

Hydrogen Borrowing Reactions of Amino Alcohols and the Total Synthesis of (–)-γ-Lycorane

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Table of Contents

Table of Contents i
Declaration v
Abstract vii
Acknowledgements ix
Abbreviations and Acronyms xi
Chapter 1: Introduction 1
1.1 How to Form a C–C Bond 1
1.1.1 Polar C–C Bond Formations 1
1.1.2 Radical C–C Bond Formations 2
1.1.3 Pericyclic C–C Bond Formations 4
1.1.4 Summary 5
1.2 Hydrogen Borrowing Alkylation Reactions 6
1.2.1 Reaction Overview 6
1.2.2 Historical Origins of Hydrogen Borrowing Catalysis 8
1.2.3 Modern Approaches to Hydrogen Borrowing Alkylations with Primary Alcohols 10
1.3 Use of Ph* Methyl Ketone 100 in Hydrogen Borrowing Catalysis 17
1.3.1 Initial Discovery and Alkylations Using Primary and Secondary Alcohols 17
1.3.2 Alkylation Reactions with Diols to form Cyclohexanes and Cyclohexenes 25
1.3.3 Earth-Abundant Metal Catalysed Reactions of Ph* Methyl Ketone 100 30
1.3.4 Summary 32
1.4 Importance of Nitrogen in Organic Synthesis 34
1.4.1 Nitrogen Containing Natural Products 34
1.4.2 Nitrogen-Containing Pharmaceuticals 36
1.4.3 Summary 38
1.5 Project Aims 38
Chapter 2: Hydrogen Borrowing Reactions of Aziridino Alcohols 40
2.1 Introduction 40
2.1.1 Properties of Aziridines 41
2.1.2 Project Aims 43
2.2 Results and Discussion: Initial Reaction Development and Scope 43
2.2.1 Reaction Optimisation 43
2.2.2 Diastereoselectivity of Simple Aziridino Alcohols 46
2.2.3 Synthesis and Evaluation of Other Nitrogen-Containing Substrates 51
2.2.4 Hydrogen Borrowing Scope Summary 54
2.3 Results and Discussion: Ph* Cleavage Reactions with Bromine 55

2.3.1 Prior Ph* Deprotection Conditions 55
2.3.2 Deprotection Scope 56
2.3.3 Additional Project Aims 57
2.4 Results and Discussion: Synthesis of Additional Aziridino Alcohols 59
2.4.1 Literature Methods for Asymmetric Aziridinations 59
2.4.2 Organocatalysed Synthesis of Aziridines and Attempted Hydrogen Borrowing 60
2.4.3 Deprotection of Aziridino Aldehydes 63
2.5 Results and Discussion: Reactions of Aziridino Alcohols 373 and 376 68
2.5.1 Hydrogen Borrowing Reactions with Ph* Methyl Ketone 100 68
2.5.2 Attempted Br_2-Mediated Cleavage of Hydrogen Borrowing Product 378 70
2.5.3 Synthesis and Reactions of Methyl-Substituted Aziridino Alcohol 396 74
2.6 Conclusions and Future Work 76
Chapter 3: Total Synthesis of (–)-*γ*-Lycorane 78
3.1 Introduction 78
3.2 Previous Approaches to *γ*-Lycorane 80
3.2.1 Original Isolation 80
3.2.2 Mori, 1995 80
3.2.3 Fujioka, 2006 81
3.2.4 Baudoin, 2018 82
3.2.5 Huang, 2020 82
3.2.6 Summary 83
3.3 Results and Discussion: Racemic Synthesis of (±)-*γ*-Lycorane 84
3.3.1 Synthesis of Hydrogen Borrowing Precursor 414 84
3.3.2 Hydrogen Borrowing Alkylation with Ph* Methyl Ketone 100 84
3.3.3 Use of a Hydrogen Donor 85
3.3.4 Bromine-Mediated Cleavage 88
3.3.5 Attempted Cyclisation Reactions of Dibromide 444 89
3.3.6 Endgame to form (±)-*γ*-lycorane 93
3.4 Results and Discussion: Total Synthesis of (–)-γ-Lycorane 97
3.4.1 Asymmetric Aziridination 97
3.4.2 Reduction of 469 98
3.4.3 Deprotection and Alkylation 101
3.4.4 Endgame to Form (–)-γ-Lycorane 104
3.5 Results and Discussion: A Pericyclic Approach to γ-Lycorane 107
3.5.1 Overman's Synthesis of (–)-Strychnine 107
3.5.2 Aziridination and Diastereoselective Vinyl Addition 108
3.5.3 Attempted Ring-Openings of Aziridino Alcohol 497 109

3.5.4 Second-Generation Efforts to Form Amine 507 113
3.6 Conclusions and Future Work 116
Chapter 4: Hydrogen Borrowing Reactions of Amino Alcohols 118
4.1 Introduction 118
4.1.1 Project Aims 123
4.1.2 Compound Stereochemistry 123
4.2 Results and Discussion: Reaction Optimisation 124
4.3 Results and Discussion: Substrate Synthesis and Scope 127
4.3.1 *N*,*N*-Dibenzyl 1,2-Amino Alcohols Synthesis 127
4.3.2 *N*,*N*-Dibenzyl 1,2-Amino Alcohols Scope 130
4.3.3 Investigating the Role of the Nitrogen Protecting Group 133
4.3.4 *N*-Trityl 1,2-Amino Alcohols Synthesis 137
4.3.5 *N*-Trityl Protected 1,2-Amino Alcohols Scope 142
4.3.6 Additional *N*-Trityl Substrate Synthesis and Scope 145
4.3.7 Synthesis and Scope of Cyclic Serine, Threonine, and Cysteine Derivatives 148
4.3.8 Crystallinity and Secondary Alkylation of Hydrogen Borrowing Products 153
4.3.9 Scope Summary 156
4.4 Results and Discussion: Product Deprotection to γ-Amino Butyric Acids 157
4.4.1 Initial Attempts at Ph* Removal with Br_2 157
4.4.2 Deprotection with HCl in HFIP 161
4.4.3 Chromatography-Free Hydrogen Borrowing and Cleavage 164
4.5 Conclusions and Future Work 165
Chapter 5: Experimental 168
5.1 General Experimental Details 168
Atom Numbering 168
Chromatography 168
Reactions and Reagents 168
Spectroscopy 168
5.2 General Procedures 169
General Procedure A – Hydrogen Borrowing of Aziridine Alcohols 169
General Procedure B – Br_2 Cleavage 169
General Procedure C – Aziridination of α,β-Unsaturated Enals 169
General Procedure D – Deprotection of Boc-Protected Aziridines with TBAF 170
General Procedure E – Hydrogen Borrowing of Amino Acid-Derived Alcohols 170
General Procedure I – Acid-Mediated Cleavage of Trityl Hydrogen Borrowing Products 171
5.3 Experimental Data 172
Appendix 1: X-Ray Crystallographic Data 332

A1.1 Compound 312 332
A1.2 Compound 351 336
A1.3 Compound 368 339
A1.4 Compound 381 342
A1.5 Compound 410 345
A1.6 Compound 553 349
A1.7 Compound 591 352
A1.8 Compound 665 358
A1.9 Compound 719 362
Appendix 2: Experimental Procedures by Indi Marriott 368
Appendix 3: References 370

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.



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Hilary Term 2021

Abstract

Hydrogen Borrowing Reactions of Amino Alcohols and the Total Synthesis of (–)-γ-Lycorane
A thesis submitted for the degree of Doctor of Philosophy by Christopher J. J. Hall, St Anne's College and The Chemistry Research Laboratory, Hilary Term 2021.

Chapter 1: Introduction
The introduction gives an overview of C–C bond forming reactions, highlighting their applications within the thesis. The historical development of C–C bond forming hydrogen borrowing reactions is then reviewed, with an emphasis on work by the Donohoe group involving Ph* methyl ketone, as well as examples in the chemical literature utilising earth-abundant metal catalysts. Finally, the role of nitrogen-containing compounds within both natural products and pharmaceuticals is discussed.

Chapter 2: Hydrogen Borrowing Reactions of Aziridino Alcohols
The hydrogen borrowing reaction between various aziridino alcohols and Ph* methyl ketone is explored, along with the formation of lactams upon removal of the Ph* group with Br_2. A number of *N*-Boc aziridines are synthesised and converted into their corresponding *N*-Bn aziridino alcohols *via* structurally complex aziridino aldehyde dimers. The unexpected reactivity of trisubstituted aziridino alcohols under hydrogen borrowing and Br_2 cleavage conditions is also explored.

Chapter 3: Total Synthesis of (–)-γ-Lycorane
Utilising a key C–C bond forming hydrogen borrowing reaction, and a subsequent Br_2-mediated Ph* cleavage/lactam formation/ring opening cascade, the total synthesis of (–)-γ-Lycorane is completed in 9 steps, 4% overall yield and in 99:1 er. An alternative pericyclic approach to (–)-γ-Lycorane is also explored, with a number of small and highly functionalised amine and aziridine substituted cyclopentanes being successfully synthesised.

Chapter 4: Hydrogen Borrowing Reactions of Amino Alcohols
The hydrogen borrowing reaction between enantioenriched 1,2-amino alcohols, derived from both natural and unnatural amino acids, and Ph* methyl ketone was investigated. The use of a bulky trityl group was found to be effective in protecting the reaction intermediates against racemisation, leading to the isolation of a large number of 1,4-amino ketone products in good yields and with high levels of enantioenrichment. The use of HCl in HFIP was found to be effective for cleavage of both the Ph* and trityl groups, giving 1,4-amino acid products in excellent yields and with no loss in enantioenrichment. The use of column chromatography could be entirely avoided by performing the two steps in sequence without intermediate purification.

Chapter 5: Experimental
This chapter contains the experimental procedures and spectroscopic data for all compounds described within the thesis.

Appendix 1: X-Ray Crystallographic Data
The X-ray crystallographic data for compounds **312**, **351**, **368**, **381**, **410**, **553**, **591**, **665**, and **719** can be found in this appendix.

Appendix 2: Experimental Procedures by Indi Marriott
Experimental data for compounds **411** and **410** prepared by Indi Marriot.

Appendix 3: References
The references cited within the thesis can be found in this appendix.

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This thesis is what it is thanks to the help of my two excellent proofreaders, Tim and Dani, who – in addition to finding every un-italicized *N*-benzyl and missing en-dash – have been stalwart fellow members of F7, as well as endless sources of named reactions (Tim) and career advice (Dani). Life in F7 wouldn't have been the same without our superb Sheriff, Santa, and Enforcer, Oskar – who has been there all the way through my DPhil and has made the last few years all the brighter through his indefatigable cheer. Similarly, Roly has been an enormous help throughout my time as a TJD – whether that be teaching me all there is to know about HPLCs, always being up for an interesting conversation, or having a very excitable Milo to go on walks with! I also must thank Ciaran, for numerous fascinating discussions about politics, chemistry, and everything in between; Simon, for many memorable evenings at the pub and weekend boardgames; Galina, for your unending optimism; Dana, for your humour and teaching us all just *how much* you love *t*BuLi; and some old hands, Johannes, Mel, Waz and CB, for making me feel so welcome to the group back in the day and introducing me to the joys of brew.

Of course, I wasn't always in F7, and many F8ers have made their mark on my DPhil. Hamish has been a great friend ever since he arrived, and we've spent many long hours playing boardgames and talking about dogs – a trend I hope will continue! I'd also like to thank my original fellow member of Team Christmas, OSSC poster design expert, and sharer of dog videos, Anna. Bruno, Lydia, Elliot, Marvin, and Lewis have also been memorable additions to the group – I know brew will be safe in your hands! For looking after me as a lowly Part II, there was no better teacher than Henrique – hopefully I didn't turn out too dodgy after all! And of course, my original fellow Part IIs and double-act, Max and Daniel, have been there throughout and been the source of much wisdom.

I've been fortunate enough to have lived with many friends during my studies, and above all else I must thank Fran for putting up with me for the last seven(!) years. You've been there through thick and thin, and it wouldn't have been the same without you. Similarly, Dom, Ash, Emma, George, Sophie, and Ashok have all made my time in Oxford incredibly special – whether that be from sunny evenings in the garden at Fairacres, to finding our unexpected housemate in Cricket Road. More recently, lockdown wouldn't have been the same without James and Andy making me feel right at home in London, and for some truly delicious cooking.

Last but never least, I'd like to thank my parents for their unconditional love and support for as long as I can remember. I may not know where I'm going, but you've been there for me every step of the way. Similarly, Momma and Pop-pops have always been there with love, support, and embarrassing stories about when I was younger! My DPhil has also given me multiple opportunities to see more of my many American cousins – thank you for all the wonderful evenings on the porch and I can't wait to see you all again. A huge thank you also to Katherine and Gregor for spiriting me out of London at the start of lockdown 2.0 and being such wonderful company for this last bit of my write-up, it's been truly memorable. Finally, these last few years have been made all the more special by Christian and David – thank you for everything.

Abbreviations and Acronyms

Å	Ångström
Ac	acetyl
acac	acetylacetone
AIBN	azobisisobutyronitrile
Ala	alanine
Ar	aryl
Arg	arginine
aq.	aqueous
B	base
bipy	2,2’-bipyridine
BINAPO	2-diphenylphosphino-2’-diphenylphosphinyl-1,1’-binaphthalene
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
°C	degree(s) Celsius
CBz	carboxybenzyl
cm^{-1}	wavenumber(s), inverse centimetre(s)
cod	1,5-cyclooctadiene
conc.	concentrated
COSY	correlation spectroscopy
Cp*	pentamethylcyclopentadienyl
CSA	camphorsulfonic acid
Cy	cyclohexyl
Cys	cysteine
d	days
δ	NMR chemical shift
DABCO	1,4-diazabicyclo[2.2. 2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane, methylene chloride
dFCF	2-(2,4-difluoro-3-(trifluoromethyl)phenyl)-4-methylpyridine
DIBAL-H	diisobutylaluminium hydride

DMAP	4-dimethylaminopyridine
dme	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMPU	*N*,*N*'-Dimethylpropyleneurea
DMSO	dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppBz	1,2-bis(diphenylphosphino)benzene
dr	diastereomeric ratio
dtbby	4,4'-di-*tert*-butylbipyridine
DTBM	3,5-di-*tert*-butyl-4-methoxyphenyl
E	electrophile
ee	enantiomeric excess
ent-	enantiomeric-
epi-	epimeric-
equiv.	equivalent(s)
er	enantiomeric ratio
ESI	electrospray ionisation
Et	ethyl
et al.	*et alii* (Latin: and others)
EXSY	Exchange SpectroscopY
FDA	Food and Drugs Administration
g	gram(s)
Gln	glutamine
Glu	glutamic acid
h	hour(s)
[H]	hydride
HFIP	hexafluoroisopropanol
His	histidine
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQY	heteronuclear single quantum coherence spectroscopy
i	*iso*
IR	infrared spectroscopy

J	coupling constant
L	ligand
L*	chiral ligand
LA	lewis acid
LDA	lithium diisopropylamide
Leu	leucine
Lys	lysine
m	multiplet
M	molarity, mol dm^{-3}
*m*CPBA	*meta*-chloroperoxybenzoic acid
M.p.	melting point
Me	methyl
Mes	mesityl
Met	methionine
min	minute(s)
mL	millilitre(s)
mol	mole(s)
mol%	mole per cent
MS	molecular sieves
n	normal, unbranched alkyl chain
Nap	naphthalene
NMR	nuclear magnetic resonance spectroscopy
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
[Ox]	oxidation
PG	protecting group
Ph	phenyl
Ph*	pentamethylphenyl
Phe	phenylalanine
phen	phenanthroline
Phg	phenylglycine
Piv	pivaloyl
PMP	4-methoxyphenyl

ppm	parts per million
ppy	2-phenylpyridine
Pr	propyl
q	quartet
Quant.	quantitative
R	generic substituent, Rest/Radical
recryst.	recrystallisation
RT	room temperature
sat.	saturated
Ser	serine
SET	single electron transfer
t	tertiary alkyl group, *tert*-alkyl
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Tf	triflyl
TFA	trifluoroaceticacid
THF	tetrahydrofuran
Thr	threonine
TLC	thin-layer chromatography
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
Tr	trityl
Trp	tryptophan
Ts	toluenesulfonyl
Tyr	tyrosine
UV	ultraviolet
Val	valine
ν_{max}	infrared absorption maximum

To Pop-pops – for making me into the scientist I am today.

(all those nights at the Cirencester Science & Technology Society paid off!)

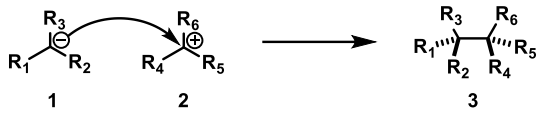
Chapter 1: Introduction

1.1 How to Form a C–C Bond

There is no process more fundamental to organic chemistry than the formation of carbon–carbon (C–C) bonds. Whilst there exist innumerable methods to achieve such a transformation, they can be broadly classified into three main types: polar, radical, and pericyclic.

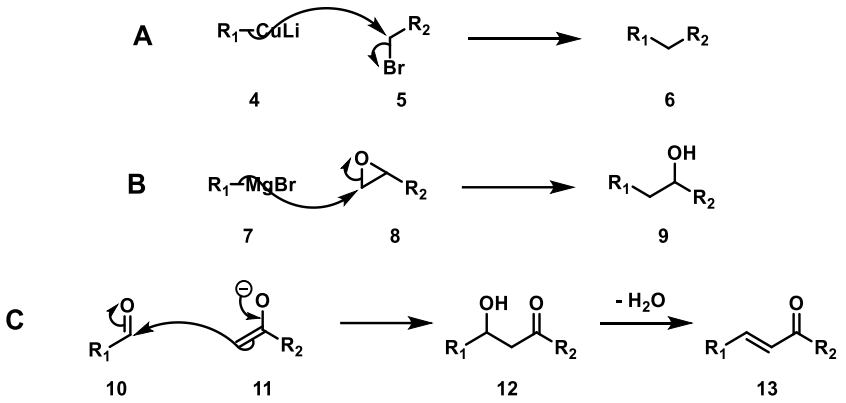
1.1.1 Polar C–C Bond Formations

Polar reactions involve the movement of an electron pair which, when it comes to the formation of C–C bonds, is most simply represented as the reaction between an all-carbon carbanion **1** and carbocation **2** (Scheme 1.1).



Scheme 1.1*: Simple representation of a polar C–C bond formation.*
All possible product stereoisomers not shown.

Such charged species are highly reactive, and so it is common practice to use functional groups in their stead. For the role of the carbanion, it is common to use either an organometallic species – such as an alkyllithium or Grignard reagent – or an enolate derived from deprotonation of a carbonyl. The partnering carbocation is often concealed in the form of a polarised C–X bond; examples being those found in alkyl halides, cyclic ethers such as epoxides, or functionalised alcohols such as tosylates; or in an easily broken π bond – the archetypal example being carbonyls, although alkenes and alkynes are also commonly used. Representative examples are shown below, ranging from the simple alkylation reaction between an organocuprate **4** and bromide **5** (A); the addition of a Grignard reagent **7** to an epoxide **8** (B); and the base-catalysed aldol reaction between an aldehyde **10** and ketone enolate **11** to give a β-hydroxy ketone **12**, which can then lose water to give enone **13** (C) (Scheme 1.2).

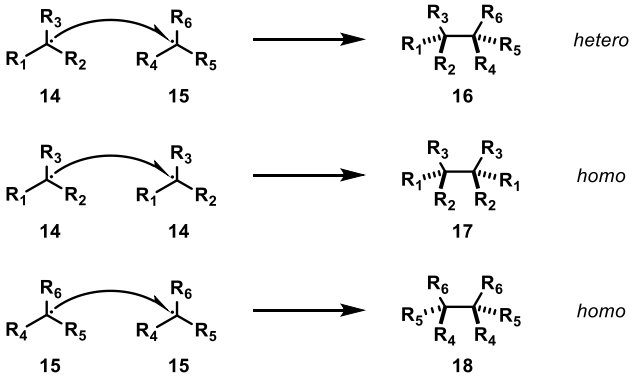


***Scheme 1.2**: Representative examples of polar bond-forming reactions.*

Of these, it is the aldol reaction (C) that is of most importance to this thesis – forming the basis of the hydrogen borrowing alkylation reactions described later in this chapter and others.

1.1.2 Radical C–C Bond Formations

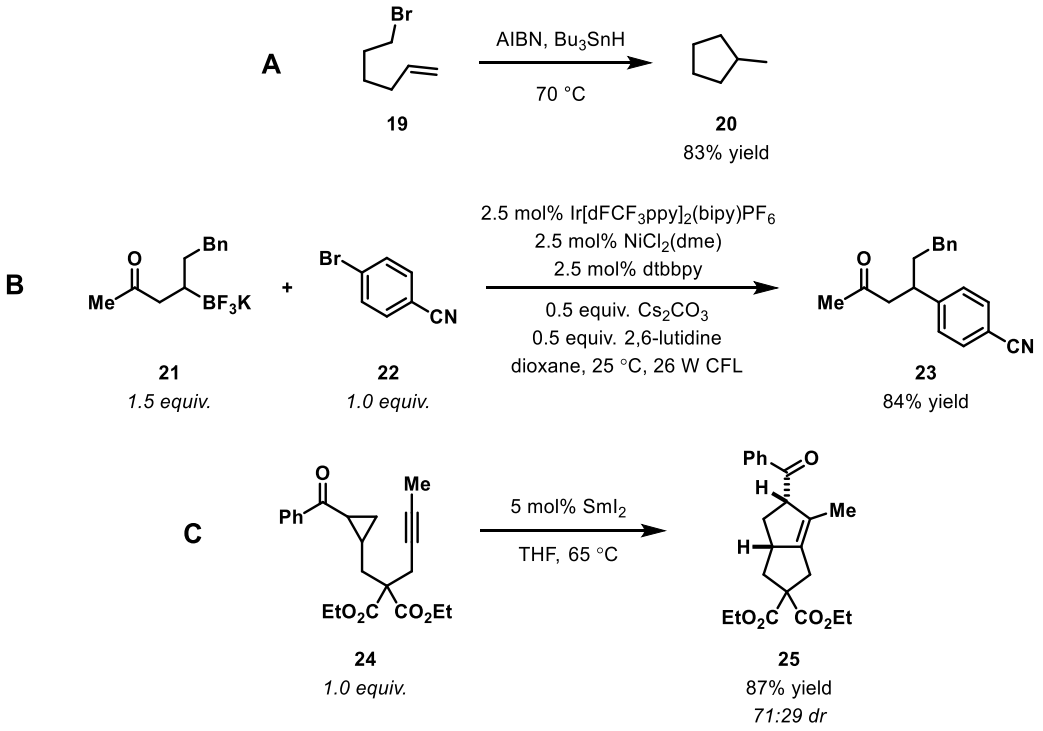
Radical reactions involve singly occupied molecular orbitals containing unpaired electrons, with the reacting species often being uncharged. This lack of charge, however, can lead to a loss in specificity – with intermolecular radical reactions suffering from a product distribution of hetero- and homo-dimers (Scheme 1.3).



***Scheme 1.3**: Simple representation of a bimolecular radical C–C bond formation. All possible product stereoisomers not shown.*

Due to this drawback, radical reactions were historically used in intramolecular reactions – with the initial radical species cyclising onto a suitable acceptor, such as an alkene or alkyne, within the same molecule. However, modern techniques allow for selective intermolecular reactions as well.[1] In order to generate the radical species needed for reaction, certain functional groups are required – with

representative examples being shown below (Scheme 1.4). The most typical are, once again, weak C–X bonds – with classic historical examples being alkyl bromides and iodides. In combination with a radical initiator (such as AIBN) and a radical chain carrier (such as Bu_3SnH), these can be used to selectively form radicals at the carbon atom of choice with the radical reaction then proceeding to form a new C–C bond (A).[2] Alternatives to this approach include the use of modern photochemical techniques to generate radicals *via* the action of an excited photocatalyst on a suitable species, such as Molander's use of an alkyl BF_3K salt **21** (B),[3] as well as Proctor's use of substoichiometric SmI_2 to generate carbon-based radicals from carbonyls **24** (C).[4]

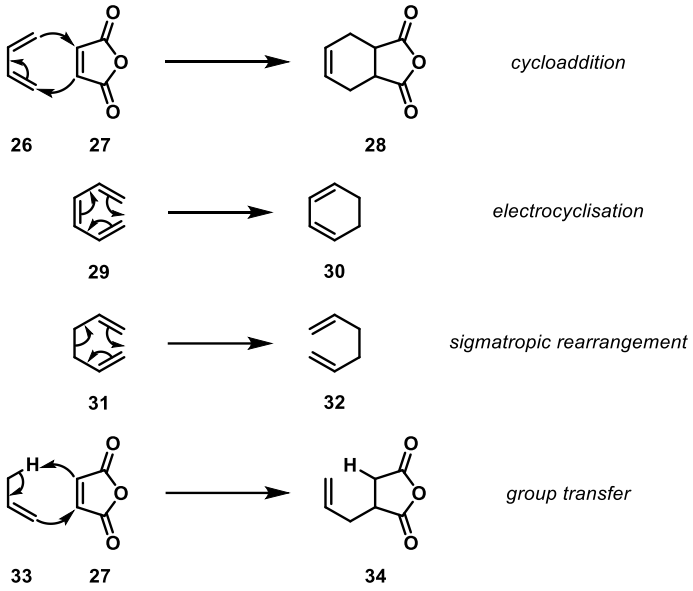


***Scheme 1.4**: Literature examples of radical bond-forming reactions.*

Whilst radical reactions are unexplored for much of this thesis, the AIBN-mediated formation of a carbon-based radical from a weak C–X bond (A) is investigated in Chapter 3 as part of the total synthesis of (–)-γ-lycorane.

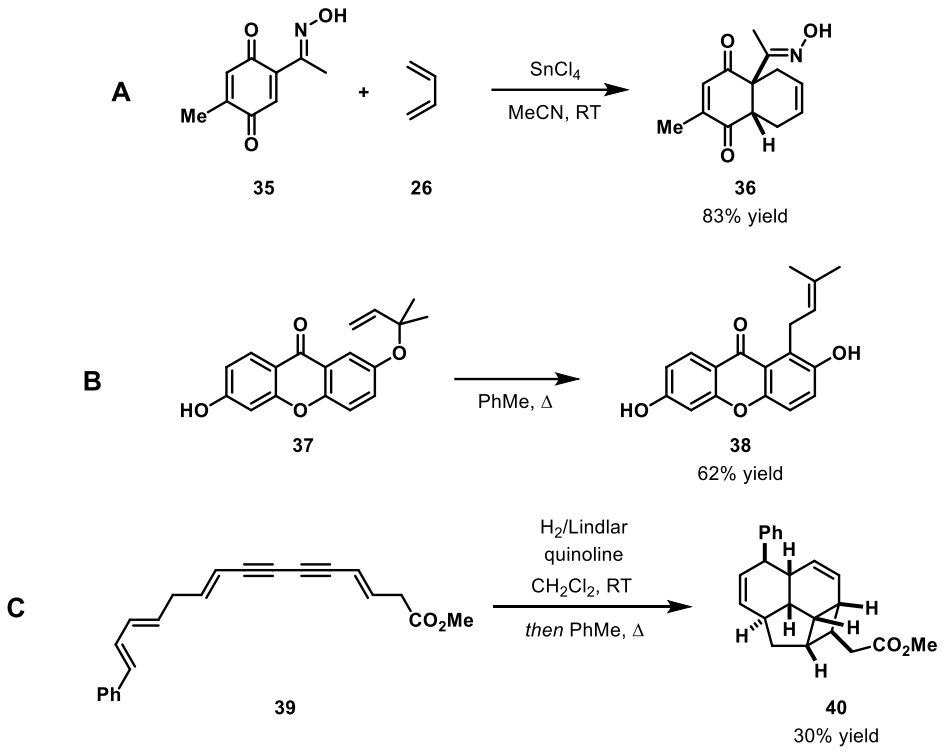
1.1.3 Pericyclic C–C Bond Formations

Pericyclic reactions are set apart from polar and radical reactions in that the reaction transition state involve a complete cycle of bond orbitals, with the reaction progressing in a concerted fashion from the starting material(s) to product(s). They are further divided into four main classes – cycloadditions, electrocyclisations, sigmatropic rearrangements, and group transfer reactions (Scheme 1.5).



***Scheme 1.5**: Examples of the four main classes of pericyclic reaction.*

Representative examples of pericyclic reactions used in synthesis are shown below (Scheme 1.6). The most commonly used, and perhaps most powerful, pericyclic reaction is the Diels–Alder reaction – as shown in Kishi's synthesis of a tetrodotoxin precursor (A) – in which a cycloaddition between a diene **26** and dienophile **35** generates two new stereocentres and two new C–C bonds.[5] [3,3]-Sigmatropic rearrangements are also used in total synthesis – with the Claisen rearrangement of allyl vinyl ethers finding many uses in total synthesis, such as in part of Suzuki's synthesis of termicalcicolanone A (B).[6] Whilst pericyclic reactions have so far found to be less common in nature than their polar and radical cousins, the biosynthesis of endiandric acid C was proposed by Black and co-workers to proceed *via* a cascade reaction involving two sequential electrocyclic reactions followed by a final Diels–Alder cyclisation[7] – a process demonstrated by Nicolaou in his elegant 1982 total synthesis (C).[8]



***Scheme 1.6**: Literature examples of pericyclic reactions in total synthesis.*

Towards the end of Chapter 3, a pericyclic aza-Cope reaction is explored as a possible avenue towards the synthesis of (–)-γ-lycorane – building on the ingenious use of such a reaction by Overman in his ground-breaking 1993 synthesis of (–)-strychnine.[9]

1.1.4 Summary

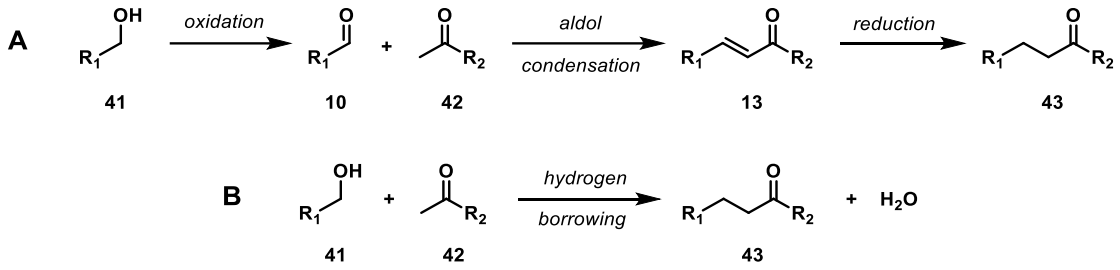
As previously mentioned, of the three main classes of C–C bond forming reactions it is polar bond formations – and in particular, the aldol reaction – which forms the basis of this thesis. However, as shown in Scheme 1.2, the product of a classical aldol reaction is an unsaturated alkene product such as **13**. Whilst olefins are immensely useful synthetic functional groups in organic chemistry,[10] the synthesis of saturated C–C bonds is arguably more valuable. A 2009 review of saturation in pharmaceutical molecules found that an increase in molecular complexity – measured in part by the number of sp^3 hybridised carbons and asymmetric centres in a molecule – was correlated with more successful transitions from discovery to drug.[11]

Fortunately, there exist synthetic methods which marry the strengths of the aldol reaction with the evident scientific need to develop methods to access more sp^3 centres – namely, hydrogen borrowing alkylation reactions.

1.2 Hydrogen Borrowing Alkylation Reactions

1.2.1 Reaction Overview

To appreciate the synthetic utility of hydrogen borrowing reactions, it is useful to compare them side-by-side with a classical aldol reaction sequence that achieves the same overall synthetic transformation (Scheme 1.7).

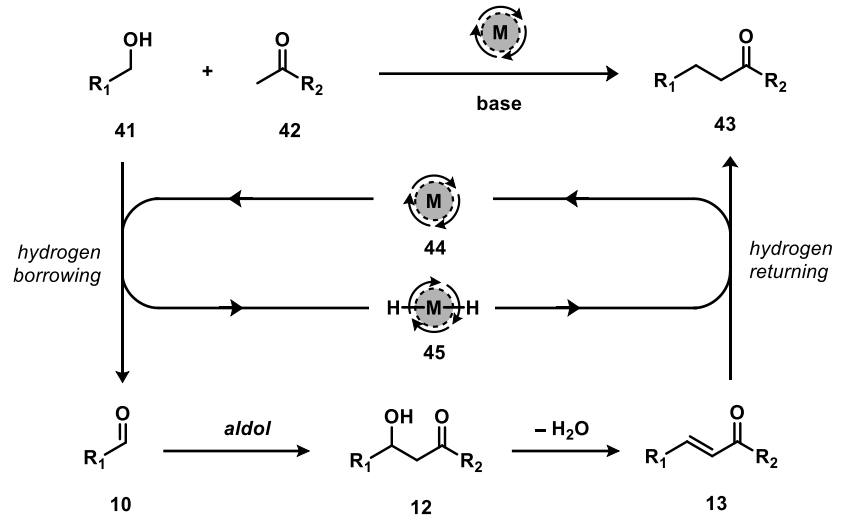


***Scheme 1.7**: Comparison of aldol and hydrogen borrowing reactions.*

Starting from alcohol **41**, the first step is oxidation to aldehyde **10**, a process that can involve expensive or environmentally injurious reagents. Once purified, aldehyde **10** can then undergo an aldol condensation with ketone **42**, giving the product enone **13**. The final step to obtain product **43** is a reduction of the olefin moiety – for which many methods exist, often involving the addition of an organic hydride source or a metal catalysed hydrogenation. In summary, the overall transformation of alcohol **41** to alkylated ketone product **43** is achieved in three separate steps – an oxidation, aldol condensation, and reduction (A).

In comparison, effecting a hydrogen borrowing process allows for the reaction of alcohol **41** and ketone **42** to proceed to the alkylated product **43** in a single step (B) – bypassing the intrinsic and inescapable inefficiencies of multi-step processes. To appreciate how such a transformation is

achieved, it is necessary to examine the generic mechanism of a hydrogen borrowing alkylation reaction (Scheme 1.8).



***Scheme 1.8**: Generic mechanism of a hydrogen borrowing alkylation reaction.*

The first step in the mechanism is oxidation of alcohol **41** by a suitable metal catalyst **44** to give aldehyde **10** and metal-hydride species **45**. Aldehyde **10** can then undergo a classical base-catalysed aldol condensation with ketone **42** to give enone **13**, which is then reduced by the metal-hydride species **45** to give alkylated product **43**, as well as regenerating the metal catalyst **44**, thereby allowing the catalytic cycle to perpetuate. The only by-product from the reaction is the water produced during the aldol condensation – an important consideration when evaluating the environmental impact of the reaction.

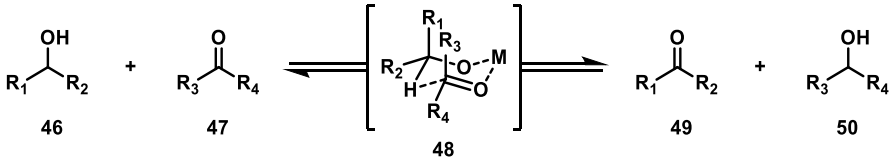
Environmental impact is also of paramount importance when comparing hydrogen borrowing alkylations to another of the more traditional methods of C–C bond formation seen in Scheme 1.2 – namely, the attack of an enolate onto an alkyl halide or other leaving group (A). Rather than using an alcohol as the alkylating agent, these require either pre-activation of the alcohol or its conversion into a suitable halide/halide equivalent – processes that entail environmental costs due to both atom economy, as well as the intrinsic toxicity of many alkylating reagents.[12] Furthermore, to control reactivity, these reactions often require the complete formation of the enolate prior to the reaction

using strong bases such as LDA or KHMDS, as well as cryogenic temperatures to prevent side reactions. Organocatalytic methods have been developed that allow for the amelioration of some of these factors, however they come with their own synthetic issues.[13] Combined, these factors lay bare the shortcomings in traditional methods for the alkylation of carbonyls – some of which have been addressed in the historical, and continuing, development of hydrogen borrowing alkylation reactions.

1.2.2 Historical Origins of Hydrogen Borrowing Catalysis

Before hydrogen can be borrowed, it needs to be transferred – and so it is unsurprising that before hydrogen borrowing catalysis came the field of transfer hydrogenations. In a typical transfer hydrogenation reaction, a catalyst – which is usually, but not always,[14] a transition metal species – accepts hydrogen from an alcohol (or amine) to generate a more reactive carbonyl (or imine). Rather than returning the hydrogen at the end of the reaction, the catalyst is regenerated by transferring the hydrogen to an acceptor molecule, which in most cases is another carbonyl (or imine) species.

The most basic example of such a transformation – and one that, from a practical point of view, can occasionally rear its head in unexpected places – is the Meerwein–Ponndorf–Verley (MPV) reaction. In this process, a metal catalyst (often an aluminium alkoxide species) facilitates the direct transfer of hydrogen (or rather, hydride) from an alcohol **46** to a carbonyl acceptor **47** to give a product carbonyl **49** and alcohol **50** *via* a 6-membered cyclic transition state **48** (Scheme 1.9).

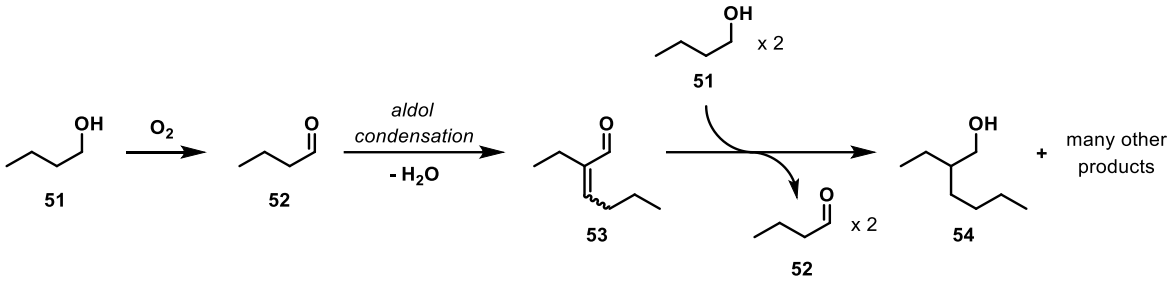


Scheme 1.9*: General mechanism of the Meerwein–Ponndorf–Verley reaction.*

Such a process is inherently reversible due to the principle of microscopic reversibility, and as such, the distribution of products arises from the inherent relative thermodynamic stabilities of all the components – however, the outcome of the reaction may be influenced by the use of an excess of either the alcohol **46** or carbonyl **47**, to push the position of equilibrium to favour the formation of the

desired product. In the case where an excess of carbonyl **47** is used to drive the oxidation of alcohol **46**, the process is known as an Oppenauer oxidation.

A very early example of a hydrogen borrowing-type reaction in the literature, and one that would have much bearing on the future direction of hydrogen borrowing alkylations, is the Guerbet Reaction, first disclosed over a century ago (Scheme 1.10).



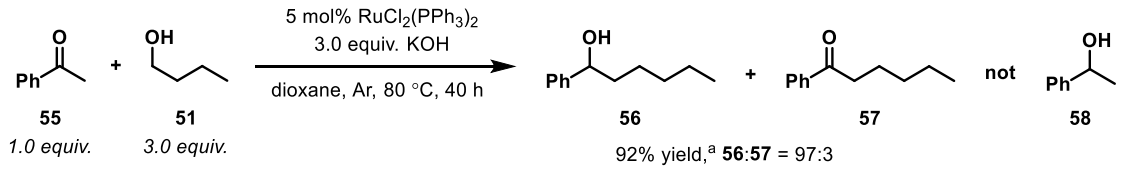
***Scheme 1.10**: General mechanism of the Guerbet reaction.*

Guerbet observed the reaction of 1-butanol **51** at elevated temperatures to give a range of products, including dimerisation product 2-ethylhexanol **54**.[15] The reaction is initiated by the spontaneous air oxidation of a small quantity of butanol **51** to give butanal **52**. Butanal **52** then reacts with itself *via* an aldol condensation to give unsaturated dimer **53**, which is then reduced twice in an MPV-type reaction by two additional equivalents of butanol **51** to give the product **54**. Two more equivalents of butanal **54** are generated during this reaction, allowing the reaction to propagate.

A key issue with the Guerbet reaction is its lack of selectivity, with a number of different product isomers and derivatives being formed – as well as compounds resulting from competing processes such as Cannizzaro and Tishchenko reactions. Fortunately, the last century – and in particular the last two decades – has seen the development of many metal-catalysed processes to form carbon–carbon bonds *via* hydrogen borrowing that have done much to overcome these deficits, a representative number of which will now be discussed.

1.2.3 Modern Approaches to Hydrogen Borrowing Alkylations with Primary Alcohols

Perhaps the first pertinent example of a transition metal catalysed hydrogen borrowing reaction involving an aldol reaction was the unexpected ruthenium-catalysed coupling between acetophenone **55** and 1-butanol **51** observed in 2001 by Shim and co-workers during their studies into transfer hydrogenation reactions (Scheme 1.11).[16]



Scheme 1.11*: Unexpected ruthenium catalysed hydrogen borrowing as reported by Shim and co-workers.*
[a]Determined by GLC analysis

Whilst the initial aim had been to perform a reductive hydrogenation of acetophenone **55** to form 1-phenylethanol **58**, what was instead observed was a mixture of condensation products **56** and **57** with consistently high combined yields in a variety of ratios depending on the metal catalyst used and the reaction temperature. Shim and co-workers concluded that this was due to a hydrogen borrowing cycle similar to that described in Scheme 1.8, albeit with the resulting ketone **57** often being reduced to the corresponding alcohol **56** – a result of the excess (3 equivalents) alcohol **51** generating additional metal hydride species capable of reduction. Shim and co-workers concluded their initial investigations by examining a number of other ketones and alcohols under their reaction conditions, many of which gave the desired products in good to high yields (Table 1.1).

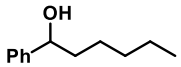
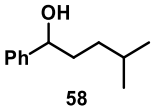
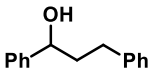
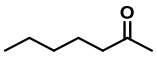
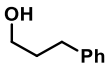
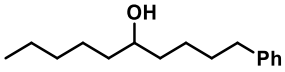
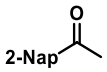
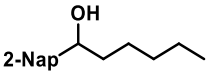
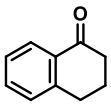
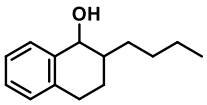
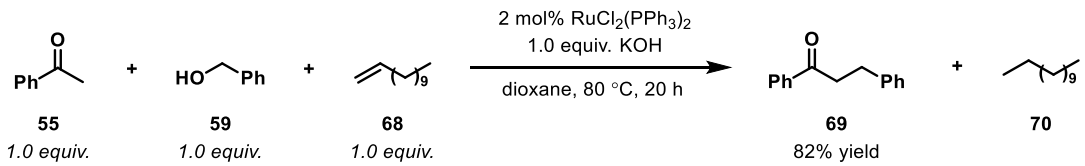
Ketone	Alcohol	Product	Yield
 **55**	 **51**	 **56**	80%
 **55**	 **57**	 **58**	76%
 **55**	 **59**	 **60**	77%[a]
 **61**	 **62**	 **63**	49%
 **64**	 **51**	 **65**	85%
 **66**	 **51**	 **67**	47%[b]

***Table 1.1**: Selected substrate scope of Shim's ruthenium catalysed alkylation reaction. Reaction conditions: 1.0 equiv. ketone, 3.0 equiv. alcohol, 5 mol% $RuCl_2(PPh_3)_2$, 3.0 equiv. KOH, dioxane, Ar, 80 °C, 40 h.*
[a]Reaction conducted for 20 h. [b]2-Butyl-1-tetralone also isolated in 45% yield.

In a subsequent publication, Shim and co-workers found that the addition of a sacrificial hydride acceptor in the form of 1-dodecene **68** was effective in preventing reduction of the final carbonyl species, as demonstrated by the ruthenium-catalysed reaction between acetophenone **55** and benzyl alcohol **59** giving alkylated product **69** in 82% yield (Scheme 1.12).[17]



***Scheme 1.12**: Shim's alkylation of acetophenone **55** in the presence of 1-dodecene **68**.*

The next main advance in the field came from the group of Ishii, who in 2004 reported that the use of $[Ir(cod)Cl_2]$, PPh_3 and KOH in the absence of solvent facilitated the α-alkylation of a range of ketones with primary alcohols without the use of a sacrificial hydride acceptor (Table 1.2).[18]

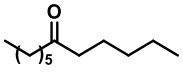
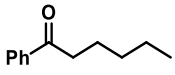
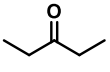
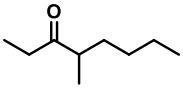
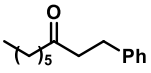
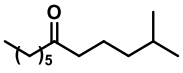
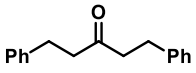
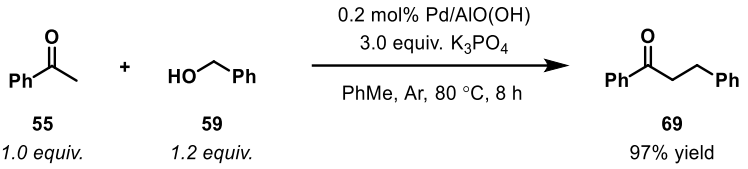
Ketone	Alcohol	Product	Yield
 71	 51	 72	80%
 55	 51	 57	88%
 73	 51	 74	47%
 71	 59	 75	81%
 71	 76	 77	84%
 78	 59	 79	86%

***Table 1.2**: Ishii's use of [Ir(cod)Cl$_2$] to facilitate α-alkylation of ketones with primary alcohols. Reaction conditions: 1.0 equiv. ketone, 2.0 equiv. alcohol, 1 mol% [Ir(cod)Cl]$_2$, 4 mol% PPh$_3$, 10 mol% KOH, 100 °C, 4 h.*

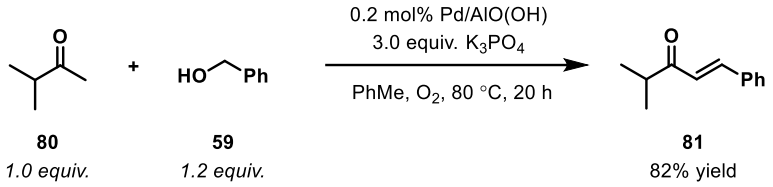
Yields were generally high, and in most cases only a single product was observed, with minimal reduction of the final ketones to the corresponding alcohols. A twofold excess of the primary alcohol was used to ensure selectivity for the desired products and prevent unwanted dimerisation of starting ketones. Of particular note was the reaction between 3-pentanone **73** and 1-butanol **51** which resulted in branched alkylation product **74**, the lower yield of 47% for this process reflecting the difficulties associated with alkylation of non-methyl ketones, which is a recurring issue for many catalytic systems in this field.

With Ishii having established a new precedent of direct alkylation of ketones with primary alcohols without the use of a sacrificial hydride acceptor, subsequent publications were to focus on the use of different metal catalysts to effect the same transformation. A noteworthy contribution was described by Park and co-workers who found that palladium could be used to catalyse the prototypical reaction between acetophenone **55** and benzyl alcohol **59** (Scheme 1.13).[19]



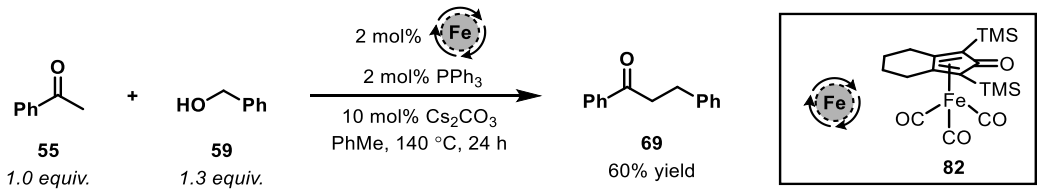
***Scheme 1.13**: Park and co-workers' use of palladium for hydrogen borrowing alkylations.*

A particular highlight of Park's work was that the heterogeneous palladium catalyst Pd/AlO(OH), composed of palladium nanoparticles encapsulated within an aluminium hydroxide framework, could be recovered and reused after the reaction with negligible decrease in product yield even after six reaction cycles, provided an equivalent of K_3PO_4 (relative to acetophenone **55**) was added with each cycle to reactivate the catalyst. Furthermore, whilst saturated products such as **69** were the majority product when the reaction was run under an atmosphere of Ar, the use of an O_2 atmosphere selectively formed enone products such as **81** in good yield – although in all cases the reaction was more sluggish, requiring up to 20 h to reach completion (Scheme 1.14).



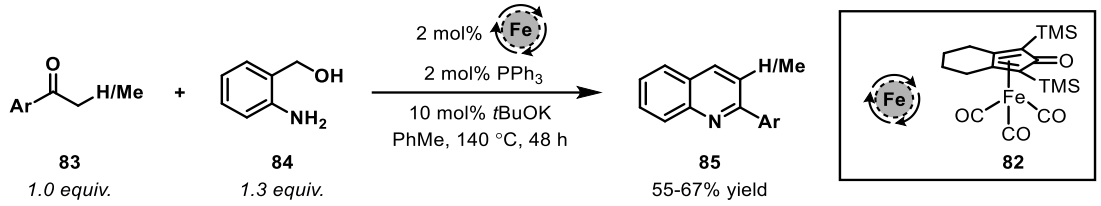
***Scheme 1.14**: Park and co-workers' use of an O_2 atmosphere to form enones.*

Another substantial advance in the field came in 2015, when Beller and co-workers showed that the Knölker-type iron catalyst **82** could be used to promote the alkylation of aryl methyl ketones with primary alcohols, which represented the first use of a first-row transition metal for this type of transformation (Scheme 1.15).[20, 21]



***Scheme 1.15**: Beller and co-workers' use of iron catalyst **82** for α-alkylation of ketones.*

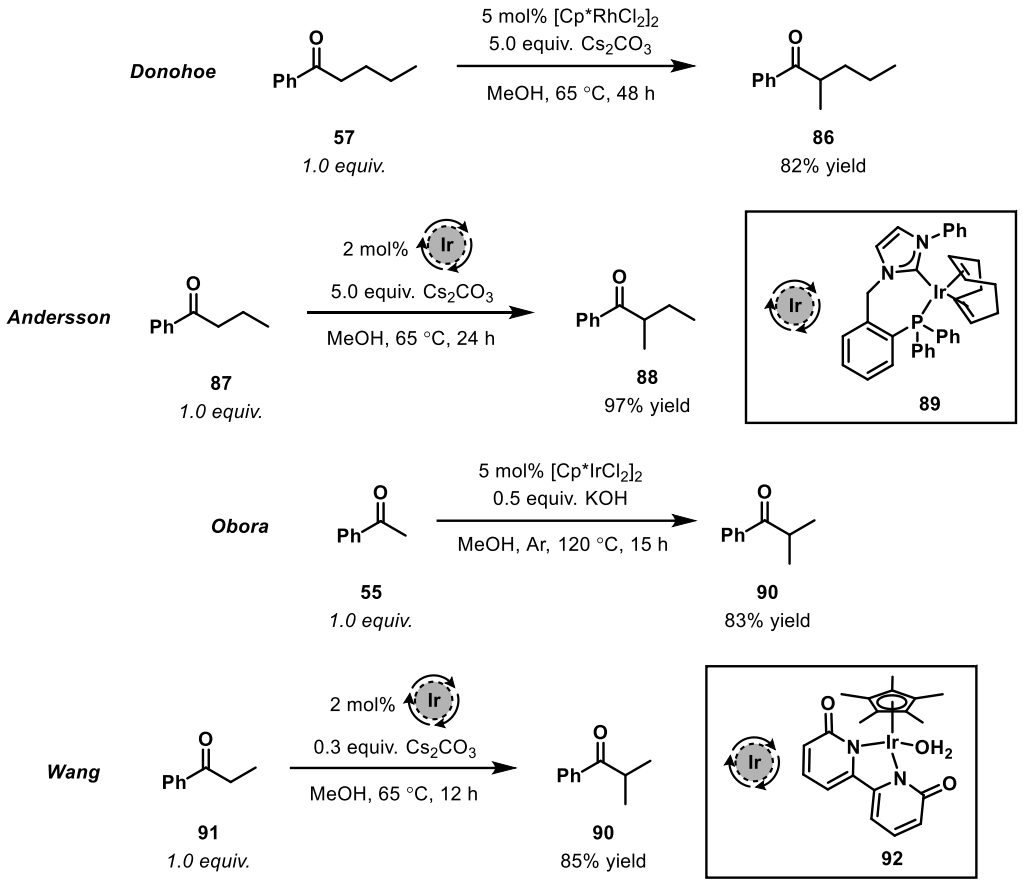
As with Ishii and co-workers' results, an excess of the primary alcohol was required to prevent unwanted dimerisation of the ketone starting materials. The authors also demonstrated the use of catalyst **82** in a modified Friedländer reaction,[22] synthesising a number of quinolines **85** from ketones **83** and 2-aminobenzyl alcohols **84** (Scheme 1.16).



***Scheme 1.16**: Synthesis of quinolines* via *an iron-catalysed modified Friedländer reaction.*

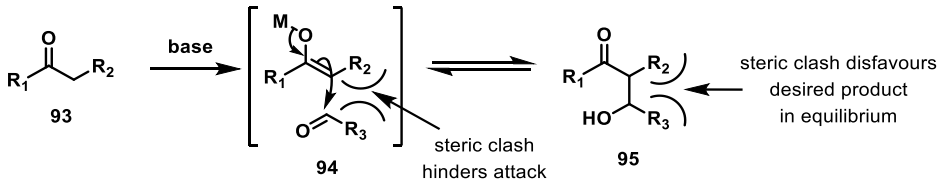
Whilst the above examples demonstrate a range of catalytic systems capable of promoting a hydrogen borrowing reaction between ketones and primary alcohols, in almost all cases they result in the formation of linear products. Compound **74**, formed from 3-pentanone **73** and 1-butanol **51** using Ishii's conditions, constitutes the only branched product; the low yield of 42% further reflecting the difficulty of such a transformation.

The first of such hydrogen borrowing reactions specifically designed to generate α-branched ketone products all involved MeOH as the alcohol coupling partner, with key examples coming from the groups of Donohoe,[23] Andersson,[24] Obora,[25] and Wang (Scheme 1.17).[26]



***Scheme 1.17**: Formation of α-branched ketone products using MeOH under hydrogen borrowing catalysis.*

The exclusivity of MeOH as the alcohol for these processes arises from the fact that the aldol reaction required for the formation of a branched product is much less favourable than that needed for linear analogues. This is due in part to the additional steric bulk of the enolate hindering the initial attack in **94**, as well as increased strain in the aldol addition intermediate **95** (Scheme 1.18).

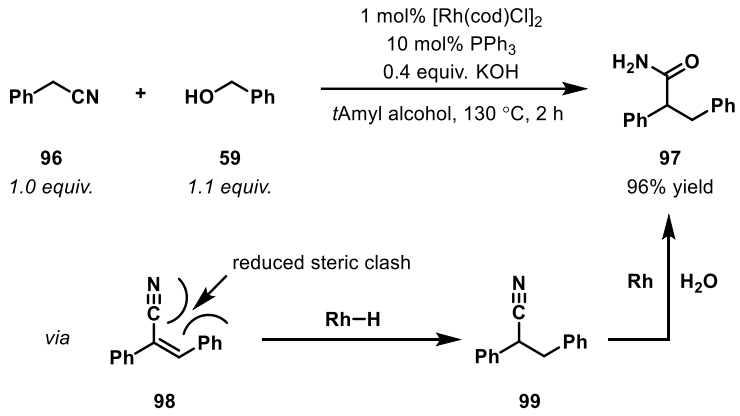


***Scheme 1.18**: Issues facing the formation of branched products using hydrogen borrowing catalysis.*

Although the initial oxidation of MeOH to formaldehyde is more challenging than the corresponding oxidations of either alkyl or benzyl alcohols – as evidenced by its increased energy of dehydrogenation (ΔH (MeOH) = +84 kJ mol^{-1}, cf. ΔH (EtOH) = +68 kJ mol^{-1})[27] – the exceptional reactivity of formaldehyde as an electrophile facilitates the initial attack of the carbonyl enolate, with formaldehyde's small steric

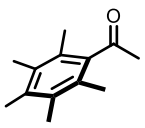
bulk then minimising allylic strain in the final product. A final benefit of formaldehyde as the electrophile is that it cannot undergo the competing self-condensation reactions that are often observed with other aldehydes, thereby increasing reaction selectivity.

As useful a process as methylation may be, the use of higher alcohols in hydrogen borrowing reactions to form branched carbonyl products still remained unanswered. The first example of progress in this area came from Wang and co-workers, who showed that rhodium could be used to catalyse the reaction of arylacetonitriles **96** and primary alcohols **59** to give α-alkylated arylacetamides **97** *via* α-alkylated arylacetonitriles **99** (Scheme 1.19).[28]



***Scheme 1.19**: Wang and co-workers' α-alkylation of arylacetonitriles with primary alcohols.*

In this case, the use of an arylacetonitrile in place of a more traditional ketone results in a more favourable aldol condensation due to acidification of the benzylic protons by the nitrile group, as well the linear nature of the nitrile moiety minimising steric interactions in the α,β-unsaturated nitrile intermediate **98** prior to the final conjugate addition of the metal hydride to give **99**. The rhodium catalyst is proposed to then hydrate nitrile **99** to the corresponding amide products **97**.



100

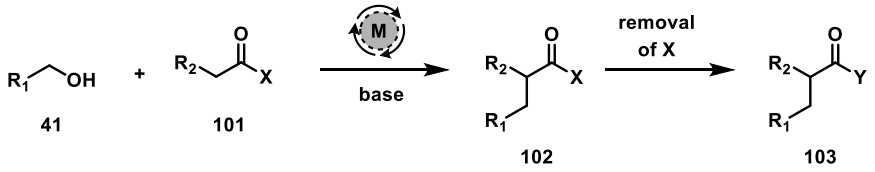
***Figure 1.1**: Pentamethyl acetophenone, also known as Ph* methyl ketone **100**.*

The next breakthrough in this area was to come from Donohoe and co-workers, particularly *via* the use of pentamethyl acetophenone, also known as Ph* methyl ketone **100**, and its various derivatives (Figure 1.1).

1.3 Use of Ph* Methyl Ketone 100 in Hydrogen Borrowing Catalysis

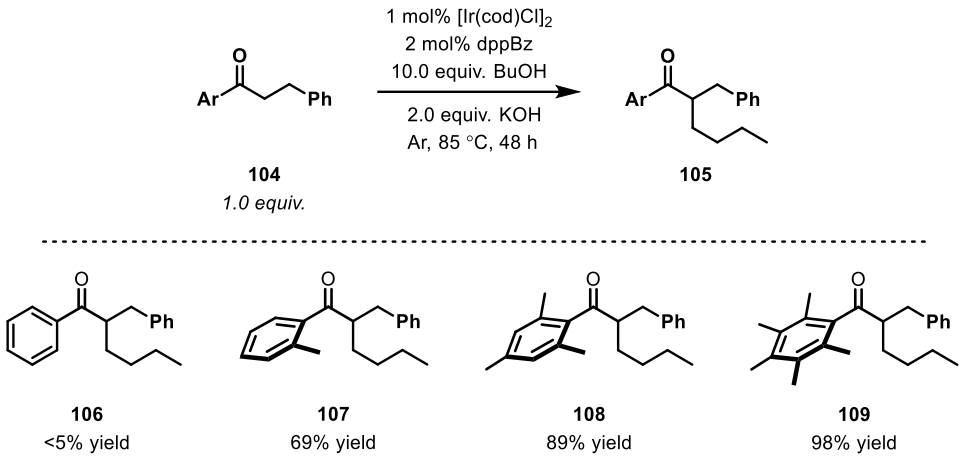
1.3.1 Initial Discovery and Alkylations Using Primary and Secondary Alcohols

As previously discussed, the two key issues preventing the use of higher alcohols in hydrogen borrowing reactions with carbonyls to form α-branched products are the steric hindrance of the initial enolate attack, and the unfavourable steric interactions of the aldol adduct favouring the reverse reaction in the equilibrium. Donohoe and co-workers hypothesised that these issues could be overcome by designing a carbonyl substrate **101** in such a way that the group X: (i) reduced steric hindrance about the carbonyl; (ii) prevented homodimerization of **101**; (iii) protected the carbonyl from reduction to the corresponding alcohol; and (iv) could be readily removed or transformed in such a way after the hydrogen borrowing sequence to access a range of useful products (Scheme 1.20).[29]



Scheme 1.20*: Donohoe and co-workers' design of a suitable carbonyl substrate* ***101*** *for the formation of branched products from higher alcohols* via *hydrogen borrowing catalysis.*

As aryl methyl ketones are perhaps the most studied family of carbonyls for hydrogen borrowing catalysis, simple aryl ketones **104** were a logical starting point for Donohoe and co-workers in their hydrogen borrowing studies (Scheme 1.21).

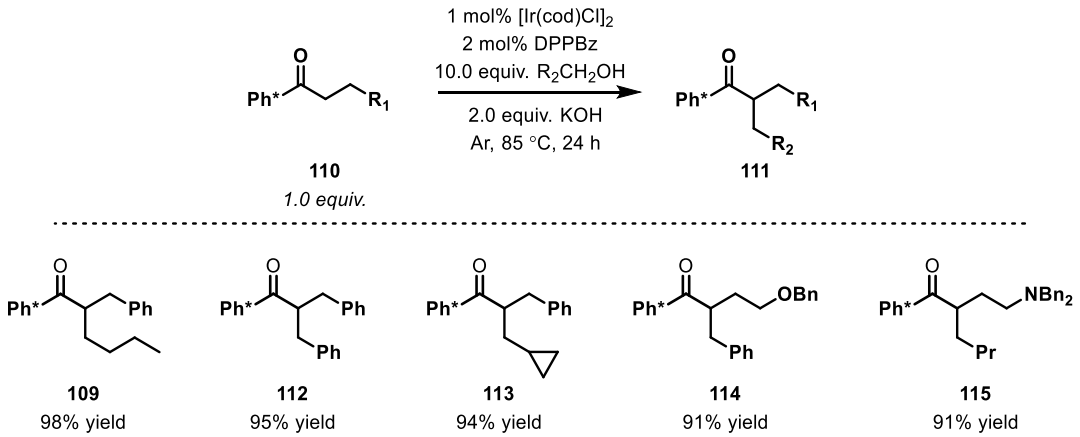


***Scheme 1.21**: Hydrogen borrowing alkylations of substituted aryl ketones with 1-butanol **51**.*

Intriguingly, whilst unsubstituted phenyl derivative **106** was formed in only trace quantities, the use of a single *ortho* methyl substituent on the ring resulted in the desired product **107** being isolated in 69% yield. Further methyl substitution on the ring, first at the other *ortho* position and then on all five possible positions resulted in formation of the desired products **108** and **109** in 89% and 98% yield, respectively. Whilst an initial analysis might suggest that additional steric bulk around the ring would only exacerbate the aforementioned problems associated with enolate attack and allylic strain in the key aldol reaction, Donohoe and co-workers suggested that the presence of *ortho* substituents served to twist the phenyl ring out of conjugation with the carbonyl moiety – an observation supported by both IR and X-Ray crystallographic analysis – which led to two key benefits.

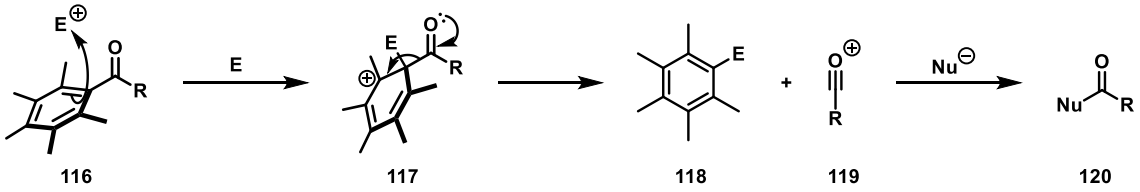
Firstly, by twisting the ring out of plane with the carbonyl, steric hindrance about the carbonyl α-carbon is reduced. This reduction in steric hindrance results in a more favourable enolate attack onto the primary alcohol-derived aldehyde, and also suppresses the deleterious retro-aldol reaction. Secondly, the *ortho* methyl groups increase reaction selectivity by shielding the carbonyl from reduction to the corresponding alcohol, a commonly observed side-process in previous methodologies,[16–18, 20] as well as preventing competing self-aldol reactions.

A short substrate scope involving a number of different primary alcohols and heteroatom-substituted aryl ketones was completed, with the desired products being formed in high yields and selectivities in all cases (Scheme 1.22).



***Scheme 1.22**: Selected substrate scope of various pentamethylphenyl ketone hydrogen borrowing reactions.*

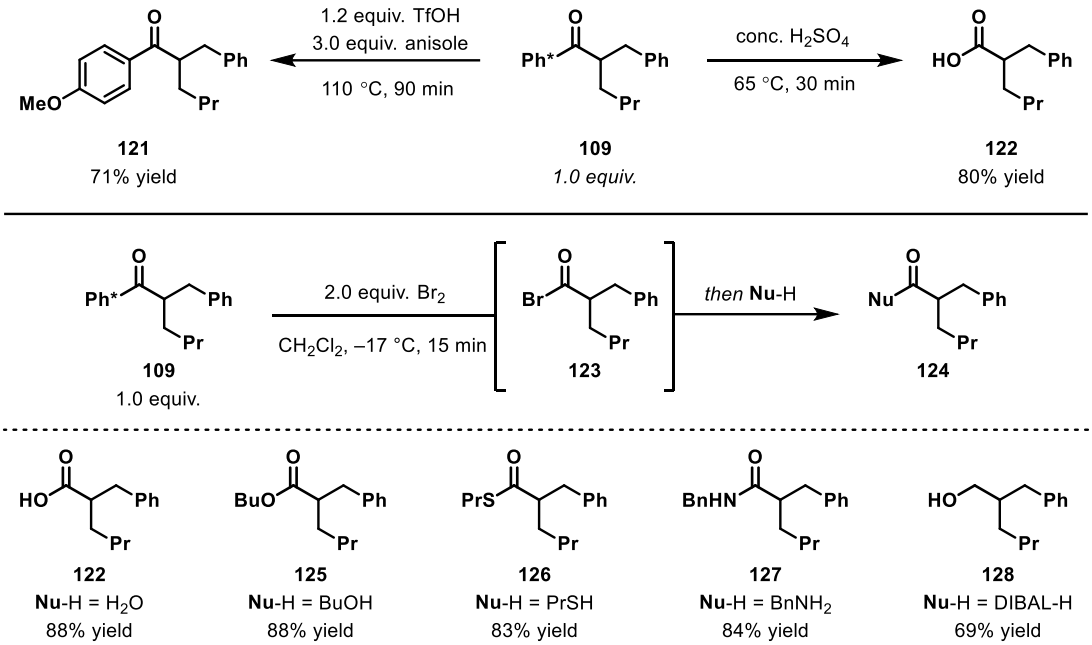
Whilst the pentamethylphenyl group had clearly fulfilled the Donohoe group's primary design objective of reducing steric hindrance about the carbonyl α-carbon and facilitating the key hydrogen borrowing transformation, conditions had to be developed to cleanly remove it from the reaction products. Fortunately, a number of suitable reaction conditions were found, all of which achieved the transformation *via* the same general mechanism (Scheme 1.23).



***Scheme 1.23**: Mechanism for the cleavage of pentamethylphenyl ketones **116**.*

Donohoe and co-workers proposed that the cleavage reaction began with an initial activation of the pentamethylphenyl ring in **116** *via* reaction at the *ipso* position with a suitable electrophile, $\mathbf{E^+}$, to give intermediate **117**. This was followed by loss of substituted pentamethylbenzene **118** to give a putative oxonium ion **119** which is then attacked by a suitable nucleophile, $\mathbf{Nu^-}$, to give **120** (Scheme 1.23).

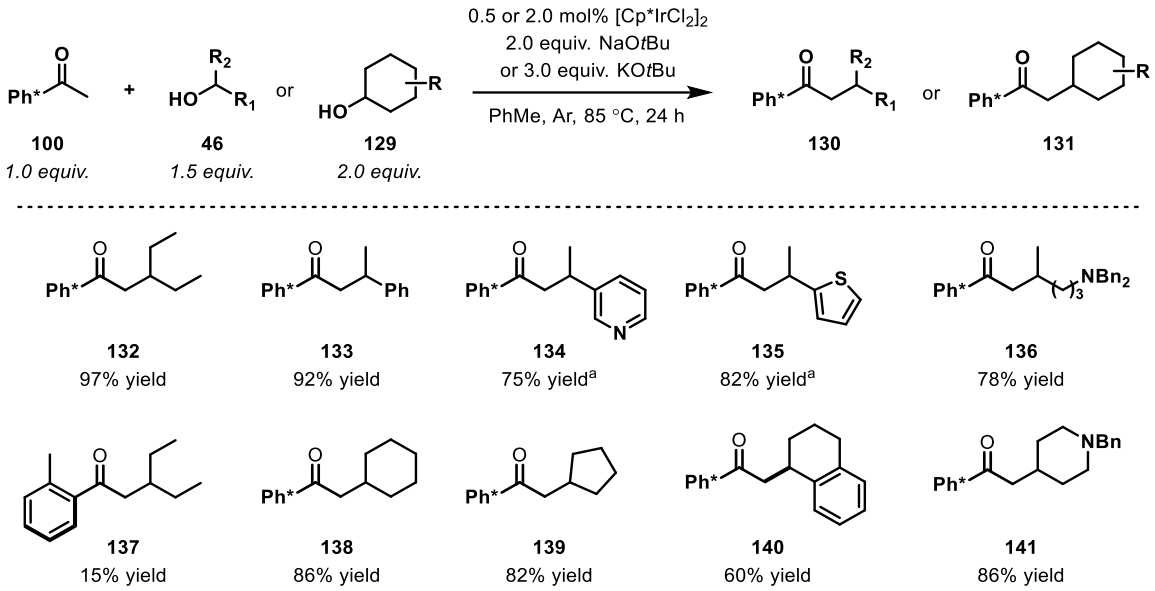
Two different modalities of reaction were developed, with the role of E^+ being played by either a proton or Br_2. Under acidic conditions, Donohoe and co-workers found that product **109** could be readily converted into either aryl ketone **121** or carboxylic acid **122** in good yields, with either anisole or water acting as the nucleophile, respectively (Scheme 1.24).



***Scheme 1.24**: Mechanism and selected scope of pentamethylphenyl ketone cleavage conditions.*

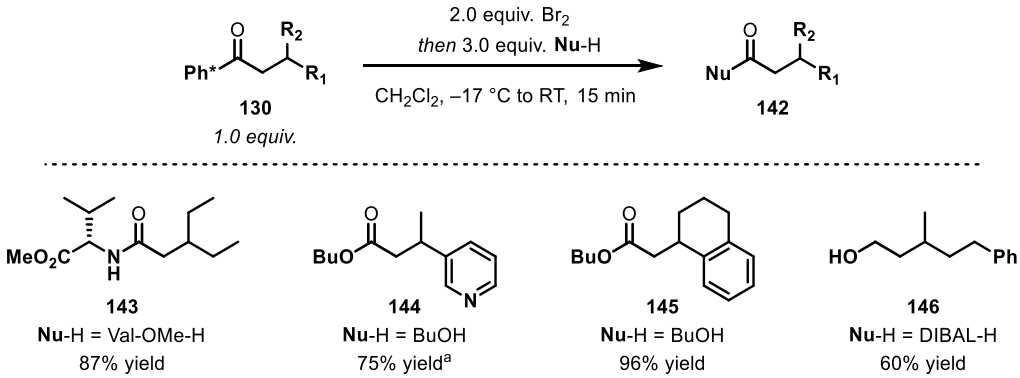
Of the conditions disclosed by Donohoe and co-workers, it was the use of elemental Br_2 that proved the most versatile. Upon activation of the ring and loss of pentamethyl bromobenzene, the oxonium was then attacked by the bromide counterion to give acyl bromide **123** – the existence of which could be detected by ^{13}C NMR. The subsequent addition of a range of nucleophiles to this reactive intermediate gave final products bearing multiple functional groups such as carboxylic acid **122**, ester **125**, thioether **126**, amide **127**, and alcohol **128**.

In a subsequent publication, the Donohoe group expanded their methodology to the hydrogen borrowing reaction between Ph* methyl ketone **100**, and secondary alcohols **46** – this time yielding β-branched carbonyl products (Scheme 1.25).[30]



***Scheme 1.25**: Selected scope of the hydrogen borrowing reaction between Ph* methyl ketone **100** and secondary alcohols **46**.*
[a]Reaction conducted at 105 °C.

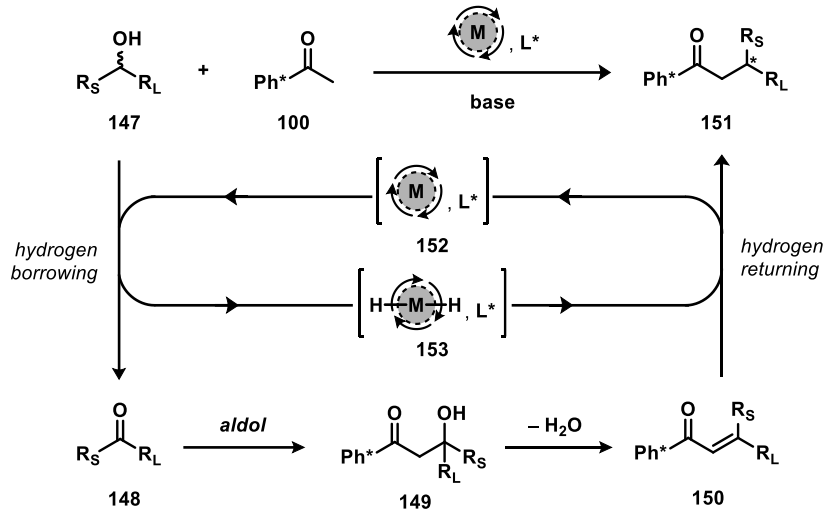
Interestingly, when compared to the high yield of **107** observed in Scheme 1.21, the use of a mono-*ortho*-substituted acetophenone resulted in very poor conversion to product **137**; however, no attempt was made by the authors to rationalise this. More consistent, however, were the results of the Br_2-mediated cleavage of the reaction products – with a wide range of esters and amides being formed, as well as the fragrance compound (±)-3-methyl-5-phenylpentanol **146** (Scheme 1.26).



***Scheme 1.26**: Selected scope of the Br_2-mediated cleavage of β-branched hydrogen borrowing products.*
[a]4.0 equiv. of Br_2 used.

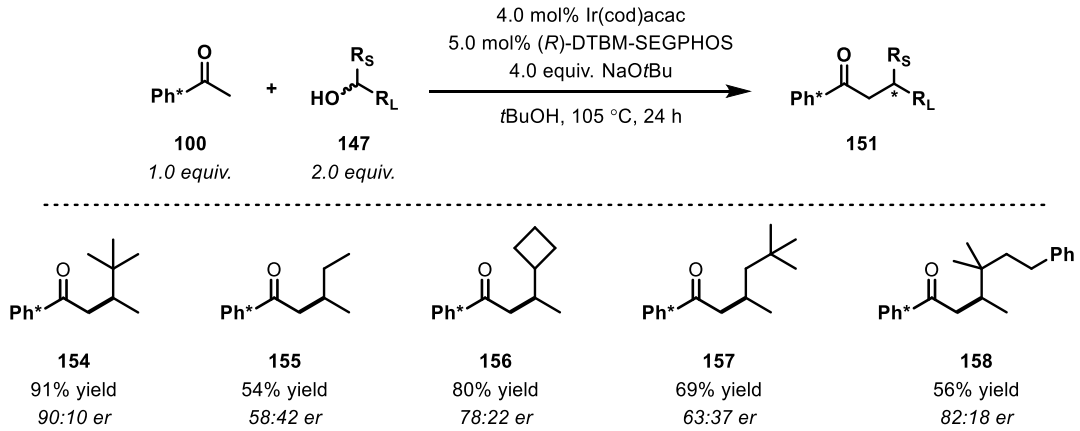
Two further advances to come from the Donohoe group in this particular field involved the synthesis of enantioenriched β-branched products from racemic secondary alcohols *via* an enantioconvergent

alkylation,[31] and the synthesis of cyclopentane derivatives from secondary alcohols bearing a cyclopropane substituent *via* a vinyl cyclopropane (VCP) rearrangement.[32]



***Scheme 1.27**: Mechanism of the enantioconvergent alkylation of Ph* methyl ketone **100** with racemic secondary alcohols **147**.*

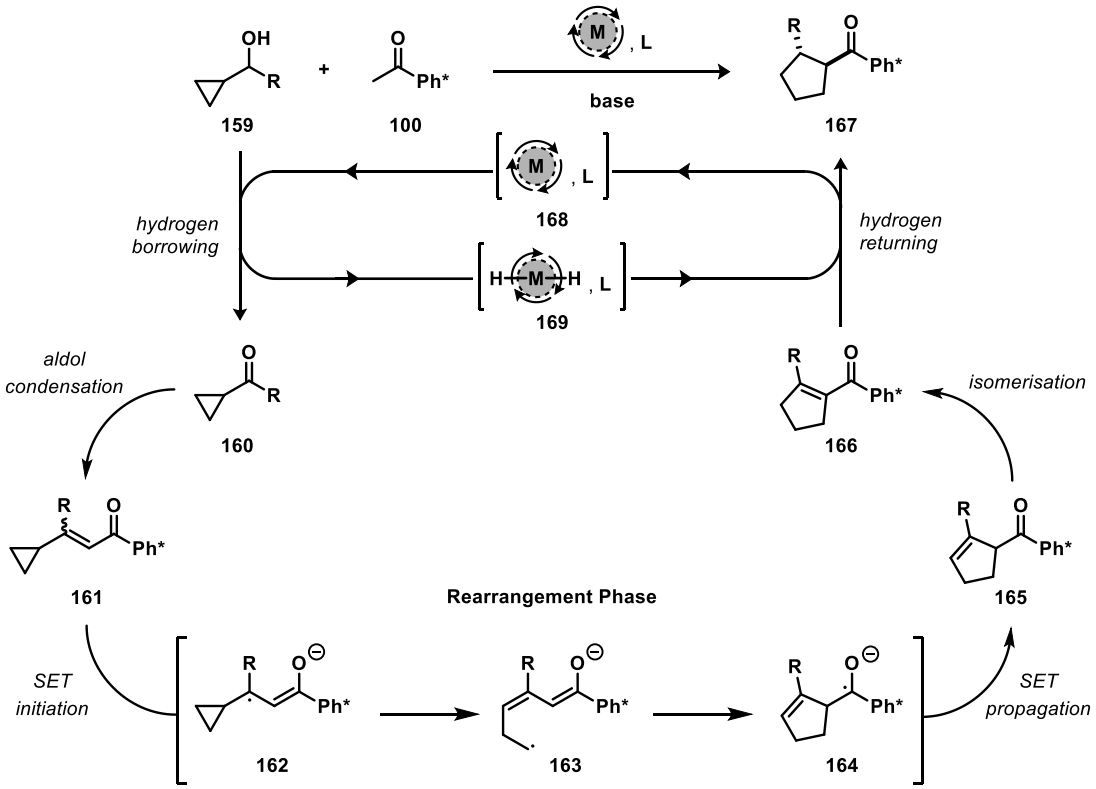
For the enantioconvergent alkylation, the reaction proceeds in the same manner as seen previously with secondary alcohols – with a racemic alcohol **147** being oxidised to the corresponding ketone **148** before then undergoing an aldol condensation to give an enone **150**. At that point, the use of a chiral ligand–iridium complex **153** results in the enantioselective addition of hydride to one face of the enone **150** resulting in the formation of an enantioenriched product **151** (Scheme 1.27).



***Scheme 1.28**: Selected scope of the enantioconvergent alkylation of Ph* methyl ketone **100** with racemic secondary alcohols **147**.*

As is clear from the substrate scope, the enantioselectivity of the reaction was strongly correlated with the substituent steric bulk of alcohol **147** – going from as high as 90:10 in the case of R_L = *tert*-butyl for **154**, to as low as 58:42 for **155** where R_L = ethyl (Scheme 1.28). The authors hypothesised that whilst facial addition of hydride **153** to enone **150** is controlled by the chiral ligand, the outcome of the reaction is equally dependent on the formation of a single enone **150** *E*/*Z*-isomer – selectivity for which only occurred in the case where R_L was substantially larger than R_S. As with prior publications, the Ph* group could be cleaved with Br_2 to yield a range of useful derivatives.

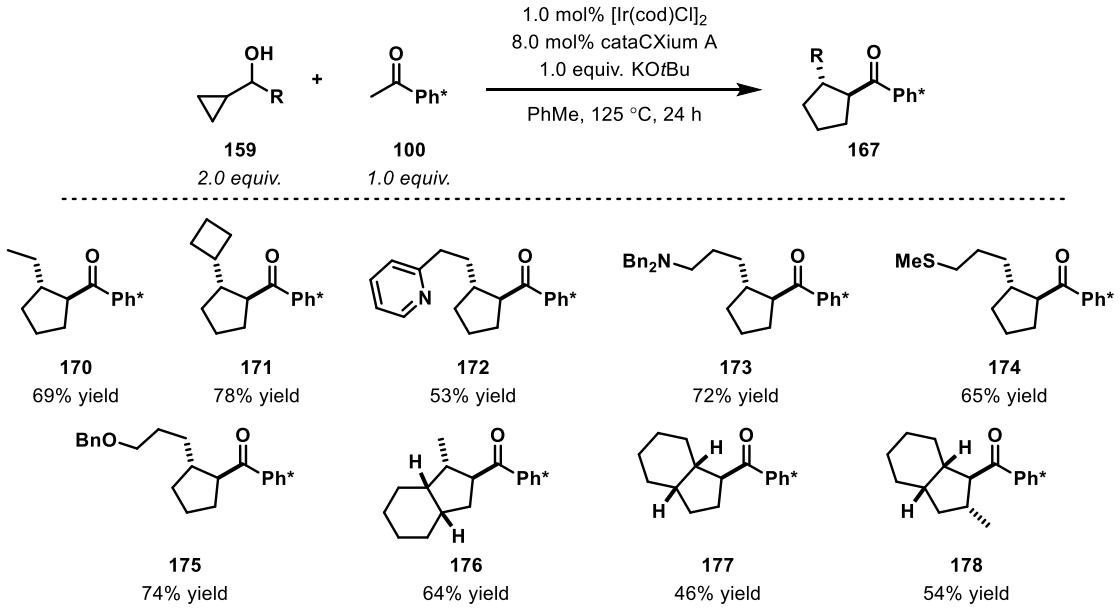
The synthesis of cyclopentanes **167** from cyclopropyl-substituted alcohols **159** represented a step up in complexity from a single hydrogen borrowing alkylation – with an intermediate rearrangement step being required to form the desired products (Scheme 1.29).



***Scheme 1.29**: Mechanism of the synthesis of cyclopentanes from the reaction of Ph* methyl ketone **100** with cyclopropyl-substituted secondary alcohols **159**.*

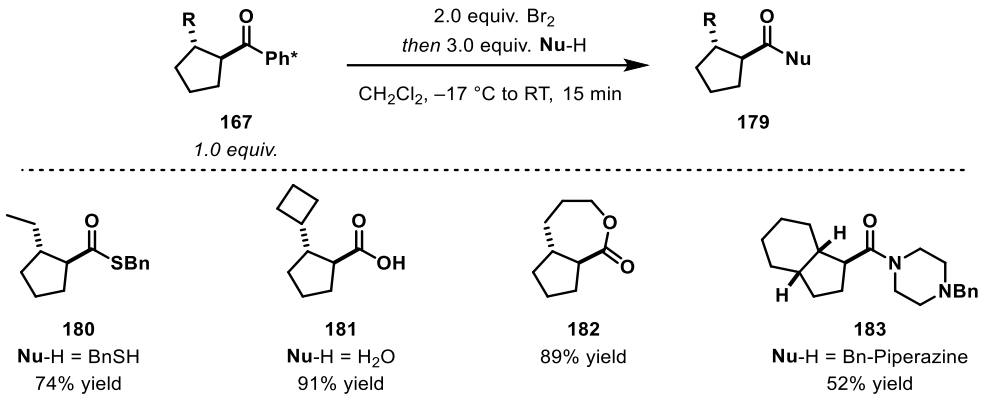
After numerous mechanistic experiments, the authors proposed that the reaction sequence began with a typical oxidation of the starting alcohol **159** to ketone **160**, followed by an aldol condensation

to give enone **161**. Divergence from a standard hydrogen borrowing sequence then comes *via* a single electron transfer (SET) from an alkoxide or enolate to give radical-anion **162**. A cyclopropyl ring-opening/ring-closing sequence then successfully rearranges the product to give a cyclopentyl radical-anion **164** – which then acts as a single electron donor to another equivalent of enone **161** *via* SET, thereby allowing the reaction to propagate. Isomerisation of alkene **165** to give enone **166** is followed by reduction to give the desired product **167**.



***Scheme 1.30**: Selected scope of the synthesis of cyclopentanes from the reaction of Ph* methyl ketone **100** with cyclopropyl-substituted secondary alcohols **159**.*

The reaction proved to be tolerant of heteroatoms, with good yields of products **172**, **173**, **174**, and **175** containing nitrogen-, sulfur-, and oxygen-bearing side-chains, respectively (Scheme 1.30). Furthermore, the use of bicyclic cyclopropyl starting materials could be used to obtain *cis*-fused cyclopentane products **176**, **177**, and **178** in good yields and as single diastereomers. The authors concluded their work by treating a number of products with Br_2, followed by suitable nucleophiles, thereby demonstrating once again the versatility of Ph* cleavage. Of particular note was the formation of lactone **182** from benzyl ether containing product **175** – presumably formed *via* a cyclisation, followed by debenzylation (Scheme 1.31).

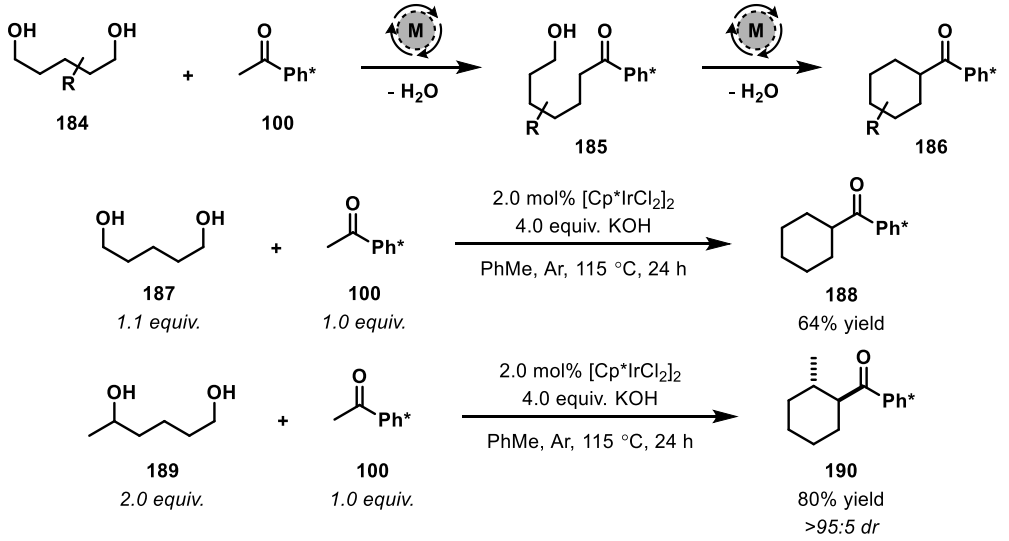


***Scheme 1.31**: Br_2-mediated Ph* cleavage and coupling of cyclopentane derivatives.*

Having demonstrated the synthesis of α- and β-branched carbonyl products *via* hydrogen borrowing catalysis using primary and secondary alcohols, respectively, as well as the synthesis of cyclopentanes *via* rearrangement of cyclopropyl-substituted alcohols, the next target in the Donohoe group's sights was the synthesis of cyclohexanes from diols.

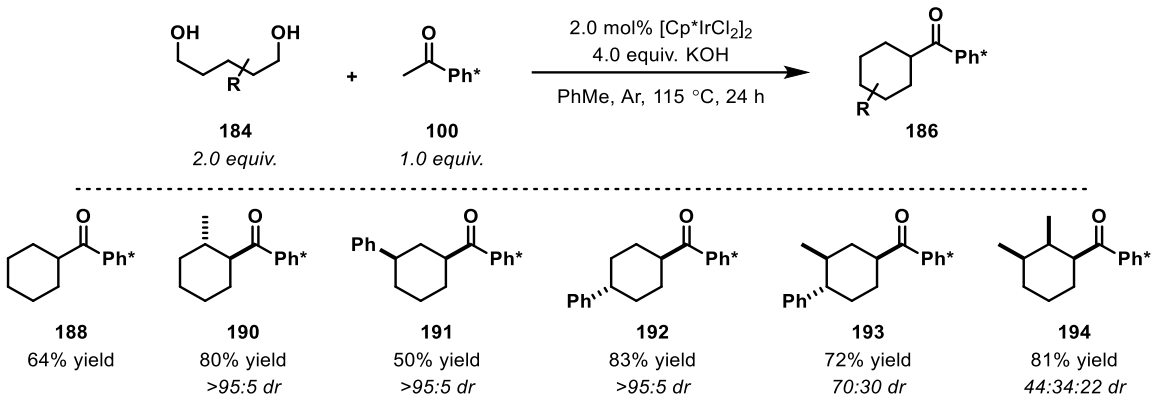
1.3.2 Alkylation Reactions with Diols to form Cyclohexanes and Cyclohexenes

Following on from the success of Ph* methyl ketone **100** in promoting single hydrogen borrowing alkylations with both primary and secondary alcohols, Donohoe and co-workers envisaged that a diol **184** might undergo a double alkylation in one pot to form a cyclic product *via* two sequential hydrogen borrowing reactions (Scheme 1.32).[33]



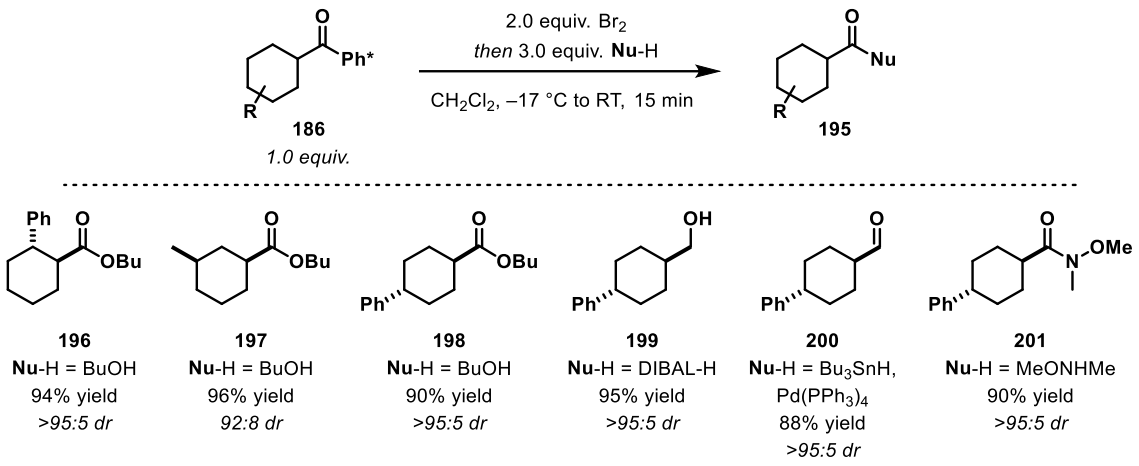
***Scheme 1.32**: Donohoe's proposed formation of cyclohexanes from diols* via *hydrogen borrowing catalysis and initial optimisation experiments.*

A short optimisation of reaction conditions using unsubstituted 1,5-pentanediol **187** found that the desired cyclohexane product **188** could be obtained in 66% yield with 4.0 equivalents of KOH as the base, 2 mol% of $[Cp^*IrCl_2]_2$ as the catalyst, 4M toluene as the solvent and a slight (1.1 equivalents) excess of the diol with respect to the Ph* methyl ketone **100**. However, upon switching to using an excess (2.0 equivalents) of methyl substituted diol **189**, the authors observed an 80% isolated yield of **190**, with >95:5 selectivity for the *trans* isomer – however when diol **187** was exposed to the same conditions the yield of **188** was only 64%. The explanation put forward for the difference in yields was that the substituted diol **189** was benefitting from a Thorpe–Ingold effect that promoted the desired cyclisation and increased its isolated yield. With these new conditions in hand, Donohoe and co-workers completed an extensive scope of aryl- and alkyl-substituted diols, synthesising several cyclohexane products in good to excellent yields (Scheme 1.33).



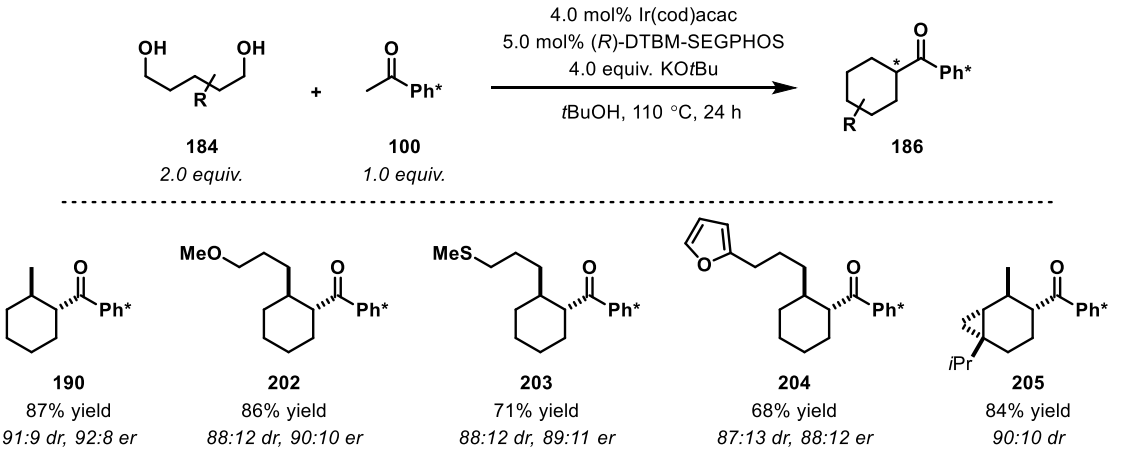
***Scheme 1.33**: Selected substrate scope of Donohoe and co-workers' synthesis of cyclohexanes from diols via hydrogen borrowing catalysis.*

The use of Br_2 once again proved effective in removing the Ph* moiety, with the corresponding butyl esters being formed from a number of products, as well as cyclohexane derivative **192** being transformed into (amongst others) the corresponding alcohol **199**, aldehyde **200**, and Weinreb amide **201** (Scheme 1.34).



***Scheme 1.34**: Selected scope of Br_2-mediated cleavage of cyclohexane derivatives.*

The next clear development lay in making the overall transformation enantioselective in a similar manner to that achieved with acyclic β-branching products from secondary alcohols. After an extensive ligand screen with methyl-substituted pentanediol **189** as the substrate, Donohoe and co-workers identified the optimal conditions of 4 mol% Ir(cod)acac as the metal precatalyst, 5 mol% (*R*)-DTBM-SEGPHOS as the chiral ligand, 4.0 equivalents of KO*t*Bu as the base, and *t*BuOH as the solvent for 24 h at 110 °C.[34] A substrate scope was conducted, featuring a range of alkyl-substituted diols, as well as some bearing oxygen-, and sulfur-containing side-chains (Scheme 1.35).

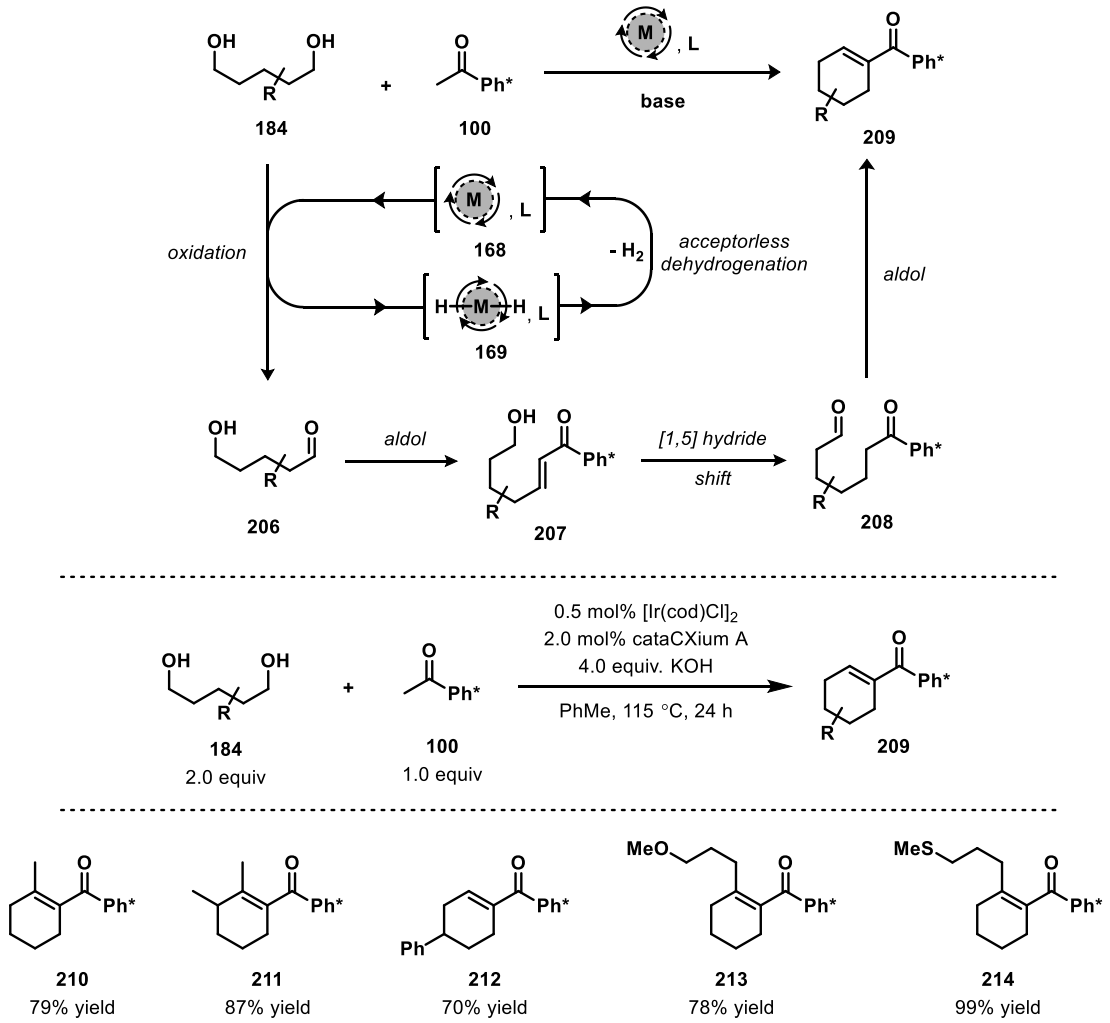


***Scheme 1.35**: Selected scope of the enantioselective synthesis of cyclohexanes from diols via hydrogen borrowing catalysis.*

Although a series of deprotections with Br_2 was not performed in this instance, cyclohexane **190** was cleaved to the corresponding acyl bromide before then being reduced with excess $LiAlH_4$ to give an

alcohol – the optical rotation of which was compared to its literature-known enantiomer and found to be equal and opposite in magnitude, proving that no erosion of absolute stereochemistry had occurred during the transformation.

A final advance to come from the Donohoe group in this area arose from the speculation that, because the penultimate intermediate in the synthesis of cyclohexanes by hydrogen borrowing is a cyclohexene, it may be possible to prevent the final reduction by the use of a sacrificial hydride acceptor, thereby providing a convenient route to access this useful class of compounds.[35]

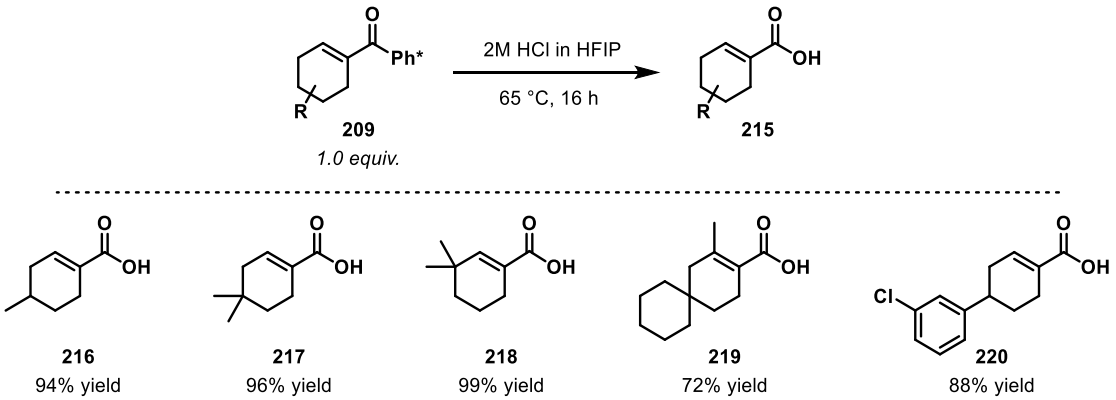


***Scheme 1.36**: Mechanism and selected substrate scope of the synthesis of cyclohexenes from diols* via *hydrogen borrowing derived catalysis.*

It was eventually found that a hydride acceptor was not required for the transformation, with a more dilute reaction mixture favouring an acceptorless dehydrogenation of the iridium hydride species **169**,

thereby preventing the final reduction. Furthermore, extensive deuterium labelling experiments found the reaction to proceed *via* a 1,5-hydride transfer in compound **207** after the initial alkylation, rather than a second hydrogen borrowing sequence as had previously been proposed in the synthesis of cyclohexanes (Scheme 1.36).[33]

An extensive substrate scope was completed, utilising a similar range of diols to those used for the enantioselective synthesis of cyclohexanes.[34] Notably, the use of butane- and hexane-diols to form cyclopentane and cycloheptane rings, respectively, gave very poor yields – which provided further evidence for the role of a 1,5-hydride transfer as part of the reaction mechanism. Finally, as the reactive enone functionality precluded the use of Br_2 as a reagent for cleavage of Ph*, Donohoe and co-workers revisited their previously disclosed acid-mediated conditions and found that the use of 2M HCl in HFIP smoothly deprotected a number of products to their corresponding α,β-unsaturated carboxylic acids **215** (Scheme 1.37).



***Scheme 1.37**: Acid-mediated cleavage of cyclohexene products to α,β-unsaturated carboxylic acids.*

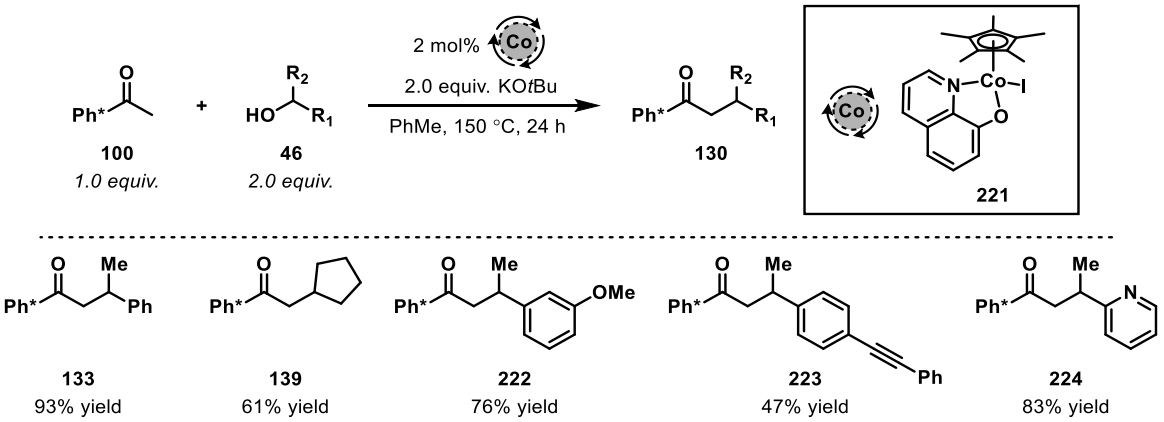
Together, the above results demonstrate how Ph* methyl ketone **100** is uniquely capable of promoting hydrogen borrowing alkylation reactions with both primary and secondary alcohols, as well as diols. The act of twisting the aryl ring out of conjugation with the carbonyl C=O bond reduces steric hindrance about the carbonyl α-carbon, allowing much more sterically congested products to be formed. The two *ortho* methyl groups also help to protect the carbonyl from reduction, thereby facilitating the

formation of a single desired product. Finally, the Ph* group may be readily removed with the use of either Br_2 or acid, providing access to a range of products.

One notable drawback, however, of Donohoe and co-workers' aforementioned methodology is the use of an iridium metal catalyst. As one of the least abundant metals in the earth's crust,[36] iridium is inherently more expensive than many other transition metals and it is therefore unsurprising that the focus of many research groups is in the development of new catalytic methods that avoid the use of iridium and other such rare-earths. Hydrogen borrowing is no exception, and recent years have seen a number of publications exploring the use of earth-abundant metals to catalyse the reaction between Ph* methyl ketone **100** and alcohols – a representative selection of which will now be discussed.

1.3.3 Earth-Abundant Metal Catalysed Reactions of Ph* Methyl Ketone 100

As a fellow group 9 element, cobalt was an obvious choice to replace iridium in hydrogen borrowing catalysis and in 2019, Sundararaju and co-workers demonstrated that the well-defined, high-valence cobalt(III)-catalyst **221** could be used to achieve the alkylation of Ph* methyl ketone **100** with a range of secondary alcohols (Scheme 1.38).[37]

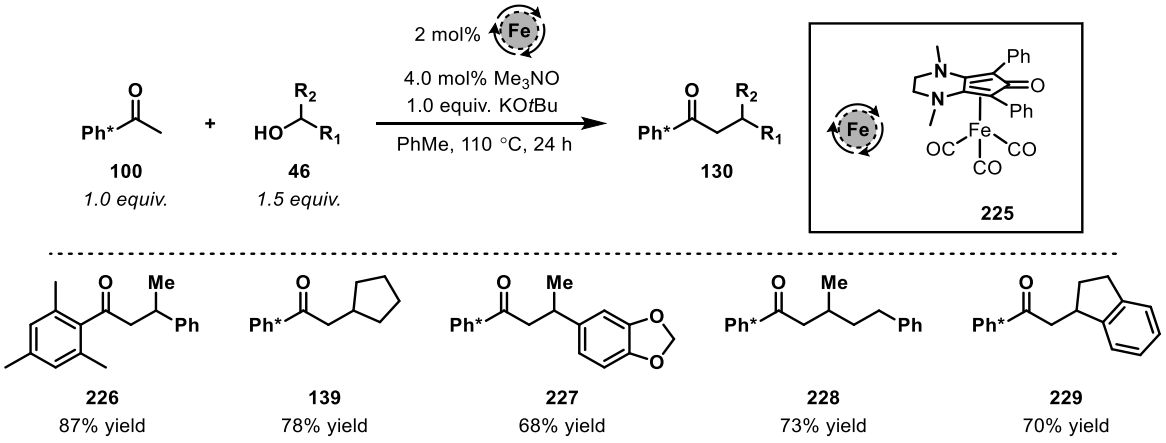


***Scheme 1.38**: Cobalt-catalysed alkylation of Ph* methyl ketone **100** with secondary alcohols.*

Despite the generally lower yields (with respect to iridium-catalysed hydrogen borrowing) and the fact that many of the alcohols were benzylic in nature (thereby making them much easier to oxidise), the novelty of using a first row transition metal for such a reaction is in itself a noteworthy achievement.

In accordance with Donohoe's established procedure, product **133** was treated with Br_2 to cleave the Ph* moiety and subsequently trapped with a small number of standard nucleophiles.

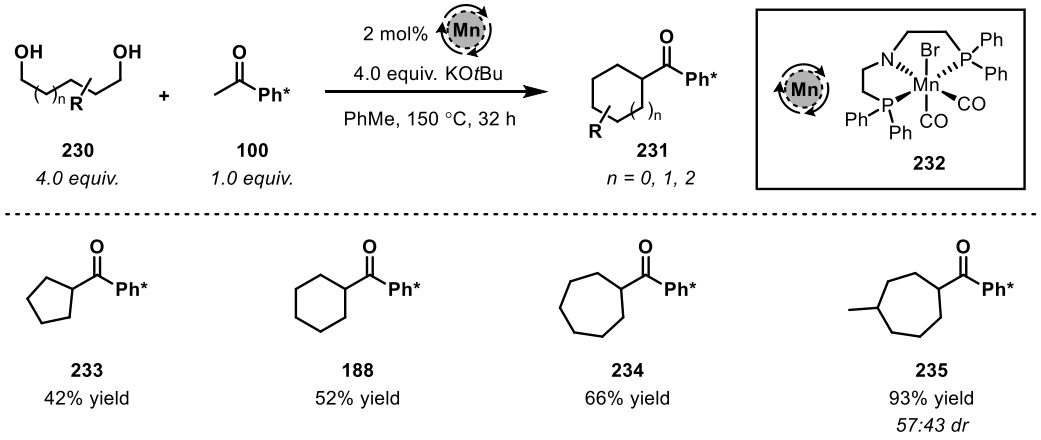
Adjacent to cobalt in the first-row transition metals is iron – and in 2020 Renaud and co-workers utilised the half sandwich iron complex **225** to perform alkylations of Ph* methyl ketone **100** with a very similar range of alcohols to those used by Sundararaju (Scheme 1.39).[38]



***Scheme 1.39**: Iron-catalysed alkylation of Ph* methyl ketone **100** with secondary alcohols **46**.*

It is interesting to note that, in addition to Ph* methyl ketone **100**, the Renaud group also made use of 1-mesitylethan1-one as the carbonyl coupling partner to give **226** – the two flanking *ortho* methyl groups conferring the same benefits as in Ph* methyl ketone **100** – and the resulting products could be functionalised in an identical way using Br_2. In contrast to other catalytic systems, the use of iron complex **225** requires the addition of two equivalents of Me_3NO per equivalent of catalyst in order to activate it to reaction by liberating a vacant site on the iron centre. Another interesting aspect of iron catalyst **225** was observed when 1-phenylethan-1-*d*-1-ol was used. In this case, the product ***d*$_1$-226** was formed with 100% D incorporation at the benzylic position, suggesting no H/D crossover at any stage during the reaction – possibly as a result of the reduced acidity of the iron-hydride complex, when compared to other transition metal-hydride complexes. This is in contrast to deuterium labelling studies conducted for many other hydrogen borrowing reactions in which deuterium scrambling is common, along with deuteration at multiple other positions.[37]

A final recent development in the field worth discussing was published by Leitner and co-workers in 2019 and involves the reaction between diols and a range of substituted aryl alcohols and ketones, including Ph* methyl ketone **100**, to form 5-, 6-, and 7-membered rings catalysed by the manganese pincer complex Mn-MACHO **232** (Scheme 1.40).[39]



***Scheme 1.40**: Manganese-catalysed alkylation of Ph* methyl ketone **100** with diols **230** to form cycloalkanes **231**.*

Intriguingly, Leitner and co-workers found that Mn-MACHO **232** allowed for the effective formation of cyclopentanes **233** and cycloheptanes **234** and **235** from 1,4- and 1,6-diols respectively. This differs from the reactivity observed by the Donohoe group in which the formation of 5- or 7-membered rings was especially challenging and therefore suggests that an intramolecular transfer mechanism may not be applicable to these substrates.[35]

1.3.4 Summary

As demonstrated by the above examples, the methodology for the construction of carbon–carbon bonds *via* hydrogen borrowing catalysis has seen immense development in recent years. Starting from the alkylation reactions of simple aryl methyl ketones with primary alcohols, the field has moved into the formation of α-branched carbonyls, first by the use of MeOH and then by primary alcohols – in the latter case enabled by the use of Ph* methyl ketone **100** and its unique properties (Figure 1.2).

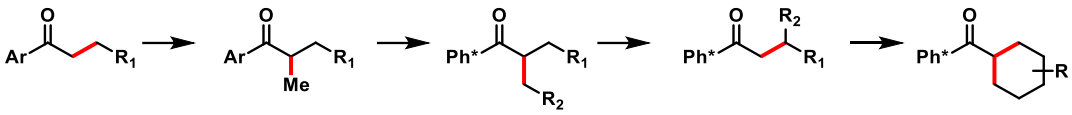


***Figure 1.2**: Summary of the key developments in C–C bond forming hydrogen borrowing alkylations of ketones discussed in this chapter. **Bold** represents asymmetric variants.*

Subsequent developments then involved the synthesis of β-branched carbonyls and cyclohexanes, starting from secondary alcohols and diols respectively. Enantioselective variants of both methods have since been developed, as well as catalytic systems utilising earth-abundant metal complexes.

One aspect of hydrogen borrowing catalysis that has remained chronically underdeveloped, however, is the substrate scope of the products. In almost all publications, little variety in substrate scope is explored beyond evaluation of aliphatic and aromatic substitutional isomers, as well as a small number of ethers and thioethers. Particularly conspicuous by their paucity are nitrogen-containing products – shown below is the total range of nitrogenous compounds (not including cleavage products) synthesised by the methodologies detailed so far in this chapter (Figure 1.3).

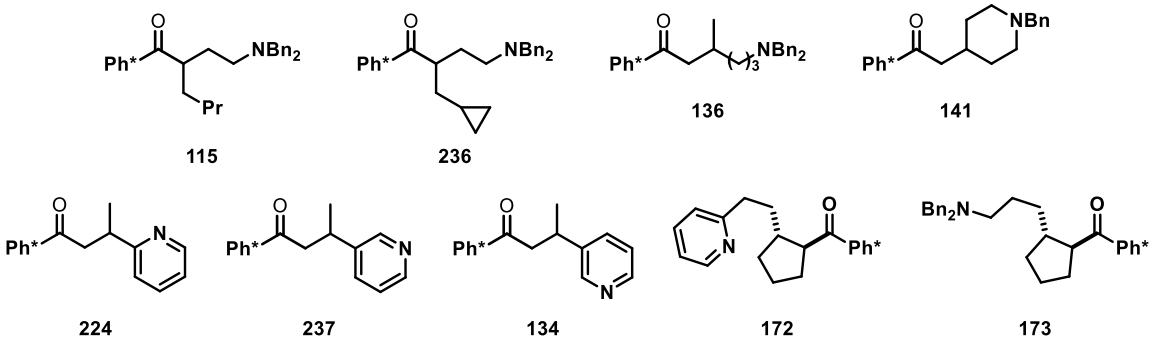


***Figure 1.3**: Nitrogen containing compounds synthesised by C–C bond forming hydrogen borrowing catalysis.*

Amongst hydrogen borrowing products, the only nitrogen-containing functionalities present are monosubstituted pyridines and aliphatic amines – the latter being represented almost exclusively by perbenzylated derivatives, often located remotely from the reactive centres. The reasons for this are unclear, and no prior publication has put forward any explanation for it. One possible cause for this

dearth of nitrogenous substrates may be substrate degradation due to N-oxidation by the catalyst. Another possibility may be that the amine lone pair, if located close enough within the substrate to the oxidisable alcohol, may act as part of a bidentate ligand that sequesters the catalyst and suppresses reaction.

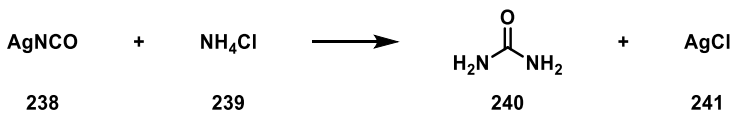
Regardless of the cause, it is clear that C–C bond forming hydrogen borrowing suffers from a lack of diversity within its substrate alcohols, particularly in the case of nitrogen. This alone would be enough to justify further development of such reactions; however, an additional incentive arises from the paramount importance of nitrogen in both natural products and pharmaceuticals, as detailed in the following section.

1.4 Importance of Nitrogen in Organic Synthesis

Whilst both the ubiquity and puissance of nitrogenous compounds in organic synthesis ought not to need any introduction, it is worth highlighting a few key examples of their occurrence within both natural and man-made compounds to demonstrate the value in developing new methods to access them.

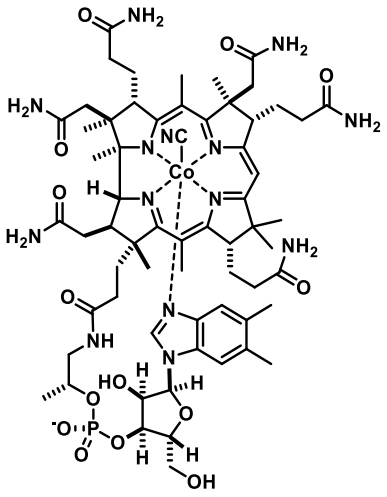
1.4.1 Nitrogen Containing Natural Products

The first natural product ever artificially produced – an historical event considered by many to be the starting point of modern organic chemistry – was urea **240**, a nitrogen-containing compound synthesised by Friedrich Wöhler in 1828 from silver cyanate **238** and ammonium chloride **239** (Scheme 1.43).[40]



***Scheme 1.43**: Wöhler's 1828 synthesis of urea.*

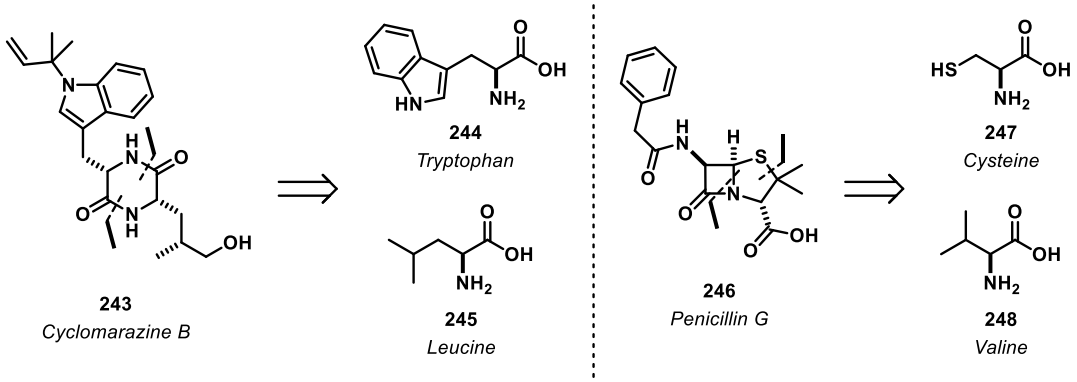
Since then, the field has seen much development, with another landmark in the total synthesis of such compounds coming in the 1972 synthesis of Vitamin B_{12} **242** by the groups of Woodward and Eschenmoser, the culmination of 12 years of work by almost 100 researchers (Figure 1.4).[41]



242

***Figure 1.4**: Vitamin B_{12}.*

In both the above examples, the nitrogen-containing functional groups are either simple amides or part of conjugated aromatic systems and are therefore not of interest from a stereochemical perspective. Many nitrogen atoms in Nature, however, are in the form of amines or amides adjacent to chiral centres derived from amino acids (the "building blocks" of proteins and many secondary metabolites) allowing for the rapid construction of complexity from the set of 20 naturally occurring amino acids (Scheme 1.44).[42, 43]



243
Cyclomarazine B

244
Tryptophan

245
Leucine

246
Penicillin G

247
Cysteine

248
Valine

***Scheme 1.44**: Amino acid derived natural products Cyclomarazine B and Penicillin G.*

Even more elaborate are the many nitrogen-containing natural products, also known as alkaloids, that derive from a multitude of building blocks such as terpenes and amino acids, followed by many further enzymatic modifications to produce molecules of immense molecular complexity – and so it is therefore unsurprising that such structures have attracted the attention of many organics chemists *via* multiple total syntheses throughout the years, a representative selection of which are shown below (Figure 1.5).[44–50]

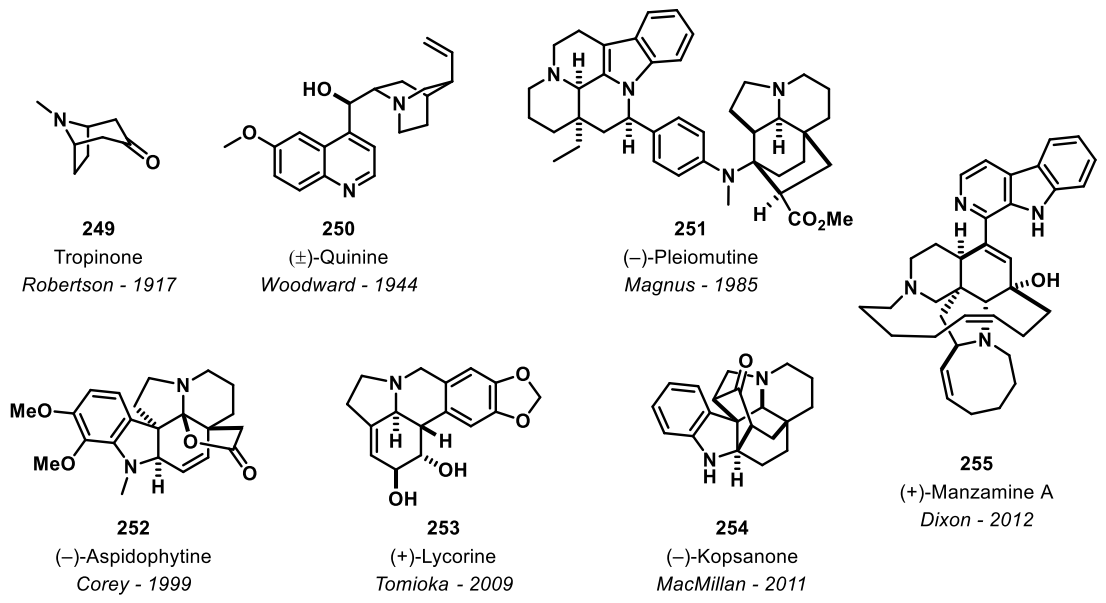
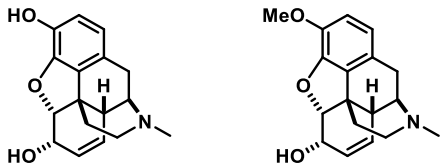


***Figure 1.5**: Naturally occurring alkaloids that have been the target of total synthesis.*

From the above, it is clear that nitrogen finds itself in a wide range of compounds synthesised by Nature, with highly variable structures and functionalities. It is no surprise, therefore, that many are biologically active, with numerous natural products – along with their derivatives and structural analogues – being used as therapeutics, as will be detailed in the next section.

1.4.2 Nitrogen-Containing Pharmaceuticals

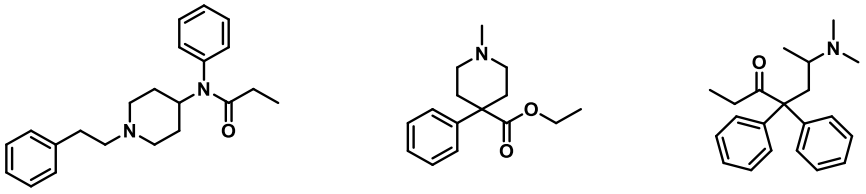
One of the world's oldest drugs to be used for therapeutic purposes was opium – the active ingredient of which is the alkaloid morphine **256**, along with smaller amounts of codeine **257**, both of which are still used as painkillers today (Figure 1.6).[51]



256 *Morphine* **257** *Codeine*

***Figure 1.6**: The opium-derived pharmaceuticals morphine and codeine.*

The complications associated with the production of opium from the opium poppy, along with the desire to create structural isomers with different therapeutic properties, has led to the development of many synthetic opioids that target the same receptors as morphine **256**. As the small selection below shows, all such compounds include some nitrogen functionality in the form of amines, highlighting their importance in the biological activity of opioids (Figure 1.7).



258 *Fentanyl* **259** *Pethidine* **260** *Methadone*

***Figure 1.7**: Synthetic nitrogen-containing opioids fentanyl, pethidine, and methadone.*

To move away from the field of opioids and look at therapeutics more generally, an excellent demonstration of the ubiquity of nitrogen within such compounds can be found in a 2014 review by Njardarson and co-workers on the frequency of heterocycles amongst FDA-approved pharmaceuticals.[52] Of the 1994 FDA approved drugs examined by the authors, 1035 are unique small molecule drugs and of these, 874 (84.4%) contain at least one nitrogen atom – with 613 (59.2%) of those containing at least one nitrogen heterocycle (Figure 1.8).

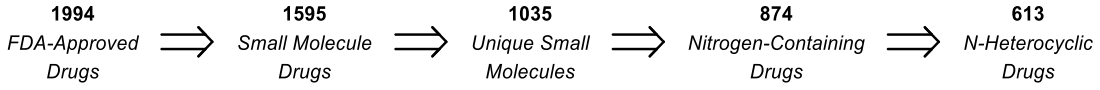


***Figure 1.8**: Njardarson and co-workers' analysis of FDA approved drugs.*

An earlier 2011 study by Roughley and Jordan found a similar result – in their examination of 3566 drug candidates with biological data, they found 1529 (42.9%) contained at least one alkyl amine

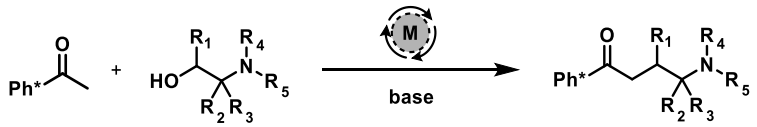
functionality, with a further 810 (22.7%) and 504 (14.1%) containing aryl and diaryl amines, respectively.[53] Together, these two reports can leave no doubt as to the importance of nitrogen containing compounds within medicinal chemistry – and therefore to the utility of any methodology capable of expanding access to them.

1.4.3 Summary

The above examples of nitrogen-containing natural products and pharmaceuticals demonstrate how pervasive nitrogen is throughout chemical space. As demonstrated earlier in this chapter, C–C bond forming hydrogen borrowing reactions have seen much development in recent years, but their substrate scope often remains limited to various permutations of simple aliphatic and aromatic hydrocarbons. The application of C–C bond forming hydrogen borrowing reactions to nitrogen-containing substrates is therefore a key unmet challenge in this area and will allow for the application of this powerful technique to a much wider, and more useful, range of target molecules.

1.5 Project Aims

In light of the previous remarks, the aim of this project was simple: to develop a carbon–carbon bond forming hydrogen borrowing reaction between Ph* methyl ketone **100** and nitrogen-containing substrate alcohols **261** (Scheme 1.45).



Scheme 1.45*: Hypothetical target hydrogen borrowing reaction between Ph* methyl ketone* ***100*** *and a nitrogen-containing substrate alcohol* ***261****.*

If possible, the substrate alcohols would be easy to synthesise – and the products from the reaction would ideally be industrially or pharmaceutically relevant, in order to further expand the utility of hydrogen borrowing. Furthermore, we envisaged that the use of amines containing a stereogenic

centre would allow for an investigation into the stereochemical consequences of hydrogen borrowing alkylations.

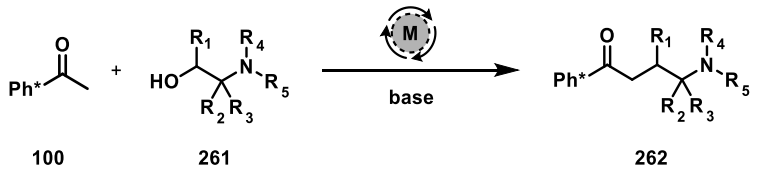
Finally, the methodology would be applied to the total synthesis of a naturally occurring alkaloid – a feat not yet accomplished utilising carbon–carbon bond forming hydrogen borrowing – as another means of demonstrating the value of the transformation.

Chapter 2: Hydrogen Borrowing Reactions of Aziridino Alcohols

2.1 Introduction

As detailed in the introductory chapter to this thesis, hydrogen borrowing reactions of alcohols have flourished into a developed field – encompassing a wide range of C-C bond forming processes. Highlighted in the same chapter, however, was the relative intolerance of such reactions to the inclusion of heteroatoms in the substrate backbone. This was attributed to the harsh reaction conditions employed for hydrogen borrowing, particularly in the creation of C–C bonds, as well the possibility of heteroatoms ligating to the catalyst and thereby interfering in the desired reaction pathway.

These considerations notwithstanding, and attracted by the ubiquity and synthetic importance of amines within both pharmaceutical chemistry and nature, it was decided to develop a C–C bond forming hydrogen borrowing reaction that specifically included substrate alcohols **261** bearing an amine within their backbone (Scheme 2.1). Furthermore, the reaction partner to the alcohol would be the Ph* methyl ketone **100** developed by the Donohoe group – its many useful synthetic attributes, once again detailed in Chapter 1, making it a logical choice.

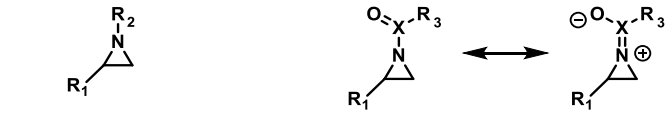


Scheme 2.1*: General scheme of a hydrogen borrowing reaction between Ph* methyl ketone and an amine-containing alcohol substrate.*

As such, work began on finding a suitable substrate **261** for this reaction. Given the lack of simple amines used as substrates in other C–C bond forming hydrogen borrowing reactions to date, it was thought that a different approach would be required – with aziridino alcohols eventually being chosen due a number of their unique characteristics, as detailed in the next section.

2.1.1 Properties of Aziridines

Once referred to as "epoxides' ugly cousins",[54] aziridines are three-membered nitrogen-containing heterocycles that are far less utilised in synthesis than their oxygenic relations. Unsurprisingly, owing to their high degree of Bæyer ring strain – estimated at being around 111 kJ mol^{-1} – their chemistry is dominated by ring opening reactions, with the nature of this reactivity being determined by the substituent on the nitrogen atom, making the aziridine either "nonactivated" or "activated" (Figure 2.1).[55]



263
Nonactivated aziridines
R_2 = H, alkyl, aryl

264
Activated aziridines
R_3 = OR, alkyl, aryl; X = C, S

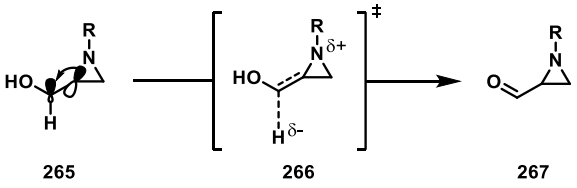
***Figure 2.1**: Nonactivated and activated aziridines.*

The nitrogen atom in nonactivated aziridines **263** is typically either an alkyl or aryl group, making it more electron rich and therefore less amenable to ring opening reactions than a comparable epoxide – this can be rationalised by the resulting negative charge residing on a less electronegative nitrogen atom, as opposed to an oxygen in the case of an epoxide. Ring opening reactions therefore require either protonation, quaternisation, or the formation of an adduct with a suitable Lewis acid to promote reactivity.[56]

Activated aziridines **264**, in contrast, bear substituents on the nitrogen atom that polarise the C–N bonds of the aziridine – carbonyls and sulfonyls are the archetypical examples. This results in the C–N ring bonds being much more amenable to being broken by incoming nucleophiles, and as such, activated aziridines often do not require the participation of Lewis acids in order to promote such reactivity. Furthermore, upon ring opening, these groups serve to delocalise the lone pair of the nitrogen and so help to stabilise any resulting negative charge.

In the context of designing a suitable substrate for hydrogen borrowing, a nonactivated aziridine seemed preferential – the strongly basic conditions used precluded the possibility of their activation by a Lewis Acid, and an alkyl or aryl substituent on the nitrogen would make the ring less susceptible to cleavage than the corresponding carbonyl or sulfonyl on an activated aziridine. Furthermore, the lone pair of nonactivated aziridines is less basic than their corresponding amine analogues – a common comparison is often made between the weakly basic aziridinium ion, with a pK_a of 7.98, and other secondary amines such as dimethylamine, with a pK_a of 10.73.[57] This is attributed to the nitrogen lone pair having more s-character than a typical amine – an effect arising from the extra p-character needed in the C–N bonds as a consequence of the small ring size, similar to that observed in cyclopropane derivatives.[58] To our minds, this reduced basicity – relative to an acyclic amine analogue – would likely prove advantageous in a hydrogen borrowing reaction, with the substrate aziridino alcohol being less liable to act as a ligand and sequester the reaction catalyst than a comparable amine.

A final consideration was that of the relation of the alcohol substituent in the substrate for hydrogen borrowing to the aziridine (Scheme 2.2).



***Scheme 2.2**: Activation of α-hydroxy aziridines to oxidation.*

It was envisaged that the use of an α-hydroxy aziridine such as **265** would be activated towards oxidation *via* the additional p-character in the C–N aziridine bonds donating into the C–H σ* bond at the hydroxy centre, making it more hydridic and therefore more likely to be involved in a metal-catalysed oxidation process to give aldehyde **267**.

2.1.2 Project Aims

With the decision made to focus on α-hydroxy aziridines **265** as substrates for a new hydrogen borrowing reaction, the project aims were clear:

i. Find and optimise conditions for a hydrogen borrowing reaction between a model α-hydroxy aziridine substrate and Ph* methyl ketone **100**.

ii. Explore cleavage conditions of the Ph* group from the hydrogen borrowing product, either by the precedented Br_2-mediated cleavage developed within the Donohoe group, or otherwise.

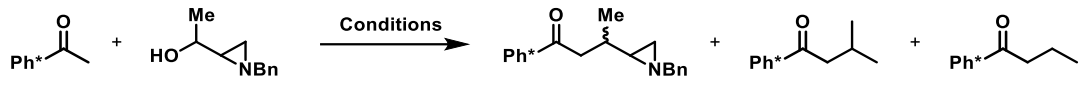
iii. Synthesise a range of α-hydroxy aziridines and evaluate their competency in the hydrogen borrowing reaction and subsequent cleavage.

A final, and more ambitious, aim of the project was to find a way to apply any developed methodology to the total synthesis of a natural product, thereby demonstrating its utility in a broader synthetic setting.

2.2 Results and Discussion: Initial Reaction Development and Scope

2.2.1 Reaction Optimisation

The initial optimisation of reaction conditions was conducted by Ben Jones, using 1.5 equivalents of secondary aziridino alcohol **268** as the model substrate and Ph* methyl ketone **100** as the reaction partner and limiting reagent (Table 2.1).[59]



100 *1.0 equiv.* **268** *1.5 equiv.* **269** **270** **271**

Entry	Catalyst (mol%)	Base (equiv.)	Temp. (°C)	Solvent (conc.)	Yield (%)			dr
					268	**269**	**270** and **271**[a]	
1	$[Cp^*IrCl_2]_2$ (0.5)	NaO*t*Bu (2.0)	85	PhMe (4M)	94	7	-	-
2	$[Cp^*IrCl_2]_2$ (0.5)	NaO*t*Bu (2.0)	70	PhMe (4M)	100	-	-	-
3	$[Cp^*IrCl_2]_2$ (0.5)	NaO*t*Bu (2.0)	100	PhMe (4M)	48	7	-	-
4	$[Cp^*IrI_2]_2$ (0.5)	NaO*t*Bu (2.0)	85	PhMe (4M)	87	6	-	6:5
5	$[Ir(cod)Cl_2]_2$ (0.5) and PPh_3 (2.0)	NaO*t*Bu (2.0)	85	PhMe (4M)	90	2	-	-
6	$[Cp^*IrCl_2]_2$ (1.0)	NaO*t*Bu (2.0)	85	PhMe (4M)	60	14	<5	-
7	$[Cp^*IrCl_2]_2$ (2.0)	NaO*t*Bu (2.0)	85	PhMe (4M)	8	51	<25	3:2
8	$[Cp^*IrCl_2]_2$ (5.0)	NaO*t*Bu (2.0)	85	PhMe (4M)	3	73	<15	3:2
9	$[Cp^*IrCl_2]_2$ (2.0)	KOH (2.0)	85	PhMe (4M)	17	68	<10	3:2
10	$[Cp^*IrCl_2]_2$ (2.0)	KOTMS (2.0)	85	PhMe (4M)	17	62	<10	3:2
11	$[Cp^*IrCl_2]_2$ (2.0)	KO*t*Bu (2.0)	85	PhMe (4M)	36	11	<10	3:2
12	$[Cp^*IrCl_2]_2$ (2.0)	KOH (1.5)	85	PhMe (4M)	19	59	<10	3:2
13	$[Cp^*IrCl_2]_2$ (2.0)	KOH (4.0)	85	PhMe (4M)	16	67	<10	3:2
14	$[Cp^*IrCl_2]_2$ (2.0)	KOH (3.0)	85	PhMe (4M)	13	73	<10	3:2
15	$[Cp^*IrCl_2]_2$ (2.0)	KOH (2.0)	85	PhMe (2M)	35	51	<10	3:2
16	$[Cp^*IrCl_2]_2$ (2.0)	KOH (2.0)	85	PhMe (1M)	61	25	<10	3:2
17	$[Cp^*IrCl_2]_2$ (2.0)	KOH (2.0)	85	PhMe (0.5M)	59	25	<10	3:2
18	$[Cp^*IrCl_2]_2$ (2.0)	KOH (2.0)	85	PhMe (8M)	9	89	<5	3:2
19	$[Cp^*IrCl_2]_2$ (2.0)	KOH (2.0)	85	Neat	6	93	<5	3:2

Table 2.1*: Optimisation of reaction conditions conducted by Ben Jones on alcohol* ***268****.*
[a]Isolated as an inseparable mixture.

Upon initially varying the temperature (Entries 1–3), it was found that 85 °C was optimal – with a decrease to 70 °C leading to a complete lack of conversion; and an increase to 100 °C giving a similar quantity of product, albeit accompanied by an observed substantial increase in decomposition of starting material **268**.

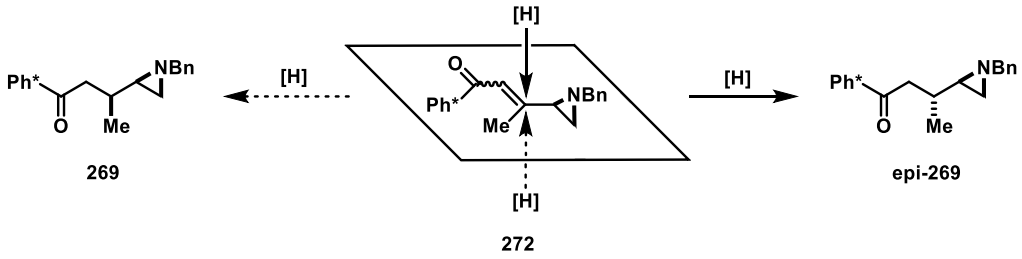
Screening of iridium catalysts (Entries 4 and 5) found no credible alternative to $[Cp^*IrCl_2]_2$ – with the other catalysts screened both resulting in reduced conversion. A survey of catalyst loading proved more fruitful (Entries 6 and 7), with an increase from 0.5 mol% to 2.0 mol% resulting in a substantial increase in product conversion – from 7% yield to a much more respectable 51% yield. Whilst further increasing the catalyst loading to 5.0 mol% resulted in a further elevation of yield to 73% (Entry 8),

such a high level of catalyst loading was deemed excessive, and as such, further optimisation was carried out with a loading of 2.0 mol%.

Next to be screened were reaction bases (Entries 9–11), covering a number of commonly used strong bases in hydrogen borrowing. Both KOTMS and KOH performed well (Entries 9 and 10), with KOH giving the best yield so far – with a catalyst loading of 2.0 mol% – of 68%. Interestingly, the performance of KO*t*Bu (Entry 11) was vastly inferior to NaO*t*Bu – an 11% yield of **269** as opposed to 51% yield – suggesting that the base counterion plays a non-trivial role in the reaction. Given this result, KOH was selected as the primary base going forward, and as such, the number of equivalents used was the next variable to be investigated. A decrease to 1.5 equivalents (Entry 12) suppressed the yield of **269**, as did an increase to 4.0 equivalents (Entry 13). The use of 3.0 equivalents (Entry 14) gave the best yield of **269** so far, at 73% yield.

The final variable to be investigated was concentration of the solvent toluene. Dilution of the reaction mixture (Entries 15–17) only resulted in a diminution in yield of the desired hydrogen borrowing product to 25% yield at 0.5 and 1.0M. In contrast, however, was the effect of increasing the reaction concentration (Entries 18 and 19), with an initial increase to 89% yield of **269** when the reaction was conducted at a concentration of 8M – and the best, and final, optimisation yield of 93% being obtained when the reaction was run neat, with 2.0 equivalents of KOH as the base and 2.0 mol% of $[Cp^*IrCl_2]_2$ as the catalyst (Entry 19).

It is interesting to note that, with the exception of the use of $[Cp^*IrI_2]_2$ as the catalyst, the dr of the product remained constant at 3:2 – with the relative stereochemistry of each diastereomer remaining undetermined. This suggested that selectivity of the final addition of hydride to the penultimate enone species was independent of any reaction conditions and so presumably controlled entirely by the substrate itself (Scheme 2.3).



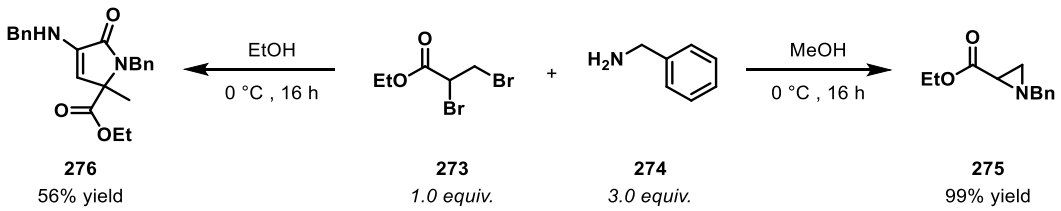
***Scheme 2.3**: Diastereodetermining addition of hydride to enone **272** in the synthesis of **269**.*
*Note: The relative stereochemistry in **269** had yet to be determined.*

This was obviously a disappointing result, given that an ideal reaction would provide diastereomerically pure product, and the (almost) complete invariance of dr from 3:2 suggested that improving it would be a non-trivial task. However, with the above reaction conditions in hand, the next step was the synthesis of a number of suitable aziridino alcohol substrates – and the subsequent subjection of them to the optimised reaction – in order to evaluate how reaction yield and diastereoselectivity would be influenced by substrate structure.

2.2.2 Diastereoselectivity of Simple Aziridino Alcohols

Given that the secondary alcohol, and therefore resulting enone intermediate **272**, in substrate **268** bore a methyl group as the substituent, it seemed intuitive to vary the size of this group and evaluate the effects of such a change on reaction yield and diastereoselectivity.

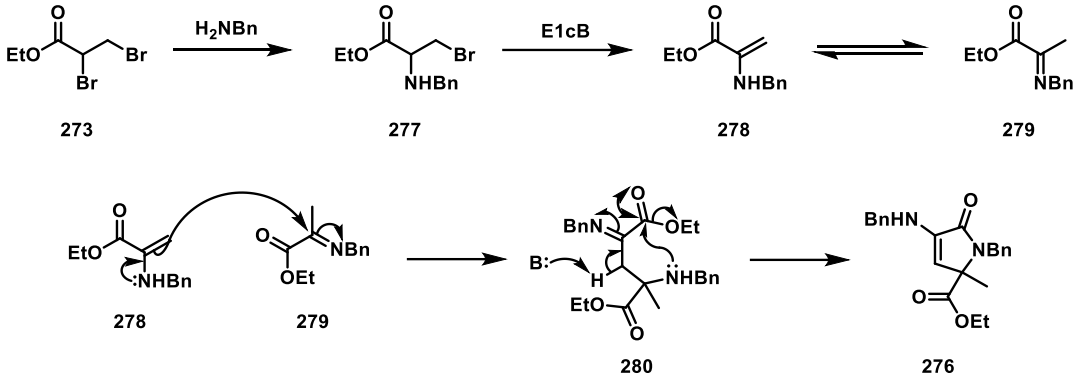
Starting where Ben Jones had left off, substrate synthesis began with the formation of aziridino ester **275** from dibromide **273** and benzylamine **274** (Scheme 2.4).



***Scheme 2.4**: Synthesis of pyrrolidinone **276** and aziridine **275** from dibromide **273**.*

When MeOH was used as the solvent, the reaction proceeded smoothly to give the desired aziridine product **275** in 99% yield. However, to our surprise, when the reaction was initially conducted using EtOH as the solvent, no aziridine formation was observed – with the major product instead being

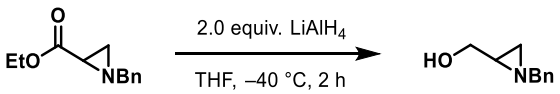
pyrrolidinone **276**, isolated in 56% yield as a red solid. Whilst no explanation for the dependence on alcoholic solvent could be provided, a possible mechanism for this transformation is shown below (Scheme 2.5).



***Scheme 2.5**: Possible mechanism for the formation of pyrrolidinone **276**.*

Initial S_N2 displacement of the more reactive α-bromide in **273** by benzylamine **274** gives amine **277**, which can then lose the less reactive β-bromide *via* an E1cB process to give enamine **278**. Tautomerisation of this enamine gives the highly reactive imine **279**, which is then trapped by another equivalent of enamine **278** to give intermediate **280**. Tautomerisation of this second imine back to the enamine, and concomitant ring closure, gives the pyrrolidinone product **276**.

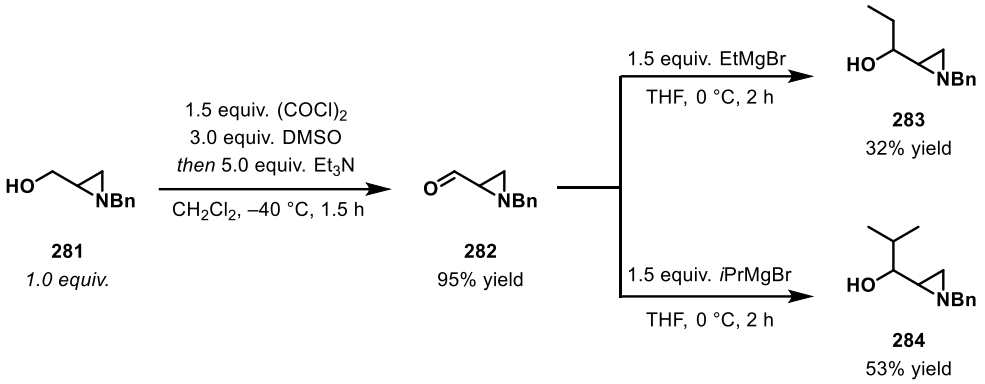
With aziridino ester **275** in hand, the next step in the synthesis was reduction to give alcohol **281**. This was achieved by treatment of the substrate with $LiAlH_4$, which gave clean reduction to alcohol **281** in 96% yield (Scheme 2.6).



***Scheme 2.6**: Reduction of aziridino ester **275** to alcohol **281** with $LiAlH_4$.*

Whilst primary aziridino alcohol **281** itself was a suitable substrate for the hydrogen borrowing alkylation, albeit one with no product diastereomers, it could also be oxidised *via* a Swern oxidation to give aziridino aldehyde **282** in 95% crude yield. Due to fears over its instability, this aldehyde was then

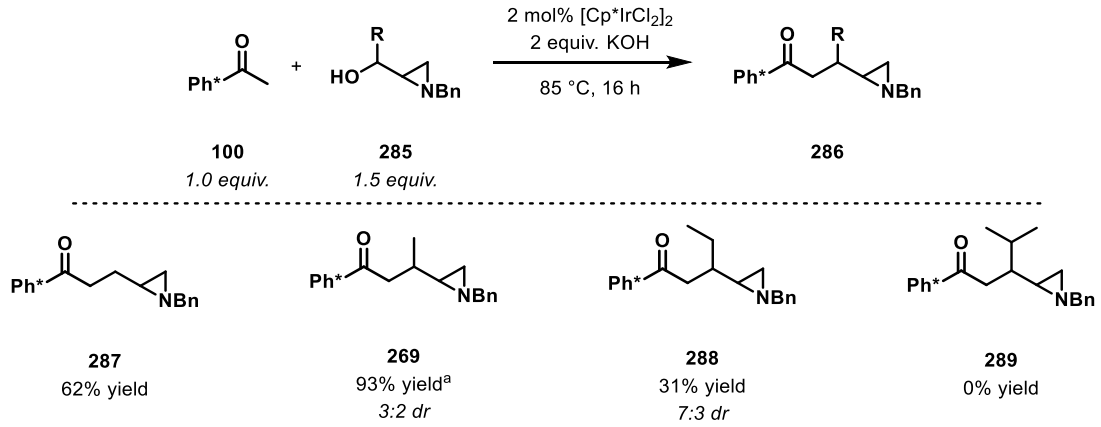
immediately treated with the appropriate Grignard reagents to give ethyl- and isopropyl-substituted secondary aziridino alcohols **283** and **284** in 32% and 53% yield respectively (Scheme 2.7).



Scheme 2.7*: Synthesis of secondary aziridino alcohols **283** and **284** from alcohol **281**.*

In both cases, the product alcohols were isolated as separable mixtures of diastereomers – with the crude ^{1}H NMR being too complicated to establish the dr of the reaction itself. Furthermore, NMR analysis alone was insufficient to determine the relative stereochemistry of each separated diastereomer – however given that the first step in the hydrogen borrowing reaction is oxidation of the alcohol with loss of stereochemistry, the major diastereomer in each case was taken forward.

With three new substrates in hand – primary alcohol **281**, ethyl substituted alcohol **283**, and isopropyl substituted alcohol **284** – their reactivity with Ph* methyl ketone **100** under hydrogen borrowing conditions could be evaluated (Scheme 2.8).

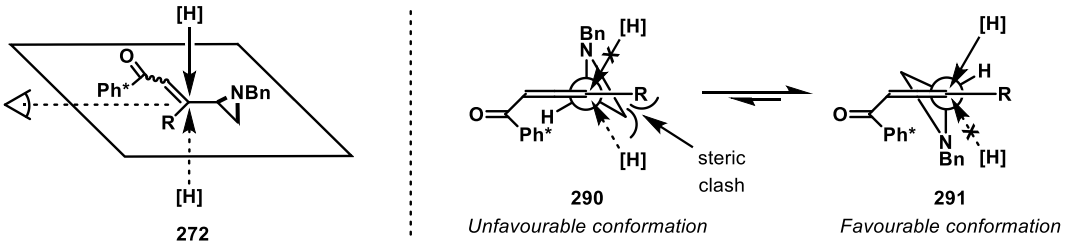


Scheme 2.8*: Subjection of simple aziridino alcohols to optimised hydrogen borrowing conditions.*
[a]Reaction conducted by Ben Jones

Disappointingly, all three substrates underperformed model alcohol **269** – with one reaction failing to give any product at all. To start with, product formation from primary alcohol **281** was observed in 62% yield – a result initially surprising to us, given that one might expect sterics to be less of a hindrance to the reaction than in model alcohol **268**. However, it was hypothesised that the reduction in yield could come from the less electron-rich primary alcohol **281** being harder to oxidise in the initial step in the reaction, or the lack of steric hindrance making alternative degradation reactions more competitive with the desired pathway.

With a 7:3 product dr, ethyl-substituted aziridino alcohol **288** proved to be the most diastereoselective substrate of the scope so far – unfortunately, the yield of product **288** was only 31%. Whilst the low yield can be easily explained by the additional steric bulk of the ethyl group hindering either the aldol reaction or final reduction, more consideration needs to be given to the change in diastereoselectivity.

In the model for diastereoselectivity provided earlier in this chapter, we proposed the diastereoselectivity of the reaction is determined by the facial selectivity of the hydride addition to enone **272**. Given that a change from methyl-substituted alcohol **269** to ethyl-substituted alcohol **283** results in an increase in diastereoselectivity, a possible explanation would be that the addition is governed by a polar Felkin–Anh model in which the electronegative aziridine nitrogen lies perpendicular to the enone π-system (Scheme 2.9).



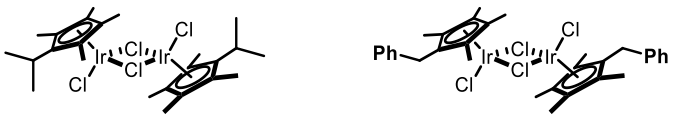
***Scheme 2.9**: Possible mechanistic origins of hydrogen borrowing diastereoselectivity.*

The two possible conformers of this are **290** and **291**, with the position of equilibrium depending on the magnitude of the steric clash between the aziridine methylene and the R group. As R increases in

size, conformer **291** is favoured over **290**, leading to more top-face reduction and an increase in the corresponding product diastereomer. However, without the relative stereochemistry of the major product being determined, the above mechanism remains speculative.

Finally, isopropyl-substituted aziridino alcohol **284** resulted in no formation of the desired product, with only starting material being observed by ^{1}H NMR. This was rationalised by the steric hindrance of the substrate preventing either oxidation by iridium or stopping the key aldol reaction from occurring as intended.

As a final attempt to improve the dr of the original hydrogen borrowing reaction with methyl-substituted aziridino alcohol **268**, the reaction was repeated with two analogues of the $[Cp^*IrCl_2]_2$ catalyst – both synthesised by Dr James Frost – bearing extra substitution on the Cp* ring (Figure 2.2).



292 **293**

***Figure 2.2**: Variants of the hydrogen borrowing $[Cp^*IrCl_2]_2$ catalyst synthesised by Dr James Frost.*

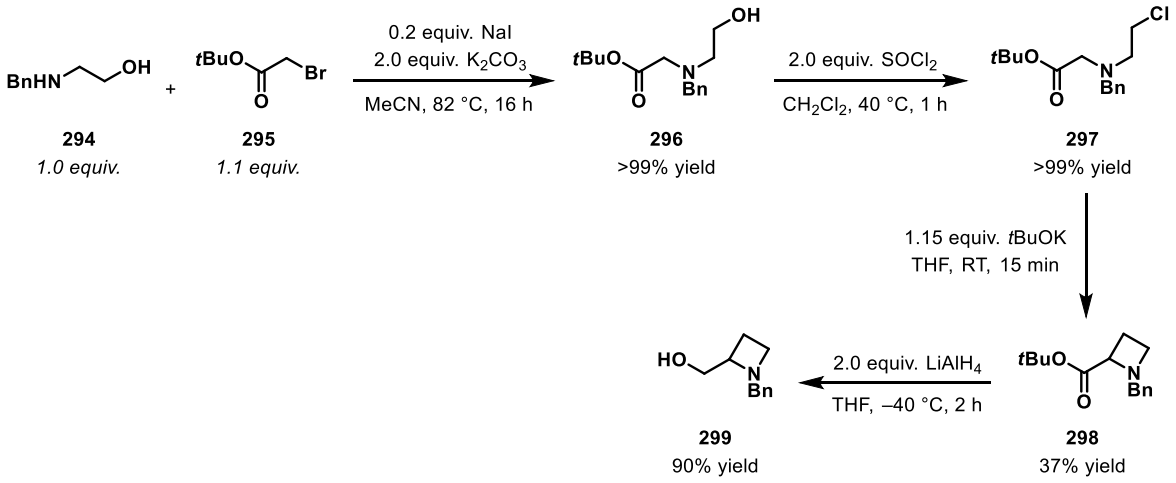
Unfortunately, despite the additional steric bulk about the catalytic centre, neither catalyst was successful in improving the reaction dr above the familiar value of 3:2. This was rationalised by free rotation about the cyclopentyl ring allowing the single bulkier substituent to point away from any reactive centre, thereby preventing it from exerting a steric influence. This problem could theoretically be overcome by replacing all the methyl groups on the Cp* ring with bulkier alternatives, however it was thought that this would compromise the activity of the catalyst, as well as prove difficult to synthesise, and so was not pursued.

The above results made it clear to us that attempting to improve the dr of the hydrogen borrowing reaction by altering the substituent of a secondary alcohol or the nature of the catalyst was likely to

come at the expense of yield. As such, it was decided to synthesise a number of other nitrogen-containing substrates – so as to ascertain a better understanding of the factors affecting the reaction, as well as to further explore the chemical space that could be accessed by it.

2.2.3 Synthesis and Evaluation of Other Nitrogen-Containing Substrates

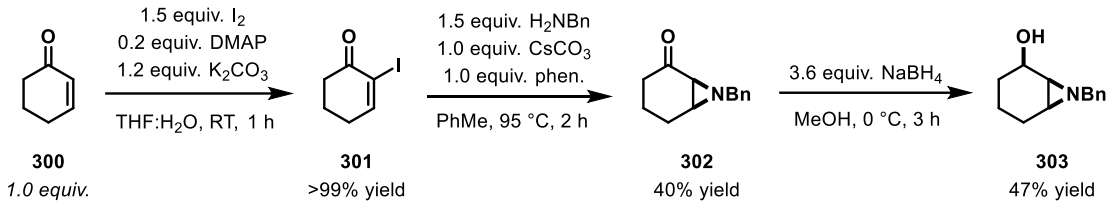
Having started with aziridines, it seemed to us that the use of azetidines – their four-membered analogues – might prove an informative comparison. Fortuitously, a route to azetidino-alcohol **299** had already been reported by Couty and co-workers,[60] and the synthesis therefore proved relatively straightforward (Scheme 2.10).



***Scheme 2.10**: Synthesis of azetidino-alcohol **299**.*

Starting with *N*-benzylaminoethanol **294**, alkylation with activated α-bromo ester **295** proceeded smoothly in >99% yield to give tertiary amine **296**. Transformation of the primary alcohol moiety to a chloride was affected with the use of $SOCl_2$ – giving chloride **297**, also in >99% yield. Cyclisation to the azetidine was achieved *via* treatment of **297** with KO*t*Bu, the resulting Baldwin-allowed 4-*exo*-tet cyclisation giving azetidine **298** in a disappointing 37% yield – perhaps due to competing E2 elimination of the chloride, as well as the unfavourable ring-strain in the product. Finally, reduction with $LiAlH_4$ proceeded smoothly to give the desired azetidino-alcohol **299** in 90% yield, with the spectroscopic data found to be in good accordance with that previously reported by Couty and co-workers.

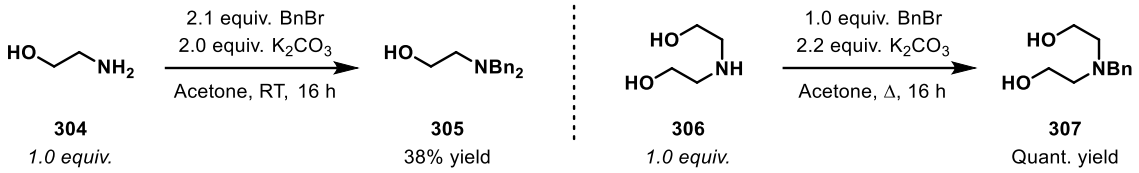
Another class of compounds that drew our interest were bicyclic aziridines – both due to the possibility that an additional ring system would add to the complexity, and therefore synthetic value of any hydrogen borrowing products, as well as the fact that they were reported by Maycock and co-workers to be readily synthesised from easily accessible α-iodo enones.[61] With this in mind, it was decided to synthesise bicyclic aziridino alcohol **303** from cyclohexenone **300** (Scheme 2.11).



***Scheme 2.11**: Synthesis of bicyclic aziridino alcohol **303** from cyclohexenone **300**.*

Using iodination conditions reported by Krafft and Cran in 2004,[62] cyclohexenone **300** reacted to form α-iodo enone **301** in >99% yield. Following Maycock's procedure, treatment of **301** with benzylamine, Cs_2CO_3, and phenanthroline in toluene (used in place of xylene, Maycock's preferred solvent) afforded the desired aziridine **302** in 40% yield *via* a Gabriel-Cromwell reaction. To our minds, the inclusion of stoichiometric phenanthroline in the reaction mixture seemed somewhat unusual – however Maycock and co-workers found it to be essential for reactivity, postulating that it was needed to act as a ligand for Cs^+ ions. Finally, reduction of the ketone in **302** with excess $NaBH_4$ yielded the desired aziridino alcohol **303** in 47% yield as a single diastereomer – with NOESY analysis showing it to be the expected *cis* isomer.

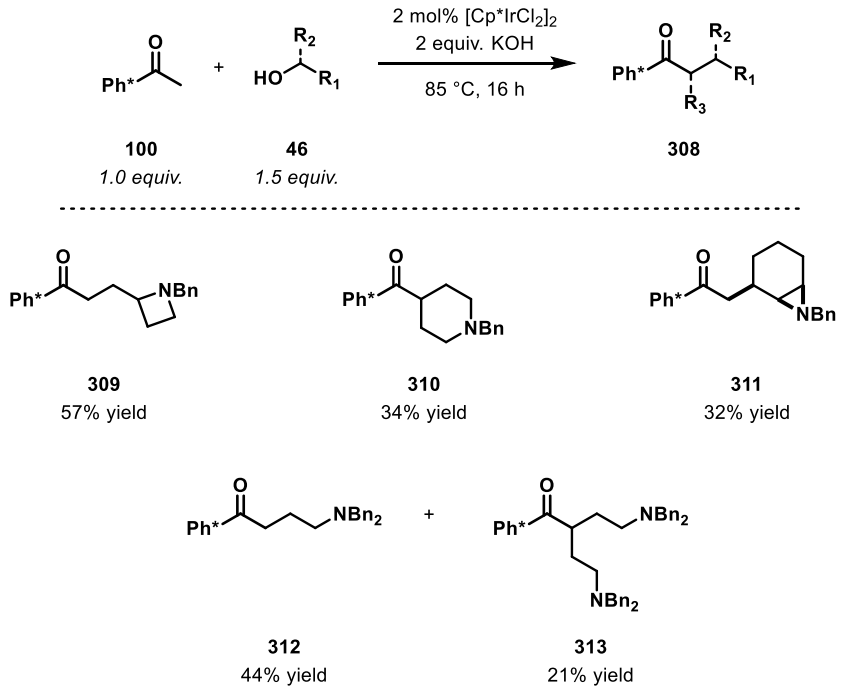
Before attempting the hydrogen borrowing alkylation with **299** and **303**, it was decided to first synthesise two other simple amino-alcohols – both to further round out the scope of the reaction, and to test our prior hypothesis that a cyclic amine structure was essential for good reactivity (Scheme 2.12).



***Scheme 2.12**: Synthesis of amino-alcohol **305** and -diol **307**.*

Pleasingly, both syntheses were straightforward: treatment of ethanolamine **304** with benzyl bromide afforded amino-alcohol **305** as a crystalline solid in 38% yield, whilst the reaction between diethanolamine **306** and benzyl bromide gave the desired amino-diol **307** in quantitative yield. The low yield of the former process was attributed to the difficulty in performing the second alkylation with benzyl bromide on an already hindered centre.

With four new amino-alcohols in hand, we set out to explore their reaction with Ph* methyl ketone **100** under hydrogen borrowing conditions (Scheme 2.13).



***Scheme 2.13**: Hydrogen borrowing reactions of assorted amino alcohols.*

Highest yielding was azetidino-alcohol **299**, giving the desired product **309** in 57% yield – quite similar, in fact, to that observed when primary aziridino alcohol **281** was reacted to give the corresponding hydrogen borrowing product **286** in 62% yield. To our surprise, the next best performing substrate was

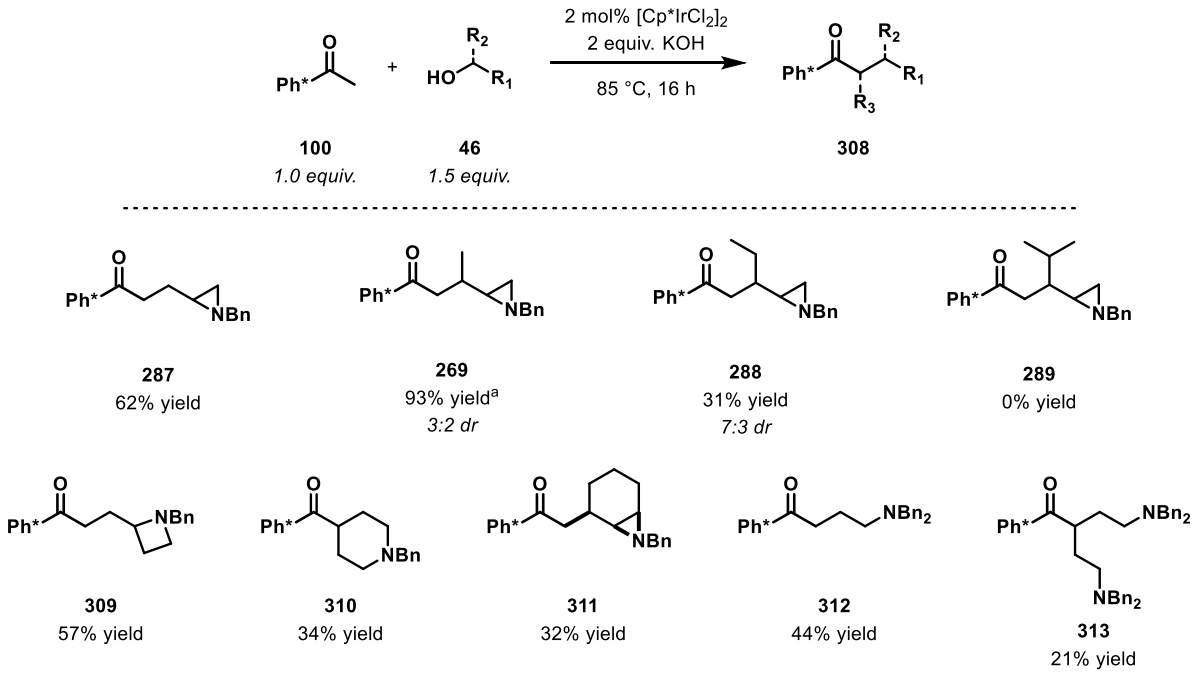
dibenzylated amino-alcohol **305** – giving the expected monoalkylated product **312** in 44% yield, along with a 21% yield of dialkylated Ph* ketone **313**.

This secondary hydrogen borrowing reaction, which until now had not been observed to occur, was most likely made possible by the aldehyde formed from the oxidation of **305** being relatively sterically unhindered. Further optimisation reactions were conducted with dibenzyl-alcohol **305** – however these form the basis of Chapter 4 of this thesis, and so will not be discussed further at this point.

Whilst expectations had been low for amino-diol **307** – owing to concerns over its stability to the reaction conditions – we were pleasantly surprised to see the formation of piperidine **310** in 34% yield. At the time, this represented the first synthesis of a six-membered ring *via* a C–C bond forming hydrogen borrowing reaction – and this methodology has since been explored by the Donohoe group in the context of forming carbocycles in racemic[33, 35]and enantiopure form,[34] as well as in the synthesis of piperidines.[63, 64, 65] Finally, the lowest yielding reaction was that of bicyclic aziridino alcohol **303**, furnishing hydrogen borrowing product **311** as a single diastereomer but in only 32% yield – perhaps attributable to the sterically hindered alcohol in **303** hindering reactivity.

2.2.4 Hydrogen Borrowing Scope Summary

With the varied successes of azetidino and amino alcohols detailed in the above section, along with the initial results from investigating the diastereoselectivity in aziridino alcohols, we now had a reasonable array of nitrogen-containing hydrogen borrowing products (Scheme 2.14).



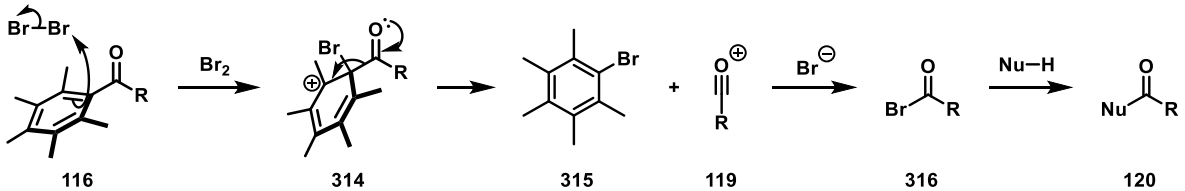
***Scheme 2.14**: Nitrogen-containing hydrogen borrowing products.*
[a]Reaction conducted by Ben Jones.

Having served its purpose in facilitating the hydrogen borrowing reaction, our focus now shifted to removing the Ph* group from the above products.

2.3 Results and Discussion: Ph* Cleavage Reactions with Bromine

2.3.1 Prior Ph* Deprotection Conditions

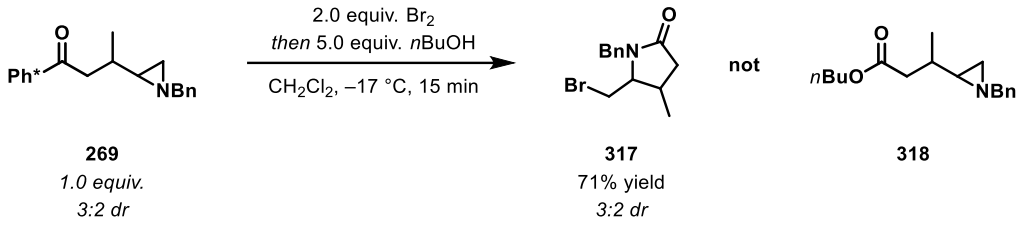
As detailed in Chapter 1, conditions to remove the Ph* group from hydrogen borrowing products using Br_2 had already been developed by the Donohoe group – with the reaction proceeding *via* an *ipso* bromination of the aromatic ring to give **314**, and a subsequent retro-Friedel-Crafts reaction to give a putative acyl bromide **316** which could be trapped with a range of nucleophiles (Scheme 2.15).



***Scheme 2.15**: Br_2-mediated removal of the Ph* auxiliary.*

The first attempted cleavage of a nitrogen-containing hydrogen borrowing product was conducted by Ben Jones, who found that when aziridine **269** was treated with Br_2 at –17 °C, followed by an excess of

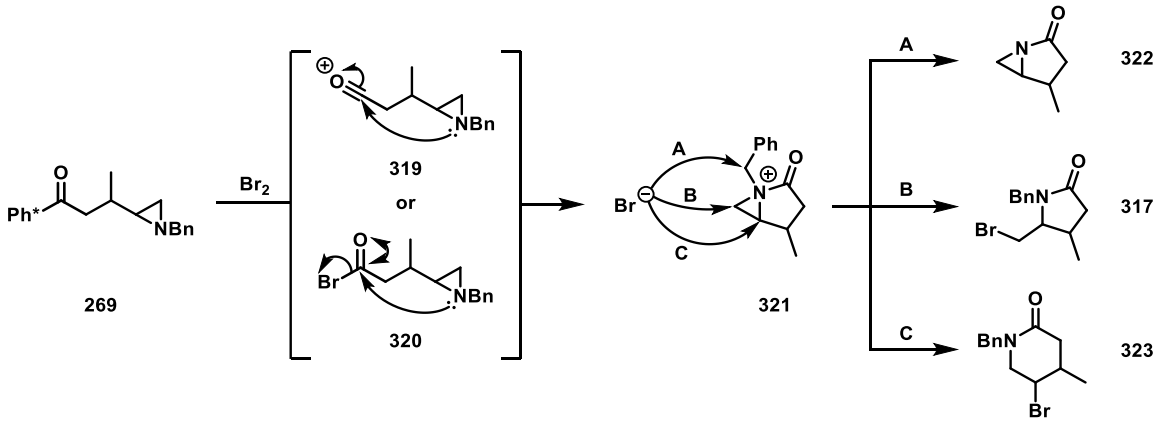
*n*BuOH to trap the acyl bromide, the product was not the expected ester **318** – but instead the cyclic lactam **317** in 71% yield and 3:2 dr (Scheme 2.16).



269 *1.0 equiv. 3:2 dr* — **317** 71% yield *3:2 dr* — **318**

Scheme 2.16*: Unexpected formation of lactam* ***317*** *in the Br_2-mediated cleavage of* ***269*** *by Ben Jones.*

The formation of lactam **317** could be explained by the cleavage of Ph* proceeding as expected, only for the intermediate acylium **319** or subsequent acyl bromide **320** to be trapped in an intramolecular attack by the aziridine nitrogen to give aziridinium **321** (Scheme 2.17).

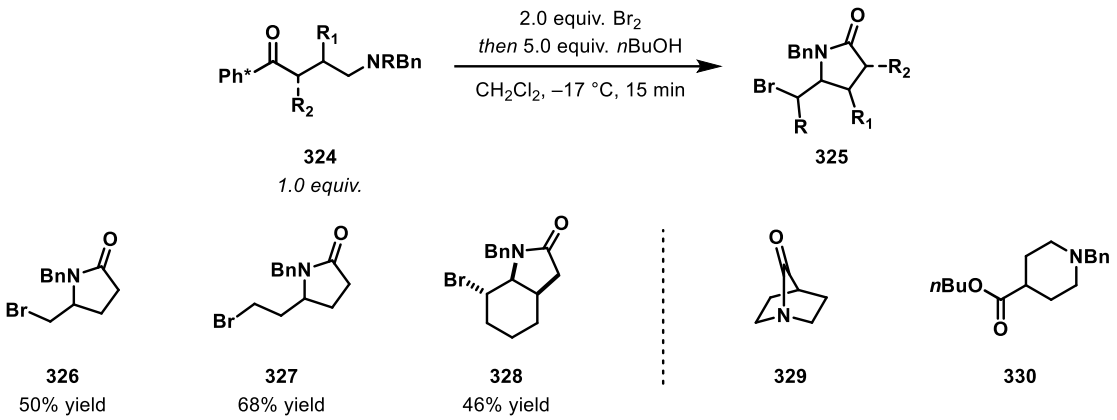


Scheme 2.17*: Possible mechanism for the formation of lactam* ***317****.*

At this point, the aziridinium could conceivably be attacked by the bromide counterion to give one of three products – however only pathway **B** was observed, presumably due to it being favoured on the grounds of both sterics and relief of ring strain. Whilst unexpected, the formation of lactam **317** was seen as an opportunity – providing a route to substituted pyrrolidones that, starting from enantiopure aziridines, could conceivably give enantioenriched products.

2.3.2 Deprotection Scope

To evaluate the scope of this transformation, a number of nitrogen-containing hydrogen borrowing products **324** were subjected to the Br_2-mediated cleavage conditions (Scheme 2.18).



***Scheme 2.18**: Scope for the Br_2-mediated cleavage of Ph*.*

Pleasingly, both unsubstituted aziridine **287** and azetidine **309** underwent the sequential cleavage/cyclisation reaction to give lactams **326** and **327** in 50% and 68% yield, respectively. Interestingly, despite an approximately 6 kJ mol^{-1} decrease in ring strain relative to an aziridine,[66] azetidine **309** still reacted to form only one regioisomer of the product – suggesting that the ring-opening step with bromide is dominated by sterics. To our dismay, the treatment of piperidine **310** with Br_2 resulted in only decomposition – with no trace of either bicyclic compound **329**, from intramolecular trapping with nitrogen; or ester **330**, from intermolecular trapping with *n*BuOH.

Of particular note was the bicyclic lactam **328** formed in 46% yield by treatment of bicyclic aziridine **311** with Br_2. The 6,5-bicylic structure of the product, along with the stereodefined secondary alkyl bromide on the six-membered ring, struck us as being useful structural motifs that could be exploited in the synthesis of more complex molecules – a topic that is more fully explored in Chapter 3 in the total synthesis of (–)-γ-lycorane.

2.3.3 Additional Project Aims

With the completion of both a small substrate and cleavage scope, all three of the initial project aims outlined at the start of this chapter had been completed. In order to further explore this chemistry, and in light of the unexpected – but interesting – products formed during the deprotection, two further project aims were identified:

iv. Establish whether existing methods for asymmetric aziridinations could be applied to the synthesis of the aziridino alcohols used in our scope.

v. Synthesise other bicyclic aziridino alcohols and investigate their reactivity, with the aim of assembling more natural product-like scaffolds similar to **328**.

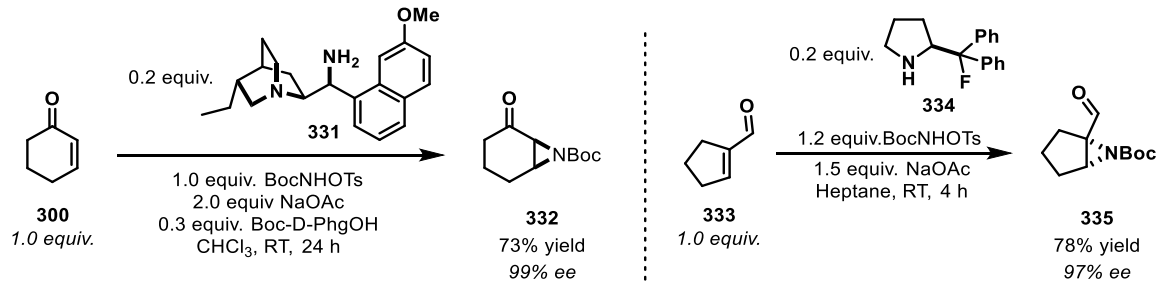
With these two additional project aims in mind, we set out to synthesise a number of other aziridino alcohols – with the emphasis being on aziridines that could be accessed *via* known asymmetric aziridinations.

2.4 Results and Discussion: Synthesis of Additional Aziridino Alcohols

2.4.1 Literature Methods for Asymmetric Aziridinations

Whilst the asymmetric synthesis of epoxides is familiar to most undergraduate chemists, with such classic examples as the Sharpless epoxidation of allylic alcohols[67] or the Shi epoxidation of simple olefins,[68] asymmetric aziridinations are far less widely known – although numerous methods are known.[69]

Of particular interest to us in this project, however, were the aziridinations developed by Melchiorre[70] and Gilmour[71] that use quinine- and proline-derived organocatalysts, respectively (Scheme 2.19).



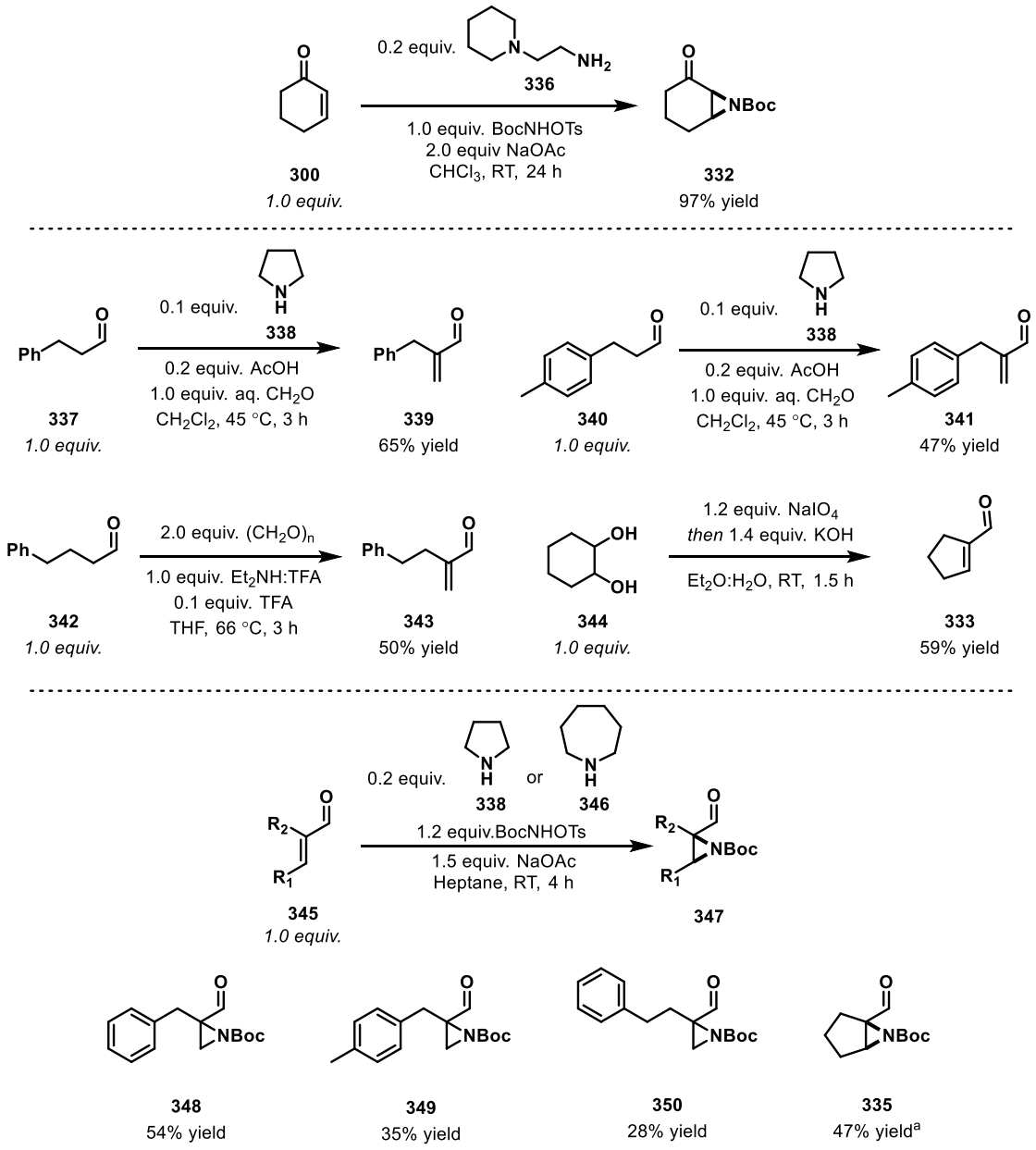
***Scheme 2.19**: Asymmetric aziridinations developed by Melchiorre and Gilmour.*

The appeal of both the above methodologies was twofold. Firstly, the organocatalysts **331** and **334** used by both methods were accessible from cheap and readily available starting materials – a key consideration in any synthesis. Secondly, the resulting aziridines from both methods were *N*-Boc protected – which we envisaged could be more easily deprotected than the *N*-Tosyl aziridines formed using most other aziridination methods.[69]

Rather than begin work immediately using a chiral aziridination catalyst, the synthesis of either requiring multiple steps, it was decided to initially proceed with achiral analogues – thereby synthesising racemic material on which to test the key hydrogen borrowing step and subsequent Br_2-mediated cleavage.

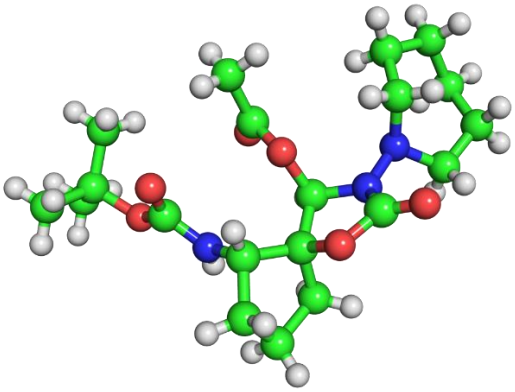
2.4.2 Organocatalysed Synthesis of Aziridines and Attempted Hydrogen Borrowing

As such, a number of suitable enones and enals were synthesised and subjected to both Melchiorre and Gilmour's aziridination conditions – using either diamine **336**, pyrrolidine **338**, or azepane **346** as an achiral organocatalyst as appropriate (Scheme 2.20).



Scheme 2.20*: Synthesis of racemic aziridines using organocatalysis.*
*[a]Synthesised using azepane **346** as the organocatalyst.*

All reactions gave the desired products, albeit with highly variable yields. Best performing was the aziridination of cyclohexenone **300** using Melchiorre's conditions and achiral diamine **336** as the organocatalyst – giving the desired product **332** in 97% yield. Unfortunately, yields for aziridinations of enal substrates using Gilmour's conditions were universally lower and, in the case of cyclic aldehyde **333**, extremely capricious. Acyclic enals **339**, **341**, and **343** all used piperidine as the organocatalyst, and the poor yields could perhaps be a consequence of piperidine being an inferior catalyst for the transformation than Gilmour's original fluorinated proline derivative **334**. In an attempt to circumvent this, cyclic aldehyde **333** was aziridinated using azepane **346** as the organocatalyst – the hypothesis being that the larger ring would make the intermediate enamine more nucleophilic, following a trend in going from pyrrolidine to piperidine enamines as detailed by Mayr and Ofial.[72] Whilst the use of azepane **346** did improve the yield of **335** to 47% from 29% with pyrrolidine, it also resulted in the reaction sometimes giving none of the desired product **335**, and instead forming an unknown, dark red compound as the only product. Attempts at structural elucidation by NMR, IR and MS proved inconclusive – with the structure finally being identified by X-Ray crystallography as spirocyclic compound **351** (Figure 2.3).

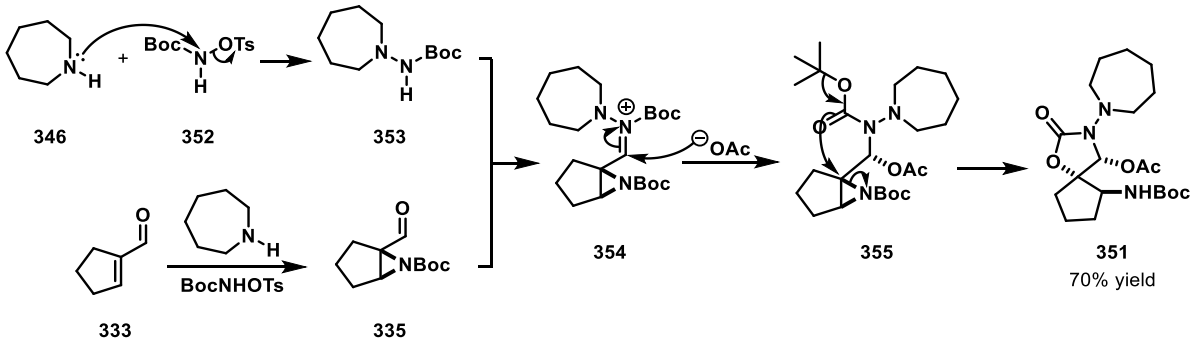


351
70% yield

***Figure 2.3**: X-Ray structure of side product **351**.*
Data collected and analysed by Dr Kirsten E. Christensen.

A number of features of the above structure were particularly striking to us – foremost among them the formation of an unusual N–N single bond. Furthermore, compound **351** bears three separate stereocentres, yet only a single diastereomer was observed. The yield, with respect to the limiting

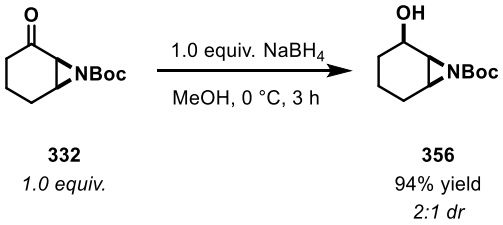
reagent of azepane **346**, was 70% – suggesting that its formation is highly favourable. A possible mechanism for its formation is outlined below (Scheme 2.21).



***Scheme 2.21**: Possible mechanism for the formation of spirocycle **336**.*

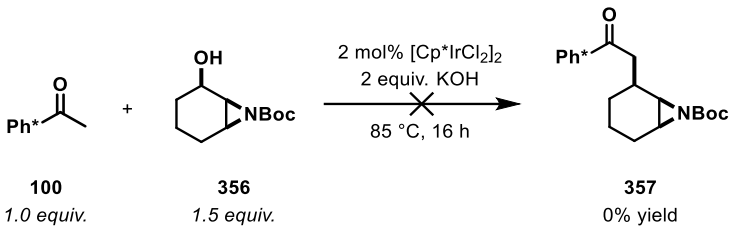
In this mechanism, initial aziridination of cyclic enal **333** occurs to give the expected *N*-Boc aziridino aldehyde **335**. Leftover BocNHOTs **352** is then attacked by the azepane catalyst **346**, forming the N–N bond in intermediate **353** with the loss of the tosylate leaving group as a driving force. This high energy hydrazide **353** then condenses with aziridino aldehyde **335** to give intermediate iminium **354**, which is attacked by the acetate base to give intermediate **355** – presumably in a stereospecific manner. The final ring in the spirocycle is formed by attack of the *N*-Boc carbonyl oxygen into the aziridine C-N σ* orbital in a 5-exo-trig cyclisation, along with loss of the stable *tert*-butyl cation to give product **351**.

With a number of new aziridino aldehydes and one aziridino ketone in hand, the next step was to synthesise the appropriate aziridino alcohols required for hydrogen borrowing. Aziridino ketone **332** was the first substrate to be reduced, and treatment with $NaBH_4$ afforded aziridino alcohol **356** as a 2:1 mixture of diastereomers in 94% yield (Scheme 2.22).



***Scheme 2.22**: Reduction of aziridino ketone **332**.*

With the desired aziridino alcohol **356** in hand, it was a simple matter of subjecting it to our optimised conditions for hydrogen borrowing (Scheme 2.23).



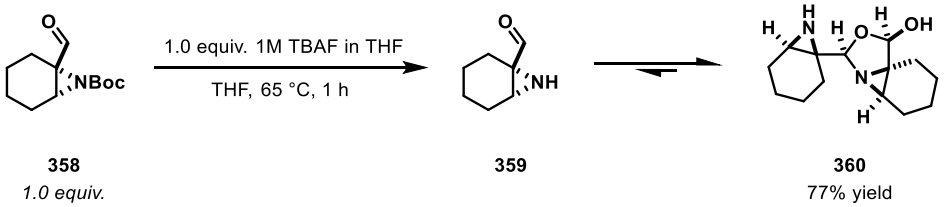
***Scheme 2.23**: Attempted hydrogen borrowing reaction of aziridino alcohol **356**.*

To our dismay, none of the desired product **357** was observed – with the reaction only resulting in decomposition of the starting aziridine **356**. It was hypothesised that this was due to the *N*-Boc protected aziridine moiety being unstable to the strongly basic reaction conditions, resulting in the free *N*–H aziridine being formed and subsequently degrading.

In order to circumvent this problem, it was decided to first perform a protecting group switch on the aziridine substrates – replacing the more unstable *N*-Boc group with a more robust alkyl protecting group.

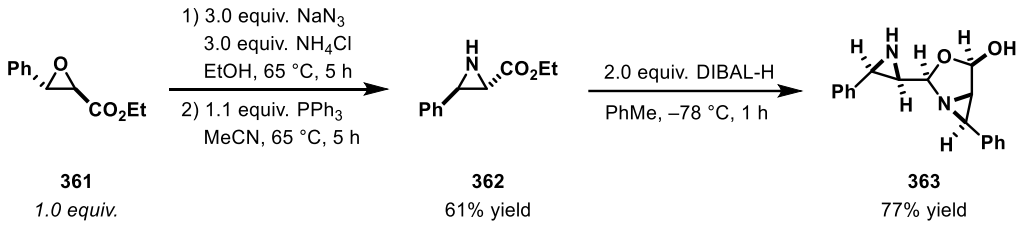
2.4.3 Deprotection of Aziridino Aldehydes

A survey of the literature found no applicable conditions for the deprotection of *N*-Boc aziridino ketones such as **356** – however, in Gilmour's publication of his asymmetric aziridinations, conditions for the deprotection of one of the *N*-Boc aziridino aldehyde products **358** using TBAF (unlikely to have been the first choice of reagent for removing a Boc group) to give dimer **360** are also described (Scheme 2.24).[71]



***Scheme 2.24**: Gilmour's deprotection of* N*-Boc aziridino aldehyde **358** to give dimer **360**.*

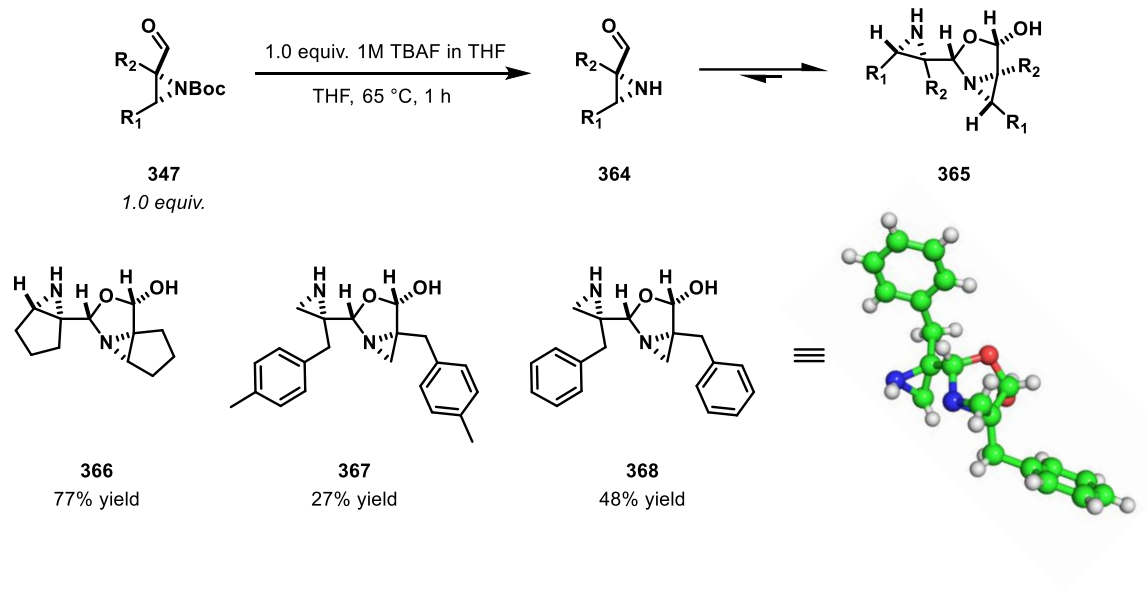
This observation was highlighted by Gilmour as being consistent with earlier work by Yudin, who investigated the dimers **363** formed from the reaction of a number of simple *N*-H aziridino aldehydes derived from the DIBAL-H reduction of aziridino esters **362** – which were in turn formed by the Staudinger-type aziridination of epoxy-esters **361** by sodium azide (Scheme 2.25).[73]



Scheme 2.25*: Yudin's earlier investigations into the dimerisation of* N*-H aziridino aldehydes.*

Two aspects of this reaction are of particular note. Firstly, the use of an aziridine – rather than a free amine – prevented an intermolecular condensation reaction between the aldehyde and free nitrogen moieties from occurring, presumably due to the increased ring-strain of the aziridine providing enough of a thermodynamic barrier to the usually favourable reaction to form an iminium. Secondly, despite the fact that the starting aziridines **361** were racemic, the product dimers **363** are isolated as single diastereomers – out of 8 possible diastereomers – implying there must be a thermodynamic driving force for homo- rather than hetero-dimerisation, and for a particular geometry about the central oxazolidine ring.

Following these examples, a number of our aziridino aldehydes were treated with TBAF and gave the expected dimeric species, in good to poor yields (Scheme 2.26). In keeping with the results observed by Gilmour and Yudin,[71, 73] all products were formed as a single dimer diastereomer – the relative stereochemistry of which for dimer **368** was confirmed by an X-Ray structure. Whilst we were unable to crystallise and therefore confidently assign the relative stereochemistry of dimers **366** and **367**, the relative stereochemistry in the X-Ray structure of dimer **368** matched that observed by Yudin and co-workers in crystallographic analysis of their products and so the stereochemistry of **366** and **367** was assumed to be the same.



***Scheme 2.26**: Deprotection of* N*-Boc aziridino aldehydes **347** using Gilmour's conditions. X-Ray data collected and analysed by Dr Kirsten E. Christensen.*

Another fascinating property of these dimeric species was discovered when analysing the NOESY spectra of compound **368**. An EXSY correlation was observed that implied that the free aziridine N–*H* proton was in chemical exchange with both the free O–*H* proton of the hemiacetal, which is to be expected, *as well as one the C–H protons on the same aziridine ring* (Figure 2.4).

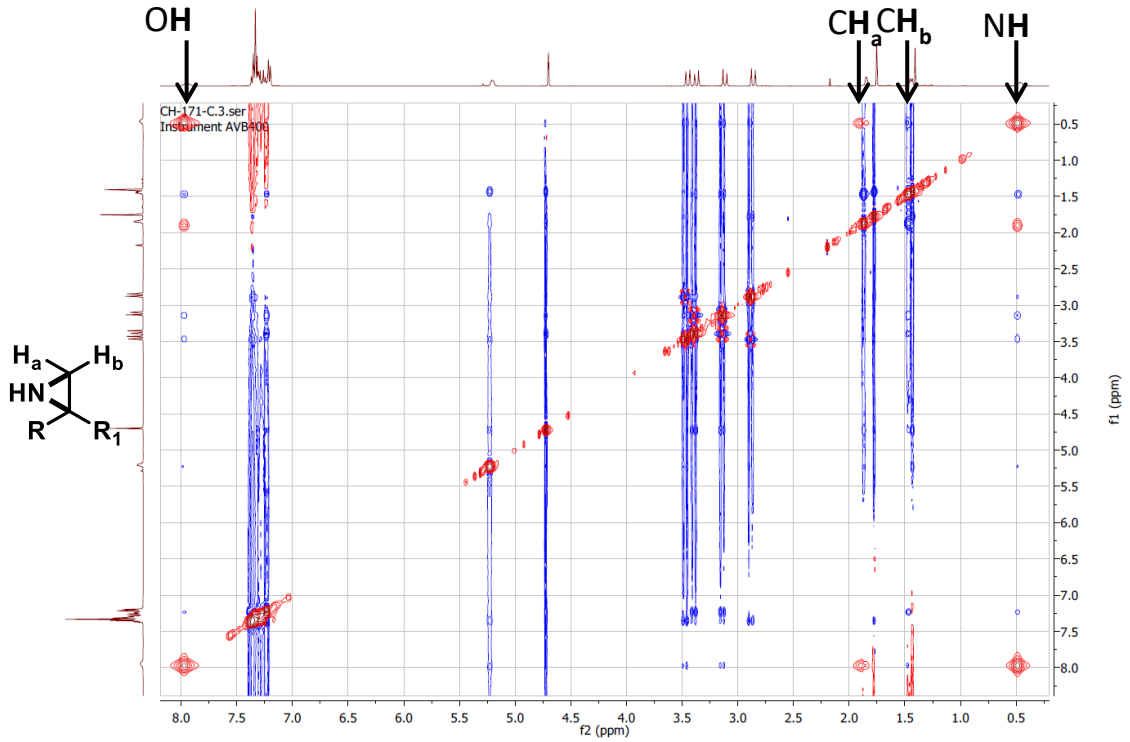
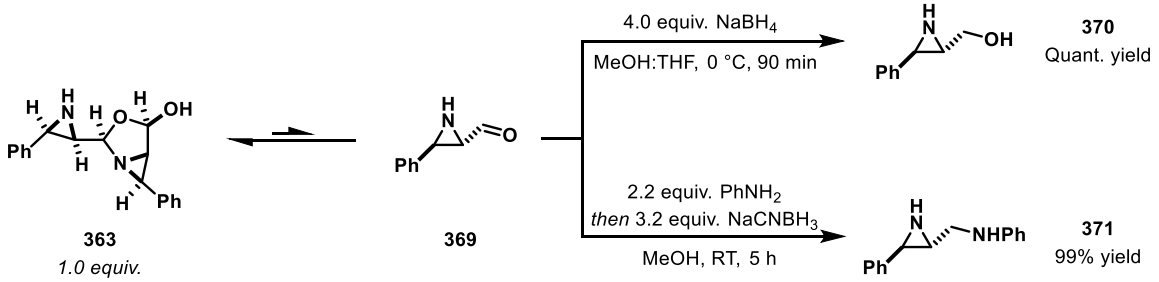


***Figure 2.4**: NOESY Spectrum of dimer **368** exhibiting an unusual EXSY correlation.*

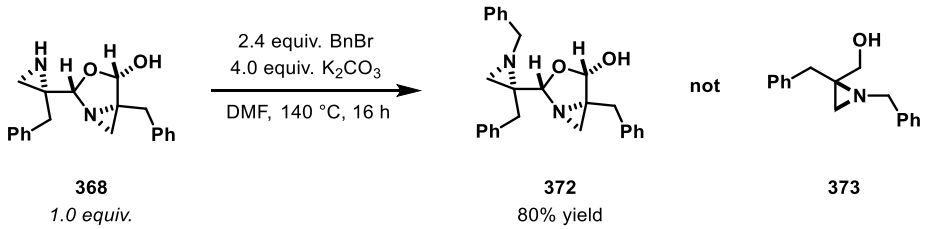
A chemical exchange process involving such a strong C–H bond was clearly impossible, prompting a search for an alternative explanation. Fortunately, an answer was found in an earlier publication by Hodgson and co-workers, who reported that the NOESY spectra of terminal *N*–H aziridines – such as found in dimer **368** – exhibit an effect known as scalar cross-relaxation of the first kind.[74] Whilst a full explanation of the effect is beyond the scope of this thesis, it arises from modulation of the C–H and *N*–H J-coupling by the pyramidal inversion of the aziridine nitrogen – a process made unusually slow in aziridines, relative to other amines, due to the small ring size destabilising the planar transition state of the inversion process.

Interesting NMR effects aside, our next task lay in the reprotection of the aziridine nitrogens with a more suitable protecting group – for which benzyl was chosen. In Yudin's earlier publication was the observation that aziridino aldehyde dimer **363** could undergo either reduction with $NaBH_4$ to give alcohol **370**, or reductive amination with aniline and $NaCNBH_3$ to give amine **371** – thereby demonstrating that the dimeric species **363** is in equilibrium with its monomer **369** (Scheme 2.27).[73]



***Scheme 2.27**: Equilibrium between dimer **363** and monomer **369**, with subsequent transformations by Yudin.*

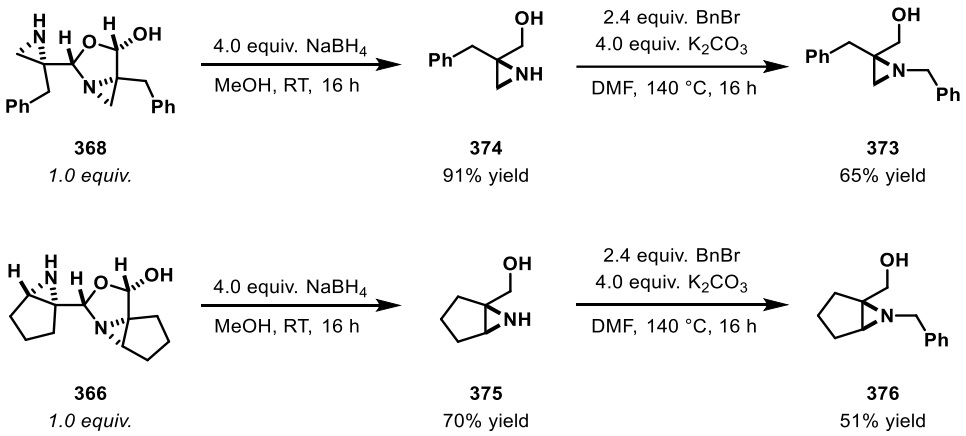
With this observation in mind, it was decided to treat dimer **368** with an excess of benzyl bromide in the hopes of trapping out the monomer as the protected *N*–Bn species **373** (Scheme 2.28).



***Scheme 2.28**: Attempted formation of* N*–Bn monomer **373** from dimer **368**.*

To our great surprise, this reaction succeeded only in benzylating the free *N*–H aziridine to give monobenzylated dimer **372** in 80% yield. Because the greatly increased reaction temperature – relative to Yudin's reactions conducted at RT – of 140 °C ought to push the equilibrium in favour of monomer **373** in accordance with Le Chatelier's Principle, another factor must have been at work to favour the dimeric species **372**. This was ascribed to the role of solvent, with the benzylation being performed in the aprotic solvent DMF, as opposed to Yudin's reductions which were conducted in MeOH – a solvent capable of effectively hydrogen-bonding with, and therefore favouring, free *N*–H aziridines.

In light of this result, it was decided to follow Yudin's example and first perform a reduction in MeOH to obtain free *N*–H aziridino alcohols, which could be subsequently protected by benzylation with benzyl bromide (Scheme 2.29).



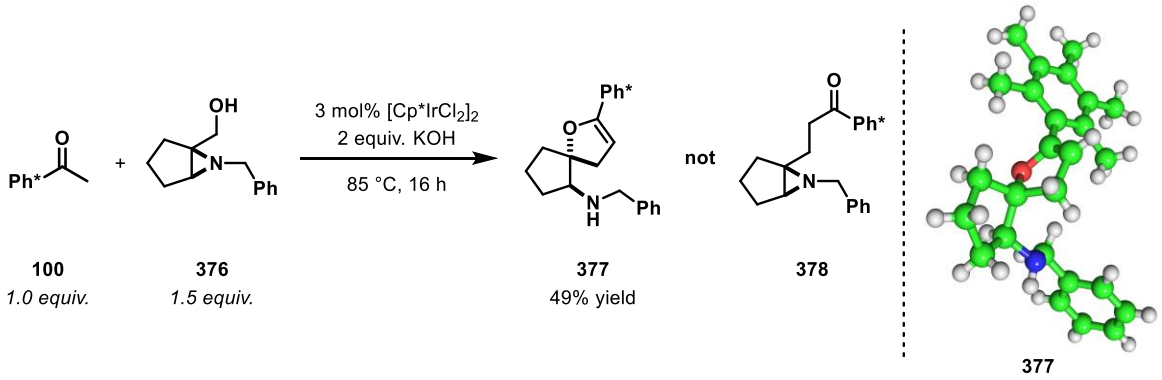
***Scheme 2.29**: Reduction and benzylation of aziridino aldehyde dimers.*

Pleasingly, the deprotection of dimers **368** and **366** proceeded as anticipated – giving the desired *N*–H aziridino alcohols in 91% and 70% yield, respectively. Unsurprisingly, due to their small size and ample ability for hydrogen-bonding, both compounds were highly viscous oils that were tricky to handle and purify. Despite this, the benzylation reactions proceeded as expected – giving benzyl-substituted aziridino alcohol **373** in 65% yield, and bicyclic aziridino alcohol **376** in 51% yield. With these substrates in hand, we were in position to investigate their reactivity to hydrogen borrowing alkylation with Ph* methyl ketone **100**, and subsequent Br_2-mediated cleavage.

2.5 Results and Discussion: Reactions of Aziridino Alcohols 373 and 376

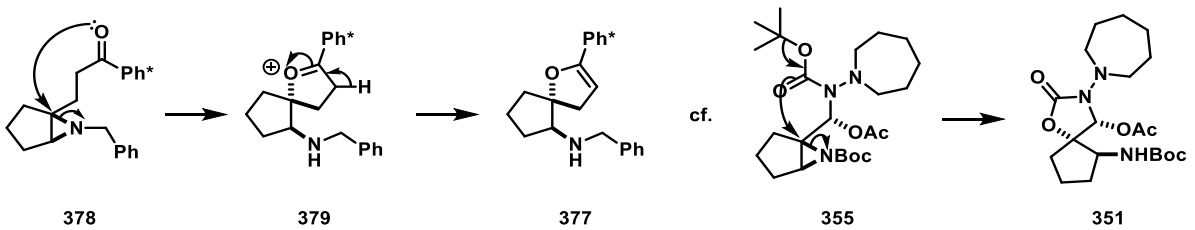
2.5.1 Hydrogen Borrowing Reactions with Ph* Methyl Ketone 100

Upon first attempting a hydrogen borrowing alkylation of Ph* methyl ketone **100** with aziridino alcohol **376**, the reaction appeared to have proceeded as planned – with the crude ^{1}H NMR showing full conversion to the desired product **378**, as ascertained from the loss of the alcohol CH_2 singlet, along with the appearance of signals with a characteristic shift of 2.77 ppm and ddd multiplicity of the methylene adjacent to the ketone carbonyl. However, upon attempted purification by column chromatography, the expected hydrogen borrowing product **378** was not obtained – with the only isolated compound being spirocyclic ether **377** in 49% yield, the structure of which was proven by X-ray crystallography (Scheme 2.30).



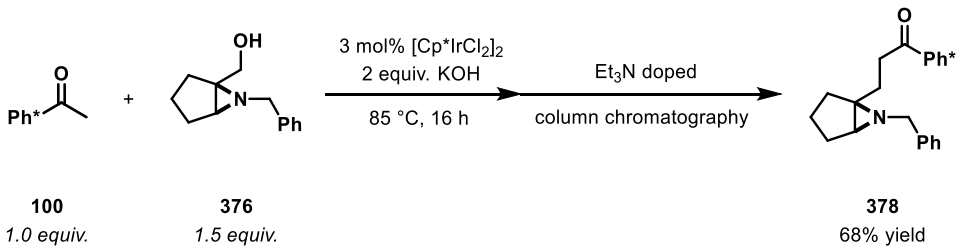
***Scheme 2.30**: Attempted hydrogen borrowing reaction of aziridino alcohol **376** and formation of unexpected spirocycle **377**.*
Data collected and analysed by Dr Kirsten R. Christensen.

It was immediately clear to us that spirocycle **377** was formed by a cyclisation of the carbonyl oxygen in **378** onto the tertiary aziridine carbon, resulting in ring-opening, with subsequent loss of one of the α-carbonyl protons to give the enol ether (Scheme 2.31).



***Scheme 2.31**: Mechanism for the formation of spirocycle **377** from hydrogen borrowing product **378**.*

This mechanism was highly reminiscent of the formation of the unusual side product **351**, observed in the aziridination reaction to form **335** from cyclic enal **333** earlier in this chapter. A key difference, however, is the protecting group on the aziridine – with the earlier cyclisation occurring when the aziridine **355** bore a highly electron withdrawing Boc group, thereby activating it to ring-opening. It was reasoned, therefore, that the aziridine in **378** must also be activated somehow in order for this cyclisation to take place – the fact that the desired product had been observed in the crude ^{1}H NMR proved that the molecule was not intrinsically unstable. It was hypothesised that protonation of the basic nitrogen could be responsible for activating the ring sufficiently to allow undesired ring-opening reaction to occur – the question was, as what point did this occur? Given that the degradation appeared to have taken place during column chromatography, and that the silica gel used for such purposes is known to be mildly acidic,[75] it was decided to repeat hydrogen borrowing reaction under the same reaction conditions as before – with the additional precaution of chromatographic purification being performed using eluent basified by the addition of Et_3N (Scheme 2.32).

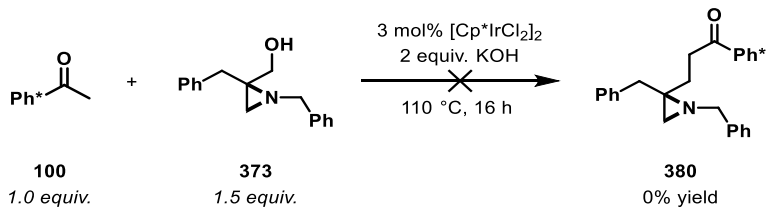


100 *1.0 equiv.* **376** *1.5 equiv.* **378** 68% yield

Scheme 2.32*: Formation and purification of hydrogen borrowing product **378** using basified silica gel.*

Pleasingly, this change in the purification procedure circumvented the unwanted cyclisation to **377** and furnished the desired hydrogen borrowing product **378** in 68% yield – somewhat disappointing given that few side-products were observed *via* crude ^{1}H NMR, but also impressive given the neopentyl nature of the alcohol being oxidised in the starting material.

To our dismay, when benzyl-substituted aziridine **373** was subjected to the optimised hydrogen borrowing conditions no desired product **380** was observed – with the reaction just returning starting material, even when the reaction temperature was raised to 110 °C (Scheme 2.33).



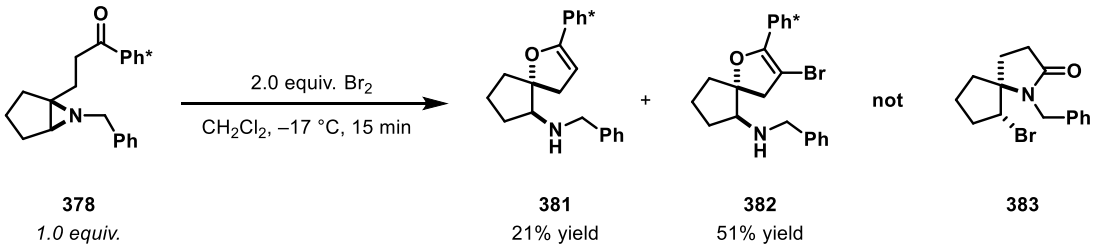
***Scheme 2.33**: Attempted hydrogen borrowing alkylation with aziridino alcohol **373**.*

This lack of reactivity was attributed to the steric bulk of the substrate – once again containing a neopentyl alcohol centre. Whilst bicyclic aziridino alcohol **376** surpassed this obstacle and still reacted successfully, this could be due to the bicyclic nature of the ring "tying back" some of the steric bulk – thereby limiting its influence on reactions at the alcohol. Benzyl-substituted aziridino alcohol **373**, however, does not benefit from such an effect – with the benzyl group free to rotate and inhibit reactivity. As such, substrate **373** was abandoned, and our efforts instead focussed on the reactions of bicyclic aziridino alcohol **376**.

With hydrogen borrowing product **378** in hand, our next ambition was to cleave the Ph* group with Br_2 and perform the same lactamisation/aziridine ring-opening cascade we had observed with more simple aziridine-bearing substrates.

2.5.2 Attempted Br_2-Mediated Cleavage of Hydrogen Borrowing Product 378

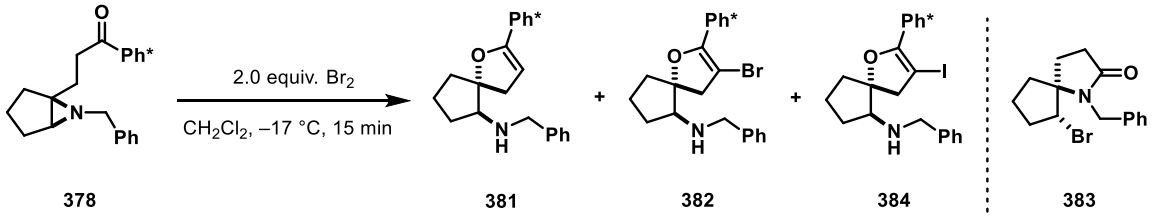
Upon exposure of aziridine **378** to our prior cleavage conditions with Br_2 we were disappointed to discover that the anticipated cleavage reaction to give spirocyclic lactam **383** did not occur – with the substrate instead undergoing the same acid-catalysed cyclisation process as before to give spirocyclic ether **381** in 21% yield, along with its brominated analogue **382** in 51% yield (Scheme 2.34).



***Scheme 2.34**: Unexpected formation of spirocycles **381** and **382** in the attempted Br_2-mediated cleavage of **378**.*

One interesting feature of the ^{1}H NMR spectra of brominated spirocycle **382** was the methyl substituents of the Ph*. Normally in Ph* containing compounds the ring is free to rotate and as such the two *ortho* and the two *meta* methyl substituents appear as two 6H singlets. In compound **382**, however, all five methyl groups were distinguishable as independent 3H singlets *via* NMR – this most likely being a consequence of the increased steric bulk of the bromine substituent on the enol ether restricting free rotation of the aromatic ring on the NMR timescale.

In an attempt to try and prevent the unwanted cyclisation from occurring, a number of bases were screened as additives, along with various solvents and temperature regimes – as well as the use of ICl and NBS as reagents to cleave the Ph* ring (Table 2.2).



378 *1.0 equiv.* **381** **382** **384** **383**

Entry	Additive/Variant to Standard Conditions	Outcome
1	None	21% yield **381**, 51% yield **382**
2	1.0 equiv. ICl in CH_2Cl_2	58% yield **384**[a]
3	3.0 equiv. neat Br_2 as solvent	**382**[a]
4	1.0 equiv. 2M HCl in Et_2O	**381**[a]
5	2.0 equiv. Et_3N	**381** and **382** (1:1)[a]
6	1.0 equiv. Proton Sponge®	**381**[a]
7	1.0 equiv. Proton Sponge® premixed with Br_2	**381**[a]
8	1.0 equiv. DBU	**378** and **381** (1:1)[a]
9	1.0 equiv. Pyridine	**381** and **382** (1:4)[a]
10	2.0 equiv. TMG	**378**, then **382** on heating to 40 °C[a]
11	1.0 equiv. DABCO	**381** and **382** (1:0.6)[a]
12	0.5 equiv. DABCO	**381** and **382** (1:1.6)[a]
13	1.0 equiv. TMP	**378**[a]
14	1.0 equiv. TMP and 2.0 equiv. Br_2	**381** and **382** (1:1)[a]
15	1.0 equiv. K_2CO_3	**381** and **382** (1:2)[a]
16	Biphasic with sat. aq. K_2CO_3	**378**[a]
17	Pentane as solvent	**381** and **382** (1:5)[a]
18	MeCN as solvent	**381** and **382** (1:4)[a]
19	MeCN as solvent and 1.0 equiv. NBS	**381** and **382** (1:0.7)[a]
20	–78 °C then warmed to RT	**382**[a]

***Table 2.2**: Ph* cleavage conditions screened to prevent unwanted spirocycle formation.*
[a]Not isolated, identified by analysis of crude ^{1}H NMR spectra.

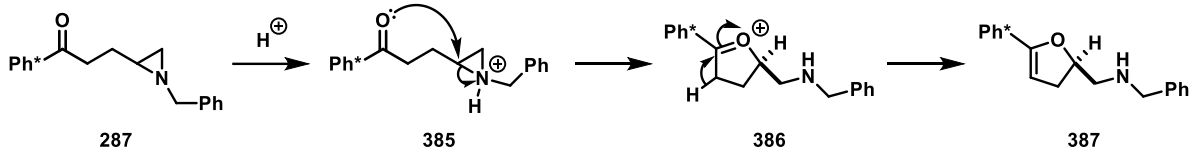
Disappointingly, none of the above conditions resulted in the formation of the desired spirocyclic lactam **383** – instead giving either starting material **378**; a mix of the two unwanted spirocyclic side products **381** and **382**; or, in the case of ICl (Entry 2), the iodinated spirocycle **384** in 58% yield – which, unsurprisingly, also exhibited restricted rotation of the Ph* group. Neat Br_2 was used as the solvent (Entry 3) in the hope that it would facilitate rapid Ph* cleavage and lactam formation, however this did not have the desired effect with the only observed product being brominated spirocycle **382**. A control reaction was conducted with 2M HCl (Entry 4) to ascertain whether a simple protic acid caused the unwanted cyclisation, which indeed it did.

The failure of various basic additives to prevent the acid-catalysed cyclisation from occurring warranted explanation. For amine bases such as Et_3N, Proton Sponge®, or DBU (Entries 5, 6, 7 and 8) with available protons next to the basic nitrogen, it was hypothesised that Br_2 was forming an adduct with the amine, followed by elimination of HBr to give the iminium – thereby removing any buffering effect of the amine. To circumvent this, amine bases with non-existent or non-removeable α-protons such as pyridine, TMG, DABCO and TMP (Entries 9 – 14) were tested – although with no further success. Another base screened was K_2CO_3 – both in the form of a solid additive (Entry 15) and as an aqueous solution (Entry 16) however neither condition led to the formation of the desired product **383**, perhaps due to issues of solubility/miscibility with CH_2Cl_2.

Finally, both pentane and MeCN were screened as reaction solvents (Entries 17 and 18), along with the use of NBS as a bromine source (Entry 19) – however none of these conditions yielded the desired product **383**. Lowering the reaction temperature to –78 °C (Entry 20) resulted in no reaction at all, as determined by TLC analysis, however it once again gave the undesired spirocycle **382** upon warming to RT.

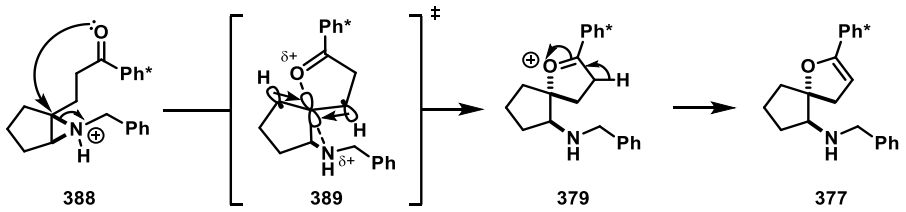
With these results, it was clear to us that the unwanted acid-catalysed cyclisation to give spirocyclic ether **381** was an extremely favourable one – occurring rapidly even under the mildly acidic conditions

of column chromatography. It was interesting to note, however, that such a transformation had not been observed in our prior investigations into Br_2-mediated cleavages with other aziridines – despite such a pathway being possible: for example, unsubstituted aziridine **287** could theoretically rearrange to give dihydrofuran **387** (Scheme 2.35).



***Scheme 2.35**: Possible acid-catalysed cyclisation of aziridine-containing hydrogen borrowing product **287**.*

It was therefore hypothesised that the structural feature responsible for facilitating the unwanted cyclisation was the tertiary aziridine centre in **378** – upon protonation to give aziridinium **388**, the excellent hyperconjugative stabilisation of the tertiary centre would lower the energy of the transition state **389** involved in aziridine ring-opening, thereby leading to the unwanted product **377** (Scheme 2.36).

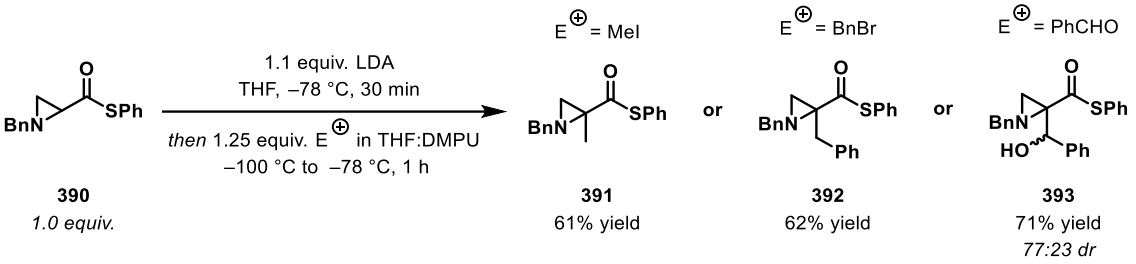


***Scheme 2.36**: Hyperconjugative stabilisation of the transition state in aziridine ring-opening.*

To test this hypothesis, it was decided to synthesise another aziridino alcohol that contained such a tertiary centre and subject it to hydrogen borrowing conditions and the Br_2-mediated cleavage. Unfortunately, although benzyl-substituted aziridine **373** had been such a substrate – it had failed to participate in hydrogen borrowing due to the additional steric bulk of the benzyl group inhibiting reactivity. It was decided, therefore, to synthesise the methyl substituted analogue of **373** in the hopes that it would be less sterically impaired in the hydrogen borrowing reaction.

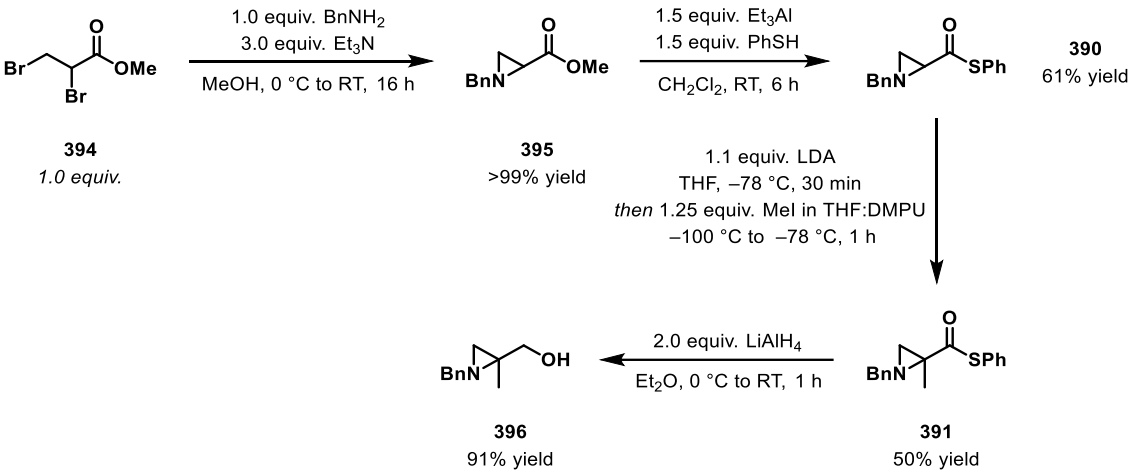
2.5.3 Synthesis and Reactions of Methyl-Substituted Aziridino Alcohol 396

Fortunately, the synthesis of methylated aziridino thioester **391** had already been reported by Seebach and Haner as part of their studies into the reactions and diastereoselectivity of small-ring ester enolates (Scheme 2.37).[76]



***Scheme 2.37**: Seebach and Haner's studies into the reactions of small-ring ester enolates.*

As such, aziridino methyl ester **395** was synthesised from dibromo-ester **394** and benzylamine in >99% yield (Scheme 2.38) – a slight variation from Seebach's route which synthesised aziridino ester **395** from serine in three steps.

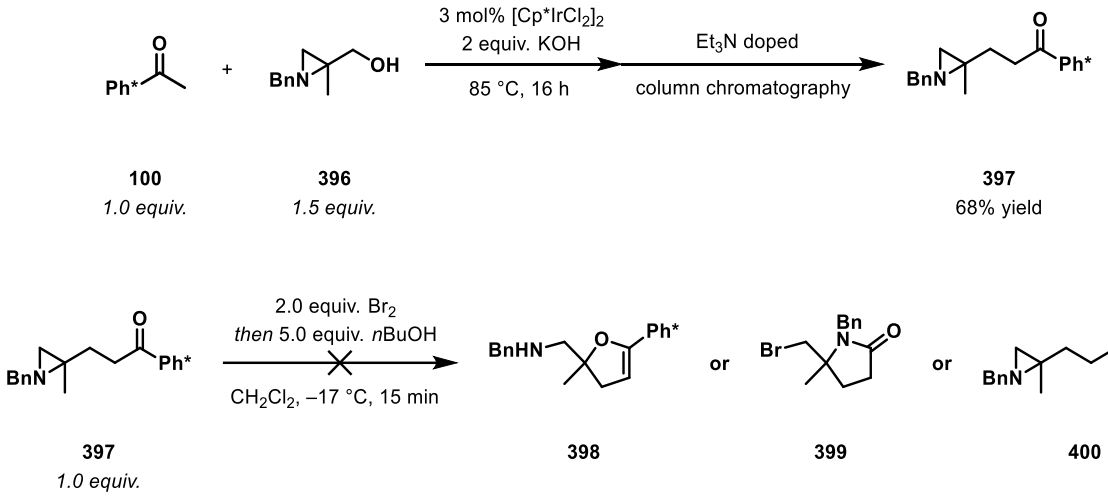


***Scheme 2.38**: Synthesis of methyl-substituted aziridino alcohol **396**.*

The next step in the synthesis was a transesterification of the methyl ester **395** to thioester **390** using Et_2AlSPh generated *in situ* by the addition of thiophenol to a solution of Et_3Al, which proceeded in 61% yield. Methylation of **390** was then achieved by first treatment with LDA, followed by a solution of MeI in DMPU – giving the desired methylated product **391** in 50% yield. The use of a thioester for this step had been found by Seebach to be essential – with the reaction actually giving products with retention

of stereochemistry, if enantiopure starting materials were used. Finally, reduction of the thioester **391** was achieved with $LiAlH_4$, giving the desired methyl-substituted aziridino alcohol **396** in 91% yield.

To our delight, when aziridino alcohol **396** was subjected to the standard hydrogen borrowing conditions – with care taken to use Et_3N in the column eluent for chromatographic purification – the desired product **397** was formed in 68% yield (Scheme 2.39).



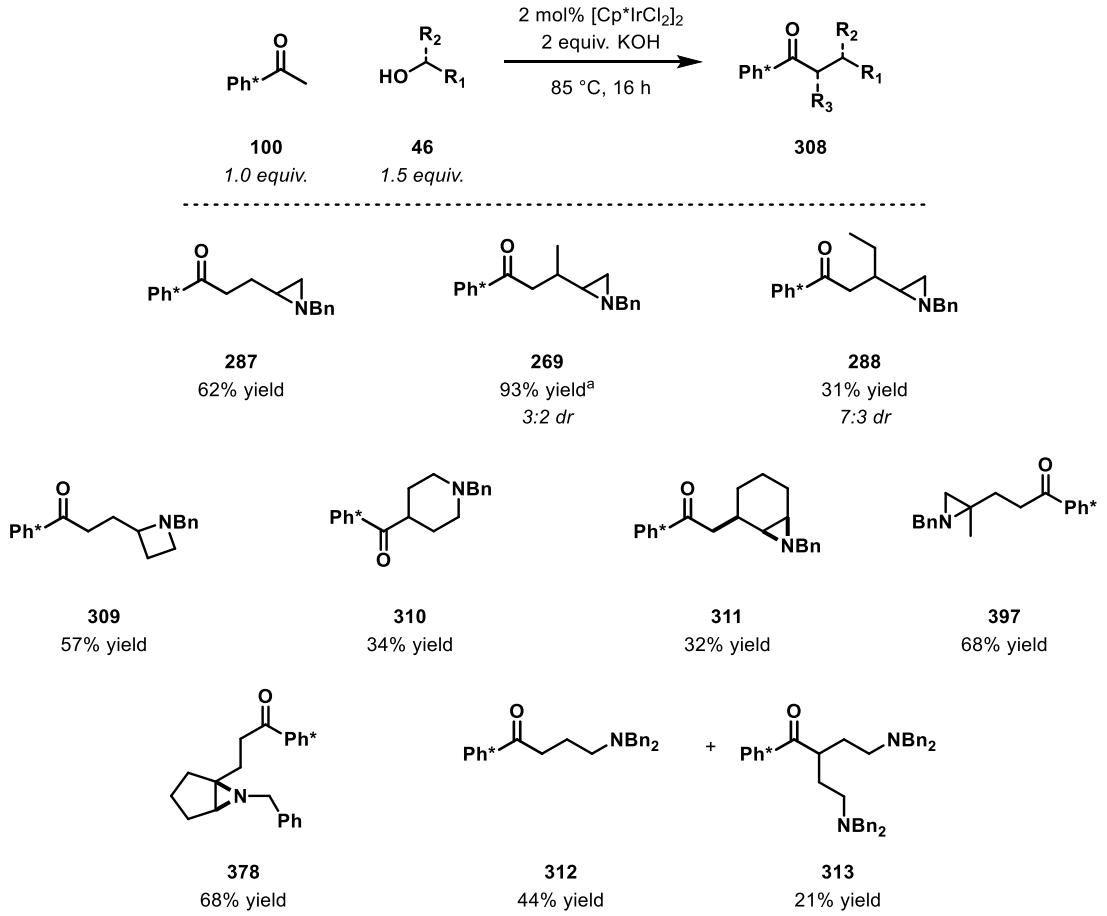
Scheme 2.39*: Hydrogen borrowing and attempted Br_2-mediated cleavage of aziridino alcohol* ***396****.*

Unfortunately, this success was not mirrored in the Br_2-mediated cleavage, with neither the desired product **399**; the cyclic enol-ether **398** (from the acid-catalysed aziridine ring-opening reaction); nor the ester **400** from *n*BuOH trapping of the acyl bromide being observed – the reaction instead giving only decomposition of the starting material to unidentifiable products.

2.6 Conclusions and Future Work

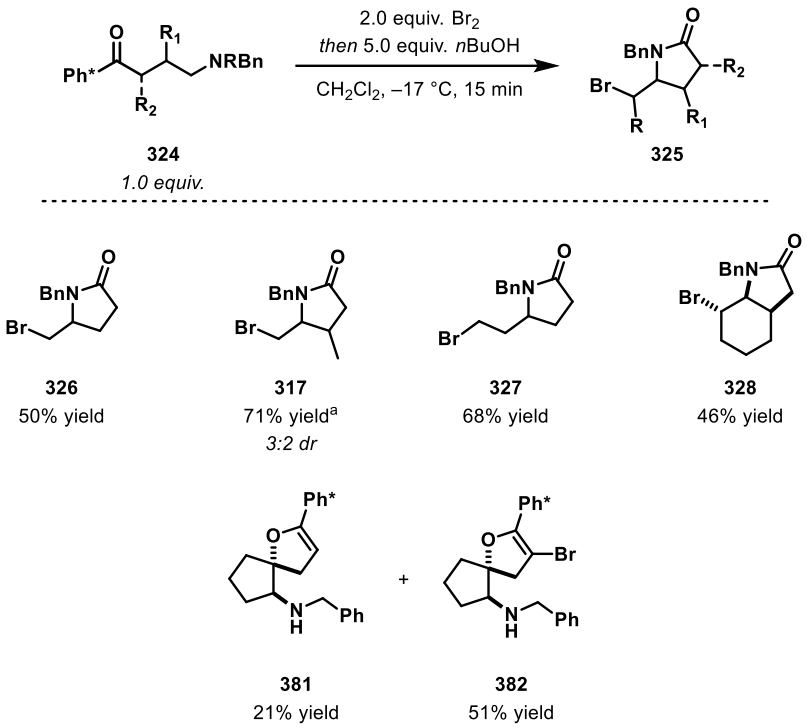
With the failure of the Br_2-mediated cleavage of **397**, it was decided that we had exhausted all immediate avenues for investigating the reactions of aziridino alcohols with Ph* methyl ketone **100** under hydrogen borrowing conditions and so this particular project was brought to a close.

To summarise progress made, a number of aziridino alcohols were synthesised and subjected to hydrogen borrowing conditions, with yields varying from poor to excellent (Scheme 2.40).



***Scheme 2.40**: Scope of hydrogen borrowing reactions of aziridino alcohols.*
[a]Reaction conducted by Ben Jones.

Upon subjecting some of the hydrogen borrowing products to Ph* cleavage conditions with Br_2, the formation of lactams was observed, as well as the formation of the unwanted spirocyclic enol ethers **381** and **382** in the case of bicyclic aziridine **378** (Scheme 2.41).



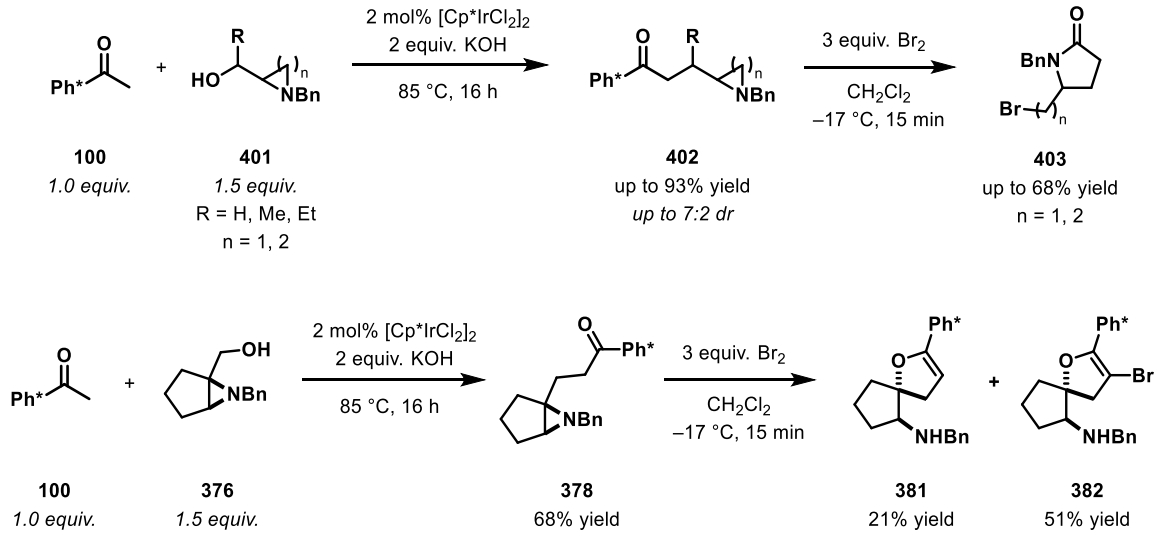
***Scheme 2.41**: Scope of the Br_2-mediated cleavage reactions of hydrogen borrowing products.*
[a]Reaction conducted by Ben Jones.

Future work in this area could focus on the promising reaction of azetidino-alcohol **299** by synthesising and reacting analogue azetidines. There is also potential, mentioned earlier in this chapter, of using enantiopure aziridines to synthesise enantiopure lactam products – a process that is utilised in the total synthesis of (–)-γ-lycorane in the following chapter.

Chapter 3: Total Synthesis of (–)-*γ*-Lycorane

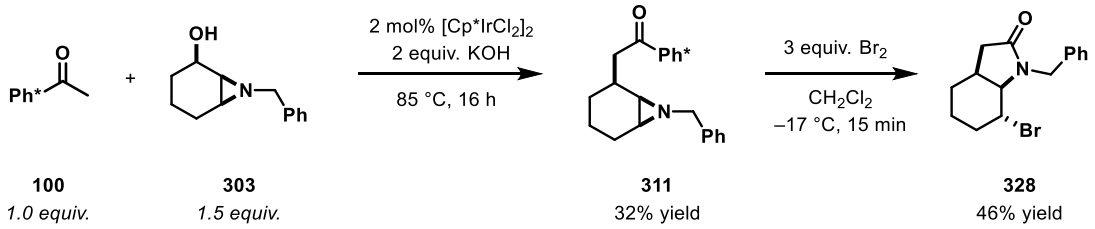
3.1 Introduction

Chapter 2 saw the development of the alkylation of Ph* methyl ketone **100** with a number of different aziridine-bearing alcohols *via* hydrogen borrowing catalysis. Subsequent reaction with Br_2 gave either lactams such as **403**, or unexpected spirocyclic ethers such as **381** and **382** (Scheme 3.1).



***Scheme 3.1**: Hydrogen borrowing reactions of aziridino alcohols and subsequent cleavage with Br_2.*

One result of particular interest, however, was the Br_2-mediated cyclisation of hydrogen borrowing product **311**, which resulted in lactam **328** containing a *cis*-6,5-bicyclic ring structure (Scheme 3.2).



***Scheme 3.2**: Cyclisation to give a* cis*-6,5-bicyclic lactam.*

This structural motif is common in natural products and as such, provided an opportunity to demonstrate the utility of hydrogen borrowing catalysis in enabling total synthesis. A survey of the literature found a number of small, nitrogen-containing natural products and natural product derivatives bearing the appropriate *cis*-6,5-bicyclic ring structure (Figure 3.1).

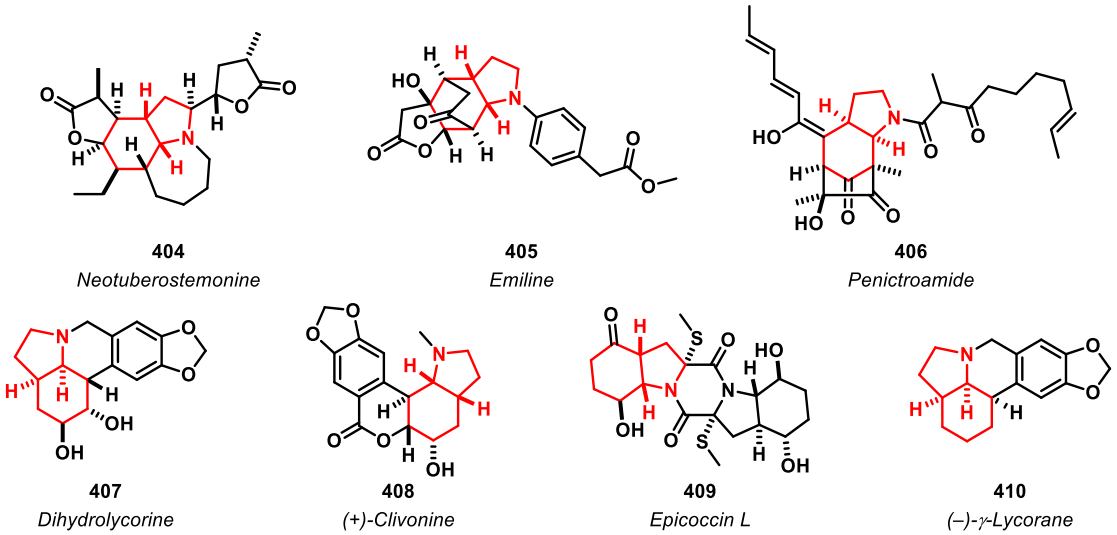
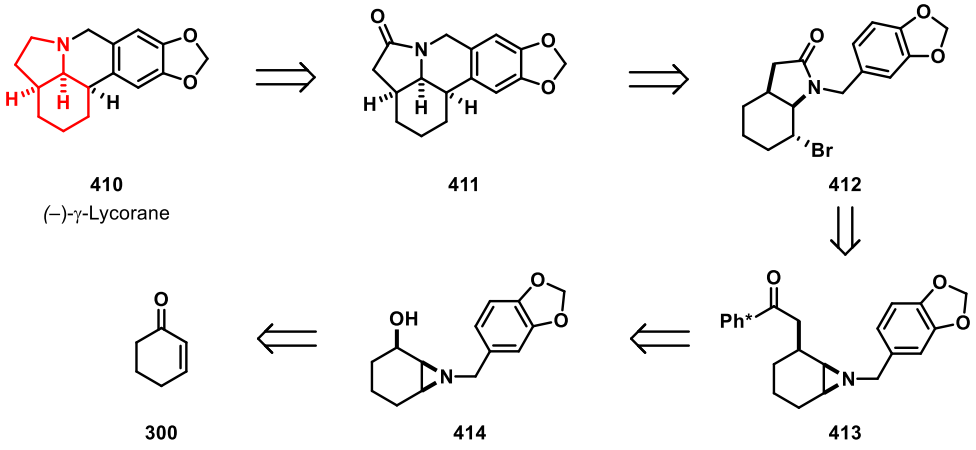


***Figure 3.1**: Alkaloid natural products and derivatives containing a* cis*-6,5-bicyclic system.*

Of these, the natural product derivative (–)-γ-lycorane **410** was chosen for a number of reasons. Firstly, the asymmetric aziridination of cyclic enones is well precedented in the literature, with key examples by Melchiorre,[70] Gilmour,[71] and Hamada,[77] thereby paving the way to an enantioenriched synthesis. Secondly, γ-Lycorane bears three contiguous stereocentres on the central cyclohexane ring and it was our belief that the third and final centre could be formed by a substrate-controlled intramolecular attack (with inversion) of the aromatic ring onto the secondary bromide **412** formed from Ph* cleavage of intermediate **413** with Br_2 (Scheme 3.3). Finally, the aromatic piperonyl group in γ-Lycorane would simply take the place of the benzyl protecting group used in our prior methodology – with the hope that alcohol **414** could be similarly obtained from readily available cyclohexenone **300**.



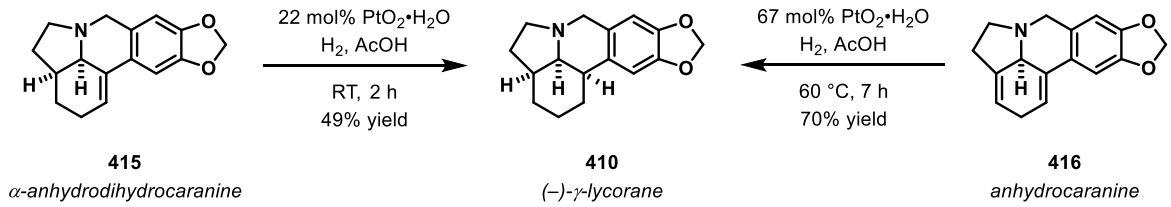
***Scheme 3.3**: Retrosynthesis of (–)-γ-lycorane involving a hydrogen borrowing reaction.*

The synthesis of (–)-γ-Lycorane was performed in collaboration with Indi Marriott, as part of his Part II thesis for the University of Oxford. His individual contribution, highlighted where appropriate in the text, consisted of the production of material and optimisation of the final steps in the synthesis. Experimental procedures for reactions conducted solely by Indi Marriott can be found in Appendix 2.

3.2 Previous Approaches to *γ*-Lycorane

3.2.1 Original Isolation

As previously stated, (–)-*γ*-lycorane is not a natural product itself, but was instead first isolated in 1961 by Kotera as part of his degradation studies into the Caranine family of natural products.[78] Starting from either α-anhydrodihydrocaranine **415** or anhydrocaranine **416**, hydrogenation with Adams catalyst in acetic acid gave (–)-*γ*-Lycorane in 49% and 70% yield, respectively (Scheme 3.4).



Scheme 3.4: *Kotera's isolation of (–)-γ-lycorane*.

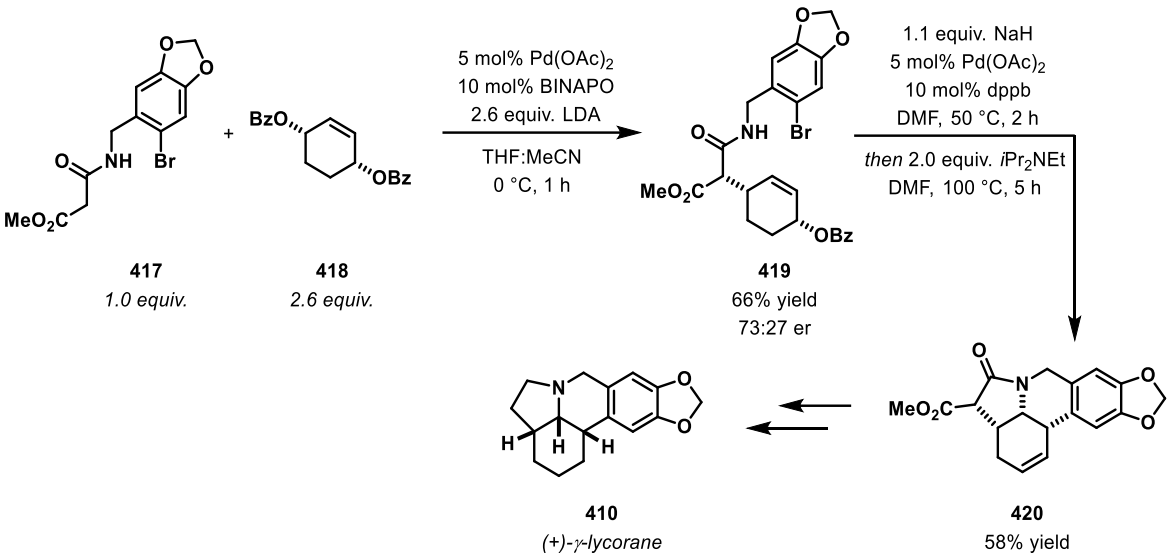
Unsurprisingly, reduction of β-anhydrodihydrocaranine with Adams catalyst gave (+)-*γ*-lycorane, with the other two lycoranes, α and β, having also been isolated by Kotera – albeit from the alkaloid lycorine.[79, 80]

Since then, the lycoranes have proven to be popular targets in total synthesis – with their compact ring system and multiple stereocentres providing a suitable architecture on which to demonstrate new chemical methodologies. A number of syntheses of *γ*-lycorane will now be presented, so as to give an overview of the field, up to and including contemporary developments.

3.2.2 Mori, 1995

The first asymmetric synthesis of *γ*-lycorane – as the (+)-stereoisomer – was reported by Mori and co-workers, who utilised a desymmetrising Tsuji-Trost reaction of *meso* cyclohexene derivative **418** with

(*S*)-BINAPO as a ligand to give **419**, thereby setting the first key stereocentre of the ring system, albeit in only 73:27 er (Scheme 3.5).[81]

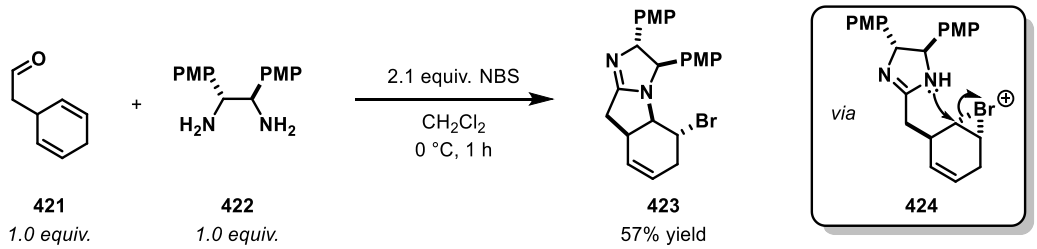


***Scheme 3.5**: Key steps in Mori's synthesis of (+)-γ-lycorane.*

A second Tsuji-Trost reaction of the amide nitrogen in **419**, followed by a Heck reaction in the same pot furnished the core of (+)-*γ*-lycorane, with a subsequent reduction and decarboxylation required to give the desired product in an overall 23% yield.

3.2.3 Fujioka, 2006

Another example of a desymmetrising approach, Fujioka's 2006 synthesis utilised the condensation of an enantiopure 1,2-diamine **422** onto aldehyde **421** (Scheme 3.6).[82] Treatment with NBS then resulted in an oxidation, bromination, and cyclisation cascade *via* intermediate **424** to give the desired 6,5-bicyclic compound **423** as the core of (–)-*γ*-lycorane in 57% yield as a single diastereomer.

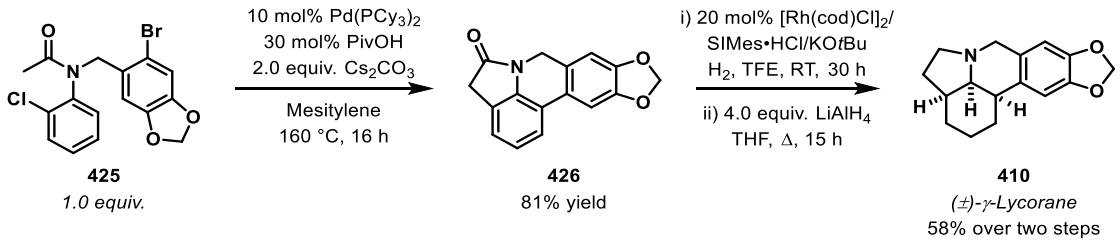


***Scheme 3.6**: Fujioka's NBS-mediated cyclisation used in his route to the 6,5-core of (-)-γ-lycorane.*

A further seven steps were required to obtain (–)-*γ*-lycorane, with dihydroimidazole **423** being first activated with MeI, and then hydrolysed to remove the chiral auxiliary. The overall yield of the route was 18%.

3.2.4 Baudoin, 2018

A recent synthesis by Baudoin and co-workers is notable for its brevity, synthesising (±)-*γ*-lycorane in just four steps.[83] The key step is the use of an intramolecular palladium-catalysed double arylation reaction, forging the central 6,5,6 ring system in compound **426** (Scheme 3.7). Selective hydrogenation of one of the aromatic rings then gives the desired all-*cis* geometry required.

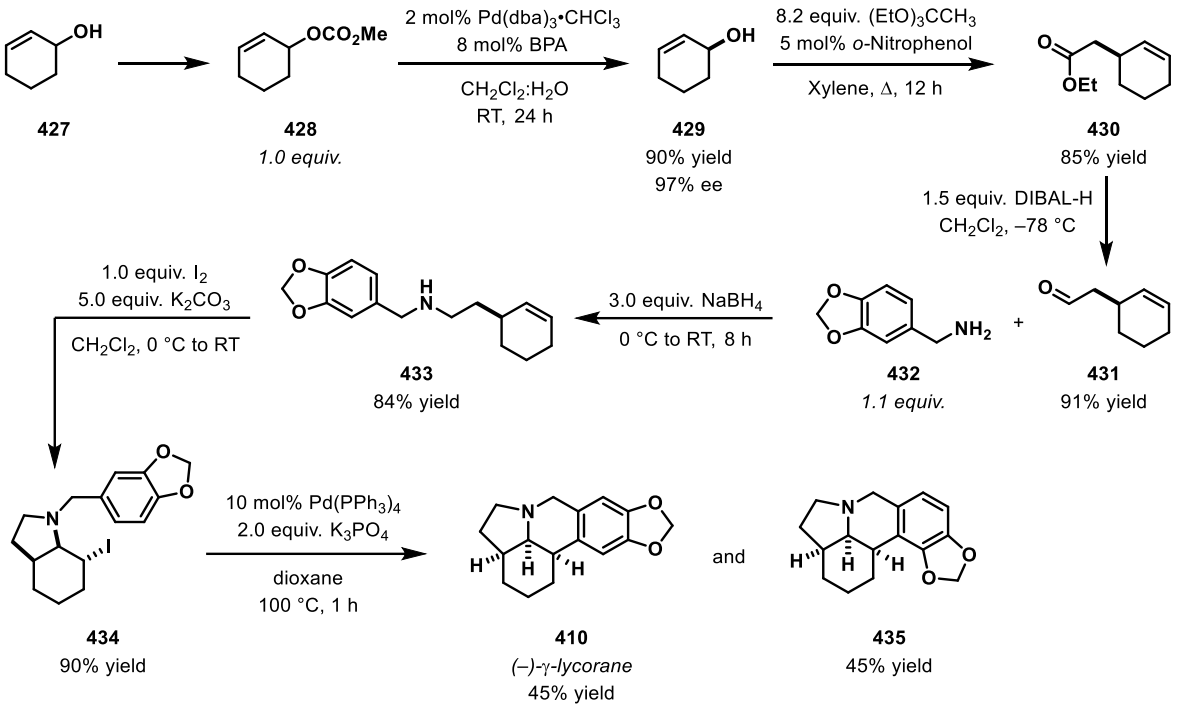


***Scheme 3.7**: Baudoin's use of a double arylation reaction in the synthesis of (±)-γ-lycorane.*

Careful evaluation of hydrogenation catalysts was needed to prevent either overreduction of both rings, or just reduction of the piperonyl motif. PdO_2, Pd/C and Ru/C all proved unsatisfactory, with the eventual use of $[Rh(cod)Cl]_2$ in combination with the NHC ligand SIMes·HCl and KO*t*Bu delivering the desired product in 73% **–** albeit as a racemic compound. A final reduction of the amide with $LiALH_4$ afforded (±)-*γ*-lycorane in 47% overall yield.

3.2.5 Huang, 2020

A more recent asymmetric synthesis of (–)-*γ*-lycorane was reported by Huang, who utilised an unusual palladium-catalysed arylation reaction of an alkyl iodide.[84] Absolute stereochemistry was determined by a deracemisation of the carbonate of cyclohexen-1-ol **427** using methodology developed by Gais,[85] followed by a Johnson-Claisen rearrangement of **429** with triethylorthoacetate to give the enantiopure ethyl ester **430** (Scheme 3.8).



***Scheme 3.8**: Huang's synthesis of (–)-γ-lycorane* via *a radical cyclisation.*

Reduction to the aldehyde and subsequent reductive amination with piperonylamine **432** furnished secondary amine **433** which underwent smooth cyclisation onto the iodonium formed upon treatment with I_2 to give cyclisation precursor **434**. The final palladium-catalysed step to give (–)-*γ*-lycorane, along with unwanted regioisomer **435**, was based on work by Alexanian,[86] in which a Pd^0 species undergoes single-electron oxidative addition into the alkyl iodide to give a carbon centred radical, which then adds to the aromatic ring to give a cyclohexadienyl radical. Rearomatisation is then proposed to occur *via* another single-electron oxidation and loss of a proton to regenerate the Pd^0 catalyst. Despite screening numerous conditions, the regioselectivity could not be improved – perhaps due to the insensitivity of radical reactions to steric hindrance – giving the overall yield for the synthesis at 23%.

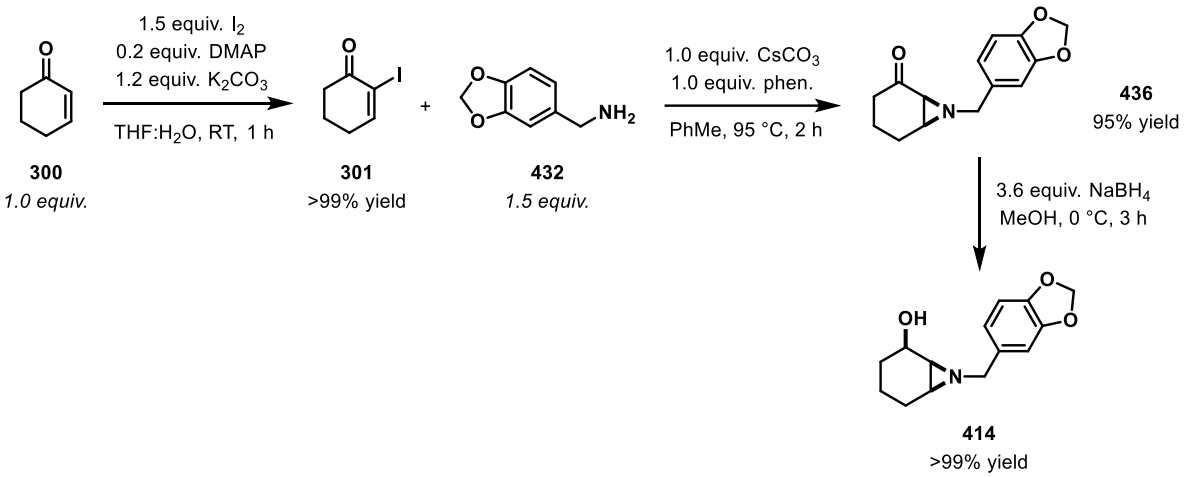
3.2.6 Summary

As illustrated by the above examples, γ-lycorane has shown to be a fruitful proving ground for synthetic methodologies, with palladium-catalysed couplings featuring heavily. It was our intention to also use a palladium catalysed reaction to forge the final ring in the system, with an initial C-C bond being formed by a hydrogen borrowing alkylation of aziridino alcohol **414**.

3.3 Results and Discussion: Racemic Synthesis of (±)-*γ*-Lycorane

3.3.1 Synthesis of Hydrogen Borrowing Precursor 414

Before working on an asymmetric route, it was decided to first synthesise (±)-*γ*-lycorane and optimise as many steps as possible with racemic material, before moving onto an enantioenriched variant. In a similar route to that which was used to prepare benzyl aziridine **303**, cyclohexenone **300** was treated with I_2 to give α-iodoenone **301**. Michael addition of piperonylamine **432**, followed by intramolecular S_N2 substitution of iodide furnished aziridino ketone **436** in 95% yield (Scheme 3.9).

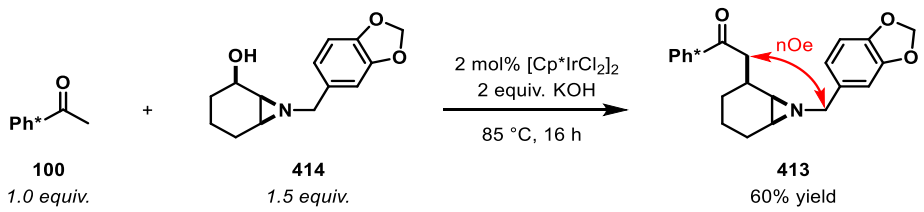


***Scheme 3.9**: Synthesis of hydrogen borrowing precursor **414** from cyclohexenone **300**.*

Reduction with $NaBH_4$ in MeOH at 0 °C gave the desired alcohol **414** as a single diastereomer in >99% yield, with the selectivity of the addition of hydride presumably determined by the steric bulk of the aziridine blocking one face of the ketone.

3.3.2 Hydrogen Borrowing Alkylation with Ph* Methyl Ketone 100

With alcohol **414** in hand, the hydrogen borrowing alkylation could be attempted. Using KOH as the base and no solvent – the conditions developed in Chapter 2 – the desired product was isolated in 60% yield. The *cis* stereochemistry was determined by nOe correlations between the benzyl and α-carbonyl methylene protons, and can be rationalised by the bottom face 1,4-conjugate addition of an iridium-hydride species to the enone generated during the reaction, again due to the steric bulk of the alkyl aziridine (Scheme 3.10).



***Scheme 3.10**: Hydrogen borrowing alkylation of aziridino alcohol **414**.*

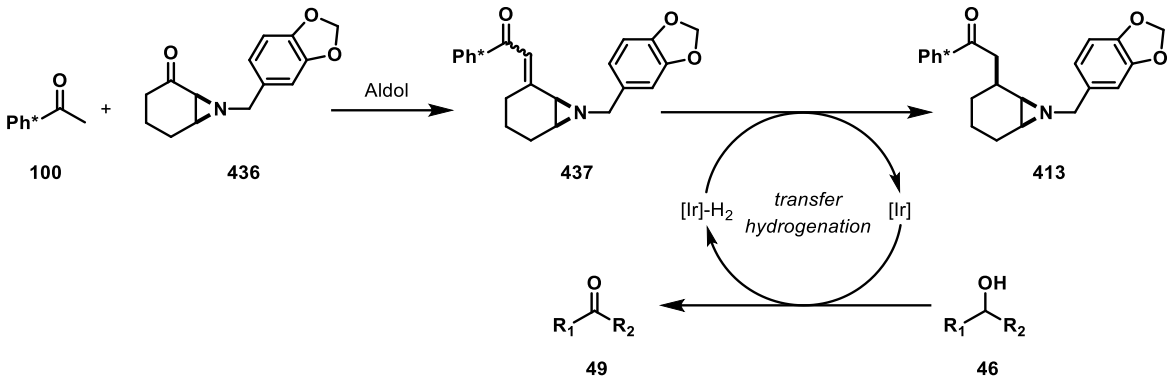
Further optimisation studies were attempted on this substrate by Indi Marriott, including changing the solvent, base, equivalents, temperature, and the use of KI as an additive – however, no reproducible increase in yield was obtained and the original conditions were retained.[87] It was also noted that the reaction was highly capricious – repeated reactions on the same scale and with the same conditions gave varying yields. One hypothesis for this activity was the inhomogeneity of the reaction, which resulted from the lack of a solvent preventing all components from dissolving and reacting uniformly (although it should be noted the Ph* methyl ketone **100** melts 83 – 85 °C and so could be seen as a solvent); however, as mentioned above, attempts by Indi Marriott to introduce common hydrogen borrowing solvents such as *t*BuOH or toluene only suppressed the overall yield.

3.3.3 Use of a Hydrogen Donor

Before continuing with the synthesis, it was observed that the previous two steps were synthetically inefficient – starting from ketone **436**, a reduction was performed to alcohol **414**, which was immediately oxidised back to ketone **436** as the first step of the hydrogen borrowing sequence. Whilst it is standard practice in the literature to make alcohols for hydrogen borrowing reactions from carbonyls *via* a reduction, before immediately oxidising them again, it was a step we felt could be eliminated from the synthesis.

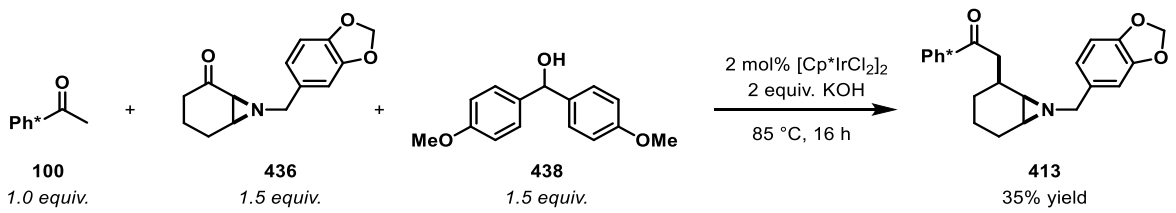
To do so, it was envisaged that a suitable hydrogen donor **46** could be added to the hydrogen borrowing reaction, and that ketone **436** rather than alcohol **414** would be used as the starting material. The reaction would then proceed *via* the usual aldol condensation between the ketone **436** and Ph* methyl ketone **100** to form enone **437**, which would then be reduced by the iridium hydride

produced by oxidation of the hydrogen donor **46** to ketone **49** – an overall process that constituted a transfer hydrogenation reaction (Scheme 3.11).



***Scheme 3.11**: Proposed use of a hydrogen donor.*

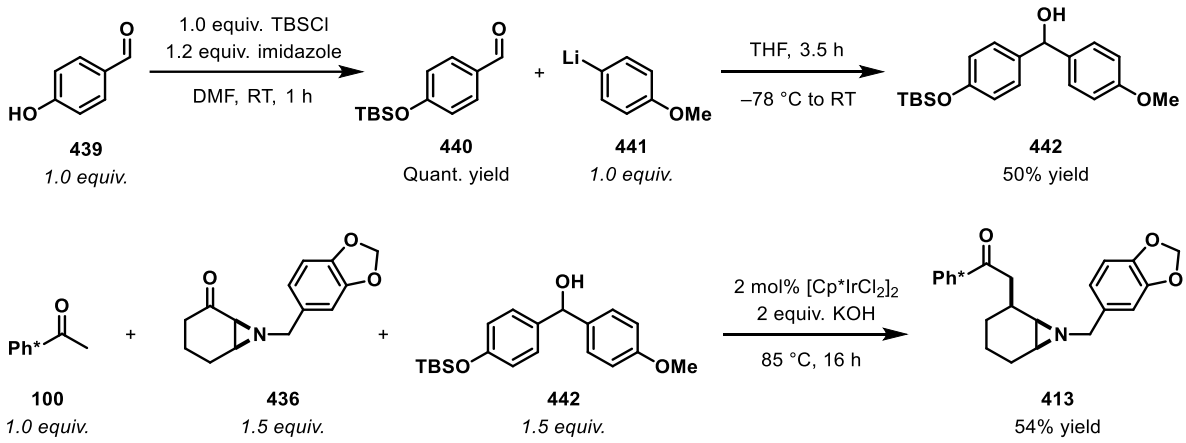
Unsurprisingly, the nature of the hydrogen donor **46** would be critical to the success of this transformation and, in our minds, two key features of the hydrogen donor **46** were needed. Firstly, an ideal hydrogen donor must be easy to oxidise, so as to favour the production of the iridium-hydride needed for reduction. Secondly, it needed to have a lower propensity to participate in an aldol reaction with Ph* methyl ketone **100** relative to that of the substrate ketone **436**, in order to prevent the formation of unwanted side products. Fortunately, a highly electron-rich alcohol fulfils both these criteria – making the loss of hydride more favourable, as well as making the resulting carbonyl less reactive towards nucleophiles such as the enolate involved in the first step of hydrogen borrowing. Commercially available 4,4'-dimethoxybenzhydrol **438** appeared to have both these properties, and as such was subjected to the standard hydrogen borrowing conditions along with ketone **436** (Scheme 3.12).



***Scheme 3.12**: Attempted use of 4,4'-dimethoxybenzhydrol as a hydrogen donor.*

Pleasingly, the use of **438** as a hydrogen donor was successful – giving the desired product **413** in 35% yield. Unfortunately, product **413** was inseparable *via* column chromatography from the oxidised form of **438** – 4,4'-dimethoxybenzophenone – and as such, a different hydrogen donor was required.

Given that the only issue with **438** had been the polarity of its oxidation product (and the somewhat reduced yield of the desired product **413**), we believed that changing one of the ring methoxy groups to an O-TBS would make the compound less polar, and hopefully easier to separate. Synthesis was straightforward, starting with the TBS protection of 4-hydroxybenzaldehyde **439** in quantitative yield to give **440**, followed by the addition of the aryllithium **441** generated by lithium-halogen exchange between *n*BuLi and 4-bromoanisole, giving the desired hydrogen donor **442** in 50% yield (Scheme 3.13).



***Scheme 3.13**: Synthesis and reaction of hydrogen donor **442**.*

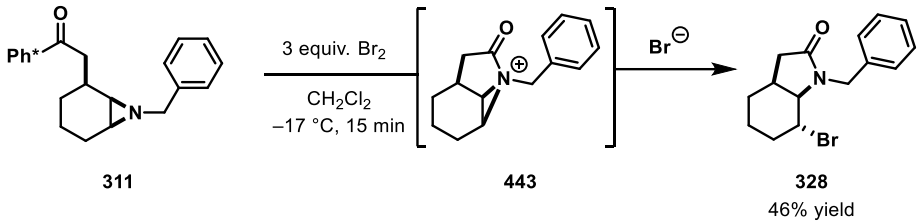
To our delight, hydrogen donor **442** worked well in the transfer hydrogenation, giving pure product **413** in 54% yield – the decrease in polarity caused by the TBS group proving sufficient to allow separation by column chromatography. A number of other hydrogen donor species were synthesised and tested by Indi Marriott, replacing the methoxy motif with combinations of $–NMe_2$ and –O*i*Pr; however, all of these resulted in reduced conversions and so were not pursued further.[87]

To compare the two routes, reduction of **436** with $NaBH_4$ followed by a standard hydrogen borrowing alkylation of the resulting alcohol **414** gave the desired product **413** in 60% yield over two steps –

whereas the single step process using hydrogen donor **442** resulted in a 54% yield of **413**. Given the synthetic ease of the $NaBH_4$ reduction, and the fact that purification *via* column chromatography was not required, it was decided to proceed with the two-step route for the production of more material. Another consideration worth mentioning is that this route has a greater atom economy because it does not require the synthesis and use of a hydrogen donor.

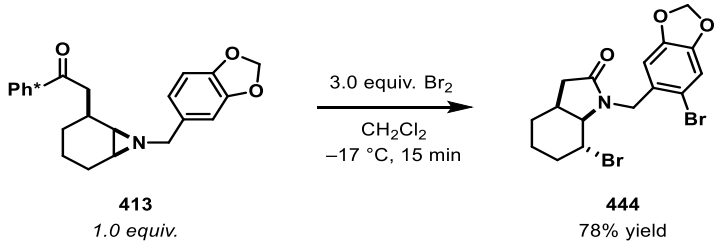
3.3.4 Bromine-Mediated Cleavage

To return to the key result from Chapter 2 that inspired us to synthesise (–)-*γ*-lycorane, when N-benzyl aziridine hydrogen borrowing product **311** was treated with Br_2 it underwent the expected Ph* cleavage reaction, followed by cyclisation of the aziridine to presumably form reactive aziridinium **443**, followed by subsequent ring opening by the bromide anion to give product **328** (Scheme 3.14).



***Scheme 3.14**: Br_2-mediated ring opening of compound **311**.*

Following the same procedure, a solution of *N*-piperonyl aziridine hydrogen borrowing product **413** in CH_2Cl_2 at –17 °C was treated with 3 equivalents of Br_2, resulting in the expected cleavage and cyclisation reaction, along with an unexpected (but not altogether surprising) bromination of the electron-rich aromatic ring to give dibrominated product **444** in 78% yield – the regioselectivity of the second bromination being proven by a subsequent cyclisation (*vide infra)* (Scheme 3.15).

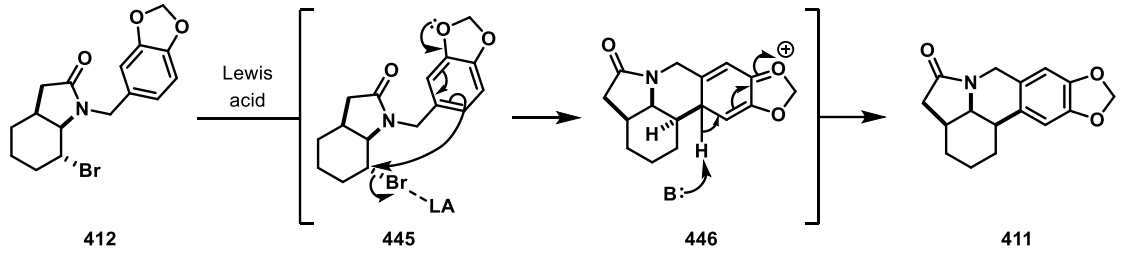


***Scheme 3.15**: Br_2-mediated ring opening and concomitant aromatic bromination of compound **413**.*

A number of conditions were investigated by Indi Marriott in order to maximise the yield and suppress the formation of piperonyl ring bromination side-products.[87] Unfortunately, whilst trace (4–8% by ^{1}H NMR) amounts of the desired, monobrominated product **412** were detected, the majority product in all cases was dibrominated **444**. The use of the weaker brominating reagent NBS, both alone and in combination with NH_4OAc,[88] in an attempt to differentiate between the reactivities of the two aromatic rings resulted in just starting material. In most cases, slight decomposition to form piperonal was observed, presumable due to Br_2 acting as an oxidising agent on the aziridine C–N bond. This was hypothesised to go *via* a radical process, owing to its suppression with the addition of TEMPO to the reaction mixture – although this also led to a large reduction in yield of **444**, down to 20%.[87]

3.3.5 Attempted Cyclisation Reactions of Dibromide 444

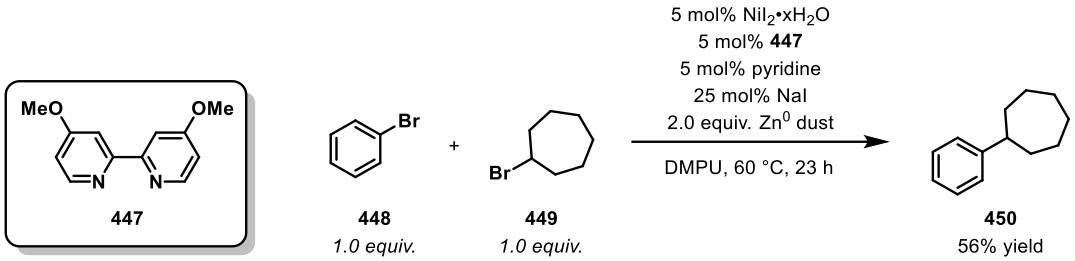
The additional bromination of the piperonyl ring at first appeared to be a hindrance to the synthesis, given that our original plan had been to perform a Friedel-Crafts type intramolecular displacement of the alkyl bromide with the aromatic ring – a pathway blocked in compound **444** by the presence of a bromide in the requisite position (Scheme 3.16).



Scheme 3.16*: Proposed intramolecular Friedel-Crafts alkylation of* ***412*** *to form the final ring of (–)-γ-lycorane.*

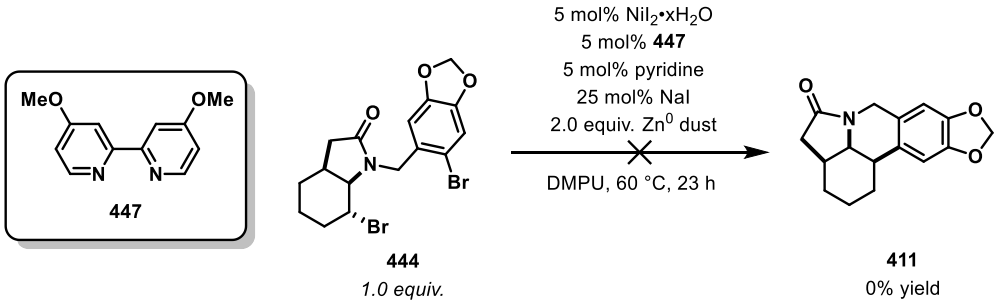
With this in mind, alternative routes to the desired cyclic product were considered. In 2012, Weix and co-workers reported the development of a nickel-catalysed coupling reaction between aryl halides **448** and alkyl bromides **449** (Scheme 3.17).[89] The authors proposed a number of possible mechanics for this reaction, ranging from direct cross coupling between an aryl-nickel species and either an alkyl-nickel or zinc; disproportionation of two nickel intermediates followed by reductive elimination;

oxidative addition of the alkyl bromide into an aryl-nickel species; and the nickel species acting as an initiator for a radical chain process.



***Scheme 3.17**: Example reaction of Weix and co-workers' coupling between aryl and alkyl halides.*

Two key limitations when applying this methodology to *γ*-lycorane were immediately obvious to us – firstly that all examples of in the original publication were of *intermolecular* reactions as opposed to the *intramolecular* reaction required to form a ring in *γ*-lycorane. Secondly, the alkyl bromide in the product **444** formed during the bromination reaction is on the opposite face of the cyclohexane ring to the aryl ring – meaning either a Finkelstein-type inversion with iodide would first be required, or the inversion of either a radical or alkylmetal intermediate species before reaction to form the desired C–C bond. Perhaps unsurprisingly, given these issues, when dibromide **444** was exposed to Weix's reaction conditions on a 0.25 mmol scale there was no formation of the desired product; only unreacted starting material was obtained (Scheme 3.18).

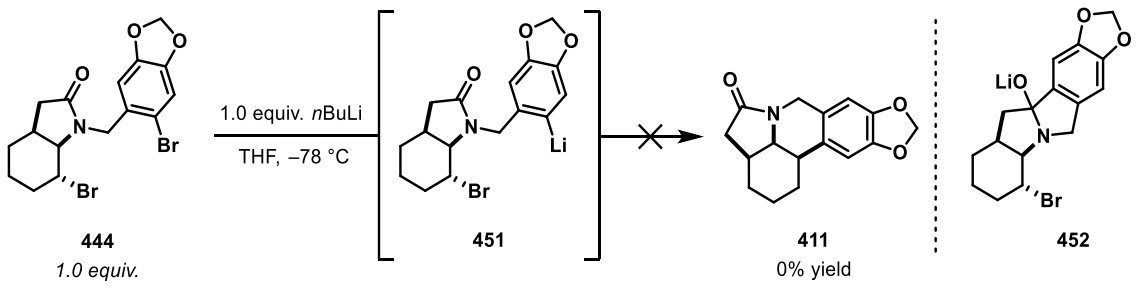


***Scheme 3.18**: Attempted intramolecular coupling of dibromide **444** using Weix's conditions.*

Weix and co-workers noted in the Supplementary Information of their publication that the colour of the reaction is a good indicator of its progress – with the active reaction being pale green due to the presence of Ni^0, formed by the reduction of Ni^{II} by zinc, and turning black upon completion. In our

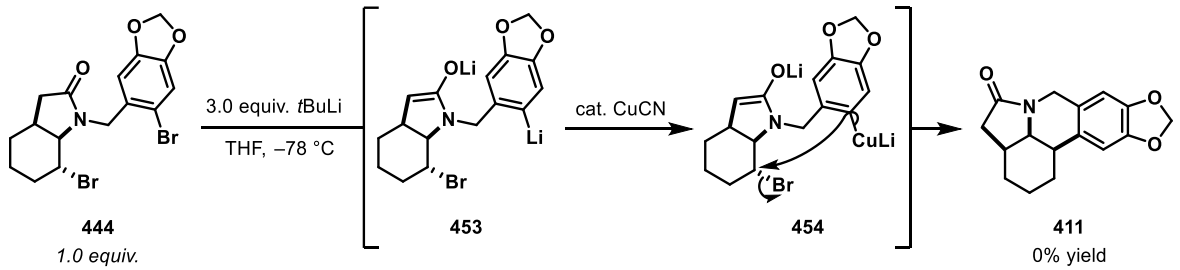
hands the pale green colour was not observed, and it was hypothesised that reaction may have been sensitive to the type of zinc dust used. A fresh batch of activated zinc was prepared and tested; however, this was met with no further success and so this approach was abandoned.

Another possibility to unite the two bromides and forge the desired C–C bond was the use of lithium-halogen exchange. It was anticipated that that treatment of dibromide **444** with one equivalent *n*BuLi would result in the formation of aryllithium **451**, which would then cyclise onto the alkyl bromide in an S_N2 manner to give the desired product **411** (Scheme 3.19). Unfortunately, none of the desired product was obtained in this manner, with crude ^{1}H NMR analysis showing only decomposition of starting material – perhaps *via* a competing cyclisation of the aryllithium species onto the amide carbonyl to give **452**.



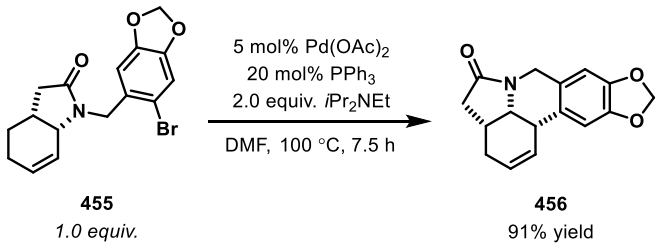
Scheme 3.19*: Attempted ring closure of dibromide* ***444*** via *lithium-halogen exchange.*

To circumvent this cyclisation pathway, it was proposed to treat dibromide **444** with three equivalents of *t*BuLi, along with a catalytic amount of CuCN, in the hopes that the extra equivalent of base would deprotonate the amide to form **453**, thereby protecting it from attack by the aryllithium. Further to this, the S_N2 reaction would be facilitated by transmetallation of the aryllithium with a copper cyanide species to form the corresponding Gilman reagent **454**, which are well known to be more competent nucleophiles for S_N2 reactions (Scheme 3.20).[90]



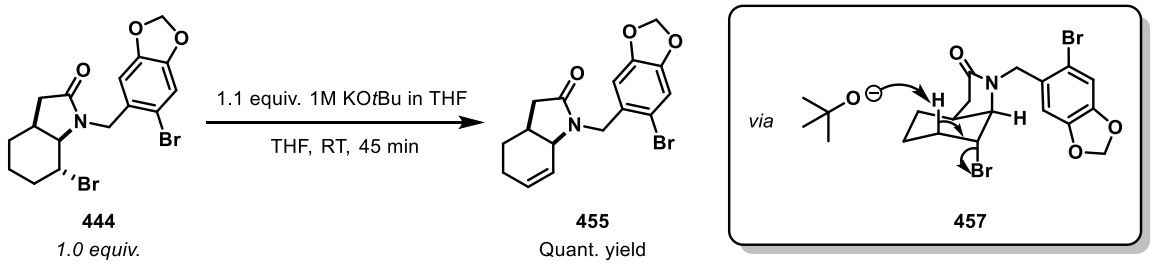
***Scheme 3.20**: Proposed use of* t*BuLi and formation of a Gilman reagent.*

Unfortunately, owing to time constraints and a hesitancy to work with pyrophoric *t*BuLi and toxic CuCN, it was decided not to pursue this approach and instead focus on a more conventional and practical route. One example of an alternative method to close the final ring can be found in Mori's 1995 synthesis of (+)-γ-Lycorane, where an alternative route disclosed by the authors in the same paper utilises an intramolecular Heck reaction from an aryl bromide onto an olefin in the six-membered ring (Scheme 3.21).[81]



***Scheme 3.21**: Mori's intramolecular Heck-reaction to close the final ring of (+)-γ-lycorane.*

Starting from dibromide **444**, it appeared to be a simple matter of conducting an E2 elimination of the alkyl bromide to form the desired alkene substrate for a Heck reaction. As a strong, non-nucleophilic base, DBU was chosen to perform this transformation. Pleasingly, treatment of **444** with 5 equivalents of DBU in toluene at 100 °C gave the desired elimination product **455** in 53% yield – however, the reaction did not proceed to complete conversion and the product **455** was inseparable from leftover starting material **444** *via* column chromatography. It is also worth noting that only one regioisomer of the alkene was formed – the *anti*-stereochemical requirement of the E2 elimination in **457** ensuring only one of the three α-protons was in the correct orientation to allow the reaction to proceed (Scheme 3.22).



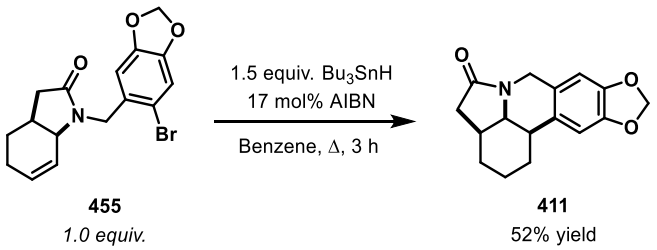
***Scheme 3.22**: E2 elimination of dibromide **444**.*

In an attempt to circumvent this purification issue, two other bases were screened. When screened by Indi Marriott, the guanidinium base TMG resulted in a much lower NMR yield of 21%;[87] this could potentially be explained by TMG's lower pK_{aH} of 15.3 in THF, compared to DBU's pK_{aH} of 16.6 in the same solvent.[91] To our delight, switching to a 1M solution of KO*t*Bu in THF at room temperature gave the desired product **455** in complete conversion and quantitative yield within 45 minutes – possibly due to the much greater basicity of the *tert*-butoxide anion.

3.3.6 Endgame to form (±)-*γ*-lycorane

With olefin **455** in hand, we had completed a formal synthesis of (±)-*γ*-lycorane – with the final steps needed to transform it into the natural product derivative having already been reported by Mori in his 1995 paper,[81] which involved a three-step procedure, as well as in only two steps by Ikeda in his 1998 synthesis.[92] However, it was decided to perform these steps for ourselves on **455** – with the dual purpose of verifying the integrity of the literature routes, and as an opportunity to apply any synthetic developments from the last two decades to further shorten our route.

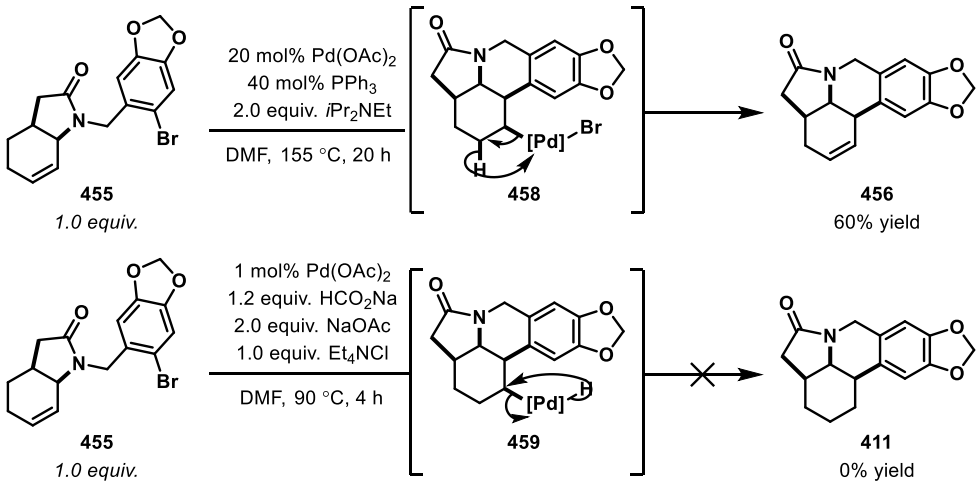
The first route attempted was that of Ikeda,[92] who utilised a classical radical cyclisation reaction whereby an AIBN initiator-generated tributyltin radical reacts with the aryl bromide in **455** to give an aryl radical, which then undergoes a 5-*exo*-trig cyclization onto the olefin to give a secondary carbon centered radical (Scheme 3.23). The radical chain then propagates *via* abstraction of a hydrogen atom from another molecule of Bu_3SnH.



***Scheme 3.23**: Ikeda's radical ring closure on the route to (–)-γ-Lycorane.*

This experiment was repeated by Indi Marriott and, to our great surprise, gave only starting material **455**.[87] This is in direct contrast to Ikeda who, under the same conditions and with the same substrate, reported a 52% yield of **411**. The reaction was reattempted twice more, both times with dry benzene and using fresh bottles of AIBN and Bu_3SnH; however, neither reaction showed any sign of product formation, once again only returning starting material. In the absence of any obvious causes for failure, it was decided to abandon the radical cyclisation route and instead focus on Mori's Heck reaction approach which was deemed more reliable.

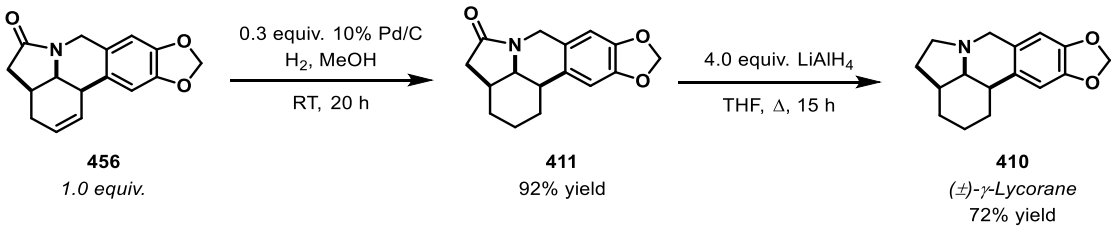
Pleasingly, upon exposing bromide **455** to Mori's conditions of catalytic $Pd(OAc)_2$ and PPh_3 with Hünig's base in DMF at 155 °C, the desired cyclisation product **456** was formed in 60% yield – somewhat lower than Mori's reported yield of 91% (Scheme 3.24). It is worth noting that this step produces a single regioisomer and establishes the all-*cis* geometry of γ-Lycorane, with the β-hydride elimination of intermediate **458** only being possible in one direction to give the desired product **456**.



***Scheme 3.24**: Palladium catalysed Heck reaction to form the final ring in (±)-γ-Lycorane.*

Also shown in Scheme 3.24 are the conditions used in an attempt to perform a reductive Heck reaction on dibromide **455** – the idea being that the intermediate formed after the Heck reaction would accept a hydride from sodium formate to give **459**, before preferentially undergoing a reductive elimination to give reduced product **411** rather than β-hydride elimination to give product **456**. Unfortunately, neither the desired product **411** nor the Heck product **456** was observed, with the reaction only returning starting material **455**. However, upon examining the original work by Faul and co-workers from which the above conditions were taken,[93] it became clear that all successful substrates were designed in such a way that the resulting carbo-palladium intermediate had no β-hydrogens with which to undergo a β-hydride elimination, and so the only productive pathway was *via* reduction by formate. As such, this approach was abandoned, and the non-reductive Heck reaction was used for the asymmetric synthetic.

The final steps in the synthesis of (±)-γ-Lycorane were carried out by Indi Marriott in accordance with Mori's synthesis.[81, 87] Hydrogenation of the double bond in **456** was achieved using a simple Pd/C hydrogenation to give **411** in 92% yield, followed by a reduction of the amide carbonyl with $LiAlH_4$ to give (±)-γ-Lycorane in 72% yield (Scheme 3.25).



***Scheme 3.25**: Synthesis of (±)-γ-Lycorane.*

All analytical data matched that previously reported – and in addition, a small sample was recrystallised from pentane/Et_2O to give a crystal suitable for X-Ray analysis, the structure of which is shown in Figure 3.2.

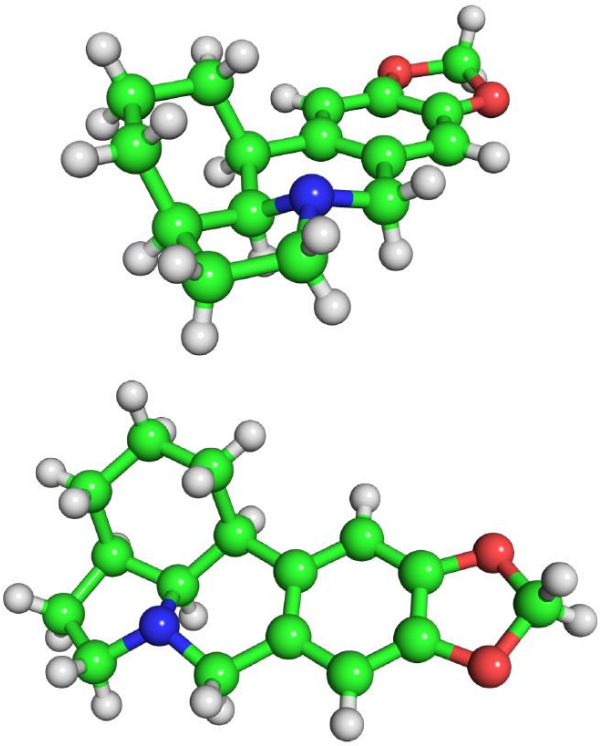


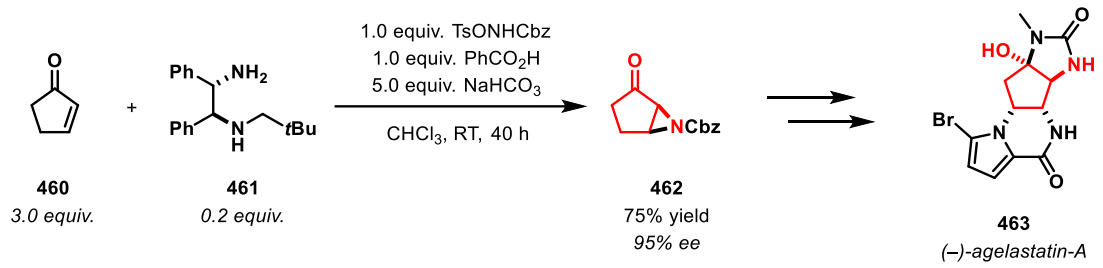
***Figure 3.2**: X-Ray Structure of (±)-γ-Lycorane.*
Data collected and analysed by Dr Kirsten R. Christensen.

Of particular note in the above structure is the clear all-*cis* configuration of the cyclohexane ring, as well as the orientation of the nitrogen's lone pair into the concave face of the bowl-like structure.

Having completed the total synthesis of (±)-*γ*-lycorane, the next challenge lay in its asymmetric synthesis – however, it was anticipated that many of the steps would be the same, with an early stage asymmetric aziridination setting the absolute stereochemistry.

3.4 Results and Discussion: Total Synthesis of (–)-γ-Lycorane

As mentioned at the start of this chapter, there exists in the literature a number of asymmetric aziridination reactions, variants of which were explored in Chapter 2. For (–)-*γ*-lycorane, it was decided to use the method developed by Hamada and co-workers, who used a chiral diamine catalyst **461** in combination with *N*-tosyloxycarbamate to aziridinate cyclopentenone **460** as a key step in their synthesis of (–)-agelastatin A (Scheme 3.26).[77]



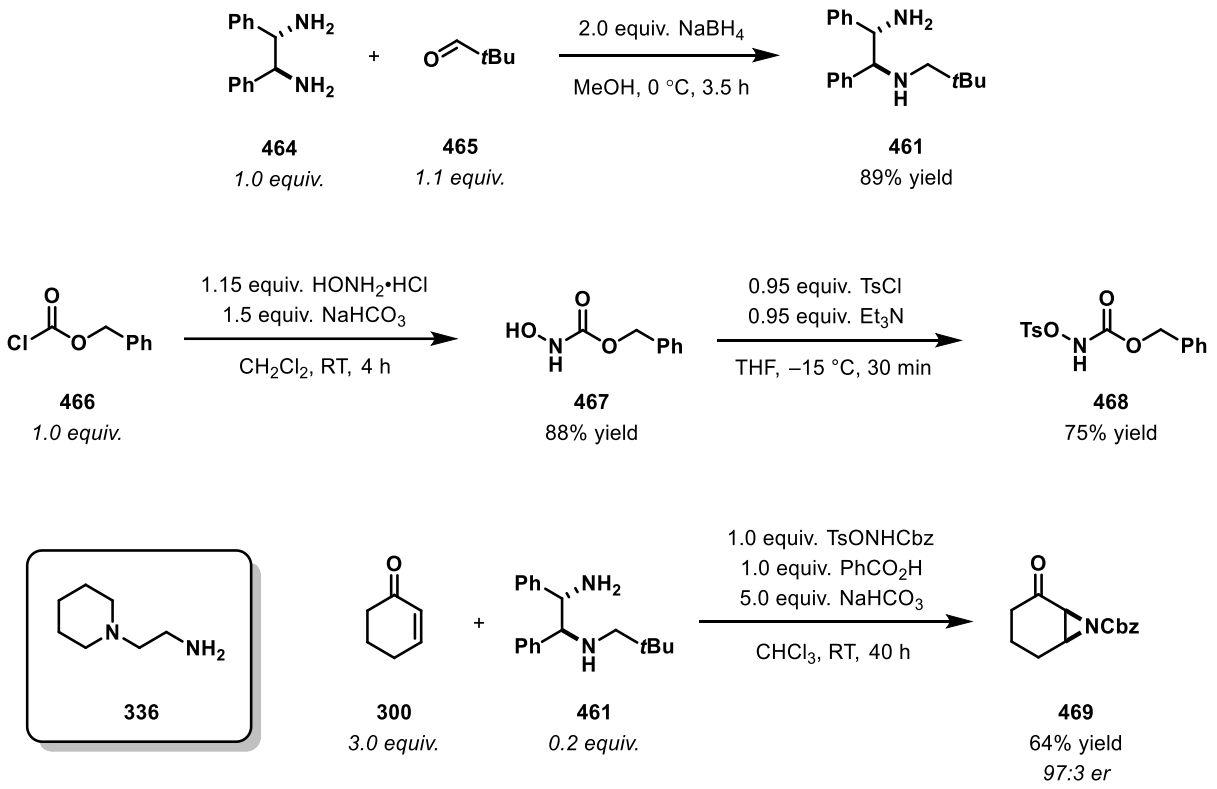
***Scheme 3.26**: Hamada's development and use of an asymmetric aziridination in the synthesis of (–)-agelastatin A.*

Hamada's methodology was particularly attractive to us for two key reasons. Firstly, the diamine catalyst **461** was derived in one step from commercially available – and relatively inexpensive – diphenylethylenediamine. This was particularly important given that the enantiodetermining step was the first in the synthesis, and so a relatively large amount of catalyst would be required. Secondly, asymmetric aziridinations require an electron-withdrawing group on the nitrogen, and Hamada's reaction makes use of a Cbz group, rather than the more typical Ts or Boc. This was of interest to us because the Cbz group can be easily cleaved either by hydrogenation or basic hydrolysis, as opposed to Ts and Boc which require either more forcing or acidic conditions, as shown in Chapter 2 of this thesis.

3.4.1 Asymmetric Aziridination

As such, work on the asymmetric synthesis of (–)-*γ*-lycorane began by synthesising both the enantiopure catalyst **461**, as well as the aziridination reagent **468** – with both syntheses proceeding smoothly. The aziridination was then conducted on cyclohexenone **300** – a substrate not featured in

Hamada's original scope – which gave the desired aziridine **469** in 64% yield on a 3.1 g scale with a very acceptable 97:3 er, as measured by HPLC against a racemic sample of **469** prepared using an achiral diamine catalyst **336** (Scheme 3.27).

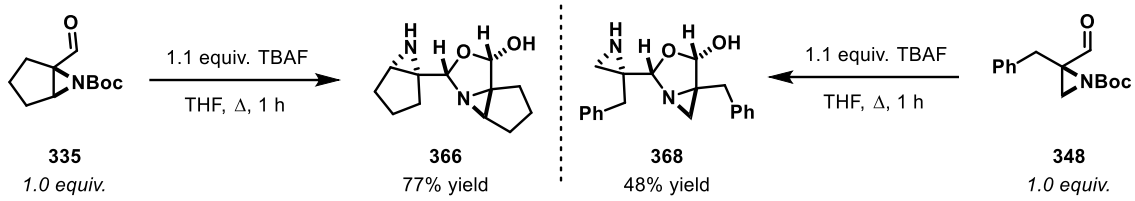


***Scheme 3.27**: Asymmetric aziridination of cyclohexenone **300**.*

With enantioenriched aziridine **469** in hand, replacement of the Cbz with piperonyl and a reduction of the carbonyl were now required to bring the asymmetric synthesis to compound **414** – converging it with the already established racemic route.

3.4.2 Reduction of 469

Our first consideration at this point was the order of events – whether to perform the Cbz removal and subsequent alkylation, and then reduce, or *vice versa*. Our prior work with aziridino aldehydes, documented in Chapter 2, showed that free N–H aziridines in the same molecule as aldehydes would form dimers – with the one of the nitrogens attacking the carbonyl to form a stable aminal, thereby simultaneously protecting both the unstable aldehyde and N–H aziridine moieties (Scheme 3.28).

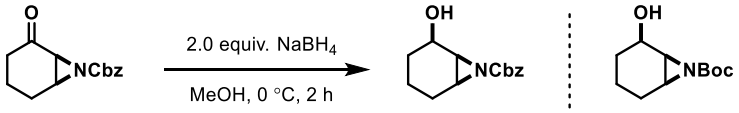


335 *1.0 equiv.* | **366** 77% yield | **368** 48% yield | **348** *1.0 equiv.*

***Scheme 3.28**: Dimers formed between free N–H aziridines and aldehydes.*

Whilst this could conceivably occur with aziridine **469** upon removal of the Cbz protecting group, it was thought to be less likely to occur – due to both the increased steric hindrance, and decreased electronic reactivity of the ketone in **469** to nucleophilic attack, which would leave the resulting unstable N–H aziridine motif free to react in unwanted ways. As such, it was decided to first perform the reduction of the carbonyl, and then to do a deprotection/reprotection sequence in one pot.

Given the success of a $NaBH_4$ reduction on the similar substrate **436** in the racemic route, this seemed like a good starting set of conditions for the reduction. Indeed, treatment of ketone **469** with two equivalents of $NaBH_4$ at 0 °C gave the desired product **470** in 80% yield – however, similar to the reduction of *N*-Boc aziridino ketone **332** to give **356** in Chapter 2, it was formed as a 2:1 mixture of diastereomers (Scheme 3.29).



469 | **470** 80% yield *2:1 dr* | **356** 94% yield *2:1 dr*

***Scheme 3.29**: Reduction of ketone **469** with $NaBH_4$.*

Given that the only difference between the two substrates was the group on the aziridine – a Cbz group in **469** as opposed to piperonyl in **436** – it was hypothesised that the increased barrier to inversion of the Cbz-protected aziridine might be restricting the rotation of the Cbz group, disfavouring the positioning of it over the ring. In comparison, piperonyl-protected substrate **436** in the racemic route features no such interaction and so is free to rotate, charting out a greater area of steric interaction (Figure 3.3).

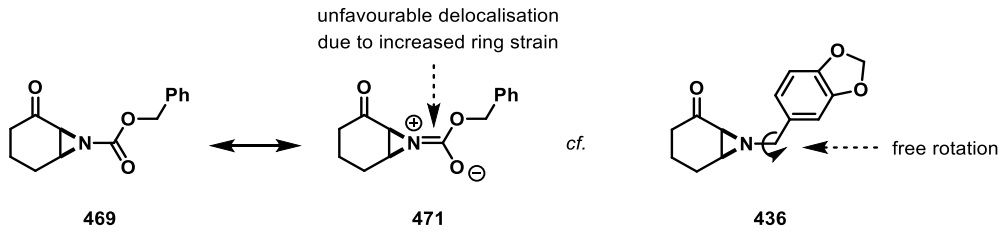
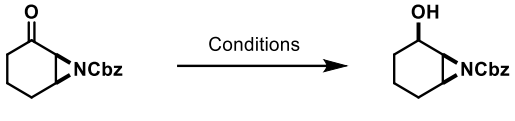


***Figure 3.3**: Differing steric interactions of differentially protected aziridines.*

Whilst the yield was acceptable, and the two diastereomers would be oxidised back to the ketone in the first step of the hydrogen borrowing reaction, it was decided to see if the diastereoselectivity could be optimised – if only to make purification in the deprotection/reprotection step easier. To this end, a number of different reduction conditions were screened, as shown in Table 3.1.



469
1.0 equiv.

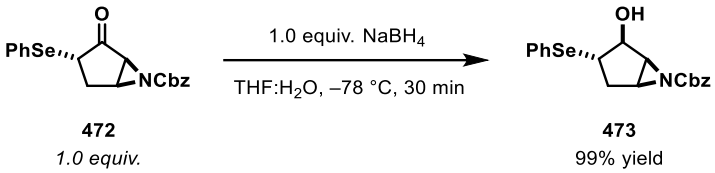
470

Entry	Conditions	Outcome
1	2.0 equiv. $NaBH_4$, MeOH, 0 °C	80% yield **470**, *2:1 dr*
2	3.0 equiv. L-Selectride®, THF, –78 °C	0% yield **470**, BnOH formed
3	1.5 equiv. L-Selectride®, THF, –78 °C	0% yield **470**, BnOH formed
4	2.0 equiv. DIBAL-H, CH_2Cl_2, –78 °C	0% yield **470**, BnOH formed
5	2.0 equiv. $NaBH_4$, MeOH, –20 °C	84% yield **470**, *2.3:1 dr*
6	1.0 equiv. $NaBH_4$, MeOH, –78 °C	79% yield **470**, *2.6:1 dr*

***Table 3.1**: Reduction conditions screened on ketone **469**.*

The first reagent screened was L-Selectride®, an extremely bulky boron-based hydride source that is well known to be effective at performing selective 1,2-reductions of carbonyls.[94] However, as Entry 2 shows, the treatment of ketone **469** with three equivalents of L-Selectride® at –78 °C did not result in the formation of the expected product **470** – instead, large amounts of benzyl alcohol were detected by both TLC and crude NMR, suggesting that the Cbz group had been decomposed by the reagent. Similar results were obtained when the number of equivalents was reduced to 1.5 (Entry 3), as well as when DIBAL-H was used under the same conditions (Entry 4), and as such these hydride sources were abandoned. Returning to $NaBH_4$, it was hypothesised that reducing the reaction temperature would lead to higher selectivity and indeed, when the reaction was cooled to –20 °C, the dr increased slightly

to 2.3:1, along with a small increase in overall yield to 84% (Entry 5). In their synthesis of (–)-Agelastatin A, Hamada and co-workers performed a completely diastereoselective reduction on a very similar protected aziridine compound **472**, with the reaction being conducted at much lower temperatures than we had so far attempted (Scheme 3.30).[77]



472
1.0 equiv.

473
99% yield

***Scheme 3.30**: A diastereoselective reduction in Hamada's synthesis of (–)-Agelastatin A.*

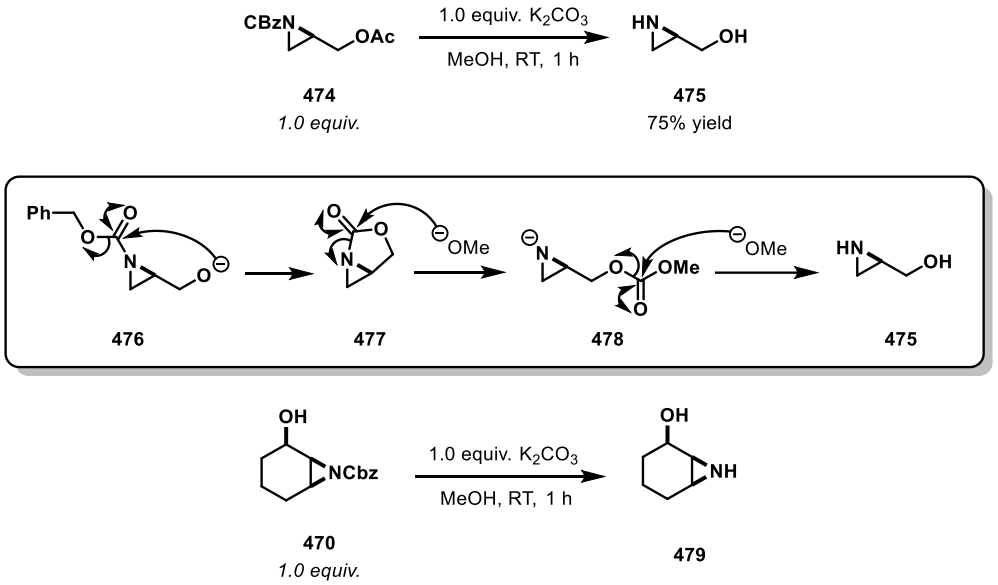
Although the use of these conditions on ketone **469** did lead to a further slight increase in dr to 2.6:1, it was accompanied by a small reduction in yield to 79% (Entry 6). This slight increase in dr was not considered sufficient justification to use cryogenic temperatures and as such, it was the conditions in Entry 5 that were used going forward. Pleasingly, these conditions worked well on a multigram scale, furnishing 1.7 and 1.9 g of alcohol **470** in 70 and 77% yield respectively, with both reactions giving the expected 2.3:1 dr.

With appreciable quantities of alcohol **470** in hand, the next step in the sequence was the removal of the Cbz protecting group and alkylation of the resulting N–H aziridine with a piperonyl group.

3.4.3 Deprotection and Alkylation

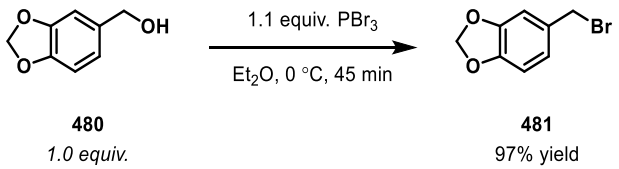
Initial work on the deprotection was conducted by Indi Marriott, who found that the usual Cbz removal conditions of hydrogenation over Pd/C in MeOH surprisingly resulted in no product formation. A survey of the literature led us to a publication by Choi and Borch, who found that Cbz-protected aziridines such as **474** with a vicinal acetate protected alcohol could be deprotected by K_2CO_3 in MeOH at RT.[95] Their mechanistic proposal, based on *in situ* NMR monitoring of the reaction, is that the free alkoxide **476** formed by the expected acetate deprotection of **474** attacks the carbonyl of the Cbz group to give transient bicyclic carbamate **477** (Scheme 3.31). This is then attacked by methanol to give the

unsymmetrical carbonate **478** which is cleaved to give the product alcohol **475** containing the free N–H aziridine.



Scheme 3.31*: Choi and Borch's cleavage of a Cbz protected aziridine, and its application to* ***470****.*

To our delight, when treated with the above conditions, alcohol **470** deprotected to give N–H aziridino alcohol **479**, as determined by crude ^{1}H NMR analysis – however, the high polarity of the compound made separation by column chromatography unfeasible.[87] As such, it was decided to perform the alkylation reaction to give **414** in the same pot, thereby avoiding any difficulties in purifying the polar intermediate. To this end, piperonyl bromide **481** was synthesised in one step (although commercially available, the cost was considered too prohibitive) from piperonyl alcohol **480** and PBr_3 in 97% yield, before being used for the one-pot alkylation (Scheme 3.32).



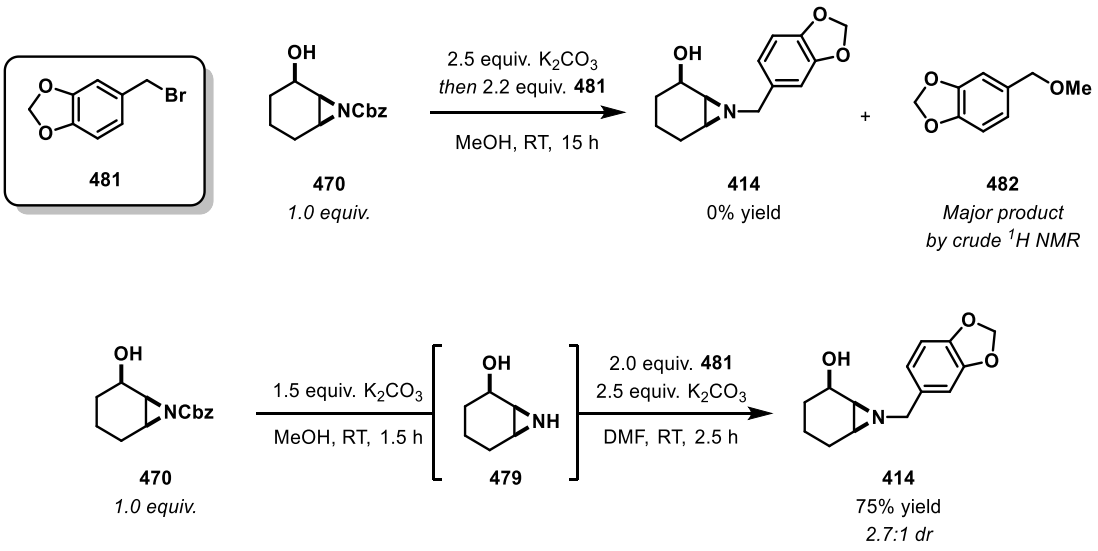
Scheme 3.32*: Synthesis of piperonyl bromide* ***481****.*

Given that alkylation reactions of amines are often conducted in MeOH, it was assumed that the same solvent could be used for both steps – with additional K_2CO_3, along with the piperonyl bromide **481**, being added once the Cbz deprotection was complete – and a test reaction conducted by Indi Marriott

using benzyl bromide rather than piperonyl bromide **481** found this to be the case, delivering the desired product in 94% yield.[87]

Unfortunately, when piperonyl bromide **481** was used, no product formation was observed – the alkyl bromide instead reacted with the solvent MeOH to give undesired ether **482**. This change in reactivity can be attributed to the mesomeric donation of the *para* oxygen in piperonyl bromide into the C–Br σ* orbital, weakening the bond and making it more susceptible to solvolysis.

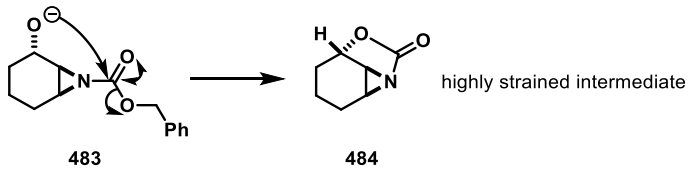
As a workaround, it was decided to perform a solvent switch before adding the reactive piperonyl bromide **481** – with DMF being chosen to due to its high polarity and lack of nucleophilicity. Pleasingly this worked as anticipated, with a 1.7 g scale reaction furnishing alcohol **414** in 75% yield as a pair of separable diastereomers in a 2.7:1 ratio (Scheme 3.33).



***Scheme 3.33**: Deprotection/alkylation sequence to give alcohol **414**.*

At this point, it is interesting to note that although the reaction resulted in a degree of diastereoenrichment, the minor *trans*-diastereomer of Cbz-protected **470** was still deprotected to some extent by K_2CO_3 and MeOH. This is clearly incompatible with the mechanism of Choi and Borch outlined earlier,[95] which involves the formation of a bicyclic carbamate and so suggests that the neighbouring group participation of the alkoxide might not be required for such a process (Scheme

3.34) – a possibility discussed by Choi and Borch due to their observation that the TBS-protected analogue of alcohol **474** underwent Cbz cleavage, albeit at a much slower rate.

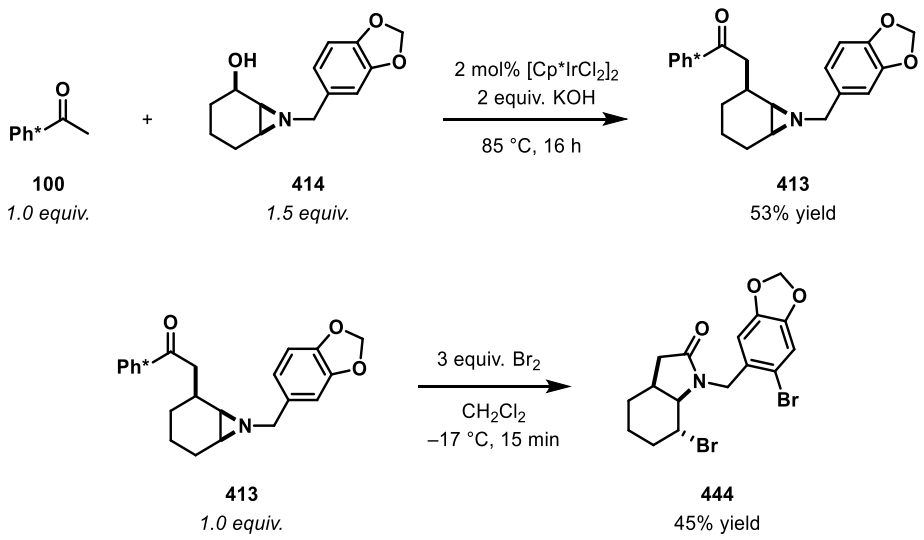


Scheme 3.34**: Highly strained intermediate required for deprotection of* trans-483*** via *Choi and Borch's mechanism.*

Having synthesised a sufficient quantity of alcohol **414** *via* the reduction, deprotection, alkylation sequence, the asymmetric synthesis had now intersected the racemic route detailed earlier in this chapter and all that remained was to take the material through the six final steps.

3.4.4 Endgame to Form (–)-γ-Lycorane

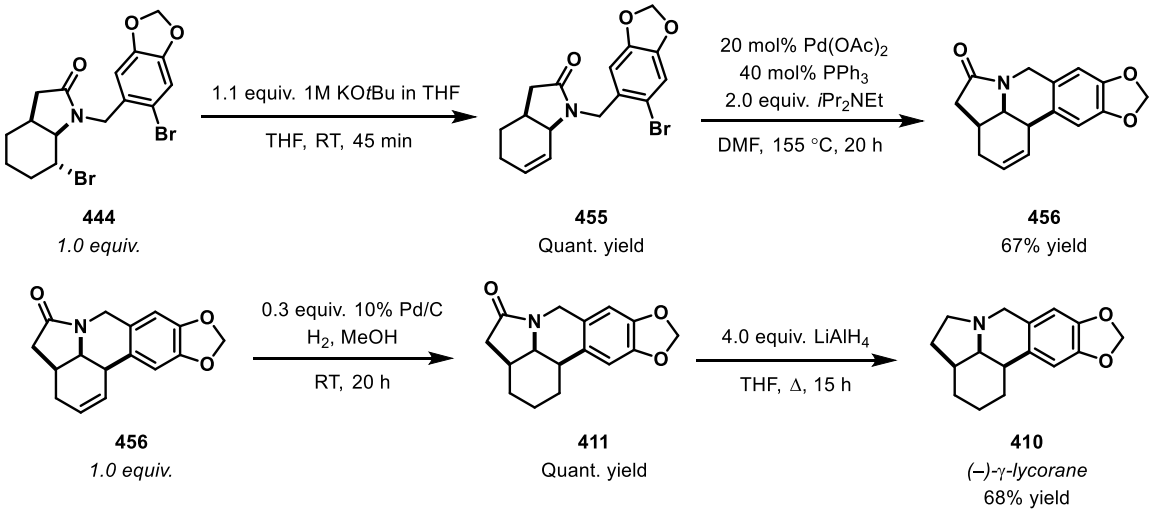
Starting with alcohol **414**, the key hydrogen borrowing transformation was attempted several times. As had been the case during the racemic synthesis, this step once again proved highly capricious, with reactions conducted under identical conditions with the same batch of starting material giving highly variable yields, or even failing altogether. The best yield obtained was with diasteromerically pure all-*cis* alcohol **414**, which gave the desired product **413** in 53% yield – however, most attempts using material with a dr of approximately 2.3:1 gave yields in the mid-40% range, only marginally lower (Scheme 3.35). Whilst we envisaged that the minor correlation between the diastereomeric purity of alcohol **414** and the yield of hydrogen borrowing product **413** might be explained by the *cis*-**414** being easier for the iridium catalyst to oxidise than its corresponding *trans*-**414** isomer due to the oxidised C–H being less sterically hindered; we did not have the opportunity to perform the hydrogen borrowing reaction with pure *trans*-**414** in an attempt to further explore this effect and the synthesis was carried on regardless.



***Scheme 3.35**: Hydrogen borrowing and bromine-mediated cleavage of enantioenriched material.*

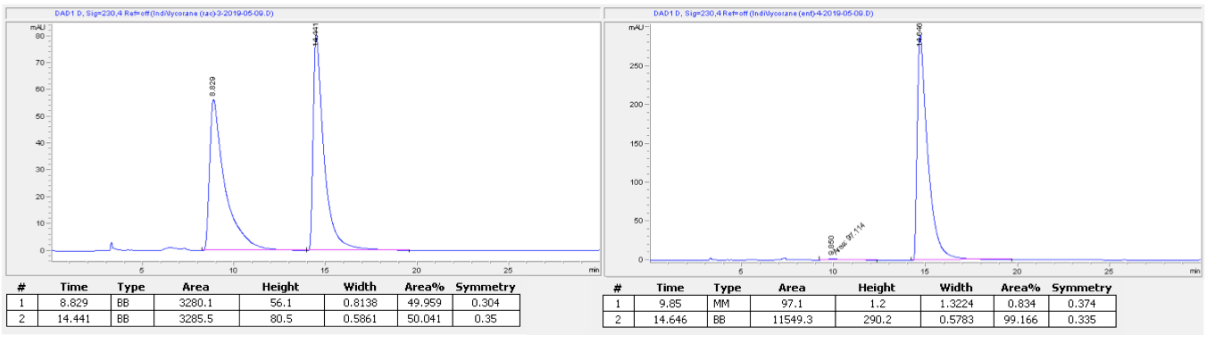
With enantioenriched hydrogen borrowing product **413** in hand, work began on the bromine-mediated cleavage reaction. Similarly to the previous step, this reaction also suffered from problems with irreproducibility – with the highest yield of 45% of dibromide **444** being obtained in a repeat by Indi Marriott, as shown above in Scheme 3.35.[87] The low yields, and regularly observed formation of key degradation product piperonal, led us to hypothesise that fault lay with the rate of addition of elemental bromine into the reaction. As most reactions were conducted on a small scale (0.2 - 0.3 mmol being typical) at –17 °C, the dropwise addition of bromine could potentially lead to local exotherms, causing unwanted reactivity. Similarly, the drop size was also observed to vary, once again leading to experimental inconsistencies. Attempts to rectify this by using a pre-prepared stock solution of bromine in CH_2Cl_2 only led to lower yields.

The final steps in the synthesis of (–)-*γ*-lycorane were conducted entirely by Indi Marriott and the yields were often similar, if not better, than those obtained during the racemic synthesis and are shown in Scheme 3.36.[87]



***Scheme 3.36**: Final steps in the synthesis of (–)-γ-lycorane.*

Elimination of the alkyl bromide **444** proceeded smoothly in quantitative yield, followed by the intramolecular heck reaction to give compound **456** in 67% yield. Hydrogenation of the formed olefin gave amide **411** in quantitative yield, which was then reduced with $LiAlH_4$ to give (–)-γ-lycorane in 68% yield. The overall yield for the sequence was 3.4% across nine steps – with the er of the final product being determined by HPLC analysis as 99:1, comparing against the racemic sample prepared earlier (Figure 3.4).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.829	BB	3280.1	56.1	0.8138	49.959	0.304
2	14.441	BB	3285.5	80.5	0.5861	50.041	0.35

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.85	MM	97.1	1.2	1.3224	0.834	0.374
2	14.646	BB	11549.3	290.2	0.5783	99.166	0.335

***Figure 3.4**: HPLC traces of (±) and (–)-γ-lycorane, collected by Indi Marriott*

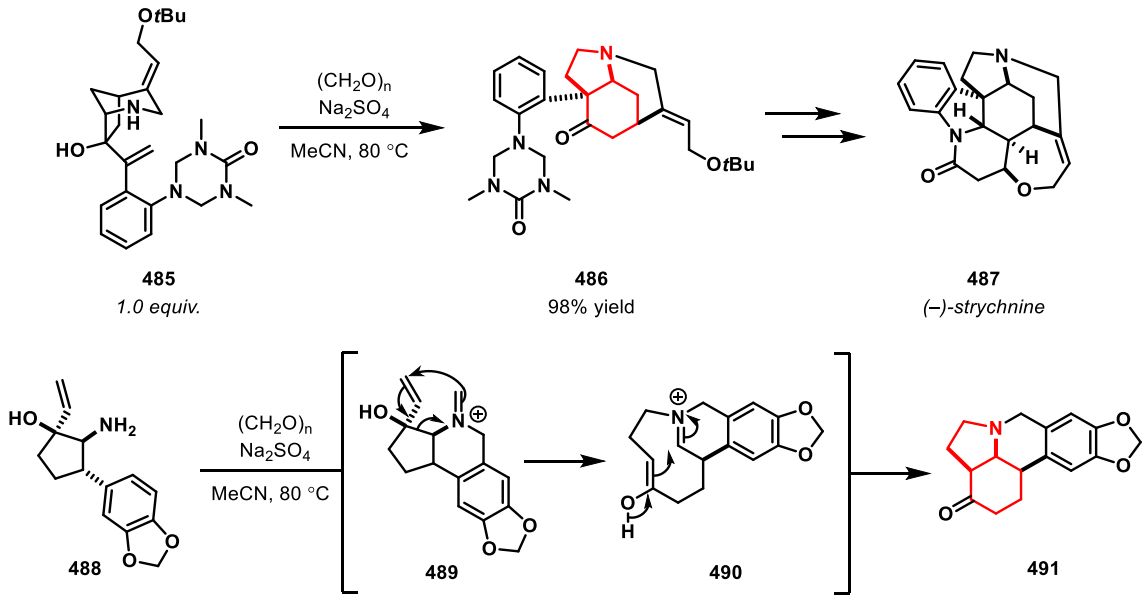
Finally, the specific rotation of the enantioenriched sample was measured – giving an $[\alpha]_D^{20}$ of –24.5, which was of similar sign and magnitude to the $[\alpha]_D^{20}$ of –19.5 reported by Fujioka and co-workers.[82]

Whilst our route is neither the shortest nor highest yielding synthesis reported for (–)-γ-lycorane, to our knowledge this route represents the first use of a hydrogen borrowing reaction to form a C–C bond in total synthesis – thereby demonstrating the utility of such methodology in a more complex setting.

3.5 Results and Discussion: A Pericyclic Approach to γ-Lycorane

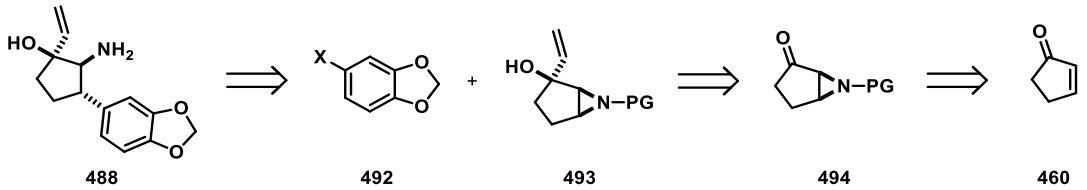
3.5.1 Overman's Synthesis of (–)-Strychnine

Although the synthesis of (–)-γ-lycorane was now completed, our interest in the use of aziridines to synthesise it was not yet satisfied. Inspired by the work of Overman in his ground-breaking 1995 synthesis of (–)-strychnine,[9] which uses a key aza-Cope-Mannich reaction to form pentacyclic intermediate **486** in 98% yield, it was envisaged that the 6,5-bicyclic core of (–)-γ-Lycorane could be formed in a similar way, starting from amine **488** (Scheme 3.37).



***Scheme 3.37**: An aza-Cope-Mannich reaction in Overman's synthesis of (–)-strychnine and its possible application to the synthesis of (–)-γ-lycorane.*

In turn, it was hypothesised that amine **488** could be obtained by a regioselective opening of aziridino alcohol **493** by a suitable aryl nucleophile **492**. Alcohol **493** was envisaged to be accessed by the diastereoselective addition of vinylmagnesium bromide to aziridino ketone **494**, itself obtained from an enantioselective aziridination of cyclopentenone **460** (Scheme 3.38).

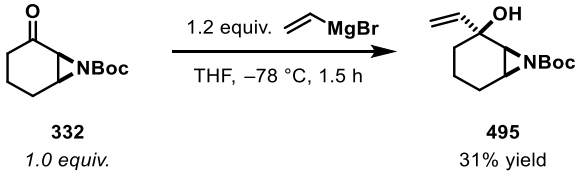


***Scheme 3.38**: Retrosynthesis of amine **488**.*

Similar to the approach used for the hydrogen borrowing route to (–)-γ-Lycorane, it was decided to first attempt a racemic synthesis to test the key aza-Cope-Mannich reaction, before repeating the steps with enantiopure material.

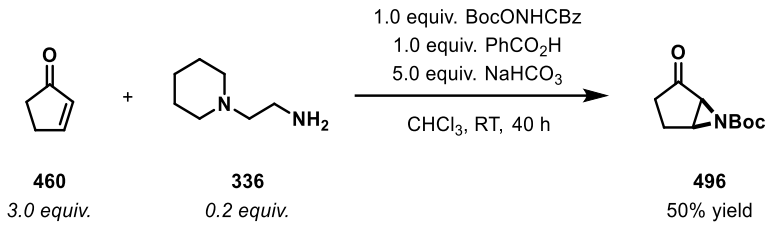
3.5.2 Aziridination and Diastereoselective Vinyl Addition

Work began with a test reaction between vinylmagnesium bromide and a sample of racemic *N*-Boc aziridine **332**, which had already been prepared during earlier work on (–)-*γ*-lycorane. Pleasingly, this resulted in clean addition to the carbonyl to give alcohol **495** as a single diastereomer – albeit in the slightly disappointing yield of 31% (Scheme 3.39).



***Scheme 3.39**: Test addition of vinylmagnesium bromide to aziridino ketone **332**.*

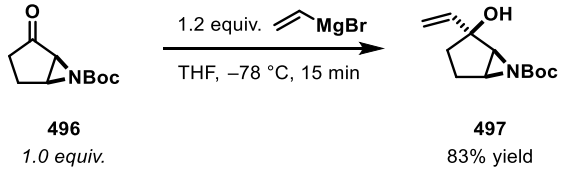
Having shown that the addition was possible, it was time to work on the real system. Once again using the achiral diamine catalyst **336** to perform a racemic aziridination, cyclopentenone **460** reacted using BocNHOTs as the nitrogen source to give aziridino ketone **496** in a moderate 50% yield (Scheme 3.40). Furthermore, leftover BocNHOTs from the reaction was inseparable from the product **496**, with the two being isolated in a 5.4:1 (**496**:BocNHOTs) ratio.



***Scheme 3.40**: Racemic aziridination of cyclopentenone.*

Despite these separation issues, it was decided to proceed with the impure material in the hope that the 1,2-addition into the ketone would not be impeded by the leftover aziridination reagent and that the product formed would be amenable to separation.

To our delight, the addition of vinylmagnesium bromide to the impure mixture of aziridino ketone **496** and leftover BocNHOTs proceeded smoothly in only 15 minutes, giving the desired alcohol **497** in 83% yield (Scheme 3.41) – the increase in reactivity and yield compared to the test reaction perhaps reflecting the additional driving force from relief of ring stain in the five-membered ring. As predicted, there were no issues with purification – the transition from a ketone to polar alcohol moiety ensured a large change in R_f, making separation by column chromatography trivial.

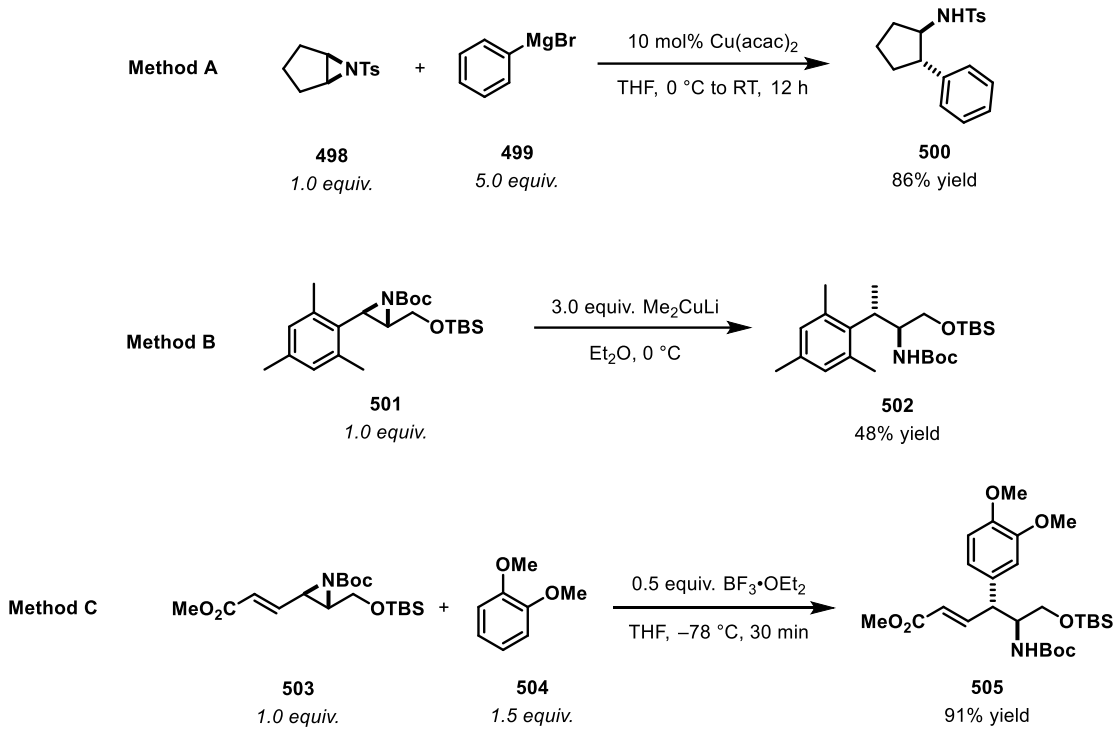


***Scheme 3.41**: Addition of vinylmagnesium bromide to aziridino ketone **496**.*

With alcohol **497** in hand, our attention turned to finding conditions that would open the aziridine to give the aza-Cope-Mannich substrate **488**.

3.5.3 Attempted Ring-Openings of Aziridino Alcohol 497

It was assumed that the regioselectivity of aziridine ring-opening by any nucleophile would be dominated by sterics and so occur only at the opposite end to the tertiary alcohol. An analysis of the literature found three possible methods of opening aziridines with suitable nucleophiles, as shown below in Scheme 3.42.



***Scheme 3.42**: Literature methods for ring-opening aziridines with various nucleophiles.*

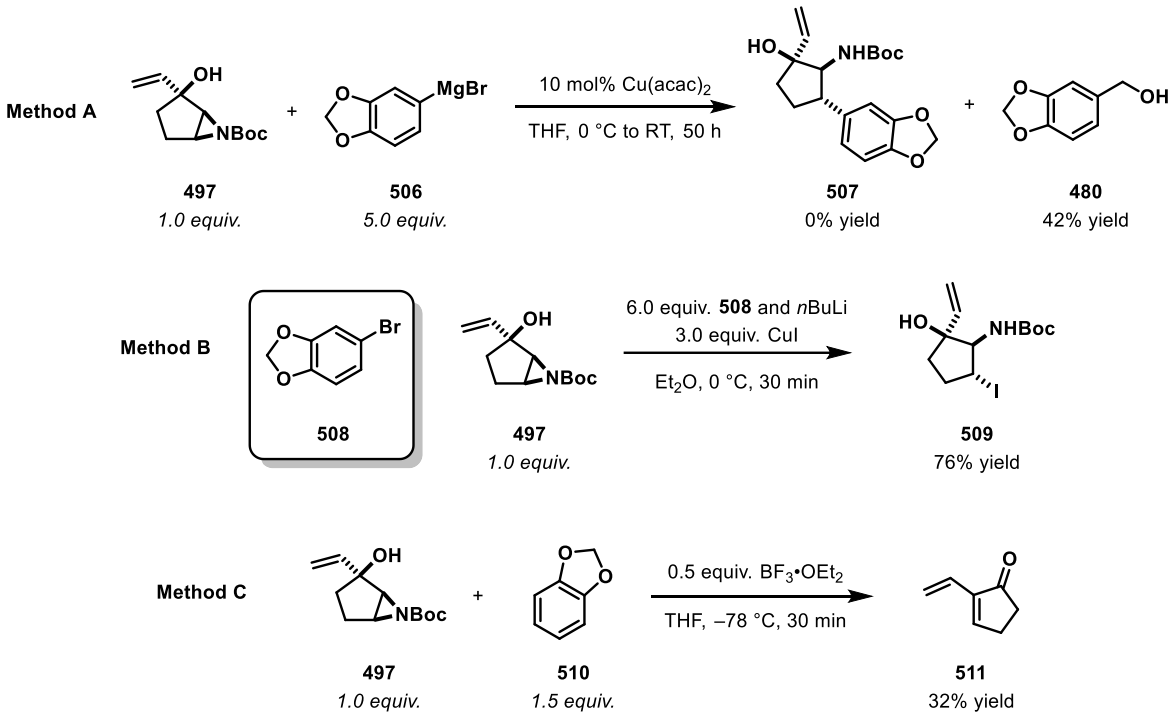
Method **A** was detailed in a 2004 patent by Pharmacopeia Inc. and used $Cu(acac)_2$ to catalyse the addition of phenylmagnesium bromide into a tosyl aziridine on a five-membered ring to give tosylamine **500**.[96] The structural similarity to our substrate was very encouraging, and it was hoped that the Boc group would be analogous enough to the Ts in their substate to allow for ring opening.

Method **B** was based on a 2000 report by Riera and co-workers who used Me_2CuLi to regioselectively open an *N*-Boc aziridine to give amine **502**.[97] In contrast to method **A**, the substrate used bears an aryl ring next to the centre to be opened – thereby facilitating bond cleavage *via* the aryl π-system stabilising the transition state associated with the breaking of the C–N bond – however, the use of the *N*-Boc aziridine, and the paucity of synthetic methods to achieve this transformation, were enough to justify its inclusion.

Method **C** comes from a 2011 paper by Nagumo and co-workers and is noticeably different from methods **A** and **B** in its lack of a metal catalyst or arylmetal nucleophile.[98] Instead, the authors used $BF_3{\cdot}OEt_2$ to facilitate the opening of an *N*-Boc aziridine with electron-rich aromatic rings in a

Friedel-Crafts type reaction. This route seemed especially attractive to us, given the corresponding nucleophile for our reaction would be the extremely electron-rich 1,3-benzodioxole.

Shown below are the results of applying each of these methods to *N*-Boc aziridine **497** – whilst none succeeded in furnishing the desired ring-opened product **507**, they did provide some examples of interesting reactivity (Scheme 3.43).



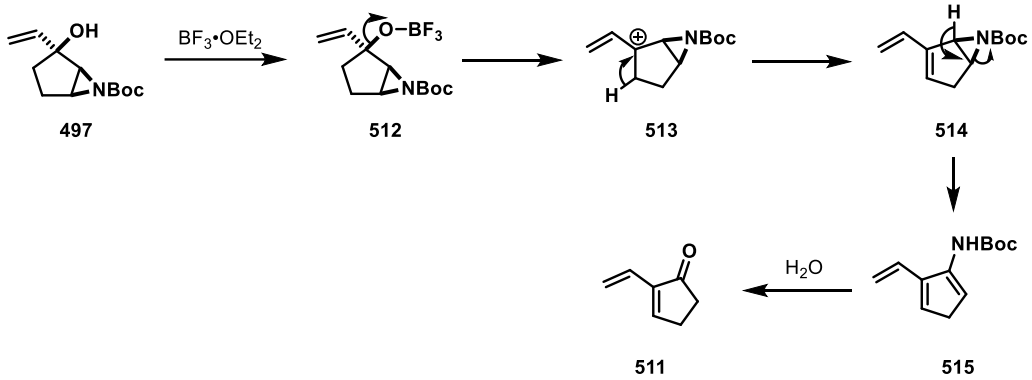
***Scheme 3.43**: Attempts to ring-open aziridine **497** using aryl nucleophiles.*

Unfortunately, Method **A** fared the worst – the reaction showed no reactivity after being left for 6 h at room temperature. An extended reaction time of 50 h resulted in the formation of a number of unidentified by-products, with piperonyl alcohol **480** being the only compound isolated by column chromatography in 42% yield – its formation proving difficult to explain.

Method **B** did result in aziridine ring-opening, albeit with the wrong nucleophile to give *trans* iodide **509** in a respectable 76% yield. The high yield of iodide **509** is not altogether surprising, given the highly effective nature of the iodide anion as a nucleophile, and could either be a consequence of the failure of the premixing protocol between the aryl bromide, *n*BuLi, and CuI to form the desired Gilman reagent

or, if it did form correctly, the iodide anion still being a better nucleophile and outcompeting it. Despite the failure to form **507**, the regiochemistry of iodide **509** was evidence that the aziridine was predisposed to open at the desired end. In addition to this, it was proposed that iodide **509** might still be used in a coupling reaction with a suitable aryl species to form **507** using modern cross-coupling chemistry.

Method **C** was also unsuccessful in forming the desired amine **507**, with the only isolatable product being the highly unexpected diene **511** in 32% yield – notable for its strong and penetrating odour, as well as the extremely deshielded vinylic proton triplet at 7.51 ppm. The formation of **511** is unclear, but mostly likely resulted from a BF_3-mediated dehydration of the tertiary alcohol to alkene **513** – as well as a rearrangement of the aziridine to enamine **515**, which presumably hydrolysed upon workup to give **511** (Scheme 3.44).



Scheme 3.44*: Possible mechanism for the formation of diene* ***511*** *from aziridine* ***497****.*

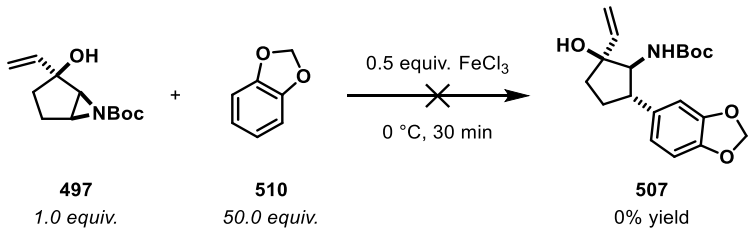
Given that Nagumo and co-workers did not see a similar rearrangement of their *N*-Boc aziridines to enamines or ketones when exposed to $BF_3{\cdot}OEt_2$,[98] it was hypothesised that the initial dehydration of the tertiary alcohol was in some way responsible – and that protection of the hydroxyl moiety might prevent such a pathway.

Based on these results, it was decided to abandon efforts to open aziridine **497** with an organocopper species, and instead focus on the Friedel-Crafts approach – as well as investigating the possibility of

using alkyl halides such as iodide **509** in an appropriate cross-coupling reaction to give the desired product **507**.

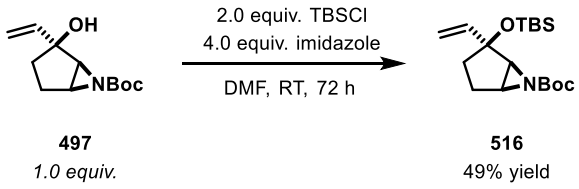
3.5.4 Second-Generation Efforts to Form Amine 507

Before attempting to protect the hydroxyl functionality in **497**, it was decided to reattempt the Friedel-Crafts reaction using the less Lewis-acidic $FeCl_3$, so as to disfavour the dehydration process; additionally, 1,3-benzodioxole was used as the solvent to encourage its nucleophilic attack on the activated aziridine (Scheme 3.45).



***Scheme 3.45**: Use of $FeCl_3$ in the attempted Friedel-Crafts reaction.*

Unfortunately, no product formation was observed – nor was the formation of diene **511**, suggesting that $FeCl_3$ was too weak a Lewis acid to activate either the alcohol or aziridine for any form of reaction. Rather than screen more Lewis acids, alcohol **497** was protected as a TBS alcohol with the reaction proceeding in 49% yield (Scheme 3.46) – the modest reaction outcome perhaps attributable to the steric hindrance of the tertiary alcohol.

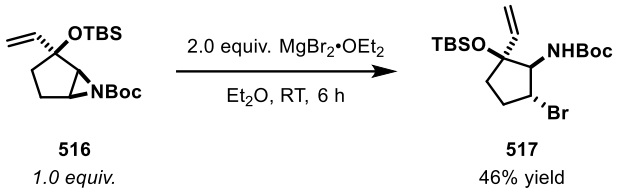


***Scheme 3.46**: TBS protection of alcohol **497**.*

With TBS-protected alcohol **516** in hand, the Friedel-Crafts reaction with 1,3-benzodioxole and $BF_3{\cdot}OEt_2$ was performed – however, once again, the only observed product was diene **511**, interestingly with the same yield as before of 32%. This was presumably due to BF_3-mediated cleavage of the TBS

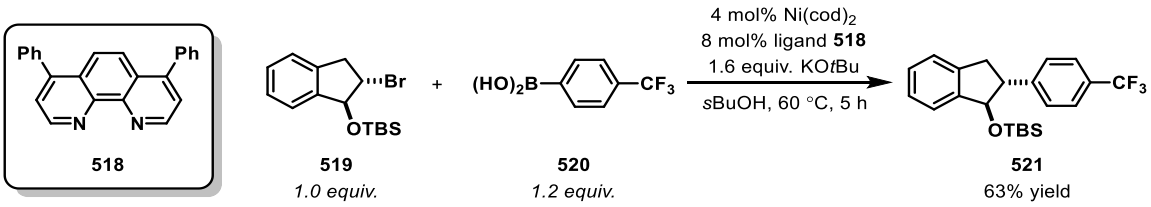
group to unveil the free tertiary alcohol – however, this process usually requires longer reaction times and non-cryogenic temperatures.[99, 100]

With this result, it was decided to also abandon the Friedel-Crafts route and instead explore a cross-coupling strategy. Rather than use alkyl iodide **509** with its free hydroxyl group, it was decided to open TBS-protected aziridine **516** with $MgBr_2$ to the corresponding alkyl bromide **517** using methodology developed by Righi and Ciambrone.[101] As shown in Scheme 3.47, the ring opening occurred in 46% yield to give the desired alkyl bromide, although a small amount of diene **511** was detectable by TLC and by its characteristic odour.



***Scheme 3.47**: Ring-opening of aziridine **516** with $MgBr_2$.*

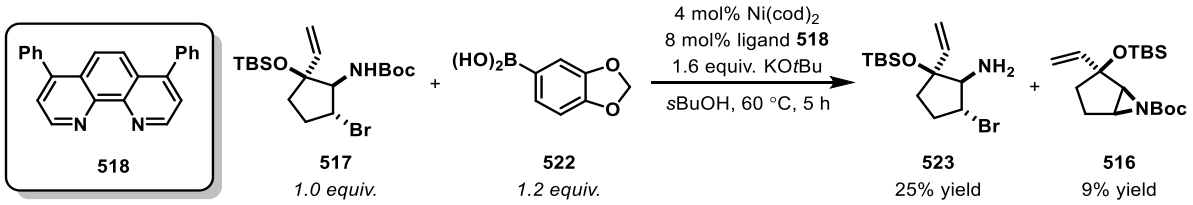
With alkyl bromide **517** in hand, a suitable cross-coupling strategy was needed to form the required bond to 1,3-benzodioxole. Such a strategy was found in work disclosed by Fu in 2004, detailing the development of a Suzuki cross-coupling between arylboronic acids and unactivated secondary alkyl bromides and iodides.[102] Of particular note in this publication was alkyl bromide **519**, which also contained a TBS-protected alcohol, in which the isolated product **521** retained the *trans* stereochemistry of starting material (Scheme 3.48).



***Scheme 3.48**: Fu's cross-coupling reaction between arylboronic acids and unactivated alkyl halides.*

Although the authors did not comment on the stereochemical outcome of the above reaction, the result could possibly be explained by either a stereospecific mechanism, or an equilibrating intermediate that preferentially forms the thermodynamically favourable *trans* product.

Unfortunately, when Fu's methodology was applied to bromide **517**, none of the desired product was observed – with the only isolated products being aziridine **516** in 9% yield, presumably formed by base-mediated ring closure, and the Boc deprotected secondary amine **523** in 25% yield (Scheme 3.49).

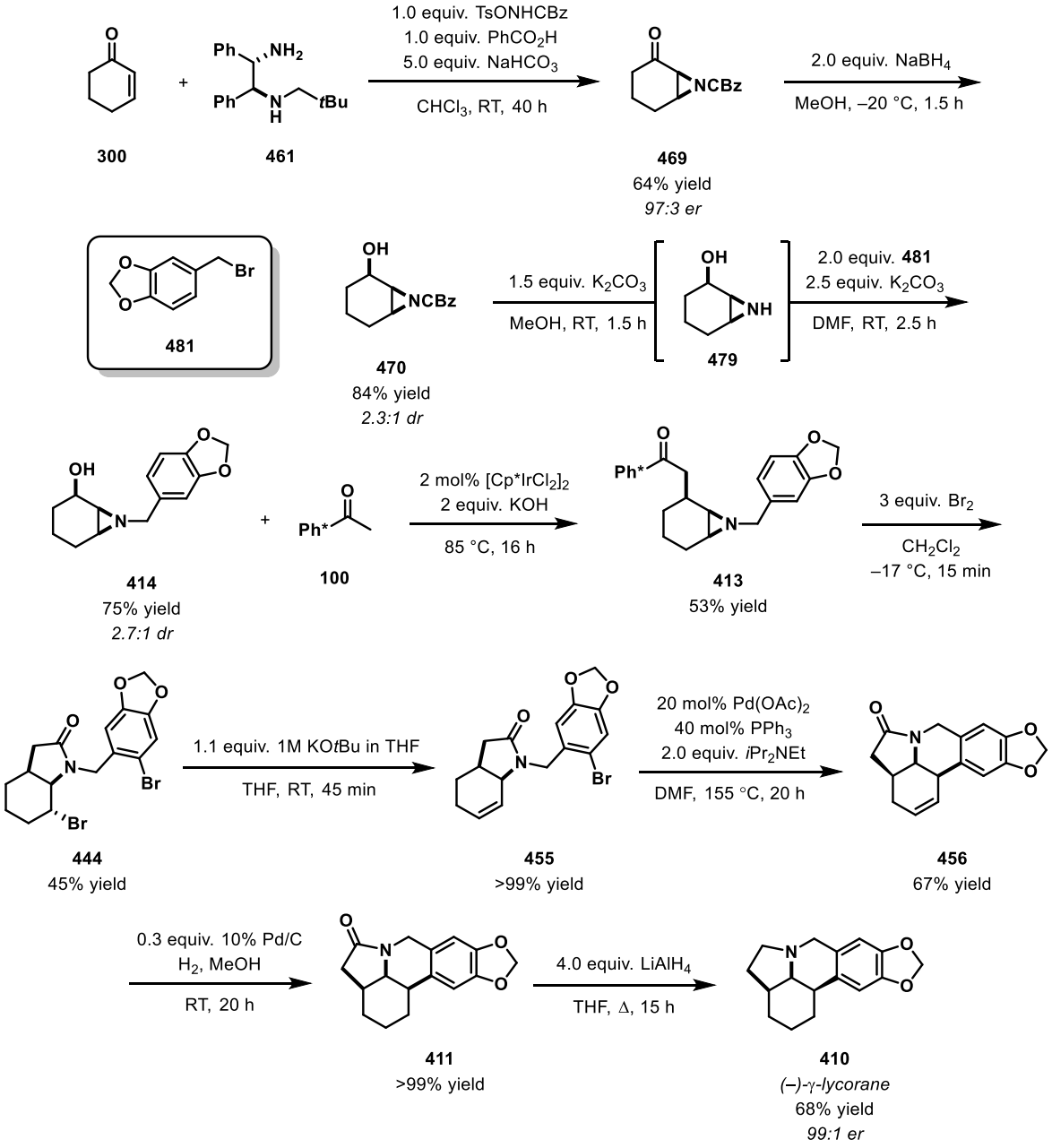


***Scheme 3.49**: Attempted Suzuki cross-coupling using bromide **517**.*

With the failure of the above reaction, it was decided to call an end to this attempted synthesis of (–)-γ-Lycorane. Despite the fact that the key aza-Cope-Mannich reaction had not been attempted, a number of interesting reactions involving small, bicyclic aziridines had been explored – and the formation of diene **511** had proven to be noteworthy surprise.

3.6 Conclusions and Future Work

In conclusion, the total syntheses of both (±) and (–)-*γ*-lycorane were completed, in 9 steps and 19% and 4% overall yield, respectively. The er of (–)-*γ*-lycorane was 99:1, as measured by HPLC analysis, and was set by an asymmetric aziridination in the first step of the synthesis. The asymmetric route is summarised in Scheme 3.50 shown below.



***Scheme 3.50**: Completed route to (–)-γ-lycorane.*

To the best of our knowledge, the above route represents the first use of a hydrogen borrowing reaction to form a C–C bond in total synthesis, thereby demonstrating the utility of a reaction which, until now, has been limited to the less complex compounds commonly found within methodological publications.

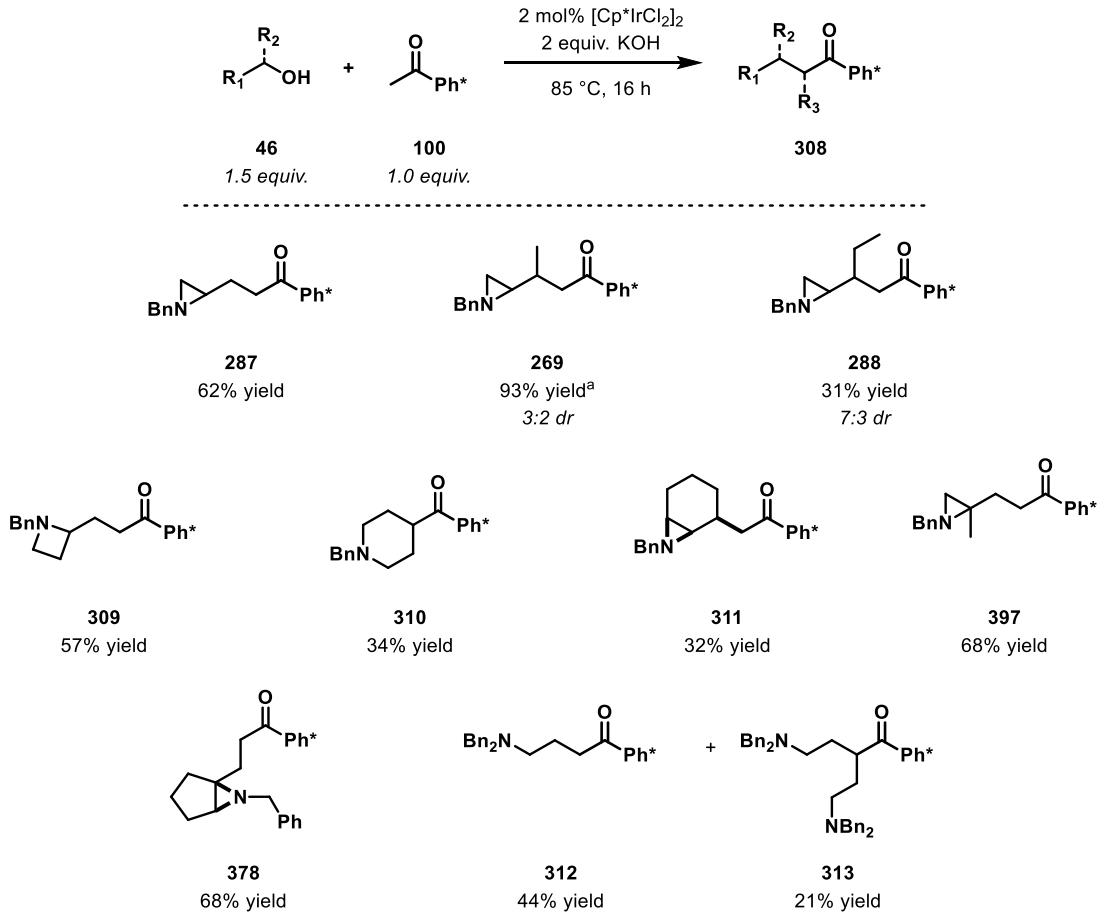
Whilst an attempt was made to explore an alternative route to (–)-*γ*-lycorane using a pericyclic reaction inspired by Overman's synthesis of (–)-strychnine, we were unable to synthesise the substrate **488** required for the key step. However, a number of interesting compounds were discovered *en route,* and this proposed synthesis remains a fruitful avenue of pursuit to (–)-*γ*-lycorane in the future.

Chapter 4: Hydrogen Borrowing Reactions of Amino Alcohols

4.1 Introduction

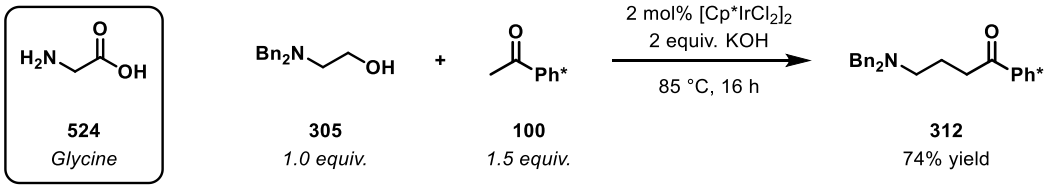
Having demonstrated in the previous chapter that aziridine-containing alcohols can be utilised in the synthesis of more complex alkaloids such as (–)-*γ*-lycorane *via* hydrogen borrowing catalysis, our attention turned once more to the utilization of other nitrogen containing alcohols in hydrogen borrowing reactions.

Whilst the small scope of amine- and aziridine-containing alcohols explored in Chapter 2 represented a new class of substrate alcohols, it was our contention that the area was still ripe for further exploration (Scheme 4.1).



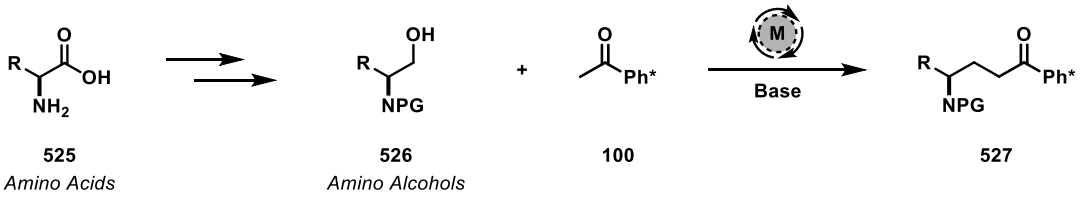
***Scheme 4.1**: Scope of hydrogen borrowing reactions of aziridino alcohols.*
[a]Reaction conducted by Ben Jones.

In particular, our attention was drawn to the formation of products **312** and **313** from dibenzylethanolamine **305**. Along with piperidine derivative **310**, these represented the only amines in the above scope that were not aziridines or azetidines, and as such were more likely to be of interest to the wider synthetic community. Whilst individual yields for each product were low (44% and 21% for **312** and **313**, respectively), we observed that this constituted an effective 65% yield of **312** – with 21% then undergoing a further hydrogen borrowing alkylation to give **313**. In an attempt to circumvent this, we hypothesised that the use of excess Ph* methyl ketone **100** might serve to suppress the unwanted second alkylation reaction and were therefore pleased to observe that, upon switching the equivalents of **305** and **100**, only the desired monoalkylation product **312** was obtained in 74% isolated yield (Scheme 4.2).



***Scheme 4.2**: The use of excess Ph* methyl ketone **100** to suppress the formation of double alkylation product **313**.*

The above increase in yield was encouraging evidence that molecules such as **312** might be a fruitful new class of hydrogen borrowing products. Upon closer inspection, we observed that dibenzyl alcohol **305** could be seen as an *N*-protected and CO_2H-reduced form of the simple amino acid glycine **524**. This then led us to consider whether other amino acids **525** – suitably protected and reduced to the corresponding 1,2-amino alcohols **526** – would be viable substrates for hydrogen borrowing reactions with Ph* methyl ketone **100** to give 1,4-amino ketones **527** (Scheme 4.3).



***Scheme 4.3**: Proposed use of amino acid-derived 1,2-amino alcohols **526** for hydrogen borrowing catalysis.*

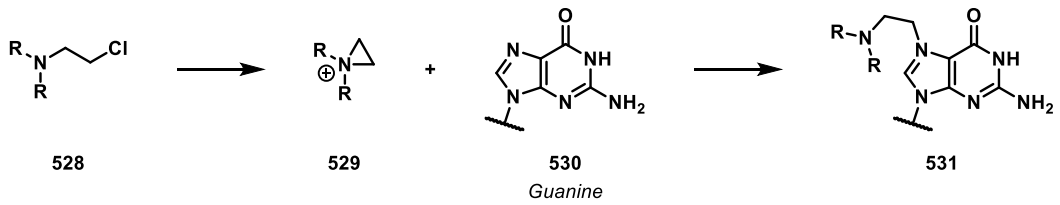
Our interest in this class of substrates was heightened by the number of advantageous characteristics associated with amino acids namely:

i. Amino acids are cheap and readily available, making them an attractive starting material for synthesis.

ii. Amino acids are naturally produced as enantiopure compounds with an L configuration at the chiral centre, providing easy access to enantioenriched products.

iii. Amino acids are the "building blocks" of a large number of both natural products and pharmaceuticals, and as such, structures derived from them are likely to be of interest to the wider synthetic community.

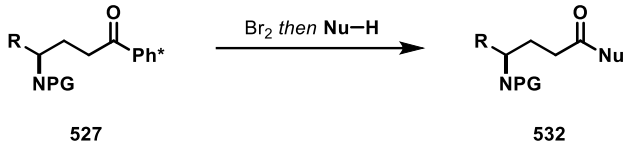
We also observed that another advantage of 1,2-amino alcohols as substrates for hydrogen borrowing was that their analogues for classical alkylation reactions are 1,2-amino halides such as **528**. Whilst at first glance these may appear benign, they are in fact potent chemical weapons – the main examples of which are the nitrogen mustards (Scheme 4.4).



***Scheme 4.4**: Hazards associated with the use of 1,2-amino halides.*

The mechanism of action of such 1,2-amino halides is *via* the intramolecular displacement of the halide to form a reactive aziridinium **529**. This is then attacked *in vivo* by the nucleophilic N7 nitrogen in the DNA nucleobase guanine **520** – a process that is then repeated to form DNA crosslinks, leading to mutations and eventually cell death. By using a 1,2-amino alcohol and hydrogen borrowing catalysis, this pathway is entirely avoided – achieving the same alkylation transformation, but without the use of such toxic reagents.

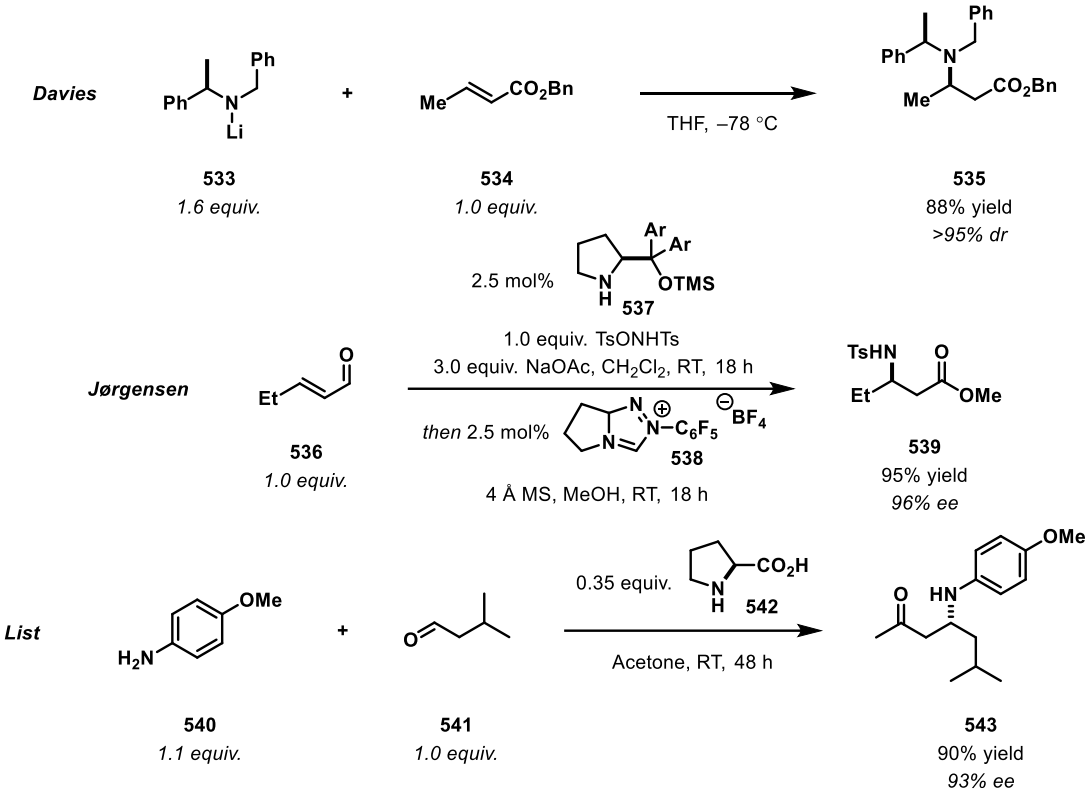
In addition to this, we envisaged that the hydrogen borrowing products **527** could be cleaved under Donohoe's previously developed[29] bromine-mediated conditions to give enantioenriched 1,4-amino acid derivatives **532** (Scheme 4.5).



527 **532**

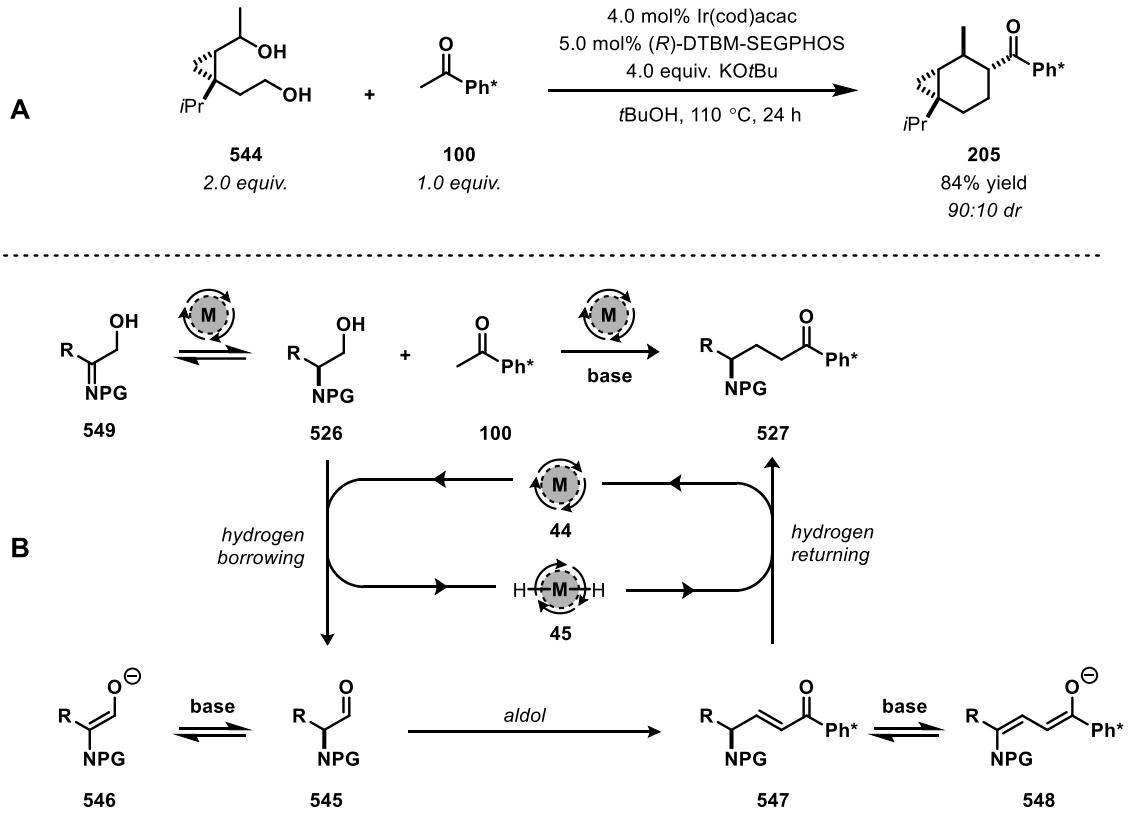
Scheme 4.5*: Proposed cleavage of hydrogen borrowing products* ***527*** *to give 1,4-amino acid derivatives* ***532****.*

Such products were immediately of interest to us due to the scarcity of literature methods for accessing them, especially when compared to the large number of synthetic methodologies known for accessing the related class of enantioenriched 1,3-amino acid derivatives – prominent historical examples of which being Davies' enantioselective addition of a chiral lithium amide species to α,β-unsaturated carbonyls,[103, 104] Jørgensen's enantioselective one-pot aziridination and subsequent ring-opening,[105] and List's proline-catalysed Mannich reaction (Scheme 4.6).[106]



Scheme 4.6*: Selected literature methods for the synthesis of enantioenriched 1,3-amino acid derivatives.*

A final consideration at the outset of this project was the possibility for racemisation of the 1,2-amino alcohol substrates **526** under the reaction conditions. In our examination of the prior hydrogen borrowing literature, we found no examples in which a stereocentre at the α-position of an oxidisable alcohol was successfully carried through the reaction without epimerisation – with the sole exception of β-Thugone-derived alcohol **544** utilised by Donohoe and co-workers in their asymmetric synthesis of cyclohexanes,[34] although in this case epimerisation was almost certainly prevented by the strained cyclopropane moiety as well as the need to form a fused 6,3-ring system in the product (Scheme 4.7, Part A).



***Scheme 4.7**: Donohoe's use of an α-chiral alcohol **544**, and the potential opportunities for epimerisation of 1,2-amino alcohols **526** in a hydrogen borrowing alkylation reaction with Ph* methyl ketone **100**.*

An examination of the reaction mechanism of a hydrogen borrowing reaction makes clear the potential avenues for epimerisation of α-chiral alcohols, such as 1,2-amino alcohols **526** (Scheme 4.7, Part B). Initial oxidation of **526** by the metal catalyst **44** forms 1,2-amino aldehyde **545** – greatly acidifying the neighbouring stereogenic proton and thereby facilitating epimerisation under the basic reaction

conditions *via* enolate **546**. The next step is then an aldol condensation to give enone **547**, which provides further potential for epimerisation *via* deprotonation to form extended enolate **548**. Only after the final reduction by metal hydride species **45** is the stereocentre in question no longer vulnerable to direct deprotonation – however we envisaged that a poorly chosen metal catalyst may still cause epimerisation at any stage *via* reversible oxidation of the C–N bond to form an imine **549**, as is often seen in C–N bond forming hydrogen borrowing reactions.[107]

4.1.1 Project Aims

With the above considerations in hand, the aims for this final project were as follows:

i. Find optimised conditions for the reaction between amino acid-derived 1,2-amino alcohols **526** and Ph* methyl ketone **100**, maximising both product yield and enantioretention.

ii. Synthesise *N*-protected 1,2-amino alcohols corresponding to the 20 naturally occurring amino acids and submit them to the previously optimised conditions.

iii. Cleave the Ph* moiety from a number of hydrogen borrowing products to form 1,4-amino acid derivatives.

4.1.2 Compound Stereochemistry

All structural formulae of amino acid derivatives depicted in this chapter with bold/dashed bonds refer to enantioenriched compounds. Racemic amino acid derivatives are depicted using single lines at the relevant stereogenic centres (Figure 4.1).



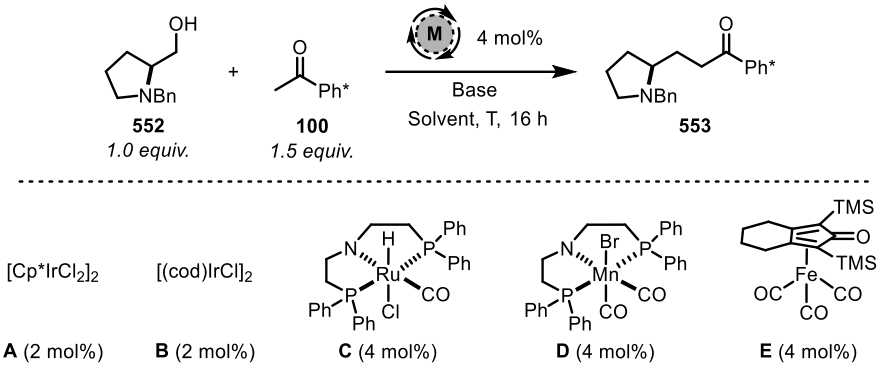
550 **551**

***Figure 4.1**: Illustrative examples of enantioenriched L-Alanine **550** and racemic DL-Serine **551**.*

Furthermore, where quoted, product er was measured by HPLC analysis against a racemic sample prepared using an identical route.

4.2 Results and Discussion: Reaction Optimisation

As a model substrate, it was decided to use *N*-benzyl-L-prolinol **552** – a commercially available amino alcohol that has been previously used by Yus and co-workers as a ligand to catalyse the enantioselective addition of dialkylzincs to imines.[108] An optimisation of reaction conditions was then conducted, examining a suitable range of catalysts, bases, solvents, concentrations, and reaction temperatures (Table 4.1).



Entry	[M]	Base (equiv.)	T/ °C	Solvent	Yield[a] 553	er[b]
1	**A**	KOH (2.0)	85	No solvent	63	82:18
2	**A**	KOH (2.0)	85	PhMe (1.0 M)	51	82:18
3	**B**[c]	KOH (2.0)	85	PhMe (1.0 M)	20	77:23
4	**C**	KOH (2.0)	85	PhMe (1.0 M)	41	81:19
5	**D**	KOH (2.0)	85	PhMe (1.0 M)	–[d]	–[d]
6	**E**[e]	KOH (2.0)	85	PhMe (1.0 M)	–[f]	–[f]
7	**A**	KOH (2.0)	110	No solvent	62	65:35
8	**A**	KOH (2.0)	65	No solvent	49	88:12
9	**A**	KO*t*Bu (2.0)	85	No solvent	18	90:10
10	**A**	NaO*t*Bu (2.0)	85	No solvent	10	96:4
11	**A**	NaO*t*Bu (1.0)	85	No solvent	42	95:5
12	**A**	NaO*t*Bu (0.5)	85	No solvent	63	92:8
13	**A**	NaO*t*Bu (0.2)	85	No solvent	60	89:11
14	**A**	NaOH (0.5)	85	No solvent	63	90:10
15	**A**	LiOH (0.5)	85	No solvent	NR	NR
16	**A**	Cs_2CO_3 (0.5)	85	No solvent	NR	NR
17	**A**	NaO*t*Bu (0.5)	85	*t*BuOH (0.5 M)	50	92:8
18	**A**	NaO*t*Bu (1.0)	85	*t*BuOH (0.5 M)	39	94:6
19	**A**	NaO*t*Bu (0.5)	85	*t*BuOH (1.0 M)	46	95:5
20	**A**	**NaO*t*Bu (0.5)**	**85**	***t*BuOH (2.5 M)**	**72**	**94:6**

Table 4.1*: Optimisation of reaction conditions between* N*-benzyl-L-prolinol* ***552*** *and Ph* methyl ketone* ***100****.*
[a] Isolated yield. [b] Determined by normal phase HPLC analysis using a chiral stationary phase.
[c] With 4 mol% dppBz. [d] Complex mixture formed. [e] With 8 mol% Me_3NO. [f] No reaction.

Optimisation began using the conditions detailed in the previous section for the hydrogen borrowing alkylation of dibenzylethanolamine **305** with Ph* methyl ketone **100** (Table 4.1, Entry 1). Pleasingly, this resulted in the formation and isolation of the desired product **553** in 63% yield, and with a very promising er of 82:18. Given that these conditions were unusual in that they were solvent free, an unconventional and sometimes disadvantageous setup, it was decided to revisit the use of toluene as a solvent – the same conditions previously used by Donohoe and co-workers for the synthesis of cyclohexanes and β-branched products from Ph* methyl ketone **100**.[30, 33] Despite a slight decrease in yield to 51%, the er remained consistent at 82:18 – suggesting that the use of solvent was not deleterious to the transformation (Table 4.1, Entry 2). Disappointingly, when the conditions used by Donohoe and co-workers for the formation of α-branched products from Ph* derivatives using $[(cod)IrCl]_2$ **B** were attempted,[29] the yield dropped substantially to only 21% accompanied by a slight reduction in product er to 77:23 (Table 4.1, Entry 3). Inspired by recent advances in the field (detailed in Chapter 1) from the groups of Gunanathan,[109] Renaud,[38] and Leitner,[39] we next surveyed a number of alternative transition metal catalysts (Table 4.1, Entries 4-6). Whilst Ru-MACHO **C** gave the desired product **553** in a poor 41% yield and acceptable 81:19 er, Mn-MACHO **D** resulted in only decomposition – with iron-based piano-stool complex **E** giving only unreacted starting materials.

With the solvent-free conditions of Entry 1 still proving most efficacious, we next investigated the role of temperature in the reaction (Table 4.1, Entries 7 and 8). Increasing the reaction temperature from 85 °C to 110 °C resulted in a very similar isolated yield of 62% – however the product er greatly decreased to 65:35. We postulated that this was a result of the sterically unfavourable deprotonation becoming more viable at elevated temperatures – a hypothesis supported by the fact that when the reaction was conducted at 65 °C, er increased to 88:12. Unfortunately, this came with the caveat of **553** being isolated in only 49% yield – and as such, a reaction temperature of 85 °C was used for future experiments.

The next variable to be investigated was the nature of the base. It was hypothesised that the degree of product racemisation might be decreased by the use of a bulkier base making the key deprotonation event more difficult. As such, bulky bases KO*t*Bu and NaO*t*Bu were screened – upon which we were delighted to observe an increase in product er to 90:10 and 96:4, respectively (Table 4.1, Entries 9 and 10). Unfortunately, in both cases this gain once again came at the expense of yield – with product **553** being isolated in only 18% and 10% yield respectively. However, it was decided that the high er of 96:4 in the case of NaO*t*Bu was worth pursuing, with this being rewarded by the discovery that a base loading of 0.5 equivalents increased **553** yield to 63% with only a slight decrease in er to 92:8 (Table 4.1, Entries 11 – 13). Before moving on to other variables, the other alkali metal bases NaOH, LiOH, and Cs_2CO_3 were all screened for activity (Table 4.1, Entries 14 – 16). Although NaOH produced a similar result to NaO*t*Bu, the use of either LiOH or Cs_2CO_3 resulted in no product formation, possibly due to neither being a strong enough base to affect the key aldol reaction.

At this point, it was observed that the absence of a solvent was causing issues for the reaction in terms of mixing – with solid base, catalyst, and starting material often failing to become a single phase. As such, it was decided to utilise *t*BuOH as a reaction solvent – the rationale being that some amount was being formed regardless due to protonation of the NaO*t*Bu base, and that the use of *t*BuOH as a solvent had been crucial in prior work by Donohoe and co-workers in the asymmetric synthesis of β-branched and cyclohexane containing Ph* derivatives.[31, 34] We were therefore delighted to find, after a short survey of *t*BuOH concentrations, that the use of a concentrated (2.5 M) solution of *t*BuOH gave the desired product **553** in 72% yield and with 94:6 er (Table 4.1, Entries 17 – 20). Whilst the use of a 2.5 M concentration yielded a slightly lower er than 1.0 M (94:6 rather than 95:5), it was decided that the higher yield (72% rather than 46%) more than compensated for this deficit.

As such, the final optimised conditions for the reaction between 1.0 equivalents of *N*-benzyl-L-prolinol **552** and 1.5 equivalents of Ph* methyl ketone **100** were found to be 2 mol% $[Cp^*IrCl_2]_2$, 0.5 equivalents NaO*t*Bu, and 2.5 M *t*BuOH at 85 °C for 16 h, giving **553** in 72% and with 94:6 er.

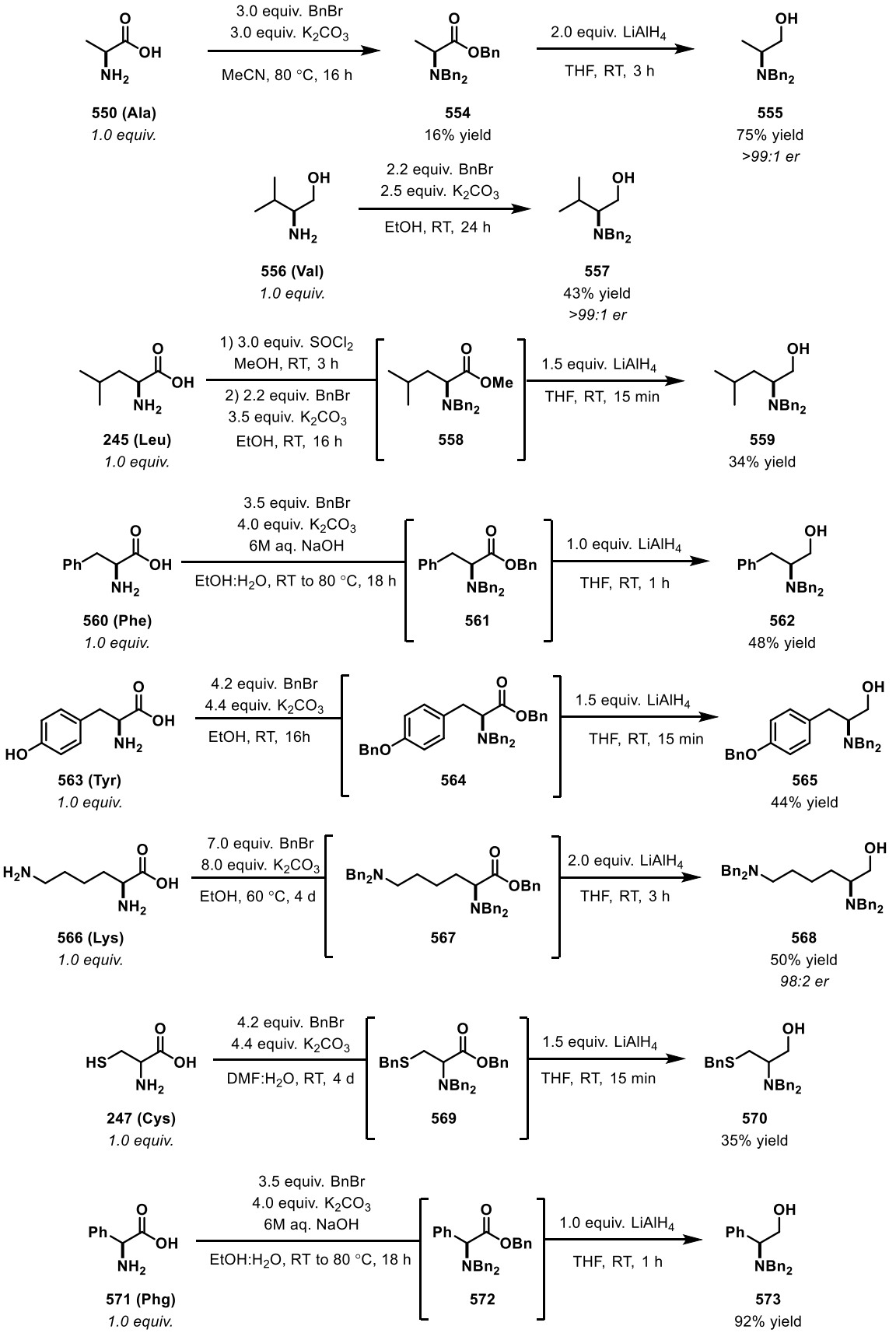
4.3 Results and Discussion: Substrate Synthesis and Scope

4.3.1 *N*,*N*-Dibenzyl 1,2-Amino Alcohols Synthesis

With optimised conditions in hand, our next step was to synthesise a number of suitably protected 1,2-amino alcohols and to subject them to the hydrogen borrowing reaction with Ph* methyl ketone **100**. It was decided to begin with the *N*,*N*-dibenzyl derivatives of a number of simple amino acids – such a protecting group being easy to install and unlikely to have any unwanted reactivity. Accordingly, the *N*,*N*-dibenzyl derivatives of alanine **550**, valinol **556**, leucine **245**, phenylalanine **560**, tyrosine **563**, lysine **566**, cysteine **247,** and the unnatural amino acid phenylglycine **571** were prepared (Scheme 4.8).

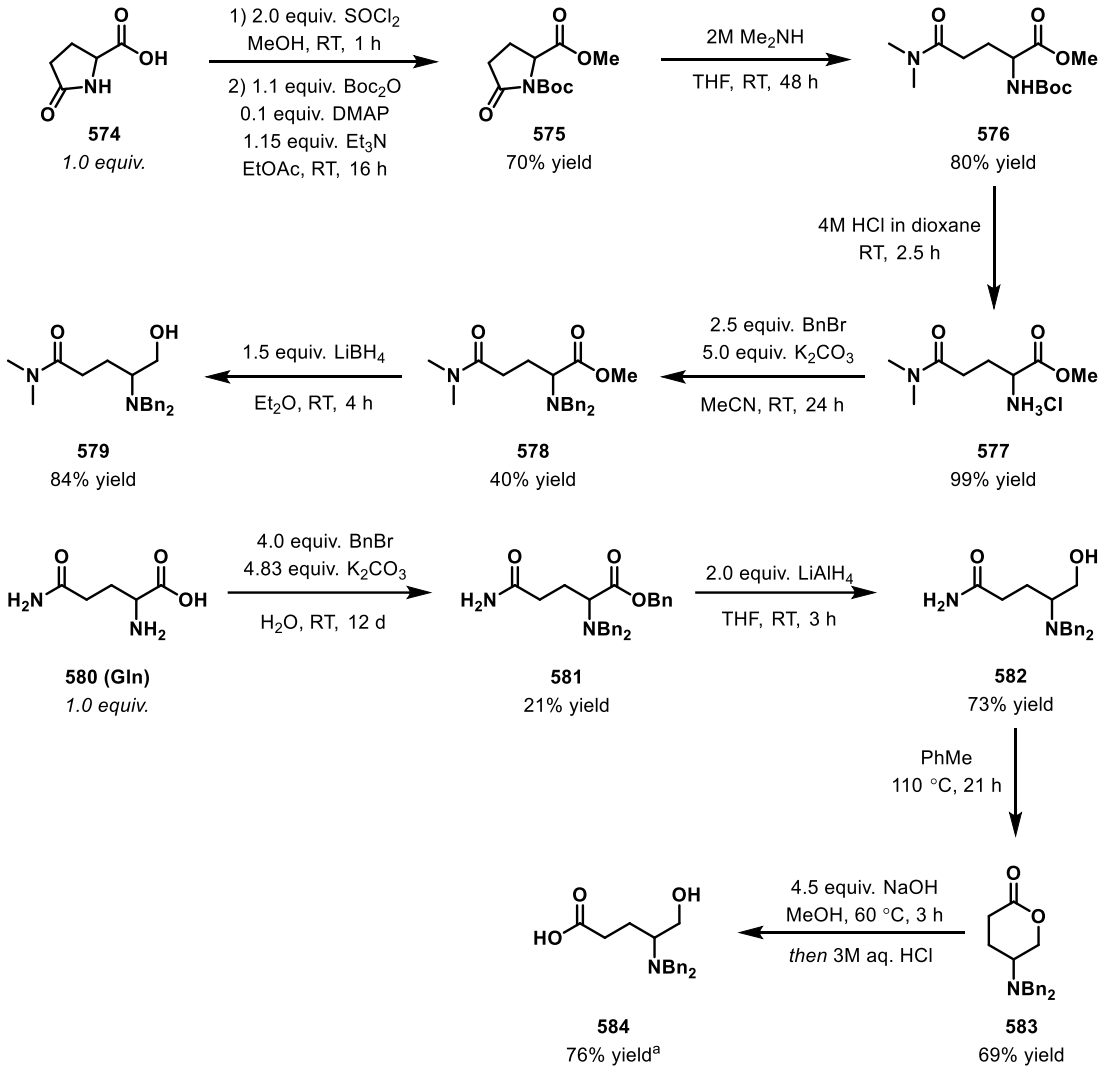
In all cases, the desired 1,2-amino alcohols were readily accessed in a small number of steps in reasonable overall yields. The low yield for benzylation of alanine **550** was attributed to escape of solvent during the reflux, causing precipitation of K_2CO_3 around the flask and as such, insufficient base in the reaction for full conversion. However, the reaction was performed on sufficiently large scale (10 mmol) that enough material was obtained for the subsequent reduction and hydrogen borrowing alkylation. In the case of phenylalanine **560**, tyrosine **563**, lysine **566**, cysteine **247**, and phenylglycine **571**, it was decided not to isolate the intermediate benzyl esters, with the crude mixture being subjected to standard reduction conditions of $LiAlH_4$ in THF – and the desired product being isolated afterwards *via* column chromatography. The formation of *N*,*N*-dibenzyl leucinol **559** was originally attempted using the same procedure *via* formation of the perbenzylated amino acid and subsequent reduction, however chromatographic separation of the product **559** from benzyl alcohol liberated during the $LiAlH_4$ reduction proved problematic, necessitating the use of a methyl ester instead.

In all cases, small amounts of the corresponding racemic samples were prepared alongside in similar yields so as to provide a racemic reference for HPLC analysis after the key hydrogen borrowing alkylation. To ensure no erosion of enantioenrichment had occurred during benzylation and reduction, *N*,*N*-dibenzyl alaninol **555**, valinol **557** and perbenzylated lysinol **568** were analysed by HPLC analysis against their racemic samples, with the products found to still be at high levels of enantioenrichment.



***Scheme 4.8**: Synthesis of* N,N*-dibenzyl protected 1,2-amino alcohols.*

More complicated were the syntheses of the *N*,*N*-dibenzyl derivatives corresponding to glutaminol **579** and glutamic alcohol **584**. In both cases, the presence of another reactive functional group within the amino acid necessitated more convoluted synthetic planning (Scheme 4.9).



***Scheme 4.9**: Syntheses of* N,N*-dibenzyl protected glutaminol **579** and glutamic acid-derived alcohol **584**.*
[a]Isolated with an unidentified, inseparable impurity.

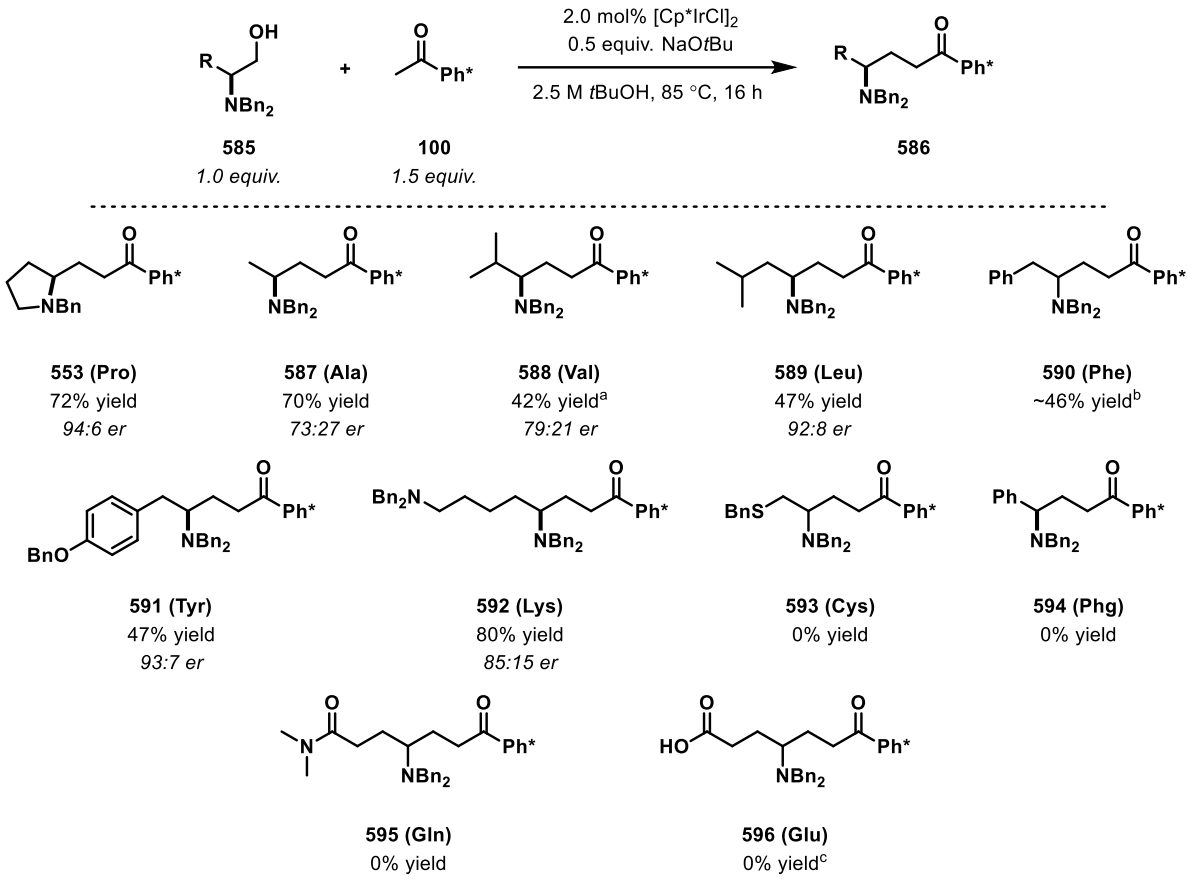
The synthesis of glutaminol **579** began with DL-pyroglutamic acid **574**. Esterification with $SOCl_2$ was immediately followed by Boc protection of the amide nitrogen to give oxopyrrolidine **575** in 70% yield. The newly weakened amide C–N bond was then smoothly cleaved by the addition of **575** to a solution of Me_2NH in THF, with the pure product **576** being isolated by a simple filtration in 80% yield. Cleavage of the Boc group was achieved by the action of 4M HCl in dioxane, giving the desired amine

hydrochloride salt **577** in 99% yield. Benzylation was achieved with the standard combination of BnBr and K_2CO_3, giving methyl ester **578** in 44% yield. In a departure from the norm, reduction of the methyl ester functionality was achieved using a 4M solution of $LiBH_4$ in THF – chosen to avoid the unwanted reduction of the dimethyl amide – with the desired amino alcohol **579** being formed in 84% yield.

Somewhat ironically, glutamine **580** was used as the starting point for glutamic-acid derivative **584**, with tribenzylation being achieved using a particularly sluggish reaction over the course of 12 days, giving perbenzylated product **581** in an extremely disappointing 21% yield. Reduction of the benzyl ester was achieved using $LiAlH_4$, giving alcohol **582** in 73% yield. This was then cyclised under reflux conditions to give cyclic lactone **583** in 69% yield, which was then saponified with NaOH and neutralised to give free carboxylic acid **584** in 76% yield alongside an unidentified, inseparable impurity.

4.3.2 *N*,*N*-Dibenzyl 1,2-Amino Alcohols Scope

With a number of suitably protected 1,2-amino alcohol substrates in hand, we could begin investigating their reactivity with Ph* methyl ketone **100** under the newly optimised hydrogen borrowing conditions (Scheme 4.10). Whilst we were delighted to observe reasonable conversion to products in a number of cases, there was still much to be desired. Alaninol **555** gave the desired product **587** in a very pleasing 70% yield, however the er was much more disheartening at only 73:27 – presumably due to the small methyl group making deprotonation of the stereogenic proton more facile. We were disappointed to observe that valinol **557** showed no reactivity at 85 °C, with the reaction having to be heated to 110 °C in order for product **588** to be formed – albeit in lower yield than for alanine-derivative **587**, but with slightly higher er. We proposed that this was once again due to sterics, with the bulky isopropyl group effectively shielding the central proton from deprotonation – and so increasing the er – but also disfavouring the key aldol condensation and thereby reducing conversion and preventing the reaction from occurring altogether at lower temperatures.

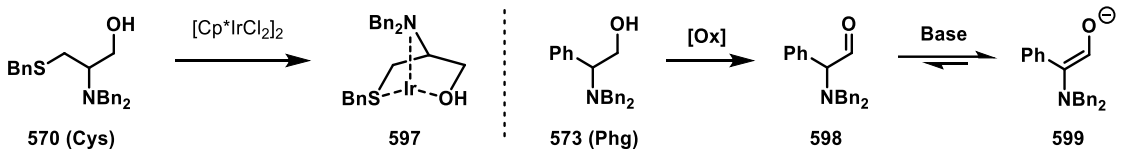


***Scheme 4.10**: Reaction of* N,N-*dibenzyl protected 1,2-amino alcohols under hydrogen borrowing conditions. [a]Reaction conducted at 110 °C. [b]Product inseparable from Ph* methyl ketone **100**, yield estimated from crude ^{1}H NMR. [c]1.5 equivalents of NaOtBu used.*

Whilst the yield of hydrogen borrowing product **589** from leucinol **559** was relatively disappointing, the er of 92:8 was much more encouraging – however improvements could still be made. Unfortunately, whilst a reasonable degree of conversion to the desired product **590** from phenylalaninol **562** was observed by crude ^{1}H NMR, the pure product proved inseparable from Ph* methyl ketone **100** *via* column chromatography despite a number of different solvent systems being attempted. Formation of the corresponding HCl salt *via* treatment with a 2.0 M solution of HCl in Et_2O was also unsuccessful in completely removing Ph* methyl ketone **100** contamination. Fortunately, the *para* –OBn substitution in tyrosinol **565** altered the product polarity enough to allow for isolation of **591** in a moderate 47% yield, but with a very reasonable 93:7 er.

Finally, lysinol **568** gave the desired product **592** in an excellent 80% yield, however this was accompanied by a lower er of 85:15 – this being an intermediate value between the 73:27 er of alanine-

derived product **587** and the 92:8 er of leucine-derived product **589**, suggesting the linear sidechain in lysine is of an intermediate steric bulk between the methyl group of alanine and the isobutyl group of leucine. The only substrates to not show any reactivity were the 1,2-amino alcohols **570** and **573** derived from cysteine and phenylglycine, as well as **579** and **584** derived from glutamine and glutamic acid, respectively. In all cases, only starting material was observed by crude ^{1}H NMR suggesting that either the initial oxidation of the alcohol moiety had failed, or that the catalyst was not being regenerated. It was hypothesised, in the case of cysteinol **570**, that the sulfur atom in the amino acid sidechain could be irreversibly coordinating to the metal catalyst in a tridentate manner along with the amine and hydroxyl moieties, preventing the initial oxidation (Scheme 4.11).



***Scheme 4.11**: Proposed barriers to reaction in cysteinol **570** and phenylglycinol **573**.*

For phenylglycinol **573**, we proposed that whilst there seemed no obvious reason why the initial oxidation would not occur, the then formed aldehyde **598** would be greatly acidified by the presence of the phenyl substituent adjacent to the enolisable proton – shifting the position of equilibrium to favour the unreactive enolate **599** and thereby preventing the desired aldol reaction from occurring. For glutamine and glutamic acid derived alcohols **579** and **584** the reason for their failure to react to form **595** and **596** was less clear – with one hypothesis being that, similar to cysteinol **570**, the heteroatom-bearing sidechain might be helping to coordinate to the metal catalyst, sequestering it and preventing reactivity. However, no further investigations into these two particular substrates were conducted.

With the above results, it was clear that 1,2-amino alcohols were suitable substrates for hydrogen borrowing catalysis – a useful contribution to the field in and of itself – however yields remained variable and, most crucially, the er of the products was still too low (<95:5 er) to be synthetically useful.

Rather than revisit the reaction conditions themselves, it was decided to investigate the role of the nitrogen protecting group, as detailed in the following section.

4.3.3 Investigating the Role of the Nitrogen Protecting Group

Due to the ubiquity of amines within synthetic organic chemistry, as detailed in Chapter 1, there is no shortage of different functional groups detailed in the literature that may be used to protect them from unwanted reactivity.[110] Whilst carbamates such as Boc or Cbz are popular protecting groups, we believed that such groups would be labile under the strongly basic conditions used during hydrogen borrowing and as such they were not pursued. Amides and tosyl protecting groups were also ruled out, on the grounds that both are somewhat electron withdrawing and so would likely hinder the first key oxidation of the alcohol moiety by the metal catalyst – a process that is favoured by electron donating substituents.[111]

Given the fact that simple *N*-benzyl protecting groups had been shown in the previous section to be tolerated under hydrogen borrowing conditions, it was decided to focus on other alkylamine protecting groups – albeit of different steric bulk. We reasoned that as the aforementioned *N*,*N*-dibenzyl amino alcohols featured two benzyl groups, the synthesis of 1,2-amino alcohols featuring the equivalent of either one or three benzyl groups would be instructive. Whilst in principle a monobenzyl nitrogen protecting group could be used, we were of the opinion that the likelihood of unwanted condensation reactions to form iminiums with the intermediate aldehyde was too high, leading to this option being discarded. We instead settled on the chosen protecting groups being *ortho*-xylene (one benzyl) and triphenylmethane (three benzyls), also known as trityl (Figure 4.2).

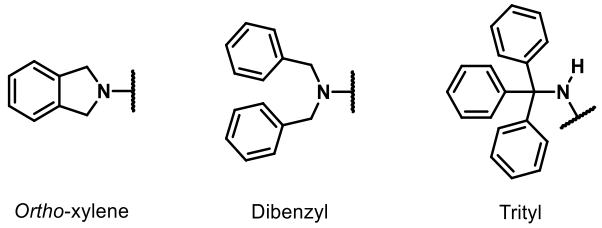
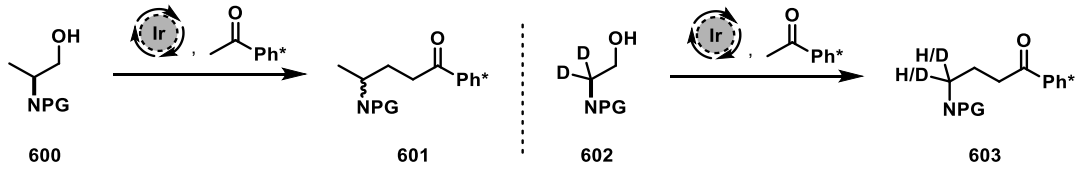


***Figure 4.2**:* Ortho-*xylene, dibenzyl, and triphenylmethane (trityl) nitrogen protecting groups.*

In order to probe the influence of these protecting groups on the degree of intermediate deprotonation, it was decided to synthesise the *N*-protected derivatives corresponding to alaninols **600** and d_2-glycinols **602** and then submit them to our optimised hydrogen borrowing alkylation conditions, with the degree of deprotonation being determined by the extent of product racemisation in the case of alanine derivatives **601** and loss of deuterium in d_2-glycine derivatives **603** (Scheme 4.12).

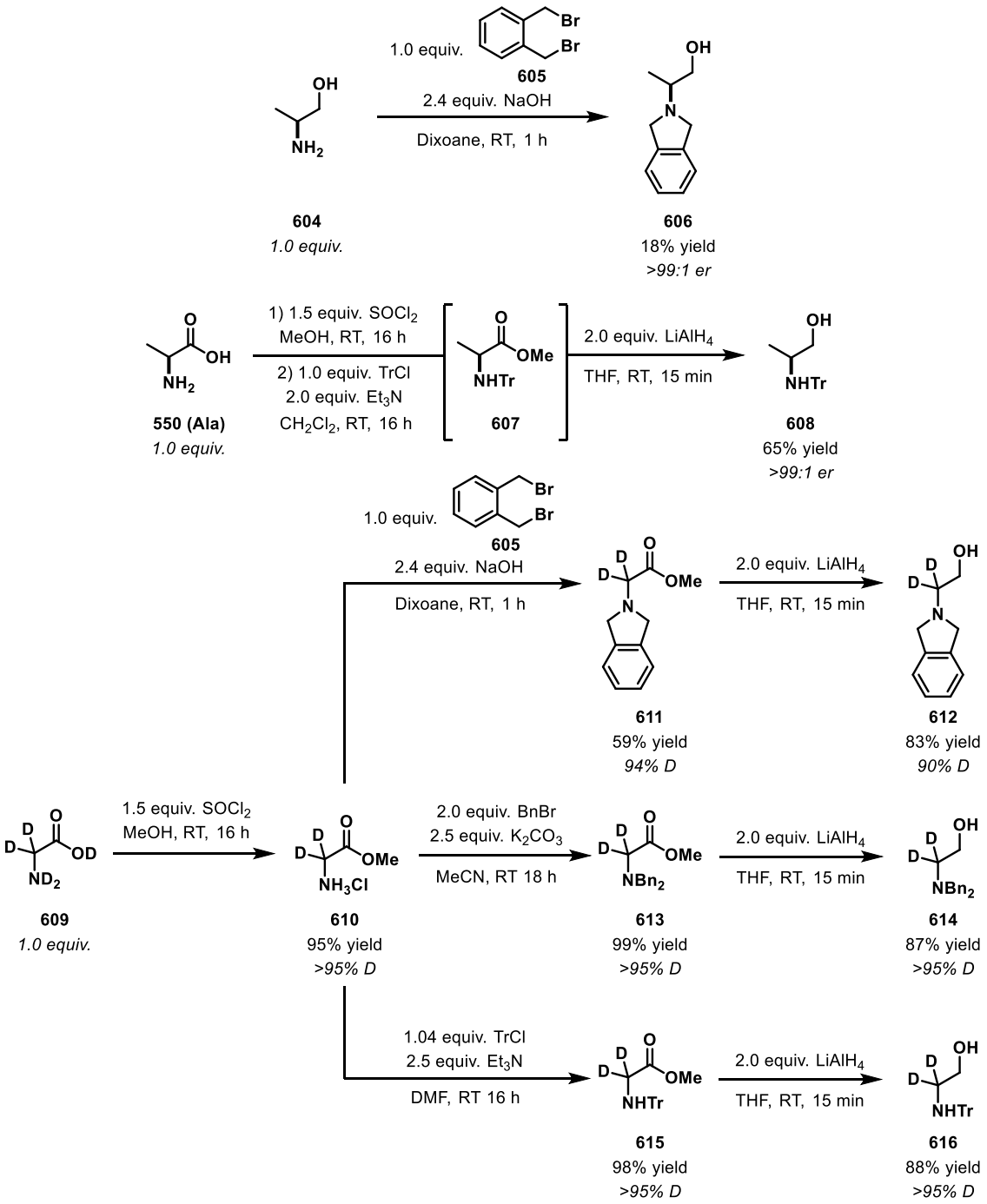


***Scheme 4.12**: Proposed use of alaninols **600** and* d*$_2$-glycinols **602** to probe intermediate deprotonation during hydrogen borrowing reactions of 1,2-amino alcohols.*

Synthesis of the suitably protected amino acids was straightforward. L-Alaninol **604** was treated with 1,2-bis(bromomethyl)benzene **605** to give the desired product **606** in a 18% yield – perhaps reflecting the unfavourable orbital alignment required for the second alkylation step (Scheme 4.13). To ensure no racemisation had occurred during the alkylation, an analytical sample was prepared from DL-alaninol **604**, with subsequent HPLC analysis finding **606** to have an er of >99:1. For the tritylated analogue, alanine **550** was first converted into its corresponding methyl ester hydrochloride *via* standard conditions before then being treated with trityl chloride to give the crude tritylated ester **607**. This was then immediately subjected to reduction with $LiAlH_4$ to give the desired tritylated glycinol **608** in 65% yield over three steps. Once again, preparation of an analytical racemic sample *via* the same route allowed for HPLC analysis to determine the er of **608** to be >99:1.

The synthesis of all three d_2-glycinols began with the formation of d_2-methyl ester hydrochloride **610** from d_5-glycine **609** in 95% yield. In the same manner as alanine-derivative **604**, d_2-ester **610** was treated with 1,2-bis(bromomethyl)benzene **605** to give the desired cyclic product **611** in 59% yield, however this was accompanied by a slight decrease in D-incorporation to 94%, as measured by ^{1}H NMR. Reduction with $LiAlH_4$ gave the desired alcohol **612** in 83% yield, however once again there was a slight decrease in deuterium incorporation to 90% D. Interestingly, both ester **611** and alcohol **612**

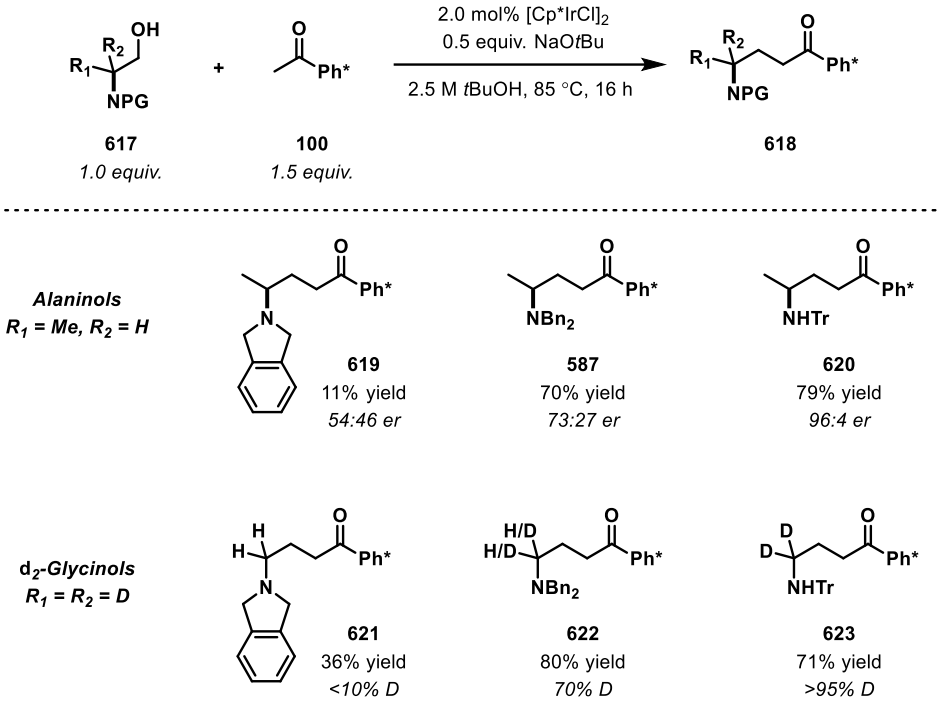
appeared to be somewhat unstable – discolouring over a number of days, even when stored in the freezer, possibly due to oxidation of the isoindolinyl moiety. Benzylation of **610** was straightforward, with the desired product **613** being obtained in 99% yield and with >95% D-incorporation.



***Scheme 4.13**: Synthesis of protected alaninols and d_2-glycinols.*

Reduction to d_2-alcohol **614** proceeded smoothly in 87% yield, again with no decrease in substrate deuteration. Finally, tritylation of d_2-ester **610** was conducted using standard tritylation conditions to give **615** in 98% yield and with >95% D-incorporation, followed by a $LiAlH_4$ reduction to give d_2-alcohol **616** in 88% yield and >95% D-incorporation.

With all six amino acid/protecting group substrate permutations in hand, we set about evaluating their performance under our optimised hydrogen borrowing conditions (Scheme 4.14).



***Scheme 4.14**: Hydrogen borrowing reactions of protected alaninols and* d_2*-glycinols with Ph* methyl ketone **100**.*

To our delight, a clear trend was observed between protecting group steric bulk and retention of enantioenrichment/deuterium incorporation. In both cases, the *ortho*-xylene (the equivalent of one benzyl group) protected amino alcohols **606** and **612** fared extremely poorly – with alanine-derivative **619** being formed in only 11% yield and with 54:46 er, and d_2-glycine-derivative **621** being obtained in a slightly better 36% yield, but with an almost complete loss of deuterium incorporation. Dibenzyl protected d_2-glycinol **614** produced a similar result to the previously discussed alaninol **555**, giving the desired product **622** in 80% yield and with 70% deuterium incorporation – reflecting an intermediate

degree of deprotonation during the reaction. Emerging as the clear victor was the use of a trityl protecting group – with tritylated alanine-derivative **620** being formed in 79% yield and a very pleasing 96:4 er, and d_2-glycine-derivative **623** being formed in 71% yield and with no decrease in deuteration.

The success of the trityl group in preventing deprotonation of the neighbouring acidic proton came as no surprise to us when seen in the light of its extensive historical use in preventing the epimerisation of peptides during coupling reactions.[112, 113] Whilst the main disadvantage of the trityl group is its impact on atom economy due to its large molecular weight of 243 Da, we believed that this was more than offset by its numerous advantages, namely: (i) prevention of epimerization; (ii) low cost and toxicity of the TrCl precursor; (iii) ease of removal with either mild acid or hydrogenolysis.[110] As such, we next set about synthesising a number of trityl protected 1,2-amino alcohols with the hope of boosting the levels of enantioretention over the previously discussed dibenzyl variants.

4.3.4 *N*-Trityl 1,2-Amino Alcohols Synthesis

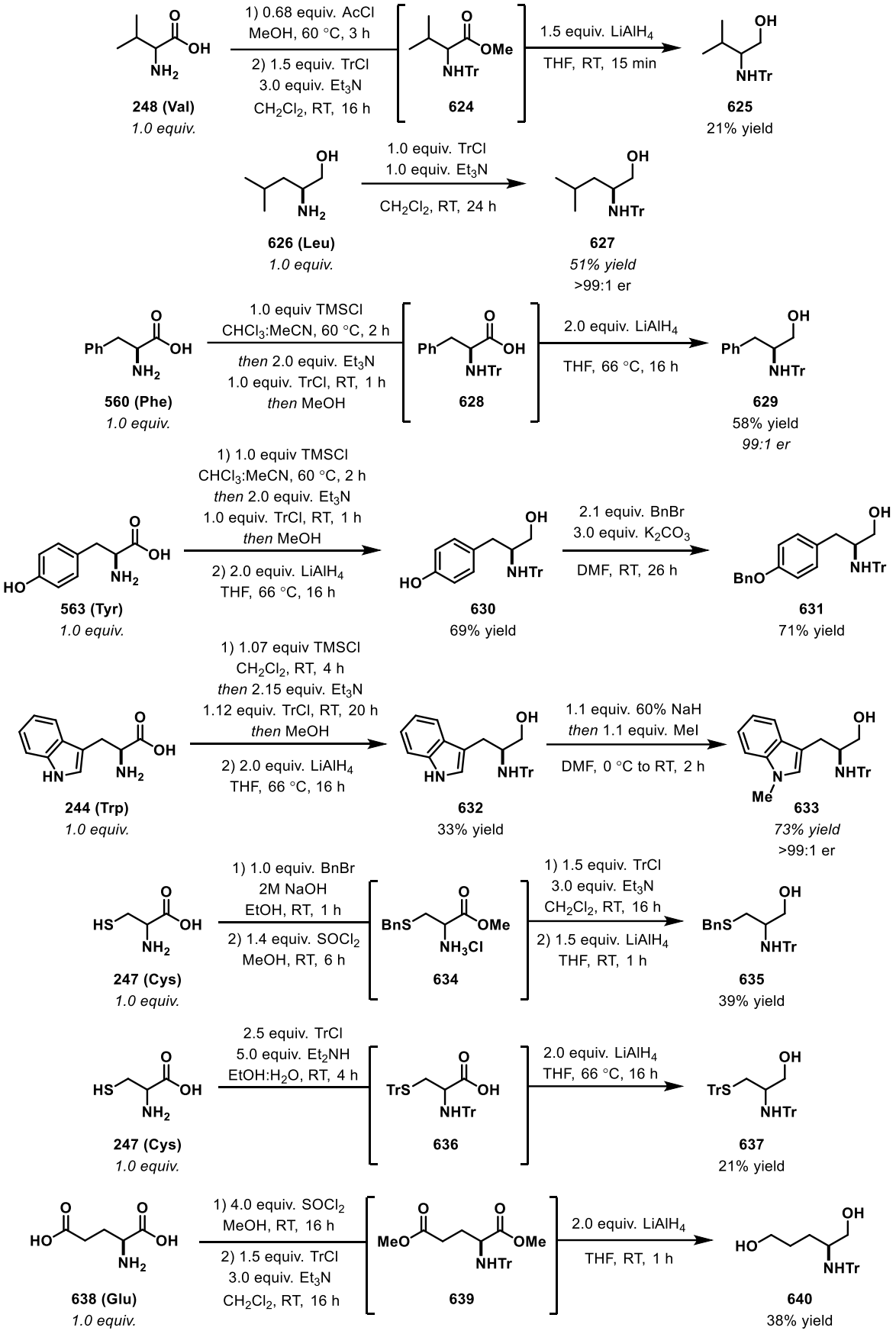
In a similar manner to the synthesis of the dibenzyl derivatives, the route to most of the trityl protected 1,2-amino alcohols consisted of tritylation of either the starting amino acid or the corresponding methyl ester hydrochloride, followed by reduction of the crude mixture to obtain the protected 1,2-amino alcohols (Scheme 4.15 and 4.16).

Starting with DL-valine **248**, esterification using acetyl chloride in methanol furnished the corresponding methyl ester hydrochloride which was then immediately tritylated using standard tritylation conditions to give crude **624**. Reduction with $LiAlH_4$ then gave amino alcohol **625** in a slightly disappointing 21% yield over three steps – possibly reflecting the difficulties involved with installing the bulky trityl group next to an already sterically congested centre. Next, leucinol **626** was readily converted into its tritylated analogue **627** in 51% yield and in 99:1 er, as measured by HPLC analysis against a racemic sample prepared by the same route.

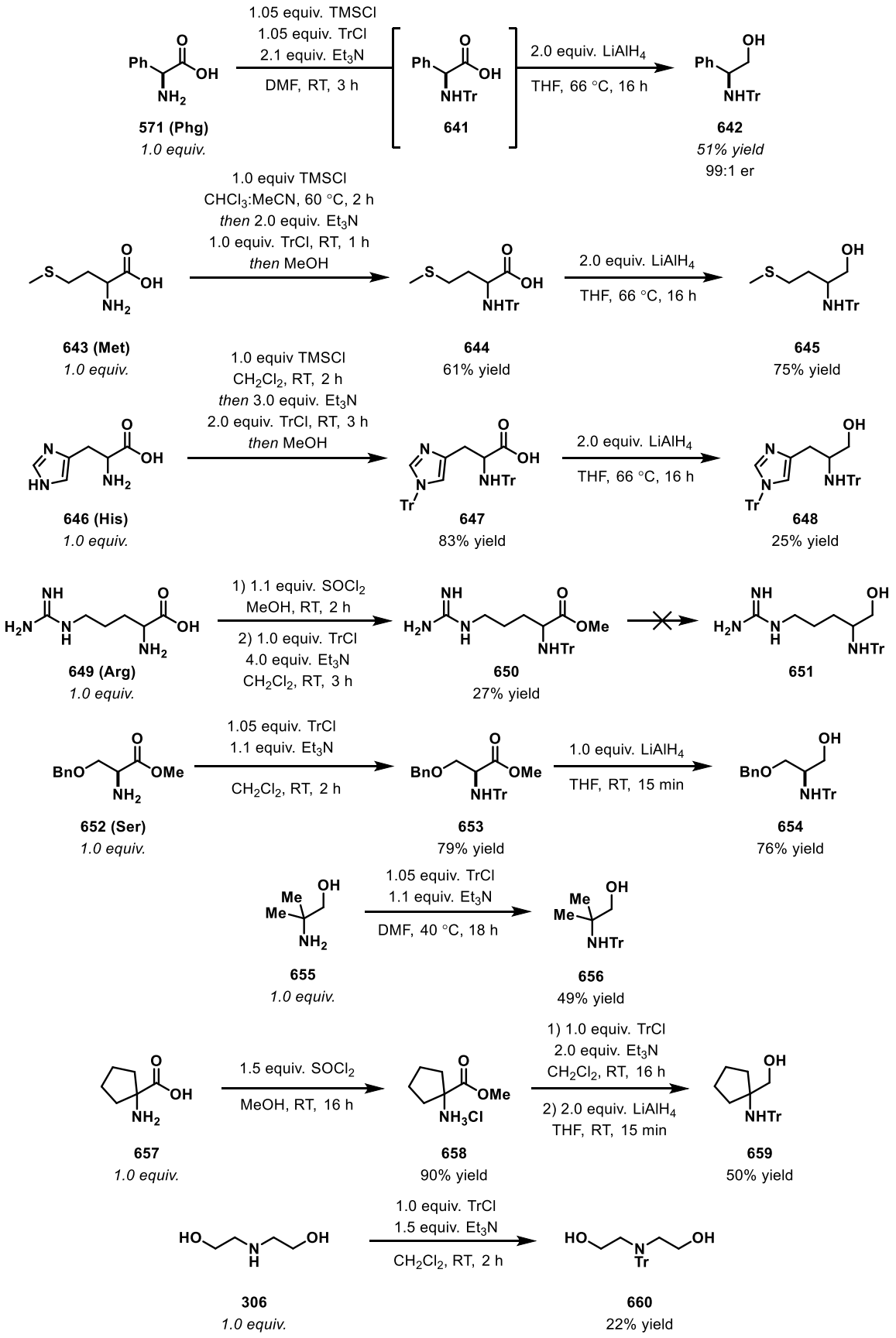
Rather than initially form a methyl ester, and then perform the tritylation, phenylalanine **560** was treated with trimethylsilyl chloride to form the TMS ester *in situ* before then performing the tritylation in the same pot with the usual combination of TrCl and Et_3N. The addition of MeOH at the end of the reaction served to cleave the TMS ester back to the free carboxylic acid **628**, which was then submitted to reduction with $LiAlH_4$ without further purification to give protected amino alcohol **629** in 58% overall yield and 99:1 er. Tyrosine **563** was also treated with the same initial tritylation conditions to give a crude carboxylic acid which was then immediately reduced with $LiAlH_4$ and purified to give alcohol **630** in 69% yield. Benzylation of the free phenolic oxygen gave the desired alcohol **631** in 71% yield.

Tryptophan **244** was also initially tritylated *via* the use of a transient TMS ester, however the conditions used were slightly different – with CH_2Cl_2 as the solvent as opposed to a mixture of $CHCl_3$ and MeCN. The resulting crude acid was then reduced with $LiAlH_4$ to give alcohol **632** in 33% yield. The free indole N–H was then protected using the sequential addition of NaH and MeI, giving the desired alcohol **633** in 74% yield and with >99:1 er. DL-cysteine **247** was initially treated with 1.0 equivalents of BnBr to protect the free thiol sidechain, before then forming the methyl ester hydrochloride **634** with $SOCl_2$. The crude hydrochloride **634** was then tritylated and subsequently reduced with $LiAlH_4$ to give amino alcohol **635** in 39% over four steps. In addition to the SBn protected variant, it was decided to also synthesise the STr protected amino alcohol. Therefore, DL-Cysteine **247** was treated with an excess of TrCl in the presence of Et_2NH to give crude amino acid **636**, this then immediately being reduced with $LiAlH_4$ to give the desired di-trityl 1,2-amino alcohol **637** in 21% yield over two steps.

Rather than try and differentiate between the two carboxylic acids in glutamic acid **638**, as had been unsuccessfully attempted with dibenzyl amino alcohol **584**, it was decided to reduce both and investigate the reactivity of the resulting diol under our hydrogen borrowing conditions. As such, glutamic acid **638** was treated with $SOCl_2$ to form the crude di-methyl ester hydrochloride which was tritylated under standard conditions to give crude **639**. Reduction of both methyl esters with $LiAlH_4$ afforded the desired diol **640** in 38% yield.



***Scheme 4.15**: Synthesis of* N*-trityl protected 1,2-amino alcohols.*



***Scheme 4.16**: Synthesis of* N*-trityl protected 1,2-amino alcohols.*

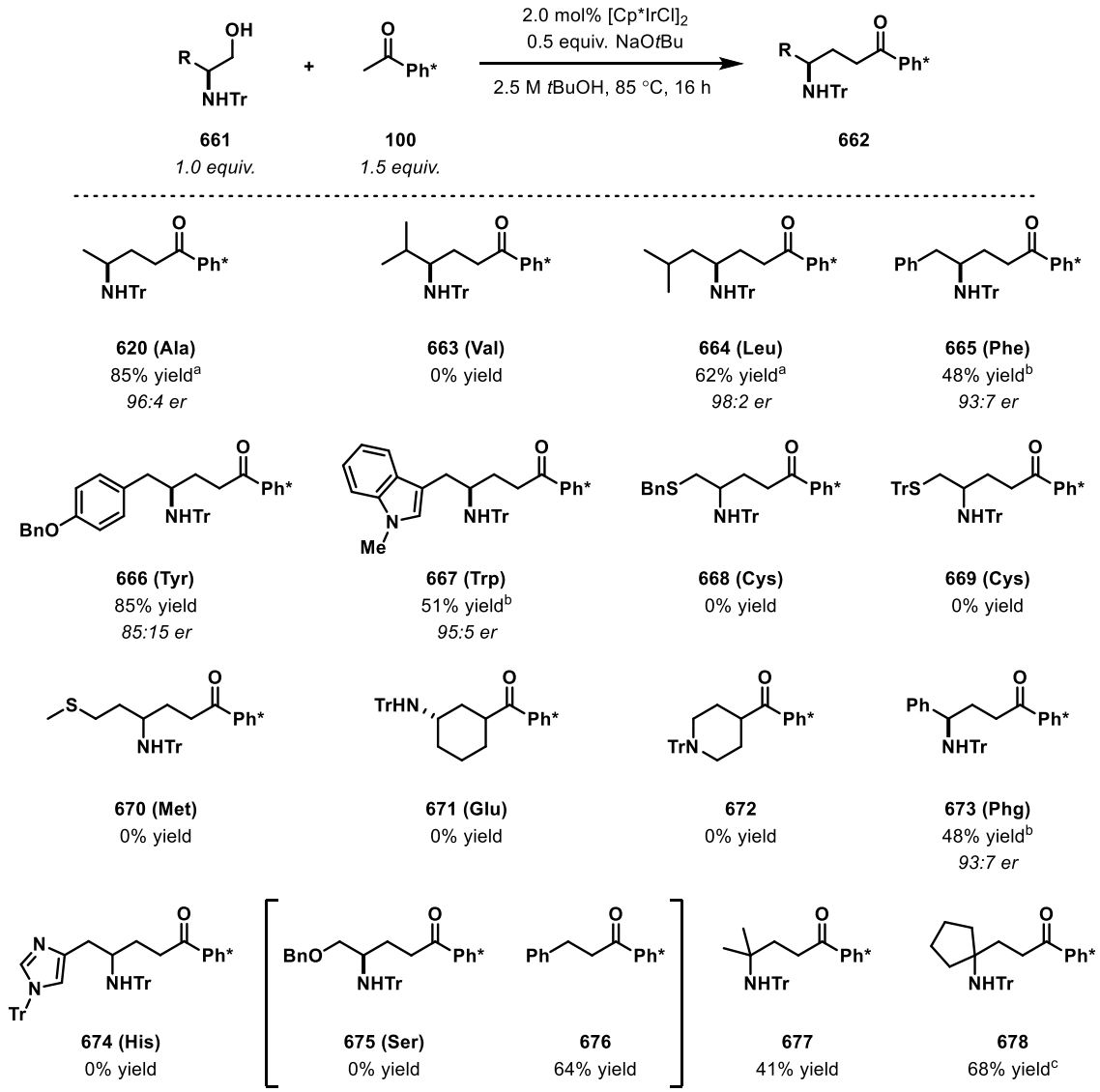
Despite the lack of reactivity as its *N*,*N*-dibenzyl derivative, it was decided to synthesise the *N*-trityl variant of unnatural amino acid phenylglycine **571**. A transient TMS ester was once again used for the initial tritylation, with the O–Si bond being cleaved by the addition of 3M aqueous HCl in the work-up, rather than by the addition of MeOH. The crude tritylated product **641** was then reduced with $LiAlH_4$ to give the desired amino alcohol **642** in 51% yield and with a very encouraging 99:1 er.

Another sulfur containing amino acid, methionine **643**, was also trityl protected using typical procedures with a 61% yield for the tritylation and 75% yield for the subsequent reduction of the carboxylic acid with $LiAlH_4$ to alcohol **645**. Next was the 1,2-amino alcohol corresponding to DL-histidine **646** – with the imidazole sidechain also being protected with a trityl group in 83% yield, followed by a surprisingly low yielding reduction to alcohol **648**. Guanidine containing amino acid arginine **649** was first treated with $SOCl_2$ in MeOH to form the methyl ester dihydrochloride which was immediately subjected to tritylation conditions to form **650** in 27% yield. A number of reducing agents ($NaBH_4$, $LiBH_4$, and $LiAlH_4$) were screened in an attempt to reduce the methyl ester to the desired alcohol **651**, however this proved unsuccessful in all cases and the endeavour was abandoned. The final natural amino acid to be tritylated was serine, with commercially available O-benzyl serine methyl ester **652** being tritylated to give **653** in 79% yield. Reduction of the methyl ester gave **654** in 76% yield.

Next to be synthesised were the *N*-trityl 1,2-amino alcohols derived from unnatural quaternary amino acids dimethyl glycinol **656** and cycloleucine **657**. Starting from commercially available 2-amino-2-methylpropanol **655**, tritylation under standard conditions directly gave the desired alcohol **656** in 49% yield. Next, cycloleucine **657** was esterified in 90% yield using $SOCl_2$ before then being subjected to the well-tested combination of tritylation and reduction to give cyclopentane containing amino alcohol **659** in 50% yield over two steps. The final tritylated amino alcohol to be synthesised was diol **660** in one step from diethanolamine **306** in 22% yield. Whilst not strictly corresponding to a natural or unnatural amino acid, it was hoped that **660** might form a cyclohexane product in a similar manner to diol **640** derived from glutamic acid **638**.

4.3.5 *N*-Trityl Protected 1,2-Amino Alcohols Scope

With a large number of *N*-trityl protected 1,2-amino alcohols in hand, we set about evaluating their reactivity under the optimised hydrogen borrowing conditions (Scheme 4.17).



***Scheme 4.17**: Reaction of* N*-trityl protected 1,2-amino alcohols under hydrogen borrowing conditions. [a]Reaction conducted on a gram scale. [b]Reaction conducted at 110 °C. [c]Reaction conducted using 1.0 equiv. **100** and 2.0 equiv. **659**.*

Following on from the aforementioned success of trityl protected alaninol **608**, we were disappointed to discover that tritylated valinol **625** failed to form the desired product **663** either at 85 °C or 110 °C. This was attributed to the combination of the isopropyl sidechain and the bulky trityl group making either the initial alcohol oxidation or the subsequent aldol condensation too sterically congested to

occur. Much more encouraging, however, was the reaction of tritylated leucinol **627** to form hydrogen borrowing product **664** in 62% yield and 98:2 er – a marked increase from its dibenzyl analogue **589**, formed in 47% yield and 92:8 er. Along with alaninol **608**, the reaction of leucinol **627** was conducted on a gram scale (4.0 mmol of starting alcohol) with no decrease in yield or er – demonstrating the robustness of the reaction. Phenylalaninol **629** also yielded good results, with the switch from dibenzyl to trityl proving enough to allow for purification *via* column chromatography, resulting in the isolation of pure product **665** in 48% yield and 93:7 er – although an elevated reaction temperature of 110 °C was required for the reaction to proceed. Tyrosinol **631** provided an intriguing result, with the corresponding hydrogen borrowing product **666** being isolated in an excellent 85% yield, but with only 85:15 er – somewhat lower than the 93:7 er observed for dibenzyl protected tyrosine product **591**.

Tryptophanol **633** also required an elevated reaction temperature to proceed, giving the desired product **667** in 51% yield and with 95:5 er – the moderate yield being more than offset by the complexity of the substrate having no match within the prior hydrogen borrowing literature. Sadly, all three sulfur containing amino alcohols **635**, **637**, and **645** failed to give any of the desired products **668**, **669**, and **670**. In all cases, only unreacted starting material was observed, even upon increasing the reaction temperature to 110 °C. Another failure was observed in the case of diol **640** derived from glutamic acid and diol **660** derived from diethanolamine – both of which resulted in decomposition of the starting material and no trace of the desired product, even when repeated with an extra equivalent of NaO*t*Bu to account for the need to perform a second hydrogen borrowing alkylation.

In contrast, we were surprised – but delighted – to see the formation of hydrogen borrowing product **673** in 48% yield and with a remarkable 93:7 er. As discussed earlier, we had anticipated that the presence of the phenyl ring would serve to acidify the vulnerable proton of the stereogenic centre to the point that deprotonation was extremely facile upon oxidation of the alcohol moiety in **642** to aldehyde **679**. The formation of product **673**, and the extremely high level of enantioretention observed, suggested to us that the steric bulk of the trityl group must be greatly disfavouring

intermediate deprotonation – possibly by preventing the aryl π-system from adopting the necessary conformation to overlap with and acidify the C–H σ* (Figure 4.3).

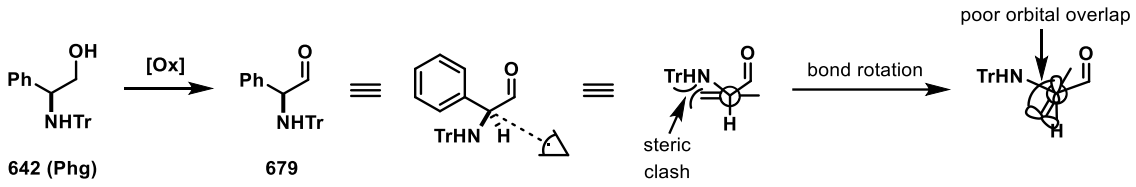
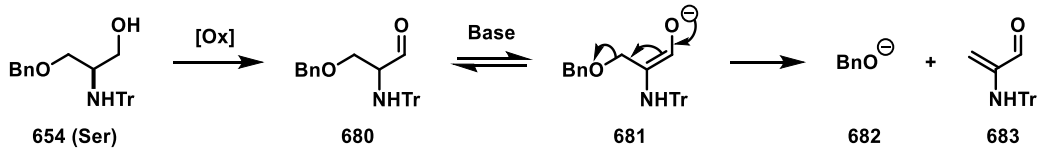


***Figure 4.3**: Proposed steric influence of the* N*-trityl group in phenylglycinol **642**-derived aldehyde **679**.*

Sadly, ditrityl protected histidinol **648** also failed to give its corresponding product **674**, although this was attributed to solubility issues of the starting alcohol – a white powder that failed to dissolve in the reaction mixture even after 16 hours. *N*-Trityl-*O*-benzyl serinol **654** did react, albeit in a wholly unexpected manner. Rather than form the direct hydrogen borrowing product **675**, we instead observed the formation of literature known compound **676** – the result of a hydrogen borrowing reaction between benzyl alcohol **59** and Ph* methyl ketone **100**. We hypothesised that benzyl alcohol **59** was being formed during the reaction *via* an E1cB-type elimination of benzyloxide **682** from amino aldehyde **680** – with the key deprotonation possibly being made more facile by a favourable overlap of the C–H σ orbital with the C–OBn σ* (Scheme 4.18).



***Scheme 4.18**: Formation of benzyloxide **681** from decomposition of serinol **654**.*

Finally, we were pleased to see that both dimethyl glycinol **656** and cycloleucinol **659** reacted to form the desired products **677** and **678** in 41% and 68% yield, respectively. In the case of cycloleucinol **659**, the standard reaction conditions were observed to lead to a large amount of the unreduced enone intermediate which could not be separated from **678** – to prevent this, the reaction stoichiometry was changed to feature a twofold excess of **659** relative to Ph* methyl ketone **100**, thereby creating a more reducing environment and allowing for isolation of the desired product **659** in good yield. It is also

worth highlighting that the classical equivalents of the 1,2-amino alcohols **656** and **659** would be neopentyl halides **684** and **685** – both unlikely to be suitable for use for alkylations due to the issues associated with 1,2-amino halides detailed earlier in this chapter, such as formation of aziridiniums, as well as the steric hindrance about the C–X σ* making the alkylation reaction extremely sluggish (Figure 4.4).



684 **685**

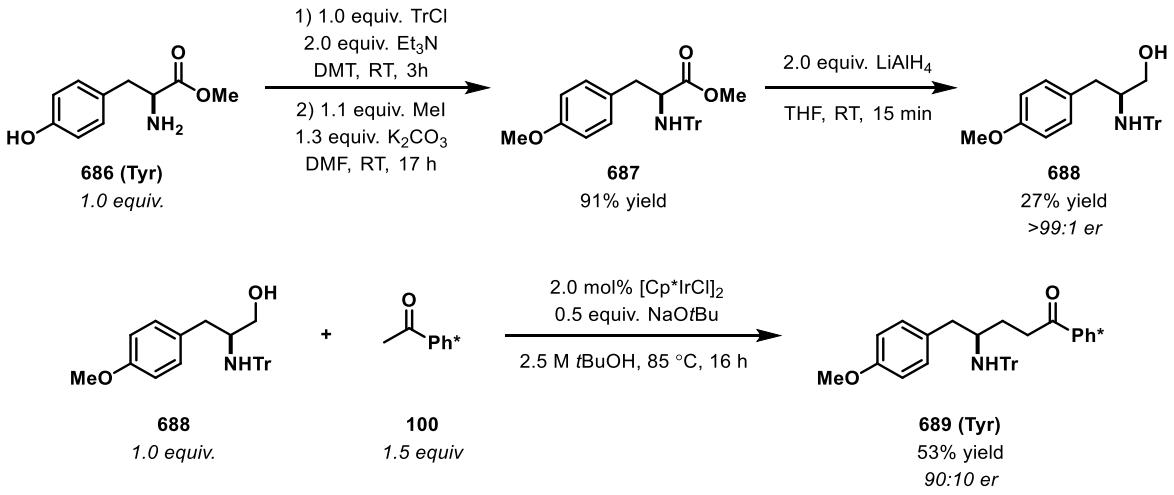
Figure 4.4*: Classical 1,2-amino halide equivalents of 1,2-amino alcohols* ***684*** *and* ***685****.*

With the above success of the *N*-trityl group in expanding our substrate scope to a number of natural and unnatural amino alcohols, we decided to revisit a small number of unsatisfactory/unreactive substrates in the hope of overcoming barriers to reactivity.

4.3.6 Additional *N*-Trityl Substrate Synthesis and Scope

The first amino acid to be revisited was tyrosine, as the decrease in er in going from *N*,*N*-dibenzyl derivative **591** to *N*-trityl derivative 6**66** was still unexplained – an opposite trend to that observed in the amino alcohols derived from alanine and leucine. We hypothesised that a possible cause for this inconsistency may be variable solubility of one or both of the tyrosinol derivatives **565** and **631** in the reaction mixture. To probe this, we decided to synthesise amino alcohol **688** – with the phenolic oxygen protected by a methyl rather than benzyl group (Scheme 4.19).

Tritylation of the commercially available tyrosine methyl ester **686** was achieved using standard tritylation conditions in >99% yield. Methylation of the phenolic oxygen was then achieved using MeI to give ester **687** in an excellent 91% yield. Reduction with $LiAlH_4$ gave the desired amino alcohol **688** in 27% yield and >99:1, as measured by HPLC analysis. Interestingly, a trityl containing side product was detected by crude ^1H NMR in significant quantities after the reduction, but not identified.

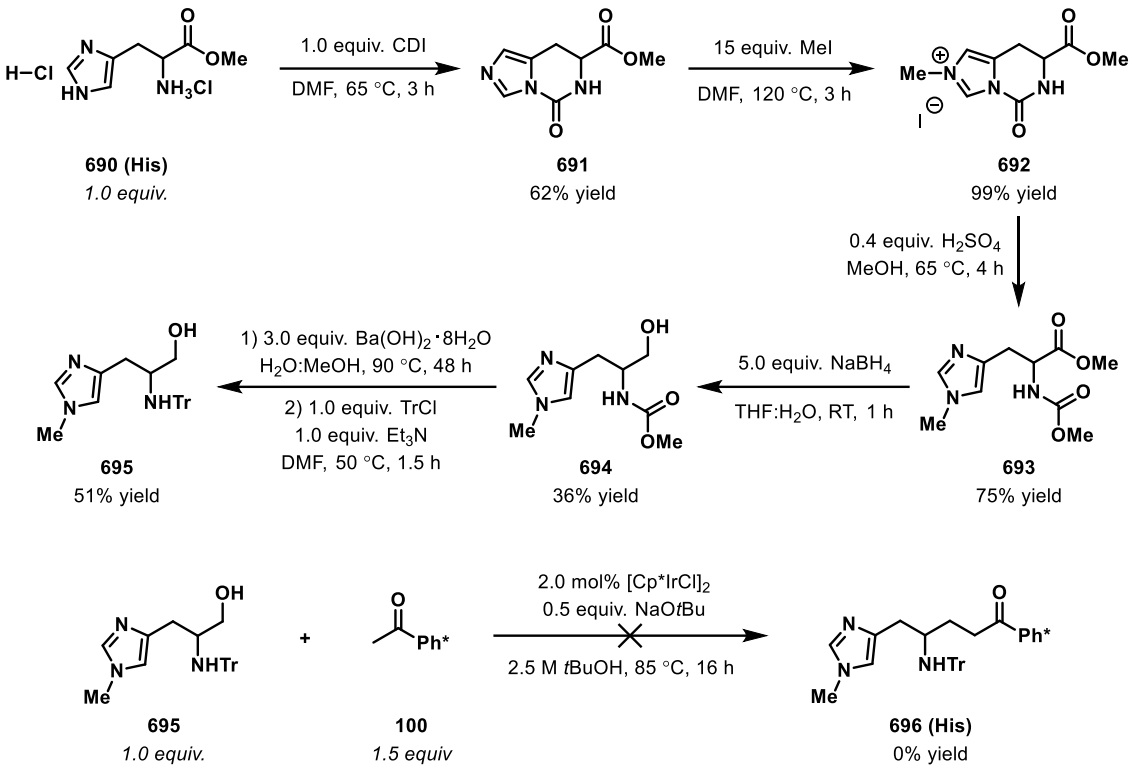


***Scheme 4.19**: Synthesis and reactivity of methylated* N-*trityl tyrosinol **688**.*

With tyrosinol **688** in hand, we were able to subject it to our hydrogen borrowing conditions to obtain product **689** in 53% yield and with a slightly improved 90:10 er – although this was still lower than the 93:7 er observed in *N*,*N*-dibenzyl hydrogen borrowing product **591**. The origins of these differences in er remained unclear, with time constraints preventing us from synthesising the corresponding methyl protected *N*,*N*-dibenzyl tyrosinol substrate – however the notable influence of what appeared to be a distant functional group on the er of the reaction suggested to us that more effects were at work in determining the outcome of the reaction than just sterics.

Another amino acid to be revisited was histidine – with the original ditrityl histidinol **648** suffering from visible solubility issues. As such, it was decided to replace the imidazole trityl protecting group with a methyl group – however this resulted in a much more convoluted synthetic route (Scheme 4.20).

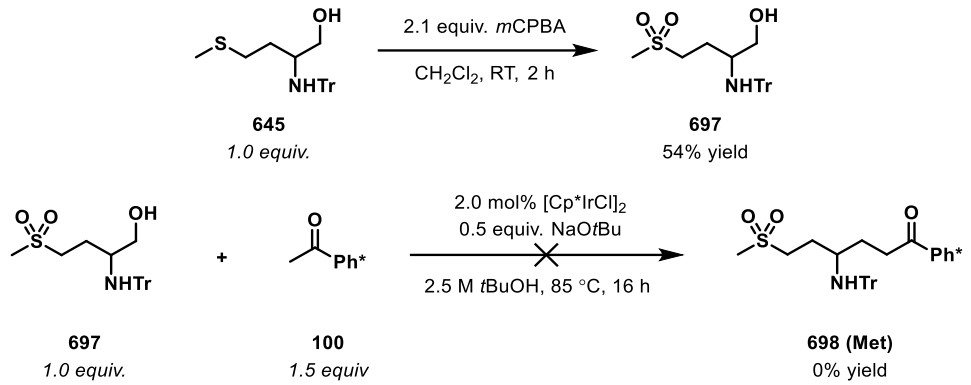
Starting from commercially available DL-histidine methyl ester dihydrochloride **690**, treatment with 1.0 equivalents of CDI resulted in the formation of cyclic compound **691** in 62% yield. Iodide salt **692** was then formed in quantitative yield *via* the treatment of **691** with excess MeI. The cyclic urea functionality was then cleaved by MeOH in the presence of catalytic sulfuric acid to give **693** in 75% yield.



***Scheme 4.20**: Synthesis and reactivity of methylated* N*-trityl histidinol **695**.*

Reduction of the methyl ester was achieved with $NaBH_4$ to give **694** in 36% yield, followed by cleavage of the methyl carbamate utilising the somewhat unusual conditions of $Ba(OH)_2$ in refluxing MeOH:H_2O to give a crude amino alcohol which was immediately tritylated to give amino alcohol **695** in 51% yield over two steps. Unfortunately, all the above proved for naught when histidinol **695** was treated with the optimised hydrogen borrowing conditions, with none of the desired product **696** being formed and only starting material being detected.

The failure of methianinol **645** to form the desired product **670** was particularly intriguing, considering thiothers have previously been shown by Donohoe and co-workers to be tolerated under hydrogen borrowing conditions.[34] Given that our working hypothesis for the failure of sulfur containing amino alcohols under our hydrogen borrowing conditions was coordination of sulfur to the iridium catalyst, it was decided to oxidise the thioether in **645** to the corresponding sulfone – a much less effective functional group for ligation (Scheme 4.21).



***Scheme 4.21**: Synthesis and reactivity of N-trityl methianinol sulfone **697**.*

Oxidation of the thioether in **645** was readily achieved using a slight excess of *m*CPBA, giving the desired sulfone **697** in 54% yield. However, once again upon subjection to hydrogen borrowing conditions, none of the desired product **698** was formed and only starting material was recovered. In light of this result, we decided to abandon any further attempts to synthesise sulfur containing 1,2-amino alcohols and instead revisit the oxygen containing amino acid, serine **551**, along with its slightly more complex analogue, threonine **700**.

4.3.7 Synthesis and Scope of Cyclic Serine, Threonine, and Cysteine Derivatives

As detailed above, *O*-benzyl protected serinol **654** had already been synthesised and found to decompose under our hydrogen borrowing conditions – releasing benzyl alcohol **59**, which in turn led to unexpected hydrogen borrowing product **676**. Inspired by our original success with prolinol **552**, we wondered whether serine **551** and threonine **700** could be protected as five-membered hemiaminal ethers **699** and **701**, respectively (Figure 4.5).

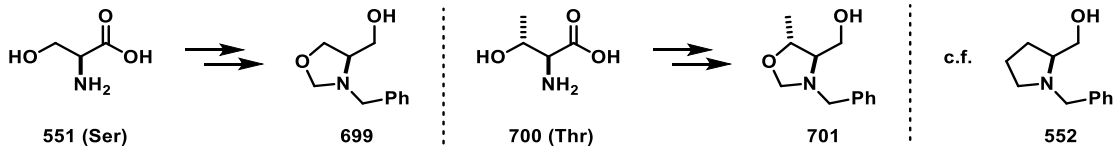
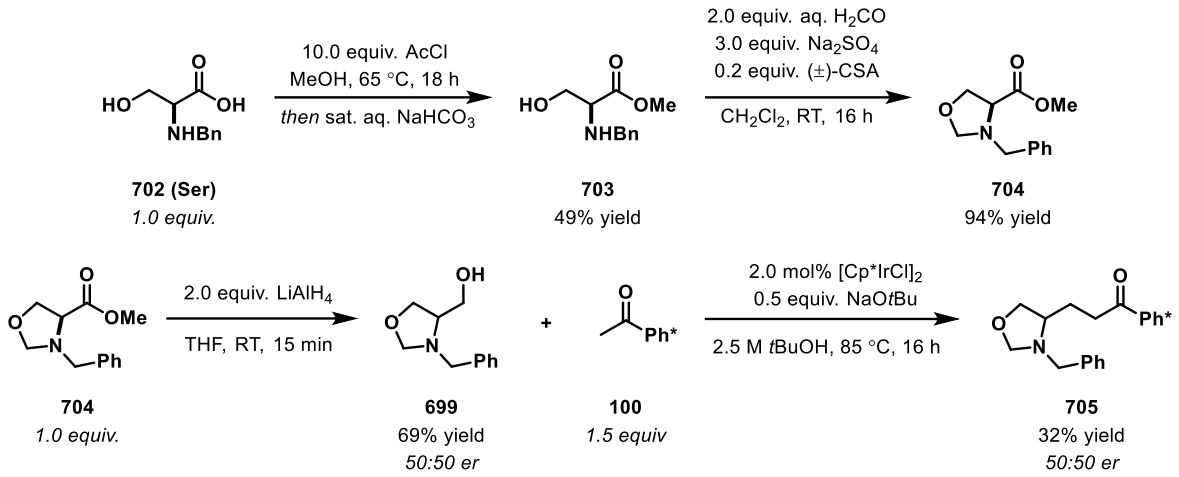


***Figure 4.5**: Proposed protection of serine **551** and threonine **700** as hemiaminal ethers **699** and **701**.*

Starting with commercially available *N*-benzyl-L-serine **702**, formation of the methyl ester hydrochloride was achieved using AcCl in MeOH, followed by neutralisation of the reaction mixture to liberate the free amine **703** in 49% yield (Scheme 4.22).



***Scheme 4.22**: Synthesis and reactivity of cyclic serinol **699**.*

Formation of the methylene bridge was achieved using conditions disclosed by Overman in his synthesis of (–)-pancracine,[114] with the desired cyclic product **704** being isolated in excellent yield. Finally, reduction with $LiAlH_4$ afforded the desired alcohol **705** in 69% yield. Upon subjection of alcohol **699** to our hydrogen borrowing conditions, the desired product **705** was isolated in a somewhat disappointing 32% yield and was – to our great surprise – completely racemic by HPLC analysis, despite starting the substrate synthesis with a single enantiomer of **702**. At this point, the er of the starting alcohol **699** had yet to be checked – in all prior cases there had been no erosion in alcohol enantioenrichment during substrate synthesis, and the same was assumed to have been true for serinol **699**. Intriguingly, HPLC analysis showed alcohol **699** to not only be racemic, but for the two enantiomeric forms to be interconverting on the HPLC timescale, producing what is known as a "batman" plot (Figure 4.6).

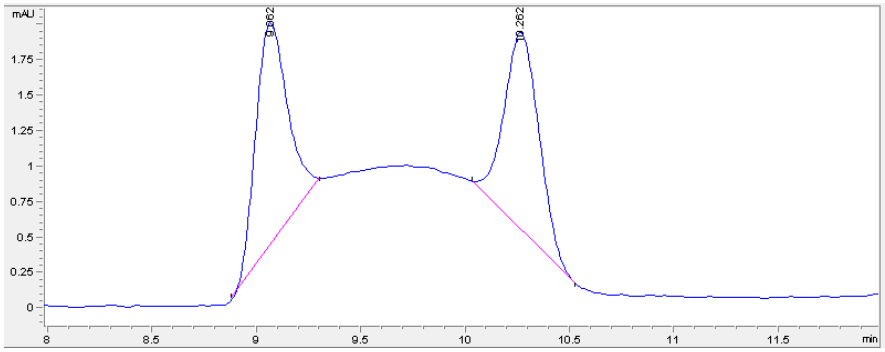
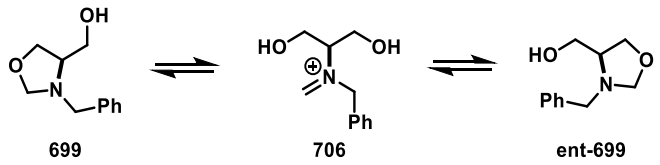


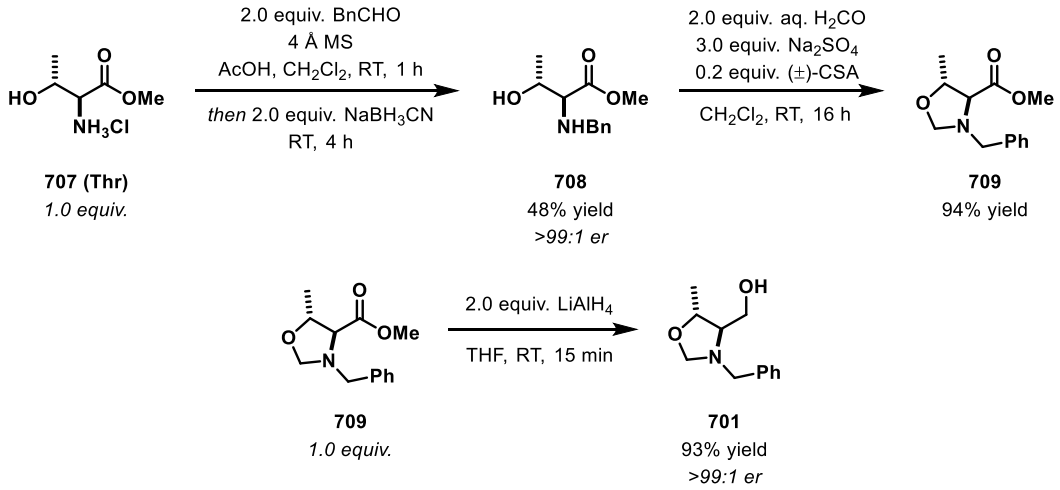
***Figure 4.6**: HPLC trace of cyclic serinol **699** showing a characteristic "batman" plot.*

Analysis kindly conducted by Dr Roly Armstrong found the half-life of racemisation to be 2.9 minutes, precluding any attempt to resynthesise **699** and submit it to our hydrogen borrowing conditions before it had time to racemise. Mechanistically, we proposed that the racemisation of **699** was occurring via an equilibrium with achiral intermediate **706** – which may close using either hydroxyl group to form either **699** or its enantiomer **ent-699** (Scheme 4.23).



***Scheme 4.23**: Mechanism for racemisation of alcohol **699** via achiral intermediate **706**.*

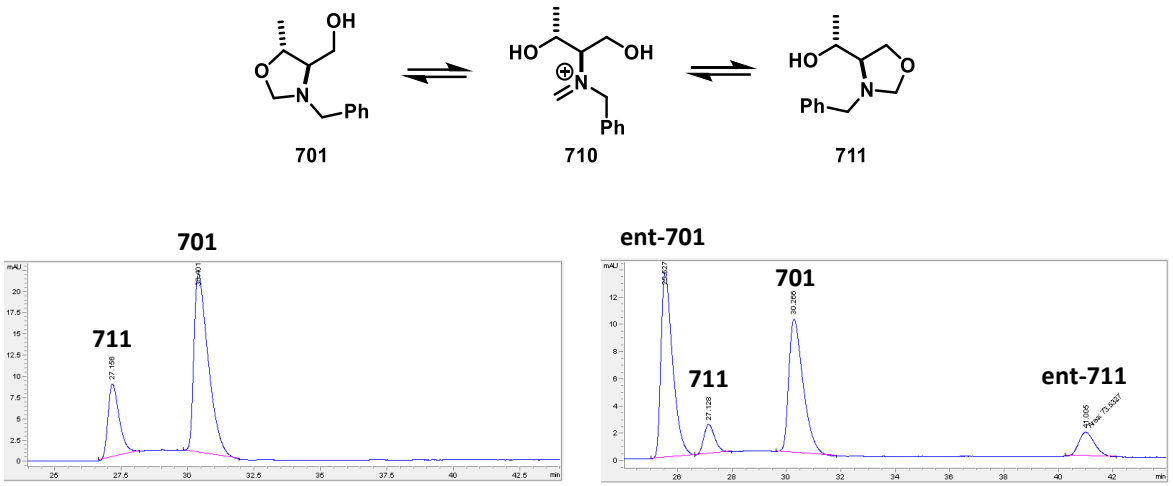
The synthesis of the threonine analogue of **699** began using a reductive amination of commercially available L-threonine methyl ester hydrochloride **707** with benzaldehyde to selectively install a single benzyl group, giving the desired product **708** in 48% yield and with >99:1 er by HPLC analysis when measured against a racemic sample (Scheme 4.24).



***Scheme 4.24**: Synthesis of cyclic threoninol **701**.*

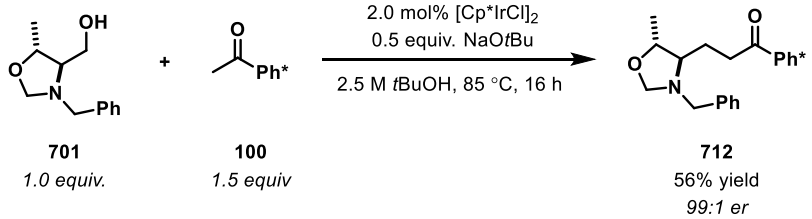
The next two steps were identical to that used in the synthesis of serinol **699**, with the methylene bridge being formed in 94% yield, followed by a final $LiAlH_4$ reduction of **709** to give the desired cyclic threoninol **701** in 93% yield. Similarly to serinol **699**, HPLC analysis of threoninol **701** revealed two interconverting peaks of different sizes – in contrast to serinol **699**, threoninol **701** was in equilibrium

with its structural isomer **711**, not its enantiomer **ent-701**, with one side of the equilibrium being favoured over the other (Scheme 4.25).



***Scheme 4.25**: Interconverting equilibrium and HPLC trace of cyclic threoninol **701** (left) and **rac-701** (right). Note: **701** is assumed to be the major species by HPLC, as it is in CD_2Cl_2 for NMR, but cannot be proven as such.*

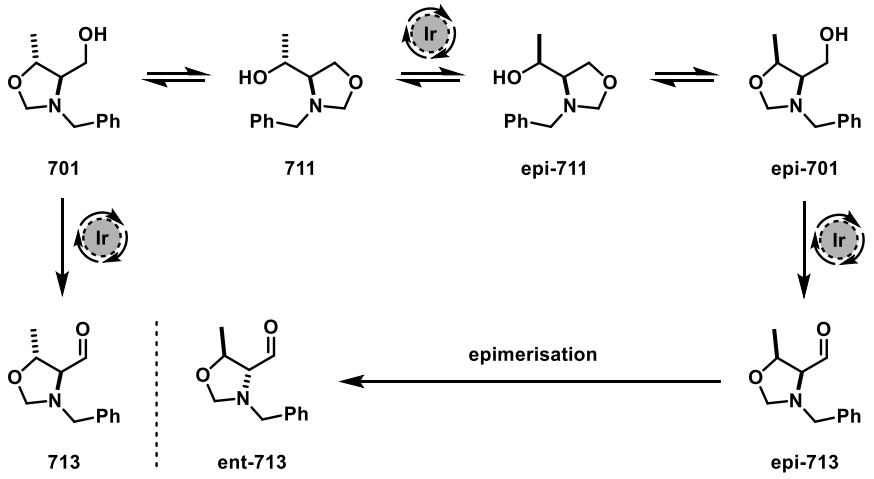
In order to confirm the above, a racemic sample of threoninol **701** was prepared using an identical route and also subjected to HPLC analysis – the resulting spectrum having four peaks, two aligned with **701** and its structural isomer **711**, and two corresponding to **ent-701** and its structural isomer **ent-711**. The presence of isomer **711** was also detectable *via* NMR, with threoninol **701** and **711** existing in a 4:1 ratio in CD_2Cl_2. Mostly importantly, however, was that threoninol **701** remained enantiopure, with the HPLC trace in Scheme 4.24 showing it to have an er of >99:1. We were therefore excited to submit it to our optimised hydrogen borrowing conditions to see whether this enantioenrichment was retained (Scheme 4.26).



***Scheme 4.26**: Hydrogen borrowing reaction of cyclic threoninol derivative **701**.*

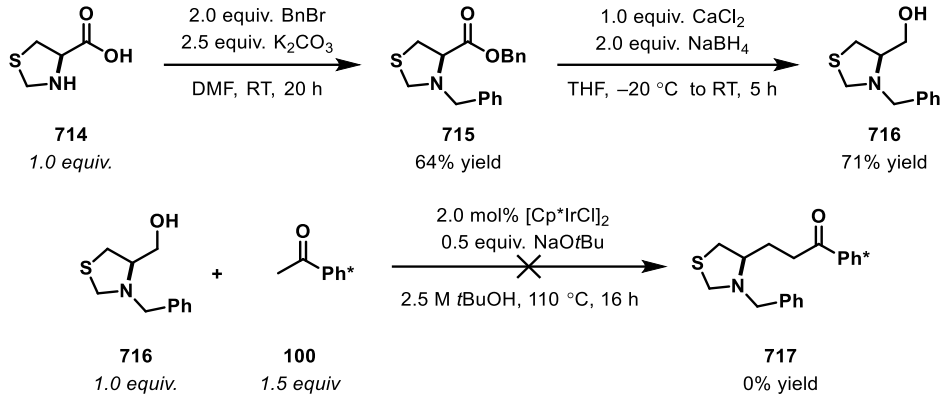
Gratifyingly, the desired hydrogen borrowing product **712** was obtained in an acceptable 56% yield, but as a single diastereomer with an excellent 99:1 er. It is worth noting that in this case, due to the

presence of a secondary chiral centre, deprotonation of the aldehyde intermediate would lead to the formation of a diastereomer, not an enantiomer, of the product **712**. That this did not occur suggested to us that the additional methyl substituent on the ring was either disfavouring intermediate deprotonation, or sterically favouring the formation of the *trans* substitution pattern observed in the product **712**. The small amount of ent-**712** formed during the reaction was proposed to arise *via* a small amount of **701** undergoing a metal catalyst mediated oxidation/reduction sequence to give **epi-711**. Equilibration in the same manner as **701** and **711** then gives **epi-701**, which undergoes oxidation to give the corresponding aldehyde **epi-713**. A final epimerisation of this aldehyde intermediate then occurs to give the favourable *trans* ring substitution pattern in aldehyde **ent-713**, which then goes on to perform the key hydrogen borrowing reaction (Scheme 4.27).



***Scheme 4.27**: Mechanism for the formation of **ent-713**.*

As a final investigation in this area, we elected to synthesise the corresponding cyclic cysteinol analogue of serinol **699** and threoninol **701** to see whether the issue associated with sulfur could be overcome (Scheme 4.28).



***Scheme 4.28**: Synthesis and reactivity of cyclic cysteinol **716**.*

Synthesis of the desired alcohol was straightforward, starting with a literature known benzylation of commercially available thioproline **714** to give benzyl ester **715** in 64% yield. Next, a reduction utilising the *in situ* generation of $Ca(BH_4)_2$ gave the desired cysteinol **716** in 71% yield. To our great disappointment, however, alcohol **716** failed to show any reactivity under our hydrogen borrowing conditions – even when the temperature was raised to 110 °C – bringing an end to our scope of amino alcohols.

4.3.8 Crystallinity and Secondary Alkylation of Hydrogen Borrowing Products

A key benefit of the Ph* group that has been previously identified by Donohoe and co-workers is the tendency of Ph* containing compounds to be crystalline.[31, 34] Crystallinity conveys two key benefits, both of which were taken advantage of by us in this work.

Firstly, crystalline products may be analysed by X-ray crystallography in order to unambiguously determine atomic connectivity and, in the presence of a suitably heavy atom, absolute configuration. Whilst none of our hydrogen borrowing products contained a suitably heavy atom to allow for confirmation of absolute configuration, we were delighted to be able to obtain X-ray crystal structures of the hydrogen borrowing products corresponding to *N*,*N*-dibenzyl glycine **312**, *N*-benzyl proline **553**, *N*,*N*-dibenzyl tyrosine **591**, and *N*-trityl phenylalanine **665** (Figure 4.7).

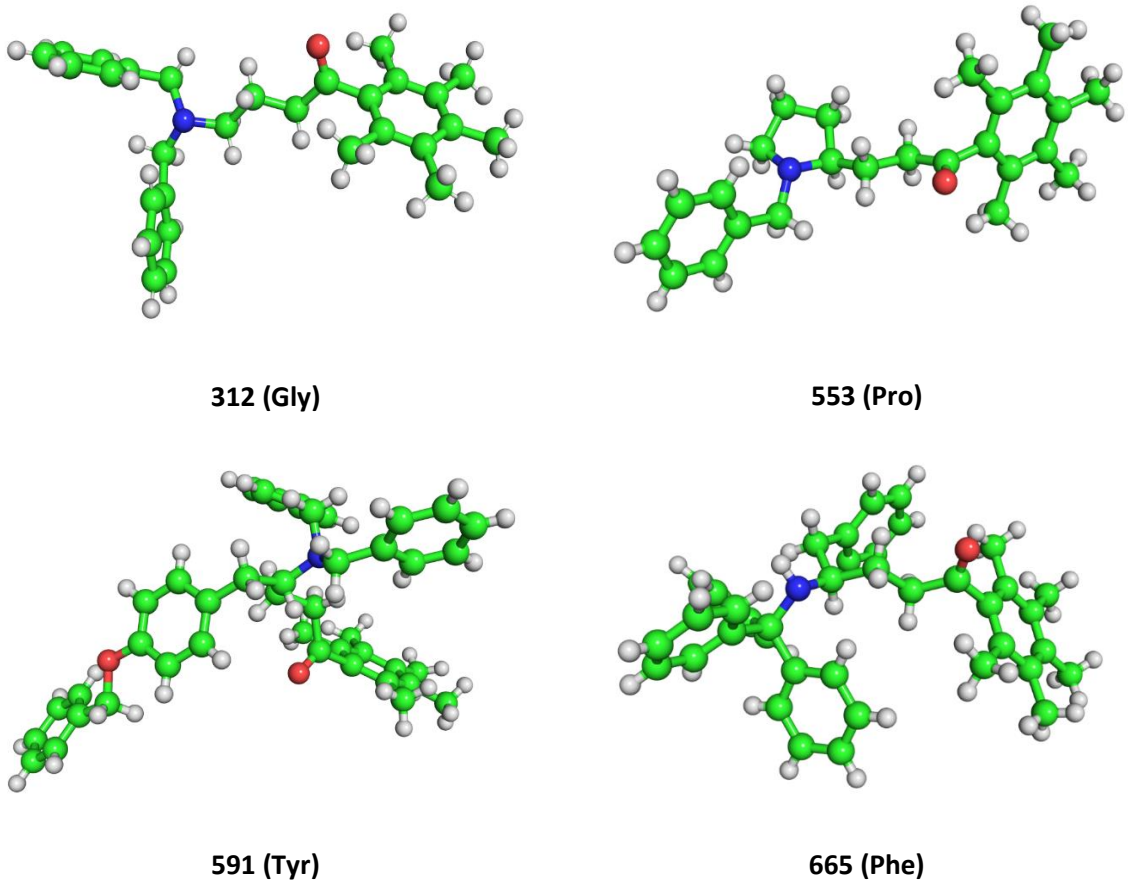
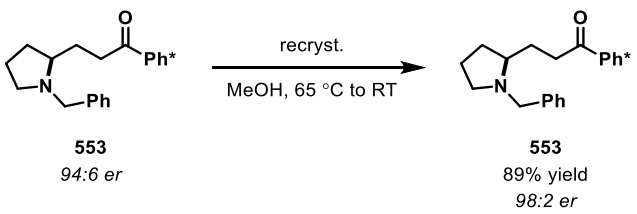


***Figure 4.7**: X-Ray structures of hydrogen borrowing products **312**, **553**, **591**, and **665**. Data collected and analysed by Dr Kirsten E. Christensen.*

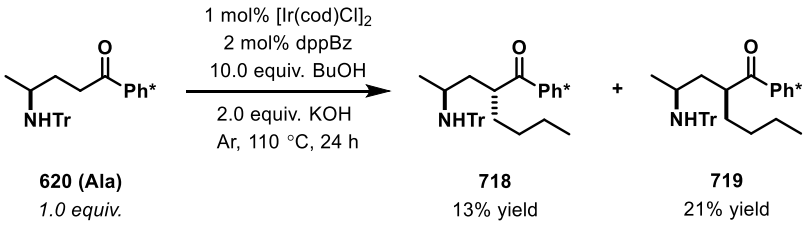
Secondly, scalemic mixtures of crystalline products may have their enantioenrichment enhanced *via* recrystallisation – so long as the compound in question has a tendency to crystallise as homochiral crystals, as is often the case.[115] This was exploited with proline-derived product **553**, with a single recrystallisation from boiling MeOH enhancing the product er from 94:6 to 98:2, with 89% mass recovery (Scheme 4.29).



***Scheme 4.29**: Enhancement of er in hydrogen borrowing product **553** via recrystallisation.*

Before moving onto product deprotection, we decided to investigate whether a secondary hydrogen borrowing alkylation could be performed. Rather than develop new reaction conditions, we decided

to expose alanine-derived product **620** to Donohoe's previously disclosed conditions for the formation of α-branched products using *n*BuOH as the coupling partner (Scheme 4.30).[29]



***Scheme 4.30**: Secondary hydrogen borrowing alkylation of alanine derived product **620**.*

Whilst the overall yield was somewhat disappointing, we were pleased to isolate the two possible product diastereomers **718** and **719** in 13% and 21% yield, respectively. Despite possessing a very similar R_f, product separation was enabled by the use of a finer grade of SiO_2 during column chromatography. Furthermore, although the stereochemistry about the amine stereocentre was known from the starting material, NMR analysis alone was insufficient to determine the relative configuration of each diastereomer. Fortunately, the major product diastereomer **719** proved to be crystalline – allowing for X-ray analysis which showed the carbonyl α-centre to be S (Figure 4.8).

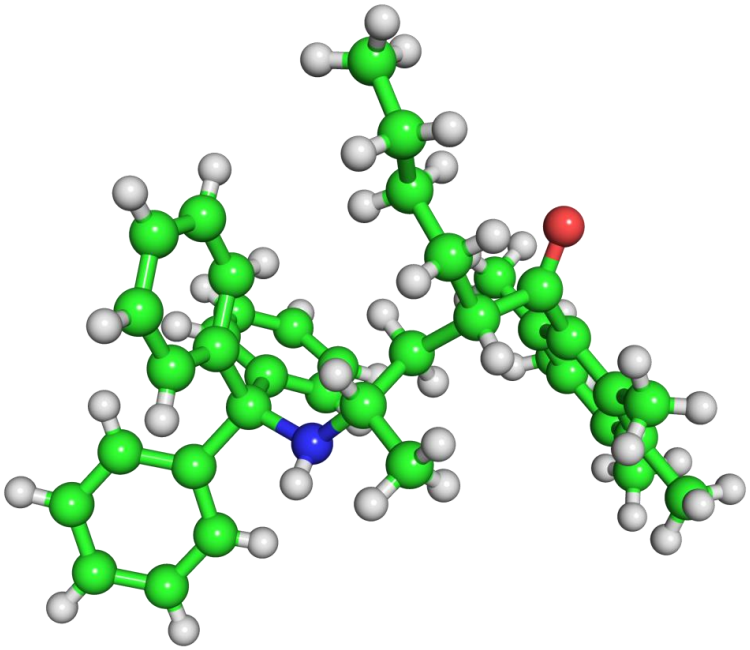
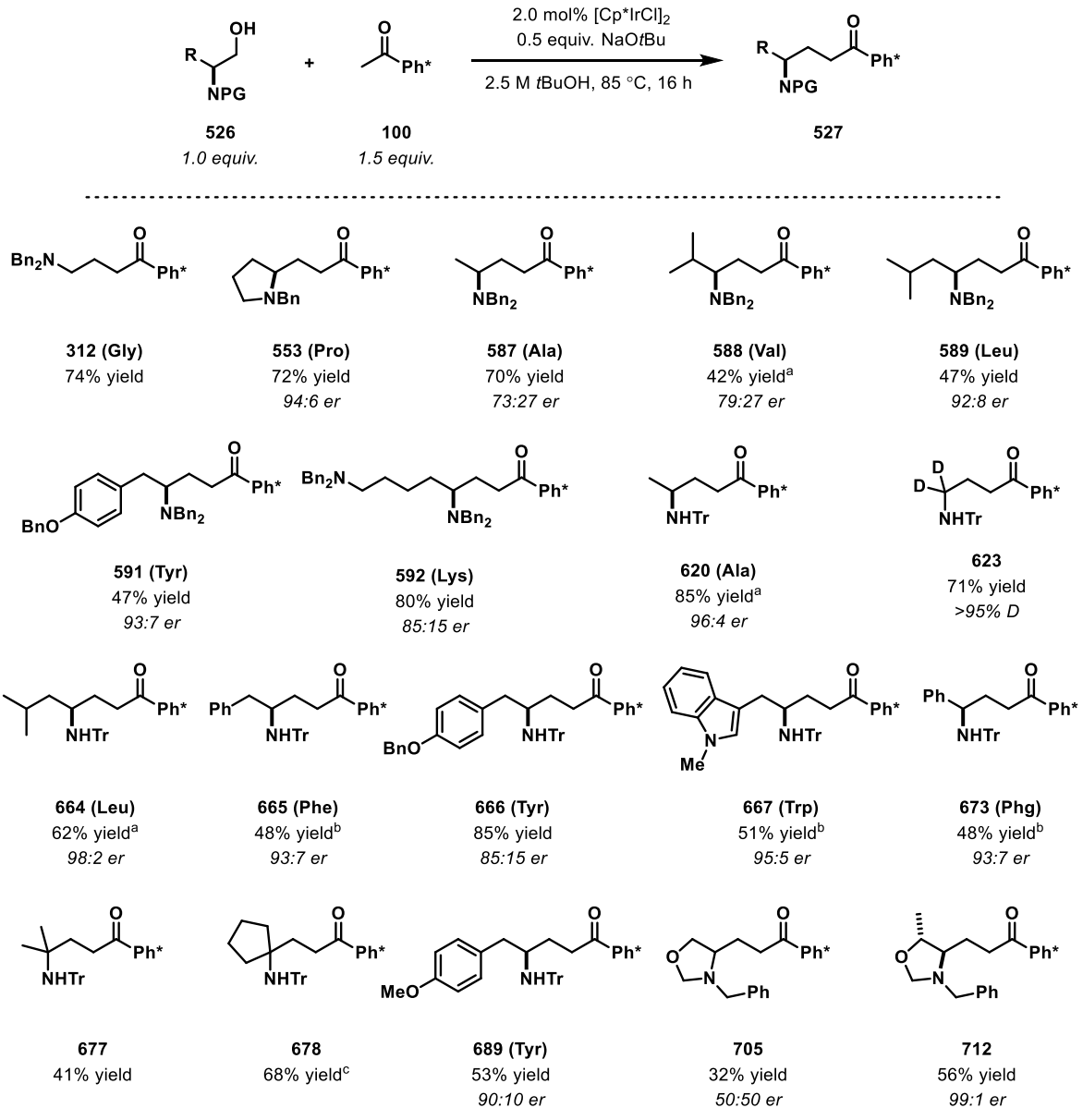


***Figure 4.8**: X-Ray structure of double hydrogen borrowing product **719**.*
Data collected and analysed by Dr Kirsten E. Christensen.

4.3.9 Scope Summary

In summary, we were delighted to find that a large number of 1,2-amino alcohols **526** derived from both natural and unnatural amino acids could react with Ph* methyl ketone **100** under hydrogen borrowing conditions to give a wide range of structurally diverse products in moderate to excellent yields and with high levels of enantioretention (Scheme 4.31).



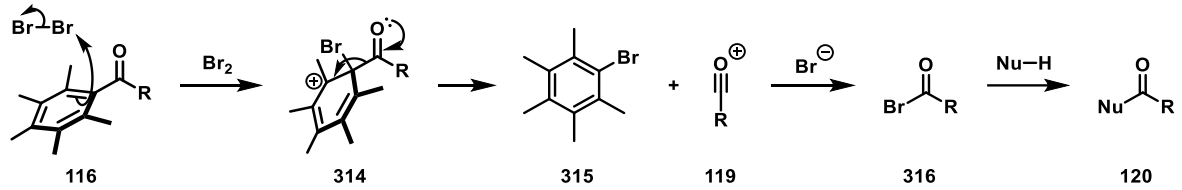
***Scheme 4.31**: Scope of the hydrogen borrowing reaction of 1,2-amino alcohols **526** with Ph* methyl ketone **100**. [a]Reaction conducted on a gram scale. [b]Reaction conducted at 110 °C. [c]Reaction conducted using 1.0 equiv. **100** and 2.0 equiv. **659**.*

Still to be resolved, however, was the question of product deprotection – with both the Ph* and either the *N*-trityl or *N*,*N*-dibenzyl groups needing to be removed in order to access synthetically useful compounds.

4.4 Results and Discussion: Product Deprotection to γ-Amino Butyric Acids

4.4.1 Initial Attempts at Ph* Removal with Br_2

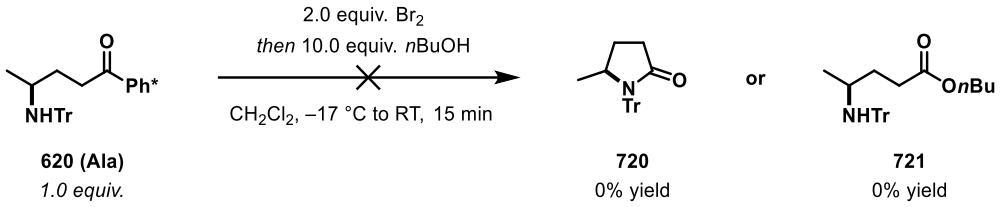
As thoroughly discussed in Chapter 1, the primary method for Ph* deprotection is the use of Br_2 to cleave the Ph* group to form pentamethylbromobenzene **315** and an acyl bromide **316**, followed by trapping with various nucleophiles to form a range of products **120** (Scheme 4.32).



Scheme 4.32*: Cleavage of the Ph* group using Br_2.*

Alanine-derived hydrogen borrowing product **620** was chosen as a model substrate for deprotection for a number of reasons: large amounts of **620** had been prepared during earlier gram scale testing of the hydrogen borrowing reaction; the methyl group side chain was highly unlikely to contribute to unwanted reactivity; the methyl group appeared as a clear and diagnostic doublet at 0.73 ppm *via* ^{1}H NMR, allowing for starting material consumption to be easily traced.

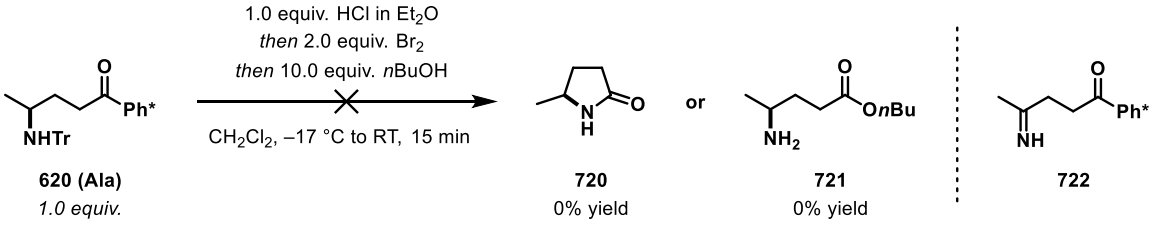
As detailed in Chapter 2, and exploited in Chapter 3 in the synthesis of (–)-*γ*-lycorane, aziridine and azetidine containing substrates had been found to cyclise onto the acyl bromide formed after Ph* cleavage, giving a cyclic amide product. We therefore anticipated that alanine-derived product **620** would likely react to form the γ-lactam product **720**, following formation of the intermediate acyl bromide using standard cleavage conditions – however it was decided to also add an excess of *n*BuOH after a period of time to trap any unreacted acyl bromide intermediates to give ester **721** if the expected cyclisation were not to occur (Scheme 4.33).



***Scheme 4.33**: Attempted deprotection of alanine-derived product **620** with Br_2.*

Unfortunately, upon exposure to the reaction conditions, only a complex mixture of products was detected by crude ^{1}H NMR – with none of the expected lactam **720**, *n*-butyl ester **721**, or starting material **620**. Given that these conditions had been previously used on *N*-benzyl aziridine containing substrates in Chapters 2 and 3 without issue, it was proposed that the *N*-trityl protecting group might be to blame. Specifically, elemental Br_2 is well known to produce the strong acid HBr upon contact with water,[116] a process highly likely to have been occurring under our reaction conditions due to the fact no efforts were taken to strenuously dry either the reactants or reaction vessel.

As a highly acid sensitive protecting group,[110] it seemed likely that the trityl group was immediately falling off in an uncontrolled fashion during the reaction, giving a mixture of the *N*-trityl protected, free NH_2 and NH_3Br ammonium salt forms of the substrate **620** – thereby leading to a mixture of products. To prevent this, it was decided to first treat the substrate with one equivalent of acid in order to fully cleave the trityl group to give the free amine, before then reattempting the Ph* cleavage with Br_2 in the same pot (Scheme 4.34).

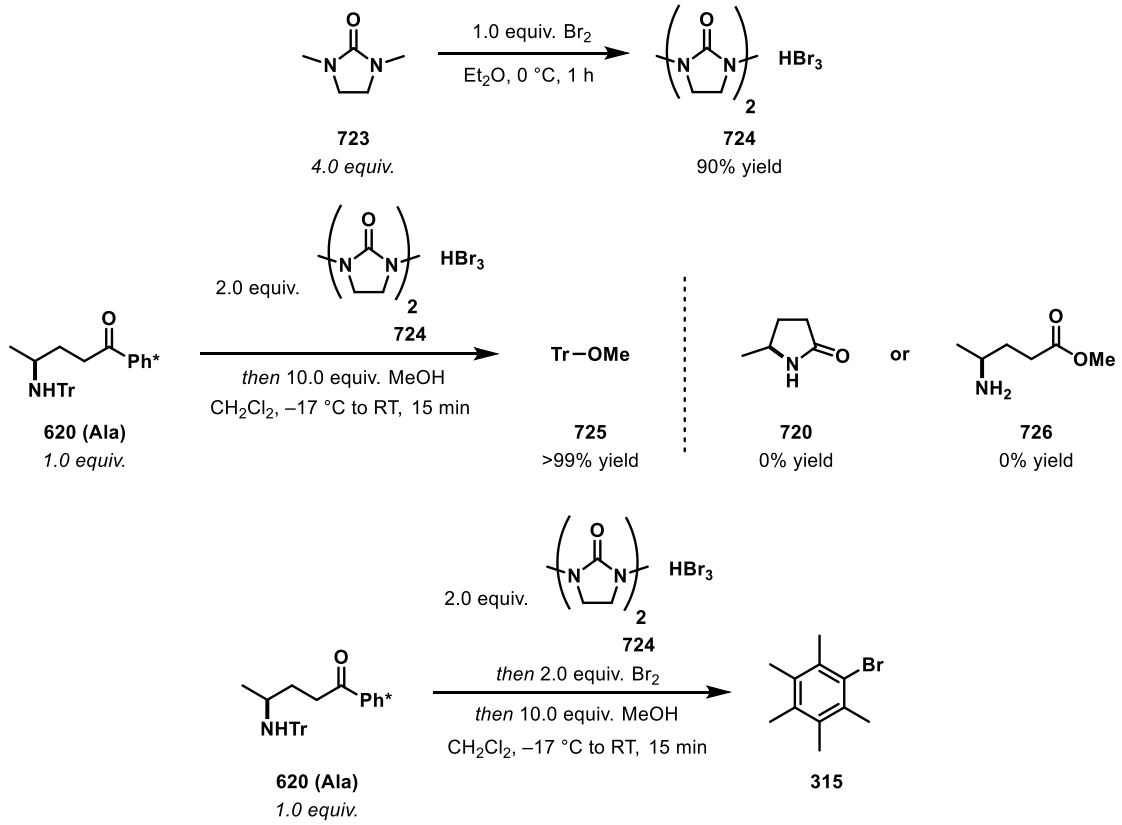


***Scheme 4.34**: Attempted acid-mediated detritylation, followed by deprotection of alanine-derived product **620** with Br_2.*

Unfortunately, once again neither of the possible products **720** or **721** were isolated or even observed by crude ^{1}H NMR – however signals consistent with the formation of imine **722** (methyl singlet at ~2 ppm, two COSY-adjacent triplets at ~2.5ppm and 3.5ppm) were observed, suggesting that the C–N

bond was being oxidised by Br_2. In an attempt to avoid this unwanted oxidation, we searched the literature for more mild sources of bromine that we hoped would still be capable of cleaving the Ph* group, but without performing the unwanted amine oxidation.

A good candidate was found in work conducted by Matsubara and co-workers, who found that treatment of Br_2 with 1,3-dimethyl-2-imidazolidinone **723** (DMI) formed a stable crystalline complex **724** that could be used for a number of classical reactions usually involving molecular bromine.[117] Synthesis of the complex was straightforward, with the addition of Br_2 to a solution of DMI in ether leading to precipitation of the desired bright orange complex **724** in 90% yield (Scheme 4.35).

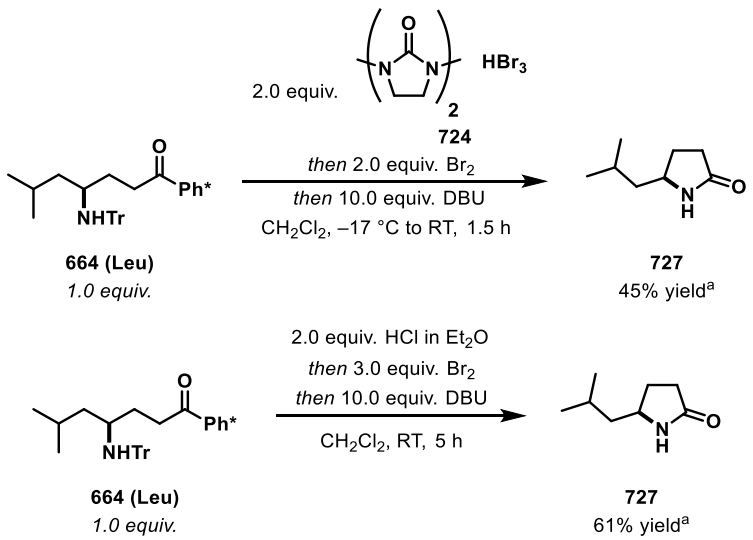


***Scheme 4.35**: Synthesis of complex **724** and its attempted use in Ph* cleavage.*

Interestingly, upon treatment of alanine-derived product **620** with complex **724**, followed by MeOH, neither of the possible Ph* cleavage products **720** or **726** were observed – however the trityl methyl ether **725** was isolated in >99% yield. This suggested to us that complex **724** had led to complete cleavage of the trityl group from the product, forming trityl bromide which then reacted with MeOH

to give **725**. Curious to investigate this process further, we then repeated the above reaction but with the addition of Br_2 after the reaction had been left to stir with complex **724** for 1 hour. Although once again neither of the desired products was formed, we did observe the formation of substantial quantities of pentamethyl bromobenzene **315** by crude ^1H NMR – a sure sign that the desired Ph* cleavage was occurring.

Inspired by this result, we elected to repeat the reaction with leucine-derived hydrogen borrowing product **664**, albeit with the replacement of the addition of MeOH with an excess of the strong base DBU – the hypothesis being that this might serve to mediate the formation of the desired γ-lactam **727** *via* a cyclisation of the amine onto the newly formed acyl bromide (Scheme 4.36).



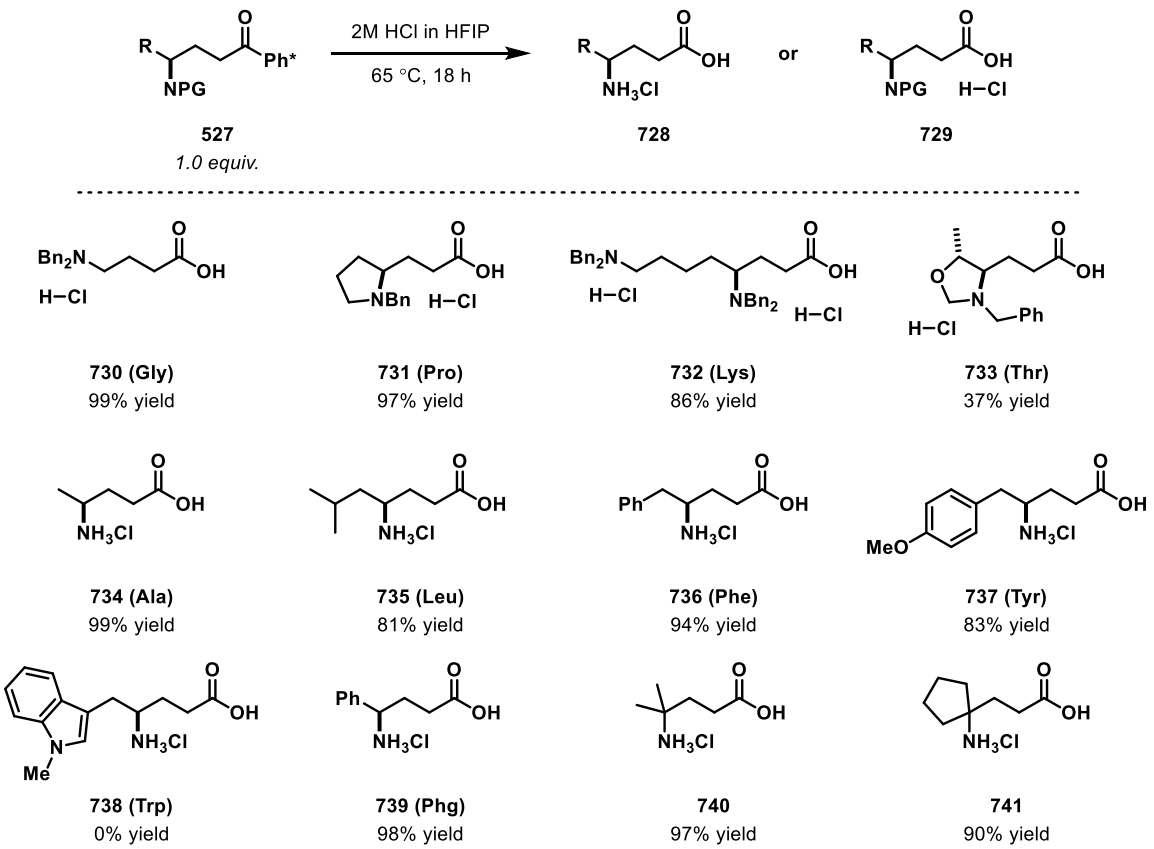
***Scheme 4.36**: DBU-mediated cyclisation to form γ-lactam **727**.*
[a]Product er not determined.

We were therefore encouraged to observe that these new conditions led to the formation of γ-lactam **727** in 45% yield – demonstrating that the cleavage of the Ph* functionality could still occur in the presence of an oxidisable amine. Next, we decided to re-examine the role of complex **724** – which only seemed to be acting as an acid to remove the trityl group whilst Br_2 went on to actually cleave the Ph* functionality. We therefore repeated the above cleavage reaction, replacing complex **724** with 2M HCl in Et_2O – followed by Br_2 and then DBU as before, and conducting the reaction at room temperature.

Pleasingly, this also gave the desired product **727** in an increased yield of 61%, thereby demonstrating that the cleavage and cyclisation of hydrogen borrowing products such as **664** to γ-lactams such as **727** is a viable process.

4.4.2 Deprotection with HCl in HFIP

Alongside the above deprotection efforts involving Br_2, we also decided to investigate alternative conditions disclosed by Donohoe and co-workers for the removal of Ph* *via* the use of a 2M solution of HCl in hexafluoroisopropanol (HFIP) to give carboxylic acids.[35] In contrast to the difficulties associated with the use of Br_2, upon conducting a test reaction we were instead delighted to observe the smooth formation of 1,4-amino acid hydrochloride **734** from alanine-derived hydrogen borrowing product **620** in 99% yield. We therefore proceeded to deprotect the majority of our hydrogen borrowing products under the same conditions in similarly impressive yields with little difficulty (Scheme 4.37).

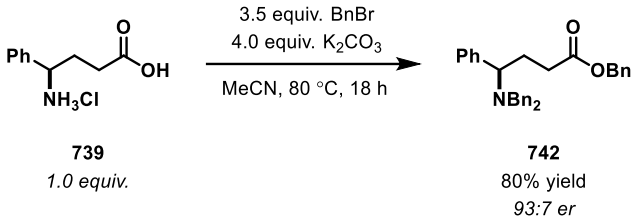


***Scheme 4.37**: Acid-mediated cleavage of the Ph* group to give 1,4-amino acid hydrochlorides **728** or **729**.*

One particular advantage in these conditions when applied to hydrogen borrowing products derived from amino alcohols was that no chromatographic purification of the products was necessary. Upon completion of the reaction, the solution was diluted with water and then repeatedly washed with Et_2O remove the triphenylmethane and pentamethylbenzene cleavage by-products, along with the HFIP solvent. The resulting aqueous solution of the desired amino acid hydrochloride in water was then concentrated *in vacuo* to remove water along with any excess HCl to give the pure products, typically as crystalline solids.

The only low yielding exceptions to the above cleavage conditions were threonine- and tryptophan-derived hydrogen borrowing products **712** and **667** – with deprotected threonine derivative **733** being formed in a disappointing 37% yield, and the desired tryptophan derivative **739** not being detected despite numerous attempts. In the former case, it was proposed that the methylene bridge in **712** might be decomposing under the reaction conditions, however no decomposition products were isolated to support this hypothesis. For tryptophan-derived product **667**, upon exposure to the reaction conditions a deep violet colour was observed and persisted throughout the reaction workup – suggesting to us that decomposition of the indole moiety was occurring, possibly *via* protonation of the heterocycle's C3 position.

Although the yields for the acid-mediated deprotection were more than satisfactory, we were cognisant of the fact that the enantioenrichment of the products had yet to be measured – unlike the previous hydrogen borrowing step, the 1,4-amino acid hydrochlorides were unsuitable for normal phase HPLC analysis due to their polarity, as well as most compounds lacking a suitable UV chromophore for peak detection after separation. Even though the possibility of product racemisation under the reaction conditions seemed unlikely, it could not be fully ruled out. We therefore elected to synthesise a suitably protected derivative of phenylglycine-derived cleavage product **739** (in our eyes the product most likely to racemise *via* an S_N1-type process due to the influence of the aryl ring on the C–N σ*) and submit it to HPLC analysis (Scheme 4.38).



***Scheme 4.38**: Protection and HPLC analysis of phenylglycine-derived cleavage product **739**.*

Protection of **739** was readily achieved *via* treatment with an excess of benzyl bromide to give the desired *N*,*N*-dibenzyl benzyl ester **742** in 80% yield. Synthesis of a racemic sample allowed for HPLC analysis which showed the er to be 93:7 – identical to that of the precursor hydrogen borrowing product **673** – thereby demonstrating that the amino acid-derived stereocentre was untouched by the cleavage conditions.

Having completed a comprehensive deprotection scope, and shown the enantioenrichment of the products to be retained, a further goal was to discover the practical applications of 1,4-amino acids. We were therefore delighted to discover that the leucine- and phenylglycine-derived 1,4-amino acid hydrochlorides **735** and **739** were close positional isomers of the gabapentionoid drugs Pregabalin **743** and Phenibut **744**, respectively (Figure 4.9).[118, 119]

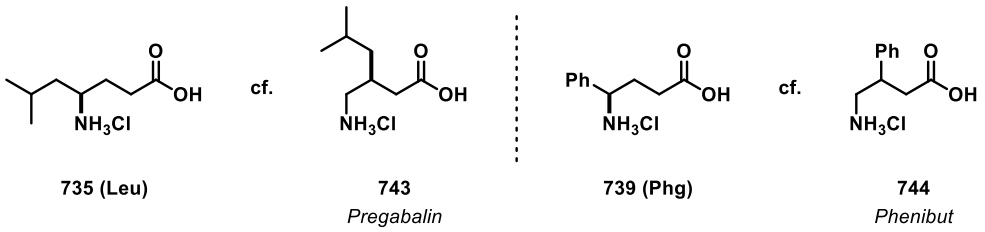


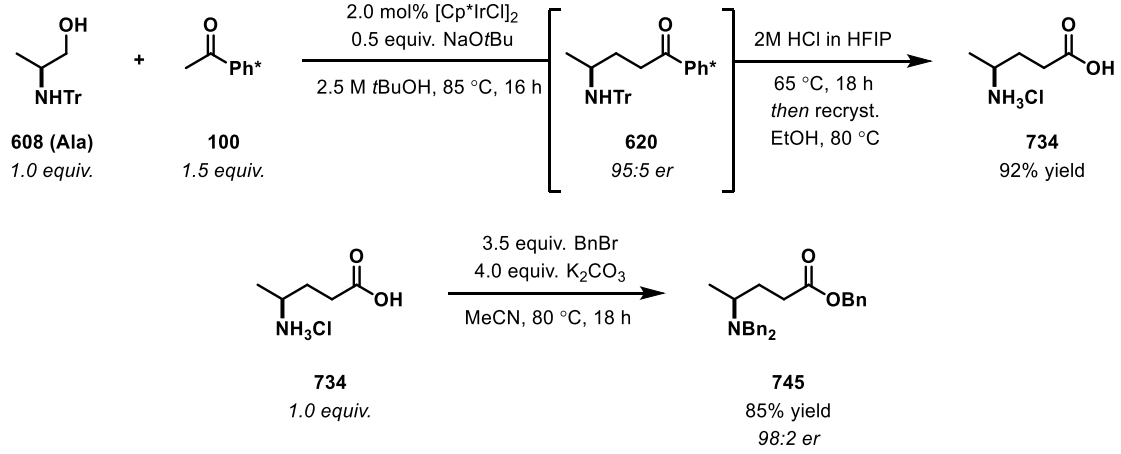
***Figure 4.9**: Structural similarity of gabapentionoid drugs Pregabalin **743** and Phenibut **744** with cleavage products **735** and **739**.*

Both drugs are structural analogues of the neurotransmitter γ-aminobutyric acid (GABA), and are used to treat a wide range of neurological conditions ranging from epilepsy to anxiety. As detailed in the introduction to this thesis, hydrogen borrowing has historically struggled to produce pharmaceutically relevant structures due to its issues with functional group compatibility, thus making the synthesis of

drug analogues such as **735** and **739** using the methodology developed within this chapter all the more exciting.

4.4.3 Chromatography-Free Hydrogen Borrowing and Cleavage

As previously mentioned, a particular advantage of the acid-mediated cleavage conditions was that no purification of the products was necessary by column chromatography – with only aqueous dilution, washing with Et_2O, and concentration *in vacuo* needed to obtain pure, crystalline products. Given the simplicity of the cleavage reaction, it was postulated whether chromatographic purification of the hydrogen borrowing intermediate was necessary – and as such a tandem process with *N*-trityl alaninol **608** was attempted, with the crude hydrogen borrowing product **620** being subjected to the cleavage conditions with the only intermediate purification being a water and brine wash of an ethereal solution of **620** to remove inorganic salts (Scheme 4.39).



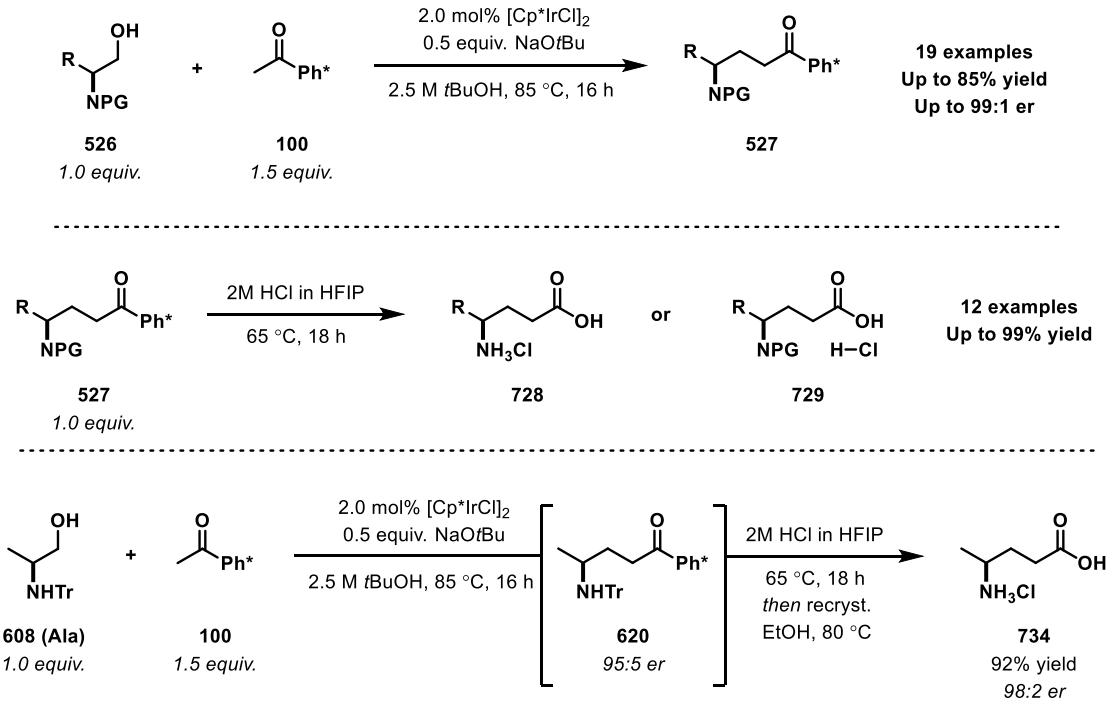
***Scheme 4.39**: Chromatography-free tandem hydrogen borrowing and cleavage of N-trityl alaninol **620**.*

To our delight, the desired 1,4-amino acid hydrochloride **734** was obtained after a single recrystallisation from EtOH in 92% yield over two steps – higher even than the 85% yield observed from the hydrogen borrowing step alone, demonstrating the intrinsic loss in yield associated with column chromatography. The reaction was also performed on a gram scale (4.0 mmol), leading to 571 mg of the product **734** being isolated.

Although the er of an aliquot of the hydrogen borrowing intermediate had been measured by preparative TLC and HPLC analysis to be 95:5, it was decided to repeat the same perbenzylation procedure that was performed on phenylglycine-derivative **739** in order to determine the er of **742**. As before, the protection proceeded smoothly to give the desired product **745** in 85% yield. HPLC analysis against a racemic sample prepared in the same manner found the product er to be 98:2 – the increase in er from that measured *via* the aliquot of intermediate **620** presumably arising during the recrystallisation of **734** from EtOH in a similar manner to that observed with the proline-derived hydrogen borrowing product **553** in Scheme 4.29.

4.5 Conclusions and Future Work

In summary, we have developed the hydrogen borrowing alkylation reaction of Ph* methyl ketone **100** with 1,2-amino alcohols **526** derived from the cheap and readily available amino acids **525** (Scheme 4.40).



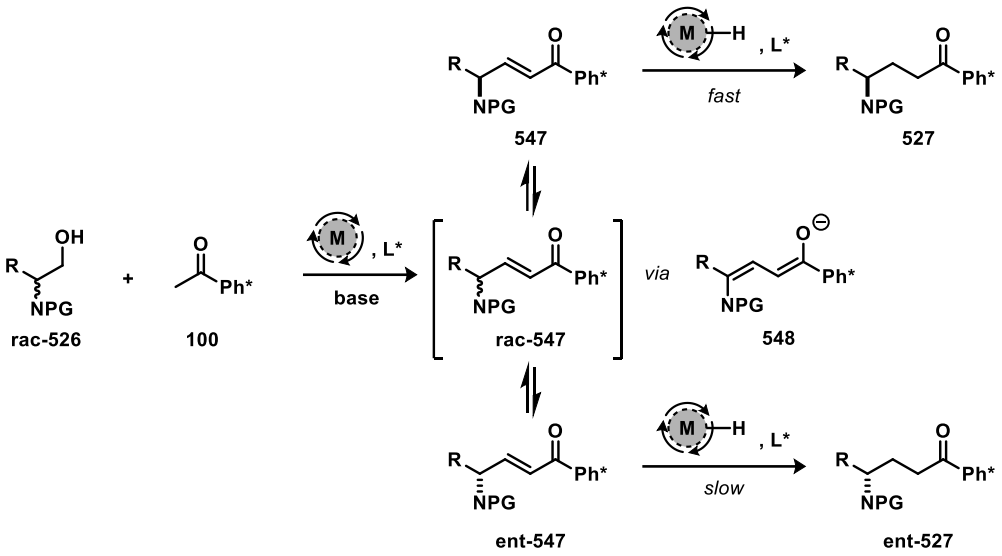
***Scheme 4.40**: Hydrogen borrowing alkylation and subsequent acid-mediated cleavage of Ph* methyl ketone **100** with amino acid-derived 1,2-amino alcohols **526**.*

The use of a bulky trityl group to protect the amine functionality was key to ensuring high levels of enantioretention, as well as increasing product yields in a number of cases. The functional group compatibility of the reaction was explored *via* the medium of amino acid side chains – with alkyl, aromatic, indole, amine, and hemiaminal ether moieties all being tolerated. Unnatural amino acids were also successfully utilised, with the reaction of phenylglycinol derivative **642** being especially surprising.

Typical cleavage conditions with Br_2 were explored, however the use of 2M HCl in HFIP proved most suitable, with a large number of products **527** being deprotected to the corresponding 1,4-amino acid hydrochlorides **728** or **729** in excellent yields with no loss in enantioenrichment. Finally, the use of column chromatography was avoided entirely by a tandem reaction without intermediate purification, giving alanine-derivative **734** in 92% yield and 98:2 er.

The most pressing aspect of future work in this area would be the testing for biological activity of the 1,4-amino acid hydrochlorides **728** and **729** formed from the acid-mediated removal of Ph*. The cleavage products **735** and **739**, derived from leucinol **626** and phenylglycine **571** respectively, are both closely related to potent drug analogues of the neurotransmitter GABA – and it is possible a number of the other cleavage products will exhibit some level of activity as pharmaceutical agents.

Synthetically, two main avenues present themselves. Firstly, seeing as amino alcohols have been shown to be tolerated under hydrogen borrowing conditions, we envisage that the reaction of racemic amino alcohols such as **rac-526** with Ph* methyl ketone **100** under the control of a chiral catalyst could be used in a dynamic kinetic resolution to form the same 1,4-amino acid derivatives **527** *via* enantioselective catalyst reduction of the interconverting intermediate enone **547** (Scheme 4.41). Studies to this effect are currently ongoing within the Donohoe group.



***Scheme 4.41**: Proposed usage of racemic amino alcohols **rac-547** in a hydrogen borrowing dynamic kinetic resolution reaction.*

Secondly, we have demonstrated that an adjacent *N*-trityl protected nitrogen allows an α-chiral alcohol to be carried through a C–C bond forming hydrogen borrowing reaction without high levels of racemisation. In a similar vein, our use of structurally diverse amino acid side chains demonstrates that hydrogen borrowing catalysis may be used with more sensitive structural motifs. We hope that these two advances will provide the impetus for new hydrogen borrowing methodologies to include similarly enantioenriched and heteroatom-containing substrates in an attempt to increase product diversity in a field that has sometimes been limited in this respect.

Chapter 5: Experimental

5.1 General Experimental Details

Atom Numbering: Atoms are numbered to illustrate peak assignments and do not necessarily correspond to IUPAC nomenclature.

Chromatography: Thin layer chromatography (TLC) was carried out using Merck aluminium backed DC60 F_{254} plates (particle size 0.25 mm). Spots were visualised by UV light, then stained and heated with vanillin or potassium permanganate as appropriate. Flash chromatography was carried out using Merck silica gel 60 (particle size 43 – 60 μm), the solvent system used is indicated and the procedure being that developed by Still *et al*.[120]

Reactions and Reagents: All reactions were carried out under a nitrogen atmosphere unless otherwise stated. CH_2Cl_2, diethyl ether, and THF were obtained from Grubbs canisters, with the solvent passing through an activated alumina column under nitrogen.

Spectroscopy: Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on Bruker AVG400 (400/101 MHz) and DPX200 (200 MHz). Spectra were referenced to the residual solvent peak ($CDCl_3$: H 7.26, C 77.2 ppm). Peak assignments were made based on chemical shifts, integrations, coupling constants, as well as COSY (correlation spectroscopy), HSQC (heteronuclear single quantum coherence) and NOESY (nuclear Overhauser effect spectroscopy) experiments. Peak multiplicities are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), or a combination thereof.

Infrared spectra were recorded using a Bruker Tensor 27 FT-IR spectrometer. All assignable absorption maxima are reported in wavenumbers (cm^{-1}).

High resolution mass spectra were recorded by Chemistry Research Laboratory staff using a Bruker Daltronics MicroTOF spectrometer (ESI). Mass to charge ratios (m/z) are reported in Daltons.

5.2 General Procedures

General Procedure A – Hydrogen Borrowing of Aziridine Alcohols

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added substrate (1.5 equiv.), $[Cp^*IrCl_2]_2$ (2.0 mol%), Ph* methyl ketone (1.0 equiv.) and KOH (2.0 equiv.) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a ResealTM septum) and an argon balloon fitted. The vial was heated to the required temperature (85 °C) in a preheated oil bath for 16 h. The mixture was cooled to RT, filtered through a SiO_2 plug (eluting with Et_2O) and concentrated *in vacuo*. Purification by column chromatography provided the title compound.

General Procedure B – Br_2 Cleavage

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added substrate (1.0 equiv.) and CH_2Cl_2 (0.2 M) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a ResealTM septum) and cooled to –17 °C (ice/NaCl bath). Following this, Br_2 (3.0 equiv.) was added dropwise and the mixture stirred until TLC analysis indicated complete consumption of the substrate (typically 15 min). The reaction was then quenched with *n*BuOH (5 .0 equiv.), diluted with Et_2O (15 mL per mmol substrate) and water (7 mL per mmol substrate). The layers were separated, and the aqueous layer extracted with Et_2O three times. The combined organics were washed with sat. aq. $Na_2S_2O_3$, sat. aq. $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography provided the title compound.

General Procedure C – Aziridination of α,β-Unsaturated Enals

To a solution of enal (1.0 equiv.) in heptane (0.12 M) was added sequentially pyrrolidine (0.2 equiv.), BocNHOTs (1.2 equiv.) and NaOAc (1.5 equiv.). The resulting suspension was left to stir for 24 at RT before being filtered through a SiO_2 plug (eluting with EtOAc:pentane, 7:1) and concentrated *in vacuo*. Purification by column chromatography provided the title compound.

General Procedure D – Deprotection of Boc-Protected Aziridines with TBAF

To a solution of Boc-protected aziridine (1.0 equiv.) in THF (0.1 M) was added TBAF in THF (1.1 equiv.) and the reaction heated at reflux (66 °C) for 1 h. The slight brown solution was quenched by the addition of sat. aq. $NaHCO_3$ (20 mL per mmol of aziridine) and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography provided the title compound.

General Procedure E – Hydrogen Borrowing of Amino Acid-Derived Alcohols

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added substrate (1.0 equiv.), $[Cp^*IrCl_2]_2$ (2.0 mol%), Ph* methyl ketone (1.5 equiv.), NaO*t*bu (0.5 equiv.) and *t*BuOH (2.5 M) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a ResealTM septum) and a nitrogen balloon fitted. The vial was heated to the required temperature (85 °C) in a preheated oil bath for 16 h. The mixture was cooled to RT, filtered through a SiO_2 plug (eluting with Et_2O) and concentrated *in vacuo*. Purification by column chromatography provided the title compound.

General Procedure F: Formation of Amino Acid Methyl Ester Hydrochlorides

To a stirred solution of amino acid (1.0 equiv.) in MeOH (10 mL/g amino acid) at 0 °C was added $SOCl_2$ (1.5 equiv.) dropwise. The reaction was then warmed to RT and left to stir overnight. The solvent was then removed *in vacuo* to give a crude solid that was redissolved in MeOH (5 mL/g amino acid) before being again concentrated *in vacuo*. This process was repeated twice before a final concentration *in vacuo* to give the pure desired product.

General Procedure G: Tritylation of Amino Acid Esters

To a stirred solution of amino acid ester hydrochloride (1.0 equiv.) and trityl chloride (1.0 equiv.) in CH_2Cl_2 (3 mL/mmol amino acid) at RT was added Et_3N (2.0 equiv.) dropwise and the reaction left to stir for 16 h. The reaction was then washed with water (3 mL/mmol amino acid), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product.

General Procedure H: $LiAlH_4$ Reduction of Amino Acids and Esters

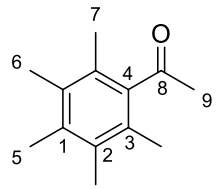
To a stirred solution of $LiAlH_4$ (2.0 equiv.) in THF (10 mL/mmol $LiAlH_4$) at 0 °C was added a solution of the amino acid ester (1.0 equiv.) in THF (1 mL/mmol $LiAlH_4$) dropwise, before being warmed to RT for esters or reflux for carboxylic acids. Reaction progress was monitored by TLC analysis and upon completion (typically 15 min for methyl esters, 3 h for benzyl esters, and 16 h for carboxylic acids), the reaction was cooled to 0 °C and diluted with Et_2O (5 mL/mmol $LiAlH_4$) before being quenched by the sequential addition of water (1 mL/g $LiAlH_4$), 15% aqueous NaOH (1 mL/g $LiAlH_4$), water (3 mL/g $LiAlH_4$) and $MgSO_4$. The thick emulsion was then filtered under reduced pressure (washing the filter cake with Et_2O), and concentrated *in vacuo* to give the crude product.

General Procedure I – Acid-Mediated Cleavage of Trityl Hydrogen Borrowing Products

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added substrate (0.1 mmol, 1.0 equiv.), HFIP (0.88 mL) and conc. HCl (0.13 mL). The reaction vessel was sealed with a microwave vial cap (containing a ResealTM septum) and heated at 65 °C for 16 h. The reaction was then cooled to RT, and diluted by the addition of water (2 mL). The mixture was then washed with Et_2O (3 × 2 mL) and concentrated *in vacuo* to give the pure desired product as the acid salt.

5.3 Experimental Data

1-(2,3,4,5,6-Pentamethylphenyl)ethan-1-one (100)

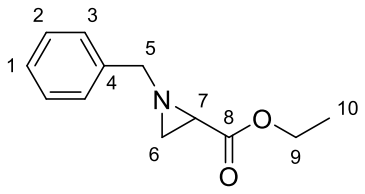


To a stirred solution of pentamethylbenzene (10.0 g, 67.6 mmol, 1.0 equiv.) and acetyl bromide (5.48 mL, 74.3 mmol, 1.1 equiv.) in CH_2Cl_2 (675 mL) at 0 °C was added $AlCl_3$ (11.25 g, 84.5 mmol, 1.25 equiv.) portionwise. After stirring for 30 min, the reaction was poured into water (500 ml, cooled with a water-ice bath) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 200 ml)and the combined organic layers washed with sat. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo* to give crude **100**. Column chromatography (SiO_2, dry load, pentane:Et_2O, 90:10) gave the desired compound **100** as a white solid (11.96g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.46 (s, 3H, H_3C(9)), 2.24 (s, 3H, H_3C(5)), 2.19 (s, 6H, 2 × Ar-CH_3), 2.14 (s, 6H, 2 × Ar-CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 210.1 (*C*(8)), 140.9 (C_{Ar}), 135.4 (C_{Ar}), 133.1 (2 × C_{Ar}), 127.0 (2 × C_{Ar}), 33.1 (*C*(9)), 17.1 (2 × CH_3C_{Ar}), 16.7 (*C*(5)), 16.0 (2 × CH_3C_{Ar}).

Data was consistent with that previously reported.[33]

Ethyl 1-benzylaziridine-2-carboxylate (275)



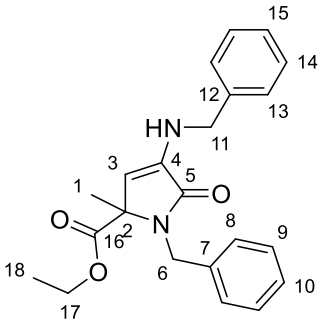
To a stirred solution of benzylamine (13.4 mL, 123 mmol, 3.0 equiv.) in MeOH (200 mL) at 0 °C was added a solution of 2,3-dibromopropionate (5.96 mL, 41 mmol, 1.0 equiv.) in MeOH (100 mL) dropwise over the course of 3 h. The reaction was then left to stir overnight at RT. The solvent was then removed *in vacuo* to give a residue which was redissolved in Et_2O (150 mL) and washed with water (300 mL).

The aqueous layer was then extracted with Et_2O (3 × 50 mL) and the combined organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo* to give aziridine **275** (8.49g, 99%) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 – 7.21 (m, 5H, 5 × *H*C_{Ar}), 4.19 (qq, J = 10.8, 7.1 Hz, 2H, *H*$_2$C(9)), 3.55 (d, J = 4.0 Hz, 2H, *H*$_2$C(5)), 2.26 (dd, J = 3.2, 1.2 Hz, 1H, *H*C(7)), 2.19 (dd, J = 6.4, 3.1 Hz, 1H, *H*$_a$H$_b$C(6)), 1.75 (dd, J = 6.5, 1.2 Hz, 1H, H$_a$*H*$_b$C(6)), 1.27 (t, J = 7.1 Hz, 3H, *H*$_3$C(10)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 170.9 (*C*(8)), 137.9 (*C*$_{Ar}$), 128.6 (2 × *C*$_{Ar}$), 128.2 (2 × *C*$_{Ar}$), 127.5 (*C*$_{Ar}$), 64.0 (*C*(5)), 61.3 (*C*(9)), 37.7 (*C*(7)), 34.6 (*C*(6)), 14.3 (*C*(10)).

Data was consistent with that previously reported.[121]

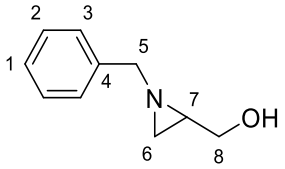
Ethyl 1-benzyl-4-(benzylamino)-2-methyl-5-oxo-2,5-dihydro-1H-pyrrole-2-carboxylate (276)



To a stirred solution of 2,3-dibromopropionate (1.30 mL, 9 mmol) in EtOH (9 mL) at 0 °C was added benzylamine (2.95 mL, 27 mmol) in EtOH (36 mL) slowly over the course of 30 min. The reaction mixture was then warmed to RT and left to stir for 16 h. The EtOH was then removed *in vacuo* to give an orange solid which was then redissolved in water (20 mL) and Et_2O (20 mL). The layers were separated, and the aqueous layer extracted with Et_2O (3 × 20 mL). The organic layers were then combined, washed with brine, and dried over $MgSO_4$ before being concentrated *in vacuo* to give a crude orange oil. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 80:20) gave the desired compound **276** (911 mg, 56%) as a thick red oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 – 7.19 (m, 10H, 10 × *H*C_{Ar}), 5.08 (s, 1H, *H*C(3)), 4.88 (d, J = 15.7 Hz, 1H, *H*$_a$H$_b$C(11)), 4.65 (t, J = 5.7 Hz, 1H, *H*N), 4.36 (d, J = 15.7 Hz, 1H, H$_a$*H$_b$*C(11)), 4.22 (d, J = 5.7 Hz, 2H, *H*$_2$C(6)), 3.94 (ddq, J = 39.7, 10.7, 7.1 Hz, 2H, *H*$_2$C(17)), 1.36 (s, 3H, *H*$_3$C(1)), 1.12 (t, J = 7.1 Hz, 3H, *H*$_3$C(18)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 171.8 (*C*(5)), 168.2 (*C*(16)), 139.8 (*C*(4)), 137.9 (*C*(12)), 137.6 (*C*(7)), 128.7 (2 × *C*$_{Ar}$), 128.5 (2 × *C*$_{Ar}$), 128.2 (2 × *C*$_{Ar}$), 127.6 (2 × *C*$_{Ar}$), 127.5 (*C*$_{Ar}$), 127.4 (*C*$_{Ar}$), 104.3 (*C*(3)), 67.6 (*C*(2)), 61.7 (*C*(17)), 48.5 (*C*(11)), 44.8 (*C*(6)), 21.8 (*C*(1)), 14.1 (*C*(18)); **IR** ν_{max} (film)/cm^{-1} 3338, 2981, 1730, 1688, 1656, 1404, 1240, 1176, 1107, 774, 734, 697; **HRMS** (ESI$^+$) $C_{22}H_{25}O_3N_2$ requires 365.18597, found $[M+H]^+$ 365.18531 (Δ –1.82 ppm).

(1-Benzylaziridin-2-yl)methanol (281)

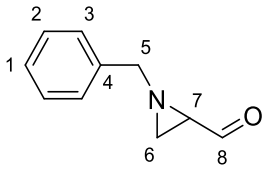


To a stirred solution of $LiAlH_4$ (2.53 g, 66.6 mmol, 2.0 equiv.) in THF (200 mL) at –40 °C was slowly added a solution of **275** (6.83 g, 33.3 mmol, 1.0 equiv.) in THF (50 mL) and the reaction left to stir for 2 h. The reaction was then warmed to RT and quenched by the sequential addition of water (2.5 ml), 15% aqueous NaOH (2.5 mL), water (7.5 mL) and $MgSO_4$ (25 g). The thick emulsion was then filtered under reduced pressure and the solvent removed *in vacuo* to give the desired alcohol **281** as an oil (5.22 g, 96%) that was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.57 – 7.06 (m, 5H, 5 × *H*C_{Ar}), 3.77 (dd, J = 11.7, 2.6 Hz, 1H, *H$_a$*H$_b$C(8)), 3.46 (s, 2H, *H*$_2$C(5)), 3.37 (dd, J = 11.6, 5.0 Hz, 1H, H$_a$*H$_b$*C(8)), 1.84 (m, J = 3.5 Hz, 2H, *H*$_2$C(6)), 1.49 (m, J = 6.0 Hz, 1H, *H*C(7)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.2 (*C*$_{Ar}$), 128.8 (2 × *C*$_{Ar}$), 128.3 (2 × *C*$_{Ar}$), 127.6 (*C*$_{Ar}$), 64.3 (*C*(8)), 63.0 (*C*(5)), 40.6 (*C*(7)), 31.5 (*C*(6)).

Data was consistent with that previously reported.[121]

1-Benzylaziridine-2-carbaldehyde (282)

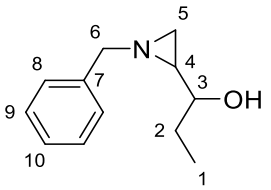


To a stirred solution of oxalyl chloride (1.9 mL, 22.5 mmol, 1.5 equiv.) in CH_2Cl_2 (40 mL) at –78 °C was added DMSO (3.2 mL, 45 mmol, 3.0 equiv.) and the reaction stirred for 10 min. A solution of alcohol **281** (2.45 g, 15 mmol, 1.0 equiv.) in CH_2Cl_2 (15 mL) was added dropwise over 15 min and the reaction left to stir for a further 20 min. Et_3N (10.4 mL, 75 mmol, 6.0 equiv.) was added dropwise and the reaction warmed to RT over 1 h. The reaction was then quenched by the addition of sat. aq. NH_4Cl (30 mL) and the layers separated. The organic layer was then washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the desired aldehyde **282** as a yellow oil (2.29g, 95%) that was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.90 (d, J = 6.4 Hz, 1H, *H*C(8)), 7.43 – 7.12 (m, 5H, 5 × *H*C_{Ar}), 3.65 – 3.40 (m, 2H, *H*$_2$C(5)), 2.28 (t, J = 3.1 Hz, 1H, *H*$_a$H$_b$C(6)), 2.19 (td, J = 6.6, 3.0 Hz, 1H, H$_a$*H*$_b$C(6)), 1.91 (d, J = 6.6 Hz, 1H, *H*C(7)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 199.8 (*C*(8)), 137.8 (C_{Ar}), 128.8 (2 × C_{Ar}), 128.3 (2 × C_{Ar}), 127.6 (C_{Ar}), 63.3 (*C*(5)), 44.5 (*C*(7)), 32.8 (*C*(6)).

Data was consistent with that previously reported.[121]

1-(1-Benzylaziridin-2-yl)propan-1-ol (283)



To a stirred solution of EtMgBr (1.6 mL of 3M in Et_2O, 4.8 mmol) in THF (10 mL) at 0 °C was slowly added 1-benzylaziridine-2-carbaldehyde **282** (0.67g, 4 mmol) in THF (3 mL). The resulting mixture was stirred for 1.5 h at 0 °C before being quenched by the addition of sat. aq. NH_4Cl. Extraction with Et_2O

(3 × 20 mL), washing with brine and drying with $MgSO_4$, followed by concentration *in vacuo* gave a crude yellow oil. Purification by column chromatography (SiO_2, dry load, pentane: EtOAc, 80:20) gave the desired compound as a separable mixture of diastereomers of **283**.

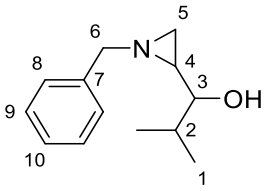
First Diastereomer (134 mg, 18%) Pale yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.41 – 7.18 (m, 5H, 5 × *H*C_{Ar}), 3.52 (dd, J = 13.0, 2.2 Hz, 1H, $H_a$$H_b$C(6)), 3.38 (d, J = 12.9 Hz, 1H, $H_a$$H_b$C(6)), 3.18 (q, J = 6.1 Hz, 1H, *H*C(3)), 2.16 (s, 1H, *H*C(5)), 1.85 (dd, J = 3.5, 1.5 Hz, 1H, *H*C(5)), 1.65 (td, J = 5.8, 4.0 Hz, 1H, *H*C(4)), 1.51 (dd, J = 6.5, 1.4 Hz, 1H, *H*C(2)), 1.46 (q, J = 7.2 Hz, 2H, H_2C(2)), 0.95 – 0.87 (m, 3H, H_3C(1)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.1 (C_{Ar}), 128.7 (2 × C_{Ar}), 128.4 (2 × C_{Ar}), 127.5 (C_{Ar}), 73.0 (*C*(3)), 64.4 (*C*(6)), 43.5 (*C*(4)), 32.2 (*C*(2)), 28.7 (*C*(5)), 10.0 (*C*(1)); **IR** ν_{max} (film)/cm^{-1} 3396, 3062, 3030, 2964, 2930, 2876, 1454, 1027, 974, 824, 735, 698; **HRMS** (ESI$^+$) $C_{12}H_{18}ON$ requires 192.13829, found $[M+H]^+$ 192.13826 (Δ –0.16 ppm).

Second Diastereomer (103 mg, 14%) Pale yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39 – 7.22 (m, 5H, 5 × *H*C_{Ar}), 3.66 (td, J = 6.2, 3.6 Hz, 1H, $H_a$$H_b$C(6)), 3.59 (d, J = 13.4 Hz, 1H, $H_a$$H_b$C(6)), 3.44 (d, J = 13.5 Hz, 1H, *H*C(3)), 1.92 (d, J = 3.6 Hz, 1H, *H*C(5)), 1.71 (dt, J = 6.9, 3.6 Hz, 1H, *H*C(5)), 1.47 (p, J = 7.3 Hz, 2H, H_2C(2)), 1.40 (d, J = 6.3 Hz, 1H, H_2C(4)), 0.96 (t, J = 7.5 Hz, 3H, H_3C(1)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.1 (C_{Ar}), 128.6 (2 × C_{Ar}), 128.0 (2 × C_{Ar}), 127.3 (C_{Ar}), 69.6 (*C*(3)), 63.8 (*C*(6)), 42.4 (*C*(4)), 29.6 (*C*(2)), 27.7 (*C*(5)), 9.9 (*C*(1)); **IR** ν_{max} (film)/cm^{-1} 3385, 2964, 2924, 2876, 1454, 1165, 1043, 1028, 971, 735, 698; **HRMS** (ESI$^+$) $C_{12}H_{18}ON$ requires 192.13829, found $[M+H]^+$ 192.13837 (Δ 0.4 ppm).

1-(1-Benzylaziridin-2-yl)-2-methylpropan-1-ol (284)



To a stirred solution of ^{i}PrMgBr (1.6 mL of 3M in Et_2O, 4.8 mmol) in THF (10 mL) at 0 °C was slowly added 1-benzylaziridine-2-carbaldehyde **282** (0.67g, 4 mmol) in THF (3 mL). The resulting mixture was stirred for 1.5 h at 0 °C before being quenched by the addition of sat. aq. NH_4Cl. Extraction with Et_2O (3 × 20 mL), washing with brine and drying with $MgSO_4$, followed by concentration *in vacuo* gave a crude yellow oil. Purification by column chromatography (SiO_2, dry load, Et_2O:pentane, 60:40) gave a separable mixture of diastereomers of **284**.

First Diastereomer (362 mg, 44%) Yellow oil

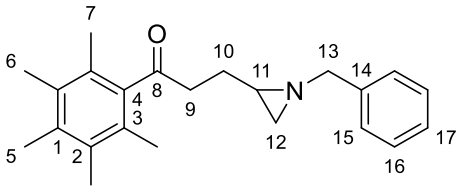
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 – 7.22 (m, 5H, 5 × *H*C$_{Ar}$), 3.61 – 3.36 (m, 2H, *H*$_2$C(6)), 2.98 (q, J = 5.1 Hz, 1H, *H*C(3)), 2.28 (d, J = 6.1 Hz, 1H, *H*C(2)), 1.88 – 1.80 (m, 1H, *H*C(5)), 1.70 (hept, J = 7.5, 7.0 Hz, 1H, *H*C(5)), 1.52 (d, J = 6.4 Hz, 1H, *H*C(4)), 1.02 – 0.84 (m, 6H, 2 × *H*$_3$C(1)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.1 (*C*$_{Ar}$), 128.6 (2 × *C*$_{Ar}$), 128.4 (2 × *C*$_{Ar}$), 127.5 (*C*$_{Ar}$), 76.3 (*C*(3)), 64.2 (*C*(6)), 41.9 (*C*(4)), 33.3 (*C*(2)), 32.5 (*C*(5)), 18.6 (*C*(1)), 18.3 (*C*(1')); **IR** ν_{max} (film)/cm^{-1} 3396, 3029, 2959, 2873, 2360, 2341, 1496, 1454, 1362, 1028, 1000, 734, 697; **HRMS** (ESI$^+$) $C_{13}H_{20}ON$ requires 206.15394, found $[M+H]^+$ 206.15351 (Δ – 2.12 ppm).

Second Diastereomer (77 mg, 9%) Yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 – 7.23 (m, 5H, 5 × *H*C$_{Ar}$), 3.59 (d, J = 13.5 Hz, 1H, *H*$_a$H$_b$C(6)), 3.52 – 3.43 (m, 1H, H$_a$*H*$_b$C(6)), 2.71 – 2.54 (m, 1H, *H*C(3)), 1.93 (d, J = 3.7 Hz, 1H, *H*C(5)), 1.74 (dt, J = 6.9, 3.5 Hz, 1H, *H*C(5)), 1.64 (h, J = 6.7 Hz, 1H, *H*C(4)), 1.00 – 0.91 (m, 6H, 2 × *H*$_3$C(1)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.1 (*C*$_{Ar}$), 128.6 (2 × *C*$_{Ar}$), 127.9 (2 × *C*$_{Ar}$), 127.3 (*C*$_{Ar}$), 72.7 (*C*(3)), 63.6 (*C*(6)), 40.8 (*C*(4)), 32.7 (*C*(2)), 29.6 (*C*(5)), 18.5 (*C*(1)), 18.4 (*C*(1')); **IR** ν_{max} (film)/cm^{-1} 3406, 2960, 2928, 2873, 2360, 2341, 1496, 1454,

1361, 1065, 1028, 1001, 734, 697; **HRMS** (ESI$^+$) $C_{13}H_{20}ON$ requires 206.15394, found $[M+H]^+$ 206.15349 (Δ –2.2 ppm).

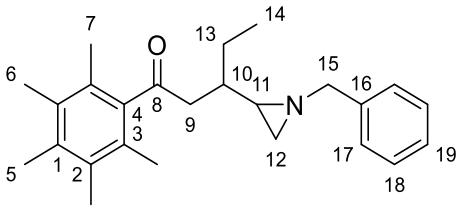
3-(1-Benzylaziridin-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one (287)



(1-benzylaziridin-2-yl)methanol **281** (147 mg, 0.9 mmol) was subjected to **General Procedure A**. Purification by column chromatography (SiO_2, dry load, pentane:Et_2O, 50:50) gave the desired compound **287** (124 mg, 62%) as pale orange semi-solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.29 – 7.14 (m, 5H, 5 × *H*C$_{Ar}$), 3.46 – 3.26 (m, 2H, *H*$_2$C(13)), 2.72 – 2.57 (m, 2H, *H*$_2$C(9)), 2.15 (s, 3H, *H*$_3$C(5)), 2.10 (s, 6H, 2 × *H*$_3$C(6)), 1.97 (s, 6H, 2 × *H*$_3$C(7)), 1.91 – 1.76 (m, 1H, *H*C(12)), 1.70 – 1.63 (m, 1H, *H*C(11)), 1.63 – 1.56 (m, 2H, *H*$_2$C(10)), 1.36 (d, J = 6.0 Hz, 1H, *H*C(12)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 211.6 (*C*(8)), 140.5 (*C*$_{Ar}$), 139.3 (*C*$_{Ar}$), 135.4 (*C*$_{Ar}$), 133.0 (2 × *C*$_{Ar}$), 128.4 (2 × *C*$_{Ar}$), 128.1 (2 × *C*$_{Ar}$), 127.3 (2 × *C*$_{Ar}$), 127.1 (*C*$_{Ar}$), 64.9 (*C*(13)), 43.2 (*C*(11)), 39.0 (*C*(9)), 34.0 (*C*(10)), 26.8 (*C*(12)), 17.2 (2 × *C*(6)), 16.7 (*C*(5)), 16.0 (2 × *C*(7)); **IR** ν_{max} (film)/cm^{-1} 2923, 1698, 1656, 1453, 1403, 1355, 1106, 732, 698; **HRMS** (ESI$^+$) $C_{23}H_{30}ON$ requires 336.23219, found $[M+H]^+$ 336.23126 (Δ –2.76 ppm).

3-(1-Benzylaziridin-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one (288)



Aziridine alcohol **283** (127 mg, 0.67 mmol) was subjected to **General Procedure A**. Purification by column chromatography (SiO_2, dry load, pentane:EtOAc, 90:10) gave product **288** as a separable mixture of diastereomers in a 7:3 (by crude ^{1}H NMR) ratio.

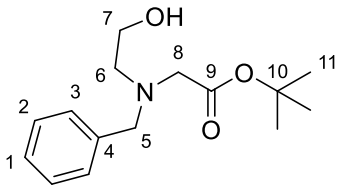
First Diastereomer (20 mg, 13%) Yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39 – 7.23 (m, 5H, 5 × *H*C$_{Ar}$), 3.43 (dd, 2H, *H*$_2$C(15)), 2.79 – 2.55 (m, 2H, *H*$_2$C(9)), 2.23 (s, 3H, *H*$_3$C(5)), 2.18 (s, 6H, 2 × *H*$_3$C(6)), 2.09 (s, 6H, 2 × *H*$_3$C(7)), 1.90 – 1.80 (m, 1H, *H*C(10)), 1.78 (d, J = 3.4 Hz, 1H, *H*C(12)), 1.48 (p, J = 7.0 Hz, 2H, *H*C(13)), 1.38 (d, J = 6.3 Hz, 1H, *H*C(12)), 1.04 – 0.95 (m, 1H, *H*C(11)), 0.86 (t, J = 7.5 Hz, 3H, *H*$_3$C(14)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 210.6 (*C*(8)), 140.8 (*C*$_{Ar}$), 139.4 (*C*$_{Ar}$), 135.4 (*C*$_{Ar}$), 133.2 (2 × *C*$_{Ar}$), 128.5 (2 × *C*$_{Ar}$), 128.4 (2 × *C*$_{Ar}$), 127.3 (2 × *C*$_{Ar}$), 127.2 (*C*$_{Ar}$), 65.2 (*C*(15)), 47.3 (*C*(11)), 43.4 (*C*(9)), 37.2 (*C*(13)), 33.3 (*C*(12)), 25.8 (2 × *C*(6)), 17.2 (*C*(5)), 16.8 (2 × *C*(7)), 11.2 (*C*(14)); **IR** ν_{max} (film)/cm^{-1} 2959, 2926, 1701, 1454, 13555, 735, 698; **HRMS** (ESI$^+$) $C_{25}H_{34}ON$ requires 364.26349, found $[M+H]^+$ 364.26208 (Δ –3.89 ppm).

Second Diastereomer (30 mg, 18%) Yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39 – 7.17 (m, 5H, 5 × *H*C$_{Ar}$), 4.12 (q, J = 7.2 Hz, 1H), 3.47 – 3.25 (m, 2H, *H*$_2$C(15)), 2.64 (d, J = 3.2 Hz, 1H, *H*$_2$C(15)), 2.59 (d, J = 8.1 Hz, 2H, *H*$_3$C(9)), 2.22 (s, 3H, *H*$_3$C(5)), 2.16 (s, 6H, 2 × *H*$_3$C(6)), 2.03 (s, 6H, 2 × *H*$_3$C(7)), 1.78 (d, J = 2.9 Hz, 1H, *H*C(12)), 1.68 (tt, J = 11.9, 5.0 Hz, 2H, *H*C(13)), 1.42 (ddd, J = 18.5, 14.3, 7.1 Hz, 1H, *H*C(12)), 0.97 (t, J = 7.2 Hz, 3H, *H*$_3$C(14)), 0.87 (dt, J = 15.0, 8.4 Hz, 1H, *H*C(11)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 210.9 (*C*(8)), 132.9 (*C*$_{Ar}$), 128.5 (2 × *C*$_{Ar}$), 128.4 (2 × *C*$_{Ar}$), 127.1 (2 × *C*$_{Ar}$), 65.2 (*C*(15)), 48.6 (*C*(11)), 43.1 (*C*(9)), 38.3 (*C*(13)), 34.9 (*C*(12)), 17.0 (2 × *C*(6)), 16.7 (*C*(5)), 15.9 (2 × *C*(7)), 11.7 (*C*(14)) [N.B. Some of the aromatic ^{13}C signals too weak to identify]; **IR** ν_{max} (film)/cm^{-1} 2960, 2926, 1700, 1454, 1381, 740, 699; **HRMS** (ESI$^+$) $C_{25}H_{34}ON$ requires 364.26349, found $[M+H]^+$ 364.26306 (Δ –1.18 ppm).

tert-Butyl N-benzyl-N-(2-hydroxyethyl)glycinate (296)

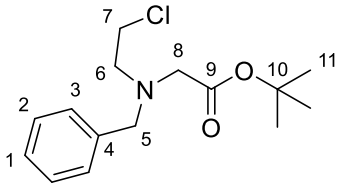


2-Benzylaminoethanol (4.7 mL, 33.1 mmol, 1.0 equiv.), NaI (1.0 g, 6.7 mmol, 0.2 equiv.), K_2CO_3 (4.7 g, 34 mmol, 1.03 equiv.) and $^tBuCO_2CH_2Br$ (5.2 mL, 35 mmol, 1.06 equiv.) were added to MeCN (150mL) and stirred for 16 h at reflux (82 °C). The solvent was then removed *in vacuo* and the residue taken up in water (60 mL) and Et_2O (60 mL). The layers were separated, and the organic layer was washed with sat. aq. $Na_2S_2O_3$ (60 mL). The aqueous layers were then combined and extracted with Et_2O (2 × 60 mL). The combined organic extracts were then washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give **296** as a yellow oil (9.16 g, Quant.) which was used without further purification.

^{1}H NMR (200 MHz, $CDCl_3$) δ_H 7.36 – 7.25 (m, 5H, 5 × *H*C_{Ar}), 3.81 (s, 2H, *H*$_2$C(5)), 3.59 (t, J = 5.6 Hz, 2H, *H*$_2$C(7)), 3.22 (s, 2H, *H*$_2$C(8)), 2.85 (d, J = 5.3 Hz, 2H, *H*$_2$C(6)), 1.45 (s, 9H, 3 × *H*$_3$C(11)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 171.9 (*C*(9)), 138.2 (*C*(4)), 128.8 (2 × C_{Ar}), 128.3 (2 × C_{Ar}), 127.3 (*C*(1)), 81.3 (*C*(10)), 58.8 (*C*(5)), 58.5 (*C*(8)), 55.3 (*C*(6)), 26.5 (*C*(7)), 28.0 (3 × *C*(11)).

Data was consistent with that previously reported.[60]

tert-Butyl N-benzyl-N-(2-chloroethyl)glycinate (297)



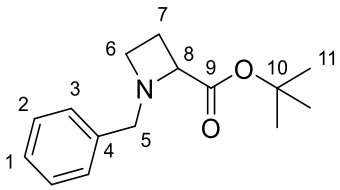
To a stirred solution of alcohol **296** (9.1 g, 33 mmol, 1.0 equiv.) in CH_2Cl_2 (200 mL) at RT was added $SOCl_2$ (4.7 mL, 64 mmol, 1.93 equiv.) dropwise and the reaction brought to reflux (40 °C) for 1 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (100 mL) and the layers separated. The

aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the organic layers combined, dried over $MgSO_4$, and concentrated *in vacuo* to give **297** (10.1 g, Quant.) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37 – 7.23 (m, 5H, 5 × *H*C$_{Ar}$), 3.87 (s, 2H, *H*$_2$C(5)), 3.52 (d, J = 7.0 Hz, 2H, *H*$_2$C(7)), 3.31 (s, 2H, *H*$_2$C(8)), 3.07 (t, J = 7.0 Hz, 2H, *H*$_2$C(6)), 1.47 (s, 9H, 3 × *H*$_3$C(11)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 170.8 (*C*(9)), 139.0 (*C*(4)), 128.9 (*C*$_{Ar}$), 128.5 (*C*$_{Ar}$), 127.4 (*C*(4)), 81.3 (*C*(10)), 58.4 (*C*(5)), 55.9 (*C*(8)), 55.6 (*C*(6)), 42.4 (*C*(7)), 28.4 (3 × *C*(11)).

Data was consistent with that previously reported.[60]

tert-Butyl 1-benzylazetidine-2-carboxylate (298)

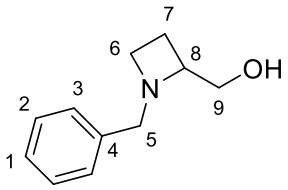


To a stirred solution of ester **297** (10.1 g, 33 mmol, 1.0 equiv.) in THF (300 mL) at 0 °C was added ^{t}BuOK (4.48 g, 40 mmol, 1.2 equiv.) portionwise and the reaction was left to stir for 15 min whilst warming to RT. The reaction was then quenched by the addition of sat. aq. NH_4Cl (15 mL) and partial removal of the THF *in vacuo*. EtOAc (100 mL) and water (100 mL) were then added, and the layers separated. The aqueous layer was extracted with EtOAC (2 × 50 mL) and the organic layers combined, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 85:15) gave the desired compound **298** (3.0 g, 37%) as a thick oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.34 – 7.15 (m, 5H, 5 × *H*C$_{Ar}$), 3.82 (d, J = 12.6 Hz, 1H, *H*$_a$H$_b$C(5)), 3.64 – 3.57 (m, 1H, *H*C(8)), 3.53 (d, J = 12.5 Hz, 1H, H$_a$*H*$_b$C(5)), 3.27 (dddd, J = 8.2, 6.6, 2.5, 0.8 Hz, 1H, *H*$_a$H$_b$C(6)), 2.87 (ddd, J = 9.4, 7.9, 6.6 Hz, 1H, H$_a$*H*$_b$C(6)), 2.31 (ddt, J = 10.5, 9.2, 8.4 Hz, 1H, *H*$_a$H$_b$C(7)), 2.13 (dtd, J = 10.5, 8.0, 2.4 Hz, 1H, H$_a$*H*$_b$C(7)), 1.40 (s, 9H, 3 × *H*$_3$C(11)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 171.8 (*C*(9)), 137.4 (*C*(4)), 129.1 (*C*(1)), 128.2 (2 × *C*$_{Ar}$), 127.1 (2 × *C*$_{Ar}$), 80.6 (*C*(10)), 65.1 (*C*(8)), 62.5 (*C*(5)), 50.6 (*C*(6)), 28.0 (3 × *C*(11)), 21.4 (*C*(7)).

Data was consistent with that previously reported.[60]

(1-Benzylazetidin-2-yl)methanol (299)

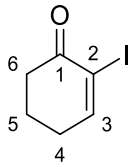


To a stirred solution of ester **298** (2.0 g, 8.1 mmol, 1.0 equiv.) in THF (30 mL) at 0 °C was added $LiAlH_4$ (615 mg, 16.2 mmol, 2.0 equiv.) portionwise and the reaction left to stir for 2 h. The reaction was then warmed to RT and quenched by the sequential addition of water (0.6 ml), 15% aqueous NaOH (0.6 mL), water (1.8 mL) and $MgSO_4$ (8 g) before being stirred at RT for 2 h. The thick emulsion was then filtered under reduced pressure and the solvent removed *in vacuo* to give the desired alcohol **299** as an oil (1.29 g, 90%) that was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37 – 7.24 (m, 5H, 5 × *H*C_{Ar}), 3.73 – 3.55 (m, 2H, *H*$_2$C(5)), 3.44 (ddd, J = 8.1, 2.7 Hz, 1H, *H*C(8)), 3.36 – 3.29 (m, 3H, *H*$_a$H$_b$C(9) and *H*$_2$C(6)), 2.96 (td, J = 8.8, 6.8 Hz, 1H, H$_a$*H*$_b$C (6)), 2.23 (dq, J = 10.5, 8.7 Hz, 1H, *H*$_a$H$_b$C(7)), 1.95 (dtd, J = 10.5, 8.0, 2.5 Hz, 1H, H$_a$*H*$_b$C(7)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.2 (*C*$_{Ar}$), 128.7 (2 × *C*$_{Ar}$), 128.5 (2 × *C*$_{Ar}$), 127.3 (*C*$_{Ar}$), 66.8 (*C*(8)), 62.2 (*C*(6)), 62.0 (*C*(5)), 51.5 (*C*(9)), 18.7 (*C*(7)).

Data was consistent with that previously reported.[60]

2-Iodocyclohex-2-en-1-one (301)



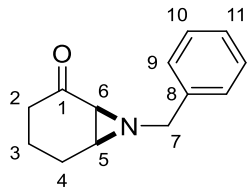
To a stirred solution of cyclohexenone **300** (1.0 mL, 10 mmol, 1.0 equiv.) in THF-water (1:1, 50 mL) was added sequentially K_2CO_3 (1.66 g, 12 mmol, 1.2 equiv.), I_2 (3.8 g, 15 mmol, 1.5 equiv.) and DMAP (240 mg, 2 mmol, 0.2 equiv.) and the reaction left to stir for 1 h. The reaction mixture was then poured into

EtOAc (100 mL), washed with sat. aq. $Na_2S_2O_3$ (2 × 100 mL), 0.1 M aq. HCl (200 mL) and brine. Drying over $MgSO_4$ and concentration *in vacuo* yielded crude **301**. Purification by column chromatography (SiO_2, dry load, pentane:EtOAc, 90:10) gave the desired compound **301** (1.44 g, 65%) as a pale yellow solid that slowly decomposed when stored at RT.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.77 (t, J = 4.5 Hz, 1H, *H*C(3)), 2.71 – 2.60 (t, 2H, H_2C(6)), 2.49 – 2.37 (dt, 2H, H_2C(4)), 2.08 (tt, J = 6.3 Hz, 2H, H_2C(5)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 192.4 (*C*(1)), 159.6 (*C*(3)), 104.0 (*C*(2)), 37.4 (*C*(6)), 30.1 (*C*(4)), 23.0 (*C*(5)).

Data was consistent with that previously reported.[62]

7-Benzyl-7-azabicyclo[4.1.0]heptan-2-one (302)

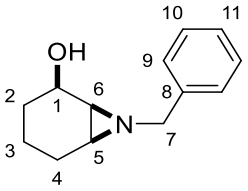


To a stirred solution of iodide **301** (1.10 g, 5 mmol, 1.0 equiv.) and benzylamine (0.82 mL, 7.5 mmol, 1.5 equiv.) in toluene (50 mL) at 95 °C was added Cs_2CO_3 (1.76 g, 5 mmol, 1.0 equiv.) and phenanthroline (0.90 g, 5 mmol, 1.0 equiv.) and the reaction left to stir for 2 h. Filtration through a plug of SiO_2 and concentration *in vacuo* yielded **302** (412 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.36 – 7.09 (m, 5H, 5 × *H*C$_{Ar}$), 3.73 (d, J = 13.7 Hz, 1H, H_aH$_b$C(7)), 3.30 (d, J = 13.7 Hz, 1H, H$_a$$H_b$C(7)), 2.48 – 2.33 (m, 1H, H_aH$_b$C(2)), 2.25 (dd, J = 5.9, 2.3 Hz, 1H, H$_a$$H_b$C(2)), 2.06 (d, J = 6.0, 1H, *H*C(6)), 2.03 – 1.87 (m, 3H, H_2C(4) and H_aH$_b$C(3)), 1.73 – 1.61 (m, 1H, H$_a$$H_b$C(3)), 1.54 (td, J = 12.0, 11.3, 5.6 Hz, 1H, *H*C(5)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 207.9 (*C*(1)), 138.6 (*C*(8)), 128.6 (2 × C_{Ar}), 127.7 (2 × C_{Ar}), 127.4 (*C*(11)) , 63.4 (*C*(7)), 46.5 (*C*(6)), 43.9 (*C*(5)), 37.2 (*C*(2)), 23.3 (*C*(4)), 18.9 (*C*(3)).

Data was consistent with that previously reported.[62]

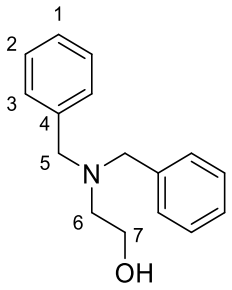
7-benzyl-7-azabicyclo[4.1.0]heptan-2-ol (303)



To a stirred solution of ketone **302** (400 mg, 2 mmol, 1.0 equiv.) in MeOH (10 mL) at 0 °C was added $NaBH_4$ (270 mg, 7.2 mmol, 3.6 equiv.) and the reaction left to stir for 3 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (5 mL) and CH_2Cl_2 (5 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with water (10 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to give a crude oil. Purification by column chromatography (SiO_2, dry load, pentane:EtOAc, 80:20 to 60:40) gave the desired compound **303** (189 mg, 47%) as a pale brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 – 7.23 (m, 5H, 5 × *H*C_{Ar}), 3.95 (dq, J = 10.3, 5.2 Hz, 1H, *H*C(1)), 3.55 (d, J = 13.5 Hz, 1H, *H*$_a$H$_b$C(7)), 3.41 (d, J = 13.5 Hz, 1H, H$_a$*H*$_b$C(7)), 2.36 (d, J = 9.9 Hz, 1H, *H*OC(1)), 2.06 (t, J = 5.8 Hz, 1H, *H*C(6)), 1.97 (t, J = 5.4 Hz, 1H, *H*C(5)), 1.85 (dt, J = 14.0, 5.7 Hz, 1H, *H*$_a$H$_b$C(4)), 1.70 – 1.57 (m, 1H, H$_a$*H*$_b$C(4)), 1.46 (dddd, J = 21.2, 10.2, 5.0, 2.2 Hz, 2H, *H*$_a$H$_b$C(3) and *H*$_a$H$_b$C(2)), 1.39 – 1.29 (m, 1H, H$_a$*H*$_b$C(2)), 1.18 (dtd, J = 13.7, 8.5, 6.1 Hz, 1H, H$_a$*H*$_b$C(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.5 (*C*(8)), 128.6 (2 × *C*$_{Ar}$), 128.0 (2 × *C*$_{Ar}$), 127.3 (*C*(11)), 64.4 (*C*1)), 64.3 (*C*(7)), 43.1 (*C*(6)), 42.2 (*C*(5)), 30.8 (*C*(2)), 23.9 (*C*(4)), 17.0 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 3387, 2935, 1453, 1064, 846, 732, 698; **HRMS** (ESI$^+$) $C_{13}H_{18}ON$ requires 204.13829, found $[M+H]^+$ 204.13841 (Δ 0.60 ppm); **M.p.** 68 – 70 °C.

2-(Dibenzylamino)ethan-1-ol (305)

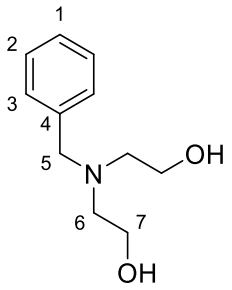


Ethanolamine **304** (1.50 mL, 25 mmol, 1.0 equiv.), benzyl bromide (6.30 mL, 53 mmol, 2.1 equiv.) and K_2CO_3 (6.9g, 50 mmol, 2.0 equiv.) were added to acetone (50 mL) and stirred for 16 h at RT. The reaction mixture was then filtered, and the solvent removed *in vacuo*. The crude product was then passed through a plug of SiO_2 (eluting with pentane:Et_2O, 70:30 to 40:60) and the solvent removed *in vacuo* to give an oil which crystallised over 3 d. Washing with pentane and water gave pure **305** (2.29 g, 38%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 – 7.21 (m, 10H, 10 × *H*C_{Ar}), 3.63 (s, 4H, 2 × *H*$_2$C(5)), 3.58 (d, J = 5.6 Hz, 2H, *H*$_2$C(7)), 2.67 (d, J = 5.5 Hz, 2H, *H*$_2$C(6)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.9 (2 × *C*(4)), 129.1 (4 × C_{Ar}), 128.6 (4 × C_{Ar}), 127.4 (2 × *C*(1)), 58.6 (*C*(7)), 58.3 (2× *C*(5)), 54.9 (*C*(6)).

Data was consistent with that previously reported.[122]

2,2'-(Benzylazanediyl)bis(ethan-1-ol) (307)



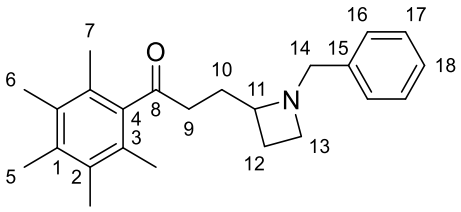
Diethanolamine **306** (4.78 mL, 50 mmol, 1.0 equiv.), benzyl bromide (5.95 mL, 50 mmol, 1.0 equiv.) and K_2CO_3 (15.0g, 109 mmol, 2.2 equiv.) were added to acetone (100 mL) and stirred for 16 h at reflux (56 °C). The reaction mixture was then filtered, and the solvent removed *in vacuo*. Water (100 mL) and $CHCl_3$ (100mL) were added and the layers separated. The aqueous layer was extracted with $CHCl_3$ (2 ×

50 mL), the organic layers were then combined, washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to give diol **307** (10.35g, Quant.).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42 – 7.18 (m, 5H, 5 × *H*C_{Ar}), 3.71 (s, 2H, *H*$_2$C(5)), 3.65 – 3.60 (m, 4H, 2 × *H*$_2$C(7)), 2.74 – 2.69 (m, 4H, 2 × *H*$_2$C(6)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.8 (*C*(4)), 129.0 (2 × C_{Ar}), 128.5 (2 × C_{Ar}), 127.3 (*C*(1)), 58.6 (*C*(5)), 58.2 (*C*(7)), 54.8 (*C*(6)).

Data was consistent with that previously reported.[123]

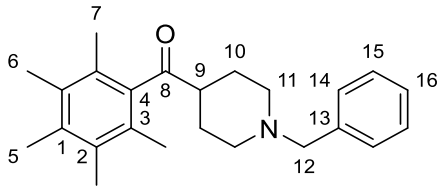
3-(1-Benzylazetidin-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one (309)



(1-Benzylazetidin-2-yl)methanol **299** (159 mg, 0.9 mmol) was subjected to **General Procedure A**. Purification by column chromatography (SiO_2, dry load, pentane:Et_2O, 50:50) gave the desired compound **309** (120 mg, 57%) as a dark orange gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.34 – 7.18 (m, 5H, 5 × *H*C_{Ar}), 3.73 (d, J = 12.7 Hz, 1H, *H*$_a$H$_b$C(14)), 3.46 (d, J = 12.7 Hz, 1H, H$_a$*H*$_b$C(14)), 3.26 (td, J = 7.4, 5.2 Hz, 2H, *H*$_2$C(13)), 2.80 (dt, J = 9.4, 7.5 Hz, 1H, *H*C(11)), 2.63 (qdd, J = 18.2, 9.4, 6.0 Hz, 2H, *H*$_2$C(9)), 2.23 (s, 3H, *H*$_3$C(5)), 2.18 (s, 6H, 2 × *H*$_3$C(6)), 2.07 (s, 6H, 2 × *H*$_3$C(7)), 2.01 (td, J = 10.0, 8.8, 6.6 Hz, 1H, *H*$_2$C(12)), 1.94 – 1.74 (m, 2H, *H*$_2$C(10)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 211.8 (*C*(8)), 140.8 (C_{Ar}), 138.6 (C_{Ar}), 135.4 (C_{Ar}), 133.2 (2 × C_{Ar}), 128.9 (2 × C_{Ar}), 128.4 (2 × C_{Ar}), 127.4 (2 × C_{Ar}), 127.1 (C_{Ar}), 66.1 (*C*(11)), 63.1 (*C*(14)), 51.5 (*C*(13)), 41.4 (*C*(9)), 29.4 (*C*(10)), 23.5 (*C*(12)), 17.4 (2 × *C*(6)), 16.8 (*C*(5)), 16.1 (2 × *C*(7)); **IR** ν_{max} (film)/cm^{-1} 2924, 2361, 2341, 1699, 1453, 1380, 1348, 1308, 1168, 1117, 1072, 1028, 733, 698; **HRMS** (ESI$^+$) $C_{24}H_{32}ON$ requires 350.24784, found [M+H]$^+$ 350.24679 (Δ –2.99 ppm).

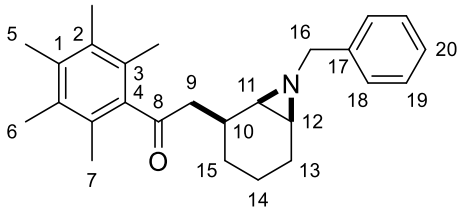
(1-Benzylpiperidin-4-yl)(2,3,4,5,6-pentamethylphenyl)methanone (310)



2,2'-(Benzylazanediyl)bis(ethan-1-ol) **307** (351 mg, 1.8 mmol) was subjected to **General Procedure A**. Purification by column chromatography (SiO_2, dry load, pentane:Et_2O, 70:30) gave the desired compound **310** (143 mg, 34%) as pale orange crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.28 – 7.15 (m, 5H, 5 × *H*C$_{Ar}$), 3.43 (s, 2H, *H*$_2$C(12)), 2.95 – 2.83 (m, 2H, 2 × *H*$_a$H$_b$C(11)), 2.50 (tt, J = 11.4, 4.0 Hz, 1H, *H*C(9)), 2.16 (s, 3H, *H*$_3$C(5)), 2.11 (s, 6H, 2 × *H*$_3$C(6)), 2.01 (s, 6H, 2 × *H*$_3$C(7)), 1.87 (td, J = 11.6, 2.7 Hz, 2H, 2 × H$_a$*H*$_b$C(11)), 1.81 – 1.64 (m, 4H, 2 × *H*$_2$C(10)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 214.1 (*C*(8)), 139.9 (*C*$_{Ar}$), 138.5 (*C*$_{Ar}$), 135.6 (*C*$_{Ar}$), 133.2 (2 × *C*$_{Ar}$), 129.2 (2 × *C*$_{Ar}$), 128.3 (2 × *C*$_{Ar}$), 128.1 (2 × *C*$_{Ar}$), 127.1 (*C*$_{Ar}$), 63.3 (*C*(12)), 53.5 (2 × *C*(11)), 51.3 (*C*(9)), 27.8 (2 × *C*(10)), 18.1 (2 × *C*(6)), 16.9 (*C*(5)), 16.2 (2 × *C*(7)); **IR** ν_{max} (film)/cm^{-1} 2957, 2917, 2360, 2342, 1697, 1453, 1027, 733, 697, 669; **HRMS** (ESI$^+$) $C_{24}H_{32}ON$ requires 350.24784, found $[M+H]^+$ 350.24780 (Δ –0.11 ppm); **M.p.** 220 – 222 °C.

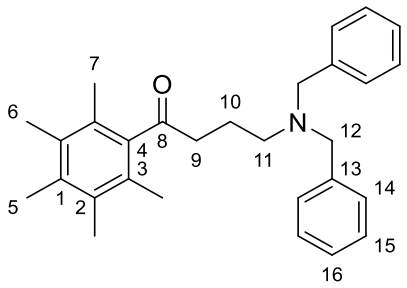
2-7-Benzyl-7-azabicyclo[4.1.0]heptan-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (311)



7-Benzyl-7-azabicyclo[4.1.0]heptan-2-ol **303** (182 mg, 0.9 mmol) was subjected to **General Procedure A**. Purification by column chromatography (SiO_2, dry load, pentane:Et_2O, 80:20) gave a single diastereomer **311** (118 mg, 53%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39 – 7.16 (m, 5H, 5 × *H*C$_{Ar}$), 3.68 (d, J = 13.9 Hz, 1H, *H*$_a$H$_b$C(16)), 3.13 (d, J = 13.9 Hz, 1H, H$_a$*H*$_b$C(16)), 2.87 – 2.58 (m, 2H, *H*$_2$C(9)), 2.45 (q, J = 4.9 Hz, 1H, *H*C(12)), 2.22 (s, 3H, *H*$_3$C(5)), 2.17 (s, 6H, 2 × *H*$_3$C(6)), 2.05 (s, 6H, 2 × *H*$_3$C(7)), 1.95 (dd, J = 6.5, 4.1 Hz, 1H, *H*C(11)), 1.87 (dt, J = 14.6, 5.3 Hz, 1H, *H*C(10)), 1.72 (q, J = 5.8 Hz, 2H, *H*$_2$C(15)), 1.52 – 1.41 (m, 2H, *H*$_2$C(13)), 1.22 – 1.07 (m, 2H, *H*$_2$C(14)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 212.0 (*C*(8)), 140.8 (*C*$_{Ar}$), 140.1 (*C*$_{Ar}$), 135.4 (*C*$_{Ar}$), 133.1 (2 × *C*$_{Ar}$), 128.3 (2 × *C*$_{Ar}$), 128.0 (2 × *C*$_{Ar}$), 127.4 (2 × *C*$_{Ar}$), 126.8 (*C*$_{Ar}$), 64.9 (*C*(16)), 50.6 (*C*(11)), 42.4 (*C*(9)), 40.0 (*C*(12)), 29.7 (*C*(13)), 26.7 (*C*(10)), 24.3 (*C*(15)), 21.0 (*C*(14)), 17.2 (2 × *C*(6)), 16.8 (*C*(5)), 16.1 (2 × *C*(7)); **IR** ν_{max} (film)/cm^{-1} 2928, 1698, 1453, 1382, 1350, 1110, 732, 698; **HRMS** (ESI$^+$) $C_{26}H_{34}ON$ requires 376.26349, found $[M+H]^+$ 376.26310 (Δ –1.06 ppm).

4-(Dibenzylamino)-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one (312)



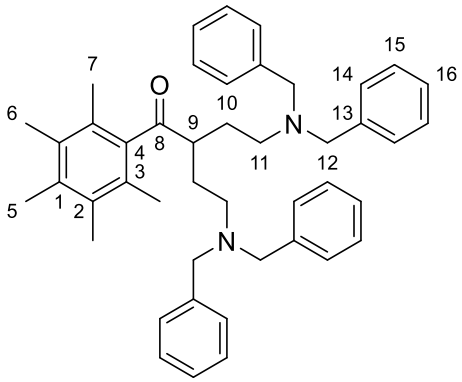
2-(Dibenzylamino)ethan-1-ol **305** (216 mg, 0.9 mmol) was subjected to **General Procedure A**. Purification by column chromatography (SiO_2, dry load, pentane:Et_2O, 90:10, R_f = 0.5) gave the desired compound **312** (138 mg, 44%) as a yellow solid.

or

2-(Dibenzylamino)ethan-1-ol **305** (241 mg, 1.0 mmol) was subjected to **General Procedure E** at 85 °C. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 92:8) gave the desired compound **312** (305 mg, 74%) as a pale yellow solid. A small sample was recrystallized from MeOH and used to provide an X-Ray crystal structure – see Appendix **A1.1** for data.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 – 7.18 (m, 10H, 10 × *H*C_{Ar}), 3.57 (s, 4H, 2 × *H*$_2$C(12)), 2.70 (t, J = 8.0 Hz, 2H, *H*$_2$C(9)), 2.51 (t, J = 6.9 Hz, 2H, *H*$_2$C(11)), 2.24 (s, 3H, *H*$_3$C(5)), 2.18 (s, 6H, 2 × *H*$_3$C(6)), 2.04 (s, 6H, 2 × *H*$_3$C(7)), 1.96 (dt, J = 7.9, 6.9 Hz, 2H, *H*$_2$C(10)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 212.3 (*C*(8)), 140.9 (*C*(4)), 139.8 (2 × *C*(13)), 135.4 (C_{Ar}), 133.2 (2 × C_{Ar}), 128.9 (4 × C_{Ar}), 128.3 (4 × C_{Ar}), 127.5 (2 × C_{Ar}), 126.9 (2 × C_{Ar}), 58.3 (2 × *C*(12)), 52.8 (*C*(11)), 43.4 (*C*(9)), 20.8 (*C*(10)), 17.4 (2 × *C*(6)), 16.8 (*C*(5)), 16.1 (2 × *C*(7)); **IR** ν_{max} (film)/cm^{-1} 3027, 2929, 2797, 1698, 1494, 1453, 1381, 1125, 745, 699; **HRMS** (ESI$^+$) $C_{29}H_{36}ON$ requires 414.27914, found $[M+H]^+$ 414.27832 (Δ –1.98 ppm); **M.p.** 68 – 70 °C.

4-(Dibenzylamino)-2-(2-(dibenzylamino)ethyl)-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one (313)

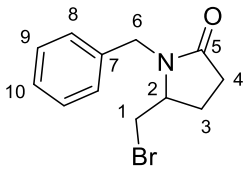


2-(Dibenzylamino)ethan-1-ol **305** (216 mg, 0.9 mmol) was subjected to **General Procedure A**. Purification by column chromatography (SiO_2, dry load, pentane:Et_2O, 90:10, R_f = 0.25) gave the desired compound **313** (41 mg, 21%) as an orange gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.30 – 7.16 (m, 20H, 20 × *H*C_{Ar}), 3.46 (d, J = 13.7 Hz, 4H, 2 × *H*$_2$C(12)), 3.33 (d, J = 13.7 Hz, 4H, 2 × *H*$_2$C(12)), 2.83 – 2.71 (m, 1H, *H*C(9)), 2.46 – 2.26 (m, 4H, 2 × *H*$_2$C(11)), 2.19 (s, 3H, *H*$_3$C(5)), 2.11 (s, 6H, 2 × *H*$_3$C(6)), 1.95 (s, 6H, 2 × *H*$_3$C(7)), 1.93 – 1.81 (m, 2H, *H*$_2$C(10)), 1.52 – 1.38 (m, 2H, *H*$_2$C(10)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 213.9 (*C*(8)), 139.7 (4 × C_{Ar}), 139.6 (C_{Ar}), 135.5 (C_{Ar}), 133.1 (2 × C_{Ar}), 128.9 (8 × C_{Ar}), 128.4 (2 × C_{Ar}), 128.2 (8 × C_{Ar}), 126.9 (4 × C_{Ar}), 58.0 (*C*(12)), 51.1 (*C*(11)), 49.4 (*C*(9)), 26.4 (*C*(10)), 18.0 (2 × *C*(6)), 16.9 (*C*(5)), 16.2 (2 × *C*(7)); **IR** ν_{max} (film)/cm^{-1} 3027, 2928, 2799,

1691, 1494, 1453, 1365, 1303, 1260, 1110, 1074, 1028, 912, 744, 698; **HRMS** (ESI^+) $C_{45}H_{53}ON_2$ requires 637.41524, found $[M+H]^+$ 637.41498 (Δ –0.41 ppm).

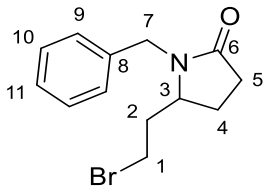
1-Benzyl-5-(bromomethyl)pyrrolidin-2-one (326)



Aziridine ketone **287** (108 mg, 0.3 mmol) was subjected to **General Procedure B**. Purification by column chromatography (SiO_2, dry load, Et_2O) gave the desired compound **326** (41 mg, 50%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.51 – 7.14 (m, 5H, 5 × *H*C_{Ar}), 5.06 (d, J = 15.2 Hz, 1H, $H_aH_bC(6)$), 3.99 (d, J = 15.2 Hz, 1H, $H_aH_bC(6)$), 3.75 (tt, J = 8.4, 3.7 Hz, 1H, *H*C(2)), 3.52 – 3.33 (m, 2H, $H_2C(1)$), 2.63 (ddd, J = 17.3, 10.2, 7.1 Hz, 1H, $H_aH_bC(4)$), 2.45 (ddd, J = 16.8, 10.4, 5.4 Hz, 1H, $H_aH_bC(4)$), 2.24 – 2.11 (m, 1H, $H_aH_bC(3)$), 1.98 (ddd, J = 11.7, 9.5, 5.0 Hz, 1H, $H_aH_bC(3)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 175.3 (*C*(5)), 136.2 (C_{Ar}), 129.0 (2 × C_{Ar}), 128.1 (2 × C_{Ar}), 127.9 (C_{Ar}), 56.7 (*C*(2)), 44.4 (*C*(6)), 35.0 (*C*(1)), 30.0 (*C*(4)), 23.1 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 2958, 1681, 1416, 1254, 705; **HRMS** (ESI^+) $C_{12}H_{15}ON^{79}Br$ requires 268.03315, found $[M+H]^+$ 268.03328 (Δ 0.41 ppm).

1-Benzyl-5-(2-bromoethyl)pyrrolidin-2-one (327)

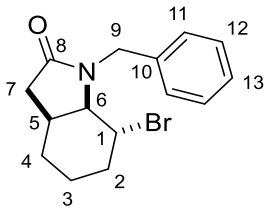


Azetidine ketone **309** (108 mg, 0.3 mmol) was subjected to **General Procedure B**. Purification by column chromatography (SiO_2, dry load, EtOAc) gave the desired compound **327** (137 mg, 68%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.46 – 7.05 (m, 5H, 5 × *H*C_{Ar}), 4.92 (d, J = 15.0 Hz, 1H, $H_aH_bC(7)$), 4.04 (d, J = 15.0 Hz, 1H, $H_aH_bC(7)$), 3.71 – 3.56 (m, 1H, *H*C(3)), 3.37 (ddd, J = 10.3, 7.3, 4.9 Hz, 1H, $H_aH_bC(1)$), 3.26

(ddd, J = 10.2, 8.7, 6.6 Hz, 1H, $H_aH_bC(1)$), 2.58 – 2.20 (m, 2H, $H_2C(5)$), 2.20 – 2.13 (m, 1H, $H_aH_bC(4)$), 1.87 (dddd, J = 14.1, 9.2, 6.7, 4.9 Hz, 1H, $H_aH_bC(4)$), 1.76 – 1.65 (m, 2H, $H_2C(2)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 175.0 (*C*(6)), 136.6 (C_{Ar}), 128.9 (2 × C_{Ar}), 128.2 (2 × C_{Ar}), 127.8 (C_{Ar}), 56.1 (*C*(3)), 44.6 (*C*(7)), 36.1 (*C*(2)), 30.0 (*C*(5)), 28.0 (*C*(4)), 23.8 (*C*(1)); **IR** ν_{max} (film)/cm^{-1} 2932, 1683, 1418, 1261, 703; **HRMS** (ESI$^+$) $C_{13}H_{17}ON^{79}Br$ requires 282.04880, found $[M+H]^+$ 282.04907 (Δ 0.95 ppm).

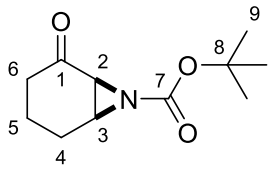
1-Benzyl-7-bromooctahydro-2H-indol-2-one (328)



Cyclic aziridine ketone **311** (84 mg, 0.22 mmol) was subjected to **General Procedure B**. Purification by column chromatography (SiO_2, dry load, EtOAc) gave the desired compound **328** (31 mg, 46%) as a creamy gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.27 – 7.07 (m, 5H, 5 × HC_{Ar}), 4.95 (d, J = 15.0 Hz, 1H, $H_aH_bC(9)$), 4.34 (d, J = 15.0 Hz, 1H, $H_aH_bC(9)$), 4.11 (td, J = 9.6, 8.6, 4.2 Hz, 1H, *H*C(1)), 3.50 (t, J = 6.5 Hz, 1H, *H*C(6)), 2.42 (m, J = 6.1 Hz, 1H, *H*C(5)), 2.22 (s, 1H, $H_aH_bC(7)$), 2.20 (d, J = 3.1 Hz, 1H, $H_aH_bC(7)$), 1.64 – 1.36 (m, 6H, $H_2C(2)$ and *H*C(3) and *H*C(4)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 175.4 (*C*(8)), 136.9 (C_{Ar}), 128.8 (2 × C_{Ar}), 128.3 (2 × C_{Ar}), 127.7 (C_{Ar}), 63.0 (*C*(6)), 52.7 (*C*(1)), 45.5 (*C*(9)), 35.8 (*C*(5)), 34.4 (*C*(2)), 33.5 (*C*(7)), 26.4 (*C*(4)), 20.5 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 2932, 2861, 1689, 1414, 1258, 1218, 1191, 702; **HRMS** (ESI$^+$) $C_{15}H1_9ON^{79}Br$ requires 308.06445, found $[M+H]^+$ 308.06456 (Δ 0.34 ppm).

tert-Butyl-2-oxo-7-azabicyclo[4.1.0]heptane-7-carboxylate (332)

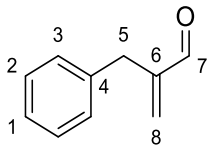


To a stirred solution of 1-(2-aminoethyl)piperidine **336** (128 µL, 0.9 mmol, 0.3 equiv.) in $CHCl_3$ (10 mL) was added cyclohexenone **330** (0.35 mL, 3.6 mmol, 1.2 equiv.), BocNHOTs (0.86 g, 3 mmol, 1.0 equiv.) and $NaHCO_3$ (0.50 g, 6 mmol, 2.0 equiv.) sequentially. The reaction was then stirred at RT for 24 h before being diluted with CH_2Cl_2 (10 mL), passed through a plug of SiO_2 (eluting with CH_2Cl_2) and concentrated *in vacuo* to give the desired aziridine **332** (611 mg, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.10 – 3.04 (m, 1H, *H*C(2)), 2.89 (d, J = 5.8 Hz, 1H, *H*C(3)), 2.50 – 2.18 (m, 2H, H_2C(6)), 2.10 – 1.86 (m, 2H, H_2C(4)), 1.82 – 1.57 (m, 2H, H_2C(5)), 1.45 (d, J = 1.3 Hz, 9H, 3 × H_3C(9)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 204.5 (*C*(7)), 160.7 (*C*(1)), 82.4 (*C*(8)), 43.3 (*C*(2)), 40.6 (*C*(6)), 37.0 (*C*(3)), 28.0 (3 × *C*(9)), 22.7 (*C*(4)), 17.4 (*C*(5)).

Data was consistent with that previously reported.[70]

2-Benzylacrylaldehyde (339)



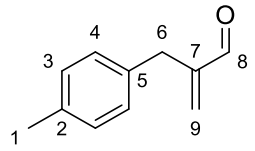
To a stirred solution of pyrrolidine **338** (166 µL, 2 mmol, 0.1 equiv.) and acetic acid (229 µL, 4 mmol, 0.2 equiv.) in CH_2Cl_2 (20 mL) was added 3-phenylpropanal **337** (2.63 mL, 20 mmol, 1.0 equiv.) and formaldehyde in water (37% w/w, 1.62 mL, 20 mmol, 1.0 equiv.), and the reaction heated at reflux (45 °C) for 3 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (100 mL) and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column

chromatography (SiO_2, eluent load, pentane:EtOAc, 97:3) gave the desired compound **339** (1.96 g, 65%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.60 (s, 1H, *H*C(7)), 7.41 – 7.07 (m, 5H, 5 × *H*C_{Ar}), 6.15 – 5.95 (m, 2H, *H*$_2$C(8)), 3.56 (t, J = 1.2 Hz, 2H, *H*$_2$C(5)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 194.0 (*C*(7)), 149.8 (*C*(6)), 138.2 (*C*(4)), 135.2 (2 × *C*$_{Ar}$), 129.3 (2 × *C*$_{Ar}$), 128.7 (*C*(1)), 126.4 (*C*(8)), 34.3 (*C*(5)).

Data was consistent with that previously reported.[124]

2-(4-Methylbenzyl)acrylaldehyde (341)

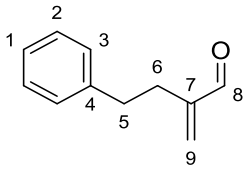


To a stirred solution of pyrrolidine **338** (39 µL, 0.55 mmol, 0.1 equiv.) and acetic acid (63 µL, 1.1 mmol, 0.2 equiv.) in CH_2Cl_2 (6 mL) was added 3-(p-tolyl)propanal **340** (0.81 g, 5.5 mmol, 1.0 equiv.) and formaldehyde in water (37% w/w, 0.45 mL, 5.5 mmol, 1.0 equiv.), and the reaction heated at reflux (45 °C) for 3 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (25 mL) and the phases separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 98:2) gave the desired compound **341** (0.411 g, 47%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.61 (s, 1H, *H*C(8)), 7.12 (d, J = 7.9 Hz, 2H, 2 × *H*C(4)), 7.07 (d, J = 8.1 Hz, 2H, 2 × *H*C(3)), 6.11 (d, J = 1.5 Hz, 1H, *H$_a$*H$_b$C(9)), 6.06 (d, J = 0.9 Hz, 1H, H$_a$*H$_b$*C(9)), 3.53 (s, 2H, *H*$_2$C(6)), 2.33 (s, 3H, *H*$_3$C(1)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 194.0 (*C*(8)), 148.7 (*C*(7)), 135.1 (*C*(5)), 129.2 (2 × *C*$_{Ar}$), 129.0 (2 × *C*$_{Ar}$), 128.6 (*C*(2)), 128.4 (*C*(9)), 33.6 (*C*(6)), 21.1 (*C*(1)).

Data was consistent with that previously reported.[124]

2-Methylene-4-phenylbutanal (343)

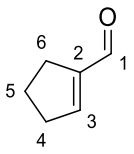


To a stirred solution of 4-phenylbutanal **342** (3.35 g, 23 mmol, 1.0 equiv.) and paraformaldehyde (1.35 g, 46 mmol, 2.0 equiv.) in THF was added diisopropylammonium 2,2,2-trifluoroacetate (4.86 g, 23 mmol, 1.0 equiv.) and trifluoroacetic acid (175 µL, 2.3 mmol, 0.1 equiv.) and the reaction stirred at reflux (66 °C) for 2 h. A second portion of paraformaldehyde (1.35 g, 46 mmol, 2.0 equiv.) was added and the reaction stirred for a further 6 h. The reaction was then cooled to RT and the solvent removed *in vacuo* to give a crude residue which was redissolved in Et_2O (50mL), washed with 1 M aq. HCl (50mL), 1 M aq. NaOH (50mL) and brine before being dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 98:2) gave the desired compound **343** (1.8 g, 50%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.59 (s, 1H, *H*C(8)), 7.40 – 7.14 (m, 5H, 5 × *H*C_{Ar}), 6.24 (d, J = 1.2 Hz, 1H, $H_a$$H_b$C(9)), 6.04 (d, J = 0.7 Hz, 1H, $H_a$$H_b$C(9)), 2.89 – 2.74 (m, 2H, H_2C(5)), 2.67 – 2.52 (m, 2H, H_2C(6)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 194.0 (*C*(8)), 147.7 (*C*(7)), 139.1 (*C*(4)), 135.4 (*C*(9)), 128.8 (2 × C_{Ar}), 128.2 (2 × C_{Ar}), 128.6 (*C*(1)), 126.4 (*C*(1)), 32.6 (*C*(6)), 32.2 (*C*(5)).

Data was consistent with that previously reported.[125]

Cyclopent-1-ene-1-carbaldehyde (333)



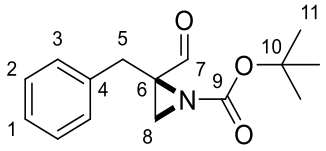
To a stirred solution of $NaIO_4$ (28.3 g, 130 mmol, 1.3 equiv.) in water (250 mL) was added 1,2-cyclohexanediol **343** (12.0 g, 103 mmol, 1.0 equiv.) in Et_2O (150 mL) and the reaction stirred at RT for 30 min. A solution of KOH (8.0 g, 142 mmol, 1.4 equiv.) in water (40 mL) was added and the solution

stirred for 1 h. The layers were separated, and the organic layer washed with water (100 mL) and brine before being dried over $MgSO_4$. Concentration *in vacuo* gave crude **333**. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 80:20) gave the desired compound **333** (5.89 g, 59%) as a pale yellow oil with a very strong almond-like aroma.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.78 (s, 1H, *H*C(1)), 6.86 (ddd, J = 4.5, 2.7, 1.7 Hz, 1H, *H*C(3)), 2.59 (tq, J = 7.5, 2.4 Hz, 2H, 2 × *H*C(6)), 2.51 (ddq, J = 8.2, 6.5, 2.2 Hz, 2H, 2 × *H*C(4), 1.98 (p, J = 7.7 Hz, 2H, 2 × *H*C(5)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 190.0 (*C*(1)), 153.3 (*C*(3)), 148.0 (*C*(2)), 33.8 (*C*(4)), 28.4 (*C*(6)), 23.0 (*C*(5)).

Data was consistent with that previously reported.[126]

tert-Butyl 2-benzyl-2-formylaziridine-1-carboxylate (348)

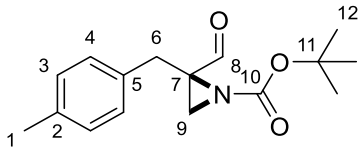


Enal **339** (1.96 g, 13 mmol) was subjected to **General Procedure C** with pyrrolidine as the amine catalyst. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 92:8) gave the desired compound **348** (1.83 g, 54%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.90 (s, 1H, *H*C(7)), 7.41 – 7.10 (m, 5H, 5 × *H*C_{Ar}), 3.17 (dd, J = 28.0, 14.7 Hz, 2H, *H*$_2$C(5)), 2.69 (s, 1H, *H*$_a$H$_b$C(8)), 2.36 (s, 1H, H$_a$*H*$_b$C(8)), 1.42 (s, 9H, 3 × *H*$_3$C(9)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 195.8 (*C*(7)), 159.1 (*C*(9)), 135.9 (*C*$_{Ar}$), 129.9 (2 × *C*$_{Ar}$), 128.5 (2 × *C*$_{Ar}$), 127.0 (*C*$_{Ar}$), 82.6 (*C*(10)), 50.0 (*C*(6)), 35.1 (*C*(6)), 34.4 (*C*(8)), 27.9 (3 × *C*(11)).

Data was consistent with that previously reported.[71]

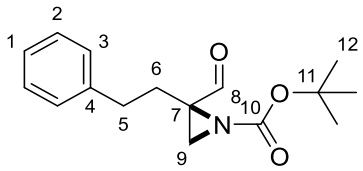
tert-Butyl 2-formyl-2-(4-methylbenzyl)aziridine-1-carboxylate (349)



Enal **341** (400 mg, 2.5 mmol) was subjected to **General Procedure C** with pyrrolidine as the amine catalyst. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 95:5) gave the desired compound **349** (238 mg, 35%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.91 (s, 1H, *H*C(8)), 7.17 (d, J = 8.1 Hz, 2H, 2 × *H*C(4)), 7.09 (d, J = 7.8 Hz, 2H, 2 × *H*C(3)), 3.20 (d, J = 14.8 Hz, 1H, H_aH$_b$C(6)), 3.07 (d, J = 14.9 Hz, 1H, H$_a$$H_b$C(6)), 2.67 (s, 1H, H_aH$_b$C(9)), 2.35 (s, 1H, H$_a$$H_b$C(9)), 2.31 (s, 3H, H_3C(1)), 1.43 (s, 9H, 3 × H_3C(12)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 196.0 (*C*(8)), 159.1 (*C*(10)), 136.5 (*C*(5)), 132.8 (*C*(2)), 129.7 (2 × *C*(3)), 129.2 (2 × *C*(4)), 82.6 (*C*(11)), 50.1 (*C*(7)), 35.0 (*C*(6)), 34.0 (*C*(9)), 27.9 (3 × *C*(12)), 21.2 (*C*(1)); **IR** ν_{max} (film)/cm^{-1} 3368, 2978, 1703, 1515, 1393, 1367, 1251, 1153, 1058, 733; **HRMS** (ESI$^+$) $C_{11}H_{14}ON$ requires 176.10699, found $[M+H]^+$ 176.10712 (Δ 0.72 ppm).

tert-Butyl 2-formyl-2-phenethylaziridine-1-carboxylate (350)

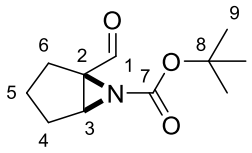


Enal **343** (1.74 g, 11.3 mmol) was subjected to **General Procedure C**. Purification by column chromatography (SiO_2, dry load, pentane:Et_2O, 80:20) gave the desired compound **350** (1.0 g, 28%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.84 (s, 1H, *H*C(8)), 7.41 – 7.12 (m, 5H, 5 × *H*C$_{Ar}$), 2.86 (t, J = 8.2 Hz, 2H, H_2C(5)), 2.71 (s, 1H, H_aH$_b$C(9)), 2.41 (s, 1H, H$_a$$H_b$C(9)), 2.21 (ddd, J = 14.1, 8.9, 7.9 Hz, 1H, H_aH$_b$C(6)), 2.09 – 1.99 (m, 1H, H$_a$$H_b$C(6)), 1.51 (s, 9H, 3 × H_3C(12)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 196.1 (*C*(8)), 159.2 (*C*(10)), 141.2 (*C*(4)), 128.6 (2 × *C*(2)), 128.5 (2 × *C*(3)), 126.3 (*C*(1)), 82.7 (*C*(11)), 49.8 (*C*(7)), 35.7 (*C*(6)),

31.8 (*C*(5)), 30.9 (*C*(9)), 28.0 (3 × *C*(12)); **IR** ν_{max} (film)/cm^{-1} 2979, 2934, 1724, 1369, 1342, 1279, 1244, 1150, 700; **HRMS** (ESI^+) $C_{11}H_{14}ON$ requires 176.10699, found $[M+H]^+$ 176.106 (Δ –0.50 ppm).

tert-Butyl 1-formyl-6-azabicyclo[3.1.0]hexane-6-carboxylate (335)

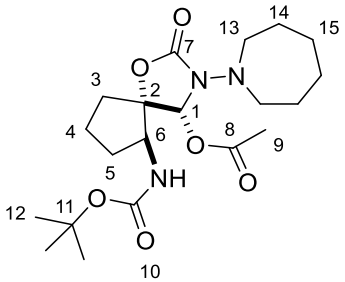


Enal **333** (0.77 g, 34 mmol) was subjected to **General Procedure C** with azepane **346** as the amine catalyst. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 90:10) gave the desired compound **335** (0.80 g, 47%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.14 (s, 1H, *H*C(1)), 3.29 – 3.23 (m, 1H, *H*C(3)), 2.27 – 2.16 (m, 2H $H_a$$H_b$C(4) and $H_a$$H_b$C(6)), 2.13 – 2.04 (m, 1H, $H_a$$H_b$C(6)), 1.88 – 1.74 (m, 3H, $H_a$$H_b$C(4) and H_2C(5)), 1.47 (s, 9H, 3 × H_3C(9)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 196.7 (*C*(1)), 158.0 (*C*(7)), 81.8 (*C*(8)), 58.8 (*C*(2)), 48.1 (*C*(3)), 28.0 (3 × *C*(9)), 25.9 (*C*(4)), 23.2 (*C*(6)), 20.2 (*C*(5))

Data was consistent with that previously reported.[71]

3-(Azepan-1-yl)-6-((tert-butoxycarbonyl)amino)-2-oxo-1-oxa-3-azaspiro[4.4]nonan-4-yl acetate (351)

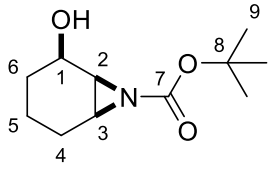


Enal **333** (0.77 g, 34 mmol) was subjected to **General Procedure C** with azepane **346** as the amine catalyst and an extended reaction time of 64 h. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 50:50) gave the unexpected spirocyclic compound **351** (1.96 g, 70%) as a pale

orange solid. A small sample was recrystallized from MeOH and used to provide an X-Ray crystal structure – see Appendix **A1.2** for data.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.32 (s, 1H, *H*C(1)), 4.42 – 4.17 (m, 1H, *H*C(6)), 3.42 – 2.95 (m, 4H, 2 × *H*$_2$C(13)), 2.26 – 2.12 (m, 1H, *H*$_a$H$_b$C(5)), 2.10 (s, 3H, *H*$_3$C(9)), 2.04 – 1.72 (m, 4H, *H*$_2$C(3) and *H*$_2$C(4)), 1.72 – 1.61 (m, 2H, H$_a$*H*$_b$C(5) and *H*$_a$H$_b$C(14)), 1.61 – 1.43 (m, 3H, H$_a$*H*$_b$C(14) and *H*$_2$C(15)), 1.41 (s, 9H, 3 × *H*$_3$C(12)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 170.3 (*C*(8)), 154.8 (*C*(10)), 154.6 (*C*(7)), 90.6 (*C*(2)), 83.4 (*C*(1)), 80.4 (*C*(11)), 56.5 (2 × *C*(13)), 55.1 (*C*(6)), 33.9 (*C*(3)), 31.0 (*C*(5)), 28.5 (3 × *C*(12)), 28.3 (2 × *C*(14)), 27.0 (2 × *C*(15)), 21.7 (*C*(9)), 19.2 (*C*(4)); **IR** ν_{max} (film)/cm^{-1} 2981, 1745, 1703, 1531, 1370, 1251, 1208, 1160, 1068, 1016; **HRMS** (ESI$^+$) $C_{20}H_{34}N_3O_6$ requires 412.2442, found $[M+H]^+$ 412.2443 (Δ 0.35 ppm); **M.p.** 156 – 158 °C.

tert-Butyl-2-hydroxy-7-azabicyclo[4.1.0]heptane-7-carboxylate (356)

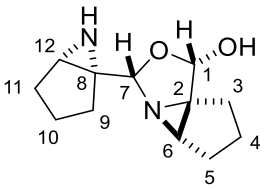


To a stirred solution of aziridine **332** (211 mg, 1 mmol, 1.0 equiv.) in dry MeOH (10 mL) at 0 °C was added $NaBH_4$ (38 mg, 1 mmol, 1.0 equiv.) and the reaction left to stir for 3 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with water (10 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give alcohol **356** (201 mg, 94% as an inseparable mix of diastereomers in a 2:1 ratio) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.08 (dt, J = 8.9, 4.4 Hz, 0.5H, *H*C(1), *minor*), 4.00 – 3.91 (m, 1H, *H*C(1), *major*), 2.82 (dt, J = 3.2, 1.0 Hz, 2H, *H*C(2) and *H*C(3), *major*), 2.67 (ddd, J = 5.8, 4.3, 1.3 Hz, 0.5H, *H*C(3), *minor*), 2.56 (dd, J = 6.0, 0.9 Hz, 0.5H, *H*C(2), *minor*), 2.22 – 2.14 (m, 1H, *H*$_a$H$_b$C(6), *major*), 2.04 – 2.00 (m, 0.5H, *H*$_a$H$_b$C(6), *minor*), 1.98 – 1.88 (m, 0.5H, *H*$_a$H$_b$C(4), *minor*), 1.86 – 1.68 (m, 3H), 1.56 – 1.48 (m, 2H), 1.45 (s, 9H, 3 × *H*$_3$C(9), *major*), 1.44 (s, 4.5H, 3 × *H*$_3$C(9), *minor*), 1.32 – 1.14 (m, 2H); **^{13}C NMR** (101

MHz, $CDCl_3$) δ_C 162.8 (*C*(7), *minor*), 162.6 (*C*(7), *major*), 81.5 (*C*(8), *major*), 81.2 (*C*(8), *minor*), 66.1 (*C*(1), *minor*), 65.2 (*C*(1), *major*), 42.2 (*C*(2, *major*), 41.9 (*C*(2), *minor*), 39.9 (*C*(3), *major*), 37.9 (*C*(3), *minor*), 29.8 (*C*(4), *minor*), 29.7 (*C*(4), *major*), 28.1 (3 × *C*(9), *minor*), 28.0 (3 × *C*(9), *major*), 23.5 (*C*(6), *minor*), 22.8 (*C*(6), *major*), 18.2 (*C*(4), *major*), 15.1 (*C*(4), *minor*); **IR** ν_{max} (film)/cm^{-1} 3411, 2938, 1715, 1368, 1289, 1257, 1227, 1155, 1069; **HRMS** (ESI^+) $C_{11}H_{19}O_3N^{23}Na$ requires 236.12571, found $[M+^{23}Na]^+$ 236.12590 (Δ 0.79 ppm).

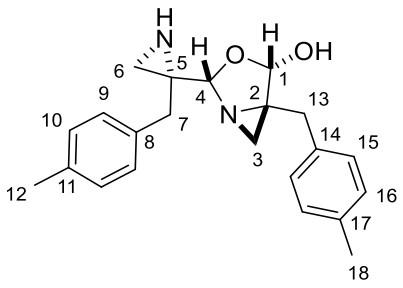
3,6-Azabicyclo[3.1.0]hexan-1-yl)tetrahydro-1H,3H-cyclopenta[2,3]azirino[1,2-c]oxazol-1-ol (366)



Aziridine **335** (1.69 g, 8.0 mmol) was subjected to **General Procedure D**. Purification by column chromatography (SiO_2, eluent load, CH_2Cl_2:MeOH, 95:5) gave the desired compound **366** (0.69 g, 77%) as a thick oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.29 (s, 1H, *H*C(1)), 4.77 (d, J = 0.9 Hz, 1H, *H*C(7)), 2.48 – 2.45 (m, 1H, *H*C(12)), 2.14 (dd, J = 12.9, 8.1 Hz, 1H, $H_aH_bC(3)$), 2.06 – 2.00 (m, 1H, $H_aH_bC(4)$), 1.98 (d, J = 3.0 Hz, 1H, *H*C(6)), 1.93 – 1.76 (m, 6H, H_aH_bC(3) and H_aH_bC(4) and H_2C(5)and H_aH_bC(10) and H_aH_bC(11)), 1.71 – 1.58 (m, 2H, H_aH_bC(10) and H_aH_bC(9)), 1.55 – 1.42 (m, 1H, H_aH_bC(9)), 1.36 (dddd, J = 15.1, 13.5, 8.1, 4.6 Hz, 1H, H_aH_bC(11)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 96.7 (*C*(7)), 95.6 (*C*(1)), 61.8 (*C*(2)), 49.4 (*C*(7)), 45.4 (*C*(6)), 40.9 (*C*(12)), 28.7 (*C*(3)), 27.4 (*C*(10)), 27.2 (*C*(5)), 25.3 (*C*(4)), 21.9 (*C*(9)), 19.3 (*C*(11)); **IR** ν_{max} (film)/cm^{-1} 3274, 2953, 2861, 2361, 1696, 1297, 1105, 1077, 984, 931, 907, 874, 855, 797, 730; **HRMS** (ESI^+) $C_{12}H_{19}O_2N_2$ requires 223.14410, found $[M+H]^+$ 223.14421 (Δ 0.47 ppm).

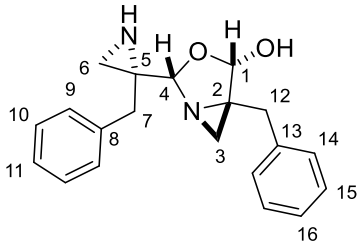
5-(4-Methylbenzyl)-2-(2-(4-methylbenzyl)aziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (367)



Aziridine **349** (227 mg, 0.83 mmol) was subjected to **General Procedure D**. Purification by column chromatography (SiO_2, eluent load, CH_2Cl_2:Acetone, 95:5) gave the desired compound **367** (78 mg, 27%) as off-white crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1H NMR 7.98 (s, 1H, *H*OC(1)), 7.21 (d, J = 8.0 Hz, 2H, 2 × *H*C_{Ar}), 7.15 (d, J = 7.9 Hz, 2H, 2 × *H*C_{Ar}), 7.12 (d, J = 8.0 Hz, 2H, 2 × *H*C_{Ar}), 7.08 (d, J = 8.0 Hz, 2H, 2 × *H*C_{Ar}), 5.19 (s, 1H, *H*C(1)), 4.69 (s, 1H, *H*C(4)), 3.40 (d, J = 14.1 Hz, 1H, H_aH_bC(13)), 3.29 (d, J = 13.9 Hz, 1H, H_aH_bC(7)), 3.11 (d, J = 13.8 Hz, 1H, H_aH_bC(7)), 2.81 (d, J = 14.1 Hz, 1H, H_aH_bC(13)), 2.35 (s, 3H, H_3C(12) or H_3C(18)), 2.34 (s, 3H, H_3C(12) or H_3C(18)), 1.81 (s, 1H, H_aH_bC(6)), 1.73 (s, 1H, H_aH_bC(3)), 1.41 (s, 1H), H_aH_bC(6), 1.39 (s, 1H, H_aH_bC(3)), 0.45 (s, 1H, *H*NC(5)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 137.0 (C_{Ar}), 135.9 (C_{Ar}), 134.9 (C_{Ar}), 132.2 (C_{Ar}), 130.1 (2 × C_{Ar}), 129.8 (2 × C_{Ar}), 129.5 (2 × C_{Ar}), 129.0 (2 × C_{Ar}), 97.8 (*C*(1)), 97.2 (*C*(4)), 52.7 (*C*(2)), 39.8 (*C*(5)), 36.9 (*C*(7)), 34.8 (*C*(13)), 33.1 (*C*(3)), 25.5 (*C*(6)), 21.2 (*C*(12) or *C*(18)), 21.1 (*C*(12) or *C*(18)); **IR** ν_{max} (film)/cm^{-1} 2928, 2361, 1495, 1454, 1105, 1083, 730, 699; **HRMS** (ESI$^+$) $C_{22}H_{27}O_2N_2$ requires 351.20670, found $[M+H]^+$ 351.20630 (Δ –1.16 ppm); **M.p.** 139 – 141 °C.

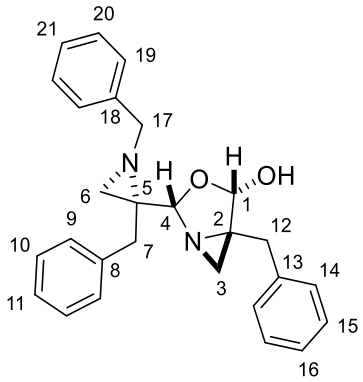
5-Benzyl-2-(2-benzylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (368)



Aziridine **348** (1.96 g, 7.5 mmol) was subjected to **General Procedure D**. Purification by column chromatography (SiO_2, eluent load, CH_2Cl_2:Acetone, 97:3) gave the desired compound **368** (582 mg, 48%) as a white solid. A small sample was recrystallized from EtOAc and used to provide an X-Ray crystal structure to determine the relative stereochemistry of C(5) – see Appendix **A1.3** for data.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.99 (d, J = 10.2 Hz, 1H, *H*OC(1)), 7.44 – 7.20 (m, 10H, 10 × *H*C_{Ar}), 5.28 – 5.20 (m, 1H, *H*C(1)), 4.74 (s, 1H, *H*C(4)), 3.49 (d, J = 14.1 Hz, 1H, $H_a$$H_b$C(12)), 3.41 (d, J = 13.8 Hz, 1H, $H_a$$H_b$C(7)), 3.16 (d, J = 13.8 Hz, 1H, $H_a$$H_b$C(12)), 2.90 (d, J = 14.0 Hz, 1H, $H_a$$H_b$C(7)), 1.89 (d, J = 4.9 Hz, 1H, $H_a$$H_b$C(6)), 1.80 (s, 1H, $H_a$$H_b$C(3)), 1.49 (d, J = 8.0 Hz, 1H, $H_a$$H_b$C(6)), 1.45 (s, 1H, $H_a$$H_b$C(3)), 0.52 (d, J = 8.3 Hz, 1H, *H*NC(5)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.1 (C_{Ar}), 135.4 (C_{Ar}), 130.2 (C_{Ar}), 129.9 (C_{Ar}), 128.8 (2 × C_{Ar}), 128.3 (2 × C_{Ar}), 127.3 (2 × C_{Ar}), 126.5 (2 × C_{Ar}), 97.8 (*C*(1)), 97.0 (*C*(4)), 52.6 (*C*(2)), 39.8 (*C*(5)), 37.6 (*C*(7)), 35.2 (*C*(12)), 33.2 (*C*(6)), 25.7 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 2926, 2361, 1495, 1454, 1104, 1079, 997, 949, 754, 729, 700; **HRMS** (ESI$^+$) $C_{20}H_{23}O_2N_2$ requires 323.17540, found $[M+H]^+$ 323.17557 (Δ 0.50 ppm); **M.p.** 169 – 171 °C.

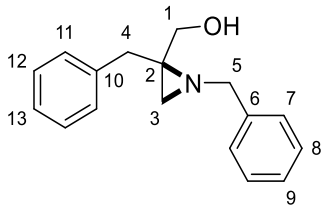
5-Benzyl-2-(1,2-dibenzylaziridin-2-yl)-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol (372)



To a stirred solution of aziridine dimer **368** (100 mg, 0.3 mmol, 1.0 equiv.) in dry DMF (4 mL) at RT was added K_2CO_3 (166 mg, 1.2 mmol, 4.0 eq) and benzyl bromide (86 µL, 0.72 mmol, 2.4 equiv.). The reaction was then left to stir for 16 h at 140 °C. The mixture was then quenched by the addition was water (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 60:40) gave the desired compound **372** (99 mg, 80%) as a cream solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.04 – 7.89 (m, 1H, *H*OC(1)), 7.50 – 7.17 (m, 15H, 15 × *H*C_{Ar}), 5.13 – 5.04 (m, 1H, *H*C(1)), 4.56 (s, 1H, *H*C(4)), 4.00 (d, J = 13.3 Hz, 1H, H_aH_bC(17)), 3.74 (d, J = 13.3 Hz, 1H, H_aH_bC(17)), 3.71 – 3.64 (m, 1H, H_aH_bC(7)), 3.19 (d, J = 14.1 Hz, 1H, H_aH_bC(12)), 3.00 (d, J = 14.2 Hz, 1H, H_aH_bC(7)), 2.46 (d, J = 14.1 Hz, 1H, H_aH_bC(12)), 2.31 (d, J = 1.5 Hz, 1H, H_aH_bC(6)), 1.68 (s, 1H, H_aH_bC(6)), 1.67 (s, 1H, H_aH_bC(3)), 1.25 (d, J = 2.5 Hz, 1H, H_aH_bC(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.2 (C_{Ar}), 138.1 (C_{Ar}), 138.0 (C_{Ar}), 129.6 (2 × C_{Ar}), 129.5 (2 × C_{Ar}), 129.0 (2 × C_{Ar}), 128.9 (2 × C_{Ar}), 128.6 (2 × C_{Ar}), 128.4 (2 × C_{Ar}), 127.8 (C_{Ar}), 126.9 (C_{Ar}), 126.5 (C_{Ar}), 96.3 (*C*(1)), 96.3 (*C*(4)), 65.5 (*C*(2)), 56.4 (*C*(17)), 53.0 (*C*(5)), 26.8 (*C*(6)), 35.4 (*C*(12)), 33.7 (*C*(7)), 33.5 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 2928, 2361, 1495, 1454, 1105, 1083, 730, 699; **HRMS** (ESI$^+$) $C_{27}H_{29}O_2N_2$ requires 413.22235, found $[M+H]^+$ 413.22308 (Δ 1.76 ppm); **M.p.** 151 – 154 °C.

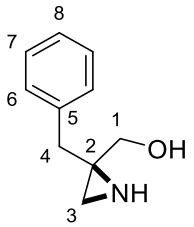
(1,2-dibenzylaziridin-2-yl)methanol (373)



To a stirred solution of aziridine **374** (164 mg, 1.0 mmol, 1.0 equiv.) in dry DMF (5 mL) at RT was added K_2CO_3 (276 mg, 2.0 mmol, 2.0 eq) and benzyl bromide (118 µL, 1.0 mmol, 1.0 equiv.). The reaction was then left to stir for 16 h at RT. The mixture was then quenched by the addition of water (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product. Purification by column chromatography (SiO_2, eluent load, EtOAc:pentane, 60:40) gave the desired compound **373** (147 mg, 65%) as colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.47 – 7.19 (m, 10H, 10 × *H*C$_{Ar}$), 3.89 (d, *J* = 14.0 Hz, 1H, *H*$_a$H$_b$C(5)), 3.81 (d, *J* = 14.0 Hz, 1H, H$_a$*H*$_b$C(5)), 3.54 (d, *J* = 10.8 Hz, 1H, *H*$_a$H$_b$C(1)), 3.32 – 3.24 (m, 1H, H$_a$*H*$_b$C(1)), 3.01 (d, *J* = 14.2, 1H, *H*$_a$H$_b$C(4)), 2.87 (d, *J* = 14.2 Hz, 1H, H$_a$*H*$_b$C(4)), 2.12 (s, 1H, *H*$_a$H$_b$C(3)), 1.67 (s, 1H, H$_a$*H*$_b$C(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.71 (*C*$_{Ar}$), 137.98 (*C*$_{Ar}$), 129.21 (2 × *C*$_{Ar}$), 128.75 (2 × *C*$_{Ar}$), 128.66 (2 × *C*$_{Ar}$), 127.74 (2 × *C*$_{Ar}$), 127.22 (*C*$_{Ar}$), 126.77 (*C*$_{Ar}$), 63.27 (*C*(1)), 56.40 (*C*(5)), 43.45 (*C*(2)), 36.46 (*C*(3)), 34.35 (*C*(4)); **IR** ν_{max} (film)/cm^{-1} 3207, 1494, 1455, 1045, 786, 743, 720, 700, 638; **HRMS** (ESI$^+$) $C_6H_{12}ON$ requires 254.1539, found [M+H]$^+$ 254.1540 (Δ 0.10 ppm); **M.p.** 86 – 88 °C.

(2-Benzylaziridin-2-yl)methanol (374)

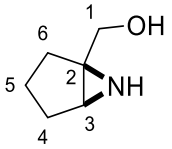


To a stirred solution of aziridine dimer **368** (100 mg, 0.3 mmol, 1.0 equiv.) in dry MeOH (10 mL) at RT was added $NaBH_4$ (45 mg, 1.2 mmol, 4.0 equiv.) and the reaction left to stir for 16 h. The solvent was

then removed *in vacuo* and water (5 mL) was added to the residue. This was then extracted with EtOAc (3 × 20 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product. Purification by column chromatography (SiO_2, eluent load, CH_2Cl_2:MeOH, 97:3) gave the desired compound **374** (75 mg, 70%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39 – 7.05 (m, 5H, 5 × *H*C$_{Ar}$), 3.66 (d, J = 11.5 Hz, 1H, $H_aH_bC(1)$), 3.43 (d, J = 11.5 Hz, 1H, $H_aH_bC(1)$), 3.10 (d, J = 14.0 Hz, 1H, $H_aH_bC(4)$), 2.80 (d, J = 14.0 Hz, 1H, $H_aH_bC(4)$), 1.67 (s, 1H, $H_aH_bC(3)$), 1.57 (s, 1H, $H_aH_bC(3)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 136.5 (*C*$_{Ar}$), 129.8 (2 × *C*$_{Ar}$), 128.7 (2 × *C*$_{Ar}$), 127.0 (*C*$_{Ar}$), 64.9 (*C*(1)), 39.5 (*C*(4)), 39.5 (*C*(2)), 27.7 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 3342, 2921, 2361, 1602, 1495, 1454, 1032, 734, 703; **HRMS** (ESI$^+$) $C_{10}H_{14}ON$ requires 164.10699, found $[M+H]^+$ 164.10698 (Δ –0.05 ppm).

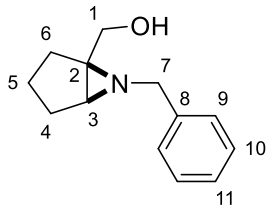
(6-Azabicyclo[3.1.0]hexan-1-yl)methanol (375)



To a stirred solution of aziridine dimer **366** (1.0 g, 4.5 mmol, 1.0 equiv.) in dry MeOH (130 mL) at RT was added $NaBH_4$ (0.68 g, 18 mmol, 4.0 equiv.) and the reaction left to stir for 16 h. The solvent was then removed *in vacuo* and water (50 mL) was added to the residue. This was then extracted with EtOAc (3 × 50 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the desired compound **375** (0.71 g, 70%) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.82 (d, J = 11.6 Hz, 1H, $H_aH_bC(1)$), 3.64 (d, J = 11.6 Hz, 1H, $H_aH_bC(1)$), 2.37 (d, J = 2.2 Hz, 1H, *H*C(3)), 1.94 – 1.83 (m, 2H, $H_2C(5)$), 1.80 – 1.65 (m, 3H, $H_aH_bC(4)$ and $H_2C(6)$), 1.40 – 1.31 (m, 1H, $H_aH_bC(4)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 63.4 (*C*(1)), 48.3 (*C*(2)), 40.5 (*C*(3)), 28.7 (*C*(5)), 27.6 (*C*(6)), 19.4 (*C*(4)); **IR** ν_{max} (film)/cm^{-1} 3340, 2926, 2856, 1496, 1453, 1356, 1300, 1043, 1030, 732, 696; **HRMS** (ESI$^+$) $C_6H_{12}ON$ requires 114.09134, found $[M+H]^+$ 114.09142 (Δ 0.66 ppm).

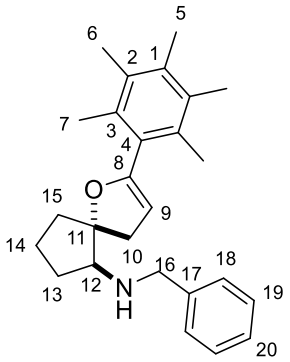
6-Benzyl-6-azabicyclo[3.1.0]hexan-1-yl)methanol (376)



To a stirred solution of aziridine **375** (226 mg, 2.0 mmol, 1.0 equiv.) in dry DMF (5 mL) at RT was added K_2CO_3 (552 mg, 4.0 mmol, 2.0 eq) and benzyl bromide (237 µL, 2.0 mmol, 1.0 equiv.). The reaction was then left to stir for 16 h at RT. The mixture was then quenched by the addition of water (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product. Purification by column chromatography (SiO_2, eluent load, EtOAc:pentane, 60:40) gave the desired compound **376** (190 mg, 47%) as an oil that crystallised upon refrigeration.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.43 – 7.21 (m, 5H, 5 × *H*C_{Ar}), 4.01 (d, J = 12.6 Hz, 1H, *H*$_a$H$_b$C(1)), 3.86 (d, J = 14.9 Hz, 1H, *H*$_a$H$_b$C(7)), 3.73 (d, J = 14.9 Hz, 1H, H$_a$*H*$_b$C(7)), 3.68 – 3.57 (m, 1H, H$_a$*H*$_b$C(1)), 2.07 – 2.04 (m, 1H, *H*C(3)), 2.01 – 1.44 (m, 6H, *H*$_2$C(4) and *H*$_2$C(5) and *H*$_2$C(6)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 140.4 (*C*$_{Ar}$), 128.6 (2 × *C*$_{Ar}$), 127.2 (2 × *C*$_{Ar}$), 126.9 (*C*$_{Ar}$), 61.4 (*C*(1)), 55.2 (*C*(7)), 52.7 (*C*(2)), 49.4 (*C*(3)), 31.1 (*C*(5)), 28.1 (*C*(6)), 21.7 (*C*(4)); **IR** ν_{max} (film)/cm^{-1} 3340, 2926, 2856, 1496, 1453, 1356, 1300, 1043, 1030, 732. 696; **HRMS** (ESI$^+$) $C_{13}H_{18}ON$ requires 204.13829, found [M+H]$^+$ 204.13806 (Δ –1.12 ppm); **M.p.** 65 – 67 °C.

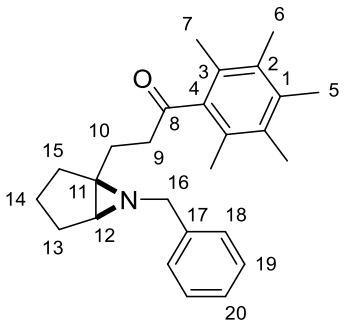
N-Benzyl-2-(2,3,4,5,6-pentamethylphenyl)-1-oxaspiro[4.4]non-2-en-6-amine (377)



Aziridine **376** (112 mg, 0.55 mmol) was subjected to **General Procedure A**. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 90:10) gave the desired compound **377** (71 mg, 49%) as a white solid. A small sample was recrystallized from MeOH and used to provide an X-Ray crystal structure – see Appendix **A1.4** for data.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.39 – 7.32 (m, 2H, 2 × *H*C$_{Ar}$), 7.36 – 7.30 (m, 2H, 2 × *H*C$_{Ar}$), 7.29 – 7.22 (m, 1H, *H*C(20)), 4.73 (t, J = 2.4 Hz, 1H, *H*C(9)), 3.88 (s, 2H, *H*$_2$C(16)), 3.33 (dd, J = 15.2, 2.3 Hz, 1H, *H*$_a$H$_b$C(10)), 3.27 (t, J = 7.9 Hz, 1H, *H*C(12)), 2.45 (dd, J = 15.2, 2.6 Hz, 1H, H$_a$*H*$_b$C(10)), 2.27 (s, 6H, 2 × *H*$_3$C(7)), 2.22 (s, 3H, *H*$_3$C(5)), 2.20 (s, 6H, 2 × *H*$_3$C(6)), 2.09 – 2.02 (m, 1H, *H*$_a$H$_b$C(13)), 2.08 – 1.88 (m, 2H, *H*$_2$C(15)), 1.80 – 1.62 (m, 2H, *H*$_2$C(14)), 1.48 (s, 1H, *H*N), 1.46 – 1.38 (m, 1H, H$_a$*H*$_b$C(13)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 154.5 (*C*(8)), 141.1 (*C*(17)), 135.6 (*C*(1)), 133.0 (2 × *C*(3)), 132.6 (2 × *C*(2)), 129.8 (*C*(4)), 128.5 (2 × *C*(19)), 128.1 (2 × *C*(18)), 127.0 (*C*(20)), 98.1 (*C*(9)), 95.5 (*C*(11)), 64.3 (*C*(12)), 52.8 (*C*(16)), 37.8 (*C*(15)), 35.3 (*C*(10)), 29.6 (*C*(13)), 19.0 (*C*(14)), 17.8 (2 × *C*(7)), 16.9 (*C*(5)), 16.6 (2 × *C*(6)); **IR** ν_{max} (film)/cm^{-1} 2947, 2872, 2360, 1665, 1453, 1261, 1149, 1008, 971, 733, 698; **HRMS** (ESI$^+$) $C_{26}H_{34}ON$ requires 376.26349, found $[M+H]^+$ 276.26471 (Δ 3.24 ppm); **M.p.** 70 – 72 °C.

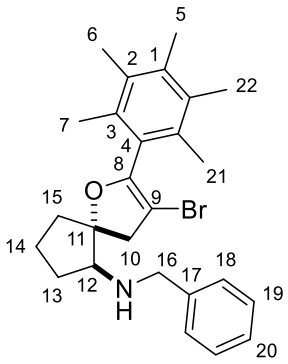
6-Benzyl-6-azabicyclo[3.1.0]hexan-1-yl)-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one (378)



Aziridine **376** (509 mg, 2.5 mmol) was subjected to **General Procedure A**. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc:Et_3N, 90:9:1) gave the desired compound **378** (529 mg, 68%) as an orange solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40 – 7.18 (m, 5H, 5 × *H*C_{Ar}), 3.85 – 3.63 (m, 2H, *H*$_2$C(16)), 2.77 (ddd, J = 18.7, 9.0, 6.8 Hz, 2H, *H*$_2$C(9)), 2.26 – 2.09 (m, 2H, *H*$_2$C(10)), 2.23 (s, 3H, *H*$_3$C(5)), 2.18 (s, 6H, 2 × *H*$_3$C(6)), 2.03 (s, 6H, 2 × *H*$_3$C(7)), 1.98 – 1.88 (m, 1H, H_aH_bC(15)), 1.92 (d, J = 1.7 Hz, 1H, *H*C(12)), 1.85 (dq, J = 7.5, 2.5 Hz, 1H, H_aH_bC(15)), 1.56 (qq, J = 6.7, 4.4, 3.5 Hz, 4H, *H*$_2$C(13) and *H*$_2$C(14)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 211.4 (*C*(8)), 140.7 (*C*$_{Ar}$), 135.6 (*C*$_{Ar}$), 133.2 (2 × *C*$_{Ar}$), 128.3 (2 × *C*$_{Ar}$), 127.4 (2 × *C*$_{Ar}$), 127.2 (2 × *C*$_{Ar}$), 126.6 (*C*$_{Ar}$), 60.5 (*C*(11)), 55.1 (*C*(16)), 50.8 (*C*(10)), 50.1 (*C*(12)), 43.8 (*C*(9)), 32.0 (*C*(15)), 28.3 (*C*(13)), 21.5 (*C*(14)), 17.3 (2 × *C*6)), 16.8 (*C*(5)), 16.1 (2 × *C*(7)); **IR** ν_{max} (film)/cm^{-1} 2924, 1699, 1452, 1406, 1382, 1351, 1309, 1117, 733, 697; **HRMS** (ESI$^+$) $C_{26}H_{34}ON$ requires 376.26349, found $[M+H]^+$ 376.26443 (Δ 2.51 ppm); **M.p.** 62 – 65 °C.

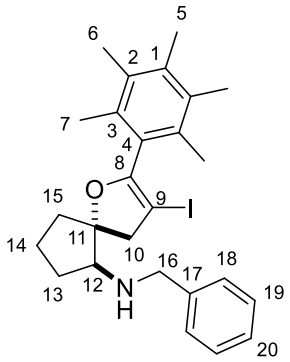
N-Benzyl-3-bromo-2-(2,3,4,5,6-pentamethylphenyl)-1-oxaspiro[4.4]non-2-en-6-amine (382)



To a stirred solution of **378** (75 mg, 0.2 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) at –17 °C was added Br_2 (10 µL, 0.2 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 mL) dropwise and the reaction left to stir for 15 min. The reaction was then diluted with water (5 mL) and Et_2O (5 mL) and the layers separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic extracts washed with sat. aq. $Na_2S_2O_3$ (10 mL), sat. aq. $NaHCO_3$ (10 mL) and brine before being dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 90:10) gave the desired compound **382** (46 mg, 51%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40 – 7.25 (m, 5H, 5 × *H*C_{Ar}), 3.89 (s, 2H, *H*$_2$C(16)), 3.67 (d, J = 14.8 Hz, 1H, *H*$_a$H$_b$C(10)), 3.27 (t, J = 7.8 Hz, 1H, *H*C(12)), 2.69 (d, J = 14.8 Hz, 1H, H$_a$*H*$_b$C(10)), 2.26 (s, 3H, *H*$_3$CC_{Ar}), 2.25 (s, 3H, *H*$_3$CC_{Ar}), 2.24 (s, 3H, *H*$_3$CC_{Ar}), 2.23 (s, 3H, *H*$_3$CC_{Ar}), 2.22 (s, 3H, *H*$_3$CC_{Ar}), 2.03 (dddd, J = 18.6, 17.1, 8.2, 5.1 Hz, 3H, *H*$_a$H$_b$C(13) and *H*$_2$C(15)), 1.75 (dtdd, J = 16.4, 10.2, 8.6, 5.6 Hz, 2H, *H*$_2$C(14)), 1.49 – 1.36 (m, 1H, H$_a$*H*$_b$C(13)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 152.9 (*C*(8)), 140.8 (*C*$_{Ar}$), 136.4 (*C*$_{Ar}$), 132.9 (*C*$_{Ar}$), 132.7 (*C*$_{Ar}$), 132.6 (*C*$_{Ar}$), 128.5 (2 × *C*$_{Ar}$), 128.1 (2 × *C*$_{Ar}$), 127.3 (*C*$_{Ar}$), 127.1 (*C*$_{Ar}$), 95.3 (*C*(9)), 91.0 (*C*(11)), 64.2 (*C*(12)), 52.8 (*C*(16)), 41.4 (*C*(10)), 37.78 (*C*(15)), 29.4 (*C*(13)), 18.9 (*C*(14)), 17.5 (H$_3$*C*C_{Ar}), 17.2 (H$_3$*C*C_{Ar}), 17.0 (H$_3$*C*C_{Ar}), 16.6 (H$_3$*C*C_{Ar}), 16.6 (H$_3$*C*C_{Ar}); **IR** ν_{max} (film)/cm^{-1} 2948, 2872, 1672, 1453, 1260, 1160, 1041, 971, 882, 733, 699; **HRMS** (ESI$^+$) $C_{26}H_{33}ON^{79}Br$ requires 454.17400, found [M+H]$^+$ 454.17435 (Δ 0.76 ppm); **M.p.** 87 – 90 °C.

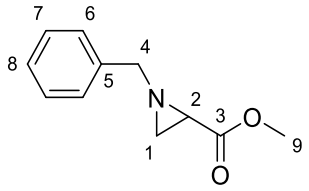
N-Benzyl-3-iodo-2-(2,3,4,5,6-pentamethylphenyl)-1-oxaspiro[4.4]non-2-en-6-amine (384)



To a stirred solution of **378** (37.5 mg, 0.1 mmol, 1.0 equiv.) in CH_2Cl_2 (1 mL) at –17 °C was added ICl (32 µL, 0.2 mmol, 2.0 equiv.) in CH_2Cl_2 (0.25 mL) dropwise and the reaction left to stir for 15 min. The reaction was then diluted with water (5 mL) and Et_2O (5 mL) and the layers separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic extracts washed with sat. aq. $Na_2S_2O_3$ (10 mL), sat. aq. $NaHCO_3$ (10 mL) and brine before being dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 90:10) gave the desired compound **384** (29 mg, 58%) as a yellow crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37 – 7.23 (m, 5H, 5 × *H*C_{Ar}), 3.86 (d, J = 1.0 Hz, 2H, *H*$_2$C(16)), 3.59 (d, J = 14.8 Hz, 1H, *H*$_a$H$_b$C(10)), 3.25 (t, J = 7.7 Hz, 1H, *H*C(12)), 2.65 (d, J = 14.8 Hz, 1H, H$_a$*H*$_b$C(10)), 2.23 (s, 3H, *H*$_3$CC_{Ar}), 2.22 (s, 3H, *H*$_3$CC_{Ar}), 2.20 (s, 6H, 2 × *H*$_3$CC_{Ar}), 2.19 (s, 3H, *H*$_3$CC_{Ar}), 2.08 – 1.91 (m, 3H, *H*$_a$H$_b$C(13) and *H*$_2$C(15)), 1.81 – 1.64 (m, 2H, *H*$_2$C(14)), 1.43 – 1.37 (m, 1H, H$_a$*H*$_b$C(13)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 157.7 (*C*(8)), 140.8 (*C*$_{Ar}$), 136.3 (*C*$_{Ar}$), 132.7 (*C*$_{Ar}$), 132.6 (*C*$_{Ar}$), 132.6 (*C*$_{Ar}$), 132.5 (*C*$_{Ar}$), 128.6 (2 × *C*$_{Ar}$), 128.4 (*C*$_{Ar}$), 128.1 (2 × *C*$_{Ar}$), 127.1 (*C*$_{Ar}$), 96.3 (*C*(11)), 64.2 (*C*(12)), 59.2 (*C*(9)), 52.8 (*C*(16)), 44.5 (*C*(10)), 37.8 (*C*(15)), 29.6 (*C*(13)), 19.0 (*C*(14)), 17.5 (H$_3$*C*C_{Ar}), 17.1 (H$_3$*C*C_{Ar}), 17.0 (H$_3$*C*C_{Ar}), 16.6 (H$_3$*C*C_{Ar}), 16.6 (H$_3$*C*C_{Ar}); **IR** ν_{max} (film)/cm^{-1} 2951, 2872, 1657, 1453, 1259, 1157, 1031, 969, 879, 734, 699; **HRMS** (ESI$^+$) $C_{26}H_{33}ON^{127}I$ requires 502.16013, found $[M+H]^+$ 502.15997 (Δ -0.32 ppm); **M.p.** 103 – 105 °C.

Methyl 1-benzylaziridine-2-carboxylate (395)

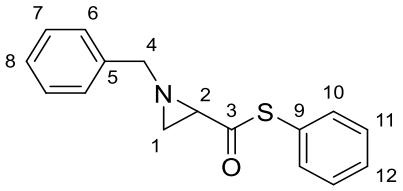


To a stirred solution of methyl 2,3-dibromopropionate **394** (2.50 g, 10 mmol, 1.0 equiv.) in MeOH (5 mL) at 0 °C was added a solution of Et_3N (4.23 mL, 30 mmol, 3.0 equiv.) in MeOH (20 mL) and the reaction left to stir for 30 min. Benzylamine (1.11 mL, 10 mmol, 1.0 equiv.) in MeOH (20 mL) was then added dropwise and the reaction left to stir for a further 30 min before being warmed to RT and left to stir for 16 h. The reaction was then concentrated *in vacuo* before being redissolved in Et_2O (50 mL) and water (100 mL) and the layers separated. The aqueous later was extracted with Et_2O (3 × 50 mL) and the combined organic extracts washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 75:25) gave the desired compound **395** (1.91 g, quant.) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40 – 7.23 (m, 5H, 5 × *H*C_{Ar}), 3.72 (s, 3H, *H*$_3$C(9)), 3.62 – 3.47 (m, 2H, *H*$_2$C(4)), 2.27 (dd, J = 3.1, 1.2 Hz, 1H, *H*C(2)), 2.21 (dd, J = 6.5, 3.1 Hz, 1H, *H*$_a$H$_b$C(1)), 1.76 (dd, J = 6.5, 1.2 Hz, 1H, H$_a$*H*$_b$C(1)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 171.3 (*C*(3)), 137.8 (*C*$_{Ar}$), 128.6 (2 × *C*$_{Ar}$), 128.2 (2 × *C*$_{Ar}$), 127.5 (*C*$_{Ar}$), 64.0 (*C*(4)), 52.4 (*C*(9)), 37.5 (*C*(2)), 34.7 (*C*(1)).

Data was consistent with that previously reported.[127]

Phenyl 1-benzylaziridine-2-carbothioate (390)



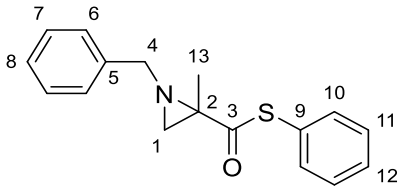
To a flame dried Schlenk flask equipped with a stirrer bar was added 1M Et_3Al in hexanes (15 mL, 15 mmol, 1.5 equiv.) and the solvent carefully removed *in vacuo*. After cooling to 0 °C, CH_2Cl_2 (15 mL) was

added and the solution left to stir for 5 min. Thiophenol (1.6 mL, 15 mmol, 1.5 equiv.) was added dropwise and the solution left to stir for a further 15 min. The reaction was then warmed to RT and a solution of methyl ester **395** (1.91 g, 10 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) was added and the reaction left to stir for 6 h at RT. After addition of Et_2O (15 mL), the reaction was carefully quenched with a 3% aq. solution of HCl (2 mL) and the precipitated solids filtered. The organic layer was washed twice with a 1% aq. solution of NaOH (15 mL) and brine (15 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Care was taken to treat all aqueous waste and glassware with bleach to remove malodorous traces of thiophenol. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 85:15) gave the desired compound **390** (1.65 g, 61%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.46 – 7.27 (m, 10H, 10 × *H*C_{Ar}), 3.72 (d, J = 13.6 Hz, 1H, $H_a$$H_b$C(4)), 3.58 (d, J = 13.6 Hz, 1H, $H_a$$H_b$C(4)), 2.49 (dd, J = 6.6, 2.8 Hz, 1H, *H*C(2)), 2.38 (dd, J = 2.9, 1.1 Hz, 1H, $H_a$$H_b$C(1)), 1.90 (dd, J = 6.6, 1.1 Hz, 1H, $H_a$$H_b$C(1)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 197.5 (*C*(3)), 137.7 (C_{Ar}), 134.8 (2 × C_{Ar}), 129.4 (C_{Ar}), 129.3 (2 × C_{Ar}), 128.6 (2 × C_{Ar}), 128.2 (2 × C_{Ar}), 127.7 (C_{Ar}), 127.6 (C_{Ar}), 63.4 (*C*(4)), 44.9 (*C*(2)), 36.5 (*C*(1)).

Data was consistent with that previously reported.[128]

Phenyl 1-benzyl-2-methylaziridine-2-carbothioate (391)



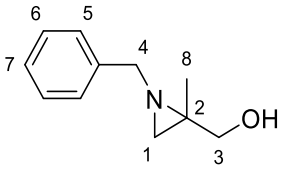
To a stirred solution of LDA, prepared *in situ* from carefully adding 2.26M *n*BuLi in hexanes (2.95 mL, 6.73 mmol, 1.1 equiv.) to a solution of diisopropylamine (1.03 mL, 7.34 mmol, 1.2 equiv.) in THF (15 mL) at –78 °C, was added a solution of thioester **390** (1.64 g, 6.12, 1.0 equiv.) dropwise at –78 °C and the solution left to stir at this temperature for 30 min. A solution of MeI (0.57 mL, 9.18 mmol, 1.5 equiv.) in THF/DMPU (3 mL: 6 mL) was then added dropwise at –78 °C and left to stir for a further 2 h.

The reaction was then warmed to RT, diluted with Et_2O (75 mL), washed sequentially with sat. aq. NH_4Cl and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 90:10) gave the desired compound **391** (0.86 g, 50%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.60 – 7.13 (m, 10H, 10 × HC_{Ar}), 3.85 (d, J = 4.7 Hz, 2H, H_2C (4)), 2.46 (s, 1H, H_aH_bC(1)), 1.71 (s, 1H, H_aH_bC(1)), 1.53 (s, 3H, H_3C(13)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.0 (C(3)), 135.0 (2 × C_{Ar}), 134.9 (2 × C_{Ar}), 129.1 (2 × C_{Ar}), 129.0 (C_{Ar}), 128.6 (C_{Ar}), 127.8 (2 × C_{Ar}), 127.7 (C_{Ar}), 127.2 (C_{Ar}), 56.5 (C(4)), 47.5 (C(2)), 42.3 (C(1)), 11.2 (C(13)).

Data was consistent with that previously reported.[128]

(1-Benzyl-2-methylaziridin-2-yl)methanol (396)

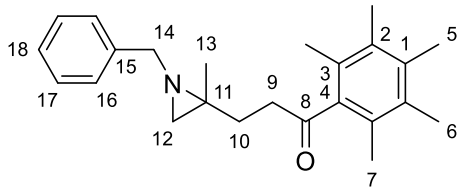


To a stirred solution of $LiAlH_4$ (182 mg, 4.8 mmol, 2.0 equiv.) in Et_2O (25 mL) at 0 °C was added a solution of thioester **391** (679 mg, 2.4 mmol, 1.0 equiv.) in Et_2O (10 mL) dropwise over the course of 15 min. The reaction was then slowly warmed to RT and left to stir for 1 h. Upon completion of the reaction, as observed by TLC in 70:30 pentane:Et_2O, the reaction was cooled to 0 °C and diluted with Et_2O (25 mL). The reaction was quenched by the sequential addition of water (182 µl), 15% aqueous NaOH (182 µl), water (546 µl mL) and $MgSO_4$ (1 g). The thick emulsion was then filtered under reduced pressure and the solvent removed *in vacuo* to give a crude oil. Purification by column chromatography (SiO_2, eluent load, CH_2Cl_2:MeOH, 96:4) gave the desired alcohol **396** as a colourless oil (466 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.48 – 7.14 (m, 5H, 5 × HC_{Ar}), 3.81 – 3.57 (m, 2H, H_2C(4)), 3.48 (d, J = 4.3 Hz, 2H, H_2C(3)), 2.05 (s, 1H, H_aH_bC(1)), 1.33 (s, 1H, H_aH_bC(1)), 1.30 (s, 3H, H_3C(8)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 140.0 (C_{Ar}), 128.5 (2 × C_{Ar}), 127.7 (2 × C_{Ar}), 127.0 (C_{Ar}), 65.4 (C(3)), 56.1 (C(4)), 53.6 (C(2)), 36.8

(*C*(1)), 13.4 (*C*(8)); **IR** ν_{max} (film)/cm^{-1} 3365, 2980, 1453, 1155, 1030, 733, 698; **HRMS** (ESI$^+$) $C_{11}H_{16}ON$ requires 178.1226, found $[M+H]^+$ 127.1228 (Δ 0.82 ppm).

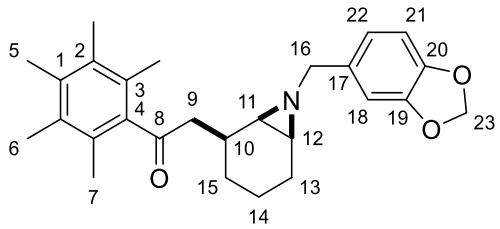
3-(1-Benzyl-2-methylaziridin-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one (397)



Aziridine **396** (195 mg, 1.1 mmol, 1.1 equiv.) was subjected to **General Procedure A**. Purification by column chromatography (SiO_2, dry load, pentane:Et_2O:Et_3N, 70:30:1) gave the desired compound **397** (239 mg, 68%) as pale brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42 – 7.19 (m, 5H, 5 × *H*C$_{Ar}$), 3.67 – 3.56 (m, 2H, *H*$_2$C(14)), 2.77 – 2.67 (m, 2H, *H*$_2$C(9)), 2.23 (s, 3H, *H*$_3$C(5)), 2.18 (s, 6H, 2 × *H*$_3$CC$_{Ar}$), 2.07 (s, 6H, 2 × *H*$_3$CC$_{Ar}$), 1.94 (ddd, J = 14.0, 10.3, 5.7 Hz, 1H, *H*$_a$H$_b$C(10)), 1.85 (s, 1H, *H*$_a$H$_b$C(12)), 1.82 – 1.72 (m, 1H, H$_a$*H*$_b$C(10)), 1.27 (s, 3H, *H*$_3$C(13)), 1.23 (s, 1H, H$_a$*H*$_b$C(12)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 212.0 (*C*(8)), 135.4 (*C*$_{Ar}$), 133.1 (2 × *C*$_{Ar}$), 128.5 (*C*$_{Ar}$), 128.4 (2 × *C*$_{Ar}$), 127.9 (2 × *C*$_{Ar}$), 127.6 (*C*$_{Ar}$), 127.4 (2 × *C*$_{Ar}$), 126.8 (*C*$_{Ar}$), 57.1 (*C*(14)), 42.0 (*C*(9)), 40.3 (*C*(12)), 38.9 (*C*(11)), 33.6 (*C*(10)), 17.3 (2 × H$_3$*C*CC$_{Ar}$), 16.8 (H$_3$*C*CC$_{Ar}$), 16.1 (2 × H$_3$*C*CC$_{Ar}$), 15.3 (*C*(13)); **IR** ν_{max} (film)/cm^{-1} 2926, 1696, 1115, 734, 696; **HRMS** (ESI$^+$) $C_{24}H_{32}ON$ requires 350.2478, found $[M+H]^+$ 250.2479 (Δ 0.26 ppm); **M.p.** 67 – 69 °C.

2-((1*R*,2*S*,6*S*)-7-(benzo[d][1,3]dioxol-5-ylmethyl)-7-azabicyclo[4.1.0]heptan-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (413)



Racemic

Cyclic aziridine alcohol **414** (147 mg, 0.6 mmol) was subjected to **General Procedure A**. Purification by column chromatography (SiO_2, dry load, pentane:Et_2O, 80:20) gave a single diastereomer **413** (151 mg, 60%) as a yellow oil.

Racemic with hydride donor 436

Cyclic aziridine ketone **436** (221 mg, 0.9 mmol) was subjected to **General Procedure A** with the addition of 1.5 eq of (4-((tert-butyldimethylsilyl)oxy)phenyl)(4-methoxyphenyl)methanol **442** (310 mg, 0.9 mmol). Purification by column chromatography (SiO_2, dry load, pentane:Et_2O, 80:20) gave a single diastereomer **413** (204 mg, 54%) as a yellow oil.

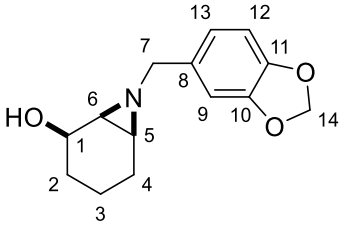
Enantioenriched

Cyclic aziridine alcohol **414** (248 mg, 1.0 mmol) was subjected to **General Procedure A**. Purification by column chromatography (SiO_2, dry load, pentane:Et_2O, 80:20) gave a single diastereomer **413** (223 mg, 53%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.87 (s, 1H, *H*C_{Ar}), 6.72 (s, 2H, 2 × *H*C_{Ar}), 5.90 (d, J = 1.3 Hz, 1H, $H_aH_bC(23)$), 5.83 (d, J = 1.3 Hz, 1H, $H_aH_bC(23)$), 3.48 (d, J = 13.3 Hz, 1H, $H_aH_bC(16)$), 3.10 (d, J = 13.4 Hz, 1H, $H_aH_bC(16)$), 2.82 – 2.54 (m, 2H, $H_2C(9)$), 2.41 (dq, J = 12.4, 7.2, 6.3 Hz, 1H, *H*C(11)), 2.22 (s, 3H, $H_3C(5)$), 2.17 (s, 6H, 2 × $H_3C(6)$), 2.06 (s, 6H, 2 × $H_3C(7)$), 1.90 (dd, J = 6.5, 4.1 Hz, 1H, *H*C(12)), 1.70 (t, J = 6.0 Hz, 1H, *H*C(10)), 1.64 (s, 2H, $H_2C(15)$), 1.44 (dt, J = 7.2, 4.9 Hz, 2H, $H_2C(13)$), 1.28 – 1.01 (m, 2H, $H_2C(14)$);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 211.8 (*C*(8)), 147.5 (C_{Ar}), 146.3 (C_{Ar}), 140.7 (C_{Ar}), 135.2 (C_{Ar}), 133.9 (C_{Ar}), 133.0 (2 × C_{Ar}), 127.2 (2 × C_{Ar}), 121.0 (C_{Ar}), 108.6 (C_{Ar}), 107.9 (C_{Ar}), 100.8 (*C*(23)), 64.4 (*C*(16)), 53.5 (*C*(11)), 50.4 (*C*(9)), 42.1 (*C*(13)), 39.8 (*C*(10)), 29.5 (*C*(15)), 26.5 (*C*(14)), 24.1 (*C*(13)), 20.8 (2 × *C*(6)), 17.1 (*C*(5)), 16.7 (2 × *C*(7)); **IR** ν_{max} (film)/cm^{-1} 2929, 1698, 1503, 1489, 1442, 1376, 1245, 1100, 1039, 928, 807; **HRMS** (ESI$^+$) $C_{27}H_{34}O_3N$ requires 420.25332, found $[M+H]^+$ 420.25206 (Δ –3.04 ppm); **$[\alpha]_D^{25}$** = +20.0 (c = 1.00, $CHCl_3$).

(1*S*,2*R*,6*S*)-7-(benzo[d][1,3]dioxol-5-ylmethyl)-7-azabicyclo[4.1.0]heptan-2-ol (414)



Racemic

To a stirred solution of cyclic aziridine ketone **436** (980 mg, 4 mmol) in MeOH (20 mL) at 0 °C was added $NaBH_4$ portionwise (3 × 181 mg, 3 × 4.8 mmol) and the reaction left to stir for 3 h until completion was indicated by TLC. Extraction with Et_2O (3 × 30 mL), drying with $MgSO_4$ and concentration *in vacuo* afforded the pure product **414** (989 mg, quant.) as a creamy solid.

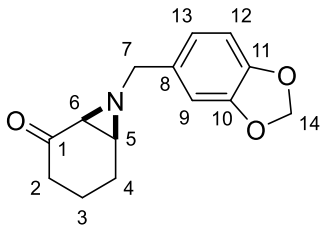
Enantioenriched

To a stirred solution of enantioenriched cyclic aziridine alcohol **470** (1.73 g, 7 mmol, 1.0 equiv.) in MeOH (30 mL) at RT was added K_2CO_3 (1.45 g, 10.5 mmol, 1.5 equiv.) and the reaction left to stir for 1 h. The reaction mixture was then passed through a short plug of silica, eluting with MeOH, to remove excess K_2CO_3 before being concentrated *in vacuo* to give a crude oil which was then dissolved in DMF (30 mL). To this mixture was added K_2CO_3 (2.42 g, 17.5 mmol, 2.5 equiv.) and piperonyl bromide **381** (3.00 g, 14 mmol, 2.0 equiv.) and the reaction left to stir at RT for 2.5 h. The reaction was then quenched by the addition of water (30 mL), extracted with EtOAc (3 × 30 mL) and washed with brine

(3 × 50 mL) before being dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 50:50 to 30:70) gave the desired product **414** as a separable mixture of diastereomers in a 2.7:1 ratio (1.30 g, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.88 (d, J = 3.7 Hz, 1H, *H*C$_{Ar}$), 6.76 (d, J = 5.7 Hz, 2H, 2 × *H*C$_{Ar}$), 5.94 (d, J = 2.7 Hz, 2H, *H*$_2$C(14)), 4.03 (t, J = 5.7 Hz, 1H, *H*$_a$H$_b$C(7)), 3.94 (dq, J = 10.2, 5.2 Hz, 1H, H$_a$*H*$_b$C(7)), 3.37 (t, J = 4.4 Hz, 1H, *H*C(6)), 2.38 – 2.28 (m, 1H, *H*C(1)), 2.02 (t, J = 5.8 Hz, 1H, *H*C(5)), 1.95 (t, J = 5.4 Hz, 1H, H$_a$*H*$_b$C(2)), 1.81 (ddt, J = 15.1, 9.5, 5.4 Hz, 1H, *H*$_a$H$_b$C(2)), 1.68 – 1.60 (m, 2H, *H*$_2$C(4)), 1.44 (ddtt, J = 15.3, 7.7, 5.2, 2.7 Hz, 1H, H$_a$*H*$_b$C(3)), 1.18 (ddt, J = 11.0, 7.3, 4.3 Hz, 1H, *H*$_a$H$_b$C(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 147.8 (*C*$_{Ar}$), 133.4 (*C*$_{Ar}$), 121.2 (*C*$_{Ar}$), 120.7 (*C*$_{Ar}$), 108.7 (*C*$_{Ar}$), 108.3 (*C*$_{Ar}$), 101.1 (*C*(14)), 64.3 (*C*(1)), 64.1 (*C*(7)), 43.0 (*C*(6)), 42.1 (*C*(5)), 30.8 (*C*(4)), 23.9 (*C*(2)), 16.9 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 3406, 2935, 1503, 1490, 1441, 1374, 1241, 1100, 1039, 927, 808; **HRMS** (ESI$^+$) $C_{14}H_{18}O_3N$ requires 248.12812, found $[M+H]^+$ 248.12815 (Δ 0.16 ppm); **M.p.** 82 – 84 °C; **$[\alpha]_D^{25}$** = +19.0 (c = 1.00, $CHCl_3$).

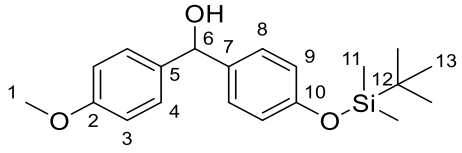
7-(Benzo[d][1,3]dioxol-5-ylmethyl)-7-azabicyclo[4.1.0]heptan-2-one (436)



2-Iodocyclohex-2-en-1-one **301** (2.21 g, 10 mmol), Cs_2CO_3 (3.87 g, 10 mmol), phenanthroline (1.8 g, 10 mmol) and piperonylamine **432** (1.87 mL, 15 mmol) were added sequentially to CH_2Cl_2 (75 mL) at RT and left to stir 4 h, after which another 0.5 equiv. of Cs_2CO_3 (1.93 g, 5 mmol) was added. After a further 4 h, 0.5 equiv. of phenanthroline (0.9 g, 5 mmol) were added and the reaction left to stir for 16 h. The resulting mixture was then diluted with CH_2Cl_2 (75 mL), washed with water (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product. Purification by column chromatography (SiO_2, dry load, pentane:Et_2O, 70:30) gave the desired product **436** (2.32 g, 95%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.84 (s, 1H, *H*C(9)), 6.75 (t, J = 6.3 Hz, 2H, *H*C(12) and *H*C(13)), 5.94 (s, 2H, H_2C(14)), 3.66 (d, J = 13.4 Hz, 1H, $H_a$$H_b$C(7)), 3.28 (d, J = 13.4 Hz, 1H, $H_a$$H_b$C(7)), 2.54 – 2.38 (m, 1H, *H*C(6)), 2.29 (d, J = 2.9 Hz, 1H, *H*C(5)), 2.15 – 1.90 (m, 4H, H_2C(2) and H_2C(4)), 1.80 – 1.51 (m, 2H, H_2C(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 207.8 (*C*(1)), 147.8 (C_{Ar}), 146.8 (C_{Ar}), 132.4 (C_{Ar}), 120.9 (C_{Ar}), 108.4 (C_{Ar}), 108.2 (C_{Ar}), 101.1 (*C*(14)), 63.3 (*C*(7)), 46.4 (*C*(6)), 43.8 (*C*(5)), 37.2 (*C*(2)), 23.31 (*C*(4)), 18.9 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 2940, 1703, 1503, 1490, 1442, 1250, 1235, 1100, 1084, 1037, 927, 808; **HRMS** (ESI$^+$) $C_{14}H_{16}O_3N$ requires 246.11247, found $[M+H]^+$ 246.11245 (Δ –0.05 ppm).

(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)(4-methoxyphenyl)methanol (442)



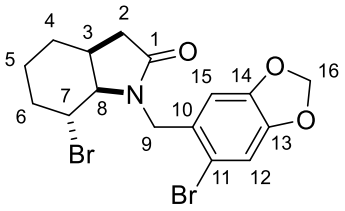
To a stirred solution of 4-hydroxybenzaldehyde **439** (3.74 g, 20 mmol, 1.0 equiv.) in DMF (50 mL) at RT was sequentially added TBSCl (3.00 g, 20 mmol, 1.0 equiv.) and imidazole (1.63 g, 24 mmol, 1.2 equiv.), and the reaction left to stir for 1 h. The reaction was quenched by the addition of water (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were then washed with brine (3 × 50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give the desired product **440** (4.72 g, Quant.) that was used without further purification.

To a stirred solution of 4-bromoanisole (3.74 g, 20 mmol, 1.0 equiv.) in THF (90 mL) at –78 °C was added 2.5 M *n*BuLi in hexanes (8.0 mL, 20 mmol, 1.0 equiv.) dropwise and the reaction stirred for 2 h. 4-((*tert*-Butyldimethylsilyl)oxy)benzaldehyde **440** (4.72 g, 20 mmol, 1.0 equiv.) in THF (5 mL) was added and the reaction warmed to RT over the course of 1.5 h. The reaction was quenched by the addition of water (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were then washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, CH_2Cl_2) gave the desired compound **442** (3.46 g, 50%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.27 (d, J = 8.4 Hz, 2H, 2 × *H*C(5)), 7.20 (d, J = 8.2 Hz, 2H, 2 × *H*C(8)), 6.86 (d, J = 8.5 Hz, 2H, 2 × *H*C(3)), 6.79 (d, J = 8.2 Hz, 2H, 2 × *H*C(9)), 5.76 (d, J = 3.3 Hz, 1H, *H*C(6)), 3.79 (s, 3H, H_3C(1)), 0.97 (s, 9H, 3 × H_3C(13)), 0.18 (s, 6H, 2 × H_3C(11)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.1 (*C*(2)), 155.2 (*C*(10)), 137.0 (*C*(5)), 136.5 (*C*(7)), 127.9 (2 × *C*(4)), 127.8 (2 × *C*(8)), 120.1 (2 × *C*(9)), 113.9 (2 × *C*(3)), 75.6 (*C*(6)), 55.4 (*C*(1)), 25.8 (*C*(12)), 18.3 (3 × *C*(13)), -4.3 (2 × *C*(11)).

Data was consistent with that previously reported.[129]

(3a*S*,7*R*,7a*R*)-7-bromo-1-((6-bromobenzo[d][1,3]dioxol-5-yl)methyl)octahydro-2H-indol-2-one (444)



Racemic

Cyclic aziridine ketone **413** (126 mg, 0.30 mmol) was subjected to **General Procedure B** – with 3 equiv. of Br_2. Purification by column chromatography (SiO_2, dry load, Et_2O) gave the desired compound **444** (100 mg, 78%) as a pale brown oil.

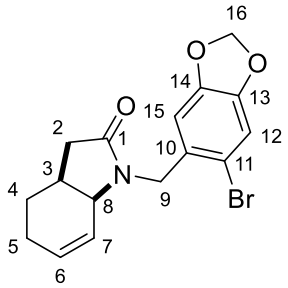
Enantioenriched

Cyclic aziridine ketone **413** (100 mg, 0.24 mmol) was subjected to **General Procedure B** – with 3 equiv. of Br_2. Purification by column chromatography (SiO_2, dry load, Et_2O) gave the desired compound **444** (42 mg, 40%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.99 (s, 1H, *H*C(12)), 6.78 (s, 1H, *H*C(15)), 5.97 (q, J = 1.3 Hz, 2H, H_2C(16)), 4.86 (d, J = 15.6 Hz, 1H, $H_a$$H_b$C(9)), 4.56 (d, J = 15.6 Hz, 1H, $H_a$$H_b$C(9)), 4.23 (ddd, J = 8.8, 6.5, 3.8 Hz, 1H, *H*C(7)), 3.67 (t, J = 6.3 Hz, 1H, *H*C(8)), 2.63 (q, J = 7.2 Hz, 1H, *H*C(3)), 2.32 (qd, J = 16.4, 7.8 Hz, 2H, H_2C(2)), 1.93 – 1.37 (m, 6H, H_2C(4) and H_2C(5) and H_2C(6)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 175.7 (*C*(1)), 147.9

(C_{Ar}), 147.7 (C_{Ar}), 129.0 (C_{Ar}), 113.7 (C_{Ar}), 113.0 (C_{Ar}), 109.8 (C_{Ar}), 102.0 (*C*(16)), 63.7 (*C*(8)), 52.3 (*C*(7)), 45.7 (*C*(9)), 35.9 (*C*(3)), 34.0 (*C*(6)), 33.2 (*C*(2)), 26.5 (*C*(4)), 20.4 (*C*(5)); **IR** ν_{max} (film)/cm^{-1} 2931, 1689, 1502, 1478, 1407, 1235, 1190, 1110, 1036, 928, 729; **HRMS** (ESI^+) $C_{16}H_{17}O_3N^{79}Br_2{}^{23}Na$ requires 451.94674, found $[M+Na]^+$ 451.94707 (Δ 0.72 ppm); **$[\alpha]_D^{25}$** = – 46.5 (c = 1.00, $CHCl_3$).

1-((6-bromobenzo[d][1,3]dioxol-5-yl)methyl)-1,3,3a,4,5,7a-hexahydro-2H-indol-2-one (455)

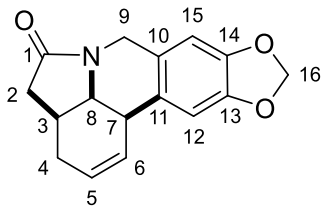


To a stirred solution of dibromide **444** (161 mg, 0.375 mmol, 1.0 equiv.) in THF (3 mL) at RT was added 1M KO*t*BU in THF (413 µL, 0.413 mmol, 1.1 equiv.) and the reaction left to stir for 45 min. The reaction was then quenched by the addition of water (10 mL), extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (5 mL) and concentrated *in vacuo* to give a crude residue. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 50:50) gave the desired compound **455** (131 mg, Quant.) as a pale oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.97 (s, 1H, *H*C(15)), 6.74 (s, 1H, *H*C(12)), 5.96 – 5.94 (m, 3H, *H*C(6) and H_2C(16)), 5.72 (ddt, J = 10.2, 3.6, 2.0 Hz, 1H, *H*C(7)), 4.75 (d, J = 15.6 Hz, 1H, H_aH_bC(9)), 4.25 (d, J = 15.6 Hz, 1H, H_aH_bC(9)), 3.85 (ddt, J = 5.1, 3.4, 1.8 Hz, 1H, *H*C(8)), 2.58 – 2.43 (m, 2H, H_2C(2)), 2.29 (td, J = 16.1, 15.5, 6.1 Hz, 1H, *H*C(3)), 2.15 – 1.88 (m, 2H, H_2C(5)), 1.76 – 1.51 (m, 2H, H_2C(4)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 174.6 (*C*(1)), 147.8 (*C*(6)), 132.0 (C_{Ar}), 129.4 (C_{Ar}), 129.0 (C_{Ar}), 123.3 (*C*(7)), 113.6 (*C*(11)), 112.7 (*C*(15)), 109.3 (*C*(12)), 101.9 (*C*(16)), 54.9 (*C*(8)), 44.1 (*C*(9)), 35.9 (*C*(2)), 31.1 (*C*(3)), 24.2 (*C*(4)), 22.3 (*C*(5)).

Data was consistent with that previously reported.[92]

3a,4,7,12b-Tetrahydro-3H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-5(3a1H)-one (456)

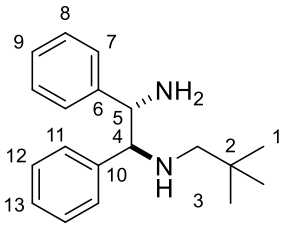


A stirred solution of bromo alkene **455** (105 mg, 0.3 mmol, 1.0 equiv.) in DMF (9 mL) at RT was sparged with N_2 for 1 h. This was followed by the sequential addition of PPh_3 (31 mg, 0.12 mmol, 40 mol%), $Pd(OAc)_2$ (13 mg, 0.06 mmol, 20 mol%), and *i*PrNEt (183 µL, 0.6 mmol, 2.0 equiv.) and the reaction was heated to 155 °C for 20 h. The reaction was then quenched by the addition of water (10 mL), extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (3 × 5 mL) and concentrated *in vacuo* to give a crude residue. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 20:80) gave the desired compound **455** (49 mg, 60%) as a pale oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.66 (s, 1H, *H*C(12)), 6.57 (s, 1H, *H*C(15)), 5.95 – 5.91 (m, 2H, H_2C(16)), 5.88 (ddt, *J* = 9.5, 6.5, 3.5 Hz, 1H, *H*C(5)), 5.64 (dtd, *J* = 9.5, 2.6, 1.3 Hz, 1H, *H*C(6)), 4.78 (d, *J* = 17.1 Hz, 1H, H_aH$_b$C(9)), 4.11 (d, *J* = 17.1 Hz, 1H, H$_a$$H_b$C(9)), 4.05 (dd, *J* = 8.1, 5.2 Hz, 1H, *H*C(8)), 3.28 (d, *J* = 2.6 Hz, 1H, *H*C(7)), 2.92 – 2.82 (m, 1H, *H*C(3)), 2.66 (ddd, *J* = 17.0, 9.6, 1.5 Hz, 1H, H_aH$_b$C(2)), 2.19 (dddt, *J* = 16.1, 6.3, 3.8, 2.5 Hz, 1H, H_aH$_b$C(4)), 2.14 – 2.07 (m, 2H, H$_a$$H_b$C(2) and H$_a$$H_b$C(4)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 174.4 (*C*(1)), 147.1 (C_{Ar}), 147.0 (C_{Ar}), 132.7 (*C*(6)), 129.9 (*C*(5)), 126.9 (C_{Ar}), 124.4 (C_{Ar}), 109.0 (*C*(15)), 106.3 (*C*(12)), 101.2 (*C*(16)), 56.7 (*C*(8)), 42.3 (*C*(9)), 38.9 (*C*(2)), 38.6 (*C*(7)), 29.2 (*C*(3)), 27.4 (*C*(4)).

Data was consistent with that previously reported.[98]

(1*S*,2*S*)-N^1-Neopentyl-1,2-diphenylethane-1,2-diamine (461)

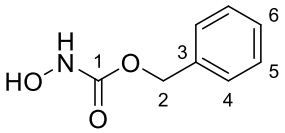


To a stirred solution of (1S,2S)-DPEN **464** (182 mg, 0.86 mmol, 1.0 equiv.) in MeOH (2 mL) at RT was added pivaldehyde **465** (103 µL, 0.95 mmol, 1.1 equiv.) and the reaction left to stir for 1 h. The reaction was then cooled to 0 °C and $NaBH_4$ (65 mg, 1.72 mmol, 2.0 equiv.) was added portionwise. The reaction was then warmed to RT and stirred for 1.5 h before being quenched by the addition of water (10 mL). The precipitated solid was collected by filtration and air-dried at 80 °C overnight to give the desired amine **461** (218 mg, 77%) as a colourless, amorphous powder.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.25 – 7.06 (m, 10H, 10 × *H*C$_{Ar}$), 3.97 (d, J = 7.0 Hz, 1H, *H*C(4)), 3.64 (d, J = 7.0 Hz, 1H, *H*C(5)), 2.17 (d, J = 11.2 Hz, 1H, *H*$_a$H$_b$C(3)), 2.06 (d, J = 11.2 Hz, 1H, H$_a$*H*$_b$C(3)), 0.85 (s, 9H, 3 × *H*$_3$C(1)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 143.8 (*C*$_{Ar}$), 142.2 (*C*$_{Ar}$), 128.2 (*C*$_{Ar}$), 128.1 (*C*$_{Ar}$), 127.9 (*C*$_{Ar}$), 127.2 (*C*$_{Ar}$), 127.0 (*C*$_{Ar}$), 126.9 (*C*$_{Ar}$), 70.6 (*C*(4)), 62.2 (*C*(5)), 60.2 (*C*(3)), 31.8 (*C*(2)), 27.9 (*C*(1)).

Data was consistent with that previously reported.[77]

Benzyl hydroxycarbamate (467)

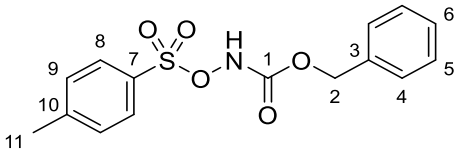


To a stirred solution of Na_2CO_3 (6.5 g, 60 mmol, 1.5 equiv.) in water (20 mL) was added hydroxylamine hydrochloride (3.2 g, 46 mmol, 1.15 equiv.), followed by a solution of benzyl chloroformate **466** (5.63 mL, 40 mmol, 1.0 equiv.) in CH_2Cl_2. The reaction was stirred at RT for 4 h, after which the reaction was acidified to approximately pH 2 by the addition of conc. HCl, extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product **467** (5.88 g, 88%) as a colourless solid which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.44 – 7.29 (m, 5H, 5 × *H*C_{Ar}), 5.18 (s, 2H, *H*$_2$C(2)), 4.60 (s, 1H, *H*N); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 159.2 (*C*(1)), 135.4 (C_{Ar}), 128.8 (2 × C_{Ar}), 128.7 (2 × C_{Ar}), 128.5 (C_{Ar}), 68.1 (*C*(2)).

Data was consistent with that previously reported.[130]

Benzyl (tosyloxy)carbamate (468)

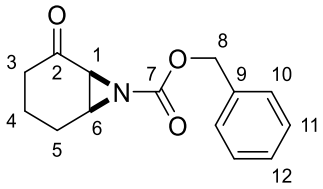


To a stirred solution of hydroxylamine **467** (5.88 g, 35 mmol, 1.06 equiv.) and Et_3N (4.56 mL, 33 mmol, 1.0 equiv.) in THF (100 mL) at –15 °C was added TsCl (6.30 g, 33 mmol, 1.0 equiv.) in THF (50 mL) and the reaction left to stir for 30 min. Any precipitated solids were then filtered off and the filtrate concentrated *in vacuo* to give the crude product. Purification by column chromatography (SiO_2, dry load, pentane:Et_2O, 67:33) gave the desired compound **468** (7.99 g, 75%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.85 – 7.80 (m, 2H, 2 × *H*C(8)), 7.35 – 7.32 (m, 2H, 2 × *H*C(9)), 7.28 – 7.16 (m, 5H, 5 × *H*C_{Ar}), 5.02 (s, 2H, *H*$_2$C(2)), 2.42 (s, 3H, *H*$_3$C(11)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 155.4 (*C*(1)), 146.2 (C_{Ar}), 134.6 (C_{Ar}), 130.3 (C_{Ar}), 129.9 (2 × C_{Ar}), 129.7 (2 × C_{Ar}), 128.9 (2 × C_{Ar}), 128.7 (2 × C_{Ar}), 128.5 (C_{Ar}), 68.8 (*C*(2)), 22.0 (*C*(11)).

Data was consistent with that previously reported.[130]

Benzyl (1*S*,6*S*)-2-oxo-7-azabicyclo[4.1.0]heptane-7-carboxylate (469)



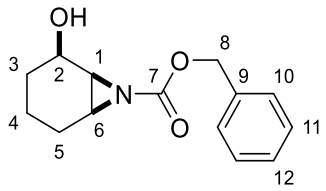
To a stirred solution of diamine catalyst **461** (1.13 g, 4 mmol, 0.2 equiv.), benzoic acid (2.44 g, 20 mmol, 1.0 equiv.), $NaHCO_3$ (8.4 g, 100 mmol, 5.0 equiv.), and protected hydroxylamine **468** (6.42 g, 20 mmol, 1.0 equiv.) in $CHCl_3$ (200 mL) at RT was added 2-cyclohexen-1-one (5.82 mL, 60 mmol, 3.0 equiv.) and the reaction left to stir for 66 h. The reaction was then quenched by the addition of water (200 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting oil was purified by column chromatography (SiO_2, dry load, pentane:Et_2O, 70:30) to give the desired compound **469** (3.17 g, 64%, 98:2 er) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42 – 7.29 (m, 5H, 5 × *H*C_{Ar}), 5.14 (d, J = 0.9 Hz, 2H, *H*$_2$C(9)), 3.15 (dtd, J = 5.7, 2.3, 0.9 Hz, 1H, *H*C(6)), 2.99 (d, J = 5.8 Hz, 1H, *H*C(1)), 2.55 – 2.44 (m, 1H, *H*$_a$H$_b$C(3)), 2.32 – 2.21 (m, 1H, H$_a$*H*$_b$C(3)), 2.12 – 2.01 (m, 1H, *H*$_a$H$_b$C(4)), 2.01 – 1.90 (m, 1H, H$_a$*H*$_b$C(4)), 1.80 (dddd, J = 14.3, 11.0, 4.8, 2.2 Hz, 1H, *H*$_a$H$_b$C(5)), 1.71 – 1.59 (m, 1H, H$_a$*H*$_b$C(5)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 203.8 (*C*(2)), 161.7 (*C*(7)), 135.5 (*C*$_{Ar}$), 128.8 (2 × *C*$_{Ar}$), 128.7 (2 × *C*$_{Ar}$), 128.5 (*C*$_{Ar}$), 68.8 (*C*(8)), 43.1 (*C*(1)), 40.8 (*C*(3)), 37.0 (*C*(6)), 22.7 (*C*(5)), 17.3 (*C*(4)); **[α]$_D^{25}$** = – 79.5 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 10.0 % IPA, 90.0 % hexane, 1.0 mL/min, 25 °C, λ = 210 nm, 10 µL injection).

Data was consistent with that previously reported.[70]

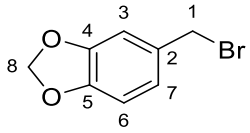
Benzyl (1*S*,2*R*,6*S*)-2-hydroxy-7-azabicyclo[4.1.0]heptane-7-carboxylate (470)



To a stirred solution of aziridine **469** (2.45 g, 10 mmol, 1.0 equiv.) in MeOH (100 mL) at –17 °C was added $NaBH_4$ (0.76 g, 20 mmol, 2.0 equiv.) portionwise and the solution left to stir for 2 h. The reaction was then quenched by the addition of sat. aq. $NaHCO_3$, extracted with EtOAc, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 40:60) gave the desired compound **470** (1.9 g, 77%) as a waxy solid, and as a 2.3:1 mixture of diastereomers at C2.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.41 – 7.28 (m, 7H, 7 × *H*C$_{Ar}$, *major and minor*), 5.14 (s, 2H, *H*$_2$C(8), *major*), 5.12 (s, 0.8H, *H*$_2$C(8), *minor*), 4.11 (dt, J = 7.2, 5.0 Hz, 0.4H, *H*C(2), *minor*), 4.03 – 3.94 (m, 1H, *H*C(2), *major*), 2.99 – 2.87 (m, 2H, *H*C(1) and *H*C(6), *major*), 2.77 (ddd, J = 5.8, 4.3, 1.3 Hz, 0.4H, *H*C(6), *minor*), 2.66 (dd, J = 6.1, 0.9 Hz, 0.4H, *H*C(1), *minor*), 2.14 (ddd, *J* = 9.9, 4.6, 2.5 Hz, 1H, *H*OC(1), *major*), 2.05 – 1.91 (m, 0.8H, *H*$_2$C(5), *minor*), 1.91 – 1.68 (m, 2.4H, *H*$_2$C(5), *major* and *H*$_a$H$_b$C(3), *minor*), 1.60 – 1.34 (m, 3.4H, *H*$_2$C(3), *major* and *H*$_a$H$_b$C(4), *major* and *H*$_a$H$_b$C(4), *minor*), 1.34 – 1.14 (m, 1.8H, H$_a$*H*$_b$C(4), *major* and H$_a$*H*$_b$C(4), *minor* and H$_a$*H*$_b$C(3), *minor*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 165.6 (*C*(1), *minor*), 163.5 (*C*(1), *major*), 136.0 (*C*$_{Ar}$, *minor*), 135.9 (*C*$_{Ar}$, *major*), 128.7 (2 × *C*$_{Ar}$, *major*), 128.6 (2 × *C*$_{Ar}$, *minor*), 128.5 (2 × *C*$_{Ar}$, *major*), 128.5 (2 × *C*$_{Ar}$, *minor*), 128.4 (*C*$_{Ar}$, *minor*), 128.3 (*C*$_{Ar}$, *major*), 68.4 (*C*(8), *major*), 68.3 (*C*(8), *minor*), 66.0 (*C*(2), *minor*), 65.2 (*C*(2), *major*), 42.4 (*C*(1), *major*), 42.0 (*C*(1), *minor*), 40.2 (*C*(6), *major*), 38.2 (*C*(6), *minor*), 29.7 (*C*(3), *minor*), 29.6 (*C*(3), *major*), 23.5 (*C*(5), *minor*), 22.8 (*C*(5), *major*), 18.2 (*C*(4), *major*), 15.0 (*C*(4), *minor*); **IR** ν_{max} (film)/cm^{-1} 3401, 2941, 1723, 1688, 1278, 1216, 1055, 752, 699; **HRMS** (ESI$^+$) $C_{14}H_{17}O_3NNa$ requires 270.1101, found [M+Na]$^+$ 270.1101 (Δ 0.24 ppm); **M.p.** 58 – 60 °C.

Piperonyl bromide (381)

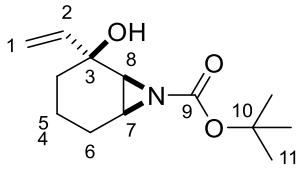


To a stirred solution of piperonyl alcohol **480** (3.04 g, 20 mmol, 1.0 equiv.) in Et_2O (30 mL) at 0 °C was added PBr_3 (2.07 mL, 22 mmol, 1.1 equiv.) in Et_2O (25 mL) *via* a dropping funnel over the course of 15 min. After stirring for an additional 30 min, the reaction was quenched by the addition of water (50 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 mL) and the organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the desired product **481** (4.15 g, 97%) as a colourless solid without any additional purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.90 – 6.84 (m, 2H, *H*C(3) and *H*C(7)), 6.75 (dd, J = 7.8, 0.6 Hz, 1H, *H*C(6)), 5.97 (s, 2H, H_2C(8)), 4.46 (s, 2H, H_2C(1)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 148.1 (*C*(4) or *C*(5)), 148.0 (*C*(4) or *C*(5)), 131.7 (*C*(2)), 122.9 (*C*(7)), 109.6 (*C*(3)), 108.5 (*C*(6)), 101.5 (*C*(8)), 34.3 (*C*(1)).

Data was consistent with that previously reported.[131]

*t*Butyl-2-hydroxy-2-vinyl-7-azabicyclo[4.1.0]heptane-7-carboxylate (495)

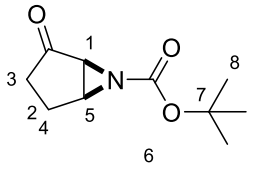


To a stirred solution of Boc aziridine ketone **332** (42 mg, 0.2 mmol, 1.0 equiv.) in THF (0.5 mL) at –78 °C was added a 1M solution of vinylmagnesium bromide in THF (240 µL, 0.24 mmol, 1.2 equiv.). The reaction mixture was left to stir 1.5 h before being quenched by the addition of sat. aq. NH_4Cl (1 mL) and extracted with Et_2O (2 × 2 mL). The combined organic extracts were then washed with water (2 mL) and brine (2 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column

chromatography (SiO_2, eluent load, pentane:Et_2O, 85:15 to 70:30) gave the desired compound **495** (15 mg, 31%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.00 (dd, J = 17.5, 10.9 Hz, 1H, *H*C(2)), 5.39 (dd, J = 17.5, 1.3 Hz, 1H, $H_aH_bC(1)$), 5.20 (dd, J = 10.9, 1.3 Hz, 1H, $H_aH_bC(1)$), 2.87 (ddd, J = 6.0, 4.5, 1.3 Hz, 1H, *H*C(7)), 2.64 (d, J = 6.2 Hz, 1H, *H*C(8)), 2.61 (s, 1H, *H*O), 1.97 – 1.86 (m, 1H, $H_aH_bC(6)$), 1.75 – 1.68 (m, 1H, $H_aH_bC(6)$), 1.59 – 1.49 (m, 1H, $H_aH_bC(4)$), 1.45 (s, 10H, 3 × $H_3C(11)$ and $H_aH_bC(5)$), 1.41 – 1.31 (m, 2H, $H_aH_bC(4)$ and $H_aH_bC(5)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 162.5 (*C*(9)), 142.0 (*C*(2)), 114.3 (*C*(1)), 81.7 (*C*(10)), 69.3 (*C*(3)), 45.6 (*C*(8)), 40.2 (*C*(7)), 34.8 (*C*(4)), 28.0 (3 × *C*(11)), 22.9 (*C*(6)), 16.9 (*C*(5)); **IR** ν_{max} (film)/cm^{-1} 3430, 1719, 1368, 1288, 1156; **HRMS** (ESI$^+$) $C_{13}H_{21}O_3NNa$ requires 262.1414, found $[M+Na]^+$ 262.1416 (Δ 0.83 ppm).

*t*Butyl-2-oxo-6-azabicyclo[3.1.0]hexane-6-carboxylate (496)



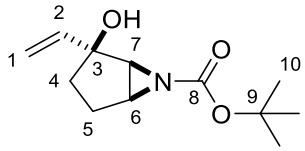
To a stirred solution of 1-(2-aminoethyl)piperidine **336** (0.43 mL, 3 mmol, 0.2 equiv.) in $CHCl_3$ (150 mL) was added cyclopentenone **460** (3.77 mL, 45 mmol, 3.0 equiv.), BocNHOTs (4.31 g, 15 mmol, 1.0 equiv.), $PhCO_2H$ (1.83 g, 15 mmol, 1.0 equiv.) and $NaHCO_3$ (0.50 g, 75 mmol, 5.0 equiv.) sequentially. The reaction was then stirred at RT for 16 h before being quenched by the addition of water (100 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 80:20) gave the desired aziridine **496** (1.47 g, 50%) as a yellow oil in a 5.4:1 ratio with inseparable BocNHOTs.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.38 (td, J = 3.1, 0.8 Hz, 1H, *H*C(5)), 3.03 – 2.98 (m, 1H, *H*C(1)), 2.52 – 2.42 (m, 2H, $H_2C(3)$), 2.22 – 2.12 (m, 1H, $H_aH_bC(4)$), 2.03 – 1.92 (m, 1H, $H_aH_bC(4)$), 1.46 (s, 9H, 3 × $H_3C(8)$);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 207.5 (*C*(2)), 158.4 (*C*(6)), 82.6 (*C*(7)), 44.2 (*C*(1)), 44.0 (*C*(3)), 31.6 (*C*(5)), 27.9 (3 × *C*(8)), 21.4 (*C*(4)).

Data was consistent with that previously reported.[70]

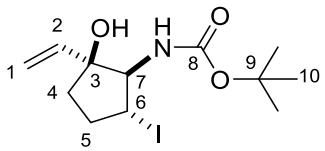
*t*Butyl-2-hydroxy-2-vinyl-6-azabicyclo[3.1.0]hexane-6-carboxylate (497)



To a stirred solution of Boc aziridine ketone **496** (197 mg, 1 mmol, 1.0 equiv.) in THF (2.5 mL) at –78 °C was added a 1M solution of vinylmagnesium bromide in THF (2.0 mL, 2 mmol, 2.0 equiv.). The reaction mixture was left to stir 15 min before being quenched by the addition of sat. aq. NH_4Cl (2 mL) and extracted with Et_2O (2 × 4 mL). The combined organic extracts were then washed with water (4 mL) and brine (4 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, toluene:Et_2O, 85:15) gave the desired compound **497** (186 mg, 83%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.93 (dd, J = 17.5, 10.9 Hz, 1H, *H*C(2)), 5.30 (ddd, J = 17.7, 1.2, 0.7 Hz, 1H, H_aH_bC(1)), 5.15 (ddt, J = 11.0, 1.2, 0.7 Hz, 1H, H_aH_bC(1)), 3.28 – 3.22 (m, 1H, *H*O), 2.97 (dd, J = 3.9, 2.4 Hz, 1H, *H*C(6)), 2.86 (d, J = 3.9 Hz, 1H, *H*C(7)), 2.20 – 2.10 (m, 1H, H_aH_bC(5)), 1.82 – 1.69 (m, 2H, H_aH_bC(4) and H_aH_bC(5)), 1.48 (s, 9H, 3 × H_3C(10)), 1.44 – 1.34 (m, 1H, H_aH_bC(4)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 161.8 (*C*(8)), 139.8 (*C*(2)), 113.5 (*C*(1)), 82.0 (*C*(3)), 80.4 (*C*(9)), 47.9 (*C*(7)), 42.0 (*C*(6)), 33.8 (*C*(4)), 28.1 (3 × *C*(10)), 25.3 (*C*(5)); **IR** ν_{max} (film)/cm^{-1} 3437, 1715, 1683, 1368, 1312, 1280, 1256, 1153; **HRMS** (ESI$^+$) $C_{12}H_{19}O_3NNa$ requires 248.1257, found $[M+Na]^+$ 248.1259 (Δ 0.69 ppm).

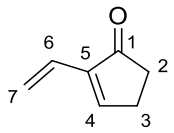
*t*Butyl-2-hydroxy-5-iodo-2-vinylcyclopentyl)carbamate (509)



To a stirred solution of 5-bromo-1,3-benzodioxole **508** (361 µL, 3 mmol, 6.0 equiv.) in Et_2O (5 mL) at 0 °C was added 2.5M *n*-BuLi in hexanes (1.2 mL, 3 mmol, 6.0 equiv.) and the reaction left to stir for 15 min. This was then added dropwise to a stirred slurry of CuI (287 mg, 1.5 mmol, 3.0 equiv.) in Et_2O (5 mL) and left to stir for a further 15 min. To the reaction was added a solution of Boc protected aziridine alcohol **497** (113 mg, 0.5 mmol, 1.0 equiv.) in Et_2O (5 mL) and the reaction left to stir for 30 min. 7.5 mL was then removed and quenched, showing only **497** by TLC and crude NMR. To the remaining reaction mixture was added $BF_3{\cdot}OEt_2$ (36 µL, 0.25 mmol, 1.0 equiv.) and the reaction left to stir for 30 min. The reaction was then quenched by the addition of sat. aq. NH_4Cl (10 mL), extracted with Et_2O (3 × 10 mL) and the combined organic extracts washed with brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 70:30) gave the ring-opened product **509** (67 mg, 76%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.06 – 5.83 (m, 1H, *H*C(2)), 5.30 (dd, J = 17.2, 0.9 Hz, 1H, H_aH_bC(1)), 5.24 – 5.07 (m, 1H, H_aH_bC(1)), 4.83 (d, *J* = 9.0 Hz, 1H, *H*N), 4.25 – 3.93 (m, 2H, *H*C(6) and *H*C(7)), 2.64 – 2.34 (m, 1H, H_aH_bC(5)), 2.30 – 1.88 (m, 2H, H_aH_bC(5) and H_aH_bC(4)), 1.92 – 1.68 (m, 1H, H_aH_bC(4)), 1.44 (s, 9H, 3 × H_3C(10)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 155.9 (*C*(8)), 141.1 (*C*(2)), 114.2 (*C*(1)), 79.7 (*C*(3)), 79.0 (*C*(9)), 68.4 (*C*(7)), 37.9 (*C*(4)), 33.3 (*C*(5)), 28.4 (3 × *C*(10)), 26.2 (*C*(6)); **IR** ν_{max} (film)/cm^{-1} 3372, 1671, 1529, 1367, 1254, 1162, 917, 681; **HRMS** (ESI$^+$) $C_{12}H_{20}O_3NINa$ requires 376.0380, found $[M+Na]^+$ 376.0381 (Δ 0.22 ppm); **M.p.** 85 – 87 °C.

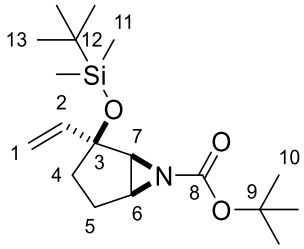
2-Vinylcyclopent-2-en-1-one (511)



To a stirred solution of aziridine alcohol **497** (45 mg, 0.2 mmol, 1.0 equiv.) in 1,3-benzodioxole (1.15 mL, 10 mmol, 50 equiv.) at 0 °C was added $BF_3{\cdot}OEt_2$ (25 µL, 0.2 mmol, 1.0 equiv.) and the reaction left to stir for 15 min. The crude reaction mixture was directly loaded onto a column, purification by which (SiO_2, neat load, pentane:Et_2O, 90:10 to 60:40) gave the unexpected diene **511** (7 mg, 32%) as a clear oil with a strong, penetrating odour.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.51 (t, J = 3.0 Hz, 1H, *H*C(4)), 6.40 (ddd, J = 17.8, 11.4, 0.9 Hz, 1H, *H*C(6)), 6.09 (dd, J = 17.8, 1.9 Hz, 1H, $H_aH_bC(1)$), 5.36 – 5.28 (m, 1H, $H_aH_bC(1)$), 2.66 – 2.58 (m, 2H, $H_2C(3)$), 2.50 – 2.44 (m, 2H, $H_2C(2)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 208.2 (*C*(1)), 159.0 (*C*(4)), 141.4 (*C*(5)), 126.8 (*C*(6)), 119.0 (*C*(7)), 35.7 (*C*(2)), 26.5 (*C*(1)); **IR** ν_{max} (film)/cm^{-1} 2922, 2853, 2361, 1708, 1478, 1438, 1231, 1039, 1001, 928; **HRMS** (ESI$^+$) C_7H_9O requires 109.06479, found $[M+H]^+$ 109.06490 (Δ 1.02 ppm).

*t*Butyl-2-((tert-butyldimethylsilyl)oxy)-2-vinyl-6-azabicyclo[3.1.0]hexane-6-carboxylate (516)

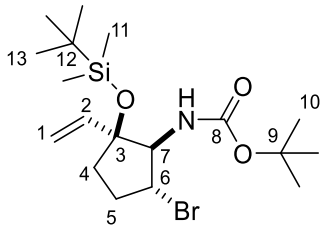


To a stirred solution of aziridine alcohol **497** (324 mg, 1.44 mmol, 1.0 equiv.) in DMF (10 mL) at RT was added *t*butyldimethylsilyl chloride (435 mg, 2.88 mmol, 2.0 equiv.) and imidazole (392 mg, 3.0 mmol, 4.0 equiv.) and the reaction left to stir for 60 h. The reaction was quenched by the addition of water (5 mL) and extracted with Et_2O (3 × 15 mL) and the combined organic extracts were washed with brine (3 × 15 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2,

eluent load, pentane:Et_2O, 75:25) gave the desired TBS protected aziridine **516** (241 mg, 49%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.90 (dd, J = 17.6, 10.8 Hz, 1H, *H*C(2)), 5.18 (dd, J = 17.6, 1.3 Hz, 1H, $H_aH_bC(1)$), 5.07 (dd, J = 10.8, 1.3 Hz, 1H, $H_aH_bC(1)$), 2.92 (dq, J = 4.9, 1.1 Hz, 1H, *H*C(6)), 2.84 (d, J = 4.6 Hz, 1H, *H*C(7)), 2.09 – 1.94 (m, 1H, $H_aH_bC(4)$), 1.64 – 1.51 (m, 3H, $H_aH_bC(4)$ and $H_2C(5)$), 1.45 (s, 9H, 3 × $H_3C(10)$), 0.90 (s, 9H, 3 × $H_3C(13)$), 0.14 (d, J = 4.6 Hz, 6H, $H_3C(11)$ and $H_3C(11')$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 162.3 (*C*(8)), 142.2 (*C*(2)), 112.8 (*C*(1)), 81.4 (*C*(3)), 81.2 (*C*(9)), 47.9 (*C*(7)), 42.0 (*C*(6)), 33.5 (*C*(5)), 28.1 (3 × *C*(10)), 26.0 (3 × *C*(13)), 25.3 (*C*(4)), 18.3 (*C*(12)), -2.4 (*C*(11)), -2.6 (*C*(11')); **IR** ν_{max} (film)/cm^{-1} 1710, 1623, 1352, 1327, 1277, 1201, 1156; **HRMS** (ESI$^+$) $C_{18}H_{34}NO_3Si$ requires 340.2302, found $[M+H]^+$ 340.2303 (Δ 0.40 ppm).

*t*Butyl-5-bromo-2-((tert-butyldimethylsilyl)oxy)-2-vinylcyclopentyl)carbamate (517)

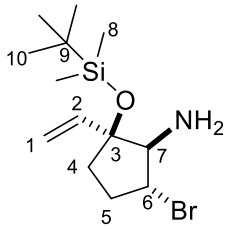


To a stirred solution of TBS protected aziridine alcohol **516** (170 mg, 0.5 mmol, 1.0 equiv.) in Et_2O (5 mL) at RT was added $MgBr_2{\cdot}Et_2O$ (258 µL, 1.0 mmol, 2.0 equiv.) and the reaction left to stir for 6 h before being filtered through a pad of celite, eluting with Et_2O, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 90:10) gave the ring-opened product **517** (97 mg, 46%) as a tan solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.90 (dd, J = 17.4, 10.9 Hz, 1H, *H*C(2)), 5.27 (d, J = 17.5 Hz, 1H, $H_aH_bC(1)$), 5.15 (d, J = 10.9 Hz, 1H, $H_aH_bC(1)$), 4.88 – 4.81 (m, 1H, *H*N), 4.08 – 3.96 (m, 2H, *H*C(6) and *H*C(7)), 2.46 (tt, J = 15.7, 7.6 Hz, 1H, $H_aH_bC(5)$), 2.24 (ddd, J = 13.8, 10.8, 7.1 Hz, 1H, $H_aH_bC(4)$), 2.09 (dddd, J = 17.5, 10.6, 6.7, 3.9 Hz, 1H, $H_aH_bC(5)$), 1.88 (ddd, J = 13.8, 8.9, 3.7 Hz, 1H, $H_aH_bC(4)$), 1.44 (s, 9H, 3 × $H_3C(10)$), 0.89 (s, 9H, 3 × $H_3C(13)$), 0.08 (s, 6H, 2 × $H_3C(11)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 155.8 (*C*(8)), 139.8

(*C*(2)), 115.2 (*C*(1)), 82.2 (*C*(3)), 79.6 (*C*(9)), 68.0 (*C*(7)), 52.6 (*C*(6), 34.7 (*C*(4)), 31.6 (*C*(5)), 28.5 (3 × *C*(10)), 26.0 (3 × *C*(13)), 18.5 (*C*(12)), -2.3 (*C*(11)), -2.6 (*C*(11')); **IR** ν_{max} (film)/cm^{-1} 1652, 1264, 1123, 1085, 832, 795; **HRMS** (ESI$^+$) $C_{18}H_{35}BrNO_3Si$ requires 420.1564, found $[M+H]^+$ 420.1564 (Δ -0.22 ppm); **M.p.** 80 – 82 °C.

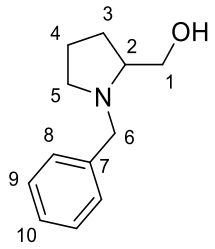
5-Bromo-2-((tert-butyldimethylsilyl)oxy)-2-vinylcyclopentan-1-amine (523)



In a glove box, Ni(cod)$_2$ (2 mg, 0.008 mmol, 4 mol%), bathophenanthroline **518** (5.3 mg, 0.016 mmol, 8 mol%), 3,4-(methylenedioxy)phenylboronic acid **522** (40 mg, 0.24 mmol, 1.2 equiv.), KO*t*Bu (36 mg, 0.32 mmol, 1.6 equiv.) and *sec*-butanol (1.5 mL) were added to a vial equipped with a stirrer bar and the reaction left to stir at RT for 10 min. To the reaction was added TBS protected ring opened amino alcohol **517** (84 mg, 0.2 mmol, 1.0 equiv.) and the reaction stirred at 65 °C for 5 h. The mixture was then passed through a short column of SiO_2, eluting with Et_2O, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 90:10 to 100% Et_2O) gave the Boc-removed product **523** (16 mg, 25%) as a pale brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.86 (dd, J = 17.6, 10.9 Hz, 1H, *H*C(2)), 5.24 (d, J = 10.9 Hz, 1H, H_aH_bC(1)), 5.19 (d, J = 17.6 Hz, 1H, H_aH_bC(1)), 4.91 – 4.85 (m, 1H, *H*C(6)), 3.88 (d, J = 7.1 Hz, 1H, *H*C(7)), 2.09 – 1.92 (m, 3H, H_aH_bC(5) and H_2C(4)), 1.90 – 1.80 (m, 1H, H_aH_bC(5)), 0.88 (s, 9H, 3 × H_3C(10)), 0.08 (d, J = 12.7 Hz, 6H, H_3C(8) and H_3C(8')); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 140.7 (*C*(2)), 115.8 (*C*(1)), 82.6 (*C*(3)), 79.7 (*C*(6)), 64.0 (*C*(7)), 32.6 (*C*(4)), 31.6 (*C*(5)), 26.0 (3 × *C*(10)), 18.3 (*C*(9)), -2.2 (*C*(8)), -2.3 (*C*(8')); **IR** ν_{max} (film)/cm^{-1} 3231, 2856, 1737, 1242, 1066, 1017, 1003, 927, 832, 773, 679; **HRMS** (ESI$^+$) $C_{13}H_{27}BrNOSi$ requires 320.1040, found $[M+H]^+$ 320.1042 (Δ 0.82 ppm); **M.p.** 105 – 107 °C.

(1-Benzylpyrrolidin-2-yl)methanol (552)



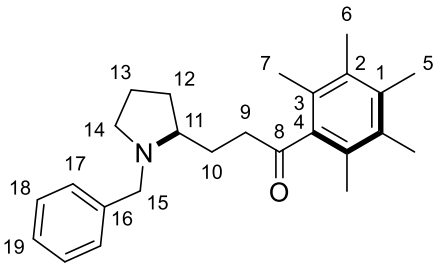
To a stirred solution of NaOH (0.78 g, 19.6 mmol, 1.0 equiv.) in water (35 mL) at 0 °C was added DL-proline **542**, followed by the simultaneous addition of benzoyl chloride (2.28 mL, 19.6 mmol, 1.0 equiv.) and a solution of NaOH ((0.78 g, 19.6 mmol, 1.0 equiv.) in water (2.5 mL). The reaction mixture was stirred at 0 °C for 2 h before being washed with Et_2O (2 × 25 mL), acidified by the dropwise addition of conc. HCl to pH 2 and extracted with EtOAC (3 × 25 mL). The combined organic extracts were then washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give crude product (4.17 g, 19 mmol) which was used without further purification.

To a stirred solution of $LiAlH_4$ (2.28 g, 60 mmol, 3.16 equiv.) in THF (70 mL) at 0 °C was added a solution of crude N-benzoyl proline (4.17 g, 19 mmol, 1.0 equiv.) in THF (10 mL) dropwise, before being left to stir at 0 °C for 1 h, after which the reaction was heated to reflux and left to stir for a further 16 h. The reaction was then cooled to 0 °C and diluted with Et_2O (60 mL) before being quenched by the sequential addition of water (2.28 ml), 15% aqueous NaOH (2.28 ml), water (6.84 mL) and $MgSO_4$ (12 g). The thick emulsion was then filtered under reduced pressure and concentrated *in vacuo* to give the desired alcohol **552** as a yellow oil (3.07 g, 82% over two steps) without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42 – 7.05 (m, 5H, 5 × *H*C_{Ar}), 3.89 (d, J = 13.0 Hz, 1H, *H*$_a$H$_b$C(6)), 3.58 (dd, J = 10.8, 3.5 Hz, 1H, *H*$_a$H$_b$C(1)), 3.35 (dd, J = 10.7, 2.1 Hz, 1H, H$_a$*H*$_b$C(1)), 3.28 (d, J = 13.0 Hz, 1H, H$_a$*H*$_b$C(6)), 2.89 (ddd, J = 9.4, 6.1, 3.0 Hz, 1H, *H*$_a$H$_b$C(5)), 2.71 – 2.61 (m, 1H, *H*C(2)), 2.21 (td, J = 9.4, 7.5 Hz, 1H, H$_a$*H*$_b$C(5)), 1.93 – 1.69 (m, 2H, *H*$_a$H$_b$C(3) and *H*$_a$H$_b$C(4)), 1.69 – 1.53 (m, 2H, H$_a$*H*$_b$C(3) and H$_a$*H*$_b$C(4)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.5 (*C*(7)), 128.8 (2 × *C*$_{Ar}$), 128.5 (2 × *C*$_{Ar}$), 127.2 (*C*(10)), 64.3 (*C*(2)), 61.8 (*C*(1)), 58.6 (*C*(6)), 54.6 (*C*(5)), 27.9 (*C*(3)), 23.6 (*C*(4)).

Data was consistent with that previously reported.[132]

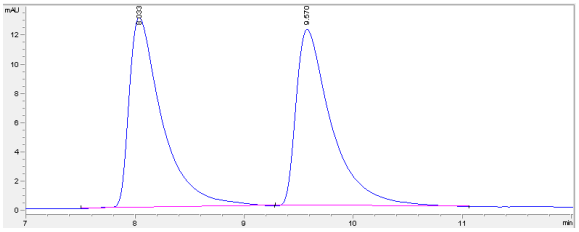
(*S*)-3-(1-Benzylpyrrolidin-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one (553)



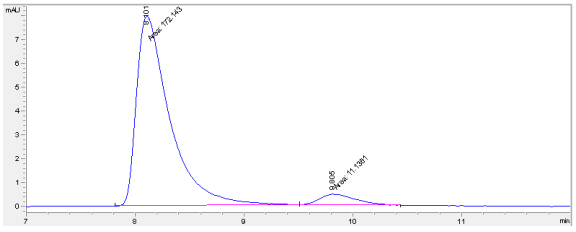
N-Benzyl-L-prolinol **552** (96 mg, 0.5 mmol, 1.0 equiv.) was subjected to **General Procedure E**. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 60:40) gave the desired compound **553** (131 mg, 72%, 94:6 er) as a tan solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37 – 7.18 (m, 5H, 5 × *H*C_{Ar}), 4.09 (d, J = 13.0 Hz, 1H, $H_a$$H_b$C(15)), 3.19 (d, J = 12.9 Hz, 1H, $H_a$$H_b$C(15)), 2.94 – 2.79 (m, 2H, $H_a$$H_b$C(14) and $H_a$$H_b$C(9)), 2.69 (ddd, J = 18.5, 10.1, 5.7 Hz, 1H, $H_a$$H_b$C(9)), 2.50 (qd, J = 7.9, 3.2 Hz, 1H, *H*C(11)), 2.24 (s, 4H, $H_a$$H_b$C(10) and H_3C(5)), 2.19 (s, 7H, $H_a$$H_b$C(14) and 2 × $H_3$$CC_{Ar}$), 2.11 (s, 6H, 2 × $H_3$$CC_{Ar}$), 1.90 (dddd, J = 12.3, 9.4, 8.0, 6.6 Hz, 1H, $H_a$$H_b$C(12)), 1.79 (dddd, J = 13.3, 10.1, 8.1, 4.9 Hz, 1H, $H_a$$H_b$C(10)), 1.69 – 1.62 (m, 2H, H_2C(13)), 1.55 – 1.41 (m, 1H, $H_a$$H_b$C(12)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 212.3 (*C*(8)), 141.0 (C_{Ar}), 139.8 (C_{Ar}), 135.5 (C_{Ar}), 133.2 (2 × C_{Ar}), 129.0 (2 × C_{Ar}), 128.3 (2 × C_{Ar}), 127.4 (2 × C_{Ar}), 126.9 (C_{Ar}), 63.2 (*C*(11)), 58.7 (*C*(15)), 54.3 (*C*(14)), 41.9 (*C*(9)), 30.1 (*C*(12)), 27.0 (*C*(10)), 22.3 (*C*(13)), 17.4 (2 × $H_3$$CC_{Ar}$), 16.8 (*C*(5)), 16.1 (2 × $H_3$$CC_{Ar}$); **IR** (film) ν_{max}/cm^{-1} **=** 2943, 2788, 1699, 1495, 1452, 1407, 1379, 1118, 737; **HRMS** (ESI$^+$) $C_{25}H_{34}ON$ requires 364.2635, found $[M+H]^+$ = 364.2635 (Δ –0.01 ppm); **$[\alpha]_D^{25}$** = –67.2 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 1.0 % IPA, 99.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).



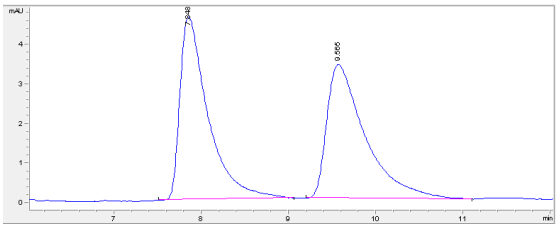
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2	9.57	BB	276.6	12.1	0.3377	49.849	0.41



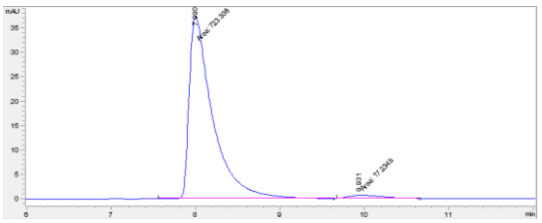
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.101	MF	172.1	8	0.3603	93.924	0
2	9.805	FM	11.1	4.7E-1	0.3923	6.076	0.595

571 mg of **553** was recrystallised from ~2 mL of boiling MeOH to give 506 mg (89% recovery) of **553**, the er of which was measured to be 98:2 by HPLC analysis.

Chiral HPLC (Chiralpak IA with guard, 1.0 % IPA, 99.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

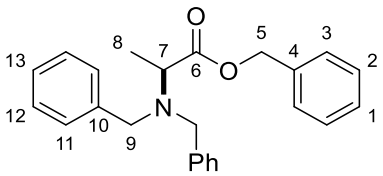


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.848	BB	103.5	4.6	0.3214	49.963	0.405
2	9.565	BB	103.7	3.4	0.4342	50.037	0.398



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.99	MM	723.3	37.2	0.324	97.673	0.355
2	9.931	MM	17.2	6.1E-1	0.4673	2.327	0.422

Benzyl dibenzyl-*L*-alaninate, 554



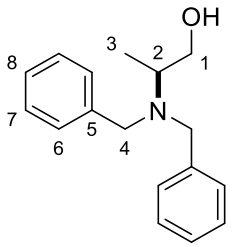
To a stirred suspension of *L*-alanine **550** (0.89 g, 10 mmol, 1.0 equiv.) and K_2CO_3 (4.14 g, 30 mmol, 3.0 equiv.) in MeCN (30 mL) at RT was added benzyl bromide (4.16 mL, 35 mmol, 3.0 equiv.) dropwise. The resulting solution was then warmed to 80 °C and left to stir for 16 h. The reaction mixture was then

cooled to RT and water (50 mL) was added. The resulting mixture was then extracted with EtOAc (3 × 50 mL), and the organic extracts washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 96:4) gave the desired compound **554** (585 mg, 16%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.43 – 7.20 (m, 15H, 15 × *H*C_{Ar}), 5.28 – 5.12 (m, 2H, *H*$_2$C(5)), 3.88 – 3.79 (m, 2H, 2 × *H*$_a$H$_b$C(9)), 3.68 – 3.60 (m, 2H, 2 × H$_a$*H*$_b$C(9)), 3.56 (qd, *J* = 5.9, 2.4 Hz, 1H, *H*C(7)), 1.39 – 1.33 (m, 3H, *H*$_3$C(8)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 173.7 (*C*(6)), 140.0 (2 × *C*$_{Ar}$), 136.3 (*C*(4)), 128.8 (4 × *C*$_{Ar}$), 128.7 (2 × *C*$_{Ar}$), 128.44 (2 × *C*$_{Ar}$), 128.38 (*C*(1)), 128.35 (4 × *C*$_{Ar}$), 127.1 (2 × *C*$_{Ar}$), 66.2 (*C*(7)), 56.3 (*C*(5)), 54.5 (2 × *C*(9)), 15.1 (*C*(8)).

Data was consistent with that previously reported.[133]

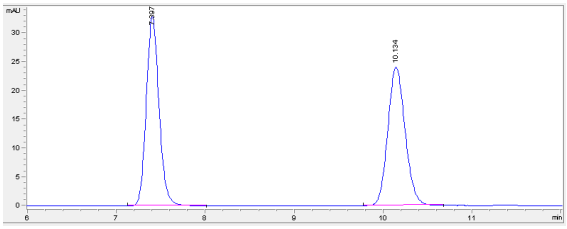
(*S*)-2-(Dibenzylamino)propan-1-ol, 555



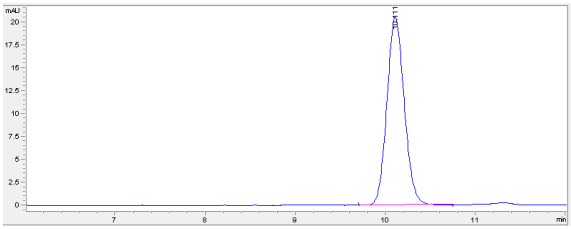
Perbenzylated alanine **554** (528 mg, 1.5 mmol, 1.0 equiv.) was subjected to **General Procedure H**. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 80:20 to 70:30) gave the desired alcohol **555** (285 mg, 75%, >99:1 er) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.55 – 7.01 (m, 10H, 10 × *H*C_{Ar}), 3.82 (d, J = 13.4 Hz, 2H, 2 × *H*$_a$H$_b$C(4)), 3.51 – 3.41 (m, 1H, *H*$_a$H$_b$C(1)), 3.39 – 3.29 (m, 3H, 2 × H$_a$*H*$_b$C(4) and H$_a$*H*$_b$C(1)), 3.14 (s, 1H, *H*OC(1)), 2.99 (dddd, J = 13.5, 11.5, 6.7, 4.8 Hz, 1H, *H*C(2)), 0.98 (d, J = 6.6 Hz, 3H, *H*$_3$C(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.4 (2 × *C*(5)), 129.1 (4 × *C*$_{Ar}$), 128.6 (4 × *C*$_{Ar}$), 127.3 (2 × *C*(8)), 62.8 (*C*(1)), 54.3 (*C*(2)), 53.0 (2 × *C*(4)), 8.8 (*C*(3)); **$[\alpha]_D^{25}$** = +51.0 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IB-N5 with guard, 5.0 % IPA, 95.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).



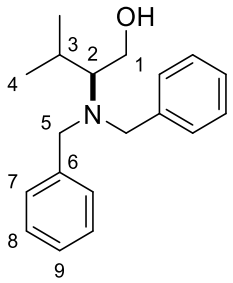
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.397	BB	325.2	32.8	0.1535	49.960	0.852
2	10.134	BB	325.7	24	0.2101	50.040	0.861



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.111	BB	275.5	20.5	0.2065	100.000	0.873

Data was consistent with that previously reported.[134]

(*S*)-2-(Dibenzylamino)-3-methylbutan-1-ol (557)

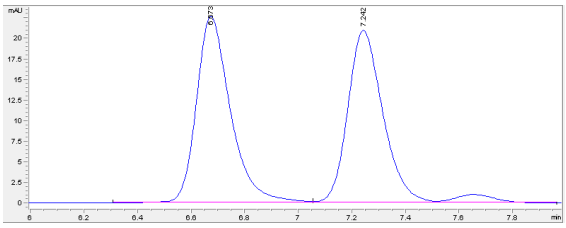


To a stirred solution of L-valinol **556** (1.03 g, 10 mmol, 1.0 equiv.) and K_2CO_3 (3.45 g, 25 mmol, 2.5 equiv.) in EtOH (50 mL) at RT was added BnBr (2.61 mL, 22 mol, 2.2 equiv.) and the reaction left to stir for 24 h. The mixture was then concentrated *in vacuo* and the residue redissolved in EtOAc (50 mL), washed with water (50 mL), sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a crude oil. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 80:20) gave the desired compound **557** (812 mg, 43%, >99:1 er) as a colourless oil.

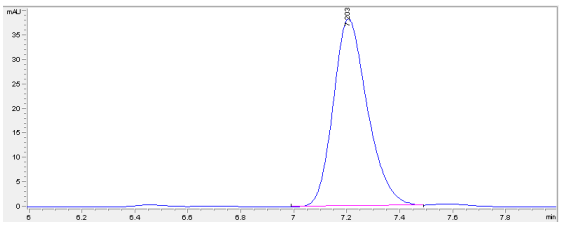
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.34 – 7.20 (m, 10H, 10 × *H*C_{Ar}), 3.88 (d, J = 13.2 Hz, 2H, 2 × H_aH_bC(5)), 3.67 (d, J = 13.2 Hz, 2H, 2 × H_aH_bC(5)), 3.56 (dd, J = 10.6, 4.6 Hz, 1H, H_aH_bC(1)), 3.49 – 3.37 (m, 1H, H_aH_bC(1)), 3.02 (s, 1H, *H*OC(1)), 2.53 (ddd, J = 9.9, 7.8, 4.6 Hz, 1H, *H*C(2)), 2.06 (dp, J = 7.8, 6.7 Hz, 1H, *H*C(3)), 1.14 (d, J = 6.8 Hz, 3H, H_3C(4)), 0.88 (d, J = 6.7 Hz, 3H, H_3C(4')); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C

139.8 (2 × *C*(6)), 129.3 (4 × C_{Ar}), 128.6 (4 × C_{Ar}), 127.3 (2 × *C*(9)), 64.7 (*C*(2)), 59.3 (*C*(4)), 54.3 (2× *C*(5)), 27.7 (*C*(3)), 22.9 (*C*(4)), 20.3 (*C*(4')); $[\alpha]_D^{25}$ = +27.4 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 5.0 % IPA, 95.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).



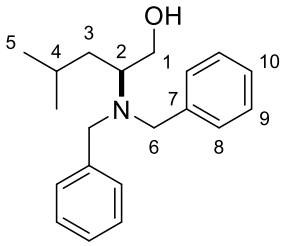
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.673	BV	202.1	22.7	0.134	50.102	0.703
2	7.242	VV R	201.2	20.9	0.1385	49.898	0.761



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.203	BB	343	38.3	0.1384	100.000	0.759

Data was consistent with that previously reported.[135]

(*S*)-2-(Dibenzylamino)-4-methylpentan-1-ol (559)



To a stirred solution of MeOH (20 mL) at 0 °C was added $SOCl_2$ (4.38 mL, 60 mmol, 3.0 equiv.) dropwise and the reaction left to stir for 15 min. L-Leucine **245** (2.62 g, 20 mmol, 1.0 equiv.) was added portionwise and the reaction warmed to RT and left to stir for 3 h. The solvent was then removed *in vacuo* before adding more MeOH (20 mL) and removing it *in vacuo*. The process was repeated twice before drying under high vacuum for 3 h to give the desired methyl ester hydrochloride which was used without further purification.

To a stirred solution of the crude methyl ester (3.62 g, 20 mmol, 1.0 equiv.) and K_2CO_3 (9.66 g, 70 mmol, 3.5 equiv.) in EtOH (40 mL) at RT was added BnBr (5.23 mL, 44 mmol, 2.2 equiv.) and the reaction left to stir for 16 h. The reaction was concentrated *in vacuo* and residue taken up in water (30 mL) before

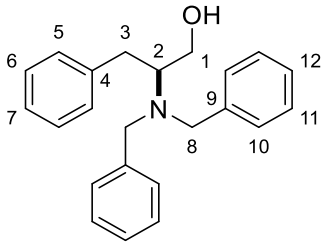
being extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a crude product **558** as an oil that was used without further purification.

To a stirred solution of $LiAlH_4$ (1.14 g, 30 mmol, 1.5 equiv.) in THF (200 mL) at 0 °C was added a solution of crude benzylated leucine (4.98 g, 20 mmol, 1.0 equiv.) in THF (40 mL) dropwise, before being allowed to warm to RT over the course of 15 min. The reaction was then cooled to 0 °C and diluted with Et_2O (100 mL) before being quenched by the sequential addition of water (1.14 ml), 15% aqueous NaOH (1.14 ml), water (3.42 mL) and $MgSO_4$ (6 g). The thick emulsion was then filtered under reduced pressure and concentrated *in vacuo* to give the desired alcohol **559** as a colourless oil (2.03 g, 34% over three steps) without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.46 – 7.14 (m, 10H, 10 × *H*C_{Ar}), 3.77 (d, J = 13.3 Hz, 2H, 2 × $H_a$$H_b$C(6)), 3.56 – 3.36 (m, 2H, H_2C(1)), 3.33 (d, J = 13.2 Hz, 2H, 2 × $H_a$$H_b$C(6)), 3.16 (s, 1H, *H*OC(1)), 2.81 (tdd, J = 10.1, 5.0, 2.5 Hz, 1H, *H*C(2)), 1.48 (qq, J = 6.8, 2.9 Hz, 2H, $H_a$$H_b$C(3) and *H*C(4)), 1.18 – 1.05 (m, 1H, $H_a$$H_b$C(3)), 0.88 (d, J = 6.1 Hz, 3H, H_3C(5)), 0.82 (d, J = 5.9 Hz, 3H, H_3C(5')); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.5 (2 × *C*(7)), 129.2 (4 × C_{Ar}), 128.6 (4 × C_{Ar}), 127.4 (2 × *C*(10)), 61.2 (*C*(1)), 57.1 (*C*(2)), 53.2 (2 × *C*(6)), 34.1 (*C*(3)), 25.6 (*C*(4)), 24.2 (*C*(5)), 22.2 (*C*(5')); **$[\alpha]_D^{25}$** = +83.6 (c = 1.00, $CHCl_3$).

Data was consistent with that previously reported.[136]

(*S*)-2-(Dibenzylamino)-3-phenylpropan-1-ol (562)



To a stirred solution of ethanol (20 mL) and 6M aq. NaOH (1.66 mL) at RT was added L-phenylalanine **560** (1.65 g, 10 mmol, 1.0 equiv.), K_2CO_3 (5.52 g, 40 mmol, 4.0 equiv.), BnBr (4.16 mL, 35 mmol, 3.5 equiv.) and water (20 mL) and the reaction left to stir for 16 h, before being brought to reflux for a

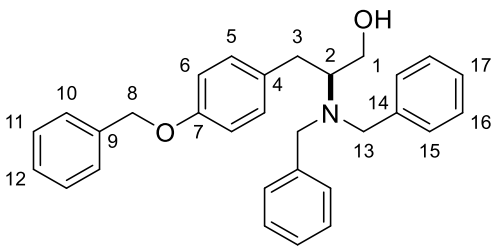
further 2 h. The ethanol was removed *in vacuo* and the leftover aqueous solution extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a crude product **561** (4.89 g) as an oil that was used without further purification.

To a stirred solution of $LiAlH_4$ (0.38 g, 10 mmol, 1.0 equiv.) in Et_2O (40 mL) at 0 °C was added crude benzylated phenylglycine (4.89 g, 10 mmol, 1.0 equiv.) dropwise, before being allowed to warm to RT over the course of 1 h, after which the reaction was shown to have gone to completion *via* TLC (pentane:Et_2O, 80:20). The reaction was then cooled to 0 °C and diluted with Et_2O (25 mL) before being quenched by the sequential addition of water (380 µl), 15% aqueous NaOH (380 µl), water (1.14 mL) and $MgSO_4$ (2 g). The thick emulsion was then filtered under reduced pressure and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 80:20) gave the desired alcohol **562** as a colourless oil (1.58 g, 48% over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.59 – 6.94 (m, 15H, 15 × *H*C_{Ar}), 3.93 (d, J = 13.2 Hz, 2H, 2 × $H_a$$H_b$C(8)), 3.49 (dd, J = 11.9, 5.5 Hz, 3H, $H_a$$H_b$C(1) and 2 × $H_a$$H_b$C(8)), 3.39 – 3.28 (m, 1H, $H_a$$H_b$C(1)), 3.17 – 2.99 (m, 3H, $H_a$$H_b$C(3) and *H*C(2) and *H*OC(1)), 2.48 – 2.38 (m, 1H, $H_a$$H_b$C(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.3 (C_{Ar}), 139.2 (C_{Ar}), 129.2 (C_{Ar}), 129.1 (C_{Ar}), 128.7 (2 × C_{Ar}), 127.5 (C_{Ar}), 126.4 (C_{Ar}), 61.0 (*C*(2)), 60.5 (*C*(1)), 53.4 (2 × *C*(8)), 31.8 (*C*(3)); **$[\alpha]_D^{25}$** = +45.4 (c = 1.00, $CHCl_3$).

Data was consistent with that previously reported.[137]

(*S*)-3-(4-(Benzyloxy)phenyl)-2-(dibenzylamino)propan-1-ol (565)



To a stirred solution of L-tyrosine **563** (1.81 g, 10 mmol, 1.0 equiv.) and K_2CO_3 (6.07 g, 44 mmol, 4.4 equiv.) in EtOH (10 mL) at RT was added BnBr (4.99 mL, 42 mmol, 4.2 equiv.) and the reaction left to

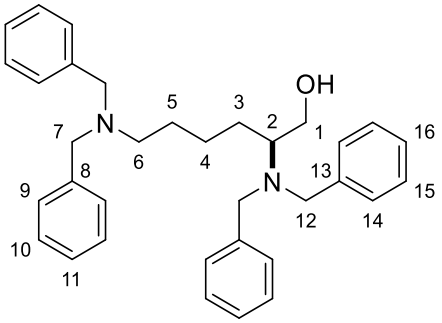
stir for 16 h. The reaction was concentrated *in vacuo* and residue taken up in water (30 mL) before being extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a crude product **564** (4.98 g) as an oil that was used without further purification.

To a stirred solution of $LiAlH_4$ (0.57 g, 15 mmol, 1.5 equiv.) in THF (100 mL) at 0 °C was added a solution of crude benzylated tyrosine (4.98 g, 10 mmol, 1.0 equiv.) in THF (20 mL) dropwise, before being allowed to warm to RT over the course of 15 min after which the reaction was shown to have gone to completion *via* TLC (pentane:Et_2O, 70:30). The reaction was then cooled to 0 °C and diluted with Et_2O (50 mL) before being quenched by the sequential addition of water (570 µl), 15% aqueous NaOH (570 µl), water (1.71 mL) and $MgSO_4$ (3 g). The thick emulsion was then filtered under reduced pressure and concentrated *in vacuo* to give an oil. Trituration of the oil with Et_2O resulted in the formation of the desired alcohol **565** as a colourless solid (1.92 g, 44% over two steps) without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.49 – 7.21 (m, 15H, 15 × *H*C_{Ar}), 7.04 – 6.97 (m, 2H, 2 × *H*C(5)), 6.93 – 6.85 (m, 2H, 2 × *H*C(6)), 5.04 (s, 2H, *H*$_2$C(8)), 3.92 (d, J = 13.3 Hz, 2H, 2 × *H*$_a$H$_b$C(13)), 3.54 – 3.44 (m, 3H, 2 × H$_a$*H*$_b$C(13) and *H*$_a$H$_b$C(1)), 3.34 (dd, J = 10.9, 4.2 Hz, 1H, H$_a$*H*$_b$C(1)), 3.10 – 2.97 (m, 3H, *H*$_a$H$_b$C(3) and *H*C(2)), 2.44 – 2.33 (m, 1H, H$_a$*H*$_b$C(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 157.5 (*C*(7)), 139.3 (2 × *C*(14)), 137.2 (*C*(9)), 131.6 (2 × *C*(5)), 130.1 (*C*$_{Ar}$), 129.2 (2 × *C*$_{Ar}$), 128.8 (*C*$_{Ar}$), 128.7 (2 × *C*$_{Ar}$), 128.1 (*C*(4)), 127.6 (*C*$_{Ar}$), 127.5 (*C*$_{Ar}$), 115.2 (2 × *C*(6)), 70.2 (*C*(8)), 61.1 (*C*(2)), 60.6 (*C*(1)), 53.4 (2 × *C*(13)), 31.0 (*C*(3)); **$[\alpha]_D^{25}$** = +54.7 (c = 1.00, $CHCl_3$).

Data was consistent with that previously reported.[138]

(*S*)-2,6-Bis(dibenzylamino)hexan-1-ol (568)



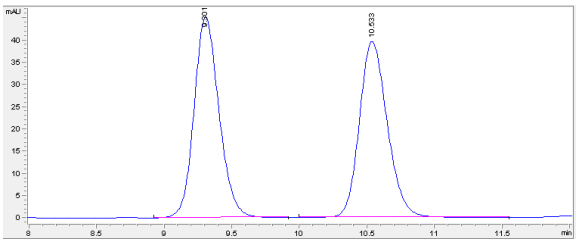
To a stirred solution of L-lysine **566** (1.83 g, 10 mmol, 1.0 equiv.) in EtOH (20 mL) at RT was added K_2CO_3 (11.0 g, 80 mmol, 8.0 equiv.) and BnBr (8.30 mL, 70 mmol, 7.0 equiv.) and the reaction heated to 60 °C for 4 d. The resulting white slurry was then filtered through a pad of celite, washing with EtOAc (50 mL) and the filtrate washed with brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a crude yellow oil **567** (8.02 g) that was used without further purification.

To a stirred solution of $LiAlH_4$ (0.76 g, 20 mmol, 2.0 equiv.) in THF (40 mL) at 0 °C was added a solution of crude perbenzyl-L-lysine **567** (8.02 g, 10 mmol, 1.0 equiv.) in THF (20 mL) dropwise, before being warmed to RT over the course of 3 h. The reaction was then cooled to 0 °C and diluted with Et_2O (50 mL) before being quenched by the sequential addition of water (0.76 ml), 15% aqueous NaOH (0.76 ml), water (2.28 mL) and $MgSO_4$ (4 g). The thick emulsion was then filtered under reduced pressure and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 60:40) gave the desired alcohol **568** (2.47 g, 50% over two steps, 98:2 er) as a pale yellow oil.

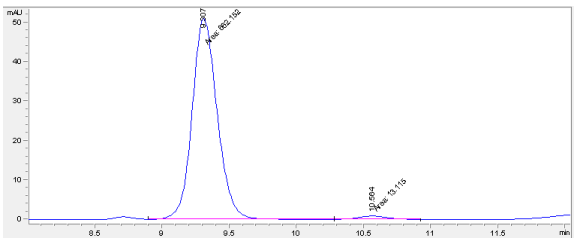
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.44 – 7.17 (m, 20H, 20 × *H*C$_{Ar}$), 3.76 (d, J = 13.3 Hz, 2H, 2 × Ph*H$_a$*H$_b$CN), 3.58 (d, J = 13.6 Hz, 2H, 2 × Ph*H$_a$*H$_b$CN'), 3.54 – 3.41 (m, 3H, 2 × PhH$_a$*H$_b$*CN' and *H$_a$*H$_b$C(1)), 3.41 – 3.29 (m, 3H, 2 × PhH$_a$*H$_b$*CN and H$_a$*H$_b$*C(1)), 3.15 (s, 1H, *H*O), 2.73 (tt, J = 9.3, 4.6 Hz, 1H, *H*C(2)), 2.49 – 2.37 (m, 2H, *H$_2$*C(6)), 1.67 – 1.39 (m, 3H, *H$_a$*H$_b$C(3) and *H$_2$*C(5)), 1.33 – 1.21 (m, 2H, *H$_2$*C(4)), 1.08 (dtd, J = 13.0, 9.6, 5.0 Hz, 1H, H$_a$*H$_b$*C(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 140.1 (2 × *C*$_{Ar}$), 139.5 (2 × *C*$_{Ar}$), 129.2 (4 × H*C*$_{Ar}$), 128.9 (4 × H*C*$_{Ar}$), 128.6 (4 × H*C*$_{Ar}$), 128.3 (4 × H*C*$_{Ar}$), 127.3 (2 × H*C*$_{Ar}$), 127.0 (2 × H*C*$_{Ar}$), 61.0 (*C*(1)),

59.1 (*C*(2)), 58.6 (2 × *C*Ph), 53.3 (2 × *C*Ph), 53.0 (*C*(6)), 27.5 (*C*(5)), 24.9 (*C*(3)), 24.8 (*C*(4)); **$[\alpha]_D^{25}$** = +66.8 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 5.0 % IPA, 95.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).



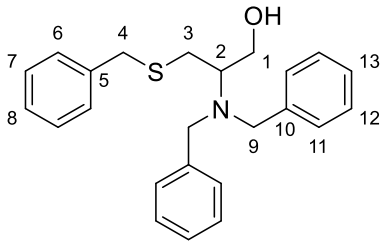
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.301	BB	578.3	44.9	0.1981	50.435	0.813
2	10.533	BB	568.3	39.5	0.222	49.565	0.789



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.307	MF	662.2	50.8	0.2171	98.058	0
2	10.564	FM	13.1	8.5E-1	0.2557	1.942	0.93

Data was consistent with that previously reported.[139]

3-(Benzylthio)-2-(dibenzylamino)propan-1-ol (570)



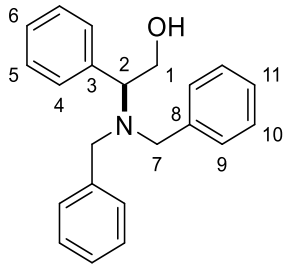
To a stirred solution of DL-Cysteine **247** (0.61 g, 5 mmol, 1.0 equiv.) and K_2CO_3 (3.04 g, 22 mmol, 4.4 equiv.) in DMF (20 mL) and water (10 mL) at RT was added BnBr (3.59 g, 21 mmol, 4.2 equiv.) and the reaction left to stir for 4 d. The reaction mixture was then partitioned between Et_2O (100 mL) and water (100 mL) and the layers separated. The aqueous layer was extracted with Et_2O (2 × 50 mL), and the combined organic layers washed with brine (3 × 50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a crude oil **569** (2.40 g) that was used without further purification.

To a stirred solution of $LiAlH_4$ (285 mg, 7.5 mmol, 1.5 equiv.) in THF (50 mL) at 0 °C was added a solution of crude perbenzylated serine **569** (2.40 g, 5 mmol, 1.0 equiv.) in THF (10 mL) dropwise, before being allowed to warm to RT over the course of 15 min. The reaction was then cooled to 0 °C and diluted

with Et_2O (40 mL) before being quenched by the sequential addition of water (0.29 ml), 15% aqueous NaOH (0.29 ml), water (0.87 mL) and $MgSO_4$ (2 g). The thick emulsion was then filtered under reduced pressure and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 70:30) gave the desired alcohol **570** as a colourless oil (654 mg, 35% over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.41 – 7.17 (m, 15H, 15 × HC_{Ar}), 3.79 (d, J = 13.4 Hz, 2H, 2 × $H_aH_bC(9)$), 3.67 (s, 2H, $H_2C(4)$), 3.64 (d, J = 8.9 Hz, 1H, $H_aH_bC(1)$), 3.52 – 3.41 (m, 3H, 2 × $H_aH_bC(9)$ and $H_aH_bC(1)$), 3.08 – 2.96 (m, 1H, $HC(2)$), 2.82 – 2.75 (m, 1H, $H_aH_bC(3)$), 2.34 (ddd, J = 12.9, 8.9, 1.5 Hz, 1H, $H_aH_bC(3)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.2 (2 × $C(10)$), 138.0 ($C(5)$), 129.1 (4 × C_{Ar}), 129.0 (2 × C_{Ar}), 128.7 (2 × C_{Ar}), 128.7 (4 × C_{Ar}), 127.5 (2 × $C(13)$), 127.3 (2 × $C(8)$), 61.0 ($C(1)$), 58.7 ($C(2)$), 53.5 (2 × $C(9)$), 37.1 ($C(4)$), 27.9 ($C(3)$); **IR** ν_{max} (film)/cm^{-1} 1482, 1447, 1288, 1210, 1854, 1004, 765; **HRMS** (ESI$^+$) $C_{24}H_{28}NOS$ requires 378.1886, found $[M+H]^+$ 378.1887 (Δ 0.34 ppm).

(*S*)-2-(Dibenzylamino)-2-phenylethan-1-ol (573)



To a stirred solution of ethanol (20 mL) and 6M aq. NaOH (1.66 mL) at RT was added L-phenylglycine **571** (1.51 g, 10 mmol, 1.0 equiv.), K_2CO_3 (5.52 g, 40 mmol, 4.0 equiv.), BnBr (4.16 mL, 35 mmol, 3.5 equiv.) and water (20 mL) and the reaction left to stir for 16 h, before being brought to reflux for a further 2 h. The ethanol was removed *in vacuo* and the leftover aqueous solution extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a crude product **572** (4.54 g) as an oil that was used without further purification.

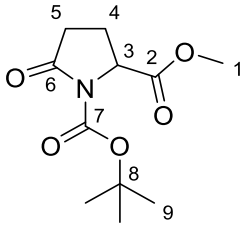
To a stirred solution of $LiAlH_4$ (0.38 g, 10 mmol, 1.0 equiv.) in Et_2O (40 mL) at 0 °C was added crude benzylated phenylglycine **572** (4.54 g, 10 mmol, 1.0 equiv.) dropwise, before being allowed to warm

to RT over the course of 1 h, after which the reaction was shown to have gone to completion *via* TLC (pentane:Et_2O, 80:20). The reaction was then cooled to 0 °C and diluted with Et_2O (25 mL) before being quenched by the sequential addition of water (380 µl), 15% aqueous NaOH (380 µl), water (1.14 mL) and $MgSO_4$ (2 g). The thick emulsion was then filtered under reduced pressure and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 85:15) gave the desired alcohol **573** as a colourless oil (2.91 g, 92% over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.50 – 7.18 (m, 15H, 15 × *H*C_{Ar}), 4.14 (t, J = 10.6 Hz, 1H, $H_a$$H_b$C(1)), 3.98 – 3.89 (m, 3H, *H*C(2) and 2 × $H_a$$H_b$C(7)), 3.60 (ddd, J = 10.6, 8.4, 5.2 Hz, 1H, $H_a$$H_b$C(1)), 3.14 (d, J = 13.4 Hz, 2H, 2 × $H_a$$H_b$C(7)), 3.06 (d, J = 8.2 Hz, 1H, *H*OC(1)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.2 (C_{Ar}), 135.1 (C_{Ar}), 129.4 (C_{Ar}), 129.1 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 127.4 (C_{Ar}), 63.1 (*C*(2)), 60.5 (*C*(1)), 53.6 (*C*(7)).

Data was consistent with that previously reported.[140]

1-(*t*Butyl) 2-methyl 5-oxopyrrolidine-1,2-dicarboxylate (575)



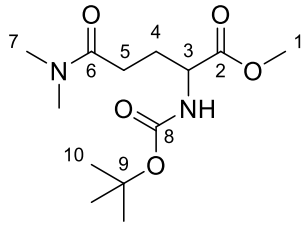
To a stirred solution of DL-pyroglutamic acid **574** (15.0 g, 116 mmol, 1.0 equiv.) in MeOH (60 mL) at RT was added $SOCl_2$ (16.9 mL, 231 mmol, 2.0 equiv.) dropwise and the reaction left to stir for 1 h. The solvent was then removed *in vacuo* and the residue redissolved in EtOAc (200 mL). Et_3N (18.5 mL, 134 mmol, 1.15 equiv.) was added dropwise, and the reaction filtered through celite to remove the formed precipitate. DMAP (1.5 g, 12.3 mmol, 0.1 equiv.) and Boc_2O (27.8 g, 127 mmol, 1.1 equiv.) were added and the reaction left to stir at RT for 3 h. The reaction mixture was then cooled to 0 °C, 1M aq. HCl (13.0 mL) was added and the reaction left to stir for 10 min. The layers were separated, and the organic layer washed with water (20 mL) and concentrated *in vacuo*. *t*Butyl methyl ether (27 mL) was added

to the residue and cooled to 0 °C with stirring, resulting in precipitation of the desired product **575** (19.7 g, 70%) which was separated by filtration.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.58 (dd, J = 9.4, 3.0 Hz, 1H, *H*C(3)), 3.75 (s, 3H, H_3C(1)), 2.59 (ddd, J = 17.5, 10.1, 9.6 Hz, 1H, $H_a$$H_b$C(5)), 2.45 (ddd, J = 17.4, 9.4, 3.6 Hz, 1H, $H_a$$H_b$C(5)), 2.29 (ddt, J = 13.4, 10.1, 9.4 Hz, 1H, $H_a$$H_b$C(4)), 2.00 (dddd, J = 13.3, 9.5, 3.6, 3.0 Hz, 1H, $H_a$$H_b$C(4)), 1.45 (s, 9H, 3 × H_3C(9)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.3 (*C*(6)), 171.9 (*C*(2)), 149.3 (*C*(7)), 83.6 (*C*(8)), 58.9 (*C*(3)), 52.6 (*C*(1)), 31.2 (*C*(5)), 28.3 (3 × *C*(9)), 21.5 (*C*(4)).

Data was consistent with that previously reported.[141]

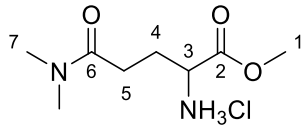
Methyl N^2-(tert-butoxycarbonyl)-N^5,N^5-dimethylglutaminate (576)



To a stirred solution of 2M Me_2NH in THF (40 mL) at RT was added Boc protected pyroglumatic acid methyl ester **575** (9.72 g, 40 mmol, 1.0 equiv.) and the reaction left to stir for 48 h. The formed white precipitate was collected by filtration and washed with pentane to provide the desired product **576** (9.26 g, 80%) as a fluffy white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.38 (d, J = 8.0 Hz, 1H, *H*N), 4.38 – 4.18 (m, 1H, *H*C(3)), 3.73 (s, 3H, H_3C(1)), 2.98 (s, 3H, H_3C(7)), 2.94 (s, 3H, H_3C(7')), 2.40 (tq, J = 16.4, 9.3, 8.3 Hz, 2H, H_2C(5)), 2.19 (dtd, J = 14.3, 7.3, 4.7 Hz, 1H, $H_a$$H_b$C(4)), 1.98 (tt, J = 14.8, 7.1 Hz, 1H, $H_a$$H_b$C(4)), 1.43 (s, 9H, 3 × H_3C(10)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.1 (*C*(2)), 172.0 (*C*(6)), 155.7 (*C*(8)), 80.0 (*C*(9)), 53.5 (*C*(3)), 52.4 (*C*(1)), 37.3 (*C*(7)), 35.7 (*C*(7')), 29.5 (*C*(5)), 28.4 (3 × *C*(10)), 27.8 (*C*(4)); **IR** ν_{max} (film)/cm^{-1} 3232, 1725, 1712, 1614, 1534, 1255, 1235, 1159, 1007; **HRMS** (ESI^+) $C_{13}H_{24}O_5N_2Na$ requires 311.1577, found $[M+Na]^+$ 311.1578 (Δ 0.3 ppm); **M.p.** 99 – 101 °C.

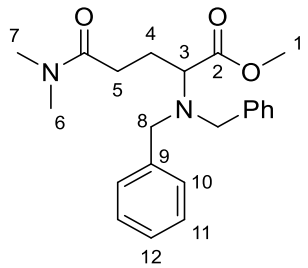
Methyl N^5,N^5-dimethylglutaminate hydrochloride (577)



To a stirred solution of 4M HCl in dioxane (10 mL) at RT was added Boc protected dimethylglutaminate **576** (0.86 g, 3 mmol, 1.0 equiv.) and the reaction left to stir for 2.5 h. The solvent was then removed *in vacuo* and the resulting solid triturated with Et_2O before being dried *in vacuo* to give desired amine hydrochloride **577** (0.97 g, quant.) as a highly hygroscopic gum.

^{1}H NMR (400 MHz, D_2O) δ_H 4.15 (t, J = 6.3 Hz, 1H, *H*C(3)), 3.79 (s, 3H, H_3C(1)), 3.01 (s, 3H, H_3C(7)), 2.88 (s, 3H, H_3C(7')), 2.63 (dd, J = 18.8, 11.6 Hz, 2H, H_2C(5)), 2.18 (tp, J = 14.5, 6.8 Hz, 2H, H_2C(4)); **^{13}C NMR** (101 MHz, D_2O) δ_C 174.0 (*C*(2)), 170.8 (*C*(6)), 54.2 (*C*(1)), 52.9 (*C*(3)), 37.8 (*C*(7)), 36.1 (*C*(7')), 29.1 (*C*(5)), 25.7 (*C*(4)); **IR** ν_{max} (film)/cm^{-1} 1745, 1619, 1436, 1229, 1082; **HRMS** (ESI$^+$) $C_8H_{17}O_3N_2$ requires 189.1234, found $[M+H]^+$ 189.1233 (Δ –0.25 ppm).

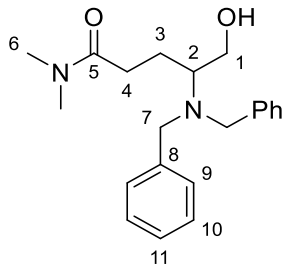
Methyl N^2,N^2-dibenzyl-N^5,N^5-dimethylglutaminate (578)



To a stirred solution of amine **577** (672 mg, 3 mmol, 1.0 equiv.) and K_2CO_3 (2.07 g, 15 mmol, 5.0 equiv.) in MeCN (20 mL) at RT was added BnBr (0.89 mL, 7.5 mmol, 2.5 equiv.) and the reaction left to stir for 24 h. Water (25 mL) was added, and the mixture was extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 40:60) gave the desired compound **578** (482 mg, 44%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.35 – 7.22 (m, 10H, 10 × *H*C$_{Ar}$), 3.90 (d, J = 13.7 Hz, 2H, 2 × *H*$_a$H$_b$C(8)), 3.77 (s, 3H, *H*$_3$C(1)), 3.55 (d, J = 13.7 Hz, 2H, 2 × H$_a$*H*$_b$C(8)), 3.37 (dd, J = 9.1, 5.8 Hz, 1H, *H*C(3)), 2.90 (s, 3H, *H*$_3$C(7)), 2.84 (s, 3H, *H*$_3$C(7')), 2.36 (ddd, J = 15.8, 8.9, 5.5 Hz, 1H, *H*$_a$H$_b$C(5)), 2.22 (ddd, J = 15.7, 9.0, 6.5 Hz, 1H, H$_a$*H*$_b$C(5)), 2.15 – 2.06 (m, 1H, *H*$_a$H$_b$C(4)), 2.06 – 1.95 (m, 1H, H$_a$*H*$_b$C(4)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.2 (*C*(2)), 172.2 (*C*(6)), 139.7 (2 × *C*(9)), 129.1 (4 × H*C*$_{Ar}$), 128.4 (4 × H*C*$_{Ar}$), 127.1 (2 × *C*(12)), 60.4 (*C*(3)), 54.7 (2 × *C*(8)), 51.3 (*C*(1)), 37.1 (*C*(7)), 35.4 (*C*(7')), 30.0 (*C*(5)), 24.8 (*C*(4)); **IR** ν_{max} (film)/cm^{-1} 2981, 1728, 1645, 1494, 1454, 1397, 1147, 1074, 748, 699; **HRMS** (ESI$^+$) $C_{22}H_{29}O_3N_2$ requires 369.2173, found $[M+H]^+$ 369.2173 (Δ 0.04 ppm).

4-(Dibenzylamino)-5-hydroxy-*N*,*N*-dimethylpentanamide (579)

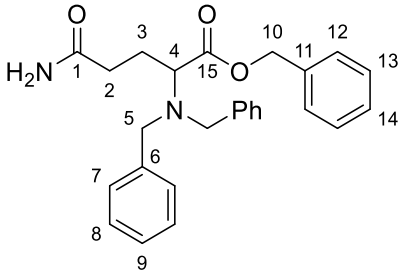


To a stirred solution of methyl ester **578** (368 mg, 1 mmol, 1.0 equiv.) in Et_2O (2 mL) and EtOH (87 µL) at 0 °C was added 4M $LiBH_4$ in THF (375 µL, 1.5 mmol, 1.5 equiv.) and the reaction warmed to RT and left to stir for 4 h. Water (4 mL) and EtOAc (4 mL) were added and layers were separated. The aqueous layer was extracted with EtOAc (2 × 4 mL) and the combined extracts dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 20:80) gave the desired compound **579** (285 mg, 84%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.35 – 7.11 (m, 10H, 10 × *H*C$_{Ar}$), 3.75 (d, J = 13.4 Hz, 2H, 2 × *H*$_a$H$_b$C(7)), 3.54 – 3.45 (m, 4H, 2 × H$_a$*H*$_b$C(7) and *H*$_2$C(1)), 3.15 (s, 1H, *H*O), 2.89 (s, 6H, *H*$_3$C(6) and *H*$_3$C(6')), 2.69 (dddd, J = 9.1, 7.6, 6.0, 4.3 Hz, 1H, *H*C(2)), 2.25 – 2.16 (m, 2H, *H*$_2$C(4)), 2.14 – 2.03 (m, 1H, *H*$_a$H$_b$C(3)), 1.64 – 1.49 (m, 1H, H$_a$*H*$_b$C(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 172.3 (*C*(5)), 139.6 (2 × *C*(8)), 129.1 (4 × H*C*$_{Ar}$), 128.5 (4 × H*C*$_{Ar}$), 127.2 (2 × *C*(11)), 61.0 (*C*(1)), 58.9 (*C*(2)), 53.4 (2 × *C*(7)), 37.1 (*C*(6)), 35.5 (*C*(6')),

30.6 (*C*(4)), 21.1 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 2981, 1628, 1494, 1454, 1397, 1152, 748, 700; **HRMS** (ESI^+) $C_{21}H_{29}O_2N_2$ requires 341.2224, found $[M+H]^+$ 341.2223 (Δ –0.19 ppm).

Benzyl dibenzylglutaminate (581)

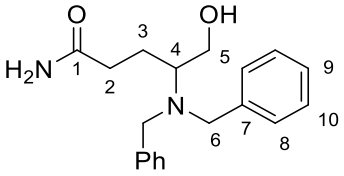


To a stirred solution of DL-glutamine **580** (7.30 g, 50 mmol, 1.0 equiv.) and K_2CO_3 (33.53 g, 243 mmol, 4.83 equiv.) in water (350 mL) at RT was added benzyl bromide (23.75 mL, 200 mmol, 4.0 equiv.) and the reaction left to stir for 12 d. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO_2, eluent load, CH_2Cl_2:MeOH, 96:4) to give the desired compound **581** (4.46 g, 21%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.46 – 7.19 (m, 15H, 15 × HC_{Ar}), 5.31 – 5.13 (m, 2H, H_2C(10)), 4.98 (d, *J* = 5.1 Hz, 2H, H_2N), 3.88 (d, *J* = 13.7 Hz, 2H, 2 × H_aH_bC(5)), 3.53 (d, *J* = 13.7 Hz, 2H, 2 × H_aH_bC(5)), 3.37 (dd, *J* = 8.8, 5.8 Hz, 1H, *H*C(4)), 2.34 – 2.20 (m, 1H, H_aH_bC(2)), 2.18 – 1.98 (m, 3H, H_aH_bC(2) and H_2C(3)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 174.6 (*C*(1)), 172.3 (*C*(15)), 139.8 (*C*(11)), 139.5 (2 × *C*(6)), 129.2 (4 × C_{Ar}), 128.8 (2 × HC_{Ar}), 128.7 (2 × HC_{Ar}), 128.5 (4 × C_{Ar}), 127.3 (2 × *C*(9)), 127.0 (*C*(14)), 66.4 (*C*(10)), 60.3 (*C*(4)), 54.7 (2 × *C*(5)), 32.3 (*C*(2)), 25.2 (*C*(3)).

Data was consistent with that previously reported.[142]

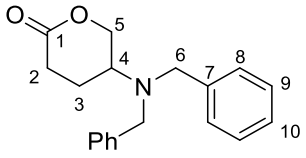
4-(Dibenzylamino)-5-hydroxypentanamide (582)



Glutamine derivative **581** (1.75 g, 4 mmol, 1.0 equiv.) was subjected to **General Procedure H**. Purification by column chromatography (SiO_2, eluent load, CH_2Cl_2:MeOH, 97:3 to 95:5) gave the desired alcohol **582** (0.90 g, 73%) as an off-white powder.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.39 – 7.16 (m, 10H, 10 × *H*C$_{Ar}$), 5.55 (br. s, 1H, *H*O), 3.80 (d, *J* = 13.3 Hz, 2H, 2 × *H*$_a$H$_b$C(6)), 3.60 – 3.45 (m, 4H, 2 × H$_a$*H*$_b$C(6) and *H*$_2$C(5)), 2.77 (m, *J* = 11.3 Hz, 1H, *H*C(4)), 2.26 – 2.04 (m, 3H, *H*$_a$H$_b$C(3) and *H*$_2$C(2)), 1.64 – 1.51 (m, 1H, H$_a$*H*$_b$C(3)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 175.1 (*C*(1)), 139.2 (2 × *C*(7)), 129.3 (4 × *C*$_{Ar}$), 128.6 (4 × *C*$_{Ar}$), 127.4 (2 × *C*(9)), 60.9 (*C*(5)), 58.9 (*C*(4)), 53.5 (2 × *C*(6)), 32.9 (*C*(2)), 21.4 (*C*(3)); **IR** (film) ν_{max}/cm^{-1} = 3308, 2932, 1679, 1636, 1451, 1407, 738, 696; **HRMS** (ESI$^+$) $C_{19}H_{25}O_2N_2$ requires 313.1911, found $[M+H]^+$ = 313.1908 (Δ –0.83 ppm); **M.p.** = 95 – 97 °C.

5-(Dibenzylamino)tetrahydro-2H-pyran-2-one, 583

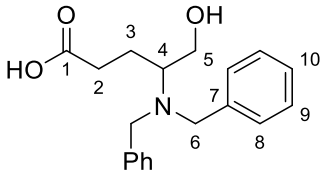


A stirred solution of glutamine derived alcohol **582** (420 mg, 1.37 mmol, 1.0 equiv.) in toluene (40 mL) was heated to reflux for 21 h. The mixture was then concentrated *in vacuo* and purified by column chromatography (SiO_2, eluent load, pentane:EtOAc, 70:30) to give the desired lactone **583** (281 mg, 69%) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.41 – 7.21 (m, 10H, 10 × *H*C$_{Ar}$), 4.38 – 4.24 (m, 2H, *H*$_2$C(5)), 3.75 – 3.62 (m, 4H, 2 × *H*$_2$C(6)), 3.24 (dtd, *J* = 9.1, 6.9, 5.6 Hz, 1H, *H*C(4)), 2.64 (ddd, *J* = 16.9, 6.3, 4.9 Hz, 1H, *H*$_a$H$_b$C(2)), 2.42 (ddd, *J* = 16.9, 10.4, 6.9 Hz, 1H, H$_a$*H*$_b$C(2)), 2.11 (ddd, *J* = 13.7, 11.7, 6.3 Hz, 1H, *H*$_a$H$_b$C(3)), 2.03 – 1.91 (m, 1H, H$_a$*H*$_b$C(3)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 172.0 (*C*(1)), 139.3 (2 × *C*(7)), 128.6 (4 ×

C_{Ar}), 128.5 (4 × C_{Ar}), 127.4 (2 × *C*(10)), 69.0 (*C*(5)), 54.5 (2 × *C*(6)), 52.0 (*C*(4)), 29.1 (*C*(2)), 20.4 (*C*(3)); **IR** (film) ν_{max}/cm^{-1} = 3027, 1733, 1454, 1247, 1171, 1138, 1055, 749; **HRMS** (ESI^+) $C_{19}H_{22}O_2N$ requires 296.1645, found $[M+H]^+$ = 296.1645 (Δ –0.19 ppm).

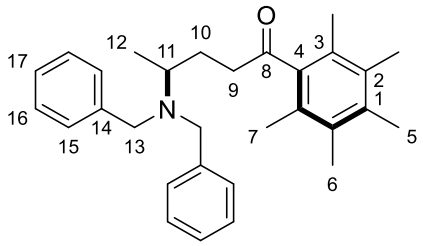
4-(Dibenzylamino)-5-hydroxypentanoic acid, 584



To a stirred solution of lactone **583** (249 mg, 0.84 mmol, 1.0 equiv.) in methanol (25 mL) was added a solution of NaOH (151 mg, 3.78 mmol, 4.5 equiv.) in water (4.5 mL). The reaction was then heated to 60 °C and left to stir for 3 h. Upon cooling to RT, the reaction mixture was neutralised by the dropwise addition of 3M aq. HCl and concentrated in vacuo. Purification by column chromatography (SiO_2, eluent load, CH_2Cl_2:MeOH, 95:5) gave the desired alcohol **584** (194 mg, 76%) as a colourless solid along with an inseparable impurity detectable by ^{13}C NMR.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.28 (br. s, *H*O_2C), 7.37 – 7.03 (m, 10H, 10 × *H*C_{Ar}), 3.61 (d, J = 13.8 Hz, 2H, 2 × $H_a$$H_b$C(6)), 3.49 (d, J = 13.8 Hz, 2H, 2 × $H_a$$H_b$C(6)), 3.47 – 3.41 (m, 2H, H_2C(5)), 2.68 – 2.55 (m, 1H, *H*C(4)), 2.21 (dt, J = 15.2, 7.1 Hz, 1H, $H_a$$H_b$C(2)), 2.15 – 2.05 (m, 1H, $H_a$$H_b$C(2)), 1.90 – 1.77 (m, 1H, $H_a$$H_b$C(3)), 1.62 (dt, J = 14.6, 7.1 Hz, 1H, $H_a$$H_b$C(3)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 177.9 (*C*(1)), 136.7 (2 × *C*(7)), 129.9 (4 × C_{Ar}), 128.8 (4 × C_{Ar}), 128.0 (2 × *C*(10)), 60.9 (*C*(5)), 59.9 (*C*(4)), 53.8 (2 × *C*(6)), 33.2 (*C*(2)), 21.4 (*C*(3)); **IR** (film) ν_{max}/cm^{-1} = 2806, 1727, 1495, 1454, 1245, 1216, 1174, 750, 699; **HRMS** (ESI^-) $C_{19}H_{24}O_3N$ requires 314.1751, Found $[M+H]^-$ = 314.1750 (Δ –0.34 ppm); **M.p.** = 95 – 97 °C.

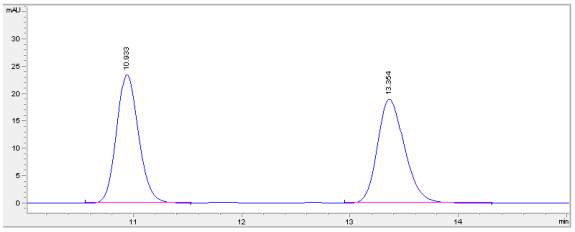
(*S*)-4-(Dibenzylamino)-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one (587)



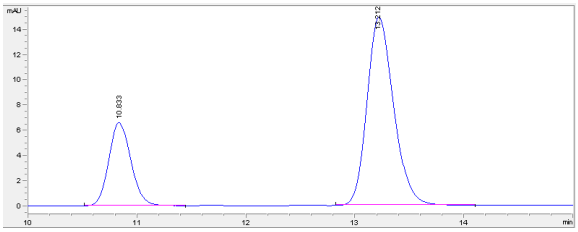
N,*N*-Dibenzyl-L-alaninol **555** (102 mg, 0.4 mmol, 1.0 equiv.) was subjected to **General Procedure E**. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 60:40) gave the desired compound **587** (120 mg, 70%, 73:27) as a tan solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39 – 7.13 (m, 10H, 10 × *H*C_{Ar}), 3.75 (d, J = 13.8 Hz, 2H, 2 × $H_a$$H_b$C(13)), 3.39 (d, J = 13.8 Hz, 2H, 2 × $H_a$$H_b$C(13)), 3.00 (ddd, J = 18.5, 10.6, 4.8 Hz, 1H, $H_a$$H_b$C(9)), 2.82 – 2.69 (m, 1H, *H*C(11)), 2.56 (ddd, J = 18.6, 10.6, 5.0 Hz, 1H, $H_a$$H_b$C(9)), 2.23 (d, J = 2.8 Hz, 3H, H_3C(5)), 2.18 (s, 6H, 2 × $H_3$$CC_{Ar}$), 2.02 (s, 7H, $H_a$$H_b$C(10) and 2 × $H_3$$CC_{Ar}$), 1.71 (ddt, J = 14.3, 10.6, 5.2 Hz, 1H, $H_a$$H_b$C(10)), 1.06 (d, J = 6.6 Hz, 3H, H_3C(12)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 212.6 (*C*(8)), 141.1 (C_{Ar}), 140.5 (2 × C_{Ar}), 135.4 (C_{Ar}), 133.1 (2× C_{Ar}), 128.8 (4 × C_{Ar}), 128.3 (4 × C_{Ar}), 127.5 (2 × C_{Ar}), 126.8 (2 × C_{Ar}), 53.4 (2 × *C*(13)), 52.4 (*C*(11)), 43.3 (*C*(9)), 27.5 (*C*(10)), 17.3 (H_3*C*C_{Ar}), 16.8 (*C*(5)), 16.1 (2 × H_3*C*C_{Ar}), 13.3 (*C*(12)); **IR** ν_{max} (film)/cm^{-1} 2980, 1698, 1454, 1381, 1154, 1072, 746, 727, 698; **HRMS** (ESI$^+$) $C_{30}H_{38}ON$ requires 428.2948, found [M+H]$^+$ 428.2944 (Δ –0.91 ppm); **M.p.** 70 – 72 °C; **[α]$_D^{25}$** = –3.6 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 1.0 % IPA, 99.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

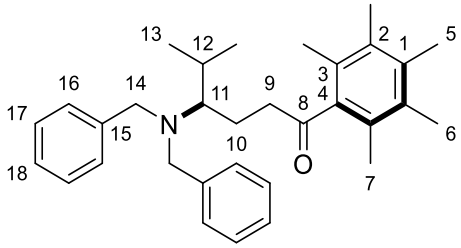


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.933	BB	328.9	23.5	0.2151	50.095	0.835
2	13.354	BB	327.7	19	0.2652	49.905	0.757



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.833	BB	92	6.6	0.2123	26.537	0.85
2	13.212	BB	254.8	14.9	0.2608	73.463	0.772

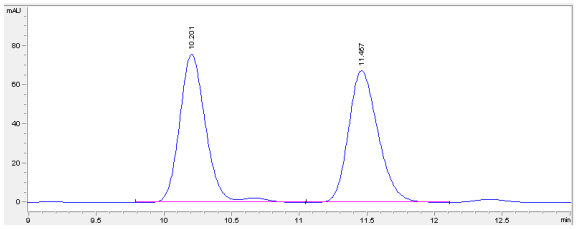
(*R*)-4-(Dibenzylamino)-5-methyl-1-(2,3,4,5,6-pentamethylphenyl)hexan-1-one (588)



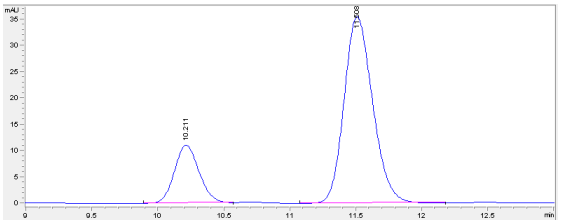
Dibenzyl valinol **557** (142 mg, 0.5 mmol, 1.0 equiv.) was subjected to **General Procedure E**. Purification by column chromatography (SiO_2, dry load, pentane:Et_2O, 90:10) gave the desired compound **588** (94 mg, 42%, 79:21 er) as a thick, clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.36 – 7.16 (m, 10H, 10 × *H*C_{Ar}), 3.67 (s, 4H, 2 × *H*$_2$C(14)), 2.90 (ddd, J = 18.7, 10.7, 4.8 Hz, 1H, *H*$_a$H$_b$C(9)), 2.56 (ddd, J = 18.7, 10.9, 4.9 Hz, 1H, H$_a$*H*$_b$C(9)), 2.32 – 2.25 (m, 1H, *H*C(11)), 2.24 (s, 3H, *H*$_3$C(5)), 2.19 (s, 6H, 2 × *H*$_3$CC_{Ar}), 2.16 – 2.09 (m, 1H, *H*$_a$H$_b$C(10)), 2.06 (s, 6H, 2 × *H*$_3$CC_{Ar}), 2.05 – 1.98 (m, 1H, *H*C(12)), 1.82 – 1.69 (m, 1H, H$_a$*H*$_b$C(10)), 0.94 (dd, J = 22.0, 6.7 Hz, 6H, 2 × *H*$_3$C(13)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 212.5 (*C*(8)), 141.0 (*C*$_{Ar}$), 140.5 (*C*$_{Ar}$), 135.4 (*C*$_{Ar}$), 133.2 (*C*$_{Ar}$), 129.0 (*C*$_{Ar}$), 128.2 (*C*$_{Ar}$), 127.4 (*C*$_{Ar}$), 126.8 (*C*$_{Ar}$), 62.4 (*C*11)), 54.3 (2 × *C*(14)), 44.8 (*C*(9)), 29.0 (*C*(12)), 22.0 (*C*(13)), 20.2 (*C*(10)), 20.2 (*C*(13')), 17.3 (2 × H$_3$*C*C_{Ar}), 16.8 (*C*(5)), 16.1 (2 × H$_3$*C*C_{Ar}); **IR** ν_{max} (film)/cm^{-1} 2954, 1699, 1454, 747, 699; **HRMS** (ESI$^+$) $C_{32}H_{42}ON$ requires 456.3261, found $[M+H]^+$ 456.3261 (Δ 0.04 ppm); **$[\alpha]_D^{25}$** = –22.6 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 1.0 % IPA, 99.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

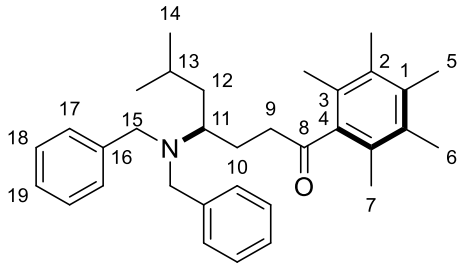


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.201	BV R	1029.2	76.1	0.2032	50.191	0.837
2	11.457	BB	1021.4	67.6	0.2322	49.809	0.755



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.211	BB	142	11	0.2002	20.950	0.874
2	11.508	BB	535.9	35.6	0.2319	79.050	0.8

(*R*)-4-(Dibenzylamino)-6-methyl-1-(2,3,4,5,6-pentamethylphenyl)heptan-1-one (589)



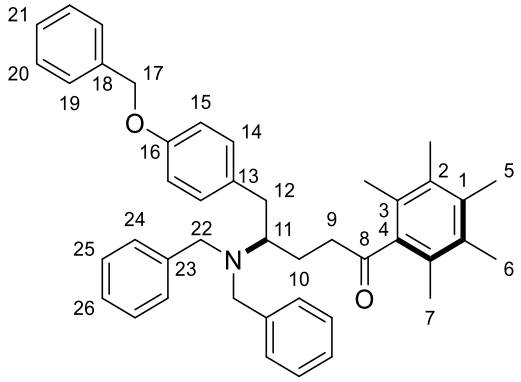
Dibenzyl leucinol **559** (149 mg, 0.5 mmol, 1.0 equiv.) was subjected to **General Procedure E**. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 96.5:3.5) gave the desired compound **589** (109 mg, 47%, 92:8 er) as a thick, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42 – 7.17 (m, 10H, 10 × *H*C$_{Ar}$), 3.67 (d, J = 13.6 Hz, 2H, 2 × *H*$_a$H$_b$C(15)), 3.56 (d, J = 13.4 Hz, 2H, 2 × H$_a$*H*$_b$C(15)), 2.93 (ddd, J = 18.7, 10.0, 5.2 Hz, 1H, *H*$_a$H$_b$C(9)), 2.62 – 2.46 (m, 2H, *H*C(11) and H$_a$*H*$_b$C(9)), 2.27 (s, 3H, *H*$_3$C(5)), 2.22 (s, 6H, 2 × *H*$_3$CC$_{Ar}$), 2.07 (s, 7H, *H*$_a$H$_b$C(10) and 2 × *H*$_3$CC$_{Ar}$), 1.84 – 1.66 (m, 2H, *H*C(13) and H$_a$*H*$_b$C(10)), 1.57 (ddd, J = 13.3, 7.2, 5.9 Hz, 1H, *H*$_a$H$_b$C(12)), 1.11 (ddd, J = 13.6, 7.4, 6.4 Hz, 1H, H$_a$*H*$_b$C(12)), 0.84 (d, J = 6.6 Hz, 3H, *H*$_3$C(14)), 0.74 (d, J = 6.5 Hz, 3H, *H*$_3$C(14')); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 212.6 (*C*(8)), 141.1 (*C*(4)), 140.6 (2 × *C*(16)), 135.4 (*C*(1)), 133.2 (2 × *C*$_{Ar}$), 129.1 (4 × H*C*$_{Ar}$), 128.2 (4 × H*C*$_{Ar}$), 127.5 (2 × *C*$_{Ar}$), 126.9 (2 × *C*(19)), 55.1 (*C*(11)), 53.4 (2 × *C*(15)), 43.6 (*C*(9)), 38.9 (*C*(12)), 25.1 (*C*(13)), 23.6 (*C*(10)), 23.2 (*C*(14')), 23.0 (*C*(14)), 17.3 (2 × H$_3$*C*C$_{Ar}$), 16.8 (*C*(5)), 16.1 (2 × H$_3$*C*C$_{Ar}$); **IR** ν_{max} (film)/cm^{-1} 2952, 1699, 1454, 1382, 1151, 1108, 1073, 748, 729,

699; **HRMS** (ESI$^+$) $C_{33}H_{44}ON$ requires 470.3417, found $[M+H]^+$ 370.3414 (Δ –0.66 ppm); $[\alpha]_D^{25}$ = –25.4 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 5.0 % IPA, 95.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

(*R*)-5-(4-(Benzyloxy)phenyl)-4-(dibenzylamino)-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one (591)



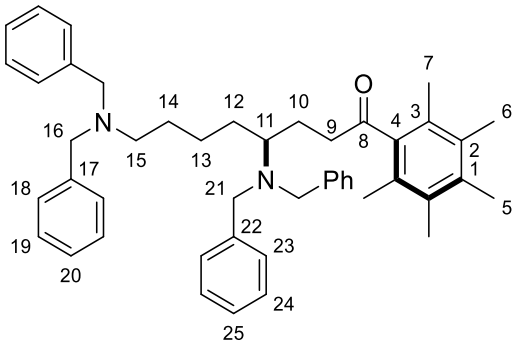
Perbenzylated tyrosinol **565** (219 mg, 0.5 mmol, 1.0 equiv.) was subjected to **General Procedure E**. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 90:10) gave the desired compound **591** (143 mg, 47%, 93:7 er) as a tan solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.51 – 7.14 (m, 15H, 15 × *H*C_{Ar}), 7.04 – 6.91 (m, 2H, 2 × *H*C(14)), 6.95 – 6.81 (m, 2H, 2 × *H*C(15)), 5.04 (s, 2H, H_2C(17)), 3.84 (d, J = 13.6 Hz, 2H, 2 × $H_a$$H_b$C(22)), 3.54 (d, J = 13.8 Hz, 2H, 2 × $H_a$$H_b$C(22)), 3.13 – 2.98 (m, 2H, $H_a$$H_b$C(9) and $H_a$$H_b$C(12)), 2.74 (tt, J = 9.3, 4.8 Hz, 1H, *H*C(11)), 2.48 – 2.30 (m, 2H, $H_a$$H_b$C(9) and $H_a$$H_b$C(12)), 2.23 (s, 3H, H_3C(5)), 2.16 (s, 6H, 2 × $H_3$$CC_{Ar}$), 2.04 (dddd, J = 14.4, 9.4, 7.1, 4.6 Hz, 1H, $H_a$$H_b$C(10)), 1.98 (s, 6H, 2 × $H_3$$CC_{Ar}$), 1.75 (ddt, J = 14.3, 11.0, 4.9 Hz, 1H, $H_a$$H_b$C(10)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 212.5 (*C*(8)), 157.2 (*C*(16)) , 141.0 (C_{Ar}), 140.1 (2 × C_{Ar}), 137.3 (C_{Ar}), 135.3 (C_{Ar}), 133.1 (C_{Ar}), 132.8 (C_{Ar}), 130.3 (2 × *C*(14)), 128.9 (C_{Ar}), 128.7 (C_{Ar}), 128.3 (C_{Ar}), 128.0 (C_{Ar}), 127.6 (C_{Ar}), 127.5 (C_{Ar}), 126.9 (C_{Ar}), 114.9 (2 × *C*(15)), 70.2 (*C*(17)), 59.4 (*C*(11)), 53.5 (2 × *C*(22)), 43.4 (*C*(9)), 34.5 (*C*(12)), 23.9 (*C*(10)), 17.3 (2 × H_3*C*C_{Ar}), 16.8 (*C*(5)), 16.0 (2 × H_3*C*C_{Ar}); **IR** ν_{max} (film)/cm^{-1}

2981, 1696, 1510, 1454, 1239, 1218, 1121, 1026, 747, 697; **HRMS** (ESI$^+$) $C_{43}H_{48}O_2N$ requires 610.3680, found $[M+H]^+$ 610.3676 (Δ –0.56 ppm); **M.p.** 135 – 137 °C; $[\alpha]_D^{25}$ = –2.7 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 10.0 % IPA, 90.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

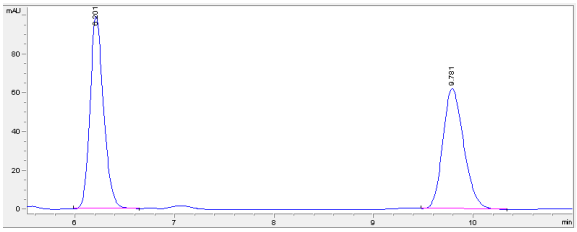
(*S*)-4,8-Bis(dibenzylamino)-1-(2,3,4,5,6-pentamethylphenyl)octan-1-one (592)



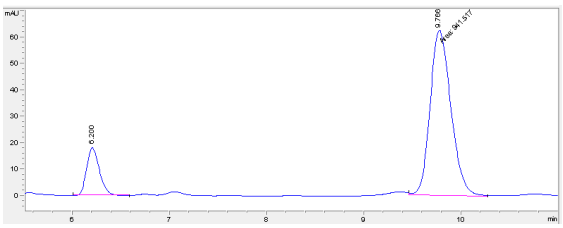
Tetrabenzyl lysinol **568** (1.48 g, 3 mmol, 1.0 equiv.) was subjected to **General Procedure E**. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 90:10) gave the desired compound **592** (1.59 g, 80%, 85:15 er) as a thick, clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.46 – 7.11 (m, 20H, 20 × *H*C$_{Ar}$), 3.66 – 3.43 (m, 8H, 2 × *H*$_2$C(16) and 2 × *H*$_2$C(21)), 2.85 (ddd, J = 18.5, 10.2, 5.0 Hz, 1H, *H*$_a$H$_b$C(9)), 2.57 – 2.29 (m, 4H, H$_a$*H*$_b$C(9) and *H*C(11) and *H*$_2$C(15)), 2.24 (s, 3H, *H*$_3$C(5)), 2.18 (s, 6H, 2 × *H*$_3$CC$_{Ar}$), 2.11 – 1.95 (m, 7H, 2 × *H*$_3$CC$_{Ar}$ and *H*$_a$H$_b$C(10)), 1.72 – 1.51 (m, 2H, H$_a$*H*$_b$C(10) and *H*$_a$H$_b$C(12)), 1.50 – 1.24 (m, 4H, *H*$_2$C(14) and *H*$_2$C(13)), 1.12 (tt, J = 13.8, 6.9 Hz, 1H, *H*$_a$H$_b$C(12)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 212.6 (*C*(8)), 141.1 (*C*(4)), 140.6 (2 × *C*$_{Ar}$), 140.2 (2 × *C*$_{Ar}$), 135.4 (*C*(1)), 133.2 (2 × *C*$_{Ar}$), 129.0 (4 × H*C*$_{Ar}$), 128.9 (4 × H*C*$_{Ar}$), 128.3 (8 × H*C*$_{Ar}$), 127.5 (2 × *C*$_{Ar}$), 126.9 (4 × H*C*$_{Ar}$), 58.5 (2 × C(16) or *C*(21)), 57.2 (*C*(11)), 53.4 (2 × C(16) or *C*(21)), 53.3 (*C*(15)), 43.6 (*C*(9)), 29.3 (*C*(12)), 27.4 (*C*(14)), 24.8 (*C*(13)), 23.5 (*C*(10)), 17.3 (2 × H$_3$*C*C$_{Ar}$), 16.8 (*C*(5)), 16.1 (2 × H$_3$*C*C$_{Ar}$); **IR** ν_{max} (film)/cm^{-1} 2933, 1698, 1494, 1453, 1028, 746, 698; **HRMS** (ESI$^+$) $C_{47}H_{57}ON_2$ requires 665.4465, found $[M+H]^+$ 665.4461 (Δ –0.65 ppm); $[\alpha]_D^{25}$ = –0.8 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 5.0 % IPA, 95.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

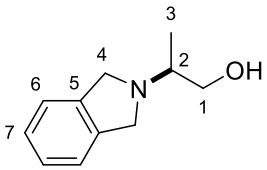


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1	6.201	BB	939.9	99	0.1448	51.009	0.757
2	9.781	BB	902.7	61.6	0.2268	48.991	0.772



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	6.2	BB	167.5	18.3	0.141	15.102	0.755
2	9.766	MM	941.5	62.8	0.2497	84.898	0.78

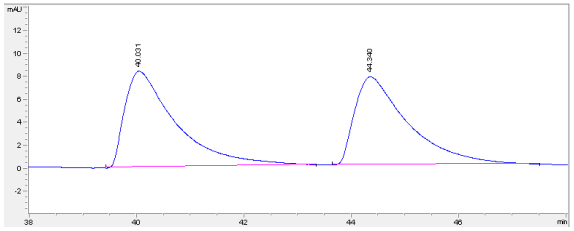
(*S*)-2-(Isoindolin-2-yl)propan-1-ol (606)



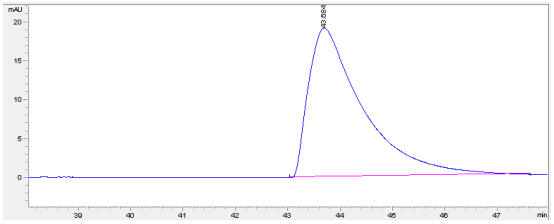
To a stirred solution of L-alaninol **604** (0.75 mg, 10 mmol, 1.0 equiv.) and α,α'-dibromo-*o*-xylene **605** (2.64 g, 10 mmol, 1.0 equiv.) in dioxane (25 mL) at RT was added NaOH (0.96 g, 24 mmol, 2.4 equiv.) and the reaction left to stir for 1 h. The reaction mixture was then filtered through a pad of celite and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, CH_2Cl_2:MeOH, 85:15) gave the desired compound **606** (319 mg, >99:1 er) as a fluffy, pale-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.22 (s, 4H, 4 × *H*C_{Ar}), 4.09 – 3.93 (m, 4H, 2 × *H*$_2$C(4)), 3.69 (dd, J = 10.8, 4.3 Hz, 1H, *H*$_a$H$_b$C(1)), 3.48 (dd, J = 10.8, 6.2 Hz, 1H, H$_a$*H*$_b$C(1)), 2.97 (pd, J = 6.5, 4.3 Hz, 1H, *H*C(2)), 1.15 (d, J = 6.6 Hz, 3H, *H*$_3$C(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 139.7 (2 × *C*(5)), 126.9 (2 × C_{Ar}), 122.5 (2 × C_{Ar}), 64.7 (*C*(1)), 58.4 (*C*(2)), 55.1 (2 × *C*(4)), 13.3 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 2979, 2804, 1462, 1378, 1069, 1048, 977, 755; **HRMS** (ESI$^+$) $C_{11}H_{16}ON$ requires 178.1226, found $[M+H]^+$ = 178.1227 (Δ 0.14) ppm; **$[\alpha]_D^{25}$** = +51.0 (c = 1.00, $CHCl_3$); **M.p.** = 123 – 125 °C.

Chiral HPLC (Chiralpak IB-N5 with guard, 0.9 % IPA, 99.1 % hexane, 1.0 mL/min, 25 °C, λ = 210 nm, 5 µL injection).

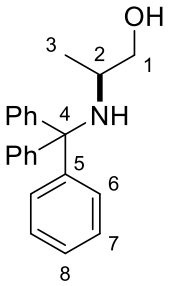


#	Time	Type	Area	Height	Width	Area%	Symmetry
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2	44.34	BB	531.4	7.7	0.9236	48.524	0.383



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	43.684	BB	1396.5	19.3	1.0026	100.000	0.365

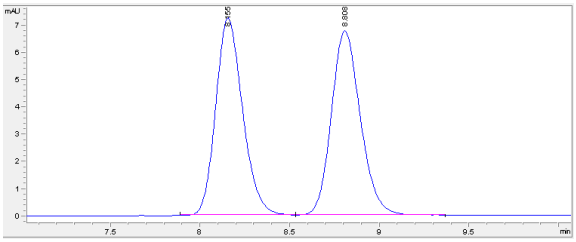
(*S*)-2-(Tritylamino)propan-1-ol (608)



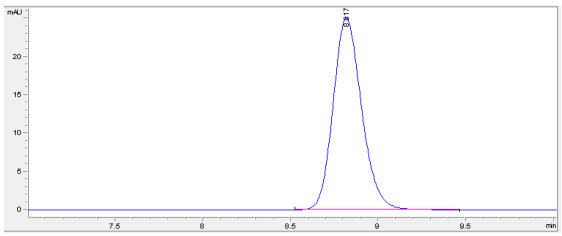
L-Alanine **550** (3.56 g, 40 mmol, 1.0 equiv.) was subjected to **General Procedure F** to give the desired amino acid methyl ester hydrochloride (5.24 g, 94%). This ester (4.86 g, 35 mmol, 1.0 equiv.) was then subjected to **General Procedure G** to give the crude tritylated alanine methyl ester **607** which was immediately subjected to **General Procedure H**. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 70:30 to 50:50) gave the desired alcohol **608** as a colourless solid (7.26 g, 65% over two steps, >99:1 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.59 – 7.49 (m, 6H, 6 × *H*C(6)), 7.34 – 7.23 (m, 6H, 6 × *H*C(7)), 7.23 – 7.15 (m, 3H, 3 × *H*C(8)), 3.16 (dd, J = 10.5, 4.3 Hz, 1H, $H_aH_bC(1)$), 3.04 (dd, J = 10.5, 4.9 Hz, 1H, $H_aH_bC(1)$), 2.76 (dtd, J = 11.0, 6.5, 4.6 Hz, 1H, *H*C(2)), 0.67 (d, J = 6.5 Hz, 3H, $H_3C(3)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 146.9 (3 × *C*(5)), 128.9 (6 × *C*(6)), 128.0 (6 × *C*(7)), 126.5 (3 × *C*(8)), 71.2 (*C*(4)), 67.1 (*C*(1)), 49.6 (*C*(2)), 19.9 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 2968, 1448, 1032, 950, 745, 706; **HRMS** (ESI$^+$) $C_{22}H_{23}ONNa$ requires 340.1672, found $[M+Na]^+$ 340.1671 (Δ –0.31 ppm); **M.p.** 82 – 84 °C; **$[\alpha]_D^{25}$** = +10.9 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 5.0 % IPA, 95.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

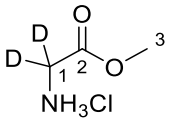


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.155	BB	76	7.3	0.1602	49.912	0.802
2	8.808	BB	76.2	6.8	0.1734	50.088	0.813



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	8.817	BB	282.3	25	0.1716	100.000	0.809

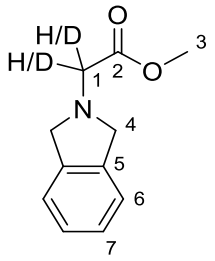
Methyl glycinate-2,2-d_2 hydrochloride (610)



Glycine-d_5 **609** (2.0 g, 25 mmol, 1.0 equiv.) was subjected to **General Procedure F** to give the desired compound **610** (3.0 g, 95%) as a colourless solid with >95% D incorporation, as determined by ^{1}H NMR analysis.

^{1}H NMR (D_2O, 400 MHz) δ_H = 3.86 (s, 3H, H_3C(3)); **^{13}C NMR** (D_2O, 101 MHz) δ_C = 168.7 (*C*(2)), 53.4 (*C*(3)), 39.6 (*C*(1)); **^{2}H NMR** (H_2O, 77 MHz) δ_D = 3.80 (s, 2D, D_2C(1)); **IR** (film) ν_{max}/cm^{-1} = 2907, 1743, 1499, 1329, 1209, 1150, 910, 792; **HRMS** (ESI$^+$) $C_3H_6D_2O_2N$ requires 92.0675, found $[M+H]^+$ = 92.0679 (Δ 4.19 ppm); **M.p.** = 182 – 184 °C.

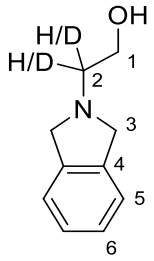
Methyl 2-(isoindolin-2-yl)acetate-d_2 (611)



A stirred solution of **610** (635 mg, 5 mmol, 1.0 equiv.), α,α'-dibromo-*o*-xylene **605** (1.32 g, 5 mmol, 1.0 equiv.) and K_2CO_3 (2.07 g, 15 mmol, 3.0 equiv.) in MeCN (100 mL) was warmed to 80 °C and the reaction left to stir for 24 h. The reaction was then quenched by the addition of water (100 mL) and the mixture extracted with EtOAc (3 × 75 mL). The combined organic extracts were then washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 50:50) gave the desired compound **611** (568 mg, 59%) as a brown oil with 94% D incorporation, as determined by ^{1}H NMR analysis.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.19 (s, 4H, 2 × H_2C(6) and 2 × H_2C(7)), 4.12 (s, 4H, 2 × H_2C(4)), 3.75 (s, 3H, H_3C(3)), 3.60 (t, J = 2.4 Hz, 0.12H, H/D_2C(1)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 171.3 (*C*(2)), 139.8 (2 × *C*(5)), 126.9 (2 × C_{Ar}), 122.4 (2 × C_{Ar}), 58.8 (2 × *C*(4)), 51.8 (*C*(3)) [*N.B.* The signal for the CD_2 carbon is a very weak multiplet at ~55.8 ppm]; **^{2}H NMR** ($CHCl_3$, 77 MHz) δ_D = 3.60 (H/D_2C(1)); **IR** (film) ν_{max}/cm^{-1} = 1741, 1466, 1434, 1285, 1265, 1202, 1168, 745; **HRMS** (ESI$^+$) $C_{11}H_{12}D_2O_2N$ requires 194.1145, found $[M+H]^+$ = 194.1146 (Δ 0.78 ppm).

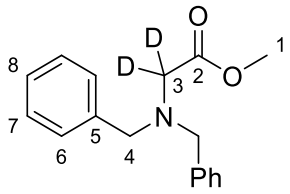
2-(Isoindolin-2-yl)ethan-2,2-d_2-1-ol (612)



Methyl ester **611** (483 mg, 2.5 mmol, 1.0 equiv.) was subjected to **General Procedure H**. Purification by column chromatography (SiO_2, eluent load, CH_2Cl_2:MeOH, 92:8) gave the desired alcohol **612** (342 mg, 83%) as a brown oil with 90% D incorporation, as determined by ^{1}H NMR analysis.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.21 (s, 4H, 2 × H_2C(5) and 2 × H_2C(6)), 4.00 (s, 4H, 2 × H_2C(3)), 3.70 (s, 2H, H_2C(1)), 2.95 – 2.87 (m, 0.2H, H/D_2C(2)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 139.8 (2 × C(4)), 127.0 (2 × C_{Ar}), 122.4 (2 × C_{Ar}), 59.8 (C(1)), 59.0 (2 × C(3)), 57.0 (C(2)); **^{2}H NMR** ($CHCl_3$, 77 MHz) δ_D = 2.91 (H/D_2C(2)); **IR** (film) ν_{max}/cm^{-1} = 3289 (br.), 2778, 1464, 1056, 1028, 741; **HRMS** (ESI$^+$) $C_{10}H_{12}D_2ON$ requires 166.1195, found $[M+H]^+$ = 166.1194 (Δ –0.70 ppm).

Methyl *N*,*N*-dibenzylglycinate-d_2 (613)

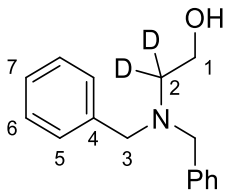


A stirred solution of **610** (635 mg, 5 mmol, 1.0 equiv.) and K_2CO_3 (1.73 g, 12.5 mmol, 2.5 equiv.) in MeCN (100 mL) was added benzyl bromide (1.19 mL, 10 mmol, 2.0 equiv.) dropwise and the reaction left to stir for 18 h. The reaction was filtered through a pad of celite (eluting with Et_2O) and concentrated *in vacuo* to give the desired pure product **613** (1.35 g, 99%) as a colourless solid with >95% D incorporation, as determined by ^{1}H NMR analysis.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.42 – 7.36 (m, 4H, 4 × HC(6)), 7.35 – 7.29 (m, 4H, 4 × HC(7)), 7.28 – 7.23 (m, 2H, 2 × HC(8)), 3.82 (s, 4H, 2 × H_2C(4)), 3.69 (s, 3H, H_3C(1)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 172.0

(*C*(2)), 139.1 (2 × *C*(5)), 129.0 (4 × *C*(6)), 128.4 (4 × *C*(7)), 127.3 (2 × *C*(8)), 57.8 (2 × *C*(4)), 51.4 (*C*(1)). [*N.B.* The signal for the CD_2 carbon is too weak to observe]; **^{2}H NMR** ($CHCl_3$, 77 MHz) δ_D = 2.91 (D_2C(2)); **IR** (film) ν_{max}/cm^{-1} = 1743, 1453, 1275, 1243, 1156, 1143, 1064, 746, 735, 696; **HRMS** (ESI$^+$) $C_{17}H_{18}D_2O_2N$ requires 272.1614, found $[M+H]^+$ = 272.1614 (Δ –0.20 ppm); **M.p.** = 31 – 33 °C.

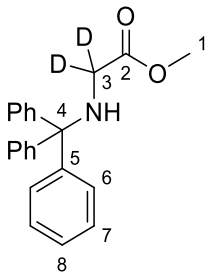
2-(Dibenzylamino)ethan-2,2-*d*$_2$-1-ol (614)



Methyl ester **613** (813 mg, 3.0 mmol, 1.0 equiv.) was subjected to **General Procedure H**. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 60:40) gave the desired alcohol **614** (631 mg, 87%) as a colourless solid with >95% D incorporation, as determined by ^{1}H NMR analysis.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.42 – 7.22 (m, 10H, 10 × *H*C$_{Ar}$), 3.64 (s, 4H, 2 × *H*$_2$C(3)), 3.58 (s, 2H, *H*$_2$C(1)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 138.9 (2 × *C*(4)), 129.1 (4 × *C*(5)), 128.6 (4 × *C*(6)), 127.4 (2 × *C*(7)), 58.5 (*C*(1)), 58.3 (2 × *C*(3)), 54.1 (*C*(2)); **^{2}H NMR** ($CHCl_3$, 77 MHz) δ_D = 2.65 (D_2C(2)); **IR** (film) ν_{max}/cm^{-1} = 3300, 2796, 1494, 1453 1369, 1058, 1025, 744, 731, 697; **HRMS** (ESI$^+$) $C_{16}H_{18}D_2ON$ requires 244.1665, found $[M+H]^+$ = 244.1666 (Δ 0.23 ppm); **M.p.** = 39–41 °C.

Methyl tritylglycinate-2,2-*d*$_2$ (615)

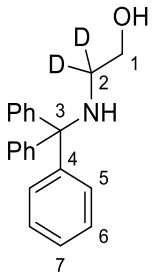


To a stirred solution of methyl ester hydrochloride **610** (635 mg, 5 mmol, 1.0 equiv.) and trityl chloride (1.45 g, 5.2 mmol, 1.04 equiv.) in DMF (10 mL) at 0 °C was added Et_3N (1.73 mL, 12.5 mmol, 2.5 equiv.)

dropwise before being warmed to RT and left to stir for 16 h. The reaction was quenched by the addition of water (20 mL) and the mixture extracted with EtOAc:Hexane (2:1, 3 × 25 mL). The combined organic extracts were then washed with brine (3 × 25 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 90:20) gave the desired pure product **615** (1.63 g, 98%) as a colourless solid with >95% D incorporation, as determined by ^{1}H NMR analysis.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.52 – 7.42 (m, 6H, 6 × *H*C(6)), 7.30 – 7.24 (m, 6H, 6 × *H*C(7)), 7.21 – 7.16 (m, 3H, 3 × *H*C(8)), 3.60 (s, 3H, H_3C(1)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 172.9 (*C*(2)), 145.5 (3 × *C*(5)), 128.8 (6 × *C*(6)), 128.1 (6 × *C*(7)), 126.7 (3 × *C*(8)), 70.8 (*C*(4)), 51.9 (*C*(1)) [*N.B.* The signal for the CD_2 carbon is too weak to observe]; **^{2}H NMR** ($CHCl_3$, 77 MHz) δ_D = 3.14 (D_2C(3)); **IR** (film) ν_{max}/cm^{-1} = 1739, 1695, 1489, 1447, 1286, 1154, 770, 746, 698, 624; **HRMS** (ESI$^+$) $C_{22}H_{19}D_2O_2NNa$ requires 356.1590, found $[M+Na]^+$ = 356.1589 (Δ –0.40 ppm); **M.p.** = 99 – 101 °C.

2-(Tritylamino)ethan-2,2-*d*$_2$-1-ol (616)

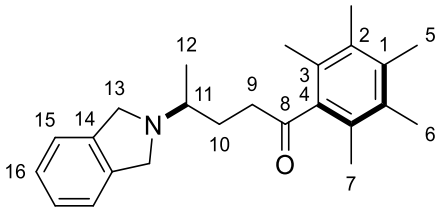


Methyl ester **615** (999 mg, 3.0 mmol, 1.0 equiv.) was subjected to **General Procedure H**. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 60:40) gave the desired alcohol **616** (804 mg, 88%) as a colourless solid with >95% D incorporation, as determined by ^{1}H NMR analysis.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.52 – 7.44 (m, 6H, 6 × *H*C(5)), 7.34 – 7.26 (m, 6H, 6 × *H*C(6)), 7.23 – 7.17 (m, 3H, 3 × *H*C(7)), 3.68 (s, 2H, H_2C(1)); **^{13}C NMR** ($CDCl_3$ 101 MHz) δ_C = 146.0 (3 × *C*(4)), 128.8 (6 × *C*(5)), 128.0 (6 × *C*(6)), 126.5 (3 × *C*(7)), 70.7 (*C*(3)), 62.7 (*C*(1)), 45.1 (*C*(2)); **^{2}H NMR** ($CHCl_3$, 77 MHz) δ_D = 2.34

(D_2C(2)); **IR** (film) ν_{max}/cm^{-1} = 3272 (br.), 1487, 1447, 1047, 1027, 760, 748, 700, 639; **HRMS** (ESI$^+$) $C_{21}H_{19}D_2ONNa$ requires 328.1641, found $[M+Na]^+$ = 328.1641 (Δ –0.08 ppm); **M.p.** = 74 – 76 °C.

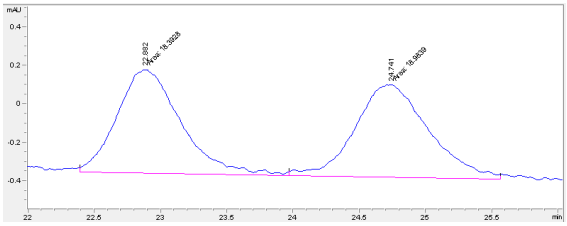
(*S*)-4-(Isoindolin-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one (619)



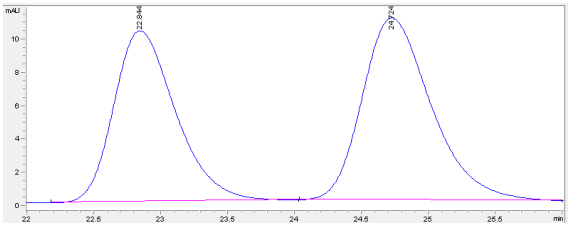
Amino alcohol **606** (89 mg, 0.5 mmol, 1.0 equiv.) was subjected to **General Procedure E**. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 70:30) gave the desired compound **619** (20 mg, 11%, 54:46 er) as a dark brown gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.23 – 7.15 (m, 4H, 4 × *H*C$_{Ar}$), 3.99 (s, 4H, 2 × *H*$_2$C(13)), 2.95 – 2.70 (m, 3H, *H*$_2$C(9) and *H*C(11)), 2.22 (s, 3H, *H*$_3$C(5)), 2.18 (s, 6H, 2 × *H*$_3$CC$_{Ar}$), 2.11 (s, 6H, 2 × *H*$_3$CC$_{Ar}$), 2.08 – 1.89 (m, 2H, *H*$_2$C(10)), 1.15 (d, J = 6.4 Hz, 3H, *H*$_3$C(12)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 212.5 (*C*(8)), 141.1 (*C*$_{Ar}$), 140.2 (2 × *C*(14)), 135.4 (*C*$_{Ar}$), 133.2 (2 × *C*$_{Ar}$), 127.4 (2 × *C*$_{Ar}$), 126.8 (2 × *C*(15) or *C*(16)), 122.5 (2 × *C*(15) or *C*(16)), 56.9 (*C*(11)), 56.1 (2 × (*C*(13)), 41.5 (*C*(9)), 28.7 (*C*(10)), 17.3 (2 × H$_3$*C*C$_{Ar}$), 17.1 (*C*(5)), 16.8 (*C*(12)), 16.1 (2 × H$_3$*C*C$_{Ar}$); **IR** ν_{max} (film)/cm^{-1} 2980, 1697, 1454, 1381, 910, 732; **HRMS** (ESI$^+$) $C_{24}H_{32}ON$ requires 250.2478, found $[M+H]^+$ 350.2480 (Δ 0.50 ppm); **$[\alpha]_D^{25}$** = +1.4 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 5.0 % IPA, 95.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

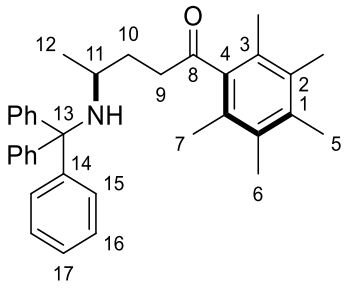


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	22.882	MF	18.4	5.4E-1	0.564	49.209	0
2	24.741	FM	19	4.9E-1	0.6513	50.791	0.936



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	22.844	BB	331.8	10.3	0.4916	45.608	0.707
2	24.724	BB	395.7	11	0.5358	54.392	0.714

(*S*)-1-(2,3,4,5,6-Pentamethylphenyl)-4-(tritylamino)pentan-1-one (620)



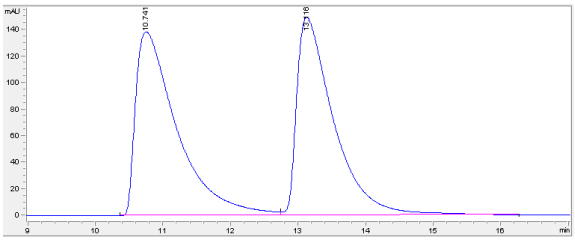
Tritylated alaninol **608** (127 mg, 0.4 mmol, 1.0 equiv.) was subjected to **General Procedure E** at 85 °C. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 95:5 to 90:10) gave the desired compound **620** (155 mg, 79%, 96:4 er) as a fluffy yellow solid.

Tritylated alaninol **608** (1.27 g, 4 mmol, 1.0 equiv.) was subjected to **General Procedure E**. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 95:5 to 90:10) gave the desired compound **620** (1.67 g, 85%, 96:4 er) as a fluffy yellow solid.

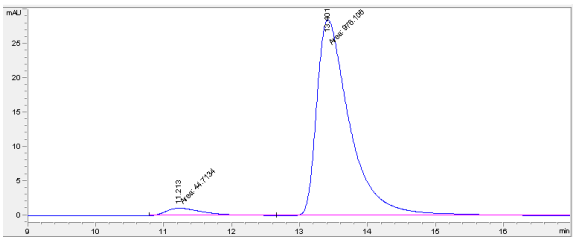
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.56 – 7.48 (m, 6H, 6 × *H*C(15)), 7.28 – 7.20 (m, 6H, 6 × *H*C(16)), 7.19 – 7.10 (m, 3H, 3 × *H*C(17)), 2.70 – 2.55 (m, 2H, H_aH_bC(9) and *H*C(11)), 2.46 (ddd, J = 17.9, 10.2, 5.9 Hz, 1H, H_aH_bC(9)), 2.23 (s, 3H, H_3C(5)), 2.18 (s, 6H, 2 × H_3CC_{Ar}), 2.04 (s, 6H, 2 × H_3CC_{Ar}), 1.54 – 1.47 (m, 2H, H_2C(10)), 0.64 (d, J = 6.4 Hz, 3H, H_3C(12)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 212.1 (*C*(8)), 147.2 (3 × *C*(14)), 141.0 (*C*(4)), 135.4 (*C*(1)), 133.2 (2 × C_{Ar}), 128.9 (6 × *C*(15)), 127.9 (6 × *C*(16)), 127.4 (2 × C_{Ar}), 126.4 (3 × *C*(17)), 71.5 (*C*(13)), 48.0 (*C*(11)), 42.2 (*C*(9)), 32.0 (*C*(10)), 21.9 (*C*(12)), 17.4 (2 × H_3CC_{Ar}), 16.8 (*C*(5)),

16.1 (2 × H_3CC_{Ar}); **IR** ν_{max} (film)/cm^{-1} 2928, 1697, 1489, 1447, 1216, 748, 706; **HRMS** (ESI^+) $C_{35}H_{39}ONNa$ requires 512.2924, found $[M+Na]^+$ 512.2925 (Δ 0.29 ppm); **M.p.** 58 – 60 °C; **$[\alpha]_D^{25}$** = –27.2 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 1.0 % IPA, 99.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

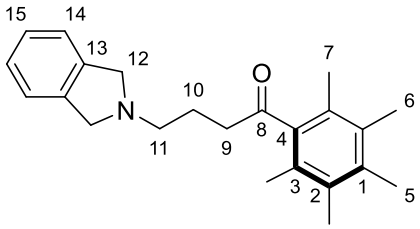


#	Time	Type	Area	Height	Width	Area%	Symmetry
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2	13.116	VB	5654.5	148.8	0.5614	48.951	0.34



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	11.213	MF	44.7	1.1	0.6717	4.380	0.478
2	13.401	FM	976.1	28.7	0.5668	95.620	0.478

4-(Isoindolin-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one (621)

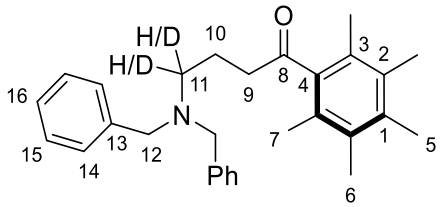


Xylyl protected deuterated glycinol **612** (99 mg, 0.6 mmol, 1.0 equiv.) was subjected to **General Procedure E** at 85 °C. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 60:40) gave the desired compound **621** (72 mg, 36%, <10% D incorporation) as a pale brown solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.20 (s, 4H, 2 × H_2C(14) and 2 × H_2C(15)), 3.97 (s, 4H, 2 × H_2C(12)), 2.83 (td, *J* = 7.2, 4.7 Hz, 4H, H_2C(9) and H_2C(11)), 2.23 (s, 3H, H_3C(5)), 2.18 (s, 6H, 2 × H_3CC_{Ar}), 2.11 (s, 6H, 2 × H_3CC_{Ar}), 2.03 (dd, *J* = 8.2, 5.9 Hz, 2H, H_2C(10)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 212.0 (*C*(8)), 140.8 (*C*(4)), 140.0 (2 × C_{Ar}), 135.5 (*C*(1)), 133.2 (2 × C_{Ar}), 127.4 (2 × C_{Ar}), 126.9 (2 × *C*(14) or *C*(15)), 122.4 (2 × *C*(14) or *C*(15)), 59.1 (2 × *C*(12)), 55.2 (*C*(11)), 43.1 (*C*(9)), 22.5 (*C*(10)), 17.3 (2 × H_3CC_{Ar}), 16.8 (*C*(5)), 16.1 (2 ×

H_3CC_{Ar}); **IR** (film) ν_{max}/cm^{-1} = 2929, 1694, 1447, 1355, 1144, 1133, 742, 701; **HRMS** (ESI^+) $C_{23}H_{30}ON$ requires 336.2322, found $[M+H]^+$ = 336.2318 (Δ –1.14 ppm); **M.p.** = 74–76 °C.

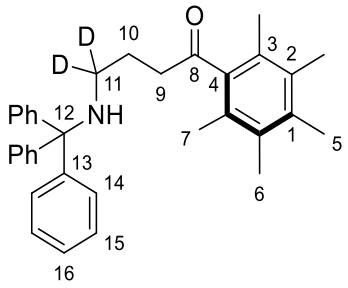
4-(Dibenzylamino)-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one-4,4-d_2 (622)



Dibenzyl protected deuterated glycinol **614** (146 mg, 0.6 mmol, 1.0 equiv.) was subjected to **General Procedure E** at 85 °C. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 92:8) gave the desired compound **622** (198 mg, 80%, 70% D incorporation) as a pale orange solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.42 – 7.21 (m, 10H, 10 × HC_{Ar}), 3.61 (s, 4H, 2 × H_2C(12)), 2.72 (dd, J = 7.2, 1.5 Hz, 2H, H_2C(9)), 2.58 – 2.49 (m, 0.6H, H/D_2C(11)), 2.26 (s, 3H, H_3C(5)), 2.21 (s, 6H, 2 × H_3CC_{Ar}), 2.08 (s, 6H, 2 × H_3CC_{Ar}), 1.97 (t, J = 7.2 Hz, 2H, H_2C(10)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 212.2 (C(8)), 140.9 (C(4)), 139.8 (2 × C(13)), 135.4 (C(1)), 133.1 (2 × C_{Ar}), 128.9 (4 × C(14)), 128.3 (4× C(15)), 127.4 (2 × C_{Ar}), 126.9 (2 × C(16)), 58.3 (2 × C(12)), 52.8 (C(11)), 43.3 (C(9)), 20.5 (C(10)), 17.3 (2 × H_3CC_{Ar}), 16.8 (C(5)), 16.1 (2 × H_3CC_{Ar}); **^{2}H NMR** ($CHCl_3$, 77 MHz) δ_D = 2.50 (H/D_2C(11)); **IR** (film) ν_{max}/cm^{-1} = 2789, 1700, 1452, 1123, 915, 749, 731, 698; **HRMS** (ESI^+) $C_{29}H_{34}D_2ON$ requires 416.2917, found $[M+H]^+$ = 416.2907 (Δ –2.32 ppm); **M.p.** = 69 – 71 °C.

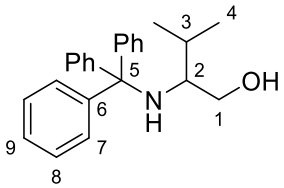
1-(2,3,4,5,6-Pentamethylphenyl)-4-(tritylamino)butan-1-one-4,4-d_2 (623)



Trityl protected deuterated glycinol **616** (183 mg, 0.6 mmol, 1.0 equiv.) was subjected to **General Procedure E** at 85 °C. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 92:8) gave the desired compound **623** (202 mg, 71%, >95% D incorporation) as a fluffy, off-white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.50 (d, *J* = 7.6 Hz, 6H, 6 × *H*C(14)), 7.30 (t, *J* = 7.6 Hz, 6H, 6 × *H*C(15)), 7.21 (t, *J* = 7.6 Hz, 3H, 3 × *H*C(16)), 2.80 (t, *J* = 7.3 Hz, 2H, H_2C(9)), 2.25 (s, 3H, H_3C(5)), 2.20 (s, 6H, 2 × H_3CC_{Ar}), 2.10 (s, 6H, 2 × H_3CC_{Ar}), 1.92 (t, *J* = 7.3 Hz, 2H, H_2C(10)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 212.0 (*C*(8)), 146.2 (3 × C(13)), 140.8 (*C*(4)), 135.5 (*C*(1)), 133.2 (2 × C_{Ar}), 128.7 (6 × C(14)), 127.9 (6 × C(15)), 127.4 (2 × C_{Ar}), 126.4 (3 × C(16)), 71.0 (*C*(11)), 43.7 (*C*(9)), 43.3 (*C*(11)), 24.4 (*C*(10)), 17.4 (2 × H_3CC_{Ar}), 16.8 (*C*(5)), 16.1 (2 × H_3CC_{Ar}); **^{2}H NMR** ($CHCl_3$, 77 MHz) δ_D = 2.22 (D_2C(11)); **IR** (film) ν_{max}/cm^{-1} = 2161, 1694, 1490, 1447, 1154, 1122, 744, 702; **HRMS** (ESI$^+$) $C_{34}H_{35}D_2ONNa$ requires 500.2893, found $[M+Na]^+$ = 500.2890 (Δ –0.63 ppm); **M.p.** = 119 – 121 °C.

(S)-3-Methyl-2-(tritylamino)butan-1-ol (625)



To a stirred solution of MeOH (25 mL) at 0 °C was added AcCl (2.37 mL, 79 mmol, 0.68 equiv.) dropwise and the reaction left to stir for 15 min. DL-Valine **248** (1.17 g, 10 mmol, 1.0 equiv.) was added portionwise and the reaction warmed to reflux and left to stir for 3 h. The solvent was then removed *in vacuo* before adding more MeOH (20 mL) and removing it *in vacuo*. The process was repeated twice

before drying under high vacuum for 3 h to give the desired methyl ester hydrochloride which was used without further purification.

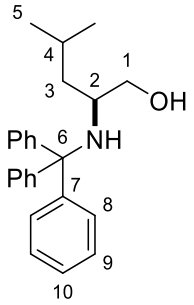
To a stirred solution of crude DL-valine methyl ester hydrochloride (1.67 g, 10 mmol, 1.0 equiv.) and trityl chloride (4.19 g, 15 mmol, 1.5 equiv.) in CH_2Cl_2 (40 mL) at 0 °C was added a solution of Et_3N (4.15 mL, 30 mmol, 3.0 equiv.) in CH_2Cl_2 (10 mL) dropwise over the course of 15 min. The mixture was then warmed to RT and left to stir for 16 h. The reaction was then quenched by the addition of sat. aq. $NaHCO_3$ (25 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic extracts washed with brine (25 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product **624** which was used without further purification.

To a stirred solution of $LiAlH_4$ (0.57 g, 15 mmol, 1.5 equiv.) in THF (100 mL) at 0 °C was added a solution of crude tritylated valine methyl ester **624** (3.45 g, 10 mmol, 1.0 equiv.) in THF (20 mL) dropwise, before being allowed to warm to RT over the course of 1 h. The reaction was then cooled to 0 °C and diluted with Et_2O (50 mL) before being quenched by the sequential addition of water (0.57 ml), 15% aqueous NaOH (0.57 ml), water (1.71 mL) and $MgSO_4$ (3 g). The thick emulsion was then filtered under reduced pressure and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 85:15) gave the desired alcohol **625** as a colourless oil (0.73 g, 21% over three steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.60 – 7.51 (m, 6H, 6 × *H*C(7)), 7.33 – 7.23 (m, 6H, 6 × *H*C(8)), 7.22 – 7.15 (m, 3H, 3 × *H*C(9)), 3.34 (dd, J = 11.0, 3.5 Hz, 1H, $H_aH_bC(1)$), 3.11 (dd, J = 11.0, 5.1 Hz, 1H, $H_aH_bC(1)$), 2.43 (dt, J = 5.1, 3.6 Hz, 1H, *H*C(2)), 1.31 (hd, J = 7.0, 3.9 Hz, 1H, *H*C(3)), 0.82 (d, J = 7.0 Hz, 3H, $H_3C(4)$), 0.68 (d, J = 7.0 Hz, 3H, $H_3C(4')$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 146.9 (3 × *C*(6)), 128.8 (6 × *C*(7)), 127.9 (6 × *C*(8)), 126.6 (3 × *C*(9)), 71.3 (*C*(5)), 60.4 (*C*(1)), 57.9 (*C*(2)), 31.0 (*C*(3)), 20.0 (*C*(4')), 17.3 (*C*(4)).

Data was consistent with that previously reported.[143]

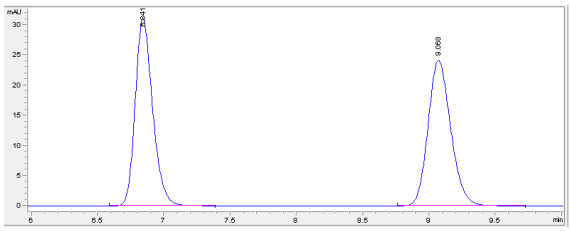
(*S*)-4-Methyl-2-(tritylamino)pentan-1-ol (627)

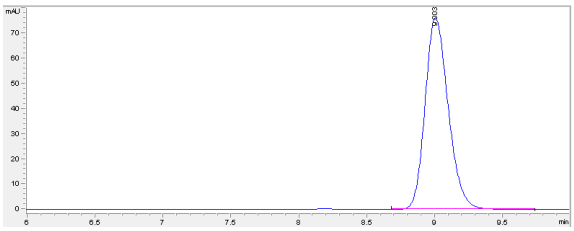


To a stirred solution of L-leucinol **626** (2.60 g, 20 mmol, 1.0 equiv.) and trityl chloride (5.58 g, 20 mmol, 1.0 equiv.) in CH_2Cl_2 (50 mL) at 0 °C was added Et_3N (2.77 mL, 20 mmol, 1.0 equiv.) dropwise over the course of 15 min. The mixture was then warmed to RT and left to stir for 24 h. The reaction was then quenched by the addition of sat. aq. $NaHCO_3$ (50 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 80:20) gave the desired alcohol **627** as a colourless oil (3.68 g, 51%, >99:1 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.62 – 7.43 (m, 6H, 6 × *H*C(8)), 7.32 – 7.24 (m, 6H, 6 × *H*C(9)), 7.23 – 7.16 (m, 3H, 3 × *H*C(10)), 3.21 (dd, J = 10.8, 2.6 Hz, 1H, $H_aH_bC(1)$), 3.05 (ddd, J = 10.9, 3.7, 0.9 Hz, 1H, $H_aH_bC(1)$), 2.65 (dtd, J = 10.5, 4.0, 2.5 Hz, 1H, *H*C(2)), 1.45 – 1.31 (m, 2H, *H*C(4) and $H_aH_bC(3)$), 0.67 (d, J = 6.4 Hz, 3H, $H_3C(5)$), 0.66 – 0.59 (m, 1H, $H_aH_bC(3)$), 0.57 (d, J = 6.4 Hz, 3H, $H_3C(5')$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 146.8 (3 × *C*(7)), 128.9 (6 × *C*(8)), 128.0 (6 × *C*(9)), 126.6 (3 × *C*(10)), 71.5 (*C*(6)), 62.9 (*C*(1)), 51.7 (*C*(2)), 42.8 (*C*(3)), 24.9 (*C*(4)), 23.8 (*C*(5)), 21.6 (*C*(5')); **$[\alpha]_D^{25}$** = +20.8 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 5.0 % IPA, 95.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).



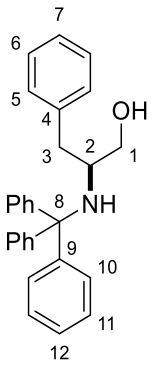


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1	6.841	BB	285.4	31.2	0.1387	49.792	0.761
2	9.068	BB	287.8	24.3	0.1824	50.208	0.819

#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.003	BB	901.9	76.3	0.182	100.000	0.774

Data was consistent with that previously reported.[144]

(*S*)-3-Phenyl-2-(tritylamino)propan-1-ol (629)

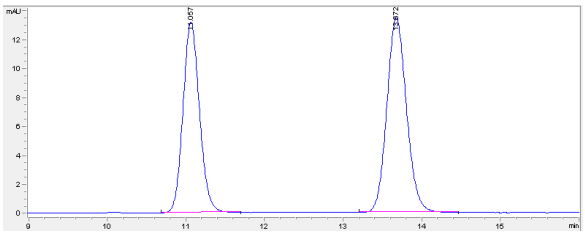


To a stirred solution of L-phenylalanine **560** (3.30 g, 20 mmol, 1.0 equiv.) in $CHCl_3$:MeCN (30:6 mL) at RT was added Me_3SiCl (2.53 mL, 20 mmol, 1.0 equiv.) and the reaction heated to reflux for 2 h before being allowed to cool back to RT. Et_3N (5.53 mL, 40 mmol, 2.0 equiv.) was slowly added, followed by trityl chloride (5.58 g, 20 mmol, 1.0 equiv.) in $CHCl_3$ (20 mL) and the reaction left to stir for 1 h. The reaction mixture was then quenched by the addition of MeOH (4 mL) and the solvent was removed *in vacuo* to give a residue which was redissolved in Et_2O (50 mL) and water (50 mL). The layers were separated, and the organic layer washed with a 5% precooled aq. solution of citric acid (2 × 30 mL) and brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude tritylated product **628** which was used without further purification.

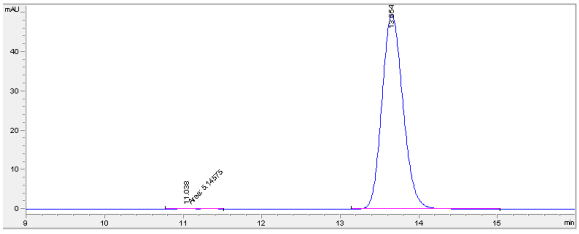
To a stirred solution of $LiAlH_4$ (1.52 g, 40 mmol, 2.0 equiv.) in THF (200 mL) at 0 °C was added a solution of crude L-tritylphenylalanine **628** (8.14 g, 20 mmol, 1.0 equiv.) in THF (20 mL) dropwise, before being heated to reflux over the course of 16 h. The reaction was then cooled to 0 °C and diluted with Et_2O (100 mL) before being quenched by the sequential addition of water (1.52 ml), 15% aqueous NaOH (1.52 ml), water (4.56 mL) and $MgSO_4$ (8 g). The thick emulsion was then filtered under reduced pressure and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 75:25) gave the desired alcohol **629** as a colourless solid (4.59 g, 58%, 99:1 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.63 – 7.48 (m, 6H, 6 × *H*C(10)), 7.28 (td, J = 8.2, 7.7, 1.9 Hz, 6H, 6 × *H*C(9)), 7.24 – 7.06 (m, 6H, 3 × *H*C(10) and 3 × *H*C_{Ar}), 6.98 – 6.90 (m, 2H, 2 × *H*C_{Ar}), 3.11 (d, J = 10.8 Hz, 1H, $H_aH_bC(1)$), 2.92 (dd, J = 10.9, 4.1 Hz, 1H, $H_aH_bC(1)$), 2.82 (dtd, J = 9.2, 4.8, 2.5 Hz, 1H, *H*C(2)), 2.51 (ddd, J = 12.5, 9.4, 2.6 Hz, 1H, $H_aH_bC(3)$), 2.31 (dt, J = 13.2, 3.9 Hz, 1H, $H_aH_bC(3)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 146.7 (3 × *C*(9)), 139.2 (*C*(4)), 129.6 (2 × *C*$_{Ar}$), 128.9 (6 × *C*(10)), 128.4 (2 × *C*$_{Ar}$), 128.1 (6 × *C*(11)), 126.6 (3 × *C*(12)), 126.2 (*C*(7)), 71.4 (*C*(8)), 62.6 (*C*(1)), 55.5 (*C*(2)), 39.4 (*C*(3)); **$[\alpha]_D^{25}$** = –28.1 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 5.0 % IPA, 95.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).



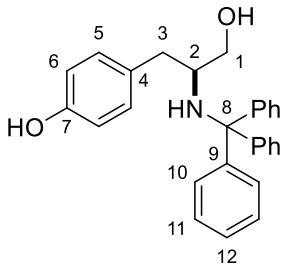
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	11.057	BB	192.2	13.2	0.2242	45.109	0.862
2	13.672	BB	233.9	13.5	0.2689	54.891	0.867



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	11.038	MM	5.1	1.9E-1	0.4585	0.555	0.399
2	13.654	BB	921.6	49.5	0.2913	99.445	0.838

Data was consistent with that previously reported.[144]

(*S*)-4-(3-Hydroxy-2-(tritylamino)propyl)phenol (630)

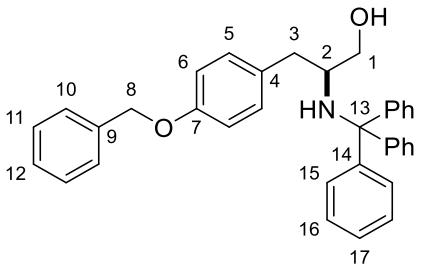


To a stirred solution of L-tyrosine **563** (3.62 g, 20 mmol, 1.0 equiv.) in $CHCl_3$:MeCN (30:6 mL) at RT was added Me_3SiCl (5.10 mL, 40 mmol, 2.0 equiv.) and the reaction heated to reflux for 2 h before being allowed to cool back to RT. Et_3N (8.30 mL, 60 mmol, 3.0 equiv.) was slowly added, followed by trityl chloride (5.58 g, 20 mmol, 1.0 equiv.) in $CHCl_3$ (20 mL) and the reaction left to stir for 1 h. The reaction mixture was then quenched by the addition of MeOH (4.0 mL, 100 mmol, 5.0 equiv.) and the solvent was removed *in vacuo* to give a residue which was redissolved in Et_2O (50 mL) and a 5% precooled solution of citric acid (50 mL). The layers were separated, and the organic layer washed with 1M aq. NaOH (2 × 25 mL) and water (2 × 25 mL). The combined aqueous layers were washed with Et_2O (25 mL), cooled to 0 °C and carefully neutralised by the addition of glacial AcOH. The resulting solution was extracted with Et_2O (2 × 50 mL) and the combined organic layers washed with water (2 × 50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product (4.48 g, 53%) as a foam that was used without further purification.

To a stirred solution of $LiAlH_4$ (0.81 g, 21.2 mmol, 2.0 equiv.) in THF (150 mL) at 0 °C was added a solution of crude trityl-L-tyrosine (4.48 g, 10.6 mmol, 1.0 equiv.) in THF (50 mL) dropwise, before being heated to reflux for 4 h. The reaction was then cooled to 0 °C and diluted with Et_2O (100 mL) before being quenched by the sequential addition of water (0.81 ml), 15% aqueous NaOH (0.81 ml), water (2.43 mL) and $MgSO_4$ (5 g). The thick emulsion was then filtered under reduced pressure and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 40:60) gave the desired alcohol **563** as an extremely fluffy colourless solid (2.98 g, 69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.59 – 7.51 (m, 6H, 6 × *H*C(10)), 7.31 – 7.24 (m, 6H, 6 × *H*C(11)), 7.23 – 7.16 (m, 3H, 3 × *H*C(12)), 6.83 – 6.73 (m, 2H, 2 × *H*C(5)), 6.66 – 6.59 (m, 2H, 2 × *H*C(6)), 3.12 (dd, J = 10.9, 2.7 Hz, 1H, $H_aH_bC(1)$), 2.94 (dd, J = 10.8, 4.1 Hz, 1H, $H_aH_bC(1)$), 2.76 (dtd, J = 9.3, 4.5, 2.6 Hz, 1H, *H*C(2)), 2.42 (dd, J = 13.3, 9.5 Hz, 1H, $H_aH_bC(3)$), 2.19 (dd, J = 13.2, 4.8 Hz, 1H, $H_aH_bC(3)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 154.3 (*C*(7)), 146.7 (3 × *C*(9)), 130.9 (*C*(4)), 130.6 (2 × *C*(5)), 128.9 (6 × *C*(10)), 128.1 (6 × *C*(11)), 126.7 (3 × *C*(12)), 115.3 (2 × *C*(6)), 71.5 (*C*(9)), 62.5 (*C*(1)), 55.5 (*C*(2)), 38.5 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 2980, 1613, 1595, 1514, 1490, 1447, 1217, 1172, 1031, 747, 706, 667, 643; **HRMS** (ESI^+) $C_{28}H_{27}O_2NNa$ requires 432.1934, found $[M+Na]^+$ 432.1934 (Δ 0.09 ppm); **M.p.** 74 – 76 °C; **$[\alpha]_D^{25}$** = 48.9 (c = 1.00, $CHCl_3$).

(*S*)-3-(4-(Benzyloxy)phenyl)-2-(tritylamino)propan-1-ol (631)



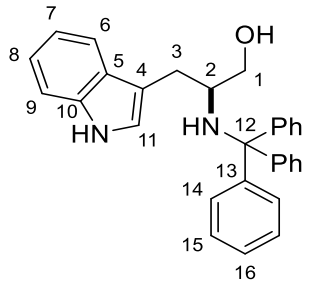
To a stirred solution of tritylated L-tyrosine **630** (1.23 g, 3 mmol, 1.0 equiv.) and K_2CO_3 (0.83 g, 6 mmol, 2.0 equiv.) in DMF (30 mL) at RT was added BnBr (392 µL, 3.3 mmol, 1.1 equiv.) and the reaction left to stir for 6 h. TLC analysis (pentane:Et_2O, 50:50) showed unconsumed starting material, resulting in the addition of more K_2CO_3 (0.41 g, 3 mmol, 1.0 equiv.) and BnBr (356 µL, 3 mmol, 1.0 equiv.) and the reaction left to stir for an additional 20 h. The reaction mixture was then diluted with EtOAc (100 mL) and washed with brine (3 × 50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 70:30 to 50:50) gave the desired alcohol **631** as a colourless foam (1.07 g, 71%, 98:2 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.60 – 7.51 (m, 6H, 6 × *H*C(15)), 7.43 – 7.33 (m, 4H, 4 × HC_{Ar}), 7.31 – 7.25 (m, 7H, 6 × *H*C(16) and *H*C(12)), 7.23 – 7.16 (m, 3H, 3 × *H*C(17)), 6.89 – 6.77 (m, 4H, 2 × *H*C(5) and 2 × *H*C(6)), 5.00 (s, 2H, $H_2C(8)$), 3.12 (dd, J = 10.9, 2.7 Hz, 1H, $H_aH_bC(1)$), 2.93 (dd, J = 10.9, 4.1 Hz, 1H,

H_aH_bC(1)), 2.76 (dtd, J = 9.3, 4.5, 2.7 Hz, 1H, *H*C(2)), 2.45 (dd, J = 13.3, 9.4 Hz, 1H, H_aH$_b$C(3)), 2.23 (dd, J = 13.3, 4.8 Hz, 1H, H_aH_bC(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 140.2 (*C*(12)), 130.2 (*C*(7)), 146.6 (3 × *C*(15)), 131.2 (*C*(4)), 131.4 (2 × *C*(5)), 129.2 (2 × C_{Ar}), 128.8 (6 × *C*(15)), 128.5 (2 × C_{Ar}), 128.3 (6 × *C*(16)), 127.8 (*C*(9)), 126.7 (3 × *C*(17)), 114.1 (2 × *C*(6)), 71.2 (*C*(13)), 62.4 (*C*(1)), 55.9 (*C*(2)), 38.8 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 2931, 1510, 1449, 1240, 1028, 747, 708, 698; **HRMS** (ESI$^+$) $C_{35}H_{33}O_2NNa$ requires 522.2404, found $[M+Na]^+$ 522.2400 (Δ –0.72 ppm); **M.p.** 53 – 55 °C; **$[\alpha]_D^{25}$** = 36.5 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 20.0 % IPA, 80.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

(S)-3-(1H-Indol-3-yl)-2-(tritylamino)propan-1-ol (632)



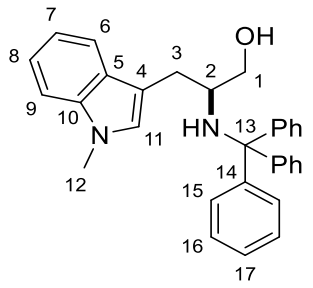
To a stirred slurry of L-tryptophan **244** (2.04 mg, 10 mmol, 1.0 equiv.) in CH_2Cl_2 (16 mL) at RT was added Me_3SiCl (1.36 mL, 10.7 mmol, 1.07 equiv.) and the reaction left to stir for 4.25 h. Et_3N (2.97 mL, 21.5 mmol, 2.15 equiv.) was added, followed by the dropwise addition of trityl chloride (3.12 g, 11.2 mmol, 1.12 equiv.) in CH_2Cl_2 (8 mL). The reaction was then left to stir at RT for 20 h, before being quenched by the addition of MeOH (10 mL) and concentrated *in vacuo*. The residue was redissolved in EtOAc (15 mL) and CH_2Cl_2 (15 mL) before being washed with a 5% precooled aq. solution of citric acid (2 × 30 mL) and brine (2 × 30 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give crude tritylated tryptophan that was used without further purification.

To a stirred solution of $LiAlH_4$ (0.76 g, 20 mmol, 2.0 equiv.) in THF (100 mL) at 0 °C was added a solution of crude L-trityltryptophan (4.46 g, 10 mmol, 1.0 equiv.) in THF (10 mL) dropwise, before being heated to reflux over the course of 4 h. The reaction was then cooled to 0 °C and diluted with Et_2O (50 mL)

before being quenched by the sequential addition of water (0.76 ml), 15% aqueous NaOH (0.76 ml), water (2.28 mL) and $MgSO_4$ (4 g). The thick emulsion was then filtered under reduced pressure and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 50:50) gave the desired alcohol **632** as a colourless solid (1.41 g, 33%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.91 (s, 1H, *H*N), 7.61 – 7.51 (m, 6H, 6 × *H*C(14)), 7.35 – 7.12 (m, 12H, 6 × *H*C(15) and 3 × *H*C(16) and 3 × *H*C$_{Ar}$), 7.02 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H, *H*C$_{Ar}$), 6.85 (d, J = 2.3 Hz, 1H, *H*C(11)), 3.22 – 3.11 (m, 1H, H_aH_bC(1)), 2.96 (dtd, J = 9.3, 5.0, 2.5 Hz, 1H, *H*C(2)), 2.82 – 2.71 (m, 2H, H_aH_bC(1) and H_aH_bC(3)), 2.62 (dd, J = 14.0, 5.1 Hz, 1H, H_aH_bC(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 146.8 (3 × *C*(13)), 136.3 (*C*(10)), 128.9 (6 × *C*(14)), 128.8 (*C*(5)), 128.3 (*C*(4)), 128.0 (6 × *C*(15)), 126.6 (3 × *C*(16)), 122.9 (*C*(11)), 122.1 (*C*$_{Ar}$), 119.4 (*C*$_{Ar}$), 119.3 (*C*$_{Ar}$), 111.1 (*C*$_{Ar}$), 71.4 (*C*(12)), 62.9 (*C*(1)), 54.2 (*C*(2)), 29.2 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 3421, 3057, 2932, 1595, 1490, 1456, 1340, 1216, 1092, 1031, 902, 744, 707; **HRMS** (ESI$^-$) $C_{30}H_{27}ON_2$ requires 431.2129, found $[M–H]^-$ 431.2130 (Δ 0.35 ppm); **M.p.** 75 – 77 °C; **$[\alpha]_D^{25}$** = –5.0 (c = 1.00, $CHCl_3$).

(*S*)-3-(1-Methyl-1H-indol-3-yl)-2-(tritylamino)propan-1-ol (633)

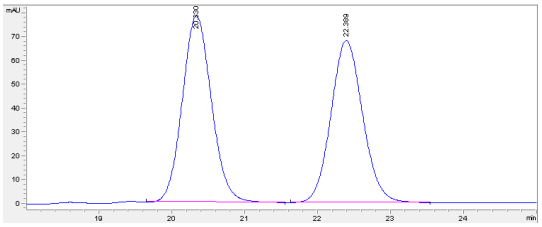


To a stirred solution of 60 wt.% NaH (176 mg, 4.4 mmol, 1.1 equiv.) in DMF (18 mL) at RT was added tritylated tryptophanol **632** (1.74 g, 4 mmol, 1.0 equiv.) in DMF (12 mL) dropwise and the reaction left to stir for 30 min. The reaction was then cooled to 0 °C and MeI (274 µL, 4.4 mmol, 1.1 equiv.) was slowly added. The reaction was then warmed to RT and left to stir for 1 h. Water (30 mL) was added, the mixture extracted with EtOAc (3 × 50 mL), and the combined organic extracts were washed with brine (3 × 50 mL), dried over $NaSO_4$, and concentrated in vacuo. Purification by column

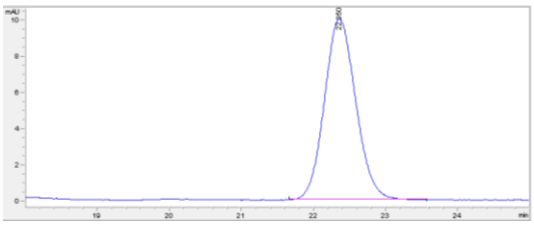
chromatography (SiO2, eluent load, pentane:Et_2O, 60:40) gave the desired compound **633** (1.31 g, 73%, >99:1 er) as a fluffy solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.56 (dq, J = 6.7, 1.2 Hz, 6H, 6 × *H*C(15)), 7.32 (ddt, J = 8.0, 2.0, 0.9 Hz, 1H, *H*C_{Ar}), 7.27 (dd, J = 8.4, 6.7 Hz, 6H, 6 × *H*C(16)), 7.23 – 7.13 (m, 5H, 3 × *H*C(17) and 2 × *H*C_{Ar}), 7.01 (ddt, J = 8.1, 6.8, 1.2 Hz, 1H, *H*C_{Ar}), 6.69 (s, 1H, *H*C(11)), 3.67 (s, 3H, H_3C(12)), 3.16 (dd, J = 10.8, 2.5 Hz, 1H, $H_a$$H_b$C(1)), 2.96 (ddp, J = 9.2, 4.7, 2.4 Hz, 1H, *H*C(2)), 2.82 – 2.71 (m, 2H, $H_a$$H_b$C(1) and $H_a$$H_b$C(3)), 2.61 (dd, J = 14.0, 5.0 Hz, 1H, $H_a$$H_b$C(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 146.9 (3 × *C*(14)), 137.1 (*C*$_{Ar}$), 129.0 (6 × *C*(15)), 128.4 (*C*$_{Ar}$), 128.0 (6 × *C*(16)), 127.7 (*C*(11)), 126.6 (3 × *C*(17)), 121.6 (H*C*$_{Ar}$), 119.4 (H*C*$_{Ar}$), 118.9 (H*C*$_{Ar}$), 111.7 (*C*$_{Ar}$), 109.2 (*C*$_{Ar}$), 71.5 (*C*(13)), 62.9 (*C*(1)), 54.4 (*C*(2)), 32.7 (*C*(12)), 29.1 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 2931, 1696, 1486, 1448, 744, 708; **HRMS** (ESI$^+$) $C_{31}H_{30}ON_2Na$ requires 469.2250, found $[M+Na]^+$ 469.2250 (Δ –0.02 ppm); **M.p.** 89 – 91 °C; **[α]$_D^{25}$** = –39.4 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 5.0 % IPA, 95.0 % hexane, 1.0 mL/min, 25 °C, λ = 210 nm, 10 µL injection).

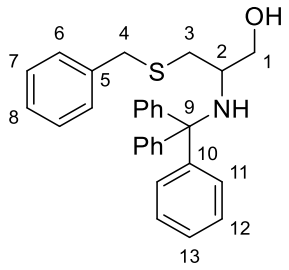


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1	20.33	BB	2186.8	78.1	0.4326	51.515	0.888
2	22.389	BB	2058.2	67.8	0.4681	48.485	0.892



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	22.35	BB	304.1	10.1	0.4725	100.000	0.87

3-(Benzylthio)-2-(tritylamino)propan-1-ol (635)



To a rapidly stirring solution of 2M aq. NaOH (15 mL) and EtOH (35 mL) at RT was added DL-cysteine **247** (0.99 g, 8.2 mmol, 1.0 equiv.) and BnBr (0.97 mL, 8.2 mmol, 1.0 equiv.) and the reaction left to stir for 1 h. Concentrated HCl was then added dropwise to bring the pH to 6-7, resulting in the formation of a precipitate which was filtered and washed with water (40 mL), ethanol (40 mL) and Et_2O (40 mL) to give the crude product (1.45 g, 71%) as a glossy white solid.

Crude benzylated cysteine (1.24 g, 5 mmol, 1.0 equiv.) was dissolved in MeOH at 0 °C and $SOCl_2$ (511 µL, 7 mmol, 1.4 equiv.) was added dropwise. The reaction was warmed to RT and left to stir for 6 h, after which the solvent was removed *in vacuo* to give the crude methyl ester product **634** (1.43 g, quant.).

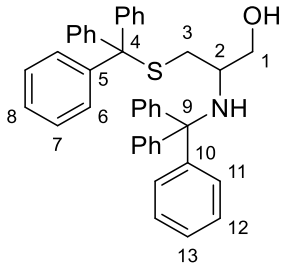
To a stirred solution of crude benzylated cysteine methyl ester hydrochloride (1.40 g, 5 mmol, 1.0 equiv.) and trityl chloride (2.09 g, 7.5 mmol, 1.5 equiv.) in CH_2Cl_2 (20 mL) at 0 °C was added a solution of Et_3N (2.08 mL, 15 mmol, 3.0 equiv.) in CH_2Cl_2 (5 mL) dropwise over the course of 15 min. The mixture was then warmed to RT and left to stir for 16 h. The reaction was then quenched by the addition of sat. aq. $NaHCO_3$ (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic extracts washed with brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product which was used without further purification.

To a stirred solution of $LiAlH_4$ (0.38 g, 10 mmol, 1.5 equiv.) in THF (50 mL) at 0 °C was added a solution of crude tritylated *S*-benzyl cysteine (2.50 g, 5 mmol, 1.0 equiv.) in THF (10 mL) dropwise, before being allowed to warm to RT over the course of 1 h. The reaction was then cooled to 0 °C and diluted with

Et_2O (30 mL) before being quenched by the sequential addition of water (0.38 ml), 15% aqueous NaOH (0.38 ml), water (1.14 mL) and $MgSO_4$ (2 g). The thick emulsion was then filtered under reduced pressure and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 75:25) gave the desired alcohol **635** as a colourless oil (0.85 g, 39% over four steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61 – 7.45 (m, 6H, 6 × *H*C(11)), 7.30 – 7.12 (m, 14H, 6 × *H*C(12) and 3 × *H*C(13) and 5 × *H*C_{Ar}), 3.45 – 3.35 (m, 3H, *H*$_2$C(4) and *H*$_a$H$_b$C(1)), 2.95 (dd, J = 11.0, 5.2 Hz, 1H, H$_a$*H*$_b$C(1)), 2.78 – 2.68 (m, 1H, *H*C(2)), 2.34 (dd, J = 13.1, 4.3 Hz, 1H, *H*$_a$H$_b$C(3)), 2.15 (dd, J = 13.1, 7.5 Hz, 1H, H$_a$*H*$_b$C(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 146.7 (3 × *C*(10)), 138.5 (*C*(5)), 128.9 (2 × *C*$_{Ar}$), 128.8 (6 × *C*(11)), 128.6 (2 × *C*$_{Ar}$), 128.1 (6 × *C*(12)), 127.1 (*C*$_{Ar}$), 126.6 (3 × *C*(13)), 71.2 (*C*(9)), 63.4 (*C*(1)), 52.8 (*C*(2)), 37.1 (*C*(4)), 35.1 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 1491, 1449, 1216, 1029, 901, 746, 704; **HRMS** (ESI$^+$) $C_{29}H_{29}ONNaS$ requires 462.1862, found $[M+Na]^+$ 462.1862 (Δ –0.04 ppm).

2-(Tritylamino)-3-(tritylthio)propan-1-ol (637)



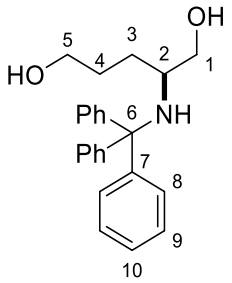
To a rapidly stirring solution of DL-cysteine **247** (605 mg, 5 mmol, 1.0 equiv.) in water (15 mL) at 0 °C was added Et_2NH (2.57 mL, 25 mmol, 5.0 equiv.) in EtOH (15 mL), followed by the portionwise addition of trityl chloride (3.49 g, 12.5 mmol, 2.5 equiv.) and the reaction left to stir for 4 h. The reaction mixture was then extracted with Et_2O (3 × 20 mL), after which the combined organic extracts were washed with water (30 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give crude ditritylated product **636**.

To a stirred solution of $LiAlH_4$ (0.38 g, 10 mmol, 1.5 equiv.) in THF (40 mL) at 0 °C was added a solution of crude tritylated cysteine **636** (3.10 g, 5 mmol, 1.0 equiv.) in THF (10 mL) dropwise, before being heated to reflux over the course of 1 h. The reaction was then cooled to 0 °C and diluted with Et_2O (30

mL) before being quenched by the sequential addition of water (0.38 ml), 15% aqueous NaOH (0.38 ml), water (1.14 mL) and $MgSO_4$ (2 g). The thick emulsion was then filtered under reduced pressure and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 75:25) gave the desired alcohol **637** as a colourless oil (0.63 g, 21% over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.50 – 7.43 (m, 6H, 6 × *H*C(6) or *H*C(11)), 7.38 – 7.32 (m, 6H, 6 × *H*C(6) or *H*C(11)), 7.28 – 7.15 (m, 18H, 18 × *H*C_{Ar}), 3.12 (dd, J = 11.0, 3.2 Hz, 1H, *H*$_a$H$_b$C(1)), 2.70 (dd, J = 11.0, 5.2 Hz, 1H, H$_a$*H*$_b$C(1)), 2.64 (dt, J = 8.0, 3.8 Hz, 1H, *H*C(2)), 2.21 – 2.06 (m, 2H, *H*$_2$C(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 146.7 (3 × *C*(5) or *C*(10)), 145.0 (3 × *C*(5) or *C*(10)), 129.8 (6 × *C*$_{Ar}$), 128.8 (6 × *C*$_{Ar}$), 128.1 (6 × *C*$_{Ar}$), 128.0 (6 × *C*$_{Ar}$), 126.8 (3 × *C*8) or *C*(13)), 126.6 (3 × *C*(8) or *C*(13)), 71.3 (*C*(4) or *C*(9)), 66.7 (*C*(4) or *C*(9)), 63.4 (*C*(1)), 52.9 (*C*(2)), 35.0 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 3057, 1595, 1489, 1446, 1216, 1032, 744, 700, 622; **HRMS** (APCI$^-$) $C_{48}H_{48}O_2N$ requires 670.3691, found [M–H]$^-$ 670.3687 (Δ –0.48 ppm); **M.p.** 74 – 76 °C.

(*S*)-2-(Tritylamino)pentane-1,5-diol (640)



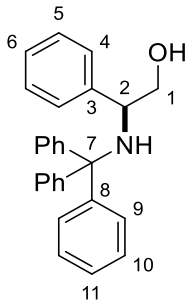
To a stirred solution of L-glutamic acid **638** (5.88 g, 40 mmol, 1.0 equiv.) in MeOH (120 mL) at 0 °C was added $SOCl_2$ (11.7 mL, 160 mmol, 4.0 equiv.) dropwise over the course of 20 min, after which the reaction was warmed to RT and left to stir for 16 h. The solvent was then removed *in vacuo* before adding more MeOH (20 mL) and removing it *in vacuo*. The process was repeated twice before drying under high vacuum for 3 h to give the desired dimethyl ester hydrochloride (8.41 g, quant.) which was used without further purification.

To a stirred solution of crude dimethyl ester hydrochloride (4.20 g, 20 mmol, 1.0 equiv.) and trityl chloride (8.37 g, 30 mmol, 1.5 equiv.) in CH_2Cl_2 (80 mL) at 0 °C was added a solution of Et_3N (8.30 mL, 60 mmol, 3.0 equiv.) in CH_2Cl_2 (20 mL) dropwise over the course of 15 min. The mixture was then warmed to RT and left to stir for 16 h. The reaction was then quenched by the addition of sat. aq. $NaHCO_3$ (40 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic extracts washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product **639** which was used without further purification.

To a stirred solution of $LiAlH_4$ (2.30 g, 60 mmol, 2.0 equiv.) in THF (200 mL) at 0 °C was added a solution of crude trityl-L-glutamic acid dimethyl ester **639** (8.30 g, 20 mmol, 1.0 equiv.) in THF (40 mL) dropwise, before being warmed to RT over the course of 1 h. The reaction was then cooled to 0 °C and diluted with Et_2O (100 mL) before being quenched by the sequential addition of water (2.30 ml), 15% aqueous NaOH (2.30 ml), water (6.90 mL) and $MgSO_4$ (12 g). The thick emulsion was then filtered under reduced pressure and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, MeOH:CH_2Cl_2, 5:95) gave the desired alcohol **640** as a colourless solid (2.71 g, 38% over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61 – 7.53 (m, 6H, 6 × *H*C(8)), 7.34 – 7.26 (m, 6H, 6 × *H*C(9)), 7.26 – 7.19 (m, 3H,3 × *H*C(10)), 3.39 (qd, *J* = 6.1, 4.4 Hz, 2H, H_2C(5)), 3.28 (dd, *J* = 10.9, 3.2 Hz, 1H, H_aH_bC(1)), 3.13 (dd, *J* = 10.9, 4.5 Hz, 1H, H_aH_bC(1)), 2.64 (dq, *J* = 8.1, 3.8 Hz, 1H, *H*C(2)), 1.47 – 1.34 (m, 1H, H_aH_bC(4)), 1.34 – 1.21 (m, 2H, H_aH_bC(3) and H_aH_bC(4)), 0.95 (ddt, *J* = 10.8, 8.0, 4.2 Hz, 1H, H_aH_bC(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 146.8 (3 × *C*(7)), 128.8 (6 × *C*(8)), 128.0 (6 × *C*(9)), 126.6 (3 × *C*(10)), 71.4 (*C*(6)), 63.4 (*C*(1)), 62.9 (*C*(5)), 53.4 (*C*(2)), 29.1 (*C*(3)), 29.0 (*C*(4)); **IR** ν_{max} (film)/cm^{-1} 3329, 1489, 1448, 1057, 1030, 747, 706; **HRMS** (ESI$^+$) $C_{24}H_{27}O_2NNa$ requires 384.1934, found $[M+Na]^+$ 384.1931 (Δ –0.66 ppm); **M.p.** 99 – 101 °C; **$[\alpha]_D^{25}$** = +22.8 (c = 1.00, $CHCl_3$).

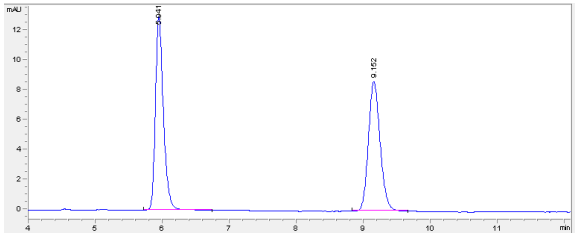
(*S*)-2-Phenyl-2-(tritylamino)ethan-1-ol (642)



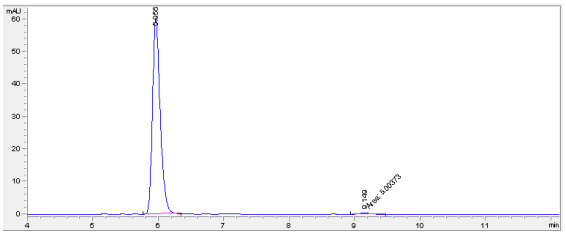
According to a literature procedure,[145] to a stirred solution of L-phenylglycine **571** (1.51 g, 10 mmol, 1.0 equiv.) in DMF (10 mL) at RT in flame-dried glassware under N_2 was added Me_3SiCl (1.33 mL, 10.5 mmol, 1.05 equiv.) and left to stir for 10 min. A solution of trityl chloride (2.93 g, 10 mmol, 1.05 equiv.) in DMF (5 mL) was added dropwise, followed by dropwise addition of Et_3N (2.91 mL, 21 mmol, 2.1 equiv.) and the reaction left to stir for 2 h. The reaction mixture was then quenched by the addition of water (20 mL) and acidified to pH 3-4 by the dropwise addition of 3M aq. HCl. The resulting mixture was then extracted with Et_2O (3 × 30 mL) and the combined organic layers washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product **641** that was used without further purification. The crude tritylated phenylglycine **641** (3.93 g) was subjected to **General Procedure H**. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 80:20) gave the desired alcohol **642** (1.94 g, 51% over two steps, 99:1 er) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.56 – 7.44 (m, 6H, 6 × *H*C(9)), 7.33 – 7.11 (m, 14H, 14 × *H*C_{Ar}), 3.79 (t, J = 4.8 Hz, 1H, *H*C(2)), 3.21 (dd, J = 10.9, 4.3 Hz, 1H, *H*$_a$H$_b$C(1)), 2.80 (dd, J = 10.9, 5.3 Hz, 1H, H$_a$*H*$_b$C(1)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 146.6 (3 × *C*(8)), 143.6 (*C*(3)), 129.0 (6 × *C*(9)), 128.4 (2 × C_{Ar}), 127.9 (6 × *C*(10)), 127.3 (2 × C_{Ar}), 126.8 (*C*(6)), 126.6 (3 × *C*(11)), 72.0 (*C*(7)), 67.1 (*C*(1)), 58.7 (*C*(2)); **$[\alpha]_D^{25}$** = +114.2 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 10.0 % IPA, 90.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).



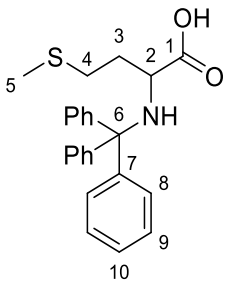
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	5.941	BB	107.1	13	0.1241	50.312	0.699
2	9.152	BB	105.8	8.7	0.1861	49.688	0.826



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	5.956	BB	495.8	60.6	0.1235	99.001	0.707
2	9.149	MM	5	3.8E-1	0.2173	0.999	0.852

Data was consistent with that previously reported.[145]

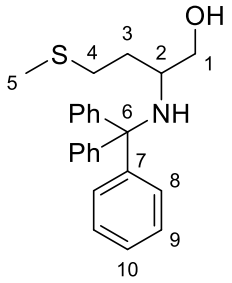
Tritylmethionine (644)



To a stirred solution of DL-methionine **643** (745 mg, 5 mmol, 1.0 equiv.) in $CHCl_3$:MeCN (7.5:1.5 mL) at RT was added Me_3SiCl (634 µL, 5 mmol, 1.0 equiv.) and the reaction heated to reflux for 2 h before being allowed to cool back to RT. Et_3N (1.38 mL, 10 mmol, 2.0 equiv.) was slowly added, followed by trityl chloride (1.40 g, 5 mmol, 1.0 equiv.) in $CHCl_3$ (5 mL) and the reaction left to stir for 1 h. The reaction mixture was then quenched by the addition of MeOH (25 mL) and the solvent was removed *in vacuo* to give a residue which was redissolved in Et_2O (25 mL) and a 5% precooled solution of citric acid (25 mL). The layers were separated, and the organic layer washed with 1M aq. NaOH (2 × 10 mL) and water (2 × 10 mL). The combined aqueous layers were washed with Et_2O (10 mL), cooled to 0 °C and carefully neutralised by the addition of glacial AcOH. The resulting solution was extracted with Et_2O (2 × 20 mL) and the combined organic layers washed with water (2 × 20 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the pure product **644** (1.20 g, 61%) as a pale yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.55 – 7.38 (m, 6H, 6 × *H*C(8)), 7.25 (t, J = 7.6 Hz, 6H, 6 × *H*C(9)), 7.18 (t, J = 7.3 Hz, 3H, 3 × *H*C(10)), 3.52 – 3.45 (m, 1H, *H*C(2)), 2.63 (ddd, J = 13.0, 9.7, 5.8 Hz, 1H, $H_aH_bC(4)$), 2.50 (ddd, J = 13.0, 9.5, 5.9 Hz, 1H, $H_aH_bC(4)$), 2.11 (s, 3H, $H_3C(5)$), 1.99 (ddq, J = 15.7, 10.9, 5.4 Hz, 1H, $H_aH_bC(3)$), 1.90 – 1.79 (m, 1H, $H_aH_bC(3)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 179.1 (*C*(1)), 145.6 (3 × *C*(7)), 128.9 (6 × *C*(8)), 128.1 (6 × *C*(9)), 126.9 (3 × *C*(10)), 71.6 (*C*(6)), 55.9 (*C*(2)), 34.3 (*C*(3)), 30.1 (*C*(4)), 15.7 (*C*(5)); **IR** ν_{max} (film)/cm^{-1} 2980, 1706, 1490, 1447, 1215, 747, 704, 611; **HRMS** (ESI^-) $C_{24}H_{24}O_2NS$ requires 390.1533, found $[M–H]^-$ = 390.1538 (Δ 1.13 ppm); **M.p.** 169 – 171 °C.

4-(Methylthio)-2-(tritylamino)butan-1-ol (645)

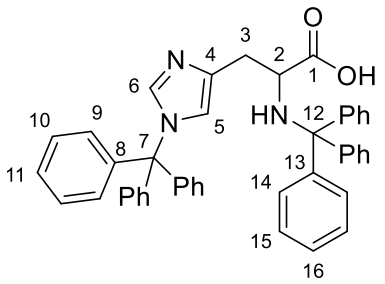


To a stirred solution of $LiAlH_4$ (0.15 g, 4 mmol, 2.0 equiv.) in THF (20 mL) at 0 °C was added a solution of DL-tritylmethioine **644** (0.78 g, 2 mmol, 1.0 equiv.) in THF (10 mL) dropwise, before being heated to reflux over the course of 4 h. The reaction was then cooled to 0 °C and diluted with Et_2O (20 mL) before being quenched by the sequential addition of water (0.15 ml), 15% aqueous NaOH (0.15 ml), water (0.45 mL) and $MgSO_4$ (1 g). The thick emulsion was then filtered under reduced pressure and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 70:30) gave the desired alcohol **645** as a colourless oil (0.56 g, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.59 – 7.49 (m, 6H, 6 × *H*C(8)), 7.33 – 7.23 (m, 6H, 6 × *H*C(9)), 7.24 – 7.16 (m, 3H, 3 × *H*C(10)), 3.22 (dd, J = 11.1, 2.9 Hz, 1H, $H_aH_bC(10)$), 3.05 – 2.96 (m, 1H, $H_aH_bC(1)$), 2.73 (dtd, J = 8.6, 4.2, 2.9 Hz, 1H, *H*C(2)), 2.34 (ddd, J = 12.9, 9.2, 5.4 Hz, 1H, $H_aH_bC(4)$), 2.22 (ddd, J = 12.9, 8.8, 6.8 Hz, 1H, $H_aH_bC(4)$), 1.95 (s, 3H, $H_3C(5)$), 1.61 (dtd, J = 14.1, 8.8, 5.4 Hz, 1H, $H_aH_bC(3)$), 1.31 (dddd, J = 13.5, 9.1, 6.8, 4.0 Hz, 1H, $H_aH_bC(3)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 146.7 (3 × *C*(7)), 128.8 (6 × *C*(8)),

128.1 (6 × *C*(9)), 126.7 (3 × *C*(10)), 71.4 (*C*(6)), 63.2 (*C*(1)), 53.0 (*C*(2)), 32.7 (*C*(3)), 30.8 (*C*(4)), 15.6 (*C*(5)); **IR** ν_{max} (film)/cm^{-1} 1489, 1447, 1216, 1051, 1031, 901, 746, 706; **HRMS** (ESI^+) $C_{24}H_{27}ONNaS$ requires 400.1706, found $[M+Na]^+$ = 400.1704 (Δ –0.36 ppm).

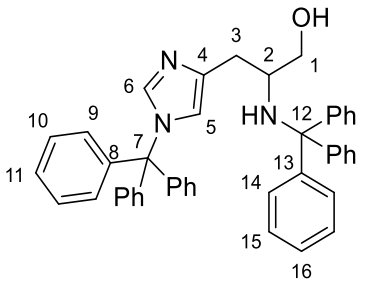
N^{α},N^{τ}-Ditritylhistidine (647)



To a stirred solution of DL-histidine **646** (775 mg, 5 mmol, 1.0 equiv.) in CH_2Cl_2 (15 mL) at RT was added Me_3SiCl (634 µL, 5 mmol, 1.0 equiv.) and the reaction heated to reflux for 2 h before being allowed to cool back to RT. Et_3N (2.08 mL, 15 mmol, 3.0 equiv.) was slowly added and the reaction heated to reflux again for 5 min. The reaction was then colled to RT followed by the addition of trityl chloride (2.79 g, 5 mmol, 2.0 equiv.) in CH_2Cl_2 (15 mL) and the reaction left to stir for 3 h. The reaction mixture was then quenched by the addition of MeOH (25 mL) and the solvent was removed *in vacuo* to give a residue which was redissolved in $CHCl_3$ (25 mL) and a 5% precooled solution of citric acid (25 mL). The layers were separated, and the organic layer washed with water (2 × 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the pure product **647** (2.66g, 83%) as a light foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.36 (dddd, J = 12.4, 10.7, 6.3, 2.8 Hz, 16H, 15 × *H*C_{Ar} and *H*C(6)), 7.24 – 7.04 (m, 15H, 15 × *H*C_{Ar}), 6.32 (d, J = 1.5 Hz, 1H, *H*C(6)), 3.62 (dd, J = 6.6, 3.4 Hz, 1H, *H*C(2)), 2.37 – 2.21 (m, 2H, H_2C(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 175.4 (*C*(1)), 145.7 (3 × *C*(8) or *C*(13)), 141.9 (3 × *C*(8) or *C*(13)), 137.1 (*C*(6)), 129.8 (6 × C_{Ar}), 129.0 (6 × C_{Ar}), 128.5 (3 × *C*(11) or *C*(16)), 128.4 (6 × C_{Ar}), 128.2 (6 × C_{Ar}), 126.9 (3 × *C*(11) or *C*(16)), 120.1 (*C*(5)), 77.4 (*C*(7)), 71.9 (*C*(12)) 56.9 (*C*(2)), 30.9 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 2981, 1492, 1446, 1211, 749, 701; **HRMS** (ESI^+) $C_{44}H_{38}O_2N_3$ requires 640.2959, found $[M+H]^+$ 640.2957 (Δ –0.22 ppm); **M.p.** 170 – 172 °C.

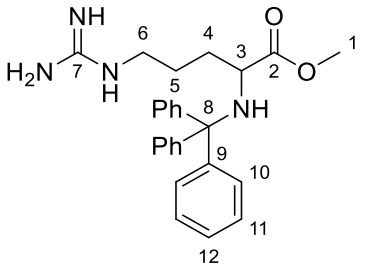
3-(1-Trityl-1H-imidazol-4-yl)-2-(tritylamino)propan-1-ol (648)



To a stirred solution of $LiAlH_4$ (0.23 g, 6 mmol, 2.0 equiv.) in THF (30 mL) at 0 °C was added a solution of DL-ditritylhistidine **647** (1.88 g, 3 mmol, 1.0 equiv.) in THF (10 mL) dropwise, before being heated to reflux over the course of 4 h. The reaction was then cooled to 0 °C and diluted with Et_2O (20 mL) before being quenched by the sequential addition of water (0.23 ml), 15% aqueous NaOH (0.23 ml), water (0.69 mL) and $MgSO_4$ (1.5 g). The thick emulsion was then filtered under reduced pressure and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:CH_2Cl_2, 30:70) gave the desired alcohol **648** as an extremely fluffy solid (0.46 g, 25%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.55 – 7.44 (m, 6H, 6 × *H*C_{Ar}), 7.37 – 7.24 (m, 10H, 10 × *H*C_{Ar} and *H*C(6)), 7.23 – 7.06 (m, 15H, 15 × *H*C_{Ar}), 6.29 (d, J = 1.4 Hz, 1H, *H*C(5)), 3.49 (dd, J = 11.3, 3.2 Hz, 1H, $H_a$$H_b$C(1)), 3.00 (dd, J = 11.3, 6.3 Hz, 1H, $H_a$$H_b$C(1)), 2.91 (m, 1H, *H*C(2)), 2.39 (ddd, J = 14.4, 3.2, 0.8 Hz, 1H, $H_a$$H_b$C(3)), 1.95 (dd, J = 14.5, 6.4 Hz, 1H, $H_a$$H_b$C(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 147.3 (3 × *C*(8) or *C*(13)), 142.5 (3 × *C*(8) or *C*(13)), 138.3 (*C*(4)), 137.8 (*C*(6)), 129.8 (6 × C_{Ar}), 128.9 (6 × C_{Ar}), 128.2 (6 × C_{Ar} and 3 × *C*(11) or *C*(16)), 127.9 (6 × C_{Ar}), 126.4 (3 × *C*(11) or *C*(16)), 120.5 (*C*(5)), 75.3 (*C*(7)), 71.2 (*C*(12)), 65.9 (*C*(1)), 52.7 ((*C*(2)), 32.0 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 1491, 1446, 1217, 1131, 1034, 747, 701; **HRMS** (APCI$^+$) $C_{44}H_{40}ON_3$ requires 626.3166, found $[M+H]^+$ 626.3147 (Δ –2.94 ppm); **M.p.** 88 – 90 °C.

Methyl tritylargininate (650)

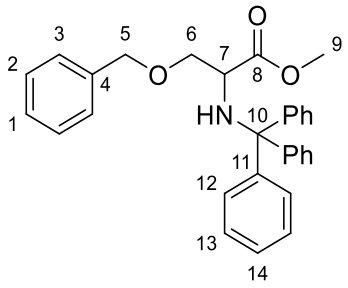


To a stirred solution of MeOH (20 mL) at –10 °C was added $SOCl_2$ (1.61 mL, 22 mmol, 1.1 equiv.) and the mixture left to stir for 10 min. DL-arginine **649** (3.48 g, 20 mmol, 1.0 equiv.) was then added portionwise and the reaction warmed to RT before being subjected to ultrasonification for 2 h. The solvent was then removed *in vacuo* and the crude dihydrochloride product (4.29 g, 96%) used without further purification.

To a stirred solution of crude arginine methyl ester (2.60 g, 10 mmol, 1.0 equiv.) in CH_2Cl_2 at RT was added Et_3N (5.53 mL, 40 mmol, 4.0 equiv.) and trityl chloride (3.07 g, 11 mmol, 1.1 equiv.) and the reaction left to stir for 3 h. The reaction was then cooled to 0 °C and quenched by the addition of MeOH (20 mL). The reaction was then concentrated *in vacuo* before being redissolved in CH_2Cl_2 (50 mL), washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, CH_2Cl_2:MeOH:aq. NH_3, 90:9.5:0.5) provided the title compound **650** (1.14 g, 27%) as colourless crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.88 (s, 1H, C*H*NCH_2), 7.49 – 7.45 (m, 6H, 6 × *H*C(10)), 7.28 – 7.23 (m, 6H, 6 × *H*C(11)), 7.17 (dd, J = 8.2, 6.6 Hz, 3H, 3 × *H*C(12)), 3.34 (t, J = 6.1 Hz, 1H, *H*C(3)), 3.14 (s, 3H, H_3C(1)), 3.02 (td, J = 15.3, 12.7, 9.0 Hz, 2H, H_2C(6)), 2.65 (s, 1H, *H*$NCPh_3$), 1.82 (dq, J = 13.7, 6.6 Hz, 1H, $H_a$$H_b$C(4)), 1.71 (dq, J = 9.5, 4.9, 4.2 Hz, 1H, $H_a$$H_b$C(4)), 1.63 (dd, J = 15.9, 8.8 Hz, 1H, $H_a$$H_b$C(5)), 1.55 – 1.43 (m, 1H, $H_a$$H_b$C(5)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 175.4 (*C*(2)), 157.6 (*C*(7)), 145.9 (3 × *C*(9)), 128.9 (6 × *C*(10)), 128.1 (6 × *C*(11)), 126.7 (3 × *C*(12)), 71.3 (*C*(8)), 55.8 (*C*(3)), 51.9 (*C*(1)), 41.1 (*C*(6)), 32.6 (*C*(4)), 24.8 (*C*(5)); **IR** ν_{max} (film)/cm^{-1} 3326 (br.), 3159, 1732, 1666, 1448, 1210, 750, 707; **HRMS** (APCI$^+$) $C_{26}H_{31}O_2N_4$ requires 431.2442, found $[M+H]^+$ 431.2427 (Δ –3.26 ppm); **M.p.** 110 – 112 °C.

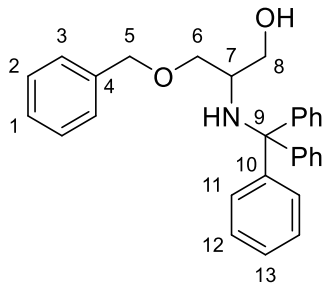
Methyl *O*-benzyl-*N*-tritylserinate (653)



To a stirred solution of commercially available DL-*O*-benzyl serine methyl ester **652** (4.18 g, 20 mmol, 1.0 equiv.) and trityl chloride (5.84 g, 21 mmol, 1.05 equiv.) in CH_2Cl_2 (80 mL) at 0 °C was added a solution of Et_3N (3.04 mL, 22 mmol, 1.1 equiv.) in CH_2Cl_2 (20 mL) dropwise over the course of 15 min. The mixture was then warmed to RT and left to stir for 2 h. The reaction was then quenched by the addition of sat. aq. $NaHCO_3$ (40 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic extracts washed with brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 70:30) gave the desired alcohol **653** as a colourless oil (7.12 g, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.57 – 7.47 (m, 6H, 6 × *H*C(12)), 7.44 – 7.24 (m, 11H, 6 × *H*C(13) and 5 × *H*C_{Ar}), 7.24 – 7.17 (m, 3H, 3 × *H*C(14)), 4.56 (d, J = 5.1 Hz, 2H, *H*$_2$C(5)), 3.81 (dd, J = 8.9, 4.5 Hz, 1H, *H*C(7)), 3.66 – 3.56 (m, 1H, *H*$_a$H$_b$C(9)), 3.25 (s, 3H, *H*$_3$C(9)), 2.82 (d, J = 9.9 Hz, 1H, H$_a$*H*$_b$C(9)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 172.6 (*C*(8)), 143.9 (3 × *C*(11)), 135.4 (*C*(4)), 128.9 (6 × *C*(12)), 128.1 (6 × *C*(13)), 127.4 (2 × *C*(3)), 126.7 (3 × *C*(14)), 125.9(3 × *C*(2)), 121.8 (*C*(1)) 72.6 (*C*(10)), 71.8 (*C*(7)), 71.6 (*C*(5)), 69.9 (*C*(6)), 53.3 (*C*(9)); **IR** ν_{max} (film)/cm^{-1} 1734, 1491, 1448, 1205, 1102, 1029, 745, 698; **HRMS** (ESI$^+$) $C_{30}H_{29}O_3NNa$ requires 474.2040, found $[M+Na]^+$ 474.2038 (Δ –0.31 ppm).

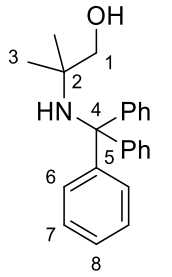
3-(Benzyloxy)-2-(tritylamino)propan-1-ol (654)



To a stirred solution of $LiAlH_4$ (0.23 g, 6 mmol, 1.0 equiv.) in THF (30 mL) at 0 °C was added a solution of tritylated *O*-benzyl serine **653** (2.76 g, 6 mmol, 1.0 equiv.) in THF (10 mL) dropwise, before being allowed to warm to RT over the course of 15 min. The reaction was then cooled to 0 °C and diluted with Et_2O (20 mL) before being quenched by the sequential addition of water (0.23 ml), 15% aqueous NaOH (0.23 ml), water (0.69 mL) and $MgSO_4$ (1.5 g). The thick emulsion was then filtered under reduced pressure and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 50:50) gave the desired alcohol **654** as a colourless oil (1.93 g, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.60 – 7.53 (m, 6H, 6 × *H*C(11)), 7.36 – 7.22 (m, 11H, 6 × *H*C(12) and 5 × *H*C_{Ar}), 7.22 – 7.16 (m, 3H, 3 × *H*C(13)), 4.28 (d, *J* = 2.2 Hz, 2H, *H*$_2$C(5)), 3.49 (m, 1H, *H*$_a$H$_b$C(8)), 3.19 (dd, *J* = 8.9, 3.2 Hz, 1H, *H*$_a$H$_b$C(6)), 3.01 (dd, *J* = 10.9, 5.4 Hz, 1H, H$_a$*H*$_b$C(8)), 2.89 – 2.82 (m, 1H, *H*C(7)), 2.82 – 2.78 (m, 1H, H$_a$*H*$_b$C(6)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 146.9 (3 × *C*(10)), 138.2 (*C*(4)), 128.8 (6 × *C*(11)), 128.5 (2 × *C*$_{Ar}$), 128.0 (6 × *C*(12)), 127.8 (*C*(1)), 127.7 (2 × *C*$_{Ar}$), 126.6 (3 × *C*(13)), 73.3 (*C*(5)), 71.6 (*C*(6)), 71.1 (*C*(9)), 64.1 (*C*(8)), 52.8 (*C*(5)); **IR** ν_{max} (film)/cm^{-1} 1491, 1450, 1091, 1059, 1029, 745, 706, 698; **HRMS** (ESI$^+$) $C_{29}H_{29}O_2NNa$ requires 446.2091, found [M+Na]$^+$ 446.2093 (Δ 0.50 ppm).

2-Methyl-2-(tritylamino)propan-1-ol (656)

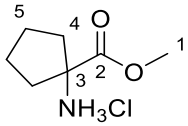


According to a literature procedure,[146] to a stirred solution of commercially available 2-amino-2-methylpropanol **655** (0.48 mL, 5 mmol, 1.0 equiv.) and Et_3N (0.76 mL, 5.5 mmol, 1.1 equiv.) in DMF (30 mL) at 0 °C was added a solution of trityl chloride (1.46 g, 5.25 mmol, 1.05 equiv.) in DMF (5 mL) and the warmed to 40 °C and left to stir for 18 h. The reaction was quenched by the addition of water (50 mL) and the mixture extracted with EtOAc (3 × 30 mL) and the combined organic extracts were washed with brine (3 × 30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 85:15) gave the desired compound **656** (807 mg, 49%) as a colourless solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.67 – 7.60 (m, 6H, 6 × *H*C(6)), 7.29 – 7.23 (m, 6H, 6 × *H*C(7)), 7.22 – 7.13 (m, 3H, 3 × *H*C(8)), 2.78 (s, 2H, H_2C(1)), 0.81 (s, 6H, 2 × *H*C(3)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 148.0 (3 × *C*(5)), 129.2 (6 × *C*(6)), 127.8 (6 × *C*(7)), 126.4 (3 × *C*(8)), 71.6 (*C*(1)), 69.8 (*C*(4)), 55.8 (*C*(2)), 26.2 (2 × *C*(3)).

Data was consistent with that previously reported.[146]

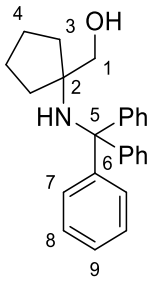
Methyl 1-aminocyclopentane-1-carboxylate hydrochloride (658)



Cycloleucine **657** (2.58 g, 20 mmol, 1.0 equiv.) was subjected to **General Procedure F** to give the desired compound **658** (3.22 g, 90%) as a colourless solid.

^{1}H NMR (D_2O, 400 MHz) δ_H = 3.87 (s, 3H, H_3C(1)), 2.45 – 2.28 (m, 2H, 2 × $H_a$$H_b$C(4)), 2.05 – 1.82 (m, 6H, 2 × $H_a$$H_b$C(4) and 2 × H_2C(5)); **^{13}C NMR** (D_2O, 101 MHz) δ_C = 173.9 (*C*(2)), 65.3 (*C*(3)), 53.8 (*C*(1)), 36.4 (2 × *C*(4)), 25.1 (2 × *C*(5)); **IR** (film) ν_{max}/cm^{-1} = 2878 (br.), 1741, 1578, 1523, 1264, 1216, 1190, 993; **HRMS** (ESI$^+$) $C_7H_{14}O_2N$ requires 144.1019, found $[M+H]^+$ = 144.1018 (Δ –0.44 ppm); **M.p.** = 200 – 202 °C.

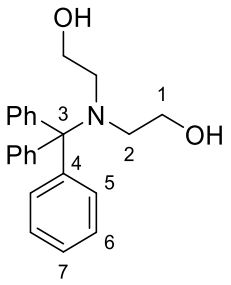
(1-(Tritylamino)cyclopentyl)methanol (659)



Cycloleucine methyl ester hydrochloride **658** (2.69 g, 15 mmol, 1.0 equiv.) was subjected to **General Procedure G** to give the crude tritylated methyl ester which was immediately subjected to **General Procedure H**. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 80:20) gave the desired alcohol **659** as a colourless solid (2.66 g, 50% over two steps).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.60 – 7.52 (m, 6H, 6 × *H*C(7)), 7.29 – 7.22 (m, 6H, 6 × *H*C(8)), 7.21 – 7.14 (m, 3H, 3 × *H*C(9)), 2.49 (br. s, 1H, *H*O), 2.42 (s, 2H, H_2C(1)), 1.66 – 1.54 (m, 2H, 2 × $H_a$$H_b$C(3)), 1.53 – 1.40 (m, 2H, 2 × $H_a$$H_b$C(4)), 1.40 – 1.17 (m, 4H, 2 × $H_a$$H_b$C(3) and 2 × $H_a$$H_b$C(4)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 147.8 (3 × *C*(6)), 129.1 (6 × *C*(7)), 127.8 (6 × *C*(8)), 126.5 (3 × *C*(9)), 70.2 (*C*(5)), 67.6 (*C*(1)), 66.7 (*C*(2)), 36.2 (2 × *C*(3)), 24.9 (2 × *C*(4)); **IR** (film) ν_{max}/cm^{-1} = 1488, 1443, 1035, 743, 699, 632; **HRMS** (ESI$^+$) $C_{25}H_{27}ONNa$ requires 380.1985, found $[M+Na]^+$ = 380.1988 (Δ 0.78 ppm); **M.p.** = 83 – 85 °C.

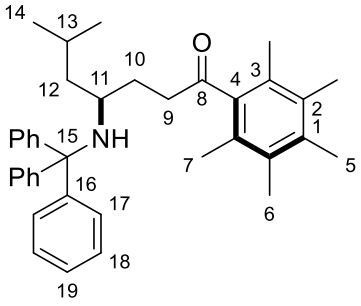
2,2'-(Tritylazanediyl)bis(ethan-1-ol) (660)



To a stirred solution of diethanolamine **306** (4.77 mL, 50 mmol, 1.0 equiv.) in CH_2Cl_2 (100 mL) at 0 °C was added Et_3N (10.40 mL, 75 mmol, 1.5 equiv.), followed by the portionwise addition of trityl chloride (15.30 g, 55 mmol, 1.1 equiv.) and the reaction left to stir and warm to RT over the course of 2 h. Water (100 mL) and EtOAc (100 mL) were added and the layers separated. The organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product. Recrystallisation from EtOAc gave pure product **660** (3.88 g, 22%) as a colourless, crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.54 – 7.44 (m, 6H, 6 × *H*C(5)), 7.25 – 7.19 (m, 6H, 6 × *H*C(6)), 7.15 – 7.07 (m, 3H, 3 × *H*C(7)), 3.73 (t, J = 6.3 Hz, 4H, 2 × H_2C(1)), 2.53 (t, J = 6.2 Hz, 4H, 2 × H_2C(2)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 143.7 (3 × *C*(4)), 129.7 (6 × C_{Ar}), 127.8 (6 × C_{Ar}), 126.3 (3 × *C*(7)), 78.9 (*C*(3)), 62.5 (*C*(1)), 55.2 (*C*(2)); **IR** ν_{max} (film)/cm^{-1} 3332, 1489, 1447, 1216, 1032, 1003, 745, 709, 631; **HRMS** (ESI$^-$) $C_{23}H_{24}O_2N$ requires 346.1813, found $[M–H]^-$ 346.1808 (Δ –1.43 ppm); **M.p.** 151 – 153 °C.

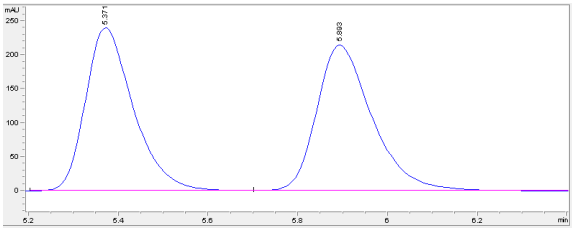
(*R*)-6-Methyl-1-(2,3,4,5,6-pentamethylphenyl)-4-(tritylamino)heptan-1-one (664)



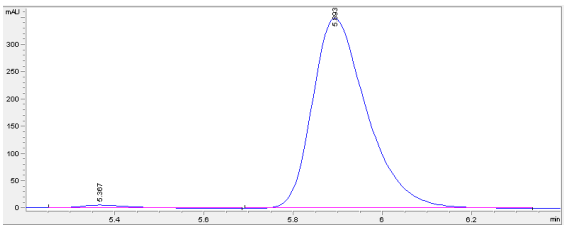
Tritylated leucinol **627** (1.44 g, 4 mmol, 1.0 equiv.) was subjected to **General Procedure E**. Purification by column chromatography (SiO_2, eluent load, toluene) gave the desired compound **664** (1.32 g, 62%, 98:2 er) as an exceptionally viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.57 – 7.45 (m, 6H, 6 × *H*C(17)), 7.26 – 7.21 (m, 6H, 6 × *H*C(18)), 7.18 – 7.14 (m, 3H, 3 × *H*C(19)), 2.92 – 2.76 (m, 1H, H_aH_bC(9)), 2.56 (dt, J = 9.2, 4.6 Hz, 1H, *H*C(11)), 2.54 – 2.41 (m, 1H, H_aH_bC(9)), 2.25 (s, 3H, H_3C(5)), 2.20 (s, 6H, 2 × H_3CC_{Ar}), 2.08 (s, 6H, 2 × H_3CC_{Ar}), 1.69 – 1.57 (m, 2H, H_2C(10)), 1.45 (s, 1H, *H*C(13)), 1.42 – 1.29 (m, 1H, H_aH_bC(12)), 1.01 (ddd, J = 14.0, 9.1, 5.2 Hz, 1H, H_aH_bC(12)), 0.58 (dd, J = 14.4, 6.5 Hz, 6H, H_3C(14) and H_3C(14')); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 212.6 (*C*(8)), 147.1 (*C*(16)), 141.0 (*C*(4)), 135.4 (C_{Ar}), 133.2 (C_{Ar}), 129.0 (6 × C_{Ar}), 127.9 (6 × C_{Ar}), 127.4 (C_{Ar}), 126.4 (3 × C_{Ar}), 71.5 (*C*(13), 49.5 (*C*(11)), 44.1 (*C*(9)), 40.9 (*C*(10)), 26.8 (*C*(12)), 25.0 (*C*(13)), 23.7 (*C*(14)), 21.8 (*C*(14')), 17.4 (2 × H_3CC_{Ar}), 16.8 (*C*(5)), 16.1 (2 × H_3CC_{Ar}); **IR** ν_{max} (film)/cm^{-1} 3057, 2954, 1698, 1596, 1490, 1448, 1407, 757, 707; **HRMS** (ESI$^-$) $C_{38}H_{44}ON$ requires 530.3428, found $[M–H]^-$ 530.3423 (Δ –1.11 ppm); **$[\alpha]_D^{25}$** = –35.4 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 1.0 % IPA, 99.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

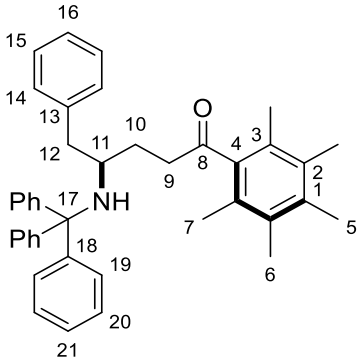


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	5.371	BV	1782.3	240.5	0.1104	49.182	0.677
2	5.893	VB	1841.5	214.6	0.1301	50.818	0.664



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	5.367	VB	48.3	5.8	0.123	1.602	0.645
2	5.893	BB	2965.2	349.5	0.129	98.398	0.652

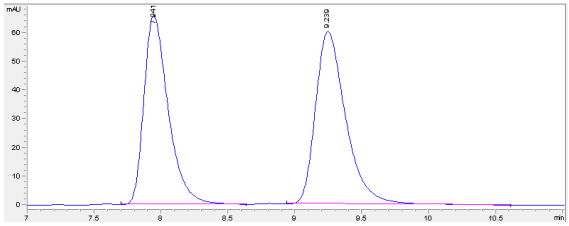
(*R*)-1-(2,3,4,5,6-Pentamethylphenyl)-5-phenyl-4-(tritylamino)pentan-1-one (665)



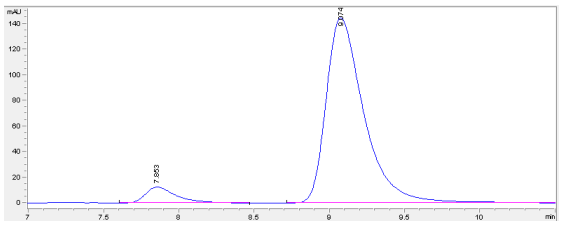
Tritylated phenylalaninol **629** (118 mg, 0.3 mmol, 1.0 equiv.) was subjected to **General Procedure E**. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 95:5 to 92:8) gave the desired compound **665** (98 mg, 58%, 96:4 er) as a fluffy yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.57 – 7.50 (m, 6H, 6 × *H*C(19)), 7.30 – 7.20 (m, 6H, 6 × *H*C(20)), 7.20 – 7.06 (m, 6H, 3 × *H*C(21) and 3 × *H*C_{Ar}), 6.91 – 6.83 (m, 2H, 2 × *H*C_{Ar}), 2.81 – 2.66 (m, 2H, *H*C(11) and $H_aH_bC(9)$), 2.53 (ddd, J = 17.8, 11.4, 4.8 Hz, 1H, $H_aH_bC(9)$), 2.35 – 2.24 (m, 2H, $H_2C(12)$), 2.23 (s, 3H, $H_3C(5)$), 2.18 (s, 6H, 2 × H_3CC_{Ar}), 2.02 (s, 6H, 2 × H_3CC_{Ar}), 1.62 – 1.52 (m, 1H, $H_aH_bC(10)$), 1.46 – 1.32 (m, 1H, $H_aH_bC(10)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 211.9 (*C*(8)), 147.0 (*C*(18)), 140.8 (*C*(4)), 139.4 (2 ×CCH_3), 135.4 (*C*(13)), 133.2 (2 ×CCH_3), 129.3 (2 ×C_{Ar}), 128.9 (6 ×C_{Ar}), 128.4 (2 ×C_{Ar}), 128.0 (6 ×C_{Ar}), 127.4 (*C*(1)), 126.5 (3 × *C*(21)), 126.2 (*C*(16)), 71.6 (*C*(17)), 53.7 (*C*(11)), 41.8 (*C*(9)), 41.3 (*C*(12)), 27.2 (*C*(10)), 17.4 (2 × H_3CC_{Ar}), 16.8 (*C*(5)), 16.1 (2 × H_3CC_{Ar}); **IR** ν_{max} (film)/cm^{-1} 3023, 2931, 1697, 1491, 1448, 746, 707; **HRMS** (APCI$^-$) $C_{41}H_{42}ON$ requires 564.3272, found $[M–H]^-$ 564.3268 (Δ –0.61 ppm); **M.p.** 80 – 82 °C; **$[\alpha]_D^{25}$** = –33.8 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 1.0 % IPA, 99.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

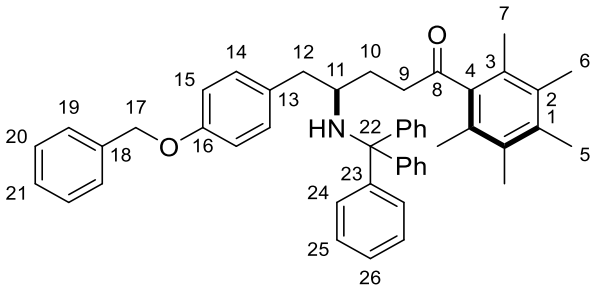


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.941	BB	831.4	65.8	0.1913	46.903	0.618
2	9.239	BB	941.2	60	0.237	53.097	0.644



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.853	BB	174.8	12.4	0.2109	6.443	0.574
2	9.074	BB	2538.4	144.6	0.2648	93.557	0.577

(*R*)-5-(4-(Benzyloxy)phenyl)-1-(2,3,4,5,6-pentamethylphenyl)-4-(tritylamino)pentan-1-one (666)



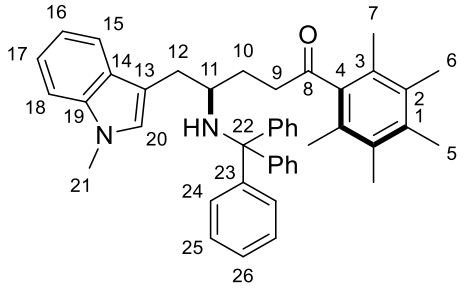
Tritylated benzyltyrosinol **631** (150 mg, 0.3 mmol, 1.0 equiv.) was subjected to **General Procedure E**. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 90:10 to 80:20) gave the desired compound **666** (130 mg, 65%, 85:15 er) as a fluffy yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.58 – 7.47 (m, 6H, 6 × *H*C(24)), 7.44 – 7.29 (m, 5H, 5 × *H*C$_{Ar}$), 7.27 – 7.20 (m, 6H, 6 × *H*C(25)), 7.20 – 7.11 (m, 3H, 3 × *H*C(26)), 6.78 (d, J = 1.3 Hz, 4H, 2 × *H*C(14) and 2 × *H*C(15)), 4.99 (s, 2H, *H*$_2$C(17)), 2.69 (ddt, J = 14.8, 11.7, 5.9 Hz, 2H, *H*C(11) and *H*$_a$H$_b$C(9)), 2.50 (ddd, J = 17.7, 11.4, 4.8 Hz, 1H, H$_a$*H*$_b$C(9)), 2.31 – 2.21 (m, 4H, *H*$_a$H$_b$C(12) and *H*$_3$C(5)), 2.18 (m, 7H, H$_a$*H*$_b$C(12) and 2 × *H*$_3$CC$_{Ar}$), 2.02 (s, 6H, 2 × *H*$_3$CC$_{Ar}$), 1.59 – 1.52 (m, 1H, *H*$_a$H$_b$C(10)), 1.46 – 1.31 (m, 1H, H$_a$*H*$_b$C(10)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 211.9 (*C*(8)), 157.3 (*C*(16)), 147.1 (3 × *C*(23)), 140.8 (*C*$_{Ar}$), 137.3 (*C*$_{Ar}$), 135.4 (*C*$_{Ar}$), 133.2 (2 × *C*$_{Ar}$), 131.7 (*C*$_{Ar}$), 130.3 (2 × *C*(14)), 128.9 (6 × *C*(24)), 128.7 (2 × H*C*$_{Ar}$), 128.0 (*C*(21)), 127.9 (6 × *C*(25)), 127.6 (2 × H*C*$_{Ar}$), 127.4 (2 × *C*$_{Ar}$), 126.5 (3 × *C*(26)), 114.9 (2 × *C*(15)), 71.5 (*C*(22)), 70.2 (*C*(17)),

53.7 (*C*(11)), 41.9 (*C*(9)), 40.3 (*C*(12)), 27.2 (*C*(10)), 17.4 (2 × H_3CC_{Ar}), 16.8 (*C*(5)), 16.1 (2 × H_3CC_{Ar}); **IR** ν_{max} (film)/cm^{-1} 3030, 1697, 1510, 1449, 1240, 1219, 748, 707, 697; **HRMS** (ESI^-) $C_{48}H_{48}O_2N$ requires 670.3691, found $[M–H]^-$ 670.3687 (Δ –0.48 ppm); **M.p.** 68 – 70 °C; **$[\alpha]_D^{25}$** = –15.4 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 10.0 % IPA, 90.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

(*R*)-5-(1-Methyl-1H-indol-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)-4-(tritylamino)pentan-1-one (667)

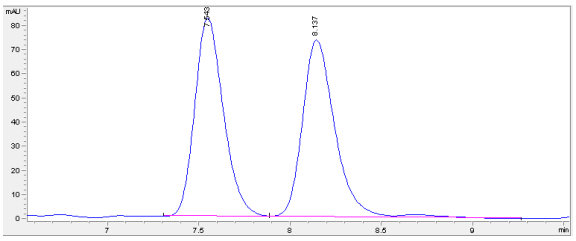


Tritylated methyltryptophanol **633** (134 mg, 0.3 mmol, 1.0 equiv.) was subjected to **General Procedure E** at 110 °C. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O:Et_3N, 85:15:0.5 to 80:20:0.5) gave the desired compound **667** (95 mg, 51%, 95:5 er) as a highly acid-sensitive, colourless, and fluffy solid.

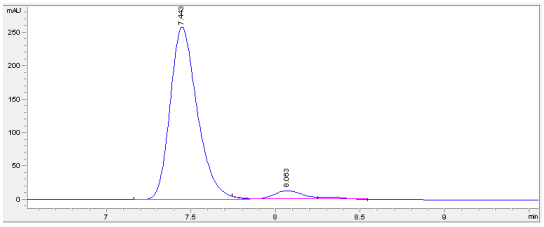
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.55 – 7.46 (m, 6H, 6 × *H*C(24)), 7.30 – 7.18 (m, 8H, 6 × *H*C(25) and 2 × *H*C_{Ar}), 7.18 – 7.11 (m, 4H, 3 × *H*C(26) and *H*C_{Ar}), 6.98 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H, *H*C_{Ar}), 6.63 (s, 1H, *H*C(20)), 3.66 (s, 3H, H_3C(21)), 2.83 (td, J = 7.0, 2.9 Hz, 1H, *H*C(11)), 2.75 – 2.61 (m, 1H, H_aH_bC(9)), 2.56 (dd, J = 9.5, 6.6 Hz, 2H, H_2C(12)), 2.47 (ddd, J = 17.7, 11.4, 4.8 Hz, 1H, H_aH_bC(9)), 2.23 (s, 3H, H_3C(5)), 2.16 (s, 6H, 2 × H_3CC_{Ar}), 1.95 (s, 6H, 2 × H_3CC_{Ar}), 1.50 (ddt, J = 11.5, 6.9, 3.6 Hz, 1H, H_aH_bC(10)), 1.45 – 1.35 (m, 1H, H_aH_bC(10)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 212.1 (*C*(8)), 147.2 (3 × *C*(23)), 140.8 (*C*$_{Ar}$), 137.0 (*C*$_{Ar}$), 135.3 (*C*$_{Ar}$), 133.1 (*C*$_{Ar}$), 129.0 (6 × *C*(24)), 128.1 (*C*$_{Ar}$), 127.9 (6 × *C*(25)), 127.5 (*C*(20)), 127.3, 126.4 (3 × *C*(26)), 121.6 (H*C*$_{Ar}$), 119.4 (H*C*$_{Ar}$), 118.7 (H*C*$_{Ar}$), 111.8 (*C*$_{Ar}$), 109.1 (H*C*$_{Ar}$), 71.5 (*C*(22)), 52.8 (*C*(11)), 42.2 (*C*(9)), 32.7 (*C*(21)), 31.0 (*C*(12)), 27.8 (*C*(10)), 17.4 (2 × H_3CC_{Ar}), 16.8 (*C*(5)), 16.1 (2 × H_3CC_{Ar}); **IR**

ν_{max} (film)/cm^{-1} 2931, 1696, 1486, 1448, 744, 708; **HRMS** (APCI$^-$) $C_{44}H_{45}ON_2$ requires 617.3537, found $[M–H]^-$ 617.3531 (Δ –0.96 ppm); **M.p.** 89 – 91 °C; **$[\alpha]_D^{25}$** = –39.4 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 5.0 % IPA, 95.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

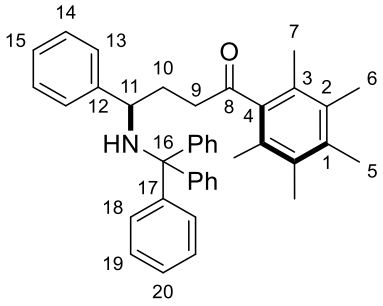


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.543	BV	895.1	82.1	0.1672	49.447	0.768
2	8.137	VV R	915.1	73.3	0.1863	50.553	0.72



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.443	BV R	2904.6	257.2	0.1702	94.938	0.724
2	8.063	VV E	154.9	12.9	0.1844	5.062	0.832

(*R*)-1-(2,3,4,5,6-Pentamethylphenyl)-4-phenyl-4-(tritylamino)butan-1-one (673)

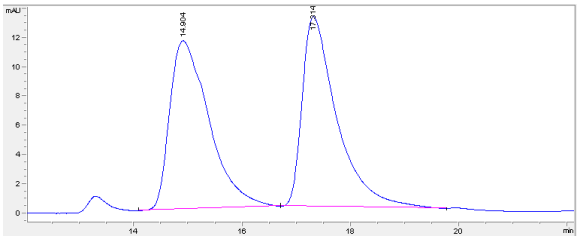


Tritylated phenylglycinol **642** (227 mg, 0.6 mmol, 1.0 equiv.) was subjected to **General Procedure E** at 110 °C. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 95:5 to 92:8) gave the desired compound **673** (159 mg, 48%, 93:7 er) as a fluffy, pale-yellow solid.

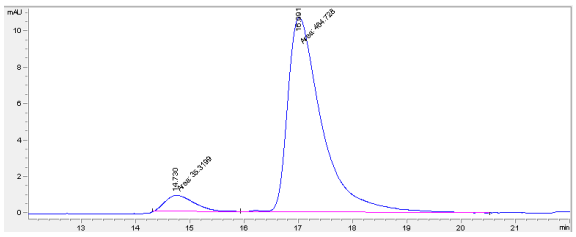
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.54 – 7.43 (m, 6H, 6 × *H*C(18)), 7.23 – 7.09 (m, 11H, 6 × *H*C(19) and 5 × *H*C_{Ar}), 7.06 (dt, *J* = 6.1, 1.6 Hz, 3H, 3 × *H*C(20)), 3.51 (dd, *J* = 9.3, 3.9 Hz, 1H, *H*C(11)), 2.18 (s, 3H, H_3C(5)), 2.12 – 2.00 (m, 8H, 2 × H_3CC_{Ar} and H_2C(9)), 1.81 (s, 6H, 2 × H_3CC_{Ar}), 1.67 – 1.58 (m, 1H, H_aH_bC(10)), 1.58 – 1.49 (m, 1H, H_aH_bC(10)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 211.5 (*C*(8)), 146.7 (3 × *C*(17)), 145.4 (*C*(12)), 140.7 (*C*(4)), 135.3 (*C*(1)), 133.0 (2 × C_{Ar}), 129.1 (6 × *C*(18)), 128.2 (2 × C_{Ar}), 127.8 (6 × *C*(19)), 127.3 (2 × C_{Ar}), 127.2 (2 × C_{Ar}), 126.44 (3 × *C*(20)), 126.39 (*C*(15)), 72.3 (*C*(16)), 57.7 (*C*(11)), 42.4 (*C*(9)), 32.4 (*C*(10)),

17.1 (2 × H_3CC_{Ar}), 16.7 (*C*(5)), 16.0 (2 × H_3CC_{Ar}); **IR** (film) ν_{max}/cm^{-1} = 2981, 1699, 1448, 1382, 1154, 1072, 772, 746, 706; **HRMS** (ESI^+) $C_{40}H_{41}ONNa$ requires 574.3080, found $[M+Na]^+$ = 574.3078 (Δ –0.34 ppm); **M.p.** = 70 – 72 °C; **$[\alpha]_D^{25}$** = +14.6 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 1.0 % IPA, 99.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

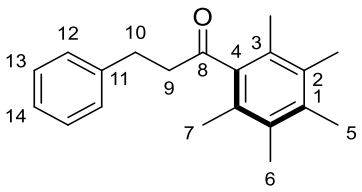


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.904	BB	582.1	11.5	0.7145	50.047	0.485
2	17.314	BB	581	13	0.6425	49.953	0.443



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	14.73	MF	35.3	9.1E-1	0.6497	7.063	0
2	16.991	FM	464.7	10.6	0.728	92.937	0.484

1-(2,3,4,5,6-pentamethylphenyl)-3-phenylpropan-1-one (676)

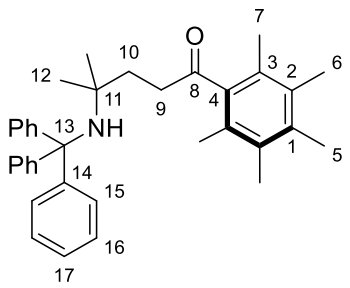


Tritylated *O*-benzyl serinol **654** (169 mg, 0.4 mmol, 1.0 equiv.) was subjected to **General Procedure E**. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 95:5) gave the unexpected compound **676** (72 mg, 64%) as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.29 – 7.11 (m, 5H, 5 × HC_{Ar}), 3.03 (ddd, *J* = 7.7, 6.4, 1.9 Hz, 2H, $H_2C(10)$), 3.00 – 2.92 (m, 2H, $H_2C(9)$), 2.18 (s, 3H, $H_3C(5)$), 2.13 (s, 6H, 2 × H_3CC_{Ar}), 2.00 (s, 6H, 2 × H_3CC_{Ar}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 211.0 (*C*(8)), 141.2 (C_{Ar}), 140.6 (C_{Ar}), 135.6 (C_{Ar}), 133.2 (2 × C_{Ar}), 128.6 (2 × C_{Ar}), 128.5 (2 × C_{Ar}), 127.5 (2 × C_{Ar}), 126.2 (*C*(14)), 47.2 (*C*(9)), 29.5 (*C*(10)), 17.2 (2 × H_3CC_{Ar}), 16.8 (*C*(5)), 16.1 (2 × H_3CC_{Ar}).

Data was consistent with that previously reported.[29]

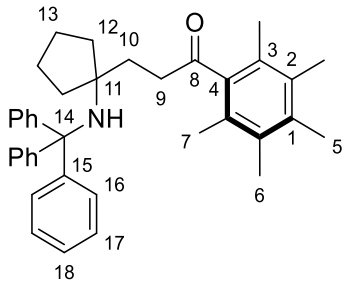
4-Methyl-1-(2,3,4,5,6-pentamethylphenyl)-4-(tritylamino)pentan-1-one (677)



Trityl protected alcohol **656** (331 mg, 1.0 mmol, 1.0 equiv.) was subjected to **General Procedure E** at 110 °C. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O:Et_3N, 97:3:0.5) gave the desired compound **677** (204 mg, 41%,) as an off-white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.65 – 7.58 (m, 6H, 6 × *H*C(15)), 7.22 (dd, *J* = 8.4, 6.8 Hz, 6H, 6 × *H*C(16)), 7.18 – 7.09 (m, 3H, 3 × *H*C(17)), 2.91 (t, *J* = 8.1 Hz, 2H, H_2C(9)), 2.26 (s, 3H, H_3C(5)), 2.21 (s, 6H, 2 × H_3CC_{Ar}), 2.13 (s, 6H, 2 × H_3CC_{Ar}), 1.69 (t, *J* = 8.1 Hz, 2H, H_2C(10)), 1.63 (br. s, 1H, *H*N), 0.69 (s, 6H, 2 × H_3C(12)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 212.6 (*C*(8)), 148.4 (3 × *C*(14)), 141.2 (*C*(4)), 135.5 (*C*(1)), 133.3 (2 × C_{Ar}), 129.3 (6 × *C*(15)), 127.6 (6 × *C*(16)), 127.5 (2 × C_{Ar}), 126.2 (3 × *C*(17)), 70.0 (*C*(13)), 54.2 (*C*(11)), 41.4 (*C*(9)), 39.9 (*C*(10)), 28.5 (2 × *C*(12)), 17.5 (2 × H_3CC_{Ar}), 16.8 (*C*(5)), 16.1 (2 × H_3CC_{Ar}); **IR** (film) ν_{max}/cm^{-1} = 1701, 1487, 1446, 1176, 1047, 1030, 748, 699, 639; **HRMS** (ESI$^-$)$C_{36}H_{40}ON$ requires 502.3104, found [M-H]$^-$ = 502.3107 (Δ 0.43 ppm); **M.p.** = 58–60 °C.

1-(2,3,4,5,6-Pentamethylphenyl)-3-(1-(tritylamino)cyclopentyl)propan-1-one (678)

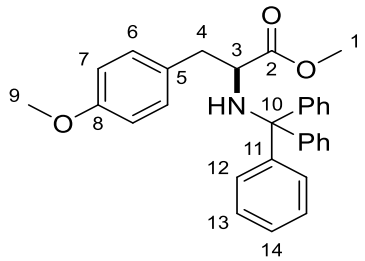


Trityl protected cycloleucinol **659** (183 mg, 0.6 mmol, 2.0 equiv.) was subjected to **General Procedure E** at 110 °C, with pentamethylacetophenone **100** (1.0 equiv.) as the limiting reagent. Purification by

column chromatography (SiO_2, eluent load, pentane:Et_2O:Et_3N, 95:5:0.5) gave the desired compound **678** (215 mg, 68%) as a colourless solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.59 – 7.52 (m, 6H, 6 × *H*C(16)), 7.24 – 7.19 (m, 6H, 6 × *H*C(17)), 7.18 – 7.12 (m, 3H, 3 × *H*C(18)), 2.79 (d, *J* = 8.0 Hz, 2H, H_2C(9)), 2.25 (s, 3H, H_3C(5)), 2.20 (s, 6H, 2 × H_3CC_{Ar}), 2.09 (s, 6H, 2 × H_3CC_{Ar}), 1.59 – 1.48 (m, 2H, 2 × H_aH_bC(12)), 1.48 – 1.38 (m, 4H, 2 × H_2C(13)), 1.33 (d, *J* = 8.0 Hz, 2H, H_2C(10)), 1.27 – 1.19 (m, 2H, 2 × H_aH_bC(12)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 212.4 (*C*(8)), 148.3 (3 × *C*(15)), 141.2 (*C*(4)), 135.5 (*C*(1)), 133.2 (2 × C_{Ar}), 129.2 (6 × *C*(16)), 127.7 (6 × *C*(16)), 127.4 (2 × C_{Ar}), 126.3 (3 × *C*(17)), 70.1 (*C*(14)), 65.4 (*C*(11)), 41.8 (*C*(9)), 38.3 (2 × *C*(12)), 35.1 (*C*(10)), 24.5 (2 × *C*(13)), 17.4 (2 × H_3CC_{Ar}), 16.8 (*C*(5)), 16.1 (2 × H_3CC_{Ar}); **IR** (film) ν_{max}/cm^{-1} = 2970, 2871, 2161, 2027, 1698, 1485, 1447, 1309, 709, 694, 652; **HRMS** (ESI^+) $C_{38}H_{44}ONNa$ requires 552.3237, found $[M+Na]^+$ = 552.3239 (Δ 0.36 ppm); **M.p.** = 149 – 151 °C.

Methyl (*S*)-3-(4-methoxyphenyl)-2-(tritylamino)propanoate (687)

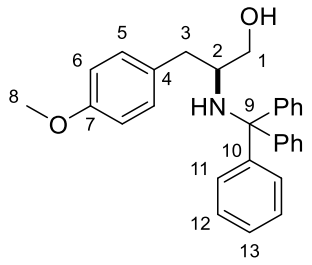


To a stirred solution of commercially available *L*-tyrosine methyl ester hydrochloride **686** (9.24 g, 40 mmol, 1.0 equiv.) and trityl chloride (11.16 g, 40 mmol, 1.0 equiv.) in DMF (300 mL) at 0 °C was added Et_3N (11.07 mL, 80 mmol, 2.0 equiv.) dropwise over the course of 15 min. The mixture was then warmed to RT and left to stir for 3 h. The reaction was then quenched by the addition of water (200 mL) and the mixture extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (3 × 100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude intermediate as an oil that crystallised under high vacuum into a colourless solid. To a stirred solution of the crude tritylated intermediate (13.11 g, 30 mmol, 1.0 equiv.) and K_2CO_3 (5.38 g, 39 mmol, 1.3 equiv.) in DMF

(90 mL) at RT was added MeI (2.05 mL, 33 mmol, 1.1 equiv.) dropwise and the reaction left to stir for 17 h. The reaction was then concentrated *in vacuo* and the residue redissolved in water (30 mL). The resulting mixture was extracted with EtOAc (3 × 30 mL) and the combined organic extracts washed with brine (3 × 30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 80:20) gave the methylated product **687** (2.04 g, 91%) as a colourless solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.46 – 7.37 (m, 6H, 6 × *H*C(12)), 7.25 – 7.18 (m, 6H, 6 × *H*C(13)), 7.18 – 7.11 (m, 5H, 3 × *H*C(14) and 2 × *H*C(6)), 6.86 (d, *J* = 8.7 Hz, 2H, 2 × *H*C(7)), 3.81 (s, 3H, H_3C(9)), 3.56 – 3.48 (m, 1H, *H*C(3)), 3.05 (s, 3H, H_3C(1)), 2.90 (dp, *J* = 13.0, 6.5 Hz, 2H, H_2C(4)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 175.1 (*C*(2)), 158.6 (*C*(8)), 146.0 (3 × *C*(11)), 130.9 (2 × *C*(6)), 129.7 (*C*(5)), 129.0 (6 × *C*(12)), 127.9 (6 × *C*(13)), 126.4 (3 × *C*(14)), 113.8 (2 × *C*(7)), 71.1 (*C*(10)), 58.5 (*C*(3)), 55.4 (*C*(9)), 51.4 (*C*(1)), 41.6 (*C*(4)); **IR** (film) ν_{max}/cm^{-1} = 2981, 2889, 1738, 1514, 1446, 1383, 1248, 1159, 1117, 822, 783, 773, 706; **HRMS** (ESI$^+$) $C_{30}H_{29}O_3NNa$ requires 474.2040, found $[M+Na]^+$ = 474.2038 (Δ –0.37 ppm); **M.p.** = 83 – 85 °C; **$[\alpha]_D^{25}$** = +61.0 (c = 1.00, $CHCl_3$).

(*S*)-3-(4-Methoxyphenyl)-2-(tritylamino)propan-1-ol (688)

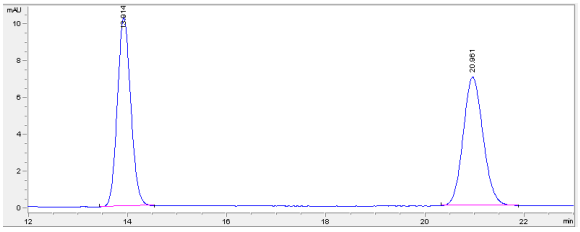


Methylated tyrosine derivative **687** (9.02 g, 20 mmol, 1.0 equiv.) was subjected to **General Procedure H**. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 80:20 to 60:30) gave the desired alcohol **688** (2.24 g, 27%, >99:1 er) as a colourless solid.

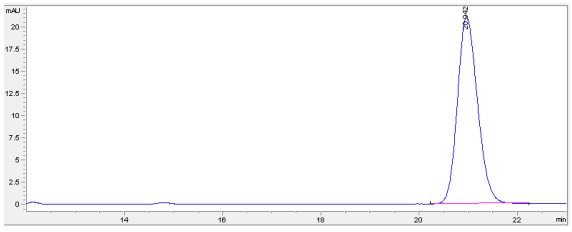
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.57 (ddd, *J* = 8.3, 2.2, 1.1 Hz, 6H, 6 × *H*C(11)), 7.34 – 7.26 (m, 6H, 6 × *H*C(12)), 7.25 – 7.17 (m, 3H, 3 × *H*C(13)), 6.86 (d, *J* = 8.4 Hz, 2H, 2 × *H*C(5)), 6.74 (d, *J* = 8.4 Hz, 2H, 2 ×

*H*C(6)), 3.75 (s, 3H, *H*$_3$C(8)), 3.13 (dd, *J* = 11.0, 2.8 Hz, 1H, *H*$_a$H$_b$C(1)), 2.94 (dd, *J* = 11.0, 4.1 Hz, 1H, H$_a$*H*$_b$C(1)), 2.77 (dtd, *J* = 8.9, 4.6, 2.5 Hz, 1H, *H*C(2)), 2.47 (dd, *J* = 13.3, 9.8 Hz, 1H, *H*$_a$H$_b$C(3)), 2.24 (dd, *J* = 13.3, 4.6 Hz, 1H, H$_a$*H*$_b$C(3)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 158.1 (*C*(7)), 146.7 (3 × *C*(10)), 131.1 (*C*(4)), 130.5 (2 × *C*(5)), 128.9 (6 × *C*(11)), 128.1 (6 × *C*(12)), 126.6 (3 × *C*(13)), 113.8 (2 × *C*(6)), 71.5 (*C*(9)), 62.5 (*C*(1)), 55.5 (*C*(2)), 55.3 (*C*(8)), 38.4 (*C*(3)); **IR** (film) ν_{max}/cm^{-1} = 2981, 1383, 1246, 1155, 1031, 954, 746, 70; **HRMS** (ESI$^+$) $C_{29}H_{29}O_2NNa$ requires 446.2091, Found $[M+Na]^+$ = 446.2088 (Δ –0.58 ppm); **M.p.** = 48 – 50 °C; **[α]$_D^{25}$** = –16.1 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 5.0 % IPA, 95.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

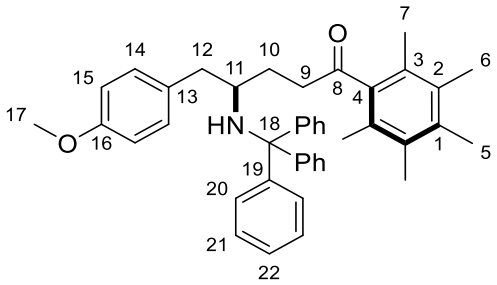


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2	20.961	BB	196.3	7	0.4284	50.232	0.889



#	Time	Type	Area	Height	Width	Area%	Symmetry
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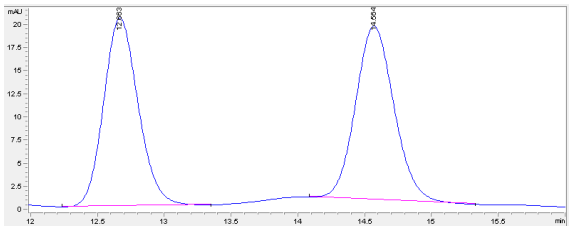
(*R*)-5-(4-Methoxyphenyl)-1-(2,3,4,5,6-pentamethylphenyl)-4-(tritylamino)pentan-1-one (689)



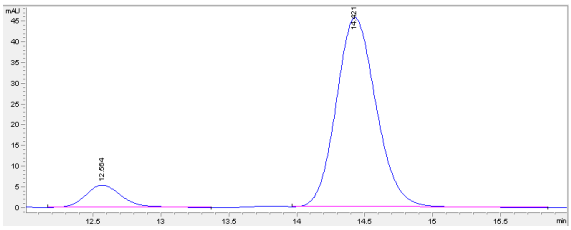
Trityl protected methyl tyrosinol **688** (170 mg, 0.4 mmol, 1.0 equiv.) was subjected to **General Procedure E** at 110 °C. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 85:15) gave the desired compound **689** (127 mg, 53%, 90:10 er) as a colourless and fluffy solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.60 – 7.48 (m, 6H, 6 × *H*C(20)), 7.29 – 7.22 (m, 6H, 6 × *H*C(21)), 7.22 – 7.12 (m, 3H, 3 × *H*C(22)), 6.80 (dt, *J* = 8.7, 2.2 Hz, 2H, 2 × *H*C(14)), 6.70 (dt, *J* = 8.7, 2.2 Hz, 2H, 2 × *H*C(15)), 3.75 (s, 3H, H_3C(17)), 2.78 – 2.63 (m, 2H, *H*C(11) and $H_a$$H_b$C(9)), 2.51 (ddd, *J* = 17.7, 11.5, 4.8 Hz, 1H, H_a*H*$_b$C(9)), 2.31 – 2.22 (m, 4H, H_3C(5) and $H_a$$H_b$C(12)), 2.22 – 2.16 (m, 7H, 2 × H_3CC_{Ar} and H_a*H*$_b$C(12)), 2.03 (s, 6H, 2 × H_3CC_{Ar}), 1.62 – 1.50 (m, 1H, $H_a$$H_b$C(10)), 1.39 (dddd, *J* = 14.5, 11.5, 5.0, 3.2 Hz, 1H, H_a*H*$_b$C(10)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 211.9 (*C*(8)), 158.1 (*C*(16)), 147.0 (3 × *C*(19)), 140.8 (*C*(4)), 135.4 (*C*(1)), 133.2 (2 × H_3CC_{Ar}), 131.4 (*C*(13)), 130.2 (2 × *C*(14)), 128.9 (6 × *C*(20)), 127.9 (6 × *C*(21)), 127.4 (2 × H_3CC_{Ar}), 126.5 (3 × *C*(22)), 113.8 (2 × *C*(15)), 71.5 (*C*(18)), 55.3 (*C*(17)), 53.7 (*C*(11)), 41.9 (*C*(9)), 40.3 (*C*(12)), 27.1 (*C*(10)), 17.4 (2 × H_3CC_{Ar}), 16.8 (*C*(5)), 16.1 (2 × H_3CC_{Ar}); **IR** (film) ν_{max}/cm^{-1} = 2981, 2889, 1696, 1511, 1382, 1247, 1157, 954, 706; **HRMS** (ESI$^+$) $C_{42}H_{45}O_2NNa$ requires 618.3343, found $[M+Na]^+$ = 618.3341 (Δ –0.26 ppm); **M.p.** = 75–77 °C; **$[\alpha]_D^{25}$** = –20.2 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 1.0 % IPA, 99.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

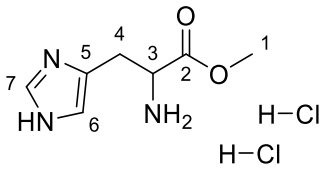


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1	12.663	BB	366.6	20.3	0.2763	49.314	0.843
2	14.564	BB	376.8	18.8	0.3082	50.686	0.875



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	12.564	BB	99.8	5.4	0.2832	9.645	0.801
2	14.421	BB	934.6	45.8	0.316	90.355	0.845

Methyl histidinate dihydrochloride (690)



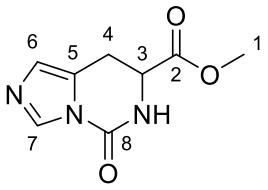
To a stirred solution of DL-histidine **646** (6.20 g, 40 mmol, 1.0 equiv.) in MeOH (160 mL) at 0 °C was added $SOCl_2$ (11.7 mL, 160 mmol, 4.0 equiv.) dropwise over the course of 20 min, after which the reaction was heated to reflux and left to stir for 16 h. The solvent was then removed *in vacuo* before

adding more MeOH (20 mL) and removing it *in vacuo*. The process was repeated twice before drying under high vacuum for 3 h to give the desired methyl ester as the dihydrochloride **690** (9.43 g, 98%) which was used without further purification.

^{1}H NMR (400 MHz, D_2O) δ_H 8.76 (d, J = 1.5 Hz, 1H, *H*C(7)), 7.50 (s, 1H, *H*C(6)), 4.56 (t, J = 6.8 Hz, 1H, *H*C(3)), 3.89 (s, 3H, H_3C(1)), 3.51 (tp, J = 12.9, 6.4 Hz, 2H, H_2C(4)); **^{13}C NMR** (101 MHz, D_2O) δ_C 168.9 (*C*(2)), 134.3 (*C*(7)), 126.2 (*C*(5)), 118.4 (*C*(6)), 54.0 (*C*(1)), 51.9 (*C*(3)), 24.9 (*C*(4)).

Data was consistent with that previously reported.[147]

Methyl 5-oxo-5,6,7,8-tetrahydroimidazo[1,5-c]pyrimidine-7-carboxylate (691)

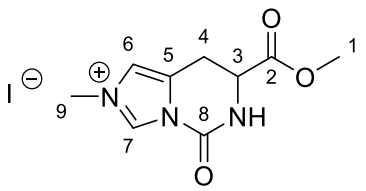


To a stirred solution of DL-histidine methyl ester dihydrochloride **690** (8.44 g, 35 mmol, 1.0 equiv.) in DMF (175 mL) at RT was added 1,1'-carbonyldiimidazole (5.67 g, 35 mmol, 1.0 equiv.) and the reaction heated to 65 °C for 3 h. The reaction was then concentrated *in vacuo* and the resulting oil dissolved in 1M aq. $NaHCO_3$ (300 mL). The solution was then extracted with $CHCl_3$ (8 × 50 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give a crude solid (6.61 g) that was recrystallized from MeOH (18 mL) to give the desired product **691** (4.24 g, 62%) as a colourless crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.17 (d, J = 0.9 Hz, 1H, *H*C(7)), 6.89 (q, J = 1.2 Hz, 1H, *H*C(6)), 6.31 (s, 1H, *H*N), 4.37 (ddd, J = 8.9, 5.2, 2.1 Hz, 1H, *H*C(3)), 3.82 (s, 3H, H_3C(1)), 3.39 (ddt, J = 15.8, 5.2, 0.9 Hz, 1H, H_aH$_b$C(4)), 3.15 (ddd, J = 15.7, 8.8, 1.4 Hz, 1H, H$_a$$H_b$C(4)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 169.6 (*C*(2)), 147.8 (*C*(8)), 135.4 (*C*(7)), 126.5 (*C*(6)), 124.1 (*C*(5)), 53.5 (*C*(1)), 52.9 (*C*(3)), 23.3 (*C*(2)).

Data was consistent with that previously reported.[148]

7-(Methoxycarbonyl)-2-methyl-5-oxo-5,6,7,8-tetrahydroimidazo[1,5-c]pyrimidin-2-ium iodide (692)

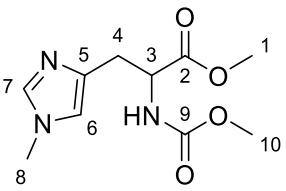


To a stirred solution of pyrimidine **691** (1.95 g, 10 mmol, 1.0 equiv.) in DMF (20 mL) at RT was added MeI (9.34 mL, 150 mmol, 15.0 equiv.) and the reaction heated to reflux for 3 h. The solution was then cooled to RT and diluted with Et_2O (100 mL). The mixture was refrigerated for 16 h, resulting in the formation of a precipitate which was filtered and washed with cold Et_2O to give the desired salt **692** (3.38 g, quant.) as a colourless, crystalline solid.

^{1}H NMR (400 MHz, D_2O) δ_H 9.41 (dd, J = 1.7, 0.9 Hz, 1H, *H*C(7)), 7.46 (t, J = 1.3 Hz, 1H, *H*C(6)), 4.79 (t, J = 5.8 Hz, 1H, *H*C(3)), 4.01 (s, 3H, H_3C(9)), 3.82 (s, 3H, H_3C(1)), 3.54 (dd, J = 5.6, 1.3 Hz, 2H, H_2C(4)); **^{13}C NMR** (101 MHz, D_2O) δ_C 172.3 (*C*(2)), 146.7 (*C*(8)), 136.1 (t, J = 33.7 Hz, *C*(7)), 129.4 (*C*(5)), 121.7 (*C*(6)), 54.8 (*C*(1)), 53.0 (*C*(3)), 37.7 (*C*(9)), 22.3 (*C*(4)).

Data was consistent with that previously reported.[148]

Methyl N^{α}-(methoxycarbonyl)-N^{τ}-methylhistidinate (693)



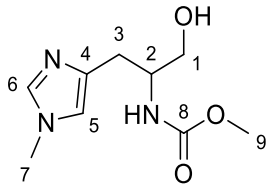
To a stirred solution of methylated salt **692** (2.70 g, 8 mmol, 1.0 equiv.) in MeOH (60 mL) at RT was added conc. H_2SO_4 (172 µL, 3.2 mmol, 0.4 equiv.) dropwise and the reaction heated to reflux for 4 h. The mixture was then cooled to RT and NaOMe (200 mg, 3.7 mmol, 0.46 equiv.) was added before the solution was concentrated *in vacuo* to a volume of approximately 15 mL. CH_2Cl_2 (15 mL) was added to dilute the mixture before being washed with a 1:1 mixture of sat. aq. $NaHCO_3$ and water (15 mL), dried

over Na_2SO_4 and concentrated *in vacuo* to give a colourless oil that solidified under high vacuum to give pure desired product **693** (1.44 g, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.32 (d, *J* = 1.4 Hz, 1H, *H*C(7)), 6.65 – 6.60 (m, 1H, *H*C(6)), 6.31 – 6.24 (m, 1H, *H*N), 4.55 (dt, *J* = 8.0, 5.1 Hz, 1H, *H*C(3)), 3.68 (s, 3H, H_3C(8)), 3.65 (s, 3H, H_3C(1)), 3.60 (s, 3H, H_3C(10)), 3.12 – 2.91 (m, 2H, H_2C(4)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 172.4 (*C*(2)), 156.9 (*C*(9)), 137.7 (*C*(7)), 137.5 (*C*(5)), 117.0 (*C*(6)), 54.1 (*C*(3)), 52.3 (*C*(1)), 52.2 (*C*(10)), 33.5 (*C*(8)), 30.0 (*C*(4)).

Data was consistent with that previously reported.[149]

Methyl (1-hydroxy-3-(1-methyl-1H-imidazol-4-yl)propan-2-yl)carbamate (694)

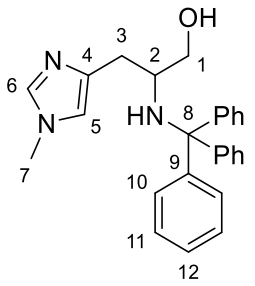


To a stirred solution of methylated histidinate **693** (1.33 g, 5.5 mmol, 1.0 equiv.) in THF (33 mL) and water (8 mL) at 0 °C was added $NaBH_4$ (1.05 g, 27.5 mmol, 5.0 equiv.) portionwise before being warmed to RT and left to stir for 1 h. The solution was then cooled to 0 °C and conc. aq. HCl (4.58 mL) was added dropwise, resulting in the evolution of H_2. K_2CO_3 was then added until the solution became saturated and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, 7M NH_3 in MeOH:CH_2Cl_2, 10:90) gave the desired compound **694** (419 mg, 36%) as a viscous oil that was highly prone to bumping.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33 (s, 1H, *H*C(6)), 6.67 (s, 1H, *H*C(5)), 5.61 (d, J = 8.2 Hz, 1H, *H*N), 4.41 (s, 1H, *H*O), 3.87 (dq, J = 8.7, 4.9 Hz, 1H, *H*C(2)), 3.72 (dd, J = 11.5, 3.6 Hz, 1H, H_aH_bC(1)), 3.62 (d, J = 1.6 Hz, 6H, H_3C(7) and H_3C(9)), 3.56 (dd, J = 11.5, 4.7 Hz, 1H, H_aH_bC(1)), 2.92 – 2.71 (m, 2H, H_2C(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 157.0 (*C*(8)), 137.8 (*C*(4)), 137.2 (*C*(6)), 118.4 (*C*(5)), 64.4 (*C*(1)), 52.6 (*C*(9)), 52.1 (*C*(2)), 33.5 (*C*(7)), 30.3 (*C*(3)).

Data was consistent with that previously reported.[149]

3-(1-Methyl-1H-imidazol-4-yl)-2-(tritylamino)propan-1-ol (695)

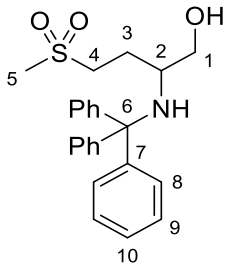


To a stirred solution of alcohol **694** (367 mg, 1.72 mmol, 1.0 equiv.) in water (20 mL) and MeOH (10 mL) at RT was added $Ba(OH)_2 \cdot 8H_2O$ (1.08 g, 3.44 mmol, 2.0 equiv.) before being heated to 90 °C and left to stir for 24 h, after which more $Ba(OH)_2 \cdot 8H_2O$ (0.54 g, 1.72 mmol, 1.0 equiv.) was added and the reaction stirred for a further 24 h. The mixture was then cooled to RT and dry ice was added, resulting in the formation of insoluble $BaCO_3$. The reaction was stirred for a further 2 h, after which it was filtered through a pad of celite and concentrated *in vacuo* to give the intermediate amino alcohol which was used without further purification. To a stirred solution of the aforementioned amino alcohol (374 mg, 1.72 mmol, 1.0 equiv.) in DMF (25 mL) at RT was added Et_3N (238 µL, 1.72 mmol, 1.0 equiv.) and the reaction heated to 50 °C. After being left to stir for 30 min, trityl chloride (480 mg, 1.72 mmol, 1.0 equiv.) was added and the reaction left to stir for 1 h. The reaction was then poured into water (50 mL) and placed in the freezer (–18 °C) for 2 h, resulting in formation of a precipitate. Filtration of the mixture afforded a crude solid which was purified by column chromatography (SiO_2, eluent load, 7M NH_3 in MeOH:CH_2Cl_2, 10:90) to give the desired compound **695** (350 mg, 51%) as a colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.63 – 7.51 (m, 6H, 6 × *H*C(10)), 7.26 (ddd, J = 7.9, 6.2, 1.3 Hz, 7H, 6 × *H*C(11) and *H*C(6)), 7.21 – 7.12 (m, 3H, 3 × *H*C(12)), 6.42 (d, J = 1.3 Hz, 1H, *H*C(5)), 3.58 (s, 3H, *H*C(7)), 3.42 (dd, J = 10.8, 2.9 Hz, 1H, $H_aH_bC(1)$), 2.97 – 2.83 (m, 2H, $H_aH_bC(1)$ and *H*C(2)), 2.45 – 2.36 (m, 1H, $H_aH_bC(3)$), 2.01 (dd, J = 14.5, 6.2 Hz, 1H, $H_aH_bC(3)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 147.3 (3 × *C*(9)), 139.4 (*C*(4)), 137.0 (*C*(6)), 128.9 (6 × *C*(10)), 127.9 (6 × *C*(11)), 126.4 (3 × *C*(12)), 118.2 (*C*(5)), 71.3 (*C*(8)), 65.1

(*C*(1)), 53.1 (*C*(2)), 33.4 (*C*(7)), 31.4 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 2981, 1510, 1489, 1448, 1216, 1159, 1031, 746, 706, 643, 621; **HRMS** (ESI$^+$) $C_{26}H_{28}ON_3$ requires 398.2227, found $[M+H]^+$ 398.2227 (Δ 0.07 ppm); **M.p.** 162 – 164 °C.

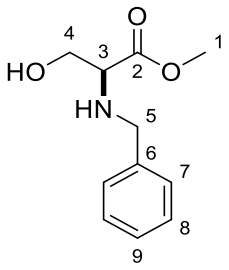
4-(Methylsulfonyl)-2-(tritylamino)butan-1-ol (697)



To a stirred solution of trityl methioninol **645** (285 mg, 0.76 mmol, 1.0 equiv.) in CH_2Cl_2 (7.5 mL) at RT was added *m*CPBA (357 mg, 77 wt. %, 1.59 mmol, 2.1 equiv.) and the reaction left to stir for 2 h after which the starting material was shown to have been consumed by TLC analysis (EtOAc:CH_2Cl_2, 25:75). To the mixture was added sat. aq. $NaHCO_3$ (1 mL) and the resulting mixture diluted with CH_2Cl_2 (10 mL). The layers were separated, and the organic phase washed with sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, EtOAc:CH_2Cl_2, 25:75) gave the desired alcohol **697** as a yellow gum (168 mg, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.59 – 7.50 (m, 6H, 6 × *H*C(8)), 7.32 – 7.26 (m, 6H, 6 × *H*C(9)), 7.24 – 7.18 (m, 3H, 3 × *H*C(10)), 3.20 (dd, J = 11.0, 3.0 Hz, 1H, $H_aH_bC(1)$), 2.94 (dtdd, J = 19.2, 14.1, 11.3, 5.3 Hz, 3H, $H_2C(4)$ and $H_aH_bC(1)$), 2.80 (dtd, J = 7.5, 4.4, 3.1 Hz, 1H, *H*C(2)), 2.75 (s, 3H, $H_3C(5)$), 1.84 (dddd, J = 12.7, 11.1, 7.5, 5.2 Hz, 1H, $H_aH_bC(3)$), 1.68 – 1.55 (m, 1H, $H_aH_bC(3)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 146.5 (3 × *C*(7)), 128.7 (6 × *C*(8)), 128.2 (6 × *C*(9)), 126.9 (3 × *C*(10)), 71.3 (*C*(6)), 64.0 (*C*(1)), 52.0 (*C*(2)), 51.8 (*C*(4)), 40.3 (*C*(5)), 26.7 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 1490, 1448, 1295, 1129, 749, 708; **HRMS** (ESI$^+$) $C_{24}H_{27}O_3NNaS$ requires 432.1604, found $[M+Na]^+$ 432.1604 (Δ –0.04 ppm); **M.p.** 122 – 124 °C.

Methyl benzyl-L-serinate (703)

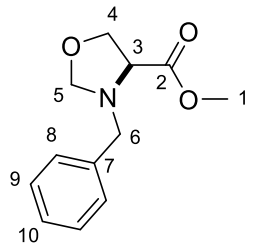


To stirring MeOH (50 mL) at RT was added acetyl chloride (8.62 mL, 120 mmol, 10 equiv.) dropwise and the resulting solution left to stir for 10 min. Commercially available *N*-benzyl-L-serine **702** (2.34 g, 12 mmol, 1.0 equiv.) was added portionwise and the reaction heated to reflux for 18 h. Upon cooling to RT, the reaction was cautiously quenched by the addition of sat. aq. $NaHCO_3$ (100 mL) and the resulting mixture extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 20:80) gave the desired methyl ester **703** (1.54 g, 49%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.27 – 7.08 (m, 5H, 5 × *H*C_{Ar}), 3.74 (dd, J = 13.0, 8.3 Hz, 1H, $H_a$$H_b$C(5)), 3.69 – 3.55 (m, 5H, $H_a$$H_b$C(4) and H_3C(1) and $H_a$$H_b$C(5)), 3.48 (dd, J = 10.8, 6.3 Hz, 1H, $H_a$$H_b$C(4)), 3.29 (ddd, J = 7.2, 6.0, 4.1 Hz, 1H, *H*C(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 173.6 (*C*(2)), 139.3 (*C*(6)), 128.7 (2 × C_{Ar}), 128.4 (2 × C_{Ar}), 127.5 (*C*(9)), 62.5 (*C*(5)), 62.0 (*C*(3)), 52.3 (*C*(2)), 52.2 (*C*(1)).

Data was consistent with that previously reported.[150]

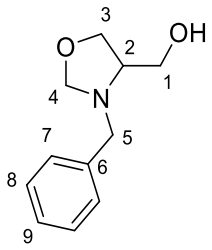
Methyl (*S*)-3-benzyloxazolidine-4-carboxylate (704)



To a stirred solution of benzylated serine **703** (1.25 g, 6 mmol, 1.0 equiv.), Na_2SO_4 (2.56 mg, 18 mmol, 3.0 equiv.) and DL-camphorsulfonic acid (278 mg, 1.2 mmol, 0.2 equiv.) in CH_2Cl_2 (60 mL) at RT was added 37% H_2CO in water (360 µL, 12 mmol, 2.0 equiv.) and the reaction left to stir for 2 h. The mixture was then filtered through a short pad of celite and the filtrate washed with 1M aq. NaOH (20 mL) and water (20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the pure product **704** (1.24 g, 94%) as a colourless oil.

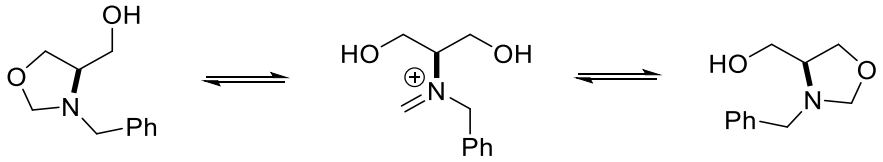
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40 – 7.36 (m, 2H, 2 × *H*C(8)), 7.32 (tt, J = 7.0, 1.1 Hz, 2H, 2 × *H*C(9)), 7.27 (tt, J = 6.4, 1.3 Hz, 1H, *H*C(10)), 4.43 (d, J = 1.1 Hz, 2H, H_2C(5)), 4.16 (tt, J = 8.2, 1.2 Hz, 1H, H_aH_bC(4)), 3.92 – 3.84 (m, 3H, H_aH_bC(4) and H_2C(6)), 3.73 – 3.65 (m, 4H, *H*C(3) and H_3C(1)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 172.5 (*C*(2)), 138.2 (*C*(7)), 128.9 (2 × *C*(8)), 128.6 (2 × *C*(9)), 127.6 (*C*(10)), 87.1 (*C*(5)), 67.3 (*C*(4)), 64.5 (*C*(3)), 58.8 (*C*(6)), 52.3 (*C*(1)); **IR** ν_{max} (film)/cm^{-1} 2953, 2887, 1736, 1454, 1437, 1200, 1177, 1049, 1013, 734, 700; **HRMS** (ESI$^+$) $C_{12}H_{16}O_3N$ requires 222.1125, found $[M+H]^+$ 222.1126 (Δ 0.49 ppm); **$[\alpha]_D^{25}$** = –29.3 (c = 1.00, $CHCl_3$).

(3-Benzyloxazolidin-4-yl)methanol (699)



Cyclic serine derivative **704** (940 mg, 4 mmol, 1.0 equiv.) was subjected to **General Procedure H**. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 50:50) gave the desired alcohol **699** (670 mg, 69%, 50:50 er) as a colourless solid.

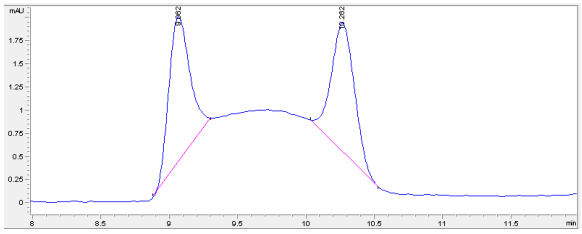
The product **699** was observed by HPLC analysis to be racemic, with the two enantiomers interconverting with a half-life of racemisation of 2.9 min, as determined by analysis of their characteristic "batman" profile. We propose that this was a result of **699** interconverting through achiral intermediate **706** to its enantiomer **ent-699**.



699 **706** **ent-699**

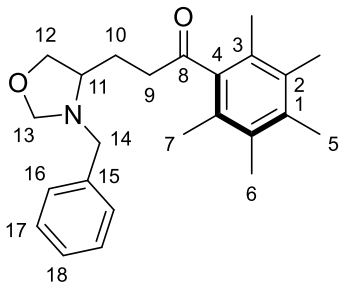
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40 – 7.24 (m, 5H, 5 × HC_{Ar}), 4.41 – 4.30 (m, 2H, $H_2C(4)$), 4.04 (dd, J = 8.4, 7.3 Hz, 1H, $H_aH_bC(1)$), 3.81 (s, 2H, $H_2C(5)$), 3.49 (dd, J = 8.4, 4.9 Hz, 1H, $H_aH_bC(1)$), 3.42 (dd, J = 6.1, 3.5 Hz, 2H, $H_2C(3)$), 3.27 (tt, J = 7.0, 5.2 Hz, 1H, $HC(2)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.7 ($C(6)$), 128.9 (2 × C_{Ar}), 128.7 (2 × C_{Ar}), 127.7 ($C(9)$), 85.7 ($C(4)$), 66.5 ($C(1)$), 64.8 ($C(2)$), 61.9 ($C(3)$), 59.2 ($C(5)$); **IR** ν_{max} (film)/cm^{-1} 2877, 1454, 1357, 1041, 1012, 699; **HRMS** (ESI^+) $C_{11}H_{16}O_2N$ requires 194.1176, found $[M+H]^+$ 194.1178 (Δ 1.09 ppm).

Chiral HPLC (Chiralpak IA with guard, 10.0 % IPA, 90.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.062	BB	16.8	1.6	0.1645	51.128	0.824
2	10.262	BB	16.1	1.4	0.1798	48.872	0.874

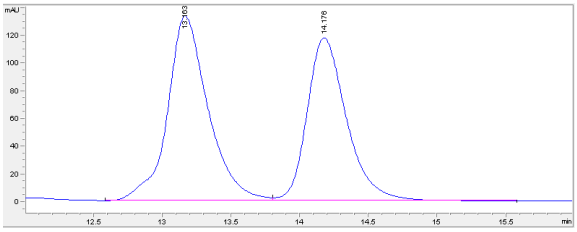
3-(3-Benzyloxazolidin-4-yl)-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one (705)



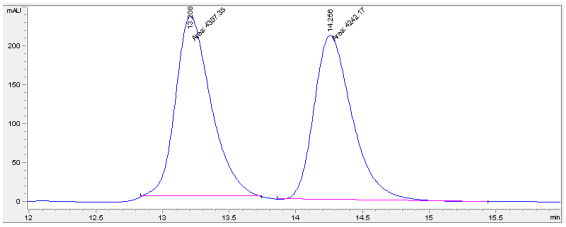
Benzyl cyclo serine **699** (116 mg, 0.6 mmol, 1.0 equiv.) was subjected to **General Procedure E** at 60 °C. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 80:20) gave the desired compound **705** (71 mg, 32%, 50:50 er) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.31 – 7.10 (m, 5H, 5 × HC_{Ar}), 4.21 (s, 2H, $H_2C(13)$), 4.01 (dd, J = 8.0, 6.9 Hz, 1H, $H_aH_bC(12)$), 3.65 (d, J = 1.7 Hz, 2H, $H_2C(14)$), 3.34 (dd, J = 8.0, 4.9 Hz, 1H, $H_aH_bC(12)$), 3.10 (ddt, J = 8.7, 6.9, 5.2 Hz, 1H, $HC(11)$), 2.77 (ddd, J = 18.6, 8.8, 5.6 Hz, 1H, $H_aH_bC(9)$), 2.64 (ddd, J = 18.6, 8.8, 6.4 Hz, 1H, $H_aH_bC(9)$), 2.16 (s, 3H, $H_3C(5)$), 2.10 (s, 6H, 2 × H_3CC_{Ar}), 1.99 (s, 6H, 2 × H_3CC_{Ar}), 1.85 – 1.67 (m, 2H, $H_2C(11)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 211.9 ($C(11)$), 140.7 (C_{Ar}), 139.3 (C_{Ar}), 135.6 (C_{Ar}), 133.2 (2 × C_{Ar}), 128.9 (2 × HC_{Ar}), 128.5 (2 × HC_{Ar}), 127.36 (d, J = 1.8 Hz, $C(18)$ and 2 × C_{Ar}), 85.5 ($C(13)$), 69.5 ($C(12)$), 63.2 ($C(11)$), 59.1 ($C(14)$), 42.5 ($C(9)$), 27.1 ($C(10)$), 17.3 (2 × H_3CC_{Ar}), 16.8 ($C(5)$), 16.1 (2 × H_3CC_{Ar}); **IR** ν_{max} (film)/cm^{-1} 2980, 1697, 1454, 1383, 1154, 1073, 699; **HRMS** (ESI$^+$) $C_{24}H_{32}O_2N$ requires 366.2428, found $[M+H]^+$ 366.2429 (Δ 0.28 ppm).

Chiral HPLC (Chiralpak IA with guard, 1.0 % IPA, 99.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

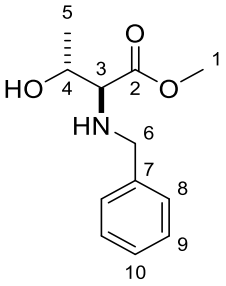


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.163	BV	2748.9	133	0.3031	53.862	0.758
2	14.176	VB	2354.7	117.3	0.3041	46.138	0.706



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	13.208	MM	4307.3	231.4	0.3103	50.381	0.716
2	14.256	FM	4242.2	210.8	0.3354	49.619	0.691

Methyl benzyl-L-threoninate (708)

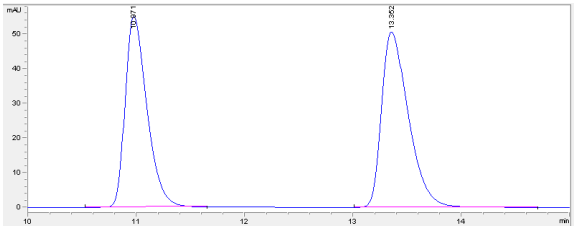


To a stirred solution of methyl L-threoninate hydrochloride **707** (2.51 g, 15 mmol, 1.0 equiv.) in glacial acetic acid (7.5 mL) and CH_2Cl_2 (12.5 mL) at RT were added benzaldehyde (3.06 mL, 30 mmol, 2.0 equiv.) and crushed 4Å molecular sieves (2.5 g), and the reaction left to stir for 1 h. The mixture was then cooled to 0 °C and $NaBH_3CN$ (1.89 g, 30 mmol, 2.0 equiv.) was added portionwise with substantial evolution of gas. The reaction was then warmed to RT and left to stir for 4 h before being carefully quenched by the slow addition of sat. aq. $NaHCO_3$ (100 mL) with further gas evolution being observed. The resulting mixture was then extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 50:50 to 30:70) gave the desired product **708** (1.60 g, 48%, >99:1 er) as a clear oil.

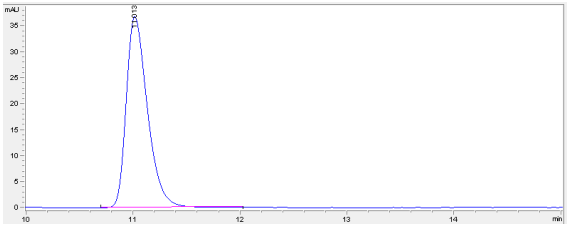
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40 – 7.26 (m, 5H, 5 × HC_{Ar}), 3.84 (d, J = 13.0 Hz, 1H, $H_aH_bC(6)$), 3.72 (s, 3H, $H_3C(1)$), 3.70 (d, J = 13.0 Hz, 1H, $H_aH_bC(6)$), 3.70 – 3.66 (m, 1H, $HC(4)$), 3.04 (d, J = 7.5 Hz, 1H, $HC(3)$),

1.20 (d, J = 6.2 Hz, 3H, H_3C(5)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 174.3 (*C*(2)), 139.3 (*C*(7)), 128.6 (2 × C_{Ar}), 128.5 (2 × C_{Ar}), 127.5 (*C*(10)), 68.2 (*C*(4)), 67.5 (*C*(3)), 52.8 (*C*(6)), 52.1 (*C*(1)), 19.4 (*C*(5)).

Chiral HPLC (Chiralpak IA with guard, 5.0 % IPA, 95.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).



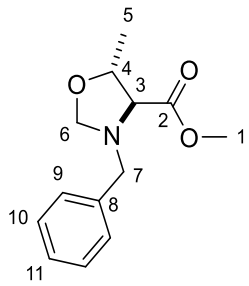
#	Time	Type	Area	Height	Width	Area%	Symmetry
1	10.971	BB	767.2	55.2	0.2143	47.076	0.605
2	13.352	BB	862.5	50.6	0.2607	52.924	0.57



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	11.013	BB	509.8	36.9	0.2112	100.000	0.63

Data was consistent with that previously reported.[151]

Methyl (2*S*,3*R*)-1-benzyl-3-methylpyrrolidine-2-carboxylate (709)

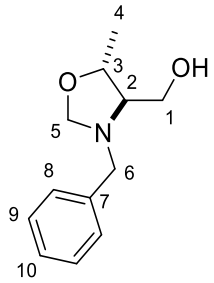


To a stirred solution of benzylated threonine methyl ester **708** (1.34g, 6 mmol, 1.0 equiv.), Na_2SO_4 (2.56 g, 18 mmol, 3.0 equiv.) and camphorsulfonic acid (278 mg, 1.2 mmol, 0.2 equiv.) in CH_2Cl_2 (60 mL) at RT was added formaldehyde (37% solution in water, 0.97 mL, 12 mmol, 2.0 equiv.) and the reaction left to stir for 16 h. The reaction mixture was then filtered through a pad of celite (eluting with CH_2Cl_2) and the resulting solution washed with 1M aq. NaOH (30 mL) and water (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 83:17) gave the desired compound **709** (1.34 g, 94%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.30 – 7.19 (m, 5H, 5 × HC_{Ar}), 4.42 (d, J = 5.3 Hz, 1H, $H_aH_bC(7)$), 4.36 (d, J = 5.3 Hz, 1H, $H_aH_bC(7)$), 4.01 (p, J = 6.2 Hz, 1H, *H*C(4)), 3.84 (s, 2H, $H_2C(6)$), 3.61 (s, 3H, $H_3C(1)$), 3.10

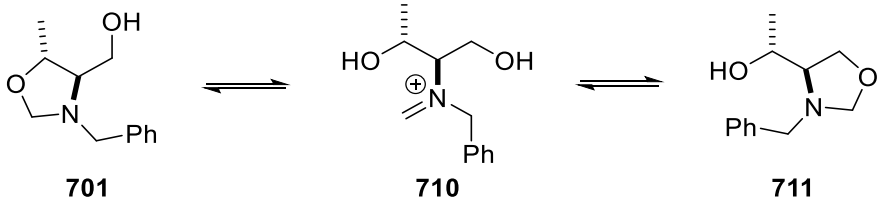
(d, J = 6.7 Hz, 1H, *H*C(3)), 1.38 (d, J = 6.1 Hz, 3H, *H*$_3$C(5)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 172.3 (*C*(2)), 138.1 (*C*(8)), 129.0 (2 × *C*(9)), 128.6 (2 × *C*(10)), 127.6 (*C*(11)), 86.6 (*C*(7)), 77.3 (*C*(4)), 71.6 (*C*(3)), 59.5 (*C*(6)), 52.3 (*C*(1)), 20.3 (*C*(5)); **IR** ν_{max} (film)/cm^{-1} 2871, 1734, 1278, 1198, 1171, 1073, 749, 699; **HRMS** (ESI$^+$) $C_{13}H_{18}O_3N$ requires 236.1281, found $[M+H]^+$ 236.1282 (Δ 0.29 ppm); **$[\alpha]_D^{25}$** = –56.7 (c = 1.00, $CHCl_3$).

((4*R*,5*R*)-3-Benzyl-5-methyloxazolidin-4-yl)methanol (701)



Cyclic threonine derivative **709** (940 mg, 4 mmol, 1.0 equiv.) was subjected to **General Procedure H**. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 70:30) gave the desired alcohol **701** (769 mg, 93%, >99:1 er) as a colourless oil.

The product **701** was observed (in CD_2Cl_2) to exist in an approximately 4:1 equilibrium ratio with its structural isomer **711**, presumably interconverting through intermediate **710** on a timescale too slow to be detectable by NMR spectroscopy, but clearly visible by HPLC analysis with a characteristic asymmetric “batman” profile.

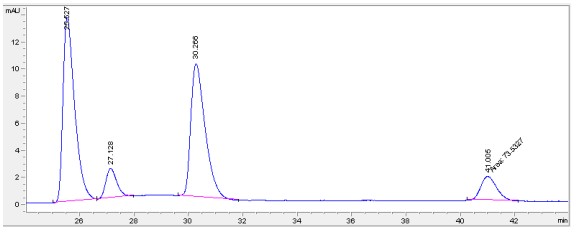


701 **710** **711**

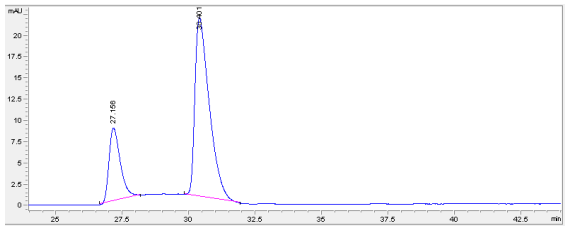
^{1}H NMR (CD_2Cl_2, 400 MHz) δ_H = 7.41 – 7.23 (m, 6H, 5 × *H*C$_{Ar}$ (*major*) and 5 × *H*C$_{Ar}$ (*minor*)), 4.36 (d, *J* = 6.6 Hz, 0.2H, *H$_a$*H$_b$C(5) (*minor*)), 4.32 (s, 2H, *H*$_2$C(5)), 4.18 (d, *J* = 6.6 Hz, 0.2H, H$_a$*H$_b$*C(5) (*minor*)), 3.99 (dd, *J* = 8.4, 7.0 Hz, 0.2H, *H$_a$*H$_b$C(1) (*minor*)), 3.90 – 3.81 (m, 2H, *H*$_2$C(6) (*major*)), 3.81 – 3.74 (m, 2H,

H_2C(1) (*major*)), 3.48 – 3.33 (m, 2H, *H*C(3) (*major*), H_aH_bC(1) (*minor*) and *H*C(3) (*minor*)), 2.91 (ddd, *J* = 8.9, 7.0, 4.2 Hz, 0.2H, *H*C(2) (*minor*)), 2.65 (ddd, *J* = 6.4, 5.4, 4.5 Hz, 1H, *H*C(2) (*major*)), 1.35 (d, *J* = 6.2 Hz, 3H, H_3C(4) (*major*)), 1.03 (d, *J* = 6.1 Hz, 0.7H, H_3C(4) (*minor*)); **^{13}C NMR** (CD_2Cl_2, 101 MHz) δ_C = 139.70 (*C*(7) (*minor*)), 139.67 (*C*(7) (*major*)), 129.5 (2 × C_{Ar} (*minor*)), 129.3 (2 × C_{Ar} (*major*)), 129.04 (2 × C_{Ar} (*minor*)), 129.00 (2 × C_{Ar} (*major*)), 128.0 (*C*(10) (*minor*)), 127.9 (*C*(10) (*major*)), 86.1 (*C*(5) (*major*)), 85.4 (*C*(5) (*minor*)), 76.2 (*C*(3) (*major*)), 72.3 (*C*(2) (*major*)), 71.6 (*C*(2) (*minor*)), 67.6 (*C*(3) (*minor*)), 66.2 (*C*(6) (*minor*)), 61.3 (*C*(6) (*major*)), 60.8 (*C*(1) (*minor*)), 60.0 (*C*(1) (*major*)), 20.3 (*C*(1) (*major*)), 19.1 (*C*(1) (*minor*)); **IR** ν_{max} (film)/cm^{-1} 3435 (br.), 2870, 1454, 1381, 1071, 1027, 700; **HRMS** (ESI$^+$) $C_{12}H_{18}O_2N$ requires 208.1332, found $[M+H]^+$ 208.1333 (Δ 0.46 ppm); **$[\alpha]_D^{25}$** = –16.1 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 1.0 % IPA, 99.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

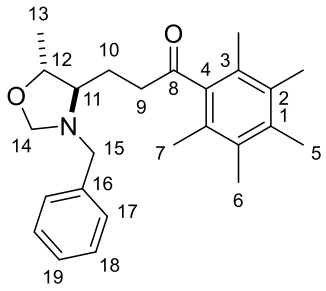


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	25.527	BB	410.1	13.6	0.4506	45.144	0.529
2	27.128	BB	61.6	2.2	0.4207	6.776	0.759
3	30.266	BB	363.2	9.9	0.5355	39.984	0.528
4	41.005	MM	73.5	1.8	0.6783	8.095	0.782



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	27.156	BB	257.6	8.7	0.4504	24.414	0.613
2	30.401	BB	797.5	21.1	0.5526	75.586	0.433

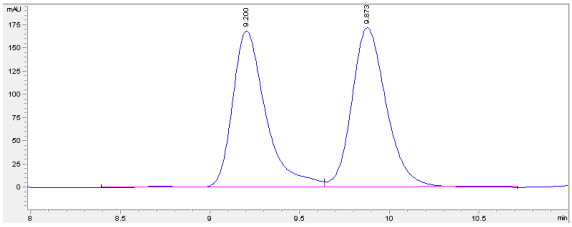
3-((4*R*,5*R*)-3-Benzyl-5-methyloxazolidin-4-yl)-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one (712)



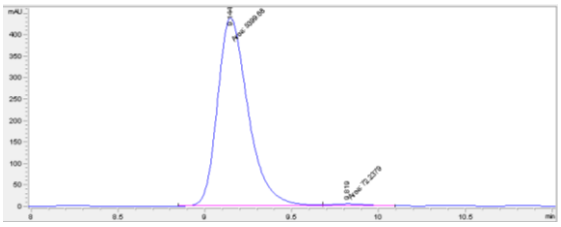
Benzyl cyclo threonine **701** (62 mg, 0.3 mmol, 1.0 equiv.) was subjected to **General Procedure E**. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 80:20) gave the desired compound **712** (64 mg, 56%, 99:1 er) as a pale brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 – 7.20 (m, 5H, 5 × *H*C$_{Ar}$), 4.29 (s, 2H, *H*$_2$C(14)), 3.80 (d, J = 1.7 Hz, 2H, *H*$_2$C(15)), 3.68 (p, J = 6.1 Hz, 1H, *H*C(12)), 2.87 (ddd, J = 18.5, 9.1, 5.8 Hz, 1H, *H*$_a$H$_b$C(9)), 2.75 (ddd, J = 18.5, 9.1, 6.2 Hz, 1H, H$_a$*H*$_b$C(9)), 2.63 (ddd, J = 7.8, 6.2, 5.2 Hz, 1H, *H*C(11)), 2.25 (s, 3H, *H*$_3$C(5)), 2.20 (s, 6H, 2 × *H*$_3$CC$_{Ar}$), 2.10 (s, 6H, 2 × *H*$_3$CC$_{Ar}$), 1.97 – 1.80 (m, 2H, *H*$_2$C(10)), 1.42 (d, J = 6.1 Hz, 3H, *H*$_3$C(13)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 212.0 (*C*(8)), 140.8 (*C*$_{Ar}$), 139.5 (*C*$_{Ar}$), 135.5 (*C*$_{Ar}$), 133.2 (2 × *C*$_{Ar}$), 128.8 (2 × H*C*$_{Ar}$), 128.4 (2 × H*C*$_{Ar}$), 127.4 (*C*(19)), 127.3 (2 × *C*$_{Ar}$), 85.1 (*C*(14)), 78.8 (*C*(12)), 70.3 (*C*(11)), 59.8 (*C*(15)), 42.4 (*C*(9)), 26.2 (*C*(10)), 20.5 (*C*(13)), 17.4 (2 × H$_3$*C*C$_{Ar}$), 16.8 (*C*(5)), 16.1 (2 × H$_3$*C*C$_{Ar}$); **IR** ν_{max} (film)/cm^{-1} 2970, 2926, 1698, 1453, 1381, 1071, 998, 699; **HRMS** (ESI$^+$) $C_{25}H_{34}O_2N$ requires 380.2584, found [M+H]$^+$ 380.2585 (Δ 0.29 ppm); **M.p.** 84 – 86 °C; **$[\alpha]_D^{25}$** = –2.5 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 1.0 % IPA, 99.0 % hexane, 1.0 mL/min, 25 °C, λ = 210 nm, 10 µL injection).

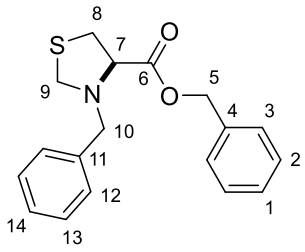


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.2	VV R	2198.5	169.1	0.1942	48.716	0.693
2	9.873	VB	2314.3	172.6	0.2045	51.284	0.766



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.144	MF	5399.7	439.5	0.2048	98.680	0
2	9.819	FM	72.2	5.2	0.2311	1.320	0.812

Benzyl (*R*)-3-benzylthiazolidine-4-carboxylate (715)



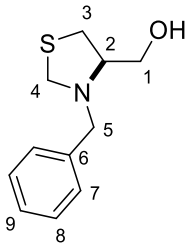
To a stirred solution of L-thioproline **714** (2.66 g, 20 mmol, 1.0 equiv.) and K_2CO_3 (6.90 g, 50 mmol, 2.5 equiv.) in DMF (60 mL) at RT was added BnBr (4.75 mL, 40 mmol, 2.0 equiv.) and the reaction left to stir for 20 h. Water (60 mL) and Et_2O (30 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (3 × 30 mL) and the combined organic layers washed with brine (3 × 20 mL),

dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 95:5) gave the desired compound **715** (4.00 g, 64%) as a pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.45 – 7.22 (m, 10H, 10 × *H*C_{Ar}), 5.16 (s, 2H, *H*$_2$C(5)), 4.29 (d, J = 9.5 Hz, 1H, *H*$_a$H$_b$C(9)), 4.05 (ddd, J = 10.5, 8.4, 2.1 Hz, 2H, *H*C(7) and H$_a$*H*$_b$C(9)), 3.75 (d, J = 13.2 Hz, 1H, *H*$_a$H$_b$C(10)), 3.65 (d, J = 13.2 Hz, 1H, H$_a$*H*$_b$C(10)), 3.30 (dd, J = 10.9, 3.2 Hz, 1H, *H*$_a$H$_b$C(8)), 3.20 (dd, J = 10.9, 7.4 Hz, 1H, H$_a$*H*$_b$C(8)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 170.8 (*C*(6)), 137.9 (*C*$_{Ar}$), 135.6 (*C*$_{Ar}$), 129.0 (2 × *C*$_{Ar}$), 128.7 (2 × *C*$_{Ar}$), 128.6 (2 × *C*$_{Ar}$), 128.5 (*C*$_{Ar}$), 128.2 (2 × *C*$_{Ar}$), 127.7 (*C*$_{Ar}$), 69.3 (*C*(7)), 67.0 (*C*(5)), 59.2 (*C*(9)), 58.0 (*C*(10)), 32.6 (*C*(8)).

Data was consistent with that previously reported.[152]

(*R*)-(3-Benzylthiazolidin-4-yl)methanol (716)



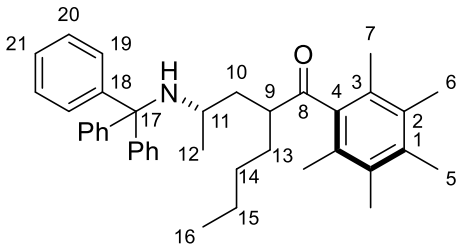
To a stirred solution of $CaCl_2$ (555 mg, 5 mmol, 1.0 equiv.) in EtOH (7.5 mL) and THF (15 mL) at –20 °C was added $NaBH_4$ (380 mg, 10 mmol, 2.0 equiv.) portionwise and the reaction left to stir for 10 min. To this was added a solution of crude benzyl ester **715** (1.57 g, 5 mmol, 1.0 equiv.) in THF (15 mL) and the reaction warmed to 0 °C over the course of 3 h, before being warmed to RT and left to stir for 2 h. To the reaction was added sat. aq. NH_4Cl (15 mL) and water (15 mL) and the resulting mixture extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give a crude oil. Purification by column chromatography (SiO_2, eluent load, pentane:EtOAc, 70:30) gave the desired compound **716** (734 mg, 71%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.36 – 7.17 (m, 5H, 5 × *H*C_{Ar}), 4.00 (d, J = 10.3 Hz, 1H, *H*$_a$H$_b$C(4)), 3.90 (dd, J = 10.3, 0.9 Hz, 1H, H$_a$*H*$_b$C(4)), 3.69 – 3.58 (m, 2H, *H*$_a$H$_b$C(5) and *H*C(2)), 3.53 (d, J = 13.0 Hz, 1H,

$H_aH_bC(5)$), 3.39 – 3.25 (m, 2H, $H_2C(1)$), 3.01 (dd, J = 10.7, 6.9 Hz, 1H, $H_aH_bC(3)$), 2.62 – 2.54 (m, 1H, $H_aH_bC(3)$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.1 (*C*(6)), 129.0 (2 × C_{Ar}), 128.6 (2 × C_{Ar}), 127.6 (*C*(9)), 70.0 (*C*(2)), 61.6 (*C*(1)), 58.4 (*C*(5)), 56.9 (*C*(4)), 31.4 (*C*(3)).

Data was consistent with that previously reported.[153]

1-(2,3,4,5,6-Pentamethylphenyl)-2-((*S*)-2-(tritylamino)propyl)hexan-1-one (718 and 719)



To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added alanine hydrogen borrowing product **620** (196 mg, 0.4 mmol, 1.0 equiv.), $[(cod)IrCl_2]_2$ (2.7 mg, 0.004 mmol, 1.0 mol%), 1,2-bis(diphenylphosphanyl)benzene (3.6 mg, 0.008 mmol, 2.0 mol%), KOH (45 mg, 0.8 mmol, 2.0 equiv.) and *n*BuOH (296 µL, 0.8 mmol, 10.0 equiv.) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a ResealTM septum) and purged with Ar for 5 min using a balloon. The vial was heated to the required temperature (105 °C) in a preheated oil bath for 24 h. The mixture was cooled to RT, filtered through a SiO_2 plug (eluting with Et_2O) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0.015-0.040 mm, eluent load, pentane:Et_2O, 95:5) provided the desired compound (74 mg, 34%) as two separable C9 diastereomers **718** and **719**, both being fluffy and colourless solids.

718 (29 mg, 13%)

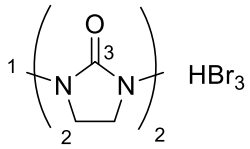
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.53 – 7.43 (m, 6H, 6 × *H*C(19)), 7.29 – 7.19 (m, 6H, 6 × *H*C(20)), 7.19 – 7.11 (m, 3H, 3 × *H*C(21)), 2.75 (dt, J = 7.1, 5.1 Hz, 1H, *H*C(9)), 2.44 (h, J = 6.3 Hz, 1H, *H*C(11)), 2.26 (s, 3H, $H_3C(5)$), 2.17 (s, 6H, 2 × H_3CC_{Ar}), 2.04 – 1.91 (m, 7H, 2 × H_3CC_{Ar} and $H_aH_bC(10)$), 1.58 – 1.53 (m, 1H, $H_aH_bC(13)$), 1.46 – 1.33 (m, 1H, $H_aH_bC(10)$), 1.20 – 1.12 (m, 5H, $H_aH_bC(13)$ and $H_2C(14)$ and $H_2C(15)$),

0.88 – 0.79 (m, 3H, H_3C(16)), 0.52 (d, J = 6.2 Hz, 3H, H_3C(12)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 213.6 (*C*(8)), 147.2 (3 × *C*(18)), 139.9 (C_{Ar}), 135.5 (C_{Ar}), 133.1 (2 × C_{Ar}), 129.0 (6 × *C*(19)), 128.6 (2 × C_{Ar}), 127.7 (6 × *C*(20)), 126.3 (3 × *C*(21)), 71.0 (*C*(17)), 50.9 (*C*(9)), 47.2 (*C*(11)), 39.7 (*C*(10)), 30.1 (*C*(13)), 29.5 (*C*(14)), 23.2 (*C*(15)), 22.9 (*C*(12)), 18.0 (2 × H_3*C*CAr), 16.9 (*C*(5)), 16.2 (2 × H_3*C*CAr), 14.1 (*C*(16)); **IR** ν_{max} (film)/cm^{-1} 2935, 2147, 1720, 1554, 1444, 1182, 821, 740, 706; **HRMS** (ESI$^+$) $C_{39}H_{48}ON$ requires 546.3730, found $[M+H]^+$ 546.3732 (Δ 3.60 ppm); **M.p.** 46 – 48 °C.

719 (45 mg, 21%)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.57 – 7.44 (m, 6H, 6 × *H*C(19)), 7.28 – 7.20 (m, 6H, 6 × *H*C(20)), 7.20 – 7.12 (m, 3H, 3 × *H*C(21)), 2.58 (dddd, J = 20.2, 9.9, 6.7, 3.5 Hz, 2H, *H*C(9) and *H*C(11)), 2.22 (s, 3H, H_3C(5)), 2.16 (s, 6H, 2 × H_3CC_{Ar}), 2.01 (s, 6H, 2 × H_3CC_{Ar}), 1.52 – 1.37 (m, 3H, H_2C(10) and H_aH_bC(13)), 1.21 – 1.06 (m, 5H, H_aH_bC(13) and H_2C(14) and H_2C(15)), 0.80 (t, J = 7.0 Hz, 3H, H_3C(16)), 0.53 (d, J = 6.2 Hz, 3H, H_3C(12)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 213.9 (*C*(8)), 147.2 (3 × *C*(18)), 139.9 (C_{Ar}), 135.4 (C_{Ar}), 133.1 (2 × C_{Ar}), 129.0 (6 × *C*(19)), 127.9 (6 × *C*(20)), 127.7 (2 × C_{Ar}), 126.4 (3 × *C*(21)), 71.6 (*C*(17)), 50.9 (*C*(9)), 47.0 (*C*(11)), 39.3 (*C*(10)), 29.3 (*C*(14)), 28.4 (*C*(13)), 23.2 (*C*(15)), 21.5 (*C*(12)), 18.0 (2 × H_3*C*CAr), 16.9 (*C*(5)), 16.2 (2 × H_3*C*CAr), 14.0 (*C*(16)); **IR** ν_{max} (film)/cm^{-1} 2931, 2160, 1721, 1691, 1449, 1185, 746, 704; **HRMS** (ESI$^+$) $C_{39}H_{48}ON$ requires 546.3730, found $[M+H]^+$ 546.3730 (Δ 0.01 ppm); **M.p.** 60 – 62 °C.

Bis (1,3-dimethyl-2-imidazolidinone) hydrotribromide (724)



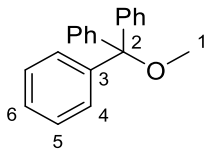
Following the literature procedure, a stirred solution of 1,3-dimethyl-2-imidazolidinone **723** (4.30 mL, 40 mmol, 4.0 equiv.) in Et_2O (40 mL) was cooled to 0 °C and Br_2 (0.52 mL, 10 mmol, 1.0 equiv.) was added dropwise, resulting in the formation of an orange precipitate. The reaction was left to stir for 1 h at 0 °C. Et_2O (60 mL) was then added and the resulting suspension was filtered, and the precipitate

washed with additional Et_2O (3 × 20 mL) to give the desired product **724** (2.86 g, 90%) as a bright orange crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.59 (s, 4H, 2 × *H*$_2$C(2)), 2.89 (s, 6H, 2 × *H*$_3$C(1)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 161.4 (*C*(3), 46.2 (2 × *C*(2)), 31.9 (2 × *C*(1)).

Data was consistent with that previously reported.[117]

(Methoxymethanetriyl)tribenzene (725)

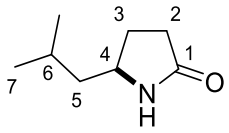


To a stirred solution of hydrogen borrowing product **620** (105 mg, 0.2 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 mL) at RT was added Br_2 source **724** (93 mg, 0.2 mmol, 1.0 equiv.) and the reaction left to stir for 20 min, after which TLC analysis (pentane:Et_2O, 90:10) showed full consumption of the starting material. MeOH (800 µL, 20 mmol, 100 equiv.) was added and the left to stir for 30 min, before being filtered through a short silica plug (eluting with MeOH) and concentrated *in vacuo* to give the product **725** (57 mg, quant.) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.50 – 7.43 (m, 6H, 6 × *H*C(4)), 7.34 – 7.29 (m, 6H, 6 × *H*C(4)), 7.28 – 7.21 (m, 3H, 3 × *H*C(6)), 3.08 (s, 3H, *H*$_3$C(1)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 144.1 (3 × *C*(3)), 128.9 (6 × C_{Ar}), 128.0 (6 × C_{Ar}), 127.0 (3 × *C*(6)), 87.2 (*C*(2)), 52.2 (*C*(1)).

Data was consistent with that previously reported.[154]

(*R*)-5-Isobutylpyrrolidin-2-one (727)

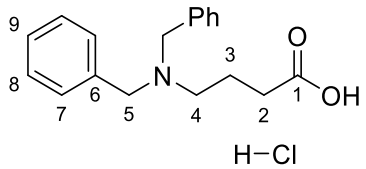


To a stirred solution of hydrogen borrowing product **664** (80 mg, 0.15 mmol, 1.0 equiv.) in CH_2Cl_2 (0.75 mL) at RT was added 2M HCl in Et_2O (150 µL, 0.3 mmol, 2.0 equiv.) and the reaction left to stir for 4 h until the formation of a precipitate turned the solution cloudy. Br_2 (23 µL, 0.45 mmol, 3.0 equiv.) was then added and the reaction left to stir for 15 min, after which DBU (228 µL, 1.5 mmol, 10 equiv.) was added and the reaction stirred for a further 1 h. The reaction mixture was then passed through a short plug of silica, eluting with CH_2Cl_2, before being concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, MeOH:CH_2Cl_2, 5:95) gave the desired amide **727** as a colourless oil (13 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.71 (p, J = 6.8 Hz, 1H, *H*C(4)), 2.35 – 2.28 (m, 2H, H_2C(2)), 2.25 – 2.22 (m, 1H, H_aH$_b$C(3)), 1.77 – 1.56 (m, 2H, *H*C(6) and H$_a$$H_b$C(3)), 1.45 (ddd, J = 14.0, 7.6, 6.6 Hz, 1H, H_aH$_b$C(5)), 1.32 (ddd, *J* = 13.7, 7.7, 6.2 Hz, 1H, H$_a$$H_b$C(5)), 0.92 (d, J = 6.6 Hz, 6H, H_3C(7) and H_3C(7')); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 178.3 (*C*(1)), 52.8 (*C*(4)), 46.1 (*C*(5)), 30.3 (*C*(2)), 28.0 (*C*(3)), 25.5 (*C*(6)), 23.0 (*C*(7)), 22.5 (*C*(7')).

Data was consistent with that previously reported.[155]

4-(Dibenzylamino)butanoic acid hydrochloride (730)

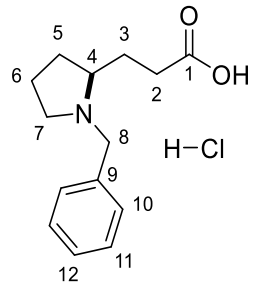


Glycine-derived hydrogen borrowing product **312** (41 mg, 0.1 mmol, 1.0 equiv.) was subjected to **General Procedure I** to give the desired compound **730** (32 mg, 99%) as a thick, clear oil.

^{1}H NMR (400 MHz, D_2O) δ_H 7.58 – 7.40 (m, 10H, 10 × *H*C_{Ar}), 4.38 (d, J = 5.9 Hz, 4H, 2 × *H*$_2$C(5)), 3.20 – 3.12 (m, 2H, *H*$_2$C(4)), 2.38 (t, J = 6.9 Hz, 2H, *H*$_2$C(2)), 2.04 (dq, J = 11.9, 6.9 Hz, 2H, *H*$_2$C(3)); **^{13}C NMR** (101 MHz, D_2O) δ_C 176.7 (*C*(1)), 131.0 (2 × *C*$_{Ar}$), 130.2 (*C*(9)), 129.4 (2 × *C*$_{Ar}$), 129.0 (*C*(6)), 57.2 (2 × *C*(5)), 51.3 (*C*(4)), 30.5 (*C*(2)), 18.6 (*C*(3)); **IR** ν_{max} (film)/cm^{-1} 2950 (br.), 1720, 1456, 1210, 1177, 741, 699; **HRMS** (ESI$^+$) $C_{18}H_{22}O_2N$ requires 284.1645, found $[M+H]^+$ 284.1642 (Δ –1.24 ppm).

Data was consistent with that previously reported.[156]

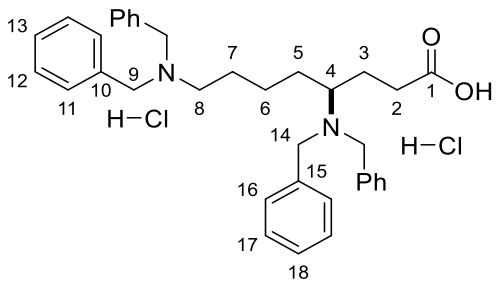
(*S*)-3-(1-Benzylpyrrolidin-2-yl)propanoic acid hydrochloride (731)



Proline-derived hydrogen borrowing product **553** (73 mg, 0.2 mmol, 1.0 equiv.) was subjected to **General Procedure I** to give the desired compound **731** (52 mg, 97%) as a pale yellow solid.

^{1}H NMR (400 MHz, D_2O) δ_H 7.57 – 7.43 (m, 5H, 5 × *H*C_{Ar}), 4.49 (d, J = 13.0 Hz, 1H, *H*$_a$H$_b$C(8)), 4.24 (d, J = 13.0 Hz, 1H, H$_a$*H*$_b$C(8)), 3.59 (dtd, J = 10.1, 8.0, 4.3 Hz, 1H, *H*C(4)), 3.43 (ddd, J = 11.7, 7.6, 5.5 Hz, 1H, *H*$_a$H$_b$C(7)), 3.26 (dt, J = 11.7, 8.0 Hz, 1H, H$_a$*H*$_b$C(7)), 2.50 – 2.30 (m, 3H, *H*$_2$C(2) and *H*$_a$H$_b$C(3)), 2.15 – 2.01 (m, 2H, *H*$_a$H$_b$C(6) and *H*$_a$H$_b$C(5)), 1.95 (dtd, J = 13.5, 8.0, 5.7 Hz, 1H, H$_a$*H*$_b$C(6)), 1.88 – 1.70 (m, 2H, H$_a$*H*$_b$C(3) and H$_a$*H*$_b$C(5)); **^{13}C NMR** (101 MHz, D_2O) δ_C 176.5 (*C*(1)), 130.6 (2 × *C*$_{Ar}$), 130.1 (*C*(12)), 129.9 (*C*(9)), 129.4 (2 × *C*$_{Ar}$), 66.7 (*C*(4)), 57.5 (*C*(8)), 54.1 (*C*(7)), 30.2 (*C*(2)), 28.9 (*C*(5)), 26.1 (*C*(3)), 21.4 (*C*(6)); **IR** ν_{max} (film)/cm^{-1} 3345, 2963 (br.), 1619, 1543, 1461, 1378, 1071, 1049, 719, 645; **HRMS** (ESI$^+$) $C_{14}H_{20}O_2N$ requires 234.1489, found $[M+H]^+$ 234.1490 (Δ 0.50 ppm); **M.p.** 160 – 162 °C; **$[\alpha]_D^{25}$** = –18.1 (c = 1.00, MeOH).

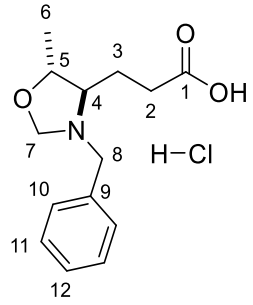
(*S*)-4,8-Bis(dibenzylamino)octanoic acid dihydrochloride (732)



Lysine-derived hydrogen borrowing product **592** (134 mg, 0.2 mmol, 1.0 equiv.) was subjected to **General Procedure I** to give the desired compound **732** (104 mg, 86%) as an opaque gum.

^{1}H NMR (D_2O, 400 MHz) δ_H = 7.56 – 7.44 (m, 18H, 18 × *H*C_{Ar}), 7.29 (d, *J* = 7.3 Hz, 2H, 2 × *H*C_{Ar}), 4.60 (d, *J* = 13.3 Hz, 1H, $H_a$$H_b$C(14)), 4.47 – 4.27 (m, 6H, H_2C(14') and 2 × H_2C(9)), 4.21 (d, *J* = 13.3 Hz, 1H, $H_a$$H_b$C(14)), 3.09 (dt, *J* = 10.6, 6.0 Hz, 3H, *H*C(4) and H_2C(2)), 2.62 – 2.50 (m, 1H, $H_a$$H_b$C(8)), 2.35 – 2.20 (m, 2H, $H_a$$H_b$C(8) and $H_a$$H_b$C(7)), 1.91 (td, *J* = 11.2, 6.8 Hz, 2H, $H_a$$H_b$C(7) and $H_a$$H_b$C(3)), 1.81 – 1.59 (m, 3H, $H_a$$H_b$C(3) and H_2C(5)), 1.38 – 1.26 (m, 1H, $H_a$$H_b$C(6)), 1.20 (q, *J* = 8.5 Hz, 1H, $H_a$$H_b$C(6)); **^{13}C NMR** ($D_2O$, 101 MHz) δ_C = 177.9 (*C*(1)), 131.0 (C_{Ar}), 130.8 (C_{Ar}), 130.6 (C_{Ar}), 130.19 (C_{Ar}), 130.16 (C_{Ar}), 129.8 (C_{Ar}), 129.7 (C_{Ar}), 129.4 (C_{Ar}), 129.3 (C_{Ar}), 129.0 (C_{Ar}), 62.1 (*C*(4)), 57.3 (2 × *C*(14) or *C*(19)), 54.8 (*C*(14) or *C*(19)), 53.9 (*C*(14') or *C*(19')), 51.3 (*C*(8)), 31.6 (*C*(2)), 27.3 (*C*(7)), 23.6 (*C*(3)), 22.9 (*C*(5)), 22.7 (*C*(6)); **IR** (film) ν_{max}/cm^{-1} = 3398, 2981 (br.), 1458, 1024, 1002, 756, 702; **HRMS** (ESI$^+$) $C_{36}H_{43}O_2N_2$ requires 535.3319, found $[M+H]^+$ = 535.3320 (Δ 0.24 ppm); **$[\alpha]_D^{25}$** = +4.1 (c = 1.00, MeOH).

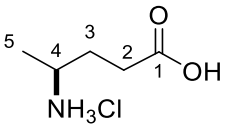
3-((4*R*,5*R*)-3-Benzyl-5-methyloxazolidin-4-yl)propanoic acid hydrochloride (733)



Threonine-derived hydrogen borrowing product **712** (76 mg, 0.2 mmol, 1.0 equiv.) was subjected to **General Procedure I** to give the desired compound **733** (20 mg, 37%) as a colourless residue.

^{1}H NMR (D_2O, 400 MHz) δ_H = 7.61 – 7.43 (m, 5H, 5 × HC_{Ar}), 5.09 (d, *J* = 6.6 Hz, 1H, $H_aH_bC(8)$), 4.85 (d, *J* = 6.6 Hz, 1H, $H_aH_bC(8)$), 4.58 (d, *J* = 13.0 Hz, 1H, $H_aH_bC(7)$), 4.41 (d, *J* = 13.0 Hz, 1H, $H_aH_bC(7)$), 4.13 (dq, *J* = 7.5, 6.2 Hz, 1H, *H*C(5)), 3.41 (dt, *J* = 7.5, 6.9 Hz, 1H, *H*C(4)), 2.26 – 2.07 (m, 2H, $H_2C(2)$), 1.90 (qd, *J* = 6.9, 2.7 Hz, 2H, $H_2C(3)$), 1.48 (d, *J* = 6.2 Hz, 3H, $H_3C(6)$); **^{13}C NMR** (D_2O, 101 MHz) δ_C = 176.1 (*C*(1)), 130.9 (2 × HC_{Ar}), 130.5 (*C*(12)), 129.6 (2 × HC_{Ar}), 129.0 (*C*(9)), 83.3 (*C*(8)), 81.3 (*C*(5)), 68.8 (*C*(4)), 58.6 (*C*(7)), 29.2 (*C*(2)), 24.0 (*C*(3)), 17.2 (*C*(6)); **IR** (film) ν_{max}/cm^{-1} = 3374, 2981 (br.), 1720, 1394, 750, 702; **HRMS** (ESI$^+$) $C_{14}H_{20}O_3N$ requires 250.1438, found $[M+H]^+$ = 250.1437 (Δ –0.31 ppm); **$[\alpha]_D^{25}$** = –7.3 (c = 1.00, MeOH).

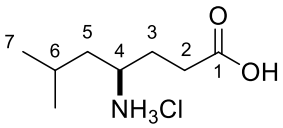
(*S*)-4-Aminopentanoic acid hydrochloride (734)



Alanine-derived hydrogen borrowing product **620** (49 mg, 0.1 mmol, 1.0 equiv.) was subjected to **General Procedure I** to give the desired compound **734** (15 mg, 99%) as a colourless powder.

^{1}H NMR (D_2O, 400 MHz) δ_H = 3.41 (h, *J* = 6.7 Hz, 1H, *H*C(4)), 2.52 (dt, *J* = 8.2, 6.7 Hz, 2H, $H_2C(2)$), 1.99 (dddd, *J* = 14.1, 8.3, 7.0, 5.8 Hz, 1H, $H_aH_bC(3)$), 1.84 (dtd, *J* = 14.7, 8.0, 5.8 Hz, 1H, $H_aH_bC(3)$), 1.30 (d, *J* = 6.7 Hz, 3H, $H_3C(5)$); **^{13}C NMR** (D_2O, 101 MHz) δ_C = 177.0 (*C*(1)), 47.1 (*C*(4)), 29.8 (*C*(2)), 28.9 (*C*(3)), 17.3 (*C*(5)); **IR** (film) ν_{max}/cm^{-1} = 2940 (br.), 1714, 1603, 1508, 1407, 1376, 1191, 1131, 800, 649; **HRMS** (ESI$^+$) $C_5H_{12}O_2N$ requires 118.0863, found $[M+H]^+$ = 118.0865 (Δ 1.75 ppm); **M.p.** = 155 – 157 °C; **$[\alpha]_D^{25}$** = –4.0 (c = 1.00, MeOH).

(*R*)-4-Amino-6-methylheptanoic acid hydrochloride (735)

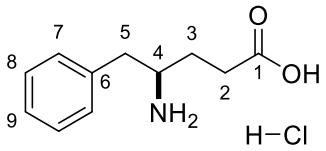


Leucine-derived hydrogen borrowing product **664** (266 mg, 0.5 mmol, 1.0 equiv.) was subjected to **General Procedure I** to give the desired compound **735** (79 mg, 81%) as a colourless powder.

^{1}H NMR (D_2O, 400 MHz) δ_H = 3.39 (p, *J* = 6.7 Hz, 1H, *H*C(4)), 2.55 (t, *J* = 7.5 Hz, 2H, H_2C(2)), 2.05 – 1.85 (m, 2H, H_2C(3)), 1.70 (dh, *J* = 13.3, 6.7 Hz, 1H, *H*C(6)), 1.58 – 1.44 (m, 2H, H_2C(5)), 0.93 (dd, *J* = 6.7, 3.1 Hz, 6H, 2 × H_3C(7)); **^{13}C NMR** (D_2O, 101 MHz) δ_C = 177.1 (*C*(1)), 49.4 (*C*(4)), 40.9 (*C*(5)), 29.5 (*C*(2)), 27.4 (*C*(3)), 23.8 (*C*(6)), 21.7 (*C*(17)), 21.2 (*C*(17')); **IR** (film) ν_{max}/cm^{-1} = 2981 (br.), 2888, 1700, 1385, 1245, 1157, 953, 705; **HRMS** (ESI$^+$) $C_8H_{18}O_2N$ requires 160.1332, found $[M+H]^+$ = 160.1332 (Δ 0.11 ppm); **M.p.** = 144 – 146 °C; **$[\alpha]_D^{25}$** = –0.8 (c = 1.00, MeOH).

Data was consistent with that previously reported.[157]

(*R*)-4-Amino-5-phenylpentanoic acid hydrochloride (736)

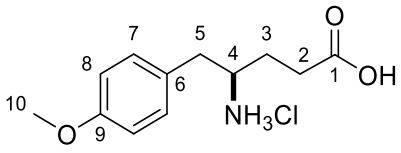


Phenylalanine-derived hydrogen borrowing product **665** (104 mg, 0.2 mmol, 1.0 equiv.) was subjected to **General Procedure I** to give the desired compound **736** (43 mg, 94%) as a tan solid.

^{1}H NMR (400 MHz, D_2O) δ_H 7.51 – 7.29 (m, 5H, 5 × *H*C_{Ar}), 3.63 (dq, J = 8.0, 6.5 Hz, 1H, *H*C(4)), 3.09 (dd, J = 14.2, 6.3 Hz, 1H, H_aH_bC(5)), 2.92 (dd, J = 14.3, 8.0 Hz, 1H, H_aH_bC(5)), 2.57 (dd, J = 8.1, 7.0 Hz, 2H, H_2C(2)), 1.99 (dddd, J = 8.4, 7.5, 6.5, 2.0 Hz, 2H, H_2C(3)); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 176.8 (*C*(1)), 135.5 (*C*(6)), 129.4 (2 × C_{Ar}), 129.1 (2 × C_{Ar}), 127.6 (*C*(9)), 52.4 (*C*(4)), 37.9 (*C*(5)), 29.7 (*C*(2)), 27.0 (*C*(3)); **IR** (film) ν_{max}/cm^{-1} = 2916 (br.), 1715, 1690, 1485, 1373, 1231, 1217, 860, 741, 724, 691, 642; **HRMS** (ESI$^+$) $C_{11}H_{16}O_2N$ requires 194.1176, found $[M+H]^+$ = 194.1179 (Δ 1.77 ppm); **M.p.** = 75 – 77 °C; **$[\alpha]_D^{25}$** = –18.1 (c = 1.00, MeOH).

Data was consistent with that previously reported.[158]

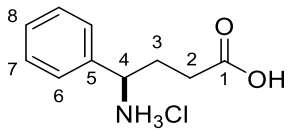
(*R*)-4-Amino-5-(4-methoxyphenyl)pentanoic acid hydrochloride (737)



Tyrosine-derived hydrogen borrowing product **689** (119 mg, 0.2 mmol, 1.0 equiv.) was subjected to **General Procedure I** to give the desired compound **737** (43 mg, 83%) as a thick, clear oil.

^{1}H NMR (D_2O, 400 MHz) δ_H = 7.31 – 7.21 (m, 2H, 2 × *H*C(7)), 7.03 – 6.99 (m, 2H, 2 × *H*C(8)), 3.83 (s, 3H, H_3C(10)), 3.58 (dd, *J* = 7.8, 6.3 Hz, 1H, *H*C(4)), 3.02 (dd, *J* = 14.3, 6.3 Hz, 1H, $H_a$$H_b$C(5)), 2.86 (dd, *J* = 14.3, 7.8 Hz, 1H, $H_a$$H_b$C(5)), 2.55 (dd, *J* = 8.3, 6.7 Hz, 2H, H_2C(2)), 1.97 (dddd, *J* = 8.3, 7.8, 6.7, 2.1 Hz, 2H, H_2C(3)); **^{13}C NMR** (D_2O, 101 MHz) δ_C = 176.8 (*C*(1)), 158.2 (*C*(9)), 130.7 (2 × *C*(7)), 128.0 (*C*(6)), 114.6 (2 × *C*(8)), 55.4 (*C*(10)), 52.5 (*C*(4)), 37.1 (*C*(5)), 29.7 (*C*(2)), 26.9 (*C*(3)); **IR** (film) ν_{max}/cm^{-1} = 2935 (br.), 1711, 1612, 1512, 1247, 908, 729; **HRMS** (ESI^+) $C_{12}H_{18}O_3N$ requires 224.1281, found $[M+H]^+$ = 224.1283 (Δ 0.99 ppm); **$[\alpha]_D^{25}$** = –0.4 (c = 1.00, MeOH).

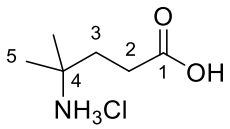
(R)-4-Amino-4-phenylbutanoic acid hydrochloride (739)



Phenylglycine-derived hydrogen borrowing product **673** (110 mg, 0.2 mmol, 1.0 equiv.) was subjected to **General Procedure I** to give the desired compound **739** (42 mg, 98%) as a colourless powder.

^{1}H NMR (D_2O, 400 MHz) δ_H = 7.60 – 7.43 (m, 5H, 5 × *H*C_{Ar}), 4.44 (td, *J* = 5.9, 3.4 Hz, 1H, *H*C(4)), 2.47 – 2.23 (m, 4H, H_2C(2) and H_2C(3)); **^{13}C NMR** (D_2O, 101 MHz) δ_c = 176.6 (*C*(1)), 135.2 (*C*(5)), 129.7 (*C*(8)), 129.4 (2 × C_{Ar}), 127.4 (2 × C_{Ar}), 54.7 (*C*(4)), 29.9 (*C*(2)), 28.4 (*C*(3)); **IR** (film) ν_{max}/cm^{-1} = 2904 (br.), 1719, 1498, 1413, 1217, 1177, 1126, 821, 765, 697; **HRMS** (ESI^+) $C_{10}H_{14}O_2N$ requires 180.1019, found $[M+H]^+$ = 180.1020 (Δ 0.73 ppm); **M.p.** = 195–197 °C; **$[\alpha]_D^{25}$** = –17.5 (c = 1.00, MeOH).

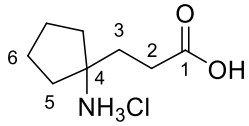
4-Amino-4-methylpentanoic acid hydrochloride (740)



Dimethyl hydrogen borrowing product **677** (80 mg, 0.16 mmol, 1.0 equiv.) was subjected to **General Procedure I** to give the desired compound **740** (26 mg, 97%) as a colourless powder.

^{1}H NMR (D_2O, 400 MHz) δ_H = 2.51 (t, *J* = 8.1 Hz, 2H, H_2C(2)), 1.97 (t, *J* = 8.1 Hz, 2H, H_2C(3)), 1.35 (s, 6H, 2 × H_3C(5)); **^{13}C NMR** (D_2O, 101 MHz) δ_C = 177.3 (*C*(1)), 53.9 (*C*(4)), 34.3 (*C*(3)), 28.5 (*C*(2)), 24.1 (2 × *C*(5)); **IR** (film) ν_{max}/cm^{-1} = 2932 (br.), 1706, 1414, 1189, 843, 648; **HRMS** (ESI$^+$) $C_6H_{14}O_2N$ requires 132.1019, found $[M+H]^+$ = 132.1019 (Δ –0.28 ppm); **M.p.** = 170 – 172 °C.

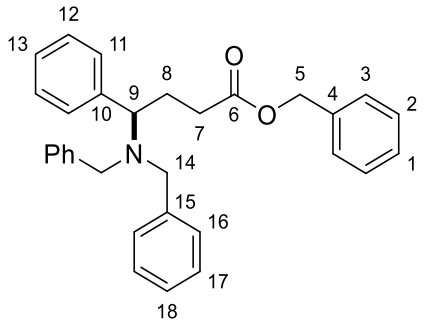
3-(1-Aminocyclopentyl)propanoic acid hydrochloride (741)



Cycloleucine-derived hydrogen borrowing product **678** (106 mg, 0.2 mmol, 1.0 equiv.) was subjected to **General Procedure I** to give the desired compound **741** (28 mg, 90%) as a colourless powder.

^{1}H NMR (D_2O, 400 MHz) δ_H = 2.56 (t, *J* = 7.9 Hz, 2H, H_2C(2)), 2.08 (t, *J* = 7.9 Hz, 2H, H_2C(3)), 1.95 – 1.73 (m, 8H, 2 × H_2C(5) and 2 × H_2C(6)); **^{13}C NMR** (D_2O, 101 MHz) δ_C = 177.3 (*C*(1)), 64.1 (*C*(4)), 35.8 (2 × *C*(5)), 32.4 (*C*(3)), 28.9 (*C*(2)), 23.7 (2 × *C*(6)); **IR** (film) ν_{max}/cm^{-1} = 2879 (br.), 1742, 1704, 1580, 1522, 1410, 1214, 1191, 886; **HRMS** (ESI$^+$) $C_8H_{16}O_2N$ requires 158.1176, found $[M+H]^+$ = 158.1175 (Δ –0.17 ppm); **M.p.** = 184–186 °C.

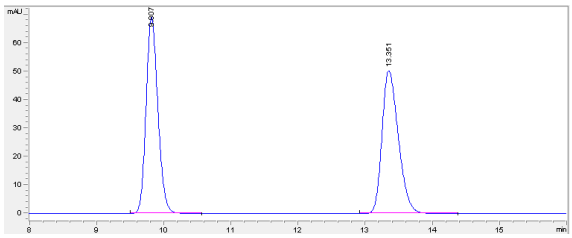
Benzyl (*R*)-4-(dibenzylamino)-4-phenylbutanoate (742)



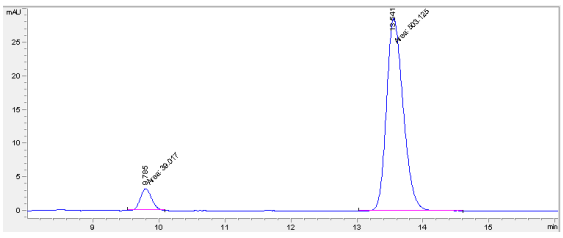
To a stirred suspension of phenylglycine derived cleavage product **739** (11 mg, 0.05 mmol, 1.0 equiv.) and K_2CO_3 (28 mg, 0.2 mmol, 4.0 equiv.) in MeCN (1 mL) at RT was added benzyl bromide (20 µL, 0.175 mmol, 3.5 equiv.). The resulting solution was then warmed to 80 °C and left to stir for 16 h. The reaction mixture was then cooled to RT and water (3 mL) was added. The resulting mixture was then extracted with EtOAc (3 × 4 mL), and the organic extracts washed with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 95:5) gave the desired compound **742** (18 mg, 80%, 93:7 er) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.34 (m, 16H, 16 × *H*C_{Ar}), 7.25 – 7.18 (m, 4H, 4 × *H*C_{Ar}), 5.04 (dd, *J* = 19.0, 12.2 Hz, 2H, *H*$_2$C(5)), 3.85 (d, *J* = 13.8 Hz, 2H, 2 × *H*$_a$H$_b$C(14)), 3.70 (t, *J* = 7.0 Hz, 1H, *H*C(9)), 3.12 (d, *J* = 13.8 Hz, 2H, 2 × H$_a$*H*$_b$C(14)), 2.63 – 2.52 (m, 1H, *H*$_a$H$_b$C(7)), 2.51 – 2.32 (m, 2H, *H*$_a$H$_b$C(8) and H$_a$*H*$_b$C(7)), 2.16 – 2.03 (m, 1H, H$_a$*H*$_b$C(8)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 173.6 (*C*(6)), 140.1 (2 × *C*(15)), 138.0 (*C*$_{Ar}$), 136.2 (*C*$_{Ar}$), 129.1 (2 × *C*$_{Ar}$), 128.9 (4 × *C*$_{Ar}$), 128.7 (2 × *C*$_{Ar}$), 128.44 (4 × *C*$_{Ar}$), 128.36 (2 × *C*$_{Ar}$), 128.3 (*C*$_{Ar}$), 128.2 (2 × *C*$_{Ar}$), 127.5 (*C*$_{Ar}$), 127.0 (2 × *C*$_{Ar}$), 66.3 (*C*(5)), 61.4 (*C*(9)), 53.7 (2 × *C*(14)), 32.0 (*C*(7)), 26.7 (*C*(8)); **IR** (film) ν_{max}/cm^{-1} = 2980, 1734, 1494, 1454, 1158, 746, 698; **HRMS** (ESI$^+$) $C_{31}H_{32}O_2N$ requires 450.2428, found [M+H]$^+$ = 450.2425 (Δ –0.52 ppm); **[α]$_D^{25}$** = +37.2 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 1.0 % IPA, 99.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).

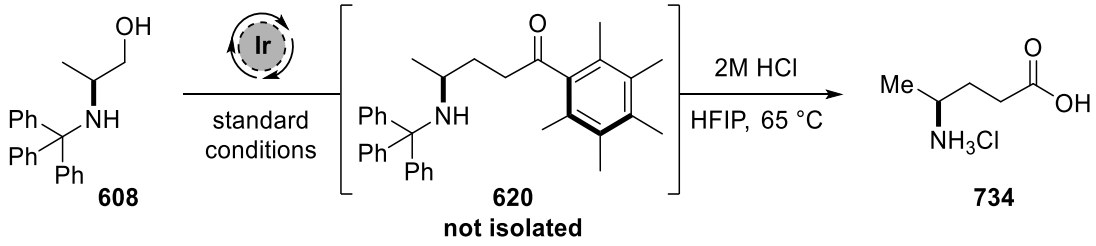


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.807	BB	844.2	69	0.1888	49.697	0.799
2	13.351	BB	854.5	50.3	0.2622	50.303	0.679

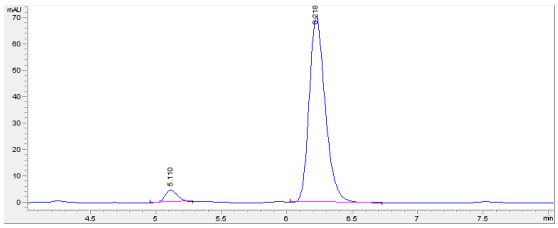


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	9.785	MM	39	3.2	0.2004	7.197	0.88
2	13.541	MM	503.1	28.6	0.2932	92.803	0.745

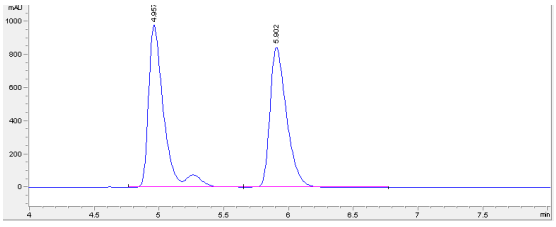
Chromatography-free two-step reaction to form 734



A 10–20 mL Biotage® microwave vial equipped with a stirrer bar, was sequentially charged with the trityl protected alaninol **608** (1.27 g, 4.0 mmol, 1.0 equiv.), pentamethylacetophenone **100** (1.14 g, 6.0 mmol, 1.5 equiv.), $[Cp^*IrCl_2]_2$ (64 mg, 0.08 mmol, 2 mol%), NaO^tBu (192 mg, 2.0 mmol, 0.5 equiv.), and *tert*-butanol (1.6 mL). The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum), pierced with a needle attached to a nitrogen balloon, and the vial was heated to 85 in a preheated oil bath for 16 h. The mixture was cooled to RT and filtered through a SiO_2 plug, eluting with Et_2O (100 mL). The resulting solution was then washed with water (2 × 50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a crude black tar that was used for the next step without further purification. An aliquot was removed, purified by small-scale preparative TLC (pentane:Et_2O, 95:5), and subjected to HPLC analysis to determine the er of intermediate **620** to be 95:5 (Chiralpak IA with guard, 5.0 % IPA, 95.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	5.11	BB	30.8	4.6	0.1018	4.858	0.787
2	6.218	BB	603.3	70.9	0.1293	95.142	0.739

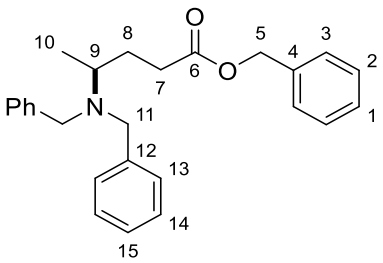


#	Time	Type	Area	Height	Width	Area%	Symmetry
1	4.957	BV R	8113.7	979.2	0.1134	51.864	0.566
2	5.902	BV R	7530.6	842.7	0.1361	48.136	0.592

In a 10–20 mL Biotage® microwave vial equipped with a stirrer bar, the crude hydrogen borrowing product **620** was dissolved in HFIP (35.2 mL) and conc. HCl (5.2 mL) was added. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and heated at 65 °C for 48 h. The reaction was then cooled to RT and diluted by the addition of water (30 mL). The mixture was then washed with Et_2O (3 × 50 mL) and concentrated *in vacuo* to give a tan solid. ^1H analysis found the product to be contaminated with detritylated, but Ph* containing, **620** in an 11:1 ratio. The crude product was therefore recrystallised from boiling EtOH:Et_2O to give the pure desired product **734** (571 mg, 92%) as fluffy white crystals.

To establish the er of the cleavage product **734**, it was perbenzylated and analysed by chiral HPLC in a similar manner to the procedure used for cleavage product **739** to give compound **742**.

Benzyl (*S*)-4-(dibenzylamino)pentanoate, (745)

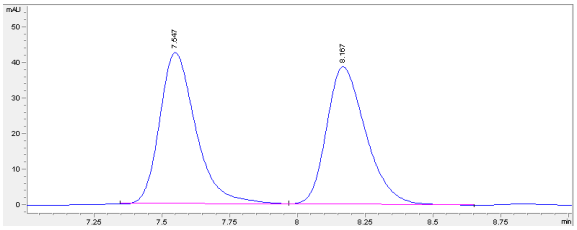


To a stirred suspension of alanine derived cleavage product **734** (153 mg, 1.0 mmol, 1.0 equiv.) and K_2CO_3 (552 mg, 4.0 mmol, 4.0 equiv.) in MeCN (10 mL) at RT was added benzyl bromide (416 µL, 3.5

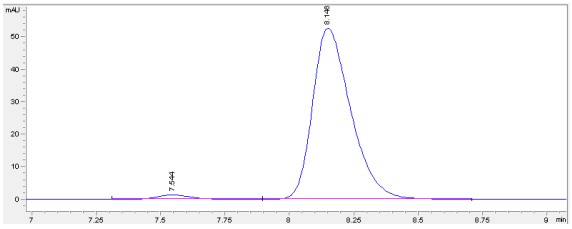
mmol, 3.5 equiv.). The resulting solution was then warmed to 80 °C and left to stir for 16 h. The reaction mixture was then cooled to RT and water (10 mL) was added. The resulting mixture was then extracted with EtOAc (3 × 15 mL), and the organic extracts washed with brine (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, pentane:Et_2O, 95:5) gave the desired compound **745** (329 mg, 85%, 98:2 er) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H = 7.47 – 7.11 (m, 15H, 15 × *H*C_{Ar}), 5.13 – 4.98 (m, 2H, *H*$_2$C(5)), 3.75 (dd, *J* = 13.8, 3.4 Hz, 2H, 2 × *H*$_a$H$_b$C(11)), 3.38 (dt, *J* = 13.8, 2.4 Hz, 2H, 2 × H$_a$*H*$_b$C(11)), 2.75 (dddd, *J* = 11.6, 9.5, 6.4, 3.9 Hz, 1H, *H*C(9)), 2.66 – 2.52 (m, 1H, *H*$_a$H$_b$C(7)), 2.42 – 2.28 (m, 1H, H$_a$*H*$_b$C(7)), 1.98 – 1.83 (m, 1H, *H*$_a$H$_b$C(8)), 1.72 – 1.54 (m, 1H, H$_a$*H*$_b$C(8)), 1.09 – 1.01 (m, 3H, *H*$_3$C(10)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ_C = 173.9 (*C*(6)), 140.4 (2 × *C*(12)), 136.3 (C(4)), 128.9 (4 × *C*$_{Ar}$), 128.7 (2 × *C*$_{Ar}$), 128.33 (*C*(1) and 4 × *C*$_{Ar}$), 128.28 (2 × *C*$_{Ar}$), 126.9 (2 × *C*$_{Ar}$), 66.2 (*C*(5)), 53.3 (2 × *C*(11)), 52.1 (*C*(9)), 31.8 (*C*(7)), 29.1 (*C*(8)), 13.0 (*C*(10)); **IR** (film) ν_{max}/cm^{-1} = 1733, 1494, 1454, 1166, 743, 696; **HRMS** (ESI$^+$) $C_{26}H_{30}O_2N$ requires 388.2271, found [M+H]$^+$ = 388.2278 (Δ 1.90 ppm); **[α]$_D^{25}$** = –9.9 (c = 1.00, $CHCl_3$).

Chiral HPLC (Chiralpak IA with guard, 1.0 % IPA, 99.0 % hexane, 1.0 mL/min, 25 °C, λ = 254 nm, 10 µL injection).



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.547	BV	399.2	42.7	0.1431	50.502	0.697
2	8.167	VB	391.3	38.8	0.1537	49.498	0.689



#	Time	Type	Area	Height	Width	Area%	Symmetry
1	7.544	BB	12.3	1.3	0.1408	2.207	0.818
2	8.146	BB	543.8	52.9	0.158	97.793	0.642

Appendix 1: X-Ray Crystallographic Data

A1.1 Compound 312

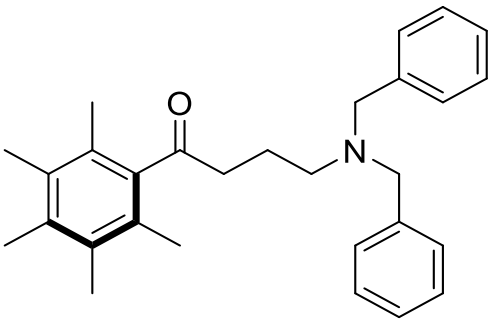


Table A1.1. Crystal data and structure refinement for 7293

Identification code	7293	
Empirical formula	C29 H35 N O	
Formula weight	413.60	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 9.3539(2) Å	α = 65.117(3)°
	b = 16.4296(5) Å	β = 85.500(2)°
	c = 17.3084(6) Å	γ = 88.814(2)°
Volume	2405.38(14) $Å^3$	
Z	4	
Density (calculated)	1.142 Mg/m^3	
Absorption coefficient	0.517 mm^{-1}	
F(000)	896	
Crystal size	0.24 × 0.18 × 0.11 mm^3	

Theta range for data collection	2.823 to 77.156°.
Index ranges	-10<=h<=11, -18<=k<=20, -21<=l<=21
Reflections collected	19873
Independent reflections	10028 [R(int) = 0.019]
Completeness to theta = 74.841°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.94 and 0.89
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10026 / 0 / 560
Goodness-of-fit on F^2	1.0069
Final R indices [I>2sigma(I)]	R1 = 0.0452, wR2 = 0.1197
R indices (all data)	R1 = 0.0515, wR2 = 0.1263
Extinction coefficient	27(6)
Largest diff. peak and hole	0.27 and -0.30 e.$Å^{-3}$

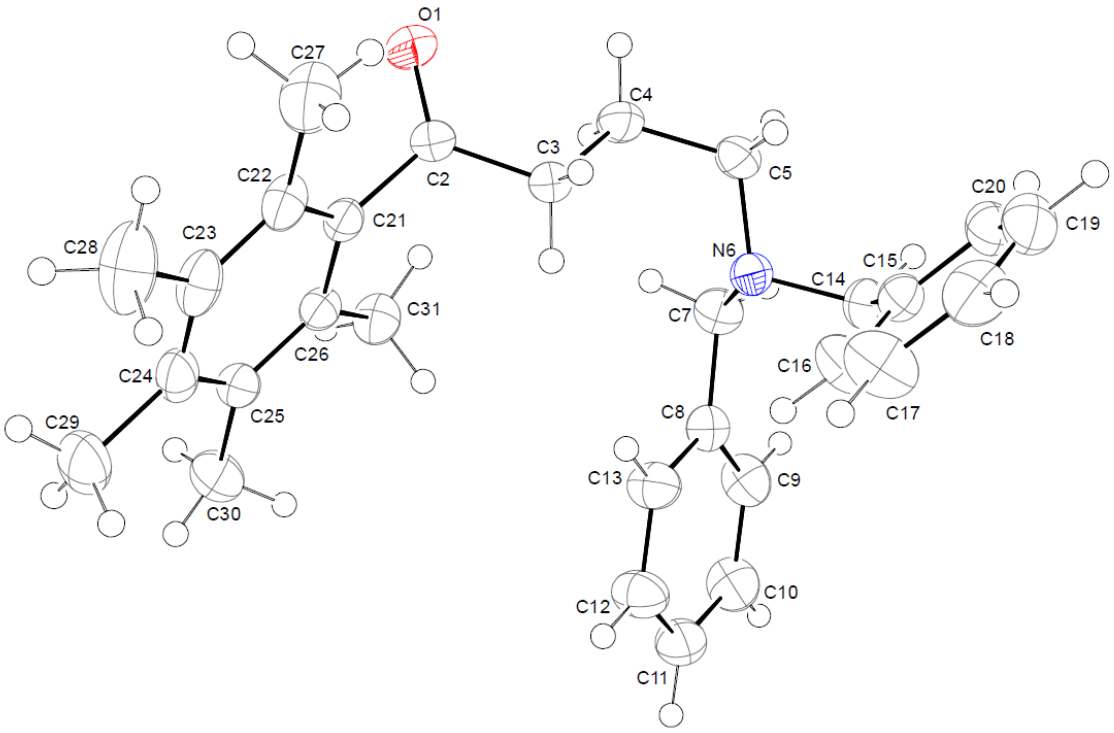


Table A1.2. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2 x10^3$) for 7293. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	9286(1)	4599(1)	2017(1)	60
C(2)	8404(1)	5077(1)	1564(1)	35
C(3)	8637(1)	6079(1)	1101(1)	30
C(4)	9609(1)	6454(1)	1539(1)	36
C(5)	9935(1)	7451(1)	1025(1)	37
N(6)	8649(1)	7993(1)	761(1)	31
C(7)	7786(2)	8040(1)	1487(1)	38
C(8)	6310(1)	8406(1)	1254(1)	34
C(9)	5712(2)	9037(1)	1513(1)	43
C(10)	4333(2)	9347(1)	1322(1)	48
C(11)	3533(2)	9029(1)	873(1)	45
C(12)	4117(2)	8401(1)	606(1)	47
C(13)	5494(2)	8094(1)	793(1)	41
C(14)	9059(2)	8899(1)	129(1)	35
C(15)	9559(1)	8926(1)	-732(1)	35
C(16)	8641(2)	8644(1)	-1165(1)	49
C(17)	9059(2)	8688(1)	-1966(1)	58
C(18)	10406(2)	9013(1)	-2348(1)	53
C(19)	11334(2)	9282(1)	-1921(1)	50
C(20)	10915(2)	9240(1)	-1118(1)	43
C(21)	7063(1)	4692(1)	1414(1)	29
C(22)	7158(2)	4167(1)	951(1)	37
C(23)	5892(2)	3840(1)	796(1)	41
C(24)	4560(2)	4024(1)	1112(1)	39
C(25)	4485(1)	4538(1)	1586(1)	35
C(26)	5745(1)	4877(1)	1737(1)	29
C(27)	8592(2)	3962(1)	612(1)	61
C(28)	5970(3)	3283(1)	284(1)	65
C(29)	3200(2)	3662(1)	945(1)	60

C(30)	3072(2)	4744(1)	1949(1)	55
C(31)	5669(2)	5406(1)	2274(1)	39
O(51)	5727(1)	6943(1)	3556(1)	75
C(52)	6599(2)	6856(1)	4065(1)	42
C(53)	6189(1)	6881(1)	4914(1)	40
C(54)	4688(1)	7232(1)	4989(1)	33
C(55)	4370(1)	7229(1)	5863(1)	33
N(56)	3029(1)	7672(1)	5956(1)	30
C(57)	1772(1)	7167(1)	5922(1)	35
C(58)	398(1)	7675(1)	5908(1)	32
C(59)	-737(1)	7283(1)	6514(1)	36
C(60)	-2003(1)	7749(1)	6499(1)	37
C(61)	-2142(1)	8613(1)	5883(1)	38
C(62)	-1013(2)	9008(1)	5278(1)	42
C(63)	251(2)	8544(1)	5292(1)	38
C(64)	2974(1)	7744(1)	6774(1)	33
C(65)	3838(1)	8528(1)	6735(1)	29
C(66)	3785(1)	9367(1)	6051(1)	34
C(67)	4490(2)	10100(1)	6053(1)	41
C(68)	5260(2)	10009(1)	6733(1)	43
C(69)	5335(2)	9177(1)	7410(1)	43
C(70)	4633(2)	8441(1)	7409(1)	37
C(71)	8159(1)	6721(1)	3877(1)	32
C(72)	8631(1)	5875(1)	3975(1)	33
C(73)	10078(2)	5769(1)	3769(1)	37
C(74)	11019(2)	6508(1)	3466(1)	43
C(75)	10540(2)	7343(1)	3407(1)	43
C(76)	9090(2)	7459(1)	3600(1)	38
C(77)	7605(2)	5082(1)	4297(1)	48
C(78)	10584(2)	4856(1)	3853(1)	54
C(79)	12560(2)	6412(2)	3178(1)	70
C(80)	11567(2)	8137(2)	3118(1)	73
C(81)	8528(2)	8368(1)	3476(1)	58

A1.2 Compound 351

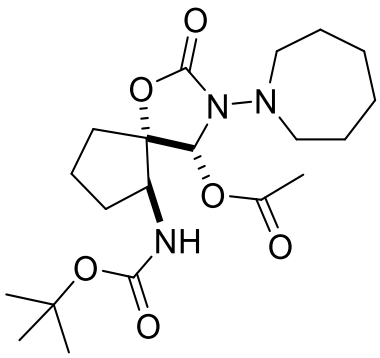


Table A1.3. Crystal data and structure refinement for 7031

Identification code	7031	
Empirical formula	C20 H33 N3 O6	
Formula weight	411.50	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 10.39620(10) Å	α = 90°.
	b = 11.62420(10) Å	β = 90°.
	c = 18.26820(10) Å	γ = 90°.
Volume	2207.67(3) $Å^3$	
Z	4	
Density (calculated)	1.238 Mg/m^3	
Absorption coefficient	0.754 mm^{-1}	
F(000)	888	
Crystal size	0.25 × 0.24 × 0.17 mm^3	
Theta range for data collection	4.509 to 76.119°	

Index ranges	-12<=h<=12, -14<=k<=14, -22<=l<=22
Reflections collected	18359
Independent reflections	4560 [R(int) = 0.020]
Completeness to theta = 74.597°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.88 and 0.82
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4560 / 0 / 264
Goodness-of-fit on F^2	1.0139
Final R indices [I>2sigma(I)]	R1 = 0.0234, wR2 = 0.0607
R indices (all data)	R1 = 0.0236, wR2 = 0.0608
Absolute structure parameter	0.03(3)
Extinction coefficient	94(6)
Largest diff. peak and hole	0.19 and -0.13 e.Å^{-3}

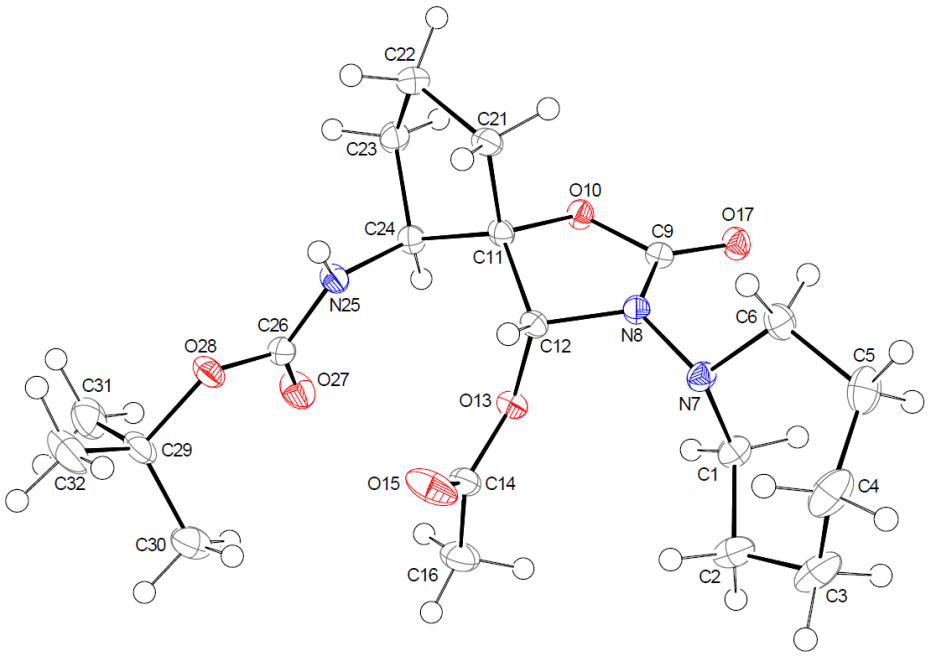


Table A1.4. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2$ $x10^3$) for 7031. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	4795(1)	6007(1)	5979(1)	21
C(2)	3678(1)	6654(1)	6328(1)	29
C(3)	3170(1)	7664(1)	5877(1)	36
C(4)	2841(1)	7394(1)	5081(1)	34
C(5)	4011(1)	7097(1)	4616(1)	31
C(6)	4430(1)	5841(1)	4624(1)	22
N(7)	4328(1)	5314(1)	5354(1)	17
N(8)	4848(1)	4197(1)	5329(1)	16
C(9)	6139(1)	3969(1)	5276(1)	16
O(10)	6330(1)	2828(1)	5388(1)	17
C(11)	5060(1)	2267(1)	5426(1)	15
C(12)	4189(1)	3254(1)	5662(1)	15
O(13)	4262(1)	3395(1)	6449(1)	18
C(14)	3155(1)	3455(1)	6839(1)	20
O(15)	2112(1)	3309(1)	6580(1)	35
C(16)	3443(1)	3720(1)	7624(1)	28
O(17)	6998(1)	4636(1)	5141(1)	21
C(21)	4773(1)	1740(1)	4673(1)	18
C(22)	5282(1)	487(1)	4715(1)	24
C(23)	5899(1)	373(1)	5477(1)	23
C(24)	5162(1)	1238(1)	5947(1)	16
N(25)	3866(1)	836(1)	6114(1)	17
C(26)	3484(1)	648(1)	6812(1)	18
O(27)	4135(1)	848(1)	7350(1)	27
O(28)	2283(1)	216(1)	6815(1)	21
C(29)	1658(1)	-84(1)	7516(1)	26
C(30)	1532(1)	975(1)	7999(1)	37
C(31)	2389(1)	-1056(1)	7885(1)	35
C(32)	337(1)	-492(1)	7270(1)	39

A1.3 Compound 368

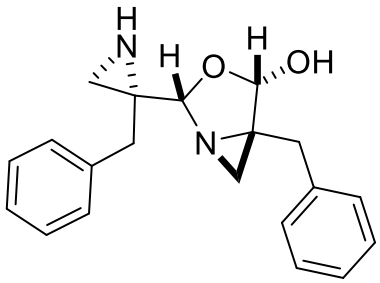


Table A1.5. Crystal data and structure refinement for 6920.

Identification code	6920
Empirical formula	C20 H22 N2 O2
Formula weight	322.41
Temperature	150 K
Wavelength	1.54184 Å
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 6.0295(2) Å α = 90°.
	b = 10.3828(4) Å β = 90°.
	c = 26.8913(11) Å γ = 90°.
Volume	1683.48(11) $Å^3$
Z	4
Density (calculated)	1.272 Mg/m^3
Absorption coefficient	0.657 mm^{-1}
F(000)	688
Crystal size	0.10 × 0.09 × 0.02 mm^3
Theta range for data collection	4.565 to 76.188°
Index ranges	-7<=h<=7, -12<=k<=11, -33<=l<=33

Reflections collected	11275
Independent reflections	3466 [R(int) = 0.027]
Completeness to theta = 74.664°	99.6%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.99 and 0.90
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3466 / 0 / 218
Goodness-of-fit on F^2	1.0052
Final R indices [I>2sigma(I)]	R1 = 0.0277, wR2 = 0.0668
R indices (all data)	R1 = 0.0307, wR2 = 0.0691
Absolute structure parameter	0.12(10)
Largest diff. peak and hole	0.20 and -0.15 e.$Å^{-3}$

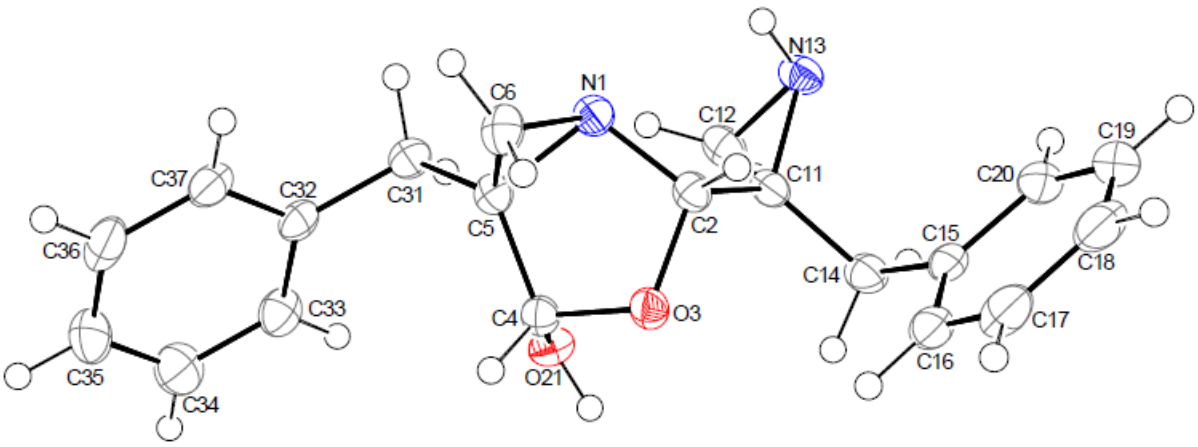


Table A1.6. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2 x10^3$) for 6920. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	9100(2)	2067(1)	6828(1)	23
C(2)	8759(2)	2701(1)	7304(1)	22
O(3)	8520(2)	4063(1)	7216(1)	23
C(4)	7674(2)	4220(1)	6724(1)	22
C(5)	8501(2)	3048(1)	6445(1)	21
C(6)	10859(2)	2719(1)	6536(1)	28
C(11)	6732(2)	2155(1)	7570(1)	22
C(12)	5055(2)	1440(1)	7277(1)	27
N(13)	6634(2)	732(1)	7602(1)	26
C(14)	6060(2)	2853(1)	8042(1)	28
C(15)	7908(2)	2889(1)	8421(1)	26
C(16)	9413(2)	3901(1)	8432(1)	31
C(17)	11217(3)	3881(1)	8752(1)	37
C(18)	11533(3)	2853(2)	9072(1)	39
C(19)	10003(3)	1852(1)	9076(1)	39
C(20)	8212(3)	1865(1)	8752(1)	33
O(21)	5364(1)	4207(1)	6705(1)	26
C(31)	7304(2)	2582(1)	5986(1)	25
C(32)	7396(2)	3539(1)	5563(1)	25
C(33)	5647(2)	4381(1)	5476(1)	31
C(34)	5728(3)	5260(2)	5086(1)	39
C(35)	7565(3)	5307(2)	4778(1)	40
C(36)	9319(3)	4481(2)	4864(1)	38
C(37)	9235(2)	3596(1)	5252(1)	30

A1.4 Compound 381

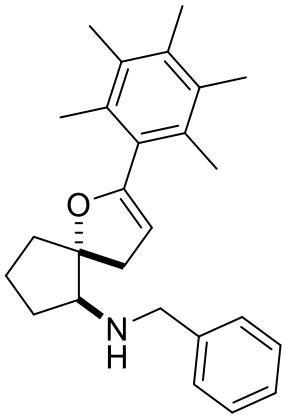


Table A1.7. Crystal data and structure refinement for 6987.

Identification code	6987	
Empirical formula	C26 H33 N O	
Formula weight	375.55	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 6.56280(10) Å	α = 90°.
	b = 14.3869(2) Å	β = 90°.
	c = 22.5311(3) Å	γ = 90°.
Volume	2127.35(5) $Å^3$	
Z	4	
Density (calculated)	1.173 Mg/m^3	
Absorption coefficient	0.533 mm^{-1}	
F(000)	816	
Crystal size	0.39 × 0.05 × 0.04 mm^3	

Theta range for data collection	3.645 to 76.116°.
Index ranges	-7<=h<=8, -15<=k<=17, -28<=l<=27
Reflections collected	24429
Independent reflections	4432 [R(int) = 0.029]
Completeness to theta = 76.116°	99.8%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.98 and 0.86
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4432 / 0 / 254
Goodness-of-fit on F^2	1.0053
Final R indices [I>2sigma(I)]	R1 = 0.0329, wR2 = 0.0872
R indices (all data)	R1 = 0.0339, wR2 = 0.0887
Absolute structure parameter	-0.06(7)
Largest diff. peak and hole	0.17 and -0.14 e.$Å^{-3}$

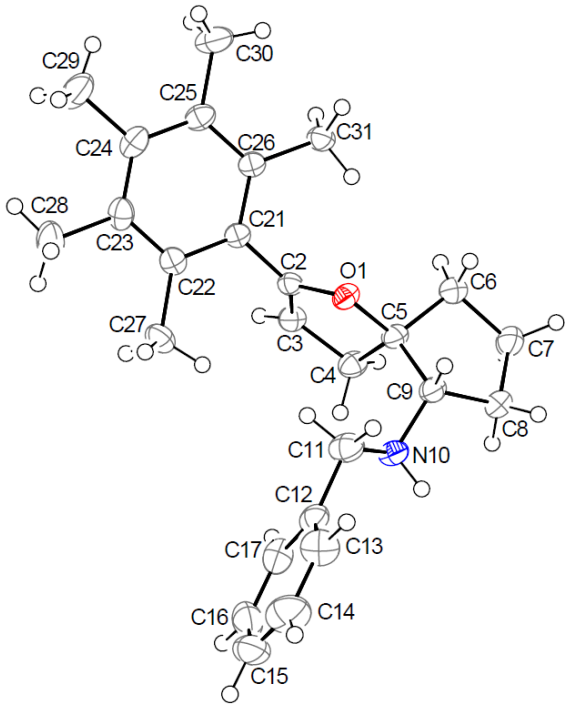


Table A1.8. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2 x10^3$) for 6987. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	6067(1)	6699(1)	3282(1)	27
C(2)	4542(2)	7350(1)	3223(1)	25
C(3)	3469(2)	7264(1)	2727(1)	28
C(4)	4202(2)	6426(1)	2392(1)	31
C(5)	6222(2)	6216(1)	2713(1)	27
C(6)	8074(2)	6561(1)	2368(1)	35
C(7)	8484(2)	5777(1)	1922(1)	39
C(8)	7684(2)	4884(1)	2221(1)	35
C(9)	6730(2)	5185(1)	2813(1)	28
N(10)	5013(2)	4601(1)	2981(1)	30
C(11)	4606(2)	4607(1)	3619(1)	39
C(12)	3031(2)	3886(1)	3788(1)	33
C(13)	3453(3)	3227(1)	4216(1)	46
C(14)	1994(4)	2578(1)	4378(1)	61
C(15)	108(3)	2585(1)	4112(1)	61
C(16)	-316(2)	3230(1)	3681(1)	55
C(17)	1127(2)	3877(1)	3520(1)	41
C(21)	4327(2)	8012(1)	3727(1)	24
C(22)	2674(2)	7918(1)	4116(1)	27
C(23)	2416(2)	8577(1)	4568(1)	32
C(24)	3800(2)	9310(1)	4629(1)	33
C(25)	5474(2)	9390(1)	4244(1)	30
C(26)	5752(2)	8730(1)	3793(1)	25
C(27)	1248(2)	7093(1)	4073(1)	35
C(28)	663(2)	8471(1)	4998(1)	48
C(29)	3504(3)	10010(1)	5124(1)	50
C(30)	6952(3)	10193(1)	4301(1)	45
C(31)	7525(2)	8817(1)	3368(1)	30

A1.5 Compound 410

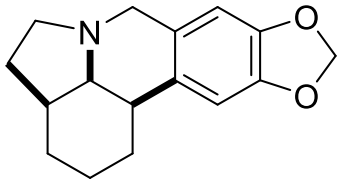


Table A1.9. Crystal data and structure refinement for 7144.

Identification code	7144	
Empirical formula	C16 H19 N O2	
Formula weight	257.33	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 9.5572(6) Å	α= 101.237(6)°.
	b = 12.2819(10) Å	β= 99.446(5)°.
	c = 12.4294(6) Å	γ = 110.609(7)°.
Volume	1295.68(17) $Å^3$	
Z	4	
Density (calculated)	1.319 Mg/m^3	
Absorption coefficient	0.689 mm^{-1}	
F(000)	551.996	
Crystal size	0.19 x 0.15 x 0.05 mm^3	
Theta range for data collection	3.748 to 76.818°.	
Index ranges	-12<=h<=12, -15<=k<=15, -15<=l<=15	
Reflections collected	21905	
Independent reflections	5401 [R(int) = 0.060]	
Completeness to theta = 75.281°	99.6 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.97 and 0.74
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	5401 / 0 / 344
Goodness-of-fit on F^2	0.9945
Final R indices [I>2sigma(I)]	R1 = 0.0665, wR2 = 0.1943
R indices (all data)	R1 = 0.0839, wR2 = 0.2173
Largest diff. peak and hole	0.28 and -0.26 e.$Å^{-3}$

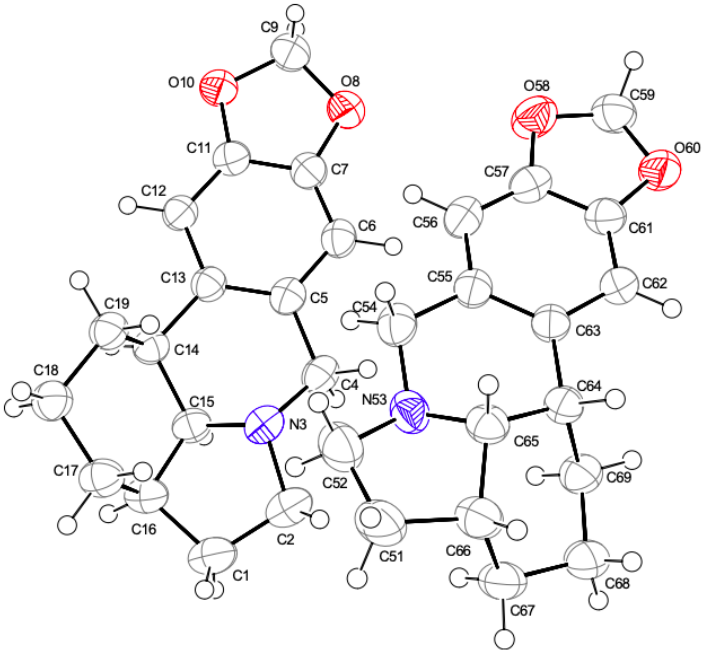


Table A1.10. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2$ $x10^3$) for 7144. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	7220(4)	6281(3)	4983(3)	58
C(2)	7802(4)	7288(3)	6104(3)	59
N(3)	7529(3)	8310(2)	5804(2)	44
C(4)	8638(3)	9476(2)	6533(2)	45
C(5)	8540(3)	10510(2)	6075(2)	41
C(6)	9257(3)	11685(2)	6807(2)	44
C(7)	9226(3)	12617(2)	6366(2)	44
O(8)	9894(2)	13836(2)	6904(2)	54
C(9)	9326(4)	14389(3)	6123(3)	55
O(10)	8717(3)	13525(2)	5032(2)	53
C(11)	8535(3)	12429(2)	5242(2)	43
C(12)	7835(3)	11289(2)	4507(2)	42
C(13)	7842(3)	10307(2)	4937(2)	39
C(14)	7060(3)	9044(2)	4130(2)	40
C(15)	7623(3)	8182(2)	4631(2)	41
C(16)	6714(3)	6835(2)	4063(3)	48
C(17)	4960(3)	6478(2)	3761(3)	50
C(18)	4517(3)	7295(2)	3113(3)	49
C(19)	5293(3)	8606(2)	3856(2)	46
C(51)	3805(4)	6128(3)	8062(3)	69
C(52)	4229(4)	7141(3)	7483(3)	63
N(53)	5577(3)	8140(2)	8293(2)	47
C(54)	5709(3)	9309(3)	8144(2)	47
C(55)	6894(3)	10331(2)	9122(2)	41
C(56)	7459(3)	11493(3)	8964(2)	46

C(57)	8468(3)	12426(2)	9869(3)	46
O(58)	9142(3)	13635(2)	9914(2)	62
C(59)	10181(4)	14208(3)	11021(3)	58
O(60)	9919(3)	13352(2)	11666(2)	59
C(61)	8932(3)	12256(2)	10906(2)	45
C(62)	8411(3)	11133(2)	11086(2)	44
C(63)	7361(3)	10146(2)	10166(2)	40
C(64)	6788(3)	8891(2)	10343(2)	42
C(65)	5351(3)	8043(2)	9406(2)	44
C(66)	4847(3)	6683(2)	9288(3)	53
C(67)	6231(4)	6319(2)	9425(3)	54
C(68)	7481(4)	7120(3)	10503(3)	54
C(69)	8082(3)	8419(2)	10432(3)	51

A1.6 Compound 553

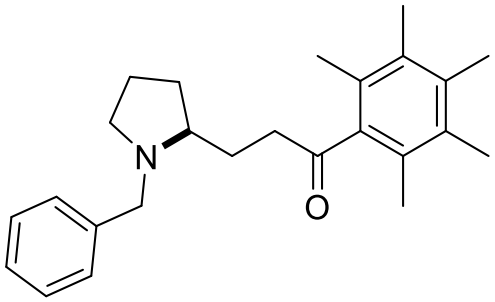


Table A1.11. Crystal data and structure refinement for 7286

Identification code	7286
Empirical formula	C25 H33 N O
Formula weight	363.54
Temperature	150 K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	P 21
Unit cell dimensions	a = 11.9463(4) Å α = 90°
	b = 5.6890(2) Å β = 92.600(3)°
	c = 15.9070(5) Å γ = 90°
Volume	1079.97(6) $Å^3$
Z	2
Density (calculated)	1.118 Mg/m^3
Absorption coefficient	0.509 mm^{-1}
F(000)	395.997
Crystal size	0.22 x 0.09 x 0.02 mm^3
Theta range for data collection	2.781 to 77.159°
Index ranges	-15<=h<=13, -7<=k<=7, -19<=l<=19

Reflections collected	8881
Independent reflections	4475 [R(int) = 0.021]
Completeness to theta = 74.073°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.99 and 0.90
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4469 / 1 / 245
Goodness-of-fit on F^2	0.9975
Final R indices [I>2sigma(I)]	R1 = 0.0416, wR2 = 0.1107
R indices (all data)	R1 = 0.0467, wR2 = 0.1155
Absolute structure parameter	0.21(14)
Largest diff. peak and hole	0.24 and -0.19 e.Å^{-3}

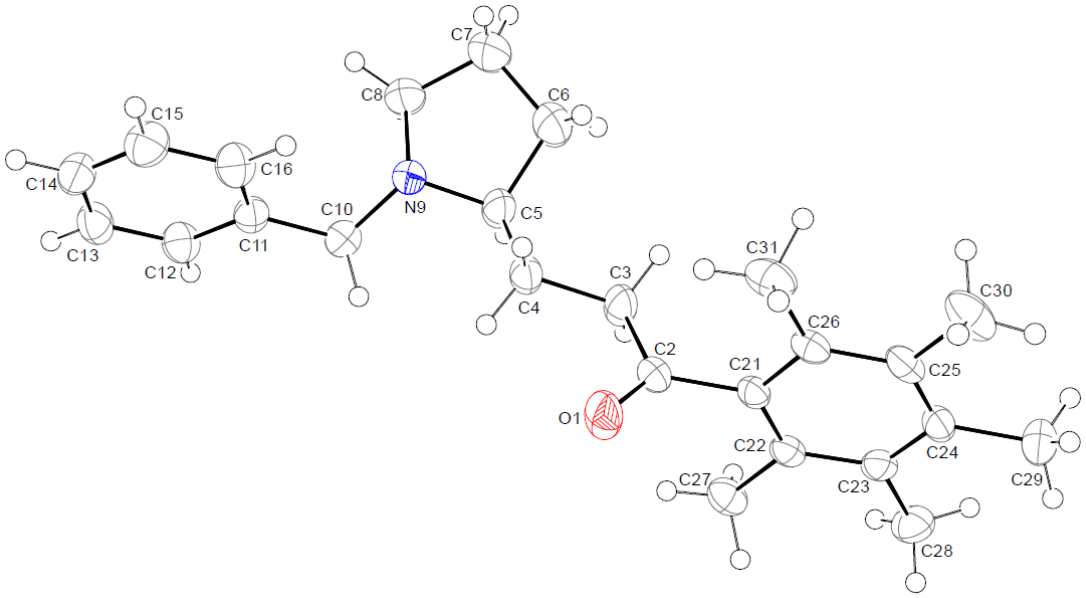


Table A1.12. Atomic coordinates (x10^4) and equivalent isotropic displacement parameters (Å^2 x10^3) for 7286. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	3793(1)	4998(3)	6554(1)	50
C(2)	3098(1)	3538(3)	6342(1)	33
C(3)	2565(2)	1960(4)	6978(1)	40
C(4)	2774(2)	2718(3)	7889(1)	35
C(5)	2222(2)	1072(4)	8498(1)	39
C(6)	942(2)	974(6)	8377(1)	63
C(7)	487(2)	958(7)	9242(2)	72
C(8)	1518(2)	677(4)	9834(1)	46
N(9)	2400(1)	1829(3)	9375(1)	33
C(10)	3517(2)	1351(3)	9743(1)	36
C(11)	3764(1)	2668(3)	10560(1)	33
C(12)	4551(2)	1793(3)	11151(1)	38
C(13)	4806(2)	3003(4)	11890(1)	41
C(14)	4276(2)	5112(4)	12045(1)	43
C(15)	3499(2)	6006(4)	11463(1)	46
C(16)	3244(2)	4788(4)	10724(1)	40
C(21)	2712(1)	3235(3)	5436(1)	27
C(22)	3202(1)	1519(3)	4947(1)	29
C(23)	2819(1)	1233(3)	4108(1)	30
C(24)	1979(1)	2720(3)	3762(1)	33
C(25)	1509(1)	4456(3)	4262(1)	33
C(26)	1859(1)	4700(3)	5107(1)	31
C(27)	4135(1)	-13(3)	5313(1)	37
C(28)	3326(2)	-673(4)	3585(1)	44
C(29)	1594(2)	2464(5)	2847(1)	53
C(30)	615(2)	6128(4)	3904(2)	52
C(31)	1342(2)	6535(4)	5656(1)	45

A1.7 Compound 591

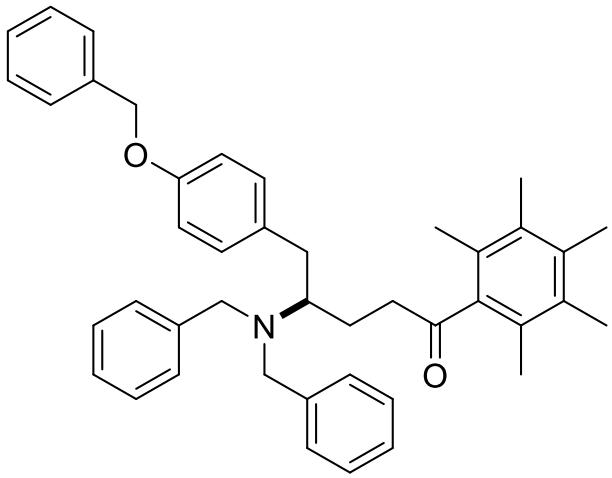


Table A1.13. Crystal data and structure refinement for 7265

Identification code	7265	
Empirical formula	C43 H47 N O2	
Formula weight	609.85	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 12.3530(4) Å	α = 82.700(3)°.
	b = 16.1578(5) Å	β = 76.898(3)°
	c = 18.0772(7) Å	γ = 83.527(3)°.
Volume	3472.6(2) $Å^3$	
Z	4	
Density (calculated)	1.166 Mg/m^3	
Absorption coefficient	0.539 mm^{-1}	
F(000)	1312.001	

Crystal size	0.39 × 0.20 × 0.04 mm^3
Theta range for data collection	2.523 to 77.276°
Index ranges	-15<=h<=12, -20<=k<=17, -22<=l<=22
Reflections collected	30643
Independent reflections	14516 [R(int) = 0.040]
Completeness to theta = 74.958°	99.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.98 and 0.84
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	14514 / 20 / 891
Goodness-of-fit on F^2	1.0009
Final R indices [I>2sigma(I)]	R1 = 0.0617, wR2 = 0.1583
R indices (all data)	R1 = 0.0778, wR2 = 0.1745
Largest diff. peak and hole	0.52 and -0.36 e.$Å^{-3}$

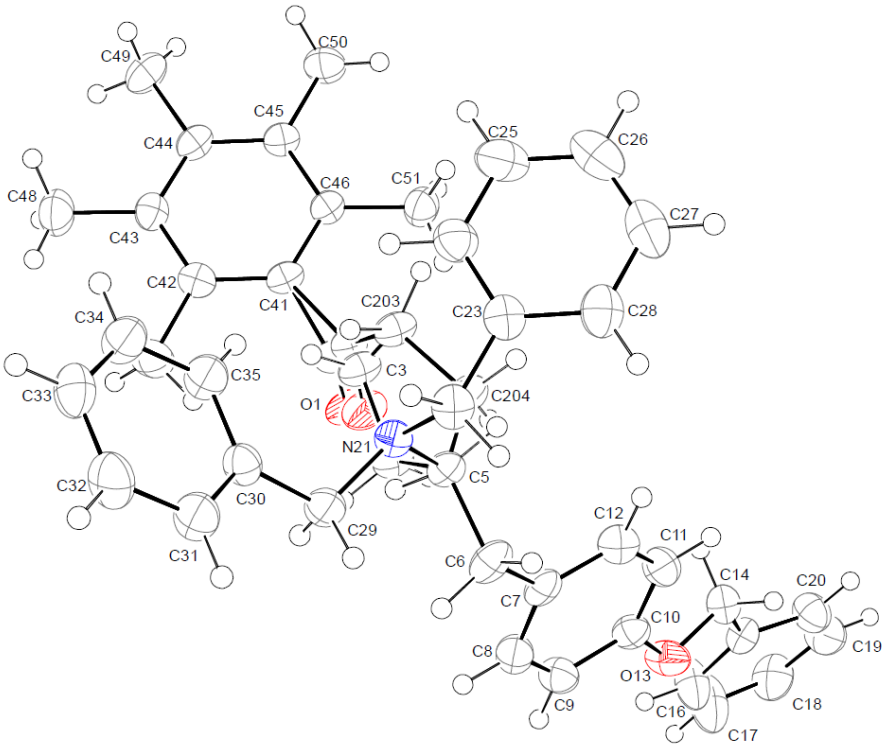


Table A1.14. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2$ $x10^3$) for 7265. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	9814(2)	9431(1)	7066(1)	38
C(2)	9525(2)	9850(2)	7594(1)	29
C(3)	8811(2)	10671(1)	7540(1)	34
C(4)	8705(2)	10986(1)	6726(1)	32
C(5)	7768(2)	11659(1)	6695(1)	30
C(6)	7568(2)	11909(1)	5886(1)	39
C(7)	7425(2)	11175(1)	5481(1)	33
C(8)	8222(2)	10932(1)	4853(1)	38
C(9)	8108(2)	10262(1)	4478(1)	40
C(10)	7174(2)	9813(1)	4734(1)	35
C(11)	6371(2)	10034(1)	5360(1)	39
C(12)	6500(2)	10715(1)	5723(1)	39
O(13)	7123(1)	9169(1)	4317(1)	45
C(14)	6368(2)	8563(1)	4668(1)	37
C(15)	6566(2)	7838(1)	4193(1)	35
C(16)	7581(2)	7654(2)	3713(2)	58
C(17)	7761(2)	6939(2)	3331(2)	73
C(18)	6939(2)	6406(2)	3430(2)	58
C(19)	5902(2)	6608(2)	3875(1)	53
C(20)	5718(2)	7321(1)	4256(1)	46
N(21)	7879(1)	12375(1)	7102(1)	29
C(22)	6811(2)	12858(1)	7372(1)	35
C(23)	6043(2)	12370(1)	8005(1)	35
C(24)	6402(2)	12014(1)	8656(1)	43
C(25)	5700(2)	11560(2)	9241(1)	55
C(26)	4626(2)	11471(2)	9178(2)	58
C(27)	4256(2)	11830(2)	8544(2)	56
C(28)	4960(2)	12280(1)	7954(1)	45
C(29)	8710(2)	12929(1)	6661(1)	37

C(30)	9158(2)	13436(1)	7162(1)	34
C(31)	9441(2)	14243(1)	6893(1)	45
C(32)	9924(2)	14699(1)	7316(2)	51
C(33)	10123(2)	14355(1)	8013(1)	46
C(34)	9829(2)	13553(1)	8293(1)	46
C(35)	9349(2)	13097(1)	7871(1)	41
C(41)	9838(2)	9583(1)	8346(1)	29
C(42)	10842(2)	9838(1)	8437(1)	32
C(43)	11228(1)	9531(1)	9095(1)	32
C(44)	10600(2)	8983(1)	9654(1)	32
C(45)	9569(2)	8768(1)	9571(1)	31
C(46)	9189(1)	9062(1)	8906(1)	29
C(47)	11498(2)	10425(1)	7822(1)	47
C(48)	12331(2)	9759(2)	9207(2)	50
C(49)	11054(2)	8621(2)	10345(1)	47
C(50)	8887(2)	8203(1)	10187(1)	44
C(51)	8102(2)	8808(1)	8787(1)	40
O(101)	4785(2)	5326(1)	2976(1)	46
C(102)	5173(2)	4978(2)	2413(2)	32
C(103)	5811(2)	4125(2)	2441(1)	40
C(104)	5982(2)	3785(1)	3235(1)	34
C(105)	6979(2)	3142(1)	3209(1)	31
C(106)	7266(2)	2848(1)	3987(1)	39
C(107)	7513(2)	3547(1)	4389(1)	33
C(108)	8597(2)	3750(1)	4316(1)	38
C(109)	8821(2)	4406(1)	4670(1)	40
C(110)	7949(2)	4874(1)	5107(1)	33
C(111)	6864(2)	4664(1)	5208(1)	37
C(112)	6664(2)	4007(1)	4844(1)	38
O(113)	8241(1)	5523(1)	5424(1)	41
C(114)	7349(2)	6090(1)	5758(1)	40
C(115)	7819(2)	6868(1)	5886(1)	39

C(116)	8653(2)	7227(1)	5328(2)	47
C(117)	8999(2)	7987(2)	5415(2)	57
C(118)	8547(2)	8390(2)	6052(2)	62
C(119)	7713(3)	8042(2)	6607(2)	72
C(120)	7342(3)	7278(2)	6526(2)	59
N(121)	6875(1)	2452(1)	2772(1)	31
C(122)	7955(2)	1999(1)	2459(1)	40
C(123)	8752(2)	2570(1)	1944(1)	40
C(124)	9739(2)	2709(2)	2132(2)	51
C(125)	10449(2)	3264(2)	1672(2)	65
C(126)	10185(2)	3688(2)	1022(2)	68
C(127)	9212(2)	3548(2)	814(2)	60
C(128)	8506(2)	2990(2)	1275(1)	46
C(129)	6092(2)	1859(1)	3208(1)	39
C(130)	5647(2)	1360(1)	2701(1)	37
C(131)	5612(2)	501(1)	2858(1)	42
C(132)	5143(2)	54(1)	2418(1)	52
C(133)	4703(2)	461(2)	1825(2)	52
C(134)	4741(2)	1318(2)	1653(2)	53
C(135)	5214(2)	1758(1)	2093(2)	49
C(141)	5082(2)	5380(1)	1628(1)	35
C(142)	4069(2)	5321(1)	1423(1)	37
C(143)	3905(2)	5712(1)	723(1)	38
C(144)	4746(2)	6147(1)	233(1)	37
C(145)	5760(2)	6196(1)	432(1)	36
C(146)	5935(2)	5813(1)	1140(1)	36
C(147)	3160(2)	4838(2)	1944(2)	56
C(148)	2817(2)	5689(2)	473(2)	61
C(149)	4550(3)	6573(2)	-524(1)	59
C(150)	6664(2)	6663(2)	-108(2)	61

C(151)	7011(2)	5871(2)	1385(2)	59
O(201)	9450(10)	9732(10)	7054(6)	48
C(202)	9186(12)	9946(11)	7697(6)	29
C(203)	8199(10)	10619(7)	7850(7)	34
C(204)	7509(9)	10871(6)	7235(6)	34
O(301)	5361(11)	5108(8)	2941(5)	46
C(302)	5703(11)	4977(7)	2275(5)	36
C(303)	6653(11)	4262(7)	2132(7)	43
C(304)	7326(9)	3961(5)	2748(6)	34

A1.8 Compound 665

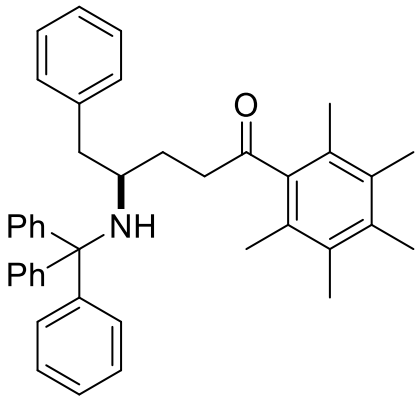


Table A1.15. Crystal data and structure refinement for 7275

Identification code	7275	
Empirical formula	C41 H43 N O	
Formula weight	565.80	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 11.5084(17) Å	α = 105.551(3)°
	b = 11.8276(17) Å	β = 111.052(3)°
	c = 13.2451(2) Å	γ = 93.290(3)°
Volume	1597.09(5) $Å^3$	
Z	2	
Density (calculated)	1.176 Mg/m^3	
Absorption coefficient	0.525 mm^{-1}	
F(000)	608	
Crystal size	0.25 × 0.22 × 0.12 mm^3	

Theta range for data collection	3.761 to 77.041°.
Index ranges	-14<=h<=14, -14<=k<=14, -16<=l<=16
Reflections collected	12458
Independent reflections	6696 [R(int) = 0.030]
Completeness to theta = 74.730°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.94 and 0.83
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6696 / 37 / 407
Goodness-of-fit on F^2	0.9997
Final R indices [I>2sigma(I)]	R1 = 0.0434, wR2 = 0.1193
R indices (all data)	R1 = 0.0457, wR2 = 0.1224
Largest diff. peak and hole	0.29 and -0.19 e.$Å^{-3}$

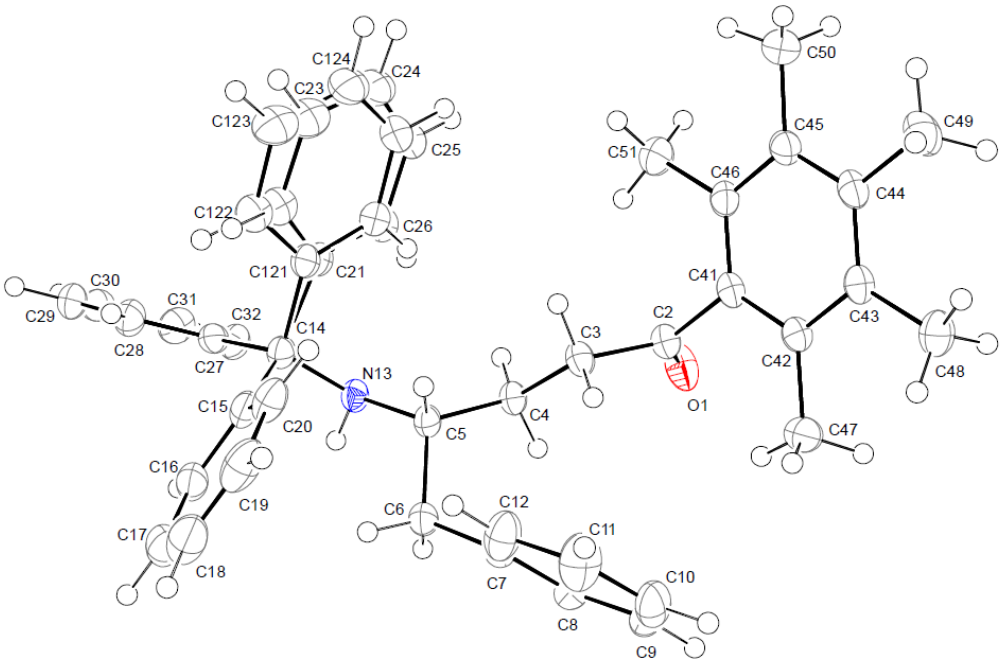


Table A1.16. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2$ $x10^3$) for 7275. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	6734(1)	7623(1)	1972(1)	41
C(2)	6969(1)	7254(1)	2783(1)	27
C(3)	6439(1)	6013(1)	2682(1)	26
C(4)	5423(1)	5316(1)	1528(1)	24
C(5)	4986(1)	4023(1)	1454(1)	24
C(6)	5658(1)	3138(1)	862(1)	27
C(7)	7077(1)	3458(1)	1426(1)	29
C(8)	7767(1)	4048(1)	986(1)	33
C(9)	9066(1)	4391(1)	1545(1)	38
C(10)	9693(1)	4146(1)	2538(1)	43
C(11)	9030(1)	3549(1)	2981(1)	49
C(12)	7725(1)	3204(1)	2422(1)	40
N(13)	3595(1)	3684(1)	874(1)	24
C(14)	2962(1)	3039(1)	1406(1)	25
C(15)	3553(1)	1920(1)	1538(1)	29
C(16)	3209(1)	916(1)	581(1)	36
C(17)	3817(1)	-64(1)	615(2)	48
C(18)	4791(1)	-60(1)	1607(2)	53
C(19)	5149(1)	929(1)	2560(2)	48
C(20)	4536(1)	1914(1)	2530(1)	36
C(21)	3078(9)	4035(10)	2531(8)	26
C(22)	2991(7)	3714(8)	3445(8)	32
C(23)	2972(7)	4581(10)	4391(6)	41
C(25)	3108(7)	6076(8)	3524(9)	46
C(26)	3128(8)	5221(10)	2574(9)	35
C(27)	1540(1)	2686(1)	635(1)	26
C(28)	781(1)	1833(1)	781(1)	33
C(29)	-512(1)	1549(1)	144(1)	35
C(30)	-1069(1)	2112(1)	-652(1)	35

C(31)	-327(1)	2951(1)	-817(1)	36
C(32)	971(1)	3242(1)	-173(1)	31
C(41)	7842(1)	8000(1)	3972(1)	26
C(42)	9148(1)	8045(1)	4303(1)	26
C(43)	9947(1)	8692(1)	5424(1)	27
C(44)	9441(1)	9287(1)	6198(1)	29
C(45)	8130(1)	9254(1)	5843(1)	30
C(46)	7324(1)	8598(1)	4726(1)	28
C(47)	9695(1)	7401(1)	3475(1)	36
C(48)	11357(1)	8763(1)	5785(1)	35
C(49)	10332(1)	9947(1)	7412(1)	40
C(50)	7576(1)	9949(1)	6647(1)	42
C(51)	5907(1)	8555(1)	4330(1)	39
C(121)	3020(3)	3848(3)	2545(3)	26
C(122)	2810(3)	3386(3)	3343(2)	32
C(123)	2811(3)	4136(4)	4351(2)	41
C(124)	3015(3)	5365(4)	4580(2)	45
C(125)	3190(3)	5833(3)	3789(3)	46
C(126)	3185(3)	5084(3)	2777(3)	35
C(24)	3070(9)	5759(9)	4440(8)	45

A1.9 Compound 719

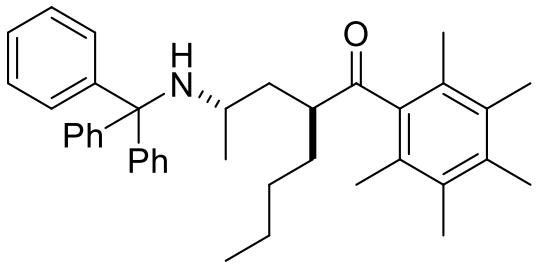


Table A1.17. Crystal data and structure refinement for DIA0429

Identification code	DIA0429	
Empirical formula	C39 H47 N O	
Formula weight	545.81	
Temperature	100 K	
Wavelength	0.68890 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 18.1194(2) Å	α = 90°
	b = 8.72040(10) Å	β = 101.8695(10)°
	c = 20.0915(2) Å	γ = 90°
Volume	3106.75(6) $Å^3$	
Z	4	
Density (calculated)	1.167 Mg/m^3	
Absorption coefficient	0.063 mm^{-1}	
F(000)	1184.001	
Crystal size	0.250 × 0.075 × 0.010 mm^3	
Theta range for data collection	1.645 to 36.008°.	

Index ranges	-30<=h<=30, -14<=k<=14, -34<=l<=33
Reflections collected	60455
Independent reflections	15691 [R(int) = 0.045]
Completeness to theta = 74.730°	99.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00 and 0.57
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	15686 / 345 / 837
Goodness-of-fit on F^2	1.0066
Final R indices [I>2sigma(I)]	R1 = 0.0584, wR2 = 0.1543
R indices (all data)	R1 = 0.0765, wR2 = 0.1673
Absolute structure parameter	0
Largest diff. peak and hole	1.03 and -0.64 e.Å^{-3}

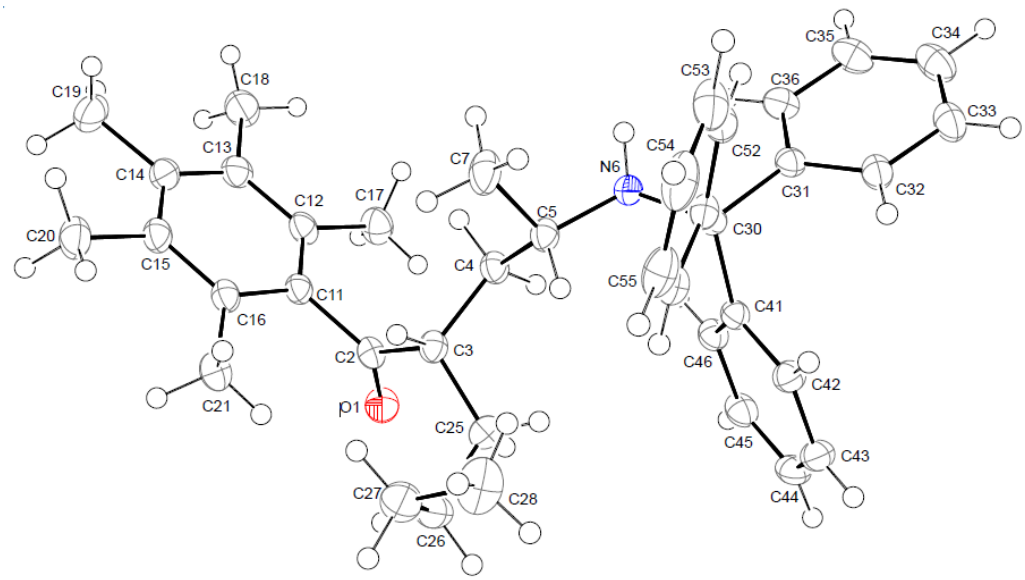


Table A1.18. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2$ $x10^3$) for DIA0429. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	6251(1)	5000(3)	5699(1)	30
C(2)	6528(1)	3720(2)	5760(1)	23
C(3)	6777(1)	2979(2)	6457(1)	23
C(4)	6171(1)	1783(2)	6549(1)	24
C(5)	6469(1)	636(2)	7125(1)	23
N(6)	5846(1)	-7(2)	7411(1)	23
C(7)	6923(1)	-626(3)	6876(1)	39
C(11)	6604(1)	2803(2)	5139(1)	23
C(12)	5950(1)	2266(2)	4701(1)	26
C(13)	6026(1)	1440(2)	4120(1)	30
C(14)	6746(1)	1168(2)	3985(1)	30
C(15)	7391(1)	1719(2)	4424(1)	28
C(16)	7323(1)	2570(2)	5001(1)	24
C(17)	5176(1)	2587(3)	4845(1)	34
C(18)	5332(1)	820(3)	3642(1)	43
C(19)	6835(2)	295(3)	3356(1)	41
C(20)	8163(1)	1392(3)	4283(1)	37
C(21)	8012(1)	3290(3)	5439(1)	29
C(25)	6898(1)	4180(2)	7026(1)	27
C(26)	7617(1)	5137(3)	7087(1)	33
C(27)	8357(1)	4238(3)	7289(1)	37
C(28)	8439(1)	3399(4)	7959(1)	49
C(30)	5948(1)	51(2)	8163(1)	21
C(31)	5289(1)	-778(2)	8381(1)	22
C(32)	5322(1)	-1009(2)	9077(1)	26
C(33)	4749(1)	-1746(3)	9309(1)	32
C(34)	4117(1)	-2261(3)	8850(1)	36
C(35)	4069(1)	-2011(3)	8164(1)	35
C(36)	4649(1)	-1272(2)	7925(1)	29

C(41)	5881(1)	1722(2)	8387(1)	21
C(42)	6216(1)	2240(2)	9036(1)	25
C(43)	6062(1)	3704(2)	9254(1)	28
C(44)	5557(1)	4657(2)	8829(1)	30
C(45)	5224(1)	4150(2)	8183(1)	28
C(46)	5381(1)	2701(2)	7965(1)	24
C(51)	6698(1)	-739(2)	8498(1)	23
C(52)	6708(1)	-2336(2)	8555(1)	29
C(53)	7366(1)	-3133(3)	8821(1)	37
C(54)	8041(1)	-2337(3)	9026(1)	40
C(55)	8047(1)	-769(3)	8947(1)	35
C(56)	7383(1)	35(3)	8687(1)	27
O(101)	9353(3)	-5829(6)	3753(3)	52
C(102)	9162(3)	-4465(6)	3720(3)	33
C(103)	9518(3)	-3318(6)	3308(3)	35
C(104)	8890(1)	-2316(3)	2775(1)	41
C(105)	9279(1)	-844(2)	2584(1)	28
N(106)	8716(1)	186(2)	2173(1)	28
C(107)	9646(1)	33(3)	3208(1)	40
C(111)	8560(3)	-3914(10)	4067(3)	27
C(112)	8733(3)	-3068(8)	4672(3)	31
C(113)	8169(3)	-2493(8)	4963(3)	34
C(114)	7414(3)	-2752(10)	4665(4)	30
C(115)	7223(7)	-3589(12)	4060(5)	24
C(316)	7794(3)	-4356(9)	3781(4)	23
C(117)	9560(3)	-2859(9)	5013(3)	49
C(118)	8373(5)	-1578(8)	5621(3)	55
C(119)	6820(4)	-2065(10)	5008(4)	51
C(120)	6406(7)	-4100(30)	3827(10)	46
C(121)	7316(4)	-5061(9)	3061(4)	37
C(125)	10124(4)	-4061(6)	2975(4)	58
C(126)	9836(5)	-5193(10)	2404(4)	85
C(127)	10640(5)	-5827(9)	2325(6)	85
C(128)	10465(10)	-7090(30)	1828(12)	79

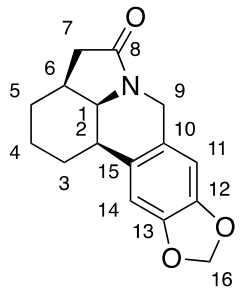
C(130)	8399(1)	-121(2)	1443(1)	26
C(131)	7647(1)	-1020(2)	1335(1)	27
C(132)	7274(1)	-1225(3)	1865(1)	35
C(133)	6591(1)	-2014(3)	1765(1)	39
C(134)	6264(1)	-2588(3)	1128(1)	36
C(135)	6619(1)	-2343(2)	586(1)	31
C(136)	7299(1)	-1563(2)	689(1)	27
C(141)	8188(1)	1457(2)	1113(1)	28
C(142)	8185(1)	1705(2)	424(1)	31
C(143)	7982(1)	3117(2)	122(1)	34
C(144)	7767(1)	4314(3)	496(1)	36
C(145)	7746(1)	4074(3)	1172(1)	36
C(146)	7959(1)	2663(2)	1482(1)	32
C(151)	8983(1)	-943(2)	1105(1)	26
C(152)	9582(1)	-132(3)	940(1)	31
C(153)	10117(1)	-871(3)	645(1)	37
C(154)	10067(1)	-2433(3)	515(1)	37
C(155)	9492(1)	-3264(3)	698(1)	34
C(156)	8954(1)	-2514(2)	990(1)	30
O(301)	8942(2)	-6108(5)	3244(2)	52
C(302)	8959(2)	-4749(5)	3411(2)	33
C(303)	9377(3)	-3574(5)	3055(3)	35
C(311)	8492(3)	-4153(9)	3902(3)	27
C(312)	8848(2)	-3453(7)	4514(2)	31
C(313)	8400(3)	-2782(7)	4918(3)	34
C(314)	7612(3)	-2880(9)	4744(4)	30
C(315)	7264(6)	-3753(12)	4167(4)	26
C(116)	7700(4)	-4161(11)	3696(5)	23
C(317)	9697(3)	-3508(9)	4746(3)	53
C(318)	8765(4)	-2022(9)	5578(3)	59
C(319)	7147(4)	-2114(8)	5184(3)	45
C(320)	6417(6)	-3860(20)	3957(9)	46
C(321)	7577(3)	-5180(8)	3139(3)	37
C(325)	9821(2)	-4350(5)	2575(2)	29

C(326)	10509(2)	-5239(5)	2934(2)	35
C(327)	10987(3)	-6015(9)	2464(3)	58
C(328)	10473(8)	-7020(30)	1976(10)	79

Appendix 2: Experimental Procedures by Indi Marriott

The following procedures are those reported by Indi Marriott in his Part II Thesis, University of Oxford, 2019 – albeit with compounds numbers changed to fit the above text.

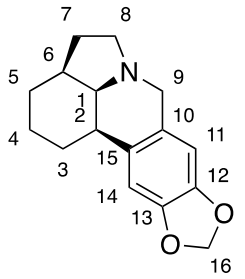
(3aS,3a1R,12bR)-2,3,3a,4,7,12b-Hexahydro-1H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-5(3a1H)-one (411)



To a stirred solution of substrate **456** (68.8 mg, 0.256 mmol, 1.0) in methanol was added 10% Pd/C (8.5 mg, 0.08 mmol, 0.3 equiv.) and hydrogen pressure was applied overnight with a balloon. The reaction mixture was filtered through Celite® using MeOH and the filtrate concentrated *in vacuo*, yielding the title compound **411** (63.5 mg, 0.234 mmol, 92%). A quantitative yield (49.0 mg, 0.181 mmol) was obtained for enantiopure material.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.62 (s, 1H, HC^{Ar}), 6.60 (s, 1H, HC^{Ar}), 5.94 (d, *J* = 1.4 Hz, 1H, H^{16}), 5.92 (d, *J* = 1.4 Hz, 1H, H^{16}), 4.54 (d, *J* = 17.3 Hz, 1H, H^{9a}), 4.33 (d, *J* = 17.3 Hz, 1H, H^{9b}), 3.77 (t, *J* = 4.6 Hz, 1H, H^{1}), 2.75 (dt, *J* = 12.7, 4.4 Hz, 1H, H^{2}), 2.58 (dd, *J* = 16.1, 6.8 Hz, 1H, H^{7a}), 2.49 – 2.37 (m, 1H, H^{6}), 2.09 (d, *J* = 16.1 Hz, 1H, H^{7b}), 1.84 – 1.66 (m, 3H, H^{3a}, H^{4a}, H^{5a}), 1.41 – 1.07 (m, 3H, H^{3b}, H^{4b}, H^{5b}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 175.88 (C^{8}), 146.89 (C^{Ar}), 146.82 (C^{Ar}), 131.80 (C^{Ar}), 123.50 (C^{Ar}), 108.69 (C^{Ar}), 106.89 (C^{Ar}), 101.24 (C^{16}), 55.92 (C^{1}), 42.90 (C^{9}), 40.50 (C^{2}), 40.06 (C^{7}), 33.17 (C^{6}), 30.48 (C^{3}), 28.08 (C^{5}), 23.84 (C^{4}); **IR** ν_{max} (thin film): 2360, 1675, 1482, 1035, 932, and 847 cm^{-1}; **HRMS** (ESI^{+}) Found $[M+Na]^{+}$ = 294.1100; $C_{16}H_{17}O_3NNa$ requires 294.1101, Δ = –0.27 ppm; **M.p.** 122-124 °C (*racemic*), 136-138 °C (*enantiopure*); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = -70.6 (*c* = 1.00; $CHCl_3$).

(–)-γ-Lycorane (410)



Substrate **411** (60.0 mg, 0.221 mmol, 1.0 equiv.) was dissolved in THF (10 mL) and placed under a nitrogen atmosphere. $LiAlH_4$ (33.6 mg, 0.885 mmol, 4.0 equiv.) was added portionwise to the stirred solution at RT. The mixture was heated at reflux for 15 h, cooled to RT, and poured over sat. aq. Na_2SO_4 (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 20 mL), filtered, concentrated *in vacuo*, yielding the crude product. Purification by column chromatography (SiO_2; wet load; 94.5% CH_2Cl_2, 4% MeOH, 0.5% NEt_3), gave the title compound **410** as a pale green solid (41.0 mg, 0.159 mmol, 72%). A yield of 68% (21.7 mg, 0.085 mmol) was obtained for enantiopure material. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.61 (s, 1H, HC^{Ar}), 6.49 (s, 1H, HC^{Ar}), 5.90 – 5.87 (m, 2H, H^{16}), 4.02 (d, *J* = 14.4 Hz, 1H, H^{9a}), 3.39 (td, *J* = 9.2, 3.9 Hz, 1H, H^{8a}), 3.22 (d, *J* = 14.3 Hz, 1H, H^{9b}), 2.74 (dt, *J* = 12.1, 4.7 Hz, 1H, H^2), 2.38 (t, *J* = 5.0 Hz, 1H, H^1), 2.27 – 2.11 (m, 2H, H^6, H^{8a}), 2.08-1.96 (m, 1H, H^{7a}), 1.81 – 1.67 (m, 2H, H^{3a}, H^{4a}), 1.67 – 1.59 (m, 1H, H^{5a}), 1.53 – 1.41 (m, 2H, H^{3b}, H^{7b}), 1.36 – 1.25 (m, 2H, H^{4b}, H^{5b}); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 146.23 (C^{Ar}), 145.82 (C^{Ar}), 133.31 (C^{Ar}), 127.41 (C^{Ar}), 108.51 (C^{Ar}), 106.43 (C^{Ar}), 100.85 (C^{16}), 63.10 (C^1), 57.29 (C^9), 53.92 (C^8), 39.60 (C^2), 37.52 (C^6), 31.87 (C^3), 30.56 (C^5), 29.45 (C^7), 25.36 (C^4); **IR** ν_{max} (thin film): 2921, 1504, 1229, 1039, 867, and 851 cm^{-1}; **HRMS** (ESI^+) Found $[M+H]^+$ = 258.1490; $C_{16}H_{20}O_2N_1$ requires 258.1489, Δ = +0.63 ppm; **M.p.** 78-80 °C (*racemic*), 100-102 °C (*enantiopure*); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ = –39.3 (*c* = 1.00; $CHCl_3$); = -24.5 (*c* = 0.65; $CHCl_3$), [lit. = -19.5].

Enantiomeric ratio was determined by HPLC with a Chiralcel® IB column (hexane:^{i}PrOH, 95.5:0.5; 1 mL/min; 230 nm; 25°C; t_r(major) = 14.6 min, t_r(minor) = 9.8 min; 99:1 er.

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