The Development of Catalytic Methods for the Synthesis of Saturated Nitrogen Heterocycles

A thesis submitted to the Board of the Faculty of Physical Sciences in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

at the

University of Oxford

by

Anna E. R. Chamberlain

St Hilda's College

and

The Chemistry Research Laboratory

Trinity Term 2019

Table of contents

Declaration

The work described herein is entirely my own, except where help is acknowledged from a specific person or a reference is given to a published source or thesis.

Anna Elisabeth Rollo Chamberlain

University of Oxford

Trinity Term 2019

Abstract

The Development of Catalytic Methods for the Synthesis of Saturated Nitrogen Heterocycles
A thesis submitted for the degree of **Doctor of Philosophy** by **Anna E. R. Chamberlain**, St Hilda's College and The Chemistry Research Laboratory, Trinity Term 2019.

Chapter 1: Introduction

The introduction gives a description of the applications of azetidines, pyrrolidines and piperidines, as well as a brief overview of existing methods for their synthesis. Selected examples from the chemical literature are discussed. This chapter also reviews the history and development of hydrogen borrowing catalysis for nitrogen alkylation.

Chapter 2: Photoredox Catalysis for the Synthesis of Azetidines

The development of visible light-mediated photoredox catalysis for azetidine synthesis was explored. A $Ru(bpy)_3^{2+}$ catalyst system was employed to induce single electron reduction of 1-phenylbut-2-en-1-one and reaction of the resulting radical anion was attempted with a number of nitrogen-containing electrophiles. Subsequently, a tethered substrate featuring an enone and an oxime portion was designed, synthesised and subjected to a screen of photoredox catalysts, with the hope of effecting an intramolecular azetidine formation.

Chapter 3: Hydrogen Borrowing Catalysis for the Synthesis of Piperidines

Hydrogen borrowing catalysis enabled the generation of a wide range of substituted piperidine scaffolds. Diols are employed as double alkylating agents and overall the process forms two new C–N bonds to furnish the heterocycle. A range of diols and amines were subjected to the reaction conditions to synthesis piperidines. The synthesis of pyrrolidines, azetidines and heterocycles bearing more than one heteroatom were also investigated under the hydrogen borrowing conditions.

Chapter 4: Stereoselective Synthesis of Piperidines using Hydrogen Borrowing Catalysis

Hydrogen borrowing catalysis for the synthesis of piperidines with stereogenic centres at the C2, C3 and C4 positions was investigated. The use of an enantiopure amine was explored for stereoinduction at the C2 centre. Through extensive optimisation, water was discovered to be an optimum reaction solvent and a new set of reaction conditions were developed enabling stereoretention in up to 93:7 er at the C3 position. Piperidines bearing a stereogenic centre at the C4 position could be synthesised from enantioenriched starting materials as this centre was found to be unharmed during the hydrogen borrowing reaction.

Chapter 5: Experimental

This chapter contains the experimental procedures and spectroscopic data for all of the compounds described within the thesis.

Chapter 6: Appendix

The X-ray crystallographic data for compound **240** can be found in the appendix.

Chapter 7: References

The references cited within the thesis can be found in this chapter.

Acknowledgements

First and foremost, I must thank my supervisor, Prof. Tim Donohoe, for your support and guidance over the last four years. Thank you for the opportunity to work as part of your group and for always being excited to talk about chemistry. I'm especially grateful for your endless enthusiasm and that your door was always open to discuss good (and bad) results.

I must also thank my industrial supervisor, Dr Heather Twin, your support and enthusiasm over the last few years has been instrumental to my DPhil. Thank you for giving me the opportunity to spend time working in the labs at Vertex and for going above and beyond to lend help or resources whenever possible. I'm also grateful to Dr Thomas Staroske for devoting valuable time to separating compounds for me and Stefan Richardson for attempting to purify my 'messy' reactions. I also want to thank Dr Ewa Chudyk and Dr Ron Knetgel for their help in conducting DFT calculations. Lastly, to everyone I met during my time at Vertex, thank you for making me feel welcome and included.

Thank you to the SBM CDT team; Prof. Martin Smith and Prof. Darren Dixon for giving me this great opportunity and Dr Lara Lourenco Venda, Dr Maitane Fernandez Chento and Laura Thomas for ensuring the course ran smoothly and for always being on hand to help with any problem, big or small. Thanks are also due to the CRL NMR, mass spectrometry and X-ray crystallography staff for running endless service samples for me, and for getting spectra back quickly when needed. The CRL would be a very different place without the support and stores staff, thanks are due to you for keeping everything working.

I've been lucky to work with several very talented post docs during my time in the Donohoe group; Hamish, Roly, Simon, James, Maria, Harry and Harish – thank you for your guidance and advice in the lab. Particular thanks to Roly (aka Dr Diol) for all of your help during my time as part of Team Hydrogen Borrowing and for the hours spent staring at complicated NMR spectra, and to Hamish for always answering my questions in the lab, no matter how stupid they may have sounded, but most importantly, for all the dog videos. Thank you also to my proofreaders, Roly, Hamish, Chris and Waz, for helpful suggestions and for picking up many a mistake or typo in this thesis.

I would like to thank all of the members of F8 (or F-great as it should be known); Max for your cheesy music choices and always being around to share in the joys of chemistry, Alex for educating me on many a philosophical topic, Hamish for your (sometimes questionable) discussion topics and fantastic musical music, Daniel for your cutting remarks (mostly at Max's expense), Ben for all the memes and putting up with my mess slowly encroaching onto your desk and Bruno, Lydia and Lewis for making the lab a brighter place recently. Special thanks are due to Kieran for your work in getting the hydrogen borrowing project off the ground and for your fantastic singing during your brief time as my fumehood neighbour.

I must also thank everyone from F7, mostly for not complaining too much when I came to 'borrow' your nice glassware! Roly, for sharing in my HPLC woes, Simon for embracing morning brew, Chris for taking over Team Christmas duties and for more dog videos. Thanks to Oskar for always being so cheerful, to little Tim for enlightening me on so many named reactions I'd never heard of before and to Daniella, Ciaran and Galina for making F7 a cheerful place to visit.

My time in the Donohoe group wouldn't have been the same without all the great chemists who I've met over the years; I'm especially grateful to Waz and Mel for always being around for a lunch break or pub trip and for all your support along the way. Thanks to CB for always jumping at the opportunity to help with an NMR problem or fix a broken Büchi, to dodgey Henrique for even more questionable conversation topics and the infamous 'would you rather…' discussions, Simon and Harish for your help and guidance in my first few weeks and Johannes for instilling the importance of brew and passing on the Team Christmas baton.

Last but not least, I thank my parents for their never-ending support over my many years at school and university and their constant encouragement, no matter the task at hand. To my brother, James, for always being on hand to cheer me up and make fun of me. To my friends, old and new, for being there to commiserate or celebrate as appropriate, and for providing much needed distraction. To Andrew, for always being there to pick me up and cheer me on after a bad day in the lab, and for celebrating every milestone with me, big or small.

Abbreviations and Acronyms

Ac	acetyl
acac	acetylacetone
ADH	alcohol dehydrogenase
^{t}Am	*tert*-amyl
AmDH	amine dehydrogenase
APIs	active pharmaceutical ingredients
Ar	aryl/aromatic
ax	axial
BMIM	1-butyl-3-methylimidazolium
Bn	benzyl
BNPPA	1,2'-binaphthyl-2,2'-diylphosphoric acid
Boc	*tert*-butyloxycarbonyl
bpy	bipyridine
br.	broad
^{n}Bu	*normal*-butyl
^{t}Bu	*tert*-butyl
BVE	Benzyl vinyl ether
cat.	catalyst
Cbz	carboxylbenzyl
Cf.	compared to (latin)
cod	1,5-cyclooctadiene
COSY	Correlation spectroscopy
Cp*	pentamethylcyclopentadienyl
CPME	cyclopentyl methyl ether
Cy	cyclohexyl
Cyp450	cytochrome P450

dF	di-fluoro
DFT	density function theory
d	doublet
DAD	diode array detector
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DPEphos	bis[(2-diphenylphosphino)phenyl] ether
dppf	1,1'-ferrocenediyl-bis(diphenylphosphine)
dqd	double quartet of doublets
dqt	double quartet of triplets
dr	diastereomeric ratio
dtbpy	4,4'-bis(*tert*-butyl)-2,2'-bipyrine
ee	enantiomeric excess
ent	enantioenriched
eq	equatorial
equiv.	equivalents
er	enantiomeric ratio
es	enantiospecificity; the extent of enantioretention during the reaction, calculated as (ee of product/ee of starting material)*100%
ESI	electrospray ionisation
Et	ethyl
EVE	Ethyl vinyl ether
FTIR	Fourier-transform infrared spectroscopy
FDA	(US) Food and Drug Administration
g	grams

HB	hydrogen borrowing (catalytic cycle)
hept	heptet
het-Ar	heteroaromatic
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
HMBC	heteronuclear multiple bond correlation
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
hrs	hours
HSQC	heteronuclear single quantum coherence
Hz	Hertz
in situ	in place (latin)
in vacuo	in a vacuum (latin)
IPA	*iso*-propyl alcohol
IR	infrared
J	coupling constant
L	litre
LDA	lithium diiospropylamide
LED	light emitting diode
m	*meta*
m	multiplet
M	molar
Me	methyl
MeCN	acetonitrile
Mes-Acr	9-mesityl-10-methylacridinium tetrafluoroborate
mg	milligrams
min	minute(s)
mL	millilitre(s)

mol%	molar percent
MS	molecular sieves
MVK	methyl vinyl ketone
NAD	nicotinamide adenine dinucleotide
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NPC	*N*-(propen-1-yl)carbazole
n.r.	no reaction
Ns	nosyl
NVC	*N*-vinylcarbazole
o	*ortho*
p	*para*
p	pentet
Ph	phenyl
phen	phenanthroline
PIDA	phenyliodine(III) diacetate
PMA	Phosphomolybdic acid
PMB	*para*-methoxybenzene
PNB	*para*-nitrobenzene
ppm	parts per million
ppm	parts per million
ppy	2-phenylpyridine
*i*Pr	*iso*-propyl
p-tol	*para*-tolyl
Py	pyridyl
q	quartet

qd	quartet of doublets
rac	racemic
r.r.	regioisomeric ratio
RSM	recovered starting material
rt	room temperature
s	singlet
SET	single electron transfer
SFC	supercritical fluid chromatography
SM	starting material
SPINOL	1,1'spirobiindane-7,7'-diol
t/*tert*	tertiary
Ts	tosyl
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	triflate
THF	tetrahydrofuran
TMS	tri-methylsilyl
TBAI	tetrabutylammonium iodide
t	triplet
TFE	2,2,2-trifluoroethanol
TLC	thin layer chromatography
TRIP	3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl
t_r	retention time
tt	triplet of triplets
UPLC-MS	ultra-performance liquid chromatography-mass spectrometry
UV	ultraviolet
via	by way of (latin)

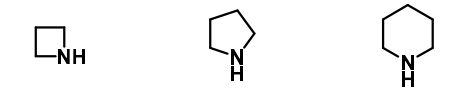
µW	microwave
w.r.t.	With respect to
% wt/wt	weight percent
xs	excess
λ	wavelength

Chapter 1: Introduction

1.1 Importance and prevalence of saturated nitrogen heterocycles

Nitrogen heterocycles are of great interest and value due to their extensive use in many fields of chemistry, including active pharmaceutical ingredients (APIs), agrochemicals, and natural products.[1,2] In particular, *N*-heterocycles are greatly important in the pharmaceutical industry as they are one of the most common structures found in API molecules. A 2014 study by Njardarson and co-workers found that 59% of FDA-approved small molecule drugs contain nitrogen heterocycle functionality.[3]

The work presented in this thesis is primarily concerned with the synthesis of four-, five- and six-membered saturated ring systems containing just one nitrogen, known as azetidines (**1**), pyrrolidines (**2**) and piperidines (**3**) repectively (**Scheme 1.1**).[4] This introductory chapter will, therefore, only focus on examples of the use of these three ring classes, with a brief overview of existing synthetic strategies and recent examples from the chemical literature.



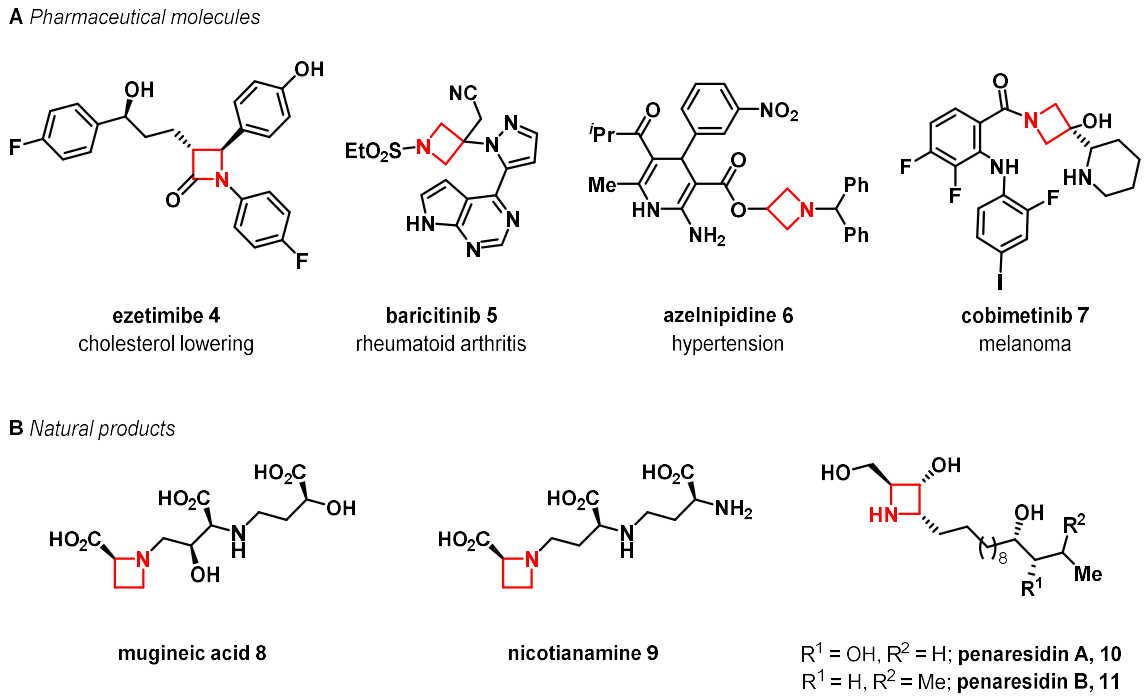
azetidine **1** pyrrolidine **2** piperidine **3**

Scheme 1.1: *Small, saturated nitrogen heterocycles bearing one nitrogen atom; azetidine, pyrrolidine and piperidine.*[4]

1.1.1 Azetidines

Four-membered nitrogen heterocycles are structurally rigid due to their small ring size and lack of rotatable bonds, and this has been correlated with increased bioavailability and metabolic stability.[5,6] However, azetidines are significantly under-represented in APIs compared to 5- and 6-membered rings.[3] The β-lactam drug class is the most commonly used 4-membered nitrogen heterocycle in pharmaceutical agents, the majority of which are used as antibiotics.[3] However, an exception to this is the cholesterol lowering agent ezetimibe **4**, which is one of few examples in

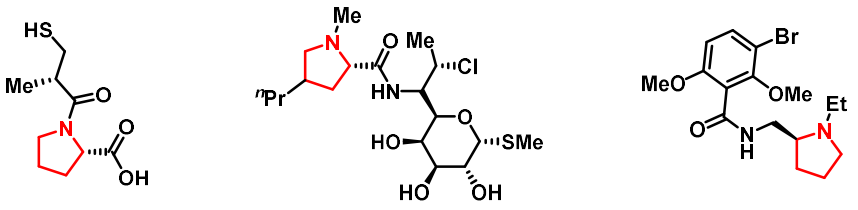
which the β-lactam core is not fused to another ring system (**Scheme 1.2A**).[3,7] Further examples of azetidine-containing pharmaceuticals include baricitinib **5**, a JAK1/JAK2 inhibitor used in the treatment of rheumatoid arthritis,[8] azelnipidine **6** for hypertension[9] and cobimetinib **7**, an MEK inhibitor used in the treatment of melanoma (**Scheme 1.2A**).[10] Azetidine rings can also be found in a range of natural products, including mugineic acid **8**, nicotianamine **9** and the panaresidins **10** and **11**, which were extracted from marine sponges (**Scheme 1.2B**).[11,12]



Scheme 1.2: (A) *Selected examples of 4-membered nitrogen heterocycles.*[8,9,10] ***(B)*** *Natural products bearing azetidine cores.*[11,12]

1.1.2 Pyrrolidines

The most common five-membered nitrogen heterocycle in FDA approved drugs were found to be pyrrolidines, closely followed by the aromatic rings, thiazole and imidazole.[3] Pyrrolidines commonly appear in drug molecules in the form of proline derivatives, such as the angiotensin converting enzyme (ACE) inhibitors for the treatment of cardiovascular diseases, for example captopril **12** (**Scheme 1.3**).[3] Other examples include the antibiotic clindamycin **13**, which also features a proline-derived core, and the antipsychotic remoxipride **14** (**Scheme 1.3**).[13,14]



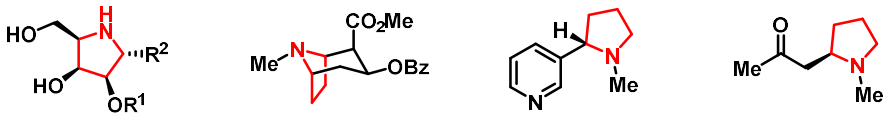
captopril 12
ACE inhibitor

clindamycin 13
antibiotic

remoxipride 14
antipyschotic

Scheme 1.3: *Examples of drug molecules bearing pyrrolidine functionality.*[3,13,14]

Besides their prevalence in APIs, pyrrolidines are present in a wide spectrum of natural products (**Scheme 1.4**).[15,16] Many members of the broussonetinine natural product family feature a common pyrrolidine core **15**, but differ in the nature of the long hydrocarbon chain at the C5-position (R^2, **Scheme 1.4**).[15] The infamous natural products, cocaine **16** and nicotine **17** also have pyrrolidine cores, as well as hygrine **18** which is an alkaloid found primarily in coca leaves (**Scheme 1.4**).[4,16,17]



broussonetinine core 15

cocaine 16

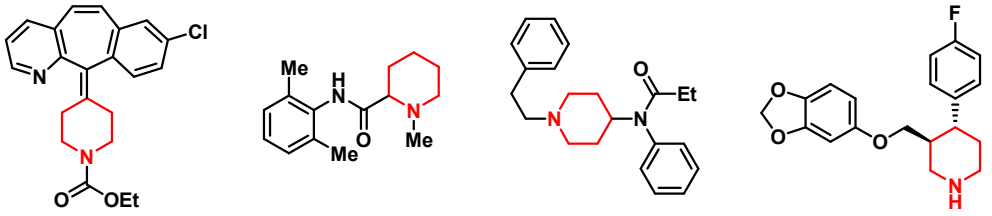
nicotine 17

hygrine 18

Scheme 1.4: *Natural products featuring pyrrolidine cores.*[4,15,16,17]

1.1.3 Piperidines

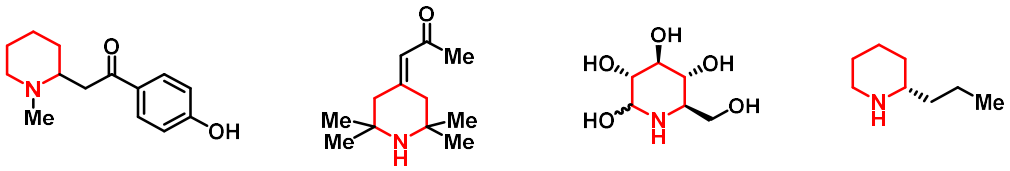
Piperidines are a highly privileged scaffold in medicinal chemistry and have found application in APIs for a wide range of indications.[18] Accordingly, in the aforementioned study by Njardarson and co-workers, piperidine was found to be the most prevalent nitrogen heterocycle in FDA-approved small molecule drugs.[3] Two important classes of piperidine drugs are antihistamines, for example loratadine **19**, and local anaesthetic agents such as mepivicaine **20** (**Scheme 1.5**).[3,19,20] Other, well known examples include the powerful analgesic fentanyl **21** and the blockbuster antidepressant, paroxetine **22** (**Scheme 1.5**).[3,21,22]



loratidine 19 antihistamine | **mepivicaine 20** anaesthetic | **fentanyl 21** analgesic | **paroxetine 22** antidepressant

Scheme 1.5: *API molecules with a piperidine core.*[19,20,21,22]

Piperidines are also found in a wide variety of natural products, for example alkaloids thalictroidine **23** and calyxamine B **24**, isolated from the Caribbean sea spinge, *Calyx podatypa*.[15,17] Further examples include the family of azasugars, such as nojirimycin **25**, and the highly poisonous coniine **26**, a nicotinic acetylcholine receptor antagonist found in hemlock (**Scheme 1.6**).[15,23]



(±)-thalictroidine 23 | calyxamine B 24 | nojirimycin 25 | coniine 26

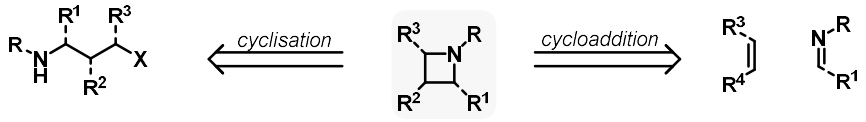
Scheme 1.6: *Natural products with piperidine cores.*[15,17,23]

1.2 Synthesis of *N*-heterocycles

Given the prevalence of *N*-heterocycles, the need for development of novel and efficient syntheses is of ongoing importance. The pharmaceutical industry, in particular, are continually seeking rapid synthetic routes to novel heterocyclic structures for early-stage drug discovery efforts, as well as safe, robust and environmentally friendly routes for large scale API production.[24] General tactics for the synthesis of azetidines, pyrrolidines and piperidines are discussed below. In the interest of brevity, only a few selected examples are presented in each case.

1.2.1 Synthesis of azetidines

Despite the biological importance of azetidines, few general synthetic routes have been reported in comparison to their larger ring homologues.[25] Cyclisation of linear substrates is a common strategy for azetidine synthesis, either through intramolecular nucleophilic substitution, or double alkylation of a nitrogen source with a three-carbon unit.[26] Alternatively, cycloaddition reactions provide an efficient azetidine construction route (**Scheme 1.7**).[27]



Scheme 1.7: *Common disconnections of azetidines include cyclisation and cycloaddition reactions.*

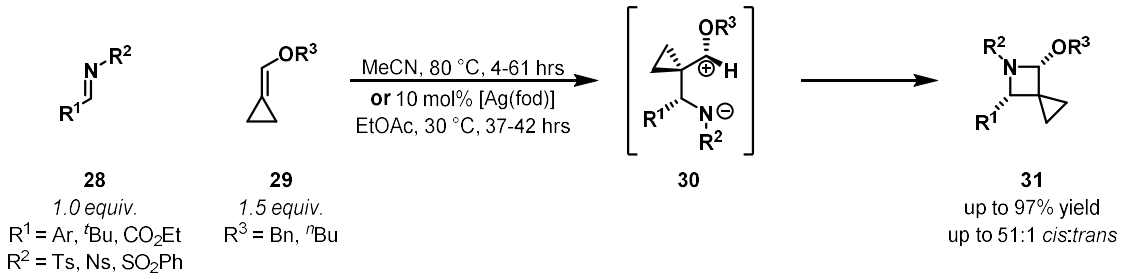
Other methods for azetidine synthesis include rearrangements of existing cyclic structures, in particular, the ring opening of strained azabicyclo[1.1.0]butanes which was pioneered by Baran and co-workers.[28,29] More recently, the Aggarwal group have developed a synthetic route to azabicyclo[1.1.0]butyl lithium and demonstrated its use in the synthesis of azetidine boronic esters.[30] Azetidines are also often accessed by reduction of higher oxidation state ring systems, such as β-lactams, which may be achieved with common reducing agents , for example $LiAlH_4$ or Raney nickel.[25] A highly potent and selective combination of DIBAL-H and chloroalanes, such as $AlHCl_2$ and AlH_2Cl, was reported by Ojima and co-workers for reduction of β-lactams in 1983.[31] The

focus of this section will be cycloaddition and cyclisation reactions, of which examples are discussed in the following sections.

Cycloaddition reactions

Cycloaddition of an imine and an alkene is an elegant and mechanistically straightforward route to azetidine ring structures.[27] [2+2] cycloadditions are commonly light-mediated due to orbital symmetry rules (see **Section 2.11** for examples), but thermally mediated reactions have been reported and selected examples are discussed below.[27] Early examples often required elevated pressure, for example the cycloaddition of imines with electron rich alkenes such as enol ethers and enamines at 12 kbar, reported by Scheeren in 1987.[32]

More recently, de Meijere and co-workers reported the [2+2] cycloaddition of sulfonyl-protected imines **28** to (alkoxymethylene)cyclopropanes **29** at atmospheric pressure (**Scheme 1.8**). This reaction was initially discovered by heating imine **28** and enol ether **29** in acetonitrile at 80 °C. However, it was also found that the reaction could be carried out at lower temperature (30 °C) in the presence of catalytic quantities of a Lewis acidic silver(I) catalyst, which was thought to enhance the electrophilicity of the imine. An enol ether bearing a *gem*-dimethyl group in place of the cyclopropane ring did not react with imine **28** under thermal or catalytic conditions. Hence, it was concluded that the cyclopropane was essential for stabilisation of zwitterionic intermediate **30**. High ratios of *cis*:*trans* products **31** were isolated and density functional theory (DFT) calculations suggested that the *cis* isomer was the thermodynamically favoured product.[33]



28 *1.0 equiv.* R^1 = Ar, ^{t}Bu, CO_2Et; R^2 = Ts, Ns, SO_2Ph

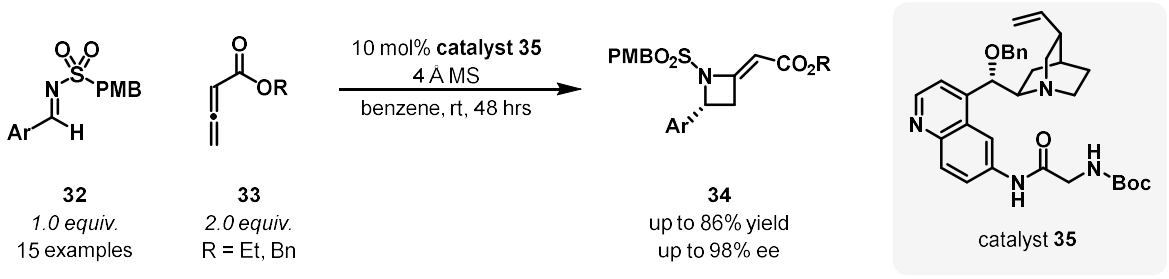
29 *1.5 equiv.* R^3 = Bn, ^{n}Bu

30

31 up to 97% yield, up to 51:1 *cis*:*trans*

Scheme 1.8: *Thermally induced or silver-catalysed [2+2] cycloaddition for azetidine synthesis.*[33]

In 2011, Masson and Zhu reported one of the first enantioselective [2+2] cycloadditions for azetidine synthesis. The reaction of *N*-sulfonyl imine **32** and allenoate **33** was carried out in the presence of cinchona alkaloid catalyst **35** and found to give rise to azetidines **34** with excellent enantioselectivity. A range of benzylaldehyde-derived imines gave rise to good yields, although strongly electron-donating substituents (Ar) led to diminished yields (**Scheme 1.9**).[34]



32
1.0 equiv.
15 examples

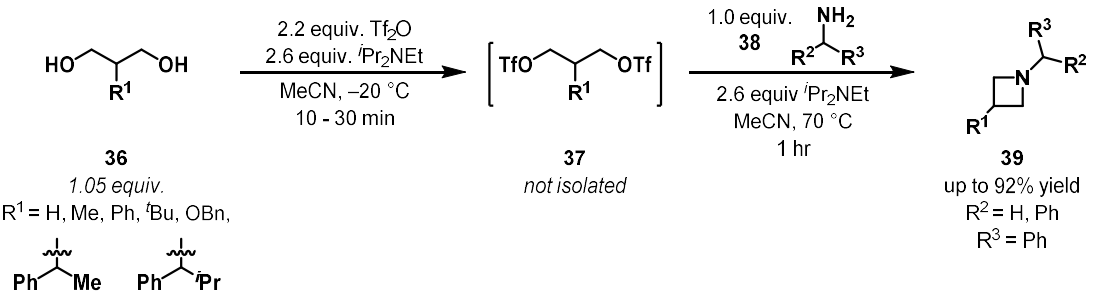
33
2.0 equiv.
R = Et, Bn

34
up to 86% yield
up to 98% ee

Scheme 1.9: *Enantioselective synthesis of azetidines via [2+2] cycloaddition.*[34]

Cyclisation reactions

The reaction of a nitrogen source and a double alkylating agent is a conceptually simple route for the synthesis of azetidines. However, degradation problems are often encountered due to elimination of the starting material. Hillier and Chen reported the one-pot, two-step reaction of primary amine **38** and diol **36**, through *in-situ* generation of bis-triflate **37**. A range of azetidines **39** were furnished in good yields and no elimination products were observed (**Scheme 1.10**).[26]



36
1.05 equiv.
R^1 = H, Me, Ph, ^{t}Bu, OBn,

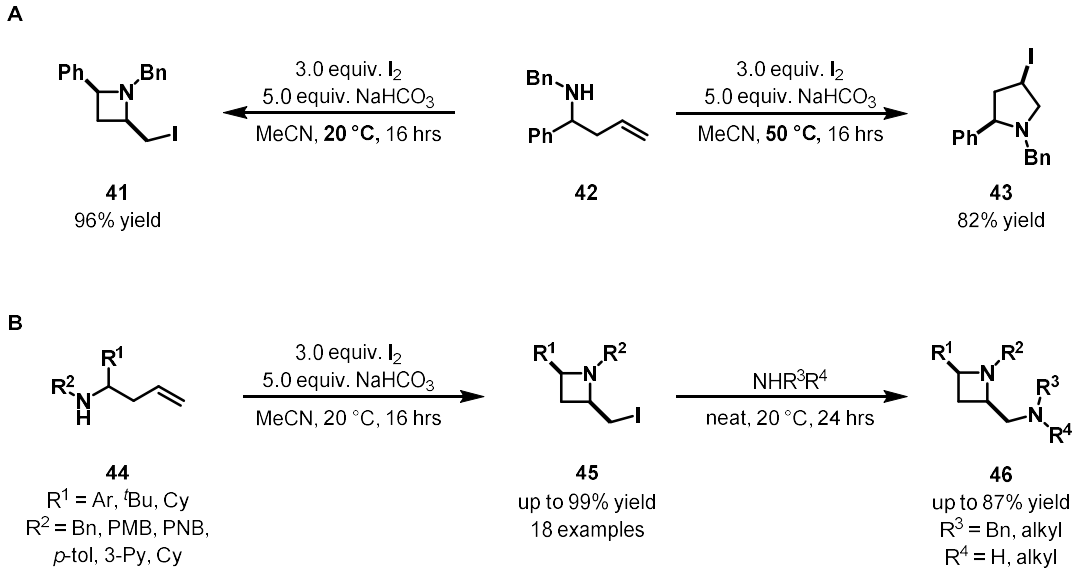
37
not isolated

39
up to 92% yield
R^2 = H, Ph
R^3 = Ph

Scheme 1.10: *Double nucleophilic substitution of bis-triflate, generated in-situ from diol* ***36****.*[26]

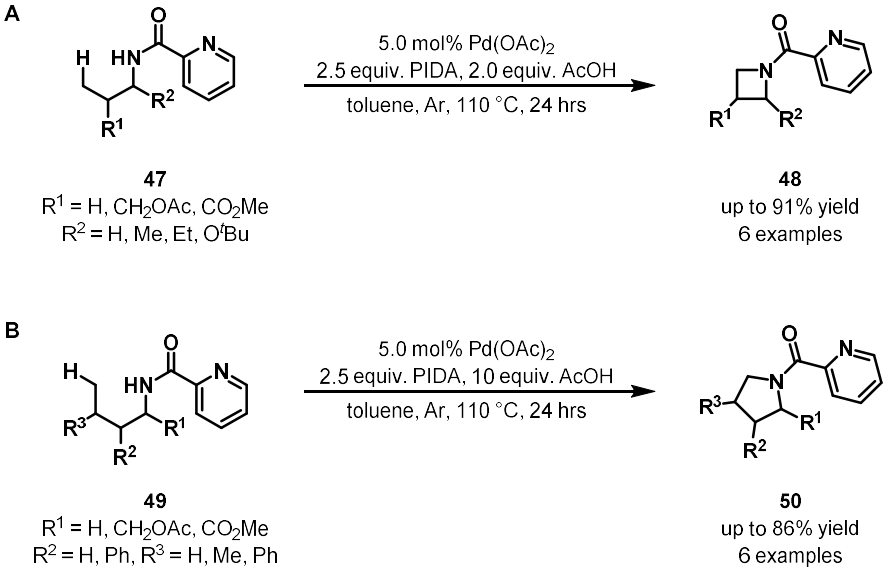
A recent report from Fossey and co-workers demonstrated the iodocyclisation of homoallyl amines **42** to yield 2,4-*cis*-iodoazetidines **41**. Interestingly, it was found that simply conducting the

reaction at a slightly elevated temperature (50 °C) led to the formation of pyrrolidine **43** instead of azetidine **41** (**Scheme 1.11A**). A range of substituted homoallylamines **44** were found to give rise to good to excellent yields of iodoazetidine **45**, although in some cases the corresponding pyrrolidine product was also observed. The *cis*-iodoazetidines **45** were prone to isomerisation to the corresponding pyrrolidine upon work-up, but it was found that the crude reaction mixture could be reacted with a range of primary and secondary amines to give rise to more stable methylamino azetidine derivatives **46** in high yield (**Scheme 1.11B**).[35]



Scheme 1.11: (A) *Increased reaction temperature results in pyrrolidine formation.*[35] ***(B)*** *Iodocyclisation of homoallyl amines yields a range of azetidines, as reported by Fossey and co-workers.*

C–H activation has emerged as a powerful synthetic tool in recent years and was recently applied to the synthesis of *N*-heterocycles by Chen and co-workers.[36,37] A picolinamide directing group was employed to facilitate intramolecular γ-C(sp^3)–H amination under an oxidative Pd(II)/Pd(IV) catalytic cycle. A small number of azetidines **48** were afforded in good to excellent yields (**Scheme 1.12A**) and this catalyst system was also applied to the intramolecular amination of δ-C(sp^3)–H bonds to furnish pyrrolidine products **50** (**Scheme 1.12B**).[37]

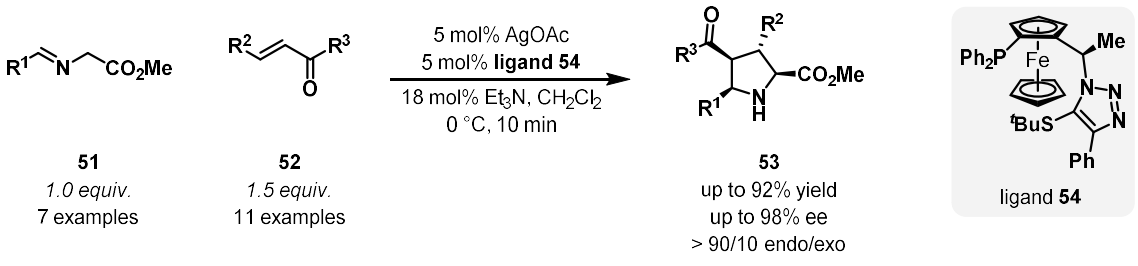


Scheme 1.12: *Intramolecular C–H amination for the synthesis of* ***(A)*** *azetidines and* ***(B)*** *pyrrolidines.*[37]

1.2.2 Synthesis of pyrrolidines

Cycloaddition reactions

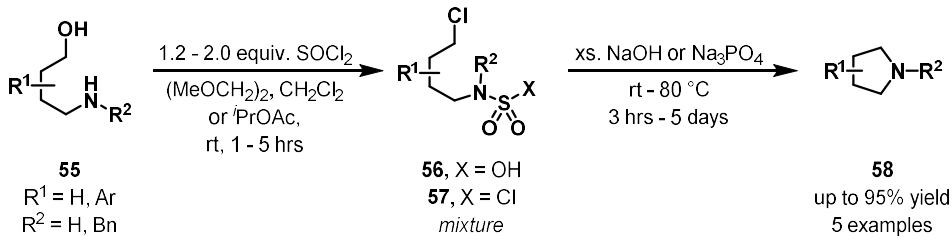
Cycloaddition reactions also represent a particularly efficient method for the synthesis of pyrrolidines, providing access to a range of multiply substituted cores. These methods have the advantage that they tend to be highly atom economic, give good diastereoselectivity and employ abundant starting materials.[38] The classic approach proceeds *via* a [3+2] cycloaddition of an olefin and an azomethine ylide, which may be generated from an imine or aziridine.[39] A number of silver catalysed reactions have been reported,[40,41] for example, Fukuzawa and co-workers developed an enantioselective cycloaddition of imine **51** with enone **52** using a silver(I)-ThioClickFerrophos (**54**) catalyst system. The reaction was found to proceed with high *endo*-selectivity and gave rise to a range of pyrrolidines **53** in high yield and enantioselectivity (**Scheme 1.13**).[42]



Scheme 1.13: E*nantioselective synthesis of multiply substituted pyrrolidines via 1.3-dipolar cycloaddition.*[42]

Cyclisation reactions

Syntheses of pyrrolidines by cyclisation tend to make use of the inherent nucleophilicity of the nitrogen atom in a nucleophilic substitution reaction. Cyclodehydration of an aminoalcohol is an attractive route due to the ease of access and stability of the starting material. However, lengthy protection/deprotection sequences are often required in order to make the –OH group a better leaving group.[43] However, more recently, Xu and co-workers reported a one-pot procedure involving *in situ* generation of chloride **56/57** from aminoalcohol **55** using $SOCl_2$. The authors observed a mixture of sulfamic chloride **57** and sulfamic acid **56** but both were found to cyclise efficiently, despite the reduced nucleophilicity of the sulfamic nitrogen, and gave rise to a range of pyrrolidines **58** in good yields (**Scheme 1.14**).[43]



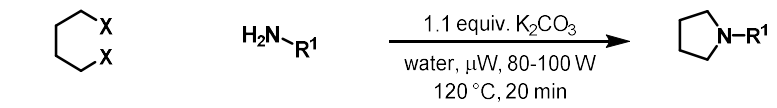
55
R^1 = H, Ar
R^2 = H, Bn

56, X = OH
57, X = Cl
mixture

58
up to 95% yield
5 examples

Scheme 1.14: *Synthesis of pyrrolidines from aminoalcohols by in situ generation of chloride **56/57** followed by cyclisation.[43]*

Alternatively, one can envision cyclisation of a nitrogen source with a bis-electrophile. Ju and Varma demonstrated the microwave-assisted reaction of primary amines **61** with dihalides or ditosylates **60** in water. A range of pyrrolidines **62** were isolated in good to excellent yields, although most examples did not bear any backbone substitution (**Scheme 1.15**). A small number of azetidine, piperidine and azepane examples were also included.[44]



60
1.1 equiv.
X = Br, Cl, I, OTs

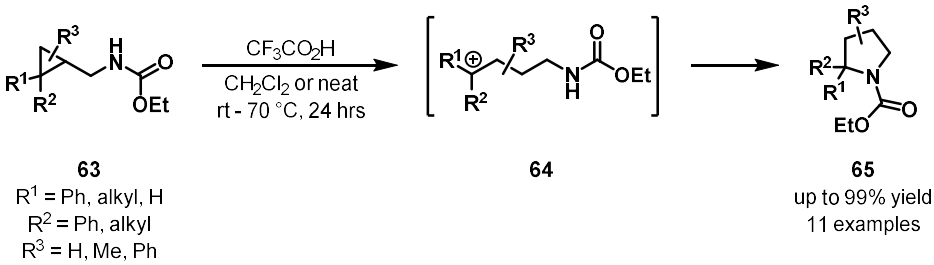
61
1.0 equiv.
R^1 = Ar, Bn, Cy

62
up to 96% yield
17 examples

Scheme 1.15: *Double alkylation of primary amines for synthesis of pyrrolidines.[44]*

Alternative synthetic routes

Other methods commonly employed for the synthesis of pyrrolidines include, but are not limited to, reduction of pyrroles and other higher oxidation state heterocycles or lactams.[45,46] Ring contraction or expansion routes are also known, for example, regioselective C–C bond cleavage of acylated aminomethyl cyclopropane **63** to furnish 2,2-disubstituted pyrrolidines **65** was recently reported by Jirgensons and Skvorcova (**Scheme 1.16**). Acid-promoted cyclopropane ring opening was proposed to give rise to carbocation intermediate **64**, which was subsequently trapped by intramolecular reaction with the carbamate nitrogen to yield pyrrolidine **65.** A range of pyrrolidines **65** were synthesised in excellent yields and the authors noted that the strength of the acid and the nature of the nitrogen substituent were key to obtaining high regioselectivity.[47]



63
R^1 = Ph, alkyl, H
R^2 = Ph, alkyl
R^3 = H, Me, Ph

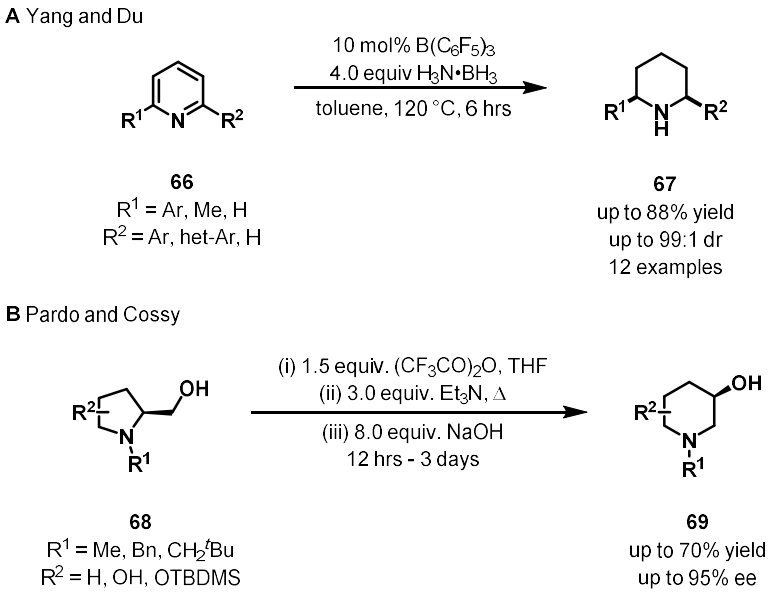
64

65
up to 99% yield
11 examples

Scheme 1.16: *Cyclopropane ring opening and subsequent intramolecular amination to yield pyrrolidines* ***65****, reported by Skvorcova and Jirgensons.*[47]

1.2.3 Synthesis of piperidines

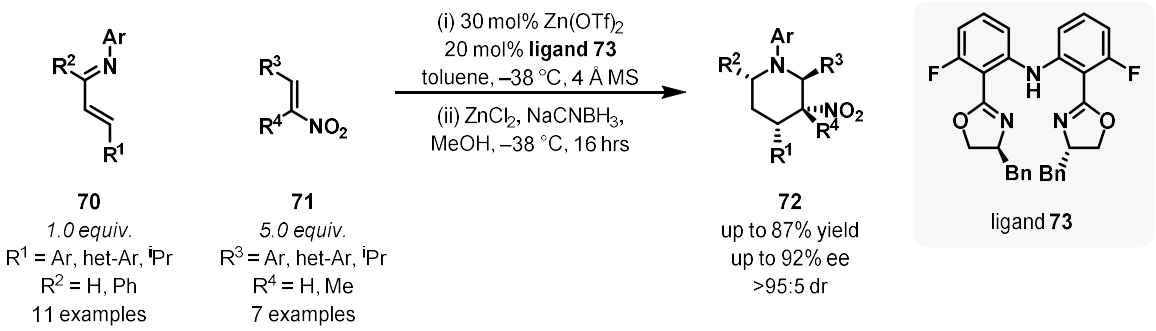
Many strategies available for the synthesis of piperidines are similar to those employed for the synthesis of the four- and five-membered *N*-heterocycles. A wealth of methodology exists for the synthesis of piperidines including cyclisation, cycloaddition, ring expansion and reduction of higher oxidation state species such as pyridines **66**. For example, Du and co-workers reported the diastereoselective reduction of pyridines under borane-catalysed transfer hydrogenation conditions to give rise to *cis*-2,6-disubstituted piperidine products **67** (**Scheme 1.17A**).[48] Furthermore, Pardo and Cossy demonstrated the stereoselective rearrangement of prolinol **68** to yield piperidin-3-ol **69** in the presence of stoichiometric triflic anhydride and triethylamine (**Scheme 1.17B**).[49,50]



Scheme 1.17: (A) *Du and co-workers' transfer hydrogenation of pyridines to give rise to piperidines.*[48] ***(B)*** *Ring rearrangement of prolinols to give piperidinols, reported by Pardo and Cossy.*[49,50]

Cycloaddition reactions

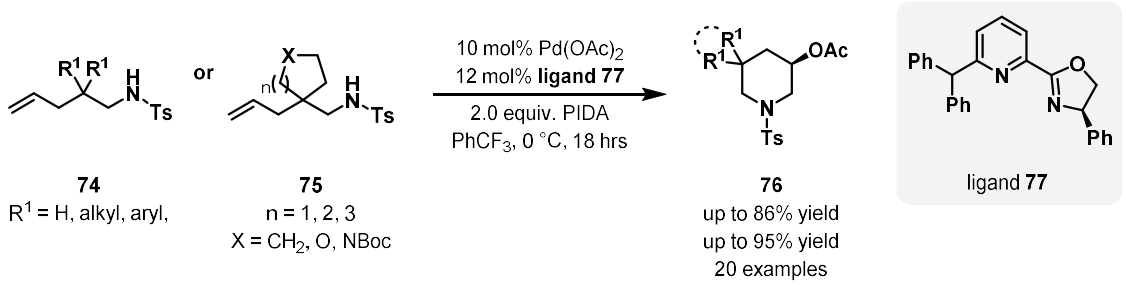
Diels–Alder cycloadditions are widely used for the construction of carbocyclic ring systems and have also been developed for the synthesis of nitrogen-heterocycles by several groups.[51] Recently, Rovis and co-workers reported the enantio- and diastereoselective formal [4+2] cycloaddition of 1-azadiene **70** and nitro-alkene **71** (**Scheme 1.18**). An inexpensive zinc(II) catalyst was employed and, in combination with an enantiopure bis(oxazolinylphenyl)amide (BOPA) ligand **73**, was found to give rise to high yield and enantioselectivity of multiply substituted piperidines **72**. An example of a piperidine bearing a quaternary centre (R^4 = Me) was also reported, although the yield and enantioselectivity were lower than other examples (31% yield, 54% ee). Furthermore, reduction of the nitro group with $NiCl_2$ and $NaBH_4$ was shown to proceed with excellent yield to give rise to medicinally interesting 3-aminopiperidines.[52]



Scheme 1.18: *Enantio- and diastereoselective synthesis of piperidines via [4+2] cycloadditions, reported by Rovis and co-workers.*[52]

Cyclisation reactions

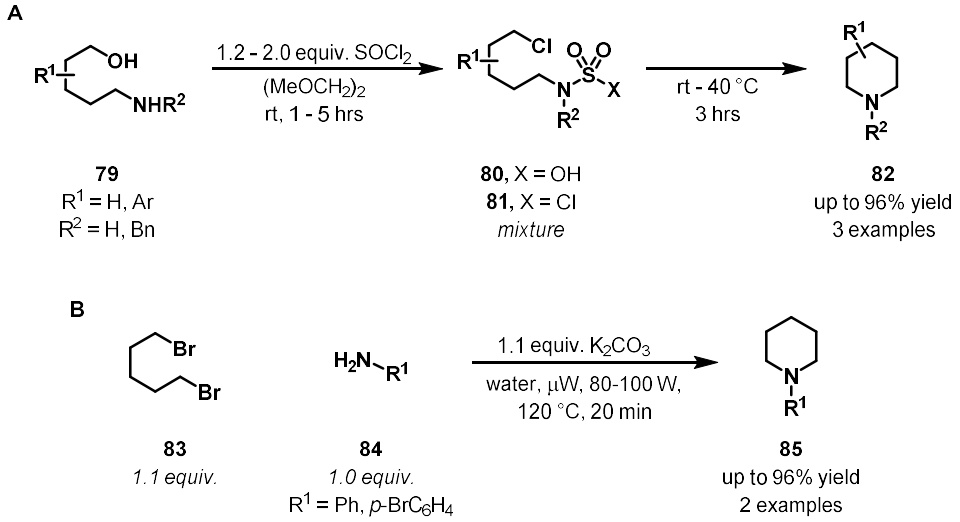
Liu and co-workers recently reported the first enantioselective palladium-catalysed 6-*endo* oxidative amination of alkenes **74**/**75**. Novel pyridine-oxazoline ligand **77** was developed for this purpose and led to the synthesis of a range of enantiomerically enriched 3-acetoxylated piperidines **76** and spiropiperidines. (**Scheme 1.19**). The authors proposed that aminopalladation was the enantiodetermining step, governed by steric repulsion between the ligand and *N*-tosyl group.[53]



Scheme 1.19: *Palladium-catalysed synthesis of 3-acetoxylated piperidines and spiro-piperidines.*[53]

Classic approaches to *N*-heterocycle formation, such as intramolecular nucleophilic substitution or reaction of a nitrogen source with a bis-electrophile have also been applied to the synthesis of piperidines. Work by Xu and co-workers was introduced in **Section 1.2.2** for the synthesis of pyrrolidines *via* generation of sulfamic chloride **80**/**81** and this was also applied to the synthesis of piperidines **82** (**Scheme 1.20A**).[43] Likewise, Ju and Varma's microwave-assisted *N*-heterocycle

synthesis was found to be applicable to the construction of a small number of piperidines **85** in excellent yields (**Scheme 1.20B**).[44]



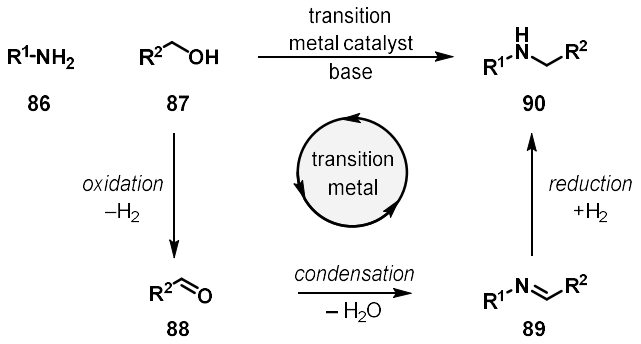
***Scheme 1.20: (A)** One-pot piperidine synthesis by in-situ generation of sulfamic chloride **80/81.**[43] **(B)** Ju and Varma included two piperidine examples in their study of microwave-assisted N-heterocycle synthesis.[44]*

It can be seen that a wide range of complementary methods exist for the synthesis of azetidines, pyrrolidines and piperidines. However, given the importance of these structures in industry and the wide range of applications, the development of new methodology is paramount. Ideally, these methods should be applicable to a range of substrates and employ environmentally-benign and readily accessible starting materials and reagents.

1.3 Hydrogen borrowing alkylation

Classically, amine alkylation reactions are carried out using alkyl halides and similar reagents, which are often highly toxic and lead to stoichiometric amounts of waste product. In addition, over-alkylation can be problematic. Reductive amination has emerged as a highly useful means of amine synthesis from carbonyl compounds but often these starting materials can be unstable or difficult to access.[54]

Hydrogen borrowing is a highly atom economic and redox neutral alternative, using alcohols **87** as the alkylating agent. Typically, a transition metal catalyst is employed which oxidises the alcohol to the more reactive carbonyl intermediate **88**. This is followed by condensation with amine **86**, generating water as the sole reaction by-product. The catalyst finally returns the 'borrowed' hydrogen to reduce imine **89** and yield the desired amine product **90** (**Scheme 1.21**).[54]



Scheme 1.21: *Hydrogen borrowing for amine alkylation.*[54]

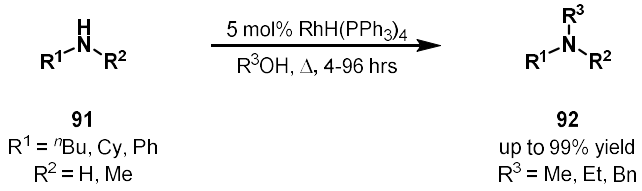
1.3.1 History

The field of hydrogen borrowing chemistry has grown over the past century from a seminal discovery by Guerbet in 1899, who discovered that *n*-butanol could be dehydrogenated in the presence of base and that the resulting aldehyde then underwent self-condensation followed by reduction to generate branched alcohol products.[55] This discovery led to the development of a range of catalytic systems that could affect similar transformations under much milder conditions.[56] The formation of C–C bonds has attracted attention from a number of groups, including our own who have recently reported methodology for the alkylation of ketones to

generate branched structures and carbocyclic compounds.[57,58,59] Although hydrogen borrowing catalysis for C–C bond formation was discovered before the corresponding C–N methodology, the overall concept is very similar and hence catalyst systems have developed synergistically over recent years.

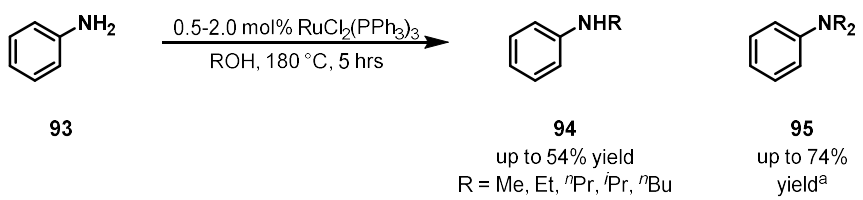
1.3.2 Hydrogen borrowing for N-alkylation

The first applications of hydrogen borrowing chemistry for C–C and C–N bond formation were reported by Grigg in the early 1980s. Alkylation of a range of primary and secondary amines **91** was demonstrated with simple alcohols, such as methanol and ethanol, and led to high yields of alkylated product **92** (**Scheme 1.22**). Alkylation of cyclohexylamine, aniline and pyrrolidine was also demonstrated.[60]



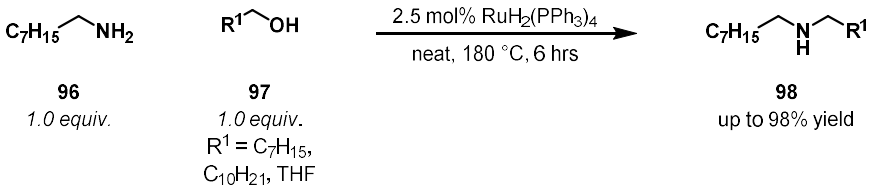
Scheme 1.22: *Amine alkylation under hydrogen borrowing catalysis by Grigg and co-workers.[60]*

This work was closely followed by a report on the use of simple alcohols for the alkylation of aniline **93** by Watanabe and co-workers (**Scheme 1.23**). Linear alcohols such as ethanol and *n*-propanol led to good yields of the corresponding alkylated anilines **94**. However, branched alcohols such as *iso*-propanol and *iso*-butanol gave rise to 25 and 28% yield respectively, presumably due to increased steric hinderance. It was noted that longer reactions time or increased catalyst loading led to increased conversion to bis-alkyl product **95**.[61]



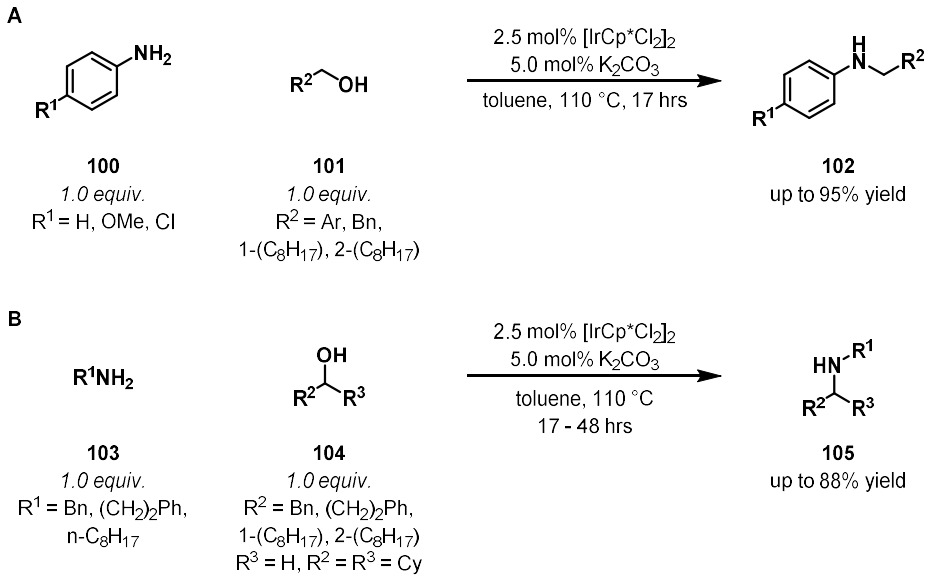
Scheme 1.23: *Alkylation of aniline, reported by Watanabe and co-workers.[61]*

Murahashi and co-workers subsequently employed $RuH_2(PPh_3)_4$ to achieve alkylation of *n*-octylamine **96** with a small number of aliphatic alcohols **97** in good yields (**Scheme 1.24**). However, as in Watanabe's work, elevated temperature (180 °C) was required.[62] These groups all proceeded to develop hydrogen borrowing protocols for *N*-heterocycle synthesis utilising diols in a double hydrogen borrowing process. For discussions of C-N annulation chemistry under hydrogen borrowing catalysis, see **Section 3.1**.



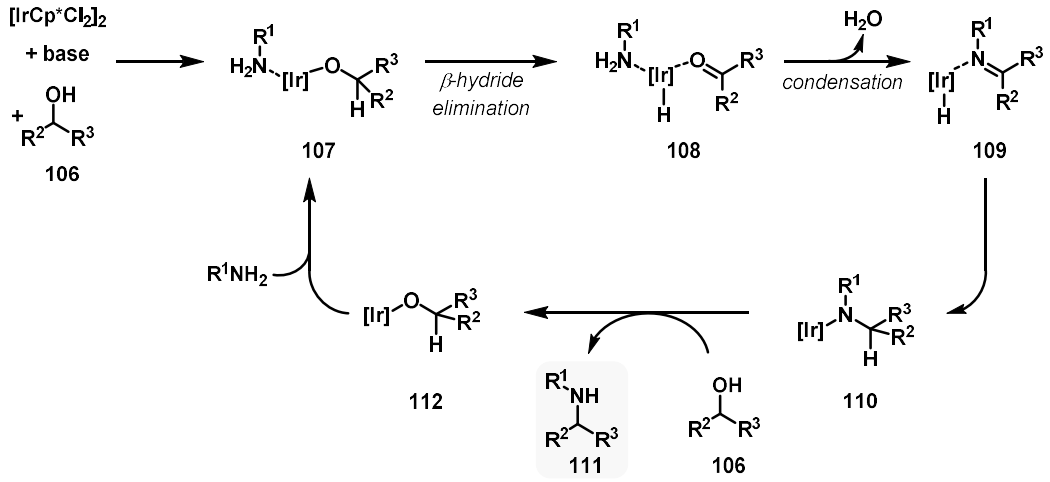
Scheme 1.24: *Alkylation of aliphatic amines by Murahashi and co-workers.*[62]

Fujita and Yamaguchi reported the first examples of iridium catalysed hydrogen borrowing alkylation of amines in 2003.[63] Following examination of a range of catalysts, $[IrCp^*Cl_2]_2$ was found to be superior and was applied to the alkylation of anilines **100** with a range of primary and secondary alcohols **101** (**Scheme 1.25A**). It is notable that this example employs the amine and alcohol starting materials in a 1:1 ratio, whereas previous work from Grigg, Watanabe and Murahashi used the alcohol in vast excess. [60,61,62] The alkylation of primary alkyl amines **103** was also studied, although the yields of product **105** were found to be slightly decreased relative to the aniline examples (**Scheme 1.25B**). This work was later expanded to include the alkylation of secondary amines and to achieve a one-pot sequential reaction for the synthesis of tertiary amines bearing three different substituents.[64]



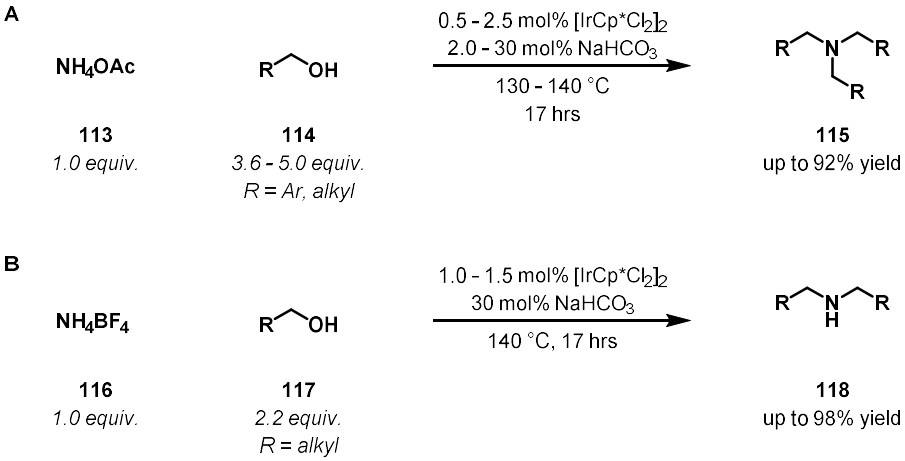
Scheme 1.25: (A) *Iridium-catalysed alkylation of anilines and* ***(B)*** *alkyl amines, reported by Fujita and Yamaguchi.*[63]

Fujita and Yamaguchi proposed a mechanism in which alcohol **106** is oxidised by the iridium catalyst to give carbonyl intermediate **108**, concomitantly generating an iridium hydride species. Condensation of the aldehyde/ketone **108** and amine species was proposed to take place within the coordination sphere of iridium, generating water as the only by-product and giving rise to imine species **109**. Imine **109** is reduced upon insertion into the [Ir]–H bond and the amine product **111** released following alkoxide exchange (**Scheme 1.26**).[63,64]



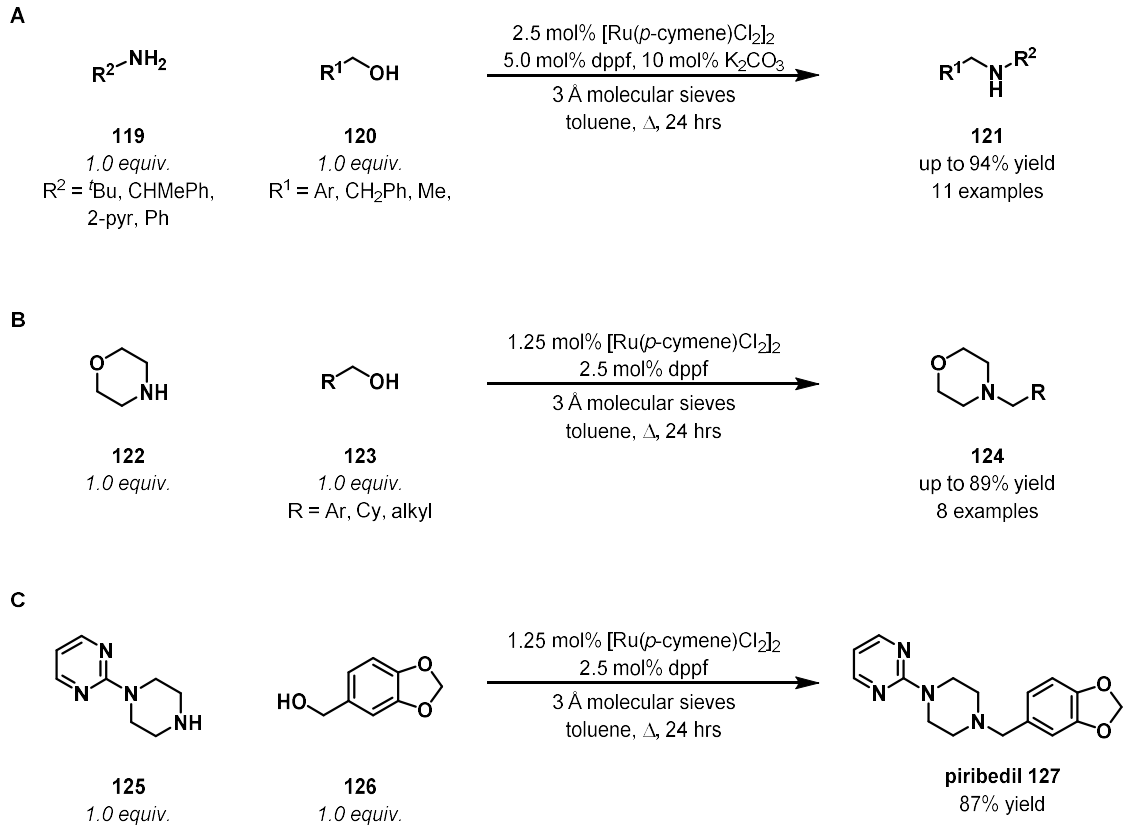
Scheme 1.26: *Mechanism for the N-alkylation of primary amines with primary or secondary alcohols.*[63,64]

Fujita and Yamaguchi subsequently applied their hydrogen borrowing methodology to the alkylation of ammonium salts, which are an attractive and simple nitrogen source for amine synthesis. It was found that ammonium salts such as NH_4OAc **113** could be reacted with primary alkyl and benzyl alcohols **114** in the presence of catalytic $[IrCp^*Cl_2]_2$ to result in high yields of trialkyl amines **115** (**Scheme 1.27A**). Use of NH_4BF_4 **116** as the nitrogen source was found to give rise to dialkylamines **118** with good selectivity (**Scheme 1.27B**).[65]



Scheme 1.27: *Hydrogen borrowing for* ***(A)*** *trialkylation of NH_4OAc and* ***(B)*** *dialkylation of NH_4BF_4.*[65]

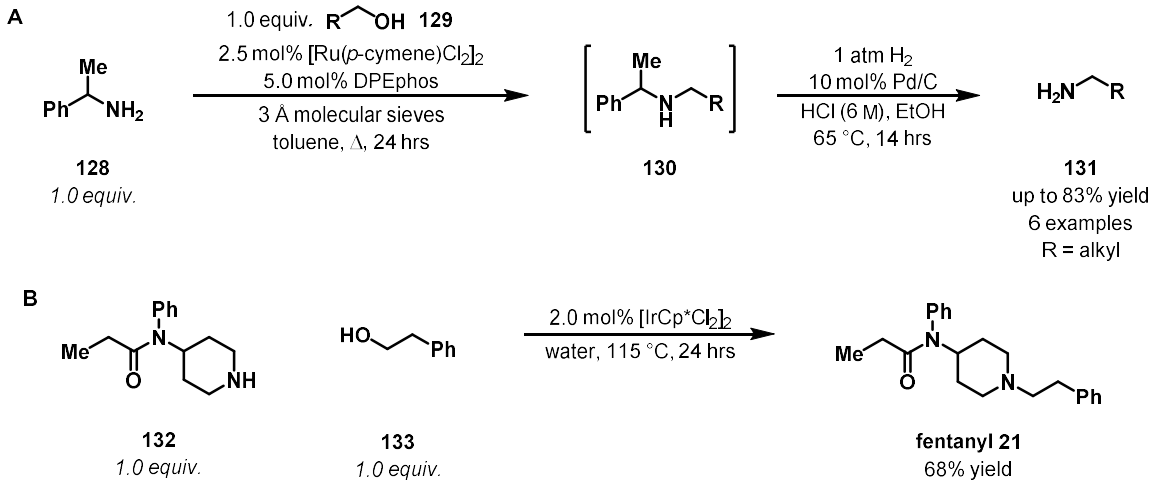
Significant contributions have been made to the field of hydrogen borrowing catalysis for both C–N and C–C bond formation by the Williams group. The *N*-alkylation of phenethylamine and tryptamine under iridium catalysis was reported in 2005, demonstrating potential application of hydrogen borrowing catalysis in the synthesis of biologically active molecules.[66] Ruthenium catalysed hydrogen borrowing conditions were later developed for the alkylation of a range of primary amines **119** with primary alcohols **120** (**Scheme 1.28A**).[54] This work was subsequently expanded to include the alkylation of a wide range of secondary amines, including morpholine **122** to generate tertiary amine products **124** (**Scheme 1.28B**). The synthesis of piribedil (**127**), a drug used in the treatment of Parkinson's disease, was also demonstrated in 87% yield by the alkylation of piperazine **125** with piperonyl alcohol **126** (**Scheme 1.28C**).[67]



Scheme 1.28: (A) *Ruthenium-catalysed hydrogen borrowing alkylation of primary amines.*[54] ***(B)*** *Alkylation of secondary amines.* ***(C)*** *Synthesis of piribedil under hydrogen borrowing alkylation conditions.*[67]

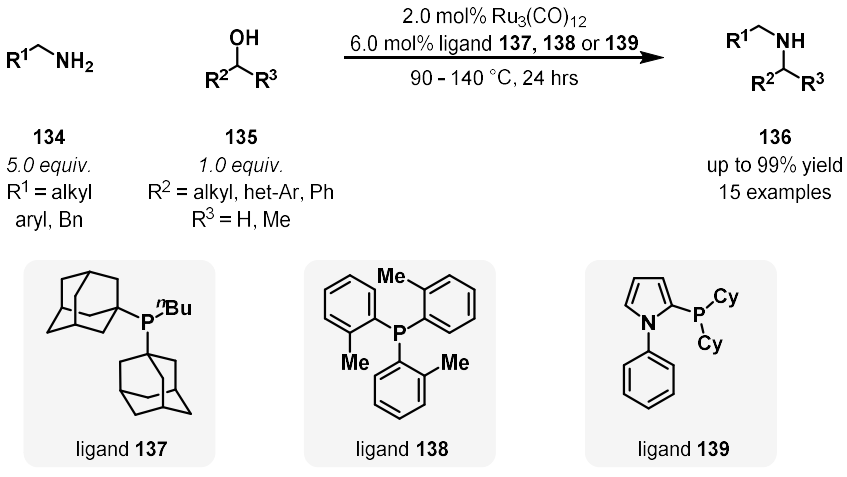
In an interesting report, Williams and co-workers developed a two-step, one-pot process for the synthesis of primary amines *via* hydrogen borrowing. Alkylation of a range of 1-phenethylamines **128** with primary alkyl alcohols **129** was demonstrated, followed by hydrogenolysis to yield amines **131** (**Scheme 1.29A**). Alkylation of sulfonamides, phosphinamides and trimethylsilylethanesulfonamides was also shown and was followed by the appropriate deprotection conditions to yield the primary amine product.[68] Subsequent work from Williams and co-workers included development of conditions for hydrogen borrowing alkylation of amines in aqueous media. A range of primary alkyl and benzyl amines were included, as well as sulfonamides and secondary amines. These conditions were also applied to the synthesis of the powerful analgesic fentanyl (**21**), in 68% yield (**Scheme 1.29B**).[69] The Williams group later reported the *N*-alkylation of a huge range of primary and secondary amines and sulfonamides, as well as

the synthesis of cyclic amine products under ruthenium-catalysed hydrogen borrowing conditions (see **Section 3.1**).[70]



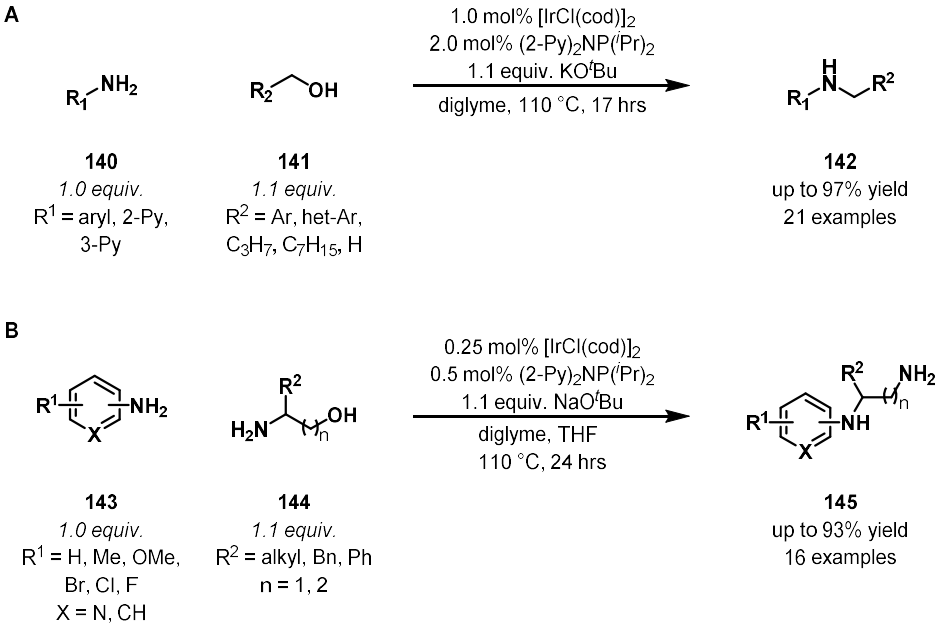
Scheme 1.29: (A) *One-pot, two-step synthesis of primary amines.*[68] ***(B)*** *Synthesis of fentanyl by hydrogen borrowing alkylation under aqueous conditions.*[69]

Several other groups have developed conditions for *N*-alkylation of amines under hydrogen borrowing catalysis in recent years. For example, Beller and co-workers employed $Ru_3(CO)_{12}$ in combination with phosphine ligands **137**–**139** to achieve the alkylation of primary alkyl amines **134** with secondary alcohols **135** (**Scheme 1.30**).[71] This work was soon expanded to cover the synthesis of a more structurally diverse range of secondary amines using $Ru_3(CO)_{12}$ and phosphine ligands.[72]



Scheme 1.30: *Alkylation of primary amines under ruthenium-catalysed hydrogen borrowing conditions.*[71]

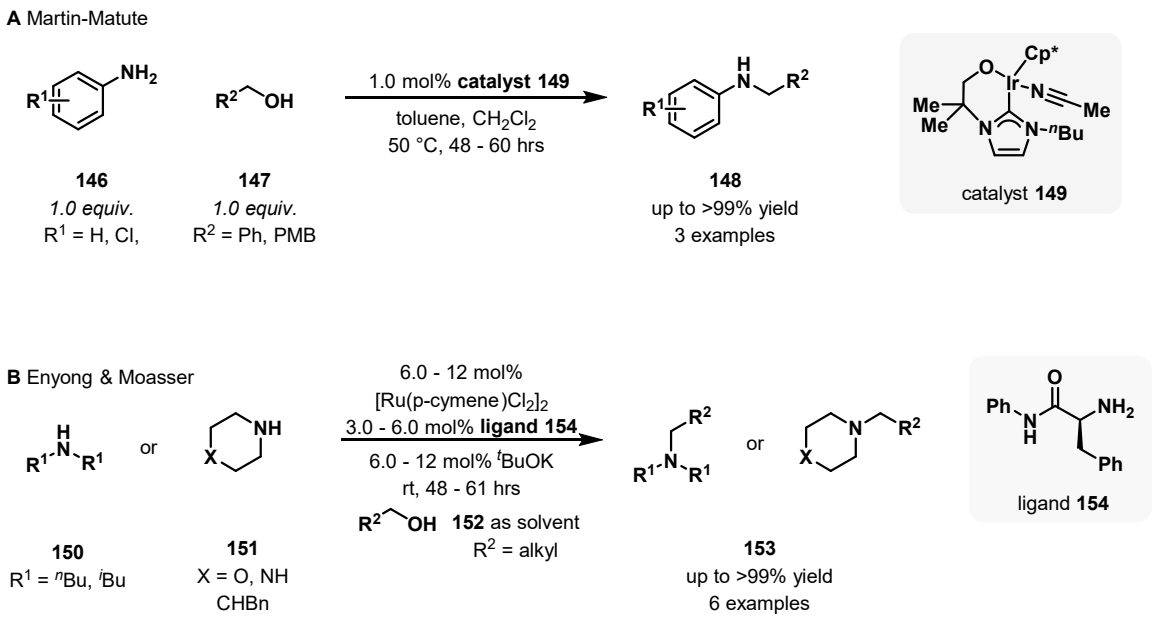
In 2009 Kempe and co-workers reported a novel P,N-ligand-stabilised iridium catalyst for the hydrogen borrowing alkylation of (hetero)aromatic amines **140** with primary alcohols **141**. The catalyst was generated *in situ* from commercially available iridium catalyst $[Ir(cod)Cl]_2$ and $(2\text{-Py})_2NP(^iPr)_2$ (Py = pyridyl) **Scheme 1.31A**). Unfortunately, these conditions were only found to be applicable to aromatic amines. Alkylation of cyclohexylamine and *n*-butylamine with benzyl alcohol did not give rise to the corresponding secondary amine products.[73] This work was subsequently expanded to the selective monoalkylation of (hetero)aromatic amines **143** with aminoalcohols **144**, thus generating tri-amine products, which are of interest in medicinal chemistry and as ligands for metal catalysts (**Scheme 1.31B**).[74]



***Scheme 1.31: (A)** iridium catalysed monoalkylation of (hetero)aromatic amines with primary alcohols.[73] **(B)** synthesis of polyamines under iridium-catalysed hydrogen borrowing alkylation of (hetero)aromatic amines.[74]*

Low-temperature hydrogen borrowing

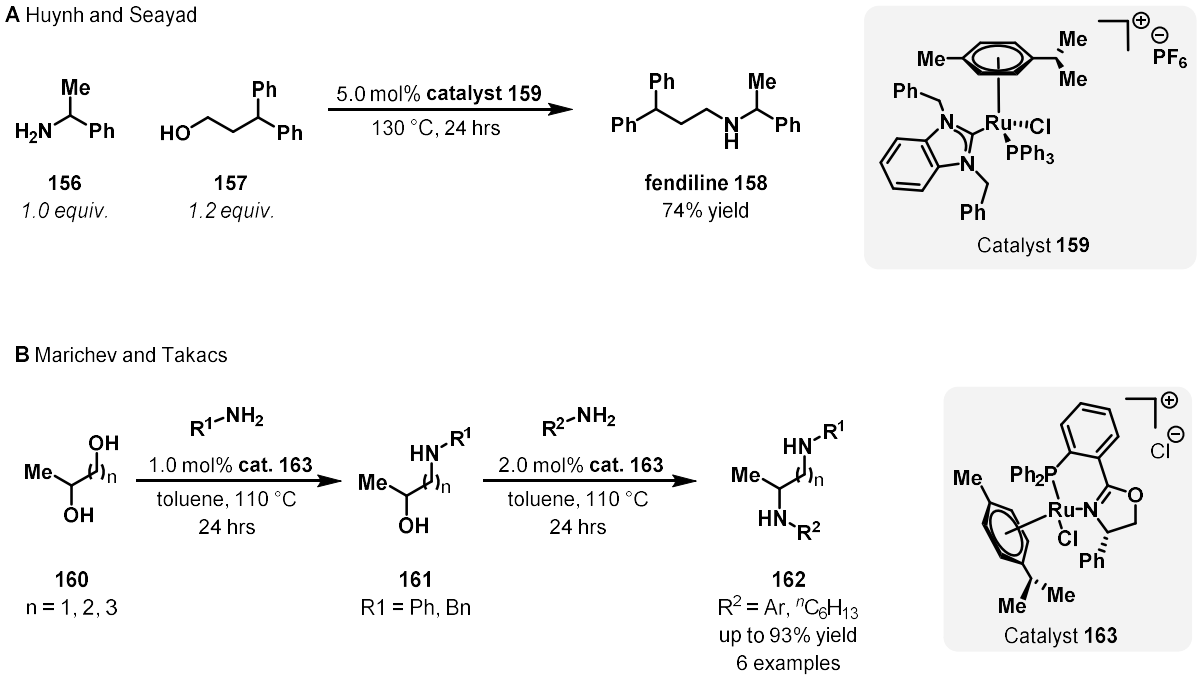
The early reports of hydrogen borrowing for amine alkylation employed elevated temperatures, for example Watanabe's work which required reaction at 180 °C.[61] Martín-Melute and co-workers developed and synthesised bifunctional iridium complex **149**, bearing an *N*-heterocyclic carbene ligand, which enabled the alkylation of a range of aryl amines **146** at temperatures as low as 50 °C (**Scheme 1.32A**).[75] Subsequently, Enyong and Moasser reported the use of $[Ru(p\text{-cymene})Cl_2]_2$ in combination with amino acid-derived ligand **154**, which was found to enable the alkylation of a large number of primary and secondary amines at temperatures between 45 and 65 °C, but a large excess of the alcohol partner was required. Increased catalyst loading was found to enable the alkylation of secondary amines **150**/**151** at room temperature (**Scheme 1.32B**).[76]



Scheme 1.32: (A) *Hydrogen borrowing alkylation reaction at 50 °C, developed by Martín-Matute.*[75] ***(B)*** *Room temperature hydrogen borrowing catalysis for the alkylation of secondary amines, reported by Enyong and Moasser.*[76]

Huynh and Seayad developed *N*-heterocyclic carbene ruthenium complex **159** for the alkylation of amines with primary alcohols under hydrogen borrowing conditions. Several primary and secondary amines were alkylated in good to excellent yields and the synthesis of fendiline (**158**), a calcium channel blocker, was demonstrated (**Scheme 1.33A**).[77] Marichev and Takacs also

reported the ruthenium-catalysed hydrogen borrowing alkylation of amines with secondary alcohols. Upon employment of diols bearing both a primary and secondary alcohol **160**, the hydrogen borrowing reaction took place selectively at the primary alcohol, enabling a two-step synthesis of diamines **162** bearing two different substituents (**Scheme 1.33B**). Despite the use of an enantiopure catalyst **163**, no asymmetric induction was observed during this work.[78]

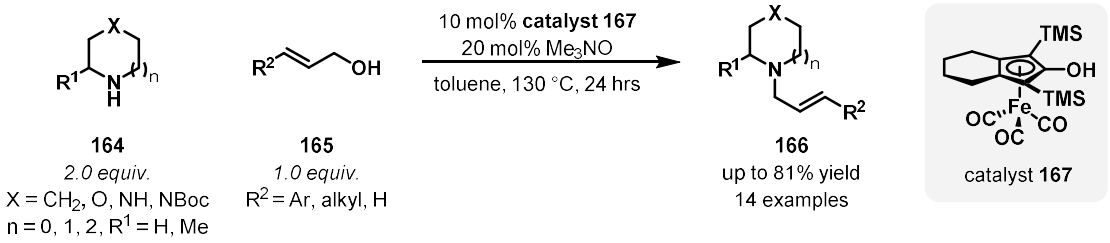


Scheme 1.33: (A) *Synthesis of fendiline under ruthenium-catalysed hydrogen borrowing conditions.*[77] ***(B)*** *Regioselective diamination of alcohols* ***160*** *under hydrogen borrowing catalysis.*[78]

Earth-abundant metal catalysts

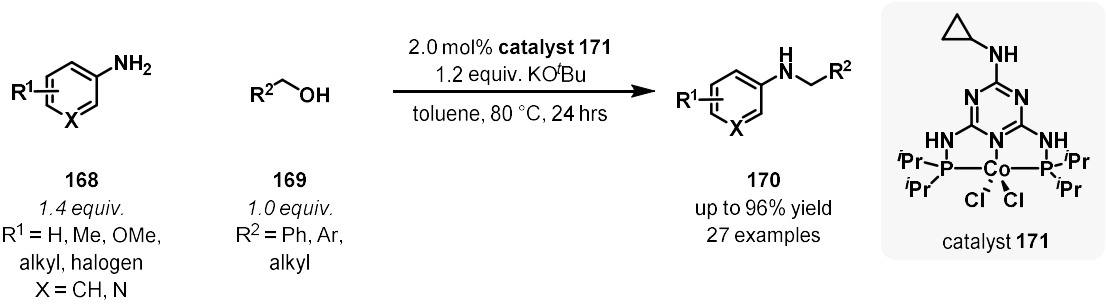
The majority of hydrogen borrowing alkylations of amines employ catalysts based on precious metals such as iridium and ruthenium. However, examples using earth-abundant metals such as iron, manganese, cobalt, nickel and copper have begun to emerge.[79] The first example of iron-catalysed hydrogen borrowing for *N*-alkylation was reported by Feringa and Barta, who employed Knöckler's catalyst **167** for the alkylation of a range of aromatic and benzyl amines (**Scheme 3.9, Section 3.1**).[80] Sandararaju and co-workers also employed Knöckler's catalyst **167** for *N*-alkylation using allyl alcohols **165**, which is noteworthy because no side reactions of the allyl

alcohols were observed (**Scheme 1.34**).[81] Further iron-catalysed examples followed from a number of groups including Wills,[82,83] Zhao,[84] Kirchner[85,86] and Morrill.[87]



Scheme 1.34: *Iron-catalysed alkylation of secondary amines using allyl alcohols.*[81]

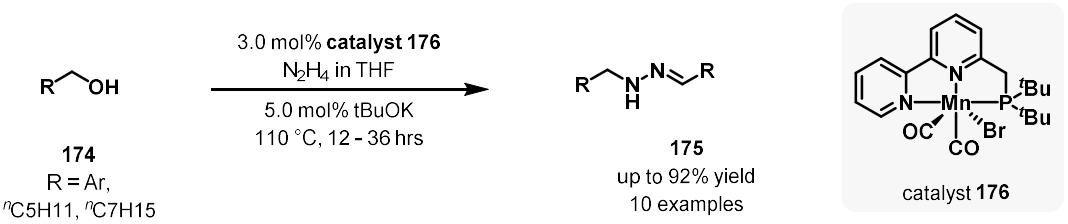
The first homogeneous cobalt-catalysed amine alkylation was reported by Kempe and co-workers who developed cobalt(II) PNP complex **171** for the alkylation of a range of aromatic amines **168** at 80 °C (**Scheme 1.35**).[88] This work was subsequently built upon by the groups of Kirchner,[89] Zhang and Zheng,[90] who employed similar PNP complexes to alkylate various aryl and aliphatic amines with primary and secondary alcohols. More recently, Balaraman and Liu developed catalytic systems involving $CoCl_2 \bullet 6H_2O$ and $Co(acac)_2$, in combination with readily available phosphine ligands, which allowed for the alkylation of a range of amines in good yields.[91]



Scheme 1.35: *Cobalt-catalysed alkylation of aromatic amines.*[88]

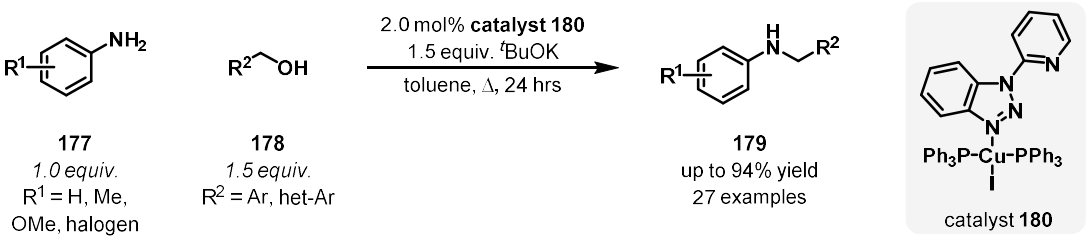
Manganese-catalysed hydrogen borrowing catalysis for amine alkylation was first reported in 2016 by Beller and co-workers, who developed a manganese PNP pincer complex and demonstrated the alkylation of a wide range of aromatic amines in high yields, including methylation using methanol as the reaction solvent.[92,93] Mono-methylation of anilines was also

demonstrated by Sortais and co-workers in 2017, also through the use of a manganese PNP pincer complex.[94] An interesting recent report from Milstein and co-workers involved development of novel Mn(^{t}Bu-PNN) catalyst **176** for the alkylation of hydrazine to yield hydrazones **175** (**Scheme 1.36**). The reaction was termed a partial hydrogen borrowing process, involving one acceptorless dehydrogenative coupling cycle and one hydrogen borrowing cycle. Notably, the product retains the C=N bond and is not fully reduced.[95]



Scheme 1.36: *Double alkylation of hydrazine under manganese-catalysed hydrogen borrowing conditions.*[95]

To the best of our knowledge, there has been just one report of copper-catalysed hydrogen borrowing *N*-alkylation to date. In 2017, Wang and co-workers reported the use of triazole-phosphine-copper catalysts for the alkylation of anilines **177** with benzyl alcohols **178** (**Scheme 1.37**). This catalytic system was also applied to the synthesis of a number of 1*H*-benzo[d]imidazole derivatives.[96]



Scheme 1.37: *Copper-catalysed hydrogen borrowing alkylation of anilines* ***177****.*[96]

Earth-abundant metal catalysts for *N*-alkylation are a relatively recent development in the field of hydrogen borrowing. However, the use of sustainable catalysts is an important endeavour for the future of hydrogen borrowing.

1.4 Project aims

The overall aim of the research presented in this thesis was to investigate and develop novel catalytic methodology for the synthesis of nitrogen heterocycles, primarily the small, saturated ring systems; azetidines, pyrrolidines and piperidines. This was broken down into two mechanistically distinct projects:

1. The application of photoredox catalysis to the synthesis of azetidines, *via* a radical anion [2+2] reaction (**Chapter 2**).
2. Hydrogen borrowing catalysis for the synthesis of pyrrolidines and piperidines by double nitrogen alkylation, using diols as the alkylating agents. This work involved the synthesis of a range of piperidines (**Chapter 3**), followed by development of stereoselective hydrogen borrowing conditions for the synthesis of enantioenriched piperidines and pyrrolidines (**Chapter 4**).

Chapter 2: Photoredox Catalysis for the Synthesis of Azetidines

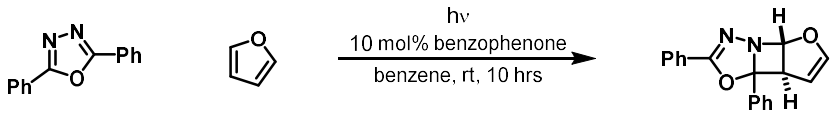
2.1 Introduction

4-Membered nitrogen heterocycles are important biologically active compounds (for examples, see **Section 1.1.1**) but have attracted much less attention from the chemical community than their 5- and 6-membered analogues.[25] For this reason it is important to develop novel methods for their construction.

In recent years, photoredox catalysis has emerged as a powerful tool in synthetic organic chemistry.[97] A range of stable metal polypyridyl complexes have been developed and applied to a wide variety of chemical transformations.[98] Irradiation with visible light generates a photoexcited state, which typically undergoes a single-electron-transfer (SET) process with the substrate, thus enabling the generation of reactive intermediates under relatively mild conditions.[99]

2.1.1 Photochemical azetidine synthesis

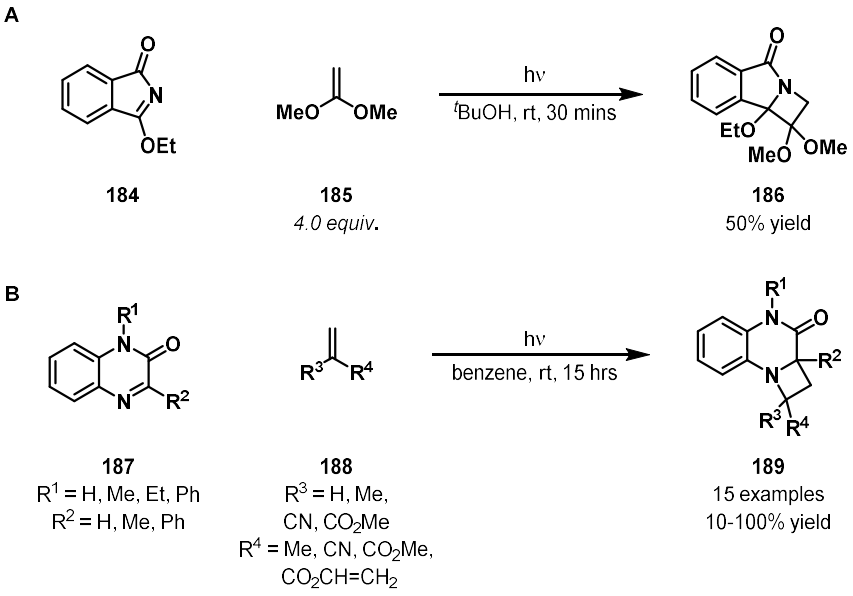
Cycloaddition of a C=N bond and a C=C bond is an attractive disconnection for the synthesis of azetidines, and the first such example was reported by Tsuge and co-workers in 1968. The photocycloaddition of 2,5-diphenyl-1,3,4-oxadiazole **181** with indene was affected by irradiation with a 300 W high-pressure mercury lamp and was proposed to proceed through an excited triplet state. This work was later expanded to include the cycloaddition reaction with furan **182** to yield azetidine **183** (**Scheme 2.1**).[100,101]



181 **182** *excess* **183** 26% yield

Scheme 2.1: *Photocycloaddition of 2,5-diphenyl-1,3,4-oxadiazole **181** with furan **182**, reported by Tsuge and co-workers in 1973.*[101]

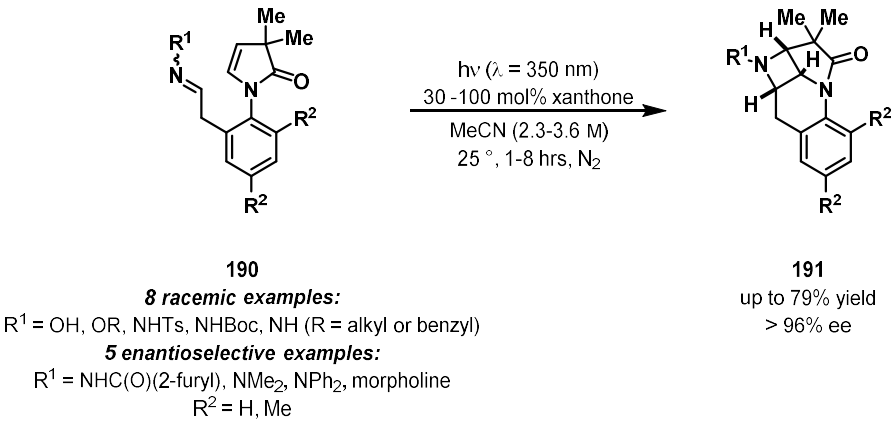
In the following years, a number of photocycloaddition syntheses of azetidines were reported, although in all cases, high energy UV light was employed. For example, Swenton and Hyatt found that the C=N bond of an aza-uracil could be reacted with an electronically diverse range of simple alkenes in high yield and regioselectivity.[102,103] Koch and co-workers also reported a number of photocycloaddition reactions involving C=N bonds, such as the reaction of 3-ethoxyisoindole **184** with 1,1-dimethoxyethene **185** to yield cycloadduct **186** in 50% yield (**Scheme 2.2A**). A number of other alkenes, for example cyclohexene and butene were also employed and gave modest yields of the corresponding azetidines.[104] Subsequently, the UV light-mediated (450 W) reaction of 2-aryl-2-oxazolidin-4-ones and 1,1-dimethoxyethene **185** was reported to give rise to azetidines up to 75% yield.[105] Nishio reported the [2+2] photocycloadditon of quinoxaline-2(1*H*)-ones **187** and electron deficient alkenes **188**, such as acrylonitriles and acrylates, under irradiation from a high-pressure mercury lamp (**Scheme 2.2B**).[106]



Scheme 2.2: *Photocycloadditions of* ***(A)*** *3-ethoxyisoindole* ***184*** *and* ***(B)*** *photocycloaddition of quinoxaline-2-(1H)-ones and electron deficient alkenes reported by Nishio.*[106]

The Sivaguru group have recently reported the first intramolecular aza-Paternò-Büchi reaction of enamides and imines.[107] The reaction employs xanthone as a triplet sensitiser (E_T = 74 kcal mol^{-1})

and is carried out under UV light (λ = 350 nm) in a Rayonet reactor. Hydrazines, oximes and hydrazones **190** were well tolerated and led to the formation of azetidines **191** in high yield and diastereoselectivity. In the case where the starting materials were enantioenriched, efficient axial-to-point chirality transfer generated the products as single diastereomers and without significant erosion of ee (**Scheme 2.3**).[107]



190
8 racemic examples:
R^1 = OH, OR, NHTs, NHBoc, NH (R = alkyl or benzyl)
5 enantioselective examples:
R^1 = NHC(O)(2-furyl), NMe_2, NPh_2, morpholine
R^2 = H, Me

191
up to 79% yield
> 96% ee

Scheme 2.3: *Intramolecular aza-Paternò-Büchi reaction of enamides with oximes, hydrazones and hydrazines, developed by Sivaguru and co-workers.*[107]

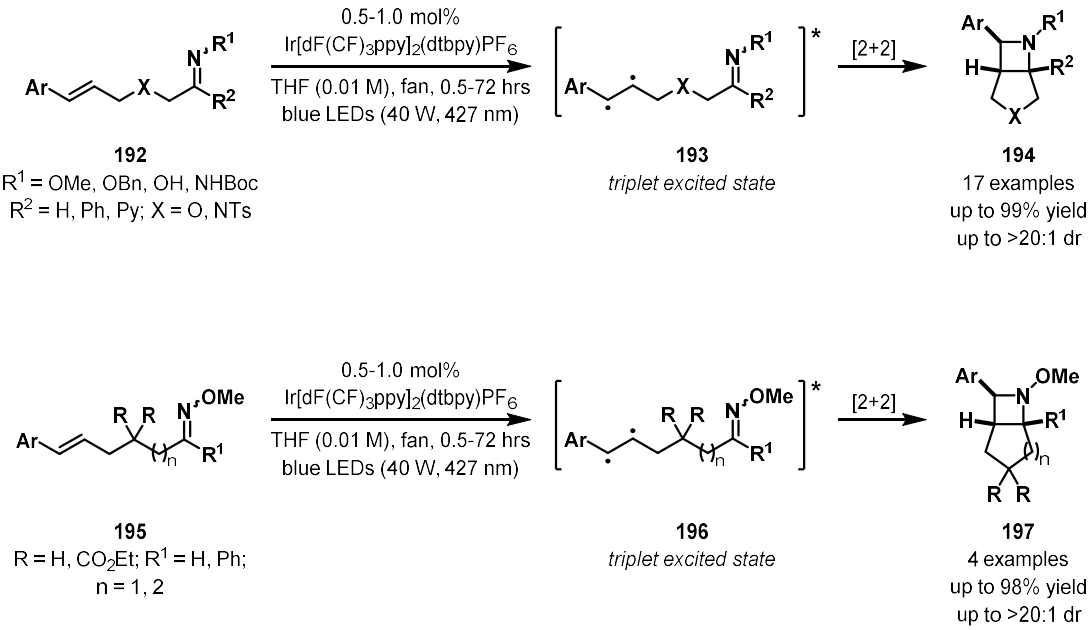
In general, reports of photocycloadditions of C=N and C=C bonds to generate azetidines employ high-energy UV light and visible light mediated reactions have remained elusive until very recently. In addition, the imine functionality is typically conjugated with an electron withdrawing group, as in the work of Tsuge,[100,101] Swenton and Hyatt,[102,103] Koch[104,105] and Nishio.[106] In more recent work from Sivaguru and co-workers,[107] stabilised C=N bonds in the form of oximes and hydrazones are employed. At the outset of our studies, photoredox-mediated cycloaddition for azetidine synthesis had not been reported. During our work on photoredox mediated azetidine synthesis (**Sections 2.5–2.8**), Schindler and co-workers reported the visible light mediated aza-Paternò-Büchi reaction. [108]

2.1.2 Visible light mediated azetidine synthesis *via* cycloaddition

Challenges inherent to the photoexcitation of imines means that, to date, few aza-Paternò-Büchi reactions have been realised.[107] It is known that excited state imines undergo radiationless decay

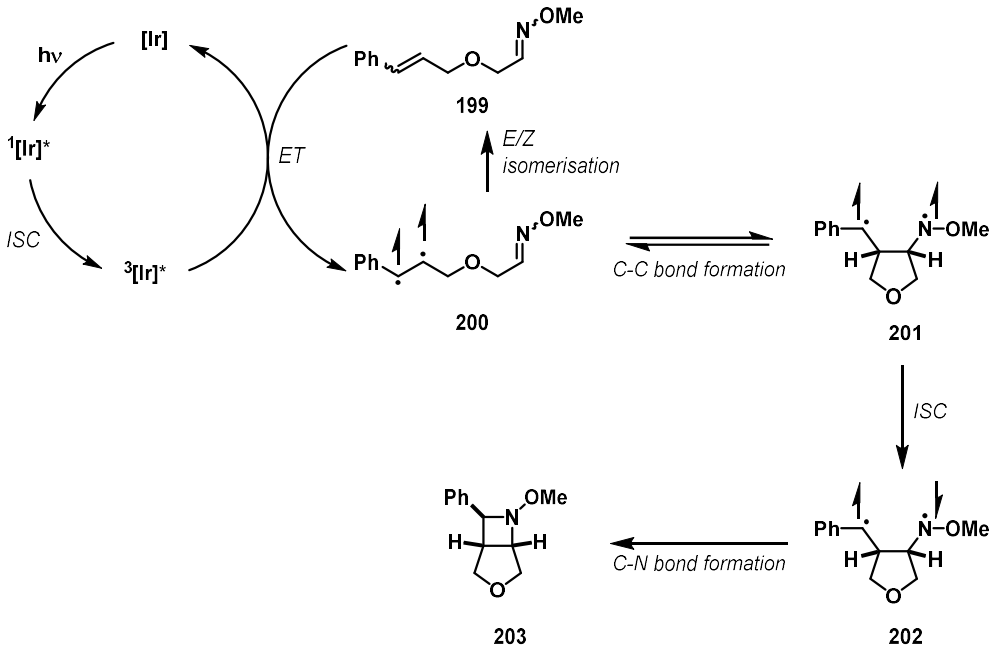
by rotation around the C=N π-bond, which results in dissipation of electronic energy and lack of reactivity in [2+2] reaction with alkenes. Successful cases tend employ high energy UV light and involve rigid systems which are predisposed for cyclisation.

In 2019, the Schindler group reported the synthesis of azetidines *via* a visible light mediated aza-Paternò-Büchi reaction. A large number of fused azetidines **194**/**197** were synthesised from the corresponding oximes and hydrazones **192** (**Scheme 2.4**). The styrene moiety was found to be essential for productive quenching of the photocatalyst excited state and both electron-rich and -poor styrenes were well tolerated. It was noted that the reaction is stereoconvergent and both *E* and *Z* isomers of the styrene gave the same diastereomer of the product. Alkyl, ether and amine tethers could be utilised to give rise to excellent yields and diastereoselectivity (**Scheme 2.4**). A small number of ketoximes were also shown to undergo cycloaddition, although extended reaction time was required.[108]



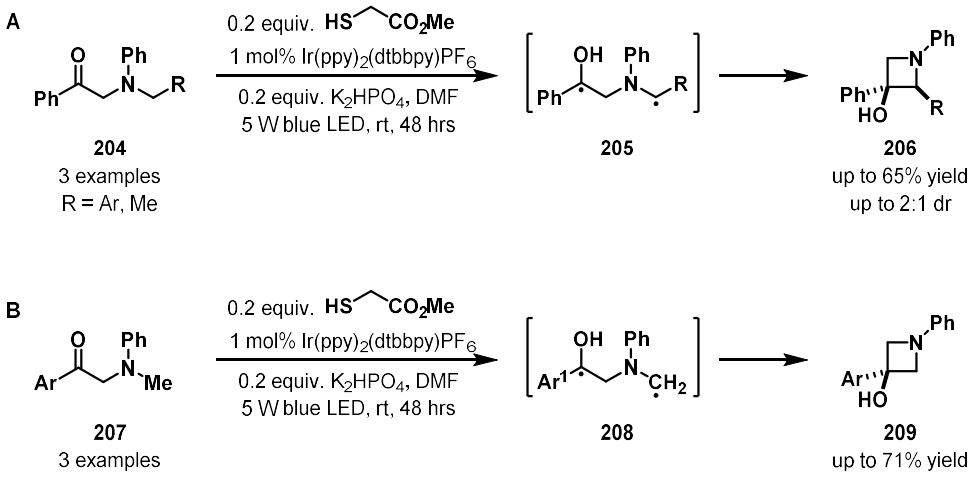
Scheme 2.4: *Light-mediated triplet energy transfer aza Paternò-Büchi reaction for the construction of azetidines.*[108]

A mechanism involving triplet energy transfer was proposed rather than a photoredox process. Energy transfer from the photoexcited catalyst to styrene **199** was thought to give rise to triplet **200**, which also allows for rapid interconversion of *E* and *Z* isomers of substrate **199.**[109] Reversible C–C bond formation gives rise to 1,4-diradical **201**, and following intersystem crossing (**202**), the observed azetidine product **203** is formed (**Scheme 2.5**).[108]



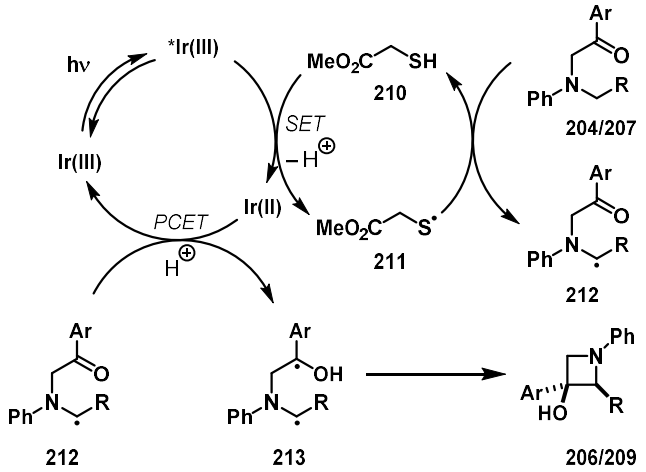
Scheme 2.5: *Proposed mechanism for visible light-enabled aza Paterno-Buchi reaction by Schindler and co-workers.*

Previously, a visible light-mediated synthesis of saturated nitrogen heterocycles was published by Zhu and co-workers, who developed a photoredox catalysed radical-radical coupling reaction for the construction of pyrrolidines, piperidines and azetidines. For example, the use of *N*-benzyl and *N*-ethyl substrates **204** led to the formation of tri-substituted azetidines **206** (**Scheme 2.6A**), whereas employment of *N*-methyl amines **204** lead to the generation of di-substituted products **209** in good yields (**Scheme 2.6B**).[110]



Scheme 2.6: *Photochemical generation of biradical **205/208** leads to the formation of **(A)** trisubstituted azetidines **206** and **(B)** disubstituted azetidines **209**.*[110]

The authors proposed a mechanism in which the iridium(III) photocatalyst is excited by irradiation and the excited state species engages with methyl 2-mercaptoacetate **210** to generate thiyl radical **211** *via* SET. Thiyl radical **211** can then abstract a hydrogen atom from the substrate **204**/**207** to give α-amino radical **212**. Simultaneously, proton-coupled electron transfer from the reduced catalyst species was proposed to give rise to ketyl radical **213** whilst regenerating the catalyst. Radical recombination leads to the observed azetidine products **206**/**207** (**Scheme 2.7**). Control reactions were carried out to support the proposed mechanism but do not rule out the possibility of a Norrish type II mechanism.

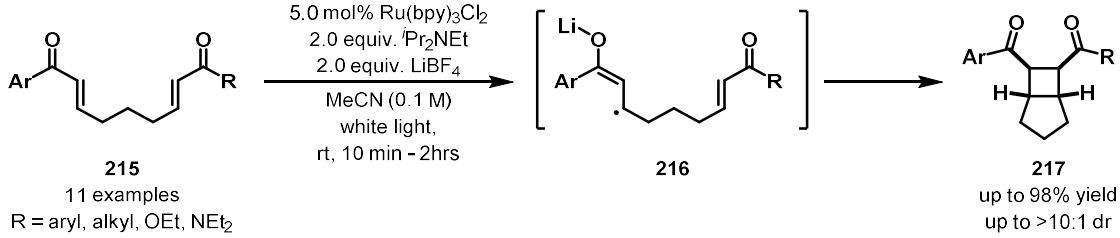


Scheme 2.7: *Proposed mechanism for the photoredox mediated radical-radical coupling cyclisation reaction published by Zhu and co-workers.*[110]

2.1.3 Synthesis of cyclobutanes under visible light photocatalysis

Photochemical [2+2] addition of C=C bonds represents an efficient method for the construction of cyclobutanes.[111] Early reports from Ledwith and co-workers involved initiation with metal salts,[112] and later triaryl amine radical cation initiation was employed by Bauld and co-workers.[113] Recently, the photoredox catalysed cycloaddition of styrenes has been realised using visible light by the groups of Nicewicz[120] and Yoon.[111]

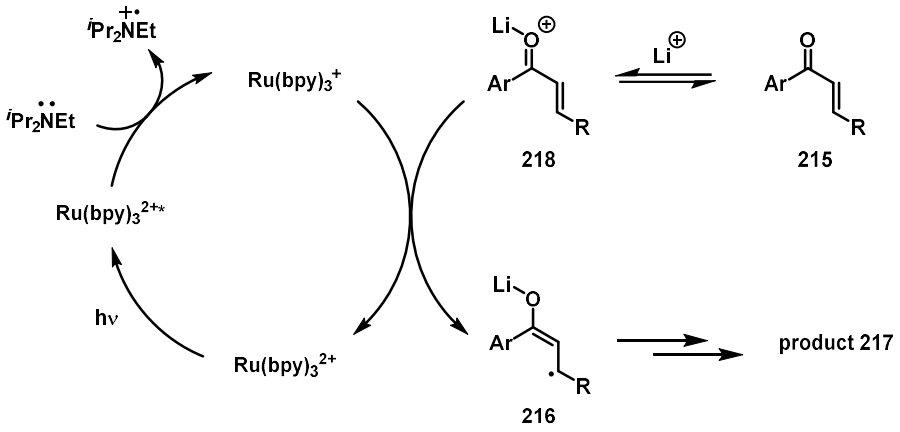
Yoon and co-workers also developed efficient methodology for the [2+2] cycloaddition of enones under visible light catalysis. This was initially demonstrated with bis-enone **215**, which was found to undergo [2+2] cycloaddition to form bicyclic system **217** in high yield and diastereoselectivity (**Scheme 2.8**). The cycloaddition was proposed to go *via* radical anion **216** and a range of bis-enones were found to give rise to cyclobutanes **217** in high yields and diastereoselectivity. The photocatalyst $Ru(bpy)_3Cl_2$ was excited by irradiation with a 23 W household light bulb, in the presence of $LiBF_4$ and $^{i}Pr_2NEt$. It was found that at least one of the enone R groups must be aromatic to enable reduction and therefore, successful reaction. This was attributed to the more positive reduction potential of such systems relative to aliphatic enones, in which it was not possible to generate the required radical anion.[114]



Scheme 2.8: *Yoon and coworker's photoredox-mediated intramolecular cycloaddition of bis-enone **215**, proposed to go via radical anion intermediate **216**.*[114]

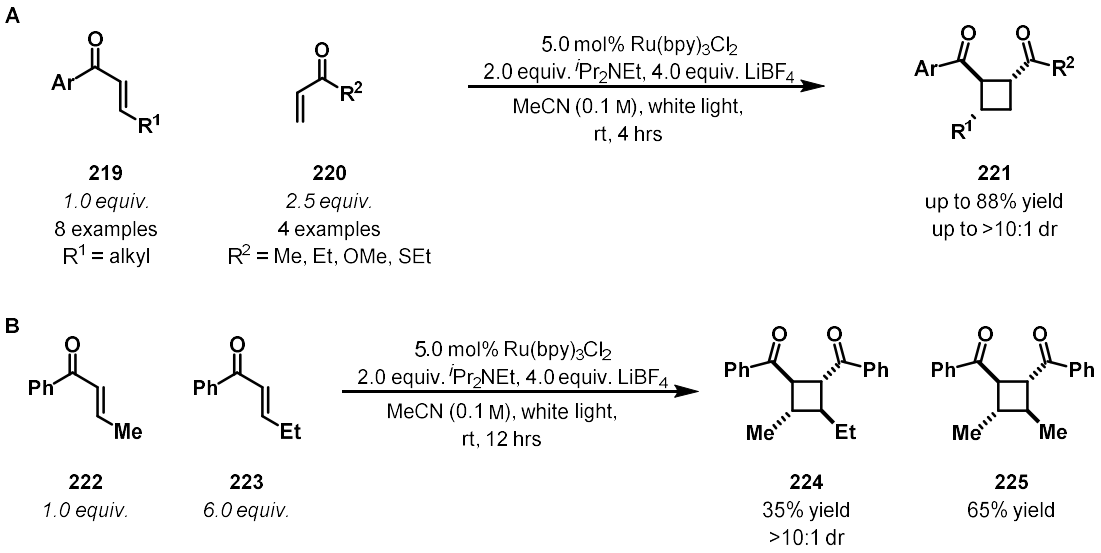
Control reactions were used to confirm the importance of the catalyst and additives; no reaction was observed in the absence of $Ru(bpy)_3Cl_2$ or in the dark, which confirmed that the reaction is initiated by photoexcitation of the catalyst. In the absence of $^{i}Pr_2NEt$, no reaction was observed

which implied that the catalytically relevant species is $Ru(bpy)_3^+$, which is formed upon reductive quenching of the photoexcited state ($Ru(bpy)_3^{2+}$) by the amine. Lastly, $LiBF_4$ was found to be essential to produce a homogeneous reaction mixture since $Ru(bpy)_3Cl_2$ is only sparingly soluble in anhydrous acetonitrile. This was attributed to the formation of a more soluble $Ru(bpy)_3(BF_4)_2$ species *in situ*. The presence of the lithium cation was also found to be important and it was proposed that Li^+ acts as a Lewis acid to activate the enone towards one-electron reduction (**Scheme 2.9**).[114]



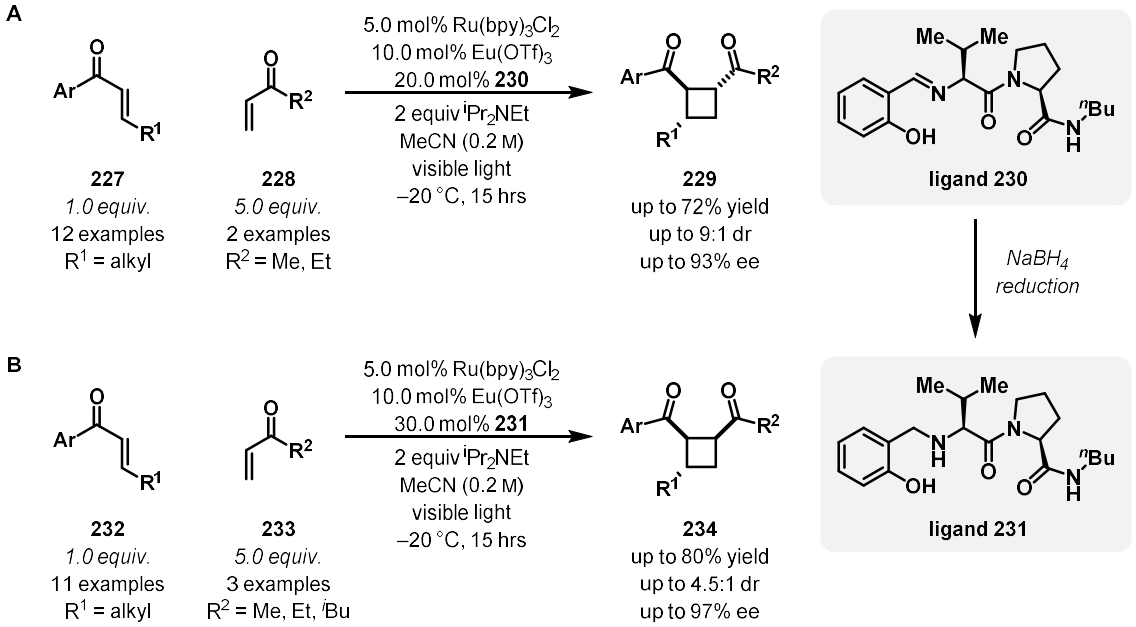
Scheme 2.9: *Proposed mechanism of formation of radical anion* ***216*** *by Yoon and co-workers.*[114]

This concept was subsequently applied to the intermolecular reactions of untethered enones **219**. As in previous work, an aromatic enone was required to act as the electrophore in this process. The resulting radical anion was coupled with a range of Michael acceptors and it was a requirement that this Michael acceptor was (a) more reactive towards the radical anion than enone **219** to minimise unwanted dimerisation of **219** and (b) not susceptible to reduction under the photoredox conditions. A range of trisubstituted cyclobutanes **221** were synthesised in good yields and, in most cases, >10:1 dr (**Scheme 2.10A**). Michael acceptors bearing β-substituents, such as **223**, were found to be less reactive due to steric hindrance and hence the dimerisation of **222** was seen to dominate (**Scheme 2.10B**).[115]



Scheme 2.10: (A) *Reation of aryl enones with a range of Michael acceptors gives rise to tri-substituted cyclobutane products.* ***(B)*** *α-Substituents lead to lower yields and* ***(C)*** *β-substituents cause formation of dimer* ***225*** *to predominate.*

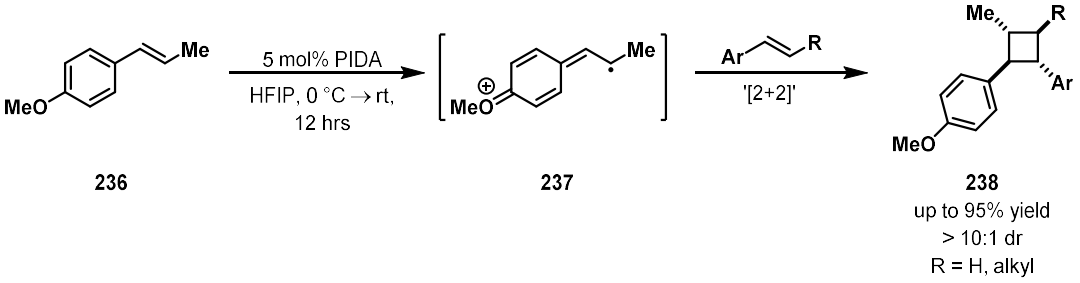
Subsequently, Yoon and co-workers developed their photoredox system to achieve enantioselective cyclobutane synthesis through the addition of a Lewis acid co-catalyst, $Eu(OTf)_3$, and chiral ligand **230**. A range of electronically diverse aryl enones **227** were coupled with vinyl ketones **228**. The trisubstituted cyclobutane products **229** were isolated in moderate to good yields and diastereoselectivity, with high levels of enantioselectivity (**Scheme 2.11A**). Reduction of ligand **230** with $NaBH_4$ gave rise to ligand **231** which was employed in the reaction and found to result in formation of the 1,2-*cis* diastereomers **234** (**Scheme 2.11B**).[116]



Scheme 2.11: *Enantioselective [2+2] photocycloadditions to furnish* ***(A)*** *all-trans cyclobutanes and* ***(B)*** *1,2-cis cyclobutanes.*[116]

2.2 Results and Discussion: Preliminary work

Previous work in the Donohoe group showed that cyclobutanes **238** can be synthesised *via* dimerisation of styrenes, initiated by catalytic quantities of hypervalent iodine oxidants, for example phenyliodine(III) diacetate (PIDA). The use of a fluorinated alcohol solvent, such as 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) or 2,2,2-trifluoroethanol (TFE), was found to be essential. [117] This was attributed to formation of a strongly hydrogen-bonded adduct, which increased the oxidising ability of PIDA.[118] It was a requirement that at least one alkene partner be electron-rich, and tri- and tetra-substituted cyclobutanes were synthesised in high yields and diastereoselectivity (**Scheme 2.12**). It was proposed that the reaction was initiated by single-electron oxidation of the styrene to form radical cation **237**, which then engaged in [2+2] reaction with another styrene molecule.[117]



Scheme 2.12: *Cycloaddition of styrenes via hypervalent iodine mediated single-electron oxidation.* [117]

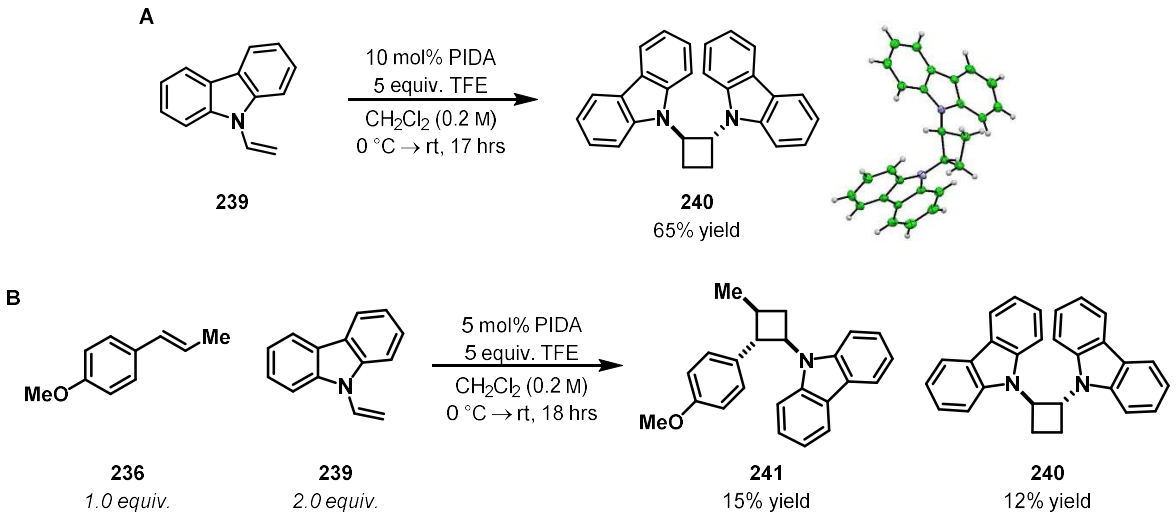
2.2.1 Preliminary project aims

The preliminary project aimed to extend the hypervalent iodine-mediated cyclobutane synthesis, previously developed in the group, to the synthesis of cyclobutanes bearing heteroatom substituents.[119] In the interest of conciseness, this project will not be discussed in detail. However, this early work directly inspired the photochemical project which is the main focus of this chapter. Therefore, the key results from this preliminary project are outlined briefly in the following sub-sections.

2.2.2 Results and Discussion: Nitrogen-substituted cyclobutanes

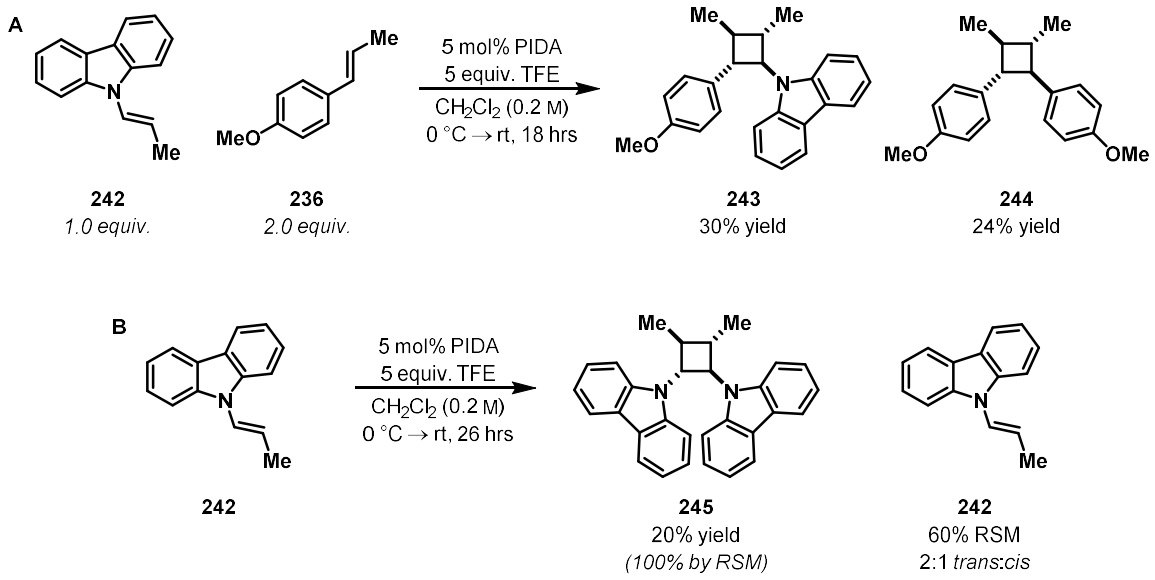
The dimerisation of *N*-vinylcarbazole (NVC) was one of the first examples of cyclobutane synthesis *via* [2+2] cycloaddition of alkenes, published by Ledwith and co-workers in 1969.[112] This transformation was catalysed by cerium(IV) or iron(III) salts and was proposed to proceed through a radical cation species. More recently, the dimerisation of NVC has been demonstrated under visible light photocatalysis conditions by Nicewicz and co-workers.[120]

We found that initial attempts to dimerise NVC **239** under our conditions using catalytic PIDA in HFIP led to polymerisation of NVC **239**. It is known that poly(*N*-vinylcarbazole) can be generated under acid catalysed polymerisation conditions, and it was suspected that the acidic nature of HFIP (pK_a = 9.3[121]) had led to the polymerisation of NVC.[122,123] Trifluoroethanol (TFE) is less acidic than HFIP (pK_a = 12.3[124]) and it was found that 5 equiv. TFE and 10 mol% PIDA led to formation of cyclobutane **240** in 65% yield (**Scheme 2.13A**). The structure of cyclobutane **240** was found to match literature NMR data and was confirmed by X-ray crystallography, which indicated *trans* geometry. Under similar conditions, NVC **239** was reacted with *trans*-anethole **236** to furnish cyclobutane **241** in 15% yield, but NVC dimer **240** was also isolated in 12% yield (**Scheme 2.13B**).



Scheme 2.13: (A) *Dimerisation of NVC to yield cyclobutane* ***240*** *and X-ray crystal structure.* ***(B)*** *Reaction of trans-anethole and NVC. trans-Anethole and TFE were added by syringe pump over 2 hours.*

Bauld and co-workers demonstrated the cycloaddition of *trans-N*-(propen-1-yl)carbazole (NPC) **242** and *trans*-anethole **236** using catalytic tris(4-bromophenyl)aminium hexachloroantimonate as an initiator.[125] Under our conditions, it was found that syringe pump addition of NPC **242** to a solution of *trans*-anethole **236**, PIDA and TFE in CH_2Cl_2 and gave rise to 30% yield of cyclobutane **243**, alongside 24% yield of *trans*-anethole dimer **244** (**Scheme 2.14A**). Under these conditions, NPC **242** was found to dimerise and gave rise to cyclobutane **245** in 20% yield. The residual starting material **242** was found to have a reduced *trans*:*cis* ratio upon re-isolation, which may suggest that only the *trans* isomer was reactive under our conditions (**Scheme 2.14B**).

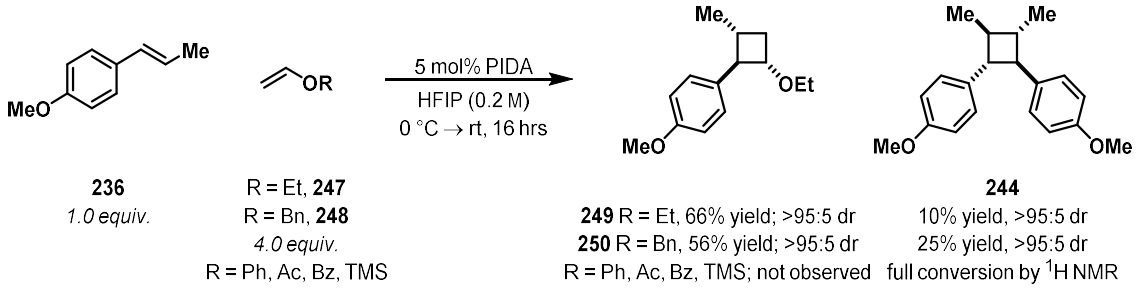


***Scheme 2.14: (A)** Reaction of NPC **242** and trans-anethole **236**. All-trans geometry of **243** assigned based on observed nOe correlations. All-trans geometry of **244** assigned by comparison to literature data.[117] **(B)** Dimerisation of NPC **242.** all-Trans geometry was assigned based on analogy to **243** and **244**.*

2.2.3 Results and Discussion: Oxygen-substituted cyclobutanes

Further to our studies of cyclobutanes bearing nitrogen substituents, we also wished to investigate the synthesis of oxygen-substituted cyclobutanes. Yoon and co-workers described the reaction of *trans*-anethole **236** with ethyl vinyl ether (EVE) **247** in 67% yield and high diastereoselectivity under photoredox catalysis, and we were interested to apply our conditions to this.[111]

Under our conditions, with 5 mol% PIDA in HFIP, it was found that *trans*-anethole **236** reacted with EVE **247** to give rise to cyclobutanol **249** in 66% yield. However, it was not possible to prevent formation of *trans*-anethole dimer **244**, which was isolated in 10% yield. We investigated a number of alternative vinyl ethers in the hope of expanding the reaction scope. Phenyl vinyl ether, vinyl benzoate, vinyl acetate and trimethyl(vinyloxy)silane did not engage in reaction with *trans*-anethole **236**. However, upon subjection of benzyl vinyl ether (BVE) **248** to the reaction with *trans*-anethole **236**, benzyl-protected cyclobutanol **250** was isolated in 56% yield, with 25% *trans*-anethole dimer **244** (**Scheme 2.15**).



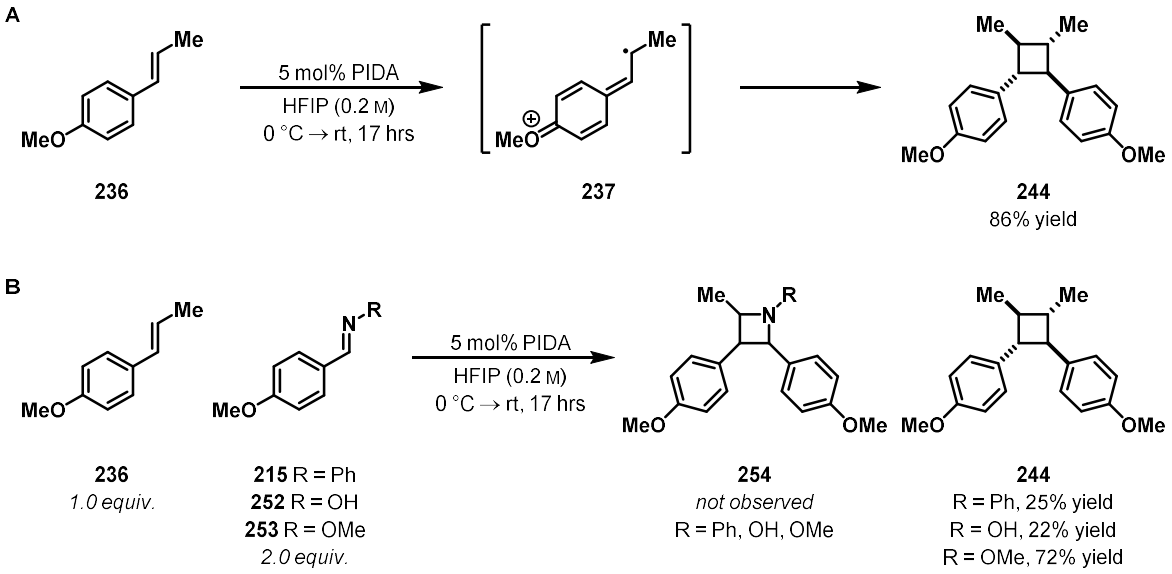
Scheme 2.15: *Synthesis of protected cyclobutanols. All-trans geometry of **250** assigned based on observed nOe correlations, head-to-head dimer assigned by HMBC analysis. All-trans geometry of **249** was assigned by comparison to literature data.*[117]

2.2.4 Results and Discussion: Synthesis of azetidines

Unfortunately, the synthesis of nitrogen- and oxygen-substituted cyclobutanes was not found to be applicable to a wide range of substrates. We subsequently investigated the application of our hypervalent iodine/fluorinated solvent conditions to the synthesis of azetidines. Early results indicated it was not possible to carry out the single electron oxidation of imines under these conditions. However, since *trans*-anethole **236** was known to undergo single electron oxidation in the presence of HFIP and 5 mol% PIDA (**Scheme 2.16A**), we proposed to engage radical cation with imines and oximes to furnish azetidines.[117]

A small range of imines and oximes **251**–**253** were investigated but the desired azetidine products **254** were not observed (**Scheme 2.16B**). Dimerisation of *trans*-anethole **236** was observed,

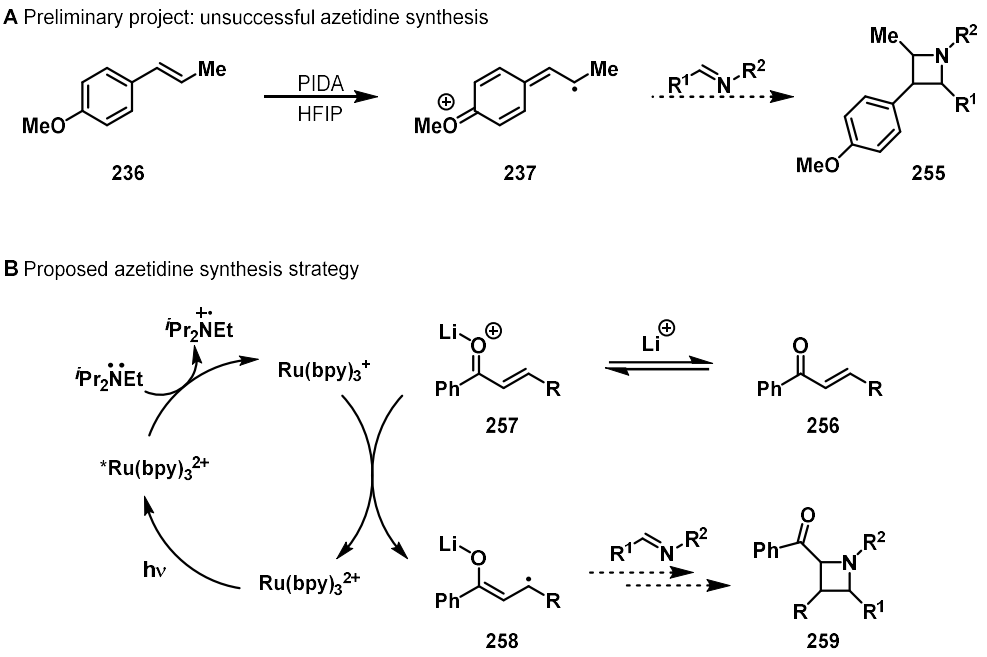
although in lower yield than the reaction in the absence of an imine or oxime partner, which led us to suspect that the presence of a nitrogen-containing electrophile lead to inhibition of the reaction, and hence, this project was not pursued further.



Scheme 2.16: (A) *The dimerisation of trans-anethole proceeds through radical cation* ***237*** *to give cyclobutane* ***244*** *in 86% yield.* ***(B)*** *Reaction of trans-anethole with imine* ***251*** *or oximes* ***252*** *and* ***253*** *led to formation of cyclobutane* ***244****, not the desired azetidine products* ***254****.*

2.3 Project aims

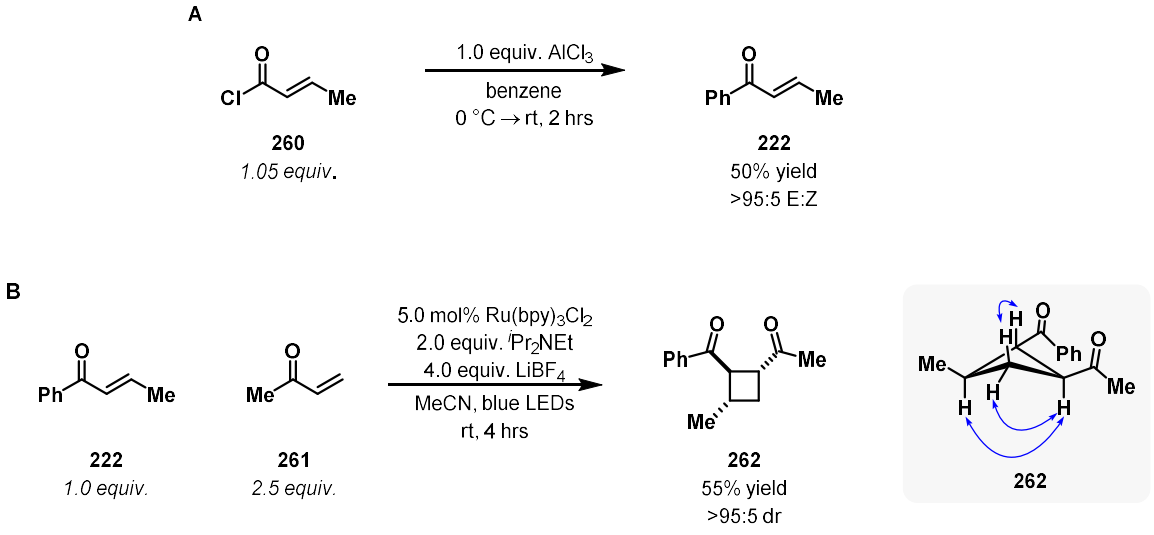
Our attempted hypervalent iodine-mediated synthesis of azetidines was based on the reaction of radical cation **237** with nitrogen-containing electrophiles, such as imines and oximes (**Scheme 2.17A**), but unfortunately this did not lead to the synthesis of azetidines **256**. It was subsequently proposed to reverse the electronics of the system and engage an electron-rich radical with an imine or oxime. Based on Yoon's cyclobutane synthesis (**Section 2.1.3**), we proposed to generate radical anion **216** from aromatic enone **215** under photoredox conditions and react it with imines or oximes to furnish azetidines **257** (**Scheme 2.17B**).[115]



Scheme 2.17: (A) *Previous work involved oxidative formation of radical cation **237** and reaction with a range of imines and oximes.* ***(B)*** *Proposed route to azetidines by generation of radical anion **258** under photoredox conditions and reaction with nitrogen electrophiles.*

2.4 Results and Discussion: Repeat of Yoon's example

At the outset of our investigations, it was prudent to carry out a repeat of Yoon's cyclobutane formation from enone **222** and methyl vinyl ketone (MVK) **261** in order to check that radical **258** could be formed in our hands. Enone **222** was synthesised in 50% yield by Friedel-Crafts reaction of *trans*-crotonyl chloride **260** with benzene, in the presence of stoichiometric aluminium trichloride (**Scheme 2.18A**).[126] Alkene geometry was confirmed by ^{1}H NMR spectroscopy; the alkene protons (7.07 and 6.90 ppm) were found to couple to each other with J = 15.3 Hz, which was indicative of *trans* geometry. Enone **222** was successfully cross-dimerised with methyl vinyl ketone (MVK) **261** under Yoon's conditions; 5 mol% $Ru(bpy)_3Cl_2$, 2.0 equiv. $^iPr_2NEt$, 4.0 equiv. $LiBF_4$, 0.1 M in acetonitrile and under irradiation with blue LEDs. Cyclobutane **262** was isolated in 55% yield and >95:5 dr, and the spectroscopic data was consistent with the literature.[114] All-*trans* geometry was confirmed by nOe analysis (**Scheme 2.18B**).

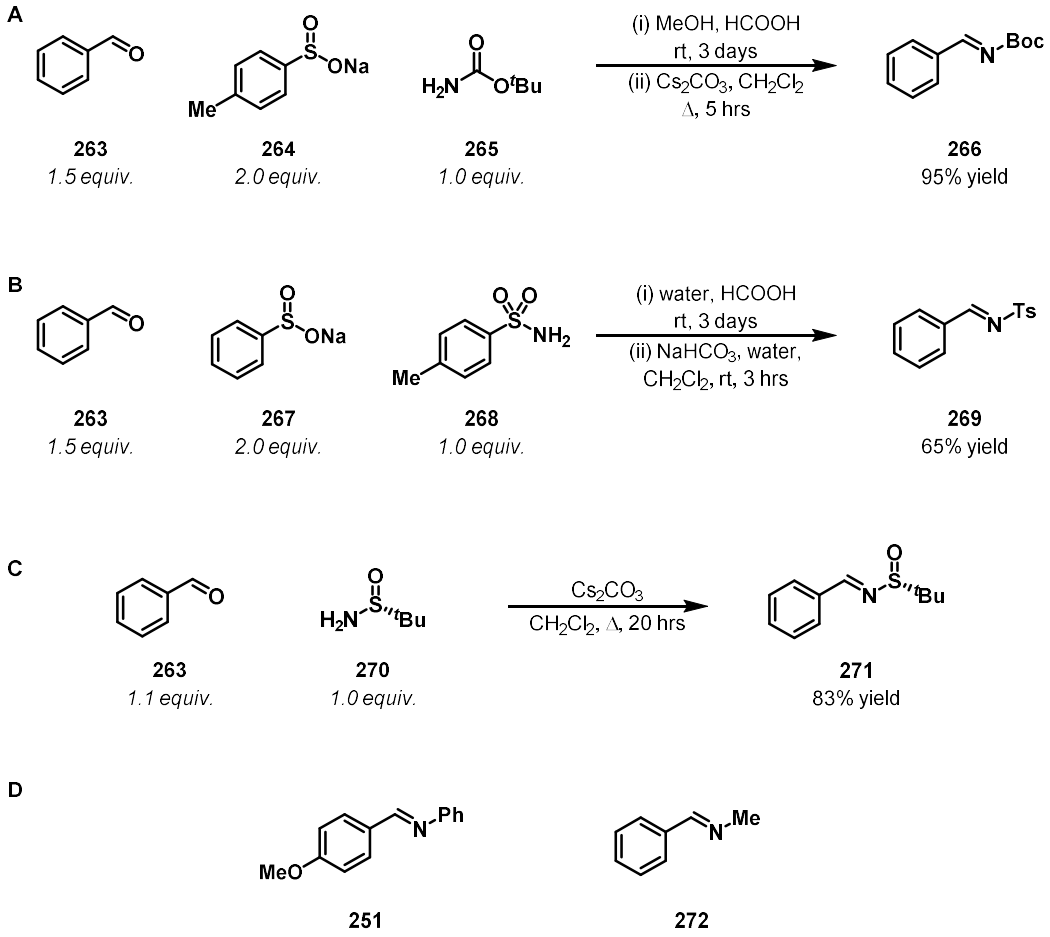


***Scheme 2.18: (A)** Synthesis of trans-enone **222** via Friedel-Crafts reaction. **(B)** Repeat of Yoon's cross-dimerisation between enone **222** and MVK. Blue arrows indicate observed nOe correlations[114]*

The synthesis of cyclobutane **262** verified that radical **258** was formed under our photochemical reaction setup and so we were able to embark upon efforts to engage radical **258** with nitrogen-containing electrophiles.

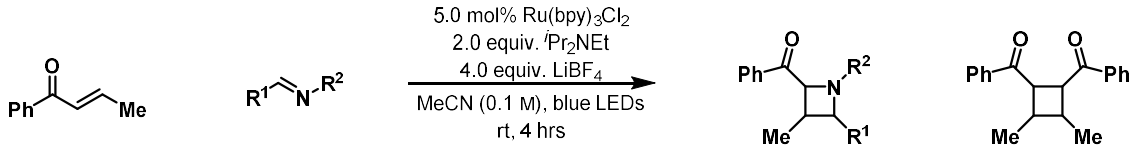
2.5 Results and Discussion: Reaction with imines

A number of benzaldehyde-derived imines were synthesised; initially it was proposed that an electron-withdrawing *N*-protecting group would be required in order to promote radical addition to the electron-deficient C=N bond. *N*-Boc imine **266**, *N*-tosyl imine **269** and Ellman's sulfinamide imine **271** were synthesised from benzaldehyde **263** using literature known procedures, which proceeded to give the corresponding imines in good yields (**Scheme 2.19A, B & C**).[127,128,129] Phenyl and methyl protected imines **251** and **272** were purchased from commercial suppliers and used without further purification (**Scheme 2.19D**).



Scheme 2.19: *Synthesis of* ***(A)*** *N-Boc imine* ***266****,* ***(B)*** *N-Tosyl imine* ***269****,* ***(C)*** *Ellman's auxiliary protected imine* ***271*** *and* ***(D)*** *commercially available imines.*[127,128,129]

Subjection of *N*-Boc imine **266** to the photoredox conditions with enone **222** was not observed to lead to the desired azetidine product **273** by ^{1}H NMR spectroscopy. A small amount of cyclobutane **225** resulting from dimerisation of enone **222** was observed, in addition to unreacted starting materials (**Table 2.1**, Entry 1). *N*-Tosyl imine **269** did not lead to azetidine or cyclobutane products and starting materials were returned (**Table 2.1**, Entry 2). Reaction of enone **222** with sulfimine **271** and methyl-protected imine **272** led to full conversion to the enone dimer **225** and the unreacted imines were returned (**Table 2.1**, Entry 3 & 4). Phenyl-protected anisaldehyde imine **251** was also found to not engage in any reactions with enone **222** and a trace of cyclobutane **225** was observed, in addition to unreacted starting materials (**Table 2.1**, Entry 5). In all cases, a small amount (5-10%) of benzaldehyde was identified by the presence of a singlet at 10.00 ppm in the ^{1}H NMR spectrum. This was attributed to hydrolysis of the imine starting materials, possibly under the reaction conditions or during the aqueous work up.



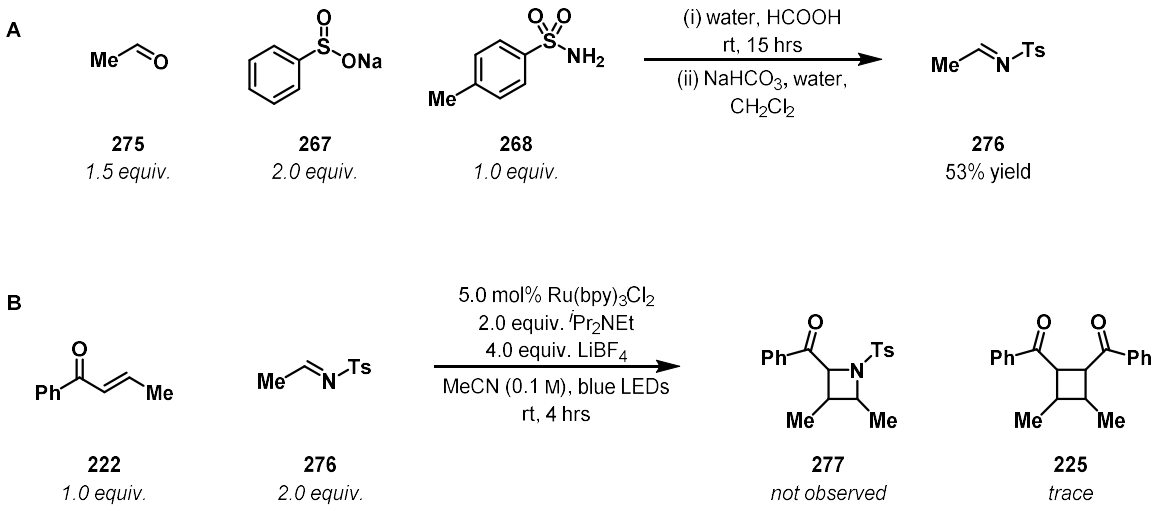
222 *1.0 equiv.* — *2.0 equiv.* — **273** *not observed* — **225**

Entry	Imine	R^1	R^2	**Outcome** (by ^{1}H NMR)
1	**266**	Ph	Boc	Trace of dimer **225**, plus unreacted SMs
2	**269**	Ph	Ts	Unreacted SMs only
3	**271**	Ph	S(O)^{t}Bu	Full conversion to dimer **225**
4	**272**	Ph	Me	Full conversion to dimer **225**
5	**251**	PMB	Ph	Trace of dimer **225**, plus unreacted SMs

Table 2.1: *Attempted reaction of enone **222** with a range of imines under photoredox conditions. Reactions were observed by NMR spectroscopy. PMB = p-methoxybenzene.*

The imines studied thus far were derived from aryl aldehydes and hence have significant steric bulk adjacent to the reaction centre. It was thought that this added bulk may hinder the azetidine formation and so imines bearing smaller substituents were subsequently studied. Imine **276** was synthesised from acetaldehyde **275** in 53% yield (**Scheme 2.20A**).[130] Reaction of ethylidene imine

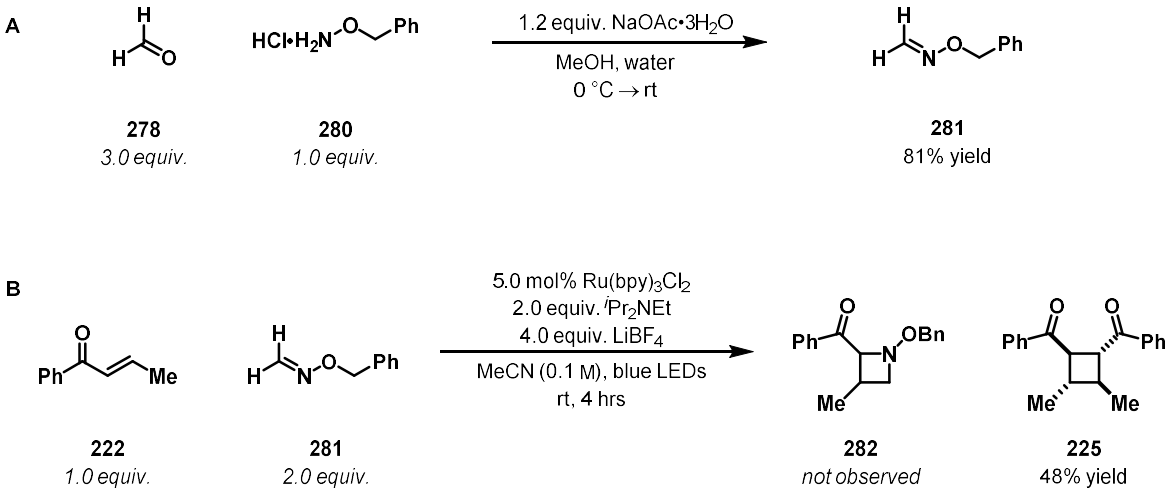
276 and enone **222** under the photoredox conditions was found not to yield any of azetidine **277** despite the decreased bulk of the methyl group (*cf.* benzyladehyde imine **269**). Traces of the dimer **225** were observed by ^{1}H NMR (< 5%), along with enone **222** (**Scheme 2.20B**).



***Scheme 2.20: (A)** Synthesis of ethylidene imine **276** and **(B)** subjection to photoredox conditions with enone **222**.*[130]

Work by Yoon and co-workers was heavily focussed on the synthesis of trisubstituted cyclobutanes. Reaction between two β-substituted enones gave rise to only a low yield of the desired heterodimer, with the major product being the dimer **225** (**Scheme 2.10**, **Section 2.1.3**). It was postulated that a trisubstituted azetidine would be a more accessible target than the previous tetrasubstituted compounds.

Oxime **281** was synthesised by condensation of formaldehyde **278** and benzyl hydroxylamine hydrochloride **280** (**Scheme 2.21A**).[131] However, subjection to the photoredox reaction with enone **222** did not yield the expected azetidine **282** and dimeric cyclobutane **225** was isolated in 48% yield (**Scheme 2.21B**).

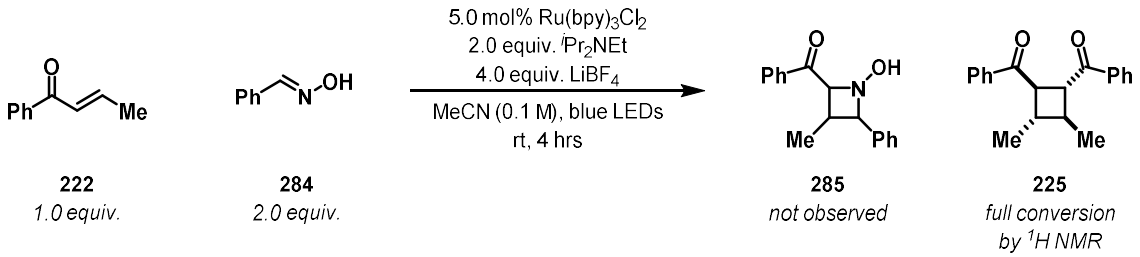


Scheme 2.21: (A) *Synthesis of unhindered oxime* ***281*** *and* ***(C)*** *subjection to the reaction with enone* ***222*** *under photoredox conditions.*

The reaction of enone **222** with imines under photoredox conditions had not been successful for the synthesis of azetidines, despite investigation of a number of electronically and sterically varied imines. Encouragingly, the formation of cyclobutane **225**, resulting from dimerisation of enone **222**, was observed in a number of cases which implied that reduction of enone **222** to generate radical anion **258** had taken place.

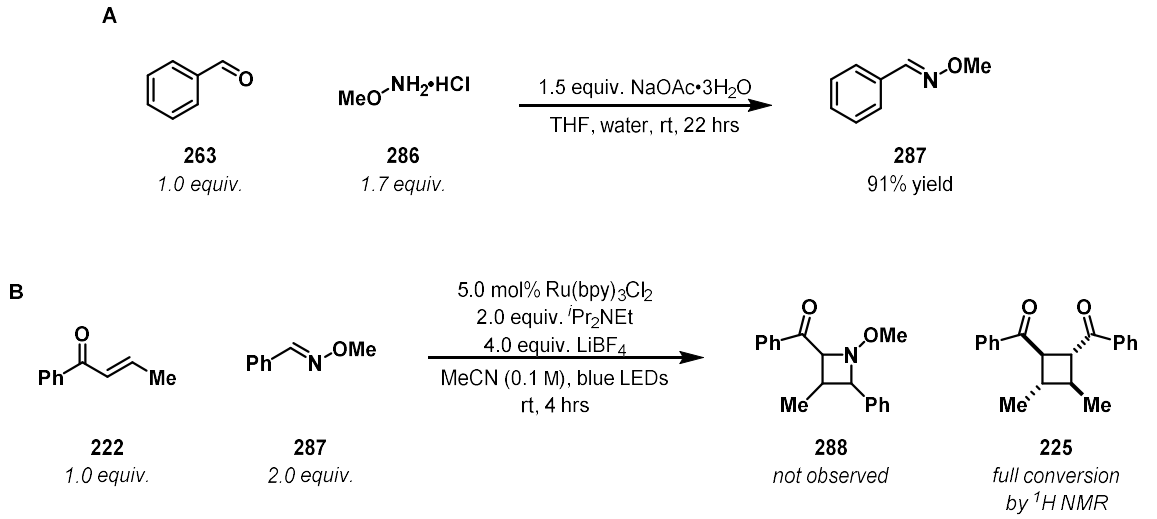
2.6 Results and Discussion: Reaction with oximes

Oximes are known to be more stable towards hydrolysis than imines and it was hoped this would limit the formation of aldehydes, as observed in the reaction with imines.[132] Subjection of commercially available benzaldehyde oxime **284** to the photoredox reaction with enone **222** was found not to lead to the desired azetidine **285**. Full conversion of enone **222** to cyclobutane **225** was observed by ^{1}H NMR spectroscopy. However, oxime **284** was not returned (**Scheme 2.22**). It was proposed that unprotected oxime **284** was not stable to the reaction conditions and may undergo fragmentation or polymerisation. Beckmann rearrangement might also be expected but the corresponding amide was not observed.



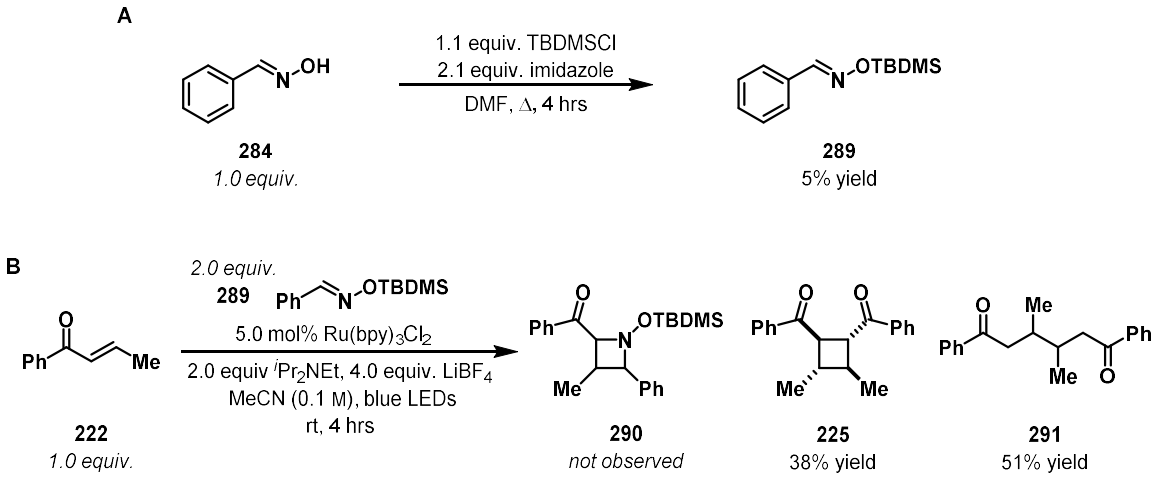
Scheme 2.22: *Attempted reaction of enone **222** with oxime **284** under photoredox catalysis.*

In order to limit the chance of oxime degradation under the photoredox conditions, a number of *O*-protected oximes were investigated. *O*-Protected oxime **287** was synthesised by condensation of benzaldehyde **263** and methyloxyamine hydrochloride **286**, which proceeded in 91% yield (**Scheme 2.23A**).[133] However, reaction with enone **222** under the $Ru(bpy)_3Cl_2$ catalysed photoredox system was not successful. Full conversion of enone **222** to cyclobutane **225** was observed by ^{1}H NMR spectroscopy. Methyl-protected oxime **287** was also returned and did not appear to undergo significant degradation, unlike unprotected analogue **284** (**Scheme 2.23B**).



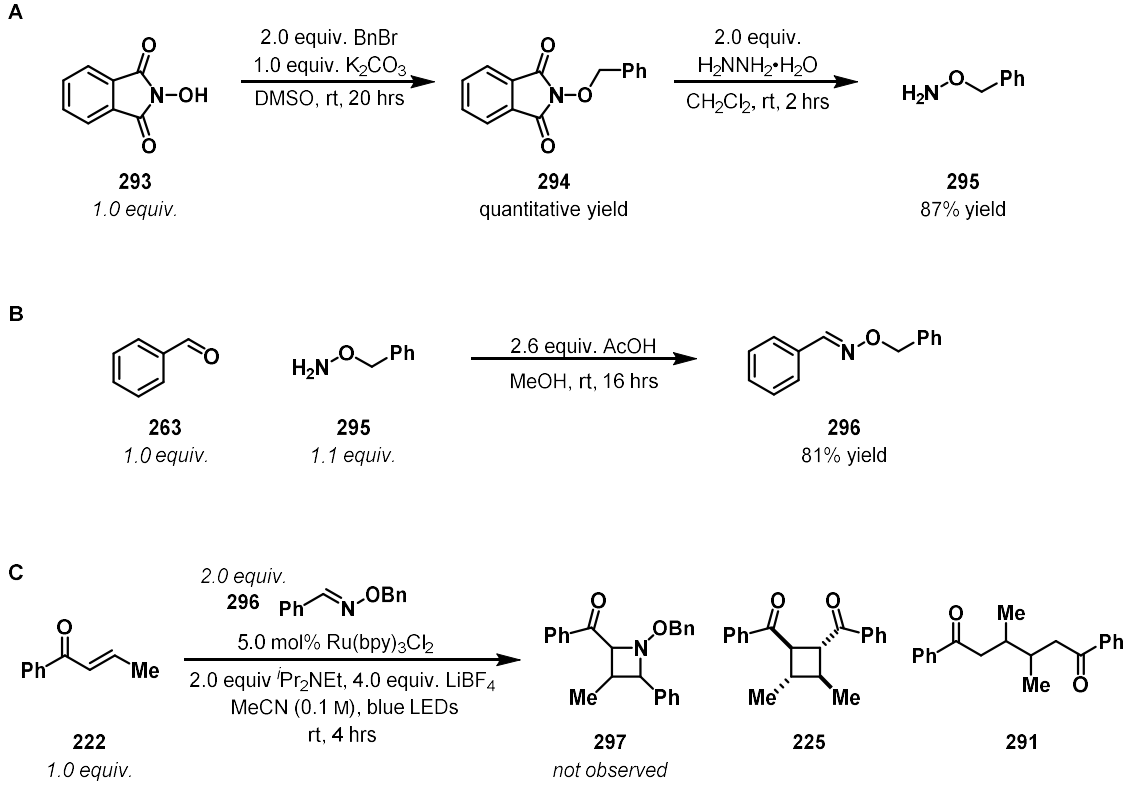
Scheme 2.23: (A) *Synthesis of O-methyl oxime* ***287*** *and* ***(B)*** *attempted reaction with enone* ***222*** *under photoredox conditions.*

O-tert-Butyldimethylsilyl (TBDMS) protected oxime **289** was synthesised by reaction of oxime **284** and TBDMSCl in the presence of imidazole (**Scheme 2.24A**). Reaction of oxime **289** with enone **222** under the standard photoredox conditions did not lead to formation of the azetidine target **290**. Instead, dimeric cyclobutane **225** was isolated in 38% yield. In addition to cyclobutane **225**, an additional by-product was isolated in 51% yield which was found to be acyclic dimer **291** (**Scheme 2.24B**, see also **Section 2.7.2**). Oxime **289** was also returned which suggests this *O*-TBDMS oxime was stable to the photoredox reaction conditions.



Scheme 2.24: (A) *Synthesis of O-TBDMS protected oxime* ***289*** *and* ***(B)*** *reaction with enone* ***222*** *under photoredox conditions.*

Benzyl protected-oximes have been demonstrated for use in radical-mediated reactions.[134] *O*-Benzylhydroxylamine **295** was synthesised in 87% yield by Gabriel synthesis from hydroxyphthalimide **293** (**Scheme 2.25A**).[135] Condensation reaction of benzaldehyde **263** and hydroxylamine **295** furnished oxime **296** in 81% yield, which was identified by the presence of a CH=N singlet at 8.16 ppm in the ^{1}H NMR spectrum (**Scheme 2.25B**). In contrast, the CHO proton of benzaldehyde appears as a singlet at 10.00 ppm.[136] Subjection of oxime **296** to the photoredox conditions with enone **222** was observed to not lead to azetidine product **297**, instead, a 5:2 mixture of cyclobutane **225** and acyclic dimer **291** was identified by ^{1}H NMR spectroscopy. Oxime **296** was also observed in the ^{1}H NMR of the crude reaction mixture which implied it did not degrade under the photoredox conditions (**Scheme 2.25C**).

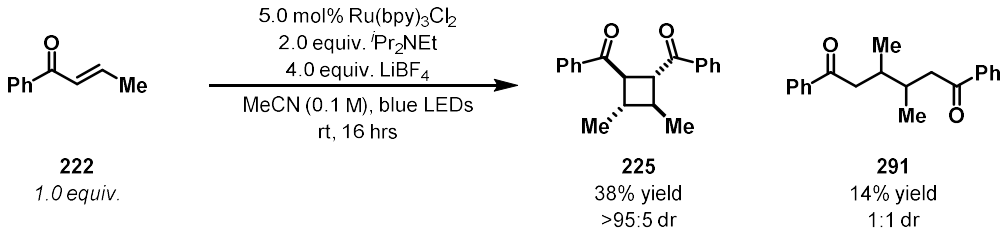


***Scheme 2.25: (A)** Gabriel synthesis of O-benzyl hydroxylamine **295** **(B)** synthesis of protected oxime **296** and **(C)** subjection to intermolecular reaction with enone **222** under photoredox catalysis.*

2.7 Results and Discussion: Mechanistic studies into the photoredox mediated [2+2] dimerisation of enones

Du and Yoon published the dimerisation of enone **222** in 2009 however, to this date little is known about the mechanism of the reaction.[115] During our studies, we often observed the formation of cyclobutane **225** and the presence of a second byproduct was noted during the attempted reaction of enone **222** and oxime **296** (**Scheme 2.24**). This product was isolated and characterised to be acyclic dimer **291**. We endeavoured to gain mechanistic insight into the synthesis of cyclobutane products in the hope that this would also be applicable to our azetidine system.

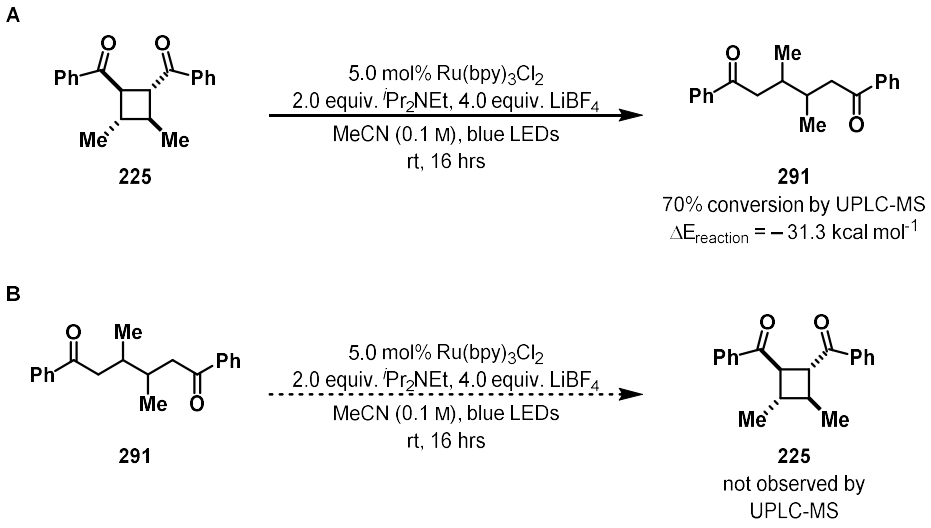
A control reaction was carried out in which enone **222** was subjected to the $Ru(bpy)_3Cl_2$ mediated photoredox conditions in the absence of an imine or oxime reaction partner. This was found to give rise to cyclobutane **225** in 38% yield and acyclic dimer in 14% yield after 16 hours reaction time (**Scheme 2.26**).



Scheme 2.26: *Control reaction. Subjection of enone **222** to photoredox condition was found to give rise to dimeric products **225** and **291**.*

2.7.1 Resubjection experiments

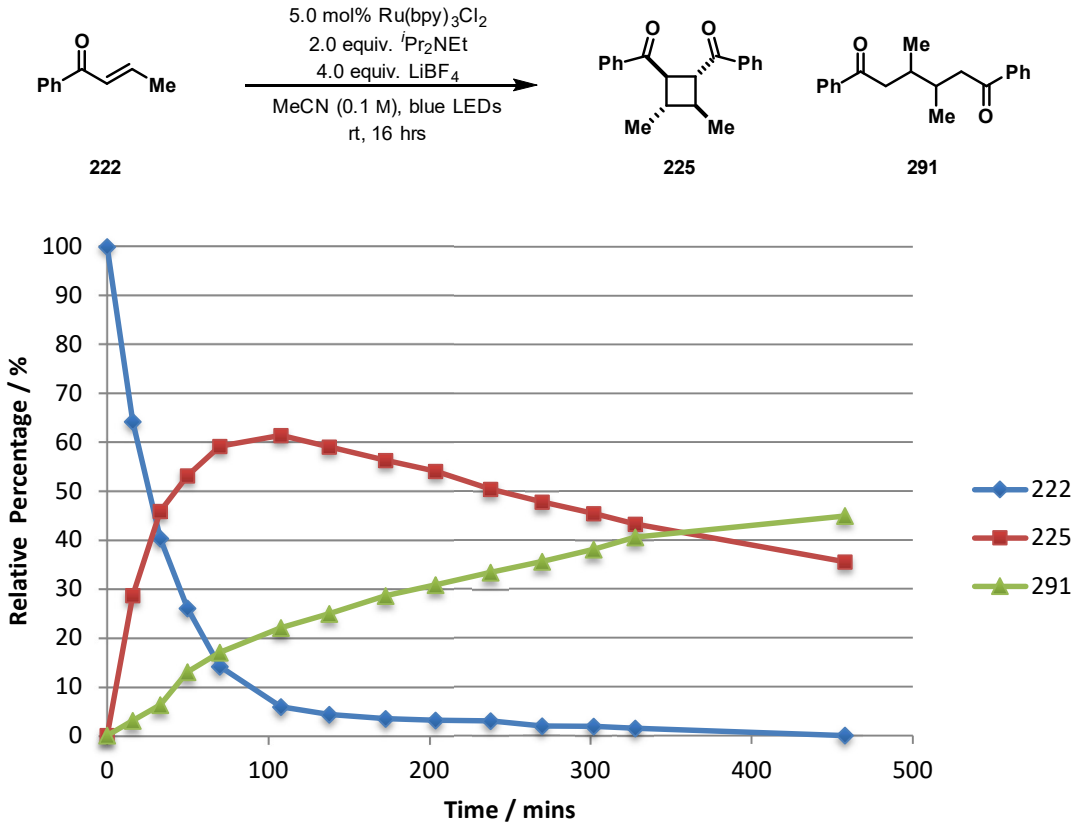
Resubjection of cyclobutane **225** to the photoredox reaction conditions was found to result in the formation of acyclic compound **291** but the reverse was not seen to be true; cyclobutane **225** cannot be formed from **291** under these conditions (**Scheme 2.27A & B**). This indicates that the two compounds are not in direct equilibrium with one another. The energies of the lowest energy conformers were calculated by Dr Ewa Chudyk (Vertex) which indicated that the reduction of cyclobutane **225** to acyclic compound **291** is thermodynamically favourable (**Scheme 2.27A**).



Scheme 2.27: (A) *Resubjection of cyclobutane* ***225*** *to the reaction conditions gave rise to acyclic compound* ***291****. **(B)** Resubjection of acyclic compound* ***291*** *to the reaction conditions was not observed to give rise to cyclobutane* ***225****. Reactions were monitored by UPLC-MS.*

2.7.2 Reaction monitoring

Aliquots were taken from the dimerisation reaction of enone **222** and analysed by UPLC-MS. The relative proportions of starting material enone **222**, cyclobutane **225** and acyclic dimer **291** were monitored over a 7-hour period and are shown in **Scheme 2.28**. It can be seen that the starting material enone **222** is consumed relatively quickly, and initially the rate of formation of cyclobutane **225** is fast. However, the formation of cyclobutane **225** begins to slow after roughly an hour and reaches a plateau after about two hours, at which time the amount of cyclobutane **225** relative to acyclic compound **291** begins to decrease. Throughout the reaction, the proportion of acyclic dimer **291** increases in an approximately linear fashion and continues to increase even after enone **222** is fully consumed. At this point, the proportion of cyclobutane **225** was seen to decrease. Overall, these results suggest that acyclic compound **291** is formed from cyclobutane **225**, and not directly from the starting material enone **222**.

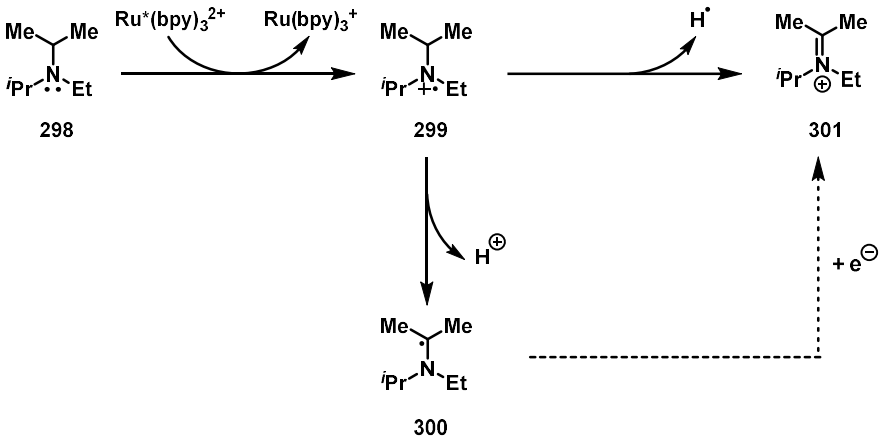


Scheme 2.28: *Relative percentage of starting material enone* ***222****, cyclobutane* ***225*** *and acyclic dimer byproduct* ***291*** *were monitored by UPLC-MS.*

After prolonged reaction time (5 days), the relative proportion of cyclobutane **225** and acyclic dimer **291** was roughly 70:30 and full conversion to acyclic compound **291** was not observed (**Scheme 2.28**). It was postulated that this may be due to the catalyst becoming inactive after prolonged reaction time. Additional aliquots of $Ru(bpy)_3Cl_2$ (2 x 5 mol%) were added after 19- and 43-hours reaction time. The addition of fresh catalyst did not have an observable effect on the relative proportion of cyclobutane **225** and acyclic dimer **291** and therefore it was concluded that a lack of active catalyst species was not the limiting factor.

The reduction of cyclobutane **225** to acyclic compound **291** requires formal addition of a proton (H^+) and a hydrogen radical ($H^\bullet$). Amines, such as Hünig's base ($^iPr_2NEt$) **298** are known to be very good electron donors and are often used in photoredox reactions as sacrificial reductants in order

to generate the active catalyst species. Oxidation to the radical cation **299** lowers the strength of the C–H bond adjacent to nitrogen, which makes **299** a good hydrogen atom ($H^{\bullet}$) source. Additionally, the pK_a at the αC–H positions is also significantly lowered in radical cation **299**, compared with the neutral amine and hence deprotonation at these sites is also facile (**Scheme 2.29**).[99]



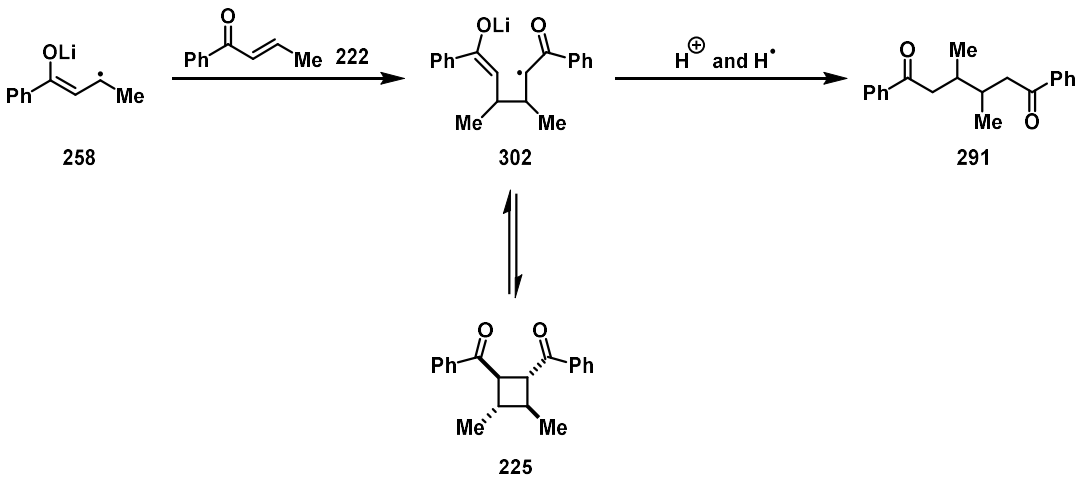
Scheme 2.29: *$^{i}Pr_2NEt$* ***298*** *can act as a proton and hydrogen radical source under photoredox conditions.*[99]

The base, $^{i}Pr_2NEt$, was proposed to be the source of the required H^+ and $H^{\bullet}$ for the reduction of cyclobutane **225** to acyclic dimer **291** and it was postulated that the reduction stalls when the $^{i}Pr_2NEt$ is fully consumed. It was found that increasing the loading of base loading from 2 equiv. to 10 equiv. in the dimerisation reaction of enone **222** gave rise to a significantly increased ratio of reduced product **291** to cyclobutane **225** of 93:7.

A mechanism was proposed in which radical anion **258** reacts with a further molecule of enone **222** to give rise to radical anion intermediate **302**. Radical recombination and loss of an electron gives rise to observed cyclobutane **225**, however, this process is reversible. Addition of a hydrogen radical and a proton, followed by tautomerisation, leads to the formation of acyclic dimer **291** in a non-reversible process (**Scheme 2.30**). Acyclic dimer **291** was calculated* to be 31.3 kcal mol^{-1}

* DFT calculations were carried out by Dr Ewa Chudyk (Vertex)

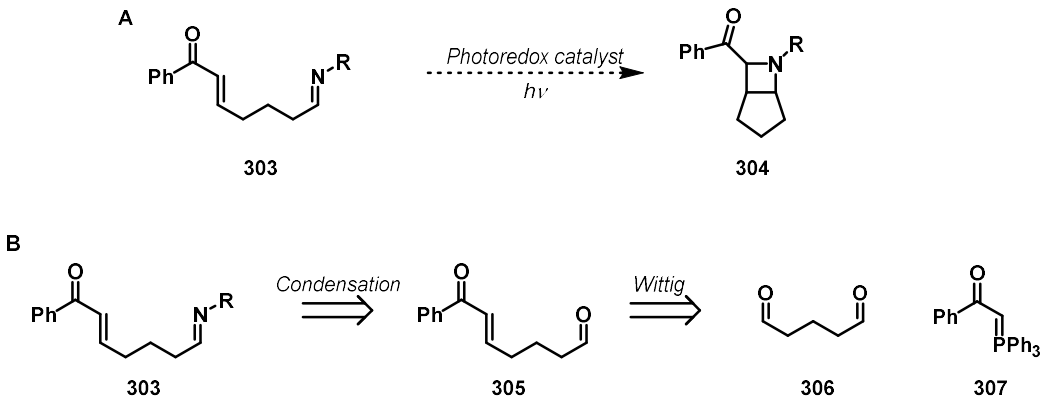
lower in energy than cyclobutane **225** and hence its formation is thought to be very energetically favourable. The necessary hydrogen radical and proton are generated during the decomposition of $^{i}Pr_2NEt$, and as shown above (**Scheme 2.30**). Increased loading of $^{i}Pr_2NEt$ was found to lead to increased conversion of cyclobutane **225** to acyclic dimer **291**, which supports this proposed role of $^{i}Pr_2NEt$.



Scheme 2.30: *Proposed mechanism for the formation of cyclobutane **225** and acyclic dimer **291**.*

2.8 Results and Discussion: Development of an intramolecular reaction

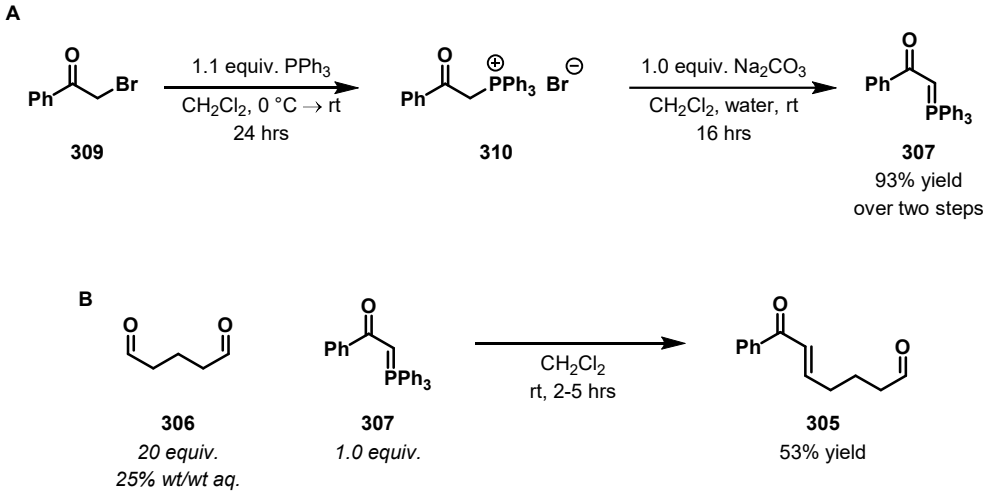
The reaction of enone **222** with imines and oximes had proven unsuccessful and hence we sought a simplified system. It was proposed that this could be accomplished by tethering the two reaction centres to enable an intramolecular reaction (**Scheme 2.31A**). This was inspired by the initial approach taken by Yoon and co-workers in which subjection of bis-enone **215** to photoredox conditions lead to the formation of cyclobutane **217** (**Section 2.1.3**).[114] A phenyl enone moiety was maintained from previous studies, since radical generation had proven successful under photoredox conditions. It was envisioned the imine **303** could be synthesised from aldehyde **305**, which in turn could be accessed *via* a Wittig reaction with glutaraldehyde **306** (**Scheme 2.31B**).



Scheme 2.31: (A) *Proposed intramolecular azetidine formation under photoredox conditions.* ***(B)*** *Retrosynthetic design of intramolecular substrate* ***303****.*

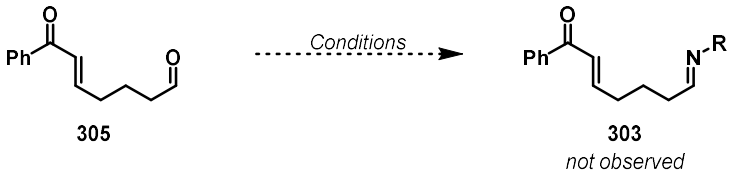
2.8.1 First generation intramolecular substrate

The reaction of α-bromoketone **309** and triphenylphosphine was carried out on multiple-gram scale to provide ylide **307** in high yield (**Scheme 2.32A**).[137] Wittig reaction with glutaraldehyde **306** was found to give rise to enone **305** in 53% yield, and was identified by the presence of alkene peaks at 7.02 ppm and 6.91 ppm which were seen to couple to each other with J = 15.4 Hz, indicating *trans* geometry (**Scheme 2.32B**).[138]



Scheme 2.32: (A) *Synthesis of ylide* ***307*** *in 93% yield via phosphonium bromide* ***310****. **(B)** Wittig reaction with glutaraldehyde* ***306*** *to form enone* ***305****.*[138]

With enone **305** in hand, imine synthesis was attempted under number of conditions. Formation of both tosyl and carbamate imines proved unsuccessful and, in all cases, a complex mixture of products was observed by ^{1}H NMR spectroscopy (**Table 2.2**, Entries 1-3). In addition, oxime formation was attempted but this was also found to give rise to highly complex mixture of products by NMR (**Table 2.2**, Entry 4). It was concluded that aldehyde **305** was not stable under the reaction conditions and so this route was not pursued further (**Table 2.2**).

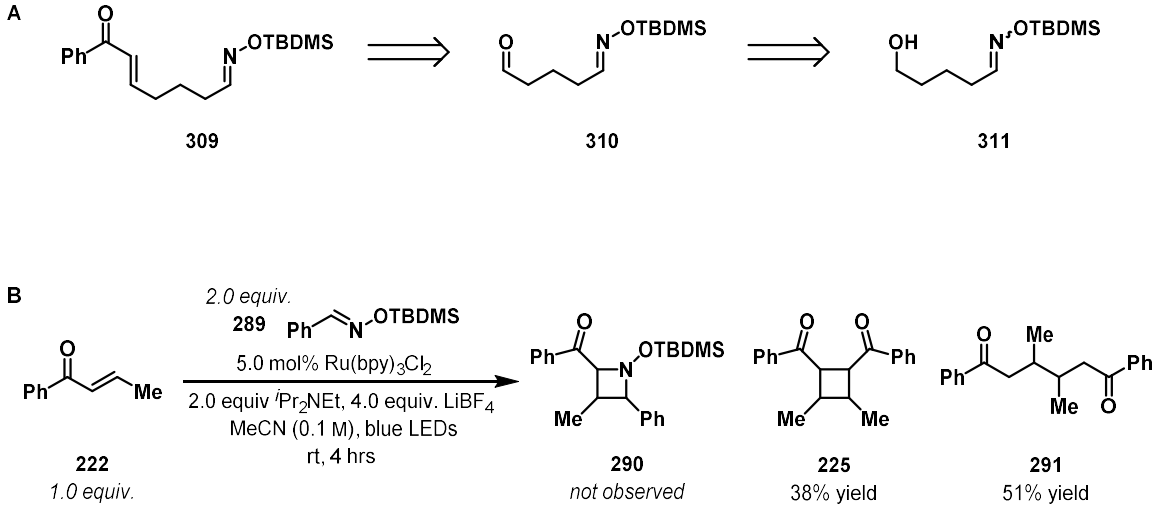


Entry	R	Conditions	Outcome
1	Ts	(i) $TsNH_2$, $PhSO_2Na$, HCOOH, water; (ii) sat. aq. $NaHCO_3$, CH_2Cl_2	Complex mixture
2	Boc	(i) $BocNH_2$, *p*-$tolSO_2Na$, HCOOH, water; (ii) Cs_2CO_3	Complex mixture
3	Cbz	(i) $CbzNH_2$, *p*-$tolSO_2Na$, HCOOH, water; (ii) K_2CO_3	Complex mixture
4	OH	$H_2NOH.HCl$, Et_3N, CH_2Cl_2	Complex mixture

Table 2.2: *Attempted imine and oxime condensation reactions with aldehyde* ***305****.*

2.8.2 Second generation intramolecular substrate

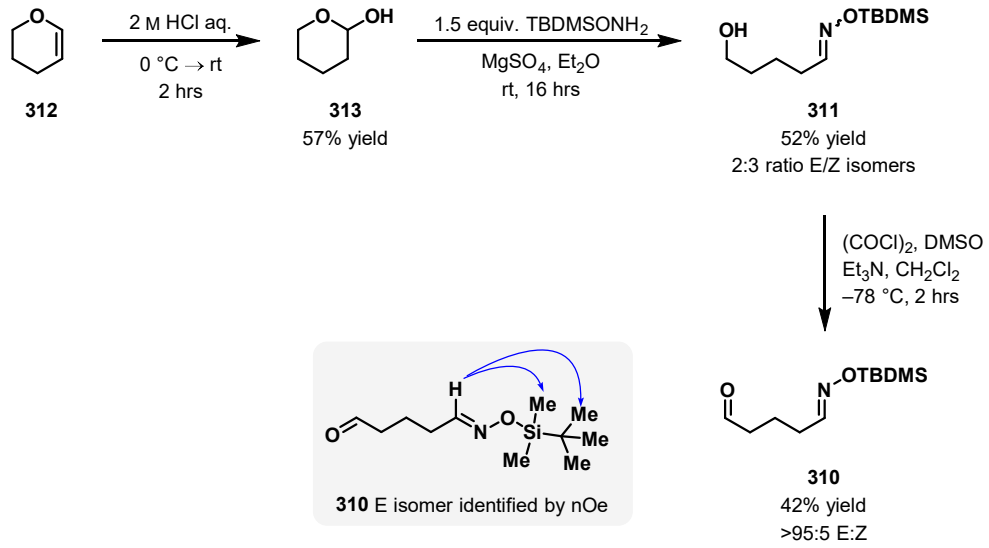
Following the problematic synthesis of imine **303**, an alternative route for the construction of a tethered substrate was sought. It was proposed that reversal of the order of events would help to overcome the problems of suspected over-reaction of dialdehyde **306** under Wittig conditions (**Scheme 2.33A**). *O*-TBDMS oxime **289** was not found to engage in reaction with enone **222**, but the formation of enone dimers **225** and **291** were observed (**Scheme 2.33B**). This indicated that the inclusion of an *O*-TBDMS oxime does not hinder the photochemical generation of radical **258**. Hence, intramolecular substrate **309** was synthesised based on the route of Ishibashi and co-workers.[139]



***Scheme 2.33: (A)** Retrosynthesis of the second-generation tethered substrate **309**. **(B)** Previously attempted reaction of enone **222** and O-TBDMS oxime **289** under photoredox conditions.*

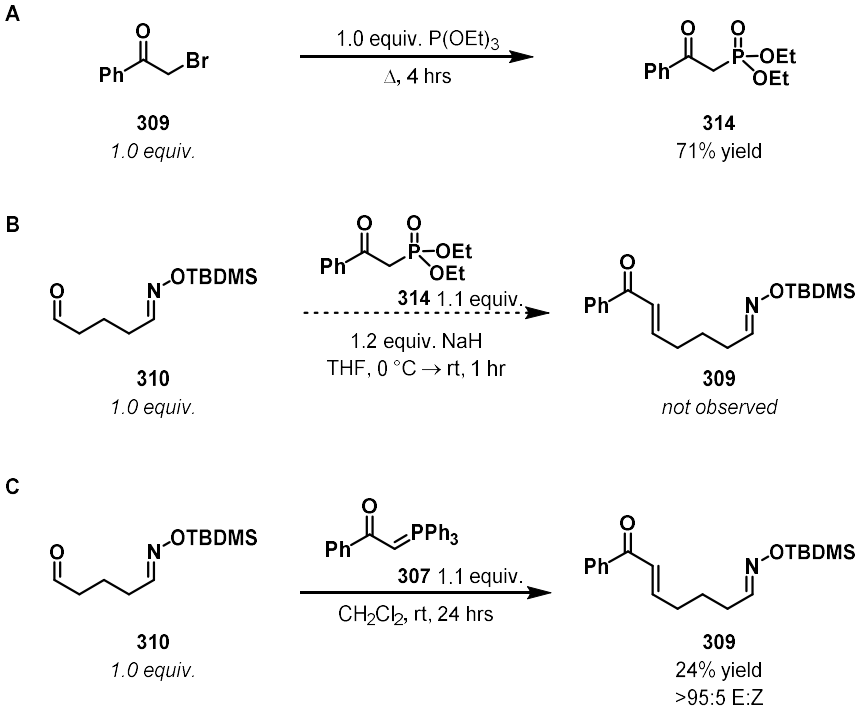
Tetrahydropyranol **313** was synthesised by acid-catalysed hydration of dihydropyran **312**.[140] Whilst the yield of **313** was low, dihydropyran **312** is cheap and readily available, and the hydrolysis could be easily carried out on multiple-gram scale in order to generate sufficient material. Subsequently, condensation with *O*-(*tert*-butyldimethylsilyl)hydroxylamine gave rise to oxime **311** in 52% yield and as an inseparable 2:3 mixture of oxime *E*/*Z* isomers. Following oxidation to aldehyde **310** under Swern conditions, the *E* isomer was isolated by column

chromatography and identified by observation of nOe correlations between the CH=N proton and the TBDMS group (**Scheme 2.34**).



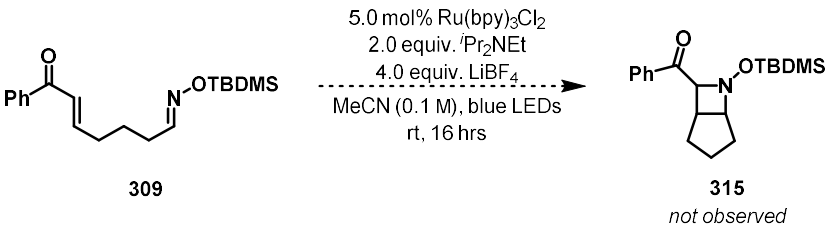
Scheme 2.34: *Synthesis of aldehyde **310** over three steps. The E isomer was isolated and identified by nOe correlations (indicated by solid, blue arrows).*[139,140]

Ishibashi and co-workers employed aldehyde **310** in a Horner-Wadsworth-Emmons reaction to synthesise the final alkene product. Accordingly, phosphonate **314** was synthesised from α-bromoketone **309** *via* a Michaelis-Arbuzov reaction with triethylphosphite (**Scheme 2.35A**), and transformation of aldehyde **310** to enone **309** was attempted *via* Horner-Wadsworth-Emmons coupling (**Scheme 2.35B**).[139,141] However, ^{1}H NMR analysis of the crude reaction mixture indicated decomposition of aldehyde **310**. Inspired by the synthesis of the first-generation intramolecular substrate **303**, a Wittig reaction of aldehyde **310** with ylide **307** was carried out and was found to give rise to enone **309** in 24% yield (**Scheme 2.35C**). In contrast to the first-generation route, the Wittig reaction involves a mono-aldehyde species **310** and therefore over-reaction problems are avoided.



Scheme 2.35: (A) *Synthesis of phosphonate* ***314****.*[139] ***(B)*** *Attempted Horner-Wadsworth-Emmons reaction of aldehyde* ***310*** *with phosphonate* ***314****.*[139] ***(C)*** *Successful Wittig reaction to form enone* ***309****.*

With enone **309** in hand, the photoredox reaction to form azetidine **315** was attempted under the standard $Ru(bpy)_3Cl_2$ conditions. However, ^1H NMR spectroscopy of the crude reaction mixture revealed a complex mixture, with little evidence of cyclic product **315** or starting material **309** (**Scheme 2.36**). It was proposed that substrate **309** was not stable under the reaction conditions and therefore, an alternative tethered substrate was sought.

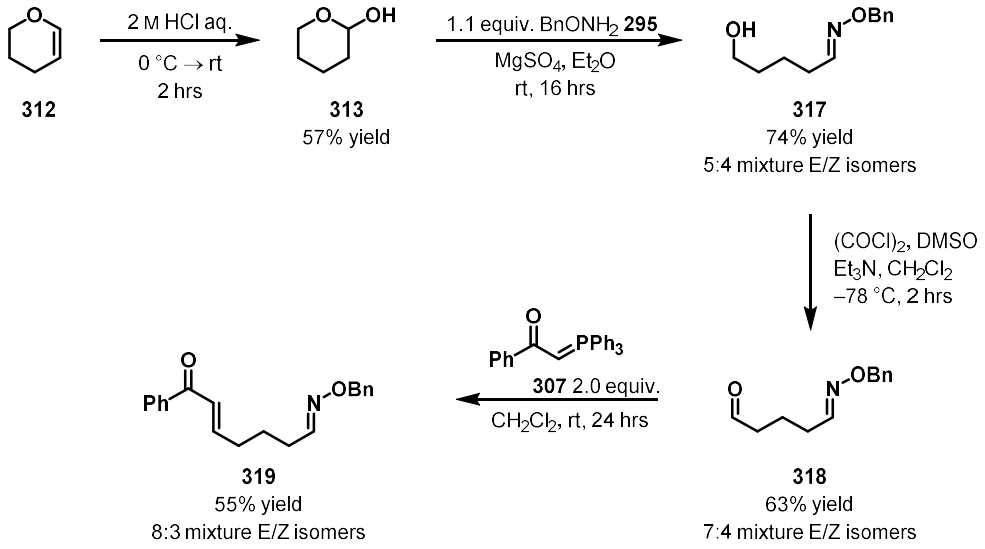


Scheme 2.36: *Attempted intramolecular azetidine formation under photoredox conditions.*

2.8.3 Third generation intramolecular substrate

It was proposed that an alternative oxime protecting group might improve stability in the photoredox reaction. It was found that a number of radical-mediated cyclisation reactions involving nitrogen substituents tend to employ *O*-benzyl protected oximes.[134] Reaction of *O*-benzyl oxime **296** with enone **222** had been attempted previously and, whilst the azetidine product was not observed, oxime **296** appeared to be stable under the photoredox conditions (**Section 2.6**). Synthesis of TBDMS-protected oxime **309** was found to proceed in low yield over five steps and the scale of reaction was limited by the availability of *O*-(*tert*-Butyldimethylsilyl)hydroxylamine.

The synthesis of intramolecular substrate **319** was carried out under a modification of Ishibashi and co-workers' route. As before, the synthesis started from readily available tetrahydropyranol **313,** which was generated by acid hydrolysis of pyran **312**. Tetrahydropyranol **313** and hydroxylamine **295** were combined to give **317** in 74% yield, which was identified by the presence of a characteristic oxime C<u>H</u>=N signal at 7.46 ppm (t, *J* = 6.4 Hz) in the ^{1}H NMR spectrum. Subsequently, Swern oxidation of alcohol **317** to the corresponding aldehyde **318** proceeded in 63% yield and gave rise to a 7:4 mixture of *E*/*Z* oxime isomers. The major isomer was assigned as the *E* isomer by analogy to *O*-TBDMS aldehyde **318**. Finally, Wittig reaction with ylide **307** gave rise to the target enone **319** in 55% yield (**Scheme 2.37**). Overall, intramolecular substrate **319** was furnished in significantly higher yield than *O*-TBDMS analogue.



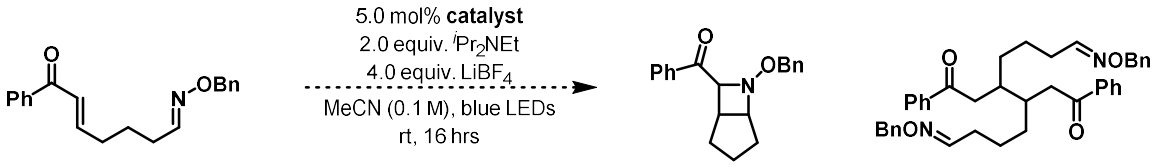
Scheme 2.37: *Synthesis of third-generation intramolecular substrate* ***319.***

2.8.4 Photoredox catalyst screen

With tethered substrate **319** in hand, a survey of photoredox catalysts was carried out with the aim of inducing cycloaddition to form azetidine **320**. Attempts to measure the redox potential of enone **319** using an ElectraSyn® device did not give satisfactory cyclic voltammetry spectra, partly because it was not possible to rigorously de-gas the solution.* Therefore, catalysts with a wide range of excited state redox potentials were screened (**Table 2.3**).

Reactions were conducted under analogous conditions to previous studies; 5 mol% catalyst, 2 equiv. Hünig's base, 4 equiv. $LiBF_4$, anhydrous acetonitrile (0.1 M) and irradiation with blue LEDs (λ_{max} = 450 nm). In the case of $Ir(ppy)_3$, $Ir[dF(^tBu)ppy]_3$ and Eosin Y reactions were also carried out in DMF due to observed lack of solubility in acetonitrile. Reactions were monitored and analysed by UPLC-MS.

* ElectraSyn measurements were carried out whilst on a placement at Vertex



319 320 Mass 307 321 Mass 616

Entry	Catalyst	$E_{1/2}$ / V
1	$Ru(bpy)_3Cl_2.6H_2O$	–1.33
2	$Ru(phen)_3Cl_2$	–1.36
3	$Ir(ppy)_3$	–2.19
4[a]	$Ir[dF(^tBu)\text{-}ppy]_3$	-
5	$[Ir(ppy)_2(dtbpy)]PF_6$	–1.51
6	$[Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbpy)]PF_6$	–1.37
7	Eosin Y	–1.06
8	Mes-Acr	–0.57
9	Rose Bengal	–0.78

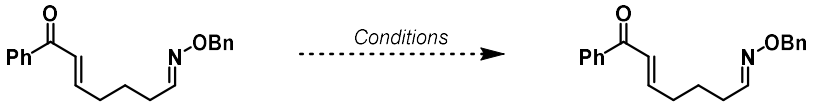
Table 2.3: *Photoredox catalysts screened for the intramolecular azetidine formation.* [142,143] [a]*Data was not available for* $Ir[dF(^tBu)\text{-}ppy]_3$.

A small peak correlating to the mass of azetidine **320** ($M+H^+$ = 308) was observed by UPLC-MS when $Ru(bpy)_3Cl_2$ was used. However, isolation by mass-directed semi-prep HPLC* gave rise to a very small amount of material which was found to be a complex mixture of compounds by NMR spectroscopy. Trace product mass ($M+H^+$ = 308) was also observed when $Ir(ppy)_3$ and $[Ir(ppy)_2(dtbpy)]PF_6$ were employed. Unfortunately, the retention time of these catalysts coincided with the observed $M+H^+$ = 308 and so isolation by semi-prep HPLC* was not attempted. Traces levels of $M+H^+$ = 617 were also observed under $Ir[dF(^tBu)\text{-}ppy]_3$ and $[Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbpy)]PF_6$ catalysis which could be attributed to a dimer structure such as **321**. Isolation by semi-prep HPLC* gave rise to a very small quantity of material which appeared to be a complex mixture by NMR spectroscopy. Organic photoredox catalysts Eosin Y, Mes-Acr and Rose Bengal were also surveyed but no evidence of desired azetidine **320** was observed by UPLC-MS.

* Semi-preparative HPLC was carried out by Stefan Richardson (Vertex)

During the photocatalyst study, a common peak was observed by UPLC-MS at 0.55 min and after prolonged reaction time (24 hrs), this was amplified and seen to be the main component. Unfortunately, mass spectrometry did not reveal any characteristic or rationalisable $M+H^+$ values. Isolation by semi-prep HPLC* gave rise to a small amount of material with a highly complex ^1H NMR spectrum. It was thought that this was likely a mixture of degradation products of oxime **319**. A series of control reactions were carried out in order to confirm this hypothesis.

Oxime **319** was subjected to the reaction conditions with $[Ir(ppy)_2(dtbpy)]PF_6$ in the absence of light for 24 hours, which was found to return starting material (**Table 2.4**, Entry 1). Likewise, subjection to catalyst-free conditions, also in the dark, did not produce any observable degradation products (**Table 2.4**, Entry 2). However, exposing an acetonitrile solution of oxime **319** to either blue or UV light in the absence of the catalyst, $^iPr_2NEt$ and $LiBF_4$ led to complete consumption of the starting material **319** and observation of a UPLC-MS peak at 0.55 min with little mass information, as seen previously (**Table 2.4**, Entries 3 and 4). It was concluded that compound **319** was not stable to blue or UV light and therefore was not suitable for applications in photoredox chemistry.



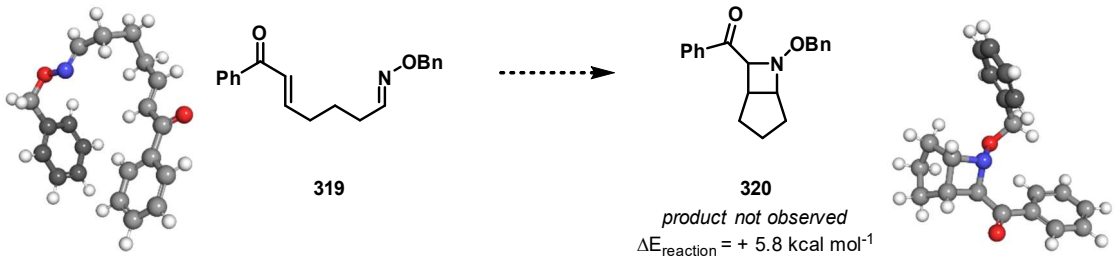
319 319

Entry	Conditions	Outcome
1	5.0 mol% $[Ir(ppy)_2(dtbpy)]PF_6$, 2.0 equiv. $^iPr_2NEt$, 4.0 equiv. $LiBF_4$, MeCN (0.1 M), **dark**, rt, 24 hrs	No change
2	2.0 equiv. $^iPr_2NEt$, 4.0 equiv. $LiBF_4$, MeCN (0.1 M), **dark**, rt, 24 hrs	No change
3	**Blue LEDs**, MeCN (0.1 M), rt, 3 days	Complete consumption of **319**
4	**UV LEDs**, MeCN (0.1 M), rt, 3 days	Complete consumption of **319**

Table 2.4: *Control reactions with oxime **319** confirm instability under blue or UV light.*

2.8.5 Computational calculations

Photocatalysis has the ability to circumvent the expected thermodynamic restrictions of a reaction and can therefore lead to formation of a product with higher energy than the starting material.[109] Computational energy calculations involving an excited state, such as proposed radical intermediate **327**, are hugely time and resource consuming and hence, were not within the remit of this project. The ground state energies of the lowest energy conformers of starting material **319** and desired azetidine product **320** were calculated and optimised using DFT by Dr Ewa Chudyk and Dr Ron Knetgel (Vertex). Interestingly, it was found that formation of azetidine **320** is thermodynamically disfavoured ($\Delta E_{reaction}$ = +5.8 kcal mol^{-1}, **Scheme 2.38**). However, without knowledge of the excited state energetics, it is not possible to draw conclusions about the energetic feasibility of this reaction.

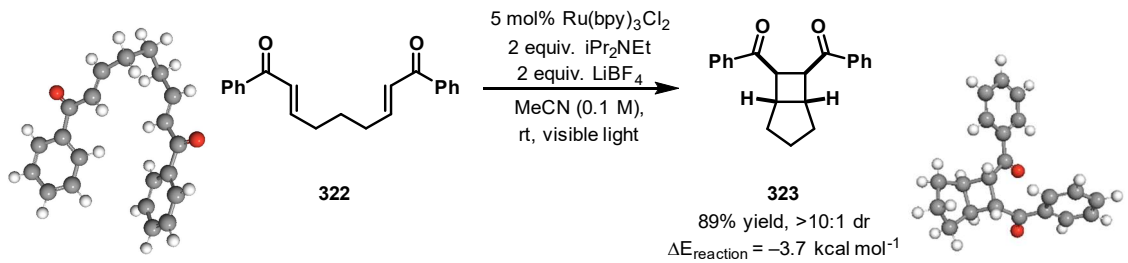


Scheme 2.38: *Calculated energies and structures of the lowest energy conformers of oxime **319** and target azetidine **320** as determined by Dr Ewa Chudyk (Vertex). Key for 3D structures: grey = carbon, blue = nitrogen, red = oxygen and white = hydrogen.*

Similarly, the ground state energies of bis-enone **322** and carbocyclic product **323** were also calculated for Yoon's reported intramolecular cycloaddition,[114] and overall the reaction was found to be thermodynamically favourable ($\Delta E_{reaction}$ = –3.7 kcal mol^{-1}, **Scheme 2.39**).* However, excited state calculations were not performed and therefore it is not prudent to draw strong conclusions from this data. However, it is interesting to note that formation of cyclobutane **323** from bis-enone

* Calculations were performed by Dr Ewa Chudyk (Vertex)

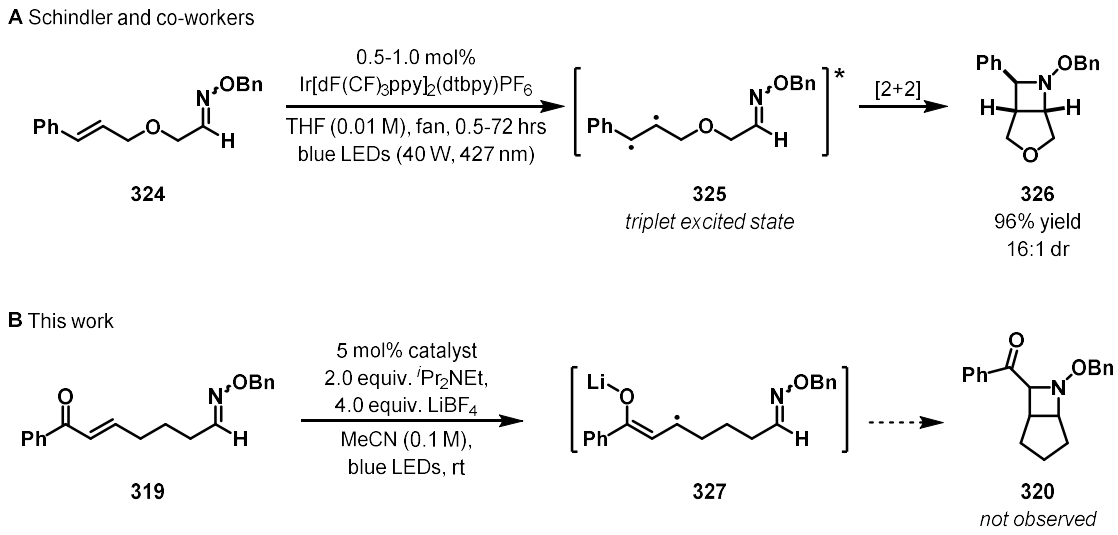
322 was calculated to be thermodynamically favourable, whilst azetidine formation is not, but this may simply be a coincidence.



Scheme 2.39*: Calculated lowest energy conformer energies and structures for intramolecular cycloaddition of bis-enone* ***322*** *as developed by Yoon and co-workers.*[114] *Calculations were carried out by Dr Ewa Chudyk. Key for 3D structures: grey = carbon, blue = nitrogen, red = oxygen and white = hydrogen.*

2.8.6 Conclusion

Schindler and co-workers successfully employed a similar tethered substrate approach in their synthesis of azetidines, which shows that our concept was valid. However, the key difference between the substrates is that the Schindler group utilised activation of styrene functionality, which is likely to be more electron rich than our enone system (**Scheme 2.40A**). It was noted that the excited state redox potential of $Ir[dF(CF)_3ppy]_2(dtbpy)_2PF_6$ ($E_{1/2}^{III*/II}$ = +1.21 V, $E_{1/2}^{IV/III*}$ = –0.89 V) is not sufficient to oxidise or reduce substrate **324** *via* the single electron transfer pathway typical of polypyridyl iridium photocatalysts.[99,108] Schindler's work is therefore, mechanistically distinct from ours in that the cycloaddition proceeds *via* triplet energy excitation, whereas we focussed on single electron reduction of enone **319**, as previously described by Yoon and co-workers (**Scheme 2.40B**).[114,115,116] Unfortunately the report of photoredox mediated azetidine synthesis from Schindler and co-workers diminished the impact of our project, and given our degradation problems, it was decided not to pursue the project further.



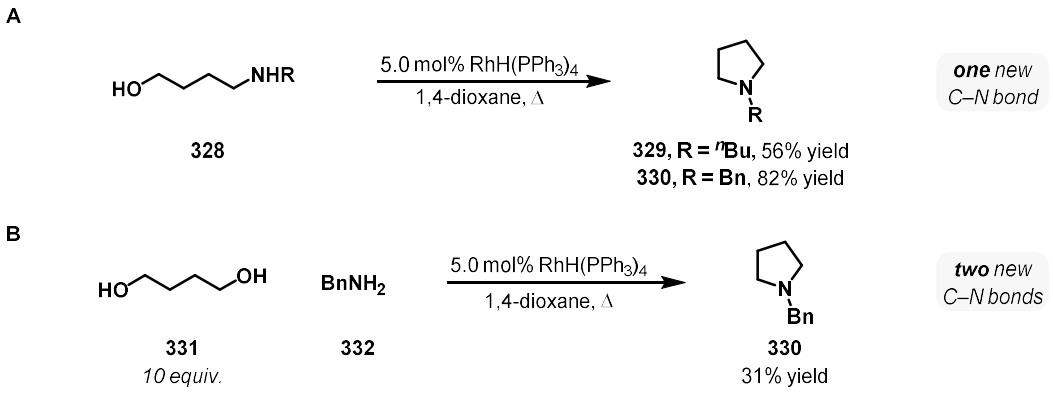
Scheme 2.40: (A) *Visible light-mediated synthesis of azetidine* ***326*** *via triplet excited state* ***325****, reported by Schindler and co-workers.*[108] ***(B)*** *Our work aimed to form azetidine* ***320*** *from enone* ***319*** *under photoredox-mediated single electron reduction.*

Chapter 3: Hydrogen Borrowing Catalysis for the Synthesis of Piperidines

3.1 Introduction

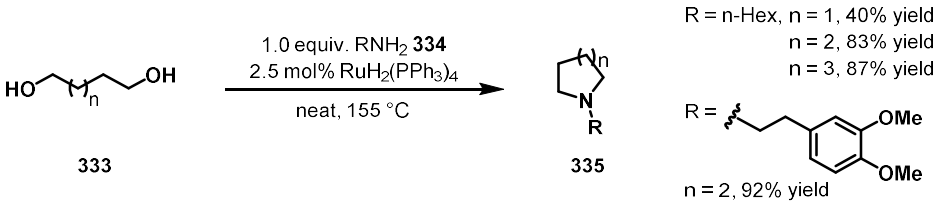
Hydrogen borrowing reactions of diols with amines to construct new C–N bonds has been studied by a number of groups (Section 1.3.2). This concept has been extended to the synthesis of unsaturated *N*-heterocycles from an amine and a diol and involves two sequential hydrogen borrowing cycles, thus leading to the formation of two new C–N bonds. This is a highly attractive disconnection for *N*-heterocycle synthesis due to the easy accessibility of the starting materials.

The field was pioneered by Grigg and co-workers in 1981 with the demonstration of the synthesis of *N*-benzylpyrrolidine **330** from aminoalcohol **328** under ruthenium-catalysed hydrogen borrowing conditions (**Scheme 3.1A**). This process involves the formation of only a single C–N bond but served as an important proof of concept for the formation of cyclic products. This was subsequently extended to the reaction of benzylamine **332** with a large excess of butane-1,2-diol **331** to yield pyrrolidine **330** in 31% yield (**Scheme 3.1B**).[60] A number of groups have contributed to the field in the years since Grigg's first publication and a range of catalyst systems have been developed.



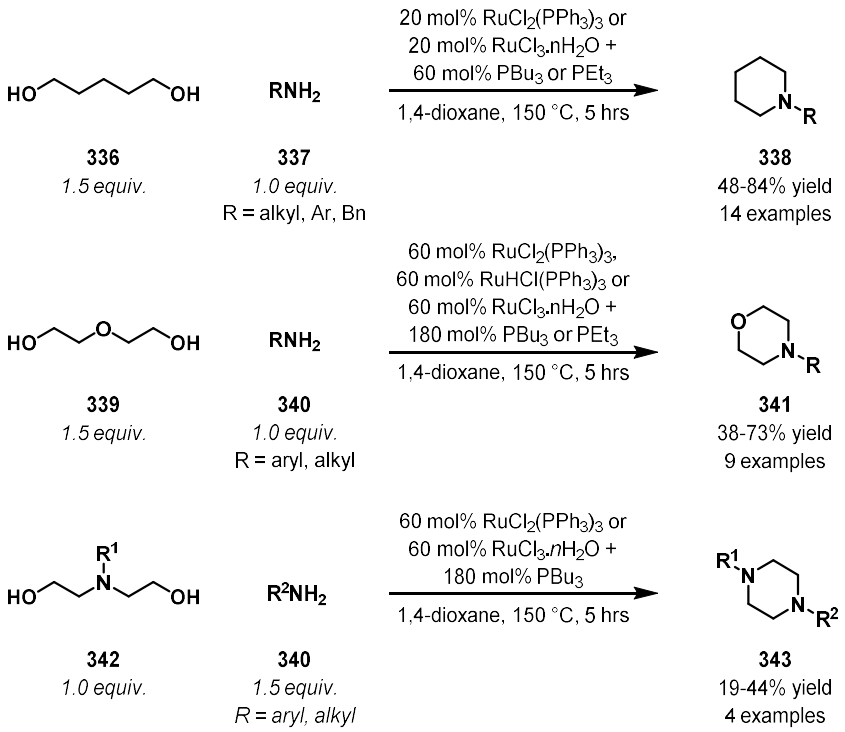
Scheme 3.1: *Early examples of hydrogen borrowing for C–N annulation by Grigg.* ***(A)*** *Cyclisation of aminoalcohol* ***328*** *under ruthenium-catalysed hydrogen borrowing involves formation of one new C–N bond.* ***(B)*** *Cyclisation of a diol* ***331*** *with benzylamine* ***332*** *via double C–N bond formation.*[60]

Soon after Grigg's seminal publication, Murahashi and co-workers employed ruthenium(II) complex $RuH_2(PPh_3)_4$ for the synthesis of unsymmetrical secondary and tertiary amines under hydrogen borrowing conditions. Like their predecessors, Murahashi's group also briefly demonstrated the cyclisation of aminoalcohols to the corresponding cyclic compounds but soon progressed to the reaction of diols **333** with simple amines. The reaction of hexylamine or alkyl amine **334** with diol **333** was shown to furnish examples of five-, six- and seven-membered rings (**Scheme 3.2**). The yield was found to increase with increasing ring size, up to 87% for *N*-hexylazepine, which was attributed to the templating effect of bidentate coordination of the diol with ruthenium.[62]



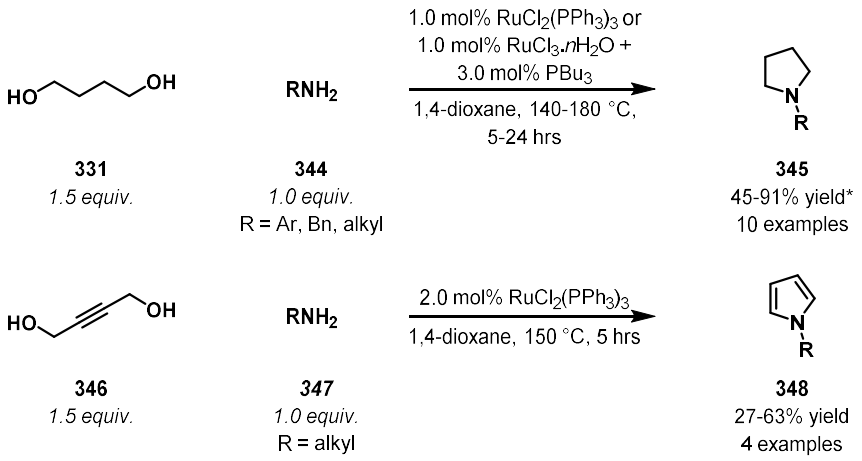
Scheme 3.2: *Synthesis of N-heterocycles from diol **333** and alkyl amines by Murahasi and co-workers.*[62]

Watanabe and co-workers described the synthesis of a number of piperidines by reaction of diol **336** with a range of amines. Aryl amines were employed, with only a small number of alkyl or benzyl amines **337** being utilised, and in all cases the diols were unfunctionalised (**Scheme 3.3**). Several ruthenium catalysts were investigated and it was found that the nature of the phosphine ligand is key; PPh_3 was sufficient for aromatic amines but in the case of alkyl amines, a more electron-rich ligand such as PBu_3 or PEt_3 was required.[144] Additionally, the synthesis of morpholines **341** and piperazines **343** was also achieved. However, high catalyst loadings were necessary, and yields were modest. Similarly, additional electron-rich phosphine ligands were required for the successful reaction of aliphatic amines.[144]



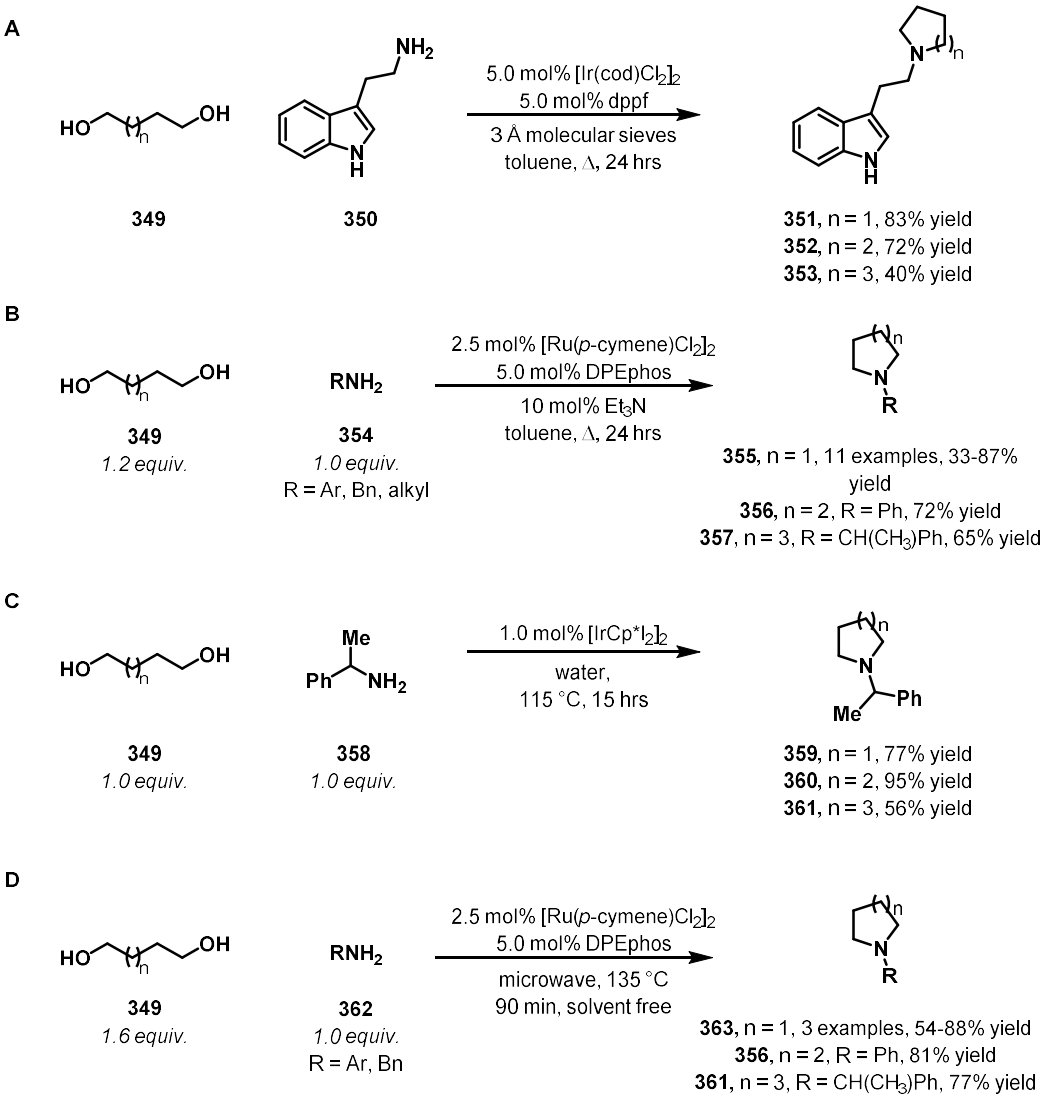
***Scheme 3.3**: Ruthenium catalysed hydrogen borrowing for the synthesis of **(A)** piperidines **(B)** morpholines and **(C)** piperazines by Watanabe and co-workers.[144]*

In a subsequent publication, Watanabe's group demonstrated the synthesis of a number of pyrolidines **345** from butanediol **331** and a range of aryl-, benzyl- and alkylamines **341** in modest to excellent yields. As noted in previous work, the inclusion of electron-rich phosphine ligand PBu_3 was essential for the examples involving alkyl amines. Interestingly, application of this hydrogen borrowing methodology to the reaction of butynediol **346** with alkyl amines was found to result in the formation of pyrroles **348** in modest yields. Ruthenium complexes are known to catalyse the isomerisation of olefins and allyl alcohols to aldehydes and such processes were invoked in the mechanism of this pyrrole formation (**Scheme 3.4**).[145]



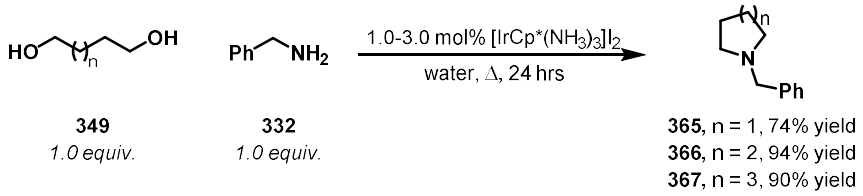
Scheme 3.4: *Application of hydrogen borrowing methodology to the synthesis of five-membered rings by Watanabe and co-workers.*[145]

The Williams group have published extensively in the area of hydrogen borrowing, with particular focus on the synthesis of pharmaceutically-relevant molecules. For example, the tryptamine substructure **350** is found in a wide range of biologically active molecules and it was demonstrated that the primary amine moiety can be alkylated with diols **349** under iridium(I)-catalysed hydrogen borrowing conditions to give rise to pyrrolidine **351**, piperidine **352** and azepane **353.** The isolated yields were found to decrease with increasing ring size (**Scheme 3.5A**).[66] The construction of *N*-heterocycles under ruthenium-catalysed hydrogen borrowing was subsequently demonstrated; a range of *N*-substituted pyrrolidines **355** were generated in good yields, along with piperidine **356** and azepane **357** (**Scheme 3.5B**).[70] It was found that the reaction can be carried out in water using the iridium catalyst $[IrCp^*I_2]_2$ whilst maintaining high yields of cyclic products **359**–**361** (**Scheme 3.5C**).[146] Under ruthenium-catalysis and microwave irradiation, solvent-free hydrogen borrowing was demonstrated, thus further increasing the atom economy of this process. Cyclic amines **356**, **361** and **363** were found to be formed in higher yields than previous thermal work after only 90 minutes of reaction time (**Scheme 3.5D**).[147] Despite the breadth of Williams' work, the variation always concerned the nature of the amine partner or ring size and there was little exploration of any functionality on the backbone of the diol partner.



***Scheme 3.5**: Development of hydrogen borrowing catalysis for synthesis of a range of ring sizes by Williams and co-workers.* [66,70,146,147]

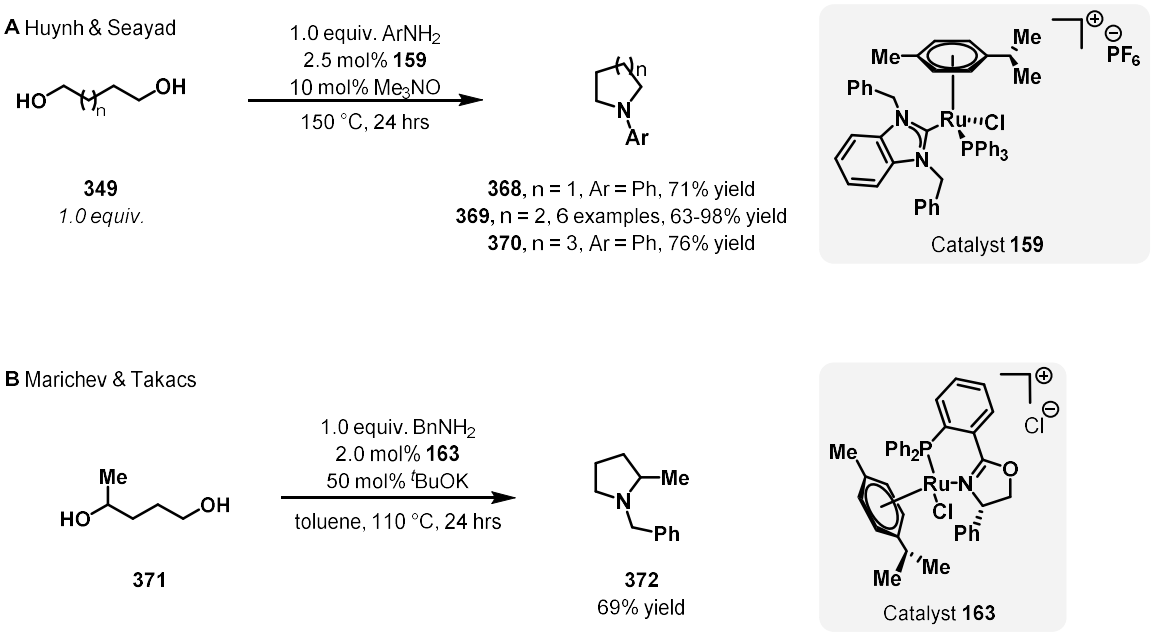
Further to Williams' report of iridium-catalysed hydrogen borrowing in aqueous media,[69] Fujita and Yamaguchi developed a water-soluble iridium-Cp* complex bearing ammonia ligands, which was shown to be effective for hydrogen borrowing in water. A wide range of substrates were demonstrated, including a small number of cyclic substrates **365**–**367**, which were isolated in good to excellent yields (**Scheme 3.6**).[148]



Scheme 3.6: *Water soluble catalyst, $[IrCp^*(NH_3)_3]I_2$, was shown to be effective for the synthesis of pyrrolidine **365**, piperidine **366** and azepane **367**.*[148]

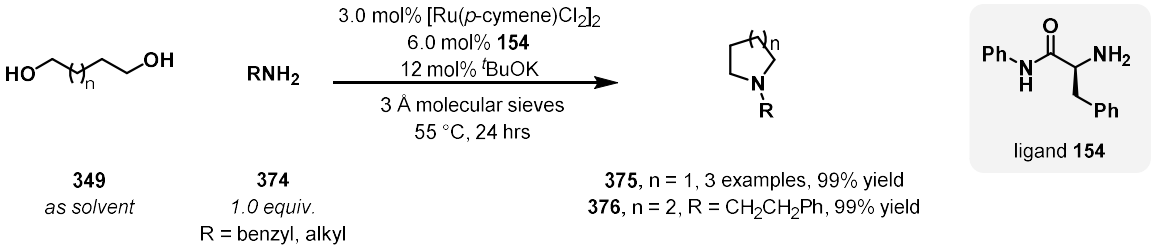
In recent years, further development of hydrogen borrowing methodology for C–N bond formation has centred on the discovery of novel catalysts systems. Elaborate ruthenium catalysts have been developed for hydrogen borrowing, for example catalyst **159** by Hunyh and Seayad, which bears an *N*-heterocyclic carbene (NHC) ligand, was shown to give rise to a range of *N*-heterocycles **368**–**370** in good yields, (**Scheme 3.7A**).[77]

In 2016, Marichev and Takacs reported the development of ruthenium catalyst **163**, which enabled the reaction of benzylamine with substituted diol **371** (in a 1:1 ratio) and furnished pyrrolidine **372** in 69% yield (**Scheme 3.7B**). This catalyst was also found to be selective for reaction at a primary alcohol when employed at lower loadings (1 mol%).[78]



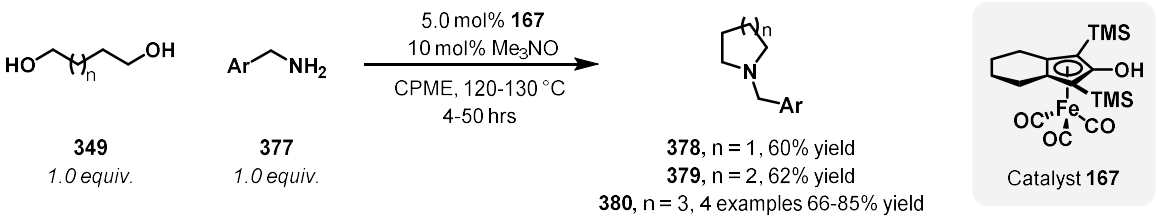
Scheme 3.7: *Novel ruthenium catalysts for hydrogen borrowing and their applications to heterocycle formation by **(A)** Huynh and Seayad[77] and **(B)** Marichev and Takacs.*[78]

The majority of *N*-heterocycle formations discussed in this section require elevated temperatures (115-180 °C) for the hydrogen borrowing reaction to proceed. Enyong and Moasser showed that a combination of readily available amino acid-derived ligand **154** and $[Ru(p\text{-cymene})Cl_2]_2$ allows for amine alkylation and efficient construction of pyrrolidines **375** and piperidine **376** at a much lower temperature (55 °C). However, it was necessary to use a large excess of diol **349** (**Scheme 3.8**).[76]



Scheme 3.8: *Use of aminoacid ligand **154**, developed by Enyong and Moasser.*[76]

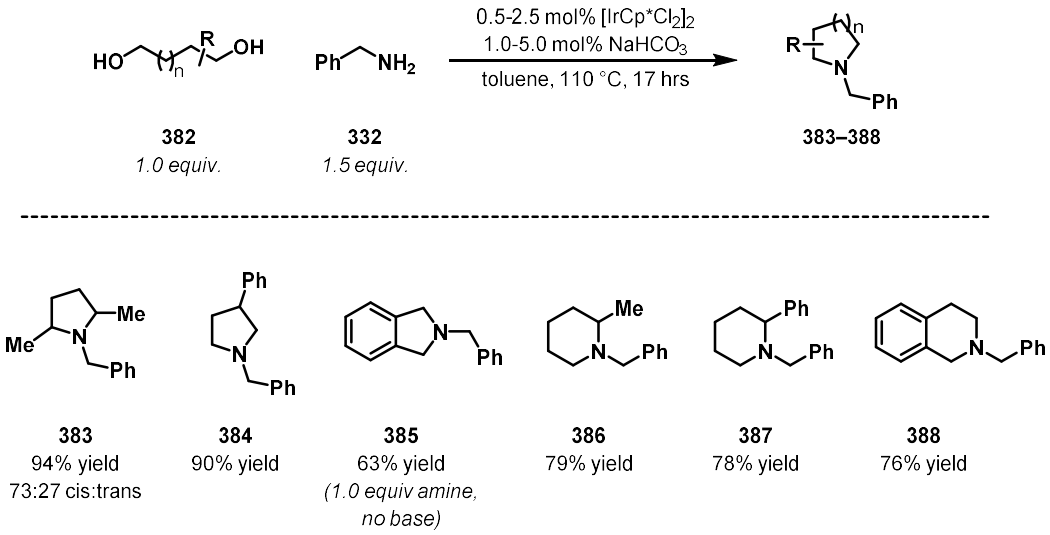
Hydrogen borrowing reactions tend to rely on precious transition metal catalysts such as iridium, ruthenium and rhodium, which can be expensive. Iron is often considered an attractive alternative for ruthenium due to its high abundance, low cost and thus, sustainability.[149] The first reports of iron catalysed hydrogen borrowing for C–N bond formation were published by Feringa and Barta in 2014, who demonstrated the use of Knölker's catalyst **167** for a range of amine alkylations, including the synthesis of pyrrolidine **378**, piperidines **379** and azepanes **380** in good yields (**Scheme 3.9**).[80]



Scheme 3.9: *Use of iron catalyst **167** for heterocycle synthesis under hydrogen borrowing catalysis by Feringa and Barta.* [80]

There has been considerable application of hydrogen borrowing catalysis to the synthesis of pyrrolidines, piperidines and azepanes, and a number of catalyst systems and reaction conditions have been developed over a 25-year period. The majority of contributions focus on the development of *N*-alkylation of acyclic substrates, with only a few heterocyclic systems being demonstrated in each case. Overall, a wide range of aromatic, benzylic and alkyl amines have been employed in their reactions with diols. However, in all of the work described in this section; only one report pertains to a substituted diol; the synthesis of 2-methylpyrrolidine **372** from diol **371** as demonstrated by Takacs (**Scheme 3.7B**).[78]

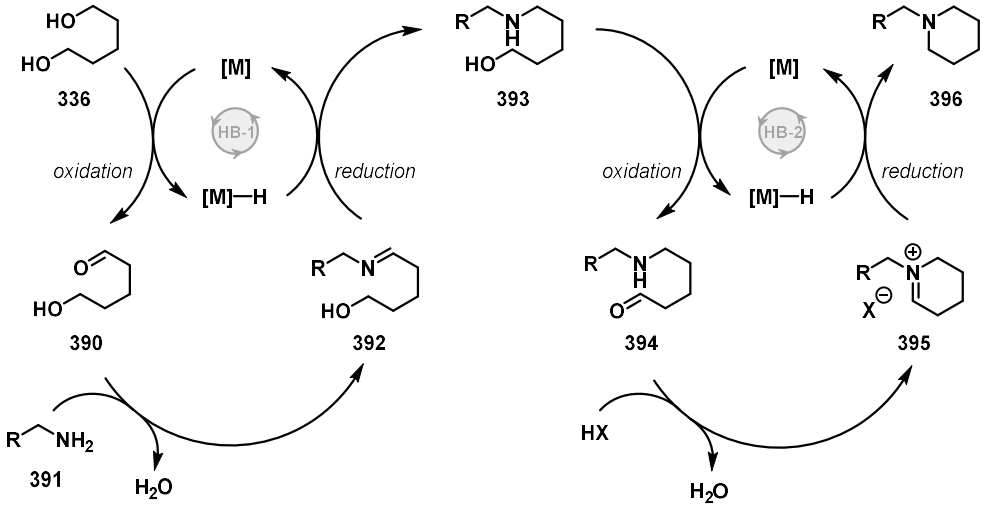
This lack of substrate diversity was partially addressed by Fujita and Yamaguchi in 2004. Using $[Cp^*IrCl_2]_2$, in combination with catalytic $NaHCO_3$, they focussed on heterocycle formation and a number of five-, six- and seven-membered nitrogen heterocycles **383**–**388** were synthesised in good yields, including a small number of substituted examples (**Scheme 3.10**). Simple methyl or aryl substituents were investigated, as well as fused bicyclic systems **385** and **388**.[150]



Scheme 3.10: *Iridium-catalysed hydrogen borrowing published by Fujita and Yamaguchi. Only carbon-substituted examples are shown.*[150]

3.1.1 Mechanism

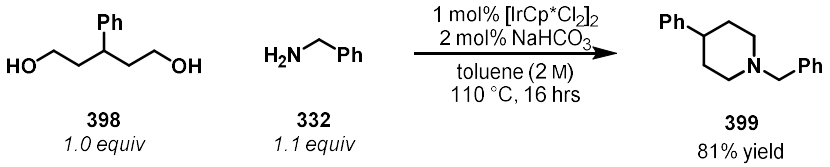
A number of groups have proposed mechanisms for the formation of C–N bonds under hydrogen borrowing catalysis, but these tend to concern acyclic systems, since this is the focus of most work.[70,77,80,148] Fujita and Williams have proposed mechanisms for cyclic products with iridium catalysts.[66,150] The process involves two hydrogen borrowing cycles and in order to aid discussion, these cycles will be referred to as HB-1 and HB-2 from here onwards (**Scheme 3.11**). In HB-1, diol **336** is oxidised by the catalyst to form carbonyl species **390** and giving rise to a metal hydride species.[148] Condensation of aldehyde **390** with the amine partner gives rise to imine **391**, which is reduced when the catalyst returns the 'borrowed' hydrogen. Intermediate **393** enters the HB-2 cycle, the difference now is that heterocycle **396** is formed following the reduction of iminium ion **395**. Overall the process is redox-neutral and generates water as the only byproduct.



Scheme 3.11: *Proposed mechanism for the intramolecular hydrogen borrowing to form piperidines, based on work from Watanabe, Fujita and Williams.*[144,66,150]

3.1.2 Previous work in the Donohoe Group

Hydrogen borrowing methodology for the formation of C–C bonds has been a mainstay of the Donohoe group since 2014, with the most recent efforts focussed on the construction of saturated carbocycles.[59,151] The synthesis of piperidines using hydrogen borrowing began as a part II project undertaken by Kieran Paterson, with the primary aim to increase and diversify the reaction substrate scope relative to that previously published by Fujita.[150] At the outset of the project, reaction optimisation studies were carried out using 3-phenylpentane-1,5-diol **398** as the model substrate. Variations in amine loading, catalyst loading, reaction time and temperature were all investigated.[152] This led to the optimum conditions shown in **Scheme 3.12**, using just 1 mol% of $[IrCp^*Cl_2]_2$ catalyst, 2 mol% $NaHCO_3$ and 1.1 equiv. amine in toluene at 110 °C.

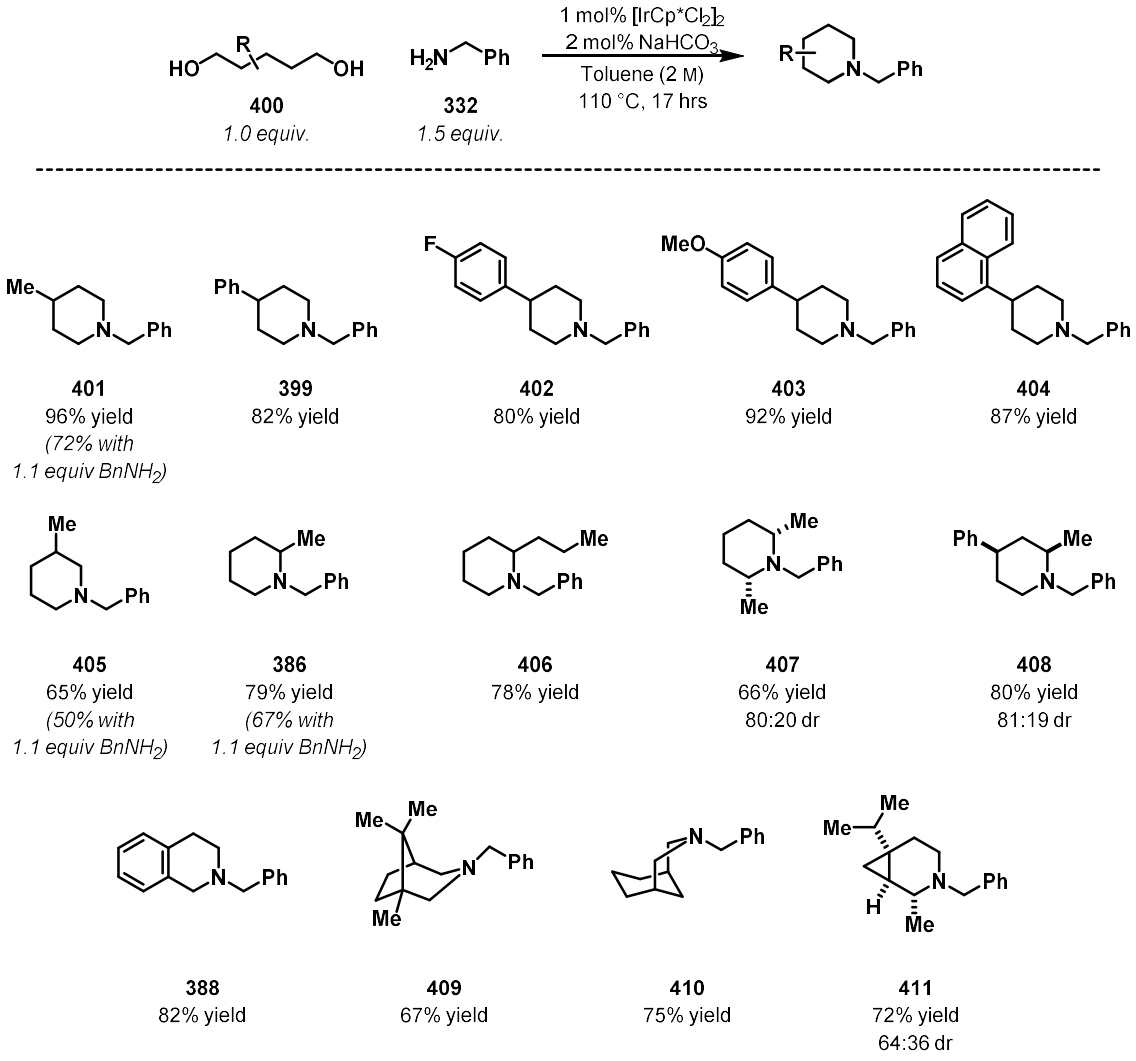


***Scheme 3.12**: Optimised reaction conditions as developed by Kieran Paterson.[152]*

During the synthesis of methyl-piperidines **386**, **401** and **405**, it was found that an increase in amine loading gave rise to significant improvements in yield and so reaction scoping studies were carried out using 1.5 equivalents benzylamine **332** (**Scheme 3.13**).[152]

Simple alkyl- and aryl-substituents were well tolerated at the 4-position, giving rise to piperidines **401** and **399** in excellent yields. This also extended well to electron-poor *p*-fluorobenzyl substrate **402**, electron-rich *p*-methoxybenzyl substrate **403** and bulkier naphthyl piperidine **404**, which gave the cyclic amine products in high yields. An alkyl substituent at the 3-position gave rise to slightly decreased yield of piperidine ***rac*-405**, but was better tolerated at the 2-position, giving **386** in 79% yield. Piperidine **406** is, in fact, *N*-benzyl protected coniine, providing a facile route to this simple natural product from the corresponding *n*-propyl substituted pentanediol. Disubstituted piperidines **407** and ***rac*-408** were furnished in good yield and diastereoselectivity, and the

methodology was further extended to bicyclic ring systems **388**, **409** and **410** with good yields. Piperidine **411** was synthesised from a thujone-derived diol in 72% yield and 64:36 dr (**Scheme 3.13**).[152]



Scheme 3.13: *Initial reaction scope carried out by Kieran Paterson. Major diastereomer depicted.*[152]

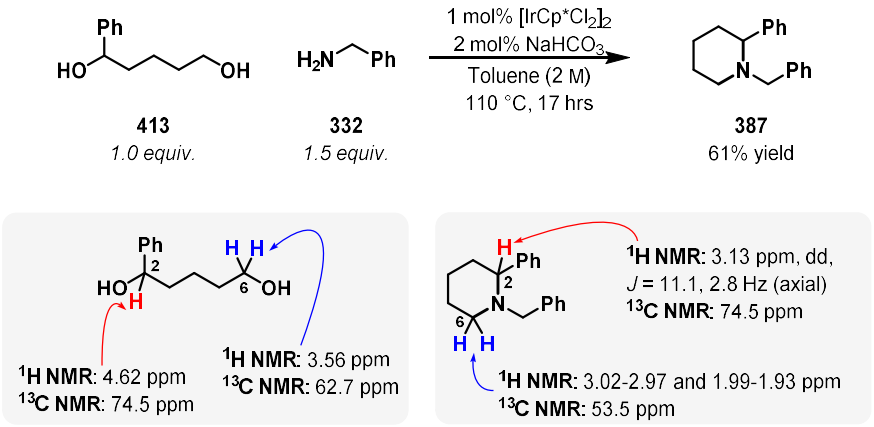
3.2 Project aims

Upon taking over this project, my aims were to:

1. Increase and diversify the existing substrate scope initiated by Kieran Paterson, with particular emphasis on the construction of complex molecular frameworks which were hoped to be of interest to pharmaceutical chemists.
2. Develop conditions for *N*-benzyl deprotection of the piperidine products. It was felt that the ability to easily cleave the nitrogen protecting group would be paramount to the utility of this methodology.
3. Investigate the application of hydrogen borrowing catalysis for the stereoselective synthesis of piperidines (discussed in **Chapter 4**).

3.3 Results and Discussion: Diol Substrate Scope Elaboration

Using the reaction conditions developed by Kieran Paterson, additional diols were investigated. Phenyl diol **413**[*] was synthesised by DIBAL-H reduction of δ-valerolactone, followed by reaction with phenylmagnesium chloride. Subjection of phenyl diol **413** to the hydrogen borrowing conditions gave rise to piperidine **387** in 61% yield (**Scheme 3.14**).



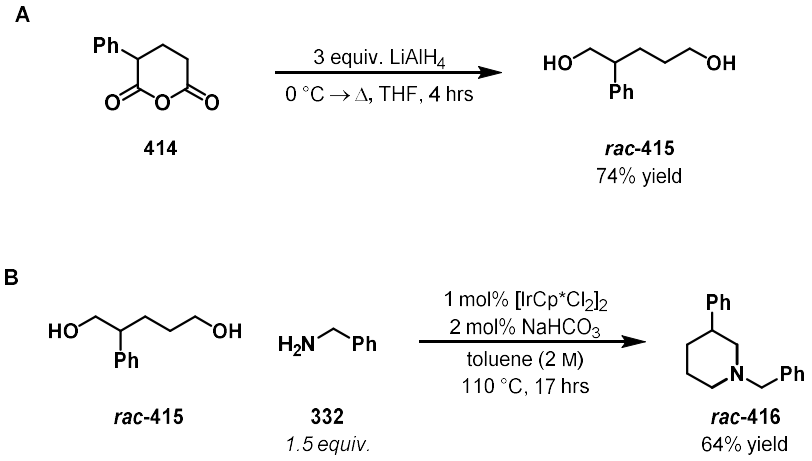
Scheme 3.14: *Synthesis of phenyl piperidine **387** and identification by ^{1}H and ^{13}C NMR spectroscopy.*

Phenyl piperidine **387** was identified by NMR spectroscopy and comparison to literature data.[153] A significant upfield shift was observed in both the ^{1}H and ^{13}C spectra at CH-2 and CH_2-6. For example, CH-2 is seen at 4.62 ppm for diol **413** and 3.13 ppm in the case of piperidine **387**. The corresponding carbon moves from 64.5 ppm in diol **413** to 62.7 ppm for piperidine **387**.[154] A similar observation was made for CH_2-6 (**Scheme 3.14**). This is characteristic of a transformation from the proton/carbon being adjacent to oxygen to becoming more shielded when adjacent to nitrogen. In addition, no O–H or N–H stretch was observed by IR spectroscopy and mass spectrometry analysis was in agreement with the expected mass for piperidine **387**. Similar analysis techniques were employed for all of the heterocycles synthesised.

2-Phenylpentane diol ***rac*-415** was synthesised in 74% yield by $LiAlH_4$ reduction of anhydride **414** (**Scheme 3.15A**). The hydrogen borrowing reaction of ***rac*-415** with benzylamine **332** furnished

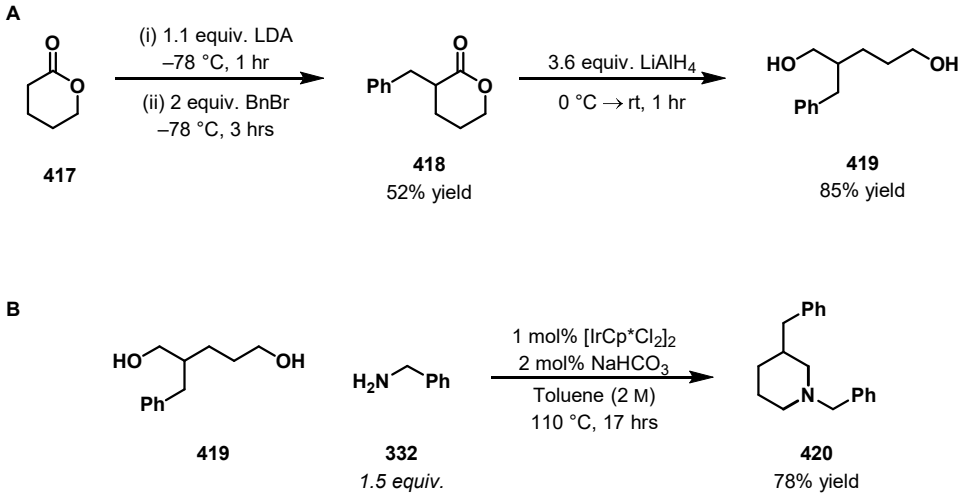
[*] Diol **413** was synthesised by Daniel Matheau-Raven

piperidine ***rac*-416** in 64% yield (**Scheme 3.15B**). This yield is comparable to the analogous 2-substituted piperidine **387.**



***Scheme 3.15: (A)** Synthesis of phenyl diol **rac-415** and **(B)** subjection to hydrogen borrowing reaction with benzylamine.*

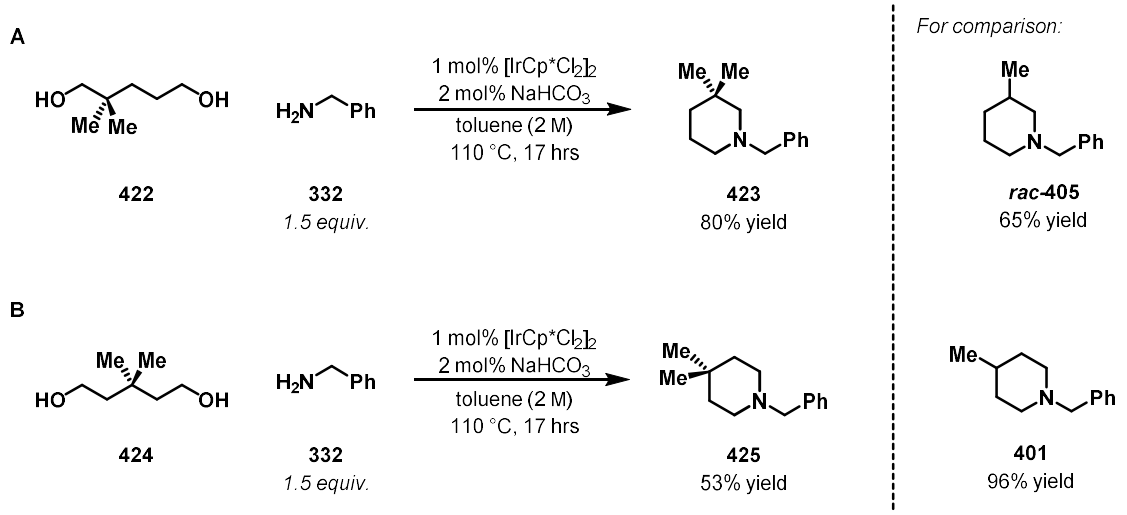
2-Benzylpentanediol **419** was synthesised in two steps from δ-valerolactone **417** by deprotonation with LDA, followed by alkylation with benzyl bromide. $LiAlH_4$ reduction of the resulting lactone **418** furnished diol **419** in 85% yield (**Scheme 3.16A**). Subjection of diol **419** to the hydrogen borrowing conditions gave rise to benzylpiperidine **420** in 78% yield (**Scheme 3.16B**).



***Scheme 3.16: (A)** Synthesis of diol **419** from δ-valerolactone. **(B)** Subjection of diol **419** to hydrogen borrowing conditions gave rise to piperidine **420**.*

3.3.1 Geminal-disubstituted piperidines

The inclusion of gem-dimethyl substituents on the diol backbone was predicted to give improved yields relative to monomethyl substrates **401** and ***rac*-405** due to the Thorpe-Ingold effect.[155] 2,2-Dimethyldiol **422** gave piperidine **423** in 80% yield, a significant improvement over monomethylsubstrate ***rac*-405** (**Scheme 3.17A**) which may be due to increased rate of cyclisation due to the presence of the additional methyl substituent. However, this trend did not hold true for 3,3-dimethyldiol **424** and dimethyl piperidine **425** was isolated in 53% yield *cf.* 96% yield of monomethyl product **401** (**Scheme 3.17B**).



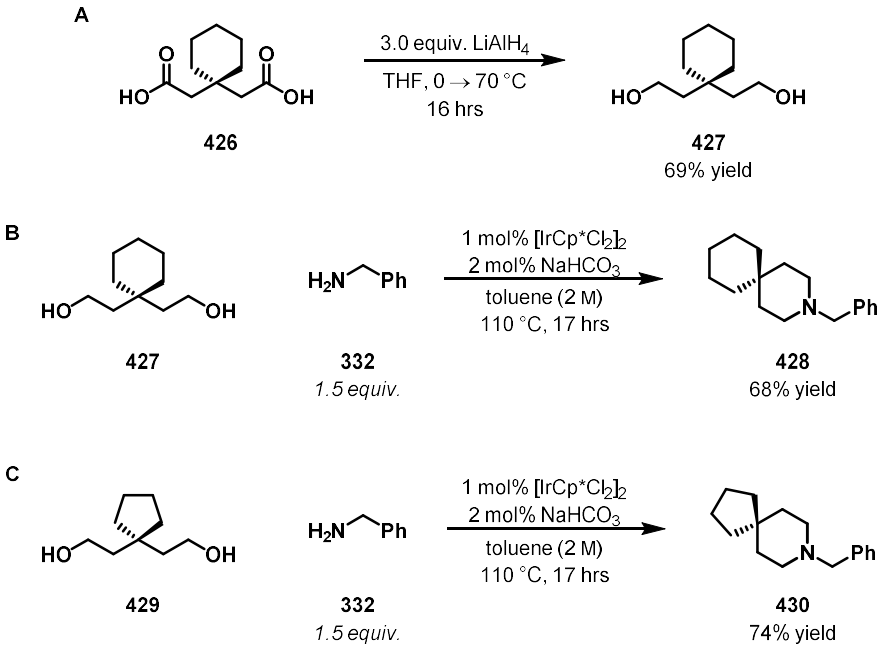
Scheme 3.17: *Subjection of gem-dimethyl diols **422** and **424*** to the hydrogen borrowing conditions gave rise to piperidines **423** and **425**. *Piperidine **rac-405** and **401** were prepared by Kieran Paterson.*

3.3.2 Spirocyclic piperidines

Cyclic diols **427** and **429** were also expected to produce a favourable Thorpe-Ingold effect. Diol **427** was synthesised in 69% yield *via* $LiAlH_4$ reduction of diacid **426** (**Scheme 3.18A**) and the corresponding diol **429** bearing a 5-membered ring was synthesised under an analogous procedure by Dr Roly Armstrong. Subjection of these diols to our hydrogen borrowing conditions with benzylamine **332** gave rise to spirocyclic piperidines **428** and **430** in 68% and 74% yield respectively (**Scheme 3.18B & C**). A number of spiro-heterocyclic natural products are known and

*Diol **422** and **424** were synthesised by Dr Roly Armstrong

have been found to exhibit a range of biological activities.[156] It is hoped that the synthesis of **428** and **430** will lead to the hydrogen borrowing catalysed synthesis of natural products featuring spiro-heterocyclic cores.



Scheme 3.18: (A) *Synthesis of diol* ***427*** *via reduction of diacid* ***426*** *with $LiAlH_4$.* ***(B)*** *and* ***(C)*** *Synthesis of spirocyclic products from diols* ***427*** *and* ***429****.*[*]

3.3.3 Multiply substituted diols

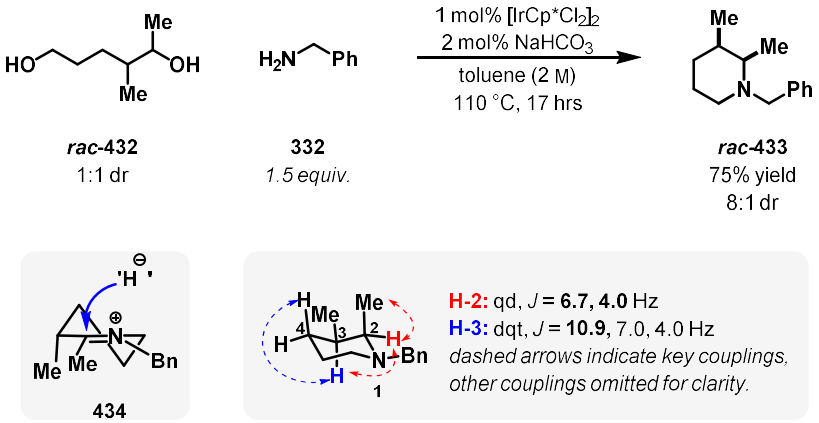
We were interested to investigate the effects of multiple ring substituents on the diastereoselectivity of the hydrogen borrowing reaction. In these cases, reduction of the final iminium ion is the diastereo-determining step. A number of di-substituted susbtrates were prepared and studied in order to investigate the effects of different substitution patterns on diastereoselectivity.

2,3-Disubstitution

Upon subjection to the hydrogen borrowing conditions with benzylamine **332**, 1,2-dimethyldiol ***rac*-432**[*] gave rise to piperidine ***rac*-433** in 75% yield and 8:1 dr (**Scheme 3.19**). The major diastereomer was determined to be the *syn* product by ^{1}H NMR spectroscopy. H-2 (2.77 ppm) was

[*] Diol ***rac*-432** was synthesised by Dr Roly Armstrong

observed to give a qd (J = 6.7, 4.0 Hz) with moderate coupling constant values which are indicative of equatorial geometry, whereas H-3 (1.89 ppm) gives rise to a dqt (J = 10.9, 7.0, 4.0 Hz) featuring a large coupling constant which indicates a dihedral angle of 180° with neighbouring H-4_{ax} and therefore, axial geometry.



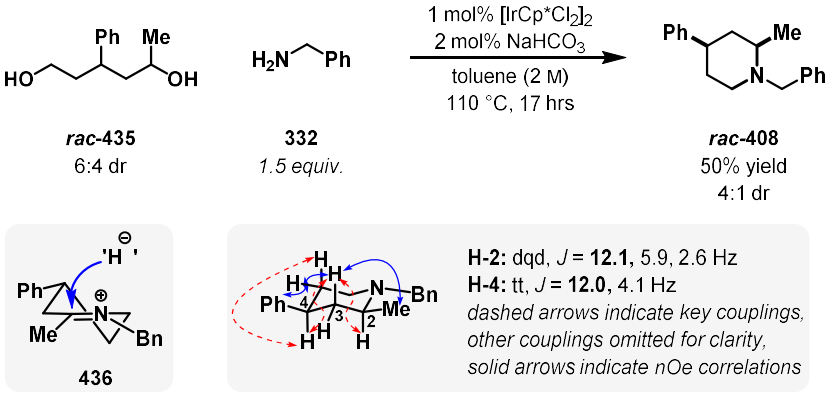
Scheme 3.19: *Synthesis of dimethyl piperidine* ***rac*-433** *from dimethyl diol* ***rac*-432**** *and Fürst-Plattner model for addition of the reductant. Major diastereomer depicted. Dashed arrows (red) indicate J couplings.*

The high diastereoselectivity can be rationalised by reduction from the top face of iminium ion **434**, in accordance with the Fürst-Plattner rule;[157] in which the 3-methyl group is forced axial in order to minimise $A^{1,2}$ strain with the neighbouring methyl group.[158] The reduction therefore takes place by axial addition of hydride from the top face of iminium ion **434** (as drawn in **Scheme 3.19**), and proceeds through a chair-like transition state.

2,4-Disubstitution

In the case of diol ***rac*-435**, piperidine ***rac*-408** was synthesised in moderate yield and 4:1 dr (**Scheme 3.20**). The major diastereomer was determined to have *cis* geometry by ^{1}H NMR coupling constant and nOe analysis. H-2 (2.37 ppm) gives rise to a dqd (J = 12.1, 5.9, 2.6 Hz) and was assigned to be axial due to the large coupling constant to H-3_{ax}. H-4 (2.58 ppm) was observed as a tt (J = 12.0, 4.1 Hz) which also includes a large coupling constant to the two adjacent axial protons (H-3_{ax} and H-5_{ax}) and therefore was also assigned to have axial geometry. In addition, nOe

correlations were observed between H-3$_{ax}$ ↔ Me and H-3$_{ax}$ ↔ Ph, which confirms that all three substituents are on the same face.



Scheme 3.20: *Synthesis of piperidine* ***rac*-408** *from diol* ***rac*-435**[*] *under hydrogen borrowing conditions and Fürst-Plattner model for addition of the reductant. Major diastereomer depicted. Dashed arrows (red) indicate J couplings, solid arrows (blue) indicate nOe correlations.*

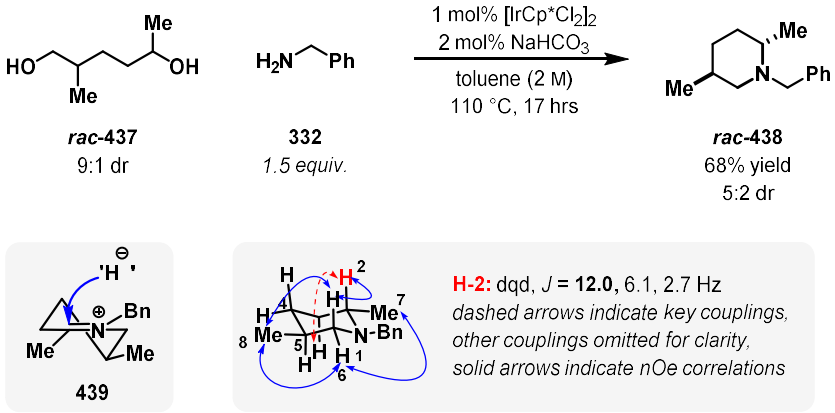
It is assumed that the bulky phenyl group adopts an equatorial position and iminium **436** is reduced by axial addition of [Ir]–H to the top face (as drawn in **Scheme 3.20**) which proceeds through a chair-like transition state. Reduction from the bottom face would go through a twist-boat transition state which is of higher energy than the chair-like transition state due to torsional and transannular strain, and therefore is disfavoured.

2,5-Disubstitution

Hydrogen borrowing reaction of diol ***rac*-437**[†] and benzylamine **332** resulted in the synthesis of 1,4-dimethyl piperidine ***rac*-438** in 68% yield and 5:2 dr. The major diastereomer is as depicted in **Scheme 3.21** and was assigned by coupling constant and nOe analysis. H-2 (2.12 ppm) was observed as a dqd (*J* = 12.0, 6.1, 2.7 Hz) in the ^{1}H NMR spectrum, with a large coupling constant to H-3, which indicates a 180° dihedral angle, and therefore H-2 was assigned to be axial. Unfortunately, H-5 was not fully resolved in the ^{1}H NMR spectrum but the peak shape appears to

[*] Diol ***rac*-435** was synthesised by Dr Roly Armstrong
[†] Diol ***rac*-437** was synthesised by Dr James Frost

contain large couplings and so axial geometry was tentatively assigned. The proposed geometry was confirmed by nOe correlations from both methyl groups to the neighbouring protons.

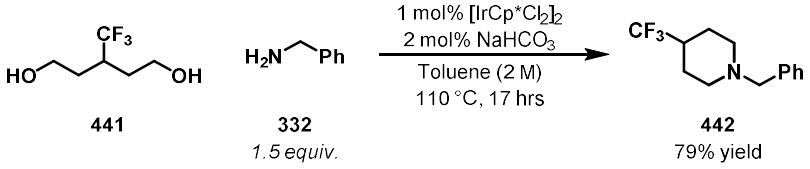


Scheme 3.21: *Synthesis of dimethyl piperidine* ***rac-438*** *from dimethyl diol* ***rac-437*** *** *and Fürst-Plattner model for addition of the reductant. Major diastereomer depicted. Dashed arrows (red) indicate J couplings, solid arrows (blue) indicate nOe correlations.*

The 2,3-dimethyl system ***rac*-433** gave the highest dr of the disubstituted systems studied and this was attributed to the locking methyl group being axially disposed. In comparison, the locking groups in both 2,4-disubstituted ***rac*-408** and 2,5-disubstituted ***rac*-438** adopt an equatorial position however, the methyl substituent is significantly less bulky than the phenyl substituent. It is noted that the decrease in dr observed for dimethyl substrate ***rac*-438** (locking Me group, 5:2 dr, A = 1.7 kcal mol^{-1}) relative to ***rac*-408** (locking Ph group, 4:1 dr, A = 2.8 kcal mol^{-1}) is in accordance with the ratio between the A-values.[159]

3.3.4 Diols featuring heteroatom substituents

We sought to synthesise medicinally relevant piperidine scaffolds and were aware of the increasing prevalence of fluorinated groups in APIs due to its utility as a bioisotere.[160,161] Fluorinated diols had proven unsuccessful in other C–C bond forming hydrogen borrowing methodology in the Donohoe group. However, our conditions for hydrogen borrowing with amines were significantly less forcing due to the presence of mild, catalytic base. We found that trifluoromethyl piperidine **442** could be isolated in 79% yield under our conditions from the corresponding trifluoromethyl diol **441** (**Scheme 3.22**).



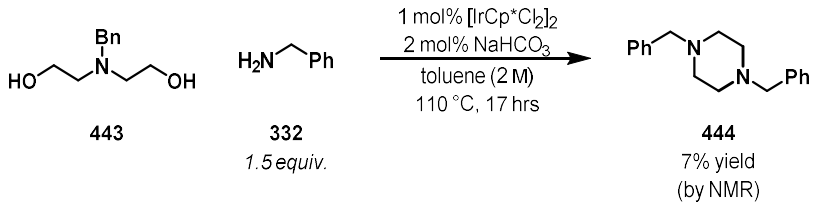
Scheme 3.22: *Synthesis of fluorinated piperidine **442** under hydrogen borrowing conditions from diol **441**.*[*]

[*] Diol **431** were synthesised by Dr Roly Armstrong

3.4 Results and Discussion: synthesis of heterocycles bearing more than one heteroatom

Heterocycles featuring more than one heteroatom, for example piperazines and morpholines, are of great interest in the pharmaceutical industry due to their prevalence in biologically active molecules. Analysis of a 2014 database of FDA-approved small molecule drugs revealed that of the 59% of structures containing at least one nitrogen heterocycle, 16% of these are piperazine scaffolds and 3% feature morpholine rings.[3]

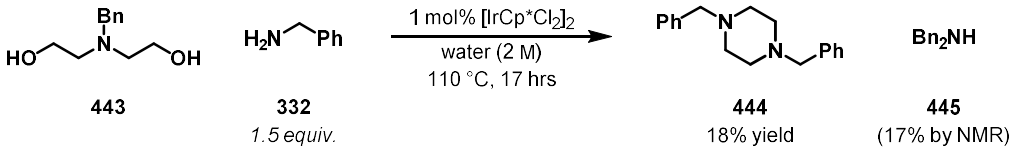
Watanabe and co-workers reported the synthesis of piperazines and morpholines under ruthenium-catalysed hydrogen borrowing catalysis in 1985 but there have been few examples in recent years (**Section 3.1**).[144] We were interested to apply our methodology to the synthesis of piperazine **444** from benzylamine **332** and aminodiol **443**.* Unfortunately, under the original hydrogen borrowing conditions in toluene, the reaction did not go to completion and only trace piperazine **444** was observed by NMR spectroscopy (7% yield calculated relative to an internal standard, **Scheme 3.23**). The majority of the material was unreacted diol **443** although it was suspected that diol **443** was partially degraded to give a complex mixture of products.



Scheme 3.23: *Synthesis of piperazine **444** under hydrogen borrowing catalysis. Yield was calculated by comparison to an internal standard; 1,1,2,2-tetracholoethane.*

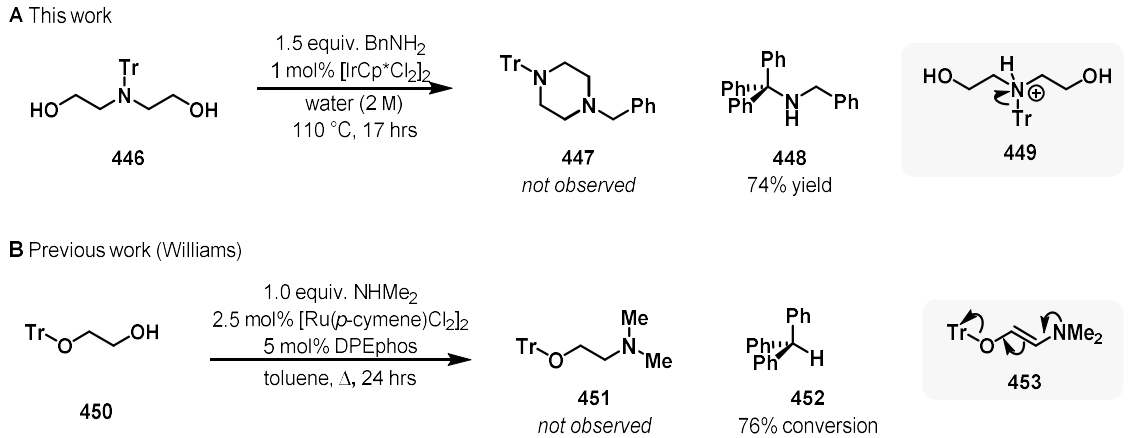
The synthesis of piperazine **444** was also attempted in water (for development of these conditions, see **Section 4.4**). Using these milder conditions, piperazine **444** was synthesised in slightly increased yield of 18% from aminodiol **443*** and benzylamine **332** (**Scheme 3.24**).

* Aminodiol **443** was synthesised by Kieran Paterson



Scheme 3.24: *Synthesis of piperazine **444** under hydrogen borrowing catalysis in water. It was not possible to separate **444** from the dibenzylamine **445** byproduct*

We postulated that the aminodiol starting materials may be able to coordinate to the iridium catalyst, thus inhibiting reaction. In order to prevent this, we sought a bulky nitrogen protecting group and so the synthesis of trityl-protected piperazine **447** from aminodiol **446**[*] and benzylamine **332** was attempted. However, the desired product **447** was not observed and instead trityl-protected benzylamine **448** was isolated in 74% yield (**Scheme 3.25A**). A similar loss of the trityl group was noted by Williams and co-workers during attempted alkylation of dimethylamine with trityl ether **450**, instead only triphenylmethane **452** was isolated (**Scheme 3.25B**). The authors postulated that the alcohol **450** is oxidised to the corresponding aldehyde and underwent condensation with the amine. Enamine **453** collapsed to eject Ph_3C^- which is too bulky to be able to recombine with the iminium species and so, gains a proton to yield **452**.[70] However, in our case the observed trityl benzylamine product **448** suggests loss of the trityl group *via* an S_N1 pathway, and the resulting bulky carbocation reacts with benzylamine to form **448**.

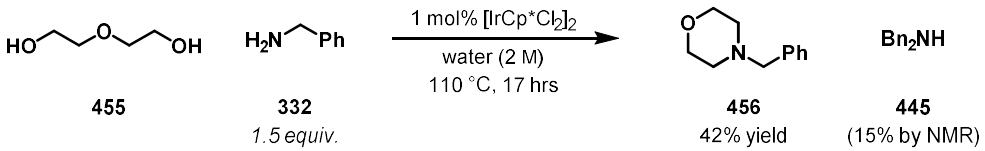


Scheme 3.25: (A) *Subjection of trityl protected aminodiol **446** to the hydrogen borrowing reaction in water.*

[*] Aminodiol **446** was synthesised by Christopher Hall

***(B)** Previous work by Williams and co-workers reported* O*-trityl deprotection under ruthenium-catalysed hydrogen borrowing.*[70]

The synthesis of morpholine substrates under the hydrogen borrowing reaction in water was also briefly investigated. Diethylene glycol **455** and benzylamine **332** were subjected to the new base-free hydrogen borrowing conditions in water and morpholine **456** was isolated in 42% yield (**Scheme 3.26**). The low yield was attributed to partial degradation of diethylene glycol **455**, but it was not possible to isolate or identify these degradation products.



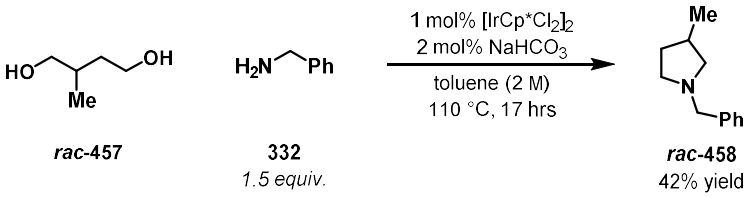
***Scheme 3.26:** Synthesis of morpholine **456** under base-free hydrogen borrowing catalysis in water.*

Under the mild hydrogen borrowing conditions in water, several heterocycles bearing more than one heteroatom have been synthesised. Although the yields are lower than those obtained for the corresponding piperidines, there is potential for further development in the future. Given the high worth of such compounds it is hoped the further screening efforts can be carried out in the future.[3]

3.5 Results and Discussion: Synthesis of Small Ring Sizes

3.5.1 Synthesis of pyrrolidines

The majority of previous heterocycles synthesised under hydrogen borrowing catalysis concern the formation of five-membered rings, including the first example by Grigg and co-workers.[60] Based on this, and bearing in mind the prevalence of pyrrolidines in APIs, we were interested to apply our original hydrogen borrowing conditions to the synthesis of pyrrolidine ***rac*-458**.[3] Applying our conditions to 1,4-diol ***rac*-457**[*] was found to give rise to pyrrolidine ***rac*-458** in 42% yield (**Scheme 3.27**).

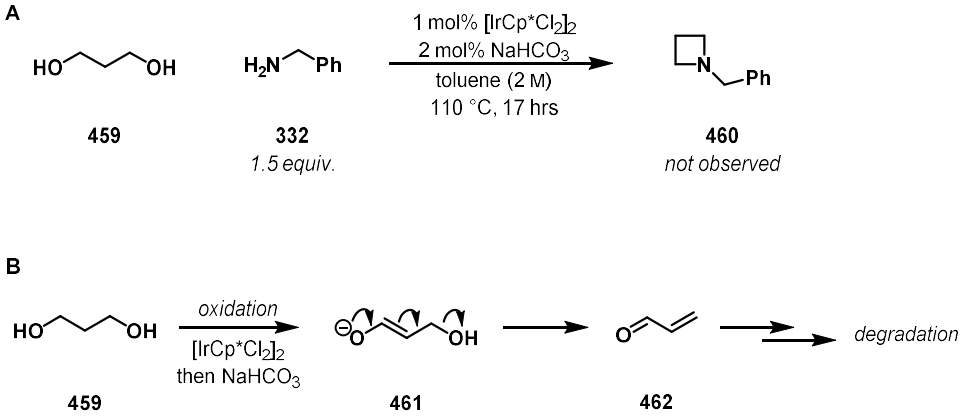


Scheme 3.27: *Synthesis of pyrrolidine* ***rac-458*** *under hydrogen borrowing catalysis from diol* ***rac-457***.[*]

3.5.2 Attempted synthesis of azetidines

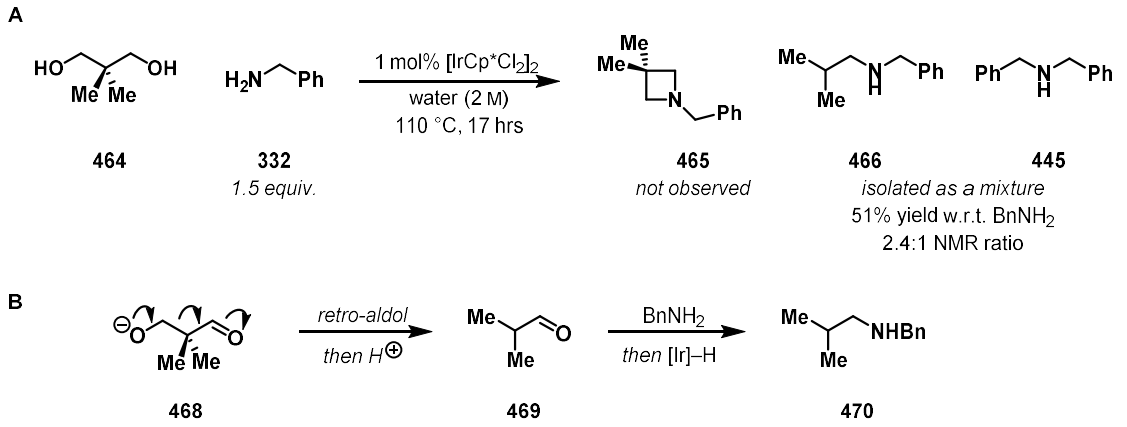
There is currently no literature precedence for the synthesis of azetidines under hydrogen borrowing catalysis, which indicates challenges inherent to this route, for example, starting material degradation. Application of 1,3-propanediol **459** in the original $NaHCO_3$/toluene hydrogen borrowing conditions was briefly investigated by Kieran Paterson (**Scheme 3.28A**), but unfortunately, the expected azetidine **460** was not observed. It was proposed that partially oxidised diol **461** degraded via an $E1_{CB}$ pathway under the reaction conditions (**Scheme 3.28B**).[152]

[*] Diol ***rac*-457** was synthesised by Dr Roly Armstrong



Scheme 3.28: (A) *Kieran Paterson's subjection of propanediol* ***459*** *to the original hydrogen borrowing conditions in toluene and* ***(B)*** *proposed degradation pathway.*[152]

The synthesis of azetidines was revisited following the development of the base-free hydrogen borrowing conditions in water. It was hoped that the absence of base would serve to prevent degradation of diol **459**. Initially, gem-dimethyl diol **464** was chosen as it was thought that the Thorpe-Ingold effect would promote cyclisation to form the azetidine.[155] This substrate is unable to form enol conjugate base **461** and therefore it was postulated this would also help prevent degradation of the starting material. However, hydrogen borrowing catalysis was not found to give rise to azetidine **465**. Instead, amines **466** and **467** were identified from the ^{1}H NMR spectroscopy of the crude reaction mixture by comparison to literature data and by mass spectrometry (**Scheme 3.29A**).[162] It was proposed that oxidised intermediate **468** can fragment *via* a retro-aldol process to yield aldehyde **469**, which then undergoes hydrogen borrowing reaction with benzylamine **332** to yield amine **470** (**Scheme 3.29B**).



Scheme 3.29: (A) *Attempted synthesis of azetidine* ***465*** *under hydrogen borrowing catalysis and* ***(B)*** *proposed mechanism for starting material degradation.*

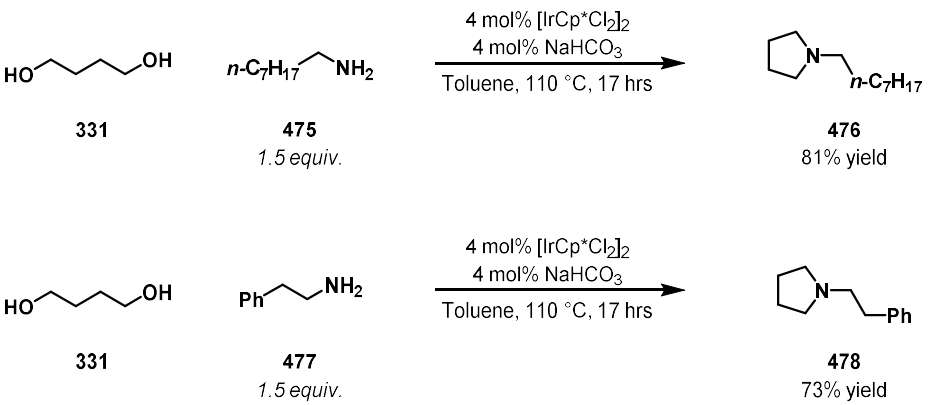
A number of other propanediols **471**–**474** were also subjected to hydrogen borrowing reaction with benzylamine **332** under the new base-free conditions in water (**Scheme 3.30**). In all cases, the desired azetidines were not observed. A wide range of amine products similar to that shown in **Scheme 3.29A** were tentatively identified but the NMR spectra were often complex and difficult to interpret. However, in all cases, evidence for the formation of dibenzylamine **445** was observed. These products were thought to have formed from either degradation of the diol by $E1_{CB}$ and subsequent reaction with benzylamine, or degradation of the intermediate aminoalcohol (**Scheme 3.29B**).

Scheme 3.30: *Unsubstituted, mono- and dimethyl propanediols investigated for the synthesis of azetidines under hydrogen borrowing chemistry.*

The problems with cyclobutane formation appeared to be due to inherent degradation of propanediols and hence the synthesis of azetidines *via* hydrogen borrowing catalysis was not investigated further.

3.6 Results and Discussion: Investigation of Alternative Amines

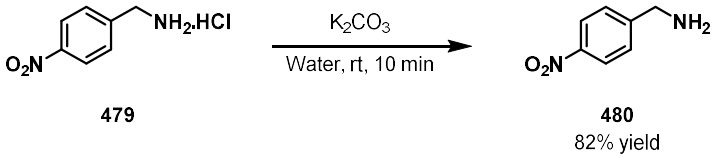
To date, efforts in our group have focussed on the use of benzylamine as the amine partner in the hydrogen borrowing reaction. There is precedent for the use of alkyl amines such as *n*-octylamine **475**, which was shown to give rise to pyrolidines **476** and **478** by Fujita and co-workers (**Scheme 3.31**).[150] Ultimately, it was felt that the utility of our methodology relied heavily upon the ability to remove the nitrogen protecting group and therefore only benzyl amines have been investigated, since *N*-benzyl groups may be readily deprotected by hydrogenolysis.



Scheme 3.31: *Use of alkyl amines **475** and **477** by Fujita was found to give rise to the corresponding pyrrolidines in good yields.*[150]

3.6.1 Amine synthesis

Before setting out to thoroughly investigate the effects of different amines on the hydrogen borrowing reaction, it was first necessary to synthesise *p*-nitrobenzylamine **480**. Other amines discussed in this section were obtained from commercial suppliers and used without further purification. *p*-Nitrobenzylamine was purchased as the hydrochloride salt **479** and the free amine **480** was obtained by reaction with potassium carbonate, which was found to proceed in good yield (**Scheme 3.32**). Unfortunately, it was found that amine **480** is not stable to air or moisture upon standing, but this problem was negated by ensuring amine **480** was carried forward to the hydrogen borrowing reaction immediately.



479 **480** 82% yield

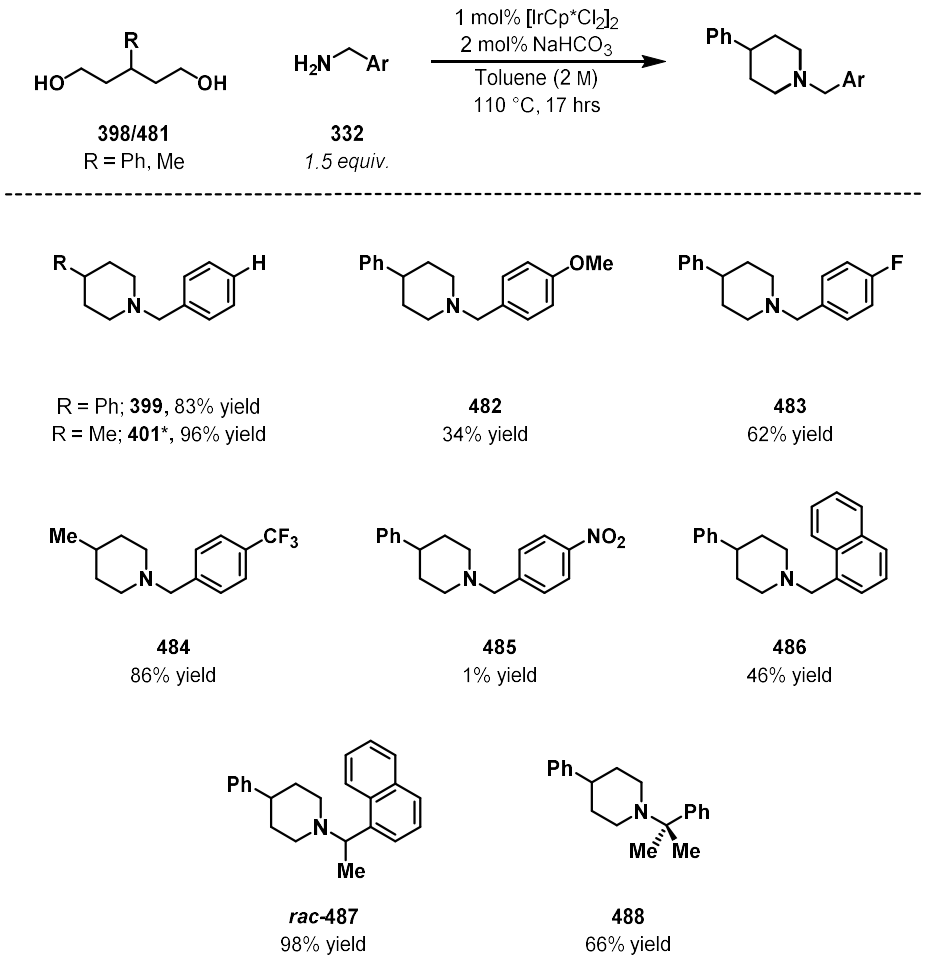
Scheme 3.32: *Synthesis of amine **480**.*

3.6.2 Amine scope

We examined a range of benzylamines bearing electron-donating, electron-withdrawing and bulky aryl groups in the hydrogen borrowing reaction with 3-phenylpentanediol **398** (**Scheme 3.33**). Given that the proposed mechanism involves nucleophilic addition of the amine to carbonyl intermediate **390** and an intramolecular nucleophilic addition of intermediate **394**, we expected that the electronic nature of the amine would have a significant effect on the yield. Substituents with a positive inductive effect would be expected to increase the nucleophilicity of the nitrogen lone pair and thus result in increased product yield relative to benzylamine product **399**/**401**. However, it was found that *p*-methoxybenzylamine gave rise to a poor yield of piperidine **482**, despite the increased nucleophilicity (σ_p = –0.28[163]). This may be because the more electron-rich substituent hinders nucleophilic addition of hydride to iminium **395** in the final reduction step. Conversely, *p*-fluorobenzylamine (σ_p = +0.15[163]), despite being more electron-deficient than benzylamine, was found to give rise to piperidine **483** in 62% yield, which is also significantly lower than *N*-benzylpiperidine **401**[*]. Conversely, the more strongly electron-deficient *p*-(trifluoromethyl)benzylamine (σ_p = +0.53[163]) gave rise to piperidine **484** in 86% yield. The very strongly electron withdrawing *p*-nitro group (σ_p = +0.81[163]) gave only trace amount of product **485**. This may be because the amine moiety is no longer sufficiently nucleophilic to attack the carbonyl intermediate **390**/**394**. Transfer hydrogenation of nitroarenes to anilines has been achieved under iridium catalysis by Cai and co-workers and it is possible a similar process occurs under our conditions.[164] The resulting aniline would likely chelate the catalyst and prevent the desired reaction from taking place. These results indicate that the electronic requirements of different

[*] Piperidine **401** was synthesised by Kieran Paterson

steps of the mechanism (**Scheme 3.11**) are very finely balanced and the relationship to amine nucleophilicity is not as simple as first thought.

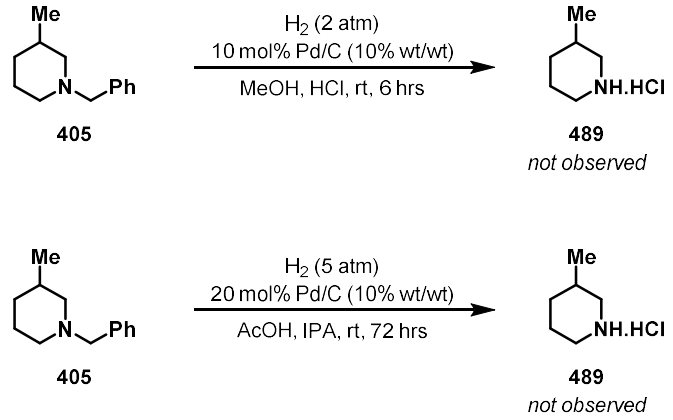


Scheme 3.33: *Investigation of alternative amines for hydrogen borrowing using diol **398** or **481**. *Synthesised by Kieran Paterson.*[152]

We were also interested to investigate the effects of more hindered amines, such as naphthalenyl-1-methanamine which gave piperidine **486** in 46% yield upon reaction with diol **398**. Inclusion of a methyl group at the α-position gave rise to a dramatic increase in yield and piperidine ***rac*-487** was isolated in 98% yield. We were also pleased to find that cumylamine gave rise to piperidine **488** in 66% yield, despite the increased bulk adjacent to the amine moiety (**Scheme 3.33**).

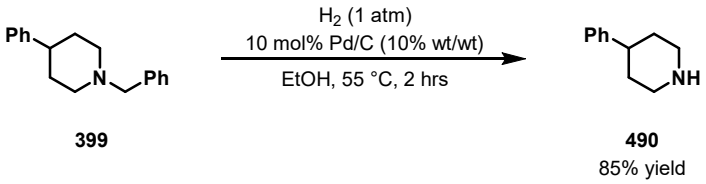
3.7 Results and Discussion: Amine Deprotection

The ease of nitrogen de-protection was paramount to the utility of our methodology and hence it was important to develop conditions to cleave the benzyl group. Kieran Paterson had previously attempted de-benzylation with palladium on carbon and either 2 or 5 atm hydrogen but was unable to obtain piperidine **489** (**Scheme 3.34**).[152]



Scheme 3.34: *Previous, unsuccessful attempts at debenzylation. Reactions carried out by Kieran Paterson.*[152]

Miao and co-workers reported hydrogenolysis of a similar compound during their synthesis of noranabasamine (discussed in more detail in **Section 4.1.2**).[165] We were pleased to find that application of these conditions to *N*-benzylpiperidine **399** resulted in a high yield of piperidine **490** after only 2 hours (**Scheme 3.35**). Formation of piperidine **490** was confirmed by the disapperarance of the benzyl CH_2 signal at 3.58 ppm in the ^{1}H NMR spectrum. The use of elevated temperature was important for this process, the hydrogenolysis was not observed to take place at room temperature.



Scheme 3.35: *Debenzylation of piperidine **399** under hydrogenolysis conditions.*

Chapter 4: Stereoselective Synthesis of Piperidines using Hydrogen Borrowing Catalysis

4.1 Introduction

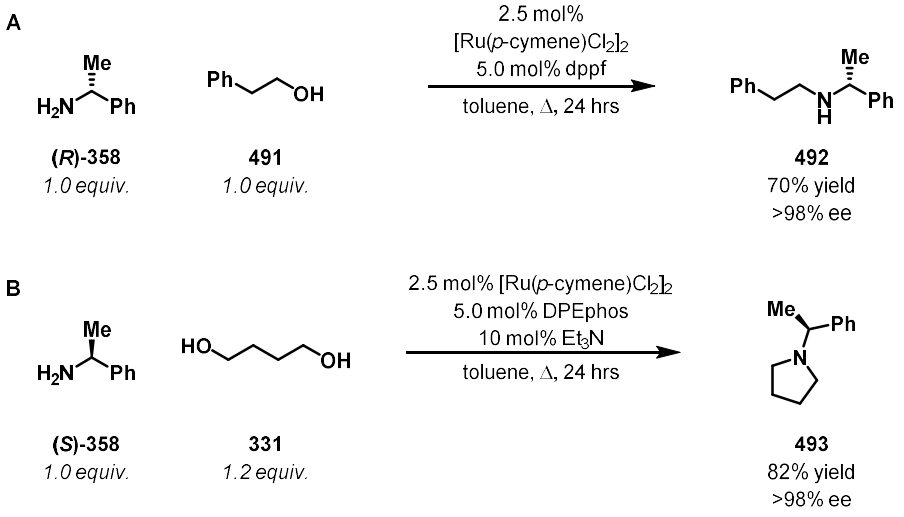
Recent years have seen a progression towards more architecturally diverse molecules in drug discovery. This move away from largely sp^2 character is known to favourably affect physical properties such as solubility, and hence compounds with a greater degree of saturation are of increasing interest. The fraction of compounds bearing one or more stereocentres has been found to increase through the drug development process, which may indicate that compounds with higher proportions of sp^3 centres are more likely to succeed. The presence of stereogenic centres also allows for improved selectivity and potency as this enables better interactions with the target to be engineered.[166] Increased complexity, and therefore increased numbers of chiral centres, has also been linked to reduced promiscuity and Cyp450 inhibition.[167] Given the prevalence of nitrogen heterocycles in pharmaceutical compounds, development of stereoselective means for their construction is therefore of great importance.[3]

We were interested to develop hydrogen borrowing conditions for the stereoselective synthesis of *N*-heterocycles, as set out in our initial project plans (**Section 3.2**), and this formed the basis of much of the work in this project. Whilst there are a few examples of asymmetric hydrogen borrowing reactions for C–N bond formation, this remains one of the major challenges in the field.[168]

4.1.1 Asymmetric amine alkylation under hydrogen borrowing catalysis

Stereoretention

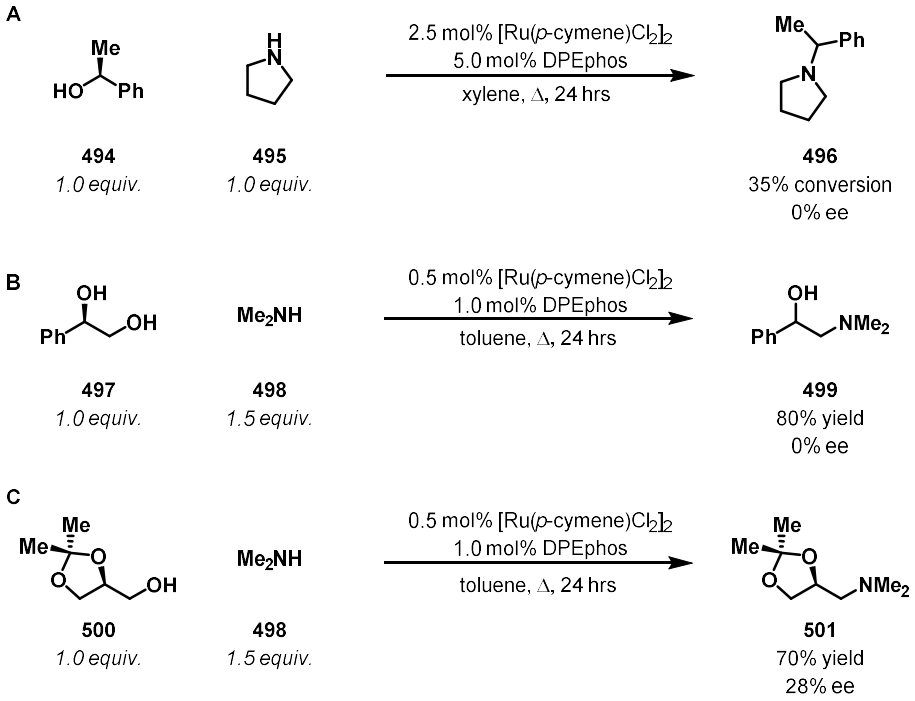
The Williams group have developed ruthenium-catalysed hydrogen borrowing for *N*-alkylation of amines and demonstrated its application to the construction of simple *N*-heterocycles (see **Section 3.1**). During this work, the use of enantiopure alcohols and amines was briefly considered as the authors were intrigued to determine whether stereochemical information could be retained. It was found that chiral amines could be employed with good results; the reaction of (*R*)-α-methylbenzylamine **(*R*)-358** with alcohol **491** was found to give rise to alkylated product **492** in 70% yield and >98% ee (**Scheme 4.1A**). Furthermore, the dual hydrogen borrowing reaction of diol **331** with (*S*)-α-methylbenzylamine **(*S*)-358** furnished pyrrolidine **493** in 82% yield and >98% ee (**Scheme 4.1B**). This indicates that there is no isomerisation of the intermediate imine, nor is direct oxidation of the amine taking place.[70]



Scheme 4.1: *Application of enantiopure amines in the hydrogen borrowing reaction with **(A)** alcohol **491** and **(B)** diol **331** by Williams and co-workers.*[70]

Reaction of an enantiomerically pure secondary alcohol **494** was found to give rise to racemic product **496**, which was expected since the reaction proceeds through oxidation of alcohol **494** to the corresponding ketone (**Scheme 4.2A**). In the case of diol **497**, amination was observed to occur selectively at the primary alcohol of the diol (**Scheme 4.2B**). However, erosion of enantiopurity at

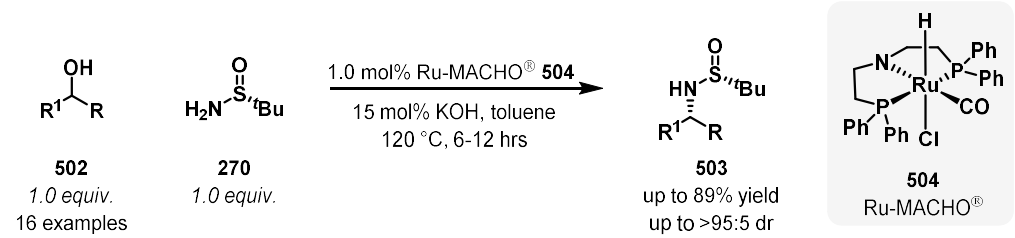
the secondary alcohol was observed and attributed to reversible oxidation to the corresponding ketone. Finally, protected enantiopure triol **500** was subjected to the ruthenium-catalysed hydrogen borrowing reaction with dimethylamine **498** and found to result in the formation of product **501** in 28% ee. This partial racemisation was attributed to enolisation of the aldehyde intermediate, or an iminium-enamine tautomerisation (**Scheme 4.2C**).[70]



Scheme 4.2: *Subjection of enantiopure alcohols to hydrogen borrowing catalysed amination.*[70]

Diastereoselective catalysis

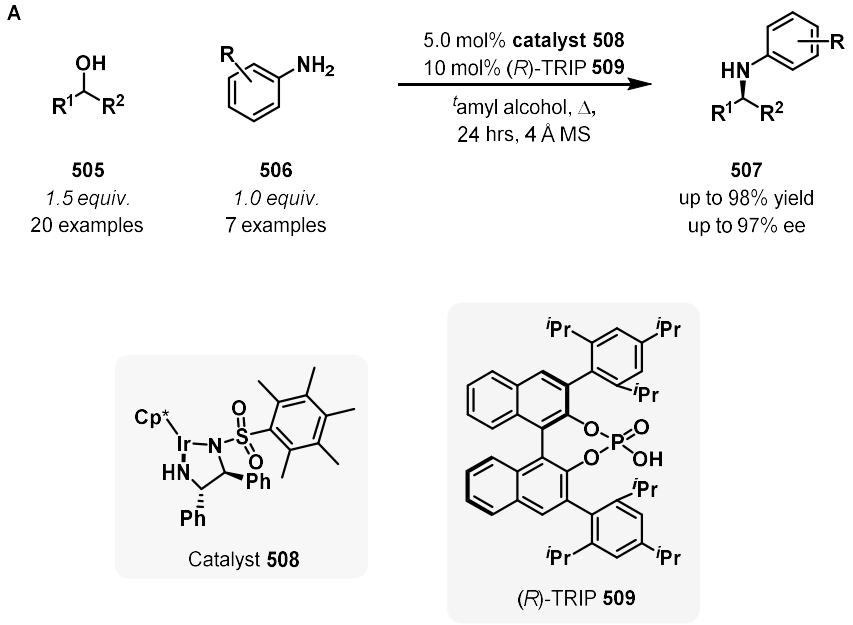
Guan and co-workers developed a diasteroselective hydrogen borrowing reaction for the sulfinamidation of alcohols using a ruthenium(II) PNP-type pincer catalyst **504**. This work employed an enantiopure Ellman's sulfinamide **270** and reaction with a range of secondary alcohols **502** gave the alkylated products **503** in good yields and, in the case where R^1 is aryl, complete diastereocontrol (**Scheme 4.3**). When R^1 = *n*-butyl or phenethyl the dr decreased to 70:30 and 75:25 respectively.[169]



Scheme 4.3: *Diastereoselective hydrogen borrowing reaction employing chiral sulfinamide* ***270****.*[169]

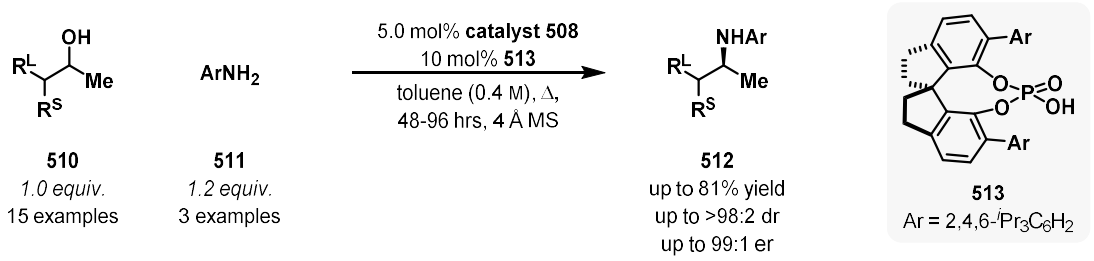
Enantioselective catalysis

The first example of enantioselective amination of alcohols under hydrogen borrowing catalysis was published by Zhao and co-workers in 2014, who employed a combination of Noyori–Ikariya-type iridium complex **508** with a bulky, chiral phosphoric acid cocatalyst, (*R*)-TRIP **509**. This work was one of the first examples of hydrogen borrowing amination under acidic conditions. The acid cocatalyst **509** was proposed to promote the condensation of the amine **506** and intermediate ketone therefore increasing reaction efficiency as well as enantioselectivity. Although a matched/mismatched relationship between the phosphoric acid and chiral catalyst was found, the chirality of the iridium catalyst was determined to be the overriding factor. A range of secondary alcohols **505** and aromatic amines **506** were investigated and high yields of aminated products **507** were isolated (**Scheme 4.4**). In most cases R^1 = methyl, and an increase in size to ethyl was found to give decreased er.[170]



Scheme 4.4: (A) *Enantioselective hydrogen borrowing catalysis for the amination of alcohols.*[170]

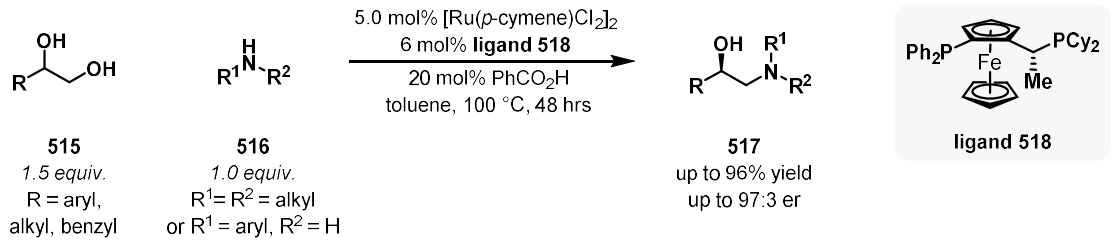
Subsequently, Zhao's group have applied iridium catalyst **508** in combination with SPINOL-derived phosphoric acid cocatalyst **513** to the first dynamic kinetic asymmetric amination of alcohols under hydrogen borrowing catalysis. This work provided an elegant and efficient method for the synthesis of α,β-branched amines **512** with high levels of enantio- and diastereoselectivity (**Scheme 4.5**).[171]



Scheme 4.5: *Dynamic kinetic amination of α-branched alcohols.*[171]

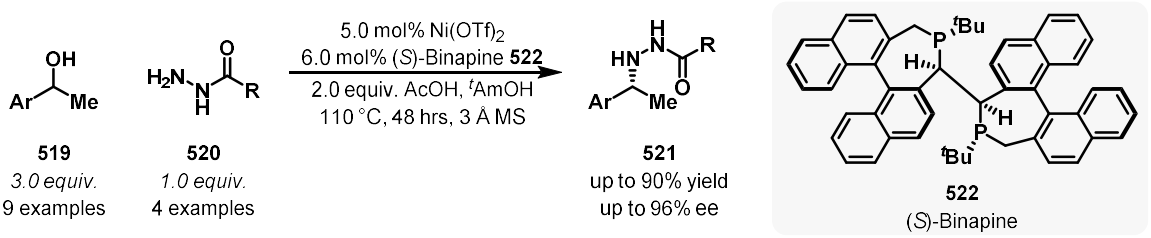
Zhao's group have also extended their dynamic kinetic resolution approach to the synthesis of valuable β-aminoalcohols **517** through the enantioselective amination of 1,2-diols **515** *via* a ruthenium-catalysed hydrogen borrowing reaction. The combination of a chiral phosphine ligand **518** and an achiral Brønsted acid catalyst ($PhCO_2H$) was found to be key for achieving high

enantioselectivity. A number of diols **515** and amines **516** were investigated and some correlation between the electronic properties of the amine and the regioselectivity of the reaction was observed; the more electron-poor amines gave rise to a mixture of regioisomers, whereas electron-rich substrates resulted in single regioisomers of product. The mechanism was proposed to involve oxidation of the primary alcohol and condensation with the amine partner, following which the iminium can racemise *via* the enamine tautomer thus setting up a dynamic kinetic asymmetric reduction pathway to give rise to the aminoalcohol **517** in very high enantioselectivity (**Scheme 4.6**).[172]



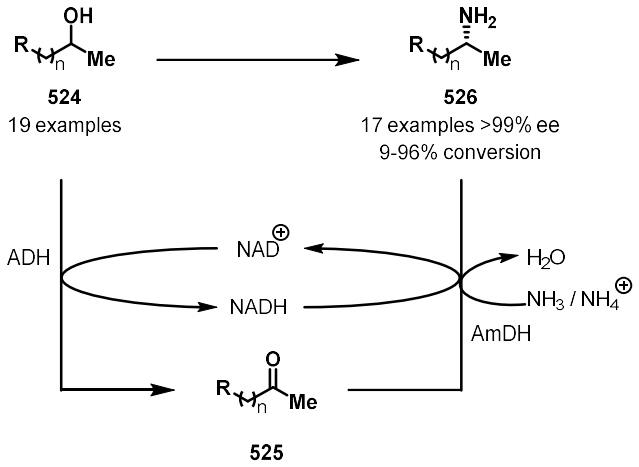
Scheme 4.6: *Enantioselective amination of 1,2-diols by Zhao and co-workers.*[172]

The majority of enantioselective hydrogen borrowing reactions employ precious, rare-earth metals such as iridium and ruthenium, however, more sustainable and affordable alternatives are beginning to emerge. For example, the nickel catalysed hydrogen borrowing reaction between secondary alcohols and acylhydrazines or aryl amines was developed by Zhou and co-workers. Initial results employed nickel triflate in the presence of a simple phosphine ligand (dppf), but a number of enantiopure phosphine ligands were also examined. (*S*)-Binapine **522** was found to be optimal and resulted in the synthesis of a range of alkylated acylhydrazines **521** in good yields and up to 96% ee (**Scheme 4.7**).[173]



Scheme 4.7: *Enantioselective N-alkylation of acylhydrazines under nickel-catalysed hydrogen borrowing conditions.*[173]

Turner and co-workers have developed a metal-free hydrogen borrowing reaction using a dual enzyme system, which was found to enable the asymmetric amination of secondary alcohols and uses ammonia as the nitrogen source. An alcohol dehydrogenase (ADH) was employed to oxidise alcohol **524** to ketone **525** *in situ.* Following condensation of ammonia with ketone **525**, the resulting imine/iminium was reduced by an amine dehydrogenase (AmDH). Nicotinamide adenine dinucleotide (NAD) was employed as the hydride shuttle. Following enzyme mutations, both aryl and alkyl-substituted secondary alcohols gave rise to very high enantioselectivity (**Scheme 4.8**). An additional benefit of this work is that it is carried out at a significantly lower temperature than the majority of hydrogen borrowing methodology (30 °C). It is also noteworthy that this route gives rise to unprotected, primary amines **526** which is not seen in other hydrogen borrowing methodology; *N*-protection is usually required.[174]



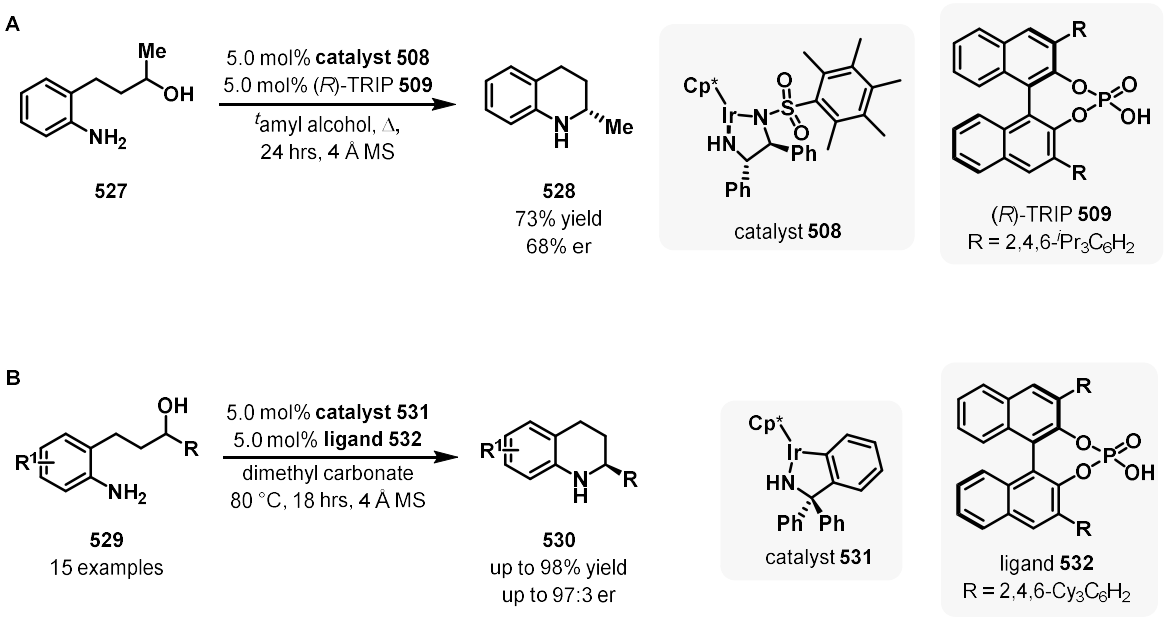
Scheme 4.8: *Dual-enzyme hydrogen borrowing reaction for the asymmetric synthesis of primary amines* ***526****. ADH = alcohol dehydrogenase, AmDH = amine dehydrogenase, NAD = nicotinamide adenine dinucleotide (oxidised form), NADH⁺ = nicotinamide adenine dinucleotide (reduced form).*[174]

4.1.2 Stereoselective C–N annulation using hydrogen borrowing catalysis

Hydrogen borrowing has been applied to the enantioselective synthesis of a number of acyclic amines, however, the synthesis of *N*-heterocycles is less well known. A few examples have emerged in recent years, which can be broken into three categories; (a) use of chiral catalysts and ligands for enantioselective catalysis, (b) use of enantiopure starting materials and retention of chirality in the hydrogen borrowing reaction and (c) use of chiral auxiliaries to induce diastereoselectivity.

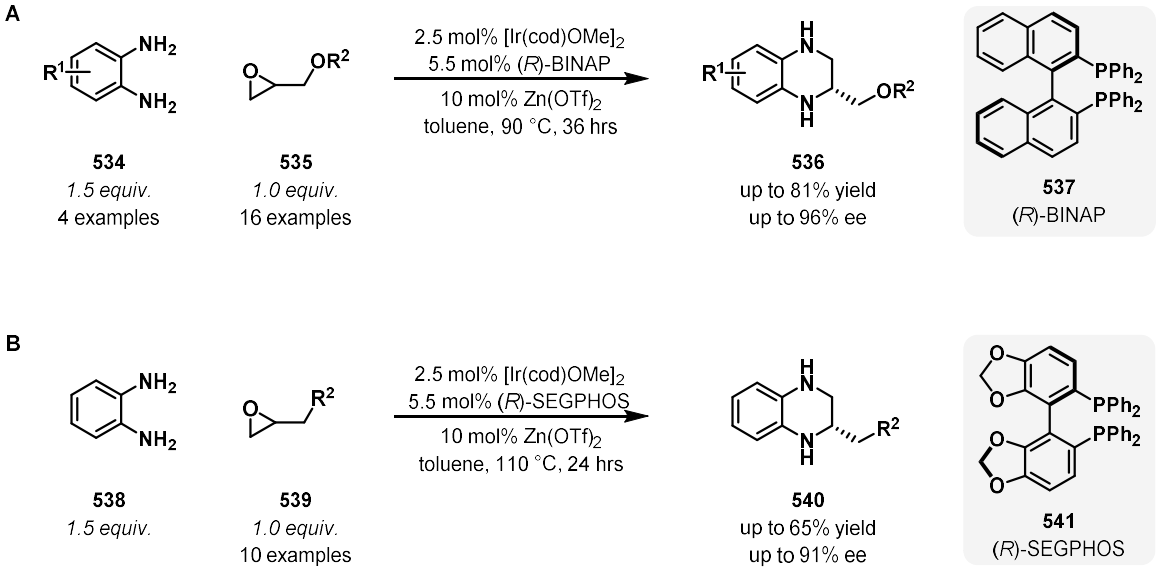
Enantioselective catalysis

Zhao and co-workers developed a dual catalytic system involving a chiral iridium-catalyst **508** (*R*)-TRIP **509** for the asymmetric amination of secondary alcohols **505** (**Scheme 4.4**). A synthesis of tetrahydroquinoline **528** was also demonstrated, albeit with modest enantioselectivity (**Scheme 4.9A**).[170] Subsequently, it was found that iridium-catalyst **531** and phosphoric acid **532** were optimal for the enantioselective synthesis of tetrahydroquinolines **530** and gave rise to significantly improved yield and ee. Whilst this work involves the formation of an *N*-heterocycle, only one hydrogen borrowing cycle is involved. The use of an achiral iridium(III) complex in combination with an enantiopure phosphoric acid cocatalyst was found to result in a high yields of a range of tetrahydroquinolines **530** with high enantioselectivity (**Scheme 4.9B**).[175]



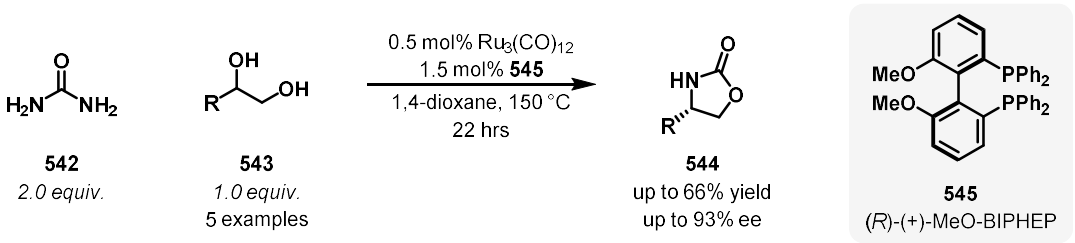
Scheme 4.9: *Enantioselective synthesis of tetrahydroquinines under hydrogen borrowing catalysis developed by Zhao and co-workers.*[175]

More recently, Zhang, Xia, Zhao and co-workers have extended their hydrogen borrowing methodology to the enantioselective synthesis of 1,2,3,4-tetrahydroquinoxalines under relay zinc and iridium catalysis. The reaction proceeds through zinc-mediated opening of epoxide **535** to generate an aminoalcohol *in situ*, which then undergoes iridium-mediated hydrogen borrowing to give the heterocyclic product **536**. The Lewis acid cocatalyst, $Zn(OTf)_2$, was thought to promote both the epoxide opening and the condensation steps. The final imine reduction step in the hydrogen borrowing cycle was proposed to be the enantiodetermining step and was controlled by the presence of the chiral phosphine ligand **537**. A range of ether-substituted products **536** were synthesised from racemic epoxides **535** in good yields and excellent enantioselectivity (**Scheme 4.10A**). When alkyl-substituted epoxides were employed, it was found that (*R*)-SEGPHOS **541** gave improved ee over (*R*)-BINAP **537** and it was also necessary to increase the reaction temperature. However, both the yields and enatioselectivity were lower for alkyl substrates **540** (**Scheme 4.10B**).[176]



Scheme 4.10: (A) *Enantioselective synthesis of ether-substituted and* ***(B)*** *alkyl-substituted 1,2,3,4-tetrahydroquinoxalines under zinc and iridium relay catalysis by Zhao and co-workers.*[176]

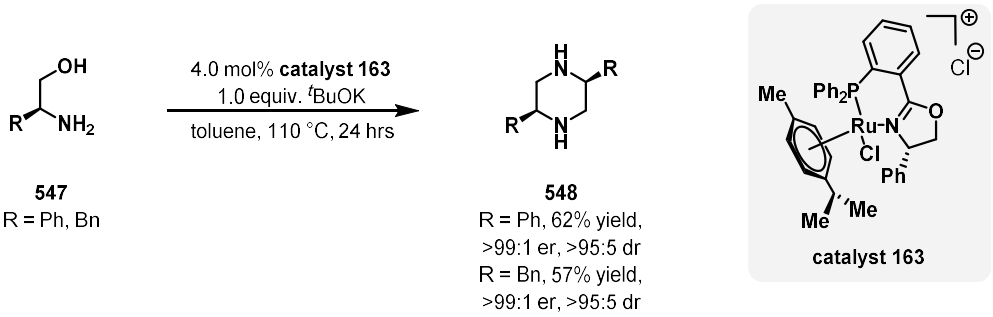
Beller's group have applied hydrogen borrowing catalysis to the reaction of 1,2-diols and urea to form oxazolidin-2-ones, which are highly useful compounds in synthetic and medicinal chemistry. The initial work employed ruthenium catalyst, $Ru_3(CO)_{12}$, and dppf to synthesise racemic oxazolidin-2-ones. It was also found that enantioenriched products **544** could be generated by employing enantiopure diphosphine ligand, (*R*)-(+)-MeO-BIPHEP **545**. A small selection of aryl and alkyl substituents were tolerated at the 4-position with good enantioselectivity and moderate to good yields (**Scheme 4.11**).[177]



Scheme 4.11: *Enantioselective synthesis of oxazolidinones under hydrogen borrowing catalysis.*[177]

Stereoretention

During their work on the amination of alcohols under ruthenium-catalysed hydrogen borrowing conditions, Marichev and Takacs demonstrated the synthesis of pyrrolidines, as well as a small number of morpholines, piperazines and diazocines. Dimerisation of enantiopure aminoalcohols **547** was also investigated and found to give rise to the corresponding *cis*-2,5-disubstituted piperazines **548** in good yields, with no evidence of racemisation at the stereocentre adjacent to nitrogen (**Scheme 4.12**). To the best of our knowledge, this is one of the only known examples of complete retention of stereochemistry α to the transient carbonyl centre during the amination of alcohols under hydrogen borrowing catalysis. Notably, enantiopure catalyst **163** was used in this work but the matched vs. mismatched effects were not discussed.[78]

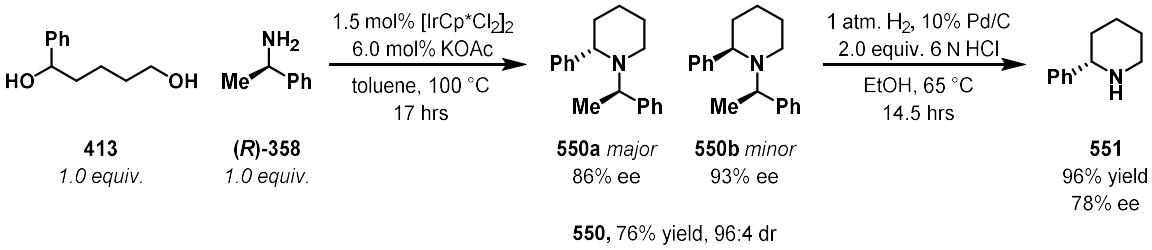


Scheme 4.12: *Dimerisation of enantiopure aminoalcohols under ruthenium-catalysed hydrogen borrowing conditions was shown to proceed with complete retention of stereochemistry by Marichev and Takacs.*[78]

Stereoinduction using a chiral amine auxiliary

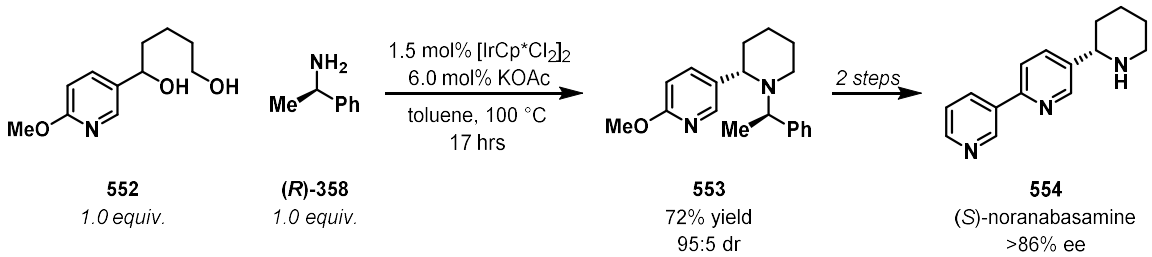
Following the synthesis of a wide range of *N*-heterocycles under iridium-catalysed hydrogen borrowing conditions (**Section 3.1**), Fujita and Yamaguchi demonstrated the diastereoselective synthesis of 2-substituted piperidine **550** using a chiral amine; (*R*)-α-methylbenzylamine **(*R*)-358**. The conditions were altered slightly and included an increased catalyst loading and KOAc instead of $NaHCO_3$, also at higher loading. Piperidine **550** was synthesised in 76% yield and 96:4 dr (**Scheme 4.13**). Hydrogenolysis of the α-methylbenzyl group gave rise to (*S*)-2-phenylpieridine **551** in 78% ee. Racemisation at the stereogenic centre of the auxiliary was observed to a small extent

and attributed to isomerisation of the iminium intermediate with the corresponding enamines (see **Scheme 4.16**).[150]



Scheme 4.13: *Diastereoselective synthesis of piperidine **550** by Fujita and Yamaguchi.[150]*

The use of a chiral auxiliary for stereoinduction during hydrogen borrowing mediated *N*-heterocycle formation was later used by Trudell and co-workers in the synthesis of noranabasamine **554**, an alkaloid isolated from the Colombian poison dart frog (*Phyllobates terribilis*). The reaction of diol **552** and (*R*)-α-methylbenzylamine **(*R*)-358** under Fujita and Yamaguchi's hydrogen borrowing conditions ($[IrCp^*Cl_2]_2$/KOAc) provided piperidine **553** in 72% yield and 95:5 dr (**Scheme 4.14**).[150] The methoxypyridine was converted to the corresponding aryl chloride by heating with $POCl_3$ and then Suzuki–Miyaura coupling with 3-pyridineboronic acid gave the final natural product **554**. The ee of **554** was determined to be >86% using NMR spectroscopy and the chiral shift reagent 1,1'-binaphthyl-2,2'-diylphosphoric acid (BNPPA). The opposite enantiomer of noranabasamine was also synthesised in >80% ee through an identical sequence starting from (*S*)-α-methylbenzylamine.[165]



Scheme 4.14: *Use of a chiral auxiliary and hydrogen borrowing amination in the asymmetric synthesis of noranabasamine **554** by Trudell and co-workers.[165]*

4.2 Results and Discussion: Stereoinduction at the C2 position

4.2.1 Use of chiral auxiliary groups on nitrogen

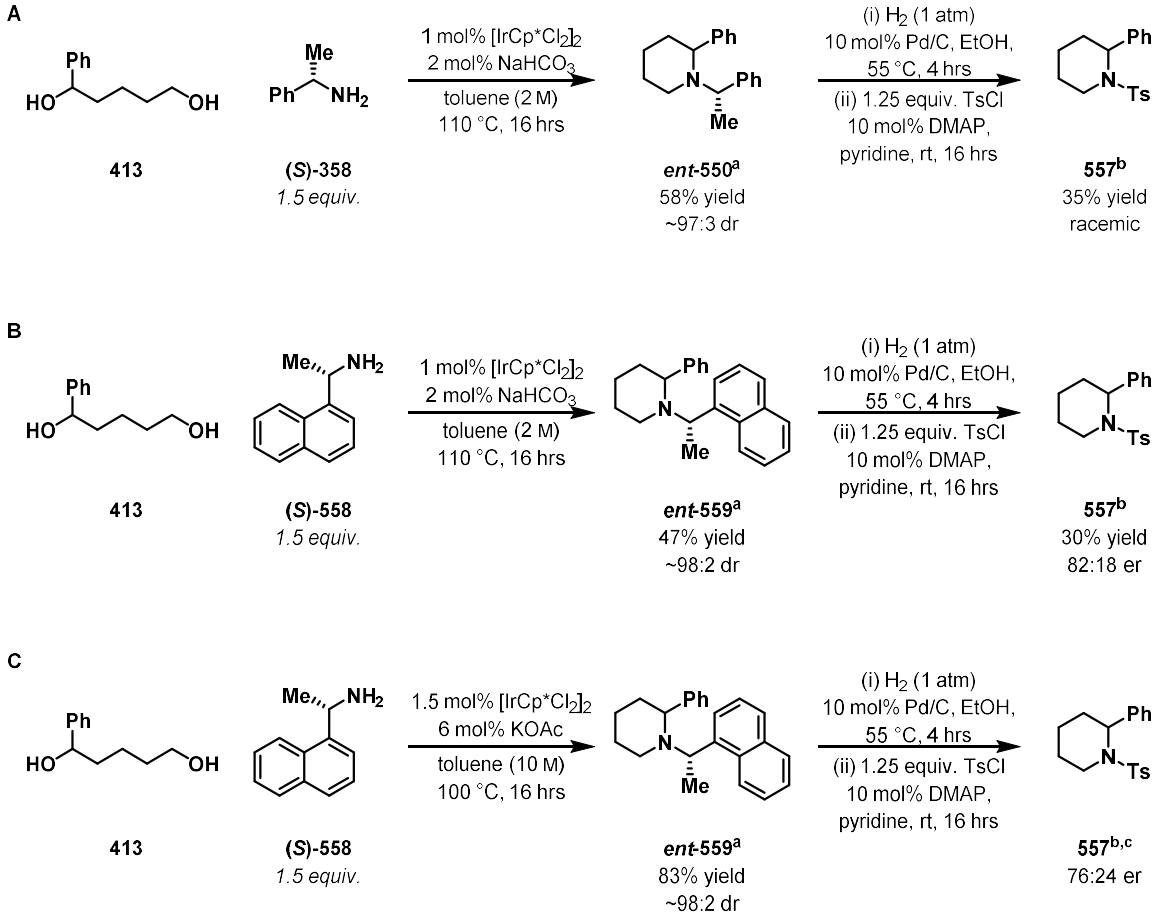
Given the successful employment of chiral auxiliaries for the diastereoselective synthesis of *N*-heterocycles under hydrogen borrowing catalysis by Fujita, Yamaguchi and Trudell, we were interested to trial this strategy under our conditions.[150,165]

The initial reaction employed 1-phenylpentane diol **413**[*] with (*S*)-α-methylbenzylamine **(*S*)-358** which was found to give rise to piperidine ***ent*-550** in 73% yield and very high dr; only a trace of the minor diastereomer was visible in the ^{1}H NMR spectrum (**Scheme 4.15A**). Unfortunately, despite analysis of a sample of authentic racemic piperidine ***rac*-556** on nine chiral HPLC columns and six chiral SFC columns under a range of conditions, it was not possible to separate the diastereomers or enantiomers of ***rac*-556.** Cleavage of the benzyl group by hydrogenolysis was successful and was followed by reaction with tosyl chloride to furnish *N*-tosyl compound **557**, the enantiomers of which were separable by chiral HPLC. However, *N*-tosyl compound **557** was found to be racemic by chiral HPLC and this was thought to have arisen through one of two ways; (a) the auxiliary stereogenic centre was racemised during the hydrogen borrowing reaction prior to the final reduction step (discussed later) but stereoinduction in this final reduction step was high, such that piperidine **556** was formed with high diastereoselectivity but low enantioselectivity at C2 or, (b) piperidine **556** was formed with high enantio- and diastereoselectivity at C2, but the C2-stereogenic centre was subsequently racemised during the hydrogenolysis/tosylation procedure – this racemisation process could be facilitated by the benzylic nature of the C2 stereogenic centre.

Next, we turned our attention to (*S*)-1-(naphthalen-1-yl)ethan-1-amine, which upon hydrogen borrowing reaction with diol **413**[*], gave rise to 47% yield of piperidine ***ent*-559** (**Scheme 4.15B**). Piperidine ***ent*-559** was found to have high dr; only a trace of the minor diastereomer was seen by

[*] Diol **413** was synthesised by Dr Wasim Akhtar

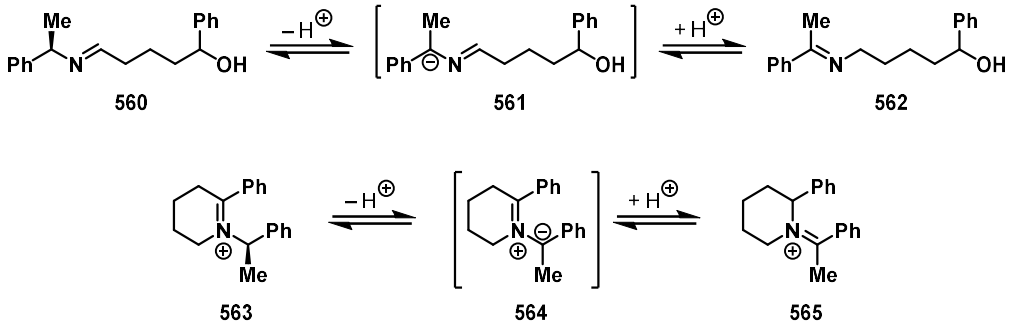
^{1}H NMR spectroscopy. As before, direct determination of the enantiomeric excess of ***ent*-559** proved impossible by chiral HPLC or SFC and it was necessary to carry out the hydrogenolysis and reaction with tosyl chloride to furnish *N*-tosyl derivative **557**. HPLC analysis of **557** revealed an er of 82:18. This result may be a consequence of the increased bulk of the naphthyl auxiliary relative to the α-methylbenzyl example, which limits racemisation at the auxiliary stereogenic centre, or the increased ease of cleavage of the naphthyl group relative to the benzyl example. However, it does not give any further insight into whether racemisation has occurred during the hydrogen borrowing reaction or subsequent hydrogenolysis.



Scheme 4.15: *(A) Hydrogen borrowing reaction with (S)-α-methylbenzylamine (B) Use of (S)-1-(naphthalen-1-yl)ethan-1-amine as a chiral auxiliary amine under standard hydrogen borrowing conditions and (C) under Fujita and Yamaguchi's hydrogen borrowing conditions.[150] [a]Relative stereochemistry not known. [b]Absolute stereochemistry unknown. [c]An analytical sample (~1 mg) of **557** was isolated by preparative TLC.*

Hydrogen borrowing reaction of diol **413** and amine **(*S*)-558** was also carried out under Fujita and Yamaguchi's hydrogen borrowing conditions, which were also used in the stereodefining step in the synthesis of noranabasamine by Trudell.[150,165] These conditions employ a higher loading of $[IrCp^*Cl_2]_2$ and base; KOAc in place of $NaHCO_3$. The reaction concentration is also increased, and the temperature decreased slightly. These conditions were optimised for a different reaction system and appear not to be directly applicable to our system, giving a slightly decreased level of stereoinduction (**Scheme 4.15C**).

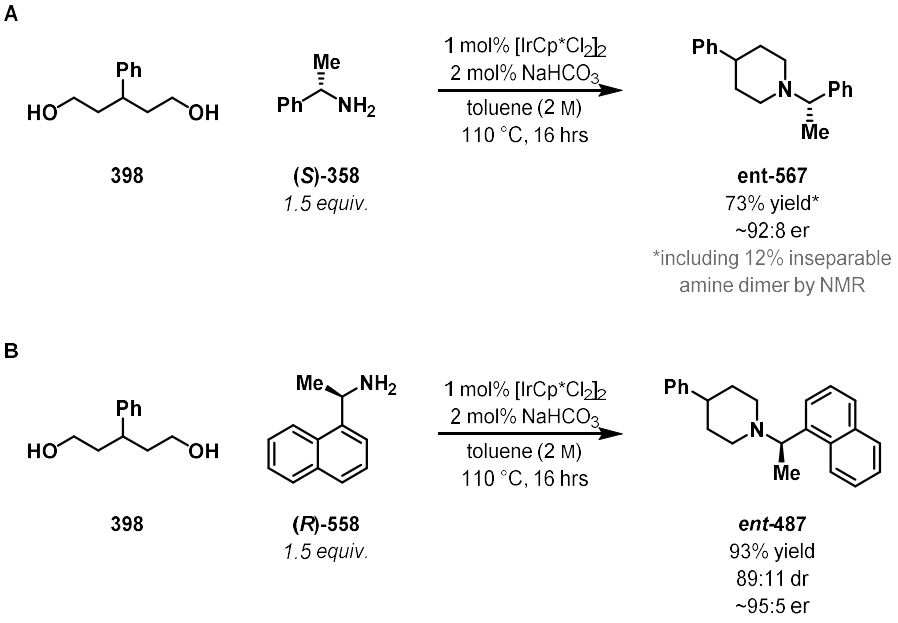
We wanted to find out at what stage the loss of stereochemical integrity occured and first considered racemisation of the auxiliary stereogenic centre during the hydrogen borrowing reaction. As noted previously, a small degree of racemisation was observed at this centre by Fujita and Yamaguchi, who attributed this to isomerisation of the imine **561** or iminium **564** intermediate, which would proceed through a planar intermediate (**Scheme 4.16**).[150]



Scheme 4.16: *Isomerisation of imine intermediate **561** and/or iminium intermediate **564** leads to racemisation of the auxiliary chiral centre, as described by Fujita and Yamaguchi.[150]*

In order to determine whether a similar racemisation pathway was operating under our conditions, we investigated the reaction of symmetric diol **398** and (*S*)-α-methylbenzylamine **(*S*)-358**. The corresponding piperidine ***ent*-567** was found to form in 73% yield under our conditions (**Scheme 4.17A**). Likewise, piperidine ***ent*-487** was synthesised in 93% yield from diol **398** and the corresponding enantiopure naphthyl amine **(*R*)-558** (**Scheme 4.17B**). HPLC analysis of piperidine ***ent*-567** and ***ent*-487** was attempted on nine chiral columns with no success but

separation by SFC on a chiral stationary phase was more promising. Baseline separation of the two enantiomers could not be achieved and so the er values shown in **Scheme 4.17** must be treated as approximations. It can be seen that there was a high level of stereoretention at the auxiliary centre and that only a small amount of racemisation occurred during the hydrogen borrowing reaction. We began to suspect that the low enantioselectivities observed for 2-phenylpiperidine systems ***ent*-556** and ***ent*-559** were due to racemisation occurring during the hydrogenolysis/tosylation procedure carried out prior to HPLC analysis.

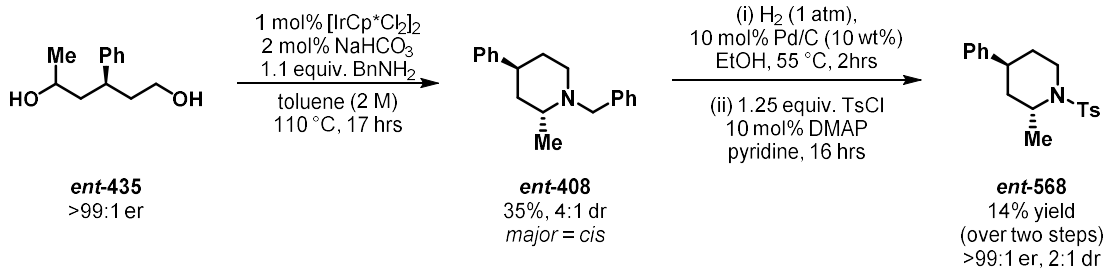


Scheme 4.17: *Synthesis of piperidine **ent-567** and **ent-487** from diol **398** and the corresponding α-chiral amines under hydrogen borrowing conditions. Chiral SFC analysis was used to calculate er however, full separation was not achieved and hence these values are approximations only.*

To investigate this further, we introduced an additional substituent at the C4-position, targeting valuable 2,4-disubstituted systems. This would enable us to investigate the possibilities for stereoretention at the C4 position and also provide an additional opportunity to study the C2 stereogenic centre by monitoring diastereoselectivity.

4.3 Results and Discussion: Retention of Chirality at C4

The hydrogen borrowing reaction of enantiopure diol ***ent*-435** with benzylamine **332** was carried out by Kieran Paterson, affording piperidine ***ent*-408** in 35% yield and as a 4:1 mixture of diastereomers. The diastereoselectivity is dictated by the final reduction step of the second hydrogen borrowing cycle (**Scheme 3.11**). The addition of hydride to the cyclic iminium species is in accordance with the Fürst-Plattner rule; axial attack of [Ir]–H from the least hindered face results in formation of the major *cis* diastereomer (see **Section 3.3.3**). However, at the time it was not possible to (a) separate the enantiomers of piperidine ***ent*-408** by chiral HPLC or, (b) cleave the *N*-benzyl group of piperidine ***ent*-408** to enable derivatisation for HPLC analysis. Following development of effective hydrogenolysis conditions for de-benzylation (**Section 3.7**), the deprotection was realised and the resulting free piperidine could be reacted with tosyl chloride to give ***ent*-568**. HPLC analysis of tosylate ***ent*-568** revealed an er of >99:1 (**Scheme 4.18**).



***ent*-435**
>99:1 er

***ent*-408**
35%, 4:1 dr
major = *cis*

***ent*-568**
14% yield
(over two steps)
>99:1 er, 2:1 dr

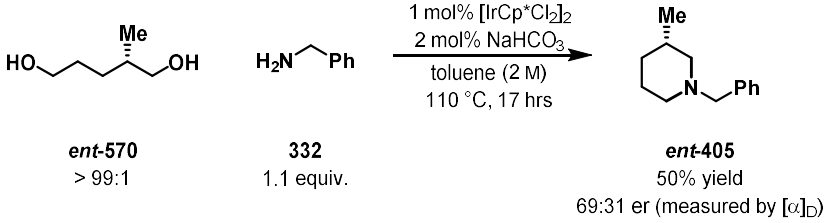
Scheme 4.18: *Synthesis of piperidine* ***ent*-408** *by Kieran Paterson and subsequent deprotection, tosylation and er analysis. The hydrogenolysis and tosylation reactions were observed to go to complete conversion by TLC analysis.*

This result demonstrates that the C4 stereogenic centre is configurationally stable during the hydrogen borrowing reaction, presumably because this position is sufficiently removed from the reacting centres and transient carbonyl groups. *N*-Tosyl piperidine ***ent*-568** was isolated as a 2:1 mixture of diastereomers. Since ***ent*-568** was isolated in low yield it was not prudent to draw any strong conclusions from this result, but it was decided that an alternative, more reliable derivatisation procedure was required moving forward.

4.4 Results and Discussion: Retention of Chirality at C3

4.4.1 Previous work in the Donohoe group

Towards the end of his Part II project, Kieran Paterson briefly investigated the subjection of an enantiopure diol ***ent*-570** to the optimised hydrogen borrowing conditions with benzylamine **332** and found that piperidine ***ent*-405** was formed in 50% yield (**Scheme 4.19**). Unfortunately, it was not possible to separate the enantiomers of *N*-benzylpiperidine ***ent*-405** by chiral HPLC and so an er of 69:31 was tentatively calculated by specific rotation and comparison to literature data. Nevertheless, this was an exciting result given the inclusion of carbonyl intermediates in the proposed mechanism. It was found that the corresponding *N*-tosyl compound was more easily separated by chiral HPLC. However, despite several attempts to cleave the benzyl group by hydrogenolysis, Kieran Paterson was unable to realise this due to time constraints.[152]

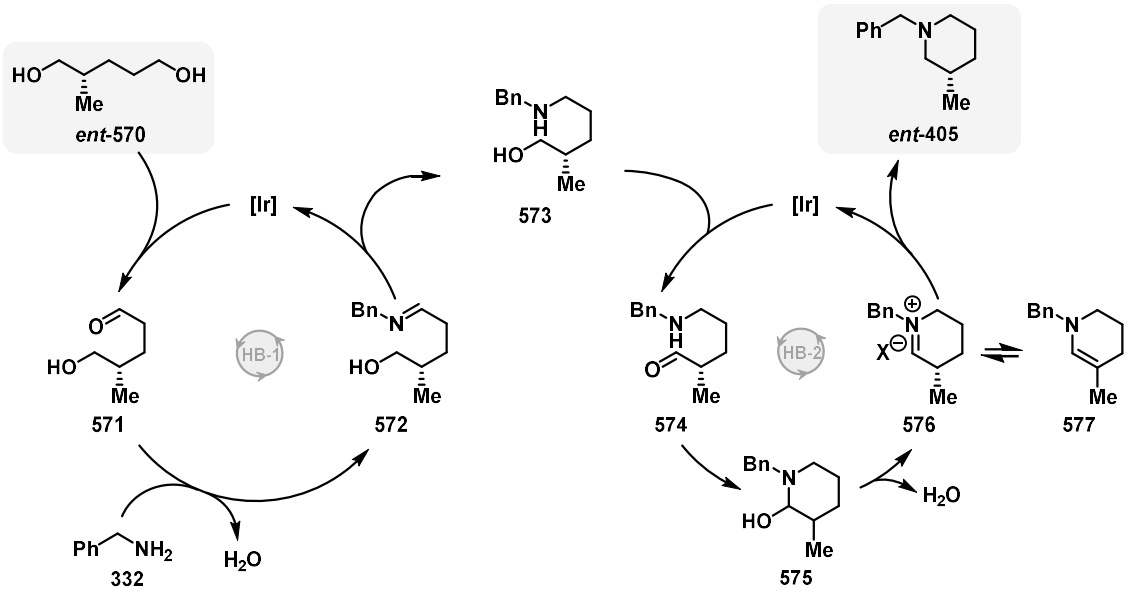


Scheme 4.19: *Synthesis of* ***ent*-405** *by Kieran Paterson. Enantiomeric ratio was calculated by specific rotation and comparison to literature values.*[152]

4.4.2 Mechanism

The partial retention of stereochemistry at the piperidine C3 position is highly surprising upon consideration of the proposed mechanism. The reaction involves two sequential hydrogen borrowing cycles, both of which proceed through aldehyde intermediates (**571**/**574**) in the case of diol ***ent*-570** (**Scheme 4.20**). The first cycle, HB-1, is likely to involve the least hindered alcohol group and therefore does not risk racemisation of the chiral centre. However, following oxidation in HB-2, the chiral centre is adjacent to an aldehyde (**574**), thus greatly increasing the acidity of the α-proton. It was therefore expected that aldehyde **574** would be highly likely to racemise since the hydrogen borrowing reaction is carried out in the presence of base. Intramolecular

condensation of α-chiral aldehyde **574** gives rise to α-chiral iminium **576** *via* hemiaminal **575**. The rate of water elimination from hemiaminal **575** may also affect the extent of racemisation of the stereogenic centre present in iminium **576**, which is also prone to tautomerisation with enamine **577**. Whilst hemiaminal **575** will not be depicted in all future mechanistic schemes it is important to bear this in mind. It is likely that a number of the mechanistic steps depicted in **Scheme 4.20** are in fact reversible but, for simplicity, these are depicted with single arrows.



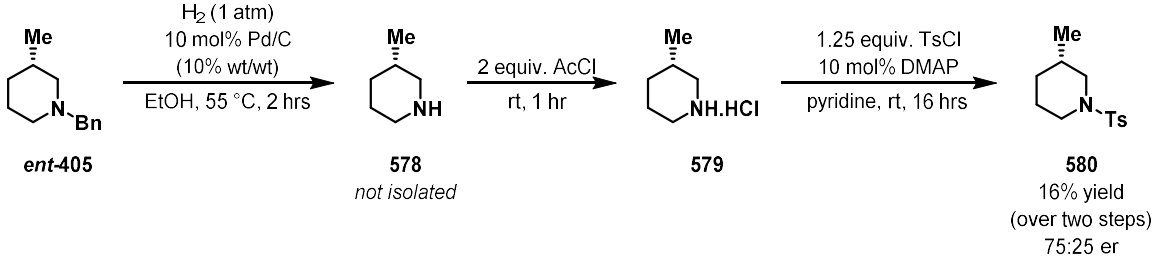
Scheme 4.20: *Proposed mechanism for the reaction of diol* ***ent-570*** *and benzylamine* ***332*** *under hydrogen borrowing catalysis.*

4.4.3 Initial results and HPLC derivatisation

Although we had doubts about the reliability of the hydrogenolysis and tosylation procedure previously used for derivatisation of *N*-benzyl piperidines, it was necessary to verify Kieran Paterson's result. In the case of 3-methylpiperidine ***ent*-405**, the stereogenic centre was hoped to be sufficiently removed from the reacting centre that it would not be harmed during the hydrogenolysis and subsequent tosylation.

The hydrogenolysis conditions developed for phenyl-substituted piperidine **399** were also found to be effective for removal of the *N*-benzyl group in 3-methyl system ***ent*-405**. A small modification

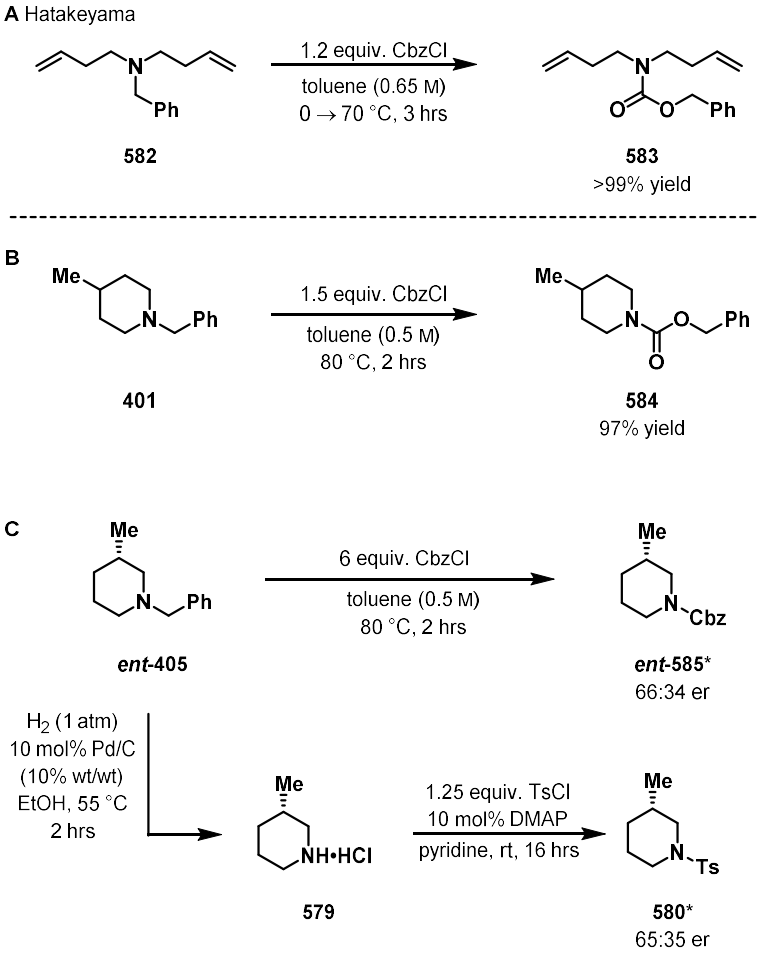
to the procedure was required since it was found that 3-methylpiperidine **578** was volatile (boiling point = 122–124 °C at atmospheric pressure[178]). Therefore, the hydrochloride salt was formed by addition of HCl in order to facilitate removal of the solvent ethanol and ethyl acetate *in vacuo*. Salt **579** was carried forward for tosyl protection without further purification. Tosyl-piperidine **580** was formed in low yield but only a small amount of material (~ 1mg) was required for HPLC analysis and so further reaction optimisation was not carried out (**Scheme 4.21**). The decreased basicity of the sulfonamide nitrogen enabled significantly improved separation and thus it was now possible to analyse Kieran Paterson's original sample by chiral HPLC. We were pleased to find the er to be 75:25, higher than the value originally estimated by specific rotation. However, due to earlier doubts about the reliability of this derivatisation process, an alternative procedure was sought.



Scheme 4.21: *N-Benzyl hydrogenolysis and tosyl protection allowed for HPLC analysis and verification of Kieran Paterson initial result.*

During their synthesis of quinine and quinidine, Hatakeyama and co-workers transformed *N*-benzyl amine **582** into the corresponding Cbz-protected species **583** by heating with an excess of benzyl chloroformate (**Scheme 4.22A**).[179] 4-Methylpiperidine **401** was employed as a test substrate and it was found that under similar conditions, benzyloxycarbonylation concomitant with debenzylation could be effected in just two hours by heating *N*-benzylpiperidine **401** with an excess of benzyl chloroformate in toluene (**Scheme 4.22B**). This process was found to be highly useful during the synthesis of a range of piperidines; it translated well to 3-methylpiperidine ***ent*-405** and piperidines protected with modified benzyl groups (**Section 4.4.10**). Most

importantly, it was found that the enantiomers of *N*-Cbz piperidine ***ent*-585** could be separated by HPLC on a chiral stationary phase. A sample of *N*-benzyl piperidine ***ent*-405** was divided and subjected to the new Cbz derivatisation procedure as well as the prior route involving hydrogenolysis and tosylation. In both cases the enantiomeric ratio was calculated to be within experimental error by HPLC on a chiral stationary phase (**Scheme 4.22C**).

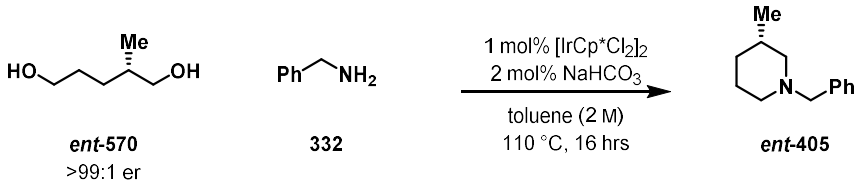


***Scheme 4.22: (A)** debenzylation and benzyloxycarbonylation of bis-homoallyl amine **582**. **(B)** Test Cbz protection of **401** and **(C)** application to 3-methyl piperidines **ent-405**. *An analytical sample (~1 mg) of **ent-585** was isolated by preparative TLC for HPLC analysis.*

A direct repeat of Kieran Paterson's conditions was carried out and whilst the yield was found to increase to 68%, the enantioselectivity decreased to 66:34 (**Table 4.1**, Entry 1). Following calculation of the yield by comparison to an internal standard (1,1,2,2-tetrachloroethane) by ^{1}H NMR spectroscopy, a portion of crude reaction mixture was carried forward for reaction with

benzyl chloroformate and an analytical sample (~ 1 mg) of *N*-Cbz piperidine ***ent*-585** could be isolated by preparative TLC. In some cases, the hydrogen borrowing reaction did not go to full conversion and the residual diol ***ent*-570** and benzylamine **332** were also Cbz-protected upon derivatisation, which made purification of ***ent*-585** by preparative TLC very challenging due to their similar polarities. In these cases, it was possible to purify *N*-benzyl piperidine by column chromatography prior to Cbz protection. This derivatisation process was found to be quicker and easier to carry out than the hydrogenolysis/tosylation procedure and hence was employed for all substrates moving forward.

Early optimisation reactions indicated that an increased amount of benzylamine **332** was beneficial for the reaction; both yield and er were seen to increase (**Table 4.1**, Entry 2). Moving forward, all hydrogen borrowing reactions were carried out with 1.5 equivalents of the amine partner.



***ent*-570**
>99:1 er

332

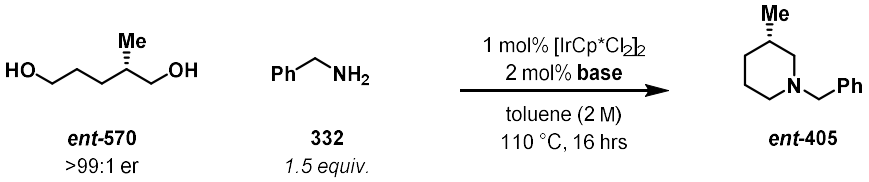
***ent*-405**

Entry	$BnNH_2$ (equiv.)	Yield / %	er
1	1.1	72 [68]	66:34
2	1.5	92 [80]	71:29

Table 4.1: *Use of 1.1 and 1.5 equiv. $BnNH_2$. Yields were calculated by ^1H NMR spectroscopy comparison to an internal standard, 1,1,2,2-tetrachloroethane, isolated yields are shown in parentheses, er was calculated by chiral HPLC analysis of the corresponding N-Cbz protected compound* ***ent-405****.*

4.4.4 Reaction optimisation: base screen

With the new Cbz derivatisation conditions in hand, we sought to increase the enantioretention by optimisation of the hydrogen borrowing reaction conditions. Based on our proposed mechanism (**Scheme 4.20**), we hypothesised that the racemisation was primarily taking place at the α-chiral aldehyde **574** and therefore that the strength of the base would be important. A wide range of inorganic bases were investigated (**Table 4.2**).



***ent*-570** >99:1 er | **332** *1.5 equiv.* | ***ent*-405**

Entry	Base	Yield / %	er
1	-	[54]	57:43
2	$NaHCO_3$	92[80]	71:29
3	$KHCO_3$	85	73:27
4	$CsHCO_3$	98	74:26
5	NaOAc	90[86]	62:38
6	KOAc	95[71]	62:38
7	Na_2CO_3	94	67:33
8	K_2CO_3	61	54:46
9	Cs_2CO_3	21	78:22
10	NaOH	94	76:24
11	KOH	92	71:29
12	$CsOH.xH_2O$	n.r.	-
13	^{t}BuOK	88	69:31
14	^{t}BuOK (5 mol%)	n.r.	-
15	^{t}BuOK (10 mol%)	n.r.	-

Table 4.2: *Base screen results. Yields were calculated by ^{1}H NMR spectroscopy by comparison to an internal standard, 1,1,2,2-tetrachloroethane, isolated yields are shown in parentheses, er was calculated by chiral HPLC analysis of the corresponding N-Cbz protected compound* ***ent*-585***.*

Removing the base from the reaction led to poor er and decreased yield which was attributed to poor conversion (**Table 4.2**, Entry 1). The original conditions with $NaHCO_3$ (**Table 4.2**, Entry 2) gave very good yield and modest er. It was found that both $KHCO_3$ and $CsHCO_3$ gave rise to high yields of piperidine ***ent*-405** with 73:27 er and 74:26 er respectively, which is a slight increase relative to $NaHCO_3$ (**Table 4.2**, Entries 3 and 4).

Acetate bases have been used to good effect in diastereoselective hydrogen borrowing by Fujita, Yamaguchi and Trudell.[150,165] In our system, NaOAc and KOAc gave rise to good yields of ***ent*-405**, but lower er than the bicarbonate bases (**Table 4.2**, Entries 5 and 6).

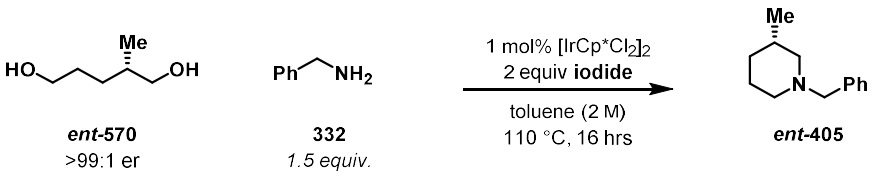
It is known that $NaHCO_3$ decomposes to give Na_2CO_3, CO_2 and water at high temperatures (above 100 °C in a closed system) and it was postulated that this could be taking place during the hydrogen borrowing reaction at 110 °C (reactions were carried out in a sealed tube).[180] Use of Na_2CO_3 was found to give a high yield of ***ent*-405**, comparable to $NaHCO_3$, but the er was lower (**Table 4.2**, Entry 7). Dramatic deceases in yield were seen moving down Group 1 to K_2CO_3 and Cs_2CO_3, however the er increased with Cs_2CO_3 giving the highest enantiospecificity across all the bases screened (**Table 4.2**, Entries 8 and 9).

It was initially thought that a weaker base would be beneficial for enantiospecificity since this should decrease the extent of deprotonation at the α centre, thus limiting racemisation. Encouraged by the high levels of enantioenrichment obtained with carbonate bases, we were motivated to try stronger bases. Both NaOH and KOH gave rise to very high yields of piperidine ***ent*-405** and good er (**Table 4.2**, Entries 10 and 11). Unfortunately, no reaction was observed with $CsOH.xH_2O$ although this was attributed to its hygroscopic nature and corresponding handling difficulty (**Table 4.2**, Entry 12). We were surprised to find that ^{t}BuOK, gave high yield of ***ent*-405** and good er, with only a slight drop relative to $NaHCO_3$ (**Table 4.2**, Entry 13). However, increased loading of ^{t}BuOK caused the reaction to cease completely and only starting materials were observed by ^{1}H NMR spectroscopy after 16 hours (**Table 4.2**, Entries 14 & 15).

Moving forward, $CsHCO_3$ (2 mol%) was chosen as the optimum base since it gave the best compromise for high yield and high er. This base also had the added benefit that it has a significantly higher molecular weight than the other bases which performed well, such as $NaHCO_3$, NaOH and KOH, which reduces the error associated with weighing out the very small portions required (3.8 mg $CsHCO_3$ *cf.* 1.7 mg $NaHCO_3$).

4.4.5 Reaction optimisation: addition of iodide

It was postulated that increasing the rate of reduction of iminium ion **576** (**Scheme 4.20**), should limit the extent of racemisation at the 3-position. Xiao and co-workers have studied transfer hydrogenation of a range heteroaromatics using $[RhCp^*Cl_2]_2$ and found that the addition of iodide, in the form of tetrabutylammonium iodide (TBAI) or KI, gave a dramatic rate enhancement. A mechanism involving reduction of a charged pyridinium was proposed, not dissimilar to our system involving iminium reduction.[181,182] Work published recently by our group found that the combination of KI with $[IrCp^*Cl_2]_2$ had a similar effect for the interrupted hydrogen transfer reduction of pyridinium and quinolinium salts.[183] Hence, we were interested to investigate the addition of iodide to our $[IrCp^*Cl_2]_2$ catalysed hydrogen borrowing reaction.

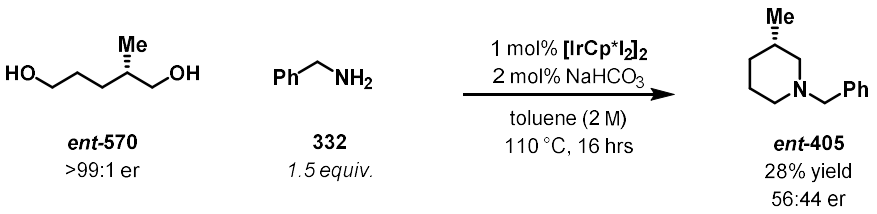


Entry	Iodide source	Yield / %	er
1	KI	9 [10]	53:47
2	TBAI	n.r.	-

Table 4.3: *Inclusion of iodide sources. Yields were calculated by ^1H NMR spectroscopy by comparison to an internal standard, 1,1,2,2-tetrachloroethane, isolated yields are shown in parentheses, er was calculated by chiral HPLC analysis of the corresponding N-Cbz protected compound* ***ent-585****.*

Initially, 2 equiv. KI was added to the reaction (**Table 4.3**, Entry 1) however, this resulted in a very low yield of piperidine ***ent*-405** which was essentially racemic. The poor results were partially attributed to low solubility of KI in toluene and as such it was not possible to efficiently stir the reaction slurry (on a 1 mmol scale; 332 mg KI in 0.5 mL toluene). In an attempt to lessen these problems with solubility, addition of TBAI to the reaction was also investigated (**Table 4.3**, Entry 2). TBAI did not appear to be soluble in the reaction mixture at room temperature, but the solubility increased at 110 °C. Unfortunately, no reaction was observed in the presence of TBAI and unreacted starting materials ***ent*-570** and **332** were returned.

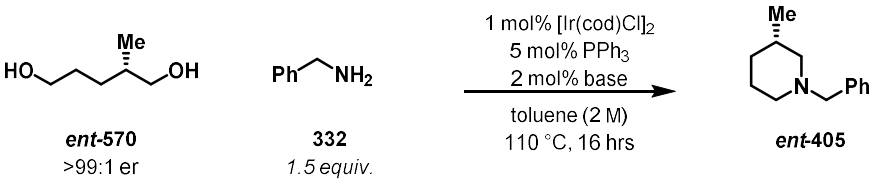
Previous work in the group attributed the beneficial effects of addition of iodide to $[IrCp^*Cl_2]_2$ may be due to formation of [Ir]–I complexes *in situ*.[183] An alternative catalyst, $[IrCp^*I_2]_2$ was also investigated, but resulted in only 28% yield of ***ent*-405** and very low er (**Scheme 4.23**). Although $[IrCp^*I_2]_2$ may be a good catalyst for the final reduction of iminium **576**, this low yield indicates it is not an effective catalyst for the other steps in the mechanism.



Scheme 4.23: *Use of alternative iridium catalyst; $[IrCp^*I_2]_2$. Yield was calculated by ^{1}H NMR spectroscopy by comparison to an internal standard, 1,1,2,2-tetrachloroethan and, er was calculated by chiral HPLC analysis of the corresponding N-Cbz protected compound* ***ent*-585**.

4.4.6 Reaction optimisation: iridium source

A large proportion of the enantioselective hydrogen borrowing methodology in the literature employs chiral ligands (**Section 4.1**). In addition, this approach had recently been successful for the enantioselective synthesis of carbocyclic compounds under iridium(I)-mediated hydrogen borrowing in the group.[151] With the hope of developing similar conditions for *N*-heterocycle formation, an iridium(I) catalyst system was investigated briefly. Unfortunately, both in the presence and absence of $NaHCO_3$, no reaction was observed using $[Ir(cod)Cl]_2$ (**Table 4.4**).

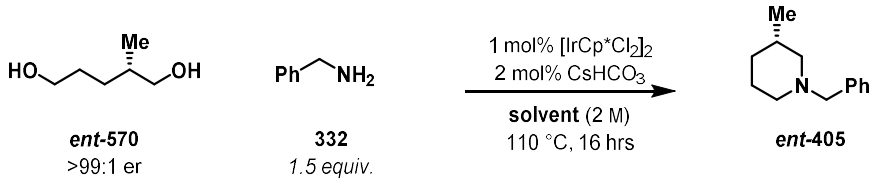


Entry	Base	Yield / %	er
1	$NaHCO_3$	n.r.	-
2	-	n.r.	-

Table 4.4: *Attempted use of iridium(I) catalyst for the hydrogen borrowing reaction of diol* ***ent*-570** *with benzylamine* ***332***.

4.4.7 Reaction optimisation: solvent screen

A range of high boiling solvents were screened, in combination with 2 mol% $CsHCO_3$. In all cases the yield was decreased relative to the original solvent, toluene (**Table 4.5**, Entry 1). Heptane (**Table 4.5**, Entry 2) gave rise to 82% piperidine ***ent*-405** in 76:24 er, which is comparable to the reaction in toluene. Whilst both heptane and toluene are non-polar solvents, it was observed that the starting materials and product are not miscible with heptane and a biphasic system is formed, whereas the toluene reaction is monophasic. *tert*-Butanol gave 84% yield of piperidine ***ent*-405** and 76:24 er (**Table 4.5**, Entry 3). However, the more polar alcoholic solvent 1,1,1-trifluoroethanol (TFE) was found to give 69% yield and a significantly reduced er of 55:45 (**Table 4.5**, Entry 4). In both alcohol solvents, the starting materials were fully soluble. Ethereal solvents, 1,4-dioxane and cyclopentylmethyl ether (CPME) both gave rise to good yields of piperidine ***ent*-405** along with high er and the reactions were monophasic (**Table 4.5**, Entries 5 and 6). Omitting the solvent was found to give a high yield and increased er relative to all reactions run using solvent (**Table 4.5**, Entry 7). However, it was felt that the solvent-free reaction was not particularly practical, particularly when the reactions were run on small scale (<1 mmol), and CPME was chosen as the optimal solvent moving forward.



***ent*-570**
>99:1 er

332
1.5 equiv.

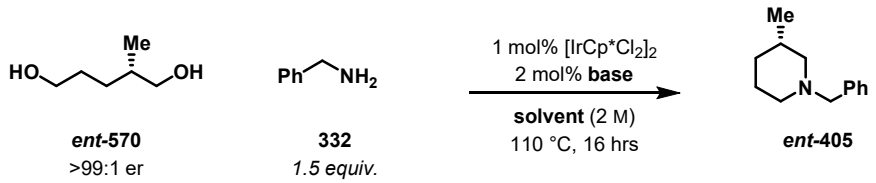
***ent*-405**

Entry	Solvent	Yield / %	er
1	Toluene	98	74:26
2	Heptane	82	76:24
3	^{t}BuOH	84	76:24
4	TFE	69	55:45
5	1,4-Dioxane	85	79:21
6	CPME	81	80:20
7	-	93	82:18

***Table 4.5**: Solvent screen results. Yields were calculated by ^{1}H NMR spectroscopy by comparison to an internal standard, 1,1,2,2-tetrachloroethane and er was calculated by chiral HPLC analysis of the corresponding N-Cbz protected compound **ent-585**.*

During the solvent-free reaction, condensation of water was observed on the walls of the reaction vial, along with immiscible droplets in the reaction mixture in some other cases. This prompted us to consider the role of water in more detail. There are two amine condensation steps in the proposed mechanism (**Scheme 4.20**) and hence 2 equivalents of water are generated (36 µL of water on a 1 mmol reaction scale). Since this does not appear to hinder the reaction, we were intrigued to investigate the extreme situation in which water is used as the solvent.

Use of water as the solvent gave rise to a high yield of piperidine ***ent*-405** and the highest er observed so far (**Table 4.6**, Entry 1). It was also found that in water, base was no longer required for the hydrogen borrowing reaction (**Table 4.6**, Entry 2). Omitting the base gives rise to near identical yield and er, which is in agreement with similar observations made by Williams and co-workers during their synthesis of *N*-heterocycles under hydrogen borrowing catalysis.[147] In the case of methyl diol ***ent*-570**, the starting materials are fully miscible with water but as the reaction proceeds, the formation of a layer of product on top of the aqueous phase was observed. It was thought that this altered mass balance may alter the equilibrium of key mechanistic steps, thus affecting the enantioselectivity. In addition, the biphasic system may serve to keep sensitive aldehyde and imine intermediates separate from the base (in the cases when base was employed). It was subsequently thought that brine should enhance the partition effect further still, however, whilst the yield of ***ent*-405** was comparable, the er was significantly reduced (**Table 4.6**, Entry 3). Ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate (BMIM PF_6) was also investigated but was found to result in poor conversion and near-racemic product and hence the use of ionic liquids was not pursued further (**Table 4.6**, Entry 4). The effects of a biphasic system were further investigated by employing a 1:1 mixture of the two best solvents so far; water and CPME (**Table 4.6**, Entry 5). This resulted in a high yield of piperidine product ***ent*-405** and 81:19 er but didn't give any added benefits over single solvent systems.



Entry	Solvent	Base	Yield / %	er
1	Water	$CsHCO_3$	79	84:16
2	Water	-	79	83:17
3	Brine	-	81	65:35
4	BMIM PF_6	-	[15]	51:49
5	1:1 Water:CPME	$CsHCO_3$	95	81:19

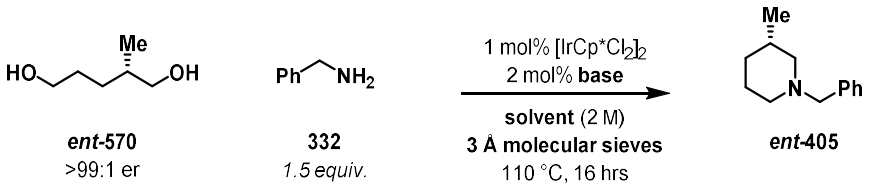
Table 4.6**: Hydrogen borrowing in aqueous media. Yields were calculated by ^{1}H NMR spectroscopy by comparison to an internal standard, 1,1,2,2-tetrachloroethane, isolated yields are shown in parentheses and er was calculated by chiral HPLC analysis of the corresponding N-Cbz protected compound **ent-585.

4.4.8 Reaction optimisation: inclusion of molecular sieves

Following the discovery that water is an excellent solvent for the hydrogen borrowing reaction of ***ent*-570** with benzylamine **332**, we were curious to investigate the other extreme case; complete removal of water. Since the reaction generates 2 equivalents of water as the by-product, dry conditions cannot be achieved by using anhydrous solvent alone and so molecular sieves were included. On a 1 mmol scale, roughly 200 mg of freshly activated 3Å molecular sieves (MS) are required to absorb the water generated.[184]

When 3Å MS were included in the reaction of diol ***ent*-570** with benzylamine **332** with $[IrCp^*Cl_2]_2$ and $CsHCO_3$ (**Table 4.7**, Entry 1), the yield was found to decrease dramatically but the er increased slightly, relative to the analogous MS-free reaction. Increasing the MS loading two-fold had a further detrimental effect on the yield, but the enantiomeric ratio increased to 90:10 (**Table 4.7**, Entry 2). Excluding the base from the reaction caused the yield and er to increase, contrary to previous base-free reaction results (**Table 4.7**, Entry 3). At 400 mg MS loading, the yield is very low, but the er remained unchanged at 90:10 relative to the analogous conditions including base (**Table 4.7**, Entry 4). Use of CPME as the solvent gave rise to a slight increase in yield of ***ent*-405**

relative to the analogous conditions in toluene, and 92:8 er at 400mg MS loading (**Table 4.7**, Entries 5 and 6).



Entry	Solvent	Base and MS	Yield / %	er
1	Toluene	2 mol% $CsHCO_3$, 200 mg 3Å MS	26 [24]	78:22
2	Toluene	2 mol% $CsHCO_3$, 400 mg 3Å MS	15 [14]	90:10
3	Toluene	200 mg 3Å MS	[67]	84:16
4	Toluene	400 mg 3Å MS	[29]	90:10
5	CPME	200 mg 3Å MS	86	85:15
6	CPME	400 mg 3Å MS	[36]	92:8

Table 4.7: *Addition of molecular sieves to hydrogen borrowing reactions in toluene and CPME. Yields were calculated by ^{1}H NMR spectroscopy by comparison to an internal standard, 1,1,2,2-tetrachloroethane, isolated yields are shown in parentheses and er was calculated by chiral HPLC analysis of the corresponding N-Cbz protected compound* ***ent-585****.*

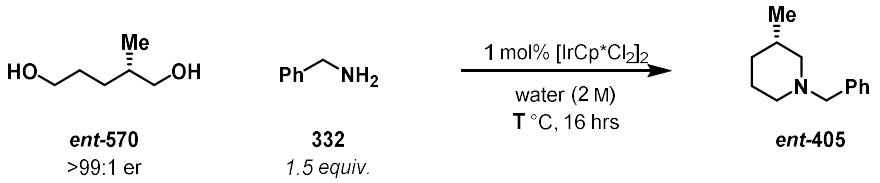
It is known that solvent dried over 3Å molecular sieves can become significantly alkaline; Inazu and co-workers found unexpected reactivity in methanol that had been dried and distilled over 3 Å MS. The solvent had become sufficiently basic to cause *O*-acetate cleavage and the authors postulated that the MS contained K_2CO_3 as an impurity leading to the formation of methoxide.[185] In our case, we postulate that the basic nature of the molecular sieves was sufficient for the hydrogen borrowing reactions to proceed, since K_2CO_3 is also an effective base for the reaction (**Table 4.2**, Entry 8). At high loadings of MS (400 mg), the reactions became more difficult to stir which would be expected to hinder reaction. Whilst a 92:8 er was obtained, ultimately the inclusion of MS was ultimately not pursued further due to the low yields of ***ent*-405** obtained.

At this point in time, we had two sets of optimum reaction conditions. The base-free conditions with water as the solvent were found to give the highest level of stereoretention. However, when organic solvent was employed, the base was found to be essential and use of 2 mol% $CsHCO_3$ in

CPME gave a slightly higher yield than the aqueous conditions, with reasonably high stereoretention. Both sets of conditions were taken forward to the temperature screen.

4.4.9 Reaction optimisation: temperature

A range of reaction temperatures from 65–110 °C were screened for the hydrogen borrowing reaction of diol ***ent*-570** with benzylamine **332** in water (**Table 4.8**). Generally, the yield was found to increase with temperature, but above 90 °C the yields of ***ent*-405** obtained were all roughly the same, within experimental error. The yield was very poor at 65 °C and 70 °C and this was because the reaction did not reach full conversion (**Table 4.8**, Entries 1 & 2). On the other hand, the er also increased with increasing temperature but reached a maximum of 90:10 at 80 °C (**Table 4.8**, Entry 4), after which it began to decrease slightly (**Table 4.8**, Entries 5–7). As we were primarily concerned with the stereoretention of the reaction, a slight compromise in yield (69%) was accepted in order to achieve the highest er. Therefore, 80 °C was chosen as the optimum reaction temperature moving forward.



***ent*-570**
>99:1 er

332
1.5 equiv.

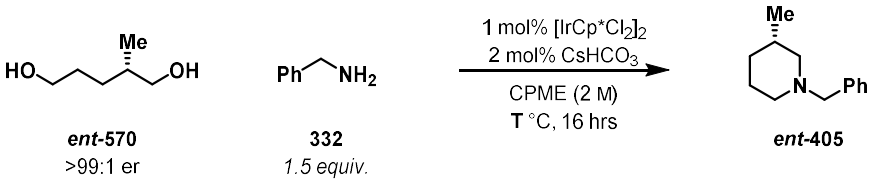
***ent*-405**

Entry	Temperature, T/ °C	Yield / %	er
1	65	11	80:20
2	70	41	85:15
3	75	61	88:12
4	80	69	90:10
5	90	78	86:14
6	100	82	85:15
7	110	79	84:16

Table 4.8: *Investigation of hydrogen borrowing reaction temperature. Yields were calculated by ^{1}H NMR spectroscopy by comparison to an internal standard, 1,1,2,2-tetrachloroethane and er was calculated by chiral HPLC analysis of the corresponding N-Cbz protected compound* ***ent*-585***.*

We were also interested to see if the temperature trend held true under the $CsHCO_3$/CPME reaction conditions (**Table 4.9**). As before, yield was found to increase with increasing temperature, but the effects were much more pronounced; at 70 and 80 °C only trace product

was observed by NMR (**Table 4.9**, Entries 1 & 2), whereas 81% yield was obtained at 110 °C (**Table 4.9**, Entry 5). Similar to the reaction in water, the er was reduced at lower temperature and an er of 84:16 was obtained at 90 °C (**Table 4.9**, Entry 3). Again, it was necessary to compromise on yield of ***ent*-405** to achieve the highest er (**Table 4.9**, Entry 5).

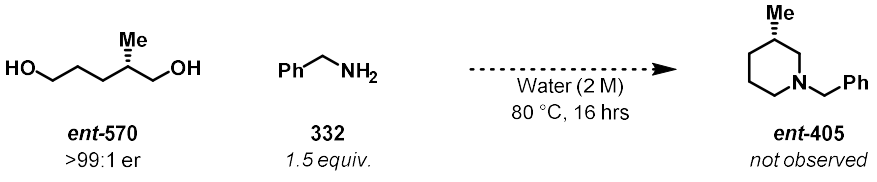


***ent*-570** >99:1 er | **332** *1.5 equiv.* | ***ent*-405**

Entry	Temperature, T/ °C	Yield / %	er
1	70	1	n.d.
2	80	3	n.d.
3	90	58	84:16
4	100	85	80:20
5	110	81	80:20

Table 4.9: *Investigation of hydrogen borrowing reaction temperature under CPME/$CsHCO_3$. Yields were calculated by ^{1}H NMR comparison to an internal standard, 1,1,2,2-tetrachloroethane, isolated yields are shown in parentheses and er was calculated by chiral HPLC analysis of the corresponding N-Cbz protected compound* ***ent*-585**.

As expected, the metal was found to be essential for hydrogen borrowing reaction between diol ***ent*-570** and benzylamine **332** under the optimised conditions in water. As a control experiment, exclusion of the $[IrCp^*Cl_2]_2$ catalyst did not lead to piperidine formation and only starting materials were returned (**Scheme 4.24**).



***ent*-570** >99:1 er | **332** *1.5 equiv.* | ***ent*-405** *not observed*

Scheme 4.24: *Metal-free reaction of diol* ***ent*-570** *and benzylamine* **332** *gave no conversion.*

In conclusion, the optimum hydrogen borrowing reaction conditions were found to employ water as the solvent (2 M) and no base, and the optimum reaction temperature was 80 °C. Under these conditions, piperidine ***ent*-405** was obtained in 69% yield (by ^{1}H NMR with an internal standard)

and 90:10 er. These reaction conditions were employed for the amine and diol substrate scope studies.

4.4.10 Amine Scope

A range of benzylamines bearing electronically diverse aromatic substituents were investigated in the hydrogen borrowing reaction with ***ent*-570,** under the optimised reaction conditions. An electron rich amine was proposed to have several effects in the proposed mechanism and the extent of racemisation:

- Increased nucleophilicity of the amine may lead to an increased rate of condensation with aldehyde **571** in HB-1 and the intramolecular ring closing of **574** in HB-2 (**Scheme 4.20**), thus limiting the extent of epimerisation of aldehyde **574**.
- A more electron rich substituent on nitrogen was thought to aid expulsion of water to form iminium **576**, thus favouring iminium **576**. Since hemiaminal **575** is not prone to racemisation, this would lead to a greater extent of racemisation *via* enamine **577**.
- An electron donating nitrogen substituent would also serve to hinder the addition of hydride in the final reduction step, which would lead to a greater extent of racemisation *via* enamine **577**.

In order to investigate the balance of the above factors, a range of electronically-diverse benzylamines were subjected to the hydrogen borrowing reaction with diol ***ent*-570** under the optimised conditions.

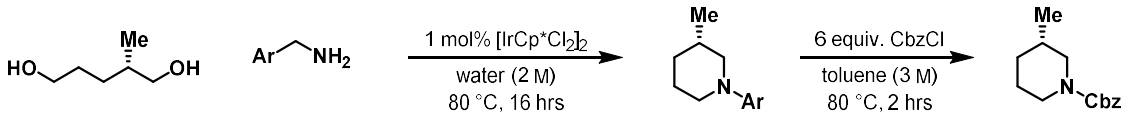
The conditions developed previously for debenzylation concomitant with Cbz protection (**Section 4.4.3**) were found to be effective for the cleavage of all the benzyl groups investigated, which highlights the utility of this derivatisation method. The Cbz-protection reactions were observed to go to complete conversion by TLC. However, only a small sample (~1 mg) of *N*-Cbz piperidine ***ent*-585** was isolated by preparative TLC in each case and used for HPLC analysis.

p-Methoxybenzylamine (σ_p = –0.28[163]) was found to give rise to piperidine **587** in comparable yield to benzylamine substrate ***ent*-405** however, the er was greatly reduced (**Table 4.10**, Entry 1 *cf.* Entry 3) . In addition, subjection of piperonylamine ($\Sigma(\sigma_{p+}\ \sigma_m)$ = –0.18, OMe σ values were used as an estimation[163]) to the hydrogen borrowing reaction with diol ***ent*-507** furnished piperidine **588** in both decreased yield and er (**Table 4.10**, Entry 2). Overall it can be seen that electron rich amines did not fit with our hypothesis and in fact had the opposite effect. We next turned our attention to electron poor amines.

A wide range of electron-deficient aryl amines were subjected to the hydrogen borrowing reaction with diol ***ent*-570**. We were pleased to find that *p*-fluorobenzylamine **589a** (σ_p = +0.15[163]) gave rise to piperidine **589** in higher yield than unsubstituted benzylamine product ***ent*-405** (**Table 4.10**, Entry 4). However, the slight decrease in electron density did not have an effect on the er.

p-(Trifluoromethyl)benzylamine **590a** (σ_p = +0.53[163]) was found to give rise to piperidine **590** in 91:9 er, but slightly lower yield *cf.* ***ent*-405** (**Table 4.10**, Entry 5). 3,5-Difluorobenzylamine **591a** ($\Sigma(\sigma_{p+}\ \sigma_m)$ = +0.68[163]) furnished piperidine **591** in 67% yield and 93:7 er which was the highest er achieved for the hydrogen borrowing reaction of methyl diol ***ent*-570** (**Table 4.10**, Entry 6). This indicates that increased electron-withdrawing characteristics of the amine appears to be beneficial for er. Use of 3,4,5-trifluorobenzylamine **592a** ($\Sigma(\sigma_{p+}\ \sigma_m)$ = +0.83[163]) piperidine **592** was isolated in 56% yield and 90:10 er which is again comparable to benzylamine substrate ***ent*-405** (**Table 4.10**, Entry 7).

Introduction of a nitrile group proved to be detrimental for er and yield - *p*-cyanobenzylamine (σ_p = +0.70[163]) **593a** gave an er of 64:36 (**Table 4.10**, Entry 8). Addition of a second CF_3 group produced a dramatic effect; use of bis-trifluoromethyl amine **594a** ($\Sigma(\sigma_{p+}\ \sigma_m)$ = +0.92[163]) lead to isolation of piperidine **594** in only 3% yield and an er of 65:35 (**Table 4.10**, Entry 9).



***ent*-570** >99:1 er | **587–594a** *1.5 equiv.* | **587–594** | ***ent*-585**

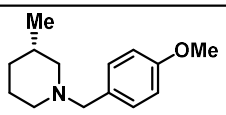
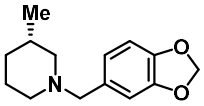
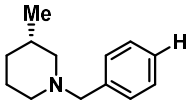
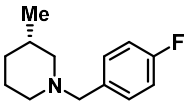
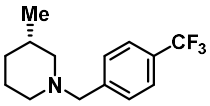
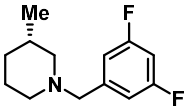
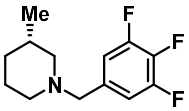
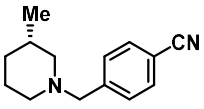
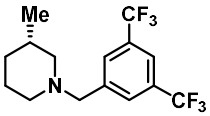
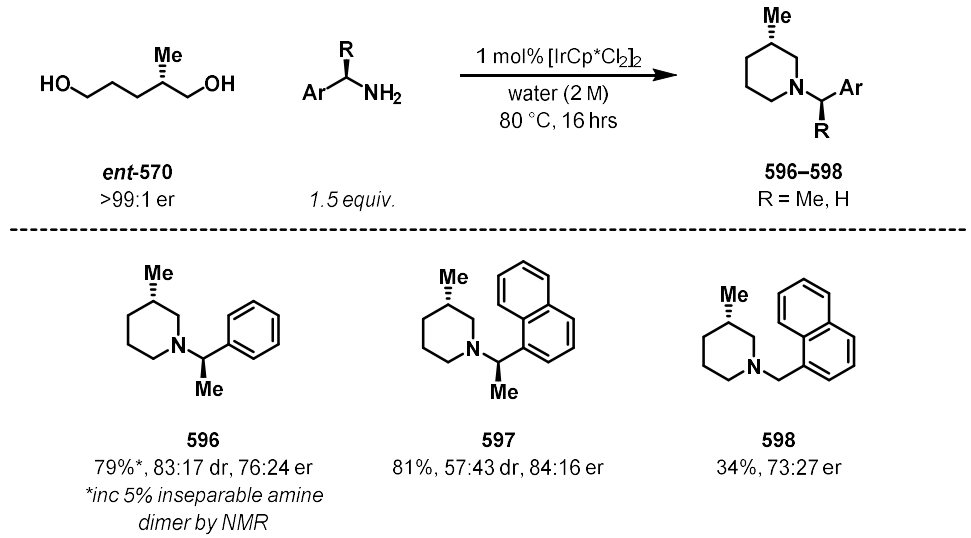
Entry		Yield / %	er	$\Sigma(\sigma_m + \sigma_p)$	amine density (ρ) / g cm^{-3}
1	 **587**	67	72:28	–0.28	1.05
2	 **588**	29	64:36	–0.18*	1.214
3	 ***ent*-405**	69	90:10	0	0.981
4	 **589**	72	90:10	0.15	1.095
5	 **590**	64	91:9	0.53	1.229
6	 **591**	67	93:7	0.68	1.21
7	 **592**	56	90:10	0.83	1.3
8	 **593**	41	64:36	0.70	solid
9	 **594**	3	65:35	0.92	solid

Table 4.10: *Subjection of a range of amines to the hydrogen borrowing conditions with diol* ***ent-570*** *to yield piperidines* ***587–594****, including Hammett parameters (*approximation from OMe values) and amine density values.* [163,186] *er was calculated by chiral HPLC following conversion to N-Cbz piperidine* ***ent-585*** *(complete conversion, analytical sample isolated by preparative TLC).*

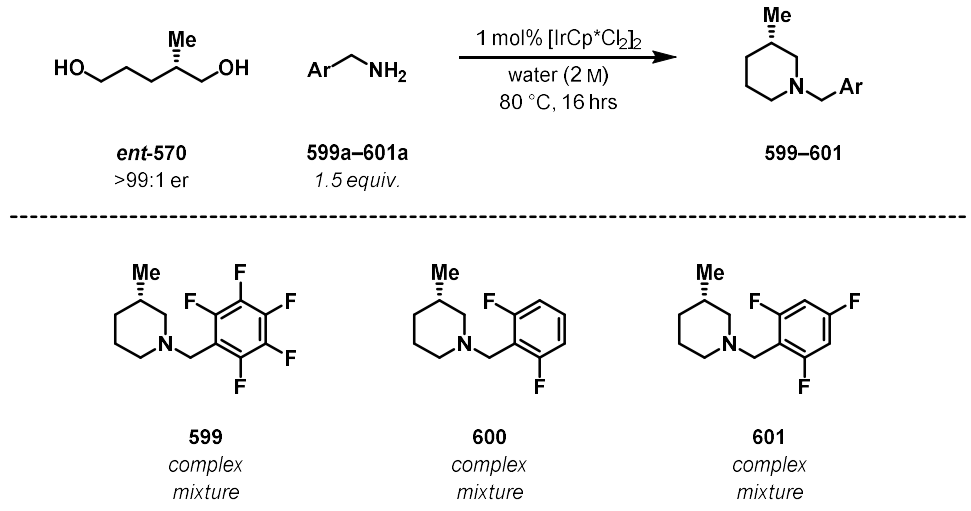
Diol ***ent*-570** and benzylamine **332** are miscible with water but the hydrogen borrowing reaction in water becomes biphasic as the product is generated. In the case of benzylamine **332** (density, $\rho = 0.981$ gcm^{-3}),[186] the organic layer forms on top of the aqueous layer, however, the other amines investigated all have $\rho > 1$ gcm^{-3} and accordingly, the organic layer was seen to form below the aqueous layer.[186] It may be that such differences in physical effects have an impact on the yield and er of the reaction, particularly because mixing is likely to be more effective nearer the magnetic stirrer at the bottom of the vial. It was assumed that the product piperidine density correlates with the amine density. Unfortunately, there does not appear to be a clear trend between amine (and therefore) product density and the yield and er of the hydrogen borrowing reaction. The two clear outliers are **593** and **594**, which both gave very low yields and er, and in both cases the amines are solids. 3,5-(Bis(trifluoromethyl))benzylamine has a low melting point (50-55 °C[186]) and the reaction was observed to be homogeneous to begin with however, after 16 hours, large amounts of solid were found around the top of the vial, well above the reaction solvent level. It was suspected that the amine had sublimed during the reaction, therefore decreasing the amount of amine available for reaction and leading to very low yield (3%, **Table 4.10**, Entry 9).

Previously, α-methyl substituted amines have been found to lead to high yields of piperidine products in the hydrogen borrowing reaction with pentanediols (**Section 3.6.2**). The reaction of diol ***ent*-570** with (*R*)-α-methylbenzylamine **(*R*)-358** gave rise to good yield of piperidine **596,** but er and dr were modest (**Scheme 4.25**). The equivalent naphthyl amine **(*R*)-558** was found to give a slight increase in yield and er. The α-methyl substituent was observed to have a beneficial effect on both yield and er, naphthyl piperidine **598** was isolated in very low yield and er.



***Scheme 4.25**: Investigation of naphthyl and α-substituted amines, er was determined by chiral HPLC following conversion to the corresponding N-Cbz piperidine **ent-585.** Relative stereochemistry assigned based on retention.*

The high er obtained for difuoro- and trifluoro-substrates **591** and **592** led us to investigate a number of other fluorinated amines (**Scheme 4.26**). In all cases, complex mixtures were obtained with little evidence for the target piperidines **599**–**601** by ^{1}H NMR spectroscopy. The additional steric bulk of the ortho substituents on the amine is likely to have hindered the reaction.

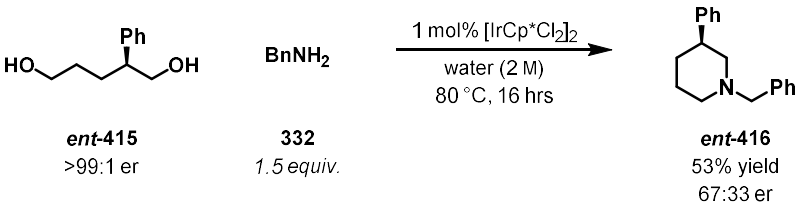


***Scheme 4.26:** Unsuccessful hydrogen borrowing reaction of fluorinated amines with diol **ent-570**.*

4.4.11 Diol Scope

Enantiopure 2-methyl diol ***ent*-570** was synthesised by $LiAlH_4$ reduction of the corresponding commercially available dimethyl ester by Dr Roly Armstrong. Unfortunately, this was the only enantiopure 2-substituted diol precursor readily available. It was highly desirable to investigate a number of different 2-substituted diols in the hydrogen borrowing reaction however, methods for enantioselective synthesis of these diols, or higher oxidation state precursors are scarce and very challenging. Therefore, it was not possible to conduct detailed diol scope investigations.

2-Phenylpentane-1,5-diol ***rac*-415** and 2-benzylpentane-1,5-diol **419** were both synthesised as racemates as described in **Section 3.3**. Samples of both were sent to industrial collaborators at Vertex (Abingdon) who carried out preparative SFC separation of the enantiomers to give the enantiopure (*R*) and (*S*) compounds. The enantiomers were identified by specific rotation and comparison to literature data.[187] In order to obtain the required amount of material for a single hydrogen borrowing reaction attempt, a large number of repeated injections were necessary at great time cost. Unfortunately, it was not possible to find satisfactory conditions for preparative scale separation of the enantiomers of benzyl diol **419**. Subjection of phenyldiol ***ent*-415**[*] to the optimised hydrogen borrowing conditions with benzylamine lead to the formation of piperidine ***ent*-416** in 53% yield and 67:33 er (**Scheme 4.27**). The lower yield and enantioselectivity are likely due to the acidity of the benzyl C3–H compared to the methyl substrate which makes racemisation at the C3 centre more facile.



Scheme 4.27: *Synthesis of phenyl piperidine* ***ent-416*** *from enantiopure diol* ***ent-415,***[§§§§] *er was calculated by chiral HPLC analysis of the corresponding N-Cbz compound (**S3**).*

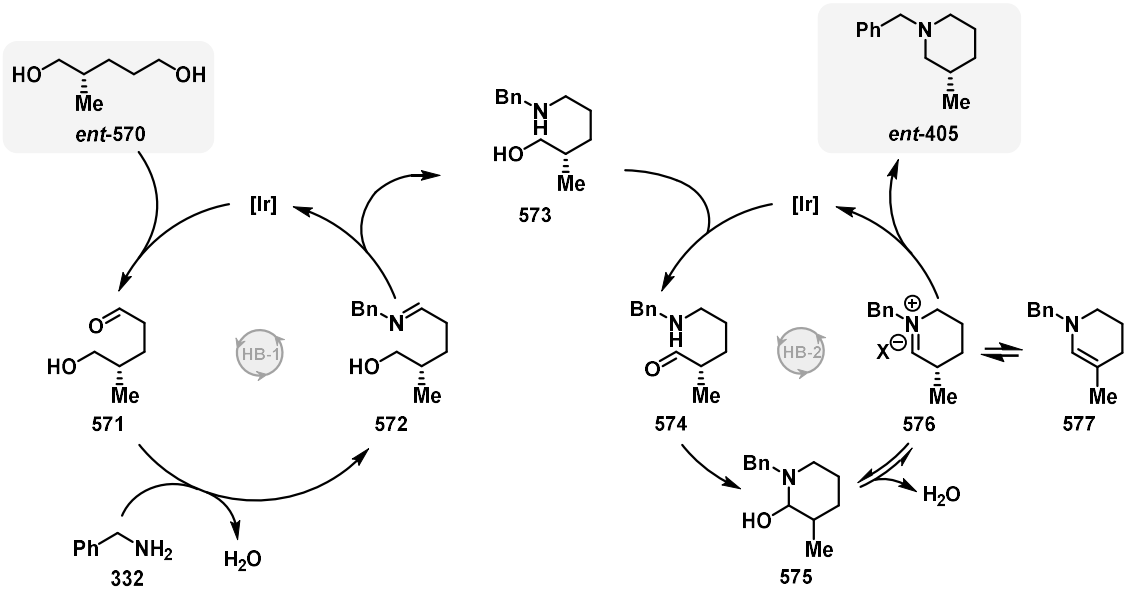
[*] The enantiomers of diol **415** were separated by Dr Thomas Staroske (Vertex)

4.5 Results and Discussion: Mechanistic studies

4.5.1 Proposed mechanism

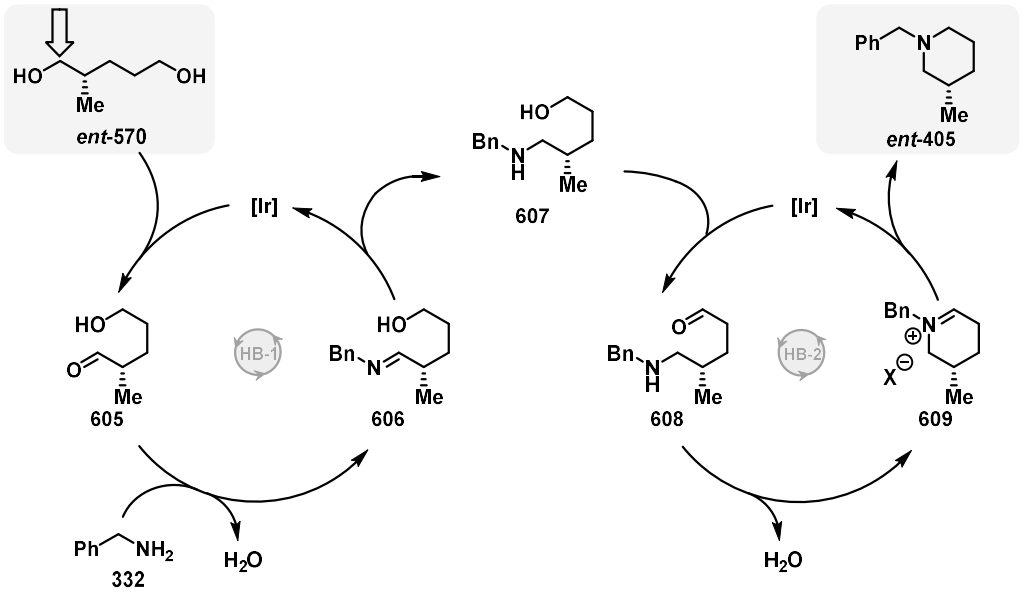
At the conclusion of our screening efforts we had reached a maximum er of 93:7 and we turned our attention to the proposed mechanism in order to identify means of further increasing stereoretention. The proposed mechanism features two sequential hydrogen borrowing cycles (labelled HB-1 and HB-2) and, in the case of an unsymmetrical diol such as ***ent*-570**, the order of events becomes important.

As alluded to earlier, it was expected that the alcohol furthest from the stereodefined substituent would react first since it is less sterically hindered (**Scheme 4.28**, indicated by arrow). In this case, the first cycle (HB-1) would proceed through aldehyde **571** and imine **572** with little chance for racemisation of the chiral centre. However, in the second cycle (HB-2), α-chiral aldehyde **574** and α-chiral iminium **576** are formed, both of which are expected to be highly susceptible to racemisation due to the acidity of the α-proton. Iminium **576** is likely to tautomerise to enamine **577**, which leads to racemisation at the C3 centre and the position of the equilibrium between hemiaminal **575** and iminium **576** may affect the extent of racemisation (**Scheme 4.28**).



Scheme 4.28: *Proposed mechanism for the case where the least hindered alcohol is involved in HB-1.*

If the alcohol group closest to the chiral group reacts first (**Scheme 4.29**, indicated by arrow), α-chiral aldehyde **605** and α-chiral imine **606** are formed in HB-1, which are expected to be sensitive to racemisation. Once the second cycle (HB-2) is reached, the er of the C-3 centre has been set and is thought to remain unaffected through aldehyde **608** and iminium **609** (**Scheme 4.29**).

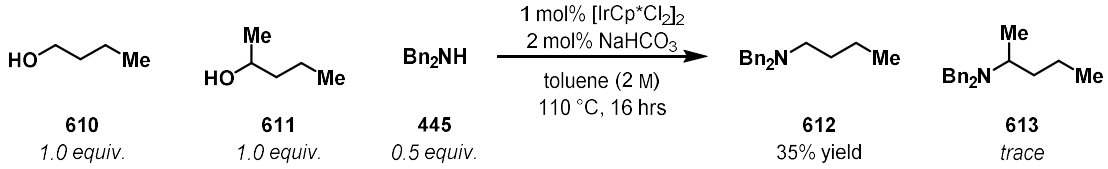


Scheme 4.29: *Proposed mechanism resulting from involvement of the most hindered alcohol in HB-1.*

We postulated that α-chiral iminium **576** was likely to be the most susceptible to racemisation through tautomerisation to enamine **577** during the hydrogen borrowing reaction (**Scheme 4.28**). The sensitive α-chiral iminium ion is only involved in the case where the least hindered alcohol is oxidised first (**Scheme 4.28**). Hence, we sought a means by which to force the reaction to proceed *via* the alternative pathway in which the most hindered alcohol is oxidised first (**Scheme 4.29**).

4.5.2 Competition experiment: primary vs secondary alcohols

Previous work in the group on the hydrogen borrowing reaction of diols with ketones to form C–C bonds revealed a complete preference for reaction of a primary alcohol over secondary.[59] However, this work was carried out under more forcing conditions; 2 mol% $[IrCp^*Cl_2]_2$, 4 equiv. KOH in toluene (4 M) at 115 °C. A competition experiment was carried out under our optimised hydrogen borrowing conditions between primary alcohol **610** and secondary alcohol **611** (**Scheme 4.30**). Dibenzylamine **445** was used in place of benzylamine **332** in order to simplify the system because the use of benzylamine may lead to the formation of crossed bisalkylated products and complicate analysis by NMR spectroscopy. The original toluene reaction conditions were employed in order to remove any physical effects, such as mixing problems, because alcohols **610** and **611** are not water miscible. The amine products **612** and **613** were identified by ^1H and ^{13}C NMR analysis and comparison to literature data and yields were calculated by comparison to an internal standard.[188,189] Only a trace amount of **613** was observed by NMR, which indicates hydrogen borrowing under these conditions is almost entirely selective for a primary alcohol over a secondary alcohol. The preference for reaction at the primary alcohol **610** was attributed to the increased reactivity of the intermediate aldehyde *cf.* the ketone formed upon oxidation of secondary alcohol **611**.[4]

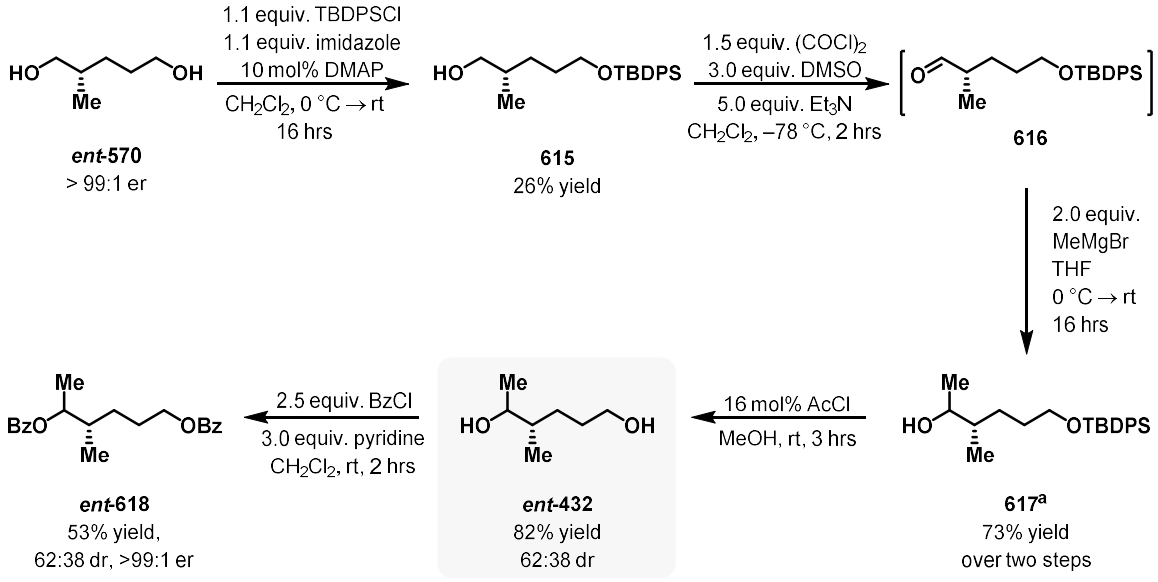


Scheme 4.30: *Control reaction involving a hydrogen borrowing competition reaction between primary alcohol **610** and secondary alcohol **611** with dibenzylamine. Yields were calculated by ^1H NMR by comparison to an internal standard, 1,1,2,2-tetrachloroethane.*

In order to test our theory that racemisation occurs primarily through tautomerisation of α-chiral iminium **576** to enamine **577**, we designed a system in which alcohol group closest to the enantioenriched β-position is now a secondary alcohol.

4.5.3 Synthesis of (4*S*)-4-methylhexane-1,5-diol *ent*-432

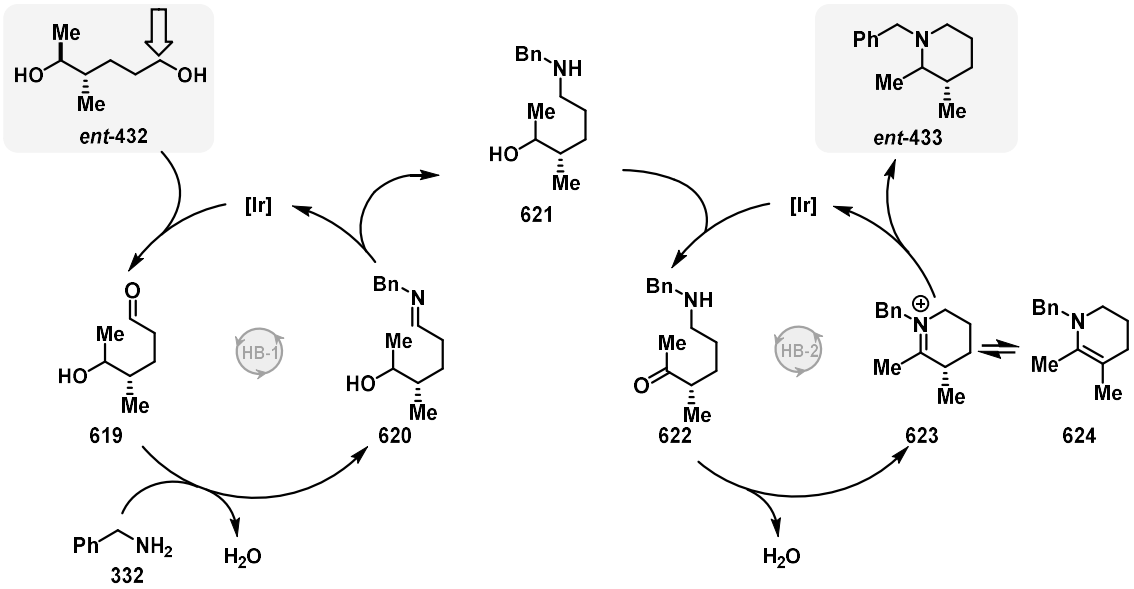
Dimethyl diol ***ent*-432** was synthesised from diol ***ent*-570** *via* the route shown in **Scheme 4.31**. *tert*-Butyldiphenylsilyl (TBDPS) chloride was found to protect the least hindered alcohol with 3:1 selectivity. After three successive purifications on silica, 26% yield of the desired regioisomer **615** was isolated (>95:5 r.r.). This regioisomer was tentatively assigned by comparison to literature NMR data.[190] Alcohol **615** was then oxidised to aldehyde **616** by a Swern oxidation; the formation of aldehyde **616** was confirmed by a characteristic aldehyde signal in the ^{1}H NMR spectrum at 9.60 ppm. The multiplicity (d, J = 1.9 Hz) of this peak confirmed the desired regioisomer of alcohol **615** had been synthesised. There was concern that aldehyde **616** may racemise or decompose on standing or upon purification on silica and hence, it was carried forward to the next step immediately. Reaction with methylmagnesium bromide furnished alcohol **617** in 73% yield over two steps. Finally, TBDPS deprotection was achieved by *in situ* generation of catalytic HCl to yield dimethyl alcohol ***ent*-432** in 82% yield and 62:38 dr. Derivatisation as the bisbenzoyl ester enabled chiral HPLC analysis, which indicated an er of >99:1 (**Scheme 4.31**).



Scheme 4.31: *Synthesis of diol* ***ent*-432***. Enantiomeric excess was calculated by chiral HPLC analysis of the corresponding bisbenzoyl ester* ***618****. [a]It was not possible to calculate dr for* ***617*** *due to overlapping peaks in the ^{1}H NMR spectrum.*

4.5.4 Hydrogen borrowing alkyaltion with (4*S*)-4-methylhexane-1,5-diol *ent*-432

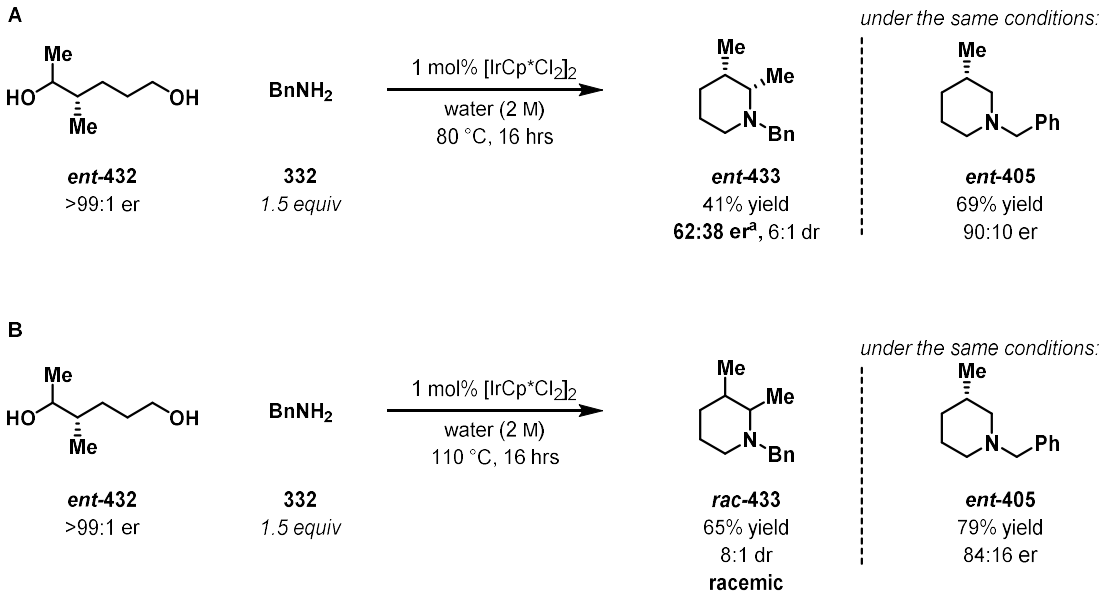
The mechanism of the hydrogen borrowing reaction between dimethyldiol ***ent*-432** and benzylamine is proposed to involve oxidation and reaction at the primary alcohol in HB-1 based on the results of the control reactions discussed previously (**Section 4.5.2**). Therefore, the mechanism is forced to proceed through α-chiral iminium ion **623** in HB-2, at which point we propose racemisation occurs *via* tautomerisation with enamine **624**. The intramolecular condensation is likely to be slower for this substrate than for the analogous monomethyl compound since it requires nucleophilic addition to a ketone, which is typically less reactive than an aldehyde (**Scheme 4.32**).[4]



Scheme 4.32: *Proposed mechanism of the hydrogen borrowing reaction between dimethyl diol* ***ent*-432** *and benzylamine* ***332****.*

Subjection of dimethyldiol ***ent*-432** to our optimised hydrogen borrowing conditions at 80 °C in water gave rise to piperidine ***ent*-433** in 41% yield and 6:1 dr. The er was significantly decreased relative to monomethyl piperidine ***ent*-405** under the same conditions (**Scheme 4.33A**). However, when the reaction temperature was increased to 110 °C, the piperidine product ***ent*-433** was isolated in higher yield and dr but, was found to be completely racemic by HPLC analysis of the corresponding *N*-Cbz compound (**Scheme 4.33B**). It was not possible to cleanly isolate the minor diastereomer by column chromatography and therefore only the er of the major diastereomer

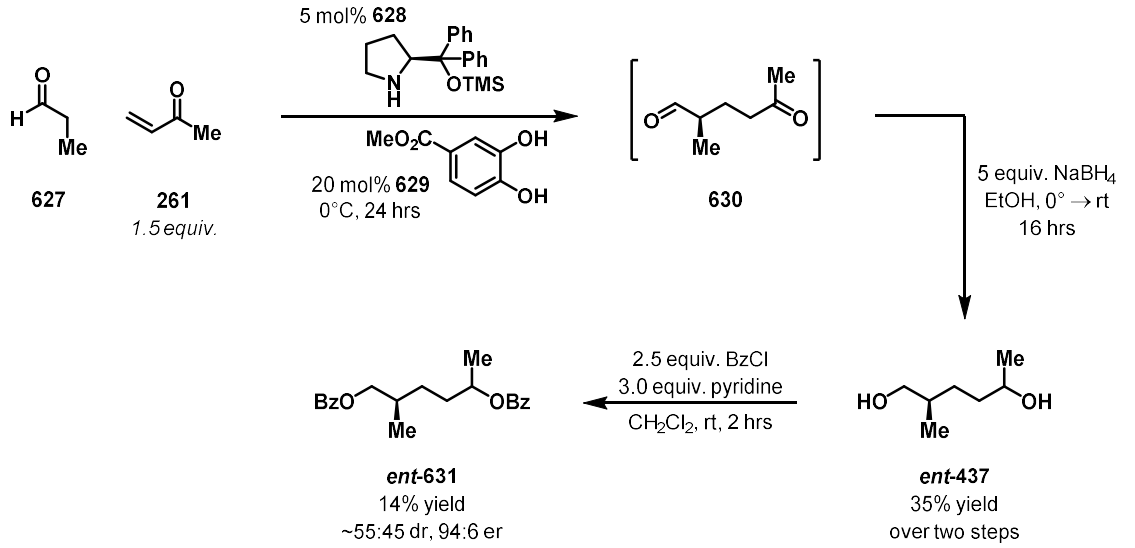
was measured. For a discussion on the factors governing diastereoselectivity in multiply substituted piperidine systems, see **Section 3.3.3**. This provides support for the hypothesis that racemisation occurs at the stage of the α-chiral iminium. Di-methyl iminium **623** is likely to be reduced more slowly than the analogous mono-methyl iminium **576** due to the additional steric bulk, which leads to a greater extent of racemisation.



Scheme 4.33: *Subjection of dimethyl diol* ***ent-432*** *to base-free hydrogen borrowing reaction with benzylamine* ***332*** *in water at* ***(A)*** *80 °C and* ***(B)*** *110* °C, *er was calculated by chiral HPLC analysis of the corresponding N-Cbz protected compound* **S4**, *major diastereomer depicted. Yield, er and es are shown for monomethyl system* ***ent-405*** *for comparison. [a]er was calculated for the major diastereomer.*

4.5.5 Synthesis of (2*R*)-2-methylhexane-1,5-diol

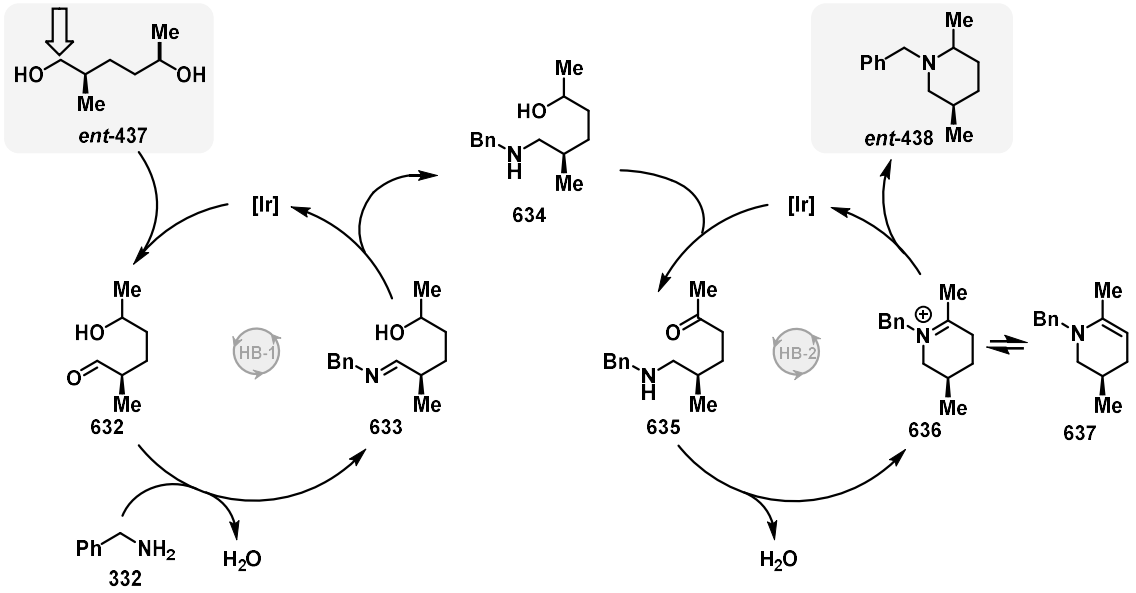
The opposite situation, in which the alcohol closest to the chiral centre reacts was next evaluated. Dimethyl diol ***ent*-437** was synthesised by an enantioselective Michael addition of propionaldehyde **627** to methyl vinyl ketone **261** in the presence of Hiyashi-Jørgenssen catalyst **628** and acid cocatalyst **629**.[191] The resulting 1,5-dicarbonyl compound **630** was reduced *in situ* to afford diol ***ent*-437** in 35% overall yield (**Scheme 4.34**). Since diol ***ent*-437** does not contain a UV chromophore, it was also derivatised as the bisbenzoyl ester ***ent*-631** for HPLC analysis, which revealed an er of 94:6. Absolute stereochemistry was assigned by comparison to the literature data.[191]



Scheme 4.34: *Synthesis of dimethyldiol* ***ent-437*** *under organocatalysis.*[191] *Enantiomeric excess was calculated by chiral HPLC analysis of the corresponding bisbenzoyl ester* ***ent-631****.*

4.5.6 Hydrogen borrowing alkyaltion with (2*R*)-2-methylhexane-1,5-diol *ent*-437

The proposed mechanism for hydrogen borrowing reaction of dimethyldiol ***ent*-437** with benzylamine **332** is shown in **Scheme 4.35**. It can be seen that the reaction is now expected to proceed through a pathway in which α-chiral aldehyde **632** is generated in HB-1, followed by α-chiral imine **633**. However, in HB-2, the iminium generated (**636**) can be tautomerised to enamine **637** without risk of racemisation of the methyl substituent. Thus, it was expected that piperidine product ***ent*-438** would be formed in high er.



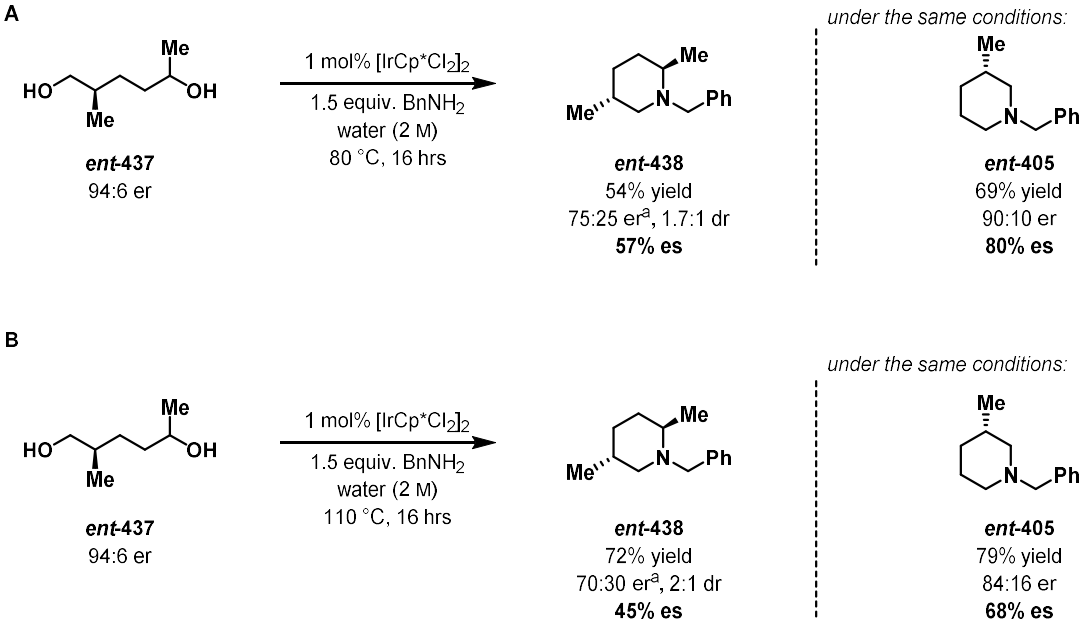
Scheme 4.35: *Proposed mechanism for the hydrogen borrowing alkylation of benzylamine* ***332*** *with dimethyldiol* ***ent-437****.*

Diol ***ent*-437** was synthesised in 94:6 er and hence, in order to allow comparison with previous reactions involving monomethyl ***ent*-570** (>99:1 er), the enantiospecificity (es) has been calculated for the following dimethylpiperidine ***ent*-438** and is defined as follows:

$$es = \frac{ee\ (product)}{ee\ (starting\ material)} \times 100\%$$

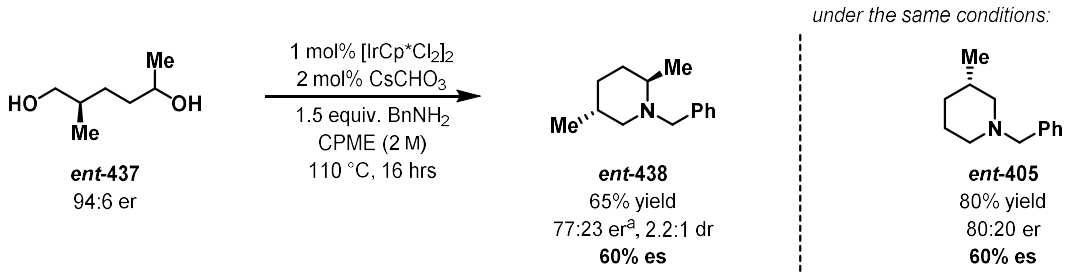
Equation 4.1: *Formula for the calculation of enantiospecificity.*

Under our optimised hydrogen borrowing conditions in water at 80 °C, dimethylpiperidine ***ent*-438** was isolated in 1.7:1 dr and 54% yield (for a discussion of the factors governing dr, see **Section 3.3.3**). Following *N*-Cbz protection (**S5**), the er was found to be 75:25 which equates to 57% es (see **Equation 4.1**). This is significantly lower than the analogous monomethyl substrate ***ent*-405** (**Scheme 4.36A**). The reaction was also carried out at 110 °C, which gave rise to piperidine ***ent*-438** in lower yield and er, as expected, but with slightly increased dr. Again, the es is significantly lower than for monomethyl substrate ***ent*-405** (**Scheme 4.36B**).



Scheme 4.36: *Subjection of dimethyl diol* ***ent-437*** *to base-free hydrogen borrowing reaction with benzylamine* ***332*** *in water at* ***(A)*** *80 °C and* ***(B)*** *110* °C, *er was calculated by chiral HPLC analysis of the corresponding N-Cbz protected compound* ***332****, major diastereomer depicted. Yield, er and es are shown for monomethyl system* ***ent-639*** *for comparison. [a]er is quoted for the major diastereomer.*

Subjection of dimethyl diol ***ent*-437** and benzylamine **332** to the hydrogen borrowing reaction with 2 mol% $CsHCO_3$ in CPME gave rise to piperidine ***ent*-438** in 65% yield and slightly higher diastereoselectivity than the reaction in water (**Scheme 4.37**). The es was 60%, which is the same as 3-methyl substrate ***ent*-405** under the analogous conditions.

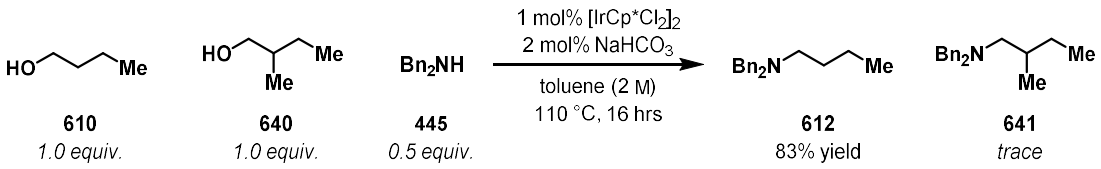


Scheme 4.37: *Subjection of dimethyl diol* ***ent-437*** *to base-free hydrogen borrowing reaction with benzylamine* ***332*** *under $CsHCO_3$/CPME conditions, er was calculated by chiral HPLC analysis of the corresponding N-Cbz protected compound* ***S5****, major diastereomer depicted. Yield, er and es are shown for monomethyl system* ***ent-405*** *for comparison. [a]er is quoted for the major diastereomer.*

Overall, the added methyl group has caused a small decrease in the stereoretention of the hydrogen borrowing reaction. Whilst this may suggest the tautomerisation between α-chiral iminium **636** and enamine **637** is not the sole loss of chiral information, it implies that epimerisation is also happening at other stages of our mechanism. On the other hand, when organic solvent is used, the addition of a methyl group did not have any effect on the stereoretention of the reaction. This suggests that there are additional differences between the water and CPME systems that were not accounted for in our model. This may include physical effects which arise as the biphasic system develops, or solvation differences. These results prompted us to carry out control reactions to investigate the comparative rate of oxidation of a linear alcohol vs. a β-branched alcohol.

4.5.7 Competition experiments

It was thought that the relatively small methyl substituent would not provide a significant steric bias for reaction at one of the alcohol groups of diol ***ent*-570** over the other, particularly since the methyl group is removed from the reacting centre, at the β-position of the alcohol. A competition reaction was set up between linear alcohol **610** and β-branched alcohol **640** in order to mimic the envirnoments of the two alcohol groups in in diol ***ent*-570** (**Scheme 4.38**). Similar to the primary vs secondary alcohol competition experiment (**Section 4.5.2**), dibenzylamine **445** was employed in order to simplify analysis.



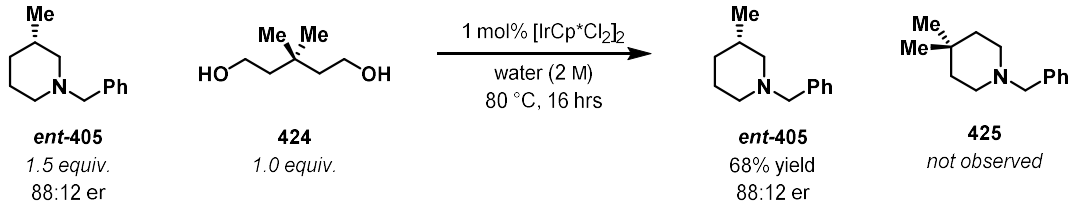
Scheme 4.38: *Competition experiment between linear alcohol **610** and β-branched alcohol **640**. Yields were calculated by ^{1}H NMR spectroscopy by comparison to an internal standard, 1,1,2,2-tetrachloroethane.*

The major product was linear amine **612** resulting from reaction of Bn_2NH with the less hindered alcohol. β-Branched amine **640** was only observed in trace amounts. This implies that the first

alkylation event in our double hydrogen borrowing mechanism occurs with almost complete selectivity for the least hindered alcohol group.

4.5.8 Resubjection experiments

Throughout our study of the synthesis of piperidine ***ent*-405** under hydrogen borrowing catalysis, there was a chance that piperidine product ***ent*-405** was also racemised under the reaction conditions. This was ultimately disproven by resubjection of material with known er (88:12) to the hydrogen borrowing reaction under the optimum conditions. *gem*-Dimethyl diol **424** was employed, so that in the event of complete reaction reversal, the resulting piperidine may be separated from ***ent*-405**. The reaction did not produce any crossover product **425** and piperidine ***ent*-405** was re-isolated in 88:12 er (**Scheme 4.39**). This implies that the final reduction step of the proposed mechanism is not reversible.



Scheme 4.39: *Resubjection of piperidine* ***ent*-405** *to the hydrogen borrowing conditions.*

4.5.9 Mechanistic conclusions

Our proposed hydrogen borrowing mechanism involves two sequential catalytic cycles. Following control experiments, it was concluded that the least hindered alcohol group of methyldiol ***ent*-570** is involved in the first cycle, that is the alcohol furthest away from the stereogenic centre. This leads to the formation of an α-chiral iminium ion which was thought to be the most likely point of racemisation. Hydrogen borrowing reaction of dimethyldiol ***ent*-432,** which is forced to go through the pathway involving an α-chiral iminium ion was found to give rise to racemic product **433**. This was partly attributed to slow reduction of α-chiral iminium **623** due to the additional steric bulk. The opposite case was also examined in which the stereogenic centre is not adjacent to the

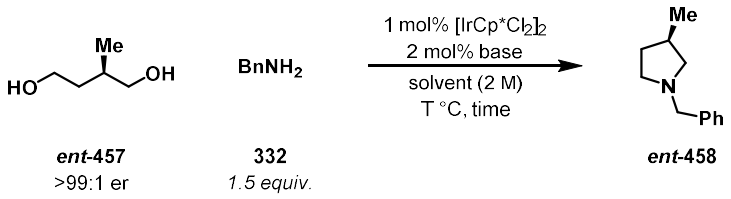
transient iminium ion **636**; hydrogen borrowing reaction of dimethyldiol ***ent*-437** led to the isolation of piperidine ***ent*-438** in 75:25 er.

4.6 Results and Discussion: Stereoselective Synthesis of Pyrrolidines

The synthesis of racemic pyrrolidine ***rac*-458** was demonstrated under the original hydrogen borrowing conditions with $NaHCO_3$ in toluene (see **Section 3.5.1**). Following development of reaction conditions for synthesis of 3-methyl piperidine ***ent*-458** in up to 93:7 er, we were interested to apply this work to the stereoselective synthesis of pyrrolidines.

Initial results with (*R*)-2-methylbutanediol ***ent*-457** were very promising. The Cbz protection developed for piperidine products was also found to be transferrable to the five-membered rings, and the reaction proceeded rapidly to afford *N*-Cbz pyrrolidines in decreased reaction time. Enantiopure diol ***ent*-457** was synthesised by $LiAlH_4$ reduction of the corresponding enantiopure bis-methylester by Dr Roly Armstrong and was confirmed to be >99:1 er by HPLC analysis of the corresponding bis-benzoyl ester on a chiral stationary phase.

Initially, diol ***ent*-457** was subjected to hydrogen borrowing reaction with benzylamine **332** under the base-free, water conditions at 110 °C, which was found to give rise to pyrrolidine ***ent*-458** in 78% NMR yield and 87:13 er (**Table 4.11**, Entry 1). However, we were pleased to find that use of CPME with 2 mol% $CsHCO_3$ increased the er to 96:4 (**Table 4.11**, Entry 2). During the optimisation for six-membered rings it was found that reducing the reaction temperature from 110 °C to 80 °C gave a slight decrease in yield but, more importantly, increased er. The same was found to be true for the yield of pyrrolidine ***ent*-458** at 80 °C however, the er remained the same under both aqueous and organic solvent conditions (**Table 4.11**, Entries 3 and 4). Increased reaction time (24 hrs) gave rise to a significantly improvement in the yield of pyrrolidine ***ent*-458** and maintained an er of 96:4 (**Table 4.11**, Entry 5). The hydrogen borrowing reaction was carried out at room temperature under both sets of conditions however, in both cases no reaction was observed and starting materials were returned (**Table 4.11**, Entries 6 and 7). Due to time constraints, it was not possible to conduct a full reaction optimisation or substrate scope evaluation.



***ent*-457**
>99:1 er

332
1.5 equiv.

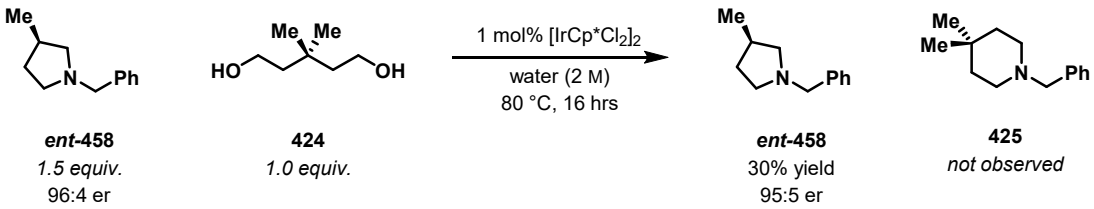
***ent*-458**

Entry	Solvent	Base	Temperature, T/ °C	Time, t / hrs	Yield / %	er
1	Water	-	110	16	[78]	87:13
2	CPME	$CsHCO_3$	110	16	72	94:6
3	Water	-	80	16	62	87:13
4	CPME	$CsHCO_3$	80	16	54	94:6
5	CPME	$CsHCO_3$	80	24	86	94:6
6	Water	-	rt	16	n.r.	-
7	CPME	$CsHCO_3$	rt	16	n.r.	-

***Table 4.11**: Hydrogen borrowing catalysis for the synthesis of pyrrolidines. Yields shown in parentheses were calculated by ^1H NMR spectroscopy by comparison to an internal standard, 1,1,2,2-tetrachloroethane, er was calculated by HPLC analysis on a chiral stationary phase of the corresponding N-Cbz protected compound* **S6**.

4.6.1. Resubjection experiment

In order to check the configurational stability of pyrrolidine product ***ent*-458**, material of known er was subjected to hydrogen borrowing conditions with gem-dimethyl diol **424**. Pyrrolidine ***ent*-458** was reisolated in 95:5 er which is within error of the er of the original material (96:4). Gem-dimethyl piperidine **425** was not observed which suggests that the reaction is not fully reversible (**Scheme 4.40**). These results are in accordance with the 6-membered ring system (**Section 4.5.8**).



***ent*-458**
1.5 equiv.
96:4 er

424
1.0 equiv.

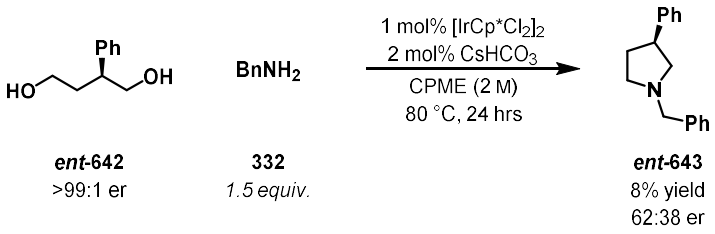
***ent*-458**
30% yield
95:5 er

425
not observed

***Scheme 4.40:** Resubjection of pyrrolidine **ent-458** to hydrogen borrowing conditions.*

4.6.2 Diol scope

Fortunately, enantiopure butanediol precursors are somewhat more readily available the pentanediol precursors. (*S*)-2-Phenylbutane-1,4-diol ***ent*-642** was obtained by $LiAlH_4$ reduction of (*S*)-phenylsuccinic acid by Dr Roly Armstong and confirmed to have 99:1 er by HPLC analysis with a chiral stationary phase. Unfortunately, subjection to the optimised hydrogen borrowing conditions for five-membered ring formation with benzylamine **332** gave rise to pyrrolidine ***ent*-643** in 8% yield and 62:38 er (**Scheme 4.41**). As with the analogous 6-membered ring (**Section 4.4.11**), this result was attributed to the increased acidity of the C3 benzyl proton which promotes racemisation. Unfortunately, further investigations into diol scope were not possible due to time constraints but are currently underway in the group.

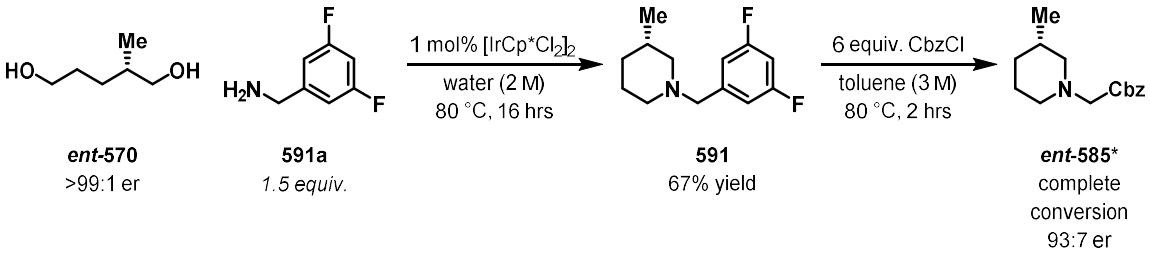


Scheme 4.41: *Synthesis of 3-phenylpyrrolidine* ***ent*-643** *under hydrogen borrowing conditions,[*] er was calculated following HPLC analysis on a chiral stationary phase of the corresponding N-Cbz pyrrolidine* **S8**.

[*] Diol ***ent*-642** was synthesised by Dr Roly Armstrong

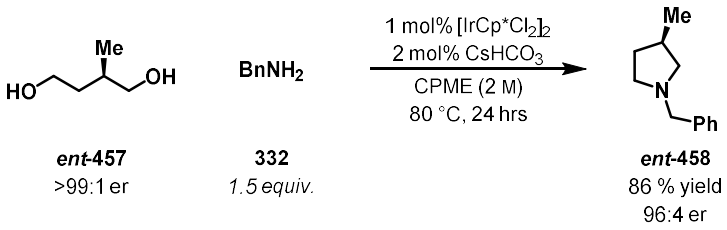
4.7 Conclusions and Future Work

In summary, the synthesis of (*S*)-3-methylpiperidine ***ent*-405** under hydrogen borrowing catalysis has been studied and extensive reaction optimisation carried out, which has led to the development of base-free reaction conditions with water as the solvent. Enantiopure diol ***ent*-570** was employed and stereoretention up to 93:7 er could be achieved in the reaction with 3,5-difluorobenzylamine (**Scheme 4.42**). This result is especially pleasing given the inclusion of α-chiral carbonyl intermediated in our proposed reaction mechanism. Deprotection conditions have been developed for the cleavage of the *N*-benzyl group under hydrogenolysis. Alternatively, it was shown that a range of *N*-benzyl variants can be converted to the corresponding *N*-Cbz compounds with ease.



Scheme 4.42: *Optimised hydrogen borrowing conditions for the reaction of diol* ***ent-570*** *and difluorobenzylamine* ***591a*** *leads to synthesis of piperidine* ***591*** *with 93:7 er by stereoretention, er was calculated by chiral HPLC analysis of the corresponding N-Cbz piperidine* ***ent-585****. **An analytical sample of* ***ent-585*** *was isolated by preparative TLC.*

The newly developed hydrogen borrowing conditions were also applied to the synthesis of pyrrolidines with excellent results. Whilst only brief optimisation studies were carried out, it was found that the organic solvent, CPME, in the presence of 2 mol% $CsHCO_3$ gave rise to higher er than the aqueous conditions developed for 6-membered ring formation. It was possible to synthesise pyrrolidine in up to 86% yield and 96:4 er (**Scheme 4.43**).



***ent*-457**
>99:1 er

332
1.5 equiv.

***ent*-458**
86 % yield
96:4 er

Scheme 4.43: *Pyrrolidine* ***ent-458*** *was synthesised in excellent yield and er under hydrogen borrowing catalysis.*

4.7.1 Future work

Given the prevalence of chiral ligands for enantioselective hydrogen borrowing catalysis in the literature, it is possible that a similar route could be developed for the enantioselective synthesis of *N*-heterocycles from racemic diols. Investigations into alternative catalysts were only brief during this project but this area should be revisited; chiral ligands have previously been used in conjunction with a range of ruthenium, iridium and even nickel catalysts (see **Section 4.1**).

Work is ongoing in the group to develop conditions for 'interrupted' synthesis of *N*-heterocycles under hydrogen borrowing conditions; that is to trap the intermediate iminium ion/enamine with a range of nucleophiles in order to construct more complex scaffolds. It is hoped that the application of the stereoselective methodology developed herein to such an endeavour will generate an elegant route to the synthesis of stereodefined, natural product-like scaffolds.

Chapter 5: Experimental

5.1 General Experimental

5.1.1 Reagents and solvents

All reactions were performed in flame-dried reaction vessels under an argon atmosphere, unless otherwise stated. Anhydrous solvents were obtained from MBRAUN SP-5 solvent purification system and were dried by passage through double filtration columns under nitrogen. Anhydrous benzylamine (≥99.5%, purified by redistillation) was purchased from Sigma Aldrich. All other reagents were acquired from Sigma Aldrich, Fluorochem, Acros Organics, Alfa Aesar or TCI and used without further purification. Brine refers to a saturated aqueous solution of NaCl.

5.1.2 Chromatography

Reactions were monitored by TLC using Merck Silicagel 60 F_{254} aluminium-backed silica plates (particle size 0.20 mm) and visualised by exposure to UV light (λ = 254 nm) and/or staining and heating with phosphomolybdic acid, vanillin or potassium permanganate as appropriate. Flash column chromatography was performed using Merck Geduran® Silicagel 60 (40–63 μm) according to the method by Still and co-workers.[192] The required solvent system is specified in parentheses and where mixtures of solvents are described, the ratios are given as volume:volume. Solvents used for column chromatography were HPLC grade and supplied by Sigma Aldrich, Acros, Honeywell or Thermo Fisher Scientific.

N-Benzyl piperidine products were purified on pre-basified silica (as noted in general procedure A, B, D and G) which was prepared as follows; silica (400 g), pentane (250 mL), Et_2O (250 mL) and trimethylamine (5 mL) were combined in a 1 L beaker and stirred for 15 minutes. The solvent was allowed to evaporate overnight, and the resulting silica could be stored in a sealed bottle for a few weeks.

5.1.3 NMR spectroscopy

Proton (^{1}H), carbon (^{13}C), fluorine (^{19}F) and phosphorous (^{31}P) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVIII HD 400 or Bruker AVIII 500 MHz spectrometer at ambient temperature, unless otherwise stated. ^{13}C spectra were run with broadband decoupling. ^{1}H and ^{13}C spectra were referenced to residual solvent peaks ($CDCl_3$, ^{1}H = 7.26 ppm and ^{13}C = 77.2 ppm or d_8-toluene, ^{1}H = 2.08 ppm and ^{13}C = 20.4 ppm). ^{19}F and ^{31}P NMR spectra are not externally referenced. Chemical shifts (δ) are recorded in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H NMR or 0.1 ppm for ^{13}C, ^{19}F and ^{31}P NMR, except where additional precision was required to distinguish two close peaks.

Coupling constants (*J*) are measured in hertz (Hz) and quoted to the nearest 0.1 Hz. Peaks are assigned as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), heptet (hept), multiplet (m), broad (br.) or a combination such as doublet of doublets (dd), doublet of triplets (dt) etc. Multiplicities are based on appearance rather than interpretation. COSY, HSQC, HMBC and NOESY experiments were used to aid structural assignment where appropriate. For cyclic compounds, the abbreviation 'ax' denotes the axial proton and 'eq' the equatorial proton. In cases where it was not possible to definitively assign axial and equatorial, the CH_2 protons are labelled 'a' and 'b'.

5.1.4 High-performance Liquid Chromatography (HPLC)

HPLC analysis was preformed using an Agilent 1260 Infinity II instrument, equipped with Chiralcel® and Chiralpak® columns (250mm x 4.6 mm, particle size 5 µm) and appropriate guard columns (4 mm x 10 mm, particle size 5 µm) and a diode array detector. Enantiomeric samples were compared to an authentic sample of the corresponding racemic compound. In most cases, these were synthesised under hydrogen borrowing conditions using the appropriate, racemic alcohol. Retention times of benzyl (*S*)-3-methylpiperidine-1-carboxylate ***ent*-585** were found to be irreproducible day-to-day and so enantioenriched samples were always run in sequence with the racemic standard.

5.1.5 Infrared spectroscopy

Fourier-transformed infrared (FT-IR) spectra were recorded as a thin film or solid on a Bruker Tensor 27 FT-IR spectrometer equipped with a Pike Miracle Attenuated Total Reflectance sampling accessory. Absorption maxima are quoted in wavenumbers (cm^{-1}). The abbreviation br. denotes a broad peak.

5.1.6 Mass spectrometry

High resolution mass spectrometry (HRMS) was carried out by staff at the Oxford University Mass Spectrometry Research Facility. Electrospray ionisation (ESI) HRMS were recorded on a Thermo Exactive orbitrap spectrometer equipped with Waters Equity liquid chromatography system using an eluent of 10:89.9:0.1 water:methanol:formic acid and a flow rate of 0.2 mL min^{-1}. The system was operated using a heated electrospray (HESI-II) probe with a resolution of 50,000 FWHM. Conditions were adjusted to maximise sensitivity, and the system was calibrated on the day of analysis to have an accuracy of better than 5 ppm for 24 hours following external calibration. Instrument control and data processing were carried out using Agilent MassHunter software. The mass reported is that containing the most abundant isoptopes and is within 5 ppm of the calculated mass, unless otherwise stated. HRMS values are quoted as a mass to charge ratio (*m/z*) in Daltons, rounded to 4 decimal places and within 5 ppm of the calculated value.

5.1.7 Melting points

Melting point analysis was carried out using a Lecia VMTG heated-stage microscope equipped with a Testo 720 thermometer. Samples were recrystallised prior to melting point analysis (solvent quoted in parentheses) and values are uncorrected.

5.1.8 Optical Rotation

Specific optical rotation was measured on a Schmidt Haensch Unipol L2000 Polarimeter, using a 100 mm quartz glass mictrotube (volume 1 cm^3) at the sodium D line (λ = 589.3 nm) and at 25 °C. $[\alpha]_{\mathrm{D}}^{25}$ values have units 10^{-1} deg cm^2 g^{-1}. The solvent used is quoted in parentheses, along with the concentration, *c*, which has units 10^{-2} g mL^{-1}.

5.1.9 Photoredox reactions

Photochemical reations were carried out using one of two set ups:

1. HepatoChem® EvoluChem™ PhotoChemistry device with Kessil H150 blue light source 34W (400–500 nm, λ_{max} = 450 nm). The device was equipped with vial holders to accommodate either 8 x 2 mL or 3 x 4 mL vials. The device featured a built-in fan to maintain ambient temperature and was placed on a stirrer hotplate.
2. A blue LED light strip wound around the inside of a crystallisation dish and placed on top of a stirrer hotplate.

5.1.10 Naming and numbering of compounds

Compound names were generated using the computer software ChemDraw according the to the International Union of Pure and Applied Chemistry (IUPAC) guidelines. The numbering shown on structures has been used to aid NMR assignment and does not necessarily correspond with the systematic name. Compounds that are not assigned a compound number are labelled S1, S2 etc.

5.1.11 X-ray crystallography

Single crystal X-ray diffraction was recorded by Amber Thompson using a Nonius KappaCCD diffractometer or Oxford Diffraction/Agilent Supernovae A. Crystal structure images presented were produced using the computer software CRYSTALS.

5.1.12 Computational calculations

Energy calculations were conducted by Dr Ewa Chudyk and Dr Ron Knetgel (Vertex) using Maestro computer software (from Schrödinger) with OPLS3 force field. Geometries were optimised at the quantum level using DFT at the B3LYP/6-31G** level of theory, using Jaguar computer software. Optimised geometry images were produced using the computer software PyMOL.

5.1.13 Ultra-performance liquid chromatography–mass spectrometry (UPLC-MS)

UPLC-MS analysis was run on a Waters Acquity UPLC-MS with Waters PDA UV detector and Waters SQD mass spectrometer at 45 °C, using either a Waters UPLC BEH C8 column (2.1 mm x 50 mm, 1.7 µm particle size) or Phenomenex Kinetex EVO C18 column (2.1 mm x 50 mm, 2.6 µm particle

size). Gradient solvent systems were used with mobile phase A = 10 mM ammonium formate in water:acetonitrile 95:5 (pH 9) and mobile phase B = acetonitrile.

5.1.14 Mass-directed semi-preparative HPLC

Semi-preparative reverse phase HPLC was carried by Dr Thomas Staroske and Stefan Richardson (Vertex) using a Waters autopurification HPLC-MS system equipped with a Waters 2998 UV detector, a Waters QDa mass spectrometer and FractionLynx™ computer software. Either a Waters Sunfire Prep C18 OBD column (19 mm x 150 mm, 5 µm particle size) or a Waters XBridge Prep C18 OBD column (19 mm x 150 mm, 5 µm particle size) were used with an appropriate water:acetonitrile gradient with either TFA or NH_4OH as a modifier.

5.2 General Procedures

General procedure A: Hydrogen borrowing alkylation of amines with diols in toluene

To a 2-5 mL Biotage® microwave vial equipped with a stirrer bar was added the appropriate alcohol substrate (1.0 equiv.), $[IrCp^*Cl_2]_2$ (1.0 mol%) and $NaHCO_3$ (2.0 mol%). The vial was sealed with a microwave vial crimp cap (containing a Reseal® septum), evacuated under vacuum and refilled with argon three times. Anhydrous toluene (2 M) was added *via* syringe, followed by the appropriate amine (1.5 equiv.). The vial was sealed with Parafilm®, placed in a preheated oil bath and stirred at 110 °C for 16 hours. The reaction mixture was cooled to room temperature and concentrated under a flow of nitrogen. Purification by column chromatography (SiO_2 was basified with Et_3N prior to use, see Section 5.1.2 for details) afforded the piperidine product.

General procedure B: Hydrogen borrowing alkylation of amines with diols in water

To a 2-5 mL Biotage® microwave vial equipped with a stirrer bar was added the appropriate alcohol substrate (1.0 equiv.) and $[IrCp^*Cl_2]_2$ (1.0 mol%). The vial was sealed with a microwave vial crimp cap (containing a Reseal® septum), evacuated under vacuum and refilled with argon three times. Deionised water (2 M) was added *via* syringe, followed by the appropriate amine (1.5 equiv.). The vial was sealed with Parafilm®, placed in a preheated oil bath and stirred at the appropriate temperature for 16 hours. The reaction mixture was cooled to room temperature and extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2 was basified with Et_3N prior to use, see Section 5.1.2 for details) afforded the title compound.

General procedure C: Carboxybenzyl (Cbz) protection for HPLC analysis

To a 2-5 mL Biotage® microwave vial equipped with a stirrer bar was added the appropriate *N*-benzyl substrate (1.0 equiv.). Benzyl chloroformate (3 M in toluene, 6.0 equiv.) was added slowly *via* syringe. The vial was sealed with a microwave vial crimp cap (containing a Reseal® septum) and equipped with a balloon (caution: gas evolution!). The reaction mixture was stirred at 80 °C

for 2 hours. The reaction mixture was cooled to room temperature and transferred directly onto a silica column. Purification by column chromatography (SiO_2) afforded the title compound.

General procedure D: Solvent-free hydrogen borrowing alkylation of amines with diols

To a 2-5 mL Biotage® microwave vial equipped with a stirrer bar was added the appropriate alcohol substrate (1.0 equiv.), $[IrCp^*Cl_2]_2$ (1.0 mol%) and $NaHCO_3$ (2.0 mol%). The vial was sealed with a microwave vial crimp cap (containing a Reseal® septum), evacuated under vacuum and refilled with argon three times. Anhydrous benzylamine (1.5 equiv.) was added *via* syringe. The vial was sealed with Parafilm®, placed in a preheated oil bath and stirred at 110 °C for 16 hours. The reaction mixture was transferred directly onto a SiO_2 column and purification by column chromatography (using SiO_2 previously basified with Et_3N, see Section 5.1.2 for details) afforded the title compound.

General procedure E: Bis-benzoylation of diols for HPLC analysis

To a solution of the required diol (1.0 equiv.) in anhydrous CH_2Cl_2 (0.04 M) was added pyridine (3 equiv.) and benzoyl chloride (2.5 equiv.). The resulting solution was stirred at room temperature for 2 hours before addition of saturated aqueous NH_4Cl solution (10 mL). The mixture was extracted with CH_2Cl_2 (3×10 mL) and the combined organic phases dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2) afforded the title compound.

General procedure F: $Ru(bpy)_3Cl_2$ catalysed 2+2 addition under photoredox conditions

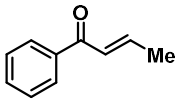
The procedure was adapted from the literature.[115] To a flame dried Schlenk tube equipped with magnetic stirrer bar was added the required enone (1.0 equiv.), appropriate Micheal acceptor (2.4 equiv.), $Ru(bpy)_3Cl_2$ (5.0 mol%), $LiBF_4$ (4.0 equiv.), $^iPr_2NEt$ (2.0 equiv.) and anhydrous acetonitrile (0.1 M). The reaction mixture was subjected to three freeze-pump-thaw cycles in the dark before exposure to blue LEDs, wih stirring, for the required time. The reaction mixture was concentrated *in vacuo* and purification by column chromatography (SiO_2) afforded the title compound.

General procedure G: Hydrogen borrowing alkylation of amines with diols in CPME

To a 2-5 mL Biotage® microwave vial equipped with a stirrer bar was added the appropriate alcohol substrate (1.0 equiv.), $CsHCO_3$ (2.0 mol%) and $[IrCp^*Cl_2]_2$ (1.0 mol%). The vial was sealed with a microwave vial crimp cap (containing a Reseal® septum), evacuated under vacuum and refilled with argon three times. Cyclopentyl methyl ether (2 M) was added *via* syringe, followed by the appropriate amine (1.5 equiv.). The vial was sealed with Parafilm®, placed in a preheated oil bath and stirred at 80 °C for 24 hours. The reaction mixture was cooled to room temperature and concentrated under a flow of nitrogen. Purification by column chromatography (SiO_2 was basified with Et_3N prior to use, see Section 5.1.2 for details) afforded the title compound.

5.3 Experimental Procedures

(*E*)-1-Phenylbut-2-en-1-one (222)



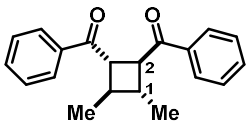
Enone **222** was synthesised according to literature procedure.[126] To a suspension of aluminium trichloride (5.50 g, 41.1 mmol) in benzene (20 mL) at 0 °C was slowly added *trans*-crotonyl chloride (4.10 mL, 42.8 mmol, 75% purity). The reaction mixture was warmed to room temperature and stirred for a further 2 hours. The reaction was quenched by slow addition into a mixture of 1M HCl (100 mL) and ice. After stirring the mixture for 1 hour, water (50 mL) and Et_2O (100 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic portions dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (97:3 pentane:Et_2O) afforded enone **222** (2.36 g, 50%, >95:5 E:Z) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96-7.88 (2H, m, Ar<u>H</u>), 7.57-7.52 (1H, m, Ar<u>H</u>), 7.48-7.44 (2H, m, Ar<u>H</u>), 7.07 (1H, dq, *J* = 15.3, 6.8 Hz, CH=C<u>H</u>CH$_3$), 6.90 (1H, dq, *J* = 15.3, 1.6 Hz, C<u>H</u>=CHCH$_3$), 2.00 (3H, dd, *J* = 6.8, 1.5 Hz, C<u>H</u>$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 190.9 (<u>C</u>=O), 145.2 (<u>C</u>H=CHCH$_3$), 138.0 (Ar<u>C</u>), 132.7 (Ar<u>C</u>H), 128.6 (4 × Ar<u>C</u>H), 127.7 (CH=<u>C</u>HCH$_3$), 18.7 (<u>C</u>H$_3$).

The data are consistent with the literature.[193]

***rac*-(3,4-Dimethylcyclobutane-1,2-diyl)bis(phenylmethanone) (225)**



Cyclobutane **225** was synthesised according to a modified literature procedure.[114] To a vial equipped with a magnetic stirrer bar was weighed (*E*)-1-phenylbut-2-en-1-one **222** (59 mg,

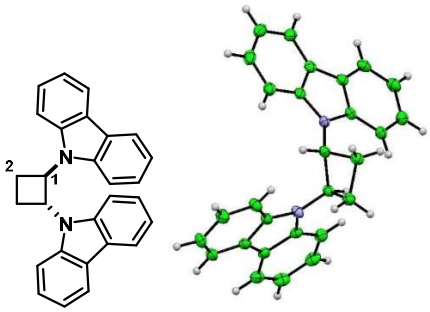
0.4 mmol), $Ru(bpy)_3Cl_2$ (15 mg, 5.0 mol%) and $LiBF_4$ (150 mg, 1.6 mmol). The vial was sealed with a screw cap (containing a septum) and acetonitrile (4.0 mL) and $^{i}Pr_2NEt$ (0.14 mL, 0.80 mmol) were added *via* syringe. Nitrogen was bubbled through the solution in the dark for approx. 10 minutes. The vial was sealed with parafilm, irradiated with blue LEDs (λ = 450 nm) and stirred for 2 hours. Purification by column chromatography (95:5 heptane:EtOAc) afforded cyclobutane **225** (22 mg, 38%, >95:5 dr) as a colourless oil. *Assigned as all-trans geometry based on comparison to literature data.*[114]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00-7.96 (4H, m, ArH), 7.56-7.52 (2H, m, ArH), 7.46-7.42 (4H, m, ArH), 4.05-4.03 (2H, m, 2 × CH-2), 2.20-2.10 (2H, m, 2 × CH-1), 1.22-1.19 (6H, m, 2 × CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.9 (2 × C=O), 136.5 (2 × ArC), 133.4 (2 × ArCH), 128.8 (4 × ArCH), 128.7 (4 × ArCH), 47.5 (2 × CH-2), 39.5 (2 × CH-1), 19.4 (2 × CH_3).

The data are consistent with the literature.[114]

(±)-1,2-Di(9*H*-carbazol-9-yl)cyclobutane (240)



To a 2–5 mL Biotage® microwave vial was added *N*-vinylcarbazole (97 mg, 0.50 mmol) and (diacetoxyiodo)benzene (16.1 mg, 10 mol%). The vial was sealed with a crimp cap (containing a Reseal® septum), flushed with argon for 10 minutes and cooled to 0 °C before addition of CH_2Cl_2 (2.32 mL) followed by TFE (0.18 mL). The resulting solution was stirred at 0 °C for 2 hours before being warmed to room temperature and stirred for a further 15 hours. The reaction mixture was directly concentrated *in vacuo* and purification by column chromatography (98:2 pentane:Et_2O)

afforded cyclobutane **240** (63 mg, 65%, >95:5) as a colourless solid. *Head-to-head dimerisation and trans geometry was confirmed by X-ray crystallography (see **Appendix 6.1**).*

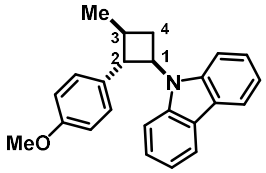
^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.06 (4H, dt, *J* = 7.7, 1.2 Hz, Ar<u>H</u>), 7.56 (4H, dt, *J* = 8.3, 0.9 Hz, Ar<u>H</u>), 7.39 (4H, ddd, *J* = 8.3, 7.1, 1.2 Hz, Ar<u>H</u>), 7.21 (4H, td, *J* = 7.7, 0.9 Hz, Ar<u>H</u>), 6.33-6.28 (2H, m, 2 × C<u>H</u>-<u>1</u>), 3.16-3.07 (2H, m, 2 × C<u>H</u>-<u>2$_a$</u>), 2.80-2.70 (2H, m, 2 × C<u>H</u>-<u>2$_b$</u>).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 140.0 (4 × Ar<u>C</u>), 127.8 (4 × Ar<u>C</u>H), 123.6 (4 × Ar<u>C</u>), 120.5 (4 × Ar<u>C</u>H), 119.4 (4 × Ar<u>C</u>H), 109.7 (4 × Ar<u>C</u>H), 54.5 (2 × <u>C</u>H-1), 20.9 (2 × <u>C</u>H$_2$-2).

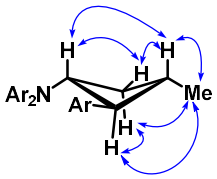
Melting point ($CDCl_3$) = 198–199 °C.

The data are consistent with the literature.[120]

<u>(±)-9-(2-(4-Methoxyphenyl)-3-methylcyclobutyl)-9H-carbazole (241)</u>



N-vinylcarbazole (116 mg, 0.60 mmol) was dissolved in CH_2Cl_2 (1 mL) in a 2–5 mL Biotage® microwave vial and (diacetoxyiodo)benzene (4.8 mg, 5.0 mol%) was added. The vial was sealed with a crimp cap (containing Reseal® septum), flushed with argon for approx. 5 minutes and the solution cooled to 0 °C. *trans*-Anethole (45 mg 0.30 mmol) was dissolved in a mixture of TFE (0.11 mL) and CH_2Cl_2 (0.39 mL) and added *via* syringe pump over 1 hour. The reaction mixture was stirred at 0 °C for 2 hours before being warmed to room temperature and stirred for a further 16 hours. The mixture was concentrated *in vacuo* and transferred directly onto a silica column. Purification by column chromatography (98:2 pentane:Et_2O) afforded cyclobutane **241** (16 mg, 15%, >95:5 dr) as a colourless solid.



nOe correlations indicate by solid arrows (blue).
Other correlations have been omitted for clarity

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.11 (2H, m, ArH), 7.65 (2H, m, ArH), 7.44 (2H, m, ArH), 7.25-7.21 (2H, m, ArH), 7.13-7.09 (2H, m, ArH), 6.81-6.77 (2H, m, ArH), 5.07 (1H, td, *J* = 9.7, 8.4 Hz, CH-1), 4.14 (1H, t, *J* = 9.4 Hz, CH-2), 3.75 (3H, s, OCH_3), 2.75-2.63 (2H, m, CH_2-4), 2.41-2.29 (1H, m, CH-3), 1.49 (3H, d, *J* = 6.6 Hz, CH_3).

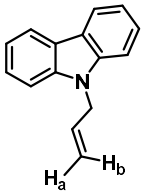
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 158.3 (ArC), 140.3 (2 × ArC), 134.7 (ArC), 127.5 (2 × ArCH), 125.6 (2 × ArCH), 123.5 (2 × ArC), 120.4 (2 × ArCH), 119.0 (2 × ArCH), 114.1 (2 × ArCH), 110.4 (2 × ArCH), 55.4 (OCH_3), 53.3 (CH-1), 52.8 (CH-2), 32.9 (CH_2-4), 31.9 (CH-3), 21.2 (CH_3).

HRMS: ESI^+ found $[M+H]^+$ = 342.1853, $C_{24}H_{24}NO$ requires 342.1852, Δ = 0.18 ppm.

FTIR (film): ν_{max} = 2951, 1513, 1452, 1335, 1249, 1035, 749, 723 cm^{-1}.

Melting point (CH_2Cl_2) = 157–158 °C.

_N_-Allyl-9H-carbazole (S1)



Carbazole **S1** was synthesised according to literature procedure.[194] Carbazole (1.67 g, 10.0 mmol) was dissolved in DMF and cooled to 0 °C before portionwise addition of potassium hydroxide pellets (1.12 g, 20.0 mmol) over 5 minutes. The solution was stirred for 20 minutes at 0 °C before addition of allyl bromide (1.73 mL, 20.0 mmol). The resulting solution was sonicated at 35 °C for 1 hour before being cooled to room temperature, diluted with Et_2O (20 mL) and washed with water (20 mL). The organic phase was washed with aqueous LiCl solution (5 wt%, 3 × 20 mL). The organic

phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (98:2 pentane:Et_2O) afforded **S1** (1.75 g, 84%) as a colourless, crystalline solid.

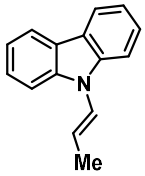
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.14 (2H, dq, *J* = 7.8, 1.0 Hz, ArH), 7.46-7.51 (2H, m, ArH), 7.39-7.42 (2H, m, ArH), 7.24-7.29 (2H, m, ArH), 6.02 (1H, ddt, *J* = 17.1, 10.1, 4.9 Hz, $NCH_2CH=CH_2$), 5.19 (1H, dq, *J* = 10.3, 1.5 Hz, $NCH_2CH=CH_{2a}$), 5.07 (1H, dq, *J* = 17.1, 1.8 Hz, $NCH_2CH=CH_{2b}$), 4.93 (2H, dt, *J* = 4.9, 1.8 Hz, $NCH_2CH=CH_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 140.5 (2 × ArC), 132.4 ($NCH_2CH=CH_2$), 125.8 (2 × ArCH), 123.1 (2 × ArC), 120.5 (2 × ArCH), 119.2 (2 × ArCH), 116.9 ($NCH_2CH=CH_2$), 108.9 (2 × ArCH), 45.4 ($NCH_2CH=CH_2$).

Melting point (CH_2Cl_2) = 54–55 °C

The data are consistent with the literature.[194]

<u>*N*-(prop-1-en-1-yl)-9H-carbazole (242)</u>



Allyl carbazole **S1** (250 mg, 1.20 mmol) and Grubbs Catalyst® 2nd generation (51 mg, 0.06 mmol) were charged to a flame-dried flask, followed by degassed, anhydrous CH_2Cl_2. Trimethyl(vinyloxy)silane (1.80 mL, 12.2 mmol) was added and the resulting solution was heated at reflux, with stirring, for 20 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. Purification by column chromatography (99:1 pentane:Et_2O) afforded alkene **242** (152 mg, 61%, 3:1 E:Z) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.04 (2H, ddt, *J* = 9.6, 7.8, 1.0 Hz, ArH), 7.54 (2H, dt, *J* = 8.3, 0.9 Hz, ArH), 7.41 (2H, ddd, *J* = 8.3, 7.1, 1.2 Hz, ArH), 7.22 (2H, ddt, *J* = 7.8, 7.0, 1.0 Hz, ArH), 6.90 (1H, dq, 14.0, 1.7 Hz, NCH=$CHCH_3$), 6.09 (1H, dq, *J* = 13.7, 6.8 Hz, NCH=CHCH_3), 1.97 (3H, dd, *J* = 6.8, 1.7 Hz, CH_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 139.9 (2 × Ar<u>C</u>), 126.1 (2 × Ar<u>C</u>H), 124.2 (N<u>C</u>H=CHCH$_3$), 123.5 (2 × Ar<u>C</u>), 120.3 (2 × Ar<u>C</u>H), 120.0 (2 × Ar<u>C</u>H), 119.0 (NCH=<u>C</u>HCH$_3$), 110.2 (2 × Ar<u>C</u>H), 16.0 (<u>C</u>H$_3$).

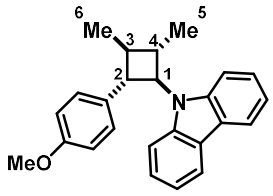
Additional signals for the cis isomer:

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.69 (1H, dq, 7.9, 1.8 Hz, NC<u>H</u>=CHCH$_3$), 5.93 (1H, m, NCH=C<u>H</u>CH$_3$), 1.61 (3H, dd, *J* = 7.0, 1.8 Hz, C<u>H$_3$</u>).

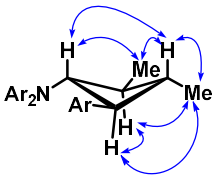
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 126.6 (NCH=<u>C</u>HCH$_3$), 123.3 (N<u>C</u>H=CHCH$_3$), 13.9 (<u>C</u>H$_3$).

The data are consistent with the literature.[125]

<u>(±)-9-(-2-(4-Methoxyphenyl)-3,4-dimethylcyclobutyl)-9*H*-carbazole (243)</u>



To a 2–5 mL microwave vial was added (diacetoxyiodo)benzene (3.2 mg, 5.0 mol%) before the vial was sealed with a crimp cap (containing Reseal® septum), flushed with argon for 5 minutes and cooled to 0 °C. *trans*-Anethole (59 mg, 0.40 mmol) was dissolved in CH_2Cl_2 (0.4 mL) and added to the vial *via* syringe, followed by TFE (0.1 mL). 9-(Prop-1-en-1-yl)-9*H*-carbazole **242** (42 mg, 0.20 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and added *via* syringe pump over 2 hours. The resulting solution was stirred at 0 °C for 2 hours before warming to room temperature and stiring for a further 16 hours, then the solvent was directly removed *in vacuo.* Purification by column chromatography (98:2 pentane:Et_2O) afforded cyclobutane **242** (13 mg, 30%, >95:5 dr) as a colourless oil. *Head-to-head geometry assigned by HMBC analysis, all-trans stereochem assigned by nOe analysis.*



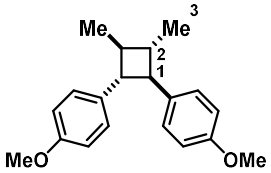
nOe correlations indicated by solid arrows (blue). *Other correlations have been omitted for clarity*

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.12 (2H, ddd, *J* = 7.8, 1.3, 0.7 Hz, ArH), 7.67 (2H, dt, *J* = 8.3, 0.9 Hz, ArH), 7.45 (2H, ddd, *J* = 8.4, 7.1, 1.3 Hz, ArH), 7.26-7.22 (2H, m, ArH), 7.06-7.03 (2H, m, ArH), 6.77-6.75 (2H, m, ArH), 4.58 (1H, t, *J* = 9.5 Hz, CH-1), 4.04 (1H, t, *J* = 9.4 Hz, CH-2), 3.73 (3H, s, OCH_3), 3.00 (1H, tq, *J* = 9.1, 6.4 Hz, CH-4), 1.94-1.85 (1H, m, CH-3), 1.51 (3H, d, *J* = 6.6 Hz, CH_3-6), 1.20 (3H, d, *J* = 6.4 Hz, CH_3-5).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 158.2 (ArC), 140.6 (2 × ArC), 134.8 (ArC), 127.4 (2 × ArCH), 125.6 (2 × ArCH), 123.6 (2 × ArC), 120.4 (2 × ArCH), 119.1 (2 × ArCH), 114.0 (2 × ArCH), 110.3 (2 × ArCH), 61.6 (CH-1), 55.4 (OCH_3), 49.8 (CH-2), 41.0 (CH-4), 39.6 (CH-3), 19.9 (CH_3-6), 18.8 (CH_3-5).

The data are consistent with the literature.[125]

(±)-4,4'-(3,4-Dimethylcyclobutane-1,2-diyl)bis(methoxybenzene) (244)



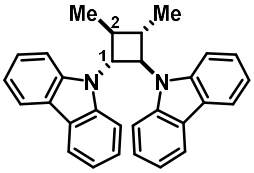
To a 2–5 mL Biotage® microwave vial was added (diacetoxyiodo)benzene (8.1 mg, 5.0 mol%), before the vial was sealed with a crimp cap (containing a Reseal® septum), flushed with argon for approx. 5 minutes and cooled to 0 °C. *trans*-Anethole (74 mg, 0.50 mmol) was dissolved in HFIP (2.5 mL) and added to the vial *via* syringe. The reaction was stirred at 0 °C for 2 hours before being warmed to room temperature and stirred for a further 18 hours. The mixture was concentrated *in vacuo,* and purification by column chromatography (97:3 pentane:Et_2O) afforded cyclobutane **244** (50 mg, 68%, >95:5 dr) as a colourless oil. *All-trans geometry was assigned by comparison to literature data, head-to-head dimerisation was assigned by HMBC analysis.*[117]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.15-7.11 (4H, m, ArH), 6.85-6.81 (4H, m, ArH), 3.78 (6H, s, 2 × OCH_3), 2.81 (2H, d, *J* = 9.0 Hz 2 × CH-1), 1.91-1.75 (2H, m, 2 × CH-2), 1.19 (6H, d, *J* = 5.8 Hz, 2 × CH_3-3).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.4 (2 × ArC), 128.2 (4 × ArCH), 114.2 (4 × ArCH), 100.4 (2 × ArC), 55.7 (2 × OCH_3), 52.9 (2 × C-1), 43.7 (2 × C-2), 19.4 (2 × CH_3-3).

The data are consistent with the literature.[117]

(±)-9,9′-(3,4-Dimethylcyclobutane-1,2-diyl)bis(9*H*-carbazole) (245)



A solution of 9-(prop-1-en-1-yl)-9*H*-carbazole **242** (25 mg, 0.12 mmol) in CH_2Cl_2 (0.56 mL) was charged to a 2–5 mL Biotage® microwave vial before the vial was sealed with a Suba-Seal® septum, flushed with argon for approx. 5 minutes and cooled to 0 °C. (Diacetoxyiodo)benzene (1.9 mg, 5 mol%) and TFE (0.04 mL) were added and the vial was resealed. The reaction solution was stirred at 0 °C for 4 days before direct concentration *in vacuo.* Purification by column chromatography (99:1 → 98:2 pentane:Et_2O) afforded cyclobutane **245** (4.9 mg, 20%, >95:5 dr) as a colourless oil. *Head-to-head geometry assigned by HMBC analysis, all-trans stereochem assigned by analogy to **241**, **234** and **244**.*

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.04 (4H, dt, *J* = 7.7, 1.1 Hz, ArH), 7.58 (4H, dq, *J* = 8.4, 0.9 Hz, ArH), 7.40 (4H, ddd, *J* = 8.4, 7.2, 1.3 Hz, ArH), 7.19 (4H, ddd, *J* = 7.9, 7.2, 0.9 Hz, ArH), 5.74-5.71 (2H, m, 2 × CH-1), 3.10-3.04 (2H, m, 2 × CH-2), 1.51-1.49 (6H, m, 2 × CH_3).

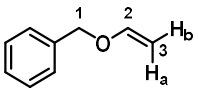
^{13}C NMR ($CDCl_3$, 101 MHz) δ = 140.4 (4 × ArC), 125.9 (4 × ArCH), 123.7 (4 × ArC), 120.6 (4 × ArCH), 119.4 (4 × ArCH), 109.6 (4 × ArCH), 58.9 (2 × CH-1), 37.4 (2 × CH-2), 19.5 (2 × CH_3).

HRMS: ESI^+ found $[M+H]^+$ = 415.2170, $C_{30}H_{27}N_2$ requires 415.2169, Δ = 0.40 ppm.

IR (film): ν_{max} = 3420, 1597, 1483, 1451, 1335, 1239, 1211, 748, 722 cm^{-1}.

Melting point ($CDCl_3$) = 185–186 °C.

((Vinyloxy)methyl)benzene (248)



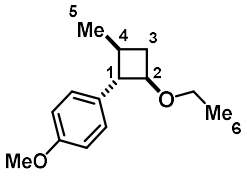
Vinyl ether **248** was synthesised according to literature procedure.[195] To a solution of Na_2CO_3 (1.27 g, 12.0 mmol) and $[Ir(cod)Cl]_2$ (134 mg, 0.2 mmol) in anhydrous toluene (20 mL) was added benzyl alcohol (2.07 mL, 20.0 mmol) and vinyl acetate (3.69 mL, 40.0 mmol). The reaction mixture was heated at 100°C with stirring for 5 hours before the reaction was concentrated *in vacuo*. Purification by column chromatography (99:1 pentane:Et_2O) afforded benzyl vinyl ether **248** (1.72 g, 64%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.43-7.28 (5H, m, ArH), 6.58 (1H, dd, *J* = 14.3, 6.8 Hz, CH-2), 4.77 (2H, s, CH_2-1), 4.31 (1H, dd, *J* = 14.3, 2.2 Hz, CH_2-3_a), 4.09 (1H, dd, *J* = 6.8, 2.2 Hz, CH_2-3_b).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 151.8 (CH-2), 137.0 (ArC), 128.7 (2 × ArCH), 128.1 (ArCH), 127.7 (2 × ArCH), 87.5 (CH_2-3), 70.2 (CH_2-1).

The data are consistent with the literature.[195]

(±)-1-(2-Ethoxy-4-methylcyclobutyl)-4-methoxybenzene (249)



A microwave vial containing *trans*-anethole (45 mg, 0.30 mmol) and a magnetic stirrer bar was sealed with a Suba-Seal® septum, flushed with argon for approx. 5 minutes and cooled to 0 °C. A solution of ethyl vinyl ether (0.12 mL, 1.20 mmol) in HFIP (1.5 mL) was added, followed by (diacetoxyiodo)benzene (4.8 mg, 5.0 mol%). The vial was resealed and stirred at 0 °C for two hours, before being warmed to room temperature and stirred for a further 16 hours. The reaction mixture was concentrated *in vacuo.* Purification by column chromatography (97:3 pentane:Et_2O)

afforded cyclobutane **249** (46 mg, 70%, >95:5 dr) as a colourless oil. *Substitution pattern confirmed by HMBC analysis, all-trans geometry assigned by comparison to **250** and literature data.*[111]

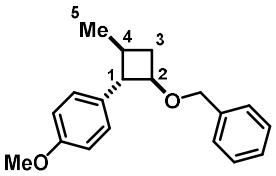
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.18-7.16 (2H, m, ArH), 6.86-6.84 (2H, m, ArH), 3.81 (1H, dt, *J* = 7.3, 6.8 Hz, CH-2), 3.79 (3H, s, OCH_3), 3.37 (2H, q, *J* = 7.0 Hz, OCH_2), 2.76 (1H, dd, *J* = 9.3, 7.7 Hz, CH--1), 2.43 (1H, dt, *J* = 10.5, 7.2 Hz, CH_2-3_a), 1.88-1.76 (1H, m, CH-4), 1.48 (1H, dt, *J* = 10.2, 8.2 Hz, CH_2-3_b), 1.15 (3H, d, *J* = 6.5 Hz, CH_3-5), 1.14 (3H, t, *J* = 7.0 Hz, CH_3-6).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 158.3 (ArC), 135.1 (ArC), 127.9 (2 × ArCH), 113.9 (2 × ArCH), 76.4 (CH-2), 63.9 (OCH_2), 56.6 (CH-1), 55.4 (OCH_3), 35.1 (CH_2-3), 29.7 (CH-4), 20.6 (CH_3-5), 15.5 (CH_3-6).

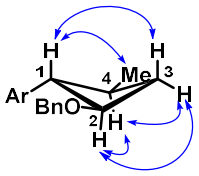
HRMS: ESI^+ found $[M+Na]^+$ = 243.1357, $C_{14}H_{20}NaO_2$ requires 243.1356, Δ = 0.41 ppm.

IR (film): ν_{max} = 2951, 2867, 1612, 1512, 1453, 1246, 1140, 1084, 1037, 833, 804 cm^{-1}.

(±)-1-(-2-(Benzyloxy)-4-methylcyclobutyl)-4-methoxybenzene (250)



A 2–5 mL Biotage® microwave vial was charged with *trans*-anethole (30 mg, 0.20 mmol). The vial was sealed with a Suba-Seal® septum, flushed with argon for approx. 5 minutes and cooled to 0 °C. To the vial was added a solution of benzyl vinyl ether **248** (107 mg, 0.80 mmol) in HFIP (1.0 mL), followed by (diacetoxyiodo)benzene (3.2 mg, 5.0 mol%) and the vial was resealed. The solution was stirred at 0 °C for 2 hours before being warmed to room temperature and stirred for a further 16 hours. The reaction mixture was directly concentrated *in vacuo,* and purification by column chromatography (97:3 pentane:Et_2O) afforded cyclobutane **250** (32 mg, 56%, >95:5 dr) as a colourless oil. *Head-to-head dimerisation was assigned based on HMBC analysis, all-trans geometry confirmed by nOe.*



nOe correlations indicated by solid, blue arrows
Other correlations have been omitted for clarity

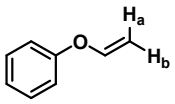
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.39-7.27 (5H, m, ArH), 7.19-7.17 (2H, m, ArH), 6.90-6.86 (2H, m, ArH), 4.47-4.41 (2H, m, OCH_2Ph), 3.93 (1H, q, *J* = 7.5 Hz, CH-2), 3.82 (3H, s, OCH_3), 2.88 (1H, dd, *J* = 9.3, 7.8 Hz, CH-1), 2.43 (1H, dt, *J* = 10.5, 7.2 Hz, $CH\text{-}3_a$), 1.91-1.81 (1H, m, CH-4), 1.55 (1H, dt, *J* = 10.2, 8.2 Hz, $CH\text{-}3_b$), 1.19 (3H, d, *J* = 6.5 Hz, $CH_3\text{-}5$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ = 158.3 (ArC), 138.5 (ArC), 135.0 (ArC), 128.4 (2 × ArCH), 128.0 (2 × ArCH), 127.9 (2 × ArCH), 127.6 (ArCH), 113.9 (2 × ArCH), 76.0 (CH-2), 70.5 (OCH_2Ph), 56.4 (CH-1), 55.4 (OCH_3), 35.0 (CH_2-3), 29.6 (CH-4), 20.6 (CH_3-5).

HRMS: ESI$^+$ found $[M+Na]^+$ = 305.1514, $C_{19}H_{22}NaO_2$ requires 305.1512, Δ = 0.66 ppm.

IR (film): ν_{max} = 2951, 1611, 1512, 1453, 1246, 1140, 1125, 1084, 1066, 803, 735, 697 cm^{-1}.

(Vinyloxy)benzene (S2)



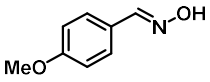
Vinyl ether **S2** was synthesised according to literature procedure.[195] To a solution of Na_2CO_3 (0.38 g, 3.60 mmol), $[Ir(cod)Cl]_2$ (40.3 mg, 0.06 mmol) and phenol (0.57 g, 6.0 mmol) in anhydrous toluene (6 mL) in a 2–5 mL Biotage® microwave vial was added vinyl acetate (1.11 mL, 12.0 mmol). The vial was sealed with a crimp cap (containing Reseal® septum) and the reaction mixture was heated at 100 °C, with stirring, for 3 hours. The reaction mixture was concentrated *in vacuo.* Purification by column chromatography (99:1 pentane:Et_2O) afforded vinyl ether **S2** (0.29 g, 41%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36-7.31 (2H, m, ArH), 7.11-7.06 (1H, m, ArH), 7.03-6.99 (2H, m, ArH), 6.66 (1H, dd, *J* = 13.7, 6.1 Hz, OCH), 4.77 (1H, dd, *J* = 13.7, 1.6 Hz, CH_{2a}), 4.44 (1H, dd, *J* = 6.1, 1.7 Hz, CH_{2b}).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.9 (Ar<u>C</u>), 148.3 (O<u>C</u>H), 129.8 (2 × Ar<u>C</u>H), 123.3 (Ar<u>C</u>H), 117.2 (2 × Ar<u>C</u>H), 95.2 (<u>C</u>H_2).

The data are consistent with the literature.[195]

(*E*)-4-Methoxybenzaldehyde oxime (252)



To a solution of *p*-anisaldehyde (0.82 g, 6.0 mmol) in anhydrous CH_2Cl_2 (26 mL) at 0 °C was added hydroxylamine hydrochloride (0.71 g, 10.2 mmol) and triethylamine (2.84 mL, 20.4 mmol). The resulting solution was warmed to room temperature and stirred for 1.5 hours before addition of saturated aqueous $NaHCO_3$ solution (35 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2:Acetone 96:4) afforded oxime **252** (0.79 g, 87%) as a colourless solid.

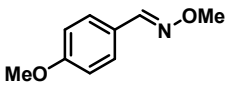
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.57 (1H, s, O<u>H</u>), 8.11 (1H, s, C<u>H</u>=N), 7.54-7.50 (2H, m, Ar<u>H</u>), 6.95-6.88 (2H, m, Ar<u>H</u>), 3.83 (3H, s, OC<u>H</u>$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.2 (Ar<u>C</u>), 150.0 (<u>C</u>=N), 128.6 (2 × Ar<u>C</u>H), 124.7 (Ar<u>C</u>), 114.4 (2 × Ar<u>C</u>H), 55.5 (O<u>C</u>H_3).

Melting point (CH_2Cl_2) = 61–62 °C.

The data are consistent with the literature.[196]

(*E*)-4-Methoxybenzaldehyde *O*-methyl oxime (253)



Oxime **253** was synthesised according to a modified literature procedure.[197] To a solution of *p*-anisaldehyde (0.61 mL, 5.0 mmol) in ethanol (15 mL) and water (45 mL) was added *O*-methylhydroxylamine hydrochloride (1.13 g, 13.5 mmol) and sodium acetate (1.80 g, 22.0

mmol). The reaction mixture was heated at reflux, with stirring, for 5 hours. The reaction mixture was cooled to room temperature and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (95:5 pentane:Et_2O) afforded oxime **253** (0.67 g, 81%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (1H, s, C<u>H</u>=N), 7.53-7.51 (2H, m, ArC<u>H</u>), 6.91-6.87 (2H, m, ArC<u>H</u>), 3.95 (3H, s, C=NOC<u>H</u>$_3$), 3.83 (3H, s, ArOC<u>H</u>$_3$).

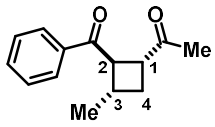
^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.0 (Ar<u>C</u>), 148.4 (<u>C</u>=N), 128.6 (2 × Ar<u>C</u>H), 124.9 (Ar<u>C</u>), 114.3 (2 × Ar<u>C</u>H), 62.0 (C=NO<u>C</u>H$_3$), 55.5 (ArO<u>C</u>H$_3$).

HRMS: ESI+ found $[M+H]^+$ = 166.0864, $C_9H_{12}NO_2$ requires 166.0863, Δ = 0.57 ppm.

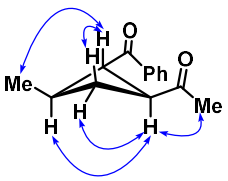
FTIR (film): ν_{max} = 2959, 2360, 1607, 1512, 1305, 1248, 1171, 1053, 1032, 917, 830 cm^{-1}.

Melting point (CH_2Cl_2) = 39–41 °C.

<u>(±)-1-(-2-benzoyl-3-methylcyclobutyl)ethan-1-one (261)</u>



Enone **222** (73 mg, 0.50 mmol), methyl vinyl ketone (0.10 mL, 1.2 mmol), $Ru(bpy)_3Cl_2$ (21.5 mg, 5.0 mol%), $LiBF_4$ (188 mg, 2.0 mmol), $^i Pr_2NEt$ (0.17 mL, 1.0 mmol) and anhydrous acetonitrile (5.0 mL) were subjected to **general procedure F**. Purification by column chromatography (80:20 pentane:Et_2O) afforded cyclobutane **261** (60 mg, 55%, >95:5 dr) as a colourless oil. *Head-to-head dimerisation was assigned by HMBC correlations, all-trans geometry assigned by nOe correlations.*



nOe correlations indicated by solid, blue arrows
Other correlations have been omitted for clarity

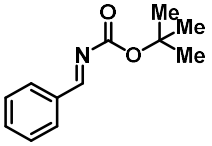
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97-7.93 (2H, m, Ar<u>H</u>), 7.57-7.51 (1H, m, Ar<u>H</u>), 7.47-7.42 (2H, m, Ar<u>H</u>), 3.89 (1H, td, *J* = 8.4, 0.9 Hz, C<u>H</u>-2), 3.60 (1H, td, *J* = 9.4, 8.4 Hz, C<u>H</u>-1), 2.47 (1H, qq, *J* = 8.3,

6.5 Hz, CH-3), 2.36 (1H, dddd, *J* = 10.7, 9.3, 8.3, 0.9 Hz, CH-4_a), 2.06 (3H, s, C(O)CH_3), 1.72 (1H, ddd, *J* = 10.7, 9.5, 8.8 Hz, CH-4_b), 1.16 (3H, d, *J* = 6.7 Hz, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.3 (MeC=O), 199.4 (PhC=O), 136.2 (ArC), 133.4 (ArCH), 128.7 (4 × ArCH), 49.8 (C-2), 43.5 (C-1), 31.0 (C-3), 29.4 (C-4), 27.7 (C(O)CH_3), 21.0 (CH_3).

The data are consistent with the literature.[115]

tert-Butyl benzylidenecarbamate (265)



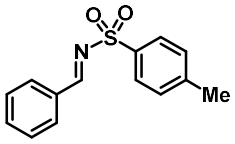
Imine **265** was synthesised according to literature procedure.[127] To solution of benzaldehyde (1.52 mL, 15.0 mmol) in methanol (7.30 mL), water (14.6 mL) and formic acid (5.10 mL) was added sodium *p*-tosylsulfinate (3.56 g, 20.0 mmol) and *tert*-butyl carbamate (1.17 g, 10.0 mmol). The reaction mixture was stirred at room temperature for 3 days before isolation of the solid by filtration. The colourless solid was washed with water (20 mL), followed by pentane (20 mL) and then dried under air. A portion of the solid (1.00 g, 2.8 mmol) was redissolved in CH_2Cl_2 (20 mL) and cesium carbonate (2.70 g, 8.3 mmol) was added and the mixture heated at reflux, with stirring, for 5 hours. The reaction mixture was cooled to room temperature, diluted with pentane (20 mL) and filtered. The filtrate was concentrated *in vacuo* to afford imine **265** (0.55 g, 95%) as a colourless oil, which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.87 (1H, s, CH=N), 7.93-7.90 (2H, m, ArH), 7.58-7.54 (1H, m, ArH), 7.49-7.45 (2H, m, ArH), 1.59 (9H, s, 3 × CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.8 (C=N), 162.8 (C=O), 134.2 (ArC), 133.6 (ArCH), 130.4 (2 × ArCH), 129.0 (2 × ArCH), 82.4 (C$(CH_3)_3$), 28.1 (3 × C$(CH_3)_3$).

The data are consistent with the literature.[198]

_N_-Benzylidene-4-methylbenzenesulfonamide (268)



Imine **268** was synthesised according to literature procedure.[128] To a solution of *p*-toluenesulfonamide (1.71 g, 10.0 mmol) and sodium benzenesulfinate (1.81 g, 11.0 mmol) in formic acid (15 mL) and water (15 mL) was added benzaldehyde (1.71 mL, 10.0 mmol). The reaction mixture was stirred at room temperature for 20 hours. The slurry was filtered, washed with water (20 mL) and pentane (15 mL). The solid residue was dissolved in CH_2Cl_2 (70 mL) and saturated aqueous $NaHCO_3$ solution (50 mL) was added. The biphasic mixture was stirred vigorously for 3 hours before the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford imine **268** (1.68 g, 65%) as a pale pink solid, which was used without further purificiation.

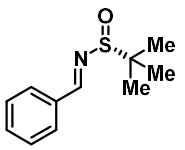
^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.03 (1H, s, C<u>H</u>=N), 7.93-7.88 (4H, m, Ar<u>H</u>), 7.63-7.59 (1H, m, Ar<u>H</u>), 7.50-7.46 (2H, m, Ar<u>H</u>), 7.35-7.33 (2H, m, Ar<u>H</u>), 2.43 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.3 (<u>C</u>=N), 144.7 (Ar<u>C</u>), 135.3 (Ar<u>C</u>), 135.1 (Ar<u>C</u>H), 132.5 (Ar<u>C</u>), 131.4 (2 × Ar<u>C</u>H), 129.9 (2 × Ar<u>C</u>H), 129.3 (2 × Ar<u>C</u>H), 128.2 (2 × Ar<u>C</u>H), 21.8 (<u>C</u>H$_3$).

Melting point (CH_2Cl_2) = 104–107 °C.

The data are consistent with the literature.[128]

(*R*)-*N*-Benzylidene-2-methylpropane-2-sulfinamide (270)



Imine **270** was synthesised according to literature procedure.[129] To a solution of benzaldehyde (1.02 mL, 6.0 mmol) and (*R*)-*tert*-butylsulfinamide (0.61 g, 5.0 mmol) in CH_2Cl_2 (25 mL) was added

caesium carbonate (1.95 g, 6.0 mmol). The reaction mixture was heated at reflux, with stirring, for 20 hours. The mixture was cooled to room temperature, filtered through a pad of Celite® (eluting with CH_2Cl_2) and the filtrate concentrated *in vacuo*. Purification by column chromatography (90:10 → 50:50 pentane:Et_2O) afforded imine **270** (0.87 g, 83%) as a yellow oil.

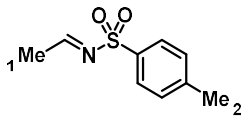
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.59 (1H, s, C<u>H</u>=N), 7.86-7.84 (2H, m, Ar<u>H</u>), 7.54-7.45 (3H, m, Ar<u>H</u>), 1.26 (9H, s, 3 × C<u>H$_3$</u>).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.9 (<u>C</u>=N), 134.2 (Ar<u>C</u>), 132.6 (Ar<u>C</u>H), 129.5 (2 × Ar<u>C</u>H), 129.1 (2 × Ar<u>C</u>H), 57.9 (<u>C</u>$(CH_3)_3$), 22.7 (3 × C(<u>C</u>$H_3)_3$).

$[\alpha]_D^{25}$ = –101.9 (*c* = 1.0, $CHCl_3$).

The data are consistent with the literature.[129]

<u>*N*-Ethylidene-4-methylbenzenesulfonamide (276)</u>



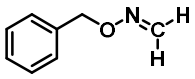
Imine **276** was synthesised according to a literature procedure.[130] *p*-Toluenesulfonamide (1.91 g, 10.0 mmol) and sodium benzenesulfinate (1.81 g, 11.0 mmol) were dissolved in water (20 mL) and formic acid (15 mL). Acetaldehyde (0.56 mL, 10.0 mmol) was added and the reaction mixture stirred at room temperature for 15 hours. The solid was removed by filtration, washed with water (10 mL) and pentane (20 mL) and dried under air. The colourless solid was redissolved in CH_2Cl_2 (100 mL) and washed with saturated aqueous $NaHCO_3$ solution (70 mL). The aqueous layer was extracted with a further portion of CH_2Cl_2 (70 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford imine **276** (1.05 g, 53%) as a white solid, which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.62 (1H, q, *J* = 5.0 Hz, C<u>H</u>=N), 7.83-7.81 (2H, m, Ar<u>H</u>), 7.36-7.34 (2H, m, Ar<u>H</u>), 2.45 (3H, s, C<u>H$_3$-2</u>), 2.25 (3H, d, *J* = 5.0 Hz C<u>H$_3$-1</u>).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.2 (C̲H=N), 144.9 (ArC̲), 134.4 (ArC̲), 129.9 (2 × ArC̲H), 128.2 (2 × ArC̲H), 25.5 (C̲H_3-2), 21.7 (C̲H_3-1).

The data are consistent with the literature.[130]

Formaldehyde *O*-benzyl oxime (281)



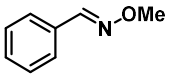
Oxime **281** was synthesised according to literature procedure.[131] To a solution of sodium acetate trihydrate (1.63 g, 12.0 mmol) in water (40 mL) and methanol (10 mL) at 0 °C was added *O*-benzylhydroxylamine hydrochloride (1.60 g, 10.0 mmol) and formaldehyde (2.20 mL, 30.0 mmol, 37% wt/wt in water). The reaction mixture was warmed to room temperature and stirred for a further 3 hours. The mixture was extracted with CH_2Cl_2 (4 × 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford imine **281** (1.10 g, 81%) as a yellow oil, which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39-7.30 (5H, m, ArH̲), 7.09 (1H, d, *J* = 8.2 Hz, N=CH̲$_{2a}$), 6.47 (1H, d, *J* = 8.2 Hz, N=CH̲$_{2b}$), 5.14 (2H, s, PhCH̲$_2$O).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.8 (C̲=N), 137.6 (ArC̲), 128.6 (2 × ArC̲H), 128.4 (2 × ArC̲H), 128.1 (ArC̲H), 76.2 (PhC̲H_2O).

The data are consistent with the literature.[131]

Benzaldehyde *O*-methyl oxime (287)



Oxime **287** was synthesised according to literature procedure.[133] To a solution of benzaldehyde (0.57 mL, 5.6 mmol) in THF (2.8 mL) and water (8.4 mL) was added sodium acetate trihydrate (1.14 g, 8.4 mmol) and methyloxyamine hydrochloride (0.794 g, 9.5 mmol). The reaction mixture was stirred at room temperature for 22 hours, diluted with Et_2O (20 mL) and the layers separated. The

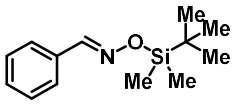
organic layer was washed with brine (3 × 20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of a portion of the crude material (0.30 g) by column chromatography (98:2 pentane:Et_2O) afforded oxime **287** (0.27 g, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.07 (1H, s, C<u>H</u>=N), 7.60-7.57 (2H, m, Ar<u>H</u>), 7.41-7.36 (3H, m, Ar<u>H</u>), 3.98 (3H, s, C<u>H</u>$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 148.7 (<u>C</u>=N), 132.3 (Ar<u>C</u>), 129.9 (Ar<u>C</u>H), 128.8 (2 × Ar<u>C</u>H), 127.1 (2 × Ar<u>C</u>H), 62.2 (<u>C</u>H$_3$).

The data are consistent with the literature.[133]

<u>Benzaldehyde *O*-(*tert*-butyldimethylsilyl) oxime (289)</u>



To a solution of (*E*)-benzaldehyde oxime (1.21 g, 10.0 mmol) and *tert*-butyldimethylsilyl chloride (1.51 g, 10.6 mmol) in DMF (2 mL) was added a solution of imidazole (1.44 g, 21.2 mmol) in DMF (3 mL) dropwise. The reaction mixture was heated at reflux, with stirring, for 4 hours. The mixture was cooled to room temperature and extracted with pentane (3 × 20 mL). The combined organic layers were washed with cold saturated aqueous $NaHCO_3$ (20 mL), 1M HCl (20 mL) and 5% aqueous LiCl solution (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (99:1 pentane:Et_2O) afforded oxime **289** (119 mg, 5%) as a colourless oil.

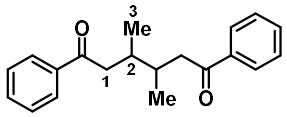
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.20 (1H, s, C<u>H</u>=N), 7.62-7.58 (2H, m, Ar<u>H</u>), 7.40-7.36 (3H, m, Ar<u>H</u>), 0.99 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.24 (6H, s, 2 × SiC<u>H</u>$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.3 (<u>C</u>=N), 132.8 (Ar<u>C</u>), 130.2 (Ar<u>C</u>H), 128.8 (2 × Ar<u>C</u>H), 127.2 (2 × Ar<u>C</u>H), 26.3 (3 × SiC(<u>C</u>H$_3$)$_3$), 18.4 (Si<u>C</u>(CH$_3$)$_3$), –5.2 (2 × Si<u>C</u>H$_3$).

HRMS: ESI+ found $[M+H]^+$ = 236.1466, $C_{13}H_{22}NO^{28}Si$ requires 236.1465, Δ = 0.25 ppm.

FTIR (film): ν_{max} = 2830, 2857, 1472, 1252, 950, 906, 831, 785, 692 cm^{-1}.

3,4-Dimethyl-1,6-diphenylhexane-1,6-dione (291)



To a vial equipped with a magnetic stirrer bar was weighed (E)-1-phenylbut-2-en-1-one **222** (59 mg, 0.40 mmol), $Ru(bpy)_3Cl_2$ (15 mg, 5.0 mol%) and $LiBF_4$ (150 mg, 1.6 mmol). The vial was sealed with a screw cap (containing a septum) and acetonitrile (4 mL) and $^{i}Pr_2NEt$ (0.14 mL, 0.80 mmol) were added *via* syringe. Nitrogen was bubbled through the solution in the dark for approx. 10 minutes. The vial was sealed with parafilm, irradiated with blue LEDs (λ = 450 nm) and stirred for 2 hours. ^{1}H NMR analysis of the crude reaction mixture indicated a 1:1 mixture of diastereomers. Purification by column chromatography (95:5 heptane:EtOAc) afforded **291** (8.4 mg, 14%, 1:1 dr) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96-7.93 (4H, m, Ar<u>H</u>), 7.58-7.53 (2H, m, Ar<u>H</u>), 7.48-7.44 (4H, m, Ar<u>H</u>), 3.07-3.00 (2H, m, 2 × C<u>H$_2$-1$_a$</u>), 2.86-2.77 (2H, m, 2 × C<u>H$_2$-1$_b$</u>), 2.38-2.27 (2H, m, 2 × C<u>H-2</u>), 0.99 (6H, d, *J* = 6.5 Hz, C<u>H$_3$-3</u>).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.3 (<u>C</u>=O), 200.1 (<u>C</u>=O), 137.4 (2 × Ar<u>C</u>), 133.1 (2 × Ar<u>C</u>H), 128.7 (4 × Ar<u>C</u>H), 128.3 (4 × Ar<u>C</u>H), 43.9 (<u>C</u>H$_2$-1), 34.4 (<u>C</u>H-2), 17.2 (<u>C</u>H$_3$-3).

Additional peaks for the minor diastereomer:

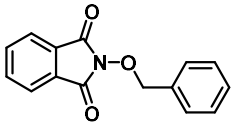
^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.96 (6H, d, *J* = 6.6 Hz, C<u>H$_3$-3</u>).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 42.7 (<u>C</u>H$_2$-1), 34.0 (<u>C</u>H-2), 15.5 (<u>C</u>H$_3$-3).

HRMS: ESI+ found $[M+H]^+$ = 295.1692, $C_{20}H_{23}O_2$ requires 295.1693, Δ = –0.23 ppm.

FTIR (film): ν_{max} = 2924, 1679, 1597, 1580, 1448, 1369, 1277, 1209, 1180, 1001, 752, 690 cm^{-1}.

2-(Benzyloxy)isoindoline-1,3-dione (294)



294 was synthesised according to literature procedure.[135] To a solution of *N*-hydroxyphthalimide (1.63 g, 10.0 mmol) in dimethyl sulfoxide (15 mL) was added K_2CO_3 (1.38 g, 10.0 mmol) and benzyl bromide (2.38 mL, 20.0 mmol). The reaction mixture was stirred at room temperature for 20 hours before addition of water (30 mL). The reaction mixture was filtered and the pale-yellow solid was washed with cold water (3 × 5 mL) and dried under air. Recrystallisation from EtOH afforded **294** (2.03 g, 80%) as pale yellow, needle-like crystals.

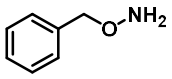
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83-7.79 (2H, m, ArH), 7.75-7.71 (2H, m, ArH), 7.56-7.51 (2H, m, ArH), 7.41-7.35 (3H, m, ArH), 5.21 (2H, s, OCH_2Ph).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.6 (2 × C=O), 134.6 (2 × ArCH), 133.8 (2 × ArC), 130.0 (2 × ArCH), 129.5 (ArCH), 129.0 (ArC), 128.7 (2 × ArCH), 123.6 (2 × ArCH), 80.0 (OCH_2Ph).

Melting point (EtOH) = 146–148 °C.

The data are consistent with the literature.[135]

***O*-Benzylhydroxylamine (295)**

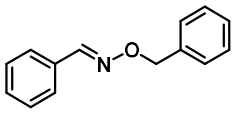


Hydroxylamine **295** was synthesised according to literature procedure.[135] To a solution of 2-(benzyloxy)isoindoline-1,3-dione **294** (1.00 g, 3.9 mmol) in CH_2Cl_2 (13 mL) was added hydrazine hydrate (0.38 mL, 7.8 mmol) dropwise and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was filtered, and the filtrate washed with 2M NaOH (2 × 50 mL) followed by brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford hydroxylamine **295** (0.42 g, 87%) as a yellow oil which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40-7.30 (5H, m, ArH), 5.39 (2H, br. s, NH_2), 4.70 (2H, s, $PhCH_2O$).

The data are consistent with the literature.[135]

Benzaldehyde *O*-benzyl oxime (296)



Oxime **296** was synthesised according to literature procedure.[199] To a solution of *O*-benzylhydroxylamine **295** (0.23 g, 1.9 mmol) in methanol (5.0 mL) was added benzaldehyde (0.17 mL, 1.7 mmol) and acetic acid (0.25 mL, 4.4 mmol). The reaction mixture was stirred at room temperature for 16 hours before addition of saturated aqueous $NaHCO_3$ solution until neutral pH was reached. The layers were separated, and the organic layer washed with water (2 × 20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by column chromatography (98:2 pentane:Et_2O) afforded oxime **296** (0.29 g, 81%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.16 (1H, s, CH=N), 7.62-.57 (2H, m, ArH), 7.48-7.43 (2H, m, ArH), 7.40-7.31 (6H, m, ArH), 5.23 (2H, s, OCH_2Ph).

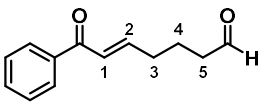
^{13}C NMR (126 MHz, $CDCl_3$) δ = 149.2 (CH=N), 137.6 (ArC), 132.4 (ArC), 130.0 (ArCH), 128.8 (2 × ArCH), 128.6 (2 × ArCH), 128.5 (2 × ArCH), 128.1 (ArCH), 127.2 (2 × ArCH), 76.5 (OCH_2Ph).

HRMS: ESI+ found $[M+H]^+$ = 212.1069, $C_{14}H_{14}NO$ requires 212.1070, Δ = –0.40 ppm.

FTIR (film): ν_{max} = 1454, 1211, 1037, 1017, 985, 944, 915, 753, 692 cm^{-1}.

The data are consistent with the literature.[199]

(*E*)-7-Oxo-7-phenylhept-5-enal (305)



To a solution of ylide **307** (0.50 g, 1.3 mmol) in anhydrous CH_2Cl_2 (10 mL) was added glutaraldehyde (2.48 mL, 26.0 mmol, 25% wt/wt in water). The reaction mixture was stirred at room temperature

for 2 hours before dilution with CH_2Cl_2 (20 mL) and water (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography afforded aldehyde **305** (0.12 g, 44%, >95:5 E:Z) as a colourless oil.

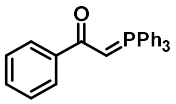
^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.80 (1H, t, *J* = 1.4 Hz, C<u>H</u>=O), 7.94-7.91 (2H, m, Ar<u>H</u>), 7.58-7.54 (1H, m, Ar<u>H</u>), 7.49-7.45 (2H, m, Ar<u>H</u>), 7.02 (1H, dt, *J* = 15.4, 6.7 Hz, C<u>H</u>-2), 6.91 (1H, dt, *J* = 15.4, 1.3 Hz, C<u>H</u>-1), 2.53 (2H, td, *J* = 7.2, 1.4 Hz, C<u>H$_2$</u>-5), 2.37 (2H, m, C<u>H$_2$</u>-3), 1.88 (2H, p, *J* = 7.3 Hz, C<u>H$_2$</u>-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 201.7 (<u>C</u>H=O), 190.7 (<u>C</u>=O), 148.1 (<u>C</u>H-2), 137.9 (Ar<u>C</u>), 132.9 (Ar<u>C</u>H), 128.7 (2 × Ar<u>C</u>H), 128.7 (2 × Ar<u>C</u>H), 126.8 (<u>C</u>H-1), 43.2 (<u>C</u>H$_2$-5), 32.0 (<u>C</u>H$_2$-3), 20.6 (<u>C</u>H$_2$-4).

HRMS: ESI+ found $[M+Na]^+$ = 225.0889, $C_{13}H_{14}O_2{}^{23}Na$ requires 225.0886, Δ = 1.33 ppm.

FTIR (film): ν_{max} = 1721, 1668, 1619, 1447, 1345, 1285, 1224, 982, 694 cm^{-1}.

<u>1-Phenyl-2-(triphenyl-λ5-phosphaneylidene)ethan-1-one (307)</u>



Wittig reagent **307** was synthesised according to literature procedure.[137] To a solution of α-bromoacetophenone (9.95 g, 50.0 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added triphenylphosphine (14.4 g, 55.0 mmol). The reaction mixture was warmed to room temperature and stirred for a further 24 hours. The pale-yellow solid was isolated by filtration, washed with Et_2O (100 mL) and dried under air. A portion of this solid (6.00 g, 13.0 mmol) was suspended in CH_2Cl_2 (30 mL) and water (30 mL). A solution of Na_2CO_3 (1.38 g, 13.0 mmol) in water (30 mL) was added and the biphasic mixture stirred vigorously for 16 hours. The layers were separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was redissolved in Et_2O (100 mL) and stirred for 1 hour, during which time a white precipitate was formed. The solid was isolated by

filtration, washed with Et_2O (3 × 20 mL) and dried under air. Wittig reagent **307** (4.59 g, 93%) was afforded as a colourless solid and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99-7.96 (2H, m, ArH), 7.76-7.70 (6H, m, ArH), 7.59-7.54 (3H, m, ArH), 7.49-7.45 (6H, m, ArH), 7.37-7.33 (3H, m, ArH), 4.43 (1H, d, *J* = 21.7 Hz, CH=PPh_3).

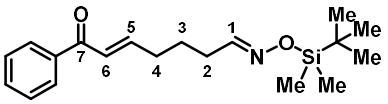
^{13}C NMR (101 MHz, $CDCl_3$) δ = 185.0 (C=O), 141.3 (d, *J* = 14.7 Hz, 3 × ArC), 133.3 (d, *J* = 10.3 Hz, 6 × ArCH), 133.2 (2 × ArCH), 129.4 (ArC), 128.9 (d, *J* = 12.5 Hz, 3 × ArCH), 127.8 (2 × ArCH), 127.1 (d, *J* = 91.3 Hz, 6 × ArCH), 126.9 (ArCH), 50.8 (d, *J* = 112.1 Hz, CH=PPh_3).

^{31}P NMR (162 MHz, $CDCl_3$) δ = 16.6 (s, PPh_3).

Melting point (CH_2Cl_2) = 189–190 °C

The data are consistent with the literature.[137]

(5E)-7-Oxo-7-phenylhept-5-enal *O*-(*tert*-butyldimethylsilyl) oxime (309)



Enone **309** was synthesised according to literature procedure.[139] To a flame dried round bottom flask, equipped with magnetic stirrer bar, was added ylide **307** (155 mg, 0.41 mmol) and anhydrous CH_2Cl_2 (1.0 mL). Aldehyde **310** (85 mg, 0.37 mmol) in anhydrous CH_2Cl_2 (1.0 mL) was added to the flask and the mixture stirred at room temperature for 24 hours. A further portion of ylide **307** (76 mg, 0.20 mmol) was added and the mixture stirred at room temperature for a further 5 hours. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (3 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (98:2 pentane:Et_2O) afforded oxime **309** (30 mg, 24%, >95:5 E:Z) as a colourless oil.

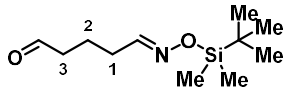
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94-7.91 (2H, m, ArH), 7.58-7.54 (1H, m, ArH), 7.49-7.45 (2H, m, ArH), 7.05 (1H, dt, *J* = 15.4, 6.8 Hz, CH-5), 6.92-6.87 (2H, m, CH-1 and CH-6), 2.46 (2H, td, *J* = 7.6,

5.4 Hz, C$\underline{H}_2$-2), 2.39-2.33 (2H, m, C$\underline{H}_2$-4), 1.73 (2H, p, *J* = 5.6 Hz, C$\underline{H}_2$-3), 0.93 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.16 (6H, s, 2 × SiC$\underline{H}_3$).

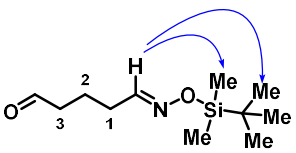
^{13}C NMR (101 MHz, $CDCl_3$) δ = 190.9 (C=O), 155.4 (C=N), 148.7 (CH-5), 138.0 (ArC), 132.8 (ArCH), 128.7 (4 × ArCH), 126.6 (CH-6), 32.6 (CH_2-4), 26.2 (3 × SiC(CH_3)$_3$), 25.2 (CH_2-2), 24.9 (CH_2-3), 18.3 (SiC(CH_3)$_3$), –5.2 (2 × SiCH_3).

The data are consistent with the literature. [139]

(*E*)-5-(((*tert*-Butyldimethylsilyl)oxy)imino)pentanal (310)



Aldehyde **310** was synthesised according to literature procedure.[139] To a flame dried round bottom flask equipped with a magnetic stirrer bar was added oxaloyl chloride (0.19 mL, 2.3 mmol) and anhydrous CH_2Cl_2 (3.5 mL). The mixture was cooled to –78 °C before addition of dimethyl sulfoxide (0.20 mL, 2.8 mmol). The mixture was stirred at –78 °C for 30 minutes before dropwise addition of alcohol **311** (410 mg, 1.8 mmol) as a solution in anhydrous CH_2Cl_2 (5 mL). After stirring at –78 °C for a further 30 minutes, triethylamine (1.23 mL, 8.9 mmol) was added dropwise and the reaction mixture warmed to 0 °C. The reaction mixture was stirred at 0 °C for 1 hour before being quenched with water (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* ^{1}H NMR analysis of the crude reaction mixture indicated the presence of a 2:1 mixture of oxime E/Z isomers. Purification by column chromatography (85:15 pentane:Et_2O) afforded **310** (171 mg, 42%, >95:5 E:Z) as a colourless oil.



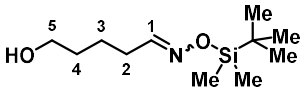
Oxime trans geometry was confirmed by nOe. *Other correlations have been omitted for clarity.*

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.78 (1H, t, *J* = 1.3 Hz, C$\underline{H}$=O), 6.85 (1H, t, *J* = 5.5 Hz, C$\underline{H}$=N), 2.48 (2H, td, *J* = 7.3, 1.4 Hz, C$\underline{H}_2$-3), 2.42 (2H, td, *J* = 7.6, 5.5 Hz, C$\underline{H}_2$-1), 1.81 (2H, p, *J* = 7.4, C$\underline{H}_2$-2), 0.92 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.15 (6H, s, 2 × SiC$\underline{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 201.8 (C=O), 155.0 (C=N), 43.4 (CH_2-3), 26.2 (3 × SiC(CH_3)$_3$), 24.8 (CH_2-1), 18.8 (CH_2-2), 18.3 (SiC(CH_3)$_3$), –5.2 (2 × SiCH_3).

The data are consistent with the literature.[139]

5-Hydroxypentanal *O*-(*tert*-butyldimethylsilyl) oxime (311)



Oxime **311** was synthesised according to literature procedure.[139] To a suspension of tetrahydropyranol **313** (0.10 g, 1.0 mmol) and $MgSO_4$ (0.38 g, 3.1 mmol) in Et_2O (3.0 mL) was added *O*-(*tert*-butyldimethylsilyl)hydroxylamine (0.22 g, 1.5 mmol) and the mixture stirred at room temperature for 16 hours. The reaction mixture was filtered and concentrated *in vacuo*. ^{1}H NMR analysis of the crude reaction mixture indicated the presence of a 1:1 mixture of oxime geometrical isomers. Purification by column chromatography (50:50 pentane:Et_2O) afforded oxime **311** (0.12 g, 52%, 2:3 mixture of oxime E/Z isomers) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51 (1H, t, *J* = 5.9 Hz, CH-1), 3.69-3.64 (2H, m, CH_2-5), 2.24 (2H, td, *J* = 6.9, 5.8 Hz, CH_2-2), 1.65-1.52 (4H, m, CH_2-3 and CH_2-4), 0.93 (9H, s, SiC(CH_3)$_3$), 0.16 (6H, s, 2 × SiCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.4 (CH-1), 62.57 (CH_2-5), 32.2 (CH_2-4), 29.4 (CH_2-2), 26.24 (3 × SiC(CH_3)$_3$), 22.8 (CH_2-3), 18.33 (SiC(CH_3)$_3$), –5.1 (2 × SiCH_3).

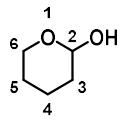
Additional signals for the minor isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.86 (1H, t, *J* = 5.4 Hz, CH-1), 2.42 (2H, td, *J* = 7.2, 5.4 Hz, CH_2-2), 0.93 (9H, s, SiC(CH_3)$_3$), 0.15 (6H, s, 2 × SiCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.2 (C=N), 62.62 (CH_2-5), 32.4 (CH_2-3 or CH_2-4), 26.17 (3 × SiC(CH_3)$_3$), 25.2 (CH_2-2), 22.5 (CH_2-3 or CH_2-4), 18.27 (SiC(CH_3)$_3$), -5.2 (2 × SiCH_3).

The data are consistent with the literature. [139]

Tetrahydro-2H-pyran-2-ol (313)



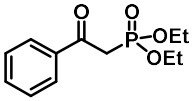
Pyranol **313** was synthesised according to literature procedure.[140] To a round bottom flask containing 2M HCl (25 mL) at 0 °C was added 3,4-dihydropyran (5.42 mL, 59.5 mmol) dropwise. The biphasic mixture was warmed to room temperature and stirred vigorously for a further 2 hours. The reaction was quenched by slow addition of saturated aqueous $NaHCO_3$ solution (55 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford tetrahydropyranol **313** (3.45 g, 57%) as a colourless oil which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.90-4.86 (1H, m, CH-2), 4.03-3.98 (1H, m, CH_2-6_a), 3.90-3.62 (1H, m, OH), 3.55-3.49 (1H, m, CH_2-6_b), 1.88-1.75 (2H, m, CH_2-3, CH_2-4 or CH_2-5), 1.55-1.47 (4H, m, CH_2-3, CH_2-4 or CH_2-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 94.6 (CH-2), 64.0 (CH_2-6), 32.0 (CH_2-3, CH_2-4 or CH_2-5), 25.3 (CH_2-3, CH_2-4 or CH_2-5), 20.4 (CH_2-3, CH_2-4 or CH_2-5).

The data are consistent with the literature.[200]

Diethyl (2-oxo-2-phenylethyl)phosphonate (314)



Phosphonate **314** was synthesised according to literature procedure.[141] A mixture of 2-bromoacetophenone (4.98 g, 25.0 mmol) and triethylphosphite (4.29 mL, 25.0 mmol) was heated at reflux, with stirring, for 4 hours. The mixture was cooled to room temperature and transferred directly onto a silica column. Purification by column chromatography (75:25 pentane:Et_2O) afforded phosphonate **314** (4.54 g, 71%) as a yellow oil.

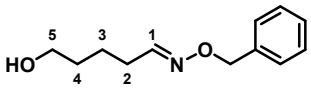
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98-7.96 (2H, m, Ar<u>H</u>), 7.57-7.52 (1H, m, Ar<u>H</u>), 7.45-7.41 (2H, m, Ar<u>H</u>), 4.13-4.06 (4H, m, 2 × O<u>C</u>H$_2$), 3.59 (2H, d, *J* = 22.7 Hz, <u>C</u>H$_2$), 1.23 (6H, t, *J* = 7.1 Hz, 2 × <u>C</u>H$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 192.0 (d, *J* = 6.8 Hz, <u>C</u>=O), 136.5 (d, *J* = 1.6 Hz, Ar<u>C</u>), 133.7 (Ar<u>C</u>H), 129.1 (2 × Ar<u>C</u>H), 128.6 (2 × Ar<u>C</u>H), 62.6 (d, *J* = 6.7 Hz, 2 × O<u>C</u>H$_2$), 38.5 (d, *J* = 132.2 Hz, <u>C</u>H$_2$P), 16.3 (d, *J* = 6.2 Hz, 2 × <u>C</u>H$_3$).

^{31}P NMR (162 MHz, $CDCl_3$) δ = 19.9 (s, <u>P</u>=O).

The data are consistent with the literature.[201]

<u>5-Hydroxypentanal *O*-benzyl oxime (317)</u>



To a solution of pyranol **313** (111 mg, 1.1 mmol) and hydroxylamine **295** (150 mg, 1.2 mmol) in Et_2O (3.6 mL) was added $MgSO_4$ (0.54 g, 4.5 mmol) and the suspension stirred at room temperature for 16 hours. The mixture was filtered, and the filtrate concentrated *in vacuo*. ^{1}H NMR analysis of the crude reaction mixture indicated a 3:2 mixture of oxime E/Z isomers. Purification by column chromatography (50:50 pentane:Et_2O) afforded oxime **317** (167 mg, 74%, 5:4 mixture of oxime E/Z isomers) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.46 (1H, t, *J* = 6.1 Hz, C<u>H</u>-1), 7.38-7.28 (5H, m, Ar<u>H</u>), 5.05 (2H, s, OC<u>H</u>$_2$Ph), 3.63 (2H, m, C<u>H</u>$_2$-5), 2.26-2.20 (2H, m, C<u>H</u>$_2$-2), 1.62-1.53 (4H, m, C<u>H</u>$_2$-3 and C<u>H</u>$_2$-4).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 151.4 (<u>C</u>=N), 137.8 (Ar<u>C</u>), 128.5 (2 × Ar<u>C</u>H), 128.4 (2 × Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 75.7 (O<u>C</u>H$_2$Ph), 62.5 (<u>C</u>H$_2$-5), 32.1 (<u>C</u>H$_2$-2), 29.3 (<u>C</u>H$_2$-4), 22.9 (<u>C</u>H$_2$-3).

Additional peaks for the minor isomer:

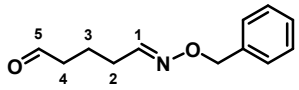
^{1}H NMR (500 MHz, $CDCl_3$) δ =6.69 (1H, t, *J* = 5.5 Hz, C<u>H</u>-1), 5.10 (2H, s, OC<u>H</u>$_2$Ph), 2.41 (2H, td, *J* = 7.3, 5.5 Hz, C<u>H</u>$_2$-2).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 152.2 (<u>C</u>=N), 138.1 (Ar<u>C</u>), 128.5 (2 × Ar<u>C</u>H), 128.1 (2 × Ar<u>C</u>H), 127.9 (Ar<u>C</u>H), 75.9 (O<u>C</u>H$_2$Ph), 62.5 (<u>C</u>H$_2$-5), 32.4 (<u>C</u>H$_2$-2), 25.6 (<u>C</u>H$_2$-4), 22.6 (<u>C</u>H$_2$-3).

HRMS: ESI+ found $[M+H]^+$ = 208.1331, $C_{12}H_{18}NO_2$ requires 208.1332, Δ = – 0.34 ppm.

FTIR (film): ν_{max} = 3357 (br.), 2933, 2865, 1454, 1367, 1048, 917, 698 cm^{-1}.

5-((Benzyloxy)imino)pentanal (318)



To a flame dried round bottom flask equipped with a magnetic stirrer bar was added oxaloyl chloride (0.08 mL, 1.0 mmol) and anhydrous CH_2Cl_2 (1.5 mL). The mixture was cooled to –78 °C before addition of dimethyl sulfoxide (0.08 mL, 1.2 mmol). The mixture was stirred at –78 °C for 30 minutes before dropwise addition of alcohol **317** (160 mg, 0.72 mmol) as a solutuion in anhydrous CH_2Cl_2 (2.0 mL). After stirring at –78 °C for a further 30 minutes, triethylamine (0.50 mL, 3.6 mmol) was added dropwise and the reaction mixture was warmed to 0 °C. The reaction mixture was stirred at 0 °C for 1 hour before being quenched with water (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* ^{1}H NMR analysis of the crude reaction mixture indicated a 2:1 mixture of oxime E/Z isomers. Purification by column chromatography (75:25 pentane:Et_2O) afforded **318** (93 mg, 63%, 7:4 ratio of E/Z isomers) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.75-9.74 (1H, m, C<u>H</u>-5), 7.43 (1H, t, *J* = 5.9 Hz, C<u>H</u>-1), 7.37-7.28 (5H, m, Ar<u>H</u>), 5.05 (2H, s, OC<u>H$_2$</u>Ph), 2.46 (2H, td, *J* = 7.3, 1.4 Hz, C<u>H$_2$</u>-4), 2.24 (2H, td, *J* = 7.4, 5.9 Hz, C<u>H$_2$</u>-2), 1.86-1.80 (2H, m, C<u>H$_2$</u>-3).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 201.7 (<u>C</u>=O), 150.2 (<u>C</u>H-1), 137.7 (Ar<u>C</u>), 128.5 (2 × Ar<u>C</u>H), 128.4 (2 × Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 75.8 (O<u>C</u>H$_2$Ph), 43.0 (<u>C</u>H$_2$-4), 28.9 (<u>C</u>H$_2$-2), 19.0 (<u>C</u>H$_2$-3).

Additional peaks for the minor isomer:

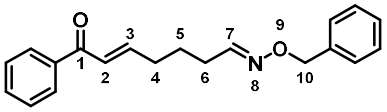
^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.68 (1H, t, *J* = 5.6 Hz, C<u>H</u>-1), 5.10 (2H, s, OC<u>H$_2$</u>Ph), 2.41 (2H, td, *J* = 7.7, 5.6, C<u>H$_2$</u>-2).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 201.7 (C=O), 151.1 (CH-1), 138.0 (ArC), 128.1 (2 × ArCH), 128.0 (2 × ArCH), 127.9 (ArCH), 76.0 (OCH_2Ph), 43.3 (CH_2-4), 25.2 (CH_2-2), 18.8 (CH_2-3).

HRMS: ESI+ found $[M+H]^+$ = 206.1176, $C_{12}H_{16}NO_2$ requires 206.1176, Δ = 0.05 ppm.

FTIR (film): ν_{max} = 2928, 1722, 1454, 1367, 1281, 1048, 752, 699 cm^{-1}.

7-Oxo-7-phenylhept-5-enal *O*-benzyl oxime (319)



To a flame dried round bottom flask, equipped with magnetic stirrer bar, was added ylide **307** (2.66 g, 7.0 mmol) and anhydrous CH_2Cl_2 (10 mL). Aldehyde **318** (719 mg, 3.5 mmol) in anhydrous CH_2Cl_2 (5 mL) was added to the flask and the mixture stirred at room temperature for 20 hours. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (3 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (80:20 pentane:Et_2O) afforded oxime **319** (0.59 g, 55%, 8:3 mixture of oxime E/Z isomers) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.93-7.91 (2H, m, ArH), 7.58-7.54 (1H, m, ArH), 7.48-7.45 (3H, m, 2 × ArH and CH=N), 7.37-7.28 (5H, m, ArH), 7.06-6.99 (1H, m, CH-3), 6.91-6.85 (1H, m, CH-2), 5.06 (2H, s, CH_2-10), 2.38-2.32 (2H, m, CH_2-4), 2.29-2.24 (2H, m, CH_2-6), 1.77-1.70 (2H, m, CH_2-5).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 190.8 (C=O), 150.6 (C=N), 148.6 (CH-3), 138.0 (ArC), 137.8 (ArC), 132.8 (ArCH), 128.7 (4 × ArCH), 128.6 (ArCH), 128.4 (2 × ArCH), 128.1 (ArCH), 127.9 (ArCH), 126.7 (CH-2), 75.8 (OCH_2Ph), 32.1 (CH_2-4), 29.1 (CH_2-6), 25.2 (CH_2-5).

Additional signals for the other isomer:

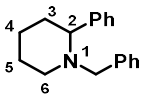
^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.71 (1H, t, *J* = 5.5 Hz, CH=N), 5.11 (2H, s, CH_2-10), 2.47-2.42 (2H, m, CH_2-6).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 151.4 ($C=N_{trans}$), 138.1 (ArC), 76.0 (OCH_2Ph).

HRMS: ESI+ found $[M+H]^+$ = 308.1645, $C_{21}H_{22}NO_2$ requires 308.1645, Δ = 0.05 ppm.

FTIR (film): ν_{max} = 2929, 1670, 1651, 1579, 1449, 1345, 1283, 1226, 1038, 696 cm^{-1}.

<u>*N*-Benzyl-2-phenylpiperidine (387)</u>



2-Phenylpentane-1,5-diol **413**[*] (180 mg, 1.0 mmol), anhydrous benzylamine (0.16 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and $NaHCO_3$ (1.7 mg, 2.0 mol%) were subjected to **general procedure D**. Purification by column chromatography (pentane:Et_2O 95:5) afforded piperidine **387** (189 mg, 75%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 (2H, d, *J* = 6.9 Hz, Ar<u>H</u>), 7.35-7.33 (2H, m, Ar<u>H</u>), 7.30-7.19 (6H, m, Ar<u>H</u>), 3.79 (1H, d, *J* = 13.5 Hz, NC<u>H_{2a}</u>Ph), 3.13 (1H, dd, *J* = 11.1, 2.8 Hz, C<u>H_2-2$_{ax}$</u>), 3.02-2.97 (1H, m, C<u>H_2-6$_a$</u>), 2.83 (1H, d, *J* = 13.5 Hz, NC<u>H_{2b}</u>Ph), 1.99-1.93 (1H, m, C<u>H_2-6$_b$</u>), 1.85-1.77 (2H, m, C<u>H_2-3$_a$</u> and C<u>H_2-5$_b$</u>), 1.70-1.54 (3H, m, C<u>H_2-3$_b$</u> and C<u>H_2-4</u>), 1.46-1.33 (1H, m, C<u>H_2-5$_b$</u>).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.9 (Ar<u>C</u>), 140.0 (Ar<u>C</u>), 128.8 (2 × Ar<u>C</u>H), 128.6 (2 × Ar<u>C</u>H), 128.1 (2 × Ar<u>C</u>H), 127.6 (2 × Ar<u>C</u>H), 127.0 (Ar<u>C</u>H), 126.6 (Ar<u>C</u>H), 69.3 (<u>C</u>H-2), 59.9 (N<u>C</u>H_2Ph), 53.5 (<u>C</u>H_2-6), 37.2 (<u>C</u>H_2-3), 26.1 (<u>C</u>H_2-4), 25.4 (<u>C</u>H_2-5).

HRMS: ESI+ found $[M+H]^+$ = 252.1746, $C_{18}H_{22}N$ requires 252.1747, Δ = –0.46 ppm.

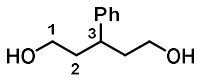
FTIR (film): ν_{max} = 2932, 2786, 1493, 1451, 1104, 1065, 1047, 1028, 757, 734, 698 cm^{-1}.

Melting point (CH_2Cl_2) = 92–94 °C

The data are consistent with the literature.[153]

[*] Diol **413** was synthesised by Daniel Mattheau-Raven

3-Phenylpentane-1,5-diol (398)



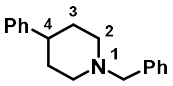
$LiAlH_4$ (1.09 g, 28.8 mmol) was suspended in anhydrous THF (100 mL) at 0 °C. 3-Phenylglutaric acid (2.00 g, 9.61 mmol) was dissolved in anhydrous THF (10 mL) and added dropwise to the $LiAlH_4$ suspension at 0 °C over 20 minutes. The reaction mixture was warmed to room temperature and then heated at reflux for 16 hours. The reaction was cooled to 0 °C, diluted with a further portion of THF (100 mL) and quenched with dropwise addition of water (1.1 mL) followed by 15% aq. NaOH (1.1 mL) and a further portion of water (3.3 mL). The mixture was warmed to room temperature and stirred for 10 minutes after which $MgSO_4$ was added and the mixture stirred for a further 30 minutes. The mixture was filtered through Celite® (eluting with Et_2O) and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2:MeOH 95:5) afforded diol **398** (1.51 g, 87%) as a viscous, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32-7.26 (2H, m, Ar<u>H</u>), 7.23-7.17 (3H, m, Ar<u>H</u>), 3.59-3.53 (2H, m, 2 × C<u>H</u>$_2$-<u>1</u>$_a$), 3.50-3.43 (2H, m, 2 × C<u>H</u>$_2$-<u>1</u>$_b$), 2.92 (1H, tt, *J* = 9.9, 5.4 Hz, C<u>H</u>-<u>3</u>), 1.98-1.79 (6H, m, 2 × C<u>H</u>$_2$-<u>2</u> and 2 × O<u>H</u>).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.6 (Ar<u>C</u>), 128.7 (2 × Ar<u>C</u>H), 127.7 (2 × Ar<u>C</u>H), 126.6 (Ar<u>C</u>H), 60.9 (2 × <u>C</u>H$_2$-1), 39.5 (2 × <u>C</u>H$_2$-2), 38.2 (<u>C</u>H-3).

The data are consistent with the literature.[202]

***N*-Benzyl-4-phenylpiperidine (399)**



3-Phenylpentane-1,5-diol **398** (180 mg, 1.0 mmol), anhydrous benzylamine (0.16 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Purification by column chromatography (pentane:Et_2O 60:40) afforded piperidine **399** (208 mg, 83%) as a yellow oil.

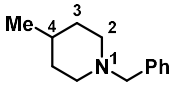
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41-7.20 (10H, m, Ar<u>H</u>), 3.58 (2H, s, NC<u>H$_2$</u>Ph), 3.06-3.01 (2H, m, 2 × C<u>H$_2$-2$_b$</u>), 2.53 (1H, m, C<u>H-4</u>), 2.14-2.08 (2H, m, 2 × C<u>H$_2$-2$_b$</u>), 1.86 (4H, m, 2 × C<u>H$_2$-3</u>).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.6 (Ar<u>C</u>), 138.6 (Ar<u>C</u>), 129.4 (2 × Ar<u>C</u>H), 128.5 (2 × Ar<u>C</u>H), 128.3 (2 × Ar<u>C</u>H), 127.1 (Ar<u>C</u>H), 127.0 (2 × Ar<u>C</u>H), 126.2 (Ar<u>C</u>H), 63.6 (N<u>C</u>H$_2$Ph), 54.4 (2 × <u>C</u>H$_2$-2), 42.8 (<u>C</u>H-4), 33.6 (2 × <u>C</u>H$_2$-3).

HRMS: ESI+ found $[M+H]^+$ = 252.1742, $C_{18}H_{22}N$ requires 252.1747, Δ = –2.09 ppm.

FTIR (film): ν_{max} = 3027, 2934, 2798, 2750, 1493, 1452, 1366, 991, 735, 696 cm^{-1}.

<u>*N*-Benzyl-4-methylpiperidine (401)</u>



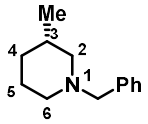
4-Methylpentane-1,5-diol (118 mg, 1.0 mmol), anhydrous benzylamine (0.16 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Purification by column chromatography (pentane:Et_2O 80:20) afforded piperidine **401** (135 mg, 71%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32-7.21 (5H, m, Ar<u>H</u>), 3.48 (2H, s, NC<u>H$_2$</u>Ph), 2.87-2.82 (2H, m, 2 × C<u>H$_2$-2$_{eq}$</u>), 1.93 (2H, td, *J* = 11.5, 2.4 Hz, 2 × C<u>H$_2$-2$_{ax}$</u>), 1.62-1.56 (2H, m, 2 × C<u>H$_2$-3$_a$</u>), 1.41-1.30 (1H, m, C<u>H-4</u>), 1.29-1.19 (2H, m, 2 × C<u>H$_2$-3$_b$</u>), 0.91 (3H, d, *J* = 6.2 Hz, C<u>H$_3$</u>).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.9 (Ar<u>C</u>), 129.4 (2 × Ar<u>C</u>H), 128.2 (2 × Ar<u>C</u>H), 127.0 (Ar<u>C</u>H), 63.7 (N<u>C</u>H$_2$Ph), 54.1 (2 × <u>C</u>H$_2$-2), 34.5 (2 × <u>C</u>H$_2$-3), 30.9 (<u>C</u>H-4), 22.1 (<u>C</u>H$_3$).

The data are consistent with the literature.[203]

(*S*)-1-Benzyl-3-methylpiperidine (405)



Procedure for enantioenriched material: (*S*)-2-Methylhexane-1,5-diol* ***ent*-570** (118 mg, 1.0 mmol, >99:1 er), anhydrous benzylamine (0.16 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and deionised water (0.5 mL) were subjected to **general procedure B** at 80 °C. Purification by column chromatography (pentane:Et_2O 90:10) afforded piperidine ***ent*-405** (134 mg, 71%, 88:12 er) as a colourless oil.

Procedure for racemic material: Racemic material for HPLC analysis was synthesised using (±)-2-methylhexane-1,5-diol ***rac*-570** under an analogous procedure.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33-7.22 (5H, m, Ar<u>H</u>), 3.48 (2H, s, NC<u>H_2</u>Ph), 2.79 (2H, m, C<u>H_2-2$_a$</u> and C<u>H_2-6$_{eq}$</u>), 1.85 (1H, td, *J* = 11.1, 3.7 Hz, C<u>H_2-6$_{ax}$</u>), 1.72-1.51 (5H, m, C<u>H_2-2$_b$</u>, C<u>H</u>-3, C<u>H_2-4$_a$</u> and C<u>H_2-5</u>), 0.90-0.86 (1H, m, C<u>H_2-4$_b$</u>), 0.83 (3H, d, *J* = 6.4 Hz, C<u>H_3</u>).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.8 (Ar<u>C</u>), 129.3 (2 × Ar<u>C</u>H), 128.2 (2 × Ar<u>C</u>H), 126.9 (Ar<u>C</u>H), 63.8 (N<u>C</u>H_2Ph), 62.1 (<u>C</u>H_2-2), 54.1 (<u>C</u>H_2-6), 33.2 (<u>C</u>H_2-5), 31.3 (<u>C</u>H-3), 25.7 (<u>C</u>H_2-4), 19.9 (<u>C</u>H_3).

HRMS: ESI+ found $[M+H]^+$ = 190.1590, $C_{13}H_{20}N$ requires 190.1590, Δ = –0.04 ppm.

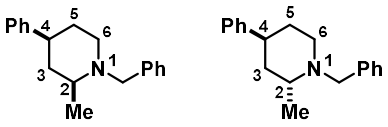
FTIR (film): ν_{max} = 2927, 2794, 2756, 1454, 1346, 1120, 1073, 1028, 976, 737, 698 cm^{-1}.

$[\alpha]_D^{25}$ **= +**8.9 (*c* = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding *N*-Cbz compound ***ent*-585** (synthesised using **general procedure C**, analytic sample isolated by preparative TLC, for HPLC conditions and full characterisation data, see p239), er = 88:12.

* Diol ***ent*-570** was synthesised by Dr Roly Armstrong

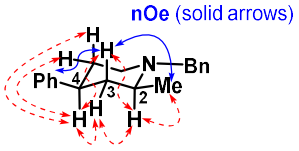
(±)-*N*-Benzyl-2-methyl-4-phenylpiperidine (408)



XXa *major* **XXb** *minor*

1-Methyl-3-phenylpentane-1,5-diol* ***rac*-435** (110 mg, 0.56 mmol), anhydrous benzylamine (0.09 mL, 0.84 mmol), $[IrCp^*Cl_2]_2$ (4.5 mg, 1.0 mol%), $NaHCO_3$ (0.9 mg, 2.0 mol%) and anhydrous toluene (0.28 mL, 2 M) were subjected to **general procedure A**. Purification by column chromatography (pentane:Et_2O 90:10) afforded piperidine ***rac*-408a** (58 mg, 39%, dr >95:5) as a colourless oil and piperidine ***rac*-408b** (16 mg, 11%, dr >95:5) as a pale yellow oil.

Data for the major diastereomer rac-408a



H-2_{ax} dqd, *J* = 12.1, 5.9, 2.6 Hz
H-4_{ax} tt, *J* = 12.0, 4.1 Hz
Large J values indicate axial geometry
Couplings shown with dashed arrows
H-6_{eq} and H-6_{ax} are removed for clarity

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.38-7.17 (10H, m, ArH), 4.17 (1H, d, *J* = 13.4 Hz, NCH_{2a}Ph), 3.21 (1H, d, *J* = 13.3 Hz, NCH_{2b}Ph), 2.94 (1H, dt, *J* = 11.7, 3.4 Hz, CH_2-6_{eq}), 2.58 (1H, tt, *J* = 12.0, 4.1 Hz, CH-4_{ax}), 2.37 (1H, dqd, *J* = 12.1, 5.9, 2.6 Hz, CH-2_{ax}), 2.07 (1H, td, *J* = 11.6, 3.4 Hz, CH_2-6_{ax}), 1.87-1.82 (1H, m, CH_2-3_{eq}), 1.78-1.65 (2H, m, CH_2-5), 1.60 (1H, td, *J* = 12.8, 10.9 Hz, CH_2-3_{ax}), 1.28 (3H, d, *J* = 6.1 Hz, CH_3).

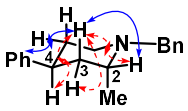
^{13}C NMR (126 MHz, $CDCl_3$) δ = 146.6 (ArC), 139.3 (ArC), 129.4 (2 × ArCH), 128.5 (2 × ArCH), 128.3 (2 × ArCH), 126.94 (2 × ArCH), 126.89 (ArCH), 126.2 (ArCH), 58.2 (NCH_2Ph), 57.3 (CH-2), 53.4 (CH_2-6), 43.2 (CH_2-3), 43.1 (CH-4), 33.5 (CH_2-5), 21.5 (CH_3).

HRMS: ESI+ found $[M+H]^+$ = 266.1903, $C_{19}H_{24}N$ requires 266.1903, Δ = –0.30 ppm.

FTIR (film): ν_{max} = 2930, 2788, 1494, 1451, 1376, 1065, 756, 732, 697 cm^{-1}.

* Diol ***rac*-435** was synthesised by Kieran Paterson

Data for the minor diastereomer rac-408b



nOe (solid arrows)
nOe is not observed between H-3_{ax} and Me
H-3_{ax} td, *J* = 12.7, 4.8 Hz
Large J values indicate **H-4** has axial geometry
Couplings shown with dashed arrows
H-6_{eq} and H-6_{ax} are removed for clarity

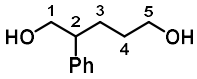
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.39 (2H, d, *J* = 7.5 Hz, ArH), 7.34-7.17 (8H, m, ArH), 3.70-3.54 (2H, m, NCH_2Ph), 3.24-3.19 (1H, m, CH-2_{eq}), 2.88-2.81 (1H, m, CH-4_{ax}), 2.64-2.61 (2H, m, CH_2-6), 2.03 (1H, td, *J* = 12.7, 4.8 Hz, CH_2-3_{ax}), 1.78-1.74 (2H, m, CH_2-5), 1.68 (1H, dt, *J* = 12.9, 3.1 Hz, CH_2-3_{eq}), 1.12 (3H, d, *J* = 6.7 Hz, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 146.9 (ArC), 140.0 (ArC), 128.8 (2 × ArCH), 128.5 (2 × ArCH), 128.3 (2 × ArCH), 127.1 (2 × ArCH), 126.9 (ArCH), 126.1 (ArCH), 59.3 (NCH_2Ph), 52.2 (CH-2), 45.8 (CH_2-6), 39.5 (CH_2-3), 36.6 (CH-4), 33.6 (CH_2-5), 10.0 (CH_3).

HRMS: ESI+ found $[M+H]^+$ = 266.1903, $C_{19}H_{24}N$ requires 266.1903, Δ = –0.30 ppm.

FTIR (film): ν_{max} = 2930, 2800, 1493, 1453, 1369, 1128, 1026, 754, 730, 697 cm^{-1}.

2-Phenylpentane-1,5-diol (415)



$LiAlH_4$ (1.45 g, 38.3 mmol) was suspended in anhydrous THF (50mL) at 0 °C. 2-Phenylglutaric anhydride (2.43 g, 12.8 mmol) was added portionwise to the $LiAlH_4$ suspension at 0°C. The reaction mixture was warmed to room temperature and then heated at reflux, with stirring, for 4 hours. The reaction was cooled to 0 °C, diluted with a further portion of THF (50 mL) and quenched with dropwise addition of water (1.5 mL) followed by 15% aq. NaOH (1.5 mL), and water (4.5 mL). The mixture was warmed to room temperature and stirred for 10 minutes after which $MgSO_4$ was added and the mixture stirred for a further 30 minutes. The mixture was filtered through Celite® (eluting with Et_2O) and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2:MeOH 95:5) afforded diol **415** (1.70 g, 74%) as a viscous, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35-7.19 (5H, m, ArH), 3.80-3.71 (2H, m, CH_2-1), 3.63-3.56 (2H, m, CH_2-5), 2.84-2.76 (1H, m, CH-2), 1.87-1.79 (1H, m, CH_2-3$_a$), 1.70-1.19 (5H, m, CH_2-3$_b$, CH_2-4, 2 × OH).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 142.3 (ArC), 128.8 (2 × ArCH), 128.2 (2 × ArCH), 126.9 (ArCH), 67.6 (CH_2-1), 62.8 (CH_2-5), 48.5 (CH-2), 30.5 (CH_2-3), 28.3 (CH_2-4).

The data are consistent with the literature.[204]

Enantiomer separation

(*S*)-415 and **(*R*)-415** were prepared by Dr Thomas Staroske (Vertex) by preparative SFC separation of diol **415** using Chiralpak® ID column, 80:20 CO_2:MeOH, 10 mL min^{-1}, 260 nm, 35°C, 20 µL injections of 100 mg/mL diol **415** in MeOH; t_r (*S*) = 4.3 min, t_r (*R*) = 5.0 min. Absolute configuration was determined by optical rotation and comparison to literature data.

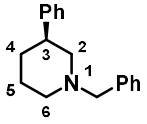
For **(*S*)-415;** $[\alpha]_D^{25}$ **=** +22.5 (*c* = 1.0, EtOH). Literature value $[\alpha]_D^{25}$ **=** +18.3 (*c* = 1.0, EtOH, 80% ee);[187]

HPLC: Enantiomeric excess was determined by SFC by Dr Thomas Staroske; Chiralpak® ID column

(5-50% MeOH:CO_2 gradient over 3.5 min, 2 mL min^{-1}, DAD 210-400 nm, 40 °C); t_r (major) = 1.3 min, t_r (minor) = 1.4 min, >99:1 er.

For **(*R*)-415;** $[\alpha]_D^{25}$ **=** –21.2 (*c* = 1.0, EtOH); **HPLC**: Enantiomeric excess was determined by SFC by Dr Thomas Staroske; Chiralpak® ID column (5-50% MeOH:CO_2 gradient over 3.5 min, 2 mL min^{-1}, DAD 210-400 nm, 40 °C); t_r (minor) = 1.3 min, t_r (major) = 1.4 min, >99:1 er.

(*S*)-*N*-Benzyl-3-phenylpiperidine (416)



Procedure for enantioenriched material: (S)-2-Phenylpentane-1,5-diol* (144 mg, 0.8 mmol, >99:1 er), anhydrous benzylamine (0.13 mL, 1.2 mmol), $[IrCp^*Cl_2]_2$ (6.3 mg, 0.8 mol%) and water (0.4 mL) were subjected to **general procedure B** at 80 °C. Purification by column chromatography (pentane:Et_2O 90:10) afforded piperidine ***ent*-416** (107 mg, 53%, 67:33 er) as a colourless solid.

Procedure for racemic material: 2-Phenylpentane-1,5-diol (180 mg, 1.0 mmol), anhydrous benzylamine (0.16 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Purification by column chromatography (pentane:Et_2O 90:10) afforded piperidine ***rac*-416** (162 mg, 64%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39-7.22 (10H, m, Ar$\underline{H}$), 3.59 (2H, s, NC$\underline{H_2}$Ph), 3.05 (1H, ddt, *J* = 11.0, 3.6, 1.7 Hz, C$\underline{H_2}$-2_{eq}), 2.98 (1H, m, C$\underline{H_2}$-6_{eq}), 2.89 (1H, tt, *J* = 11.6, 3.7 Hz, C$\underline{H}$-3_{ax}), 2.09 (1H, t, *J* = 11.1 Hz, C$\underline{H_2}$-2_{ax}), 2.07-1.94 (2H, m, C$\underline{H_2}$-6_{ax} and C$\underline{H_2}$-4_a), 1.85-1.71 (2H, m, C$\underline{H_2}$-5), 1.55-1.45 (1H, m, C$\underline{H_2}$-4_b).

* The enantiomers of diol **415** were separated by Dr Thomas Staroske (Vertex)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.0 (Ar<u>C</u>), 138.5 (Ar<u>C</u>), 129.3 (2 × Ar<u>C</u>H), 128.4 (2 × Ar<u>C</u>H), 128.3 (2 × Ar<u>C</u>H), 127.4 (2 × Ar<u>C</u>H), 127.0 (Ar<u>C</u>H), 126.4 (Ar<u>C</u>H), 63.7 (N<u>C</u>H_2Ph), 61.2 (<u>C</u>H_2-2), 53.9 (<u>C</u>H_2-6), 43.1 (<u>C</u>H-3), 31.8 (<u>C</u>H_2-4), 25.9 (<u>C</u>H_2-5).

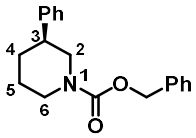
Melting point (CH_2Cl_2) = 45–47 °C.

$[\alpha]_D^{25}$ **=** –10.6 (*c* = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding *N*-Cbz compound, **S3** (see p202–203 for HPLC conditions and full characterisation data); 67:33 er.

The data are consistent with the literature.[205]

<u>Benzyl (*S*)-3-phenylpiperidine-1-carboxylate (S3)</u>



Procedure for enantioenriched material: (*S*)-*N*-benzyl-3-phenylpiperidine ***ent*-416** (30 mg, 0.12 mmol) and benzyl chloroformate (3M in toluene, 0.5 mL, 1.5 mmol) were subjected to **general procedure C**. Purification by column chromatography (pentane:Et_2O 75:25) afforded pyrrolidine **S3** (36 mg, 99%, 67:33 er) as a colourless oil.

Procedure for racemic material: Racemic material for HPLC analysis was synthesised using *N*-benzyl-3-phenylpiperidine ***rac*-416** under an analogous procedure*. The data is consistent with the literature.*[217]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37-7.21 (10H, m, Ar<u>H</u>), 5.16 (2H, s, OC<u>H_2</u>Ph), 4.38-4.20 (2H, br. m, C<u>H_2-2$_a$</u> and C<u>H_2-6$_a$</u>), 2.89-2.66 (3H, br. m, C<u>H_2-2$_b$</u>, C<u>H-3</u> and C<u>H_2-6$_b$</u>), 2.07-2.02 (1H, m, C<u>H_2-4$_a$</u>), 1.84-1.55 (3H, m, C<u>H_2-4$_b$</u> and C<u>H_2-5</u>). *Some of the signals appear broad due to the rotameric nature of the carbamate.*

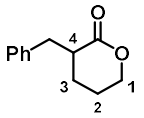
^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.4 (<u>C</u>=O), 143.4 (Ar<u>C</u>), 137.1 (Ar<u>C</u>), 128.7 (2 × Ar<u>C</u>H), 128.6 (2 × Ar<u>C</u>H), 128.1 (Ar<u>C</u>H), 128.0 (2 × Ar<u>C</u>H), 127.2 (2 × Ar<u>C</u>H), 126.8 (Ar<u>C</u>H), 67.2 (O<u>C</u>H_2Ph), 50.8

($\underline{C}H_2$-2), 44.5 ($\underline{C}H_2$-6), 42.8 (br., $\underline{C}$H-3), 31.9 (br., $\underline{C}H_2$-4), 25.6 (br., $\underline{C}H_2$-5). *Some of the signals appear broad due to the rotameric nature of the carbamate.*

$[\alpha]_D^{25}$ = –18.8 (*c* = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IB-N column (99:1 hexane:IPA, 1.0 mL min^{-1}, 210 nm, room temperature); t_r (minor) = 16.3 min, t_r (major) = 18.1 min; 67:33 er.

3-Benzyltetrahydro-2H-pyran-2-one (418)



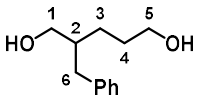
Di-*iso*propylamine (7.70 mL, 54.9 mmol) was dissolved in anhydrous THF (50 mL) and cooled to 0 °C. *n*-Butyllithium (2.5 M in hexanes, 21.0 mL, 52.5 mmol) was added dropwise and the mixture was allowed to stir for 15 minutes. The reaction mixture was cooled to –78 °C before slow addition of a solution of δ-valerolactone (4.43 mL, 47.7 mmol) in anhydrous THF (50 mL) over 1 hour. Benzyl bromide (11.3 mL, 95.4 mmol) was dissolved in anhydrous THF (20 mL) and added to the reaction mixture over 1 hour. The reaction mixture was allowed to stir at –78 °C for a further 3 hours before slow addition of saturated aqueous NH_4Cl solution (200 mL). The mixture was warmed to room temperature and concentrated *in vacuo* to remove the majority of the THF. The residue was extracted with Et_2O (3 × 200 mL), the combined organic phases dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (pentane:Et_2O 75:25) afforded lactone **418** (4.74 g, 52%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32-7.19 (5H, m, Ar$\underline{H}$), 4.33-4.22 (2H, m, $C\underline{H_2}$-1), 3.37 (1H, q, *J* = 9.0 Hz, PhC$\underline{H_{2a}}$), 2.77-2.68 (2H, m, PhC$\underline{H_{2b}}$ and C$\underline{H}$-4), 1.95-1.75 (3H, m, $C\underline{H_2}$-2, and $C\underline{H_2}$-3_a), 1.57-1.47 (1H, m, $C\underline{H_2}$-3_b).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 174.1 ($\underline{C}$=O), 139.0 (Ar$\underline{C}$), 129.3 (2 × Ar$\underline{C}$H), 128.6 (2 × Ar$\underline{C}$H), 126.6 (Ar$\underline{C}$H), 68.6 ($\underline{C}H_2$-1), 41.6 ($\underline{C}$H-4), 37.3 (Ph$\underline{C}H_2$), 24.2 ($\underline{C}H_2$-3), 22.0 ($\underline{C}H_2$-2).

The data are consistent with the literature.[206]

2-Benzylpentane-1,5-diol (419)



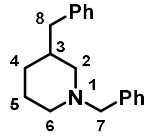
$LiAlH_4$ (1.20 g, 38.0 mmol) was suspended in anhydrous THF (150mL) at 0 °C. 3-Benzyltetrahydro-2H-pyran-2-one **418** (2.00 g, 10.5 mmol) was dissolved in anhydrous THF (25 mL) added dropwise to the $LiAlH_4$ suspension at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 hour. The reaction was cooled to 0 °C, diluted with a further portion of THF (100 mL) and quenched with dropwise addition of water (1.2 mL) followed by 15% aq. NaOH (1.2 mL) and water (3.6 mL). The mixture was warmed to room temperature and stirred for 10 minutes after which $MgSO_4$ was added, and the mixture was stirred for a further 30 minutes at room temperature. The mixture was filtered through Celite® eluting with Et_2O and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2:MeOH 95:5) afforded diol **419** as a viscous, colourless oil (1.74 g, 85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.30-7.26 (2H, m, ArH), 7.21-7.17 (3H, m, ArH), 3.66-3.55 (3H, m, CH_2-1_a and CH_2-5), 3.50 (1H, dt, *J* = 10.7, 5.3 Hz, CH_2-1_b), 2.67-2.59 (2H, m, CH_2-6), 2.03-2.01 (1H, m, OH), 2.00-1.98 (1H, m, OH), 1.86-1.79 (1H, m, CH-2), 1.67-1.54 (2H, m, CH_2-4), 1.52-1.45 (1H, m, CH_2-3_a), 1.41-1.34 (1H, m, CH_2-3_b).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.8 (ArC), 129.2 (2 × ArCH), 128.4 (2 × ArCH), 126.0 (ArCH), 64.5 (CH_2-1), 63.0 (CH_2-5), 42.3 (CH-2), 37.9 (CH_2-6), 29.8 (CH_2-4), 26.9 (CH_2-3).

The data are consistent with the literature.[207]

1,3-Dibenzylpiperidine (420)



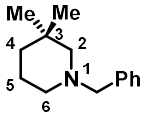
2-Benzylpentane-1,5-diol **419** (194 mg, 1.0 mmol), anhydrous benzylamine (0.16 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Purification by column chromatography (pentane:Et_2O 90:10) afforded piperidine **420** (208 mg, 78%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34-7.13 (10H, m, ArH), 3.57-3.40 (2H, m, PhCH_2-7), 2.81 (1H, dd, *J* = 10.9, 3.0 Hz, CH_2-2_{eq}), 2.76 (1H, d, *J* = 11.0 Hz, CH_2-6_a), 2.61-2.43 (2H, m, PhCH_2-8), 1.96-1.86 (2H, m, CH-3 and CH_2-6_b), 1.79 (1H, t, *J* = 10.4 Hz, CH_2-2_{ax}), 1.71-1.61 (2H, m, CH_2-4_a and CH_2-5_a), 1.56-1.45 (1H, m, CH_2-4_b), 1.00-0.92 (1H, m, CH_2-5_b).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.8 (ArC), 138.8 (ArC), 129.3 (2 × ArCH), 129.2 (2 × ArCH), 128.3 (2 × ArCH), 128.2 (2 × ArCH), 127.0 (ArCH), 125.9 (ArCH), 63.7 (PhCH_2-7), 60.4 (CH_2-2), 54.1 (CH_2-6), 41.1 (PhCH_2-8), 38.2 (CH-3), 30.7 (CH_2-5), 25.3 (CH_2-4).

The data are consistent with the literature.[208]

***N*-Benzyl-3,3-dimethylpiperidine (423)**



2-Dimethylpentane-1,5-diol **423**[*] (132 mg, 1.0 mmol), anhydrous benzylamine (0.16 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Purification by column chromatography (pentane:Et_2O 90:10) afforded piperidine **423** (162 mg, 80%) as a pale yellow oil.

[*] Diol **423** was synthesised by Dr Roly Armstrong

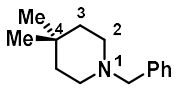
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.21-7.35 (5H, m, Ar<u>H</u>), 3.44 (2H, s, NC<u>H$_2$</u>Ph), 2.33 (2H, br. s, C<u>H$_2$</u>-6), 2.01 (2H, br. s, C<u>H$_2$</u>-2), 1.63-1.57 (2H, m, C<u>H$_2$</u>-5), 1.24-1.21 (2H, m, C<u>H$_2$</u>-4), 0.93 (6H, s, 2 × C<u>H$_3$</u>).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.7 (Ar<u>C</u>), 128.8 (2 × Ar<u>C</u>H), 128.2 (2 × Ar<u>C</u>H), 126.7 (Ar<u>C</u>H), 66.1 (<u>C</u>H$_2$-2), 63.5 (N<u>C</u>H$_2$Ph), 54.8 (<u>C</u>H$_2$-6), 37.8 (<u>C</u>H$_2$-4), 31.1 (<u>C</u>-3), 27.4 (2 × <u>C</u>H$_3$), 22.8 (<u>C</u>H$_2$-5).

HRMS: ESI+ found $[M+H]^+$ = 204.1748, $C_{14}H_{22}N$ requires 204.1747, Δ = 0.67 ppm.

FTIR (film): ν_{max} = 2934, 2793, 2750, 1453, 1362, 1347, 1308, 1179, 1119, 1025, 739, 697 cm^{-1}.

<u>*N*-Benzyl-4,4-dimethylpiperidine (425)</u>



3,3-Dimethylpentane-1,5-diol **424**[*] (132 mg, 1.0 mmol), anhydrous benzylamine (0.16 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Purification by column chromatography (pentane:Et_2O 80:20) afforded piperidine **425** (149 mg, 74%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35-7.21 (5H, m, Ar<u>H</u>), 3.51 (2H, s, NC<u>H$_2$</u>Ph), 2.40-2.37 (4H, m, 2 × C<u>H$_2$</u>-2), 1.41-1.38 (4H, m, 2 × C<u>H$_2$</u>-3), 0.92 (6H, s, 2 × C<u>H$_3$</u>).

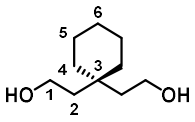
^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.9 (Ar<u>C</u>), 129.4 (2 × Ar<u>C</u>H), 128.2 (2 × Ar<u>C</u>H), 127.0 (Ar<u>C</u>H), 63.7 (N<u>C</u>H$_2$Ph), 50.2 (2 × <u>C</u>H$_2$-2), 38.9 (2 × <u>C</u>H$_2$-3), 28.6 (2 × <u>C</u>H$_3$), 28.4 (broad, <u>C</u>-4).

HRMS: ESI+ found $[M+H]^+$ = 204.1749, $C_{14}H_{22}N$ requires 204.1747, Δ = 0.85 ppm.

FTIR (film): ν_{max} = 2948, 2910, 2803, 2760, 1473, 1454, 1385, 1118, 1028, 988, 919, 736 cm^{-1}.

[*] Diol **424** was synthesised by Dr Roly Armstrong

2,2'-(Cyclohexane-1,1-diyl)bis(ethan-1-ol) (427)



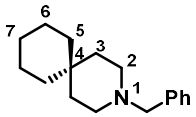
$LiAlH_4$ (1.71 g, 45.0 mmol) was suspended in anhydrous THF (150 mL) at 0 °C. 1,1-Cyclohexanediacetic acid (3.00 g, 15.0 mmol) was added portionwise to the $LiAlH_4$ suspension at 0 °C. The reaction mixture was warmed to room temperature and then heated at reflux for 16 hours. The reaction was cooled to 0 °C, diluted with a further portion of THF (100 mL) and quenched with dropwise addition of water (1.7 mL) followed by 15% aq. NaOH (1.7 mL) and water (5.1 mL). The mixture was warmed to room temperature and stirred for 10 minutes after which $MgSO_4$ was added and the mixture stirred for a further 30 minutes. The mixture was filtered through Celite® (eluting with Et_2O) and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2:MeOH 95:5) afforded diol **427** (1.78 g, 69%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.70 (4H, t, *J* = 7.0 Hz, 2 × C$\underline{H_2}$-1), 2.51 (2H, br. s, 2 × O$\underline{H}$), 1.63 (4H, t, *J* = 7.0 Hz, 2 × C$\underline{H_2}$-2), 1.45-1.36 (6H, m, 2 × C$\underline{H_2}$-5, and C$\underline{H_2}$-6), 1.33-1.29 (4H, m, 2 × C$\underline{H_2}$-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 58.9 (2 × $\underline{C}H_2$-1), 39.9 (2 × $\underline{C}H_2$-2), 36.6 (2 × $\underline{C}H_2$-4), 34.1 ($\underline{C}$-3), 26.5 ($\underline{C}H_2$-6), 21.6 (2 × $\underline{C}H_2$-5).

The data are consistent with the literature.[59]

3-Benzyl-3-azaspiro[5.5]undecane (428)



2,2'-(Cyclohexane-1,1-diyl)bis(ethan-1-ol) **427** (172 mg, 1.0 mmol), anhydrous benzylamine (0.16 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Purification by column chromatography (pentane:Et_2O 80:20) afforded piperidine **428** (166 mg, 68%) as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.33-7.22 (5H, m, ArH), 3.50 (2H, s, NCH_2Ph), 2.37 (4H, t, *J* = 5.6 Hz, 2 × CH_2-2), 1.46 (4H, t, *J* = 5.7 Hz, 2 × CH_2-3), 1.42-1.39 (6H, m, 2 × CH_2-6 and CH_2-7), 1.33-1.31 (4H, m, 2 × CH_2-5).

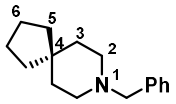
^{13}C NMR (125 MHz, $CDCl_3$) δ = 138.8 (ArC), 129.4 (2 × ArCH), 128.2 (2 × ArCH), 127.0 (ArCH), 63.8 (NCH_2Ph), 49.5 (2 × CH_2-2), 36.4 (2 × CH_2-3), 30.9 (C-4), 27.0 (2 × CH_2-5), 21.7 (2 × CH_2-6 and CH_2-7).

HRMS: ESI+ found $[M+H]^+$ = 244.2058, $C_{17}H_{26}N$ requires 244.2060, Δ = –0.72 ppm.

FTIR (film): ν_{max} = 2919, 2848, 2802, 2763, 1450, 1125, 987, 914, 736, 697 cm^{-1}.

Melting point (CH_2Cl_2) = 44–46 °C.

8-Benzyl-8-azaspiro[4.5]decane (430)



2,2'-(Cyclopentane-1,1-diyl)bis(ethan-1-ol) **429**[*] (158 mg, 1.0 mmol), anhydrous benzylamine (0.16 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Purification by column chromatography (pentane:Et_2O:Et_3N 79.5:19.5:1) afforded piperidine **430** as a pale yellow oil (170 mg, 74%).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.33-7.22 (5H, m, ArH), 3.48 (2H, s, NCH_2Ph), 2.37 (4H, br. s, 2 × CH_2-2), 1.59-1.55 (4H, m, 2 × CH_2-6), 1.49-1.46 (4H, m, 2 × CH_2-3), 1.41-1.38 (4H, m, 2 × CH_2-5).

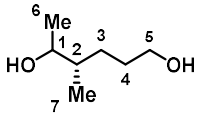
[*] Diol **429** was synthesised by Dr Roly Armstrong

^{13}C NMR (125 MHz, $CDCl_3$) δ = 138.9 (Ar<u>C</u>), 129.4 (2 × Ar<u>C</u>H), 128.2 (2 × Ar<u>C</u>H), 127.0 (Ar<u>C</u>H), 63.8 (N<u>C</u>H_2Ph), 51.6 (2 × <u>C</u>H_2-2), 40.9 (<u>C</u>-4), 37.8 (2 × <u>C</u>H_2-3), 24.5 (2 × <u>C</u>H_2-5 and 2 × <u>C</u>H_2-6).

HRMS: ESI+ found $[M+H]^+$ = 230.1905, $C_{16}H_{24}N$ requires 230.1903, Δ = 0.65 ppm.

FTIR (film): ν_{max} = 2940, 2917, 2867, 2801, 2759, 1468, 1366, 1342, 1122, 735, 697 cm^{-1}.

(4*S*)-4-Methylhexane-1,5-diol (432)



Alcohol ***ent*-432** was synthesised according to modified literature procedure.[220] To a solution of TBDPS-protected alcohol **617** (2.40 g, 6.5 mmol) in methanol (11 mL) was added acetyl chloride (0.08 mL, 1.08 mmol). The reaction solution was stirred at room temperature for 3 hours before addition of EtOAc (50 mL). The solution was cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$ solution (50 mL). The layers were separated, and the aqueous layer extracted with EtOAc (3 × 50 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (90:10 CH_2Cl_2:MeOH) afforded diol ***ent*-432** (0.70 g, 82%, 62:38 dr, >99:1 er) as a viscous, colourless oil and an inseparable mixture of diastereomers. *It was not possible to accurately determine the dr from the crude reaction mixture or purified compound due to overlapping peaks in the ^{1}H NMR spectrum, ~62:38 dr was estimated by HPLC analysis of the corresponding bis-benzoyl ester,* ***ent*-618**.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.77-3.61 (3H, m, C<u>H</u>-1 and C<u>H$_2$</u>-5), 3.47 (2H, br. s, 2 × O<u>H</u>), 1.72-1.40 (4H, m, C<u>H</u>-2, C<u>H$_2$</u>-3$_a$ and C<u>H$_2$</u>-4), 1.28-1.10 (1H, m, C<u>H$_2$</u>-3$_b$), 1.15 (3H, d, *J* = 6.4 Hz, C<u>H$_3$</u>-6), 0.90 (3H, d, *J* = 6.8 Hz, C<u>H$_3$</u>-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 71.1 (<u>C</u>H-1), 63.0 (<u>C</u>H_2-5), 40.0 (<u>C</u>H-2), 30.5 (<u>C</u>H_2-4), 28.5 (<u>C</u>H_2-3), 20.0 (<u>C</u>H_3-6), 14.5 (<u>C</u>H_3-7).

Additional signals for the other diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.14 (3H, d, *J* = 6.3 Hz, C<u>H$_3$</u>-6), 0.89 (3H, d, *J* = 6.8 Hz, C<u>H$_3$</u>-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 71.8 (C-1), 63.0 (CH_2-5), 39.4 (C-2), 30.1 (CH_2-4), 28.7 (CH_2-3), 20.0 (CH_3-6), 15.0 (CH_3-7).

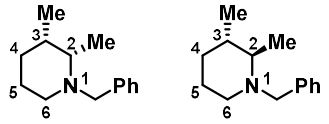
HRMS: ESI+ found $[M+Na]^+$ = 155.1043, $C_7H_{16}O_2Na$ requires 155.1043, Δ = 0.28 ppm.

FTIR (film): ν_{max} = 3321, 2966, 2934, 2874, 1458, 1377, 1097, 1054, 1027, 929, 892 cm^{-1}.

$[\alpha]_D^{25}$ = –20.0 (*c* = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding bis-benzoyl ester, see ***ent*-618** for details. 62:38 dr, >99:1 er.

<u>*N*-Benzyl-2,3-dimethylpiperidine (433)</u>



433a *major* **433b** *minor*

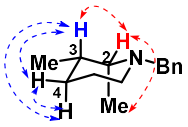
Procedure for enantioenriched material: (4*S*)-4-methylhexane-1,5-diol ***ent*-432** (132 mg, 1.0 mmol, 99:1 er), anhydrous benzylamine (0.16 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and deionised water (0.5 mL) were subjected to **general procedure B** at 110 °C. NMR analysis of the crude reaction mixture indicated the presence of two diastereomers in 8:1 dr. Purification by column chromatography (pentane:Et_2O 90:10) afforded piperidine **433a** (108 mg, 53%, >95:5 dr) as a colourless oil and piperidine **433b** (24 mg, 12%, >95:5 dr) as a colourless oil. The minor diastereomer **433b** was isolated as a mixture with N-benzyl-3-methylpiperidine (37% w.r.t. **433b**) and an unknown impurity (18% w.r.t. **433b**) and hence only the major diastereomer was derivatised for enantiomeric excess determination.

Procedure for racemic material: 4-methylhexane-1,5-diol ***rac*-432**[*] (132 mg, 1.0 mmol), anhydrous benzylamine (0.16 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. NMR analysis of

[*] Diol ***rac*-432** was synthesised by Dr Roly Armstrong

the crude reaction mixture indicated the presence of two diastereomers in 8:1 dr. Purification by column chromatography (pentane:Et_2O 90:10) afforded piperidine ***rac*-433a** (132 mg, 65%) as a colourless oil and piperidine ***rac*-433b** (20 mg, 10%) as a colourless oil.

Data for the major isomer, (2R,3R)-1-benzyl-2,3-dimethylpiperidine (433a):



H-2, qd, *J* = 6.7, 4.0 Hz
H-3, dqt, *J* = 10.9, 7.0, 4.0 Hz
Other protons are omitted for clarity

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37-7.20 (5H, m, ArH), 3.66-3.50 (2H, m, NCH_2Ph), 2.77 (1H, qd, *J* = 6.7, 4.0 Hz, CH-2), 2.45 (1H, ddd, *J* = 11.7, 9.9, 3.9 Hz, CH_2-6_{ax}), 2.32 (1H, dt, *J* = 11.7, 4.1 Hz, CH_2-6_{eq}), 1.89 (1H, dqt, *J* = 10.9, 7.0, 4.0 Hz, CH-3), 1.61-1.40 (3H, m, CH_2-4_{eq}, CH_2-4_{ax} and CH_2-5_{eq}), 1.27 (1H, dtd, *J* = 13.0, 10.4, 4.8 Hz, CH_2-5_{ax}), 0.90 (3H, d, *J* = 6.7 Hz, CH_3-7), 0.86 (3H, d, *J* = 7.0 Hz, CH_3-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.5 (ArC), 128.7 (2 × ArCH), 128.2 (2 × ArCH), 126.7 (ArCH), 59.3 (NCH_2Ph), 57.8 (CH-2) 46.8 (CH_2-6), 35.1 (CH-3), 28.1 (CH_2-4), 25.2 (CH_2-5), 18.1 (CH_3-8), 6.7 (CH_3-7).

HRMS: ESI+ found $[M+H]^+$ = 204.1747, $C_{14}H_{22}N$ requires 204.1747, Δ = 0.26 ppm.

FTIR (film): ν_{max} =2926, 2793, 1494, 1452, 1373, 1142, 1122, 1090, 1027, 955, 731, 697 cm^{-1}.

$[\alpha]_D^{25}$ = +3.3 (*c* = 1.1, $CHCl_3$).

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding *N*-Cbz compound **S4**.

Data for the minor isomer, (2R,3S)-1-benzyl-2,3-dimethylpiperidine (433b):

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34-7.21 (5H, m, ArH), 3.99 (1H, d, *J* = 13.6 Hz, $NCH_{2a}Ph$), 3.28 (1H, d, *J* = 13.6 Hz, $NCH_{2b}Ph$), 2.75 (1H, dtd, *J* = 11.6, 3.9, 1.5 Hz, CH_2-6_{eq}), 2.07-1.96 (2H, m, CH-2 and CH_2-6_{ax}), 1.71-1.64 (1H, m, CH_2-4_a), 1.54-1.48 (2H, m, CH_2-5), 1.44-1.35 (1H, m, CH-3), 1.21 (3H, d, *J* = 6.1 Hz, CH_3-7), 1.09-0.97 (1H, m, CH_2-4_b), 0.95 (3H, d, *J* = 6.6 Hz, CH_3-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.9 (Ar<u>C</u>), 129.2 (2 × Ar<u>C</u>H), 128.2 (2 × Ar<u>C</u>H), 126.7 (Ar<u>C</u>H), 62.8 (<u>C</u>H-2), 58.1 (N<u>C</u>H_2Ph), 52.3 (<u>C</u>H_2-6), 37.0 (<u>C</u>H-3), 33.1 (<u>C</u>H_2-4), 24.8 (<u>C</u>H_2-5), 20.1 (<u>C</u>H_3-8), 17.0 (<u>C</u>H_3-7).

Additonal peaks for the N-benzyl-3-methylpiperidine impurity (405):

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.48 (2H, s, NC<u>H_2</u>Ph), 1.87 (1H, td, *J* = 11.1, 3.8 Hz, C<u>H_2-6$_{ax}$</u>), 0.84 (3H, d, *J* = 6.3 Hz, C<u>H_3</u>). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 138.7 (Ar<u>C</u>), 129.2 (2 × Ar<u>C</u>H), 128.1 (2 × Ar<u>C</u>H), 126.8 (Ar<u>C</u>H), 63.6 (N<u>C</u>H_2Ph), 62.0 (<u>C</u>H_2-2), 54.0 (<u>C</u>H_2-6), 33.1 (<u>C</u>H_2-5), 31.2 (<u>C</u>H_2-3), 25.6 (<u>C</u>H_2-4), 19.7 (<u>C</u>H_3).

Additonal peaks for the unknown impurity:

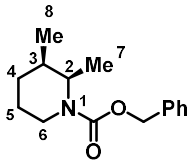
^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.08 (1H, d, *J* = 13.5 Hz), 3.14 (1H, d, *J* = 13.5 Hz), 0.77 (3H, d, *J* = 6.1 Hz). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 139.5, 128.6, 126.6, 61.0, 58.2, 56.6, 35.2, 33.6, 31.3, 30.4, 22.4, 21.1, 19.7, 14.1.

HRMS: ESI+ found $[M+H]^+$ = 204.1747, $C_{14}H_{22}N$ requires 204.1747, Δ = 0.11 ppm.

FTIR (film): ν_{max} = 2928, 2787, 1494, 1454, 1368, 1119, 1028, 733, 698 cm^{-1}.

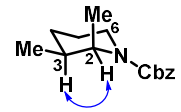
$[\alpha]_D^{25}$ **=** +5.3 (*c* = 0.3, $CHCl_3$).

<u>Benzyl-2,3-dimethylpiperidine-1-carboxylate (S4)</u>



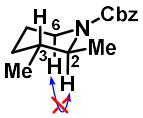
Procedure for enantioenriched material: *N*-Benzyl (2*R*,3*R*)-2,3-dimethylpiperidine ***ent*-433** (50 mg, 0.25 mmol) and benzyl chloroformate (3M in toluene, 0.5 mL, 1.5 mmol) were subjected to **general procedure C**. Purification by column chromatography (75:25 pentane:Et_2O) afforded piperidine **S4** (59 mg, 96%, 63:37 er, >95:5 dr) as a colourless oil.

Procedure for racemic material: Racemic material for HPLC analysis was synthesised using *N*-benzyl-2,3-dimethylpiperidine ***rac*-433** under an analogous procedure. An analytical sample (~1 mg) was isolated by preparative TLC.



Proposed geometry

nOe not observed between H-2 and H-6ax (see right)
Other protons and correlations omitted for clarity



Not observed

^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ = 5.18-5.10 (2H, m, PhC$\underline{H}_2$), 4.34 (1H, p, *J* = 6.6 Hz, C$\underline{H}$-2$_{eq}$), 4.00 (1H, d, *J* = 12.9 Hz, C$\underline{H}_2$-6$_{eq}$), 2.59 (1H, td, *J* = 12.8, 4.2 Hz, C$\underline{H}_2$-6$_{ax}$), 1.57-1.50 (1H, m, C$\underline{H}$-3$_{ax}$), 1.29-1.13 (3H, m, C$\underline{H}_2$-4$_a$, C$\underline{H}_2$-5), 1.03-0.92 (1H, m, C$\underline{H}_2$-4$_b$), 0.83 (3H, dd, *J* = 7.0, 1.2 Hz, C$\underline{H}_3$-7), 0.60 (3H, d, *J* = 6.7 Hz, C$\underline{H}_3$-8). *Signals corresponding to the aromatic protons are partially obscured by the d_8-toluene solvent signals. The aromatic signals can be clearly observed in the room temperature $CDCl_3$ data below.*

^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ = 155.3 (C=O), 138.4 (ArC), 128.7 (2 × ArCH), 128.3 (2 × ArCH), 128.0 (ArCH), 67.1 (PhCH_2O), 51.7 (CH-2), 38.8 (CH_2-6), 34.5 (CH-3), 27.3 (CH_2-5), 26.3 (CH_2-4), 18.8 (CH_3-8), 10.3 (CH_3-7).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ = 7.41-7.27 (5H, m, ArH), 5.18-5.10 (2H, m, OC$\underline{H}_2$Ph), 4.39-4.21 (m, 1H, C$\underline{H}$-2), 4.10-3.92 (m, 1H, C$\underline{H}_2$-6$_a$), 2.82 (1H, t, *J* = 13.3 Hz, C$\underline{H}_2$-6$_b$), 1.82-1.24 (5H, m, C$\underline{H}$-3, C$\underline{H}_2$-4 and C$\underline{H}_2$-5), 1.02 (3H, d, *J* = 7.0 Hz, C$\underline{H}_3$-7), 0.86 (3H, d, *J* = 6.9 Hz, C$\underline{H}_3$-8).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ = 155.4 (C=O), 137.3 (ArC), 128.6 (2 × ArCH), 127.9 (ArCH), 127.9 (2 × ArCH), 67.0 (OCH_2Ph), 51.3 (CH-2), 38.5 (CH_2-6), 34.1 (CH-3), 26.8 (CH_2-5), 26.0 (CH_2-4), 19.0 (CH_3-8), 10.4 (CH_3-7).

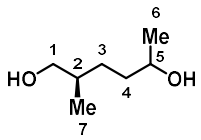
HRMS: ESI+ found $[M+H]^+$ = 248.1646, $C_{15}H_{22}NO_2$ requires 248.1645, Δ = 0.37 ppm.

FTIR (film): ν_{max} = 2931, 1692, 1418, 1345, 1308, 1258, 1173, 1146, 1102, 1044, 1004 cm^{-1}.

$[\alpha]_D^{25}$ = +11.2 (*c* = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IC column (99.7:0.3 hexane:IPA, 1.0 mL min^{-1}, 210 nm, room temperature); t_r (minor) = 84.5 min, t_r (major) = 90.5 min; 63:37 er.

(2*R*)-2-Methylhexane-1,5-diol (437)



Diol ***ent*-437** was prepared using a modified literature procedure.[191] To a pre-cooled vial at 0 °C was added (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (1.00 g, 3.10 mmol), methyl-3,4-dihydroxybenzoate (1.90 g, 12.3 mmol), propanal (4.43 mL, 61.4 mmol) and methyl vinyl ketone (7.48 mL, 92.2 mmol). The vial was sealed and stirred at 0 °C for 24 hours. The reaction solution was transferred into pre-cooled ethanol (500 mL) at 0 °C *via* syringe and sodium borohydride (11.6 g, 0.31 mol) was added portionwise. The reaction mixture was allowed to warm to room temperature and stirred for a further 16 hours. The mixture was poured onto ice and allowed to warm to room temperature. The solution was concentrated *in vacuo* to remove the majority of the EtOH and extracted with Et_2O (3 × 400 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2:MeOH 95:5) afforded diol ***ent*-437** (1.23 g, 15%, ~55:45 dr, 94:6 er) as a viscous, colourless oil and an inseparable mixture of diastereomers. *It was not possible to calculate dr of the crude reaction mixture or purified compound due to overlapping peaks in the ^{1}H NMR spectrum, a dr of ~55:45 was estimated by HPLC for the benzoyl ester derivative* ***ent*-631.**

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.81-3.77 (1H, m, C<u>H</u>-5), 3.49-3.43 (2H, m, C<u>H$_2$</u>-1), 2.29-1.39 (6H, m, 2 × O<u>H</u>, C<u>H</u>-2, C<u>H$_2$</u>-3, and C<u>H$_2$</u>-4$_a$), 1.29-1.11 (1H, m, C<u>H$_2$</u>-4$_b$), 1.19 (3H, d, *J* = 6.2 Hz, C<u>H$_3$</u>-6), 0.94-0.90 (3H, m, C<u>H$_3$</u>-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 68.6 (C<u>H</u>-5), 68.1 (C<u>H</u>$_2$-1), 36.6 (C<u>H</u>$_2$-3), 35.9 (C<u>H</u>-2), 29.2 (C<u>H</u>$_2$-4), 23.7 (C<u>H</u>$_3$-6), 16.8 (C<u>H</u>$_3$-7).

Additional peaks for the minor diastereomer:
^{13}C NMR (101 MHz, $CDCl_3$) δ = 36.3 (C<u>H</u>$_2$-3), 35.6 (C<u>H</u>-2), 29.0 (C<u>H</u>$_2$-4), 23.8 (C<u>H</u>$_3$-6), 16.7 (C<u>H</u>$_3$-7).

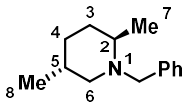
HRMS: ESI+ found $[M+Na]^+$ = 155.1040, $C_7H_{16}O_2{}^{23}Na$ requires 155.1043, Δ = –1.69 ppm.

FTIR (film): ν_{max} = 3318, 2927, 2872, 1459, 1374, 1112, 1021, 984, 943 cm^{-1}.

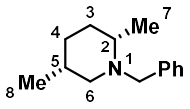
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ **=** +11.0 (*c* = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding bis-benzoyl ester ***ent*-631** (see p256–257 for HPLC conditions and full characterisation data); 94:6 er.

(2*R*,5*R*)-*N*-Benzyl-2,5-dimethylpiperidine (438)



438a
major

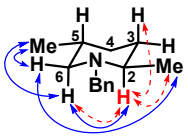


438b
minor

Procedure for enantioenriched material: (2*R*)-2-Methylhexane-1,5-diol ***ent*-437** (132 mg, 1.0 mmol, 94:6 er), anhydrous benzylamine (0.16 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and water (0.5 mL) were subjected to **general procedure B** at 110 °C. ^{1}H NMR analysis of the crude reaction mixture indicated the presence of two diastereomers in 2:1 dr. Purification by column chromatography (pentane:Et_2O 95:5) afforded piperidine **438a** (105 mg, 52%, >95:5 dr) as a colourless oil and piperidine **438b** (49.6 mg, 24%, >95:5 dr) as a colourless oil.

Procedure for racemic material: 2-Methylhexane-1,5-diol ***rac*-437**[*] (132 mg, 1.0 mmol), anhydrous benzylamine (0.16 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A** at 110 °C. ^{1}H NMR analysis of the crude reaction mixture indicated the presence of two diastereomers in 5:2 dr. Purification by column chromatography (pentane:Et_2O 90:10) afforded piperidine ***rac*-438** (138 mg, 68%, 5:2 dr) as a colourless oil.

***Data for the major diastereomer* 438a**



H-2$_{ax}$ dqd, *J* = **12.0**, 6.1, 2.7 Hz
(shown with dashed arrows)
H-5$_{ax}$ was not fully resolved but contains large J values indicative of axial geometry.
nOe correlations shown with solid arrows.
Note: other protons and correlations are removed for clarity

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34-7.21 (5H, m, ArH), 4.07 (1H, d, *J* = 13.5 Hz, NCH_{2a}Ph), 3.14 (1H, d, *J* = 13.5 Hz, NCH_{2b}Ph), 2.74-2.70 (1H, m, CH_2-6$_a$), 2.12 (1H, dqd, *J* = 12.0, 6.1, 2.7 Hz, CH-2$_{ax}$), 1.70-1.33 (5H, m, CH_2-3, CH_2-4$_a$, CH-5, and CH_2-6$_b$), 1.21 (3H, d, *J* = 6.1 Hz, CH_3-7), 0.96-0.85 (1H, m, CH_2-4$_b$), 0.76 (3H, d, *J* = 6.2 Hz, CH_3-8).

[*] Diol ***rac*-437** was prepared by Dr James Frost

^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.5 (Ar<u>C</u>), 129.3 (2 × Ar<u>C</u>H), 128.2 (2 × Ar<u>C</u>H), 126.7 (Ar<u>C</u>H), 61.1 (<u>C</u>H$_2$-6), 58.3 (N<u>C</u>H$_2$Ph), 56.7 (<u>C</u>H-2), 35.3 (<u>C</u>H$_2$-3), 33.7 (<u>C</u>H$_2$-4), 31.4 (<u>C</u>H-5), 22.3 (<u>C</u>H$_3$-7), 19.9 (<u>C</u>H$_3$-8).

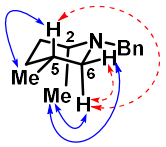
HRMS: ESI+ found $[M+H]^+$ = 204.1748, $C_{14}H_{22}N$ requires 204.1747, Δ = 0.63 ppm.

FTIR (film): ν_{max} = 2925, 1494, 1454, 1370, 1144, 1125, 1064, 732, 697 cm^{-1}.

$[\alpha]_D^{25}$ = –65.2 (*c* = 2.1, $CHCl_3$).

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding *N*-Cbz compound, **S5a** (see p218–219 for HPLC conditions and full characterisation data). er = 70:30.

***Data for the minor diastereomer* 438b**



H-6$_{ax}$ dd, *J* = 11.6, 9.0 Hz
(shown with dashed arrows)

nOe correlations shown with solid arrows.
Me-7 ↔ Me-8 not observed.
Note: other protons and correlations removed for clarity

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37-7.21 (5H, m, Ar<u>H</u>), 3.66-3.46 (2H, m, NC<u>H</u>$_2$Ph), 2.81-2.88 (1H, m, C<u>H</u>-2), 2.34 (1H, dd, *J* = 11.6, 4.2 Hz, C<u>H</u>$_2$-6$_{eq}$), 2.17 (1H, dd, *J* = 11.6, 9.0 Hz, C<u>H</u>$_2$-6$_{ax}$), 1.81-1.61 (2H, m, C<u>H</u>$_2$-4$_a$ and C<u>H</u>-5), 1.55-1.44 (2H, m, C<u>H</u>$_2$-3$_a$ and C<u>H</u>$_2$-4$_b$), 1.30-1.16 (1H, m, C<u>H</u>$_2$-3$_b$), 1.01 (3H, d, *J* = 6.6 Hz, C<u>H</u>$_3$-7), 0.87 (3H, d, *J* = 6.7 Hz, C<u>H</u>$_3$-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.4 (Ar<u>C</u>), 128.7 (2 × Ar<u>C</u>H), 128.2 (2 × Ar<u>C</u>H), 126.7 (Ar<u>C</u>H), 59.2 (N<u>C</u>H$_2$Ph), 54.7 (<u>C</u>H$_2$-6), 52.8 (<u>C</u>H-2), 31.4 (<u>C</u>H$_2$-4), 30.8 (<u>C</u>H-5), 28.4 (<u>C</u>H$_2$-3), 19.4 (<u>C</u>H$_3$-8), 11.9 (<u>C</u>H$_3$-7).

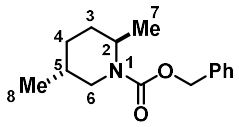
HRMS: ESI+ found $[M+H]^+$ = 204.1748, $C_{14}H_{22}N$ requires 204.1747, Δ = 0.63 ppm.

FTIR (film): ν_{max} = 2925, 1494, 1454, 1374, 1330, 1215, 1122, 1066, 735, 697 cm^{-1}.

$[\alpha]_D^{25}$ = +2.4 (*c* = 0.7, $CHCl_3$).

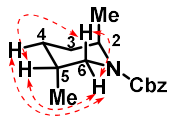
HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding *N*-Cbz compound, **S5b** (see p219–220 for HPLC conditions and full characterisation data). er = 67:33.

Benzyl (2*S*,5*S*)-2,5-dimethylpiperidine-1-carboxylate (S5a)



Procedure for enantioenriched material: *N*-benzyl-(2*S*,5*S*)-2,5-dimethylpiperidine ***ent*-438a** (26 mg, 0.13 mmol) and benzyl chloroformate (3 M in toluene, 0.5 mL, 1.5 mmol) were subjected to **general procedure C**. Purification by column chromatography afforded piperidine **S5a** (31 mg, 98%, 70:30 er, >95:5).

***Procedure for racemic material*:** Racemic material for HPLC analysis was synthesised using (±)-*N*-benzyl-2,5-dimethylpiperidine ***rac*-438a** under an analogous procedure.



H-6$_{eq}$ dtd, *J* = 13.6, 2.3, 0.9 Hz
H-6$_{ax}$ dd, *J* = 13.5, 3.4 Hz
Indicates H-5 is equatorial
H-2 (m) does not appear to contain large couplings, tentatively assigned equatorial

^{1}H NMR (500 MHz, d$_8$-toluene, 363 K) δ = 5.18-5.08 (2H, m, OC<u>H$_2$</u>Ph), 4.33 (1H, pd, *J* = 6.6, 3.1 Hz, C<u>H</u>-2$_{eq}$), 3.64 (1H, d, *J* = 13.4 Hz, C<u>H$_2$</u>-6$_{ax}$), 2.94 (1H, dd, *J* = 13.5, 3.5 Hz, C<u>H$_2$</u>-6$_{eq}$), 1.71-1.62 (1H, m, C<u>H$_2$</u>-3$_a$), 1.57-1.43 (2H, m, C<u>H</u>-5 and C<u>H$_2$</u>-4$_a$), 1.01-0.92 (2H, m, C<u>H$_2$</u>-3$_b$ and C<u>H$_2$</u>-4$_b$), 0.98 (3H, d, *J* = 6.9 Hz, C<u>H$_3$</u>-7), 0.84 (3H, d, *J* = 6.9 Hz, C<u>H$_3$</u>-8).

^{13}C NMR (125 MHz, d$_8$-toluene, 363 K) δ = 155.8 (<u>C</u>=O), 138.3 (Ar<u>C</u>), 66.8 (O<u>C</u>H$_2$Ph), 47.3 (<u>C</u>H-2), 44.7 (<u>C</u>H$_2$-6), 28.4 (<u>C</u>H-5), 25.9 (<u>C</u>H$_2$-4), 25.8 (<u>C</u>H$_2$-3), 17.1 (<u>C</u>H$_3$-8), 16.7 (<u>C</u>H$_3$-7). *Signals corresponding to the aromatic protons and carbons are partially obscured by the d$_8$-toluene solvent signals. The aromatic signals can be clearly observed in the room temperature CDCl$_3$ data below.*

^{1}H NMR (400 MHz, CDCl$_3$, 298 K) δ = 7.37-7.28 (5H, m, Ar<u>H</u>), 5.16-5.10 (2H, m, OC<u>H$_2$</u>Ph), 4.46-4.39 (1H, m, C<u>H</u>-2), 3.73 (1H, dt, *J* = 13.6, 2.3 Hz, C<u>H$_2$</u>-6$_{eq}$), 3.13 (1H, dd, *J* = 13.5, 3.4 Hz, C<u>H$_2$</u>-6$_{ax}$), 1.96-1.78 (3H, m, C<u>H$_2$</u>-3$_a$, C<u>H$_2$</u>-4$_a$ and C<u>H</u>-5), 1.32-1.25 (2H, m, C<u>H$_2$</u>-3$_b$ and C<u>H$_2$</u>-4$_b$), 1.13 (3H, d, *J* = 6.9 Hz, C<u>H$_3$</u>-7), 0.98 (3H, d, *J* = 6.9 Hz, C<u>H$_3$</u>-8).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ = 156.1 (C=O), 137.3 (ArC), 128.6 (2 × ArCH), 127.9 (ArCH), 127.8 (2 × ArCH), 66.9 (OCH_2Ph), 46.8 (CH-2), 44.0 (CH_2-6), 27.8 (CH-5), 24.9 (CH_2-4), 24.8 (CH_2-3), 16.7 (CH_3-8), 16.3 (CH_3-7).

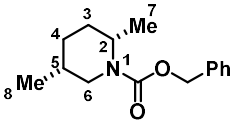
HRMS: ESI+ found $[M+H]^+$ = 248.1646, $C_{15}H_{22}O_2N$ requires 248.1645, Δ = 0.24 ppm.

FTIR (film): ν_{max} = 2936, 1693, 1423, 1355, 1336, 1308, 1260, 1244, 1159, 1076, 1029, 697 cm^{-1}.

$[\alpha]_D^{25}$ = –14.2 (*c* = 1.4, $CHCl_3$).

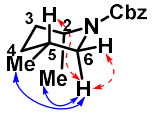
HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IA column (99:1 hexane:IPA, 0.7 mL min^{-1}, 210 nm, room temperature); t_r (minor) = 12.8 min, t_r (major) = 13.6 min; 70:30 er.

(2R,5S)-2,5-dimethylpiperidine-1-carboxylate (S5b)



Procedure for enantioenriched material: *N*-benzyl-2,5-dimethylpiperidine ***ent*-438b** (25 mg, 0.12 mmol) and benzyl chloroformate (3M in toluene, 0.5 mL, 1.5 mmol) were subjected to **general procedure C**. Purification by column chromatography afforded piperidine **S5b** (29 mg, 95%, 67:33 er, >95:5 dr).

***Procedure for racemic material*:** Racemic material for HPLC analysis was synthesised using (±)-*N*-benzyl-2,5-dimethylpiperidine ***rac*-438b** under an analogous procedure.



H-6_{ax} dd, *J* = 13.4, 11.5 Hz
Large J values indicate axial goemetry
Couplings shown with dashed arrows
H_2-3 and H_2-4 are removed for clarity
nOe (solid arrows)

^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ = 5.09 (2H, s, OCH_2Ph), 4.49-4.43 (m, 1H, CH-2_{eq}), 4.00 (1H, d, *J* = 12.6 Hz, CH_2-6_{eq}), 2.29 (1H, dd, *J* = 13.4, 11.5 Hz, CH_2-6_{ax}), 1.58-1.43 (1H, m, CH_2-3_a), 1.32-1.16 (3H, m, CH_2-3_b, CH_2-4_a and CH-5), 1.01-0.92 (1H, m, CH_2-4_b), 0.93 (3H, d, *J* = 7.0 Hz, CH_3-7), 0.63 (3H, d, *J* = 6.4 Hz, CH_3-8).

^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ = 155.1 (C=O), 138.2 (ArC), 66.9 (OCH_2Ph), 46.4 (CH_2-6), 46.3 (CH-2), 31.8 (CH-5), 30.6 (CH_2-3), 28.2 (CH_2-4), 19.3 (CH_3-8), 15.8 (CH_3-7). *Signals corresponding to the aromatic protons and carbons are obscured by the d_8-toluene solvent signals. The aromatic signals can be clearly observed in the room temperature $CDCl_3$ data below.*

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ = 7.39-7.28 (5H, m, ArH), 5.13 (2H, s, OCH_2Ph), 4.53-4.40 (1H, m, CH-2), 4.02-3.86 (1H, m, CH_2-6_a), 2.53-2.43 (1H, m, CH_2-6_b), 1.74-1.63 (1H, m, CH_2-3_a), 1.60-1.44 (3H, m, CH_2-3_b, CH_2-4_a and CH-5), 1.30-1.19 (1H, m, CH_2-4_b), 1.13 (3H, d, *J* = 7.0 Hz, CH_3-7), 0.89 (3H, d, *J* = 6.3 Hz, CH_3-8).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ = 156.1 (C=O), 137.3 (ArC), 128.6 (2 × ArCH), 128.0 (2 × ArCH), 127.9 (ArCH), 67.0 (OCH_2Ph), 45.8 (CH-2 and CH_2-6), 31.5 (CH-5), 30.2 (CH_2-3), 27.6 (CH_2-4), 19.4 (CH_3-8), 16.2 (CH_3-7).

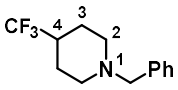
HRMS: ESI+ found $[M+H]^+$ = 248.1646, $C_{15}H_{22}O_2N$ requires 248.1645, Δ = 0.55 ppm.

FTIR (film): ν_{max} = 2936, 1693, 1423, 1336, 1308, 1260, 1244, 1159, 1146, 1076, 1029, 697 cm^{-1}.

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IC column (99:1 hexane:IPA, 0.7 mL min^{-1}, 210 nm, room temperature); t_r (minor) = 17.8 min, t_r (major) = 18.7 min; 67:33.

$[\alpha]_D^{25}$ **=** +5.0 (*c* = 1.6, $CHCl_3$).

<u>*N*-benzyl-4-(trifluoromethyl)piperidine (442)</u>



4-(Trifluoromethyl)-pentane-1,5-diol **441**[*] (172 mg, 1.0 mmol), anhydrous benzylamine (0.16 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Purification by column chromatography (pentane:Et_2O 90:10) afforded piperidine **442** (192 mg, 79%) as a pale yellow oil.

[*] Diol **441** was synthesised by Dr Roly Armstrong

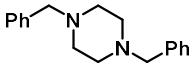
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36-7.24 (5H, m, Ar<u>H</u>), 3.51 (2H, s, NC<u>H$_2$</u>Ph), 2.97 (2H, m, 2 × C<u>H$_2$-2$_{eq}$</u>), 2.05-1.96 (1H, m, C<u>H-4</u>), 1.95 (2H, td, *J* = 11.9, 2.6 Hz, 2 × C<u>H$_2$-2$_{ax}$</u>), 1.85-1.78 (2H, m, 2 × C<u>H$_2$-3$_{eq}$</u>), 1.64 (2H, qd, *J* = 12.7, 3.9 Hz, 2 × C<u>H$_2$-3$_{ax}$</u>).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.3 (Ar<u>C</u>), 129.2 (2 × Ar<u>C</u>H), 128.4 (2 × Ar<u>C</u>H), 127.7 (q, *J* = 278.4, <u>C</u>F$_3$), 127.2 (Ar<u>C</u>H), 63.2 (N<u>C</u>H$_2$Ph), 52.5 (2 × <u>C</u>H$_2$-2), 40.5 (q, *J* = 27.1 Hz, <u>C</u>H-4), 24.8 (2 × <u>C</u>H$_2$-3).

^{19}F NMR (400 MHz, $CDCl_3$) δ = -73.7 (d, *J* = 8.2 Hz, C<u>F$_3$</u>).

The data are consistent with the literature.[153]

<u>*N, N'*-Dibenzylpiperazine (444)</u>



2,2'-Azanediylbis(ethan-1-ol) **443**[*] (195 mg, 1.0 mmol), anhydrous benzylamine (0.16 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and deionised water (0.5 mL) were subjected to **general procedure B** at 110 °C. Purification by column chromatography (pentane:Et_2O 80:20) afforded piperazine **444** (48 mg, 18%) as a pale yellow solid as an inseparable mixture with dibenzylamine **445** (17% by ^{1}H NMR w.r.t. piperazine **444**, *the spectral data are consistent with the literature*[209]).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35-7.22 (10H, m, Ar<u>H</u>), 3.51 (4H, s, 2 × NC<u>H$_2$</u>Ph), 2.48 (8H, br. s, 4 × C<u>H$_2$-2</u>).

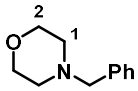
^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.3 (2 × Ar<u>C</u>), 129.4 (4 × Ar<u>C</u>H), 128.3 (4 × Ar<u>C</u>H), 127.1 (2 × Ar<u>C</u>H), 63.2 (2 × N<u>C</u>H$_2$Ph), 53.2 (4 × <u>C</u>H$_2$).

Melting point (CH_2Cl_2) = 90–91 °C.

The data are consistent with the literature.[210]

[*] Diol **443** was synthesised by Kieran Paterson

_N_-Benzylmorpholine (456)



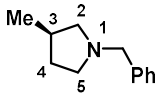
Diethylene glycol (106 mg, 1.0 mmol), anhydrous benzylamine (0.16 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and deionised water (0.5 mL) were subjected to **general procedure B** at 110 °C. Purification by column chromatography (pentane:Et_2O 80:20) afforded piperazine **456** as a colourless oil (48 mg, 42%) as an inseparable mixture with dibenzylamine (15% by ^1H NMR w.r.t. morpholine **456**, *the spectral data are consistent with the literature*[209]).

^1H NMR (400 MHz, $CDCl_3$) δ = 7.36-7.24 (5H, m, ArH), 3.72-3.70 (4H, m, 2 × CH_2-1), 3.50 (2H, s, NCH_2Ph), 2.46-2.43 (4H, m, 2 × CH_2-2).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.9 (ArC), 129.3 (2 × ArCH), 128.4 (2 × ArCH), 127.3 (ArCH), 67.2 (2 × CH_2-1), 63.6 (NCH_2Ph), 53.8 (2 × CH_2-2).

The data are consistent with the literature.[211]

(_R_)-1-Benzyl-3-methylpyrrolidine (458)



Procedure for enantioenriched material: (*R*)-2-Methylpentane-1,4-diol* ***ent*-457** (104 mg, 1.0 mmol, >99:1 er), anhydrous benzylamine (0.16 mL, 1.5 mmol), $CsHCO_3$ (3.9 mg, 2.0 mol%), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and CPME (0.5 mL) were subjected to **general procedure G**. Purification by column chromatography (pentane:Et_2O 80:20) afforded pyrrolidine ***ent*-458** (96 mg, 54%, 96:4 er) as a colourless oil.

Procedure for racemic material: 2-Methylpentane-1,4-diol* ***rac*-457** (104 mg, 1.0 mmol), anhydrous benzylamine (0.16 mL, 1.5 mmol), $NaHCO_3$ (1.7 mg, 2.0 mol%), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Purification

* Diol ***ent*-457** was synthesised by Dr Roly Armstrong

by column chromatography (pentane:Et_2O 90:10) afforded pyrrolidine ***rac*-458** (74 mg, 42%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35-7.21 (5H, m, ArH), 3.63-3.56 (2H, m, NCH_2Ph), 2.82 (1H, dd, *J* = 9.0, 7.4 Hz, CH_2-2_a), 2.70 (1H, ddd, *J* = 9.2, 8.0, 5.4 Hz, CH_2-5_a), 2.45 (1H, td, *J* = 8.8, 6.4 Hz, CH_2-5_b), 2.32-2.19 (1H, m, CH-3), 2.07-1.96 (2H, m, CH_2-2_b and CH_2-4_a), 1.34 (1H, dddd, *J* = 12.6, 8.5, 6.3, 5.4 Hz, CH_2-4_b), 1.01 (3H, d, *J* = 6.8 Hz, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.6 (ArC), 129.0 (2 × ArCH), 128.3 (2 × ArCH), 126.9 (ArCH), 62.4 (CH_2-2), 61.0 (NCH_2Ph), 54.3 (CH_2-5), 32.8 (CH_2-4), 32.0 (CH-3), 20.6 (CH_3).

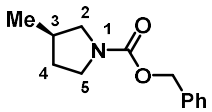
HRMS: ESI+ found $[M+H]^+$ = 176.1434, $C_{12}H_{18}N$ requires 176.1434, Δ = – 0.03 ppm.

FTIR (film): ν_{max} = 2955, 2783, 1453, 1375, 1155, 1136, 1124, 1029, 907, 739, 698 cm^{-1}.

$[\alpha]_D^{25}$ = –5.2 (*c* = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding *N*-Cbz compound, **S6** (see p223–224 for HPLC conditions and full characterisation data). er = 96:4.

Benzyl (*R*)-3-methylpyrrolidine-1-carboxylate (S6)



Procedure for enantioenriched material: (*R*)-*N*-benzyl-3-methylpyrrolidine ***ent*-458** (19 mg, 0.08 mmol) and benzyl chloroformate (3 M in toluene, 0.5 mL, 1.5 mmol) were subjected to **general procedure C**. Purification by column chromatography (pentane:Et_2O 80:20) afforded pyrrolidine **S6** (28 mg, 38%, 96:4 er) as a colourless oil.

Procedure for racemic material: Racemic material for HPLC analysis was synthesised using *N*-benzyl-3-methylpyrrolidine ***rac*-458** under an analogous procedure*. The data are consistent with the literature.*[212]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39-7.26 (5H, m, ArH), 5.13 (2H, s, NCH_2Ph), 3.63-3.50 (2H, m, CH_2-2_a and CH_2-5_a), 3.35 (1H, dtd, *J* = 10.6, 8.7, 7.1 Hz, CH_2-5_b), 2.92 (1H, ddd, *J* = 15.2, 10.5, 8.1 Hz, CH_2-2_b), 2.31-2.17 (1H, m, CH-3), 2.02-1.94 (1H, m, CH_2-4_a), 1.55-1.45 (1H, m, CH_2-4_b), 1.05 (3H, m, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.0 (C=O), 137.3 (ArC), 128.6 (2 × ArCH), 128.0 (3 × ArCH), 66.72 (NCH_2Ph), 66.69 (NCH_2Ph), 53.4 (CH_2-2), 53.0 (CH_2-2), 46.2 (CH_2-5), 45.8 (CH_2-5), 33.8 (CH-3), 33.7 (CH-3), 33.0 (CH_2-4), 32.9 (CH_2-4), 17.8 (CH_3). *Some of the signals are doubled due to the rotameric nature of the carbamate.*

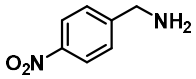
HRMS: ESI+ found $[M+Na]^+$ = 242.1153, $C_{13}H_{17}NO_2Na$ requires 242.1152, Δ = 0.54 ppm.

FTIR (film): ν_{max} = 2959, 2874, 1702, 1419, 1358, 1216, 1177, 1149, 1133, 1103, 1074 cm^{-1}.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ **=** +18.5 (*c* = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IG column (99:1 hexane:IPA, 1.0 mL min^{-1}, 210 nm, room temperature); t_r (minor) = 40.3 min, t_r (major) = 42.0 min; 96:4 er.

(4-Nitrophenyl)methanamine (480)

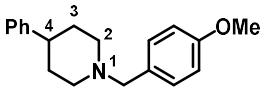


To a solution of *para*-nitrobenzylamine hydrochloride salt (0.50 g, 2.65 mmol) in water (20 mL) was added K_2CO_3 until a basic pH was reached. The resulting solution was stirred at room temperature for 1 hour and extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting yellow solid (0.34 g, 85%) was used immediately without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.20-8.17 (2H, m, ArH), 7.52-7.48 (2H, m, ArH), 4.00 (2H, s, $ArCH_2$), 1.51 (2H, br. s, NH_2).

The spectroscopic data are consistent with the literature.[213]

_N_-(4-methoxybenzyl)-4-phenylpiperidine (482)



3-Phenylpentane-1,5-diol **398** (180 mg, 1.0 mmol), *para*-methoxybenzylamine (0.20 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Purification by column chromatography (pentane:Et_2O 60:40) afforded piperidine **482** (95.4 mg, 34%) as a colourless oil.

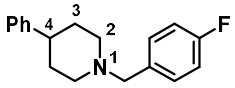
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30-7.15 (7H, m, Ar<u>H</u>), 6.88-6.84 (2H, m, Ar<u>H</u>), 3.80 (3H, s, OC<u>H</u>$_3$), 3.48 (2H, s, NC<u>H</u>$_2$Ph), 3.02-2.97 (2H, m, 2 × C<u>H</u>$_2$-2$_a$), 2.51-2.44 (1H, m, C<u>H</u>-4), 2.08-2.02 (2H, m, 2 × C<u>H</u>$_2$-2$_b$), 1.81-1.76 (4H, m, 2 × C<u>H</u>$_2$-3).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 158.8 (Ar<u>C</u>), 146.7 (Ar<u>C</u>), 130.6 (Ar<u>C</u>), 130.6 (2 × Ar<u>C</u>H), 128.5 (2 × Ar<u>C</u>H), 127.0 (2 × Ar<u>C</u>H), 126.2 (Ar<u>C</u>H), 113.7 (2 × Ar<u>C</u>H), 63.0 (N<u>C</u>H$_2$Ph), 55.4 (O<u>C</u>H$_3$), 54.3 (2 × <u>C</u>H$_2$-2), 42.9 (<u>C</u>H-4), 33.7 (2 × <u>C</u>H$_2$-3).

HRMS: ESI+ found $[M+H]^+$ = 282.1847, $C_{19}H_{24}NO$ requires 282.1852, Δ = –1.76 ppm.

FTIR (film): ν_{max} = 2933, 2796, 2754, 1611, 1510, 1453, 1243, 833, 757, 699 cm^{-1}.

_N_-(4-Fluorobenzyl)-4-phenylpiperidine (483)



3-Phenylpentane-1,5-diol **398** (180 mg, 1.0 mmol), *p*-fluorobenzylamine (0.17 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Purification by column chromatography (pentane:Et_2O 90:10 → 80:20) afforded piperidine **483** (167 mg, 62%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34-7.28 (4H, m, Ar<u>H</u>), 7.25-7.18 (3H, m, Ar<u>H</u>), 7.05-6.99 (2H, m, Ar<u>H</u>), 3.52 (2H, s, NC<u>H</u>$_2$Ar), 3.02-2.97 (2H, m, 2 × C<u>H</u>$_2$-2$_a$), 2.56-2.45 (1H, m, C<u>H</u>-4), 2.12-2.05 (2H, m, 2 × C<u>H</u>$_2$-2$_b$), 1.85-1.72 (4H, m, 2 × C<u>H</u>$_2$-3).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 163.1 (d, *J* = 244.6 Hz, Ar<u>C</u>F), 146.6 (Ar<u>C</u>), 134.3 (d, *J* = 3.0 Hz, Ar<u>C</u>), 130.8 (d, *J* = 8.0 Hz, 2 × Ar<u>C</u>H), 128.5 (2 × Ar<u>C</u>H), 127.0 (2 × Ar<u>C</u>H), 126.2 (Ar<u>C</u>H), 115.1 (d, *J* = 21.1 Hz, 2 × Ar<u>C</u>H), 62.8 (N<u>C</u>H_2Ar), 54.4 (2 × <u>C</u>H_2-2), 42.8 (<u>C</u>H-4), 33.6 (2 × <u>C</u>H_2-3).

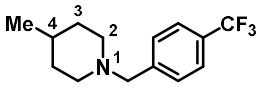
^{19}F NMR (400 MHz, $CDCl_3$) δ = –116.13 (tt, *J* = 8.8, 5.5 Hz, Ar<u>F</u>).

HRMS: ESI+ found $[M+H]^+$ = 270.1651, $C_{18}H_{21}FN$ requires 270.1653, Δ = –0.67 ppm.

FTIR (film): ν_{max} = 2936, 2795, 2756, 1603, 1507, 1221, 1154, 1090, 992, 835, 755, 699 cm^{-1}.

Melting point (CH_2Cl_2) = 69–70 °C.

***N*-Methyl-1-(4-(trifluoromethyl)benzyl)piperidine (484)**



3-Methylpentane-1,5-diol (118 mg, 1.0 mmol), *p*-(trifluoromethyl)benzylamine (0.21 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Purification by column chromatography (pentane:Et_2O 90:10) afforded piperidine **484** (220 mg, 86%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57-7.54 (2H, m, Ar<u>H</u>), 7.45-7.42 (2H, m, Ar<u>H</u>), 3.52 (2H, s, NC<u>H_2</u>Ph), 2.83-2.78 (2H, m, 2 × C<u>H_2-2$_{eq}$</u>), 1.95 (2H, td, *J* = 11.5, 2.5 Hz, 2 × C<u>H_2-2$_{ax}$</u>), 1.63-1.57 (2H, m, 2 × C<u>H_2-3$_a$</u>), 1.42-1.31 (1H, m, C<u>H-4</u>), 1.29-1.19 (2H, m, 2 × C<u>H_2-3$_b$</u>), 0.92 (3H, d, *J* = 6.4 Hz, C<u>H_3</u>).

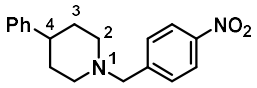
^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.4 (Ar<u>C</u>), 129.3 (4 × Ar<u>C</u>H), 125.2 (q, *J* = 3.9 Hz, Ar<u>C</u>), 124.5 (q, *J* = 271.7 Hz, <u>C</u>F_3), 63.1 (N<u>C</u>H_2Ph), 54.2 (2 × <u>C</u>H_2-2), 34.5 (2 × <u>C</u>H_2-3), 30.9 (<u>C</u>H-4), 22.1 (<u>C</u>H_3).

^{19}F NMR (400 MHz, $CDCl_3$) δ = –62.3 (s, C<u>F_3</u>).

HRMS: ESI+ found $[M+H]^+$ = 258.1466, $C_{14}H_{19}F_3N$ requires 258.1475, Δ = –3.61 ppm.

FTIR (film): ν_{max} = 2924, 2797, 1324, 1161, 1123, 1102, 1066, 847, 812 cm^{-1}.

_N_-(4-Nitrobenzyl)-4-phenylpiperidine (485)



3-Phenylpentane-1,5-diol **398** (180 mg, 1.0 mmol), *para*-nitrobenzylamine **485** (167 mg, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Purification by column chromatography (pentane:Et_2O 70:30) afforded piperidine **485** (3.8 mg, 1%) as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21-8.17 (2H, m, ArH), 7.56-7.52 (2H, m, ArH), 7.33-7.18 (5H, m, ArH), 3.63 (2H, s, NCH_2Ph), 2.99-2.95 (2H, m, 2 × CH_2-2$_a$), 2.56-2.48 (1H, m, CH-4), 2.19-2.12 (2H, m, 2 × CH_2-2$_b$), 1.87-1.76 (4H, m, 2 × CH_2-3).

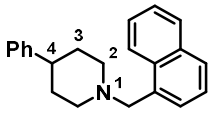
^{13}C NMR (126 MHz, $CDCl_3$) δ = 147.3 (ArC), 146.3 (ArC), 129.6 (2 × ArCH), 128.6 (2 × ArCH), 127.0 (2 × ArCH), 126.4 (ArCH), 125.7 (ArC), 123.7 (2 × ArCH), 62.7 (NCH_2Ph), 54.6 (2 × CH_2-2), 42.6 (CH-4), 33.6 (2 × CH_2-3).

HRMS: ESI+ found $[M+H]^+$ = 297.1594, $C_{18}H_{21}N_2O_2$ requires 297.1598, Δ = –1.32 ppm.

FTIR (film): ν_{max} = 2936, 2797, 1603, 1518, 1493, 1346, 853, 739, 699 cm^1.

Melting point (CH_2Cl_2) = 69–70 °C.

_N_-(Naphthalen-1-ylmethyl)-4-phenylpiperidine (486)



3-Phenylpentane-1,5-diol **398** (180 mg, 1.0 mmol), 1-naphthylethylamine (0.22 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Purification by column chromatography (pentane:Et_2O 95:5) afforded piperidine **486** (137 mg, 46%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.38-8.36 (1H, m, ArH), 7.87 (1H, d, *J* = 7.8 Hz, ArH), 7.79 (1H, d, *J* = 7.8 Hz, ArH), 7.57-7.42 (4H, m, ArH), 7.32-7.17 (5H, m, ArH), 3.96 (2H, s, NCH_2Ar), 3.09 (2H, dt,

J = 11.0, 3.6 Hz, 2 × C$\underline{H_2}$-2$_{eq}$), 2.55 (1H, tt, *J* = 10.8, 5.6 Hz, C$\underline{H}$-4), 2.23-2.16 (2H, m, 2 × C$\underline{H_2}$-2$_{ax}$), 1.85-1.74 (4H, m, 2 × C$\underline{H_2}$-3).

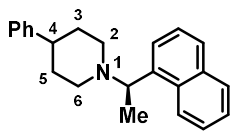
^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.8 (Ar$\underline{C}$), 134.8 (Ar$\underline{C}$), 134.0 (Ar$\underline{C}$), 132.8 (Ar$\underline{C}$), 128.5 (3 × Ar$\underline{C}$H), 127.9 (Ar$\underline{C}$H), 127.4 (Ar$\underline{C}$H), 127.0 (2 × Ar$\underline{C}$H), 126.2 (Ar$\underline{C}$H), 125.8 (Ar$\underline{C}$H), 125.7 (Ar$\underline{C}$H), 125.3 (Ar$\underline{C}$H), 125.0 (Ar$\underline{C}$H), 61.6 (N$\underline{C}$H$_2$Ar), 54.8 (2 × $\underline{C}$H$_2$-2), 43.0 ($\underline{C}$H-4), 33.8 (2 × $\underline{C}$H$_2$-3).

HRMS: ESI+ found $[M+H]^+$ = 302.1901, $C_{22}H_{24}N$ requires 302.1903, Δ = –0.67 ppm.

FTIR (film): ν_{max} = 1598, 1493, 1452, 1365, 1334, 1167, 1108, 988, 784, 699cm^{-1}.

Melting point (CH_2Cl_2) = 106–107 °C.

(*R*)-*N*-(1-(Naphthalen-1-yl)ethyl)-4-phenylpiperidine (487)



Procedure for enantioenriched material: 3-Phenylpentane-1,5-diol **398** (180 mg, 1.0 mmol), (*R*)-(1-naphthyl)ethylamine (0.24 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Analysis of the crude reaction mixture by ^{1}H NMR indicated a dr of 89:11. Purification by column chromatography (pentane:Et_2O 90:10) afforded piperidine ***ent*-487** (293 mg, 93%, >95:5 dr) as a colourless oil.

Procedure for racemic material: 3-Phenylpentane-1,5-diol **398** (180 mg, 1.0 mmol), (1-naphthyl)ethylamine (0.24 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Analysis of the crude reaction mixture by ^{1}H NMR indicated a dr of 93:7. Purification by column chromatography (pentane:Et_2O 90:10) afforded piperidine ***rac*-487** (308 mg, 98%, >95:5 dr) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.50 (1H, dd, *J* = 8.3, 1.6 Hz, Ar$\underline{H}$), 7.88 (1H, dd, *J* = 8.0, 1.6 Hz, Ar$\underline{H}$), 7.76 (1H, dt, *J* = 8.2, 1.0, Ar$\underline{H}$), 7.64 (1H, dd, *J* = 7.1, 1.3 Hz, Ar$\underline{H}$), 7.55-7.45 (3H, m, Ar$\underline{H}$), 7.33-7.17 (5H, m, Ar$\underline{H}$), 4.18 (1H, q, *J* = 6.7 Hz, NC$\underline{H}$(CH_3)Ar), 3.37-3.32 (1H, m, C$\underline{H_2}$-2$_{eq}$), 2.99-2.96 (1H, m,

CH_2-6$_a$), 2.55-2.46 (1H, m, CH-4), 2.18 (1H, td, *J* = 11.4, 2.8 Hz, CH_2-2$_{ax}$), 2.13-2.07 (1H, m, CH_2-6$_b$), 1.93-1.70 (4H, m, CH_2-3 and CH_2-5), 1.52 (3H, d, *J* = 6.7 Hz, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.9 (ArC), 141.2 (ArC), 134.2 (ArC), 132.0 (ArC), 128.9 (ArCH), 128.5 (2 × ArCH), 127.3 (ArCH), 127.0 (2 × ArCH), 126.1 (ArCH), 125.6 (2 × ArCH), 125.4 (ArCH), 124.7 (ArCH), 124.4 (ArCH), 61.8 (NCH(CH_3)Ar), 53.2 (CH_2-2), 50.6 (CH_2-6), 43.1 (CH-4), 34.1 (CH_2-3), 34.0 (CH_2-5), 19.1 (CH_3).

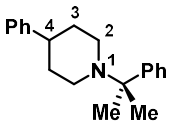
HRMS: ESI+ found $[M+H]^+$ = 316.2059, $C_{23}H_{26}N$ requires 316.2060, Δ = –0.14 ppm.

FTIR (film): ν_{max} = 2931, 2798, 1509, 1451, 1372, 1314, 1256, 1129, 800, 780, 699 cm^{-1}.

$[\alpha]_D^{25}$ = –34.7 (*c* = 1.0, $CHCl_3$).

HPLC: *Unable to determine er, compound not separable by HPLC.*

4-Phenyl-*N*-(2-phenylpropan-2-yl)piperidine (488)



3-Phenylpentane-1,5-diol **398** (180 mg, 1.0 mmol), cumylamine (0.22 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Purification by column chromatography (pentane:Et_2O 95:5) afforded piperidine **488** (185 mg, 66%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60-7.57 (2H, m, ArH), 7.35-7.17 (8H, m, ArH), 2.95-2.93 (2H, m, 2 × CH_2-2$_{eq}$), 2.47 (1H, tt, *J* = 11.8, 4.3 Hz, CH-4$_{ax}$), 2.22 (2H, td, *J* = 11.4, 2.7 Hz, 2 × CH_2-2$_{ax}$), 1.82-1.68 (4H, m, 2 × CH_2-3), 1.39 (6H, s, 2 × CH_3).

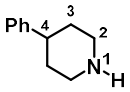
^{13}C NMR (101 MHz, $CDCl_3$) δ = 150.0 (ArC), 147.1 (ArC), 128.5 (2 × ArCH), 128.1 (2 × ArCH), 127.1 (2 × ArCH), 126.2 (2 × ArCH), 126.13 (ArCH), 126.08 (ArCH), 60.1 (NC(CH_3)$_2$Ph), 47.3 (2 × CH_2-2), 43.5 (CH-4), 34.6 (2 × CH_2-3), 24.5 (2 × CH_3).

HRMS: ESI+ found $[M+H]^+$ = 280.2060, $C_{20}H_{26}N$ requires 280.2060, Δ = 0.17 ppm.

FTIR (film): ν_{max} = 2972, 2930, 1493, 1446, 1271, 1177, 1073, 1024, 959, 759, 698 cm^{-1}.

Melting point (CH_2Cl_2) = 101–102 °C.

4-Phenylpiperidine (490)

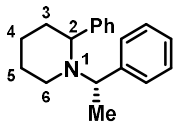


4-Phenyl-*N*-phenylpiperidine **399** (100 mg, 0.38 mmol) and 10% wt/wt palladium on carbon (40.4 mg, 10 mol% Pd) were dissolved in ethanol (13 mL). The solution and reaction vessel headspace were purged with hydrogen gas for 5 minutes before heating the reaction at 55 °C with vigorous stirring under an atmosphere of hydrogen for 2 hours. The reaction mixture was cooled to room temperature and filtered through a pad of Celite® (eluting with 100 mL EtOAc). The filtrate was concentrated *in vacuo*. Piperidine **490** (57 mg, 85%) was carried forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35-7.18 (5H, m, Ar<u>H</u>), 3.21-3.17 (2H, m, 2 × C<u>H$_2$-2$_{eq}$</u>), 2.74 (2H, td, *J* = 12.2, 2.5 Hz, 2 × C<u>H$_2$-2$_{ax}$</u>), 2.62 (1H, tt, *J* = 12.1, 3.7 Hz, C<u>H-4$_{ax}$</u>), 1.86-1.59 (4H, m, 2 × C<u>H$_2$-3</u>).

The data are consistent with the literature.[214]

2-Phenyl-1-((*S*)-1-phenylethyl)piperidine (556)



1-Phenylpentane-1,5-diol* **413** (180 mg, 1.0 mmol), *(S)*-α-methylbenzylamine (0.19 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Analysis of the crude reaction mixture by ^1H NMR indicated a dr of ~97:3. Purification by column chromatography (pentane:Et_2O 80:20) afforded piperidine **556** (154 mg, 58%, 95:5 dr) as a pale yellow solid and an inseparable mixture of diastereomers.

^1H NMR (400 MHz, $CDCl_3$) δ = 7.49-7.43 (4H, m, ArH), 7.34-7.17 (6H, m, ArH), 3.84 (1H, q, *J* = 6.8 Hz, NCH(CH_3)Ph), 3.51 (1H, dd, *J* = 10.7, 2.8 Hz, CH_2-2_{ax}), 2.60-2.55 (1H, m, CH_2-6_{eq}), 2.23 (1H, td, *J* = 11.5, 2.8 Hz, CH_2-6_{ax}), 1.82-1.76 (2H, m, CH_2-5_a and CH_2-3_a), 1.73-1.63 (1H, m, CH_2-3_b), 1.61-1.57 (1H, m, CH_2-4_{eq}), 1.53-1.43 (1H, m, CH_2-5_b), 1.35 (1H, qt, *J* = 13.0, 4.0 Hz, CH_2-4_{ax}), 1.19 (3H, d, *J* = 6.8 Hz, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.4 (ArC), 144.9 (ArC), 128.6 (2 × ArCH), 127.9 (2 × ArCH), 127.70 (2 × ArCH), 127.65 (2 × ArCH), 127.0 (ArCH), 126.2 (ArCH), 65.8 (CH-6), 55.1 (NCH(CH_3)Ph), 45.3 (CH_2-2), 37.4 (CH_2-5), 26.5 (CH_2-3 or CH_2-4), 25.8 (CH_2-3 or CH_2-4), 8.2 (CH_3).

HRMS: ESI+ found $[M+H]^+$ = 266.1903, $C_{19}H_{24}N$ requires 266.1903, Δ = 0.04 ppm.

FTIR (film): ν_{max} = 2932, 1492, 1450, 1382, 1364, 1177, 1021, 758, 699cm^{-1}.

Melting point (CH_2Cl_2) = 71–74 °C

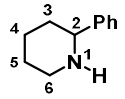
$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ **=** –33.1 (*c* = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding *N*-Ts compound **557** (see p232–233 for HPLC conditions and full characterisation data), er = 50:50.

The data are consistent with the literature. [150]

* Diol **413** was synthesised by Dr Roly Armstrong

2-Phenylpiperidine (S7)

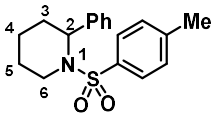


2-Phenyl-1-((*S*)-1-phenylethyl)piperidine **556** (93 mg, 0.35 mmol) and 10% wt/wt palladium on carbon (37 mg, 10 mol% Pd) were dissolved in ethanol (13 mL). The solution and reaction vessel headspace were purged with hydrogen gas for 5 minutes before heating the reaction at 55 °C with vigorous stirring under an atmosphere of hydrogen for 4 hours. The reaction mixture was cooled to room temperature and filtered through a pad of Celite® (eluting with 100 mL EtOAc). The filtrate was concentrated *in vacuo*. Piperidine **S7** (41.4 mg, 67%) was carried forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38-7.16 (5H, m, ArH), 3.60 (1H, dd, *J* = 10.5, 2.5 Hz, CH_2-6_{eq}), 3.21 (1H, ddt, *J* = 11.8, 4.1, 1.8 Hz, CH_2-2_{ax}), 2.81 (1H, td, *J* = 11.6, 2.9 Hz, CH_2-6_{ax}), 1.97-1.23 (6H, m, CH_2-3, CH_2-4, CH_2-5).

The data are consistent with the literature.[215]

2-Phenyl-*N*-tosylpiperidine (557)



2-Phenylpiperidine **S7** (41 mg, 0.25 mmol), tosyl chloride (60 mg, 0.31 mmol) and 4-(dimethylamino)pyridine (3.1 mg, 0.025 mmol) were dissolved in pyridine (1 mL). The resulting solution was stirred at room temperature for 16 hours before concentration *in vacuo*. The residue was redissolved in CH_2Cl_2 and washed with 1M HCl (3 $\times$ 20 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (pentane:Et_2O 90:10) afforded piperidine **557** (28 mg, 35%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71-7.66 (2H, m, ArH), 7.28-7.13 (7H, m, ArH), 5.19 (1H, m, CH-2), 3.79-3.73 (1H, m, CH_2-6_{eq}), 2.94 (1H, ddd, *J* = 14.3, 12.4, 3.1 Hz, CH_2-6_{ax}), 2.36 (3H, s, CH_3), 2.17-2.10 (1H, m, CH_2-3_a), 1.64-1.54 (1H, m, CH_2-3_b), 1.45-1.11 (4H, m, CH_2-4 and CH_2-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.1 (Ar<u>C</u>), 139.1 (Ar<u>C</u>), 138.9 (Ar<u>C</u>), 129.8 (2 × Ar<u>C</u>H), 128.7 (2 × Ar<u>C</u>H), 127.2 (2 × Ar<u>C</u>H), 127.1 (2 × Ar<u>C</u>H), 126.9 (Ar<u>C</u>H), 55.4 (<u>C</u>H-2), 42.0 (<u>C</u>H_2-6), 27.4 (<u>C</u>H_2-3), 24.4 (<u>C</u>H_2-5), 21.6 (<u>C</u>H_3), 19.1 (<u>C</u>H_2-4).

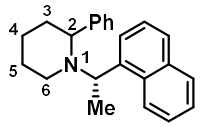
Melting point (CH_2Cl_2) = 137–138 °C

$[\alpha]_D^{25}$ **=** +1.1 (*c* = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IB-N column (99:1 hexane:IPA, 1.0 mL min^{-1}, 210 nm, room temperature); t_r (major) = 16.7 min, t_r (minor) = 21.2 min; er = 82:18.

The data are consistent with the literature.[216]

<u>1-((*S*)-1-(Naphthalen-1-yl)ethyl)-2-phenylpiperidine (559)</u>



Procedure for enantioenriched material: 1-Phenylpentane-1,5-diol* **413** (180 mg, 1.0 mmol), (S)-(1-naphthyl)ethylamine (0.24 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Purification by column chromatography (pentane:Et_2O 95:5) afforded piperidine ***ent*-559** (148 mg, 47%, dr ~98:2) as a pale orange oil and an inseparable mixture of diastereomers. *It was not possible to calculate dr from the ^{1}H NMR of the crude reaction mixture due to overlapping peaks.*

***Procedure for racemic material*:** Racemic material for HPLC analysis was synthesised using 1-Phenylpentane-1,5-diol **398‡‡‡‡‡‡‡** and (**±**)-(1-naphthyl)ethylamine under an analogous procedure.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.32-8.29 (1H, m, Ar<u>H</u>), 7.81-7.79 (1H, m, Ar<u>H</u>), 7.73-7.66 (3H, m, Ar<u>H</u>), 7.49-7.31 (7H, m, Ar<u>H</u>), 4.47 (1H, q, *J* = 6.8 Hz, NC<u>H</u>(CH_3)Ar), 3.59-3.56 (1H, m, C<u>H-2</u>),

* Diol **413** was synthesised by Dr Roly Armstrong

2.61-2.56 (1H, m, C$\underline{H_2}$-6$_{eq}$), 2.33 (1H, td, *J* = 11.4, 2.8 Hz, C$\underline{H_2}$-6$_{ax}$), 1.82-1.72 (3H, m, C$\underline{H_2}$-3 and C$\underline{H_2}$-4$_a$), 1.52-1.46 (1H, m, C$\underline{H_2}$-5$_a$), 1.42 (3H, d, *J* = 6.8 Hz, C$\underline{H_3}$), 1.36-1.22 (2H, m, C$\underline{H_2}$-4$_b$ and C$\underline{H_2}$-5$_b$).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.2 (Ar$\underline{C}$), 139.7 (Ar$\underline{C}$), 134.1 (Ar$\underline{C}$), 132.7 (Ar$\underline{C}$), 128.6 (2 × Ar$\underline{C}$H), 128.5 (2 × Ar$\underline{C}$H), 128.3 (Ar$\underline{C}$H), 127.51 (Ar$\underline{C}$H), 127.46 (Ar$\underline{C}$H), 126.0 (Ar$\underline{C}$H), 125.6 (Ar$\underline{C}$H), 125.3 (Ar$\underline{C}$H), 125.0 (Ar$\underline{C}$H), 124.7 (Ar$\underline{C}$H), 66.2 ($\underline{C}$H-2), 53.5 (N$\underline{C}$H(CH_3)Ar), 45.6 ($\underline{C}H_2$-6), 36.1 ($\underline{C}H_2$-3), 26.4 ($\underline{C}H_2$-5), 25.6 ($\underline{C}H_2$-4), 9.5 ($\underline{C}H_3$).

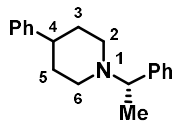
HRMS: ESI+ found $[M+H]^+$ = 316.2059, $C_{23}H_{26}N$ requires 316.2060, Δ = –0.14 ppm.

FTIR (film): ν_{max} = 2932, 2794, 1541, 1491, 1397, 1381, 1339, 1290, 1214, 1173, 798, 749 cm^{-1}.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ **=** +0.9 (*c* = 1.0, $CHCl_3$).

HPLC: Unable to determine er directly, compound not separable by HPLC. Enantiomeric excess at the C5–Ph position was determined by chiral HPLC analysis of the corresponding *N*-Ts compound, **557** (see p232–233 for HPLC conditions and full characterisation data). er = 82:18.

4-phenyl-*N*-(1-phenylethyl)piperidine (567)



Procedure for enantioenriched material: 3-Phenylpentane-1,5-diol **398** (180 mg, 1.0 mmol), (*S*)–α–methylbenzylamine (0.19 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%), $NaHCO_3$ (1.7 mg, 2.0 mol%) and anhydrous toluene (0.5 mL) were subjected to **general procedure A**. Analysis of the crude reaction mixture by ^{1}H NMR indicated a dr of roughly 87:13. Purification by column chromatography (pentane:Et_2O 60:40) afforded piperidine ***ent*-567** (184 mg, 73%, 89:11 dr) as a yellow oil as an inseparable mixture with (*S*)-1-phenyl-N-((*S*)-1-phenylethyl)ethan-1-amine (20% by ^{1}H NMR w.r.t. piperidine ***ent*-567**, *spectral data are consistent with the literature*[219]).

***Procedure for racemic material*:** Racemic material for HPLC analysis was synthesised using (±)–α–methylbenzylamine under an analogous procedure.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35-7.15 (10H, m, ArH), 3.48 (1H, q, *J* = 6.8 Hz, NCH(CH_3)Ph), 3.19 (1H, dtd, *J* = 11.1, 3.5, 2.1 Hz, CH_2-2_{eq}), 2.94 (1H, dtd, *J* = 11.3, 3.4, 2.0, CH_2-6_{eq}), 2.43 (1H, m, CH-4), 2.08 (1H, m, CH_2-2_{ax}), 1.96 (1H, td, *J* = 11.2, 3.4 Hz, CH_2-6_{ax}), 1.85 (2H, m, CH_2-3), 1.75 (2H, m, CH_2-5), 1.42 (3H, d, *J* = 6.5 Hz, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 146.8 (ArC), 144.0 (ArC), 128.5 (2 × ArCH), 128.1 (2 × ArCH), 127.8 (2 × ArCH), 126.9 (2 × ArCH), 126.8 (ArCH), 126.0 (ArCH), 65.1 (NCH(CH_3)Ph), 51.4 (CH_2-2), 51.3 (CH_2-6), 43.1 (CH-4), 33.9 (CH_2-3), 33.8 (CH_2-5), 19.7 (CH_3).

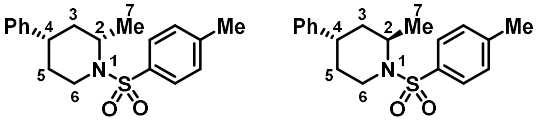
HRMS: ESI+ found $[M+H]^+$ = 266.1904, $C_{19}H_{24}N$ requires 266.1903, Δ = 0.27 ppm.

FTIR (film): ν_{max} = 3026, 2932, 2796, 1493, 1451, 1129, 1022, 756, 699 cm^{-1}.

$[\alpha]_D^{25}$ = +1.2 (*c* = 1.0, $CHCl_3$).

HPLC: *Unable to determine er, compound not separable by HPLC or SFC.*

(2*S*,4*S*)-2-Methyl-4-phenyl-1-tosylpiperidine (568)



568a Major **568b** Minor

(2*S*,4*S*)-*N*-Benzyl-2-methyl-4-phenylpiperidine ***ent*-408**[*] (90 mg, 0.34 mmol, 4:1 dr) and 10% wt/wt palladium on carbon (36.1 mg, 10 mol% Pd) were dissolved in ethanol (12 mL). The reaction mixture was heated at 55 °C under a hydrogen atmosphere with vigorous stirring for 2 hours. The reaction mixture was cooled to room temperature and filtered through a pad of Celite® (eluting with 100 mL EtOAc). The filtrate was concentrated *in vacuo*. The residue (60 mg, 0.34 mmol) was dissolved in pyridine (1.4 mL) before addition of tosyl chloride (81 mg, 0.43 mmol) and 4-(dimethylamino)pyridine (4.2 mg, 10 mol%). The resulting solution was stirred at rt for 16 hours before concentration *in vacuo*. The residue was redissolved in CH_2Cl_2 and washed with 2M HCl (3

[*] Piperidine ***ent*-408** was synthesised by Kieran Paterson

× 10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (pentane:Et_2O 80:20) afforded piperidine ***ent*-568** (16.1 mg, 14%, 2:1 dr, >99:1 er) as a colourless oil and an inseparable mixture of diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76-7.72 (2H, m, ArH), 6.35-7.26 (4H, m, ArH), 7.22-7.17 (1H, m, ArH), 7.73-7.08 (2H, m, ArH), 4.06 (1H, dt, *J* = 12.7, 4.7 Hz, CH_2-6_{eq}), 3.09-3.01 (1H, m, CH-2), 2.92-2.80 (1H, m, CH_2-6_{ax}), 2.57-2.42 (1H, m, CH-4), 2.45 (3H, s, $ArCH_3$), 1.98-1.91 (1H, m, CH_2-5_a), 1.85-1.51 (3H, m, CH_2-3 and CH_2-5_b), 1.39 (3H, d, *J* = 6.5 Hz, CH_3-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.0 (ArC), 143.3 (ArC), 136.6 (ArC), 129.74 (2 × ArCH), 128.69 (2 × ArCH), 127.5 (2 × ArCH), 126.8 (2 × ArCH), 126.6 (ArCH), 54.8 (CH_2-2), 47.2 (CH_2-6), 41.8 (CH_2-3), 41.4 (CH-4), 32.4 (CH_2-5), 22.1 (CH_3-7), 21.7 ($ArCH_3$).

Additional signals for the minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.46-4.39 (1H, m, CH-2), 3.90 (1H, dddd, *J* = 13.5, 4.8, 2.4, 1.0 Hz, CH_2-6_{eq}), 3.13 (1H, td, *J* = 13.2, 2.7 Hz CH_2-6_{ax}), 2.92-2.80 (1H, m, CH-4), 2.45 (3H, s, $ArCH_3$), 1.85-1.51 (4H, m, CH_2-3 and CH_2-5), 1.18 (3H, d, *J* = 7.0 Hz, CH_3-7).

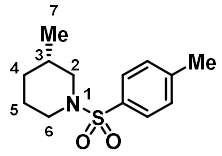
^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.3 (ArC), 143.1 (ArC), 138.5 (ArC), 129.8 (2 × ArCH), 128.7 (2 × ArCH), 127.2 (2 × ArCH), 126.9 (2 × ArCH), 126.6 (ArCH), 48.8 (CH_2-2), 40.4 (CH_2-6), 38.1 (CH_2-3), 36.1 (CH-4), 32.8 (CH_2-5), 21.7 ($ArCH_3$), 15.9 (CH_3-7).

HRMS: ESI+ found $[M+H]^+$ = 330.1522, $C_{19}H_{24}O_2N^{32}S$ requires 330.1522, Δ = –0.11 ppm.

FTIR (film): ν_{max} = 2938, 1600, 1495, 1453, 1335, 1162, 1116, 879, 816, 759, 699 cm^{-1}.

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IB N-5 column (99:5 hexane:IPA, 1.0 mL min^{-1}, 230 nm, room temperature) ~64:36 dr; major diastereomer t_r (minor) = 18.2 min, t_r (major) = 20.4 min, >99:1 er; minor diastereomer, t_r (major) = 19.2 min, t_r (minor) = 21.3 min, >99:1 er.

(S)-3-Methyl-1-tosylpiperidine (580)



N-benzyl-3-methylpiperidine ***ent*-405** (45 mg, 0.24 mmol) and 10% wt/wt palladium on carbon (25 mg, 10 mol% Pd) were dissolved in ethanol (8 mL). The solution and reaction vessel headspace were purged with hydrogen gas for 5 minutes before heating the reaction at 55 °C with vigorous stirring under an atmosphere of hydrogen for 3 hours. The reaction mixture was cooled to room temperature and filtered through a pad of Celite® (eluting with 100 mL EtOAc). To the filtrate was added acetyl chloride (0.03 mL, 0.48 mmol) and the mixture was stirred for 30 minutes before concentration *in vacuo*. Hydrochloride salt **578** was carried forward without further purification.

3-Methylpiperidine hydrochloride **579** (34 mg, 0.25 mmol), tosyl chloride (60 mg, 0.31 mmol) and 4-(dimethylamino)pyridine (3.1 mg, 0.025 mmol) were dissolved in pyridine (1 mL). The resulting solution was stirred at room temperature for 16 hours before concentration *in vacuo*. The residue was redissolved in CH_2Cl_2 and washed with 1M HCl (3 × 20 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (pentane:Et_2O 80:20) afforded piperidine ***ent*-580** (10 mg, 16%) as a colourless solid.

***Procedure for racemic material*:** Racemic material for HPLC analysis was synthesised by Kieran Paterson, using *N*-benzyl-3-methylpiperidine ***rac*-405** and an analogous procedure.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66-7.62 (2H, m, Ar<u>H</u>), 7.33-7.30 (2H, m, Ar<u>H</u>), 3.67-3.58 (2H, m, C<u>H</u>$_2$-2$_{eq}$ and C<u>H</u>$_2$-6$_{eq}$), 2.43 (3H, s, TsC<u>H</u>$_3$), 2.21 (1H, td, *J* = 11.3, 2.8 Hz, C<u>H</u>$_2$-6$_{ax}$), 1.88 (1H, t, *J* = 10.7 Hz, C<u>H</u>$_2$-2$_{ax}$), 1.80-1.57 (4H, m, C<u>H</u>$_2$-5, C<u>H</u>-3 and C<u>H</u>$_2$-4$_a$), 0.87 (3H, d, C<u>H</u>$_3$-7), 0.84-0.76 (1H, m, C<u>H</u>$_2$-4$_b$).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 143.4 (Ar<u>C</u>), 133.5 (Ar<u>C</u>), 129.7 (2 × Ar<u>C</u>H), 127.8 (2 × Ar<u>C</u>H), 53.4 (<u>C</u>H$_2$-2), 46.6 (<u>C</u>H$_2$-6), 32.2 (<u>C</u>H$_2$-4), 30.8 (<u>C</u>H-3), 24.8 (<u>C</u>H$_2$-5), 21.7 (Ts<u>C</u>H$_3$), 19.1 (<u>C</u>H$_3$-7).

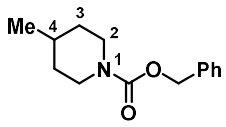
Melting point (CH_2Cl_2) = 96–99 °C.

$[\alpha]_D^{25}$ = –13.4 (*c* = 0.8, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IB-N column (99:1 hexane:IPA, 1.0 mL min^{-1}, 210 nm, room temperature); t_r (major) = 20.10 min, t_r (minor) = 21.52 min; 74:26 er.

The data are consistent with the literature.[217]

Benzyl 4-methylpiperidine-1-carboxylate (584)



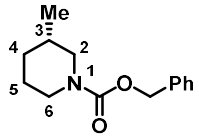
To a solution of *N*-benzyl-4-methylpiperidine **401** (50 mg, 0.26 mmol) in toluene (0.5 mL) was added benzyl chloroformate (0.06 mL, 0.40 mmol). The vial was sealed, equipped with an argon balloon and stirred at 80 °C for 2 hours. After this time, the reaction was cooled to room temperature and a further portion of benzyl chloroformate (0.03 mL, 0.20 mmol) added. After stirring at 80 °C for a further 2 hours, the reaction mixture was transferred directly onto a silica column. Purification by column chromatography afforded piperidine **584** (59 mg, 97%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39-7.29 (5H, m, Ar<u>H</u>), 5.12 (2H, s, OC<u>H_2</u>Ph), 4.20-4.08 (2H, m, 2 × C<u>H_2-2$_a$</u>), 2.83-2.69 (2H, m, 2 × C<u>H_2-2$_b$</u>), 1.67-1.57 (2H, m, 2 × C<u>H_2-3$_a$</u>), 1.57-1.46 (1H, m, C<u>H-4</u>), 1.12-1.08 (2H, m, 2 × C<u>H_2-3$_b$</u>), 0.94 (3H, d, *J* = 6.5 Hz, C<u>H_3</u>).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.4 (<u>C</u>=O), 137.1 (Ar<u>C</u>), 128.6 (2 × Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 127.9 (2 × Ar<u>C</u>H), 67.0 (O<u>C</u>H_2), 44.4 (2 × <u>C</u>H_2-2), 34.1 (2 × <u>C</u>H_2-3), 31.0 (<u>C</u>-4), 22.0 (<u>C</u>H_3).

The data are consistent with the literature.[218]

Benzyl (*S*)-3-methylpiperidine-1-carboxylate (585)



Procedure for enantioenriched material: (*S*)-1-Benzyl-3-methylpiperidine ***ent*-405** (26 mg, 0.14 mmol) and benzyl chloroformate (3 M in toluene, 0.5 mL, 1.5 mmol) were subjected to **general procedure C**. Purification by column chromatography (75:25 pentane:Et_2O) afforded piperidine ***ent*-585** (27 mg, 82%, 88:12 er) as a colourless oil.

Procedure for racemic material: To a suspension of K_2CO_3 (0.41 g, 1.2 mmol) in anhydrous THF (5 mL) was added 3-methylpiperidine (99 mg, 1.0 mmol), followed by benzyl chloroformate (0.17 mL, 1.2 mmol). The reaction mixture was stirred at room temperature for 1 hour before addition of water (1 mL). After stirring for a further hour, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (pentane:Et_2O 80:20) afforded piperidine ***rac*-585** (231 mg, 99%) as a colourless oil.

^{1}H NMR (500 MHz, d_8-toluene, 363 K) δ = 5.11-5.06 (2H, m, OCH_2Ph), 3.97-3.92 (2H, m, CH_2-2_{eq} and CH_2-6_{eq}), 2.55 (1H, ddd, *J* = 13.1, 11.2, 3.5 Hz, CH_2-6_{ax}), 2.25 (1H, dd, *J* = 13.0, 10.1 Hz, CH_2-2_{ax}), 1.45-1.41 (1H, m, CH_2-4_a), 1.37-1.16 (3H, m, CH-3, CH_2-5), 0.78-0.70 (1H, m, CH_2-4_b), 0.63 (3H, d, *J* = 6.6 Hz, CH_3). *Signals corresponding to the aromatic protons are obscured by the d_8-toluene solvent signals. The aromatic signals can be clearly observed in the room temperature $CDCl_3$ data below.*

^{13}C NMR (125 MHz, d_8-toluene, 363 K) δ = 155.3 (C=O), 138.3 (ArC), 128.6 (2 × ArCH), 128.3 (2 × ArCH), 128.0 (ArCH), 67.1 (OCH_2Ph), 51.8 (CH_2-2), 44.8 (CH_2-6), 33.4 (CH_2-4), 31.2 (CH-3), 25.4 (CH_2-5), 18.8 (CH_3).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ = 7.36-7.28 (5H, m, ArH), 5.13 (2H, s, OCH_2Ph), 4.10-4.02 (1H, m, CH_2-6_{eq}), 3.99-3.92 (1H, m, CH_2-2_a), 2.76 (1H, td, *J* = 12.9, 3.0 Hz, CH_2-6_{ax}), 2.50-2.36 (1H, m,

C$\underline{H_2}$-2$_b$), 1.82-1.75 (1H, m, C$\underline{H_2}$-4$_a$), 1.66-1.54 (2H, m, C$\underline{H_2}$-5$_a$ and C$\underline{H}$-3), 1.49-1.40 (1H, m, C$\underline{H_2}$-5$_b$) 1.11-1.01 (1H, m, C$\underline{H_2}$-4$_b$), 0.88 (3H, d, *J* = 6.6 Hz, C$\underline{H_3}$).

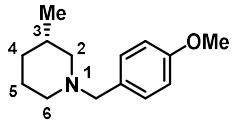
^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ = 155.4 (C=O), 137.2 (ArC), 128.6 (2 × ArCH), 128.0 (ArCH), 127.9 (2 × ArCH), 67.0 (OCH_2Ph), 51.4 (CH_2-2), 44.5 (CH_2-6), 33.1 (CH_2-4), 31.1 (CH-3), 25.5 (CH_2-5), 19.1 (CH_3).

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ **=** +19.1 (*c* = 1.7, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IC column (99:1 hexane:IPA, 0.7 mL min^{-1}, 210 nm, room temperature); t_r (major) = 27.0 min, t_r (minor) = 28.2 min; 88:12 er.

The data are consistent with the literature.[218]

(*S*)-1-(4-Methoxybenzyl)-3-methylpiperidine (587)



(*S*)-2-Methylhexane-1,5-diol ***ent*-570**[*] (118 mg, 1.0 mmol, >99:1 er), *p*-methoxybenzylamine (0.20 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and deionised water (0.5 mL) were subjected to **general procedure B** at 80 °C. Purification by column chromatography (pentane:Et_2O 75:25) afforded piperidine **587** (148 mg, 67%, 72:28 er) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24-7.20 (2H, m, ArH), 6.87-6.83 (2H, m, ArH), 3.80 (3H, s, OCH_3), 3.42 (2H, s, NCH_2Ph), 2.82-2.74 (2H, m, C$\underline{H_2}$-2$_a$ and C$\underline{H_2}$-6$_{eq}$), 1.83 (1H, td, *J* = 11.2, 3.5 Hz, C$\underline{H_2}$-6$_{ax}$), 1.72-1.49 (5H, m, C$\underline{H_2}$-2$_b$, C$\underline{H}$-3, C$\underline{H_2}$-4$_a$, C$\underline{H_2}$-5), 0.89-0.80 (1H, m, C$\underline{H_2}$-4$_b$), 0.83 (3H, d, *J* = 6.4 Hz, C$\underline{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.7 (ArC), 130.8 (ArC), 130.5 (2 × ArCH), 113.6 (2 × ArCH), 63.1 (NCH_2Ph), 62.0 (CH_2-2), 55.4 (OCH_3), 54.0 (CH_2-6), 33.3 (CH_2-4), 31.3 (CH-3), 25.7 (CH_2-5), 19.9 (CH_3).

[*] Diol ***ent*-570** was synthesised by Dr Roly Armstrong

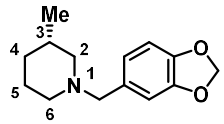
HRMS: ESI+ found $[M+H]^+$ = 220.1696, $C_{14}H_{22}NO$ requires 220.1696, Δ = 0.12 ppm.

FTIR (film): ν_{max} = 2927, 1613, 1511, 1464, 1300, 1243, 1179, 1121, 1038, 830, 815 cm^{-1}.

$[\alpha]_D^{25}$ = +5.2 (*c* = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding *N*-Cbz compound ***ent*-585** (synthesised using **general procedure C**, analytic sample isolated by preparative TLC, for HPLC conditions and full characterisation data, see p239), er = 72:28.

(*S*)-1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-3-methylpiperidine (588)



(*S*)-2-Methylhexane-1,5-diol ***ent*-570**[*] (118 mg, 1.0 mmol, >99:1 er), piperonylamine (0.19 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and deionised water (0.5 mL) were subjected to **general procedure B** at 80 °C. Purification by column chromatography (pentane:Et_2O 50:50) afforded piperidine **588** (68 mg, 29%, 64:36 er) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.85 (1H, t, *J* = 1.0 Hz, ArH), 6.74 (2H, d, *J* = 1.0 Hz, ArH), 5.93 (2H, s, OCH_2O), 3.38 (2H, s, NCH_2Ph), 2.81-2.73 (2H, m, CH_2-2_a and CH_2-6_{eq}), 1.83 (1H, td, *J* = 11.2, 3.4 Hz, CH_2-6_{ax}), 1.72-1.49 (5H, m, CH_2-2_b, CH-3, CH_2-4_a, CH_2-5), 0.89-0.83 (1H, m, CH_2-4_b), 0.83 (3H, d, *J* = 6.4 Hz, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 147.6 (ArC), 146.5 (ArC), 132.8 (ArC), 122.3 (ArCH), 109.7 (ArCH), 107.9 (ArCH), 100.9 (OCH_2O), 63.5 (NCH_2Ph), 62.0 (CH_2-2), 54.0 (CH_2-6), 33.2 (CH_2-4), 31.3 (CH-3), 25.7 (CH_2-5), 19.9 (CH_3).

HRMS: ESI+ found $[M+H]^+$ = 234.1488, $C_{14}H_{20}NO_2$ requires 234.1489, Δ = –0.03 ppm.

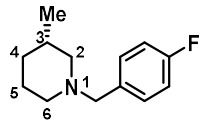
FTIR (film): ν_{max} = 2927, 2762, 1502, 1488, 1440, 1369, 1339, 1240, 1181, 1159, 1112, 1039, 932 cm^{-1}.

[*] Diol ***ent*-570** was synthesised by Dr Roly Armstrong

$[\alpha]_D^{25}$ **= +**3.9 (*c* = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding *N*-Cbz compound ***ent*-585** (synthesised using **general procedure C**, analytic sample isolated by preparative TLC, for HPLC conditions and full characterisation data, see p239), er = 64:36.

(*S*)-1-(4-Fluorobenzyl)-3-methylpiperidine (589)



(*S*)-2-Methylhexane-1,5-diol ***ent*-570**[*] (118 mg, 1.0 mmol, >99:1 er), 4-fluorobenzylnitrile (0.17 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and deionised water (0.5 mL) were subjected to **general procedure B** at 80 °C. Purification by column chromatography (pentane:Et_2O 90:10) afforded piperidine **589** (150 mg, 72%, 90:10 er) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29-7.21 (2H, m, ArH), 7.01-6.96 (2H, m, ArH), 3.43 (2H, s, NCH_2Ph), 2.79-2.71 (2H, m, CH_2-2_a and CH_2-6_{eq}), 1.84 (1H, td, *J* = 11.2, 3.3 Hz, CH_2-6_{ax}), 1.72-1.49 (5H, m, CH_2-2_b, CH-3, CH_2-4_a, CH_2-5), 0.91-0.82 (1H, m, CH_2-4_b), 0.84 (3H, d, *J* = 6.4 Hz, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.0 (d, *J* = 244.0 Hz, ArCF), 134.6 (d, *J* = 3.2 Hz, ArC), 130.7 (d, *J* = 7.9 Hz, 2 × ArCH), 115.0 (d, *J* = 20.8 Hz, 2 × ArCH), 62.9 (NCH_2Ar), 62.0 (CH_2-2), 54.1 (CH_2-6), 33.2 (CH_2-4), 31.3 (CH-3), 25.7 (CH_2-5), 19.9 (CH_3).

^{19}F NMR (400 MHz, $CDCl_3$) δ = –116.40 (ddd, *J* = 14.4, 9.0, 5.5 Hz, ArF).

HRMS: ESI+ found $[M+H]^+$ = 208.1497, $C_{13}H_{19}FN$ requires 208.1496, Δ = 0.48 ppm.

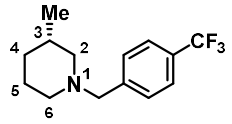
FTIR (film): ν_{max} = 2928, 1604, 1508, 1465, 1458, 1356, 1293, 1221, 1154, 1120, 1091, 1078, 1039, 844, 822 cm^{-1}.

$[\alpha]_D^{25}$ **=** +8.7 (*c* = 1.0, $CHCl_3$).

[*] Diol ***ent*-570** was synthesised by Dr Roly Armstrong

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding *N*-Cbz compound ***ent*-585** (synthesised using **general procedure C**, analytic sample isolated by preparative TLC, for HPLC conditions and full characterisation data, see p239), er = 90:10.

(*S*)-3-Methyl-1-(4-(trifluoromethyl)benzyl)piperidine (590)



(*S*)-2-Methylhexane-1,5-diol ***ent*-570**[*] (118 mg, 1.0 mmol, >99:1 er), *para*-(trifluoromethyl)benzylamine (0.21 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and deionised water (0.5 mL) were subjected to **general procedure B** at 80 °C. Purification by column chromatography (pentane:Et_2O 90:10) afforded piperidine **590** (166 mg, 64%, 91:9 er) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57-7.55 (2H, m, Ar$\underline{H}$), 7.45-7.43 (2H, m, Ar$\underline{H}$), 3.51 (2H, s, NC$\underline{H_2}$Ph), 2.79-2.71 (2H, m, C$\underline{H_2}$-2$_a$ and C$\underline{H_2}$-6$_{eq}$), 1.89 (1H, td, *J* = 11.1, 3.4 Hz, C$\underline{H_2}$-6$_{ax}$), 1.73-1.51 (5H, m, C$\underline{H_2}$-2$_b$, C$\underline{H}$-3, C$\underline{H_2}$-4$_a$, C$\underline{H_2}$-5), 0.92-0.84 (1H, m, C$\underline{H_2}$-4$_b$), 0.84 (3H, d, *J* = 6.3 Hz, C$\underline{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.4 (Ar$\underline{C}$), 129.3 (4 × Ar$\underline{C}$H), 125.2 (q, *J* = 3.8 Hz, Ar$\underline{C}CF_3$), 124.5 (q, *J* = 272.1 Hz, $\underline{C}F_3$), 63.2 (N$\underline{C}H_2$Ph), 62.2 ($\underline{C}H_2$-2), 54.2 ($\underline{C}H_2$-6), 33.1 ($\underline{C}H_2$-4), 31.3 ($\underline{C}$H-3), 25.7 ($\underline{C}H_2$-5), 19.8 ($\underline{C}H_3$).

^{19}F NMR (400 MHz, $CDCl_3$) δ = –62.3 (s, C$\underline{F_3}$).

HRMS: ESI+ found $[M+H]^+$ = 258.1463, $C_{14}H_{19}F_3N$ requires 258.1464, Δ = –0.31 ppm.

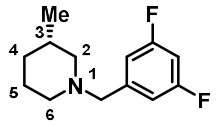
FTIR (film): ν_{max} = 2930, 1323, 1162, 1123, 1103, 1066, 1019, 836, 819 cm^{-1}.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ **= +**6.7 (*c* = 1.0, $CHCl_3$).

[*] Diol ***ent*-570** was synthesised by Dr Roly Armstrong

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding *N*-Cbz compound ***ent*-585** (synthesised using **general procedure C**, analytic sample isolated by preparative TLC, for HPLC conditions and full characterisation data, see p239), er = 91:9.

(*S*)-1-(3,5-Difluorobenzyl)-3-methylpiperidine (591)



(*S*)-2-Methylhexane-1,5-diol ***ent*-570**[*] (118 mg, 1.0 mmol, >99:1 er), 3,5-difluorobenzylamine (0.18 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and deionised water (0.5 mL) were subjected to **general procedure B** at 80 °C. Purification by column chromatography (pentane:Et_2O 95:5) afforded piperidine **591** (152 mg, 67%, 93:7 er) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.90-6.84 (2H, m, ArH), 6.66 (1H, tt, *J* = 9.0, 2.4 Hz, ArH), 3.42 (2H, s, NCH_2Ph), 2.77-2.69 (2H, m, CH_2-2_a and CH_2-6_{eq}), 1.89 (1H, td, *J* = 11.1, 3.4 Hz, CH_2-6_{ax}), 1.72-1.52 (5H, m, CH_2-2_b, CH-3, CH_2-4_a, CH_2-5), 0.92-0.82 (1H, m, CH_2-4_b), 0.85 (3H, d, *J* = 6.2 Hz, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.1 (dd, *J* = 247.8, 12.7 Hz, 2 × ArCF), 142.7 (t, *J* = 8.7 Hz, ArC), 110.5-110.3 (m, 2 × ArCH), 101.2 (t, *J* = 25.6 Hz, ArCH), 61.8 (t, *J* = 1.9 Hz, NCH_2Ar), 61.1 (CH_2-2), 53.2 (CH_2-6), 32.0 (CH_2-4), 30.3 (CH-3), 24.7 (CH_2-5), 18.8 (CH_3).

^{19}F NMR (400 MHz, $CDCl_3$) δ = –110.8 - –110.9 (m, 2 × ArF).

HRMS: ESI+ found $[M+H]^+$ = 226.1403, $C_{13}H_{18}F_2N$ requires 226.1402, Δ = 0.61 ppm.

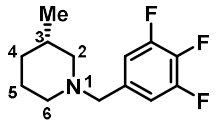
FTIR (film): ν_{max} = 2930, 1626, 1597, 1458, 1438, 1346, 1317, 1115, 976, 965, 846 cm^{-1}.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ **= +**11.5 (*c* = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding *N*-Cbz compound ***ent*-585** (synthesised using **general procedure C**, analytic sample isolated by preparative TLC, for HPLC conditions and full characterisation data, see p239), er = 93:7.

[*] Diol ***ent*-570** was synthesised by Dr Roly Armstrong

(*S*)-3-Methyl-1-(3,4,5-trifluorobenzyl)piperidine (592)



(*S*)-2-Methylhexane-1,5-diol ***ent*-570**[*] (118 mg, 1.0 mmol, >99:1 er), 3,4,5-trifluorobenzylnitrile (0.19 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and deionised water (0.5 mL) were subjected to **general procedure B** at 80 °C. Purification by column chromatography (pentane:Et_2O 90:10) afforded piperidine **592** (137 mg, 56%, 90:10 er) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.00-6.92 (2H, m, ArH), 3.47 (2H, s, NCH_2Ph), 2.75-2.66 (2H, m, CH_2-2_a and CH_2-6_{eq}), 1.88 (1H, td, *J* = 11.1, 3.2 Hz, CH_2-6_{ax}), 1.73-1.49 (5H, m, CH_2-2_b, CH-3, CH_2-4_a, CH_2-5), 0.92-0.83 (1H, m, CH_2-4_b), 0.84 (3H, d, *J* = 6.3 Hz, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.2 (ddd, *J* = 249.4, 10.1, 4.0 Hz, 2 × ArCF), 138.6 (dt, *J* = 249.6, 15.4 Hz, ArCF), 135.9 (td, *J* = 6.8, 4.6 Hz, ArC), 112.4 (d, *J* = 20.8 Hz, 2 × ArCH), 62.4 (NCH_2Ar), 62.0 (CH_2-2), 54.1 (CH_2-6), 33.0 (CH_2-4), 31.3 (CH-3), 25.6 (CH_2-5), 19.8 (CH_3).

^{19}F NMR (400 MHz, $CDCl_3$) δ = –135.26 - –135.39 (m, ArF), –163.27 (tt, *J* 20.6, 6.7 Hz, ArF).

HRMS: ESI+ found $[M+H]^+$ = 244.1308, $C_{13}H_{17}F_3N$ requires 244.1308, Δ = 0.34 ppm.

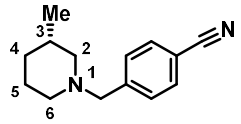
FTIR (film): ν_{max} = 2930, 1621, 1526, 1445, 1372, 1360, 1350, 1231, 1131, 1122, 1039, 980 cm^{-1}.

$[\alpha]_D^{25}$ **=** +10.4 (*c* = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding *N*-Cbz compound ***ent*-585** (synthesised using **general procedure C**, analytic sample isolated by preparative TLC, for HPLC conditions and full characterisation data, see p239), er = 90:10.

[*] Diol ***ent*-570** was synthesised by Dr Roly Armstrong

(*S*)-4-((3-Methylpiperidin-1-yl)methyl)benzonitrile (593)



(*S*)-2-Methylhexane-1,5-diol ***ent*-570**[*] (118 mg, 1.0 mmol, >99:1 er), 4-(aminomethyl)benzylnitrile (198 mg, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and deionised water (0.5 mL) were subjected to **general procedure B** at 80 °C. Purification by column chromatography (pentane:Et_2O 95:5) afforded piperidine **593** (87 mg, 41%, 64:36 er) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61-7.58 (2H, m, ArH), 7.45-7.42 (2H, m, ArH), 3.49 (2H, s, NCH_2Ph), 2.75-2.67 (2H, m, CH_2-2$_a$ and CH_2-6$_{eq}$), 1.90 (1H, td, *J* = 11.1, 3.2 Hz, CH_2-6$_{ax}$), 1.73-1.51 (5H, m, CH_2-2$_b$, CH-3, CH_2-4$_a$, CH_2-5), 0.94-0.82 (1H, m, CH_2-4$_b$), 0.84 (3H, d, *J* = 6.2 Hz, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.2 (ArC), 132.2 (2 × ArCH), 129.7 (2 × ArCH), 119.3 (C≡N), 110.8 (ArC), 63.2 (NCH_2Ar), 62.3 (CH_2-2), 54.4 (CH_2-6), 33.1 (CH_2-4), 31.4 (CH-3), 25.7 (CH_2-5), 19.9 (CH_3).

HRMS: ESI+ found $[M+H]^+$ = 215.1543, $C_{14}H_{19}N_2$ requires 215.1543 Δ = 0.31 ppm.

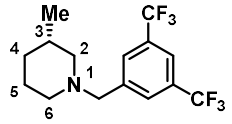
FTIR (film): ν_{max} = 2928, 2794, 2758, 2228, 1608, 1505, 1465, 1437, 1414, 1371, 1299, 1160, 1122, 1079, 1041, 1020, 976 cm^{-1}.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ **=** +5.7 (*c* = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding *N*-Cbz compound ***ent*-585** (synthesised using **general procedure C**, analytic sample isolated by preparative TLC, for HPLC conditions and full characterisation data, see p239), er = 64:36.

[*] Diol ***ent*-570** was synthesised by Dr Roly Armstrong

(*S*)-1-(3,5-Bis(trifluoromethyl)benzyl)-3-methylpiperidine (594)



(*S*)-2-Methylhexane-1,5-diol ***ent*-570**[*] (118 mg, 1.0 mmol, >99:1 er), 3,5-bis(trifluoromethyl)benzylamine (428 mg, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and deionised water (0.5 mL) were subjected to **general procedure B** at 80 °C. Purification by column chromatography (pentane:Et_2O 95:5) afforded piperidine **594** (11 mg, 3%, 65:35 er) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80-7.79 (2H, m, ArH), 7.76-7.74 (1H, m, ArH), 3.55 (2H, s, NCH_2Ph), 2.76-2.68 (2H, m, CH_2-2$_a$ and CH_2-6$_{eq}$), 1.94 (1H, td, *J* = 11.1, 3.3 Hz, CH_2-6$_{ax}$), 1.74-1.55 (5H, m, CH_2-2$_b$, CH-3, CH_2-4$_a$, CH_2-5), 0.95-0.84 (1H, m, CH_2-4$_b$), 0.86 (3H, d, *J* = 6.0 Hz, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 142.2 (ArC), 131.5 (q, *J* = 33.1 Hz, 2 × Ar*C*-CF_3), 129.0-128.9 (m, 2 × Ar*C*H), 124.3 (q, *J* = 270.9 Hz, 2 × *C*F_3), 121.0 (hept., *J* = 3.7 Hz, Ar*C*H), 62.6 (NCH_2Ar), 62.1 (*C*H_2-2), 54.2 (*C*H_2-6), 32.9 (*C*H_2-4), 31.2 (*C*H-3), 25.5 (*C*H_2-5), 19.7 (*C*H_3).

^{19}F NMR (400 MHz, $CDCl_3$) δ = –62.9 (s, 2 × CF_3).

HRMS: ESI+ found $[M+H]^+$ = 326.1338, $C_{15}H_{18}F_6N$ requires 326.1338, Δ = – 0.02 ppm.

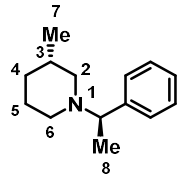
FTIR (film): ν_{max} = 2933, 1376, 1345, 1277, 1172 (br.), 1131 (br.), 896, 843, 707, 683 cm^{-1}.

$[\alpha]_D^{25}$ = +2.9 (*c* = 0.7, $CHCl_3$).

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding *N*-Cbz compound ***ent*-585** (synthesised using **general procedure C**, analytic sample isolated by preparative TLC, for HPLC conditions and full characterisation data, see p239), er = 65:35.

[*] Diol ***ent*-570** was synthesised by Dr Roly Armstrong

(*S*)-3-Methyl-1-((*R*)-1-phenylethyl)piperidine (596)



(*S*)-2-Methylhexane-1,5-diol ***ent*-570**[*] (118 mg, 1.0 mmol, >99:1 er), (*R*)-α-methylbenzylamine (0.19 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and deionised water (0.5 mL) were subjected to **general procedure B** at 80 °C. Analysis of the crude reaction mixture by ^{1}H NMR indicated a dr of 83:17. Purification by column chromatography (pentane:Et_2O 80:20) afforded piperidine **596** (161 mg, 79%, 76:24 er, 85:15 dr) as a colourless oil and as a mixture with (*R*)-bis((*R*)-1-phenylethyl)amine (5% by ^{1}H NMR w.r.t piperidine **596**, *spectral data are consistent with the literature*[219]).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35-7.21 (5H, m, ArH), 3.41 (1H, q, *J* = 6.8 Hz, NCH(CH_3)Ph), 2.98-2.88 (1H, m, CH_2-6$_{eq}$), 2.76-2.70 (1H, m, CH_2-2$_{eq}$), 1.85 (1H, td, *J* = 11.1, 3.3 Hz, CH_2-6$_{ax}$), 1.70-1.51 (4H, m, CH-3, CH_2-4$_a$, CH_2-5), 1.45 (1H, t, *J* = 10.6 Hz, CH_2-2$_{ax}$), 1.37 (3H, d, *J* = 7.0 Hz, CH_3-8), 0.87-0.74 (1H, m, CH_2-4$_b$), 0.78 (3H, d, *J* = 6.4 Hz, CH_3-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.1 (ArC), 128.1 (2 × ArCH), 127.9 (2 × ArCH), 126.8 (ArCH), 65.0 (NCH(CH_3)Ph), 59.0 (CH_2-2), 51.09 (CH_2-6), 33.44 (CH_2-4), 31.5 (CH-3), 26.02 (CH_2-5), 20.04 (CH_3-7), 19.50 (CH_3-8).

Additional signals for the minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.50 (1H, q, *J* = 6.8 Hz, NCH(CH_3)Ph), 2.98-2.88 (1H, m, CH_2-2$_a$), 2.76-2.70 (1H, m, CH_2-6$_{eq}$), 1.76 (1H, td, *J* = 11.3, 3.0 Hz, CH_2-6$_{ax}$), 1.27 (3H, d, *J* = 6.7 Hz, CH_3-8), 0.68 (3H, d, *J* = 6.3 Hz, CH_3-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 65.1 (NCH(CH_3)Ph), 59.2 (CH_2-2), 51.06 (CH_2-6), 33.38 (CH_2-4), 25.97 (CH_2-5), 19.47 (CH_3-8), 20.01 (CH_3-7).

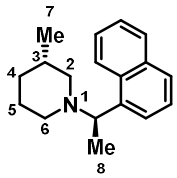
HRMS: ESI+ found $[M+H]^+$ = 204.1748, $C_{14}H_{22}N$ requires 204.1747, Δ = 0.78 ppm.

[*] Diol ***ent*-570** was synthesised by Dr Roly Armstrong

FTIR (film): ν_{max} = 2927, 1492, 1453, 1373, 1125, 1081, 760, 700 cm^{-1}.

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding *N*-Cbz compound ***ent*-585** (synthesised using **general procedure C**, analytic sample isolated by preparative TLC, for HPLC conditions and full characterisation data, see p239), er = 76:24.

(*S*)-3-Methyl-1-((*R*)-1-(naphthalen-1-yl)ethyl)piperidine (597)



(*S*)-2-Methylhexane-1,5-diol ***ent*-570**[*] (118 mg, 1.0 mmol, >99:1 er), (*R*)-(1-naphthyl)ethylamine (0.22 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and deionised water (0.5 mL) were subjected to **general procedure B** at 80 °C. NMR analysis of the crude reaction mixture indicated the presence of two diastereomers in 73:27 dr. Purification by column chromatography (pentane:Et_2O 95:5) afforded piperidine **597** (206 mg, 81%, 84:16 er, 57:43 dr) as a colourless oil and an inseparable mixture of diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.50-8.45 (1H, m, ArH), 7.87-7.85 (1H, m, ArH), 7.76-7.73 (1H, m, ArH), 7.61-7.58 (1H, m, ArH), 7.59-7.42 (3H, m, ArH), 4.14-4.04 (1H, m, NCH(CH_3)Ar), 3.09-3.03 (1H, m, CH_2-6_a), 2.77-2.73 (1H, m, CH_2-2_a), 1.99-1.92 (1H, m, CH_2-6_b), 1.71-1.51 (5H, m, CH_2-2_b, H_2-4_a, CH_2-5_{eq}, CH_2-5_{ax} and CH-3), 1.46 (3H, d, *J* = 6.7 Hz, CH_3-8), 0.87-0.83 (1H, m, CH_2-4_b), 0.74 (3H, d, *J* = 6.0 Hz, CH_3-7).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 141.4 (ArC), 134.2 (ArC), 132.0 (ArC), 128.78 (ArCH), 127.18 (ArCH), 125.53 (ArCH), 125.4 (ArCH), 125.3 (ArCH), 124.6 (ArCH), 124.56 (ArCH), 61.7 (NCH(CH_3)Ar), 60.7 (CH_2-2), 50.1 (CH_2-6), 33.5 (CH_2-4), 31.5 (CH-3), 26.1 (CH_2-5), 19.93 (CH_3-7), 18.8 (CH_3-8).

[*] Diol ***ent*-570** was synthesised by Dr Roly Armstrong

Additional signals for the minor diastereomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.50-8.45 (1H, m, ArH), 7.87-7.85 (1H, m, ArH), 7.76-7.73 (1H, m, ArH), 7.61-7.58 (1H, m, ArH), 7.59-7.42 (3H, m, ArH), 4.14-4.04 (1H, m, NCH(CH_3)Ar), 3.09-3.03 (1H, m, CH_2-6_a), 2.77-2.73 (1H, m, CH_2-2_a), 1.99-1.92 (1H, m, CH_2-2_b), 1.71-1.51 (5H, m, CH_2-6_b, CH_2-4_a, CH_2-5 and CH-3), 1.47 (3H, d, *J* = 6.7 Hz, CH_3-8), 0.89 (3H, d, *J* = 5.9 Hz, CH_3-7), 0.87-0.83 (1H, m, CH_2-4_b).

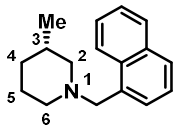
^{13}C NMR (126 MHz, $CDCl_3$) δ = 141.4 (ArC), 134.2 (ArC), 132.0 (ArC), 128.76 (ArCH), 127.19 (ArCH), 125.51 (ArCH), 125.4 (ArCH), 125.3 (ArCH), 124.6 (ArCH), 124.53 (ArCH), 61.7 (NCH(CH_3)Ar), 58.2 (CH_2-6), 52.8 (CH_2-2), 33.4 (CH_2-4), 31.5 (CH-3), 26.0 (CH_2-5), 20.04 (CH_3-7), 18.6 (CH_3-8).

HRMS: ESI+ found $[M+H]^+$ = 254.1904, $C_{18}H_{24}N$ requires 254.1903, Δ = 0.47 ppm.

FTIR (film): ν_{max} = 2926, 2792, 1458, 1373, 1195, 1123, 1079, 972, 799, 776 cm^{-1}.

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding *N*-Cbz compound ***ent*-585** (synthesised using **general procedure C**, analytic sample isolated by preparative TLC, for HPLC conditions and full characterisation data, see p239), er = 84:16.

(*S*)-3-Methyl-1-(naphthalen-1-ylmethyl)piperidine (598)



(*S*)-2-Methylhexane-1,5-diol ***ent*-570**[*] (118 mg, 1.0 mmol, >99:1 er), naphthalene-1-ylmethanamine (0.22 mL, 1.5 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and deionised water (0.5 mL) were subjected to **general procedure B** at 80 °C. Purification by column chromatography (pentane:Et_2O 90:10) afforded piperidine **598** (82 mg, 34%, 73:27 er) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.35-8.32 (1H, m, ArH), 7.86-7.84 (1H, m, ArH), 7.77 (1H, dt, *J* = 7.9, 1.1 Hz, ArH), 7.54-7.39 (4H, m, ArH), 3.86 (2H, d, *J* = 1.6 Hz, NCH_2Ph), 2.89-2.83 (2H, m, CH_2-2_a and CH_2-6_{eq}), 1.97 (1H, td, *J* = 11.1, 3.4 Hz, CH_2-6_{ax}), 1.73-1.49 (5H, m, CH_2-2_b, CH-3, CH_2-4_a, CH_2-5), 0.96-0.82 (1H, m, CH_2-4_b), 0.85 (3H, d, *J* = 6.1 Hz, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 135.0 (ArC), 134.0 (ArC), 132.8 (ArC), 128.5 (ArCH), 127.7 (ArCH), 127.2 (ArCH), 125.7 (ArCH), 125.6 (ArCH), 125.3 (ArCH), 125.0 (ArCH), 62.5 (NCH_2Ph), 61.8 (CH_2-2), 54.5 (CH_2-6), 33.3 (CH_2-4), 31.3 (CH-3), 25.8 (CH_2-5), 19.9 (CH_3).

HRMS: ESI+ found $[M+H]^+$ = 240.1746, $C_{17}H_{22}N$ requires 240.1747, Δ = 0.48 ppm.

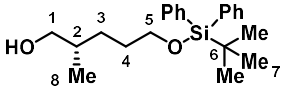
FTIR (film): ν_{max} = 2926, 2801, 2756, 1509, 1465, 1457, 1370, 1341, 1168, 1126, 1117, 975, 791, 783, 772 cm^{-1}.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ **= +**10.1 (*c* = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding *N*-Cbz compound ***ent*-585** (synthesised using **general procedure C**, analytic sample isolated by preparative TLC, for HPLC conditions and full characterisation data, see p239), er = 73:27.

[*] Diol ***ent*-570** was synthesised by Dr Roly Armstrong

(*S*)-5-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpentan-1-ol (615)



Alcohol **615** was prepared according to a modified literature procedure.[220] To a solution of (*S*)-2-methylpentane-1,5-diol ***ent*-570**[*] (5.00 g, 42.3 mmol, >99:1 er), imidazole (3.17 g, 46.5 mmol) and 4-dimethylaminopyridine (0.53 g, 4.2 mmol), in anhydrous CH_2Cl_2 (420 mL) at 0 °C was added *tert*-butyl(chloro)diphenylsilane (12.1 mL, 46.5 mmol). The reaction mixture was warmed to room temperature and stirred for 16 hours. The reaction was quenched with saturated aqueous NH_4Cl solution (300 mL). The layers were separated, and the aqueous layer extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (3 ×, pentane:Et_2O 80:20), afforded alcohol **615** (3.97 g, 26%) as a viscous, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69-7.66 (4H, m, Ar<u>H</u>), 7.45-7.36 (6H, m, Ar<u>H</u>), 3.67 (2H, t, *J* = 6.4 Hz, C<u>H$_2$-5</u>), 3.49 (1H, dt, *J* = 10.9, 5.5 Hz, C<u>H$_2$-1$_a$</u>), 3.41 (1H, dt, *J* = 10.8, 5.8 Hz, C<u>H$_2$-1$_b$</u>), 1.70-1.42 (4H, m, C<u>H</u>-2, C<u>H$_2$-3$_a$</u>), and C<u>H$_2$-4</u>), 1.36-1.30 (1H, m, O<u>H</u>), 1.24-1.14 (1H, m, C<u>H$_2$-3$_b$</u>), 1.06 (9H, s, 3 × C<u>H$_3$-7</u>), 0.91 (3H, d, *J* = 6.7 Hz, C<u>H$_3$-8</u>).

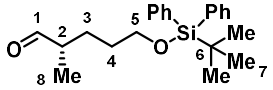
^{13}C NMR (101 MHz, $CDCl_3$) δ = 135.7 (4 × Ar<u>C</u>H), 134.2 (2 × Ar<u>C</u>), 129.7 (2 × Ar<u>C</u>H), 127.7 (4 × Ar<u>C</u>H), 68.4 (<u>C</u>H$_2$-1), 64.3 (<u>C</u>H$_2$-5), 35.6 (<u>C</u>H-2), 30.1 (<u>C</u>H$_2$-4), 29.4 (<u>C</u>H$_2$-3), 27.0 (<u>C</u>H$_3$-8), 19.4 (3 × <u>C</u>H$_3$-7), 16.7 (<u>C</u>-6).

$[\alpha]_D^{25}$ **=** –4.9 (*c* = 2.0, CH_3Cl).

The data are consistent with the literature.[190]

[*] Diol ***ent*-570** was synthesised by Dr Roly Armstrong

(*S*)-5-((*tert*-Butyldiphenylsilyl)oxy)-2-methylpentanal (616)

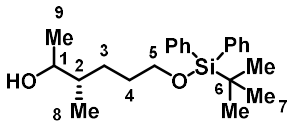


To a solution of oxaloyl chloride (1.16 mL, 13.7 mmol) in anhydrous CH_2Cl_2 (200 mL) at –78 °C was slowly added dimethyl sulfoxide (1.93 mL, 27.3 mmol) in anhydrous CH_2Cl_2 (10 mL). The resulting mixture was stirred for 30 minutes at –78 °C before dropwise addition of alcohol **615** (3.25 g, 9.1 mmol) in anhydrous CH_2Cl_2 (50 mL). The reaction mixture was stirred for 30 minutes at –78 °C before dropwise addition of trimethylamine (6.30 mL, 45.5 mmol). After stirring for a further 1 hour at –78 °C, the reaction mixture was warmed to 0 °C and quenched with saturated aqueous NH_4Cl (200 mL). The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Aldehyde **616** was carried forward to the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.60 (1H, d, *J* = 1.9 Hz, C<u>H</u>-1), 7.67-7.64 (4H, m, Ar<u>H</u>), 7.45-7.35 (6H, m, Ar<u>H</u>), 3.67 (2H, t, *J* = 6.2 Hz, C<u>H$_2$</u>-5), 2.36-2.30 (1H, m, C<u>H</u>-2), 1.85-1.76 (1H, m, C<u>H$_2$</u>-3$_a$), 1.64-1.54 (2H, m, C<u>H$_2$</u>-4), 1.50-1.39 (1H, m, C<u>H$_2$</u>-3$_b$), 1.08 (3H, d, *J* = 7.0 Hz, C<u>H$_3$</u>-8), 1.05 (9H, s, 3 × C<u>H$_3$</u>-7).

The data are consistent with the literature.[221]

(*3S*)-6-((*tert*-Butyldiphenylsilyl)oxy)-3-methylhexan-2-ol (617)



A solution of aldehyde **616** (3.55 g, 9.1 mmol) in anhydrous THF (50 mL) was cooled to 0 °C before dropwise addition of methyl magnesium bromide (6.1 mL, 18.2 mmol, 3M in Et_2O). The reaction mixture was warmed to room temperature and stirred for a further 16 hours. After this time, the reaction mixture was cooled to 0 °C and quenched with saturated aqueous NH_4Cl solution (100 mL). The mixture was concentrated *in vacuo* before being diluted with Et_2O (100 mL). The layers were separated, and the aqueous layer washed with Et_2O (3 × 100 mL). The organic layers

were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (75:25 pentane:Et_2O) afforded alcohol **617** (2.45 g, 73% over two steps) as a pale-yellow oil and an inseparable mixture of diastereomers. *It was not possible to accurately determine the dr from the crude reaction mixture or purified compound due to overlapping peaks in the ^{1}H NMR spectrum.*

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69-7.66 (4H, m, ArH), 7.45-7.36 (6H, m, ArH), 3.67 (3H, m, CH-1 and CH_2-5), 1.71-1.38 (5H, m, CH-2, CH_2-3 and CH_2-4), 1.14 (3H, dd, *J* = 6.4, 1.0 Hz, CH_3-8), 1.06 (9H, s, 3 × CH_3-7), 0.89-0.85 (3H, m, CH_3-9).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.7 (4 × ArCH), 134.2 (2 × ArC), 129.7 (2 × ArCH), 127.7 (4 × ArCH), 71.5 (CH-1), 64.3 (CH_2-5), 39.7 (CH-2), 30.4 (CH_2-4), 28.9 (CH_2-3), 27.0 (3 × CH_3-7), 20.5 (C-6), 19.4 (CH_3-8), 14.4 (CH_3-9).

Additional signals for the other diastereomer

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.12 (3H, dd, *J* = 6.3, 1.1 Hz, CH_3-8), 1.06 (9H, s, 3 × CH_3-7), 0.89-0.85 (3H, m, CH_3-9).

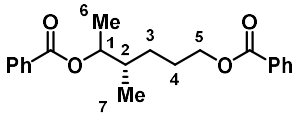
^{13}C NMR (101 MHz, $CDCl_3$) δ = 71.8 (CH-1), 39.9 (CH-2), 30.3 (CH_2-4), 28.8 (CH_2-3), 19.5 (CH_3-8), 14.7 (CH_3-9).

HRMS: ESI+ found $[M+Na]^+$ = 393.2219, $C_{23}H_{34}{}^{23}NaO_2{}^{28}Si$ requires 393.2220, Δ = –0.34 ppm.

FTIR (film): ν_{max} = 3355, 2931, 2858, 1472, 1428, 1389, 1107, 1090, 1007, 936 cm^{-1}.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ **=** –8.2 (*c* = 1.0, $CHCl_3$).

(4*S*)-4-Methylhexane-1,5-diyl dibenzoate (618)



(4S)-4-methylhexane-1,5-diol ***ent*-432** (26 mg, 0.20 mmol), pyridine (0.05 mL, 0.60 mmol), benzoyl chloride (0.06 mL, 0.50 mmol) and CH_2Cl_2 (5 mL) were subjected to **general procedure E**. Purification by column chromatography (CH_2Cl_2) afforded ester ***ent*-618** (36 mg, 53%, 62:38 dr, >99:1 er) as a colourless oil and an inseparable mixture of diastereomers. *It was not possible to accurately determine the dr from the crude reaction mixture or purified compound due to overlapping peaks in the ^{1}H NMR spectrum, ~ 62:38 dr was estimated by HPLC, see below.*

***Procedure for racemic material*:** Racemic material for HPLC analysis was synthesised using 4-methylhexane-1,5-diol ***rac*-432**[*] under an analogous procedure.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.05-7.99 (4H, m, ArH), 7.57-7.52 (2H, m, ArH), 7.44-7.38 (4H, m, ArH), 5.17 (1H, qd, *J* = 6.4, 4.2 Hz, CH-1), 4.37-4.30 (2H, m, CH_2-5), 2.07-1.64 (4H, m, CH-2, CH_2-3_a and CH_2-4), 1.43-1.28 (1H, m, CH_2-3_b), 1.33 (3H, d, *J* = 6.4 Hz, CH_3-6), 1.06 (3H, d, *J* = 6.8 Hz, CH_3-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.8 (2 × C=O), 133.0 (2 × ArCH), 130.5 (2 × ArC), 129.7 (4 × ArCH), 128.5 (4 × ArCH), 74.3 (CH-1), 65.2 (CH_2-5), 37.7 (CH-2), 29.2 (CH_2-3), 26.6 (CH_2-4), 17.1 (CH_3-6), 15.0 (CH_3-7).

Additional signals for the minor diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.13-5.07 (1H, m, CH-1), 1.31 (3H, d, *J* = 6.5 Hz, CH_3-6), 1.03 (3H, d, *J* = 6.8 Hz, CH_3-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.2 (C=O), 132.9 (ArCH), 131.0 (ArC), 74.8 (CH-1), 65.2 (CH_2-5), 37.5 (CH-2), 29.0 (CH_2-3), 26.5 (CH_2-4), 16.5 (CH_3-6), 15.1 (CH_3-7).

HRMS: ESI+ found $[M+Na]^+$ = 363.1566, $C_{21}H_{24}O_4Na$ requires 363.1567, Δ = –0.18 ppm.

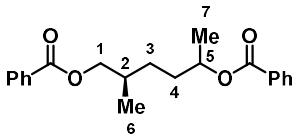
FTIR (film): ν_{max} = 2964, 1713, 1451, 1382, 1314, 1270, 1110, 1070, 1026 cm^{-1}.

$[\alpha]_D^{25}$ = –3.8 (*c* = 1.0, $CHCl_3$).

[*] Diol ***rac*-432** was synthesised by Dr Roly Armstrong

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IA column (99.7:0.3 hexane:IPA, 1.0 mL min^{-1}, 230 nm, room temperature) ~62:38 dr; major diastereomer t_r (major) = 43.5 min, t_r (minor) = 55.1 min, >99:1 er; minor diastereomer, t_r (minor) = 40.9 min, t_r (major) = 46.9 min, >99:1 er.

(2R)-2-Methylhexane-1,5-diyl dibenzoate (631)



Diol ***ent*-437** (26 mg, 0.20 mmol), pyridine (0.05 mL, 0.60 mmol), benzoyl chloride (0.06 mL, 0.50 mmol) and CH_2Cl_2 (5 mL) were subjected to **general procedure E**. Purification by column chromatography (CH_2Cl_2) afforded ester ***ent*-631** (9.5 mg, 14%, ~55:45 dr, 94:6 er) as a colourless oil and an inseparable mixture of diastereomers. *It was not possible to calculate dr of the crude reaction mixture or purified compound due to overlapping peaks in the ^{1}H NMR spectrum, a dr of ~55:45 was estimated by HPLC (see below).*

***Procedure for racemic material*:** Racemic material for HPLC analysis was synthesised using 2-methylhexane-1,5-diol ***rac*-437**[*] under an analogous procedure.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04-8.00 (4H, m, ArH), 7.57-7.52 (2H, m, ArH), 7.43-7.38 (4H, m, ArH), 5.22-5.13 (1H, m, CH-5), 4.22-4.13 (2H, m, CH_2-1), 2.03-1.94 (1H, m, CH-2), 1.90-1.56 (4H, m, CH_2-3, CH_2-4_a and CH-5), 1.45-1.28 (1H, m, CH_2-4_b), 1.36 (3H, d, *J* = 6.3 Hz, CH_3-7), 1.05 (3H, d, *J* = 6.8 Hz, CH_3-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.7 (C=O), 166.3 (C=O), 133.0 (ArCH), 132.9 (ArCH), 130.9 (ArC), 130.5 (ArC), 129.6 (4 × ArCH), 128.5 (2 × ArCH), 128.4 (2 × ArCH), 71.5 (CH-5), 69.5 (CH_2-1), 33.6 (CH_2-3), 33.8 (CH-2), 29.4 (CH_2-4), 20.3 (CH_3-7), 17.2 (CH_3-6).

Additional signals for the minor diastereomer:

[*] Diol ***rac*-437** was synthesised by Dr James Frost

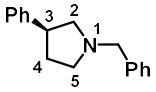
^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.7 (C=O), 166.3 (C=O), 133.0 (ArCH), 132.9 (ArCH), 130.9 (ArC), 130.5 (ArC), 129.6 (4 × ArCH), 128.5 (2 × ArCH), 128.4 (2 × ArCH), 71.7 (CH-5), 69.6 (CH_2-1), 33.4 (CH_2-3), 33.7 (CH-2), 29.2 (CH_2-4), 20.3 (CH_3-7), 17.0 (CH_3-6).

HRMS: ESI+ found $[M+H]^+$ = 341.1749, $C_{21}H_{25}O_4$ requires 341.1747, Δ = 0.47.

FTIR (film): ν_{max} = 1714, 1451, 1314, 1272, 1109, 1070, 1026, 710 cm^{-1}.

HPLC: Enantiomeric excess was determined by HPLC with a Chiralpak® IA column (99.7:0.3 hexane:IPA, 1.0 mL min^{-1}, 230 nm, room temperature), ~55:45 dr; major diastereomer t_r (major) = 65.8 min, t_r (minor) = 90.9 min, 94:6 er; minor diastereomer t_r (minor) = 58.7 min, t_r (major) = 75.4 min; 94:6 er.

(*S*)-*N*-Benzyl-3-phenylpyrrolidine (643)



Procedure for enantioenriched material: (*S*)-2-Phenylbutane-1,4-diol ***ent*-642**[*] (166 mg, 1.0 mmol, >99:1 er), anhydrous benzylamine (0.16 mL, 1.5 mmol), $CsHCO_3$ (3.9 mg, 2.0 mol%), $[IrCp^*Cl_2]_2$ (8.0 mg, 1.0 mol%) and CPME (0.5 mL) were subjected to **general procedure G**. Purification by column chromatography (pentane:Et_2O 75:25) afforded pyrrolidine ***ent*-643** (19 mg, 8%, 62:38 er) as a yellow oil.

Procedure for racemic material: Racemic material ***rac*-643** for HPLC analysis was synthesised using 2-Phenylbutane-1,4-diol ***rac*-642*** under an analogous procedure*. The data are consistent with the literature.*[150]*

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39-7.17 (10H, m, ArH), 3.69 (2H, s, NCH_2Ph), 3.38 (1H, dq, *J* = 9.9, 7.6 Hz, CH-3), 3.05 (1H, dd, *J* = 9.2, 7.8 Hz, CH_2-2_a), 2.85 (1H, ddd, *J* = 9.2, 8.0, 5.9 Hz, CH_2-5_a), 2.71 (1H, td, *J* = 8.9, 5.9 Hz, CH_2-5_b), 2.52 (1H, dd, *J* = 9.2, 7.8 Hz, CH_2-2_b), 2.35 (1H, dddd, *J* = 12.8, 9.8, 7.9, 5.9 Hz, CH_2-4_a), 1.91 (1H, dddd, *J* = 12.9, 8.7, 7.2, 5.9 Hz, CH_2-4_b).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.8 (ArC), 139.5 (ArC), 128.9 (2 × ArCH), 128.5 (2 × ArCH), 128.4 (2 × ArCH), 127.5 (2 × ArCH), 127.0 (ArCH), 126.2 (ArCH), 62.5 (CH_2-2), 60.8 (NCH_2Ph), 54.8 (CH_2-5), 43.6 (CH-3), 33.4 (CH_2-4).

HRMS: ESI+ found $[M+H]^+$ = 238.1598, $C_{17}H_{20}N$ requires 238.1590, Δ = 3.08 ppm.

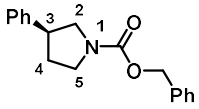
FTIR (film): ν_{max} = 3027, 2958, 2787, 1493, 1454, 1345, 1145, 1029, 742, 698 cm^{-1}.

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ **=** –8.4 (*c* = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by chiral HPLC analysis of the corresponding *N*-Cbz compound, **S8** (see p259 for HPLC conditions and full characterisation data). er = 62:38.

[*] Diols ***ent*-642** and ***rac*-642** were synthesised by Dr Roly Armstrong

Benzyl (*S*)-3-phenylpyrrolidine-*N*-carboxylate (S8)



Procedure for enantioenriched material: (*S*)-*N*-Benzyl-3-phenylpyrrolidine ***ent*-643** (19 mg, 0.08 mmol) and benzyl chloroformate (3M in toluene, 0.5 mL, 1.5 mmol) were subjected to **general procedure C**. Purification by column chromatography (pentane:Et_2O 75:25) afforded pyrrolidine **S8** (8.6 mg, 38%, 62:38 er) as a colourless oil.

Procedure for racemic material: Racemic material for HPLC analysis was synthesised using *N*-benzyl-3-phenylpyrrolidine ***rac*-643** under an analogous procedure. *The data is consistent with the literature.*[217]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42-7.22 (10H, m, ArH), 5.18-5.16 (2H, m, NCH_2Ph), 3.96-3.85 (1H, m, CH_2-2_a), 3.75-3.64 (1H, m, CH_2-5_a), 3.53-3.35 (3H, m, CH_2-2_b, CH-3, and CH_2-5_b), 2.34-2.25 (1H, m, CH_2-4_a), 2.07-1.96 (1H, dt, *J* = 12.9, 9.6, 7.0 Hz, CH_2-4_b).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.9 (C=O), 141.31 (ArC), 141.25 (ArC), 137.2 (ArC), 137.1 (ArC), 128.8 (2 × ArCH), 128.6 (2 × ArCH), 128.1 (ArCH), 128.0 (2 × ArCH), 127.2 (2 × ArCH), 127.00 (ArCH), 126.96 (ArCH), 66.9 (NCH_2Ph), 52.5 (CH_2-2), 52.4 (CH_2-2), 46.3 (CH_2-5), 45.9 (CH_2-5), 44.4 (CH-3), 43.4 (CH-3), 33.4 (CH_2-4), 32.5 (CH_2-4). *Some of the signals are doubled due to the rotameric nature of the carbamate.*

$[\alpha]_D^{25}$ = –2.9 (*c* = 1.0, $CHCl_3$).

HPLC: Enantiomeric excess was determined by HPLC with a Chiralcel® OD column (99:1 hexane:IPA, 1.0 mL min^{-1}, 210 nm, room temperature); t_r (minor) = 31.0 min, t_r (major) = 36.3 min; 62:38 er.

The data is consistent with the literature.[217]

Chapter 6: Appendix

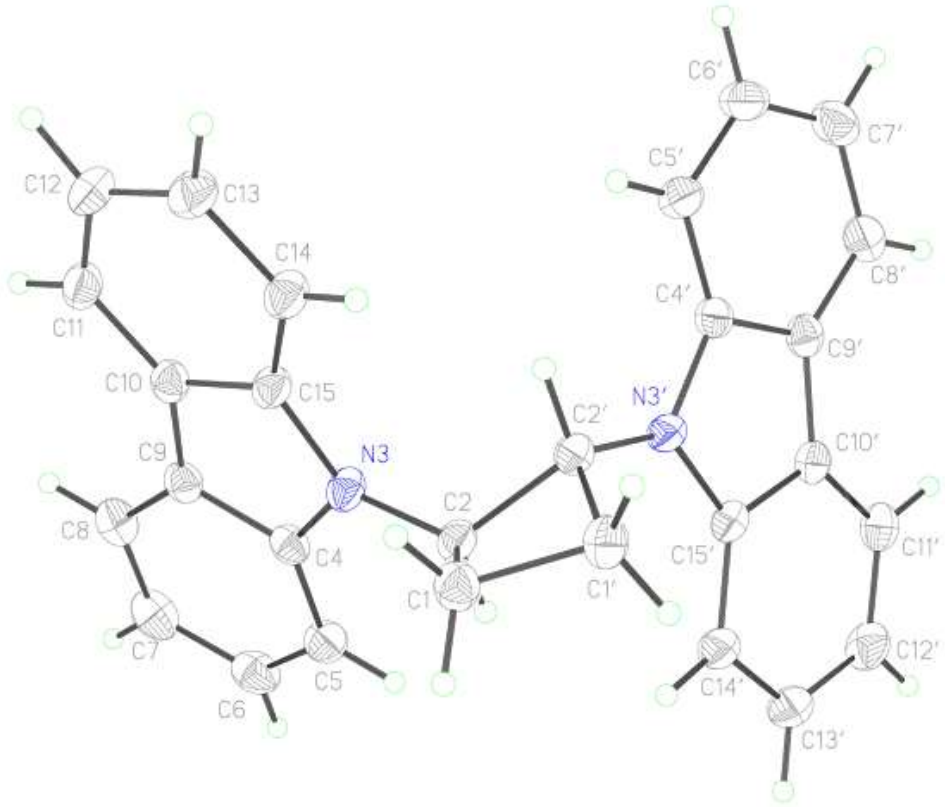
6.1 X-ray Crystallographic Data for Compound 240

Table 1: Crystal data and structure refinement for **240**

Empirical formula	C28 H22 N2	
Formula weight	386.50	
Temperature	386.50	
Wavelength	150 K	
Crystal system	Tetragonal	
Space group	P 42 b c	
Unit cell dimensions	a = 18.54580(10) Å	α = 90°
	b = 18.54580(10) Å	β = 90°
	c = 11.35240(10) Å	γ = 90°
Volume	3904.62(5) $Å^3$	
Z	8	
Density (calculated)	1.315 Mg/m^3	
Absorption coefficient	0.590 mm^{-1}	
F(000)	1632	
Crystal size	0.24 x 0.04 x 0.04 mm^3	
Theta range for data collection	4.769 to 76.309°	
Index ranges	-23<=h<=23, -23<=k<=23, -14<=l<=14	
Reflections collected	73364	
Independent reflections	4081 [R(int) = 0.045]	
Completeness to theta = 76.309°	99.8%	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.98 and 0.49	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4081 / 1 / 272	
Goodness-of-fit on F^2	1.0045	
Final R indices [I>2sigma(I)]	R1 = 0.0296, wR2 = 0.0766	
R indices (all data)	R1 = 0.0301, wR2 = 0.0775	
Absolute structure parameter	-0.2(4)	
Largest diff. peak and hole	0.17 and -0.17 e.$Å^3$	

Table 2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **240**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5411(1)	10069(1)	5275(1)	25
C(2)	5408(1)	9910(1)	6619(1)	21
N(3)	5902(1)	10271(1)	7408(1)	21
C(4)	6430(1)	9919(1)	8067(1)	21
C(5)	6553(1)	9182(1)	8212(1)	25
C(6)	7128(1)	8975(1)	8916(1)	30
C(7)	7580(1)	9481(1)	9451(1)	31
C(8)	7458(1)	10209(1)	9304(1)	26
C(9)	6873(1)	10434(1)	8620(1)	21
C(10)	6595(1)	11132(1)	8296(1)	21
C(11)	6799(1)	11834(1)	8582(1)	26
C(12)	6419(1)	12406(1)	8111(1)	29
C(13)	5844(1)	12281(1)	7345(1)	28
C(14)	5628(1)	11590(1)	7035(1)	25
C(15)	6005(1)	11011(1)	7530(1)	21
N(103)	5928(1)	5206(1)	7228(1)	22
C(115)	6111(1)	5936(1)	7199(1)	21
C(110)	6743(1)	6022(1)	6514(1)	21
C(109)	6964(1)	5311(1)	6139(1)	22
C(104)	6450(1)	4827(1)	6595(1)	22
C(105)	6506(1)	4087(1)	6392(1)	27
C(106)	7099(1)	3843(1)	5770(1)	31
C(107)	7627(1)	4317(1)	5346(1)	32
C(108)	7559(1)	5055(1)	5515(1)	28
C(111)	7040(1)	6708(1)	6350(1)	25
C(112)	6700(1)	7295(1)	6856(1)	28
C(113)	6079(1)	7205(1)	7528(1)	26
C(114)	5780(1)	6528(1)	7724(1)	24
C(102)	5397(1)	4867(1)	7981(1)	23
C(101)	5417(1)	4994(1)	9331(1)	30


C6'
C7'
C5'
C12
C13
C14
C8'
C4'
C11
C9'
C10
C15
N3'
C2'
C9
N3
C10'
C2
C8
C4
C15'
C11'
C1
C1'
C7
C5
C12'
C6
C14'
C13'

Chapter 7: References

[1] B. Zhang, A. Studer, *Chem. Soc. Rev.* **2015**, *44*, 3505–3521.
[2] A. Hameed, S. Javed, R. Noreen, T. Huma, S. Iqbal, H. Umbreen, T. Gulzar, T. Farooq, *Molecules* **2017**, *22*, 1691–1713.
[3] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274.
[4] J. Clayden, N, Greeves, S. Warren, P. Wothers, *Organic Chemistry*, 1st Edition, Oxford University Press, Oxford, United Kingdom, 2001.
[5] D. F. Veber, S. R. Johnson, H.-Y. Cheng, B. R. Smith, K. W. Ward, K. D. Kopple, *J. Med. Chem.* **2002**, *45*, 2615–2623.
[6] D. J. St. Jean, C. Fotsch, *J. Med. Chem.* **2012**, *55*, 6002–6020.
[7] E. Lioudaki, E. S. Ganotakis, D. P. Mikhailidis, *Curr. Vasc. Pharmacol.* **2011**, *9*, 62–86.
[8] E. C. Keystone, P. C. Taylor, E. Drescher, D. E. Schlichting, S. D. Beattie, P.-Y. Berclaz, C. H. Lee, R. K. Fidelus-Gort, M. E. Luchi, T. P. Rooney, W. L. Macias, M. C. Genovese, *Ann. Rheum. Dis.* **2015**, *74*, 333–340.
[9] K. Oizumi, H. Nishino, H. Koike, T. Sada, M. Miyamoto, T. Kimura, *Jpn. J. Pharmacol.* **1989**, *51*, 57–64.
[10] K. D. Rice, N. Aay, N. K. Anand, C. M. Blazey, O. J. Bowles, J. Bussenius, S. Costanzo, J. K. Curtis, S. C. Defina, L. Dubenko, S. Engst, A. A. Joshi, A. R. Kennedy, A. I. Kim, E. S. Koltun, J. C. Lougheed, J.-C. L. Manalo, J.-F. Martini, J. M. Nuss, C. J. Peto, T. H. Tsang, P. Yu, S. Johnston., *ACS Med. Chem. Lett.* **2012**, *3*, 416–421.
[11] F. Matsuura, Y. Hamada, T. Shioiri, *Tetrahedron* **1994**, *50*, 9457–9470.
[12] J. Kobayashi, M. Tsuda, J. Cheng, M. Ishibashi, H. Takikawa, K. Mori, *Tetrahedron Lett.* **1996**, *37*, 6775–6776.
[13] A. A. Sinkula, W. Morozowich, E. L. Rowe, *J. Pharm. Sci.* **1973**, *62*, 1106–1111.
[14] M. H. Norman, J. L. Kelley, E. B. Hollingsworth, *J. Med. Chem.* **1993**, *36*, 3417–3423.
[15] D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435–446.
[16] C. Bhat, S. G. Tilve, *RSC Adv.* **2014**, *4*, 5405–5452.
[17] T. Ponpandian, S. Muthusubramanian, *Tetrahedron Lett.* **2011**, *52*, 1520–1522.
[18] P. Goel, O. Alam, M. J. Naim, F. Nawaz, M. Iqbal, M. I. Alam, *Eur. J. Med. Chem.* **2018**, *157*, 480–502.
[19] Y. Wang, J. Wang, Y. Lin, L.-F. Si-Ma, D. Wang, L.-G. Chen, D.-K. Liu, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4454–4456.
[20] N. Shankaraiah, R. A. Pilli, L. S. Santos, *Tetrahedron Lett.* **2008**, *49*, 5098–5100.
[21] C. A. Valdez, R. N. Leif, B. P. Mayer, *PLOS ONE* **2014**, *9*, e108250.
[22] D. Chamorro-Arenas, L. Fuentes, L. Quintero, S. Cruz-Gregorio, H. Höpfl, F. Sartillo-Piscil, *Eur. J. Org. Chem.* **2017**, *2017*, 3558–4110.
[23] H. Hotti, H. Rischer, *Molecules* **2017**, *22*, 1962–1985.
[24] A. P. Taylor, R. P. Robinson, Y. M. Fobian, D. C. Blakemore, L. H. Jones, O. Fadeyi, *Org. Biomol. Chem.* **2016**, *14*, 6611–6637.
[25] A. Brandi, S. Cicchi, F. M. Cordero, *Chem. Rev.* **2008**, *108*, 3988–4035.
[26] M. C. Hillier, C. Chen, *J. Org. Chem.* **2006**, *71*, 7885–7887.
[27] J. Cabral, P. Laszlo, M. T. Montaufier, *Tetrahedron Lett.* **1988**, *29*, 547–550.
[28] R. Gianatassio, J. M. Lopchuk, J. Wang, C.-M. Pan, L. R. Malins, L. Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran, *Science* **2016**, *351*, 241–246.
[29] J. M. Lopchuk, K. Fjelbye, Y. Kawamata, L. R. Malins, C.-M. Pan, R. Gianatassio, J. Wang, L. Prieto, J. Bradow, T. A. Brandt, M. R. Collins, J. Elleraas, J. Ewanicki, W. Farrell, O. O. Fadeyi, G. M. Gallego, J. J.Mousseau, R. Oliver, N. W. Sach, J. K. Smith, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran., *J. Am. Chem. Soc.* **2017**, *139*, 3209–3226.
[30] A. Fawcett, A. Murtaza, C. H. U. Gregson, V. K. Aggarwal, *J. Am. Chem. Soc.* **2019**, *141*, 4573–4578.
[31] M. Yamashita, I. Ojima, *J. Am. Chem. Soc.* **1983**, *105*, 6339–6342.
[32] R. W. M. Aben, R. Smit, J. W. Scheeren, *J. Org. Chem.* **1987**, *52*, 365–370.
[33] I. Nakamura, T. Nemoto, Y. Yamamoto, A. de Meijere, *Angew. Chem. Int. Ed.* **2006**, *45*, 5176–5179.
[34] J.-B. Denis, G. Masson, P. Retailleau, J. Zhu, *Angew. Chem. Int. Ed.* **2011**, *50*, 5356–5360.
[35] A. Feula, S. S. Dhillon, R. Byravan, M. Sangha, R. Ebanks, M. A. H. Salih, N. Spencer, L. Male, I. Magyary, W.-P. Deng, F. Müller, J. S. Fossey, *Org. Biomol. Chem.* **2013**, *11*, 5083–5093.
[36] R. H. Crabtree, A. Lei, *Chem. Rev.* **2017**, *117*, 8481–8482.
[37] G. He, Y. Zhao, S. Zhang, C. Lu, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 3–6.

[38] J. Li, Y. Ye, Y. Zhang, *Org. Chem. Front.* **2018**, *5*, 864–892.
[39] M. S. Singh, S. Chowdhury, S. Koley, *Tetrahedron* **2016**, *72*, 1603–1644.
[40] K. V. Kudryavtsev, P. M. Ivantcova, A. V. Churakov, V. A. Vasin, *Tetrahedron Lett.* **2012**, *53*, 4300–4303.
[41] W. Zeng, Y.-G. Zhou, *Tetrahedron Lett.* **2007**, *48*, 4619–4622.
[42] I. Oura, K. Shimizu, K. Ogata, S. Fukuzawa, *Org. Lett.* **2010**, *12*, 1752–1755.
[43] F. Xu, B. Simmons, R. A. Reamer, E. Corley, J. Murry, D. Tschaen, *J. Org. Chem.* **2008**, *73*, 312–315.
[44] Y. Ju, R. S. Varma, *J. Org. Chem.* **2006**, *71*, 135–141.
[45] D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557–2590.
[46] R. Kuwano, M. Kashiwabara, M. Ohsumi, H. Kusano, *J. Am. Chem. Soc.* **2008**, *130*, 808–809.
[47] M. Skvorcova, A. Jirgensons, *Org. Lett.* **2017**, *19*, 2478–2481.
[48] Q. Zhou, L. Zhang, W. Meng, X. Feng, J. Yang, H. Du, *Org. Lett.* **2016**, *18*, 5189–5191.
[49] T.-X. Métro, D. Gomez Pardo, J. Cossy, *J. Org. Chem.* **2007**, *72*, 6556–6561.
[50] J. Cossy, C. Dumas, D. G. Pardo, *Eur. J. Org. Chem.* **1999**, *1999*, 1693–1699.
[51] K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2000**, *39*, 3558–3588.
[52] J. C. K. Chu, D. M. Dalton, T. Rovis, *J. Am. Chem. Soc.* **2015**, *137*, 4445–4452.
[53] X. Qi, C. Chen, C. Hou, L. Fu, P. Chen, G. Liu, *J. Am. Chem. Soc.* **2018**, *140*, 7415–7419.
[54] M. H. S. A. Hamid, J. M. J. Williams, *Chem. Commun.* **2007**, 725–727.
[55] M. Guerbet, *Comptes Rendus Math. Acad. Sci. Paris* **1899**, *128*, 1002.
[56] A. Corma, J. Navas, M. J. Sabater, *Chem. Rev.* **2018**, *118*, 1410–1459.
[57] J. R. Frost, C. B. Cheong, W. M. Akhtar, D. F. J. Caputo, N. G. Stevenson, T. J. Donohoe, *J. Am. Chem. Soc.* **2015**, *137*, 15664–15667.
[58] W. M. Akhtar, C. B. Cheong, J. R. Frost, K. E. Christensen, N. G. Stevenson, T. J. Donohoe, *J. Am. Chem. Soc.* **2017**, *139*, 2577–2580.
[59] W. M. Akhtar, R. J. Armstrong, J. R. Frost, N. G. Stevenson, T. J. Donohoe, *J. Am. Chem. Soc.* **2018**, *140*, 11916–11920.
[60] R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit, N. Tongpenyai, *J. Chem. Soc., Chem. Commun.* **1981**, 611–612.
[61] Y. Watanabe, Y. Tsuji, Y. Ohsugi, *Tetrahedron Lett.* **1981**, *22*, 2667–2670.
[62] S.-I. Murahashi, K. Kondo, T. Hakata, *Tetrahedron Lett.* **1982**, *23*, 229–232.
[63] K. Fujita, Z. Li, N. Ozeki, R. Yamaguchi, *Tetrahedron Lett.* **2003**, *44*, 2687–2690.
[64] K. Fujita, Y. Enoki, R. Yamaguchi, *Tetrahedron* **2008**, *64*, 1943–1954.
[65] R. Yamaguchi, S. Kawagoe, C. Asai, K. Fujita, *Org. Lett.* **2008**, *10*, 181–184.
[66] G. Cami-Kobeci, P. A. Slatford, M. K. Whittlesey, J. M. J. Williams, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 535–537.
[67] M. H. S. A. Hamid, J. M. J. Williams, *Tetrahedron Lett.* **2007**, *48*, 8263–8265.
[68] G. W. Lamb, A. J. A. Watson, K. E. Jolley, A. C. Maxwell, J. M. J. Williams, *Tetrahedron Lett.* **2009**, *50*, 3374–3377.
[69] O. Saidi, A. J. Blacker, G. W. Lamb, S. P. Marsden, J. E. Taylor, J. M. J. Williams, *Org. Process Res. Dev.* **2010**, *14*, 1046–1049.
[70] M. H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson, J. M. J. Williams, *J. Am. Chem. Soc.* **2009**, *131*, 1766–1774.
[71] A. Tillack, D. Hollmann, D. Michalik, M. Beller, *Tetrahedron Lett.* **2006**, *47*, 8881–8885.
[72] D. Hollmann, A. Tillack, D. Michalik, R. Jackstell, M. Beller, *Chem. Asian J.* **2007**, *2*, 403–410.
[73] B. Blank, M. Madalska, R. Kempe, *Adv. Synth. Catal.* **2008**, *350*, 749–758.
[74] B. Blank, S. Michlik, R. Kempe, *Adv. Synth. Catal.* **2009**, *351*, 2903–2911.
[75] A. Bartoszewicz, R. Marcos, S. Sahoo, A. K. Inge, X. Zou, B. Martín-Matute, *Chem.: Eur. J.* **2012**, *18*, 14510–14519.
[76] A. B. Enyong, B. Moasser, *J. Org. Chem.* **2014**, *79*, 7553–7563.
[77] S. P. Shan, X. Xiaoke, B. Gnanaprakasam, T. T. Dang, B. Ramalingam, H. V. Huynh, A. M. Seayad, *RSC Adv.* **2014**, *5*, 4434–4442.
[78] K. O. Marichev, J. M. Takacs, *ACS Catal.* **2016**, *6*, 2205–2210.
[79] B. G. Reed-Berendt, K. Polidano, L. C. Morrill, *Org. Biomol. Chem.* **2019**, *17*, 1595–1607.
[80] T. Yan, B. L. Feringa, K. Barta, *Nat. Commun.* **2014**, *5*, 5602.
[81] B. Emayavaramban, M. Roy, B. Sundararaju, *Chem.: Eur. J.* **2016**, *22*, 3952–3955.
[82] A. J. Rawlings, L. J. Diorazio, M. Wills, *Org. Lett.* **2015**, *17*, 1086–1089.
[83] T. J. Brown, M. Cumbes, L. J. Diorazio, G. J. Clarkson, M. Wills, *J. Org. Chem.* **2017**, *82*, 10489–10503.
[84] H.-J. Pan, T. W. Ng, Y. Zhao, *Chem. Commun.* **2015**, *51*, 11907–11910.

[85] M. Mastalir, B. Stöger, E. Pittenauer, M. Puchberger, G. Allmaier, K. Kirchner, *Adv. Synth. Catal.* **2016**, *358*, 3824–3831.
[86] M. Mastalir, M. Glatz, N. Gorgas, B. Stöger, E. Pittenauer, G. Allmaier, L. F. Veiros, K. Kirchner, *Chem.: Eur. J.* **2016**, *22*, 12316–12320.
[87] K. Polidano, B. D. W. Allen, J. M. J. Williams, L. C. Morrill, *ACS Catal.* **2018**, *8*, 6440–6445.
[88] S. Rösler, M. Ertl, T. Irrgang, R. Kempe, *Angew. Chem. Int. Ed.* **2015**, *54*, 15046–15050.
[89] M. Mastalir, G. Tomsu, E. Pittenauer, G. Allmaier, K. Kirchner, *Org. Lett.* **2016**, *18*, 3462–3465.
[90] G. Zhang, Z. Yin, S. Zheng, *Org. Lett.* **2016**, *18*, 300–303.
[91] S. P. Midya, A. Mondal, A. Begum, E. Balaraman, *Synthesis* **2017**, *49*, 3957–3961.
[92] S. Elangovan, J.-B. Sortais, M. Beller, C. Darcel, *Angew. Chem. Int. Ed.* **2015**, *54*, 14483–14486.
[93] J. Neumann, S. Elangovan, A. Spannenberg, K. Junge, M. Beller, *Chem.: Eur. J.* **2017**, *23*, 5410–5413.
[94] A. Bruneau-Voisine, D. Wang, V. Dorcet, T. Roisnel, C. Darcel, J.-B. Sortais, *J. Catal.* **2017**, *347*, 57–62.
[95] U. K. Das, Y. Ben-David, Y. Diskin-Posner, D. Milstein, *Angew. Chem. Int. Ed.* **2018**, *57*, 2179–2182.
[96] Z. Xu, D.-S. Wang, X. Yu, Y. Yang, D. Wang, *Adv. Synth. Catal.* **2017**, *359*, 3332–3340.
[97] M. H. Shaw, J. Twilton, D. W. C. MacMillan, *J. Org. Chem.* **2016**, *81*, 6898–6926.
[98] T. Koike, M. Akita, *Inorg. Chem. Front.* **2014**, *1*, 562–576.
[99] C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363.
[100] O. Tsuge, M. Tashiro, K. Oe, *Tetrahedron Lett.* **1968**, *9*, 3971–3974.
[101] O. Tsuge, K. Oe, M. Tashiro, *Tetrahedron* **1973**, *29*, 41–46.
[102] J. A. Hyatt, J. S. Swenton, *J. Chem. Soc., Chem. Commun.* **1972**, 1144–1145.
[103] J. S. Swenton, J. A. Hyatt, *J. Am. Chem. Soc.* **1974**, *96*, 4879–4885.
[104] K. A. Howard, T. H. Koch, *J. Am. Chem. Soc.* **1975**, *97*, 7288–7298.
[105] R. M. Rodehorst, T. H. Koch, *J. Am. Chem. Soc.* **1975**, *97*, 7298–7304.
[106] T. Nishio, *J. Org. Chem.* **1984**, *49*, 827–832.
[107] E. Kumarasamy, S. K. Kandappa, R. Raghunathan, S. Jockusch, J. Sivaguru, *Angew. Chem. Int. Ed.* **2017**, *56*, 7056–7061.
[108] M. R. Becker, A. D. Richardson, C. S. Schindler, **2019**, DOI 10.26434/chemrxiv.7218272.v3.
[109] K. Singh, S. J. Staig, J. D. Weaver, *J. Am. Chem. Soc.* **2014**, *136*, 5275–5278.
[110] W. Li, Y. Duan, M. Zhang, J. Cheng, C. Zhu, *Chem. Commun.* **2016**, *52*, 7596–7599.
[111] M. A. Ischay, M. S. Ament, T. P. Yoon, *Chem. Sci.* **2012**, *3*, 2807–2811.
[112] F. A. Bell, R. A. Crellin, H. Fujii, A. Ledwith, *J. Chem. Soc. D* **1969**, 251–252.
[113] R. A. Pabon, D. J. Bellville, N. L. Bauld, *J. Am. Chem. Soc.* **1984**, *106*, 2730–2731.
[114] M. A. Ischay, M. E. Anzovino, J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **2008**, *130*, 12886–12887.
[115] J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **2009**, *131*, 14604–14605.
[116] J. Du, K. L. Skubi, D. M. Schultz, T. P. Yoon, *Science* **2014**, *344*, 392–396.
[117] I. Colomer, R. Coura Barcelos, T. J. Donohoe, *Angew. Chem. Int. Ed.* **2016**, *55*, 4748–4752.
[118] I. Colomer, C. Batchelor-McAuley, B. Odell, T. J. Donohoe, R. G. Compton, *J. Am. Chem. Soc.* **2016**, *138*, 8855–8861.
[119] A. E. R Chamberlain, *Synthesis of Heteroatom-Substituted Cyclobutanes using Hypervalent Iodine Catalysis*, Probationary Research Student Transfer of Status Report, University of Oxford, 2017.
[120] M. Riener, D. A. Nicewicz, *Chem. Sci.* **2013**, *4*, 2625–2629.
[121] I. Colomer, A. E. R. Chamberlain, M. B. Haughey, T. J. Donohoe, *Nat. Rev. Chem.* **2017**, *1*, 0088.
[122] J. M. Reyna-González, M. Aguilar-Martínez, J. A. Bautista-Martínez, E. Rivera, I. González, P. Roquero, *Polymer* **2006**, *47*, 6664–6672.
[123] K. Karon, M. Lapkowski, *J. Solid State Electrochem.* **2015**, *19*, 2601–2610.
[124] A. Di Salvo, M. David, B. Crousse, D. Bonnet-Delpon, *Adv. Synth. Catal.* **2006**, *348*, 118–124.
[125] Y. Roh, D. Gao, N. L. Bauld, *Adv. Synth. Catal.* **2001**, *343*, 481–489.
[126] D. von der Heiden, S. Bozkus, M. Klussmann, M. Breugst, *J. Org. Chem.* **2017**, *82*, 4037–4043.
[127] D. Best, S. Kujawa, H. W. Lam, *J. Am. Chem. Soc.* **2012**, *134*, 18193–18196.
[128] E. Kiss, I. E. Markó, M. Guillaume, *Tetrahedron* **2011**, *67*, 9173–9178.
[129] L. Nielsen, K. B. Lindsay, J. Faber, N. C. Nielsen, T. Skrydstrup, *J. Org. Chem.* **2007**, *72*, 10035–10044.
[130] N. Kato, T. Shirai, Y. Yamamoto, *Chem.: Eur. J.* **2016**, *22*, 7739–7742.
[131] D. Teze, M. Dion, F. Daligault, V. Tran, C. André-Miral, C. Tellier, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 448–451.
[132] J. Kalia, R. T. Raines, *Angew. Chem. Int. Ed.* **2008**, *47*, 7523–7526.

[133] B. S. Pilgrim, A. E. Gatland, C. H. A. Esteves, C. T. McTernan, G. R. Jones, M. R. Tatton, P. A. Procopiou, T. J. Donohoe, *Org. Biomol. Chem.* **2016**, *14*, 1065–1090.
[134] A. G. Fallis, I. M. Brinza, *Tetrahedron* **1997**, *53*, 17543–17594.
[135] D. Kang, H. Zhang, Z. Zhou, B. Huang, L. Naesens, P. Zhan, X. Liu, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5182–5186.
[136] T. Guo, Y. Gao, Z. Li, J. Liu, K. Guo, *Synlett* **2019**, *30*, 329–332.
[137] H. Wei, Y. Li, K. Xiao, B. Cheng, H. Wang, L. Hu, H. Zhai, *Org. Lett.* **2015**, *17*, 5974–5977.
[138] E. L. Richards, P. J. Murphy, F. Dinon, S. Fratucello, P. M. Brown, T. Gelbrich, M. B. Hursthouse, *Tetrahedron* **2001**, *57*, 7771–7784.
[139] O. Tamura, T. Mitsuya, X. Huang, Y. Tsutsumi, S. Hattori, H. Ishibashi, *J. Org. Chem.* **2005**, *70*, 10720–10725.
[140] T. Oishi, M. Kanemoto, R. Swasono, N. Matsumori, M. Murata, *Org. Lett.* **2008**, *10*, 5203–5206.
[141] P. Huang, J. Xu, *RSC Adv.* **2016**, *6*, 63736–63748.
[142] *Electrochemical Series of Photocatalysts and Common Organic Compounds,* Merck, http://chemlabs.princeton.edu/macmillan/wp-content/uploads/sites/6/Merck-Photocatalysis-Chart.pdf, accessed July 2018.
[143] L. Ludvíková, P. Friš, D. Heger, P. Šebej, J. Wirz, P. Klán, *Phys. Chem. Chem. Phys.* **2016**, *18*, 16266–16273.
[144] Y. Tsuji, K. T. Huh, Y. Ohsugi, Y. Watanabe, *J. Org. Chem.* **1985**, *50*, 1365–1370.
[145] Y. Tsuji, Y. Yokoyama, K.-T. Huh, Y. Watanabe, *B. Chem. Soc. Jpn.* **1987**, *60*, 3456–3458.
[146] A. J. A. Watson, A. C. Maxwell, J. M. J. Williams, *J. Org. Chem.* **2011**, *76*, 2328–2331.
[147] O. Saidi, A. J. Blacker, G. W. Lamb, S. P. Marsden, J. E. Taylor, J. M. J. Williams, *Org. Process Res. Dev.* **2010**, *14*, 1046–1049.
[148] R. Kawahara, K. Fujita, R. Yamaguchi, *Adv. Synth. Catal.* **2011**, *353*, 1161–1168.
[149] S. Enthaler, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2008**, *47*, 3317–3321.
[150] K. Fujita, T. Fujii, R. Yamaguchi, *Org. Lett.* **2004**, *6*, 3525–3528.
[151]R. Armstrong, W. Akhtar, T. Young, F. Duarte, T. J. Donohoe, *Angew. Chem. Int. Ed.* **2019**, 58, 12558–12562.
[152] K. J. Paterson, *Synthesis of Aza-Heterocycles via Hydrogen Borrowing Catalysis,* Part II Thesis, University of Oxford, **2018**.
[153] D. Talwar, H. Y. Li, E. Durham, J. Xiao, *Chem.: Eur. J.* **2015**, *21*, 5370–5379.
[154] D. L. Matheau-Raven, *Development and application of interrupted hydrogen borrowing catalysis towards the synthesis of substituted cyclohexenes,* Rotation Report, University of Oxford, **2018**.
[155] R. M. Beesley, C. K. Ingold, J. F. Thorpe, *J. Chem. Soc., Trans.* **1915**, *107*, 1080–1106.
[156] C. Bathula, P. Dangi, S. Hati, R. Agarwal, P. Munshi, A. Singh, S. Singh, S. Sen, *New J. Chem.* **2015**, *39*, 9281–9292.
[157] A. Fürst, P. A. Plattner, *Helv. Chim. Acta* **1949**, *32*, 275–283.
[158] S. G. Davies, M. J. Durbin, S. J. S. Hartman, A. Matsuno, P. M. Roberts, A. J. Russell, A. D. Smith, J. E. Thomson, S. M. Toms, *Tetrahedron: Asymmetry* **2008**, *19*, 2870–2881.
[159] E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds,* Wiley & Sons, New York, United States, 1994.
[160] B.-C. Wang, L.-J. Wang, B. Jiang, S.-Y. Wang, N. Wu, X.-Q. Li, D.-Y. Shi, *Mini-Rev. Med. Chem.* **2017**, *17*, 683–692.
[161] N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822–5880.
[162] É. Dorkó, M. Szabó, B. Kótai, I. Pápai, A. Domján, T. Soós, *Angew. Chem. Int. Ed.* **2017**, *56*, 9512–9516.
[163] J. March, *Advanced Organic Chemistry; Reactions, Mechanisms and Structure*, 4th Edition, Wiley & Sons, New York, United States, 1992.
[164] S. Chen, G. Lu, C. Cai, *New J. Chem.* **2015**, *39*, 5360–5365.
[165] L. Miao, S. C. DiMaggio, H. Shu, M. L. Trudell, *Org. Lett.* **2009**, *11*, 1579–1582.
[166] F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756.
[167] F. Lovering, *Med. Chem. Commun.* **2013**, *4*, 515–519.
[168] D. Hollmann, *ChemSusChem* **2014**, *7*, 2411–2413.
[169] N. J. Oldenhuis, V. M. Dong, Z. Guan, *J. Am. Chem. Soc.* **2014**, *136*, 12548–12551.
[170] Y. Zhang, C.-S. Lim, D. S. B. Sim, H.-J. Pan, Y. Zhao, *Angew. Chem. Int. Ed.* **2014**, *53*, 1399–1403.
[171] Z.-Q. Rong, Y. Zhang, R. H. B. Chua, H.-J. Pan, Y. Zhao, *J. Am. Chem. Soc.* **2015**, *137*, 4944–4947.
[172] L.-C. Yang, Y.-N. Wang, Y. Zhang, Y. Zhao, *ACS Catal.* **2017**, *7*, 93–97.
[173] P. Yang, C. Zhang, Y. Ma, C. Zhang, A. Li, B. Tang, J. S. Zhou, *Angew. Chem. Int. Ed.* **2017**, *56*, 14702–14706.

[174] F. G. Mutti, T. Knaus, N. S. Scrutton, M. Breuer, N. J. Turner, *Science* **2015**, *349*, 1525–1529.
[175] C. S. Lim, T. T. Quach, Y. Zhao, *Angew. Chem. Int. Ed.* **2017**, *56*, 7176–7180.
[176] G. Xu, G. Yang, Y. Wang, P.-L. Shao, J. N. N. Yau, B. Liu, Y. Zhao, Y. Sun, X. Xie, S. Wang, Y. Zhang, L. Xia, Y. Zhao, *Angew. Chem. Int. Ed.* **2019**, *58*, 14082–14088.
[177] M. Peña-López, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2016**, *55*, 7826–7830.
[178] T. Masamune, M. Takasugi, A. Murai, *Tetrahedron* **1971**, *27*, 3369–3386.
[179] S. M. Sarkar, Y. Taira, A. Nakano, K. Takahashi, J. Ishihara, S. Hatakeyama, *Tetrahedron Lett.* **2011**, *52*, 923–927.
[180] E. M. Barall, L. B. Rogers, *J. Inorg. Nucl. Chem.* **1966**, *28*, 41–51.
[181] J. Wu, C. Wang, W. Tang, A. Pettman, J. Xiao, *Chem.: Eur. J.* **2012**, *18*, 9525–9529.
[182] J. Wu, W. Tang, A. Pettman, J. Xiao, *Adv. Synth. Catal.* **2013**, *355*, 35–40.
[183] A. Grozavu, H. B. Hepburn, P. J. Smith, H. K. Potukuchi, P. J. Lindsay-Scott, T. J. Donohoe, *Nat. Chem.* **2019**, *11*, 242.
[184] Sigma Aldrich Molecular Sieves – Technical Information Bulletin, https://www.sigmaaldrich.com/chemistry/chemical-synthesis/learning-center/technical-bulletins/al-1430/molecular-sieves.html, accessed March 2019.
[185] M. Mizuno, K. Kobayashi, H. Nakajima, M. Koya, T. Inazu, *Synth. Commun.* **2002**, *32*, 1665–1670.
[186] Amine density values and melting points were taken from the Safety Data Sheets available on sigmaaldrich.com or fluorochem.co.uk (accessed 2nd August 2019).
[187] X. Bao, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2019**, *58*, 2139–2143.
[188] G. Zhang, B. L. Scott, S. K. Hanson, *Angew. Chem. Int. Ed.* **2012**, *51*, 12102–12106.
[189] N. Yoshikai, A. Mieczkowski, A. Matsumoto, L. Ilies, E. Nakamura, *J. Am. Chem. Soc.* **2010**, *132*, 5568–5569.
[190] M. Oikawa, T. Ueno, H. Oikawa, A. Ichihara, *J. Org. Chem.* **1995**, *60*, 5048–5068.
[191] S. Feuillastre, B. Pelotier, O. Piva, *Eur. J. Org. Chem.* **2014**, *2014*, 1753–1759.
[192] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.
[193] S. Guha, I. Kazi, P. Mukherjee, G. Sekar, *Chem. Commun.* **2017**, *53*, 10942–10945.
[194] S. Zhao, J. Kang, Y. Du, J. Kang, X. Zhao, Y. Xu, R. Chen, Q. Wang, X. Shi, *J. Heterocyclic Chem.* **2014**, *51*, 683–689.
[195] Y. Okimoto, S. Sakaguchi, Y. Ishii, *J. Am. Chem. Soc.* **2002**, *124*, 1590–1591.
[196] Y. Nakano, Y. Kato, K. Imai, E. Ochiai, J. Namekawa, S. Ishizuka, K. Takenouchi, A. Tanatani, Y. Hashimoto, K. Nagasawa, *J. Med. Chem.* **2006**, *49*, 2398–2406.
[197] W. Zhang, D. Wu, J. Zhang, Y. Liu, *Eur. J. Org. Chem.* **2014**, *2014*, 5827–5835.
[198] C. R. Jones, G. Dan Pantoş, A. J. Morrison, M. D. Smith, *Angew. Chem. Int. Ed.* **2009**, *48*, 7391–7394.
[199] S. Wertz, A. Studer, *Helv. Chim. Acta* **2012**, *95*, 1758–1772.
[200] A. Sokolsky, X. Wang, A. B. Smith, *Tetrahedron Lett.* **2015**, *56*, 3160–3164.
[201] B. D. Cons, A. J. Bunt, C. D. Bailey, C. L. Willis, *Org. Lett.* **2013**, *15*, 2046–2049.
[202] N. Ríos-Lombardía, V. Gotor-Fernández, V. Gotor, *J. Org. Chem.* **2011**, *76*, 811–819.
[203] R. Cano, M. Yus, D. J. Ramón, *Tetrahedron* **2011**, *67*, 8079–8085.
[204] K. Shin, S. Joung, Y. Kim, S. Chang, *Adv. Synth. Catal.* **2017**, *359*, 3428–3436.
[205] M. Renom-Carrasco, P. Gajewski, L. Pignataro, J. G. de Vries, U. Piarulli, C. Gennari, L. Lefort, *Chem.: Eur. J.* **2016**, *22*, 9528–9532.
[206] E. E. Kwan, J. R. Scheerer, D. A. Evans, *J. Org. Chem.* **2013**, *78*, 175–203.
[207] T. Kano, F. Shirozu, M. Akakura, K. Maruoka, *J. Am. Chem. Soc.* **2012**, *134*, 16068–16073.
[208] B. Sundararaju, M. Achard, G. V. M. Sharma, C. Bruneau, *J. Am. Chem. Soc.* **2011**, *133*, 10340–10343.
[209] Y. Pan, Z. Luo, J. Han, X. Xu, C. Chen, H. Zhao, L. Xu, Q. Fan, J. Xiao, *Adv. Synth. Catal.* **2019**, *361*, 2301–2308.
[210] D. Chamorro-Arenas, U. Osorio-Nieto, L. Quintero, L. Hernández-García, F. Sartillo-Piscil, *J. Org. Chem.* **2018**, *83*, 15333–15346.
[211] O. O. Kovalenko, A. Volkov, H. Adolfsson, *Org. Lett.* **2015**, *17*, 446–449.
[212] W. Xue, H. Xu, Z. Liang, Q. Qian, H. Gong, *Org. Lett.* **2014**, *16*, 4984–4987.
[213] N. Richy, M. Ghoraf, J. Vidal, *J. Org. Chem.* **2012**, *77*, 10972–10977.
[214] S. O'Sullivan, E. Doni, T. Tuttle, J. A. Murphy, *Angew. Chem. Int. Ed.* **2014**, *53*, 474–478.
[215] Z.-Y. Liu, Z.-H. Wen, X.-C. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 5817–5820.
[216] S. E. Denmark, H. M. Chi, *J. Am. Chem. Soc.* **2014**, *136*, 8915–8918.

[217] J. J. Verendel, T. Zhou, J.-Q. Li, A. Paptchikhine, O. Lebedev, P. G. Andersson, *J. Am. Chem. Soc.* **2010**, *132*, 8880–8881.
[218] S. J. Aitken, G. Grogan, C. S.-Y. Chow, N. J. Turner, S. L. Flitsch, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3365–3370.
[219] Z. Pan, L. Shen, D. Song, Z. Xie, F. Ling, W. Zhong, *J. Org. Chem.* **2018**, *83*, 11502–11509.
[220] A. Roushanbakhti, Y. Liu, P. C. M. Winship, M. J. Tucker, W. M. Akhtar, D. S. Walter, G. Wrigley, T. J. Donohoe, *Angew. Chem. Int. Ed.* **2017**, *56*, 14883–14887.
[221] L. Raffier, O. Piva, *Eur. J. Org. Chem.* **2013**, *2013*, 1124–1131.