

**ASYMMETRIC SYNTHESIS OF
TETRAHYDROQUINOLINES VIA AZA-
MICHAEL REACTIONS**

A DISSERTATION FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

FROM IMPERIAL COLLEGE LONDON

BY

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DEPARTMENT OF CHEMISTRY
IMPERIAL COLLEGE LONDON

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Imperial College of Science, Technology and Medicine

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Asymmetric Synthesis of Tetrahydroquinolines *via aza*-Michael Reactions

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ABSTRACT

The tetrahydroquinolines structural unit is found in a number of natural products that exhibit a variety of biological activities including anti-allergic, anti-inflammatory and antitumour. As a result there is significant interest in their synthesis. This PhD thesis describes the work undertaken in the development of a new synthetic route that can be applied to the asymmetric synthesis of structurally diverse tetrahydroquinolines. The introductory chapter outlines the main current synthetic strategies towards tetrahydroquinolines and their application to the synthesis of some biologically interesting compounds.

Chapter 2 discusses work on the total asymmetric synthesis of the Galipea alkaloids. An *aza*-Michael reaction was used to install the required stereochemistry. Extensive optimisation of the *aza*-Michael reaction resulted in high enantioselectivities, with optically pure material obtained upon recrystallisation. Various synthetic procedures were investigated for formation of the tetrahydroquinoline ring system and the remainder of the synthesis, with the Galipea alkaloids obtained from a common precursor.

Work towards the formal synthesis of the Martinelline alkaloids, using the *aza*-Michael reaction to set the first stereocentre, is detailed in Chapter 3. A range of different α , β -unsaturated carbonyl and anilines were investigated for the *aza*-Michael reaction, with 85% enantioselectivity obtained on optimisation. Formation of the tetrahydroquinoline core was achieved and the installation of the second chiral centre investigated.

Chapter 4 describes any miscellaneous work conducted, including preliminary investigations towards the synthesis of levonantradol. The last Chapter contains the experimental procedures and characterisation data for all the compounds synthesised during the course of this project.

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ABBREVIATIONS

Ac	Acetyl group
AcOH	Acetic acid
AIBN	2,2'-Azobis(2-methylpropionitrile)
aq.	Aqueous solution
Ar	General aryl group
atm	Atmosphere(s)
BINAP	2, 2'- <i>Bis</i> (diphenylphosphino)-1, 1'-binaphthyl
BINAPO	2, 2'- <i>Bis</i> (diphenylphosphinyl)-1, 1'-binaphthyl
BINOL	1, 1'-Bi-2-naphthol
BKCa	Calcium-activated potassium channels
[BMIM]PF ₆	1-butyl-3-methylimidazolium hexafluorophosphate
Bn	Benzyl
Boc	<i>tert</i> -Butoxycarbonyl
br	Broad (spectral)
BSA	<i>Bis</i> (trimethylsilyl)acetamide
Bz	Benzoyl
Calcd.	Calculated
Cat.	Catalytic
CBz	Benzyloxycarbonyl
CETP	Cholesteryl ester transfer protein
CI	Chemical ionization
Cl-MeO-BIPHEP	5, 5'-Dichloro-6, 6'-dimethoxy-2, 2'- <i>bis</i> (diphenylphosphino)-1, 1'-biphenyl
COD	1,5-cyclooctadiene
COSY	Correlation spectroscopy

d	Doublet (spectral)
Db	Dibenzylideneacetone
DBU	1, 8-diazabicyclo-[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DHF	Dihydrofuran
DHP	Dihydropyran
DIBAL	Diisobutylaluminum hydride
DifluoroPhos	5, 5'-Bis(diphenylphosphino)-2, 2', 2'-tetrafluoro-4, 4'-bi-1, 3-benzodioxole
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMF	<i>N,N</i> -Dimethyl formamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
d.r	Diastereomeric ratio
Ee	Enantiomeric excess
EI	Electron impact
eq.	Number of molar equivalents
ESI	Electrospray ionisation
FAB	Fast atom bombardment
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
IBX	2-Iodoxybenzoic acid

IPA	Propan-2-ol
IR	Infrared
<i>J</i>	Coupling constants (Hz)
LAH	Lithium Aluminium Hydride
LC-MS	Liquid chromatography-mass spectroscopy
LDA	Lithium diisopropylamide
LHMDS	Lithium <i>bis</i> (trimethylsilyl)amide
Lit.	Literature
LUMO	Lowest unoccupied molecular orbital
m	Multiplet (spectral)
M	Molar (moles per litre)
M ⁺	Parent molecular ion
<i>m/z</i>	Mass-to-charge ratio
Max.	Maximum
MeO-Biphep	6, 6'-Dimethoxy-2, 2'- <i>bis</i> (diphenylphosphino)-1, 1'-biphenyl
2-Methyl CBS	3,3-Diphenyl-1-methyltetrahydro-3 <i>H</i> -pyrrolo[1,2- <i>c</i>][1,3,2]oxazaborole
Moc	Methoxycarbonyl
mol	Mole(s)
mp	Melting point
Ms	Mesyl
MS	Mass spectrometry
NaHMDS	Sodium <i>bis</i> (trimethylsilyl)amide
Nap	Naphthyl
NDMA	<i>N</i> -Methyl- <i>D</i> -Aspartate
NMO	4-Methylmorpholine <i>N</i> -oxide

NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
P-Phos	2,2',6,6'-Tetramethoxy-4,4'-bis(diphenylphosphino)-3,3'-Bipyridine
9- PBN	2,6-dimethyl-9-phenyl-9-phosphabicyclo[3.3.1]nonane
Pent	Pentyl
PPA	Polyphosphoric acid
Psi	Pounds per square inch
Py	Pyridine
q	Quartet (spectral)
R	Alkyl group
R_f	Retention factor
Rt	Room temperature
s	Singlet (spectral)
sat.	Saturated
SegPhos	5,5'-Bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole
SM	Starting material
SYNPHOS	6, 6'-Bis(diphenylphosphino)-2, 2', 3, 3'-tetrahydro-5, 5'-bi-1, 4-benzodioxin
S/C	Substrate to catalyst ratio
T	Temperature
t	Triplet (spectral)
TBAF	Tetrabutylammonium fluoride
TBDMS	<i>tert</i> -butyldimethyl silyl
TBDPS	<i>tert</i> -butyldiphenyl silyl

TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
TES	Triethylsilyl
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
THQ	Tetrahydroquinoline
TLC	Thin layer chromatography
Tol	Tolyl group
Tol-BINAP	2, 2'-Bis(di- <i>p</i> -tolylphosphino)-1, 1'-binaphthyl
TPAP	Tetrapropylammonium perruthenate
Ts	4-toluenesulfonyl
Vs	Versus
X	Generic functional group
X-Phos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
Y	Generic functional group
[α]	Specific rotation
δ	Chemical shift
ν	Wavenumber

CHAPTER ONE

INTRODUCTION

1.0 Biologically Interesting Tetrahydroquinolines

Quinolines and their derivatives are an important class of benzofused nitrogen heterocycles.¹ The tetrahydroquinoline structural unit is found in a number of natural products² that exhibit a variety of biological properties, including anti-allergic, anti-inflammatory³ and anti-tumour activities.⁴ They also attract attention as important synthetic intermediates.⁵ Many of these compounds contain substituents in the 2-, 3- and/or 4- positions of the ring (Figure 1.1), each constituting a stereogenic centre.

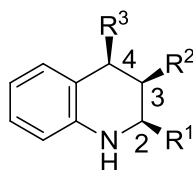


Figure 1.1: Tetrahydroquinoline core structure.

The pharmaceutical industry has a long-standing interest in compounds containing the tetrahydroquinoline core unit. Several libraries of substituted tetrahydroquinolines have been synthesised and screened for their potential as drug candidates. Some have found therapeutic uses, such as the 2-substituted tetrahydroquinoline oxaminiquine **1.1** (Figure 1.2), which is used to treat schistosomiasis, a parasitic disease.⁶

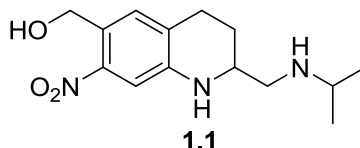


Figure 1.2: 2-substituted tetrahydroquinoline Oxaminiquine.

A selection of other tetrahydroquinolines with interesting biological activities is shown below (Figure 1.3).

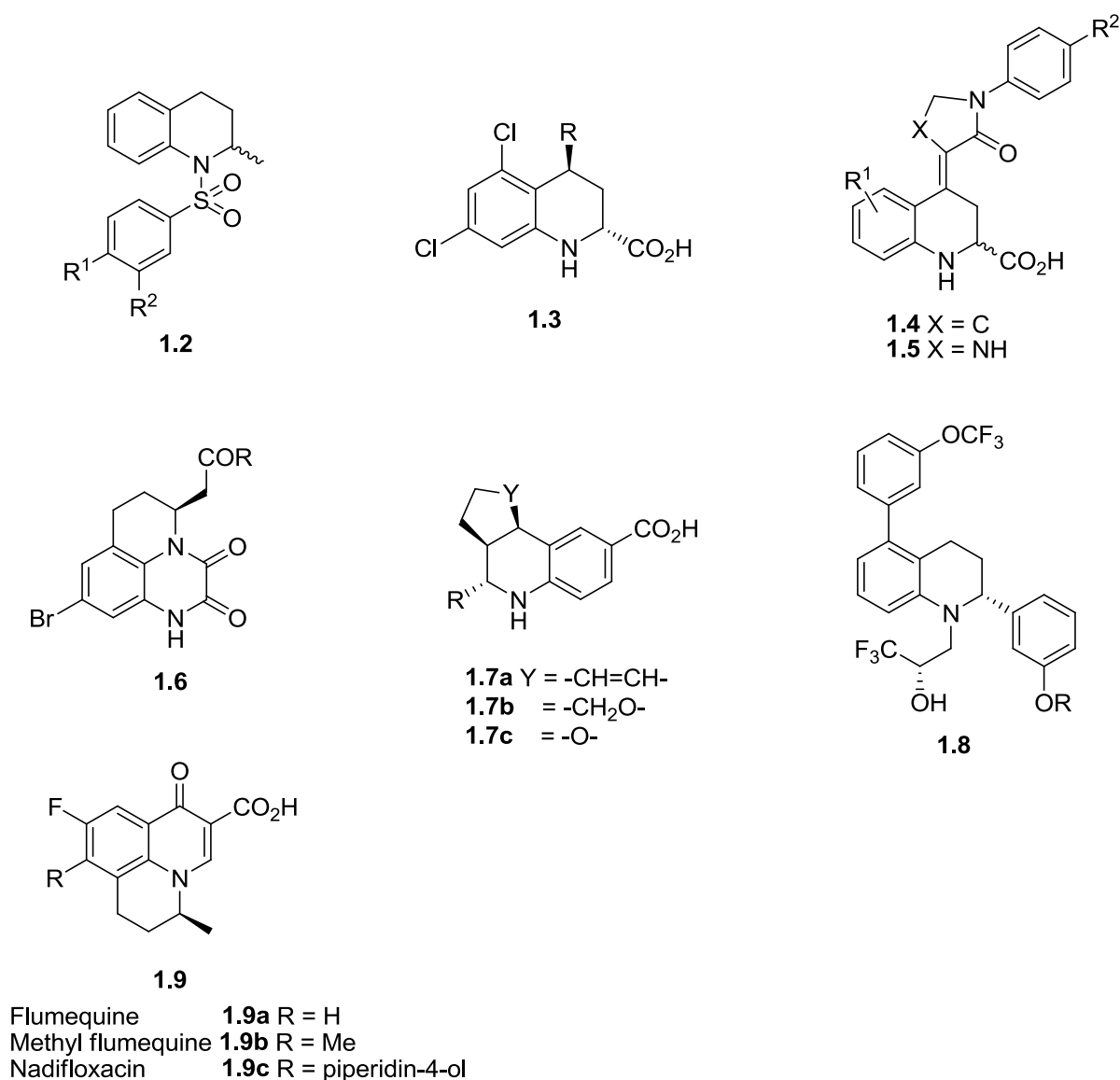


Figure 1.3: Biologically interesting tetrahydroquinolines.

2-Methyltetrahydroquinolines of type **1.2** show antiparasitic activity,⁷ whilst the compounds **1.3-1.6** are all potent antagonists of the NMDA receptor, which plays a role in neuronal cell death during conditions such as stroke.⁸⁻¹² The tricyclic family of tetrahydroquinolines with core structure **1.7a-c** are BKCa receptor antagonist, currently under investigation as novel agents to treat migraines by the regulation of neuronal excitability and synaptic transmission.¹³ The 2-phenyltetrahydroquinoline **1.8** is a potent CETP inhibitor, which could have potential therapeutic uses for the treatment of high cholesterol.¹⁴ The tricyclic fluoroquinolones **1.9a-c** are antimicrobial agents with high antibacterial activity,¹⁵ particularly towards gram-positive bacteria; all three quinolines show a significant difference in

effectiveness between the two enantiomers, with the (*S*)-enantiomer 64 to 256 times more potent than the (*R*)-enantiomer.¹⁶

Despite significant interest in tetrahydroquinolines, there are surprisingly few examples of their asymmetric synthesis. The following sections will be dedicated to the discussion of four tetrahydroquinolines of particular interest and relevance to the topic of our investigation. Two of these are naturally occurring alkaloids, while the others are synthetic molecules. Following this, the major enantioselective synthetic routes to tetrahydroquinolines will be presented. By far, the asymmetric hydrogenation of quinolines is the most utilised for the synthesis of optically pure 2-substituted tetrahydroquinolines; both metal and non-metal catalytic systems will be discussed. The next most commonly used synthesis for 2-, 3-, and 4-substituted tetrahydroquinolines is the inverse electron demand Diels-Alder reaction and this is discussed next. Following these will be other methodologies including: *aza*-Michael reactions, hydroamination reactions and miscellaneous examples used for the synthesis of specific tetrahydroquinolines. The Chapter will conclude with a discussion of the aims of the project.

1.0.1 Galipea Alkaloids

The Galipea alkaloids (Figure 1.4) are a group of four, 2-alkyl-tetrahydroquinolines, known to exhibit anti-malaria and cytotoxic activities, consisting of angustureine **1.10**, galipeine **1.11**, cuspareine **1.12** and galipinine **1.13**.¹⁷ Angustureine and galipeine were the first to be extracted from *Galipea officinalis* Hancock, a Venezuelan shrubby tree, in 1999 by Jacquemond-Collet *et al.*¹⁸ The natural configuration of angustureine was determined to be (*R*) by Theeraladanon *et al.* through the construction of the (*S*)-enantiomer in a complete stereo-defined manner.¹⁷ The other three alkaloids were all determined to be the (*S*)-enantiomer, by their total synthesis from quinolines using asymmetric hydrogenation.^{19, 20}

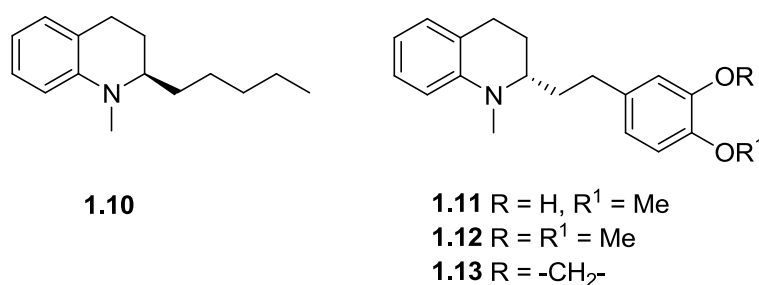


Figure 1.4: The Galipea alkaloids.

1.0.2 Martinelline Alkaloids

Preparations made from the root bark of the *Martinella* species have been used by Amazon Indian tribes for the treatment of eye ailments. In 1995, martinelline **1.14** and martinelllic acid **1.15** (Figure 1.5) were isolated from *Martinella iquitosensis* by Merck scientists. They were found to be the first non-peptidic Bradykinnin B1 and B2 receptor antagonist,²¹ with potent antibiotic activity against Gram-positive and Gram-negative bacteria²² and have an unprecedented hexahydropyrrolo[3,2-c]quinolines core structure.²³ ¹H NMR and NOE experiments confirmed the relative stereochemistry of the fused ring junction to be *syn*, whereas the stereochemistry of the adjacent 2-substituent was found to be *anti*, with respect to the ring junction.²¹ The absolute stereochemistry of martinelline was assigned by the total synthesis of both enantiomers and comparison of their optical rotation to that of the isolated natural product.

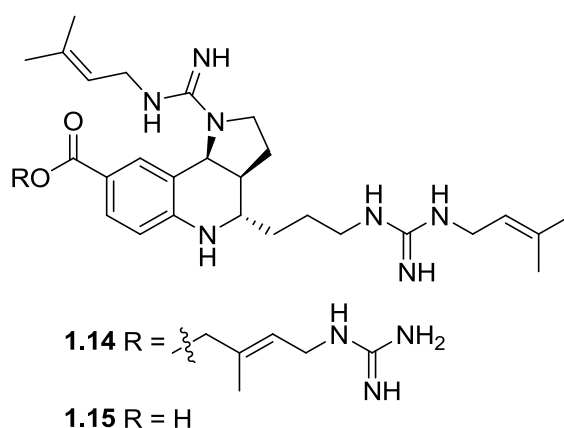


Figure 1.5: Martinelline alkaloids.

1.0.3 Torcetrapib

Torcetrapib **1.16** is a 2, 4-disubstituted tetrahydroquinoline (Figure 1.6), which was investigated as a potential substitute for Lipitor in the treatment of coronary heart disease. It inhibits the cholesteryl ester transfer protein (CETP), increasing the levels of “good” cholesterol and lowering the levels of “bad” cholesterol. However, development of Torcetrapib was stopped during phase III clinical trials, due to the increased risk of patient death.²⁴

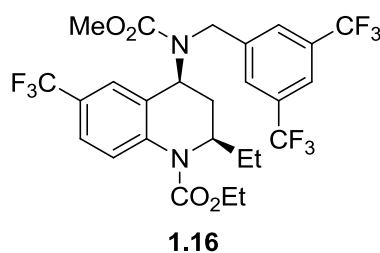


Figure 1.6: Torcetrapib.

1.0.4 Levonantradol

Levonantradol **1.17** is a tricyclic tetrahydroquinoline containing 5 chiral centres (Figure 1.7).²⁵ It is a synthetic cannabinoid developed by Pfizer in the 80's, possessing analgesic and antiemetic properties, with 9-14 times greater potency than morphine.²⁶ However, unlike morphine it is devoid of interactions with the opiate receptor. There has been significant interest in levonantradol over the last few decades, with a number of studies conducted into potential therapeutic uses, however, it has limited utility due to adverse effects.²⁷

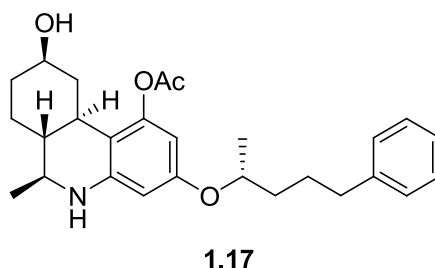


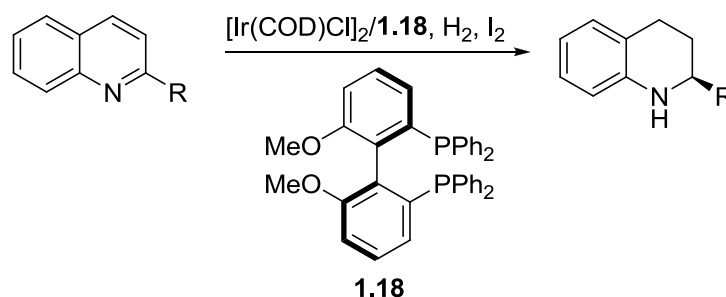
Figure 1.7: Levonantradol.

1.1 Quinoline hydrogenation

There is significant interest in the development of catalytic asymmetric hydrogenation reactions to yield optically pure heterocycles.²⁸ Although a variety of Rh, Ru and Ir complexes have been reported for the enantioselective hydrogenation of olefins, ketones and imines, a majority of these failed with heteroaromatic compounds.²⁹ Several factors contribute to the increased difficulty, for example resonance stability and catalytic poisoning, due to binding of the heteroatom to the metal centre.³⁰ However, in recent years a variety of examples of the asymmetric hydrogenation of quinolines have been reported. These will be presented in this section, in addition to their application to the synthesis of some of the biologically interesting compounds mentioned earlier. This Chapter concludes with a discussion of the mechanism.

1.1.1 Metal catalysed hydrogenations

The first asymmetric hydrogenation of quinolines was reported by Zhou in 2003, using a catalyst formed *in situ* from $[\text{Ir}(\text{COD})\text{Cl}]_2$ (0.5 mol%) and (*R*)-MeO-Biphep **1.18** (1.1 mol%), with I_2 as an activator (Scheme 1.1).²⁰ In the absence of iodine, the reaction only proceeded in < 5% yield.



Scheme 1.1: First asymmetric hydrogenation of 2-substituted quinolines.

The hydrogenation of a variety of 2-substituted quinolines proceeded with excellent yields and enantioselectivities of up to 94%. High ee's were achieved regardless of the length or nature of the side chain (Table 1.1, entries 1-3); branched (entry 4), arenethyl (entry 5), ester (entry 6) and alcohol functionalities (entry 7) can be tolerated. However, 2-aryl substituted quinolines gave lower ee values (entry 8). This system worked specifically for 2-substituted quinolines, with little to no enantioselectivity obtained with 3- or 4- substituted quinolines.

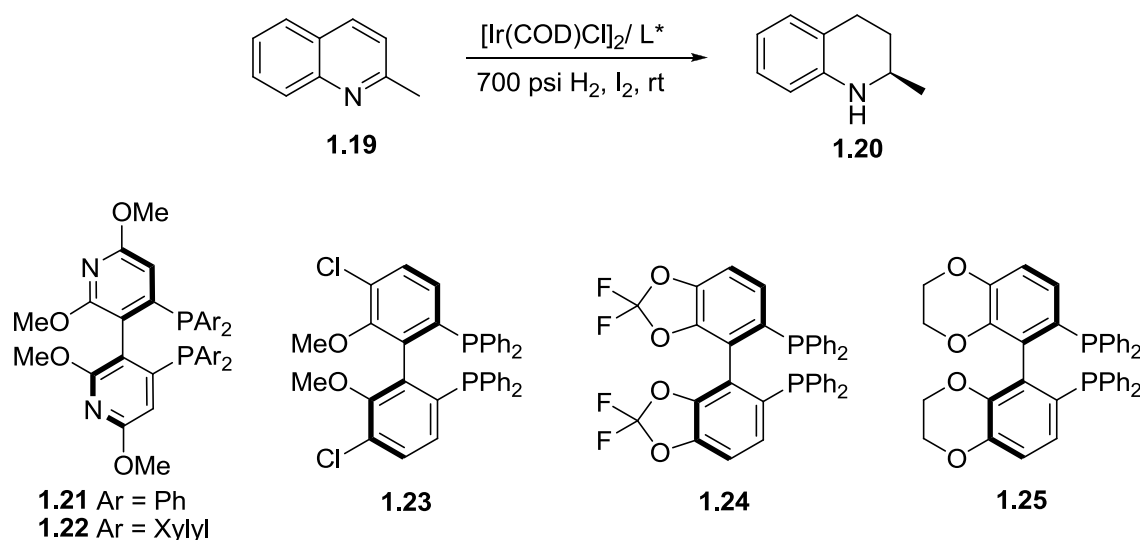
Table 1.1: Asymmetric hydrogenation of various 2-substituted quinolines.^a

Entry	R	% Yield ^b	% ee, (Config) ^c
1	Me	94	94 (<i>R</i>)
2	Et	88	96 (<i>R</i>)
3	<i>n</i> -Pr	92	93 (<i>R</i>)
4	<i>i</i> -Pr	92	94 (<i>S</i>)
5	$\text{CH}_2\text{CH}_2\text{Ph}$	95	93 (<i>R</i>)
6	$\text{CH}_2\text{OCOCH}_3$	90	87 (<i>S</i>)
7		87	94 (<i>S</i>)
8	Ph	95	72 (<i>S</i>)

^aReagents and conditions: Quinoline (1.0 mmol), $[\text{Ir}(\text{COD})\text{Cl}]_2$ (0.5 mol%), (*R*)-MeO-Biphep (1.1 mol%), I_2 (10 mol%), toluene (5 mL), H_2 (600-700 psi). ^bIsolated yields. ^cDetermined by chiral HPLC analysis.

There are two suggested functions for the iodine additive; the first is that the iodine activates the substrate *via* complexation to the nitrogen and the second involves the formation of a new highly active catalyst by oxidative addition. To determine the mode of action, Wang *et al.* pre-formed the iodo-quinoline complex and also the iodo-catalyst complex. No hydrogenation of the iodo-quinoline occurred on addition of catalyst, however the iodo-catalyst complex successfully hydrogenated 2-methylquinoline, suggesting that the iodine plays a role in catalyst activation.³¹

Various other ligands have also been investigated for the hydrogenation of 2-methylquinoline using the conditions developed by Zhou (Scheme 1.2, Table 1.2). Chiral bidentate phosphine ligands, in particular, have received much attention.



Scheme 1.2: Hydrogenation of 2-methylquinoline.

Chan *et al.* described a catalytic system generated *in situ* from $[\text{Ir}(\text{COD})\text{Cl}]_2$ and the electronically deficient biaryl phosphine ligand P-Phos **1.21** (Scheme 1.2, Table 1.2). The results were found to be comparable to that attained with MeO-Biphep (Table 1.2, entries 1 vs 2). Moreover, no degradation in ee was observed on exposing the catalytic system to air for 24 hours.³² However, the partial decomposition of the catalyst, in the presence of oxygen, during the hydrogenation process becomes significant on lowering the catalytic loading. Conducting the reactions under anaerobic conditions, and decreasing the iodine levels to 1.25-2.5%, allowed good results to be obtained at a S/C ratio as low as 50,000.³³ The catalyst

could be separated and recycled by conducting the reaction in a poly (ethylene glycol) dimethyl ether (DMPEG)-hexane mixture.³²

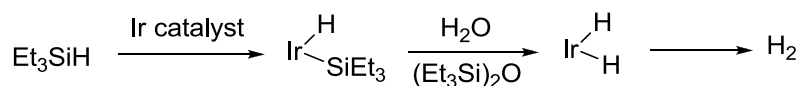
Subsequently, the use of Xylyl-P-Phos **1.22**, Cl-MeO-Biphep **1.23**, DifluorPhos **1.24** and SYNPHOS **1.25** was investigated by the same research team (Table 1.2, entries 3-6). Excellent conversions and comparable enantioselectivities were obtained irrespective of the ligand used.³⁴ Using DifluorPhos as ligand, catalytic loading may be lowered to 0.01 mol% without significant change in enantioselectivity (entry 7).³⁵ Re-use of the catalyst, however, resulted in a small decrease in activity after each cycle.³⁴

Table 1.2: Hydrogenation of 2-methylquinoline using various ligands.^a

Entry	Ligand	Catalytic loading/ mol %	I ₂ / mol %	Solvent	% Yield	ee %, (Config) ^b
1	(R)- 1.18	0.5	10	Toluene	94	94 (R)
2	(R)- 1.21	0.5	5.0	THF	97	91 (R)
3	(R)- 1.22	1.0	10	THF	99	92 (R)
4	(R)- 1.23	1.0	10	THF	99	91 (R)
5	(R)- 1.24	1.0	10	CH ₂ Cl ₂ /THF (1:1)	89	99 (R)
6	(R)- 1.25	1.0	10	CH ₂ Cl ₂ /THF (1:1)	89	99 (R)
7	(R)- 1.24	0.01	2.5	Toluene	99	94 (R)

^aReagents and conditions: Quinoline (1.0 mmol), [Ir(COD)Cl]₂ (0.01-1.0 mol%), ligand (1.1-2.1 mol%), I₂ (2.5-10 mol%), solvent (See table), H₂ (600-700 psi), rt, 20-24 hr. ^bDetermined by chiral HPLC.

More recently, the hydrogenation of 2-substituted quinolines was achieved by Zhou, using an [Ir(COD)Cl]₂/(S)-SegPhos (Figure 1.8), with water/silane as the hydrogen source. The reaction of a metal silane complex with H₂O resulted in formation of an Ir-dihydride complex, which liberated hydrogen gas by reductive elimination (Scheme 1.3). Good enantioselectivities of 83-93% and yields up to 98% were obtained using this system, with the exception of 2-phenylquinoline, which again proceeded with lower yield and ee.³⁶



Scheme 1.3: Generation of hydrogen from a silane and water.

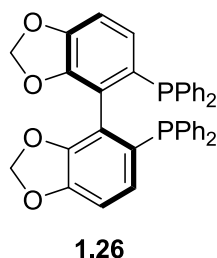


Figure 1.8: (S)-Segphos.

A range of other types of ligands have also been used for the hydrogenation of 2-methylquinoline (Figure 1.9, Table 1.3). Notably, several of these are derived from chiral BINOL (1.28, 1.30 and 1.31).

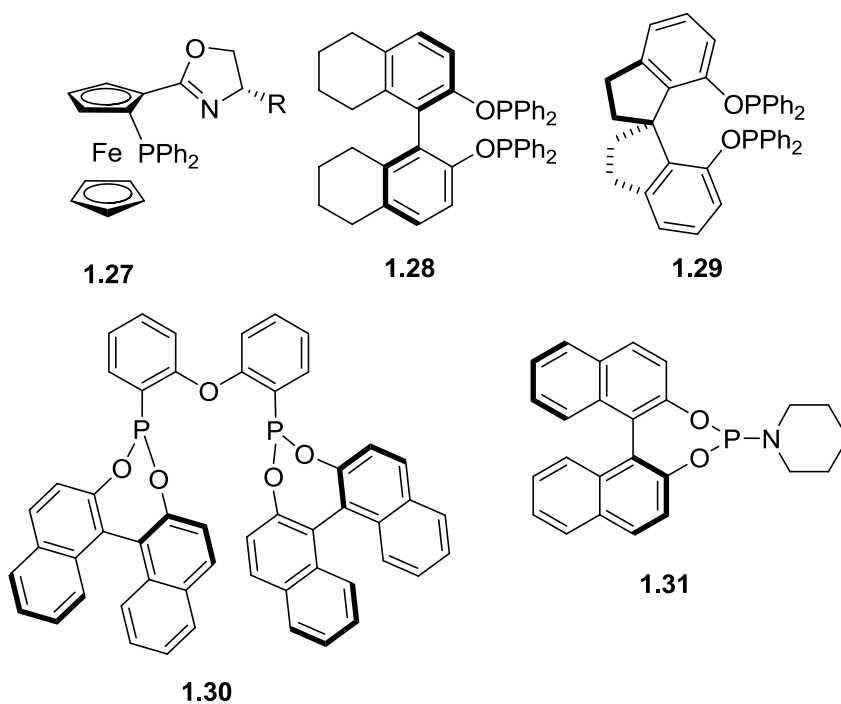


Figure 1.9: Ligands used for the asymmetric hydrogenation of 2-substituted quinolines.

Table 1.3: Asymmetric hydrogenation of 2-methyl quinolines **1.19** using various ligands.^a

Entry	Ligand (mol%)	Cat. loading (mol%)	Additive (mol%)	Pressure/ Psi	Temp/ °C	% Yield ^b	% ee, (Config) ^c
1	(<i>S</i> , <i>Sp</i>)- 1.27 (1.1)	0.5	I ₂ (5.0)	600	rt	95 ^d	90 (<i>R</i>)
2	(<i>R</i>)- 1.28 (1.1)	1.0	I ₂ (1.0)	700	rt	100	95 (<i>R</i>)
3	(<i>R</i>)- 1.29 (0.1)	0.05	I ₂ (1.0)	700	rt	100	92 (<i>R</i>)
4	(<i>S</i>)- 1.30 (1.0)	0.5	I ₂ (1.0)	870	rt	96	92 (<i>S</i>)
5	(<i>S</i>)- 1.31 (4.0)/ Tri- <i>o</i> -tolylphosphine (2.0)	1.0	Piperidine HCl (10)	725	60	100	89 (<i>S</i>)

^aReagents and conditions: Quinoline (1.0 mmol), [Ir(COD)Cl]₂ (0.05-1.0 mol%), ligand, additive, H₂, 20-24 hr.^bDetermined by ¹H NMR. ^cDetermined by chiral HPLC. ^dIsolated Yield.

All five ligands catalysed the hydrogenation of 2-methylquinoline in good yield and ee (Table 1.3).³⁷⁻⁴⁰ These reactions were conducted using [Ir(COD)Cl]₂/L*, H₂ and I₂, with the exception of ligand **1.31** (entry 5), where iodine was substituted with piperidine hydrochloride and the addition of an achiral ligand, tri-*o*-tolylphosphine, was also required to achieve high yields and enantioselectivities.³⁸ All systems accommodate changes in the 2-alkyl-substituent of the quinolines, and good results were obtained even for 2-aryl substituted quinolines, which has thus far proved problematic.³⁹

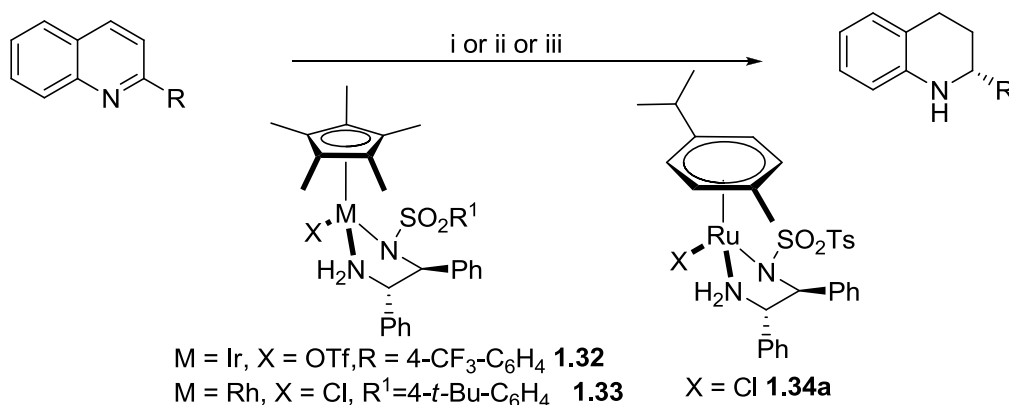
Attempts to lower the S/C ratio were met with limited success (Table 1.4). Increasing the ratio to 2000 for the MeO-Biphep catalysed reaction decreased the conversion to 7% (entry 1 vs 2). Significantly lowered yields and enantioselectivities were also obtained with (*R*)-H₈-BINAPO **1.28**, on increasing the S/C ratio to only 500 (entry 3 vs 4). The reaction with Spiropo **1.29**, however, proved the most robust; only a slight decrease in yield was observed on changing the S/C ratio from 100 to 5000 (entry 5 vs 6).³⁹

Table 1.4: Effect of S/C ratio on hydrogenation of 2-methylquinoline.^a

Entry	Ligand	S/C ratio	I ₂ / mol%	% Yield	% ee (Config) ^b
1	(<i>R</i>)- 1.18	200	10	94	94 (<i>R</i>) ^c
2 ^c	(<i>R</i>)- 1.18	2000	1.0	7	-
3	(<i>R</i>)- 1.28	100	1.0	100	95 (<i>R</i>)
4	(<i>R</i>)- 1.28	500	1.0	48	76 (<i>R</i>)
5	(<i>R</i>)- 1.29	100	1.0	100	92 (<i>R</i>)
6	(<i>R</i>)- 1.29	5000	1.0	91	92 (<i>R</i>)

^aReagent and conditions: Quinoline (1.0 mmol), [Ir(COD)Cl]₂ (see table), ligand (see table), I₂ (1.0-10 mol%), CH₂Cl₂ (5 mL), H₂ (600-700 psi), rt, 20 h. ^bDetermined by chiral HPLC. ^cReaction conducted in toluene.

The air-sensitivity of many of the catalysts described has driven much research into the development of more stable systems. To this end, three diamine-based catalysts were synthesised and used in the hydrogenation of 2-substituted quinolines (Scheme 1.4).⁴¹

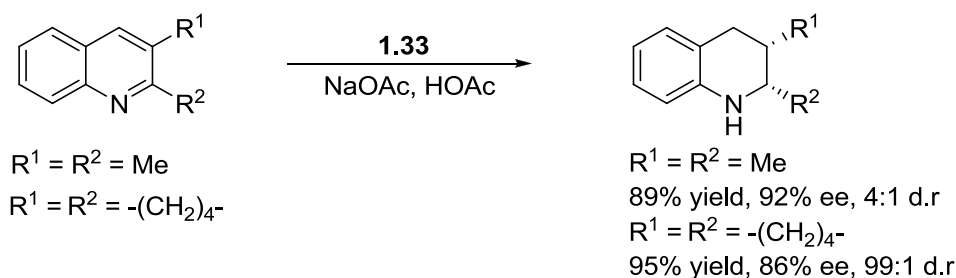


Scheme 1.4: Reagents and conditions: (i) **1.32**, TFA, H₂, MeOH, 15 °C; (ii) **1.33**, HCOONa, pH 5 buffer solution, 40 °C; (iii) **1.34a**, H₂, [BMIM]PF₆, 25 °C.

The hydrogenation of 2-substituted tetrahydroquinolines proceeded well with 1 mol% of the iridium catalyst **1.32**, in undegassed MeOH. The results were unaffected by exposing the reaction mixture to oxygen, or on stirring the catalyst under oxygen for 1 hour prior to use. Enantioselectivities and yields of 94-99% were consistently obtained, with the exception of 2-phenyl quinolines, which proceed in 90% yield and 79% ee.⁴¹ The hydrogenation also proceeded well with the ruthenium catalyst **1.34a**. Enantioselectivities of 96-99% and yields

of 87-97% were obtained, when the reaction was conducted in the ionic liquid [BMIM]PF₆, without the need for additives. Furthermore, catalyst was found to be highly stable in the ionic liquid, with the same activity observed even after exposure to air for 30 days. The catalyst proved highly recyclable with retention of reactivity and ee observed over 6 cycles.⁴²

The asymmetric hydrogenation of various 2-substituted quinolines was also performed under transfer hydrogenation conditions using the rhodium catalyst **1.33** in water. Excellent yields and enantioselectivities were obtained, irrespective of the nature of the side chain, using a buffered system to maintain the reaction at pH 5. 96% yield and 90% ee was obtained for the notoriously difficult hydrogenation of 2-phenyl quinoline. The hydrogenation of 2, 3-disubstituted quinolines was also achieved in excellent yields, ee's and d.r's., giving the *syn* disubstituted product as the major diastereoisomer (Scheme 1.5).⁴³



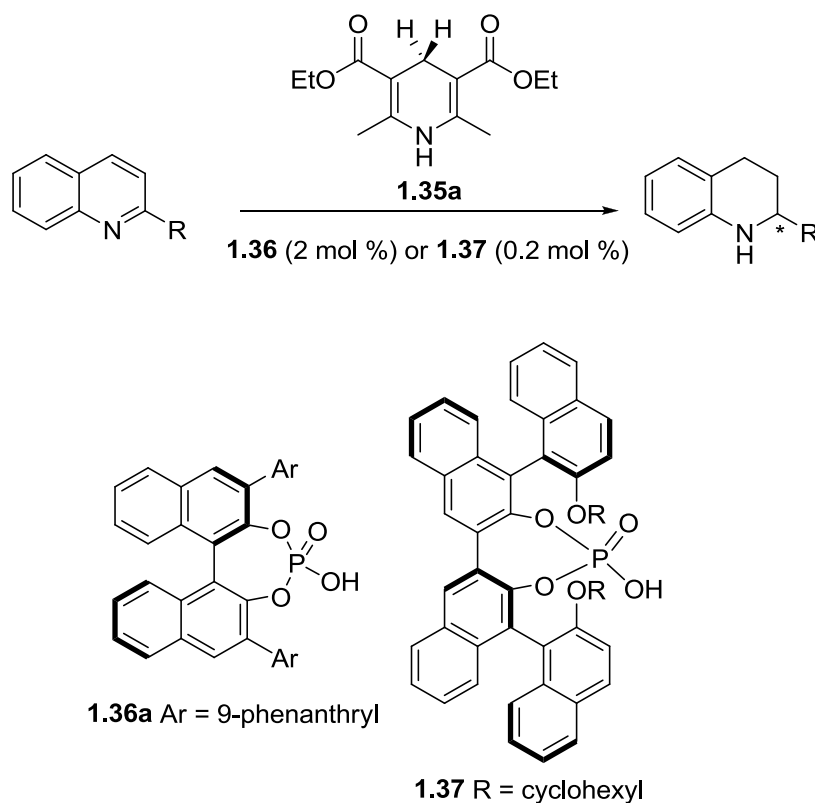
Scheme 1.5: Hydrogenation of 2, 3-disubstituted quinolines.

In summary, the first asymmetric hydrogenation of quinolines was developed by Zhou, using a Ir[COD]Cl₂/(*R*)-MeO-Biphep catalytic system and I₂ as activator. A range of 2-alkyl substituted tetrahydroquinolines were formed in excellent ee's and yields. In contrast, the reduction of 2-phenylquinoline proceeded with lower enantioselectivity. Subsequently, a variety of different diphosphine ligands have been reported. The use of P-Phos as ligand created an air stable catalyst, which afforded comparable enantioselectivities to MeO-Biphep. This catalyst could also be recycled and reused in the reaction with comparable ee. Very good results were achieved with the ligand **1.29** at low catalytic loadings. To date, there is only one example where 2, 3- tetrahydroquinolines were successfully formed in good yields, ee's and dr's, using a Ph catalyst.

In the next section, the hydrogenation of quinolines using non-metal, phosphoric acid catalysts will be presented.

1.1.2 Non-metal catalysed hydrogenations

The non-metal catalysed asymmetric hydrogenation of various 2-substituted quinolines can be achieved using chiral phosphoric acids **1.36a** and **1.37** as catalyst and the Hantzsch ester **1.35a** as the hydrogen source (Scheme 1.6).^{29, 44}



Scheme 1.6: Phosphoric acid-catalysed hydrogenation of 2-substituted quinolines.

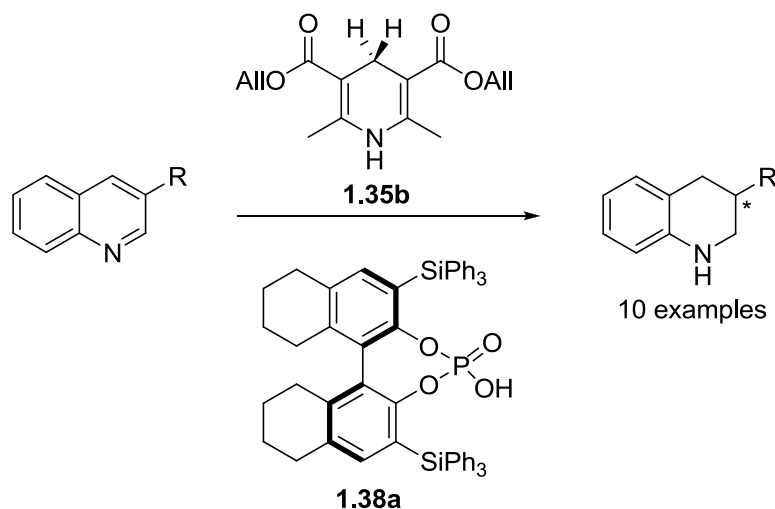
Table 1.5: Hydrogenation of 2-substituted quinolines using chiral phosphoric acids.^a

Entry	Chiral phosphoric acid (mol%)	R	Temp/ °C	% Yield	% ee, (Config) ^b
1	(<i>R</i>)- 1.36a (2.0 mol%)	<i>n</i> -Bu	60	91	87 (<i>R</i>)
2	(<i>R</i>)- 1.36a (2.0 mol%)	<i>n</i> -pent	60	88	90 (<i>R</i>)
3	(<i>R</i>)- 1.36a (2.0 mol%)	Ph	60	92	98 (<i>S</i>)
4	(<i>R</i>)- 1.37 (0.2 mol%)	<i>n</i> -Bu	35	99	94 (<i>R</i>)
5	(<i>R</i>)- 1.37 (0.2 mol%)	<i>n</i> -pent	35	99	92 (<i>R</i>)
6	(<i>R</i>)- 1.37 (0.2 mol%)	Ph	35	99	96 (<i>S</i>)

^aReagents and conditions: Quinoline (0.1 mmol), **1.35a** (2.4 eq), phosphoric acid (see table), 20 h. ^bDetermined by chiral HPLC.

Changing the length of the side chain from an *n*-butyl group to an *n*-pentyl group, had little effect on the results obtained (Table 1.5, entry 1 vs 2 and 4 vs 5). Good enantioselectivities and yields were also obtained for the hydrogenation of 2-phenylquinoline (entries 3 and 6). Thus, this appears to be a complementary methodology to the metal catalysed reactions.

Unusually, the hydrogenation of 3-substituted quinolines was also attempted using the chiral phosphoric acid catalyst **1.38a**, with the allyl-substituted **1.35b** as the hydrogen source (Scheme 1.7). The reaction proceeded to give the tetrahydroquinolines in moderate ee (77-86%) and variable yields (30-76%).⁴⁵

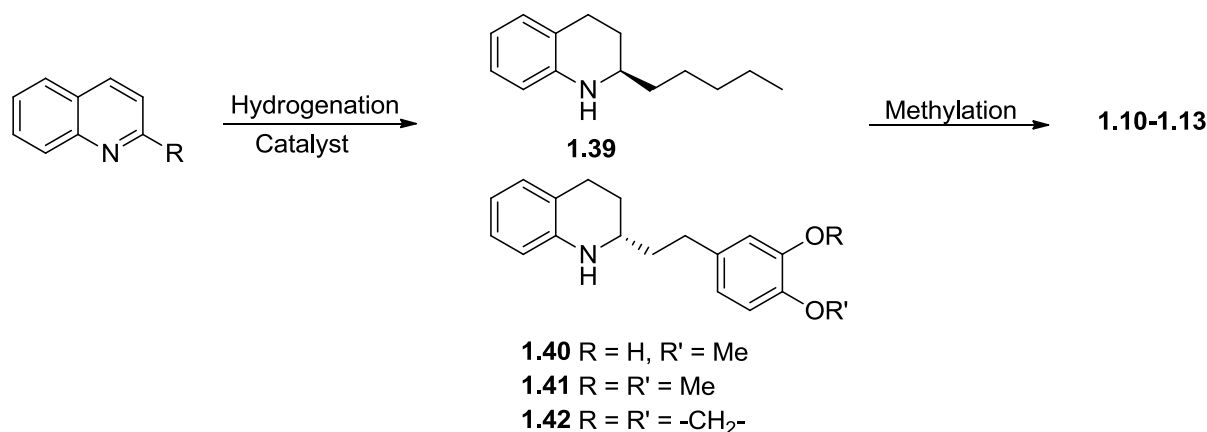


Scheme 1.7: Hydrogenation of 3-substituted quinolines.

In summary, chiral phosphoric acids catalyse the hydrogenation of 2-substituted quinolines, with Hantzsch esters as the hydrogen source, to give optically pure tetrahydroquinolines. The hydrogenation of 2-phenylquinoline, which often proves difficult for metal-catalysed processes, was achieved in good ee's and yields with both phosphoric acids **1.36a** and **1.37**. The rarely reported hydrogenation of 3-substituted tetrahydroquinolines was achieved with the chiral phosphoric acid **1.38a** in moderate ee's and variable yields.

1.1.3 Applications to natural product synthesis

The Galipea alkaloids precursors **1.39-1.42** have all been synthesised by asymmetric hydrogenation of quinolines. The Galipea alkaloids are easily obtainable from the reduced product, by the methylating of the nitrogen (Scheme 1.8).²⁹



Scheme 1.8: Synthesis of the Galipea Alkaloids *via* asymmetric hydrogenation.

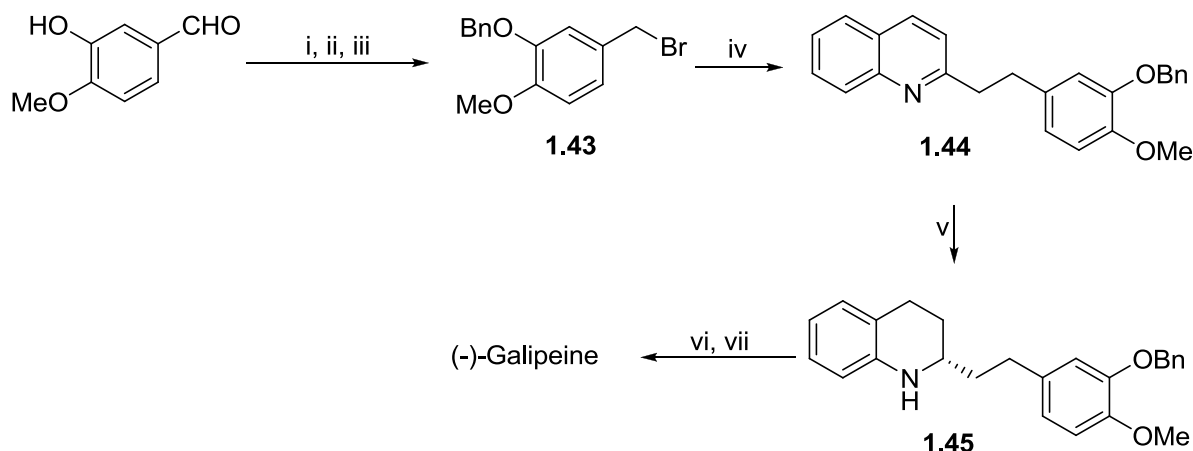
A large number of the systems previously described have been applied to the synthesis of the angustureine precursor **1.39**, in excellent enantioselectivities of 90-96%.^{33-35, 38, 39} Fewer systems, however, were used for the synthesis of the other Galipea alkaloids (Table 1.6). The original [Ir(COD)Cl]₂/MeO-Biphep system developed by Zhou²⁰ was applied to the synthesis of angustureine, cuspareine and galipinine precursors **1.39**, **1.41** and **1.42**, respectively, in good yields and enantioselectivities (Table 1.6, entries 1-3). In comparison, hydrogenation using the [Ir(COD)Cl]₂ system with Segphos **1.26**³⁶ proceeded in lower yields and enantioselectivities (entries 4-6). This was also the case with the ferrocenyloxazoline ligand **1.27**,⁴⁰ which proceeded to give two of the tetrahydroquinolines **1.39** and **1.41**, in lower enantioselectivities of 92% and 87% (entries 7-8). On the other hand, the use of the air stable diamine iridium and ruthenium catalysts **1.32**⁴¹ (entries 9-11) and **1.34a**⁴² (entries 14-16) proceeded to give the precursors **1.39**, **1.41** and **1.42** in excellent yields and enantioselectivities, whilst the Rh complex **1.33**⁴³ afforded **1.39** and **1.42** with similar results (entries 12 and 13). Last but not least, the phosphoric acid catalysts **1.36a**²⁹ and **1.37**⁴⁴ were used for the synthesis of **1.39**, **1.41** and **1.42**, with the reactions proceeding to give the tetrahydroquinolines in excellent yields but somewhat lower enantioselectivities (entries 17-22).

Table 1.6: Synthesis of Galipea alkaloids *via* asymmetric hydrogenation reactions.^a

Entry	Product	Cat. System	Cat. Loading/ mol%	% Yield	% ee, (Config) ^b
1	1.39	[Ir(COD)Cl] ₂ /(<i>R</i>)- 1.18 , H ₂ , I ₂	0.5	92	94 (<i>R</i>)
2	1.41	[Ir(COD)Cl] ₂ /(<i>R</i>)- 1.18 , H ₂ , I ₂	0.5	86	96 (<i>R</i>)
3	1.42	[Ir(COD)Cl] ₂ /(<i>R</i>)- 1.18 , H ₂ , I ₂	0.5	88	93 (<i>R</i>)
4	1.39	[Ir(COD)Cl] ₂ /(<i>S</i>)- 1.26 , H ₂ , H ₂ O, Et ₃ SiH	1	96	88 (<i>S</i>)
5	1.41	[Ir(COD)Cl] ₂ /(<i>S</i>)- 1.26 , H ₂ , H ₂ O, Et ₃ SiH	1	84	83 (<i>S</i>)
6	1.42	[Ir(COD)Cl] ₂ /(<i>S</i>)- 1.26 , H ₂ , H ₂ O, Et ₃ SiH	1	94	86 (<i>S</i>)
7	1.39	[Ir(COD)Cl] ₂ /(<i>S</i> , <i>S</i>)- 1.27 , H ₂ , I ₂	0.5	94	92 (<i>R</i>)
8	1.41	[Ir(COD)Cl] ₂ /(<i>S</i> , <i>S</i>)- 1.27 , H ₂ , I ₂	0.5	82	87 (<i>R</i>)
9	1.39	(<i>S</i> , <i>S</i>)- 1.32	0.2	98	96 (<i>S</i>)
10	1.41	(<i>S</i> , <i>S</i>)- 1.32	0.2	96	96 (<i>S</i>)
11	1.42	(<i>S</i> , <i>S</i>)- 1.32	0.2	97	97 (<i>S</i>)
12	1.39	(<i>S</i>)- 1.33	1	92	97 (<i>S</i>)
13	1.42	(<i>S</i>)- 1.33	1	85	97 (<i>S</i>)
14	1.42	(<i>S</i> , <i>S</i>)- 1.34a	1	96	98 (<i>S</i>)
15	1.41	(<i>S</i> , <i>S</i>)- 1.34a	1	96	97 (<i>S</i>)
16	1.39	(<i>S</i> , <i>S</i>)- 1.34a	1	97	98 (<i>S</i>)
17	1.39	(<i>R</i>)- 1.36a /1.35a	2	88	90 (<i>R</i>)
18	1.41	(<i>R</i>)- 1.36a /1.35a	2	95	90 (<i>R</i>)
19	1.42	(<i>R</i>)- 1.36a /1.35a	2	94	91 (<i>R</i>)
20	1.39	(<i>R</i> , <i>R</i>)- 1.37 /1.35a	0.2	99	92 (<i>R</i>)
21	1.42	(<i>R</i> , <i>R</i>)- 1.37 /1.35a	0.2	99	95 (<i>R</i>)
22	1.41	(<i>R</i> , <i>R</i>)- 1.37 /1.35a	0.2	99	90 (<i>R</i>)

^aReagent and conditions: Quinoline (1.0 mmol), catalyst (see table). ^bDetermined by chiral HPLC.

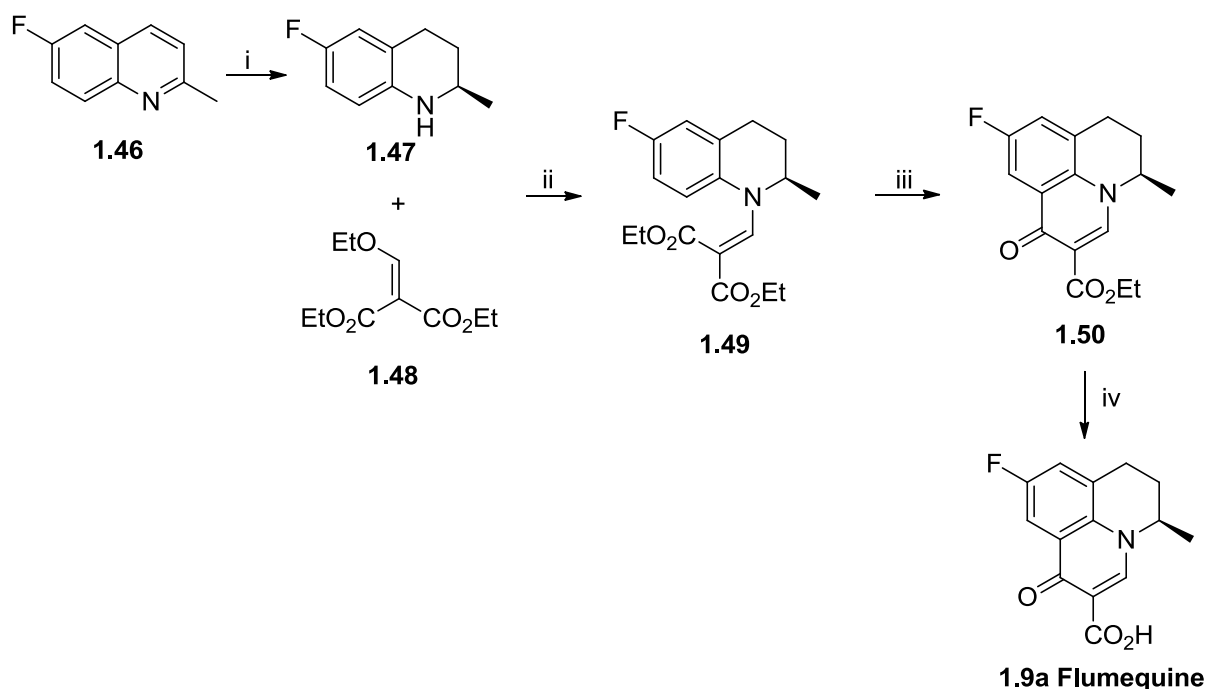
There is only one reported total synthesis of (-)-galipeine, which was achieved by asymmetric hydrogenation (Scheme 1.9).¹⁹



Scheme 1.9: Reagents and conditions: (i) BnCl, NaHCO₃, KI, MeCN, 89%; (ii) NaBH₄, MeOH, 96%; (iii) PBr₃, Et₂O/pyridine, 85%; (iv) Quinaldine, *n*-BuLi, Et₂O, 86%; (v) [Ir(COD)Cl]₂/(*S*)-MeO-Biphep, I₂, H₂ (500 psi), toluene, 94%, (vi) HCHO, AcOH, NaBH₃CN, MeCN, 96%; (vii) 5% Pd/C, EtOAc, AcOH, 95%.

The benzyl bromide **1.43** was synthesised from the commercially available isovanillin in three steps. Lithiation of quinaldine with *n*-BuLi, followed by the addition of **1.43** gave the 2-substituted quinoline **1.44**. Asymmetric hydrogenation, using the [Ir(COD)Cl]₂/(*S*)-MeO-Biphep system developed by Zhou, proceeded to give the tetrahydroquinoline **1.45** in 94% yield and 96% ee. Finally, methylation of the tetrahydroquinoline nitrogen and removal of the benzyl protecting group gave (-)-galipeine in 7 steps with 54% overall yield.

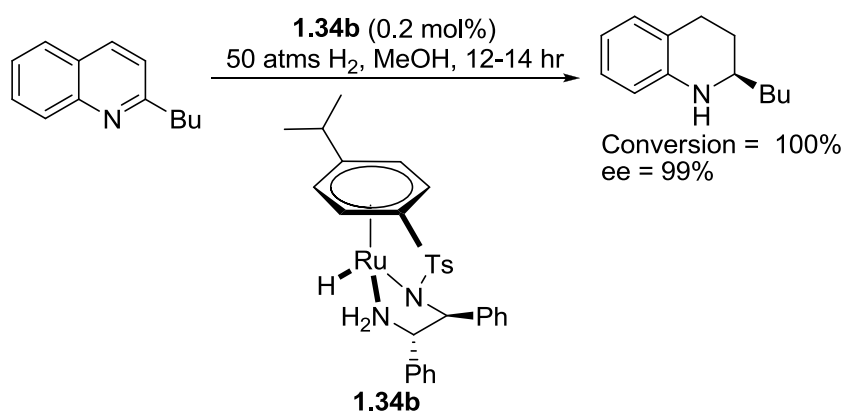
The total synthesis of flumequine **1.9a**, has also been achieved by asymmetric hydrogenation as the key step (Scheme 1.10). Using the chiral phosphoric acid catalyst **1.38a**, the THQ **1.47** was formed in 83% yield and 95% ee. Alkylation of **1.47** with diethyl(ethoxymethylene) malonate **1.48** gave **1.49**, which was subjected to electrophilic cyclisation and hydrolysis to form the tricyclic fluoroquinoline in 5 steps with an overall yield of 61%.⁴⁶



Scheme 1.10: Reagent and conditions: (i) **1.38a**, **1.35a**, benzene, 60 °C, 95%; (ii) 125 °C then 10 mbar; (iii) PPA, 110 °C; (iv) H₂O, H⁺, 100 °C.

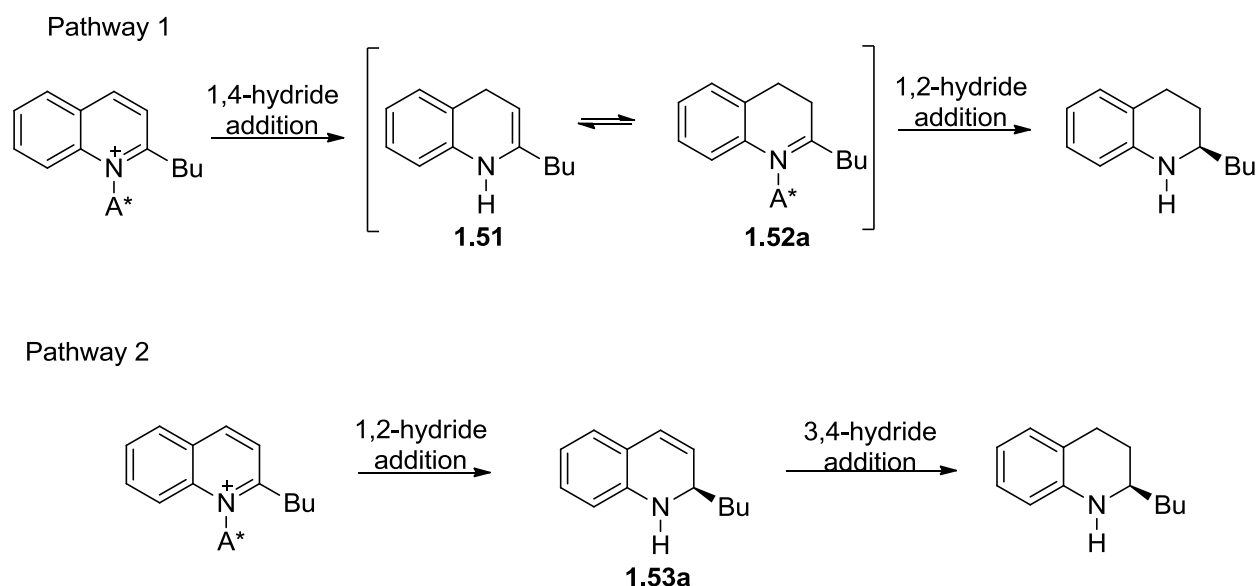
1.1.4 Mechanism

The hydrogenation of various 2-substituted tetrahydroquinolines by the Ru-hydride catalyst **1.34b** has been investigated very recently (Scheme 1.11).⁴⁷



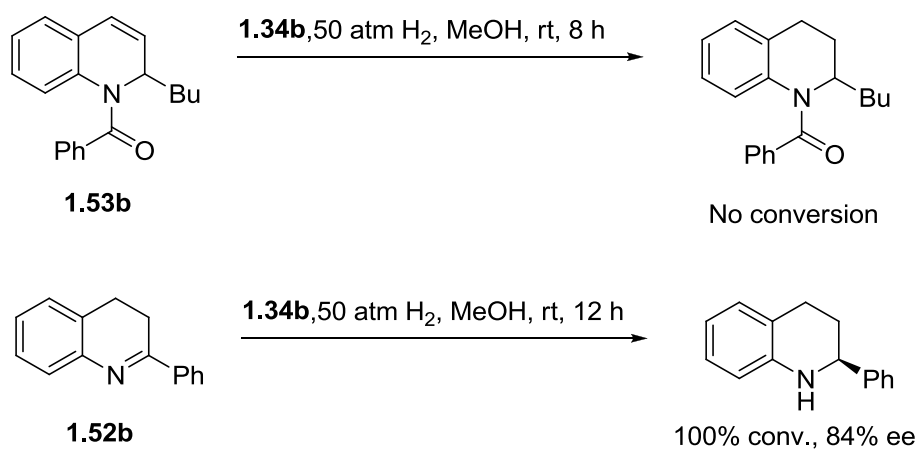
Scheme 1.11: Hydrogenation system investigated for mechanistic studies.

Activation of the quinoline by binding to the catalyst is required prior to the hydrogenation step. The subsequent additions of H₂ may proceed *via* two possible pathways (Scheme 1.12).



Scheme 1.12: Two possible hydrogenation mechanisms.

To determine the operating mechanism, the *N*-benzoyl protected **1.53b** was prepared and subjected to the hydrogenation conditions. No conversion to the product was observed (Scheme 1.13). In contrast, the hydrogenation of the imine **1.52b** proceeded to give the desired tetrahydroquinoline in comparable ee and yield to that obtained on hydrogenation of the quinoline. In addition, the presence of the imine intermediate **1.52b** was detected in the reaction mixture by ^1H NMR and ESI-HRMS. This confirmed that the hydrogenation proceeds along pathway 1, through the imine.⁴⁷ Therefore, the key step in the mechanism is proposed to take place *via* enantioselective hydride transfer to the imine, catalysed by the (re)coordination of the catalyst to the nitrogen of the dihydroquinoline intermediate (Scheme 1.12).

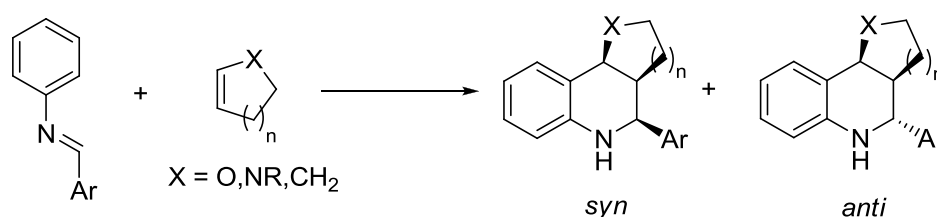


Scheme 1.13: Determination of reaction pathway

Although the hydrogenation of 2-substituted tetrahydroquinolines proceeded smoothly, allowing for the synthesis of some biologically interesting tetrahydroquinolines, there are very few examples where asymmetric hydrogenation has been applied to the synthesis of 3-substituted tetrahydroquinolines and, as yet, there are no examples of the asymmetric hydrogenation of 4-substituted quinolines. This limits the application of the methodology to the synthesis of more complex natural products. In the next section we will discuss the formation of tetrahydroquinolines using *aza*-Diels-Alder reactions, often used for the synthesis of highly substituted tetrahydroquinolines.

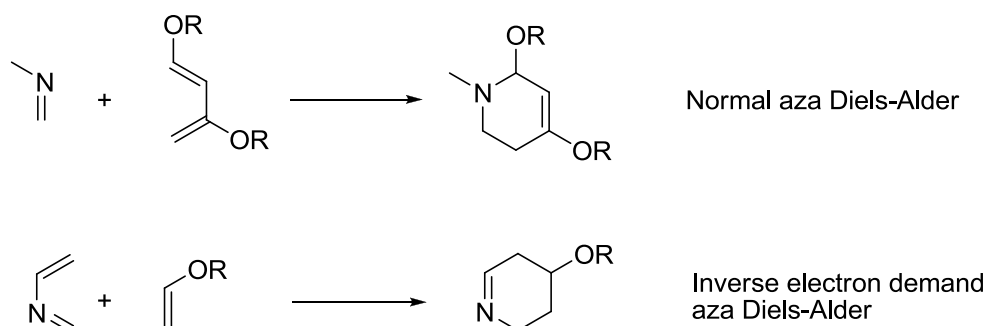
1.2 Diels-Alder reaction

The *aza*-Diels-Alder reaction known as the Povarov reaction,⁴⁸ describes a [4+2] cycloaddition reaction between *N*-arylimines and electron rich dienophiles. It is one of the most popular and powerful synthetic methods for the synthesis of 1, 2, 3, 4-substituted tetrahydroquinolines (Scheme 1.14).



Scheme 1.14: General *aza*-Diels-Alder reaction for the formation of tetrahydroquinolines.

These cyclisations are also described as ‘inverse electron demand’ (IED) reactions, where the HOMO of the dienophile reacts with the LUMO of the diene. They occur when the *aza*-diene is very electron poor and the dienophile contains electron donating groups (Scheme 1.15).⁴⁹



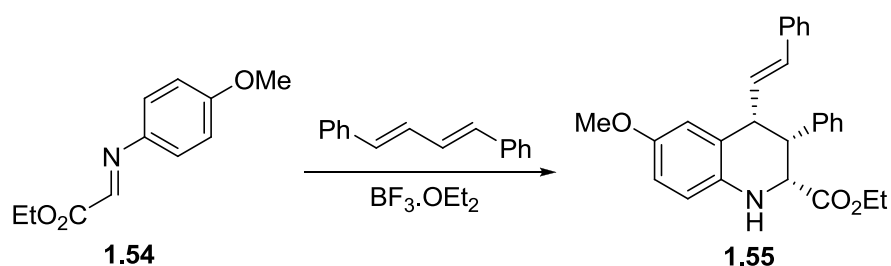
Scheme 1.15: Normal and inverse electron demand *aza*-Diels-Alder reactions.⁴

Lewis acid catalysts are widely used for IED *aza*-Diels-Alder reactions, during which, up to three chiral centres can be created. The catalyst acts by coordination to the *aza*-diene, enhancing the interaction between the HOMO and LUMO orbitals.⁵⁰

In this section, the synthesis of 2, 4-substituted tetrahydroquinolines and 2, 3, 4-substituted tetrahydroquinolines *via* IED Diels-Alder reactions will be described. The mechanism of the reaction will be discussed initially, followed by examples of metal-catalysed reactions. This will be followed by non-metal catalysed IED Diels-Alder reactions, and finally the chapter concludes with examples where these Diels-Alder reactions have been applied to the synthesis of some biologically interesting tetrahydroquinolines.

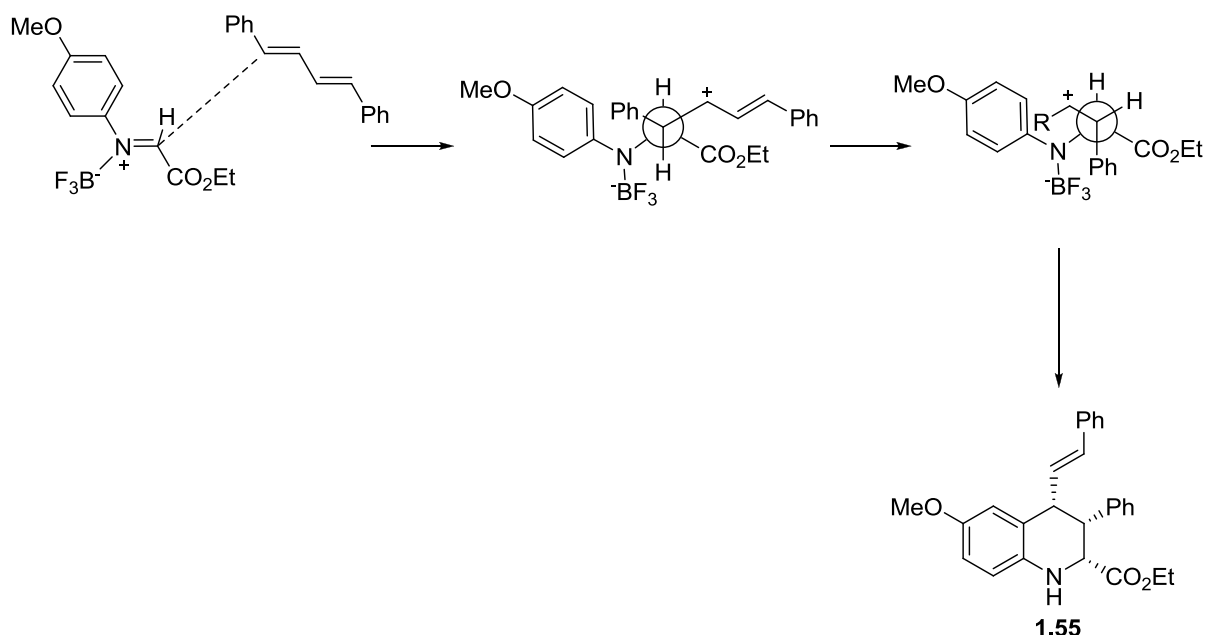
1.2.1 Mechanism

Whilst the Diels-Alder reaction is generally believed to proceed with retention of the alkene geometry, the $\text{BF}_3 \cdot \text{OEt}_2$ catalysed reaction of *N*-arylimines with *trans* 1, 4-disubstituted dienes gave the *syn* 2, 3, 4-substituted tetrahydroquinoline exclusively, *i.e.* the stereochemistry of the diene was not conserved in the product (Scheme 1.16).⁵¹



Scheme 1.16: Diels-alder reaction of an imine with a 1-mono substituted diene.

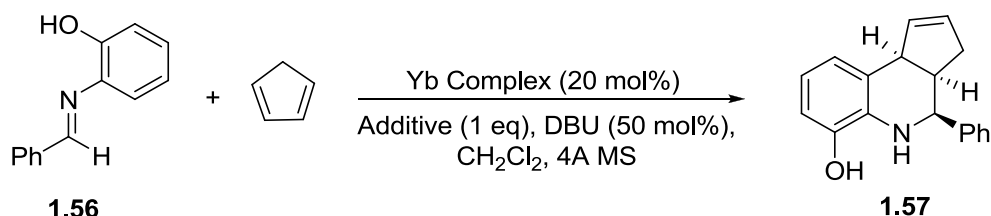
Based on these observations, an ionic mechanism was proposed, where the diene approaches the activated imine along the least hindered pathway to create a cationic intermediate (Scheme 1.17). Attack by the aromatic ring, after C-C bond rotation, yielded the tetrahydroquinoline derivative.



Scheme 1.17: Ionic pathway for the *aza*-Diels-Alder reaction.⁵¹

1.2.2 Metal catalysed *aza*-Diels-Alder reactions

The first catalytic asymmetric *aza*-Diels-Alder reaction of *N*-benzylidene-2-hydroxyaniline with cyclopentadiene was reported by Kobayashi and co-workers, using a chiral ytterbium-BINOL complex (Scheme 1.18).⁵²



Scheme 1.18: Diels-Alder reaction of cyclopentadiene with *N*-benzylidene-2-hydroxyaniline.

Without any additives, the reaction between **1.56** and cyclopentadiene proceeded to give the *syn* isomer, as shown in **1.57**, almost exclusively (>98:2) in 62% ee. The use of *N*-benzylideneaniline gave no chiral induction, so it was suggested that the presence of the phenol group on **1.56** allowed for the bidentate binding of the catalyst, leading to enantioselective control. The addition of 2, 6-di-*tert*-butylpyridine to interact with the phenolic hydrogen, improved the results, giving the cycloadduct in 92% yield and 71% ee. The phenolic hydrogen-additive interaction is believed to fix the *aza*-diene in place (Figure

1.10). In addition, the BINOL-ligated Yb complex is believed to form two hydrogen bonds with DBU, transferring the axial chirality of the ligand into the reaction sphere and shielding the top face of the imine from attack.

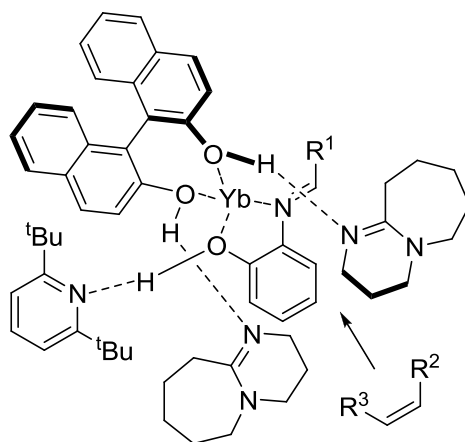
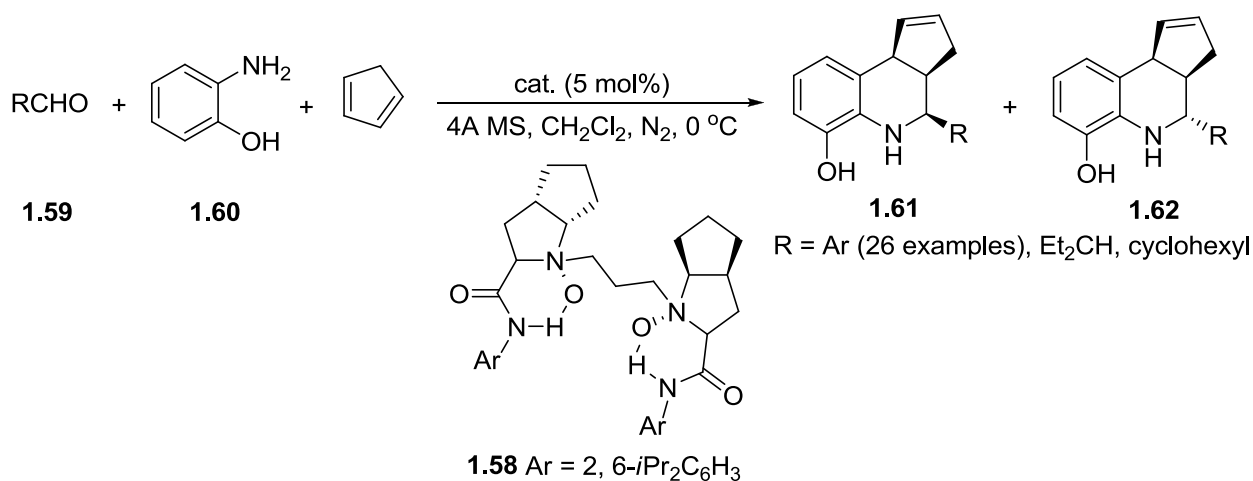


Figure 1.10: Binding of chiral Lewis acid and additive to the *aza*-diene.

Recently, Xie *et al.* reported the synthesis of fused tetrahydroquinolines using a $\text{Sc}(\text{OTf})_3$ complex with a chiral *N,N'*-dioxide ligand (Scheme 1.19).⁵³

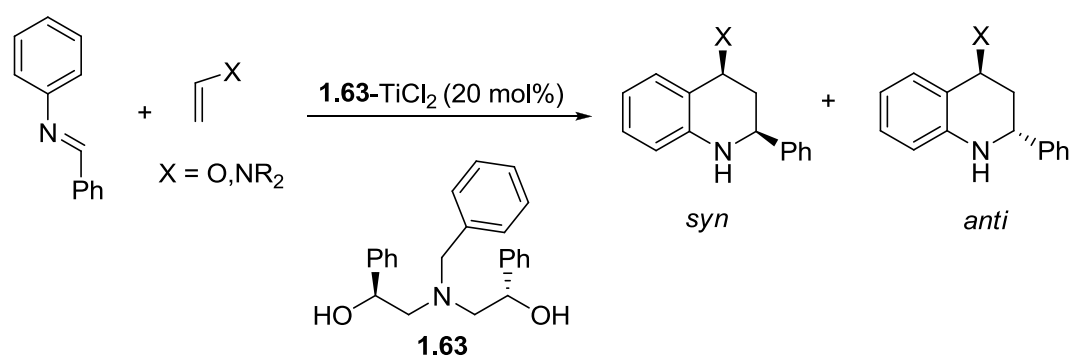


Scheme 1.19: $\text{Sc}(\text{OTf})_3$ catalysed synthesis of THQ.

A range of aromatic aldehydes were reacted with 2-hydroxyaniline and cyclopentadiene to produce the tetrahydroquinolines with preferential formation of the syn isomer 1.61 (>90:10), in excellent enantioselectivities (>90%). Aliphatic aldehydes were also suitable substrates, giving the tetrahydroquinolines with enantioselectivities between 94-99%. The reaction is both air- and moisture- tolerant, and catalytic loading can be reduced to 2.5 mol% without loss of selectivity. Although the reaction can tolerate a range of aldehydes, the choice of

aniline is limited to those containing a hydroxyl group in the 2-position, and attempts to use other dienophiles were also unsuccessful.

In 2001, Sundererjan *et al.* reported the asymmetric synthesis of tetrahydroquinolines using a chiral titanium complex generated from a mixture of di-isopropoxide titanium dichloride with the amino diol ligand **1.63**.⁵⁰ The cycloadditions of several dienophiles with benzylidene aniline were examined in the presence of this titanium complex (Scheme 1.20). The reaction gave mixtures of the *syn*- and *anti*- isomers in varying ratios and enantioselectivities (Table 1.7).



Scheme 1.20: Titanium catalysed Diels-Alder reaction of *N*-aryl imines.

Table 1.7: Results of Ti catalysed IED Diels-Alder reaction of various dienophiles.^a

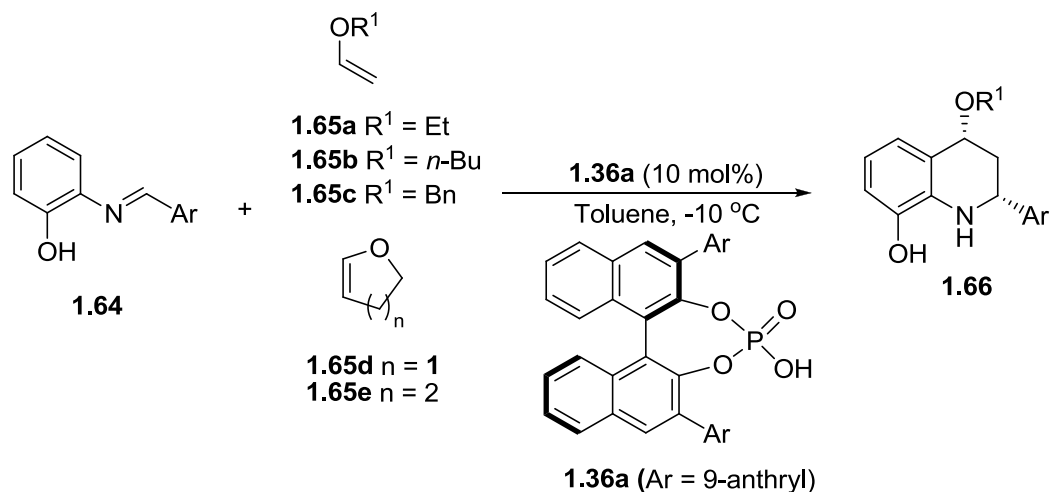
Entry	Dienophile	T/ °C	% Conversion	Ratio of <i>syn/anti</i>	% ee of <i>syn</i> ^b	% ee of <i>anti</i> ^b
1	Dihydropyran	0	60	0.25	92	10
2	Ethylvinyl ether	35	65	0.67	90	50
3	Dihydrofuran	0	50	2.33	82	90
4	Cyclopentadiene	35	58	1	51	-

^aReagents and conditions: **1.63**-TiCl₂ (0.6 mmol), benzylidene aniline (2.0 mmol), dienophile (2.0 mmol), CH₂Cl₂/toluene (2:1) (5 mL). ^bDetermined by chiral HPLC.

The reaction of benzylidene aniline with dihydropyran or ethylvinyl ether proceeded to give the *anti* isomer as the major product in low ee, while a higher ee was obtained for the minor *syn* isomer (Table 1.7, entries 1 and 2). Conversely, the *syn* isomer was preferentially formed when dihydrofuran was used, and both isomers were produced in good enantioselectivities (entry 3). With cyclopentadiene as the dienophile, the *syn* isomer was formed exclusively in moderate ee (entry 4).

1.2.3 Non-metal catalysed Diels-Alder reactions

Several reports of the synthesis of tetrahydroquinolines using chiral phosphoric acids of type **1.36** have been published (Scheme 1.21 and Scheme 1.22).



Scheme 1.21: Phosphoric acid catalysed reaction of aldimine and ethyl vinyl ethers.

The reaction of imines of type **1.64** with enol ethers of type **1.65**, catalysed by **1.36a**, resulted in the formation of THQ's **1.66** in a *syn*/*anti* ratio of 99:1, with up to 97% ee and 95% yield. A range of aromatic groups and a variety of different enol ethers, both cyclic and acyclic, were well tolerated. However, the presence of the OH group on the *N*-aryl again proved essential for the attainment of high enantioselectivities. The reaction is believed to proceed through a 9-membered cyclic intermediate (Figure 1.11), where the chiral catalyst binds to the phenolic hydrogen and nitrogen of the imine by hydrogen bonds. This hydrogen bonding encases the imine within a chiral environment, leading to the selectivity observed.⁴

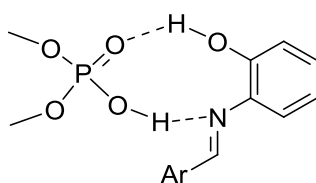
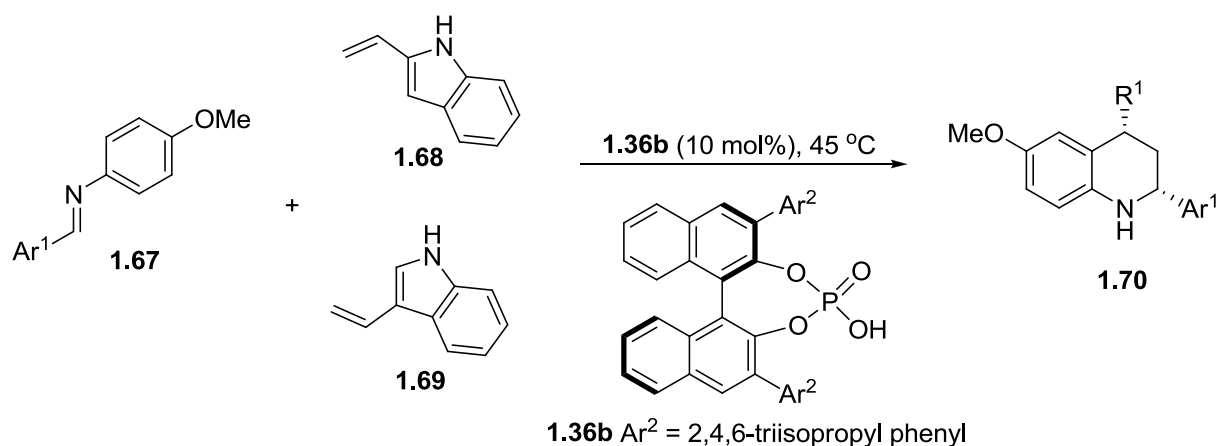


Figure 1.11: Suggested 9-membered cyclic intermediate in the reaction of **1.64** and **1.65**.

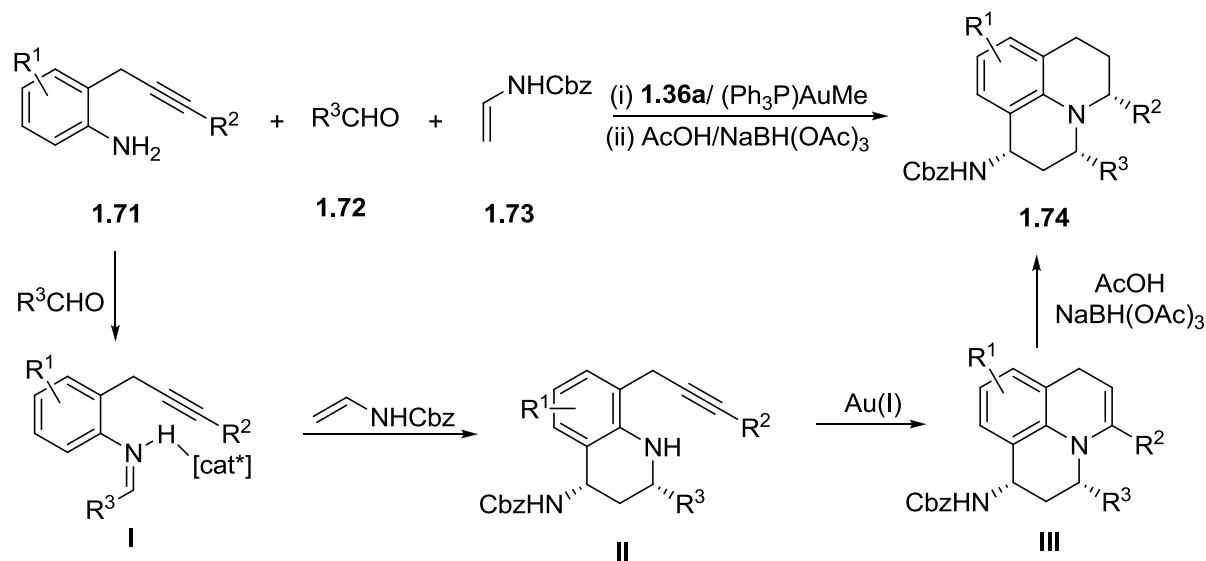
Vinylindoles **1.68** and **1.69** have also been successfully adopted as dienophiles with **1.36b** as catalyst (Scheme 1.22).



Scheme 1.22: Chiral phosphoric acid catalysed Diels-Alder reaction with vinylindole.

All tetrahydroquinoline products were produced in excellent d.r. of >90:10 and enantioselectivities of >90%, regardless of the steric or electronic nature of the aromatic imine.⁵⁴

These chiral phosphoric acid catalysed reactions have been used for the synthesis of more complex structures, such as tricyclic Julolidine derivatives of type **1.74** (Scheme 1.23).⁵⁵



Scheme 1.23: Synthesis of Julolidines.

In these reactions the aniline **1.71** first condenses with the aldehyde **1.72** to form the imine intermediate **I** *in situ*. Activation of the imine by the binding of the phosphoric acid catalyst **1.36a** initiates the reaction with the enamide **1.73**, producing the intermediate **II**, which subsequently undergoes a hydroamination reaction catalysed by the gold complex to give the intermediate **III**. Reduction of the imine proceeds to give *syn*-**1.74** as the major product.

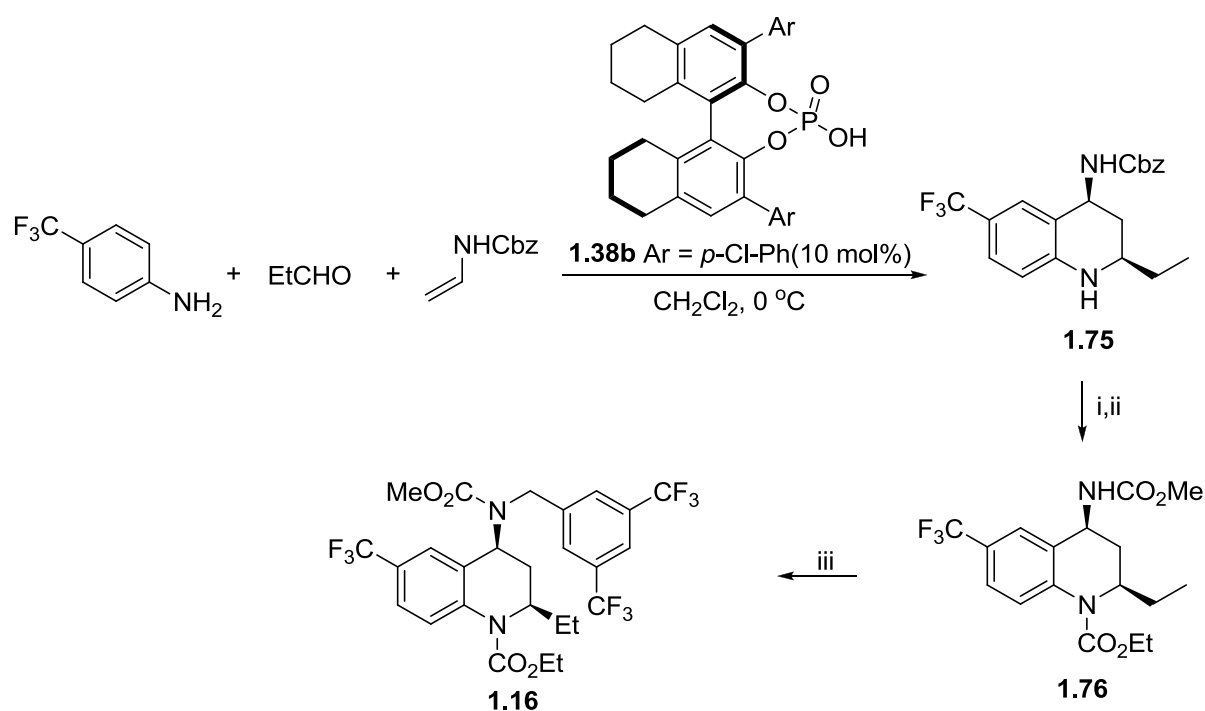
A range of Julolidine derivatives were synthesised in good yields (60-72%) and excellent enantioselectivities (92-99%) (Table 1.8). The use of both electron-donating and withdrawing aldehydes had no effect on the enantioselectivities obtained in the reaction (Table 1.8, entry 3 vs 2 and 4) and the presence of electron-withdrawing groups in the R¹ and R² positions were also well tolerated (entries 5 and 6).⁵⁵

Table 1.8: Formation of Julolidine derivatives by Diels-Alder reactions.^a

Entry	R ¹	R ²	R ³	% Yield ^{b,d}	% ee ^{c,d}
1	H	Ph	Ph	67 (12)	92 (92)
2	H	Ph	4-Cl-Ph	70 (15)	96 (97)
3	H	Ph	4-MeO-Ph	61 (7)	94 (92)
4	H	Ph	4-CN-Ph	70 (14)	97 (97)
5	H	4-F-Ph	4-Br-Ph	61 (16)	97 (96)
6	4-Cl	Ph	4-Br-Ph	62 (20)	99 (99)

^aReagents and conditions: Aniline (0.1 mmol), aldehyde (1 eq), enamine (3 eq), (Ph₃P)AuMe (10 mol%), 3 Å MS, **1.36a** (15 mol%), -40 °C, 24 h. ^bIsolated yield. ^cDetermined by Chiral HPLC. ^dThe data in parentheses are the values corresponding to the minor diastereoisomer of **1.74**.

The synthesis of Torcetrapib **1.16** can be achieved in four steps, employing a three component Diels-Alder reaction with *N*-vinyl carbamates as the dienophile (Scheme 1.24).



Scheme 1.24: Reagent and conditions: (i) ClCO₂Et, py., 88%; (ii) Pd/C, H₂, ClCO₂Me, py., 81%; (iii) KH, 3,5-di-CF₃-benzyl bromide, 79%.

The two chiral centres were installed using an IED Diels-Alder reaction in the presence of 10 mol% of the BINOL-derived phosphoric acid **1.38b**. The reaction furnished the tetrahydroquinoline in 57% yield and 93% enantioselectivity. Torcetrapib was obtained from the cycloadduct **1.75** in three further synthetic steps with 56% overall yield, by removal of the Cbz protecting group, followed by alkylation of the heteroatoms (Scheme 1.25).⁵⁶

There are other literature reports for the diastereoselective formation of tetrahydroquinolines using *aza*-Diels-Alder reactions.^{13, 57-63} However, these racemic compounds will not be discussed here, likewise for reactions with limited substrate scope.

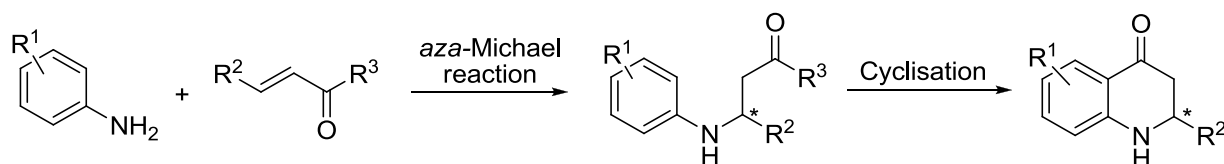
Miscellaneous reports of the enantioselective synthesis of biologically interesting tetrahydroquinolines will be discussed in the next section, all involving the addition of a X-H across an unsaturated C-C bond.

1.3 Heterofunctionalisation of alkenes and alkynes

The addition of amines to C-C unsaturated bonds is atom-economical and as a result is a highly topical research area.^{64, 65} Addition of the amine to the C-C bond can either occur in an intermolecular or intramolecular manner, and both have been utilised in the synthesis of optically active tetrahydroquinolines.

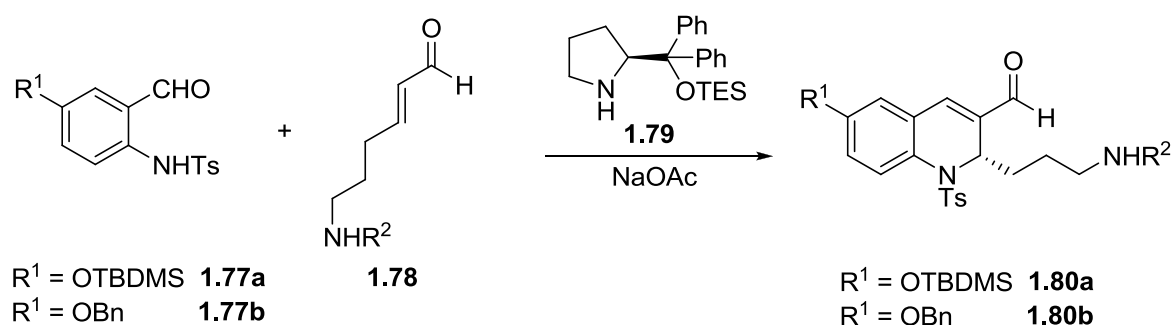
1.3.1 Intermolecular reactions

There are three examples where the intermolecular *aza*-Michael reactions have been used for the synthesis of tetrahydroquinolines. The first two examples involve the addition of an aniline to an α , β -unsaturated carbonyl compound (Scheme 1.25). This forms a chiral centre which will become the C-2 position of the tetrahydroquinoline.



Scheme 1.25: Tetrahydroquinoline synthesis using an *aza*-Michael reaction.

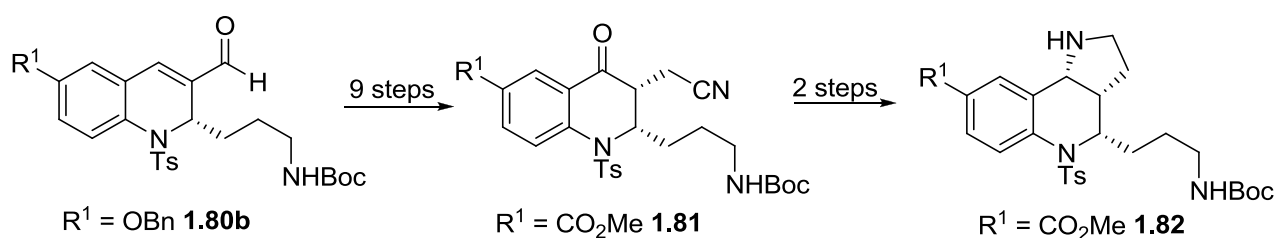
The core structure of the Martinelline alkaloids has been synthesised in good enantioselectivity, using an asymmetric tandem Michael-aldol reaction.⁶⁶



Scheme 1.26: Synthesis of the core structure of the Martinelline alkaloids.

The reaction of the requisite α, β -unsaturated carbonyl **1.78** with the 2-amino benzaldehydes derivatives **1.77** was conducted in the presence of the organocatalyst (*S*)-diphenylprolinol triethyl silyl ether **1.79** (Scheme 1.26). Interestingly, the nature of the substituent R^1 was found to have a dramatic effect on the ee obtained. When an *O*-TBDMS group was present, the reaction proceeded to give the 2-substituted dihydroquinoline **1.80a** as a racemic mixture, however, on changing to an *O*-benzyl group, 86% ee was obtained. With extensive optimisation of the reaction conditions, the dihydroquinoline was produced in 92% yield and 97% ee.⁶⁶

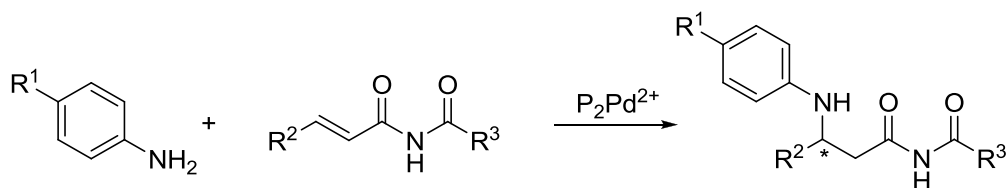
Further functional group manipulation of the alkene allowed for the synthesis of the pyrroloquinoline core (Scheme 1.27). It was envisioned that the stereochemistry set at the C-2 position would direct bond formations at the C-3 and C-4.⁶⁶



Scheme 1.27: Application of the tandem Michael aldol reaction to the synthesis of Martinelline alkaloids.

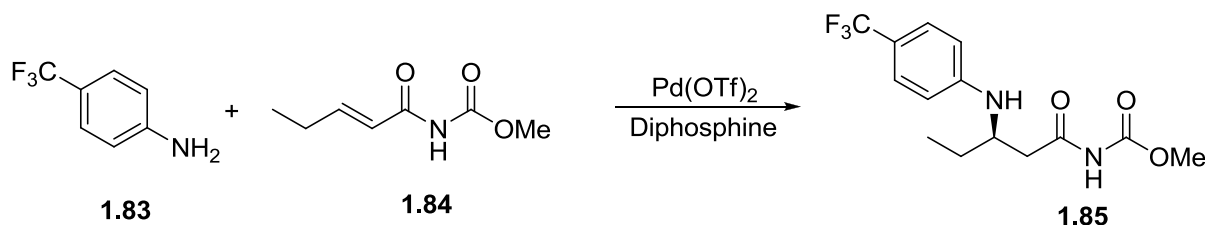
Previously, our research group have been working on the development of an asymmetric *aza*-Michael reaction, between anilines and α, β -unsaturated di-carbonyl compounds, using a chiral Pd-complex catalyst (Scheme 1.28).^{67, 68} Previous work has shown the best

enantioselectivities and yields are obtained when *N*-carbamates⁶⁹ are used in combination with *C*₂-symmetrical biaryl diphosphine ligands.⁷⁰



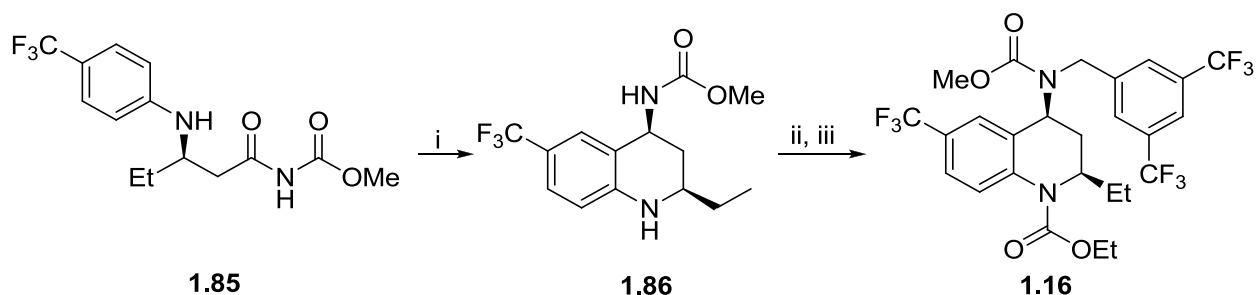
Scheme 1.28: Asymmetric *aza*-Michael reaction.

This reaction has been applied to the synthesis of Torcetrapib **1.16**, which contains 2 chiral centres at the C-2 and C-4 positions. The addition of 4-trifluoromethylaniline to the α , β -unsaturated carbamate **1.84** was investigated (Scheme 1.29). The asymmetric *aza*-Michael reaction was used to set the stereochemistry at the C-2 position, which directed the formation of the second chiral centre in a stereospecific ring cyclisation.



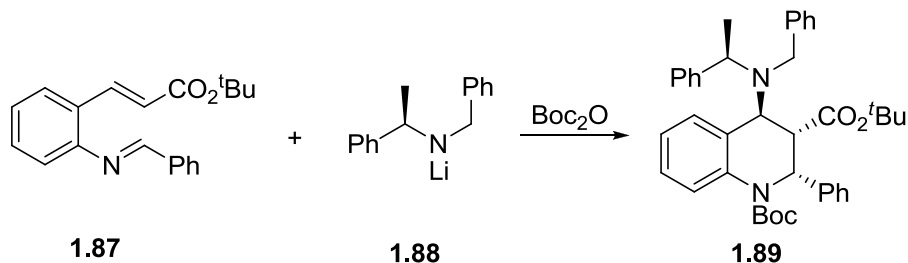
Scheme 1.29: Aza-Michael reaction used in the synthesis of Torcetrapib.

The chiral palladium catalyst was formed *in situ* from Pd(OTf)₂ and the diphosphine ligand. (S)-BINAP and (S)-P-Phos **1.21** proved to be the best ligands giving yields of ca. 80% and 90% ee. Optically pure *aza*-Michael product **1.85** was obtained upon recrystallisation from cyclohexane/toluene. Torcetrapib was then synthesised in three further steps (Scheme 1.30); a Lewis acid catalysed reductive cyclisation reaction proceeded to give the 2, 4-disubstituted tetrahydroquinoline **1.86**, as a single diastereoisomer, in 92% yield. Derivatization of both nitrogens gave Torcetrapib **1.16**. The overall synthetic sequence comprises of 7 steps and proceeded in 26% overall yield.²⁴



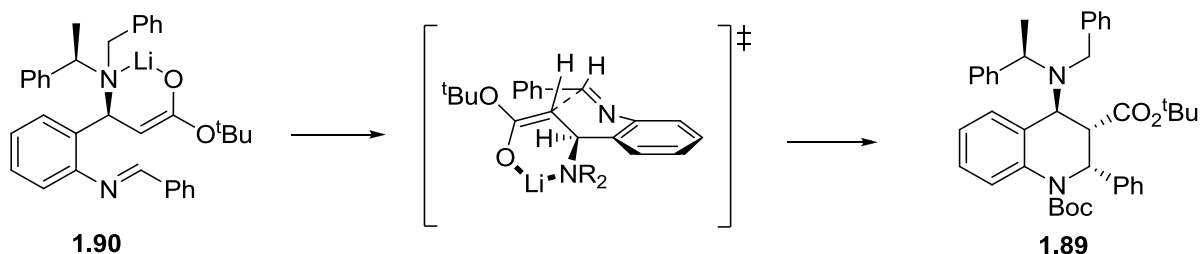
Scheme 1.30: Synthesis of Torcetrapib: (i) NaBH₄, MgCl₂, 92%; (ii) ClCO₂Et, py., 82%; (iii) 3,5-bis(trifluoromethyl) benzyl bromide, KO^tBu, 52%.

The tandem conjugate addition/cyclisation reaction of the homochiral lithium amide **1.88** (98% ee) with α , β -unsaturated esters of type **1.87** produced the densely substituted 4-aminotetrahydroquinoline **1.89** as a single diastereoisomer in 98% enantioselectivity and 75% yield, after *N*-Boc protection (Scheme 1.31).



Scheme 1.31: Enantioselective tetrahydroquinoline formation utilising optically pure starting materials.

The reaction proceeds *via* the conjugate addition of the amide, which installs the first stereocentre at the C-4 position and produces the (*Z*)-lithium enolate **1.90**. The cyclisation reaction proceeds through a boat transition state, with the *Re* face of the enolate is directed towards the imine as a result of the lithium-chelation (Scheme 1.32), producing the tetrahydroquinoline as the 2, 3-*syn*, 3, 4-*anti* isomer.

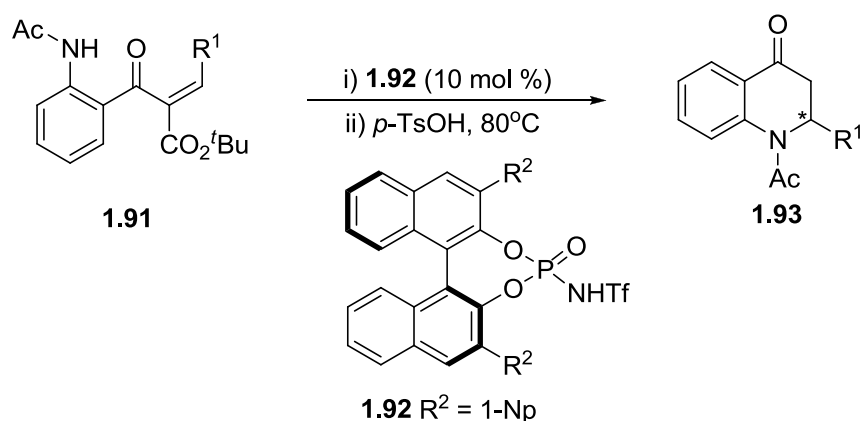


Scheme 1.32: Stereochemical pathway for the cyclisation reaction

A range of addition/cyclisation precursors were synthesised, with the phenyl group at C-2 replaced by various other aryl functionalities, including furan-2-yl. In all cases the 2, 3-*syn* 3, 4-*anti* tetrahydroquinoline was formed selectively in excellent yields (73-98%).⁷¹

1.3.2 Nucleophilic cyclisations

The asymmetric intramolecular *aza*-Michael reaction of *tert*-butyl ester activated α , β -unsaturated ketones of type **1.91**, proceeded to give optically active tetrahydroquinolones in the presence of a chiral phosphoric acid **1.92** (Scheme 1.33).⁷²



Scheme 1.33: Intramolecular *aza*-Michael cyclisation.

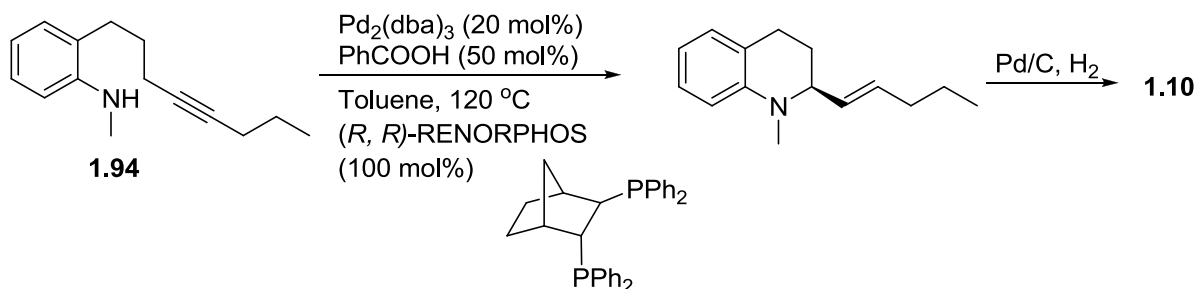
A range of different substrates were subjected to the cyclisation (Table 1.9), with different aryl groups accommodated at C-2. The tetrahydroquinolones were obtained in excellent yields after removal of the *tert*-butyl carboxylate group, post cyclisation. The enantioselectivity was found to be highly dependent on the nature of the substrate. The presence of an electron withdrawing group, such as a bromide or nitro, on the aromatic R^1 led to a decrease in ee (Table 1.9, entry 1 vs 2 and 3). The highest enantioselectivity of 82% was obtained when a 4-tolyl substituent was present (entry 4). Surprisingly, the location of the substituent on the phenyl ring also appeared to have a significant effect on the enantioselectivity; 60% ee was obtained when a methoxy group was present at the *para* position of the phenyl ring, whereas a methoxy group on the *ortho* position afforded near racemic material (entry 5 vs 6).

Table 1.9: Substrate scope for intramolecular *aza*-Michael reaction.^a

Entry	R^1	Yield % ^b	ee % ^{c,d}
1	Ph	95	72 (-)
2	4-Br-C ₆ H ₄	90	58 (-)-(S) ^e
3	4-NO ₂ -C ₆ H ₄	77	20 (-)
4	4-Me-C ₆ H ₄	98	82 (-)
5	4-MeO-C ₆ H ₄	94	60 (-)
6	2-MeO-C ₆ H ₄	95	4 (+)

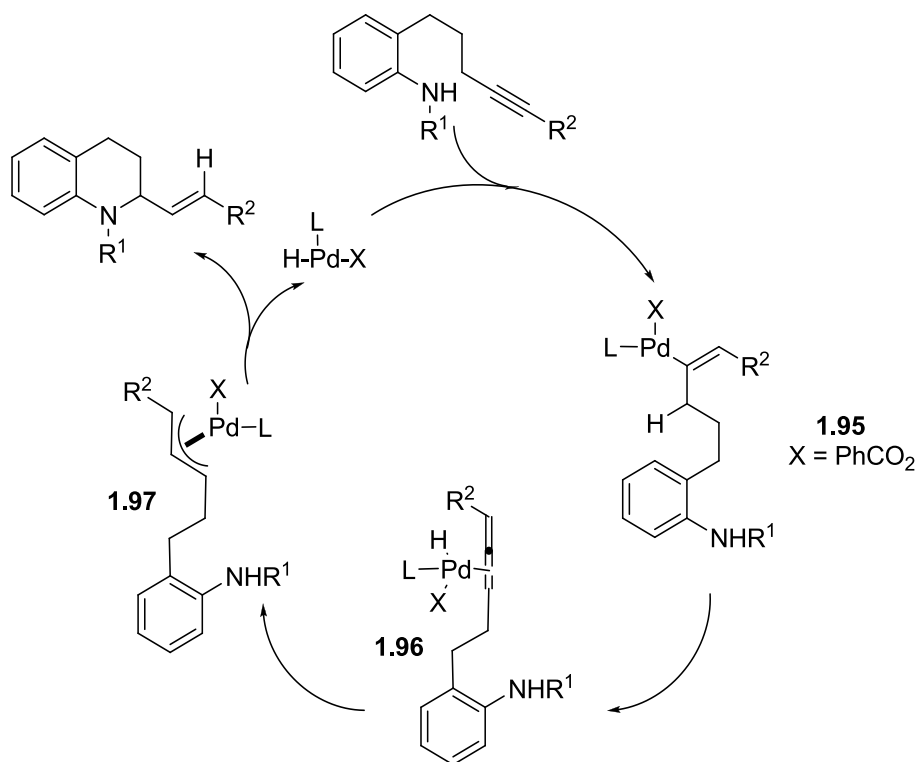
^aReagents and conditions: **1.92** (10 mol%), aniline (0.1 mol/L in toluene). ^bIsolated yields. ^cDetermined by chiral HPLC. ^dOptical rotation. ^eAbsolute configuration was determined by X-ray analysis.

In 2007, Yamamoto *et al.* showed that anilino-alkynes cyclise upon treatment with $\text{Pd}(\text{PPh}_3)_4$ and (*R,R*)-RENORPHOS, in the presence of benzoic acid, to give 2-substituted tetrahydroquinolines as a single *E*-isomer. Enantioselectivities of up to 78% and yields of 61–73% were obtained. The method was used to prepare (–)-angustureine in two steps from **1.94** with 48% yield and 52% ee (Scheme 1.34).⁷³



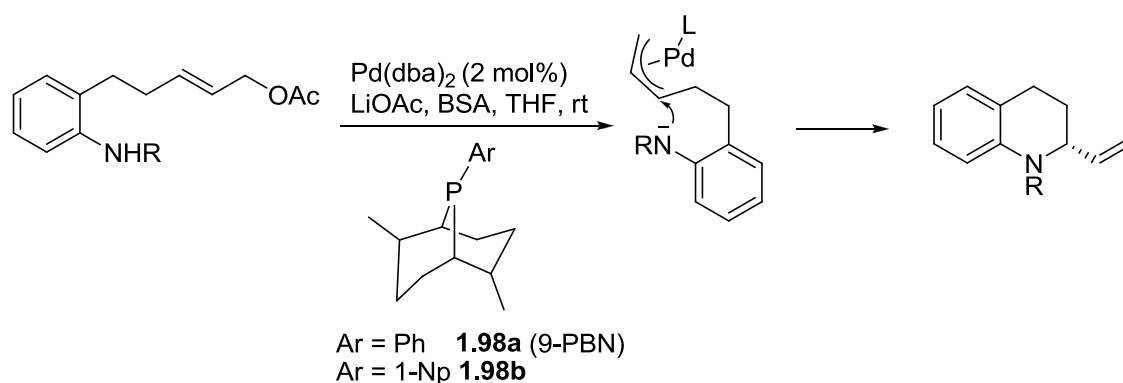
Scheme 1.34: Intramolecular cyclisation reaction to form angustureine.

The proposed catalytic cycle involves the initial formation of a hydridopalladium species, created by reaction of Pd^0 with benzoic acid (Scheme 1.35). This inserts into the alkyne to give a vinylpalladium intermediate **1.95**, which undergoes β -hydride elimination to give an allene **1.96**. The π -allyl moiety **1.97** then forms from the re-insertion of Pd-H and the product is produced by an intramolecular nucleophilic attack of the amine.⁷³



Scheme 1.35: Proposed mechanism for cyclisation of aniline-alkynes.

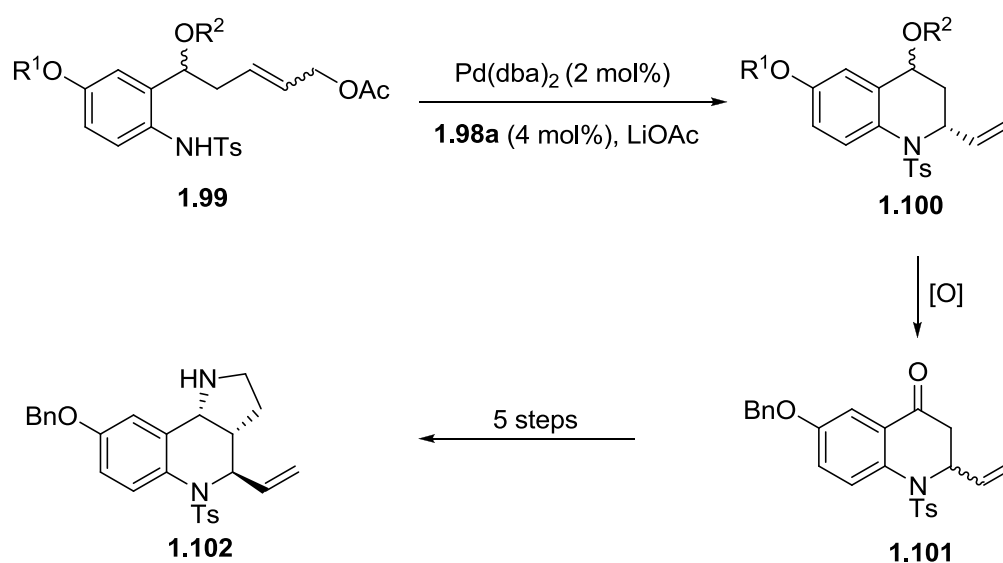
An intramolecular palladium-catalysed asymmetric allylic substitution reaction has been utilised by Hamada *et al.* for the synthesis of optically active tetrahydroquinolines (Scheme 1.36).⁷⁴



Scheme 1.36: Cyclisation of *ortho*-substituted aniline sulfonamides.

The cyclisation proceeded using Pd(dba)₂ and the bicyclic phosphine ligand **1.98a** or **1.98b**, in the presence of *bis*(trimethylsilyl)acetamide and lithium acetate. The tetrahydroquinoline products were obtained in good enantioselectivities of up to 92% but, in relatively low yields (55-68%). This cyclisation proceeded through a π -allyl palladium species, formed by displacement of the acetate group with palladium. Nucleophilic attack of the deprotonated amine onto the π -allyl species gave the tetrahydroquinoline.

This methodology was applied to the synthesis of the Martinelline alkaloids in 9 steps and 43% yield from commercially available starting materials (Scheme 1.37).⁷⁵



Scheme 1.37: Synthesis of Martinelline alkaloid core.

The cyclisation of racemic **1.99** using (-)-9-PBN **1.98a**, in the presence of LiOAc, gave the tetrahydroquinoline **1.100** as a 68:32 mixture of *syn:anti* isomers, in 60% ee (Scheme 1.37). The alkene geometry of the starting material had no effect on the diastereoselectivity obtained. However, changes in the nature of the alkoxy protecting group R² were found to have a significant effect. Oxidation of **1.100** gave the ketone **1.101**, from which the pyrroloquinoline core structure was synthesised in 5 steps with only 9% overall yield.⁷⁵

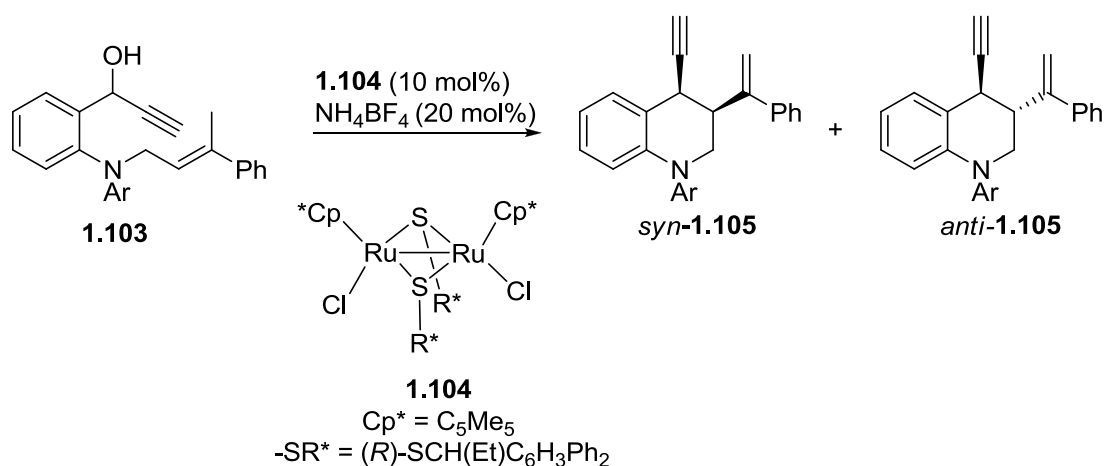
In summary, a number of different heterofunctionalisation reactions have been used for the synthesis of tetrahydroquinolines. These reactions have been applied to the synthesis of several biologically interesting tetrahydroquinolines. Three intermolecular *aza*-Michael reactions were discussed, with the synthesis of 2, 3, 4-trisubstituted tetrahydroquinolines achieved by the tandem conjugate addition/cyclisation reaction of a chiral lithium amide. The reaction proceeded to give the 2, 3-*syn*, 3, 4-*anti* isomer only. In addition 2, 4-*syn* disubstituted tetrahydroquinolines were formed using the *aza*-Michael reaction of anilines with α , β -unsaturated carbamates, followed by a stereospecific cyclisation reaction. This methodology was applied to the synthesis of the 2, 4-disubstituted natural product Torcetrapib **1.16**. The core structure of the Martinelline alkaloids **1.14-1.15** was successfully synthesised in good yields and enantioselectivity using a tandem *aza*-Michael/aldol reaction.

In addition, synthesis of the core structure of the Martinelline alkaloids was achieved in moderate yield and enantioselectivity but low diastereoselectivity, *via* the intramolecular addition of aniline to a π -allyl palladium species. Also, angustureine was formed by an intramolecular cyclisation reaction in excellent yield but very poor enantioselectivity. Despite the application of these addition reactions to the synthesis of a number of natural products, the reactions were highly specific, with variations often proceeding to give poor results.

1.4 Miscellaneous approaches

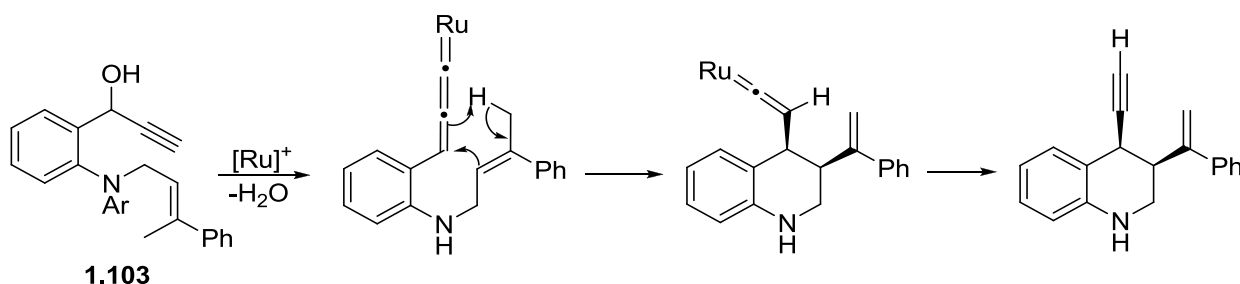
1.4.1 Metal catalysed cyclisation

In the presence of 10 mol% of an optically active thiolate-bridged diruthenium complex **1.104** and 20 mol% of NH₄BF₄, the acyclic substrate **1.103** reacted to give the 3, 4-disubstituted tetrahydroquinolines **1.105** (Scheme 1.38).⁷⁶



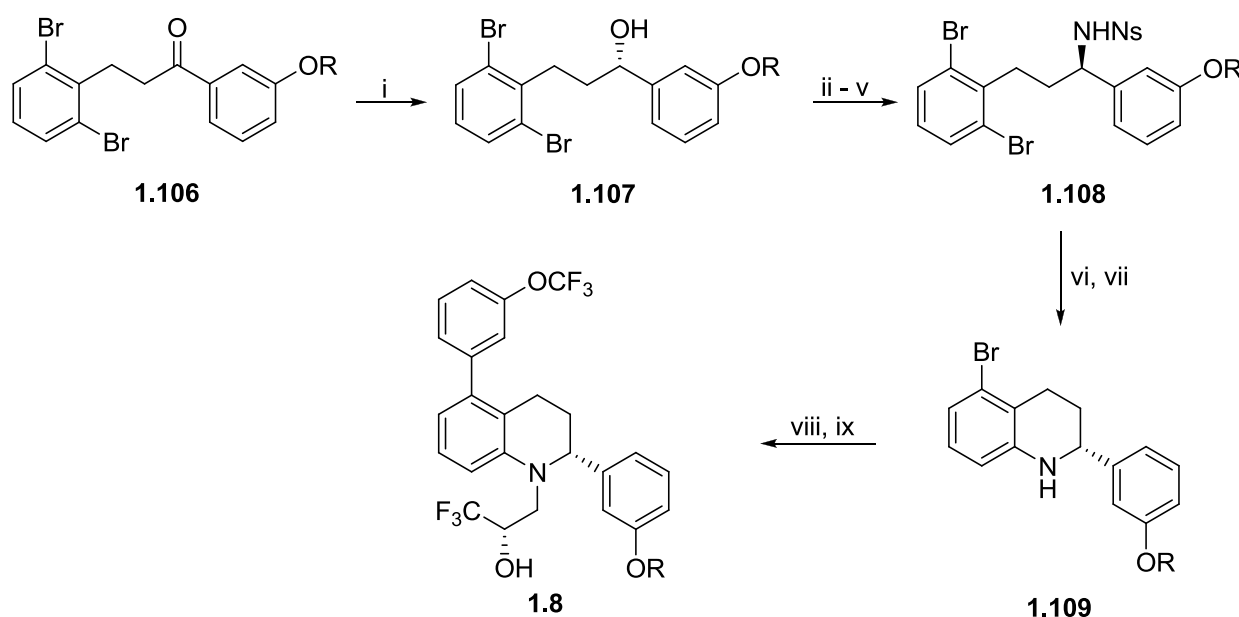
Scheme 1.38: Ruthenium catalysed formation of 1, 2, 3, 4-tetrahydroquinolines.

The reaction proceeded in the good *syn/anti* ratio of 13/1, and the *syn* isomer was formed with up to >95% ee, regardless of the nature of the Ar group. This cyclisation reaction is believed to proceed *via* Ru-alkylidene intermediates, which rearrange to give the tetrahydroquinoline core (Scheme 1.39).⁷⁷



Scheme 1.39: Tetrahydroquinoline formation *via* cyclisation of propargylic alcohols bearing allylic amines.⁷⁸

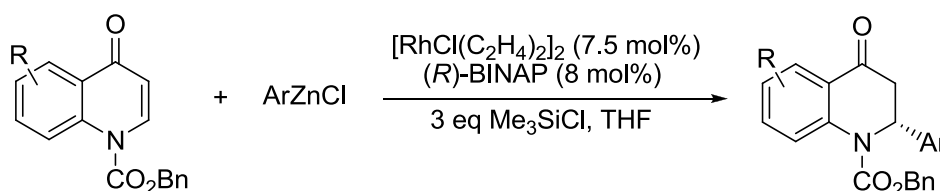
The potent CETP inhibitor **1.8** has been synthesised using an intramolecular cyclisation, under Fukuyama conditions (copper iodide and caesium carbonate in hot DMSO) (Scheme 1.40). Asymmetric reduction of the prochiral ketone **1.106** proceeded in 91% ee and the resultant alcohol was converted to the amine **1.108** in 4 steps. Synthesis of the tetrahydroquinoline was achieved using a copper-mediated cyclisation reaction. Cross-coupling to attach the aryl group in the 6 position was achieved by a Suzuki-Miyaura reaction, followed by alkylation of the tetrahydroquinoline nitrogen to give **1.8** predominantly as the *syn* isomer in 73% yield.⁷⁹



Scheme 1.40: Reagent and conditions: (i) (*R*)-Me-CBS, $\text{Me}_2\text{S}\cdot\text{BH}_3$, 82-90%; (ii) MsCl , triethylamine, 100%; (iii) NaN_3 , DMF, 95%; (iv) $\text{Me}_2\text{S}\cdot\text{BHCl}_2$, 95%; (v) NaCl , triethylamine, 95%; (vi) CuI , Cs_2CO_3 , 96%; (vii) $\text{HSCH}_2\text{CO}_2\text{H}$, LiOH , 88%; (viii) $\text{Pd}(\text{PPh}_3)_4$, *m*- $\text{CF}_3\text{OC}_6\text{H}_4\text{B}(\text{OH})_2$, K_2CO_3 , 91%; (ix) $\text{Yb}(\text{OTf})_3$, 1, 1, 1-trifluoroethoxypropane, DCE, 50 °C, 73%.

1.4.2 1,4-Addition reactions

The 1, 4-addition of phenylzinc chloride to 2, 3-dihydro-4-pyridone, catalysed by a BINAP-Rh complex, with chlorotrimethylsilane as an additive, proceeded to give 2-aryl substituted tetrahydroquinolines (Scheme 1.41). It is believed that the additive activates the substrate towards 1, 4-addition, by acting as a Lewis acid, and/or stabilises the product, by forming a silyl enol ether.⁸⁰



Scheme 1.41: Asymmetric 1, 4-addition reaction.

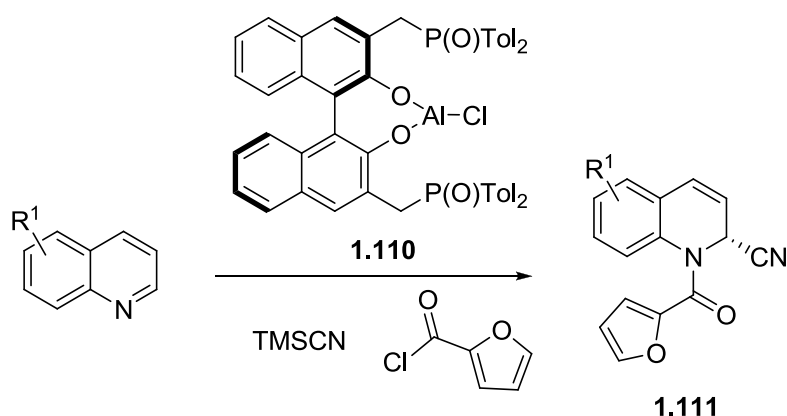
Table 1.10: Synthesis of 2-substituted tetrahydroquinolines using 1, 4-addition reactions.^a

Entry	R	Ar	% Yield	% ee, (Config) ^b
1	H	Ph	88	98 (R)
2	H	3,5-Me-Ph	100	98 (R)
3	H	2-Tol	74	86 (R)
4	4-Cl	Ph	89	99 (R)
5	4-Cl	4-Tol	82	88 (R)
6	3,5-OMe	Ph	87	99 (R)
7	3,5-OMe	Nap	92	98 (R)

^aReagent and conditions: $[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2$ (7.5 mol%), (*R*)-BINAP (8.2 mol%), Me_3SiCl (3.0 eq), THF, 20 °C, 20 h. ^bDetermined by chiral HPLC.

Excellent yields and enantioselectivities were obtained for the addition of a range of different arylzinc reagents. The reaction proceeded well with tolyl zinc reagents (Table 1.10, entries 2 and 3), although 2-tolyl zinc chloride gave a slightly lower ee and yield than the reaction with 4-tolyl zinc, probably as a result of steric congestion. The presence of both electron-withdrawing and donating groups on the 4-quinolone had little effect on the results obtained, (entries 4 and 6) and the reaction proceeded smoothly with naphthyl-zinc chloride to give the 2-substituted tetrahydroquinolone in 98% ee.

The 1, 4-addition of cyano groups to quinolines, catalysed by a chiral aluminium phosphonate complex **1.110** proceeded to give 2-substituted tetrahydroquinolines in good yields and enantioselectivities (Scheme 1.42).

**Scheme 1.42:** 1, 4-addition reaction of the cyano group catalysed by **1.110**.

The presence of electron-donating groups on the quinoline, increased both the yield and enantioselectivity obtained (Table 1.11, entries 2-4), while the presence of electron withdrawing groups, gave less satisfactory results (entry 5).¹¹

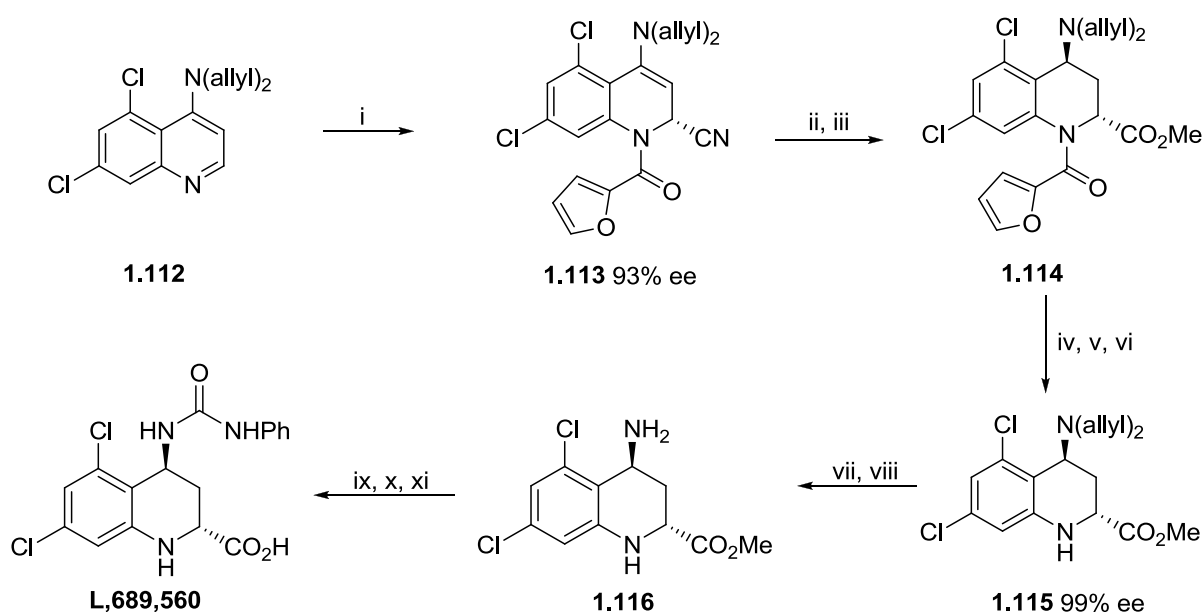
Table 1.11: 1, 4-addition reaction of TMSCN.^a

Entry	R ¹	% Yield ^b	% ee, (Config) ^c
1	H	91	85 (<i>R</i>)
2	4-MeO	74	89
3	3,4-MeO	99	91
4	4-NH ₂	72	89
5	4-Cl	57	67

^aReagents and conditions: Catalyst **1.110** (9.0 mol%), TMSCN (2.0 eq), 2-furoyl chloride (2.0 eq), -40 °C.

^bIsolated yield. ^cDetermined by chiral HPLC.

This catalytic reaction was used for the synthesis of L-689,560 a potent NMDA receptor antagonist (Scheme 1.43).

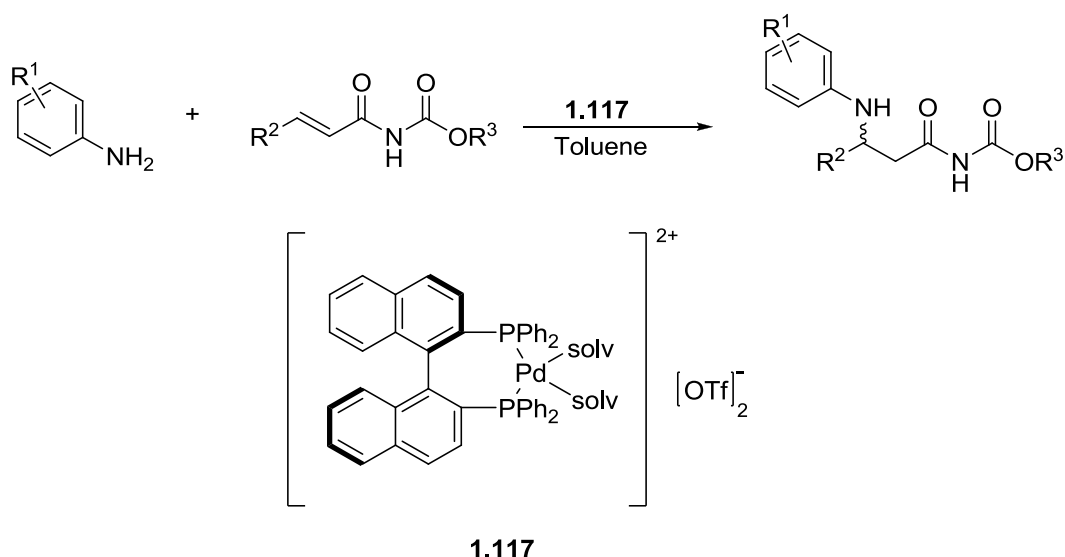


Scheme 1.43: Reagents and conditions: (i) 1 mol% **1.110**, TMSCN, 2-furoyl chloride, CH₂Cl₂, -40 °C, (ii) NaBH₃CN, AcOH, MeOH, 91%; (iii) HCl, MeOH, 93%; (iv) NaOH, EtOH; (v) HCl, MeOH; (vi) recrystallisation, 81%; (vii) Pd(PPh₃)₄ (5 mol%), 1,3-dimethyl-barbituric acid; (viii) HCl, 92%; (ix) PhNCO, NEt₃, 87%; (x) LiOH; (xi) H₃O⁺, 85%.

Reaction of the di-chloroquinoline with TMS-CN produced the dihydroquinoline **1.113** in 91% yield and 93% ee. Enamine reduction proceeded to give the tetrahydroquinoline selectively as the *anti* isomer. Conversion of the cyano group to the carboxylic ester, followed by removal of the *N*-furoyl group gave **1.115**; at this juncture, the enantioselectivity of the compound was enhanced to 99% by recrystallisation. Removal of the allyl groups, followed by formation of the urea at the C-4 position and hydrolysis of the ester, gave L,689,560.¹¹

1.5 Aim

The aim of this project is the development of a new synthetic route to structurally diverse tetrahydroquinolines using a catalytic asymmetric *aza*-Michael reaction, previously developed in our group (Scheme 1.44).⁸¹



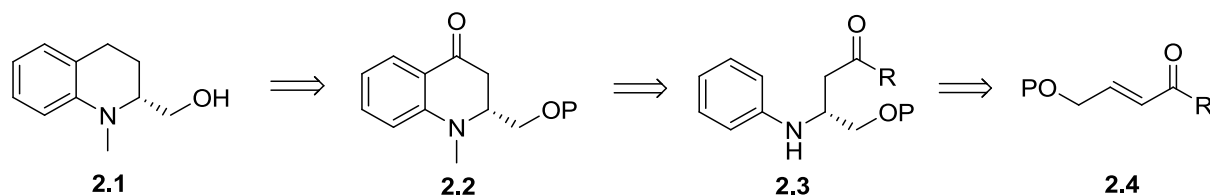
Scheme 1.44: Palladium BINAP catalysed *aza*-Michael reaction.

This work will focus on applying the strategy for the asymmetric synthesis of interesting tetrahydroquinolines including; the Galipea alkaloids, as well as more complex structures such as the Martinelline alkaloids and levonantradol. The key to these latter targets is to utilise the stereogenic centre at C-2 to direct the introduction of further substituents at C-3 and C-4. This is guided by several examples of diastereoselective ring syntheses, where chiral centres already installed can be used to direct the formation of a second or third chiral centre.^{11, 24, 82-85}

CHAPTER TWO
SYNTHESIS OF THE GALIPEA
ALKALOIDS

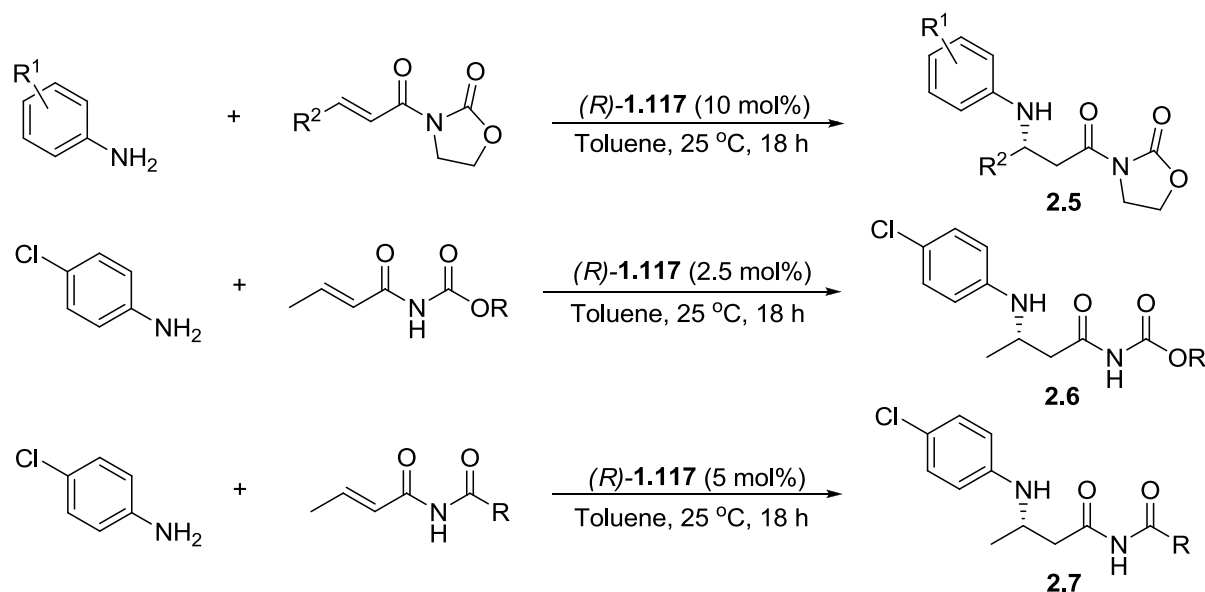
2.0 Synthesis of the Galipea alkaloids

This project was initiated with an investigation into the asymmetric total synthesis of the Galipea alkaloids (Figure 1.4). It would be advantageous to synthesise all four of the alkaloids from a common precursor, allowing for a more divergent route. We envisioned that **2.1** would be an appropriate common precursor as all four alkaloids could be easily obtained by attachment of the appropriate side chain. Retrosynthetic analysis of the tetrahydroquinoline **2.1** led to the tetrahydroquinolone **2.2** (Scheme 2.1). This in turn should be accessible from **2.3**, formed by the asymmetric *aza*-Michael reaction of aniline with Michael acceptors of type **2.4**. This will be used to install the required stereochemistry of the alkaloids, starting from pro-chiral reagents.



Scheme 2.1: Retrosynthetic analysis of **2.1**.

Prior work in our research group investigated the enantioselective *aza*-Michael reaction of primary aromatic amines with α , β -unsaturated compounds. The addition of anilines to *N*-alkenoyl oxazolidinones,⁶⁷ *N*-alkenoyl carbamates⁶⁹ and α , β -unsaturated *N*-imides⁸⁶ occurred readily in very high selectivity, using a dicationic [(BINAP)Pd(solvent)₂]²⁺ [TfO]⁻₂ catalyst **1.117** (Scheme 2.2, Table 2.1).



Scheme 2.2: Palladium-catalysed addition of anilines to *N*-alkenoyl oxazolidinones, carbamates and imides.

Table 2.1: *Aza*-Michael reaction of *N*-alkenoyl oxazolidinones, *N*-alkenoyl carbamates and α , β -unsaturated *N*-imides.^a

Entry	Product	Cat. (mol%)	R ¹	R ²	% Yield ^b	% ee ^c
1	2.5	10	H	Me	93	93
2	2.5	10	4-Me	Me	85	73
3	2.5	10	4-OMe	Me	89	37
4	2.5	10	4-Cl	Me	96	90
5	2.5	10	H	Et	66	41
6	2.5	10	H	Pr	72	27
7	2.6	2.5	4-Cl	Me	>99	>99
8	2.7	5	4-Cl	Me	84	73

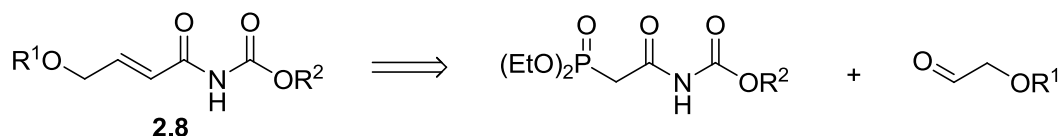
^aReagent and conditions: ArNH₂ (1 eq), alkene (1 eq), Cat. (x mol%), toluene, 25 °C, 18 h. ^bDetermined by ¹H NMR. ^cDetermined by chiral HPLC.

Similar reactivity trends were observed in each system, where the presence of an electron donating group on the aromatic amine (*e.g.* OMe) led to a decrease in the ee (Table 2.1, entry 1 vs entries 2 and 3). However, the presence of an electron-withdrawing group, such as a chloride, had little effect on the results compared to using aniline (entry 1 vs 4). Increasing the chain length of R² resulted in a significant decrease in the enantioselectivity (entry 1 vs entries 5 and 6). The highest enantioselectivities were obtained with *N*-alkenoyl carbamates (entry 7 vs 4 and 8).

In this Chapter, the synthesis of the prochiral Michael acceptors from readily available starting materials will be described. Four different α , β -unsaturated carbamates were synthesised, using various alkene forming reactions, to investigate the effect the nature of the carbamate group has on the *aza*-Michael system. The optimisation of the reaction between aniline and the Michael acceptors is detailed next. On obtainment of optically pure *aza*-Michael adducts, the formation of the tetrahydroquinolone ring was investigated, from which the common precursor **2.1** was obtained. Finally, the chapter concludes with the formation of the Galipea alkaloids *via* attachment of the side chains.

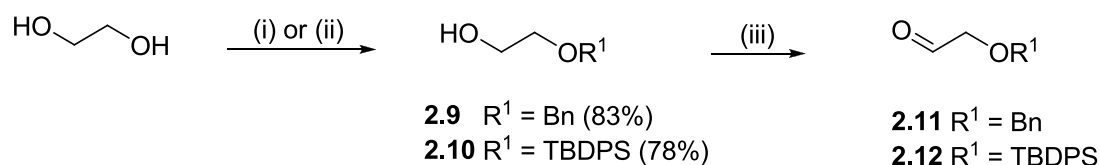
2.1 Synthesis of α , β -unsaturated carbamates

In this work, *N*-alkenoyl carbamates were chosen as Michael acceptors for the synthesis of the Galipea alkaloids, as these previously gave the best results. Firstly, a range of α , β -unsaturated carbamates, with general structure **2.8**, were prepared. These were accessible from the Horner-Wadsworth-Emmons (HWE) reaction of phosphonate carbamates and protected α -hydroxyl aldehydes (Scheme 2.3).



Scheme 2.3: Retrosynthesis of the α , β -unsaturated carbamates.

Synthesis of the protected α -hydroxy acetaldehydes was achieved by oxidation of a mono-protected ethylene glycol (Scheme 2.4). Benzyl and *tert*-butyldiphenyl silyl were chosen as *O*-protecting groups.



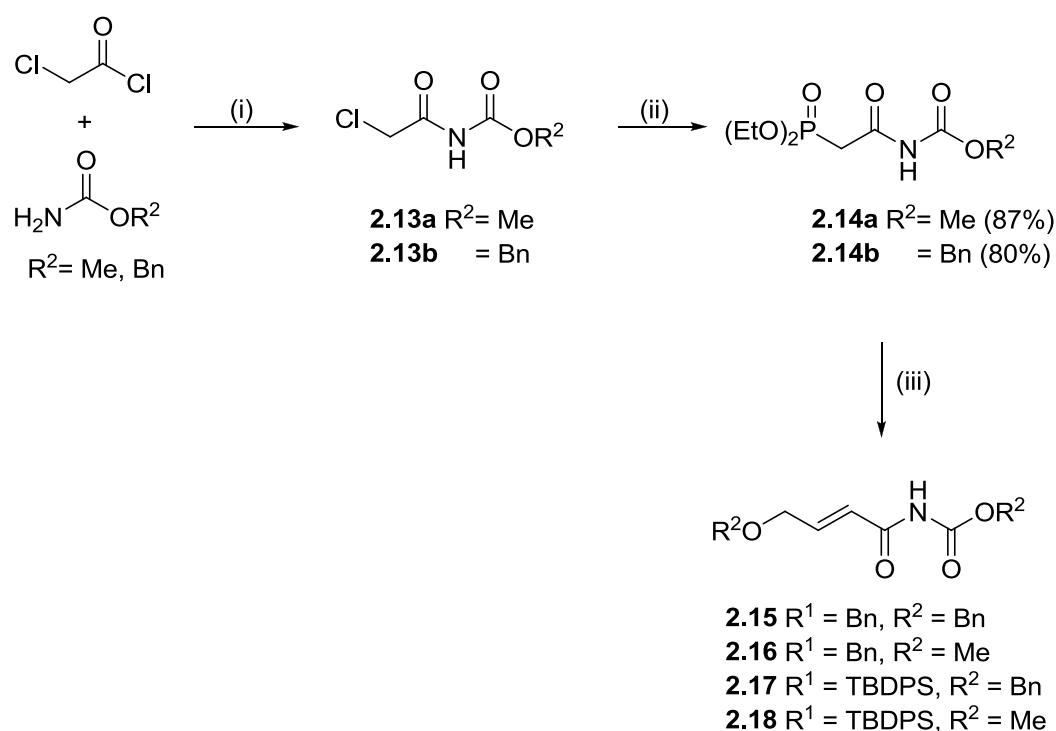
Scheme 2.4: Reagents and conditions: (i) BnBr, NaH, reflux, 16 h; (ii) TBDPSCl, imidazole, rt, 24h; (iii) Oxalyl chloride, DMSO, NEt_3 , CH_2Cl_2 , -78°C .

The desymmetrised alcohol **2.9** was obtained using published procedures, by the reaction of ethylene glycol with sodium hydride and benzyl bromide.⁸⁷ The reaction gave a mixture of **2.9** and the diprotected ethylene glycol in a 9:1 ratio, which separated by distillation to give the desired **2.9** in 83% yield. Alternatively, ethylene glycol was reacted with *tert*-butyldiphenylsilyl chloride and imidazole to give **2.10** in a 78% yield, after purification by column chromatography.⁸⁸ In this case, there is no evidence of any disilylated product in the reaction mixture.

The next step involved the oxidation of the protected alcohols to the corresponding aldehydes. Swern oxidation conditions^{87, 89} were used to produce the aldehydes **2.11** and **2.12**.

Product formation was confirmed, in both cases, by the presence of an aldehyde proton resonance in the ^1H NMR spectrum at 9.7 ppm. As these aldehydes were found to be unstable to isolation and storage, they were immediately employed in the HWE reaction without purification.

Adopting published procedures,²⁴ the phosphonate carbamates were prepared by the reaction of chloroacetyl chloride with the required carbamate at 100 °C to yield **2.13a** and **2.13b** (Scheme 2.5). These were subsequently heated with triethyl phosphite in an Arbuzov reaction, to afford **2.14a** and **2.14b** in 87% and 80% yields, respectively.



Scheme 2.5: Reagents and conditions: (i) 100 °C; (ii) $\text{P}(\text{OEt})_3$, 80 °C; (iii) **2.11** or **2.12**, DBU, THF, 5 °C.

The HWE reaction was attempted in accordance with previous precedence,⁸⁶ by the treatment of the aldehyde with DBU and the phosphonate carbamate in THF at 5 °C. However, this produced the desired Michael acceptors **2.15**, **2.17** and **2.18** in low isolated yields of 20-23% (Table 2.2, entries 1, 2 and 5). Formation of the Michael acceptor was identified by the presence of characteristic olefinic proton resonances in the ^1H NMR spectrum: For the benzyl-protected Michael acceptor **2.15** these appear at 7.06 ppm as a doublet and at 7.15 ppm as a double triplet with a mutual 3J coupling constant of 15.5 Hz. For the *tert*-

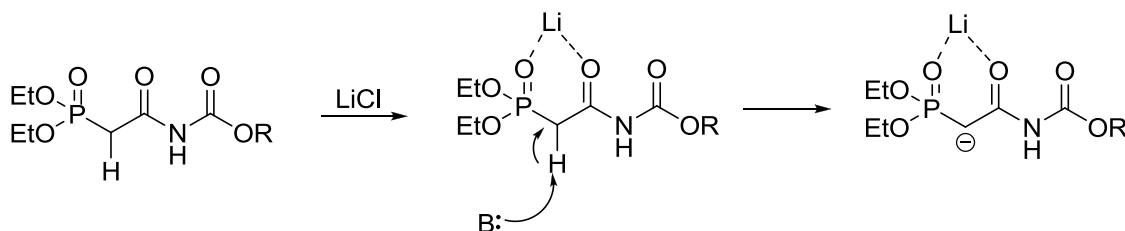
butyldiphenylsilyl protected Michael acceptors the olefinic protons appear as a triplet at 7.16 ppm and a doublet at 7.23 ppm, also with a mutual 3J coupling of 15.5 Hz. These 3J coupling constants confirmed the exclusive formation of the *E*-isomer in both cases.

Table 2.2: Conditions for Horner-Wadsworth-Emmons reaction.^a

Entry	Product	Base	LiCl /eq	% Yield ^b
1	2.17	DBU	0	20
2	2.18	DBU	0	21
3	2.17	<i>i</i> -Pr ₂ NEt	7.43	32
4	2.18	<i>i</i> -Pr ₂ NEt	7.43	45
5	2.15	DBU	0	23
6	2.15	<i>i</i> -Pr ₂ NEt	7.43	44
7	2.16	<i>i</i> -Pr ₂ NEt	7.43	42

^aGeneral reaction conditions: Aldehyde (6.6-19 mmol, 1.1 eq), phosphonate carbamate (7.9-23 mmol, 1.3 eq), LiCl (44-130 mmol, 7.4 eq), *i*-Pr₂NEt (5.9-17.5 mmol, 1.0 eq), MeCN, rt, 12 h. ^b% Isolated yield calculated over 2 steps.

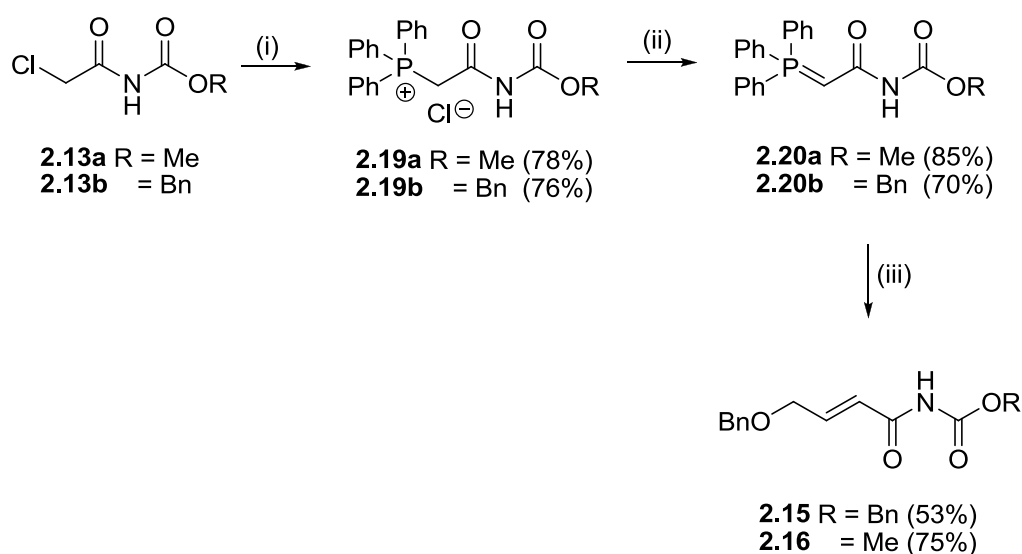
The low yields obtained for the HWE reaction were attributed to the limited stability of the aldehydes under basic conditions. Hence, the olefination reaction was attempted under Masamune-Roush conditions.⁹⁰ In this protocol LiCl is used as an additive, and the chelation of the phosphonate to the cation increases the acidity of the methylene proton (Scheme 2.6). This allows for the use of a weaker base, *e.g.* *i*-Pr₂NEt. Using the modified procedure, a moderate improvement in yield was obtained (Table 2.2, entries 3, 5 and 6).



Scheme 2.6: Mechanism of the Masamune-Roush modified HWE reaction.

The order of reagent addition was varied to determine if this affected the yield of the reaction. The base was stirred with an excess of phosphonate carbamate for 30 minutes, prior to the addition of the aldehyde, to allow for complete consumption of the base. Unfortunately, no improvement was achieved and degradation of the aldehyde was still a competitive process.

In light of these results, it was believed that formation of the Michael acceptors under neutral conditions, utilising a Wittig reaction, would be advantageous. Following a literature procedure,⁹¹ the phosphonium salts **2.19a** and **2.19b** were prepared, in 78% and 76% yield respectively, by the reaction of **2.13a** and **2.13b** with triphenylphosphine in THF under refluxing conditions (Scheme 2.7). The ylid salt formation was confirmed by the presence of a broad doublet ¹H resonance signal at 5.45 ppm, corresponding to the CH₂ group adjacent to the phosphorus (²J_{PH} = 14 Hz). Reaction of these chloride salts with KO^tBu gave the ylids **2.20a** and **b**, causing the shift of the broad doublet from 5.45 ppm to 4.59 ppm. The ylids were isolated as white solids in 85% and 70% yield respectively, and used without further purification in a Wittig reaction with the aldehyde **2.11**. This afforded the Michael acceptors **2.15** and **2.16** with improved yields of 53% and 75% respectively, as a 3.5:1 mixture of *E*- and *Z*- isomers. The *E*-isomer was identified by the presence of the *trans*-olefinic protons with a ³J coupling constant of 15.5 Hz, whereas the minor *Z*-isomer olefin protons displayed a smaller ³J coupling of 11.7 Hz. The isomers were separable by column chromatography.



Scheme 2.7: Reagents and conditions: (i) PPh₃, reflux, 16 h, 77%; (ii) KO^tBu, THF, 1 h, 84%; (iii) **2.11**, CH₂Cl₂, rt, 16 h.

A tandem Swern/Wittig reaction has been reported by Ireland, where the ylid was added to the Swern reaction mixture, on complete formation of the aldehyde.⁹² This would obviate the need to isolate the unstable aldehyde. Accordingly, the ylid **2.20a** was added to the Swern reaction mixture containing **2.11**, and the Michael acceptor **2.16** was isolated in the lower yield of 30%, with a slightly decreased *E*:*Z* ratio of 2:1.

It is possible that the low yields obtained for the synthesis of the Michael acceptors were a result of aldehyde degradation under the Swern conditions, where a large excess of NEt_3 was used. Thus the neutral Dess-Martin periodinane (DMP) and IBX reagents were employed for the oxidation-olefination reactions (Table 2.3).

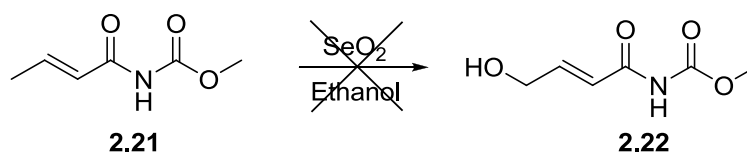
Table 2.3: Results for the oxidation of **2.9** to the aldehyde.^a

Entry	Conditions	Time/h	Temp/°C	% Yield ^b
1	IBX	60	70	10
2	DMP	12	Rt	100

^aGeneral reaction conditions: **Entry 1:** Alcohol **2.9** (1.3 mmol, 1.0 eq), IBX (1.7 mmol, 1.3 eq), EtOAc (5 mL), reflux; **Entry 2:** Alcohol **2.9** (1.1 mmol, 1.0 eq), DMP (1.2 mmol, 1.1 eq), CH_2Cl_2 (5 mL), rt. ^bYields determined by ^1H NMR.

The oxidation using IBX (Table 2.3, entry 1) gave low conversion to the aldehyde, with starting material persisting in the reaction mixture. In contrast, the oxidation using DMP (entry 2) proceeded well with full conversion. However, significant decomposition occurred upon workup and the aldehyde was obtained as a complex mixture. This degradation could be prevented by performing the oxidation and Wittig reactions in a tandem one-pot protocol, removing the need to isolate the aldehyde.⁹³ Accordingly, the Michael acceptor **2.16** was formed in 78% yield as the *E*-isomer exclusively. Oxidation of the alcohol was also attempted in a mild tandem oxidation process (TOPs), in which MnO_2 is used as oxidant and the resultant aldehyde is immediately reacted with a ylid.⁹⁴ However, no product or aldehyde was observed after 72 hours and starting material persisted.

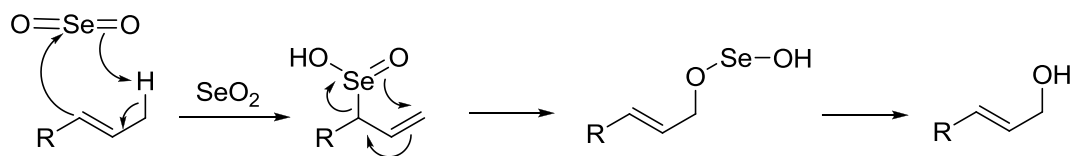
An alternative synthesis of the Michael acceptors involves the allylic oxidation of an alkene, using selenium dioxide (SeO_2) (Scheme 2.8).⁹⁵



Scheme 2.8: Michael acceptor formation by allylic oxidation.

Formation of the Michael acceptors *via* this method is attractive as it avoids the use of unstable aldehydes. **2.21** was easily synthesised, in good yield, by the HWE reaction of the phosphonium carbamates **2.14a** with acetaldehyde.²⁴ The mechanism of the allylic oxidation

proceeds as shown (Scheme 2.9). The selenium dioxide reacts with the alkene to give an allylic selenine acid. This undergoes a [2,3] sigmatropic rearrangement to produce an unstable selenium ether, which rapidly decomposed to give the desired allylic alcohol.



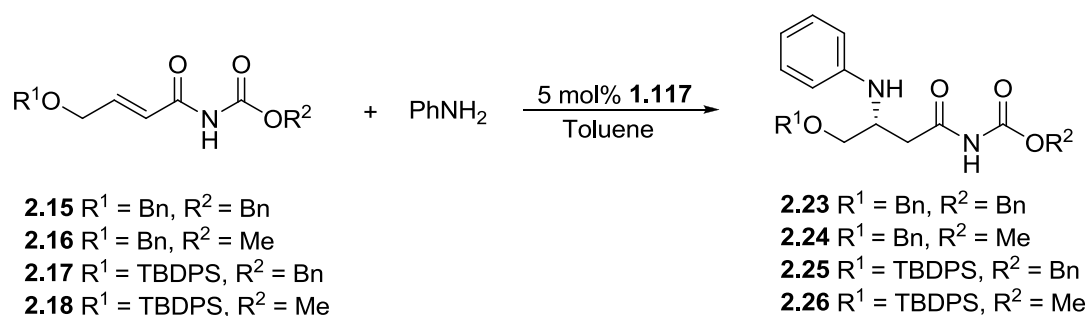
Scheme 2.9: Mechanism of the selenium dioxide mediated allylic oxidation.

The allylic oxidation was attempted on the alkene **2.21**, which was refluxed with the selenium dioxide in ethanol for several days.⁹⁵ However, only starting material was recovered from the reaction mixture.

In summary, the instability of the aldehydes proved problematic for the synthesis of the *aza*-Michael acceptors. The HWE reactions proceed to give the desired Michael acceptors in the desired *E*-isomer exclusively, however the yields are low. Using a weaker base in the Masamune-Roush modified HWE reaction had little effect. Changing to the neutral Wittig reaction increased the yield significantly, but gave a mixture of *E*- and *Z*- isomers. Finally, a tandem oxidation/Wittig reaction using DMP proved to be the most successful method, giving an overall yield of 78% over 2 steps. The next section details the optimisation of the *aza*-Michael reaction of aniline with these α , β -unsaturated carbamates.

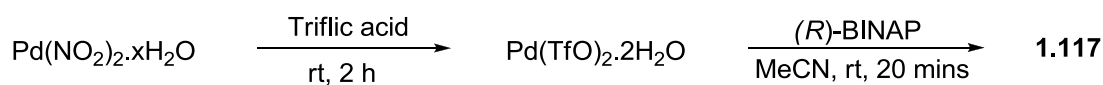
2.2 *Aza*-Michael reactions

The asymmetric *aza*-Michael reaction was the key step in the synthesis of the *Galipea* alkaloids, as it was used to install the stereochemistry. Significant optimisation of the *aza*-Michael reaction was undertaken to allow for the obtainment of material with high optical purity. The addition of aniline to Michael acceptors **2.15-2.18** catalysed by **1.117** was investigated to determine if the nature of the protecting group R^1 or the nature of the carbamate R^2 had any significant effect (Scheme 2.10).



Scheme 2.10: Aza-Michael reaction of aniline with Michael acceptors **2.15-2.18**.

The palladium-BINAP complex **1.117** was used in the initial screening, as it was found to be the best general catalyst for the addition of anilines to α , β -unsaturated carbonyls.⁸¹ The catalyst was prepared in two steps. Following a literature procedure, palladium nitrate was treated with triflic acid to generate palladium triflate as a hygroscopic purple solid (Scheme 2.11).⁹⁶ The catalyst **1.117** was then generated by reaction of the palladium triflate with (*R*)-BINAP in acetonitrile under anhydrous conditions, followed by recrystallisation from CH₂Cl₂/ether. The palladium-BINAP catalyst formed was air stable and identifiable by ³¹P NMR, which shows a characteristic broadened singlet at +33.0 ppm.⁹⁷



Scheme 2.11: Palladium BINAP catalyst synthesis.

Previously, it has been shown that the solvent used in the *aza*-Michael reaction has a significant effect on the enantioselectivity, toluene was found to be optimal for most of the reactions of α , β -unsaturated 1,3-dicarbonyl compounds.^{67, 69, 86} Accordingly, aniline was added to a mixture of the catalyst **1.117** and Michael acceptor **2.15-2.18** in toluene. The reaction was initially conducted at room temperature. However, starting materials persisted in the mixture after 16 h, as significant levels of both the catalyst and alkene were insoluble. Subsequently, the reaction temperature was increased to 50 °C (Table 2.4).

Table 2.4: Results of the *aza*-Michael reaction of **2.15-2.18** with aniline.^a

Entry	Michael acceptor	Aniline	Time /h	% Yield ^b	% ee ^c
1	<i>E</i> - 2.17	PhNH ₂	71	93	ND
2	<i>E</i> - 2.18	PhNH ₂	71	78	ND
3	<i>E</i> - 2.15	PhNH ₂	16	100	69
4	<i>Z</i> - 2.15	PhNH ₂	16	100	25
5	<i>E</i> - 2.16	PhNH ₂	16	100	61
6	<i>E</i> - 2.16	PhNHMe	48	63	ND

^aGeneral reaction conditions: **For entries 1-5:** Michael acceptor (0.2-0.4 mmol, 1.0 eq), **1.117** (5.0 mol%), aniline (0.2-0.4 mmol, 1.0 eq), toluene (1 mL), 50 °C. **Entry 6:** Michael acceptor (0.4 mmol, 1.0 eq), **1.117** (5 mol%), *N*-methylaniline (0.4 mmol, 1.0 eq), toluene (1 mL), 50 °C. ^bDetermined by ¹H NMR. ^cDetermined by chiral HPLC using a Daicel Chiralpak AD-H column.

Even at the elevated temperature, the additions of aniline to the silyl-protected **2.17** and **2.18** proceeded very sluggishly and conversions were incomplete after 3 days (Table 2.4, entries 1 and 2). In comparison, the addition to *E*-**2.15** and *E*-**2.16** proceeded with quantitative conversions within 16 h (entries 3 and 5). In all cases, the formation of the *aza*-Michael product was confirmed by loss of the olefin protons and the appearance of an ABX pattern in the ¹H NMR spectra, corresponding to the formation of the stereogenic centre and the diastereotopic methylene group. Separation of the enantiomers of *E*-**2.17** and *E*-**2.18** was not possible by chiral HPLC, preventing the determination of their enantiomer excesses. However, encouraging enantioselectivities of 69% and 61% were obtained for the products from the *E*-isomers of **2.15** and **2.16** (entries 3 and 5). Performing the reaction with the *Z*-isomer of **2.15** led to a significantly lower enantioselectivity of 25% (entry 4). As a result, it is important to ensure that the *E*-isomer is used in the conjugate additions, in order not to compromise the enantioselectivities.

The use of *N*-methylaniline in the *aza*-Michael reaction would install the methyl group present on the tetrahydroquinoline nitrogen of all four of the Galipea alkaloids. This would remove the need to methylate this nitrogen at a later stage, reducing the total number of steps in the synthesis. However, the reaction of *E*-**2.16** with *N*-methylaniline proved to be slow, attaining only 63% conversion after 2 days at 50 °C (Table 2.4, entry 6). Additionally, separation of the two enantiomers by chiral HPLC was unsuccessful and thus determination of the enantioselectivity was not possible. For this reason, it was decided that the methyl group should be installed later in the synthesis.

Previously, the assignment of the stereochemistry of the *aza*-Michael products was achieved by the synthesis of the known β -amino acid **2.27**.⁸¹ It was established that the use of (*R*)-BINAP led to formation of the (*S*)-isomer of the β -amino acid. Thus we expect the *aza*-Michael reaction of our α , β -unsaturated carbamates to also proceed with the same stereodifferentiation, *i.e.* using the (*R*)-isomer of the catalyst **1.117**, we would expect the (*R*)-isomer of **2.23-2.26** (Figure 2.1). This assumption will be confirmed by the synthesis of the natural products (*vide infra*).

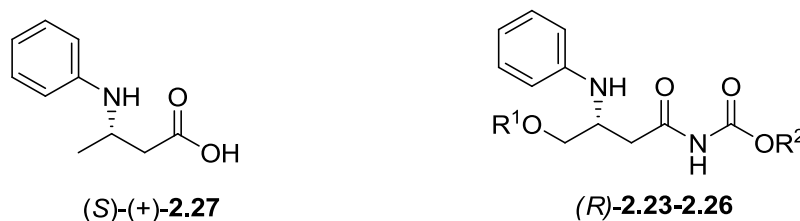


Figure 2.1: β -amino acid synthesised for the assignment of the stereochemistry.

For the synthesis of the *Galipea* alkaloids, high enantioselectivities were required. As better yields and shorter reaction times were achieved with the benzyl protected substrates, these were adopted in the subsequent optimisation studies. The next three sections detail the optimisation of the reaction, to obtain optically pure *aza*-Michael adducts.

2.2.1 Dilution study

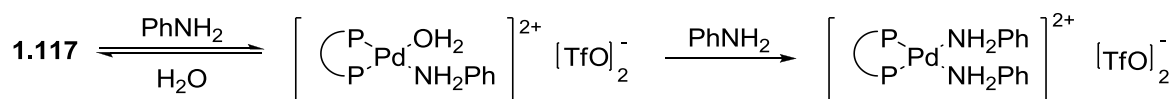
The effect of dilution on the *aza*-Michael reaction of **2.15** catalysed by **1.117** was investigated. Changing the dilution of the reaction had very little effect on the reaction yield, however significant changes to the enantioselectivity can be observed (Table 2.5). Decreasing the concentration of the reactant from 600 to 200 mM, led to further increase in the enantioselectivity (Table 2.5, entry 4 vs entries 2 and 3). Conversely, by increasing the concentration to 1 M, a large decrease in ee to 39% was observed (entry 1), whilst further dilution below 200 mM exerted little effect on the enantioselectivity (entries 4, 5 and 6). All 6 reactions remained homogeneous at 50 °C, suggesting this is not a solubility effect.

Table 2.5: Dilution results.^a

Entry	Dilution/ mM	Time /h	% Yield ^b	% ee, ^c (Config)
1	1000	16	96	39 (R)
2	600	16	98	58 (R)
3	300	16	98	67 (R)
4	200	16	95	74 (R)
5	150	16	91	74 (R)
6	75	16	97	76 (R)

^aGeneral reaction condition: Michael acceptor (0.3 mmol, 1.0 eq), (R)-**1.117** (5 mol%), aniline (1.0 eq), toluene, 50 °C, 16 h. ^bDetermined by ¹H NMR. ^cDetermined by chiral HPLC using Daicel Chiralpak AD-H column.

Previous mechanistic studies⁹⁸ revealed that a single equivalent of aniline binds to the catalyst **1.117** reversibly. However, the addition of the second equivalent leads to the formation of a diamine complex (Scheme 2.12), which is kinetically stable and catalytically inactive. Therefore, a high concentration of aniline in the reaction mixture can cause catalyst deactivation. The increase in ee with dilution is thus attributed to a reduction in the effective concentration of aniline, resulting in slower inhibition of the catalytic activity. This could be achieved more efficiently by the slow addition of aniline to a solution of the Michael acceptor and catalyst.⁹⁸

**Scheme 2.12:** Consecutive binding of aniline to **1.117**.

Slow addition of aniline to **2.15** and **2.16** was conducted over 20 hours using a syringe pump. This further improved the ee obtained to 81% and 84% respectively (Table 2.6).

Table 2.6: Slow addition results.^a

Entry	Product	Time/ h	% Yield ^b	% ee ^c , (Config)
1	2.23	17	96	81 (R)
2	2.24	18	96	84 (R)

^aSlow addition conditions: **Entry 1:** Michael acceptor **2.15** (0.15 mmol, 1.0 eq), (R)-**1.117** (5 mol%), aniline (0.15 mmol, 1.0 eq), toluene (2.5 mL), 50 °C, 48 h. **Entry 2:** Michael acceptor **2.16** (0.4 mmol, 1.0 eq), (R)-**1.117** (5 mol%), aniline (0.4 mmol, 1.0 eq), toluene (4.5 mL), 50 °C, 48 h. ^bDetermined by ¹H NMR.

^cDetermined by chiral HPLC using Daicel Chiralpak AD-H column.

2.2.2 Ligand screen

Axial chirality was previously shown to be the most effective for the enantioselective *aza*-Michael reactions.⁷⁰ Thus, range of chiral biaryl diposphines were examined as chiral ligands in the reaction of **2.15** and **2.16** with aniline (Figure 2.2). In these experiments, the $[P_2Pd(sol)_2]^{2+} [TfO]^-_2$ complexes (where P = biaryl phosphine ligand) were generated *in situ*, by stirring 5.5 mol% of the ligand with 5.0 mol% of $Pd(OTf)_2 \cdot 2H_2O$ in toluene for 30 minutes, prior to addition of the reactants.

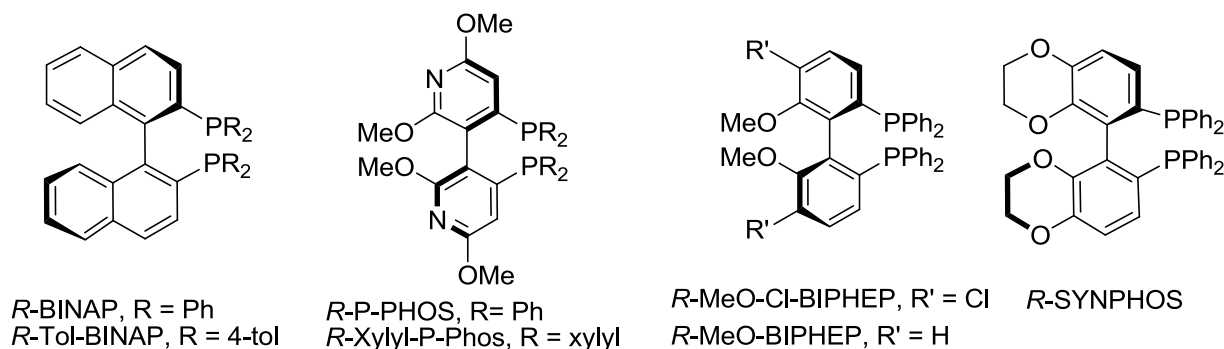


Figure 2.2: Various ligands used in the screening reactions.

Table 2.7: Results of ligand screen with Michael acceptors **2.15** and **2.16**.^a

Entry	Michael acceptor	Ligand	Time/ h	% Yield ^b	% ee ^c , (Config)
1	2.15	<i>R</i> -BINAP	19	100	69 (<i>R</i>)
2	2.16	<i>R</i> -BINAP	16	100	58 (<i>R</i>)
3	2.15	<i>R</i> -Tol-BINAP	19	95	69 (<i>R</i>)
4	2.16	<i>R</i> -Tol-BINAP	16	98	53 (<i>R</i>)
5	2.15	<i>R</i> -MeO-Biphep	19	100	66 (<i>R</i>)
6	2.16	<i>R</i> -MeO-Biphep	30	93	77 (<i>R</i>)
7	2.16	<i>R</i> -MeO-Cl-Biphep	16	93	72 (<i>R</i>)
8	2.15	<i>R</i> -Synphos	19	97	69 (<i>R</i>)
9	2.16	<i>R</i> -Synphos	30	85	40 (<i>R</i>)
10	2.15	<i>R</i> -P-Phos	19	100	64 (<i>R</i>)
11	2.16	<i>R</i> -P-Phos	30	74	11 (<i>R</i>)
12	2.15	<i>R</i> -Xylyl-P-Phos	19	94	72 (<i>R</i>)
13	2.16	<i>R</i> -Xylyl-P-Phos	19	94	41 (<i>R</i>)

^aGeneral reaction conditions: **For Michael acceptor 2.15:** $Pd(OTf)_2 \cdot 2H_2O$ (5.0 mol%), ligand (5.5 mol%), **2.15** (0.3 mmol, 1.0 eq), aniline (1.0 eq), toluene (1.5 mL), 50 °C; **For Michael acceptor 2.16:** $Pd(OTf)_2 \cdot 2H_2O$ (5.0 mol%), ligand (5.5 mol%), **2.16** (0.4 mmol, 1.0 eq), aniline (1.0 eq), toluene (1.5 mL), 50 °C. ^bYields determined by ¹H NMR. ^cEnantioselectivity determined by chiral HPLC using Daicel Chiralpak AD-H column.

Comparable results were obtained for the $[\text{Pd}(\text{R-BINAP})(\text{OH}_2)_2]^{2+}[\text{OTf}]^-_2$ complex generated *in situ*, compared to the use of the preformed catalyst **1.117** (Table 2.7 entries 1 and 2 vs. Table 2.4 entries 3 and 5). Generally, changes in the biaryl diphosphine ligand structure had little effect on the ee or yield for additions to the CBz-protected **2.15**, with the ee varying from 64 to 72% and yields from 94 to 100% (entries 3, 5, 8, 10 and 12). In contrast, the ligand structure had a very significant effect on the ee values obtained with the Moc-protected **2.16**. (*R*)-MeO-Biphep and (*R*)-Cl-MeO-Biphep complexes proceeded to give the highest ee of 77% and 72% respectively, and good yields of over 90% (entries 6 and 7), while (*R*)-P-Phos, (*R*)-Synphos and (*R*)-Xylyl-P-Phos gave moderate to good yields but low ee (entries 9, 11 and 13). (*R*)-Tol-BINAP gave similar results to those obtained with (*R*)-BINAP (entry 2 vs 4), suggesting that the size of the phosphine groups has little bearing on the results.

From this study, the highest enantioselectivity was obtained for the *aza*-Michael reaction of **2.16**, with (*R*)-MeO-Biphep. As the slow addition of aniline to the reaction mixture was previously shown to be beneficial for enantioselectivity (Table 2.6), this protocol was also adopted for the reaction of **2.16** with the (*R*)-MeO-Biphep catalyst. Unfortunately, no improvement in yield or ee was observed (66% yield and 77% ee).

Despite testing a range of biaryl-phosphine ligands for the *aza*-Michael reaction, no improvement in enantioselectivity was achieved. However, it is interesting to note that the enantioselectivities obtained with the various ligands were higher dependent on the nature of the terminal carbamate group.

2.2.3 Recrystallisation (enrichment of optical purity)

Good enantioselectivities (up to 84%) have been achieved for the *aza*-Michael reaction. However, for the total synthesis of the *Galipea* alkaloids, optically pure material was required. Previously, the optical purity of similar Michael adducts was shown to improved upon recrystallisation from cyclohexane-toluene.²⁴ For these compounds, racemic products are more crystalline and so precipitate more readily, leaving optically enriched compound in the mother liquors. Thus, the Michael adduct **2.24** was similarly recrystallised using a range of solvent conditions. Recrystallisation from EtOAc-hexane was found to be the most

effective - after several recrystallisations the initial mixture of 86% ee deposited crystals with an ee of 27%, leaving the mother liquor containing **2.24** in 77% recovered yield with 99% ee (Figure 2.3).

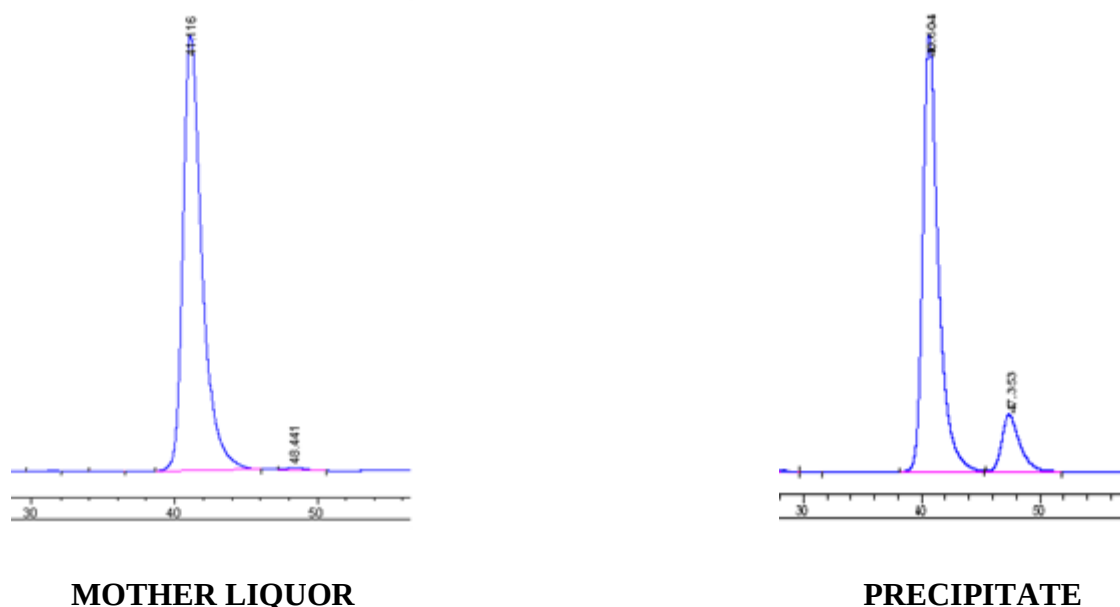


Figure 2.3: HPLC traces of mother liquor and precipitated solid after recrystallisation of a sample of **2.24** with 86% ee.

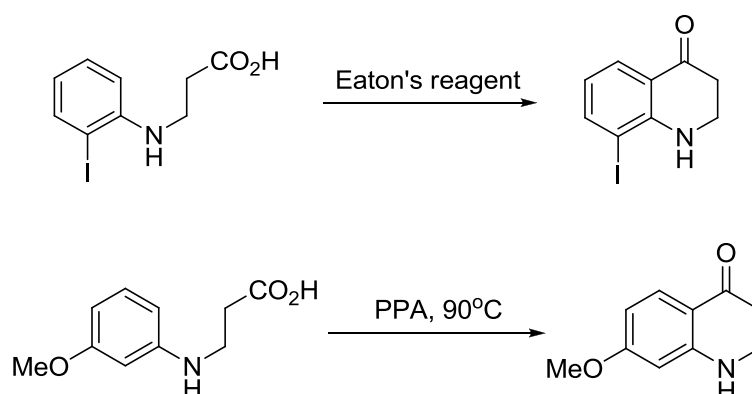
In conclusion, optimisation of the *aza*-Michael reaction allowed for the increase in ee from the initial 61% and 69% to the 84% and 81%, respectively, by the slow addition of aniline to the catalyst and alkene. Subsequently, optically pure material was obtained *via* recrystallisation of the *aza*-Michael adducts.

2.3 Electrophilic ring cyclisation

The next step in the synthesis of the Galipea alkaloids was the formation of the tetrahydroquinoline core structure. This section details our attempts at the cyclisation of the *aza*-Michael derivatives.

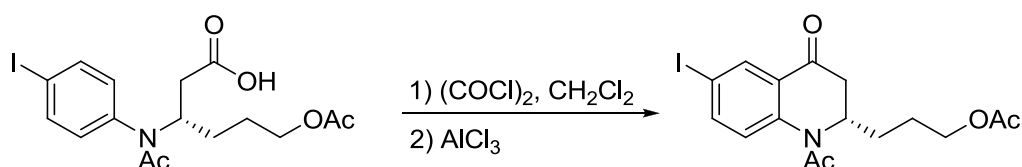
2.3.1 Friedel-Crafts type cyclisations

Several methods have been reported for the formation of tetrahydroquinolone ring systems, *via* the electrophilic cyclisation of β -amino acids. The first uses dehydrating reagents such as PPA⁹⁹ and Eaton's reagent (7% P_2O_5 in CH_3SO_3H)¹⁰⁰ to facilitate the ring cyclisation (Scheme 2.13).



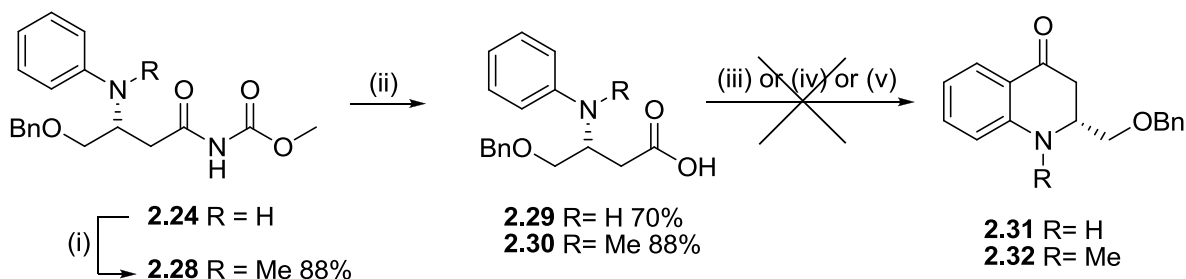
Scheme 2.13: Electrophilic ring cyclisation using dehydrating reagents.

The second method involves the formation of an acid chloride from the β -amino acid, which can then undergo a Friedel-Crafts reaction in the presence of a Lewis acid, such as $AlCl_3$. Ma *et al.* have used this method for the synthesis of a tetrahydroquinolone in 62% yield (Scheme 2.14).¹⁰¹



Scheme 2.14: Friedel-Crafts cyclisation of an amino acid.

First, methylation of **2.24** was attempted using a large excess of MeI and 2.5 equivalents of Ag_2O , however low yields of **2.28** were obtained. In comparison, reductive alkylation proceeded under literature conditions¹⁹ to give **2.28** in 88% yield (Scheme 2.15). Hydrolysis of the carbamates proceeded to give the *N*-aryl β -amino acids **2.29** and **2.30** in 70% and 88% yield, respectively. The loss of the methyl carbamate group was confirmed by 1H NMR and the appearance of a ^{13}C signal at 175.8 ppm corresponding to the carboxylic acid moiety. In addition, the characteristic broad OH stretch between 3000 and 2800 cm^{-1} , accompanied by a $C=O$ absorption at 1709 cm^{-1} , were observed in the infrared spectrum.



Scheme 2.15: Reagents and conditions: (i) Formaldehyde, NaCNBH₃, AcOH, MeCN, 5 °C, 1 h; (ii) 1 M KOH, MeOH, rt, 2 h; (iii) Eaton's reagent 7% P₂O₅ in CH₃SO₃H, rt-60 °C; (iv) (COCl)₂, DMF, CH₂Cl₂, AlCl₃, 0 °C-rt, 15 h; (v) PPA, 65-90 °C.

With the acyclic precursors **2.29** and **2.30** in hand, the electrophilic ring cyclisation using Eaton's reagent¹⁰⁰ or PPA⁹⁹ was investigated (Table 2.8).

Table 2.8: Results of the electrophilic ring cyclisation using Eaton reagent and PPA.^a

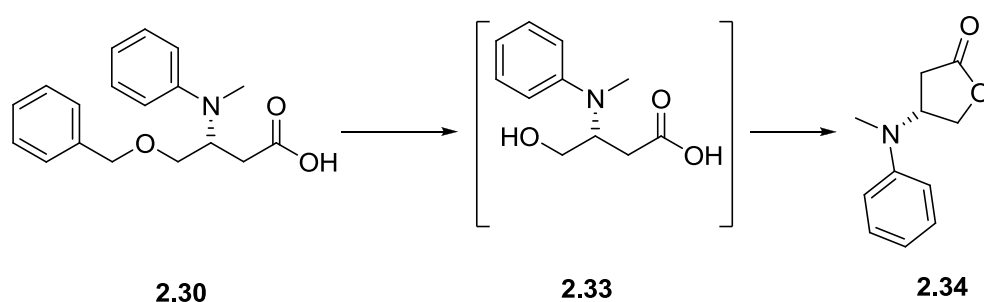
Entry	Starting material	Reagent	Temp/°C	Time/h	% Yield
1	2.29	Eaton's	60	3	-
2	2.29	Eaton's	Rt	4	-
3	2.24	Eaton's	60	3	-
4	2.30	Eaton's	Rt	5	-
5	2.30	PPA	90	2	-
6	2.30	PPA	65	2	-
7	2.30	PPA	90	1	-
8	2.24	PPA	65	2	-
9	2.23	PPA	90	2	-
10	2.35	PPA	90	2	-

^aGeneral reaction conditions: **For entries 1-4:** Cyclisation precursor (1.0 eq), Eaton's reagent (4.0 eq); **For entries 5-10:** Cyclisation precursor (0.16 mmol, 1.0 eq), PPA (8.0 mmol, 50 eq). ^bDetermined by ¹H NMR.

None of the desired tetrahydroquinolone was obtained when the electrophilic ring cyclisation of **2.29** was attempted using Eaton's reagent (Table 2.8, entry 1). Instead, complete degradation of the starting material occurred. It was hoped that this degradation could be suppressed by lowering the reaction temperature (entry 2), or by subjecting the carbamate **2.24** to the reaction (entry 3). However, neither of these attempts were successful; complex

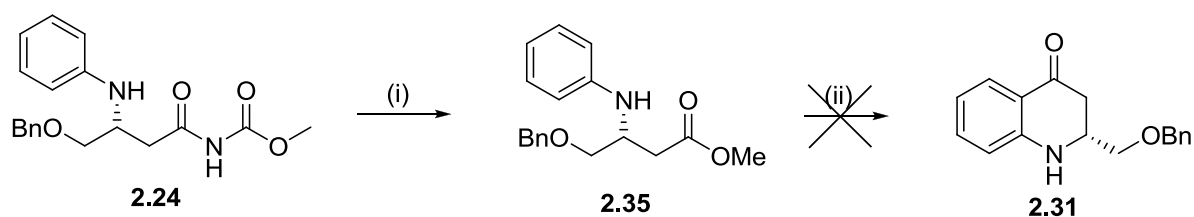
reaction mixtures were obtained, with signals observed in the ^1H NMR spectra relating to aniline and an alkene, suggesting a retro-*aza*-Michael reaction had occurred. It was postulated that the methylated **2.30** would be more resistant to the retro-*aza*-Michael reaction. However, **2.30** was still inherently unstable to the strongly acidic conditions and although none of the retro *aza*-Michael products were observed, complete degradation of the starting material to unidentifiable compounds occurred (entry 4).

As the cyclisation with Eaton's reagent proved unsuccessful, the reaction was attempted with PPA, in the hope that the carboxylic acid would prove more stable against these reaction conditions. Unfortunately, no product was obtained when the reaction was conducted under described conditions (entry 5),⁹⁹ with lowered temperature (entry 6) or with shortened reaction time (entry 7). Complex mixtures were obtained in all three cases, from which an unknown compound can be isolated in low yields (~ 30%). This was subsequently identified as **2.34** (Scheme 2.16), characterised by a strong carbonyl stretch at 1770 cm^{-1} in its infrared spectrum typical of a γ -lactone moiety, further supported by a ^{13}C NMR resonance signal at 175.7 ppm and the observation of a M^+ ion peak of 191 (EI). The presence of the lactone implies that the benzyl protecting group in **2.30** was unstable under the reaction conditions, and on cleaving formed the β -hydroxy acid intermediate **2.33**, which cyclise spontaneously to form **2.34**.



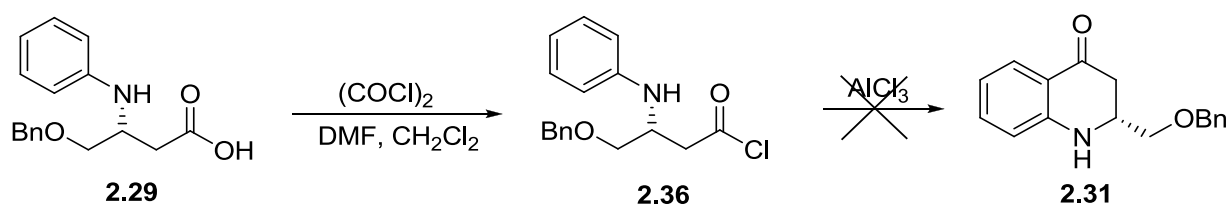
Scheme 2.16: Formation of the lactone ring.

The direct cyclisation of carboxylic esters to produce tetrahydroquinolones is known in the literature.⁹⁹ Thus, the PPA cyclisation was attempted with the methyl carboxylic ester **2.35**, formed from **2.24** in 60% yield (Scheme 2.17),¹⁰² and also the carbamate derivatives **2.23** and **2.24**. In these cases, the formation of the γ -lactone **2.34** was not observed, but neither was any tetrahydroquinolone – once again, complete degradation of the precursors occurred (Table 2.8, entries 8-10).



Scheme 2.17: Reagent and conditions: (i) CaCl_2 , NaOMe, MeOH, 60%; (ii) PPA, 120°C .

Due to the lack of success with acid-catalysed electrophilic cyclisations, it was hoped the formation of the cyclised material may be achieved under the milder Friedel-Crafts conditions. To this end, the amino acid **2.29** was converted into the acid chloride **2.36**, which was then subjected to the Friedel-Crafts reaction (Scheme 2.18).

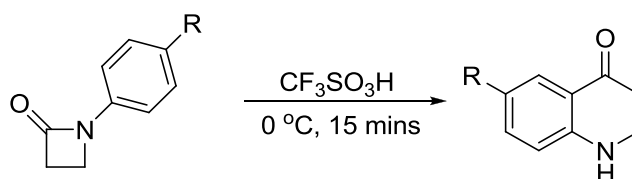


Scheme 2.18: Formation of tetrahydroquinolone using a Friedel-Crafts reaction.

Complete consumption of starting material occurred but, once again, the reaction proceeded to give the γ -lactone **2.34** (23% yield) *i.e.* cleavage of the benzyl protecting group by the strong Lewis acid occurred under these conditions.

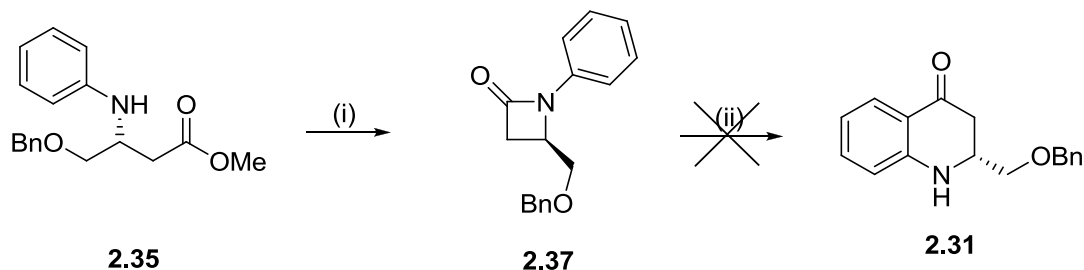
Up to this juncture, despite a large number of attempts, none of the desired heterocycle was obtained by the electrophilic cyclisation of acid derivatives. Complete degradation occurred *via* a retro-*aza*-Michael reaction when Eaton's reagent was employed, due to the strongly acidic reaction conditions. When using PPA or a Lewis acid, competitive debenzylolation, leading to the formation of a lactone, prevented obtainment of the tetrahydroquinoline. In other cases, degradation of the starting material occurred.

The formation of tetrahydroquinolone rings by the Fries rearrangement of an *N*-arylated β -lactams had been reported (Scheme 2.19).^{103, 104}



Scheme 2.19: Fries rearrangement of β -lactams to give tetrahydroquinolones.

Accordingly, the required β -lactam **2.37** was obtained from the methyl ester **2.35** by cyclisation with LHMDS (Scheme 2.20).¹⁰⁵ On subjecting **2.37** to the Fries rearrangement conditions, none of the tetrahydroquinolone was formed, and starting material persisted in solution. Increasing the reaction time led to complete degradation of the starting material.

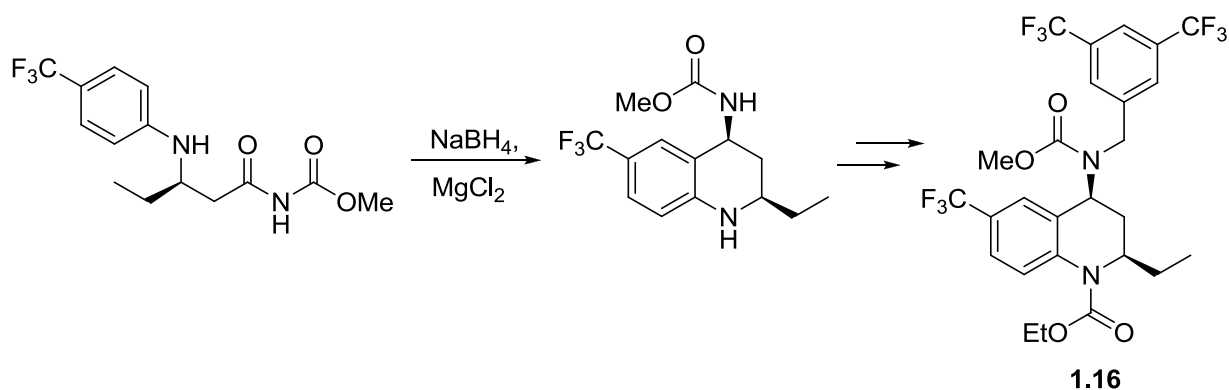


Scheme 2.20: Reagent and Conditions: (i) LHMDS, THF, $-20\text{ }^\circ\text{C}$; (ii) $\text{CF}_3\text{SO}_3\text{H}$, DCE, $0\text{ }^\circ\text{C}$.

The instability of these *aza*-Michael products, their corresponding carboxylic acid and β -lactams to strongly acidic conditions, renders the formation of the tetrahydroquinolone ring system impossible *via* electrophilic cyclisation reactions. As a result, alternative, milder methods were sought.

2.3.2 Lewis acid mediated reduction/cyclisation reaction

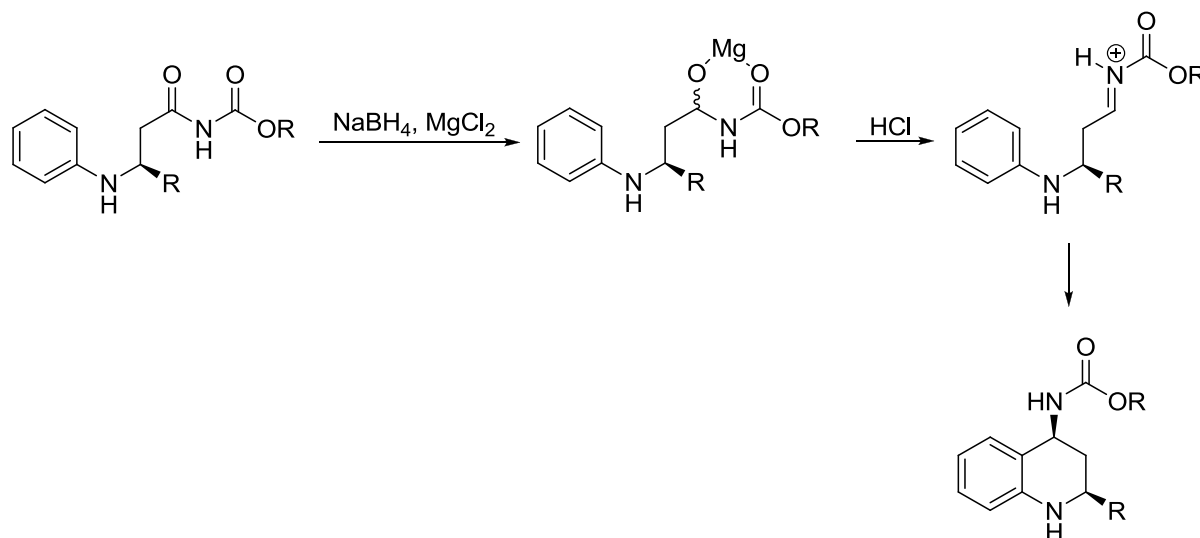
Previous work in our group reported the formation of 2, 4-disubstituted tetrahydroquinolines from *aza*-Michael adducts in the synthesis of a CETP inhibitor, Torcetrapib **1.16** (Scheme 2.21).²⁴



Scheme 2.21: Synthesis of Torcetrapib **1.16**.

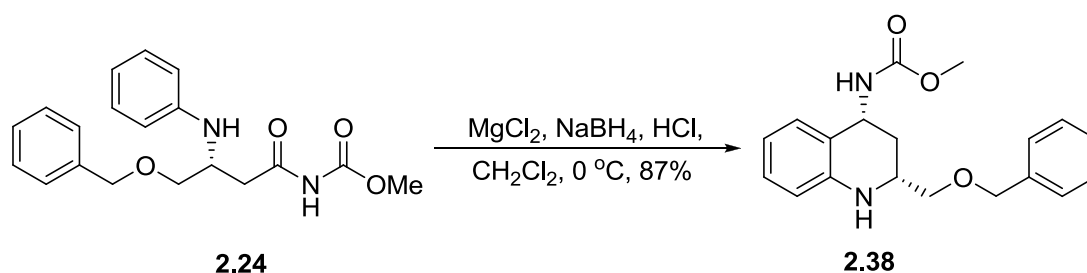
The cyclisation step was facilitated by MgCl_2 , which acted as a Lewis acid forming a chelate with the 1, 3-dicarbonyl moiety of the *aza*-Michael adduct, promoting the reduction of one of the carbonyl groups by NaBH_4 (Scheme 2.22). Elimination of the resultant hydroxyl group produced an acyl immonium ion, which underwent electrophilic cyclisation to produce the 2,

4-tetrahydroquinoline as the *syn* isomer exclusively. Molecular modelling revealed the activation energy of the *syn* cyclisation pathway to be considerably lower than the *anti* cyclisation pathway.



Scheme 2.22: Lewis acid mediated reductive cyclisation of *aza*-Michael adducts.

Similarly, Michael adduct **2.24** was subjected to the reductive/cyclisation conditions. Gratifyingly, this afforded the expected nitrogen heterocycle **2.38** in 87% yield, as a single compound, presumably the *syn*-isomer (Scheme 2.23). The formation of the desired tetrahydroquinoline was indicated by the loss of one of the two carbonyl stretches in the IR spectrum, corresponding to the imide functionality, and the emergence of the new *N*-carbamate entity, with a ^{13}C resonance at 156.4 ppm.



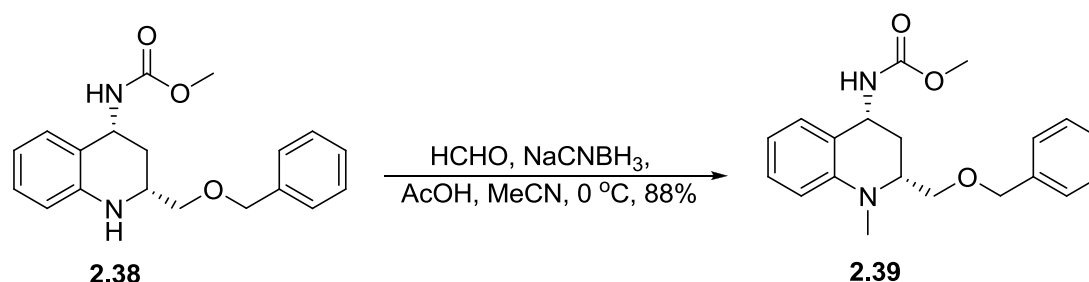
Scheme 2.23: Reductive cyclisation of *aza*-Michael adducts.

Formation of the tetrahydroquinoline ring was finally achieved using this mild reductive/cyclisation reaction, in excellent yield. This cyclisation also installed another stereocentre in the C-4 position of the ring, which has to be removed for the synthesis of the Galipea alkaloids.

2.4 Synthesis of the common precursor 2.1

Synthesis of the common precursor **2.1** from the tetrahydroquinoline **2.38** requires methylation of the tetrahydroquinoline nitrogen, the removal of the Moc protected amine at C-4 and deprotection of the C-2 ether to liberate the hydroxyl group.

It was decided that methylation of the tetrahydroquinoline nitrogen should be performed first, as an unsubstituted nitrogen could cause problems in later steps. This was easily achieved under reductive methylation conditions,¹⁹ to give the desired tetrahydroquinolines **2.39** in 88% yield (Scheme 2.24).

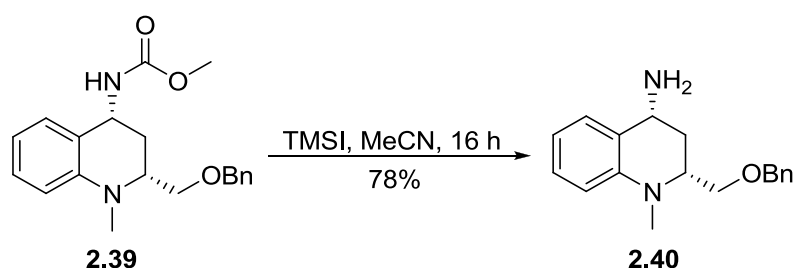


Scheme 2.24: Reductive methylation reaction.

The installation of the Me group was confirmed by the presence of a singlet resonance at 2.99 ppm in the ¹H NMR spectrum, and a resonance signal at 31.9 ppm in the ¹³C NMR spectrum.

2.4.1 Deamination

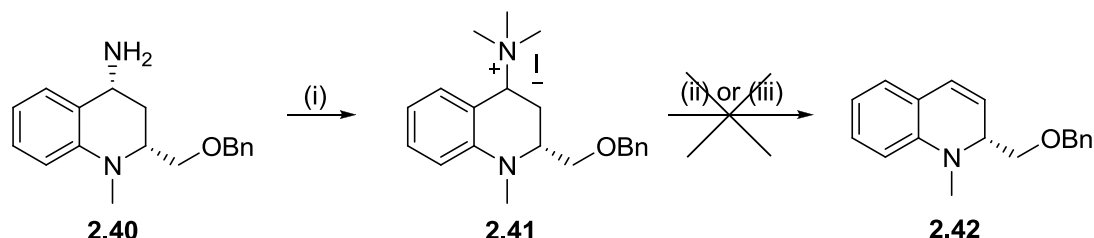
The deprotection of the *N*-Moc group was attained using trimethylsilyl iodide,¹⁰⁶ to afford the amine **2.40** in 78% yield (Scheme 2.25). The loss of the CO₂Me was confirmed by ¹H and ¹³C NMR spectroscopy.



Scheme 2.25: Moc deprotection using TMSI.

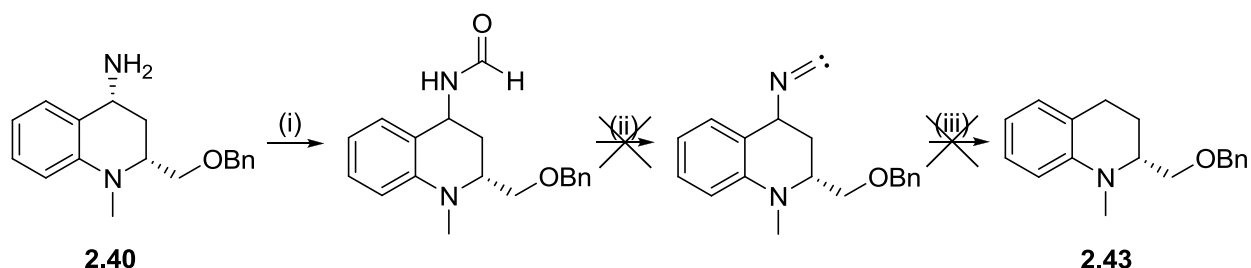
Several deamination procedures are known in the literature, the simplest of which involves the reaction of the amine with excess methyl iodide, followed by the Hofmann elimination of the resultant quaternary ion. This could be achieved using various bases¹⁰⁷ or amberlite¹⁰⁸ (Scheme 2.26). Hydrogenation of the resultant alkene would both remove the double bond

created and the benzyl protecting group to give the common intermediate **2.1** in a single step. Unfortunately, reaction of the amine **2.40** with a large excess of MeI and K₂CO₃ did not proceed to give the desired alkene, leading only to complete degradation of the starting material.



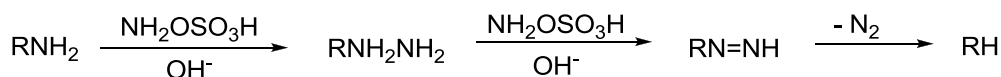
Scheme 2.26: Reagents and conditions: (i) MeI, K₂CO₃, MeOH; (ii) Amberlite, MeOH; (iii) Base.

In a Barton deamination reaction, the amine is converted into an isocyanide, which undergoes a radical reaction with AIBN and tin-*n*-butyl hydride to give the corresponding deaminated product (Scheme 2.27).¹⁰⁹ Accordingly, formation of the isocyanide was attempted *via* formylation of the amine using formic acetic anhydride, followed by dehydration with toluene-*p*-sulphonyl chloride in pyridine.¹⁰⁹ However, only a complex mixture was obtained.



Scheme 2.27: Barton deamination reaction: (i) Formic acid, acetic anhydride, reflux, 12 h; (ii) Py., TsCl, rt, 2 h (iii) AIBN, HSnBu₃.

Deamination reactions have been achieved using hydroxyl-amine-*O*-sulfonic acid and sodium hydroxide. Initially the amine is converted to the hydrazine under basic conditions and then elimination of nitrogen gives the alkane (Scheme 2.28).¹¹⁰



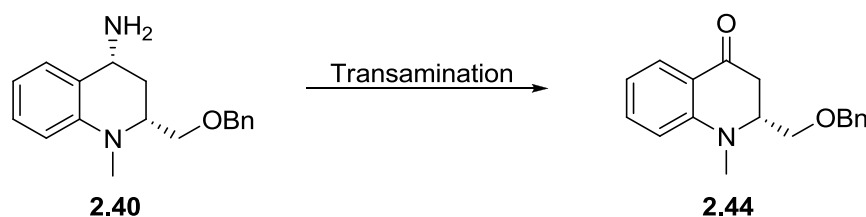
Scheme 2.28: Deamination using hydroxyl-amine-*O*-sulfonic acid.

Under the literature conditions,¹¹⁰ none of the desired deamination product **2.43** was obtained, with **2.40** persisting in the reaction solution, even when the reaction was performed under reflux.¹¹¹

Although these deamination reactions would provide a direct route to the Galipea alkaloids, the instability of the amine to the harsh reaction conditions proved problematic.

2.4.2 Transamination

A number of methods for the transformation of amines into ketones are known in the literature, whereby amines are converted into imines, which hydrolyse to give the corresponding ketones. Removal of a ketone group from the C-4 position should be facile, with a large number of procedures known to facilitate this, including the Wolff-Kishner reduction.¹¹² A variety of transamination reactions were attempted on the amine **2.40** (Scheme 2.29, Table 2.9).



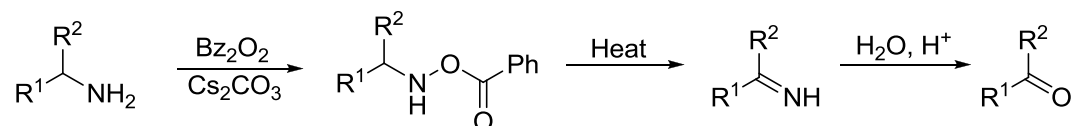
Scheme 2.29: Transamination of amine **2.40** to the tetrahydroquinolone.

Table 2.9: Transamination of the amine **2.40**.

Entry	Conditions	Temp/ °C	Time/ h	% Yield ^b
1	Bz ₂ O ₂ , Cs ₂ CO ₃ , DMF	0-50	18	-
2	Bz ₂ O ₂ , Cs ₂ CO ₃ , DMF	0	2	-
3	Fremy's salt, 2% Na ₂ CO ₃ , Py.	rt	16	-
4	Fremy's salt, 2% Na ₂ CO ₃	rt	5	-
5	IBX	rt	72	-
6	IBX	rt	2	< 5
7	Rapoport's reagent, DBU, H ⁺	rt	18	44
8	Corey's reagent	rt	4	43

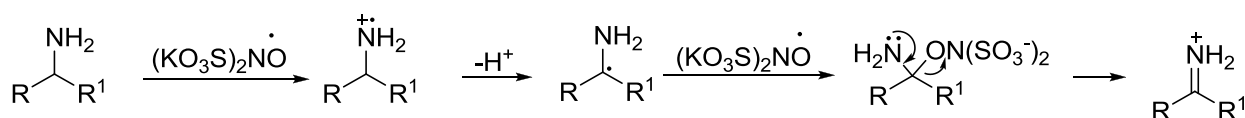
^aReagents and conditions: **For entries 1-2:** Amine (1.2 eq), Bz₂O₂ (0.15 mmol, 1.0 eq), Cs₂CO₃ (1.5 eq), DMF (1 mL); **For entries 3-4:** Amines (0.18 mmol, 1.0 eq), Fremy's salt (10 eq), 5% Na₂CO₃ (20 mL); **For entries 5-7:** Amine (0.18 mmol, 1.0 eq), IBX (1.1 eq), DMSO (0.5 mL); **Entry 8:** Amine (0.18 mmol, 1.0 eq), Rapoport's reagent (1.0 eq), DBU (2.0 eq), sat. oxalic acid (2 mL), DMF (1 mL), CH₂Cl₂ (1 mL); **Entry 9:** Amine (0.18 mmol, 1.0 eq), Corey's reagent (1.0 eq). ^bYields determined by ¹H NMR.

The reaction of amines with benzoyl peroxide and caesium carbonate leads to the formation of hydroxylamines. These can decompose on heating to give imines, which hydrolyse to form ketones (Scheme 2.30).¹¹³ Unfortunately, only degradation products were observed in the reaction mixture when **2.40** was subjected to the literature conditions (Table 2.9, entry 1).¹¹³ Failure to isolate the intermediate hydroxylamine implies that the decomposition occurred at the onset of the reaction (entry 2).



Scheme 2.30: Conversion of amines into ketones using benzoyl peroxide.

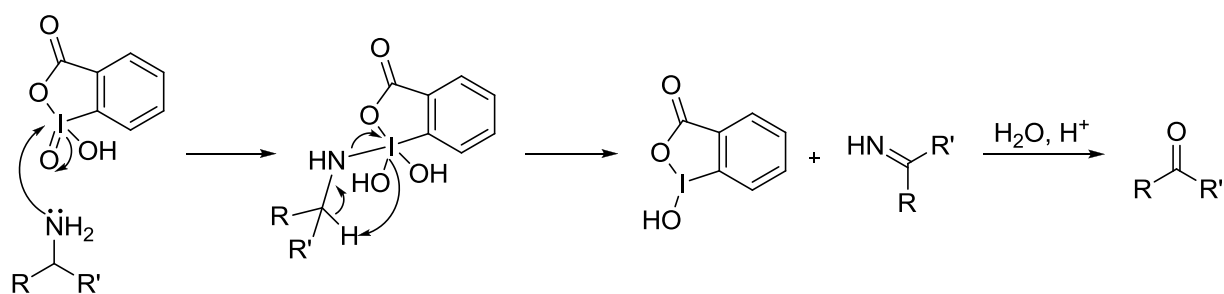
Using Fremy's salt, $(\text{KO}_3\text{S})_2\text{NO}\cdot$ a stable radical,¹¹⁴ an electron can be extracted from the amine to form a radical cation, which produces an alkyl radical after loss of a proton. Addition of the Fremy's salt gives a neutral quaternary species, which immediately eliminates $\text{ON}(\text{SO}_3^-)_2$ to give an imine (Scheme 2.31).



Scheme 2.31: Conversion of amines to ketones using Fremy's salt.

The reaction was attempted using Fremy's salt with Na_2CO_3 in pyridine. Unfortunately, degradation of the amine starting material was facile under these conditions (Table 2.9, entry 3). The reaction was also attempted in the absence of pyridine (entry 4), in case the presence of the organic base was facilitating degradation of the starting material, however, no improvement was observed.

IBX has been shown to convert a variety of primary amines into ketones (Scheme 2.32).¹¹⁵



Scheme 2.32: Mechanism of ketone formation using IBX.

Once again, only extensive degradation was observed when the amine was reacted with IBX at room temperature for 72 hours (Table 2.9, entry 5). On reducing the reaction time, only trace levels of the ketone were observed by ^1H NMR (entry 6).

Finally, 4-formyl-1-methylpyridinium benzenesulfonate, Rapoport's reagent **2.45**¹¹⁶ and 3,5-di-*t*-butyl-1,2-benzoquinone, Corey's reagent **2.46**,¹¹⁷ were investigated as transamination reagents (Figure 2.4).

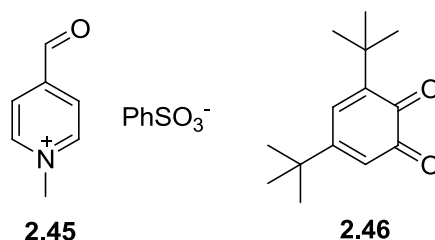
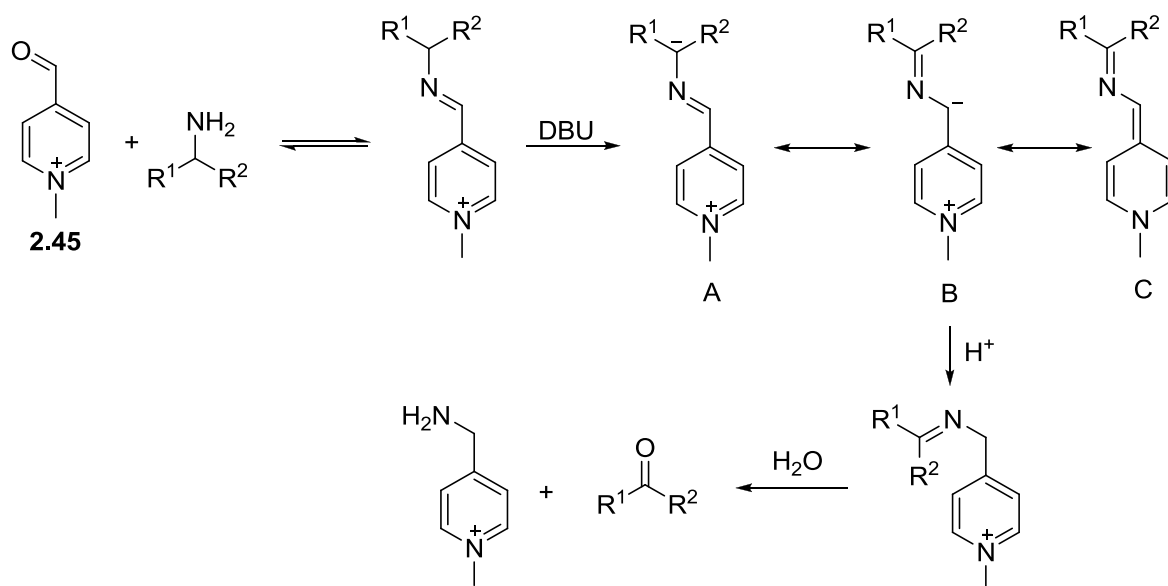


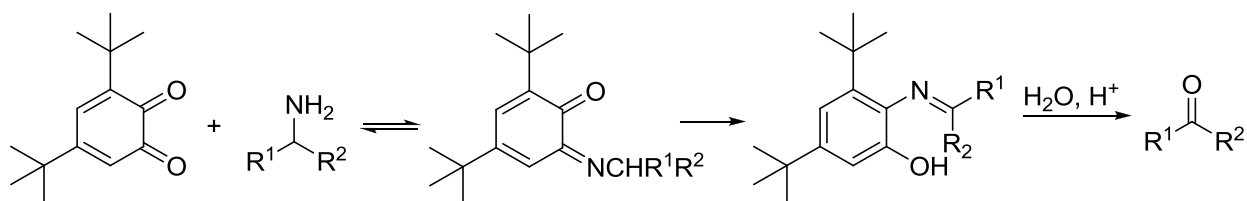
Figure 2.4: Transaminating reagents.

The Rapoport's reagent **2.45** mimics the pyridoxal phosphate co-factor responsible for transamination of amino acids.¹¹⁶ It reacts with the amine to form an imine intermediate (Scheme 2.33). Upon the addition of a base (DBU), deprotonation occurred and an equilibrium is established between the resonance structures A, B and C. Upon the addition of an aqueous acid, protonation of these resonance structures proceeded to give an imine. Protonation of the resonance structure A would reform the starting material, whereas protonation of the resonance structure B would lead to the formation of product, upon hydrolysis. Therefore the success of the reaction is dependent on this equilibrium.



Scheme 2.33: Mechanism of transamination using **2.45**.

Condensation of amines with Corey's reagent **2.46** also produces an imine. In this case, the addition of base is unnecessary. The imine intermediate undergoes a spontaneous 1, 5-prototropic rearrangement, with aromatisation of the ring the driving force. The resultant imine hydrolyses to produce the desired ketone (Scheme 2.34).



Scheme 2.34: Transamination with Corey's reagent.

The transamination of the amine **2.40** with Rapoport's reagent proceeded to give the ketone in a moderate yield (Table 2.9, entry 7). A clean mixture of product and starting material was obtained; the latter could be recovered and reused. It was thought that the transamination of the amine with Corey's reagent could proceed to give higher levels of conversion, as the quinine/aromatic redox system thermodynamically favours the 1, 5-prototropic rearrangement. However, this proved not to be the case, and a comparable yield to that obtained with Rapoport's reagent was achieved, however, none of the starting material was recovered (entry 8). Thus, the Rapoport's transamination reagent was chosen for the synthesis of the Galipea alkaloids.

A variety of different conditions were investigated for the transamination using **2.45**, in an attempt to optimise the yield of the ketone (Table 2.10).

Table 2.10: Transamination of **2.40** with **2.45**.^a

Entry	2.45 (eq)	DBU (eq)	% Isolated yield
1	1	2	44
2	2	2	47
3	2	2	35 ^b
4	2	3	67
5	10	10	75

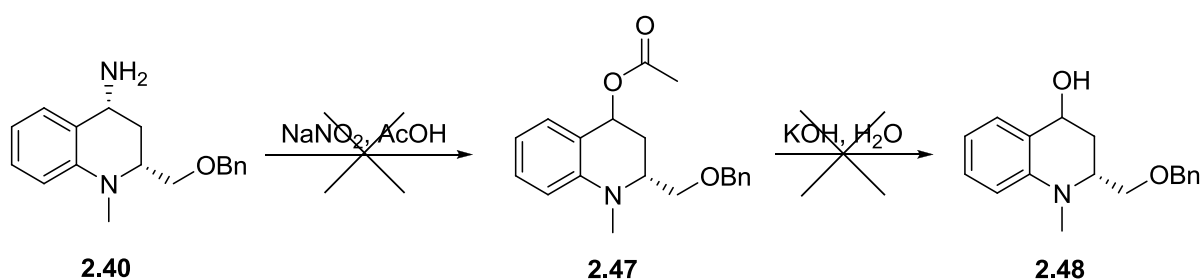
^aReagents and conditions: Amine (0.18 mmol, 1.0 eq), **2.45** (1-10 eq), CH₂Cl₂ (1 mL) and DMF (1 mL).

^bConducted at twice the concentration.

The original procedure employed one equivalent of the transamination reagent and 2 equivalents of DBU, to afford an isolated yield of 44% (Table 2.10, entry 1). It was thought the low yield could be due to a problem with formation of the imine, prior to addition of base, with the equilibrium favouring the precursors **2.40** and **2.45**. Thus, the amount of transaminating reagent was increased (2 equivalents), in an attempt to drive the equilibrium towards the imine. However, little difference in the yield was observed (entry 2). Next, the reaction was performed at a higher concentration, whereupon the yield decreased to 35% (entry 3). This is attributed to the poor solubility of transamination reagent.

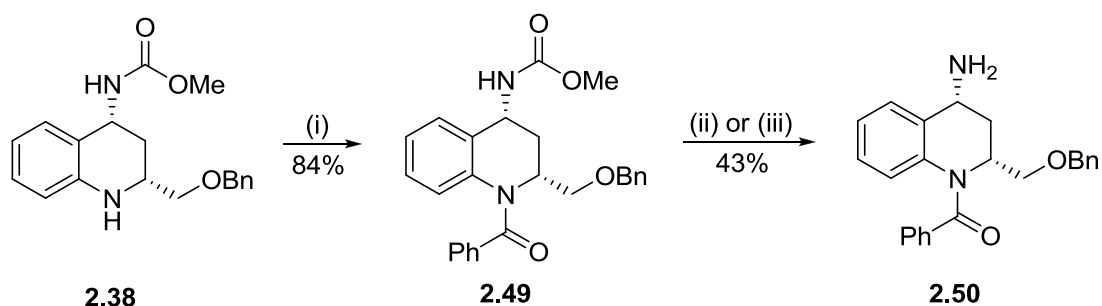
The effect of base on the reaction was explored. By increasing the equivalents of DBU from 2 to 3, an increase in the yield to 67% was observed (Table 2.10, entry 4). This suggests that an excess of DBU is required to ensure deprotonation occurs to establish the equilibrium between the resonance structures. Finally, a good yield of 75% was obtained when a large excess of both reagents was used (entry 5).

The amine group at C-4 may be converted into a hydroxyl group *via* an acetate. Reaction of the amine with sodium nitrite produced a diazonium ion, which was immediately substituted by an acetate group. Hydrolysis of the acetate gave the desired alcohol.¹¹⁸ Conversion of the amine **2.40** into the alcohol **2.48** was attempted under the described conditions (Scheme 2.35), however degradation of the starting material occurred, even when the reaction was conducted at -5 °C.



Scheme 2.35: Conversion of the amine into a hydroxyl group.

It was noted that the literature examples contained an electron-withdrawing group on the tetrahydroquinoline nitrogen. In this case, it is possible that the unprotected nitrogen was interfering with the reaction, leading to degradation of the starting material. With this in mind, **2.50** was prepared with a benzoyl protecting group on the nitrogen (Scheme 2.36).



Scheme 2.36: Reagents and conditions: (i) BzCl, NEt₃, Et₂O; (ii) TMSI, MeCN; (iii) 2M NaOH, EtOH, reflux.

Protection of the nitrogen was required to take place prior to removal of the *N*-Moc group from the amine in the C-4 position, to ensure selective protection of the tetrahydroquinoline nitrogen. **2.49** was prepared in 84% yield, with the formation confirmed by the appearance of an additional carbonyl signal at 169.9 ppm in the ¹³C NMR. Removal of the *N*-Moc protecting group was initially attempted using TMSI. The reaction proceeded to give the amine **2.50**, in the low yield of 43%. This prompted us to attempt a different *N*-Moc deprotection using 2M NaOH at reflux, but this did not lead to any improvement in yield.

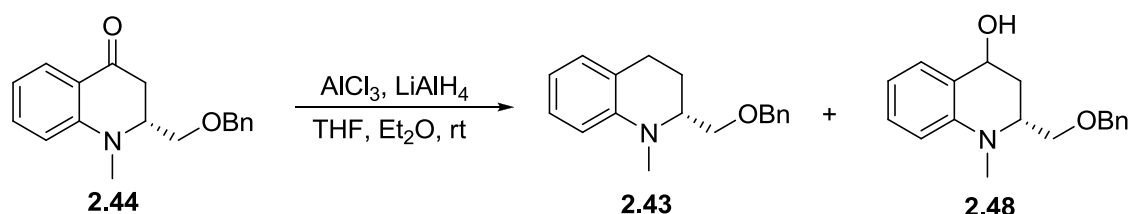
With the protected amine **2.50** in hand, conversion of the amine to the alcohol was attempted. Disappointingly, this led to a complex mixture, which appeared to contain only trace levels of the alcohol. The significant levels of decomposition made this method unattractive.

Direct substitution of an NH₂ by an OH has also been reported to occur using KOH.¹¹⁹ Following this procedure, the amine **2.40** was heated to 120 °C in ethylene glycol with KOH. On leaving the reaction for 16 hours, complete degradation of the starting material occurred. The reaction time was consequently reduced. After 3 hours, trace amounts of the alcohol was observed by ¹H NMR, however, this was accompanied by a significant level of degradation. No reaction occurred upon lowering the reaction temperature to 50 °C.

The formation of the alcohol proved unsuccessful and large levels of decomposition occurred under all the reaction conditions. As a good yield was obtained for the transamination of the amine **2.40** into the ketone **2.44** using Rapoport's reagent, **2.44** was chosen as the intermediate for the synthesis of the Galipea alkaloids.

2.4.3 Ketone removal and benzyl deprotection

There are a wide range of conditions reported for the removal of ketone groups. The reduction of ketones to alkyls has previously been reported using AlCl_3 and LiAlH_4 (Scheme 2.37).¹²⁰



Scheme 2.37: Ketone removal from the tetrahydroquinolone.

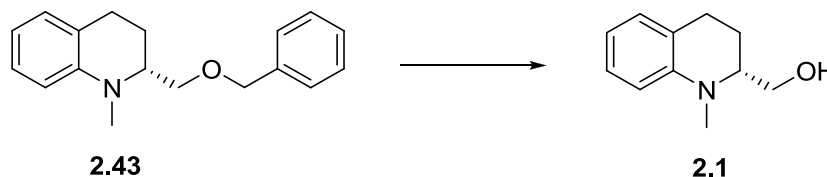
Reduction of our ketone **2.44** using LiAlH_4 and AlCl_3 produced a mixture of the tetrahydroquinoline **2.43** and the partially reduced **2.48** in a 2:1 ratio (Table 2.11, entry 1). The major component was confirmed as **2.43**, by the presence of its M^+ ion at 267 (EI) and two multiplets between 2.83-2.64 ppm and 2.19-1.96 ppm in the ^1H NMR spectrum, corresponding to the adjacent methylene groups in the heterocycle. The alcohol **2.48**, obtained as a 1:1 mixture of diastereoisomers, was identified as the minor component by the observation of the M^+ ion at 283 (EI) and an OH stretch in the IR spectrum at 3410 cm^{-1} . On extending the reaction time to 16 hours, the yield of **2.43** was improved, however complete formation was still not obtained (entry 2). Eventually, on increasing the equivalents of LiAlH_4 and the reaction time, complete conversion to the desired product occurred, and **2.43** was isolated in 87% yield (entry 3).

Table 2.11: Ketone removal from the tetrahydroquinolone.^a

Entry	Total LiAlH_4 (eq)	AlCl_3 (eq)	Time/h	2.43 : 2.48 ^b
1	2.5	2	2	2:1
2	2.5	2	16	5:1
3	3.5	2	18	100:0

^aGeneral reaction conditions: Tetrahydroquinolone **2.44** (0.36 mmol, 1.0 eq); AlCl_3 (0.71-1.42 mmol); LiAlH_4 (0.89-1.78 mmol). ^bRatio determined by ^1H NMR.

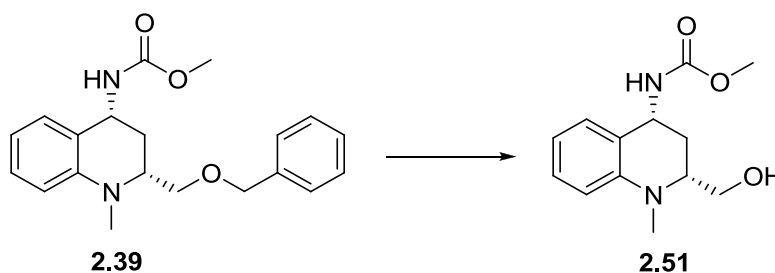
Formation of the common precursor **2.1** was now achievable by cleavage of the benzyl protecting group (Scheme 2.38).



Scheme 2.38: Removal of the benzyl group.

Classically, the removal of benzyl protecting groups is achieved by hydrogenation over activated Pd/C.¹²¹ When the tetrahydroquinoline **2.43** was subjected to hydrogenation conditions (5% Pd/C in ethanol under an atmosphere of hydrogen, at ambient temperature and pressure), none of the desired alcohol was obtained and starting material was recovered. No improvement was achieved on the addition of acetic acid. Turning to other non-reductive methods, some success was achieved by the use of TMSI, which afforded a mixture of the starting material **2.43** and the alcohol **2.1** in a 1:1 ratio. Increasing the reaction time, the amount of TMSI and the temperature had no effect on the product distribution. In all cases starting material persisted, and increasing the temperature for prolonged periods resulted in complex mixtures.

It was postulated that removal of the benzyl group could be facile at an earlier stage in the synthesis (Scheme 2.39). Hence, deprotection of the 2, 4-disubstituted tetrahydroquinoline **2.39** was attempted under a range of conditions (Table 2.12 and 2.13).



Scheme 2.39: Removal of the benzyl group from the tetrahydroquinoline **2.39**.

Initially, hydrogenation was attempted using palladium on charcoal (Table 2.12). It was postulated that removal of the Moc protected amine could also occur under these conditions, as it resides in the activated benzylic position.

Table 2.12: Hydrogenation of the tetrahydroquinoline **2.39**.^a

Entry	Conditions	Temp/ °C	Pressure/psi	Time/ h	% Yield ^b
1	5 % Pd/C, H ₂ , AcOH	rt	14.7	5	-
2	10 % Pd/C, H ₂	50	14.7	7	-
3	10 % Pd/C, H ₂	50	14.7	72	-
4	10 % Pd/C, H ₂	rt	30	72	-
5	10 % Pd/C, H ₂	50	30	72	-
6	10% Pd/C, 1,4-cyclohexadiene	rt	-	72	-

^aReagents and conditions: **Entry 1:** THQ (100 mg, 0.3 mmol), Pd/C (100 mg), AcOH (cat.), H₂, EtOH (2 mL); **For entries 2-3:** THQ (50 mg, 0.14 mmol), Pd/C (50 mg), THF (2 mL), H₂; **For entries 4-5:** THQ (50 mg, 0.14 mmol), Pd/C (50 mg), THF (2 mL), H₂ (30 psi); **Entry 6:** THQ (100 mg, 0.3 mmol), Pd/C (100 mg), 1,4-cyclohexadiene (0.3 mL), EtOH (1.5 mL). ^bYields determined by ¹H NMR.

No reaction occurred on attempting the hydrogenation with 5% Pd/C at room temperature under an atmosphere of hydrogen, even with the addition of acid (Table 2.12, entry 1). Changing the catalyst to 10% Pd/C and increasing the temperature to 50 °C had no effect (entry 2), even at extended reaction times (entry 3). As a result, the hydrogenation was conducted under 30 psi of hydrogen at room temperature, to see if increasing the pressure would allow for deamination. None of the desired product was obtained; starting material was recovered, even when the reaction was left exposed to the hydrogenative conditions for 72 hours at 50 °C (entries 4 and 5), although the onset of degradation was evident. Transfer hydrogenation was attempted under literature conditions,¹²² using Pd/C as catalyst and 1, 4-cyclohexadiene as the hydrogen source. This hydrogenation process also proved unsuccessful with benzyl protecting group remained in place (entry 6), suggesting it is surprisingly stable.

As hydrogenation with Pd/C did not proceed to remove the benzyl group a number of other methods for debenzylolation were investigated (Table 2.13).

Table 2.13: Results for benzyl deprotection of **2.39**.^a

Entry	Conditions	Time/h	Temperature/ °C	% of 2.51 obtained ^b	% of SM remaining ^b
1	AlCl ₃ , <i>N,N</i> -dimethylaniline	24	rt	-	100
2	FeCl ₃	24	rt	-	-
3	Nickel sponge	16	80	90	10

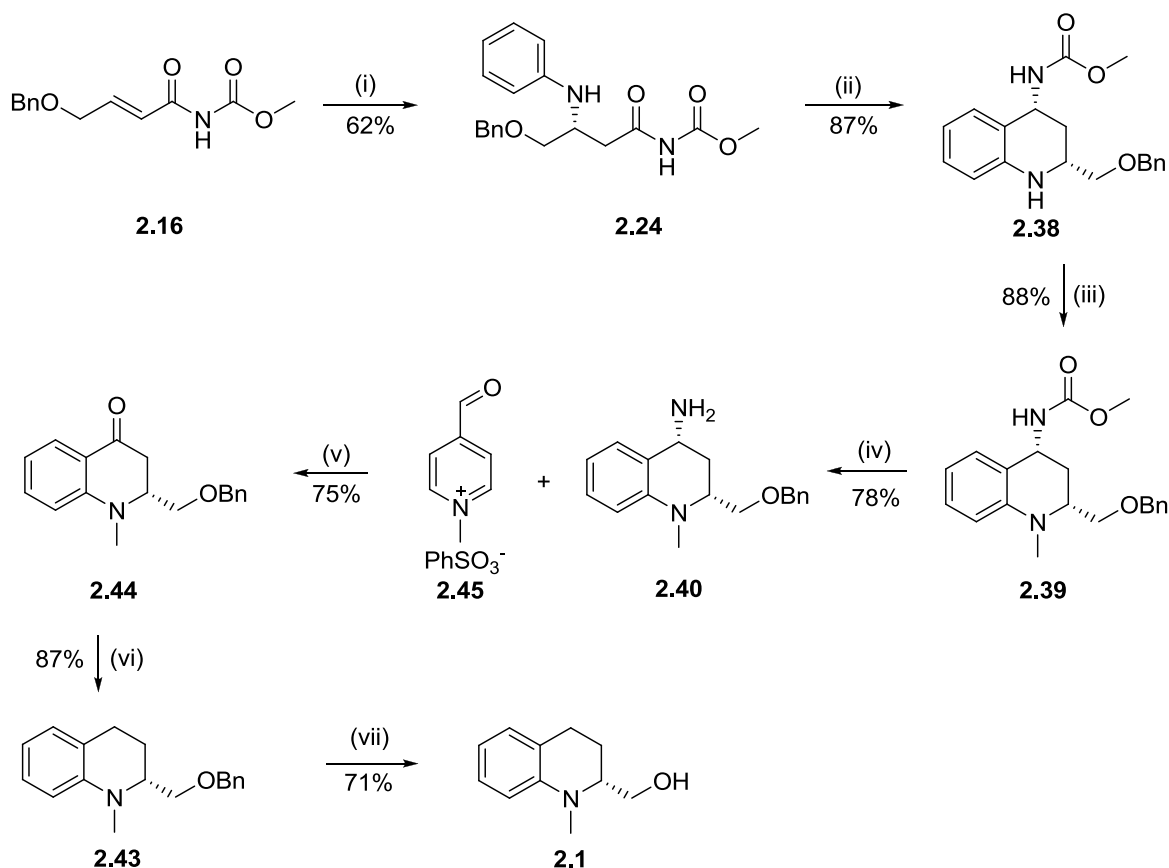
^aReagent and Conditions: **Entry 1: 2.39** (50 mg, 0.14 mmol), AlCl₃ (78 mg, 0.58 mmol), *N,N*-dimethylaniline (55 μ L, 0.44 mmol), CH₂Cl₂ (1 mL); **Entry 2: 2.39** (50 mg, 0.14 mmol), FeCl₃ (71 mg, 0.41 mmol), CH₂Cl₂ (3 mL); **Entry 3: 2.39** (50 mg, 0.14 mmol), nickel sponge (500 mg), EtOH (2 mL), THF (1 mL). ^bDetermined by ¹H NMR.

The removal of benzyl ethers using AlCl₃ and *N,N*-dimethylaniline has been reported.¹²³ This reaction is believed to proceed *via* coordination of the AlCl₃ to the ether oxygen. Nucleophilic attack of the dimethylaniline at the benzylic carbon liberates the alcohol upon acidic work up. Unfortunately, when **2.39** was subjected to these conditions no reaction was obtained and starting material was recovered (Table 2.13, entry 1). Benzyl deprotection can also occur in the presence of FeCl₃ in dichloromethane, believed to proceed in a similar manner to the AlCl₃ reaction.^{124, 125} In this case, complete degradation of the starting material to unknown compounds occurred (entry 2). Finally, cleavage of the benzyl group was achieved using Nickel sponge in a mixture of ethanol/THF.^{126, 127} Under refluxing conditions, the reaction proceeded to give **2.51** with 90% conversion after 16 hours (entry 3). Furthermore, the reaction progressed cleanly to give an easily separable mixture of starting material and product.

The debenzylolation procedure was also applied successfully to the deaminated tetrahydroquinoline **2.43**. In contrast to the debenzylolation of **2.39**, the reaction was extremely slow requiring 5 days to proceed to 80% conversion, giving the alcohol **2.1** in 71% yield. Attempts to reduce the reaction time by increase the pressure gave complex reaction mixtures, with significant degradation of the starting material. The formation of the deprotected **2.1** was confirmed by the presence of an OH stretch in the IR spectrum and the M⁺ ion 177.1 (EI).

Hence, the common precursor **2.1** was formed from ethylene glycol in 9 steps with 12% overall yield (Scheme 2.40). The *aza*-Michael reaction afforded **2.24** in good

enantioselectivity, and optically pure material was obtained upon recrystallisation. The formation of the *N*-heterocycle was achieved under reductive cyclisation conditions to give the 2, 4-disubstituted tetrahydroquinoline **2.38**. Methylation, followed by *N*-Moc deprotection produced the amine **2.40** in good yield. This amine was subjected to a transamination reaction using Rapoport's reagent. Finally, **2.1** was obtained from the tetrahydroquinolone by reductive removal of the ketone and benzyl deprotection.

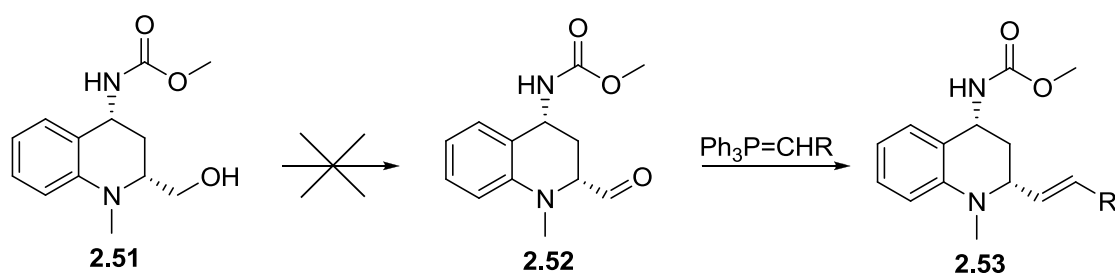


Scheme 2.40: Reagent and conditions: (i) PhNH_2 , **1.117**, toluene, 50 °C; (ii) NaBH_4 , $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$, EtOH/THF , HCl , -10 °C; (iii) HCHO , NaCNBH_3 , AcOH , MeCN , 0 °C; (iv) TMSI , MeCN , rt; (v) 4-formyl-1-methyl pyridinium benzenesulfonate **2.45**, DBU , oxalic acid, $\text{CH}_2\text{Cl}_2/\text{DMF}$, rt; (vi) AlCl_3 , LiAlH_4 , Et_2O , THF , rt; (vii) Nickel sponge, EtOH , THF , reflux.

2.5 C-2 Side chain attachment

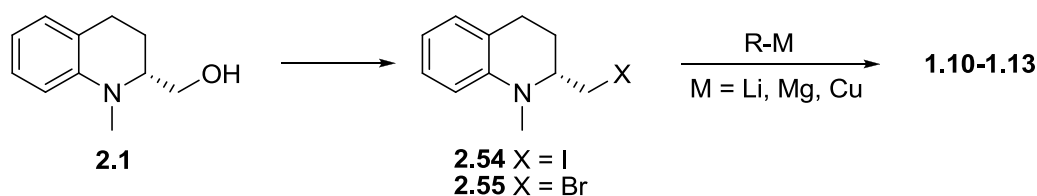
With **2.51** in hand, an attempt was made to attach the requisite C-2 substituents at this stage. This could be achieved by oxidation of the alcohol to the corresponding aldehyde, followed

by a Wittig reaction (Scheme 2.41). However, oxidation of **2.51** under Swern conditions did not proceed to give the aldehyde, but only led to complete degradation of the starting material.

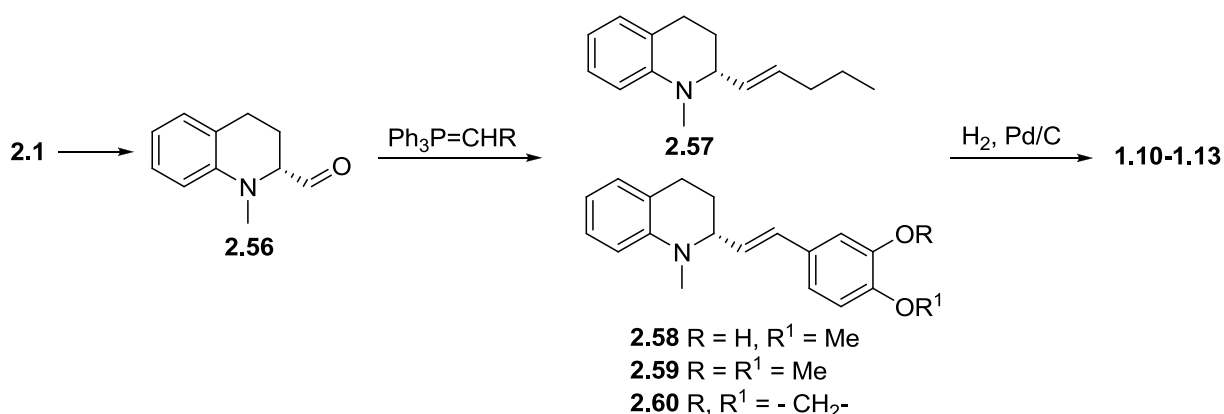


Scheme 2.41: Attachment of the C-2 side chain to **2.51**.

Thus, attachment of the C-2 substituent was attempted with **2.1**. Two potential methods were identified; The conversion of the C-2 alcohol into a leaving group, followed by the reaction with a suitable organometallic reagent (Scheme 2.42), or the tandem oxidation/Wittig sequence, followed by hydrogenation of the resultant double bond (Scheme 2.43).



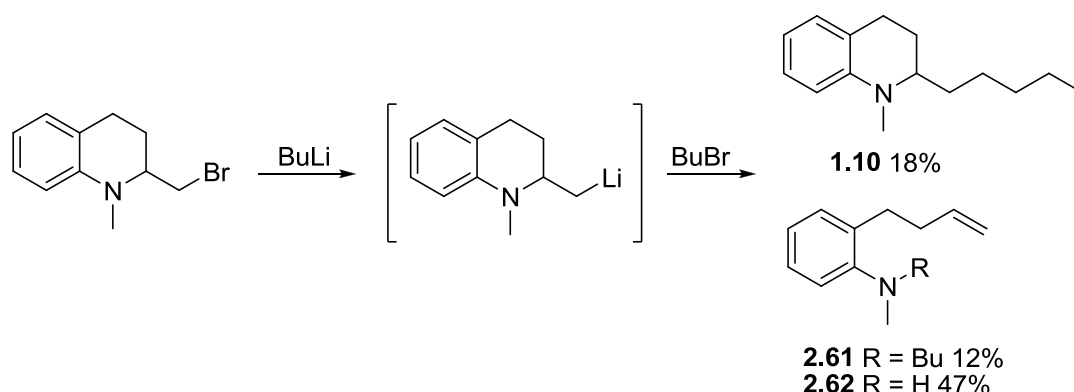
Scheme 2.42: Formation of the Galipea alkaloids by a $\text{S}_{\text{N}}2$ reaction.



Scheme 2.43: Formation of the Galipea alkaloids using a tandem oxidation-Wittig-reduction sequence.

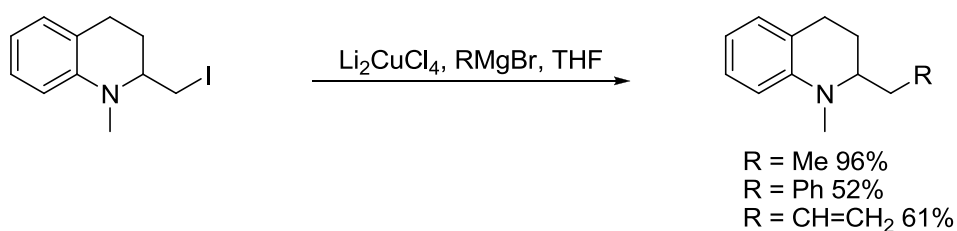
The first strategy has been previously adopted for the synthesis of racemic angustureine and various analogues. **2.54** and **2.55** were treated with a cuprate, to produce angustureine in 18%

yield. The main side products of this reaction were the anilines **2.61** and **2.62**, formed by competitive elimination (Scheme 2.44).¹²⁸



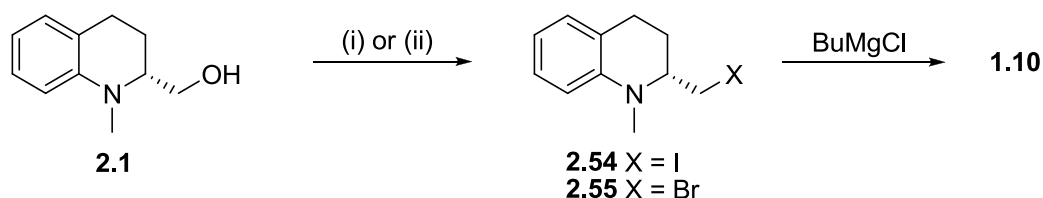
Scheme 2.44: Attempted Galipea alkaloid synthesis.

In the reported work, the addition of allyl, phenyl and methyl groups to the iodide proceeded to give the substituted products in moderate to good yields, using a cuprate formed from Li_2CuCl_4 and a Grignard reagent (Scheme 2.45).¹²⁸



Scheme 2.45: Extension of C-2 side chain by $\text{S}_{\text{N}}2$ substitution.

The alcohol of **2.1** was converted into a good leaving group, either an iodide or bromide, following literature conditions (Scheme 2.46).¹²⁸ These compounds are unstable, and were used immediately on formation. Attempts to convert the alcohol into a tosyl or mesyl group led to extensive degradation. The bromide and iodide were reacted with *n*-butylmagnesium chloride under a number of reaction conditions (Table 2.14).



Scheme 2.46: Reagents and conditions: (i) I_2 , PPh_3 , imidazole, toluene, MeCN, 0 °C; (ii) MsCl , NEt_3 , LiBr , THF, -40 °C.

Table 2.14: Attempted attachment of the C-2 side chain *via* S_N2 substitution.^a

Entry	Starting material	Reagents	Grignard/eq	Time/h	% Yield ^b
1	2.55	CuCl	6.25	18	30
2	2.54	CuCl	6.25	18	-
3	2.55	CuI	6.25	72	-
4	2.54	CuI	6.25	72	< 5
5	2.55	CuCl ₂ , LiBr	1.05	18	-
6	2.54	CuCl ₂ , LiBr	1.05	18	< 5
7	2.55	AgNO ₃	1.3	18	-
8	2.54	AgNO ₃	1.3	18	-

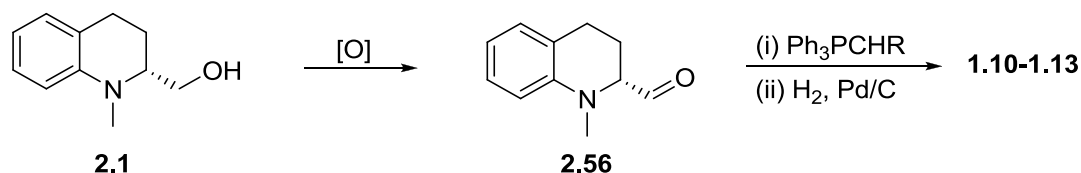
^aReagent and conditions: **For entries 1-2:** Alkyl halide (1.0 eq), CuCl (2.7 eq), *n*-BuMgCl (6.25 eq), THF, NMP, -78°C-rt; **For entries 3-4:** Alkyl halide (1.0 eq), CuI (1.44 eq), *n*-BuMgCl (6.25 eq), THF, -78°C-rt; **For entries 5-6:** Alkyl halide (1.0 eq), CuCl₂ (cat.), LiBr (cat.), *n*-BuMgCl (1.05 eq), THF, NMP, -78°C-rt; **For entries 7-8:** Alkyl halide (1.0 eq), AgNO₃ (cat.), *n*-BuMgCl (1.3 eq), Et₂O, rt. ^bYield calculated by ¹H NMR.

Reaction of the bromide **2.55** with the Grignard reagent, in the presence of CuCl, proceeded to give **1.10** as a mixture containing large amounts of starting material (Table 2.14, entry 1). Characteristic signals corresponding to alkene protons could be seen in the ¹H NMR spectrum, suggesting degradation of the bromide *via* elimination of HX. Conversely, none of the desired **1.10** was obtained when the iodo **2.54** was subjected to the same reaction conditions; a majority of the iodide decomposing (entry 2). No product was formed when the bromide was reacted with the cuprate generated from the Grignard reagent and CuI (entry 3). On the other hand, trace levels of product were observed when the iodide was reacted with this cuprate, but a significant level of starting material was recovered (entry 4). Finally, no reaction occurred between **2.55** and the Grignard reagent with CuCl₂ and LiBr,¹²⁹ while the iodide gave trace quantities of **1.10**, with recovery of starting material (entries 5 and 6).

Recently silver salts have been reported to efficiently catalyse the cross coupling reaction of alkyl halides with Grignard reagents.¹³⁰ Accordingly, the cross coupling reaction of the iodide **2.54** and bromide **2.55** with butyl magnesium chloride was attempted in the presence of AgNO₃. Unfortunately only starting material was recovered from the reaction mixture.

Failing to synthesise angustureine, in good yield, by cross-coupling with organometallic reagents, we started to investigate the second strategy involving redox transformations.

Namely, the oxidation of **2.1** to the aldehyde, followed by a Wittig reaction and hydrogenolysis of the C=C bond (Scheme 2.47). The preparation of the aldehyde was attempted using several different oxidising reagents (Table 2.15).



Scheme 2.47: Formation of the Galipea alkaloids *via* redox transformations.

Table 2.15: Oxidation of **2.1**.^a

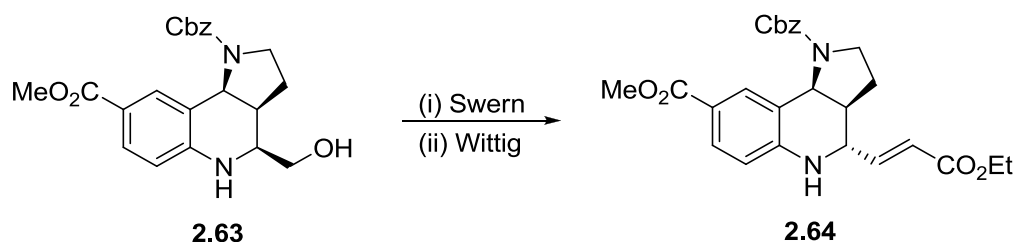
Entry	Oxidation conditions	Temp/ ^o C	Time/h	% Conversion ^b
1	TEMPO, NaOCl, KBr	rt	20	-
2	TPAP, NMO	rt	16	10
3	DMP	rt	18	30
4	DMP, H ₂ O	5	3	30
5	DMP, TFA	rt	18	100
6	Swern	-78 to rt	1.5	100

^aReagents and conditions: **Entry 1:** Alcohol (0.17 mmol, 1.0 eq), TEMPO (10 mol%), NaClO (0.19 mmol, 1.1 eq), potassium bromide (0.17 mmol, 1.0 eq), CH₂Cl₂ (1 mL); **Entry 2:** Alcohol (0.06 mmol, 1.0 eq), NMO (0.12 mmol, 2.0 eq), TPAP (10 mol%), CH₂Cl₂ (0.5 mL); **For entries 3-5:** Alcohol (0.16 mmol, 1.0 eq), DMP (0.16 mmol, 1.0 eq), CH₂Cl₂ (1 mL); **Entry 6:** Alcohol (0.17 mmol, 1.0 eq), oxalyl chloride (0.19 mmol, 1.1 eq), DMSO (0.34 mmol, 2.0 eq), NEt₃ (0.85 mmol, 5.0 eq), CH₂Cl₂ (1 mL). ^bDetermined by ¹H NMR.

Formation of the aldehyde under mild reaction conditions would prove advantageous, as this could help minimise degradation of the aldehyde. Initially the mild oxidation of the alcohol was attempted using TEMPO, but starting material was recovered (Table 2.15, entry 1). Only 10% conversion was obtained when TPAP was employed (entry 2). A DMP oxidation procedure was next attempted, which proceeded with 30% conversion (entry 3). The addition of water has been shown to improve DMP oxidation reactions,^{131, 132} however it had no effect in this instance (entry 4). The result contradicts an earlier report, where DMP oxidation of a similar alcohol to **2.1** has been achieved, when the nitrogen was protected with a deactivating group.¹³³ This implies that the presence of the *N*-methyl substituent could be the cause of our failure. Hence, trifluoroacetic acid (1.5 eq) was added to the reaction mixture, in the hope of protonating and deactivating the nitrogen. Indeed, this led to a complete consumption of the

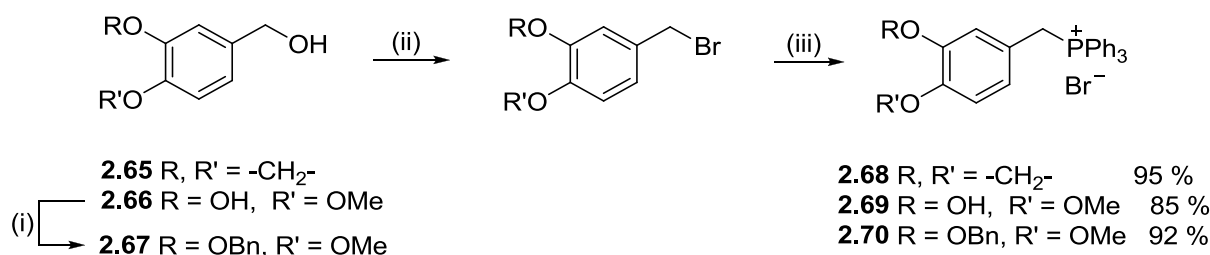
alcohol, but the aldehyde was not formed cleanly. Finally, Swern conditions were used for the oxidation to afford complete conversion to the aldehyde in a much cleaner reaction (entry 6), confirmed by the observation of an aldehyde resonance at 9.8 ppm in the ^1H NMR spectrum. Due to the instability of the aldehyde, it was used immediately in the following step without purification.

There are several examples where the Swern oxidation of similar alcohols proceeded with epimerisation or racemisation of their chiral centres. An example is the Swern/Wittig reaction of alcohol **2.63**, where the epimerisation of the C-2 chiral centre was attributed to the presence of the large excess of triethylamine used in the Swern reaction, to give the more stable 2, 3-*anti* isomer (Scheme 2.48).⁸² To ensure no racemisation occurred during the oxidation of **2.1**, it is necessary to perform careful removal of the triethylamine during the workup, by multiple washes with sat. NH_4Cl .



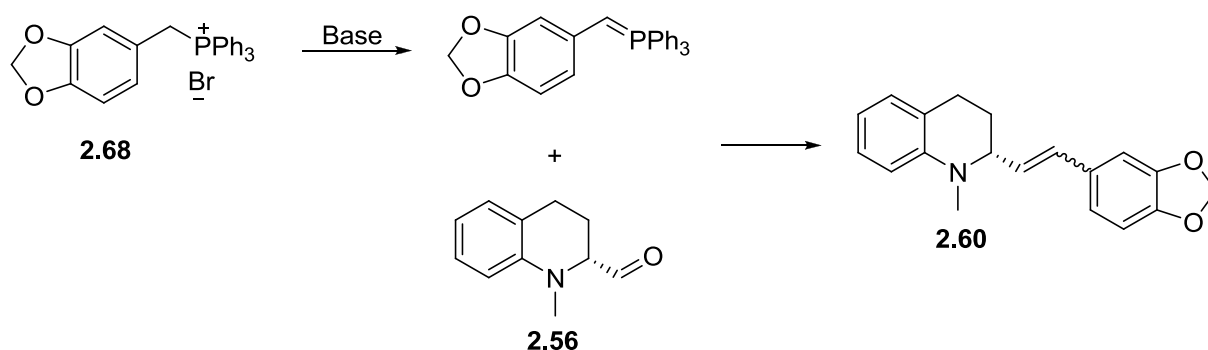
Scheme 2.48: Epimerisation of a C-2 chiral centre under Swern oxidation conditions.

The phosphonium salts required for the addition of the side chain, were prepared from commercially available alcohols in excellent yields (Scheme 2.49).



Scheme 2.49: Reagent and conditions: (i) K_2CO_3 , BnBr, acetone, reflux, 71%; (ii) PBr_3 , CH_2Cl_2 ; (iii) PPh_3 , toluene.

The Wittig reactions were subsequently performed, with the ylid salts stirred for 1 hour with the base, prior to addition of the aldehyde.¹³⁴ A variety of different reaction conditions were examined (Scheme 2.50, Table 2.16).

**Scheme 2.50:** Wittig reaction for the formation of **2.60**.**Table 2.16:** Optimisation of the Wittig reaction.^a

Entry	Base	Base eq	Ylid eq	Temp/°C	Time/ h	Yield % ^b
1	<i>n</i> -BuLi	1.1	1.2	-78 to 5	18	38
2	<i>n</i> -BuLi	1.1	1.2	-78 to -25	18	33
3	<i>n</i> -BuLi	1.5	1.2	-78 to 5	18	40
4	<i>n</i> -BuLi	2.0	1.2	-78 to 5	18	33
5	<i>n</i> -BuLi	1.5	1.6	-78 to 5	18	44
6	<i>n</i> -BuLi	2.0	2.2	-78 to 5	18	69
7	KO ^{<i>t</i>} Bu	1.1	1.2	0	18	43
8	KO ^{<i>t</i>} Bu	1.1	1.2	-78 to rt	18	33
9	KO ^{<i>t</i>} Bu	2.0	2.2	0	18	65
10	NaHMDS	1.1	1.2	-78 to 5	18	41
11	NaHMDS	2.0	2.2	-78 to 5	18	69

^aReagent and conditions: Aldehyde (0.28 mmol, 1.0 eq), ylid (1.2-2.2 eq), base (1.1-2.0 eq), THF (3 mL).^bYields over 2 steps after column chromatography, as a mixture of *E/Z* isomers.

Initially *n*-BuLi was used as base in a slight excess,¹³⁴ to ensure complete consumption of the aldehyde (Table 2.16, entry 1). This afforded a low yield of product. To minimise the degradation of the aldehyde, the reaction temperature was maintained at -25 °C after addition of the aldehyde (entry 2), but this did not lead to any improvement in yield. The amount of base used in the reaction was next investigated. When a slight excess of base was used (with respect to the ylid), there was no change in the outcome (entry 1 vs entry 3). However, the presence of a large excess of base led to a reduction in yield (entry 4). This result suggested that the aldehyde was unstable to basic conditions. In addition, the slow rate of the reaction could be responsible for the poor results, prompting us to employ an excess of the Wittig

reagent (entries 5 and 6). This led to a small increase in the product yield and thus far, the highest yield for the oxidation/Wittig reaction was achieved with a 2-fold excess of the ylid (entry 6).

Other strong bases were also investigated in this study, such as KO^tBu (entries 7, 8 and 9) and NaHMDS (entries 10 and 11). The nature of the base was found to have no significant effect on the results and comparable yield to *n*-BuLi were obtained. In all cases, the highest yields were achieved when a 2-fold excess of the ylid was used (entries 9 and 11). The reaction with KO^tBu as base proceeded to give the best result when conducted at 0 °C (entry 8 vs 9).

In all cases the alkene **2.60** was obtained as a mixture of *E*- and *Z*-isomers, typically in a ratio of 2:3 (Figure 2.5). The major isomer had a ³*J* value of 11.6 Hz and so was assigned as the *Z*-isomer, while the minor *E*-isomer exhibited a ³*J* value of 15.8 Hz.

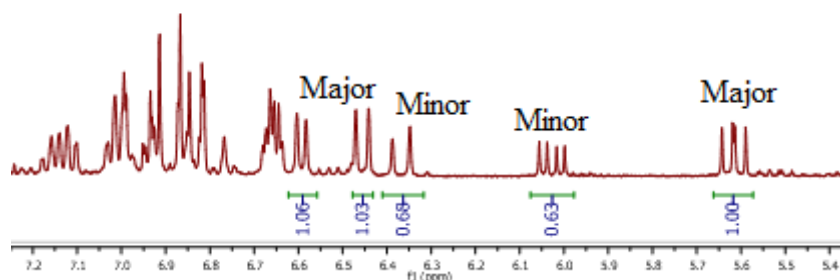
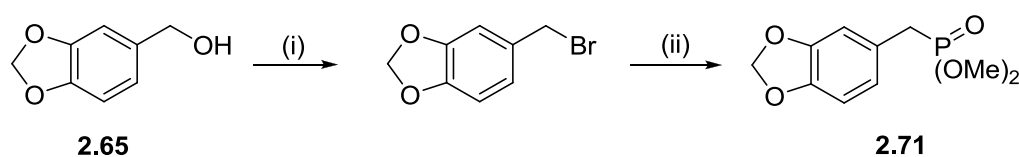


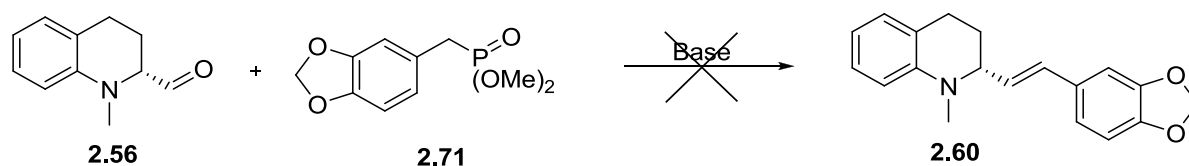
Figure 2.5: NMR of **2.60** showing the *E*- and *Z*-isomers.

In addition to the Wittig reaction, a HWE reaction was also attempted in the hope of improving the yield of the alkene. The formation of the alkene as a single *E*-isomer would also allow for easier analysis. The phosphonate HWE reagent was prepared from the alcohol **2.65**, via the bromide, in quantitative yields (Scheme 2.51).



Scheme 2.51: Reagent and conditions: (i) PBr₃, CH₂Cl₂, 0 °C; (ii) P(OMe)₃, 90 °C, quant.

The HWE reaction of the aldehyde **2.56** and the phosphonate **2.71**, was investigated under a variety of different conditions (Scheme 2.52, Table 2.17).



Scheme 2.52: HWE reaction of the aldehyde **2.56** with the phosphonate **2.71**.

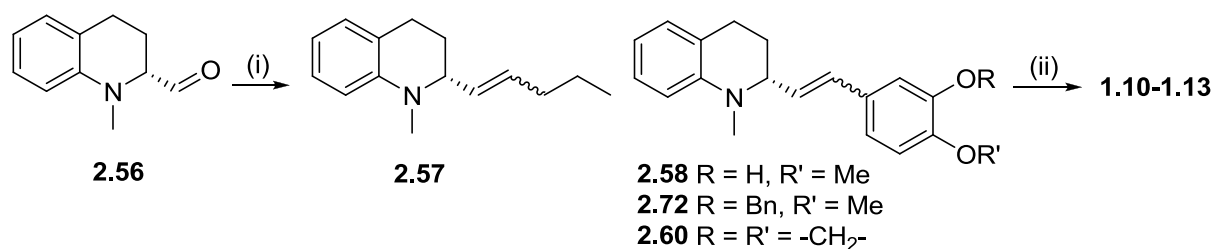
Table 2.17: HWE reaction of the aldehyde **2.56** under various conditions.^a

Entry	Base/additive	Temp/ ° C	Time/h	% Yield
1	NEt ₃	rt	72	-
2	KO ^t Bu	rt	16	-
3	KO ^t Bu	-78 °C	16	-
4	DBU/LiCl	rt	16	-

^aReagents and conditions: **Entry 1:** Aldehyde (0.28 mmol, 1.0 eq), **2.71** (0.28 mmol, 1.0 eq), NEt₃ (0.28 mmol, 1.0 eq), THF (1 mL), rt; **Entry 2:** Aldehyde (0.28 mmol, 1.0 eq), **2.71** (0.28 mmol, 1.0 eq), KO^tBu (0.37 mmol, 1.3 eq), DMF (1 mL), rt; **Entry 3:** Aldehyde (0.28 mmol, 1.0 eq), **2.71** (0.30 mmol, 1.1 eq), KO^tBu (0.32 mmol, 1.1 eq), THF (1 mL), -78 °C; **Entry 4:** Aldehyde (0.28 mmol, 2.0 eq), **2.71** (0.14 mmol, 1.0 eq), DBU (0.42 mmol, 3.0 eq), LiCl (0.42 mmol, 3.0 eq), MeCN (1 mL), rt.

Initially triethylamine was used,¹³⁵ as it was deemed advantageous to use a milder base to minimise the base catalysed degradation of the aldehyde. Unfortunately, none of the desired alkene was formed and starting material persisted (Table 2.17, entry 1). Using the stronger KO^tBu^{136, 137} led to complete degradation of the aldehyde, even at -78 °C (entries 2 and 3). Finally, a Masamune-Roush modified reaction¹³⁸ also proved unsuccessful, due to competitive degradation of the starting material (entry 4).

Telescoping the oxidation/Wittig reaction with the hydrogenation would produce the natural products **1.10-1.13** in a single synthetic sequence. Hence, the final synthesis of the Galipea alkaloids was achieved using the optimum conditions developed for the alkene formation followed by immediate hydrogenation to give **1.10**, **1.11** and **1.13** (Scheme 2.53, Table 2.18).



Scheme 2.53: Reagent and conditions: (i) Aldehyde **2.56**, KO^tBu, Ylid, THF, 0 °C; (ii) Pd/C, H₂, EtOH, THF, reflux.

Table 2.18: Application of optimised Wittig reaction conditions for the synthesis of the other Galipea alkaloids.^a

Entry	Ylid	Product	Yield % ^b	[α] _D ²⁵	[α] _D ²⁵ (lit.)
1	<i>n</i> -BuPPh ₃ Cl	 (<i>S</i>)- 1.10	44	+7.5	-7.16 ¹⁸
2	2.69	 (<i>rac</i>)- 2.58	26 ^c	-	-
3	2.70	 (<i>S</i>)- 1.11	32	-27.0	-26.1 ¹⁹ -13.6 ¹⁸
4	2.68	 (<i>rac</i>)- 1.13	31	-	-33.4 ¹³⁹

^aReagent and conditions: **For entries 1-2 and 4:** Aldehyde (0.28 mmol, 1.0 eq), KO^tBu (0.57 mmol, 2.0 eq), Ylid (2.2 eq), THF, 0 °C, then Pd/C (50 mg), EtOH (1 mL), THF (0.5 mL). **Entry 3:** Aldehyde (0.28 mmol, 1.0 eq), KO^tBu (0.85 mmol, 3.0 eq), Ylid (2.2 eq) THF, 0 °C, then Pd/C (50 mg), EtOH (1 mL), THF (0.5 mL).

^bYield determined by ¹H NMR over 3 steps. ^cNo hydrogenation performed, yield based on formation of the alkene.

The reaction proceeded to furnish angustureine in 44% yield over three steps, which recorded an $[\alpha]_{\text{D}}^{25}$ value of $+7.5^\circ$ (Table 2.18, entry 1). In comparison, the natural product was reported to have a specific rotation of -7.16° . This confirms we have achieved the synthesis of the unnatural (*S*)-(+)-enantiomer of angustureine, as expected from the assumption of the *aza*-Michael product stereochemistry (section 2.2).

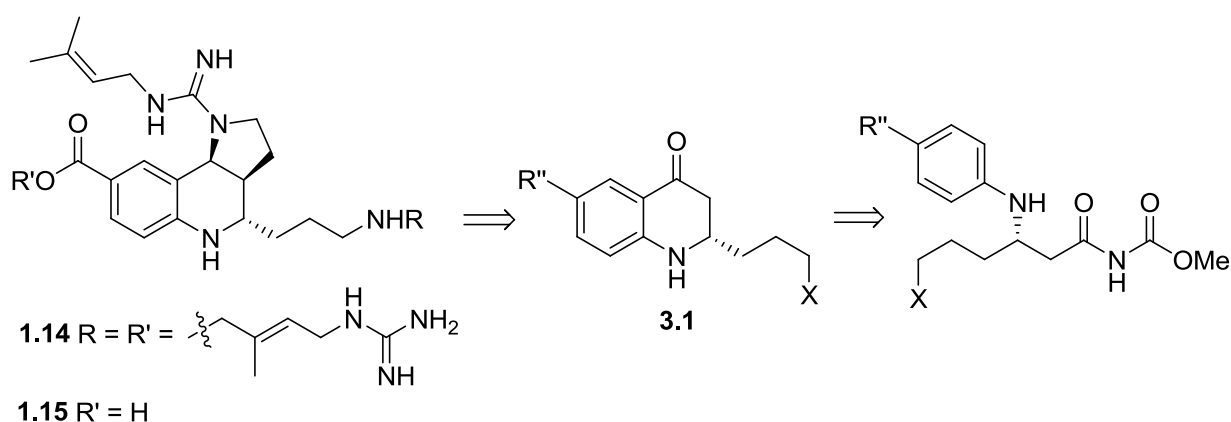
For the reaction with the ylid **2.69**, an additional equivalent of base was needed to take into account the presence of the free phenolic group.¹⁴⁰ As a result, the alkene **2.58** was obtained in a very low yield (entry 2) and so the hydrogenation was not attempted. To overcome this problem, it was decided to employ the benzyl protected ylid **2.70**. This afforded **1.11** in 32% yield after hydrogenation (entry 3), with the $[\alpha]_{\text{D}}^{25}$ of -27.0° , this compares well to the reported optical rotation, -26.1° (96% ee), of a synthetic sample of the (*S*)-isomer.¹⁹ Interestingly the natural product has a lower optical rotation of -13.6° , suggesting that it was not isolated as a single enantiomer. A third *Galipea* alkaloid galipinine **1.13** was also synthesised in 31% yield over the three steps (entry 4). Due to the limited amount of the alcohol **2.1** available, formation of galipinine was only achieved racemically and the formation of cuspareine was not attempted.

In summary, this Chapter has detailed the synthesis of three *Galipea* alkaloids (two optically pure and one racemic), achieved in 12 steps with 4-5% yield. Although this route is not the shortest, nor the highest yielding for the synthesis of these molecules, it allows for the divergent synthesis of a range of tetrahydroquinolines from a common precursor. Furthermore, the overall synthetic route proceeds through a number of optically pure intermediates, which could prove interesting for the development of other tetrahydroquinoline molecules. This method also proved successful for the synthesis of galipeine, whose total synthesis has only been reported on one other occasion.¹⁹

CHAPTER THREE
SYNTHESIS OF THE
MARTINELLINE ALKALOIDS

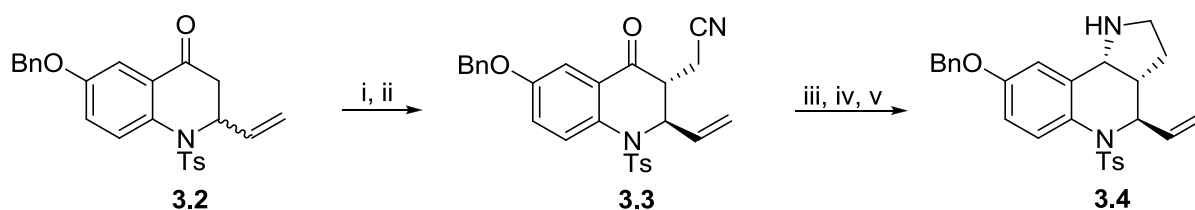
3.0 Synthesis of the Martinelline Alkaloids

This Chapter details the work towards the formal synthesis of the Martinelline alkaloids, martinelline **1.14** and martinellic acid **1.15**. These alkaloids are substituted in the 2-, 3- and 4-positions of the tetrahydroquinoline core and therefore have three stereogenic centres. We aim to use the methodology detailed in the previous chapter, to form the 2-substituted tetrahydroquinolone **3.1**, from which both Martinelline alkaloids should be accessible (Scheme 3.1). The *aza*-Michael reaction developed previously by our group will be used to install the first of the chiral centres in the 2-position, which will be used to direct the formation of further stereogenic centres.



Scheme 3.1 : Retrosynthetic analysis of the Martinelline alkaloids.

Previously, a similar approach has been adopted for the racemic synthesis of the martinelline core structure,⁷⁵ where the installation of the 5-membered heterocyclic ring was achieved by treatment of the ketone **3.2** with paraformaldehyde (Scheme 3.2).

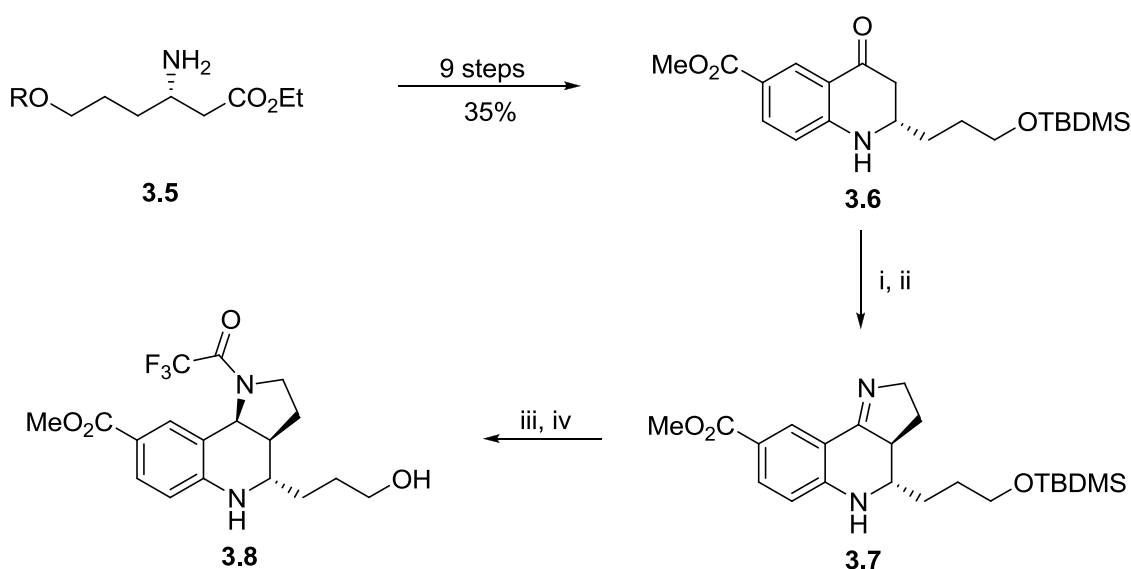


Scheme 3.2: Reagents and conditions: (i) HCHO, PhMeNH.TFA, 85%; (ii) KCN, AcOH, 71%; (iii) LiAlH₄; (iv) MnO₂, 9%; (v) NaBH₃CN, 100%.

This was followed by the 1, 4-conjugate addition of KCN to the resultant activated methylene, to give the nitrile **3.3**, exclusively as the *anti* isomer. Upon reduction of the nitrile with LiAlH₄ and re-oxidation of the benzylic alcohol, spontaneous cyclisation occurred to

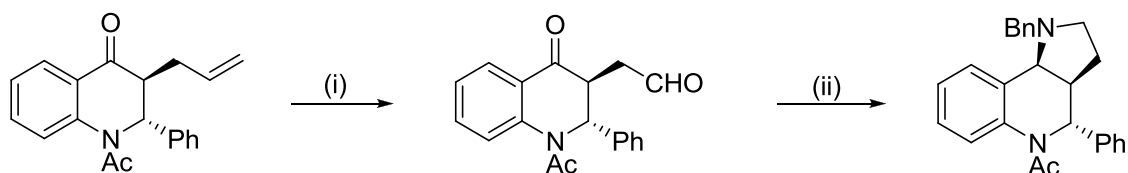
give an imine. Finally, reduction of the imine with NaCNBH_3 produced the tricyclic structure **3.4**. The tandem reduction/alcohol re-oxidation steps proceeded with only 9% overall yield. Other selective nitrile reduction methods were also investigated, but competitive reduction of the allyl alkene occurred in all cases.⁷⁵

In another report, Ma *et al.* detailed the diastereoselective synthesis of martinelllic acid from a 2-substituted tetrahydroquinolone intermediate **3.6**, which was obtained from the optically pure **3.5** in 9 steps with 35% overall yield. Installation of the third ring was achieved by the formation of a cyclic imine using a Staudinger reaction (Scheme 3.3). Following the removal of the TBDMS protecting group and reduction of the imine, the tricyclic core was attained as a single diastereoisomer. Removal of the protecting group was required in order to give high stereoselectivities in the reduction reaction. This was attributed to the coordination of the free hydroxyl to the borohydride.¹⁰¹



Scheme 3.3: Reagent and conditions: (i) LHMDS, THF then $\text{BrCH}_2\text{CH}_2\text{OTf}$; (ii) NaN_3 , DMF then PPh_3 , H_2O , 48 %; (iii) TBAF, HOAc; (iv) NaBH_4 , $(\text{CF}_3\text{CO})_2\text{O}$, 94 %.

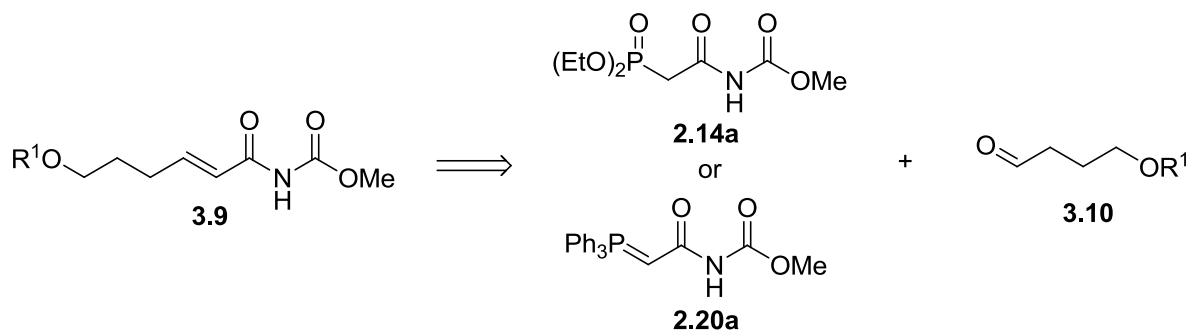
Additionally, Lei *et al.* have shown that formation of the pyrroloquinoline core can be achieved from an C-3 allyl substituted tetrahydroquinoline by ozonolysis of the allyl group, followed by reductive amination (Scheme 3.4).¹⁴¹



Scheme 3.4: Reagent and conditions: (i) O_3 , CH_2Cl_2 , $-78\text{ }^\circ\text{C}$ then Me_2S , $0\text{ }^\circ\text{C}$ -rt; (ii) $\text{BnNH}_2\cdot\text{HCl}$, NaBH_3CN , MeOH , rt.

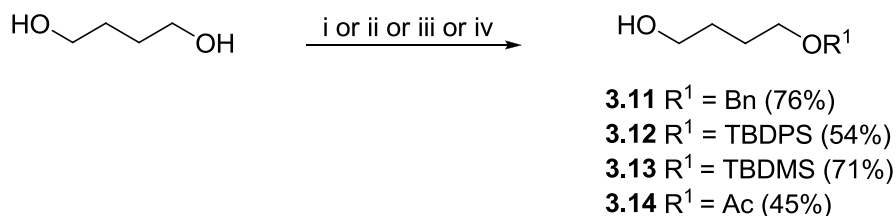
3.1 Synthesis of α , β -unsaturated carbamates

Compared to the Galipea alkaloids, the Martinelline alkaloids have a longer C-2 side chain, and so Michael acceptors of type **3.9** were required. These will be synthesised from γ -hydroxy acetaldehydes, either by a Wittig reaction with the ylid **2.20a**, or a HWE reaction with the phosphonate carbamate **2.14a** (Scheme 3.5).



Scheme 3.5: Retrosynthetic analysis of the *aza*-Michael acceptors.

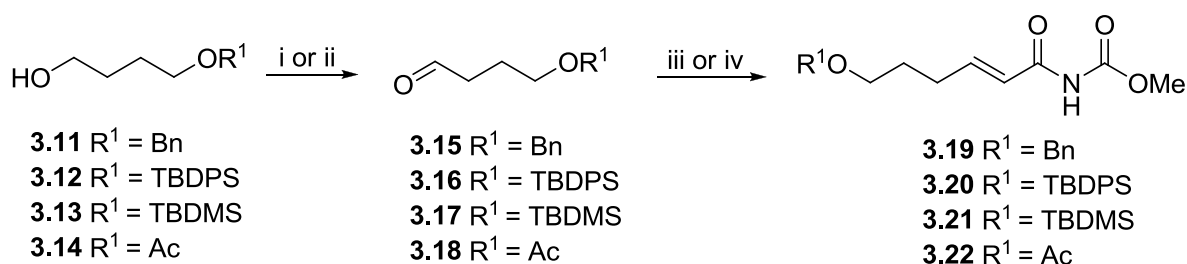
The required γ -hydroxy acetaldehydes were synthesised from 1, 4-butanediol in two steps; the mono-protection of the diol and the oxidation of the free alcohol. From the work conducted previously, the nature of the hydroxyl protecting group has a significant effect on the *aza*-Michael reaction. As a result, four different protecting groups were used in the synthesis of the desymmetrised alcohol, including a benzyl ether **3.11**, two silyl ethers **3.12** and **3.13** and an acetyl **3.14** (Scheme 3.6).



Scheme 3.6: Reagent and conditions: (i) BnBr, NaH, THF, 0 °C, 16 h; (ii) DIPEA, TBDPSCl, CH₂Cl₂, rt, 2 h; (iii) TBDMSCl, imidazole, DMF, rt, 2 h; (iv) AcCl, py., CH₂Cl₂, 0 °C, 16 h.

The benzyl protected alcohol **3.11** was prepared using published procedures, by the reaction of 1, 4-butanediol with NaH and BnBr. A mixture of the mono- and di-protected butandiol was formed in a 10:1 ratio, which separated by column chromatography to give the desired **3.11** in 76% yield.¹⁴² On the other hand, both silyl-protected alcohols were formed as the mono-protected species only. The TBDPS protected alcohol was obtained in 54% yield via the reaction of TBDPSCl and DIPEA with 1, 4-butanediol,¹⁴³ whereas the formation of the TBDMS protected alcohol proceeded smoothly with imidazole as base, to give the mono-protected alcohol in 71% yield.¹⁴⁴ Last but not least, mono-protection with the acetyl group was achieved using acetyl chloride and pyridine in 45% yield, which is lower than the yield reported in the literature (74%).¹⁴⁵ The next step involved the oxidation of the alcohols to give the protected γ -hydroxy acetaldehyde. Due to the instability of these aldehydes, they were used immediately in the olefination reaction, without any further purification.

It was shown in the previous chapter that the *aza*-Michael reaction gave higher enantioselectivities with the *E*-isomer of the α , β -unsaturated carbamates was employed. Therefore, formation of the alkene using a HWE reaction would be advantageous. The low yields previously experienced with the HWE reaction were thought to be due to degradation of the aldehyde mediated by base and the close proximity of the protected alcohol to the aldehyde moiety. It was hoped that the increased distance between the aldehyde and the alcohol in these γ -hydroxy acetaldehydes would help increase their stability. Consequently, several different oxidation and olefination methods were attempted for the formation of the required α , β -unsaturated carbamates **3.19-3.22** (Scheme 3.7, Table 3.1).



Scheme 3.7: Reagent and Conditions: (i) Oxalyl chloride, DMSO, NEt₃, CH₂Cl₂, -78 °C-rt; (ii) IBX, DMSO, rt; (iii) **2.14a**, DBU, THF, rt; (iii) **2.20a**, CH₂Cl₂, rt.

Table 3.1: Synthesis of *aza*-Michael acceptors.^a

Entry	Alcohol	Oxidation method	Alkene Synthesis	<i>E:Z</i> ratio ^b	% Yield ^c
1	3.11	Swern	HWE	100:0	40
2	3.11	Swern	Wittig	10:1	34
3	3.11	IBX	HWE	100:0	20
4	3.11	IBX	Wittig	100:0	15 ^d
5	3.12	Swern	HWE	100:0	49
6	3.12	IBX	HWE	100:0	15
7	3.12	Swern	Wittig	10:1	70
8	3.13	Swern	Wittig	10:1	55
9	3.14	Swern	Wittig	10:1	45

^aReagent and conditions: **Swern reaction:** Alcohol (5.6 mmol, 1.0 eq), oxalyl chloride (12 mmol, 2.2 eq), DMSO (27 mmol, 4.8 eq), NEt₃ (28 mmol, 5.0 eq), CH₂Cl₂ (15 mL); **IBX oxidation:** Alcohol (3.9 mmol, 1.0 eq), IBX (4.3 mmol, 1.1 eq), DMSO (20 mL); **HWE reaction:** Phosphonate carbamate (5.6 mmol, 1.0 eq), DBU (5.6 mmol, 1.0 eq), THF (10 mL); **Wittig reaction:** Ylid (5.6 mmol, 1.0 eq), CH₂Cl₂ (20 mL).

^bDetermined by ¹H NMR. ^cIsolated yield obtained over 2 steps after column chromatography. ^dTandem Oxidation/Wittig reaction.

Formation of **3.19** was initially attempted using a Swern oxidation followed by a HWE reaction. The reactions proceeded to give **3.19** as the *E*- isomer exclusively in the low yield of 40% (Table 3.1, entry 1). Using a Wittig reaction, a 10:1 mixture of the *E*- and *Z*-isomers was formed in the lower yield of 34% (entry 2). Even poorer result were obtained when IBX was used in the oxidation step (entries 3 and 4), while the alkene was produced in only 15% yield with the tandem IBX oxidation-Wittig sequence (entry 4).

Synthesis of the alkene **3.20** was also attempted using a HWE reaction, where the aldehyde **3.16** was formed under Swern or IBX oxidation conditions. In both cases, the alkene was formed exclusively as the *E*-isomer, with the Swern oxidation proving optimum (entry 5 vs

6). Finally, an improvement in the yield was obtained with a combination of Swern oxidation and Wittig reaction (entry 7), which afforded the alkene **3.20** in 70% yield, as a 10:1 inseparable mixture of the *E*- and *Z*-isomers. Likewise, the other alkenes **3.21** and **3.22** were obtained in a 10:1 mixture of *E*- and *Z*-isomers, *via* a Wittig reaction (entries 8 and 9). Rather unexpectedly, the acetyl protected aldehyde remained largely unreacted, giving a very low yield of the Wittig product **3.22** (entry 9). Characteristic alkene peaks were observed in the ^1H NMR spectra of **3.19-3.22**, appearing as a doublet at 6.8 ppm and a double triplet at 7.1 ppm for the major *E*-isomer ($^3J_{\text{HH}} = 15.4$ Hz). The alkene signals for the minor *Z*-isomer appear as a doublet at 6.5-6.6 ppm and a double triplet at 6.3 ppm ($^3J_{\text{HH}} = 11.5$ Hz).

The synthesis of these α , β -unsaturated compounds proceeded in low yields in all cases (Table 3.1), potentially caused by the close proximity of the protected alcohol to the aldehyde. Hence, the synthesis of an alternative α , β -unsaturated compound **3.26** was investigated. The use of this Michael acceptor would install an allyl group into the C-2 position of the tetrahydroquinoline, giving **3.23** (Figure 3.1). The required C-2 side chain could then be constructed following hydroboration of the allyl group.⁸³

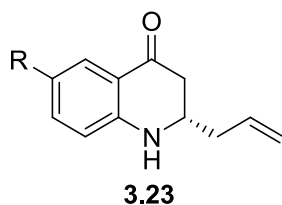
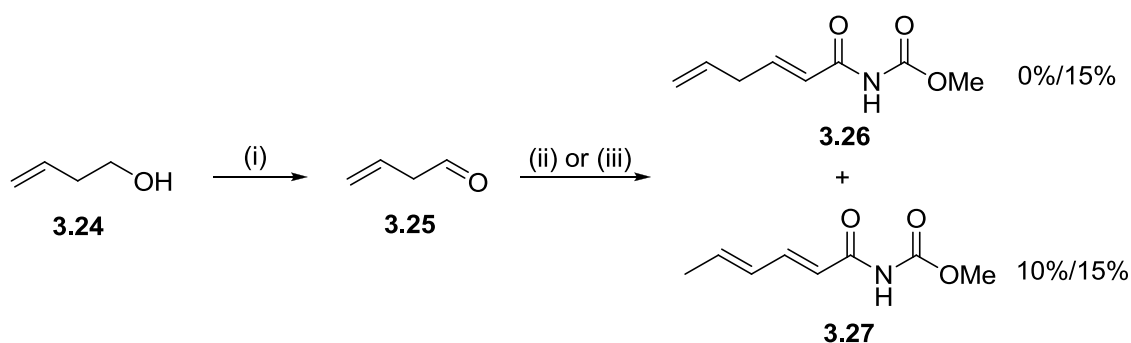


Figure 3.1: Potential tetrahydroquinoline intermediate in the Martinelline alkaloid synthesis.

3-Buten-1-ol **3.24** was converted into the aldehyde **3.25** using a TEMPO-catalysed oxidation procedure.¹⁴⁶ Following this, the HWE reaction with the phosphonate carbamates **2.14a**, produced none of the desired compound, but a different α , β -unsaturated alkene **3.27** was isolated in 10% yield (Scheme 3.8). The formation of the diene **3.27** was confirmed by the presence of a doublet in the ^1H NMR spectrum corresponding to the terminal CH_3 group. This diene was formed by the base-catalysed migration of the terminal double bond into conjugation with the other unsaturated alkene.¹⁴⁶



Scheme 3.8: Reagents and Conditions: (i) TEMPO, $\text{PhI}(\text{OAc})_2$, pentane, CH_2Cl_2 , rt; (ii) ylid, **2.20a**, CH_2Cl_2 ; (iii) **2.14a**, DBU, THF.

To avoid this, the formation of the desired alkene **3.26** was attempted using the neutral Wittig reaction with **2.20a** (Scheme 3.8). In this case, the reaction proceeded to give a complex mixture. The desired alkene **3.26** was isolated in 15% yield, confirmed by the presence of the CH_2 methylene group, observed as a multiplet in the ^1H NMR at 3.05 ppm. An equal amount of the conjugated diene **3.27** was also isolated, even under these ‘neutral’ conditions. This suggests the double bond easily migrates into the more conjugated position.

In summary, a range of different α,β -unsaturated carbamates have been synthesised in moderate yields (Figure 3.2), with the Swern/Wittig protocol proving to be the most effective method.

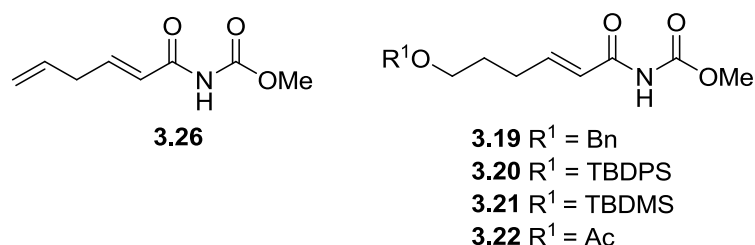


Figure 3.2: The α,β -unsaturated carbamates synthesised.

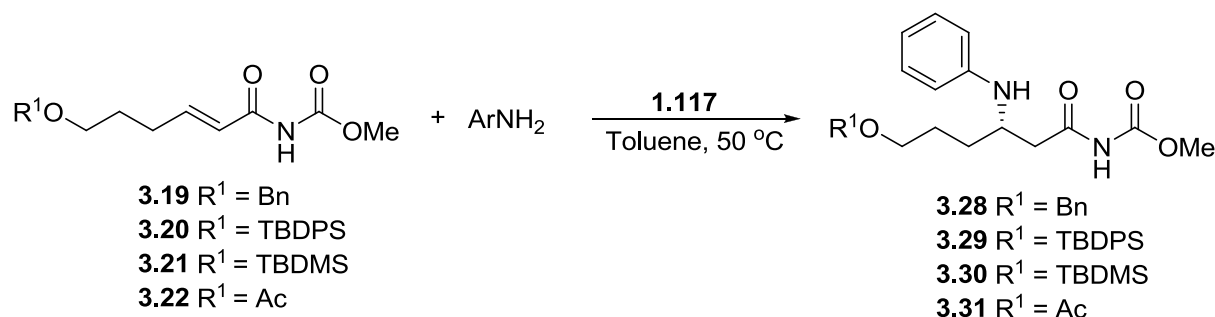
The next section details the reaction of these α,β -unsaturated carbamates with a range of anilines, in an attempt to produce optically pure Michael adducts, that can then be used for the synthesis of the Martinelline alkaloids.

3.2 Aza-Michael reactions

As with the Galipea alkaloids, significant optimisation of the *aza*-Michael reactions were undertaken to allow for the obtainment of material with high optical purity. Initially the effect of changing the alcohol protecting group was investigated.

3.2.1 Screening of different protecting group

The four *aza*-Michael acceptors **3.19**-**3.22** were reacted with aniline using the set of conditions proven to be optimum for the *aza*-Michael reaction in the Galipea alkaloids syntheses, *i.e.* the reaction was conducted at 50 °C in toluene using the [Pd(*R*-BINAP)(OH₂)₂]²⁺[OTf]⁻ **1.117** complex as catalyst (Scheme 3.9).



Scheme 3.9: Reaction of various α , β -unsaturated carbamates with aniline.

Table 3.2: *Aza*-Michael reaction of aniline with different acceptors.^a

Entry	Carbamate	Time/d	% Yield ^b	% ee ^c
1	3.19	2	33	8
2	3.20	3	73	66
3	3.21	1	65	46
4	3.22	5	47	44
5	3.26	7	50	61

^aReagent and conditions: Alkene (100 mg, 1.0 eq), aniline (1.0 eq), catalyst (5 mol%), toluene (1 mL), 50 °C.

^bDetermined by ¹H NMR. ^cDetermined by chiral HPLC using either Hichrom-CHI-PGG-2759 (entries 1, 3-5) or Daicel Chiralpak AD-H column (entry 2 or 5).

Initially the reaction was attempted using the benzyl protected alkene **3.19**. Only 33% conversion was achieved after 2 days and the *aza*-Michael product was formed in very low enantioselectivity (Table 3.2, entry 1). This result was rather unexpected as the *aza*-Michael reaction for the Galipea alkaloids proceeded well with the benzyl-protected Michael acceptor. Next, the reaction was repeated using **3.20**, containing the bulky *tert*-butyldiphenyl silyl protecting group. An improvement in both conversion and ee to 73% and 66% respectively was observed (entry 2). Using the *tert*-butyldimethyl silyl protected **3.21**, 65% conversion of the starting material was obtained after 24 hours (Table 3.2, entry 3), and no further

improvement was observed on prolonging the reaction time. The reaction gave the *aza*-Michael product **3.30** in 46% enantioselectivity. On leaving the reaction for an additional 3 days, the conversion increased to 85%. These results suggest that increasing the steric bulk of the silyl protecting group on the side chain leads to increased conversions and enantioselectivities. In contrast, lower conversion and enantioselectivity, 47% and 44% respectively, was obtained with the substrate containing the acetyl protecting group, **3.22** (entry 4).

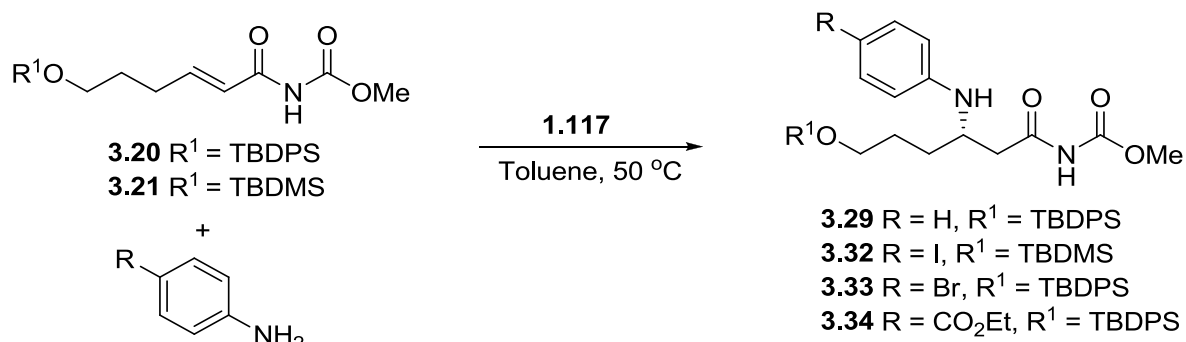
The results concur with our earlier observations that the nature of the substituent on the alkene has a significant effect on both the yield and enantioselectivity of the reaction. The result obtained with **3.19** was significantly lower than with the other three Michael acceptors, suggesting that the catalyst was somehow deactivated in this system, lowering the yield and ee.

Reaction of aniline with the *aza*-Michael acceptor **3.26** was also attempted, to determine if the reaction would proceed better in the absence of the protected alcohol. However, only 50% conversion and 61% ee was obtained after 7 days at 50 °C (Table 3.2, entry 5). The low conversion, increased reaction time and low enantioselectivity make this unattractive for the synthesis of the Martinelline alkaloids.

In all cases the reactions proceeded in a sluggish manner with incomplete formation of product. The highest conversion and enantioselectivity was obtained when the bulky *tert*-butyldiphenyl silyl was used as the protecting group, in the Michael acceptor **3.20**. The facile and selective removal of this silyl protecting group using TBAF¹⁴⁷ could prove advantageous later in synthesis. Therefore, the *tert*-butyldiphenyl silyl protected alkene was used in the subsequent optimisation studies.

3.2.2 Screening of different anilines

The Martinelline alkaloids contain substituents on the aromatic ring, *para* to the nitrogen heteroatom. Martinelline contains a carboxylic ester, while martinellie acid contains a carboxylic acid (Scheme 3.1). Thus, the *aza*-Michael reactions of a variety of *para*-substituted anilines with the Michael acceptors **3.20** and **3.21** were investigated (Scheme 3.10).



Scheme 3.10: Aza-Michael reaction of model substrates with various *para*-substituted anilines.

Table 3.3: Aza-Michael reaction of model substrates with a range of anilines^a

Entry	Alkene	R	Time/d	% Yield ^b	% ee ^c , (Config)
1	3.20	CO ₂ Et	1.5	77	57 (S)
2	3.20	Br	2	77	68 (S)
3	3.21	I	7	40	33 (S)
4	3.20	H	2	77	67 (S)

^aReagent and conditions: Alkene (50 mg, 1.0 eq), aniline (1.0 eq), **1.117** (5 mol%), toluene (1 mL), 50 °C.

^bDetermined by ¹H NMR. ^cDetermined by chiral HPLC using Daicel chiralpak AD-H column (entry 2 and 4) or Hichrom-CHI-PGG-2759 (entries 1 and 3).

The use of ethyl 4-aminobenzoate in the *aza*-Michael reaction would give **3.34**, which would allow for the formation of the tetrahydroquinoline ring with a carboxylic ester already in place. Thus, the reaction of **3.20** and ethyl 4-aminobenzoate was initially attempted at 50 °C in toluene. This afforded **3.34** in 78% conversion and 57% enantioselectivity (Table 3.3, entry 1). In the hope of obtaining better conversions and enantioselectivities, alternative anilines were also investigated.

If a bromo or iodo group could be installed in the position *para* to the nitrogen, it could be converted into a carboxylic ester at a later stage in the synthesis. This could be achieved using either: (i) a palladium catalysed carbonylation reaction under a carbon monoxide atmosphere,^{101, 148} or (ii) *via* lithium halogen exchange with BuLi, followed by reaction with dimethyl carbonate.¹⁴⁹ Alternatively, bromination at the C-7 position of tetrahydroquinolines is known to occur using NBS and CCl₄.¹⁵⁰ Thus, it was envisaged that the introduction of the ester group may also be performed after cyclisation of the *aza*-Michael adduct.

The reaction of the alkene **3.20** with 4-bromoaniline proceeded to give **3.33** in 77% yield and 68% enantioselectivity (Table 3.3, entry 2), while the corresponding reaction with iodoaniline gave a complex mixture of inseparable products. In comparison, the reaction of the silyl-protected **3.21** with iodoaniline gave the product in very low conversion and ee, even on prolonged reaction times (entry 3). The formation of **3.29** proceeded with comparable yield but higher enantioselectivity than the reaction with ethyl 4-aminobenzoate (entry 1 vs 4).

The *aza*-Michael reaction of **3.20** with aniline, 4-bromoaniline and ethyl 4-aminobenzoate all proceeded to the similar levels of completion, with 4-bromoaniline giving the highest enantioselectivity (68%). Surprisingly, the reaction of **3.21** with 4-iodoaniline gave a significantly lower ee and yield. Further optimisation was conducted on the *aza*-Michael reaction of **3.20** with 4-bromoaniline and ethyl 4-aminobenzoate.

3.2.3 Effect of catalyst loading

Attributing the low conversions to catalyst deactivation, the reactions of 4-bromoaniline and ethyl 4-aminobenzoate with the Michael acceptor **3.20** were repeated with an increased catalyst loading of 10 mol% (Table 3.4). However, no improvement in the conversion or reaction time was observed in either case (Table 3.4, entry 1 vs 2 and entry 3 vs 4). As a consequence the enantioselectivities were not determined.

Table 3.4: Effect of catalyst loading on the *aza*-Michael reaction.^a

Entry	Product	Cat loading/ mol %	Time/d	% Yield ^b
1	3.33	5.0	2	68
2	3.33	10	2	70
3	3.34	5.0	2	77
4	3.34	10	2	75

^aReagent and conditions: Alkene (0.13 mmol), aniline (0.13 mmol), **1.117** (See table), toluene (1 mL), 50 °C.

^bDetermined by ¹H NMR.

3.2.4 Effect of Alkene : Aniline ratio

The pathways to deactivation of the palladium BINAP catalyst during *aza*-Michael reactions have been previously studied.⁹⁸ The alkene is activated towards nucleophilic attack by the

formation of a chelate through the 1, 3-dicarbonyl of the α , β -unsaturated carbamate. Similarly, the catalyst can also bind to the product, and if this binding was stronger than the binding to the alkene starting material, gradual catalyst deactivation would occur over the course of the reaction. It was postulated that by increasing the ratio of alkene : aniline, an excess of the starting material would always be present in the reaction mixture, and therefore the competitive binding of the starting material to the catalyst would be increased.

Table 3.5: Effect of alkene : aniline ratio on the reaction of ethyl 4-aminobenzoate with **3.20**.^a

Entry	Alkene (eq)	Time/d	% Yield ^b
1	1.0	2	77
2	1.2	2	50
3	1.5	2	55
4	2.0	2	60

^aReagent and conditions: Alkene (50 mg, 0.13 mmol), aniline (0.06-0.13 mmol), **1.117** (5 mol%), toluene (1 mL), 50 °C. ^bDetermined by ¹H NMR.

Initially, the reaction of **3.20** with ethyl 4-aminobenzoate was examined (Table 3.5). Surprisingly, increasing the equivalents of the alkene with respect to the aniline had a significant detrimental effect on the levels of conversion obtained. Even a slight excess of the alkene led to a reduction in conversion to 50% (entry 1 vs 2), however, no additional deprivation in yield was observed on further increasing the equivalents of alkene (entries 3 and 4). As increasing the alkene to aniline ratio was found to have a detrimental effect on the yields obtained, the enantioselectivities were not determined. This data suggests that the lack of full conversion observed for this reaction was not a result of product inhibition.

Table 3.6: Effect of alkene : aniline ratio on the reaction of 4-bromoaniline with **3.20**.^a

Entry	Alkene (eq)	Time/d	% Yield ^b	% ee ^c , (Config)
1	1.0	2	68	70 (S)
2	1.5	5	64	74 (S)
3	2.0	2	80	85 (S)

^aReagent and conditions: Alkene (50 mg, 0.13 mmol), aniline (0.06 mmol-0.13 mmol), **1.117** (5 mol%), toluene (1 mL). ^bDetermined by ¹H NMR. ^cDetermined by chiral HPLC using Chiral Daicel AD-H column.

The same study was carried out on the reaction between **3.20** and 4-bromoaniline. Although a slight excess of the alkene did not lead to any noticeable changes (Table 3.6, entry 1 vs 2), doubling the equivalents of the alkene did, in this instance, lead to an increase in the yield to 80%. Gratifyingly, this was also accompanied by an increase in the enantioselectivity to 85%. This suggested that product inhibition of the catalyst was an issue in this system. The differences observed between the reaction of 4-bromoaniline and ethyl 4-aminobenzoate show that the nature of the aniline has a significant effect on the catalyst deactivation process.

3.2.5 Dilution study

Previously, the dilution of the reaction mixture has been shown to affect the enantioselectivities of the *aza*-Michael reaction. This effect was particularly prominent in the synthesis of the Galipea alkaloids, where the slow addition of the aniline to the reaction mixture led to a significant increase in the enantioselectivity, from 61% to 84%. As a result, the effect of dilution on the reaction of **3.20** with 4-bromoaniline and ethyl 4-aminobenzoate was investigated (Table 3.7).

Table 3.7: Effect of dilution on the *aza*-Michael reaction of **3.20** with both anilines.^a

Entry	Product	Dilution/ mM	Time/d	% Yield ^b	% ee ^c , (Config)
1	3.33	260	1.5	77	67 (S)
2	3.33	130	2	68	68 (S)
3	3.34	260	2	78	57 (S)
4	3.34	130	2	82	71 (S)

^aReagent and conditions: Alkene (0.13 mmol, 1.0 eq), aniline (0.13 mmol, 1.0 eq), **1.117** (5 mol%), toluene (See table). ^bDetermined by ¹H NMR. ^cDetermined by chiral HPLC using Chiral Daicel AD-H column.

Surprisingly, increasing the dilution of the reaction with 4-bromoaniline did not lead to any improvement in the enantioselectivity (Table 3.7, entry 1 vs 2). In fact, the reaction proceeded with higher conversion when a more concentrated solution was prepared. In contrast, increasing the dilution of the reaction with ethyl 4-aminobenzoate led to a significant improvement in the enantioselectivity obtained, with no change in the yield (entry 3 vs 4).

The slow addition of the anilines to a mixture of the catalyst and alkene was undertaken next (Table 3.8).

Table 3.8: Slow addition of the anilines to **3.20**.^a

Entry	Product	Time/d	% Yield ^b	% ee ^b , (Config)
1	3.33	2	65	70 (S)
2^d	3.34	4	70	81 (S)

^aReagent and conditions: Alkene (0.13 mmol, 1.0 eq), aniline (0.13 mmol, 1.0 eq), catalyst (5 mol%), toluene (2 mL). ^bDetermined by ¹H NMR. ^cDetermined by chiral HPLC using Chiral Daicel AD-H column. ^d10 mol% catalyst used.

The enantioselectivity of **3.33** was not improved by the slow addition of the 4-bromoaniline to the reaction (Table 3.8, entry 1). However, the slow addition of ethyl 4-aminobenzoate did lead to an increase in the enantioselectivity observed, although the reaction was significantly slower (entry 2).

These results show that inhibition of the catalyst is occurring in both cases. In the case of 4-bromoaniline binding of the *aza*-Michael product in preference to the alkene starting material was causing the low conversions, whereas catalytic deactivation in the reaction of ethyl 4-aminobenzoate was probably due to binding of the aniline.

3.2.6 Effect of temperature

Previously the *aza*-Michael reaction was conducted at 50 °C, due to poor solubility of the alkene at room temperature in toluene. This was not the case for the alkene **3.20**, which is fully soluble at room temperature. Therefore, the reaction temperature could be lowered. The reaction of **3.20** with 4-bromoaniline was conducted at 30 °C and room temperature (Table 3.9).

Table 3.9: Effect of temperature on the *aza*-Michael reaction of **3.20** with 4-bromoaniline.^a

Entry	Temp/ ° C	Time/d	% Yield ^b	% ee ^c , (Config)
1	rt	7	84	85 (S)
2	30	0.5	71	85 (S)
3^d	30	1.5	80	87 (S)

^aReagent and conditions: Alkene (50 mg, 0.13 mmol), aniline (20 mg, 0.13 mmol), catalyst (5 mol%), toluene (1 mL). ^bDetermined by ¹H NMR. ^cDetermined by chiral HPLC Chiral Daicel Chiralpak AD-H column. ^d2 eq of alkene used.

The reaction conducted at room temperature proceeded to give good conversion and high enantioselectivity, however the reaction was very slow, taking 7 days to reach 84% conversion (Table 3.9, entry 1). On raising the temperature slightly to 30 °C, 71% conversion and 85% ee was obtained after 12 hours (entry 2). Repeating the reaction with 2 equivalents of the Michael acceptor, with respect to the aniline, led to a slight improvement in the yield and enantioselectivity (entry 2 vs 3). However, the purification of the *aza*-Michael product proved difficult in the presence of an excess of the starting alkene. As a result, an optimal substrate ratio of 1:1 and temperature of 30 °C were employed for the synthesis of the Martinelline alkaloids.

High enantioselectivities were obtained for the reaction of both anilines with the Michael acceptor, however, the long reaction times required with the ethyl 4-aminobenzoate made this reaction unpractical. Therefore, 4-bromoaniline was chosen as the nucleophile for the *aza*-Michael reaction. This reaction can be performed on a multigram scale.

3.2.7 Recrystallisation (ee enhancement)

Attempts to enhance the optical purity of the *aza*-Michael adduct **3.33** by recrystallisation from toluene-cyclohexane, as well as ether-pentane, were investigated, but to no avail. In both cases, the racemic material was insufficiently crystalline to precipitate, even when the process was conducted in pure cyclohexane.

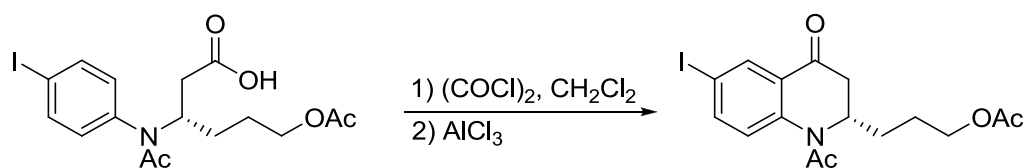
In summary, the nature of the alcohol protecting group on the α , β -unsaturated carbamates was shown to significantly affect the enantioselectivities and yields of the *aza*-Michael reactions. The use of a benzyl protecting group gave a surprisingly low yield and ee. On the other hand, the bulky *tert*-butyldiphenyl silyl was identified as the best protecting group for the alkene, with **3.20** giving the highest enantioselectivities and yields. Eventually, 4-bromoaniline and ethyl 4-aminobenzoate were identified as suitable nucleophiles for the *aza*-Michael reaction; good yields and enantioselectivities were obtained after extensive optimisation. The longer reaction times required with ethyl 4-aminobenzoate made this reaction less attractive and so the reaction of **3.20** with 4-bromoaniline was chosen for the synthesis of the Martinelline alkaloids. Unfortunately, attempts to further improve the ee of the Michael adduct **3.33** by recrystallisation were unsuccessful. It was decided that this will be attempted at a later stage.

3.3 Tetrahydroquinolone formation

With the *aza*-Michael adducts in hand, the next step in the synthesis of the Martinelline alkaloids was the formation of the tetrahydroquinolone ring.

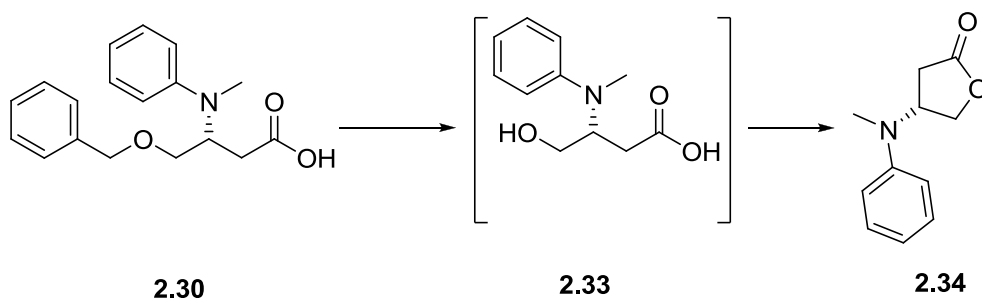
3.3.1 Friedel-Crafts cyclisation

Ma *et al.* reported the synthesis of a very similar tetrahydroquinolone in 62% yield, using an electrophilic Friedel-Crafts cyclisation of an acid chloride (Scheme 3.11).¹⁰¹



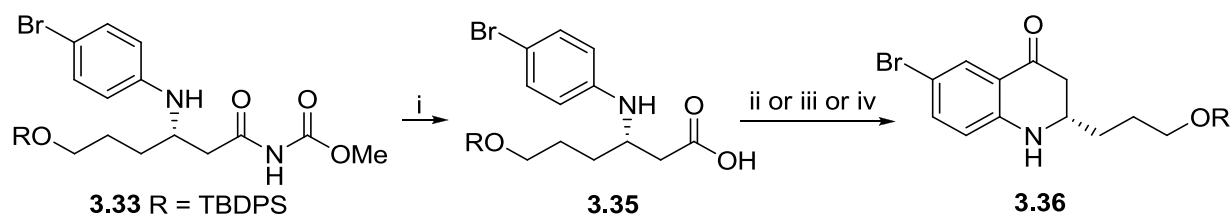
Scheme 3.11: Friedel-Craft cyclisation of an amino acid.

Previous attempts at the formation of the tetrahydroquinolone ring in the Galipea alkaloid synthesis, *via* electrophilic cyclisation of β -amino acids, proved unsuccessful with degradation of the starting material occurring in all cases (See Section 2.3.1). Some of the problems arose due to loss of the benzyl protecting group to produce a γ -lactone (Scheme 3.12).



Scheme 3.12: Formation of the lactone ring.

In this case, a *tert*-butyldiphenyl silyl protecting group was used, which would hopefully prove more stable to the acidic reaction conditions. The formation of the tetrahydroquinolone **3.36** was investigated using different reagents. First, the *N*-aryl β -amino acid **3.35** was prepared by the hydrolysis of the *aza*-Michael product **3.33** (Scheme 3.13).



Scheme 3.13: Reagent and conditions: (i) 1 M KOH, MeOH, rt, 82 %; (ii) PPA, 60 °C; (iii) Eaton's reagent, 65 °C; (iv) AlCl_3 , oxalyl chloride, $\text{CH}_2\text{Cl}_2/\text{DMF}$, 0 °C.

The carboxylic acid was formed in 82% yield, with the structure confirmed by the loss of the methyl carbamate group from the ^1H NMR spectrum, the appearance of a characteristic OH stretch at 3380 cm^{-1} and a carbonyl stretch at 1680 cm^{-1} in the infrared spectrum. It was envisaged that the optical purity of this intermediate may be enhanced by the formation of a diastereomeric salt with quinine.¹⁵¹ Consequently, the carboxylic acid **3.35** was reacted with (+)-quinine. However, the resultant salt did not resolve upon recrystallisation.

Next, the electrophilic ring cyclisation of the carboxylic acid **3.35** was attempted under several different conditions (Table 3.10).

Table 3.10: Electrophilic cyclisation of **3.35**.^a

Entry	Conditions	Temp/ °C	Time/h	% Yield ^b
1	PPA	60	2	-
2	AlCl_3 , oxalyl chloride	0-rt	16	-
3	Eaton's reagent	65	3	23 ^c

^aReagent and conditions: **Entry 1:** Acid (100 mg, 0.18 mmol), PPA (500 mg), CH_2Cl_2 (1 mL); **Entry 2:** Acid (100 mg, 0.18 mmol), oxalyl chloride (24 μL , 0.28 mmol), AlCl_3 (78 mg, 0.59 mmol), DMF (cat.), CH_2Cl_2 (1 mL); **Entry 3:** Acid (100 mg, 0.18 mmol), Eaton's reagent (2 mL). ^bIsolated yield after column chromatography. ^cTetrahydroquinolone obtained with loss of the alcohol protecting group.

Initially, the cyclisation of **3.35** was attempted using PPA (Table 3.10, entry 1).⁹⁹ None of the desired tetrahydroquinolone **3.36** was formed and complete degradation of the starting material occurred. Large levels of 4-bromoaniline were observed by ^1H NMR, suggesting that a retro-*aza*-Michael reaction had occurred.

The AlCl_3 -catalysed Friedel-Crafts cyclisation of an acid chloride, formed by the reaction of **3.35** with oxalyl chloride and DMF, was attempted next (entry 2).¹⁰¹ The acid chloride proved to be unstable under these conditions, and degradation of the starting material was

observed with loss of the *tert*-butyldiphenyl silyl protecting group. ^1H NMR of the reaction mixture showed trace levels of a side product, which is believed to be the lactone **3.37** (Figure 3.3), as suggested by the presence of two double doublets at 3.35 ppm and 3.55 ppm corresponding to the CH_2 group next to the lactone. Formation of the seven-membered ring of **3.37** would be significantly less favourable than the formation of the 5-membered lactone **2.34**, accounting for the low yield $< 10\%$.

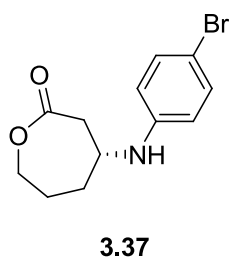


Figure 3.3: Lactone formed under Friedel-Crafts cyclisation conditions.

Finally, the cyclisation of **3.35** was attempted with Eaton's reagent.¹⁰⁰ Again, ^1H NMR revealed the loss of the *tert*-butyldiphenyl silyl protecting group; however, in this case, formation of the lactone **3.37** was not observed. A single product was isolated from the reaction mixture. IR analysis showed a carbonyl stretch at 1670 cm^{-1} , which corresponds to an aryl ketone, suggesting that it was the deprotected tetrahydroquinolone **3.38** (Figure 3.4). The formation of **3.38** was also confirmed by the presence of an OH stretch at 3340 cm^{-1} in the IR spectrum and the observation of a MH^+ peak of 284 (ESI).

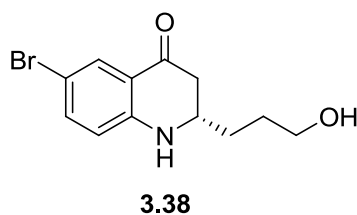
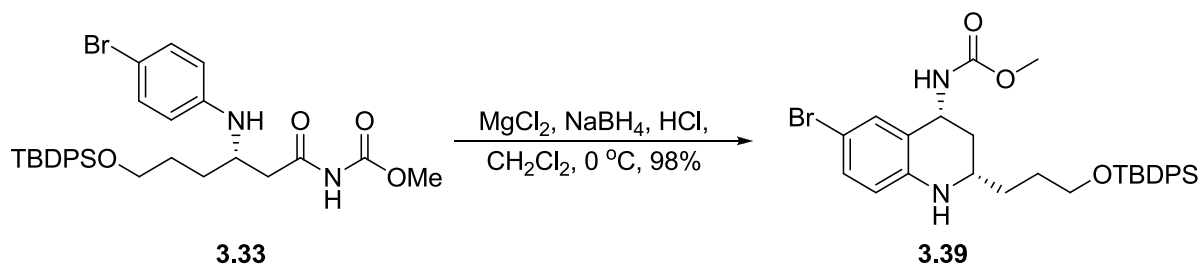


Figure 3.4: Product from electrophilic ring cyclisation with Eaton's reagent.

3.38 was obtained in the very low yield of 23% making this route unattractive. Disappointingly, the silyl protecting group proved unstable to the reaction conditions, and complete starting material degradation occurred under the strongly acidic reaction conditions. As a result, an alternative method for the formation of the tetrahydroquinoline ring under milder conditions was required.

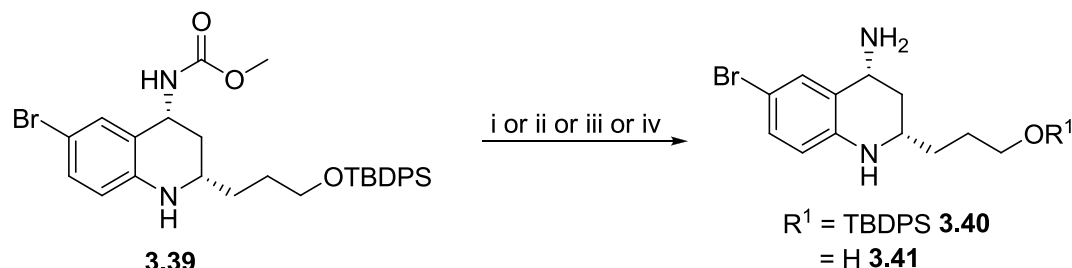
3.3.2 Lewis acid mediated reductive cyclisation

The *aza*-Michael product **3.33** was reacted with MgCl_2 and NaBH_4 to give the 2, 4-disubstituted tetrahydroquinoline **3.39** as a single diastereoisomer in 98% yield (Scheme 3.14).²⁴ The formation of the tetrahydroquinoline was confirmed by the loss of a carbonyl signal at 172.7 ppm in the ^{13}C NMR spectrum and the appearance of a unique absorption band at 1770 cm^{-1} in the IR spectrum.



Scheme 3.14: Reductive cyclisation of the *aza*-Michael adduct.

With the 2, 4-disubstituted tetrahydroquinoline in hand, the next step in the synthesis was the removal of the *N*-Moc protecting group (Scheme 3.15).



Scheme 3.15: Reagent and conditions: (i) TMSI, MeCN, rt, 16 h; (ii) 2M KOH, MeOH, 90 °C, 23 h; (iii) 4M HCl, dioxane, CH₂Cl₂; (iv) F₃CCO₂H, CH₂Cl₂.

Previously deprotection of the amine was achieved in good yield using TMSI. Accordingly, the reaction was performed in MeCN at room temperature for 16 hours,¹⁰⁶ which, proceeded to give **3.41** exclusively, as cleavage of the TBDPS group also occurred (Table 3.11, entry 1). The reaction was subsequently repeated with a significantly shortened reaction time of 1 hour (entry 2). However, the silyl group proved more labile than the carbamate under these conditions, with **3.42** obtained as the only product (Figure 3.5). This lack of success led us to investigate other methods for the removal of the Moc protecting group (Table 3.11).

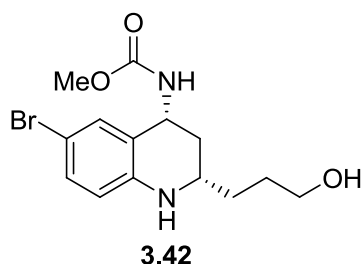


Figure 3.5: 2, 4-disubstituted tetrahydroquinoline after loss of the TBDPS protecting group.

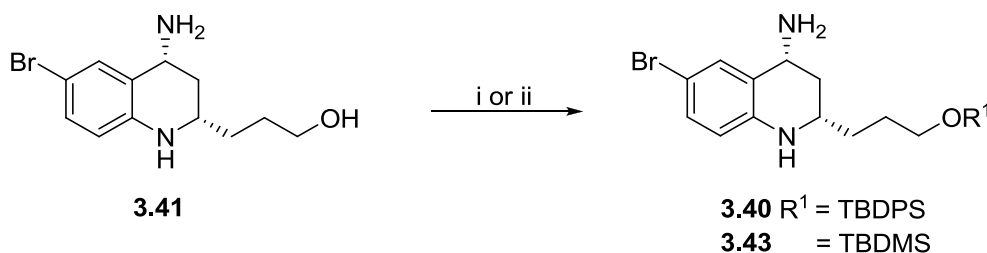
Table 3.11: Various conditions attempted for the deprotection of the *N*-Moc group.^a

Entry	Conditions	Temp/ ^o C	Time/h	% Yield of 3.40 ^b	% Yield of 3.41 ^c	% Yield of 3.42 ^c
1	TMSI	rt	16	-	78	-
2	TMSI	rt	1	-	-	100 ^b
3	6M KOH	90	18	-	50	-
4	2M KOH	90	23	-	80	-
5	2M KOH	rt	96	Trace	-	30
6	HCl, dioxane	rt	1	-	-	100 ^b
7	TMSI	rt	16	-	-	50
8	TFA	rt	96	-	-	-

^aReagents and conditions: **For entries 1-2 and 7:** Starting material (1.3 mmol, 1.0 eq), TMSI (5.2 mmol, 4.0 eq), MeCN (15 mL); **For entry 3-5:** Starting material (0.4 mmol, 1.0 eq), KOH (See table), MeOH (3 mL); **Entry 6:** Starting material (0.4 mmol, 1.0 eq), CH₂Cl₂ (35 mL), 4M HCl in dioxane (8.6 mL, 80 eq); **Entry 8:** Starting material (0.2 mmol, 1.0 eq), TFA (2.5 mL), CH₂Cl₂ (2.5 mL). ^bYields determined by ¹H NMR. ^cIsolated yields.

Removal of the *N*-Moc protecting group of **3.39** was attempted with KOH.¹⁵² Using 6M KOH led to the globally deprotected species **3.41** in 50% yield, when the reaction was conducted at 90 °C (Table 3.11, entry 3). The same reaction outcome resulted using 2M KOH, where **3.41** was formed exclusively in the significantly improved yield of 80% (entry 4). On lowering the temperature of the reaction, only a trace of the desired **3.40** was observed, with the *tert*-butyldiphenyl silyl deprotected **3.42** isolated in 30% yield and the remainder of the starting material recovered. These results show that under basic conditions the deprotection of the silyl group is, again, quicker than the deprotection of the Moc group.

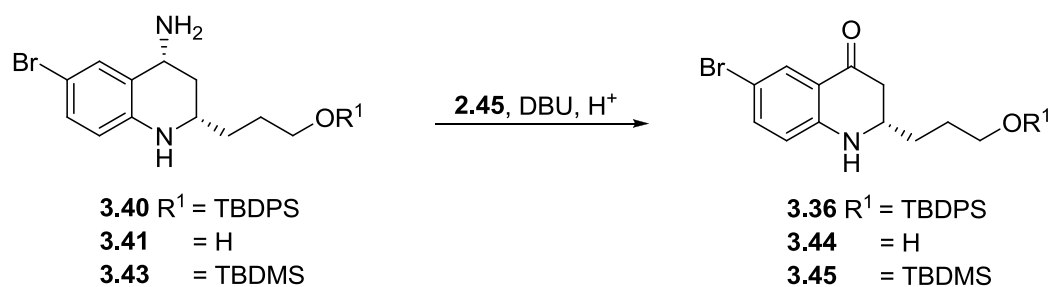
Next, the hydrolysis of the *N*-Moc group under acidic conditions was investigated. Exposing the tetrahydroquinoline **3.39** to 4M HCl in dioxane for 1 hour (entry 6),¹⁵³ led to the exclusive removal of the TBDPS group. This is quite a significant observation as HCl was used in the work up of the TMSI and KOH reactions. Hence, it was possible that the observed loss of the *tert*-butyldiphenyl silyl group occurred during work up, and not during the reaction. If this was the case, avoiding an acidic work up should have allowed for the formation of the desired **3.40**. With this in mind, the TMSI deprotection was repeated without an acidic work up. This led to a complex reaction mixture, where a significant level of the alcohol deprotected product was still observed (entry 7). Finally, the deprotection of **3.39** was attempted using the milder acid TFA.¹⁵⁴ This led to complete degradation of the starting material to an unidentifiable mixture of products. Hence, the selective deprotection of the amine could not be achieved in the presence of the TBDPS protecting group, despite the range of methods attempted. Thus, the re-protection of the alcohol was required (Scheme 3.16).



Scheme 3.16: Reagent and conditions: (i) Imidazole, TBDPSCl, CH₂Cl₂, Quant. (ii) Imidazole, TBDMSCl, DMAP, CH₂Cl₂, 65%.

Re-protection of the alcohol **3.41** with a *tert*-butyldiphenylsilyl group¹⁵⁵ and a *tert*-butyldimethyl silyl group¹⁵⁶ proceeded with quantitative and 65% yields, respectively. Formation of the protected alcohols was confirmed by the loss of the OH peak at 3310 cm⁻¹ in the IR spectra.

With the protected amines **3.40** and **3.43** in hand, their conversion into the tetrahydroquinolones **3.36** and **3.45** was attempted, *via* transamination with Rapoport's reagent¹¹⁶ (Scheme 3.17, Table 3.12).

**Scheme 3.17:** Transamination of the amines.**Table 3.12:** Transamination of protected amine.^a

Entry	Amine	Time/h	Quench	Base/eq	Product	% Yield ^b	% SM recovered ^b
1	3.40	3	Citric acid	DBU/ 3eq	3.36	5	95
2	3.40	18	Citric acid	DBU/ 3 eq	3.36	72	28
3	3.40	18	Oxalic acid	DBU/ 3 eq	3.36	90	10
4	3.40	18	Oxalic acid	DBU/ 10 eq	3.36	Trace	-
5	3.40	18	Oxalic acid	KO ^t Bu/ 3 eq	3.36	-	17 ^c
6	3.43	18	Oxalic acid	DBU/ 3 eq	3.44	100	-

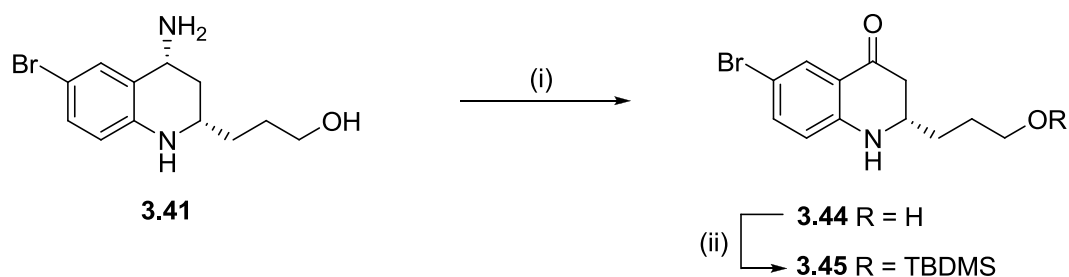
^aReagents and conditions: Amine (50 mg, 0.2 mmol), Rapoport's reagent (0.3 mmol, 1.5 eq), base (See table), CH₂Cl₂ (1 mL), DMF (1 mL), sat. acid (5 mL), rt. ^bIsolated yield.

The transamination of **3.40** was performed¹⁵⁷ with oxalic acid replaced by citric acid and the (quenching) process reduced from 16 hours to 2 hours, to avoid decomposition of the desired ketone **3.36** via acid catalysed cleavage of the TBDPS group. Unfortunately, only a very low yield of the ketone was formed, and the majority of the starting material was recovered (Table 3.12, entry 1). However, no loss of the TBDPS protecting group was observed, showing it to be stable to these conditions. On repeating the reaction and extending the quench to 16 hours, a significant improvement in the yield to 72% was obtained (entry 2). A further improvement, to 90%, was achieved by re-adopting oxalic acid in the workup (entry 3) and the reaction proceeded to give a clean mixture of starting material and product.

Next, the amount of base was increased from 3 to 10 equivalents, in the hope of pushing the reaction to completion. In this case, only a trace level of the desired ketone **3.36** was observed in the reaction mixture, accompanied by large amounts of degraded products (Table 3.12, entry 4). KO^tBu was also used, to determine if a stronger base would improve the yield (entry 5). Again, large levels of degradation occurred and none of the desired ketone was obtained, although a low level of the starting material was recovered. These results show the reaction yield is optimal by employing DBU (3 eq) and oxalic acid for the quench; moreover, the time of the reaction quench proved significant.

Thus, the transamination of **3.43** was attempted under the optimal conditions. However, TBDMS proved unstable under these conditions, as the deprotected **3.44** was isolated quantitatively as the only product (Table 3.12, entry 6).

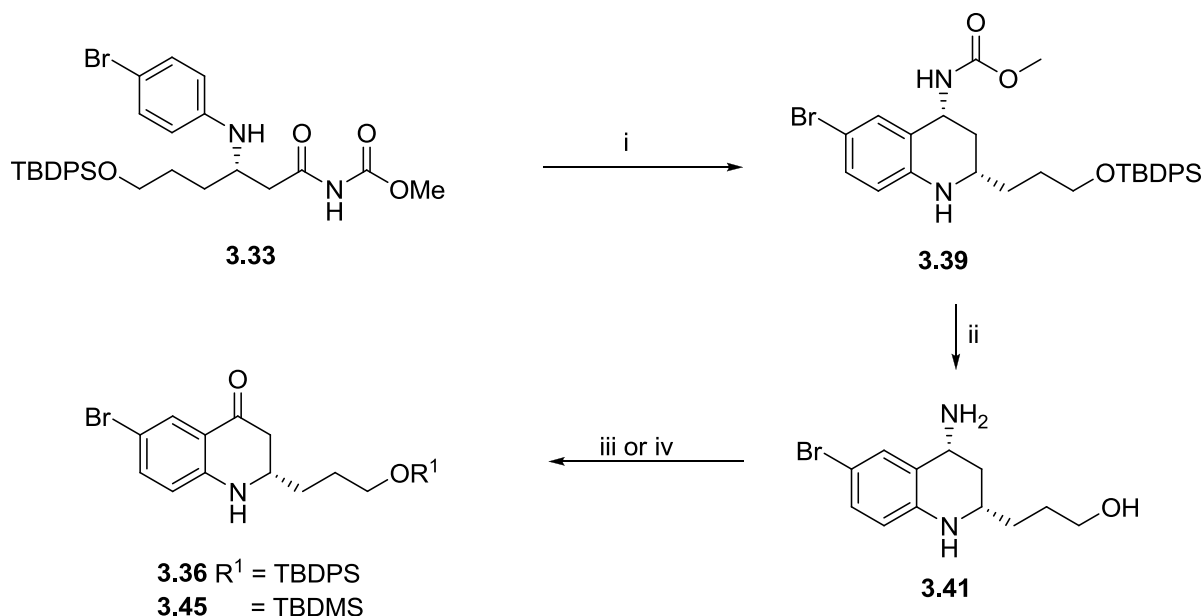
The formation of the ketone **3.45** was finally achieved in two steps, by the transamination of the amine **3.41** to give the ketone **3.44**. Re-protection of the free hydroxyl with a TBDMS group at this point allowed for the synthesis of **3.45** (Scheme 3.18). The transamination of **3.41** gave **3.44** in the good yield of 75% and the re-protection was achieved using imidazole, DMAP and TBDMSCl in 70% yield.



Scheme 3.18: Reagent and conditions: (i) **2.45**, DBU, DMF, CH₂Cl₂, 75%; (ii) TBDMSCl, DMAP, Imidazole, CH₂Cl₂, 70%.

To summarise, the formation of the tetrahydroquinolones was achieved from the commercially available 1, 4-butandiol in 8 steps with 8-18% overall yield (Scheme 3.19). Mono-protection of 1, 4-butandiol, followed by Swern oxidation and a Wittig reaction gave the TBDPS-protected alkene **3.20** in 40% yield. [(BINAP)Pd(solvent)₂]²⁺ [TfO]₂⁻ catalysed the *aza*-Michael reaction of 4-bromoaniline in 85% yield and 85% ee. The 2, 4-disubstituted tetrahydroquinoline **3.39** was then synthesised by the Lewis acid catalysed reductive cyclisation reaction of the *aza*-Michael product **3.33**, and global deprotection of the Moc and silyl protecting group using TMSI gave **3.41** in good yield. Here, the synthesis of the two

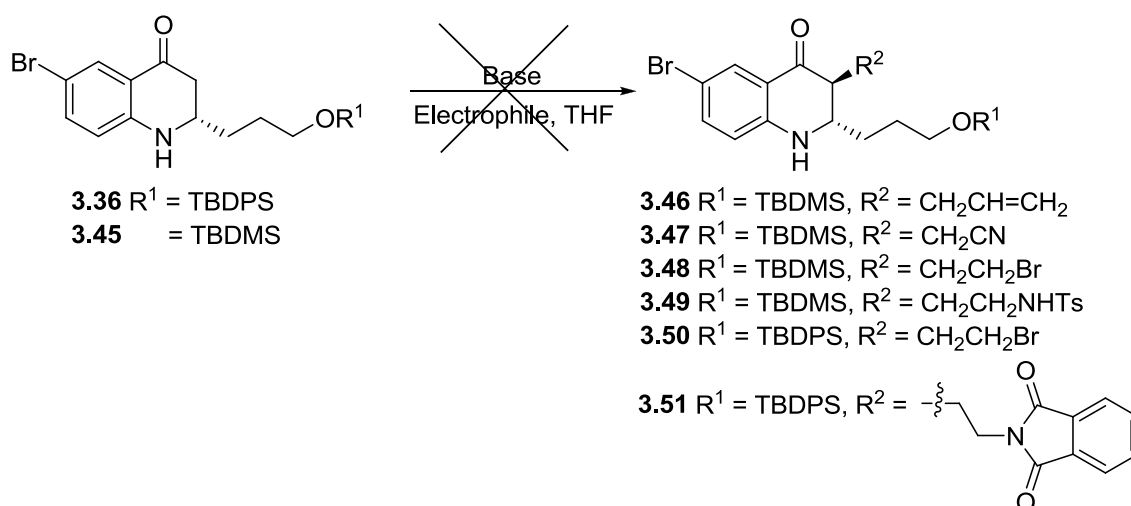
ketones **3.36** and **3.45** diverged, with **3.36** formed firstly by reprotection of the free hydroxyl and then transamination using Rapoport's reagent. Synthesis of **3.45** was achieved by the transamination of the unprotected amine **3.41** to give the ketone, followed by reprotection of the free alcohol with a TBDMS group.



Scheme 3.19: Reagent and conditions: (i) MgCl_2 , NaBH_4 , THF, EtOH, 0°C , 5 h, 98%; (ii) TMSI, MeCN, 16 h, 78%; (iii) Imidazole, TBDPSCl, CH_2Cl_2 , 16 h, rt then **2.45**, DBU, DMF, CH_2Cl_2 , oxalic acid, 18 h, rt, 75%; (iv) **2.45**, DBU, DMF, CH_2Cl_2 , oxalic acid, 18 h, rt then TBDMSCl, imidazole, DMAP, CH_2Cl_2 , 16 h, rt, 35%.

3.4 Work towards formation of the third ring

The final step in the formal synthesis of the Martinelline alkaloids was the installation of the third ring. It was expected that the stereochemistry set at the C-2 position would direct the stereochemistry at the C-3 and C-4 positions. In this part of the work, alkylation of the ketones **3.36** and **3.45** was attempted with a range of different electrophiles (Scheme 3.20, Table 3.13).

**Scheme 3.20:** Alkylation of the C-3 position.**Table 3.13:** Attempted alkylation of the C-3 position.^a

Entry	Ketone	Electrophile	Base/eq	Time/h	% Yield ^b
1	3.45		LHMDS/ 2.1 eq	3	-
2	3.45		LHMDS/ 2.1 eq	3	-
3	3.45		LHMDS/ 2.2 eq	3	-
4	3.36		LHMDS/ 3.1 eq	4	Trace

^aReagents and conditions: **For entries 1-2:** **3.45** (0.13 mmol, 1.0 eq), 1M LHMDS in THF (0.26 mmol, 2.1 eq), electrophile (0.28 mmol, 2.2 eq), THF (0.7 mL), -78°C - -40 °C, rt; **For entry 3:** **3.45** (0.13 mmol, 1.0 eq), 1M LHMDS in THF (0.28 mmol, 2.2 eq), electrophile (0.32 mmol, 2.5 eq), THF (0.7 mL), -78°C - -40°C; **For entry 4:** **3.36** (0.2 mmol, 1.0 eq), 1M LHMDS (0.4 mmol, 2.1 eq), electrophile (0.42 mmol, 2.2 eq), THF (1.5 mL), -78°C - -40°C, 3 h, then 1M LHMDS (1.0 eq), -40 °C, 1 h.

The alkylation of the C-3 position was first attempted using allyl bromide and LHMDS as base. Complete consumption of the starting material occurred to give a mixture of products (Table 3.13, entry 1). The major component was tentatively assigned as the quinoline **3.53**, which was isolated in 56% yield (Figure 3.6). Formation of the quinoline was confirmed by

the presence of the MH^+ peak 396 (ESI) and a singlet in the 1H NMR at 6.24 ppm corresponding to H_a .

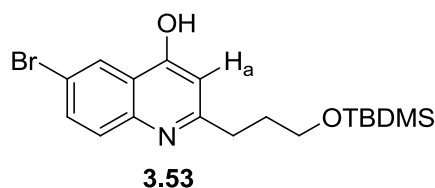


Figure 3.6: Quinoline formed during the alkylation attempt.

LC-MS analysis of the reaction mixture identified the presence of three other components. The observation of a MH^+ of 478 corresponds to the formation of a dialkylated tetrahydroquinoline produced in 16% isolated yield. Alkylation of the nitrogen and either the C-3 position of the tetrahydroquinolone or the oxygen of the enol, would give **3.54** or **3.55** (Figure 3.7). The observation of a 1H resonance signal corresponding to H_a at 4.9 ppm supported the formation of **3.54**.

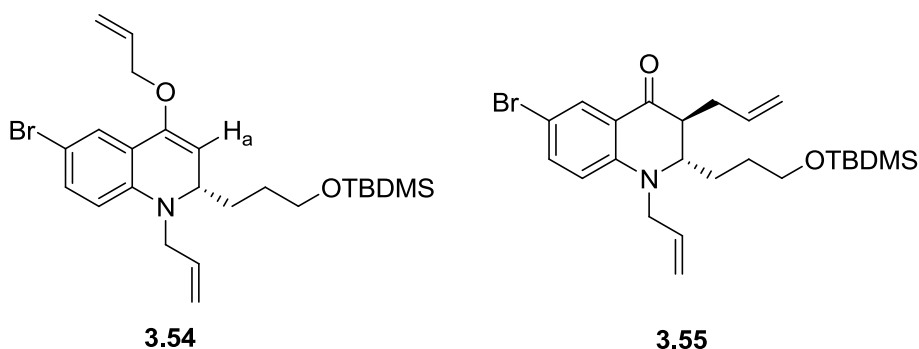


Figure 3.7: Two possible dialkylated tetrahydroquinolines.

The two other components were believed to be the mono-alkylated tetrahydroquinoline **3.56** (MH^+ 438) and **3.57** (MH^+ 438) (Figure 3.8). No C-3 alkylation was observed, so other electrophiles were investigated.

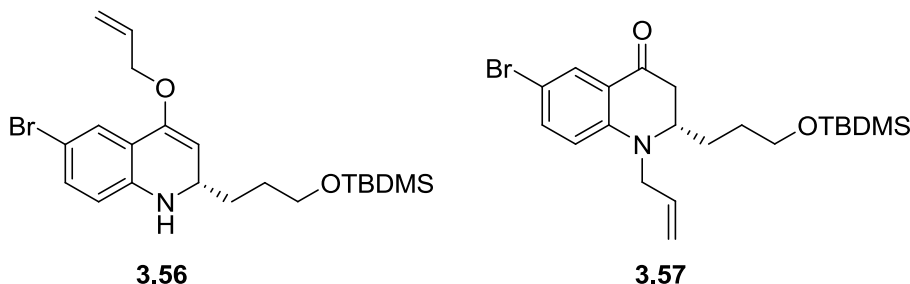
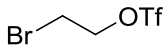
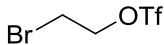
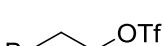
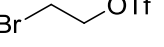


Figure 3.8: Two possible mono-alkylated tetrahydroquinolines.

Next, bromoacetonitrile was used as the electrophile (Table 3.13, entry 2). In this case, only starting material was recovered from the reaction mixture. Upon addition of the bromoacetonitrile the reaction turned black, suggesting that base-catalysed polymerisation of the electrophile may have occurred. To avoid this, 1-tosylaziridine was subsequently used, (entry 3), however, only the starting materials were recovered. Last but not least, the use of a masked amine electrophile *N*-(2-bromoethyl)phthalimide **3.52** was investigated. In this case, the reaction with the tetrahydroquinoline **3.36** proceeded to give trace levels of the desired product, but a majority of the starting material was recovered (entry 4).

The lack of reaction thus far was attributed to low reactivity of the electrophiles towards alkylation at C-3. Previously, alkylation of the similar THQ **3.6** has been achieved with $\text{BrCH}_2\text{CH}_2\text{OTf}$ (Scheme 3.3), and so the reaction of the tetrahydroquinolines **3.36** and **3.45** was attempted with this electrophile (Table 3.14).

Table 3.14: Alkylation with $\text{BrCH}_2\text{CH}_2\text{OTf}$.^a

Entry	Ketone	Electrophile	Base/eq	Time/h	% Yield ^b
1	3.36		LHMDS/ 2.1 eq	3	-
2	3.45		LHMDS/ 2.1 eq	3	-
3	3.36		LHMDS/ 3.1 eq	4	-
4	3.36		LHMDS/ 4.2 eq	16	-
5	3.36		LHMDS/ 6.3 eq	16	-
6	3.45		LDA/ 2.1 eq	3	-

^aReagents and conditions: Ketone (0.12 mmol, 1.0 eq), electrophile (0.25 mmol, 2.2 eq), base (See table), THF (1 mL), -78 °C - -40°C. ^bYield determined by ¹H NMR.

None of the desired alkylated product was formed with either tetrahydroquinolines under the conditions reported (entries 1 and 2).⁸² Suspecting that the lack of alkylation could be due to incomplete deprotonation, an additional equivalent of base was added but this did not lead to the formation of the desired product and only starting material was recovered (entry 3). None of the electrophile was observed by ¹H NMR, suggesting degradation had occurred. With this in mind, the enol was pre-formed and then slowly introduced into a solution of the

electrophile (*via* a cannular). Again, no alkylation was achieved even with prolonged reaction times and the addition of extra electrophile (entries 4 and 5). Finally LDA was used as base, but only the starting material persisted in the reaction mixture.

To determine if deprotonation of the C-3 position was occurring, a D₂O quench was conducted after addition of the base to **3.36** and **3.45**. Deprotonation was attempted using LHMDS, LDA and NaHMDS – in all cases, incorporation of deuterium at C-3 was not observed in either the ¹H NMR or LC-MS spectra.

A range of different electrophiles were used in an attempt to achieve C-3 alkylation, however the formation of the third ring proved difficult, with no alkylation achieved in any of the cases. When allyl bromide was used as electrophile only O- and N-alkylation products were obtained. On the other hand, bromoacetonitrile decomposed in the presence of the strong base, and only starting material was recovered when 1-tosylaziridine was used. Trace levels of product was observed with the masked amine *N*-(2-bromoethyl)phthalimide **3.53**, however, the majority of the starting material was recovered. Alkylation of the C-3 position was also attempted using the BrCH₂CH₂OTf electrophile, which was successfully used by Ma *et al.*⁸² However, no alkylation was achieved under a variety of different conditions. Finally, deuterium quenches of the reaction revealed that none of the bases tested were able to deprotonate at C-3, explaining the failure of these reactions.

In summary, five different α , β -unsaturated carbamates were synthesised and assessed as acceptors for the *aza*-Michael reaction. The nature of the protecting group was found to have a significant effect, with variations in the enantioselectivity between 8% and 66%. The reaction with aniline identified the TBDPS-protected **3.20** as the best Michael acceptor. The *aza*-Michael reaction of **3.20** with four different anilines was subsequently investigated, and 4-bromoaniline was found to give the product in the highest yield and enantioselectivity.

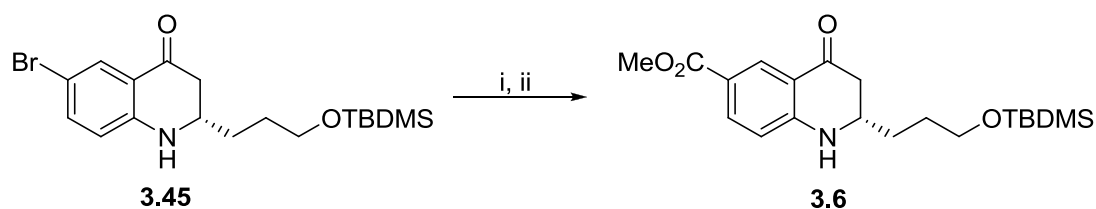
Electrophilic cyclisation of the β -amino acid using PPA, Eaton's reagent and oxalyl chloride with AlCl₃ all proved unsuccessful and as a result, the Lewis acid catalysed reductive/cyclisation was used to give the 2, 4-di-substituted tetrahydroquinoline. Synthesis of the two silyl protected tetrahydroquinolones was achieved by transamination and reprotection of the alcohol. Finally formation of the third ring was attempted by alkylation of the C-3 position. This was attempted using several different electrophiles; however, in all

cases no alkylation of the C-3 position was observed and additional work is required to allow for the formal synthesis of the Martinelline Alkaloids.

3.5 Future Work

For the formal synthesis of the Martinelline alkaloids, optically pure material is required. Improvements to the enantioselectivity by the recrystallisation of various intermediates should be attempted. On formation of the tetrahydroquinoline ring the material becomes more crystalline, thus recrystallisation of **3.39** could prove successful for the enhancement of the enantioselectivity. Alternatively, improvements could also be made by the formation of diastereomeric salts, *via* the reaction of the amines **3.40**, **3.41** or **3.43** with a chiral acid, *e.g.* tartaric acid. Recrystallisation of the salt could allow for the separation of the diastereoisomers, giving optically pure material on liberation of the free amine.

To achieve the formal synthesis of the Martinelline alkaloids, formation of the third ring is required. So far, attempts to alkylate **3.36** and **3.45** were unsuccessful. This is attributed to the inability of the base to deprotonate the C-3 position. Previously, alkylation of the C-3 position of **3.6** was achieved. Thus, the presence of the bromine may be detrimental to the alkylation procedure and hence, the conversion of the bromide of the ketone **3.45** into the methoxy ester would allow for the formal synthesis, as the reaction is precedented.¹⁵⁸ This should be achievable in two steps, by protection of the nitrogen¹⁵⁹ and then reaction with BuLi and dimethyl carbonate (Scheme 3.21).⁸³ Alternatively, the effect of protection of the nitrogen of **3.45** with a variety of protecting groups, *i.e.* Boc, benzoyl or benzyl groups, could be investigated in an attempt to achieve C-3 alkylation.



Scheme 3.21: Reagent and conditions: (i) Boc₂O, NEt₃, THF; (ii) *n*-BuLi, CH₃OCO₂CH₃, THF.

The reaction of **3.6** with other electrophiles including *N*-(2-bromoethyl)phthalimide, *N*-(2-iodoethyl)phthalimide and *N*-tosyl aziridine should also be attempted at this stage, to provide a quicker route to the pyrroloquinoline core structure.

CHAPTER FOUR
SYNTHESIS OF LEVONANTRADOL

4.0 Synthesis of levonantradol

Levonantradol **1.17** is a structurally novel analgesic drug developed by a team of Pfizer scientists in the 1980's, containing a tricyclic core structure with chiral centres in the 2-, 3- and 4- positions of the tetrahydroquinoline ring.²⁵ In addition to these, **1.17** contains a chiral centre on the side chain and another on the fused carbocyclic ring. The potency of levonantradol's analgesic properties is highly dependent on the stereochemistry of all the chiral centres, with the 2-(*S*), 3-(*R*), 4-(*R*) isomer giving the highest activity. The X-ray structure of the diastereoisomer **4.1**, containing the opposite stereochemistry on the side chain (Figure 4.1), was obtained. This allowed for the assignment of the absolute stereochemistry. This diastereoisomer showed a 10-fold decrease in activity compared to levonantradol. In comparison, the enantiomer of levonantradol was found to be 100 times less active, highlighting the importance of asymmetric synthesis for the formation of pharmaceutically active compounds.²⁵

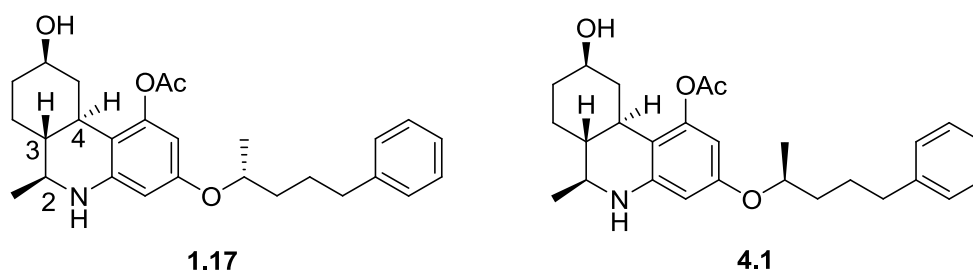
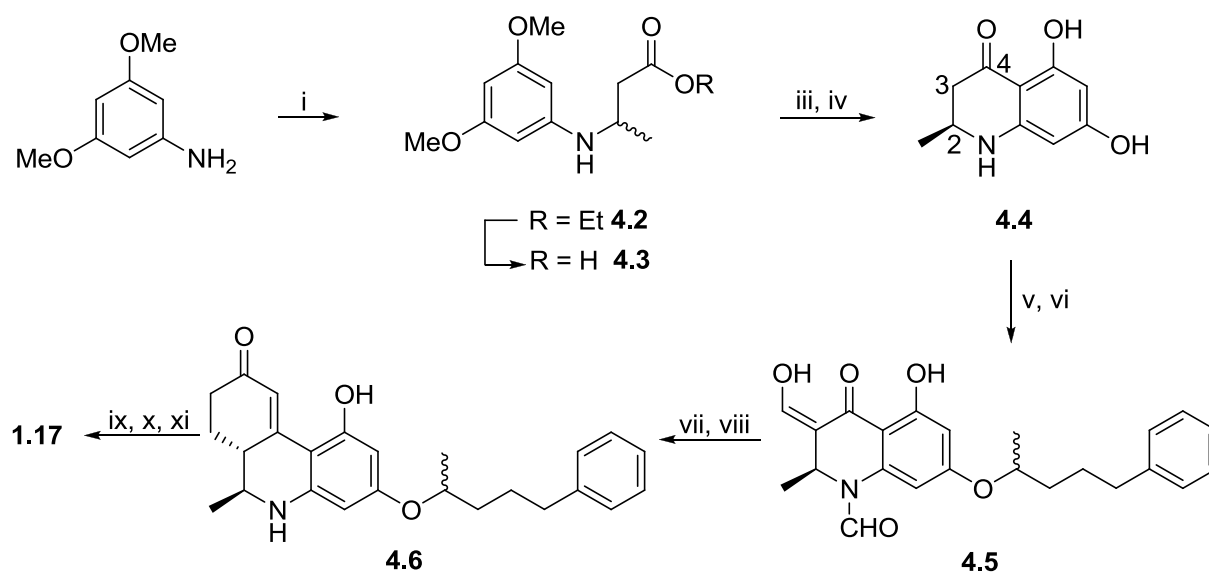


Figure 4.1: Levonantradol **1.17** and the less active diastereoisomer.

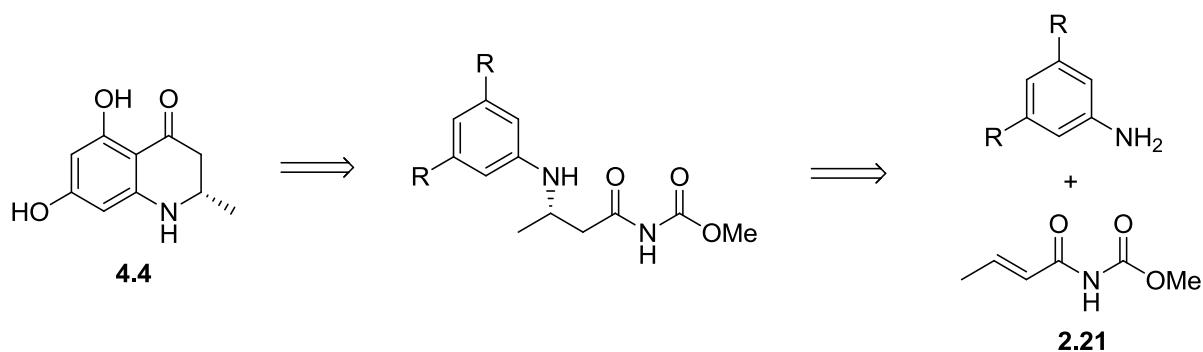
The synthesis of levonantradol was published by its inventors in a communication and also described in a patent, using 3, 5-dimethoxyaniline as the starting material (Scheme 4.1).^{25, 160} The reaction of 3, 5-dimethoxyaniline with ethyl acetoacetate in the presence of acetic acid, followed by reduction with sodium borohydride produced the β -amino ester **4.2**. Hydrolysis of the carboxylic ester gave the carboxylic acid **4.3**. Resolution of the racemic material, to give optically pure acid, was conducted at this stage by recrystallisation, using the chiral amino alcohol 1-ephedrine as a resolving agent.¹⁶⁰ Cyclisation to form the tetrahydroquinolone **4.4** was facilitated using 48% HBr at reflux, and was accompanied by the deprotection of the methoxy groups. Regiospecific attachment of the aromatic side chain was achieved by the addition of mesylated 5-phenyl 2-pentanol to **4.4**. Formation of the third ring, via a Robinson annulation reaction, furnished the tricyclic core structure of; with stereocentre at C-3 occurring *anti* to the C-2 methyl group. Dissolving metal reduction was used to remove the C=C double bond of the cyclic enone and levonantradol was synthesised

in two further steps by reduction of the ketone with NaBH_4 , and regiospecific *O*-acetylation of the aromatic alcohol.¹⁶⁰



Scheme 4.1: Reagent and conditions: (i) 3, 5-dimethoxyaniline, ethyl acetoacetate, AcOH then NaBH_4 , AcOH; (ii) Hydrolysis; (iii) 1-ephedrine, CH_2Cl_2 ; (iv) Glacial AcOH, 48% HBr, reflux; (v) 5-phenyl 2-pentanol, NEt_3 , MsCl, 0 °C then K_2CO_3 , DMF, 80 °C; (vi) Ethyl formate, NaH, rt; (vii) NEt_3 , MeOH, methyl vinyl ketone, rt; (viii) K_2CO_3 , MeOH, rt; (ix) NH_3 , Li, -78 °C - rt; (x) NaBH_4 THF, -78 °C; (xi) DMAP, NEt_3 , Ac_2O , 0 °C.

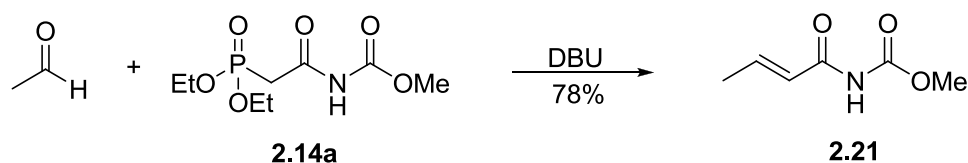
We envisioned the asymmetric synthesis of the key intermediate tetrahydroquinolone **4.4** to be achievable using the methodology developed in the previous chapters. The *aza*-Michael reaction would install the C-2 stereocentre, with the tetrahydroquinolone formed by electrophilic ring cyclisation (Scheme 4.2). The synthesis of levonantradol from **4.4** would then be achievable following literature conditions.



Scheme 4.2: Retrosynthetic analysis of **4.4**.

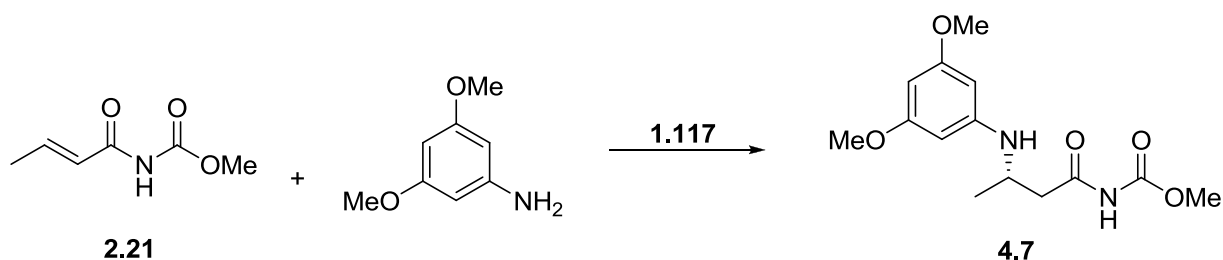
4.1 Synthesis of *aza*-Michael precursors

For the synthesis of levonantradol, the installation of a methyl group into the C-2 position requires the Michael acceptor **2.21**. Following the published procedure, the HWE reaction of acetaldehyde with the phosphonate carbamate **2.14a** proceeded in 78% yield (Scheme 4.3).⁹⁸ The formation of the alkene was confirmed by the presence of the olefinic protons, appearing as a multiplet at 7.18 ppm and a double doublet at 6.88 ppm in the ¹H NMR spectrum.



Scheme 4.3: Synthesis of the *aza*-Michael acceptor.

The required tetrahydroquinolone **4.4** is substituted with hydroxyl groups in the *meta* positions (relative to the amine). Ideally, **4.4** would be formed from the *aza*-Michael product **4.7**, which in turn would be synthesised *via* reaction of **2.21** with 3,5-dimethoxyaniline (Scheme 4.4).

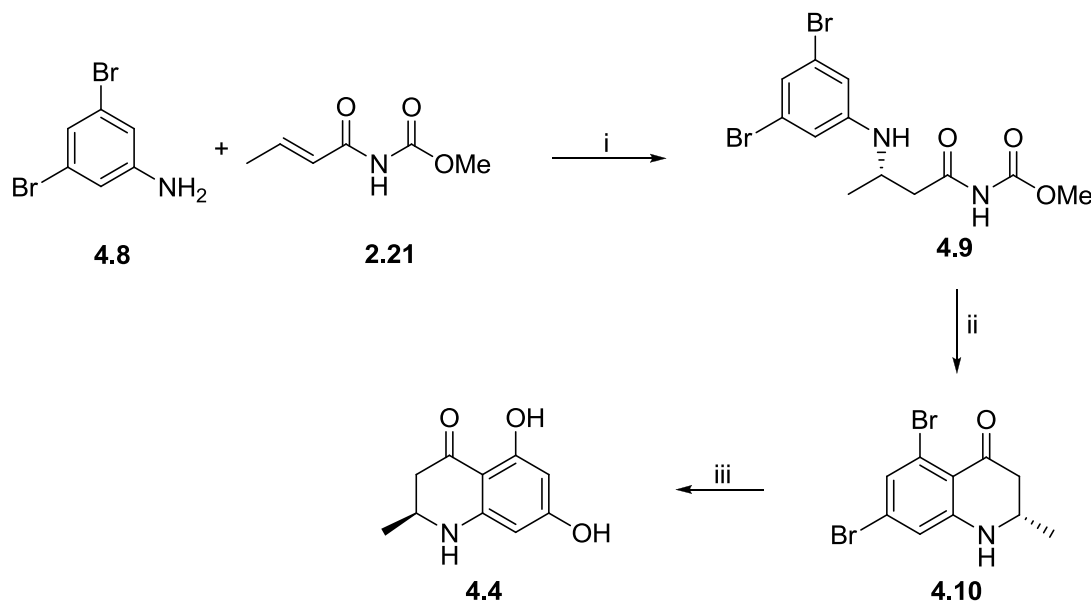


Scheme 4.4: Ideal *aza*-Michael reaction for levonantradol synthesis.

However, the *aza*-Michael reaction of electron rich anilines is known to proceed with low yields and enantioselectivities (see section 2.0), due to catalyst deactivation by irreversible binding of the amine to the catalyst, and also the operation of a background, uncatalysed *aza*-Michael reaction.⁷⁰ Thus, an alternative approach was required.

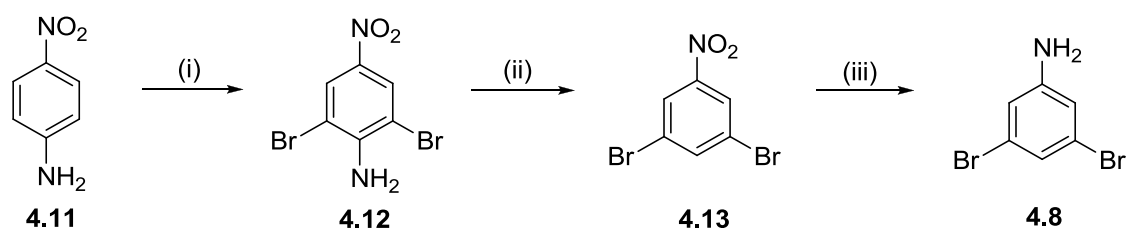
The presence of electron-withdrawing groups on the aniline was found to be well tolerated in previous work (see section 2.0), and so 3, 5-dibromoaniline was chosen as the nucleophile for the conjugate addition. The tetrahydroquinolone **4.4** should be obtainable *via* conversion of the aryl bromides into the required hydroxyl groups (Scheme 4.5). There are a number of literature examples, where aryl bromides have been converted into phenols and ethers. For

example, by employing Pd_2dba_3 /bulky phosphine as catalyst, KOH can be used as a nucleophilic reagent.¹⁶¹



Scheme 4.5: Reagent and conditions: (i) $[\text{Pd}(\text{R-BINAP})(\text{OH}_2)_2]^{2+}[\text{OTf}]^-_2$, toluene; (ii) PPA; (iii) Pd_2dba_3 , KOH, PR_3 , 100 °C.

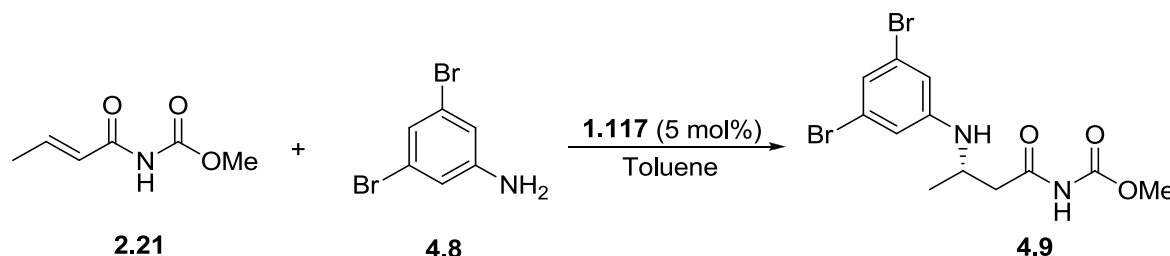
The 3, 5-dibromoaniline **4.8** is not commercially available, thus it was synthesised from 4-nitroaniline **4.11** in 3 steps (Scheme 4.6). Bromination of **4.11** with Br_2 and acetic acid gave **4.12** in the excellent yield of 95%. Removal of the amine was achieved, *via* the formation of an intermediary diazonium salt, using NaNO_2 in sulfuric acid. The diazonium salt decomposed on heating, releasing nitrogen to afford **4.13** in 96% yield, confirmed by the appearance of a triplet resonance at 8.03 ppm in the ^1H NMR spectrum. Reduction of the nitro group using tin(II) chloride gave the 3, 5-dibromoaniline **4.8** in 81% yield. The reduction of the electron-withdrawing NO_2 to a electron-releasing NH_2 was indicated by an upfield shift of the aromatic proton resonances from 8.36 ppm and 8.03 ppm to 7.05 ppm and 6.77 ppm, as well as the presence of the MH^+ ion peak at 251 (ESI).



Scheme 4.6: Reagents and conditions: (i) AcOH, Br_2 , 65 °C, 95%; (ii) NaNO_2 , H_2SO_4 , EtOH, 90 °C, 96% (iii) SnCl_2 , THF/EtOH, rt, 81%.

4.2 Aza-Michael reaction

At room temperature, no reaction was observed when a mixture of 3, 5-dibromoaniline, the α , β -unsaturated carbamate **2.21** and $[\text{Pd}(\text{R-BINAP})(\text{OH}_2)_2]^{2+}[\text{OTf}]_2$ **1.117** (5 mol%) was stirred in toluene for 24 hours (Scheme 4.7). Upon raising the temperature to 50 °C, the formation of the product **4.9** in 80% conversion and 75% ee was achieved (Table 4.1, entry 1). However, full conversion was unobtainable, even with prolonged reaction time. Formation of the product was confirmed by loss of the alkene signals at 7.18 ppm and 6.88 ppm, and the appearance of an ABX pattern in the ^1H NMR spectrum, with resonances between 2.95 ppm and 3.14 ppm corresponding to the CH_2 group adjacent to the chiral centre.



Scheme 4.7: Aza-Michael reaction of **2.21** with 3, 5-dibromoaniline.

In an attempt to improve the conversion obtained for the *aza*-Michael reaction, further optimisation was carried out (Table 4.1).

Table 4.1: Effect of solvent and aniline : alkene ratio on the *aza*-Michael reaction.^a

Entry	Solvent	Alkene (eq)	Temp/ °C	Time/h	% Yield ^b	% ee ^c , (Config)
1	Toluene	1.0	50	36	80	75 (S)
2	CH ₂ Cl ₂	1.0	40	24	50	56 (S)
3	Toluene	1.0	50	16	75	ND ^d
4	Toluene	1.5	50	16	50	ND ^d
5	Toluene	2.0	50	16	23	ND ^d

^aReagents and conditions: Alkene (0.35 mmol, 1.0-2.0 eq), aniline (0.17-0.35 mmol, 1.0 eq), **1.117** (5 mol%), solvent (1 mL). ^bDetermined by ^1H NMR. ^cDetermined by chiral HPLC using Hichrom-CHI-PGG-2759 column.

^dEnantioselectivities were not determined as the conversions were too low.

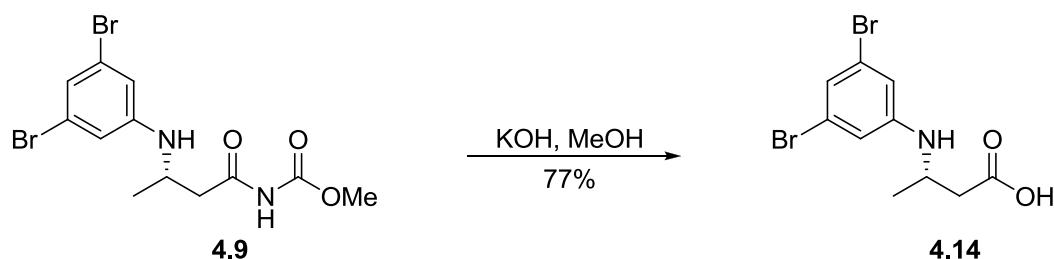
The lack of reaction observed at room temperature for the *aza*-Michael reaction was the result of poor solubility of both the catalyst and α , β -unsaturated carbamate. It was hoped that

changing the solvent would increase the solubility of both reagents and thus give improved results. Previously, CH_2Cl_2 was shown to be an effective solvent for similar *aza*-Michael reactions, offering comparable results to toluene.⁸¹ In this case, the reaction in CH_2Cl_2 proceeded to give the product in a lower yield and enantioselectivity (Table 4.1, entry 1 vs 2), despite the increased solubility of the alkene.

Next, the effect of varying the aniline to alkene ratio was investigated. Previously, in the synthesis of the Martinelline alkaloids, this led to improved enantioselectivities (see section 3.2.4). In this case, increasing the equivalents of the alkene from 1.0 to 1.5 led to a decrease in yield from 75% to 50% (Table 4.1, entry 3 vs 4). A further decrease to 23% was observed on using two equivalents of alkene (entry 4 vs 5).

In the synthesis of the Galipea alkaloids, a significant improvement in the enantioselectivity was obtained on the slow addition of the aniline to the reaction mixture (see section 2.2.1).⁹⁸ Replicating this procedure, the reaction proceeded to give **4.9** with the improved enantioselectivity of 85%, although full conversion was still not obtained and the *aza*-Michael product was isolated in only 68% yield.

In the previous synthesis of levonantradol, resolution of the racemic acid was achieved using the chiral amino alcohol 1-ephedrine, where recrystallisation of the ion pair gave optically pure material (Scheme 4.1).²⁵ An attempt was made to employ this procedure to enrich the optical purity of the *aza*-Michael adduct **4.9**. Hydrolysis of the carbamate to give the corresponding carboxylic acid proceeded in 77% yield (Scheme 4.8). The formation of the carboxylic acid was confirmed by the appearance of a ^{13}C signal at 176.4 ppm and the M^+ ion peak of 337 (ESI).



Scheme 4.8: Hydrolysis of the *aza*-Michael product.

The carboxylic acid **4.14** was reacted with (1*R*, 2*S*)-(-)-ephedrine to form a diastereomeric salt. Recrystallisation of the ion pair was attempted with ethyl acetate/*n*-hexane and toluene/*n*-hexane mixtures. In both cases, oiling of the compound occurred and the process did not give any improvement in enantioselectivity.

An enhancement in the enantioselectivity of the *aza*-Michael product **4.9** was eventually achieved by recrystallisation (Table 4.2).

Table 4.2: Recrystallisation of **4.9** from various solvents.^a

Entry	Solvent conditions	% ee of mother liquor ^b , (Config)	% ee of solid ^b , (Config)
1	EtOAc/ <i>n</i> -Hexane	-	85 (S)
2	Et ₂ O/ <i>n</i> -Pentane	-	85 (S)
3	Toluene/ <i>n</i> -Hexane	-	85 (S)
4	EtOAc	85 (S)	-
5	Et ₂ O	85 (S)	-
6	Toluene	91 (S)	69 (S)

^aReagents and conditions: **Entries 1-3 and 6: 4.9** (0.9 g, 2.3 mmol), total solvent (10 mL), reflux; **Entry 4: 4.9** (0.4 g, 1.0 mmol), EtOAc (1.5 mL), reflux; **Entry 5: 4.9** (0.4 g, 1.0 mmol), Et₂O (21 mL), reflux. ^bDetermined by chiral HPLC using Hichrom-CHI-PGG-2759 column.

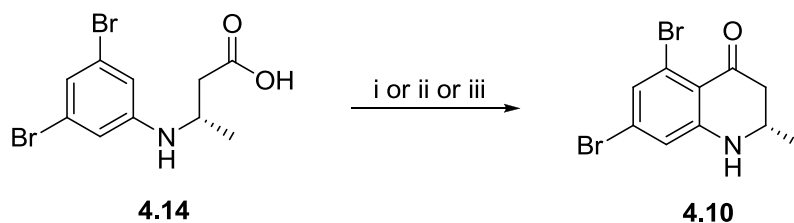
Recrystallisation of **4.9** from an ethyl acetate/*n*-hexane mixture did not lead to any improvement in the enantioselectivity (Table 4.2, entry 1). There was no solubility difference between the racemic and optically pure compound in this solvent system, as the material was extremely crystalline. Similar results were obtained with the ether/*n*-pentane and toluene/*n*-hexane systems, with no change in enantioselectivity observed upon recrystallisation (entries 2 and 3).

It was thought the use of the anti-solvent in the above systems could have been the cause of the problem. As a result the recrystallisation was tried in neat EtOAc and Et₂O, however, in both cases, oiling occurred and no enhancement in enantioselectivity was observed (entries 4 and 5). Finally, the recrystallisation was attempted in neat toluene and gratifyingly the enantioselectivity of the material remaining in the mother liquor was enhanced to 91% ee. Correspondingly, the solid precipitate was obtained in 62% recovered yield with 69% ee. Repeating the recrystallisation process allowed for the obtainment of optically pure **4.9**.

Thus, the *aza*-Michael reaction of 3, 5-dibromoaniline with **2.21** proceeded to give the product **4.9** in 80% conversion and 74% enantioselectivity. The ee was increased to 85% *via* the slow addition of the aniline, although the reaction still did not proceed to completion. Finally, optically pure material was obtained by recrystallisation from toluene.

4.3 Work towards the synthesis of 4.4

The next step in the synthesis of levonantradol was the formation of the tetrahydroquinolone ring, from the optically pure *aza*-Michael product **4.9**. The cyclisation of the carboxylic acid **4.14** under several different conditions was thus attempted (Scheme 4.9, Table 4.3).



Scheme 4.9: Reagent and conditions: (i) PPA, 90 °C; (ii) Oxalyl chloride, AlCl₃, CH₂Cl₂; (iii) Eaton's reagent, 65 °C.

Table 4.3: Electrophilic cyclisation reactions.^a

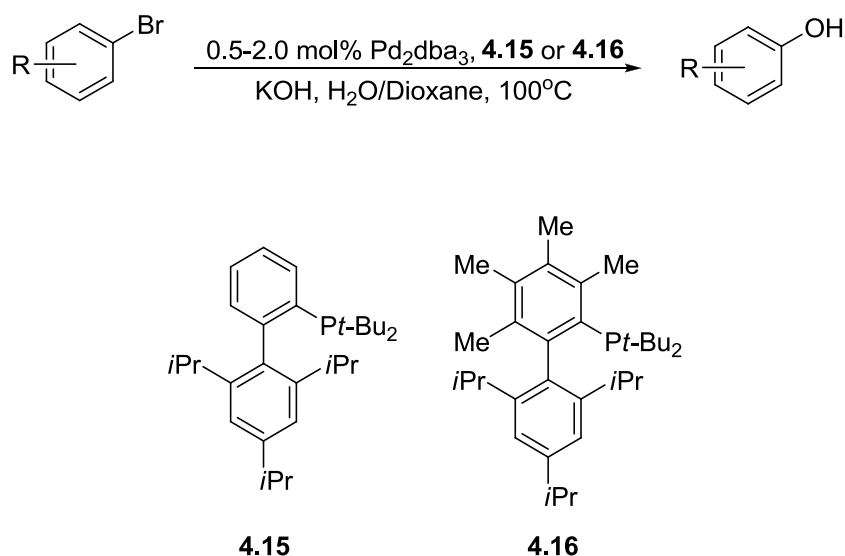
Entry	Reaction Conditions	% Yield ^b
1	Eaton's reagent	32
2	(COCl) ₂ , AlCl ₃ , DMF	42
3	PPA	64
4	PPA, Toluene	25
5	PPA, CH ₂ Cl ₂	50

^aReagents and conditions: **Entry 1:** Acid (0.26 mmol, 1.0 eq), oxalyl chloride (0.4 mmol, 1.5 eq), AlCl₃ (0.83 mmol, 3.2 eq), DMF (cat.), CH₂Cl₂, 0 °C; **Entry 2:** Acid (0.26 mmol, 1.0 eq), Eaton's reagent (2 mL); **Entry 3:** Acid (0.26 mmol, 1.0 eq), PPA (1.0 g), 90 °C; **Entry 4:** Acid (2.5 mmol, 1.0 eq), PPA (2.0 g), toluene (10 mL), 90 °C; **Entry 5:** Acid (0.4 mmol, 1.0 eq), PPA (0.5 g), CH₂Cl₂ (1 mL), 90 °C. ^bIsolated yields.

In the previous syntheses, formation of the tetrahydroquinolone ring using an electrophilic ring cyclisation was unsuccessful, which was attributed to the proximity of an oxygen atom. In this case, the absence of a heteroatom in the side chain permits the use of Eaton's reagent,

PPA and $(\text{COCl})_2$ with AlCl_3 , leading to the formation of **4.10** in all cases (Table 4.3). The cyclisation using Eaton's reagent or under Friedel-Crafts conditions proceeded in low yields (entries 1 and 2), whilst the cyclisation with PPA gave the tetrahydroquinolone in 64% yield (entry 3). In an attempt to produce a more homogenous reaction mixture, the cyclisation was attempted in various solvents. The yield obtained in toluene was very low (entry 4), which was due to the formation of a significant level of side product (as observed by ^1H NMR). On the other hand, the reaction performed in CH_2Cl_2 did not lead to any improvement in yield (entry 3 vs 5).

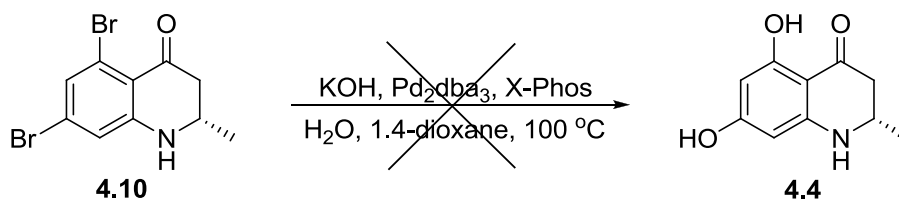
With the cyclised product in hand, we investigated the formation of **4.4** by the substitution of the bromides in a hydroalkoxylation reaction. Previously, Anderson *et al.* have demonstrated the conversion of aryl bromides to phenols using Pd_2dba_3 and a bulky phosphine ligands, such as $t\text{-Bu-X-Phos}$ **4.15** or tetramethyl di- $t\text{-Bu-X-Phos}$ **4.16** (Scheme 4.10). A range of different Ar-Br and Ar-Cl were found to undergo the reaction with KOH to give the phenol derivatives in 79-99% yield.¹⁶¹



Scheme 4.10: Synthesis of phenols.

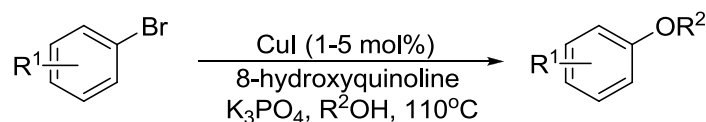
Formation of the desired tetrahydroquinolone **4.4** from **4.10** was attempted using the described conditions (Scheme 4.11). The tetrahydroquinolone **4.10** was reacted with KOH, using a catalyst generated *in situ* from Pd_2dba_3 (5 mol%) and X-Phos, at 100 °C for 16 hours. However, none of the desired **4.4** was obtained, and only the starting material was recovered from the reaction mixture. Upon the addition of the X-Phos to the solution of **4.10**, KOH and Pd_2dba_3 , the reaction turned black, which suggested catalyst deactivation. To prevent this, the

catalytic complex was pre-formed, prior to addition to the tetrahydroquinolone. Unfortunately, no improvement was observed, and the starting material was again recovered.



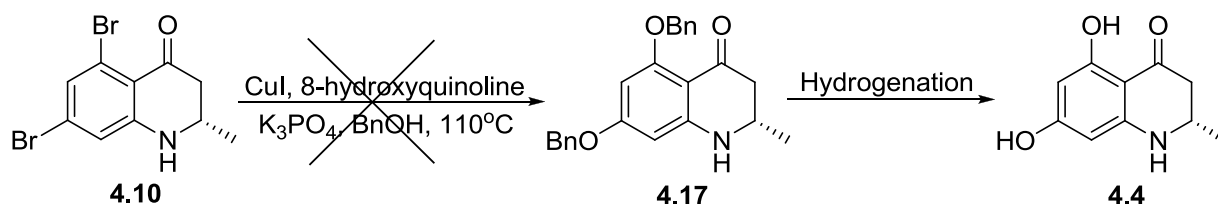
Scheme 4.11: Hydroalkoxylation reaction of **4.10**.

Surveying the literature, there are several other examples of cross coupling reactions with aryl bromides and aliphatic alcohols. Niu *et al.* reported the reaction of aryl bromides with a wide range of aliphatic alcohols, catalysed by copper iodide (Scheme 4.12). This reaction proceeded to give the ethers in the good yields of 78-92%. The reaction was tolerant to both electron withdrawing and donating groups on the aryl ring.¹⁶²



Scheme 4.12: Cross coupling of aryl bromides with aliphatic alcohols.

It was envisaged that this copper catalysed reaction could be used to convert the aryl bromide **4.10** into the tetrahydroquinolone **4.4**. Reaction of **4.10** with benzyl alcohol, catalysed by CuI, would produce **4.17**, from which the required tetrahydroquinolone **4.4** could be synthesised by hydrogenation of the benzyl groups (Scheme 4.13).



Scheme 4.13: Postulated formation of **4.4** using a Cu-catalysed coupling reaction.

The reaction of **4.10** with benzyl alcohol, was attempted under the literature conditions, with CuI as catalyst in the presence of an excess of benzyl alcohol (10 eq) without solvent, in a sealed pressure tube at 110 °C. Initial evaluation of the reaction suggested that **4.10** was being consumed. However, removal of the excess benzyl alcohol proved difficult, preventing

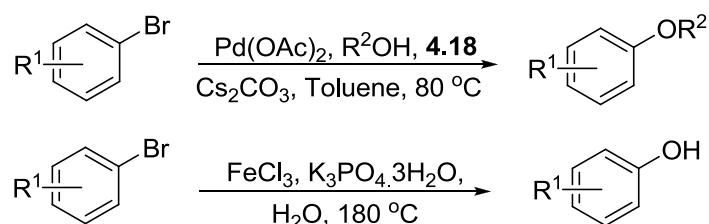
analysis of the reaction mixture. The reaction was subsequently repeated using only 2 equivalents of benzyl alcohol. Unfortunately, the starting material was recovered and time constraints prevented further investigation into this coupling reaction.

In summary, the α , β -unsaturated carbamate **2.21** and the 3, 5-dibromoaniline required were formed in good yields of 79% and 74% respectively. These were subsequently used in the *aza*-Michael reaction, which proceeded to give the desired product in **4.9** 80% conversion and 75% ee after 36 hours. Further optimisation led to an improvement in the enantioselectivity to 85% by the slow addition of the aniline, and optically pure material was obtained by recrystallisation from toluene.

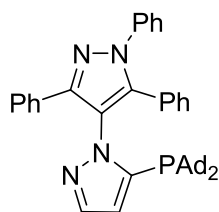
Hydrolysis of the *aza*-Michael adduct using KOH and MeOH proceeded to give the carboxylic acid in 77% yield, and the electrophilic cyclisation to the tetrahydroquinolone **4.10** was achieved in 64% yield using PPA. Two different cross coupling reactions were attempted for the synthesis of the desired intermediate **4.4**. The direct formation of **4.4** by reaction of **4.10** with KOH using a Pd_2dba_3 and X-Phos complex was unsuccessful. Subsequently the coupling with benzyl alcohol, catalysed by CuI was attempted; however, no product was obtained.

4.4 Future work

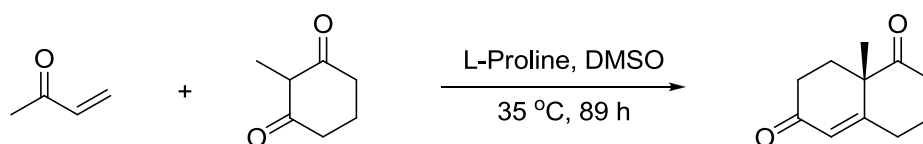
To complete the formal synthesis of levonantradol, further investigation into the CuI, 8-hydroquinoline coupling reaction of **4.10** with benzyl alcohol is required. In addition, a number of other coupling procedures should also be investigated. Gowrisankar *et al.* have reported the coupling of various alcohols with aryl bromides using a complex generated from $\text{Pd}(\text{OAc})_2$ and **4.18** - a bulky phosphine based on a *bis*-pyrazole backbone (Figure 4.2).¹⁶³ Also, the direct conversion of aryl bromides to phenols has been reported using an iron-catalysed reaction (Scheme 1.14).¹⁶⁴



Scheme 4.14: Two coupling reaction of aryl bromides.

**4.18****Figure 4.2:** New ligand used for cross coupling reaction.

Although formation of the third ring system of levonantradol from **4.4** has been reported (Scheme 4.1), the synthetic scheme is long. It would be advantageous if this ring could be synthesised using a more direct route, thereby reducing the overall number of steps in the synthesis. In 2000, Bui *et al.*¹⁶⁵ reported a proline catalysed Robinson annulation reaction, which proceeded to form the bicyclic ring system in a single transformation (Scheme 4.15).^{166, 167} Therefore, the reaction of **4.10** with methyl vinyl ketone in the presence of *L*-proline could allow for the introduction of the third ring, into the C-3, C-4 position in a single step.

**Scheme 4.15:** Robinson annulations reaction.

CHAPTER FIVE

EXPERIMENTAL

5.0 General remarks

Anhydrous acetonitrile and DMF were purchased from Sigma-Aldrich in SureSeal[®] bottles and stored under nitrogen. All other anhydrous solvents were dried in a solvent purification system, by passing through columns of molecular sieves. Commercially available reagents were used as received. Palladium salts and Nickel sponge were provided by Johnson Matthey plc, through a precious metals loan agreement.

All manipulations involving air-sensitive reagents were performed using standard Schlenk techniques and oven dried glassware. Column chromatography was performed on silica gel (Kieselgel 60, 63-200 μ m).

¹H, ¹³C and ³¹P NMR spectra were obtained on Bruker AVACE 400 instruments (¹H at 400 MHz, ¹³C at 100.6 MHz and ³¹P at 161.9 MHz). The chemical shifts (δ) are given in parts per million (ppm), referenced to TMS and the coupling constants (*J*) are reported in Hertz (Hz). Full assignment of resonance signals was aided by relevant 2D NMR experiments, namely, COSY and HMQC.

Infrared spectra were recorded on a Perkin Elmer Spectrum 100 series FT-IR spectrometer fitted with an ATR accessory. Optical rotations were measured on a Perkin Elmer 343 polarimeter using a 10 cm solution cell. [α]_D values are given in 10⁻¹ deg cm² g⁻¹ and concentrations in g per 100 mL. HPLC analyses were performed on a Gilson or a Hewlett Packard series 1050 HPLC system equipped with an autoinjector with a 20 μ L loop, using Daicel Chiralpak AD and AD-H columns or a Hichrom-CHI-PGG-2759 column. Detection was effected by UV absorption at 254 nm.

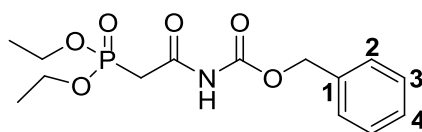
Mass spectra (MS) were recorded on either a Micromass Autospec Premier or a VG Platform II spectrometer using EI, ESI, CI or FAB techniques. Melting points were determined on an Electrothermal Gallenham apparatus and were uncorrected. Elemental analyses were conducted by the Science Technical Support Unit at the London Metropolitan University.

5.1 Compounds used in Chapter 2

General synthesis of phosphonate carbamates.²⁴

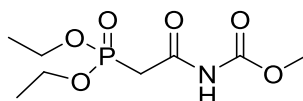
A mixture of the requisite alkyl carbamate (0.40 mol) and chloroacetyl chloride (32.3 mL, 0.40 mol) was heated to 100 °C under a N₂ atmosphere, whereupon the mixture became homogenous and then solidified. Heating was continued for a further 30 min before cooling to room temperature. The solid was placed under vacuum for 30 min to remove volatile side products, and the residue was triturated with Et₂O. The resultant suspension was filtered to obtain an off-white solid. The solid and P(OEt)₃ (15.9 mL, 92.7 mmol) were then combined in a round bottomed flask fitted with an air condenser. The mixture was heated to 80 °C under N₂ until complete consumption of starting material (followed by TLC). The solution was then cooled and hexane added. The clear hexane top layer was decanted and the process repeated 7 times, to remove the excess P(OEt)₃. The remaining residue was purified by recrystallisation from toluene/*n*-hexane to afford the desired phosphonate imide.

Benzyl 2-(diethoxyphosphoryl)acetylcarbamate (2.14b)



The product was obtained as an off white solid (12.4 g, 79%); mp 103-105 °C (lit. 101-102 °C)²⁴; $\nu_{\max}/\text{cm}^{-1}$ 3120, 2980, 1770, 1690, 1210; δ_{H} (400 MHz, CDCl₃) 9.40 (1H, br. s, NH), 7.43-7.28 (5H, m, Ar-H), 5.17 (2H, s, CO₂CH₂), 4.15-4.03 (4H, m, OCH₂CH₃), 3.29 (2H, br. d, *J* 22.1, PCH₂), 1.27 (6H, t, *J* 7.1, CH₃); δ_{C} (100 MHz, CDCl₃) 164.6 (CONH), 151.1 (CO₂), 135.0 (C-1), 128.7 (C-3), 128.6 (C-2/C-4), 128.5 (C2/C4), 67.8 (CO₂CH₂), 63.0 (d, *J* 7, OCH₂CH₃), 36.0 (d, *J* 130, PCH₂), 16.3 (d, *J* 6, CH₃); *m/z* (EI) 329.1031 (*M*⁺, C₁₄H₂₀NO₆P requires 329.1028), 152 (50), 91 (100).

Methyl 2-(diethoxyphosphoryl)acetylcarbamate (2.14a)



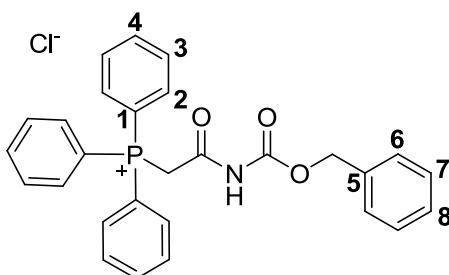
The product was obtained as an off-white solid (84%); mp 46-48°C (lit. 45-47 °C)²⁴; $\nu_{\max}/\text{cm}^{-1}$ 3170, 2995, 1780, 1210; δ_{H} (400 MHz, CDCl₃) 8.38 (1H, br. s, NH), 4.33-4.14 (4H, m, OCH₂), 3.82 (3H, s, OCH₃), 3.37 (2H, d, *J* 21.7, PCH₂), 1.37 (6H, t, *J* 7.1, CH₃CH₂); δ_{C} (100 MHz, CDCl₃) 164.6 (CONH), 151.8 (CO₂), 63.0 (d, *J* 6, OCH₂), 52.9 (OCH₃), 35.9 (d, *J* 130,

PCH₂), 16.3 (d, *J* 6, CH₃CH₂); *m/z* (EI) 253.0724 (*M*⁺, C₈H₁₆NO₆P requires 253.0715), 226 (30), 208 (25), 179 (55), 152 (100), 123 (90).

General Synthesis of Phosphonium Salts

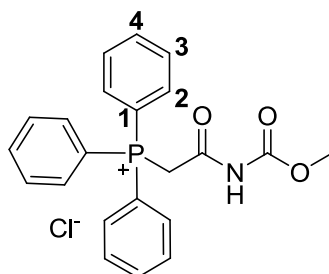
PPh₃ (38.4 g, 0.15 mol) was added to benzyl 2-chloroacetylcarbamate (27.8 g, 0.12 mol) in THF (300 mL). The reaction was heated to reflux until complete consumption of starting material (¹H NMR spectroscopy). The reaction mixture was cooled to room temperature, whereupon the resultant precipitate was collected by filtration.

(2-(Benzyloxycarbonylamino)-2-oxoethyl)triphenylphosphonium chloride (2.19b)



The product was obtained as a white solid (45.5 g, 76%); mp 144-146 °C; $\nu_{\max}/\text{cm}^{-1}$ 2870, 1778, 1437, 1109; δ_{H} (400 MHz, CDCl₃) 12.25 (1H, s, NH), 7.85–7.70 (10H, m, Ar-H), 7.61–7.55 (5H, m, Ar-H), 7.40–7.19 (5H, m, Ar-H), 5.44 (2H, d, *J* 14.0, PCH₂), 5.11 (2H, s, OCH₂Ar); δ_{C} (100 MHz, CDCl₃) 163.0 (CONH), 150.6 (CO₂), 135.1 (C-4), 135.0 (C-5), 134.0 (d, *J* 11, C-3), 130.3 (d, *J* 13, C-2), 128.6 (C-7), 128.4 (C-6), 128.1 (C-8), 117.9 (d, *J* 89, C-1), 67.0 (OCH₂Ar), 33.5 (d, *J* 58, PCH₂); *m/z* (ESI) 454.1568 ([*M*-Cl]⁺, C₂₈H₂₅NO₃P requires 454.1572), 326 (6), 224 (15).

(2-(Methoxycarbonylamino)-2-oxoethyl)triphenylphosphonium chloride (2.19a)



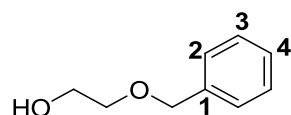
The product was obtained from methyl 2-chloroacetylcarbamate as a white solid (39.0 g, 78%); mp 184-186 °C; $\nu_{\max}/\text{cm}^{-1}$ 3090, 2060, 2890, 3830, 2770, 1780, 1620, 1530, 1440; δ_{H} (400 MHz, CDCl₃) 12.25 (1H, br. s, NH), 7.83-7.70 (9H, m, Ar-H), 7.55-7.65 (6H, m, Ar-H), 5.45 (2H, d, *J* 16.0, PCH₂), 3.62 (3H, s, OCH₃); δ_{C} (100 MHz, CDCl₃) 163.1 (d, *J* 4, CONH),

151.2 (CO₂), 135.1 (C-4), 134.0 (d, *J* 10, C-3), 130.2 (d, *J* 13, C-2), 118.0 (d, *J* 88, C-1), 52.7 (3H, s, OCH₃), 33.4 (d, *J* 58, PCH₂); *m/z* (ESI) 378.1253 ([M-Cl]⁺, C₂₂H₂₁NO₃P requires 378.1259), 326 (4), 303 (6).

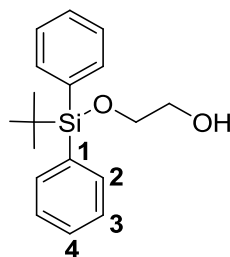
KO^tBu (9.92 g, 88.2 mmol) was added slowly in several portions to a suspension of the phosphonium salt (44.1 mmol) in THF (150 mL) at -5 °C, whereupon the phosphonium salt gradually dissolved. The resultant homogeneous reaction mixture was stirred for 1 hour and CH₂Cl₂ (300 mL) and H₂O (150 mL) then added. The aqueous layer was extracted with CH₂Cl₂ (200 mL) and the combined organic extracts were dried over MgSO₄ and concentrated under vacuum. The phosphonium ylids were used directly in the Wittig olefination reactions without further purification.

Synthesis of protected aldehydes

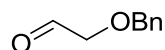
2-(Benzyloxy)ethanol (2.9)⁸⁷



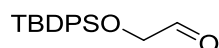
Ethylene glycol (30.0 mL, 0.54 mol) was added under N₂ to a slurry of sodium hydride (4.40 g, 0.19 mol) in dry THF (500 mL) slowly over 1.5 h. Upon complete addition, the mixture was heated to reflux and benzyl bromide (21.3 mL, 0.18 mol) was added over 3 h. After refluxing for 16 h, the reaction mixture was allowed to cool to room temperature and diluted with Et₂O (250 mL). The organic layer was washed with H₂O (200 mL), dried over MgSO₄, and concentrated. The resulting oily residue was distilled at 110 °C, 0.2 torr (lit. 82-83°C, 0.1 torr)¹⁶⁸ to give the alcohol as a colourless oil (22.7 g, 83%). *v*_{max}/cm⁻¹ 3364, 2941, 2870; *δ*_H (400 MHz, CDCl₃) 7.43-7.40 (5H, m, Ar-H), 4.58 (2H, s, ArCH₂), 3.77 (2H, t, *J* 5.0, HOCH₂), 3.61 (2H, t, *J* 5.0, OCH₂), 2.29 (1H, br. s, CH₂OH); *δ*_C (100 MHz, CDCl₃) 138.0 (C-1), 128.5 (C-3), 127.9 (C-2/C-4), 127.8 (C2/C4), 73.3 (CH₂O), 71.5 (HOCH₂), 61.8 (CH₂Ar); *m/z* (EI) 152 (M⁺, 30%), 107 (32), 91 (100).

2-(2,2-dimethyl-1,1-diphenylpropoxy)ethanol (2.10)⁸⁸

tert-Butylchlorodiphenylsilane (10.0 mL, 38.5 mmol) was added to a mixture of ethylene glycol (12.0 mL, 0.23 mol) and imidazole (2.88g, 42.4 mmol) in THF (200 mL). The reaction mixture was stirred for 29 h before quenching, by the addition of H₂O (200 mL) and Et₂O (200 mL). The aqueous layer was extracted with Et₂O (3 x 200 mL) and the combined organic extracts were dried over MgSO₄ and concentrated under vacuum. The resulting oil was purified by column chromatography, EtOAc/*n*-pentane 4:1, *R_f* = 0.35, to give the alcohol (9.08 g, 78%) as a yellow oil. $\nu_{\text{max}}/\text{cm}^{-1}$ 3330 br, 2960, 2860, 1100, 1060; δ_{H} (400 MHz, CDCl₃) 7.77- 7.65 (4H, m, Ar-H), 7.53-7.37 (6H, m, Ar-H), 3.80 (2H, dd, *J* 4.0, 5.6, OCH₂), 3.75- 3.68 (2H, br. m, CH₂OH), 2.21 (1H, br. s, OH), 1.11 (9H, s, C(CH₃)₃); δ_{C} (100 MHz, CDCl₃) 135.6 (C-2), 133.3 (C-1), 129.8 (C-4), 127.8 (C-3), 65.0 (CH₂), 63.7 (CH₂OH), 26.9 (C(CH₃)₃), 19.2 (C(CH₃)₃); *m/z* (EI) 300 (M⁺, <1%), 243 (70), 199 (100), 181 (23), 165 (98).

2-(Benzyloxy)acetaldehyde (2.11)⁸⁷

Under a N₂ atmosphere, DMSO (29.5 mL, 0.42 mol) was added to a solution of oxalyl chloride (18.1 mL, 0.21 mol) in CH₂Cl₂ (600 mL) over 20 min, at -78°C. The reaction was stirred for 10 min, followed by the addition of the alcohol **2.9** (21.0 g, 0.14 mol) in CH₂Cl₂ (10 mL) over 10 min. After stirring for a further 30 min, NEt₃ (91 mL, 0.65 mol) was added over 20 min. The reaction was allowed to warm to room temperature, diluted with Et₂O (600 mL) and filtered through a pad of MgSO₄. The filtrate was concentrated under vacuum to yield the aldehyde **2.11** as a yellow oil. This was employed in the next step without purification.

2-(tert-butyldiphenylsilyloxy)acetaldehyde (2.12)⁸⁸

Under a N₂ atmosphere, DMSO (2.3 mL, 31.9 mmol) was added to a solution of oxalyl chloride (1.4 mL, 15.9 mmol) in CH₂Cl₂ (54 mL) at -78°C. When the addition was complete, alcohol **2.10** (4.0 g, 13.3 mmol) was added as a solution in CH₂Cl₂ (6 mL). After stirring for 20 min, NEt₃ (10 mL, 66.5 mmol) was slowly added. The reaction was allowed to warm to room temperature and the solvent removed under vacuum. The resulting slurry was triturated with EtOAc/*n*-hexane 1:4, and then filtered. The filtrate was evaporated under reduced pressure to yield the aldehyde as a yellow oil. This was employed in the next step without purification.

General methods for the synthesis of the Michael acceptors

Method A: (HWE reaction) DBU (1.0 eq) was added to a solution of the phosphonate carbamate (1.1 eq) in THF (10 mL), followed by the aldehyde (1.1 eq). The reaction was stirred for 18 h, before the mixture was diluted with EtOAc (20 mL) and H₂O (20 mL). The aqueous layer was separated, washed with EtOAc and the combined organic layers dried over MgSO₄, filtered, and concentrated under vacuum.

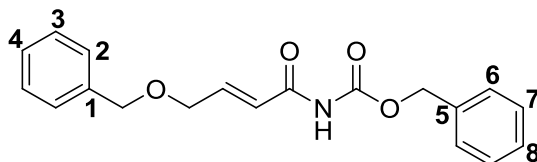
Method B: (Masamune-Roush HWE reaction) To a solution of aldehyde (1.1 eq) in MeCN (10 mL), was added the phosphonate carbamate (1.3 eq), LiCl (7.5 eq) and ⁱPr₂NEt (1.0 eq). The mixture was stirred for 16 h and then quenched with H₂O. The aqueous layer was extracted with EtOAc and the combined organic extracts washed with brine, dried over MgSO₄ and concentrated under vacuum.

Method C: (Wittig reaction) A solution of the ylid (1.0 eq) in CH₂Cl₂ (10 mL) was added to aldehyde (1.0 eq). The solution was stirred for 16 h, before it was concentrated under vacuum to give the alkene as mixture of *E* and *Z* isomers, which were separable by column chromatography.

Method D: (Tandem DMP-Wittig reaction) To a solution of the alcohol **2.9** (10.0 g, 66.0 mmol) dissolved in CH₂Cl₂ (150 mL) was added pyridine (15.0 mL, 185 mmol) and DMP

(28.0 g, 66.0 mmol). The reaction was stirred at 15 °C for 2 h, before a solution of the ylid **2.20a** (37.4 g, 99.0 mmol) in CH₂Cl₂ (150 mL) was added. On complete consumption of the starting material (¹H NMR spectroscopy) the CH₂Cl₂ was removed by evaporation.

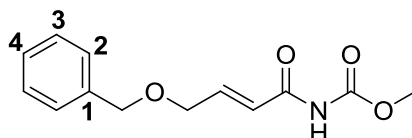
(E)-Benzyl 4-(benzyloxy) but-2-enoylcarbamate (2.15)



The residue was purified by column chromatography, EtOAc/*n*-hexane 3:2, *R_f* = 0.30, to give the alkene as a white solid. Major *E* isomer; mp 98-100 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ 3260, 1747, 1650, 1510; δ_{H} (400 MHz, CDCl₃) 7.76 (1H, br. s, NH), 7.44-7.29 (10H, m, Ar-H), 7.15 (1H, dt, *J* 3.9, 15.5, CH₂CH), 7.06 (1H, br. d, *J* 15.5, CHCO), 5.22 (2H, s, CO₂CH₂), 4.60 (2H, s, OCH₂Ar), 4.23 (2H, dd, *J* 1.6, 3.9, CH₂CH); δ_{C} (100 MHz, CDCl₃) 165.3 (CONH), 151.4 (CO₂), 146.1 (CH₂CH), 137.7 (C-1), 135.0 (C-5), 128.7 (C-7/C-3), 128.6 (C-7/C-3), 128.5 (C-4), 128.4 (C-8), 127.9 (C-2), 127.8 (C-6), 121.2 (CHCO), 72.8 (OCH₂Ar), 68.8 (CH₂CH), 67.9 (COOCH₂); *m/z* (ESI) 326.1387 (MH⁺, C₁₉H₂₀NO₄ requires 326.1392), 243 (78), 91 (100).

Minor *Z* isomer; *R_f* = 0.35; mp 72-74 °C; δ_{H} (400 MHz, CDCl₃) 8.26 (1H, br. s, NH), 7.50-7.26 (10H, m, Ar-H), 6.73 (1H, br. d, *J* 11.7, CHCO), 6.60 (1H, dt, *J* 4.5, 11.7, CH₂CH), 5.22 (2H, s, CO₂CH₂), 4.67 (2H, dd, *J* 2.2, 4.5, CH₂CH), 4.57 (2H, s, OCH₂Ar); δ_{C} (100 MHz, CDCl₃) 165.6 (CONH), 151.6 (CO₂), 150.5 (CH₂CH), 137.9 (C-1), 135.0 (C-5), 129.6 (C-7/C-3), 128.7 (C-7/C-3), 128.5 (C-4), 128.4 (C-8), 127.9 (C-2), 127.8 (C-6), 119.5 (CHCO), 72.9 (OCH₂Ar), 69.3 (CH₂CH), 67.9 (CO₂CH₂).

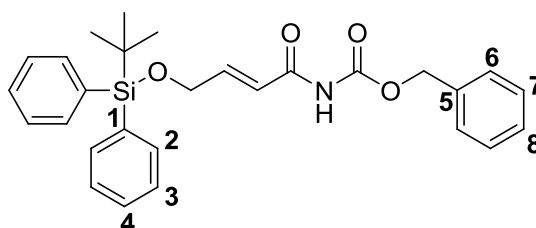
(E)-Methyl 4-(benzyloxy)but-2-enoylcarbamate (2.16)



Synthesised using method D. The residue was purified by column chromatography, EtOAc/*n*-hexane 3:2, *R_f* = 0.28, to give the alkene as a white solid (12.2 g, 74%); mp 83-85 °C;

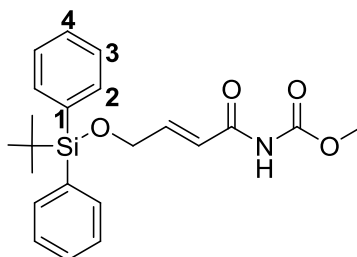
$\nu_{\max}/\text{cm}^{-1}$ 3250, 1770, 1650, 1200; δ_{H} (400 MHz, CDCl_3) 8.66 (1H, s, NH), 7.39-7.25 (5H, m, Ar-H), 7.14 (1H, dt, J 4.2, 15.4, CH_2CH), 7.01 (1H, br. d, J 15.4, CHCO), 4.57 (2H, s, OCH_2Ar), 4.21 (2H, dd, J 1.8, 4.2, CH_2CH), 3.77 (3H, s, OCH_3); δ_{C} (100 MHz, CDCl_3) 165.8 (CONH), 152.2 (CO_2), 145.9 (CH_2CH), 137.7 (C-1), 128.5 (C-3), 127.8 (C-4), 127.7 (C-2), 121.5 (CHCO), 72.8 (OCH_2Ar), 68.8 (OCH_2CH), 53.1 (OCH_3); m/z (ESI) 250.1078 (MH^+ , $\text{C}_{13}\text{H}_{16}\text{NO}_4$ requires 250.1079), 158 (38), 143 (78), 91 (100).

(E)-Benzyl 4-(tert-butyldiphenylsilyloxy)but-2-enoylcarbamate (2.17)



The residue was purified by recrystallisation from EtOAc/*n*-hexane to give the alkene as a white solid: mp 93-95 °C; $\nu_{\max}/\text{cm}^{-1}$ 3261, 1750, 1655, 1216; δ_{H} (400MHz, CDCl_3) 7.79-7.65 (5H, m, Ar-H and NH), 7.52-7.35 (11H, m, Ar-H), 7.23 (1H, d, J 15.2, CHCO), 7.17 (1H, br. d, J 15.2, CH_2CH), 5.25 (2H, s, OCH_2Ar), 4.45-4.40 (2H, m, OCH_2CH), 1.13 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 165.6 (CONH), 151.4 (CO_2), 148.8 (CH_2CH), 135.5 (C-2), 135.1 (C-5), 133.0 (C-1), 130.1 (C-4), 128.7 (C-7/C-8), 128.6 (C-7/C-8), 128.4 (C-6), 127.8 (C-3), 119.8 (CHCO), 67.9 (OCH_2Ar), 63.3 (OCH_2CH), 26.7 ($\text{C}(\text{CH}_3)_3$), 19.3 ($\text{C}(\text{CH}_3)_3$); m/z (EI) 473.2026 (M^+ , $\text{C}_{28}\text{H}_{31}\text{NO}_4\text{Si}$ requires 473.2022), 256 (4), 199 (100).

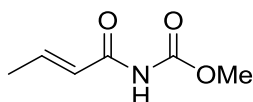
(E)-methyl 4-(tert-butyldiphenylsilyloxy)but-2-enoylcarbamate (2.18)



The residue was purified by recrystallisation from EtOAc/*n*-hexane to give the alkene as a white solid; mp 134-136 °C; $\nu_{\max}/\text{cm}^{-1}$ 3169, 1746, 1655, 1540, 1230; δ_{H} (400MHz; CDCl_3) 7.69 (4H, dd, J 1.3, 7.7, Ar-H), 7.62 (1H, br. s, NH), 7.51-7.36 (6H, m, Ar-H), 7.23 (1H, d, J 15.2, CHCO), 7.16 (1H, dt, J 2.7, 15.2, CH_2CH), 4.45-4.38 (2H, m, OCH_2CH), 3.83 (3H, s, OCH_3), 1.12 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 165.8 (CONH), 152.2 (CO_2), 148.9

(CHCO), 135.5 (C-2), 132.9 (C-1), 129.9 (C-4), 127.8 (C-3), 119.7 (CH₂CH), 63.2 (OCH₂), 53.1 (OCH₃), 26.7 (C(CH₃)₃), 19.3 (C(CH₃)₃); *m/z* (ESI) 398.1790 (MH⁺, C₂₂H₂₈NO₄Si requires 398.1788), 256 (10) 199 (100).

(*E*)-Methyl but-2-enoylcarbamate (2.21)⁸¹



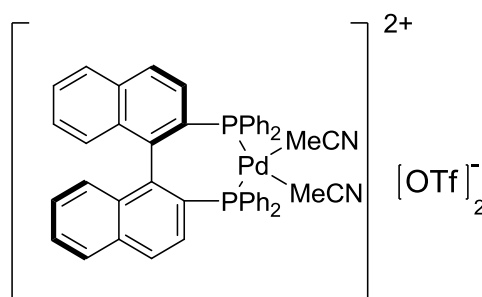
To a solution of the phosphonate carbamate **2.14a** (5.00 g, 20.0 mmol) in THF (20 mL), cooled in a water bath, was added acetaldehyde (5.60 mL, 100 mmol) and DBU (3.00 mL, 20.0 mmol). The reaction mixture was stirred for 16 h, then diluted with EtOAc (50 mL) and H₂O (50 mL). The aqueous layer was separated and washed with EtOAc (2 x 50 mL) and the combined organic extracts washed with brine, dried over MgSO₄, filtered and evaporated to dryness. The residue was purified by column chromatography, EtOAc/*n*-hexane 1:1, *R_f* = 0.5, to give the alkene as a white solid (1.67 g, 59%); mp 147-149 °C (lit. 149-150 °C)²⁴; *v*_{max}/cm⁻¹ 3270, 3070, 3030, 2980, 1770, 1680, 1640, 1500; *δ*_H (400 MHz, CDCl₃) 7.60 (1H, br. s, NH), 7.18 (1H, dq, *J* 6.9, 15.2, CH₃CH), 6.87 (1H, dd, *J* 1.5, 15.2, CHCO), 3.81 (3H, s, OCH₃), 1.97 (3H, dd, *J* 1.5, 6.9, CH₃CH); *δ*_C (100 MHz, CDCl₃) 165.8 (CONH), 152.3 (CO₂), 146.8 (CH₃CH), 122.7 (CHCO), 53.1 (OCH₃), 18.5 (CH₃CH); *m/z* (EI) 143.0580 (M⁺, C₆H₉NO₃ requires 143.0582), 69 (100), 41 (66).

Catalyst synthesis

Palladium triflate dihydrate⁹⁷

A Schlenk tube was charged with Pd(NO₃)₂·2H₂O (2.50 g, 10.8 mmol), which was dried under vacuum overnight. The Schlenk tube was attached to an aq. K₂CO₃ bubbler and purged with N₂. Triflic acid (13.3 mL, 0.15 mol) was added drop wise and the resultant mixture was stirred for a further 2 h under a stream of N₂. The slurry was transferred to boiling tubes and the excess triflic acid was decanted off after centrifuge. The residue was dried in the dessicator at 100 °C for 16 h to give Pd(OTf)₂·2H₂O (4.00 g, 84%) as a light purple powder.

$[(R\text{-BINAP})\text{Pd}(\text{NCMe})_2]^{2+} [\text{TfO}]_2$ (1.117)⁶⁷



To $\text{Pd}(\text{OTf})_2 \cdot 2\text{H}_2\text{O}$ (2.90 g, 6.70 mmol) in a N_2 -purged Schlenk tube was added dry MeCN (60 mL). (*R*)-BINAP (4.15 g, 6.70 mmol) was added and the resultant orange solution was stirred for 30 min and filtered through celite. EtOH (~ 400 mL) was added and the resultant precipitate was collected by filtration to give the complex as a yellow solid (6.32 g, 89%). $\nu_{\text{max}}/\text{cm}^{-1}$ 3350, 3070, 2290, 1440, 1250, 1230, 1170; δ_{H} (400MHz; CDCl_3) 8.03-7.75 (7H, m, Ar-H), 7.73-7.47 (15H, m, Ar-H), 7.21 (2H, t, J 7.2, Ar-H), 7.02 (2H, t, J 7.3, Ar-H), 6.90 (4H, br. s, Ar-H), 6.73 (2H, d, J 8.6, Ar-H), 1.97 (3H, s, CH_3); δ_{C} (100 MHz, CDCl_3) 139.7, 135.0, 134.9, 134.8, 133.0, 132.9, 132.18, 132.13, 130.5, 130.4, 129.5, 129.3, 129.2, 128.5, 127.8, 127.7, 127.0, 124.6, 124.0, 122.9, 122.2, 122.0, 121.2, 118.9, 118.9, 118.3, 2.33; δ_{P} (162 MHz, CDCl_3) + 32.0 (s); m/z (FAB) 877 ($\text{C}_{45}\text{H}_{32}\text{F}_3\text{O}_3\text{P}_2\text{PdS}^+$), (56), 728 (37), 437 (100), 154 (48).

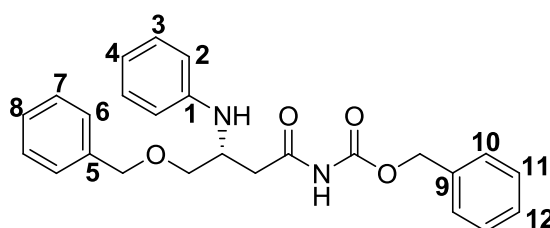
General methods for the Aza-Michael reaction

Method A: A Radley's reaction tube was charged with a stir bar and $[(R\text{-BINAP})\text{Pd}(\text{NCMe})_2]^{2+} [\text{TfO}]_2$, placed under vacuum for 30 min and then flushed with N_2 . Toluene was added, the reaction tube placed in a carousel and heated to 50 °C. On reaching temperature, the Michael acceptor and aniline were added. Upon completion (^1H NMR spectroscopy), the reaction mixture was evaporated to dryness and the residue was purified by column chromatography.

Method B: (Ligand Screening) A Radley's reaction tube was purged with N_2 and charged with $\text{Pd}(\text{OTf})_2 \cdot 2\text{H}_2\text{O}$ (5 mol%), the appropriate ligand (5.5 mol%), and a stir bar. The Radley's tube was re-purged with N_2 before the addition of dry toluene. The reaction tube was placed in the carousel, stirred for 45 min and then heated to 50 °C. The Michael acceptor and aniline were added. Upon completion (^1H NMR spectroscopy), the reaction mixture was evaporated to dryness and the residue purified by column chromatography.

Method C: (Slow addition) A round bottom flask was charged with [(*R*-BINAP)Pd(NCMe)₂]²⁺ [TfO⁻]₂ (0.35 g, 0.33 mmol) and the Michael acceptor (6.58 mmol). Dry toluene (20 mL) was added and the mixture was heated to 50 °C. Once a clear solution was obtained, a solution of aniline (0.6 mL, 6.58 mmol) in toluene (15 mL) was added slowly using a syringe pump, over 20 h. The reaction mixture was stirred at 50 °C for an additional 18 h, cooled to room temperature and concentrated under vacuum. The residue was purified by column chromatography.

Benzyl 4-(benzyloxy)-3-(phenylamino)butanoylcarbamate (2.23)



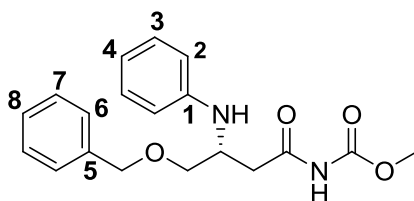
Using method C, the product was obtained as a brown oil (96%); [α]_D²⁵ + 3.5° (*c* = 1.3, CH₂Cl₂, 85% ee); Daicel Chiralpak AD-H, 10 % IPA in *n*-hexane, 1.0 mL/min, *t*_R(major) = 28.7 min, *t*_R(minor) = 33.9 min; Column chromatography, Et₂O/*n*-pentane 1:1, *R*_f = 0.38; $\nu_{\text{max}}/\text{cm}^{-1}$ 3380, 3280, 1750, 1660, 1210; δ_{H} (400MHz, CDCl₃) 7.90 (1H, br. s, NHCO), 7.45-7.29 (10H, m, Ar-H), 7.19 (2H, dd, *J* 7.3, 7.8, H-3), 6.76 (1H, t, *J* 7.3, H-4), 6.66 (2H, d, *J* 7.8, H-2), 5.19 (2H, s, CO₂CH₂), 4.54 (2H, s, OCH₂Ar), 4.16 (2H, br. s, ArNH and CH), 3.71-3.57 (2H, m, OCH₂CH), 3.18-3.00 (2H, m, CHCH₂CO); δ_{C} (100 MHz, CDCl₃) 172.3 (CONH), 151.3 (CO₂), 146.5 (C-1), 137.9 (Ar-C), 134.9 (Ar-C), 129.4 (C-3), 128.7 (Ar-C), 128.5 (Ar-C), 128.48 (Ar-C), 128.45 (Ar-C), 127.8 (Ar-C), 127.7 (Ar-C), 118.3 (C-4), 114.1 (C-2), 73.3 (OCH₂Ar), 70.9 (OCH₂CH), 67.9 (CO₂CH₂), 50.0 (CH), 37.9 (CHCH₂CO); *m/z* (EI) 418.1898 (M⁺, C₂₅H₂₆N₂O₄ requires 418.1893), 310 (35), 297 (100), 189 (89), 146 (92), 104 (82), 77 (75); Anal. Calcd. for C₂₅H₂₆N₂O₄: C, 71.75; H, 6.26; N, 6.69%. Found: C, 71.71; H, 6.16; N, 6.79%.

General procedure for optical enrichment by recrystallisation:

A sample of optically active **2.24** (4.12 g, 84% ee) was suspended in EtOAc (6 mL) and heated to reflux. Hexane was then added drop wise until the solution just started to turn cloudy (~ 18 mL). The mixture was cooled to room temperature, whereupon white needle like crystals were formed, and collected by filtration (2.05 g, 70% ee). The filtrate was

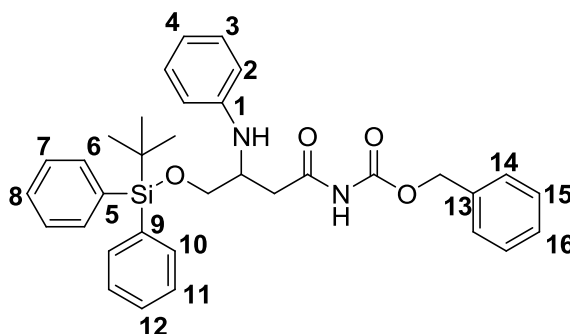
evaporated to give optically enrich material (2.04 g, 99% ee). This process was repeated with the less optically pure product until the enantioselectivity of the recrystallised solid reached 27%. The *aza*-Michael product can be recovered in 77% yield in 99% ee, as a yellow oil.

Methyl 4-(benzyloxy)-3-(phenylamino)butanoylcarbamate (2.24)



Using method C, the product was obtained as a yellow oil (67%); $[\alpha]_D^{25} + 4.2^\circ$ ($c = 1.2$, CHCl_3 , 97% ee); Daicel Chiralpak AD-H, 2% IPA in *n*-hexane, 1.0 mL/min, $t_R(\text{major}) = 22.3$ min, $t_R(\text{minor}) = 25.5$ min; Column chromatography, $\text{Et}_2\text{O}/n\text{-pentane}$ 2:1, $R_f = 0.33$; $\nu_{\text{max}}/\text{cm}^{-1}$ 3260, 3180, 1755, 1600; δ_H (400MHz, CDCl_3) 7.92 (1H, br. s, NHCO), 7.41-7.30 (5H, m, Ar-H), 7.19 (2H, dd, J 7.4, 7.8, H-3), 6.76 (1H, t, J 7.4, H-4), 6.67 (2H, d, J 7.8, H-2), 4.54 (2H, s, OCH_2Ar), 4.09-4.23 (2H, br. m, ArNH and CH), 3.77 (3H, s, OCH_3), 3.59-3.68 (2H, m, OCH_2), 2.99-3.15 (2H, m, CH_2CO); δ_C (100 MHz, CDCl_3) 172.4 (NHCO), 152.0 (CO_2), 145.6 (C-1), 137.9 (C-5), 129.4 (C-3), 128.4 (C-7), 127.8 (C-8), 127.7 (C-6), 118.3 (C-4), 114.1 (C-2), 73.3 (OCH_2Ar), 70.9 (OCH_2CH), 53.0 (OCH_3), 50.1 (CH), 37.9 (CH_2CO); m/z (EI) 342.1581 (M^+ , $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_4$ requires 342.1580), 310 (15), 221 (69), 189 (48), 146 (100), 104 (41), 91 (60).

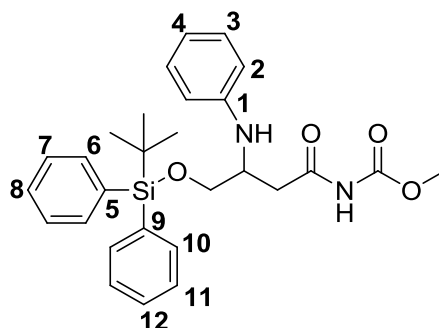
Benzyl 4-(*tert*-butyldiphenylsilyloxy)-3-(phenylamino)butanoylcarbamate (2.25)



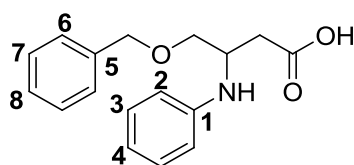
The product was obtained as a yellow oil; Column chromatography, $\text{Et}_2\text{O}/n\text{-pentane}$ 3:2, $R_f = 0.30$; Separation of enantiomers by Chiral HPLC was not possible; $\nu_{\text{max}}/\text{cm}^{-1}$ 2960, 2940, 2870, 1780, 1700, 1610, 1500; δ_H (400MHz; CDCl_3) 7.85 (1H, br. s, CONH), 7.69-7.57 (4H, m, Ar-H), 7.49-7.31 (11H, m, Ar-H), 7.14 (1H, dd, J 7.3, 7.8, H-3), 6.74 (1H, t, J 7.3, H-4),

6.54 (2H, d, J 7.8, H-2), 5.20 (2H, s, OCH₂Ar), 4.17 (1H, br. s, ArNH), 4.06-3.98 (1H, br. m, CH), 3.82 (1H, dd, J 4.8, 10.2, SiOCH₂), 3.77 (1H, dd, J 3.1, 10.2, SiOCH₂), 3.17 (1H, dd, J 6.4, 16.2, CH₂CO₂), 3.08 (1H, dd, J 5.6, 16.2, CH₂CO₂), 1.09 (9H, s, C(CH₃)₃); δ_{C} (100 MHz, CDCl₃) 172.7 (CONH), 151.5 (CO₂), 146.6 (C-1), 135.6 (C-6/C-10), 135.6 (C-6/C-10), 135.4 (Ar-C), 135.0 (Ar-C), 133.1 (C-5/C-9), 133.0 (C-5/C-9), 129.9 (C-8/C-12), 129.8 (C-8/C-12), 129.4 (C-3), 128.7 (Ar-C), 128.5 (Ar-C), 127.9 (C-7/C-11), 127.8 (C-7/C-11), 118.2 (C-4), 114.1 (C-2), 67.8 (OCH₂Ar), 64.5 (SiOCH₂), 51.5 (CH), 37.8 (CH₂CO), 26.9 (C(CH₃)₃), 19.3 (C(CH₃)₃); m/z (ESI) 567.2668 (MH⁺, C₃₄H₃₈N₂O₄Si requires 567.2679), 537 (8), 496 (10).

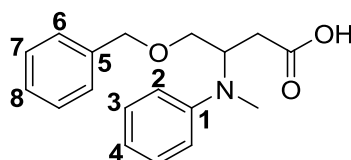
Methyl 4-(*tert*-butyldiphenylsilyloxy)-3-(phenylamino)butanoylcarbamate (2.26)



The product was obtained as a yellow oil; Column chromatography, EtOAc/*n*-hexane 2:3, R_f = 0.34; Separation of enantiomers by Chiral HPLC was not possible; $\nu_{\text{max}}/\text{cm}^{-1}$ 2960, 2940, 2870, 1770, 1700, 1610, 1500, 1210, 1110; δ_{H} (400 MHz, CDCl₃) 8.11 (1H, br. s, NHCO), 7.71-7.60 (4H, m, Ar-H), 7.52-7.33 (6H, m, Ar-H), 7.17 (2H, dd, J 7.3, 7.8, H-3), 6.76 (1H, t, J 7.3, H-4), 6.59 (2H, d, J 7.8, H-2), 4.17 (1H, br. s, ArNH), 3.85 (1H, dd, J 4.9, 10.2, CH), 3.82-3.75 (5H, m, OCH₃ and OCH₂), 3.18 (1H, dd, J 6.6, 16.2, CH₂CO), 3.11 (1H, dd, J 5.6, 16.2, CH₂CO), 1.12 (9H, s, C(CH₃)₃); δ_{C} (100 MHz, CDCl₃) 172.7 (CONH), 152.1 (CO₂), 146.6 (C-1), 135.6 (C-6/C-10), 135.5 (C-6/C-10), 133.1 (C-5/C-9), 133.0 (C-5/C-9), 129.9 (C-8/C-12), 129.8 (C-8/C-12), 129.4 (C-3), 127.8 (C-7/C-11), 127.7 (C-7/C-11), 118.3 (C-4), 114.1 (C-2), 64.5 (OCH₂), 53.0 (OCH₃), 51.6 (CH), 37.8 (CH₂CO), 26.9 (C(CH₃)₃), 19.3 (C(CH₃)₃); m/z 490.2292 (M⁺, C₂₈H₃₄N₂O₄Si requires 490.2288), 433 (25), 340 (27), 316 (92), 221 (90), 146 (100).

4-(Benzyloxy)-3-(phenylamino)butanoic acid (2.29)

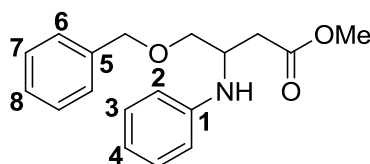
To the carbamate **2.24** (1.00 g, 2.90 mmol) in MeOH (30 mL) was added 1M aq. KOH (29.0 mL, 29.0 mmol). The resultant solution was stirred at room temperature for 1 hour and then the MeOH was removed by evaporation. H₂O (30 mL) was added to the residue and the aqueous layer washed with Et₂O (2 x 30 mL). The aqueous layer was then acidified to pH 4 by the addition of 1M aq. HCl, before it was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine, dried over MgSO₄ and the solvent evaporated to give the acid as a yellow oil (0.58 g, 70%); $\nu_{\text{max}}/\text{cm}^{-1}$ 3400, 3050, 2920, 2850, 1710, 1600, 1500; δ_{H} (400MHz, CDCl₃) 7.45-7.29 (5H, m, Ar-H), 7.22 (2H, dd, *J* 7.4, 8.0, H-3), 6.81 (1H, t, *J* 7.4, H-4), 6.71 (2H, d, *J* 8.0, H-2), 4.55 (2H, s, OCH₂Ar), 4.05-3.96 (1H, m, NHCH), 3.63 (2H, d, *J* 4.0, OCH₂), 2.74 (2H, dd, *J* 2.6, 6.5, CH₂CO); δ_{C} (100 MHz, CDCl₃) 176.1 (CO₂H), 146.0 (C-1), 137.8 (C-5), 129.5 (C-3), 128.5 (C-7), 127.9 (C-8), 127.7 (C-6), 119.1 (C-4), 114.9 (C-2), 73.4 (OCH₂Ar), 70.4 (OCH₂), 50.9 (CHNH), 36.0 (CH₂CO₂), *m/z* (ESI) 286.1432 (MH⁺, C₁₇H₂₀NO₃ requires 286.1443), 268 (10), 198 (8).

4-(Benzyloxy)-3-(methyl(phenyl)amino)butanoic acid (2.30)

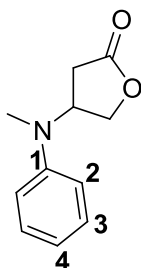
To a solution of the carbamate **2.24** (1.30 g, 3.80 mmol) in MeCN (25 mL) was added formaldehyde (37% w/w solution in H₂O, 2.80 mL, 38.0 mmol). Sodium cyanoborohydride (0.70 g, 11.0 mmol) and acetic acid (0.80 mL, 13.0 mmol) were then added sequentially to the reaction mixture at 0 °C. After 30 min, an additional portion of acetic acid (0.80 mL, 13.0 mmol) was added and the reaction stirred for 1 h. Et₂O (100 mL) was added and the organic layer was washed with 1M aq. KOH (3 x 20 mL), dried over MgSO₄, filtered and evaporated to dryness. 1M aq. KOH (29.0 mL, 29.0 mmol) was added to the residue, and the resultant solution was stirred at room temperature for 1 h before evaporation. H₂O (30 mL) was added to the residue and the aqueous layer was extracted with Et₂O (2 x 30 mL). The aqueous layer was then acidified to pH 4 by the addition of 1M HCl and extracted with EtOAc (3 x 50 mL).

The combined organic extracts were washed with brine, dried over MgSO_4 and the solvent evaporated to give the acid as a yellow oil (0.85 g, 77%); $\nu_{\text{max}}/\text{cm}^{-1}$ 3040, 2870, 1710, 1600, 1510, 1110; δ_{H} (400MHz, CDCl_3) 7.52-7.32 (7H, m, Ar-H), 7.06 (2H, d, J 8.2, C-2), 6.92 (1H, t, J 7.2, C-4), 4.72-4.62 (1H, m, NCH), 4.58 (2H, s, OCH_2Ar), 3.74 (1H, dd, J 6.2, 9.8, OCH_2), 3.65 (1H, dd, J 6.3, 9.8, OCH_2), 2.90 (3H, s, NCH_3), 2.79 (2H, m, CH_2CO_2); δ_{C} (100 MHz, CDCl_3) 177.2 (CO_2H), 150.0 (C-1), 138.1 (C-5), 129.3 (Ar-C), 128.5 (Ar-C), 127.8 (Ar-C), 127.7 (C-3), 118.4 (C-4), 114.8 (C-2), 73.2 (OCH_2Ar), 70.2 (OCH_2), 56.3 (NHCH), 34.9 (CH_2CO_2), 32.1 (NCH_3); m/z (ESI) 300.1596 (MH^+ , $\text{C}_{18}\text{H}_{22}\text{NO}_3$ requires 300.1600), 240 (4), 192 (3).

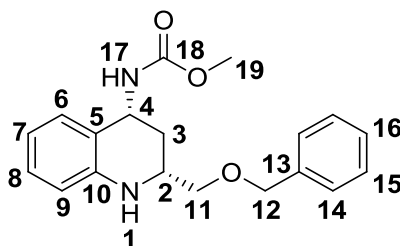
Methyl 4-(benzyloxy)-3-(phenylamino)butanoate (2.35)



CaCl_2 (0.50 g, 4.40 mmol) was added to a solution of the carbamate **2.24** (1.00 g, 3.00 mmol) in MeOH (15 mL). A solution of NaOMe (0.40 g, 7.30 mmol) in MeOH (5 mL) was added drop wise. Upon completion of the reaction (TLC) the MeOH was removed by evaporation, and aq. NH_4Cl (30 mL) was added to the residue. The aqueous layer was washed with Et_2O (3 x 30 mL) and the combined organic layers washed with brine, dried over MgSO_4 , filtered and evaporated to dryness. The crude product was purified by column chromatography, $\text{EtOAc}/n\text{-hexane}$ 1:1, $R_f = 0.32$, to give the ester as a yellow oil (0.52 g, 60%); $\nu_{\text{max}}/\text{cm}^{-1}$ 3050, 3030, 2920, 2850, 1730, 1600, 1510, 1440, 1270; δ_{H} (400MHz, CDCl_3) 7.59-7.30 (5H, m, Ar-H), 7.21 (2H, t, J 7.2, H-3), 6.76 (1H, t, J 7.2, H-4), 6.68 (2H, d, J 7.2, H-2), 4.57 (2H, s, OCH_2Ar), 4.30-4.00 (2H, m, CH and NH), 3.81-3.55 (5H, m, OCH_3 and OCH_2), 2.73 (2H, d, J 6.2, CH_2CO_2); δ_{C} (100 MHz, CDCl_3) 172.4 (CO_2Me), 146.7 (C-1), 138.0 (Ar-C), 129.4 (C-3), 128.5 (Ar-C), 127.8 (Ar-C), 127.7 (Ar-C), 118.0 (C-4), 113.8 (C-2), 73.4 (OCH_2Ar), 70.9 (OCH_2CH), 51.7 (CO_2CH_3), 50.2 (NCH), 36.1 (CH_2CO_2); m/z (EI) 300.1585 (MH^+ , $\text{C}_{18}\text{H}_{22}\text{NO}_3$ requires 300.1600), 250 (5).

4-(Methyl(phenyl)amino)dihydrofuran-2(3H)-one (2.34)

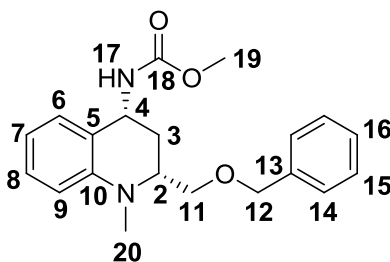
To a suspension of the acid **2.30** (0.10 g, 0.33 mmol) and catalytic DMF in CH_2Cl_2 (2 mL) was added oxalyl chloride (43.0 μl , 0.50 mmol) at 0 °C. The mixture was stirred for 10 min at 0 °C and 1 h at room temperature. The solvent was evaporated to dryness and then the residue re-dissolved in CH_2Cl_2 (2 mL). AlCl_3 (0.13 g, 1.00 mmol) was added to the solution at 0 °C and the resulting mixture stirred at room temperature for 16 h. The reaction mixture was quenched by pouring into an ice- CHCl_3 mixture. The aqueous layer was extracted with CHCl_3 (2 x 10 mL) and the combined organic extracts dried with MgSO_4 and concentrated under vacuum to give the lactone (0.02 g, 31%) as a yellow oil; $\nu_{\text{max}}/\text{cm}^{-1}$ 2933, 1773, 1597; δ_{H} (400 MHz, CDCl_3) 7.39 (1H, m, H-4), 7.34–7.26 (2H, m, H-3), 6.91 (2H, m, H-2), 4.69 (1H, m, CH), 4.54 (1H, dd, J 7.0, 10.0, OCH_2), 4.38 (1H, dd, J 4.0, 10.0, OCH_2), 2.84–2.76 (4H, m, NCH_3 and CH_2CO), 2.63 (1H, dd, J 4.5, 18.0, CH_2CO); δ_{C} (100 MHz, CDCl_3) 175.7 (CO), 149.6 (C-1), 129.3 (C-3), 119.9 (C-4), 116.3 (C-2), 71.1 (CO_2CH_2), 56.2 (NCH), 33.4 (NCH₃), 39.1 (CH_2CO); m/z (EI) 191.0943 (M^+ , $\text{C}_{11}\text{H}_{13}\text{NO}_2$ requires 191.0946), 132 (100).

(2-Benzyloxymethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid methyl ester (2.38)

To a solution of the carbamate **2.24** (6.50 g, 19.0 mmol) dissolved in an ethanol/THF mixture (1:1, 65 mL) was added NaBH_4 (0.50 g, 13.0 mmol) at -10 °C. A solution of $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ (4.00 g, 20.0 mmol) in H_2O (10 mL) was slowly added, maintaining the temperature below 0 °C. When the addition was complete, the reaction was stirred at 0 °C for 30 min., then quenched by addition of CH_2Cl_2 (80 mL), 1M aq. HCl (80 mL) and citric acid (9.00 g, 47.0

mmol). The biphasic mixture was stirred at room temperature for 4 h. The organic layer was separated, before the addition of H₂O (100 mL) and citric acid (5.50 g, 28.0 mmol). The mixture was stirred at room temperature for 45 min. The organic layer was then separated, dried over MgSO₄ and concentrated under vacuum. The volatiles remaining in the residue were displaced by co-distillation with hexane under reduced pressure, to give the 2, 4-disubstituted tetrahydroquinoline as an off-white solid (5.40 g, 87%); $[\alpha]_{\text{D}}^{25} -13.5^\circ$ ($c = 0.7$, CHCl₃); mp 90-92 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ 3370, 3330, 2950, 2940, 2860, 1710, 1520, 1470, 1240, 1090; δ_{H} (400 MHz, CDCl₃) 7.47-7.29 (5H, m, Ar-H), 7.19 (1H, dd, J 1.6, 7.7, H-6), 7.05 (1H, dt, J 1.6, 7.7, H-8), 6.70 (1H, dt, J 1.2, 7.7, H-7), 6.54 (1H, dd, J 1.2, 7.7, H-9), 5.12-5.00 (2H, m, H-4 and H-17), 4.59 (2H, s, H-12), 4.41 (1H, br. s, H-1), 3.78-3.69 (4H, m, H-2 and H-19), 3.57 (1H, dd, J 3.3, 9.1, H-11), 3.40 (1H, t, J 9.1, H-11), 2.29-2.09 (1H, m, H-3), 1.55-1.35 (1H, m, H-3); δ_{C} (100 MHz, CDCl₃) 157.2 (C-18), 144.5 (C-10), 137.9 (C-13), 128.6 (C-15), 128.4 (C-8), 127.9 (C-16), 127.8 (C-14), 126.9 (C-6), 121.8 (C-5), 117.8 (C-7), 114.7 (C-9), 74.0 (C-11), 73.3 (C-12), 52.2 (C-2), 50.4 (C-19), 47.6 (C-4), 32.7 (C-3); m/z (EI) 326.1620 (M^+ , C₁₉H₂₂N₂O₃ requires 326.1630), 205 (7), 143 (8), 130 (100), 91 (20); Anal. Calcd for C₁₉H₂₂N₂O₃: C, 69.92; H, 6.79; N, 8.58%. Found: C, 70.14; H, 6.91; N, 8.68%.

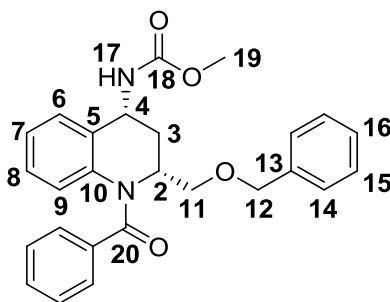
Methyl 2-(benzyloxymethyl)-1-methyl-1,2,3,4-tetrahydroquinolin-4-ylcarbamate (2.39)



A mixture of tetrahydroquinoline **2.38** (6.20 g, 19.0 mmol) and formaldehyde (37% w/w solution in H₂O, 14.2 mL, 0.19 mol) in MeCN (150 mL) was cooled to 5 °C. Sodium cyanoborohydride (3.60 g, 57.0 mmol) was added portion-wise to the solution, followed by glacial acetic acid (3.80 mL, 66.0 mmol), maintaining the temperature below 10 °C. After 30 min an additional portion of glacial acetic acid (3.80 mL, 66.0 mmol) was added. Stirring was continued at 5 °C for another 30 min and Et₂O (400 mL) was added. The organic layer was washed with 1M aq. KOH (3 x 100 mL), dried over MgSO₄, filtered and then evaporated *in vacuo*. The residue was purified by column chromatography, EtOAc/*n*-hexane 1:1.5, $R_f = 0.35$, to afford the product as an off white solid (5.70 g, 88%); $[\alpha]_{\text{D}}^{25} + 10.0^\circ$ ($c = 1.1$,

CHCl₃); mp 90-92°C; $\nu_{\max}/\text{cm}^{-1}$ 3320, 3030, 2920, 1710, 1700, 1520, 1490, 1240, 1210; δ_{H} (400 MHz, CDCl₃) 7.44-7.25 (6H, m, H-6 and Ar-H), 7.21 (1H, m, H-8), 6.72 (1H, t, J 7.3, H-7), 6.65 (1H, d, J 8.2, H-9), 5.63 (1H, br. d, J 7.7, H-17), 4.99-4.85 (1H, m, H-4), 4.53 (2H, s, H-12), 3.85-3.54 (6H, m, H-11, H-2 and H-19), 2.99 (3H, s, H-20), 2.40-2.28 (1H, m, H-3), 2.28-2.16 (1H, m, H-3); δ_{C} (100 MHz, CDCl₃) 156.7 (C-18), 145.9 (C-10), 137.8 (C-13), 128.9 (Ar-C), 128.4 (Ar-C), 127.8 (Ar-C), 127.7 (Ar-C), 127.6 (Ar-C), 122.3 (C-5), 116.4 (C-7), 111.5 (C-9), 73.4 (C-12), 71.3 (C-11), 56.8 (C-2), 51.9 (C-19), 45.9 (C-4), 37.8 (C-20), 32.1 (C-3); m/z (EI) 340.1789 (M^+ , C₂₀H₂₄N₂O₃ requires 340.1787), 219 (19), 187 (6), 144 (100), 91 (15); Anal. Calcd for C₂₀H₂₄N₂O₃: C, 70.56; H, 7.11; N, 8.23%. Found: C, 70.74; H, 6.96; N, 8.16%.

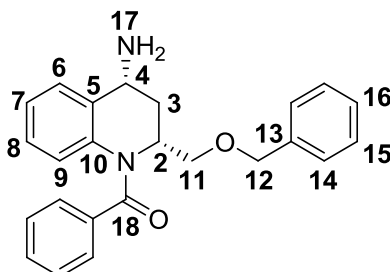
Methyl-1-benzoyl-2-(benzyloxymethyl)-1,2,3,4-tetrahydroquinolin-4-ylcarbamate (2.49)



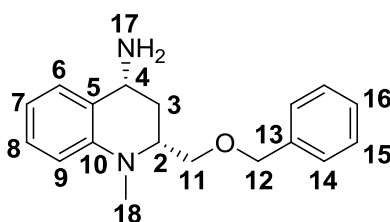
The tetrahydroquinoline **2.38** (0.50 g, 1.50 mmol) was dissolved in Et₂O (10 mL) and cooled to 0 °C, whereupon triethylamine (3.20 mL, 23.0 mmol) and benzoyl chloride (0.20 mL, 1.90 mmol) were added consecutively. The reaction was then allowed to warm to room temperature where it was stirred for 16 h. Additional benzoyl chloride (0.20 mL, 1.90 mmol) was added and after a further 16 h, the reaction was quenched by the addition of 10 % aq. NaOH (30 mL). The organic layer was washed with 10 % aq. HCl (3 x 10 mL), dried over MgSO₄, filtered and evaporated to dryness. The product was purified by column chromatography, EtOAc/*n*-hexane 1:1, R_f = 0.33, to give **2.49** as a brown gum (0.55 g, 84%); $\nu_{\max}/\text{cm}^{-1}$ 2960, 2870, 1720, 1640, 1400, 1360; δ_{H} (400 MHz, CDCl₃) 7.34-7.12 (11H, m, Ar-H), 7.07 (1H, t, J 7.5, H-8), 6.88 (1H, t, J 7.5, H-7), 6.51 (1H, d, J 7.5, H-6), 5.56 (1H, d, J 9.2, H-17), 5.11-5.01 (1H, m, H-2), 5.01-4.90 (1H, m, H-4), 4.55-4.36 (2H, m, H-12), 3.80-3.67 (4H, m, H-19 and H-11), 3.50 (1H, dd, J 6.7, 9.3, H-11), 2.76-2.58 (1H, m, H-3), 1.83-1.72 (1H, m, H-3); δ_{C} (100 MHz, CDCl₃) 169.9 (C-20), 156.8 (C-18), 138.1 (Ar-C), 137.6 (Ar-C), 135.6 (Ar-C), 134.3 (Ar-C), 130.2 (Ar-C), 128.7 (Ar-C), 128.3 (Ar-C), 127.9 (Ar-C), 127.5 (Ar-C), 127.3 (Ar-C), 126.9 (C-7), 126.6 (C-6), 125.3 (C-8), 123.4 (C-9), 73.0 (C-12),

71.6 (C-11), 52.4 (C-19), 50.9 (C-2), 46.8 (C-4), 35.9 (C-3); m/z (ESI) 431.1970 (MH^+ , $C_{26}H_{27}N_2O_4$ requires 431.1971), 356 (15), 296 (8), 250 (9).

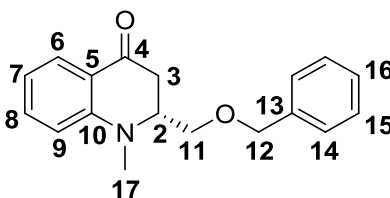
4-Amino-2-(benzyloxymethyl)-3,4-dihydroquinolin-1(2H)-yl(phenyl)methanone (2.50)



To a solution of the Moc-protected tetrahydroquinoline **2.49** (1.80 g, 4.20 mmol) in MeCN (30 mL) was added TMSI (2.30 mL, 17.0 mmol). The resultant solution was stirred at room temperature for 18 h. The reaction was quenched by the addition of MeOH (20 mL), before the solvents were removed by rotary evaporation. Et₂O (30 mL) and 1M aq. HCl (30 mL) were added to the residue and the aqueous layer was separated. The pH was adjusted to 12 by the addition of 1M aq. KOH and the aqueous layer then extracted with CH₂Cl₂ (3 x 60 mL). The combined organic extracts were dried over MgSO₄, filtered, and evaporated to dryness. The amine was purified by column chromatography using EtOAc/*n*-hexane 1:1.5, R_f = 0.2, to give the amine as a brown oil (0.95 g, 61%); ν_{max}/cm^{-1} 3060, 3040, 2920, 2860, 1640, 1490, 1340, 1100; δ_H (400 MHz, CDCl₃) 7.51 (1H, d, J 7.7, H-9), 7.40-7.13 (11H, m, Ar-H), 6.91 (1H, t, J 7.7, H-7), 6.51 (1H, d, J 7.7, H-6), 5.08 (1H, m, H-2), 4.57-4.48 (2H, m, H-12), 4.08 (1H, dd, J 4.7, 12.0, H-4), 3.76 (1H, dd, J 5.0, 9.2, H-11), 3.48 (1H, dd, J 6.8, 9.2, H-11), 2.76-2.65 (1H, m, H-3), 1.98 (2H, br. s, H-17), 1.62 (1H, dt, J 8.0, 12.0, H-3); δ_C (100 MHz, CDCl₃) 169.8 (C-18), 138.3 (Ar-C), 137.9 (Ar-C), 137.6 (Ar-C), 135.8 (Ar-C), 130.0 (Ar-C), 128.6 (Ar-C), 128.3 (Ar-C), 127.9 (Ar-C), 127.5 (Ar-C), 127.4 (Ar-C), 126.5 (C-7 and C-6), 125.5 (C-8), 122.5 (C-9), 73.0 (C-12), 71.9 (C-11), 54.1 (C-2), 47.2 (C-4), 39.6 (C-3); m/z (ESI) 373.1899 (MH^+ , $C_{24}H_{25}N_2O_2$ requires 373.1916), 356 (84), 250 (77).

2-(benzyloxymethyl)-1-methyl-1,2,3,4-tetrahydroquinolin-4-amine (2.40)

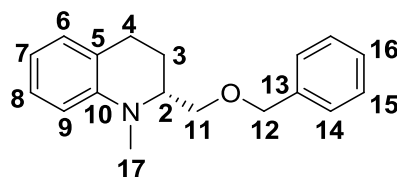
The above procedure was repeated for the deprotection of the tetrahydroquinoline **2.39** (1.00 g, 3.00 mmol) to give the amine as a brown oil (0.65 g, 78%); $\nu_{\max}/\text{cm}^{-1}$ 2920, 1600, 1500, 1450, 1370, 1070; δ_{H} (400 MHz, CDCl_3) 7.38-7.24 (6H, m, H-6 and Ar-H), 7.20 (1H, t, J 7.6, H-8), 6.74 (1H, t, J 7.6, H-7), 6.63 (1H, d, J 7.6, H-9), 4.58 (1H, d, J 11.9, H-12), 4.51 (1H, d, J 11.9, H-12), 4.14 (1H, apparent triplet, J 5.5, H-4), 3.77 (1H, dd, J 4.6, 9.7, H-11), 3.70 (1H, dd, J 5.3, 9.7, H-11), 3.59 (1H, m, H-2), 3.38 (2H, br. s, H-17), 2.98 (3H, s, H-18), 2.33 (1H, dt, J 5.5, 13.7, H-3), 2.08 (1H, dt, J 5.7, 13.7, H-3); δ_{C} (100 MHz, CDCl_3) 145.3 (C-10), 137.9 (C-13), 128.5 (C-6), 128.4 (C-15), 127.9 (C-8), 127.7 (C-16), 127.6 (C-14), 125.4 (C-5), 116.4 (C-7), 111.6 (C-9), 73.3 (C-12), 72.2 (C-11), 57.2 (C-2), 46.6 (C-4), 37.7 (C-18), 34.5 (C-3); m/z (EI) 282.1731 (M^+ , $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}$ requires 282.1732), 265 (5), 161 (55), 144 (100), 91 (32).

2-(Benzyloxymethyl)-1-methyl-2,3-dihydroquinolin-4(1H)-one (2.44)

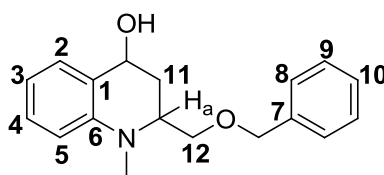
To a solution of the amine **2.40** (2.50 g, 8.80 mmol) in a $\text{CH}_2\text{Cl}_2/\text{DMF}$ mixture (1:1, 50 mL) was added 4-formyl-1-methylpyridinium benzenesulfonate (3.70 g, 13.0 mmol). After stirring for 1 h, DBU (3.90 mL, 26.0 mmol) was added and the resulting dark purple solution was stirred for a further hour at room temperature. The reaction was quenched by the addition of sat. aq. oxalic acid (50 mL) and stirred for 16 h. The biphasic mixture was evaporated to dryness and the residue purified by column chromatography, EtOAc/*n*-hexane 1:1.5, R_f = 0.40, to afford the tetrahydroquinolone as a yellow oil (1.85 g, 75%); $[\alpha]_{\text{D}}^{25}$ – 88.0° (c = 1.0, CHCl_3); $\nu_{\max}/\text{cm}^{-1}$ 2870, 1670, 1600, 1490, 1450, 1350, 1210; δ_{H} (400 MHz, CDCl_3) 7.88 (1H, dd, J 1.7, 7.8, H-6), 7.42 (1H, m, H-8), 7.34-7.24 (5H, m, Ar-H), 6.68 (1H, m, H-7), 6.65 (1H, d, J 8.5, H-9), 4.46 (2H, s, H-12), 3.83 (1H, m, H-2), 3.71 (1H, dd, J 6.6, 9.5, H-11), 3.53 (1H, dd, J 5.9, 9.5, H-11), 3.11 (3H, s, H-17), 3.00 (1H, dd, J 6.6, 16.6, H-3), 2.73

(1H, dd, J 2.4, 16.6, H-3); δ_C (100 MHz, $CDCl_3$) 192.9 (C-4), 150.2 (C-10), 137.8 (Ar-C), 135.8 (C-8), 128.4 (Ar-C), 127.7 (Ar-C), 127.6 (Ar-C), 127.4 (Ar-C), 119.0 (C-5), 116.2 (C-7), 112.8 (C-9), 73.4 (C-12), 68.9 (C-11), 60.6 (C-2), 38.9 (C-3), 38.8 (C-17); m/z (EI) 281.1416 (M^+ , $C_{18}H_{19}NO_2$ requires 281.1416), 174 (12), 160 (100), 91 (20); Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84%; H, 6.81%; N, 4.98%. Found: C, 76.94%; H, 6.66%; N, 4.85%.

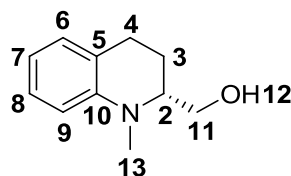
2-(benzyloxymethyl)-1-methyl-1,2,3,4-tetrahydroquinoline (2.43)



Aluminium trichloride (60.0 mg, 0.43 mmol) was suspended in Et_2O (1 mL) and lithium aluminium hydride (30.0 mg, 0.75 mmol) in THF (0.75 mL) was slowly added under vigorous stirring at room temperature. After 20 min a solution of the tetrahydroquinolone **2.44** (60.0 mg, 0.21 mmol) in THF (1 mL) was added at a rate such as to maintain a gentle reflux. The reaction was monitored by TLC. When the reaction was judged to be complete, the mixture was cooled to 0 °C and H_2O (5 mL) and Et_2O (3 mL) were added. The Et_2O layer was decanted and the aqueous layer was washed several times with Et_2O until the washings were colourless. The combined organic extracts were dried over $MgSO_4$, filtered, concentrated and purified by column chromatography, $EtOAc/n$ -hexane 1:1, R_f = 0.45, to give the tetrahydroquinoline as a colourless oil (50.0 mg, 87%); $[\alpha]_D^{25}$ – 4.5° (c = 1.4, CH_2Cl_2); ν_{max}/cm^{-1} 2920, 2850, 1720, 1600, 1500, 1380, 1250; δ_H (400 MHz, $CDCl_3$) 7.43–7.30 (5H, m, Ar-H), 7.13 (1H, t, J 7.6, H-8), 7.00 (1H, d, J 7.6, H-6), 6.64 (1H, t, J 7.6, H-7), 6.58 (1H, d, J 7.6, H-9), 4.60 (1H, d, J 12.0, H-12), 4.52 (1H, d, J 12.0, H-12), 3.65–3.56 (2H, m, H-11 and H-2), 3.53–3.45 (1H, m, H-11), 3.03 (3H, s, H-17), 2.82–2.65 (2H, m, H-4), 2.20–2.11 (1H, m, H-3), 1.97–1.85 (1H, m, H-3); δ_C (100 MHz, $CDCl_3$) 145.1 (C-10), 138.4 (Ar-C), 128.6 (Ar-C), 128.4 (Ar-C), 127.7 (C-6), 127.6 (Ar-C), 127.2 (C-8), 121.7 (C-5), 115.5 (C-7), 110.3 (C-9), 73.4 (C-12), 70.5 (C-11), 58.2 (C-2), 38.3 (C-17), 23.7 (C-4), 22.9 (C-3); m/z (EI) 267.1620 (M^+ , $C_{18}H_{21}NO$ requires 267.1623), 146 (100), 131 (8), 91 (8); Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24%. Found: C, 80.66; H, 8.02; N, 5.26%.

2-(benzyloxymethyl)-1-methyl-1,2,3,4-tetrahydroquinolin-2-ol (2.48)

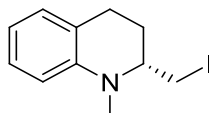
The product was isolated in a 1:1 mixture of diastereoisomers, as a brown oil (25.0 mg, 25%); $\nu_{\max}/\text{cm}^{-1}$ 3410, 3040, 2870, 1600, 1490, 1230, 1030; δ_{H} (400 MHz, CDCl_3) 7.45-7.12 (14H, m, Ar-H), 6.78-6.68 (2H, m, Ar-H), 6.63 (1H, d, J 4.4, H-9), 6.61 (1H, d, J 4.4, H-9), 4.81-4.68 (2H, br. m, H-4), 4.62-4.45 (4H, m, H-12), 3.80 (1H, dd, J 4.7, 10.0, H-2) (isomer one), 3.75 (1H, dd, J 4.2, 10.0, H-2) (isomer two), 3.69-3.41 (4H, m, H-11), 3.0 (3H, s, H-17) (isomer one), 2.98 (3H, s, H-17) (isomer two), 2.37-2.26 (3H, m, H-3), 2.02-1.94 (1H, m, H-3); δ_{C} (100 MHz, CDCl_3) 145.0 (C-10), 144.8 (C-10), 138.1 (Ar-C), 137.6 (Ar-C), 130.1 (Ar-C), 129.2 (Ar-C), 129.0 (Ar-C), 128.5 (Ar-C), 128.47 (Ar-C), 128.43 (Ar-C), 127.7 (Ar-C), 127.6 (Ar-C), 127.05 (Ar-C), 127.01 (Ar-C), 124.7 (C-5), 123.8 (C-5), 166.0 (C-7), 116.0 (C-7), 111.2 (C-9), 110.7 (C-9), 73.4 (C-12), 71.7 (C-2), 71.3 (C-2), 64.6 (C-4), 64.6 (C-4), 56.9 (C-11), 56.4 (C-11), 37.9 (C-17), 37.4 (C-17), 33.5 (C-3), 33.4 (C-3); m/z (EI) 283.1575 (M^+ , $\text{C}_{18}\text{H}_{21}\text{NO}_2$ requires 283.1572), 279 (19), 252 (21), 162 (48), 146 (100), 108 (38), 91 (55).

(1-methyl-1,2,3,4-tetrahydroquinolin-2-yl)methanol (2.1)

The tetrahydroquinoline **2.43** (0.80 g, 3.00 mmol) was dissolved in a mixture of EtOH (7 mL) and THF (8 mL). Ni sponge (4.00 g) was added and the reaction was heated to reflux under a H_2 atmosphere. On completion of the reaction (TLC), the mixture was filtered through celite to remove the catalyst, and the filtrate was evaporated to dryness. Purification by column chromatography, EtOAc/*n*-hexane 1:1, $R_f = 0.4$, gave the alcohol as a colourless oil (0.37 g, 71%); $[\alpha]_{\text{D}}^{25} -16.7^\circ$ ($c = 0.9$, CHCl_3); $\nu_{\max}/\text{cm}^{-1}$ 3370, 2940, 2890, 1600, 1510, 1310, 1220, 1040; δ_{H} (400 MHz, CDCl_3) 7.14 (1H, t, J 7.6, H-8), 7.01 (1H, d, J 7.6, H-6), 6.71-6.62 (2H, m, H-9 and H-7), 3.77-3.67 (2H, m, H-11), 3.44-3.37 (1H, m, H-2), 3.04 (3H, s, H-13), 2.91-2.64 (2H, m, H-4), 2.14-2.05 (1H, m, H-3), 1.97-1.85 (1H, m, H-3), 1.65 (1H, br. s, H-12); δ_{C} (100 MHz, CDCl_3) 145.5 (C-10), 128.7 (C-6), 127.3 (C-8), 122.5 (C-5), 116.2 (C-9), 111.3 (C-7), 63.3 (C-11), 60.1 (C-2), 38.6 (C-13), 24.3 (C-4), 23.0 (C-3); m/z (EI) 177.1154 (M^+ ,

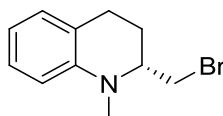
C₁₁H₁₅NO requires 177.1154); Anal. Calcd for C₁₁H₁₅NO: C, 74.54; H, 8.53; N, 7.90%. Found: C, 74.65; H, 8.46; N, 7.80%.

2-(Iodomethyl)-1-methyl-1,2,3,4-tetrahydroquinoline (2.54)¹⁶⁹



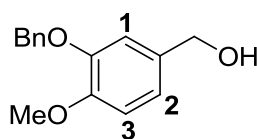
To the alcohol **2.1** (0.25 g, 1.40 mmol) in toluene (2.5 mL) and MeCN (0.5 mL) was added triphenylphosphine (0.93 g, 3.50 mmol) and imidazole (0.24 g, 3.50 mmol). The suspension was cooled to 0 °C and a solution of I₂ (0.72 g, 2.90 mmol) in toluene/MeCN (5:1, 1 mL) added. The reaction was stirred at 0 °C for 1 h and then for an additional 1.5 h at room temperature. The reaction was quenched with sat. aq. Na₂S₂O₃ (10 mL), the organic layer separated and evaporated to dryness. The residue was subjected to column chromatography, EtOAc/*n*-hexane 1:9, *R_f* = 0.33, to give the iodide as an oil, which was used without further purification.

2-(Bromomethyl)-1-methyl-1,2,3,4-tetrahydroquinoline (2.55)¹²⁸



To a mixture of the alcohol **2.1** (0.25 g, 1.40 mmol) and triethylamine (0.39 mL, 2.80 mmol) in THF (7 mL) was added MsCl (0.14 mL, 1.80 mmol) at -40 °C. The reaction was stirred for 2 h at -40 °C, before the addition of LiBr (0.49 g, 5.60 mmol). After 30 min the reaction was warmed to room temperature, over 3 h. The reaction was quenched by the addition of sat. aq. NaHCO₃ (10 mL) and the organic layer separated. The aqueous layer was washed with CH₂Cl₂ (3 x 10 mL) and the combined organic extracts dried over MgSO₄, filtered and evaporated to dryness to give the bromide, which was used without further purification.

(3-(Benzyloxy)-4-methoxyphenyl)methanol (2.67)



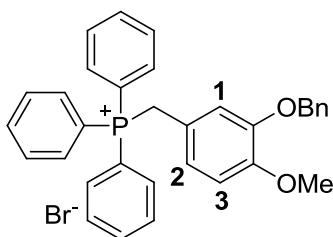
To a mixture of the alcohol **2.66** (0.50 g, 3.20 mmol) and K₂CO₃ (0.67 g, 4.80 mmol) in acetone (30 mL) was added benzyl bromide (0.39 mL, 3.20 mmol). The resultant mixture was

heated to reflux under N_2 for 4 h. The reaction was then cooled to room temperature and stirred overnight. EtOAc (50 mL) and H_2O (50 mL) were added and the aqueous layer extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness to give the product as a white solid (0.56 g, 71%); mp 68-70 °C (lit. 65-66°C)¹⁷⁰; ν_{max}/cm^{-1} 3360, 2940, 2880, 2840, 1590, 1520, 1420, 1260, 1140; δ_H (400 MHz, $CDCl_3$) 7.47 (2H, d, J 7.3, Ar-H), 7.39 (2H, t, J 7.3, Ar-H), 7.36-7.28 (1H, m, Ar-H), 6.95 (1H, s, H-1), 6.92-6.84 (2H, m, H-2 and H-3), 5.14 (2H, s, OCH_2Ar), 4.54 (2H, s, $HOCH_2$), 3.88 (3H, s, OCH_3); δ_C (100 MHz, $CDCl_3$) 149.2 (Ar-C), 148.3 (Ar-C), 137.1 (Ar-C), 133.7 (Ar-C), 128.6 (Ar-C), 127.9 (Ar-C), 127.4 (Ar-C), 120.0 (C-3), 113.1 (C-1), 111.7 (C-2), 70.9 (OCH_2Ar), 65.0 ($HOCH_2$), 56.1 (OCH_3); m/z (EI) 244.1094 (M^+ , $C_{15}H_{16}O_3$ requires 244.1099), 136 (5), 91 (100), 65 (10).

General procedure for the formation of Ylids from benzyl alcohols

To the alcohol (2.00 g, 1.0 eq) in CH_2Cl_2 (30 mL) at -5 °C was added PBr_3 (2.0 eq) drop wise, maintaining the temperature below 0 °C. After 20 min the reaction was allowed to warm to room temperature and then stirred for an additional 2 h. The reaction was quenched by the drop wise addition of sat. aq. $NaHCO_3$ (30 mL) and the aqueous layer extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. The resultant bromide was then dissolved in toluene (30 mL) and triphenylphosphine (1.0 eq) was added. The resultant slurry was heated to reflux for 18 h. The reaction mixture was cooled to room temperature and the solid collected by filtration. The ylids were recrystallised from EtOH.

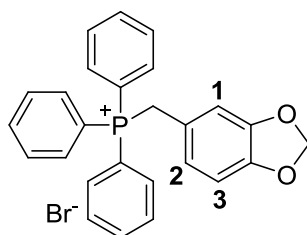
(3-(benzyloxy)-4-methoxybenzyl)triphenylphosphonium bromide (2.70)



The product was obtained as a white solid (4.30 g, 92%); mp 223-225 °C; ν_{max}/cm^{-1} 3030, 2980, 1750, 1520, 1420, 1380, 1240; δ_H (400 MHz, $CDCl_3$) 7.84-7.57 (15H, m, Ar-H), 7.28-7.23 (5H, m, Ar-H), 6.85 (1H, s, H-1), 6.69 (1H, d, J 8.3, H-2), 6.63 (1H, d, J 8.3, H-3), 5.31 (2H, d, J 13.7, CH_2P), 4.77 (2H, s, OCH_2Ar), 3.81 (3H, s, OCH_3); δ_C (100 MHz, $CDCl_3$)

149.6 (Ar-C), 148.1 (Ar-C), 136.7 (Ar-C), 134.9 (Ar-C), 134.5 (d, J 10, Ar-C), 130.1 (d, J 12, Ar-C), 128.4 (Ar-C), 127.8 (Ar-C), 127.6 (Ar-C), 124.5 (d, J 6, C-2), 118.9 (d, J 9, Ar-C), 118.4 (Ar-C), 116.7 (d, J 5, C-1), 111.7 (C-3), 70.7 (OCH₂Ar), 55.9 (OCH₃), 30.3 (CH₂P); m/z (ESI) 489.1968 ([M-Br]⁺, C₃₃H₃₀O₂P requires 489.1983).

(Benzo 1,3 dioxol-5-ylmethyl) triphenylphosphonium bromide (2.68)¹⁷¹



The product was obtained as a white solid (5.90 g, 95%); mp 221-223 °C (lit. 227-229 °C)¹³⁴; $\nu_{\text{max}}/\text{cm}^{-1}$ 2890, 2850, 2780, 1510, 1490, 1440, 1250, 1110; δ_{H} (400 MHz, CDCl₃) 7.83-7.60 (15H, m, Ar-H), 6.65-6.60 (1H, m, H-2), 6.58-6.51 (2H, m, H-1 and H-3), 5.88 (2H, s, OCH₂), 5.31 (2H, d, J 13.9, CH₂P); δ_{C} (100 MHz, CDCl₃) 147.7 (Ar-C), 135.0 (Ar-C), 134.4 (d, J 10, Ar-C), 130.1 (d, J 12, Ar-C), 125.5 (d, J 7, C-2), 120.1 (d, J 9, Ar-C), 117.8 (Ar-C), 111.4 (C-3), 108.6 (C-1), 101.3 (OCH₂), 30.5 (d, J 47, CH₂P); m/z (ESI) 397.1353 ([M-Br]⁺, C₂₆H₂₂O₂P requires 397.1357).

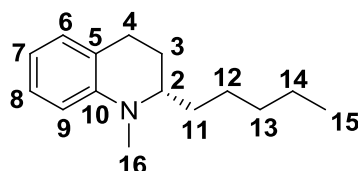
General procedure for the synthesis of the Galipea alkaloids

To a solution of oxalyl chloride (28.0 μL , 0.31 mmol) in CH₂Cl₂ (1 mL) at -78 °C was added DMSO (40.0 μL , 0.56 mmol) in CH₂Cl₂ (0.5 mL), maintaining the temperature below -60 °C. The reaction was stirred at -78 °C for 1 h and the alcohol **2.1** (50.0 mg, 0.28 mmol) in CH₂Cl₂ (0.5 mL) was added drop wise, again maintaining the temperature below -60 °C. The reaction was stirred for a further 1 h, before the addition of triethylamine (0.19 mL, 1.40 mmol). The reaction mixture was allowed to warm to room temperature, whereupon it was quenched by the addition of sat. aq. NH₄Cl (2 mL) and the organic layer washed with addition sat. aq. NH₄Cl (3 x 2 mL). The organic layer was dried over MgSO₄, filtered and evaporated to dryness. The aldehyde was used immediately in the next step without further purification.

To the ylid (0.62 mmol, 2.2 eq) in THF (2 mL) was added KO^tBu (63.0 mg, 0.56 mmol) in THF (0.5 mL) at 0 °C. After 30 min a solution of the aldehyde in THF (0.5 mL) was added and the reaction was stirred for 16 h at room temperature. The solvent was removed and the

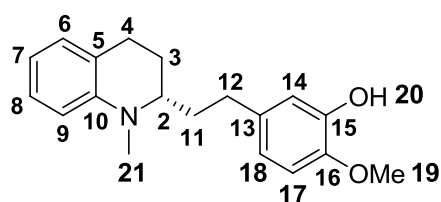
residue purified by column chromatography, eluting with 10% EtOAc in hexane, to give the olefinated product as a mixture of the *E*- and *Z*- isomers. The alkene was dissolved in EtOH (0.5 mL) and THF (0.5 mL) and 10 % Pd/C (0.20 g) was added. The reaction was stirred under an atmosphere of H₂ for 16 h. The Pd/C was removed by filtration through celite and the solution evaporated to dryness.

Angustureine (1.10)



The product was purified by column chromatography, EtOAc/*n*-Hexane 1:100, $R_f = 0.40$, to give angustureine as a colourless oil (27 mg, 44%); $[\alpha]_D^{25} + 7.5^\circ$ ($c = 0.4$, CHCl₃) Lit $[\alpha]_D^{25} - 7.16$ ($c = 1.0$, CHCl₃, natural product)^{18, 172}; $\nu_{\max}/\text{cm}^{-1}$ 2930, 2860, 950, 750; δ_H (400 MHz, CDCl₃) 7.11 (1H, t, J 7.6, H-7), 6.99 (1H, d, J 7.6, H-9), 6.60 (1H, t, J 7.6, H-8), 6.55 (1H, d, J 7.6, H-6), 3.31-3.19 (1H, m, H-2), 2.95 (3H, s, H-16), 2.91-2.74 (1H, m, H-4), 2.75-2.63 (1H, m, H-4), 1.97-1.86 (2H, m, H-3), 1.62 (1H, m, H-11), 1.46-1.26 (10H, m, H-11, H-12, H-13, H-14 and H-15); δ_C (100 MHz, CDCl₃) 145.4 (C-10), 128.6 (C-9), 127.1 (C-7), 121.9 (C-5), 115.2 (C-8), 110.4 (C-6), 59.0 (C-2), 38.0 (C-16), 31.2 (CH₂), 32.1 (CH₂), 29.7 (CH₂), 25.8 (CH₂), 24.4 (C-3), 23.6 (C-4), 22.7 (C-15); m/z (ESI) 217.1828 (M^+ , C₁₅H₂₃N requires 217.1830), 146 (100), 83 (60).

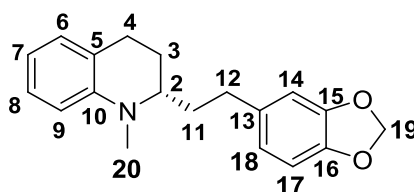
Galipeine (1.11)



The product was purified by column chromatography Et₂O/*n*-pentane, 3:7, $R_f = 0.28$, to give galipeine as a colourless gum (27.0 mg, 32%); $[\alpha]_D^{25} - 27^\circ$ ($c = 0.7$, CHCl₃) Lit $[\alpha]_D^{25} - 26.1$ ($c = 0.44$, CHCl₃, 96%)¹⁹; $\nu_{\max}/\text{cm}^{-1}$ 3500, 2940, 2850, 1600, 1500, 1280; δ_H (400 MHz, CDCl₃) 7.12 (1H, t, J 8.0, H-8), 7.02 (1H, d, J 7.2, H-6), 6.88-6.76 (2H, m, H-17 and H-14), 6.70 (1H, dd, J 2.0, 8.2, H-18), 6.63 (1H, t, J 7.2, H-7), 6.57 (1H, d, J 8.0, H-9), 5.61 (1H, br. s, H-20), 3.91 (3H, s, H-19), 3.39-3.23 (1H, m, H-2), 2.94 (3H, s, H-21), 2.92-2.82 (1H, m,

H-4), 2.79-2.60 (2H, m, H-4 and H-12), 2.60-2.46 (1H, m, H-12), 2.04-1.86 (3H, m, H-11 and H-3), 1.84-1.67 (1H, m, H-11); δ_{C} (100 MHz, CDCl_3) 145.5 (Ar-C), 145.4 (Ar-C), 144.8 (Ar-C), 135.4 (C-13), 128.8 (C-6), 127.1 (C-8), 121.8 (C-5), 119.6 (C-18), 115.4 (C-7), 114.5 (C-17/C-14), 110.7 (C-17/C-14), 110.6 (C-9), 58.2 (C-2), 56.0 (C-19), 38.0 (C-21), 32.9 (C-11), 31.6 (C-12), 24.4 (C-3), 23.6 (C-4); m/z (ESI) 298.1796 (MH^+ , $\text{C}_{19}\text{H}_{24}\text{NO}_2$ requires 298.1807), 194 (2).

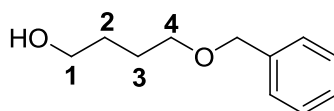
Galipinine (1.13)



The product was purified by column chromatography, $\text{Et}_2\text{O}/n\text{-hexane}$ 1:20, $R_f = 0.31$, as a colourless gum (26.0 mg, 31%); $\nu_{\text{max}}/\text{cm}^{-1}$ 2940, 2880, 1610, 1500, 1490, 1450, 1240; δ_{H} (400 MHz, CDCl_3) 7.12 (1H, t, J 7.9, H-8), 7.01 (1H, d, J 7.2, H-6), 6.78-6.62 (4H, m, Ar-H), 6.56 (1H, d, J 7.9, H-9), 5.95 (2H, s, H-19), 3.36-3.26 (1H, m, H-2), 2.95 (3H, s, H-20), 2.93-2.85 (1H, m, H-12), 2.78-2.60 (2H, m, H-4 and H-12), 2.61-2.46 (1H, m, H-4), 2.03-1.84 (3H, m, H-3 and H-11), 1.80-1.67 (1H, m, H-3); δ_{C} (100 MHz, CDCl_3) 147.6 (Ar-C), 145.6 (Ar-C), 145.4 (Ar-C), 135.9 (C-13), 128.7 (C-6), 127.1 (C-8), 121.7 (C-5), 120.9 (Ar-C), 115.4 (Ar-C), 110.6 (C-9), 108.7 (Ar-C), 108.2 (Ar-C), 100.8 (H-19), 58.2 (H-2), 38.1 (H-20), 33.2 (C-3), 32.0 (C-4), 24.4 (C-11), 23.6 (C-12). m/z (ESI) 296.1647 (MH^+ , $\text{C}_{19}\text{H}_{22}\text{NO}_2$ requires 296.1651).

5.2 Compounds used in Chapter 3

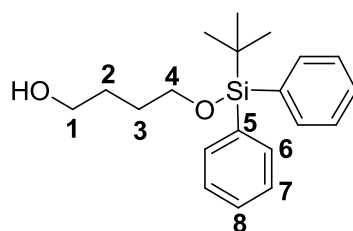
4-(benzyloxy)butan-1-ol (3.11)



To NaH (2.50 g, 55.5 mmol) in THF (35 mL) was added 1,4-butanediol (5.00 mL, 56.4 mmol), followed by BnBr (6.60 mL, 55.5 mmol) in dry THF (15 mL) at 0 °C. The suspension was stirred at room temperature under N_2 for 18 hours, then quenched by the addition of NH_4Cl (50 mL) and the aqueous layer extracted with Et_2O (50 mL). The combined organic

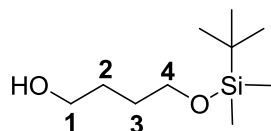
extracts were dried over MgSO_4 , filtered and concentrated to give the crude product as a yellow oil, purified by column chromatography, *n*-Hexane /EtOAc 1:1, $R_f = 0.4$, to give a yellow oil (7.77 g, 76%); $\nu_{\text{max}}/\text{cm}^{-1}$ 3380, 2940, 2860, 1450, 1060, 690; δ_{H} (400 MHz, CDCl_3) 7.36 (5H, m, Ar-H), 4.53 (2H, s, OCH_2Ar), 3.64 (2H, t, J 6.0, H-1), 3.54 (2H, t, J 5.9, H-4), 2.68 (1H, s, OH), 1.71 (4H, m, H-2 and H-3); δ_{C} (100 MHz, CDCl_3) 138.2 (Ar-C), 128.4 (Ar-C), 127.76 (Ar-C), 127.72 (Ar-C), 73.0 (OCH_2Ar), 70.3 (C-4), 62.4 (C-1), 29.8 (C2/C3), 26.5 (C2/C3); m/z (EI) 180 (M^+ , 12), 107 (75), 91 (100), 71 (27), 43 (27).

4-(*tert*-Butyldiphenylsilyloxy)butan-1-ol (3.12)¹⁴³



To a solution of 1, 4-butandiol (9.80 mL, 111 mmol) in CH_2Cl_2 (20 mL) was added DIPEA (20.0 mL, 115 mmol). TBDPSCl (10.0 mL, 38.0 mmol) was added drop wise to the solution and the mixture was stirred at room temperature for 2 h. The solvent was removed by evaporation and the residue purified by column chromatography with *n*-hexane/EtOAc 2:1, $R_f = 0.33$, to give the alcohol as a colourless oil (6.90 g, 55%); $\nu_{\text{max}}/\text{cm}^{-1}$ 3380, 2940, 2860, 1430, 1110; δ_{H} (400 MHz, CDCl_3) 7.89-7.61 (4H, m, Ar-H), 7.61-7.37 (6H, m, Ar-H), 3.77 (2H, t, J 3.7, H-4), 3.71 (2H, t, J 5.9, H-1), 2.47 (1H, br. s, OH), 1.73 (4H, m, H-2 and H-3), 1.13 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 135.6 (C-6), 133.7 (C-5), 129.7 (C-8), 127.7 (C-7), 64.1 (C-4), 62.8 (C-1), 29.8 (C-2/C-3), 29.3 (C-2/C-3), 26.9 ($\text{C}(\text{CH}_3)_3$), 19.2 ($\text{C}(\text{CH}_3)_3$); m/z (EI) 329.1930 (MH^+ , $\text{C}_{20}\text{H}_{29}\text{O}_2\text{Si}$ requires 329.1937), 216 (12), 210 (10).

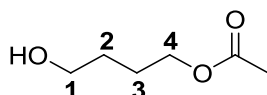
4-(*tert*-butyldimethylsilyloxy)butan-1-ol (3.13)¹⁴⁴



To a mixture of 1, 4-butandiol (9.80 mL, 111 mmol) and imidazole (5.30 g, 78 mmol) in DMF (30 mL) was added *tert*-butyldimethyl silyl chloride (4.20 g, 28.0 mmol). The reaction was stirred at room temperature for 2 h, and quenched by the addition of H_2O (150 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over MgSO_4 , filtered and evaporated to dryness. The residue was purified by column

chromatography, *n*-hexane/EtOAc 1.5:1, $R_f = 0.41$, to give the alcohol as a colourless oil (4.00 g, 71%); $\nu_{\max}/\text{cm}^{-1}$ 3350, 2960, 2940, 2670, 1470, 1260, 1100; δ_{H} (400 MHz, CDCl_3) 3.71-3.58 (4H, m, H-1 and H-4), 2.97 (1H, br. s, OH), 1.72-1.57 (4H, m, H-2 and H-3), 0.9 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.07 (6H, br. s, $\text{Si}(\text{CH}_3)_2$); δ_{C} (100 MHz, CDCl_3) 63.3 (C-1/C-4), 62.6 (C-1/C-4), 30.1 (C-2/C-3), 29.8 (C-2/C-3), 25.9 ($\text{C}(\text{CH}_3)_3$), 18.2 ($\text{C}(\text{CH}_3)_3$), -5.4 ($\text{Si}(\text{CH}_3)_2$); m/z (EI) 205 (MH^+ , 5%), 189 (28), 147 (62), 105 (82), 75 (100).

4-Hydroxybutyl acetate (3.14)¹⁴⁵

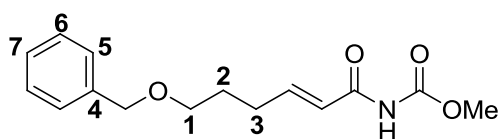


Acetyl chloride (4.60 mL, 65.0 mmol) was added drop wise to a solution of 1, 4-butandiol (10.0 g, 111 mmol) and pyridine (5.30 mL, 65.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction was stirred at room temperature over night, evaporated to dryness and purified by column chromatography with EtOAc/*n*-hexane 1:1, $R_f = 0.33$. The product was obtained as a colourless oil (3.90 g, 45%); $\nu_{\max}/\text{cm}^{-1}$ 3420, 2950, 2880, 1730, 1240, 1050; δ_{H} (400 MHz, CDCl_3) 4.12 (2H, t, J 6.5, H-4), 3.70 (2H, t, J 6.1, H-1), 2.07 (3H, s, COCH_3), 1.81-1.60 (4H, m, H-2 and H-3), 1.48 (1H, br. s, OH); δ_{C} (100 MHz, CDCl_3) 171.2 (COOCH_3), 64.2 (C-4), 62.3 (C-1), 29.1 (C-2/C-3), 25.0 (C-2/C-3), 20.9 (COCH_3); m/z (CI) 133.0868 (MH^+ , $\text{C}_6\text{H}_{13}\text{O}_3$ requires 133.0865), 71 (3), 52 (5).

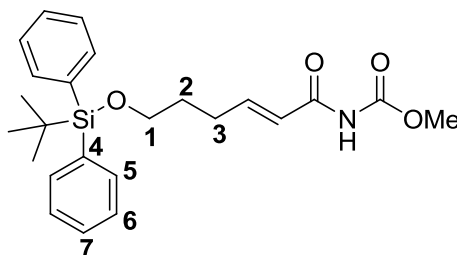
General methods for the synthesis of the Michael acceptors

DMSO (2.40 mL, 33.0 mmol) in CH_2Cl_2 (6 mL) was added to a solution of oxalyl chloride (1.40 mL, 16.7 mmol) in CH_2Cl_2 (35 mL) at -78 °C, maintaining the temperature below -60 °C. After 30 min the alcohol (15.0 mmol) in CH_2Cl_2 (12 mL) was added, maintaining the temperature below -60 °C. The reaction was stirred for another 30 min, before triethylamine (10.5 mL, 76.0 mmol) was added. The reaction was warmed to room temperature and diluted with sat. aq. NH_4Cl (50 mL). The organic layer was separated and evaporated to dryness to give the aldehyde, which was used without further purification.

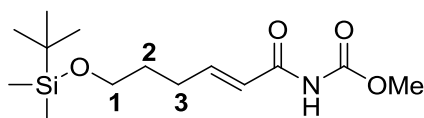
Synthesis of the Michael acceptor was achieved using general method A or C (See Section 5.1).

Methyl 6-(benzyloxy)hex-2-enoylcarbamate (3.19)

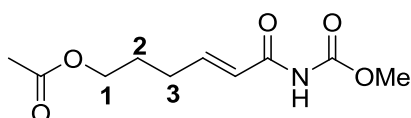
The product was obtained using general method A and purified by recrystallisation from toluene/*n*-hexane to give a white solid (1.50 g, 40%); mp 63-65 °C; $\nu_{\max}/\text{cm}^{-1}$ 3280, 3085, 2960, 2860, 1780, 1700, 1650, 1530; δ_{H} (400 MHz, CDCl_3) 7.78 (1H, br. s, NH), 7.43-7.27 (5H, m, Ar-H), 7.17 (1H, dt, J 7.0, 15.4, CH_2CH), 6.85 (1H, d, J 15.4, CHCO), 4.53 (2H, s, OCH_2Ar), 3.81 (3H, s, OCH_3), 3.53 (2H, t, J 6.2, H-1), 2.41 (2H, m, H-3), 1.83 (2H, m, H-2); δ_{C} (100 MHz, CDCl_3) 165.8 (CONH), 152.2 (CO_2), 150.8 (CH_2CH), 138.4 (C-4), 128.4 (C-6), 127.7 (C-5), 127.6 (C-7), 121.5 (CHCO), 73.0 (OCH_2Ar), 69.2 (C-1), 53.1 (OCH_3), 29.3 (C-3), 28.1 (C-2); m/z (EI) 277.1313 (M^+ , $\text{C}_{15}\text{H}_{19}\text{NO}_4$ requires 277.1314), 202 (12), 143 (30), 91 (100).

(*E*)-methyl 6-(*tert*-butyldiphenylsilyloxy)hex-2-enoylcarbamate (3.20)

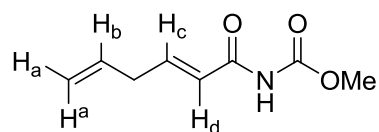
The product was obtained using general method C and purified by column chromatography, EtOAc/*n*-hexane 1.5:1, R_f = 0.31, to give a white solid (4.40 g, 70%); mp 93-95°C; $\nu_{\max}/\text{cm}^{-1}$ 3250, 2970, 2930, 2880, 1780, 1690, 1640, 1500, 1440, 1170; δ_{H} (400 MHz, CDCl_3) 7.75-7.63 (4H, m, Ar-H), 7.57 (1H, br. s, NH), 7.51-7.34 (6H, m, Ar-H), 7.17 (1H, dt, J 6.9, 15.4, CH_2CH), 6.81 (1H, d, J 15.4, CHCO), 3.82 (3H, s, OCH_3), 3.71 (2H, t, J 6.1, H-1), 2.50-2.34 (2H, m, H-3), 1.81-1.71 (2H, m, H-2), 1.08 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 165.8 (CONH), 152.3 (CO_2), 151.9 (CH_2CH), 135.5 (C-5), 133.8 (C-4), 129.6 (C-7), 127.7 (C-6), 121.3 (CHCO), 62.9 (C-1), 53.1 (OCH_3), 30.9 (C-2), 29.1 (C-3), 26.9 ($\text{C}(\text{CH}_3)_3$), 19.2 ($\text{C}(\text{CH}_3)_3$). m/z (EI) 426 (MH^+ , < 5%), 368 (100), 293 (65), 213 (35).

Methyl 6-(*tert*-butyldimethylsilyloxy)hex-2-enoylcarbamate (3.21)

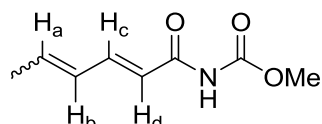
The product was obtained using general method C and purified by column chromatography, EtOAc/*n*-hexane 1.5:1, $R_f = 0.4$, to give a white solid (2.40 g, 55%); mp 83-85 °C; $\nu_{\max}/\text{cm}^{-1}$ 3230, 2940, 2850, 1770, 1690, 1660, 1530, 1240; δ_{H} (400 MHz, CDCl_3) 8.04 (1H, br. s, NH), 7.28 (1H, dt, J 6.9, 15.4, CH_2CH), 6.85 (1H, J 15.4, CHCO), 3.80 (3H, s, OCH_3), 3.65 (2H, t, J 6.2, H-1), 2.43-2.26 (2H, m, H-3), 1.80-1.62 (2H, m, H-2), 0.9 (9H, s, $(\text{C}(\text{CH}_3)_3)$), 0.06 (6H, s, $\text{Si}(\text{CH}_3)_2$); δ_{C} (100 MHz, CDCl_3) 166.2 (CONH), 152.5 (CO_2), 151.2 (CH_2CH), 121.4 (CHCO), 62.2 (C-1), 53.0 (OCH_3), 31.1 (C-2), 29.1 (C-3), 25.9 ($\text{C}(\text{CH}_3)_3$), 18.3 ($\text{C}(\text{CH}_3)_3$), 5.34 ($\text{Si}(\text{CH}_3)_2$); m/z (ESI) 302.1779 (MH^+ , $\text{C}_{14}\text{H}_{28}\text{NO}_4\text{Si}$ requires 302.1788), 224 (14), 196 (5).

6-(Methoxycabonylamino)-6-oxohex-4-enyl acetate (3.22)

The product was obtained using general method C and purified by column chromatography EtOAc/*n*-hexane 2.5:1, $R_f = 0.32$, to give a white solid in a 10:1 mixture of *E* and *Z* isomers (1.50 g, 45%); mp 55-57 °C; $\nu_{\max}/\text{cm}^{-1}$ 3560, 3270, 2960, 1770, 1720, 1650, 1510; δ_{H} (400 MHz, CDCl_3) 8.19 (1H, br. s, NH) (major isomer), 8.08 (1H, br. s, NH) (minor isomer), 7.13 (1H, dt, J 6.8, 15.5, CH_2CH) (major isomer), 6.87 (1H, d, J 15.5, CHCO) (major isomer), 6.60 (1H, d, J 11.5, CHCO) (minor isomer), 6.32 (1H, dt, J 7.5, 11.5, CH_2CH) (minor isomer), 4.09 (2H, t, J 6.5, H-1), 3.79 (3H, s, OCH_3) (major isomer), 3.78 (3H, s, OCH_3) (minor isomer), 2.78-2.67 (2H, m, H-3) (minor isomer), 2.42-2.30 (2H, m, H-3) (major isomer), 2.06 (3H, s, COCH_3) (major isomer), 2.04 (3H, s, COCH_3) (minor isomer), 1.91-1.75 (2H, m, H-2); δ_{C} (100 MHz, CDCl_3) 171.1 (COCH_3), 165.8 (CONH), 152.3 (CO_2CH_3), 149.8 (CH_2CH), 121.8 (CHCO), 63.5 (C-1), 53.1 (CO_2CH_3), 29.1 (C-3), 27.0 (C-2), 21.0 ($\text{C}=\text{OCH}_3$); m/z (ESI) 230.1030 (MH^+ , $\text{C}_{10}\text{H}_{16}\text{NO}_5$ requires 230.1028), 169 (100), 113 (55), 94 (98), 43 (95). Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{NO}_5$: C, 52.40; H, 6.60; N, 6.11%. Found: C, 52.51; H, 6.46; N, 5.97%.

Methyl hexa-2,5-dienoylcarbamate (3.26)

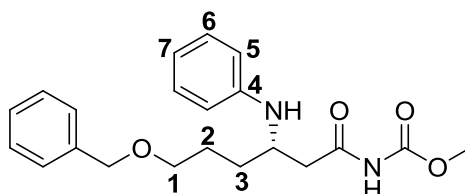
To the alcohol (1g, 13 mmol) in a Pentane/CH₂Cl₂ (9:1, 50 mL) mixture was added PhI(OAc)₂ (4.9 g, 15 mmol), immediately followed by TEMPO (0.2 g, 1.4 mmol). The reaction was stirred at room temperature for 2.5 hours. The reaction was quenched by the addition of sat. NaHCO₃ at 0 °C. The organic layer was separated and the aldehyde in the Pentane/CH₂Cl₂ mixture (25 mL) was added to a solution of the ylid in CH₂Cl₂ (30 mL). The reaction was stirred over night and the solvent removed by evaporation. The crude product was purified by column chromatography, EtOAc/Hexane 1:1 to give a white solid (0.18 g, 15%); mp 123-128 °C; $\nu_{\max}/\text{cm}^{-1}$ 3200, 2980, 1760, 1630; δ_{H} (400 MHz, CDCl₃) 7.34 (1H, s, NH), 7.18 (1H, dt, *J* 6.5, 15.5), 6.89 (1H, d, *J* 15.5, H_d), 5.95-5.80 (1H, m, H_b), 5.19-5.16 (1H, m, H_a), 5.14 (1H, dd, *J* 1.4, 6.4, H_a), 3.82 (3H, s, CO₂CH₃), 3.11-3.00 (2H, m, CH₂); δ_{C} (100 MHz, CDCl₃) 165.6 (CONH), 152.4 (CO₂), 144.4 (H_c), 137.3 (H_b), 129.3 (H_d), 118.5 (H_a), 53.1 (CO₂CH₃), 35.9 (CH₂); *m/z* (EI) 169.0739 (M⁺, C₈H₁₁NO₃ requires 169.0739), 154 (100), 95 (75), 67 (10), 41 (32).

Methyl hexa-2,4-dienoylcarbamate (3.27)

To a solution of 3-Buten-1-ol (1.00 g, 13.0 mmol) in a pentane/CH₂Cl₂ (9:1, 50 mL) mixture was added PhI(OAc)₂ (4.90 g, 15.0 mmol), immediately followed by TEMPO (0.20 g, 1.40 mmol). The reaction was stirred at room temperature for 2.5 h and then quenched by the addition of sat. aq. NaHCO₃ at 0 °C. The organic layer was separated and this solution (25 mL) containing the aldehyde was added to a mixture of the phosphonate carbamate (1.75 g, 7.00 mmol) and DBU (1.00 mL, 6.60 mmol) in CH₂Cl₂ (30 mL). The reaction was stirred overnight at room temperature, and then the solvent was removed by evaporation. The crude product was purified by column chromatography, EtOAc/*n*-hexane 1.5:1, *R_f* = 0.35, to give a white solid (0.11 g, 10%); mp 169-171 °C; $\nu_{\max}/\text{cm}^{-1}$ 3260, 2960, 1770, 1650, 1610, 1500; δ_{H} (400 MHz, CDCl₃) 7.86 (1H, dd, *J* 11.4, 15.0, H_c) (minor isomer), 7.47 (2H, br. dd, *J* 10.1, 15.1, H_c and NH), 6.96 (1H, d, *J* 15.0, H_d) (minor isomer), 6.86 (1H, d, *J* 15.1, H_d) (major isomer), 6.28 (2H, m, H_a and H_b), 6.05 (1H, dd, *J* 7.5, 11.4, H_b) (minor isomer), 3.81 (3H, s,

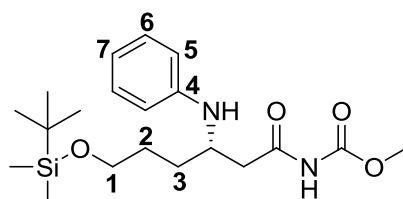
CO₂CH₃), 1.91 (3H, d, *J* 5.9, CHCH₃); δ_{C} (100 MHz, CDCl₃) 166.4 (CONH), 152.3 (CO₂), 146.9 (C-H_c), 141.2 (C-H), 130.2 (C-H), 118.6 (C-H_d), 53.0 (OCH₃), 18.8 (CHCH₃); *m/z* (EI) 169.0739 (M⁺, C₈H₁₁NO₃ requires 169.0739), 154 (100), 95 (55), 67 (60), 41 (47).

Methyl 6-(benzyloxy)-3-(phenylamino)hexanoylcarbamate (3.28)



Using method A, the product was obtained as a yellow oil (20%); Column chromatography, EtOAc/*n*-hexane 1:1.5, *R_f* = 0.33; $\nu_{\text{max}}/\text{cm}^{-1}$ 3320, 3080, 2880, 1750, 1660, 1630, 1540, 1420, 1220; δ_{H} (400MHz, CDCl₃) 7.81 (1H, br.s, NHCO), 7.41-7.29 (5H, m, Ar-C), 7.19-7.14 (2H, m, H-6), 6.71 (1H, t, *J* 7.2, H-7), 6.61 (2H, d, *J* 8.0, H-5), 4.50 (2H, s, OCH₂Ar), 4.00-3.85 (1H, m, CHNH), 3.76 (3H, s, OCH₃), 3.56-3.44 (3H, m, H-1 and ArNH), 3.01 (1H, dd, *J* 5.8, 15.9), 2.94 (1H, dd, *J* 5.4, 15.9, CH₂CO), 1.89-1.64 (4H, m, H-2 and H-3); δ_{C} (100 MHz, CDCl₃) 172.4 (CONH), 152.1 (CO₂CH₃), 147.0 (C-4), 138.4 (Ar-C), 129.4 (C-6), 128.4 (Ar-C), 127.7 (Ar-C), 127.6 (Ar-C), 117.7 (C-7), 113.5 (C-5), 73.1 (OCH₂Ar), 70.1 (C-1), 53.1 (CO₂CH₃), 50.3 (CHNH), 40.4 (CH₂CO), 31.9 (C-2/C-3), 26.4 (C-2/C-3); *m/z* (ESI) 371.1953 (MH⁺, C₂₁H₂₇N₂O₄ requires 371.1971) 300 (70), 224 (100).

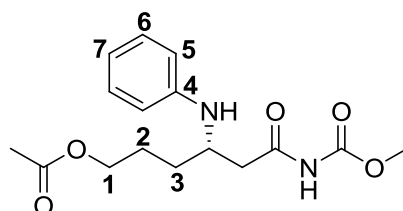
Methyl 6-(*tert*-butyldimethylsilyloxy)-3-(phenylamino)hexanoylcarbamate (3.30)



Using method A, the product was obtained as a yellow oil (40%); Column chromatography, EtOAc/*n*-hexane 1:1.5, *R_f* = 0.26; $[\alpha]_{\text{D}}^{25} + 3.3^{\circ}$ (*c* = 0.4, CHCl₃, 46% ee); $\nu_{\text{max}}/\text{cm}^{-1}$ 3260, 3000, 1750, 1710, 1590, 1200; δ_{H} (400MHz, CDCl₃) 7.22-7.12 (2H, m, Ar-C), 6.79-6.63 (3H, m, Ar-C), 3.99-3.89 (1H, m, NHCH), 3.76 (3H, s, OCH₃), 3.71-3.59 (2H, m, H-1), 3.03 (1H, dd, *J* 6.0, 16.1, CH₂CO), 2.94 (1H, dd, *J* 6.2, 16.1, CH₂CO), 1.83-1.55 (4H, m, H-2 and H-3), 0.92 (9H, s, (C(CH₃)₃), 0.11 (6H, s, Si(CH₃)₂); δ_{C} (100 MHz, CDCl₃) 172.8 (CONH), 152.2 (CO₂), 145.8 (C-4), 129.4 (C-6), 118.6 (C-7), 114.4 (C-5), 62.5 (C-1), 53.1 (OCH₃), 50.7

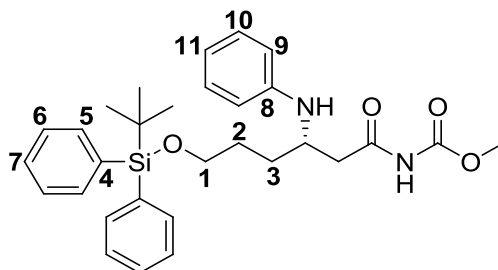
(CHNH), 40.3 (CH₂CO), 31.6 (C2/C3), 29.3 (C2/C3), 25.7 (C(CH₃)₃), 18.3 (C(CH₃)₃), -3.6 (Si(CH₃)₂); *m/z* (ESI) 395 (MH⁺, 45), 224 (100).

6-(methoxycarbonylamino)-6-oxo-4(phenylamino)hexyl acetate (3.31)



Using method A, the product was obtained as a colourless oil (43%); Column chromatography, EtOAc/*n*-hexane 1:1.5, *R_f* = 0.35; [α]_D²⁵ - 0.9° (*c* = 1.1, CHCl₃, 44% ee) $\nu_{\max}/\text{cm}^{-1}$ 3330, 3070, 2860, 1770, 1740, 1650, 1550, 1450, 1200; δ_{H} (400MHz, CDCl₃) 8.62 (1H, br.s, NHCO), 7.30 (2H, m, H-6), 6.72 (1H, t, *J* 7.2, H-7), 6.66 (2H, d, *J* 8.0, H-5), 4.14-4.07 (3H, m, ArNH and H-1), 4.05-3.93 (1H, m, NHCH), 3.77 (3H, s, OCH₃), 3.03 (1H, dd, *J* 5.6, 16.0, CH₂CO), 2.95 (1H, dd, *J* 5.2, 16.0, CH₂CO), 2.40 (3H, s, COCH₃), 1.88-1.63 (4H, m, H2 and H-3); δ_{C} (100 MHz, CDCl₃) 173.1 (CONH), 161.1 (COCH₃), 152.5 (CO₂), 147.8 (C-4), 129.4 (C-6), 117.8 (C-7), 113.5 (C-5), 64.4 (C-1), 53.1 (CO₂CH₃), 49.8 (CHNH), 40.6 (CH₂CO), 31.5 (C2/C3), 25.4 (C2/C3), 21.4 (COCH₃); *m/z* (ESI) 323.1599 (MH⁺, C₁₆H₂₃N₂O₅ requires 323.1607) 293 (12), 252 (22).

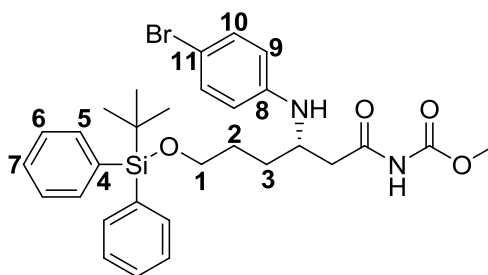
Methyl 6-(*tert*-butyldiphenylsilyloxy)-3-(phenylamino)hexanoylcarbamate (3.29)



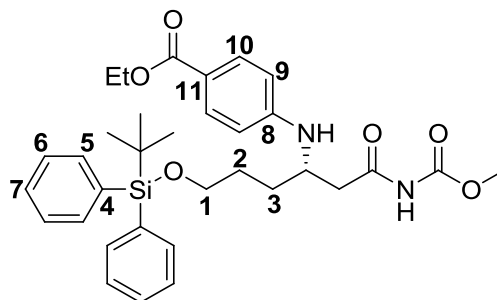
To the alkene (50.0 mg, 0.13 mmol) and [Pd(*R*-BINAP)(OH₂)₂]²⁺[OTf]⁻₂ (7.00 mg, 6.5 μ mol) in toluene (0.5 mL) was added the aniline (12.0 μ L, 0.13 mmol). The reaction was stirred for 48 h and then the solvent removed by evaporation. The crude reaction mixture was purified by column chromatography, EtOAc/*n*-hexane 1:1.5, *R_f* = 0.29, to give a colourless oil (44.0 mg, 65%); Chiral HPLC Hichrom-CHI-PGG-2759, 10% IPA in *n*-hexane, 1 mL/min, *t_R*(major) = 51.1 min, *t_R*(minor) = 63.1 min; [α]_D²⁵ - 1.5° (*c* = 1.3, CHCl₃, 71% ee); $\nu_{\max}/\text{cm}^{-1}$ 3300, 2950, 2860, 1770, 1710, 1600, 1490, 1210, 1110; δ_{H} (400 MHz, CDCl₃) 7.99 (1H, br.

s, CONH), 7.71-7.64 (4H, m, Ar-H), 7.50-7.36 (6H, m, Ar-H), 7.19 (2H, dd, J 7.4, 8.0, H-10), 6.74 (1H, t, J 7.4, H-11), 6.64 (2H, d, J 8.0, H-9), 3.99-3.90 (1H, m, NHCH), 3.85 (1H, br. s, ArNH), 3.79 (3H, s, OCH₃), 3.72-3.67 (2H, m, H-1), 3.03 (1H, dd, J 5.8, 15.8, CH₂CO), 2.95 (1H, dd, J 5.2, 15.8, CH₂CO), 1.79-1.61 (4H, m, H-2 and H-3), 1.08 (9H, s, C(CH₃)₃); δ_C (100 MHz, CDCl₃) 172.7 (CONH), 152.2 (CO₂), 147.1 (C-8), 135.6 (Ar-C), 133.9 (Ar-C), 129.6 (Ar-C), 129.4 (C-10), 127.7 (Ar-C), 117.8 (C-11), 113.7 (C-9), 63.5 (C-1), 53.1 (OCH₃), 50.3 (NHCH), 40.5 (CH₂CO), 31.3 (C-2/C-3), 29.1 (C-2/C-3), 26.9 (C(CH₃)₃), 19.2 (C(CH₃)₃); m/z (ESI) 519.2664 (MH⁺, C₃₀H₃₉N₂O₄Si requires 519.2679), 448 (28).

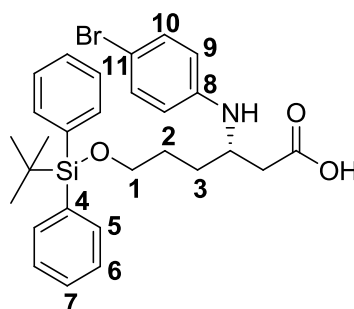
Methyl 3-(4-bromophenylamino)-6-(*tert*-butyldiphenylsiloxy)hexanoylcarbamate (3.33)



To a solution of the alkene **3.20** (1.50 g, 3.50 mmol) in toluene (25 mL) was added [Pd(BINAP)(OH₂)₂]²⁺[OTf]⁻₂ (0.19 g, 0.18 mmol). The mixture was heated to 30 °C, whereupon a solution of 4-bromoaniline (0.60 g, 3.50 mmol) in toluene (5 mL) was added slowly over 5 h. The reaction was stirred for 48 h and then cooled to room temperature. The solvent was removed by evaporation and the residue purified by column chromatography, EtOAc/*n*-hexane 1:1.5, R_f = 0.40, to give a yellow oil (1.70 g, 85%); Chiral HPLC Daicel Chiralpak AD-H, 5% IPA in *n*-hexane, 0.5 mL/min, t_R (minor) = 42.8 min, t_R (major) = 48.6 min; $[\alpha]_D^{25} + 3.0^\circ$ (c = 1.0, CHCl₃, 71% ee); $\nu_{\max}/\text{cm}^{-1}$ 2950, 2930, 2860, 1766, 1710, 1600, 1490, 1210; δ_H (400 MHz, CDCl₃) 7.84 (1H, br. s, NHCO), 7.74-7.61 (4H, m, Ar-H), 7.51-7.32 (6H, m, Ar-H), 7.23 (2H, d, J 8.6, H-10), 6.48 (2H, d, J 8.6, H-9), 3.96-3.84 (2H, br. m, ArNH and CHNH), 3.78 (3H, s, CO₂CH₃), 3.72-3.66 (2H, m, H-1), 3.04 (1H, dd, J 5.5, 15.9, COCH₂), 2.93 (1H, dd, J 4.9, 15.9, COCH₂), 1.79-1.56 (4H, m, H-2 and H-3), 1.07 (9H, s, C(CH₃)₃); δ_C (100 MHz, CDCl₃) 172.7 (CONH), 152.3 (CO₂), 146.2 (C-8), 135.6 (C-5), 133.8 (C-4), 132.0 (C-10), 129.6 (C-7), 127.7 (C-6), 115.1 (C-9), 109.1 (C-11), 63.4 (C-1), 53.2 (OCH₃), 50.4 (NHCH), 40.3 (COCH₂), 31.3 (C-2/C-3), 29.0 (C-2/C-3), 26.8 (C(CH₃)₃), 19.2 (C(CH₃)₃); m/z (EI) 596.1704 (M⁺, C₃₀H₃₇N₂O₄SiBr requires 596.1706), 509 (40), 507 (40), 424 (95), 422 (100), 226 (50), 224 (55), 199 (60).

Methyl 6-(*tert*-butyldiphenylsilyloxy)-3-(ethyl-4-aminobenzoate)hexanoylcarbamate (3.34)


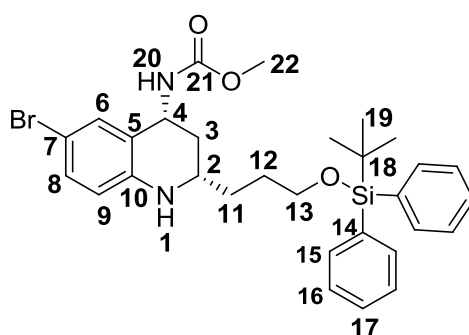
Using method A, the product was obtained as an off-white solid (72%); $[\alpha]_{\text{D}}^{25}$ - 2.7° ($c = 1.1$, CHCl_3 , 57% ee); Daicel Chiralpak AD-H, 10% IPA in *n*-hexane, 1 mL/min, $t_{\text{R}}(\text{minor}) = 21.8$ min, $t_{\text{R}}(\text{major}) = 25.8$ min; Column chromatography, EtOAc/*n*-hexane 1:1.5, $R_{\text{f}} = 0.42$; $\nu_{\text{max}}/\text{cm}^{-1}$ 3300, 3100, 3000, 1770, 1720, 1660, 1550, 1280; δ_{H} (400 MHz, CDCl_3) 7.85 (2H, d, J 8.7, H-10), 7.76-7.61 (4H, m, Ar-H), 7.50-7.34 (6H, m, Ar-H), 6.54 (2H, d, J 8.7, H-9), 4.34 (2H, q, J 7.1, CO_2CH_2), 4.07-3.93 (1H, m, CHNH), 3.78 (3H, s, OCH_3), 3.75-3.63 (2H, m, H-1), 3.10 (1H, dd, J 6.0, 16.0, CH_2CO), 2.98 (1H, dd, J 5.6, 16.0, CH_2CO), 1.83-1.57 (4H, m, H-2 and H-3), 1.39 (3H, t, J 7.1, CH_3CH_2), 1.07 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 172.5 (CONH), 166.8 (CO_2CH_2), 152.3 (CO_2CH_3), 150.1 (C-8), 135.6 (Ar-C), 133.8 (Ar-C), 131.6 (C-10), 129.6 (Ar-C), 127.7 (Ar-C), 118.8 (C-11), 111.9 (C-9), 63.4 (C-1), 60.2 (CO_2CH_2), 53.2 (OCH_3), 49.6 (CHNH), 40.3 (CH_2CO), 31.3 (C-2/C-3), 29.0 (C-2/C-3), 26.9 ($\text{C}(\text{CH}_3)_3$), 19.2 ($\text{C}(\text{CH}_3)_3$), 14.5 (CH_3CH_2); m/z (ESI) 591.2901 (MH^+ , $\text{C}_{33}\text{H}_{43}\text{N}_2\text{O}_6\text{Si}$ requires 591.2890), 448 (68), 207 (11).

6-(*tert*-Butyldiphenylsilyloxy)-3-(phenylamino)hexanoic acid (3.35)


To a solution of the carbamate **3.33** (0.22 g, 0.36 mmol) in MeOH (5 mL) was added 1M aq. KOH (5.30 mL, 5.30 mmol). The resultant solution was stirred at room temperature for 1 h and the MeOH was removed by evaporation. CH_2Cl_2 (10 mL) was added and the organic layer separated, dried over MgSO_4 and the solvent removed under vacuum to give a yellow

oil (0.16 g, 82%); $[\alpha]_D^{25} + 1.8^\circ$ ($c = 1.1$, CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ 3070, 2950, 2860, 1680, 1600, 1500, 1110; δ_{H} (400 MHz, CDCl_3) 7.79-7.65 (4H, m, Ar-H), 7.54-7.37 (6H, m, Ar-H), 7.27 (2H, d, J 8.6, H-10), 6.53 (2H, d, J 8.6, H-9), 6.40 (1H, br. s, NH/OH), 5.92 (1H, br. s, NH/OH), 3.88-3.64 (3H, m, H-1 and NHCH), 2.51-2.32 (2H, m, CH_2CO), 1.88-1.57 (4H, m, H-2 and H-3), 1.11 (9H, s, $\text{C}(\text{CH}_3)_3$); δ_{C} (100 MHz, CDCl_3) 174.6 (CO_2H), 146.2 (C-8), 135.6 (Ar-C), 133.9 (Ar-C), 132.1 (C-10), 129.7 (Ar-C), 127.7 (Ar-C), 115.4 (C-9), 109.4 (C-11), 63.5 (C-1), 50.9 (CH), 40.2 (CH_2CO), 31.0 (C-2/C-3), 29.1 (C-2/C-3), 26.9 ($\text{C}(\text{CH}_3)_3$), 19.3 ($\text{C}(\text{CH}_3)_3$); m/z ESI 539 (88), 541(100), 539 (83), 519 (25), 245 (18).

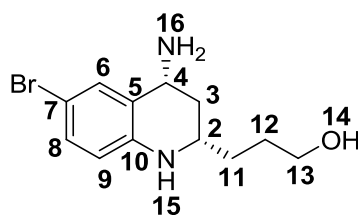
Methyl 6-bromo-2-(3-(*tert*-butyldiphenylsilyloxy)propyl)-1,2,3,4-tetrahydroquinolin-4-ylcarbamate (3.39)



To a solution of the carbamate **3.33** (1.60 g, 2.60 mmol) dissolved in an ethanol/THF mixture (1:1, 15 mL) was added NaBH_4 (70.0 mg, 1.80 mmol) at -10°C . $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ (0.56 g, 2.80 mmol) in H_2O (2 mL) was slowly added, maintaining the temperature below 0°C . Upon complete addition, the reaction was stirred at 0°C for 30 min before quenching, by the addition of CH_2Cl_2 (20 mL), 1M aq. HCl (20 mL) and citric acid (1.30 g, 6.50 mmol). The biphasic layer was stirred at room temperature for 4 h. The organic layer was separated and then H_2O (10 mL) was added, followed by citric acid (0.76 g, 4.00 mmol). The mixture was stirred at room temperature for 45 min and then the organic layer was separated, dried over MgSO_4 and concentrated under vacuum. The volatiles remaining in the residue were displaced by co-distillation with hexane under reduced pressure to give the 2, 4-disubstituted tetrahydroquinoline as a colourless gum (1.50 g, 98%); $[\alpha]_D^{25} + 6.0^\circ$ ($c = 1.0$, CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ 2940, 2860, 1720, 1600, 1500, 1111; δ_{H} (400 MHz, CD_3CN) 7.81-7.61 (4H, m, Ar-H), 7.59-7.35 (6H, m, Ar-H), 7.15 (1H, br. d, J 2.2, H-6), 7.08 (1H, dd, J 2.2, 8.6, H-8), 6.46 (1H, d, J 8.6, H-9), 5.76 (1H, d, J 9.2, H-20), 4.84 (1H, m, H-4), 4.62 (1H, br. s, H-1), 3.75 (2H, t, J 5.9, H-13), 3.69 (3H, s, H-22), 3.39 (1H, m, H-2), 2.10 (1H, ddd, J 2.5, 5.5, 11.9, H-3), 1.76-1.54 (4H, m, H-11 and H-12), 1.48 (1H, q, J 11.9, H-3), 1.06 (9H, s, H-19); δ_{C} (100

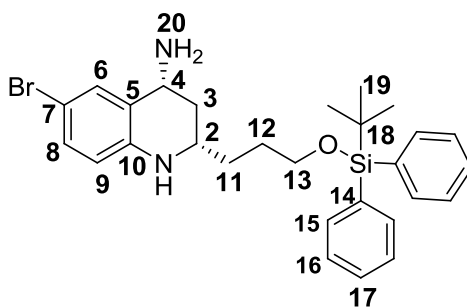
MHz, CDCl₃) 157.0 (H-21), 143.9 (C-10), 135.6 (C-15), 133.8 (C-14), 131.0 (C-8), 129.7 (C-17), 129.4 (C-6), 127.7 (C-16), 123.7 (C-5), 115.9 (C-9), 109.0 (C-7), 63.6 (C-13), 52.3 (C-22), 50.8 (C-2), 47.9 (C-4), 36.1 (C-3), 32.6 (C-11), 28.3 (C-12), 26.9 (C-19), 19.2 (C-18); *m/z* (EI) 580.1757 (*M*⁺, C₃₀H₃₇N₂O₃BrSi requires 580.1757), 550 (17), 448 (100), 250 (96), 208 (89). Anal. Calcd. for C₃₀H₃₇N₂O₃BrSi: C, 61.95; H, 6.41; N, 4.82%. Found: C, 61.84; H, 6.28; N, 4.72%.

4-Amino-6-bromo-1,2,3,4-tetrahydroquinolin-2-yl)propan-1-ol (3.41)



To a solution of the tetrahydroquinoline **3.39** (3.15 g, 5.40 mmol) in MeCN (30 mL) was added TMSI (3.00 mL, 22.0 mmol). The reaction was stirred at room temperature for 16 h and then quenched by the additional of MeOH (20 mL). The solvent was removed by evaporation and 1M aq. HCl (30 mL) was added to the residue. The aqueous layer was washed with Et₂O (30 mL) and the pH adjusted to 8 by the addition of 1M aq. KOH. Finally, the aqueous phase was washed with CH₂Cl₂ (3 x 50 mL) and the combined organic extracts dried over MgSO₄, filtered and evaporated to dryness to give the amine as a brown gum (1.20 g, 78%); [α]_D²⁵ - 30.0° (*c* = 0.67, CHCl₃); ν_{max} /cm⁻¹ 3310, 2940, 2860, 1600, 1490, 1360, 1310, 1060; δ_{H} (400 MHz, CDCl₃) 7.46 (1H, s, H-6), 7.09 (1H, d, *J* 8.5, H-8), 6.36 (1H, d, *J* 8.5, H-9), 4.01 (2H, m, H-2 and H-14), 3.70 (2H, t, *J* 5.8, H-13), 3.43 (1H, br. s, H-4), 2.25-2.08 (1H, br. m, H-3), 2.09-1.81 (2H, br. s, H-15), 1.64-1.54 (4H, m, H-11 and H-12), 1.55-1.36 (1H, m, H-3); δ_{C} (100 MHz, CDCl₃) 143.4 (C-10), 130.4 (C-8), 129.2 (C-6), 122.6 (C-5), 115.6 (C-9), 109.1 (C-7), 62.5 (C-13), 51.1 (C-4), 48.1 (C-2), 39.8 (C-3), 33.0 (C-11/C-12), 28.5 (C-11/C-12); *m/z* (ESI) 281.0278 ([*M*-3H]⁺, C₁₂H₁₄BrN₂O requires 281.0289), 270 (90), 268 (100), 250 (10).

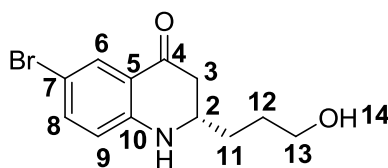
**6-Bromo-2-(3-(*tert*-butyldiphenylsilyloxy)propyl)-1,2,3,4-tetrahydroquinolin-4-amine
(3.40)**



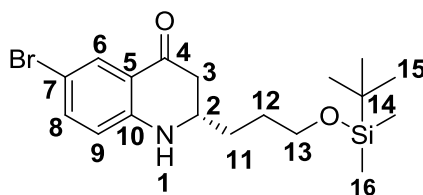
To a solution of the amine (0.60 g, 2.10 mmol) in CH_2Cl_2 (45 mL) was added imidazole (0.21 g, 0.32 mmol), followed by TBDPSCl (0.57 mL, 2.20 mmol). The reaction was stirred overnight at room temperature and quenched by the addition of H_2O (40 mL). The organic layer was separated, dried over MgSO_4 , filtered and evaporated to dryness to give the product as a brown oil (1.05 g, quant.); $[\alpha]_{\text{D}}^{25} - 14.7^\circ$ ($c = 0.75$, CHCl_3); $\nu_{\text{max}}/\text{cm}^{-1}$ 2940, 2860, 1590, 1480, 1120; δ_{H} (400 MHz, CDCl_3) 7.77-7.66 (4H, m, Ar-H), 7.56-7.37 (7H, m, Ar-H), 7.10 (1H, d, J 8.4, H-8), 6.34 (1H, d, J 8.4, H-9), 3.91-3.67 (3H, m, H-13 and H-4), 3.41 (1H, br. s, H-2), 2.15 (1H, br. s, H-3), 1.78-1.52 (4H, m, H-11 and H-12), 1.46 (1H, br. s, H-3), 1.10 (9H, s, H-19); δ_{C} (100 MHz, CDCl_3) 143.4 (Ar-C), 135.6 (Ar-C), 133.9 (Ar-C), 130.4 (C-8), 129.7 (Ar-C), 129.2 (Ar-C), 127.7 (Ar-C), 115.5 (C-9), 108.9 (C-7), 63.7 (C-4 and C-13), 51.1 (C-2), 40.3 (C-3), 32.9 (C-11/C-12), 28.4 (C-11/C-12), 27.0 (C-19), 19.3 (C-18); m/z (ESI) 523.1780 (MH^+ , $\text{C}_{28}\text{H}_{36}\text{N}_2\text{OSiBr}$ requires 523.1780), 508 (100), 250 (10).

General method for transamination of amine

To a solution of the amine (2.1 mmol) in CH_2Cl_2 /DMF (10 mL, 1/1) was added 4-formyl-1-methylpyridinium benzenesulfonate (0.88 g, 3.20 mmol). After stirring for 1 h, DBU (0.95 mL, 6.30 mmol) was added, and the resulting dark purple solution was stirred for a further 1 h at room temperature. The reaction was quenched with sat. aq. oxalic acid (10 mL) and stirred for 16 h. Et_2O (20 mL) was added to the reaction, the organic layer was separated and washed with H_2O (2 x 10 mL), brine (10 mL) then dried over MgSO_4 , filtered and evaporated to dryness. The residue was purified by column chromatography.

6-Bromo-2-(3-hydroxypropyl)-2,3-dihydroquinolin-4(1H)-one (3.44)

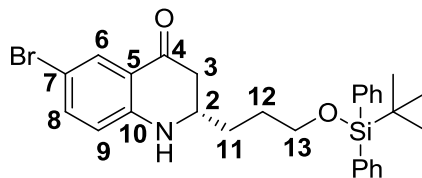
The product was purified by column chromatography, MeOH/CH₂Cl₂ 1:10, R_f = 0.45, to give a yellow solid (0.30 g, 50%); $[\alpha]_D^{25}$ – 63.4° (c = 0.71, CHCl₃); mp 108-110 °C; $\nu_{\max}/\text{cm}^{-1}$ 3340, 2940, 2880, 1660, 1610, 1500, 1410, 1290; δ_{H} (400 MHz, CDCl₃) 7.93 (1H, d, J 2.4, H-6), 7.37 (1H, dd, J 2.4, 8.7, H-8), 6.60 (1H, d, J 8.7, H-9), 4.82 (1H, br. s, H-1), 3.81-3.72 (2H, m, H-13), 3.72-3.63 (1H, m, H-2), 2.70 (1H, dd, J 3.8, 16.2, H-3), 2.50 (1H, dd, J 12.3, 16.2, H-3), 1.83-1.61 (5H, m, H-11, H-12 and H-14); δ_{C} (100 MHz, CDCl₃) 192.9 (C-4), 150.2 (C-10), 137.8 (C-8), 129.7 (C-6), 120.1 (C-5), 117.7 (C-9), 110.0 (C-7), 62.4 (C-13), 53.0 (C-2), 43.6 (C-3), 31.6 (C-12/C-11), 28.4 (C-12/C-11); m/z (ESI) 284.0282 (MH⁺, C₁₂H₁₅NO₂Br requires 284.0286), 215 (10), 213 (19).

6-Bromo-2-(3-(*tert*-butyldimethylsilyloxy)propyl)-2,3-dihydroquinolin-4(1H)-one (3.45)

To a solution of the ketone (1.00 g, 3.50 mmol) in dry CH₂Cl₂ (30 mL) was added imidazole (0.60 g, 8.70 mmol), 4-DMAP (42.0 mg, 0.35 mmol) and TBDMSCl (1.10 g, 7.00 mmol). The reaction was stirred at room temperature for 36 h and quenched by the addition of sat. aq. NH₄Cl (30 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 30 mL) and the combined organic extracts dried over MgSO₄, filtered and evaporated to dryness. The product was purified by column chromatography, MeOH/CH₂Cl₂ 1:10, R_f = 0.35, to give a yellow solid (1.00 g, 72%); $[\alpha]_D^{25}$ – 46.0° (c = 1.0, CHCl₃); mp 126-128 °C; $\nu_{\max}/\text{cm}^{-1}$ 3350, 2938, 2936, 2860, 1670, 1620; δ_{H} (400 MHz, CDCl₃) 7.94 (1H, d, J 2.4, H-6), 7.37 (1H, dd, J 2.4 and 8.7, H-8), 6.58 (1H, d, J 8.7, H-9), 4.76 (1H, s, H-1), 3.77-3.60 (3H, m, H-2 and H-13), 2.70 (1H, dd, J 3.1, 16.1, H-3), 2.50 (1H, dd, J 12.2, 16.1, H-3), 1.89-1.61 (4H, m, H-11 and H-12), 0.93 (9H, s, H-15), 0.10 (3H, s, C-16), 0.09 (3H, s, C-16); δ_{C} (100 MHz, CDCl₃) 192.8 (C-4), 150.1 (C-10), 137.7 (C-6), 129.8 (C-8), 120.1 (C-5), 117.7 (C-9), 109.9 (C-7), 62.7 (C-13), 52.9 (C-2), 43.6 (C-3), 31.7 (C-11), 28.6 (C-12), 25.9 (C-15), 18.3 (C-14), –5.3 (C-16); m/z

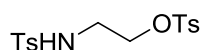
(EI) 397.1068 (M^+ , $C_{18}H_{28}NO_2SiBr$ requires 397.1073), 342 (100), 343 (90), 266 (50), 226 (70), 75 (50).

6-bromo-2-(3-*tert*-butyldiphenylsiloxy)propyl)-2,3-dihydroquinolin-4(1*H*)-one (3.36)

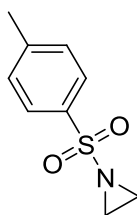


The product was purified by column chromatography, EtOAc/*n*-hexane, 1:1, R_f = 0.35, to give a yellow oil (75 %); $[\alpha]_D^{25}$ – 19.2° (c = 1.2, $CHCl_3$); ν_{max}/cm^{-1} 3070, 2950, 2940, 2860, 1670, 1600, 1490, 1430, 1110; δ_H (400MHz, $CDCl_3$) 7.96 (1H, d, J 2.4, H-6), 7.76-7.66 (4H, m, Ar-H), 7.52-7.39 (6H, m, Ar-H), 7.36 (1H, dd, J 2.4, 8.7, H-8), 6.50 (1H, d, J 8.7, H-9), 4.58 (1H, s, NH), 3.77 (2H, t, J 5.7, H-13), 3.68-3.49 (1H, m, H-2), 2.66 (1H, dd, J 3.8, 16.2, H-3), 2.46 (1H, dd, J 12.4, 16.2, H-3), 1.85-1.58 (4H, m, H-11 and H-12), 1.13 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 193.0 (C-4), 150.1 (C-10), 137.8 (C-8), 135.4 (Ar-C), 133.6 (Ar-C), 129.8 (C-6), 129.7 (Ar-C), 127.7 (Ar-C), 120.1 (C-5), 117.8 (C-9), 110.0 (C-7), 63.5 (C-13), 52.8 (C-2), 43.4 (C-3), 31.4 (C-11/C-12), 28.3 (C-11/C-12), 26.6 ($C(CH_3)_3$), 19.1 ($C(CH_3)_3$); m/z (ESI) 522.1447 (MH^+ , $C_{28}H_{33}NO_2SiBr$ requires 522.1464), 524 (100), 446 (40), 323 (12).

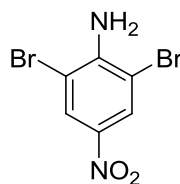
2-(4-Methylphenylsulfonamido)ethyl 4-methylbenzenesulfonate¹⁷³



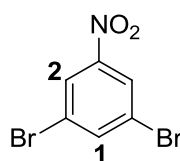
To a solution of 2-aminoethanol (1.00 g, 16.3 mmol) in pyridine (7 mL) at 0 °C was added *p*-toluenesulfonyl chloride (6.50 g, 34.4 mmol) portion wise, maintaining the temperature below 10 °C. The reaction mixture was warmed to room temperature over 3 h and then partitioned between EtOAc (40 mL) and 1M aq. HCl (40 mL). The organic layer was washed consecutively with 1M aq. HCl, sat. aq. $NaHCO_3$ and brine, then dried, filtered and evaporated to dryness. The orange residue was filtered through a pad of silica using CH_2Cl_2 as eluant. Evaporation of the CH_2Cl_2 , followed by trituration with Et_2O gave the product as an off-white solid (4.38 g, 73%) which was used in the next step without further purification. δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, J 8.1, Ar-H), 7.72 (2H, d, J 8.1, Ar-H), 7.38 (2H, d, J 8.1, Ar-H), 7.33 (2H, d, J 8.1, Ar-H), 4.87 (1H, br. t, J 6.3, NH), 4.07 (2H, t, J 5.3, OCH_2), 3.25 (2H, m, NCH_2), 2.49 (3H, s, CH_3), 2.46 (3H, s, CH_3).

1-Tosylaziridine¹⁷⁴

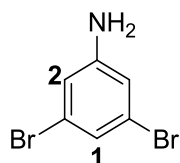
A solution of 20% aq. KOH (3.5 mL) was added to a solution of the tosylate (0.88 g, 2.38 mmol) in toluene (20 mL). The biphasic solution was stirred at room temperature until the reaction was complete (monitored by TLC). The mixture was diluted with H₂O (20 mL) and the organic phase separated, dried over Na₂SO₄, filtered and evaporated to dryness to give an off-white solid. This was stored in the freezer and used without further purification. δ_{H} (400 MHz, CDCl₃) 7.86 (2H, d, *J* 8.2, Ar-H), 7.38 (2H, d, *J* 8.2, Ar-H), 2.48 (3H, s, CH₃), 2.40 (4H, br. s, NCH₂).

5.3 Compounds used in Chapter 4**2,6-Dibromo-4-nitroaniline (4.12)**¹⁷⁵

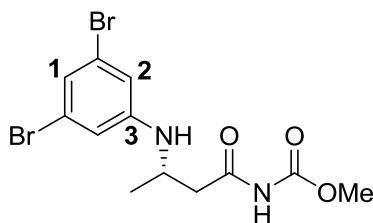
To a vigorously stirred solution of nitroaniline (10.0 g, 72.0 mmol) in glacial acetic acid (90 mL) was added a solution of bromine (7.40 mL, 145 mmol) in glacial acetic acid (50 mL) over 4 h. Half way through the addition, H₂O (20 mL) was added to dissolve the precipitate formed. Upon complete addition, the reaction mixture was poured into an ice/H₂O mixture, stirred and filtered. The solid collected was thoroughly washed with H₂O to give the aniline as a yellow/green solid (20.3 g, 95%); mp 199-201°C (lit 202-203 °C)¹⁷⁶; $\nu_{\text{max}}/\text{cm}^{-1}$ 3550, 3270, 2960, 1720, 1650, 1520; δ_{H} (400 MHz, DMSO-*d*₆) 8.26 (2H, s, CH), 6.77 (2H, br. s, NH₂); δ_{C} (100 MHz, CDCl₃) 149.6 (C-NH₂), 136.9 (C-NO₂), 128.4 (CH), 103.7 (C-Br); *m/z* (EI) 293.8638 (M⁺, C₆H₄N₂O₂Br₂ requires 293.8639), 268 (45), 266 (72), 264 (40), 252 (20), 250 (40), 248 (20), 170 (50), 168 (48), 90 (50).

1,3-Dibromo-5-nitrobenzene (4.13)¹⁷⁵

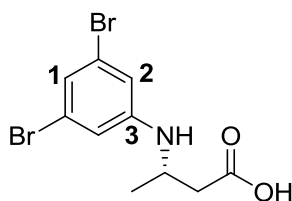
To the aniline (1.00 g, 3.30 mmol) in EtOH (12 mL) and conc. sulfuric acid (1.2 mL) at 90 °C, was added NaNO₂ (0.50 g, 11.0 mmol) portion wise. When the addition was complete, the reaction mixture was stirred for 40 h at 90 °C. The cooled reaction mixture was poured into an ice/H₂O mixture and the resultant slurry was filtered. The collected solid was dissolved in hot EtOH (15 mL), filtered and the filtrate was evaporated to give the required compound as a light brown solid (0.71 g, 75%); mp 99-101 °C, (lit. 95 °C)¹⁷⁷; $\nu_{\text{max}}/\text{cm}^{-1}$ 3080, 1530, 1340, 890; δ_{H} (400 MHz, CDCl₃) 8.36 (2H, d, *J* 1.7, H-2), 8.03 (1H, t, *J* 1.7, H-1); δ_{C} (100 MHz, CDCl₃) 149.0 (C-NO₂), 140.1 (C-1), 125.6 (C-2), 123.5 (C-Br); *m/z* (EI) 278.8529 (M⁺, C₆H₃NO₂Br₂ requires 278.8531), 235 (75), 154 (30), 75 (80).

3,5-Dibromoaniline (4.8)¹⁷⁵

To a solution of 3, 5-dibromonitrobenzene (7.32 g, 26.1 mmol) in EtOH (60 mL) and THF (60 mL) was added tin(II) chloride dihydrate (28.6 g, 127 mmol). After stirring for 20 h at room temperature, the solvent was removed by evaporation and 1M aq. KOH (50 mL) added. After stirring for two hours, the aqueous layer was separated and extracted with Et₂O (3 x 25 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated under vacuum to give the product as a light brown solid (5.51 g, 86%); mp 51-53 °C (lit 55-56 °C)¹⁷⁸; $\nu_{\text{max}}/\text{cm}^{-1}$ 3420, 3300, 3200, 1620, 1590, 1560, 1450; δ_{H} (400 MHz, CDCl₃) 7.04 (1H, t, *J* 1.6, C-1), 6.77 (2H, d, *J* 1.6, C-2), 3.79 (2H, br. s, NH₂); δ_{C} (100 MHz, CDCl₃) 148.6 (C-NH₂), 123.7 (C-Br), 123.4 (C-1), 116.5 (C-2); *m/z* (EI) 251 (MH⁺, 100), 249 (66), 172 (30), 170 (30), 91 (50), 90 (45), 63 (40).

Methyl 3-(3,5-dibromophenylamino)butanoylcarbamate (4.9)

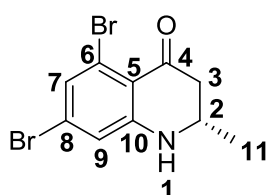
The alkene (1.25 g, 8.70 mmol) and $[\text{Pd}(\text{R-BINAP})(\text{H}_2\text{O})_2]^{2+}[\text{TfO}]_2^-$ (0.46 g, 0.43 mmol) were dissolved in toluene (22 mL) and heated to 50 °C. A solution of 3, 5-dibromoaniline (2.15 g, 8.60 mmol) in toluene (22 mL) was added over 24 h (via a syringe pump). The reaction was stirred for an additional 48 h at 50 °C and then the solvent was removed by evaporation. The residue was purified by column chromatography, $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 9:1, $R_f = 0.35$. The product was recrystallised from toluene, with the mother liquors evaporated to dryness, to give the product as an off-white solid (1.73 g, 50%); $[\alpha]_{\text{D}}^{25} - 9.85^\circ$ ($c = 1$, CHCl_3 , 97% ee); Chiral HPLC Hichrom-CHI-PGG-2759, 10% IPA in *n*-hexane, 1.0 mL/min, t_{R} (major) = 24.7 min, t_{R} (minor) = 33.4 min; mp 117-118 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ 3410, 3220, 2730, 1770, 1670, 1590, 1650, 1380, 1230; δ_{H} (400 MHz, CDCl_3) 7.47 (1H, br. s, NHCO), 6.97 (1H, t, J 1.6, H-1), 6.69 (2H, d, J 1.6, H-2), 4.12 (1H, br. d, J 9.2, NH), 4.04-3.93 (1H, m, CH), 3.82 (3H, s, OCH_3), 3.14 (1H, dd, J 5.9, 16.0, CH_2CO), 2.95 (1H, dd, J 6.0, 16.0, CH_2CO), 1.32 (3H, d, J 6.4, CHCH_3); δ_{C} (100 MHz, CDCl_3) 172.6 (CONH), 152.4 (CO_2), 149.0 (C-3), 123.6 (C-Br), 122.6 (C-1), 114.8 (C-2), 53.3 (OCH_3), 45.7 (NHCH), 41.8 (CH_2CO), 20.6 (CHCH_3); m/z (ESI) 397 (55), 395 (MH^+ , 100), 393 (50), 321 (3), 319 (10), 317 (5), 280 (10), 278 (20), 276 (10).

3- (3, 5-Dibromoohenylamino)botanic acid (4.14)

To a solution of the carbamate (0.46 g, 1.20 mmol) in MeOH (10 mL) was added 1M aq. KOH (12.0 mL, 12.0 mmol). The resultant solution was stirred at room temperature for 1 h and evaporated to dryness. H_2O was added to the residue and the aqueous layer was extracted with Et_2O (2 x 10 mL). The aqueous layer was then acidified to pH 4 by the addition of 1M

aq. HCl and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried over MgSO₄ and evaporated to give the acid as a brown gum (0.30 g, 77%); δ_{H} (400 MHz, CDCl₃) 7.00 (1H, t, *J* 1.6, H-1), 6.70 (2H, d, *J* 1.6, H-2), 3.97-3.85 (1H, m, CH), 2.65 (1H, dd, *J* 5.5, 15.6, CH₂CO), 2.57 (1H, dd, *J* 6.2, 15.6, CH₂CO), 1.33 (3H, d, *J* 6.5, CH₃CH); δ_{C} (100 MHz, CDCl₃) 176.4 (CO₂H), 148.7 (C-3), 123.6 (C-Br), 122.9 (C-1), 114.9 (C-2), 45.6 (CH), 40.2 (CH₂CO), 20.3 (CH₃); *m/z* (ESI) 337 (M⁺, 100%), 321 (5), 319 (8), 317 (5), 280 (10), 278 (20), 276 (10).

5,7-Dibromo-2-methyl-2,3-dihydroquinolin-4(1H)-one (4.10)



Polyphosphoric acid (2.00 g) was added to the acid (100 mg, 0.25 mmol) and the resultant slurry heated to 90 °C for 4 h. After cooling to 60 °C, an ice/H₂O mixture was added and the reaction mixture was stirred for a further 15 min. The product was then extracted with EtOAc (3 x 5 mL). The combined organic extracts were basified to pH 14 using 1M aq. NaOH, washed with brine, dried over MgSO₄, filtered and concentrated under vacuum. The crude product was purified by column chromatography, EtOAc/*n*-hexane 3:7, *R_f* = 0.35, to give the tetrahydroquinolone as a bright yellow solid (60.0 mg, 42%); $[\alpha]_{\text{D}}^{25}$ -19.0° (*c* = 1, CHCl₃); mp 157-159 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ 3360, 1660, 1490; δ_{H} (400 MHz, CDCl₃) 7.14 (1H, d, *J* 1.8, H-7), 6.80 (1H, d, *J* 1.8, H-9), 4.42 (1H, br. s, H-1), 3.86-3.74 (1H, m, H-2), 2.70 (1H, dd, *J* 3.8, 15.4, H-3), 2.53 (1H, dd, *J* 12.3, 15.4, H-3), 1.34 (3H, d, *J* 6.4, H-11); δ_{C} (100 MHz, CDCl₃) 153.1 (C-4), 128.4 (C-10), 128.4 (C-8), 127.0 (C-7), 123.3 (C-6), 117.7 (C-9), 115.0 (C-5), 48.1 (C-2), 46.1 (C-3), 21.1 (C-11); *m/z* (EI) 319 (M⁺, 48%), 304 (100).

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