The application of Green Chemistry to Organic Syntheses and Mass-Based Reaction Metrics.

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Doctor of Philosophy

University of York
Chemistry

November 2021

Abstract

This thesis explores the use of mass-based reaction metrics to analyses a chemical process and identify areas for improvement. The use of mass-based metrics to guide organic synthesis can lead to improvements in the green credentials and potential of a reaction.

Mass-based reaction metrics have become an increasingly popular method of evaluating the performance and green credentials of a reaction or process. However, the use of metrics is not perfect, and several pitfalls have been identified. Through the analysis of published procedures for amide formation reactions, it was shown that Atom Economy (AE) and Reaction Mass Efficiency (RME) have the potential to be applied incorrectly due to operator error, and the data obtained from Process Mass Intensity (PMI) can be misinterpreted if no context to reaction conditions are applied. These issues can be amplified when the metric results are used in direct comparisons of processes.

The use of reaction metrics has enabled improvements in various organic reactions to be identified and realised. The use of ethanol and HCl lead to improvements in the synthesis of cytosine, while 3,3-diethoxypropanitrile was synthesised from acrylonitrile in an improved catalytic process. 2,2,5,5-Tetramethyloxolane (TMO) was used as a substitute for traditional solvents in several chemical transformations; enzymatic catalysed synthesis of 1,3-oxathiolanes, the Mitsunobu reaction and various OH activated nucleophilic substitution reactions. The reactivity of cytosine and its protected derivatives towards 1,3-oxathiolanes under Mitsunobu conditions was also successfully investigated.

Finally, the use of a potentially bio-based Brønsted acid *p*-cymene sulphonic acid (*p*-CSA) was used for OH activation reactions with numerous nucleophiles reacting with allylic and propargylic alcohols as well as alcohols derived from carvone.

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List of Abbreviations

^{o}C	degrees Celsius
NEt_3	triethylamine
2-MeTHF	2-Methyl tetrahydrofuran
Ac	acetyl
ACS	American chemical society
AE	atom economy
API	active pharmaceutical ingredient
app.	apparent
Ar	aryl
aq.	aqueous
br.	broad
bp	boiling point
Bn	benzyl
Bu	butyl
Bz	benzoyl
cat.	catalytic
CDI	carbonyldiimidazole
$COCl_2$	oxalyl chloride
d	doublet
DBPEAC	ethyl 2-(3,4-dibromophenyl)azocarboxylate
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
DCPEAC	ethyl 2-(3,4-dichlorophenyl)azocarboxylate
dd	doublet of doublets
DEAD	diethyl azodicarboxylate
DIAD	disopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio

dt	doublet of triplets
EDC	1-ethyl-3-(3’-dimethylaminopropyl)carbodiimide hydrochloride
EDG	electron donating group
ee	enantiomeric excess
EI	electrical ionisation
equiv.	equivalents
ESI	electrospray ionisation
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
EWG	electron withdrawing group
FePc	iron phthalocyanine
GC-FID	gas chromatography with flame ionised detector
GC-MS	gas chromatography with mass spectroscopy
h	hour(s)
HBOt	1-hydroxybenzotriazole
HCl	hydrochloric acid
HSP	hansen solubility parameters
HSPiP	hansen solubility parameters in practice
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
i	*iso*-
IBCF	isobutyl chloroformate
*i*PrOH	*iso*-Propanol
IR	infra-red
LCA	life cycle analysis
LDA	lithium diisopropylamide
m	multiplet
Me	methyl
MeOH	methanol

min	minute(s)
m.p.	melting point
Ms	methanesulfonyl
NBS	*N*-Bromosuccinimide
n-BuLi	*n*-butyl lithium
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
o-	*ortho*-
p-	*para*-
Pc	phthalocyanine
p-CSA	*para*-cymene sulfonic acid
Ph	phenyl
PivCl	pivaloyl chloride
PMI	process mass intensity
PPh_3	triphenyl phosphine
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
PrOH	propanol
p-TSA	*para*-toluene sulfonic acid
Py	pyridine
q	quartet
REACh	registration, evaluation, authorisation & restriction of chemicals
RME	reaction mass efficiency
R_f	retention factor
rt	room temperature
s	singlet
$SOCl_2$	thionyl chloride
T3P	propylphosphonic anhydride
t	triplet
t_r	retention time
tt	triplet of triplets
^{t}	*tert*-
TBAF	tetrabutylammonium fluoride

TBS	*tert*-butyldimethylsilyl
td	triplet of doublets
Tf	trifluoromethanesulfonate (triflate)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMO	2,2,5,5-Tetramethyloxolane
TMS	trimethylsilyl
TMSI	trimethylsilyl iodide
tt	triplet of triplets
wt	weight

Acknowledgments

I must start by thanking my supervisors Professor James Clark, Dr Rob McElroy and in the earlier years Mrs Louise Summerton. I am extremely grateful for your guidance, advice and support over the last 7 years and for providing me with the opportunity to complete this Ph.D.

Reaching this point would have been impossible without help from numerous people and departments. I would like to thank the administrative, academic and technical staff at the University of York for all their assistance. I would also like to thank my colleagues at Valtris Specialty Chemicals, the guys in QC and especially Dr Charles Carraz and Mr Paul Fyfe for their continuous encouragement and motivation.

I would also like to thank my family for their unwavering support and belief in me throughout this journey. Finally, I wish to express my wholehearted thanks to my wife Ellie. Her unconditional support throughout this journey has been immeasurable, for which I will be eternally grateful.

Declaration

I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this, or any other University. All sources are acknowledged as references**.** Some of the work in this thesis was carried out by, or in collaboration with, other workers who are fully acknowledged below, all other results were obtained by the author.

Part of the work disclosed herein has previously been published in the following article;

1. E. R. Monteith, P. Mampuys, L. Summerton, J. H. Clark, B. U. W. Maes and C. R. McElroy, *Green Chemistry*, 2020, **22**, 123-135.

The author would like to declare the additional contributions to this thesis from the following worker;

Chapter 2: Process Mass Intensity (PMI): Dr Pieter Mampuys for his help collating all the data on amide reactions and his assistance with the metric analysis.

Chapter 1

General Introduction

Global population is undergoing exponential growth which started early in the 20th century. The population of the world doubled in 40 years (1959 – 1999) from 3 to 6 billion people. Growth is expected to continue and in another 40 years (2039) the population is predicted to double again to 9 billion.[1] The United Nations (UN) predict global population will pass 10 billion by 2050.[2] Over the last century this population growth subsequently led an enormous twenty fold increases in economic output and eight fold increases in material consumption.[3]

The consequences of this rapid expansion on the environment are becoming increasingly visible with anthropogenic activity generally being accepted as the root cause.[4] This activity can be attributed to; depletion of the ozone layer through use of CFC's, changes in the oceans (acidification and rising water levels) caused by emissions from burning fossil fuels and global warming (climate change).[5] Alarmingly, as population growth is forecast to continue, so will the increasing demand for resources and this will place more strain on an already damaged environment. In 1972 the first international meeting to address how human activity was harming the environment and putting lives at risk was held in Stockholm. Later in 1987 the report titles "Our Common Future" was published by the World Commission on Environment and Development.[6] This report introduced the theory of "sustained development". The most current version of this concept being prompted by the UN are their 17 sustainable development goals from the 2030 Agenda for Sustainable Development.[7] Many industries acknowledge the need to change and the concepts of sustainable development along with legalisation will allow them to eventually reach that goal.[8, 9]

Figure 1.1: UN Sustainability goals.[7]

1.1. Green Chemistry and the Chemical Industry

If a sustainable society is to be achieved, a widespread change of attitude will be necessary. One of the largest sectors in the global economy is the chemical industry. With the chemical industry playing a vital role in the modern world, from bulk chemical manufacture, producing fuels for heating and transport, to pharmaceuticals manufacturing vaccines and personal care products, a significant amount work will be required to identify how the industry is to become fully sustainable given that petrochemical resources still significantly outweigh renewables[10] 90% of the materials used in chemicals manufacturing is derived from a crude oil feedstock, given the direct link to climate change and large fluctuations in the price of oil this alone is a strong incentive to seek an alternative resource.[11] Additionally, given the nature of the chemical industry it is not surprising that the waste produced is often hazardous. It has been calculated that to equal the output of harmful emissions from the chemical industry, it would take the combined emissions of the next nine largest industrial sectors.[12]

The challenge today is the modification of established processes and development of new products and technology, which will meet legislative and consumer demands and requirements but also not adversely affect the environmentally.[13] These three factors are commonly referred to as the three pillars of sustainability, (social, economic and environmental). The field of chemistry that is driving innovation and development into sustainable, renewable and environmentally more friendly processes is known as green chemistry or (sustainable chemistry).

1.1.1. Principles of Green Chemistry

Green chemistry is a multi-disciplinary field that can be used and applied to all branches of chemistry. The aim of green chemistry is to improve the current state of the art, in a way that makes the impact of the process less harmful. One definition of green chemistry is;[14]

"Is the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances. Green Chemistry applies across the lifecycle of a chemical product, including its design manufacture and use."

Green chemistry can motivate and allows scientists to find better alternatives and more efficient ways to reach the same targets. It helps reduce waste and find replacements for hazardous materials but then goes a lot further by considering the energy efficiency of a process and the whole lifecycle from sourcing raw materials through to the end of life of a product. The idea of green chemistry began to gather momentum in the 1990's as there where several publications which brought attention to the subject. Sheldon, Anastas, Warner, Clark and Trost to highlight a few[11, 15-17] Also public and social perception that process should be more renewable along with government and international legislation (SIN list, REACh) all helped develop green chemistry into the common area of research which it is today. A key set of principles the "12 Principles of Green Chemistry" was published as a guide for the design of new chemical products and processes in accordance with sustainability.[18]

Table 1.1: 12 Principles of green chemistry.

Principle	**Explanation**
Prevention	*"It is better to prevent waste than to treat or clean up waste after it has been created."*
Atom Economy	*"Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product."*
Less Hazardous Chemical Synthesis	*"Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment."*
Designing Safer Chemicals	*"Chemical products should be designed to effect their desired function while minimizing their toxicity."*
Safer Solvents and Auxiliaries	*"The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used."*
Design for Energy Efficiency	*"Energy requirements of chemical processes should be recognized or their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure."*
Use of Renewable Feedstocks	*"A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable."*
Reduce Derivatives	*"Unnecessary derivatisation (use of blocking groups, protection/deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste."*
Catalysis	*"Catalytic reagents (as selective as possible) are superior to stoichiometric reagents."*
Design for Degradation	*"Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment."*
Real-Time Analysis for Pollution Prevention	*"Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances."*
Inherently Safer Chemistry for Accident Prevention	*"Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires."*

1.1.2. Thesis intent

The aim of the work in this thesis was to investigate the synthesis of pharmaceutically relevant compounds and through analysis with green chemistry metrics identify areas for improvement. Given the vast number of active pharmaceutical ingredients (APIs) on the market, compounds were identified from the World Health Organisations (WHOs) list of essential medicines.[19] 5-Fluorocytosine and Emtricitabine where initially selected by the Chem21 consortium and research at Durham University was conducted into the direct fluorination of cytosine.[20] Therefore it was logical that the synthesis of cytosine also be investigated. Following on from investigations with cytosine, the synthesis of 1,3-oxathiolanes were examined focusing on solvent substitution. As coupling with cytosine or its fluorinated derivative gives assess to Lamivudine or Emtricitabine, two APIs which are used as antiretroviral medicines, the Mitsunobu reaction was then explored as a possible pathway to join these compounds. Finally, the last chapter in this thesis examined the use of Brønsted acid *p*-CSA in a range of OH activation nucleophilic substitution reactions alongside Lewis acid $InCl_3$ using a potentially green, bio-based solvent TMO.

1.2. Green Chemistry developments

In 2005 the American Chemical Society (ACS) Green Chemistry Institute (GCI) set up the ACS GCI Pharmaceutical Roundtable (ACS GCIPR).[21] This roundtable consisted of members of several leading pharmaceutical corporations, their aim was to encourage innovation while integrating green chemistry into the heart of drug discovery and production. In 2007 the round table developed a list of key research areas with the aim of catalysing research and development of green chemistry within them.[22] The list was revisited in 2015 to review and update the list of key green chemistry research areas Table 1.2.[23]

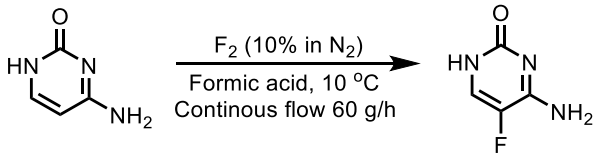
Table 1.2: Key Green Chemistry Research areas as voted by ACS GCIPR.[23]

	2005 Research area	"Equivalent" research area 2015
1	Amide Formation avoiding reagents with poor atom economy	General methods for catalytic/ sustainable (direct) amide or peptide formation
2	OH activation for nucleophilic substitution	Direct substitution of alcohols
3	Reduction of amides without hydride reagents	Amide reductions avoiding LiAlH4 and diborane
4	Asymmetric hydrogenation of unfunctionalized olefins/ enamines/imines	Asymmetric hydrogenation of unfunctionalized olefins/enamines/ imines
5	New greener fluorination methods	Improved methods for fluorination and trifluoromethoxylation
6	C–H activation of aromatics	Aliphatic and aromatic C–H activation using green oxidants and giving predictable site selectivity
7	Replacements for dipolar aprotic solvents	Viable replacements for dipolar aprotic solvents

Given the prevalence of amide formation in the pharmaceutical industry it is no surprise to find it at the top of the list.[24] There have been several reviews into the catalytic formation of amide bonds using a wide range of reactants.[25-28] The choice of solvent for amide formation has also received attention as traditionally chlorinated and polar aprotic solvents have been used for amidation reactions. MacMillan *et al* showed that dichloromethane (DCM) and dimethylformamide (DMF) could be reliably substituted with dimethylcarbonate (DMC), ethyl acetate (EtOAc) or 2-methyl tetrahydrofuran (2-MeTHF) when (1-cyano-2-ethoxy-2-oxoethylidenaminooxy) dimethylamino-morpholino-carbenium hexafluorophosphate (COMU) was used as coupling agent.[29] The replacement of dipolar aprotic (and halogenated) solvents also made the ACS GCIPR list in 2006 and in a revised format in 2015 including the work "viable" highlighting that this is an area of concern but given the unique properties of the solvent not an easy challenge to overcome.

Green fluorination was mentioned in 2006 as aspirational and was again updated in 2015 with a more defined definition Table 1.2 entry 5. With the high occurrence of fluorine atoms in active pharmaceutical compounds (APIs), combined with the lack of mild fluorination procedures to tolerate many functional groups, it is an area with significant scope to grow. Between 2014 - 2016 32% of all new drugs approved by

the FDA contained at last one F-Ar or CF_3 group.[30, 31] The use of elemental fluorine has been developed through the Chem21 consortium to improve the synthesis of 5-fluorocytoine **1.1** in a flow reactor from cytosine **1.2**. This development enables the use of the simplest and most economical reagent (F_2) although many of the hazards with fluorine gas have been reduced, they have not been eliminated.[20]



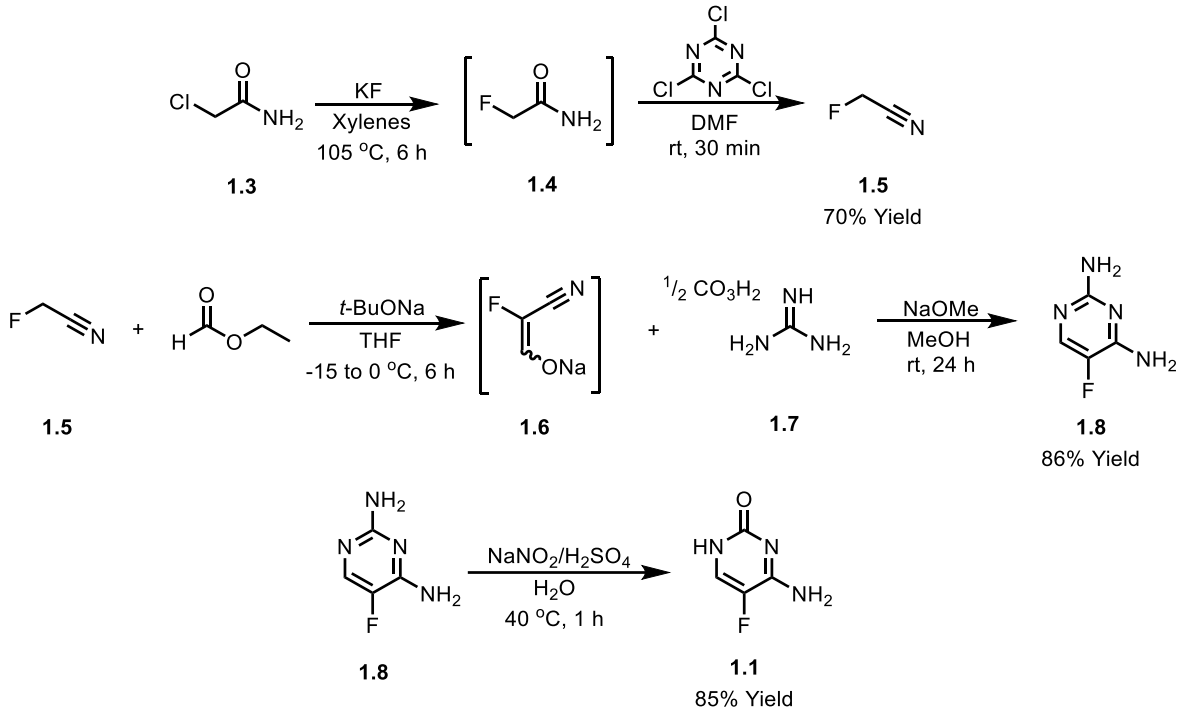
1.2 **1.1**
83% Yield

Scheme 1.1: Synthesis of 5-fluorocytosine **1.1** from cytosine **1.2**.

While the use of fluorine gas has been demonstrated at scale, it is not a technique that is easily accessible. Fortunately there has been an increase in the number of strategies and stable reagents that can be used for fluorination.[32] A few examples of these fluorination reagents are; xtalfluor-E & M, Fluolead, TFFH, PhenoFluor, PyFluor and AlkylFluor.[33-39] They can be handled safely without any special precautions and are useful for late stage functionalisation in the presence of other reactive functional groups. However, they are not perfect and typically require unfavourable solvents and prompters. The reagents also add a significant quantity of waste into a process which dramatically lowers the atom economy and other metric performance.

A synthesis of 5-fluorocytosine **1.1** has been reported by The Medicines for all Institute which avoids the use of fluorine gas.[40] Their aim was to produce 5-florocytosine **1.1** through a process with lower raw material costs than those associated with current 5-fluorocytoine **1.1** synthesis (cytosine **1.2** & direct fluorination). Their route begins with the fluorination of chloroacetamide **1.3** to generate fluoroacetonitrile **1.5** via fluoroacetamide **1.4** which is converted into sodium salt **1.6**. Through a telescoped procedure salt **1.6** is reacted with guanidine carbonate **1.7** to give 2,4-diamino-5-fluoropyrimidine **1.8** which finally leads to 5-fluorocytosine **1.1** Scheme 1.2. The authors acknowledge that the current process requires further improvement to reduce the environmental impact. Their synthesis may be able to derive 5-fluorocytosine **1.1** from more cost-efficient starting materials but given the known

toxicity profiles of **1.3**, **1.4** & **1.5**, can this process really be considered an improvement just because it lowers the cost of the perspective of starting materials?

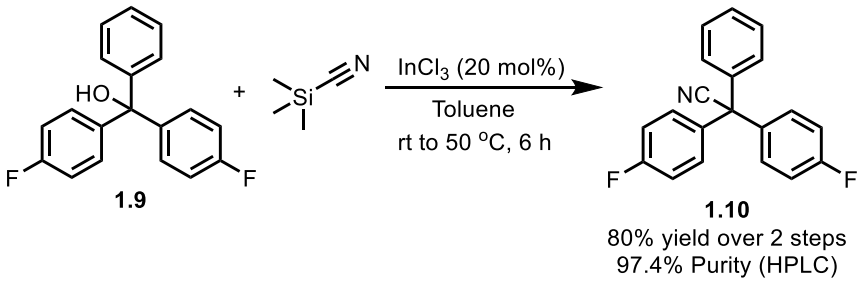


Scheme 1.2: Synthesis of 5-fluorocytosine **1.1** from chloroacetamide **1.3**.

1.2.1. OH activation / Mitsunobu reaction

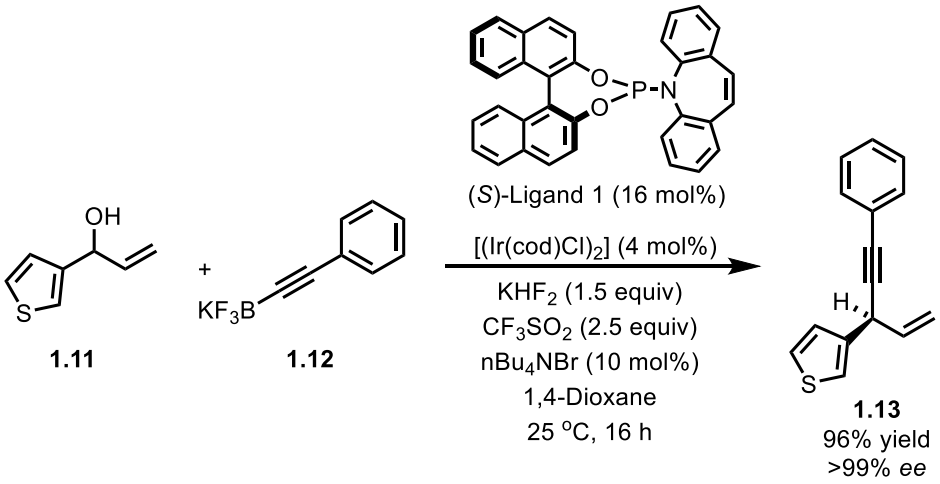
The direct substitution of alcohols is an ideal process as the direct displacement of a hydroxyl group would result in the formation of water as the only side product therefore there has been a significant advance in the catalytic activation of hydroxyl groups reported in the literature.[41-44] OH activation reactions proceeding through a S_N1 type nucleophilic substitution reaction using catalytic amounts of a Brønsted or Lewis acid to displace the hydroxide group in allylic, benzylic and propargylic alcohols has been reported in an academic and industrial setting.

Direct cyanation of alcohol **1.9** was performed through the use of several Lewis acids however indium trichloride ($InCl_3$) was the most successful providing the cleanest reaction profile in catalytic quantities. Further benefit of using $InCl_3$ was the ability to use toluene as the solvent which meant the previous step could be carried through, telescoping the process and eliminating the need for strictly anhydrous conditions which simplifies the process.[45]



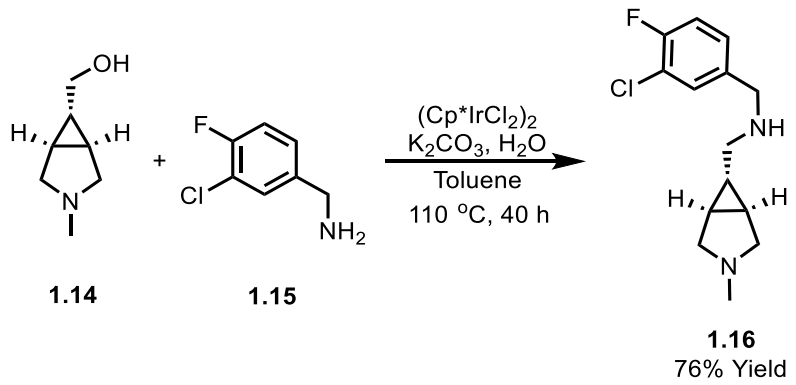
Scheme 1.3: Lewis acid catalysed cyanation of **1.9** to give **1.10**.

Iridium catalysts have been widely used for the enantioselective substitution of racemic allylic alcohols bearing a variety of functional groups. Scheme 1.4 shows an example of thiophene **1.11** and alkyne **1.12** coupling to give **1.13** with excellent selectivity. The reaction conditions can be performed at gram scale, open to air and using regular reagent grade solvent, highlighting the robustness of the catalyst and ligand.[46, 47] While this catalytic transformation is useful, from a green chemistry perspective the choice of solvent is not ideal nor is the quantity of auxiliary reagents required. The direct enantioselective iridium catalysed amination of racemic allylic alcohols is also possible.[48]



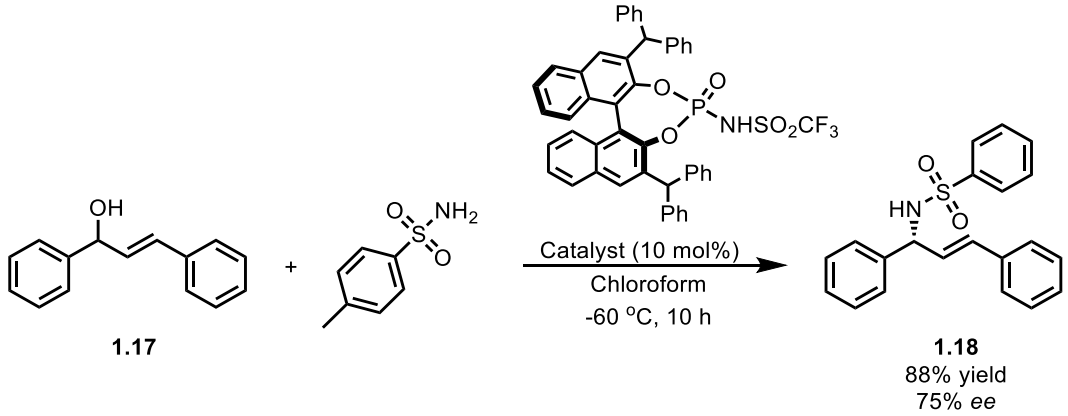
Scheme 1.4: Direct enantioselective substitution to racemic alcohol **1.11** with Lewis acids.

The use of an iridium catalyst has also been used at scale for the coupling of alcohol **1.14** with amine **1.15**, to give **1.16** Scheme 1.5.[49]



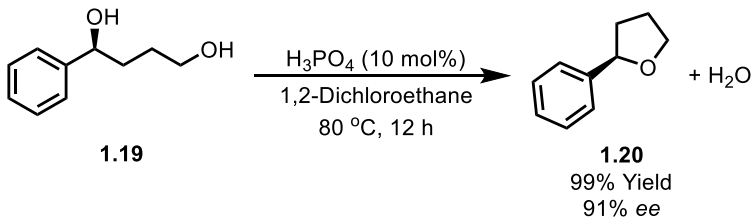
Scheme 1.5: Coupling of alcohol **1.14** with amine **1.15**.

Along with enantioselective Lewis acids, similar aminations have been performed by chiral Brønsted acids for direct allylic amination reactions.[50] Though these type of catalysts currently have a scope limited to highly π-active aromatic allylic alcohols such as **1.17** Scheme 1.6.



Scheme 1.6: Direct enantioselective substitution of racemic alcohol **1.17**.

Direct substitution of hydroxyl groups while maintaining the stereochemistry has also been reported with Brønsted acids via intramolecular S_N2 substitution.[51] The procedure allows nucleophilic substitution of the hydroxyl group in a range of aryl, allylic and propargylic alcohols in order to form C-O, C-S and C-N bonds in enantiomerically enriched five membered heterocycles. An example of the intermolecular reaction of (*S*)-1-phenylbutane-1,4-diol **1.19** to form furan **1.20** is shown in Scheme 1.7. As with the other enantioselective OH reactions the reaction conditions, do not always align completely with the principles of green chemistry, as the use of 1,2-dichloroethane (DCE) is highly undesirable.

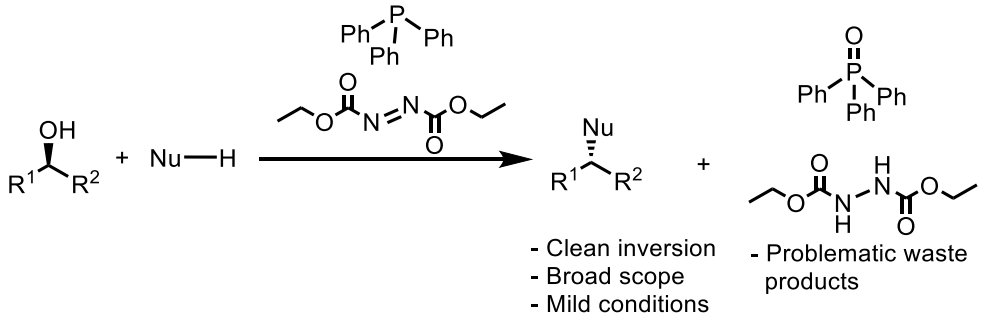


Scheme 1.7: Intermolecular coupling of **1.19** to form enantioenriched furan **1.20**.

The Mitsunobu reaction involves the condensation of alcohols with active hydrogen on a nucleophile with the assistance of triphenylphosphine (PPh_3) and dialkyl azodicarboxylate Scheme 1.8. This reaction has been widely employed by organic chemists over the past 40 years for a few reasons.

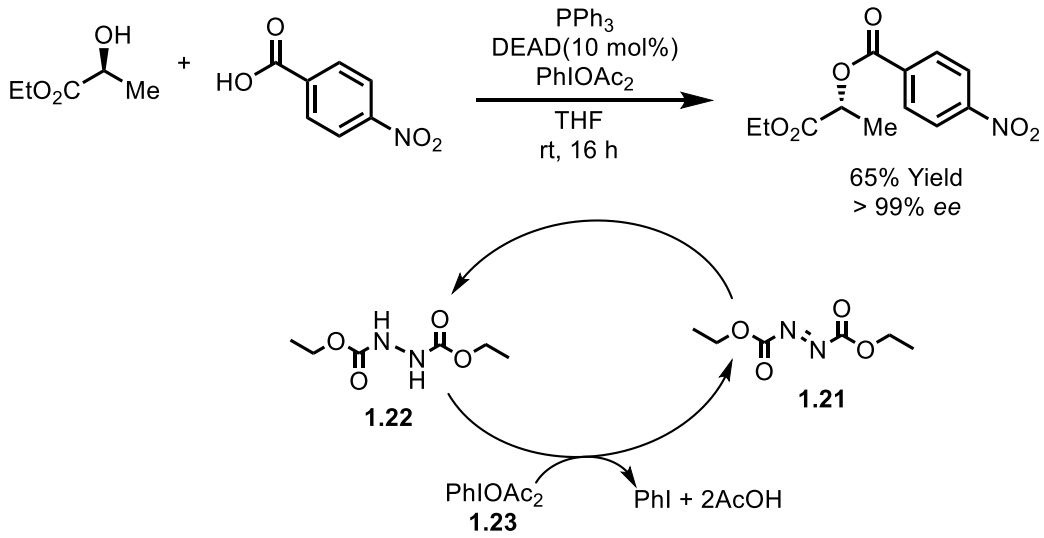
- Inversion of stereochemistry on secondary alcohols with very high specificity.
- Large range of application, nucleophiles can be derived from O, N, S and C along with a wide variety of alcohols and functional groups.
- Easy of operation. No special requirements, just addition of reagents at room or near to room temperature.
- Operates with a variety of solvents and has a wide temperature range.

One of the main issues with this reaction is the use of stoichiometric quantities of PPh_3 and azodicarboxylates. Furthermore, the work up to isolate the desired product requires a considerable amount of processing, usually including chromatography. Many of the azodicarboxylates used can be toxic and present an explosion risk as they are transformed into a hydrazine. This side product can also difficult to remove. Because of such issues commercial manufacturing employing this process is not very common, as reported only 0.2% of industrial processes use the Mitsunobu type reaction.[24]



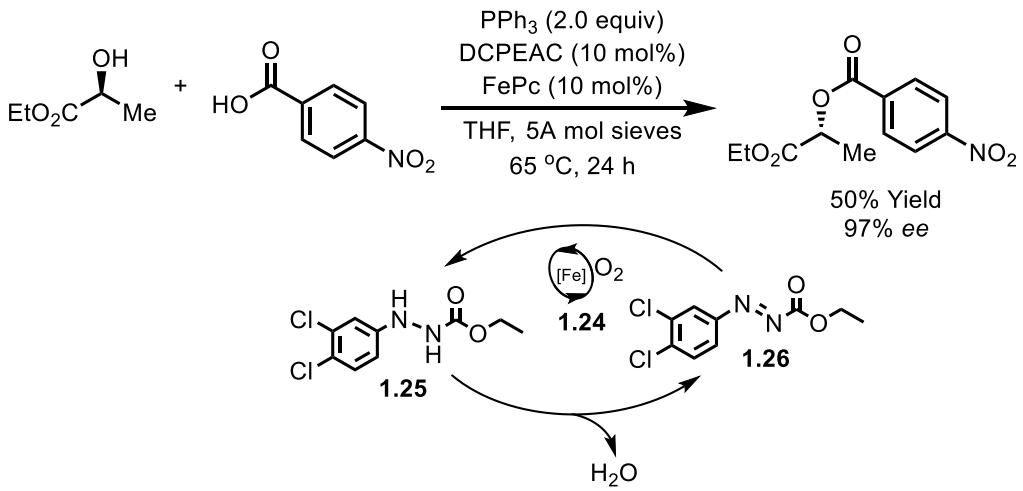
Scheme 1.8: Traditional Mitsunobu reaction.

There have been some improvements with the Mitsunobu reaction over the last number of years. PPh_3 and azodicarboxylates can now be bound to polymers and so be classed as solid-state reagents. This makes purification considerably easier as one of the major problems is removal of triphenylphosphine oxide and hydrazine side products. There has also been development in the scope of azodicarboxylate used, numerous options now exist besides the traditional diethyl/diisopropyl azodicarboxylaye (DEAD) or (DIAD). Toy *et* al where able to successfully reduce the quantity of azodicarboxylate **1.21** required to 10 mol% by using iodobenzene diacetate $PhI(OAc)_2$) **1.23** as oxidant, Scheme 1.9.[52, 53]



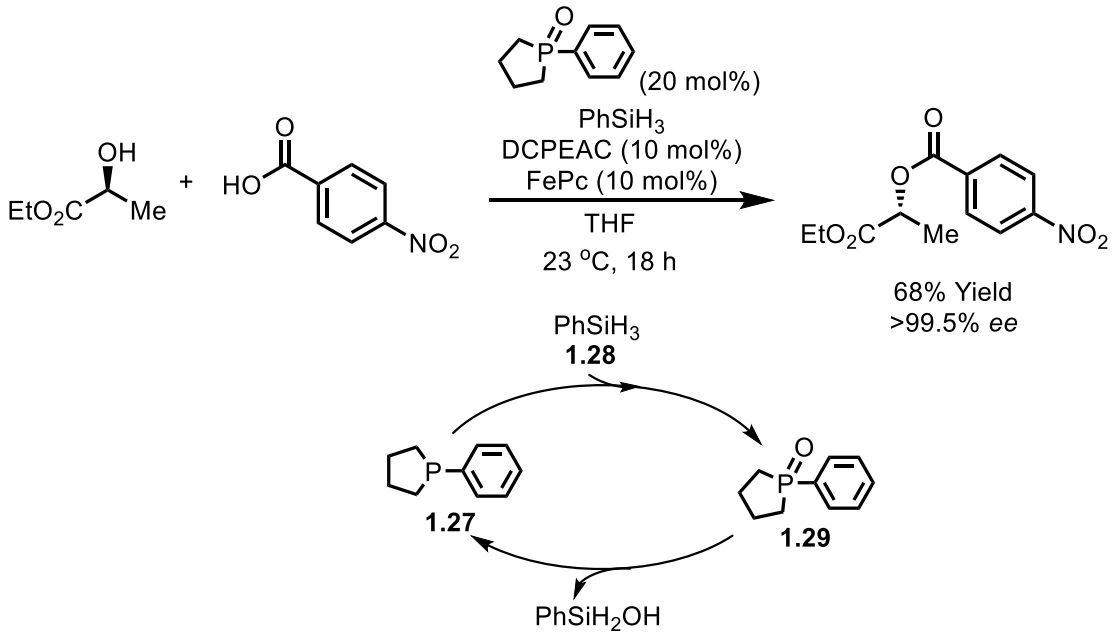
Scheme 1.9: Toy's azodicarboxylate catalyzed Mitsunobu reaction.

Another catalytic Mitsunobu reaction was established by Ishibashi *et al*.[54] In this process Ishibashi used an iron catalyst, iron phthalocyanine (FePc) **1.24** to oxidise the hydrazine **1.25** back to an azodicarboxylate **1.26** using atmospheric air as a source of oxygen, Scheme 1.10.



Scheme 1.10: Ishibashi's FePc/azodicarboxylate catalyzed Mitsunobu reaction.

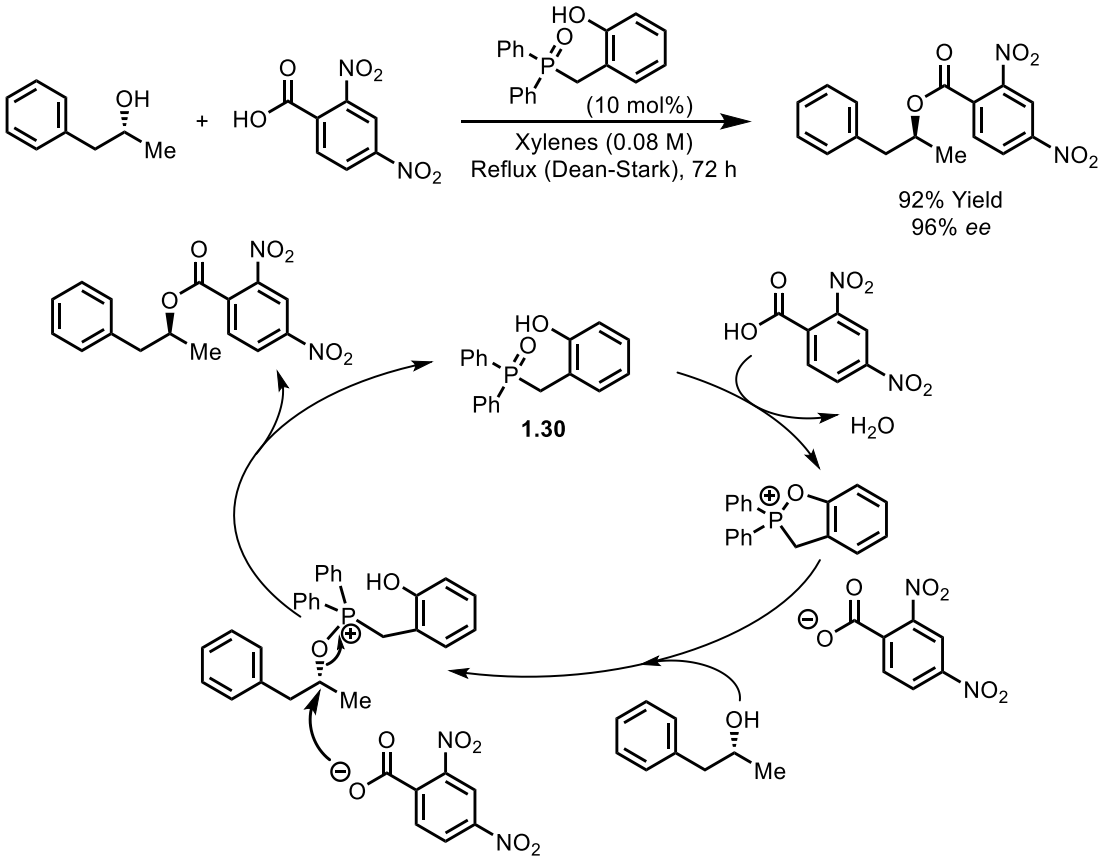
Both variations were a significant improvement over traditional Mitsunobu reaction design. In combination with catalytic azodicarboxylates the Mitsunobu reaction has also been proposed with a catalytic phosphine **1.27**.[55] Though this is not a truly catalytic process as stoichiometric quantities of silane **1.28** are required to reduce the phosphine oxide **1.29**, Scheme 1.11.



Scheme 1.11: Mitsunobu reaction with a catalytic phosphine.

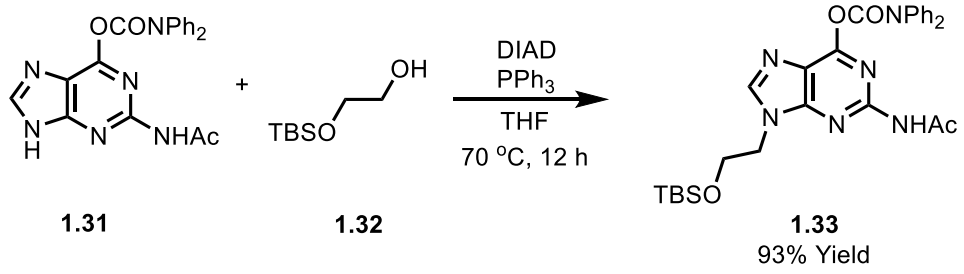
In 2019 Denton *et al* introduced the concept of a redox neutral Mitsunobu reaction Scheme 1.12.[56] This process uses a specially designed phosphine oxide **1.30** which eliminates the need for additional reductants or oxidants as presented in schemes 1.8 & 1.9. This advancement was reported to improve the mass efficiency of the

Mitsunobu by 65%. This has been verified by computer models by Zou *et al* who also used in silico techniques to predict improved catalysts.[57]



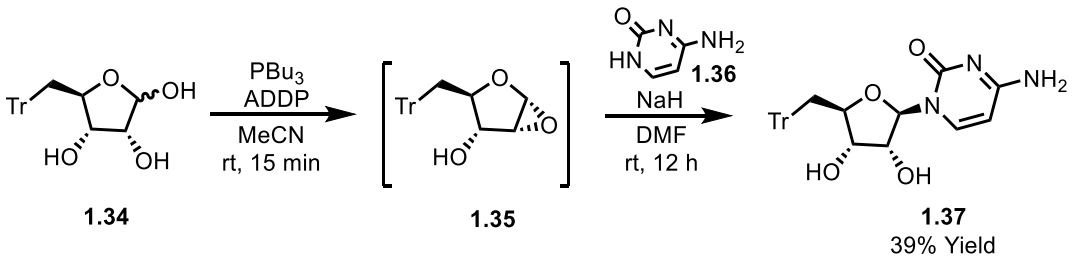
Scheme 1.12: Redox neutral Mitsunobu reaction.

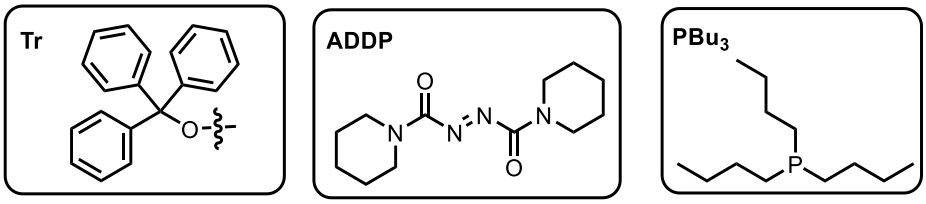
The first detailed study for coupling alcohols with nucleobases through the Mitsunobu reaction was reported in 2007 by Shi *et al*.[58] The coupling between purines **1.31** and alcohols **1.32** was successfully performed at room temperature, although as the solubility of substrates decreased, reflux conditions were required. The coupling also cleanly inverted the stereochemistry as expected with Mitsunobu S_N2 reaction and the coupling was also regioselective to give primarily *N*9-substitution product **1.33** Scheme 1.13.



Scheme 1.13: Mitsunobu reaction with purine **1.31**.

The Mitsunobu coupling of sugar motifs with nucleobases nucleophiles has been developed by Downey *et al* and covers a considerable scope of substrates.[59, 60] In their initial communication the scope was limited to soluble purines, pyrimidine cytosine failed to react due to poor solubility.[61] Using a modified procedure glycosylation was possible for substrates which previously failed, cytosine, guanine, 5-fluorouracil were able to undergo Mitsunobu coupling Scheme 1.14. This was possible as first 5-*O*-tritylribose **1.34** was converted to stable intermediate **1.35** through reaction with $P(Bu)_3$ and ADDP followed by addition of the deprotonated nucleophile **1.36** which stereoselectivly opened the epoxide and lead to product **1.37**.



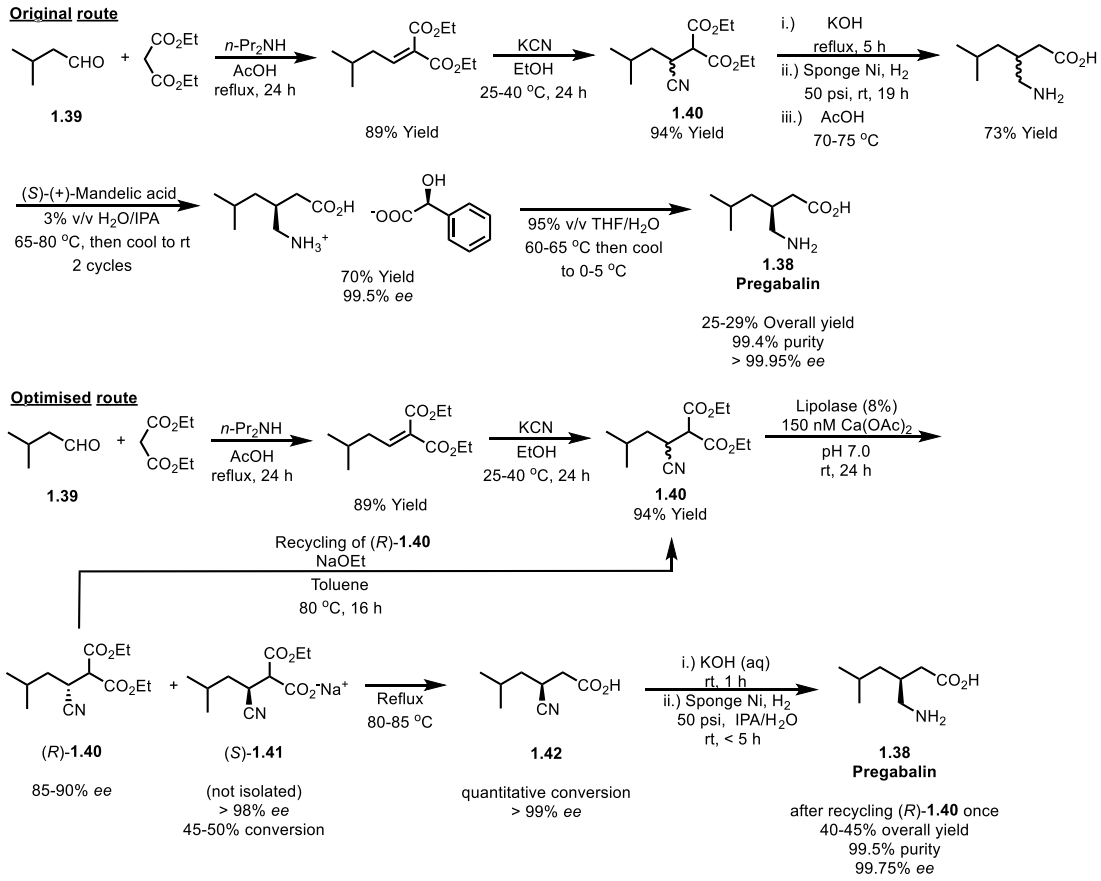


Scheme 1.14: Mitsunobu reaction with purines and pyrimidines.

1.2.2. Enzymes

Due to safety and efficacy concerns surrounding drugs that contain chiral centres, requirements mean that they must be evaluated as single enantiomers. The use of biocatalysts and enzymes can be an extremely efficient and reliable method to obtain an enantiomerically pure compounds. [62, 63] The use of biocatalysts can also enable the reaction to be performed in water rather than organic solvents. Water is the most abundant substance on the planet and is therefore the cheapest and most environmentally friendly solvent available.[18]

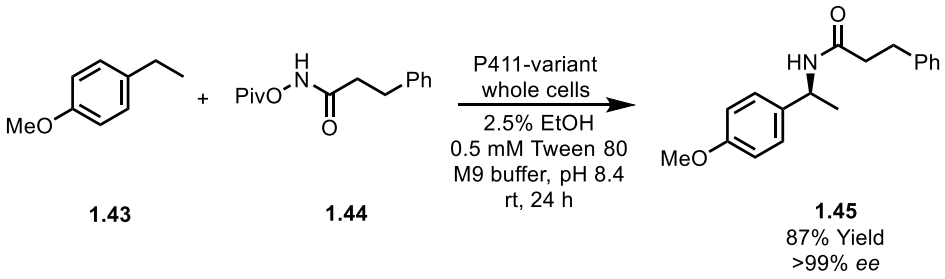
The drug Pregabalin **1.38** marketed by Pfizer as Lyric, an anticonvulsant and anxiolytic medication, is an excellent example of green chemistry and process development.[64] The original synthesis of Pregabalin **1.38** was racemic and required resolution with a chiral salt. While it may have been cost effective, it is not efficient, so an improved process was developed.[64] The optimised route to Pregabalin **1.38** made use of an enzymatic kinetic resolution early in the synthesis Scheme 1.15. This allowed the separation of the desired enantiomer as the sodium salt through an aqueous wash. The unwanted enantiomer remained in the organic layer and was recycled. Advantageously the desired enantiomer was then converted into Pregabalin using water as the solvent.



Scheme 1.15: Development of the synthetic routes to Pregabalin **1.38**

The optimised chemoenzymatic route to Pregabalin **1.38** had several advantages. The overall yield was increased by recycling the unwanted enantiomer, this also reduced the waste from the process. The use of a biocatalyst enabled the final steps of the process to be conducted in water; kinetic resolution, hydrolysis and hydrogenation reactions. These developments dramatically improved the efficiency of the process as shown through Pfizer's metric analysis. The E-Factor was reduced from 86 to 17, the optimised route uses x5 less chemicals and x8 less solvent, also the volume of organic solvent was significantly reduced due to the use of water in the final three steps. Interest has remained in the chemoenzymatic route to intermediates of Pregabalin as recently Vinigiri *et al* have developed an enzymatic synthesis using readily available enzyme CAL B.[65] The synthetic potential of enzyme catalysis is constantly growing and leading to cleaner and more efficient processes within the pharmaceutical industry.[63, 66-68]

Other example of biocatalysts included the synthesis of aliphatic and aromatic oligoethers using CAL B in a solventless system.[69] The reduction of amides to amines. Anaerobic bacteria *Clostridium sporogenes* has been shown reduce benzamide to benzylamine.[70] Biocatalysts has been applied to the synthesis of enantioenriched amides **1.45**.[71] This was achieved through directed evolution of P411 enzymes leading to intermolecular benzylic C-H amidation, an example of the C-H activation of **1.43** and addition of amide **1.44** is shown in Scheme 1.16.



Scheme 1.16: Biocatalytic benzylic amidation.

Finally, a process using CAL B has been developed to allow access to enantiomerically pure (*S*) & (*R*) 4-(acyloxy)pentanoic acids from bio derived racemic γ-valerolactone.[72] The process also provides a pathway to separate the enantiomers of GVL as (*S*) & (*R*)-GVL can both be obtained. The work highlights multiple aspect of green chemistry; biobased resource, biocatalysts, green alternative solvents, also the authors evaluating the reagents and solvent used in each reaction and use reaction metrics in order to validate the improvements in their process.

1.2.3. Solvents

The search for alternative solvents could be considered one of the most active topics of research within green chemistry.[18] This is due to the many roles solvents play within the chemical industry.[73] The demand for alternative solvents can also be linked to the need to move to more renewable and cleaner resources as the current solvent market is dominated almost exclusively by petroleum-derived products.[74] Solvents are often the largest single component in the production of cleaning agents, adhesives, paints and varnishes. They account for the vast majority of waste generated in a chemical process and typically account for around 80-90% of the mass of all materials in a production batch.[75]

The greenest solvent choice would be to use no solvent at all. There has been a great interest in recent years in the development and use of solvents that have a less harmful environmental effect and safer health and safety properties. An approach that is becoming more common is the use of solvent selection guides, with numerous publications with multiple selection criteria and a ranking system of solvents based on their "greenness" over the last decade.[76-80]

In recent years there has been increasing interest in and applications of bio-based solvents. These are solvent which can be derived from renewable feedstocks. Bio-based solvents can either be used as a direct replacement for traditional solvent or be functionalized to improve their characteristics. Examples of bio-based solvents included; ethanol, 2-MeTHF, *D*-limonene, *p*-cymene, γ-valerolactone, propylene carbonate and dihydrolevoglucosenone otherwise known as (Cyrene™).[74]

Despite the progress in developing new bio-based solvents, their uptake by industry is generally slow. This could be due to difficulty in procurement. If an industrial process was developed using a solvent the company would need to confidence that the supply of the material was secure as it is not always possible to alter a manufacturing route once it has been approved. Another factor delaying uptake of these solvents could be the unknown toxicology and ecological properties they possess. Just because a material is bio-derived does not guarantee that it is safer or *greener* when compared to traditional petroleum based solvents.[74, 80] One of the areas identified by the ACS GCIPR was "*viable replacements for dipolar aprotic solvents*", Table 1.2 entry 7 (page 8). The inclusion of the word viable could relate to the previous issues discussed about implementation and uncertainty. The desire to have an alternative to traditional dipolar aprotic is due to the increasing restrictions on their usage.[81] Dipolar aprotic solvents have a unique ability to promote a wide range of chemistry which is due to the solvents very high polarity and solvation ability.[74] Traditional dipolar aprotic include dimethylformamide (DMF), dimethylacetamide (DMA) and *N*-methylpyrrolidone (NMP). The pursuit for replacements of DMF, DMA and NMP will not be an easy task given the unique combination of properties that a replacement will have to fulfil. In the search for replacement dipolar aprotic solvents Byrne *et al* identified a group of compounds containing two amide groups with *N*-butyl side

chains, that could be synthesised from bio-based succinic acid and alkylbutylamine.[82] The results obtained were mixed, the compounds did not show any alarming toxicity issues and performed well in some common reaction but did not have as high polarity as anticipated.

A promising replacement for dipolar aprotic solvents is Cyrene which is derived from cellulose and its Hansen solubility parameters are similar to NMP.[83, 84] In a practical environment Cyrene has been used successfully in amide synthesis through acyl chloride and HATU mediated couplings and Sonogashira and Cacchi type annulation reactions.[85] [86] However, some limitations have also been reported which include incompatibilities with strong acid or base.[87]

In an effort to move away from petrochemical based solvents a viable alternative to replace toluene in polymer chemistry was developed at the University of York. 2,2,5,5-Tetramethyloxolane (TMO) is a potentially bio-derivable solvent with comparable properties to THF and toluene. The tetramethyl groups give TMO excellent resistance to peroxide formation.[88-91] To conclude, propylene carbonate can be synthesised from propylene oxide and carbon dioxide.[92, 93] It a is biodegradable solvent which has be successfully used in numerous applications; hydrogenation reactions, as well as palladium catalysed substitution, aldol, and Heck reactions.[94-96]

1.2.4. Reaction metrics

One of the key developments in green chemistry is reaction metrics.[97-100] They allow chemists to quantify their reactions and see how efficient it is or what the environmental or health and safety impact of a process are.[101] Metrics should be simple to use and understand and they can be applicable to every level of chemical education and industry; from laboratories in high school through to large scale industrial manufacturing. The pharmaceutical industry has adopted Process Mass Intensity (PMI) as its chosen metric due to the lack of ambiguity in generating data.[97, 99, 102, 103] The abundance of metrics can make selection a difficult choice, so in order to overcome manual selection, to simplify the analysis and to standardise the reaction metrics analysis process a toolkit was developed through the Chem21 consortium.[101, 104]

Chapter two explores the metrics; PMI, Atom Economy (AE) and Reaction Mass Efficiency (RME) in detail and the introductory section describes these metrics along with several others in considerable detail therefore the specifics of individual metrics will not be covered in this section.

Metrics and metric toolkits have been used by numerous researchers and industrial chemists to gauge the efficiency of their process. Parve *et al* used a detailed metric analysis to assess their chemistry and compare their methodology with previously reported procedures by comparison of the metric PMI.[72, 105] They also critically evaluated the reagents and solvents used in their work from the principled of green chemistry. After using PMI to highlight the improvements in their chemistry the authors went a step further and used the PMI data to highlight an area within the process which would benefit from future research. The Chem21 metrics toolkit was also applied to chemistry developed by Gadde *et al.*[106] The metric analysis was designed to appraise the greenness of their work. Carefully selected examples from each of the alternative methodologies found in the literature were selected and analysed by the metrics toolkit. This allowed the authors to determine the green potential of the new vs the state-of-the-art methodologies. This metric analysis for both these exampled was written up in detail and included within the supporting information of each publication.

1.3. Thesis objectives

The core objectives of this thesis are to use the principles of green chemistry to improve the synthesis of pharmaceutically relevant compounds. The methods involved will be guided by mass-based reaction metrics using the toolkit developed by the Chem21 consortium. Improvements should involve the use of alternative solvents and reagents, ideally derived from renewable or bio-based resources.

The topics covered in this thesis will be split into three main chapters and the background for each chapter will be discussed within that chapter's introduction.

Chapter two will focus on the limitations of mass-based metrics, in particular, PMI but also AE and RME. A detailed metric investigation into amide formation will be performed and the results of the mass-based metrics obtained will be critically evaluated. The limitations of the data will be discussed along with guidance on how to obtain reliable metric data that can be fairly compared to another process.

Chapter three will be guided by the results obtained from metric analysis of several synthetic processes. First of all, focus will be on the synthesis of the nucleobase cytosine. The solvent, reagent and raw material used in the synthesis will all be investigated. Then attention will move onto the applicability of the Mitsunobu reaction in nucleoside coupling between 1,3-oxathiolanes and cytosine.

Finally, chapter four will focus on the use of a potentially bio-derived Brønsted acid *p*-CSA, applying it to common and traditional reactions within organic synthesis. *p*-CSA's ability to catalyse OH activation and esterification reactions along with acting as a catalyst in protecting group formation will be explored.

Chapter 2

Process Mass Intensity (PMI)

2.1. Introduction

2.1.1. Development of reactions metrics

There have been several methods developed to quantify how "green" a process is. Anastas and Warner developed 12 principles of green chemistry and these where very quickly adopted as a methodology determining what makes a process green.[107]

Before the introduction of *green chemistry* metrics, the efficiency and sustainability of a process was a difficult concept to evaluate and quantify. The development and introduction of *green chemistry* metrics provided a method to describe and evaluate the credentials of a reaction or process generating a numerical value and thus allowing aspects of *greenness* to be quantified.[15, 17, 22, 101, 108-110]

There has been much debate about methods that can be used to evaluate a process or synthetic route and which metric or combination works best to give the clearest insight into a system.[101] The underlying theme these discussions have is the need for a metric to be objective, clearly defined and for its data to have the ability to drive improvement. Each metric has its individual strengths and weaknesses; a person's individual thoughts will also play a role with regards to how they conceive a hazard and how they apply mass based metrics.

2.1.2. Types of metric and their use

The strict definition of a metric is a system of measurement. The purpose of reaction metrics is to measure the parameters of a chemical reaction or process and use the measurements to quantify the green credentials of a reaction or process. Given the number of green chemical metrics available it is only natural that there may be some confusion when selecting a metric or analysis package to use and then also in evaluating the results derived from the metric analysis. The purpose of using a reaction metric(s) is to generate a quantification and description for the green credentials of the reaction or process. This data could then indicate how efficient a given process or reaction is compared to another. This comparison may appear to be valid at first glance but throughout this chapter the pitfalls of comparing metric data will be shown this will highlight why a comparison may not be as straight forward as first thought.

2.1.2.1. Historical and classical metrics

Established metrics which are commonly used in academia and the chemical and the chemical include percentage yield (Equation 1) which is generated by dividing the moles of product obtained from the reaction by the number of moles of the limiting reagent used. A perfect reaction should give a yield of 100%. Conversion (Equation 2), expresses the quantity of limiting reactant which has been consumed in a reaction as a percentage. The maximum value possible is 100% conversion (consumption of all the limiting reactant). Conversion can be a useful metric for optimising reaction conditions as a high value with low yield can indicate decomposition of reactant or generation of an unwanted side products. Similarly, a low conversion and low yield could indicate that the reaction conditions may have scope for improvement as the selectivity (Equation 3) would be high. Selectivity is a metric which links yield and conversion. Low yields and high conversions will give generate a poor selectivity, whereas a reaction with a high yield with high conversions will produce a high selectivity, or vice versa.

These three metrics are included in many papers and metric analysis tools as they are familiar and easy to use and calculate. These three metrics also are easy to relate to, as a high yield, high conversion and high selectivity are all desirable qualities of a process. The opposite to this is also true, if a process has low yield, conversion or

selectivity this would be undesirable. These metrics can be useful in early screening and give an indication towards what improvements are required.

$$\%\ \text{Yield} = \frac{\text{moles of product}}{\text{moles of limiting reactant}} \times 100$$

Equation 1: Percentage yield.

$$\text{Conversion} = \left(1 - \frac{\text{final moles of limiting reactant}}{\text{inital moles of limiting reactant}}\right) \times 100$$

Equation 2: Conversion.

$$\text{Selectivity} = \frac{\%\ \text{yield}}{\%\ \text{conversion}} \times 100$$

Equation 3: Selectivity.

However, all three metrics focus on the product which is formed and/or the limiting reactant that is consumed. The metrics yield, conversion and selectivity all ignore any other inputs or outputs of the process such as; the solvent (volume or hazards), waste produced, quantity of reagents used, health and safety aspects of the reaction and energy requirements. For example, if a given reaction had a fourfold excess of one reactant and quantitative results for yield and conversion, therefore 100% selective, it would appear to be a very promising process when assessed from the data generated using these three metrics. But the same reaction also makes use of highly toxic and energetic reagents and is performed at cryogenic temperatures, these details would not be accounted for. This simplistic scenario shows why a more holistic and system wide view should be considered.

Another limitation with the metrics yield, conversion and selectivity is that they cannot account for recovery and recycling of reactants. A good example of this was shown in Chapter 1, Scheme 1.15 for the manufacturing of Pregabalin **1.38**. The process has one step with a conversion of 45-50% but the unreacted material is recycled, this act cannot be captured in the metrics as they are written in equations 1 – 3.

2.1.2.2. Atom Economy (AE) & Reaction Mass Efficiency (RME)

One of the early green metrics developed to progress beyond yield, conversion and selectivity was Atom Economy (AE) introduced by Trost in 1991.[17] This metric began to consider more components of a reaction or process than solely the product or the limiting reactant as discussed in section 2.1.2.1.

AE is a straightforward calculation which determines how efficiently a reaction uses the reactants (Equation 4). AE is reported as a percentage and the higher the figure the more economical a step is, or series of reactions are as there are less atoms unused or converted into side products and considered waste. As AE is a simple metric there are several limitations that should be considered. The metric only looks at the efficiency of atom transfer from reactant to product and numerous other factors are not considered, such as solvent, reagents overall yield and stoichiometric excess of reagent or reactants. Issues can occur when calculating the AE of two-step or multi-step processes. AE also suffers the limitation of subjectivity, what one person deems as a reagent or reactant may differ based on experience, knowledge or understanding. AE produces a theoretical value which assumes than the reaction begins with an exact stoichiometric quantity of starting reactant and proceeds with a yield of 100%.

$$\mathrm{AE} = \frac{\text{Molecular weight of desired product}}{\text{Molecular weight of all reactants}} \times 100$$

Equation 4: Atom Economy.

An improvement to AE is Reaction Mass Efficiency (RME, Equation 5). RME was first introduced in 2001 by a group from GlaxoSmithKline (GSK).[111] It is a massed based metric and considers the yield of product and the total mass of reactants, and therefore the stoichiometry of reactants. This means that RME can add value in screening reactions but does not consider solvent usage, work-up or waste produced.

$$\mathrm{RME} = \frac{\text{Mass of isolated product}}{\text{Total mass of reactants}} \times 100$$

Equation 5: Reaction Mass Efficiency.

AE is a theoretical maximum value whereas RME is calculated from observed data, a comparison of the two metrics can be observed through the metric, optimum efficiency (OE) which was first introduced in 2015 by Clark *et al* (Equation 6).[101]

$$\mathrm{OE} = \frac{\mathrm{RME}}{\mathrm{AE}} \times 100$$

Equation 6: Optimum efficiency.

One consideration that is essential for reaction metrics is that the parameters should be clearly defined. One issue that can be identified is the definition of a reactant. In some calculation of AE/RME the user will only select the primary reactants, but in other calculations the user may include reagents that are needed at stoichiometric (or higher) loading because they are consumed in the process and donate atoms to an intermediate, e.g. the *in-situ* formation of an acyl chloride in amidation reaction.

2.1.2.3. E-Factor and Mass Intensity (MI)

Another early mass based reaction is E-Factor which was introduced by Sheldon in 1992.[15, 99, 112] E-Factor (Equation 7), was developed to focus on the waste produced from a given process or reaction and differs from AE by taking account of several additional factors. Firstly, E-Factor can consider the yield of the reaction and auxiliary inputs into a process, e.g. solvents and material used during the work-up (although not all users of E factors include solvent and few use the process water) Secondly, E-Factor can be applied across a multi-step process whereas AE is generally applied to a single step.

$$\text{E Factor} = \frac{\text{Mass of total waste (kg)}}{\text{Mass of total product (kg)}}$$

Equation 7: E-Factor.

E-Factor is relatively straight forward to determine and analyse; a perfect E-Factor would be zero, high number indicates a large volume of waste produced and higher environmental impact. One drawback of E-Factor is that it does not have defined boundaries or definition for what is considered a waste. Therefore, variation can be observed when this metric is implemented by different users. Is a side product considered waste if it can be isolated and utilised in another process or if unreacted starting material is recovered and recycled back into the original process? Are gasses that pass through a scrubber included in the calculation? If the solvent is distilled from the reaction and then used next time is it a waste product? These questions highlight some issues that can arise when analysing the outputs of a process. Therefore, when two processes are being compared, it is crucial that the material being considered a waste should be defined and be the same for both calculations.

Industries have been ranked according to their E-Factor which is shown in Table 2.1. Oil refining has the lowest E-Factor because there are practically no losses when oil is fractionated, every faction is considered a product and there is only one major process. In stark contrast to this the pharmaceutical industry has the greatest E-Factor. This is because a product is generally achieved through a process involving multiple steps and transformation, each of which may require an additional purification.

Table 2.1: E-Factor for sectors in the chemical industry.[15]

Chemical sector	Approximate production (t)	Approximate waste (t)	E-Factor
Oil refining	10^6 - 10^8	10^5 - 10^7	< 0.1
Bulk chemicals	10^4 - 10^6	10^4 – $5x10^6$	< 1 – 5
Fine chemicals	10^2 - 10^4	$5x10^2$ – $5x10^5$	5 – 50
Pharmaceutical	10 - 10^3	$2.5x10^2$ – 10^5	25 – 100

Oil refining also begins with a crude oil, and the calculation does not consider the resources and waste products in the mining operations used to obtain the resource. Therefore, is it justifiable to claim that oil refining is the least wasteful or most efficient? This example again highlights a pitfall when using a single metric to analyses a process and the issues that can arise when definitions are not defined.

Mass intensity (Equation 8) considers yield, stoichiometry, solvent and reagents and is expressed as a mass rather than a percent, the ideal result would be 1. MI can be compared with E-Factor (Equation 9). When the MI for a process is considered it is referred to as Process Mass Intensity (PMI).

$$\text{Mass intensity} = \frac{\text{Mass of reagents and reactants}}{\text{Mass of product}}$$

Equation 8: Mass intensity.

$$\text{E Factor} = \text{Mass intensity} - 1$$

Equation 9: E-Factor related to Mass intensity.

2.1.2.4. Process Mass Intensity (PMI)

PMI is the most complete mass-based metric and is the metric that has been adopted by, The American Chemical Society Green Chemistry Institute's Pharmaceutical Roundtable (ACS GCI PR).[102] They chose PMI because of its focus on material input into a process rather than a metric such as E-Factor which focuses on waste produced. This is due to studies showing that the environmental life cycle impacts of producing an active pharmaceutical ingredients (API) raw material is considerably greater than the environmental impacts attributed to the waste produced using the raw material.[113] However, it could be interesting to investigate of this is valid for extremely toxic and hazardous waste, i.e. Chromic waste from oxidations or acidic aluminous waste from a Friedel Crafts reaction.

PMI is popular as it encompasses the mass of all the material used in a process relative to the amount of isolated product (Equation 10). Materials considered in its calculation include reagents, reactants, catalysts, solvents (reaction & purification) and work-up materials. The PMI value can also be viewed in terms of its four inputs or expressed as the amount of reagents, reactants and catalyst (PMI_{RRC}) and solvent (PMI_{Solv}) relative to amount of isolated product (PMI).

$$\text{PMI} = \frac{\text{total mass in a process or process step}}{\text{mass of product}}$$

Equation 10: Process Mass Intensity.

$$\text{PMI} = \frac{\text{mass}_{\text{reactants}} + \text{mass}_{\text{reagents}} + \text{mass}_{\text{catalyst}} + \text{mass}_{\text{solvent}}}{\text{mass of isolated product}}$$

Equation 11: PMI expanded.

$$\text{PMI} = \frac{\text{mass}_{\text{reactants}} + \text{mass}_{\text{reagents}} + \text{mass}_{\text{catalyst}}}{\text{mass of isolated product}} + \frac{\text{mass}_{\text{solvent}}}{\text{mass of isolated product}}$$

Equation 12: PMI as PMI_{RRC} & PMI_{solv}.

$$\text{PMI} = \text{PMI}_{\text{RRC}} + \text{PMI}_{\text{solv}}$$

Equation 13: PMI.

PMI is also a popular metric as is it much easier to avoid confusion when calculating and selecting which parameters need to be included. The values from PMI can be used in conjunction with other metrics to give insights into processes. While these metrics alone may or may not be useful their inclusion in a metric toolkit or data base would be of benefit as these databases should be designed to enable a used to filter the results and obtain a range of data.

$$\text{Waste percentage} = \frac{\text{WI}}{\text{PMI}} \times 100$$

Equation 14: Waste percentage.

2.1.2.5. Solvent selection & hazardous materials

The largest source of waste in the chemical industry is the solvent.[114] This can be identified through the use of mass-based metrics and therefore it is unsurprising that the search for alternative solvents could be considered the most popular topic within green chemistry.[18] This can be supported by the fact the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (ACS GCIPR) has shown that the synthesis of 1 kg of active pharmaceutical ingredient (API) will generate around 46 kg of waste, of which 56% will be due to organic solvents, and 32% from aqueous waste.[75] The issue around solvent waste has also been highlighted by GlaxoSmithKline (GSK). They estimate that solvent usage accounts for 80 – 90% by mass of waste produced from a batch in a pharmaceutical of fine-chemical synthetic process.[75]

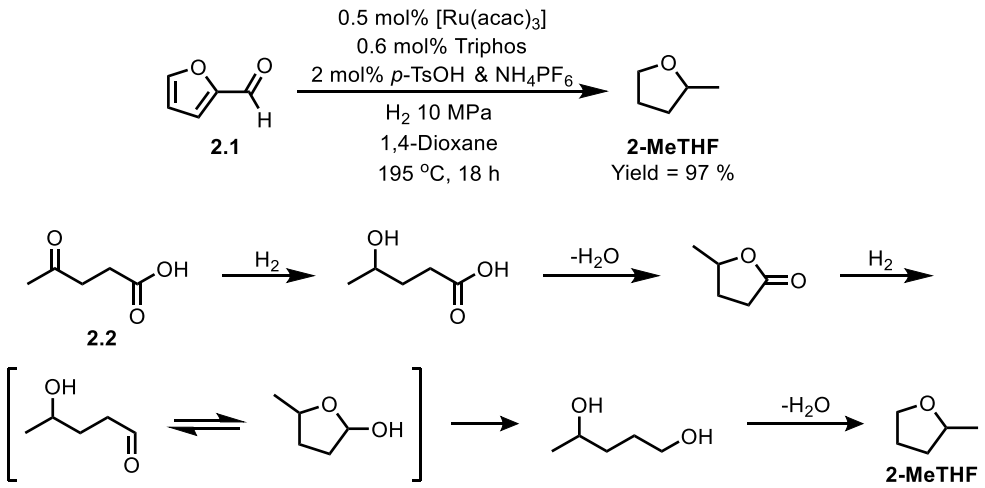
Most metrics focus on quantities of the materials use, *i.e.* molecular weights, mass or volumes of reactants, reagents and solvents. While this is useful for identifying the efficiency of a process it does not highlight any health and safety or environmental concerns with the solvent(s) or reagents chosen. This is a very important parameter and one that needs to be considered when evaluating the green credentials of a process as many conventional solvents are flammable, toxic and/or corrosive. Numerous solvents are also classified as volatile organic compounds (VOCs) which present additional hazards to operator and the environment. Therefore, the environmental impact of a process is almost always linked to the choice of solvent and consequently

any improvement in the environmental impact can be more easily obtained by altering the solvent rather than the chemistry.[18]

Given the large impact that solvent has on mass-based reaction metrics and the environment performance of a process, especially in the pharmaceutical industry, several large pharmaceutical companies have developed solvent selection guides with the aim of allowing users to make informed choices about the solvents they select. This is achieved by highlighting problematic, acceptable and desirable solvents. These guides have been created and published in an effort educate and encourage movement away from hazardous and undesirable solvents.[76-80, 115]

A problem that exists with various solvent selection guides is criteria used to assess and rank solvents. In the guides a solvents rating depends on the parameters that have been included in the screening process and these may be influenced by the creator's perception of what is important to their industry or process. A process, medicinal and analytical chemist will each have parameters that are important to them therefore each operator may view different parameters with a different attitude, i.e. the use of diethyl ether may be acceptable to a analytical chemist whereas it will generally never be acceptable to a process chemist. Another factor to consider is that a biobased solvent should not be confused with a greener solvent. *E.g.* Bioethanol from primary fermentation can be viewed as controversial due to the large proportion of land required to grow corn for its production, therefore is it truly a green solvent?

2-Methyltetrahydrofuran (2-MeTHF) has long been considered a viable replacement for tetrahydrofuran (THF). It is an aprotic ether which sits between THF and diethyl ether in terms of polarity and Lewis base strength and is suitable for a variety of organometallic reactions. 2-MeTHF can be produced from feedstock derived from biomass such as furfural **2.1** or levulinic acid **2.2** Scheme 2.1.[116] While 2-MeTHF has some benefits over THF it still has some limitations. Compared to THF, 2-MeTHF can more readily form peroxides in air because of the tertiary H present in 2-MeTHF.[117]



Scheme 2.1: Bio derived synthesis of 2-MeTHF.

While furfural **2.1** is considered renewable and sustainable it is also classified as toxic and carcinogenic. In contrast to this 3-methoxy-3-methyl-1-butanol is derived from petroleum feedstock but has a good human safety profile.[118] Therefore, which solvent is greener? Is one solvent better just because it can be classified as sustainable/biobased? Finally, when a life cycle analysis (LCA) was performed on the manufacture of 2-MeTHF it highlighted the need for careful selection of biomass resource and the results of a detailed LCA showed not all biobased chemicals could synonymously be called "green".[119]

2.1.2.6. Other metrics

The list of reaction metrics available to choose from is extensive, a very comprehensive review by Gonzalez *et al* has four tables covering most of them.[120] A small example of four less common reaction metrics are given below (Equation 15-18). Carbon efficiency (CE) & Atom utilisation (AU).[111] Environmental quotient (EQ).[112, 121] Also Effective mass yield[122]

$$\text{Carbon efficiency} = \frac{\text{Mass of carbon in the product}}{\text{Total mass of carbon in key reactants}} \times 100$$

$$\text{Atom utilisation} = \frac{\text{Mass of final product}}{\text{Total mass of all the substances produced}}$$

$$\text{Enviromental quotent} = \frac{\text{Total mass of waste}}{\text{Mass of product}} \times \text{unfriendliness quotient}$$

$$\text{Effective mass yield} = \frac{\text{Mass of product}}{\text{Total mass of hazardous reagents}}$$

Equation 15-18: Carbon efficiency 15, Atom utilization 16, Environmental quotient 17 & Effective mass yield 18.

2.1.3. Accessibility and practicality of mass-based reaction metrics

An extremely comprehensive list of metrics has been published by Gonzalez *et al.*[120] Their publication includes 140 metrics covering environmental, efficiency, economic and energy indicators for sustainable assessment of a chemical process. This large range of metrics makes the possibilities for analysing a process somewhat endless and makes the analysis of the data generated more difficulty as it would be unlikely that the same metrics would be compared and therefore how can any meaningful result be derived from the data.

A way to standardise the use of metrics and provide clarity in how a process was screened was through the development of metric toolkits or a screening program that generated data through multiple metrics.

As part of the CHEM21 consortium a 'unified metrics toolkit' was developed which combined multiple metrics into a single user-friendly database.[101] Toolkits are especially useful as not all metrics are equal, and each industry or company has their own preferred metric. Combining several well-known metrics and the development of three new ones (optimum efficiency, renewable percentage and waste percentage) allows direct comparisons to be made between processes and through this highlight any bottlenecks or problematic areas within it.[101] Also it has been designed to analyse reactions with a light touch at very early stages of development (mg scale) through to very in depth analysis at multi-kg scale. It is also hoped that this toolkit will become an educational tool, allowing chemists to continually think about and analyse their chemistry, eventually leading to the use of green and more sustainable techniques becoming second nature.[101]

The unified toolkit is comprised of 4 screening passes, starting off simply at "discovery" stage and increasing in complexity as you move into "scale up" and finally "commercialization". This toolkit is an extremely useful and fast way of describing the green aspects of a reaction and immediately reveals areas that could be improved. The toolkit was designed to incorporate traditional mass-based metrics such as yield, and atom economy alongside more detailed metrics like PMI. In addition to the mass-based metrics environmental, Health & Safety, sustainability and energy parameters were considered; such as solvents, elements of concern, substance of concern and temperature of reaction. Combining all these factors gives a much clearer picture of the overall process and should highlight many other issues that traditional metrics would miss.

Other toolkits have also been developed to aid users measure the greenness of a process and quantify their chemistry with the aim of identify areas for improvement. Merck developed *Merck's DOZN*™ which is a web-based app/tool that has been designed around the 12 principles of green chemistry and allows users to calculate a green score. This score is reflective on how sustainable a process is; therefore, a lower score could indicate areas that require improvement.[123]

Other companies such as Croda measure their greenness and suitability through the United Nations (UN) 17 Sustainable Development Goals (SDGs).[9, 124] These are a set of 17 global goals with 169 specific targets measured through 230 indicators. These SGD's have also been adopted by 195 governments worldwide and could be described as a global sustainability strategy.[7]

2.1.4. Chapter Aims

Throughout this chapter I will look at how mass based reaction metrics have been applied to the analysis of chemical reactions and processes. The work presented in this chapter will highlight the possible issues and pitfalls that can arise with metric analysis and the problems setting targets based on metrics can create. The metric that most of the analysis has been performed on is PMI. The metric PMI was chosen as this is the pharmaceutical industry's favoured metric to evaluate the green credentials of a synthetic methodology and is frequently employed for guiding route selection both in a discovery and process and development research environment. [102, 105, 125] The pitfalls and drawbacks of other metrics (AE and RME) will also be discussed and the term "green potential" introduced and described as an alternative way of viewing a process at any stage through from discover to production.

2.2. Results and Discussion

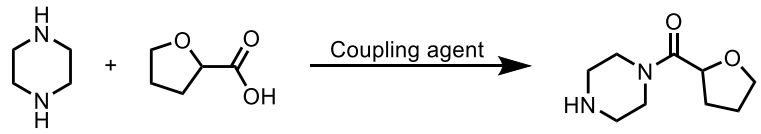
2.2.1. PMI in the Pharmaceutical industry: Case Study

PMI is the Pharmaceutical industry's chosen metric to measure sustainability and quantify the *greenness* of a given process.[102, 125-127] One of the main factors for the ACS GCI PR choosing PMI was due to the metrics focus on input rather than output, therefore trying to create an efficient process from the beginning rather than working backwards.

Some companies have set targets based on idealised metric values such as Eli Lilly (Lilly).[125] It was reported that Lilly set a target for the PMI of all new commercial API's to be <100 g g^{-1}, but quickly discovered this target was not feasible and a different approach was required. Consequently, Lilly discovered it was more appropriate to adjust targets based on market demand and developed a system based on molecular complexity and predicted marked demand to determine a practical PMI target for their process.[128] Given the vast number of reaction metrics it is no surprise that issues can arise when a target is set against a single metric, even if that metric encompassed several aspects of a reaction or process.

Issues can also arise when direct comparisons are made between two reactions yielding the same product using the same reactants, only differing with reagents. This may appear to be a sound comparison, but can the data be reliably compared without all the parameters of the reaction being taken into consideration?

Table 2.2: An adapted comparison of green credentials for amide bond formation with six coupling reagents using the CHEM21 Metrics Toolkit.[105]



2.3 **2.4** **2.5**

	Coupling agent					
	Entry 1 **Silica[a]**	**Entry 2** **Enzyme[b]**	**Entry 3** **$SOCl_2$[c]**	**Entry 4** **$B(OH)_3$[d]**	**Entry 5** **PPh_3 & NBS[e]**	**Entry 6** **HMDS[f]**
Yield (%)	15	14	70	74	82	93
Calculated with only **2.1** & **2.2** excluding the reagents and ignoring intermediates						
Traditional Atom Economy (%)	91	91	91	91	91	91
Traditional RME (%)	14	13	64	68	75	85
Modified AE & RME considering the reagents and intermediate formed in the reaction						
Modified Atom Economy (%)	91	91	57	91	26	51
Modified RME (%)	14	13	23	68	21	47
PMI reaction (g g^{-1})	122	115	31	27	39	22
PMI solvent (g g^{-1})	114	106	27	26	35	20
Solvent choice						
Catalyst?						
Recoverable catalyst?						
Critical element						
Energy						
Work-up						
Health and Safety						
Chemical of concern?						

Flag system: Green flag preferred, amber flag acceptable but some issues and red flag is undesirable.
A full key and explanation of the metrics analysis and flag classification can be found in the appendix.

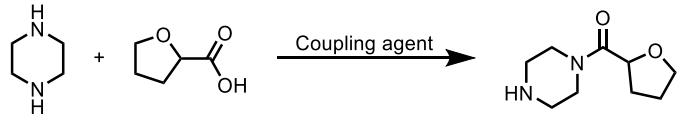
Reaction conditions: **1** (5 mmol), **2** (5 mmol), [a] K60 silica (0.1 g, activated at 700 °C), neat, 110 °C, 14 h, then acetone (20 mL). [b] Immobilized novoenzyme 435 (0.1 g), heptane (20 mL), rt, 72 h. [c] Thionyl chloride (15 mmol), toluene (20 mL), 110 °C, 1 h. [d] Boric acid (0.5 mmol), toluene (20 mL), 110 °C, 11 h. [e] Triphenylphosphine (5 mmol), *N*-Bromosuccinimide (5 mmol), pyridine (5 mmol), CH_2Cl_2 (20 mL), 5 °C then rt, 1 h. [f] Hexamethylsilazane (5 mmol), 110 °C, 8 h.

Table 2.2 is a good example of the many problems which can arise when comparing different reactions. Table 2.2. has been adapted and expanded from the publication *Why we might be misusing process mass intensity (PMI) and a methodology to apply it effectively as a discovery level metric* by McElroy *et al*.[105]

The coupling of piperazine **2.3** and tetrahydrofuran-2-carboxylic acid **2.4** to form amide **2.5** was performed under using several different amide coupling protocols. The

data from the six reactions was placed into the Chem21 Metrics Toolkit and the results are displayed in Table 2.2. These six different amides coupling reagents clearly display the issues which can occur when metric data is directly compared. The largest value for PMI was found in Entry 1, the silica coupling which had a PMI of 122 g g^{-1} and the lowest PMI was recorded with boric acid in Entry 4 at 27 g g^{-1}. If the PMI was the sole metric used to judge the green credentials of the reaction boric acid would perform better than the enzymatic route. This PMI result is interesting and somewhat counterintuitive as most would have assumed that an enzyme would be more favorable than boric acid, the flagging system too agrees with this as the enzymatic process has numerous green flags whereas boric acid has two red flags one for health and safety and the other chemical of concern. When looking deeper into the results for PMI it becomes clear that in Table 2.2 Entry 1 & 2 the high PMI results of 122 g g^{-1} and 115 g g^{-1} are due to the low yields, 15% and 14% respectively. These low yields are rather surprising and would certainly warrant further optimization. In Table 2.3 Entry 1 – 6 have been given a theoretical yield of 90%, by leveling the yield it allows a fair comparison to be made of each reaction.

Table 2.3: Metric data from Table 2.2 scaled to an overall yield of 90%.



2.3 **2.4** **2.5**

	Coupling agent					
	Entry 1 Silica	**Entry 2 Enzyme**	**Entry 3 $SOCl_2$**	**Entry 4 $B(OH)_3$**	**Entry 5 PPh_3 & NBS**	**Entry 6 HMDS**
Theoretical yield (%)	90	90	90	90	90	90
Calculated with only **2.1** & **2.2** excluding the reagents and ignoring intermediates						
Traditional Atom Economy (%)	91	91	91	91	91	91
Traditional RME (%)	82	82	82	82	82	82
Modified AE & RME considering the reagents and intermediate formed in the reaction						
Modified Atom Economy (%)	91	91	57	91	26	51
Modified RME (%)	82	82	30	82	23	46
PMI reaction (g g^{-1})	20	18	24	22	37	23
PMI solvent (g g^{-1})	19	17	21	21	32	21

**A full explanation of the metrics analysis can be found in the appendix*

When the yields are equaled for each entry our instinctive thoughts about the silica and enzymatic reaction are proven correct, that they should be the *greener* reactions. In Table 2.3 Entry 1 & 2 the PMI results are now the lowest values, a direct contrast to being the highest in Table 2.2 Entry 1 & 2.

Why do the PMI results then contradict our instinct about which reaction should be more favorable and how do you judge a reaction to be favorable over an alternative? Under what circumstances can a comparison between reaction metrics be made and if a comparison is made for two reactions yielding different products or using different reagents is it a fair comparison? These are questions which will be explored throughout this chapter.

Another problem with comparing metric analysis is shown in Table 2.2 for the two metrics AE and RME. The value for AE & RME value can differ depending on the factors considered in calculating it, as mentioned briefly when introduction the metric in section 2.1.2.2. The traditional definition for AE & RME is displayed in Equation 4 & Equation 5.

$$\mathrm{AE} = \frac{\text{Molecular weight of desired product}}{\text{Molecular weight of all reactants}} \times 100$$

Equation 4: Atom Economy.

$$\mathrm{RME} = \frac{\text{Mass of isolated product}}{\text{Total mass of reactants}} \times 100$$

Equation 5: Reaction Mass Efficiency.

Both these metrics look at the mass of isolated or desired product over total mass of reactants. But what about intermediates formed in the reaction? Are stoichiometric reagents considered reactants or reagents? Also how are catalysts defined and accounted for within these metrics? The definition of reactant and reagent can sometimes be misinterpreted, which can cause confusion about what components of a reaction are included in the calculation.

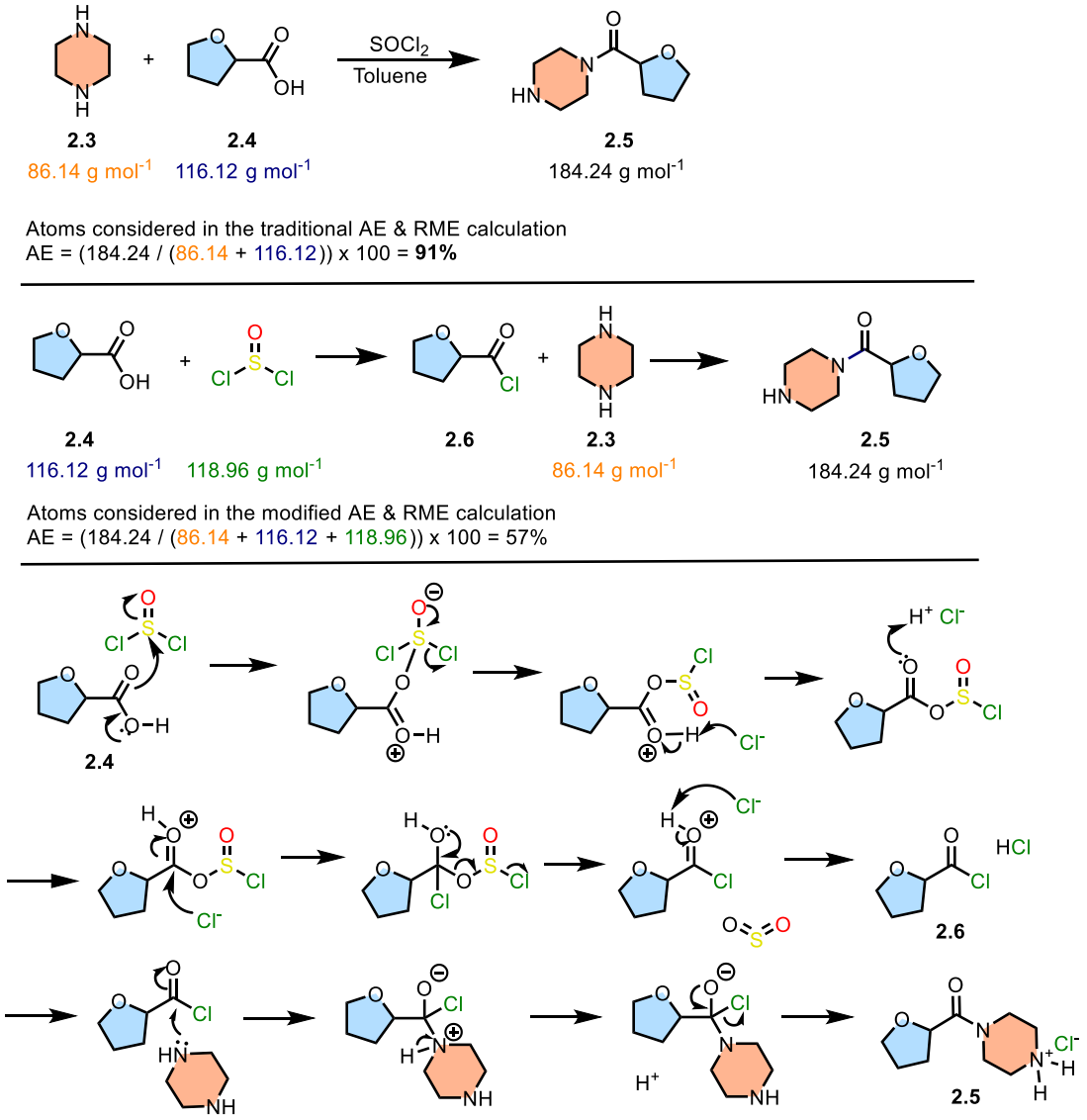
Reactant = a substance that takes part in and is changed by a chemical reaction.[129]

Reagent = a substance used to cause a chemical reaction, especially in order to find out if another substance is present.[130]

Catalyst = a substance that makes a chemical reaction happen faster without being changed itself.[131]

If we take the example reactions from Table 2.2, the values for AE and RME reported in blue (traditional definition) exclude the stoichiometric reagents in the calculation as they are considered reagents, they are not in the final product. But if one was to consider the mechanism for each process this could lead to different AE and RME as shown in Table 2.2 for modified AE (m.AE) and modified RME (m.RME) values displayed in orange (modified calculation). In the modified calculations intermediate species are being considered which include atoms from the reagent, and therefore the reagent is acting as a reactant. This can lead to ambiguity when considering a process and entering data into a metric calculator.

An example of this ambiguity is displayed in Scheme 2.2. In Table 2.2 entry 3 thionyl chloride ($SOCl_2$) has an AE of 91% when the only piperazine **2.3** and tetrahydrofuran-2-carboxylic acid **2.4** are considered in the calculation Scheme 2.2. But when the mechanism of the reaction is considered it is clear to see that the acyl chloride **2.6** is formed from the reaction of $SOCl_2$ and carboxylic acid **2.4** producing HCl and SO_2 Scheme 2.2. Therefore, our first calculation for AE and RME (traditional) including only **2.3** & **2.4** is inherently misleading and does not give an accurate representation of the reaction.



Scheme 2.2: Mechanism of amide formation using $SOCl_2$ and AE calculation.

The importance of including $SOCl_2$ in the AE/RME calculation would have also been seen if a properly balance equation had been written. Correctly balanced equations greatly simplify the process of categorising reactants and reagents. In Figure 2.1 the example of two equations are shown. The first equation is how a chemist would typically write the reaction and it could imply that this is a single step process. The second equation is a correctly balanced reaction. When observing the second equation two aspects are more easily observed. Firstly, it is obvious that $SOCl_2$ should be considered a reactant and not a reagent, as $SOCl_2$ is a reactant in the formation of intermediate **2.6**, therefore should be included in AE & RME calculations. Secondly intermediate **2.6** could be isolated if desired, therefore forming amide **2.5** using $SOCl_2$ should be considered a two-step process.

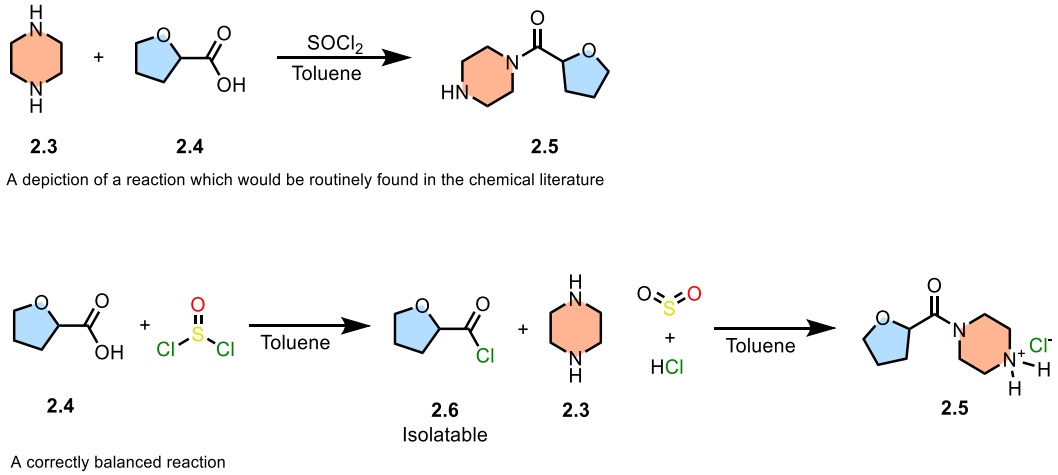
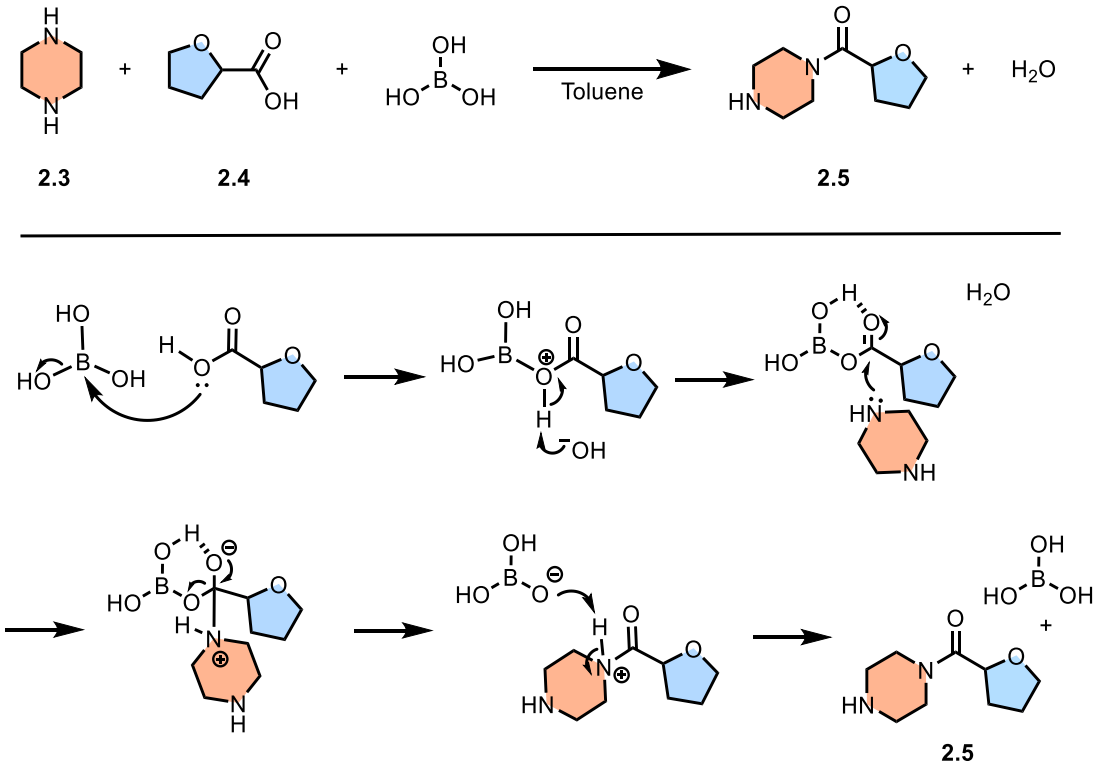


Figure 2.1: Two equations for the reaction of **2.3** with **2.4**.

Not all reactions in Table 2.2 pose problems. Entry 1 silica & entry 2 enzyme the originally (traditionally) calculated AE and RME are the same even when the mechanism is considered as they involve the use of catalysts which should remain unaltered during the reaction. In these examples nothing is consumed by through formation of an intermediate and the structure of silica and enzyme will remain unchanged (and therefore reusable) on formation of the amide.

In Table 2.2 entry 4, boric acid ($B(OH)_3$) is used as a catalyst (0.1 eq) and an intermediate complex is formed, the quantity of $B(OH)_3$ used is not stoichiometric such as in entry 3 $SOCl_2$, entry 5 triphenylphosphine (PPh_3) and *N*-bromosuccinimide (NBS) or in entry 6 hexamethyldisilazane (HMDS). In this example $B(OH)_3$ is a true catalyst therefore including it in the calculation would be unfair. The mechanism and balanced equation for amide formation using boric acid is displayed in Scheme 2.3.



Scheme 2.3: Mechanism and balanced equation for amide formation with $B(OH)_3$.

When comparing entry 3, $SOCl_2$ and entry 4, $B(OH)_3$ in Table 2.2, once the AE and RME have been recalculated including intermediates, the modified AE and modified RME calculations of $B(OH)_3$ improve significantly when compared with $SOCl_2$. $SOCl_2$ modified AE 57% & modified RME 23% vs $B(OH)_3$ modified AE 91% & modified RME 68%. These improvements should be expected given $B(OH)_3$ is used as a catalyst. However, is a direct comparison of these reactions fair given the other differences in the reactions? When considering the AE of both reactions, entry 4 $B(OH)_3$ is catalytic whereas the reaction in entry 3 with $SOCl_2$ involves a two-step, non-catalytic process. Another difficulty with determining the AE for entry 3 is the classification of $SOCl_2$, is it a reagent or reactant? If the reaction is considered one step it could be a reagent but in reality, it can be a two-step process so classifying it as a reactant is also correct. For entry 3 and entry 4 there is a 4% difference in yield, therefore the RME should be comparable, although this may not be true given the possible issues with AE. Both entry 3 and 4 have a similar PMI, 31 g g^{-1} and 27 g g^{-1} respectively, again one is catalytic the other is not so can these values be compared fairly?

The next major difference between the amidation reaction with $SOCl_2$ and $B(OH)_3$ comes from analysis of their health and safety profile. The metric analysis toolkit used in Table 2.2 was a first pass analysis from the CHEM21 unified metrics toolkit.[101] A full breakdown of the metrics toolkit and the flag grading system can be found in the appendix. Health and safety data was reviewed and assigned either a – undesirable, – acceptable but some issues or – preferred flag based on H-statements of the reagents in use. In Table 2.2 entry 4 is the only reaction to have a red flag for chemical of concern as $B(OH)_3$ has been included on the substances of very high concern (SVHC) list due to its reprotoxicity issues .

$B(OH)_3$ is also the only reagent to score a red flag in health and safety, again due to being classified as H360. (H360FD – Reproductive toxicity). This flag was assigned in the initial screening zero pass. $SOCl_2$ received a yellow flag in the first pass metric screen due to its classification of H331 (H331 – Acute toxicity by inhalation).

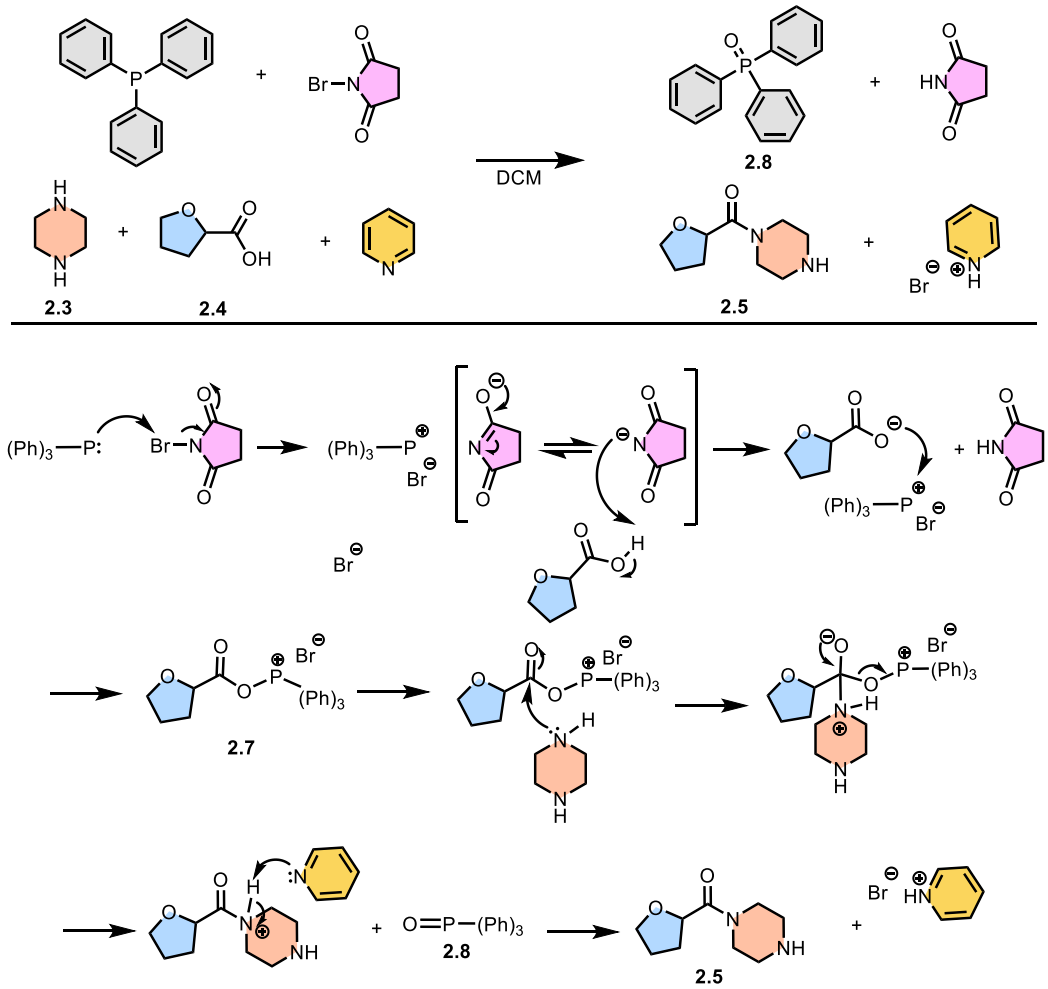
The designation of flags based on a Globally Harmonized System (GHS) H-statement can provide useful information. But caution could always be taken as classification of substances can change when new information is available. When this metric analysis was performed toluene was classified as amber (acceptable but some issues) by many solvent selection guides.[76, 77, 132] If the same screening was to be performed today a different conclusion could be reached and some amber flags in the solvent category might be changed to red.

Hazard classification & labelling of toluene according to the European Chemicals Agency.[104]

"According to the harmonised classification and labelling (CLP00) approved by the European Union, this substance may be fatal if swallowed and enters airways, is a highly flammable liquid and vapour, is suspected of damaging the unborn child, may cause damage to organs through prolonged or repeated exposure, causes skin irritation and may cause drowsiness or dizziness."

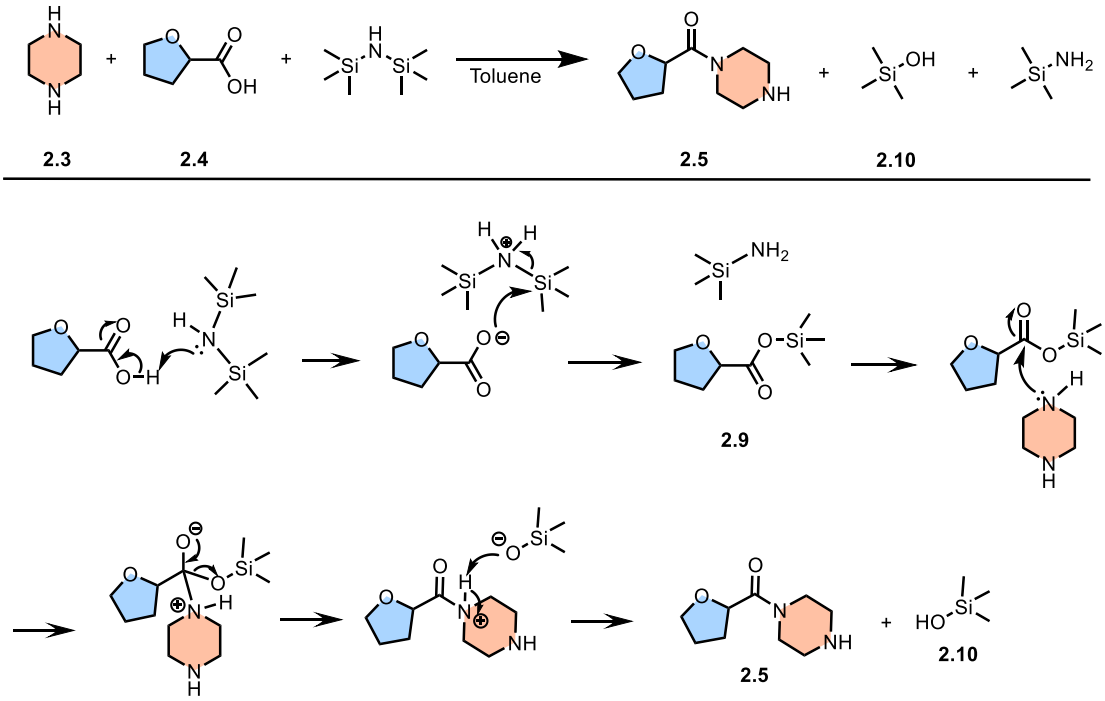
Scheme 2.4 shows a balanced equation and a proposed mechanism for the reaction displayed in Table 2.2 entry 5 using PPh_3 and NBS, an amide coupling where **2.5** is formed via an acyloxyphosphonium salt **2.7** which is produced through a reaction of PPh_3, NBS and carboxylic acid **2.4**. The reaction mechanism is shown in Scheme 2.4. The key intermediate in the mechanism is the acyloxyphosphonium salt **2.7**. Initially PPh_3 attacks NBS leaving a charged NBS intermediate which deprotonates alcohol **2.4** generating succinimide. Deprotonated alcohol **2.4** then reacts with the phosphonium bromide leading to the generation of acyloxyphosphonium salt **2.7**. A lone pair of electrons from a nitrogen on piperazine **2.3** then attacks into the acyloxyphosphonium salt **2.7** eliminating triphenylphosphine oxide **2.8**. This intermediate is finally deprotonated by pyridine leaving the desired amide **2.5** and pyridine hydrobromide.

Originally traditional AE and RME were calculated to be 91% & 75% respectively but when the mechanism is examined it is again clear to see that the reagents are consumed and therefore should be included even though their atoms do not end up in the final product. When PPh_3 and NBS are included in the metrics modified AE plummets from 91 to 26% and modified RME from 75 to 21%. Including the reagents into the AE & RME calculation gives the user a more accurate view of what is occurring in the flask.



Scheme 2.4: Mechanism and balanced equation for amide formation with PPh_3 & NBS.

HMDS was used Table 2.2 entry 6. It is thought that the reaction proceeds through a trimethylsilyl protected carboxylic acid intermediate **2.9** which is attacked by piperazine **2.3** and subsequently deprotonated by the TMS leaving group to form trimethylsilyl alcohol **2.10**. Again, after the mechanism for the reaction has been studied it highlights the need to include HMDS in the calculation for AE and RME.



Scheme 2.5: Mechanism and balanced equation for amide formation with HMDS.

These examples show the weakness and possible pitfalls of the traditional AE and RME calculation as a simple oversight can have a dramatic effect on the outcome of the metric analysis. This is contrasted by PMI, and this contrast is one of the strengths of the PMI metric: the values for PMI are constant and not variable or subjective. The parameters included in the calculation are not dependant on an assumption by the operator, therefore compared to traditional AE or RME it is more difficult to make an error in the calculation. This lack of ambiguity goes a long was in supporting the selection of PMI as the adopted metric of choice for the pharmaceutical industry.

2.2.2. PMI analysis of amidation reactions

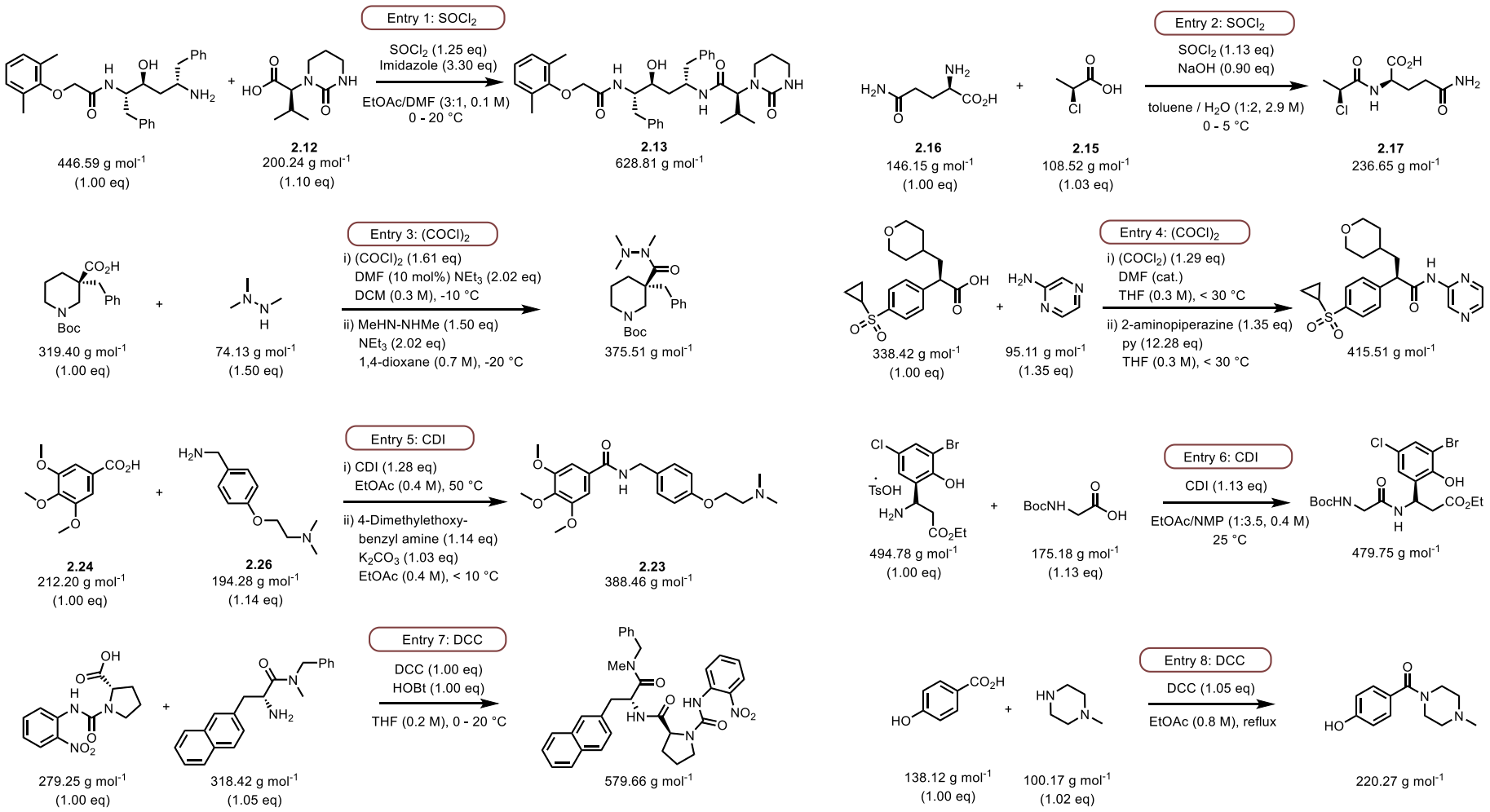
Moving on from the unexpected results obtained in Table 2.2 an in-depth analysis on PMI was conducted. The investigation began looking at the metrics of amide bond formation as this transformation is the largest category of reactions carried out in the pharmaceutical industry. 16% of all transformations involve the formation of a amide and over 65% of processes contain at least one reaction.[24, 133] Given that amide bond formation is so prevalent and there are many different reagents to choose from, it is not unreasonable to assume that most practicing chemists will encounter this type of reaction at some point in their career. Amide formation therefore should be an ideal transformation for a case study.

Several reactions for each amide coupling reagent were chosen from a comprehensive review on amide coupling reagents by Weisenburger *et al.* Scheme 2.6.[134] The most popular amide coupling reagents according to number of publications in June 2015 are displayed in Table 2.4.

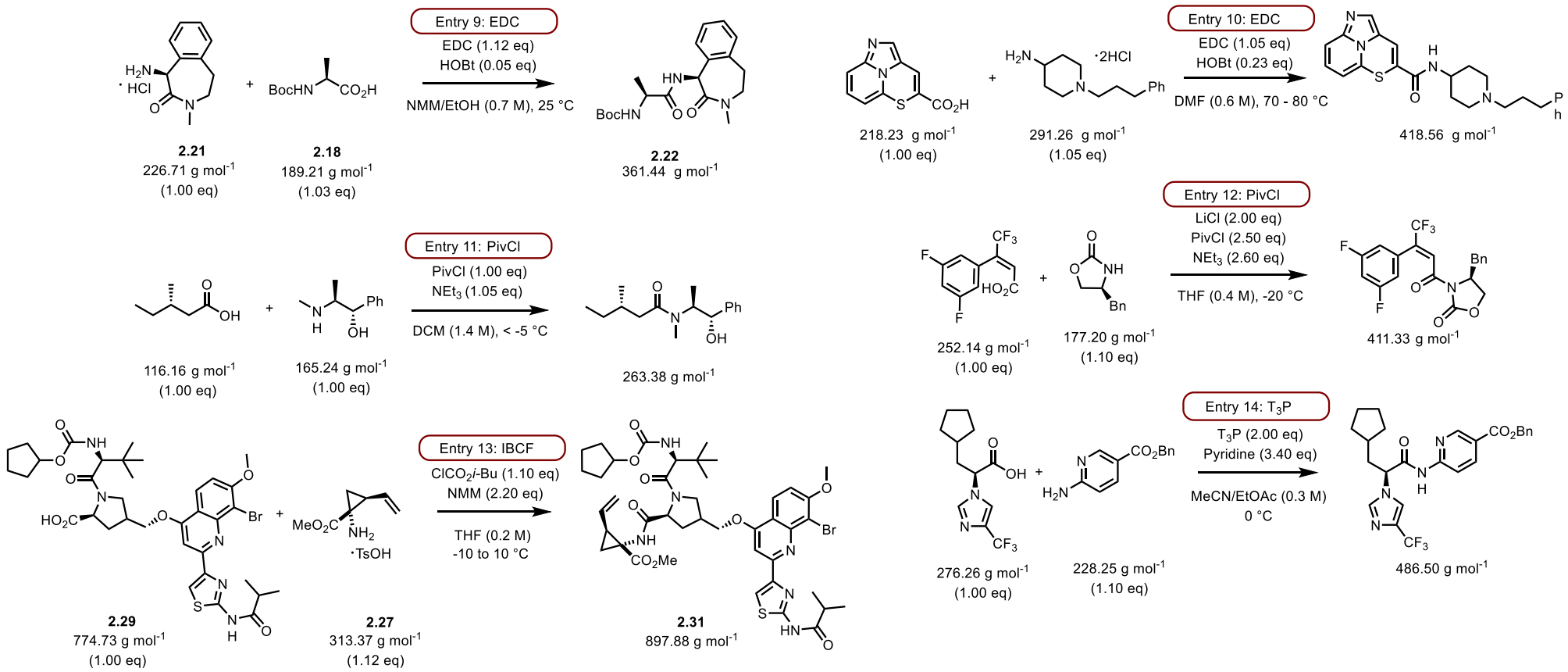
Table 2.4: Amide coupling reagents ranked in order of popularity.

Entry	Coupling reagent	Number of appearances in the review
1	1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (EDC)	54
2	Thionyl chloride ($SOCl_2$)	42
3	Carbonyldiimidazole (CDI)	38
4	Oxalyl chloride ($(COCl)_2$)	22
5	*N*,*N*'-dicyclohexylcarbodiimide (DCC)	14
6	Pivaloyl chloride (PivCl)	13
7	Isobutyl chloroformate (IBCF)	14
8	Propylphosphonic anhydride (T3P)	15

Given that a large variety of coupling reagents were covered in the review we also sought to cover a wide range of substrates which would allow the metric analysis to identify and highlight any potential pitfalls for a mass-based metric. Also given that all the reactions analysed were derived from pharmaceutical process publications the results obtained will reflect present manufacturing methods and with relevant compounds.



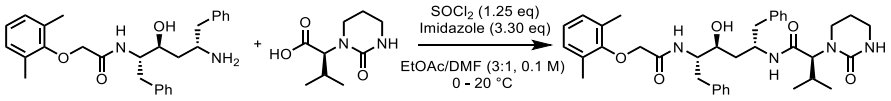
Scheme 2.6: Overview of selected amide bond forming reactions to evaluate the green metric parameters.[134]



Scheme 2.6: Overview of selected amide bond forming reactions to evaluate the green metric parameters (continued).[134]

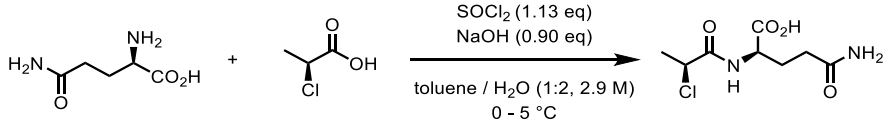
Table 2.5: Literature data and simulation A-D with $SOCl_2$ as coupling reagent.[a]

Reaction 1



446.59 g mol^{-1} (1.00 eq) + **2.12** 200.24 g mol^{-1} (1.10 eq) → **2.13** 628.81 g mol^{-1}

Reaction 2



2.16 146.15 g mol^{-1} (1.00 eq) + **2.15** 108.52 g mol^{-1} (1.03 eq) → **2.17** 236.65 g mol^{-1}

	AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{Solv} (g g^{-1})	Yield (%)
Literature data reported						
Reaction 1: [Acid] = 0.1 M	97	87	17.3	1.8	15.5	92
Reaction 2: [Acid] = 2.9 M	93	75	3.9	2.2	1.7	81
Modified AE & RME considering the reagents and intermediate formed in the reaction						
Reaction 1: [Acid] = 0.1 M	75	56	-	-	-	-
Reaction 2: [Acid] = 2.9 M	57	45	-	-	-	-
Simulation A: [Acid] = 0.4 M, Literature yield						
Reaction 1	97	87	5.7	1.8	3.9	92
Reaction 2	93	75	14.6	2.2	12.4	81
Simulation B: [Acid] = Literature data, Yield = 90%						
Reaction 1	97	85	17.7	1.8	15.8	90
Reaction 2	93	83	3.5	2.0	1.5	90
Simulation C: [Acid] = 0.4 M, Yield = 90%						
Reaction 1	97	85	5.8	1.8	4.0	90
Reaction 2	93	83	13.2	2.0	11.2	90
Simulation D: [Acid] = 0.4 M, Yield = 50%						
Reaction 1	97	47	10.5	3.3	7.2	50
Reaction 2	93	46	23.7	3.5	20.2	50

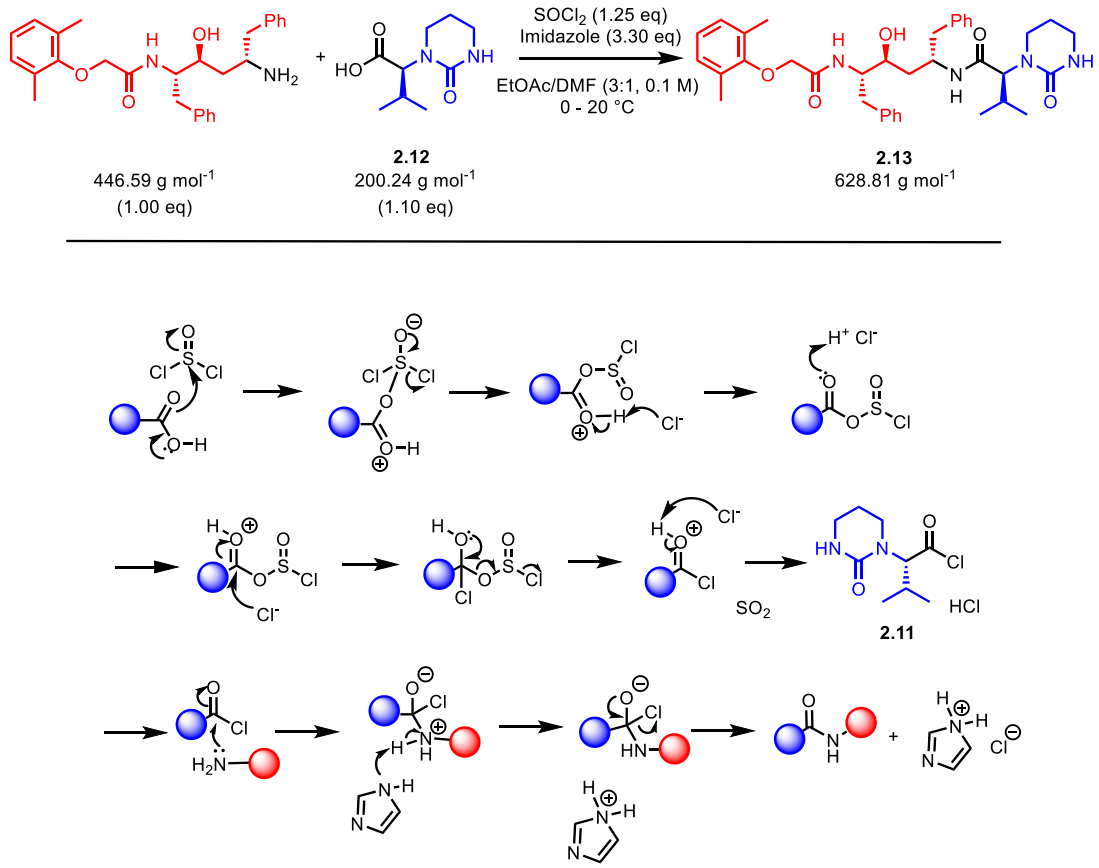
**A full explanation of the metrics analysis can be found in the appendix*

[a] Reaction refer to Scheme 2.6

Presented in Table 2.5 is the metric data for two amide formation reactions which use $SOCl_2$ as the coupling reagent. Looking at the literature data for these reactions, 1 and 2, there is similarity between both reactions AE, RME and yield. Although there is quite a difference in the PMI of 13.4 g g^{-1}. A similar difference is also noticeable between the PMI_{Solv} of both reactions (15.5 versus 1.7 g g^{-1}), this is due to a large concentration difference which is, 0.1 and 2.9 M respectively. The dominance of the solvent in the PMI calculation, as reported by Manley *et al.*[102] is nicely illustrated in this table.

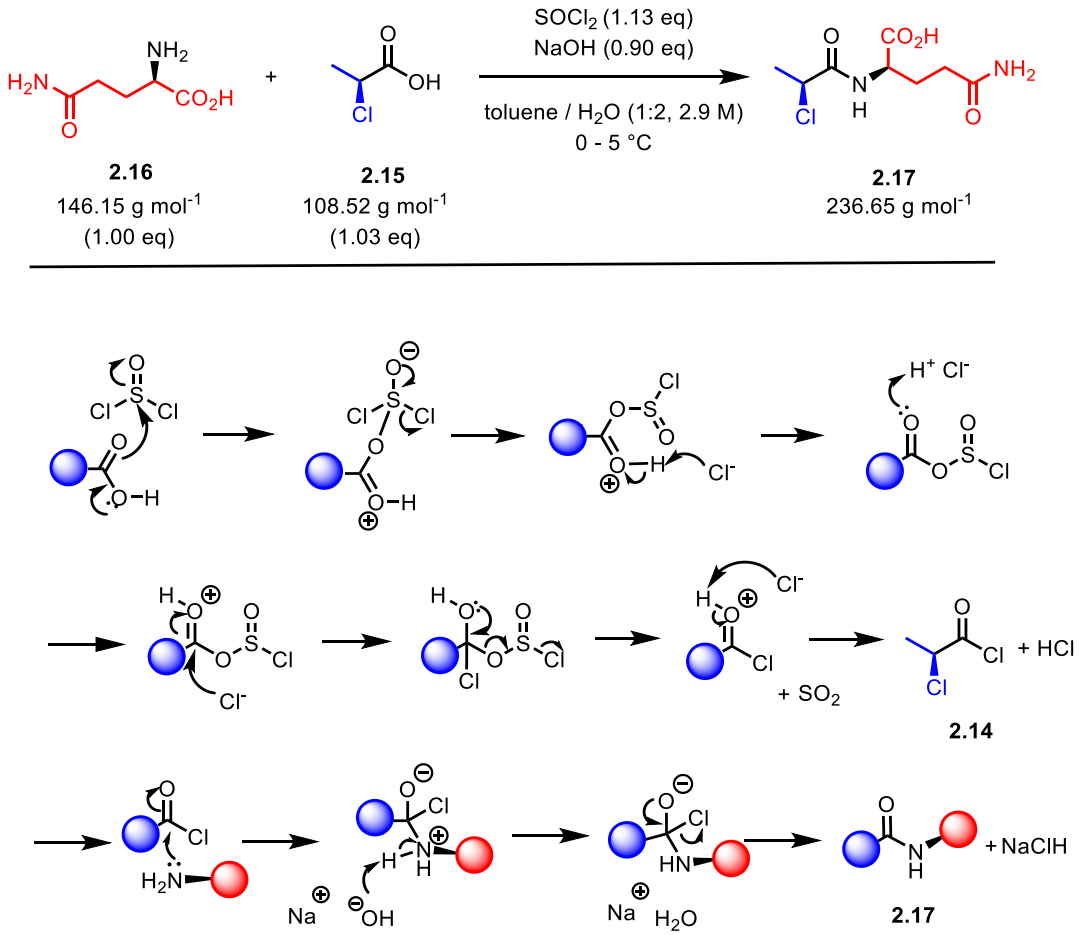
In order to determine the impact of altering reaction parameters and the effect this has on reaction metrics four simulations were performed, Table 2.5 simulation A – D. In simulation A both reactions were scaled to have an identical concentration of 0.4 M, and all other quantities remained constant (reactants, reagents, solvent, product, yield). Scaling the concentration to 0.4 M had a dramatic effect on the PMI of both reactions. In reaction 1 the PMI decreased from 17.3 to 5.7 g g^{-1} and in reaction 2 the PMI increased from 3.9 g g^{-1} to 14.6 g g^{-1}. When the PMI_{RRC} was viewed for both reactions there was no change as this ignores the effect of solvent. Looking at PMI_{solv} for simulation A the relative values are opposite of those from the literature, reaction A improves but reaction B gets worse. This is due to reaction A becoming more concentrated and reaction B becoming more dilute, this again clearly shows the large impact that solvent usage has on the PMI of a reaction or process. In Table 2.5 simulation B the only value that was altered was the yield, this was scaled to 90% and a minimal effect on the reaction metrics. In simulation C and D concentration was fixed at 0.4 M and the yields were changed to 90% & 50% respectively. In simulation C as seen in simulation B altering the yield 81% and 92% to 90% had a minimal effect but this was more drastic when the yield was decreased to 50% in simulation D. Simulation D has the largest change in metric results when compared to the literature data. This highlights the pitfalls and unreliable nature of comparing chemical processes without defining what parameters are being compared.

As mentioned in the discussion for Table 2.2 the absence of reagents which partake in the reaction can lead to a misleading result for traditional AE & RME. In Table 2.5 modified AE & RME have been calculated considering the reaction mechanisms and intermediate formed in the reaction. For reaction 1 in Table 2.5 the mechanism is displayed in Scheme 2.7, an acyl chloride intermediate **2.11** is formed by reaction with carboxylic acid **2.12** and $SOCl_2$. This intermediate then reacts with the primary amide forming the desired amide **2.13**.[135] The AE decreases from 97% traditional AE to 75% modified AE and RME decreases from 87% traditional RME to 56% modified RME when thionyl chloride is included in the calculation.



Scheme 2.7: Mechanism for amide formation in Table 2.5 reaction 1.

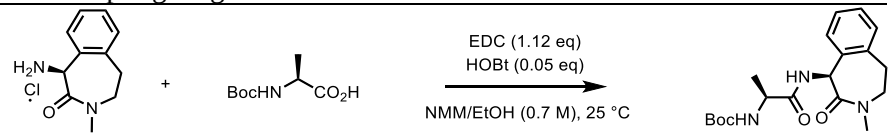
The mechanism for reaction 2 is shown below in Scheme 2.8, it proceeds through an acyl chloride **2.14** formed by reaction of carboxylic acid **2.15** and $SOCl_2$ which then subsequently reacts with L-glutamine **2.16** forming the desired amide **2.17**. The paper which reported the reaction in Scheme 2.8 performed the process in two steps, first formation of the acyl chloride intermediate **2.14** followed by amide bond formation. This distinct two-step process alone is a strong reason for including $SOCl_2$ in the AE & RME calculation even before examination of the mechanism or balanced equation. The traditional AE and RME metrics excluding $SOCl_2$ were 93% & 75% but decreased to 57% & 45% when the reagent was included in the modified AE and RME calculation. It is interesting to note that the amide bond formation is performed in biphasic toluene/aqueous NaOH solution, a Schotten-Baumann procedure.[136] These conditions were chosen to prevent decomposition of the acid chloride and eliminate other issues the authors had isolating a pure product.[137]



Scheme 2.8: Mechanism for amide formation in Table 2.5 reaction 2.

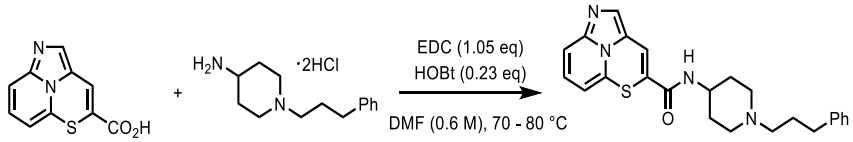
Table 2.6: Literature data and simulation A-D with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide EDC as coupling reagent.[a]

Reaction 9



2.21 226.71 g mol^{-1} (1.00 eq) + **2.18** 189.21 g mol^{-1} (1.03 eq) → **2.22** 361.44 g mol^{-1}

Reaction 10



218.23 g mol^{-1} (1.00 eq) + 291.26 g mol^{-1} (1.05 eq) → 418.56 g mol^{-1}

	AE (%)	RME (%)	PMI (g g^{-1})	PMI$_{RRC}$ (g g^{-1})	PMI$_{Solv}$ (g g^{-1})	Yield (%)
Literature data reported						
Reaction 9: [Acid] = 0.7 M	87	79	5.8	2.6	3.2	92
Reaction 10: [Acid] = 0.6 M	82	61	8.3	3.0	5.3	76
Modified AE & RME considering the reagents and intermediate formed in the reaction						
Reaction 9: [Acid] = 0.7 M	59	53	-	-	-	-
Reaction 10: [Acid] = 0.6 M	60	44	-	-	-	-
Simulation A: [Acid] = 0.4 M, Literature yield						
Reaction 9	87	79	8.5	2.6	5.9	92
Reaction 10	82	61	10.4	3.0	7.4	76
Simulation B: [Acid] = Literature data, Yield = 90%						
Reaction 9	87	77	5.9	2.6	3.3	90
Reaction 10	82	72	7.0	2.6	4.5	90
Simulation C: [Acid] = 0.4 M, Yield = 90%						
Reaction 9	87	77	8.7	2.6	6.1	90
Reaction 10	82	72	8.8	2.6	6.3	90
Simulation D: [Acid] = 0.4 M, Yield = 50%						
Reaction 9	87	43	15.6	4.7	10.9	50
Reaction 10	82	40	15.9	4.6	11.3	50

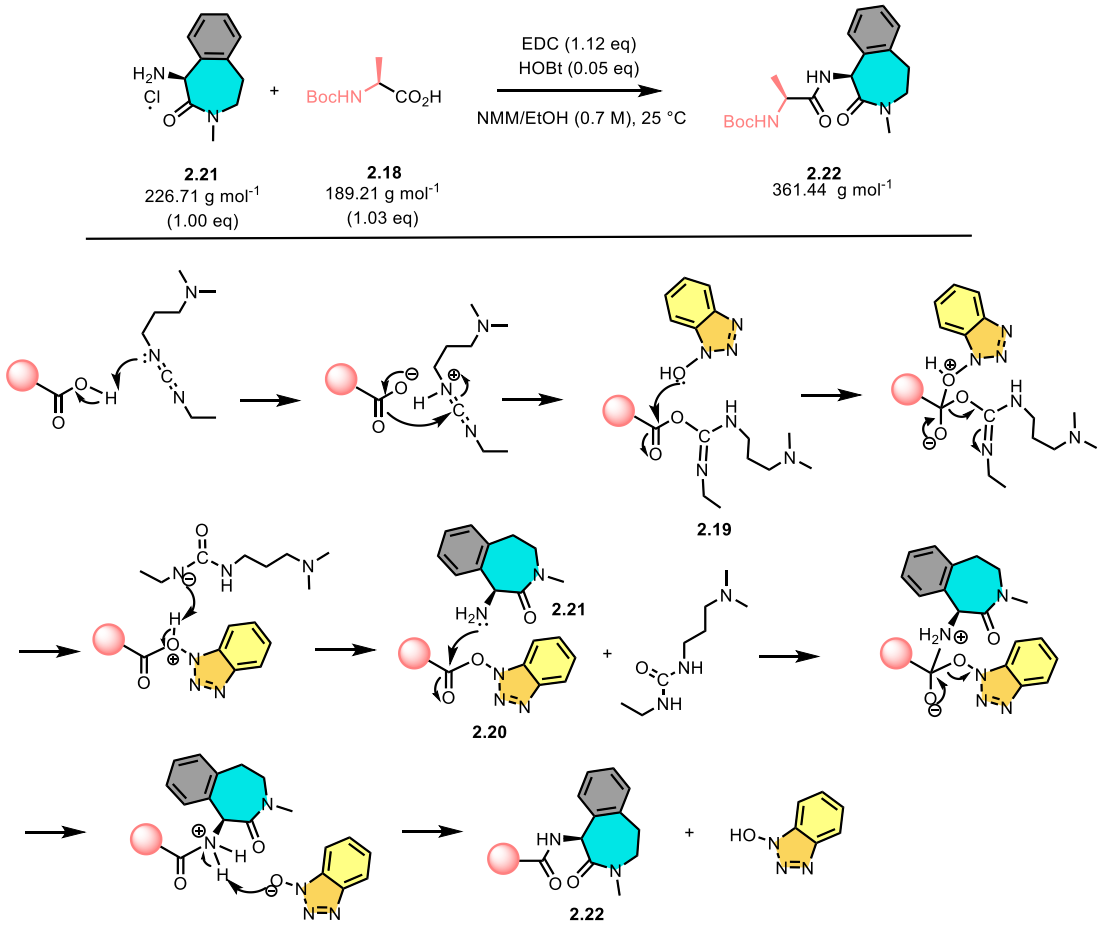
**A full explanation of the metrics analysis can be found in the appendix*

[a] Reaction refer to Scheme 2.6

Table 2.6 displays the metric data for reactions 9 & 10 from Scheme 2.6. Both these reactions use EDC as the coupling reagent and are run at a similar concentration, reaction 9 at 0.7 M & reaction 10 at 0.6 M. The most notable difference in metric results from the literature is the overall yield and RME, reaction 9 has a yield of 92% vs 76% for reaction 10 and the traditional RME is 79% vs 61% respectively. The lower traditional RME of reaction 10 can be attributed to the reduced yield and the slightly greater stoichiometric excess (1.05 eq) which can also account for a slightly higher PMI. In Table 2.6 simulation B, the yield for each reaction was scaled to 90%. This levelling of yield reduced the difference in traditional RME from 18 to 5%, the difference in PMI was also reduced from 2.5 to 1.1 g g^{-1}.

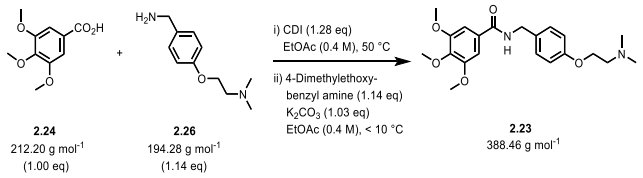
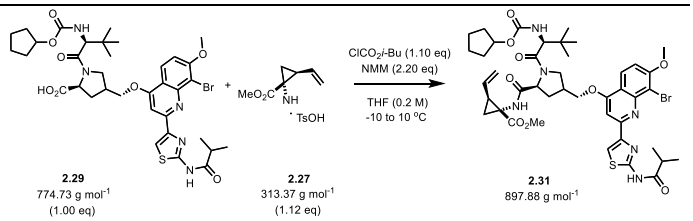
The slight differences in PMI can be linked to a concentration difference of 0.1 M between reactions and the difference in traditional RME is attributed to the molecular weight of the starting material versus product. This example shows the effect that a differing yield can have on the same process.

In Scheme 2.9 the mechanism for amide formation via 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (EDC) is shown. Initially the carboxylic acid **2.18** forms a urea type intermediate **2.19** which is converted into an activated ester **2.20** by hydroxybenzotriazole (HOBt). The amine **2.21** then attacks the carbonyl of the activated ester **2.20**, eliminating HOBt and forming the desired amide **2.21**. No atoms in the final product are derived from EDC or HOBt, but EDC should be included in the calculation for AE and RME as without this reagent the reaction would not proceed and it is present in stoichiometric quantities, whereas HOBt is present as a catalyst and can therefore be excluded.[138]



Scheme 2.9: Mechanism for amide formation in Table 2.6 reaction 9 & 10.

Table 2.7: Yield and concentration simulations for reactions with smallest and largest molecular weight difference between the reactants.[a]

	Δ MW reactants	
Reaction 5 (CDI)	17.92 g mol^{-1} MW CDI 162.15 g mol^{-1}	 **2.24** 212.20 g mol^{-1} (1.00 eq) **2.26** 194.28 g mol^{-1} (1.14 eq) **2.23** 388.46 g mol^{-1}
Reaction 13 (IBCF)	Δ MW reactants 461.36 g mol^{-1} MW IBCF 138.58 g mol^{-1}	 **2.29** 774.73 g mol^{-1} (1.00 eq) **2.27** 313.37 g mol^{-1} (1.12 eq) **2.31** 897.88 g mol^{-1}

	AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{Solv} (g g^{-1})	Yield (%)
Literature data reported						
Reaction 5: [Acid] = 0.4 M	96	81	8.8	2.2	6.6	89
Reaction 13: [Acid] = 0.2 M	83	67	8.3	2.0	6.3	84
Modified AE & RME considering the reagents and intermediate formed in the reaction						
Reaction 5: [Acid] = 0.4 M	55	45	-	-	-	-
Reaction 13 [Acid] = 0.2 M	68	50	-	-	-	-
Simulation A: [Acid] = 0.4 M, Literature yield						
Reaction 5	96	81	8.7	2.2	6.4	89
Reaction 13	83	67	4.9	2.0	2.9	84
Simulation B: [Acid] = Literature data, Yield = 90%						
Reaction 5	96	82	8.6	2.2	6.4	90
Reaction 13	83	72	7.8	1.9	5.9	90
Simulation C: [Acid] = 0.4 M, Yield = 90%						
Reaction 5	96	82	8.6	2.2	6.4	90
Reaction 13	83	72	4.6	1.9	2.7	90
Simulation D: [Acid] = 0.4 M, Yield = 50%						
Reaction 5	96	46	15.5	4.0	11.5	50
Reaction 13	83	40	8.3	3.4	4.9	50
Simulation E: [Acid] = 0.8 M, Yield = 90%						
Reaction 5	96	82	5.4	2.2	3.2	90
Reaction 13	83	72	3.2	1.9	1.4	90
Simulation F: CDI (1.1 eq) as coupling reagent for both reactions, [Acid] = 0.4 M in THF, Yield = 90%						
Reaction 5	96	82	8.6	2.2	6.4	90
Reaction 13	83	72	4.5	1.8	2.7	90
Simulation G: CDI (1.1 eq) as coupling reagent for both reactions, [Acid] = 0.4 M in THF, Yield = 50%						
Reaction 5	96	46	15.4	3.9	11.5	50
Reaction 13	83	40	8.2	3.3	4.9	50
Simulation H: IBCF (1.1 eq) as coupling reagent for both reactions, [Acid] = 0.4 M in THF, Yield = 90%						
Reaction 5	96	82	8.4	2.0	6.4	90
Reaction 13	83	72	4.5	1.7	2.8	90
Simulation I: IBCF (1.1 eq) as coupling reagent for both reactions, [Acid] = 0.4 M in THF, Yield = 50%						
Reaction 5	96	46	15.1	3.5	11.5	50
Reaction 13	83	40	8.0	3.1	4.9	50

A full explanation of the metrics analysis can be found in the appendix

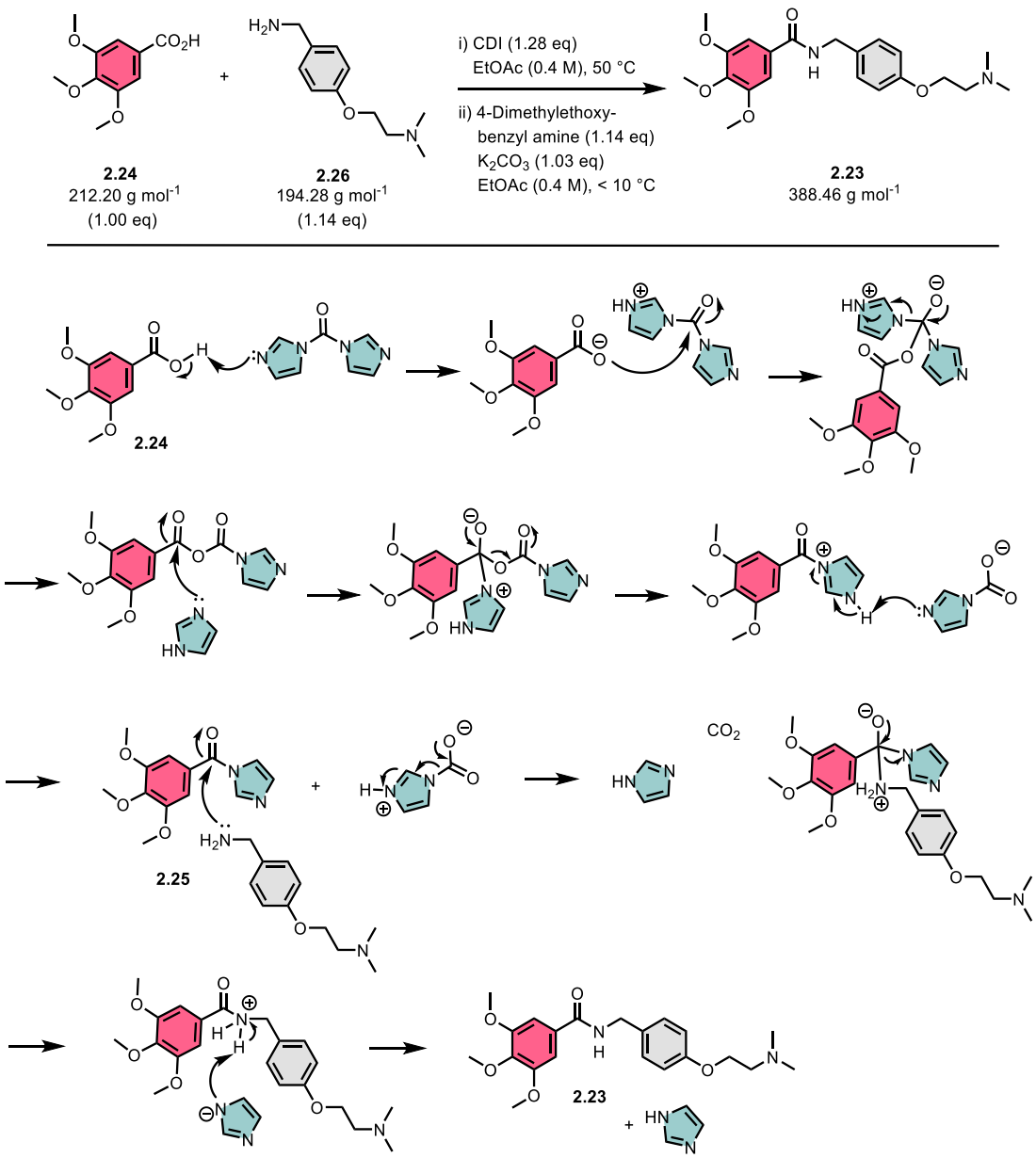
[a] Reaction refer to Scheme 2.6

Table 2.7 contains reactions 5 & 13 from Scheme 2.6. These two reactions have been selected as they represent the largest and smallest difference in molecular weight of reactants. Reaction 5 has the smallest difference of 17.92 g mol^{-1} and reaction 13 the largest 461.36 g mol^{-1}. These two reactions use different coupling reagents reaction 5, carbonyldiimidazole (CDI) and reaction 13 isobutyl chloroformate (IBCF). However, the difference in molecular weigh between both coupling reagents is a small (23.57 g mol^{-1}).

When the literature metrics are compared for both reactions there is very little difference, yield 89% vs. 84%, PMI 8.8 vs. 8.3 g g^{-1}, PMI_{RRC} 2.2 vs. 2.0 g g^{-1} and PMI_{Solv} 6.6 vs. 6.3 g g^{-1}. However, when the concentrations are standardised at 0.4 M as previously shown a difference in PMI can appear. In the case of reaction 5 & 13 the PMI of 8.8 & 8.3 g g^{-1} was altered to 8.7 & 4.9 g g^{-1} for both reactions as can be seen in Table 2.7 simulation A.

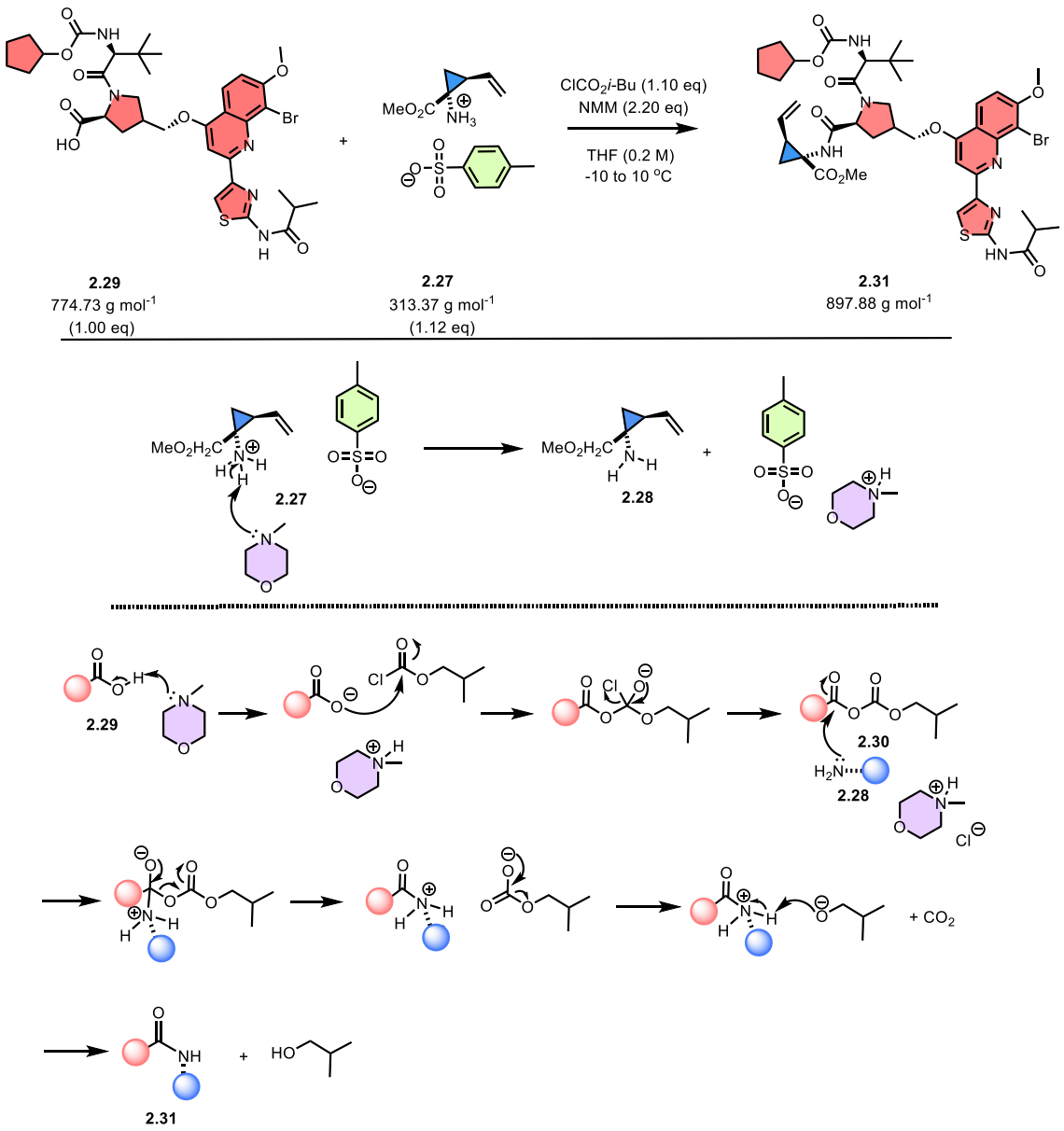
When alterations are taken to an extreme Table 2.7 simulation D the PMI values change to 15.5 vs. 8.3 g g^{-1}.This example again highlights the problem of comparing a PMI value without stating the concentration it has been calculated for.

For the amide coupling reaction involving CDI the mechanism shown in Scheme 2.10 highlights the integral role that CDI plays in the formation of the desired amide **2.23**. CDI deprotonates carboxylic acid **2.24** and is then converted into a mixed anhydride intermediate which is quickly attacked by imidazole to form intermediate **2.25**. Then the desired amide is formed when amine **2.26** reacts with intermediate **2.25** eliminating imidazole and CO_2.[139] While no atoms from CDI end up in the final compound the reagent should be included in AE and RME metric analysis.



Scheme 2.10: Mechanism for amide formation in Table 2.7 reaction 5.

In Scheme 2.11 the mechanism involving ICBF to form an amide bond is shown. Two equivalents of *N*-methylmorpholine (NMM) are used as one equivalent is required to convert the salt of the cyclopropane amide **2.27** into its free base **2.28**. The second equivalent then deprotonates carboxylic acid **2.29** and this reacts with ICBF to form a mixed, very unstable anhydride intermediate **2.30**. When the cyclopropane amide **2.28** attacks intermediate **2.30** it rearranges to eliminate CO_2, isobutane and the desired amide **2.31**.[140] Observing how ICBF is used and broken down in a similar fashion to $SOCl_2$ it is difficult to argue that it should not be included in the AE and RME calculations given the role it plays in the reaction.



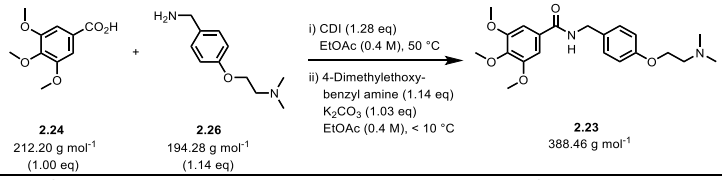
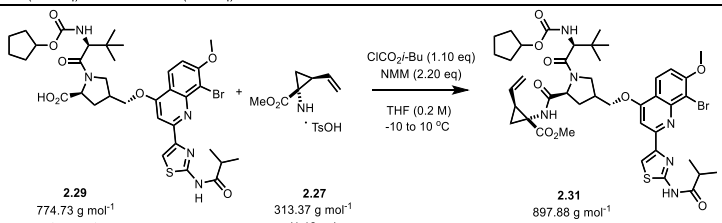
Scheme 2.11: Mechanism for amide formation in Table 2.7 reaction 13.

For the examples explored in this chapter a concentration of 0.4 M was chosen as it is expected to represent a modest concentration that could maybe be arbitrarily chosen in research and development labs. One point to mentioned about the concentration chosen for metric analysis is that it is irrelevant if the concentration is standardised. But importantly this is not to say the concentration is irrelevant in the process as it has already been shown that a more concentrated reaction significantly improves a processes metric credentials. For example, in Table 2.7 simulation C the concentration is 0.4 M and in simulation E the concentration is 0.8 M and both simulations yields are 90%. In both simulations C & E the PMI_{RRC} are identical at 2.2 & 1.9 g g^{-1} meaning

that it a reliable comparison. Comparing different processes can be useful but as we have seen, some reactions have numerous reagents available to perform the transformation, therefore the effect of changing the coupling agent on the synthesis of the same amide product was evaluated. This analysis would enable a chemist to quantitatively assess the green chemistry metrics of a process and make a more informed choice before any reagents are selected.

Following on from our simulations with reactions 5 and 13 both were simulated and evaluated using alternative coupling reagents. The coupling reagents chosen had a larger MW range than the reagents originally selected (between 118.97 g mol^{-1} and 318.18 g mol^{-1}) Table 2.8. For these simulations yield, concentration and excess reagent remained constant.

Table 2.8: Simulations for different coupling reagents for reactions with smallest and largest molecular weight difference between the reactants.[a]

Reaction 5	Δ MW reactants 17.92 g mol^{-1}	 **2.24** 212.20 g mol^{-1} (1.00 eq) + **2.26** 194.28 g mol^{-1} (1.14 eq) → **2.23** 388.46 g mol^{-1}
Reaction 13	Δ MW reactants 461.36 g mol^{-1}	 **2.29** 774.73 g mol^{-1} (1.00 eq) + **2.27** 313.37 g mol^{-1} (1.12 eq) → **2.31** 897.88 g mol^{-1}

	AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{Solv} (g g^{-1})	Yield (%)
Simulation A: $SOCl_2$ (1.1 eq, MW = 118.97 g mol^{-1}), [Acid] = 0.4 M in THF						
Reaction 5	96	82	8.0	1.6	6.4	90
Reaction 13	83	72	4.3	1.5	2.8	90
Modified AE & RME considering the reagents and intermediate formed in the reaction						
Reaction 5	74	63	-	-	-	-
Reaction 13	74	65	-	-	-	-
Simulation B: $(COCl)_2$ (1.1 eq, MW = 126.93 g mol^{-1}), [Acid] = 0.4 M in THF						
Reaction 5	96	82	8.0	1.6	6.4	90
Reaction 13	83	72	4.3	1.6	2.8	90
Modified AE & RME considering the reagents and intermediate formed in the reaction						
Reaction 5	73	62	-	-	-	-
Reaction 13	74	64	-	-	-	-
Simulation C: CDI (1.1 eq, MW = 162.15 g mol^{-1}), [Acid] = 0.4 M in THF						
Reaction 5	96	82	8.1	1.7	6.4	90
Reaction 13	83	72	4.4	1.6	2.8	90
Modified AE & RME considering the reagents and intermediate formed in the reaction						
Reaction 5	68	58	-	-	-	-
Reaction 13	72	62	-	-	-	-
Simulation D: DCC (1.1 eq, MW = 206.33 g mol^{-1}), [Acid] = 0.4 M in THF						
Reaction 5	96	82	8.3	1.9	6.4	90
Reaction 13	83	72	4.4	1.7	2.8	90
Modified AE & RME considering the reagents and intermediate formed in the reaction						
Reaction 5	63	54	-	-	-	-
Reaction 13	69	60	-	-	-	-
Simulation E: EDC (1.1 eq, MW = 191.70 g mol^{-1}), [Acid] = 0.4 M in THF						
Reaction 5	96	82	8.2	1.8	6.4	90
Reaction 13	83	72	4.4	1.6	2.8	90
Modified AE & RME considering the reagents and intermediate formed in the reaction						
Reaction 5	65	55	-	-	-	-
Reaction 13	70	61	-	-	-	-
Simulation F: PivCl (1.1 eq, MW = 120.58 g mol^{-1}), [Acid] = 0.4 M THF						
Reaction 5	96	82	8.0	1.6	6.4	90
Reaction 13	83	72	4.3	1.5	2.8	90
Modified AE & RME considering the reagents and intermediate formed in the reaction						
Reaction 5	74	63	-	-	-	-
Reaction 13	74	65	-	-	-	-
Simulation G: IBCF (1.1 eq, MW = 138.58 g mol^{-1}), [Acid] = 0.4 M in THF						
Reaction 5	96	82	8.0	1.6	6.4	90
Reaction 13	83	72	4.3	1.6	2.8	90
Modified AE & RME considering the reagents and intermediate formed in the reaction						
Reaction 5	72	61	-	-	-	-
Reaction 13	73	64	-	-	-	-
Simulation H: T_3P (1.1 eq, MW = 318.18 g mol^{-1}), [Acid] = 0.4 M in THF						
Reaction 5	96	82	8.6	2.2	6.4	90
Reaction 13	83	72	4.6	1.8	2.8	90
Modified AE & RME considering the reagents and intermediate formed in the reaction						
Reaction 5	54	45	-	-	-	
Reaction 13	64	55	-	-	-	

A full explanation of the metrics analysis can be found in the appendix

[a] Reaction refer to Scheme 2.6

For reaction 5 in Table 2.8 simulations A – H the PMI_{RRC} has a range of only 0.6 g g^{-1} (from 1.6 – 2.2 g g^{-1}) and 0.3 g g^{-1} for reaction 13 (1.5 – 1.8 g g^{-1}). Overall PMI has a range of 0.6 g g^{-1} (from 8.0 – 8.6 g g^{-1}) for reaction 5 and 0.3 g g^{-1} (4.3 – 4.6 g g^{-1}) for reaction 13. It is noteworthy that these ranges are very small. The range of PMI results can be related to the variance of the molecular weight of the reactants. When there is a large difference in molecular weight of reactants the values for PMI will be larger than if both substrates had a more equal molecular weight. The PMI value is also more weighted on the reactants than reagents, this could therefore be a consideration when screening a synthetic route. PMI_{RRC} on its own could be considered a possible alternative to PMI at a planning stage. This observation that PMI is only marginally affected in these simulations could enable chemists to take an unbiased look at how efficient their reaction is. However, when their process includes a solvent, concentration would need to be assessed independently.

As PMI_{RRC} is generally a much lower value than PMI_{Solv} or PMI_{WU} it could be used alone to comparing the chemistry of two different routes. This comparison would then identify the greatest *green potential*. For example, in a theoretical reactions 1 & 2 had metric analysis been performed and the PMI_{RRC} for reaction 2 produced a lower value, this would indicate that the actual chemistry of reaction 2 was an improvement compared to reaction 1.

When comparing the best yielding reactions from the eight separate amide coupling agents that have been covered in this metric study, several trends and observations are apparent in Table 2.9. Firstly, the overall yields for all the process are high, though this should be expected given how optimised a process being run on a large scale should be. The best yield was quantitative, and the worst was 84%.

Secondly the results for traditional AE are also high and range from 83 – 97% when only the reactants are considered. The range changes to 52 – 75% when s modified AE is calculated with the reactants included Table 2.9 (orange data). The next observation is that there is a large range in the traditional RME data with a range of 67 – 96% when only considering reactants. This range increases further to 30 – 56% when a modified RME is calculated which considers the reagents Table 2.9 (orange

data). These large changes in reported traditional and modified AE and RME have been seen throughout this chapter and the summary of amide reactions in Table 2.9 for a final time highlights the misleading values that could be generated if incorrect data is input into the calculation.

Table 2.9: Amide coupling reagents and corresponding metric values. Data generated from the literature.[141]

	AE (%)	Modified AE (%)	RME (%)	Modified RME (%)	PMI (g g^{-1})	PMI$_{RRC}$ (g g^{-1})	PMI$_{solv}$ (g g^{-1})	Yield (%)
Reaction 1 ($SOCl_2$)	97	75	87	56	5.7	1.8	3.9	92
Reaction 3 ($(COCl)_2$)	95	60	79	33	12.2	3.2	9.0	91
Reaction 5 (CDI)	96	55	96	45	8.7	2.2	6.4	89
Reaction 7 (DCC)	91	59	77	47	6.7	2.1	4.5	86
Reaction 9 (EDC)	87	59	79	53	8.5	2.6	5.9	92
Reaction 11 (PivCl)	94	52	94	43	15.0	2.3	12.6	100
Reaction 13 (IBCF)	83	68	67	50	4.9	2.0	2.9	84
Reaction 14 (T_3P)	96	54	81	30	8.1	3.3	4.7	88

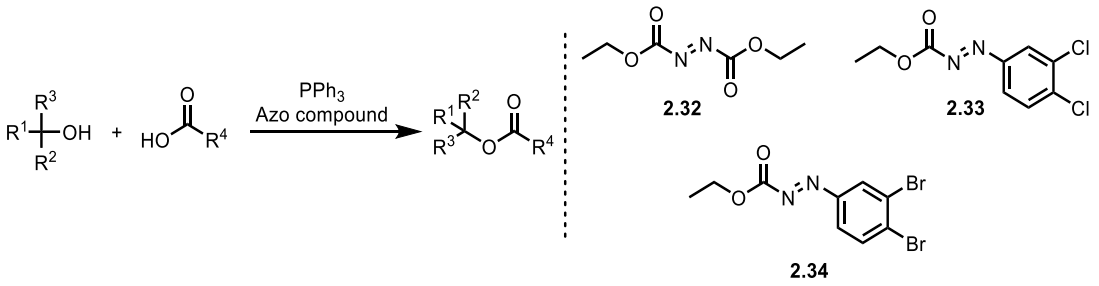
A full explanation of the metrics analysis can be found in the appendix

The final trend is with PMI and its derivatives. Overall PMI has a range from 4.9 – 15.0 g g^{-1} which is quite impressive for a synthetic process. The best and worst PMI$_{RRC}$ are 1.8 & 3.3 g g^{-1} respectively. As previously mentioned PMI$_{RRC}$ relates to only a small part of the overall PMI and therefore the reaction with lowest PMI$_{RRC}$ could be regarded as having the greatest *green potential*. By this logic looking at the data presented in Table 2.9 the reaction with lowest PMI$_{RRC}$ should have the greatest potential to be the *greenest* reaction, excluding all other influencing factors (solvent, concentration, temperature etc). The reaction with lowest PMI$_{RRC}$ is reaction 1 which uses $SOCl_2$. Therefore (based solely on metrics) this value would indicate that this coupling agent would be one of the best choices for amide coupling or that this coupling agent has the *greenest potential* based on the comparative PMI$_{RRC}$ values. The notion that $SOCl_2$ could be one of the more favourable coupling agents is supported by the OPRD review which states that $SOCl_2$ is one of the most common and widely used reagents for amide synthesis.[134] The reagent is generally cheap and easy to use. The side products produced are gaseous (HCl & SO_2) which eliminates the need for additional purification and can help reduce processing steps and therefore time which will reduce costs. However, the side products are toxic and corrosive which will require specialised equipment to contain and the waste will need treatment before it can be disposed of (or recycled).

2.2.3. PMI analysis of Mitsunobu reaction

The Mitsunobu reaction was selected as a second model reaction for our simulations to see if the same trends and observations could be detected in another process.

The Mitsunobu reaction allows the conversion of primary and secondary alcohols to esters. This reaction was well suited to a metrics analysis as it utilises two reagents, compared to one for an amide coupling. This additional reagent was important because reagent variation was not observed to impact the metrics for amide coupling. Triphenylphosphine (PPh_3) is combined with an azo-compound such as diethyl azodicarboxylate (DEAD) **2.32**, ethyl 2-(3,4-dichlorophenyl)diazene-1-carboxylate (DCPEAC) **2.33** or ethyl 2-(3,4-dibromophenyl)diazene-1-carboxylate (DBPEAC) **2.34** to generate a phosphonium intermediate that binds to the alcohol oxygen, activating it as a leaving group. Subsequent nucleophilic substitution with a carboxylate generates the desired ester together with triphenylphosphine oxide as a reasonably safe and stable side product.



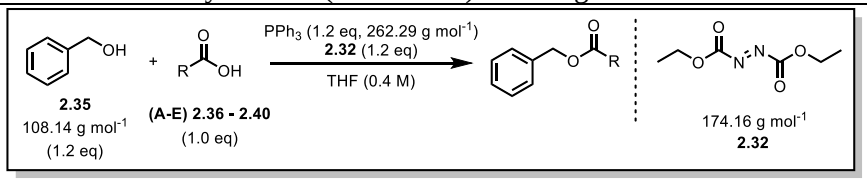
Scheme 2.12: Mitsunobu process and reagents.

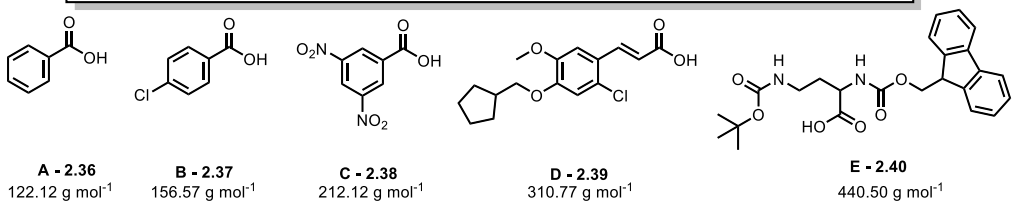
For the Mitsunobu simulations benzyl alcohol **2.35** was coupled with several carboxylic acids **2.36** – **2.40** with molecular weights ranging from 122.12 to 440.50 g mol^{-1}. The reaction conditions for Mitsunobu reactions using DEAD **2.32**, DCPEAC **2.33** and DBPEAC **2.34** were collected and processed using the Chem21 metrics toolkit. The simulations considered variations in yield, concentration and excess of reagents as before. The results for the various simulations using DEAD **2.32** are displayed in Table 2.10. The simulations for the other Mitsunobu reactions using DCPEAC **2.33** and DBPEAC **2.34** can be found in appendix, A1 & A2.

A comparison of the same reaction of benzyl alcohol **2.35** with benzoic acid **2.36** at the same concentration, but with varying yield 90 – 50% is shown in Table 2.10 simulations 1 – 4. For these four simulations the PMI varies from 15.7 g g^{-1} to 28.3 g g^{-1} with a yield varying from 90 – 50%. For the reaction with benzoic acid **2.36** altering the concentration from 0.4 M to 0.8 M when the yield remains constant at 90% increases the PMI by 5.8 g g^{-1}, entry A **2.36** in Table 2.10 simulations 1 and 6. This observation that the yield and concentration have a similar effect on a reactions PMI was also observed in the study with amide coupling reagents. This simulation again highlights a potential for incorrect identification of a problematic or unfavourable reaction.

If the incorrect example to determine the greenness of a reaction was chosen, a conclusion could be made that the coupling between benzyl alcohol **2.35** and benzoic acid **2.36** with a PMI of 15.7 g g^{-1} is less favourable than the coupling between benzyl alcohol **2.35** and an amino-protected ornithine **2.40** with a PMI of 6.9 g g^{-1}, Table 2.10 simulation 1 entry A **2.36** & E **2.40**. In this simulation both reactions are assigned the same yield, concentration and reaction stoichiometry. However, this comparison does not appreciate the *green potential* from the reaction as this difference in PMI is solely dependent on the MW of the reactants as was observed previously with amide coupling. This once again highlights a limiting factor with PMI and displays how a favourable PMI could be obtained.

Table 2.10: Green metrics simulations applied on the Mitsunobu reaction of benzyl alcohol **2.35** with various carboxylic acids (**2.36 – 2.40**) featuring a different molecular weight.





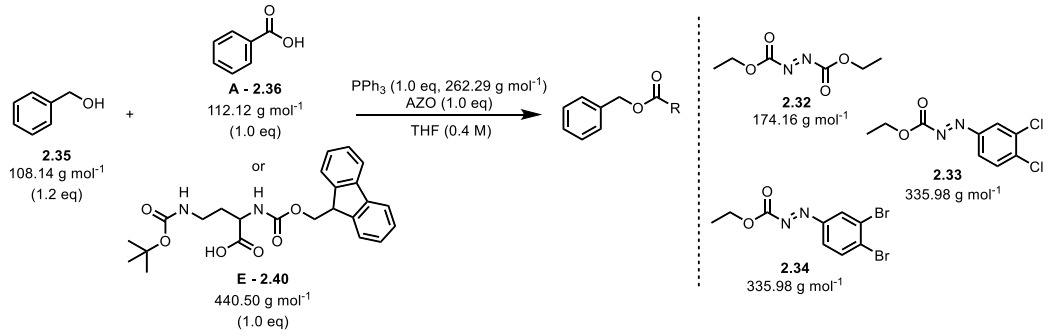
A - 2.36 122.12 g mol^{-1} | **B - 2.37** 156.57 g mol^{-1} | **C - 2.38** 212.12 g mol^{-1} | **D - 2.39** 310.77 g mol^{-1} | **E - 2.40** 440.50 g mol^{-1}

Carboxylic Acid	Traditional AE (%)	Traditional RME (%)	PMI (g g^{-1})	PMI$_{RRC}$ (g g^{-1})	PMI$_{Solv}$ (g g^{-1})	Yield (%)
Simulation 1: [Acid] = 0.4 M, Yield = 90%						
A **2.36**	92	76	15.7	4.1	11.6	90
B **2.37**	93	78	13.7	3.6	10.0	90
C **2.38**	94	80	11.4	3.2	8.2	90
D **2.39**	96	82	8.8	2.7	6.2	90
E **2.40**	97	84	6.9	2.3	4.7	90
Simulation 2: [Acid] = 0.4 M, Yield = 80%						
A **2.36**	92	67	17.7	4.6	13.1	80
B **2.37**	93	69	15.4	4.1	11.3	80
C **2.38**	94	71	12.8	3.6	9.2	80
D **2.39**	96	73	9.9	3.0	6.9	80
E **2.40**	97	74	7.8	2.6	5.2	80
Simulation 3: [Acid] = 0.4 M, Yield = 70%						
A **2.36**	92	59	20.2	5.2	15.0	70
B **2.37**	93	60	17.6	4.7	12.9	70
C **2.38**	94	62	14.6	4.1	10.5	70
D **2.39**	96	64	11.4	3.4	7.9	70
E **2.40**	97	65	8.9	2.9	6.0	70
Simulation 4: [Acid] = 0.4 M, Yield = 50%						
A **2.36**	92	42	28.3	7.3	20.9	50
B **2.37**	93	43	24.6	6.6	18.0	50
C **2.38**	94	44	20.4	5.7	14.7	50
D **2.39**	96	46	15.9	4.8	11.1	50
E **2.40**	97	47	12.5	4.1	8.4	50
Simulation 5: Scale reaction x 5:, [Acid] = 0.4 M, Yield = 90%						
A **2.36**	92	76	15.7	4.1	11.6	90
B **2.37**	93	78	13.7	3.6	10.0	90
C **2.38**	94	80	11.4	3.2	8.2	90
D **2.39**	96	82	8.8	2.7	6.2	90
E **2.40**	97	84	6.9	2.3	4.7	90
Simulation 6: [Acid] = 0.8 M, Yield = 90%						
A **2.36**	92	76	9.9	4.1	5.8	90
B **2.37**	93	78	8.6	3.6	5.0	90
C **2.38**	94	80	7.3	3.2	4.1	90
D **2.39**	96	82	5.7	2.7	3.1	90
E **2.40**	97	84	4.6	2.3	2.3	90

A full explanation of the metrics analysis can be found in the appendix

To illustrate the effect that the molecular weight of the reagents has on the metric data benzyl alcohol **2.35** was simulated reacting with two carboxylic acids **2.36** & **2.40** Table 2.11. For each simulation the first entry A was a low molecular weight compound benzoic acid **2.36** (112.12 g mol^{-1}) and the second entry E with a much higher molecular weighted compound amino-protected ornithine **2.40** (440.50 g mol^{-1}). In Table 2.11 each simulation 1 – 3 PPh_3 (262.29 g mol^{-1}) was either combined with DEAD **2.32** (174.16 g mol^{-1}), DCPEAC **2.33** (335.98 g mol^{-1}) or DBPEAC **3.34** (335.98 g mol^{-1}). The yield, concentration and excess reagent were fixed in these simulations so any change in the PMI result could be fairly assessed.

Table 2.11: Mitsunobu simulations altering the AZO-coupling reagent for reactions with a small and large molecular weight difference between the reactants.



Carboxylic Acid	Traditional AE (%)	Traditional RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{Solv} (g g^{-1})	Yield (%)
Simulation 1: [Acid] = 0.4 M, Yield = 90%, DEAD as coupling reagent						
A **2.36**	92	76	15.7	4.1	11.6	90
E **2.40**	97	84	6.9	2.3	4.7	90
Simulation 2: [Acid] = 0.4 M, Yield = 90%, DCPEAC as coupling reagent						
A **2.36**	92	76	6.2	4.5	11.6	90
E **2.40**	97	84	7.1	2.5	4.7	90
Simulation 3: [Acid] = 0.4 M, Yield = 90%, DBPEAC as coupling reagent						
A **2.36**	92	76	16.7	5.1	11.6	90
E **2.40**	97	84	7.4	2.7	4.7	90

A full explanation of the metrics analysis can be found in the appendix

The PMI_{RRC} results ranged from 4.1 – 5.1 g g^{-1} with benzoic acid **2.36** and from 2.3 - 2.7 g g^{-1} with ornithine **2.40**. The overall PMI ranged from 15.7 – 16.7 g g^{-1} with benzoic acid A **2.36** and from 6.9 – 7.4 g g^{-1} ornithine E **2.40**. These findings were similar to amide coupling results in that the effect on PMI is more dependent on the reactants than the reagents, regardless of the number of reagents used in the reaction. When comparing two processes it may be logical to assume the process employing only one reagent would perform more favourable than the process using two reagents.

This may not be the case when looking at PMI as only the mass is considered and the sum of two moderate weight reagents may actually be lower than the mass of one bulky metal complex!

2.3. Conclusions

Throughout this chapter several worked examples have shown the limitations and pitfalls of mass-based reaction metrics and how several common metrics could be misunderstood and misused.

During the analysis of mass-based reaction metrics and metric toolkits one early pitfall was the problems that can arise with issuing flags for reaction components and parameters. This is because new data can emerge, and legislation is constantly changing in the context of a chemical's hazards and risks in use and therefore the rules and/or rankings that were in place when the system was designed may have changed. This is not to say flags and colour coding systems should be avoided in analysis toolkits, but rather operators and users need to be familiar with the underlying principles which are being used to score their work and guide their choices.

The need for understanding the underlying principles of a metric was also explored with the use of AE & RME. For these metrics the user's input is critical for determining an accurate result. This was shown through the analysis of several amide formation reactions taken from the literature and practical experimentation. The consequence of an incorrect assumption, balancing of an equation or misinterpretation of a component was demonstrated by calculating the traditional and modified AE & RME for the given reactions and then performing a series of simulations with the data. The most critical parameter for AE & RME is inclusion of the correct components into the calculation. Throughout this chapter reaction mechanisms have been included to highlight the importance of understanding what is happening during a process and then applying this to correctly include the relevant components into the calculation for a modified AE & RME.

When the direct comparison of mass-based reaction metrics and PMI were examined, some potential pitfalls were discovered. Subsequently ways to avoid these pitfalls and ensure a fair metric comparison could be made between reactions has been described. PMI has been adopted by the pharmaceutical industry as their favoured metric due to its lack of ambiguity, but care needs to be taken when using PMI to compare different reactions and processes. Through a similar process as for AE & RME, analysis and simulations were performed on data taken from the literature for amide formation and Mitsunobu reactions. This metric data revealed how misleading PMI data could be when comparing values without considering all the parameters of the process. If a comparison between two processes is to be fairly made, then several parameters need to be considered. The yield, concentration and molecular weight of the reactants should be as close as reasonably possible in order to compare the performance of the process. This is to ensure the PMI value being compared is reflective of the process not the difference in concentration or molecular weight. By performing a simulation which scales these parameters the *green potential* of a methodology can be observed. This analysis could help in early stage discovery work as a procedure taken from the literature may have on first analysis have an undesirably high PMI but after the key parameter are scaled the user discovers that the high PMI results was due to the reported concentration. Therefore, the *green potential* of the process may be worth exploring.

Reaction metrics and toolkits are a powerful resource for generating information about the efficiency of a process. They can be applied to a process regardless of the amount optimisation it has undergone and to any scale, from milligram to multi tonne. But as discussed in this chapter caution should be taken when comparing different processes and the user must remember that no metric should be used in isolation. Rather a holistic review of a process should be considered. This holistic review will generally be scaled to suit the process, as described in the CHEM21 metrics toolkit where small scaled reactions are analysed by a zero-pass suite of metrics the whole way up to third pass for commercial processes.[101] The ideal scenario would be a life cycle analysis (LCA) which should cover every aspect of a process ranging from economic to environmental and health and safety parameters but given how detailed and time consuming this can be is generally only performed when a process is commercialised.

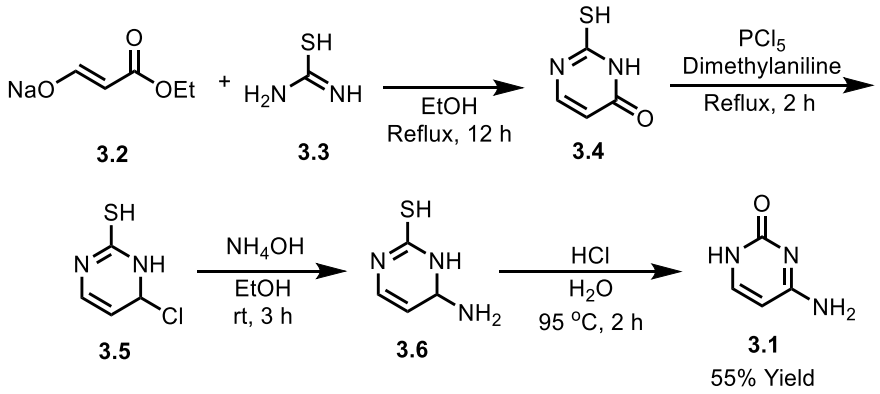
Chapter 3

Synthesis of Cytosine and 1,3-oxathiolanes leading to Lamivudine

3.1. Introduction

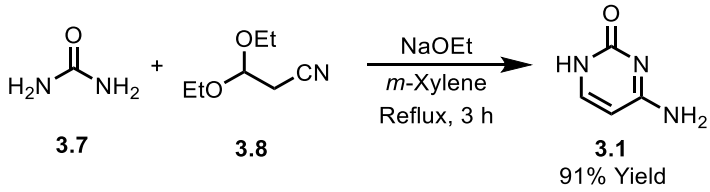
3.1.1. Cytosine and Fluorocytosine

Cytosine **3.1** was discovered in 1894 by Kossel and Neumann and first synthesised in 1903 in the same laboratory.[142] The first reported synthesis of **3.1** is shown in Scheme 3.1. It involved the condensation of the sodium salt of ethyl formylacetate **3.2** with pseudothiourea **3.3**, resulting in the formation of a 2-mercapto-6-oxypyrimidine **3.4**. Then addition of phosphorus pentachloride converted this intermediate to the 2-mercapto-6-chloropyrimidine **3.5**, which was converted into aminopyrimidine **3.6** by the action of ammonia. This pyrimidine could then be treated with hydrochloric acid and converted to cytosine **3.1**.



Scheme 3.1: First reported synthesis of cytosine **3.1**.

More resent methods for manufacturing cytosine **3.1** involve the condensation between urea **3.7** and 3,3-diethoxypropionitrle **3.8** under basic conditions Scheme 3.2.[143]



Scheme 3.2: Synthesis of cytosine **3.1** by condensation of **3.7** with **3.8**.

Fluorocytosine **3.9** alongside amphotericin B has been recommended by the World Health Organisation (WHO) as the first line treatment against *Cryptococcal meningitis* (CM). This is the leading cause of adult meningitis in sub-Saharan Africa, and contributes up to 20% of AIDS-related mortality in low-income and middle-income countries every year.[144, 145] Fluorocytosine **3.9** is also of interest to industry as a

precursor for Capecitabine **3.10** (anticancer) and Emtricitabine **3.11** the fluorinated analogue of Lamivudine **3.12**.

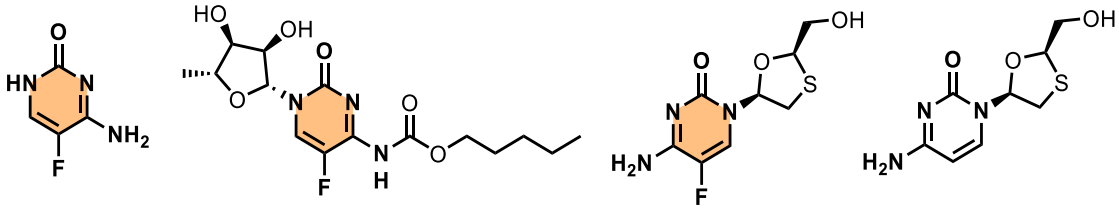
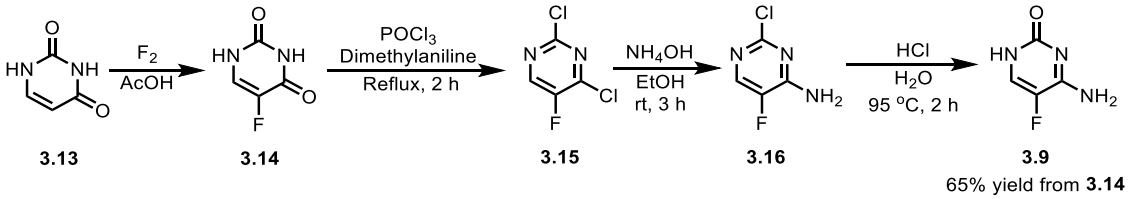


Figure 3.1: Fluorocytosine core in medicine.

While it is difficult to confirm, the reported methods for the synthesis of fluorocytosine **3.9** found in the patent literature involve a 4-step process beginning with uracil **3.13**. Uracil **3.13** is directly fluorinated with F_2 gas in acetic acid to give 5-fluorouracil **3.14** which is chlorinated with $POCl_3$ to give 2,4-dichloro-5-fluoropyrimidine **3.15**. This intermediate is then reacted with aqueous ammonia solution to give **3.16** which is hydrolysed with concentrated hydrochloric acid to produce fluorocytosine **3.9** in 65% overall yield from 5-fluorouracil **3.14** Scheme 3.3.[146-148]



Scheme 3.3: Manufacturing process for fluorocytosine **3.9**.

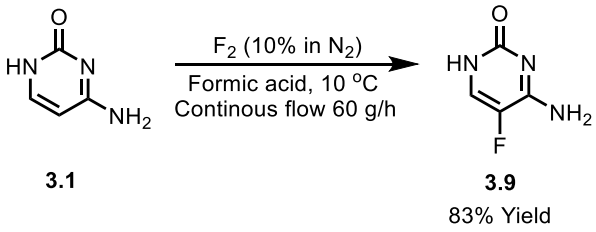
While an overall yield of 65% may be reasonable for a three-step process, applying metric analysis highlights several issues, Table 3.1. The route has several drawbacks; multistep sequence, low yield, poor traditional atom economy and a very low traditional reaction mass efficiency. There was also use of hazardous solvent (diethyl ether) and some reagents were used in great excess. The poor traditional AE is due to the combination of three-steps and the introduction of two chlorine atoms which do not make it into the final product.

Table 3.1: Metric analysis of the old industrial route to fluorocytosine **3.9**.

Metric parameter	Scheme 3.3
Yield (%)	65
Traditional Atom Economy (%)	31
Traditional RME (%)	7
PMI reaction (g g^{-1})	192
Solvent choice	
Catalyst?	
Recoverable catalyst?	
Critical element	
Energy	
Work-up	
Health and safety	
Chemical of concern?	

* *Flag system:* Green flag preferred, amber flag acceptable but some issues and red flag is undesirable. *A full key and explanation of the metric analysis and flag classification can be found in the appendix.*

In the light of these issues and through the Chem21 consortium Sanford *et al* at Durham University developed a process for a direct fluorination of cytosine **3.1** using elemental fluorine gas Scheme 3.4 which has been successfully scaled up for use on a pilot plant.[20] This process has been developed to be used with a flow reactor has the capacity of producing 60 g per hour per reaction channel.[20, 104]

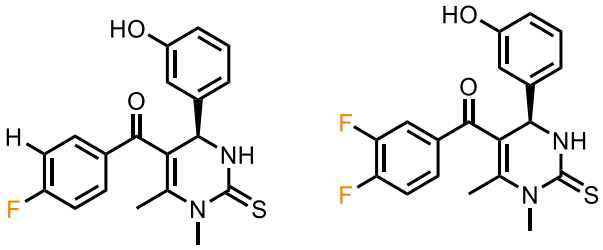


3.1 **3.9**
83% Yield

Scheme 3.4: Direct fluorination of cytosine **3.1**.

Given the only difference between and Emtricitabine **3.11** and Lamivudine **3.12** is the presence of a fluorine atom at C-5 on the pyrimidine ring easy access to fluorocytosine **3.9** could make access to Emtricitabine **3.11** significantly more economical. It is common for medicinal chemists to add a fluorine atom to a molecule as it is well known that a fluorine can significantly improve the potency of a drug.[149] Figure 3.2

shows compound **3.17** and **3.18,** the difluorinated analogue **3.18** showed a 5-fold improvement in the inhibition of tumour and nontumor cell lines compared to the monofluorinated compound.[150]



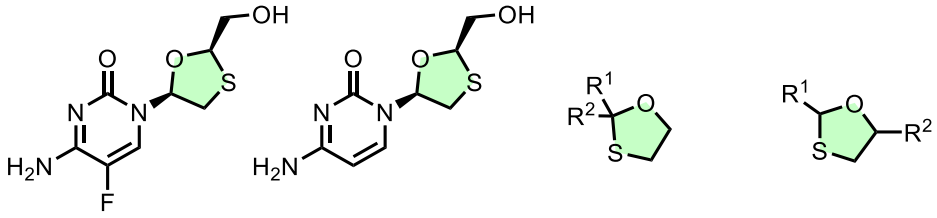
3.17
(*R*)-mono97

3.18
(*R*)-fluorastrol

Figure 3.2: Improvement in potency including a fluorine.

3.1.2. 2,5-Disubstituted-1,3-oxathiolanes

1,3-Oxathiolanes are a unique class of compounds which are not commonly found in the literature. One use of oxathioacetals **3.19** have been as protecting groups whereas 2,5-disbustituted-1,3-oxathiolanes have received attention over the last three decades when incorporated as "unnatural" sugar moieties into modified nucleosides Figure 3.3. 1,3-Oxathiolanes have demonstrated great potential as potential therapeutic agents. Areas of possible use include; antitumor agents, inhibitors of hepatitis B (HBV) and as nucleoside reverse transcriptase inhibitors (NRTIs) which are used as treatment for human immunodeficiency virus (HIV).[151-165]



3.11
Emtricitabine

3.12
Lamivudine

3.19
Oxathioacetal

3.20
2,5-disubstituted oxathiolane

Figure 3.3: Oxathiolane heterocycle core structure.

There are numerous reactions that can be explored to form a 2,5-disubstituted-1,3-oxathiolane, several methods are shown in Scheme 3.5. These reactions all lead to the 2,5-disubstituted-1,3-oxathiolene core through a condensation reaction between a thiol/hydroxythiol and an aldehyde or ketone. These routes summarise the synthetic

pathway to obtain the desired motif required to build emtricitabine **3.11** and / or lamivudine **3.12**.

Figure 3.4 contains a summary for oxathiolane **3.21** which will feature in the rest of the chapter. The figure shows the possible isomers their stereochemical configuration and relationships to each other, is also serves as a quick reference to the nomenclature used in this chapter.

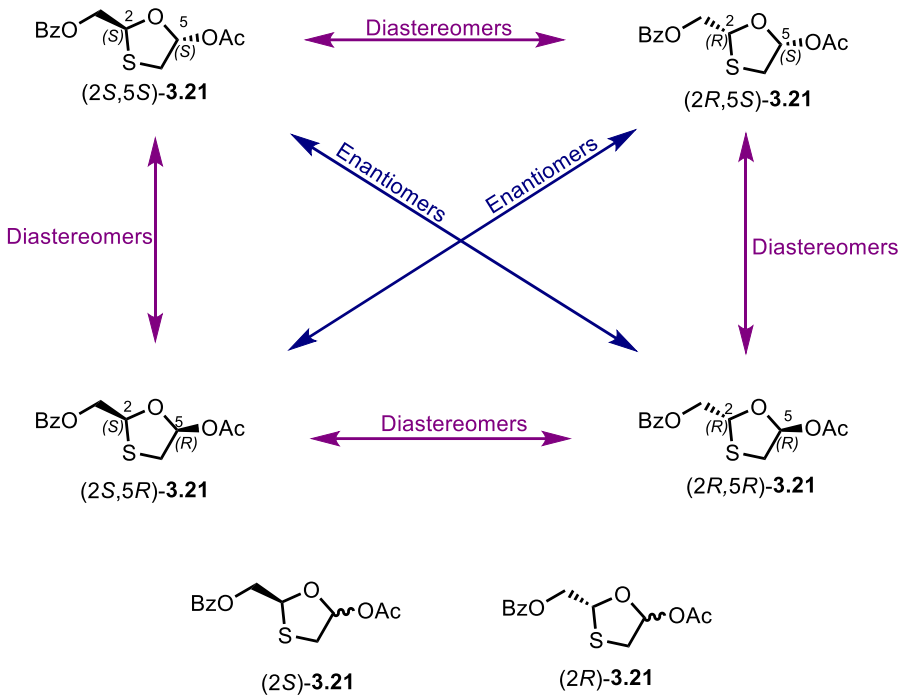
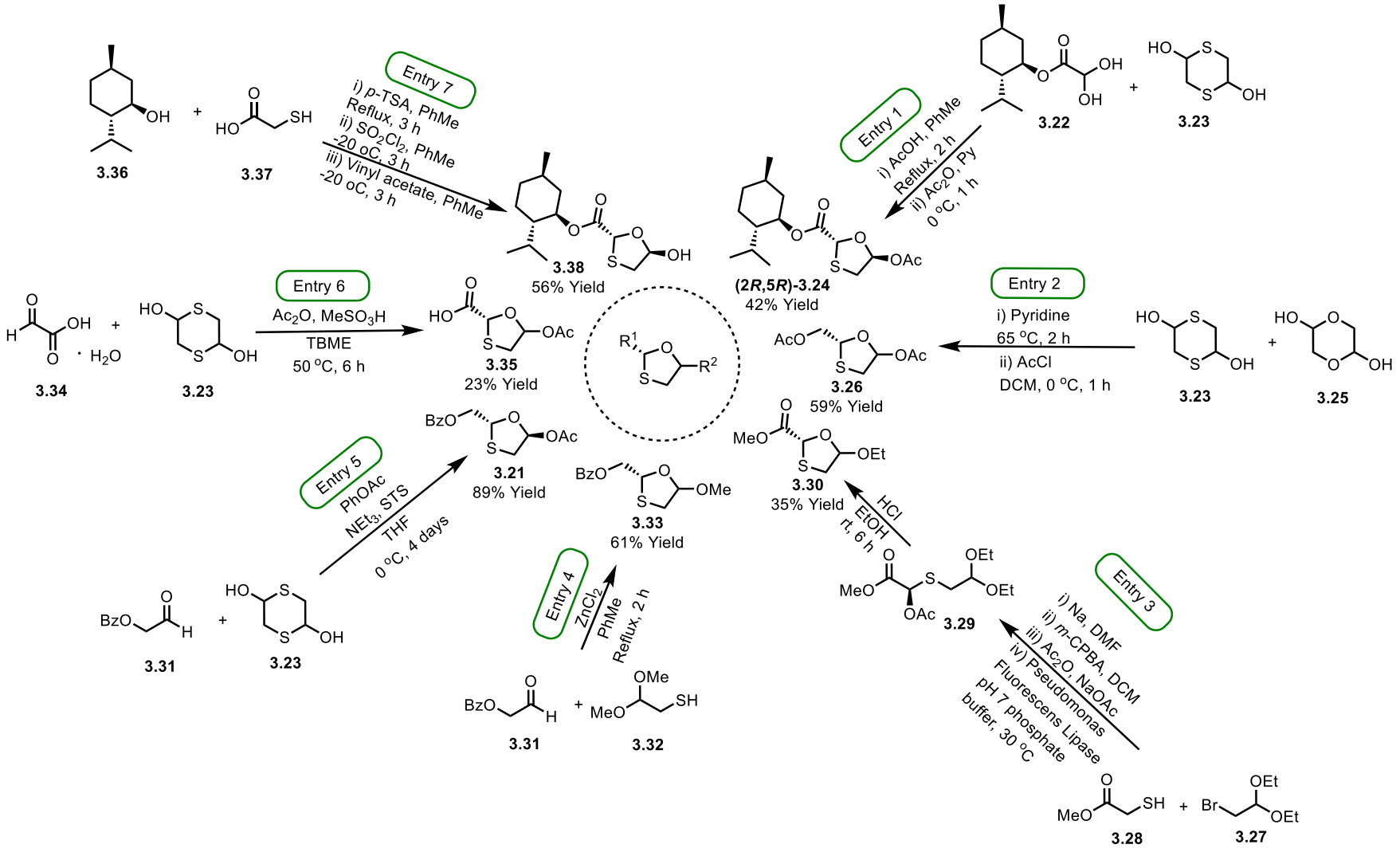


Figure 3.4: Stereoselective assignments of 2,5-disubstituted-1,3-oxathiolane **3.21**.

In Scheme 3.5 entry 1 L-menthyl glyoxylate monohydrate **3.22** and 1,4-diathiane-2,5-diol **3.23** are coupled together followed by acetylation to give **3.24** which can fortunately be obtained as a single isomer (2*R*,5*R*)-**3.24** by recrystallisation from hexane containing a catalytic quantity of triethylamine.[166] In entry 2 the condensation of glycolaldehyde **3.25** and thiol **3.23** is driven by pyridine which also acts as the solvent for the reaction, the alcohol produced is immediately acetylated with acyl chloride to give oxathiolane **3.26** as a racemic mixture.[167] Entry 3 takes a different approach to form oxathiolane **3.30** than the other entries. For entry 3 the stereochemistry at C2 is formed through a enzymatic resolution with lipase and then deprotection of the chiral acetal with HCl leading to *in situ* cyclisation forming the oxathiolane with C2 maintain the desired configuration.[155]

Entry 4 was one of the early routes used to obtain a large quantity of oxathiolane **3.33** for conversion into Lamivudine **3.12**.[168, 169] It is a straightforward condensation between aldehyde **3.31** and thiol **3.32**. The reaction shown in entry 5 is the second enzymatic process examined. It was reported that the configuration of C-(2*S)* could be controlled with different enzymes. C-(2*S*) could be obtained with CAL B using toluene and (2*R*) with subtilisin Carlsberg using THF. [153] Oxathiolane **3.21** could be formed through a cascade reaction using, aldehyde **3.31** and thiol **3.23** with base, enzyme and acetate donor. Entry 6 saw the condensation of glyoxylic acid monohydrate **3.24** with thiol **3.23** under azeotropic conditions to give a hydroxy acid which was acetylated with acetic anhydride and a catalytic amount of methane sulphonic acid to form carboxylic acid **3.35**. Extensive resolution was required to separate the isomers. Finally, entry 7 highlights a recent example of a route which utilises low cost and widely available starting material to obtain an oxathiolane intermediate **3.38**.[170] The route presented in entry 7 to oxathiolane **3.38** can be accomplished in a one pot with a 56% overall yield and >99% purity by reacting L-menthol **3.38** with thiol **3.37** followed with a controlled addition of sulfuryl chloride and vinyl acetate.

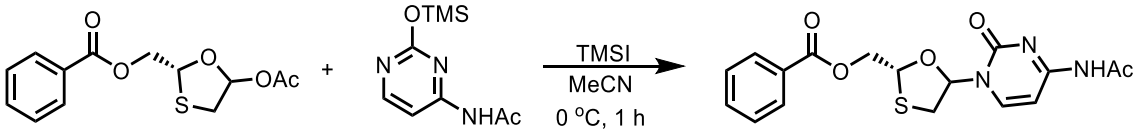


Scheme 3.5: Routes for the synthesis of 2,5-disubstituted-1,3-oxathiolanes.

3.1.3. Emtricitabine 3.11 and Lamivudine 3.12

Emtricitabine **3.11** and Lamivudine **3.12** are antiretroviral drugs used to prevent and treat HIV/AIDS.[171, 172] Both these compounds are used as part of combinational therapies for the treatment of HIV. Sales in 2019 for the drug Atripla (combination of Bristol Myers Squibb's efavirenz plus Gilead's emtricitabine and tenofovir disoproxil fumarate) was 501 million sales in 2019.[173]

Coupling of cytosine **3.1** or Fluorocytosine **3.9** with a 2,5-distustututed-1,3-oxathiolane is the most frequent method of synthesising this type of molecule. Several papers and patents have described the coupling of 2,5-distustututed-1,3-oxathiolanes with silylated of cytosines by a silyl-Hilbert-Johnson (or Vorbrüggen) reaction. [152, 153, 155, 159, 160] An example of this is shown in Scheme 3.6, oxathiolane **3.34** is coupled with protected cytosine **3.39** and trimethylsilyl iodide (TMSI) used to promote the reaction.



3.34 **3.39** **3.40**
51% Yield
(mixture of diastereomers)

Scheme 3.6: Example of a Vorbrüggen coupling between a 2,5-distustututed-1,3-oxathiolane and protected cytosine.

3.1.4. Chapter aims

The synthesis of emtricitabine **3.11** and lamivudine **3.12** is not straightforward given the unusual nature of both parts of the molecule and presence of two stereocentres. There are several possible routes which can be chosen to obtain the target compound, each of which possess their own unique challenges. The following chapter will look to optimise areas within the synthetic route to Lamivudine **3.12**. Firstly, we focused on cytosine **3.1** as this is a key intermediate of Lamivudine **3.12**. Then attention was turned to the synthesis of 2,5-disubstututed-1,3-oxathiolanes and synthesising optically pure material without the need for chiral resolution. Once access to both compounds was possible, we examined the method of coupling cytosine **3.1** with a 1,3-oxathiolane. The Vorbrüggen reaction has been a standard procedure in nucleoside

synthesis so we were interested to see if an alternative procedure could be developed or if modifications could be made to it.

Routinely a process is initiated from the cheapest commercially available material, which is generally produced in the fine chemical sector in relatively small quantities < 1000 kg per annum. While this is acceptable it does not truly reflect the complete synthesis of a compound nor show the full impact of its manufacture. The following research and optimisation studies will begin from commercially available bulk chemicals (>10,000 kg per annum) and will be compared to the state of the art methods described in the literature via metric analysis using the Chem21 Metrics Toolkit.[101] This metric analysis will highlight any fundamental improvements in the synthesis and allow a direct comparisons between the processes.

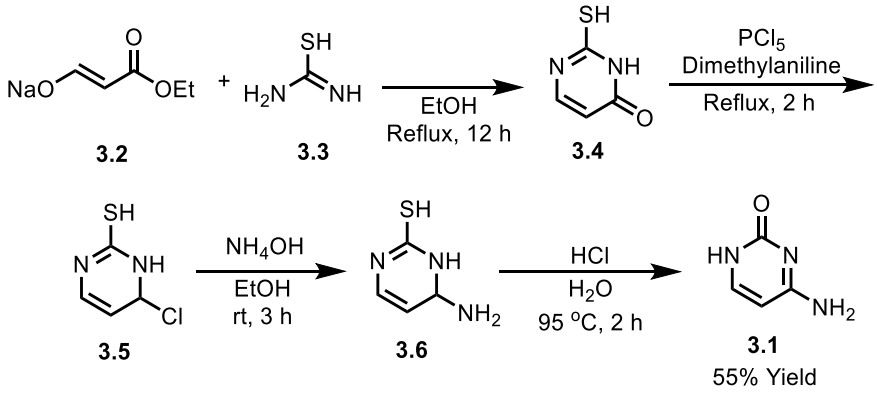
3.2. Results and Discussion

3.2.1. Synthesis of Cytosine

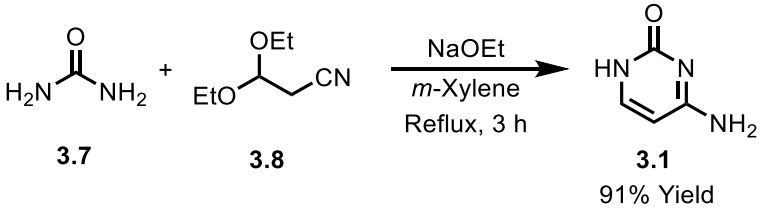
Analysis of reactions using metrics allows problematic areas within a synthetic route to be identified. Table 3.2 contains the Chem21 first pass metric analysis of the original route and a modern patent route to cytosine **3.1**. Table 3.2 Entry 1 is the original synthesis of cytosine and Entry 2, an improved patented route. While the numerical metrics have all improved in Entry 2, the flag classifications are identical for both entries. In Table 3.2 Entry 2, the synthetic route to cytosine **3.1** consists of a single step which involves a condensation reaction between urea **3.7** and 3,3-diethoxypropionitrile **3.8** Scheme 3.8.

This newer process represents a significant improvement when compared to the original synthesis, Table 3.2 Entry 2 vs Entry 1. Even though Table 3.2 Entry 2, shows an improvement some issues are still present; solvent choice, energy required (reaction temperature) and the atom economy is poor. The low atom economy can be attributed to the choice of nitrile starting material.

Given these issues optimisation studies were performed to investigate the use of alternative solvents, reaction temperature and starting material in this reaction.



Scheme 3.7: First reported synthesis of cytosine **3.1**.



Scheme 3.8: Synthesis of cytosine **3.1** by condensation with urea **3.7** and 3,3-diethoxypropionitrile **3.8**.

Table 3.2: Metric data for the synthetic routes to cytosine **3.1** Scheme 3.8.

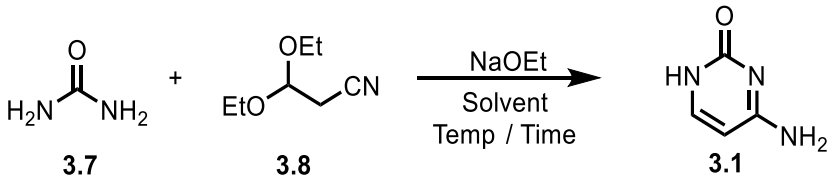
Metric parameter	Entry 1 Scheme 3.7	Entry 2 Scheme 3.8
Yield (%)	54.8	90.8
Traditional Atom Economy (%)	29.3	41.4
Traditional RME (%)	3.8	34.4
PMI reaction (g g^{-1})	826.1	111.8
PMI reagents, reactant, catalyst (g g^{-1})	11.0	3.7
PMI solvent (g g^{-1})	813.3	106.5
Solvent choice		
Catalyst?		
Recoverable catalyst?		
Critical element		
Energy		
Work-up		
Health and safety		
Chemical of concern?		

Flag system: Green flag preferred, amber flag acceptable but some issues and red flag is undesirable.
A full key and explanation of the metrics analysis and flag classification can be found in the appendix.

3.2.1.1. Optimisation of reaction conditions – Solvent

The use of *m*-xylene and other aromatic hydrocarbons can be advantageous as their properties aided in purification by forming an azeotrope with ethanol. Ethanol is produced during the reaction by hydrolysis of nitrile **3.8.** The azeotrope formed with *m*-xylene enables a simplified purification procedure as ethanol can be removed along with *m*-xylene and the remaining solvent can then form a biphasic mixture when water is added, to dissolve and remove the pyrimidone salt. The metric analysis Table 3.2 highlighted *m*-xylene as unfavourable as aromatic hydrocarbons have been classed as problematic by the Chem21 solvent selection guide, meaning special precautions would be required at pilot plant scale.[80] Therefore a series of reactions were performed to search for a suitable alternative solvent. We began by screening solvents which were recommended and classified as a green flag by the Chem21 solvent guide Table 3.3.[80, 101]

Table 3.3: Solvent screen on the synthesis of cytosine **3.1**.



3.7 **3.8** **3.1**

Entry	Solvent	Temperature	Time	Yield (%)
1	*m*-Xylene	90 °C	8 h	91
		130 °C	3 h	91
2	Toluene	90 °C	8 h	72
		110 °C	4 h	94
3	*p*-Cymene	90 °C	8 h	89
		130 °C	4 h	90
4	Limonene	90 °C Room temperature	8 h 24 h	0
5	Diethyl succinate	90 °C Room temperature	8 h 24 h	0
6	Diethyl carbonate	90 °C Room temperature	8 h 24 h	0
7	Ethyl acetate	75 °C Room temperature	8 h 24 h	0
8	Isopropyl acetate	90 °C Room temperature	8 h 24 h	0
9	Cyrene	90 °C Room temperature	8 h 24 h	0
10	Anisole	150 °C	2 h	17
11	Ethanol	Room temperature	12 h	0
		70 °C	6 h	88
12[a]	*t*-Butanol	Room temperature	12 h	0

[a] Sodium *t*-butoxide was used in place of ethoxide

Due to *m*-xylene performing well in the reaction toluene and *p*-cymene were the first solvents to be investigated due to their similar physical properties and proximity in solvent space. Table 3.3 Entry 2 & 3 shows that toluene and *p*-cymene are viable substitutes for *m*-xylene as the yields obtained are equivalent although a slightly longer reaction time is required. *p*-Cymene is a bioderived aromatic hydrocarbon derived from limonene which in turn is derived from citrus peel.[174] The use of limonene, diethyl succinate, diethyl carbonate and ethyl/isopropyl acetate were all also examined Table 3.3 Entry 4 – 8 but all were unsuccessful.

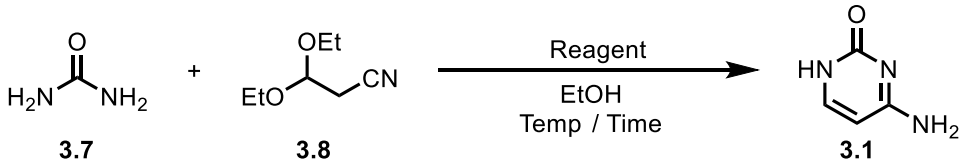
When limonene was used numerous side products where formed, while it was not possible to identify every product the majority were formed by addition to one or both of the alkenes present in limonene. Analysis of the crude proton NMR showed that the typical signal for both alkenes in had vanished.

Anisole Table 3.3 Entry 10 showed some promise but due to the high temperatures required was deemed unsuitable. When the reaction was performed in a solution of sodium ethoxide and ethanol a yield of 88% was obtained at room temperature and elevated temperature, Table 3.3 Entry 11. The use of *t*-butanol Table 3.3 Entry 12 was unsuccessful presumable as *t*-butanol is too hindered and cannot react with nitrile 3.8. The discovery that ethanol could be used as the reaction solvent was surprising and eliminated the need to use any aromatic solvent. It should also be noted that when this work was first performed toluene was categorised as amber but today would most likely be considered red – unsuitable due its suspected reprotoxicity properties.

3.2.1.2. Optimisation of reaction conditions – Reagent

With a more suitable solvent to in place a brief attempt was made to screen possible alternatives to sodium ethoxide. Several acids and bases where screened and 0.4 M ethanolic hydrochloric acid performed just as well as sodium ethoxide Table 3.4 Entry 1 & 8. Sodium, potassium and lithium hydroxides Table 3.4 Entry 2 - 4 all failed to yield any product and the urea decomposed giving off ammonia and carbon dioxide. Potassium *t*-butoxide Table 3.4 Entry 7 rapidly produced a black tar when nitrile **3.8** was added, this tar could be a polymeric residue formed by the polymerisation of deprotected nitrile **3.8** reacting with itself instead of urea **3.7**. When aluminium and iron (III) chloride were examined Table 3.4 Entry 5 & 6 no product could be detected in either case, and the starting nitrile could be recovered, it would appear that Lewis acids are not able to deprotect nitrile **3.8** whereas this reaction is favourable when a Brønsted acid such as HCl is chosen.

Table 3.4: Reagent effect on the synthesis of cytosine **3.1**.



3.7 **3.8** **3.1**

Entry	Reagent	Temperature	Time	Yield (%)
1	NaOEt	70 °C	6 h	88
2	NaOH	70 °C	6 h	0
3	KOH	70 °C	6 h	0
4	LiOH	70 °C	6 h	0
5	$AlCl_3$	70 °C	6 h	0
6	$FeCl_3$	70 °C	6 h	0
7	*t*-BuOK	70 °C	6 h	0
8	0.4 M HCl	70 °C	6 h	87
9	0.4 M HCl	Room temperature	12 h	6

With the reaction proceeding with 0.4 M ethanolic hydrochloric acid a metric comparison of two reactions was performed. The metric analysis was used to determine the effect that replacing NaOEt with 0.4 M ethanolic hydrogen chloride had on the overall process. The results are presented in Table 3.5 and it is clear entry 2, using 0.4 M HCl significantly reduces the reactions PMI. This decreases was due to the simplified work up as the product can be isolated by direct filtration and therefore minimises the volume of solvent required in the process. This is shown by the PMI decreasing from 90.6 g g^{-1} with NaOEt to 14.8 g g^{-1} with 0.4 M HCl.

Table 3.5: Metric comparison NaOEt vs 0.4M HCl as reagent for synthesis of **3.1**.

3.7 **3.8** **3.1**

Entry	Reagent	Yield (%)	Traditional AE (%)	Traditional RME(%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{solv} (g g^{-1})
1	NaOEt	88	41.4	33.2	90.6	3.8	85.1
2	0.4 M HCl	87	46.4	37.3	14.8	3.1	11.7

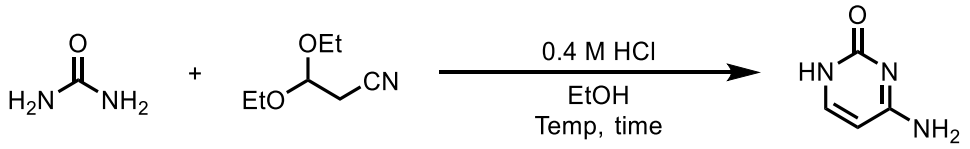
A full key and explanation of the metrics analysis and flag classification can be found in the appendix.

3.2.1.3. Optimisation of reaction conditions – Temperature

The temperature of the process was also highlighted as problematic in Table 3.2 as Entry 2 was performed at reflux. Performing a reaction at reflux is very energy intensive. Around 6 times more energy is required as an input for a process at reflux when compared to the same process operating at 5 °C below reflux.[175]

During the optimisation of solvent Table 3.3 and reagent Table 3.4 temperature was also investigated. Table 3.6 Entry 7 shows that the optimum temperature for the reaction of urea **3.7** and nitrile **3.8** was 70 °C. At temperatures below 70 °C the reaction was slow and above 70 °C the was a significant loss of product and starting material possible due to decomposition.

Table 3.6: Effect of temperature on formation of cytosine **3.1**.



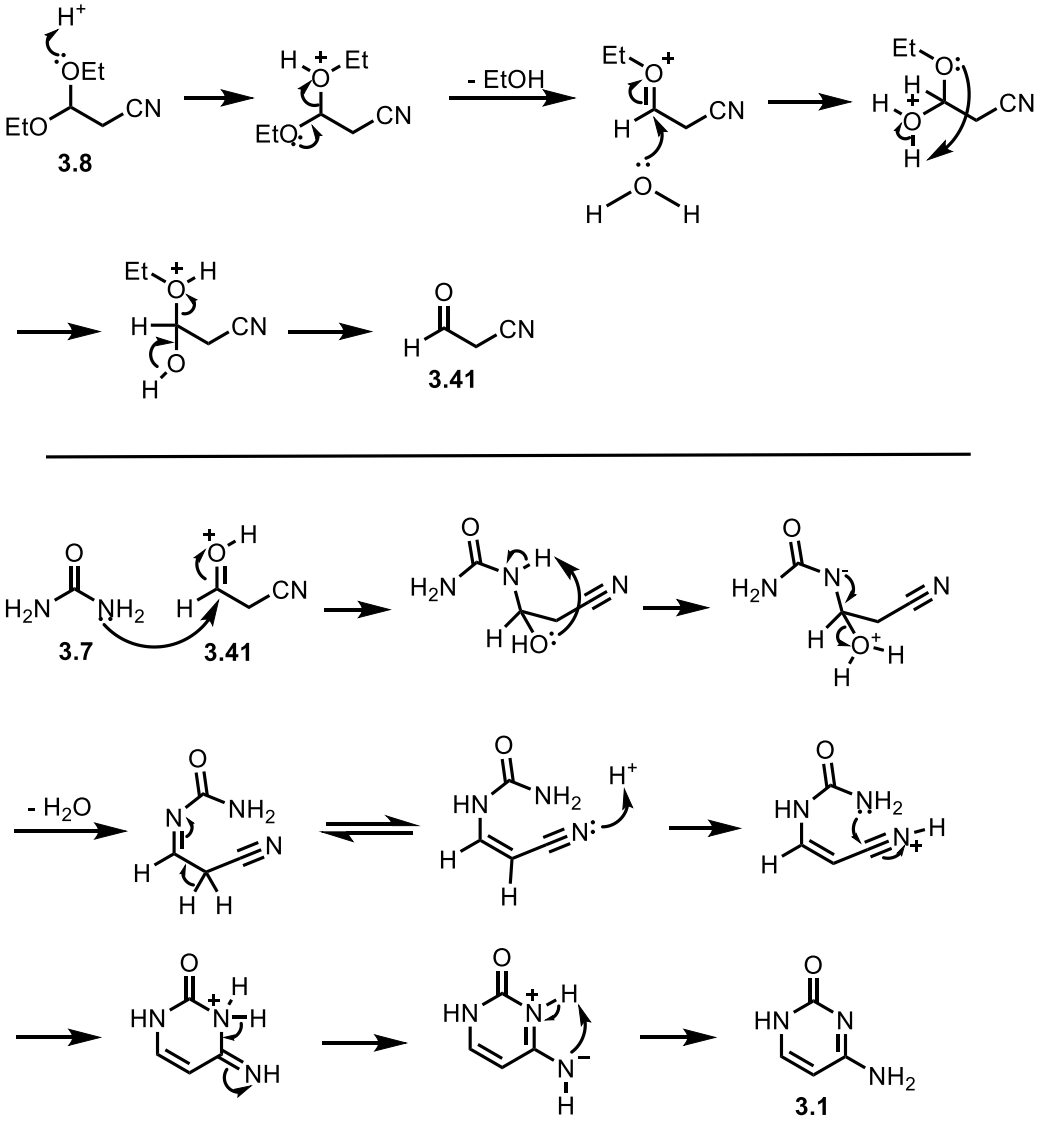
3.7 **3.8** **3.1**

Entry	Reagent	Temperature	Time	Yield (%)
1	0.4 M HCl	Room temperature	12 h	0
2	0.4 M HCl	30 °C	12 h	5
3	0.4 M HCl	40 °C	12 h	26
4	0.4 M HCl	50 °C	12 h	30
5	0.4 M HCl	50 °C	24 h	34
6	0.4 M HCl	60 °C	12 h	40
7	0.4 M HCl	70 °C	6 h	87
8	0.4 M HCl	70 °C	12 h	85
9	0.4 M HCl	Reflux	6 h	27

3.2.1.4. Optimisation of reaction conditions – Starting material

As previously shown in Table 3.2 Entry 2 the patent route has a poor atom economy which can be linked to the choice of starting material.[176] Therefore, the use of alternative, more atom efficient reactants was explored. Nitrile **3.8** contains two ethoxy groups which are lost as ethanol during the reaction to form cytosine **3.1**. The acetal is hydrolysed *in situ* to form a reactive aldehyde **3.41** as shown in Scheme 3.9. Aldehyde **3.41** is then condensed with urea **3.7** followed by cyclisation onto the nitrile to produce cytosine **3.1** Scheme 3.9.

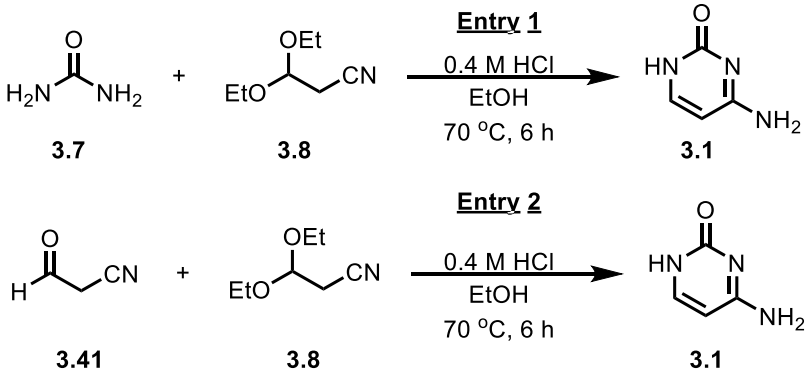
Scheme 3.9 shows how an acid can deprotect nitrile **3.8** and this aldehyde can then condense with urea **3.7.** The use of nitrile **3.8** can be justified as it is stable under ambient conditions. The acetal can easily be hydrolysed in the reaction flask and used instantly. Whereas if compound **3.41** were chosen as the starting material it would likely self-polymerize and decompose during storage if special conditions were not employed. These special measures would add additional expense and complication to the process, especially on a large scale.



Scheme 3.9: Acid catalysed hydrolysis of nitrile **3.8** & mechanism to form cytosine **3.1**.

When metrics analysis was performed substituting nitrile **3.8** for aldehyde **3.41** Table 3.7**,** the AE significantly improved along with RME and a very slight improvement in PMI. This verified the negative effect the protecting group has on the reaction metrics and supported the investigation into an alternative reactant.

Table 3.7: Metric analysis altering starting nitrile.



3.7 + 3.8 → 3.1 (Entry 1)

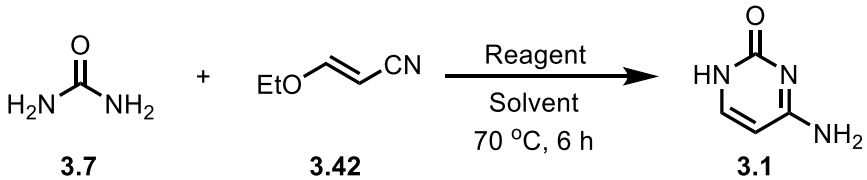
3.41 + 3.8 → 3.1 (Entry 2)

Metric parameter	Entry 1 Nitrile **3.8** as starting material	Entry 2 Aldehyde **3.41** as starting material
Traditional AE (%)	46.3	67.1
Traditional RME (%)	39.0	54.6
PMI reaction (g g^{-1})	97.7	97.0
PMI reagents, reactant, catalyst (g g^{-1})	3.0	2.3
PMI solvent (g g^{-1})	93.3	93.3

A full key and explanation of the metrics analysis and flag classification can be found in the appendix.

Given the improvements that could be gained from substituting the starting material, alternate substrates were screened for suitability. Firstly 3-ethoxyacrylonitrile **3.42** was chosen as it was very similar to nitrile **3.8**, as it can isomerise to form the same intermediate **3.41** that can be obtained from nitrile **3.8**. Nitrile **3.42** was reacted with urea **3.7** under various conditions and the results are displayed in Table 3.8.

Table 3.8: Synthesis of cytosine **3.1** from urea **3.7** and 3-ethoxyacrylonitrile **3.42**.



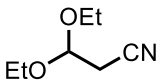
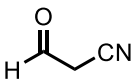
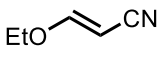
3.7 + 3.42 → 3.1

Entry	Reagent	Solvent	Yield (%)
1	NaOEt	*m*-Xylene	56
2	NaOEt	Toluene	51
3	NaOEt	EtOH	46
4	0.4 M HCl	EtOH	0
5	NaOH	EtOH	0
6	$AlCl_3$	EtOH	0
7	$FeCl_3$	EtOH	0
8	*p*-TSA	EtOH	0

When nitrile **3.42** was used in place of **3.8** a lower overall yield was observed. Table 3.8. Entry 1 used *m*-xylene as solvent with NaOEt and gave 56% yield compared to 91% when nitrile **3.8** was used. A lower yield was also observed with toluene and NaOEt Table 3.8. Entry 2, 51% vs a previously obtained 72% albeit at 90 ^{o}C. When ethanolic HCl was chosen there was no product detected and no decreases in the concentration of starting nitrile **3.21**. The trend of inactivity continued with numerous Lewis and Brønsted acids Table 3.8.Entry 4 – 8.

Subsequently attention turned to acrylonitrile **3.43** to see if it was possible to react directly with urea **3.7** to give the target compound. Acrylonitrile **3.43** is readily available in bulk quantities and is very cheap. Urea **3.7** is also cheap therefore if it was possible to use both substrates to form cytosine **3.1** this would be ideal from a financial perspective. When considering the atom economy, the reaction between urea **3.7** and acrylonitrile **3.43** would be almost 100% (based solely on reactants) as only 2 equivalents of hydrogen are lost per mole of product. Although when the reagent HCl is included the AE drops, but the improvement with acrylonitrile **3.43** can still be observed in Table 3.9, Entry 4.

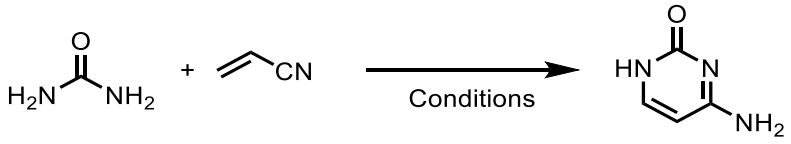
Table 3.9: Atom economy comparison of starting material.

	Entry 1	**Entry 2**	**Entry 3**	**Entry 4**
				
	3.8	**3.41**	**3.42**	**3.43**
Traditional AE (%) [a]	46.4	67.1	57.4	74.3

[a] Reaction conditions, 1.0 equiv nitrile, 1.2 equiv urea, 1.2 eq HCl

The difficulties with using acrylonitrile **3.43** may be the possibility for it to polymerise and for urea to add into the double bond. The amide nitrogen in urea **3.7** may not be nucleophilic enough to successfully perform a 1,4-conjugate addition onto acrylonitrile. Initially acrylonitrile **3.43** was screened with urea **3.7** using the same conditions as for 3-ethoxyacrylonitrile **3.42** Table 3.10.

Table 3.10: Synthesis of cytosine **3.1** from urea **3.7** and acrylonitrile **3.43**.



3.7 **3.43** **3.1**

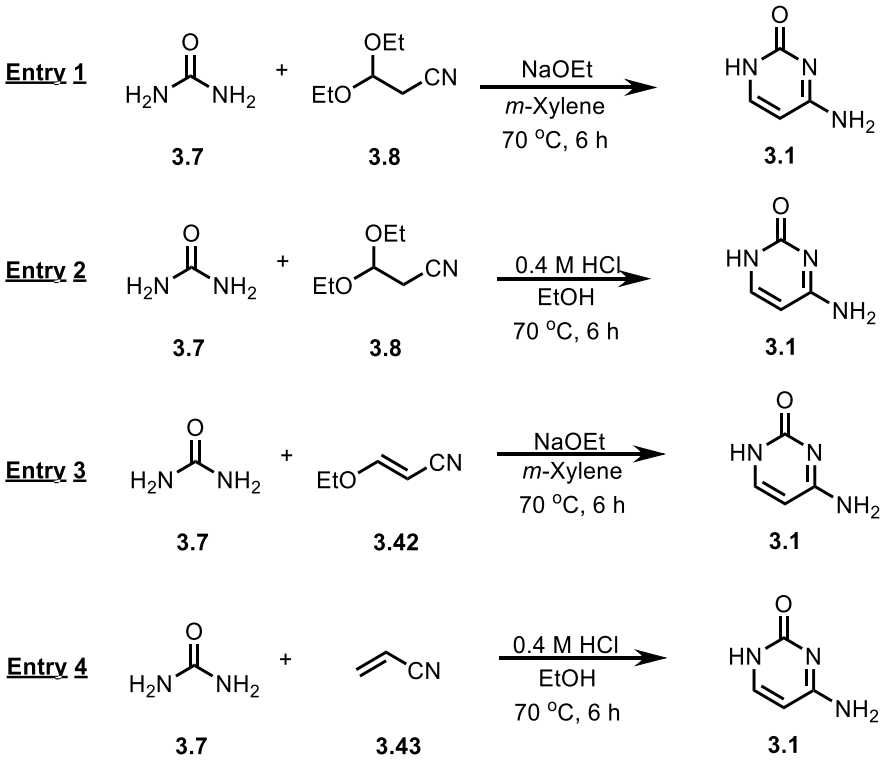
Entry	Reagent	Solvent	Temperature	Time	Yield (%)
1	NaOEt	*m*-Xylene	70 °C	6 h	0
2	NaOEt	Toluene	70 °C	6 h	0
3	NaOEt	EtOH	70 °C	6 h	0
4	0.4 M HCl	EtOH	70 °C	6 h	5
5	0.4 M HCl	Et_2O	Room temperature	24 h	0
6	NaOH	EtOH	70 °C	6 h	0
7	$AlCl_3$	EtOH	70 °C	6 h	0
8	$AlCl_3$	DCM	Room temperature	24 h	0
9	$FeCl_3$	EtOH	70 °C	6 h	0
10	*p*-TsOH	EtOH	70 °C	6 h	0
11	*p*-TsOH	H_2O	Room temperature	24 h	0

The results with acrylonitrile **3.43** were disappointing but not unexpected. There was an uncertainty if urea would be suitable substrate for an aza-micheal reaction. Looking at the results in Table 3.10 it confirms that urea **3.7** is not suitable as none of the reactions were successful. One weakly positive result was with Entry 4, but this yield was not successfully repeated and has been considered an anomaly.

3.2.1.5. Metric analysis of the screened synthetic routes to cytosine

When a metric analysis is performed on the three main routes to cytosine **3.1** the reaction with urea **3.7**, nitrile **3.8** using ethanolic HCl comes out as the most preferable reaction Table 3.11 Entry 2. It has the second most favourable yield at 87%, it also has the most favourable RME and PMI. Although Table 3.11 Entry 2 is the third least atom efficient this is due to losing two equivalents of ethanol deprotecting the reactive aldehyde, given the side product is ethanol and the solvent is ethanol which can be recovered this can metric result can be considered acceptable. The health and safety and solvent choice for entry 2 also make it the preferred choice.

Table 3.11: Metric comparison of investigated routes to cytosine **3.1**.

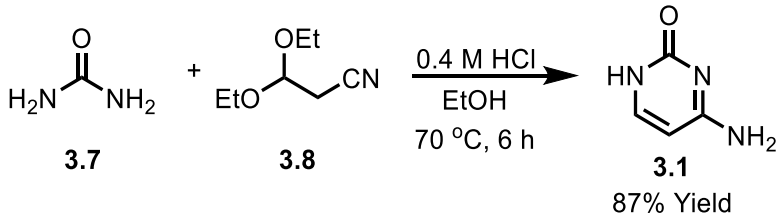


Metric parameter	**Entry 1** Nitrile **3.8** as starting material NaOEt/*m*-Xylene	**Entry 2** Nitrile **3.8** as starting material HCl/EtOH	**Entry 3** Nitrile **3.42** as starting material	**Entry 4** Acrylonitrile **3.43** as starting material
Yield (%)	90.8	87.2	56.3	5.4
Traditional AE (%)	41.4	46.4	50.0	74.3
Traditional RME (%)	34.4	37.4	25.3	3.6
PMI reaction (g g^{-1})	111.8	14.8	160.0	411.5
PMI_{RRC} (g g^{-1})	3.7	3.1	5.2	35.4
PMI_{Solv} (g g^{-1})	106.5	11.7	153.8	376.2
Solvent choice				
Catalyst?				
Recoverable catalyst?				
Critical element				
Energy				
Work-up				
Health and safety				
Chemical of concern?				

Flag system: Green flag preferred, amber flag acceptable but some issues and red flag is undesirable.
A full key and explanation of the metrics analysis and flag classification can be found in the appendix.

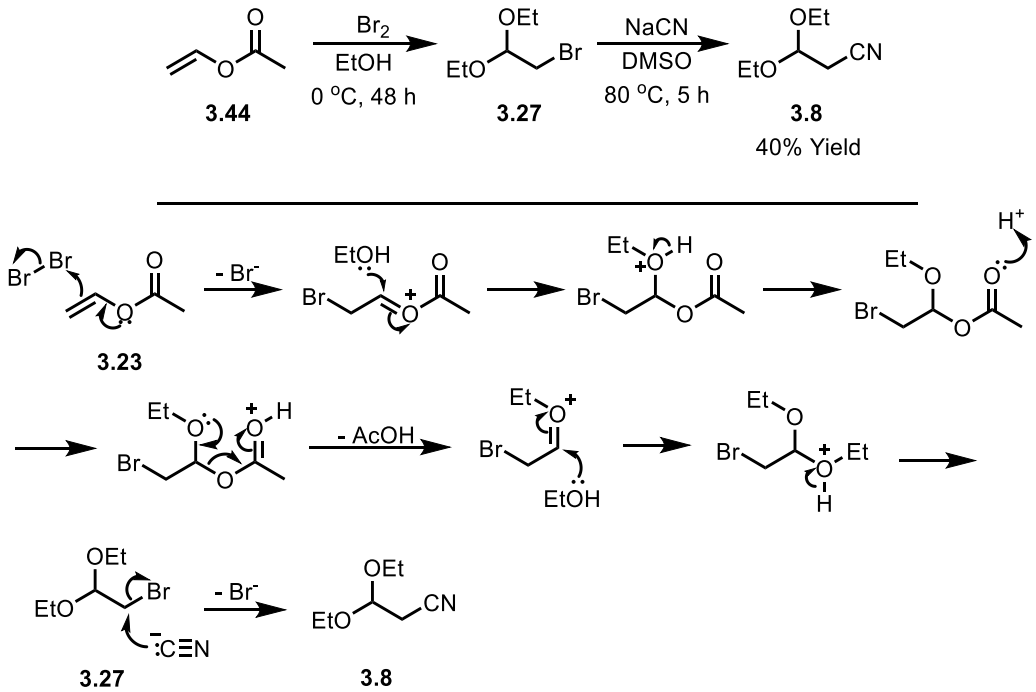
3.2.2. Synthesis of 3,3-diethoxypropanitrile

Following the evaluation of alternative nitriles focus was then turned to the synthesis of nitrile **3.8**. This was because the highest yielding and simplest procedure identified for the synthesis of cytosine **3.1** can be achieved using the reaction displayed in Scheme 3.10.



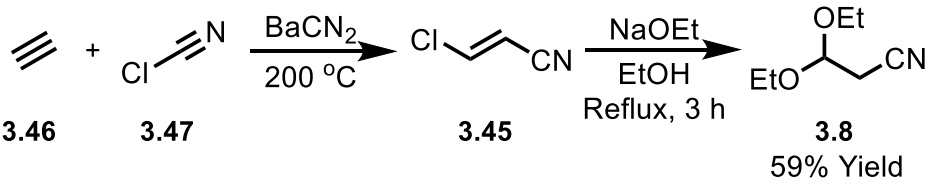
Scheme 3.10: Synthesis of cytosine **3.1** from urea **3.7** and nitrile **3.8**.

The manufacturing process to obtain nitrile **3.8** could be through one of two possible synthetic pathways which have been found in the patent literature.[177] The first route is a 2-step process which begins with vinyl acetate **3.44**, Scheme 3.11. Vinyl acetate **3.44** is converted to a brominated acetal **3.27** which then undergoes a substitution reaction with sodium cyanide to give nitrile **3.8**.



Scheme 3.11: Synthesis of nitrile **3.8** from vinyl acetate.

The second route to nitrile **3.8**, Scheme 3.12 uses 3-chloroacrylonitrile **3.45** as starting material, which can be derived from acetylene **3.46** and cyanogen chloride **3.47**.[178, 179]



3.46 **3.47** **3.45** **3.8**
59% Yield

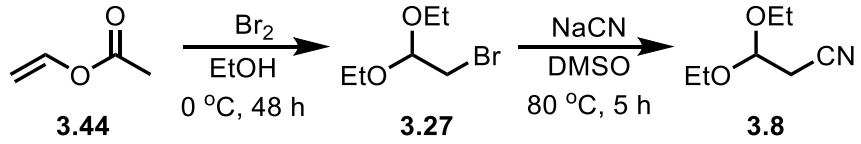
Scheme 3.12: Synthesis of nitrile **3.8** from 3-chloroacrylonitrile **3.45**.

Employing **3.45** as a reactant is relatively straightforward but its synthesis however has numerous problems. Both substrates are gas, acetylene is explosive and cyanogen chloride is toxic. High temperature ~ 200 ^{o}C has been reported in its syntheses and the product needs to be fractionally distilled. The product has also been reported to be unstable and liable to polymerise which again is not ideal and leads to problems handling and storing the material.

Metric analysis of these processes highlights several issues, the most pressing being the toxic nature of the reagents involved Table 3.12. Elemental bromine, sodium cyanide, acetylene and cyanogen chloride are all extremely toxic and will require special handling requirements. Handling of gaseous reagents requires specialist equipment and expertise. The data for metric analysis for entry 2 in Table 3.12 was complicated due to the gaseous reaction to form olefin **3.45.** The patent did not provide any physical quantities only that the gases are combined in approximately equal volume rates a good yield is obtained after condensation and subsequent fractional distillation.

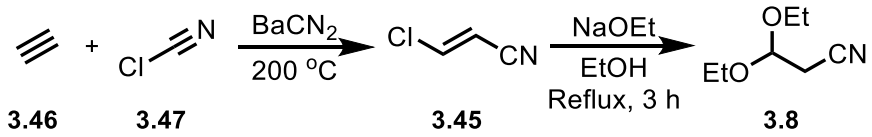
Table 3.12: Metris analysis of the manufacture of nitrile **3.8**.

Entry 1



3.44 3.27 3.8

Entry 2

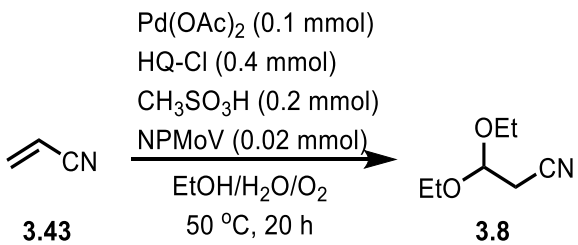


3.46 3.47 3.45 3.8

Metric parameter	Entry 1	Entry 2
Yield (%)	40.4	58.6
Traditional AE (%)	37.0	69.3
Traditional RME (%)	8.2	28.4
PMI reaction (g g^{-1})	576.1	9.9
PMI reagents, reactant, catalyst (g g^{-1})	7.6	5.0
PMI solvent (g g^{-1})	529.2	4.2
Solvent choice		
Catalyst?		
Recoverable catalyst?		
Critical element		
Energy		
Work-up		
Health and safety		
Chemical of concern?		

Flag system: Green flag preferred, amber flag acceptable but some issues and red flag is undesirable. *A full key and explanation of the metrics analysis and flag classification can be found in the appendix.*

An alternative synthetic route to nitrile **3.8** has been reported by Ishii *et al.*[180-183] They claim that monosubstituted alkenes such as acrylonitrile **3.43** can undergo acetalization via a Wacker type process Scheme 3.13

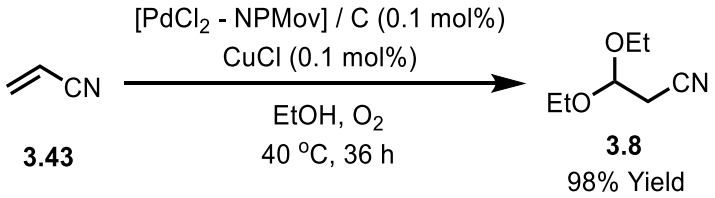


3.43 **3.8** 87% Yield

Scheme 3.13: Production of nitrile **3.8** as reported by Ishii.[183]

When the reported conditions were attempted in the lab the reaction gave a slightly lower yield than reported, 81% as opposed to 99% Scheme 3.13.[183] While this is still reasonable, the conditions were examined and after some optimization it was possible to get a quantitative conversion of acrylonitrile **3.43** to nitrile **3.8**. The optimisation involved supporting palladium (II) chloride and molybdovanadophosphate (NPMoV) on activated carbon and substituting chlorohydroquinone with copper (I) chloride. These modifications allowed the reaction to run cleanly to completion in 36 hours at 40 ^{o}C.

Supporting a Pd(II) catalyst and NPMoV on activated carbon allowed for a simple work up once the reaction was complete. This solid support also gave improved yields at a slightly lower temperature. A theory for an improved yield at lower temperature is that the activated carbon is promoting the desired interactions between substrates. Replacement of chlorohydroquinone with copper (I) chloride increased the speed of the reaction presumably by allowing for a faster oxidation of the Pd(0) and NPMoV catalytic species back into their active form.



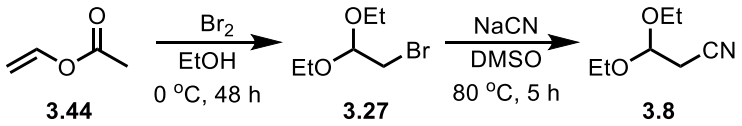
Scheme 3.14: Wacker route to nitrile **3.8**.

Once the Pd(II) catalysed acetyl reaction was complete it could be filtered acidified with HCl to form reactive aldehyde **3.41**. Addition of urea **3.7** and warming to 70 ^{o}C allowed the formation of cytosine **3.1**. Due to the filtration transferring the reaction mixture from one flask to another the conversion acrylonitrile **3.43** to cytosine **3.1** is not far from being a one pot process.

A comparison of the initial route reported by Ishii and optimised route to nitrile **3.8** is shown in Table 3.13.

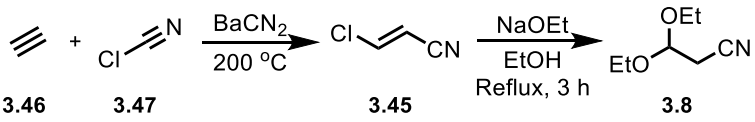
Table 3.13: Comparison of routes to nitrile **3.8**.

Entry 1



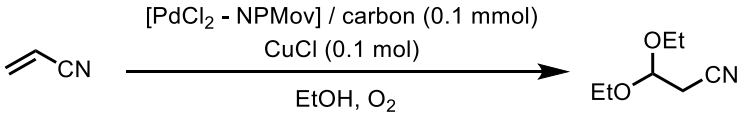
3.44 3.27 3.8

Entry 2



3.46 3.47 3.45 3.8

Entry 3



3.43 3.8

Metric parameter	Entry 1	Entry 2	Entry 3
Yield (%)	40.4	58.6	97.9
Traditional AE (%)	37.0	69.3	97.8
Traditional RME (%)	8.2	28.4	95.7
PMI reaction (g g^{-1})	576.1	9.2	6.7
PMI reagents, reactant, catalyst (g g^{-1})	7.6	5.0	1.1
PMI solvent (g g^{-1})	529.2	4.2	5.6
Solvent choice			
Catalyst?			
Recoverable catalyst?			
Critical element			
Energy			
Work-up			
Health and safety			
Chemical of concern?			

Flag system: Green flag preferred, amber flag acceptable but some issues and red flag is undesirable.
A full key and explanation of the metrics analysis and flag classification can be found in the appendix

The improvement from the initial to the optimised process is substantial. Every metric for the reaction has been improved with the exception of critical element which changed from green to red. The catalytic system uses 4 metals, palladium, molybdenum, vanadium and copper, which may pose a problem of contamination for pharmaceutical uses and is not desirable from a sustainability aspect as the natural resources for Pd, Mo and Cu are at risk of depletion in the next 50-100 years.[184]

3.2.3. Synthesis of 2,5-disubstituted-1,3-oxathiolanes

With the route to cytosine **3.1** developed it was a logical step to consider the synthetic endeavour required to obtain an 2,5-disubstituted-1,3-oxathiolane motif as this in combination with cytosine **3.1** or Fluorocytosine **3.9** form the commercially important antiretroviral medicines, Emtricitabine **3.11** and Lamivudine **3.12**. The initial approach was to perform a metric screen of the reactions presented in Scheme 3.5 and use this to guide to identify opportunities for improvement.

3.2.3.1. Metric analysis of synthetic routes to 2,5-disubstituted-1,3-oxathiolanes

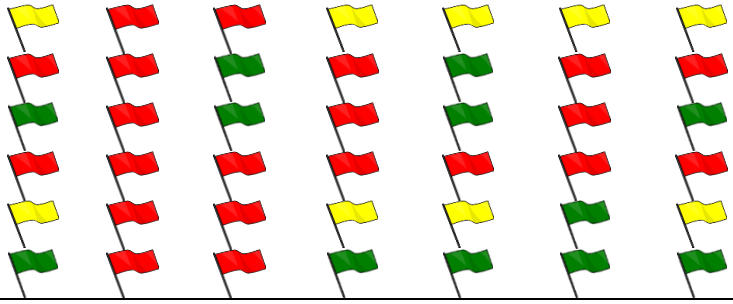
As discussed in section 3.1.2 and presented in Scheme 3.5 the various published routes to obtain a 2,5-disubstituted-1,3-oxathiolane all follow a distinct pattern of condensation of an aldehyde or glyoxylate with a thiol or 1,4-diathiane-2,5-diol **3.23** with the exception of Entry 3 & 7 which both take unique routes to form the oxathiolane ring. In Scheme 3.5, Entry 3 sets the stereochemistry at C2 through a enzymatic resolution with lipase and then deprotection of the chiral acetal with HCl leads to *in situ* cyclisation forming the oxathiolane **3.30**.[155] The route presented in Scheme 3.5 Entry 7 was deliberately designed to avoid the previously developed routes and starting materials. The authors aim was to design new routes from simple, high-volume low-cost starting materials which could potentially decrease raw material costs, increases supply chain security of Emtricitabine **3.11** and Lamivudine **3.12** and also allow alternative manufactures to enter the market therefore increasing global production of the medicines.

In order to identify any opportunities for improvement within the processes shown in Scheme 3.5 a metric analysis was performed using the procedures provided in the literature. The results from this analysis are presented in Table 3.14. In the metric data presented in Table 3.14. For this analysis work up details have been excluded. This is because the information provided for work up and purification varies greatly between authors and publications. If a general assumption was made about the quantities use this would have to be scaled to the size of the reaction and could in the case of small-scale reactions overestimate which would unfairly disfavour a reaction. The fairest option was to completely exclude all work up information regarding solvents, washes and reagents.

As stereochemical transformations are a vital part of these synthesis an additional column has been added to Table 3.14. resolution. This column is graded with the two-flag system;

- Green: no resolution required (separation of enantiomers).
- Red flag: Resolution performed, eg fractional crystallisation.

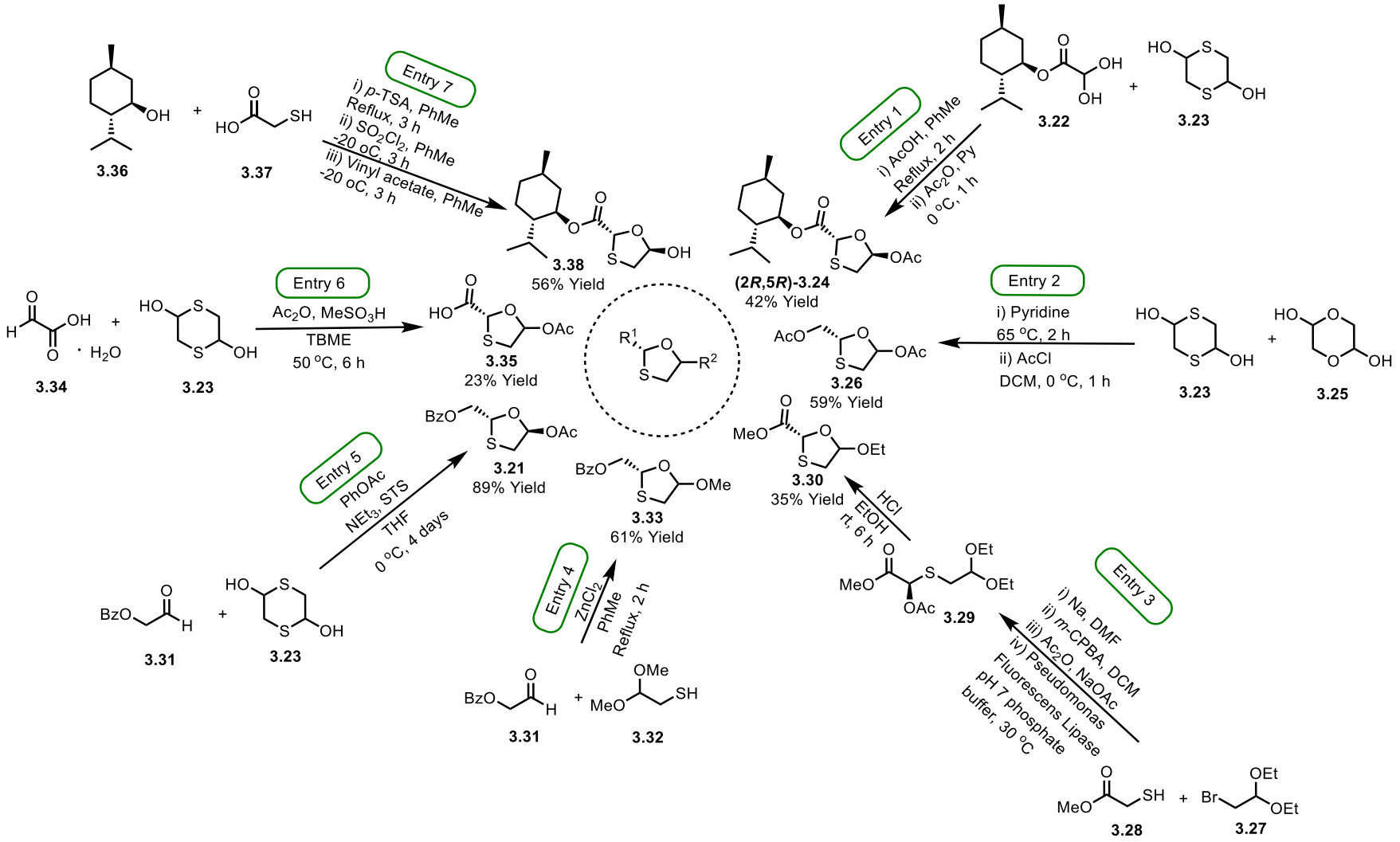
Table 3.14: Metric analysis of routes to 2,5-disubstituted-1,3-oxathiolanes.

Metric parameter	**Entry 1**[166]	**Entry 2**[167]	**Entry 3**[155]	**Entry 4**[168, 169]	**Entry 5**[153]	**Entry 6**[185]	**Entry 7**[170]
Yield (%)	42.0	59.1	35.1	61.3	88.9	22.9	56.4
Traditional AE (%)	53.1	62.8	41.1	60.2	51.0	42.9	61.4
Traditional RME (%)	17.7	22.4	13.5	28.3	29.5	16.4	22.5
PMI reaction (g g^{-1})	21.2	19.6	89.4	49.2	31.3	33.6	8.7
PMI reagents, reactant, catalyst (g g^{-1})	5.6	4.5	7.6	3.5	4.0	6.1	4.5
PMI solvent (g g^{-1})	15.6	15.1	81.8	45.6	27.2	27.5	4.3
Solvent choice							
Resolution							
Catalyst?							
Recoverable catalyst?							
Health and safety							
Chemical of concern?							

Flag system: Green flag preferred, amber flag acceptable but some issues and red flag is undesirable.
A full key and explanation of the metrics analysis and flag classification can be found in the appendix.

In Table 3.14 the route which performed least favourable was entry 3 which uses a lipase enzyme to set the stereochemistry at C2. The process in Table 3.14 entry 3 to obtain **3.30** in involves four steps whereas each of the other entries involves one or two steps. All entries show fixed stereochemistry at C2 which is obtained through chiral resolution apart from entries 3 and 5 which sets the stereochemistry by the action of an enzyme. Analysis of the data presented in Table 3.14 reveals that entry 5 has the best overall yield and RME. Entry 2 has the best AE and PMI metrics. Given RME is dependent on yield it is unsurprising that these are most favourable in the same entry. Entry 2 has the best AE and PMI as the reaction is a condensation between two aldehydes which are both consumed during the reaction, and the alcohols formed are acetylated with acyl chloride generating HCl as the only by product.

While the metric data presented in Table 3.14 gives a good insight into how the reactions compare to another caution must be taken when comparing reactions through metrics analysis as discussed in Chapter 2. These examples are further complicated by the stereochemical requirement and that some examples have been taken from the literature and performed on a milligram scale whereas others taken from patent and process literature were reported at kilogram scale.

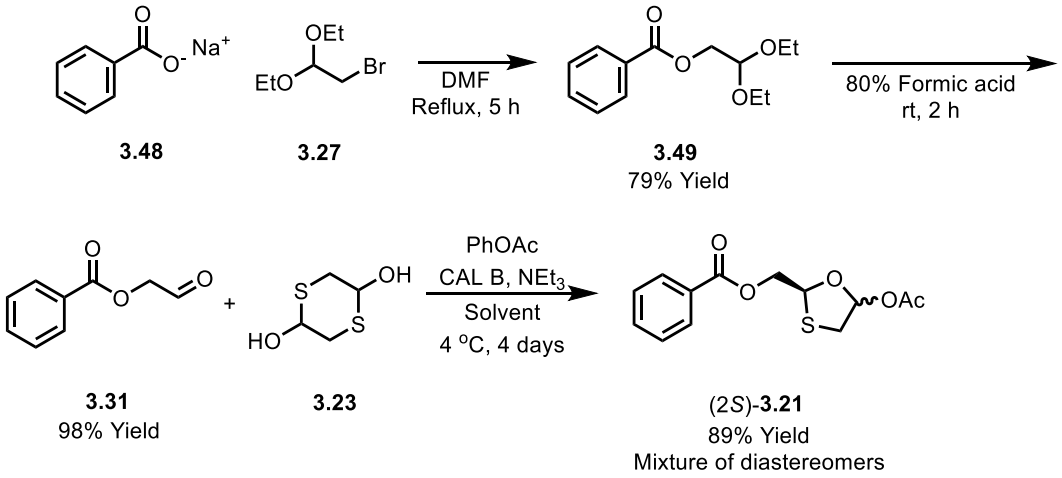


Scheme 3.5: Routes for the synthesis of 2,5-disubstituted-1,3-oxathiolanes.

3.2.3.2. Solvent study on the enzymatic synthesis of 2,5-disubstituted-1,3-oxathiolanes

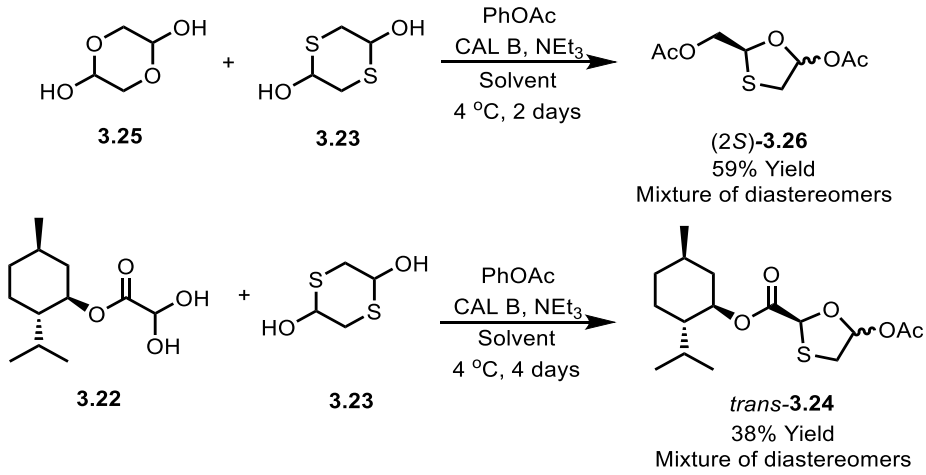
Through the metric analysis of oxathiolane synthesis presented in Scheme 3.5, Entry 5 was identified as the most ideal reaction in a laboratory setting. The chemistry in Scheme 3.5 Entry 5 works well on a small scale ~ 2 mmol, but this does not provide any indication as to how the reaction would perform on a larger scale.

Given the green potential of the enzymatic reaction described by Hu *et al* a solvent screen was carried out to try and identify if an alternative to toluene could be found.[153] The reaction presented in Scheme 3.15 was used to model the performance of different solvents. CAL-B was chosen for convenience as it is commercially available and gave access to the compounds of interest. Benzoyl protected aldehyde **3.31** is obtained from sodium benzoate **3.48** in two steps. The first step is addition of bromoacetal **3.27** to sodium benzoate **3.48** to give acetal **3.49** which is hydrolysis with aqueous formic acid to give aldehyde **3.31** which is very unstable and self-polymerises within a matter of hours at room temperature. Therefore, it was made prior to each use.



Scheme 3.15: Enzymatic synthesis of oxathiolane (2*S*)-**3.34**.

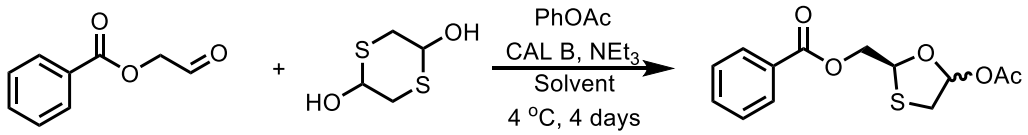
An alternative to aldehyde **3.31** was glycolaldehyde dimer **3.25** or L-menthyl glyoxylate **3.22** and both performed just as well as **3.31** and could have been used as a suitable alternative for screening reactions, Scheme 3.16 Aldehyde **3.25** and glyoxylate **3.22** have an indefinite stability when stored in a fridge and are solids whereas aldehyde **3.31** is a liquid. Despite these benefits the route using **3.31** was pursued due to the phenyl ring making analysis by NMR and HPLC simpler.



Scheme 3.16: Synthesis of oxathiolane (2*S*)-**3.24** & **3.26**

A wide range of solvents with varing properties where selected for initial screening.The results from the solvent screen are presented in Table **3.15**.

Table 3.15: Solvent study on enzymatic synthesis **3.21**.



3.31 **3.24** (2*S*)-**3.21**

Entry	Solvent	Yield (%)	dr (%)	*ee* (%) [a]
1	Toluene	89	8:1	87
2	*m*-Xylene	87	8:1	87
3	Hexane	74	8:1	85
4	Heptane	52	8:1	85
5	THF	0	-	-
6	TMO	74	7:1	80
7	NMP	0	-	-
8	DMF	0	-	-
9	Acetonitrile	42	2.5:1	50
10	Ethanol	21	2:1	50
11	DMSO	2	-	-
12	Chloroform	0	-	-
13	Ethyl acetate	13	-	-
14	TBME	63	1:1	50
15	Diethyl ether	22	1:1	50

General conditions: **3.31** (1.00 mmol), **3.24** (0.60 mmol), NEt_3 (1.00 mmol), PhOAc (3.00 mmol), CAL B (50 mg) & solvent (5 mL) 4 days at 4 °C.

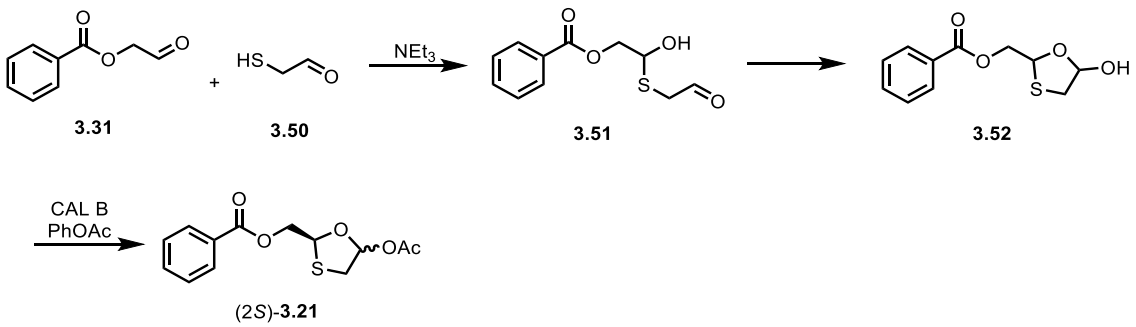
[a] *ee* of major diastereomer

Looking at the data presented

Table **3.15** there is no obvious pattern for which class of solvent is most suited to the reaction. Lipase catalysis is highly solvent dependant, with toluene performing the best giving a yield of 89% with a reasonable enantiomeric excess (*ee)* of 87% towards C-(2*S*), which was fractionally better than *m*-xylene which had a yield of 87%. These findings are in agreement with the reported procedure and other work showing that the lipase Cal B performs optimally in hydrocarbons.[153, 186] Other hydrocarbons heptane and hexane both give moderate yields of 52 & 74% respectively along with identical diastereoratios (dr) and *ee*'s . The good performance of hydrocarbons could be attributed to their low miscibility with water and therefore having less interreference with the enzymes active site and water which may be bound.

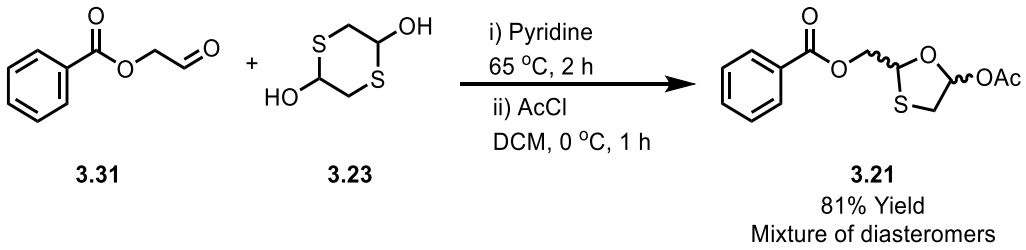
Table **3.15** Entry 5, 2,2,5,5-Tetramethyloxolane (TMO) is a solvent which was developed at the University of York as an alternative for toluene.[88, 90] A yield of 74% was obtained using TMO which was a pleasant surprise and encouraging to find it can be tolerated under these conditions. A dr of 7:1 and *ee* 80% obtained using TMO, was slightly lower than those obtained with the "traditional" hydrocarbon solvents but a promising result for the new solvent given the limited amount applications it has been evaluated with.

The reaction is thought to proceed through a cascade Scheme 3.17. Initially triethylamine (base) deprotonates the sulphur dimer **3.23** to leave the reactive thiol **3.50** then the lone pair on the sulphur can attack the carbonyl on aldehyde **3.31** to give intermediate **3.51** which cyclises to form **3.52**. Oxathiolane **3.52** can be stereoselectivly acylated with CAL B to generate the desired oxathiolane (2*S*)-**3.21** as a mixture of diastereomers at C5. Triethylamine can be substituted with pyridine, di-*n*-butylamine, diisopropylamine and *N*,*N*-Diisopropylethylamine (Hunigs Base) with no change on the yield or selectivity. In place of phenyl acetate acetic anhydride and acyl chloride were tested and worked successfully.



Scheme 3.17: Overview of cascade reaction to oxathiolane **3.21**.

The stereochemical out come of this reaction and configuration of compounds was determined by conversion of **3.21** into Lamivudine **3.12** which was analysed by chiral HPLC against an analytical standard of Lamivudine **3.12**. To begin aldehyde **3.31** and thiol **3.23** were condensed in pyridine and then the oxathiolane intermediate was acetylated with acetyl chloride to give a racemic mixture of *rac*-**3.21** Scheme 3.18. The racemic mixture was syntheised in this fashion to ensure that all four compounds could be detected by chiral HPLC Figure 3.5.



Scheme 3.18: Determination of configuration of **3.21**.

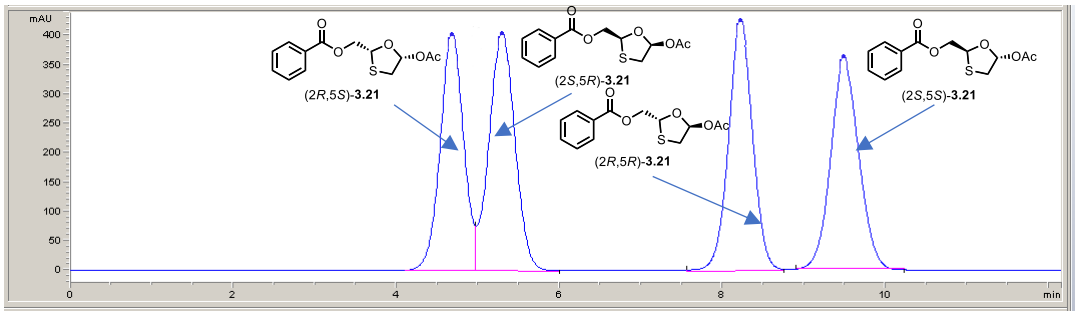
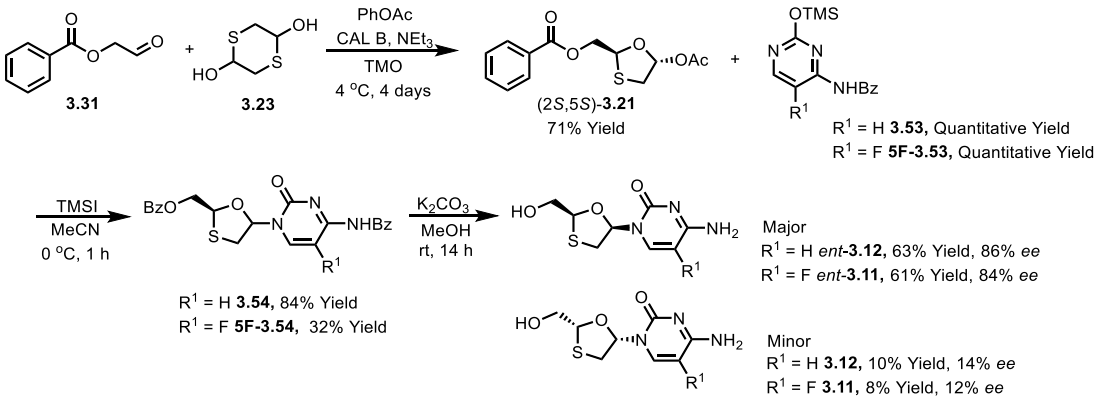


Figure 3.5:Chiral HPLC of *rac*-**3.21**.

With a reliable chiral HPLC method in place the products from the enzymatic reactions could be analysed. But there was still uncertainty about which peak related to each isomer. From the reaction with CAL B the diastereomers produced were separated by column chromatography or recrystallisation. The most abundant

diastereomer *trans*-**3.21** was reacted under Vorbrüggen conditions with protected cytosine **3.53** to give *N4*-benzoyl protected Lamivudine **3.54** which was deprotected with potassium carbonate to leave either (2*S*,5*S*)-Lamivudine *ent*-**3.12** or (2*R*,5*R*)-Lamivudine **3.12** Scheme 3.19. Chiral HPLC analysis showed that the enantiomer of Lamivudine was the major compound which been formed *ent*-**3.12** or (2*S*,5*S*)-**3.12**, which confirmed that (2*S*)-**3.21** was the major product from reaction with CAL B Figure 3.6.



Scheme 3.19: Synthesis of Lamivudine for chiral HPLC

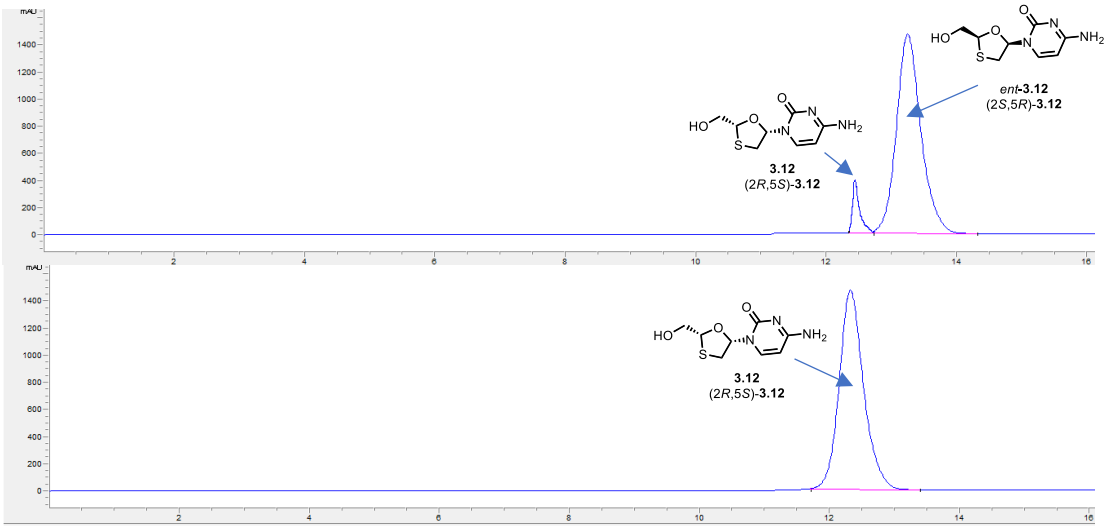
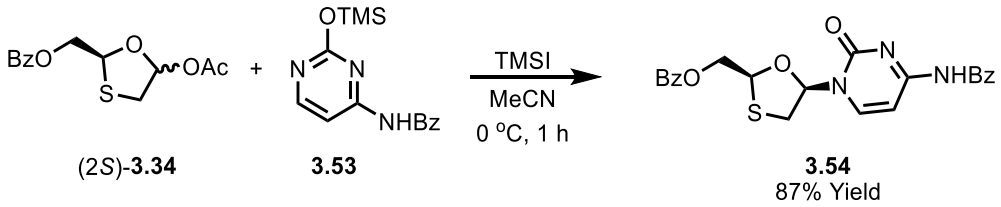


Figure 3.6: Chiral HPLC of Lamivudine and Lamivudine derived from enzymatic reaction.

3.2.4. Coupling of nucleobase & 1,3-oxathiolanes

3.2.4.1. Traditional coupling nucleoside coupling reactions

Traditionally Vorbrüggen or the Silyl-Hilbert-Johnson reaction has been the standard protocol to form a nucleoside by reacting a sugar or similar motif with a pyrimidine or purine Scheme 3.20.[153] Common Lewis acids which have been involved in this transformation include $SnCl_4$, $TiCl_4$, $Cu(OTf)_2$, TMSI, $Sc(SO_3CF_3)_3$ and $BF_3.OEt_2$. These regents are problematic as they tend to be hazardous and expensive. The reaction also favours chlorinated or acetonitrile as solvent. The hazards associated with the use of chlorinated are well known and acetonitrile can be prohibitive due to the cost especially at a larger scale. Due to the conditions generally used for Vorbrüggen reaction being unfavourable and that this transformation is not always stereoselective it would be desirable to explore alternative pathways to couple 1,3-oxathiolanes with pyrimidines without several protecting groups, stoichiometric reagents and harsh conditions.

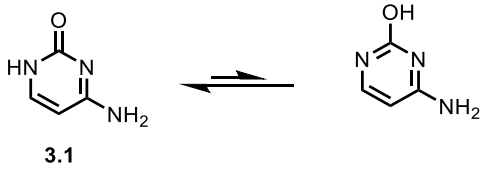


Scheme 3.20: Standard Vorbrüggen coupling reaction

Having worked with CAL B in section 3.2.3 to produce 1,3-oxathiolane intermediates**,** focus moved to the possibility of reacting 1,3-oxathiolane (2*S*,5*S*)-**3.55** with cytosine **3.1** via the Mitsunobu reaction. The hope was that this would result in the formation of lamivudine *ent*-**3.12** by inverting the stereocentre at C5 from (5*S*) to (5*R*) in 1,3-oxathiolane (2*S*,5*S*)-**3.55,** Scheme 3.23. The Mitsunobu reaction was also selected because it is a reaction that was identified by medicinal chemist as desirable for improvement.[23] A typical Mitsunobu reaction makes use of toxic and stoichiometric reagents and requires the removal of phosphine oxide side product which makes this reaction undesirable for larger scale processes. If improvements could be made it would be welcomed as the Mitsunobu reaction can be a very useful transformation when the conversion of a stereocentre is required.

3.2.4.2. Mitsunobu reaction considerations

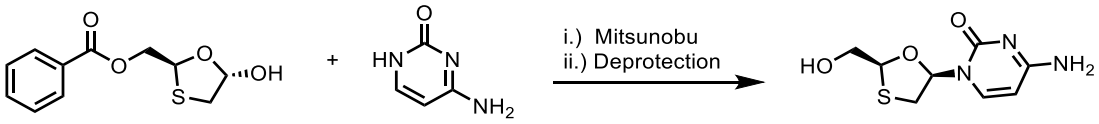
It has been previously reported that the coupling of cytosine **3.1** via a Mitsunobu reaction was very difficult and not favourable.[61] One of the limitations of cytosine **3.1** is its poor solubility, without a protecting group cytosine **3.1** is almost insoluble in most common organic solvents. Even when protected, cytosine derivatives are still hampered by solubility problems. Another drawback could be the possibility of cytosine tautomerizing which allows for the formation of *N*-alkylated and *O*-alkylated products Scheme 3.21.



3.1

Scheme 3.21: Tautomerization of cytosine **3.1**.

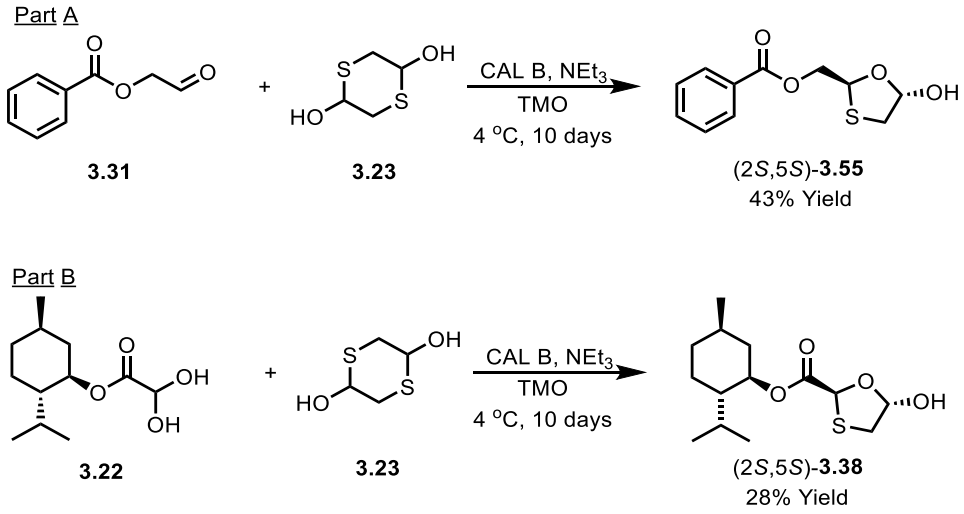
With these considerations in mind a cautious approach was taken to investigate the likelihood of our ideal pathway being feasible Scheme 3.22.



(2*S*,5*S*)-**3.55** **3.1** *ent*-**3.12**

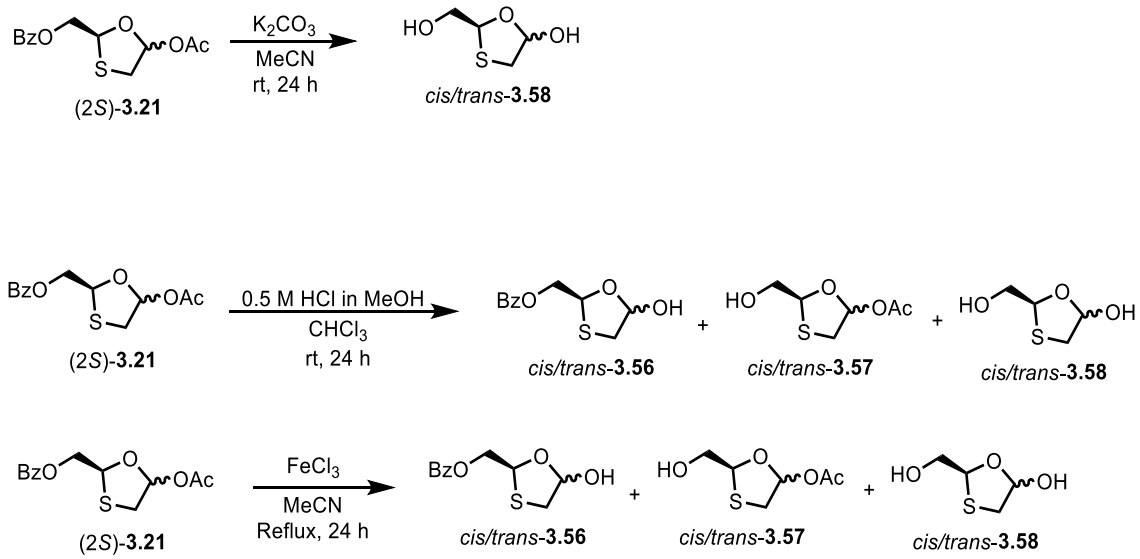
Scheme 3.22: Ideal reaction towards Lamivudine *ent*-**3.12**.

Oxathiolane alcohol (2*S*,5*S*)-**3.55** was accesses through reaction of aldehyde **3.31** and thiol **3.23** with CAL B and NEt_3 part A, Scheme 3.23. The desired C-(2*S*) enriched compound was obtained with an *ee* of 80% and (2*S*,5*S*)-**3.55** isomer was obtained through recrystallisation of the crude oil with hexane in a freezer overnight. Aldehyde **3.31** could also be substituted with L-menthyl glyoxylate **3.22** to give oxathiolane alcohol **3.38** through the same reaction and purification procedure part B, Scheme 3.23.



Scheme 3.23: Synthesis of alcohol **3.38** or **3.55**.

An attempt was made to selectively remove the acetyl group from C5 on oxathiolane **3.21**. The methods tried included reaction with potassium carbonate, but this gave predominantly **3.58**. Next removal of the protecting group with iron (III) chloride in acetonitrile and HCl in methanol/chloroform was attempted.[187, 188] Unfortunately, both methods using $FeCl_3$ then HCl failed and gave a mixture of compounds **3.56**, **3.57** & **3.58** Scheme 3.24.

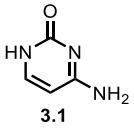
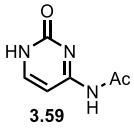
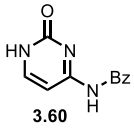
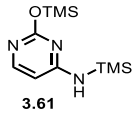


Scheme 3.24: Selective *O*-deacetylation of **3.21**.

3.2.4.3. Solvent considerations for Mitsunobu coupling

To begin, an investigation on the effect of solvent on the reaction and substrates was performed, this investigation was performed in two parts. Firstly, solubility of cytosine and its protected derivatives **3.1** & **3.59** – **3.61** was screened in a range of organic solvents, Table 3.16.

Table 3.16: Solubility of **3.1** and protected derivatives in organic solvent.

Entry	Solvent (0.01M) @ 30 °C	 **3.1**	 **3.59**	 **3.60**	 **3.61**
1	THF	Insoluble	Insoluble	Insoluble	Soluble
2	2-MeTHF	Insoluble	Insoluble	Insoluble	Soluble
3	TMO	Insoluble	Insoluble	Insoluble	Soluble
4	1,4-Dioxane	Insoluble	Insoluble	Insoluble	Soluble
5	Diethyl ether	Insoluble	Insoluble	Insoluble	Soluble
6	Acetone	Insoluble	Insoluble	Insoluble	Soluble
7	Chloroform	Insoluble	Insoluble	Insoluble	Soluble
8	DCM	Insoluble	Partly soluble	Partly soluble	Soluble
9	MeCN	Insoluble	Soluble	Soluble	Soluble
10	DMF	Insoluble	Partly soluble	Partly soluble	Soluble
11	DMSO	Soluble	Soluble	Partly soluble	Soluble
12	Toluene	Insoluble	Insoluble	Insoluble	Soluble
13	Hexane	Insoluble	Insoluble	Insoluble	Soluble
14	Cyclohexane	Insoluble	Insoluble	Insoluble	Soluble
15	Pyridine	Insoluble	Insoluble	Insoluble	Soluble
16	NMP	Insoluble	Insoluble	Insoluble	Soluble

As previously reported cytosine **3.1** is poorly soluble in every solvent tested apart from Entry 12, DMSO. N^4-acetylcytosine **3.59** has a slightly improved solubility profile which improves again with N^4-Benzoylcytosine **3.60**. TMS protected cytosine **3.61** was very soluble in every solvent tested, this can be explained by the presence of the two TMS groups making the compound much less polar, although **3.61** was prone to hydrolysis therefore storage was problematic. The very limited solubility if cytosine **3.1** can be visualised below with a Hansen solubility sphere

Figure **3.7**. Cytosine has an extremely small sphere which expands with **3.60** and even further with **3.61**.

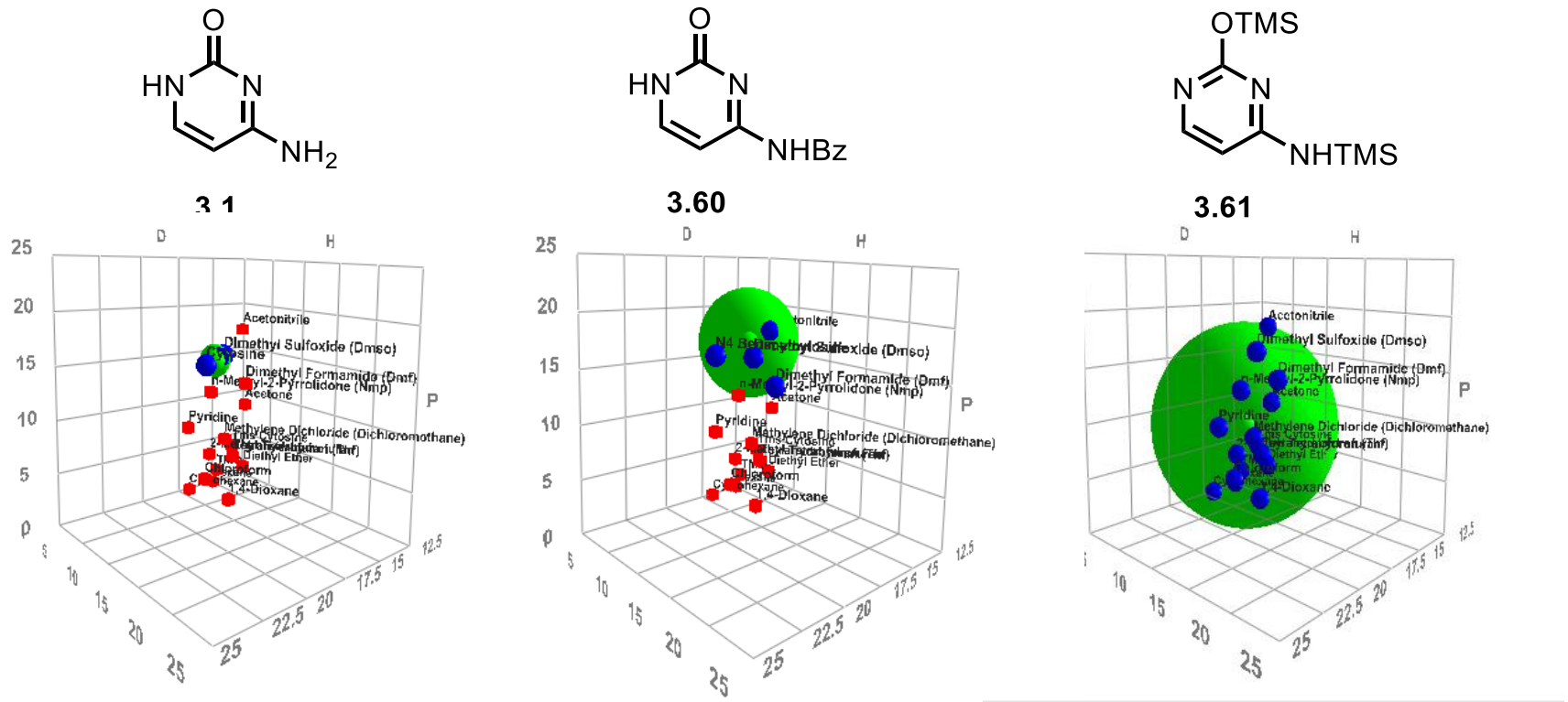
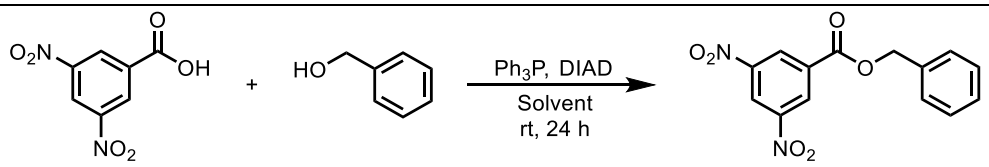


Figure 3.7: Hansen solubility spheres for protected cytosines.

Secondly the solvent effect on the Mitsunobu reaction was studied. The Mitsunobu reaction chosen for this study was the reaction between 3,5-dinitrobenzoic acid **3.62** and benzyl alcohol **3.63** which produces benzyl 3,5-dinitrobenzyl benzoate **3.64**.

Table 3.17: Mitsunobu reaction solvent screen.



3.62 **3.63** **3.64**

Entry	Solvent (0.01M)	Conversion (%) [a]	Yield (3.64) [b]
1	THF	100	98
2	2-MeTHF	100	86
3	TMO	100	79
4	1,4-Dioxane	100	60
5	Diethyl ether	100	60
6	Acetone	80	54
7	Chloroform	90	74
8	DCM	100	88
9	Acetonitrile	0	0
10	DMF	0	0
11	DMSO	0	0
12	Toluene	100	76
13	Hexane	0	0
14	Cyclohexane	0	0
15	Pyridine	0	0
16	NMP	0	0
17	Propylene carbonate	0	0
18	Isopropyl acetate	0	0
19	Ethyl acetate	0	0
20	Water	0	0
21	*p*-Cymene	93	74
22	Cyrene	0	0
23	MEK	0	0

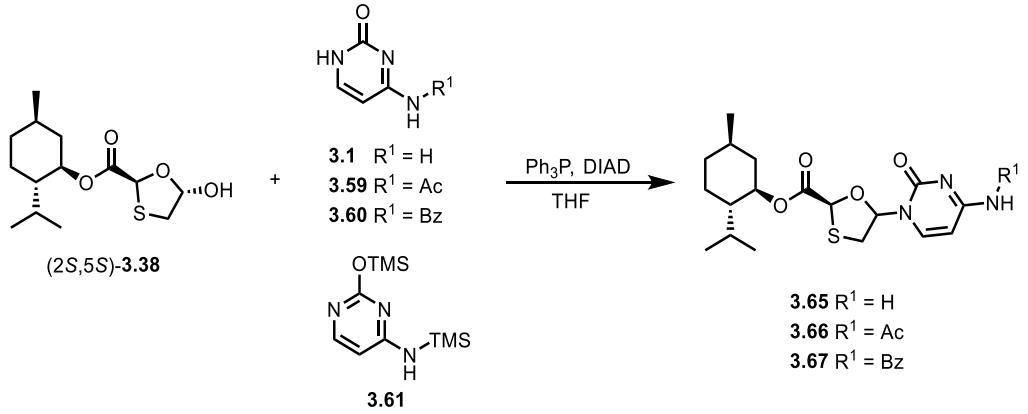
3.63 (1.0 equiv), **3.63** (1.5 equiv), PPh_3 (1.5 equiv), DIAD (1.5 eqiuiv) and solvent (0.01M)
[a] Conversion determined by GC-FID. [b] Yield determined by GC-FID.

Factors influencing the Mitsunobu reaction could be the solvents ability to stabilise the intermediate formed between phosphine and the azodicarboxylate and the ability dissolve the nucleophile and alcohol. Analysing the results from the reaction either proceeds or doesn't. The most favourable solvent is THF, Table 3.17 Entry 1 followed by Me-THF Entry 2. TMO, toluene, and *p*-cymene, Entries 3, 12 & 21 all have very similar yields ranging between 74 – 79%.

3.2.4.4. Coupling of cytosines with 1,3-oxathiolanes

Using the information gathered from the solvent study in the previous section 3.2.4.3, it was possible to identify reaction conditions which would be the most feasible for the Mitsunobu reaction to succeed with substrates of interest to this work. The initial reactions are shown below in Table 3.18.

Table 3.18: Mitsunobu screening conditions.



Entry	Cytosine derivative	DIAD (eq)	PPh_3 (eq)	Temp (ºC)	Solvent	Product	Yield (%)[a]
1	**3.1**	1.5	1.5	rt	THF	**3.65**	0
2	**3.59**	1.5	1.5	rt	THF	**3.66**	31
3	**3.60**	1.5	1.5	rt	THF	**3.67**	44
4	**3.61**	1.5	1.5	rt	THF	**3.65**	26
5	**3.60**	1.5	1.5	rt	DCM	**3.66**	10
6	**3.61**	1.5	1.5	rt	DCM	**3.67**	12
7	**3.60**	1.5	1.5	rt	TMO	**3.66**	25
8	**3.61**	1.5	1.5	rt	TMO	**3.67**	22
9	**3.60**	1.5	1.5	rt	Toluene	**3.66**	12
10	**3.61**	1.5	1.5	rt	Toluene	**3.67**	16

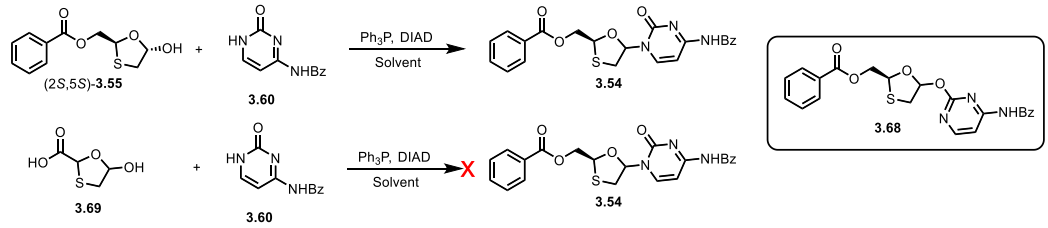
[a] Determined by HPLC

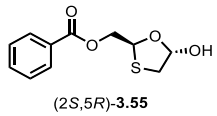
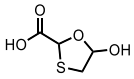
The screening reactions were focused on determining if the reaction was viable with our substrates and if the predicted product could be detected. The results agree with previous reports that unprotected cytosine **3.1** is unreactive under standard Mitsunobu conditions, presumable due its insolubility in THF Table 3.18 Entry 1. Acyl and benzoyl protected cytosine **3.59** & **3.60** performed more favourably. TMS protected cytosine **3.61** showed promise however the yields were lower than with **3.59** & **3.60** and the unprotected **3.65** was formed. The low yields could be due to the double TMS protecting groups on **3.61** making it less able to act as a nucleophile. Interesting TMO

performed better than toluene Table 3.18 Entry 7 & 8 which could be due to its similarity to THF.

Several other 1,3-oxathiolane substrates were subjected to Mitsunobu conditions and the conditions varied to try and improve the yields and obtain more of the desired N^4-addition product. One factor that could be contributing to the lower yields is the formation of *O*-addition product **3.68**. This could be formed through the tautomerization of the protected cytosine derivatives.

Table 3.19: Development of Mitsunobu reaction with 1,3-oxathiolanes



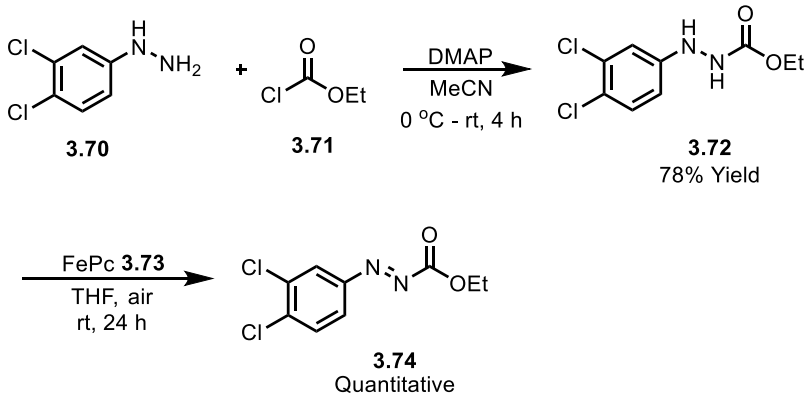
Entry	Alcohol	DIAD (eq)	PPh_3 (eq)	Temp (ºC)	Solvent	N^4-product (%)[a]	*O*-product (%)[a]
1a		1.5	1.5	rt	THF	12	3
1b		1.5	1.5	40	THF	40	22
1c		3.0	3.0	60	THF	51	35
1d		1.5	1.5	rt	TMO	4	0
1e		1.5	1.5	60	TMO	41	28
2a		1.5	1.5	rt	THF	0	0
2b		1.5	1.5	40	THF	0	0
2c		3.0	3.0	60	THF	0	0
2d		1.5	1.5	rt	TMO	0	0
2e		1.5	1.5	60	TMO	0	0

[a] Determined by HPLC

When alternative 1,3-oxathiolane substrates were examined Table 3.19 entry 1, benzyl protected 1,3-oxathiolane **3.55** gave slightly improved yields compared to **3.38** in Table 3.18 entry 1. Oxathiolane carboxylic acid **3.69**, Table 3.19 Entry 2 failed to give any product, only a complex mixture of products was formed which was most likely due to the free carboxylic acid being deprotonated and taking part in various side reactions. One important consideration was the order of addition for the reagents, this played a key role in determining the success of failure of the reaction. The cytosine substrate should be dissolved in solvent with PPh_3, followed by dropwise addition of DIAD and left to stir in the dark. This was found to promote the solubility of the substrate presumably as it was deprotonated and could tautomerize.

3.2.4.5. Scope of the Mitsunobu reaction

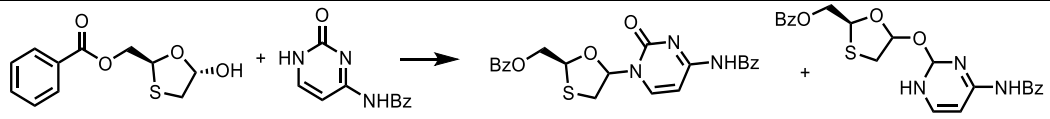
With confidence that the reaction should work with substrates of interest coupled with understanding gained around solubility of various starting materials, substitutes for PPh_3 and DIAD were sought. Firstly, Hirose *et al* had described a reaction in which the hydrazine was reoxidised in the presence of catalytic iron phthalocyanine and atmospheric oxygen.[54] Secondly Buonomo & Aldrich *et al* reported a process where the phosphine could be recycled using phenylsilane.[55] These methods were of interest as they aimed to improve the Mitsunobu reaction by moving away from stoichiometric quantities of reagent which will improve the reactions metrics.



Scheme 3.25: Synthesis of DCPEAC **3.74**

Ethyl 2-(3,4-dichlorophenyl)azocarboxylate (DCPEAC) **3.74** Scheme 3.25 was chosen as a direct substitute for DIAD in stoichiometric quantities. The exchange of DIAD for DCPEAC **3.74** had no impact on the outcome of the reaction as shown in Table 3.20 Entry 1 & 2. Next the use of catalytic quantities of DCPEAC **3.74** was investigated and a catalytic amount of FePc **3.73** was included to oxidise hydrazine **3.72** which is formed during the reaction back into the starting azo **3.74** using air as the source of oxygen Table 3.20 Entry 3. The use of catalytic quantities of DCPEAC **3.74** and FePc **3.73** was successful and the yields from Table 3.20 Entry 3 are comparable to the yields from Table 3.20 Entry 1 & 2 when DIAD & PPh_3 were used. Finally, several alternative solvents were selected Table 3.20 Entry 4 - 6, to our delight the reaction proceeded very well with toluene and TMO, Entry 4 & 5. The reaction with DMF Table 3.20 Entry 6 failed and only starting material could be detected.

Table 3.20: Mitsunobu reactions DIAD vs DCPEAC.



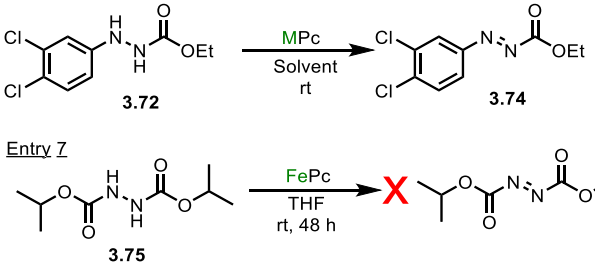
(2*S*,5*S*)-**3.55** **3.60** (2*S*)-**3.54** **3.68**

Entry	azodicarboxylate	PPh_3 (eq)	FePc (eq)	Temp (°C)	Solvent	N^4-product (%)[a]	*O*-product (%)[a]
1	DIAD 1.5 eq	1.5	0	rt	THF	51	29
2	**3.72** 1.5 eq	1.5	0	rt	THF	47	33
3	**3.72** 0.1 eq	1.5	0.1	rt	THF	48	32
4	**3.72** 0.1 eq	1.5	0.1	rt	TMO	48	32
5	**3.72** 0.1 eq	1.5	0.1	rt	Toluene	45	3
6	**3.72** 0.1 eq	1.5	0.1	rt	DMF	0	0

[a] Determined by HPLC

Other phthalocyanine dyes were screened to investigate their impact on the reaction Table 3.21. Fe, Cu, Zn all worked at room temperature, the only difference was time to completion. Table 3.21 Entry 1 was the fastest with FePc **3.73**, entry 5 CuPc was slightly slower reaching completion in 3 hours compared to FePc's 2 hours. Zn Table 3.21 entry 3 was the slowest taking 5 hours. Fe, Cu & Zn all successfully oxidise the hydrazine **3.72** to azo **3.74**. Interestingly Table 3.21 entry 7 FePc **3.73** did not oxidise the reaction using the hydrazine **3.75**. **3.75** was not able to be oxidised due to the absence of an aromatic ring which is thought to help stabilise a hydrazyl radical that could be formed during the Fe(III) catalysed oxidation of a hydrazine. Also the choice of solvent did not appear to have any influence on the reaction as can be seen in Table 3.21 Entry 1 - 4.

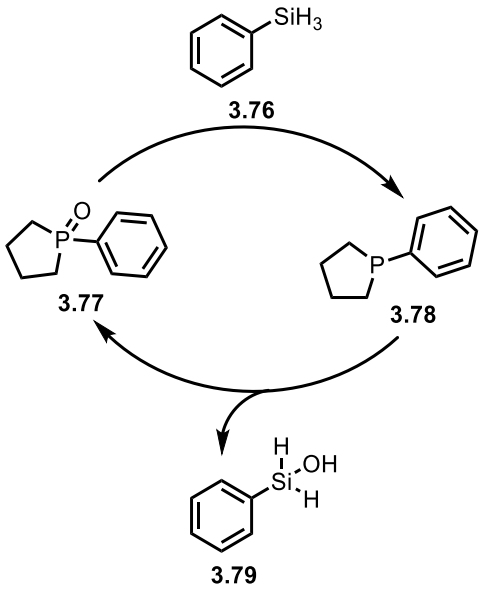
Table 3.21: Phthalocyanine screen.



Entry	Metal	Solvent	Conversion (%)[b]	Time (h)
1	Fe	THF	100	2.5
2	Fe	TMO	100	2.5
3	Fe	PhMe	100	2.5
4	Fe	DMF	100	2.5
5	Cu	THF	100	3
6	Zn	THF	100	5
7[a]	Fe	THF	0	48

[a] *E*thyl 2-(3,4-dichlorophenyl)azocarboxylate (DCPEAC) **3.72** was replaced with hydrazine **3.76** derived from DIAD.
[b] Determined by GC-FID

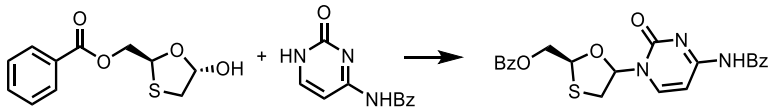
After exploring the reaction scope with different azo compounds and phthalocyanine oxidants focus moved to look at the possibility of substituting PPh_3 with a catalytic phosphine. The process reported by Buonomo & Aldrich *et al* made use of $PhSiH_3$ to recycle 1-phenylphospholane 1-oxide **3.77** to 1-phenylphospholane **3.78**.[55]



Scheme 3.26: Catalytic cycle of phosphine **3.77**.

One issue with recycling the phosphine was the formation of $PhSiH_2OH$ **3.79** as by product which still needed to be removed during work up and purification of the reaction. All this does is to move a problem elsewhere, it is not a truly catalytic reaction as you still need stoichiometric quantities of $PhSiH_3$ to recycle oxide **3.77**.

Table 3.22: Catalytic phosphine screen.



(2*S*,5*S*)-**3.55** **3.60** (2*S*)-**3.54**

Entry	azo	Phosphine 3.77	Catalyst	Oxidant	Temp (ºC)	Solvent	N^4 product (%)[a]
1	DIAD	(1.5eq)	-	-	rt	THF	2
2	DIAD	(1.5eq)	-	-	60	THF	8
3	DIAD	(10 mol%)	-	$PhSiH_3$	rt	THF	0
4	DCPEAC	(10mol%)	FePc	$PhSiH_3$	rt	THF	0
5	DCPEAC	(10mol%)	FePc	$PhSiH_3$	70	THF	0

[a] Determined by HPLC

Table 3.22 shows the results from substituting PPh_3 with phosphine **3.77.** Table 3.22 entry 1 & 2 are straight swaps of PPh_3 for **3.77**, a trace of product was detected in Entry 1 which was performed at room temperature and a little more product was detected in Entry 2 when the reaction was warmed to 60 ^oC. Only starting material was detected in Table 3.22 entry 3 & 4, these reactions were unsuccessful.

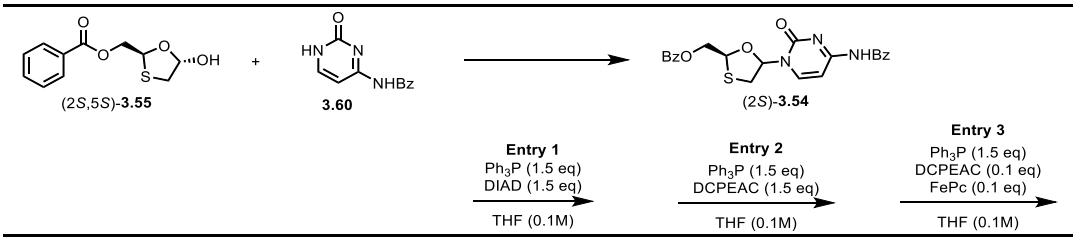
3.2.4.6. Metrics

Comparing the variations of Mitsunobu reaction through reaction metrics should highlight the effect that any change of reagent or conditions make on the overall process. As explained earlier in this thesis, all workup materials and solvents have been excluded so the metrics can focus on the reaction and the parameters that directly effect the process. The metric analysis has been carried out using experimental data generated from the work presented in this chapter. Table 3.23 Entry 1 explores the generic Mitsunobu reaction with 1.5 eq of DIAD and PPh_3. Table 3.23 Entry 2 is a Mitsunobu reaction were 1.5 eq of DIAD is replaced with 1.5 eq of DCPEAC **3.74**. Table 3.23 Entry 3 is were the first major change occurs, DCPEAC **3.74** is reduced from 1.5 to 0.1 eq and 0.1 eq of FePc **3.73** is used to regenerate the active hydrazine *in situ.*

At a glance the data presented in Table 3.23 for Entry 1 – 3 is very similar. The yield for each entry had a range of 4% from lowest to highest. The AE for all three entries is identical at a respectable 96.0% and the RME varies by 3.4% from 41.0 to 44.4%. The PMI ranges from 44.6 g g^{-1} for Entry 1 a typical Mitsunobu reaction to 48.7 g g^{-1} in Entry 2 when DIAD is replaced with DCPEAC **3.74**. The increases in PMI can be explained by the increases in molecular weight of the reagent, 46.88 g mol^{-1} is the difference between DIAD and DCPEAC **3.74**.

The PMI of Entry 2 is 46.3 g g^{-1} were a semi catalytic cycle has been introduced. This increase in PMI is unfortunate as the process has become partly catalytic and one would hope to see an improvement in the metric data. The slight increases compared to the generic route Entry 1, can be explained by the marginally lower yield in Entry 3. If the yield in Entry 3 was identical to Entry 1 the PMI would be 43.6 g g^{-1} and therefore would be an improvement.

Table 3.23: Metrics of Mitsunobu reactions.



Metric parameter	Entry 1	Entry 2	Entry 3
Yield (%)	51.2	47.2	48.2
Traditional AE (%)	96.0	96.0	96.0
Traditional RME (%)	44.4	41.0	41.9
PMI reaction (g g^{-1})	44.6	48.7	46.3
PMI_{RRC} (g g^{-1})	5.4	6.2	4.6
PMI_{Solv} (g g^{-1})	39.2	42.5	41.6
Solvent choice	🚩	🚩	🚩
Catalyst?	🚩	🚩	🏳
Recoverable catalyst?	🚩	🚩	🚩
Critical element	🏳	🏳	🏳
Energy	🏳	🏳	🏳
Work-up	🚩	🚩	🚩
Health and safety	🏳	🏳	🏳
Chemical of concern?	🏳	🏳	🏳

Flag system: Green flag 🏳 preferred, amber flag 🏳 acceptable but some issues and red flag 🚩 is undesirable.
A full key and explanation of the metrics analysis and flag classification can be found in the appendix.

Looking at only the effect of reagents, PMI_{RRC} can demonstrated that Entry 3 has the lowest value of 4.6 g g^{-1} and this highlights the improvement moving to a catalytic process can have. One issue with many metal catalysts and large ligands is the molecular weight of the compounds, in this work FePc **3.73** has a MW of 572.41 g mol^{-1} which means a significant mass is required to meet a desired loading of 10 mol%. The effect of molecular weight causing a distortion with reaction metrics and in particularly PMI has already been covered in detail in Chapter 2. The solvent used in Entry 3 is also an improvement, although only highlighting it for one entry is unfair as THF can be substituted for TMO successfully in all three entry's in Table 3.23.The overall picture presented by the metric analysis shows that the changes have a little effect. PMI is dominated by the solvent choice which remains constant as all the reactions are performed at a constant concentration. The RME stays relatively constant as the yields are similar and there is not a large excess of substrate.

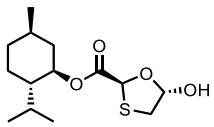
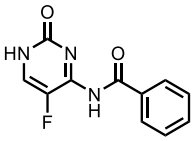
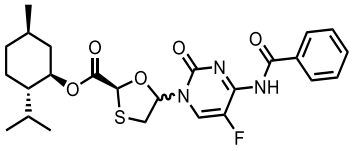
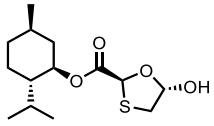
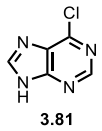
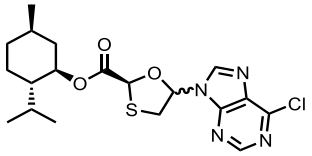
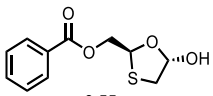
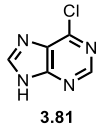
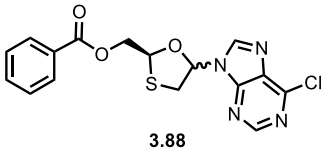
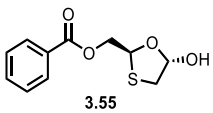
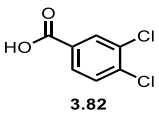
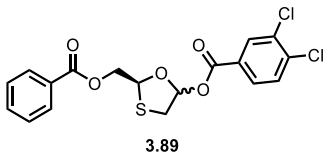
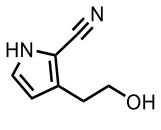
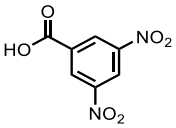
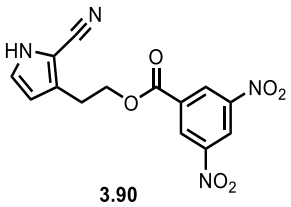
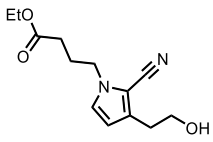
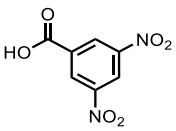
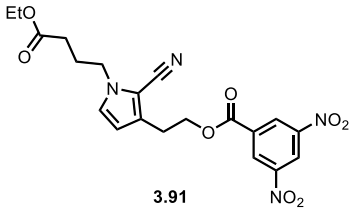
3.2.4.7. Mitsunobu reaction scope of nucleoside coupling

After investigating the coupling of 1,3-oxathiolanes with cytosine **3.1** attention moved to examine the scope of the Mitsunobu reaction between 1,3-oxathiolanes and other compounds. It has been mentioned in the literature that cytosine **3.1** is not favoured for the Mitsunobu reaction, suggesting this would not be a fruitful area of investigation.[189] In this work, with a careful selection of conditions it was possible for cytosine **3.1** to participate in the Mitsunobu reaction. However, the reactions of 1,3-oxathiolane alcohol with purines and other substrates proved to be slightly more successful that with cytosine **3.1**.

To further explore Mitsunobu reaction with unusual substrates six reactions were performed, Table 3.24 entry 1 – 6. The conditions were identical for each reaction and DCPEAC **3.74** was used in conjunction with FePc **3.73** both at 10 mol% with TMO as the solvent. Entry 1 involved oxathiolane alcohol **3.38** coupling to benzoyl protected 5-fluorocytosine **3.80** and proceeded smoothly giving a yield of 45%. For entry 2 and entry 3, 6-chloropurine **3.81** was used with alcohols **3.38** & **3.55**. These reactions again provided access to the desired product in 40% yield after purification. Alcohol **3.55** was then coupled to 3,4-dichlorobenzoic acid **3.82** which once again gave a yield of 40% after purification. These four reactions showed that oxathiolanes **3.38** and **3.55** have the scope to react with a variety of substrates. In the four reactions Table 3.24 entry 1 – 4, a single diastereoisomer was obtained but the configuration of this isomer is unknown.

To conclude the investigation into the Mitsunobu reaction, coupling was attempted between 2,3-disubstituted pyrroles **3.83** & **3.84** with 3,5-dinitrobenzoic acid **3.62**. These pyrroles were selected due their novel structure and to see if a pyrrole was compatible with these Mitsunobu conditions as pyrroles are known to decompose and oxidise relatively easily.[190] under the semi catalytic conditions using DCPEAC **3.74** and FePc **3.73** in 10 mol% with air/oxygen as oxidant. Pyrrole **3.83** and **3.84** could be accessed from propargyl alcohol **3.85** in 6 and 7 steps respectively. It was surprising to find that unprotected pyrrole **3.83** gave the desired produced **3.90** in 55% yield and protected pyrrole **3.84** yielded 86% of **3.91**. Both nitrile pyrroles and their corresponding products could not be found in the literature and it was promising to discover these novel compounds reacted as hoped.

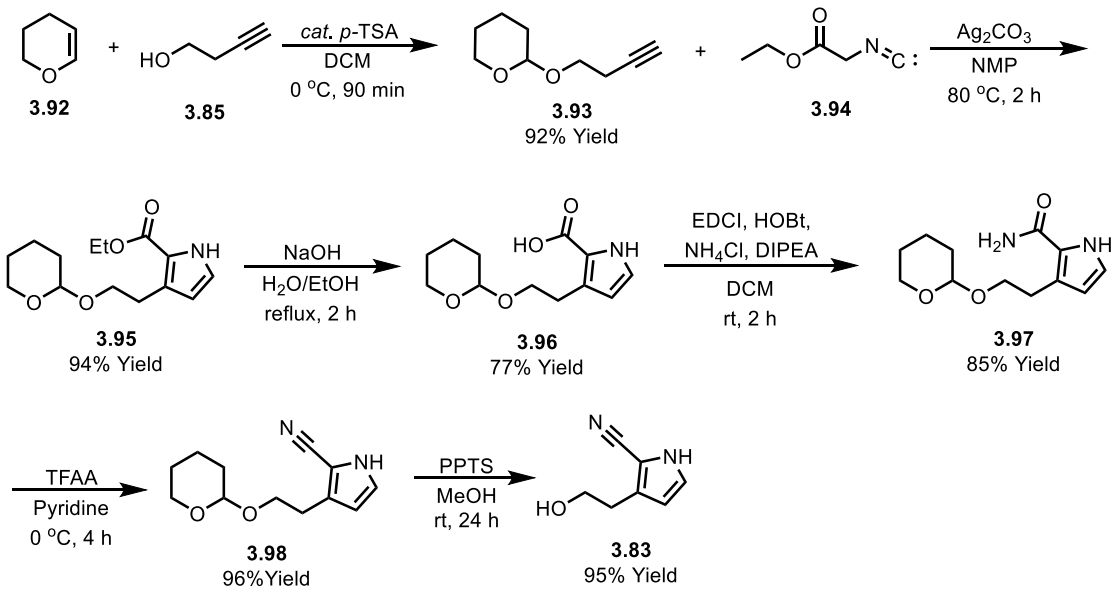
Table 3.24: Expansion of Mitsunobu reactions.

Entry	Alcohol	Substrate	Time (h)	Product	Yield (%)[a]
1	 **3.38**	 **3.80**	24	 **3.86**	45[b]
2	 **3.38**	 **3.81**	24	 **3.87**	40[b]
3	 **3.55**	 **3.81**	24	 **3.88**	40[b]
4	 **3.55**	 **3.82**	24	 **3.89**	40[b]
5	 **3.83**	 **3.62**	24	 **3.90**	55
6	 **3.84**	 **3.62**	24	 **3.91**	86

General reaction conditions: Alcohol (1.0 equiv), carboxylic acid (1.5 equiv), PPh_3 (1.5 equiv), DCPEAC **3.74** (10 mol%), FePc **3.73** (10 mol%), 60 °C, 24h in TMO (0.01M)
[a] Isolated yield after chromatography.
[b] Single diastereoisomer was obtained but the configuration of this isomer is unknown.

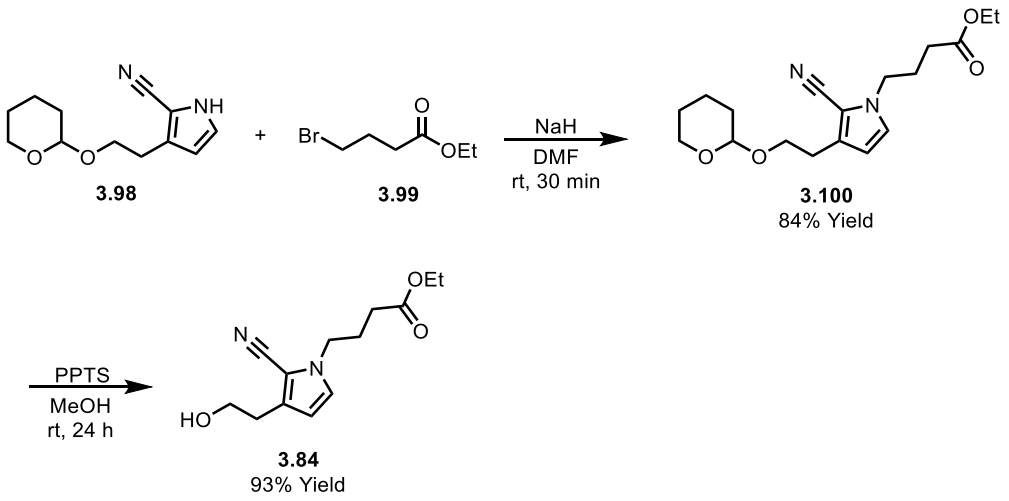
The synthesis of pyrrole **3.83** began with propargyl alcohol **3.85** which was protected with a tetrahydropyran ether by reaction with 3,4-dihydropyran **3.92** with catalytic *p*-TSA to give **3.93**. Ether **3.93** then reacted with ethyl isocyanoacetate **3.94** and a catalytic amount of silver carbonate to give the 2,3-disbustituted pyrrole **3.95**. To access nitrile **3.98**, ester **3.95** was hydrolysed under basic conditions to give carboxylic

acid **3.96** which was converted to amide **3.97** using EDC and HBOt as activating agents. Amide **3.97** was dehydrated with trifluoroacetic anhydride (TFAA) in pyridine to give nitrile **3.98** which could be deprotected with pyridine *p*-toluenesulfonate (PPTS) in methanol to give alcohol **3.83** with an overall yield of 52% over 6 steps Scheme 3.27.



Scheme 3.27: Synthesis of 2,3-disubstituted pyrroles **3.82**.

To access pyrrole **3.84**, THP protected nitrile **3.98** was *N*-alkylated with ethyl 4-bromobutyrate **3.99** using sodium hydride in DMF to give pyrrole **3.100** which could be deprotected with PPTS to give alcohol **3.84** Scheme 3.28.



Scheme 3.28: Synthesis of 2,3-disubstituted pyrroles **3.84**.

3.3. Conclusions

The work presented in this chapter highlights the improvements that can be made to some processes that are already efficient and may appear almost optimal from an initial glance. The improvements highlighted in this chapter were first identified by performing a reaction metric analysis on the process, as discussed, this analysis can highlight pinch points or possible area for improvement.

With the synthesis of cytosine **3.1** an initial metric review of the reaction which used urea **3.7** and nitrile **3.8** with sodium ethoxide in *m*-xylene indicated that areas with scope for improvement. Through experimentation it was shown that the solvent *m*-xylene and reagent sodium ethoxide could both be substituted for more environmentally friendly and safer alternatives. Ethanolic HCl proved to be a suitable alternative acting as both reagent and solvent. The improvements and benefits over *m*-xylene and sodium ethoxide have been demonstrated through a review of the modified process metrics profile. This change is nothing extraordinary, but the improvements lessen the hazards and potential negative impact of the process from an environmental and health and safety viewpoint. The next improvement was acetylating acrylonitrile **3.43** through a modification of a known procedure. The solid supported catalysts were easily filtered out and the crude filtrate could be acidified with HCl and then reacted with urea to form cytosine in a direct and efficient process.

The discovery that the safe and potentially bio-based solvent TMO was a viable replacement solvent in the chemoenzymatic formation of 1,3-oxathiolanes and the Mitsunobu reaction was another important discovery. The use successful use of TMO is significant and welcome as this solvent could reduce and potentially eliminate the need to use hazardous solvents such as toluene and THF.

The scope of the Mitsunobu reaction and catalytic versions of the process were also investigated and these reported catalytic procedures used to attempt the coupling of oxathiolanes to cytosine, purines and other carboxylic acids. The results were mixed with success and failure, but the successful reactions demonstrated that the Mitsunobu reaction could be applied to couple cytosines and oxathiolane which creates the opportunity for further research into the reactivity of oxathiolanes with other

substrates. The success of TMO as a suitable solvent for all the Mitsunobu reactions performed in this chapter. TMO showed no detrimental effect on the Mitsunobu reaction when simple reactants such as benzyl alcohol and 3,5-dinitrobenzoic acid were used or more functionalised reactants such as 2,3-disubstituted pyrroles or oxathiolane alcohols.

By using the metrics tool kit developed by the Chem21 consortium the improvements in organic synthesis throughout this chapter have been quantified and highlighted. When an improvement can be made visible it is more likely to be used and the method of analysis also more likely to be shared and used.

Chapter 4

OH Activation

4.1. Introduction

4.1.1. OH activation

In 2005 & 2015 through the American Chemical Society Green Chemistry Pharmaceutical Roundtable (ACS GCIPR) developed a list of reactions and topics they believed the most benefit from future advancements could be made from. The most popular transformation for improvement was amide formation which is not surprising given that this is the most frequently used reaction in the pharmaceutical industry. As stated in Chapter 2 amide bond formation is the largest category of reactions carried out in the pharmaceutical industry (16% of all transformations).[133] Second on the list was OH activation for nucleophilic substitution (2005) updated to direct substitution of alcohols (2015) Table 4.1.

Table 4.1: Reactions which are in use, but companies have a strong interest in developing better reagents.[22]

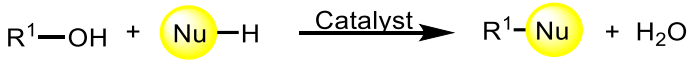
Research area	**Number of Roundtable companies voting for this research area as a priority area**
Amide formation avoiding poor atom economy reagents	6 Votes
2005 - OH activation for nucleophilic substitution 2015 - Direct substitution of alcohols	5 Votes
Reduction of amides without hydride reagents	4 Votes
Oxidation/Epoxidation methods without the use of chlorinated solvents	4 Votes
Safer and more environmentally friendly Mitsunobu reactions	3 Votes
Friedel–Crafts reaction on unactivated systems	2 Votes
Nitration	2 Votes

The substitution of activated alcohols is a frequently used approach for the preparation of active pharmaceutical ingredients (API's). A survey of reactions scaled up at Pfizer's Groton site over a 17 year period found that 2% of transformations involved the conversion of alcohol to a reactive halide, tosylate or mesylate.[191] The conversion

of an alcohol into these reactive intermediates allows for a nucleophilic substitution reaction to occur. A major disadvantage of activating an alcohol is the use of additional resources and decrease in efficiency of a process that this entails. Having to proceed through derivatisation results in generation of waste and a lower atom economy.

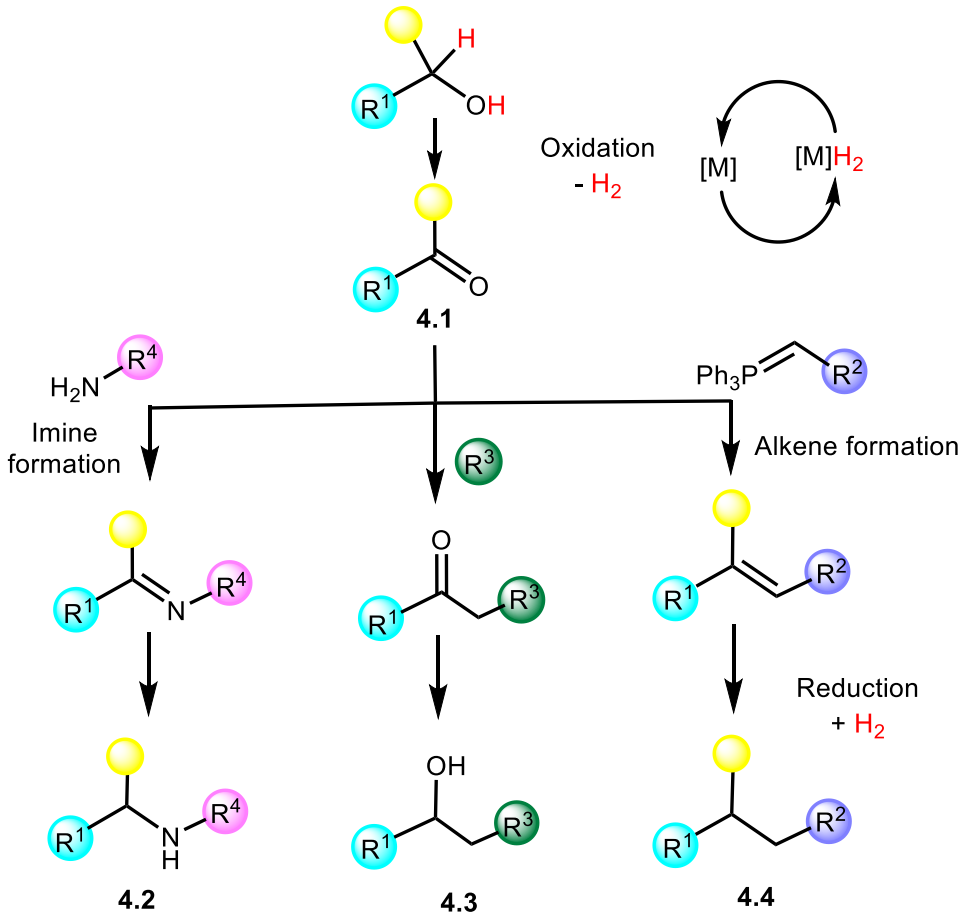
Another limitation of direct OH activation is that several procedures require an excess of sulfuric or polyphosphoric acid or a stoichiometric amount of a Lewis acid.[192-194] The use of these reactants and conditions therefore severely limits the scope of nucleophile that can be used. Alkylating reagents used to activate alcohols also tend to be toxic which is a further drawback.

These numerous drawbacks therefore currently limit direct nucleophilic substitution of an alcohol. However, the if it could be optimised, direct nucleophilic substitution of an alcohol is a very appealing, as the only side products from the reaction would be water Scheme 4.1. The obstacle that direct OH activation needs to overcome is hydroxide being a poor leaving group as this limits the potential of the reaction.



Scheme 4.1: Nucleophilic substitution of an alcohol.

Currently *in situ* OH activation can be achieved through the Mitsunobu reaction. This requires a stoichiometric quantity of activating reagents negatively impacting upon the reaction metrics which lowers the metric performance. Also, the azodicarboxylates tend to be toxic and the phosphine oxides formed can cause difficulties during purification of the final product. One approach to OH activation has been termed "Borrowing Hydrogen Method" or "Hydrogen Auto-transfer Process".[195, 196] In this method the hydrogen is removed from the alcohol to form an intermediate carbonyl **4.1**, which can react more easily with various nucleophiles Scheme 4.2. In this process the removal of hydrogen is catalytic, and it is returned to the product meaning there is no overall oxidation or reduction happening. This application covers the formation of C-C and C-N bonds although limitations of this process can be high temperatures and catalyst loading along with using expensive platinum group metals.[197-201]

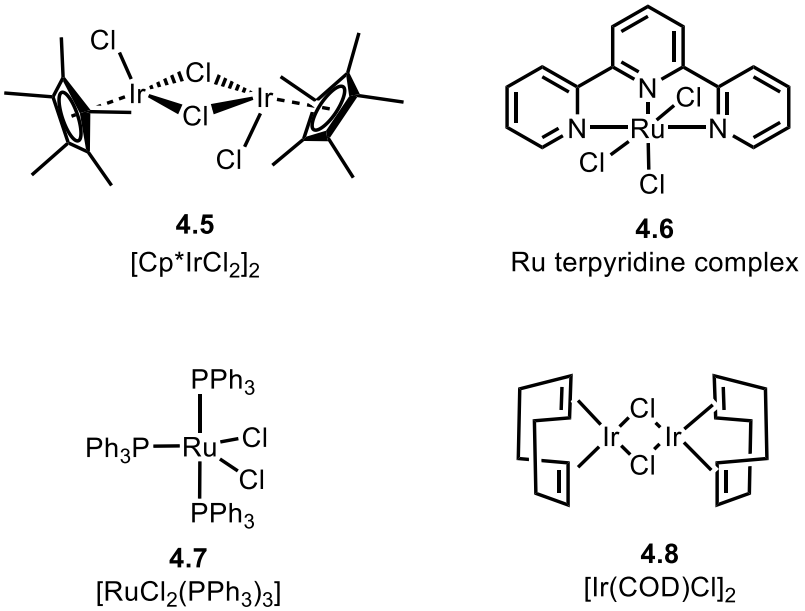


Scheme 4.2: Borrowing hydrogen method for formation of C-C & C-N bonds.

4.1.1.1. Catalysts for OH activation

Recent advances in OH activation have focused on the use of transition metals and complexes as catalysts. A vast number of catalysts have been used successfully for nucleophilic substitution with alcohols. The catalysts range in complexity from a simple Lewis or Brønsted acid such as $FeCl_3$ or *p*-TSA through to complexes with various ligands such as $[Cp^*IrCl_2]_2$ **4.5**, $[RuCl_2(PPh_3)_3]$ **4.6**, ruthenium terpyridine **4.7** & $[Ir(COD)Cl]_2$ **4.8** as shown in Figure 4.1. A review of direct S_N1 type nucleophilic substitution of alcohols by Cozzi *et al* examined over thirty different catalysts.[202] The catalysts covered in the review were Lewis acids; montmorillonite clay and numerous metal triflates and chlorides ($Bi(OTf)_3$, $Cu(OTf)_2$, Ag(OTf), $Hg(OTf)_2$, $La(OTf)_3$, $Yb(OTf)_3$, $In(OTf)_3$, BF_3, $FeCl_3$ & $InCl_3$), along with Brønsted acid; *p*-TSA and TfOH and metal complexes of Ru, Au, Mo, Ni, Pd, Re. The fact that so many catalysts can be used for similar transformations highlights the enormous potential that already exists for OH activation.

As promising and useful as Lewis acids may appear from a green chemistry perspective their sustainability should also be considered. It is common for Lewis acids to be destroyed before a reaction is worked up which leads to several issues. If the catalyst is destroyed it cannot be recovered and recycled. Being destroyed will also result in inorganic salts being dissolved in the aqueous waste streams which can be hazardous and expensive to dispose of. The suitability of the metal is another cause for concern as the vast majority of common metals used are at risk of depletion and sourced from mining.[184] Some of the metals within the highest risk category (depletion of known reserves in 5 – 50 years) are bismuth, indium, iridium, ruthenium, rubidium and zinc.[101, 184] None of these issues support the twelve principles of green chemistry although they do provide many opportunities for improvement and research.



4.5
$[Cp^*IrCl_2]_2$

4.6
Ru terpyridine complex

4.7
$[RuCl_2(PPh_3)_3]$

4.8
$[Ir(COD)Cl]_2$

Figure 4.1: Example of catalysts used for OH activation.

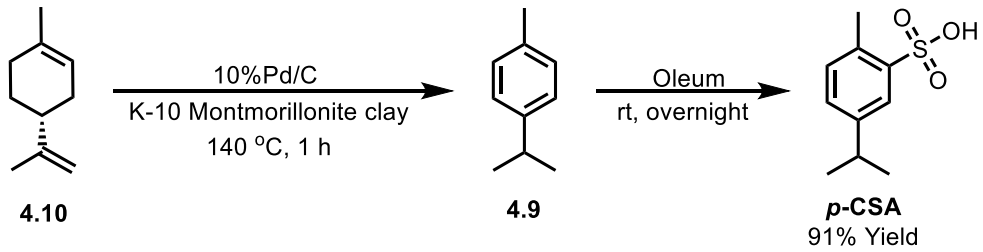
Several transition metal catalysts have also been shown to aid in the direct nucleophilic substitution with various primary and secondary alcohols.[203-209] Secondary benzylic alcohols containing a propargylic or allylic alcohol has been shown to react with various different nucleophiles catalysed by La, Sc, or Hf salts and catalysts derived from Fe or Au.[210-213] In addition, $InCl_3$ and $In(OTf)_3$ have emerged as powerful catalysts to perform direct nucleophilic substitution of allylic, propargylic and benzylic alcohols.[41, 42, 44, 202, 214] Such transformations have been discovered due to an increased understanding of the electrophilic carbonium ion that is formed when these alcohols are treated with acid. This understanding was made possible by work

performed by Olah and Mayr.[215-217] When the electrophilic and nucleophilic character of compounds was studied, and understood, the development of new reactions became possible. Using the Mayr reactivity scale it is possible to rationally design various S_N1 type reactions.[216, 217] The reactivity scale is limited though as there have been reports S_N1 type reactions involving of less activated alcohols.[218, 219] This anomaly illustrates the opportunity for further research into reactions with very reactive and electrophilic carbocations.

4.1.2. *p*-Cymene sulphonic acid (*p*-CSA)

p-Toluenesulphonic acid (*p*-TSA) is a strong Brønsted acid which is soluble in organic solvents and routinely used in organic synthesis as a catalyst or reagent. Some uses of *p*-TSA include the protection of carbonyls, esterification of carboxylic acids and transesterification of esters.[220] *p*-TSA has also been reported to catalyse the nucleophilic substitution of allylic and propargylic alcohols.[42] *p*-TSA is produced industrially by the sulphonation of toluene as an intermediate in the production of *p*-cresol.[221] A major drawback of this process is its use of petrochemical feedstocks. Recently pressure from governments and consumers has been pushing manufactures to become more sustainable. This has led manufactures to source and make use of bio-based chemicals and resources. As bio-based materials become more common place it is not unreasonable to assume that a bioderived equivalent of *p*-TSA would be welcomed and widely adopted.

A renewable alternative for toluene is *p*-cymene **4.9** a monoterpene which can be obtained from limonene **4.10** an extract from citrus waste. *p*-Cymene **4.9** has been successfully used as an alternative for toluene and can be sulphonated to give *p*-cymene-2-sulphonic acid (*p*-CSA) Scheme 4.3.[222, 223] Sulphonation of *p*-CSA occurs mostly at C-2 relative to the methyl group and can be isolated as a single isomer by recrystallisation with conc. HCl.



Scheme 4.3: Synthesis of *p*-CSA with from limonene **4.10**.

Sherwood *et al* have shown that *p*-CSA has been successfully used in place of *p*-TSA for a number of chemical applications such as, esterification of carboxylic acid in ionic liquids, the condensation of aldehyde with a ketone and also acetal protection using ethylene diol.[224, 225] Sherwood *et al*'s paper detailing the synthesis of *p*-CSA was available online in January 2012, almost 10 years ago, but since then there has been no uptake in the use of *p*-CSA (according to a SciFinder search 09/11/2021).

The two major reasons for this could be;

i.) No incentive or motivation from researchers or industry.

ii.) Lack of availability.

p-TSA is not considered a substance of concern and there are no toxicity or serious health hazards associated with the it. *p*-TSA is also commercially available as a cheap commodity chemical. A researcher can purchase 1 kg of ≥98.0% *p*-TSA monohydrate from Sigma Aldrich for £50.50.[226] In contrast to this *p*-CSA is not available even in small quantities, therefore given these considerations perhaps the lack of interest in *p*-CSA is not surprising.

4.1.3. Chapter aims

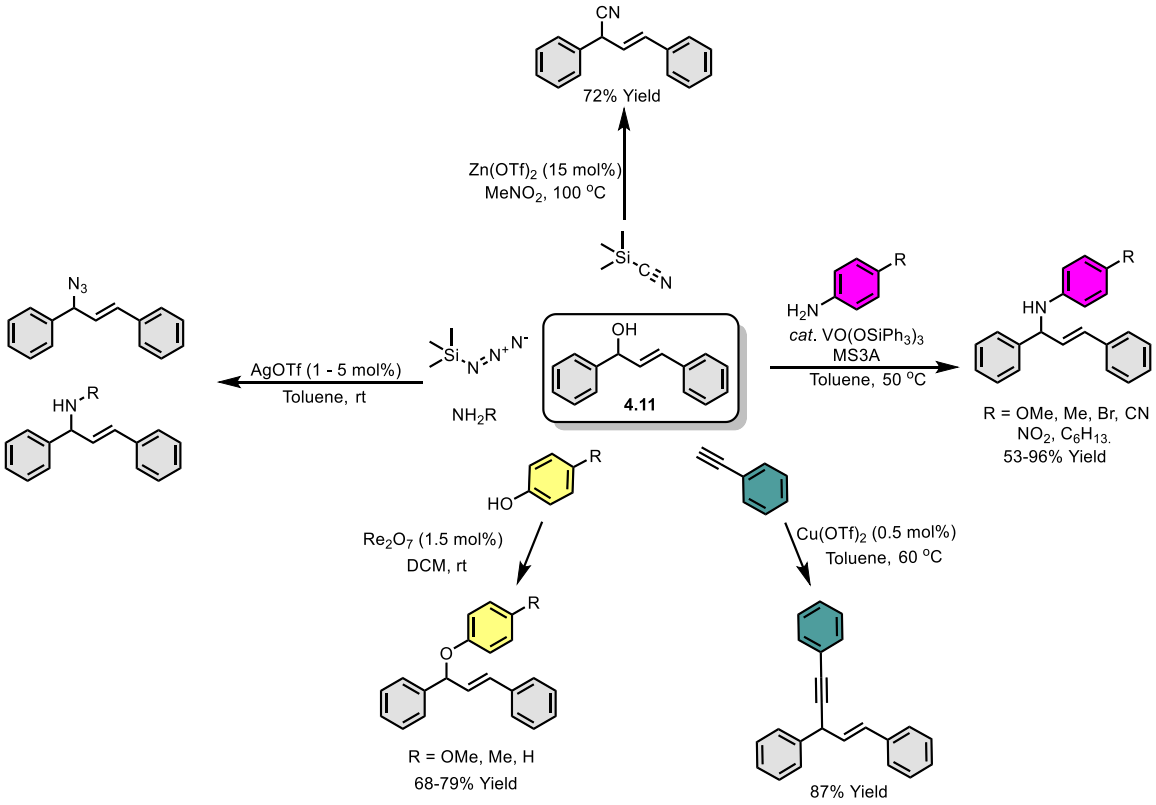
The aim of this chapter will be to explore the substitution of traditional solvents and catalysts with greener alternatives which have received limited application testing.

Initially, the use of *p*-CSA and alternative solvents were investigated in S_N1 type nucleophilic substitution reactions with allylic, propargylic and naturally occurring alcohols. Toluene is a wildly used solvent in organic chemistry and is frequently used for OH activation reactions. Therefore the application of TMO was of interest because it had been developed specifically as a replacement for toluene.[90] The application of *p*-CSA was then investigated as an alternative for *p*-TSA in the protection of a carbonyl and alcohol functional groups in synthetically important intermediates. Also, in collaboration with Valtris Specialty Chemicals *p*-CSA was trialled as a catalyst in an esterification of fatty acid (C10-20 acids) with 2-ethylhexanol. The substitution of *p*-TSA for *p*-CSA could improve the sustainability profile of the product as it would be possible to obtain the catalyst from a bio-based resource.

4.2. Results and discussion

4.2.1. OH activation of allylic, propargylic and natural alcohols

Brønsted acid-catalysed nucleophilic substitution of allylic and propargylic alcohols has been reported in the literature using *p*-TSA as a catalyst to facilitate the formation of C-C, C-N, C-O and C-S bonds.[42, 44] We wanted to explore the scope of these transformations using a potentially bio based catalyst *p*-CSA and alternative solvents; TMO, 2-MeTHF and CPME. Allylic alcohol **4.11** was chosen as the ideal substrate as it has been used in numerous OH activation studies Scheme 4.4.[227-231]

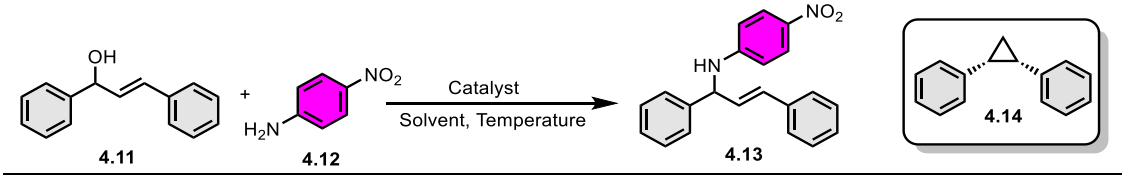


Scheme 4.4: Reactions of alcohol **4.11**.

4.2.1.1. Nucleophilic addition to allylic alcohol 4.11

Use of *p*-CSA as catalyst in the activation of alcohol **4.11** began with directly substituting *p*-TSA with *p*-CSA, Table 4.2 entry 1 and then various screening reactions were performed, Table 4.2 entry 1-12. Nucleophile 4-nitroaniline **4.12** was chosen for the screening reactions as in the literature the highest yields were obtained using it, as such any effects caused by changing the catalyst or solvent should be more easily identifiable.[42]

Table 4.2: Nucleophilic coupling *p*-CSA solvent screening reactions.



Entry	Catalyst	mol%	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	*p*-TSA	5 mol%	MeCN	rt	24	90
2	*p*-CSA	5 mol%	MeCN	rt	24	90
3	*p*-CSA	1 mol%	MeCN	rt	36	90
4	*p*-CSA	1 mol%	PhMe	60	12	85
5	*p*-CSA	1 mol%	TMO	60	12	88
6	*p*-CSA	30 mol%	2-MeTHF	60	24	0
7	*p*-CSA	30 mol%	CPME	60	24	0
8	*p*-CSA	1 mol%	THF	60	12	10
9	*p*-CSA	1 mol%	Et_2O	rt	24	0
10	*p*-CSA	1 mol%	DCM	rt	24	79
11	$InCl_3$	1 mol%	PhMe	60	12	91
12	$InCl_3$	1 mol%	TMO	60	12	90

General reaction conditions: 1.0 equiv. of alcohol, 1.5 equiv. of nucleophile in solvent (5 mL).
[a] Yield determined by GCMS.

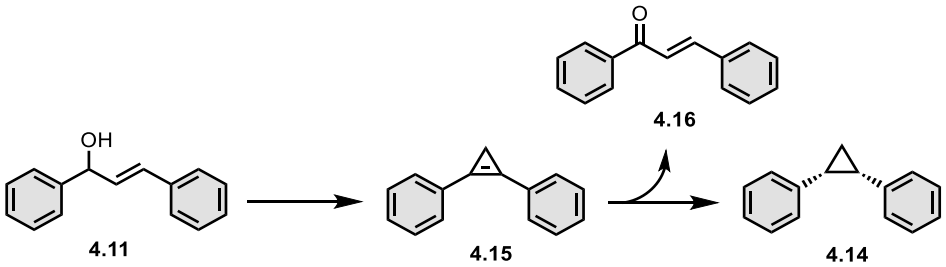
The reaction between 4-nitroaniline **4.12** and alcohol **4.11** gave compound **4.13** in a yield of 90% when the reaction was performed in acetonitrile at room temperature irrespective of whether the catalyst used was *p*-TSA or *p*-CSA, Table 4.2 entry 1 & 2. The catalyst loading for *p*-CSA was reduced to 1 mol% which gave an isolated yield of 90%, although the reaction time had increased by 12 hours Table 4.2 entry 3. The reaction between 4-nitroaniline **4.12** and alcohol **4.11** catalysed by *p*-CSA was then performed in several alterative solvents. Given the frequent use of toluene in OH activation reactions, it was the first solvent to be selected. In Table 4.2 entry 4, which shows toluene, the reaction required 12 hours at 60 °C to reach completion which was indicated by disappearance of alcohol **4.11**.

The reaction gave a yield of 85% as determined by GCMS. When TMO was used under the same condition as toluene Table 4.2 entry 5, the yield improved slightly to 88%. This was a promising result and is a good example of the versatility of TMO. 2-MeTHF and CPME entry 6 & 7 both failed to produce any desired product at room temperature and 1 mol % or at elevated temperature and 30 mol%, only starting material was recovered.

Traditional solvents, THF, diethyl ether and dichloromethane were also investigated, Table 4.2 entry 8 – 10. THF gave a yield of 10% but 100% conversion, with a significant amount of side product **4.14** detected. Diethyl ether was identical to CPME with only starting material being recovered. In Table 4.2 entry 10, DCM was used and a yield 61% obtained after 24h at room temperature.

Finally, Table 4.2 entry 11 & 12 indium (III) chloride ($InCl_3$) was used as catalyst with toluene and TMO both screened as solvent. In these examples an excellent yield of 91 & 90% was obtained which confirmed previous reports that $InCl_3$ is a powerful catalyst for OH activation on allylic substrates.

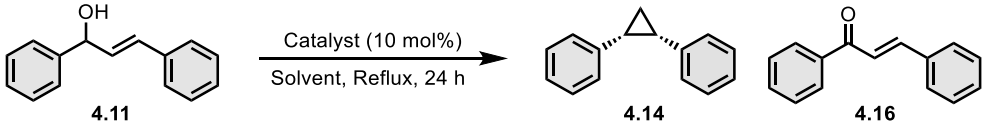
In Table 4.2 entry 6, 7 & 9 failed completely and only starting material was recovered. For the other reactions the conversion of starting alcohol **4.11** was 100%, therefore a brief investigation into the formation of side product **4.14** was performed. Cyclopropane **4.14** was initially detected by GCMS and its molecular weight was confirmed by mass spectroscopy. The structure and stereochemistry of **4.14** was verified and defined as *cis* by NMR spectroscopy. The protons adjacent to the phenyl groups on the cyclopropane gave a doublet of doublets with coupling constants of 8.4 & 6.4 Hz which is indicative of a *cis* configuration. It is thought that side product **4.14** is formed by an intermolecular Friedel-Crafts alkylation of alcohol **4.11** to give alkene **4.15** which is converted into cyclopropane **4.14** by a transfer hydrogenation process. The hydrogen is obtained either from starting alcohol **4.11** which results in ketone **4.16** or from acidic solvents or impurities present in the reaction Scheme 4.5.[232]



Scheme 4.5: Side product **4.14** formation during OH activation.

In order to verify if alcohol **4.11** was being consumed through the pathway described in Scheme 4.5 it was dissolved in solvent with $InCl_3$ and the mixture refluxed for 24 hours.

Table 4.3: Investigating the formation of side product **4.14**.



4.11 **4.14** **4.16**

Entry	Catalyst	Solvent	Yield 4.14 (%)[a]	Yield 4.16 (%)[a]	Ratio 4.14:4.16
1	$InCl_3$	MeCN	12	10	6:5
2		PhMe	24	18	4:3
3		TMO	25	20	5:4
4		2-MeTHF	32	8	4:1
5		CPME	21	7	3:1
6		THF	34	10	3.4:1
7		Et_2O	15	9	5:3
8		DCM	33	26	1.7:1.3
9	*p*-CSA	THF	35	8	4.3:1

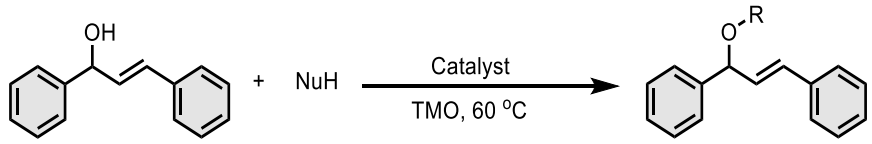
General reaction conditions: 1.0 equiv. of alcohol, 10 mol% catalyst, 24 hours at reflux.
[a] Yield determined by GCMS.

The results from Table 4.3 reveal that the intermolecular Friedel-Crafts alkylation is possible with alcohol **4.11** and that it is feasible to obtain cyclopropane **4.14** as a side product. Also is it interesting to observe the results from Table 4.3 entry 6 where THF is used as solvent. In entry 6 there is the largest difference between cyclopropane **4.14** and ketone **4.16** which may indicate that the cyclopropene **4.15** is being hydrogenated more from sources other than **4.11** possibly from the solvent as traces of furan were detected by GCMS. Table 4.3 entry 9, *p*-CSA was used as catalyst and the yield of cyclopropane **4.14** obtained was 35% vs 34% with $InCl_3$. This finding could suggest that THF, CPME and 2-MeTHF are unable to stabilise the carbonium intermediate that is formed when alcohol **4.11** is activated, therefore stopping direct nucleophilic substitution from proceeding.

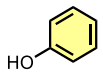
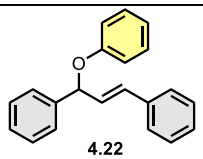
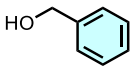
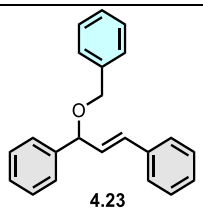
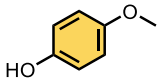
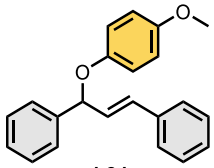
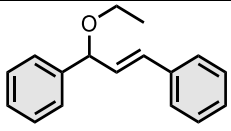
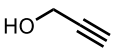
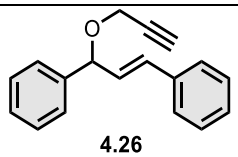
Having identified that the nucleophilic substitution between 4-nitroaniline **4.12** and alcohol **4.11** can be successfully performed by catalytic quantities of *p*-CSA in TMO, the reaction with several other nucleophiles to form C-O, C-N, C-S & C-C bonds was explored. Given the excellent yields obtained by $InCl_3$ this catalyst was also investigated alongside *p*-CSA. This provided a comparison of a Brønsted and Lewis acid catalyst for OH activation.

Table 4.4 shows five examples of C-O bonds that have been formed through OH activation with *p*-CSA and $InCl_3$ using TMO as the solvent. The five nucleophiles represent a varity of compounds which are compatable with this catalytic process. Table 4.4 entry 1 – 3 involved the formation of a C-O bond with phenol **4.17**, 4- benzyl alcohol **4.18**, and methoxyphenol **4.19** in moderate yields 68-75% with $InCl_3$ and 57 – 70% with *p*-CSA. Simple alcohol ethanol Table 4.4 entry 4 was successfully reacted along with propargyl alcohol in entry 5. *p*-CSA and $InCl_3$ were sucessful in each example although the Lewis acid consistantly out performed the Brønstead acid.

Table 4.4: Nucleophilic coupling with alcohol **4.11** to form C-O bonds.

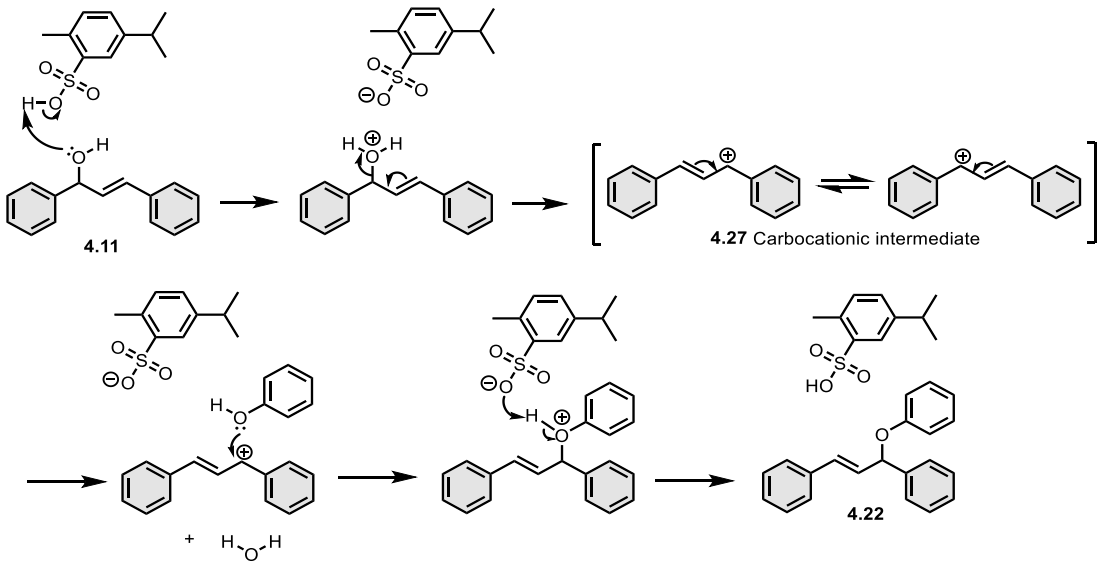


4.11

Entry	NuH	Catalyst	mol%	Time (h)	Product	Yield (%)[a]
1 i 1 ii	 **4.17**	*p*-CSA $InCl_3$	1 mol%	24	 **4.22**	70 75
2 i 2 ii	 **4.18**	*p*-CSA $InCl_3$	1 mol%	24	 **4.23**	60 68
3 i 3 ii	 **4.19**	*p*-CSA $InCl_3$	1 mol%	24	 **4.24**	57 68
4 i 4 ii	 **4.20**	*p*-CSA $InCl_3$	1 mol%	24	 **4.25**	74 80
5 i 5 ii	 **4.21**	*p*-CSA $InCl_3$	1 mol%	24	 **4.26**	61 65

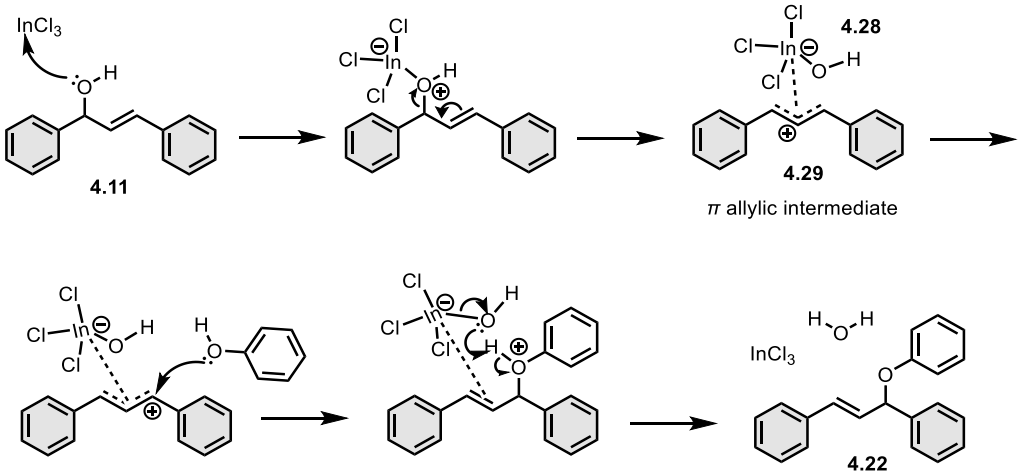
General reaction conditions: 1.0 equiv. of alcohol, 1.5 equiv. of nucleophile in solvent (5 mL).
[a] Yield determined by GCMS.

A possible mechanism for the activation of the allylic alcohol **4.11** by *p*-CSA and subsequent attcak by a nucleophile is shown in Scheme 4.6. It is thought that the alcohol is protonated by *p*-CSA causing elimination which leaves a carbocationic intermediate **4.27**. This intermediate can stabilise the positive charge throughout the whole molecule as it is fully conjugated. **4.27** Then undergoes nucleophilic attack followed by deprotonation to form the desired product and regenerate the acid.



Scheme 4.6: Possible mechanism for OH activation by Brønsted acid catalysis.

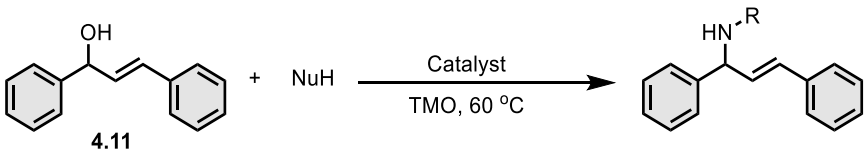
A possible alternative mechanism involving allylic alcohol **4.11** and $InCl_3$ is displayed in Scheme 4.7. When $InCl_3$ or a Lewis acid is used to activate alcohol **4.11** two intermediates are generated. The first is a Lewis acid hydroxide complex **4.28** which stabilises the carbocationic intermediate **4.29**. This increased stabilisation may explain the higher yields obtained by $InCl_3$ as the intermediate **4.27** is only stabilised by resonance.

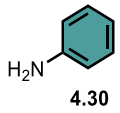
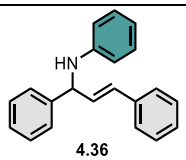
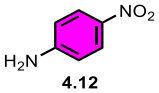
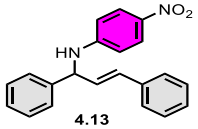
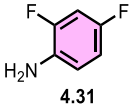
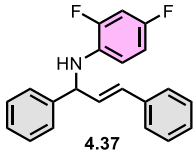
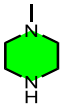
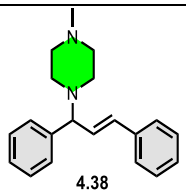
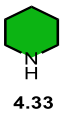
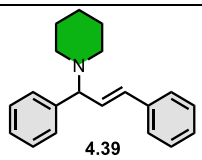
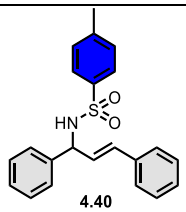
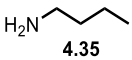
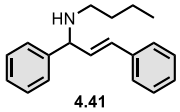


Scheme 4.7: Possible mechanism for OH activation by Lewis acid catalysis.

Following on from the promising results observed with *p*-CSA & $InCl_3$ in TMO the formation of C-N bonds was investigated. Aromatic substrates aniline **4.30**, 4-nitroaniline **4.12** and 2,4-difluoroaniline **4.31** Table 4.5 entry 1 – 3 all gave the desired nucleophilic substitution product with both *p*-CSA and $InCl_3$. Nonaromatic heterocyclic *N*-methylpiperidine **4.32** entry 4 and piperidine **4.33** entry 5 were also successful along with 4-methylbenzenesulfonamide **4.34** entry 6. One limitation of this method was simple primary aliphatic amides such as butylamine **4.35** which failed to react. In Table 4.5 entry 7 no desired product could be detected. This was unexpected given how successful ethanol **4.20** had been in Table 4.4 entry 4 and also following the high yielding reactions with both piperazine substrates **4.32** & **4.33**.

Table 4.5: Nucleophilic coupling with alcohol **4.11** to form C-N bonds.

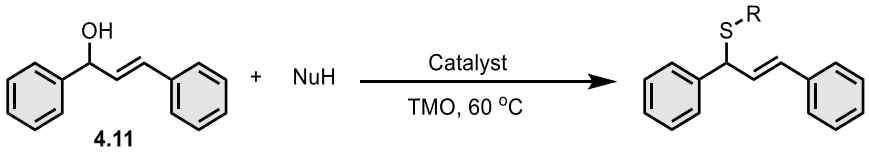


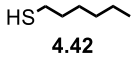
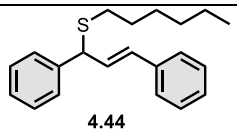
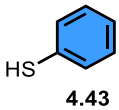
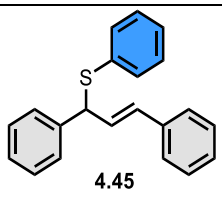
Entry	NuH	Catalyst	mol%	Time (h)	Product	Yield (%)[a]
1 i 1 ii	 4.30	*p*-CSA $InCl_3$	1 mol%	24	 4.36	80 82
2 i 2 ii	 4.12	*p*-CSA $InCl_3$	1 mol%	24	 4.13	88 90
3 i 3 ii	 4.31	*p*-CSA $InCl_3$	1 mol%	24	 4.37	48 52
4 i 4 ii	 4.32	*p*-CSA $InCl_3$	1 mol%	24	 4.38	82 87
5 i 5 ii	 4.33	*p*-CSA $InCl_3$	1 mol%	24	 4.39	70 79
6 i 6 ii	 4.34	*p*-CSA $InCl_3$	1 mol%	24	 4.40	63 78
7 i 7 ii	 4.35	*p*-CSA $InCl_3$	1 mol%	24	 4.41	0 0

General reaction conditions: 1.0 equiv. of alcohol, 1.5 equiv. of nucleophile in solvent (5 mL).
[a] Yield determined by GCMS.

In Table 4.6 1-hexanethiol **4.42** and thiophenol **4.43** were used as nucleophiles and sucessfully reacted with alcohol **4.11**. Both substrates gave excellent yields with *p*-CSA and $InCl_3$ with the largest difference being 2% between entry 2 i and 2 ii. It is interesting to note that with ethanol **4.20** and 1-hexanethiol **4.42**, both alkyl nucleophiles performed well whereas butylamine **4.35** failed to react at all.

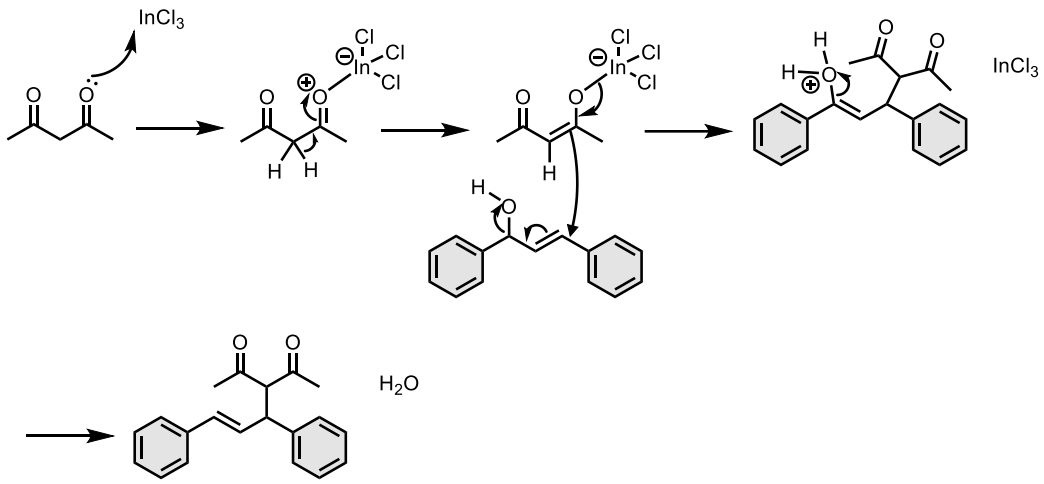
Table 4.6: Nucleophilic coupling with alcohol **4.11** to form C-S bonds.



Entry	NuH	Catalyst	mol%	Time (h)	Product	Yield (%)[a]
1 i 1 ii	 4.42	*p*-CSA $InCl_3$	1 mol%	24	 4.44	89 90
2 i 2 ii	 4.43	*p*-CSA $InCl_3$	1 mol%	24	 4.45	88 90

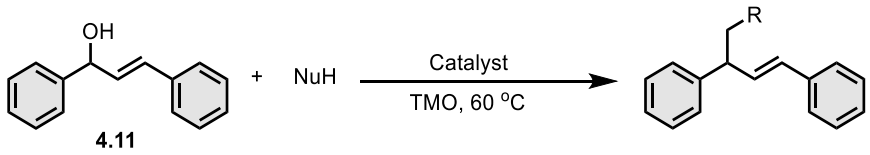
General reaction conditions: 1.0 equiv. of alcohol, 1.5 equiv. of nucleophile in solvent (5 mL)
[a] Yield determined by GCMS

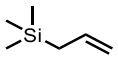
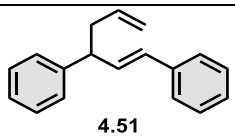
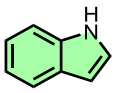
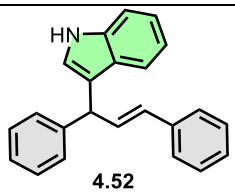
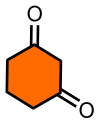
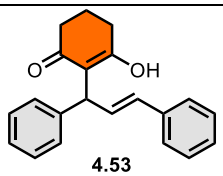
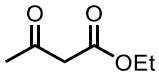
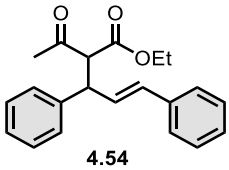
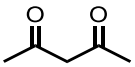
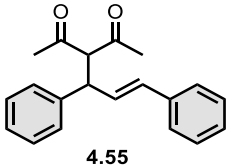
The last subset of nucleophiles investigated with alcohol **4.11** are shown in Table 4.7. The five substrates investigated all required the presence of $InCl_3$ to be able to form C-C bonds with alcohol **4.11**. Two substrates, Table 4.7. entry 1 & 2 did react with alcohol **4.11** when *p*-CSA was used as catalyst and their yield was equal to the yield obtained with $InCl_3$. In comparison Table 4.7 entry 3-5 the reaction of 1,3-dicarbonyl substrates with alcohol **4.11** only occurred when $InCl_3$ was present, this indicates that the mechanism of substitution is different with 1,3-dicarbonyl compounds and the reaction proceeded through a Lewis acid catalysed Michael addition Scheme 4.8.



Scheme 4.8: Possible mechanism reactivity of 1,3-dicarbonyl compounds.

Table 4.7: Nucleophilic coupling with alcohol **4.11** to form C-C bonds.



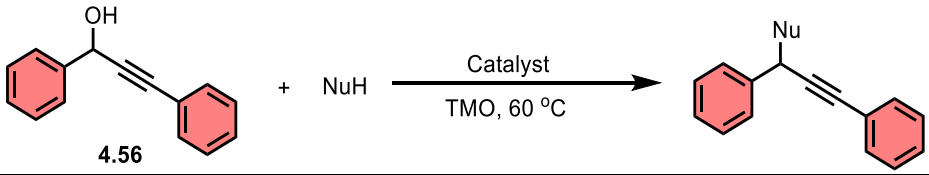
Entry	NuH	Catalyst	mol%	Time (h)	Product	Yield (%)[a]
1 i 1 ii	 **4.46**	*p*-CSA $InCl_3$	1 mol%	24	 **4.51**	99 99
2 i 2 ii	 **4.47**	*p*-CSA $InCl_3$	1 mol%	24	 **4.52**	84 85
3 i 3 ii	 **4.48**	*p*-CSA $InCl_3$	1 mol%	24	 **4.53**	0 70
4 i 4 ii	 **4.49**	*p*-CSA $InCl_3$	1 mol%	24	 **4.54**	0 70
5 i 5 ii	 **4.50**	*p*-CSA $InCl_3$	1 mol%	24	 **4.55**	0 81

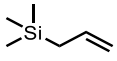
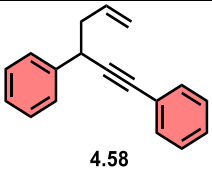
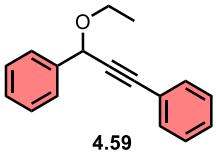
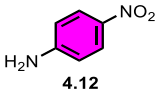
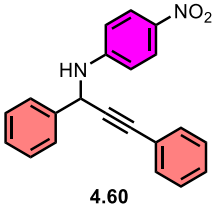
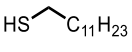
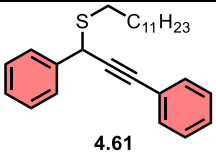
General reaction conditions: 1.0 equiv. of alcohol, 1.5 equiv. of nucleophile in solvent (5 mL).
[a] Yield determined by GCMS.

4.2.1.2. Nucleophilic addition to propargylic alcohol 4.56

Given the positive results with alcohol **4.11** the best performing nucleophiles from each category when then used in conjunction with alcohol **4.56**. The yields obtained using alcohol **4.56** were excellent, almost quantatitative. The lowest yield was obtained with 4-nitroaniline **4.12**, 85% Table 4.8 entry 3. While the exact mechanism behind this transformation is unclear, the improved yields with alcohol **4.56** could be due to greater stability directed into the carbocation from the alkyne.

Table 4.8: Nucleophilic coupling with alcohol **4.56**.



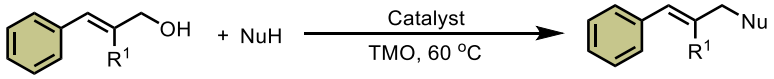
Entry	NuH	Catalyst	mol%	Time (h)	Product	Yield (%)[a]
1 i 1 ii	 4.46	*p*-CSA $InCl_3$	1 mol%	12	 4.58	99 99
2 i 2 ii	 4.20	*p*-CSA $InCl_3$	1 mol%	12	 4.59	99 99
3 i 3 ii	 4.12	*p*-CSA $InCl_3$	1 mol%	12	 4.60	85 85
4 i 4 ii	 4.57	*p*-CSA $InCl_3$	1 mol%	12	 4.61	99 99

General reaction conditions: 1.0 equiv. of alcohol, 1.5 equiv. of nucleophile in solvent (5 mL).
[a] Yield determined by GCMS.

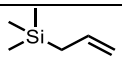
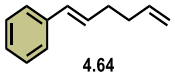
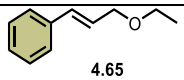
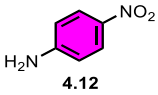
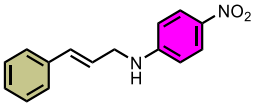
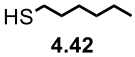
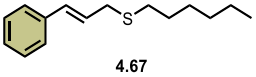
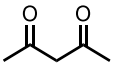
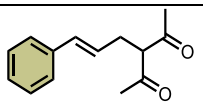
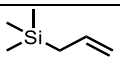
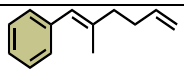
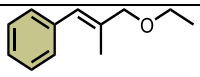
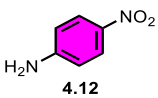
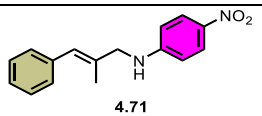
4.2.1.3. Nucleophilic addition to primary allylic alcohols

The final allylic alcohol investagated was cinnamyl alcohol **4.62** and methyl cinnamyl alcohol **4.63**. Both of these alcohols failed to react when *p*-CSA was used as a catalyst, only starting material was recoverd. When $InCl_3$ was used as catalyst each substrate in Table 4.9 formed the corresponding product, in excellent yields. For reactions with alcohols **4.62** & **4.63** the use of Lewis acid was vital as it presumable coordinated to the alkene allowing elimination of the alcohol. In contrast, when a Brønstead acid was used the alcohol may have only been protonated and given it is a primary alcohol elimination to form a stabilised intermediate was not favoured.

Table 4.9: Nucleophilic coupling with alcohol **4.62** & **4.63**.



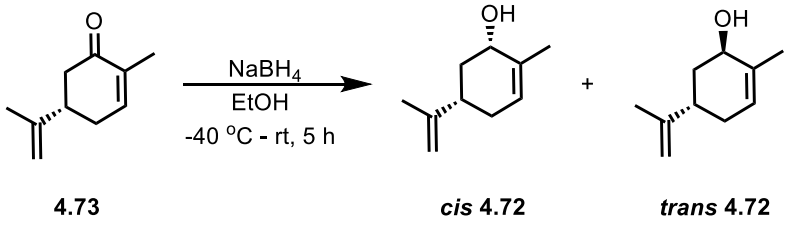
4.62 R^1 = H
4.63 R^1 = Me

Entry	NuH	Catalyst	mol%	Time (h)	Product	Yield (%)[a]
1 i 1 ii	 **4.46**	*p*-CSA $InCl_3$	1 mol%	24	 **4.64**	0 99
2 i 2 ii	 **4.20**	*p*-CSA $InCl_3$	1 mol%	24	 **4.65**	0 99
3 i 3 ii	 **4.12**	*p*-CSA $InCl_3$	1 mol%	24	 **4.66**	0 75
4 i 4 ii	 **4.42**	*p*-CSA $InCl_3$	1 mol%	24	 **4.67**	0 80
5 i 5 ii	 **4.50**	*p*-CSA $InCl_3$	1 mol%	24	 **4.68**	0 72
6 i 6 ii	 **4.46**	*p*-CSA $InCl_3$	1 mol%	24	 **4.69**	0 87
7 i 7 ii	 **4.20**	*p*-CSA $InCl_3$	1 mol%	24	 **4.70**	0 80
8 i 8 ii	 **4.12**	*p*-CSA $InCl_3$	1 mol%	24	 **4.71**	0 85

General reaction conditions: 1.0 equiv. of alcohol, 1.5 equiv. of nucleophile in solvent (5 mL).
[a] Yield determined by GCMS.

4.2.1.4. Carvone 4.72

Given the successful use of *p*-CSA in activating alcohols **4.11**, **4.56**, **4.62** & **4.63** a brief investagation was performed on a more challenging alcohol. Carveol **4.72** is a nautrally occuring unsaturated monocyclic monoterpenoid, it can be obtained by reduction of (*S*)-carvone **4.73**. This reduction was performed with sodium borohydride in ethanol at -40 ^{o}C to give a mixture of *cis* **4.72** and *trans* **4.73** Scheme 4.9.



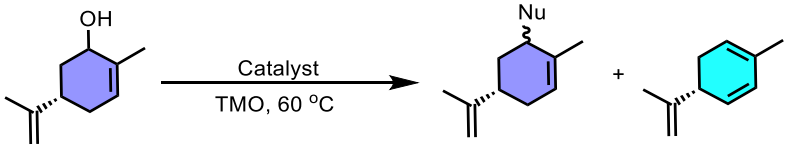
4.73 ***cis* 4.72** ***trans* 4.72**

Scheme 4.9: Reduction of (*S*)-carvone.

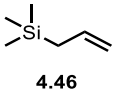
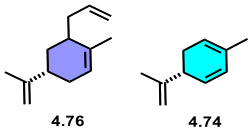
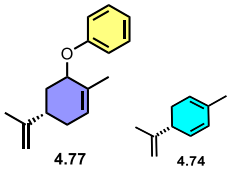
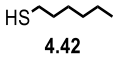
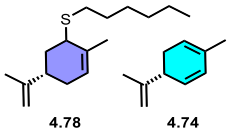
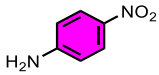
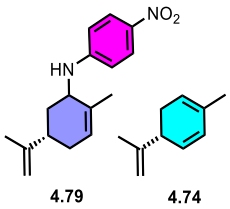
These diastereomers could be sepearted by column chromatography but for the purposes of this work were used as a mixture. A mixture of *cis/trans* carveol **4.72** was reacted with four compounds previously used to investagate the activation and substitution of alcohol **4.11**. Allyltrimethylsilane **4.46**, phenol **4.17**, 1-hexanethiol **4.42** and 4-nitroaniline **4.12** were selected as they would allow access to different hetroatom bonds and also proved most successful in previous work.

The results for the attempted OH activation and nucleophilic substitition of *cis/trans* **4.72** is shown in Table 4.10 entry 1-4. For allyltrimethylsilane Table 4.10 entry 1 the use of *p*-CSA entry 1i, delivered none of the desired product, only the elimination product **4.74**. For entry 1ii, $InCl_3$ was more successful yielding 30% of the desired product and no trace of the elimination product was detected. This trend in selectivity continued for Table 4.10 entry 2, 3 & 4, when *p*-CSA was used, only the elimination product **4.74** was detected, while a low yield of desired product was obtained when using $InCl_3$. It is thought that the Brønstead acid protonates the alcohol which is then eliminated from as the compound as water, and the resulting cation stabilises itself through resonance. This is not the case with Lewis acids as they form complexes with the lone pairs on the alcohol promoting an alternative reaction pathway and avoiding elimination of the OH group.

Table 4.10: Nucleophilic coupling with carveol **4.72**.

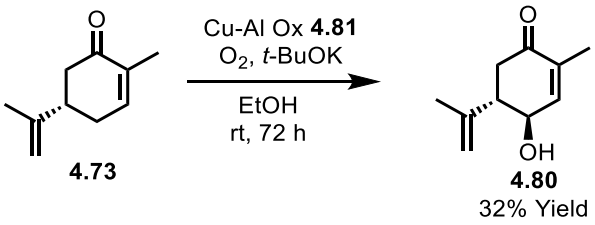


4.72 **4.74**

Entry	NuH	Catalyst	mol%	Time (h)	Product	Yield (%)[a]
1 i	 **4.46**	*p*-CSA	1 mol%	24	 **4.76** **4.74**	**4.76** 0 **4.74** 80
1 ii		$InCl_3$				**4.76** 30 **4.74** 0
2 i	 **4.17**	*p*-CSA	1 mol%	24	 **4.77** **4.74**	**4.77** 0 **4.74** 78
2 ii		$InCl_3$				**4.77** 35 **4.74** 0
3 i	 **4.42**	*p*-CSA	1 mol%	24	 **4.78** **4.74**	**4.78** 0 **4.74** 79
3 ii		$InCl_3$				**4.78** 24 **4.74** 0
4 i	 **4.12**	*p*-CSA	1 mol%	24	 **4.79** **4.74**	**4.79** 0 **4.74** 80
4 ii		$InCl_3$				**4.79** 23 **4.74** 0

General reaction conditions: 1.0 equiv. of alcohol, 1.5 equiv. of nucleophile in solvent (5 mL).
[a] Yield determined by GCMS.

After a limited success with *cis/trans* carveol **4.72** the same reaction conditions were applied to *trans*-γ-hydroxycarvone **4.80** which was obtained from (*S*)-carvone **4.73** using catalyst **4.81**. Following a method developed bt Zhang *et al*, (*S*)-carvone was converted into to *trans*-γ-hydroxycarvone **4.80** in a low yield (32%) Scheme 4.10.[233]



Scheme 4.10: Synthesis of *trans*-γ-hydroxycarvone **4.80**.

Unfortunately, any attempt to add a substrate to *trans*-γ-hydroxycarvone **4.80** failed Table 4.11 and only starting material was recovered. Allyltrimethylsilane **4.46**, phenol **4.17**, 1-hexanethiol **4.42** and 4-nitroaniline **4.12** were again selected due to their success in previous experiments.

The cause of any reactivity is unclear. It is unlikley due to sterics preventing reagents interacting with the alcohol as both the *iso*-propenyl and alcohol are axial Figure 4.2. It is feasable that the conjugated ketone is more likely to interact and bind to the reagents than any of the other functionalities present. Also, none of the reagents used are strong enough to deprotonate and form an the enolate this too appears an unlikely explanation. Another possible course of reaction could have been dehydration leading to elimination produce **4.75** but through analysis of the reaction by GCMS no such product could not be detected. Inversion of the alcohol by Mitsunobu reaction is known so perhaps the lack of reactivity is due to experimental error and it would be worthwhile revisiting.[234, 235]

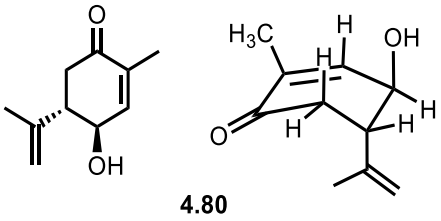
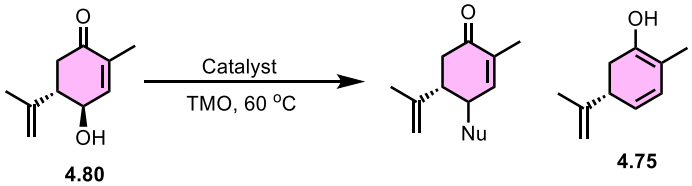
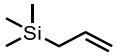
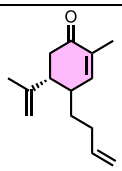
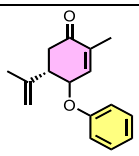
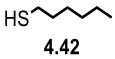
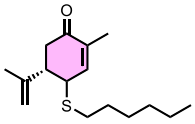
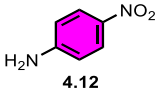
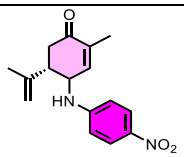


Figure 4.2: Chair configuration of *trans*-γ-hydroxycarvone **4.80**

Table 4.11: Nucleophilic coupling with alcohol **4.80**.



4.80 **4.75**

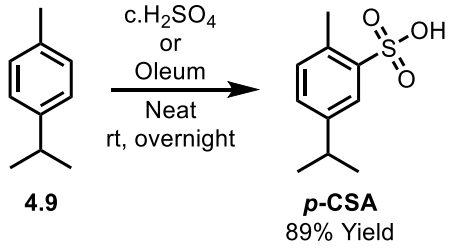
Entry	Nuh	Catalyst	mol%	Time (h)	Product	Yield (%)[a]
1 i 1 i	 **4.46**	*p*-CSA $InCl_3$	1 mol%	24	 **4.82**	0 0
2 i 2 ii	 **4.17**	*p*-CSA $InCl_3$	1 mol%	24	 **4.83**	0 0
3 i 3 ii	 **4.42**	*p*-CSA $InCl_3$	1 mol%	24	 **4.84**	0 0
4 i 4 ii	 **4.12**	*p*-CSA $InCl_3$	1 mol%	24	 **4.85**	0 0

General reaction conditions: 1.0 equiv. of alcohol, 1.5 equiv. of nucleophile in solvent (5 mL).
[a] Determined by GCMS.

4.2.2. *p*-CSA in the esterification of fatty acids

Given the success substituting *p*-TSA with *p*-CSA in the activation of an alcohol to achieve a range of coupling reactions, it was also investigated in ester formations. The difference in reactivity between *p*-TSA and *p*-CSA was investagated in a commerical process. *p*-TSA is used as catalyst in the esterfication of fatty acids **4.86** (mixture of C10-20 unsaturated fatty acids) with 2-ethylhexanol **4.87**.

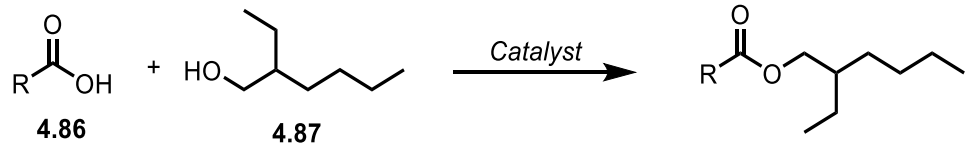
In order to evaluate *p*-CSA in the reaction several grams were synthesis. Initally an attempt was made to sulfonate *p*-cymene **4.9** with concentrated sulphuric acid (c.H_2SO_4). 3 equivalents of c.H_2SO_4 were used and the solution was heated to 170 ^oC, just under the boiling point of *p*-cymene **4.9** which resulted in a yield of 72% after 12 hours. However a more efficient process involved reacting *p*-cymene **4.9** with 3 equivalents of 20% fuming sulphuric acid (oleum) at room temperature for 12 hours with the yield increasing to 89%, Scheme 4.11. After isolation of the crude product, it was recrystallised from a minimal amount of c.HCl and made into a 65% (w/w) aqueous solution.



Scheme 4.11: Synthesis of *p*-CSA.

With a sufficent quantity of 65% *p*-CSA solution avaible the lab based esterfication reactions could be performed. These reactions were carried out in 5 L round bottom flask using fatty acid **4.86** and 2-ethylhexanol **4.87**. The scale of the reaction was 10,000 times smaller than the commercial reaction, but stoichiometric quantities were scaled, and processing conditions kept the same. The results of the reactions are shown in Table 4.12. The conversion of fatty acid to ester was only 0.2% different when p-CSA was used, 99.6% compared to *p*-TSA conversion of 99.8%. This slight difference remained even with an additional 4 hours of processing time.

Table 4.12: Results of esterification with *p*-TSA vs *p*-CSA.



4.86 **4.87**

Entry	Conditions	Conversion [a]	Colour Lovibond ¼' cell
1	Standard conditions *p*-TSA	99.8%	Red = 0.7 (2.0 max) Yellow = 2.8 (10.0 max)
2	Standard conditions *p*-CSA	99.6%	Red = 1.5 (2.0 max) Yellow = 5.0 (10.0 max)
4	4 hour delay *p*-TSA	99.8%	Red = 1.2 (2.0 max) Yellow = 3.3 (10.0 max)
5	4 hour delay *p*-CSA	99.6%	Red = 2.2 (2.0 max) Yellow = 16.9 (10.0 max)

[a] Determined by GCMS.

The noticable difference between the standard reaction and the reaction catalysed by *p*-CSA was the colour of the ester. The colour of the ester is important because it influences the colour of the final commerical product. After the ester is made it is epoxidised, and this process naturally bleachs the material but if the colour is too dark to begin, with the epoxidised material will also be too dark and therefore not suitable for certain applications. The scale used to measure the colour of the ester and epoxidised oil is the lovibond scale. A specification of 10.0 yellow for a ¼' cell has been set for the maximium accecptable colour of ester.

Under standard reaction conditions the ester produced using *p*-CSA was within the colour limits at 5.0 yellow. This result is higher than the colour value obtained with *p*-TSA, 2.8 yellow. Each reaction performed with *p*-CSA produced slightly darker material generally 2.2 units higher. When the esterfication was performed and an additional 4 hours of processing time was included to simulate a delay, the colour increassed significantly from 5.2 yellow under standard conditions to 16.9 yellow. Delays can be a common occurance with manufacturing as there can be mechanical breakdowns, shift changes and process issues, which all results in increassed processing time. This simulated delay involved holding the reaction at 130 ^{o}C for an additional 4 hours. It is known that an increass in processing time leads to a slight increass in colour due to oxidation of unreacted fatty acid but the darkening appears to accelerate when *p*-CSA is used Figure 4.3.

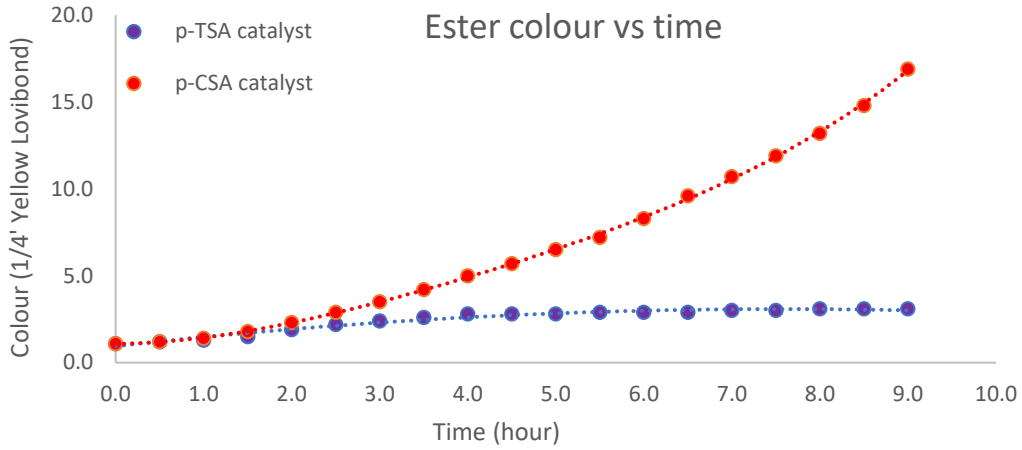


Figure 4.3: Graph showing the colour of ester over time.

The variation in colour and continual rise when the reaction time was extended was unexpected. Instances when colour values of >15.0 yellow had been obtained previously were linked to air leaking into the flask. The reaction simulating a delay was repeated several times and the reaction apparatus was checked for leaks to ensure that air was not entering and causing the colour change. The results for the reaction simulating a delay were consistant, 16.8, 16.9 & 16.9 yellow were obtained. A reaction with an intentional air leak was performed using *p*-TSA and *p*-CSA. For *p*-TSA a value of 12.4 was recorded and with *p*-CSA, 25.2 yellow. This confirmed that the presence of air adversly effects the reaction.

Further analysis was performed on the two ester produced to try and identify any differences in the composition of the material which would account for an increase in colour. The analysis indicated that the esters produced with *p*-CSA as catalyst and *p*-TSA were identical except for colour Table 4.13. The iodine value for both esters was 103 g I_2 / 100 g, therefore each ester had the same degree of unsaturation. This eliminated the possibility that any undesired side reactions may have been ocurring with *p*-CSA. The distribution of fatty acid in the ester was then analysed and this too showed that both the esters where identical, the largest difference was with the C20 component with a difference of 0.11%, but this was not siginficatnt and would not explaine the difference in colour.

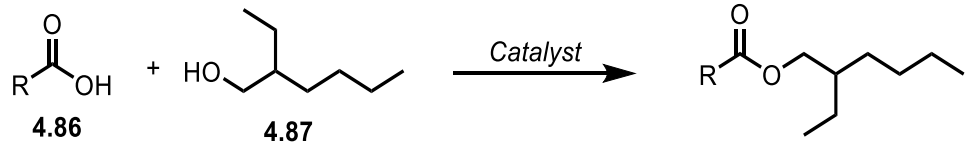
Table 4.13: Analysis of esters after an additional 4 hours processing time.

Analysis	Ester (*p*-TSA)	Ester (*p*-CSA)	Difference
Acid value (mg KOH/g)	0.1	0.1	0
Iodine value (g I_2/100 g)	103	103	0
Free alcohol (%)	5.2	5.1	0.1
Colour (1/4' Lovibond)	1.2 Red 3.3 Yellow	2.2 Red 16.9 Yellow	1.0 Red 13.6 Yellow
Constitutent from Fatty acid	**(%)**[a]	**(%)**[a]	**Difference**
C10	0.03	0.03	0
C12	0.04	0.05	0.01
C14	0.20	0.19	0.01
C14:1	-	-	-
C15	0.08	0.08	0
C16	8.10	8.15	0.05
C16:1	1.21	1.11	0.10
C16:2	0.18	0.21	0.03
C16:3	0.43	0.40	0.03
C17	0.16	0.17	0.01
C17:1	0.24	0.24	0
C18	5.18	5.20	0.02
C18:1	24.77	24.70	0.07
C18:2	22.07	21.98	0.09
C18:3	20.47	20.56	0.09
C20	1.75	1.86	0.11
C20:1	12.60	12.60	0
C20:2	1.55	1.54	0.01
C20:3	0.90	0.90	0
C22	0.03	0.03	0

[a] Determined by GCMS

The last avenue of exploration was with the method used to purify *p*-CSA. One hypothesis was that some residue from the syntesis of *p*-CSA may still be present and this is causing the material to darken. Firstly, *p*-CSA was recrystallised twice more from c.HCl (total of three times) and washed each time with a minimal amount of ice cold water. This process consumed a large quantity of *p*-CSA due to its solubility in water. When the esterfication reaction was repeated with purified *p*-CSA a high colour was again obtained, 4.8 yellow from standard conditions and 16.7 yellow with a delay. One final step in the purification of *p*-CSA was to degass the aqueous through three cycles of freeze pump thaw before use. This method of degassing was initally chosen as it is extremely rigorous but other methods of degassing such as purging with nitrogen were later found to be sufficient. Degassing the solution of *p*-CSA had a dramatic effect on the colour of ester obtained, Table 4.14.

Table 4.14: Results of esterification with degassed *p*-CSA vs *p*-TSA.



4.86 4.87

Entry	Conditions	Conversion[a]	Colour Lovibond ¼' cell
1	Standard conditions *p*-TSA	99.8%	Red = 0.7 (2.0 max) Yellow = 2.8 (10.0 max)
2	Standard conditions *p*-CSA	99.6%	Red = 1.5 (2.0 max) Yellow = 5.0 (10.0 max)
3	Standard conditions *p*-CSA (degassed)	99.7% (+0.1%)	Red = 0.9 (2.0 max) (-0.6) Yellow = 3.2 (10.0 max) (-1.8)
4	4 hour delay *p*-TSA	99.8%	Red = 1.2 (2.0 max) Yellow = 3.3 (10.0 max)
5	4 hour delay *p*-CSA	99.6%	Red = 2.2 (2.0 max) Yellow = 16.9 (10.0 max)
6	4 hour delay *p*-CSA (degassed)	99.7% (+0.1%)	Red = 1.5 (2.0 max) (-0.7) Yellow = 4.4 (10.0 max) (-12.2)

[a] Determined by GCMS

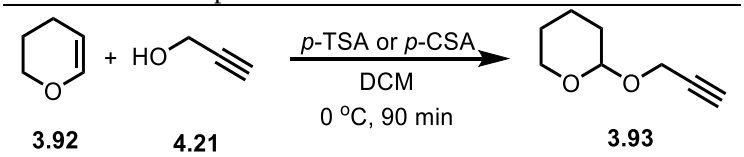
The colour of ester produced with *p*-CSA under standard conditions decreassed by 1.8 units from 5.0 to 3.2 yellow and more importantly the colour did not drasticaly increass when the reaction was delayed. During an esterfication with extended processing time using *p*-CSA Table 4.14 Entry 6, the colour increassed to a maximium of 4.4 yellow whereas previously the colour reached 16.9 yellow, 12.2 units higher under identical conditions.

The results obtained using degassed *p*-CSA solution indicate that an impurity is present within the crystal structure of *p*-CSA after recrystillisation. Perhaps very low levels of air which have been shown to adversly effect the colour. Other options could be HCl, or SO_3 dissolved in the crystal. These gases are then transfered into the aqueous solution and at elevated temperatures these react with minor impurities either from the fatty acid or 2-ethylhexanol to form highly coloured compounds at levels which are too low to routinely detect. Ultimatly *p*-CSA is a suitable alternative to *p*-TSA, a product with almost identical properties can be obtained using identical processing conditions. The issues encountered in this work also illustrate unforsceen problems which can arise with even the simpliest of tasks.

4.2.3. *p*-CSA as catalyst for alcohol protecting groups

To conclude the investigation into the uses of *p*-CSA it was used as a catalyst for two protecting group transformations. The reaction that was investigated first was protecting propargyl alcohol **4.21** with 3,4-dihydropyran **3.92**. This was a logical reaction to examine as it had previously been performed using *p*-TSA during the synthesis of 2,3-disubstituted pyrroles Scheme 3.27. When *p*-CSA as used in place of *p*-TSA the overall yield was identical, both catalysts allowed access to alcohol **3.93** in a quantitative yield Table 4.15.

Table 4.15: THP protection of alcohol **3.93**.

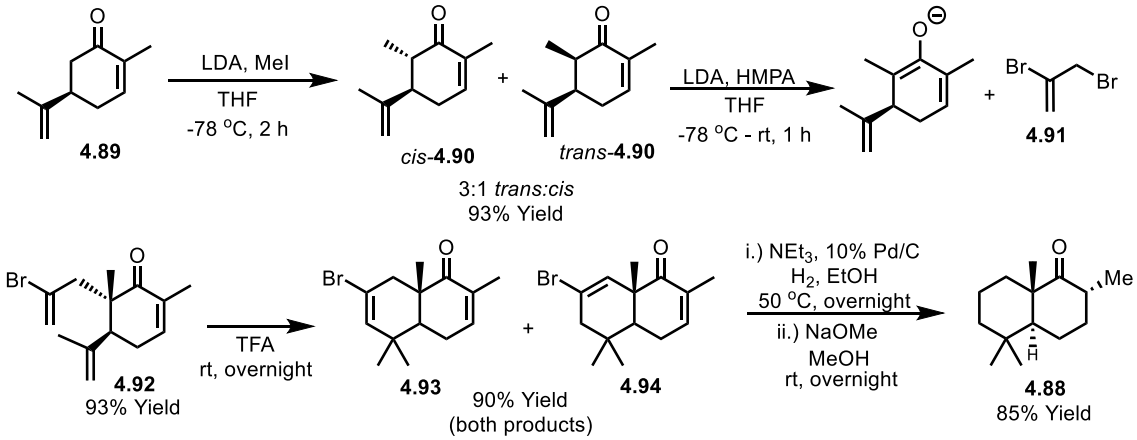


3.92 **4.21** **3.93**

Entry	Catalyst	Conversion (%)[a]	Yield (%)[b]
1	*p*-TSA	100	Quant.
2	*p*-CSA	100	Quant.

General reaction conditions: 1.00 equiv. alcohol, 1.05 equiv. THP & 0.1 equiv. catalyst, stirred for 90 minutes at 0 °C.
[a] Conversion determined by GCMS.
[b] Isolated yield.

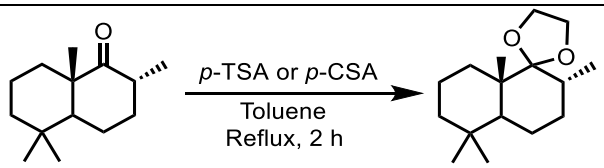
The second reaction explored was the formation of a ketal protecting group. For this decalin **4.88** was chosen due to its importance as a synthetic intermediate in numerous synthesise.[236-239] Decalin **4.88** could be obtained from (*R*)-carvone **4.89** through a 4-step process as described by Gresson *et al* Scheme 4.12.[240] (*R*)-Carvone **4.89** was first methylated using LDA and iodomethane (MeI) to give methyl carvone **4.90** as a mixture of diastereomers *cis*-**4.90** & *trans*-**4.90**. Treatment of **4.90** with LDA formed the corresponding enolate which reacts diastereoselectivly with 2,3-dibromopropene **4.91** to form bromide **4.92**. The stereochemistry at the new quaternary carbon on **4.92** is due to steric hinderance of the *iso*-propenyl group originating from (*R*)-carvone **4.89**. Acid catalysed cyclisation of **4.92** was performed using trifluoracetic acid (TFA) which gave two isomers, cyclic bromides **4.93** & **4.94**. Isomers **4.93** & **4.94** where then hydrogenated using H_2 & Pd/Carbon which yielded after base catalysed equilibrium in a solution of sodium methoxide (NaOMe) decalin **4.88** in a 66% overall yield.



Scheme 4.12: Synthesis of decalin **4.88**.

The carbonyl of decalin **4.88** was transformed into ketal **4.95** by heating under Dean-Stark conditions in the presence of ethylene glycol and an acid catalyst. *p*-TSA and *p*-CSA as before with alcohol **3.93** both provided access to **4.96** in identical yielding reactions Table 4.16. The success of *p*-CSA in catalysing the protection of both functional groups (alcohol and ketone) demonstrates that the acidic properties of *p*-CSA are very similar to *p*-TSA and that both acids could be interchanged.

Table 4.16: Ketal formation on decalin **4.88**.



4.88 **4.95**

Entry	Catalyst	Conversion (%)[a]	Yield (%)[b]
1	*p*-TSA	100	92
2	*p*-CSA	100	92

General reaction conditions: 15 equiv. of ethylene glycol, 0.1 equiv. catalyst, refluxed for 2 hours under Dean-Stark conditions.
[a] Conversion determined by GCMS.
[b] Isolated yield after chromatography

4.3. Conclusions

Through the work presented in this chapter it has been demonstrated that *p*-CSA is an extremely versatile organic acid which acts in a very similar fashion to *p*-TSA. *p*-CSA successfully replaced *p*-TSA in OH activation of allylic, and propargylic alcohols and was successfully used to catalyse the formation of two protecting groups. Namely a ketal and THP ether with synthetically useful decalin **4.88** and propargyl alcohol **3.93**.

More significantly *p*-CSA was evaluated in a commercial process and once again proved to give comparable results to *p*-TSA therefore being approved as a viable alternative if the need should arise. Although the one issue that was discovered was the impurities contained within the material. If *p*-CSA had been commercially available a more efficient purification may have been performed on the material, which may have simplified the approval process, conversely this investigation served as a good example and highlighted an aspect of material acceptance which had not been considered before, dissolved gas impurity.

The discovery that TMO is a suitable replacement for toluene in the limited range of OH activation reactions covered in this chapter is a positive result. The results obtained throughout this work support TMO's initial goal of being an alternative solvent to toluene in polymer chemistry. Given that toluene has recently been reclassified as, "suspected to be toxic to reproduction" it is likely legislative pressure will continue to grow and it is only a matter of time before alternatives to toluene will be widely sought.[241] As the migration from toluene begins the migration from *p*-TSA may not be too far behind.

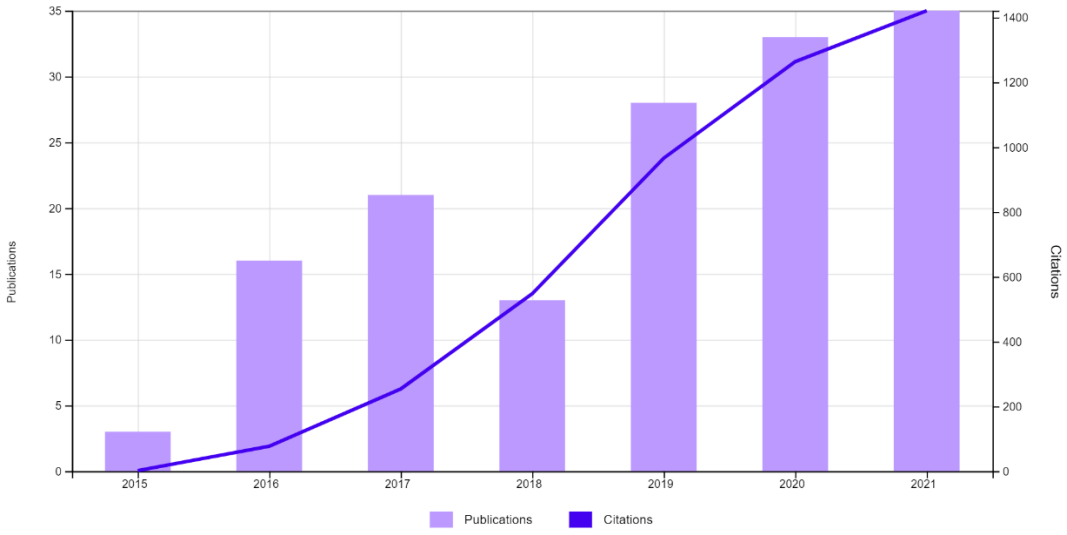
Chapter 5

Concluding Remarks and Future Work

Throughout this thesis the principles of green chemistry have been applied to several examples of organic synthesis and the results have been quantified using mass-based reaction metrics. Also, the application of mass-based reaction metrics has been critically evaluated. To conclude this thesis, the important findings from each chapter will be summarised and the possibilities for future work discussed.

Chapter 2: Process Mass Intensity (PMI).

In 2015 "*Towards a holistic approach to metrics for the 21st century pharmaceutical industry"* was published by McElroy *et al.*[101] To date (24th November 2021) this publication has received 160 citations and is showing the trend of steadily growing each year Figure 5.1.[242] The work presented in chapter 2 critically evaluates mass based reaction metrics, in the same way that these metrics are used to evaluate a chemical processes. The aim of the evaluation in both cases being the identification of possible issues or pitfalls, therefore highlight areas for improvement.



*Graph obtained as a downloadable PNG from WebofScience.com

Figure 5.1: Citation of Chem21 metrics paper Published 2015 – Nov 2021.

Through the Chem21 metric toolkit reaction metrics were generated for amide bond formation and the Mitsunobu reaction. Analysis of the data highlighted several pitfalls that an operator could encounter with AE, RME and PMI. The consequence of making an incorrect assignment for reagent, reactant, substrate or catalyst can have a dramatic effect on the metric result obtained for AE and RME. This error can be amplified and cause more confusion when results of the metric analysis are either compared with another process or recalculated by a different operator who obtains a different result.

In order to prevent this a correctly balanced equation should be examined to identify every input and output of the process which was shown through the use of a modified AE and RME. Pitfalls were also identified with PMI, when the metric data from one process was being compared with another process several flaws became apparent. As PMI is a mass-based metric the molecular weight of reactants, reagents or the concentration used can lead to an unfavourably high result in some instances. This can become a problem when working to a target value or assessing the performance of several processes. No single metric or toolkit is perfect, and caution should always be applied when comparing the data for different processes. Given the insight obtained through this work, to obtain a fair comparison of metric data between processes the parameters being compared should be as close as possible, molecular weights of reagents, concentration, yield etc. Looking at the trend in Figure 5.1 the uptake of reaction metrics is growing. It would be interesting to review the subject fields that the Chem21 metrics toolkit or any metrics toolkit has been used in and identify any weakness which are preventing or limiting use in other fields.

Chapter 3: Synthesis of cytosine and 1,3-oxathiolanes leading to Lamivudine.

Through chapter 3 several incremental improvements have been applied to the synthesis of cytosine and 3,3-diethoxypropane nitrile. The movement away from *m*-xylene and sodium ethoxide towards ethanol and HCl leads to a slightly improved metric performance for the reaction from a mass-based metric viewpoint. From an environmental and health & safety viewpoint the change in flag colour from amber to green is subtle but the impact is large. These improvements were discovered through metrics analysis using the Chem21 toolkit on a patented procedure. As described in Chapter 2 metric toolkits are designed to aid in identifying weaknesses and areas for improvement in a process.

The synthesis of 1,3-oxathiolanes was also investigated in Chapter 3. The use of CAL B to obtain (2*S*)-5-disubstituted 1,3-oxathiolanes using TMO was explored and the 1,3-oxathiolane alcohols obtained were used in a series of Mitsunobu reactions with various protected cytosine derivatives. Numerous variations of the Mitsunobu reaction were performed using traditional reagents and more modern catalytic protocols were trialled with varied success. Substitution of DIAD for a DCPEAC which was used in

catalytic quantities with FePc present to regenerate it was extremely successful. The one alternative to PPh_3 explored in this work failed to react with any of the substrates. Further investigation into the Mitsunobu between protected cytosine (pyrimidines) and 1,3-oxathiolane alcohols may be worthwhile given that the nature of this work focused on a limited scope of reaction conditions. Additionally, TMO was successfully used in all the Mitsunobu reactions and further research into applications of TMO could widen its appeal to researchers and industrial chemists.

Chapter 4: OH-Activation.

Throughout Chapter 4, *p*-CSA repeatedly proved that is was a very effective Brønsted acid with a reactivity almost identical to that of *p*-TSA. Numerous examples of allylic, and propargylic alcohol activation where shown leading to many examples of C-C, C-O, C-N and C-S bond formation. *p*-CSA also showed excellent Brønsted acid activity in the formation of ketal and THP ether protecting groups. Finally, *p*-CSA was trialled in a lab setting for a commercial process and its viability as a replacement for *p*-TSA once again proven. Further development into the synthesis of *p*-CSA would be worthwhile and possibly with time *p*-CSA can fulfil the commercial need for a bioderived Brønsted acid. One method of synthesising *p*-CSA that would avoid the use of Oleum could be electrochemical sulfonation.[243]

An application for TMO was once again discovered in Chapter 4. TMO was successfully used in all the reported OH activation reactions with allylic and propargylic alcohols. When reactions with carvone where investigated TMO was used and again proved to be a suitable solvent. One area for future work would be to revisit the synthesis of trans-γ-hydroxycarvone and perform a detailed investigation around addition to the hydroxy group. It was unexpected that only starting material could be recovered from the reactions and unusual that no side products were detected.

Chapter 6

Experimental

6.1. General information

All chemicals were purchased from commercial suppliers and used as received unless otherwise noted. Air and moisture sensitive reactions were carried out in flame-dried glassware under an argon atmosphere with magnetic stirring using standard Schlenk techniques. All solvents were dried prior to use by passage through a column filled with activated alumina and stored over molecular sieves. Reaction temperatures correspond to the external temperature of the reaction vessel. Brine refers to a saturated solution of aqueous sodium chloride.

Analytical TLC was performed on aluminum backed plates pre-coated (0.25 mm) with Merck KGaA silica gel 60 F_{254}. Compounds were visualized by exposure to UV-light (254 nm) and/or stained using $KMnO_4$, Vanillin, Hessian stain or phosphomolybdic acid (PMA) followed by heating. Flash column chromatography was performed using Fluorochem silica gel LC60A (40-60 μM). Retention factor (R_f) values reported were measured using a 10 x 3 cm TLC plate in a developing chamber containing the solvent system described.

Nuclear Magnetic Resonance (NMR) spectra were acquired at various field strength as indicated using a JEOL ECS 400 MHz spectrometer. ^1H spectra were referenced internally to the residual protic solvent resonance ($CDCl_3$ = 7.27 ppm, DMSO-d_6 = 2.50 ppm, D_2O = 4.79 ppm, CD_3CN = 1.94 ppm, THF-d_8 = 3.58 ppm). ^{13}C-spectra were referenced internally to the solvent resonance ($CDCl_3$ = 77.16 ppm, DMSO-d_6 = 39.52 ppm, CD_3CN = 118.26 ppm, THF-d_8 = 67.21 ppm). ^1H, ^{13}C, ^{19}F and ^{31}P NMR coupling constants are reported in Hertz (Hz). Coupling constants are reported using the following notation, or combination of; s = singlet, br = broad, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, sept = septet, oct = octet, non = nonet, m = multiplet. Assignment of signals in ^1H- and ^{13}C-spectra was performed using ^1H-^1H COSY, DEPT-135, ^1H ^{13}C HMQC and HMBC experiments where appropriate.

High resolution mass spectra were recorded using Electrospray Ionisation (ESI) or Atmospheric Pressure Chemical Ionisation (APCI) on a Bruker micrOTOF mass spectrometer in tandem with an Agilent series 1200 Liquid Chromatography (LC) system.

Normal phase Chiral HPLC was performed using a Phenomenex Lux Cellulose 1 or Lux Amylose 1 column (4.6 mm x 150 mm x 3 um) fitted with the corresponding guard column on an Agilent 1200 with UV detector. Exact column, flow rate, detection wavelength and retention times can be found with the corresponding compounds.

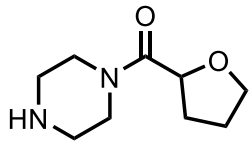
Gas chromatography was performed on a Shimadzu 2010 with FID detector using hydrogen as carrier gas. Column was a Phenomenex ZB-5HT 30 m x 0.25 *u*m x 0.25 mm. General method conditions were; Flow rate, Hydrogen @ 1.3 mL/min. Oven conditions 60 ^{o}C to 220 ^{o}C @ 10.0 ^{o}C/min, then 220 – 320 ^{o}C @ 30 ^{o}C/min hold for 3 minutes. Inlet 220 ^{o}C and detector 250 ^{o}C.

GCMS was performed on a ThermoFischer Focus GC with ThermoFischer DSQII mass spectrometer using helium as carrier gas. The column was Phenomenex ZB-5MS 30 m x 0.25 *u*m x 0.25 mm. General method conditions were; Flow rate, helium @ 1.2 mL/min 60 ^{o}C to 200 ^{o}C @ 6.0 ^{o}C/min, then 200 – 320 ^{o}C @ 20 ^{o}C/min hold for 10 minutes. MS transfer line 280 ^{o}C.

Optical rotations were obtained on a Jasco DIB370 polarimeter, with concentrations given in g 100 mL^{-1}. Melting points were determined using a Stuart SMP10 hot stage apparatus hot stage apparatus and were not corrected.

6.2. Chapter 2

(Oxolan-2-yl)(piperazin-1-yl)methanone (2.5)



2.5

Physical state: Colourless oil

$\mathbf{R}_f$ = 0.26 (5:1:0.5 EtOAc:MeOH:Et_3N, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.49 (t, *J* = 6.9 Hz, 1H), 3.83 (q, *J* = 7.3 Hz, 1H), 3.73 (q, *J* = 7.0 Hz, 1H), 3.58-3.46 (m, 2H), 3.46-3.34 (m, 2H), 2.79-2.69 (m, 4H), 2.20-2.08 (m, 1H), 1.94-1.87 (m, 2H), 1.83-1.73 (m, 1H).

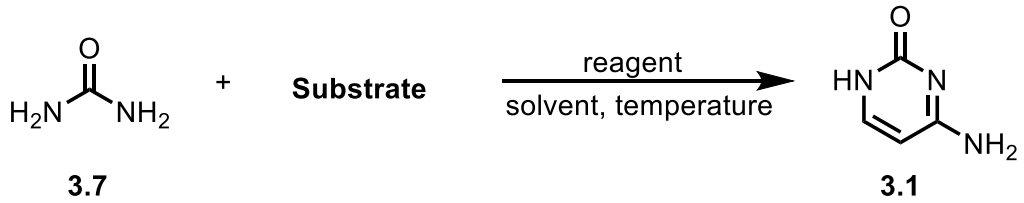
^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 75.6, 68.9, 46.6, 46.2, 45.8, 43.0, 28.4, 25.6.

HRMS ESI (*m/z*): calculated for $C_9H_{16}N_2NaO_2$ $[M+Na]^+$, 207.1104; found, 207.1103.

Spectroscopic data is consistent with those found in the literature.[244]

6.3. Chapter 3

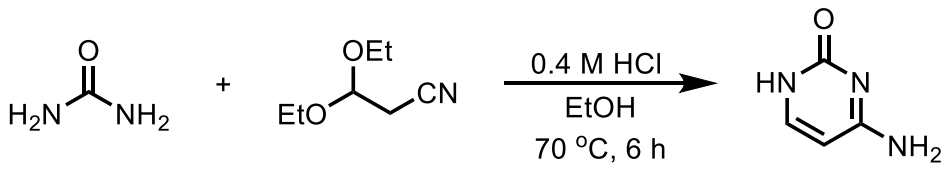
6.3.1. Generic reaction; 4-aminopyrimidin-2(1*H*)-one (Cytosine 3.1)



3.7 **3.1**

Urea (0.50 g, 8.40 mmol) and reagent (8.40 mmol) were suspended in solvent (20 mL) and the mixture was heated to the desired temperature. Substrate (7.00 mmol) was added over 1 hour and the mixture was stirred maintaining the desired temperature. After a specified time, the mixture was cooled to room temperature and water (50 mL) added to dissolve any solid that formed. The mixture was washed with ethyl acetate (3 x 20 mL) and the aqueous phase collected. The aqueous phase was cooled in an ice bath and acetic acid (7.00 mmol) was added in small portions. If a precipitate formed, it was filtered and washed with water (2 x 10 mL) on a sintered funnel then dried under vacuum at 40 °C.

6.3.2. Optimised reaction; 4-Aminopyrimidin-2(1*H*)-one (Cytosine 3.1)



3.7 **3.8** **3.1**

3,3-Diethoxypropionitrile (1.00 g, 7.00 mmol) was dissolved in ethanolic HCl (0.4 M, 21 mL) and heated to 70 °C. Urea (0.50 g, 8.40 mmol) was added portion wise over 1 hour then the mixture was stirred at 70 °C for 6 hours. After this time the mixture was cooled to room temperature and the precipitate was filtered to leave the desired product. This was washed with water (2 x 10 mL) on a sintered funnel then dried in a vacuum oven at 40 °C.

Yield: 0.81 g (87%)

Physical state: Yellow solid

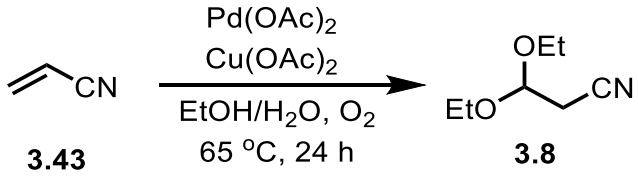
m.p. > 300 °C

^{1}H NMR (400 MHz, D_2O/DCl): δ 7.60 (d, *J* = 7.5 Hz, 1H), 6.02 (d, *J* = 7.5 Hz, 1H).

^{13}C NMR (101 MHz, D_2O/DCl): δ 160.2, 149.3, 146.2, 94.0

HRMS ESI (*m/z*): calculated for $C_4H_5NaN_2O$ $[M+Na]^+$, 134.0330; found, 134.0326.

3,3-Diethoxypropanitrile (3.8)



3.43 **3.8**

Prepared by modification of a known procedure.[245]

A 100 mL round bottom flask was evacuated and refilled three times with an oxygen balloon. Acrylonitrile (0.11 g, 2.00 mmol), palladium(II) acetate (22 mg, 0.10 mmol), and copper (II) acetate (18 mg, 0.10 mmol) were dissolved in a 50:50 mixture of water and ethanol (10 mL) and this solution was added to the flask via syringe. The solution was warmed to 65 °C and vigorously stirred for 24 hours under a slightly positive pressure using an oxygen balloon. After this time water (50 mL) was added and mixture extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, washed with a saturated sodium bicarbonate solution (50 mL), brine (50 mL) and dried over magnesium sulphate. The solvent was removed under reduced pressure to leave a crude oil which was purified by flash chromatography.

Yield: 285 mg (99%)

Physical state: Colourless oil

$\mathbf{R}_f$ = 0.27 (5:1 Hexane:EtOAc, PMA)

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.77 (t, *J* = 5.4 Hz, 1H), 3.70 (dq, *J* = 9.3, 7.0 Hz, 2H), 3.57 (dq, *J* = 9.3, 7.0 Hz, 2H), 2.65 (d, *J* = 5.4 Hz, 2H), 1.22 (t, *J* = 7.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 116.5, 98.1, 62.9, 24.8, 15.2.

HRMS ESI (*m/z*): calculated for $C_7H_{13}NNaO_2$ $[M+Na]^+$, 166.0838; found, 166.0833.

Molybdovanadophosphate (NPMoV)

Sodium metavanadate (7.32 g, 60.00 mmol) and sodium molybdate (7.21 g, 35.00 mmol) were dissolved in water (100 mL). 85% Phosphoric acid, (7.89 g, 70.00 mmol) was added dropwise and the solution was heated to 95 °C for 1 hour. After which the solution was cooled to 0 °C and saturated aqueous ammonium chloride (150 mL) was added to give NPMoV as a brown precipitate. The product was purified by recrystallisation from water and dried in a vacuum oven at 60 °C.

NPMoV – Complex mixture of molybdovanadophosphate.

Yield: 8.52 g

Physical state: Brown solid

^{31}P NMR (162 MHz, CD_3CN): δ -1.7, -2.2, -2.4, -3.0.

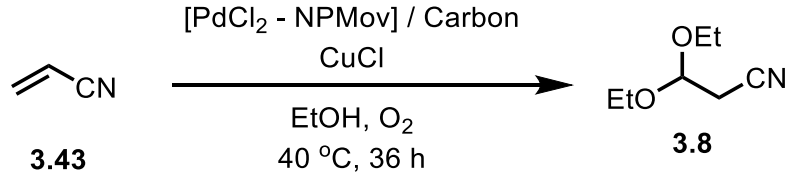
[$PdCl_2$ – NPMoV]/Carbon

Palladium (II) chloride (355 mg, 2.00 mmol) was dissolved in acetone (150 mL) and then active charcoal (10.00 g) was added. The suspension was stirred overnight at room temperature. $PdCl_2$/C was then filtered off and dried in a vacuum oven at 60 °C. $PdCl_2$/Carbon (5.00 g) was then suspended in water (100 mL) and NPMoV (500 mg) added and vigorously stirred for 2 hours at room temperature. [$PdCl_2$ – NPMoV]/Carbon was then filtered, washed with water (3 x 20 mL) and dried in a vacuum oven at 60 °C.

Yield: 10.9 g (quantitative)

XRF analysis: 1.94% Pd

6.3.3. Optimised reaction; 3,3-Diethoxypropanitrile (3.8)



3.43 **3.8**

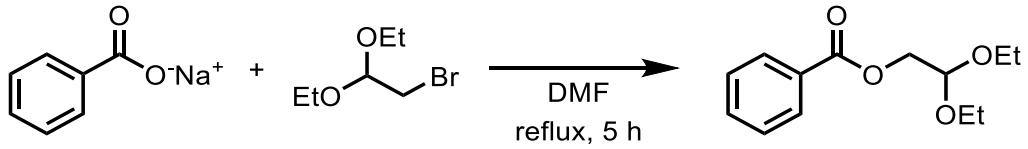
A 100 mL round bottom flask was evacuated and refilled three times with an oxygen balloon. Acrylonitrile (106 mg, 2.00 mmol), [$PdCl_2$ – NPMoV]/Carbon (10 mg), and copper (I) chloride (10 mg, 0.1 mmol) were dissolved in ethanol (10 mL) and this solution was added to the flask via syringe. The solution was warmed to 40 ^oC and vigorously stirred for 36 hours under a slightly positive pressure with an oxygen balloon. After this time water (50 mL) was added and mixture extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, washed with a saturated sodium bicarbonate solution (50 mL), brine (50 mL) and dried over magnesium sulphate. The solvent was removed under reduced pressure to leave a crude oil.

Alternative procedure for immediate use of the product in ethanol:

A 100 mL round bottom flask was evacuated and refilled three times with an oxygen balloon. Acrylonitrile (106 g, 2.00 mmol), [$PdCl_2$ – NPMoV]/Carbon (10 mg), and copper (II) acetate (18 mg, 0.10 mmol) were dissolved in ethanol (10 mL) and this solution was added to the flask via syringe. The solution was warmed to 40 ^oC and vigorously stirred for 36 hours under a slightly positive pressure of an oxygen balloon. After this time the solution was filtered through a pad of celite and silica. The filter pad was washed with ethanol (2 x 10 mL) and filtrate was either used assuming quantitative yield or solvent removed under reduced pressure.

Yield: 285 mg (99%)

2,2-Diethoxyethyl benzoate (3.49)



3.48 **3.27** **3.49**

Bromoacetyldehyde diethyl acetal (19.50 g, 15.0mL, 100.00 mmol) was dissolved in DMF (200 mL). The solution was heated to reflux and sodium benzoate (15.80 g, 110.00 mmol) added portion wise over 3 hours. The mixture was then refluxed for a further 2 hours before being cooled to room temperature. Water (1000 mL) was added and mixture extracted with ethyl acetate (4 x 200 mL). The organic layers were combined, washed with water (3 x 150 mL) and brine (150 mL) then dried over magnesium sulphate. The solvent was removed under reduced pressure and the crude oil dried azeotropically with toluene (3 x 30 mL) to leave the desired product as a dark oil which was used without further purification.

Yield: 18.92 g (79%)

Physical state: Dark brown oil

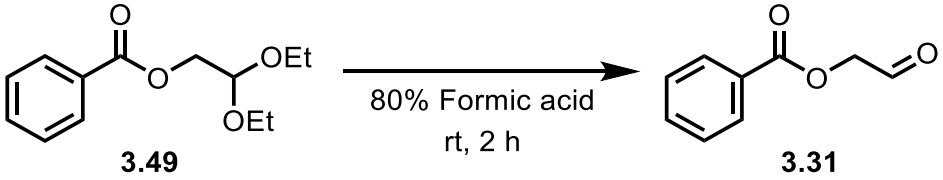
$\mathbf{R}_f$ = 0.85 (3:2 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06-7.94 (m, 2H), 7.54-7.45 (m, 1H), 7.42-7.33 (m, 2H), 4.79 (t, *J* = 5.4 Hz, 1H), 4.29 (d, *J* = 5.4 Hz, 2H), 3.77-3.47 (m, 4H), 1.18 (t, *J* = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1, 133.0, 129.9, 129.6, 128.3, 99.6, 64.3, 62.5, 15.3.

HRMS ESI (*m/z*): calculated for $C_{13}H_{18}NaO_4$ $[M+Na]^+$, 261.1103; found, 261.1093.

2-Oxoethyl benzoate (3.31)



3.49 **3.31**

2,2-Diethoxyethyl benzoate (20.00 g, 83.90 mmol) was added to a solution of aqueous 80% formic acid (150 mL). The solution was stirred at room temperature and monitored by TLC. When the reaction was complete water (200 mL) was added and the solution extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, washed with water (3 x 100 mL), saturated sodium bicarbonate solution (2 x 100 mL) and brine (100 mL) then dried over magnesium sulphate. The solvent was removed under reduced pressure and the crude oil dried azeotropically with toluene (3 x 20 mL) to leave the desired product which was either used immediately or stored under argon in a freezer below –18 ^{o}C.

Yield: 13.54 g (98%)

Physical state: Dark brown oil

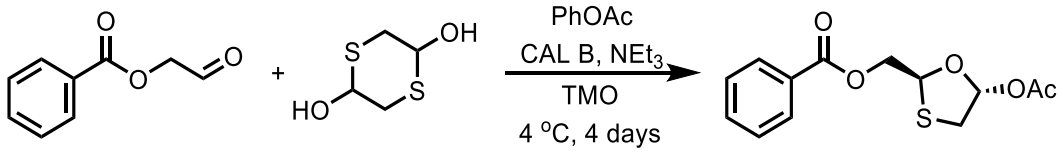
$\mathbf{R}_f$ = 0.14 (3:2 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.13-8.02 (m, 3H), 7.64-7.55 (m, 1H), 7.50-7.40 (m, 3H), 4.89 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 196.1, 171.4, 166.1, 133.8, 130.0, 128.6, 69.1.

HRMS APCI (*m/z*): calculated for $C_9H_9O_3$ $[M+H]^+$, 165.0552; found, 165.0541.

((2*S*,5*S*)-(Acetyloxy)-1,3-oxathiolan-2-yl) methyl benzoate (3.21)



3.31 **3.23** (2*S*,5*S*)-**3.21**

2-Oxoethyl benzoate (164 mg, 1.00 mmol), 1,4-dithiane-2,5-diol (91 mg, 0.6 mmol), triethylamine (101 mg, 139 µL, 1.00 mmol) and phenyl acetate (408 mg, 382 µL, 3.00 mmol) were dissolved in TMO (5 mL). This solution was added to a 10 mL round bottom flask containing enzyme CAL B (50 mg) and left for 4 days in a fridge at 4 °C. The mixture was then filtered, washed with saturated ammonium chloride (2 mL) and brine (2 mL). The organic layer was dried over magnesium sulphate and concentrated under reduced pressure. The crude oil was then dissolved in hexane and a minimal amount of diethyl ether added until the solution was clear. The solution was then stored in a freezer at –20 °C for 3 days after which a white precipitate of (2*S*,5*S*)-**3.21** was filtered, washed with cold hexane (2 mL) and dried under reduced pressure.

Yield: 200 mg (71%)

Physical state: Colourless oil

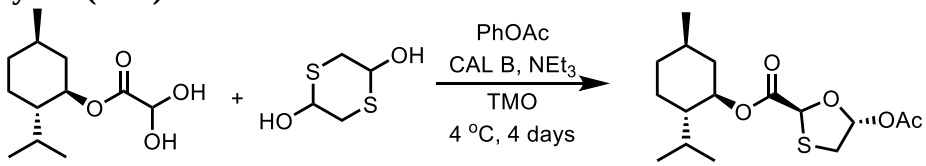
R_f = 0.26 (8:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06-7.98 (m, 2H), 7.59-7.50 (m, 1H), 7.41 (t, *J* = 7.9 Hz, 2H), 6.68 (d, *J* = 4.1 Hz, 1H), 5.67-5.51 (m, 1H), 4.60-4.54 (m, 2H), 3.69-3.62 (m, 2H), 2.06 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 166.1, 133.4, 129.9, 129.6, 128.5, 99.4, 83.4, 67.8, 37.6, 21.1

HRMS ESI (*m/z*): calculated for $C_{13}H_{14}NaO_5S$ $[M+Na]^+$, 305.0460; found, 305.0455.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl-5-acetoxy-1,3-oxathiolane-2-carboxylate (3.24)



3.22 **3.23** (2*S*,5*S*)-**3.24**

L-Menthyl glyoxylate monohydrate (230 mg, 1.00 mmol), 1,4-dithiane-2,5-diol (91 mg, 0.60 mmol), triethylamine (101 mg, 139 µL, 1.00 mmol) and phenyl acetate (408 mg, 382 µL, 3.00 mmol) were dissolved in TMO (5 mL). This solution was added to a 10 mL round bottom flask containing enzyme CAL B (50 mg) and left for 4 days in a fridge at 4 °C. The mixture was then filtered, washed with saturated ammonium chloride (2 mL) and brine (2 mL). The organic layer was dried over magnesium sulphate and concentrated under reduced pressure. This oil was then dissolved in hexane and a minimal amount of diethyl ether added until the solution was clear. The solution was then stored in a freezer at –20 °C for 3 days after which the white precipitate of (2*S*,5*S*)-**3.24** was filtered, washed with cold hexane (2 mL) and dried under reduced pressure.

Yield: 124 mg (38%)

Physical state: White solid

m.p. 102 – 105 °C

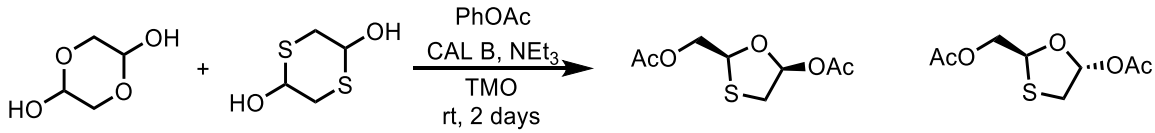
R_f = 0.20 (6:1 Hexane:EtOAc, PMA)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92-6.77 (m, 1H), 5.60 (s, 1H), 4.71-4.63 (m, 1H), 3.43 (dd, *J* = 4.0, 11.7 Hz, 1H), 3.15 (d, *J* = 11.7 Hz, 1H), 2.10 (s, 3H), 2.00-1.93 (m, 2H), 1.90-1.82 (m, 1H), 1.70-1.65 (m, 2H), 1.41-1.33 (m, 2H), 1.08-1.02 (m, 2H), 0.99-0.91 (m, 6H), 0.76 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.6, 168.5, 99.8, 79.7, 75.9, 46.8, 40.0, 37.0, 34.0, 31.2, 26.1, 23.2, 21.8, 21.1, 20.6, 16.1.

HRMS ESI (*m/z*): calculated for $C_{16}H_{26}NaO_5S$ $[M+Na]^+$, 353.4282; found, 353.4288.

((2*S*)-5-Acetoxy-1,3-oxathiolan-2-yl)methyl acetate (3.26)



3.23 **3.25** *cis*-**3.26** *trans*-**3.26**

Glycolaldehyde dimer (120 mg, 1.00 mmol), 1,4-dithiane-2,5-diol (91 mg, 0.60 mmol), triethylamine (101 mg, 139 µL, 1.00 mmol) and phenyl acetate (408 mg, 382 µL, 3.00 mmol) were dissolved in TMO (5 mL). The solution was added to a 10 mL round bottom flask containing enzyme CAL B (50 mg) and stirred for 2 days at room temperature. The mixture was then filtered, washed with saturated ammonium chloride (2 mL) and brine (2 mL). The organic layer was dried over magnesium sulphate and concentrated under reduced pressure. The crude product was purified by flash chromatography to give a mixture of diastereoisomers (8:1, *cis/trans*).

Yield: 130 mg (59%)

Physical state: Colourless oil

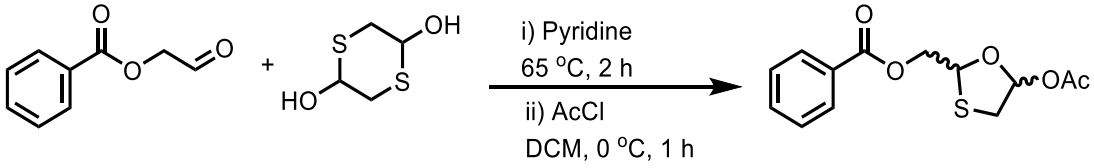
R$_f$ = 0.25 (10:1 Hexane:EtOAc, PMA)

^{1}H NMR (400 MHz, CDCl$_3$): *cis* isomer δ 6.62 (d, *J* = 4.5 Hz, 1H), 5.54 (d, *J* = 3.9 Hz, 1H), 4.42-3.99 (m, 2H), 3.32 (d, *J* = 4.2 Hz, 1H), 3.29 (d, *J* = 4.3 Hz, 1H), 2.09 (s, 3H), 2.07 (s, 3H). *trans* isomer δ 6.67 (d, *J* = 4.2 Hz, 1H), 5.54-5.49 (m, 1H), 3.95-3.79 (m, 1H), 3.32 (dd, *J* = 11.6, 4.2 Hz, 1H), 3.29 (m, 1H), 2.34-2.24 (m, 1H), 2.09 (s, 3H), 2.07 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): *cis* isomer δ 170.7, 169.3, 99.3, 84.3, 67.1, 35.6, 21.3, 20.9. *trans* isomer δ 170.7, 169.3, 99.3, 83.2, 66.0, 37.6, 21.3, 20.9

HRMS ESI (*m/z*): calculated for $C_8H_{12}NaO_5S$ $[M+Na]^+$, 243.2282; found, 243.2294.

(5-(Acetyloxy)-1,3-oxathiolan-2-yl) methyl benzoate (3.21)



3.31 **3.23** **3.21**

A solution of 2-oxoethyl benzoate (1.00 g, 6.10 mmol) was dissolved in anhydrous pyridine (20 mL) under argon. 1,4-Dithiane-2,5-diol (0.60 g, 3.70 mmol) was added and the mixture heated to 65 °C. After 2 hours the flask was cooled to 0 °C, then acetyl chloride (1.44 g, 1.3 mL, 18.30 mmol) in dichloromethane (20 mL) was added dropwise over 30 minutes. After the addition was complete the mixture was stirred for 1 hour at 0 °C before being quenched with saturated sodium hydrogen carbonate (10 mL). The organic layer was separated and washed with brine (10 mL) then dried over magnesium sulphate and concentrated under reduced pressure to give the product as a crude oil and a mixture of diastereoisomers (1.5:1, *cis/trans*).

Yield: 1.40 g (81%)

Physical state: Colourless oil

R_f = *cis* isomer 0.25 (8:1 Hexane:EtOAc, UV)
trans isomer 0.23 (8:1 Hexane:EtOAc, UV)

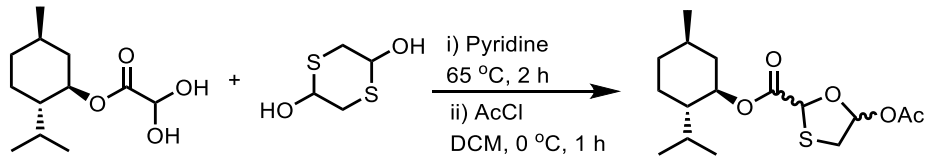
^{1}H NMR (400 MHz, $CDCl_3$): δ *cis* isomer δ 8.06-7.98 (m, 2H), 7.59-7.50 (m, 1H), 7.41 (t, *J* = 7.9 Hz, 2H), 6.68 (d, *J* = 4.1 Hz, 1H), 5.56-5.48 (m, 1H), 4.63-4.31 (m, 2H), 3.28 (dd, *J* = 4.2, 11.8 Hz, 1H), 3.15 (d, *J* =11.8 Hz, 1H); 2.06 (s, 3H). *trans* isomer δ 8.06-7.98 (m, 2H), 7.59-7.50 (m, 1H), 7.41 (t, *J* = 7.9 Hz, 2H), 6.68 (d, *J* = 4.1 Hz, 1H), 5.67-5.51 (m, 1H), 4.60-4.54 (m, 2H), 3.69-3.62 (m, 2H), 2.06 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): *cis* isomer δ 169.9, 166.1, 133.4, 129.9, 129.6, 128.5, 99.4, 84.7, 66.2, 38.2, 21.1. *trans* isomer δ 169.9, 166.1, 133.4, 129.9, 129.6, 128.5, 99.4, 83.4, 67.8, 37.6, 21.1

HRMS ESI (*m/z*): calculated for $C_{13}H_{14}NaO_5S$ $[M+Na]^+$, 305.0460; found, 305.0454.

Chiral HPLC: Phenomenex Lux Cellulose 1, hexane/isopropanol, 90:10 v/v, 1.0 mL/min, 40 °C, UV 254 nm. Retention times: (2*R*,5*S*) t_r = 4.52 min, (2*S*,5*R*) t_r = 5.68 min, (2*R*,5*R*) t_r = 8.19 min & (2*S*,5*S*) t_r = 9.24 min.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl-5-acetoxy-1,3-oxathiolane-2-carboxylate (3.24)



3.22 **3.23** **3.24**

L-Menthyl glyoxylate monohydrate (1.40 g, 6.10 mmol) was dissolved in anhydrous pyridine (20 mL) under argon.1,4-Dithiane-2,5-diol (0.60 g, 3.70 mmol) was added and the mixture heated at 65 °C for 2 hours after which the flask was cooled to 0 °C. Acetyl chloride (1.40 g, 1.3 mL, 18.30 mmol) dissolved in dichloromethane (20 mL) was then added dropwise to the reaction flask over 30 minutes. After the addition was complete the mixture was stirred for 1 hour maintaining a temperature of 0 °C before being quenched with saturated sodium hydrogen carbonate (10 mL). The organic layer was separated and washed with brine (10 mL) then dried over magnesium sulphate and concentrated under reduced pressure to give the product as a crude oil and as a mixture of diastereoisomers (2:1 *cis*/*trans*).

Yield: 1.51 g (75%)

Physical state: Amber oil

R$_f$ = *cis* isomer 0.30 (6:1 Hexane:EtOAc, PMA)
trans isomer 0.20 (6:1 Hexane:EtOAc, PMA)

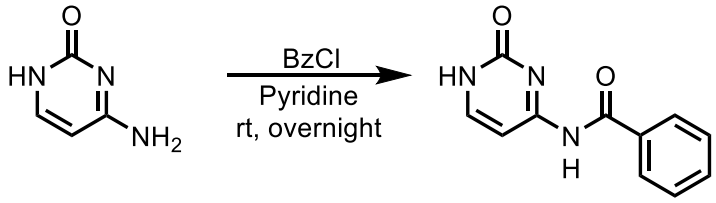
^{1}H NMR (400 MHz, CDCl$_3$):t*rans* isomer δ 6.92-6.77 (m, 1H), 5.60 (s, 1H), 4.71-4.63 (m, 1H), 3.43 (dd, *J* = 4.0, 11.7 Hz, 1H), 3.15 (d, *J* = 11.7 Hz, 1H), 2.10 (s, 3H), 2.00-1.93 (m, 2H), 1.90-1.82 (m, 1H), 1.70-1.65 (m, 2H), 1.41-1.33 (m, 2H), 1.08-1.02 (m, 2H), 0.99-0.91 (m, 6H), 0.76 (d, *J* = 7.0 Hz, 3H). *cis* isomer δ 6.92-6.78 (m, 1H), 5.63 (s, 1H), 4.80-4.74 (m, 1H), 3.45 (dd, *J* = 11.6, 3.8 Hz, 1H), 3.16 (d, *J* = 11.7 Hz, 1H), 2.11 (s, 3H), 2.12-2.00 (m, 2H), 1.93-1.85 (m, 1H), 1.79-1.70 (m, 2H), 1.41-1.33 (m, 2H), 1.08-1.02 (m, 2H), 0.99-0.91 (m, 6H), 0.76 (d, *J* = 8.5 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): t*rans* isomer δ 169.6, 168.5, 99.8, 79.7, 75.9, 46.8, 40.0, 37.0, 34.0, 31.2, 26.1, 23.2, 21.8, 21.1, 20.6, 16.1. *cis* isomer δ 169.7, 168.6, 99.9, 80.0, 75.1, 47.3, 40.2, 37.3, 34.1, 31.4, 26.2, 23.2, 21.9, 21.5, 20.9, 16.2.

HRMS ESI (*m/z*): calculated for $C_{16}H_{26}NaO_5S$ $[M+Na]^+$, 353.4282; found, 353.4288.

Chiral HPLC: Phenomenex Lux Cellulose 1, hexane/isopropanol, 90:10 v/v, 1.0 mL/min, 40 °C, UV 210 nm. Retention times: (2R,5*S*) t_r = 5.41 min, (2*S*,5*R*) t_r = 6.52 min, (2*R*,5*R*) t_r = 10.89 min & (2*S*,5*S*) t_r = 11.44 min.

***N*4-Benzoylcytosine (3.60)**



3.1 **3.60**

Cytosine (2.22 g, 20.00 mmol) was suspended in pyridine (100 mL) and the mixture cooled to 0 °C. Benzoyl chloride (8.40 g, 7.0 mL, 60.00 mmol) was added dropwise and the suspension was stirred at room temperature overnight. The reaction mixture was then cooled in an ice bath, and ammonium hydroxide (1 mL) added. The solution was stirred for 2 hours then concentrated under reduced pressure. The crude product was purified by flash chromatography to give the desired product.

An alternative purification method is: The crude material should be dissolved in a minimal amount of boiling water and the product allowed to crystallise over 48 hours.

Yield: 4.10 g (95%)

Physical state: White solid

m.p. >300 ^{o}C

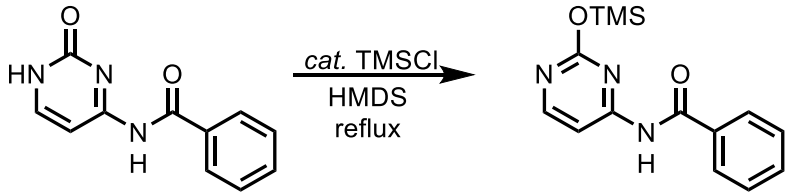
R_f = 0.25 (8:1 DCM:MeOH, UV)

^{1}H NMR (400 MHz, DMSO-d$_6$): δ 8.03-7.92 (m, 2H), 7.76 (d, *J* = 7.0 Hz, 1H), 7.62-7.53 (m, 1H), 7.50-7.39 (m, 2H), 6.91 (d, *J* = 7.0 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d$_6$): δ 166.7, 160.2, 158.7, 148.4, 132.5, 131.4, 128.6, 128.0, 95.4.

HRMS ESI (*m/z*): calculated for $C_{11}H_9N_3NaO_2$ $[M+Na]^+$, 238.0587; found, 238.0590.

***N*-(2-((Trimethylsilyl)oxy)pyrimidin-4-yl)benzamide (3.53)**



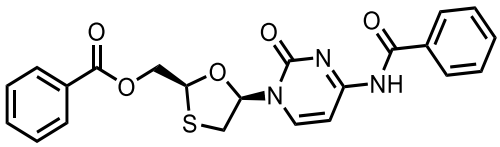
3.60 **3.53**

*N*4-Benzoylcytosine (2.15 g, 10.00 mmol) was added to a flask containing trimethylsilyl chloride (108 mg. 126 µL, 0.10 mmol) and (hexamethyldisilazane (HMDS) (8.07 g, 10.5 mL, 50.00 mmol) and refluxed under argon until all solids had dissolved. The solution was then cooled to room temperature and excess HMDS removed under vacuum. The residue was dissolved in dry dichloromethane (20 mL) to give a 0.5M solution of TMS protected *N*4-benzoylcytosine which could be used immediately or stored under argon for later use.

Yield: 2.86 g (quant)

Physical state: White solid

((*2S*,5*R*)-(4-Benzamido-2-oxopyrimidin-1(2*H*)-yl)-1,3-oxathiolan-2-yl)methyl benzoate (3.54)



3.54

(2*S*)-**3.21** (0.69 mmol) was dissolved in anhydrous acetonitrile (10 mL) and a solution of **3.53** (0.5M, 2.76 mL, 1.38 mmol) was added then the flask cooled to 0 °C in an ice bath. Trimethylsilyl iodide (276 mg, 196 µL, 1.38 mmol) dissolved in anhydrous acetonitrile was then added dropwise and the solution stirred at 0 °C under argon for 1 hour. The solution was quenched with a saturated sodium bicarbonate solution (5 mL) and diluted with water (20 mL). The mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (2 x 10 mL) and brine (20 mL) then dried over magnesium sulphate. The solvent was removed under reduced pressure to leave a crude solid which was purified by flash chromatography.

Yield: 96 mg (48%)

Physical state: White solid

m.p. >200 °C dec

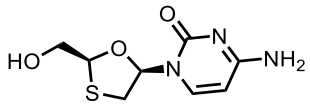
R_f = 0.19 (3:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11-8.03 (m, 2H), 7.80-7.76 (m, 3H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.51-7.47 (m, 3H), 7.51-7.40 (m, 2H), 7.10 (s, 1H), 6.34 (d, *J* = 7.4 Hz, 1H), 5.32-5.27 (m, 1H), 4.64 (dd, *J* = 11.1, 2.9 Hz, 1H), 4.39 (dd, *J* = 11.2, 2.8 Hz, 1H), 3.34-3.28 (m, 1H), 3.00-2.84 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.3, 166.0, 162.0, 155.0, 145.7, 133.2, 133.2, 132.5, 130.0, 129.8, 128.9, 128.3, 128.2, 97.7, 88.0, 85.8, 71.4, 34.1.

HRMS ESI (*m/z*): calculated for $C_{22}H_{19}N_3NaO_5S$ $[M+Na]^+$, 460.0938; found, 460.0936.

4-Amino-1-((2*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl)pyrimidin-2(1*H*)-one (3.12)



3.12

3.54 (381 mg, 1.00 mmol) was dissolved in methanol (5 mL) and potassium carbonate (136 mg, 0.50 mmol) added. The solution stirred at room temperature and monitored by TLC. Once the starting material and been consumed the solution was diluted with water (20 mL) and extracted with ethyl acetate (2 x 10mL). The organic layer was separated and washed with brine (5 mL) then dried over magnesium sulphate and concentrated under reduced pressure to give the product.

Yield: 188 mg (63%)

Physical state: White solid

m.p. 210 – 212 ^{o}C

R$_f$ = 0.15 (1:1 Hexane:EtOAc, UV)

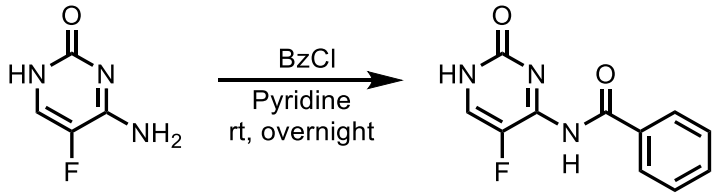
^{1}H NMR (400 MHz, DMSO-d$_6$): δ 7.82 (d, *J* = 7.4 Hz, 1H), 7.29 (s, 1H), 6.20 (t, *J* = 5.2 Hz, 1H), 5.75 (d, *J* = 7.4 Hz, 1H), 5.34 (s, 1H), 5.17 (t, *J* = 4.5 Hz, 1H), 3.73 (d, *J* = 4.1 Hz, 1H), 3.40 (dd, *J* = 11.7, 5.5 Hz, 1H), 3.04 (dd, *J* = 11.7, 4.9 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d$_6$): δ 165.8, 154.9, 141.1, 94.1, 86.6, 85.0, 62.9, 36.4.

HRMS ESI (*m/z*): calculated for $C_8H_{11}N_3NaO_3S$ $[M+Na]^+$, 252.0413; found, 252.0411.

Chiral HPLC: Phenomenex Lux Cellulose 1, hexane/isopropanol, 95:5 v/v, 1.0 mL/min, 40 ^{o}C, UV 254 nm. Retention times: (2R,5*S*) t_r = 12.59 min (*ee* = 14%) & (2*S*,5*R*) t_r = 13.40 min (*ee* = 86%).

***N*4-5-Fluorobenzoylcytosine (3.80)**



3.9 **3.80**

5-Fluorocytosine (0.26 g, 2.00 mmol) was suspended in pyridine (10 mL) and the mixture cooled to 0 °C. Benzoyl chloride (0.84 g, 0.7 mL, 6.00 mmol) was added dropwise and the suspension was stirred at room temperature overnight. The reaction mixture was then cooled in an ice bath, and ammonium hydroxide (1 mL) added. The solution was stirred for 2 hours then concentrated under reduced pressure. The crude product was purified by flash chromatography. Alternatively, the crude solution could be dissolved in a minimal amount of boiling water and the product allowed to crystallise over 48 hours.

Yield: 0.44 g (95%)

Physical state: White solid

m.p. >300 ^{o}C

R$_f$ = 0.25 (7:1 DCM:MeOH, UV)

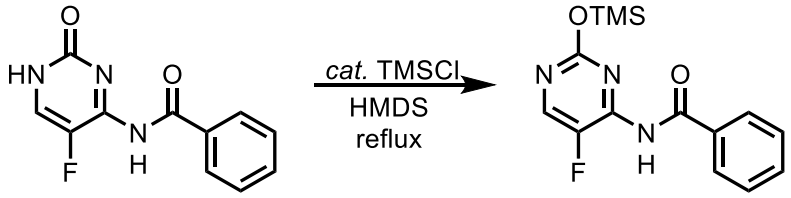
^{1}H NMR (400 MHz, DMSO-d$_6$): δ 7.92-7.42 (m, 5H), 7.61 (t, *J* = 7.5 h=Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d$_6$): δ 165.0, 162.1, 152.3 (d, *J* = 21.2 Hz), 149.4, 139.5, (d, *J* = 225.9 Hz), 135.1, 133.0, 129.4, 128.9

^{19}F NMR (376 MHz, DMSO-d$_6$): δ -171.0 (s, 1F)

HRMS ESI (*m/z*): calculated for $C_{11}H_8FN_3NaO_2$ $[M+Na]^+$, 256.0493; found, 256.0499.

N-(5-fluoro-2-((trimethylsilyl)oxy)pyrimidin-4-yl)benzamide (5F-3.53)



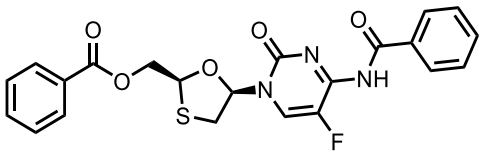
3.80 **5F-3.53**

*N*4-Benzoyl-5-fluorocytosine (2.33 g, 10.00 mmol) was added to a flask containing trimethylsilyl chloride (108 mg. 126 µL, 0.10 mmol) and (hexamethyldisilazane (HMDS) (8.07 g, 10.5 mL, 50.00 mmol) and refluxed under argon until all solids had dissolved. The solution was then cooled to room temperature and excess HMDS removed under vacuum. The residue was dissolved in dry dichloromethane (20 mL) to give a 0.5M solution of TMS protected *N*4-benzoyl-5-fluorocytosine which could be used immediately or stored under argon for later use.

Yield: 3.05 g (quant)

Physical state: White solid

((2*S*,5*R*)-(4-Benzamido-5-fluoro-2-oxopyrimidin-1(2*H*)-yl)-1,3-oxathiolan-2-yl)methyl benzoate (5F-3.54)



5F-3.54

3.21 (0.69 mmol) was dissolved in anhydrous acetonitrile (10 mL) and a solution of **5F-3.53** (0.5 M, 2.76 mL, 1.38 mmol) was added then the flask cooled to 0 °C in an ice bath. Trimethylsilyl iodide (276 mg, 196 µL, 1.38 mmol) dissolved in anhydrous acetonitrile was then added dropwise and the solution stirred at 0 °C under argon for 1 hour. The solution was quenched with a saturated sodium bicarbonate solution (5 mL) and diluted with water (20 mL). The mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (2 x 10 mL) and brine (20 mL) then dried over magnesium sulphate. The solvent was removed under reduced pressure to leave a crude solid which was purified by flash chromatography.

Yield: 67 mg (32%)

Physical state: White solid

m.p. >200 °C dec

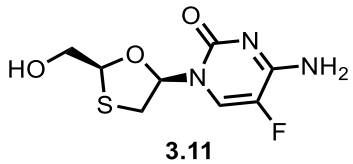
R_f = 0.24 (3:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03-7.94 (m, 3H), 7.82-7.76 (m, 2H), 7.64-7.58 (m, 2H), 7.61-7.49 (m, 4H), 6.22 (d, *J* = 7.4 Hz, 1H), 5.43-5.38 (m, 1H), 4.70-4.65 (m, 2H), 4.55 (dd, *J* = 11.2, 2.8 Hz, 1H), 3.95-3.85 (m, 1H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.3, 166.0, 155.0 (d, *J* = 15.1 Hz), 152.5 147.5, 133.2, 133.2, 132.9, 131.0, 129.8, 128.9, 128.3, 125.7 (d, *J* = 31.8 Hz) 97.7, 88.0, 86.4, 64.4, 35.1.

HRMS ESI (*m/z*): calculated for $C_{22}H_{18}FN_3NaO_5S$ $[M+Na]^+$, 478.0843; found, 478.0845.

4-Amino-5-fluoro-1-((2*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl)pyrimidin-2(1*H*)-one (3.11)



3.11

5F-3.54 (400 mg, 1.00 mmol) was dissolved in methanol (5 mL) and potassium carbonate (136 mg, 0.50 mmol) added. The solution stirred at room temperature and monitored by TLC. Once the starting material had been consumed the solution was diluted with water (20 mL) and extracted with ethyl acetate (2 x 10mL). The organic layer was separated and washed with brine (5 mL) then dried over magnesium sulphate and concentrated under reduced pressure to give the product.

Yield: 151 mg (61%)

Physical state: White solid

m.p. >196 – 200 ^{o}C

R$_f$ = 0.15 (1:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, DMSO-d$_6$): δ 8.20 (d, *J* = 7.2 Hz, 1H), 7.83 (br, 1H), 7.58 (br, 1H), 6.12-6.05 (m, 1H), 5.43 (t, *J* = 5.1 Hz, 1H), 5.18 (t, *J* = 3.8 Hz, 1H), 3.75-3.68 (m, 2H), 3.42 (dd, *J* = 11.9, 5.4 Hz, 1H), 3.12 (dd, *J* = 11.8, 4.3 Hz, 1H).

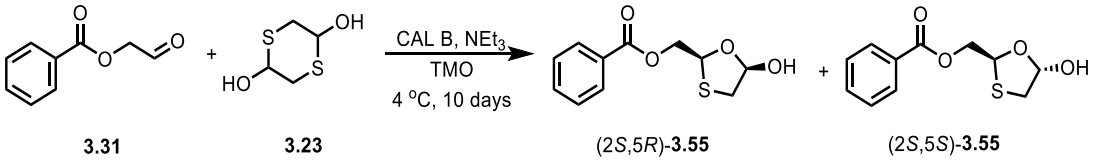
^{13}C NMR (101 MHz, DMSO-d$_6$): δ, 157.3 (d *J* = 13.4 Hz), 152.8, 136.8 (d, *J* = 240.6 Hz), 125.7 (d, *J* = 32.5 Hz), 86.8, 86.4, 62.0, 36.6.

^{19}F NMR (376 MHz, DMSO-d$_6$): δ -167.5.

HRMS ESI (*m/z*): calculated for $C_8H_{10}FN_3NaO_3S$ $[M+Na]^+$, 270.0319; found, 270.0320.

Chiral HPLC: Phenomenex Lux Cellulose 1, hexane/ethanol, 95:5 v/v, 0.8 mL/min, 40 ^{o}C, UV 254 nm. Retention times: (2R,5*S*) t_r = 16.98 min (*ee* = 16%) & (2*S*,5*R*) t_r = 17.69 min (*ee* = 84%).

((2*S*)-5-Hydroxy-1,3-oxathiolan-2-yl)methyl benzoate (3.55)



3.31 **3.23** (2*S*,5*R*)-**3.55** (2*S*,5*S*)-**3.55**

3.31 (164 mg, 1.00 mmol), 1,4-dithiane-2,5-diol (91 mg, 0.6 mmol) and triethylamine (101 mg, 139 µL, 1.00 mmol) were dissolved in TMO (5 mL). The solution was added to a 10 mL round bottom flask containing enzyme CAL B (50 mg) and left in a fridge at 4 °C for 10 days. The mixture was then filtered, washed with saturated ammonium chloride (2 mL) and brine (2 mL). The organic layer was dried over magnesium sulphate and concentrated under reduced pressure to leave a crude oil. This oil was then dissolved in hexane. The solution was stored in a freezer at –20 °C for 3 days after which a white precipitate of (2*S*,5*S*)-**3.55** was filtered, washed with cold hexane (2 mL) and dried under reduced pressure.

Yield: 103 mg (43%)

Physical state: Colourless oil

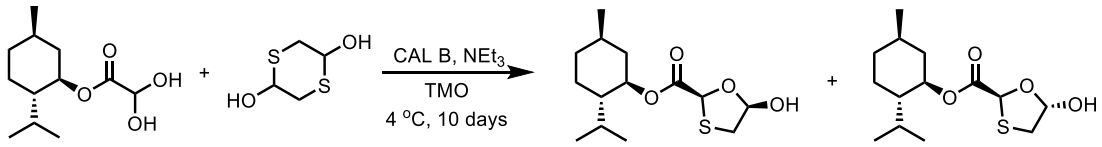
R$_f$ = *cis* isomer 0.24 (1:1 Hexane:EtOAc, UV)
trans isomer 0.26 (1:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ *cis* isomer δ 8.06-7.98 (m, 2H), 7.59-7.50 (m, 1H), 7.41 (t, *J* = 7.9 Hz, 2H), 6.68 (d, *J* = 4.1 Hz, 1H), 5.56 (d, *J* = 4.0 Hz, 1H), 4.63-4.31 (m, 2H), 3.28 (dd, *J* = 11.8, 4.2 Hz, 1H), 3.15 (d, *J* =11.8 Hz, 1H). *trans* isomer δ 8.06-7.98 (m, 2H), 7.59-7.50 (m, 1H), 7.41 (t, *J* = 7.9 Hz, 2H), 6.68 (d, *J* = 4.1 Hz, 1H), 5.51 (m, 1H), 4.65 (s, 2H), 3.73 (dd, *J* = 10.6, 5.9 Hz, 1H), 3.66 (dd, *J* = 10.6, 4.2 Hz, 1H).

^{13}C NMR (101 MHz, CDCl$_3$): *cis* isomer δ 166.1, 133.4, 129.9, 129.6, 128.5, 99.4, 84.7, 66.2, 38.2. *trans* isomer δ 166.1, 133.4, 129.9, 129.6, 128.5, 99.4, 83.4, 67.8, 37.6.

HRMS ESI (*m/z*): calculated for $C_{13}H_{14}NaO_5S$ $[M+Na]^+$, 305.0460; found, 305.0455.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl-5-hydroxy-1,3-oxathiolane-2-carboxylate (3.38)



3.22 **3.23** (2*S*,5*R*)-**3.38** (2*S*,5*S*)-**3.38**

L-Menthyl glyoxylate monohydrate (230 mg, 1.00 mmol), 1,4-dithiane-2,5-diol (91 mg, 0.60 mmol) and triethylamine (101 mg, 139 µL, 1.00 mmol) were dissolved in TMO (5 mL). This solution was added to a 10 mL round bottom flask containing enzyme CAL B (50 mg) and left in a fridge at 4 °C for 10 days. The mixture was then filtered, washed with saturated ammonium chloride (2 mL) and brine (2 mL). The organic layer was dried over magnesium sulphate and concentrated under reduced pressure to leave a crude oil. This oil was then dissolved in hexane and a minimal amount of diethyl ether added until the solution was clear. The solution was then stored in a freezer at –20 °C for 3 days after which a white precipitate of (2*S*,5*S*)-**3.38** was filtered, washed with cold hexane (2 mL) and dried under reduced pressure.

Yield: 80 mg (28%)

Physical state: White solid

m.p. 90 – 91 °C

R$_f$ = *cis* isomer 0.18 (3:1 Hexane:EtOAc, PMA)
trans isomer 0.15 (3:1 Hexane:EtOAc, PMA)

^{1}H NMR (400 MHz CDCl$_3$): t*rans* isomer δ 5.95-5.88 (m, 1H), 5.57-5.54 (m, 1H), 4.74-4.69 (m, 1H), 3.29-3.24 (m, 1H), 3.10-3.04 (m, 2H), 2.05-1.98 (m, 2H), 1.70-1.60 (m, 2H), 1.50-1.41 (m, 2H), 1.06-1.00 (m, 2H), 0.93-0.86 (m, 6H), 0.77 (s, 3H). *cis* isomer δ 6.00-5.95 (m, 1H), 5.57-5.54 (m, 1H), 4.74-4.70 (m, 1H), 3.37-3.30 (m, 1H), 3.19-3.14 (m, 2H), 2.07-1.98 (m, 2H), 1.71-1.60 (m, 2H), 1.53-1.38 (m, 2H), 1.09-0.90 (m, 2H), 0.90-0.81 (m, 6H), 0.69 (s, 3H);

^{13}C NMR (101 MHz, CDCl$_3$): t*rans* isomer δ 169.4, 101.2, 80.2, 76.0, 47.0, 40.7, 38.5, 34.4, 31.4, 26.0, 23.3, 22.0, 20.7, 16.1.*cis* isomer δ 169.5, 101.5, 76.4, 75.0,, 46.7, 40.4, 38.0, 33.4, 31.1, 26.2, 23.2, 22.2, 20.9, 16.6.

HRMS ESI (*m/z*): calculated for $C_{14}H_{24}NaO_4S$ $[M+Na]^+$, 311.1288; found, 311.1292

6.3.4. Selective *O*-deacetylation of (3.21)

General procedure A:

3.21 (282 mg, 1.00 mmol) was dissolved in chloroform (10 mL) and methanolic HCl (0.5 M, 1000 µL, 0.50 mmol) added. The solution was stirred at room temperature and monitored by TLC. Once the starting material had been consumed the solution was quenched with saturated sodium hydrogen carbonate (2 mL) and diluted with water (10 mL) and chloroform (20 mL). The organic layer was separated and washed with brine (10 mL) then dried over magnesium sulphate and concentrated under reduced pressure to give the product as a crude oil as a mixture of products.

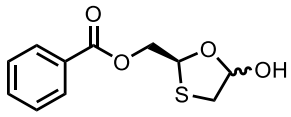
General procedure B:

3.21 (282 mg, 1.00 mmol) was dissolved in acetonitrile (10 mL) and iron(III) trichloride hexahydrate (136 mg, 0.50 mmol) added. The solution was heated to reflux and monitored by TLC. Once the starting material had been consumed the solution was quenched with saturated sodium hydrogen carbonate (2 mL) and diluted with water (10 mL) and ethyl acetate (20 mL). The organic layer was separated and washed with brine (10 mL) then dried over magnesium sulphate and concentrated under reduced pressure to give the product as a crude oil as a mixture of products.

General procedure C:

3.21 (282 mg, 1.00 mmol) was dissolved in methanol (10 mL) and potassium carbonate (69 mg, 0.50 mmol) added. The solution stirred at room temperature and monitored by TLC. Once the starting material had been consumed the solution was quenched with water (15 mL) and diluted with ethyl acetate (20 mL). The organic layer was separated and washed with brine (10 mL) then dried over magnesium sulphate and concentrated under reduced pressure to give the product as a crude oil as a mixture of products.

((2*S*)-5-Hydroxy-1,3-oxathiolan-2-yl)methyl benzoate (3.56)



3.56

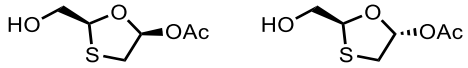
Following *O*-deacetylation general procedure B**.**

Mixture of diastereoisomers (2:1 *cis*/*trans*).

Yield: 25 mg (10%)

Physical state: Colourless oil

(2*S*)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl acetate (3.57)



cis-**3.57** *trans*-**3.57**

Following *O*-deacetylation general procedure C**.**

Mixture of diastereoisomers (6:1 *cis*/*trans*).

Yield: 18 mg (10%)

Physical state: Colourless oil

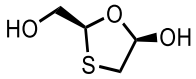
R$_f$ = *cis* isomer 0.15 (2:1 Hexane:EtOAc, PMA)
trans isomer 0.10 (2:1 Hexane:EtOAc, PMA)

^{1}H NMR (400 MHz, CDCl$_3$):*cis* isomer δ 6.62 (d, *J* = 4.5 Hz, 1H), 5.54 (d, *J* = 3.9 Hz, 1H), 4.42-3.99 (m, 2H), 3.32 (d, *J* = 4.2 Hz, 1H), 3.29 (d, *J* = 4.3 Hz, 1H), 2.09 (s, 3H). *trans* isomer δ 6.67 (d, *J* = 4.2 Hz, 1H), 5.54-5.49 (m, 1H), 3.95-3.79 (m, 1H), 3.32-3.29 (m, 2H), 2.34-2.24 (m, 1H), 2.09 (s, 3H).

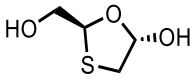
^{13}C NMR (101 MHz, CDCl$_3$): δ 168.2, 99.3, 83.4, 64.0, 37.6, 21.3.

HRMS ESI (*m/z*): calculated for $C_6H_{10}NaO_4S$ $[M+Na]^+$, 201.0192; found, 201.0194.

2-(Hydroxymethyl)-1,3-oxathiolan-5-ol (3.58)



cis-**3.58**



trans-**3.58**

Following *O*-deacetylation general procedure A**.**

Mixture of diastereoisomers (4:1 *cis*/*trans*).

Yield: 109 mg (80%)

Physical state: Colourless oil

R$_f$ = *cis* isomer 0.20 (8:1 DCM:MeOH, PMA)
trans isomer 0.15 (8:1 DCM:MeOH, PMA)

^{1}H NMR (400 MHz, CDCl$_3$): δ *cis* isomer δ 6.62 (d, *J* = 4.5 Hz, 1H), 5.54 (d, *J* = 3.9 Hz, 1H), 4.42-3.99 (m, 2H), 3.32 (d, *J* = 4.2 Hz, 1H), 3.29 (d, *J* = 4.3 Hz, 1H). *trans* isomer δ 6.67 (d, *J* = 4.2 Hz, 1H), 5.54-5.49 (m, 1H), 3.95-3.79 (m, 1H), 3.36-3.09 (m, 2H), 2.34-2.24 (m, 1H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 100.3, 83.4, 63.8, 38.1.

HRMS ESI (*m/z*): calculated for $C_4H_8NaO_4S$ $[M+Na]^+$, 175.1532; found, 175.1533.

6.3.5. Mitsunobu reactions

General Mitsunobu reaction A: PPh_3, DIAD

Triphenylphosphine (181 mg, 0.69 mmol) and substrate (0.69 mmol) were dissolved in solvent (5 mL). Then alcohol (0.46 mmol) and DIAD (140 mg, 136 µL, 0.69 mmol) were added and the solution stirred at specified temperature. The reaction was monitored by HPLC and when complete, the solvent was removed under reduced pressure and the residue purified by flash chromatography.

General Mitsunobu reaction A: PPh_3, DIAD via reactive intermediate.

Triphenylphosphine (181 mg, 0.69 mmol) and DIAD (140 mg, 136 µL, 0.69 mmol) were dissolved in solvent (5 mL) and stirred for 1 hour. Then alcohol (0.46 mmol) was added and the solution stirred for a further 30 minutes. After which substrate (0.69 mmol) was added and the solution heated to reflux. The reaction was monitored by HPLC and when complete, the solvent was removed under reduced pressure and the residue purified by flash chromatography.

General Mitsunobu reaction B: PPh_3, DCPEAC

Triphenylphosphine (181 mg, 0.69 mmol) and substrate (0.69 mmol) were dissolved in solvent (5 mL). Then alcohol (0.46 mmol) was added and when fully dissolved ethyl 2-(3,4-dichlorophenyl)hydrazine-1-carboxylate (DCPEAC) (172 mg, 0.69 mmol) was added and the solution stirred at specified temperature. The reaction was monitored by HPLC and when complete, the solvent was removed under reduced pressure and the residue purified by flash chromatography.

General Mitsunobu reaction C: PPh_3, DCPEAC (10 mol%) & FePc (10 mol%)

DCPEAC (10 mg, 0.04 mmol), FePc (25 mg, 0.04 mmol), triphenylphosphine (181 mg, 0.69 mmol), and substrate (0.69 mmol) were dissolved in solvent (5 mL). Then the alcohol (0.46 mmol) was added and when fully dissolved the solution stirred at specified temperature. The reaction was monitored by HPLC and when complete, the solvent was removed under reduced pressure and the residue purified by flash chromatography.

General Mitsunobu reaction D: Phosphine 3.77, DIAD

Phosphine oxide **3.77** (124 mg, 0.69 mmol) and substrate (0.69 mmol) were dissolved in solvent (5 mL). Then alcohol (0.46 mmol) was added and when fully dissolved DIAD (140 mg, 136 µL, 0.69 mmol) was added and the solution stirred at specified temperature. The reaction was monitored by HPLC and when complete, the solvent was removed under reduced pressure and the residue purified by flash chromatography.

General Mitsunobu reaction E: Phosphine 3.77, DCPEAC

Phosphine oxide **3.77** (124 mg, 0.69 mmol) and substrate (0.69 mmol) were dissolved in solvent (5 mL). Then alcohol (0.46 mmol) was added and when fully dissolved DCPEAC (172 mg, 0.69 mmol) was added and the solution stirred at specified temperature. The reaction was monitored by HPLC and when complete, the solvent was removed under reduced pressure and the residue purified by flash chromatography.

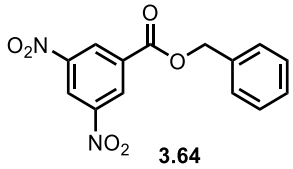
General Mitsunobu reaction F: Phosphine 3.77 (10 mol%), DCPEAC

Phosphine oxide **3.77** (7 mg, 0.04 mmol) and substrate (0.69 mmol) were dissolved in solvent (5 mL). Then alcohol (0.46 mmol) was added and when fully dissolved DCPEAC (172 mg, 0.69 mmol) and phenylsilane (75 mg, 85 µL,0.69 mmol) were added and the solution stirred at the specified temperature. The reaction was monitored by HPLC and when complete, the solvent was removed under reduced pressure and the residue purified by flash chromatography.

General Mitsunobu reaction G: Phosphine 3.77, DCPEAC & FePc (10 mol%) + $PhSiH_3$

DCPEAC (10 mg, 0.04 mmol), FePc (25 mg, 0.04 mmol), phosphine oxide **3.77** (7 mg, 0.04 mmol) and substrate (0.69 mmol) were dissolved in solvent (5 mL). Then alcohol (0.46 mmol) was added followed by phenylsilane (75 mg, 85 µL,0.69 mmol) and when fully dissolved the solution stirred at the specified temperature. The reaction was monitored by HPLC and when complete, the solvent was removed under reduced pressure and the residue purified by flash chromatography.

Benzyl 3,5-dinitrobenzoate (3.64)



3.64

Triphenylphosphine (362 mg, 1.38 mmol) and 3,5-dinitrobenzoic acid (293 mg, 1.38 mmol) were dissolved in solvent (10 mL). Then benzyl alcohol (100 mg, 0.92 mmol) and DIAD (279 mg, 271 µL, 1.38 mmol) were added and the solution stirred at the desired temperature. The reaction was monitored by GCMS and when complete, the solvent was removed under reduced pressure and the residue purified by flash chromatography.

Yield: 265 mg (93%)

Physical state: Yellow solid

m.p. 112 – 114 ^{o}C

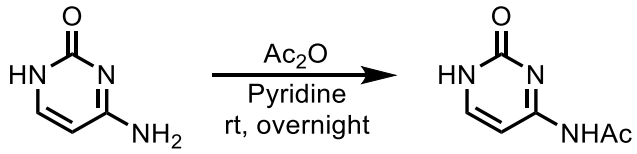
R$_f$ = 0.35 (8:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 9.22 (t, *J* = 2.1 Hz, 1H), 9.17 (d, *J* = 2.1 Hz, 2H), 7.52-7.37 (m, 5H), 5.48 (s, 2H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 162.5, 148.7, 134.6, 133.9, 129.6, 129.1, 129.0, 128.9, 122.6, 68.7.

HRMS APCI (*m/z*): calculated for $C_{14}H_{11}N_2O_6$ $[M+H]^+$, 303.0612; found, 033.0612.

***N*4-Acetylcytosine (3.59)**



3.1 **3.59**

Cytosine (0.22 g, 2.00 mmol) was suspended in pyridine (10 mL) and the mixture cooled to 0 °C. Acetic anhydride (0.61 g, 0.7 mL, 6.00 mmol) was added dropwise and the suspension was stirred at room temperature overnight. The reaction mixture was then cooled in an ice bath, and ammonium hydroxide (1 mL) added. The solution was stirred for 2 hours then diluted with water (20 mL) and stirred for 1 hour to allow a precipitate to form. This was filtered, washed with cold water and dried under reduced pressure to leave a crystalline solid.

Yield: 0.29 g (95%)

Physical state: White solid

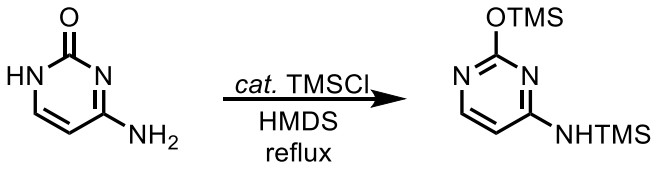
m.p. >300 ^{o}C

^{1}H NMR (400 MHz, DMSO-d$_6$): δ 11.50 (br, 1H), 7.80 (d, *J* = 7.4 Hz, 1H), 7.09, (d, *J* = 7.4 Hz, 1H), 2.08 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d$_6$): δ 169.8, 161.1, 156.2, 147.3, 94.4, 23.2.

HRMS ESI (*m/z*): calculated for $C_6H_7N_3NaO_2$ $[M+Na]^+$, 176.0430; found, 176.0438.

2,4-*O*,*N*-bis(Trimethylsilyl)cytosine (3.61)



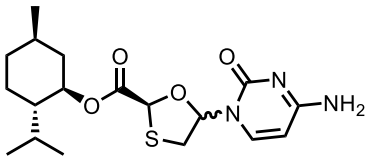
3.1 **3.61**

Cytosine (1.11 g, 10.00 mmol) was added to a flask containing trimethylsilyl chloride (108 mg. 126 µL, 0.10 mmol) and hexamethyldisilazane (HMDS) (8.07 g, 10.5 mL, 50.00 mmol) and refluxed under argon until all solids had dissolved. The solution was then cooled to room temperature and excess HMDS removed under vacuum. The residue was dissolved in dry dichloromethane (20 mL) to give a 0.5 M solution of TMS protected cytosine which could be used immediately or stored under argon for later use.

Yield: 2.55 g (quant)

Physical state: White solid

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (2*S*)-5-(4- amino-2-oxo-1,2-dihydro-1-pyrimidinyl)-1,3-oxathiolane-2-carboxylate (3.65)



3.65

TMS protected cytosine **3.53** (0.5 M, 2.8 mL, 1.38 mmol) was added to anhydrous acetonitrile (10 mL) followed by **3.24** (228 mg, 0.69 mmol) and the solution cooled in an ice bath. Trimethylsilyl iodide (276 mg, 196 µL, 1.38 mmol) in anhydrous acetonitrile was added dropwise then the solution was stirred at 0 ^{o}C under argon for 1 hour. After this time the solution was quenched with a saturated sodium bicarbonate solution (5 mL) and diluted with water (40 mL). The solution was then extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with, water (2 x 10 mL) and brine (20 mL) then dried over magnesium sulphate. The solvent was removed under reduced pressure to leave a crude solid which was purified by flash chromatography. (Single diastereoisomer, unsure of the of configuration).

Yield: 137 mg (52%)

Physical state: White solid

m.p. >200 ^{o}C dec

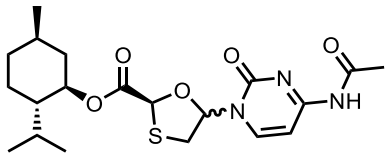
R$_f$ = 0.20 (9:1 EtOAc:MeOH, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.35 (d, *J* = 7.4 Hz, 1H), 6.47-6.37 (m, 1H), 5.73 (d, *J* = 7.4 Hz, 1H), 5.46 (s, 1H), 4.76-4.61 (m, 1H), 3.64-3.50 (m, 1H), 3.11-3.01 (m, 1H), 2.04-1.99 (m, 1H), 1.95-1.87 (m, 1H), 1.71-1.60 (m, 2H), 1.51-1.48 (m, 1H), 1.43-1.30 (m, 1H), 1.10-0.98 (m, 2H), 0.97-0.85 (m, 7H), 0.77 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 170.0, 165.2, 154.5, 142.4, 93.5, 90.4, 78.6, 76.7, 47.0, 40.5, 36.7, 33.1, 31.5, 26.1, 23.1, 22.0, 20.9, 16.0.

HRMS ESI (*m/z*): calculated for $C_{18}H_{27}N_3NaO_4S$ $[M+Na]^+$, 404.1614; found, 404.1620.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (2*S*)-5-(4-acetamido-2-oxopyrimidin-1(2*H*)-yl)-1,3-oxathiolane-2-carboxylate (3.66)



3.66

General procedure A using **3.59** (77 mg, 0.69 mmol) and **3.38** (133 mg, 0.46 mmol) at room temperature for 24 hours. (Single diastereoisomer, unsure of the of configuration).

Yield: 82 mg (42%)

Physical state: White solid

m.p. >200 ^{o}C dec

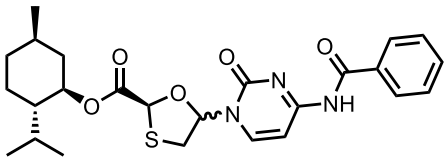
R$_f$ = 0.30 (9:1 DCM:MeOH, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.01 (d, *J* = 7.4 Hz, 1H), 8.13 (br, 1H), 7.50-7.38 (m, 1H), 6.62-6.40 (m, 1H), 5.55 (s, 1H), 4.83-4.75 (m, 1H), 3.65 (dd, *J* = 12.3, 4.6 Hz, 1H), 3.20 (dd, *J* = 12.3, 5.8 Hz, 1H), 2.22 (s, 3H), 2.10-2.01 (m, 1H), 1.90-1.81 (m, 1H), 1.74-1.62 (m, 2H), 1.55-1.44 (m, 1H), 1.40-1.33 (m, 1H), 1.10-0.97 (m, 2H), 0.96-0.79 (m, 7H), 0.74 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 169.9, 169.1, 163.0, 154.8, 145.5, 96.5, 90.4, 79.6, 76.9, 46.9, 40.6, 37.2, 33.8, 31.3, 26.1, 25.3, 23.0, 21.9, 20.7, 16.1.

HRMS ESI (*m/z*): calculated for $C_{20}H_{29}N_3NaO_5S$ $[M+Na]^+$, 446.1720; found, 446.1726.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (2*S*)-5-(4-benzamido-2-oxopyrimidin-1(2*H*)-yl)-1,3-oxathiolane-2-carboxylate (3.67)



3.67

General procedure A using **3.60** (166 mg, 0.69 mmol) and **3.38** (133 mg, 0.46 mmol) at room temperature for 24 hours. (Single diastereoisomer, unsure of the of configuration).

Yield: 98 mg (44%)

Physical state: White solid

m.p. >200 ºC dec

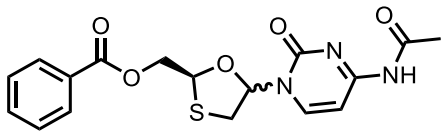
R$_f$ = 0.25 (7:1 Hexane:MeOH, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.70 (d, *J* = 7.5 Hz, 1H), 8.69 (br, 1H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 6.42-6.29 (m, 1H), 5.54 (s, 1H), 4.80-4.74 (m, 1H), 3.69-3.62 (m, 1H), 3.24 (dd, *J* = 12.3, 5.9 Hz, 1H), 2.12-2.02 (m, 1H), 1.99-1.87 (m, 1H), 1.76-1.62 (m, 2H), 1.59-1.49 (m, 1H), 1.45-1.40 (m, 1H), 1.15-0.99 (m, 2H), 0.98-0.82 (m, 7H), 0.78 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 169.3, 166.3, 162.6, 154.9, 154.6, 143.6, 133.2, 133.0, 129.1, 127.5, 96.6, 90.7, 79.7, 77.0, 47.1, 40.8, 37.1, 34.0, 31.5, 26.2, 23.2, 21.9, 20.7, 16.1.

HRMS ESI (*m/z*): calculated for $C_{25}H_{31}N_3NaO_5S$ $[M+Na]^+$, 508.5882; found, 508.5890.

((2*S*)-5-(4-Acetamido-2-oxopyrimidin-1(2*H*)-yl)-1,3-oxathiolan-2-yl)methyl benzoate (3.54Ac)



3.54Ac

General procedure A using **3.59** (106 mg, 0.69 mmol) and **3.55** (133 mg, 0.46 mmol) at room temperature for 24 hours. (Single diastereoisomer, unsure of the of configuration).

Yield: 122 mg (47%)

Physical state: White solid

m.p. >200 ^{o}C dec

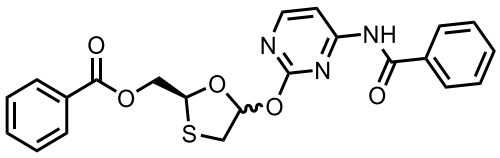
R$_f$ = 0.24 (6:1 EtOAc:MeOH, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.21 (d, *J* = 7.4 Hz, 1H), 8.07-7.52 (m, 5H), 7.30 (d, *J* = 8.2 Hz, 1H), 6.39 (dd, *J* =5.3, 2.8 Hz, 1H), 5.53 (dd, *J* = 4.2, 3.0 Hz, 1H), 4.81 (m, 2H), 3.69-3.62 (m, 1H), 3.30-3.22 (m, 1H), 2.26 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 170.5, 166.0, 162.5, 154.5, 144.7, 133.7, 130. 129.1, 128.7, 97.1, 96.8, 85.2, 63.5, 39.1, 29.7, 24.9.

HRMS ESI (*m/z*): calculated for $C_{17}H_{17}N_3NaO_5S$ $[M+Na]^+$, 398.0781; found, 398.0781.

((*2S*)5-(4-Benzamidopyrimidin-2-yl)oxy)-1,3-oxathiolan-2-yl)methyl benzoate (3.68)



3.68

General procedure A using **3.60** (166 mg, 0.69 mmol) and **3.55** (133 mg, 0.46 mmol) at room temperature for 24 hours. (Single diastereoisomer, unsure of the of configuration).

Yield: 96 mg (48%)

Physical state: White solid

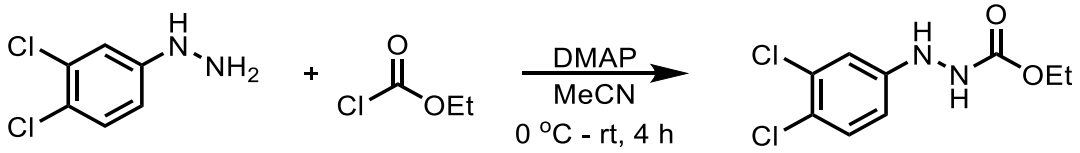
R_f = 0.19 (3:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 4.2 Hz, 1H), 8.08-8.00 (m, 2H), 8.00-7.92 (m, 2H), 7.59-7.46 (m, 2H), 7.49-7.39 (m, 4H), 7.07 (s, 1H), 6.45-6.40 (m, 1H), 5.41-5.36 (m, 1H), 4.76-4.70 (m, 1H), 4.50-4.42 (m, 1H), 3.35-3.28 (m, 1H), 3.19-3.10 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.5, 167.0, 162.0, 155.9, 154.8, 133.9, 133.4, 131.0, 129.8, 129.2, 128.9, 128.7, 128.0, 103.0, 102.6, 83.2, 70.7, 35.4.

HRMS ESI (*m/z*): calculated for $C_{22}H_{19}N_3NaO_5S$ $[M+Na]^+$, 460.0938; found, 460.0936.

Ethyl 2-(3,4-dichlorophenyl)hydrazine-1-carboxylate (3.72)



3.70 **3.71** **3.72**

2-(3,4-Dichlorophenyl)hydrazine hydrochloride (1.07 g, 5.00 mmol), pyridine (0.89 mL, 11.0 mmol) and DMAP (30.5 mg, 0.25 mmol) were dissolved in acetonitrile (25 mL) and cooled in an ice bath to 0 °C. Ethyl chloroformate (0.53 mL, 5.50 mmol) was then added dropwise and the mixture was stirred for 10 min then allowed to warm to room temperature and stir for 4 hours. The solution was then poured into water (50 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with a saturated sodium bicarbonate solution (50 mL) and brine (50 mL) then dried over magnesium sulphate. The solvent was removed under reduced pressure to leave a crude oil which was purified by flash chromatography.

Yield: 0.97 g (78%)

Physical state: White solid

m.p. 107 – 110 °C

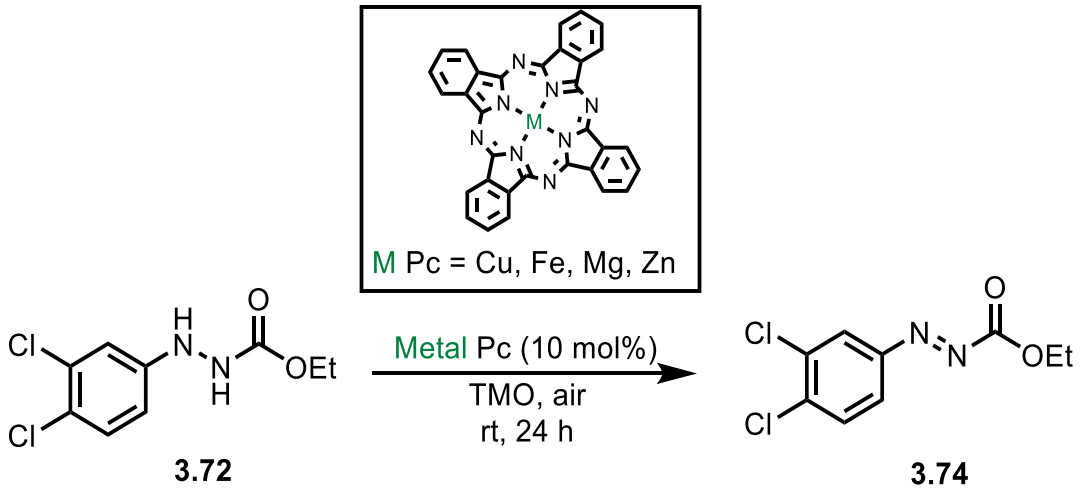
R_f = 0.36 (2:1 Hexane:EtOAc, $KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.7 Hz, 1H), 6.87-6.78 (m, 1H), 6.69 (br, 1H), 6.59 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.09 (br, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 1.26 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.2, 147.8, 133.0, 130.8, 123.6, 114.6, 112.6, 62.4, 14.6.

HRMS ESI (*m/z*): calculated for $C_9H_{10}Cl_2N_2NaO_2$ $[M+Na]^+$, 271.0012; found, 271.0019.

Ethyl 2-(3,4-dichlorophenyl) diazene-1-carboxylate (3.74)



3.72 (249 mg, 1.00 mmol) and FePc (57 mg. 0.01 mmol) were dissolved in TMO (5 mL) and stirred for 24 hours in a flask open to the air. After this time the solvent was removed under reduced pressure and the residue was purified by flash chromatography.

Yield: 247 mg (quant)

Physical state: Red powder

m.p. 130 – 132 ºC

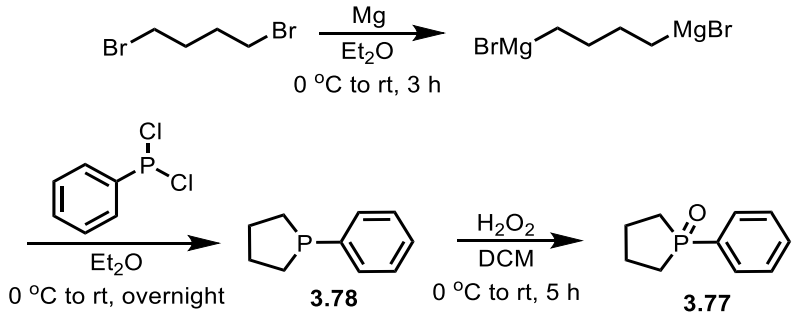
R_f = 0.45 (6:1 Hexane:EtOAc, NA, red dot on TLC plate)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 2.2 Hz, 1H), 7.79 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 4.51 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.7, 150.4, 138.2, 134.1, 131.3, 125.0, 123.7, 64.9, 14.24.

HRMS ESI (*m/z*): calculated for $C_9H_8Cl_2N_2NaO_2$ $[M+Na]^+$, 268.9855; found, 268.9560.

1-Phenylphospholane-1-oxide (3.77)



Magnesium turnings (1.22 g, 50.00 mmol) were added to a flame dried round bottom flask and dried under vacuum overnight with stirring. The flask was backfilled with argon then anhydrous Et_2O (40 mL) was added. The flask was then cooled to 0 °C and 1,4-dibromobutane (2.70 g, 121.4 mL, 50.00 mmol) in Et_2O (10 mL) was added dropwise. Once the addition was complete the flask was warmed to room temperature and stirred. After 3 hours stirring at room temperature the Grignard solution was cooled to 0 °C and dichlorophosphine (2.24 g, 1.6 mL, 12.50 mmol) in Et_2O (15 mL) was added dropwise after which the solution was warmed to room temperature and stirred overnight. The solution was quenched with water (100 mL) and organic phase removed, the aqueous phase was washed with Et_2O (3 x 20 mL) and the organic layers combined. The combined organic layers were washed with water (2 x 50 mL) and brine (100 mL) then dried over magnesium sulphate before being concentrated under reduced pressure. The crude material was used without purification.

Crude **3.78** (0.50 g, 3.05 mmol) was dissolved in DCM (20 mL) and cooled to 0 °C. With vigorous stirring 35% H_2O_2 (0.6 mL, 6.10 mmol) was added dropwise and the solution warmed to room temperature and stirred for 5 hours. The solution was then transferred to a separating funnel and washed sequentially with saturated sodium hydrogen carbonate (3 x 30 mL), water (30 mL) and brine (30 mL) then dried over magnesium sulphate and the solvent removed under reduced pressure. The crude material was purified by column chromatography.

Yield: 0.31 g (40% over 2 steps)

Physical state: White solid

m.p. 62 – 64 °C

R_f = 0.20 (9:1 MeOH:DCM + 0.1% NEt_3, UV)

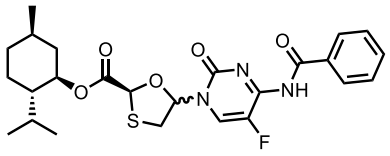
^{1}H NMR (400 MHz, d_8-THF): δ 7.75-7.65 (m, 2H), 7.50-7.39 (m, 3H), 2.20-1.95 (m, 8H).

^{13}C NMR (101 MHz, d_8-THF): δ 132.3 (d, *J* = 90.2 Hz), 130.6 (d, *J* = 3.0 Hz), 127.9 (d, *J* = 10.5 Hz), 126.6 (d, *J* = 11.0 Hz), 25.9 (d, *J* = 67.8 Hz), 25.1 (d, *J* = 8.7 Hz).

^{31}P NMR (162 MHz, d_8-THF): δ 58.7.

HRMS ESI (*m/z*): calculated for $C_{10}H_{13}NaOP$ $[M+Na]^+$, 203.0596; found, 203.0599.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (2*S*)-5-(4-benzamido-5-fluoro-2-oxopyrimidin-1(2*H*)-yl)-1,3-oxathiolane-2-carboxylate (3.86)



3.86

General procedure C using **3.80** (161 mg, 0.69 mmol) and **3.38** (133 mg, 0.46 mmol) at 60 ºC for 24 hours. (Single diastereoisomer, unsure of the of configuration).

Yield: 104 mg (45%)

Physical state: White solid

m.p. >200 ºC dec

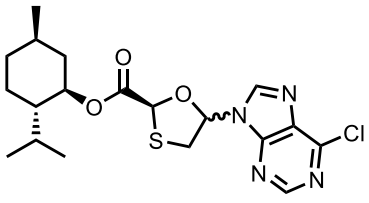
R$_f$ = 0.38 (2:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.70 (d, *J* = 6.3 Hz, 1H), 8.25 (d, *J* = 7.4 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 6.59-6.41 (m, 1H), 5.44 (s, 1H), 4.85-4.72 (m, 1H), 3.61-3.53 (m, 1H), 3.22 (dd, *J* = 12.2, 6.9 Hz, 1H), 2.10-2.01 (m, 1H), 1.99-1.88 (m, 1H), 1.77-1.70 (m, 2H), 1.59-1.45 (m, 1H), 1.46-1.38 (m, 1H), 1.15-0.97 (m, 2H), 0.96-0.80 (m, 7H), 0.78 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 169.5, 152.6 (d, *J* = 19.4 Hz), 147.1, 139.7 (d, *J* = 41.7 Hz), 135.6, 133.0, 129.9, 128.3, 126.2 (d, *J* = 41.3 Hz), 89.7, 78.6, 77.0, 47.0, 40.6, 35.6, 33.9, 31.4, 26.0, 23.1, 21.8, 20.6, 16.0.

HRMS ESI (*m/z*): calculated for $C_{25}H_{30}FN_3NaO_5S$ $[M+Na]^+$, 526.1782; found, 526.1785.

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (2*S*)-5-(6-chloro-9*H*-purin-9-yl)-1,3-oxathiolane-2-carboxylate (3.87)



3.87

General procedure C using 6-chloropurine (107 mg, 0.69 mmol) and **3.38** (133 mg, 0.46 mmol) at 60 ºC for 24 hours. (Single diastereoisomer, unsure of the of configuration).

Yield: 78 mg (40%)

Physical state: Yellow solid

m.p. >300 ºC

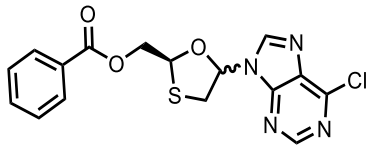
R$_f$ = 0.30 (1:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.76 (s, 1H), 8.70 (s, 1H), 5.81-5.62 (m, 1H), 6.65 (d, *J* = 4.0 Hz, 1H), 6.61 (d, *J* = 4.0 Hz, 1H), 5.69-5.58 (m, 1H), 2.10-2.01 (m, 1H), 1.99-1.88 (m, 1H), 1.83-1.77 (m, 2H), 1.59-1.45 (m, 1H), 1.46-1.38 (m, 2H), 1.15-0.97 (m, 2H), 0.96-0.80 (m, 7H), 0.78 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): δ172.4, 151.9, 151.1, 150.8, 144.8, 136.4 103.2, 80.1, 76.0, 47.7, 40.5, 38.9, 34.5, 31.3, 26.5, 24.1, 23.0, 20.8, 16.4.

HRMS ESI (*m/z*): calculated for $C_{19}H_{25}ClN_4NaO_3S$ $[M+Na]^+$, 447.1228; found, 447.1230

((2*S*)-5-(6-Chloro-9*H*-purin-9-yl)-1,3-oxathiolan-2-yl)methyl benzoate (3.88)



3.88

General procedure C using 6-chloropurine (107 mg, 0.69 mmol) and **3.55** (133 mg, 0.46 mmol) at 60 ^{o}C for 24 hours. (Single diastereoisomer, unsure of the of configuration).

Yield: 78 mg (40%)

Physical state: Yellow solid

m.p. >300 ^{o}C

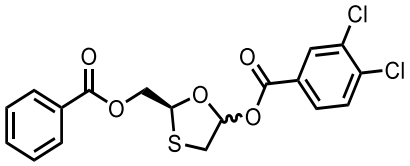
R$_f$ = 0.35 (1:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.76 (s, 1H), 8.53 (s, 1H), 8.01-7.82 (m, 2H), 7.55-7.49 (m, 1H), 7.43-7.29 (m, 2H), 6.92 (d, *J* = 4.1 Hz, 1H), 5.81-5.62 (m, 1H), 5.60 (d, *J* = 4.0 Hz, 1H), 4.60-4.31 (m, 2H), 3.26 (dd, *J* = 10.6, 4.2 Hz, 1H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 166.0, 152.5, 149.9, 149.6, 143.2, 133.9, 130.1, 129.8, 129.4, 128.7, 87.0, 86.3, 83.3, 83.0, 69.7, 29.7.

HRMS ESI (*m/z*): calculated for $C_{16}H_{13}ClN_4NaO_3S$ $[M+Na]^+$, 399.0289; found, 399.0292.

(2*S*)-*2*-((Benzoyloxy)methyl)-1,3-oxathiolan-5-yl 3,4-dichlorobenzoate (3.89)



3.89

General procedure C using 3,4-dichlorobenzoic acid (132 mg, 0.69 mmol) and **3.55** (133 mg, 0.46 mmol) at 60 ºC for 24 hours. (Single diastereoisomer, unsure of the of configuration).

Yield: 76 mg (40%)

Physical state: White solid

m.p. >300 ºC

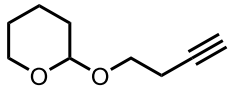
R_f = 0.30 (1:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03-7.72 (m, 5H), 7.50-7.40 (m, 3H), 6.90-6.79 (m, 1H), 6.61-5.52 (m, 1H), 4.72-4.55 (m, 2H), 5.72-5.60 (m, 1H), 3.35-3.14 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.2, 166.1, 138.0, 133.9, 133.7, 133.4, 131.5, 130.3, 129.9, 129.8, 128.6, 100.6, 100.3, 83.5, 67.4, 66.3, 37.6.

HRMS ESI (*m/z*): calculated for $C_{18}H_{14}Cl_2NaO_5S$ $[M+Na]^+$, 434.9831; found, 434.9835.

2-(3-Butyn-1-yloxy)tetrahydropyran (3.93)



3.93

3-Butyne-1-ol (5.00 g, 71.34 mmol) and dihydropyran (6.60 g, 78.47 mmol) where dissolved in dichloromethane (90 mL) and cooled to 0 ^{o}C in an ice bath. *p*-Cymene or *p*-toluene sulfonic acid (0.71 mmol) was added and the solution stirred for 90 minutes after which time the solution was quenched with saturated sodium bicarbonate (100 mL) and the organic layer removed. The aqueous phase was extracted with DCM (20 mL) and the organics layers combined then washed with brine (100 mL), dried with magnesium sulphate and filtered. The solvent was removed under reduced pressure. The product was sufficiently pure to use without purification.

Yield: 10.12 g (92%)

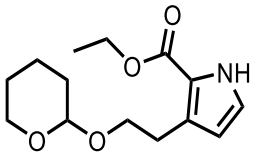
Physical state: Colourless liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.63-4.55 (m, 1H), 3.90-3.69 (m, 2H), 3.56-3.39 (m, 2H), 2.44 (td, *J* = 7.1, 2.7 Hz, 2H), 1.94 (t, *J* = 2.7 Hz, 1H), 1.86-1.41 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 98.8, 81.4, 69.3, 65.5, 62.2, 30.6, 25.4, 20.0, 19.4.

HRMS ESI (*m/z*): calculated for $C_9H_{14}NaO_2$ $[M+Na]^+$, 177.0886; found, 177.0886.

Ethyl 3-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)-1*H*-pyrrole-2-carboxylate (3.95)



3.95

Silver carbonate (28 mg, 0.10 mmol) was added to a flask and placed under argon. THP protected alkyne **3.93** (154 mg, 1.00 mmol) dissolved in dry NMP (5 mL) was added to the flask and the solution was heated to 80 ^{o}C. After 15 minutes ethyl isocyanide (226 mg, 219 µL, 2.00 mmol) in dry DMF (5 mL) was added over 30 minutes. Then the solution was stirred for a further 2 hours after which the solution was cooled to room temperature and filtered through a cotton plug. The filtrate was diluted with ether (50 mL) and successively washed with water (5 x 20 mL) and brine (20 mL) then dried over magnesium sulphate and concentrated under reduced pressure to give the product which was purified by flash chromatography.

Yield: 251 mg (94%)

Physical state: Red oil

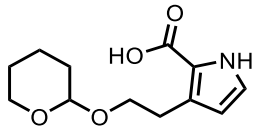
R$_f$ = 0.33 (4:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 9.15 (s, 1H), 6.83 (t, *J* = 2.8 Hz, 1H), 6.18 (t, *J* = 2.7 Hz, 1H), 4.66-4.60 (m, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.97-3.88 (m, 1H), 3.87-3.79 (m, 1H), 3.67-3.57 (m, 1H), 3.51-3.43 (m, 1H), 3.11 (t, *J* = 7.3 Hz, 2H), 1.86-1.46 (m, 6H), 1.35 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 161.7, 129.1, 121.8, 119.4, 112.2, 98.7, 67.8, 62.3, 60.2, 30.8, 27.7, 25.6, 19.7, 14.6.

HRMS ESI (*m/z*): calculated for $C_{14}H_{21}NNaO_4$ $[M+Na]^+$, 290.1363; found, 290.1362.

3-(2-((Tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)-1*H*-pyrrole-2-carboxylic acid (3.96)



3.96

Ethyl ester **3.95** (535 mg, 2.00 mmol) was dissolved in ethanol/water 50:50 v/v (20 mL) and sodium hydroxide (400 mg, 10.00 mmol) added and the solution refluxed for 2 hours. Then the solvent was removed, and residue dissolved in water. The pH was adjusted to pH 6 by addition of 0.5 M HCl then the aqueous phase extracted with ethyl acetate (3 x 20 mL). The combined organic washes were combined and washed with water (2 x 30 mL) and brine (30 mL) then dried over magnesium sulphate and the solvent removed under reduced pressure. The crude material was purified by column chromatography.

Yield: 369 mg (77%)

Physical state: White solid

m.p. 119 - 121 ^{o}C

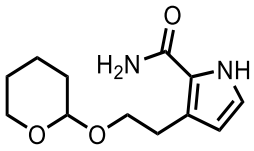
R$_f$ = 0.35 (3:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 11.10 (s, 1H), 9.58 (s, 1H), 6.89 (t, *J* = 2.8 Hz, 1H), 6.21 (t, *J* = 2.6 Hz, 1H), 4.68 (t, *J* = 3.6 Hz, 1H), 3.97 (dt, *J* = 9.5, 7.1 Hz, 1H), 3.89-3.78 (m, 1H), 3.66 (dt, *J* = 9.5, 7.0 Hz, 1H), 3.56-3.46 (m, 1H), 3.14 (t, *J* = 7.1 Hz, 2H), 1.89-1.66 (m, 2H), 1.66-1.58 (m, 1H), 1.58-1.46 (m, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 166.0, 131.1, 123.3, 118.7, 112.5, 98.7, 67.7, 62.2, 30.7, 27.6, 25.5, 19.5.

HRMS ESI (*m/z*): calculated for $C_{12}H_{17}NNaO_4$ $[M+Na]^+$, 262.1050; found, 262.1047.

3-(2-((Tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)-1*H*-pyrrole-2-carboxamide (3.97)



3.97

Carboxylic acid **3.96** (211 mg, 0.88 mmol), EDC (253 mg 1.32 mmol) and HBOt (202 mg, 1.32 mmol) where dissolved in DCM (10 mL). The solution was stirred at room temperature for 10 minutes then (235 mg, 4.40 mmol) and Hünig's base (568 mg, 4.40 mmol) was added. After 2 hours the solution was quenched with water (10 mL) and then washed with ethyl acetate (3 x 20 mL).The organics were combined and washed with water (2 x 30 mL) and brine (30 mL) then dried over magnesium sulphate and the solvent removed under reduced pressure. The crude material was purified by column chromatography.

Yield: 185 mg (85%)

Physical state: White solid

m.p. 108 - 112 ^{o}C

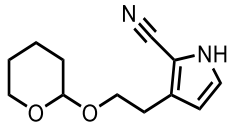
R$_f$ = 0.37 (100% EtOAc, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 9.83 (s, 1H), 6.84 (t, *J* = 2.8 Hz, 1H), 6.07 (t, *J* = 2.7 Hz, 1H), 4.57 (t, *J* = 3.0 Hz, 1H), 4.06 (dq, *J* = 9.1, 4.2 Hz, 1H), 3.67-3.55 (m, 2H), 3.48-3.39 (m, 1H), 2.98 (dt, *J* = 6.4, 4.1 Hz, 2H), 1.73-1.61 (m, 2H), 1.60-1.46 (m, 3H), 1.49-1.41 (m, 1H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 164.5, 124.3, 123.9, 121.0, 111.5, 99.1, 69.5, 62.0, 30.3, 28.0, 25.3, 19.4.

HRMS ESI (*m/z*): calculated for $C_{12}H_{18}N_2NaO_3$ $[M+Na]^+$, 261.1210; found, 261.1210.

3-(2-((Tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)-1*H*-pyrrole-2-carbonitrile (3.98)



3.98

Amide **3.97** (48 mg, 0.20 mmol) was dissolved in pyridine (10 mL) and cooled to 0 ^{o}C under argon. Trifluoroacetic anhydride (84 mg, 56 µL, 0.40 mmol) was added and the solution stirred for 4 hours. The solution was then quenched with ethyl acetate (20 mL) and washed with sodium bicarbonate solution (2 x 10 mL), water (2 x 10 mL) and brine (10 mL) then dried over magnesium sulphate and the solvent removed under reduced pressure. The crude material was purified by column chromatography.

Yield: 42 mg (96%)

Physical state: Colourless oil

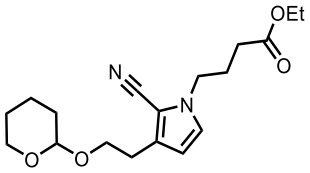
R$_f$ = 0.28 (6:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 9.53 (s, 1H), 6.82 (t, *J* = 2.9 Hz, 1H), 6.16 (t, *J* = 2.6 Hz, 1H), 4.66-4.60 (m, 1H), 3.92 (dt, *J* = 9.6, 6.9 Hz, 1H), 3.87-3.77 (m, 1H), 3.61 (dt, *J* = 9.6, 6.8 Hz, 1H), 3.54-3.44 (m, 1H), 2.89 (t, *J* = 6.9 Hz, 2H), 1.89-1.74 (m, 1H), 1.74-1.66 (m, 1H), 1.65-1.55 (m, 1H), 1.55-1.46 (m, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 133.4, 123.6, 114.6, 110.5, 99.8, 99.0, 67.4, 62.4, 30.7, 27.1, 25.5, 19.5.

HRMS ESI (*m/z*): calculated for $C_{12}H_{16}N_2NaO_2$ $[M+Na]^+$, 243.1104; found, 243.1101.

Ethyl 4-(2-cyano-3-(2-((tetrahydro-2*H*-pyran-2-yl)oxy)ethyl)-1*H*-pyrrol-1-yl)butanoate (3.100)



3.100

Sodium hydride (60% dispersion in mineral oil) (100 mg, 2.50 mmol) was washed with hexane (3 x 10 mL) under argon. Nitrile **3.98** (426 mg, 1.93 mmol) in DMF (10 mL) was added and the solution stirred for 30 minutes at room temperature. Ethyl-4-bromobutyrate (490 mg, 360 µL, 2.50 mmol) in DMF (5 mL) was then added and the solution stirred for 1 hour before being quenched with water (100 mL) and extracted with ethyl acetate (5 x 25 mL). The organics were combined and washed with water (4 x 50 mL) and brine (50 mL) then dried over magnesium sulphate and the solvent removed under reduced pressure. The crude material was purified by column chromatography.

Yield: 542 mg (84%)

Physical state: Colourless oil

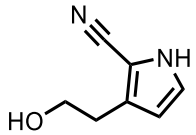
R$_f$ = 0.35 (2:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 6.72 (d, *J* = 2.7 Hz, 1H), 6.08 (d, *J* = 2.7 Hz, 1H), 4.60 (dd, *J* = 6.9, 3.2 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 4.03 (t, *J* = 6.9 Hz, 2H), 3.87 (dt, *J* = 9.6, 7.0 Hz, 1H), 3.81-3.71 (m, 1H), 3.55 (dt, *J* = 9.6, 6.8 Hz, 1H), 3.50-3.41 (m, 1H), 2.84 (t, *J* = 6.9 Hz, 2H), 2.25 (t, *J* = 7.2 Hz, 2H), 2.09 (t, *J* = 7.1 Hz, 2H), 1.87-1.74 (m, 1H), 1.72-1.63 (m, 1H), 1.61-1.43 (m, 4H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 172.4, 133.7, 126.4, 113.7, 110.0, 102.7, 98.7, 67.1, 62.1, 60.8, 47.9, 30.7, 30.7, 27.4, 26.3, 25.5, 19.4, 14.2.

HRMS ESI (*m/z*): calculated for $C_{18}H_{26}N_2NaO_4$ $[M+Na]^+$, 357.1785; found, 357.1789.

3-(2-Hydroxyethyl)-1*H*-pyrrole-2-carbonitrile (3.83)



3.83

Nitrile **3.98** (100 mg, 0.45 mmol) and pyridinium *p*-toluenesulfonate (12 mg, 0.05 mmol) were dissolved in methanol (5 mL) and stirred at room temperature for 24 hours. Water (50 mL) was then added and the solution extracted with ethyl acetate (3 x 20 mL). The organics were combined and washed with water (2 x 20 mL) and brine (20 mL) then dried over magnesium sulphate and the solvent removed under reduced pressure. The crude material was purified by column chromatography.

Yield: 58 mg (95%)

Physical state: Colourless oil

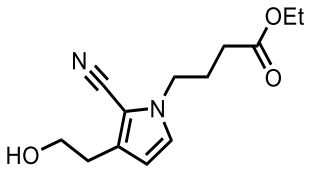
$\mathbf{R}_f$ = 0.20 (2:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.42 (s, 1H), 6.82 (t, *J* = 2.9 Hz, 1H), 6.16 (t, *J* = 2.6 Hz, 1H), 3.90-3.82 (m, 2H), 2.92-2.84 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 133.1, 123.9, 114.5, 110.5, 100.0, 62.8, 30.0.

HRMS ESI (*m/z*): calculated for $C_7H_8N_2NaO$ $[M+Na]^+$, 159.0529; found, 159.0531.

Ethyl 4-(2-cyano-3-(2-hydroxyethyl)-1*H*-pyrrol-1-yl)butanoate (3.84)



3.84

Nitrile **3.100** (150 mg, 0.45 mmol) and pyridinium *p*-toluenesulfonate (12 mg, 0.05 mmol) were dissolved in methanol (5 mL) and stirred at room temperature for 24 hours. Water (50 mL) was then added and the solution extracted with ethyl acetate (3 x 20 mL). The organics were combined and washed with water (2 x 20 mL) and brine (20 mL) then dried over magnesium sulphate and the solvent removed under reduced pressure. The crude material was purified by column chromatography.

Yield: 105 mg (93%)

Physical state: Colourless oil

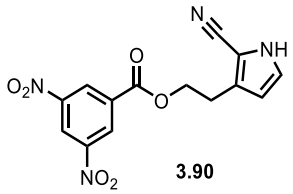
$\mathbf{R}_f$ = 0.32 (1:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.74 (d, *J* = 2.0 Hz, 1H), 6.07 (d, *J* = 2.1 Hz, 1H), 4.10 (q, *J* = 7.5 Hz, 2H), 4.03 (t, *J* = 6.9 Hz, 2H), 3.79 (t, *J* = 6.5 Hz, 2H), 2.80 (t, *J* = 6.5 Hz, 2H), 2.27 (t, *J* = 7.1 Hz, 2H), 2.14-2.04 (m, 2H), 1.25-1.20 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.5, 133.2, 126.7, 113.6, 110.0, 102.8, 62.6, 60.8, 48.0, 30.8, 30.3, 26.2, 14.2.

HRMS ESI (*m/z*): calculated for $C_{13}H_{18}N_2NaO_3$ $[M+Na]^+$, 273.1210; found, 273.1210.

2-(2-Cyano-1*H*-pyrrol-3-yl)ethyl 3,5-dinitrobenzoate (3.90)



3.90

General procedure C using nitrile **3.83** (94 mg, 0.69 mmol) and 3,5-dinitrobenzoic acid (133 mg, 0.46 mmol) at 60 ºC for 24 hours.

Yield: 125 mg (55%)

Physical state: Yellow oil

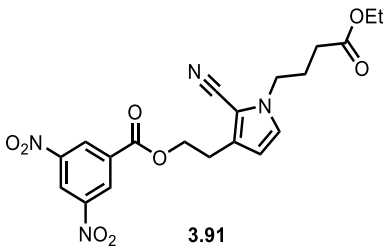
$\mathbf{R}_f$ = 0.25 (4:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.42 (s, 1H), 9.34-9.22 (m, 1H), 9.15-9.03 (m, 2H), 6.80 (t, *J* = 2.7 Hz, 1H), 6.15 (t, *J* = 2.5 Hz, 1H), 3.88-3.80 (m, 2H), 2.91-2.83 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.1, 147.8, 133.3, 132.8, 128.5, 123.5, 121.4, 114.5, 110.5, 99.9, 62.6, 29.7.

HRMS ESI (*m/z*): calculated for $C_{14}H_{10}N_4NaO_6$ $[M+Na]^+$, 353.0493; found, 353.0495.

2-(2-Cyano-1-(4-ethoxy-4-oxobutyl)-1*H*-pyrrol-3-yl)ethyl 3,5-dinitrobenzoate (3.91)



3.91

General procedure C using nitrile **3.84** (173 mg, 0.69 mmol) and 3,5-dinitrobenzoic acid (133 mg, 0.46 mmol) at 60 ºC for 24 hours.

Yield: 187 mg (86%)

Physical state: Yellow oil

R_f = 0.30 (1:1 Hexane:EtOAc, UV)

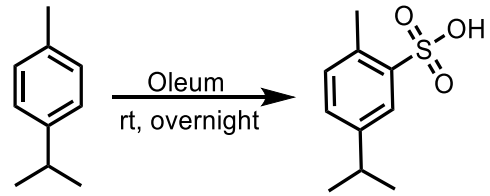
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.33-9.22 (m, 1H), 9.15-9.03 (m, 2H), 6.78 (d, *J* = 2.1 Hz, 1H), 6.17 (d, *J* = 2.2 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 4.01 (t, *J* = 6.9 Hz, 2H), 3.88-3.80 (m, 2H), 2.91-2.83 (m, 2H), 2.27 (t, *J* = 7.0 Hz, 2H), 2.04-1.95 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.1, 162.8, 143.7, 138.2, 132.5, 128.1, 126.4, 121.5, 114.4, 109.4, 102.1, 62.5, 60.9, 48.1, 30.9, 26.2, 23.8, 14.4.

HRMS ESI (*m/z*): calculated for $C_{20}H_{20}N_4NaO_8$ $[M+Na]^+$, 467.1173; found, 467.1173.

6.4. Chapter 4

***p*-Cymene sulphonic acid.**



4.9 ***p*-CSA**

Oleum (9.80 g, 5.1 mL, 100.00 mmol) was added dropwise to a solution of *p*-cymene (4.30 g, 5.0 mL, 32.00 mmol) and the mixture stirred at room temperature overnight. Then the solution was cooled in an ice bath and water (10 mL) added dropwise. The diluted mixture was transferred to a conical flask and left in a fridge at 4 ºC for 24 hours. During this time a crystalline solid formed which was filtered and dried under vacuum. The solid material was recrystallised from concentrated hydrochloric acid to give the desired product.

Yield: 6.08 g (89%)

Physical state: Colourless solid

m.p. 51 - 53 ºC

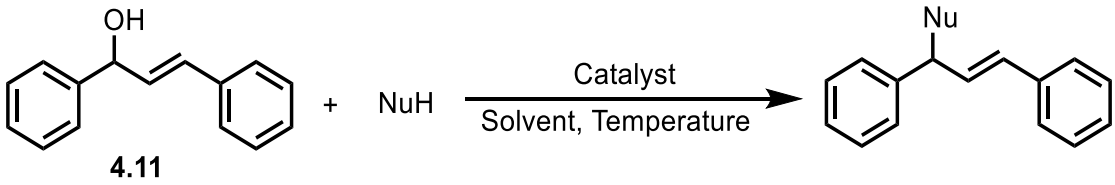
^{1}H NMR (400 MHz, DMSO-d$_6$): δ 7.57 (s, 1H), 7.04-6.95 (m, 2H), 6.10 (s, 1H), 2.46 (s, 3H), 1.14-1.08 (m, 6H).

^{13}C NMR (101 MHz, DMSO-d$_6$): δ 145.5, 145.5, 133.4, 131.4, 127.5, 124.9, 33.5, 24.5, 20.1

HRMS ESI (*m/z*): calculated for $C_{10}H_{15}O_3S$ $[M+H]^+$, 215.0742; found, 215.0737.

Spectroscopic data is consistent with those found in the literature.[224]

6.4.1. General procedure for nucleophilic substitution with diphenyl allylic alcohol (4.11).

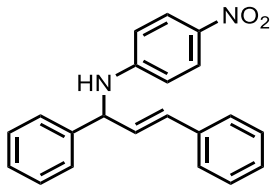


4.11

See Table 4.4, Table 4.5, Table 4.6 & Table 4.7 for optimal conditions.

Alcohol (1.00 mmol) and catalyst (0.01 - 0.05 mmol) were dissolved in a suitable solvent (5 mL), and the corresponding nucleophile (1.50 mmol) was added. The reaction mixture was stirred at the specified temperature overnight. The mixture was quenched with saturated aqueous sodium carbonate solution (20 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over magnesium sulphate and concentrated under reduced pressure. The crude material was purified by flash chromatography.

(*E*)-*N*-(1,3-Diphenylallyl)-4-nitroaniline (4.13)



4.13

Yield: 297 mg (90%)

Physical state: Yellow solid

m.p. 145 – 147 ^{o}C

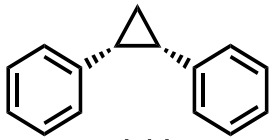
R$_f$ = 0.30 (8:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.09-8.00 (m, 2H), 7.42-7.24 (m, 10H), 6.64-6.54 (m, 3H), 6.37 (dd, *J* = 15.9, 6.1 Hz, 1H), 5.20 (t, *J* = 5.1 Hz, 1H), 4.95-4.89 (m, 1H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 152.1, 140.4, 138.7, 136.1, 132.4, 129.2, 128.7, 128.5, 128.2, 128.1 127.1, 126.6, 126.2 112.2, 60.1.

HRMS ESI (*m/z*): calculated for $C_{21}H_{18}N_2NaO_2$ $[M+Na]^+$, 353.1260; found, 353.1265.

***Cis*-1,2-diphenylcyclopropane (4.14)**



4.14

trans-1,3-Diphenyl-2-propen-1-ol (210 mg, 1.00 mmol) and catalyst (0.10 mmol) were dissolved in a suitable solvent (5 mL) and refluxed for 24 hours. The mixture was quenched with saturated aqueous sodium carbonate solution (20 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over magnesium sulphate and concentrated under reduced pressure. The crude material was purified by flash chromatography.

Yield: 68 mg (35%) 1.00 mmol

Physical state: Colourless oil

$\mathbf{R}_f$ = 0.80 (100% Hexane UV)

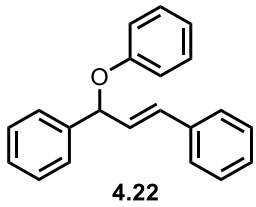
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15-7.05 (m, 6H), 6.99-6.97 (m, 4H), 2.50 (dd, *J* = 8.4, 6.4 Hz, 2H), 1.52-1.48 (m, 1H), 1.43-1.38 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 138.4, 129.0, 127.6, 125.6, 24.3, 11.4.

HRMS APCI (*m/z*): calculated for $C_{15}H_{15}$ $[M+H]^+$, 195.1168; found, 195.1168.

Spectroscopic data is consistent with those found in the literature.[246]

(*E*)-(3-Phenoxyprop-1-ene-1,3-diyl)dibenzene (4.22)



4.22

Yield: 215 mg (75%)

Physical state: White solid

m.p. 94 - 96 ºC

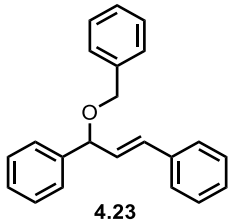
R_f = 0.35 (25:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62-7.22 (m, 13H), 6.88-6.75 (m, 3H), 6.66 (d, *J* = 16.0 Hz, 1H), 6.34 (dd, *J* = 15.8, 6.3 Hz, 1H), 5.76 (d, *J* = 6.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.7, 154.2, 143.9, 137.4, 135.8, 133.0, 131.3, 129.9, 129.8, 128.7, 128.6, 128.6, 127.4, 126.5, 126.4, 120.8, 115.4, 53.4.

HRMS APCI (*m/z*): calculated for $C_{21}H_{19}O$ $[M+H]^+$, 287.1430; found, 287.1430.

***(E)*-(3-(Benzyloxy)prop-1-ene-1,3-diyl)dibenzene (4.23)**



4.23

Yield: 204 mg (68%)

Physical state: Colourless oil

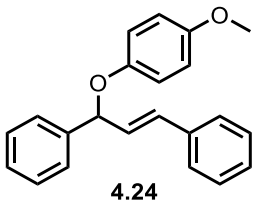
R_f = 0.35 (25:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.23 (m, 15H), 6.68 (d, *J* = 15.9 Hz, 1H), 6.39 (dd, *J* = 15.9, 7.0 Hz, 1H), 5.06 (d, *J* = 7.0 Hz, 1H), 4.63-4.51 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.4, 136.7, 134.9, 129.8, 128.2, 126.8, 126.6, 126.5, 126.5, 126.4, 125.9, 125.8, 125.3, 124.9, 79.9, 68.4.

HRMS ESI (*m/z*): calculated for $C_{22}H_{20}NaO$ $[M+Na]^+$, 323.1406; found, 323.1410.

(*E*)-(3-(4-Methoxyphenoxy)prop-1-ene-1,3-diyl)dibenzene (4.24)



4.24

Physical state: White solid

Yield: 228 mg (68%)

m.p. 93 – 95 ^{o}C

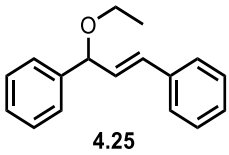
R_f = 0.25 (30:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.20 (m, 10H), 7.14-7.06 (m, 2H), 6.78-6.65 (m, 2H), 6.66 (d, *J* = 15.8 Hz, 1H), 6.34 (dd, *J* = 15.8, 6.3 Hz, 1H), 5.20 (t, *J* = 5.5 Hz, 1H), 3.65 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.7, 155.2, 149.0, 135.4, 135.1, 133.0, 131.3, 129.9, 129.8, 128.7, 128.6, 128.6, 127.4, 126.5, 126.4, 120.8, 115.4, 53.4.

HRMS ESI (*m/z*): calculated for $C_{22}H_{20}NaO_2$ $[M+Na]^+$, 339.1356, found, 3396.1357.

(*E*)-(3-Ethoxyprop-1-ene-1,3-diyl)dibenzene (4.25)



4.25

Yield: 190 mg (80%)

Physical state: Colourless oil

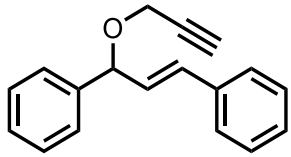
R_f = 0.50 (50:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.21 (m, 10H), 6.60 (d, *J* = 15.9 Hz, 1H), 6.33 (dd, *J* = 15.9, 7.0 Hz, 1H), 4.90 (d, *J* = 7.2 Hz, 1H), 3.60-3.56 (m, 1H), 3.50-3.44 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.6, 136.9, 131.1, 130.6, 128.7, 127.8, 127.7, 126.9, 126.6, 82.6, 64.1, 15.4.

HRMS ESI (*m/z*): calculated for $C_{17}H_{18}NaO$ $[M+Na]^+$, 261.1250; found, 261.1248.

(*E*)-(3-(Prop-2-yn-1-yloxy)prop-1-ene-1,3-diyl)dibenzene (4.26)



4.26

Yield: 160 mg (65%)

Physical state: Colourless oil

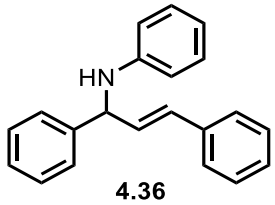
R_f = 0.25 (50:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.21 (m, 10H), 6.66 (d, *J* = 15.8 Hz, 1H), 6.29 (dd, *J* = 16.0, 7.3 Hz, 1H), 5.18, (d, *J* = 7.1 Hz, 1H), 4.20 (dd, *J* = 15.8, 2.5 Hz, 1H), 4.15 (dd, *J* = 15.8, 2.5 Hz, 1H), 2.45-2.44 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.2, 136.4, 132.4, 129.2, 128.7, 128.7, 128.0, 127.9, 127.1, 126.7, 81.0, 79.9, 74.5, 55.4

HRMS ESI (*m/z*): calculated for $C_{18}H_{16}NaO$ $[M+Na]^+$, 271.1093; found, 271.1094.

(*E*)-*N*-(1,3-Diphenylallyl)aniline (4.36)



4.36

Yield: 233 mg (82%)

Physical state: Colourless oil

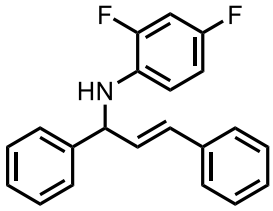
R_f = 0.30 (7:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.35 (m, 2H), 7.30-7.24 (m, 4H), 7.23-7.20 (m, 3H), 7.18-7.15 (m, 1H), 7.13-7.09 (m, 2H), 6.65 (t, *J* = 7.2 Hz, 1H), 6.62-6.51 (m, 3H), 6.30 (dd, *J* = 15.5, 6.0 Hz, 1H), 5.02 (d, *J* = 6.3 Hz, 1H), 4.05 (s, 1H);

^{13}C NMR (101 MHz, $CDCl_3$): δ 147.5, 142.2, 137.0, 131.2, 131.2, 129.4, 128.9, 128.5, 127.8, 127.5, 127.2, 126.9, 116.9, 113.1, 60.6.

HRMS ESI (*m/z*): calculated for $C_{21}H_{19}NNa$ $[M+Na]^+$, 308.1410; found, 308.1411.

(*E*)-*N*-(1,3-Diphenylallyl)-2,4-difluoroaniline (4.37)



4.37

Yield: 167 mg (52%)

Physical state: Yellow oil

R_f = 0.28 (6:1 Hexane:EtOAc, UV)

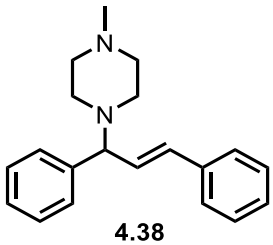
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.25 (m, 10H), 6.84-6.78 (m, 1H), 6.67-6.57 (m, 3H), 6.41 (dd, *J* = 15.6, 6.0 Hz, 1H), 5.06 (d, *J* = 6.0 Hz, 1H), 4.23 (s, 1H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 153.2, (d, *J* = 19.2 Hz) 149.6 (d *J* = 19.3 Hz), 141.4, 136.3, 132.1, 132.0, 131.3, 130.1, 128.9, 128.5, 127.8, 127.7, 127.0, 126.5, 113.4, 110.5, 103.3, 60.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ -115.7 (s, 1F), -128.8 (s, 1F).

HRMS ESI (*m/z*): calculated for $C_{21}H_{17}F_2NNa$ $[M+Na]^+$, 344.1221; found, 344.1230.

(*E*)-1-(1,3-Diphenylallyl)-4-methylpiperazine (4.38)



4.38

Yield: 254 mg (87%)

Physical state: Colourless oil

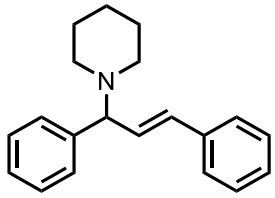
R_f = 0.15 (4:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.17 (m, 10H), 6.56 (d, *J* = 15.6 Hz, 1H), 6.30 (dd, *J* = 15.6, 8.7, Hz, 1H), 3.80 (d, *J* = 8.7 Hz, 1H), 2.44 (br, 8H), 2.29 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.9, 136.8, 131.8, 131.2, 128.6, 128.5, 127.9, 127.4, 127.2, 126.3, 74.4, 55.3, 51.5, 45.9

HRMS ESI (*m/z*): calculated for $C_{20}H_{24}N_2Na$ $[M+Na]^+$, 315.1832; found, 315.1830.

(*E*)-1-(1,3-Diphenylallyl)piperidine (4.39)



4.39

Yield: 218 mg (79%)

Physical state: Colourless oil

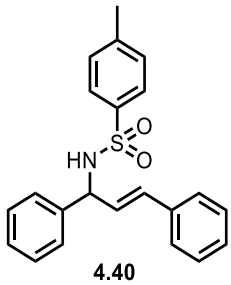
R_f = 0.20 (6:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.12 (m, 10H), 6.55 (d, *J* = 16.0 Hz, 1H), 6.26 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.81 (d, *J* = 8.5 Hz, 1H), 2.43 (br, 2H), 2.30 (br, 2H), 1.61-1.54 (m, 4H), 1.38-1.33 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.7, 137.4, 132.6, 131.2, 128.8, 128.8, 128.5, 128.0, 127.7, 126.7, 75.0, 53.0, 26.5, 25.0

HRMS ESI (*m/z*): calculated for $C_{20}H_{23}NNa$ $[M+Na]^+$, 300.1723; found, 300.1723.

(*E*)-*N*-(1,3-Diphenylallyl)-4-methylbenzenesulfonamide (4.40)



4.40

Yield: 283 mg (78%)

Physical state: While solid

m.p. 143 – 144 ^oC

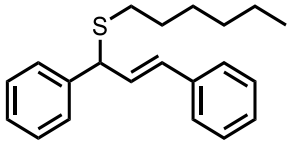
R_f = 0.25 (3:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.30-7.18 (m, 12H), 6.34 (d, *J* = 16.0 Hz, 1H), 6.08 (dd, *J* = 15.9, 6.5 Hz, 1H), 5.10 (t, *J* = 6.7 Hz, 1H), 5.03-5.00 (m, 1H), 2.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.4, 139.7, 137.9, 136.2, 132.0, 129.6, 128.9, 128.6, 128.3, 128.2, 128.1, 127.5, 127.1, 126.7, 60.0, 21.4.

HRMS ESI (*m/z*): calculated for $C_{22}H_{21}NNaO_2S$ $[M+Na]^+$, 386.1185; found, 386.1185.

(*E*)-(1,3-Diphenylallyl)(hexyl)sulfane (4.44)



4.44

Yield: 280 mg (90%)

Physical state: Colourless oil

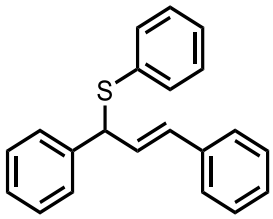
R_f = 0.40 (60:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.18 (m, 10 H), 6.50 (d, *J* = 15.7 Hz, 1H), 6.41 (dd, *J* = 15.7, 8.3, 1H), 4.60 (d, *J* = 8.4 Hz, 1H), 2.56-2.41 (m, 2H), 1.73-1.56 (m, 2H), 1.44-1.19 (m, 6H), 0.93-0.83 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.9, 136.7, 130.8, 129.9, 128.7, 128.6, 127.9, 127.7, 127.5, 126.6, 52.4, 39.3, 31.6, 29.3, 28.3, 22.7, 14.2.

HRMS APCI (*m/z*): calculated for $C_{21}H_{26}S$ $[M+H]^+$, 310.1755; found, 310.1762.

(*E*)-(1,3-Diphenylallyl)(phenyl)sulfane (4.45)



4.45

Yield: 272 mg (90%)

Physical state: White solid

m.p. 75 - 78 °C

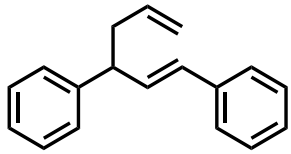
R_f = 0.24 (10:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.25 (m, 15H), 6.53 (dd, *J* = 15.5, 8.5 Hz, 1H), 6.36 (d, *J* = 15.7 Hz, 1H), 4.99 (d, *J* = 8.3 Hz, 1H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.3, 136.7, 134.9, 133.2, 131.6, 129.2, 128.8, 128.7, 128.5, 128.0, 127.6, 127.5, 127.5, 126.5, 56.7.

HRMS APCI (*m/z*): calculated for $C_{21}H_{18}S$ $[M+H]^+$, 302.1129; found, 302.1135.

(*E*)-Hexa-1,5-diene-1,3-diyldibenzene (4.51)



4.51

Yield: 231 mg (99%)

Physical state: Colourless oil

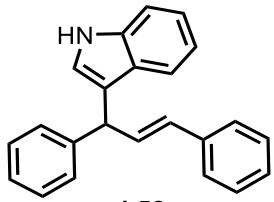
R_f = 0.45 (Hexane UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.20 (m, 10H), 6.51-6.36 (m, 2H), 5.83-5.70 (m, 1H), 5.06-4.99 (m, 2H), 3.50-3.41 (m, 1H), 2.56-2.49 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.0, 137.6, 136.7, 133.6, 129.9, 128.7, 128.6, 127.9, 127.3, 126.5, 126.3, 116.5, 49.1, 40.4.

HRMS APCI (*m/z*): calculated for $C_{18}H_{19}$ $[M+H]^+$, 235.1481; found, 235.1473.

(*E*)-3-(1,3-Diphenylallyl)-1*H*-indole (4.52)



4.52

Yield: 261 mg (85%)

Physical state: red oil

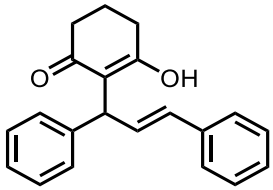
R_f = 0.35 (5:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.46-7.08 (m, 13H), 7.03 (t, *J* = 7.1 Hz, 1H), 6.87 (d, *J* = 1.6 Hz, 1H), 6.73 (dd, *J* = 15.8, 7.4 Hz, 1H), 6.44 (d, *J* = 15.8 Hz, 1H), 5.12 (d, *J* = 7.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.5, 137.6, 136.7, 132.6, 130.7, 128.6, 128.6, 127.3, 126.9, 126.5, 126.4, 122.2, 122.1, 119.9, 119.5, 118.8, 111.2, 46.3.

HRMS APCI (*m/z*): calculated for $C_{23}H_{20}N$ $[M+H]^+$, 310.1590; found, 310.1590.

(*E*)-2-(1,3-Diphenylallyl)-3-hydroxycyclohex-2-en-1-one (4.53)



4.53

Yield: 243 mg (70%)

Physical state: White solid

m.p. 151 – 153 ^{o}C

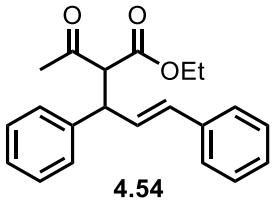
R$_f$ = 0.19 (1:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.51-7.24 (m, 11H), 6.95 (dd, *J* = 15.7, 8.1 Hz, 1H), 6.53 (d, *J* = 15.7 Hz, 1H), 5.23 (d, *J* = 8.1 Hz, 1H), 2.45-2.31 (m, 4H), 1.96-1.87 (m, 2H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 143.4, 137.6, 131.1, 131.0, 128.5, 128.1, 127.6, 127.2, 126.3, 125.9, 117.7, 42.4, 33.1, 20.6.

HRMS ESI (*m/z*): calculated for $C_{21}H_{20}NaO_2$ $[M+Na]^+$, 327.1356; found, 327.3152.

(*E*)-Ethyl-2-acetyl-3,5-diphenylpent-4-enoate (4.54)



4.54

Yield: 225 mg (70%)

Physical state: Colourless oil

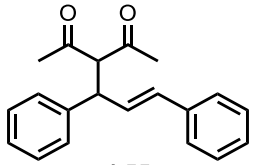
R$_f$ = 0.25 (2:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.39-7.35 (m, 2H), 7.33-7.29 (m, 10H), 7.27-7.24 (m, 4H), 7.24-7.14 (m, 4H), 6.42 (t, *J* = 15.4 Hz, 2H), 6.29-6.20 (m, 2H), 4.30-4.26 (m, 2H), 4.14 (q, *J* = 7.0 Hz, 2H), 4.80 (dd, *J* = 11.0, 9.6 Hz, 2H), 3.95 (q, *J* = 7.2 Hz, 2H), 2.30 (s, 3H), 2.02 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.98 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 201.8, 201.5, 168.0, 167.7, 140.5, 140.2, 136.8, 136.7, 131.8, 131.4, 129.5, 129.3, 129.0, 128.7, 128.5, 128.2, 128.0, 127.6, 127.5, 127.3, 127.1, 126.7, 126.5, 65.7, 65.4, 61.9, 61.6, 49.3., 49.0, 30.0, 29.9, 14.2, 13.9.

HRMS ESI (*m/z*): calculated for $C_{21}H_{22}NaO_3$ $[M+Na]^+$, 345.1461; found, 345.1463.

(*E*)-3-(1,3-Diphenylallyl)pentane-2,4-dione (4.55)



4.55

Yield: 236 mg (81%)

Physical state: White solid

R_f = 0.22 (5:1 Hexane:EtOAc, UV)

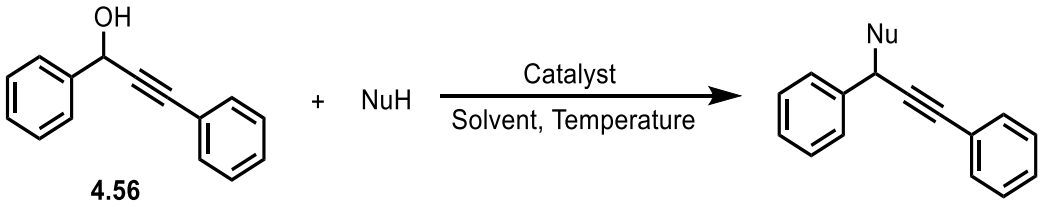
m.p. 80 – 83 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.29 (m, 2H), 7.27-7.24 (m, 6H), 7.22-7.18 (m, 2H), 6.43 (d, *J* = 15.8 Hz, 1H), 6.26-6.14 (m, 1H), 4.44-4.25 (m, 2H), 2.25 (s, 3H), 1.92 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.8, 202.9, 139.0, 136.6, 131.7, 129.2, 129.0, 128.9, 128.0, 127.5, 127.1, 126.5, 74.2, 49.2, 30.0, 29.6.

HRMS ESI (*m/z*): calculated for $C_{20}H_{20}NaO_2$ $[M+Na]^+$, 315.1356; found, 315.1362.

6.4.2. General procedure for nucleophilic substitution with propargylic alcohol (4.56).

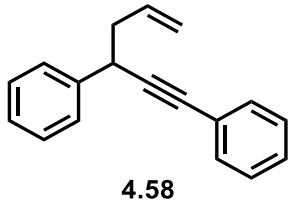


4.56

See Table 4.8 for optimal conditions.

Alcohol (1.00 mmol) and catalyst (0.01 - 0.05 mmol) were dissolved in a suitable solvent (5 mL), and the corresponding nucleophile (1.50 mmol) was added. The reaction mixture was stirred at the specified temperature overnight. The mixture was quenched with saturated aqueous sodium carbonate solution (20 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over magnesium sulphate and concentrated under reduced pressure. The crude material was purified by flash chromatography

1,3-Diphenyl-5-hexen-1-yne (4.58)



4.58

Yield: 230 mg (99%)

Physical state: Colourless oil

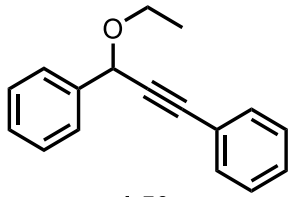
R_f = 0.40 (Hexane, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58-7.19 (m, 10H), 6.05-5.81 (m, 1H), 5.18-5.05 (m, 2H), 3.95 (t, *J* = 7.2 Hz, 1H), 2.65-2.51 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.5, 135.6, 131.8, 128.6, 128.3, 127.9, 127.7, 127.0, 123.8, 117.2, 91.0, 83.9, 42.9, 38.7.

HRMS APCI (*m/z*): calculated for $C_{18}H_{17}$ $[M+H]^+$, 233.1325; found, 233.1326.

Ethyl 1,3-diphenyl-2-proptntl ether (4.59)



4.59

Yield: 233 mg (99%)

Physical state: Colourless oil

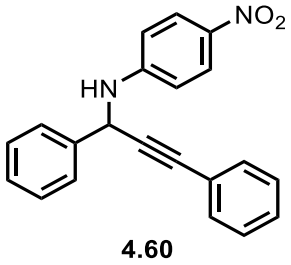
R_f = 0.20 (50:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70-7.30 (m, 10H), 5.45 (s, 1H), 3.88 (dq, *J* = 9.1, 7.0 Hz, 1H), 3.68 (dq, *J* = 9.1, 7.0 Hz, 1H), 1.35 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.2, 131.7, 128.5, 128.5, 128.4, 128.3, 127.4, 122.7, 87.3, 87.2, 71.8, 64.0, 15.4.

HRMS ESI (*m/z*): calculated for $C_{17}H_{16}NaO$ $[M+Na]^+$, 259.1093; found, 259.1093.

***N*-(1,3-diphenylprop-2-yn-1-yl)-4-nitroaniline (4.60)**



4.60

Yield: 279 mg (85%)

Physical state: Orange oil

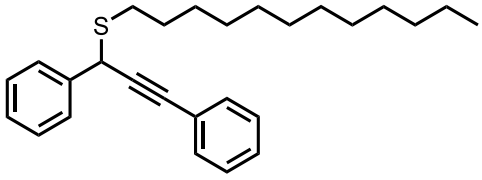
R_f = 0.30 (10:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.34 (m, 10H), 7.24-7.20 (m, 2H), 7.12 (d, *J* = 9.0 Hz, 2H), 6.94 (dd, *J* = 9.0, 2.1 Hz, 1H), 6.73 (d, *J* = 9.0 Hz, 1H), 5.58 (br, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 160.4, 151.8, 139.9, 139.3, 132.0, 130.5, 129.0, 128.6, 126.4, 122.4, 119.7, 114.1, 113.4, 112.7, 86.7, 86.2, 55.6.

HRMS ESI (*m/z*): calculated for $C_{21}H_{16}N_2NaO_2$ $[M+Na]^+$, 351.1104; found, 351.1110.

(1,3-Diphenylprop-2-yn-1-yl)(dodecyl)sulfane (4.61)



4.61

Yield: 388 mg (99%)

Physical state: Colourless oil

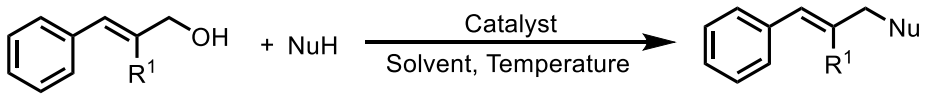
R_f = 0.40 (60:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.20 (m, 10H), 5.02 (s, 1H), 2.80-2.70 (m, 1H), 2.64-2.56 (m, 1H), 1.77-1.55 (m, 2H), 1.50-1.11 (m, 18H), 0.87 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 138.7, 131.9, 128.7, 128.6, 128.4, 128.0, 127.8, 123.1, 87.5, 85.8, 39.5, 32.0, 31.9, 29.8, 29.7, 29.6, 29.5, 29.3, 29.2, 29.1, 22.8, 14.3.

HRMS APCI (*m/z*): calculated for $C_{27}H_{37}S$ $[M+H]^+$, 393.2610; found, 393.2610.

6.4.3. General procedure for nucleophilic substitution with cinnamyl alcohols (4.62) & (4.63).

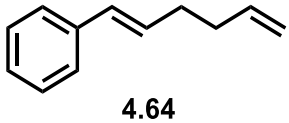


4.62 R^1 = H
4.63 R^1 = Me

See Table 4.9 for optimal conditions.

Alcohol (1.00 mmol) and catalyst (0.01 - 0.05 mmol) were dissolved in a suitable solvent (5 mL), and the corresponding nucleophile (1.50 mmol) was added. The reaction mixture was stirred at the specified temperature overnight. The mixture was quenched with saturated aqueous sodium carbonate solution (20 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over magnesium sulphate and concentrated under reduced pressure. The crude material was purified by flash chromatography.

(*E*)-Hexa-1,5-dien-1-ylbenzene (4.64)



4.64

Yield: 156 mg (99%)

Physical state: Colourless oil

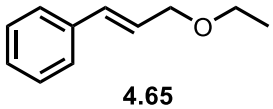
R_f = 0.40 (Hexane, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.15 (m, 5H), 6.40 (d, *J* = 15.4 Hz, 1H), 6.23 (dt, *J* = 15.5, 6.4 Hz, 1H), 5.95-5.80 (m, 1H), 5.10-4.95 (m, 2H), 2.36-2.20 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 138.1, 137.8, 130.2, 130.1, 128.5, 126.9, 126.0, 114.9, 33.6, 32.4.

HRMS APCI (*m/z*): calculated for $C_{12}H_{15}$ $[M+H]^+$, 159.1168; found, 159.1170.

(*E*)-(3-Ethoxyprop-1-en-1-yl)benzene (4.65)



4.65

Yield: 134 mg (83%)

Physical state: Colourless oil

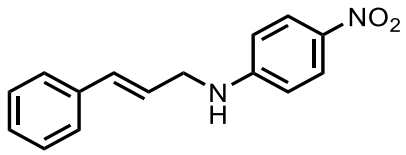
R_f = 0.30 (20:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.30 (m, 5H), 6.67 (d, *J* = 15.9 Hz, 1H), 6.37 (m, 1H), 4.20 (dd, *J* = 6.0, 1.4 Hz, 2H), 3.61 (q, *J* = 7.0 Hz, 2H), 1.31 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 136.9, 131.9, 128.7, 127.6, 126.5, 126.4, 71.5, 65.5, 15.2.

HRMS ESI (*m/z*): calculated for $C_{11}H_{14}NaO$ $[M+Na]^+$, 185.0937; found, 185.0938.

***N*-Cinnamyl-4-nitroaniline (4.66)**



4.66

Yield: 190 mg (75%)

Physical state: Yellow oil

m.p. 144 – 145 ^{o}C

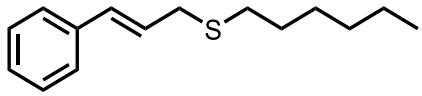
R$_f$ = 0.30 (6:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.12-8.04 (m, 2H), 7.40-7.29 (m, 3H), 7.34 -7.22 (m, 2H), 6.65-6.54 (m, 3H), 6.25 (dt, *J* = 15.9, 5.7 Hz, 1H), 4.02 (td, *J* = 5.8, 1.7 Hz, 2H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 153.2, 138.3, 136.3, 132.7, 128.8, 128.1, 126.5, 124.7, 113.5, 111.5, 45.6.

HRMS ESI (*m/z*): calculated for $C_{15}H_{14}N_2NaO_2$ $[M+Na]^+$, 277.0947; found, 277.0947.

Cinnamyl(hexyl)sulfane (4.67)



4.67

Yield: 187 mg (80%)

Physical state: Colourless oil

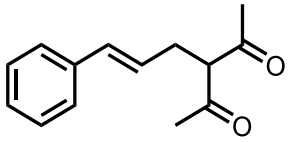
R$_f$ = 0.30 (Hexane UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.48-7.29 (m, 5H), 6.62 (d, *J* = 16.2 Hz, 1H), 6.37 (m, 1H), 4.20 (dd, *J* = 6.0, 1.4 Hz, 2H), 2.56-2.41 (m, 2H), 1.73-1.56 (m, 2H), 1.44-1.19 (m, 6H), 0.93-0.83 (m, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 136.9, 131.9, 128.7, 127.6, 126.5, 126.4, 52.4, 39.4, 31.6, 29.3, 28.5, 23.0, 14.2.

HRMS APCI (*m/z*): calculated for $C_{15}H_{23}S$ $[M+H]^+$, 235.1515; found, 235.1520.

3-Cinnamylpentane-2,4-dione (4.68)



4.68

Yield: 155 mg (72%)

Physical state: Colourless oil

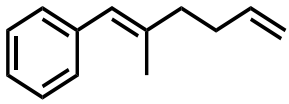
R$_f$ = 0.30 (15:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.34-7.20 (m, 5H), 6.49-6.00 (m, 2H), 3.16 (d, *J* = 4.8 Hz, 1H), 2.75 (t, *J* = 7.1 Hz, 1H), 2.20 (s, 3H), 2.12 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 203.6, 191.6, 137.1, 136.8, 132.8, 130.1, 128.6, 128.5, 127.6, 127.5, 127.3, 126.2, 126.1, 125.4, 107.4, 68.4, 31.6, 30.5, 29.4, 23.1.

HRMS ESI (*m/z*): calculated for $C_{16}H_{16}NaO_2$ $[M+Na]^+$, 239.1043; found, 239.1049.

(*E*)-(2-Methylhexa-1,5-dien-1-yl)benzene (4.69)



4.69

Yield: 150 mg (87%)

Physical state: Colourless oil

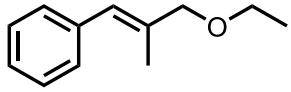
R$_f$ = 0.50 (100:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.38-7.21 (m, 5H), 6.33 (s, 1H), 5.98-5.87 (m, 1H), 5.14 (dt, *J* = 16.2, 3.2 Hz, 1H), 5.04 (dd, *J* = 10.4, 2.0 Hz, 1H), 2.36-2.28 (m, 4H), 1.91 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 138.4, 138.3, 128.8, 128.0, 125.9, 126.9, 125.2, 114.7, 40.0, 32.4, 17.8.

HRMS APCI (*m/z*): calculated for $C_{13}H_{17}$ $[M+H]^+$, 173.1325; found, 173.1324.

(*E*)-(3-Ethoxy-2-methylprop-1-en-1-yl)benzene (4.70)



4.70

Yield: 140 mg (80%)

Physical state: Colourless oil

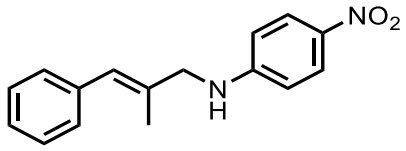
R_f = 0.6 (10:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.28 (m, 5H), 6.62 (d, *J* = 16.0 Hz, 1H), 4.20 (dd, *J* = 6.0, 1.4 Hz, 2H), 3.61 (q, *J* = 7.0 Hz, 2H), 1.89 (s, 3H) 1.31 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 136.9, 131.9, 128.7, 127.6, 126.5, 126.4, 71.5, 65.5, 15.6, 15.2.

HRMS ESI (*m/z*): calculated for $C_{12}H_{16}NaO$ $[M+Na]^+$, 199.1093; found, 199.1098.

(*E*)-*N*-(2-Methyl-3-phenylallyl)-4-nitroaniline (4.71)



4.71

Yield: 268 mg (85%)

Physical state: Yellow solid

m.p. 114 – 116 ^oC

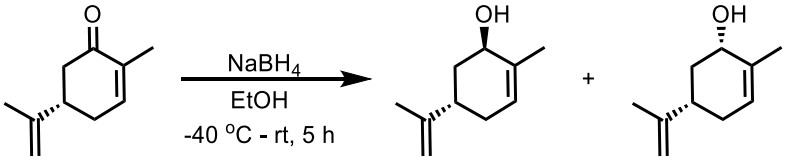
R_f = 0.40 (60:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07-7.98 (m, 2H), 7.35-7.32 (m, 2H), 7.25-7.20 (m, 3H), 6.62 (d, *J* = 9.0 Hz, 2H), 6.45 (br, 1H), 4.85 (s, 1H), 3.90 (d, *J* = 5.6 Hz, 2H), 1.91 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 153.5, 138.1, 137.0, 133.6, 128.7, 128.2, 126.7, 126.6, 126.4, 111.3, 51.4, 16.2.

HRMS ESI (*m/z*): calculated for $C_{16}H_{16}N_2NaO_2$ $[M+Na]^+$, 291.1104; found, 291.1106.

***Cis* and *trans* carveol (4.72)**



4.73 *trans*-**4.72** *cis*-**4.72**

(*S*)-(+)-Carvone (2.25 g, 15.00 mmol) was dissolved in absolute ethanol (80 mL) and the solution cooled to -40 °C. Sodium borohydride (1.13 g, 30.00 mmol) was added portion wise and the resultant suspension stirred for 1 hour then warmed to room temperature and stirred for a further 4 hours. When the reaction was complete as indicated by TLC, the solution was quenched with water (100 mL) and dilute hydrochloric acid (20 mL). The mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organic extracts were washed with brine (50 mL) then dried over magnesium sulphate and concentrated under reduced pressure. The crude material was purified by flash chromatography to give a mixture of diastereomers (3.5:1 *cis*/*trans*).

Yield: 1.78 g (78.0 %)

Physical state: Colourless oil

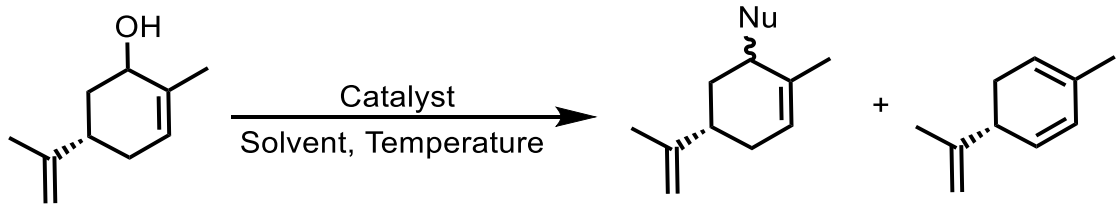
R$_f$ = *trans* isomer, 0.23 (10:1 Hexane:EtOAc, UV)
cis isomer, 0.19 (10:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, CDCl$_3$): *trans* isomer δ 5.55 (d, *J* = 5.6 Hz, 1H), 4.70 (s, 2H), 3.99 (br ,1H), 2.40-1.74 (m, 4H), 1.78 (s, 3H), 1.73 (s, 3H), 1.65 (s, 1H), 1.57-1.50 (m, 1H). *cis* isomer δ 5.50 (br, 1H), 4.70 (s, 2H), 4.19 (br, 1H), 2.35-1.91 (m, 4H), 1.75 (br, 3H), 1.74 (s, 3H), 1.60 (br 1H), 1.50-1.42 (m, 1H).

^{13}C NMR (101 MHz, CDCl$_3$): *trans isomer* δ 149.0, 134.3, 124.9, 109.0, 68.0, 36.6, 35.1, 30.8, 20.7. *cis isomer* δ 149.0, 136.3, 124.1, 109.3, 71.1, 40.7, 38.0, 31.2, 20.7, 19.1.

HRMS ESI (*m/z*): calculated for $C_{10}H_{16}NaO$ $[M+Na]^+$, 175.1093; found, 175.1093.

6.4.4. General procedure for nucleophilic substitution with carveol (4.72).

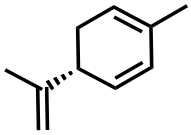


4.73 **4.74**

See Table 4.10 for optimal conditions.

Alcohol (1.00 mmol) and catalyst (0.01 - 0.05 mmol) were dissolved in a suitable solvent (5 mL), and the corresponding nucleophile (1.50 mmol) was added. The reaction mixture was stirred at the specified temperature overnight. The mixture was quenched with saturated aqueous Na_2CO_3 solution (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over magnesium sulphate and concentrated under reduced pressure. The crude material was purified by flash chromatography.

(5*R*)-2-methyl-5-(1-methylethenyl)-1,3-cyclohexadiene (4.74)



4.74

Yield: 40 mg (30%)

Physical state: Colourless oil

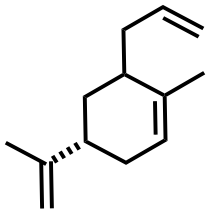
R_f = 0.40 (20:1 Hexane:Diethyl ether, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74-5.70 (m, 1H), 5.65-5.61 (m, 1H), 5.55-5.49 (m, 1H), 4.62-4.58 (m, 1H), 4.51-4.45 (m, 1H), 2.89-2.84 (m, 1H), 2.68-2.24 (m, 2H), 1.76 (s, 3H), 1.72 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.5, 134.8, 131.8, 134.7, 122.3, 108.6, 39.6, 34.0, 21.5, 19.5.

HRMS ESI (*m/z*): calculated for $C_{10}H_{15}$ $[M+H]^+$, 135.1168; found, 135.1174.

1-Methyl-(4*S*)-(methylethenyl)-6-(2-propenyl)-cyclohexene (4.76)



4.76

Yield: 52 mg (30%)

Physical state: Colourless oil

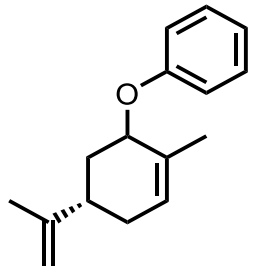
R_f = 0.40 (50:1 Hexane:Diethyl ether, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76-5.70 (m, 1H), 5.38-5.47 (m, 1H), 5.02 (dd, *J* = 4.2, 2.0 Hz, 2H), 4.67 (s, 2H), 2.34-2.29 (m, 1H), 2.14-2.05 (m, 2H), 2.01-1.94 (m, 3H), 1.85-1.80 (m, 1H), 1.72 (s, 3H), 1.66 (s, 3H), 1.40-1.31 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 216.5, 149.0, 137.6, 121.6, 115.2, 108.0, 76.5, 38.6, 36.9, 35.4, 30.4, 21.5, 20.5.

HRMS ESI (*m/z*): calculated for $C_{13}H_{21}$ $[M+H]^+$, 177.1638; found, 177.1645.

2-Methyl-(5*S*)-(methylethenyl)-1-phenoxycyclohexene (4.77)



4.77

Yield: 80 mg (35%)

Physical state: Colourless oil

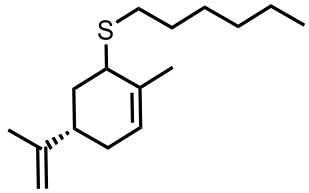
R_f = 0.20 (5:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-6.70 (m, 5H), 5.62-5.57 (m, 1H), 4.66 (s, 2H), 4.45-4.39 (m, 1H), 2.45-1.82 (m, 5H), 1.76 (s, 3H), 1.70 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.5, 148.0, 136.5, 129.3, 129.1, 123.0, 120.1, 115.1, 114.9, 107.5, 80.1, 36.9, 33.5, 30.9, 21.0, 17.5.

HRMS ESI (*m/z*): calculated for $C_{16}H_{20}NaO$ $[M+Na]^+$, 251.1406; found, 251.1407.

2-Methyl-(5*S*)-(methylethenyl)-6-hexylsulfanecyclohexene (4.78)



4.78

Yield: 60 mg (24%)

Physical state: Colourless oil

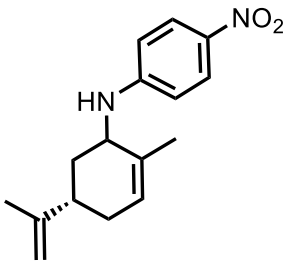
R_f = 0.35 (25:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.58-5.50 (m, 1H), 4.86 (s, 1H), 4.72 (s, 1H), 3.29-3.18 (m, 1H), 2.59-2.42 (m, 1H), 2.25-2.18 (m, 1H), 2.02-1.95 (m, 1H), 1.93-1.85 (m, 2H), 1.73 (s, 3H), 1.69 (s, 3H), 1.48-1.29 (m, 10H) 0.88 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.6, 135.1, 118.9, 112.6, 46.3, 40.1, 35.2, 31.8, 31.5, 30.7, 29.9, 28.3, 23.4, 21.5, 21.0, 14.5.

HRMS ESI (*m/z*): calculated for $C_{16}H_{29}S$ $[M+H]^+$, 253.1984; found, 253.1985.

***N*-2-Methyl-(5*S*)-(methylethenyl)-4-nitroanilinecyclohexene (4.79)**



4.79

Yield: 63 mg (23%)

Physical state: Yellow solid

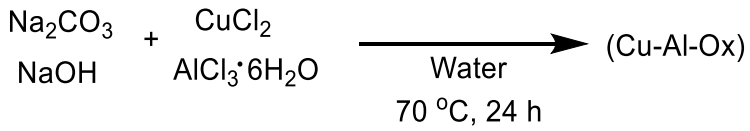
R_f = 0.40 (50:1 Hexane:Diethyl ether, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.6 Hz, 2H), 7.05 (d, *J* = 8.6 Hz, 2H), 5.27-5.16 (m, 1H), 4.92 (br, 1H), 4.86-4.72 (m, 2H), 3.49-3.40 (m, 1H), 2.36-2.29 (m, 1H), 2.25-2.02 (m, 2H), 1.93-1.85 (m, 2H), 1.75 (s, 3H), 1.72 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 152.2, 146.3, 136.6, 135.9, 128.2, 112.8, 110.4. 108.7, 63.3, 45.1, 43.3, 31.5, 20.1, 15.8.

HRMS ESI (*m/z*): calculated for $C_{16}H_{20}N_2NaO_2$ $[M+Na]^+$, 295.1417; found, 295.1419.

(Cu-Al-Ox) catalyst (4.81)



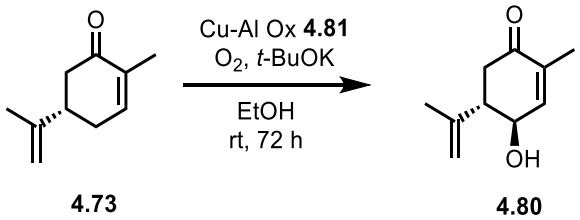
Prepared by following a known procedure.[247]

A solution of sodium carbonate (1.27 g, 12.00 mmol) and sodium hydroxide (5.20 g, 130.00 mmol) in water (100 mL) was prepared and added dropwise over 1.5 hours to a second solution of copper (II) chloride (4.84 g, 36.00 mmol) and aluminium trichloride hexahydrate (4.00 g, 16.60 mmol) in water (50 mL). The resulting pale blue suspension was stirred at 70 °C for 24 h. After which time the solution was filtered and a black precipitate collected. The residue was washed with water (3 x 30 mL). The black solid was then dried in an oven at 110 °C for 24 h, after which it was ground into a fine power. Finally, the powder was left on a tray exposed to air for 7 days before use.

Yield: 2.60 g

Physical state: Black powder

***trans*-γ-Hydroxycarvone (4.80)**



4.73 **4.80**

4.80 Was prepared by a modification of a known procedure.[247]

Catalyst **4.81** (3.36 g, 84.0 mg/mmol substrate) was added to a solution of absolute ethanol (500 mL). The suspension was stirred at room temperature for 30 min under an oxygen balloon before (*S*)-carvone (6.00 g, 40.00 mmol) and *t*-BuOK (2.24 g, 20.00 mmol) were added and the mixture stirred vigorously for 72 h. After this time the reaction was filtered through a pad of celite which was then washed with ethanol (2 x 150 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by a flash chromatography.

Yield: 2.12 g (32%)

Physical state: Yellow oil

$\mathbf{R}_f$ = 0.25 (3:1 Hexane:EtOAc, UV)

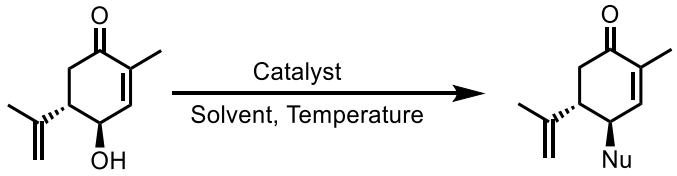
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$**=** -252 (c. 0.5, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (s, 1H), 5.09-5.00 (m, 1H), 4.94 (s, 1H), 4.45 (d, *J* = 9.7 Hz, 1H), 2.75-2.69 (m, 1H), 2.51 (dd, *J* = 16.3, 4.0 Hz, 1H), 2.40 (dd, *J* = 16.3, 13.9 Hz, 1H), 2.02 (br, 1H), 1.80 (s, 3H), 1.75 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.0, 148.1, 143.5, 135.2, 114.5, 68.5, 53.0, 41.3, 19.6, 16.1.

HRMS ESI (*m/z*): calculated for $C_{10}H_{14}NaO_2$ $[M+Na]^+$, 189.0886; found, 189.0889.

6.4.5. General procedure for nucleophilic substitution with *trans*-γ-hydroxycarvone (4.80).

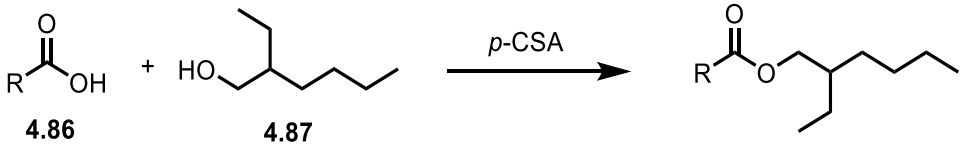


4.80

Alcohol (1.00 mmol) and catalyst (0.01 - 0.05 mmol) were dissolved in a suitable solvent (5 mL), and the corresponding nucleophile (1.50 mmol) was added. The reaction mixture was stirred at the specified temperature overnight. The mixture was quenched with saturated aqueous Na_2CO_3 solution (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over magnesium sulphate and concentrated under reduced pressure. The crude material was purified by flash chromatography.

No product was detected for any of these reactions. See Table 4.11.

2-Ethylhexylester of fatty acid



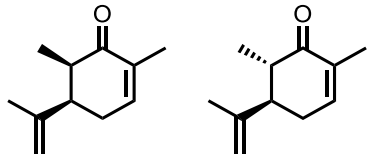
4.86 **4.87**

Fatty acid (1287 g, 4.53 mmol), 2-ethylhexanol (774 g, 5.94 mol) and 65% solution of *p*-cymene sulphonic acid (4.8 mL, 14.49 mmol) was added to a 5 L round bottom flask and set up for vacuum distillation. The flask was purged with nitrogen and warmed to 85 ^{o}C. A vacuum was applied, and the pressure of the flask reduced to 100 mmHg after which the internal temperature of the flask was gradually raised to 100 ^{o}C. These conditions were maintained until no distillate was being collected. The temperature was then raised to 130 ^{o}C and held for 30 minutes, after which time vacuum was released and the flask placed under nitrogen and allowed to cool to 80 ^{o}C. Water (400 mL) was added and the mixture stirred for 5 minutes. The aqueous layer was allowed to separate and then drained off. This washing was repeated twice more, and the product collected.

Yield: 1989 g (>99%)

Physical state: Amber oil

(5*R*,6*R*)-6-Methyl carvone & (5*R*,6*S*)-6-Methyl carvone (4.90)



cis-**4.90** *trans*-**4.90**

Diisopropylamine (3.54 g, 5.0 mL, 35.00 mmol) and dry THF (25 mL) where added to a flame dry flask under argon then cooled to -78 ^{o}C. *n*-BuLi (2.0 M in hexane, 15.0 mL, 30.00 mmol) was added dropwise and the solution stirred for 10 minutes. (*R*)-Carvone (3.76 g, 3.5 mL, 25.00 mmol) in THF (5 mL) was then added dropwise and stirred for 10 minutes before being warmed to room temperature and stirred for a further 1 hour. The solution was re-cooled to -78 ^{o}C and iodomethane (17.75 g, 7.8 mL, 125.00 mmol) added. The solution was stirred for 2 hours then warmed to room temperature overnight. The reaction was then quenched with a saturated ammonium chloride solution (20 mL) and extracted with diethyl ether (3 x 30 mL). The organics where combined and washed with water (3 x 50 mL), 10% copper sulphate (3 x 30 mL), water (2 x 20 mL), brine (2 x 30 mL) then dried with magnesium sulphate, filtered and solvent removed under produced pressure to give a crude oil. The crude product was purified by flash column chromatography to give a mixture of diastereomers (3:1 *trans/cis*).

Yield: 3.82 g (93%)

Physical state: Colourless oil

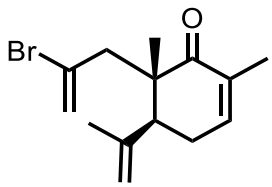
R$_f$ = *trans* isomer 0.23 (50:1 Hexane:EtOAc, UV)
cis isomer 0.19 (50:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, CDCl$_3$): *trans* isomer δ 6.68-6.61 (m, 1H), 4.76 (dq, *J* = 3.3, 1.4 Hz, 2H), 2.49-2.16 (m, 4H), 1.75-1.70 (m, 3H), 1.68-1.63 (m, 3H), 1.00 (d, *J* = 6.6 Hz, 3H). *cis* isomer δ 6.69-6.63 (m, 1H), 4.85 (s, 1H), 4.67 (s, 1H), 2.70-2.55 (m, 2H), 2.47-2.33 (m, 1H), 2.30-2.18 (m, 1H), 1.72 (s, 3H), 1.64 (s, 3H), 0.86 (d, *J* = 7.2 Hz, 3H)

^{13}C NMR (101 MHz, CDCl$_3$): *trans* isomer δ 201.8, 145.7, 143.4, 134.8, 113.2, 50.6, 44.2, 31.2, 18.2, 16.2, 12.5. *cis* isomer δ 203.5, 144.9, 144.1, 133.6, 111.5, 44.8, 43.0, 26.3, 21.9, 16.0, 10.5.

HRMS APCI (*m/z*): calculated for $C_{11}H_{17}O$ $[M+H]^+$, 165.1274; found, 165.1274.

(5*S*,6*S*)-6-(2-Bromoallyl)-2,6-dimethyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-one (4.92)



4.92

Diisopropylamine (3.54 g, 4.9 mL, 34.93 mmol) and dry THF (30 mL) where added to a flame dry flask under argon and cooled to -78 ^{o}C. *n*-BuLi (2.0 M in hexane, 15.2 mL, 30.28 mmol) was added dropwise and the solution stirred for 10 minutes. Methyl carvone **4.90** (3.83 g, 23.29 mmol) and HMPA (6.62 g, 6.1 mL, 34.93 mmol) dissolved in THF (10 mL) was then added and the solution stirred for 15 minutes. After which 2,3-dibromopropene (7.0 g, 3.4 mL, 34.93 mmol) in THF (5 mL) was added and the solution stirred for 10 minutes then warmed to room temperature and stirred for a 1 hour. The reaction was quenched with a saturated ammonium chloride solution (20 mL) then diluted with water (20 mL) and extracted with ether (3 x 30 mL). The organics where combined and washed with water (5 x 50 mL), 10% copper sulphate (2 x 30 mL), water (2 x 50 mL) and brine (2 x 25 mL) then dried with magnesium sulphate, filtered and solvent removed under produced pressure to give a crude oil. The crude product was purified by flash column chromatography.

Yield: 6.14 g (93%)

Physical state: Colourless oil

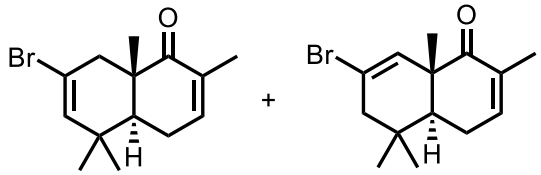
R$_f$ = 0.25 (20:1 Hexane:EtOAc, PMA)

^{1}H NMR (400 MHz, CDCl$_3$): δ 6.59-6.54 (m, 1H), 5.55 (d, *J* = 5.1 Hz, 1H), 5.47-5.45 (m, 1H), 4.77-4.75 (m, 1H), 4.71-4.70 (m, 1H), 2.89 (m, 1H), 2.82 (dd, *J* = 15.1, 1.0 Hz, 1H), 2.70 (dd, *J* = 15.2, 1.0 Hz, 1H), 2.76-2.66 (m, 1H), 2.33-2.21 (m, 1H), 1.80 (m, 3H), 1.58 (m, 3H), 1.07 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 202.0, 145.9, 141.2, 134.3, 128.4, 121.0, 114.4, 49.3, 48.7, 48.0, 28.4, 21.9, 19.4, 16.4.

HRMS ESI (*m/z*): calculated for $C_{14}H_{19}BrNaO$ $[M+Na]^+$, 305.0511; found, 305.0511.

(4aS,8aS)-7-bromo-2,5,5,8a-tetramethyl-4a,5,8,8a-tetrahydronaphthalen-1(4H)-one (4.93) & (4aS,8aR)-7-bromo-2,5,5,8a-tetramethyl-4a,5,6,8a-tetrahydronaphthalen-1(4H)-one (4.94)



4.93 **4.94**

4.92 (7.47 g, 26.36 mmol) and trifluoroacetic acid (25 mL) was stirred at room temperature overnight. The reaction was diluted with water (150 mL) and quenched with sodium hydrogen carbonate (28.79 g, 342.66 mmol). The solution was then extracted with diethyl ether (3 x 50 mL). The organics where combined and washed with water (3 x 50 mL), saturated sodium bicarbonate solution (2 x 50 mL) and brine (2 x 30 mL) then dried with magnesium sulphate, filtered and solvent removed under produced pressure to give a crude oil. The crude product was purified by flash column chromatography.

Yield: 6.73 g (90%)

Physical state: Colourless oil

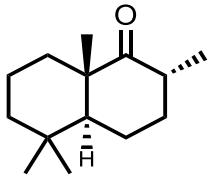
$\mathbf{R}_f$ = **4.95** 0.36 (30:1 Hexane:EtOAc, UV)
4.96 0.33 (30:1 Hexane:EtOAc, UV)

^{1}H NMR (400 MHz, $CDCl_3$): **4.95** δ 6.75-6.72 (m, 1H), 5.74 (t, *J* = 1.7 Hz, 1H), 2.32-2.29 (m, 2H), 2.55 (d, *J* = 1.6 Hz, 2H), 1.86-1.80 (m, 1H), 1.71-1.65 (m, 3H), 1.07 (s, 3H), 1.01 (s, 3H), 0.98 (s, 3H). **4.96** δ 6.70–6.65 (m, 1H), 6.51-6.45 (m, 1H), 2.38-2.30 (m, 1H), 2.28-2.17 (m, 1H), 2.39- 2.25 (m, 2H), 1.78-1.75 (m, 3H), 1.87-1.80 (m, 1H), 1.14 (s, 3H), 1.05 (s, 3H), 0.95 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): **4.95** δ 203.1, 143.8, 137.2, 133.4, 118.4, 46.7, 45.4, 43.2, 38.4, 30.9, 24.1, 24.0, 17.7, 16.2. **4.96** δ 200.9, 143.3,133.1, 131.3, 120.5, 50.7, 49.5, 46.0, 35.4, 29.9, 24.0, 23.0, 18.2, 16.4.

HRMS ESI (*m/z*): calculated for $C_{14}H_{19}BrNaO$ $[M+Na]^+$, 305.0511; found, 305.0511.

(2*R*,4a*S*,8a*S*)-2,5,5,8a-tetramethyloctahydronaphthalen-1(2*H*)-one (4.88)



4.88

4.93 & **4.94** (47.42 mmol, 13.43 g) were dissolved in ethanol/ethyl acetate (70/30 mL), triethylamine (94.84 mmol, 12.3 mL, 9.60 g) was added and the flask evacuated and refilled three times with nitrogen. 10% Pd/Carbon (23.71 mmol, 2.52 g) was then carefully added and the flask evacuated and refilled with hydrogen. The solution was heated to 50 ^{o}C and stirred for 12 hours under the positive pressure of a hydrogen balloon. After complete reduction as judged by GC the solution was cooled to room temperature and filtered through celite then washed with ethyl acetate (3 x 50 mL). The filtrate was combined and washed with 1M HCl (2 x 50 mL), saturated sodium bicarbonate solution (2 x 50 mL), water (2 x 50 mL) and brine (2 x 30 mL) then dried with magnesium sulphate, filtered and solvent removed under produced pressure to give a crude oil which was used without further purification.

The crude oil was dissolved in a solution of sodium methoxide (0.25 M, 170 mL) and stirred overnight. Methanol was removed under reduced pressure and the residue dissolved in water (200 mL) and extracted with diethyl ether (200 mL). The aqueous phase was removed, and the organic layer washed with water (3 x 100 mL) and brine (2 x 50 mL) then dried with magnesium sulphate, filtered and the solvent removed under produced pressure to give a crude oil. The crude was purified by flash chromatography.

Yield: 8.40 g (85%)

Physical state: White solid

m.p. 54 ^{o}C

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ = -38.41^{o} (*c* = 1.0 $CHCl_3$) Lit -38.47^{o} (*c* = 1.0 $CHCl_3$)

$\mathbf{R}_f$ = 0.42 (50:1 Hexane:EtOAc, PMA)

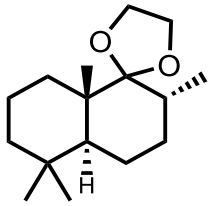
^{1}H NMR (400 MHz, $CDCl_3$):δ 2.65-2.59 (m, 1H), 2.07-2.01 (m,1H), 1.74-1.68 (m, 2H), 1.54-1.51 (m, 3H), 1.39-1.34 (m, 1H), 1.24-1.13 (m, 2H), 1.11 (s, 3H), 1.11-1.05 (m, 2H), 0.95 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 3H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 216.8, 54.2, 48.7, 41.5, 39.9, 35.7, 34.2, 33.2, 33.0, 22.0, 21.3, 18.7, 18.1, 15.0.

HRMS ESI (*m/z*): calculated for $C_{14}H_{24}NaO$ $[M+Na]^+$, 231.0992; found, 231.0989.

Spectroscopic data is consistent with those found in the literature.[240]

(2*R*,4a*S*,8a*S*)-2,5,5,8a-tetramethyloctahydro-2*H*-spiro[naphthalene-1,2'-[1,3]dioxolane] (4.95)



4.95

p-TSA or *p*-CSA (0.1 mmol) and ethylene glycol (9.32 g, 8.4 mL, 150.00 mmol) were added to solution of **4.88** (2.08 g, 10.00 mmol) in toluene (50 mL). The resulting mixture was refluxed for 2 hours under Dean-Stark conditions. After which the solution was cooled and washed with saturated sodium bicarbonate solution (2 x 50 mL) and brine (2 x 30 mL) then dried with magnesium sulphate. The solution was filtered and solvent removed under produced pressure to give a crude oil. The crude product was purified by flash column chromatography.

Yield: 2.32 g (92%)

Physical state: Colourless oil

R$_f$ = 0.40 (9:1 Hexane:EtOAc, PMA)

^{1}H NMR (400 MHz, CDCl$_3$): δ 3.97-3.86 (m, 2H), 3.86-3.77 (m, 2H), 2.65-2.59 (m, 1H), 2.07-1.99 (m,1H), 1.74-1.68 (m, 2H), 1.54-1.51 (m, 3H), 1.39-1.34 (m, 1H), 1.24-1.13 (m, 2H), 1.11 (s, 3H), 1.11-1.05 (m, 2H), 0.95 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 3H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$): δ 113.6, 65.3, 64.9, 49.0, 43.5, 42.0, 33.4, 33.3, 30.7, 30.5, 23.2, 21.9, 20.9, 18.5, 18.2, 16.6.

HRMS ESI (*m/z*): calculated for $C_{16}H_{28}NaO_2$ $[M+Na]^+$, 275.1982; found, 275.1982.

Appendix

A.1 Metrics spreadsheet and key to flag designations.

The metrics tables and parameters used in this thesis are taken from the Chem21 metrics toolkit.[101]

The full toolkit in an excel format can be found in the supplementary information at the link below.

https://pubs.rsc.org/en/content/articlelanding/2015/gc/c5gc00340g

Metrics calculation (Yield, AE, RME, PMI, PMI_{RRC}, PMI_{Solv} &PMI_{WU}

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm^3)	Density ($g\ ml^{-1}$)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm3)	Density ($g\ ml^{-1}$)	Mass (g)
			#DIV/0!								0.00						0.00
			#DIV/0!								0.00						0.00
			#DIV/0!								0.00						0.00
			#DIV/0!								0.00						0.00
			#DIV/0!								0.00						0.00
			#DIV/0!								0.00						0.00
			#DIV/0!								0.00						0.00
Total	0.00	0.00			0.00		0.00				0.00		0.00				0.00

		Flag			
Yield	#DIV/0!	#DIV/0!			
Conversion	#DIV/0!	#DIV/0!			
Selectivity	#DIV/0!	#DIV/0!			
AE	#DIV/0!				
RME	#DIV/0!	OE	#DIV/0!		
PMI total	#DIV/0!				
PMI	#DIV/0!				
PMI_{RRC}	#DIV/0!				
PMI_{Solv}	#DIV/0!				
PMI_{WU}	#DIV/0!				
PMI Workup chemical	#DIV/0!				
PMI workup solvents	#DIV/0!				

	Mass	MW	Mol
Product			#DIV/0!
	mass		
Unreacted limiting reactant	0.00		

Solvent flag classification

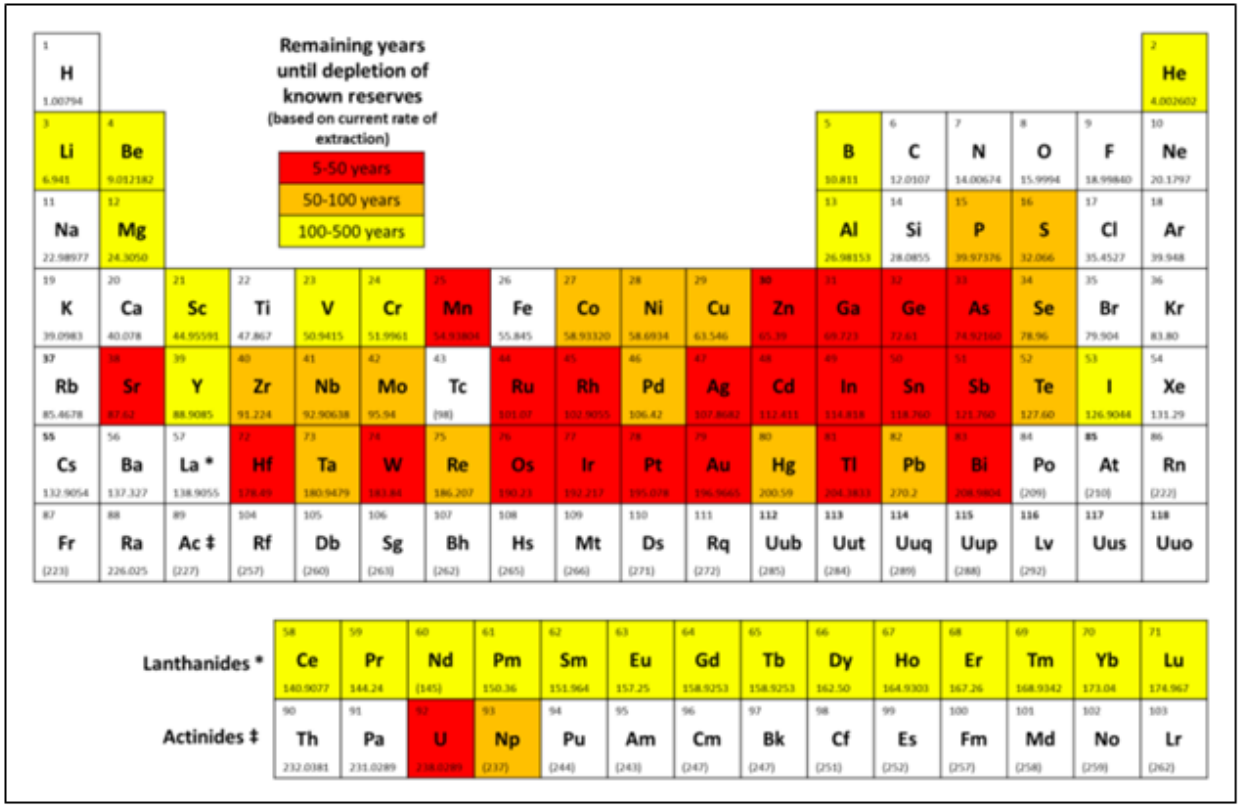
Solvents	
Preferred solvents	**water,** EtOH, nBuOH, AcOipr, AcOnBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, **AcOEt,** sulfolane
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, **cyclohexane**, chlorobenzene, formic acid, pyridine, Me-THF
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane, CS_2, HMPA

Catalyst and its recyclability flag classification

Catalyst/enzyme				
Catalyst or enzyme used, **or** reaction takes place without **any** catalyst/reagents.	Green Flag		Facile recovery of catalyst/enzyme	Green Flag
Use of stoichiometric quantities of reagents	Amber Flag		catalyst/enzyme not recovered	Amber Flag
Use of reagents in excess	Red Flag			

Critical element flag classification

Critical elements	
Supply remaining	**Flag colour**
5-50 years	Red Flag
50-500 years	Amber Flag
+500 years	Green Flag



Energy flag classification

Energy (First Pass)			
Reaction run between 0 to 70°C	Green Flag	Reaction run at reflux	Red Flag
Reaction run between -20 to 0 or 70 to 140°C	Amber Flag	Reaction run 5°C or more below the solvent boiling point	Green Flag
Reaction run below -20 or above 140°C	Red Flag		

Work up flag classification

Work Up	
quenching	Green Flag
filtration	
centrifugation	
crystallisation	
Low temperature distillation/evaporation/	
solvent exchange, quenching into aqueous solvent	Amber Flag
chromatography/ion exchange	Red Flag
high temperature	
multiple recrystallisation	

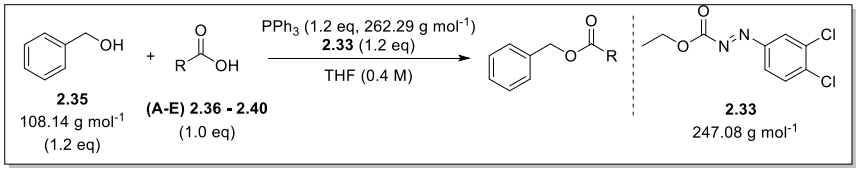
Health and safety flag classification

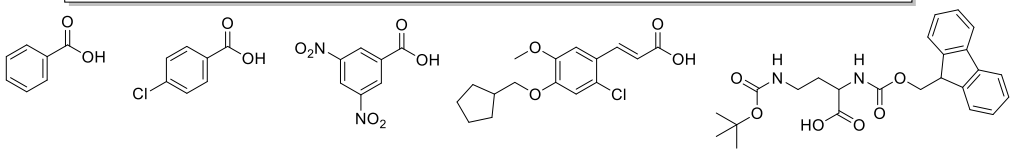
Health & safety			
	Red Flag	Amber Flag	Green Flag
Highly explosive	H200, H201, H202, H203	H205, H220, H224	If no red or amber flagged H codes present then green flag
Explosive thermal runaway	H230, H240, H250	H241	
Toxic	H300, H310, H330	H301, H311, H331,	
Long Term toxicity	H340, H350, H360, H370, H372	H341, H351, H361, H371, H373	
Environmental implications	H400, H410, H411, H420	H401, H412	

Chemical of concern flag classification

Use of chemicals of environmental concern	
Chemical identified as Substances of Very High Concern by ChemSec which are utilised	Red Flag

A.2 Green metrics simulations applied on the Mitsunobu reaction with ethyl 2-(3,4-dichlorophenyl)diazene-1-carboxylate (DCPEAC) as coupling reagent.

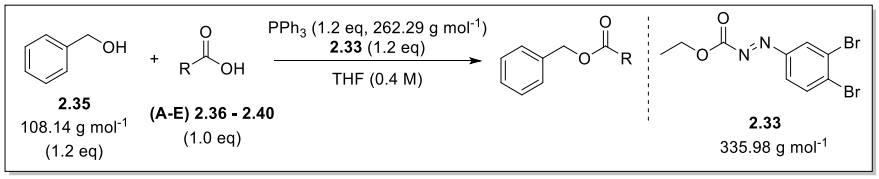


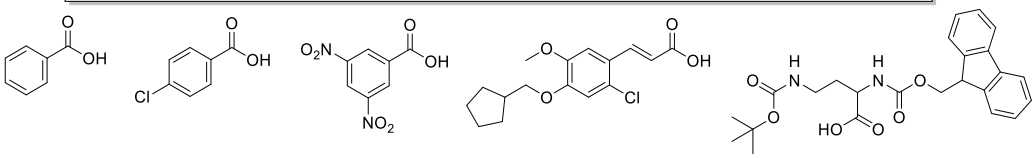


A - 2.36 122.12 g mol^{-1} | B - 2.37 156.57 g mol^{-1} | C - 2.38 212.12 g mol^{-1} | D - 2.39 310.77 g mol^{-1} | E - 2.40 440.50 g mol^{-1}

Carboxylic acid	AE (%)	RME (%)	PMI (g g^{-1})	PMI$_{RRC}$ (g g^{-1})	PMI$_{solv}$ (g g^{-1})	Yield (%)
Simulation 1: [Acid] = 0.4 M, Yield = 90%						
A	92	76	16.2	4.5	11.6	90
B	93	78	14.1	4.0	10.0	90
C	94	80	11.7	3.5	8.2	90
D	96	82	9.1	2.9	6.2	90
E	97	84	7.1	2.5	4.7	90
Simulation 2: [Acid] = 0.4 M, Yield = 80%						
A	92	67	18.2	5.1	13.1	80
B	93	69	15.8	4.5	11.3	80
C	94	71	13.1	3.9	9.2	80
D	96	73	10.2	3.3	6.9	80
E	97	74	8.0	2.8	5.2	80
Simulation 3: [Acid] = 0.4 M, Yield = 70%						
A	92	59	20.8	5.8	15.0	70
B	93	60	18.1	5.2	12.9	70
C	94	62	15.0	4.5	10.5	70
D	96	64	11.7	3.7	7.9	70
E	97	65	9.2	3.2	6.0	70
Simulation 4: [Acid] = 0.4 M, Yield = 50%						
A	92	42	29.1	8.1	20.9	50
B	93	43	25.3	7.3	18.0	50
C	94	44	21.0	6.3	14.7	50
D	96	46	16.3	5.2	11.1	50
E	97	47	12.8	4.5	8.4	50
Simulation 5: Scale reaction x5, [Acid] = 0.4 M, Yield = 90%						
A	92	76	16.1	4.5	11.6	90
B	93	78	14.1	4.0	10.0	90
C	94	80	11.7	3.5	8.2	90
D	96	82	11.9	2.9	9.0	90
E	97	84	12.1	2.5	9.7	90
Simulation 6: [Acid] = 0.8 M, Yield = 90%						
A	92	76	10.3	4.5	5.8	90
B	93	78	9.0	4.0	5.0	90
C	94	80	7.6	3.5	4.1	90
D	96	82	6.0	2.9	3.1	90
E	97	84	4.8	2.5	2.3	90

A.3 Green metrics simulations applied on the Mitsunobu reaction with ethyl 2-(3,4-dibromophenyl)diazene-1-carboxylate (DBPEAC) as coupling reagent.





A - 2.36 122.12 g mol^{-1} | **B - 2.37** 156.57 g mol^{-1} | **C - 2.38** 212.12 g mol^{-1} | **D - 2.39** 310.77 g mol^{-1} | **E - 2.40** 440.50 g mol^{-1}

Carboxylic acid	AE (%)	RME (%)	PMI (g g^{-1})	PMI_{RRC} (g g^{-1})	PMI_{solv} (g g^{-1})	Yield (%)
Simulation 1: [Acid] = 0.4 M, Yield = 90%						
A	92	76	16.7	5.1	11.6	90
B	93	78	14.5	4.5	10.0	90
C	94	80	12.1	3.9	8.2	90
D	96	82	9.4	3.2	6.2	90
E	97	84	7.4	2.7	4.7	90
Simulation 2: [Acid] = 0.4 M, Yield = 80%						
A	92	67	18.8	5.7	13.1	80
B	93	69	16.4	5.1	11.3	80
C	94	71	13.6	4.4	9.2	80
D	96	73	10.5	3.6	6.9	80
E	97	74	8.3	3.0	5.2	80
Simulation 3: [Acid] = 0.4 M, Yield = 70%						
A	92	59	21.5	6.5	15.0	70
B	93	60	18.7	5.8	12.9	70
C	94	62	15.5	5.0	10.5	70
D	96	64	12.0	4.1	7.9	70
E	97	65	9.5	3.5	6.0	70
Simulation 4: [Acid] = 0.4 M, Yield = 50%						
A	92	42	30.1	9.1	20.9	50
B	93	43	26.2	8.1	18.0	50
C	94	44	21.7	7.0	14.7	50
D	96	46	16.9	5.8	11.1	50
E	97	47	13.2	4.9	8.4	50
Simulation 5: Scale reaction x5, [Acid] = 0.4 M, Yield = 90%						
A	92	76	16.7	5.1	11.6	90
B	93	78	14.5	4.5	10.0	90
C	94	80	12.1	3.9	8.2	90
D	96	82	12.2	3.2	9.0	90
E	97	84	12.4	2.7	9.7	90
Simulation 6: [Acid] = 0.8 M, Yield = 90%						
A	92	76	10.9	5.1	5.8	90
B	93	78	9.5	4.5	5.0	90
C	94	80	8.0	3.9	4.1	90
D	96	82	6.3	3.2	3.1	90
E	97	84	5.0	2.7	2.3	90

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