable alcohol partner within the reaction, with the diether product (**97**) being isolated. Although the reaction yield was modest, this could be attributed to the stability of the ketal intermediate, as cyclic ketals are known to be more stable than acyclic analogues. Presumably the formation of the diether product proceeds through the monoether, however, none of this was isolated from the reaction.

4-Benzyloxy butanol participated in the reductive etherification reaction, forming the desired ether (**95**) in 28% yield. Benzyl ethers are commonly used as protecting groups in organic synthesis and are removed under hydrogenation conditions. As the reductive etherification reaction is essentially a hydrogenation reaction, it was encouraging to see that some intact benzyl-protected product was isolated from the reaction. It is also of note that all ethers shown derived from acetophenone and its analogues are also essentially benzylic ethers and are stable to the optimised reaction conditions.

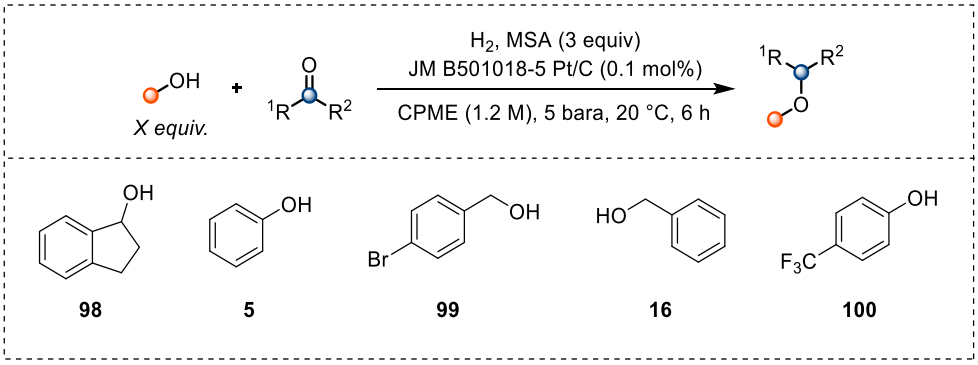


Figure 44: Phenols and benzylic alcohols trialled within the acidified reductive etherification reaction.

Phenols and benzylic alcohols were shown to be unproductive within the reaction (Figure 44). This could be attributed to the low reactivity of phenol and its derivatives, with the oxygen lone pair of phenol having reduced nucleophilicity due to delocalisation with the aromatic ring. Phenols and benzylic alcohols also have increased steric bulk compared to the other successful alcohol components outlined in the substrate scope. Should the reaction proceed through the ketal as the reactive intermediate, formation of this could be greatly hindered by these more sterically demanding reactants.

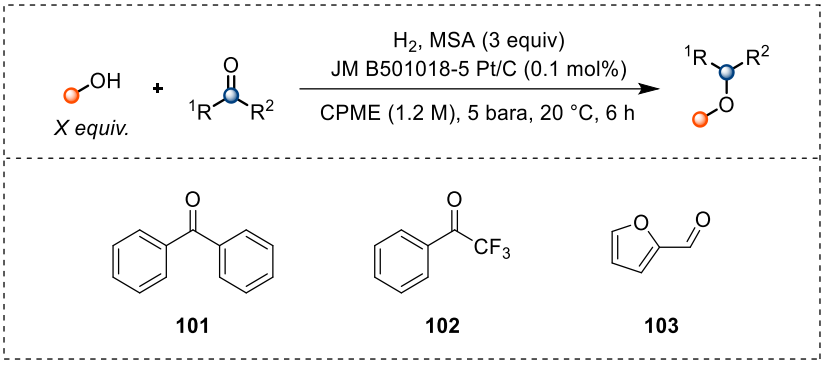


Figure 45: Carbonyls trialled within the acidified reductive etherification reaction that do not possess α hydrogen atoms with which to enolise.

For the enol ether to be accessible within the reaction mixture, the carbonyl component must possess hydrogen atoms α to the carbonyl (Figure 45). If the components do not have these hydrogen atoms, formation of an enol ether intermediate would not be possible. No ether products were detected when ketones **101**, **102** and **103** were employed in the reductive etherification reaction. It is hypothesised that, although hydrogenolysis of the ketal is possible, it will be much slower due to the increased steric hindrance around the reacting centre. This, in tandem with the lower reactivities of the conjugated carbonyl groups, may have rendered these reactions unproductive.

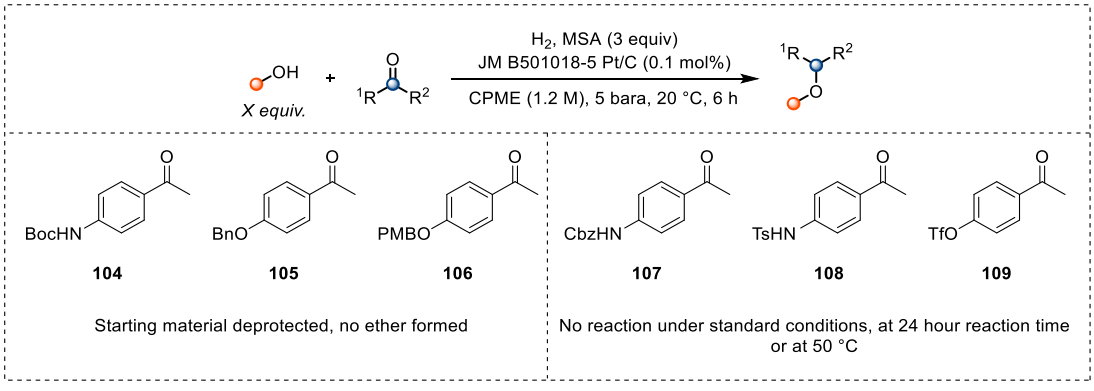
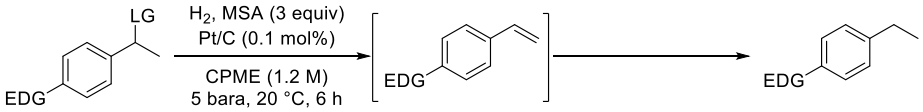


Figure 46: Unsuccessful protected acetophenone analogues within the reductive etherification reaction.

A number of protecting groups were trialled for use within this reaction including NBoc (**104**), NTs (**108**), NCbz (**107**), OBn (**105**), OPMB (**106**) and OTf (**109**) (Figure 46). Unfortunately, these were shown to be unsuitable for use within the optimised conditions with NBoc (**104**), OPMB (**106**) and OBn (**105**) deprotecting within the reaction. NTs (**108**), NCbz (**107**), and OTf (**109**) analogues were unreactive to the standard conditions, with only the *N*-Tosyl analogue showing deprotection with increased temperatures and reaction times.



Scheme 38: Proposed mechanism by which substrates bearing an electron donating group para- to the acetyl group eliminated and reduced to the corresponding ethyl benzene. EWG is -OMe or -OH and LG is -OH or -OR.

Significantly electron donating groups on *para*- substituted acetophenone analogues were also found to be inappropriate for use within this reaction (Scheme 38). Use of the *p*-OMe, *p*-OH or deprotected *p*-OH derivatives returned the corresponding ethylbenzenes. This is hypothesised to be due to elimination of the ether or alcohol derived from direct reduction of the carbonyl. E1-type elimination of these intermediates in the presence of acid would be aided by the electron donation through the aromatic ring, resulting in formation of the styrene. This styrene would then be hydrogenated by the Pt/C catalyst to form the corresponding ethylbenzene.

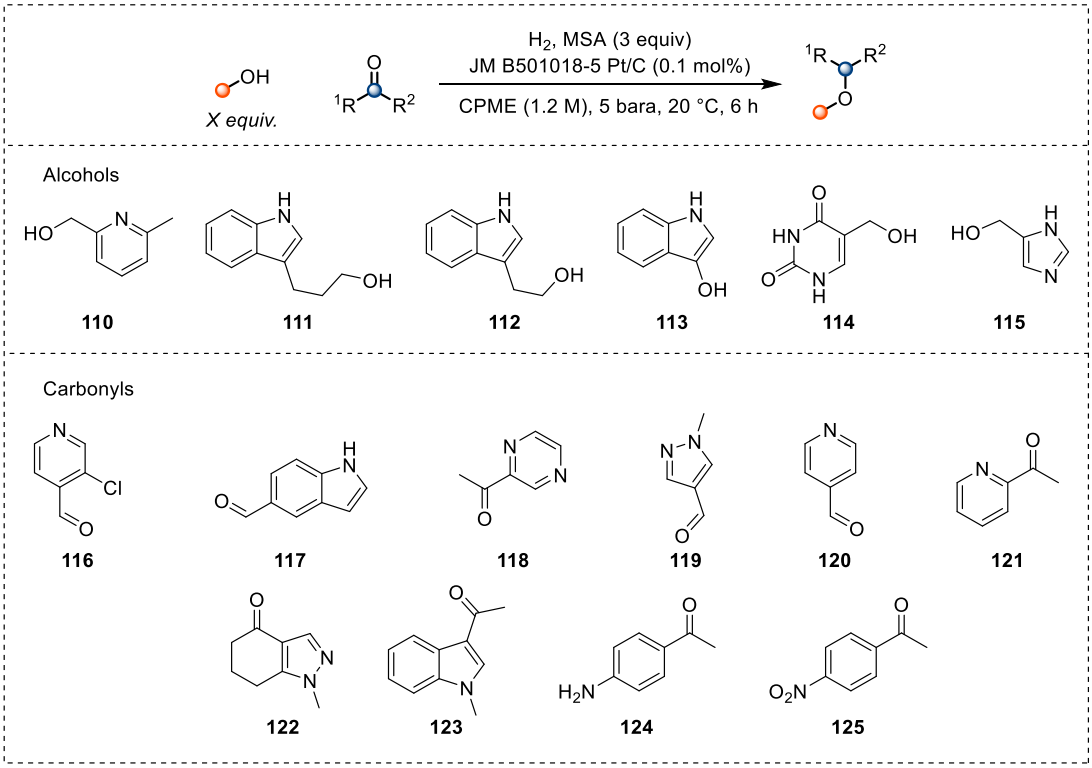
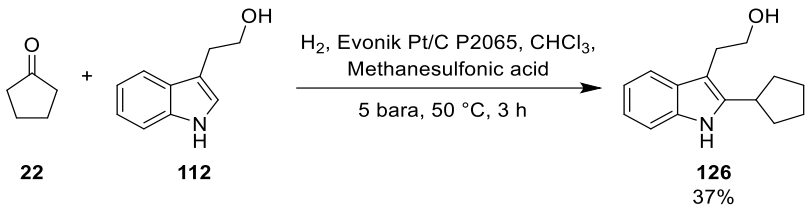


Figure 47: Substrates containing basic nitrogen centres trialled within the acidified reductive etherification reaction.

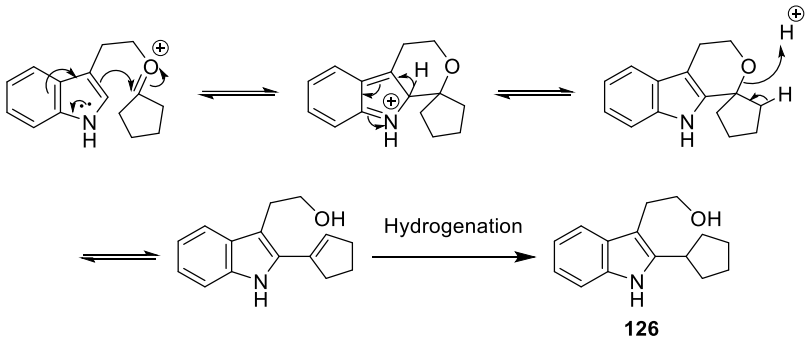
Other aromatic substrates were shown to be unsuitable for the reductive etherification (Figure 47). As observed within the saturated substrate scope, heterocycles containing a basic nitrogen atom were protonated under the acidic reaction medium. This rendered the stating materials unproductive within the reaction manifold, by precipitation from the reaction mixture.

An interesting exception to this was tryptophol, or 3-(hydroxyethyl)indole (**112**). When subjected to the more dilute, unoptimised reaction conditions, the desired ether product was not observed but instead, this substrate participated in a previously unexpected side reaction (Scheme 39). The product of this reaction was shown to incorporate the cyclopentyl ring of cyclopentanone at the C2 position of the indole ring (**126**).



Scheme 39: Observed C2 cyclopentyl product isolated from the reductive etherification of cyclopentanone and tryptophol.

This substituted indole was thought to be the product of a similar reaction to that developed by Scheidt *et al*. within a tandem isomerisation/Prins reaction, catalysed by acid and an iridium complex (Scheme 40).[86]



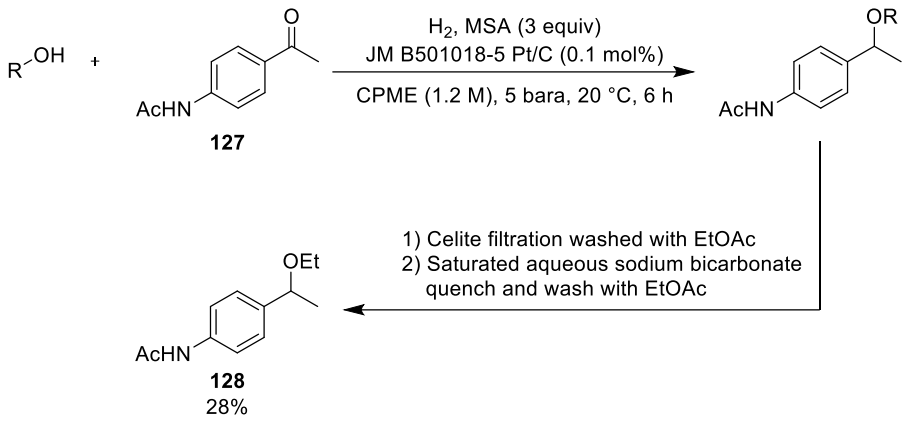
Scheme 40: Proposed mechanism of formation for the C2 functionalisation of tryptophol.

The isomerisation/Prins reaction is reported to terminate at the cyclised product, however; under the acidified reductive etherification reaction conditions, an additional elimination and hydrogenation is thought to occur to provide the C2 cyclopentyl product (**126**) in good yield.

1.4.22 Ether Substitution with Acetate Work Up

The celite filtration and solvent extraction after the hydrogenation of compounds was usually performed with CPME but was also trialled with ethyl acetate. After using ethyl acetate for the work up of ethers derived from 4'-acetamidoacetophenone, the expected products were

not isolated. Although the butyl and cyclohexylmethyl ethers were isolated previously with CPME and were observed to be formed in good amounts by LCMS before the work up was initiated, the only product isolated from both of these reactions was determined to be the ethyl ether, implying a trans-etherification process was occurring during the work up (Scheme 41).

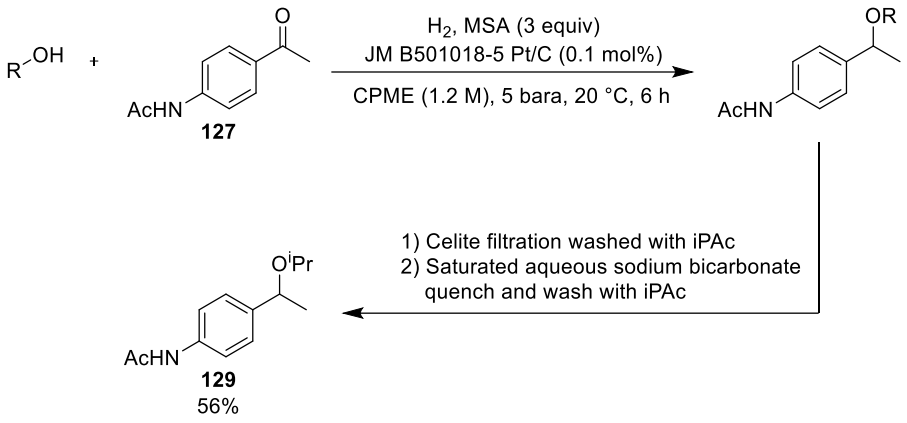


Scheme 41: Observed ether exchange from the reductive etherification reaction of 4'-acetamidoacetophenone when work up was performed with ethyl acetate solvent. R = butyl or cyclohexylmethyl.

The mechanism of this transetherification is unknown; however, a nucleophilic substitution reaction can be hypothesised at the benzylic carbon. It is known from previous studies (Section 1.4.14) that esters are incompatible solvents for the acidified reductive etherification reaction. Under the reaction conditions, esters were shown to cleave and liberate alcohol into the reaction mixture. With ethyl acetate used as the organic solvent during the solvent separation, this is likely the source of the ethyl group incorporated into the isolated ether product.

With ethanol present within the reaction mixture during/after the aqueous work up, a nucleophilic substitution reaction at the ether position can be hypothesised. This reaction may be aided through electron donation from the *p*-NHAc group. Due to the use of EtOAc as

a solvent, the sheer quantity of liberated EtOH within the work up may shift the equilibrium of the reaction to produce the ethyl ether in substantial yields.

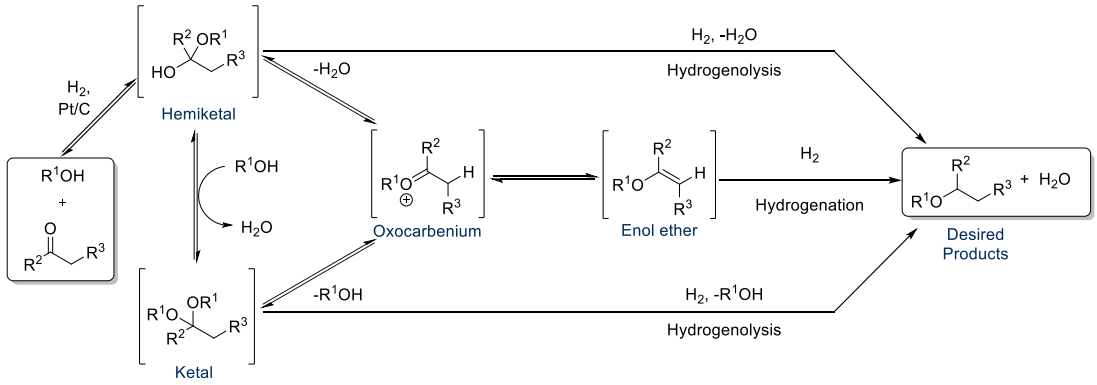


Scheme 42: Observed ether exchange from the reductive etherification reaction of 4'-acetamidoacetophenone when work up was performed with iso-propyl acetate solvent. R = butyl or cyclohexylmethyl.

To confirm the origin of the ethyl ether substituent, the reaction was repeated and *iso*-propyl acetate was used as the work up solvent (Scheme 42). This resulted in isolation of the isopropyl ether product in substantial yield. This confirms and extends upon the previous acetate solvent screening showing that acetate solvents are unsuitable for use within any part of the reductive etherification reaction.

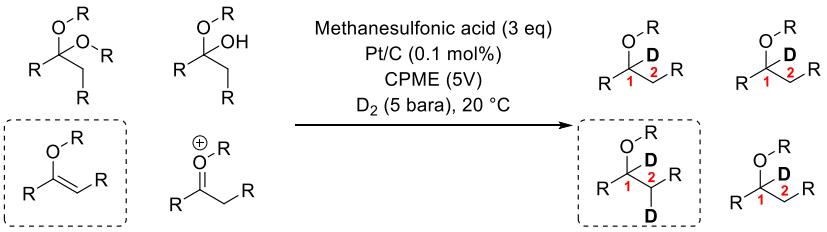
1.4.23 Deuterium Labelling Studies

To investigate the mechanism with respect to those proposed by Fujji, Bethmont and Gooβen within their reported work, a deuterium labelling study was proposed (Scheme 43).[54, 57-58, 64] This deuterium study would aim to label the product ether from the reductive etherification reaction and elucidate the nature of reactive intermediates within the reaction, including the enol ether, the ketal, the hemiketal or the oxocarbenium intermediate.



Scheme 43: Proposed mechanism for the reductive etherification containing all possible reaction intermediates.

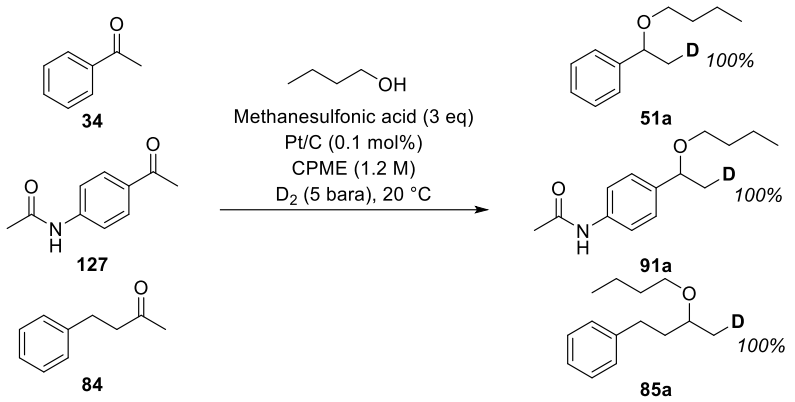
Through the incorporation of deuterium within the product ether, it will be possible to determine which intermediate was reduced and investigate the effect of the acid additive. It was hypothesised that lowering the reaction pH would allow access to the enol ether intermediate, which, with its reduced steric demand compared to the ketal intermediate, could allow a faster reaction to form the ether product. Reduction of the enol ether product would result in a doubly deuterated product, with deuterium labels present at carbons 1 and 2 (Scheme 44).



Scheme 44: Proposed deuteration experiments to determine the reaction mechanism.

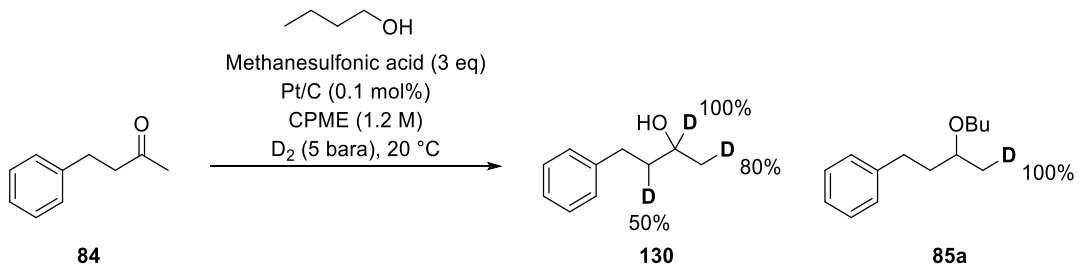
This deuterium labelling experiment was performed on 3 successful carbonyl systems from the substrate scope, in conjunction with butanol and methanesulfonic acid (Scheme 45). However, reduction of these three substrates did not result in the expected deuteration patterns shown in Scheme 44. Deuteration at C1 should occur for all proposed intermediates

in the proposed reaction mechanism (Scheme 43); however, all products showed no deuterium labelling at C1 and 100% D incorporation at C2.



Scheme 45: Reductive etherification reactions in the presence of deuterium gas to determine reaction mechanism.

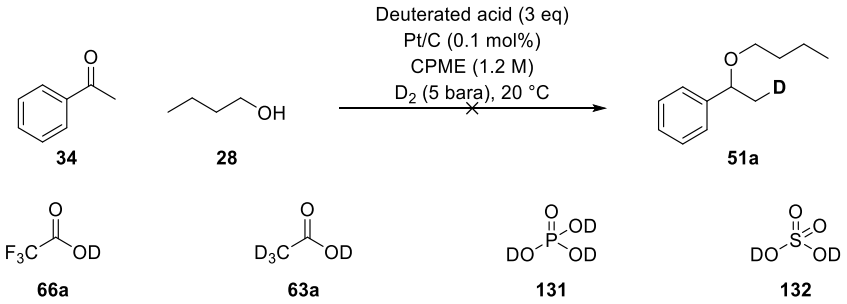
To determine whether this deuteration pattern was an artefact of the optimised reductive reaction conditions, the direct reduction side product for the reaction of 4-phenylbutan-2-one was also isolated (Scheme 46). The deuteration pattern of this side product showed an expected distribution of deuterium atoms within the reduced molecule, consistent with reduction of an enol intermediate.



Scheme 46: Deuterium labelling pattern of the direction reduction side product from the reductive etherification of 4-phenylbutan-2-one.

The surprising deuterium distribution within the product ethers suggests a different mechanism is occurring to that proposed within the previous literature reports. With any reactive hydrogens within the reaction mixture determined to be protic in nature, the labelling pattern of these molecules suggests that a deuteride reduction is in operation at C2 in concert with a protonation event at C1.

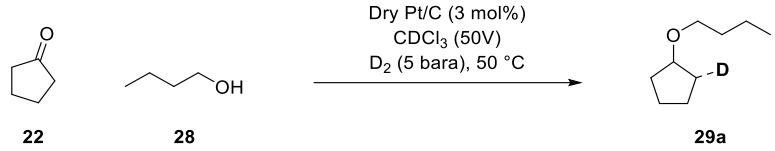
With the acid additive being the factor with most statistical significance within the DoE analysis, and being the largest most abundant protons within the reaction, exchange of this for a deuterated counterpart was investigated. As d_4-methanesulfonic acid is not a commonly available deuterated acid, substitution of this with deuterated sulfuric-, phosphoric-, trifluoroacetic- and acetic acids were investigated while awaiting delivery of d_4-MSA from a specialist supplier.



Scheme 47: Unsuccessful reductive etherification reactions using 4 common deuterated acid additives.

Unfortunately, use of these acids did not result in any ether formation under the optimised reaction conditions. This incompatibility of other acid additives to the reaction conditions was rather concerning at this point, as this could have suggested a more important role for methanesulfonic acid under the optimised reaction conditions. This more important role for MSA could signal a change in the reaction mechanism during the optimisation. To investigate

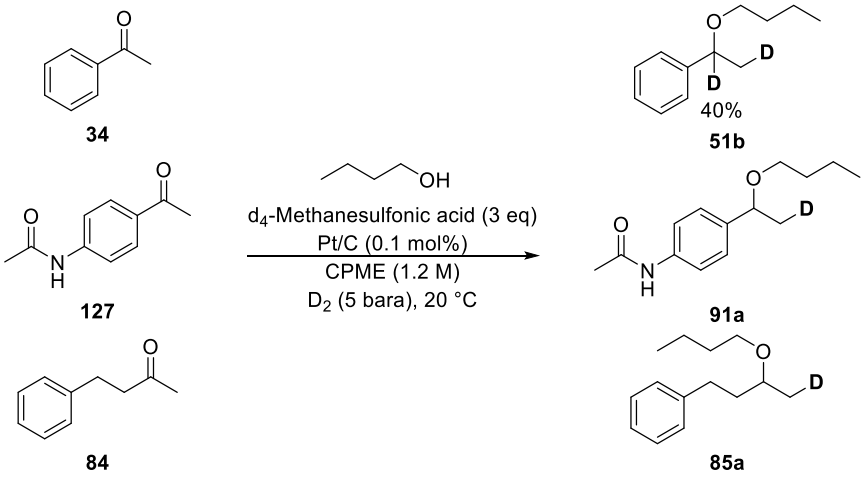
this hypothesis, the initial Gooβen conditions were performed under a deuterium atmosphere and deuteration of the product ether was analysed (Scheme 48).



Scheme 48: Reductive etherification of cyclopentanone and n-butanol under neutral Gooβen conditions.

On return to the initial Gooβen conditions with the dry catalyst and chloroform solvent, the incorporation of one deuterium atom at C2 and no deuterium atom at C1 was still observed. Although this result does not explain the origin of the unexpected deuteration pattern, it does confirm the same phenomenon is observed under the previously reported reaction manifold.

To investigate the optimised conditions further, a sample of deuterated methanesulfonic acid was acquired and the labelling experiments were repeated.



Scheme 49: Individual reductive etherification reactions in the presence of deuterium gas and d_4-methanesulfonic acid to investigate reaction mechanism.

With a return to the standard reaction conditions, but with d_4-MSA and under deuterium atmosphere, the reductive etherification was performed comparably to earlier reactions (Scheme 49). Interestingly, a change in the deuteration pattern was observed for the reaction of acetophenone with butanol. Within this reaction, some erosion of the ^{1}H ether proton integral was observable within the NMR spectra for the C1 ether hydrogen. This erosion was quantified to ~ 40% deuterium labelling of the C1 position by comparison of integrals against the butyl CH_2-O protons. Interestingly, neither of the other substrates showed a different labelling pattern to reactions without deuterated methanesulfonic acid and in all cases, 100% D incorporation at C2 was observed. It was hypothesised that this could be a result of the time required for gas purge/vent cycles on the ChemSCAN pressure equipment and the number of exchangeable protons present within the reaction mixture.

Due to the explosive nature of hydrogen gas, for safety reasons, the pressure equipment performs 3 purges with nitrogen gas before 2 purges with hydrogen or deuterium gas. Through these purge cycles, the oxygen levels within the reaction are heavily reduced to <1 % oxygen and the hazards associated with using flammable hydrogen gas significantly lowered. These purge cycles take a significant amount of time on the ChemSCAN pressure reactor. Additionally, the vent stages between these inert and reactive purges are also slowed down to ensure the gas mixtures are being vented in a safe manner.

With these purge and vent cycles taking a substantial amount of time to complete (40-60 min), this drastically increases the time for side reactions. The reaction mixture will be unable to perform reductive etherification as the high speed agitation is not initiated, however exchange of protons within the reaction can still be substantial under low speed agitation and diffusion. For this reason, it was hypothesised that the acidic deuteron present on the

d_4-methanesulfonic acid may have exchanged with other exchangeable protons within the reaction mixture during the preparation of the high pressure equipment cycles.

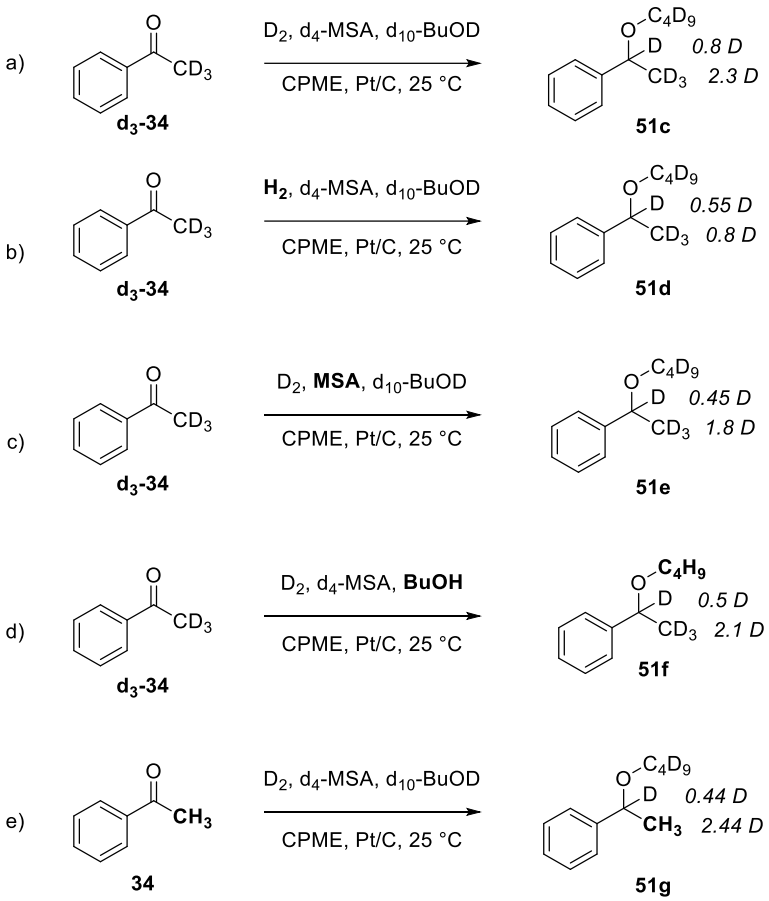
Although methanesulfonic acid is the most acidic component of the reaction and present in 3 equivalents excess, there are a large number of exchangeable protons within the reaction mixture originating from the alcohol, carbonyl and catalyst. Butanol only has one exchangeable OH proton but is however present in 2 equivalents within the reaction mixture. The carbonyl component has exchangeable protons α to the carbonyl group, in addition to any other present in functional groups within the molecule. This results in 3 exchangeable protons from acetophenone, 4 from the acetanilide analogue and 5 from 4-phenylbutan-2-one. The catalyst has been optimised to a wet paste catalyst for safety reasons, meaning that the optimised catalyst is 50% water by weight. This means that there are 0.22 equivalents of water within the reaction mixture, originating from the catalyst.

It is hypothesised that by the time the preparation of the high pressure reactor is completed and reductive etherification is initiated, the 3 equivalents of deuterated methanesulfonic acid will have reached a natural equilibrium with the 5.22 – 7.22 equivalents of other proton sources within the reaction mixture. As acetophenone is on the lowest side of this range, the exchange is thought to have been slower, or the equilibrium thought to favour a higher concentration of deuterated MSA, in comparison to non-deuterated. For this reason, some erosion of the C1 proton signal in the product ether is observed for this reaction.

To attempt to combat this exchange, materials were purchased to allow a fully deuterated reaction manifold to be studied to investigate whether the fully deuterated reaction would result in deuteration at C1 and C2. Replacement of each component within the reaction with its non-deuterated counterpart should allow determination of the source of the C1 proton/deuteron. Alternative high pressure hydrogenation equipment was also evaluated

through a comparison of the Biotage Endeavor and ChemSCAN apparatus. Comparable reactions to those in Scheme 49 were performed in the Biotage Endeavor hydrogenator and comparable results were observed in the presence of deuterium gas.

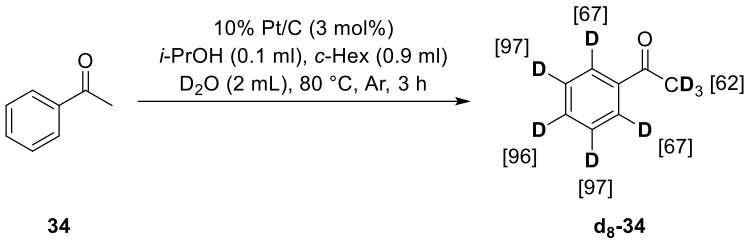
Further labelling studies were performed in the Biotage Endeavor, starting from a fully deuterated reaction manifold, and replacing one reaction component at a time to probe the individual contribution to the mechanism. These were performed with acetophenone and butanol as the model substrates (Scheme 50).



Scheme 50: Deuteration reactions of acetophenone and butanol under the reductive etherification conditions starting from a fully deuterated reaction manifold and replacing reaction components sequentially with their protic counterparts.

Within these reactions, it can be noted that incorporation of deuterium at the α position is always substantial when deuterium gas is used as the reductant. When hydrogen gas is utilised, the deuteration levels drop significantly with more hydrogen being detected at the α position (reaction b, Scheme 50). This could be some evidence for the reduction of an enol ether intermediate; however, there is far more H incorporated at the α position of the product ether than the ether position (2.2 atoms vs 0.45 atoms). Should an enol ether have been reduced, an equal amount of hydrogen would have been incorporated into these positions. This result suggests that, once the hydrogen gas is entrained into the reaction mixture, a number of exchange reactions are occurring resulting in the hydrogen being distributed across the exchangeable sites within the reaction mixture. This process is also occurring for the reaction with deuterium gas and H_3C-acetophenone as substantial deuterium incorporation is also observed (reaction e, Scheme 50).

Interestingly, the fully deuterated reaction conditions (reaction a, Scheme 50) did not result in 100% deuterium incorporation within the ether product. This observation could be due to several reasons. Firstly, the JM B501018-5 Pt/C catalyst used for these reactions was chosen to be a safer alternative to other dry precious metal catalysts. As such, this catalyst is used as a wet paste and is 50% water by weight. This water is protonated, not deuterated, and could contribute to some incorporation of hydrogen within the product ether. Secondly, the catalyst is also sold in pre-reduced form. This means that some hydrogen may already be present on the surface, contributing again to the H incorporation within the fully deuterated reaction manifold. Finally, it is reported within the literature that Pt/C catalysts can participate in hydrogen isotope exchange reactions (Scheme 51).[87-89]

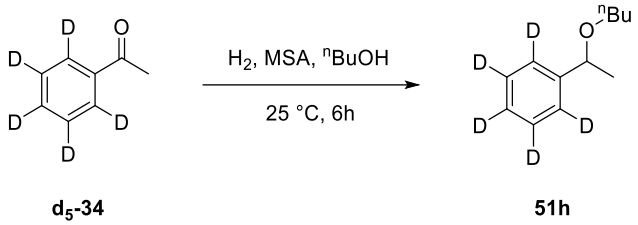


Scheme 51: Deuteration of acetophenone reported by Sajiki utilising Pt/C in the presence of an alcohol and D_2O.

Although the reaction conditions for this Pt/C catalysed HIE are different, some parallels can be observed to the reductive etherification. Both reactions feature acetophenone in the presence of an alcohol, Pt/C and at least one exchangeable deuterium source. The HIE reaction is performed at higher temperatures (80 °C vs 20 °C), however, the reductive etherification is performed for much longer reaction times (6 h vs 3 h). The reductive etherification reaction also contains many more exchangeable protium/deuterium sources.

It may be the case that the reductive etherification conditions are different enough that the HIE reaction becomes unfavourable. Should this not be the case and the reductive etherification could still favour the HIE process, this may account for some of the hydrogen incorporation within the fully deuterated reaction manifold. Any HIE from the aromatic hydrogen atoms would not only result in H/D scrambling throughout carbons of interest within the labelling studies but would also mean that the integration of peaks within the NMR spectra would no longer be accurate. As the aromatic peaks were the only consistent proton signals within the labelling studies, NMR samples were run in DCM-d_2, integration of the aromatic signals was set to 5H and integrals of the ether and α signals were calculated in comparison. Should there be any incorporation of deuterium within these aromatic protons, any calculated incorporations at the ether or α positions would be inaccurate.

To confirm whether aromatic HIE was occurring under the optimised reductive etherification conditions, d_5-acetophenone was subjected to the reaction. As the only source of deuterium within the reaction would be those present on the aromatic ring of acetophenone, any signals in the aromatic region of the ^{1}H NMR spectrum after the reaction was complete would suggest a Pt catalysed aromatic HIE reaction.

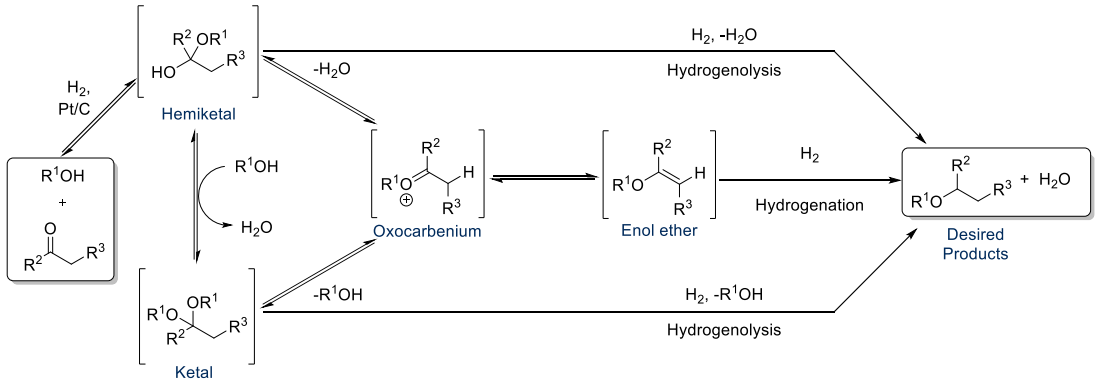


d_5-34 **51h**

Scheme 52: Reductive etherification reaction of d5-acetophenone to probe aromatic HIE.

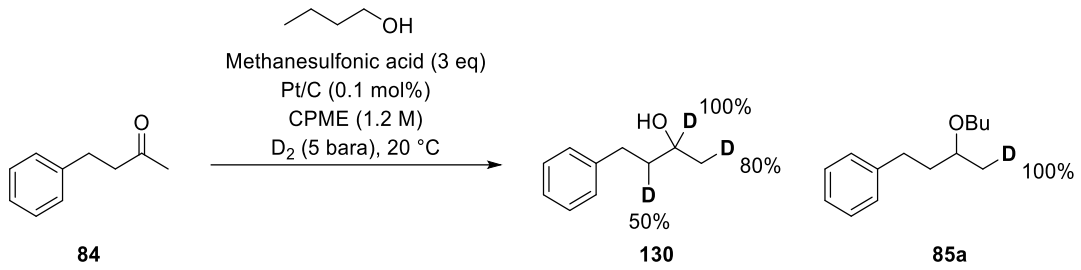
Upon subjection of d_5-acetophenone to the reaction conditions for 6 hours (Scheme 52), no aromatic signals were present within the product ether's ^{1}H NMR spectrum. This confirms that no aromatic HIE was taking place under the optimised reaction manifold, and the previously observed deuteration patterns were accurately integrated.

With no aromatic HIE observable under the optimised reaction conditions, the outcome of these deuteration studies, and subsequent comparison of ^{1}H NMR signals to the aromatic signals within the spectra, were shown to be valid. Although these deuteration studies were thorough and investigated each reaction component individually, the role of these within the reaction could not be determined in isolation. Due to the nature of the developed reductive etherification reaction, numerous exchangeable protium/deuterium sources were present, and in our hands, no deuterated product could be attributed to any single source of deuterium.



Scheme 53: Proposed mechanism for the reductive etherification containing all possible reaction intermediates.

In the end, the results of this extensive deuterium labelling study did not provide any labelling patterns to suggest the mechanisms suggested by Fujii *et al.*[54] The hydrogenolysis pathways proposed within the previous literature (Scheme 53) would result in no deuterium incorporation at the β carbon and, as such, are unlikely to be occurring under the optimised reaction manifold. Some evidence to disprove the enol ether pathway could be deduced through the deuterium incorporation observed within the products from the reaction of 4-phenylbutan-2-one (Scheme 54). The ether product of this reaction deuterated exclusively at the β-methyl position however, the carbonyl reduction product showed deuterium incorporation both sides of the alcohol product. It could be argued that strong evidence for the reduction of an enol intermediate while no evidence for the reduction of an enol ether could suggest that hydrogenation of an enol ether is not likely to be occurring within this reaction mixture. This being said however, the enol ether reduction pathway is the only proposed mechanism resulting in labelling of the β carbon and therefore may still be contributing to this, as yet unproven, reaction mechanism.



Scheme 54: Deuterium labelling pattern of the direction reduction side product from the reductive etherification of 4-phenylbutan-2-one.

The results outlined within these deuterium studies are no doubt of interest mechanistically but also synthetically. The deuterium incorporation observed exclusively at the β position of the ether is not something currently possible through such a simple hydrogenation process. A highly selective deuterium labelling process, providing β-deuterated ethers with a very high incorporation is no doubt useful. As these deuterium atoms are not thought to be reactive, this labelling reaction may be of interest to members of the radiochemistry community.

1.5 Conclusions

The optimisation of the reductive etherification reaction outlined in this report have resulted in a process which is more applicable with regards to safety, environmental impact and availability of catalyst. This improvement, although directed towards large scale synthesis, is now more favourable for performance on multiple scales within industrial or academic labs. Molecular sieves have been removed from the reaction mixture, eradicating the associated issues with grinding, cleaning and cost of disposal. By replacing chloroform with CPME as the reaction solvent, the environmental impact of the whole process has been reduced, as well as providing an improvement to the overall safety of the reaction, as CPME is not carcinogenic. Reduction of the solvent volumes from 50 V to 10 V has resulted in a significant reduction in the PMI of the reductive etherification reaction. These optimisations represent

significant progress towards developing an environmentally benign, easy and safe catalytic method of synthesising ethers from carbonyl compounds and alcohols.

An acid additive was employed within the reaction mixture to provide favourable conditions in which to form all three possible reaction intermediates (ketal, hemiketal and enol ether). A number of acid additives were trialed for use within the reaction, with 3 equivalents of methanesulfonic acid resulting in an increased product formation in the least amounts of equivalents. Within the acidified media, anhydrous conditions were shown not to be required. This allowed an optimisation from a dry precious metal catalyst to a commercially available wet catalyst paste at a much lower catalyst loading, in addition to the removal of molecular sieves. This was a substantial improvement in the overall safety of the reaction set up without any observed decrease in reaction performance. The studies of the reaction intermediates also allowed identification of an unreported symmetrical ether side product (Figure 48).

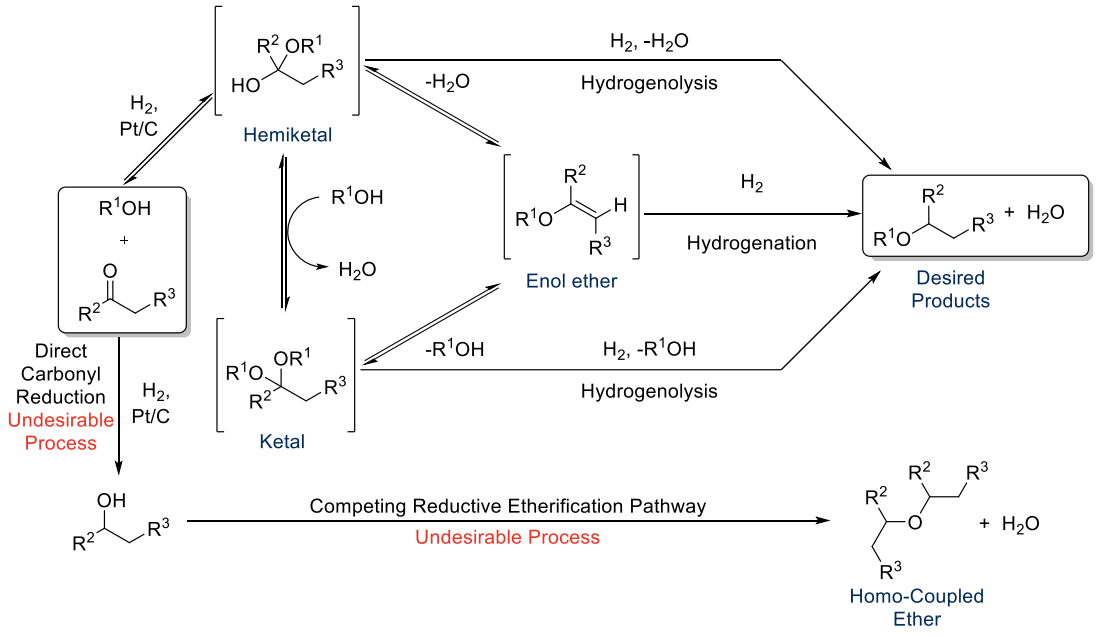


Figure 48: Expanded proposed reaction mechanism of the reductive etherification reaction, including formation of the symmetrical ether product.

CPME was selected as an alternative solvent when used in decreased solvent volumes with lower catalyst loadings. This solvent is a much greener solvent, posing less risk to human health, while also forming a much more favorable, mobile, catalyst suspension in a more concentrated reductive etherification reaction.

Through use of the acid additive, the rate of reaction was shown to be improved over the initially developed conditions through quantitative real-time analysis of solution yields. This time course data was able to be collected through improved catalyst wetting within the reaction mixture.

Potentially hazardous dry precious metal catalysts have also been optimised towards their safer, wet paste counterparts. This reduces the issues relating to the pyrophoricity of dry precious metal catalysts, improving the safety of the overall process. This makes weighing and dispensing more favorable, especially when working on a large scale. Through this extensive reproducibility screening of the precious metal catalysts on a number of different scales, JM B501018-5 was chosen as the most appropriate catalyst for the reductive etherification reaction.

Through design of experiment analysis of the reaction parameters, relative quantities of the reaction components were optimized. The acid additive was shown to be the most statistically significant factor within the analysis, with the maximum equivalents studied providing a higher product yield. Solvent volumes were also deemed to be a factor of statistical significance with lower solvent volumes giving better reaction yields. At the lower temperature range, temperature, catalyst loading and alcohol equivalents were shown to have little to no effect on the outcome of the reductive etherification reaction. This resulted

in optimal conditions of: 1 equivalent of *n*-butanol, 3 equivalents of methanesulfonic acid, 0.1 mol% of Pt/C catalyst, 20 °C and 5 solvent volumes of CPME.

Through this in depth analysis of the reaction and optimization of the reaction parameters, improvement of the reductive etherification was demonstrated on a 45 mmol scale and followed by a quantitative time course. This time course not only confirmed the rate increase from 8 hours to 30 minutes but showed an increased solution yield from 62% to 85%.

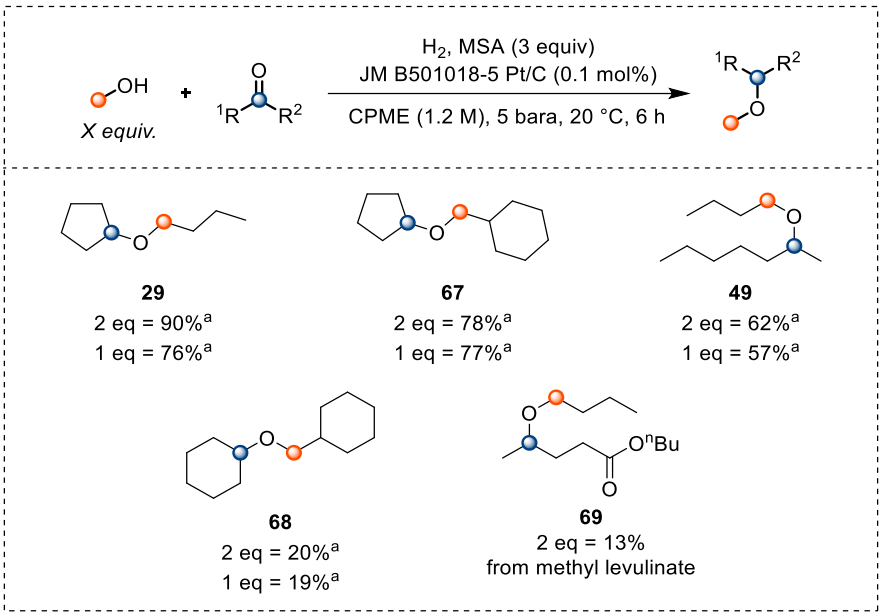


Figure 49: Saturated substrate scope of the developed reductive etherification reaction. Yields are reported as an average of two runs. [a]Denotes solution yield measured against an internal standard of tridecane. [b]Denotes yields for reactions performed once.

As a result of this optimisation, a demonstration of the reaction manifold was performed on saturated substrates (Figure 49). Cyclopentanone was shown to be an ideal substrate for this reaction, resulting in high etherification yields with *n*-butanol and cyclohexylmethanol at 1 and 2 equivalents. Due to changes within the ring system, cyclohexanone was shown to perform poorly under the optimised reaction conditions. A move to linear carbonyl

substrates such as heptan-2-one and methyl levulinate also showed reduced yields. The linear nature of these carbonyl sites makes them more sterically accessible, allowing direct carbonyl reduction to become a more substantial side reaction. In the case of heptan-2-one, this resulted in a 50:50 mixture of the desired ether product and heptan-2-ol, confirmed by quantitative time course study.

A number of aromatic substrates performed well under the optimized reaction conditions, showing a vast improvement upon the current literature precedent for reductive etherification reactions (Figure 50). It is also of note that use of 4-phenylbutan-2-one as the carbonyl component did not result in reduction of the aromatic ring to the corresponding cyclohexane as reported by Gooßen *et al*.[64] Under the optimised conditions, acetophenone and its derivatives formed ethers in good to excellent yields. These derivatives showed a tolerance for a number of functional groups including and aryl chloride, amide and pivalate. Compatibility of this functionality to these reaction conditions was particularly exciting as these groups are very useful functional handles for subsequent chemical reactions.

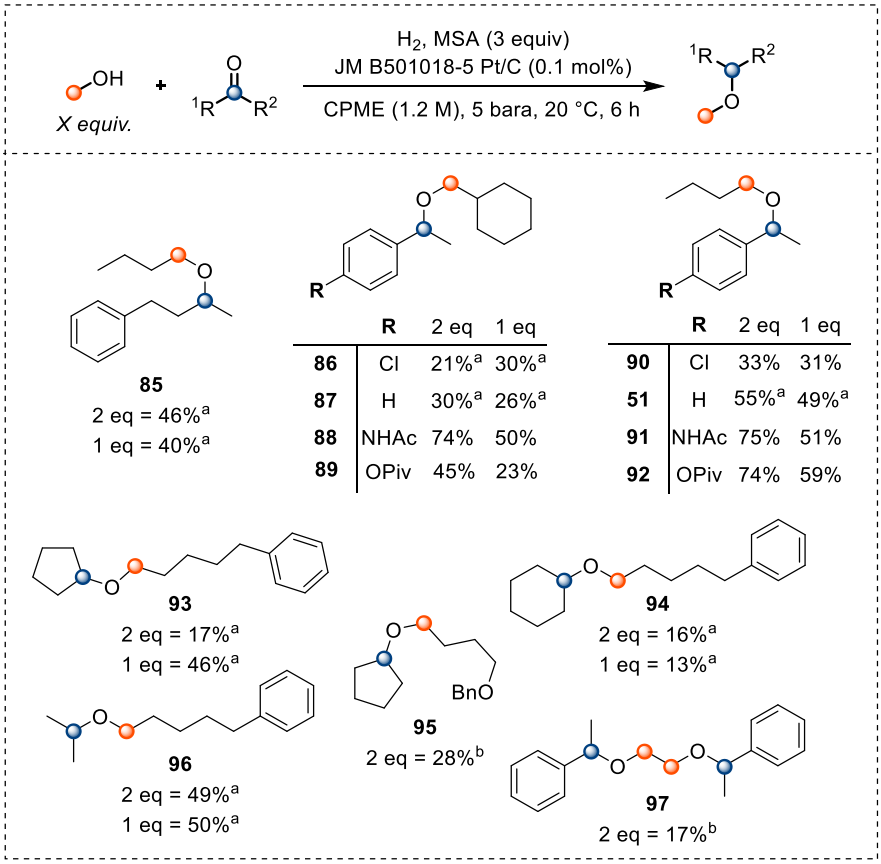


Figure 50: Aromatic substrate scope of the developed reductive etherification reaction. Yields are reported as an average of two runs. [a]Denotes solution yield measured against an internal standard of tridecane. [b]Denotes yields for reactions performed once.

Formation of ethers from acetophenone and its analogues and the subsequent stability of these ethers to the reaction conditions observed within QTC studies was very encouraging. As these ethers are essentially benzylic in nature, some incompatibility to the reaction conditions was anticipated. A benzyl ether protecting group was also demonstrated for use within the reductive etherification reaction, forming an ether with cyclopentanone in 28% yield.

A number of substrates were demonstrated to be unsuitable for use within this reductive etherification reaction including, heteroaromatic substrates, significantly electron rich

aromatic substrates, substrates containing esters or basic nitrogen centres, as well as carbonyl substrates unable to form the enol ether intermediate (Figure 51). This may be something which can be achieved in collaboration with the Kerr group by development of a milder etherification method, utilising a homogeneous iridium catalyst.

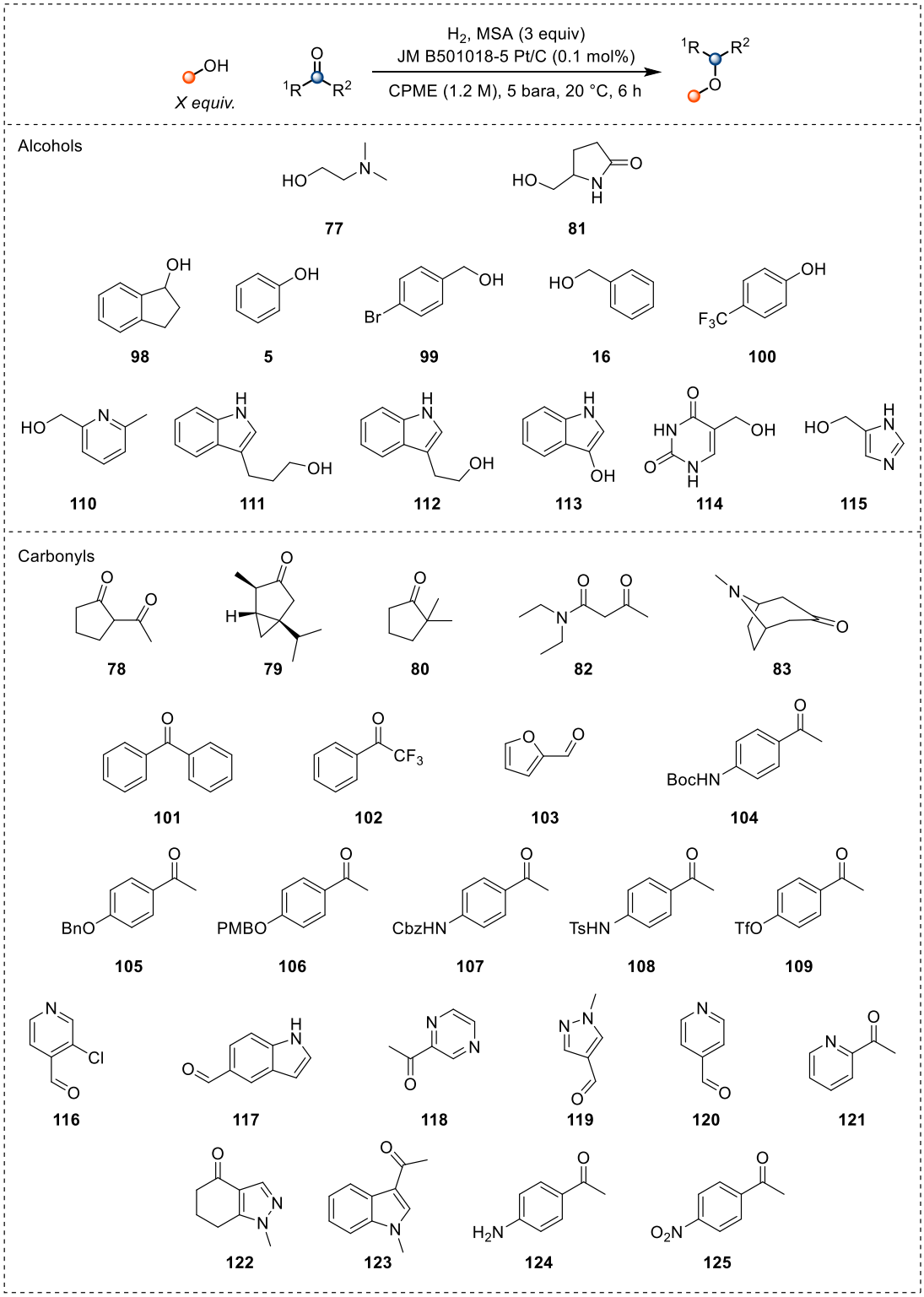
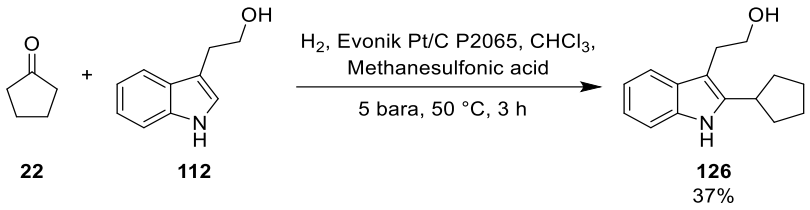


Figure 51: Unsuccessful substrates within the optimised reductive etherification reaction.

One aromatic substrate which yielded a rather surprising product when subjected to the reductive etherification conditions was that of 3-(2-hydroxyethyl)indole (Scheme 55). This is a very interesting reaction to observe with a heterogeneous catalyst as catalysts commonly used for C2 indole functionalisation are homogeneous.[90] This results suggests that a mechanism of formation of the C2 functionalised product is not one previously reported and could benefit from further exploration. This may be an interesting reaction to investigate with regards to the requirement of this reaction regarding catalyst, acid and/or hydrogen as well as structural features of the substrate.



22 **112** **126**
37%

Scheme 55: C2 functionalised indole product isolated from the attempted reductive etherification reaction of cyclopentanone and 3-(2-hydroxyethyl)indole.

Ether substitution reactions of *N*-(4-(1-alkoxyethyl)phenyl)acetamide derivatives were demonstrated when acetate solvents were utilised within the filtration and solvent separation. This substitution reaction was not only verified with ethyl acetate but also *iso*-propyl acetate to form the corresponding ethyl and *iso*-propyl ethers. Although this was only observed with ethers derived from 4'-acetamidoacetophenone, it can be concluded that acetate solvents are not compatible with any stages of the reductive etherification reaction unless the substituted products are desired.

Although the precise mechanism of the reductive etherification was not able to be probed through deuterium labelling studies, a very thorough investigation was performed. All possible proton sources within the molecules of interest were replaced with their deuterated

counterparts and products were analysed by ^{1}H NMR to determine any deuterium incorporation. The number of exchangeable protons within the reaction conditions proved to be too high to successively follow the sources and destinations of the deuterium atoms. Additional studies were performed to assess the possibilities of HIE occurring at aromatic sites within the model substrate but no evidence for this was observed and the results reported here were validated.

1.6 Future Work

Although it is an advancement upon current literature, the substrate tolerance of the optimized reductive etherification reaction has been shown to be incompatible with some substrate classes. By nature of the reaction manifold, some functionality is incompatible to the optimized conditions. With the reaction being performed analogously to a hydrogenation, any substrates containing reducible functional groups such as alkenes or nitriles will not be tolerated. With the inclusion of an acid additive, it was demonstrated that substrates with basic nitrogen centers are unproductive with respect to etherification. The acidity of the reaction mixture precipitates the substrate and shuts down the etherification reaction. Carbonyl substrates without α-hydrogens are also unsuitable for the reductive etherification reaction as this does not allow formation of the enol ether, believed to be a key intermediate within the reductive etherification reaction. With this knowledge in hand, other substrates may be selected or designed to expand the scope of the reaction. This may successfully allow some aldehyde substrates to be utilized within this methodology.

Through the mechanistic deuterium labelling studies conducted in section 1.4.23, clues towards the actual mechanism were obtained. This unexpected labelling may suggest a different mechanism of operation or may merely be a curious artifact of enol ether hydrogenation. If a new mechanism is in effect, one possible hypothesis would be involving

platinum nanoparticles. Leaching of the precious metals from the catalyst into solution has previously been observed in section 1.4.11 in relation to a vanadium doped catalyst. This vanadium leaching was obvious as it produced a vibrant green aqueous layer within the reaction mixture however, platinum may be much harder to distinguish. Residual metal analysis of the reaction mixture could give insight into the amount of leached platinum within the reaction mixture and may or may not discount this reaction pathway.

The transetherification reaction observed upon work up of acetanilide ethers with acetate solvents may be interesting to explore. It is as yet unknown if this transetherification is substrate specific to ethers derived from 4'-acetamidoacetophenone and this must first be determined. The acetate solvent screening performed for the reaction solvent will be repeated for use as the work up solvent. This may provide some accessibility to more hindered products such as menthyl, *iso*-amyl or *tert*-butyl ethers which are not within scope of this methodology.

Additional investigation should be performed into the side reaction observed when tryptophol was employed as the alcohol coupling partner in the reductive etherification reaction. Subjection of tryptophol and cyclopentanone to the reaction conditions resulted in incorporation of the cyclopentyl ring at the C2 position of the indole ring in a 37% yield. This reaction was also shown to produce a comparable yield when heptan-2-one and tryptophol were subjected to the same reaction conditions.

The mechanism for this C2 functionalisation is thought to be similar to that proposed by Scheidt with the additional elimination and hydrogenation steps.[86] Additional investigation should be performed to confirm this. More specifically, Scheidt proposes attack of the oxocarbenium intermediate directly from the C2 position of the indole ring. Although this is not impossible, it is thought to be highly unlikely as indoles are known to react preferentially

through the C3 position of the ring system.[91] It is proposed that nucleophilic attack occurs through the C3 position of the indole ring followed by a bond migration to C2 (Figure 52).

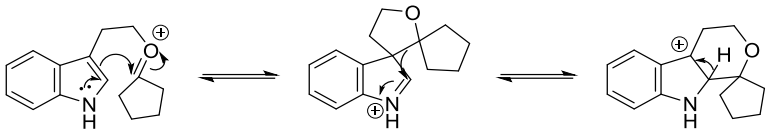


Figure 52: Hypothesised mechanismfor the formation of the C2 functionalised indole product within the reductive etherification reaction.

This could be investigated through varying the ether ring size resulting from the carbon chain length between the indole and alcohol. Depending on whether a 1, 2 or 3 carbon chain in present between the indole and alcohol group, the spirocyclic intermediate will either contain a 4, 5 or 6 membered ring respectively (Figure 53). If followed through a QTC, the formation of this intermediate may be observable. It is known that the formation of 5 membered rings is faster than 6 membered which is itself faster than 4 membered ring formation.[92] Should the intermediates be observed at different rates within the reaction mixtures, it may be evidence for the reaction at the C3 position.

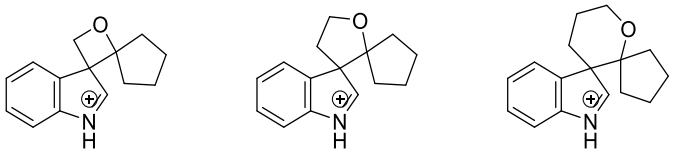
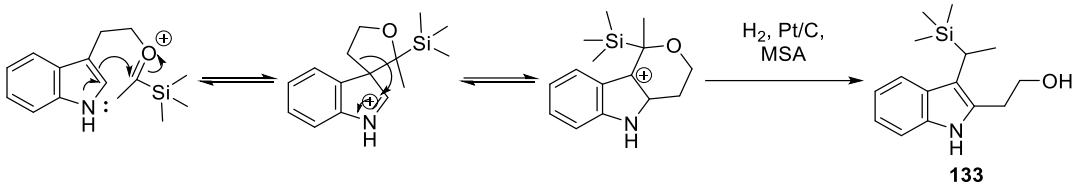


Figure 53: Proposed spirocyclic intermediates resulting from use of 1, 2 and 3 carbon chain lengths within the C2 indole functionalisation reaction.

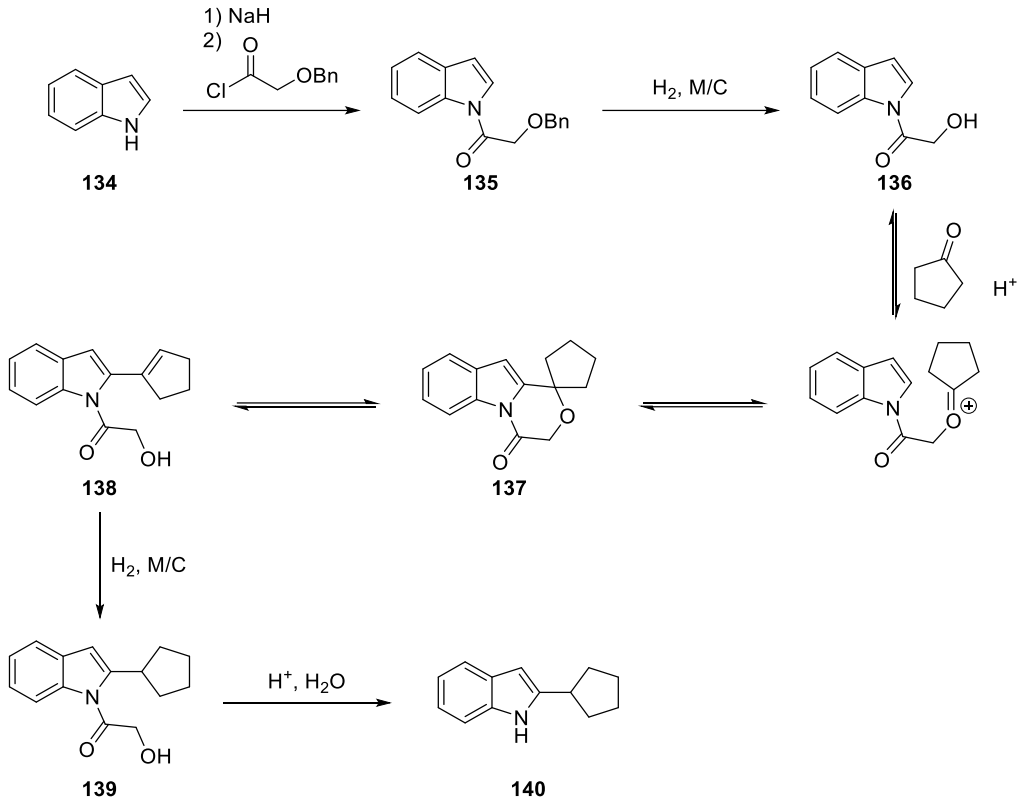
Another way in which this mechanism could be elucidated would be through altering the migratory aptitude of the substituents present at the C3 position within the reactive intermediate. If the group originating from the carbonyl starting material is better at stabilizing a positive charge at the 3 position, then this would result in migration of

the -C_2H_4OH group instead (Scheme 56). A functional group that may be suited for this investigation would be one containing a Si atom. Silicon is known to stabilize formation of a positive charge β to its position within the molecule.[93] This would result in a lower migratory aptitude within the proposed intermediate and possible migration of the -C_2H_4OH group.



Scheme 56: Proposed mechanism for the C2 functionalisation of 3-(2-hydroxyethyl)indole with acetyltrimethylsilane.

With determination of the mechanism for this transformation performed, optimization of the reaction conditions could be attempted. The reaction could be analysed through design of experiment to identify the key parameters within the reaction. This optimization would be followed by a small substrate scope, easily performed through variation of the carbonyl component.



Scheme 57: Proposed C2 functionalisation reaction of indole using a removable directing group. M/C is Pd/C or Pt/C catalyst.

Should the pendant alcohol directing group be required for the C2 functionalisation reaction, use of a removable directing group may be possible (Scheme 57). As the pendant alcohol is attached to tryptaphol via a C-C bond, removal of this after the reaction would be difficult and the product would most likely have to include this moiety. Should the *N* centre be used to attach a pendant alcohol through an amide bond, this would in theory be much easier to remove after the C2 functionalisation. This would allow incorporation of the directing group, C2 functionalisation and subsequent removal of the directing group to essentially perform a traceless C2 indole functionalisation.

1.7 Experimental

All reagents were obtained from commercial suppliers (ABCR, Aldrich, Alfa Aesar, BASF, Sigma Aldrich, Merck, Evonik or Johnson Matthey) and used without further purification.

GC samples of filtered reaction mixtures were diluted in methanol (10 µL/mL) and analysed on the Agilent 7890 system using a DB5-HT (LTM) column (15.0 m x 250 µm, 0.10 µm film). Samples were injected at 275 °C and detected using a flame ionisation detector. Chromatograms were analysed by ChromView software.

Liquid chromatography (LC) analysis was conducted on an Acquity UPLC CSH C18 column (50 mm x 2.1 mm internal diameter, 1.7 µm packing diameter) at 40 °C using a 0.3 µL injection volume.

The solvents employed were: A = 10 mM ammonium bicarbonate in water adjusted to pH 10 with ammonia solution. B = Acetonitrile.

The gradient employed was:

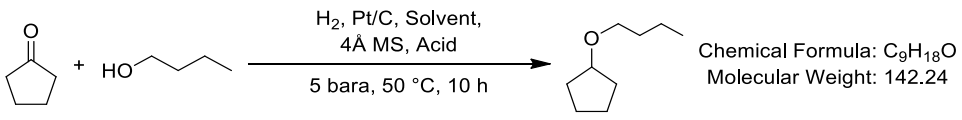
Time (min)	Flow Rate (mL min^{-1})	%A	%B
0.00	1	97	3
0.05	1	97	3
1.50	1	5	95
1.90	1	5	95
2.00	1	97	3

UV detection was a summed signal from a wavelength of 210 nm to 350 nm. Mass spectra were recorded on a Waters ZQ mass spectrometer using alternate-scan positive and negative electrospray ionisation (ES+ and ES–) with a scan range of 100 to 1000 amu, scan time of 0.27 s and an inter-scan delay of 0.10 s.

HRMS data was acquired through Waters Atmospheric Solids Analysis Probe in combined Electrospray/APcI mode (ESCi®). Masses were then analysed by Thermo Xcalibur QualBrowser software. All measured masses were determined to be within 5 ppm of the calculated mass.

NMR spectra were recorded using a Bruker AV-400 spectrometer (^{1}H = 400 MHz, ^{13}C = 101 MHz). Chemical shifts (δ) are reported in parts per million (ppm) relative to $CDCl_3$, d_2-DCM or DMSO-d_6. Coupling constants are reported in Hz and refer to $^{3}J_{HH}$ interactions unless stated otherwise. The following abbreviations are used for multiplicities: s = singlet; br. = broad signal; d = doublet; t = triplet; q = quartet; quin = quintet; spt = septet; m = multiplet. If not specifically stated, the NMR experiments were acquired at 30 °C and ^{13}C was run in [^{1}H]-decoupled mode.

1.7.1 General Procedure 1 for Use of the CAT96 High Pressure Reactor



Catalyst (3.75 µmol metal content), cyclopentanone (11 µL, 0.125 mmol), *n*-butanol (23 µL, 0.250 mmol), solvent (0.5 mL), acid (as stated in the reaction database) and 4 Å molecular sieves (0 or 60 mg) were added to HPLC vials along with a 3 x 8 mm magnetic stirrer bar, as stated in the reaction database. The reaction vials were sealed, the septa were pierced with

a blunt needle seven times and the vials were transferred to the sample plate in the CAT96 reactor, which was sealed and purged with N_2 (three times at 4 bara) followed by H_2 (twice at 5 bara). The reactions were stirred at 50 °C under 5 bara of hydrogen for 10 hours before the reactor was cooled, vented and reaction mixtures were sampled for GC analysis (10 µL in 0.5 mL methanol within a Whatman Uniprep syringeless filter vial).

GC (DB5-HT column, hydrogen carrier gas): RT = 0.570 – 0.625 (cyclopentanone/ol), 0.896 (1,1-dimethoxycyclopentane), 1.196 (cyclopentyl butyl ether), 1.538 (dicyclopentyl ether), 1.881 (tridecane)

1.7.2 General Procedure 2 for Use of the ChemSCAN II High Pressure Reactor

Pt catalyst (0.03 mmol Pt content), ketone (1 mmol), alcohol (2 mmol), 4 Å molecular sieves (0 or 500 mg) and solvent (4 mL) were added to each of the HEL ChemSCAN II 16 mL Hastelloy reactors. The reactors were sealed and purged with N_2 (three times at 4 bara) followed by H_2 (twice at 5 bara). The reaction mixtures were heated to T °C, pressurised to P bara and stirred at 1000 rpm for t hours before the reactors were cooled, vented, purged with N_2 (three times at 4 bara) and sampled for GC analysis (10 µL in 1 mL methanol).

GC (DB5-HT column, hydrogen carrier gas): RT = 0.570 – 0.625 (cyclopentanone/ol), 0.896 (1,1-dimethoxycyclopentane), 1.196 (cyclopentyl butyl ether), 1.538 (dicyclopentyl ether), 1.881 (tridecane)

1.7.3 General Procedure 3 for Use of the ChemSCAN II High Pressure Reactor

JM B501018-5 Pt/C catalyst (30 mg, 3.80 µmol), ketone (3.8 mmol), alcohol (3.8 or 7.6 mmol), methanesulfonic acid (0.74 mL, 11.4 mmol) and CPME (3.2 mL) were added to each of the HEL ChemSCAN II 16 mL Hastelloy reactors. The reactors were sealed and purged with N_2 (three times at 4 bara) followed by H_2 (twice at 5 bara). The reaction mixtures were heated to 25 °C, pressurised to 5 bara and stirred at 1000 rpm for 6 hours before the reactors were cooled, vented, purged with N_2 (three times at 4 bara) and sampled for GC or LCMS analysis (10 µL in 1 mL methanol).

1.7.4 General Procedure 4 for Calculation of Solution Yield

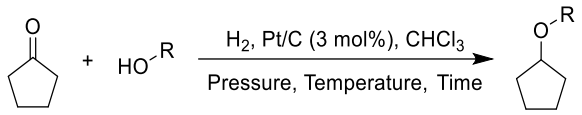
All solution yields were calculated against an internal standard of tridecane using response factor calculated by the following equation:

$$\mathrm{K_X} = \frac{\mathrm{Peak\ Area_{ISTD}} \times \mathrm{Weight_X}}{\mathrm{Peak\ Area_X} \times \mathrm{Weight_{ISTD}}}$$

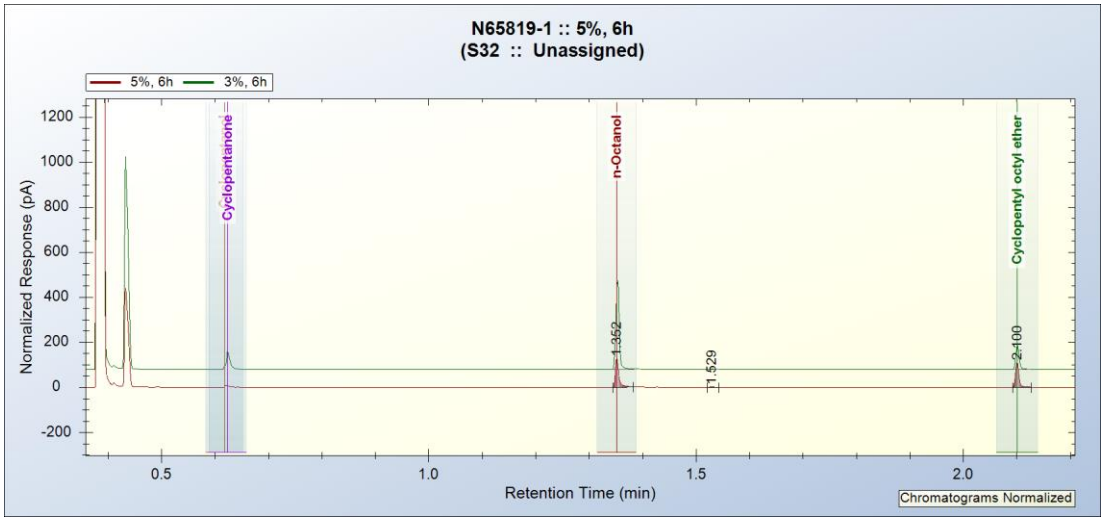
Reference samples were made of a known weight and purity of the compound of interest and a known weight of tridecane diluted in methanol within a volumetric flask. Three samples of this solution were then analysed by GC and average peak areas were recorded. Response factors (K_X) were then calculated. The K_X value then allowed weights of the reaction components of interest within the study to be calculated against a known amount of tridecane internal standard added to each reaction using this equation:

$$Weight_X = K_X \times Weight_{ISTD} \times \frac{Peak\ Area_X}{Peak\ Area_{ISTD}}$$

1.7.5 Investigation of Gooβen Conditions



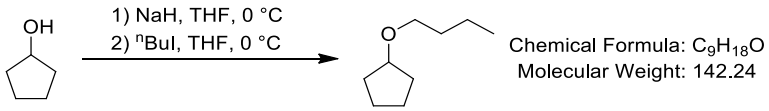
1. Reaction was performed as stated in General Procedure 2. Pt/C = Evonik Noblyst P2053 5% Pt (0.117 g) or Evonik Noblyst P2085 3% Pt (0.195 g), ketone = cyclopentanone (0.088 mL), alcohol = *n*-octanol (0.315 mL), solvent = chloroform, P = 1, T = 50, t = 6



3% catalyst showed a greater degree of direct carbonyl reduction resulting in more cyclopentanol observed within GC trace. 5% catalyst was taken for further use.

2. Reaction was performed as stated in General Procedure 2. Pt/C = Evonik Noblyst P2053 5% Pt (0.117 g), ketone = cyclopentanone (0.088 mL), alcohol = *n*-octanol (0.315 mL), solvent = chloroform, P = 2, T = 50, t = 6
3. Reaction was performed as stated in General Procedure 2. Pt/C = Evonik Noblyst P2053 5% Pt (0.117 g), ketone = cyclopentanone (0.088 mL), alcohol = *n*-butanol (0.183 mL), solvent = chloroform P = 2, T = 50, t = 10

1.7.6 Williamson Ether Synthesis of Cyclopentyl Butyl Ether (29)



To a 50 mL round bottomed flask at 0 °C was added sodium hydride (400 mg, 10 mmol) and tetrahydrofuran (10 mL). To this mixture, cyclopentanol (0.908 mL, 10 mmol) was added dropwise and the resulting slurry was stirred at room temperature for 1 h. The reaction mixture was cooled to 0 °C and a solution of 1-iodobutane (1.1 mL, 10 mmol) in tetrahydrofuran (5 mL) was added dropwise. The resulting reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was cooled in an ice bath, diluted with EtOAc (10 mL) and quenched with water (10 mL). The phases were separated and the combined organic phase was washed with water (10 mL) a further two times before being dried over $MgSO_4$ and concentrated on a rotary evaporator (200 mbar at 40 °C). The residue was purified by flash column chromatography, Biotage Isolera (KP-Sil, 10 g), (0 - 10% EtOAc : Hexane) before evaporation of chromatography solvent at 40 °C under a reduced pressure of 200 mbar to yield cyclopentyl butyl ether (52 mg, 0.366 mmol, 4% yield) as a colourless oil. Distillate from rotary evaporation was shown to contain product ether and butanol.

Cyclopentyl Butyl Ether (29)[94]

This data was concurrent with the impure sample synthesised here however, was measured from distillation of a large scale time course reaction mixture in section 1.7.11.

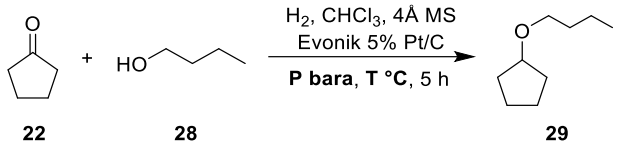
^{1}H NMR (400 MHz, $CDCl_3$), δ = 3.92 - 3.82 (m, 1H, *H*C-O), 3.38 (t, *J* = 6.7, 2H, O-C*H*$_2$), 1.78 – 1.47 (m, 10H, 5 x C*H*$_2$), 1.45 – 1.31 (m, 2H, C*H*$_2$), 0.92 (t, *J* = 7.4, 3H, C*H*$_3$)

^{13}C NMR (101 MHz, $CDCl_3$), δ = 81.2, 68.6, 32.3, 32.2, 23.5, 19.5, 13.9.

ν_{max}/cm^{-1}: 2957, 2933, 2870, 1465, 1347, 1181, 1092, 1043, 983.

1.7.7 Investigation of Pressure

Results and discussion section 1.4.2 page 34.



22 **28** **29**

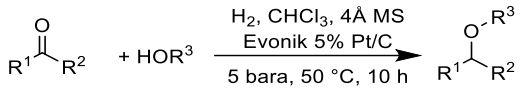
Reaction was performed as stated in General Procedure 2. Pt/C = Evonik Noblyst P2053 5% Pt (0.117 g), ketone = cyclopentanone (0.088 mL), alcohol = *n*-butanol (0.183 mL), solvent = chloroform

1. P = 2, T = 50, t = 5
2. P = 3, T = 50, t = 5
3. P = 5, T = 50, t = 5
4. P = 2, T = 40, t = 5
5. P = 3, T = 40, t = 5
6. P = 4, T = 40, t = 5
7. P = 5, T = 40, t = 5

Reactions at 50 °C were shown to produce more product than comparable reaction at 40 °C by comparison of GC traces.

Higher pressures also showed a greater conversion of starting materials to products by comparison of cyclopentanol peak comparisons within GC spectra.

1.7.8 Initial Substrate Scope



Reaction was performed as stated in General Procedure 1, containing Evonik, Noblyst P2053 Pt/C (0.015 g) and 4 Å molecular sieves (60 mg) in chloroform. More information can be found in Table 2 page 39.

Reaction	Ketone	Alcohol
1	cyclopentanone (0.011 mL)	methanol (0.010 mL)
2	cyclopentanone (0.011 mL)	ethanol (0.015 mL)
3	cyclopentanone (0.011 mL)	*n*-propanol (0.019 mL)
4	cyclopentanone (0.011 mL)	*n*-butanol (0.023 mL)
5	cyclopentanone (0.011 mL)	cyclopentanol (0.023 mL)
6	cyclopentanone (0.011 mL)	benzyl alcohol (0.026 mL)
7	2-heptanone (0.017 mL)	methanol (0.010 mL)
8	2-heptanone (0.017 mL)	ethanol (0.015 mL)
9	2-heptanone (0.017 mL)	*n*-propanol (0.019 mL)
10	2-heptanone (0.017 mL)	*n*-butanol (0.023 mL)
11	2-heptanone (0.017 mL)	cyclopentanol (0.023 mL)
12	2-heptanone (0.017 mL)	benzyl alcohol (0.026 mL)
13	acetone (0.009 mL)	methanol (0.010 mL)
14	acetone (0.009 mL)	ethanol (0.015 mL)
15	acetone (0.009 mL)	*n*-propanol (0.019 mL)
16	acetone (0.009 mL)	*n*-butanol (0.023 mL)
17	acetone (0.009 mL)	cyclopentanol (0.023 mL)
18	acetone (0.009 mL)	benzyl alcohol (0.026 mL)
19	acetophenone (0.015 mL)	methanol (0.010 mL)
20	acetophenone (0.015 mL)	ethanol (0.015 mL)
21	acetophenone (0.015 mL)	*n*-propanol (0.019 mL)

22	acetophenone (0.015 mL)	*n*-butanol (0.023 mL)
23	acetophenone (0.015 mL)	cyclopentanol (0.023 mL)
24	acetophenone (0.015 mL)	benzyl alcohol (0.026 mL)

Table 6: Reaction database detailing conditions used for RXN-16.

Product formation was indicated by comparison of GC traces for reactions featuring the same carbonyl substrates. Larger products were signalled by migration of peaks to larger retention times.

CPME was referenced to a known sample.

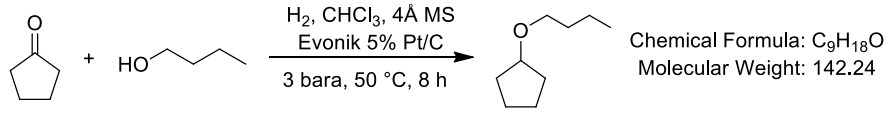
Ethers formed from acetone with methanol or ethanol are assumed to have a retention time similar to that of the solvent front within the GC spectra. Their formation is thought to occur as all other non-aromatic carbonyl and alcohol substrates showed signs of product formation.

GC trace overlays can be found in Results and Discussion section 1.4.3, page 37.

Reactions featuring benzyl alcohol and acetophenone showed no signs of product formation and reduction of benzyl alcohol to methylcyclohexane could be observed by comparison of GC retention times.

1.7.9 Neutral Large Scale Reaction

Results and discussion, section 1.4.4, page 42.



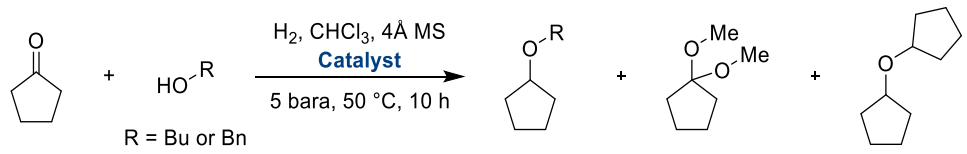
Evonik Noblyst P2053 5% Pt/C (0.375 mmol, 1.463 g), cyclopentanone (1.1 mL, 12.50 mmol), *n*-butanol (2.3 mL, 25 mmol), chloroform (50 mL) and 4 Å activated molecular sieves (6.25 g) were added to the 100 mL EasyMax high pressure Hastelloy reactor. The reactor was sealed

and purged with N_2 (three times at 4 bara) followed by H_2 (twice at 5 bara). The mixture was stirred at 1000 rpm under a constant H_2 pressure of 3 bara at 50 °C for 5 hours and GC samples were taken periodically by Mettler Toledo EasySampler (20 µL with 80 fold dilution in methanol). The reactor was cooled, vented and purged with nitrogen before a GC sample was taken (10 µL in 1 mL methanol).

In initial GC samples, a reaction intermediate was observed. This was referenced to a known sample of 1,1-dimethoxycyclopentane.

1.7.10 Heterogeneous Catalyst Screen

Results and Discussion, section 1.4.5, page 45.



Reaction was performed as stated in General Procedure 1, containing 4 Å molecular sieves (60 mg), cyclopentanone (0.011 mL) and *n*-butanol (0.023 mL) or benzyl alcohol (0.026 mL) in chloroform. 48 catalysts of varying metal identity, support and percentage metal content were evaluated at 3 mol% relative to cyclopentanone.

Visualisations of this data can be found in Figure 11, page 46 and Figure 12, page 47.

Reaction	Ketone	Alcohol	Cat.	Support	Type
1	cyclopentanone	*n*-butanol	Pt	Graphite	5R289 Dry
2	cyclopentanone	benzyl alcohol	Pt	Graphite	5R289 Dry
3	cyclopentanone	*n*-butanol	Pt	Carbon	5R103 wet
4	cyclopentanone	benzyl alcohol	Pt	Carbon	5R103 wet
5	cyclopentanone	*n*-butanol	Pt	Carbon	5R128M Wet

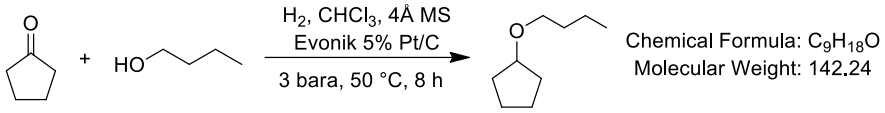
6	cyclopentanone	benzyl alcohol	Pt	Carbon	5R128M Wet
7	cyclopentanone	*n*-butanol	Pt/Sn	Alumina	110001.APO.Sn
8	cyclopentanone	benzyl alcohol	Pt/Sn	Alumina	110001.APO.Sn
9	cyclopentanone	*n*-butanol	Pt/Re	Titania	110008.TiOPtRe
10	cyclopentanone	benzyl alcohol	Pt/Re	Titania	110008.TiOPtRe
11	cyclopentanone	*n*-butanol	Pd	Carbon	5R338M wet
12	cyclopentanone	benzyl alcohol	Pd	Carbon	5R338M wet
13	cyclopentanone	*n*-butanol	Pd	Carbon	5R37 dry
14	cyclopentanone	benzyl alcohol	Pd	Carbon	5R37 dry
15	cyclopentanone	*n*-butanol	Pd	Carbon	5R374 dry
16	cyclopentanone	benzyl alcohol	Pd	Carbon	5R374 dry
17	cyclopentanone	*n*-butanol	Pd	Carbon	5R338M dry
18	cyclopentanone	benzyl alcohol	Pd	Carbon	5R338M dry
19	cyclopentanone	*n*-butanol	Pd	Carbon	5R58 dry
20	cyclopentanone	benzyl alcohol	Pd	Carbon	5R58 dry
21	cyclopentanone	*n*-butanol	Pd	Carbon	5R487 dry
22	cyclopentanone	benzyl alcohol	Pd	Carbon	5R487 dry
23	cyclopentanone	*n*-butanol	Pd	Carbon	10307
24	cyclopentanone	benzyl alcohol	Pd	Carbon	10307
25	cyclopentanone	*n*-butanol	Pd	Carbon	10R87L dry
26	cyclopentanone	benzyl alcohol	Pd	Carbon	10R87L dry
27	cyclopentanone	*n*-butanol	Pd	Carbon	10R394 dry
28	cyclopentanone	benzyl alcohol	Pd	Carbon	10R394 dry
29	cyclopentanone	*n*-butanol	Pd	Carbon	10R87L wet
30	cyclopentanone	benzyl alcohol	Pd	Carbon	10R87L wet
31	cyclopentanone	*n*-butanol	Pd	Alumina	A302099-5
32	cyclopentanone	benzyl alcohol	Pd	Alumina	A302099-5
33	cyclopentanone	*n*-butanol	Pd	Alumina	5R325
34	cyclopentanone	benzyl alcohol	Pd	Alumina	5R325
35	cyclopentanone	*n*-butanol	Pd	Silica Alumina	2R31
36	cyclopentanone	benzyl alcohol	Pd	Silica Alumina	2R31

37	cyclopentanone	*n*-butanol	Pd	Barium Sulfate	5R29A
38	cyclopentanone	benzyl alcohol	Pd	Barium Sulfate	5R29A
39	cyclopentanone	*n*-butanol	Pd(Pb)	Calcium Carbonate	A305050-5
40	cyclopentanone	benzyl alcohol	Pd(Pb)	Calcium Carbonate	A305050-5
41	cyclopentanone	*n*-butanol	Rh	Carbon	5R20A
42	cyclopentanone	benzyl alcohol	Rh	Carbon	5R20A
43	cyclopentanone	*n*-butanol	Rh	Alumina	C301099-5
44	cyclopentanone	benzyl alcohol	Rh	Alumina	C301099-5
45	cyclopentanone	*n*-butanol	Ru	Alumina	D302011-5
46	cyclopentanone	benzyl alcohol	Ru	Alumina	D302011-5
47	cyclopentanone	*n*-butanol	Rh/Ru	Carbon	M06188
48	cyclopentanone	benzyl alcohol	Rh/Ru	Carbon	M06188

Table 7: Reaction database detailing catalysts screened for RXN-18.

1.7.11 Initial Large Scale Quantitative Time Course

Results and discussion, section 1.4.6, page 49.



Evonik Noblyst P2053 5% Pt/C (0.375 mmol, 1.463 g), cyclopentanone (1.1 mL, 12.50 mmol), *n*-butanol (2.3 mL, 25 mmol), tridecane (2.3 mL), chloroform (50 mL) and 4 Å activated molecular sieves (6.25 g) were added to the EasyMax reactor fitted with EasySampler sampling probe. The reactor was sealed and purged with N_2 (three times at 4 bara) followed by H_2 (twice at 5 bara). The mixture was stirred at 1000 rpm under a constant H_2 pressure of 4 bara at 50 °C. Samples were taken periodically over 8 hours (20 µL diluted 80 fold in methanol). The reactor was cooled, vented and purged with nitrogen before GC sample was taken (10 µL in 1 mL methanol). GC solution yields were calculated against the tridecane

internal standard as stated in General Procedure 2 using calculated K_x values stated below. The reaction mixture was filtered through a pad of Celite® and concentrated. The reaction mixture was purified by Biotage Isolera (KP-Sil, 10 g, 0 - 10% EtOAc : Hexane) before product containing fractions were evaporated at 40 °C under a reduced pressure of 200 mbar. The product was obtained as a colourless oil (53 mg, 3%). Distillate from rotary evaporation was shown to contain product ether.

Compound	Average K_x
n-Butanol	1.44
Cyclopentanol	1.22
Cyclopentanone	1.34
1,1-Dimethoxycyclopentane	1.87
Butoxycyclopentane	1.21

^{1}H NMR (400 MHz, $CDCl_3$), δ = 3.92 - 3.82 (m, 1H, *H*C-O), 3.38 (t, *J* = 6.7, 2H, O-C*H*$_2$), 1.78 – 1.47 (m, 10H, 5 x C*H*$_2$), 1.45 – 1.31 (m, 2H, C*H*$_2$), 0.92 (t, *J* = 7.4, 3H, C*H*$_3$)

1.7.12 Catalyst pH Screen

Results and discussion, section 1.4.7, page 52.

Each catalyst (3.75 µmol metal content) and water (0.5 mL) were added to HPLC vials along with a 3 x 8 mm magnetic stirrer bar. The reaction vials were sealed and stirred at room temperature for 6 hours. The pH was tested using Whatman indicator strips.

Visualisation of this data can be found in Figure 13, page 51.

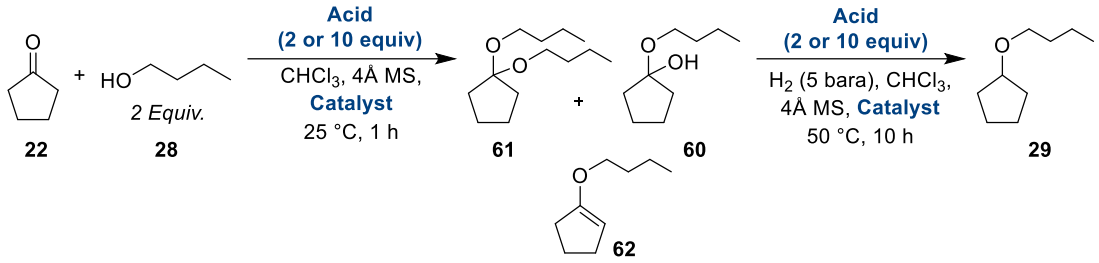
Vial	Metal	Supplier	Metal Content	Support	Catalyst Reference	pH
1	Pt	Evonik	5.000%	carbon	P2053 dry C	10
3	Pt	BASF	5.000%	carbon powder	D/R C 10325	10

4	Pt	JM	4.000%	titania	110001.TPO 1-5	10
5	Pt	JM	1.000%	alumina	110001APR	10
6	Pt	JM	5.000%	graphite	5R289 dry C	7
7	Pt	JM	1.875%	carbon	5R103 wet C	7
8	Pt	JM	2.190%	carbon	128M wet C	10
9	Pt	JM	2.000%	alumina	2% Sn 110001.APO.Sn	10
10	Pt	JM	2.000%	titania	4% Re 110008.TiOPtRe	10
11	Pd	JM	2.130%	carbon	5R338M wet C	10
12	Pd	JM	5.000%	carbon	5R37 dry C	10
13	Pd	JM	5.000%	carbon	5R374 dry C	10
14	Pd	JM	5.000%	carbon	5R338M dry C	10
15	Pd	JM	5.000%	carbon	5R58 dry C	7
16	Pd	JM	5.000%	carbon	5R487 dry C	10
17	Pd	BASF	5.000%	carbon powder	D/R C 10307	10
18	Pd	JM	10.000%	carbon	10R87L dry C	6
19	Pd	JM	10.000%	carbon	10R394 dry C	7
20	Pd	JM	4.330%	carbon	10R87L wet C	10
21	Pd	Alfa Aesar	5.000%	alumina	A302099-5 alumina	9
22	Pd	JM	5.000%	alumina	5R325 alumina	10
23	Pd	JM	2.000%	silica/alumina	2R31 silica/alumina	11
24	Pd	JM	5.000%	barium sulfate	5R29A barium sulfate	10
25	Pd	JM	5.000%	calcium carbonate	A305050-5	10
26	Rh	JM	5.000%	carbon	5R20A dry C	10
27	Rh	Alfa Aesar	5.000%	alumina	C301099-5 alumina	10
28	Ru	Alfa Aesar	5.000%	alumina	D301099-5 alumina	10
29	Rh	JM	2.000%	carbon	M06188 2% Ru dry C	9
30	N/A			4 Å Sieves	4 Å Sieves	12
31	N/A			Biotage Acid Support	ISOLUTE® Si-Propylsulfonic Acid	6
32	N/A			JM Acid Support	QuadraSil™ MP (S)	7

Table 8: Catalyst pH screening and the resulting pH of each catalyst slurry.

1.7.13 Acid Screen

Results and discussion, section 1.4.8, page 54.



Reaction was performed as stated in General Procedure 1, containing 4 Å molecular sieves (60 mg) in chloroform. Relative quantities of intermediate and products were determined by GC area%.

Visualisation of results can be found in Figure 15, page 55 for ketal formation and Figure 16, page 56 for ether formation.

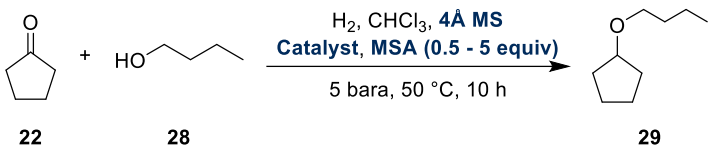
Reaction	Catalyst Reference	Acid
1	Evonik P2053 Pt/C	Acetic acid (0.014 mL)
2	JM 5R289 Pt/C	Acetic acid (0.014 mL)
3	JM 5R128M Pt/C	Acetic acid (0.014 mL)
4	JM 110008TiOPtRe Pt/Re/Titania	Acetic acid (0.014 mL)
5	JM 5R20A Rh/C	Acetic acid (0.014 mL)
6	Evonik P2053 Pt/C	Acetic acid (0.072 mL)
7	JM 5R289 Pt/C	Acetic acid (0.072 mL)
8	JM 5R128M Pt/C	Acetic acid (0.072 mL)
9	JM 110008TiOPtRe Pt/Re/Titania	Acetic acid (0.072 mL)
10	JM 5R20A Rh/C	Acetic acid (0.072 mL)
11	Evonik P2053 Pt/C	Methanesulfonic acid (0.016 mL)
12	JM 5R289 Pt/C	Methanesulfonic acid (0.016 mL)
13	JM 5R128M Pt/C	Methanesulfonic acid (0.016 mL)

14	JM 110008TiOPtRe Pt/Re/Titania	Methanesulfonic acid (0.016 mL)
15	JM 5R20A Rh/C	Methanesulfonic acid (0.016 mL)
16	Evonik P2053 Pt/C	Methanesulfonic acid (0.084 mL)
17	JM 5R289 Pt/C	Methanesulfonic acid (0.084 mL)
18	JM 5R128M Pt/C	Methanesulfonic acid (0.084 mL)
19	JM 110008TiOPtRe Pt/Re/Titania	Methanesulfonic acid (0.084 mL)
20	JM 5R20A Rh/C	Methanesulfonic acid (0.084 mL)
21	Evonik P2053 Pt/C	TFA (0.019 mL)
22	JM 5R289 Pt/C	TFA (0.019 mL)
23	JM 5R128M Pt/C	TFA (0.019 mL)
24	JM 110008TiOPtRe Pt/Re/Titania	TFA (0.019 mL)
25	JM 5R20A Rh/C	TFA (0.019 mL)
26	Evonik P2053 Pt/C	TFA (0.096 mL)
27	JM 5R289 Pt/C	TFA (0.096 mL)
28	JM 5R128M Pt/C	TFA (0.096 mL)
29	JM 110008TiOPtRe Pt/Re/Titania	TFA (0.096 mL)
30	JM 5R20A Rh/C	TFA (0.096 mL)
31	Evonik P2053 Pt/C	Benzoic acid (0.031 g)
32	JM 5R289 Pt/C	Benzoic acid (0.031 g)
33	JM 5R128M Pt/C	Benzoic acid (0.031 g)
34	JM 110008TiOPtRe Pt/Re/Titania	Benzoic acid (0.031 g)
35	JM 5R20A Rh/C	Benzoic acid (0.031 g)
36	Evonik P2053 Pt/C	Benzoic acid (0.153 g)
37	JM 5R289 Pt/C	Benzoic acid (0.153 g)
38	JM 5R128M Pt/C	Benzoic acid (0.153 g)
39	JM 110008TiOPtRe Pt/Re/Titania	Benzoic acid (0.153 g)
40	JM 5R20A Rh/C	Benzoic acid (0.153 g)

Table 9: Reaction database detailing acids screened for RXN-21.

1.7.14 Investigation of Number of Acid Equivalents

Results and discussion, section 1.4.10, page 59.



22 28 29

Reaction was performed as stated in General Procedure 1, containing methanesulfonic acid, tridecane (0.025 mL) and 4 Å activated molecular sieves (0 or 60 mg) in chloroform. Solution yield was calculated against an internal standard of tridecane as stated in General Procedure 4 using K_x values stated in 1.7.11.

Visualisation of these results can be found in Figure 18 on page 60.

Compound	Average K_x
n-Butanol	1.44
Cyclopentanol	1.22
Cyclopentanone	1.34
1,1-Dimethoxycyclopentane	1.87
Butoxycyclopentane	1.21

Reaction	Catalyst Reference	Sieves	MSA Quantity
1	Evonik P2053	60 mg	0.004 mL
2	JM 5R289 Dry	60 mg	0.004 mL
3	JM 5R128M Wet	60 mg	0.004 mL
4	Evonik P2053	0 mg	0.004 mL
5	JM 5R289 Dry	0 mg	0.004 mL
6	JM 5R128M Wet	0 mg	0.004 mL
7	Evonik P2053	60 mg	0.008 mL
8	JM 5R289 Dry	60 mg	0.008 mL
9	JM 5R128M Wet	60 mg	0.008 mL
10	Evonik P2053	0 mg	0.008 mL
11	JM 5R289 Dry	0 mg	0.008 mL
12	JM 5R128M Wet	0 mg	0.008 mL

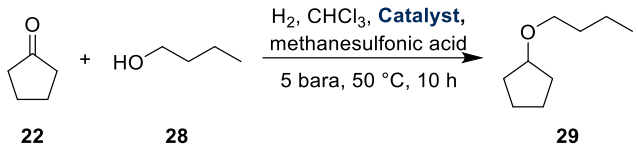
13	Evonik P2053	60 mg	0.012 mL
14	JM 5R289 Dry	60 mg	0.012 mL
15	JM 5R128M Wet	60 mg	0.012 mL
16	Evonik P2053	0 mg	0.012 mL
17	JM 5R289 Dry	0 mg	0.012 mL
18	JM 5R128M Wet	0 mg	0.012 mL
19	Evonik P2053	60 mg	0.016 mL
20	JM 5R289 Dry	60 mg	0.016 mL
21	JM 5R128M Wet	60 mg	0.016 mL
22	Evonik P2053	0 mg	0.016 mL
23	JM 5R289 Dry	0 mg	0.016 mL
24	JM 5R128M Wet	0 mg	0.016 mL
25	Evonik P2053	60 mg	0.020 mL
26	JM 5R289 Dry	60 mg	0.020 mL
27	JM 5R128M Wet	60 mg	0.020 mL
28	Evonik P2053	0 mg	0.020 mL
29	JM 5R289 Dry	0 mg	0.020 mL
30	JM 5R128M Wet	0 mg	0.020 mL
31	Evonik P2053	60 mg	0.024 mL
32	JM 5R289 Dry	60 mg	0.024 mL
33	JM 5R128M Wet	60 mg	0.024 mL
34	Evonik P2053	0 mg	0.024 mL
35	JM 5R289 Dry	0 mg	0.024 mL
36	JM 5R128M Wet	0 mg	0.024 mL
37	Evonik P2053	60 mg	0.032 mL
38	JM 5R289 Dry	60 mg	0.032 mL
39	JM 5R128M Wet	60 mg	0.032 mL
40	Evonik P2053	0 mg	0.032 mL
41	JM 5R289 Dry	0 mg	0.032 mL
42	JM 5R128M Wet	0 mg	0.032 mL
43	Evonik P2053	60 mg	0.041 mL
44	JM 5R289 Dry	60 mg	0.041 mL
45	JM 5R128M Wet	60 mg	0.041 mL

46	Evonik P2053	0 mg	0.041 mL
47	JM 5R289 Dry	0 mg	0.041 mL
48	JM 5R128M Wet	0 mg	0.041 mL

Table 10: Reaction database detailing the catalyst and acid combinations used in the catalyst screen RXN-24.

1.7.15 Heterogeneous Catalyst Screen with Acid Additive

Results and discussion, section 1.4.11, page 62.



Reaction was performed as stated in General Procedure 1, containing 4 Å molecular sieves (60 mg), tridecane (0.025 mL) and methanesulfonic acid (quantity defined in table) in conjunction with 24 wet or dry platinum catalysts on a carbon support in chloroform. Solution yields were calculated as stated in General Procedure 4 using K_x values stated in 1.7.11.

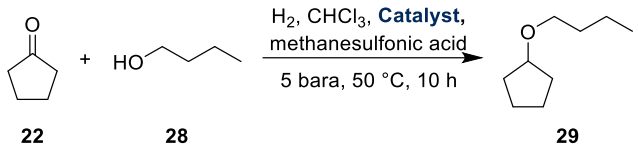
Visualisation of these results can be found in Figure 20, page 64.

Reaction	Catalyst Reference	MSA Quantity
1	Evonik P2053	N/A
2	BASF 10324	0.008 mL
3	BASF 10311	0.008 mL
4	BASF 10316	0.008 mL
5	BASF 10317	0.008 mL
6	BASF 10326	0.008 mL
7	BASF 10327	0.008 mL
8	Evonik P2057	0.008 mL
9	Evonik P2058	0.008 mL
10	Evonik P2060	0.008 mL

11	Evonik P2061	0.008 mL
12	Evonik P2065	0.008 mL
13	Evonik P8071	0.008 mL
14	Evonik P8078	0.008 mL
15	JM 5R122	0.008 mL
16	JM B103032-3	0.008 mL
17	JM B103032-5	0.008 mL
18	JM 5R18	0.008 mL
19	JM5R128M	0.008 mL
20	JM B501032-5	0.008 mL
21	JM B501018-5	0.008 mL
22	JM B106032-5	0.008 mL
23	Evonik P2053	0.008 mL
24	JM 5R289	0.008 mL
25	N/A	0.024 mL
26	BASF 10324	0.024 mL
27	BASF 10311	0.024 mL
28	BASF 10316	0.024 mL
29	BASF 10317	0.024 mL
30	BASF 10326	0.024 mL
31	BASF 10327	0.024 mL
32	Evonik P2057	0.024 mL
33	Evonik P2058	0.024 mL
34	Evonik P2060	0.024 mL
35	Evonik P2061	0.024 mL
36	Evonik P2065	0.024 mL
37	Evonik P8071	0.024 mL
38	Evonik P8078	0.024 mL
39	JM 5R122	0.024 mL
40	JM B103032-3	0.024 mL
41	JM B103032-5	0.024 mL
42	JM 5R18	0.024 mL
43	JM5R128M	0.024 mL

44	JM B501032-5	0.024 mL
45	JM B501018-5	0.024 mL
46	JM B106032-5	0.024 mL
47	Evonik P2053	0.024 mL
48	JM 5R289	0.024 mL

Table 11: Reaction database detailing the catalyst and acid combinations used in the catalyst screen RXN-23.



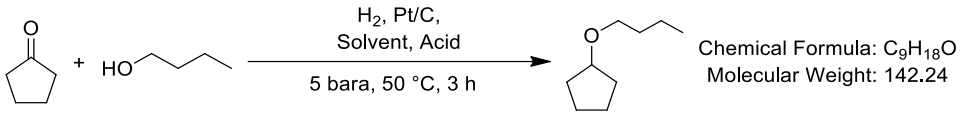
22 **28** **29**

Reaction was performed as stated in General Procedure 2. Platinum catalysts utilised in these reactions are the Evonik Noblyst P2053 5% Pt on activated carbon (0.117 g), Evonik Noblyst P2065 3% Pt on activated carbon (0.195 g), JM B501018-5 5% Pt on a carbon support (0.117 g), BASF 10311 3% Pt on a carbon support (0.195 g) or BASF 10327 5% Pt on a carbon support (0.117 g). These reactions were performed with methanesulfonic acid (1 – 3 eq) in the absence of molecular sieves. Ketone = cyclopentanone (0.088 mL), alcohol = *n*-butanol (0.183 mL), solvent = chloroform, P = 5, T = 50, t = 10. Tridecane was added upon completion (0.200 mL) and solution yields were calculated as stated in General Procedure 4 using K_x values stated in 1.7.11.

Visualisation of results can be found in Figure 22, page 66.

1.7.16 Large Scale Reaction In AutoMATE

Results and discussion, section 1.4.12, page 67.

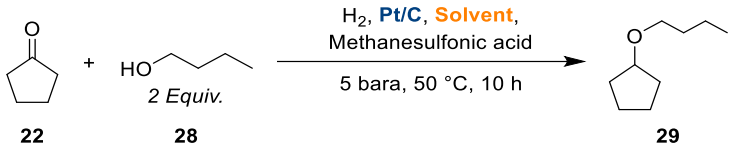


Evonik Noblyst P2053 5% Pt/C (0.375 mmol, 1.456 g), cyclopentanone (1.1 mL, 12.50 mmol), *n*-butanol (2.3 mL, 25 mmol), methanesulfonic acid (2.4 mL), tridecane (2.5 mL) and chloroform (50 mL) were added to the 160 mL HEL AutoMATE high pressure reactor fitted with EasySampler and ReactIR probes. The reactor was sealed and purged with N_2 (three times at 4 bara) followed by H_2 (twice at 3 bara). The mixture was heated to 50 °C, pressurised to 4 bara and stirred at 1000 rpm for 3 hours. The reactor was cooled, vented and purged with nitrogen before a manual sample was removed for GC analysis (10 µL in 1 mL methanol). Final solution yield was calculated (62%) as stated in General Procedure 4 using K_x values stated in 1.7.11.

Hydrogen uptake graph can be found in Figure 24, page 69.

1.7.17 Solvent Screening

Results and discussion, section 1.4.13, page 72.



Reaction was performed as stated in General Procedure 1, containing methanesulfonic acid (1 or 3 equivalents) and tridecane (0.025 mL) in solvent (0.5 mL). Solution yields were calculated as stated in General Procedure 4 using K_x values stated in 1.7.11.

Reaction	Catalyst (3 mol%)	MSA Quantity	Solvent
1	BASF 10311	0.024 mL	Chloroform
2	BASF 10327	0.024 mL	Chloroform
3	JM B501018-5	0.024 mL	Chloroform
4	Evonik P2053	0.024 mL	Chloroform
5	Evonik P2061	0.024 mL	Chloroform
6	Evonik P2061	0.008 mL	Chloroform
7	BASF 10311	0.024 mL	CPME
8	BASF 10327	0.024 mL	CPME
9	JM B501018-5	0.024 mL	CPME
10	Evonik P2053	0.024 mL	CPME
11	Evonik P2061	0.024 mL	CPME
12	Evonik P2061	0.008 mL	CPME
13	BASF 10311	0.024 mL	TBME
14	BASF 10327	0.024 mL	TBME
15	JM B501018-5	0.024 mL	TBME
16	Evonik P2053	0.024 mL	TBME
17	Evonik P2061	0.024 mL	TBME
18	Evonik P2061	0.008 mL	TBME
19	BASF 10311	0.024 mL	Ethyl Acetate
20	BASF 10327	0.024 mL	Ethyl Acetate

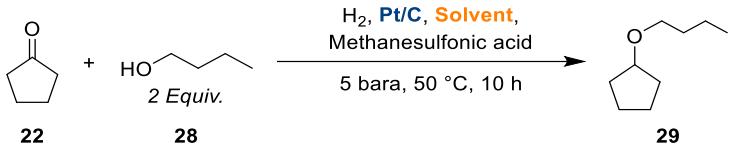
21	JM B501018-5	0.024 mL	Ethyl Acetate
22	Evonik P2053	0.024 mL	Ethyl Acetate
23	Evonik P2061	0.024 mL	Ethyl Acetate
24	Evonik P2061	0.008 mL	Ethyl Acetate
25	BASF 10311	0.024 mL	*n*-Butyl acetate
26	BASF 10327	0.024 mL	*n*-Butyl acetate
27	JM B501018-5	0.024 mL	*n*-Butyl acetate
28	Evonik P2053	0.024 mL	*n*-Butyl acetate
29	Evonik P2061	0.024 mL	*n*-Butyl acetate
30	Evonik P2061	0.008 mL	*n*-Butyl acetate
31	BASF 10311	0.024 mL	2-MeTHF
32	BASF 10327	0.024 mL	2-MeTHF
33	JM B501018-5	0.024 mL	2-MeTHF
34	Evonik P2053	0.024 mL	2-MeTHF
35	Evonik P2061	0.024 mL	2-MeTHF
36	Evonik P2061	0.008 mL	2-MeTHF
37	BASF 10311	0.024 mL	THF
38	BASF 10327	0.024 mL	THF
39	JM B501018-5	0.024 mL	THF
40	Evonik P2053	0.024 mL	THF
41	Evonik P2061	0.024 mL	THF
42	Evonik P2061	0.008 mL	THF
43	BASF 10311	0.024 mL	Toluene
44	BASF 10327	0.024 mL	Toluene
45	JM B501018-5	0.024 mL	Toluene
46	Evonik P2053	0.024 mL	Toluene
47	Evonik P2061	0.024 mL	Toluene
48	Evonik P2061	0.008 mL	Toluene

Table 12: Reaction database detailing the solvent, catalyst and acid combinations used in the solvent screen RXN-29.

Visualisation of these results can be found in Figure 28, page 74.

1.7.18 Ester Solvent Screen

Results and discussion, section 1.4.14, page 76.



22 **28** **29**

Reaction was performed as stated in General Procedure 1, containing methanesulfonic acid (1 or 3 equivalents) and tridecane (0.025 mL) in solvent (0.5 mL). Solution yields were calculated as stated in General Procedure 4 using K_x values stated in 1.7.11.

Reaction	Catalyst Reference	MSA Quantity	Solvent
1	BASF 10311	0.024 mL	Ethyl *iso*-butyrate
2	BASF 10327	0.024 mL	Ethyl *iso*-butyrate
3	JM B501018-5	0.024 mL	Ethyl *iso*-butyrate
4	Evonik P2065	0.024 mL	Ethyl *iso*-butyrate
5	Evonik P2061	0.024 mL	Ethyl *iso*-butyrate
6	Evonik P2061	0.008 mL	Ethyl *iso*-butyrate
7	BASF 10311	0.024 mL	Benzyl *iso*-butyrate
8	BASF 10327	0.024 mL	Benzyl *iso*-butyrate
9	JM B501018-5	0.024 mL	Benzyl *iso*-butyrate
10	Evonik P2065	0.024 mL	Benzyl *iso*-butyrate
11	Evonik P2061	0.024 mL	Benzyl *iso*-butyrate
12	Evonik P2061	0.008 mL	Benzyl *iso*-butyrate
13	BASF 10311	0.024 mL	*iso*-Propyl acetate
14	BASF 10327	0.024 mL	*iso*-Propyl acetate
15	JM B501018-5	0.024 mL	*iso*-Propyl acetate
16	Evonik P2065	0.024 mL	*iso*-Propyl acetate
17	Evonik P2061	0.024 mL	*iso*-Propyl acetate
18	Evonik P2061	0.008 mL	*iso*-Propyl acetate
19	BASF 10311	0.024 mL	*sec*-Butyl acetate
20	BASF 10327	0.024 mL	*sec*-Butyl acetate

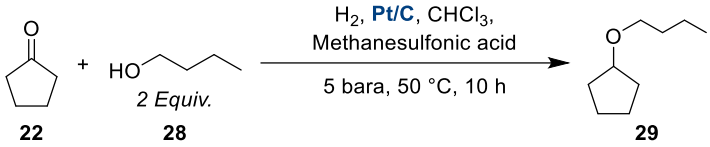
21	JM B501018-5	0.024 mL	*sec*-Butyl acetate
22	Evonik P2065	0.024 mL	*sec*-Butyl acetate
23	Evonik P2061	0.024 mL	*sec*-Butyl acetate
24	Evonik P2061	0.008 mL	*sec*-Butyl acetate
25	BASF 10311	0.024 mL	*tert*-Butyl acetate
26	BASF 10327	0.024 mL	*tert*-Butyl acetate
27	JM B501018-5	0.024 mL	*tert*-Butyl acetate
28	Evonik P2065	0.024 mL	*tert*-Butyl acetate
29	Evonik P2061	0.024 mL	*tert*-Butyl acetate
30	Evonik P2061	0.008 mL	*tert*-Butyl acetate
31	BASF 10311	0.024 mL	*iso*-Amyl acetate
32	BASF 10327	0.024 mL	*iso*-Amyl acetate
33	JM B501018-5	0.024 mL	*iso*-Amyl acetate
34	Evonik P2065	0.024 mL	*iso*-Amyl acetate
35	Evonik P2061	0.024 mL	*iso*-Amyl acetate
36	Evonik P2061	0.008 mL	*iso*-Amyl acetate
37	BASF 10311	0.024 mL	Phenyl acetate
38	BASF 10327	0.024 mL	Phenyl acetate
39	JM B501018-5	0.024 mL	Phenyl acetate
40	Evonik P2065	0.024 mL	Phenyl acetate
41	Evonik P2061	0.024 mL	Phenyl acetate
42	Evonik P2061	0.008 mL	Phenyl acetate
43	BASF 10311	0.024 mL	Menthyl acetate
44	BASF 10327	0.024 mL	Menthyl acetate
45	JM B501018-5	0.024 mL	Menthyl acetate
46	Evonik P2053	0.024 mL	Menthyl acetate
47	Evonik P2061	0.024 mL	Menthyl acetate
48	Evonik P2061	0.008 mL	Menthyl acetate

Table 13: Reaction database detailing the catalyst, acid and solvent combinations used in the catalyst screen RXN-35.

Visualisation of these results can be found in Figure 29, page 77.

1.7.19 Reproducibility Screen

Results and discussion section 1.4.15, page 78.



22 **28** **29**

Reaction was performed as stated in General Procedure 1 with tridecane internal standard (0.025 mL). Plate schematic can also be found in Figure 31, page 80. Additional results can be found in Figure 32 page 81. Solution yields were calculated as stated in General Procedure 4 using K_x values stated in 1.7.11.

Reaction	Catalyst Reference	MSA Quantity	Solvent
1/8/15/22	BASF 10311	0.024 mL	Chloroform
2/9/16/23	BASF 10327	0.024 mL	Chloroform
3/10/17/24	JM B501018-5	0.024 mL	Chloroform
4/11/18/19	Evonik P2053	0.024 mL	Chloroform
5/12/13/20	Evonik P2061	0.024 mL	Chloroform
6/7/14/21	Evonik P2061	0.008 mL	Chloroform

Table 14: Reaction database detailing the catalyst, acid and solvent combinations used in the reproducibility screen RXN-36.

1.7.20 Catalyst Wetting Investigation

Results and discussion, section 1.4.16, page 82.

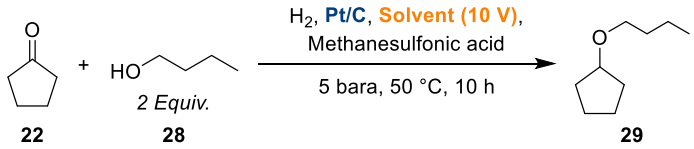
3.75 µmol of BASF 10311 or JM B501018-5 Pt/C catalyst and 24 µL methanesulfonic acid were stirred in 0.5 mL solvent within HPLC vials. Catalyst/solvent mixtures were stirred at 50 °C for 10 hours, catalyst properties were noted and photos were taken.

BASF 10311	**Methanol** Good suspension, uniform distribution	**Ethanol** Good suspension, some settling observable	**^{t}Amyl Alcohol** suspension, some settling observed	**^{t}Butanol** Good suspension, some settling observed	**Acetonitrile** Good suspension, uniform distribution	**Chloroform** Catalyst clumped in one corner
	DCM Catalyst coated bottom and lower sides of vial	**TBME** Catalyst has granular consistency and settles very quickly	**CPME** Catalyst has granular consistency and settles very quickly	**2-MeTHF** Good suspension but some settling observed	**THF** Good suspension but some settling observed	**Anisole** Good suspension but some settling observed
	Toluene Catalyst coated bottom of vial	**Acetone** Good suspension, uniform distribution. Polymerisation was observed by GC	**MIBK** Good suspension, some settling observed	**Diethyl Carbonate** Catalyst has granular consistency and settles very quickly	**Propylene Carbonate** Good suspension and uniform distribution but vial is pressurised by solvent decomposition	**NMP** Good suspension but some settling observed
	Tamisolve Good suspension, uniform distribution	**TAME** Catalyst clumping observed				
JM B501018-5	**Methanol** Good suspension, uniform distribution	**Ethanol** Good suspension, uniform distribution	**^{t}Amyl Alcohol** Good suspension, some settling observed	**^{t}Butanol** Good suspension, some settling observed	**Acetonitrile** Good suspension, uniform distribution	**Chloroform** Catalyst coated the inside of the vial
	DCM Catalyst coated the inside of the vial	**TBME** Good suspension, uniform distribution	**CPME** Catalyst has granular consistency and is clumped at the bottom	**2-MeTHF** Good suspension, some settling observed	**THF** Good suspension, uniform distribution	**Anisole** Good suspension but some settling observed
	Toluene Catalyst coated the inside of the vial	**Acetone** Good suspension, uniform distribution	**MIBK** Good suspension, some settling observed	**Diethyl Carbonate** Good suspension, some settling observed	**Propylene Carbonate** Good suspension and uniform distribution but vial is pressurised by solvent decomposition	**NMP** Good suspension but some settling observed
	Tamisolve Good suspension, uniform distribution	**TAME** Catalyst coated the inside of the vial				

Table 15: Evaluation of catalyst wetting properties for BASF 10311 and JM 501018-5 with methanesulfonic acid additive in a number of different solvents. Green indicates good catalyst wetting and red indicated bad catalyst wetting.

1.7.21 Solvent Screening at Lower Solvent Volumes and Catalyst Loadings

Results and discussion, section 1.4.16, page 82.



Catalyst (2.5 µmol), cyclopentanone (0.044 mL, 0.5 mmol) , *n*-butanol (0.092 mL, 1.0mmol), methanesulfonic acid (1.5 mmol, 0.097 mL), tridecane (0.100 mL) and solvent (0.5 mL) were added to HPLC vials within the CAT96 reactor vessel, sealed and flushed with N_2 (three times at 4 bara) followed by H_2 (twice at 5 bara). The reactions were stirred at 50 °C under 5 bara of hydrogen for 10 hours overnight. The reactor was cooled, tridecane (0.100 mL, 0.410 mmol) was added to each vial before the reaction mixtures were filtered and GC sample was taken (10 µL/mL in methanol). Solution yields were calculated as stated in General Procedure 4 using K_x values stated in 1.7.11.

Reaction	Catalyst (3 mol%)	Catalyst Quantity	Solvent
1	BASF 10311	16 mg	Chloroform
2	BASF 10327	10 mg	Chloroform
3	JM B501018-5	10 mg	Chloroform
4	Evonik P2061	10 mg	Chloroform
5	BASF 10311	16 mg	Ethyl Acetate
6	BASF 10327	10 mg	Ethyl Acetate
7	JM B501018-5	10 mg	Ethyl Acetate
8	Evonik P2061	10 mg	Ethyl Acetate
9	BASF 10311	16 mg	*n*-Butyl Acetate
10	BASF 10327	10 mg	*n*-Butyl Acetate
11	JM B501018-5	10 mg	*n*-Butyl Acetate

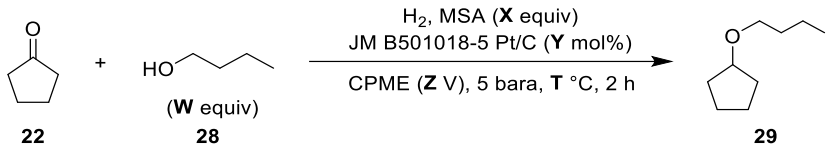
12	Evonik P2061	10 mg	*n*-Butyl Acetate
13	BASF 10311	16 mg	2-MeTHF
14	BASF 10327	10 mg	2-MeTHF
15	JM B501018-5	10 mg	2-MeTHF
16	Evonik P2061	10 mg	2-MeTHF
17	BASF 10311	16 mg	THF
18	BASF 10327	10 mg	THF
19	JM B501018-5	10 mg	THF
20	Evonik P2061	10 mg	THF
21	BASF 10311	16 mg	CPME
22	BASF 10327	10 mg	CPME
23	JM B501018-5	10 mg	CPME
24	Evonik P2061	10 mg	CPME
25	BASF 10311	16 mg	TBME
26	BASF 10327	10 mg	TBME
27	JM B501018-5	10 mg	TBME
28	Evonik P2061	10 mg	TBME
29	BASF 10311	16 mg	Toluene
30	BASF 10327	10 mg	Toluene
31	JM B501018-5	10 mg	Toluene
32	Evonik P2061	10 mg	Toluene

Table 16: Reaction database detailing the solvent, catalyst and acid combinations used in the solvent screen RXN-52.

Visualisation of results can be found in Figure 33, page 85.

1.7.22 Design of Experiments Optimisation

Results and discussion, section 1.4.17, page 86.



B501018-5 Johnson Matthey Pt/C (0.1 – 0.5 mol%), cyclopentanone (1 equivalent), *n*-butanol (1 – 2 equivalents), methanesulfonic acid (1 – 3 equivalents), tridecane and CPME (5 – 15 volumes) were added to the high pressure ChemSCAN 16 mL reactor vessels in 4 blocks of 8 as specified in the reaction database. Each block contained 6 factorial reactions and 2 centre points and all volumes were calculated to a constant 5 mL total reaction volume. Reactors were sealed and purged to 5 bara with N_2 (three times) followed by H_2 to 5 bara (twice). The reactions were stirred at 1000 rpm under a constant H_2 pressure of 5 bara at 40 – 60 °C for 2 hours. Solution yields were calculated against tridecane internal standard using GC as outlined in General Procedure 4 using the K_x values stated below. The design output was then analysed using Stat-Ease, Design Expert software (DX10).

Compound	Average K_x
n-Butanol	1.21
Cyclopentanol	1.13
Cyclopentanone	1.26
1,1-DMOCyclopentane	2.18
Butoxycyclopentane	1.28

Reaction	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
CPME (mL)	2.9	3.1	3.0	3.5	3.0	3.2	2.8	3.4
Cyclopentanone (mL)	0.314	0.337	0.324	0.250	0.324	0.348	0.303	0.246
n-butanol (mL)	0.641	0.316	0.497	0.512	0.497	0.534	0.464	0.231
MSA (mL)	0.455	0.488	0.470	0.182	0.470	0.127	0.768	0.536
Tridecane (mL)	0.701	0.753	0.724	0.559	0.724	0.779	0.676	0.550
Total Volume (mL)	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**
Pt (mol%)	0.3	0.3	0.3	0.1	0.3	0.3	0.3	0.5
Pt/C (mg)	**82**	**88**	**85**	**22**	**85**	**91**	**79**	**107**
Temperature (° C)	50	50	50	60	50	50	50	40

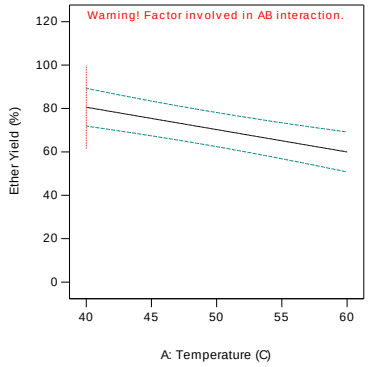
Reaction	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
CPME (mL)	2.1	3.0	3.5	3.0	3.3	3.7	3.0	2.2
Cyclopentanone (mL)	0.451	0.324	0.248	0.324	0.233	0.265	0.324	0.465
n-butanol (mL)	0.423	0.497	0.380	0.497	0.477	0.249	0.497	0.951
MSA (mL)	0.980	0.470	0.359	0.470	0.508	0.192	0.470	0.338
Tridecane (mL)	1.007	0.724	0.554	0.724	0.522	0.592	0.724	1.039
Total Volume (mL)	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**
Pt (mol%)	0.5	0.3	0.3	0.3	0.5	0.5	0.3	0.5
Pt/C (mg)	**196**	**85**	**65**	**85**	**102**	**116**	**85**	**203**
Temperature (° C)	60	50	50	50	60	60	70	60

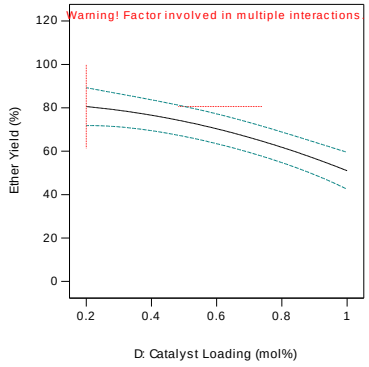
Reaction	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
CPME (mL)	2.2	3.30	3.0	1.9	2.5	2.1	2.2	2.5
Cyclopentanone (mL)	0.465	0.233	0.324	0.410	0.518	0.451	0.456	0.518
n-butanol (mL)	0.951	0.477	0.497	0.838	0.486	0.423	0.699	0.486
MSA (mL)	0.338	0.508	0.470	0.892	0.376	0.980	0.661	0.376
Tridecane (mL)	1.039	0.522	0.724	0.916	1.158	1.007	1.019	1.158
Total Volume (mL)	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**
Pt (mol%)	0.1	0.1	0.05	0.1	0.1	0.1	0.3	0.5
Pt/C (mg)	**41**	**20**	**14**	**36**	**45**	**39**	**119**	**226**
Temperature (° C)	40	40	50	60	60	40	50	40

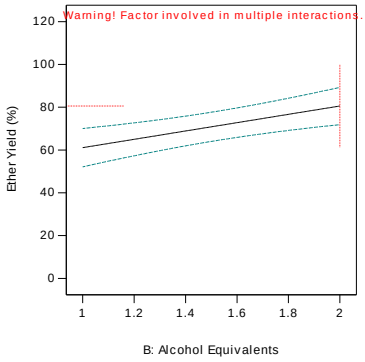
Reaction	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**
CPME (mL)	3.0	1.9	3.4	3.5	3.0	3.0	3.7	3.0
Cyclopentanone (mL)	0.324	0.410	0.246	0.250	0.324	0.324	0.265	0.324
n-butanol (mL)	0.497	0.838	0.231	0.512	0.497	0.497	0.249	0.497
MSA (mL)	0.470	0.892	0.536	0.182	0.470	0.470	0.192	0.470
Tridecane (mL)	0.724	0.916	0.550	0.559	0.724	0.724	0.592	0.724
Total Volume (mL)	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**
Pt (mol%)	0.55	0.5	0.1	0.5	0.3	0.3	0.1	0.3
Pt/C (mg)	**155**	**179**	**21**	**109**	**85**	**85**	**23**	**85**
Temperature (° C)	50	40	60	40	50	30	40	50

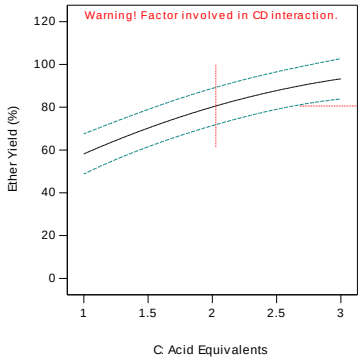
Design-Expert® Software
Factor Coding: Actual
Ether Yield (%)
95% CI Bands

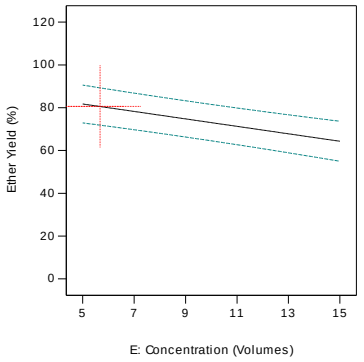
Actual Factors
A: Temperature = 40
B: Alcohol Equivalents = 2
C: Acid Equivalents = 2.02703
D: Catalyst Loading = 0.2
E: Concentration = 5.67568

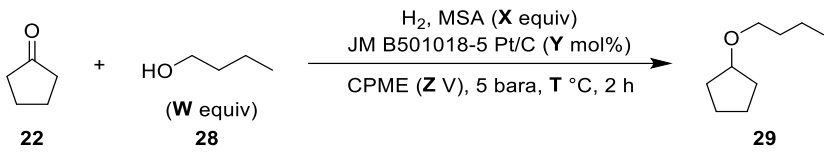












22 28 29

Results and discussion, section 1.4.17, page 89.

B501018-5 Johnson Matthey Pt/C (0.05 – 0.25 mol%), cyclopentanone (1 equivalent), *n*-butanol (1 – 2 equivalents), methanesulfonic acid (1 – 3 equivalents), tridecane and CPME (5 – 15 volumes) were added to the ChemSCAN 16 mL reactor vessels in 4 blocks of 6 and all volumes were calculated to a constant 5 mL fill level as detailed below. Each block contained 4 factorial reactions and 2 centre points. Reactors were sealed and purged to 5 bara with N_2 (three times) followed by H_2 to 5 bara (twice). The reactions were stirred at 1000 rpm under a constant H_2 pressure of 5 bara at 20 – 30 °C for 2 hours. Solution yields were calculated against tridecane internal standard using GC as outlined in General Procedure 4 using the K_x values stated below. This was then analysed using Stat-Ease, Design Expert software (DX10).

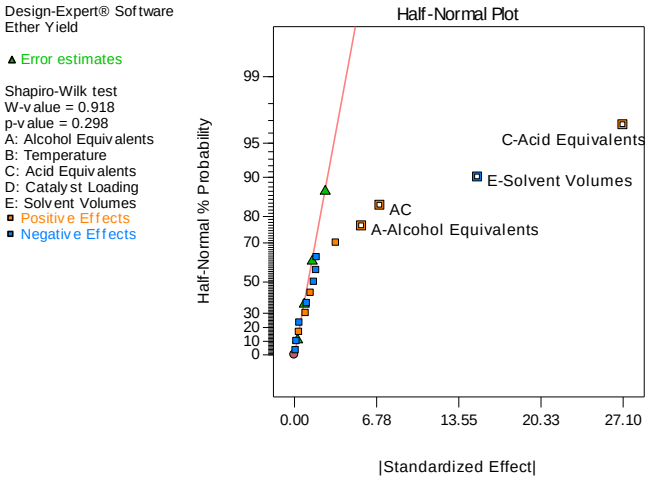
Compound	Average K_x
Cyclopentanol	1.64
Cyclopentanone	1.97
Butoxycyclopentane	1.55

Reaction	**1**	**2**	**3**	**4**	**5**	**6**
CPME (mL)	2.986	3.702	2.139	3.260	2.986	2.208
Cyclopentanone (mL)	0.324	0.265	0.451	0.233	0.324	0.465
n-butanol (mL)	0.497	0.249	0.423	0.477	0.497	0.951
MSA (mL)	0.470	0.192	0.980	0.508	0.470	0.338
Tridecane (mL)	0.724	0.592	1.007	0.522	0.724	1.039
Total Volume (mL)	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**
Pt (mol%)	0.15	0.05	0.25	0.05	0.15	0.25
Pt/C (mg)	**42**	**12**	**98**	**10**	**42**	**101**
Temperature (° C)	25	30	20	20	25	30

Reaction	**7**	**8**	**9**	**10**	**11**	**12**
CPME (mL)	2.208	3.702	3.260	2.986	2.139	2.986
Cyclopentanone (mL)	0.465	0.265	0.233	0.324	0.451	0.324
n-butanol (mL)	0.951	0.249	0.477	0.497	0.423	0.497
MSA (mL)	0.338	0.192	0.508	0.470	0.980	0.470
Tridecane (mL)	1.039	0.592	0.522	0.724	1.007	0.724
Total Volume (mL)	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**
Pt (mol%)	0.05	0.25	0.25	0.15	0.05	0.15
Pt/C (mg)	**20**	**58**	**51**	**42**	**19**	**42**
Temperature (° C)	20	20	30	25	30	25

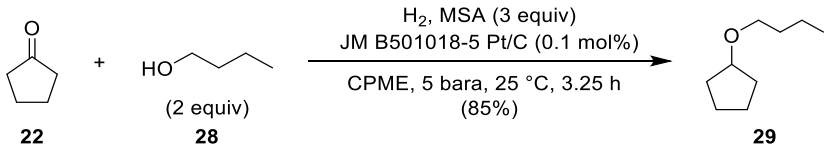
Reaction	**13**	**14**	**15**	**16**	**17**	**18**
CPME (mL)	1.946	2.986	2.986	1.946	3.437	3.437
Cyclopentanone (mL)	0.410	0.324	0.324	0.410	0.246	0.246
n-butanol (mL)	0.838	0.497	0.497	0.838	0.231	0.231
MSA (mL)	0.892	0.470	0.470	0.892	0.536	0.536
Tridecane (mL)	0.916	0.724	0.724	0.916	0.550	0.550
Total Volume (mL)	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**
Pt (mol%)	0.05	0.15	0.15	0.25	0.25	0.05
Pt/C (mg)	**18**	**42**	**42**	**89**	**54**	**11**
Temperature (° C)	30	25	25	20	30	20

Reaction	**19**	**20**	**21**	**22**	**23**	**24**
CPME (mL)	2.986	2.461	3.497	2.461	3.497	2.986
Cyclopentanone (mL)	0.324	0.518	0.250	0.518	0.250	0.324
n-butanol (mL)	0.497	0.486	0.512	0.486	0.512	0.497
MSA (mL)	0.470	0.376	0.182	0.376	0.182	0.470
Tridecane (mL)	0.724	1.158	0.559	1.158	0.559	0.724
Total Volume (mL)	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**	**5.000**
Pt (mol%)	0.15	0.05	0.25	0.25	0.05	0.15
Pt/C (mg)	**42**	**23**	**55**	**113**	**11**	**42**
Temperature (° C)	25	20	20	30	30	25



1.7.23 Large Scale Quantitative Time Course with Optimised Conditions

Results and discussion, section 1.4.18, page 91.



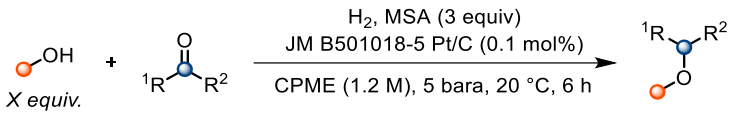
22 **28** **29**

JM B501018-5 Pt/C (0.429 g, 0.055 mmol), tridecane (3.0 mL, 12.30 mmol), cyclopentanone (4.86 mL, 55 mmol), *n*-butanol (10.07 mL, 110 mmol), methanesulfonic acid (10.71 mL, 165 mmol) and cyclopentyl methyl ether (22 mL) were added to the EasyMax high pressure Hastelloy reactor fitted with EasySampler probe. The reactor was sealed and purged with N_2 (three times at 4 bara) followed by H_2 (twice at 5 bara). The mixture was stirred at 800 rpm under a constant H_2 pressure of 5 bara at 25 °C for 3 hours. GC samples were taken periodically (20 µL diluted 80 fold in methanol) before the reaction vessel was vented and purged with N_2 (three times at 4 bara). The reaction mixture was filtered through Celite® and quenched with sodium bicarbonate. The organic layer was washed further with sodium bicarbonate and brine before being dried over $MgSO_4$. The solution yield was determined against the tridecane internal standard as outlined in General Procedure 4 using the K_x values stated below (final sample = 85%). Time course graph can be found in Figure 37, page 92.

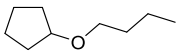
Compound	Average K_x
Cyclopentanol	1.73
Cyclopentanone	1.47
1,1-Dimethoxycyclopentane	1.78
Butoxycyclopentane	1.28

1.7.24 Saturated Substrate Scope

Results and discussion, section 1.4.19, page 93. All yields are summarised in Figure 38, page 93.



Cyclopentyl Butyl Ether (29)[94]



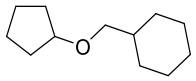
Chemical Formula: $C_9H_{18}O$
Molecular Weight: 142.24

The reactions were performed as stated in General Procedure 3 using tridecane internal standard (0.200 mL). Solution yields were calculated against an internal standard of tridecane as outlined in General Procedure 4. K_x = 1.28

1. Cyclopentanone (0.336 mL) and *n*-butanol (0.695 mL, 2 equiv) were reacted. GC solution yield = 90%, 90%
2. Cyclopentanone (0.336 mL) and *n*-butanol (0.348 mL, 1 equiv) were reacted. Duplicate experiments were performed, GC solution yields = 75%, 76%

Full data recorded in section 1.7.61.7.11 .

((Cyclopentyloxy)methyl)cyclohexane (67)[95]



Chemical Formula: $C_{12}H_{22}O$
Molecular Weight: 182.31

The reactions were performed as stated in General Procedure 3 using cyclopentanone (0.337 mL) and cyclohexylmethanol (0.935 mL). Product was purified by Biotage Isolera (10 g Sfar, EtOAc 0 - 5% in hexane) to yield a colourless oil (289 mg, 42%).

Once pure reference material was obtained, reactions were performed as stated in General Procedure 3 using tridecane internal standard (0.200 mL). Solution yields were calculated against an internal standard of tridecane as outlined in General Procedure 4. K_x = 1.38

1. Cyclopentanone (0.337 mL) and cyclohexylmethanol (0.935 mL, 2 equiv) were reacted in duplicate. GC solution yield = 81%, 75%
2. Cyclopentanone (0.337 mL) and cyclohexylmethanol (0.468 mL, 1 equiv) were reacted in duplicate. GC solution yield = 78%, 75%

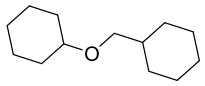
ν_{max}/cm^{-1}: 2920, 2850, 1449, 1342, 1177, 1098, 1066, 984, 891, 843.

^1H NMR (400 MHz, $CDCl_3$), δ = 3.95 – 3.80 (m, 1H C*H*-O), 3.18 (d, *J* = 6.6, 2H, CH_2-O), 1.81 – 1.46 (m, 14H), 1.34 – 1.41 (m, 3H), 0.99 – 0.83 (m, 2H)

^{13}C NMR (101 MHz, $CDCl_3$), δ = 81.3, 74.8, 38.2, 32.3, 30.3, 26.8, 25.9, 23.6.

HRMS (ESCi®): m/z calculated for $[C_{12}H_{23}O]^+$, Calculated mass = 183.1679, Measured mass = 183.1739 $[M+H]^+$

((Cyclohexyloxy)methyl)cyclohexane (68)[96]



Chemical Formula: $C_{12}H_{22}O$
Molecular Weight: 182.31

The reactions were performed as stated in General Procedure 3 using cyclohexanone (0.394 mL) and cyclohexylmethanol (0.936 mL). Product was purified by Biotage Isolera (10 g Sfar, EtOAc 0 - 5% in hexane) to yield a colourless oil (130 mg, 18%).

Once pure reference material was obtained, reactions were performed as stated in General Procedure 3 using tridecane internal standard (0.200 mL). Solution yields were calculated against an internal standard of tridecane as outlined in General Procedure 4. K_x = 1.38

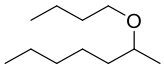
1. Cyclohexanone and cyclohexylmethanol (0.936 mL, 2 equiv) were reacted in duplicate. GC solution yield = 22%, 21%
2. Cyclohexanone and cyclohexylmethanol (0.468 mL, 1 equiv) were reacted in duplicate. GC solution yield = 18%, 19%

ν_{max}/cm^{-1}: 2921, 2851, 1448, 1362, 1116, 1095, 1072, 954, 890, 844.

^{1}H NMR (400 MHz, $OC(CD_3)_2$), δ = 3.25 – 3.13 (m, 3H C*H*-O-C*H*$_2$), 1.8 – 1.59 (m, 9H), 1.54 – 1.43 (m, 2H), 1.33 – 1.11 (m, 8H), 1.00 – 0.86 (m, 2H)

^{13}C NMR (101 MHz, $OC(CD_3)_2$), δ = 76.9, 73.5, 38.7, 32.2, 30.2, 28.6, 26.7, 26.0, 23.8.

2-Butoxyheptane (49)[3]



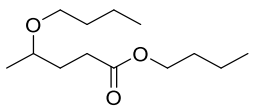
Chemical Formula: $C_{11}H_{24}O$
Molecular Weight: 172.31

The reactions were performed as stated in General Procedure 3 using tridecane internal standard (0.2 mL). Solution yields were calculated against an internal standard of tridecane as outlined in General Procedure 4 using reference material isolated from 1.7.25. K_x = 1.31

1. Heptan-2-one and *n*-butanol (0.695 mL, 2 equiv) were reacted in duplicate. GC solution yield = 61%, 62%
2. Heptan-2-one and *n*-butanol (0.348 mL, 1 equiv) were reacted in duplicate. GC solution yield = 58%, 56%

Full data found in 1.7.25.

Butyl 4-butoxypentanoate (69)[97]



Chemical Formula: $C_{13}H_{26}O_3$
Molecular Weight: 230.35

The reaction was performed as stated in General Procedure 3 using methyl levulinate (0.471 mL) and butanol (0.695 mL). Product was purified by Biotage Isolera (25 g Sfar, EtOAc 0-5% in hexane) to yield a colourless oil (96 mg, 13%).

ν_{max}/cm^{-1}: 2957, 2921, 2852, 1466, 1378, 721.

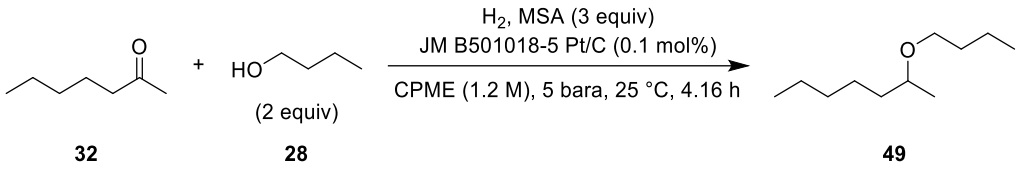
^1H NMR (400 MHz, $CDCl_3$), δ = 4.07 (t, *J* = 6.6, 2H, CO_2CH_2), 3.48 (dt, *J* = 9.2, 6.5, 1H, C*H*-O), 3.43 – 3.35 (m, 1H, C*H*-O), 3.30 (dt, *J* = 9.1, 6.8, 1H, C*H*-O) , 2.46 – 2.33 (m, 2H, CH_2), 1.8 –

1.74 (m, 2H, CH_2), 1.64 – 1.57 (m, 2H, CH_2), 1.55 – 1.48 (m, 2H, CH_2), 1.43 – 1.32 (m, 4H, 2 x CH_2), 1.14 (d, *J* = 6.2, 3H, CH_3), 0.98 – 0.86 (m, 6H, 2 x CH_3)

^{13}C NMR (101 MHz, $CDCl_3$), δ = 174.0, 74.2, 68.3, 64.2, 32.2, 31.8, 30.7, 30.5, 19.6, 19.4, 19.2, 13.9, 13.7.

1.7.25 Large Scale Quantitative Time Course of Heptan-2-one and *n*-Butanol

Results and discussion, section 1.4.19, page 93. QTC graph can be found as Figure 39, page 94.



32 **28** **49**

B501018-5 Johnson Matthey Pt/C (0.351 g, 0.090 mmol), heptan-2-one (6.30 mL, 45 mmol), *n*-butanol (8.24 mL, 90 mmol), methanesulfonic acid (8.77 mL, 135 mmol), tridecane (3 mL), and CPME (25 mL) were added to the 100 mL EasyMax pressure reactor equipped with the reactor baffle set and EasySampler probe, sealed and purged to 5 bara with N_2 (three times) followed by H_2 to 5 bara (twice). The reaction was stirred at 25 °C under 5 bara of hydrogen for 3 hours. GC samples were taken periodically (20 µL reaction sample, 80 fold dilution in methanol) *via* the Mettler Toledo EasySampler. Solution yields were calculated against tridecane internal standard using GC as outlined in General Procedure 4 (35%). Reactor was vented and purged with N_2 (three times at 4 bara). The reaction mixture was filtered through celite, quenched with saturated aqueous sodium bicarbonate solution and the organics were dried over $MgSO_4$. The product was purified by vacuum distillation (house vacuum) and

product ether was collected at 140 °C. Response factor was calculated for this reference material (82% putrity based on NMR) and solution yields were calculated against an internal standard of tridecane as outlined in General Procedure 4. K_x = 1.31.

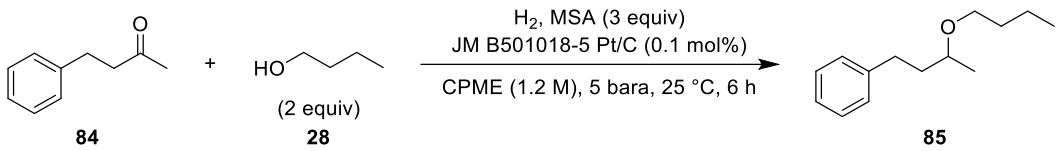
ν_{max}/cm^{-1}: 2958, 2929, 2859, 1459, 1374, 1339, 1119, 1091, 908, 734.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 3.52 – 3.43 (m, 1H, C*H*-O), 3.37 – 3.29 (m, 2H, CH_2-O), 1.57 – 1.47 (m, 2H), 1.42 – 1.25 (m, 10H), 1.14 – 1.07 (d, *J* = 6.2, 3H, CH_3-CH-O), 0.95 – 0.85 (m, 6H)

^{13}C NMR (101 MHz, $CDCl_3$), δ = 75.3, 68.1, 36.7, 32.3, 32.0, 25.3, 22.7, 19.8, 19.5, 14.1, 14.0.

1.7.26 Large Scale Quantitative Time Course of 4-Phenylbutan-2-one and *n*-Butanol

Results and discussion, section 1.4.20, page 98. QTC graph can be found as Figure 42, page 99.

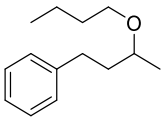


84 **28** **85**

B501018-5 Johnson Matthey Pt/C (0.297 g, 0.076 mmol), 4-phenylbutan-2-one (5.71 mL, 38 mmol), *n*-butanol (6.95 mL, 76 mmol), methanesulfonic acid (7.40 mL, 114 mmol), tridecane (1.000 mL), and CPME (27 mL) were added to the 100 mL EasyMax pressure reactor equipped with the reactor baffle set, sealed and purged to 5 bara with N_2 (three times) followed by H_2 5 bara (twice). Reactions were stirred at 800 rpm at 25 °C under 5 bara of hydrogen for 6 hours. GC samples were taken periodically (20 µL reaction sample, 80 fold dilution in methanol) via Mettler Toledo EasySampler. The solution yield was calculated against an

internal standard of tridecane (35%) as outlined in General Procedure 4 using K_x = 1.37 Reactor was purged to 5 bara with N_2 (three times).

(3-Butoxy)butylbenzene (85)[98]



Chemical Formula: $C_{14}H_{22}O$
Molecular Weight: 206.33

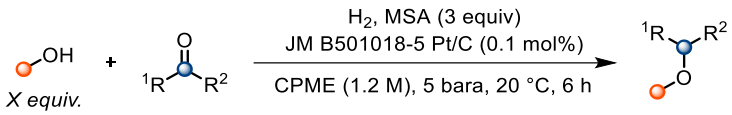
ν_{max}/cm^{-1}: 2960, 2928, 2863, 1454, 1372, 1136, 1092, 745, 698.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.33 – 7.27 (m, 2H, Ar*H*), 7.24 – 7.16 (m, 3H, Ar*H*), 3.56 – 3.45 (m, 1H, C*H*-O), 3.45 – 3.30 (m, 2H, CH_2-O), 2.82 – 2.62 (m, 2H, Ar-CH_2), 1.87 (dddd, 1H, *J* = 13.5, 9.8, 7.5, 5.7), 1.77 – 1.67 (m, 1H), 1.64 – 1.51 (m, 2H), 1.49 – 1.36 (m, 2H), 1.21 – 1.16 (d, *J* = 6.2, 3H), 1.0 – 0.94 (t, *J* = 7.3, 3H)

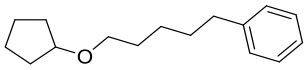
^{13}C NMR (101 MHz, $CDCl_3$), δ = 142.5, 128.4, 128.2, 125.6, 74.4, 68.2, 38.5, 32.4, 31.9, 19.7, 19.5, 14.0.

1.7.27 Aromatic Substrate Scope Including Transetherification Reactions

Results and discussion, section 1.4.21, page 100. Yields are summarised in Figure 43, page 100.



(5-(Cyclopentyloxy)pentyl)benzene (93)



Chemical Formula: $C_{16}H_{24}O$
Molecular Weight: 232.37

The reactions were performed as stated in General Procedure 3 using cyclopentanone (0.337 mL) and 5-phenylpentan-1-ol (1.284 mL). The product was purified by Biotage Isolera (25 g Sfar, EtOAc 0 - 5% in hexane). The product was a colourless oil (417 mg, 47%).

Once pure reference material was obtained, reactions were performed as stated in General Procedure 3 using tridecane internal standard (0.200 mL). The solution yields were calculated against an internal standard of tridecane as outlined in General Procedure 4. K_x = 1.54

1. Cyclopentanone and 5-phenylpentan-1-ol (1.284 mL, 2 equiv) were reacted in duplicate. GC solution yield = 17%, 16%
2. Cyclopentanone and 5-phenylpentan-1-ol (0.642 mL, 1 equiv) were reacted in duplicate. GC solution yield = 43%, 48%

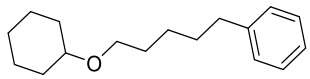
ν_{max}/cm^{-1}: 3026, 2934, 2858, 1496, 1453, 1348, 1180, 1097, 746, 698.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.32 – 7.23 (m, 2H, Ar*H*), 7.21 – 7.12 (m, 3H, Ar*H*), 3.90 – 3.80 (m, 1H C*H*-O), 3.29 (t, *J* = 6.8, 2H, CH_2-O), 2.65 (t, *J* = 7.6, 2H, CH_2-Ar), 1.77 – 1.45 (m, 12H), 1.44 – 1.33 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 142.8, 128.4, 128.2, 125.6, 81.2, 68.8, 35.9, 32.3, 31.4, 30.0, 26.0, 23.6.

HRMS (ESCi®): m/z calculated for $[C_{16}H_{25}O]^+$, Calculated mass = 233.1835, Measured mass = 233.1895$[M+H]^+$

(5-(Cyclohexyloxy)pentyl)benzene (94)[99]



Chemical Formula: $C_{17}H_{26}O$
Molecular Weight: 246.39

The reactions were performed as stated in General Procedure 3 using cyclohexanone (0.394 mL) and 5-phenylpentanol (1.280 mL). The product was purified by Biotage Isolera (25 g Sfar, EtOAc 0 - 5% in heptane). The product was a colourless oil (121 mg, 13%).

Once pure reference material was obtained, reactions were performed as stated in General Procedure 3 using tridecane internal standard (0.200 mL). The solution yields were calculated against an internal standard of tridecane as outlined in General Procedure 4. K_x = 1.60

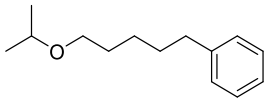
1. Cyclohexanone and 5-phenylpentan-1-ol (1.280 mL, 2 equiv) were reacted in duplicate. GC solution yield = 17%, 14%.
2. Cyclohexanone and 5-phenylpentan-1-ol (0.640 mL, 1 equiv) were reacted in duplicate. GC solution yield = 13%, 12%

ν_{max}/cm^{-1}: 2929, 2855, 1496, 1451, 1363, 1092, 752, 697.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.31 – 7.25 (m, 2H, Ar*H*), 7.21 – 7.15 (m, 3H, Ar*H*), 3.45 (t, 2H, *J* = 6.6, O-CH_2), 3.25 – 3.15 (m, 1H, O-C*H*), 2.63 (t, 2H, *J* = 7.6, CH_2-Ar), 1.95 – 1.83 (m, 2H), 1.71 – 1.51 (m, 6H), 1.45 – 1.36 (m, 2H), 1.32 – 1.15 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 142.8, 128.4, 128.2, 125.6, 77.4, 67.7, 36.0, 32.4, 31.4, 30.1, 26.0, 25.9, 24.3.

(5-*iso*-Propoxy)pentylbenzene (96)



Chemical Formula: $C_{14}H_{22}O$
Molecular Weight: 206.33

The reactions were performed as stated in General Procedure 3 using propan-2-one (0.279 mL) and 5-phenylpentanol (1.280 mL). The product was purified by Biotage Isolera (25 g Sfar, EtOAc 0 - 5% in hexane). The product was a colourless oil (50 mg, 6%).

Once pure reference material was obtained, reactions were performed as stated in General Procedure 3 using tridecane internal standard (0.2 mL). The solution yields were calculated against an internal standard of tridecane as outlined in General Procedure 4. K_x = 1.19

1. Propan-2-one and 5-phenylpentan-1-ol (1.280 mL, 2 equiv) were reacted in duplicate. GC solution yield = 51%, 47%
2. Propan-2-one and 5-phenylpentan-1-ol (0.642 mL, 1 equiv) were reacted in duplicate. GC solution yield = 49%, 51%

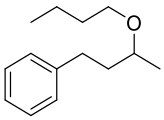
ν_{max}/cm^{-1}: 2924, 2854, 1454, 1379, 1367, 1128, 1084, 745, 697.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.29 – 7.25 (m, 2H, Ar-*H*), 7.18 – 7.08 (m, 2H, Ar-*H*), 3.53 (spt, *J* = 6.1, 1H, C*H*-O), 3.39 (t, *J* = 6.8, 2H, CH_2-O), 2.61 (t, *J* = 7.6, 2H, CH_2), 1.68 – 1.54 (m, 4H, 2 x CH_2), 1.43 – 1.35 (m, 2H, CH_2), 1.14 (d, *J* = 6.2, 2H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 142.7, 128.4, 128.2, 125.6, 71.3, 68.1, 35.9, 31.4, 30.1, 26.0, 22.1.

HRMS (ESCi®): m/z calculated for $[C_{14}H_{23}O]^+$, Calculated mass = 207.1679, Measured mass = 207.1739 $[M+H]^+$

(3-Butoxy)butylbenzene (85)[98]



Chemical Formula: $C_{14}H_{22}O$
Molecular Weight: 206.33

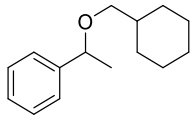
The reactions were performed as stated in General Procedure 3 using 4-phenylbutan-2-one (0.569 mL, 3.8 mmol) and butan-1-ol (0.348 mL, 3.80 mmol). The product was purified by Biotage Isolera (25g Sfar, 0-10% EtOAc in hexane) to yield a colourless oil (148 mg, 19%)

The reactions were performed as stated in General Procedure 3 using tridecane internal standard (0.200 mL). The solution yields were calculated against an internal standard of tridecane as outlined in General Procedure 4. K_x = 1.66

1. 4-Phenylbutan-2-one and *n*-butanol (0.695 mL, 2 equiv) were reacted in duplicate. GC solution yield = 47%, 45%.
2. 4-Phenylbutan-2-one and *n*-butanol (0.348 mL, 1 equiv) were reacted in duplicate. GC solution yield = 38%, 41%

Full data can be found in section 1.7.26

(1-(Cyclohexylmethoxy)ethyl)benzene (87)



Chemical Formula: $C_{15}H_{22}O$
Molecular Weight: 218.34

The reactions were performed as stated in General Procedure 3 using acetophenone (0.444 mL) and cyclohexylmethanol (0.935 mL). The product was purified by Biotage Isolera (25 g Sfar, heptane). The product was a colourless oil (383 mg, 46%).

Once pure reference material was obtained, reactions were performed as stated in General Procedure 3 using tridecane internal standard (0.2 mL). The solution yields were calculated against an internal standard of tridecane as outlined in General Procedure 4. K_x = 1.73

1. Acetophenone and cyclohexylmethanol (0.935 mL, 2 equiv) were reacted in duplicate. GC solution yield = 29%, 30%.
2. Acetophenone and cyclohexylmethanol (0.468 mL, 1 equiv) were reacted in duplicate. GC solution yield = 28%, 23%

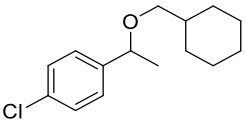
ν_{max}/cm^{-1}: 2974, 2922, 2851, 1920, 1449, 1110, 759, 700.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.38 – 7.21 (m, 5H, Ar*H*), 4.35 (q, *J* = 6.4, 1H Ar-C*H*-O), 3.09 (d, *J* = 6.4, 2H O-CH_2), 1.82 – 1.52 (m, 5H), 1.42 (d, *J* = 6.6, 3H, CH_3-CH-O), 1.32 – 1.05 (m, 4H), 0.95 – 0.81 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 144.5, 128.3, 127.2, 126.1, 78.0, 74.7, 38.2, 30.3, 30.2, 25.9, 25.9, 24.2.

HRMS (ESCi®): m/z calculated for $[C_{15}H_{23}O]^+$, Calculated mass = 219.1679, Measured mass = 219.1741 $[M+H]^+$

1-Chloro-4-(1-(cyclohexylmethoxy)ethyl)benzene (90)



Chemical Formula: $C_{15}H_{21}ClO$
Molecular Weight: 252.78

The reactions were performed as stated in General Procedure 3 using 1-(4-chlorophenyl)ethan-1-one (0.493 mL, 3.8 mmol) and cyclohexylmethanol (0.935 mL). The product was purified by Biotage Isolera (25 g Sfar, EtOAc 0 - 10% in hexane) followed by EZPrep reverse phase chromatography (50 - 100% MeCN + 0.05% TFA in water). The product containing fraction was evaporated to remove acetonitrile, neutrilised with saturated aqueous sodium bicarbonate and extracted into DCM. The DCM extracts were evaporated to yield product as a colourless oil.

1. 1-(4-Chlorophenyl)ethan-1-one and cyclohexylmethanol (0.935 mL, 2 equiv) were reacted in duplicate. Isolated yield = (302 mg, 32%), (258 mg, 27%)
2. 1-(4-Chlorophenyl)ethan-1-one and cyclohexylmethanol (0.468 mL, 1 equiv) were reacted in duplicate. Isolated yield = (231 mg, 24%), (174 mg, 18%)

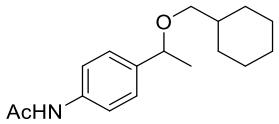
ν_{max}/cm^{-1}: 2921, 2850, 1491, 1449, 1109, 1090, 1052, 1014, 827, 779, 540.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.32 – 7.22 (m, 4H, Ar-*H*), 4.32 (q, *J* = 6.4, 1H, C*H*-O), 3.07 (qd, *J* = 9.1, 6.6, 2H, CH_2-O), 1.85 – 1.73 (m, 2H), 1.70 – 1.52 (m, 4H), 1.39 (d, *J* = 6.6, 3H), 1.31 – 1.07 (m, 3H), 0.93 – 0.81 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 143.0, 132.8, 128.5, 127.5, 77.2, 74.7, 38.2, 30.2, 30.1, 26.6, 25.9, 25.8. 24.1.

HRMS (ESCi®): m/z calculated for $[C_{15}H_{20}ClO]^-$, Calculated mass = 251.1273, Measured mass = 251.1194 $[M-H]^-$

_N_-(4-(1-(Cyclohexylmethoxy)ethyl)phenyl)acetamide (88)



Chemical Formula: $C_{17}H_{25}NO_2$
Molecular Weight: 275.39

The reactions were performed as stated in General Procedure 3 using *N*-(4-acetylphenyl)acetamide (0.673 g) and cyclohexylmethanol. The product was purified by Biotage Isolera (25 g Sfar, EtOAc 0 - 50% in heptane). The product was a white solid.

1. *N*-(4-Acetylphenyl)acetamide and cyclohexylmethanol (0.935 mL, 2 equiv) were reacted in duplicate. Isolated yield = (769 mg, 74%), (764 mg, 73%)
2. *N*-(4-Acetylphenyl)acetamide and cyclohexylmethanol (0.468 mL, 1 equiv) were reacted in duplicate. Isolated yield = (530 mg, 51%), (501 mg, 48%)

Melting point = 104.4 °C

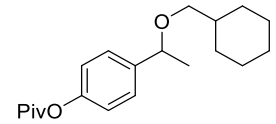
ν_{max}/cm^{-1}: 2921, 2849, 1661, 1607, 1557, 1510, 1409, 1369, 1322, 1265, 1108, 1091, 836, 547.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.48 (d, *J* = 8.4, 2H, Ar-*H*), 7.32 – 7.22 (m, 3H, Ar-*H* + N*H*), 4.34 (q, *J* = 6.5, 1H, C*H*-O), 3.15 – 3.05 (m, 2H, CH_2-O), 2.20 (s, 3H, CH_3CON), 1.82 – 1.54 (m, 6H), 1.41 (d, *J* = 6.4, 3H, CH_3), 1.31 – 1.10 (m, 3H), 0.94 – 0.82 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 168.2, 140.5, 136.9, 128.3, 126.8, 119.9, 77.5, 74.6, 38.2, 30.3, 30.1, 26.7, 25.91, 25.86, 24.6, 24.1

HRMS (ESCi®): m/z calculated for $[C_{17}H_{26}NO_2]^+$, Calculated mass = 276.1895, Measured mass = 276.1954 $[M+H]^+$

4-(1-(Cyclohexylmethoxy)ethyl)phenyl pivalate (89)



Chemical Formula: $C_{20}H_{30}O_3$
Molecular Weight: 318.46

The reactions were performed as stated in General Procedure 3 using 4-acetylphenyl pivalate (0.837 g) and cyclohexylmethanol. The product was purified by Biotage Isolera (25 g Sfar, EtOAc 0 - 50% in heptane). The product was a colourless oil.

1. 4-Acetylphenyl pivalate and cyclohexylmethanol (0.935 mL, 2 equiv) were reacted in duplicate. Isolated yield = (533 mg, 44%), (517 mg, 46%)
2. 4-Acetylphenyl pivalate and cyclohexylmethanol (0.468 mL, 1 equiv) were reacted in duplicate. Isolated yield = (294 mg, 24%), (250 mg, 21%)

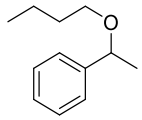
ν_{max}/cm^{-1}: 2973, 2923, 2851, 1753, 1506, 1479, 1196, 1164, 1113, 895, 851, 548.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.32 – 7.28 (m, 2H, Ar-*H*), 7.05 – 7.00 (m, 2H, Ar-*H*), 4.35 (q, *J* = 6.4, 1H, C*H*-O), 3.08 (d, *J* = 6.9, 2H, CH_2-O), 1.83 – 1.60 (m, 5H), 1.40 (d, *J* = 6.4, 3H, CH_3), 1.35 (s, 9H, CO(CH_3)$_3$), 1.32 – 1.09 (m, 4H), 0.94 – 0.80 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 177.1, 150.2, 141.8, 127.1, 121.3, 77.5, 74.7, 39.1, 38.2, 30.3, 30.1, 27.2, 26.7, 25.93, 25.86, 24.3

HRMS (ESCi®): m/z calculated for $[C_{20}H_{29}O_3]^-$, Calculated mass = 317.2187, Measured mass = 317.2110 $[M-H]^-$

(1-Butoxyethyl)benzene (51)[100]



Chemical Formula: $C_{12}H_{18}O$
Molecular Weight: 178.28

The reactions were performed as stated in General Procedure 3 using acetophenone (0.444 mL) and *n*-butanol (0.695 mL) with a reaction time of 2 h. The product was purified by Biotage Isolera (25 g Sfar, EtOAc 0 - 5% in hexane). The product was a colourless oil (217 mg, 32%).

Once pure reference material was obtained, reactions were performed as stated in General Procedure 3 using tridecane internal standard (0.200 mL). the solution yields were calculated against an internal standard of tridecane as outlined in General Procedure 4. $K_x = 1.83$

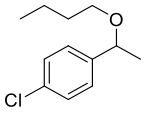
1. Acetophenone and *n*-butanol (0.695 mL, 2 equiv) were reacted in duplicate. GC solution yield = 57%, 52%
2. Acetophenone and *n*-butanol (0.348 mL, 1 equiv) were reacted in duplicate. GC solution yield = 49%, 48%

ν_{max}/cm^{-1}: 2959, 2931, 2866, 1451, 1350, 1206, 1100, 756, 699.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.38 – 7.2 (m, 5H, Ar*H*), 4.37 (q, *J* = 6.4, 1H, Ar-C*H*-O), 3.30 (t, *J* = 6.6, 2H, CH_2-O), 1.57 – 1.52 (m, 2H), 1.43 (d, *J* = 6.4, 3H, CH_3-CH-O), 1.41 – 1.29 (m, 2H), 0.88 (t, *J* = 7.4, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 144.4, 128.3, 127.2, 126.1, 79.7, 68.5, 32.1, 24.2, 19.4, 13.9.

(1-(1-Butoxyethyl)-4-chlorobenzene (90)[101]



Chemical Formula: $C_{12}H_{17}ClO$
Molecular Weight: 212.72

The reactions were performed as stated in General Procedure 3 using 1-(4-chlorophenyl)ethan-1-one (0.493 mL, 3.8 mmol) and *n*-butanol. The product was purified by Biotage Isolera (25 g Sfar, EtOAc 0 - 10% in heptane) followed by EZPrep reverse phase chromatography (50 - 100% MeCN + 0.05% TFA in water). The product was a colourless oil (220 mg, 27%).

Once pure reference material was obtained, reactions were performed as stated in General Procedure 3 using tridecane internal standard (0.200 mL). The solution yields were calculated against an internal standard of tridecane as outlined in General Procedure 4. K_x = 1.49

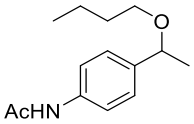
1. 1-(4-Chlorophenyl)ethan-1-one (0.493 mL) and *n*-butanol (0.695 mL, 2 equiv) were reacted in duplicate. Solution yield = 32%, 33%
2. 1-(4-Chlorophenyl)ethan-1-one (0.493 mL) and *n*-butanol (0.348 mL, 1 equiv) were reacted in duplicate. Solution yield = 30%, 32%

ν_{max}/cm^{-1}: 2959, 2931, 2867, 1489, 1090, 1014, 827, 781, 540.

^1H NMR (400 MHz, $CDCl_3$), δ = 7.32 – 7.22 (m, 4H, Ar-*H*), 4.35 (q, *J* = 6.4, 1H, C*H*-O), 3.32 – 3.23 (m, 2H, CH_2-O), 1.57 – 1.48 (m, 2H), 1.40 (d, *J* = 6.4, 3H, CH_3), 1.38 – 1.26 (m, 2H), 0.88 (t, *J* = 7.4, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 142.9, 132.9, 128.5, 127.5, 77.2, 68.6, 32.0, 24.1, 19.4, 13.9.

_N_-(4-(1-Butoxyethyl)phenyl)acetamide (91)



Chemical Formula: $C_{14}H_{21}NO_2$
Molecular Weight: 235.33

Reaction was performed as stated in General Procedure 3 using *N*-(4-acetylphenyl)acetamide (0.673 g, 3.80 mmol) and *n*-butanol. Product was purified by Biotage Isolera (25 g Sfar, EtOAc 0 - 50% in heptane). Product was a colourless oil which solidified upon standing.

1. *N*-(4-acetylphenyl)acetamide and *n*-butanol (0.695 mL, 2 equiv) were reacted in duplicate. Isolated yield = (728 mg, 77%), (767 mg, 76%)
2. *N*-(4-acetylphenyl)acetamide and *n*-butanol (0.348 mL, 1 equiv) were reacted in duplicate. Isolated yield = (457 mg, 51%), (442 mg, 50%)

Melting point = 53.8 °C

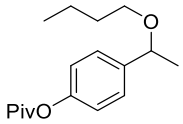
ν_{max}/cm^{-1}: 3251, 2961, 2930, 2866, 1661, 1605, 1547, 1511, 1410, 1369, 1318, 1265, 1099, 833.

^1H NMR (400 MHz, $CDCl_3$), δ = 7.46 (d, *J* = 8.4, 2H, Ar-*H*), 7.26 (overlapping br. s and d, *J* = 8.4, 3H Ar-*H* + N*H*), 4.35 (q, *J* = 6.4, 1H, C*H*-O), 3.27 (t, *J* = 6.6, 2H, CH_2-O), 2.17 (s, 3H, CH_3CO), 1.58 – 1.46 (m, 2H), 1.40 (d, *J* = 6.4, 3H, CH_3), 1.37 – 1.19 (m, 2H, CH_2), 0.88 (t, *J* = 7.4, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 168.2, 140.4, 136.9, 126.8, 119.9, 77.4, 68.4, 32.1, 24.6, 24.1, 19.4, 13.9.

HRMS (ESCi®): m/z calculated for $[C_{14}H_{22}NO_2]^+$, Calculated mass = 236.1580, Measured mass = 236.1645 $[M+H]^+$

4-(1-Butoxyethyl)phenyl pivalate (92)



Chemical Formula: $C_{17}H_{26}O_3$
Molecular Weight: 278.39

The reactions were performed as stated in General Procedure 3 using 4-acetylphenyl pivalate (0.837 g) and *n*-butanol. Product was purified by Biotage Isolera (25 g Sfar, EtOAc 0 - 20% in heptane). The product was a colourless oil.

1. 4-Acetylphenyl pivalate and *n*-butanol (0.695 mL, 2 equiv) were reacted in duplicate. Isolated yield = (769 mg, 73%), (781 mg, 74%)
2. 4-Acetylphenyl pivalate and *n*-butanol (0.348 mL, 1 equiv) were reacted in duplicate. Isolated yield = (597 mg, 56%), (651 mg, 62%)

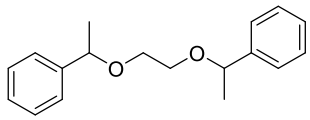
ν_{max}/cm^{-1}: 2974, 1750, 1683, 1598, 1263, 1202, 1164, 1107, 897, 602, 589.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.32 – 7.29 (m, 2H, Ar-*H*), 7.04 – 7.01 (m, 2H, Ar-*H*), 4.37 (q, *J* = 6.5, 1H, C*H*-O), 3.28 (t, *J* = 6.6, 2H, CH_2-O), 1.57 – 1.50 (m, 2H), 1.41 (d, *J* = 6.6, 3H, CH_3), 1.38 – 1.25 (m, 11H, 3 x CH_3 + CH_2), 0.88 (t, *J* = 7.3, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 177.1, 150.2, 141.7, 127.1, 121.3, 77.2, 68.5, 39.1, 32.0, 27.1, 24.3, 19.4, 13.9.

HRMS (ESCi®): m/z calculated for $[C_{17}H_{25}O_3]^-$, Calculated mass = 277.1874, Measured mass = 277.1793 $[M-H]^-$

1,2-Di(1-phenylethoxy)ethane (97)[102]



Chemical Formula: $C_{18}H_{22}O_2$
Molecular Weight: 270.37

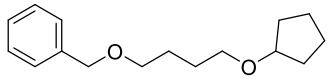
The reactions were performed as stated in General Procedure 3 using acetophenone (0.443 mL) and ethylene glycol (0.212 mL). The product was purified by Biotage Isolera (25 g Sfar, EtOAc 0 -25% in hexane). The product was a colourless oil (85 mg, 17%).

ν_{max}/cm^{-1}: 2974, 2928, 2862 1492, 1450, 1369, 1206, 1102, 760, 701.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.36 – 7.23 (m, 10H, Ar-*H*), 4.44 (quin, *J* = 6.5, 2H, C*H*-O), 3.44 (d, *J* = 5.9, 4H, CH_2-O), 1.44 (t, *J* = 6.3 6H CH_3).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 143.9, 128.4, 127.3, 126.2, 78.2, 67.9, 24.2, 24.1.

((4-(Cyclopentyloxy)butoxy)methyl)benzene (95)[103]



Chemical Formula: $C_{16}H_{24}O_2$
Molecular Weight: 248.37

The reactions were performed as stated in General Procedure 3 using cyclopentanone (0.336 mL, 3.80 mmol) and 4-(benzyloxy)butan-1-ol (1.336 mL, 7.60 mmol). The product was purified by Biotage Isolera (25 g Sfar, EtOAc 0 - 5% in hexane). The product was a colourless oil (260 mg, 28%).

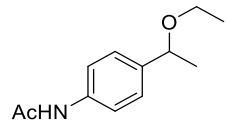
ν_{max}/cm^{-1}: 2949, 2866, 1453, 1358, 1089, 733, 697.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.35 – 7.26 (m, 5H, Ar-*H*), 4.50 (s, 2H- Ar-CH_2-O), 3.89 – 3.82 (m, 1H, C*H*-O), 3.49 (t, *J* = 6.28, 2H, CH_2-O), 3.38 (t, *J* = 6.15, 2H, CH_2-O), 1.75 – 1.46 (m, 12H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 138.7, 128.3, 127.6, 127.5, 81.2, 72.9, 70.3, 68.5, 32.3, 26.8, 26.7, 23.5.

_N_-(4-(1-Ethoxyethyl)phenyl)acetamide (128)

Section 1.4.22, Scheme 41, page 107.



Chemical Formula: $C_{12}H_{17}NO_2$
Molecular Weight: 207.27

The reactions were performed as stated in General Procedure 3 using *N*-(4-acetylphenyl)acetamide (0.673 g) and cyclohexylmethanol (0.935 mL, 2 equiv). Celite® filtration and work up was performed with EtOAc solvent. The product was purified by Biotage Isolera (25 g Sfar, EtOAc 0 - 50% in heptane). The product was an off white solid (220 mg, 28%).

Melting point = 98.4 °C

ν_{max}/cm^{-1}: 3293, 3256, 2974, 2879, 1667, 1606, 1550, 1511, 1411, 1370, 1318, 1264, 1098, 834, 756, 555.

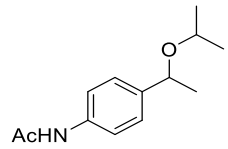
^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.46 (d, *J* = 8.6, 2H, Ar-*H*), 7.27 (d, *J* = 8.1, 2H, Ar-*H*), 7.11 (br. s, 1H, N*H*), 4.37 (q, *J* = 6.4, 1H, C*H*-O), 3.34 (q, *J* = 7.1, 2H, CH_2-O), 2.18 (s, 3H, CH_3-CO), 1.41 (d, *J* = 6.4, 3H, CH_3), 1.17 (t, *J* = 7.0, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 168.1, 140.3, 136.9, 126.8, 119.9, 77.3, 63.8, 24.6, 24.1, 15.4.

HRMS (ESCi®): m/z calculated for $[C_{12}H_{18}NO_2]^+$, Calculated mass = 208.1267, Measured mass = 208.1328 $[M+H]^+$

***N*-(4-(1-*iso*-Propoxyethyl)phenyl)acetamide (129)**

Section 1.4.22, Figure 39, page 94.



Chemical Formula: $C_{13}H_{19}NO_2$
Molecular Weight: 221.30

The reactions were performed as stated in General Procedure 3 using *N*-(4-acetylphenyl)acetamide (0.673 g) and cyclohexylmethanol (0.935 mL, 2 equiv). Celite® filtration and work up was performed with ^{i}PrOAc solvent. The product was purified by Biotage Isolera (25 g Sfar, EtOAc 20 - 50% in heptane). The product was a white solid (472 mg, 56%). 15% Ethyl acetamide was detected by comparison of NHAc proton signals in ^{1}H NMR.

Melting point = 86.3 °C

ν_{max}/cm^{-1}: 3291, 3255, 2971, 1662, 1604, 1551, 1511, 1409, 1368, 1318, 1087, 1022, 835, 753, 556.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.45 (d, *J* = 8.4, 2H, Ar-*H*), 7.30 – 7.25(m, 2H, Ar-*H*), 7.12 (br. s, 1H, N*H*), 4.50 (q, *J* = 6.6, 1H, C*H*-O), 3.47 (dt, *J* = 12.1, 6.1, 1H, C*H*-O), 2.17 (s, 3H, CH_3-CO), 1.38 (d, *J* = 6.4, 3H, CH_3), 1.14 (d, *J* = 6.2, 3H, CH_3), 1.08 (d, *J* = 6.2, 3H, CH_3).

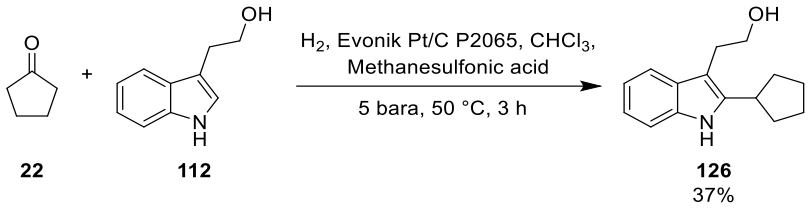
^{13}C NMR (101 MHz, $CDCl_3$), δ = 168.1, 128.3, 126.8, 120.1, 119.9, 74.2, 68.5, 24.6 23.3, 21.4.

HRMS (ESCi®): m/z calculated for $[C_{13}H_{20}NO_2]^+$, Calculated mass = 222.1424, Measured mass = 222.1487 $[M+H]^+$

1.7.28 C2 Indole Functionalisation

Results and discussion, Scheme 39, page 106.

2-(2-Cyclopentyl-1H-indol-3-yl)ethan-1-ol (126):



22 **112** **126**
37%

The reaction was performed as stated in General Procedure 2 using Evonik P2065, methanesulfonic acid (0.065 mL), 3-(2-hydroxyethyl)indole (0.322 g) and cyclopentanone (0.089 mL). The C2 functionalised product was purified by column chromatography (Biotage Isolera, KP SNAP Ultra 10 g), eluting with 20% EtOAc : Heptane. The C2 functionalised product was isolated as a pale yellow solid (84 mg, 37%).

Melting point: 139.7 °C

IR: ν_{max}/cm^{-1} 3402, 3328, 2953, 2923, 2864, 1496, 1037, 1015, 746, 498.

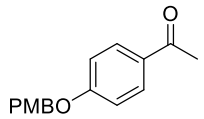
^{1}H NMR (400 MHz, DMSO-d_6), δ = 10.58 (br. s, 1H, *H*N), 7.38 (d, *J* = 7.9, 1H, ArC*H*), 7.24 (d, *J* = 7.9, 1H, ArC*H*), 6.97 (t, *J* = 7.6, 1H, ArC*H*), 6.91 (t, *J* = 7.4, 1H, ArC*H*), 4.57 (t, *J* = 5.4, 1H, O*H*), 3.50 (td, *J* = 7.5, 5.7, 2H, CH_2OH), 3.29 – 3.17 (m, 1H, C*H* cyclopentyl), 2.81 (t, *J* = 8.4, 2H, Ar-CH_2-CH_2OH), 2.01 – 1.92 (m, 2H, CH_2 cyclopentyl), 1.86 – 1.79 (m, 2H, CH_2 cyclopentyl), 1.75 – 1.65 (m, 4H, (CH_2)$_2$-(CH_2)$_2$-CH-O cyclopentyl).

^{13}C NMR (101 MHz, DMSO-d_6), δ = 139.3, 135.4, 128.3, 119.8, 117.9, 117.4, 110.5, 106.6, 62.0, 36.7, 33.0, 28.1, 25.2.

HRMS (ESCi®): m/z calculated for $[C_{15}H_{19}NO]^+$, Calculated mass = 230.1539, Measured mass = 230.1528 $[M]^+$

1.7.29 4-Hydroxyacetophenone Protection Reactions

1-(4-((4-Methoxybenzyl)oxy)phenyl)ethan-1-one (106):[104]



Chemical Formula: $C_{16}H_{16}O_3$
Molecular Weight: 256.30

To a solution of 1-(4-hydroxyphenyl)ethan-1-one (2.00 g, 14.69 mmol) in dry *N,N*-dimethylformamide (DMF) (20.0 mL), potassium carbonate (4.06 g, 29.4 mmol) and 4-methoxybenzyl chloride (2.00 mL, 14.69 mmol) were added and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, the mixture was quenched in ice water and the product was extracted into ethyl acetate (3 x 10 mL). The combined ethyl acetate extracts were washed with brine solution (2 x 10 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was partitioned between water and EtOAc, the organic phase separated and the aqueous layer was washed with EtOAc (thrice). The combined organic extracts were concentrated and the resulting solid was dry loaded onto a Biotage Isolera 50 g Sfar column and purified by column chromatography (10 - 100% EtOAc in heptane). The product was isolated as a white solid (3.149 g, 84%).

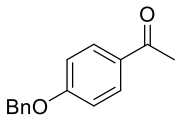
Melting point: 123.5 °C (literature melting point = 122 – 124 °C)[104]

ν_{max}/cm^{-1}: 2933, 1674, 1593, 1514, 1362, 1245, 1166, 1031, 992, 812, 590, 525.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.96 (d, *J* = 8.9, 2H, Ar-*H*), 7.38 (d, *J* = 8.6, 2H, Ar-*H*), 7.03 (d, *J* =8.9, 2H, Ar-*H*), 6.95, (d, *J* = 8.6, 2H, Ar-*H*), 5.08 (s, 2H, C*H*$_2$), 3.85 (s, 3H, OC*H*$_3$), 2.55 (s, 3H, C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 196.8, 162.7, 159.7, 130.6, 130.5, 129.3, 128.1, 114.5, 114.1, 70.0, 55.3, 26.3.

1-(4-(Benzyloxy)phenyl)ethan-1-one (105):[105]



Chemical Formula: $C_{15}H_{14}O_2$
Molecular Weight: 226.28

N,N-Dimethylformamide (DMF) (20.0 mL), 1-(4-hydroxyphenyl)ethan-1-one (2.00 g, 14.69 mmol), potassium carbonate (4.06 g, 29.4 mmol) and benzyl chloride (1.88 mL, 16.16 mmol) were stirred at room temperature for 16 h. After completion of the reaction, the mixture was quenched in ice water and the product was extracted into ethyl acetate (3 x 10 mL). The combined ethyl acetate extracts were washed with brine solution (2 x 10 mL), dried over sodium sulfate, concentrated under reduced pressure and the residue was purified by column chromatography (Biotage Isolera, 50 g Sfar, 10 - 100% EtOAc in heptane). The product was isolated as a white solid (1.008 g, 30%)

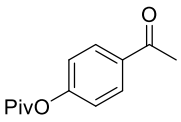
Melting point: 93.8 °C (literature melting point = 93.6 – 94 °C)[105]

ν_{max}/cm^{-1}: 1674, 1594, 1508, 1420, 1357, 1170, 1008, 827, 758, 709, 590, 559, 513.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.96 (d, *J* = 8.9, 2H, Ar-*H*), 7.47 – 7.39 (m, 5H, Ar-*H*), 7.04 (d, *J* = 9.1, 2H, Ar-*H*), 5.16 (s, 2H, C*H*$_2$), 2.58 (s, 3H, C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 196.7, 162.6, 136.2, 130.6, 130.5, 128.7, 128.2, 127.5, 114.6, 70.2, 26.4.

4-Acetylphenyl pivalate:[106]



Chemical Formula: $C_{13}H_{16}O_3$
Molecular Weight: 220.27

1-(4-Hydroxyphenyl)ethan-1-one (4.00 g, 29.4 mmol), dichloromethane (DCM) (100 mL) and triethylamine (4.50 mL, 32.3 mmol) were stirred at room temperature. Then, pivaloyl chloride (4 mL, 32.3 mmol) was added dropwise to the reaction mixture which was then stirred at room temperature overnight. The solvent was removed in vacuo. The residue was partitioned between water and DCM before organics were concentrated and purified by Biotage Isolera (50 g Sfar, 10 - 100% EtOAc in heptane). Product was isolated as a white solid (6.23 g, 96%).

Melting point: 54.9 °C (literature melting point = 53 – 55 °C)[106]

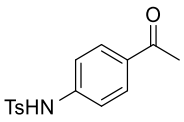
ν_{max}/cm^{-1}: 2972, 1742, 1678, 1597, 1478, 1358, 1264, 1166, 1123, 1015, 902, 604, 590.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.99 (d, *J* = 8.6, 2H, Ar-*H*), 7.16 (d, *J* = 8.6, 2H, Ar-*H*), 2.60 (s, 3H, C*H*$_3$), 1.37 (s, 9H, 3 x C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 196.9, 176.5, 154.9, 134.6, 129.9, 121.7, 39.2, 27.1, 26.6.

1.7.30 4-Aminoacetophenone Protection Reactions

4'-(4-Toluenesulfonamido)-acetophenone (108):[107]



Chemical Formula: $C_{15}H_{15}NO_3S$
Molecular Weight: 289.35

To a solution of 1-(4-aminophenyl)ethan-1-one (2.00 g, 14.80 mmol) in dichloromethane (DCM) (100.0 mL) was added pyridine (1.50 mL, 18.50 mmol) and 4-toluenesulfonyl chloride (3.53 g, 18.50 mmol). The reaction mixture was stirred for 3 h at room temperature to give a precipitate. The precipitate was filtered from the reaction mixture, and the filtrate was then washed with H_2O (300 ml × 3) and DCM (300 ml × 3). The combined DCM extracts were evaporated under reduced pressure to yield *N*-(4-acetylphenyl)-4-methylbenzenesulfonamide (3.78 g, 13.07 mmol, 88 % yield).

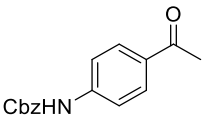
Melting point: 201.2 °C (literature melting point = 199 – 202 °C)[107]

ν_{max}/cm^{-1}: 3216, 1668, 1597, 1277, 1156, 1088, 910, 682, 629, 569, 547, 496.

^1H NMR (400 MHz, $CDCl_3$), δ = 7.87 (d, *J* = 8.6, 2H, Ar-*H*), 7.75 (d, *J* = 8.4, 2H, Ar-*H*), 7.28 (d, *J* = 8.1, 2H, Ar-*H*), 7.16 (d, *J* = 8.6, 2H, Ar-*H*), 6.91 (br. s, 1H, N*H*), 2.56 (s, 3H, CH_3), 2.41 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 196.7, 144.5, 141.0, 135.8, 133.4, 130.0, 129.9, 127.3, 119.0, 26.4, 21.6.

4-Carbobenzyloxyaminoacetophenone (107):[108]



Chemical Formula: $C_{16}H_{15}NO_3$
Molecular Weight: 269.30

To a solution of 1-(4-aminophenyl)ethan-1-one (2.00 g, 14.80 mmol) and sodium hydroxide (0.592 g, 14.80 mmol) in 50 mL of dioxane/H_2O (70:30), benzyl chloroformate (2.11 mL, 14.80 mmol) was added dropwise over 30 min at 0 °C followed by vigorous stirring of the reaction mixture overnight at room temperature. The solvent was evaporated under reduced pressure, the residue was dissolved in ethyl acetate and then washed with water once and brine once. The organic phase was then evaporated under reduced pressure and the residue was purified by Biotage Isolera (50 g Sfar, 20 - 100% EtOAc in heptane). The product was obtained as a pale yellow solid (2.618 g, 66%).

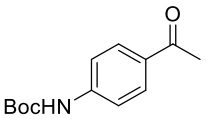
Melting point: 129.0 °C (literature melting point = 130 – 132 °C)[108]

ν_{max}/cm^{-1}: 3284, 2966, 1719, 1667, 1589, 1537, 1413, 1319, 1217, 1047, 843, 722, 605, 590, 484.

^1H NMR (400 MHz, $CDCl_3$), δ = 7.95 (d, *J* = 8.6, 2H, Ar-*H*), 7.51 (d, *J* = 8.6, 2H, Ar-*H*), 7.45 – 7.36 (m, 5H, Ar-*H*), 6.85 (br. s, 1H, N*H*) 5.25 (s, 2H, CH_2), 2.59 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 196.8, 152.8, 142.2, 135.6, 132.4, 130.8, 129.9, 128.7, 128.6, 128.4, 117.6, 67.4, 26.4.

***tert*-Butyl (4-acetylphenyl)carbamate (104): [109]**



Chemical Formula: $C_{13}H_{17}NO_3$
Molecular Weight: 235.28

1-(4-Aminophenyl)ethan-1-one (2.00 g, 14.80 mmol), di-*tert*-butyl dicarbonate (3.44 mL, 14.80 mmol) and 50 mL of dioxane were stirred and heated to reflux overnight. The solvent was evaporated under reduced pressure and the residue was purified by Biotage Isolera (50 g Sfar, 20 - 100% EtOAc in heptane). The product was isolated as an off-white solid (2.15 g, 62%)

Melting point: 145.6 °C (literature melting point = 145 – 147 °C)[109]

ν_{max}/cm^{-1}: 2974, 1718, 1661, 1584, 1368, 1319, 1236, 1150, 1052, 1033, 858, 587.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.91 (d, *J* = 8.6, 2H, Ar-*H*), 7.45 (d, *J* = 8.6, 2H, Ar-*H*), 6.69 (br. s, 1H, N*H*), 2.56 (s, 3H, CH_3), 1.53 (s, 9H, 3 x CH_3).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 196.8, 152.1, 142.9, 131.9, 129.8, 117.4, 81.3, 28.3, 26.3.

1.7.31 Deuterium Labelling Studies

Results and discussion, section 1.4.23, page 108.

1.7.31.1 General Procedure 5 for Deuterium Labelling Studies

JM B501018-5 Pt/C (0.030 g, 7.60 µmol), carbonyl compound (3.80 mmol), *n*-butanol (0.695 mL, 7.60 mmol), methanesulfonic acid (0.740 mL, 11.40 mmol), and cyclopentyl methyl ether (3.2 mL) were added to the ChemSCAN or Endeavor reactor vessels, sealed and purged with

N_2 (three times at 4 bara) followed by H_2 (twice at 5 bara). The reactions were stirred at 20 °C under 5 bara of hydrogen for 6 hours. The reactor was cooled and an LCMS sample was taken (10 µL/mL in methanol). The reaction mixture was filtered through Celite®, washed with saturated aqueous sodium bicarbonate and dried over $MgSO_4$. The organic phase was then evaporated under reduced pressure. The product was purified by Biotage Isolera and product containing fractions were evaporated and analysed by NMR.

1.7.31.2 Replacement of Hydrogen with Deuterium

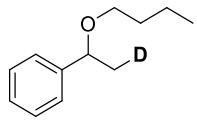
Results and discussion, section 1.4.23, page 108.

Reactions were performed as stated in GP5 within the HEL ChemSCAN II high pressure reactor. Hydrogen gas was replaced with deuterium.

Deuteration patterns were also confirmed within the Biotage Endeavour hydrogenator using the same protocol.

Results are shown in Scheme 45 and Scheme 46 on page 110.

(1-Butoxyethyl-2-*d*)benzene:



Chemical Formula: $C_{12}H_{17}DO$
Molecular Weight: 179.28

Acetophenone (0.443 mL, 3.80 mmol) was used as the carbonyl component. Product was purified by Biotage Isolera (50 g Sfar, 0 – 10% EtOAc in heptane).

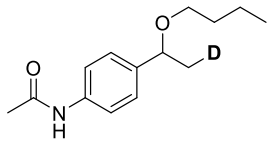
^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.37 – 7.23 (m, 5H), 4.34 (q, *J* = 6.4, 1H), 3.29 (t, *J* = 6.6, 2H), 1.59 – 1.51 (m, 2H), 1.43 (d, *J* = 6.4, 2H), 1.42 – 1.32 (m, 2H), 0.88 (t, *J* = 7.4, 3H).

Reduced integral for CH_3 proton signal was observed from comparison with non-deuterated analogue.

Non-deuterated ^{1}H NMR data of (1-butoxy)ethylbenzene for reference purposes:

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.38 – 7.20 (m, 5H, Ar*H*), 4.37 (q, *J* = 6.4, 1H, Ar-C*H*-O), 3.30 (t, *J* = 6.6, 2H, CH_2-O), 1.57 – 1.52 (m, 2H), 1.43 (d, *J* = 6.4, 3H, CH_3-CH-O), 1.41 – 1.29 (m, 2H), 0.88 (t, *J* = 7.4, 3H, CH_3).

***N*-(4-(1-Butoxyethyl-2-*d*)phenyl)acetamide:**



Chemical Formula: $C_{14}H_{20}DNO_2$
Molecular Weight: 236.33

N-(4-Acetylphenyl)acetamide (0.673 g, 3.80 mmol) was used as the carbonyl component. Product was purified by Biotage Isolera (50 g Sfar, 10 – 100% EtOAc in heptane).

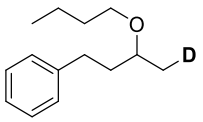
^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.48 – 7.38 (m, 2H, Ar-*H*), 7.28 – 7.24 (m, 2H, Ar-*H*), 7.20 – 7.05 (m, 1H, N*H*), 4.35 (q, *J* = 6.2, 1H, C*H*-O), 3.27 (t, *J* = 6.6, 2H, CH_2-O), 2.17 (s, 3H, CH_3-CO), 1.57 – 1.46 (m, 2H), 1.40 (d, *J* = 6.4, 2H, CH_2D), 1.38 – 1.19 (m, 2H), 0.88 (t, *J* = 7.4, 3H, CH_3).

Reduced integral for CH_3 proton signal was observed from comparison with non-deuterated analogue.

Non-deuterated ^{1}H NMR data of *N*-(4-(1-Butoxyethyl)phenyl)acetamide for reference purposes:

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.46 (d, *J* = 8.4, 2H, Ar-*H*), 7.26 (overlapping br. s and d, *J* = 8.4, 3H Ar-*H* + N*H*), 4.35 (q, *J* = 6.4, 1H, C*H*-O), 3.27 (t, *J* = 6.6, 2H, CH_2-O), 2.17 (s, 3H, CH_3CO), 1.58 – 1.46 (m, 2H), 1.40 (d, *J* = 6.4, 3H, CH_3), 1.37 – 1.19 (m, 2H, CH_2), 0.88 (t, *J* = 7.4, 3H, CH_3).

(3-Butoxybutyl-4-*d*)benzene:



Chemical Formula: $C_{14}H_{21}DO$
Molecular Weight: 207.34

4-Phenylbutan-2-one (0.569 mL, 3.80 mmol) was used as the carbonyl component. Product was purified by Biotage Isolera (25 g Sfar, 0 – 10% EtOAc in heptane).

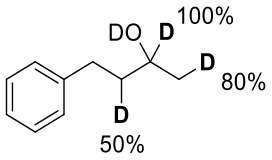
^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.30 – 7.25 (m, 2H, Ar-*H*), 7.21 – 7.15 (m, 3H, Ar-*H*), 3.50 (dt, *J* = 9.2, 6.5, 1H, C*H*-O), 3.40 – 3.27 (m, 2H, CH_2-O), 2.78 – 2.70 (m, 1H), 2.68 – 2.61 (m, 1H), 1.90 – 1.79 (m, 1H), 1.74 – 1.65 (m, 1H), 1.60 – 1.51 (m, 2H), 1.45 – 1.35 (m, 2H), 1.16 (d, *J* = 6.2, 2H, CH_2D), 0.93 (t, *J* = 7.4, 3H, CH_3).

Reduced integral for CH_3 proton signal was observed from comparison with non-deuterated analogue.

Non-deuterated ^{1}H NMR data of (3-butoxybutyl)benzene for reference purposes:

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.33 – 7.27 (m, 2H, Ar*H*), 7.24 – 7.16 (m, 3H, Ar*H*), 3.56 – 3.45 (m, 1H, C*H*-O), 3.45 – 3.30 (m, 2H, CH_2-O), 2.82 – 2.62 (m, 2H, Ar-CH_2), 1.87 (dddd, 1H, *J* = 13.5, 9.8, 7.5, 5.7), 1.77 – 1.67 (m, 1H), 1.64 – 1.51 (m, 2H), 1.49 – 1.36 (m, 2H), 1.21 – 1.16 (d, *J* = 6.2, 3H), 1.0 – 0.94 (t, *J* = 7.3, 3H).

4-Phenylbutan-1,2,3-*d*$_3$-2-ol-*d*:



Chemical Formula: $C_{10}H_{10}D_4O$
Molecular Weight: 154.25

4-Phenylbutan-2-one (0.569 mL, 3.80 mmol) was used as the carbonyl component.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.31 – 7.25 (m, 2H), 7.22 – 7.16 (m, 3H), 2.93 – 2.86 (m, 2H), 2.79 – 2.71 (m, 1.5H), 2.15 – 2.10 (m, 2.2H).

1.7.31.3 Replacement of Hydrogen with Deuterium within Unoptimised Reaction

Results and discussion, section 1.4.23, page 108. Exact reaction found in Scheme 48, page 112.

Evonik Noblyst P2053 5% Pt (0.117 g), cyclopentanone (0.089 mL), *n*-butanol (0.183 mL), 4 Å activated molecular sieves (500 mg) and chloroform (4 mL) were added to the ChemSCAN reactor vessels, sealed and purged with N_2 (three times at 4 bara) followed by H_2 (twice at 5 bara). The reaction was stirred at 50 °C under 5 bara of hydrogen for 6 hours. The reactor was cooled and the reaction mixture was filtered through Celite®, partitioned with sodium bicarbonate and dried over $MgSO_4$. The organic extracts were then evaporated under reduced pressure (200 mbar at 45 °C). The crude reaction mixture was analysed by NMR spectroscopy and compared to a previously synthesised sample of unlabelled cyclopentyl butyl ether. 1H signals either side of the ether linkage were observable in a 1:2 ratio.

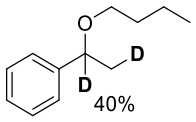
^{1}H NMR (400 MHz, $CDCl_3$), δ = 3.92-3.82 (m, 1H, *H*C-O), 3.38 (t, *J* = 6.6, 2H, O-C*H*$_2$). Other signals present but not definable within crude spectra

1.7.31.4 Replacement of Hydrogen and Acid with Deuterated Equivalents

Results and discussion, section 1.4.23, page 108.

Reactions were performed as stated in GP5 within the HEL ChemSCAN II high pressure reactor. Hydrogen gas was replaced with deuterium and methanesulfonic acid was replaced with d_4-methanesulfonic acid (0.771 mL). Results can be found summarised in Scheme 49, page 112.

(1-Butoxyethyl-1,2-*d*$_2$)benzene:



Chemical Formula: $C_{12}H_{17}DO$
Molecular Weight: 179.28

Acetophenone (0.443 mL, 3.80 mmol) was used as the carbonyl component.

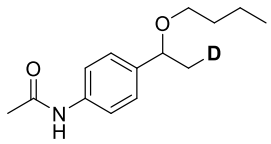
^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.37 – 7.23 (m, 5H), 4.42 – 4.33 (m, 0.6H), 3.35 – 3.27 (m, 2H), 1.59 – 1.51 (m, 2H), 1.44 – 1.32 (m, 4H), 0.91 – 0.85 (m, 3H).

Reduced integral for C*H*-O and C*H*$_3$ proton signals were observed from comparison with non-deuterated analogue.

Non-deuterated ^{1}H NMR data of (1-butoxy)ethylbenzene for reference purposes:

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.38 – 7.20 (m, 5H, Ar*H*), 4.37 (q, *J* = 6.4, 1H, Ar-C*H*-O), 3.30 (t, *J* = 6.6, 2H, CH_2-O), 1.57 – 1.52 (m, 2H), 1.43 (d, *J* = 6.4, 3H, CH_3-CH-O), 1.41 – 1.29 (m, 2H), 0.88 (t, *J* = 7.4, 3H, CH_3).

_N_-(4-(1-Butoxyethyl-2-_d_)phenyl)acetamide:



Chemical Formula: $C_{14}H_{20}DNO_2$
Molecular Weight: 236.33

N-(4-Acetylphenyl)acetamide (0.673 g, 3.8 mmol) was used as the carbonyl component.

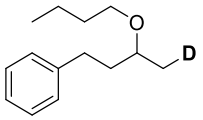
^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.48 – 7.38 (m, 2H), 7.28 – 7.24 (m, 2H), 7.20 – 7.05 (m, 1H), 4.35 (q, *J* = 6.2, 1H), 3.27 (t, *J* = 6.6, 2H), 2.17 (s, 3H), 1.57 – 1.46 (m, 2H), 1.40 (d, *J* = 6.4, 2H), 1.38 – 1.19 (m, 2H), 0.88 (t, *J* = 7.4, 3H).

Reduced integral for CH_3 proton signal was observed from comparison with non-deuterated analogue.

Non-deuterated ^{1}H NMR data of *N*-(4-(1-Butoxyethyl)phenyl)acetamide for reference purposes:

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.46 (d, *J* = 8.4, 2H, Ar-*H*), 7.26 (overlapping br. s and d, *J* = 8.4, 3H Ar-*H* + N*H*), 4.35 (q, *J* = 6.4, 1H, C*H*-O), 3.27 (t, *J* = 6.6, 2H, CH_2-O), 2.17 (s, 3H, CH_3CO), 1.58 – 1.46 (m, 2H), 1.40 (d, *J* = 6.4, 3H, CH_3), 1.37 – 1.19 (m, 2H, CH_2), 0.88 (t, *J* = 7.4, 3H, CH_3).

(3-Butoxybutyl-4-*d*)benzene:



Chemical Formula: $C_{14}H_{21}DO$
Molecular Weight: 207.34

4-Phenylbutan-2-one (0.569 mL, 3.80 mmol) was used as the carbonyl component. Non-deuterated methanesulfonic acid was used.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.30 – 7.25 (m, 2H), 7.21 – 7.15 (m, 3H), 3.50 (dt, *J* = 9.2, 6.5, 1H), 3.40 – 3.27 (m, 2H), 2.78 – 2.70 (m, 1H), 2.68 – 2.61 (m, 1H), 1.90 – 1.79 (m, 1H), 1.74 – 1.65 (m, 1H), 1.60 – 1.51 (m, 2H), 1.45 – 1.35 (m, 2H), 1.16 (d, *J* = 6.2, 2H), 0.93 (t, *J* = 7.4, 3H).

Reduced integral for C*H*$_3$ proton signal was observed from comparison with non-deuterated analogue.

Non-deuterated ^{1}H NMR data of (3-butoxybutyl)benzene for reference purposes:

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.33 – 7.27 (m, 2H, Ar*H*), 7.24 – 7.16 (m, 3H, Ar*H*), 3.56 – 3.45 (m, 1H, C*H*-O), 3.45 – 3.30 (m, 2H, C*H*$_2$-O), 2.82 – 2.62 (m, 2H, Ar-C*H*$_2$), 1.87 (dddd, 1H, *J* = 13.5, 9.8, 7.5, 5.7), 1.77 – 1.67 (m, 1H), 1.64 – 1.51 (m, 2H), 1.49 – 1.36 (m, 2H), 1.21 – 1.16 (d, *J* = 6.2, 3H), 1.0 – 0.94 (t, *J* = 7.3, 3H).

1.7.31.5 Further Deuteration Studies in the Preparation of (1-Butoxyethyl)benzene

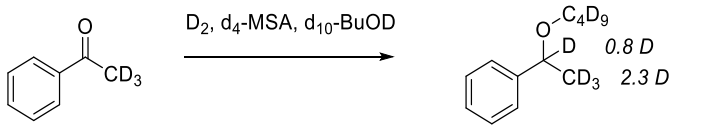
Results and discussion, section 1.4.23, page 108.

Reactions were performed as stated in GP5 within the Biotage Endeavor high pressure reactor. Unless specified, deuterium gas, d_4-methanesulfonic acid (0.748 mL), d_3-acetophenone (0.444 mL) and d_{10} *n*-butanol (0.695 mL) was used instead of their unlabelled counterparts. Protium containing compounds are highlighted in bold when used below. Results can be found summarised in Scheme 50, page 115.

Non-deuterated ^{1}H NMR data of (1-butoxy)ethylbenzene for reference purposes:

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.38 – 7.20 (m, 5H, Ar*H*), 4.37 (q, *J* = 6.4, 1H, Ar-C*H*-O), 3.30 (t, *J* = 6.6, 2H, C*H*$_2$-O), 1.57 – 1.52 (m, 2H), 1.43 (d, *J* = 6.4, 3H, C*H*$_3$-CH-O), 1.41 – 1.29 (m, 2H), 0.88 (t, *J* = 7.4, 3H, C*H*$_3$).

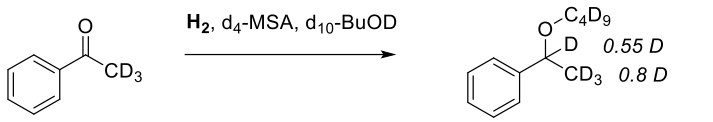
(1-((Butyl-*d*$_9$)oxy)ethyl-1,2,2,2-*d*$_4$)benzene:



Chemical Formula: $C_{12}H_5D_{13}O$
Molecular Weight: 191.35

^{1}H NMR (400 MHz, d_2-DCM), δ = 7.37 – 7.23 (m, 5H), 4.42 – 4.33 (m, 0.2H), 1.62 (s, 0.7H).

Reduced integrals were observed for C*H*-O and C*H*$_3$ from comparison with non-deuterated analogue.

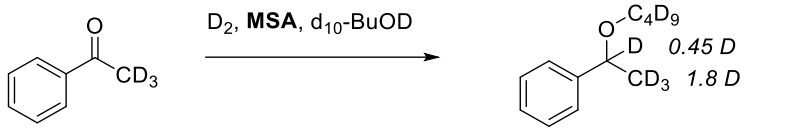


Chemical Formula: $C_{12}H_5D_{13}O$
Molecular Weight: 191.35

Hydrogen gas was used.

^{1}H NMR (400 MHz, d_2-DCM), δ = 7.37 – 7.23 (m, 5H), 4.42 – 4.33 (m, 0.45H), 1.44 – 1.32 (m, 2.2H).

Reduced integrals were observed for C*H*-O and CH_3 from comparison with non-deuterated analogue.



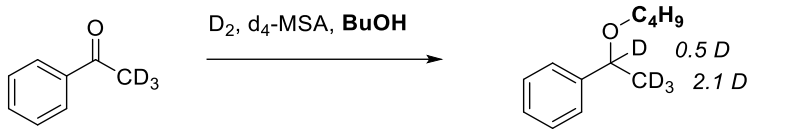
Chemical Formula: $C_{12}H_5D_{13}O$
Molecular Weight: 191.35

Methanesulfonic acid was used.

^{1}H NMR (400 MHz, d_2-DCM), δ = 7.37 – 7.23 (m, 5H), 4.42 – 4.33 (m, 0.55H), 1.44 – 1.32 (m, 1.2H).

Reduced integrals were observed for C*H*-O and CH_3.

(1-((Butoxy)ethyl-1,2,2,2-*d*$_4$)benzene:



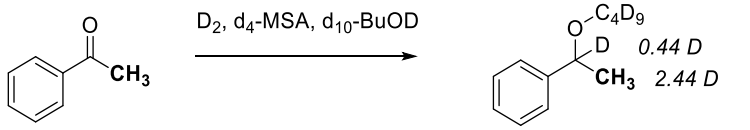
Chemical Formula: $C_{12}H_{14}D_4O$
Molecular Weight: 182.30

n-Butanol was used.

^{1}H NMR (400 MHz, d_2-DCM), δ = 7.37 – 7.23 (m, 5H), 4.42 – 4.33 (m, 0.5H), 3.35 – 3.27 (m, 2H), 1.59 – 1.51 (m, 2H), 1.44 – 1.32 (m, 0.9H), 0.91 – 0.85 (m, 3H).

Reduced integrals were observed for C*H*-O and CH_3 from comparison with non-deuterated analogue.

(1-((Butyl-*d*$_9$)oxy)ethyl-1-*d*)benzene:



Chemical Formula: $C_{12}H_8D_{10}O$
Molecular Weight: 188.34

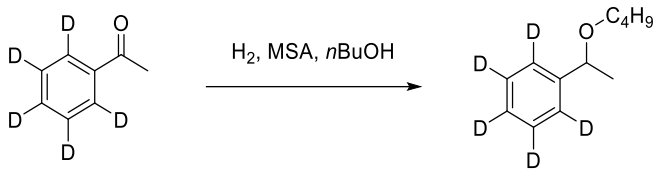
Acetophenone was used.

^{1}H NMR (400 MHz, d_2-DCM), δ = 7.37 – 7.23 (m, 5H), 4.42 – 4.33 (m, 0.56H), 1.44 – 1.32 (m, 0.56H).

No butyl proton signals were observed as well as reduced integrals for C*H*-O and CH_3 from comparison with non-deuterated analogue.

1.7.31.6 Investigation of Aromatic Hydrogen Isotope Exchange

1-(1-Butoxyethyl)benzene-2,3,4,5,6-d_5:



Chemical Formula: $C_{12}H_{13}D_5O$
Molecular Weight: 183.31

d_5-Acetophenone (0.451 mL), methanesulfonic acid (0.748 mL), *n*-butanol (0.695 mL) and hydrogen gas were used.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 4.37 (q, *J* = 6.4, 1H, Ar-C*H*-O), 3.30 (t, *J* = 6.6, 2H, CH_2-O), 1.57 – 1.52 (m, 2H), 1.43 (d, *J* = 6.4, 3H, CH_3-CH-O), 1.41 – 1.29 (m, 2H), 0.88 (t, *J* = 7.4, 3H, CH_3).

No aromatic proton signals were observed from comparison with non-deuterated analogue.

Non-deuterated ^{1}H NMR data of (1-butoxy)ethylbenzene for reference purposes:

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.38 – 7.20 (m, 5H, Ar*H*), 4.37 (q, *J* = 6.4, 1H, Ar-C*H*-O), 3.30 (t, *J* = 6.6, 2H, CH_2-O), 1.57 – 1.52 (m, 2H), 1.43 (d, *J* = 6.4, 3H, CH_3-CH-O), 1.41 – 1.29 (m, 2H), 0.88 (t, *J* = 7.4, 3H, CH_3).

2 Iridium Catalysed Allylic Alcohol Etherification

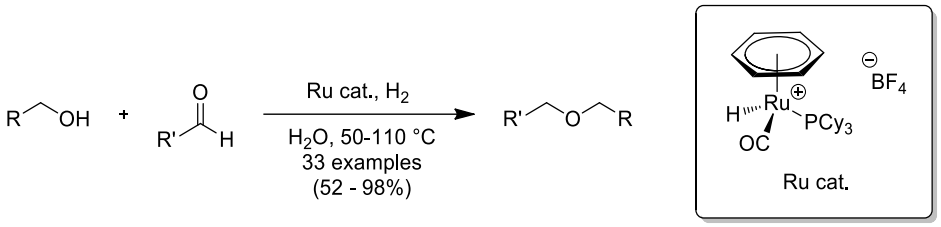
2.1 Introduction

Homogeneous catalysis has been an alternative to heterogeneous catalysis for many years. As homogeneous catalysts are commonly ligated by organic compounds, the structure of these organic compounds can be easily varied. These tuneable ligands around the metal centre can allow for site-selectivity and induction of chirality.[110] The benefits, however, come with a price, as some complex ligands for homogeneous catalysis can be more expensive than the metal itself, especially when utilising chiral variants. Homogeneous catalysis is also more amenable to mechanism elucidation as, by nature, the reaction mixtures are homogeneous and can be monitored by a broad range of analytical techniques, for example, NMR spectroscopy. On the other hand, homogeneous reaction mixtures can result in difficulty in separation of the catalyst from the product.

2.1.1 Reductive Methods

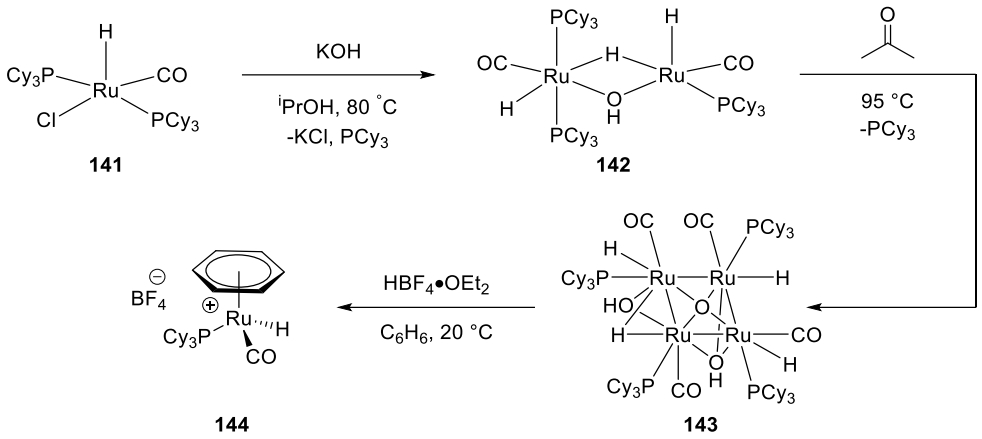
Catalytic ether formations have been reported utilising a range of different homogeneous catalysts from a number of different starting materials. Methodologies most similar to the reductive etherification (described in Chapter 1) would entail coupling of a carbonyl component with an alcohol. Yi *et al.* reported the use of a cationic ruthenium-centred catalyst and hydrogen gas to perform a homogeneous etherification reaction (Scheme 58).[111] This method reportedly has good scope and functional group tolerance, and is applicable to aliphatic, and electron-poor and electron-rich aryl aldehydes. Additionally, selective mono-etherification of a diol has also been demonstrated. Most desirably, the only by-product of this reaction is water, and the hydrogen used as the reducing agent can be readily produced

from water, *via* electrolysis. The downside to this method is the stability of the cationic ruthenium-centred catalyst. Its preparation requires strict inert atmosphere techniques, and the reductive etherification reactions are reported to require the use of a glovebox.[112-114] Although feasible, handling of highly air-sensitive materials on manufacturing scale is particularly challenging, and comes with considerable added financial implications.



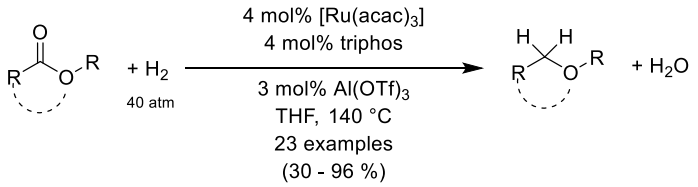
Scheme 58: Catalytic reductive etherification via ruthenium-centred catalyst and hydrogen gas.

Another issue with the cationic ruthenium centred catalyst in this work is the use of benzene in the final reaction stage of catalyst preparation (Scheme 59). Benzene is a carcinogenic reagent and, as such, is prohibited for use within pharmaceutical production.[115] This means that, for this project, synthesis of the exact catalyst utilised in the Yi method would not be practical, and benzene in the product complex would have to be replaced with toluene or another suitable ligand. Indeed, some investigation has already been performed by Yi and co-workers into ligand replacement. They report that replacement of the benzene ring with three water ligands, three alcohol ligands, or one triol ligand, results in catalysts which display similar catalytic activity to the parent benzene-containing complex (Scheme 59).[111] These results are an encouraging example of catalyst development towards a safer and more practical reductive etherification method, and, as such, warrant further attention.



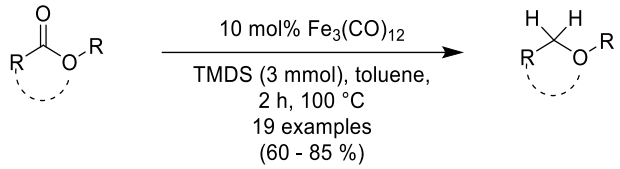
Scheme 59: Synthesis of the cationic ruthenium catalyst used in the Yi reductive etherification method.

Ethers have also been reported to be accessible through reduction of esters or carboxylic acids in the presence of alcohols, and work in this area has been pioneered by both Beller and Sakai. Beller *et al.* reported a ruthenium catalyst/Lewis acid system for the reduction of esters or acids in the presence of alcohols, to afford the ether product (Scheme 60).[116]



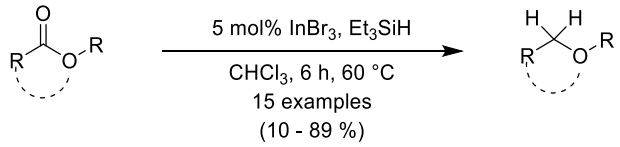
Scheme 60: Ruthenium catalysed hydrogenation of esters to form ethers.

Although this is an effective method of synthesising ethers from readily available starting materials, and the use of hydrogen gas as a reductant is very atom economical, use of 40 atmospheres of pressure requires specialist equipment and specific training for the operator. These issues were, however, addressed in an subsequent report from the Beller group, using an earth abundant, base metal (specifically, iron) catalyst (Scheme 61).[117]



Scheme 61: Iron catalysed reduction of esters to form ether products.

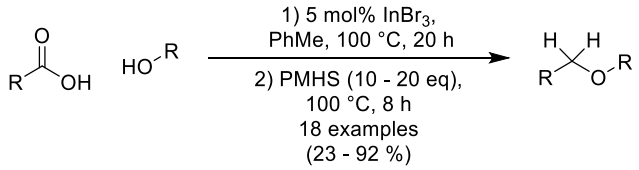
This second etherification method from the Beller group utilises a silane, thus avoiding the high pressures required when hydrogen is employed as the reductant. It also makes use of a relatively cheap and available iron catalyst, which is used without the need for any additional ligands. This iron catalyst does come with associated hazards, as it is a flammable solid, a source of volatile Fe(0) and also a potential source of carbon monoxide. Although the reaction conditions for this iron-catalysed etherification could be more readily implemented than the previously discussed ruthenium system, the substrate scope is not nearly as broad, with the large majority of substrates being saturated, unfunctionalised esters.



Scheme 62: Indium catalysed reduction reaction of esters to form corresponding ethers.

Further work on hydrosilylation reactions of esters to form ethers was performed by Sakai *et al.*[118] This reported method employs triethylsilane with an indium(III) bromide catalyst to afford the ether product under very mild reaction conditions. Although the substrate scope for this reaction is broader than that of the Beller reports, and includes a primary halide, a thiophene and a reduction of butyrolactone to THF; other substrates, such as benzylic or

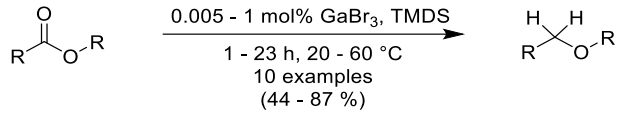
allylic esters, were not tolerated. Use of these benzylic and allylic esters resulted in a deoxygenation reaction where the deacetoxylated product was formed preferentially.



Scheme 63: Indium catalysed reduction reaction of carboxylic acid and alcohol starting materials to form ether products.

The substrate scope was, however, expanded in a second publication by the Sakai group (Scheme 63).[119] This reaction, between an alcohol and a carboxylic acid, in the presence of an indium catalyst with a silane reductant, was shown to tolerate allylic and benzylic substrates to form the corresponding ethers in moderate to good yields. Although this method has many beneficial features, such as readily available starting materials, an inexpensive catalyst and good substrate scope, the use of a silane reductant in 10 - 20 equivalents excess is particularly wasteful and decreases the atom economy of the reaction drastically.

A method to address the many issues relating to performing this methodology on a large scale, such as expensive reagents, hazardous reagents or high pressures, was developed by Metzger *et al.* (Scheme 64).[120] Metzger aimed to address the high catalyst loadings, wasteful excess of silane reductant, use of chlorinated solvents, depleting sources of indium and toxicity of $Fe_3(CO)_{12}$ in the context of unsaturated fatty ester reduction. The corresponding ethers formed by reduction of these esters are of potential importance to the cosmetics, flavours and fragrances, and lubricants industries. As such, a method amenable to large scale synthesis would be desirable.

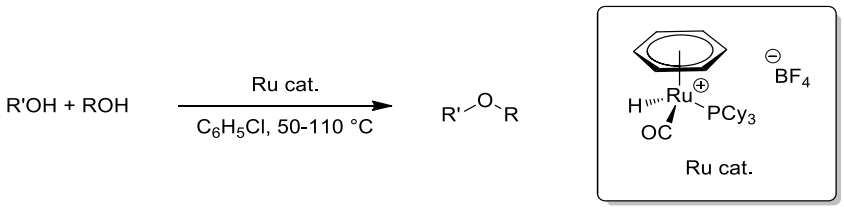


Scheme 64: Gallium catalysed reduction reaction of carboxylic acids to form ether products.

To make this methodology viable for large scale synthesis, Metzger utilised 0.005 – 1 mol% $GaBr_3$ catalyst, with 1,1,3,3-tetramethyldisiloxane (TMDS) as a reductant. These reactions were performed at room temperature, without solvent and with relatively short reaction times. This reaction also requires no aqueous work up or purification by column chromatography; products are isolated via simple distillation.

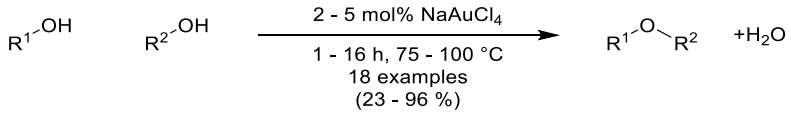
2.1.2 Etherification of Alcohols

Yi *et al.* reported a dehydrative etherification reaction of two alcohols, using the same ruthenium catalyst designed by the group for etherifications between carbonyls and alcohols. Although this report uses the same catalyst system, the reaction is performed in the absence of hydrogen (Scheme 65).[121] As there is no reducing agent in the reaction mixture, this suggests that the reaction most probably does not progress through similar mechanisms to the previously discussed protocol but instead, a dehydrative substitution reaction is proposed.



Scheme 65: Catalytic dehydrative etherification reaction utilising Yi's cationic ruthenium centred catalyst.

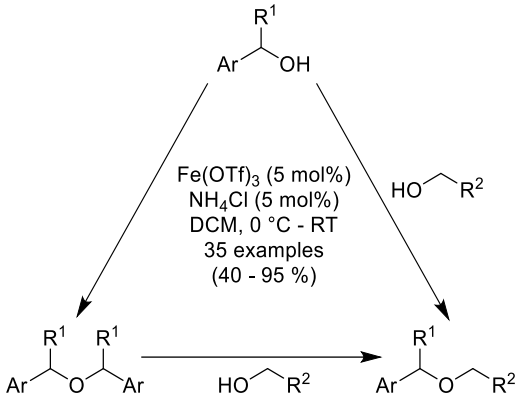
Other catalytic etherification methods have also been reported, from alcohol starting materials. A gold-catalysed etherification reaction was reported by Medio-Simón *et al.*, showing a preference for unsymmetrical ether products (Scheme 66).[122] This methodology has an impressive substrate scope, with primary benzylic, secondary benzylic, primary alkyl, secondary alkyl and tertiary alkyl alcohols all being tolerated. However, increasing steric bulk around the reacting sites generally results in a lower yield. It is also reported that chiral alcohol starting materials are racemised under the reaction conditions, forming racemic ethers. This reaction is also performed in the absence of solvent, using only starting materials to solvate the catalyst. Although this makes for a more economical process, neat reactions are not commonly used in pharmaceutical process chemistry settings. The solvent not only plays an important role by homogenising the reaction components but also can act as a heat sink, which is important from a process safety perspective.



Scheme 66: Gold catalysed etherification reaction of two alcohols.

Through use of an iron catalyst, the Gunanathan group demonstrated that one alcohol could be dimerised to form the symmetrical ether.[123] Interestingly, in the presence of a second alcohol, the unsymmetrical ether was obtained preferentially. Through thorough mechanistic investigation, it was determined that the unsymmetrical ether was obtained through initial formation of the symmetrical product which went on to react with the second alcohol to form the unsymmetrical ether product. This methodology was subsequently identified as an ether formation or a transetherification reaction, depending on the choice of alcohols or ether and alcohol as the starting materials. The scope of the reaction was very good, with

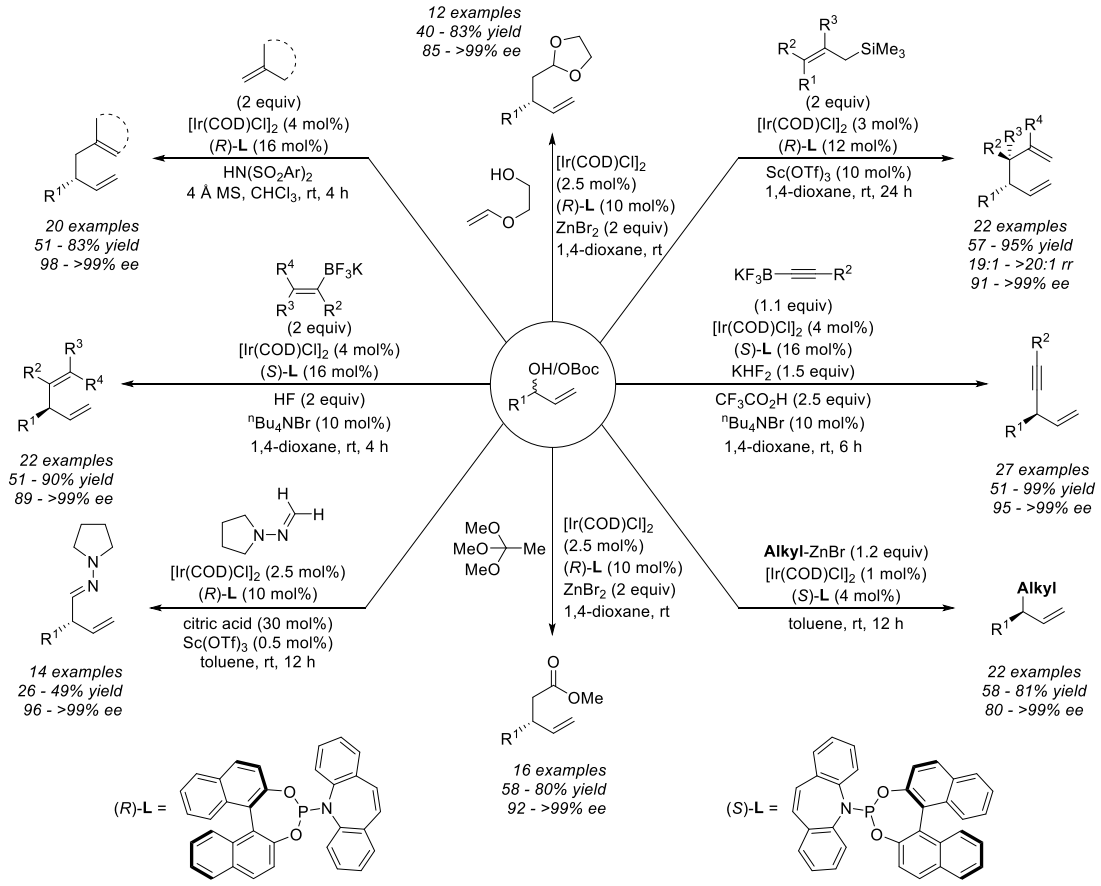
alkynes, alkenes and halides being tolerated, along with nitrile and nitro groups. This methodology does, however, require one of the alcohol coupling partners to be a benzylic alcohol.



Scheme 67: Iron catalysed etherification and transetherification reactions to form benzylic ethers.

2.1.3 Allylic Alcohol Substitution Reactions

Nucleophilic allylic substitution reactions, such as those pioneered by Carreira *et al.*, have been shown to include etherification reactions through activation of allylic alcohol substrates with an iridium catalyst (Scheme 68).[124] This impressive body of work has shown the allylic alcohol and iridium catalyst system to be an effective way of accessing not only ethers, but also amines and thioethers.[125] This approach can also be used with a number of carbon-centred nucleophiles to access C-C bond forming reactions.[126-127]

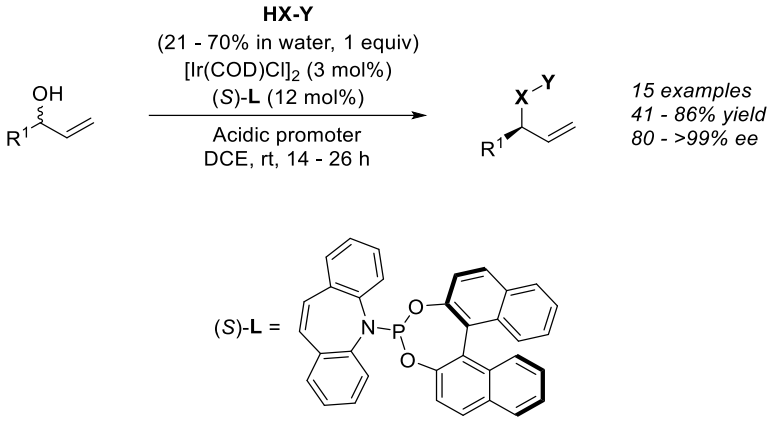


Scheme 68: C-C bond forming iridium catalysed allylic alcohol substitution reactions.

The myriad of allylic alcohol substitution reactions outlined in Scheme 68 are all proposed to proceed via the same reaction intermediate.[128] When the activated or unactivated allylic alcohol, in the presence of a Lewis- or Brønsted acid, is reacted with the iridium complex, a π-allyl iridium complex is thought to be formed. This π-allyl iridium complex is then though to be attacked by the nucleophile to form a diverse selection of products. A number of applications of this reaction have been developed by the Carreira group and are now discussed.

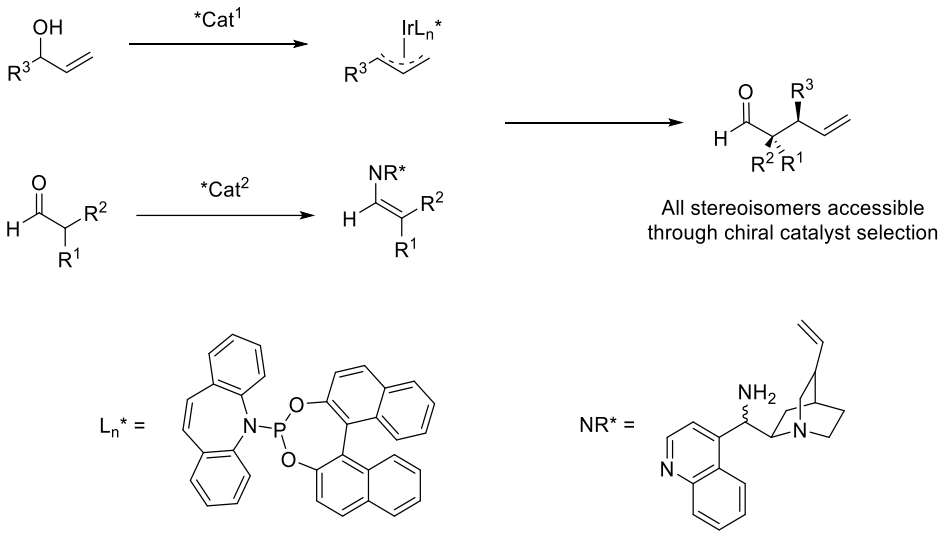
By taking advantage of the fact that nucleophilic addition of water to the allyl-iridium complex returns the allylic alcohol starting material, the Carreira group were able to utilise

nucleophiles commonly available as aqueous solutions (Scheme 69).[129] This allowed the practical synthesis of a number of hydrazines, peroxides, thioethers and hydroxylamines.



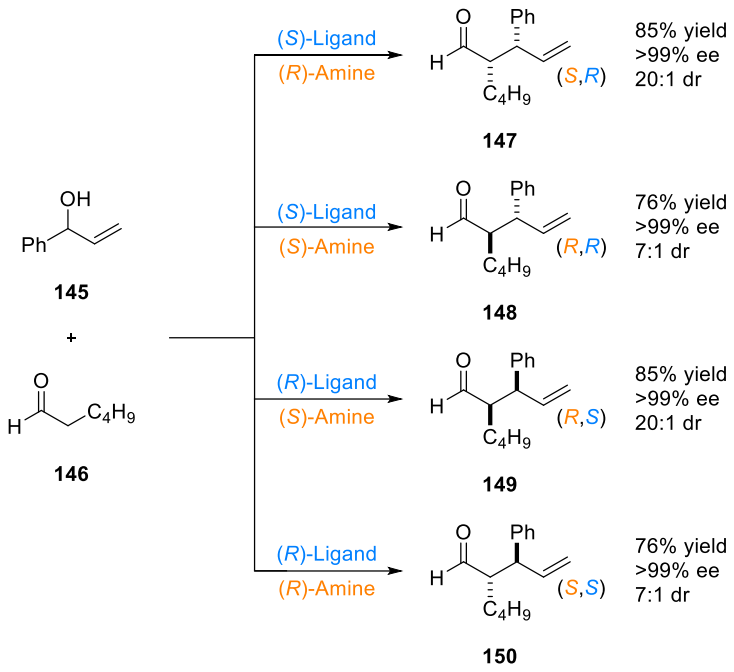
Scheme 69: Iridium catalysed allylic alcohol substitution reactions of nucleophiles commonly available as aqueous solutions.

A highly attractive aspect of the work developed by Carreira *et al*. is the amenability of the system to asymmetric catalysis. Through use of a novel phosphoramidite olefin ligand (**L**), chiral products are afforded in excellent yields and with high stereoselectivity. In fact, through use of enantioselective nucleophile generation, the Carreira group were able to access all four possible stereoisomers in a series of 2,3-functionalised aldehydes, selectively controlling the two adjacent stereocentres (Scheme 70).[130]



Scheme 70: Dual catalysed allylic alcohol substitution reactions, allowing access to all stereoisomers.

Through reaction of the allylic alcohol with the chiral iridium complex and an acidic promoter, a chiral iridium π-allyl complex is formed. Concurrently, through reaction with the chiral amine, the aldehyde substrate is transformed into a chiral enamine. Reaction of these two intermediates occurs through a stereospecific transition state and results in formation of only one of the possible four stereoisomers. Through manipulation of the chiral iridium ligand and/or the chiral amine catalyst, all stereoisomers of the products can be formed selectively in high yields, enantiomeric excess and diastereomeric ratios (Scheme 71).



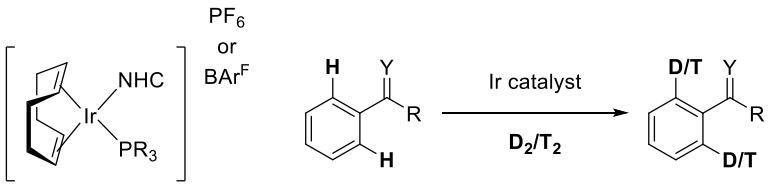
Scheme 71: Stereoselective synthesis of all stereoisomers of 2-(1phenylallyl)hexanal via the dual catalysed allylic alcohol substitution reaction.

Studies into the mechanism of the reaction led to isolation of a number of iridium complexes.[131] These studies not only showed the need for a Lewis or Brønsted acidic promoter but also showed that the catalyst was stable to oxygen complexation. The O_2-bound iridium catalyst was synthesised and characterised by X-ray crystallography. When this was used as the catalyst for the nucleophilic substitution reaction, catalytic activity was retained.

The use of this method in terms of an etherification reaction is particularly exciting as it has been demonstrated to function on a number of allylic alcohol substrates, forming ethers in good to excellent yields and enantioselectivities. However, this method does come with some limitations. The use of a ligand which is not commercially available is difficult to justify within a process chemistry setting. Ligand synthesis would take extra time, money and resource, which is obviated through use of commercially available starting materials. Also,

use of an acidic activator can be viewed as wasteful as this would reduce the PMI of the reaction, especially with a high molecular weight additive such as the *meta*-chlorobenzoic acid often employed in this methodology. The solvent selected for this reaction is also not suitable within a process chemistry laboratory. DCE is a chlorinated solvent, of low volatility and high impact to health. As such, it is classed as highly hazardous and should be avoided for use.[132] This solvent was actually prohibited from use by the European Chemicals Agency in 2017, unless a previous exemption applies.

A range of iridium-catalysed processes have been developed by the Kerr group in recent years. In particular, their novel iridium(I) complexes, ligated by an *N*-heterocyclic carbene and bulky phosphine, have revolutionised methodologies to isotopically label substrates with deuterium or tritium (Scheme 72).[133] This labelling can often be directed through functional groups already present within the target molecule, avoiding the requirement for directing group installation and removal. Further, the variants of these iridium complexes bearing a range of weakly coordinating anions have enabled these catalysts to be employed in a wide range of organic solvents.

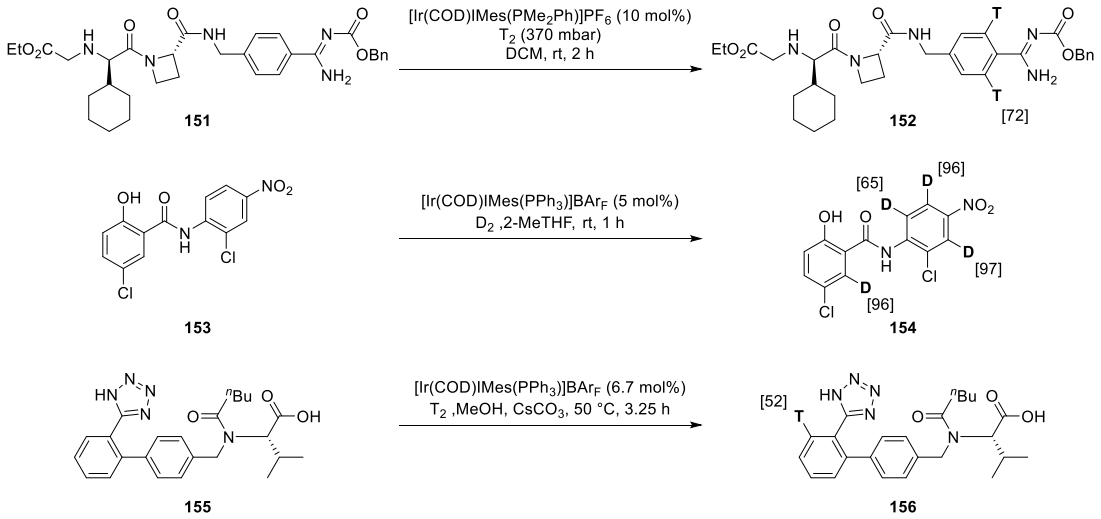


Scheme 72: General structure of the iridium catalysts developed by the Kerr group and the labelling reactions they are usually utilised in. Y and R represent a number of common functional groups including heteroatoms and ring systems.

Through the enhanced catalytic activity, selectivity and solvent applicability of the Kerr group catalysts in comparison to other literature precedence of catalytic hydrogen isotope exchange (HIE), a number of molecules have been isotopically labelled. Amides, ketones,

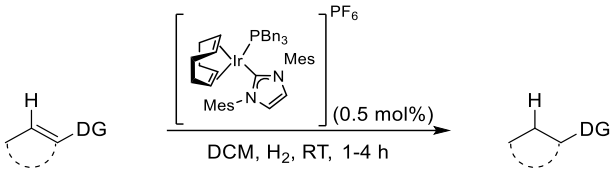
esters, heterocycles and nitro groups have all been proven to be good directing groups for use within hydrogen isotope exchange reactions with the Kerr catalysts demonstrating a substantial improvement upon comparable HIE catalysts.[134-135]

Due to the applicability and solvent compatibility of the Kerr iridium complexes, a number of pharmaceutically relevant molecules have been labelled using their inherent functionality to direct the isotopic labelling (Scheme 73).[133]



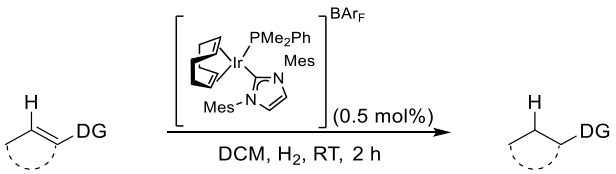
Scheme 73: Isotopic labelling of pharmaceutically relevant molecules through catalytic hydrogen isotope exchange.

The catalysts developed by the Kerr group have also proven to be effective for hydrogenations of alkenes (Scheme 74).[136] This transformation was initially reported utilising an iridium catalyst with a PF_6 counterion in DCM solvent. This methodology demonstrated alkene and alkyne reductions with hydrogen gas in the presence of other commonly reducible functional groups such as aryl halides, nitro groups and benzyl ethers.



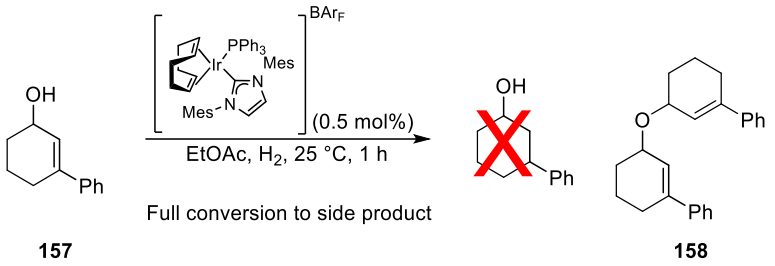
Scheme 74: Alkene hydrogenation utilising the Kerr group catalysts using a PF_6 counterion.

Further advancement of this hydrogenation was reported through use of an iridium catalyst with a BAr_F counterion (Scheme 75).[137] This bulkier counterion allowed a much larger variety of solvents to be utilised within this methodology due to the weaker co-ordination of BAr_F. This expanded methodology was also demonstrated on reducible functional groups such as an aryl bromide, ketones and a nitro group.



Scheme 75: Further developed alkene hydrogenation utilising the Kerr group catalysts using a BAr_F counterion.

As the hydrogen isotope exchange reactions of the Kerr group catalysts proceed through coordination to a heteroatom, and direct hydrogenation of alkenes and alkynes has also shown to be effective with equivalent catalysts, a directed hydrogenation was proposed.[138] This hydrogenation would utilise the stereochemistry of an allylic alcohol to direct the catalyst to deliver the hydrogen reductant in a syn-fashion.



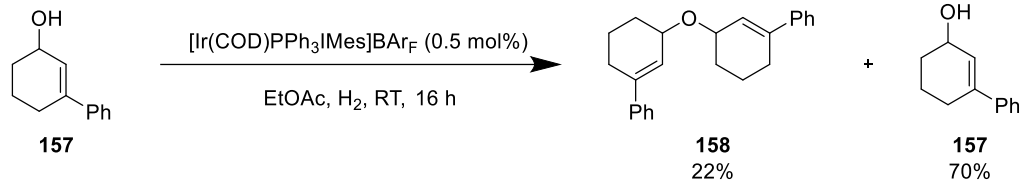
Scheme 76: Attempted iridium catalysed directed hydrogenation reaction performed by Giorgia Kidd and observed ether side product.

It is through use of 3-phenylcyclohexanol within the directed hydrogenation reaction that an ether dimer was observed as a substantial side product (Scheme 76). This transformation shows some parallels with the work by the Carreira group but utilising a commercial catalyst system, in the absence of an acid activator with a more environmentally friendly solvent and shorter reaction times.

2.2 Results and Discussion

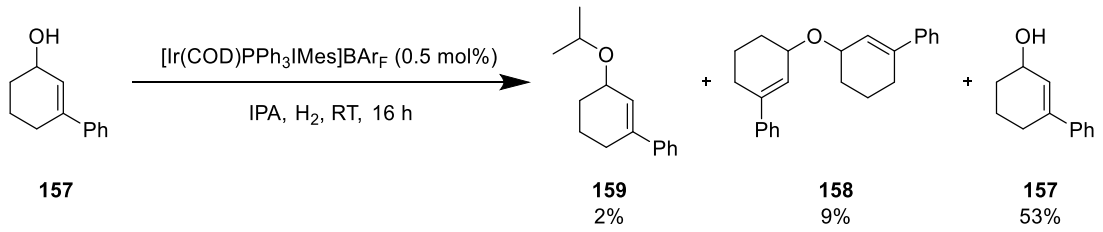
2.2.1 Initial Scoping Reactions

To initiate the investigation into the observed ether product formation, it was first necessary to replicate the initial result. To do this, 3-phenylcyclohexanol and the iridium catalyst were synthesized. The resulting 3-phenylcyclohexenol was subjected to a hydrogen atmosphere with [Ir(COD)IMesPPh$_3$]BAr$_F$ catalyst. This reaction yielded the dimerised ether product in 22% yield and returned 70% of the 3-phenylcyclohexenol starting material (Scheme 77).



Scheme 77: Formation of the dimerised ether side product under the iridium catalysed allylic alcohol etherification conditions.

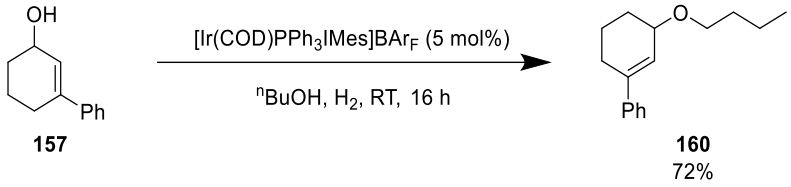
Formation of the ether product under such mild conditions is encouraging, however, symmetrical ethers are not always the desired product from etherification reactions. As such, formation of the unsymmetrical ether was investigated through replacement of the ethyl acetate solvent with IPA (Scheme 78).



Scheme 78: Attempted formation of the iso-propyl ether within the iridium catalysed allylic alcohol etherification reaction.

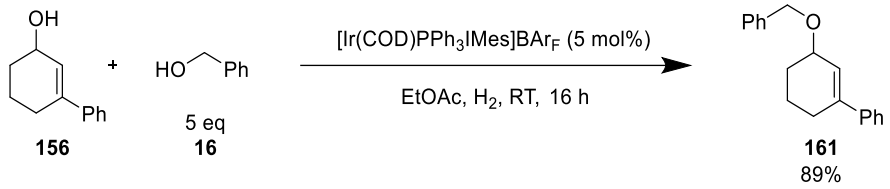
Rather disappointingly, the largest component of the reaction mixture after 16 hours was shown to be the 3-phenylcyclohexenol starting material. A 9% yield of the dimerised ether was obtained along with 2% of the desired *iso*-propyl ether. It was hypothesised that *iso*-propyl alcohol was too sterically hindered to be an effective etherification partner within the reaction manifold.

In another attempt to access an unsymmetrical ether, *n*-butanol was employed as the reaction solvent (Scheme 79). This primary alcohol is not as sterically hindered as the secondary *iso*-propanol and was found to be a much more effective etherification partner. Pleasingly, butyl ether **160** was isolated in a 72% yield after 16 hours.



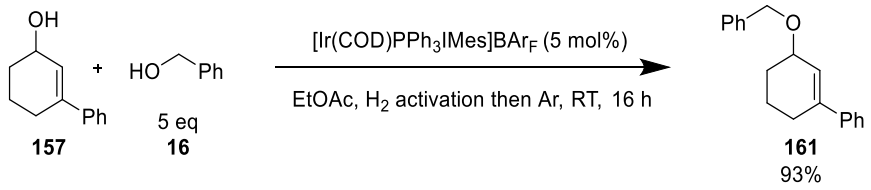
Scheme 79: Iridium catalysed etherification of 3-phenylcyclohexenol and n-butanol.

Formation of the unsymmetrical butyl ether was a very encouraging result with respect to further application of the reaction; however, as many molecules of interest to the pharmaceutical industry have a number of aromatic rings within their carbon skeleton, an aromatic alcohol was next trialled. Benzyl alcohol was chosen; however, as this alcohol has a very high boiling point of 205 °C, use of this as a solvent would not allow simple removal for purification of products. Instead, ethyl acetate was used as the reaction solvent and benzyl alcohol was used in a stoichiometry of 5 equivalents. Catalyst loading was also increased to aid product formation (Scheme 80). Under these conditions, pleasingly, the corresponding benzyl ether (**160**) was isolated in an impressive 89% yield.



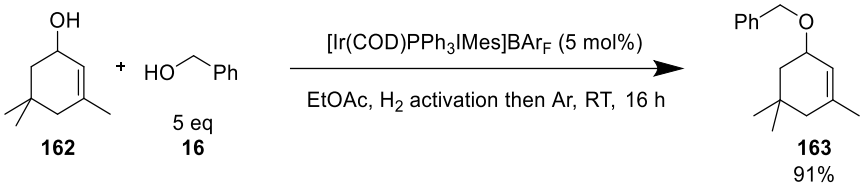
Scheme 80: Iridium catalysed etherification of 3-phenylcyclohexenol and benzyl alcohol.

It was next hypothesised that the hydrogen atmosphere was only required for activation of the catalyst and not for the coupling itself. In this case, the hydrogen atmosphere could be removed after catalyst activation. This removal of the hydrogen atmosphere would allow allylic alcohols known to be reducible under the reaction conditions to be coupled under a compatible atmosphere. This approach was first trialled on 3-phenylcyclohexanol **157**, resulting in a slightly improved 93% yield (Scheme 81).



Scheme 81: Iridium catalysed etherification of 3-phenylcyclohexenol and benzyl alcohol utilising hydrogen atmosphere solely for catalyst activation.

With the replacement of the hydrogen atmosphere for argon still resulting in a high yielding process with respect to ether formation, a reaction between 3,5,5-trimethylcyclohex-2-en-1-ol **162** and benzyl alcohol **16** was next performed (Scheme 82). 3,5,5-Trimethylcyclohex-2-en-1-ol **162** has previously been shown to be reduced under hydrogenation conditions by the Kerr group and, as such, the presence of a hydrogen atmosphere would result in an alkene hydrogenation reaction taking place over the desired etherification.[138]



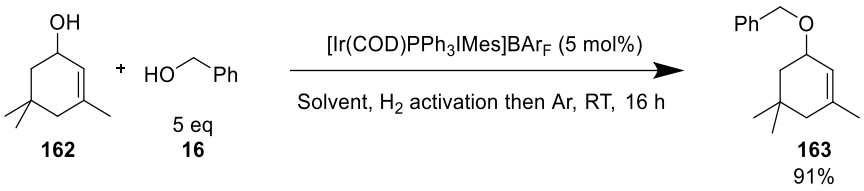
Scheme 82: Iridium catalysed etherification of 3,5,5-trimethylcyclohex-2-en-1-ol and benzyl alcohol utilising hydrogen atmosphere solely for catalyst activation.

Through this replacement of reactive atmosphere, the coupling of benzyl alcohol **16** with the reducible allylic alcohol, 3,5,5-trimethylcyclohex-2-en-1-ol **162** progressed in an impressive 91% yield.

With a high yielding reaction in hand which utilised the alcohol etherification partner in quantities lower than solvent levels, the other reaction components were investigated using this as the model reaction manifold.

2.2.2 Solvent Screening

Next, solvent screening of the reaction was initiated to evaluate its role within the reaction. 10 solvents were chosen and 3,5,5-trimethylcyclohex-2-en-1-ol and benzyl alcohol were reacted in the presence of [Ir(COD)IMesPPh$_3$]BAr$_F$ catalyst.



162 **16** **163** 91%

Reaction	Solvent	Isolated Yield
1	THF	59%
2	2-MeTHF	57%
3	Isopropyl acetate	89%
4	Dioxane	63%
5	DCM	65%
6	CPME	80%
7	TBME	96%
8	Ethyl acetate	65%
9	Toluene	80%
10	Dimethyl carbonate	>99%

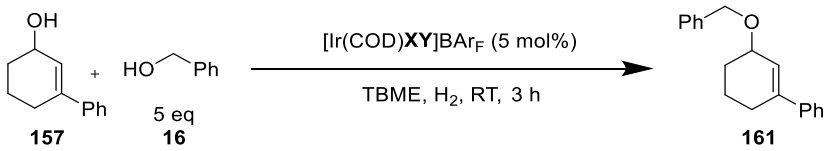
Table 17: Solvent screening for the iridium catalysed allylic alcohol etherification reaction.

Encouragingly, the etherification reaction was shown to be applicable across all solvents investigated, with the product being isolated in good to high yields in all cases. The highest yielding solvents were found to be *tert*-butyl methyl ether and dimethyl carbonate. Of these two solvents, TBME was chosen as the solvent for further optimisation studies as the melting point for this solvent is much lower, allowing a more consistent stirring upon catalyst activation at -78 °C.

2.2.3 Catalyst Screening

To evaluate the most effective catalyst for the iridium catalysed allylic alcohol etherification reaction, a selection of catalysts developed within the Kerr group were trialed (Table 18). These catalysts all share an Ir(COD) moiety, but differ in the bulky phosphine and *N*-heterocyclic carbene ligands. One catalyst (Table 18, entry 4) even featured a tethered bulky phosphine *N*-heterocyclic carbene ligand.

At this point in the investigation, the work was moved to be performed at GSK Stevenage; following the initial development of the reaction during a secondment at the University of Strathclyde. Due to the nature of hydrogenation reactors there, activation of the catalyst with hydrogen gas followed by removal of the hydrogen atmosphere and addition of the allylic alcohol substrate was difficult to achieve. For these reasons, reactions were performed in the ChemSCAN II hydrogenator at constant hydrogen pressure, with 3-phenylcyclohexenol as the allylic alcohol substrate.



Reaction	Phosphine (X)	NHC (Y)	Yield (%)			Average (%)
1	PPh_3	IPr	98%	89%	>99%	96%
2	PPh_3	IBn	66%	38%	40%	48%
3	PPh_3	IMes	0%	72%	>99%	57%
4	$-CH_2(C_6H_4-PPh_2)$	-D^{i}PP	98%	55%	75%	76%

Table 18: Catalyst screening for the iridium catalysed allylic alcohol etherification reaction.

As the most reproducible and highest yielding catalyst within the screen, [Ir(COD)IPrPPh$_3$]BAr$_F$ was chosen as the catalyst for further reaction optimisation.

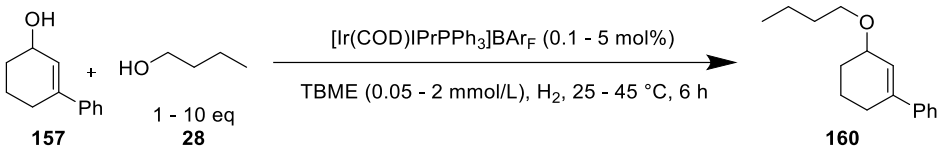
2.2.4 Design of Experiment Optimisation

To fully investigate and evaluate the reaction parameters for the iridium catalysed allylic alcohol etherification reaction, a design of experiment optimisation was performed.[83] This was performed with a view to lower the catalyst loading and increase the reaction concentration, all whilst maintaining a high performing reaction. The equivalents of alcohol etherification partner was also investigated, as it had been noted previously in similar reaction manifolds that more than 10 equivalents of alcohol co-reactant inhibits the reaction.[139] As such, the reaction parameter ranges for initial investigation were chosen as shown in Table 19.

Parameter	Low	Centre	High
Catalyst Loading	0.1%	2.55%	5%
Alcohol Equivalents	1	5.5	10
Concentration	0.05 mmol/L	1.025 mmol/L	2 mmol/L
Temperature	25 °C	35 °C	45 °C

Table 19: Design of experiment optimisation parameters and the ranges at which they were investigated.

As the reaction featuring benzyl alcohol as the etherification partner was already high yielding, a more moderately performing alcohol was chosen with which to run the DoE experiments. *n*-Butanol has been shown previously to take part in the etherification reaction but was used in solvent levels of excess (>100 equivalents). As such, this was chosen as the stoichiometric alcohol nucleophile to investigate the response of the reaction under the DoE ranges studied (Scheme 83).



Scheme 83: Model reaction for the design of experiment optimisation of the iridium catalysed allylic alcohol etherification.

To streamline the workflow and efficiently run the DoE, the CAT96 hydrogenator was selected. This hydrogenator would allow hydrogenation of multiple reaction mixtures at once, all performed on a small, 1 mL scale. To utilise this hydrogenator, it was necessary to run the reactions under constant hydrogen atmosphere to ensure consistent activation of the iridium catalyst. As such, 3-phenylcyclohexenol **157** was selected as the model allylic alcohol as this was known to be stable to hydrogenation conditions. As temperature control for individual reactions is not possible due to all the reactions being performed in the same reactor chamber, this would mean that plates of reactions would be run separately at high and low temperatures. As reactions within this design would not be randomised, it would require a different statistical model to analyse, and a split plot analysis was designed with the help of an expert DoE user.[140] This split plot design of 32 reactions consisted of 8 centre points at 35 °C as well as full factorial designs (8 factorial reactions and 4 centre points) at 25 °C and 45°C.

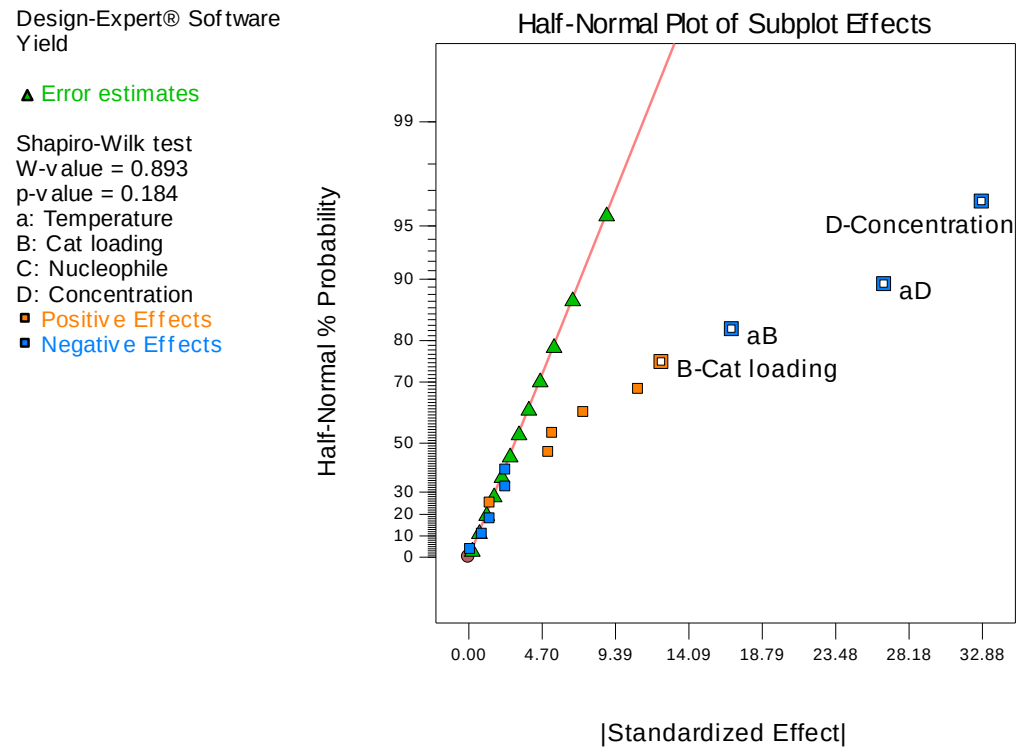


Figure 54: Half normal plot of subplot effects for the design of experiment optimisation.

Upon analysing the DoE half normal plot, catalyst loading (Figure 54), concentration and temperature were identified as factors with large statistical significance on the outcome of the reaction (p value < 0.05). More concentrated reaction mixtures produced less of the desired ether and higher catalyst loadings were required for higher yields. The interaction of temperature with both of these factors was also statistically significant within the model.

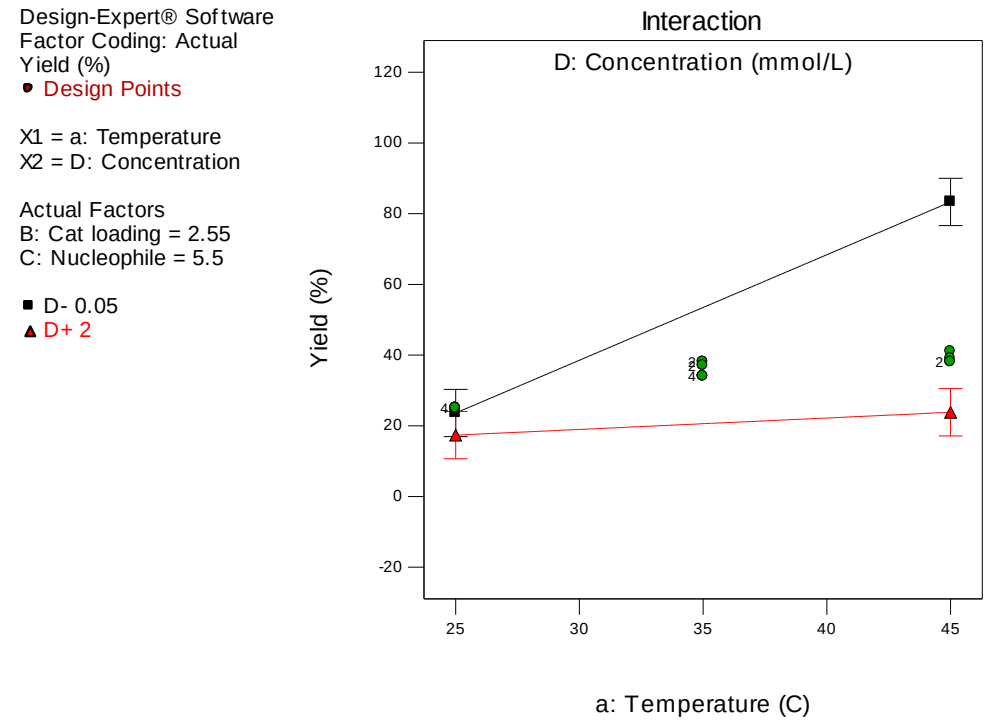


Figure 55: Interaction plot of temperature and concentration within the design of experiment optimisation. Low concentration is shown as a black line and high concentration as a red line.

As can be deduced by the interaction plot of concentration and temperature (Figure 55), at lower concentrations of 0.05 mmol/L (black line), higher temperatures are very important for the reaction to be high yielding. At higher concentrations (red line), temperature makes very little, if any, difference to the success of the reaction, and a combination of high temperature and low concentration is key to achieve a high yielding reaction.

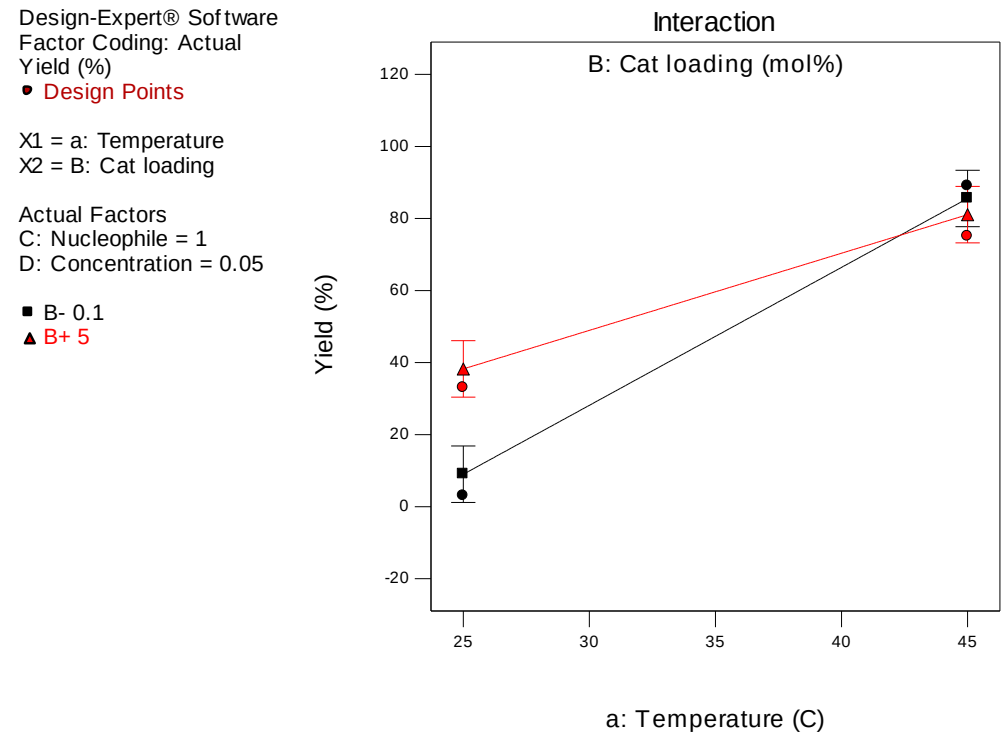


Figure 56: Interaction plot of temperature and catalyst loading within the design of experiment optimisation. Low catalyst loading is shown as a black line and high catalyst loading as a red line.

As can be deduced by the interaction plot of catalyst loading and temperature (Figure 56), at temperatures of 25 °C, lower catalyst loadings of 0.1 mol% (black line) are shown to be much lower yielding that higher catalyst loadings (5 mol%, red line). However, increase of the reaction temperature to 45 °C shows the reaction performs similarly at either catalyst loading. This is an important outcome of the analysis with regards to optimisation of the reaction, as the iridium catalyst is expensive and utilisation in small amounts is preferable.

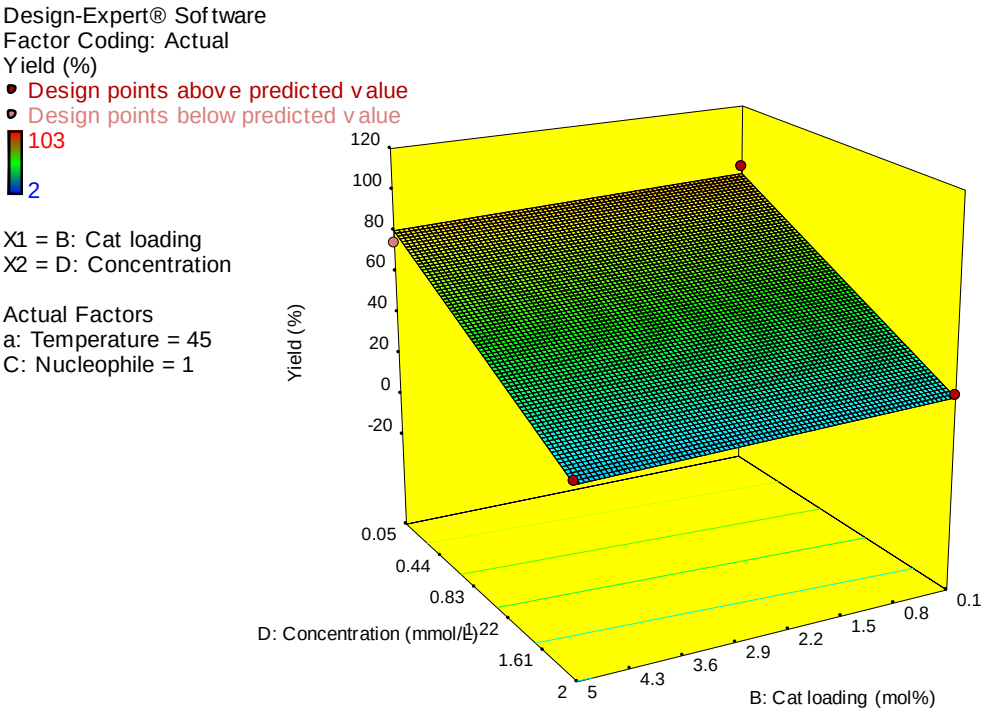
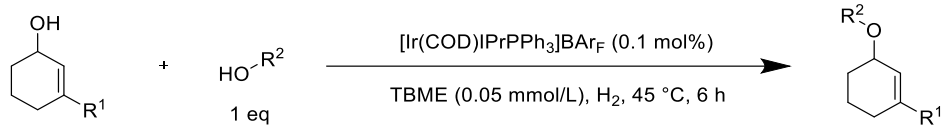


Figure 57: 3D surface plot of the design of experiment optimisation. Catalyst loading is plotted against concentration at high temperature and low nucleophile equivalents.

Encouragingly, alcohol nucleophile equivalents had no significant impact upon the outcome of the reaction, with 1 equivalent performing comparably to 10 equivalents. This is in contrast to other iridium catalysed allylic alcohol etherification reactions from the literature. Use of 1 equivalent of alcohol nucleophile in the reaction is beneficial, as this allows more expensive or precious alcohol nucleophiles to be used in only a stoichiometric amount.



Scheme 84: Predicted optimised reaction conditions for the iridium catalysed allylic alcohol etherification reaction based on DoE analysis.

Taking these considerations into account, the predicted optimal conditions from DoE analysis are, low catalyst loading (0.1 mol%), low concentration (0.05 mmol/L), high temperature (45 °C) and no preference on nucleophile equivalents (Scheme 84).

Although it is very encouraging to see low alcohol equivalents and catalyst loadings are tolerated within the reaction, the catalyst loading for future substrate scoping reaction in the ChemSCAN was raised to 0.5 mol% as this is the lowest amount of catalyst that could accurately be weighed (1.8 mg). This catalyst loading is still a substantial improvement upon the 5 mol% starting point.

Nucleophile equivalents was a factor within the analysis which showed no effect on the success of the reaction. As the study was performed with *n*-butanol as the nucleophile, any variation on the properties of the alcohol will not have been taken into account. Through variation of the alcohol nucleophile in upcoming substrate scoping reactions, steric and electronic properties of the nucleophile will vary. This will change the reactivity of the nucleophile and will most likely have an effect upon the outcome of the reaction. For this reason, slightly higher alcohol equivalents were selected, and future substrate scoping reactions will be performed with 2 equivalents of alcohol. This stoichiometry would still represent a significant improvement upon the 5, 10 or >100 equivalents studied previously with this reaction and reported for use within comparable processes in the literature.[128]

2.2.5 Alcohol Nucleophile Screening

To investigate the substrate scope of the reaction with respect to the alcohol nucleophile, 3-phenylcyclohexenol was reacted with a number of different alcohol nucleophiles. These reactions were performed within the ChemSCAN hydrogenator under constant hydrogen atmosphere.

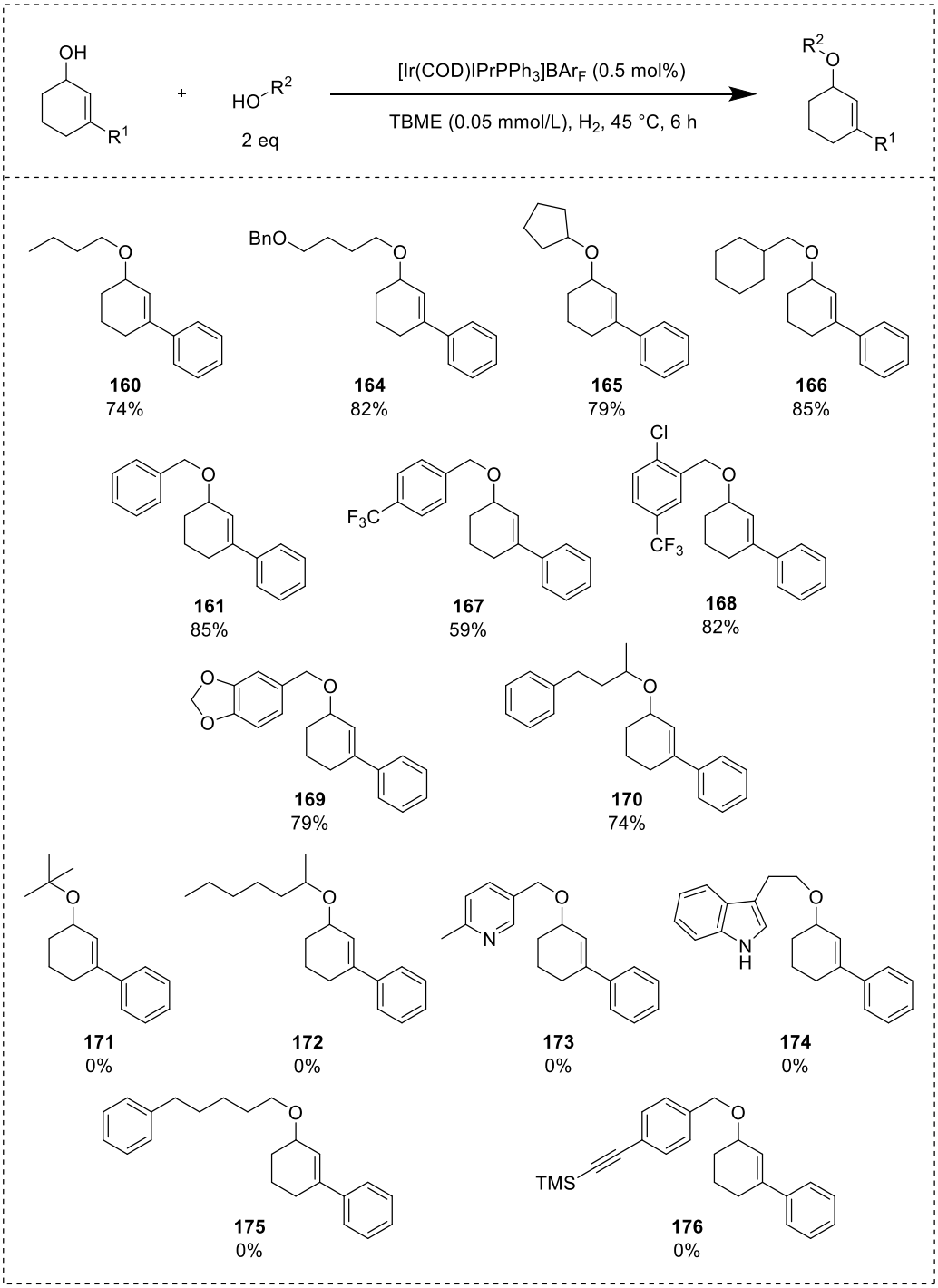


Figure 58: Alcohol nucleophile scoping reactions performed with 3-phenylcyclohexenol within the ChemSCAN hydrogenator.

A good selection of alcohol nucleophiles were shown to perform well within the iridium catalysed allylic alcohol etherification reactions. This substrate scope showed that secondary

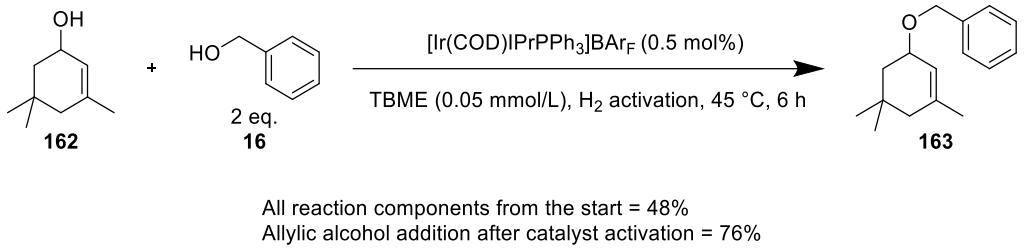
alcohols (**165** and **170**) were also tolerated as well as primary alcohols, but the tertiary alcohol, *t*-butanol (**171**) was not tolerated. A number of aromatic and benzylic alcohols were trialled for use within the reaction with the majority being successful. These aromatic alcohols featured a number of functionalities, such as aryl trifluoromethyls (**167** and **168**) and/or aryl-chloride (**168**), as well as ketals (**169**) and ethers (**164**). Sadly, no nitrogen heterocycles proved to be viable within the etherification reaction, with indole and pyridine substrates returning no product within the reaction, only starting materials.

2.2.6 Reactions with Hydrogen Activation

To further expand the scope of the iridium catalysed allylic alcohol etherification reaction, a different allylic alcohol was demonstrated for use with a selection of successful alcohols from Section 2.2.5. The allylic alcohol selected was one demonstrated within the initial scoping reaction (Section 2.2.1), 3,5,5-trimethylcyclohex-2-en-1-ol **162**. This allylic alcohol is known to be hydrogenated under similar conditions developed within the Kerr group and, as such, removal of the hydrogen atmosphere after activation of the catalyst and before the addition of the allylic alcohol is required.

To achieve this within the ChemSCAN hydrogenator, some test reactions were performed (Scheme 85). As this hydrogenator does not posess injector ports, addition of the allylic alcohol under inert atmosphere was not possible without opening the reactor vessels. As such, activation of the catalyst was trialed within the presence of all reaction components by purging the reaction vessel with hydrogen to 5 bara twice with stirring at 25 °C, before venting and purging with nitrogen three times at 5 bara. This was followed by heating to 45 °C under a nitrogen atmosphere for 6 hours. In tandem with this a second test reaction was performed. Opening of the reaction vessel to air was trialed after activation of the

catalyst under hydrogen followed by addition of the allylic alcohol and heating to 45 °C for 6 hours under nitrogen atmosphere.



Scheme 85: Test reactions within the ChemSCAN to determine order of addition and catalyst stability.

Within these reactions, lower yields were observed for the reactions with the catalyst activation in the presence of the allylic alcohol component. As 3,5,5-trimethylcyclohex-2-en-1-ol **162** is known to be reduced under similar conditions, the lower yield can be attributed to partial hydrogenation of the alkene during the catalyst activation. Encouragingly, exposure of the reaction mixture to oxygen for a short amount of time was shown to be possible, allowing addition of the allylic alcohol after catalyst activation and formation of the ether product in good yield.

With a reaction manifold in place for catalyst activation and addition of the allylic alcohol in the absence of a hydrogen atmosphere, an evaluation of alcohol etherification partners was conducted (Figure 59).

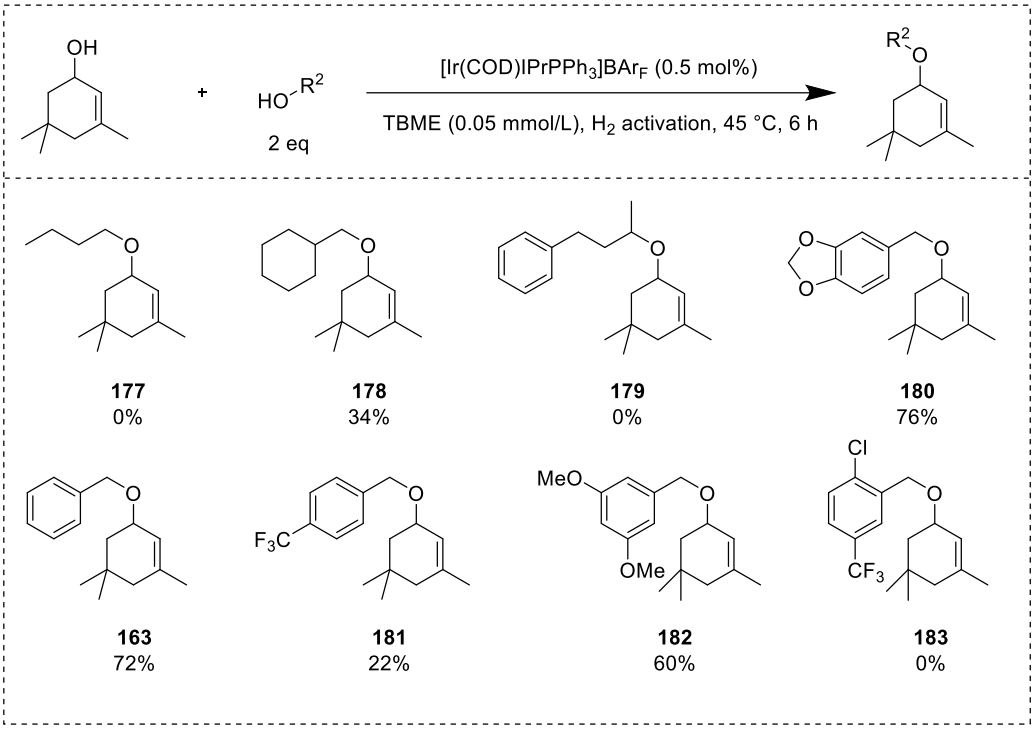


Figure 59: Alcohol nucleophile scoping reactions performed with 3,5,5-trimethylcyclohex-2-en-1-ol within the ChemSCAN hydrogenator.

Pleasingly, the procedure for hydrogen activation translated well to other substrates and ether derivatives of 3,5,5-trimethylcyclohex-2-en-1-ol **162** were formed in good to excellent yields, comparable to those observed previously. These nucleophiles spanned the classes of aromatic and aliphatic alcohols, as well as containing C-O and C-F functionalities. Curiously, three of the eight nucleophiles trialed for use under the hydrogen activation manifold showed no product formation.

The change in reactivity of these substrates through switching the reaction manifold to hydrogen activation was thought to be due to one of two things:

1. Stirring during the hydrogen purge cycles was not performed for a sufficient time to ensure consistent activation for all catalysts across the reactor block.

2. Presence of the alcohol nucleophile during the activation stage may result in the catalytic species within the reaction being an iridium-nucleophile complex. The stability of these complexes to oxygen will no doubt vary and opening of the reaction vessels to add the allylic alcohol may result in catalyst deactivation.

2.3 Conclusion

In conclusion, an effective iridium-catalysed allylic alcohol etherification reaction has been developed to form ether products in good to excellent yields. This etherification reaction was developed through a solvent evaluation, catalyst screen and design of experiment statistical analysis. Through this extensive evaluation of the allylic alcohol etherification reaction, TBME was chosen as the reaction solvent in conjunction with $[Ir(COD)IPrPPh_3]BAr_F$ as the catalyst. Design of experiment analysis showed that this catalyst could be employed in very small catalysts loadings (0.1 mol%) if the temperature of the reaction was raised to 45 °C. The concentration of the reaction was shown to be very important, with less concentrated reaction mixtures resulting in higher yields.

For ease of weighing and to allow the reaction to be generally applicable to a wide range of nucleophiles, catalyst loading was raised to 0.5 mol% and nucleophile stoichiometry was demonstrated at 2 equivalents. At these conditions, a range of nucleophiles were demonstrated to be compatible within the allylic alcohol etherification reaction. These nucleophiles possessed aromatic and aliphatic functionalities with C-F, C-Cl and C-O functionalities being tolerated. A benzylic ether was also shown to be a viable protecting group for use within this etherification reaction, even under hydrogenation conditions.

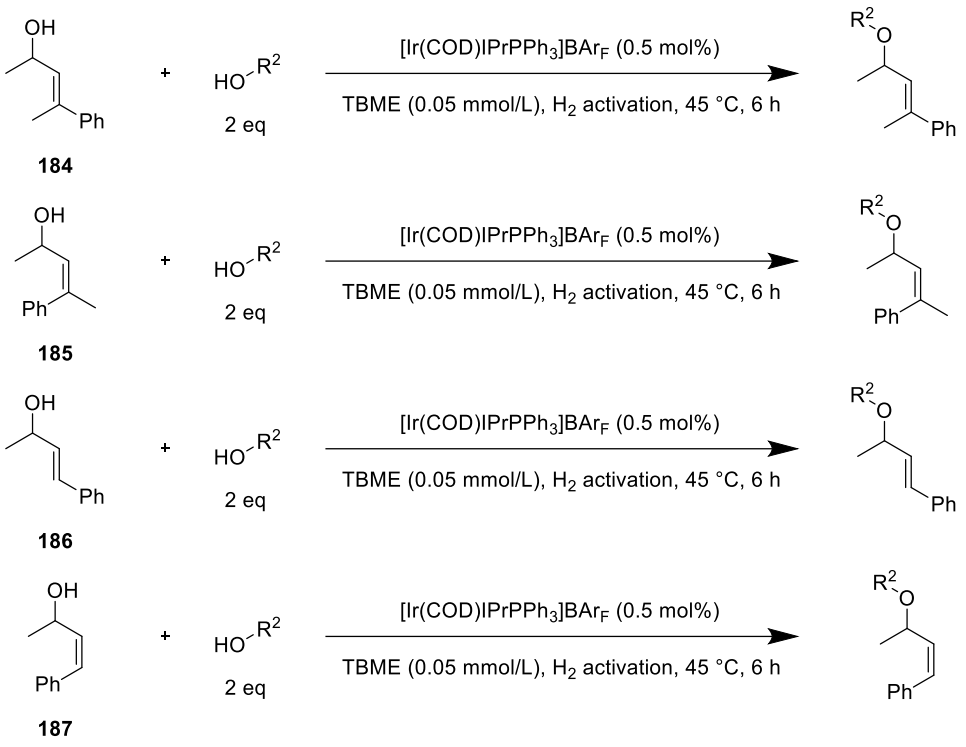
By removal of the hydrogen atmosphere before addition of the allylic alcohol, tolerance of reducible allylic alcohols was enabled. 3,5,5-Trimethylcyclohex-2-en-1-ol is known to be

reduced to the corresponding cyclohexanol using the same catalyst under a hydrogen atmosphere. By replacement of the hydrogen atmosphere before addition of the allylic alcohol, 3,5,5-trimethylcyclohex-2-en-1-ol was shown to partake in the etherifcations with a number of successful alcohol partners from the previous screen. This is a very important advancement with regards to expanding the scope of the allylic alcohol.

Overall, this iridium catalysed allylic alcohol etherification has been shown to be of similar performance to previously reported iridium catalysed allylic alcohol etherification reactions, but without the requirement for an acidic activator or preactivation of the allylic alcohol substrate. This newly developed manifold also utilises an easily synthesised iridium catalyst system without the need for custom made, chiral phosphoramidite ligands.

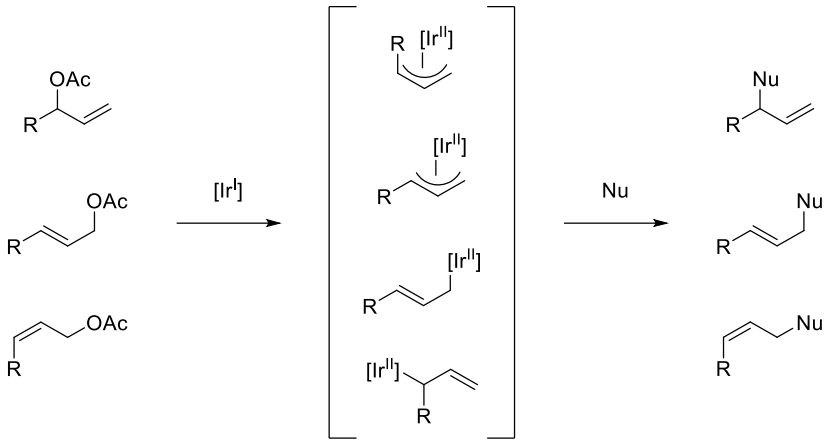
2.4 Future Work

Additional investigation into the iridium catalysed allylic alcohol etherification reaction could be performed with regards to the allylic alcohol substrate. Although two allylic alcohol substrates were demonstrated to be suitable within this methodology, a wide ranging area of chemical space is yet to be explored. It may be of interest to apply the reaction to an open chain allylic alcohol to see if acyclic variants are tolerated under the developed reaction conditions (Scheme 86). This will also open up avenues to explore the stereoisomerism of the alkene with respect to E and Z as well as substitution patterns (tri vs di-substituted).



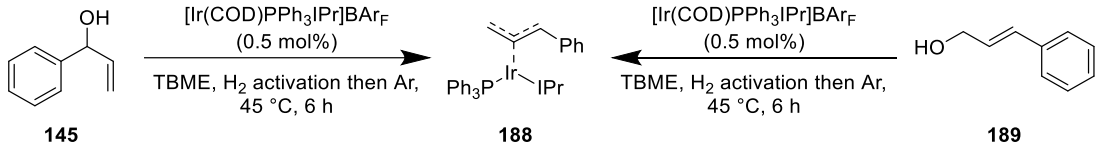
Scheme 86: Proposed investigation into the tolerance of open chain, di- and tri- substituted allylic alcohols with E and Z isomerism.

This investigation into the tolerances of the allylic alcohol starting material may also give some insights into the mechanism of the reaction. Although this has not been touched upon within the development outlined in this thesis, it has been assumed that the reaction progresses through an iridium π-allyl intermediate. Some indications of this within the open chain allylic alcohol investigation may become apparent from the isolated products. Within similar iridium catalysed reactions of allylic substrates, a number of metal-allyl intermediates are reported with the products of nucleophilic substitution displaying different isomerism (Scheme 87).[141-142]



Scheme 87: Proposed products of nucleophilic substitution of all reported intermediates of similar iridium catalysed substitution reactions of allyl substrates.

Should any investigation result in scrambling of the E/Z geometry across the double bond, this may be a strong indication of an iridium π-allyl reaction intermediate. This may also be indicated by any regioisomers formed during the reaction and this may be further investigated by applying the developed reaction manifold to (E)-3-phenylprop-2-en-1-ol (**189**) and 1-phenylprop-2-en-1-ol (**145**). These two allylic alcohols would form the same iridium π-allyl intermediate which should interact with the nucleophile in the same way. Should the same intermediate be present within both reactions, it is hypothesised that the products would be the same also (Scheme 88).



*Scheme 88: Proposed reactions of (E)-3-phenylprop-2-en-1-ol (**189**) and 1-phenylprop-2-en-1-ol (**145**) with the iridium catalyst and the proposed iridium π-allyl intermediate (**188**).*

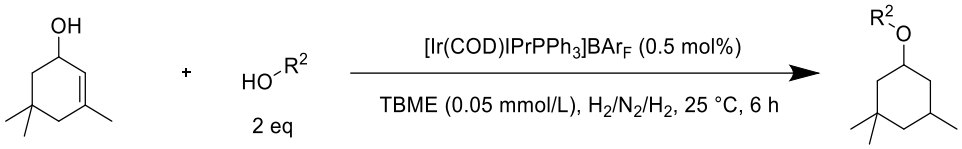
As the catalyst is homogeneous, it may be possible to further investigate the catalytic cycle of the etherification reaction through *in situ* NMR analysis to monitor changes within the system in real time.

Understanding the catalytic cycle in more depth may open up avenues to improve the catalyst system. As the Kerr group catalysts are fairly easy to customise, a number of them can be produced for specific use within the etherification reaction. As the current uses for the catalysts are for hydrogen isotope exchange reactions and hydrogenations, it is not unreasonable to hypothesise that these may not be optimally designed for the purposes of the etherification reaction of allylic alcohols. Understanding the catalytic cycle further may reveal the requirements of the catalytic system with regards to sterics and electronics. A more bespoke iridium catalyst (or selection of) may then be designed based on the current selection of Kerr group catalysts. This catalyst system could be further improved through the choice of NHC and phosphine ligands to influence the sterics and electronics of the reaction catalyst. Development of this catalyst may expand the scope of the reaction and allow *N*-heterocyclic alcohols to be utilised.

As the catalyst was shown to be amenable to etherification reactions, it would be of interest to investigate other nucleophiles which are not centred on oxygen. Utilisation of other nucleophiles could result in a wide-ranging iridium-catalysed allylic alcohol substitution reaction without the requirement for any additional activators. This allylic alcohol substitution reaction could facilitate important C-C and C-N bond forming reactions with allylic alcohol substrates.

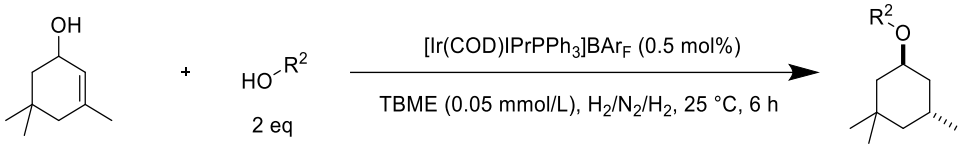
As the Kerr group catalysts are known to partake in hydrogenation reactions with some allylic alcohol substrates, it may be possible to perform the etherification reaction on these substrates as outlined in this investigation, but then reapply the hydrogen atmosphere to

reduce the saturated ethers. This may provide a facile route to saturated ethers starting from allylic alcohol substrates (Scheme 89).



Scheme 89: Proposed iridium catalysed etherification of allylic alcohol substrates followed by in-situ hydrogenation to form the saturated ether.

Stereoselectivity has not yet been explored within the iridium-catalysed allylic alcohol etherification reaction. This may be investigated during the catalyst optimisation through replacement of the phosphine or NHC with a chiral counterpart to influence the stereoselectivity of the reaction. It may also be possible to influence the stereoselectivity by use of a chiral allylic alcohol starting material. Interaction of this chiral alcohol with the iridium catalyst may occur in a stereospecific fashion and result in a chiral intermediate. Nucleophilic substitution of this intermediate may then happen in a stereospecific fashion to deliver a chiral ether product (Scheme 90).



Scheme 90: Possible stereochemical outcome of the proposed iridium catalysed etherification of allylic alcohol substrates followed by in-situ hydrogenation to form the saturated ether.

Should the tandem iridium-catalysed allylic alcohol etherification-hydrogenation reaction prove to be successful, this could display interesting stereospecificity. Within other Kerr group work, allylic alcohols were hydrogenated with the iridium catalyst using the alcohol as a director for the iridium catalyst to deliver the hydrogen in a stereospecific manner. After

the etherification is complete and hydrogen atmosphere is reapplied, this newly formed ether bond may also be able to coordinate the iridium catalyst in a similar fashion to allow a stereoselective delivery of the hydrogen from the same face as the oxygen atom and formation of the anti- product.

2.5 Experimental

All reagents were obtained from commercial suppliers (Aldrich, Alfa Aesar, Sigma Aldrich, Strem or Merck) and used without further purification.

Liquid chromatography (LC) analysis was conducted on an Agilent Technologies 1260 Infinity fitted with a Waters CSH C18 column (30 mm x 2.1 mm internal diameter, 8.5 µm packing diameter) at 40 °C using a 0.5 µL injection volume.

The solvents employed were: A = water. B = Acetonitrile.

The gradient employed was:

Time (min)	Flow Rate (mL min^{-1})	%A	%B
3.70	1	5	95
4.00	1	5	95
4.10	1	97	3

UV detection was a summed signal from a wavelength of 220 nm.

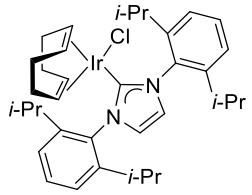
HRMS data was acquired through Waters Atmospheric Solids Analysis Probe in combined Electrospray/APcI mode (ESCi®). Masses were then analysed by Thermo Xcalibur QualBrowser software. All measured masses were determined to be within 5 ppm of the calculated mass.

NMR spectra were recorded using a Bruker AV-400 spectrometer (^{1}H = 400 MHz, ^{13}C = 101 MHz, ^{31}P = 162 MHz, ^{11}B = 128 MHz, ^{19}F = 376 MHz). Chemical shifts (δ) are reported in parts per million (ppm) relative to $CDCl_3$. Coupling constants are reported in Hz and refer to $^{3}J_{HH}$

interactions unless stated otherwise. The following abbreviations are used for multiplicities: s = singlet; br. = broad signal; d = doublet; t = triplet; q = quartet; quin = quintet; m = multiplet. Unless otherwise stated, the NMR experiments were acquired at 30 °C and ^{13}C was run in [^{1}H]-decoupled mode.

2.5.1 Catalyst Synthesis

Chloro(1,5-cyclooctadiene)[1,3-bis(2,6-di-*iso*-propylphenyl)imidazol-2-ylidene] iridium(I):



Chemical Formula: $C_{35}H_{49}ClIrN_2$
Molecular Weight: 725.46

In a vacuum heated and nitrogen dried 25 mL Schlenk tube, 1,5-cyclooctadiene-iridium(I) chloride dimer (400 mg, 0.596 mmol) and 1,3-bis(2,6-di-*iso*-propylphenyl)imidazolium chloride (506 mg, 1.191 mmol) was stirred under vacuum for 10 minutes. Tetrahydrofuran (THF) (10 mL) was added and reaction was stirred for a further 30 minutes. Potassium *tert*-butoxide (134 mg, 1.191 mmol) was added and reaction mixture was stirred for 4 hours. The reaction mixture was evaporated under reduced pressure and the crude residue was purified by Biotage Isolera (10 g Sfar, 0 - 20% EtOAc in heptane). The product containing fractions were combined and evaporated under reduced pressure to yield the product as a yellow solid (598 mg, 69%). The compound was not completely pure by NMR analysis but was used in next step of catalyst synthesis.

Melting point: Decomposed >200 °C

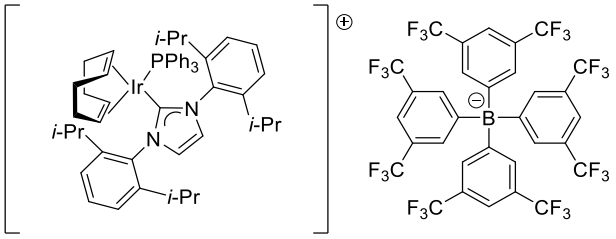
^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.44 (t, *J* = 7.6, 2H, Ar-*H*), 7.35 – 7.20 (m, 2H, Ar-*H*), 7.01 (s, 2H, Ar-*H*), 4.23 – 4.17 (m, 2H, Alkenyl C-*H*), 3.44 (br. s , 2H), 2.91 – 2.86 (m, 2H, Alkenyl C-*H*), 2.72 (br. s, 2H), 1.74 – 1.64 (m, 2H), 1.57 – 1.15 (m, 22H), 1.11 (t, *J* = 6.6, 13H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 182.5, 136.2, 129.7, 124.3, 82.8, 51.4, 33.5, 28.9, 28.7, 26.4.

IR: ν_{max}/cm^{-1} 2963, 2928, 2868, 2830, 1464, 1445, 1396, 1364, 1322, 937, 910, 801, 757, 732, 710.

HRMS (ESCi®): m/z calculated for $[C_{35}H_{51}ClIrN_2]^+$, Calculated mass = 725.4580, Measured mass = 725.3207 $[M]^+$

Triphenylphosphine(1,5-cyclooctadiene)[1,3-bis(2,6-di-*iso*-propylphenyl)imidazol-2-ylidene] iridium(I) tetrakis(3,5-bis(trifluoromethyl)phenylborate:



Chemical Formula: $C_{85}H_{76}BF_{24}IrN_2P$
Molecular Weight: 1815.52

Chloro(1,5-cyclooctadiene)[1,3-bis(2,6-di-*iso*-propylphenyl)imidazol-2-ylidene] iridium(I) (597 mg, 0.823 mmol) and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (729 mg, 0.823 mmol) were stirred in a heat dried, nitrogen cooled 25 mL Schlenk tube for 30 minutes. Dichloromethane (DCM) (10 mL) was added and stirring was continued for 30 minutes. Triphenylphosphine (216 mg, 0.823 mmol) was added and stirring was continued for 2 h. The reaction mixture was filtered through Celite®, evaporated to dryness and the residue was purified by Biotage Isolera (25 g Sfar, DCM). The product-containing fractions were combined

and evaporated to yield product as a red solid. This solid was triturated with heptane, then filtered and dried to yield the product as a red solid (1.372 g, 0.756 mmol, 92% yield).

Melting point: 163.5 °C

IR: ν_{max}/cm^{-1} 2971, 1464, 1438, 1353, 1274, 1160, 1120, 908, 886, 839, 734, 713, 695, 682, 669, 541, 527, 515.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.73 – 7.70 (m, 8H, BAr_F Ar-*H*), 7.53 – 7.43 (m, 9H, Ar-*H*), 7.43 – 7.33 (m, 8H, Ar-*H*), 7.33 - 7.26 (m, 2H, Ar-*H*), 7.19 (td, *J* = 7.8. 2.1, 4H), 7.02 (br. dd, *J* = 7.8, 1.4, 4H), 4.48 (br. s, 2H), 3.35 (br. s, 2H), 3.04 (dt, *J* = 13.2, 6.6, 2H, Alkenyl C-*H*), 2.31 (dt, *J* = 13.4, 6.6, 2H, Alkenyl C-*H*), 1.49 – 1.42 (m, 4H), 1.38 (d, *J* = 6.6, 7H), 1.34 – 1.15 (m, 5H), 1.11 (d, *J* = 6.6, 6H, C*H*$_3$), 0.87 (d, *J* = 6.6, 7H), 0.33 (d, *J* = 6.6, 6H, C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 162.4, 161.0, 146.1, 145.8, 135.9, 135.5, 135.4, 134.8, 134.7, 134.6, 131.7, 131.2, 131.2, 131.1, 129.0, 128.8, 128.7, 128.4, 128.3, 127.5, 125.9, 124.9, 124.4, 123.2, 117.5, 117.4, 79.3, 79.2, 78.6, 31.3, 30.0, 30.0, 29.7, 29.3, 27.4, 26.8, 22.0, 20.7.

^{31}P NMR (162 MHz, $CDCl_3$) δ = 16.5

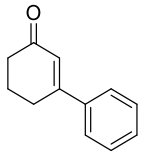
^{11}B NMR (128 MHz, $CDCl_3$) δ = -6.61

^{9}F NMR (396 MHz, $CDCl_3$) δ = -62.4

HRMS (ESCi®): m/z calculated for $[C_{85}H_{78}BF_{24}IrN_2P]^+$, Calculated mass = 1815.5194, Measured mass = 1815.5809 $[M]^+$

2.5.2 3-Phenylcyclohexenol Synthesis

5,6-Dihydro-[1,1'-biphenyl]-3(4H)-one: [143]



Chemical Formula: $C_{12}H_{12}O$
Molecular Weight: 172.23

3-Ethoxycyclohex-2-en-1-one (5.19 mL, 35.7 mmol) and tetrahydrofuran (THF) (10 mL) were stirred at 0 °C. 1.8 M Phenyllithium In dibutyl ether (20.65 mL, 39.2 mmol) was added dropwise with stirring at 0 °C and stirring was continued for 15 minutes. The reaction mixture was allowed to warm to room temperature and stirred for a further 1 hour. 1 M aqueous HCl (40 mL) was added and the mixture was stirred for 10 minutes. The reaction mixture was then extracted with EtOAc (50 mL), dried over $MgSO_4$ and evaporated to dryness. The resulting yellow oil was purified by Biotage Isolera (50 g Sfar, 20 - 80% EtOAc in heptane). The product-containing fractions were evaporated to yield the product as a yellow/white solid 5,6-dihydro-[1,1'-biphenyl]-3(4H)-one (5.46 g, 31.7 mmol, 89% yield).

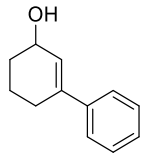
Melting point: 62.6 °C (literature melting point = 64 – 65 °C)[143]

IR: ν_{max}/cm^{-1} 1652, 1603, 1452, 1413, 1350, 1327, 1257, 1245, 1188, 1134, 883, 767, 758, 699, 517.

^1H NMR (400 MHz, $CDCl_3$), δ = 7.56 – 7.52 (m, 2H, Ar-*H*), 7.44 – 7.38 (m, 3H, Ar-*H*), 6.42 (t, *J* = 1.5, 1H, alkene C-*H*), 2.78 (td, *J* = 6.0, 1.5, 2H, CH_2), 2.52 – 2.46 (m, 2H, CH_2), 2.21 – 2.11 (m, 2H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 199.9, 159.7, 138.8, 130.0 128.8, 126.1, 125.5, 37.3, 28.1, 22.8.

3,4,5,6-Tetrahydro-[1,1'-biphenyl]-3-ol (157):[144]



Chemical Formula: $C_{12}H_{14}O$
Molecular Weight: 174.24

5,6-Dihydro-[1,1'-biphenyl]-3(4H)-one (4.07 g, 23.63 mmol) was dissolved in methanol (150 mL) and the solution was cooled to -10 °C in a salt-ice bath. Sodium borohydride (1.073 g, 28.4 mmol) was added portion-wise and the reaction was stirred for 90 mins. Saturated aqueous NH_4Cl solution was added and the reaction mixture was extracted with EtOAc (x 2). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in DCM and purified by Biotage Isolera (50 g Sfar, 0 - 80% EtOAc in heptane). The product-containing fractions were evaporated to yield the product as a white solid (4.07 g, 23.36 mmol, 99% yield).

Melting point: 60.3 °C (literature melting point = 60 – 62 °C)[144]

IR: ν_{max}/cm^{-1} 3171, 2932, 2860, 1492, 1444, 1332, 1281, 1052, 1029, 969, 905, 757, 750, 696, 687.

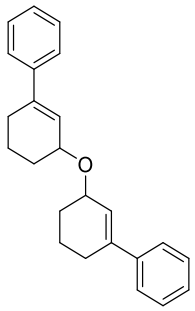
^1H NMR (400 MHz, $CDCl_3$), δ = 7.46 – 7.42 (m, 2H, Ar-*H*), 7.39 – 7.32 (m, 2H, Ar-*H*), 7.32 – 7.27 (m, 1H, Ar-*H*), 6.16 (dt, *J* = 3.5, 1.7, 1H, alkene-*H*), 4.42 (br. s, 1H, O*H*), 2.54 – 2.46 (m, 1H), 2.43 – 2.35 (m, 2H), 2.02 – 1.88 (m, 2H), 1.81 – 1.67 (m, 2H)

^{13}C NMR (101 MHz, $CDCl_3$), δ = 141.4, 140.2, 128.3, 127.4, 126.6, 125.4, 66.3, 31.7, 27.5, 19.5.

2.5.3 Initial Scoping Reactions

Results and discussion, section 2.2.1, page 227.

5,5''-Oxybis(2,3,4,5-tetrahydro-1,1'-biphenyl) (158):[145]



Chemical Formula: $C_{24}H_{26}O$
Molecular Weight: 330.47

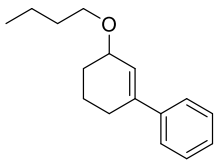
3,4,5,6-Tetrahydro-[1,1'-biphenyl]-3-ol (350 mg, 2.0 mmol) was stirred with [Ir(COD)PPh$_3$IMes]BAr$_F$ (17 mg, 0.5 mol%) in a flame-dried, argon-cooled Schlenk flask. EtOAc (5.0 mL) was added and the reaction mixture was stirred for 1 hour. The solution was cooled to -78 °C and a hydrogen atmosphere was applied *via* a balloon attached to a three way tap. The reaction vessel was sealed at the tap and allowed to warm to room temperature. Stirring was continued for 2 hours before the solution was evaporated under reduced pressure. The residue was triturated with diethyl ether before being filtered through silica and concentrated. The reaction mixture was purified by column chromatography (0 – 20% EtOAc in hexane) to yield product as a colourless oil (73 mg, 22%) and starting material (245 mg, 70%).

IR: ν_{max}/cm^{-1} 3024, 2930, 2860, 1709, 1665, 1597, 1493, 1445, 1157, 1069, 800, 754, 694.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.48 – 7.42 (d, *J* = 8.0, 4H, Ar-*H*), 7.38 – 7.22 (m, 6H, Ar-*H*), 6.22 – 6.14 (dt, *J* = 16.6, 1.6, 2H, alkene-*H*), 4.34 – 4.24 (m, 2H, O-C*H*), 2.56 – 2.46 (m, 2H), 2.45 – 2.35 (m, 2H), 2.07 – 1.90 (m, 4H), 1.88 – 1.71 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 140.7, 139.1, 138.9, 127.2, 126.2, 124.7, 124.6, 124.45, 124.35, 70.7, 70.6, 28.4, 28.0, 26.7, 26.6, 19.0, 18.7.

5-Butoxy-2,3,4,5-tetrahydro-1,1'-biphenyl (160):



Chemical Formula: $C_{16}H_{22}O$
Molecular Weight: 230.35

3,4,5,6-Tetrahydro-[1,1'-biphenyl]-3-ol (70 mg, 0.40 mmol) was stirred with [Ir(COD)PPh_3IMes]BAr_F (35 mg, 0.5 mol%) in a flame-dried, argon-cooled Schlenk flask. *n*-Butanol (4.0 mL) was added, the solution was cooled to -78 °C and a hydrogen atmosphere was applied. The reaction vessel was sealed and allowed to warm to room temperature. Stirring was continued for 16 hours before the solution was washed with DCM and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (toluene) to yield the product as a colourless oil (66 mg, 72%).

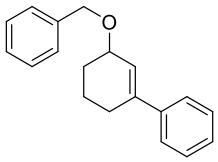
IR: ν_{max}/cm^{-1} 2930, 2861, 1711, 1598, 1494, 1445, 1341, 1161, 1091, 1034, 985, 917, 847, 756, 694.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.44 – 7.39 (m, 2H, Ar-*H*), 7.34 – 7.28 (m, 2H, Ar-*H*), 7.25 – 7.21 (m, 1H, Ar-*H*), 6.17 – 6.10 (m, 1H, alkene-*H*), 4.05 – 3.97 (m, 1H, C*H*-O), 3.61 – 3.48 (m, 2H, CH_2-O), 2.51 – 2.41 (m, 1H), 2.40 – 2.30 (m, 1H), 1.98 – 1.85 (m, 2H), 1.75 – 1.65 (m, 2H), 1.63 – 1.54 (m, 2H), 1.45 – 1.36 (m, 2H), 0.93 (t, *J* = 7.4, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 141.7, 140.0, 128.2, 127.2, 125.4, 125.1, 73.7, 68.2, 32.4, 28.1, 27.7, 19.9, 19.5, 14.0.

HRMS (ESCi®): m/z calculated for $[C_{16}H_{23}O]^+$, Calculated mass = 231.1679, Measured mass = 231.1743 $[M+H]^+$

5-(Benzyloxy)-2,3,4,5-tetrahydro-1,1'-biphenyl (161):



Chemical Formula: $C_{19}H_{20}O$
Molecular Weight: 264.37

3,4,5,6-Tetrahydro-[1,1'-biphenyl]-3-ol (70 mg, 0.40 mmol) was stirred with $[Ir(COD)PPh_3IMes]BAr_F$ (35 mg, 0.5 mol%) in a flame-dried, argon-cooled Schlenk flask. EtOAc (4.0 mL) and benzyl alcohol (208 µL, 2.0 mmol) was added, the solution was cooled to -78 °C and a hydrogen atmosphere was applied. The reaction vessel was sealed and allowed to warm to room temperature. Stirring was continued for 16 hours before the solution was washed with DCM and evaporated under reduced pressure. The reaction mixture was purified by column chromatography (toluene) to yield the product as a yellow/brown oil (93 mg, 89%).

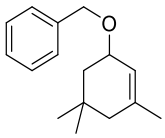
IR: ν_{max}/cm^{-1} 3029, 2932, 2860, 1495, 1452, 1342, 1203, 1161, 1072, 1028, 954, 915, 753, 735, 695.

^1H NMR (400 MHz, $CDCl_3$), δ = 7.44 – 7.14 (m, 10H, Ar-*H*), 6.18 (dt, *J* = 3.4, 1.6, 1H, alkene-*H*), 4.71 (d, *J* = 11.8, 1H, Ar-C*H*^{a}H^b), 4.65 (d, *J* = 11.8, 1H, Ar-CH^a*H*^{b}), 4.18 – 4.12 (m, 1H, C*H*-O), 2.53 – 2.44 (m, 1H), 2.42 – 2.33 (m, 1H), 2.02 – 1.88 (m, 2H), 1.84 – 1.67 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 141.6, 140.5, 139.1, 129.0, 128.4, 128.2, 127.7, 127.5, 127.3, 125.5, 124.7, 73.1, 70.2, 28.1, 27.7, 19.8.

HRMS (ESCi®): m/z calculated for $[C_{19}H_{19}O]^-$, Calculated mass = 263.1506, Measured mass = 263.1413 $[M-H]^-$

(((3,5,5-Trimethylcyclohex-2-en-1-yl)oxy)methyl)benzene (163):[146]



Chemical Formula: $C_{16}H_{22}O$
Molecular Weight: 230.35

$[Ir(COD)PPh_3IMes]BAr_F$ (35 mg, 0.5 mol%) was stirred in a flame-dried, argon-cooled Schlenk flask. EtOAc (3.0 mL) and benzyl alcohol (217 µL, 2.10 mmol) was added, the solution was cooled to -78 °C and a hydrogen atmosphere was applied. The reaction vessel was sealed and allowed to warm to room temperature before the atmosphere was replaced with argon. 3,5,5-Trimethylcyclohex-2-en-1-ol (56 mg, 0.40 mmol in 1 mL EtOAc) was added and stirring was continued for 16 hours before the solution was evaporated under reduced pressure. The reaction mixture was purified by column chromatography (toluene) to yield the product as a colourless oil (84 mg, 91%).

IR: ν_{max}/cm^{-1} 2955, 1702, 1650, 1452, 1368, 1277, 1069, 714.

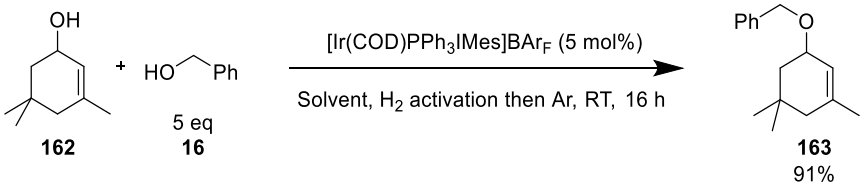
^1H NMR (400 MHz, $CDCl_3$), δ = 7.37 – 7.30 (m, 4H, Ar-*H*), 7.29 – 7.23 (m, 1H, Ar-*H*), 5.55 – 5.51 (m, 1H, alkene-*H*), 4.63 (d, *J* = 12.0, 1H, Ar-C*H*^{a}H^b), 4.58 (d, *J* = 12.0, 1H, Ar-CH^a*H*^{b}), 4.07 – 3.98 (m, 1H, C*H*-O), 1.95 – 1.82 (m, 1H), 1.77 (br. d, *J* = 17.2, 1H), 1.68 (s, 3H), 1.62 (br. d, *J* = 17.2, 1H), 1.38 (dd, *J* = 12.6. 8.9, 1H), 1.01 (s, 3H), 0.88 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 139.2, 136.5, 128.3, 127.6, 127.3, 121.2, 73.8, 70.0, 44.3, 41.4, 31.2, 30.9, 26.5, 23.7.

HRMS (ESCi®): m/z calculated for $[C_{16}H_{21}O]^-$, Calculated mass = 229.1663, Measured mass = 229.1586 $[M-H]^-$

2.5.4 Solvent Screening

Results and discussion, section 2.2.2, page 230.

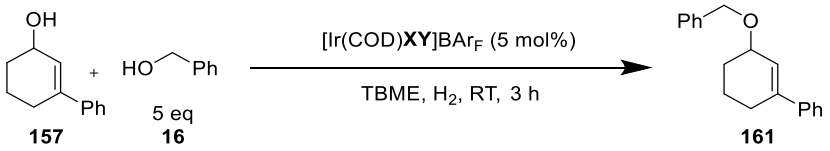


[Ir(COD)IMesPPh$_3$]BAr$_F$ (17 mg, 0.5 mol%), benzyl alcohol (108 µL, 1.0 mmol) and solvent (2.0 mL) were stirred in flame-dried, argon-cooled Radleys carousel tubes. The carousel was cooled to -78 °C and a hydrogen atmosphere was applied. The reactions were sealed, allowed to warm to room temperature and stirred for 15 minutes before the argon atmosphere was reapplied. 3,5,5-Trimethylcyclohex-2-en-1-ol (30 µL, 0.2 mmol) was added and stirring was continued for 16 hours. The reaction mixtures were washed with DCM, concentrated under reduced pressure and filtered through silica plug with DCM. The filtrate was then evaporated under reduced pressure and purified by flash column chromatography (toluene) to yield the product as a colourless oil.

Reaction	Solvent	Isolated Yield
1	THF	59%
2	2-MeTHF	57%
3	Isopropyl acetate	89%
4	Dioxane	63%
5	DCM	65%
6	CPME	80%
7	TBME	96%
8	Ethyl acetate	65%
9	Toluene	80%
10	Dimethyl carbonate	>99%

2.5.5 Catalyst Screening

Results and discussion, section 2.2.3, page 232.



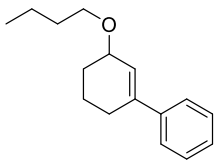
3,4,5,6-Tetrahydro-[1,1'-biphenyl]-3-ol (0.035 g, 0.201 mmol), phenylmethanol (0.104 mL, 1.004 mmol), Ir catalyst (5 mol%) and *t*-butylmethyl ether (4 mL) were added to the 16 mL ChemSCAN Hastelloy reactor vessel, sealed and purged with N_2 (three times at 4 bara) followed by H_2 (twice at 5 bara). The reactions were stirred at 25 °C under 1 bara of hydrogen for 3 hours. The reactor was cooled, vented and purged with nitrogen (3 x at 4 bara) before opening. The reactions were evaporated under reduced pressure and purified by Biotage Isolera (10 g SNAP Ultra, EtOAc 0 - 10% in heptane) to yield the product as a colourless oil.

- [Ir(COD)D^{i}PP]BAr$_F$
    - Product was isolated as a colourless oil (52 mg, 98%)
    - Product was isolated as a colourless oil (29 mg, 55%)
    - Product was isolated as a colourless oil (40 mg, 75%)
    - Average = 76%
- [Ir(COD)IMesPPh$_3$]BAr$_F$
    - No product was isolated
    - Product was isolated as a colourless oil (38 mg, 72%)
    - Product was isolated as a colourless oil (53 mg, 100%)
    - Average = 57%
- [Ir(COD)IPrPPh$_3$]BAr$_F$
    - Product was isolated as a colourless oil (52 mg, 98%)
    - Product was isolated as a colourless oil (47 mg, 89%)
    - Product was isolated as a colourless oil (52 mg, 100%)
    - Average = 96%
- [Ir(COD)IBnPPh$_3$]BAr$_F$
    - Product was isolated as a colourless oil (35 mg, 66%)
    - Product was isolated as a colourless oil (20 mg, 38%)
    - Product was isolated as a colourless oil (21 mg, 40%)
    - Average = 48%

2.5.6 Design of Experiment

Results and discussion, section 2.2.4, page 233.

5-Butoxy-2,3,4,5-tetrahydro-1,1'-biphenyl (160):



Chemical Formula: $C_{16}H_{22}O$
Molecular Weight: 230.35

3,4,5,6-Tetrahydro-[1,1'-biphenyl]-3-ol, butan-1-ol, [(COD)IrIPrPPh$_3$]BAr$_F$, biphenyl internal standard and *t*-butyl methyl ether were added into HPLC vials (quantities and equivalence as stated in reaction database). Rubber septa were fitted to the vials before being pierced with a blunt needle 7 times before the vials were placed in the CAT96 reactor vessel, sealed and purged with N_2 (three times at 4 bara) followed by H_2 (twice at 5 bara, stirred at 1000 rpm). Reactions were stirred at T °C under 1 bara of hydrogen for 6 hours. The reactor was vented and purged with nitrogen (twice at 4 bara), samples were taken for LCMS analysis (10 µL in 1 mL methanol) and solution yields were calculated against biphenyl internal standard.

All solution yields were calculated against an internal standard of biphenyl using response factor calculated using the equation:

$$\mathrm{K_X} = \frac{\text{Peak Area}_{\mathrm{ISTD}} \times \text{Weight}_{\mathrm{X}}}{\text{Peak Area}_{\mathrm{X}} \times \text{Weight}_{\mathrm{ISTD}}}$$

Reference samples were made of a known weight of the compound of interest and a known weight of biphenyl diluted with methanol in a volumetric flask. Three samples of this solution were then analysed by LC on the same day as the samples of the reaction of interest and average peak areas were recorded. Response factors (K_X) were then calculated.

Compound	Average K_x
Product Ether	1.27
Allylic Alcohol Starting Material	0.87

The K_X value then allowed weights of the reaction components of interest within the study to be calculated against a known amount of biphenyl internal standard added to each reaction using this equation:

$$Weight_X = K_X \times Weight_{ISTD} \times \frac{Peak\ Area_X}{Peak\ Area_{ISTD}}$$

Two CAT96 reactors were used and blocks of reactions were performed as such:

Day	Temperature (T)	CAT96 Reactor 1	CAT96 Reactor 2
1	35 °C	Reactions 1 - 4	Reactions 5 - 8
2	45 °C	Reactions 9 - 14	Reactions 15 - 20
3	25 °C	Reactions 21 - 26	Reactions 27 - 32

Solution yields were then analysed using a split plot model by the Design Expert 10 computer software.

Centre Points (Repeated in 2 blocks of 4 reactions)

Reactions 1-8						
	Mr	**Equivalents**	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
Allylic Alcohol	174.243	1	1.025	179		
Nucleophile	74.123	5.5	5.6375	418	0.516	0.81
Ir Cat	1814.53	0.0255	0.0261375	47		
Solvent					1	
		Concentration	1.025			
				Fill Level	1.516	
Adjusted for fill 0.87 mL level						
			mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol			0.58826947	103		
Nucleophile				240	0.296	
Ir Cat				27		
Solvent					0.574	
				Fill Level	0.87	

Reaction	Product Yield	Remaining Starting Material
1	37	11
2	37	13
3	38	11
4	38	12
5	34	12
6	34	11
7	34	13
8	34	13

DoE Reactions At 45°C

Reaction 9				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	0.05	9		
1	0.05	4	0.005	0.81
0.001	0.00005	0.09		
			1	
Concentration	0.05			
		Fill Level	1.005	
Adjusted for fill 0.87 mL level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	0.043301873	8		
Nucleophile		3	0.004	
Ir Cat		0.08		
Solvent			0.866	
		Fill Level	0.87	
	Biphenyl	9.932		
Reaction 10				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	2	348		
1	2	148	0.183	0.81
0.05	0.1	181		
			1	
Concentration	2			
		Fill Level	1.183	
Adjusted for fill 0.87 mL level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	1.470812297	256		
Nucleophile		109	0.135	
Ir Cat		133		
Solvent			0.735	

		Fill Level	0.87	
	Biphenyl	11.704		
Reaction 11				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	1.025	179		
5.5	5.6375	418	0.516	0.81
0.0255	0.0261375	47		
			1	
Concentration	1.025			
		Fill Level	1.516	
Adjusted for fill 0.87 mL level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	0.58826947	103		
Nucleophile		240	0.296	
Ir Cat		27		
Solvent			0.574	
		Fill Level	0.87	
	Biphenyl	9.981		
Reaction 12				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	1.025	179		
5.5	5.6375	418	0.516	0.81
0.0255	0.0261375	47		
			1	
Concentration	1.025			
		Fill Level	1.516	
Adjusted for fill 0.87 mL level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	0.58826947	103		
Nucleophile		240	0.296	
Ir Cat		27		
Solvent			0.574	
		Fill Level	0.87	
	Biphenyl	10.018		
Reaction 13				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	2	348		
10	20	1482	1.830	0.81
0.001	0.002	4		
			1	
Concentration	2			
		Fill Level	2.830	
Adjusted for fill 0.87 mL level				
	mMoles	**Mass (mg)**	**Volume (mL)**	

Allylic Alcohol	0.614798077	107		
Nucleophile		456	0.563	
Ir Cat		1		
Solvent			0.307	
		Fill Level	0.87	
	Biphenyl	10.09		
Reaction 14				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	0.05	9		
10	0.5	37	0.046	0.81
0.05	0.0025	5		
			1	
Concentration	0.05			
		Fill Level	1.046	
Adjusted for fill 0.87 mL level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	0.041596744	7		
Nucleophile		31	0.038	
Ir Cat		4		
Solvent			0.832	
		Fill Level	0.87	
	Biphenyl	10.073		
Reaction 15				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	1.025	179		
5.5	5.6375	418	0.516	0.81
0.0255	0.0261375	47		
			1	
Concentration	1.025			
		Fill Level	1.516	
Adjusted for fill 0.87 mL level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	0.58826947	103		
Nucleophile		240	0.296	
Ir Cat		27		
Solvent			0.574	
		Fill Level	0.87	
	Biphenyl	9.912		
Reaction 16				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	0.05	9		
1	0.05	4	0.005	0.81
0.001	0.00005	0.1		
			1	

Concentration	0.05			
		Fill Level	1.005	
Adjusted for fill 0.87 mL level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	0.043301873	8		
Nucleophile		3	0.004	
Ir Cat		0.08		
Solvent			0.866	
		Fill Level	0.87	
	Biphenyl	10.217		
Reaction 17				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	1.025	179		
5.5	5.6375	418	0.516	0.81
0.0255	0.0261375	47		
			1	
Concentration	1.025			
		Fill Level	1.516	
Adjusted for fill 0.87 mL level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	0.58826947	103		
Nucleophile		240	0.296	
Ir Cat		27		
Solvent			0.574	
		Fill Level	0.87	
	Biphenyl	10.038		
Reaction 18				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	2	348		
10	20	1482	1.830	0.81
0.001	0.002	4		
			1	
Concentration	2			
		Fill Level	2.830	
Adjusted for fill 0.87 mL level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	0.614798077	107		
Nucleophile		456	0.563	
Ir Cat		1		
Solvent			0.307	
		Fill Level	0.87	
	Biphenyl	10.024		
Reaction 19				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**

1	2	348		
1	2	148	0.183	0.81
0.05	0.1	181		
			1	
Concentration	2			
		Fill Level	1.183	
Adjusted for fill 0.87 mL level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	1.470812297	256		
Nucleophile		109	0.135	
Ir Cat		133		
Solvent			0.735	
		Fill Level	0.87	
	Biphenyl	10.238		
Reaction 20				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	0.05	9		
10	0.5	37	0.046	0.81
0.05	0.0025	5		
			1	
Concentration	0.05			
		Fill Level	1.046	
Adjusted for fill 0.87 mL level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	0.041596744	7		
Nucleophile		31	0.038	
Ir Cat		4		
Solvent			0.832	
		Fill Level	0.87	
	Biphenyl	10.131		

Reaction	Product Yield (%)	Remaining Starting Material (%)
9	89	23
10	23	3
11	39	3
12	38	3
13	36	34
14	98	2
15	25	31
16	3	108
17	25	31
18	6	44
19	22	15
20	50	21

DoE Reactions At 25°C

Reaction 21				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	0.05	9		
10	0.5	37	0.046	0.81
0.001	0.00005	0.09		
			1	
Concentration	0.05			
		Fill Level	1.046	
Adjusted for constant 0.87 mL fill level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	0.041596744	7		
Nucleophile		31	0.038	
Ir Cat		0.08		
Solvent			0.832	
		Fill Level	0.87	
	Biphenyl	10.132		

Reaction 22				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	1.025	179		
5.5	5.6375	418	0.516	0.81
0.0255	0.0261375	47		
			1	
Concentration	1.025			
		Fill Level	1.516	
Adjusted for constant 0.87 mL fill level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	0.58826947	103		

Nucleophile		240	0.296	
Ir Cat		27		
Solvent			0.574	
		Fill Level	0.87	
	Biphenyl	10.922		
Reaction 23				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	1.025	179		
5.5	5.6375	418	0.516	0.81
0.0255	0.0261375	47		
			1	
Concentration	1.025			
		Fill Level	1.516	
Adjusted for constant 0.87 mL fill level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	0.58826947	103		
Nucleophile		240	0.296	
Ir Cat		27		
Solvent			0.574	
		Fill Level	0.87	
	Biphenyl	9.792		
Reaction 24				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	0.05	9		
1	0.05	4	0.005	0.81
0.05	0.0025	5		
			1	
Concentration	0.05			
		Fill Level	1.005	
Adjusted for constant 0.87 mL fill level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	0.043301873	8		
Nucleophile		3	0.004	
Ir Cat		4		
Solvent			0.866	
		Fill Level	0.87	
	Biphenyl	9.891		
Reaction 25				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	2	348		
1	2	148	0.183	0.81
0.001	0.002	4		
			1	
Concentration	2			

		Fill Level	1.183	
Adjusted for constant 0.87 mL fill level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	1.470812297	256		
Nucleophile		109	0.135	
Ir Cat		3		
Solvent			0.735	
		Fill Level	0.87	
	Biphenyl	9.883		
Reaction 26				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	2	348		
10	20	1482	1.830	0.81
0.05	0.1	181		
			1	
Concentration	2			
		Fill Level	2.830	
Adjusted for constant 0.87 mL fill level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	0.614798077	107		
Nucleophile		456	0.563	
Ir Cat		56		
Solvent			0.307	
		Fill Level	0.87	
	Biphenyl	10.071		
Reaction 27				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	2	348		
10	20	1482	1.830	0.81
0.05	0.1	181		
			1	
Concentration	2			
		Fill Level	2.830	
Adjusted for constant 0.87 mL fill level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	0.614798077	107		
Nucleophile		456	0.563	
Ir Cat		56		
Solvent			0.307	
		Fill Level	0.87	
	Biphenyl	10.301		
Reaction 28				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	0.05	9		

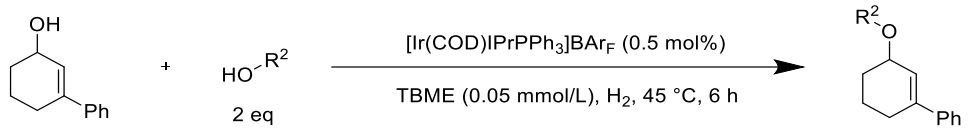
1	0.05	4	0.005	0.81
0.05	0.0025	5		
			1	
Concentration	0.05			
		Fill Level	1.005	
Adjusted for constant 0.87 mL fill level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	0.043301873	8		
Nucleophile		3	0.004	
Ir Cat		4		
Solvent			0.866	
		Fill Level	0.87	
	Biphenyl	10.393		
Reaction 29				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	1.025	179		
5.5	5.6375	418	0.516	0.81
0.0255	0.0261375	474		
			1	
Concentration	1.025			
		Fill Level	1.516	
Adjusted for constant 0.87 mL fill level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	0.58826947	103		
Nucleophile		240	0.296	
Ir Cat		27		
Solvent			0.574	
		Fill Level	0.87	
	Biphenyl	9.918		
Reaction 30				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	1.025	179		
5.5	5.6375	418	0.516	0.81
0.0255	0.0261375	47		
			1	
Concentration	1.025			
		Fill Level	1.516	
Adjusted for constant 0.87 mL fill level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	0.58826947	103		
Nucleophile		240	0.296	
Ir Cat		27		
Solvent			0.573	
		Fill Level	0.87	

	Biphenyl	9.88		
Reaction 31				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	0.05	9		
10	0.5	37	0.046	0.81
0.001	0.00005	0.09		
			1	
Concentration	0.05			
		Fill Level	1.046	
Adjusted for constant 0.87 mL fill level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	0.041596744	7		
Nucleophile		31	0.038	
Ir Cat		0.08		
Solvent			0.832	
		Fill Level	0.87	
	Biphenyl	10.087		
Reaction 32				
Equivalents	**mMoles**	**Mass (mg)**	**Volume (mL)**	**Density**
1	2	348		
1	2	148	0.183	0.81
0.001	0.002	3.6		
			1	
Concentration	2			
		Fill Level	1.183	
Adjusted for constant 0.87 mL fill level				
	mMoles	**Mass (mg)**	**Volume (mL)**	
Allylic Alcohol	1.470812297	2564		
Nucleophile		1094	0.135	
Ir Cat		2.7		
Solvent			0.735	
		Fill Level	0.87	
	Biphenyl	10.621		

Reaction	Product Yield (%)	Remaining Starting Material (%)
21	103	6
22	38	3
23	41	3
24	75	6
25	27	33
26	41	1
27	29	23
28	33	38
29	25	38
30	24	34
31	2	120
32	6	41

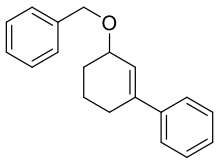
2.5.7 Alcohol Nucleophile Evaluation

Results and discussion, section 2.2.5, page 239. Yields can be found summarised in Figure 58, page 240.



3,4,5,6-Tetrahydro-[1,1'-biphenyl]-3-ol (0.035 g, 0.20 mmol), alcohol (2 equivalents, 0.40 mmol), [(COD)IrIPrPPh$_3$]BAr$_F$ (1.8 mg, 1.0 µmol) and *t*-butylmethyl ether (4 mL) were added into the 16 mL ChemSCAN Hastelloy reactor vessels, sealed and purged with N_2 (three times at 4 bara) followed by H_2 (twice at 5 bara). The reactions were stirred at 45 °C under 1 bara of hydrogen for 6 hours. The reactor was cooled, vented and purged with nitrogen (three times at 4 bara), samples were taken for LCMS analysis (10 µL in 1 mL methanol) and reactions were evaporated under reduced pressure. Products were purified by Biotage Isolera (10 g Sfar, 0 – 10% EtOAc in heptane) and product containing fractions were evaporated under reduced pressure to yield product.

5-(Benzyloxy)-2,3,4,5-tetrahydro-1,1'-biphenyl (161):



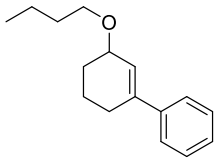
Chemical Formula: $C_{19}H_{20}O$
Molecular Weight: 264.37

Phenylmethanol (0.041 mL, 0.40 mmol) was used as alcohol nucleophile. The product was isolated as a colourless oil (45 mg, 85%).

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.44 – 7.14 (m, 10H, Ar-*H*), 6.18 (dt, *J* = 3.4, 1.6, 1H, alkene-*H*), 4.71 (d, *J* = 11.8, 1H, Ar-C*H*^{a}H^b), 4.65 (d, *J* = 11.8, 1H, Ar-CH^a*H*^{b}), 4.18 – 4.12 (m, 1H, C*H*-O), 2.53 – 2.44 (m, 1H), 2.42 – 2.33 (m, 1H), 2.02 – 1.88 (m, 2H), 1.84 – 1.67 (m, 2H).

Full data reported in 2.5.3

5-Butoxy-2,3,4,5-tetrahydro-1,1'-biphenyl (160):



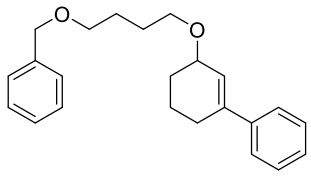
Chemical Formula: $C_{16}H_{22}O$
Molecular Weight: 230.35

Butan-1-ol (0.037 mL, 0.40 mmol) was used as alcohol nucleophile. The product was isolated as a colourless oil (34 mg, 74%).

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.44 – 7.39 (m, 2H, Ar-*H*), 7.34 – 7.28 (m, 2H, Ar-*H*), 7.25 – 7.21 (m, 1H, Ar-*H*), 6.17 – 6.10 (m, 1H, alkene-*H*), 4.05 – 3.97 (m, 1H, C*H*-O), 3.61 – 3.48 (m, 2H, C*H*$_2$-O), 2.51 – 2.41 (m, 1H), 2.40 – 2.30 (m, 1H), 1.98 – 1.85 (m, 2H), 1.75 – 1.65 (m, 2H), 1.63 – 1.54 (m, 2H), 1.45 – 1.36 (m, 2H), 0.93 (t, *J* = 7.4, 3H).

Full data reported in 2.5.3

5-(4-(Benzyloxy)butoxy)-2,3,4,5-tetrahydro-1,1'-biphenyl (164):



Chemical Formula: $C_{23}H_{28}O_2$
Molecular Weight: 336.48

4-(Benzyloxy)butan-1-ol (0.070 mL, 0.40 mmol) was used as alcohol nucleophile. The product was isolated as a colourless oil (55 mg, 82%).

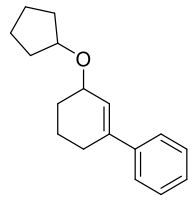
IR: ν_{max}/cm^{-1} 3029, 2935, 2858, 1494, 1453, 1358, 1201, 1091, 1028, 754, 696.

^1H NMR (400 MHz, $CDCl_3$), δ = 7.46 – 7.25 (m, 10H, Ar-*H*), 6.16 (dt, *J* = 3.5, 1.7, 1H, alkene-*H*), 4.54 (s, 2H, Ar-CH_2-O), 4.07 – 4.01 (m, 1H, C*H*-O), 3.66 – 3.50 (m, 4H, 2 x CH_2-O), 2.54 – 2.45 (m, 1H), 2.42 – 2.32 (m, 1H), 1.97 – 1.85 (m, 2H), 1.77 – 1.69 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 141.7, 140.1, 138.7, 128.3, 128.2, 127.6, 127.5, 127.2, 125.4, 125.0, 73.7, 72.9, 70.2, 68.1, 28.1, 27.7, 27.0, 26.6, 19.8.

HRMS (ESCi®): m/z calculated for $[C_{23}H_{27}O_2]^-$, Calculated mass = 335.2081, Measured mass = 335.2005 $[M-H]^+$

5-(Cyclopentyloxy)-2,3,4,5-tetrahydro-1,1'-biphenyl (165):



Chemical Formula: $C_{17}H_{22}O$
Molecular Weight: 242.36

Cyclopentanol (0.036 mL, 0.40 mmol) was used as alcohol nucleophile. The product was isolated as a colourless oil (38 mg, 79%).

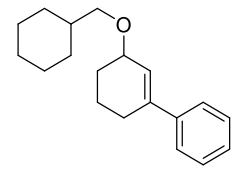
IR: v_{max}/cm^{-1} 2936, 2863, 1598, 1494, 1445, 1339, 1159, 1073, 1034, 1003, 967, 917, 847, 755, 694.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.43 – 7.38 (m, 2H, Ar-*H*), 7.33 – 7.28 (m, 2H, Ar-*H*), 7.26 – 7.20 (m, 1H, Ar-*H*), 6.10 (dt, *J* = 3.3, 1.7, 1H, alkene-*H*), 4.15 – 4.10 (m, 1H, C*H*-O), 4.09 – 4.05 (m, 1H, C*H*-O), 2.50 – 2.42 (m, 1H), 2.38 – 2.29 (m, 1H), 1.95 – 1.86 (m, 2H), 1.81 – 1.64 (m, 8H), 1.57 – 1.49 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 141.7, 139.7, 129.0, 128.2, 127.1, 125.9, 125.4, 79.1, 71.9, 33.2, 28.9, 27.6, 23.6, 23.5, 20.0.

HRMS (ESCi®): m/z calculated for $[C_{17}H_{21}O]^-$, Calculated mass = 241.1663, Measured mass = 241.1588 $[M-H]^+$

5-(Cyclohexylmethoxy)-2,3,4,5-tetrahydro-1,1'-biphenyl (166):



Chemical Formula:
$C_{19}H_{26}O$
Molecular Weight: 270.42

Cyclohexylmethanol (0.049 mL, 0.40 mmol) was used as alcohol nucleophile. The product was isolated as a colourless oil (46 mg, 85%).

IR: v_{max}/cm^{-1} 2920, 2849, 1494, 1447, 1354, 1277, 1161, 1110, 1086, 1074, 959, 913, 891, 754, 693.

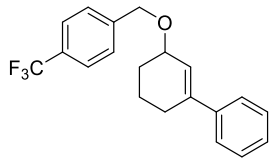
^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.44 – 7.38 (m, 2H, Ar-*H*), 7.34 – 7.27 (m, 2H Ar-*H*), 7.26 – 7.20 (m, 1H, Ar-*H*), 6.14 (dt, *J* = 3.4, 1.63, 1H, alkene-*H*), 4.02 – 3.96 (m, 1H, C*H*-O), 3.38 – 3.30 (m,

2H, C*H*$_2$-O), 2.52 – 2.41 (m, 1H), 2.39 – 2.30 (m, 1H), 1.97 – 1.78 (m, 4H), 1.75 – 1.54 (m, 6H), 1.31 – 1.14 (m, 3H), 0.93 (qd, *J* = 12.1, 3.2, 2H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 141.7, 139.9, 128.2, 127.2, 125.4, 125.2, 74.4, 73.8, 38.5, 30.33, 30.30, 28.1, 27.7, 26.7, 25.9, 19.9.

HRMS (ESCi®): m/z calculated for $[C_{19}H_{25}O]^-$, Calculated mass = 269.1976, Measured mass = 269.1901 $[M-H]^+$

5-((4-(Trifluoromethyl)benzyl)oxy)-2,3,4,5-tetrahydro-1,1'-biphenyl (167):



Chemical Formula: $C_{20}H_{19}F_3O$
Molecular Weight: 332.37

(4-(Trifluoromethyl)phenyl)methanol (0.055 mL, 0.40 mmol) was used as alcohol nucleophile. The product was purified by EZPrep reverse phase chromatography (50 – 100% MeCN + 0.1% TFA in water) to yield a colourless oil (39 mg, 59%).

IR: ν_{max}/cm^{-1} 2933, 2861, 1494, 1419, 1324, 1162, 1122, 1087, 1066, 1018, 958, 913, 823, 757, 696.

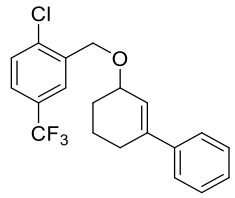
^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.63 (d, *J* = 8.1, 2H, Ar-*H*), 7.53 (d, *J* = 8.1, 2H, Ar-*H*), 7.45 – 7.41 (m, 2H, Ar-*H*), 7.38 – 7.32 (m, 2H, Ar-*H*), 7.32 – 7.26 (m, 1H, Ar-*H*), 6.22 – 6.17 (m, 1H, alkene-*H*), 4.76 (d, *J* = 12.0, 1H, Ar-C*H*^{a}H^b), 4.70 (d, *J* = 16.0, 1H, Ar-CH^a*H*^{b}), 4.24 – 4.15 (m, 1H, C*H*-O), 2.58 – 2.48 (m, 1H), 2.46 – 2.36 (m, 1H), 2.05 – 1.92 (m, 2H), 1.89 – 1.71 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 143.4, 141.6, 141.1, 129.8 (q, ^{2}JC-F = 32.3 Hz), 128.4, 127.7, 127.6, 125.6, 125.4 (q, ^{3}JC-F =3.8 Hz), 124.4, 124.4 (q, ^{1}JC-F = 267.3 Hz), 73.7, 69.5, 28.2, 27.8, 19.8.

^{19}F NMR (376 MHz, $CDCl_3$), δ = -62.5

HRMS (ESCi®): m/z calculated for $[C_{20}H_{18}F_3O]^-$, Calculated mass = 331.1380, Measured mass = 331.1312 $[M-H]^+$

5-((2-Chloro-5-(trifluoromethyl)benzyl)oxy)-2,3,4,5-tetrahydro-1,1'-biphenyl (168):



Chemical Formula: $C_{20}H_{18}ClF_3O$
Molecular Weight: 366.81

(2-Chloro-5-(trifluoromethyl)phenyl)methanol (0.084 g, 0.40 mmol) was used as alcohol nucleophile. The reaction mixture was additionally purified by EZ prep reverse phase chromatography (50 – 100% MeCN + 0.01% formic acid in water). The product was isolated as a colourless oil (60 mg, 82%).

IR: ν_{max}/cm^{-1} 2930, 2863, 1608, 1417, 1326, 1255, 1167, 1125, 1080, 1045, 955, 904, 825, 753, 694.

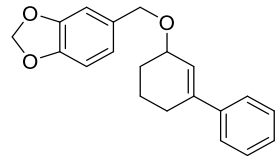
^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.86 (s, 1H, Ar-*H*), 7.48 – 7.40 (m, 4H, Ar-*H*), 7.36 – 7.30 (m, 2H, Ar-*H*), 7.29 – 7.25 (m, 1H, Ar-*H*), 6.21 (dt, *J* = 3.5, 1.6, 1H, alkene-*H*), 4.80 (d, *J* = 16.0, 1H, C*H*^{a}H^{b}-O), 4.75 (d, *J* = 16.0, 1H, CH^{a}*H*^{b}-O), 4.26 – 4.20 (m, 1H, C*H*-O), 2.58 – 2.47 (m, 1H), 2.45 – 2.35 (m ,1H), 2.05 – 1.94 (m, 2H), 1.92 – 1.82 (m, 1H), 1.81 – 1.71 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 141.4, 141.2, 138.1, 136.1, 129.5, 129.2, 128.3, 127.5, 125.7, 125.5, 125.1, 124.0, 74.3, 66.8, 29.7, 28.1, 27.7, 19.7.

^{19}F NMR (376 MHz, $CDCl_3$), δ = -62.5

HRMS (ESCi®): m/z calculated for $[C_{20}H_{17}ClF_3O]^-$, Calculated mass = 365.0990, Measured mass = 365.0912 $[M-H]^+$

5-(((3,4,5,6-Tetrahydro-[1,1'-biphenyl]-3-yl)oxy)methyl)benzo[d][1,3]dioxole (169):



Chemical Formula: $C_{20}H_{20}O_3$
Molecular Weight: 308.38

Benzo[d][1,3]dioxol-5-ylmethanol (0.061 g, 0.40 mmol) was used as alcohol nucleophile. The product was isolated as a colourless oil (49 mg, 79%).

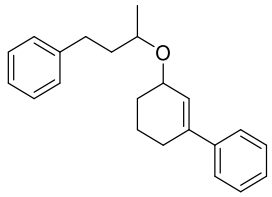
IR: ν_{max}/cm^{-1} 2932, 1501, 1489, 1442, 1337, 1248, 1122, 1096, 1073, 1037, 929, 860, 807, 757, 694.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.42 – 7.38 (m, 2H, Ar-*H*), 7.34 – 7.16 (m, 3H, Ar-*H*), 6.92 – 6.74 (m, 3H, Ar-*H*), 6.15 (dt, *J* = 3.5, 1.6, 1H, alkene-*H*), 5.94 (s, 2H, O-CH_2-O), 4.60 (d, *J* = 12.0, 1H, CH^aH^b-O), 4.55 (d, *J* = 12.0, 1H, CH^aH^b-O), 4.15 – 4.07 (m, 1H, C*H*-O), 2.52 – 2.43 (m, 1H), 2.41 – 2.32 (m, 1H), 2.00 – 1.86 (m, 2H), 1.82 – 1.67 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 147.7, 141.6, 140.5, 132.9, 129.0, 128.2, 127.3, 125.5, 124.7, 121.2, 108.5, 108.0, 100.9, 72.8, 70.0 28.1, 27.7, 19.7

HRMS (ESCi®): m/z calculated for $[C_{20}H_{19}O_3]^-$, Calculated mass = 307.1404, Measured mass = 307.1330 $[M-H]^+$

5-((4-Phenylbutan-2-yl)oxy)-2,3,4,5-tetrahydro-1,1'-biphenyl (170):



Chemical Formula: $C_{22}H_{26}O$
Molecular Weight: 306.45

4-Phenylbutan-2-ol (0.062 mL, 0.40 mmol) was used as alcohol nucleophile. The product was isolated as a colourless oil (45 mg, 74%). The purified product was determined to contain a mixture of diastereoisomers.

IR: ν_{max}/cm^{-1} 3025, 2929, 2861, 1601, 1494, 1453, 1371, 1337, 1131, 1071, 1030, 985, 908, 748, 697.

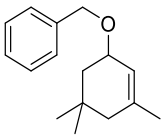
^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.44 – 7.38 (m, 2H, Ar-*H*), 7.34 – 7.15 (m, 8H, Ar-*H*), 6.09 (td, *J* = 3.3, 2.0, 1H, alkene-*H*), 4.12 – 4.05 (m, 1H, C*H*-O), 3.68 – 3.57 (m, 1H, C*H*-O), 2.86 – 2.62 (m, 2H), 2.52 – 2.44 (m, 1H), 2.40 – 2.31 (m, 1H), 1.97 – 1.69 (m, 6H), 1.23 (d, *J* = 5.9, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 142.5, 141.71, 141.65, 128.44, 128.40, 128.3, 128.18, 128.15, 127.2, 125.8, 125.7, 125.45, 125.41, 73.0, 72.8, 71.8, 71.3, 39.0, 38.9, 32.2, 32.0, 29.6, 28.8, 27.7, 21.2, 20.8, 19.9, 19.8.

HRMS (ESCi®): m/z calculated for $[C_{22}H_{25}O]^-$, Calculated mass = 305.1976, Measured mass = 305.1901 $[M-H]^+$

2.5.8 ChemSCAN Validation Reactions

Results and discussion, section 2.2.6, page 241.

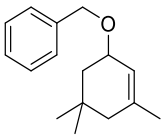


Chemical Formula: $C_{16}H_{22}O$
Molecular Weight: 230.35

[(COD)IrIPrPPh$_3$]BAr$_F$ (1.8 mg, 1.00 µmol), benzyl alcohol (0.041 mL, 0.40 mmol), 3,5,5-trimethylcyclohex-2-en-1-ol (0.031 mL, 0.200 mmol) and *t*-butylmethyl ether (4 mL) were added to the 16 mL ChemSCAN Hastelloy reactor vessels. These were purged with N_2 (3 x at 4 bara), hydrogen (stirred, 2 x at 5 bara) and then N_2 (3 x at 4 bara). The reactions were then purged with N_2 (2 x at 4 bara), heated to 45 °C and stirred for 6 hours. The reactors were then cooled and opened before the reaction mixtures were evaporated under reduced pressure. The residue was purified by Biotage Isolera (10 g Sfar, 0 – 10% EtOAc in heptane). The product was isolated as a colourless oil (22 mg, 48%).

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.37 – 7.30 (m, 4H, Ar-*H*), 7.29 – 7.23 (m, 1H, Ar-*H*), 5.55 – 5.51 (m, 1H, alkene-*H*), 4.63 (d, *J* = 12.0, 1H, Ar-C*H*^{a}H^b), 4.58 (d, *J* = 12.0, 1H, Ar-CH^a*H*^{b}), 4.07 – 3.98 (m, 1H, C*H*-O), 1.95 – 1.82 (m, 1H), 1.77 (br. d, *J* = 17.2, 1H), 1.68 (s, 3H), 1.62 (br. d, *J* = 17.2, 1H), 1.38 (dd, *J* = 12.6. 8.9, 1H), 1.01 (s, 3H), 0.88 (s, 3H).

Full data found in section Initial Scoping Reactions 2.5.3



Chemical Formula: $C_{16}H_{22}O$
Molecular Weight: 230.35

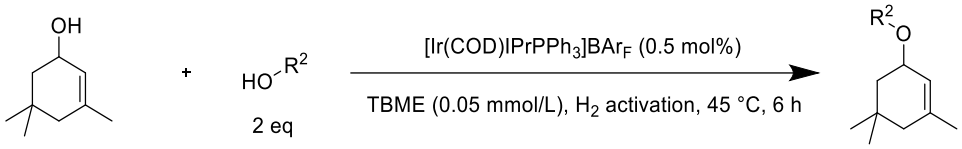
[(COD)IrIPrPPh$_3$]BAr$_F$ (1.8 mg, 1.00 µmol), benzyl alcohol (0.041 mL, 0.40 mmol) and *t*-butylmethyl ether (4 mL) were added to the 16 mL ChemSCAN Hastelloy reactor vessels. These were purged with N_2 (3 x at 4 bara), hydrogen (stirred, 2 x at 5 bara) and then N_2 (3 x at 4 bara). The reaction vessels were opened and 3,5,5-trimethylcyclohex-2-en-1-ol (0.031 mL, 0.200 mmol) was added. The reactions were then purged with N_2 (2 x at 4 bara), heated to 45 °C and stirred for 6 hours. The reactors were then cooled and opened before the reaction mixtures were evaporated under reduced pressure. The residue was purified by Biotage Isolera (10 g Sfar, 0 – 10% EtOAc in heptane). Product was a colourless oil (35 mg, 76%)

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.37 – 7.30 (m, 4H, Ar-*H*), 7.29 – 7.23 (m, 1H, Ar-*H*), 5.55 – 5.51 (m, 1H, alkene-*H*), 4.63 (d, *J* = 12.0, 1H, Ar-C*H*^{a}H^b), 4.58 (d, *J* = 12.0, 1H, Ar-CH^a*H*^{b}), 4.07 – 3.98 (m, 1H, C*H*-O), 1.95 – 1.82 (m, 1H), 1.77 (br. d, *J* = 17.2, 1H), 1.68 (s, 3H), 1.62 (br. d, *J* = 17.2, 1H), 1.38 (dd, *J* = 12.6. 8.9, 1H), 1.01 (s, 3H), 0.88 (s, 3H).

Full data found in section Initial Scoping Reactions 2.5.3

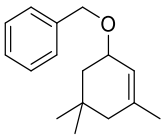
2.5.9 Reactions with Hydrogen Activation

Results and discussion, section 2.2.6, page 241. Yields can be found summarised in Figure 59, page 243.



[(COD)IrIPrPPh$_3$]BAr$_F$ (1.8 mg, 1.00 µmol), alcohol (2 equivalents, 0.40 mmol) and *t*-butylmethyl ether (4 mL) were added to the 16 mL ChemSCAN Hastelloy reactor vessels. These were purged with N_2 (3 x at 4 bara), hydrogen (stirred, 2 x at 5 bara) and then N_2 (3 x at 4 bara). The reaction vessels were opened and 3,5,5-trimethylcyclohex-2-en-1-ol (0.031 mL, 0.200 mmol) was added. The reactions were then purged with N_2 (2 x at 4 bara), heated to 45 °C and stirred for 6 hours. The reactors were then cooled and opened before the reaction mixtures were evaporated under reduced pressure. The residue was purified by Biotage Isolera (10 g Sfar, 0 – 10% EtOAc in heptane).

(((3,5,5-Trimethylcyclohex-2-en-1-yl)oxy)methyl)benzene (163):



Chemical Formula: $C_{16}H_{22}O$
Molecular Weight: 230.35

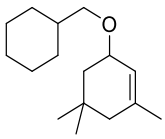
Phenylmethanol (0.041 mL, 0.40 mmol) was used as alcohol nucleophile. The product was isolated as a colourless oil (33 mg, 72%).

^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.37 – 7.30 (m, 4H, Ar-*H*), 7.29 – 7.23 (m, 1H, Ar-*H*), 5.55 – 5.51 (m, 1H, alkene-*H*), 4.63 (d, *J* = 12.0, 1H, Ar-C*H*^{a}H^b), 4.58 (d, *J* = 12.0, 1H, Ar-CH^a*H*^{b}), 4.07 – 3.98

(m, 1H, C*H*-O), 1.95 – 1.82 (m, 1H), 1.77 (br. d, *J* = 17.2, 1H), 1.68 (s, 3H), 1.62 (br. d, *J* = 17.2, 1H), 1.38 (dd, *J* = 12.6. 8.9, 1H), 1.01 (s, 3H), 0.88 (s, 3H).

Full data found in section Initial Scoping Reactions 2.5.3

3-(Cyclohexylmethoxy)-1,5,5-trimethylcyclohex-1-ene (178):



Chemical Formula: $C_{16}H_{28}O$
Molecular Weight: 236.40

Cyclohexylmethanol (0.049 mL, 0.40 mmol) was used as alcohol nucleophile. Product was purified by EZPrep reverse phase chromatography (50 – 100% MeCN + 0.1% TFA in water) to yield a colourless oil (16 mg, 34%).

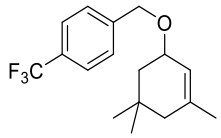
IR: ν_{max}/cm^{-1} 2920, 2850, 1672, 1449, 1377, 1364, 1172, 1131, 1104, 1085, 1071, 1010, 953, 890, 818.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 5.48 (dd, *J* = 2.2, 1.2, 1H, alkene-*H*), 3.90 – 3.82 (m, 1H, C*H*-O), 3.34 – 3.24 (m, 2H, CH_2-O), 1.87 (br. d, *J* = 17.2, 1H), 1.80 (br. dd, *J* = 12.6, 1.5, 2H), 1.76 – 1.50 (m, 9H), 1.34 – 1.11 (m, 4H), 1.00 (s, 3H), 0.98 – 0.90 (m, 2H), 0.89 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 136.0, 121.6, 77.2, 74.3, 44.3, 41.4, 38.5, 31.3, 30.9, 30.4, 30.3, 26.7, 26.4, 26.0, 23.7

HRMS (ESCi®): m/z calculated for $[C_{16}H_{27}O]^-$, Calculated mass = 235.2132, Measured mass = 235.2057 $[M-H]^+$

1-(Trifluoromethyl)-4-(((3,5,5-trimethylcyclohex-2-en-1-yl)oxy)methyl)benzene (181):



Chemical Formula: $C_{17}H_{21}F_3O$
Molecular Weight: 298.35

(4-(Trifluoromethyl)phenyl)methanol (0.055 mL, 0.40 mmol) was used as alcohol nucleophile. Product was purified by EZPrep reverse phase chromatography (50 – 100% MeCN + 0.1% TFA in water) to yield a colourless oil (13 mg, 22%).

IR: ν_{max}/cm^{-1} 2925, 1653, 1419, 1365, 1325, 1163, 1125, 1067, 1017, 819, 592.

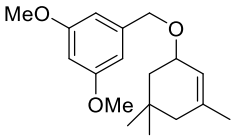
^1H NMR (400 MHz, $CDCl_3$), δ = 7.59 (d, *J* = 8.1, 2H, Ar-*H*), 7.47 (d, *J* = 7.9, 2H, Ar-*H*), 5.53 (dd, *J* = 2.3, 1.1, 1H, alkene-*H*), 4.68 (d, *J* = 12.0, 1H, C*H*^{a}H^b-O), 4.63 (d, *J* = 12.0, 1H, CH^a*H*^{b}-O), 4.08 – 4.01 (m, 1H, C*H*-O), 1.89 (br. d, *J* = 17.2, 1H), 1.81 – 1.74 (m, 1H), 1.69 (s, 3H), 1.64 (d, *J* = 17.2, 1H), 1.40 (dd, *J* = 12.6, 8.9, 1H), 1.02 (s, 3H), 0.89 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 143.4, 137.0, 129.4, 127.5, 125.6, 125.2, 120.8, 74.3, 69.2, 44.3, 41.4, 31.2, 30.9, 26.5, 23.7.

^{19}F NMR (376 MHz, $CDCl_3$), δ = -62.5

HRMS (ESCi®): m/z calculated for $[C_{17}H_{20}F_3O]^-$, Calculated mass = 297.1536, Measured mass = 297.1455 $[M-H]^+$

1,3-Dimethoxy-5-(((3,5,5-trimethylcyclohex-2-en-1-yl)oxy)methyl)benzene (182):



Chemical Formula: $C_{18}H_{26}O_3$
Molecular Weight: 290.40

(3,5-Dimethoxyphenyl)methanol (0.067 g, 0.40 mmol) was used as alcohol nucleophile. The product was isolated as a colourless oil (35 mg, 60%).

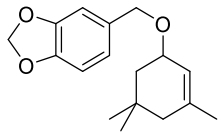
IR: v_{max}/cm^{-1} 2950, 1596, 1460, 1429, 1353, 1204, 1152, 1055, 831.

^{1}H NMR (400 MHz, $CDCl_3$), δ = 6.53 (d, *J* = 2.5, 2H, Ar-*H*), 6.37 (t, *J* = 2.3, 1H, Ar-*H*), 5.53 (dd, *J* = 2.2, 1.1, 1H, alkene-*H*), 4.57 (d, *J* = 12.0, 1H, C*H*^{a}H^b-O), 4.52 (d, *J* = 12.0, 1H, CH^a*H*^{b}-O), 4.02 (br. dd, *J* = 4.2, 2.0, 1H, C*H*-O), 3.79 (s, 6H, 2 x O-C*H*$_3$), 1.88 (br. d, *J* = 17.2, 1H), 1.76 (dd, *J* = 12.6, 5.9, 1H), 1.68 (s, 3H), 1.62 (br. d, *J* = 17.2, 1H), 1.38 (dd, *J* = 12.6, 8.9, 1H), 1.01 (s, 3H), 0.88 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 160.8, 141.7, 136.5, 121.1, 105.3, 99.5, 73.8, 69.9, 55.3, 44.3, 41.3, 31.2, 30.9, 26.5, 23.7.

HRMS (ESCi®): m/z calculated for $[C_{18}H_{27}O_3]^+$, Calculated mass = 291.1890, Measured mass = 291.1958 $[M+H]^+$

5-(((3,5,5-Trimethylcyclohex-2-en-1-yl)oxy)methyl)benzo[d][1,3]dioxole (180):



Chemical Formula: $C_{17}H_{22}O_3$
Molecular Weight: 274.36

Benzo[d][1,3]dioxol-5-ylmethanol (0.061 g, 0.40 mmol) was used as alcohol nucleophile. The product was isolated as a colourless oil (42 mg, 76%).

IR: ν_{max}/cm^{-1} 2950, 2866, 1503, 1490, 1442, 1377, 1363, 1248, 1131, 1096, 1066, 1038, 929, 863, 807.

^1H NMR (400 MHz, $CDCl_3$), δ = 6.87 (d, *J* = 1.5, 1H, Ar-*H*), 6.82 – 6.78 (m, 1H, Ar-*H*), 6.78 – 6.74 (m, 1H, Ar-*H*), 5.93 (s, 2H, O-C*H*$_2$-O), 5.51 (dd, *J* = 2.3, 1.1, 1H, alkene-*H*), 4.52(d, *J* = 12.0, 1H, C*H*^{a}H^b-O), 4.47 (d, *J* = 12.0, 1H, CH^a*H*^{b}-O), 4.05 – 3.95 (m, 1H, C*H*-O), 1.87 (br. d, *J* = 17.2, 1H), 1.77 – 1.71 (m, 1H), 1.68 (s, 3H), 1.61 (br. d, *J* = 17.2, 1H), 1.36 (dd, *J* = 12.6, 8.9, 1H), 1.00 (s, 3H), 0.88 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$), δ = 147.7, 146.9, 136.5, 133.1, 121.14, 121.07, 108.5, 108.0, 100.9, 73.6, 69.8, 44.3, 41.4, 31.2, 30.9, 26.5, 23.7.

HRMS (ESCi®): m/z calculated for $[C_{17}H_{21}O_3]^-$, Calculated mass = 273.1561, Measured mass = 273.1486 $[M-H]^-$

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