The University Of Sheffield.

Kinetic Resolution of Nitrogen Heterocycles using Chiral Organolithium Chemistry

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Abstract

The kinetic resolution and α-deprotonation of nitrogen–containing heterocycles using organolithium chemistry has been an important area of work in the Coldham group over the last decade. Some successful research published has been focussed around the kinetic resolution reactions of *N*-Boc-2-arylpiperidines and *N*-Boc-2-aryltetrahydroquinolines.

This report describes the extension of this chemistry to different heterocycles, namely 1,3-oxazinane **A**, benzoxazines **B**, quinoxalines **C**, and indoline **D** derivatives (Figure A).

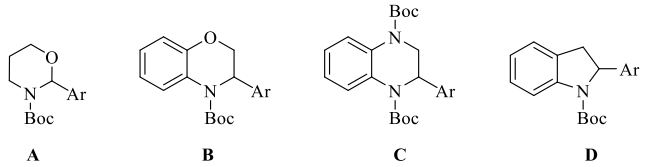


Figure A

The kinetic resolutions were attempted using a chiral base complex (*n*-BuLi/(+)-sp), which led to the recovered starting materials in good yields and excellent enantiomer ratios (Figure B).

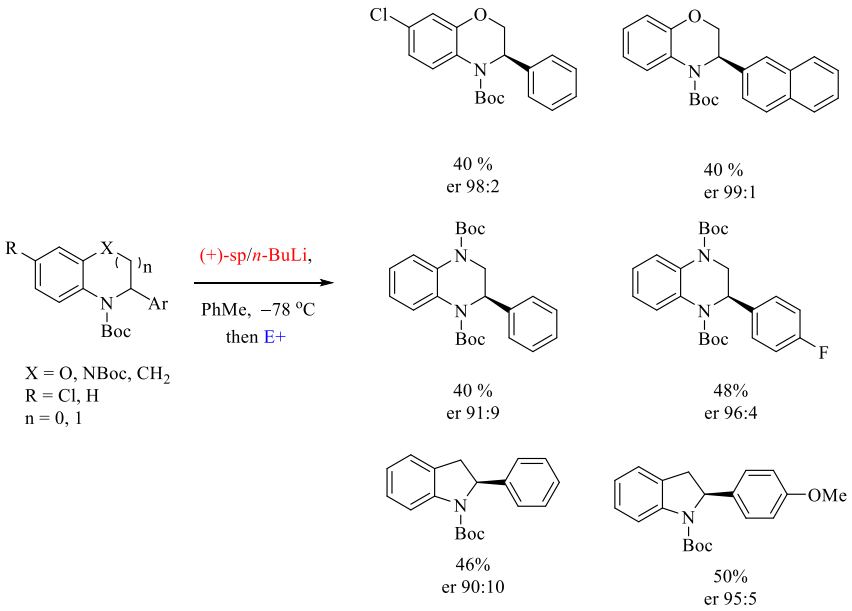
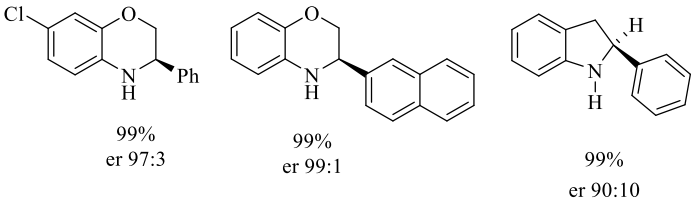


Figure B

It was possible to remove the Boc group using acid (TFA) to give the corresponding secondary amine with the enantiopurity being maintained (Figure C).



Acknowledgements

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Finally, I wished my brother Yasser was alive to see this day when my dream came true.

"And they ask you, [O Muhammad], about the soul. Say, “The soul is of the affair of my Lord. And mankind have not been given of knowledge except a little.”

ABBREVIATIONS

Ac	acetyl
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bt	benzotriazole
CIPE	complex induced proximity effect
cm	centimetre(s)
CSP	chiral stationary phase
d	day(s)
DFT	density functional theory
DKR	dynamic kinetic resolution
DME	dimethoxyethane
DMPU	*N*, *N*′-dimethylpropylene urea
DNA	deoxyribonucleic acid
dr	diastereomeric ratio
DTR	dynamic thermodynamic resolution
E^+	electrophile
EI	electron impact
ent-	enantiomer
epi-	epimer
eq. or equiv.	equivalent(s)
er	enantiomeric ratio
ES	electrospray
Et	ethyl
F_{254}	fluorescence indicator 254 nm
FT	Fourier transform
g	gram(s)
$\Delta\Delta G^{\neq}$	relative free energy change
ΔG^0	standard-state free energy of reaction
$\Delta G^{\ddagger}$	Gibbs energy of activation
h	hour(s)
$\Delta H^{\ddagger}$	enthalpy of activation
HFIP	hexafluoro-2-propanol
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
i.d.	internal diameter
^{i}Pr or *i*-Pr	isopropyl
IR	infrared
k	reaction rate constant
K	Kelvin
kJ	kilojoule(s)
KR	kinetic resolution
L	litre(s)
L^*	chiral ligand
LCT	liquid chromatography tandem
LDA	lithium diisopropylamide
lit.	literature
LRMS	low resolution mass spectrometry
µL	microlitre(s)

M	molar
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	millilitre(s)
mm	millimetre(s)
mmol	millimole(s)
mol	mole(s)
m.p.	melting point
MPV	Meerwein–Ponndorf–Verley
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
m/z	mass to charge ratio
n-Bu	normal butyl
nm	nanometre(s)
NMDA	*N*-methyl-D-aspartate
NMR	nuclear magnetic resonance
OTf	triflate
p-	*para*-
PARP	poly (ADP-ribose) polymerase
Ph	phenyl
Piv	pivaloyl
PMDTA	*N*, *N*, *N*′, *N*′, *N*′′-pentamethyldiethylenetriamine
PPA	polyphosphoric acid
psi	pounds per square inch
rac-	racemic
R_f	retardation factor
RSM	recovered starting material
rt or r.t.	room temperature
s	selectivity factor
$\Delta S^{\ddagger}$	entropy of activation
s-Bu	secondary butyl
SM	starting material
(–)-sp	(–)-sparteine
(+)-sp	(+)-sparteine
SPS	solvent purification system
SnAP reagents	2-[(tributylstannyl)methoxy]-Ethanamine
surr	surrogate
t	time
^{t}Bu or *t*-Bu	tertiary butyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THB	tetrahydrobenzoxazine
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline
THQ	tetrahydroquinoline
TLC	thin layer chromatography
TMEDA	*N, N, N', N'*-Tetramethylethylenediamine
TMS	trimethylsilyl
Ts	tosyl
UV	ultraviolet

v/v volume to volume ratio

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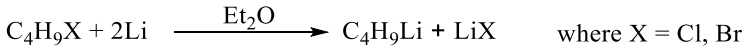
Chapter 1 - Introduction

1.1 Organolithium reagents in chemistry

Organolithium reagents have played a key role in many areas of organic chemistry over many years.[1,2] The first report of organolithium reagents was in 1917 by Schlenk, where MeLi, EtLi, and PhLi were obtained by exchange reactions from the mercury derivatives. Further contributions from Ziegler showed that *n*-BuLi and other alkyllithiums could be prepared from alkyl chlorides and bromides (Scheme 1.1).[3] In 1930, Wittig and Gilman independently discovered aromatic metalleation and the lithium−halogen exchange reaction.[4,5] These chemists found that organolithium reagents can often perform the same reactions as Grignard reagents, with increased rates and higher yields.[5]



Scheme 1.1

1.2 Structures of organolithium reagents

In 1963, the first acquired single-crystal X-ray structure of an organolithium reagent was that of ethyllithium.[3,6,7] It was found that ethyllithium adopts a cubic tetramer structure with strong association between tetramer units. Since then, several hundred solid state organolithium structures have been reported with aggregation states ranging from monomeric to polymeric (Figure 1.1).[3]

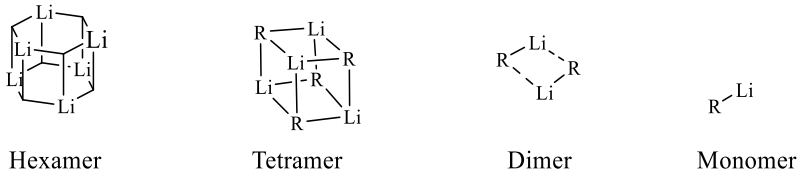


Figure 1.1

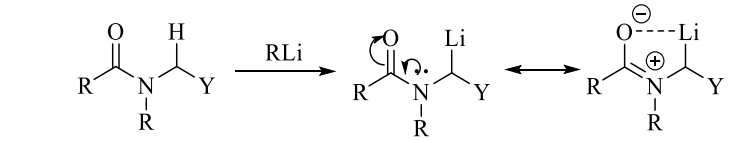
In general, hydrocarbon solvents are used to store organolithium reagents as they are soluble and stable in these solvents.[3] However, methyllithium and phenyllithium are remarkably stable and soluble in ether or THF.[2] A single carbanionic ligand cannot adequately stabilise the electron-deficient lithium atom of an organolithium compound or the lithium salts of carbanions. Hence, in non-polar solvents, lithium salts generally form dimers, tetramers, and even higher aggregates (Table 1.1). Usually, a saturated tetrahedral coordination geometry with four donor ligands is preferred by the lithium cation.[1]

Table 1.1 Typical aggregation state of organolithiums in hydrocarbon solution.[1,2]

Hexameric	Tetrameric	Dimeric	Monomeric
EtLi	*s*-BuLi	$PhCH_2Li$	-
n-BuLi	i-PrLi		
	t-BuLi		

1.3 Lithiation *α*- to a nitrogen atom

Lithiation is more favoured when it takes place adjacent (*α*-) to a nitrogen-based functional group which can co-ordinate strongly to the organolithium. The formation of the lithiated intermediate can be fast if the proton removed is benzylic, allylic, vinylic, or attached to an aromatic or small-ring saturated heterocycle, due to the increase in the acidity of the *α*-proton. Some α-lithiations use allyl or benzyl stabilisation as well as the heteroatom effect.[1]



Y = Ph, vinyl, heterocyclic, H lithiated intermediate

Scheme 1.2

Formation of the lithiated intermediate is important as it is this that can readily react with electrophiles to form various substituted amines.[1] There are three main classifications of intermediate: unstabilised, dipole-stabilised and mesomerically-stabilised.

When the nitrogen atom is not acylated, these intermediates are classed as unstabilised *α*-amino-organolithium compounds. The nitrogen lone pair can strongly interact with an adjacent C–Li bond and this destabilises the organolithium by a filled-filled orbital interaction.[1] However, these are referred to as 'unstabilised' due to the lack of any further stabilisation of the organolithium (Figure 1.2).[8]

In a dipole-stablised carbanion, the oxygen lone pair is coordinated to the lithium atom. This interaction makes the nitrogen atom more positively polarised and weakens the C–Li bond.[1] The intermediate is stabilised by pushing the lone pair of the nitrogen atom into the amide carbonyl (or similar functional group) to give a dipolar resonance form with a positively charged nitrogen atom adjacent to the carbanion.[8]

Mesomerically-stabilised *α*-amino-organolithiums are compounds that contain lithiated allylic or benzylic amines, and 2-azaallyl anions. These involve varying degrees of resonance stabilisation of the negative charge and the position of the lithium atom is not always clear.[9]

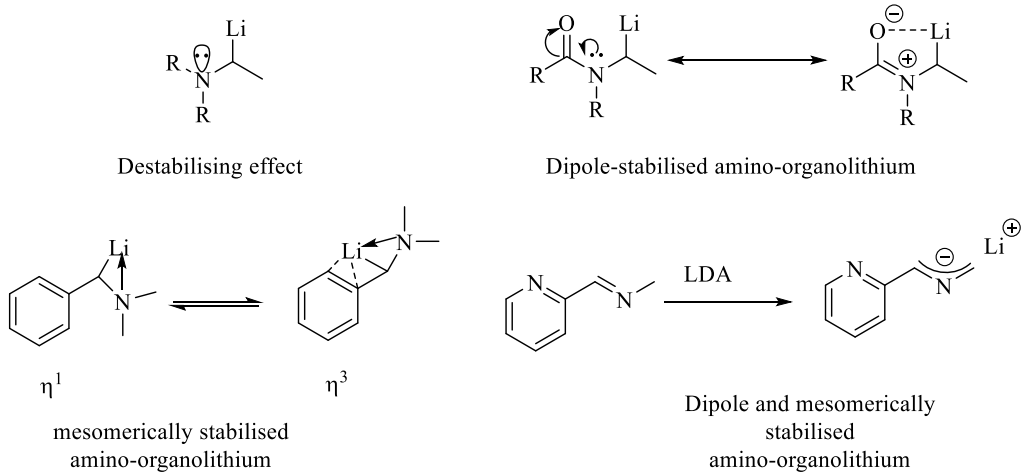


Figure 1.2

Co-ordinating ligands or solvents can stabilise an electron-deficient lithium atom as they can be an alternative source of electron density.[10] The interactions between organolithium reagents with ligands or co-ordinating solvents leads to the formation of hetero-aggregates which increases the reactivity of the organolithiums.[11] The most commonly used ligands are shown in Figure 1.3.[12–15]

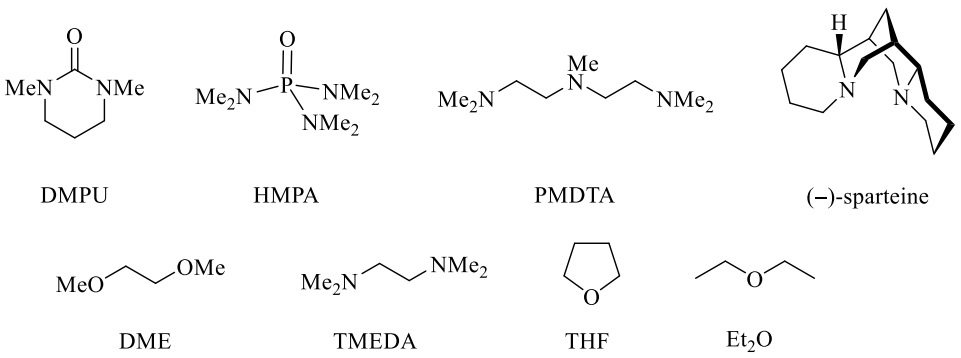
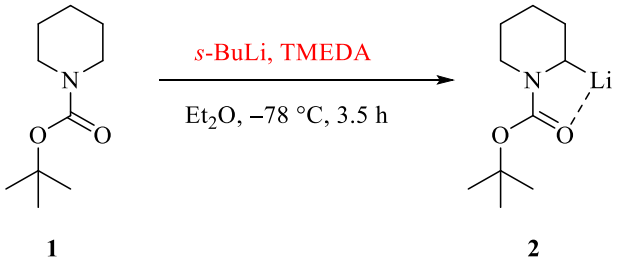


Figure 1.3

In 1989, Beak and Lee were the first to describe the effect of the *tert*-butoxycarbonyl (Boc) group on α-amino organolithiums, which is not only used to protect the nitrogen atom, but also acts as a convenient directing group for the *α*-lithiation of the amines.[16] Stabilisation of the organolithium intermediate occurs due to the lithium atom being able to co-ordinate to the electron-rich oxygen of the carbonyl group (Scheme 1.3).[17] Alternatively, groups such as amides,[18] formamides,[19] and nitrosamines[20] can be used for dipole-stabilisation of *α*-amino organolithium intermediates.[1]



Scheme 1.3

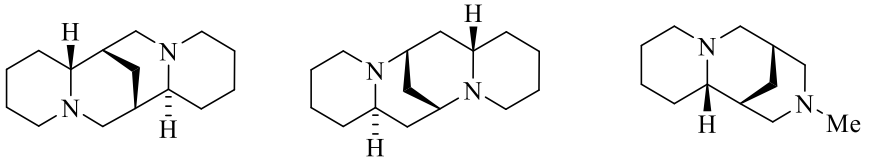
1.4 TRANSFER OF STEREOCHEMICAL INFORMATION

Four pathways are possible for the transfer of stereochemical information:

1) Asymmetric Deprotonation (AD).
2) Kinetic Resolution (KR).
3) Dynamic Kinetic Resolution (DKR).
4) Dynamic Thermodynamic Resolution (DTR).

1.4.1 ASYMMETRIC DEPROTONATION

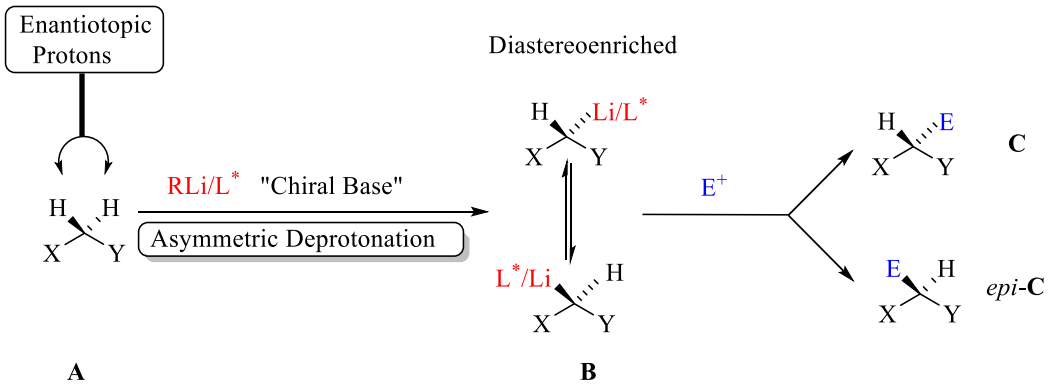
Using organolithium reagents with external chiral ligands such as (–)-sparteine **3**, (+)-sparteine **4** or (+)-sparteine surrogate **5** can form a chiral base which can asymmetrically deprotonate a compound with enantiotopic protons as initially reported by Hoppe and co-workers in 1989.[21] Deprotonative lithiations are central to many aspects of organolithium chemistry in order to generate enolates, dipole-stabilised or delocalised carbanion intermediates for several applications.[22]



(–)-sparteine **3** (+)-sparteine **4** (+)-sparteine surrogate **5**

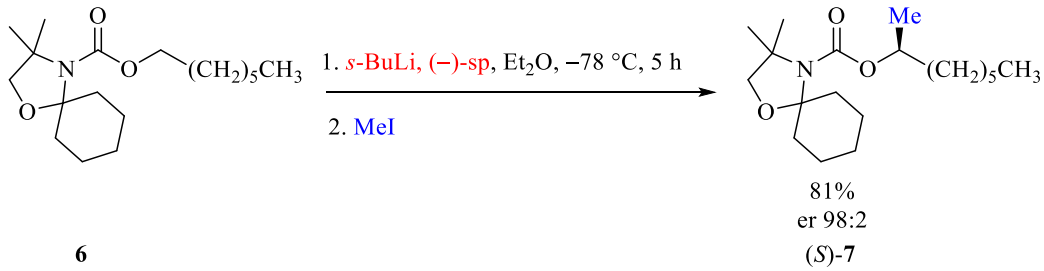
Figure 1.4

A chiral base is formed when an organolithium reagent complexes with a chiral ligand. This chiral base can selectively deprotonate an enantiotopic proton from the achiral substrate **A** to give diastereoenriched complex **B** (Scheme 1.4). The intermediate can be quenched with an electrophile to afford the chiral compounds **C** or *epi*-**C** with retention or inversion of configuration at the carbon atom.[22]



Scheme 1.4

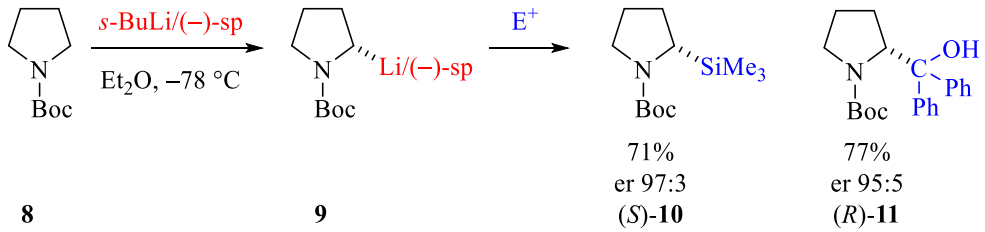
The first report on the achievement of high enantioselectivities using *s*-BuLi/(–)-sparteine in a lithiation-substitution sequence of *O*-alkyl-carbamates was reported by Hoppe and co-workers.[21] For example, carbamate **6** was treated with the *s*-BuLi/(–)-sparteine complex in ether at –78 ºC and quenching the reaction using methyl iodide gave carbamate (*S*)-**7** in was good yield (81%) and excellent enantiomer ratio (er) (98:2) (Scheme 1.5).



6 (*S*)-**7**

Scheme 1.5

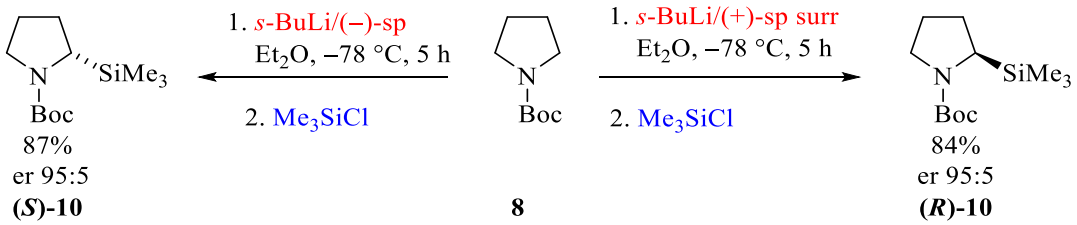
In 1994, Beak and co-workers achieved lithiation of *N*-Boc-pyrrolidine **8** by using *sec*-butyllithium with (–)-sparteine to give (*S*)-2-lithio-*N*-Boc-pyrrolidine **9** which was quenched using various electrophiles to provide 2-substituted *N*-Boc-pyrrolidines with er up to 97:3 and in good yields 71-77% (Scheme 1.6).[22,23]



8 **9** (*S*)-**10** (*R*)-**11**

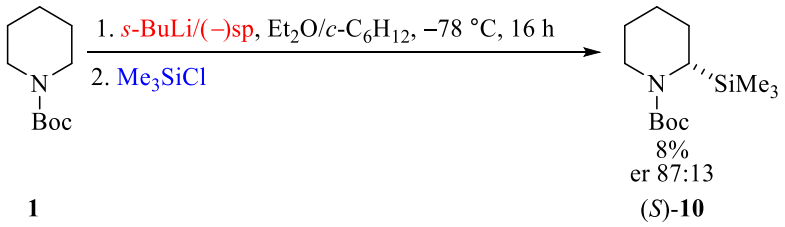
Scheme 1.6

In 2002, O'Brien and co-workers carried out some detailed studies regarding the use of the (+)-sparteine surrogate rather than (–)-sparteine in the asymmetric deprotonation of *N*-Boc-pyrrolidine **8** in Et_2O at –78 ºC, then quenching with trimethylsilyl chloride.[24] In comparison with work carried out by Beak, the two ligands generated almost identical yields (84% *R*-**10a** and 87% *S*-**10b**) and enantiomeric ratios of each enantiomer (Scheme 1.7).



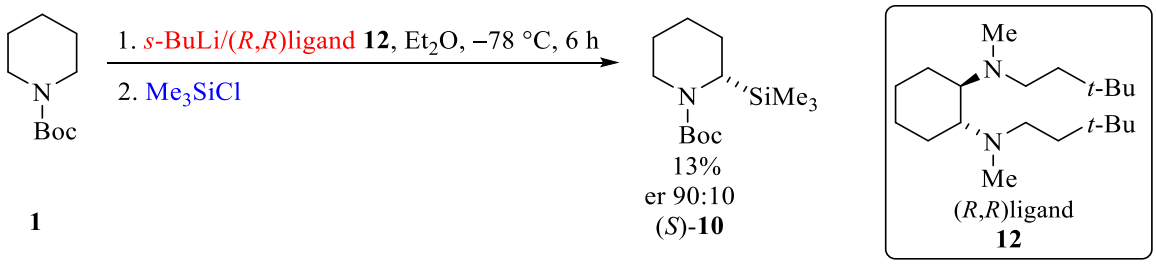
Scheme 1.7

In terms of the six-membered ring, the first asymmetric deprotonation of *N*-Boc-piperidine **1** was reported in 2002 by Bailey et al.[25] Using *s*-BuLi with (–)-sparteine **3** in Et_2O/cyclohexane at –78 ºC for 16 h and treating the intermediate complex with trimethylsilyl chloride, gave (*S*)-**10** in poor yield (8%) with reasonable er (87:13). Although a large amount of the starting material (40%) was recovered which was unsatisfactory, this study proved that the methodology was promising (Scheme 1.8).



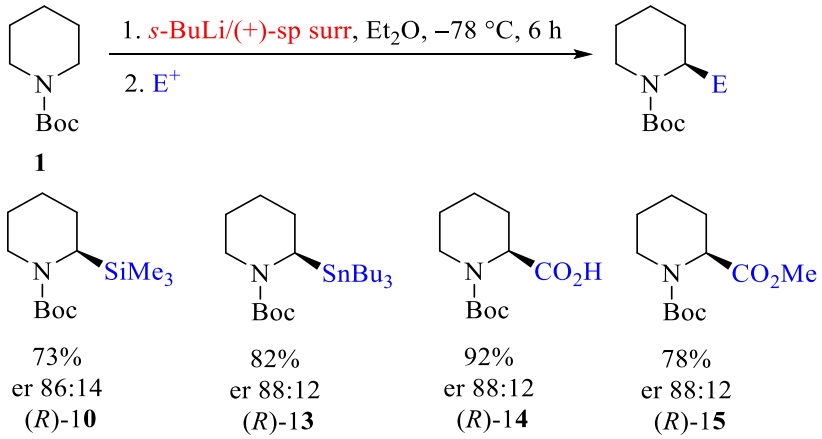
Scheme 1.8

Further research into the asymmetric deprotonation of **1** was reported by the Coldham group in 2007.[26] Using hindered ligands such as **12** with *s*-BuLi in Et_2O at –78 ºC for 6 h, and then using trimethylsilyl chloride to trap the lithiated intermediate, gave slight improvements for both the yield (13%) and enantioselectivity (90:10) of (*S*)-**10** (Scheme 1.9).



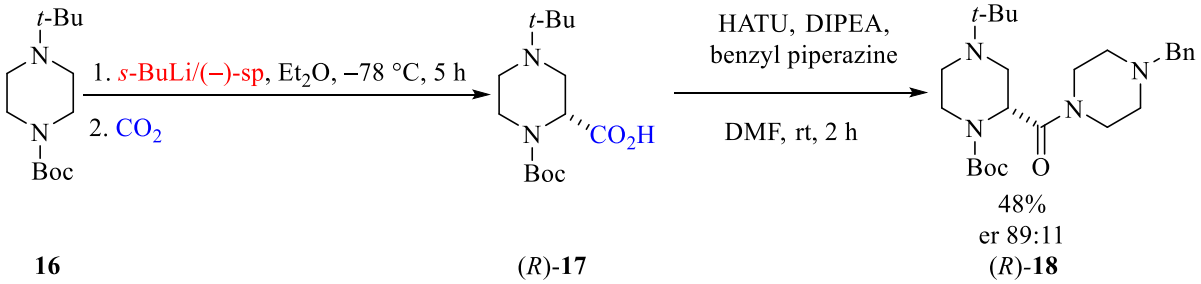
Scheme 1.9

Later, in 2010, O'Brien and co-workers found that using the (+)-sparteine surrogate **5** can give better yields than (–)-sparteine **3**.[27] It was reported that using this ligand on *N*-Boc-piperidine **1** with a range of electrophilic quenches gave up to 88:12 er and up to 92% yield of products (Scheme 1.10).[28]



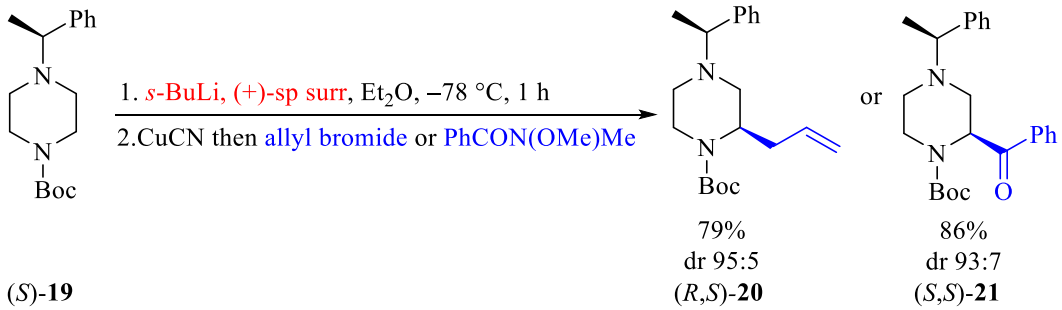
Scheme 1.10

In 2008, McDermott and co-workers successfully carried out reactions on a different six-membered ring, *N*-Boc-*N'*-*t*-butylpiperazine **16**.[29] Asymmetric deprotonation with *s*-BuLi complexed with (–)-sparteine at –78 °C for 5 h, followed by electrophilic trapping with CO_2 gave acid (*R*)-**17**. This was then treated with *N*-benzylpiperazine to give amide (*R*)-**18** with a high degree of selectivity (89:11 er) in 48% yield (Scheme 1.11).



Scheme 1.11

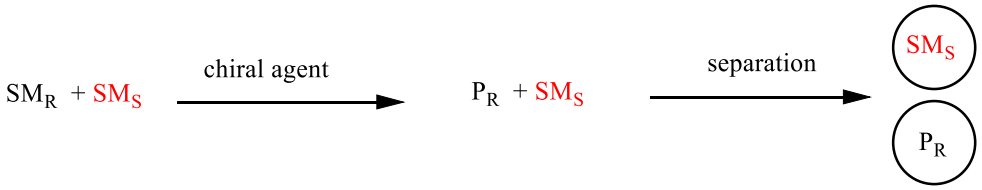
In 2015, O'Brien and co-workers reported that using *s*-BuLi with the (+)-sparteine surrogate **5** to deprotonate *N*-Boc-piperazine derivatives in Et_2O at –78 °C for 1 h, before quenching the intermediate with a range of electrophiles, gave some promising results (Scheme 1.12).[30]



Scheme 1.12

1.4.2 KINETIC RESOLUTION

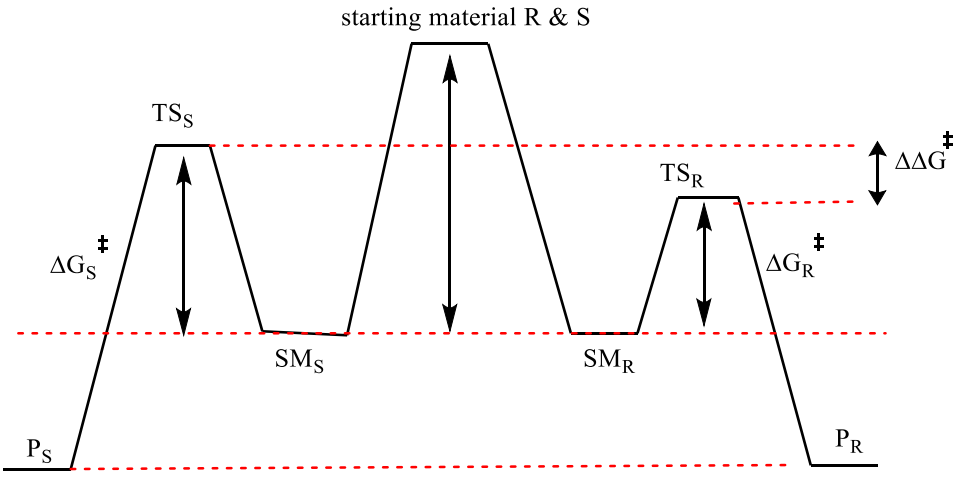
In organic chemistry, a kinetic resolution is a method to separate enantiomers in a racemic mixture due to them reacting at different rates in the presence of a chiral agent (Scheme 1.13).[31] These reactions can also be known as kinetically controlled asymmetric transformations.[32]



Scheme 1.13

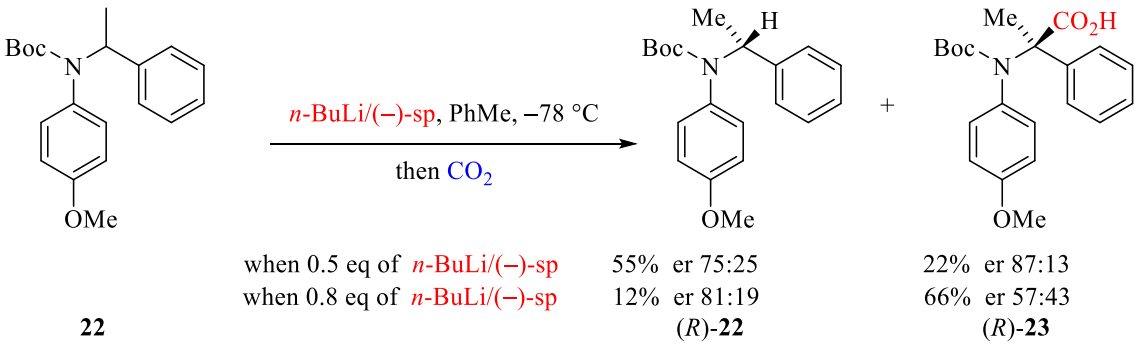
In terms of lithiation, a kinetic resolution leads to one of the enantiomers being preferentially deprotonated and quenched to give the product while the other enantiomer of starting material is recovered.[31,33] Therefore, both the quenched product and the recovered starting material can be isolated with good enantioselectivity.[31,33] However, the theoretical maximum yield of this procedure for both the product and the recovered starting material is 50%.[33,34] This is in contrast to DKR which theoretically has up to 100% yield.[35] The achievement of partial or complete resolution is by virtue of unequal rates of reaction of the enantiomers.[36] Gibbs free energy of both enantiomers are at the same level, and the products of the reaction with both enantiomers are also at equal levels. While the $\Delta G^{\ddagger}$ of transition state energies are different, from the

diagram below, the *R* enantiomer has a lower $\Delta G^{\ddagger}$ and would hence react faster than the *S* enantiomer (Scheme 1.14).[37]



Scheme 1.14

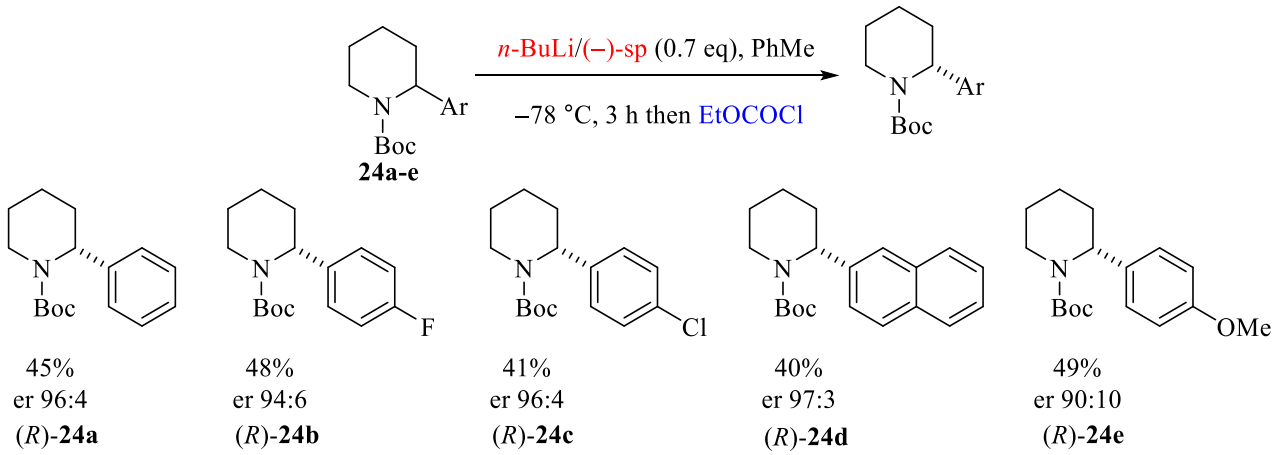
In 1997, Beak and co-workers studied the kinetic resolution of *N*-Boc-*α*-methylbenzylamine **22** using the *n*-BuLi/(–)sparteine complex.[38] The starting material (*R*)-**22** was recovered in 55% yield with 75:25 er, while the product (*R*)-**23** was isolated in 22% yield with 87:13 er. This result was obtained when 0.5 equivalents of the chiral base was used with CO_2 as the electrophile. However, with 0.8 eq of the chiral base, a lower yield (12%) of the starting material (*R*)-**22** was recovered with a good 81:19 er while a 66% yield of the product (*R*)-**23** was obtained with poor enantioselectivity (Scheme 1.15).



Scheme 1.15

Work in the Coldham group has involved the kinetic resolution of *N*-Boc-2-arylpiperidines **24a-e**. Lithiation of the 2-arylpyridines by using the chiral base system *n*-BuLi/(–)-sparteine

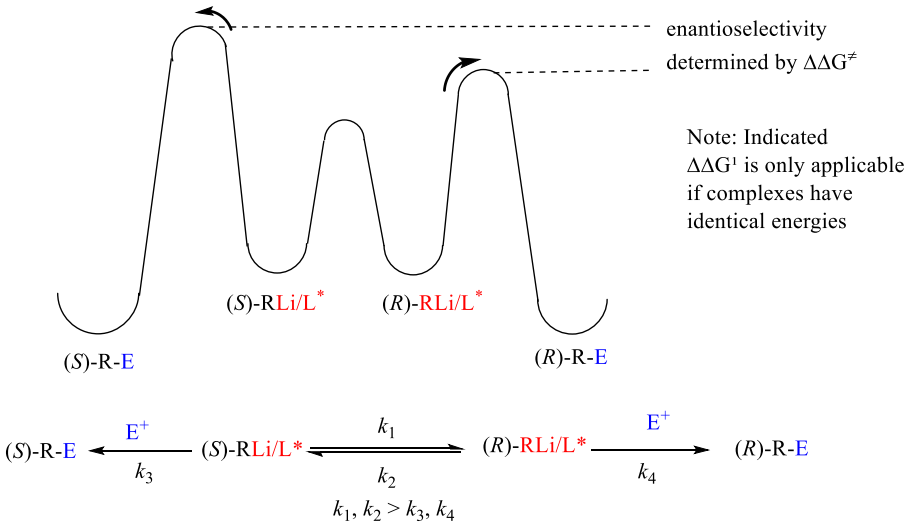
gave an organolithium intermediate which was then quenched with the electrophile ethyl chloroformate. This allowed recovery of the starting material in good yields with excellent enantiomeric ratios (Scheme 1.16).[39]



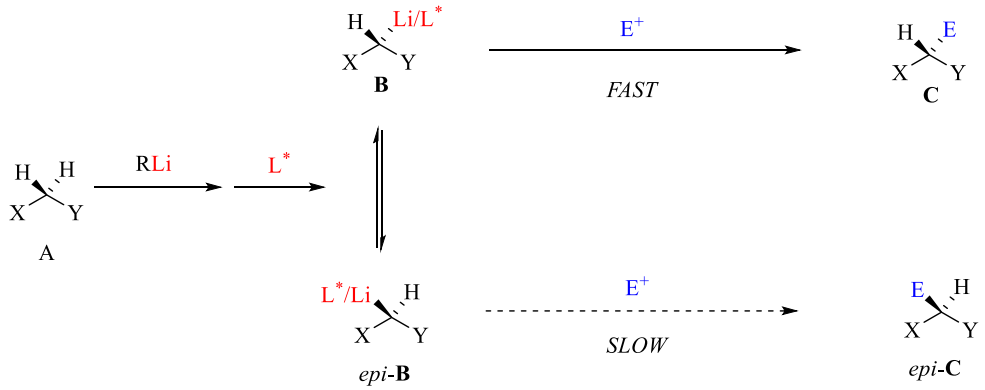
Scheme 1.16

1.4.3 DYNAMIC KINETIC RESOLUTION (DKR)

In dynamic kinetic resolution (DKR), the diastereomeric intermediates **B** / *epi*-**B** (Scheme 1.18) are in equilibrium and the stereoselectivity depends on the difference in the transition state energies of electrophilic substitution. In this case, the product's enantiomeric ratio represents the different reaction rates of the complexes with the electrophile, not the equilibrium complex ratio. This reaction is under kinetic control and can be illustrated by the reaction profile shown in Scheme 1.18.[40,41]

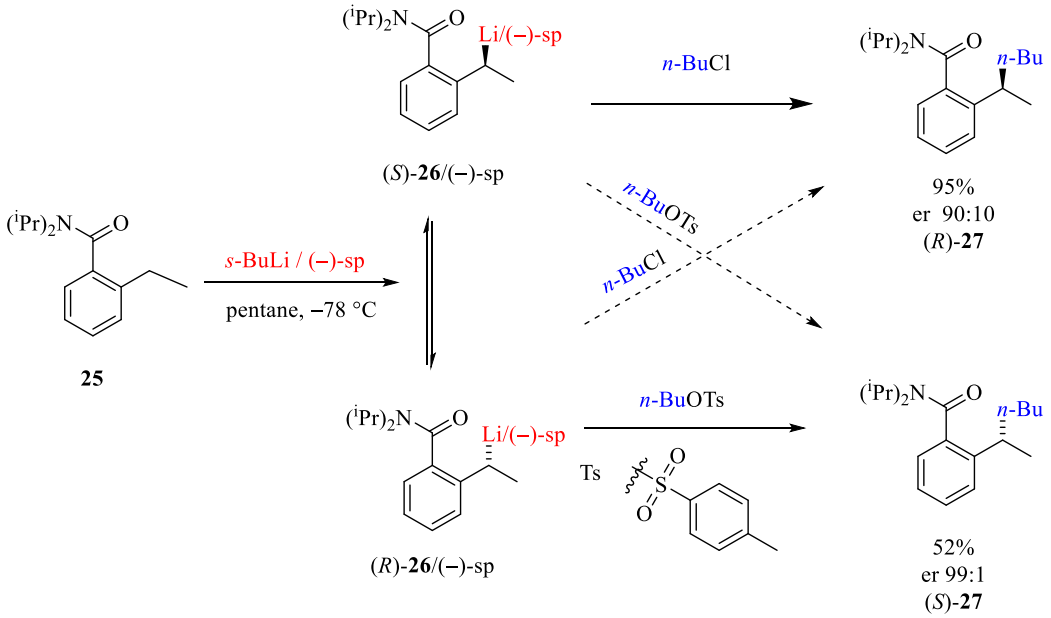


Scheme 1.17



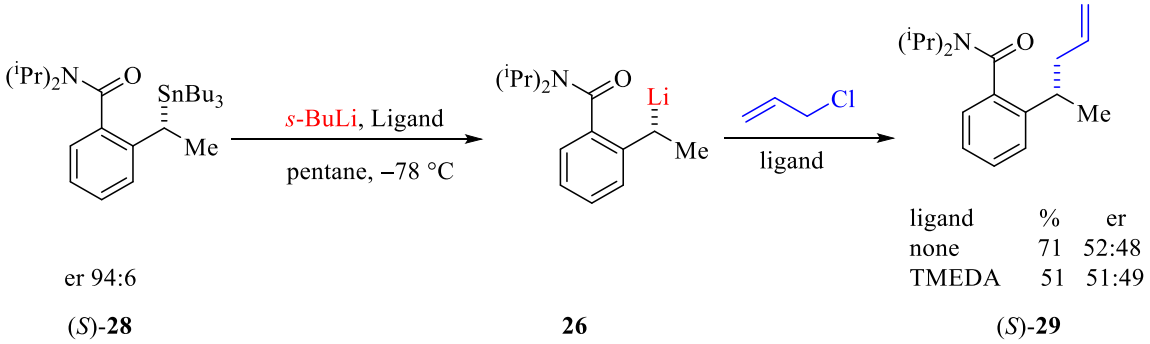
Scheme 1.18

In 1994, Beak and co-workers reported a good example of DKR which achieved high levels of enantioselectivity.[42] The amide **25** was lithiated by using the *s*-BuLi/(–)-sparteine complex to generate the intermediate complexes **26**. Then, alkyl halides were used to quench the reaction mixture to give the product **27** in a good yield of 95% and an enantiomeric ratio of 90:10. It can be recognised that using different leaving groups has a relevant effect in this reaction. In other words, when *n*-BuCl was used, this afforded the product (*R*)-**27** while *n*-BuOTs afforded the opposite configuration (*S*)-**27**. This is due to the difference in diastereomeric transition state energies for the substitution step (Scheme 1.19).



Scheme 1.19

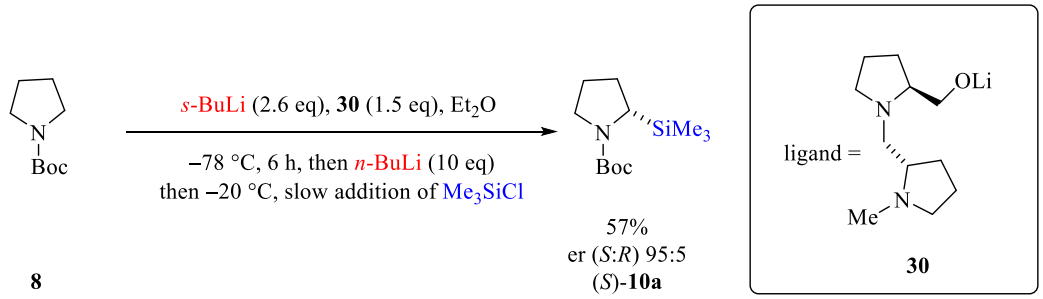
Following on from this, the lithiated intermediate **26** was prepared by using tin-lithium exchange from the enantioenriched stannane (*S*)-**28** (er 94:6). This was achieved using either *n*-BuLi or *n*-BuLi in the presence of TMEDA at –78 °C, subsequent addition of allyl chloride as the electrophile generated (*S*)-**29** in 71% and 51% yields with 52:48 and 51:49 er, respectively. This reaction showed that the enantioselectivity could not be due to an enantioselective deprotonation (Scheme 1.20).



Scheme 1.20

The DKR of *N*-Boc-2-lithiopyrrolidine was carried out using a variety of chiral ligands by Coldham and co-workers in 2006.[43] It was reported that the DKR was dependent on how fast the electrophile reacted with the two diastereomeric complexes. The best chiral ligand found

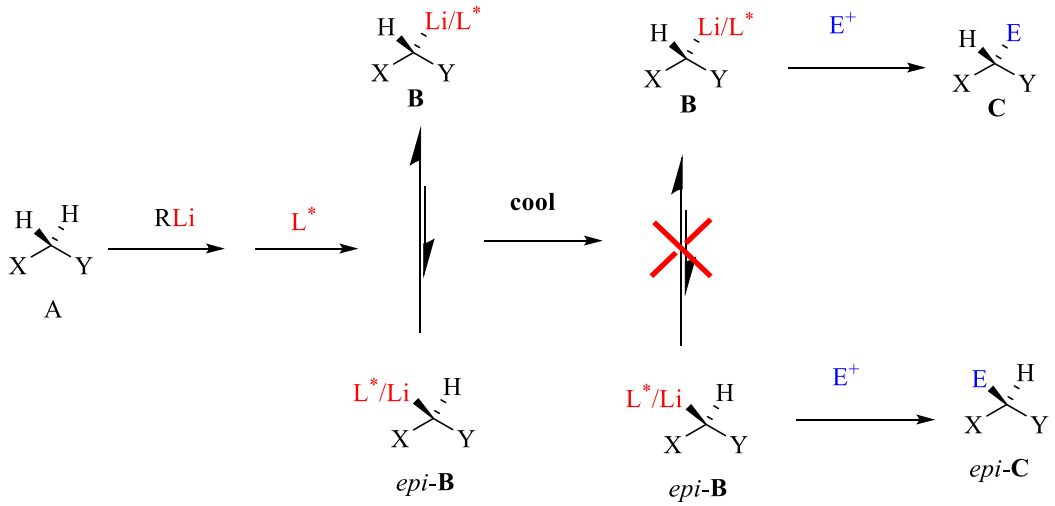
was diproline derivative **30** (Scheme 1.21). The *N*-Boc-pyrrolidine **8** was treated with *s*-BuLi and chiral ligand **30** in Et_2O at –78 °C for 6 h. A large amount of *n*-BuLi was then added, followed by Me_3SiCl which was added slowly over 30 minutes to generate the product (*S*)-**10a** in an excellent er (Scheme 1.21). Increasing the number of equivalents of *n*-BuLi up to 10 equivalents gave better selectivities when compared to using 3.25 or 6.25 equivalents.



Scheme 1.21

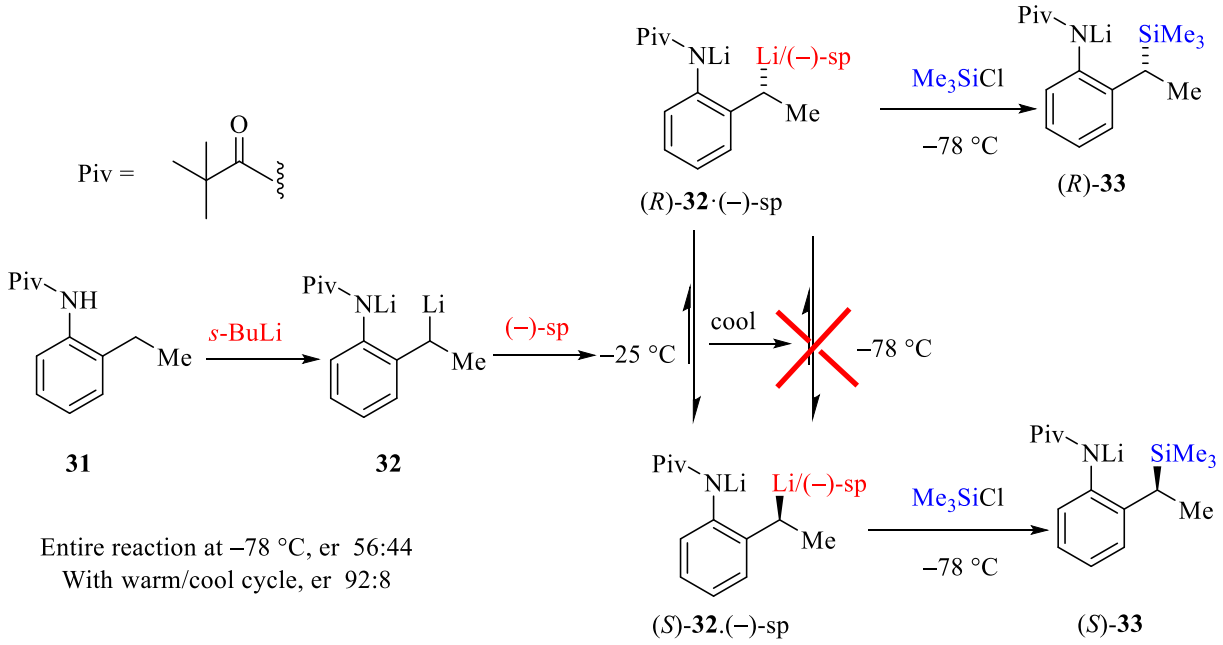
1.4.4 DYNAMIC THERMODYNAMIC RESOLUTION (DTR)

The enantioenrichment that arises from a DTR is from the thermodynamic preference for the more configurationally stable of the diastereomeric lithiated intermediates. The DTR is a two-stage process, which includes a warm and cool protocol. The first stage is deprotonation of the starting material at –78 °C to form the diastereomeric lithiated intermediates **B** and *epi*-**B** (Scheme 1.22). After warming the mixture to allow the diastereomers in the second stage to equilibrate, the equilibrium composition is locked by cooling again to –78 °C. Finally, electrophilic trapping gives either **C** or *epi*-**C** (Scheme 1.22).[35] The first report of the DTR phenomenon was on *β*-keto ester reduction in 1979 by Tai and co-workers.[44]



Scheme 1.22

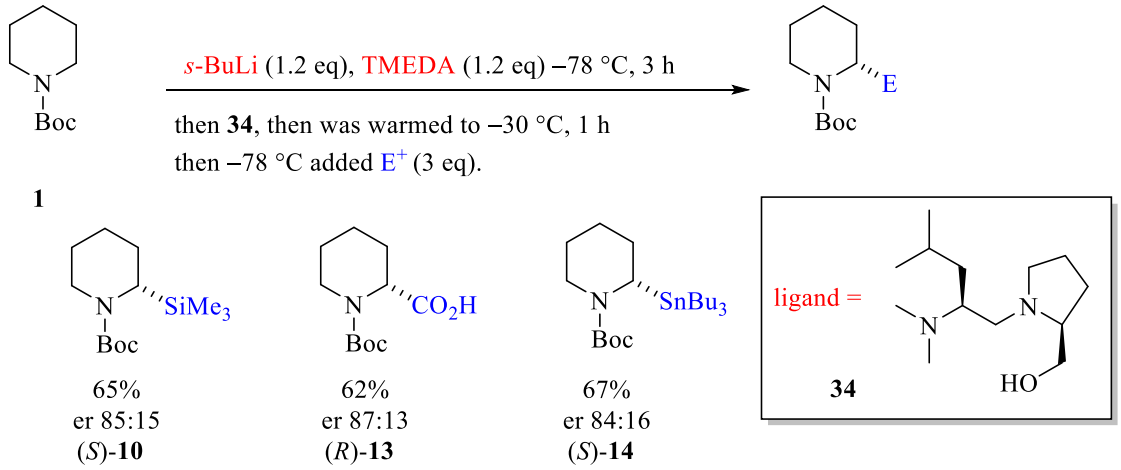
In 1997, DTR was carried out by the Beak group to achieve high levels of enantioerichment for the lithiation of *N*-pivaloyl-*o*-ethylaniline **31**.[45] The compound was deprotonated with *s*-BuLi at –25 °C to form the racemic lithiated intermediate followed by addition of (–)-sparteine to give two diastereomeric complexes. Then, after 45 min at –78 °C, trimethylsilyl chloride was added to generate the product (*S*)-**33** in a high enantiomeric ratio of er 92:8.



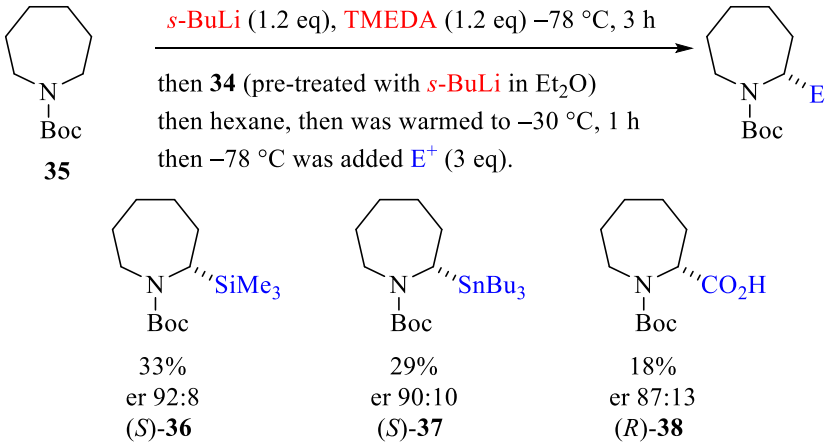
Scheme 1.23

Previous DTR work by Coldham and co-workers has involved optimisation of the asymmetric substitution of *N*-Boc-piperidines and *N*-Boc-azepines.[46] Trapping the lithiated intermediate

from *N*-Boc-piperidine **1** with different electrophilies gave a variety of 2-substituted *N*-Boc-piperidines in reasonable yields and good enantiomeric ratios (Scheme 1.24). In comparison, the products obtained from *N*-Boc-azepine **35** were isolated in lower yields but with good enantiomeric ratios (Scheme 1.25).



Scheme 1.24

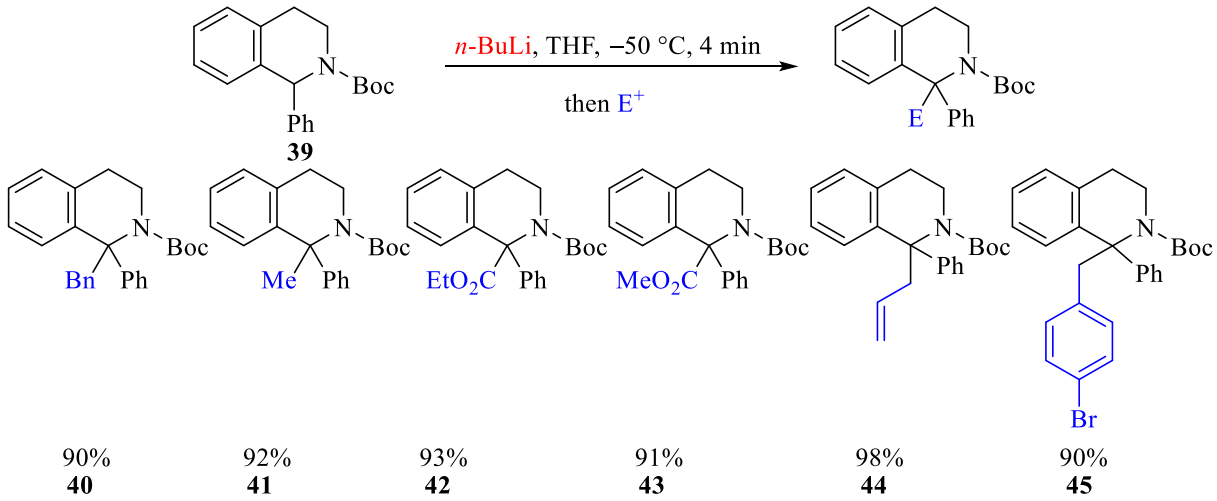


Scheme 1.25

1.5 PREVIOUS WORK IN THE COLDHAM GROUP

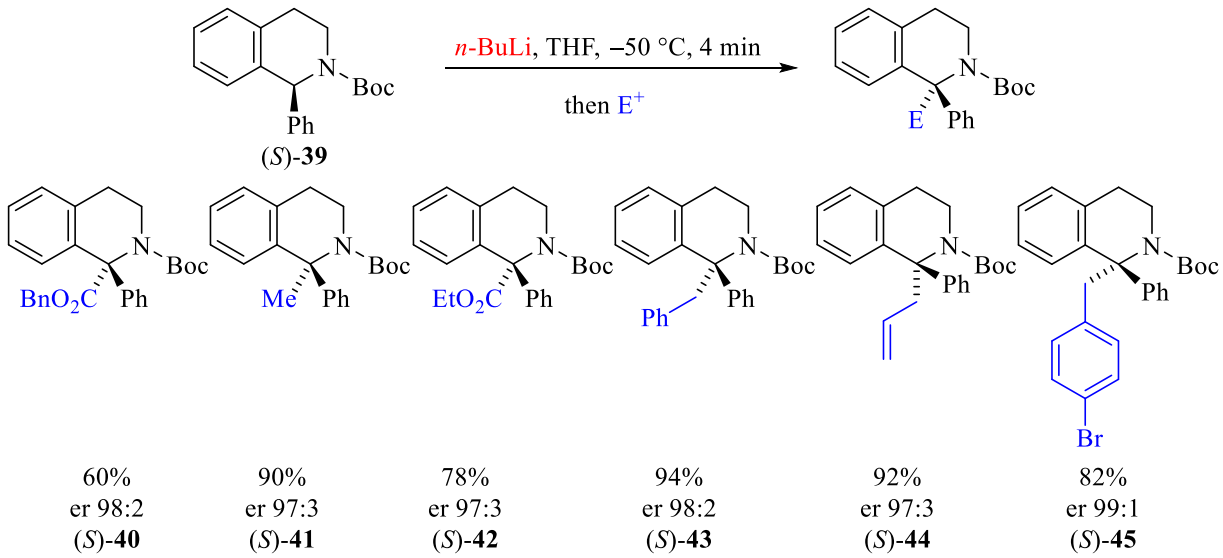
Asymmetric deprotonation using organolithium chemistry has been an important area of work in the Coldham group over the past fifteen years. The research is mainly based upon the use of a chiral base to asymmetrically deprotonate *α*- to a nitrogen atom in heterocyclic compounds in order to investigate reactions, reactivity, structures and properties of nitrogen heterocyclic compounds. Recently, the group has had an interest in the study of kinetic resolutions.

In 2014, a study of the lithiation of *N*-Boc-1-phenyltetrahydroisoquinoline **39** was carried out using *n*-BuLi at –50 ºC for 4 min.[47] The lithiated intermediate was trapped with different electrophiles to give products **40**-**45** in excellent yields (Scheme 1.26).



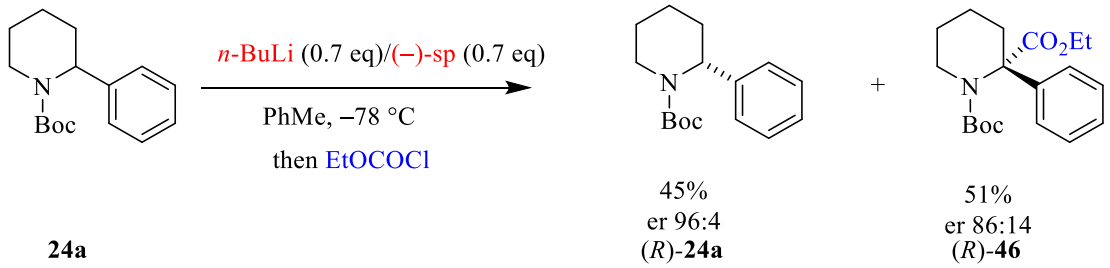
Scheme 1.26

Following this work, the enantioenriched (*S*)-**39** with 99:1 er was lithiated at –78 ºC in THF and quenched with the same electrophiles as used above. This gave promising results with yields of 60-94% and ers up to 99:1 obtained (Scheme 1.27).



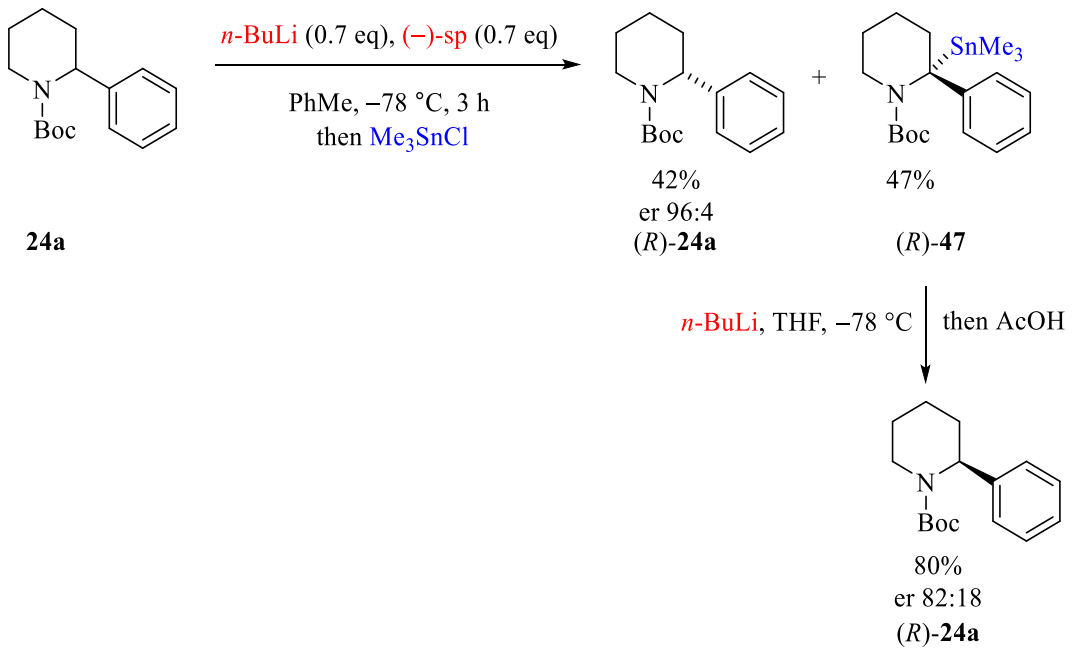
Scheme 1.27

In 2014, kinetic resolutions were reported using *N*-Boc-2-aryl-piperidines.[39] The study showed that by using 0.7 eq of *n*-BuLi complexed with (–)-sparteine in toluene at –78 ºC and quenching after 3 h with ethyl chloroformate, an excellent yield (45%) of recovered starting material was obtained in very good er (96:4) while the product was obtained in 51% yield with 86:14 er (Scheme 1.28).



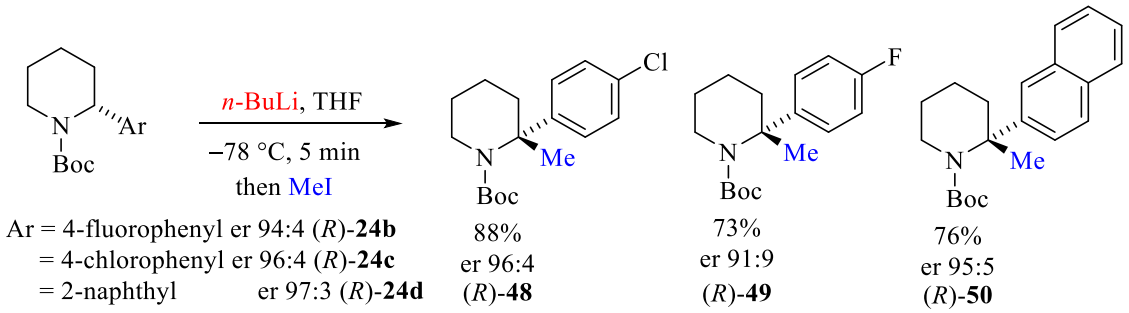
Scheme 1.28

Furthermore, it was found that by using trimethyltin chloride as the electrophile in the kinetic resolution, starting material (*R*)-**24a** was recovered in 42% yield in 96:4 er. The isolated stannane product (*R*)-**27** was then subjected to tin-lithium exchange to recover the other enantiomer of the starting material, (*S*)-**24a,** after quenching with AcOH, in 80% yield and 82:18 er. In addition, tin-lithium exchange at room temperature followed by protonation gave racemic **24a** to allow recycling of the product.



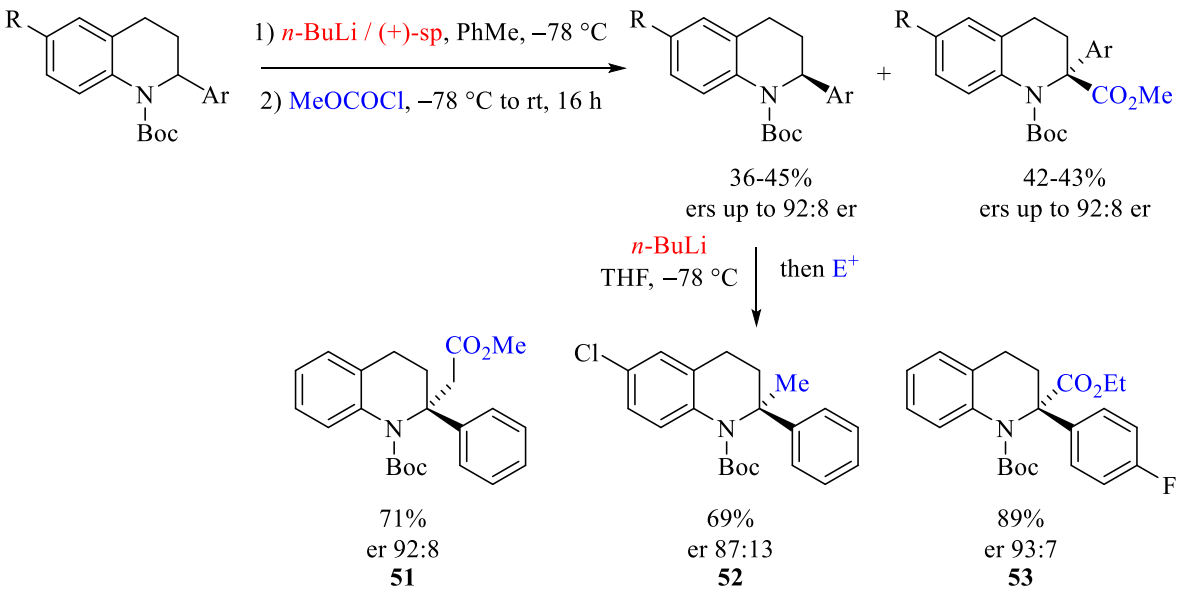
Scheme 1.29

Finally, lithiation of the enantioenriched (*R*)-**24b-d** was followed by electrophilic quench to give 2,2-disubstituted piperidines (*R*)-**48**-**50** in excellent yields with little to no loss of enantiopurity (Scheme 1.30).



Scheme 1.30

Recently, lithiation of *N*-Boc-2-aryl-tetrahydroquinoline was carried out by using *n*-BuLi in the presence of (+)-sparteine. The kinetic resolution reactions were successful achieving very high levels of enantioselectivity with recovered starting material obtained with up to er 98:2. Furthermore, the enantioenriched THQ derivatives were converted to the corresponding 2,2-disubstituted products with maintenance of the enantiopurity (Scheme 1.31).[48]


R
N
Ar
Boc
1) n-BuLi / (+)-sp, PhMe, −78 °C
2) MeOCOCl, −78 °C to rt, 16 h
R
N
Ar
Boc
36-45%
ers up to 92:8 er
+
R
Ar
N
CO2Me
Boc
42-43%
ers up to 92:8 er
n-BuLi
THF, −78 °C
then E+
CO2Me
N
Boc
71%
er 92:8
51
Cl
Me
N
Boc
69%
er 87:13
52
CO2Et
N
Boc
F
89%
er 93:7
53

Scheme 1.31

Chapter 2 - Synthesis and Lithiation–Substitution of oxazinanes & quinoxalines

2.1 Oxazinane & quinoxaline chemistry

Substituted oxazinane and quinoxaline structures are found in many important biologically active natural products and pharmaceutical compounds. Some examples are shown in Figure 2.1.[38,49–51] In this chapter, the lithiation-substitution reactions of oxazinane and quinoxaline structures will be investigated.

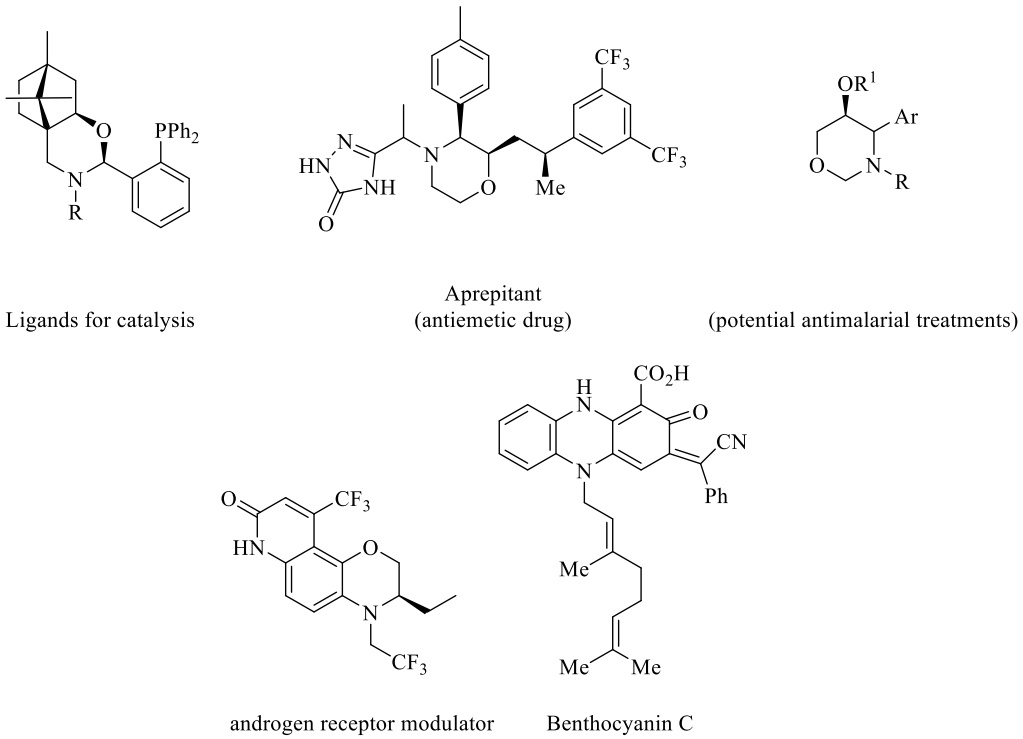
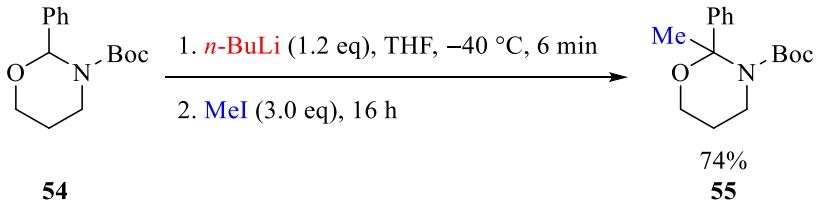


Figure 2.1

2.2 Previous work in the group

Work in this area started by a previous Masters student in the group,[52] with the aim of investigating the lithiation–substitution and kinetic resolution of *N*-Boc-2-phenyl-1,3-oxazinane **54** (Scheme 2.1). The lithiation reactions were carried out using *n*-BuLi (1.2 eq) in THF at –40 °C. The reaction mixture was left to stir for 6 min, before the lithiated intermediate

was trapped using MeI to give product **55** in 74% yield, which was the best yield obtained when a range of different electrophiles was tested.

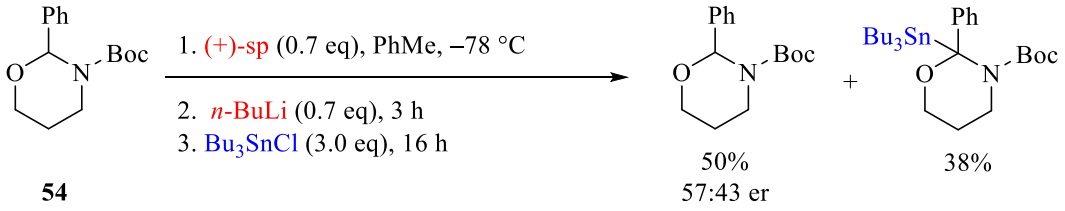


54 **55**

Scheme 2.1

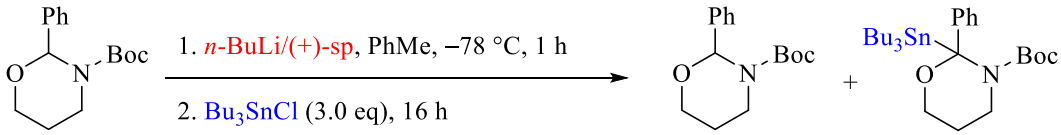
Kinetic resolutions were then carried out with the chiral base complex *n*-BuLi/(+)-sparteine using both the 'normal' and 'inverse' addition methods (Scheme 2.2). However, the enantioselectivity was very poor in both cases, which could be due to the oxygen atom in the ring of the 1,3-oxazinane **54** (as well as the oxygen atom of the carbonyl group) co-ordinating with the chiral base complex which can cause the non-selective deprotonation of either enantiomer.

Normal addition method



54 **54** **56**

Inverse addition method

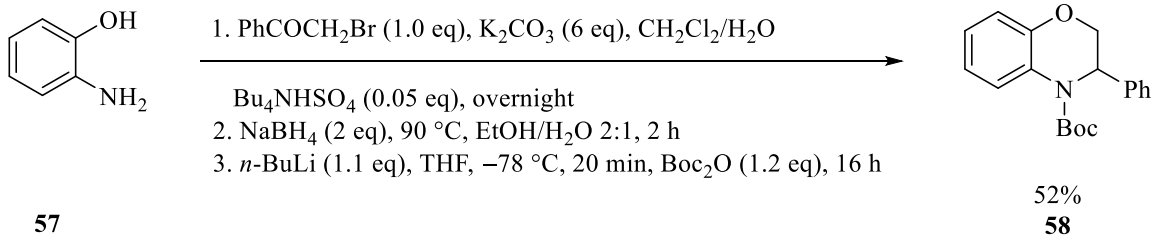


54 **54** **56**

Scheme 2.2

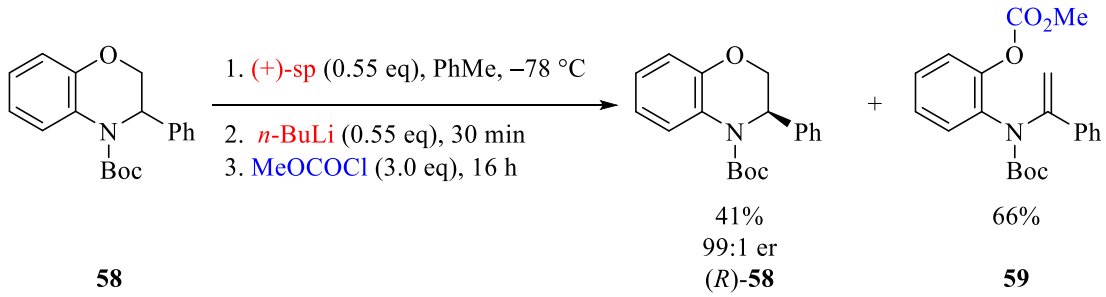
A PhD student in the group carried out work on the related *N*-Boc-3-phenyl-1,2,3,4-tetrahydro-1,4-benzoxazine **58**,[53] due to its structural similarity to the *N*-Boc-2-aryltetrahydroquinolines which had previously yielded excellent results in the kinetic resolutions.[54] *N*-Boc-3-phenyl-

1,2,3,4-tetrahydro-1,4-benzoxazine **58** was first synthesised over three steps using a literature method which gave the desired compound in a good overall yield.



Scheme 2.3

Kinetic resolutions were then attempted with substrate **58** using *n*-BuLi complexed with (+)-sp. Optimization of the reaction conditions led to approximately 0.55 equivalents of *n*-BuLi being added to a mixture of the racemic benzoxazine **58** and 0.55 equivalents of (+)-sparteine in toluene at –78 °C. After 30 min, methyl chloroformate was added. The recovered benzoxazine (*S*)-**58** was obtained in 41% yield with 99:1 er and the eliminated product **59** in 66% yield, although this is overall >100% yield due to compound **59** being sticky and the sample therefore being contaminated with solvent (Scheme 2.4). The absolute configuration of recovered benzoxazine **58** was confirmed by single-crystal X-ray analysis. The stereochemistry matches the expected configuration from using (+)-sparteine.[53]



Scheme 2.4

To expand on this, the aim of this project was to investigate kinetic resolution chemistry on *N*-Boc-2-aryl-1,3-oxazinanes, *N*-Boc-2-arylmorpholines, *N*-Boc-2-aryl-1,5-oxazinanes, *N*-Boc-2-arylbenzoxazines and 1,4-*N*,*N*-*di*-Boc-2-arylquinoxalines (Figure 2.2).

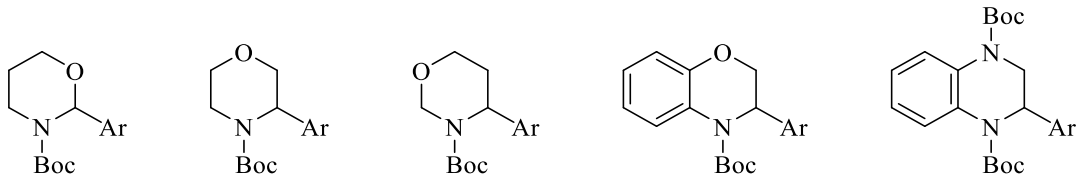
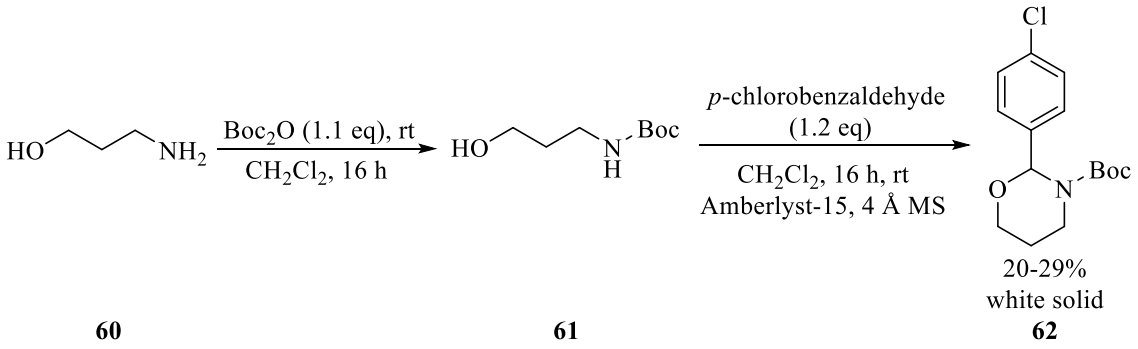


Figure 2.2

2.3 Results and Discussion of 1,3-Oxazinane

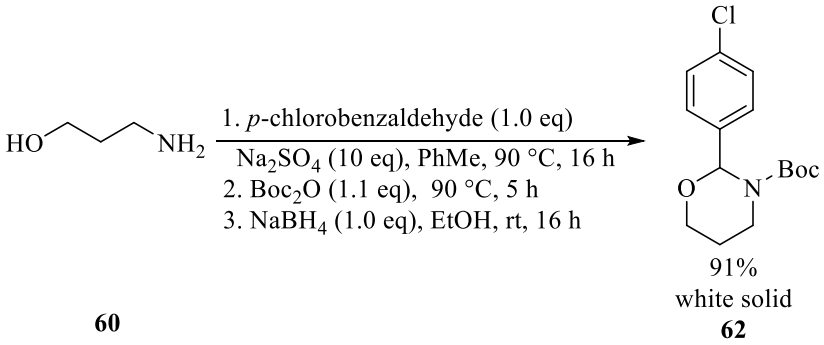
2.3.1 Synthesis of *N*-Boc-2-(4-chlorophenyl)-1,3-oxazinane 62

This project was started at the same time as a Masters student was carrying out similar work and so an example related to that work was chosen to be investigated. Therefore, by having a *para*-chloro substituent on a phenyl substituted oxazinane, this gave compound **62** that might have similar behaviour to oxazinane **54**. The oxazinane **62** was unavailable commercially and needed to be prepared from readily available starting materials. The first method used to prepare compound **62** is shown below (Scheme 2.5). 3-Amino-1-propanol **60** was protected using the Boc protecting group to give carbamate **61** in 96% yield. The protected compound was then cyclised with 4-chlorobenzaldehyde in the presence of 4 Å molecular sieves and Amberlyst-15 at room temperature overnight, which gave the target compound **62.** The reaction was repeated multiple times, but the maximum yield obtained was just 29%.[55] It was possible to separate (analytically) the enantiomers of product **62** using chiral stationary phase high performance liquid chromatography (CSP-HPLC).



Scheme 2.5

The major limitation of this synthesis was the second step as it generated the desired compound **62** in a low yield. This was potentially due to similar polarity of the product and *p*-chlorobenzaldehyde, which were difficult to separate using normal phase silica column chromatography. The low yield of compound **62** could also be due to the carbamate nitrogen atom being unreactive. As a result, an alternative strategy to synthesise **62** was devised based around similar work that was reported by Diness and co-workers (Scheme 2.6).[56]

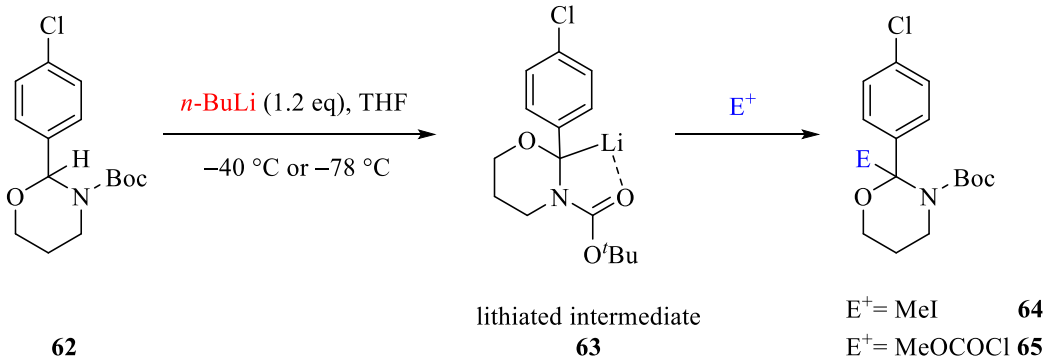


Scheme 2.6

This route was potentially more attractive as the entire synthesis was carried out in one reaction flask and limiting the amount of compound transfers may improve the yield. In this new synthetic route, the cyclisation was first performed at 90 °C. After 16 h, Boc_2O was added followed by the addition of $NaBH_4$. A benefit of this method was that it reduced any excess *p*-chlorobenzaldehyde in the reaction to *p*-chlorobenzyl alcohol which made the separation easier. Furthermore, the reaction eliminated the use of the Amberlyst-15 resin that may have introduced additional unknown impurities into the reaction.

2.3.1.1 Lithiation of *N*-Boc-2-(4-chlorophenyl)-1,3-oxazinane 62

It was first decided to try to optimise the conditions for the lithiation of compound **62** at different temperatures. To achieve this, compound **62** was dissolved in THF and lithiated using *n*-BuLi (1.2 eq) at –40 °C or –78 °C, with MeOCOCl or MeI being used as the electrophile (E^+) (Scheme 2.7).



62 lithiated intermediate **63** E^+= MeI **64** E^+= MeOCOCl **65**

Scheme 2.7

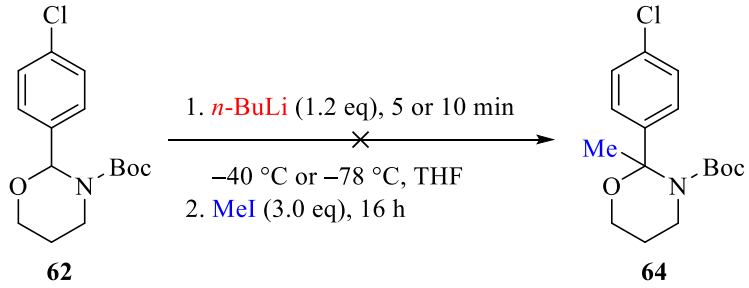
The reaction was quenched at different times between 5 and 10 min. According to the results, the best conditions were found to be lithiation at –78 °C, followed by addition of the electrophile after 10 min, followed by warming to room temperature slowly over 16 h (Scheme 2.7, Table 2.1).

Table: 2.1

Entry	E^+	*n*-BuLi eq	T	Lt	E^+t	Yield (%)
1.	MeI	1.2	−40 °C	6 min	30 min	0
2.	MeI	1.5	−40 °C	6 min	16 h	0
3.	MeI	3.0	−78 °C	10 min	16 h	0
4.	MeOCOCl	1.2	−40 °C	5 min	30 min	0
5.	MeOCOCl	3.0	−40 °C	10 min	16 h	24
6.	MeOCOCl	3.0	−78 °C	10 min	16 h	95

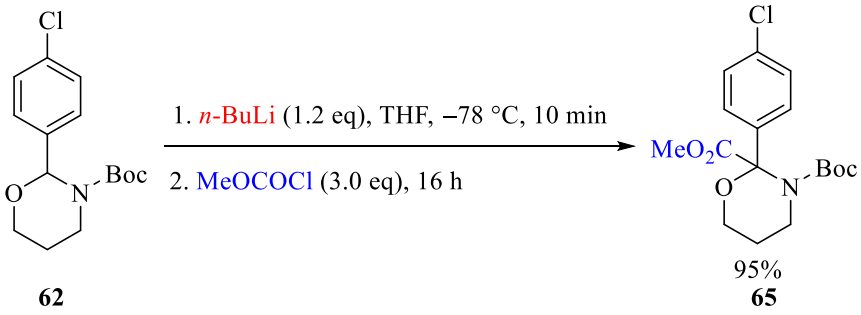
E^+ = Electrophile, eq = Equivalents, T = Temperature, Lt = Lithiation time, E^+t = Electrophile time

In **Table 2.1**, trapping with various numbers of equivalents of methyl iodide showed no conversion of the organolithium intermediate to compound **64** (Entries 1 to 3). Changing the reaction temperature from −40 °C to −78 °C was also attempted. Unfortunately, crude ^{1}H-NMR spectroscopy showed that only starting material was present.



Scheme 2.8

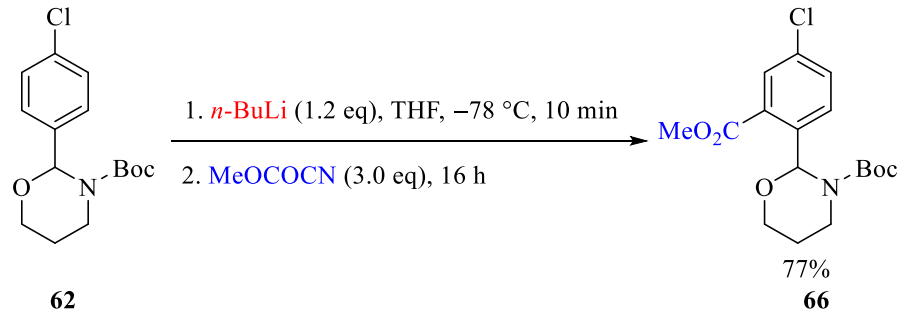
In contrast, the results in **Table 2.1** (Entries 4 to 6) when using MeOCOCl as the electrophile clearly showed that the lithiation of carbamate **62** was complete within 10 min at −78 °C in THF as a 95% yield of product **65** was obtained (Entry 6, Scheme 3.9). However, the reaction was unsuccessful using *n*-BuLi (1.2 eq) at –40 °C for 5 min, which it might be due to the organolithium intermediate being unstable at this temperature (Entry 4).



Scheme 2.9

A small number of lithiation-substitution reactions were carried out on the oxazinane **62**. Methyl iodide was the first electrophile used and although methyl iodide is known as a small and reactive electrophile, no product was obtained using the optimized conditions that were used in the reaction shown in Scheme 2.9. In contrast, when the Masters student carried out similar lithiation reactions on oxazinane **54** using *n*-BuLi (1.2 eq) at –40 °C, this gave a 74% yield of the product as shown in Scheme 2.2.

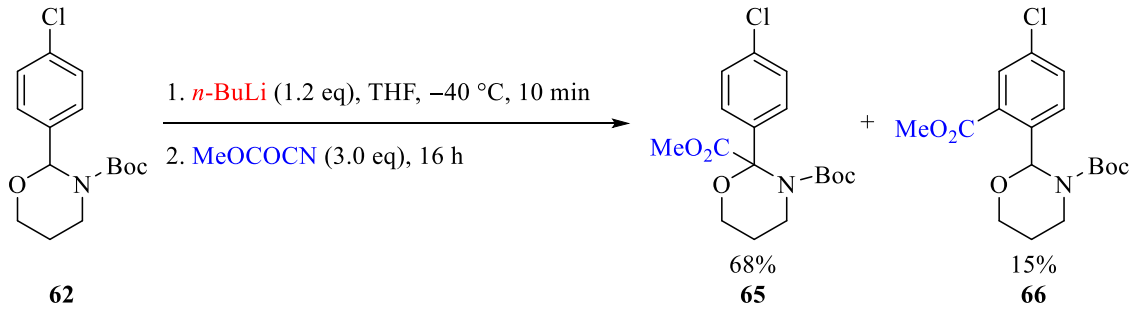
In addition, it was interesting to note that lithiation of oxazinane **62** using methyl cyanoformate as the electrophile at −78 °C did not afford the expected product **65**. Instead, the *ortho*-substituted product **66** was formed (Scheme 2.10).



62 66

Scheme 2.10

However, repeating the reaction at −40 °C as the lithiation temperature and MeOCOCN as the electrophile revealed that there were two products [R_f 0.18 & R_f 0.33, petrol−EtOAc (9:1)]. The major one was the *α*- substituted prouduct **65** in 68% yield, and the other product was the *ortho*-substituted compound **66** in 15% yield (Scheme 3.11).



62 65 66

Scheme 2.11

The ^{1}H-NMR spectrum of compound **66** showed that the benzylic proton (H^a) appeared at 6.91 ppm as a singlet (Figure 2.3). In addition, the aromatic protons had a pattern typical for a 1,2,4-trisubstituted benzene ring which confirmed the substitution had taken place in the position *ortho*- to the oxazinane ring. The ^{1}H-NMR spectroscopic data of the benzene ring indicated the presence of three aromatic protons [(ABX) spin system, δ = 7.60, 7.45 & 7.20 ppm]. The first proton was a doublet (H^d) which was significantly deshielded at 7.60 ppm with W-coupling of *J* 2.2 Hz. The second aromatic proton (H^c) appeared as a doublet of doublets at 7.45 ppm with the same W-coupling *J* value as the first proton and *ortho*-coupling *J* 8.0 Hz. Finally, the more shielded aromatic proton (H^b) at 7.20 ppm appeared as a doublet with *ortho*-coupling of *J* 8.0 Hz.

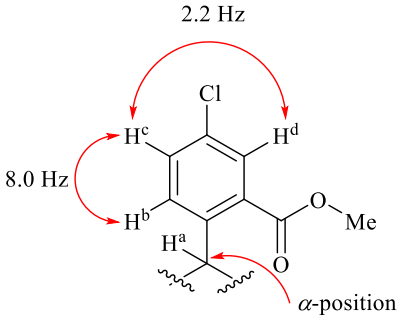


Figure 2.3

It is difficult to explain the difference in regioselectivity in these cases. There is a possibility that the activation energy of *ortho*-substitution is lower than *α*-substitution. The intermediate is likely to have some η^3 character with the lithium atom coordinated at the *α*-, *ipso*- and *ortho*-positions. This can be trapped by methyl cyanoformate prior to rearranging to the re-aromatized product **65** (Figure 2.4).[54,57]

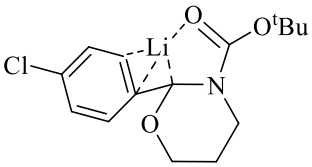
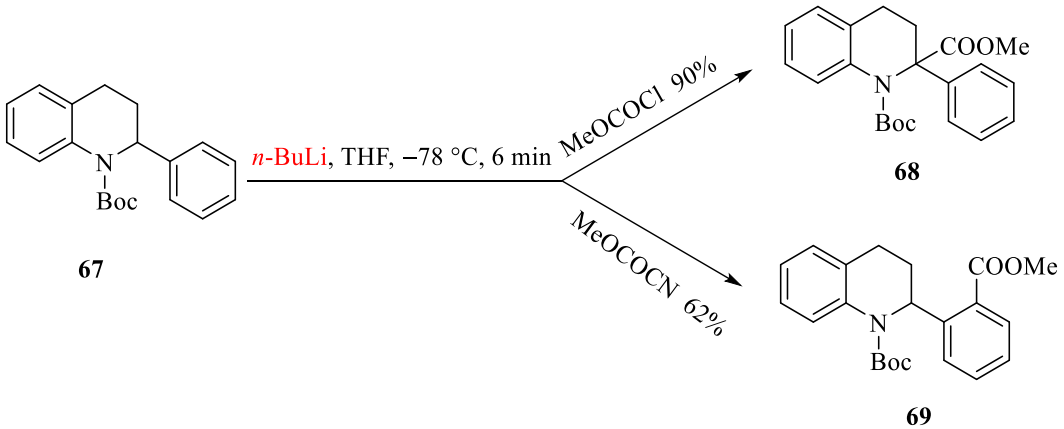


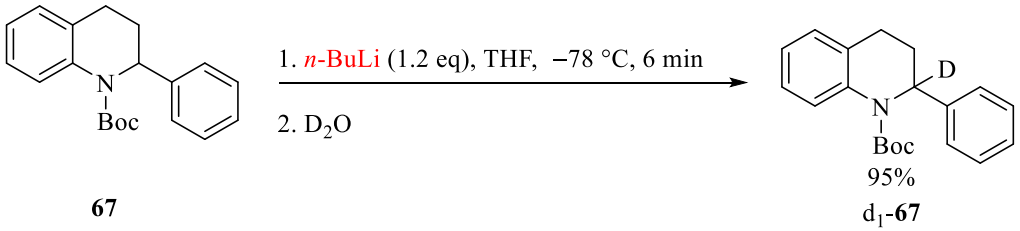
Figure 2.4

Interestingly, a similar *ortho*-substituted product **69** was formed from the deprotonation of *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **67** with *n*-BuLi and trapping by methyl cyanoformate. This work was discovered in the Coldham group by Carter (Scheme 2.12).[53]



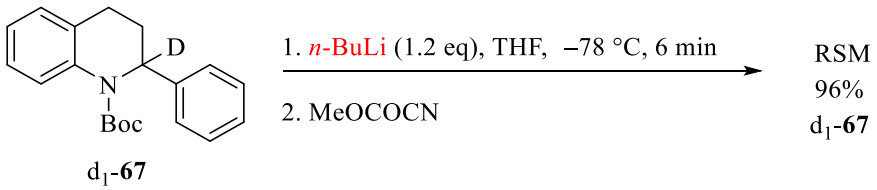
Scheme 2.12

In order to confirm that the reaction was taking place *via* an *ortho*-substitution pathway rather than by an *ortho*-lithiation pathway, *N*-Boc-THQ **67** was deuterated by using *n*-BuLi at –78 °C in THF for 6 minutes followed by addition of D_2O. This gave the deuterated THQ d_1-**67** in good yield with around 95% deuterium incorporation (Scheme 2.13).[53]



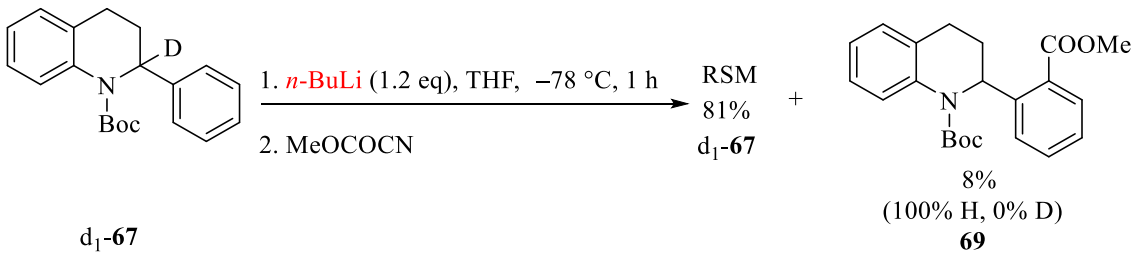
Scheme 2.13

An attempt was made to deprotonate THQ d_1-**67** with *n*-BuLi using the same conditions as had been used previously for THQ-**67** in Scheme 2.12. The reaction was quenched with methyl cyanoformate. However, only the starting material was recovered in 96% yield which helps to support the theory that only *alpha*-lithiation was taking place (Scheme 2.14).



Scheme 2.14

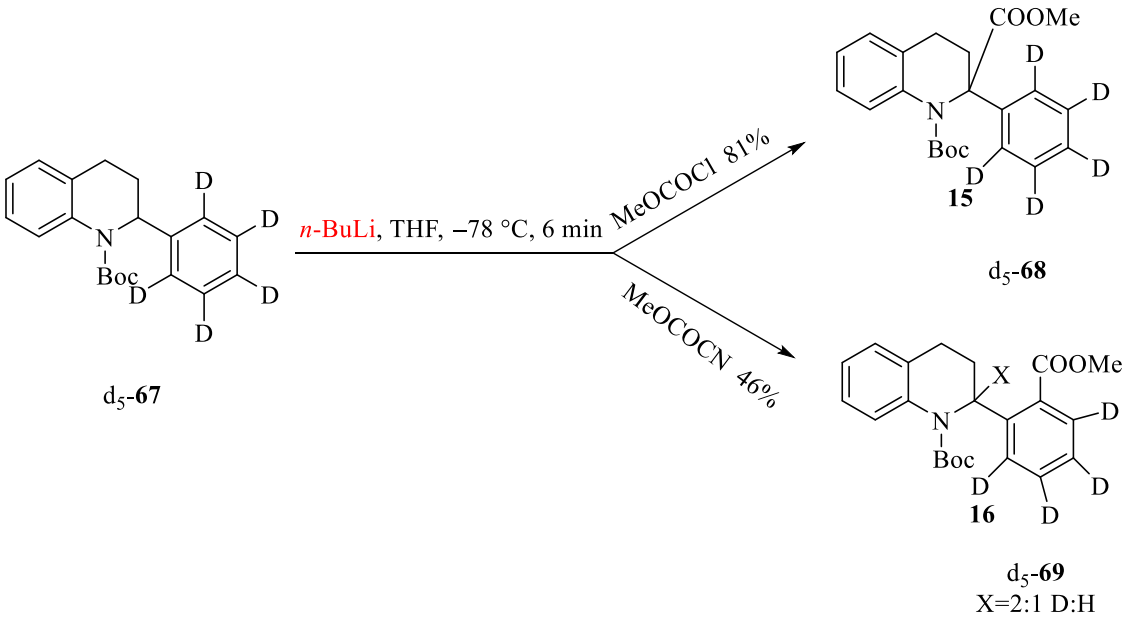
In a further attempt to lithiate THQ d_1-**67**, it was decided to add more equivalents of the base (3.0 equivalents of *n*-BuLi) and to use a longer lithiation time (1 h) before methyl cyanoformate was added. The *ortho*-substituted product **69** was obtained in a low yield (8%) with complete disappearance of the deuterium in the *α*-position (Scheme 2.15). This result also supported the theory that no *ortho*-lithiation was taking place when methyl cyanoformate was used and supported the hypothesis of the η^3 intermediate shown above in Figure 2.4.



d$_1$-**67**

Scheme 2.15

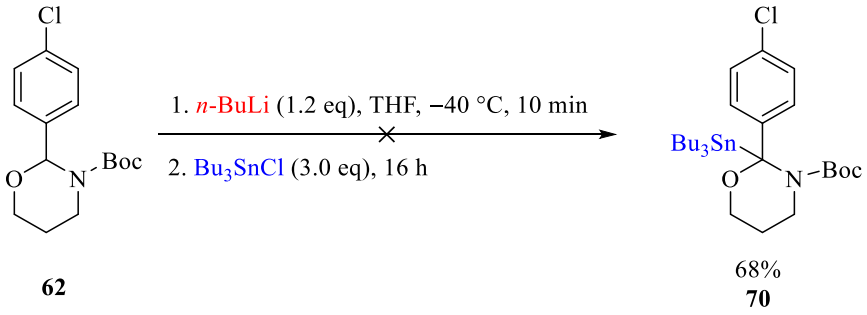
More investigation was done by Carter,[53] which used the penta-deuterated phenyl ring of THQ d$_5$-**67**. By using the same conditions as described earlier, deprotonation of compound d$_5$-**67** was then carried out using 1.2 equivalents of *n*-BuLi in THF at –78 ºC. After 6 minutes, methyl chloroformate was added and this gave the α-substituted product d$_5$-**68** in 81% yield. When the reaction was repeated and quenched with methyl cyanoformate as the electrophile, this gave, as expected, the *ortho*-substituted product d$_5$-**69** (Scheme 2.16). There was some deuterium incorporation in the *alpha*-position which almost certainly confirmed the hypothesis that it was *alpha*-lithiation, rather than *ortho*-lithiation, taking place.



d$_5$-**67**

Scheme 2.16

Unfortunately, no product was isolated when the electrophile tributyltin chloride was used at −40 °C or −78 °C under the same conditions. This might have been due to the steric hindrance of the electrophile.

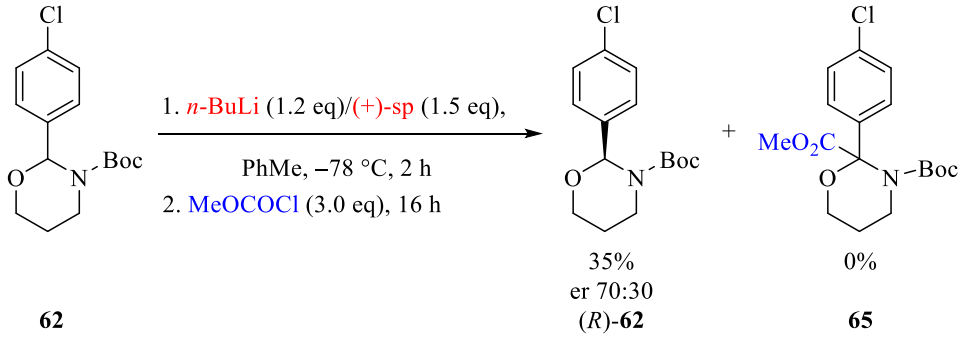


62 **70**

Scheme 2.17

2.3.1.2 Kinetic resolution of *N*-Boc-2-(4-chlorophenyl)-1,3-oxazinane 62

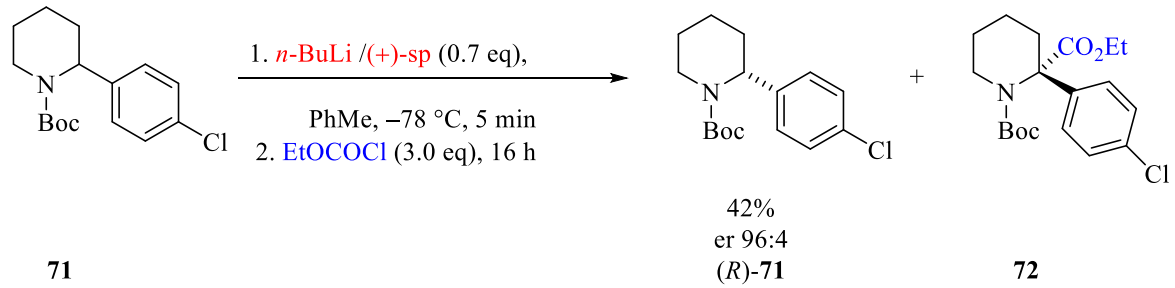
Having had some success with the racemic lithiation-substitution reactions of oxazinane **62**, the chiral ligand (+)-sparteine was used in order to attempt kinetic resolutions (KR). The initial conditions used to carry out the KR are shown in Scheme 2.18. Deprotonation of oxazinane **62** was carried out by first pre-mixing *n*-BuLi/(+)-sparteine (1.2 eq : 1.5 eq) in toluene at –78 °C for 30 min. The starting material **62** was then added to the mixture. After 2 h, MeOCOCl (3 eq) was added and the mixture was allowed to warm to room temperature over 16 h. The starting material (*R*)-**62** was recovered in 35% yield with moderate selectivity (er 70:30); the product **65** was not detected. Hence, the KR was not particularly successful and further optimisation would be required.



62 (*R*)-**62** **65**

Scheme 2.18

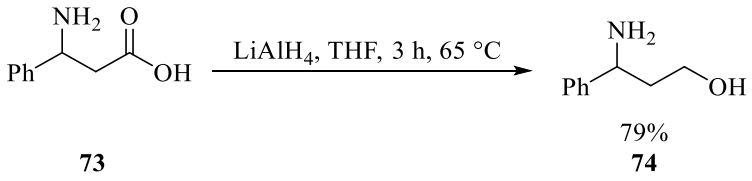
At the same time, a previous Masters student (A. Choi)[52] carried out KR on oxazinane **54** using the same conditions and this gave the recovered starting material with poor selectivity (er 54:46). This may have been due to the ease of deprotonation at C-2 with diastereomeric transition states of similar energy and if we compare this with the excellent result that was obtained for 2-arylpiperidines **71** (Scheme 2.19),[39] the only difference is the oxygen atom in the ring that could possibly be co-ordinating to *n*-BuLi/(+)-sp. As a result, work on the 2-aryl-1,3-oxazinanes was discontinued.



Scheme 2.19

2.3.2 Synthesis of *N*-Boc-2-phenyl-1,4-oxazinane 74

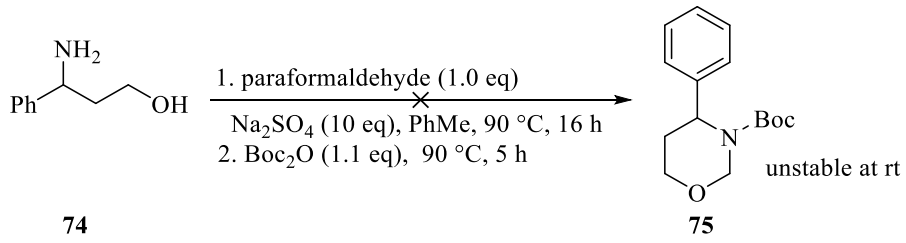
The attention was then shifted to 4-phenyl-1,3-oxazinanes. To synthesise these, 3-amino-3-phenylpropanoic acid **73** was treated with $LiAlH_4$ to give 3-amino-3-phenylpropan-1-ol **74** in 79% yield (Scheme 2.20).



Scheme 2.20

Amine **74** was then cyclised with paraformaldehyde at 90 °C. After 16 h, Boc_2O was added to give product **75**, but this was unstable (Scheme 2.21). TLC analysis of the crude product showed only one spot which was believed to correspond to the desired product. However, after

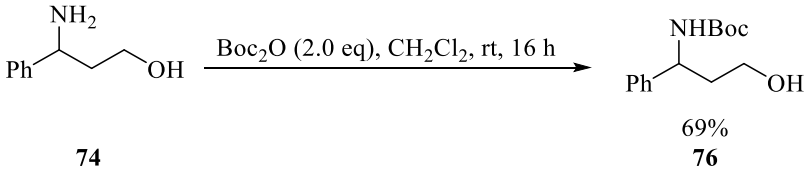
purification using column chromatography on either silica or alumina, the product **75** was isolated but it decomposed rapidly at room temperature.



Scheme 2.21

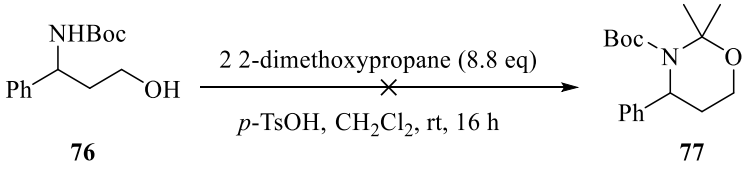
2.3.3 Synthesis of *N*-Boc-2,2-dimethyl-4-phenyl-1,3-oxazinane 77

Due to the instability of oxazinane **75**, the synthesis of the compound **77** with two methyl groups in the 2-position of the 1,5-oxazinane was attempted. Starting from the amino alcohol **74**, the amino group was protected using Boc_2O to give compound **76** in 69% yield (Scheme 2.22).



Scheme 2.22

The protected amino alcohol **76** was then treated with 2,2-dimethoxypropane and tosic acid in CH_2Cl_2 at room temperature for 16 h. However, multiple spots close to each other were observed on the TLC plate which were difficult to separate. Hence, the desired product **77** was not isolated (Scheme 2.23). The ^{1}H-NMR spectrum of the crude mixture was not clear enough to detect the expected product peaks.

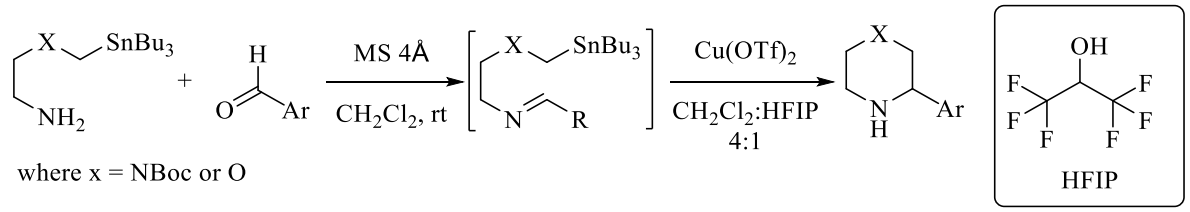


Scheme 2.23

It was therefore decided at this point to shift the attention to 1,4-oxazinanes (morpholines) as previous work in the group had given promising results.[52]

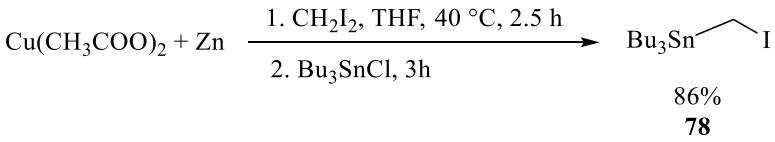
2.3.4 Synthesis of *N*-Boc-3-(4-methoxyphenyl)morpholine 75

Some research has been reported to synthesise the desired 3-arylmorpholine starting material. A study by Bode and co-workers reported use of SnAP reagents to synthesise these types of compound (Scheme 2.24).[58]



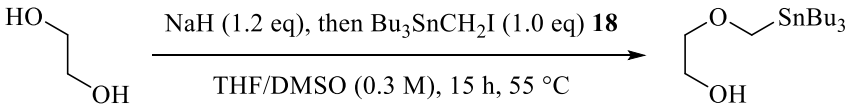
Scheme 2.24

Utilising SnAP reagents would have been the cheapest way to make morpholines and it would also be easy to use different aldehydes to prepare a range of 3-aryl derivatives.[58] The procedure began by treating $Cu(OAc)_2$ with zinc dust, then washing with warm acetic acid. A solution of CH_2I_2 in THF was added to the mixture at 40 °C. After 2.5 h, tributyltin chloride solution was added and the mixture was left to stir for 3 h to give iodide **78** in 86% yield (Scheme 3.19).



Scheme 2.25

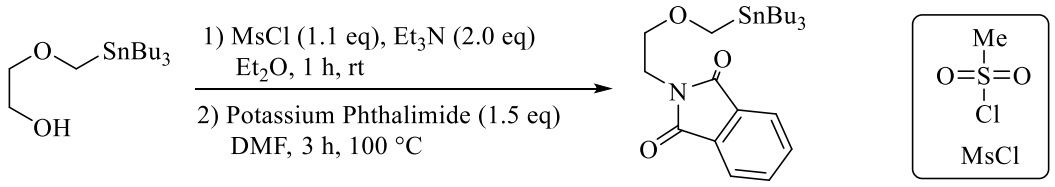
The next step was then to synthesise alcohol **80**.[58] This began with deprotonating ethylene glycol **79** using NaH and was followed by the dropwise addition of tributyl(iodomethyl)stannane **78**. The yield of product **80** was 27% and this was carried forward to the next step (Scheme 2.26).



79 **80**

Scheme 2.26

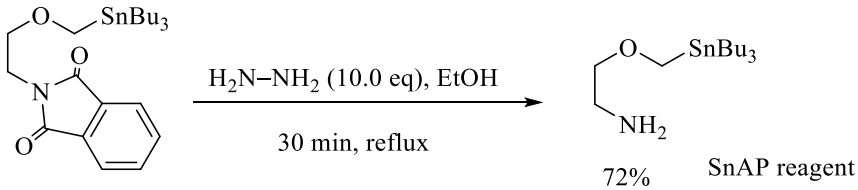
Next the mesylation of alcohol **80** was carried out by adding methanesulfonyl chloride (MsCl) and Et_3N in Et_2O.[58] The crude mesylated product was then used in the next step without further purification and was dissolved in DMF. Potassium phthalimide was added at 100 °C, to give compound **81** in an excellent yield (Scheme 2.27).



80 **81**

Scheme 2.27

The phthalimide **81** was rapidly converted to the corresponding SnAP reagent **82** by adding hydrazine monohydrate in EtOH, followed by heating under reflux for 30 min. The ^{1}H-NMR spectrum fully corresponded to the expected structure (Scheme 2.28).

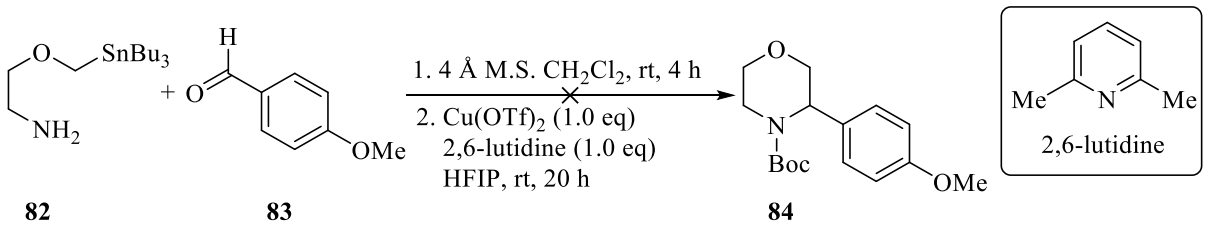


81 **82**

Scheme 2.28

The cyclisation of SnAP reagent **82** with *p*-anisaldehyde **83** was then explored. At first, compound **82** was reacted with aldehyde **83** in CH_2Cl_2, in the presence of 4 Å molecular sieves at room temperature (Scheme 2.29). In a separate flask, a homogeneous suspension was formed by adding 2,6-lutidine to $(CF_3)_2CHOH$ and anhydrous $Cu(OTf)_2$. The imine solution was then added to the homogeneous suspension in one portion and the resulting mixture was stirred at

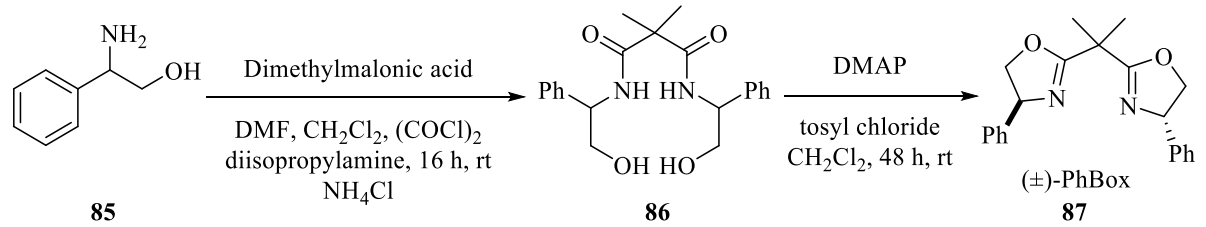
room temperature for 12 h. Unfortunately, no product was isolated and the ^{1}H-NMR spectrum showed no cyclised product.



82 **83** **84**

Scheme 2.29

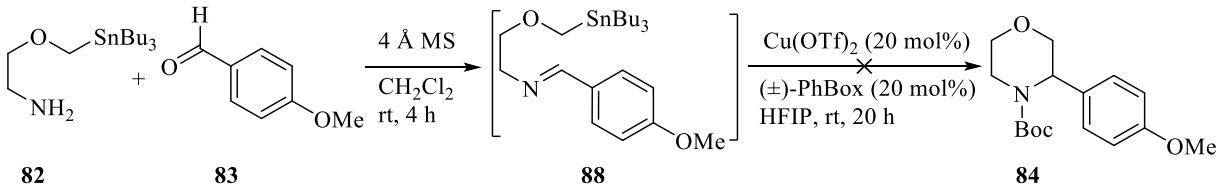
At this point, it was thought that a change of ligand might help the cyclisation step.[58] Bode and co-workers had also reported that (±)-PhBox **87** would initiate the cyclisation step, so it was decided to use (±)-PhBox **87** as the ligand instead of 2,6-lutidine. To prepare the ligand **87**, 2-amino-2-phenylethanol **85** was used. A dimethyl malonic acid solution was mixed with oxalyl chloride and the reaction mixture was left to stir for 1.5 h at room temperature. Then, the compound **85** was added dropwise to the reaction mixture. The mixture was stirred for 5 h to give diamide **86**. This was reacted with 4-dimethylaminopyridine and tosyl chloride to give (±)-PhBox **87**. The structure was confirmed by ^{1}H-NMR spectroscopy.



85 **86** **87**

Scheme 2.30

The reaction between compounds **82** and **83** was attempted again using the ligand (±)-PhBox **87** under the same conditions as reported in the literature. Unfortunately, no product was obtained using 10 mol% or up to 20 mol% of (±)-PhBox **87** (Scheme 2.31). ^{1}H-NMR spectrum of the crude product showed that no product had formed.



82 **83** **88** **84**

Scheme 2.31

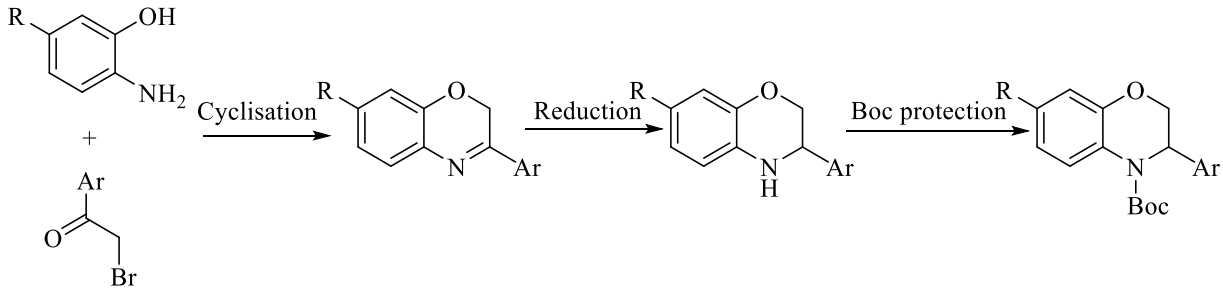
The use of $Cu(OTf)_2$ in the reaction was then investigated. As copper triflate is moisture sensitive, drying the copper triflate may improve the reaction. Another attempt of the reaction was performed where copper triflate was first dried by heating it at 110 °C under high vacuum (ca. 0.1 mmHg) for 2 hours.[58] However, this reaction was also unsuccessful. After contacting Prof. Bode to try and find a solution to the problem, it was found that the source of the copper triflate was important. Although a different source of $Cu(OTf)_2$ could have been tested, the investigation was discontinued at this point as promising preliminary results had been obtained with the related benzoxazines.

2.4 Results and discussion of 1,4-benzoxazines

2.4.1 Synthesis of *N*-Boc-3-aryltetrahydro-1,4-benzoxazine derivatives

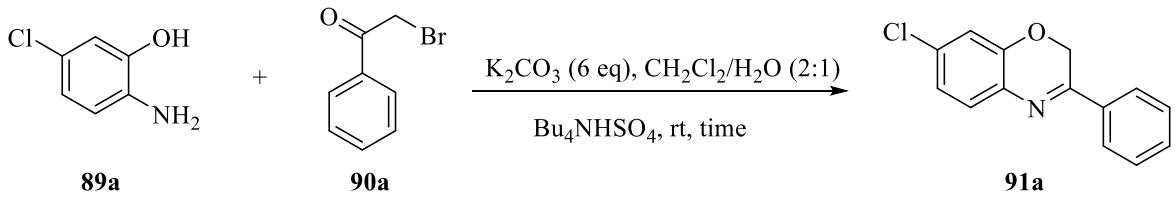
The project was then moved to synthesise and carry out kinetic resolutions on *N*-Boc-3-aryl-1,4-benzoxazine derivatives. This research would allow us to explore and extend the scope of earlier work carried out by Carter in our group (Scheme 2.4).[53]

The desired *N*-Boc-3-arylbenzoxazines were unavailable commercially and needed to be prepared from commercially available starting materials. Literature research showed that preparation of 3-aryl-1,2,3,4-tetrahydro-1,4-benzoxazine compounds could be achieved in two steps.[59,60] The obtained compounds could then be protected to give the desired *N*-Boc-3-aryl-1,4-benzoxazines (Scheme 2.32).



Scheme 2.32

To begin, we selected the 7-chlorobenzoxazine as a target. 2-Amino-5-chlorophenol **89a** and 2-bromoacetophenone **90a** were dissolved in CH_2Cl_2/H_2O and six equivalents of the base K_2CO_3 was added in the presence of a phase-transfer reagent (tetrabutylammonium hydrogensulfate). The mixture was stirred at room temperature and the reaction was monitored by TLC. The yield was optimised by changing the equivalents of phase-transfer reagent and the time of the reaction, to give the desired 3-phenyl-1,4-benzoxazine compound **91a** in an excellent yield of up to 95% (Scheme 2.33 and Table 2.2).



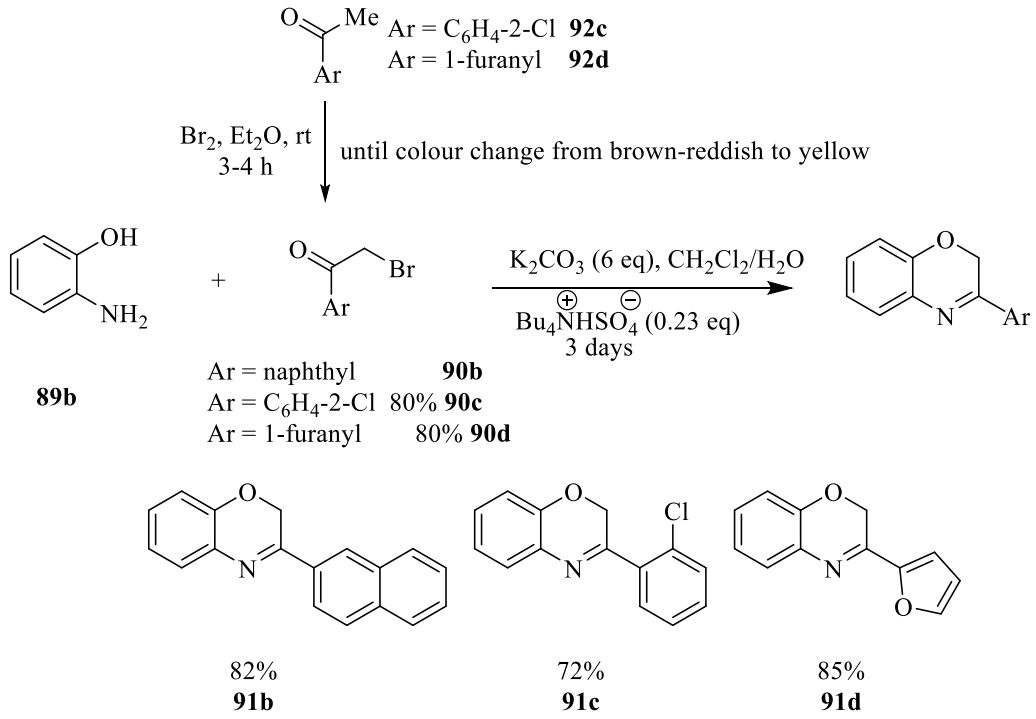
89a **90a** **91a**

Scheme 2.33

Table 2.2:

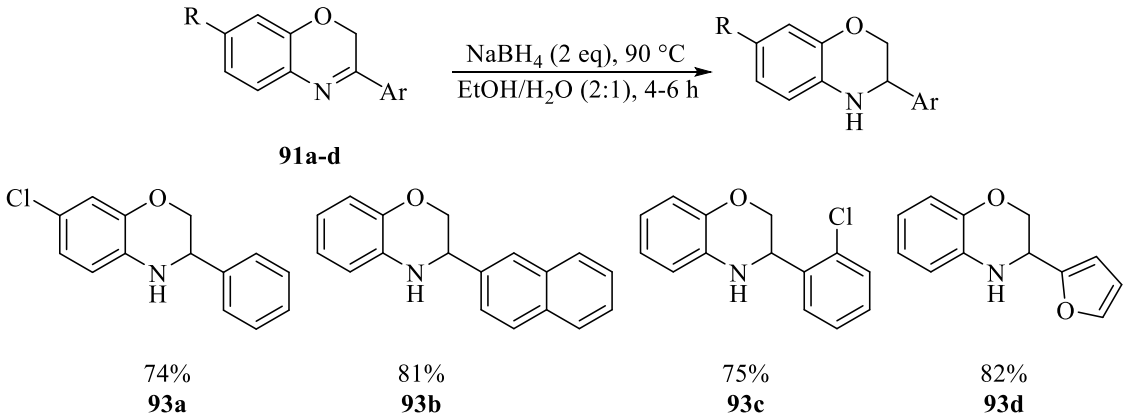
Entry	Bu_4NHSO_4 (eq)	Time	Yield
1	0.05	18 h	50%
2	0.23	18 h	73%
3	0.23	3 days	95%

Furthermore, by using the optimised conditions in Table 2.2 entry 3, it was possible to make other benzoxazine derivatives by using 2-aminophenol **89b** and 2-bromo-1-arylethanones **90b-d**. It was necessary to prepare the 2-bromo-1-(2-chlorophenyl)ethanone **90c** and 2-bromo-1-(furan-2-yl)ethanone **90d** from the corresponding aryl ketones **92a,b** using bromination reactions as shown in Scheme 2.34.



Scheme 2.34

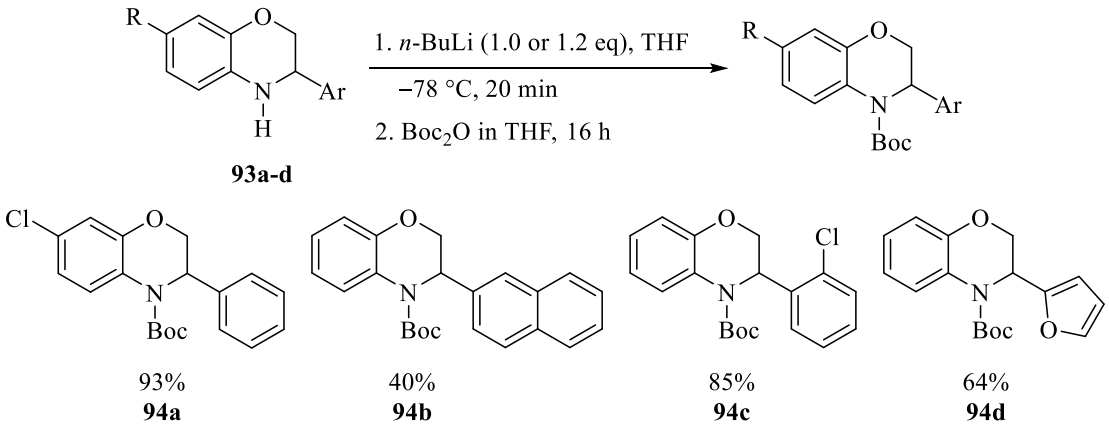
To reduce compounds **91a-d**, the starting material was dissolved in a solvent mixture of EtOH / H_2O (2:1) and $NaBH_4$ was added. The mixture was then heated at 90 °C for 4-6 h until the starting material was consumed (TLC monitoring) to give 3-aryl-1,2,3,4-tetrahydro-1,4-benzoxazines **86a-d** in good yields (Scheme 2.35).



Scheme 2.35

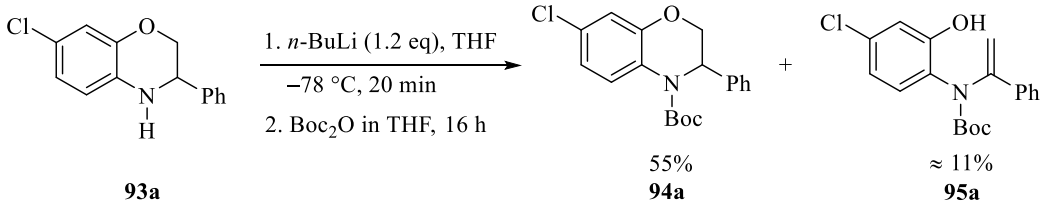
The final step was to protect the nitrogen atom in compounds **93a-d** using the *tert*-butoxycarbonyl protecting group. Just one equivalent of *n*-BuLi was used to avoid deprotonation adjacent to the nitrogen atom and formation of the eliminated product. An

exception was with the *ortho*-chloro derivative **93c** where 1.2 equivalents of *n*-BuLi was used to give a better yield (Scheme 3.36). After leaving the mixture to stir for 20 minutes in THF at –78 °C, a solution of Boc_2O in THF was added to give the desired products **94a-d** in reasonable to very good yields.



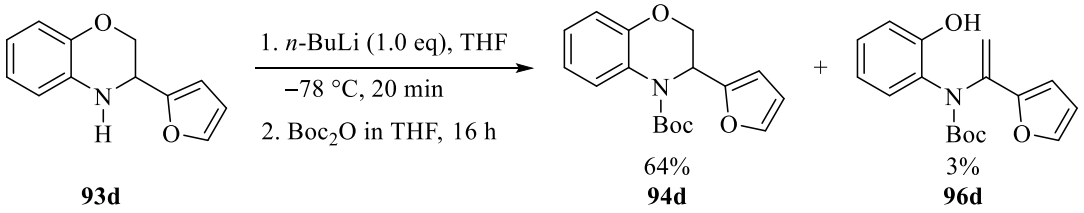
Scheme 2.36

It was noticeable that using 1.2 equivalents of *n*-BuLi led to a significant amount of alkene product **95a** being formed, which was avoided by adding one equivalent of the base as mentioned above (Scheme 2.37). The ^{1}H NMR spectrum of the alkene product **95a** contained impurities but the NMR and mass spectra indicated that this was formed in appreciable amounts.



Scheme 2.37

Interestingly, the alkene product **96a** was obtained in a trace amount when the furan derivative **93d** was used even with one equivalent of *n*-BuLi (Scheme 2.38).



Scheme 2.38

These results are supported by the ^{1}H NMR spectra shown below (Figure 2.5). In the desired product **96a**, the benzylic proton remained and there were two aliphatic protons which appeared as a doublet of doublets for both protons (Figure 2.5a). In contrast, the eliminated product showed that there were two protons in the alkene range which appeared as singlets (Figure 2.5b).

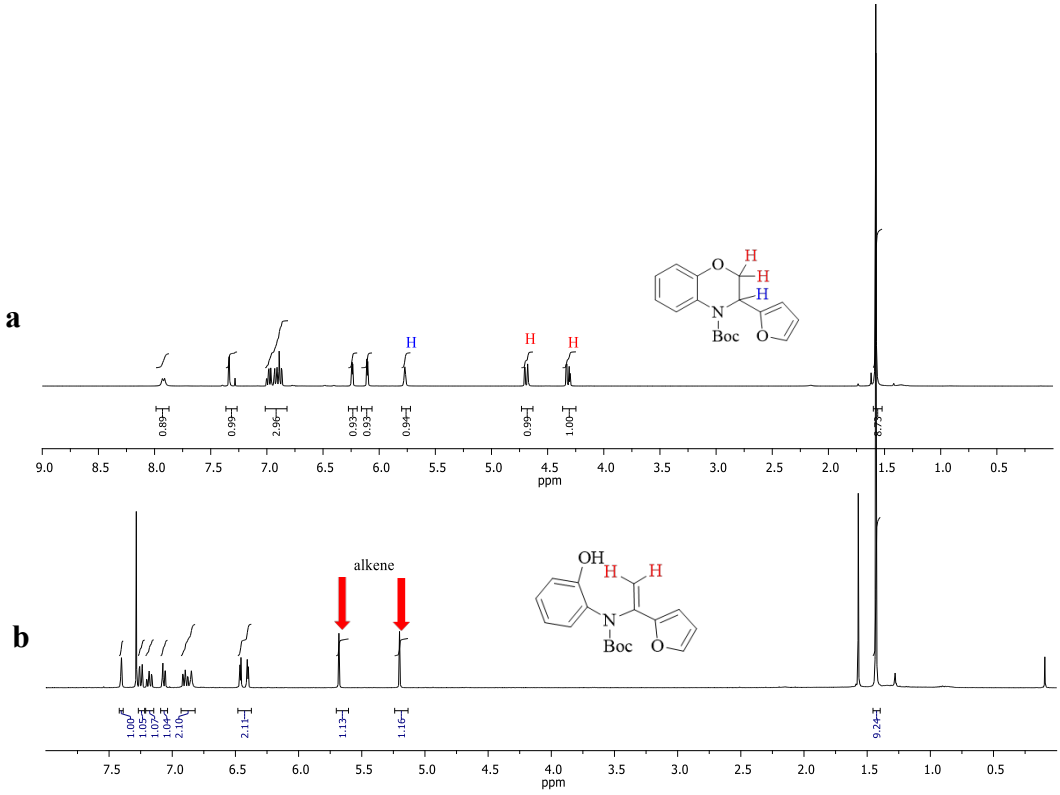


Figure 2.5

The aromatic group should be pseudo-axial to avoid A^{1,3} strain with the Boc group (and this is apparent from the small coupling constant for CHN), so the C–Li bond is pseudo-equatorial and is anti-periplanar with the breaking C–O bond aiding the E2 mechanism. In addition, the phenoxide can stabilise the negative charge (Figure 2.6).

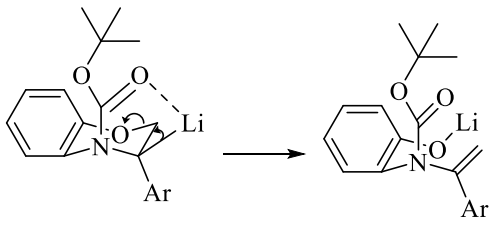
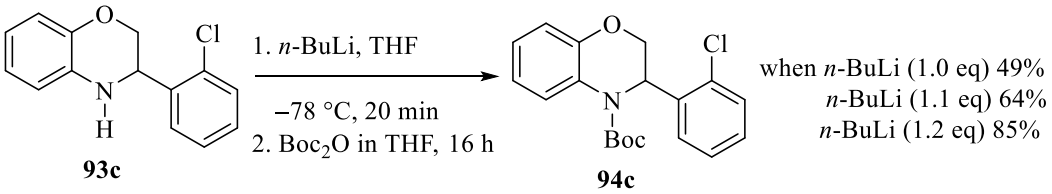


Figure 2.6 Mechanistic proposal for ring-fragmentation in lithiation of *N*-Boc-3-aryl-1,4-benzoxazines

In contrast to the other derivatives, when the equivalents of *n*-BuLi was increased with benzoxazine **93c**, this gave a better yield of **94c** without any eliminated product being obtained as shown in Scheme 3.39.

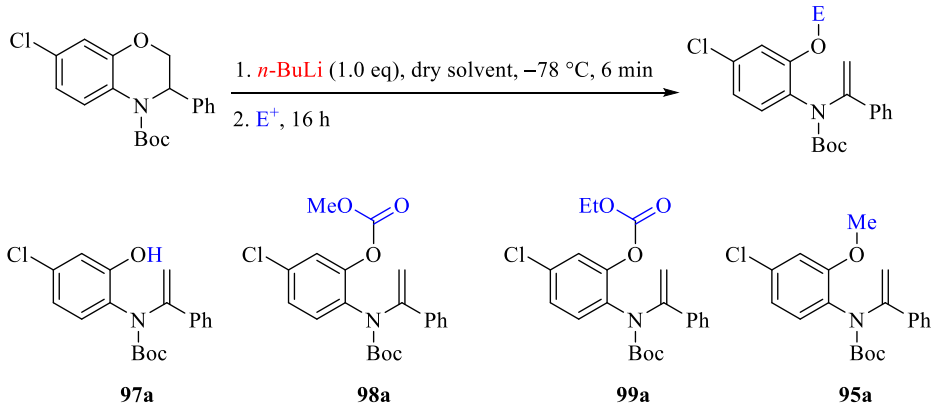


93c **94c**

Scheme 2.39

2.4.2.1 Lithiation of *N*-Boc-7-chloro-3-phenylbenzoxazine 94a

With the desired compounds **94a-d** in hand, it was necessary to optimise the conditions for lithiation and trapping, even though the *α*-substituted products could not be formed due to the elimination side product. This was tested with substrate **94a** by using *n*-BuLi at –78 ºC with 6 min as the lithiation time (Scheme 2.40, Table 2.3).



97a **98a** **99a** **95a**

Scheme 2.40

Table 2.3:

Entry	E^+	ST*	SA*	Yield	Comment
1	MeOCOCl	THF	4 mL	0	decompose
2	EtOCOCl	THF	4 mL	0	decompose
3	EtOCOCl	THF	8 mL	0	decompose
4	MeI	THF	8 mL	0	decompose
5	EtOCOCl	2-MeTHF	8 mL	40	28% RSM*
6	Allyl bromide	2-MeTHF	4 mL	0	only RSM*
7	MeOH	Et_2O	8 mL	0	45% RSM
8	MeOH	Et_2O/TMEDA	8 mL	50	12% RSM

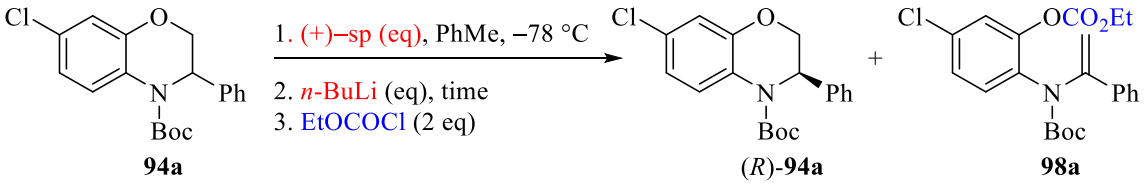
E^+ = electrophile, ST = solvent, SA* = solvent amount in 100 mg of **94a***

From Table 2.3, it was clear that carrying out the reaction in THF was not ideal to form the eliminated product (Entries 1-4). When 2-MeTHF was used, this gave the expected alkene **98a** in 40% yield with EtOCOCl as an electrophile and also a 28% yield of recovered starting material **94a** (Entry 5). However, no product was obtained when allyl bromide was used as the electrophile (Entry 6). Furthermore, no product was obtained when Et_2O was used as the solvent and only the starting material **94a** was recovered in a 45% yield (Entry 7). In comparison, when Et_2O/TMEDA was used, this gave the eliminated product **95a** in 50% yield (Entry 8). It may have been due to the fact that THF co-ordinates more strongly than 2-MeTHF. Also, 2-MeTHF is more hindered, so there may have been formation of different aggregates due to the different electrostatic interactions between the lithium atom and surrounding solvent molecules. Furthermore, ether was maybe not strong enough to deaggregate the organolithium reagent alone and so TMEDA was needed to increase further the reactivity of the organolithium by co-ordination.

2.4.2.2 Kinetic resolution of *N*-Boc-7-chloro-3-phenylbenzoxazine 94a

Due to the unpromising results obtained from the initial lithiation reactions, it was decided to concentrate on kinetic resolution reactions in which the starting materials could be recovered

in high er, regardless of whether the eliminated product is formed or not. The conditions for the kinetic resolution of tetrahydrobenzoxazine **94a** were therefore optimised. The results are summarised in Table 2.4.



Scheme 2.41

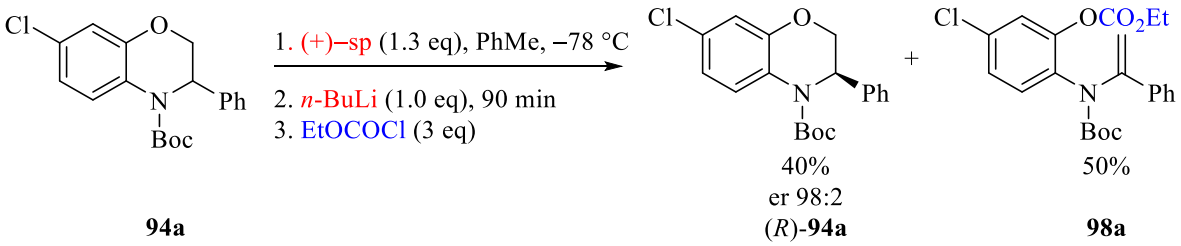
Table 2.4:

Entry	(+)-sp eq	*n*-BuLi eq	time	RSM%	er	98a%
1	0.6	0.55	30 min	83	66:34	5
2	0.7	0.60	30 min	81	63:37	11
3	0.7	0.60	60 min	75	61:39	15
4	0.7	0.65	60 min	65	66:34	25
5	0.8	0.70	30 min	62	72:28	35
6	0.9	0.80	60 min	55	73:29	38
7	1.0	0.90	60 min	50	76:24	39
8	1.1	1.0	60 min	49	86:14	41
9	1.3	1.0	90 min	40	98:2	50

eq = Equivalent, RSM = recovered starting material

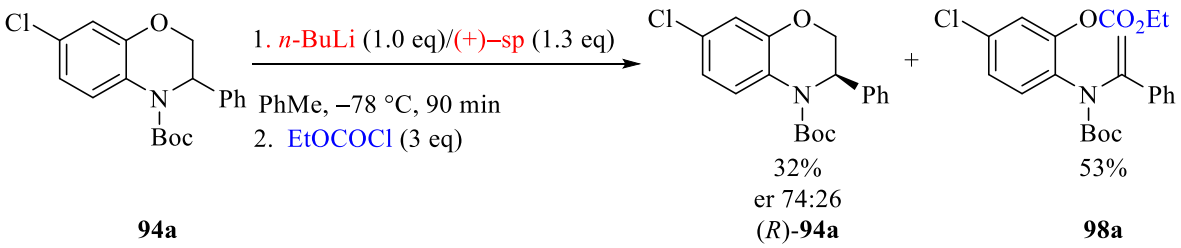
It was decided to try kinetic resolutions with the addition of *n*-BuLi to the mixture of **94a** and (+)-sp and with fewer equivalents of *n*-BuLi to not only try and avoid decomposition of the starting material, as found in the previous lithiations, but also to increase the amount of product **98a** formed. When 0.55 equivalents of *n*-BuLi and 0.6 equivalents of (+)-sparteine were used, the starting material **94a** was recovered in 83% yield with 66:34 er and the alkene product **98a** was obtained in only 5% yield (Table 3.4, Entry 1). However, when the equivalents of *n*-BuLi was slightly increased, the yield of recovered starting material **94a** was slightly lower, along with an increase in the yield of product **98a** as expected, with only a small change of the enantiomeric ratio of the starting material being observed (Entry 2). Theoretically, if the lithiation time was increased then the yield of the recovered starting material **94a** would be

reduced and this is shown in entry 3. Increasing both the equivalents of *n*-BuLi and the lithiation time gave promising results, which allowed the starting material to be recovered with better enantioselectivity (Entries 4-9). Furthermore, by using one equivalent of *n*-BuLi and an excess of (+)-sparteine (1.3 equivalents), to make sure there was enough of the chiral ligand, with a 90 min lithiation time, this gave the best result, with 40% of the starting material being recovered with 98:2 er (Entry 9 and summarised in Scheme 2.42). It was assumed that the configuration of **94a** recovered in this kinetic resolution was the same as tetrahydrobenzoxazine **58** as shown in Scheme 2.4, as (+)-sparteine was used in both cases.



Scheme 2.42

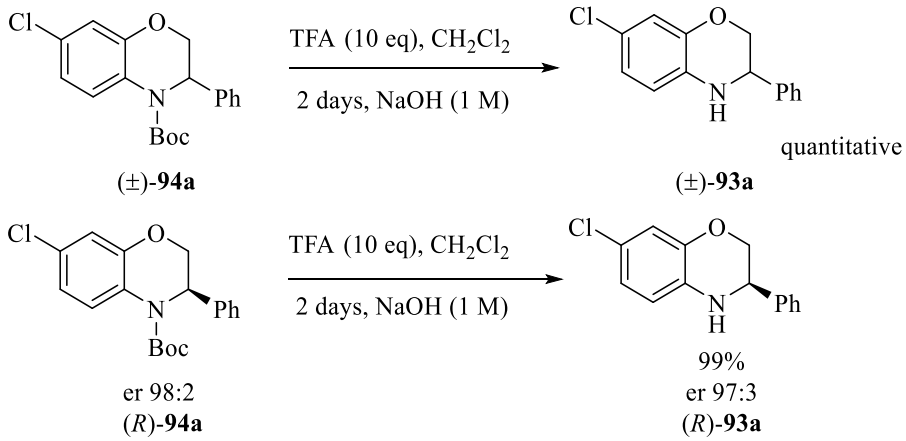
Furthermore, a pre-mix addition (also known as inverse addition) method was applied to the optimised conditions, which had worked well for the tetrahydroquinoline substrates (Scheme 1.31).[54] However, the reaction gave the recovered starting material in a low yield of 32%, with moderate enantioselectivity (74:26 er) as shown in Scheme 2.43. As this pre-mix reaction did not give promising results with tetrahydrobenzoxazine **94a**, it was decided to not carry out further kinetic resolution reactions in this case.



Scheme 2.43

Continuing with the work, it was possible to remove the Boc group by adding TFA to a solution of tetrahydroquinoline **94a** in CH_2Cl_2 to give the corresponding amine. Monitoring the reaction

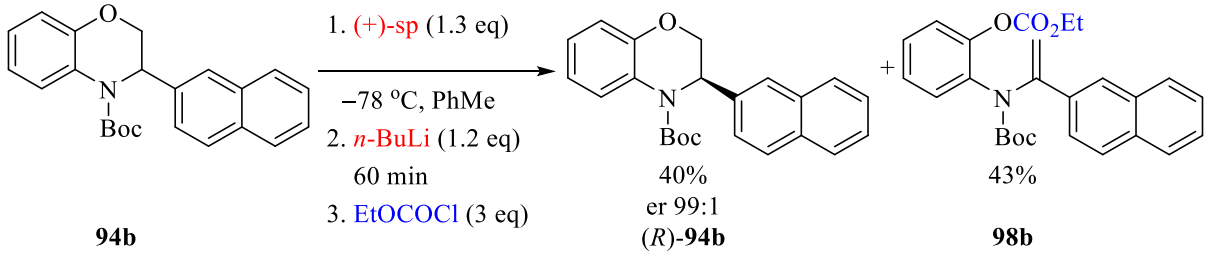
by TLC showed that the starting material was consumed after two days. This reaction was then applied to enantioenriched (*R*)-**94a** to give secondary amine (*R*)-**93a** with the enantiopurity being maintained (Scheme 2.44).



Scheme 2.44

2.4.2.3 Kinetic resolution of *N*-Boc-3-(2-naphthyl)benzoxazine 94b

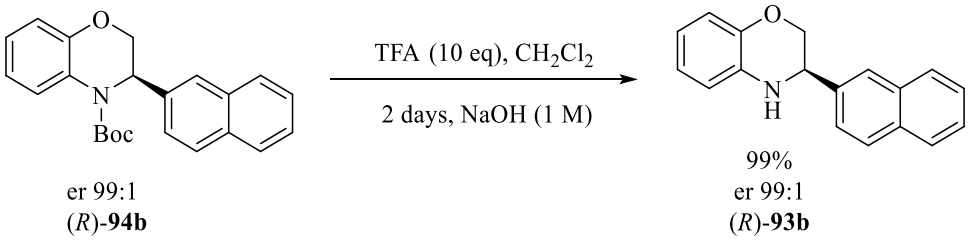
The kinetic resolution of tetrahydrobenzoxazine **94b** was then investigated using 1.3 equivalents of the chiral ligand (+)-sparteine, which was dissolved first in toluene and 1.2 equivalents of *n*-BuLi was then added at –78 °C. The starting material (*R*)-**94b** was recovered in an excellent enantiomer ratio of 99:1 in 40% yield with a 43% yield of the eliminated product **96** also obtained (Scheme 2.40).



Scheme 2.45

In the same way as tetrahydrobenzoxazine **94a**, the Boc group of benzoxazine (*R*)-**94b** was able to be removed under acidic conditions to give the secondary amine (*R*)-**93b** (Scheme 2.46).

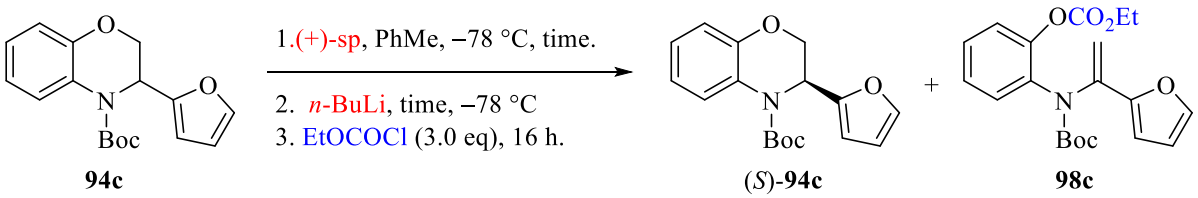
The amine (*R*)-**93b** was obtained with no loss of enantiopurity as determined by chiral stationary phase HPLC.



Scheme 2.46

2.4.2.4 Kinetic resolution of *N*-Boc-3-(2-furanyl)benzoxazine 94c

Moving on to the heterocycle derivatives, kinetic resolutions of tetrahydrobenzoxazine **94c** were attempted next. The investigation started by using the same conditions as for tetrahydrobenzoxazine **94b**. 1.2 Equivalents of *n*-BuLi and 1.3 equivalents of (+)-sparteine were used with a lithiation time of 60 min. The starting material (*S*)-**94c** was recovered with high enantioselectivity (er 92:8) but in a low yield of 11% (Scheme 2.47 and Table 2.5, entry 1).



Scheme 2.47

Table 2.5:

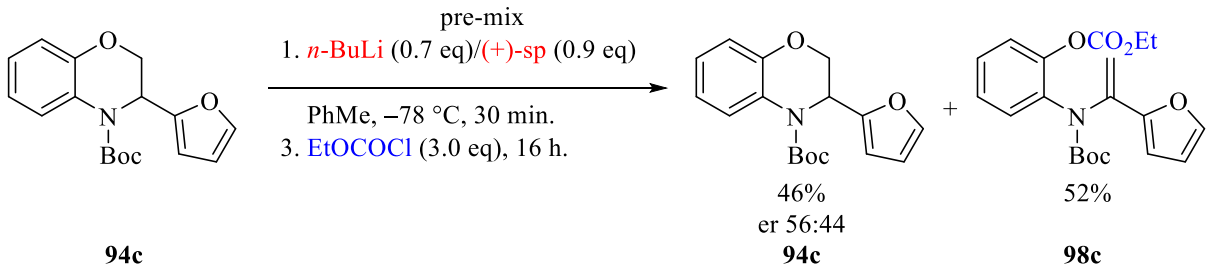
Entry	(+)-sp eq	*n*-BuLi eq	time	RSM%	er	98c%
1	1.3	1.2	60 min	11	92:8	81
2	0.9	0.7	60 min	47	71:29	50
3	0.9	0.7	30 min	43	80:20	52

eq = Equivalent, RSM = recovered starting material

Repeating the reaction with fewer equivalents of *n*-BuLi, as Table 2.5 illustrates, the yield of the recovered starting material (*S*)-**94c** was increased along with the decline in the

enantioselectivity as expected (Entry 2). The lower enantiomeric ratios of recovered tetrahydrobenzoxazine **94c** might be due to the co-ordination of the heteroatom in the furanyl ring with the *n*-BuLi. Finally, reducing the lithiation time did not affect either the yield or the enantioselectivity of the recovered starting material (Entry 3).

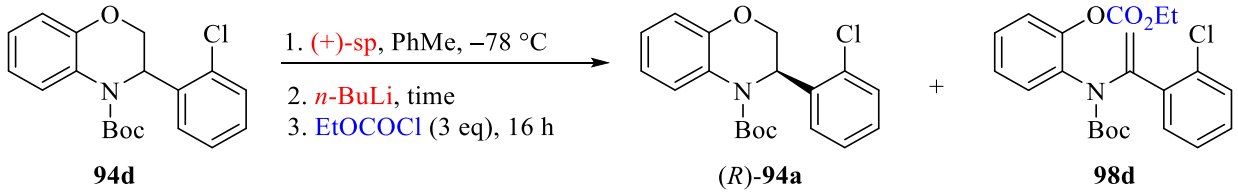
The pre-mix method was attempted next. The chiral base was first made by mixing the *n*-BuLi with (+)-sp in PhMe. The starting material **94c** was then added at –78 ºC. Unfortunately, almost racemic starting material was recovered with an er 56:44 in 46% yield, as shown in Scheme 2.48.



Scheme 2.48

2.4.2.5 Kinetic resolution of *N*-Boc-3-(2-chlorophenyl)benzoxazine 94d

Kinetic resolution reactions on tetrahydrobenzoxazine **94d** gave similar results to tetrahydro-benzoxazine **87c**, as shown in Scheme 2.44 and Table 2.6; high er was obtained only when the yield of 41d was low. This may be due to the chlorine atom, which has three possible effects, one is a steric effect that can be caused from an *ortho*-position of the chlorine atom that may affect the selectivity. The second is that chlorine has a strong inductive effect, which may increase the acidity of α-proton that influences the enantioselectivity and the rate of lithiation. The third effect that could be any coordination of the chlorine with the *n*-BuLi.



Scheme 2.49

Table 2.6:

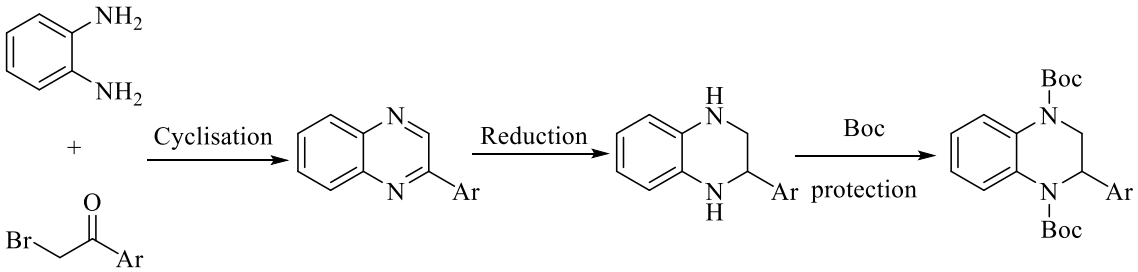
Entry	(+)-sp eq	*n*-BuLi eq	time	RSM%	er	45%
1	1.1	1.0	60 min	11	97:3	83
2	1.1	0.8	60 min	21	93:7	66
3	1.1	0.8	30 min	32	85:15	61
4	1.0	0.6	60 min	41	75:25	53

eq = Equivalent, RSM = recovered starting material

2.5 Results and discussion of 2-aryltetrahydroquinoxalines

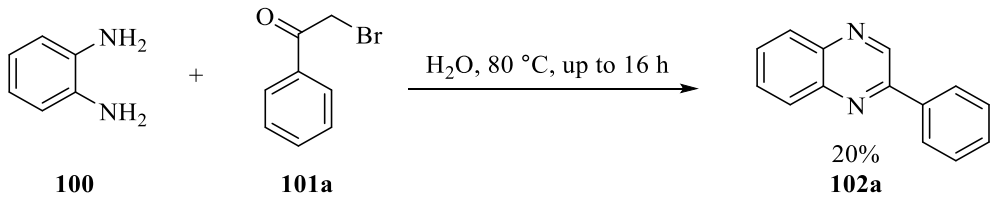
2.5.1 Synthesis of 1,4-*N*,*N*-di-Boc-2-aryltetrahydroquinoxalines

Quinoxalines are key structural units of a number of compounds with various biological activities[61], including compounds with antitumoural, antibacterial, anticandida, antitrypanosomal, anti-inflammatory, antioxidant, anti-viral, and anticancer properties.[62,63] Additionally, quinoxaline derivatives are known as anthelmintic agents, semiconductors, dyes, and biocides.[64,65] Described in this section are efforts towards the kinetic resolution of tetrahydroquinoxalines, which could be similar to the chemistry of the tetrahydrobenzoxazine structures that gave excellent enantioselectivities as discussed in the previous section. At the start of the project, there were no examples of compounds containing the 1,4-*N*,*N*-di-Boc-2-aryltetrahydroquinoxaline motif, so the quinoxaline substrates **104a-c** needed to be synthesised from readily available starting materials and a conceptual general scheme was devised after reading the literature (Scheme 2.50).[66–70]



Scheme 2.50

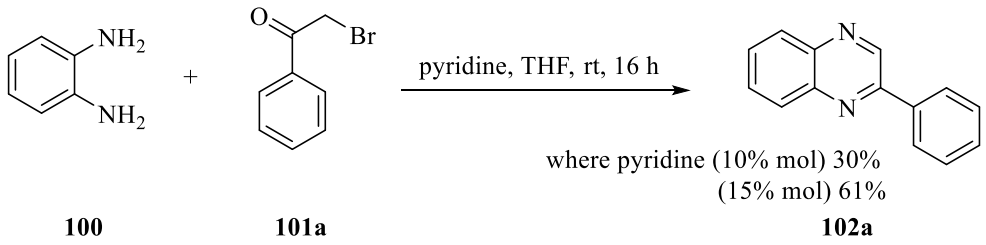
The cyclisation step was attempted first by using 1,2-phenylenediamine **100** and phenacyl bromide **101a** dissolved in water and heated at 80 °C for 16 h. Unfortunately, the reaction only gave a low yield of 20% for quinoxaline **102a**. This was much lower then the yield reported in the literature (Scheme 2.51).[69]



100 **101a** **102a**

Scheme 2.51

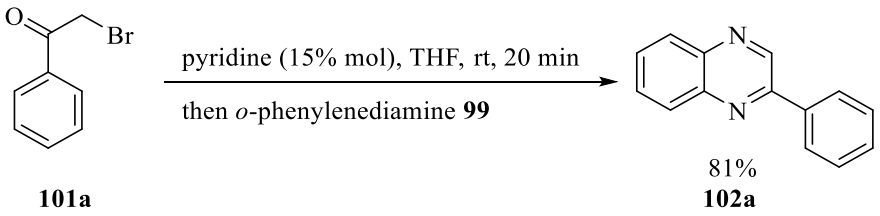
Another method was attempted to try and improve the yield. Using pyridine as a base in THF,[70] this was mixed with 1,2-phenylenediamine **100** and phenacyl bromide **101a**, at room temperature in one pot, as shown in Scheme 2.52. At first, a literature method was followed by adding 10% mole equivalents of pyridine to the reaction to afford product, but 2-phenylquinoxaline **102a** was only obtained in 30% yield as shown in Scheme 2.52. The performance of the catalyst pyridine using different mole ratios was examined. The investigation showed that 15% mole equivalents of pyridine was sufficient to improve the yield to an acceptable 61%.



100 **101a** **102a**

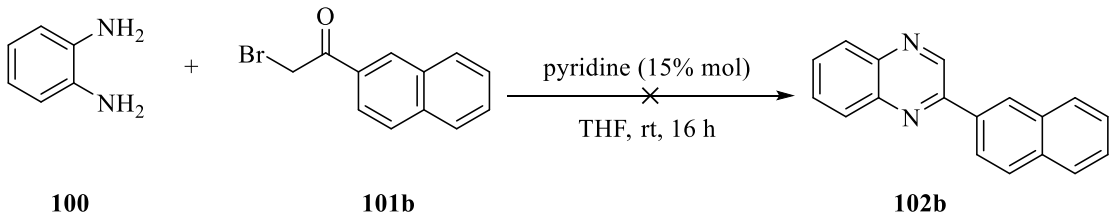
Scheme 2.52

To improve the yield of quinoxaline **102a** further, phenacyl bromide **101a** was left to stir with pyridine (15% mol) for 20 min until the solution became light green. Subsequent addition of diamine **100** then gave a good yield of **102a** (Scheme 2.53).



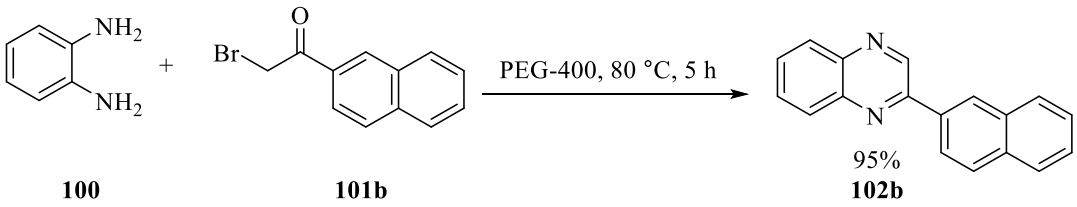
Scheme 2.53

By applying the same procedure to prepare the quinoxaline **102b**, no product was obtained and only the starting material was recovered. The reaction was repeated twice and the same results were obtained each time (Scheme 2.54).



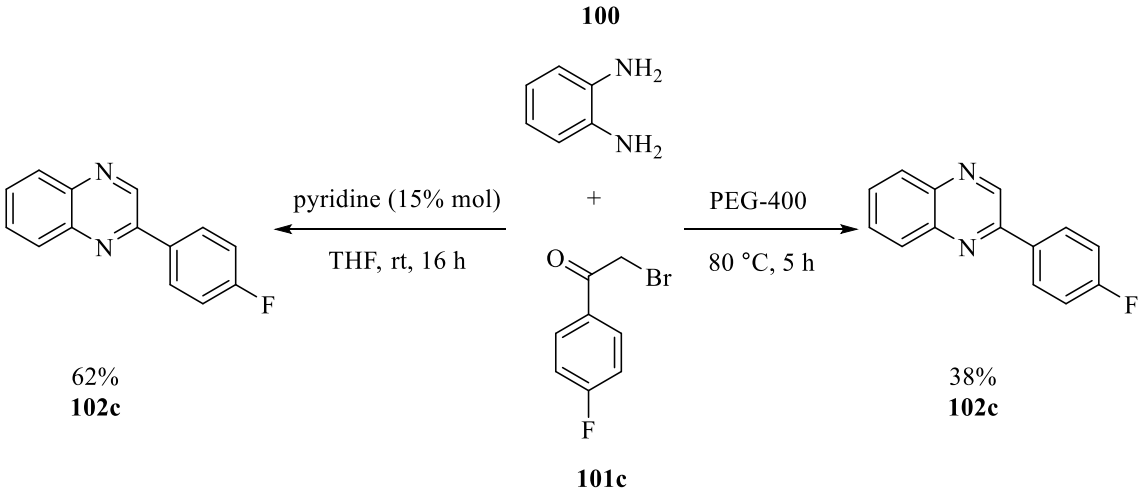
Scheme 2.54

However, after moving to a different method using polyethylene glycol (PEG) as a solvent and heating the reaction at 80 ºC for 5 h, gave **102b** in 95% yield (Scheme 2.55).[71]



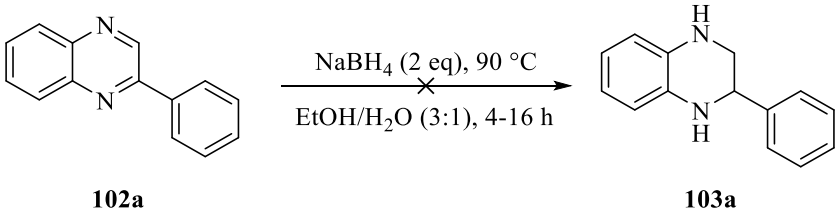
Scheme 2.55

In comparison, when applying both methods to prepare 2-(4-fluorophenyl)quinoxaline **102c,** the method using pyridine gave a 62% yield, while a much lower yield of 38% was obtained using the PEG-400 method (Scheme 2.56).[70,71]



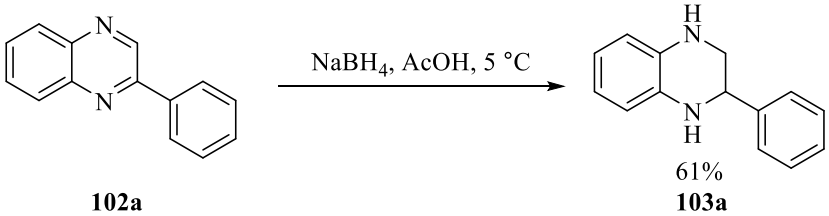
Scheme 2.56

The next step was to reduce the quinoxaline substrates. The first substrate tested was quinoxaline **102a** using sodium borohydride in the solvent mixture of EtOH/H_2O (3:1).[53] The reaction mixture was heated at 90 ºC and by monitoring the reaction using TLC, no progress was observed even after 16 h (Scheme 2.57).



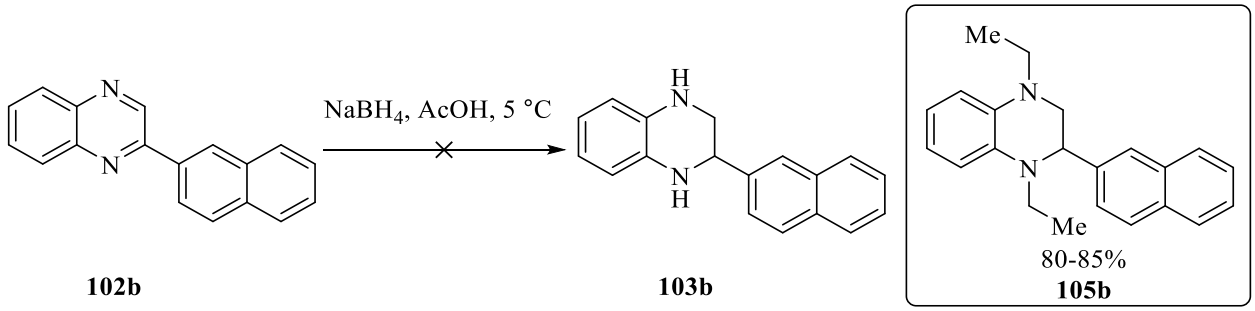
Scheme 2.57

Fortunately, the reduction reaction was successful when sodium borohydride was added in small portions to a stirred solution of quinoxaline **102a** in glacial acetic acid at 5 ºC. The reduced product **103a** was obtained in 61% yield (Scheme 2.58).[72]



Scheme 2.58

When this method was applied to quinoxaline **102b,** the side product **105b** was obtained instead of the corresponding amine **103b** (Scheme 2.59).



Scheme 2.59

^{1}H-NMR spectroscopy of the product showed 10 extra protons in the range of 1 ppm to 3.7 ppm, as shown in Figure 3.7. It was proposed that *N*-alkylation took place after reduction of the quinoxaline. The six proton signals of the CH_3 appear as a multiplet at δ1.17–1.09 ppm and the three CH_2 signals of the NCH_2 appear as a multiplet at δ 3.64 – 3.04 ppm which integrated for six protons. It is not clear how **105b** was formed from **102b**. It is possible that **103b** was formed which then underwent reductive amination, although there should not be any acetaldehyde in the acetic acid and any amide formation would be expected to give the acetamide and not the *N*-ethyl product. At this point, based on this result, this route to the desired compound was discontinued.

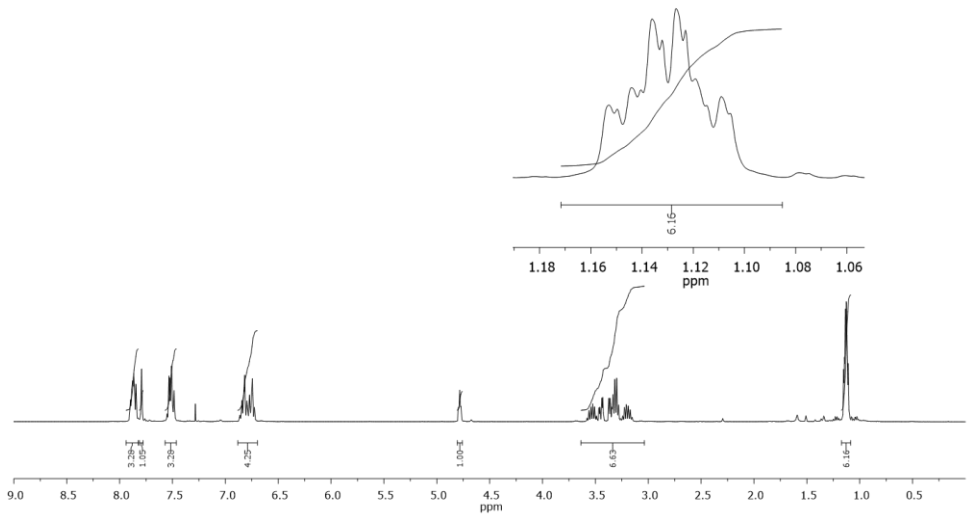
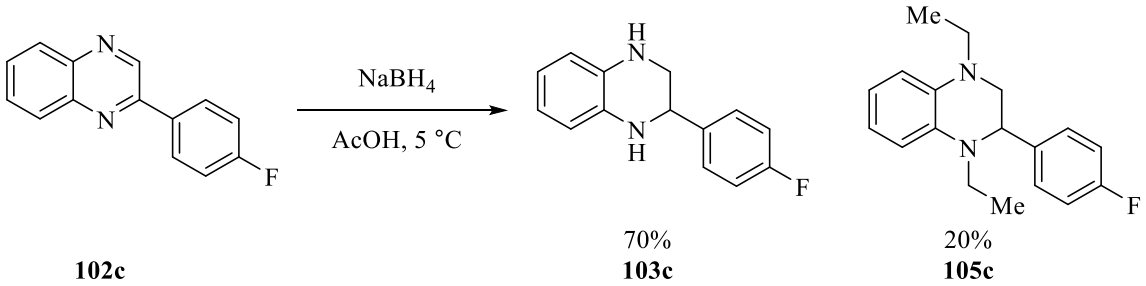


Figure 2.7

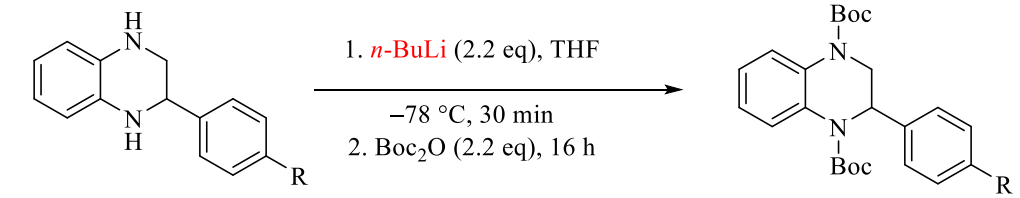
The reduction of quinoxaline **102c** with $NaBH_4$ in acetic acid was tested and this gave 70% yield of the corresponding amine **103c**, with 20% yield of alkylation product **105c** also being obtained.



102c 70% **103c** 20% **105c**

Scheme 2.60

The final step of the synthesis was the Boc protection reaction. *n*-BuLi was used to deprotonate tetrahydroquinoxaline **103a** and **103c** at –78 °C. It was decided that 2.2 equivalents of the base would be used and after leaving the mixture to stir for 20 min, a solution of Boc_2O in THF was added which gave moderate to good yields of the desired products **104a** and **104c** (Scheme 2.61). No eliminated product was obtained in the case of the tetrahydroquinoxalines, in contrast to the tetrahydrobenzoxazines **94a-d**, as mentioned above in Scheme 2.36.



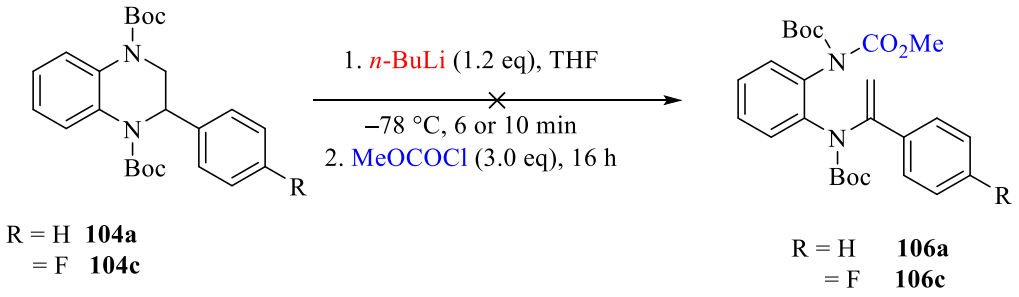
R = H **103a**
= F **103c**

R = H 85% **104a**
= F 60% **104b**

Scheme 2.61

With the tetrahydroquinoxalines **104a** and **104c** in hand, the lithiation chemistry could now be tested using *n*-BuLi in THF at –78 ºC. The reaction mixture was left to stir for between 6 and 10 minutes before adding MeOCOCl as the electrophile. However, neither of the desired alkenes **106a** and **106c** were obtained (Scheme 2.62). After warming the reaction mixtures overnight, the colour had changed from colourless to black-green, and many spots were

observed on the TLC plate. Potentially, the compounds could undergo decomposition with no desired products being obtained.

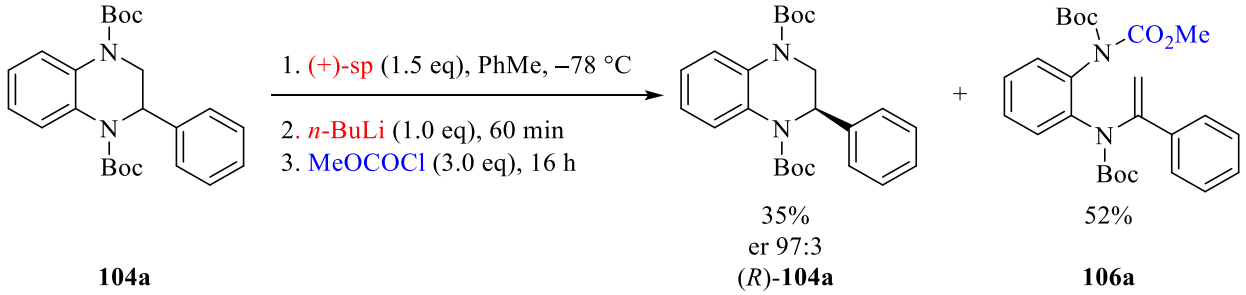


Scheme 2.62

As no products were obtained from any of the reactions, it was decided to move to investigate the kinetic resolutions, which could have high enantioselectivity like the benzoxazines.

2.5.2 Kinetic resolution of 1,4-*N*,*N*-di-Boc-2-arylquinoxalines

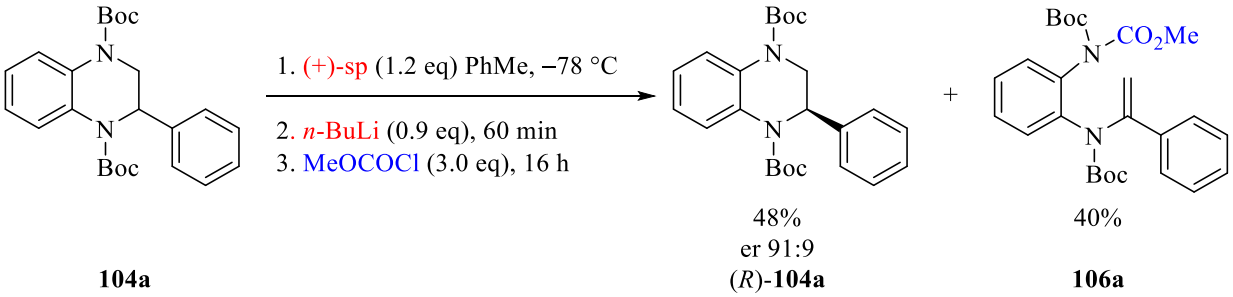
First, it was decided to try kinetic resolutions using the same conditions as the 1,4-benzoxazines by adding the *n*-BuLi last ('normal addition method'). The starting material **105a** and excess (+)-sparteine were dissolved in toluene and cooled to –78 ºC, then one equivalent of *n*-BuLi was added and after 60 min, MeOCOCl was then added as the electrophile to trap the intermediate. The starting material was recovered in 35% yield with an excellent enantiomeric ratio (97:3) while the eliminated product **106a** was obtained in 52% yield (Scheme 2.63).



Scheme 2.63

In order to try and obtain a better yield, fewer equivalents of base and (+)-sparteine were used. The reaction was run using 0.9 equivalents of *n*-BuLi with the same lithiation time of 60 min.

The recovered starting material was obtained in 48% yield with good enantiomeric ratio (91:9) and the alkene product **106a** was obtained in 40% yield (Scheme 2.64).



Scheme 2.64

The absolute configuration of dicarbamate (*R*)-**104a** was confirmed by single crystal X-ray analysis (Figure 2.8).

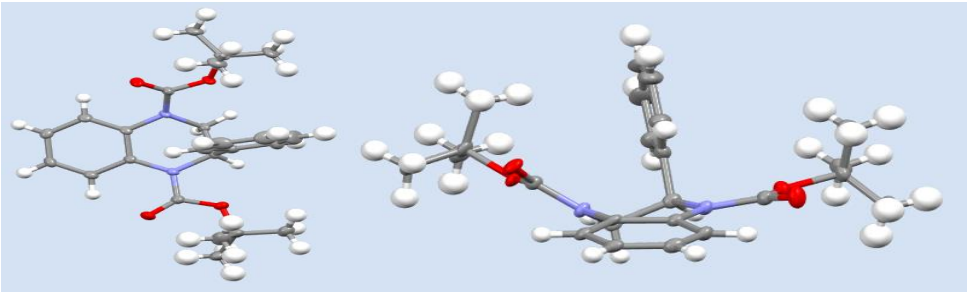


Figure 2.8

Interestingly, the single crystal X-ray data showed that in compound (*R*)-**104a**, the two *tert*-butyl groups and phenyl ring are located on the same side as shown in Figure 2.8. This may be due to the possibility of aromatic π-system interaction with the *tert*-butyl group as the distance between the centre of the benzene ring and one of the C– H's of the *tert*-butyl group is about 3.04 Å (Figure 2.9).[73]

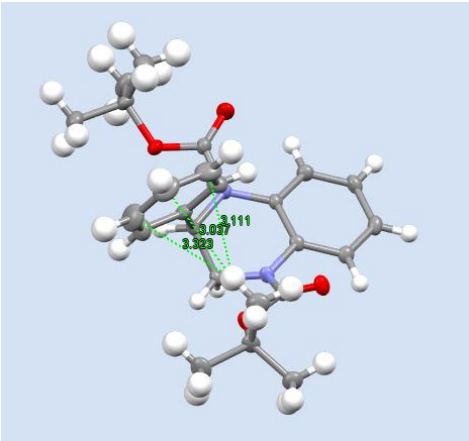
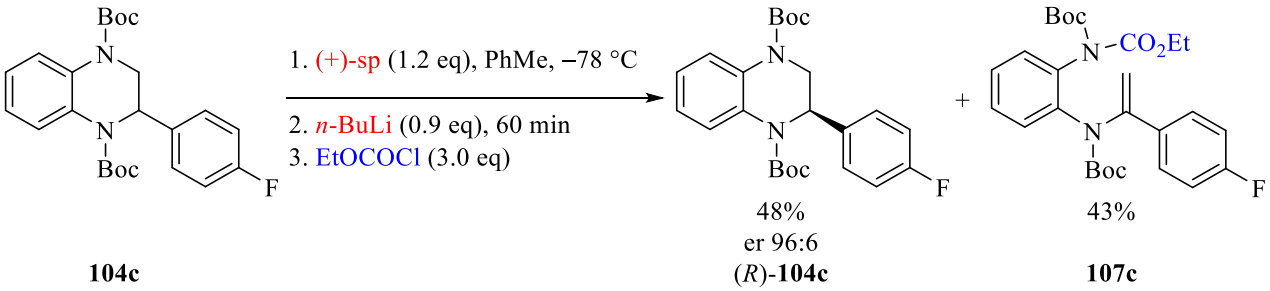


Figure 2.9

Using these conditions, the kinetic resolution was carried out with tetrahydroquinoxaline derivative **104c**, which gave the recovered (*R*)-**104c** with high enantioselectivity (96:4 er) in 48% yield while the sacrificial product **107c** was obtained in 43% yield.



Scheme 2.65

2.6 Conclusions and Future Work

In conclusion, although the lithiation quench reactions of 2-aryl-1,3-oxazinane **62** succeeded, the kinetic resolution results were disappointing. A potential reason for having poor enantioselectivity in these reactions may be due to co-ordination of the chiral organolithium complex to the oxygen atom of the 1,3-oxazinane ring which may have led to unselective deprotonation of either enantiomer (Figure 3.10a). Alternatively, this complex could preferentially deprotonate the opposite enantiomer in comparison with the complex between *n*-BuLi/(+)-sp and the carbonyl oxygen of the *tert*-butoxycarbonyl group (Figure 2.10b).

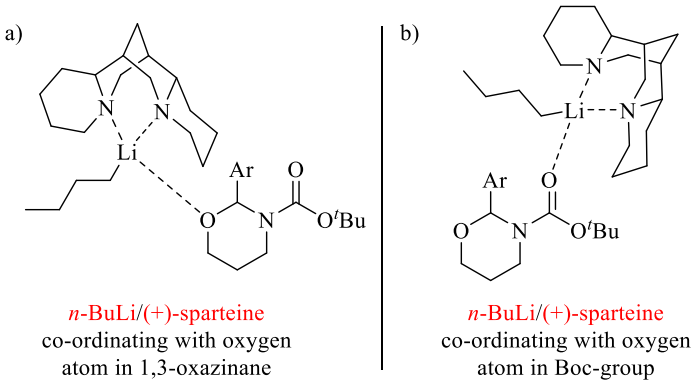
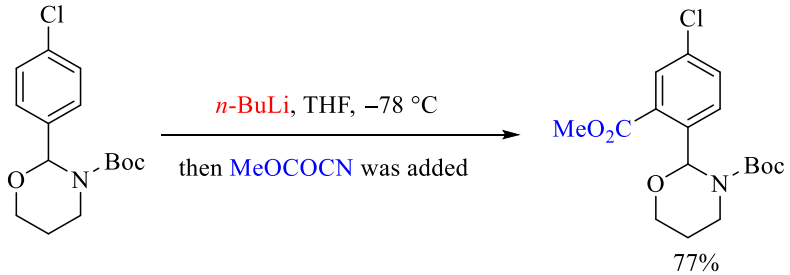


Figure 2.10

Alternatively, the benzylic proton may be more acidic (in comparison with the corresponding piperidine) due to its position between two highly electronegative atoms (oxygen and nitrogen). This might cause the $\Delta G^{\ddagger}$ of both diastereomeric transition states to have a similar energy. In other word, the hypothesis of the kinetic resolution of one enantiomer having a lower $\Delta G^{\ddagger}$ that can react faster than other is not realized in this case.

Future work should be done to confirm this theory by using DFT calculations. These could investigate whether the oxygen atom in the 1,3-oxazinane ring can be co-ordinated to the chiral base complex during the kinetic resolutions or whether the diastereomeric transition states have a similar energy.

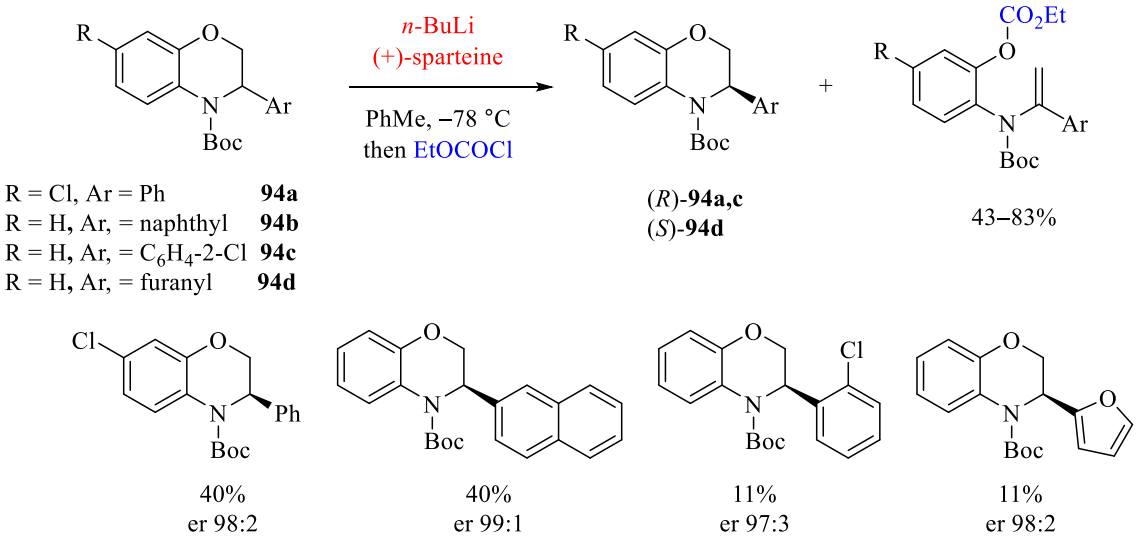
An interesting result was when methyl cyanoformate was used as the electrophile as this produced the *ortho*-substituted product **66**.



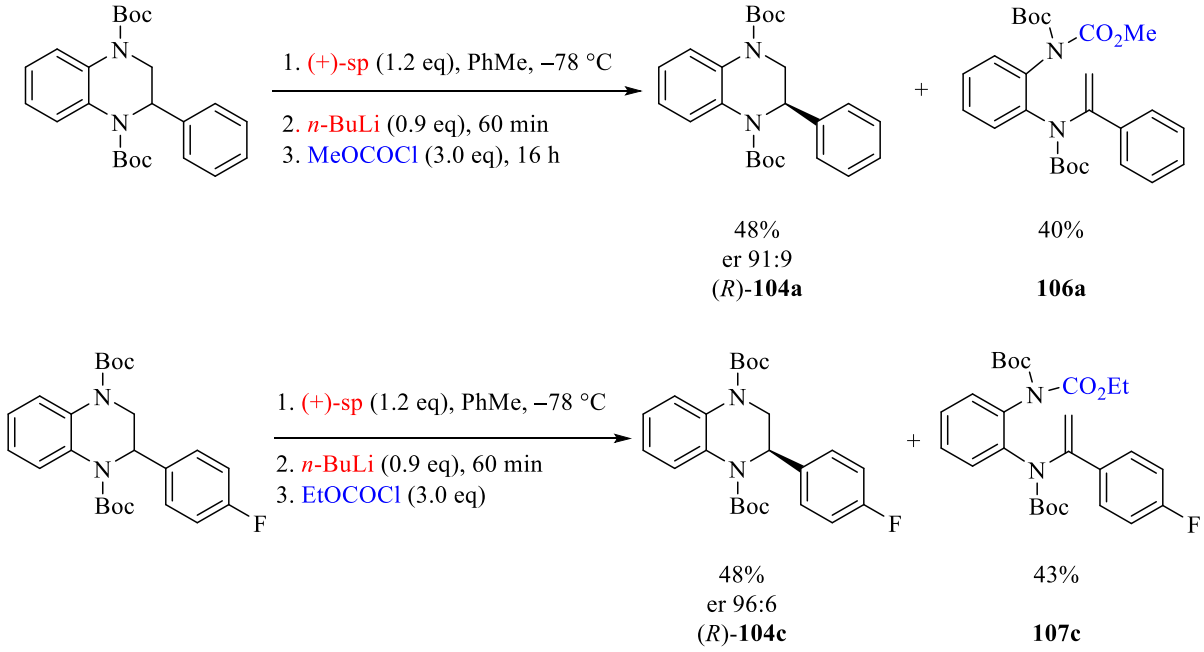
62 **66**

N-Boc-3-aryl-1,4-benzoxazines **94a-d** were synthesised in a 3-step procedure from readily available starting materials. The kinetic resolution reactions were carried out using *n*-BuLi/(+)-

sp as the chiral base which gave excellent enantioselectivity with reasonable yields being obtained.

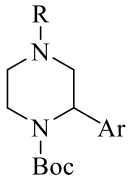


Two quinoxaline derivatives were able to be prepared from readily available starting materials. The kinetic resolutions were carried out by addition of *n*-BuLi to a mixture of the *N*,*N*-di-Boc-2-aryl-1,2,3,4-tetrahydroquinoxaline **104a**,**c** and (+)-sparteine in toluene, followed by electrophilic quench with an alkyl chloroformate.



The configurational structure showed that the two Boc groups and aromatic ring are placed on the same side which might be due to the possible interaction between the aromatic π-system and the *tert*-butyl group (Appendix A).

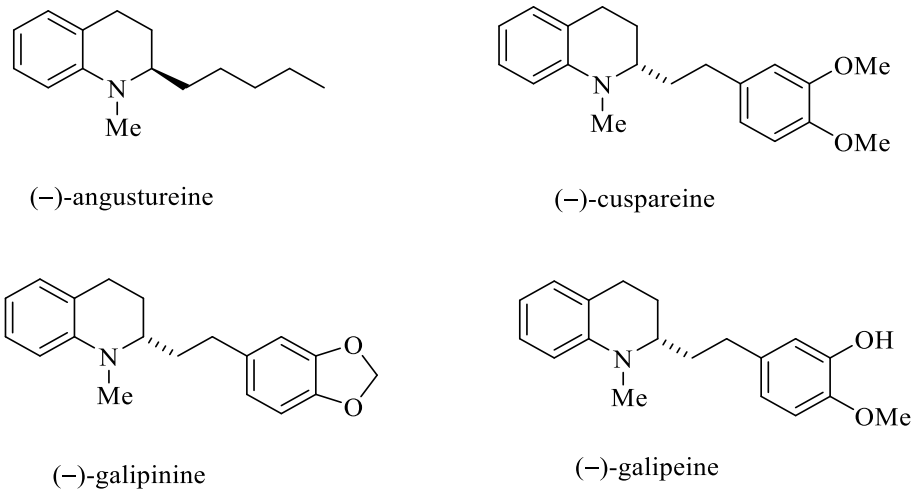
Further work could be to extend the methodology to a variety of other derivatives to examine the scope of the kinetic resolutions. Reactions could also be attempted on other 2-aryl *N*-Boc heterocycles such as piperazines **A**.



A

Chapter 3 - Synthesis and lithiation–substitution of *N*-Boc-2-styrenyldihydroquinoline

Tetrahydroquinoline and dihydroquinoline derivatives are ubiquitous in natural products and pharmaceuticals. In addition, they are of great interest in synthetic organic chemistry. There are multiple natural products which contain the THQ motif such as (–)-angustureine, (–)-cuspareine, (–)-galipinine, and (–)-galipeine (Figure 3.1). [74,75]



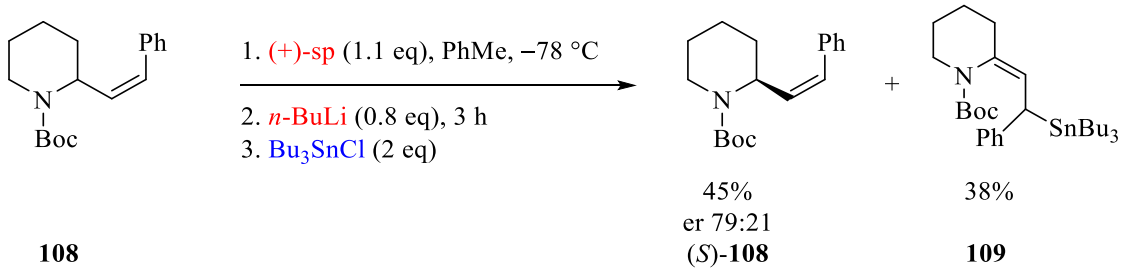
(−)-angustureine (−)-cuspareine

(−)-galipinine (−)-galipeine

Figure 3.1

3.1 Previous work in the group

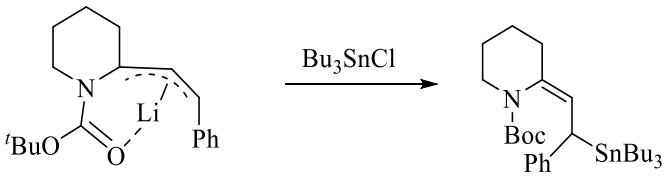
Although previous work in the Coldham group has been based around deprotonation of benzylic protons, recent work has involved investigating alternative structures inspired by natural products like (–)-galipinine and sedamine.[76] The *α*-carbon in the substrate was connected to an alkene, an sp^2 hybridised carbon, which is similar to the benzylic carbon. Therefore, a previous Ph.D student in the group started to work on *N*-Boc-2-[(*Z*)-2-phenylethenyl]piperidine **108**. [76] The kinetic resolution of compound **108** is shown below (Scheme 3.1).



108 45% er 79:21 (*S*)-**108** 38% **109**

Scheme 3.1

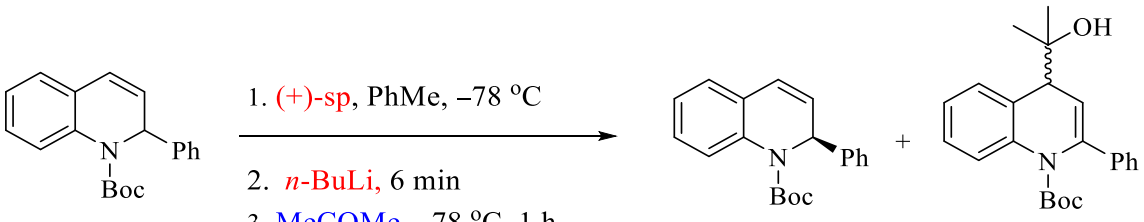
The lithiated intermediate **110** led to the *Z*-substituted product **109** after quenching with tributyltin chloride and it is likely that the lithium atom is co-ordinated to the allyl structure to give an η^3 intermediate **110**.



110 **109**

Scheme 3.2

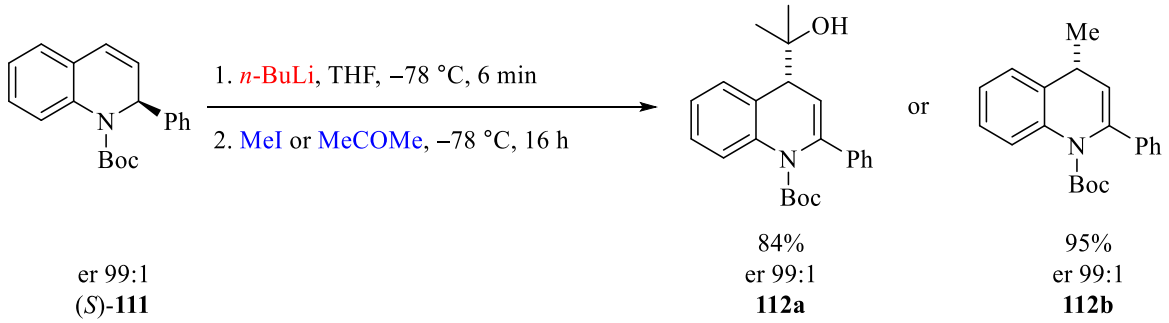
More recently, work in this area was continued by a Masters student in the group, with the aim of investigating the lithiation–substitution and kinetic resolution of *N*-Boc-2-phenyldihydroquinoline **111**.[136] It is important to note that the substitution occurred in the 4-position instead of the α-position where the deprotonation has taken place.



111 48% er 99:1 (*S*)-**111** **112a**

Scheme 3.3

The enantioenriched recovered starting material (*S*)-**111** was then lithitated and quenched with methyl iodide and acetone being used as electrophiles. Both products were obtained in high er (Scheme 3.4).



Scheme 3.4

To expand on this work, this project has aimed to try and synthesise one of the model compounds **A**, **B** and **C**, then to investigate the lithiation quench and kinetic resolution chemistry of these compounds (Figure 3.2).

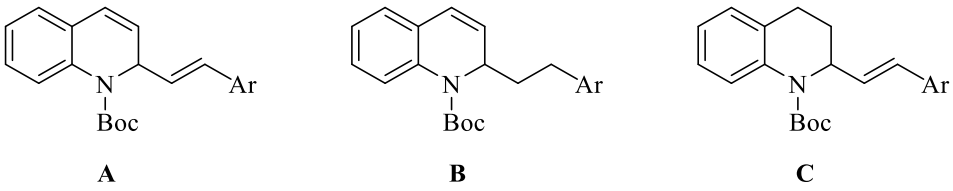
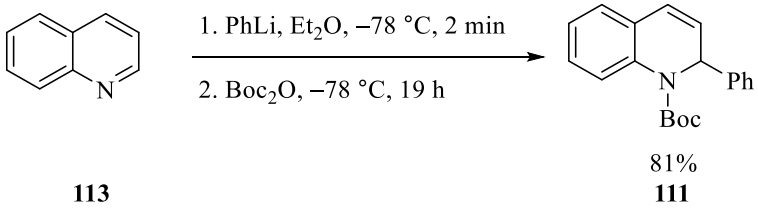


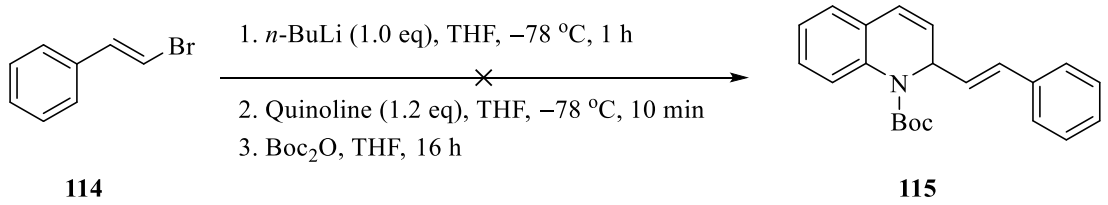
Figure 3.2

The starting materials were unavailable to buy from the suppliers and so they needed to be synthesised from commercially available materials. Firstly, the same method that was used to synthesise *N*-Boc-2-phenyldihydroquinoline **111** was used.[77] This method synthesised the desired compound in one pot from quinoline using organolithium chemistry (Scheme 3.5).



Scheme 3.5

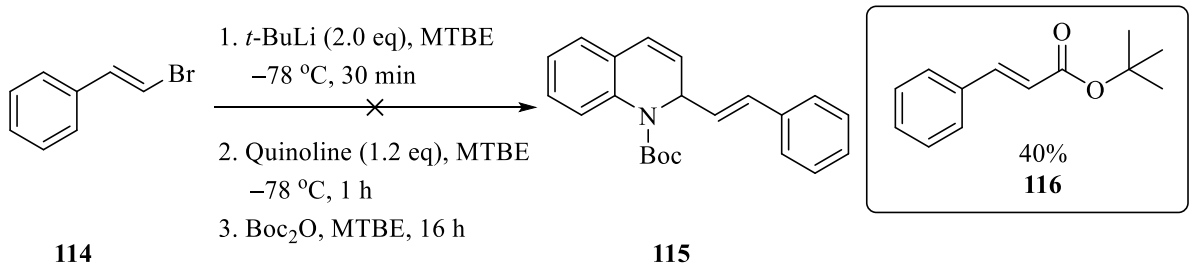
To start, halogen-lithium exchange was attempted on compound **114**, using *n*-BuLi in THF at –78 ºC and this was left to stir for 30 min.[78] Quinoline **113** in THF was then added at –78 ºC, and finally after 10 min, Boc_2O in THF was added. Unfortunately, only starting materials were recovered and the same results were obtained when Et_2O was used as a solvent.



114 **115**

Scheme 3.6

After researching the literature,[79] it was found that halogen-lithium exchanges is usually carried out using *s*-BuLi or *t*-BuLi. In order to try this, *β*-bromostyrene was first dissolved in methyl *tert*-butyl ether (MTBE) and *t*-BuLi was added at –78 ºC. After 30 min, quinoline in MTBE was slowly added and left to stir for 1 h before Boc_2O was added. Unfortunately, the desired compound was not obtained, and the product **116** was obtained instead in 40% yield as the major product, with other non-desired compounds present as determined by ^{1}H-NMR spectroscopy (Scheme 3.7). Due to the side product **116** being formed, it was assumed that the halogen-lithium exchange took place and this is further supported by the colour changing to yellowish (Figure 3.3) but there was not any further colour change when the quinoline was added. However, the reaction gave many spots on the TLC plate when Et_2O was used as solvent and none of them could be recognized.

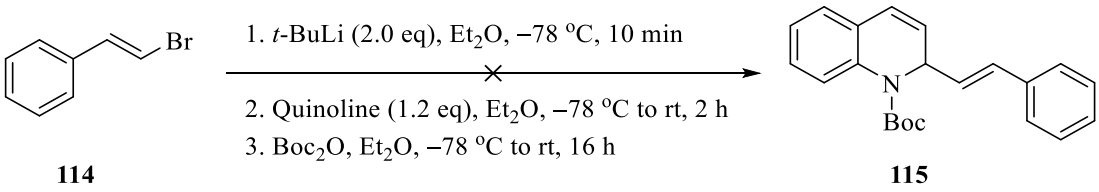


114 **115**

Scheme 3.7

Figure 3.3

The strategy then shifted to addition of the quinoline at –78 ºC, before warming the mixture to room temperature and leaving it to stir for 2 h. The colour changed to reddish (Figure 3.4 a & b) which might mean that the quinoline **113** was reacting with styrenyllithium. Boc_2O was then added after cooling the mixture to –78 ºC. Unfortunately, the reaction gave many spots on the TLC plate with none of them being recognised as the product.



Scheme 3.8

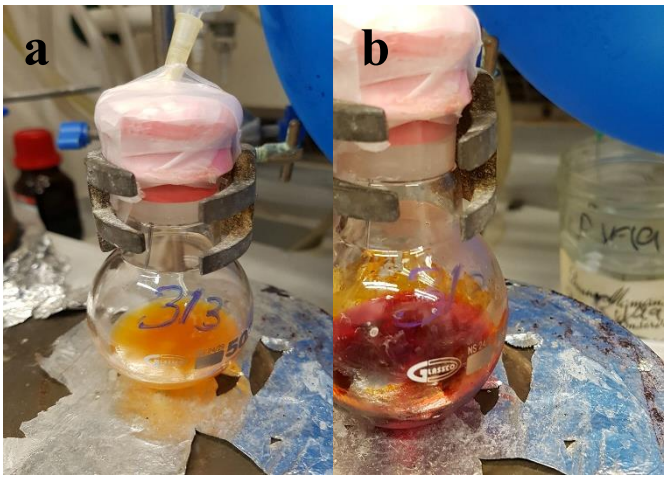
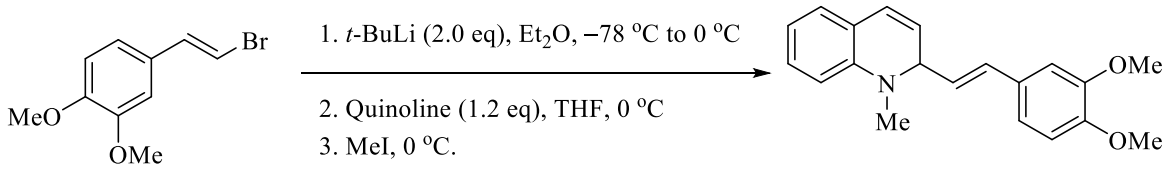


Figure 3.4: a) The reaction colour starts to change from yellow to red. b) The reaction colour becomes more reddish.

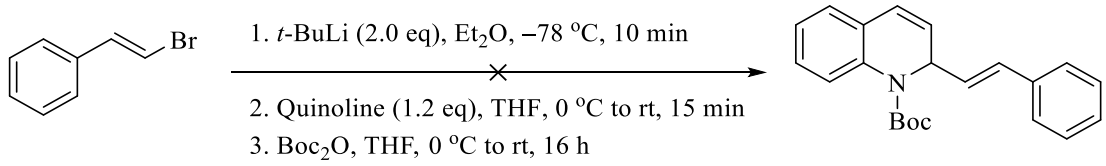
Looking in the literature, O'Byrne and Evans had reported a synthesis of quinoline **118** using halogen-lithium exchange.[80]Adding *t*-BuLi to compound **117** at –78 ºC, in Et_2O, and then quinoline was added at 0 ºC, before MeI was added at 0 ºC (Scheme 3.9).



117 **118**

Scheme 3.9

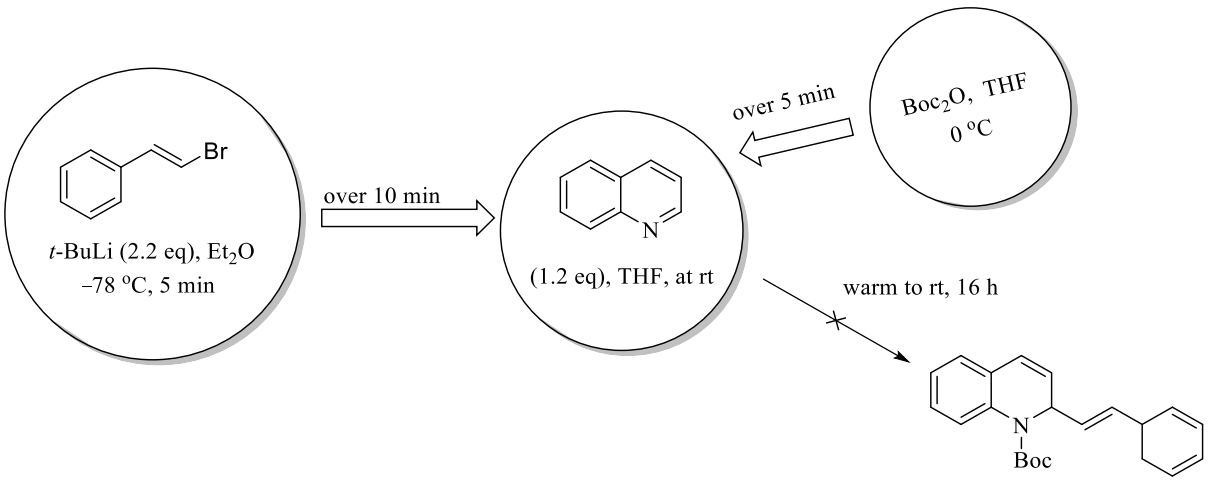
Unfortunately, applying these conditions using Boc_2O instead of MeI, no product was obtained and many spots were observed on the TLC plate. Furthermore, LCMS analysis of the crude product indicated a mixture of products had been formed and that no desired product was obtained (Scheme 3.10).



114 **115**

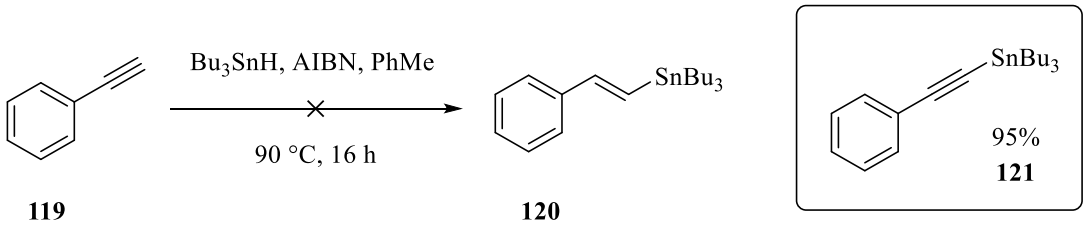
Scheme 3.10

It was thought that the order of addition of the substrates might have an effect on the result. Therefore, the halogen-lithium exchange on **115** was carried out first at –78 ºC in Et_2O and after 5 min, the mixture was added slowly over 10 min to a solution of quinoline in THF at room temperature (Scheme 3.11). However, no desired product was isolated.



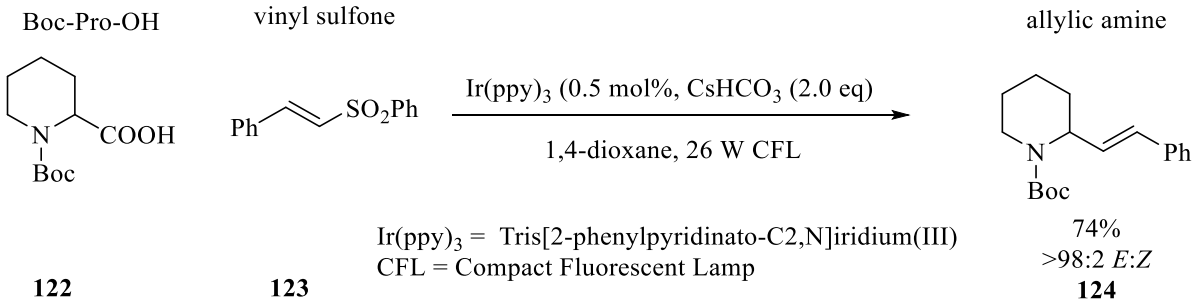
Scheme 3.11

It was thought that the reason for these disappointing results might be due to the fact that *t*-BuLi is an extremely strong base and so results in many side products. Since halogen-lithium exchange of styrene **114** was not possible with *n*-BuLi, we considered whether using tin-lithium exchange may avoid decomposition caused by *t*-BuLi. By following a literature procedure,[81]azobisisobutyronitrile (AIBN) was added to a mixture of phenylacetylene **119** and Bu_3SnH in toluene. The mixture was then heated at 90 °C overnight. However, after quenching the reaction mixture, only tributyl(2-phenylethynyl)stannane **121** was isolated instead of compound **120** (Scheme 3.12).



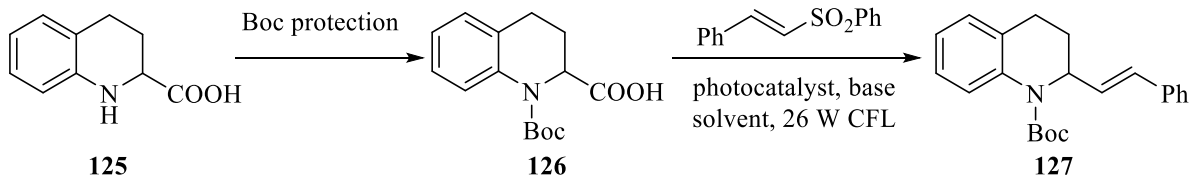
Scheme 3.12

Another route in the literature utilised photochemistry to synthesise a similar compound. MacMillan and Noble reported that amino acid **122** could be coupled to vinyl sulfones **123** *via* photoredox-generated *α*-amino radical to provide allylic amine **124** (Scheme 3.13).[82]



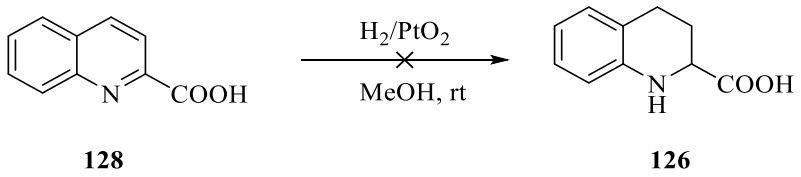
Scheme 3.13

This could be applied to 1,2,3,4-tetrahydroquinoline-2-carboxylic acid **126** by following a coupling protocol shown in scheme 3.13. So, the plan was to use the Boc group to protect compound **125** to give *N*-Boc-THQ-2-carboxylic acid **126** which then can be used in the photochemistry procedure to give the desired compound **127** (Scheme 3.14).



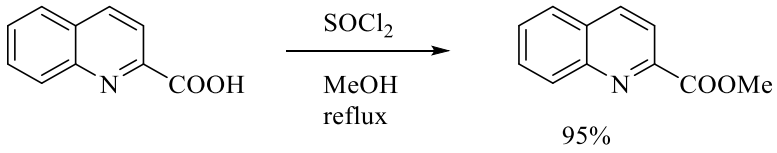
Scheme 3.14

To start with, the carboxylic acid **126** was required. While this compound is commercially available, it is very expensive and is marketed only in milligrams. However, using a literature procedure we attempted to reduce quinaldic acid **128** using H_2/PtO_2 in MeOH at room temperature.[83] However, only starting material was recovered and so it may not be possible to reduce the carboxylic acid **126** using just H_2 gas without subjecting the reaction to high pressure (Scheme 3.15).



Scheme 3.15

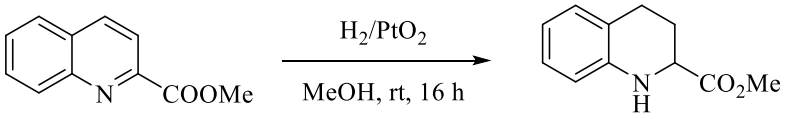
It was thought that reduction of the corresponding ester **129** may be easier than reduction of the carboxylic acid. Therefore, compound **128** was reacted with $SOCl_2$ in MeOH and this gave ester **129** in 95% yield (Scheme 3.16).



128 **129**

Scheme 3.16

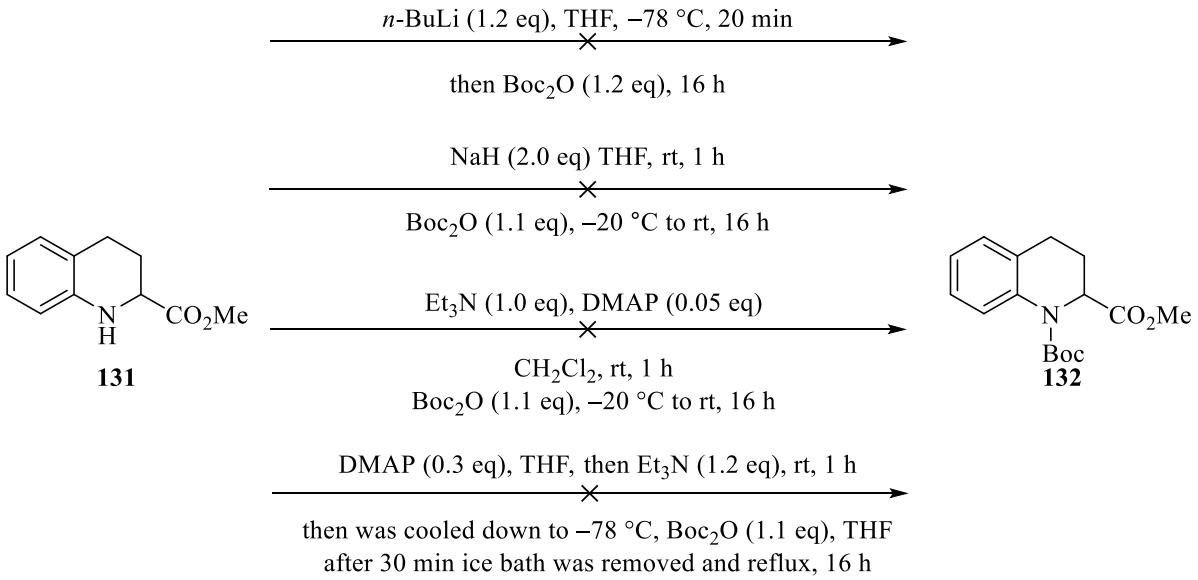
Stirring compound **129** with PtO_2 in MeOH under a H_2 atmosphere at room temperature, gave ester **130** in 92% yield (Scheme 3.17).



129 **130**

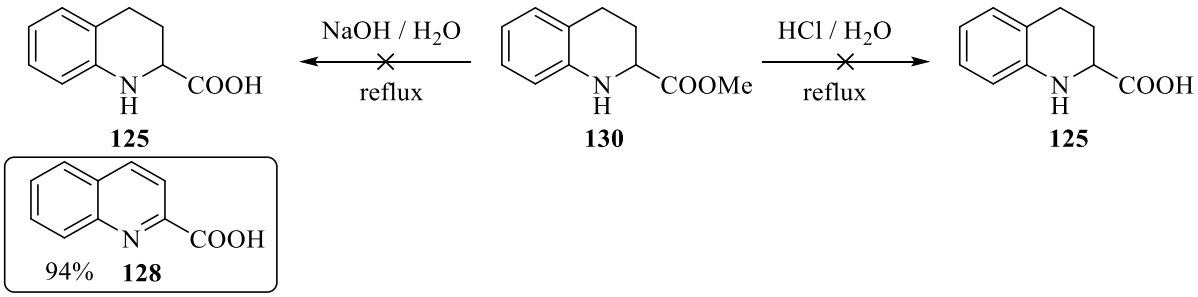
Scheme 3.17

With compound **130** in hand, many reactions were carried out using different bases to try and protect the nitrogen with a Boc group (Scheme 3.18). Unfortunately, none of these conditions worked as the ester **130** was resistant to Boc protection. After carrying out a literature search on how to protect the structure **131** or a similar structure, there was no reported method, but it was possible to protect the corresponding acid.



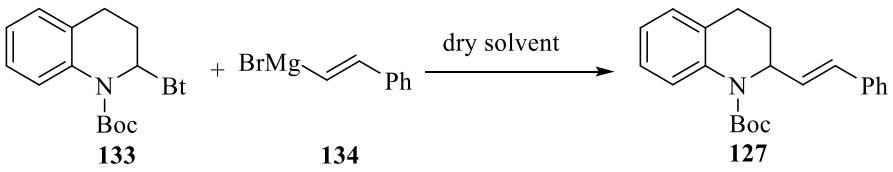
Scheme 3.18

Therefore, it was decided to convert the ester back into an acid; this was done under both acid and base hydrolysis conditions. However, the desired compound was not obtained in either case. The acid hydrolysis gave an unknown solid, which could not be characterised by ^{1}H NMR or ^{13}C NMR spectroscopy, or by mass spectrometry. In comparison, when using base hydrolysis conditions, compound **128** was obtained in 94% yield (Scheme 3.19). With the unsuccessful results obtained so far, it was decided to investigate an alternative synthetic route.



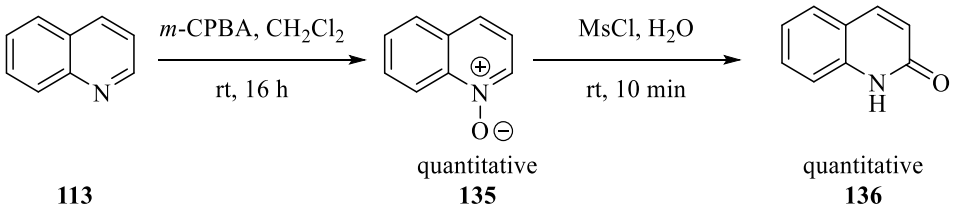
Scheme 3.19

It was thought that the starting material **127** could be prepared using a Grignard reagent by having a good leaving group such as benzotriazole in the 2-position of the THQ **133** (Scheme 3.20). This was based on related addition of PhMgBr to *N*-Boc-2-benzotriazolpiperidine.[84]



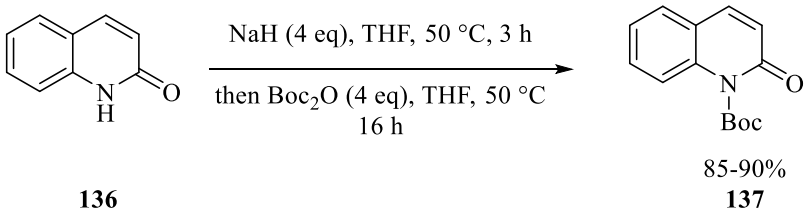
Scheme 3.20

Six steps were required to prepare compound **133**, starting from quinoline **113**. In the beginning, the reactions went smoothly as shown in Scheme 3.21. The first two steps gave quantitative yields and the products were used without any further purification. In the first step, quinoline *N*-oxide **128** was obtained by stirring the quinoline **113** with *m*-chloroperbenzoic acid for 16 h at room temperature. After the workup, methanesulfonyl chloride (MsCl) was added to an aqueous solution of quinoline *N*-oxide and after stirring, a solid precipitated which was the lactam **136.**[85]



Scheme 3.21

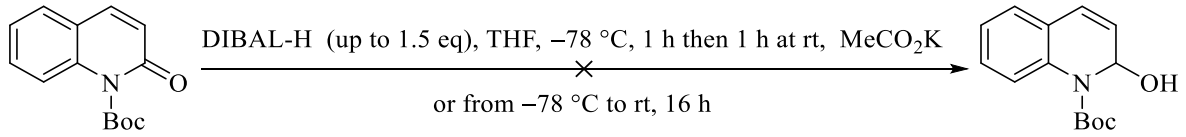
Lactam **136** was protected with the Boc group by using NaH in THF at 50 ºC to give carbamate 30 in 85-90% yield (Scheme 3.22).[86]



Scheme 3.22

The next step attempted was reduction of the carbonyl group of carbamate 30 to the hydroxy group using DIBAL-H in THF at –78 ºC for 1 h and another 1 h at room temperature. Unfortunately, this gave only starting material. The reaction conditions were changed by

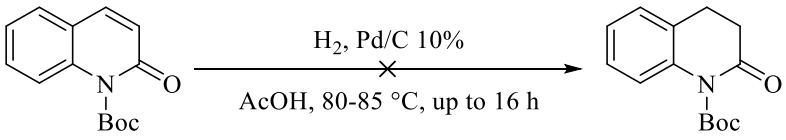
altering the equivalents of DIBAL-H which was increased up to 1.5 equivalents and warming the reaction gradually to room temperature over 16 h. Unfortunately, all attempts only gave recovered starting material (Scheme 3.23).



137 **138**

Scheme 3.23

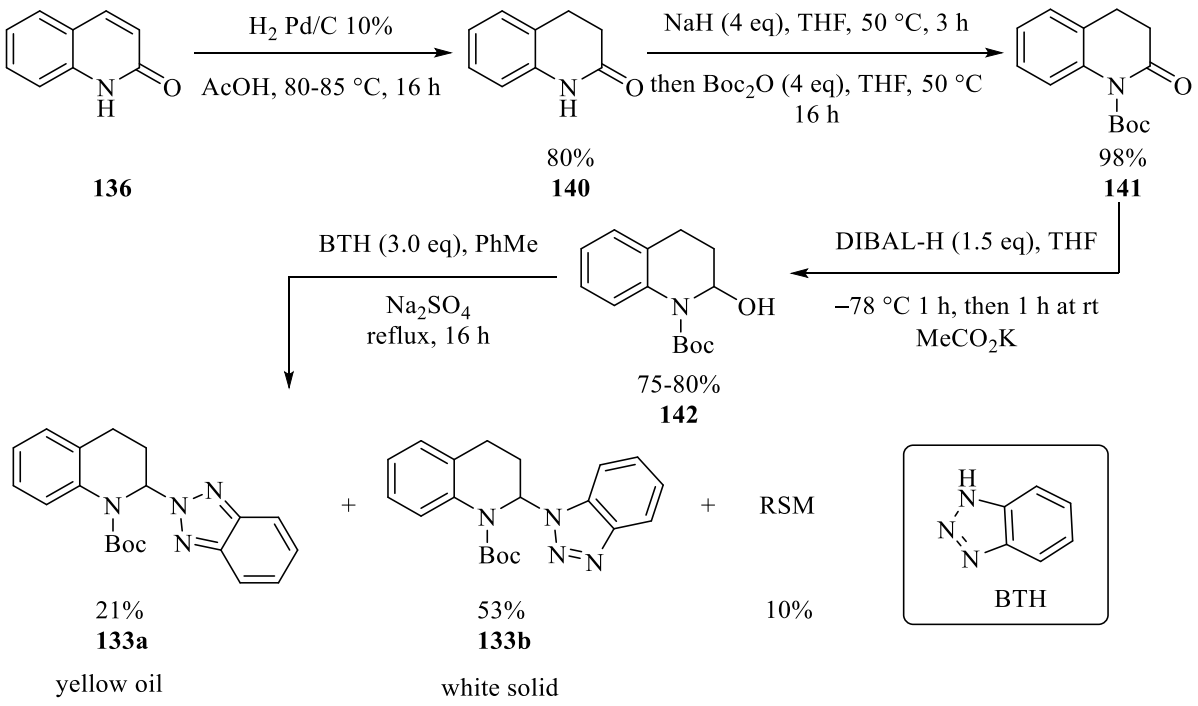
It was then decided to reduce the double bond in compound **137**, which might have been affecting the DIBAL-H reduction. Regrettably, the reduction did not work when using H_2 with palladium supported on activated carbon as a catalyst and only starting material was recovered (Scheme 3.24).



137 **139**

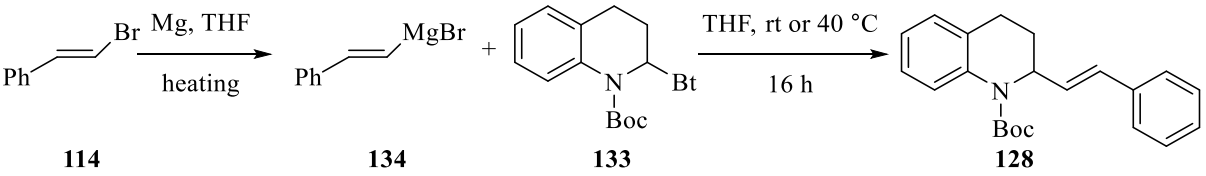
Scheme 3.24

The strategy changed to instead carry out the reduction on lactam **136** using hydrogen gas with Pd/C catalyst in AcOH and, after the reaction was heated at 85 ºC for 16 h, this gave lactam **140** in 80% yield. Pleasingly, the remaining steps went smoothly to prepare *N*-Boc-2-benzotriazolyl-THQ 26. This started by protection of lactam **140** to give carbamate **141** in 98% yield. Alcohol **142** was obtained in 80% yield by using DIBAL-H to reduce compound **141.** Finally, substitution of alcohol **142** was carried out with benzotriazole, using Na_2SO_4 in toluene under reflux for 16 h and this gave *N*-Boc-2-benzotriazolyl-THQ **133a** in 21% yield which was an oil and 53% of an isomer **133b** which was a solid (Scheme 3.25).



Scheme 3.25

With *N*-Boc-2-benzotriazolyl-THQ **133a,b** in hand, replacing the benzotriazole using the Grignard reagent was the next step. The Grignard reagent needed to be prepared from *β*-bromostyrene **114**, using Mg metal in THF while heating the reaction to 40 ºC (Scheme 3.26, Table 3.1).



Scheme 3.26

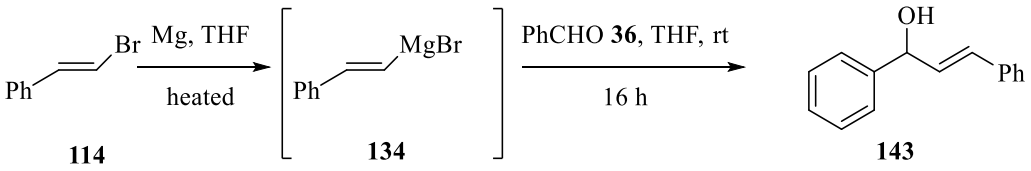
Table: 3.1

Entry	**133a**	**133b**	**133a,b**	T	Outcome
1.	–	–	√	rt	RSM
2.	–	–	√	40 °C	RSM
3.	√	–	–	rt	RSM
4.	√	–	–	40 °C	RSM
5.	–	√	–	rt	RSM
6.	–	√	–	40 °C	RSM

RSM = recovered starting material

The reaction was repeated multiple times using different conditions (Table 3.1). First, the reaction was tried with a mixture of the benzotriazole isomers both at room temperature and at 40 ºC and the reaction was monitored for 16 h, which only gave starting material (Entries 1 & 2). Unfortunately, the same results were obtained when each isomer was used separately (Entries 3–6).

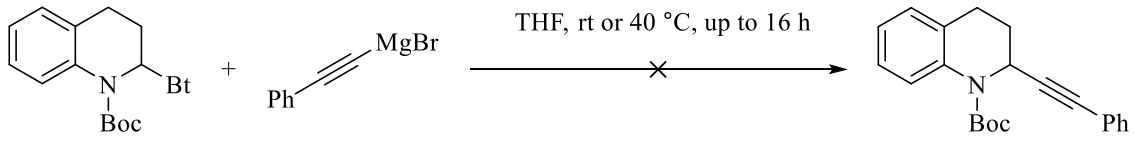
We potentially thought there may have been a problem with the formation of Grignard reagent **134**, therefore a test reaction was done where benzaldehyde was added to the reaction instead of compound **133**. The reaction gave alcohol **144** in 77% yield, which indicated that Grignard reagent was being formed and that the problem was most likely the addition step to give compound **128** (Scheme 3.27).



114 **134** **143**

Scheme 3.27

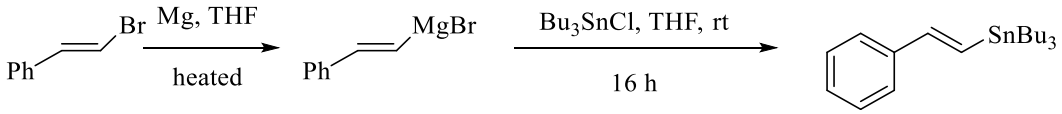
The *N*-Boc-2-benzotriazolyl-THQ **142** was then tested with another Grignard reagent **144** that was bought from a commercial supplier. However, this reaction only gave starting material (Scheme 3.28).



133 **144** **145**

Scheme 3.28

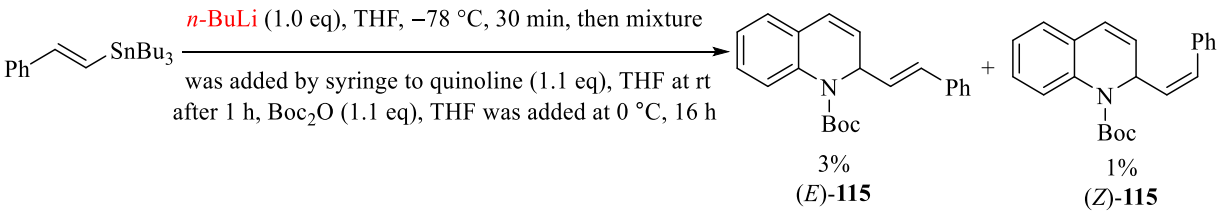
At this point, it was decided to try the vinyl lithium addition to quinoline again, but this time using tin-lithium exchange. Therefore, compound **121** was formed from the Grignard reagent **134** (Scheme 3.29). This was synthesised in the group by post-doctoral research associate Josh Priest.



114 **134** **121**

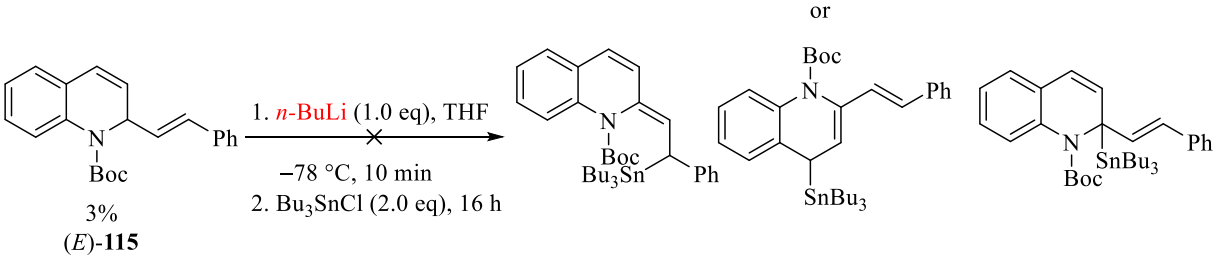
Scheme 3.29

n-BuLi was added to a solution of stannane **121** at –78 ºC in THF and left to stir for around 30 min. The mixture was then taken by a syringe and added to a solution of the quinoline at room temperature. The reaction was monitored by TLC and this showed that the quinoline was consumed after 1 h. The reaction was cooled to 0 ºC and Boc_2O was then added. The TLC plate showed many spots, with only 2 of them being recognised. The desired compound was obtained in two isomers (*E* and *Z*) in a small amount (3% of (*E*)-**8** and 1% of (*Z*)-**8)** (Scheme 3.30). The *Z*-isomer was found due to a small amount of the (*Z*)-isomer that always can be found in (*E*)-*β*-bromostyrene **8**.



Scheme 3.30

With 100 mg in hand, it was possible to carry out one reaction with *n*-BuLi in THF at –78 ºC. The lithiation time used was 10 min and the reaction was quenched with Bu_3SnCl. However, the reaction did not work as it was hard to find the best conditions without ReactIR studies (Scheme 3.31).



Scheme 3.31

At this point, due to these disappointing results, it was decided to stop this project.

3.2 Conclusions and Future Work

In conclusion, it was disappointing that it was not possible to find a suitable method to synthesise the desired substrate. Many routes were studied for trying to synthesise the compound in one-step or multi-steps either by using organolithium chemistry, Grignard reagents or trying to carry out photocatalyst chemistry. Although it was not possible to test the kinetic resolution of DHQ-**115**, it was successfully prepared albeit in small amounts.

DHQ-**115** was not formed when *t*-BuLi was used to do halogen-lithium exchanges. We believe that this may have been due to side reactions due to *t*-BuLi being an extremely strong base. However, *n*-BuLi was too weak to do the exchange with *β*-bromostyrene.

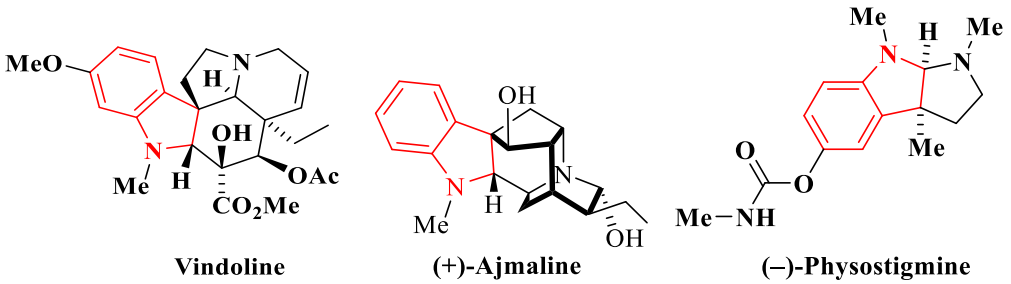
We then designed a quinaldic acid system although reduction was not possible. Instead, it was possible to reduce ester compound **129**, but it was not possible to protect the product with Boc_2O.

Future work could be to synthesise the vinyl-THQ **115** by using a Grignard reagent, which was attempted in this work by using benzotriazole as a leaving group. Unfortunately, the substitution was not possible and currently, the reason is unknown and so more investigation is needed in future. Finally, the group still harbours ambitions to synthesise a number of other 2-vinylTHQs or DHQs. As a trace amount of (*E*)-**115** and (*Z*)-**115** were obtained after adding Boc_2O using the tin–lithium exchange route, initial studies should focus on further optimisation of this route.

Chapter 4 - Synthesis and Lithiation–Substitution of *N*-Boc-2-arylindolines

4.1 Indolines in chemistry

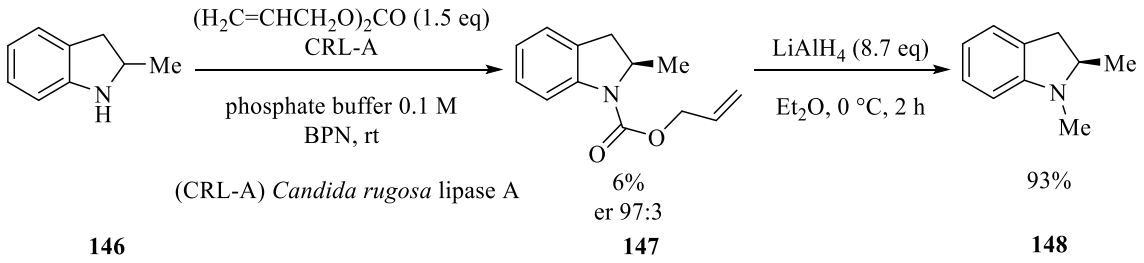
Indoline heterocycles are important structures in both natural products and medicines.[87,88] For example, vindoline is an alkaloid that is obtained from the *Aspidosperma* genus and is an important anti-tumur pharmaceutical.[89] Another example is (+)-ajmaline which is an anti-sympathomimetic drug and has antiarrhythmic effects on the heart.[90] The indoline structure can also be seen in (–)-physostigmine, which is used to treat glaucoma and other medical conditions. It is also an antidote for *Datura stramonium* poisoning.[91] These structures are shown in Figure 4.1.[92,93]



(Figure 4.1)

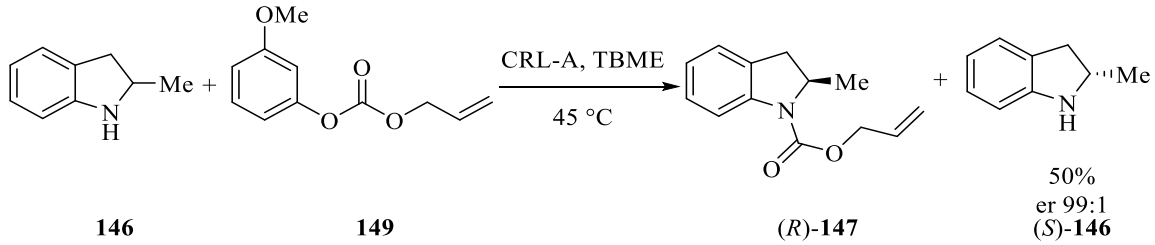
Over the years, as a result of their possible use in pharmaceuticals, several methods to synthesise indoline derivatives have been reported.[94,95] Kinetic resolution is the most generally used method to give enantiomerically pure 2-substituted indolines from racemic mixtures.[9] In 1996, Wong and co-workers reported the first chemoenzymatic resolution of 2-alkylindolines. They used lipase and protease enzymes for the enantioselective acylation of racemic 2-methylindoline **146**.[96] The enzymatic reaction was carried out with the *Candida cylindracea* lipase (CRL-A) and diallyl carbonate in (4-nitrophenyl)methanol (BPN) to give **147** in 6%

yield with er 97:3 er (Scheme 4.1). Carbamate **147** was reduced afterwards to the *N*-methyl derivative **148** by using $LiAlH_4$ in 93% yield.



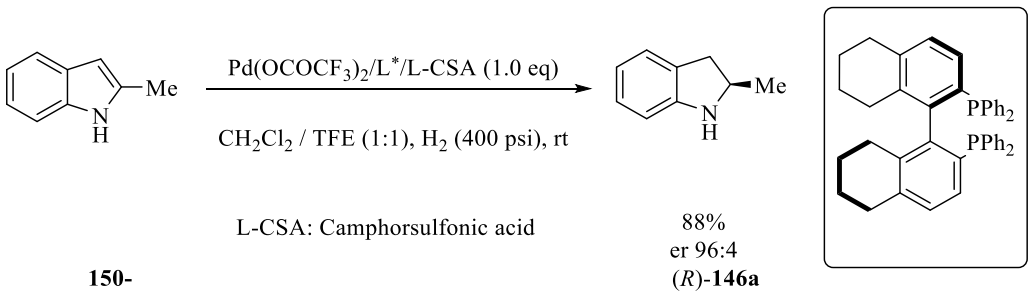
Scheme 4.1

Another efficient chemoenzymatic route for the synthesis of enantioselective 2-substituted indolines has been reported by Gotor et al.[97] Enzymatic kinetic resolution of 2-methylindoline using carbonate **149** and the enzyme CRL-A in *tert*-butyl methyl ether (TBME) at 45 °C gave indoline (*S*)-**146** in 50% yield with 99:1 er (Scheme 4.2).



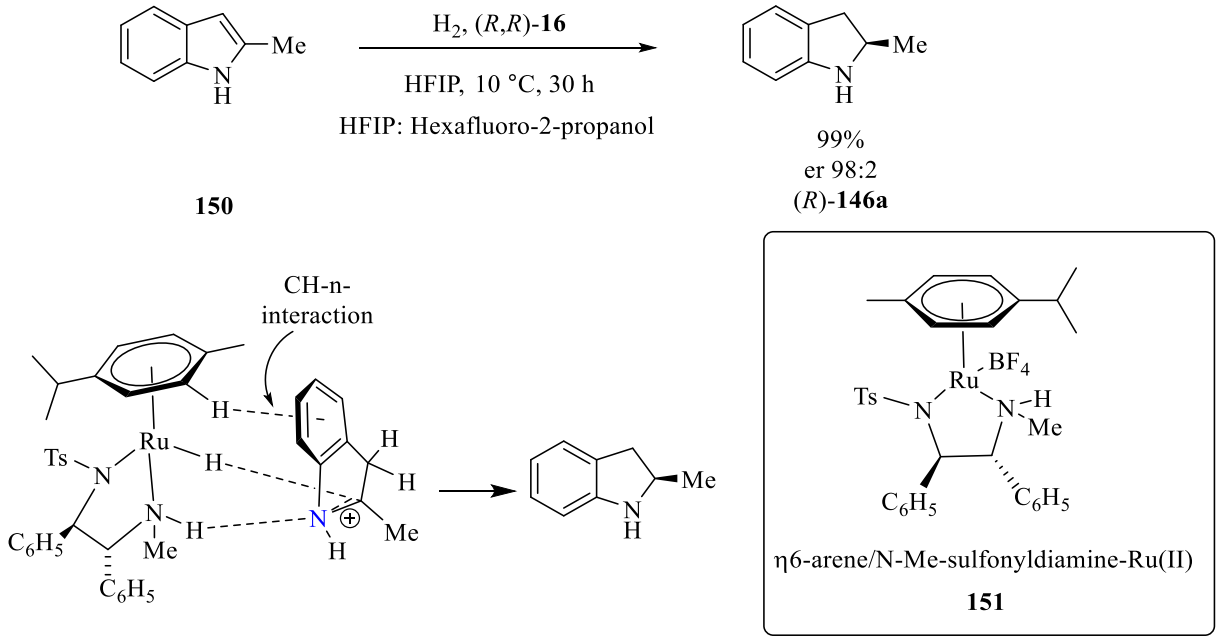
Scheme 4.3

Zhou and Zhang published in 2010 the first highly enantioselective hydrogenation of unprotected 2-methylindole **150** by using a palladium catalyst with a Brønsted acid as an activator (Scheme 4.5).[98]



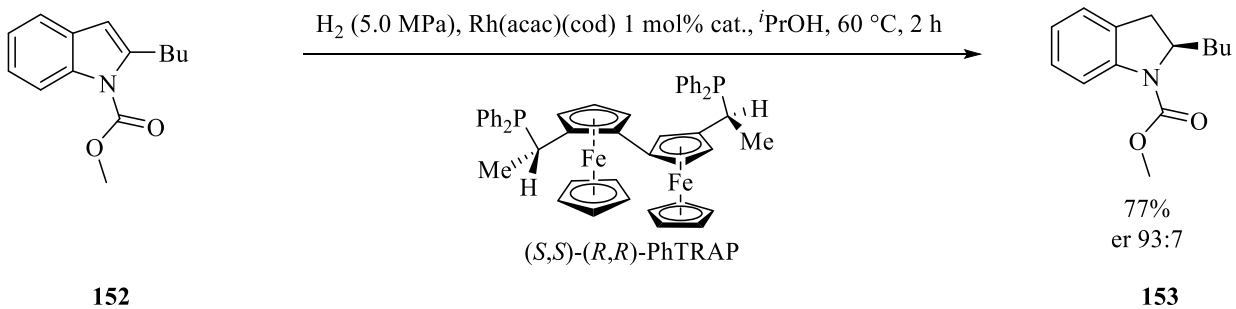
Scheme 4.5

Based on the work of Zhang and Zhou, Touge and Arai in 2016 used η^6-arene/sulfonyldiamine-Ru(II) complex **151** as a catalyst in the asymmetric transfer hydrogenation of 2-methylindole **150**. They obtained (*R*)-**146a** in high enantioselectivity (up to 99:1 er) and in 99% yield (Scheme 4.7).[99]



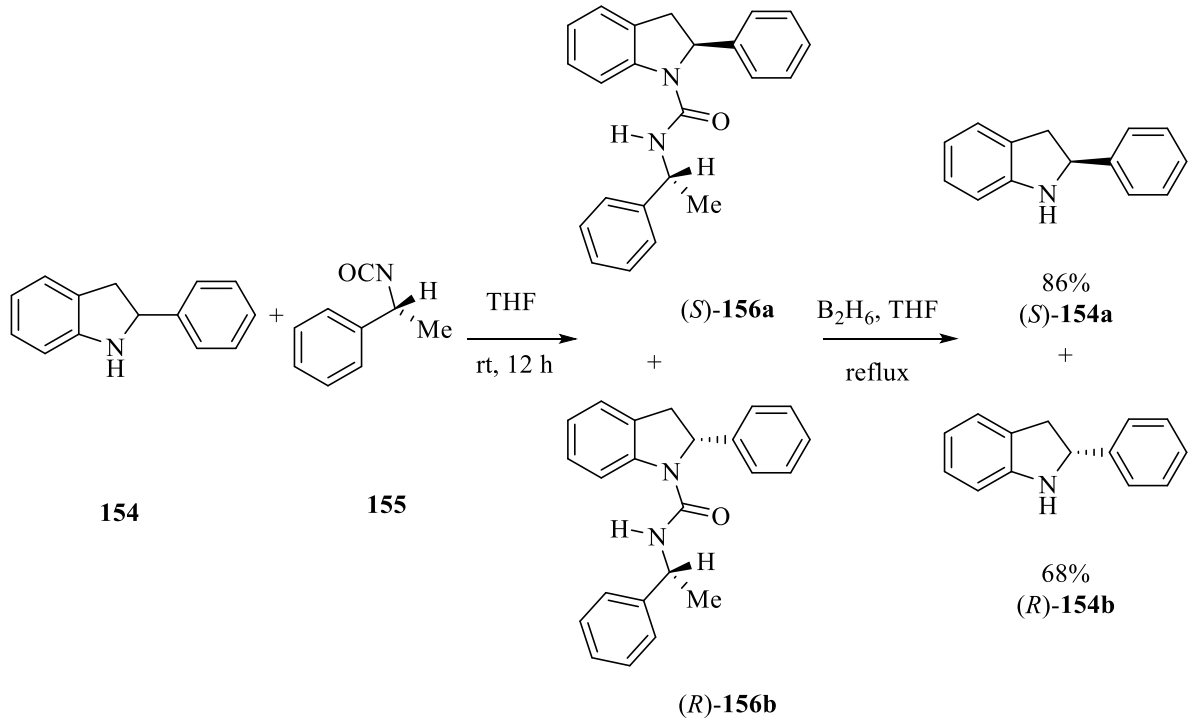
Scheme 4.7

An alternative, high yielding method for the preparation of chiral indolines could be *via* the asymmetric hydrogenation of indoles by using a chiral catalyst. An example is shown in Scheme 4.2 where heating the indole **152** at 60 °C for 2 h in 2-propanol under a hydrogen atmosphere with a chiral rhodium bisphosphate catalyst gave (*R*)-*N*-acetyl-2-butylindoline **153** in 77% yield with 93:7 er (Scheme 4.2).[100]



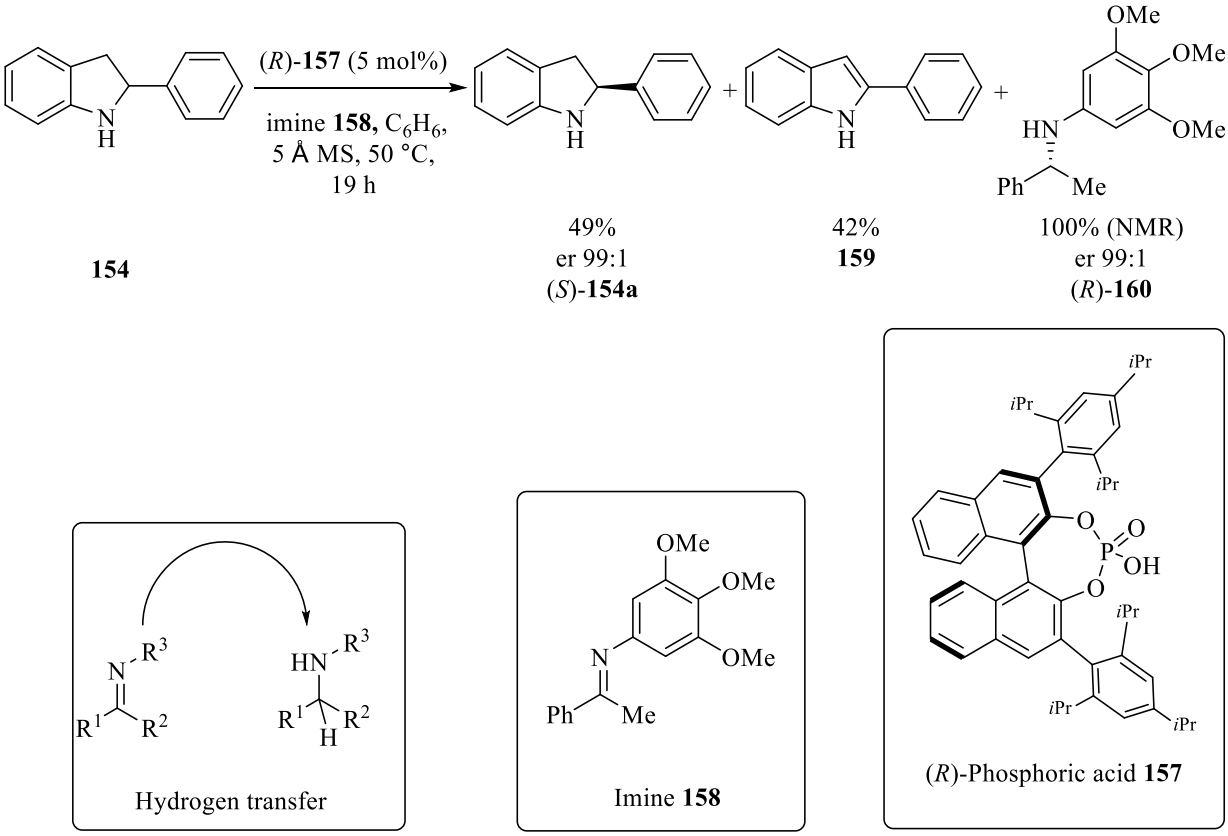
Scheme 4.2

Unelius and co-workers carried out the kinetic resolution of racemic 2-phenylindoline **154** in 2008 using (*R*)-(+)-α-methylbenzyl isocyanate **155**. The enantiomeric ratios of the two resolved 2-phenylindoline enantiomers (*S*)-**156a** and (*R*)-**156b** were 99:1 and 95:5 respectively. This was confirmed by chiral gas chromatography (Scheme 4.4). Furthermore, the two diastereomers of the 2-phenylindoline urea derivatives (*S*)-**156a** and (*R*)-**156b** were refluxed separately in diborane:THF to give isomer (*S*)-**154a** in 86% yield and isomer (*R*)-**154b** in 68% yield.[101]



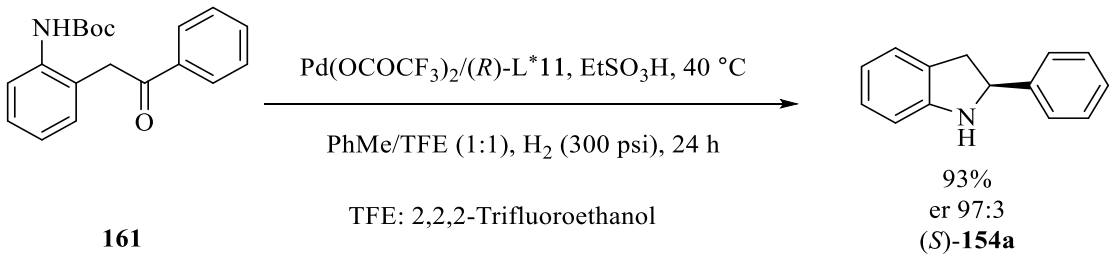
Scheme 4.4

Akiyama and co-workers reported the oxidative kinetic resolution of 2-phenylindoline **154** using chiral phosphoric acid **157** in 2013. They managed to obtain (*S*)-2-phenylindoline **154a** in high enantioselectivity (99:1 er) and in a good yield of 49% (Scheme 4.6).[102]



Scheme 4.6

Recently in 2018, Zhou and co-workers synthesised indoline derivatives in a highly efficient and enantioselective method through cyclisation and reduction. An example is shown in Scheme 4.8 where Boc deprotection of **161**, followed by cyclisation and Pd-catalysed asymmetric hydrogenation gave (*S*)-2-phenylindoline **154a** in 93% yield with 97:3 er. The one-pot reaction used $Pd(OCOCF_3)$/(*R*)-L*, H_2, and $EtSO_3H$ in TFE/toluene and was heated at 40 °C for 24 h (Scheme 4.8).[103]

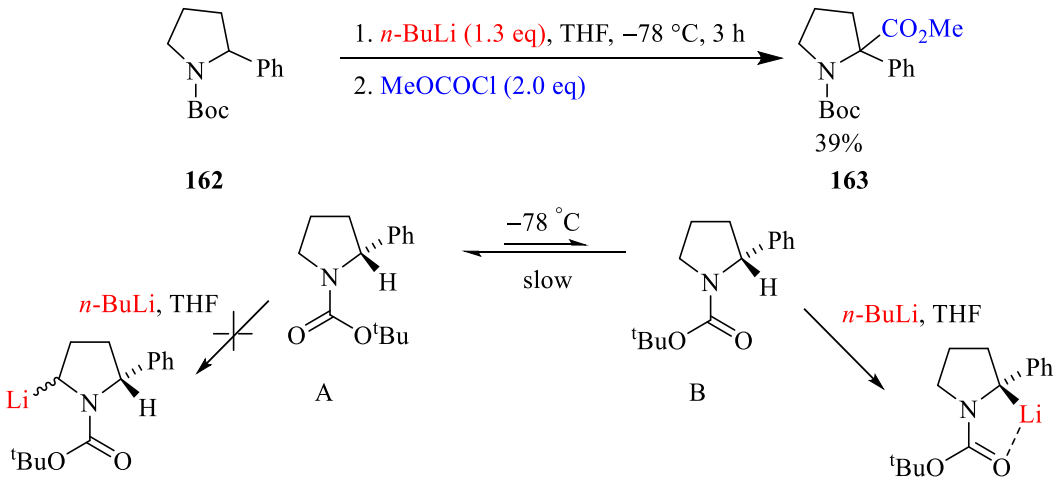


Scheme 4.8

In this chapter, the synthesis of substituted and highly enantiopure indoline derivatives will be discussed. In particular, the focus will be on the electrophilic quench of organolithium intermediates by using a variety of electrophiles and the kinetic resolution of indoline derivatves by using the chiral base-ligand system *n*-BuLi/(+)-sparteine.

4.2 Aims

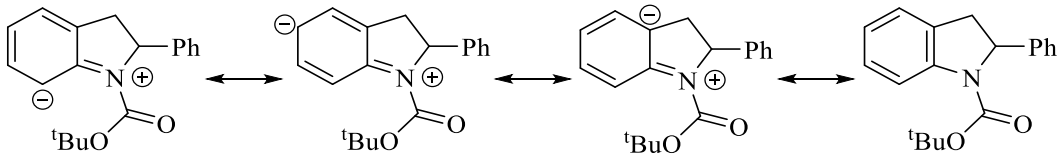
Collaboration between the Coldham and O'Brien groups in 2012 showed that by monitoring the lithiation of *N*-Boc-2-phenylpyrrolidine **162** at −78 °C using *in-situ* IR spectroscopy, the rotation of the Boc group was found to be very slow compared to *N*-Boc-2-phenylpiperidine. The Boc rotation rate of **162** was determined using VT-NMR, which confirmed that the half-life ($t_{1/2}$) for rotation of the Boc group was ~10 h at −78 °C and 3.5 min at −50 °C. From these investigations, they managed to obtain excellent results for electrophilic quenching at −50 °C. As result, no attempts were made to do kinetic resolution reactions as the elevated temperatures needed may possibly reduce the enantioselectivity (Scheme 4.9).[73]



Scheme 4.9

Based on these results, it was hypothesised that by using a more conjugated system and fusing a benzene ring to the pyrrolidine (i.e., forming an indoline), we may be able to increase the

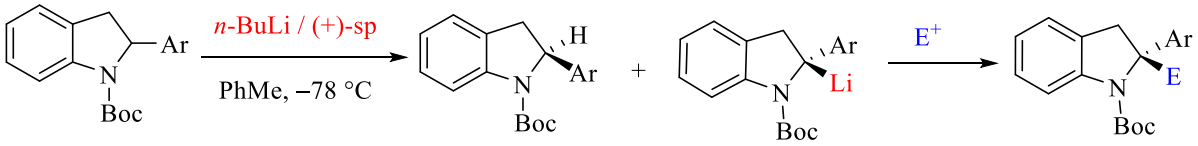
speed of the Boc rotation. This is due to interaction of the nitrogen lone pair with the benzene ring at the expense of delocolisation into the carbonyl group (Scheme 4.10).



(Scheme 4.10)

Therefore, the aim of this work was to prepare racemic of *N*-Boc-2-arylindolines and test the rate of Boc rotation and the possibility of carrying out kinetic resolution using *n*-BuLi/(+)-sparteine (Scheme 2.11).

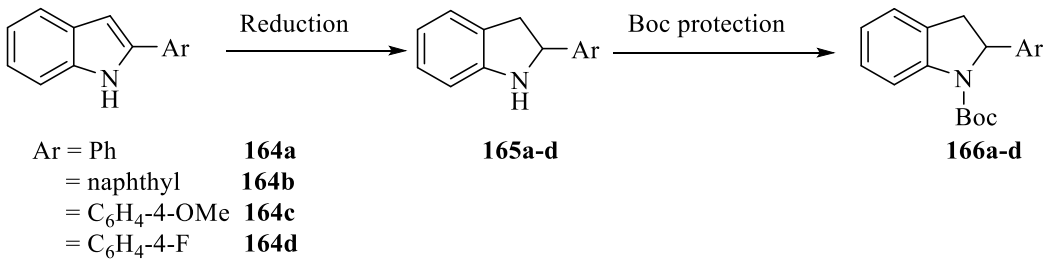
General Scheme for the Kinetic Resolution of N-Boc-2-arylindoline



(Scheme 2.11)

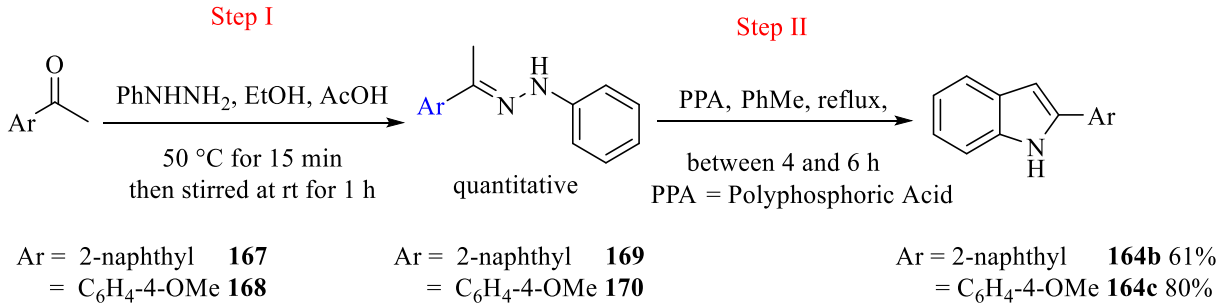
4.3 Results and discussion

Before any lithiation reactions could be done, the starting materials *N*-Boc-2-arylindolines **166a-d** needed to be synthesised. These indolines could be accessed through a two-step process as shown in Scheme 4.11. The plan was to reduce the 2-substituted indoles **164a-d** to give the corresponding 2-arylindolines **166a-d**.[104] These could then be protected to give the desired *N*-Boc-2-arylindolines **166a-d**.



(Scheme 4.12)

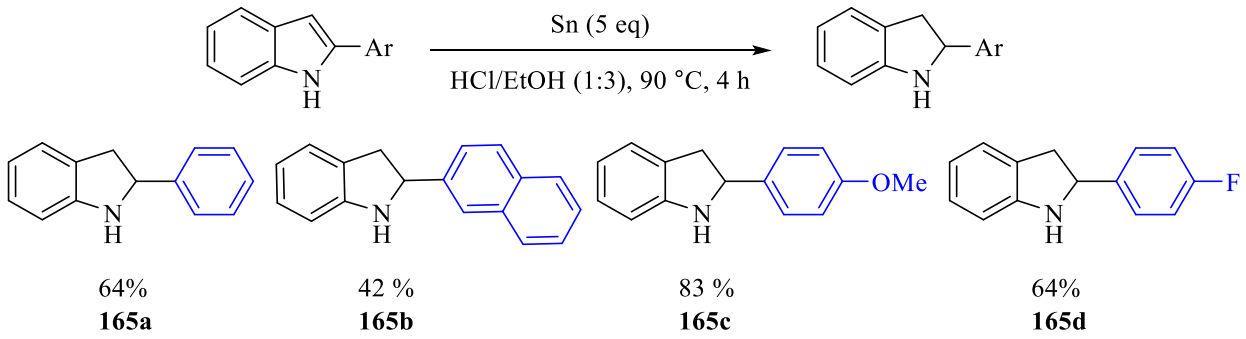
Fortunately, the 2-arylindoles **164a**,**d** were commercially available and did not need to be synthesised. However, the other 2-arylindolines **164b**,**c** needed to be synthesised by using Fischer indole condensation methods.[105–107] The first step of the Fischer indole synthesis involved the preparation of arylhydrazones **169** and **170** using a known literature method where a small amount of acetic acid was added to separate mixtures of aryl methyl ketones **167** and **168** and phenylhydrazine. Once the arylhydrazones **169** and **170** were isolated, they were used in the next step without any further purification. In the second step, arylhydrazones **169** and **170** were each heated to 145 °C for 4 h in the presence of polyphosphoric acid (PPA). These reactions proceeded very well to obtain 2-arylindoles **164b**,**c** in 61% and 80% yields respectively (Scheme 4.13).



(Scheme 4.13)

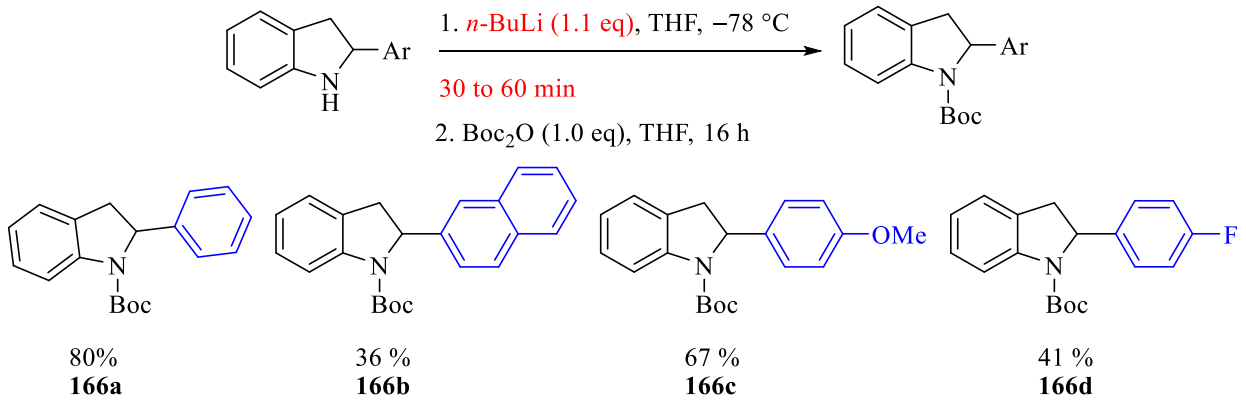
With indoles **164c** (Ar = *p*-methoxphenyl) and **164b** (Ar = 2-naphthyl) in hand, and having obtained indoles **164a** (Ar = phenyl) **164d** (Ar = *p*-fluorophenyl) from commercial suppliers, we were now able to reduce these compounds to form a small series of 2-arylindolines

165a-d. This is summarised in Scheme 2.12 where 2-arylindoles **164a-d** were reduced using tin powder and concentrated hydrochloric acid in ethanol at 90 °C for 4 h. A major limitation of this reaction was the loss of material during the work up. This resulted in lower yields for some of the 2-arylindolines **165a,c-d**, especially for the 2-naphthyl indoline **165b**, which was obtained in 42% yield (4.14).



(Scheme 4.14)

Finally, we were now able to carry out the protection step. The protection of the 2-arylindolines **165a-d** was achieved by first deprotonating the secondary amine using *n*-BuLi in THF at –78 °C. After 30–60 minutes, a solution of Boc_2O in THF was added to the mixture and the products **166a-d** were obtained in reasonable yields from 36% to 80%. (Scheme 4.15).

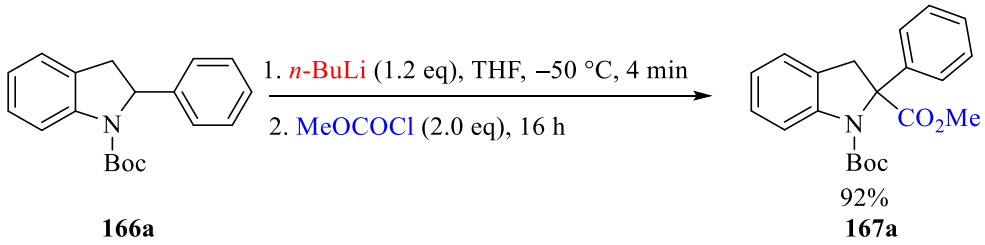


(Scheme 4.15)

Now that the *N*-Boc-2-arylindoline starting materials **166a-d** had been synthesised, we could begin to investigate the lithiation-electrophilic quench of these compounds. However, it was firstly important to optimise the lithiation conditions.

4.3.1 Lithiation trapping and kinetic resolution of *N*-Boc-2-phenylindoline 166a

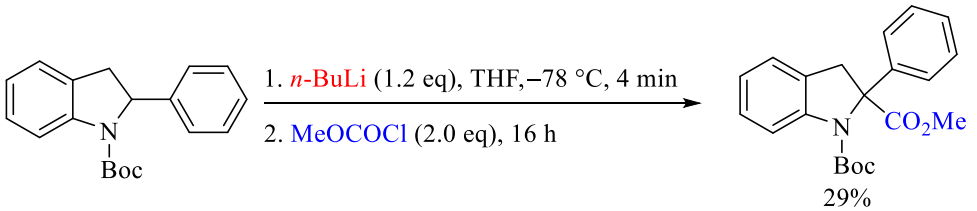
Initially, the lithiation of **166a** was carried out at –50 °C using *n*-BuLi, which gave an excellent yield of indoline **167a** when quenched after 4 minutes with methyl chloroformate (Scheme 4.16).



166a **167a**

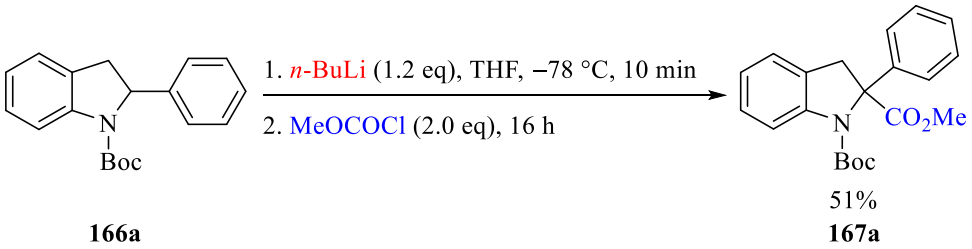
(Scheme 4.16)

In contrast, repeating the same reaction at –78 °C gave the product in 29% yield and the starting material was recovered as well (Scheme 4.17). Increasing the lithiation time to 10 minutes gave an increase in yield for compound **167a** to 51% and starting material was recovered in 46% yield (Scheme 2.18).



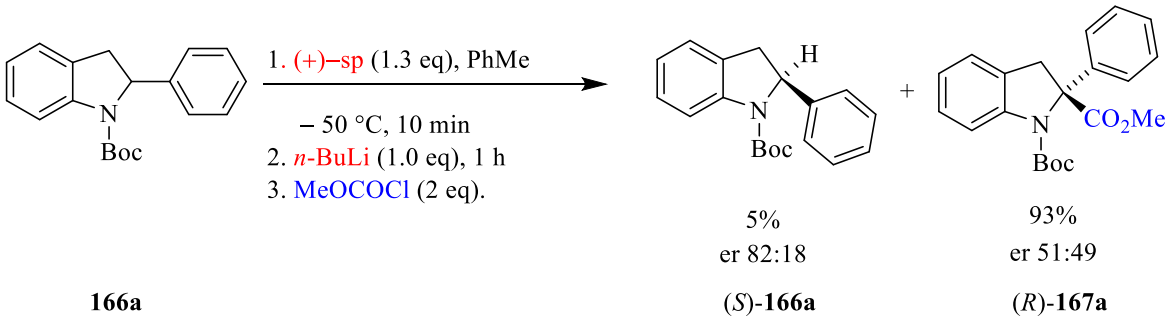
166a **167a**

(Scheme 4.17)



(Scheme 4.18)

Next, the kinetic resolution was tested at –50 °C using the chiral base *n*-BuLi (1.0 eq)/(+)–sp (1.3 eq). The mixture was stirred for 1 h before the reaction was quenched with MeOCOCl. This is shown in Scheme 4.19 where the yield of the indoline **167a** was only 5% with a moderate er of 82:18, while the ester product was obtained in 93% yield with an er of 51:49. These results supported our theory that poor enantioselectivity may be obtained when carrying out the kinetic resolution at high temperatures.



(Scheme 4.19)

Following on from the results obtained from racemic lithiation/trapping, we hoped to determine the accurate lithiation time by using ReactIR. Therefore, the lithiation of *N*-Boc-2-phenylindoline **166a** was carried out with 1.2 equivalents of *n*-BuLi at –78 °C in THF. The 2D and 3D plots (Figure 4.1) describe the lithiation of compound **166a**. The blue line represents the intensity of the C=O stretching frequency corresponding to compound *rac*-**166a** (1703 cm^{-1}), while the red line represents the intensity of the C=O stretching frequency

corresponding to the lithiated intermediate (1641 cm^{-1}). The spectrum shows that almost full lithiation occurs after 20 minutes (Figure 4.1).

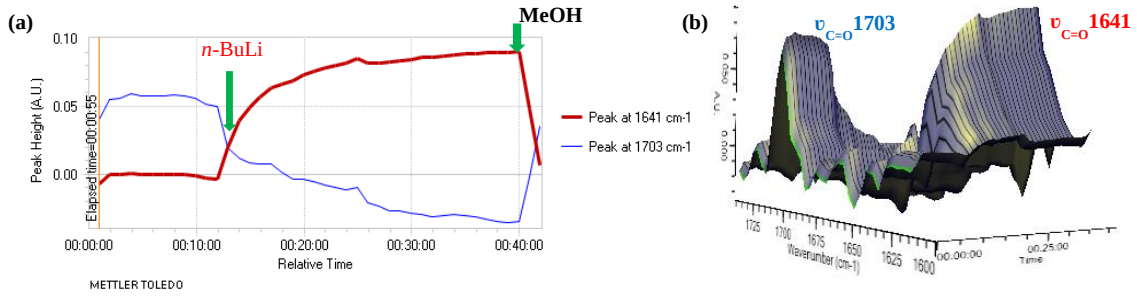
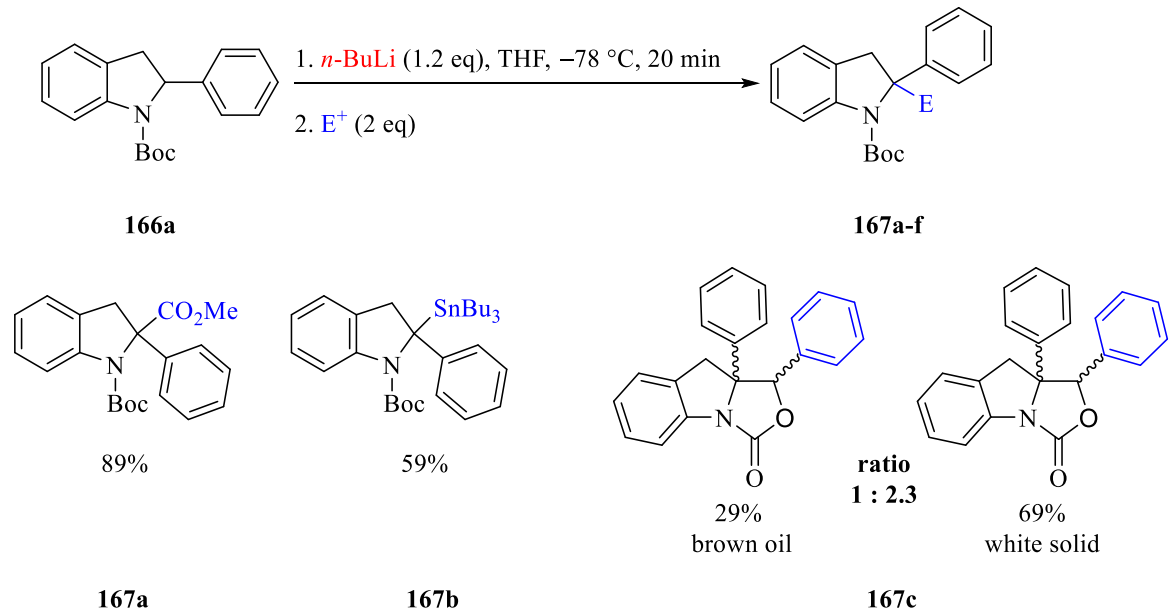


Figure 2.1: 3D and 2D plots of lithiation of **166a** at –78 ºC by *in situ* IR spectroscopy. **(a)** 2D plot showing the time evolution of the C=O peak for **71** (blue) and for the lithiated intermediate **166a** (red). **(b)** 3D plot showing changes in the absorption spectrum with time.

With this information, we repeated the initial lithiation-quench reactions on 2-phenylindoline **166a**. By deprotonating with *n*-BuLi in THF at –78 °C and stirring for 20 minutes, a variety of electrophiles were then added to give 2-substituted products **167a**–**c** in moderate to excellent yields although products **167d-f** did not form (Table 2.1 and Scheme 2.19). The electrophile methyl chloroformate gave an 88% yield as the best result (Entry 1, Table 4.1).



Scheme 4.20

Table 4.1:

Entry	Product	E^+	Yield (%)
1	**167a**	MeOCOCl	88
2	**167a**	MeOCOCN	61
3	**167b**	Bu_3SnCl	59
4	**167c**	PhCHO	29 & 69 1:2.3
5	**167d**	Prenyl bromide	0
6	**167e**	PhNCO	0
7	**167f**	1,2-dibromobutane	0

4.3.1.1 Variable temperature ^{1}H NMR spectroscopy study of indoline 166a

As illustrated by the results from the ReactIR spectroscopy, a lithiation time of 20 minutes was required for full lithiation of compound **166a**. This meant that the rotation of the Boc group was slow, but was much faster when compared to the Boc group in 2-phenylpyrrolidine **162**. To evaluate the rate of rotation of the Boc group, a variable temperature ^{1}H NMR spectroscopy (VT NMR) study was performed, where a sample of *N*-Boc-2-phenylindoline **166a** in THF-d_8 was warmed from –50 °C to room temperature. The coalescence of the *t*-butyl signal took place at around 5 °C (Figure 4.3). From the Eyring plot for the major rotamer to the minor, the activation parameters were found to be $\Delta H^{\neq} = 53.4$ kJ mol^{-1} and $\Delta S^{\neq} = -6.6$ J K^{-1} mol^{-1}. These values led to $\Delta G^{\neq} = 54.7$ kJ mol^{-1} at –78 °C and the half-life ($t_{1/2}$) of the Boc group rotation was determined to be around 7.5 min (Appendix D). This was in agreement with the ReactIR results, which indicated a lithiation time of 20 minutes would be required for full lithiation. Furthermore, NMR spectroscopic analysis showed that the ratio of the two rotamers was 6:1. The major and minor rotamers are shown in Scheme 4.21.

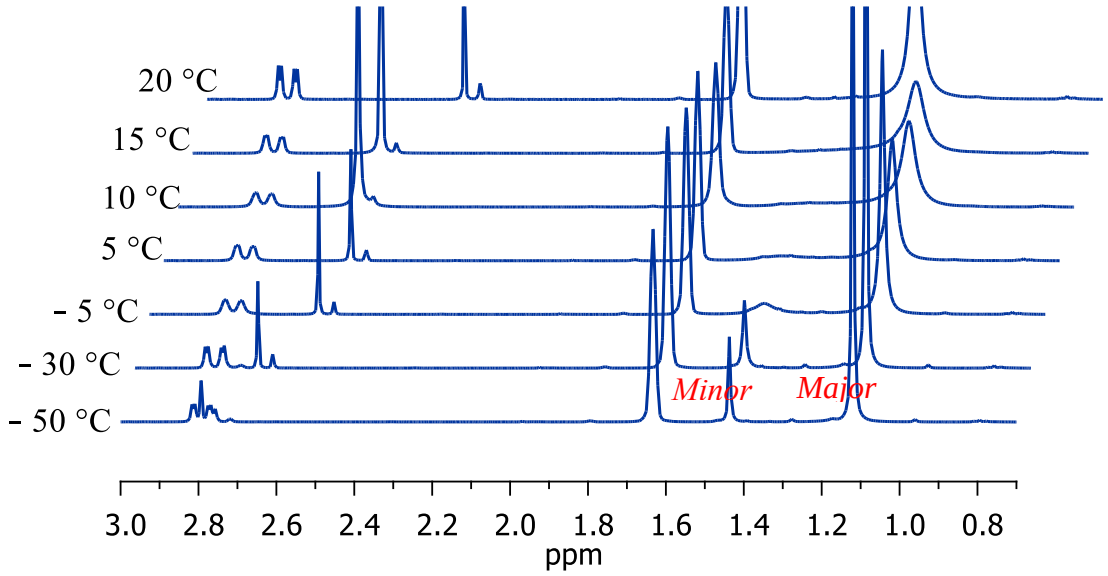
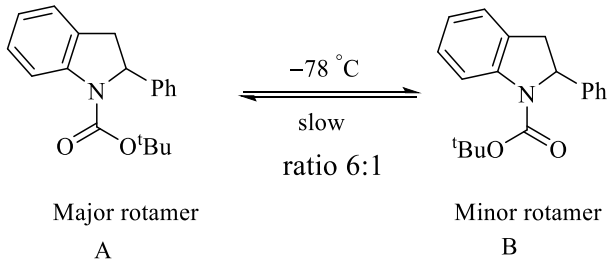


Figure 4.3: *t*-Butyl proton peak in ^{1}H NMR spectra obtained at various temperatures in THF-d_8, 500 MHz. The ratio between two rotamers is 6:1.



(Scheme 4.21)

Due to show lithiation at –78 °C, it is likely that A is the major rotamer. This is also supported by the single-crystal X-ray analysis of *N*-Boc-2-phenylpiperidine that shows a preference for the same rotamer.[73]

Furthermore, from the VT-NMR results (Figure 4.4), it can be seen that the benzylic proton of the major rotamer appears as a doublet of doublets and the other rotamer appears as a broad doublet. This splitting is as a result of the two different proton environments on the adjacent carbon and it is clear at –50 °C. As the temperature was increased, the multiplets of the benzylic proton started to broaden before the benzylic proton of the two rotamers became a broad singlet

peak which could be seen at 5 °C. This is known as the coalescence temperature. Splitting becomes more obvious and a broad doublet of doublets can be seen at room temperature.

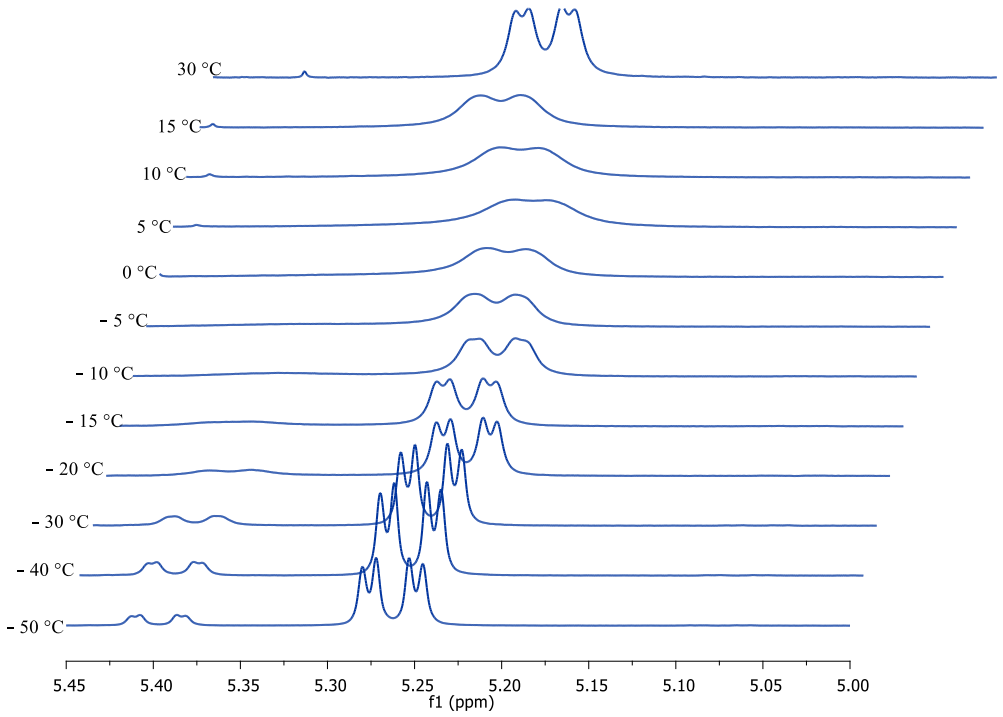
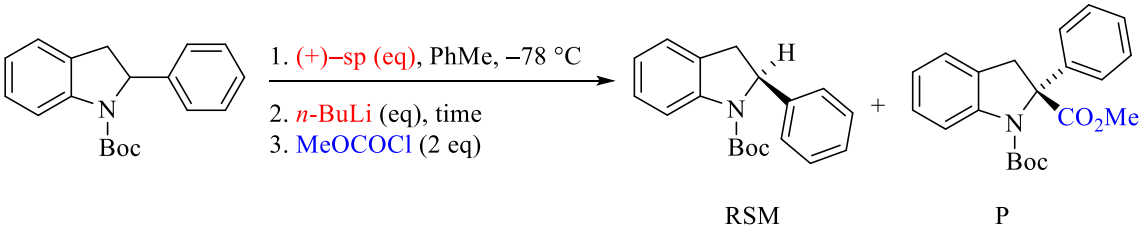


Figure 4.4: Benzylic proton peak in ^{1}H NMR spectra obtained at various temperatures in THF-d_8, 500 MHz. The ratio between two rotamers is 6:1.

4.3.1.2 Kinetic Resolution of *N*-Boc-2-phenylindoline 166a

The conditions for the kinetic resolution of *N*-Boc-2-phenylindoline **166a** were then optimised. The results are summarised in Table 4.2. Methyl chloroformate was used to quench the reaction in each case as this gave the best results from the racemic lithiation-quench reactions.



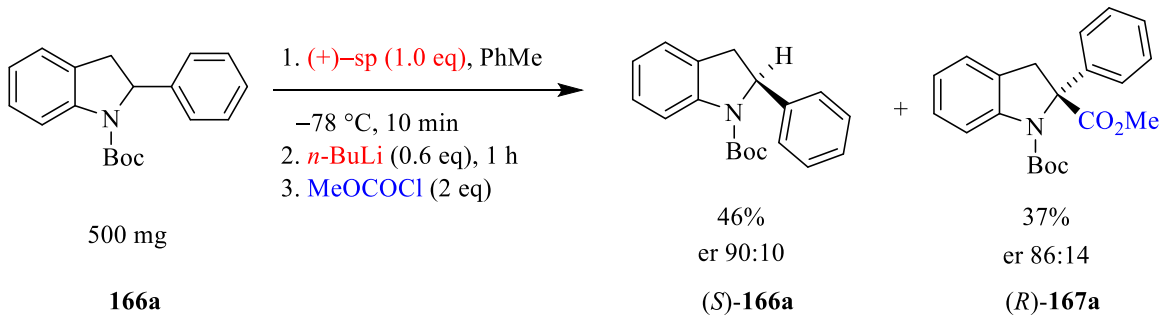
Scheme 4.22

Table 4.2.

Entry	(+)-sp eq	*n*-BuLi eq	time	RSM %	er	P %	er
1	1.3	1.0	1 h	30	92:8	64	76:24
2	1.1	0.8	1 h	35	93:7	54	75:25
3	1.1	0.8	30 min	52	81:19	47	83:17
4	1.1	0.8	45 min	43	89:11	55	75:25
5	1.1	0.7	1 h	35	93:7	56	71:29
6	1.0	0.6	45 min	48	85:15	51	82:18
7	1.3	1.0	30 min	54	79:21	46	81:19
8	1.0	0.6	1 h	44	90:10	36	88:12

Using 1 equivalent of *n*-BuLi and 1.3 equivalents of (+)-sparteine and then quenching with MeOCOCl gave an excellent er of (*S*)-**166a** (92:8), but with a low yield of 30% (Entry 1). Reducing the number of molar equivalents of *n*-BuLi to 0.8 gave a better yield of 35% with 93:7 er (Entry 2). However, decreasing the lithiation time gave poor results for both the yield and enantioselectivity (Entry 3). Also it can be seen that the enantioselectivity seems to depend on the number of equivalents of *n*-BuLi and the lithiation time (Entry 3-6). Overall, the best results were obtained when the reaction was carried out using 0.6 equivalents of *n*-BuLi, 1.0 equivalent of (+)-sparteine and with quenching by MeOCOCl after 1 h, which gave 44% yield of the indoline (*S*)-**166a** with a very good er (Entry 8).

It was pleasing to see when scaling up the optimised kinetic resolution to 500 mg, a similar result was obtained (Scheme 2.22). The absolute configuration of carbamate (*S*)-**166a** was confirmed by single crystal X-ray analysis (Figure 4.5, Appendix C).



500 mg

166a

46%
er 90:10
(*S*)-**166a**

37%
er 86:14
(*R*)-**167a**

(Scheme 4.23)

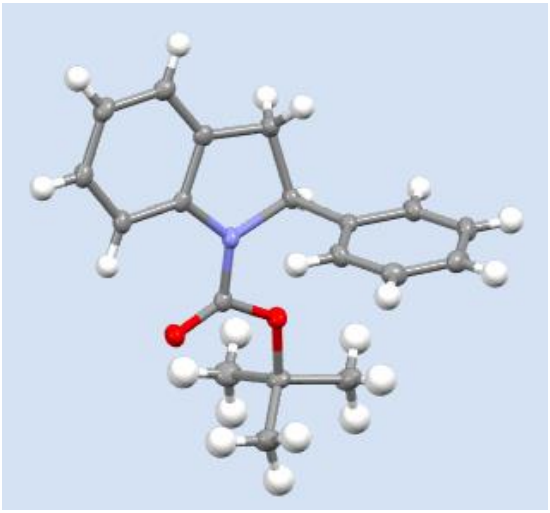
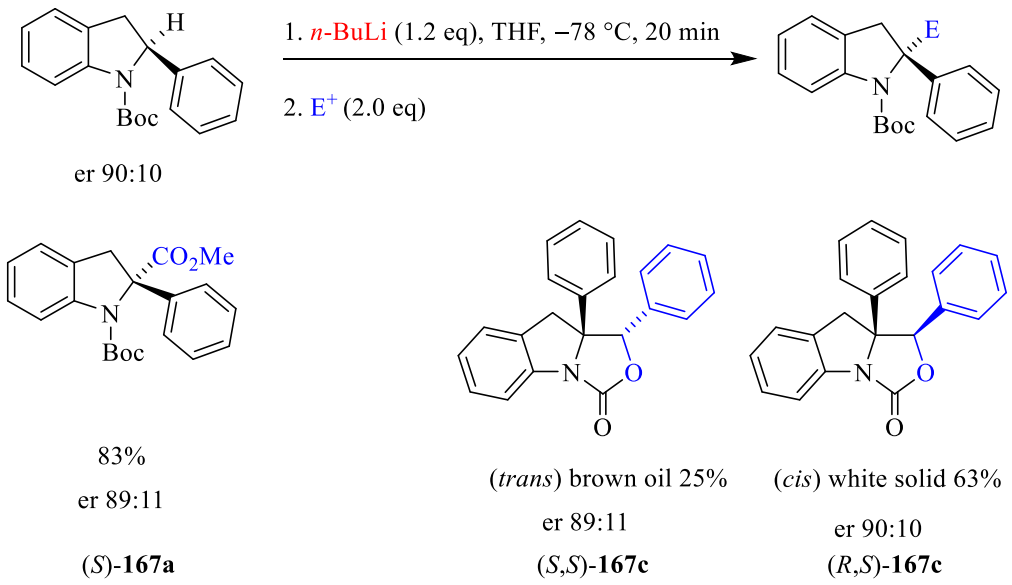


Figure 4.5: The absolute configuration of (***S***)-**166a** obtained by single crystal X-ray analysis.
(2*S*)-*N*-Boc-2-phenylindoline

Lithiation-substitution reactions were then attempted on the enantioenriched starting material (*S*)-**166a** using the electrophiles methyl chloroformate and benzaldehyde. The products (*S*)-**167a**, (*S*,*S*)-**167c** and (*S*,*R*)-**167c** were obtained with no loss in enantioenrichment (Scheme 2.23). For the (*S*,*S*)-**167c** and (*S*,*R*)-**167c**, it was confirmed that the major isomer was *cis*- (*R*,*S*)-**167c** (dr 1:2.3) by X-ray crystallography (Figure 4.5, Appendix B).



Scheme 4.24

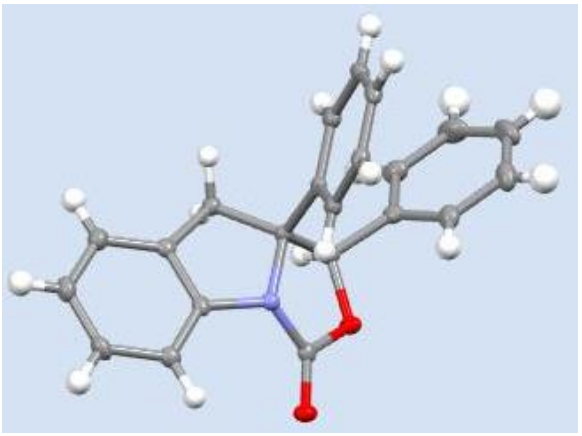
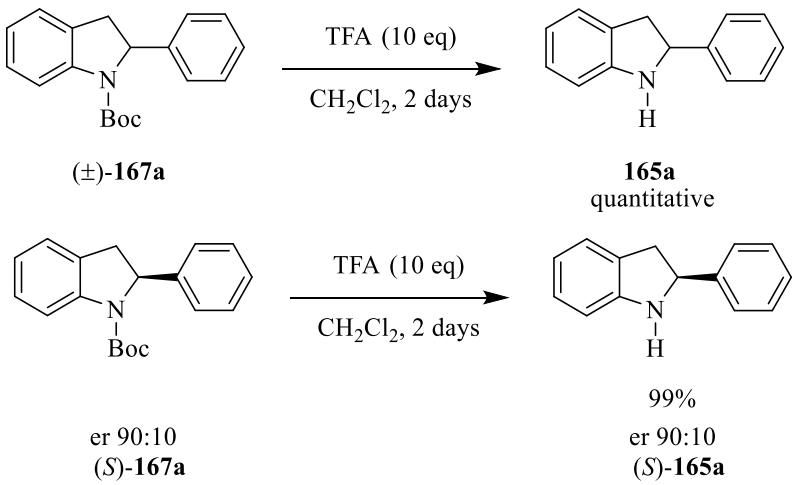


Figure 4.6: The absolute configuration of (*R*,*S*)-**167c** obtained by single crystal X-ray analysis. (1*R*,9a*S*)-1,9a-diphenyl-1H,9H-[1,3]oxazolo[3,4-a]indol-3-one

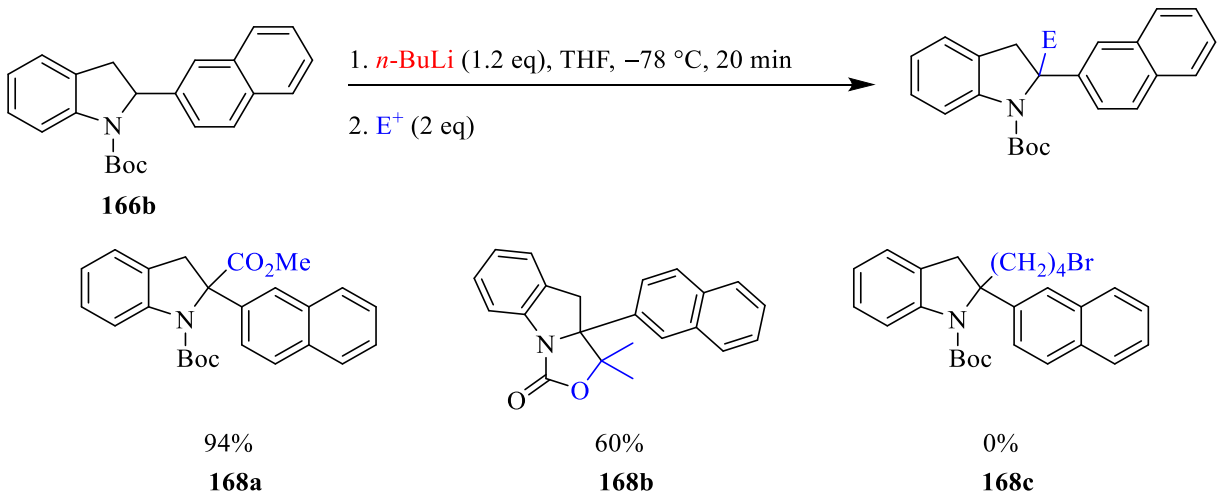
Furthermore, the Boc group of *rac*-**166a** was able to be removed under acidic conditions to give secondary amine **165a**. This was achieved by adding TFA to a solution of indoline **166a** in CH_2Cl_2. The reaction was monitored by TLC and the starting material was consumed after 2 days. These reaction conditions were then applied to enantioenriched (*S*)-**167a** to give the corresponding amine (*S*)-**165a** with retention of configuration (Scheme 2.24).



Scheme 4.25

4.3.2 Lithiation trapping and Kinetic resolution of *N*-Boc-2-(2-naphthyl)indoline 166b

The indoline **166b** was then investigated by trapping the corresponding lithiated intermediate with different electrophiles, using the same lithiation conditions as for compound **166a**. Quenching with methyl chloroformate gave a 94% yield of indoline **168a**. Furthermore, when the lithiated intermediate was quenched with acetone cyclised product **168b** was isolated in a good yield. Unfortunately, no product **168c** was formed when using the electrophile 1,4-dibromobutane under these conditions (Scheme 4.26).



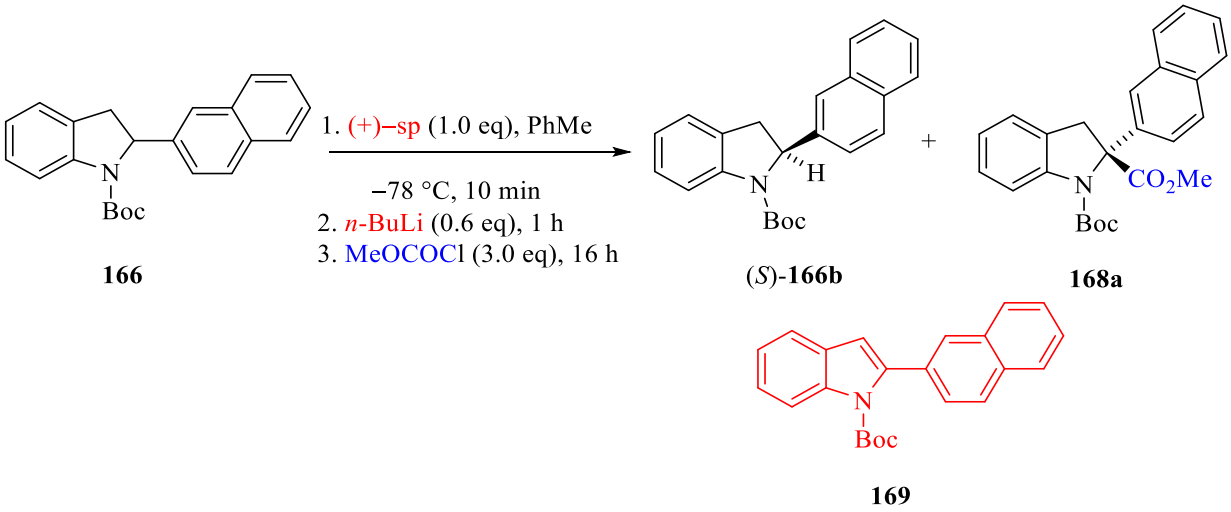
166b

94% 168a | 60% 168b | 0% 168c

Scheme 4.26

4.3.2.1 Kinetic Resolution of *N*-Boc-2-(2-naphthyl)indoline 166b

Kinetic resolutions with indoline **166b** were attempted using the optimum conditions as used for indoline **166a**. The compound **166b** and (+)-sparteine were dissolved first in toluene and then the *n*-BuLi was added at –78 °C. The major limitation of the naphthyl derivative was that it produced the eliminated product **169** during the kinetic resolution reaction will have affected the yield and possibly the enantioselectivity of the recovered indoline **166b** (Scheme 4.27). Although we tried to repeat this reaction three times using stricter precautionary measures to avoid any oxygen in the reaction's surrounding, the indole compound **169** was constantly formed in the reaction in 10-12% yield. As a result of this potential limitation, we decided not to examine this reaction any further.



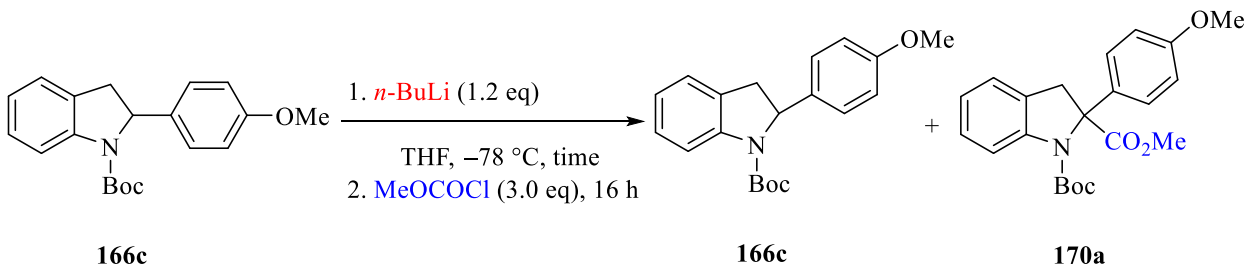
166 (*S*)-**166b** **168a** **169**

Scheme 4.27

168a	166b	169
31% er 85:15	57% er 60:40	11 %
35% er 80:20	56 % er 60:40	12 %
30% er 84:16	58% er 67:33	10 %

4.3.3 Lithiation Trapping and kinetic resolution of *N*-Boc-2-(4-methoxyphenyl)indoline 166c

The next derivative investigated was indoline **166c,** which was lithiated at –78 °C in THF. Trapping with methyl chloroformate after 20 minutes gave 43% yield of indoline **170a** (Entry 1, Table 2.3) and when the reaction was repeated, a similar result was obtained with 42% yield of indoline **170a** with some starting material being recovered (Entry 2). However, when the lithiation reaction was quenched after 30 and 35 minutes better yields of 80 and 85% were obtained respectively (Entry 3-4). These results show that reactions with the methoxy derivative seemed to be slower when compared to the other substituted indolines. Unfortunately, ReactIR spectroscopy was not available at the time to examine the lithiation time, due to a technical problem.



166c **166c** **170a**

Scheme 4.28

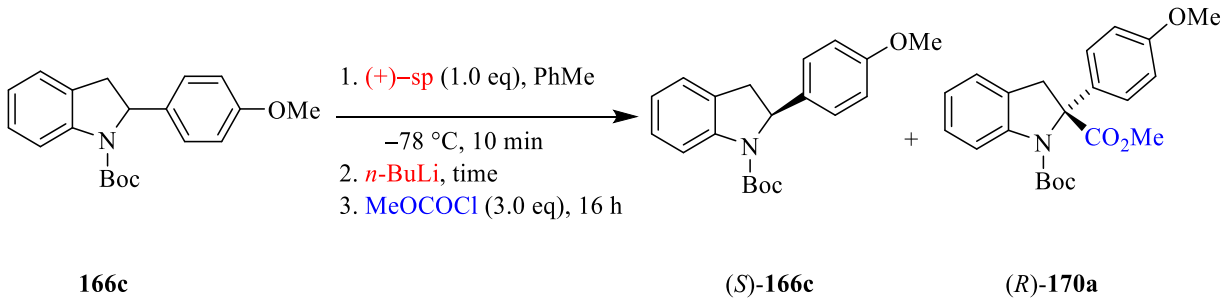
Table 4.3 Lithiation-quench of *N*-Boc-2- substituted indoline **166c**

Entry	Time	166c %	170a %
1	20 min	52	43
2	20 min	56	42
3	30 min	18	80
4	35 min	8	85

4.3.3.1 Kinetic Resolution of *N*-Boc-2-(4-methoxyphenyl)indoline 166c

Kinetic resolutions of the 2-substituted indoline **166c** were next attempted in order to try and recover enantioenriched starting materials. As with previous indolines, different conditions were used to find the optimum conditions for the kinetic resolution (Table 4.4 and Scheme 4.29). Using the conditions for phenylindoline **166a** where 0.6 equivalents of *n*-BuLi was used and trapping with MeOCOCl after 1 h (Entry 1) gave the starting material in high yield with moderate er, while the ester product (*R*)-**170a** was obtained in low yield (29%) with an excellent enantiomeric ratio of 99:1. The high yield of the recovered starting material supported the theory that reactivity of compound **166c** was low which meant that it needed more lithiation time or extra equivalents of the base. As a result, we then slightly increased the number of equivalents of base by adding 0.7 and 0.8 equivalents of *n*-BuLi and kept the lithiation time parameter at 1 h, which gave the same result (Entries 2-3). It is noted that both the yields and the enantioselectivity of the indoline **166c** were improved when the reaction time was increased

(Entry 4). Interestingly, the selectivity increased when the electrophile was added after 3 h, which gave an excellent yield of indoline **166c** (44%) with a high enantiomeric ratio of 98:2, while the 2,2-disubstituted product was obtained in 55% yield with a moderate 86:14 er (Entry 5). When the reaction mass was scaled up to 300 mg, both the the recovered starting material (*S*)-**166c** and ester product (*R*)-**170a** were obtained with excellent selectivity (Entry 6).



166c (*S*)-**166c** (*R*)-**170a**

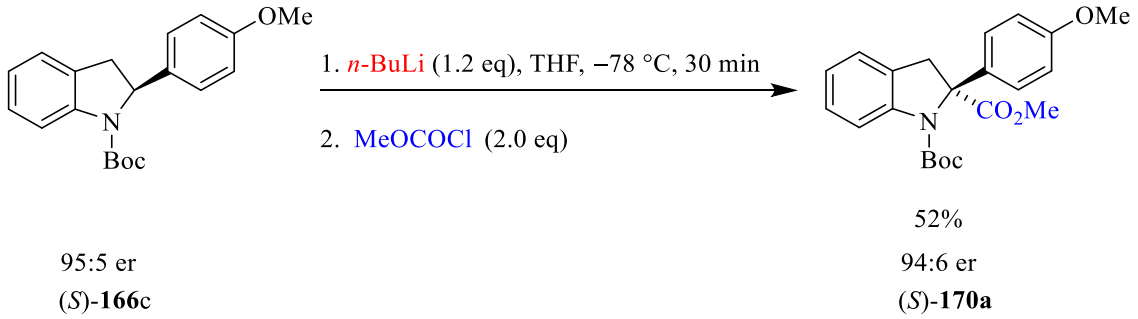
Scheme 4.29

Table 4.4

Entry	Mass (mg)	*n*-BuLi (eq)	time	166c yield %	er	170a yield %	er
1	100	0.6	1 h	70	71:29	29	99:1
2	100	0.7	1 h	67	70:30	32	99:1
3	100	0.8	1 h	62	77:23	35	99:1
4	100	0.6	2 h	52	85:15	40	94:6
5	100	0.6	3 h	44	98:2	55	86:14
6	300	0.6	3 h 10 min	50	95:5	49	95:5

It was obvious that the lithiation time for kinetic resolution with this derivative was longer than that of the parent compound **166a**. This may have been due to a number of reasons including the predicted lowered acidity of the benzylic proton in this substrate leading to a slower deprotonation. Alternatively, the longer lithiation time may have been caused by the Boc group rotating more slowly.

A lithiation–substitution reaction was then attempted on the enantioenriched starting material (*S*)-**166c** that was obtained from the kinetic resolution reaction in entry 6. Pleasingly, the ester product was obtained without loss in enantiomeric ratio (Scheme 4.30).



Scheme 4.30

4.3.3.2 Variable temperature ^{1}H NMR spectroscopy study of indoline 166c

Interesting results were obtained when investigating the energy barrier for rotation of the Boc group for *N*-Boc-2-(4-methoxyphenyl)indoline **166c** by carrying out a variable temperature NMR study. A sample of compound **166c** in THF-d_8 was warmed from –78 ºC to observe coalescence of the signals for the *t*-butyl signal proton with ratio 6:1. These signals for the two rotamers can be seen at 1.25 and 1.52 ppm at low temperature. It was observed that coalescence of the signals occurred at about 0 °C (Figure 2.5). From the Eyring plot for the major rotamer to the minor, the activation parameters were found to be $\Delta H^{\neq} = 58.7$ kJ mol^{-1} and $\Delta S^{\neq} = -14.0$ J K^{-1} mol^{-1}. This corresponds to a barrier of $\Delta G^{\neq} = 58.9$ kJ mol^{-1} at –78 °C and the half-life ($t_{1/2}$) of the Boc group rotation was determined to be around 17.05 min (Appendix). This compares with $t_{1/2}$ 7.5 min for **166a** and suggests that the longer reaction times needed for **166c** are a result of slower rotation**.**

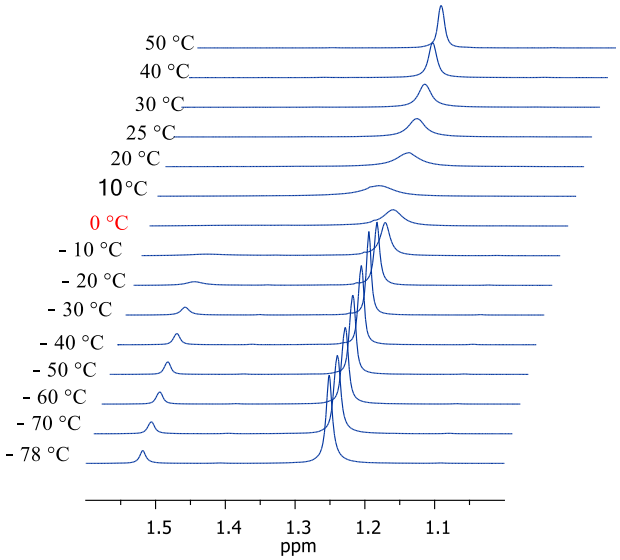
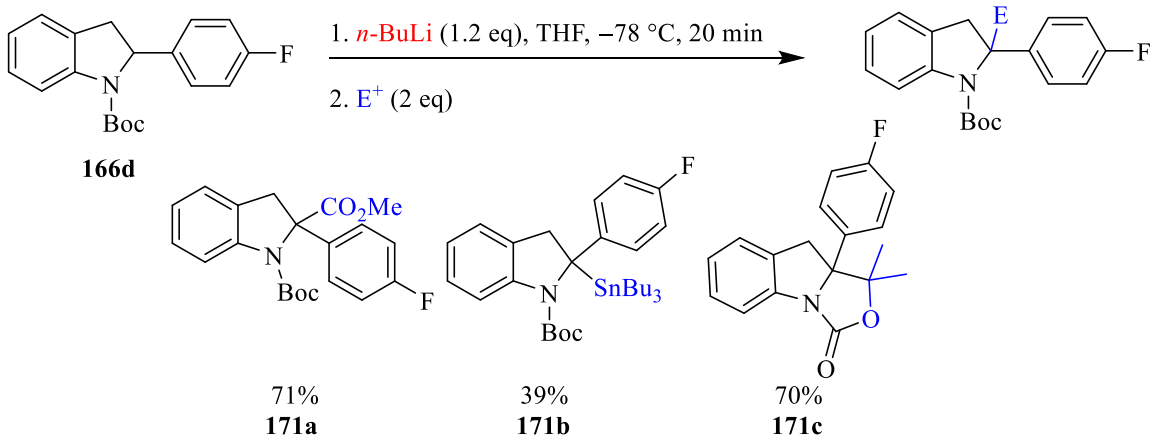


Figure 4.5: *t*-Butyl proton peak in ^{1}H NMR spectra obtained at various temperatures in THF-d_8, 500 MHz. The ratio between two rotamers is 6:1.

4.3.4 Lithiation trapping and KR of *N*-Boc-2-(4-fluorophenyl)-2,3-dihydroindoline 166d

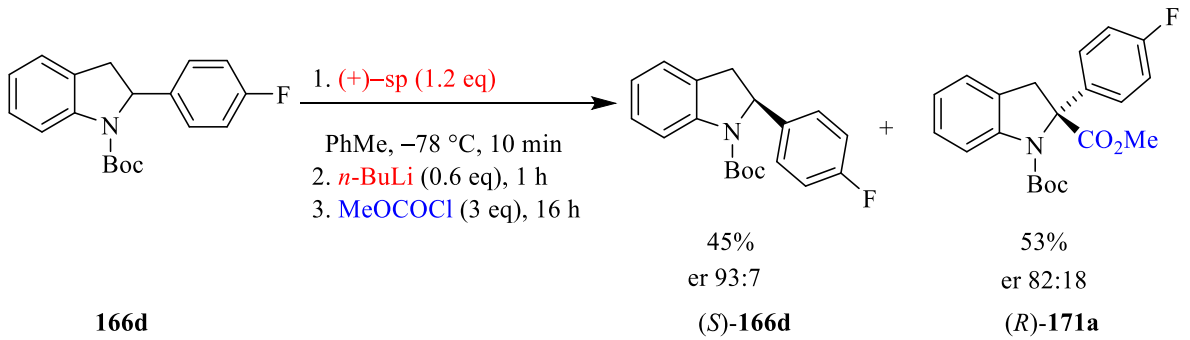
The last indoline derivative investigated was *N*-Boc-2-(4-fluorophenyl)indoline **166d**. By using the same lithiation conditions as used for **166a** and trapping with different electrophiles, products **171a-c** were obtained (Scheme 4.31). The results showed that both methyl chloroformate and acetone electrophiles gave good yields (70%), whereas the product obtained with tributyltin chloride was isolated in poor yield, which may have been due to the steric hindrance.



Scheme 4.31

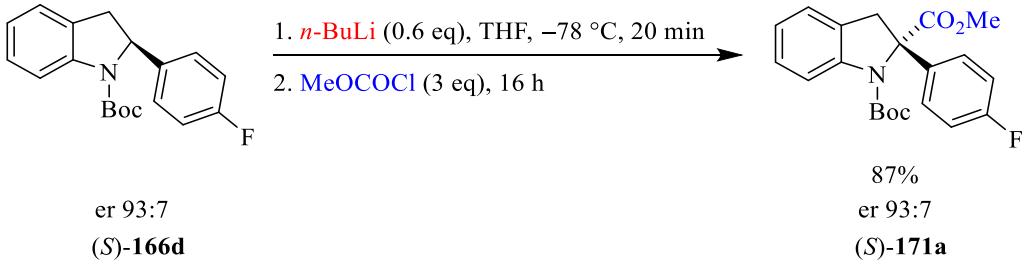
4.3.4.1 Kinetic Resolution of *N*-Boc-2-(4-fluorophenyl)indoline 166d

Kinetic resolution reactions on indoline **166d** were attempted using *n*-BuLi / (+)-sparteine in toluene at –78 °C. This gave an excellent result, with 45% of the starting material being recovered with 93:7 er after trapping with methyl chloroformate after 1 h. The ester was obtained in 53% yield with 82:18 er (Scheme 4.32).



Scheme 4.32

A visiting student, Yuhang Wang, then took over this part of the project with the aim to scale-up the kinetic resolution, and to subsequently carry out a lithiation-quench of the enantioenriched (*S*)-**166d** with methyl chloroformate.[137] This would then allow the other enantiomer of the ester product (*S*)-**171a** to be isolated. Unfortunately, when scaling-up the kinetic resolution to 0.4 g, compound (*S*)-**166d** was isolated in a low yield (25%) with a reduced er 84:16. Terefore, taking the original sample from Scheme 4.32, the (*S*)-enantiomer of the ester was obtained with retention of the enantiomeric ratio, in excellent yield (Scheme 4.33).



Scheme 4.33

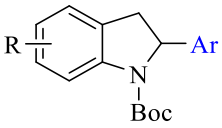
4.4 Conclusions and Future Work

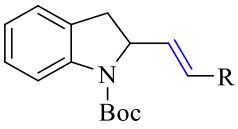
In conclusion, a variety of *N*-Boc-2-arylindolines have been synthesised by using an efficient, 2-step method, starting from their corresponding indoles. All of these compounds were able to be lithiated using *n*-BuLi. Quenching the lithiated intermediates with different electrophiles allowed a variety of 2-substituted products to be formed in reasonable yields.

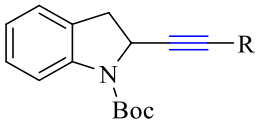
Results obtained from *in situ* ReactIR spectroscopy showed that the lithiation of 2-phenylindoline **166a** at −78 °C was slow. This corroborated the results obtained from VT NMR spectroscopy, which showed that the rate of Boc rotation was slow (the half-life ($t_{1/2}$) was 7.5 min and $\Delta G^{\neq} \approx 54.7$ kJ mol^{-1} at −78 °C). In comparison, VT NMR spectroscopy results for the *para*-methoxy derivative **166c** indicated the Boc group rotated at a slower rate (the half-life ($t_{1/2}$) of 17.0 min and $\Delta G^{\neq} \approx 58.9$ kJ mol^{-1} at −78 °C) leading to a longer lithiation time for reactions.

Kinetic resolutions were successfully carried out with the chiral base *n*-BuLi / (+)- sparteine and this gave a range of highly enantioenriched recovered *N*-Boc-2-aryl indolines in good yields. Surprisingly, the 2-naphthylindoline **166b** derivative gave the corresponding indole when subjected to the kinetic resolution and the enantioselectivity of the recovered starting material was low. Lithiation–substitution reactions using enantiomerically enriched starting materials were carried out, which gave α-substituted products with retention of configuration.

To carry on with this work in the future it would be good to expand the indoline scope by investigating similar organolithium reactions using alternative 2-substituted indolines containing different aryl groups or other substituents, such as 2-vinyl and 2-alkynyl functional groups.







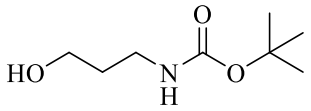
Chapter 5 - Experimental

5.1 General Experimental Details

All reagents were obtained from commercial suppliers and were used without further purification unless otherwise specified. Dry solvents were obtained from a Grubbs dry solvent system (model: SPS-200-6 or SPS-400-6). Methyl chloroformate, ethyl chloroformate, methyl bromoacetate, chlorotrimethylsilane, acetyl chloride, benzaldehyde and allyl bromide were freshly distilled from CaH_2, *n*-BuLi was regularly titrated, (+)-sparteine was freshly distilled by Kugelrohr distillation. Thin layer chromatography was performed on Merck silica gel 60 F_{254} plates and visualised by UV irradiation at 254 nm or by staining with an alkaline $KMnO_4$ or Vanillin dip. Flash column chromatography was performed using DAVISIL or Geduran silica gel (40-63 micron mesh). ^{1}H NMR spectra were recorded on a Bruker Avance 400, a Bruker Avance III 400, a Bruker Avance III HD 400 (all 400 MHz) or a Bruker Avance III HD 500 (500 MHz) instrument. Chemical shifts are reported in ppm with respect to the residual solvent peaks, with multiplicities given as s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad. Coupling constants (*J* values) are quoted to nearest 0.5 Hz with values in Hertz (Hz) and were corrected. ^{13}C NMR and ^{19}F NMR spectra were recorded on the above instruments at 100 or 126 MHz and 377 MHz respectively. Low and high resolution (accurate mass) mass spectra were recorded on a Micromass Autospec for Electron Impact (EI) and on a Waters LCT instrument for Electrospray ionization (ES) with Time-of-Flight (TOF) analysis. Infra–Red spectra were recorded on Perkin Elmer Spectrum RX Fourier Transform – IR System. Only selected peaks are reported and absorption maxima are given in cm^{-1}. Specific rotations were calculated from optical rotations recorded on an AA-10 automatic polarimeter. Melting points were recorded on a Gallenkamp hot stage and were uncorrected. Resolution between the enantiomers was achieved using a Beckman system fitted with a Phenomenex Lux Cellulose-1 column (250 mm × 4.60 mm i.d.), a Phenomenex Lux

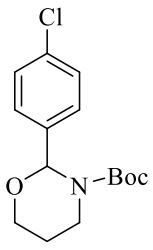
Cellulose-2 column (250 mm × 4.60 mm i.d.), Cellulose-4 column (250 mm × 4.60 mm i.d.), a Daicel ChiralPak IA column (250 mm × 4.60 mm i.d.) or a Daicel ChiralCel OJ column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane: isopropanol as the mobile phase at the flow rates specified, ambient temperature, detection by UV absorbance at 254 nm. *In situ* ReactIR infra-red spectroscopic monitoring was performed on a Mettler-Toledo ReactIR iC 4000 spectrometer equipped with a diamond-tipped (DiComp) probe.

tert-Butyl _N_-(3-hydroxypropyl)carbamate 61



Di-*tert*-butyl dicarbonate (16.0 g, 73 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise to 3-amino-1-propanol **60** (5.0 mL, 67 mmol) in CH_2Cl_2 (20 mL) at room temperature. After 16 h, the solvent was removed under reduced pressure and Et_2O (20 mL) was added. The organic layer was washed with saturated aqueous solution of $NaHCO_3$ (3 × 10 mL), saturated brine solution (10 mL) and was dried ($MgSO_4$). After filtering, the solvent was removed under reduced pressure to give the crude product as a clear oil. Purification by flash column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (9.7:0.3), gave the cabamate **61** (8.11 g, 46 mmol, 70%) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.45 (1H, t, *J* 6.0 Hz, NH), 4.09 (1H, t, *J* 6.0 Hz, OH), 3.45 (2H, q, *J* 6.0 Hz, OCH_2), 3.04 (2H, q, *J* 6.0 Hz, NCH_2), 1.49 (2H, quin, *J* 6.0 Hz, CH_2), 1.24 (9H, s, *t*–Bu). Data consistent with the literature.[108]

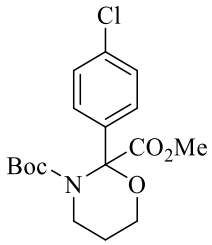
tert-Butyl 2-(4-chlorophenyl)-1,3-oxazinane-3-carboxylate 62



3-Amino-1-propanol **60** (0.49 mL, 6.5 mmol) and anhydrous Na_2SO_4 (7.0 g, 49.8 mmol) were added to a solution of *p*-chlorobenzaldehyde (700 mg, 4.98 mmol) in toluene (20 mL). The mixture was heated to 90 °C for 17 h. Di-*tert*-butyl dicarbonate (2.17 g, 9.96 mmol) was then added and the mixture was stirred for 5 h. The mixture was filtered and the solvent was removed under reduced pressure. The crude product was re-dissolved in EtOH (44 mL) and $NaBH_4$ (188 mg, 5.0 mmol) was added at room temperature. After 16 h, the solvent was removed under reduced pressure. The mixture was extracted with EtOAc (3 × 10 mL), and was washed with water (10 mL) and saturated brine solution (10 mL). The product was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by using flash column chromatography on silica gel, eluting with petrol−EtOAc (9.5:0.5) and the product was recrystallized from hexane, to give the carbamate **62** (1.9 g, 6.3 mmol, 96%) as plates; m.p. 57−58 °C; R_f 0.5 [petrol−EtOAc (9:1)]; FT-IR ν_{max} cm^{-1} 2985, 2975, 2855, 1695 (C=O); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.40 (2H, d, *J* 8.0 Hz, ArH) 7.30 (2H, d, *J* 8.0 Hz, ArH), 6.65 (1H, s, CH), 4.13 (1H, dd, *J* 13.0, 3.0 Hz, CH), 3.84−3.77 (1H, m, CH), 3.71 (1H, td, *J* 11.5, 2.5 Hz, CH), 2.98 (1H, td, *J* 13.0, 3.0 Hz, CH), 2.06–1.93 (1H, m, CH), 1.51 (9H, s, *t*-Bu), 1.43−1.36 (1H, m, CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.9 (C=O), 135.8 (C), 133.8 (C), 129.0 (CH), 128.4 (CH), 81.7 (CH), 80.7 (C), 60.5 (CH_2), 37.8 (CH_2), 28.3 (CH_3), 25.4 (CH_2); HRMS *m/z* (ES) Found: MNa^+, 320.1023, $C_{15}H_{20}{}^{35}ClNO_3Na$ requires MNa^+ 320.1024; LRMS *m/z* (ES) 322 (MNa^+ for ^{37}Cl, 4%), 320 (MNa^+ for ^{35}Cl, 12%), 198 (100%).

Resolution between the enantiomers of the the carbamate **62** was achieved using a Beckman system fitted with a Lux Cellulose–2 column (250 mm × 460 mm i.d.) as the stationary phase with a mixture of *n*-hexane–isopropanol (99:1.0 v/v) as the mobile phase at a flow rate of 1.0 $mL \cdot min^{-1}$; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 µL of the sample prepared in a 2 $g \cdot L^{-1}$ solution of the eluent. Under these conditions, the components were eluted at 8.9 min and 12.2 min with an analysis time of 30 min.

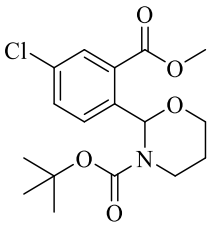
3-*tert*-Butyl 2-methyl 2-(4-chlorophenyl)-1,3-oxazinane-2,3-dicarboxylate 65



n-BuLi (0.17 mL, 0.41 mmol, 2.4 M in hexanes) was added to carbamate **62** (100 mg, 0.34 mmol) in THF (2 mL) at –78 °C. After stirring for 10 min, methyl chloroformate (0.08 mL, 1.02 mmol) was added. The mixture was allowed to warm gradually to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by by column chromatography on silica gel, eluting with petrol−EtOAc (9.5:0.5 to 9.3:0.7), to give the oxazinane **65** (114 mg, 0.32 mmol, 95%) as an oil; R_f 0.18 [petrol−EtOAc (9:1)]; FT-IR ν_{max} ATR/cm^{-1} 2980, 2930, 2870, 1760 (C=O), 1710 (C=O), 1492; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42–7.34 (4H, m, ArH), 4.03 (1H, dt, *J* 13.5, 4.0 Hz, CH), 3.95 (1H, dt, *J* 11.0, 4.0 Hz, CH), 3.75 (3H, s, OCH_3), 3.61 (1H, td, *J* 11.0, 4.0 Hz, CH), 3.28−3.20 (1H, m, CH), 2.09–1.97 (1H, m, CH) 1.52−1.50 (10H, m, *t*-Bu & CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.6 (C=O), 154.9 (C=O), 134.8 (C), 134.7 (C), 129.8 (CH), 128.5 (CH), 89.6 (C), 81.8 (C), 61.6 (CH_2), 52.8 (CH_3), 40.6 (CH_2), 28.1 (CH_3), 24.0 (CH_2); HRMS *m/z* (ES) Found: MNa^+, 378.1083, $C_{17}H_{22}{}^{35}ClNO_5Na$ requires MNa^+ 378.1079; LRMS *m/z* (ES) 380 (MNa^+ for ^{37}Cl, 5%), 378 (MNa^+ for ^{35}Cl, 13%), 256 (100%).

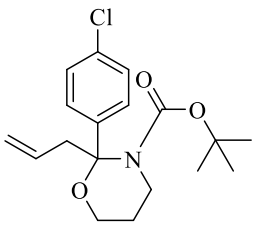
Alternatively, compound **65** was prepared as follows: carbamate **62** (100 mg, 0.34 mmol), *n*-BuLi (0.17 mL, 0.41 mmol, 2.4 M in hexanes) and methyl cyanoformate (0.08 mL, 1.02 mmol) gave the carbamate **65** (81.6 mg, 68%), as a clear oil, data as above.

***tert*-Butyl 2-(4-chloro-2-(methoxycarbonyl)phenyl)-1,3-oxazinane-3-carboxylate 66**



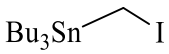
n-BuLi (0.17 mL, 0.41 mmol, 2.4 M in hexanes) was added to carbamate **62** (100 mg, 0.34 mmol), in THF (2 mL) at –78 °C. After 10 min methyl cyanoformate (0.08 mL, 1.02 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by by column chromatography on silica gel, eluting with petrol−EtOAc (9.7:0.3 to 9.4:0.6) to give the ester **66** (80 mg, 0.05 mmol, 15%) as an oil; R_f 0.33 [petrol−EtOAc (9:1)]; FT-IR ν_{max} ATR/cm^{-1} 2978, 2932, 2873, 1759 (C=O), 1704 (C=O), 1492; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (1H, d, *J* 2.2 Hz, CH), 7.45 (1H, dd, *J* 8.0, 2.2 Hz, CH), 7.20 (1H, d, *J* 8.0 Hz, CH), 6.91 (1H, s, CH), 4.15−4.08 (1H, m, CH), 3.88 (3H, s, OCH_3), 3.74–3.67 (1H, m, CH), 3.50−3.42 (1H, m, CH), 3.14−3.05 (1H, m, CH), 1.97–1.84 (1H, m, CH) 1.48−1.45 (10 H, m, *t*-Bu & CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.6 (C=O), 154.3 (C=O), 134.7 (C), 134.2 (C), 134.1 (C), 130.5 (CH), 129.4 (CH), 128.8 (CH), 81.0 (C), 80.8 (CH), 61.3 (CH_2), 52.7 (CH_3), 38.6 (CH_2), 28.3 (CH_3), 24.9 (CH_2); HRMS *m/z* (ES) Found: MNa^+, 378.1078, $C_{17}H_{22}{}^{35}ClNO_5Na$ requires MNa^+ 378.1079; LRMS *m/z* (ES) 380 (MNa^+ for ^{37}Cl, 6%), 378 (MNa^+ for ^{35}Cl, 12% MH^+), 256 (100%).

***tert*-Butyl 2-allyl-2-(4-chlorophenyl)-1,3-oxazinane-3-carboxylate 67**



n-BuLi (0.08 mL, 0.17 mmol, 2.4 M in hexanes) was added to carbamate **62** (100 mg, 0.34 mmol), in dry THF (2 mL) at –78 °C. After 10 min, allyl bromide (0.09 mL, 1.02 mmol) was added. The mixture was allowed to warm gradually to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol−EtOAc (9.7:0.3 to 9.4:0.6), to give the carbamate (48 mg, 0.14 mmol, 41%) as an oil; R_f 0.51 [petrol−EtOAc (9:1)]; FT-IR ν_{max} ATR/cm^{-1} 2978, 2972, 2935, 1697 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37−7.33 (2H, m, 2 ×CH), 7.32−7.20 (2H, m, 2 × CH), 6.01 (1H, ddt, *J* 16.0, 12.0, 7.0 Hz, C*H*=CH_2), 5.16−5.14 (1H, m, CH=C*H*$_2$), 5.13−5.10 (1H, m, C*H*$_2$=CH) 3.77−3.68 (2H, m, 2 × CH), 3.55 (1H, ddd, *J* = 12.0, 7.0, 5.0 Hz, CH), 3.40–3.32 (2H, m, 2 × CH), 2.81 (1H, ddt, *J* 14.0, 6.0, 1.5 Hz, CH), 1.96−1.85 (1H, m, CH) 1.45−1.40 (10H, m, *t*-Bu & CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.3 (C=O), 139.8 (C), 133.6 (C), 133.2 (CH), 128.3 (CH), 128.2 (CH), 118.0 (CH_2), 91.5 (C), 80.4 (C), 59.6 (CH_2), 46.1 (CH_2), 40.1 (CH_2), 28.3 (CH_3), 24.0 (CH_2); HRMS *m/z* (ES) Found: MNa^+, 360.8307, $C_{18}H_{24}{}^{35}ClNO_3Na$, requires MNa^+ 360.8310. LRMS *m/z* (ES) 362 (MNa^+ for ^{37}Cl, 4%), 360 (MNa^+ for ^{35}Cl, 12%), 238 (100%).

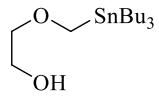
Tributyl(iodomethyl)stannane 78



$Cu(OAc)_2$ (220 mg, 1.22 mmol) was dissolved in acetic acid (4 mL) with gentle heating. Zinc dust (1.5 g, 23.4 mmol) was added and the mixture was heated gently for 3 min. The acetic acid was decanted and fresh acetic acid (4 mL) was added.[58] The resulting mixture was then stirred with gentle heating for 3 min and the acetic acid was decanted again. After repeating this procedure two more times, the cooled mixture was washed with Et_2O (2 × 5 mL) and dried over a stream of nitrogen. The mixture was dissolved in dry THF (10 mL) and diiodomethane was added dropwise until the mixture became a faint purple colour. Another portion of diiodomethane (1.90 mL, 23.3 mmol) in THF (7 mL) was added dropwise over 30 min at 40

°C. After 2.5 h, the solution was filtered and tributyltin chloride (3.33 mL, 12.3 mmol) in THF (10 mL) was added dropwise over 30 min at 40 °C. After 3 h, the solvent was removed under reduced pressure, toluene (20 mL) was added and the mixture was washed with aqueous HCl (3 × 40 mL, 2 M). The organic layer was separated, washed with brine (10 ml) and was dried ($MgSO_4$). After filtering, the solvent was evaporated to give the colourless crude product. This was purified through a short plug of silica, eluting with petrol to afford the iodide **78** (4.57 g, 13 mmol, 86%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.96 (2H, s, with broad d, $J^{117/119}$ Sn–^{1}H 18.0 Hz, CH_2) 1.65−1.43 (6H, m, 3 × CH_2), 1.34 (6H, sext, *J* 7.0 Hz, 3 × CH_2), 1.10−0.95 (6H, m, 3 × CH_2), 0.92 (9H, t, *J* 7.0 Hz, 3 × CH_3). Data in accordance with the literature.[109]

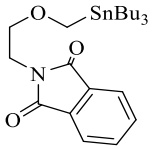
2-((Tributylstannyl)methoxy)ethanol 80



Hexane (3 × 3 mL) was used to wash sodium hydride (495 mg of a 60% suspension in mineral oil, 12.4 mmol), and this was dried under nitrogen and suspended in THF−DMSO (10:1, 20 mL).[58] Ethylene glycol (2.12 mL, 31.0 mmol) was then added dropwise to the suspension at 0 °C, and the mixture was allowed to warm to room temperature for 1 h. The mixture was cooled to 0 °C, followed by the dropwise addition of tributyl(iodomethyl)stannane (4.45 g, 10.3 mmol) in THF (11 mL) over 10 min. The suspension was heated at 55 °C for 16 h, then the reaction was slowly quenched with H_2O (20 mL) at room temperature. The layers were separated and the aqueous layer was washed with EtOAc (3 × 30 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), and were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by using flash column chromatography on silica gel, eluting with petrol−EtOAc (9:1) to give the alcohol **80** (1.0 g, 2.7 mmol, 26%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.78 (2H, s, with broad d,

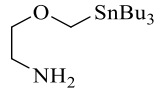
$J^{117/119}$ Sn–^{1}H 18.0 Hz, CH_2), 3.73–3.68 (2H, m, 2 × CH), 3.48–3.45 (2H, m, 2 × CH), 1.93 (1H, t, *J* 6.0 Hz, OH), 1.59–1.48 (6H, m, 3 × CH_2), 1.38–1.25 (6H, m, 3 × CH_2), 1.03–0.79 (15H, m, 3 × CH_2 and 3 × CH_3). Data consistent with the literature.[58]

2-(2-((Tributylstannyl)methoxy)ethyl)isoindoline-1,3-dione 81



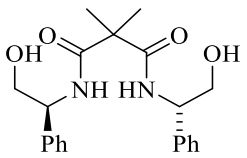
2-((Tributylstannyl)methoxy)ethanol (990 mg, 2.70 mmol) was dissolved in Et_2O (25 mL) and Et_3N (0.76 mL, 5.40 mmol) was added in one portion at room temperature, followed by the dropwise addition of methanesulfonyl chloride (0.23 mL, 2.97 mmol) over 3 min. The mixture was left to stir for 1 hour at room temperature. The reaction was slowly quenched with H_2O (5 mL). The layers were then separated and the aqueous layer was washed with EtOAc (3 × 30 mL). The combined organic layers were washed with H_2O (10 mL) and saturated brine (10 mL), were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford the crude mesylate (1.08 g). This was used in the next step without further purification. Potassium phthalimide (950 mg, 5.13 mmol) was added in one portion to a solution of the crude mesylate in DMF (35 mL) at room temperature. The reaction mixture was stirred at 100 °C for 3 h. The mixture was cooled to room temperature and was slowly quenched with H_2O (5 mL) and was extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL). The product was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by using flash column chromatography on silica gel, eluting with petrol−EtOAc (8:2), to give phthalimide **81** (1.2 g, 2.4 mmol, 90%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (2H, dd, *J* 5.0, 3.0 Hz, 2 × CH), 7.72 (2H, dd, *J* 5.0, 3.0 Hz, 2 × CH), 3.90 (2H, t, *J* 5.0 Hz, CH_2), 3.73 (2H, s, with broad d, $J^{117/119}$ Sn–^{1}H 18.0 Hz, CH_2), 3.57 (2H, t, *J* 5.0 Hz, CH_2), 1.52−1.32 (6H, m, 3 × CH_2), 1.28–1.17 (6H, m, 3 × CH_2), 0.92–0.74 (15H, m, 3 × CH_2 and 3 × CH_3). Data consistent with the literature.[58]

2-((Tributylstannyl)methoxy)ethan-1-amine 82



Hydrazine monohydrate (0.6 mL, 12 mmol) was added to a solution of phthalimide **81** (500 mg, 1.0 mmol) in EtOH (5 mL). The reaction mixture was heated under reflux for 30 min. The solvent was removed under reduced pressure. The resulting residue was suspended in CH_2Cl_2 (15 mL) and was filtered through Celite. The filtrate was concentrated under reduced pressure to afford the pure SnAP reagent **82** (270 mg, 7.4 mmol, 72%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.76 (2H, s, with broad d, $J^{117/119}$ Sn–^{1}H 18.0 Hz, CH_2), 3.37 (2H, t, *J* 5.0 Hz, CH_2), 2.83 (2H, t, *J* 5.0 Hz, CH_2), 1.65−1.48 (6H, m, 3 × CH_2), 1.46 (2H, br s, NH_2), 1.39−1.26 (6H, m, 3 × CH_2), 0.97−0.87 (15H, m, 3 × CH_2 and 3 × CH_2). Data consistent with the literature.[58]

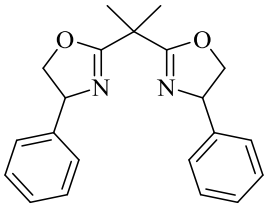
***N,N′*-Bis(2-hydroxy-1-phenylethyl)-2,2-dimethylpropanediamide 86**



Following a literature procedure, dimethylmalonic acid (2.5 g, 19.0 mmol) was suspended in dry CH_2Cl_2 (75 mL) followed by addition of three drops of dimethylformamide. Oxalyl chloride (4.0 mL, 47.0 mmol) was added dropwise to the reaction mixture at room temperature. After 1.5 h, the solvent was removed under reduced pressure to afford the crude acid chloride. This was dissolved in dry CH_2Cl_2 (60 mL) and was added dropwise to a solution of 2-amino-2-phenylethanol (5.5 g, 39.7 mmol) and diisopropylamine (16 mL, 114 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature for 5 h. The reaction mixture was quenched slowly with saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford the crude product which

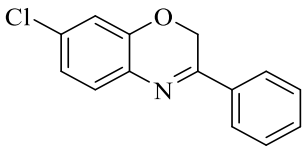
was washed with Et_2O (3 × 10 mL) to afford pure amide **86** as a white solid (7.0 g, 19 mmol, 99%). The amide was used in the next step without any purification.[110]

4-Phenyl-2-[2-(4-phenyl-4,5-dihydro-1,3-oxazol-2-yl)propan-2-yl]-4,5-dihydro-1,3-oxazole 87



The diamide **86** (1.0 g, 2.7 mmol), triethylamine (1.50 mL, 10.8 mmol) and 4-dimethylaminopyridine (60 mg, 0.54 mmol) in dichloromethane (5 mL) were stirred at room temperature. After 1.5 h, 4-toluenesulfonyl chloride (1.53 g, 8.1 mmol) in CH_2Cl_2 (5 mL) was added. After 16 h, the solution was washed with saturated aqueous NH_4Cl (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The resultant solution was concentrated under vacuum and was purified by silica gel column chromatography, eluting with petrol–EtOAc (70:30) to afford the bisoxazole **87** (0.25 g, 0.72 mmol, 90%) as an oil; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.37−7.32 (4H, m, 4 × CH), 7.32−7.26 (6H, m, 6 × CH), 5.22 (2H, dd, *J* 10.0, 8.0 Hz, CH), 4.70 (2H, dd, *J* 10.0, 8.0 Hz, CH), 4.19 (2H, t, *J* 8.0 Hz, CH), 1.70 (6H, s, 2 × CH_3). Data consistent with the literature.[111]

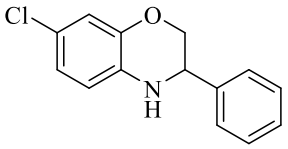
7-Chloro-3-phenyl-2H-1,4-benzoxazine 91



2-Amino-5-chlorophenol (7.0 g, 48.8 mmol) and $NBu_4^+HSO_4^-$ (3.8 g, 11.2 mmol) was added To a solution of potassium carbonate (40 g, 293 mmol) in water (200 mL) and CH_2Cl_2 (200 mL). The reaction mixture was stirred vigorously and a solution of 2-bromoacetophenone (9.7 g, 48.8 mmol) in CH_2Cl_2 (100 mL) was added. After 16 h, the layers were separated and the

aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give the crude product which was used without purification in the next step; R_f 0.64 [petrol–EtOAc (90:10)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94–7.79 (2H, m, 2 × CH) 7.54−7.44 (3H, m, 3 × CH), 7.35 (1H, d, *J* = 8.5 Hz, CH), 7.00 (1H, dd, *J* = 8.5, 2.0 Hz, CH) 6.93 (1H, d, *J* = 2.0 Hz, CH), 5.08 (2H, s, CH_2).

7-chloro-3-phenyl-3,4-dihydro-2H-1,4-benzoxazine 93a



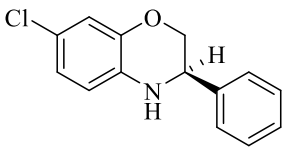
Sodium borohydride (1.38 g, 36.56 mmol) was added to 7-chloro-3-phenyl-2H-1,4-benzoxazine (4.46 g, 18.0 mmol) in ethanol (50 mL) and water (15 mL). The reaction mixture was heated at 90 °C for 4 h and then was cooled to room temperature. The solvent was removed under reduced pressure. The crude mixture was extracted between CH_2Cl_2 (60 mL) and water (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), gave the amine **93** (3.3 g, 13.4 mmol, 74%) as white solid; m.p. 61–63 °C; R_f *0.44* [petrol–EtOAc (90:10)]; FT-IR ν_{max} (ATR)/cm^{-1} 3343, 3064, 3027, 2988, 1590, 1492, 1491, 1284, 1134, 1050, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ = δ 7.45–7.30 (5H, m, 5 × CH), 6.85 (1H, d, *J* = 2.0 Hz, CH), 6.77 (1H, dd, *J* = 8.5, 2.0 Hz, CH), 6.58 (1H, d, *J* = 8.5 Hz, CH), 4.48 (1H, ddd, *J* = 8.5, 3.0, 1.3 Hz, CH), 4.28 (1H, ddd, *J* = 11.0, 3.0, 1.3 Hz, CH), 4.08–3.81 (2H, m, CH & NH).[138]

Resolution between the enantiomers of the amine **93a** was achieved using a Beckman system fitted with a ChiralCel OJ column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (98.5:1.5 v/v) as the mobile phase at a flow rate of 1

mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 74.9 min and 89.4 min with an analysis time of 100 min.

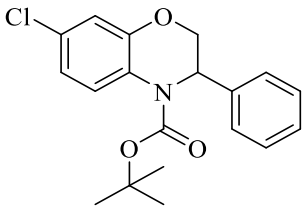
Trifluoroacetic acid (0.12 mL, 1.59 mmol) was added to a stirred solution of carbamate **94a** (55 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) at room temperature. After 2 d, the solvent was evaporated and NaOH (2 mL, 1 M) was added to basify the residue. The mixture was extracted with CH_2Cl_2 (2 × 15 mL). Using $MgSO_4$ to dry the combining organic layers then filtered and removed the solvent under reduced pressure. The crude product was purified by using column chromatography on silica gel, eluting with petrol–EtOAc (97:3) to give the amine the crude amine **93a** as an oil.

(3*R*)-7-Chloro-3-phenyl-3,4-dihydro-2H-1,4-benzoxazine (*R*)-93a



Trifluoroacetic acid (0.01 mL, 0.12 mmol) was added to a solution of the *tert*-butyl (3*R*)-3-phenyl-2,3-dihydro-1,4-benzoxazine-4-carboxylate (*R*)-**94a** (4 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) at room temperature. After 2 d, the solvent was evaporated and NaOH (2 mL, 1 M) was added to basify the residue. The mixture was extracted with CH_2Cl_2 (2 × 15 mL). $MgSO_4$ was used to dry the combined organic layers, which were then filtered and the solvent was removed under reduced pressure. The crude product was purified by using column chromatography on silica gel, eluting with petrol–EtOAc (97:3) to give the amine (*R*)-**93a** (29 mg, 100%), as white needles; mp 55–56 °C; the enantiomeric ratio was determined to be 98:2 by CSP-HPLC (major component eluted at 78.4 min); $[\alpha]_D^{23}$ –73.17 (0.21, $CHCl_3$).

***tert*-Butyl 7-chloro-3-phenyl-2,3,4a,8a-tetrahydro-1,4-benzoxazine-4-carboxylate 94a**

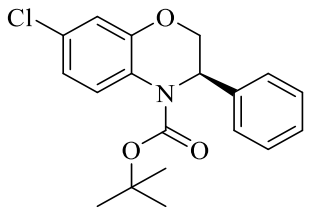


n-BuLi (3.69 mL, 8.85 mmol, 2.4 M) was added to a stirred solution of **93** (3.0 g, 8.85 mmol) in THF (30 mL) at –78 °C. After 30 min, Boc_2O (2.3 g, 10.6 mmol) in THF (15 mL) was added over 10 min. After allowing the mixture to warm to room temperature gradually over 16 h, the reaction was quenched with aqueous saturated $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the carbamate **94a** (2.84 g, 93%) as a white needles; m.p. 118–120 °C; R_f 0.26 [petrol–EtOAc (90:10)]; FT-IR ν_{max} (ATR)/cm^{-1} 2973, 2970, 2930, 1708 (C=O), 1577, 1492, 1368, 1257, 1140, 1061, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.03 (1H, d, *J* = 8.5, CH), 7.36–7.20 (5H, m, 5 × CH), 6.97–6.83 (2H, m, 2 × CH), 5.62 (1H, brs, CH), 4.60 (1H, dd, *J* = 11.0, 2.5 Hz, CH), 4.36 (1H, dd, *J* = 11.0, 3.0 Hz, CH), 1.49 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.5 (C=O), 146.5 (C), 138.4 (C), 128.6 (CH), 128.5 (C), 127.5 (CH), 126.3 (CH), 124.8 (C), 123.9 (CH), 121.2 (CH), 117.1 (CH), 82.3 (C), 68.4 (CH_2), 54.5 (CH), 28.2 (CH_3); HRMS (ES) Found: MNa^+, 368.1022. $C_{19}H_{20}{}^{35}ClNO_3Na$ requires MNa^+, 368.1024; LRMS *m/z* (ES) 370.1 (MNa^+ for ^{37}Cl, 25%), 368.1 (MNa^+ for ^{35}Cl, 75%), 290 (100, MH+-*t*-BuO, ^{37}Cl), 246 (10, MH^+-Boc,^{37}Cl).

Resolution between the enantiomers of the carbamate **94a** was achieved using a Beckman system fitted with a ChiralPak IA column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99.3:0.7 v/v) as the mobile phase at a flow rate of 1 $mL \cdot min^{-1}$; ambient temperature, detection by UV absorbance at 254 nm. Injection volume

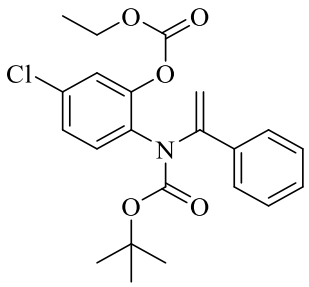
was 20 μL of the sample prepared in a 2 $g \cdot L^{-1}$ solution of the eluent. Under these conditions, the components were eluted at 8.41 min and 9.50 min with an analysis time of 15 min.

***tert*-Butyl (3*R*)-7-Chloro-3-phenyl-2,3-dihydro-1,4-benzoxazine-4-carboxylate** (*R*)-**94a**



n-BuLi (0.12 mL, 0.29 mmol, 2.5 M in hexane) was added to a mixture of (+)-sparteine (88 mg, 0.38 mmol) and the racemic carbamate **94a** (100 mg, 0.29 mmol) in dry PhMe (8 mL) at –78 °C. After 90 min, EtOCOCl (0.09 mL, 0.87 mmol) was added and the reaction mixture was allowed to warm to room temperature over 16 h and then MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (95:5) to give recovered carbamate (*R*)-**94a** (40 mg, 40%) as an amorphous, off-white solid; m.p. 110–111 °C; data as above; the enantiomeric ratio was determined to be 98:2 by CSP-HPLC (major component eluted at 9.94 min); $[\alpha]_D^{27}$ –15.3 (1.5, $CHCl_3$). In addition, the carbonate **98a** (63 mg, 50%) was isolated as an oil, data as below.

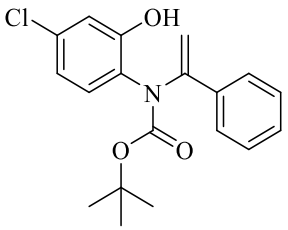
2-[(*tert*-Butoxycarbonyl)(1-phenylethenyl)amino]-5-chlorophenyl ethyl carbonate 98a



Carbamate **98a** (63 mg, 50%) was prepared as described above, as an oil; R_f 0.3 [petrol–EtOAc (90:10)]; FT-IR ν_{max} (ATR)/cm^{-1} 3083, 3060, 3026, 2980, 2933, 1780 (C=O), 1700 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58–7.46 (2H, m, 2 × CH) 7.33−7.25 (4H, m, 4 × CH), 7.23–7.18 (1H, m, CH), 7.13 (1H, dd, *J* = 8.5, 2.0 Hz, CH) 5.21 (1H, brs, C=CH), 4.83 (1H, brs,

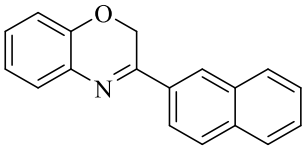
C=CH), 4.18 (2H, q, *J* = 7.0 Hz, CH_2), 1.22 (3H, t, *J* = 7.0, CH_3), 1.16 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, one quaternary carbon single missing) δ = 153.2 (C=O), 153.0 (C=O), 149.1 (C), 146.8 (C), 134.5 (C), 132.5 (C), 129.2 (CH), 128.8 (CH), 128.2 (CH), 127.2 (CH), 126.3 (CH), 124.3 (CH), 110.7 (CH_2), 82.1 (C), 65.5 (CH_2), 28.1 (CH_3), 14.5 (CH_3); HRMS (ES) Found: MNa^+, 440.1230, $C_{22}H_{24}{}^{35}ClNO_5Na$ requires MNa^+, 440.1235; LRMS *m/z* (ES) 442.1 (MNa^+ for ^{37}Cl, 25%), 440.1 (MNa^+ for ^{35}Cl, 75%), 318.1 (100, MH^+-*t*-BuO, ^{35}Cl).

tert-Butyl-_N_-(4-chloro-2-hydroxyphenyl)-_N_-(1-phenylethenyl)carbamate 95a



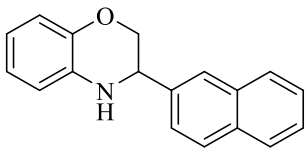
n-BuLi (0.12 mL, 0.29 mmol, 2.5 M) was added to a stirred solution of *N*-Boc-7-chloro-3-phenyl-2,3,4-tetrahydro-1,4-benzoxazine **94a** (100 mg, 0.29 mmol) in dry THF (4 mL) at –78 °C. After 10 min, MeOH (0.03 mL, 0.35 mmol) was added. The mixture was allowed to warm to room temperature over 16 h. After evaporating the solvent, the mixture was purified by column chromatography on silica gel eluting with petrol–EtOAc (97:3), to give the carbamate **95a** (52 mg, 0.15 mmol, 50%) as oil, R_f 0.17 [Petrol–EtOAc (90:10)]; FT-IR ν_{max} (ATR)/cm^{-1} 3255 (O–H), 3065, 2980, 2930, 1666 (C=O), 1510, 1360, 1265, 1165, 1075, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53–7.41 (2H, m, 2 × CH) 7.53–7.41 (3H, m, 3 × CH), 7.40–7.29 (3H, m, 2 × CH+OH), 6.83 (1H, dd, *J* 8.0, 2.5 Hz, CH) 5.62 (1H, s, C=CH), 5.16 (1H, s, C=CH) 1.30 (9H, s, *t*-Bu).

3-(Naphthalen-2-yl)-2H-1,4-benzoxazine 91b



2-Aminophenol (5.0 g, 46 mmol) and $NBu_4^+HSO_4^-$ (2.2 g, 11 mmol) was added to a solution of potassium carbonate (38.0 g, 276 mmol) in water (200 mL) and CH_2Cl_2 (200 mL). The reaction mixture was stirred vigorously and a solution of 2-bromo-2′-acetonaphthone (11.5 g, 46 mmol.) in CH_2Cl_2 (100 mL) was added. After 16 h, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, gave the crude product, which was used without any purification, as a yellow solid, mp 140-142 °C; R_f 0.51 [petrol–EtOAc (85:15)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30–8.14 (2H, m, 2 × CH), 7.97–7.82 (3H, m, 3 × CH), 7.61–7.43 (3H, m, 3 × CH), 7.17 (1H, t, *J* = 7.5 Hz, CH), 7.05 (1H, t, *J* = 7.5 Hz, CH), 6.95 (1H, d, *J* = 7.5 Hz, CH), 5.22 (2H, s, CH_2). Data consistent with the literature.[112]

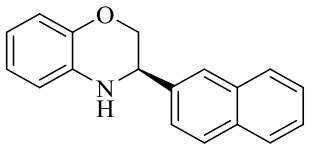
3-(Naphthalen-2-yl)-3,4-dihydro-2H-1,4-benzoxazine 93b



Sodium borohydride (2.9 g, 76 mmol) was added to 3-(naphthalen-2-yl)-2H-1,4-benzoxazine **91** (9.8 g, 37.8 mmol) in ethanol (100 mL) and water (25 mL). The reaction mixture was heated at 90 °C for 5 h and then was cooled to room temperature. The solvent was removed under reduced pressure. The crude mixture was partitioned between CH_2Cl_2 (60 mL) and water (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the amine **93b** (7.99, 30.62 mmol, 81%) as a light yellow solid; m.p. 82–84 °C; R*f* 0.55 [petrol–EtOAc (85:15)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92–7.80 (4H, m, 4 × CH), 7.55–7.46 (3H, m, 3 × CH), 6.92–6.80 (2H, m, 2 × CH), 6.77 – 6.69 (2H, m, 2 × CH), 4.69 (1H, dd, *J* = 8.5, 3.0 Hz, CH), 4.37 (1H, ddd, *J* = 11, 3.0, 2.0 Hz, CH), 4.13 – 4.05 (2H, m, CH & NH).[113]

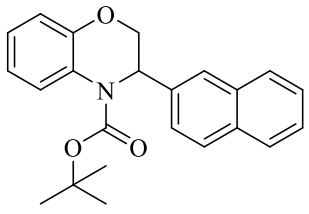
Resolution between the enantiomers of the amine **93** was achieved using a Beckman system fitted with a ChiralPak IA column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99.3:0.7 v/v) as the mobile phase at a flow rate of 1 $mL \cdot min^{-1}$; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 μL of the sample prepared in a 2 $g \cdot L^{-1}$ solution of the eluent. Under these conditions, the components were eluted at 13.7 min and 17.6 min with an analysis time of 30 min.

(3*R*)-3-(naphthalen-2-yl)-3,4-dihydro-2H-1,4-benzoxazine (*R*)-93b



Trifluoroacetic acid (0.04 mL, 0.47 mmol) was added to a solution of the *tert*-Butyl (3*R*)-3-(naphthalen-2-yl)-2,3-dihydro-1,4-benzoxazine-4-carboxylate (*R*)-**94b** (17 mg, 0.05 mmol) in CH_2Cl_2 (5 mL) at room temperature. After 2 d, the solvent was evaporated and NaOH (2 mL, 1 M) was added to basify the residue. The mixture was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried ($MgSO_{4)}$, filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3) to give the amine (*R*)-**93b** (13.1 mg, 100%), as a white solid; m.p. 70–71 °C; the enantiomeric ratio was determined to be 99:1 by CSP-HPLC (major component eluted at 13.0 min); $[\alpha]_D^{27}$ –106 (1.5, $CHCl_3$).

***tert*-Butyl 3-(naphthalen-2-yl)-2,3-dihydro-1,4-benzoxazine-4-carboxylate 94b**

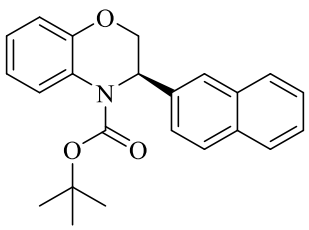


n-BuLi (3.8 mL, 9.6 mmol, 2.5 M) was added to a stirred solution of benzoxazine **93b** (2.5 g, 9.6 mmol) in THF (30 mL) at –78 °C. After 30 min, Boc_2O (2.5 g, 11.5 mmol) in THF (15 mL) was added over 10 min. After allowing the mixture to warm to room temperature gradually

over 16 h, the reaction was quenched with aqueous saturated $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the carbamate **94b** (1.38 g, 3.83 mmol, 40%) as white cubes; m.p. 100–102 °C; R*f* 0.38 [petrol–EtOAc (90:10)]; FT-IR ν_{max} (ATR)/cm^{-1} 3000, 2979, 2930, 1710 (C=O), 1586, 1493, 1368, 1252, 1140, 1065, 764; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.16–8.04 (1H, m, CH), 7.89–7.67 (4H, m, 4 × CH), 7.51–7.36 (3H, m, 3 × CH), 7.02–6.91 (2H, s, 2 × CH), 6.90–6.83 (1H, m, CH), 5.79 (1H, m, CH), 4.68 (1H, dd, *J* = 11.0, 2.5 Hz, CH), 4.45 (1H, dd, *J* = 11.0, 2.5 Hz, CH), 1.49 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, CDCl3) δ = 152.9 (C=O), 146.2 (C), 136.3 (C), 133.3 (C), 132.8 (C), 128.5 (CH), 128.1 (CH), 127.7 (CH), 126.2 (CH), 126.2 (C), 126.0 (CH), 125.5 (CH), 124.7 (CH), 124.1 (CH), 123.2 (CH), 121.3 (CH), 117.2 (CH), 82.1 (C), 68.4 (CH_2), 55 (CH), 28.3 (CH_3); HRMS (ES) Found: MNa^+, 384.1575 $C_{23}H_{23}NO_3Na$ requires MNa^+, 384.1750; LRMS *m/z* (ES) 384.2 (8%, MNa^+), 306.1 (64%), 262.1 (12%, MH+-*t*-BuO), 178.0 (100%).

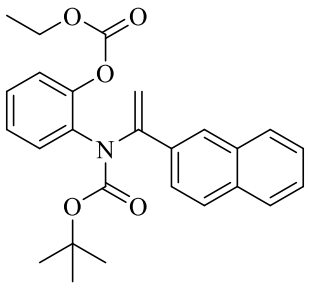
Resolution between the enantiomers of the carbamate **94b** was achieved using a Beckman system fitted with a ChiralPak IA column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99.6:0.4 v/v) as the mobile phase at a flow rate of 1 $mL \cdot min^{-1}$; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 μL of the sample prepared in a 2 $g \cdot L^{-1}$ solution of the eluent. Under these conditions, the components were eluted at 19.4 min and 21.4 min with an analysis time of 15 min.

***tert*-Butyl (3R)-3-(naphthalen-2-yl)-2,3-dihydro-1,4-benzoxazine-4-carboxylate (*R*)-94b**



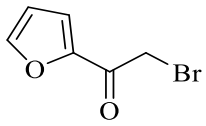
n-BuLi (0.13 mL, 0.34 mmol, 2.5 M in hexane) was added to a mixture of (+)-sparteine (88 mg, 0.38 mmol) and the racemic carbamate **94b** (100 mg, 0.29 mmol) in dry PhMe (8 mL) at –78 °C. After 60 min, EtOCOCl (0.08 mL, 0.84 mmol) was added and the reaction mixture was allowed to warm to room temperature over 16 h and then MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), to give recovered carbamate (*R*)-**94a** (40 mg, 40%) as an amorphous, off-white solid; mp 108–109 °C; data as above; the enantiomeric ratio was determined to be 99:1 by CSP-HPLC (major component eluted at 18.3 min); $[\alpha]_D^{27}$ –45.2 (0.6, $CHCl_3$). In addition, the carbonate **98b** (52 mg, 43%) was isolated as solid, data as below.

2-[(*tert*-Butoxycarbonyl)[1-(naphthalen-2-yl)ethenyl]amino]phenyl ethyl carbonate 98b



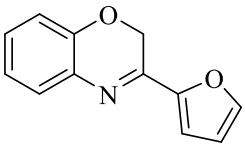
Carbamate **98b** (52 mg, 43%) was prepared as described above, as oil; R_f 0.26 [petrol–EtOAc (90:10)]; FT-IR ν_{max} (ATR)/cm^{-1} 3055, 3005, 2975, 2930, 2870, 1775 (C=O), 1700 (C=O), 1490, 1320, 1250, 1155, 1010, 815, 750; ^{1}H NMR (400 MHz, $CDCl_3$)) δ = 8.08 (1H, brs, CH), 7.90−7.83 (3H, m, 3 × CH), 7.74 (1H, dd, *J* = 8.5, 2.0 Hz, CH), 7.54–7.46 (2H, m, 2 × CH), 7.44 (1H, dd, *J* = 8.0, 1.5 Hz, CH), 7.37–7.22 (3H, m, 3 × CH), 5.45 (1H, s, C=CH), 5.07 (1H, s, C=CH), 4.24 (2H, q, *J* = 7.0 Hz, CH_2), (3H, t, *J* = 7.0, CH_3), 1.19 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.1 (C=O), 153.0 (C=O), 148.8 (C), 146.3 (C), 136.2 (C), 135.4 (C), 133.3 (C), 133.2 (C), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 127.3 (CH), 126.5 (CH), 126.3 (CH), 126.1 (CH), 124.8 (CH), 124.1 (CH), 123.4 (CH), 110.7 (C), 81.4 (C), 64.8 (OCH_2), 27.7 (CH_3), 14.1 (*t*-Bu); HRMS (ES) Found: MNa^+, 456.1794, $C_{26}H_{27}NO_5Na$ requires MNa^+, 456.1781; LRMS *m/z* (ES) 456.2 (80%), 440.1 (23%), 334.1 (100, MH+-*t*-BuO,).

2-Bromo-1-(furan-2-yl)ethanone 90d



Bromine (2.32 mL, 45.4 mmol) was added dropwise to a solution of ketone **92d (**5.0 g, 45.45 mmol) in dry Et_2O (50 mL) at 0 °C. After 3 h at room temperature, the reaction mixture was quenched by adding H_2O (30 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ (25 mL), saturated $Na_2S_2O_3$ (25 mL), brine (25 mL), and then dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (99.5:0.5), gave bromide **90d** (6.87 g, 80%) as an oil; R_f 0.29 [petrol– CH_2Cl_2 (50:50)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66–7.62 (1H, m, CH), 7.37–7.32 (1H, m, CH), 6.60 (1H, dd, *J* = 3.5, 2.0 Hz, CH), 4.32 (2H, s, CH_2). Data consistent with the literature.[114]

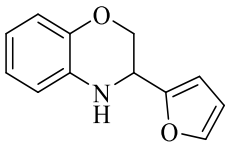
3-(Furan-2-yl)-2H-1,4-benzoxazine 91d



2-Aminophenol (4.18g, 16.8 mmol) and $NBu_4^+HSO_4^-$ (0.8 g 3.86 mmol) were added to a solution of potassium carbonate (14.0 g, 100.68 mmol) in water (50 mL) and CH_2Cl_2 (160 mL) at room temperature. The reaction mixture was stirred vigorously and a solution of 2-bromo-1-(furan-2-yl)ethanone (3.17 g, 16.8 mmol) in CH_2Cl_2 (40 mL) was added. After 16 h, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the furan **91d** (2.40 g , 12.1 mmol, 72%) as a white solid; m.p. 81–83 °C; R_f 0.26 [petrol–EtOAc (90:10)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65–7.62 (1H, m, CH), 7.45 (1H, dd, *J* 7.5, 1.5 Hz, CH), 7.14

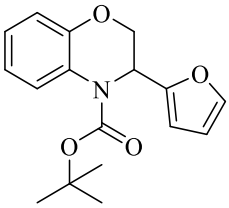
(1H, td, *J* 7.5, 1.5 Hz, CH), 7.05–6.99 (2H, m, 2 × CH), 6.91 (1H, dd, *J* 7.5, 1.5 Hz, CH), 6.58 (1H, dd, *J* 3.5, 1.5 Hz, CH), 4.91 (2H, s, CH_2). Data consistent with the literature.[115]

3-(Furan-2-yl)-3,4-dihydro-2H-1,4-benzoxazine 93d



Sodium borohydride (1.0 g, 24.1 mmol) was added to benzoxazine **91d** (2.4 g, 12.0 mmol) in ethanol (40 mL) and water (20 mL). The reaction mixture was heated at 90 °C for 4 h and then was cooled to room temperature. The solvent was removed under reduced pressure. The crude mixture was extracted between CH_2Cl_2 (60 mL) and water (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the amine **93d** (1.99 g, 82%) as an oil; R_f 0.38 [Petrol–EtOAc (90:10)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42–7.37 (1H, m, CH), 6.88–6.79 (2H, m, 2 × CH), 6.76–6.63 (2H, m, 2 × CH), 6.38–6.37 (2H, m, 2 × CH), 4.64 (1H, dt, *J* = 7.0, 3.0 Hz, CH) 4.43 (1H, ddd, *J* = 11.0, 3.0, 1.5 Hz, CH) 4.25 (1H, dd, *J* = 11.0, 7.0 Hz, CH), 4.08 (1H, brs, NH). Data consistent with the literature.[115]

tert-butyl 3-(furan-2-yl)-2,3-dihydro-1,4-benzoxazine-4-carboxylate 94d

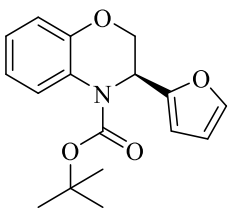


n-BuLi (3.5 mL, 8.35 mmol, 2.4 M) was added to benzoxazine **93d** (1.68 g, 8.35 mmol) in THF (20 mL) at –78 °C. After 30 min, Boc_2O (1.82 g, 8.35 mmol) in THF (10 mL) was added over 5 min. After allowing the mixture to warm to room temperature gradually over 16 h, the reaction was quenched with aqueous saturated $NaHCO_3$ (30 mL). The aqueous layer was

extracted with Et_2O (3 × 50 mL). The combined organic layers were dried (MgSO4), filtered, concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), to give the carbamate **94d** (1.61 g, 5.34 mmol, 64%) as white solid; m.p. 69–71 °C R*f* 0.75 [petrol–EtOAc (90:10)]; FT-IR ν_{max} (ATR)/cm^{-1} 3149, 3119, 2959, 2918, 2856, 1680 (C=O), 1584, 1491, 1364, 1255, 1152, 1013, 850; ^{1}H NMR (400 MHz, CDCl3) δ = 7.9 (1H, d, *J* = 7.8 Hz, CH), 7.32–7.30 (1H, m, CH), 7.00 – 6.93 (1H, m, CH), 6.92 – 6.82 (2H, m, 2 × CH), 6.23–6.21 (1H, m, CH), 6.09 – 6.07 (1H, m, CH), 5.75 (1H, s, CH), 4.67 (1H, dd, *J* = 11.0, 1.70 Hz, CH), 4.29 (1H, dd, *J* = 11.0, 3.0 Hz, CH), 1.55 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, CDCl3) δ = 152.4 (C=O), 151.1 (C), 154.3(C), 142.0 (CH), 124.8 (C), 124.4 (CH), 123.6 (CH), 120.8 (CH), 1117.0 (CH), 110.5 (CH), 107.7 (CH), 82.3 (C), 66.7 (CH_2), 48.9 (CH), 28.4 (CH_3); HRMS (ES) Found: MNa+, 324.1208 $C_{17}H_{19}NO_4Na$ requires MNa+, 324.1206; LRMS *m/z* (ES) 324.1208 (3%, MNa+), 202.0865 (7%, MH+-*t*-BuO), 178.0500 (41%) 134.0601 (100%).

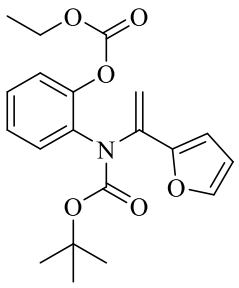
Resolution between the enantiomers of the carbamate **94d** was achieved using a Beckman system fitted with a ChiralPak IA column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99.6:0.4 v/v) as the mobile phase at a flow rate of 1 $mL \cdot min^{-1}$; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 μL of the sample prepared in a 2 $g \cdot L^{-1}$ solution of the eluent. Under these conditions, the components were eluted at 10.1 min and 13.0 min with an analysis time of 15 min.

tert-Butyl (3S)-3-(furan-2-yl)-2,3-dihydro-1,4-benzoxazine-4-carboxylate (*S*)-94d



n-BuLi (0.09 mL, 0.23 mmol, 2.5 M in hexane) was added to a stirred solution of (+)-sparteine (70 mg, 0.30 mmol) and the racemic carbamate **94d** (100 mg, 0.33 mmol) in dry PhMe (8 mL) at –78 °C. After 30 min, EtOCOCl (0.1 mL, 0.99 mmol) was added and the reaction mixture was allowed to warm to room temperature over 16 h and the then MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (95:5) to give recovered carbamate (*S*)-**94d** (43 mg, 43%) as an amorphous off-white solid; m.p. 71–73 °C; data as above; the enantiomeric ratio was determined to be 80:20 by CSP-HPLC (major component eluted at 13.0 min); $[\alpha]_D^{21}$ –20.5 (2, $CHCl_3$). In addition, the carbonate **97d** (64 mg, 52%) was isolated as an oil, data as below.

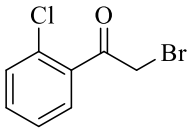
2-[(*tert*-Butoxycarbonyl)[1-(furan-2-yl)ethenyl]amino]phenyl ethyl carbonate 97d



Carbamate **97d** (64 mg, 52%) was prepared as described above, as oil; R_f 0.35 [petrol–EtOAc (90:10)]; FT-IR ν_{max} (ATR)/cm^{-1} 3642, 2984, 2932, 1763 (C=O), 1698(C=O), 1614, 1525 1202, 1096, 897, 769; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 (1H, brs, CH), 7.37−7.33 (1H, m, CH), 7.30−7.26 (2H, m, 2 × CH), 7.23–7.18 (1H, m, CH), 6.51 (1H, d, *J* = 3.3 Hz, CH), 6.43 (1H, dd, *J* = 3.3, 1.8 Hz, CH), 5.25 (1H, s, C=CH), 5.10 (1H, s, C=CH), 4.30 (2H, q, *J* = 7.0 Hz, CH_2), 1.39 (9H, brs, *t*-Bu), 1.36 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, two quaternary carbon could not be observed) δ = 153.1 (C=O), 152.8 (C=O), 146.3 (C), 142.2 (CH), 138.8 (C), 127.7 (CH), 127.4 (CH), 126.4 (CH), 123.3 (CH), 111.4 (CH), 109.9 (=CH_2), 107.5 (CH), 81.3 (C), 64.79 (OCH_2), 27.9 (CH_3), 14.2 (*t*-Bu); HRMS (ES) Found: MNa^+,

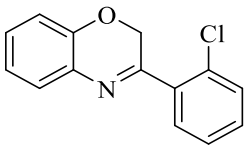
396.1430, $C_{20}H_{23}NO_6Na$ requires MNa^+, 396.1418; LRMS *m/z* (ES) 396.1 (MNa^+, 100%), 274.1 (MH^+-*t*-Bu, 72%).

2-Bromo-1-(2-chlorophenyl)ethanone 90c



Bromine (3.3 mL, 65.0 mmol) was added dropwise to a solution of ketone **92c** (10.0 g, 65.5 mmol) in dry Et_2O (70 mL) at 0 °C. After 3 h at room temperature, the reaction mixture was quenched by adding H_2O (40 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ (25 mL), saturated $Na_2S_2O_3$ (25 mL), brine (25 mL), and then dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (99:1), gave bromide **37c** (12.0 g, 80%) as an oil; R_f 0.45 [petrol–EtOAc (90:10)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.63–7.55 (1H, m, CH) 7.49–7.43 (2H, m, 2 × CH), 7.41–7.33 (1H, m, CH), 4.52 (2H, brs, CH_2). Data consistent with the literature.[114]

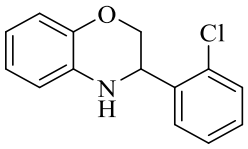
3-(2-Chlorophenyl)-2H-1,4-benzoxazine 91c



2-Aminophenol (10.5 g, 31.0 mmol) and $NBu_4^+HSO_4^-$ (4.4 g, 13 mmol) was added to a solution of potassium carbonate (21 g, 156 mmol) in water (100 mL) and CH_2Cl_2 (100 mL). The reaction mixture was stirred vigorously and a solution of 2-bromo-2′-chloroacetophenone (6.0 g, 26.0 mmol) in CH_2Cl_2 (50 mL) was added. After 16 h, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the benzoxazine **91c** (5.4 g, 85%) as an oil; R_f 0.5

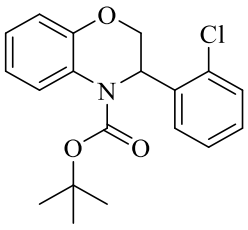
[petrol–EtOAc (90:10)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73–7.66 (1H, m, CH) 7.48–7.35 (4H, m, 4 × CH), 7.20 (1H, td, *J* = 7.5, 1.5 Hz, CH), 7.10 (1H, td, *J* = 7.5, 1.5 Hz, CH) 6.96 (1H, dd, *J* = 7.5, 1.5 Hz, CH), 4.95 (2H, brs, CH_2). Data consistent with the literature.[115]

3-(2-chlorophenyl)-3,4-dihydro-2H-1,4-benzoxazine 93c



Sodium borohydride (1.25 g, 32.9 mmol) was added to benzoxazine **91c** (4.0 g, 16.5 mmol) in ethanol (60 mL) and water (30 mL). The reaction mixture was heated at 90 °C for 4 h and then was cooled to room temperature. The solvent was removed under reduced pressure. The crude mixture was extracted between CH_2Cl_2 (60 mL) and water (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the amine **93c** (3.0 g, 75%) as an oil; R*f* 0.53 [Petrol–EtOAc (90:10)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58 (1H, dd, *J* = 7.5, 2.0 Hz, CH), 7.44 (1H, dd, *J* = 7.5, 2.0 Hz, CH), 7.37–7.23 (2H, m, 2 × CH), 6.93–6.83 (2H, m, 2 × CH), 6.80–9.70 (2H, m, 2 × CH), 5.05 (1H, dt, *J* = 7.0, 3.0 Hz, CH), 4.43 (1H, ddd, *J* = 11.0, 3.0, 1.5 Hz, CH) 4.09–3.95 (2H, m, CH&NH). Data consistent with the literature.[115]

***tert*-Butyl 3-(2-chlorophenyl)-2,3-dihydro-1,4-benzoxazine-4-carboxylate 94c**

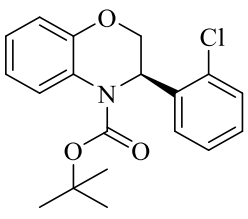


n-BuLi (6.1 mL, 14.6 mmol, 2.4 M) was added to a stirred solution of amine **91c** (3.0 g, 12.2 mmol) in THF (30 mL) at –78 °C. After 30 min, Boc_2O (3.0 g, 13.4 mmol) in THF (15 mL) was added over 10 min. After allowing the mixture to warm to room temperature gradually

over 16 h, the reaction was quenched with aqueous saturated $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), gave the carbamate **94c** (3.6 g, 85%) as a white needles; m.p. 110–112 °C; R_f 0.43 [petrol–EtOAc (90:10)]; FT-IR ν_{max} (ATR)/cm^{-1} 3063, 2930, 2875, 2970, 1714 (C=O), 1490, 1587, 1336, 1148, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (1H, d, *J* = 8.0 Hz, CH), 7.41 (1H, dd, *J* = 8.0, 1.5 Hz, CH), 7.22 (1H, td, *J* = 8.0, 1.5 Hz, CH), 7.17–7.08 (2H, m, 2 × CH), 7.07–6.98 (2H, m, 2 × CH), 6.95–6.91 (1H, m, CH), 5.91 (1H, t, *J* = 3.0 Hz, CH), 4.39 (1H, dd, *J* = 11.0, 3.0 Hz, CH), 4.30 (1H, dd, *J* = 11.0, 3.0 Hz, CH), 1.37 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.3 (C=O), 146.4 (C), 137.6 (C), 131.7 (C), 129.6 (CH), 128.7 (CH), 127.8 (C), 127.4 (CH), 127.1 (CH), 123.4 (CH), 122.0 (CH), 121.4 (CH), 117.4 (CH), 82.0 (C), 67.2 (CH_2), 55.0 (CH), 28.0 (CH_3); HRMS (ES) Found: MNa^+, 368.1027. $C_{19}H_{20}{}^{35}ClNO_3Na$ requires MNa^+, 368.1024; LRMS *m/z* (ES) 370.1 (MNa^+ for ^{37}Cl, 25%), 368.1 (MNa^+ for ^{35}Cl, 75%), 290 (100, MH^+-*t*-BuO, ^{37}Cl), 246 (10, MH^+-Boc,^{37}Cl).

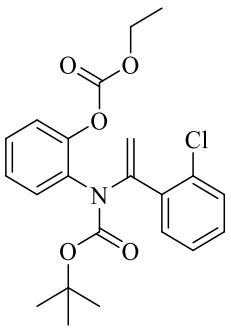
Resolution between the enantiomers of the carbamate **94c** was achieved using a Beckman system fitted with a ChiralPak IA column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 0.5 $mL \cdot min^{-1}$; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 μL of the sample prepared in a 2 $g \cdot L^{-1}$ solution of the eluent. Under these conditions, the components were eluted at 5.3 min and 7.3 min with an analysis time of 15 min.

tert-Butyl (3R)-3-(2-chlorophenyl)-2,3-dihydro-1,4-benzoxazine-4-carboxylate (*R*)-94c



n-BuLi (0.07 mL, 0.17 mmol, 2.5 M in hexane) was added to a stirred solution of (+)-sparteine (80 mg, 0.29 mmol) and the racemic carbamate **94c** (100 mg, 0.29 mmol) in dry PhMe (8 mL) at –78 °C. After 60 min, EtOCOCl (0.09 mL, 0.87 mmol) was added and the reaction mixture was allowed to warm to room temperature over 16 h and then MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), to give recovered carbamate (*R*)-**94a** (41 mg, 41%) as an amorphous off-white solid; m.p. 89–91 °C; data as above; the enantiomeric ratio was determined to be 75:25 by CSP-HPLC (major component eluted at 8.60 min); $[\alpha]_D^{23}$ +35.4 (1.95, $CHCl_3$). In addition, the carbonate **98d** (63 mg, 53%) was isolated as a solid, data as below.

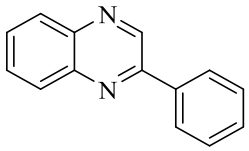
2-[(*tert*-Butoxycarbonyl)[1-(2-chlorophenyl)ethenyl]amino]phenyl ethyl carbonate 98d



Carbamate **98d** (63 mg, 53%) was prepared as described above, as solid; m.p. 73–74 °C; R_f 0.36 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (ATR)/cm^{-1} 3069, 2999, 2978, 2933, 1765 (C=O), 1711(C=O), 1091, 799; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58–7.53 (2H, m, 2 × CH) 7.41−7.36 (1H, m, CH), 7.33–7.20 (5H, m, 5 ×CH), 5.00 (1H, brs, C=CH), 4.93 (1H, brs, C=CH), 4.30 (2H, q, *J* = 7.0 Hz, CH_2), 1.35 (3H, t, *J* = 7.0, CH_3), 1.23 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.0 (C=O), 152.0 (C=O), 147.0 (C), 145.2 (C), 137.8 (C), 134.5 (C),132.1 (C) 130.3 (CH), 129.9 (CH), 128.9 (CH), 128.8 (CH), 127.8 (CH), 126.6 (CH), 126.6 (CH), 123.1 (CH), 110.8 (CH_2), 81.4 (C), 64.8 (CH_2), 27.7 (CH_3), 14.2 (CH_3); HRMS (ES) Found: MNa^+,

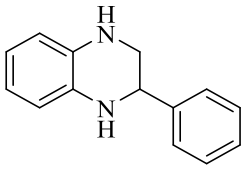
440.1233, $C_{22}H_{24}{}^{35}ClNO_5Na$ requires MNa^+, 440.1235; LRMS *m/z* (ES) 442.1 (MNa^+ for ^{37}Cl, 25%), 440.1 (MNa^+ for ^{35}Cl, 75%), 318.1 (100, MH^+-*t*-Boc, ^{35}Cl).

2-Phenyl-quinoxaline 102a



Pyridine (3 mL, 3.8 mmol) was added to a solution of phenacyl bromide (5.0 g, 25.1 mmol) in THF (60 mL). The mixture was left to stir for 20 min until it became light green and *o*-phenylenediamine (3.25 g, 30.2 mmol) was added in one portion. After16 h, the solvent was removed under reduced pressure. The mixture was extracted between CH_2Cl_2 (2 × 100 mL) and water (30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the quinoxaline **102a** (2.40 g, 81%) as a yellow solid; m.p. 73–75 °C R_f 0.47 [petrol–EtOAc (95:5)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.25 (1H, s, CH) 8.22–7.99 (4H, m, 4 × CH), 7.77–7.57 (2H, m, 2 × CH), 7.56–7.31 (3H, m, 3 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.6 (C), 143.2 (CH), 142.2 (C), 141.5 (C), 136.7(C), 130.2 (CH), 130.1 (CH), 129.6 (CH), 129.4 (CH), 129.1 (CH), 129.0 (CH), 127.5 (CH). Data consistent with the literature.[116]

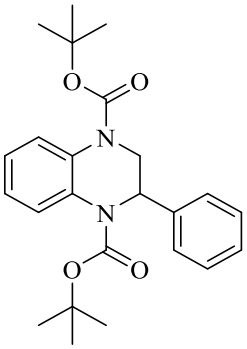
2-Phenyl-1,2,3,4-tetrahydroquinoxaline 103a



$NaBH_4$ (1.8g, 48.8 mmol) was added a portionwise to 2-phenyl quinoxaline **101a** (2.51 g, 12.2 mmol) in AcOH (75 mL) at 0 °C. The reaction was monitored by TLC (CH_2Cl_2/AcOH, 3:1). After 15 min, the starting material was completely consumed and the mixture was diluted with water (80 mL) and washed with CH_2Cl_2 (50 mL). The aqueous layer was

treated with aqueous NaOH (50 mL, 5 M) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the 2-phenyl-1,2,3,4-tetrahydroquinoxaline **103a** (1.59 g, 7.58 mmol, 62%) as a yellow solid; m.p. 76–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44–7.28 (5H, m, 5 × CH) 6.68–6.61 (2H, m, 2 × CH), 6.61–6.54 (2H, m, 2 × CH), 4.49 (1H, dd, *J* 8.0, 3.0 Hz, CH), 3.99–3.77 (2H, m, 2 × NH), 3.47 (1H, dd, *J* 11.0, 3.0 Hz, CH), 3.36 (1H, dd, *J* 11.0, 8.0 Hz, CH). Data consistent with the literature.[117]

1,4-di-*tert*-Butyl 2-phenyl-2,3-dihydroquinoxaline-1,4-dicarboxylate 104a

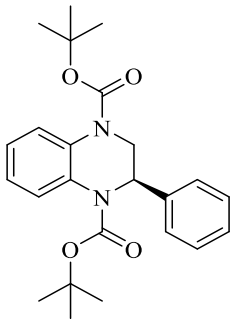


n-BuLi (7.86 mL, 18.8 mmol, 2.4 M) was added to a stirred solution of tetrahydroquinoxaline **102a** (1.8 g, 8.6 mmol) in THF (35 mL) at –78 °C. After 20 min, Boc_2O (4.0 g, 18.8 mmol) in THF (10 mL) was added over 5 min. After allowing the mixture to warm to room temperature gradually over 18 h, the reaction was quenched with a saturated $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the carbamate **104a** (2.99 g, 7.3 mmol, 85%) as white needles; m.p. 166–167 °C; R_f 0.73 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (ATR)/cm^{-1} 3008, 2925, 1714 (C=O), 1716 (C=O), 1600, 1499, 1250, 1140, 1065, 765; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11 (1H, d, *J* = 8.0, CH), 7.52 (1H, brs, CH), 7.33–7.20 (5H, m, 5 × CH), 7.17–7.12 (1H, m, CH), 7.08–7.03 (1H, m, CH), 5.40 (1H, t, *J* = 5.0 Hz, CH), 4.04–3.75 (2H, brs, 2 × CH), 1.35

(9H, s, *t*-Bu), 1.26 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, one quaternary carbon could not be observed) δ = 153.1 (C=O), 152.5 (C=O), 141.8 (C), 132.09 (C), 128.5 (2 × CH), 127.2 (CH), 125.7 (2 × CH), 124.4 (CH), 124.1 (CH), 123.0 (CH), 122.7 (CH), 81.5 (C), 81.0 (C), 61.4 (CH), 49.4 (CH_2), 28.1 (CH_3), 27.9 (CH_3); HRMS (ES) Found: MNa^+, 433.2103 $C_{24}H_{30}N_2O_4Na$ requires MNa^+, 433.2098; LRMS *m/z* (ES) 433 (9%, MNa^+), 299 (100%, MH^+-*t*-Bu^+H), 211 (46%, MH^+-Boc^+H).

Resolution between the enantiomers of the carbamate **104a** was achieved using a Beckman system fitted with a Lux Cellulose-2 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99.4:0.6 v/v) as the mobile phase at a flow rate of 0.8 $mL \cdot min^{-1}$; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 μL of the sample prepared in a 2 $g \cdot L^{-1}$ solution of the eluent. Under these conditions, the components were eluted at 11.9 min and 15.5 min with an analysis time of 20 min.

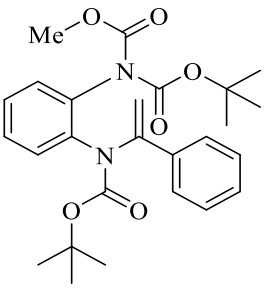
1,4-Di-*tert*-butyl (2*R*)-2-phenyl-2,3-dihydroquinoxaline-1,4-dicarboxylate (*R*)-103a



n-BuLi (86 μL, 0.22 mmol, 2.5 M in hexane) was added to a mixture of (+)-sparteine (68 mg, 0.29 mmol) and the racemic carbamate **104a** (100 mg, 0.24 mmol) in dry PhMe (8 mL) at –78 °C. After 60 min, EtOCOCl (60 μL, 0.72 mmol) was added and the reaction mixture was allowed to warm to room temperature over 16 h and then MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting

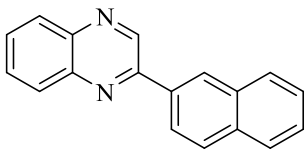
with petrol–EtOAc (95:5) to give recovered carbamate (*R*)-**104a** (48 mg, 48%) as a white needles; m.p. 177–178 °C; data as above; the enantiomeric ratio was determined to be 94:6 by CSP-HPLC (major component eluted at 11.8 min); $[\alpha]_D^{23}$ –8.2 (0.85, $CHCl_3$). In addition, the carbamate **106** (45 mg, 40%) was isolated as an oil, data as below.

***tert*-Butyl *N*-{2-[(*tert*-butoxycarbonyl)(methoxycarbonyl)amino]phenyl}-*N*-(1-phenylethenyl)carbamate 106a**



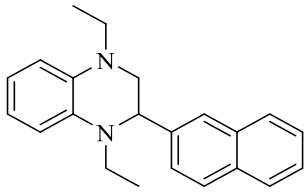
Dicarbamate **106** (45 mg, 40%) was prepared as described above, as an oil; R_f 0.39 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (ATR)/cm^{-1} 3062, 2979, 2933, 1790 (C=O), 1758 (C=O), 1716 (C=O), 1497, 1346, 1252, 1120, 1027, 854, 770; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58–7.47 (2H, m, 2 × CH), 7.39−7.25 (7H, m, 7 × CH), 5.16 (1H, s, CH), 4.92 (1H, s, CH), 3.68 (1H, s, CH_3), 1.42 (9H, s, *t*-Bu), 1.17 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.3 (C=O), 153.0 (C=O), 151.2 (C=O), 148.5 (C), 140.5 (C), 139.4 (C), 134.9 (C), 130.8 (CH), 129.1 (CH), 128.9 (CH), 128.2 (CH), 128.0 (CH), 127.0 (CH), 125.9 (CH), 109.9 (CH_2), 83.2 (C), 81.4 (C), 53.5 (CH_3), 27.8 (CH_3), 27.7 (CH_3); HRMS (ES) Found: MNa^+, 491.2156, $C_{26}H_{32}N_2O_6Na$ requires MNa^+, 491.2153; LRMS *m/z* (ES) 491.2 (38%, MNa^+), 369.2 (14%, MH^+-Boc) 269.1 (100%, MH^+-2 ×Boc).

2-(Naphthalen-2-yl)quinoxaline 102b



2-Bromo-2′-acetonaphthone (4.0 g, 16.1 mmol) was added to *o*-phenylenediamine (2.1 g, 19.3 mmol) in polyethylene glycol (PEG-400) (80 mL). The reaction mixture was heated at 80 °C for 5 h and then was cooled to room temperature. The reaction was quenched with H_2O (50 mL) and was extracted with EtOAc (3 ×60 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the quinoxaline **102b** (3.9 g, 95%) as a yellow solid; m.p. 133–135 °C R_f 0.46 [petrol–EtOAc (80:20)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.49 (1H, s, CH), 8.67 (1H, s, CH), 8.38 (1H, dd, *J* = 8.5, 1.5 Hz, CH), 8.21 (1H, d, *J* = 8.0 Hz, CH), 8.15 (1H, d, *J* = 8.0 Hz, CH), 8.08–7.96 (2H, m, 2 × CH), 7.95–7.87 (1H, m, CH), 7.87–7.68 (2H, m, 2 × CH), 7.62–7.44 (2H, m, 2 × CH). Data consistent with the literature.[71]

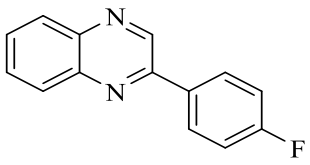
1,4-Diethyl-2-(naphthalen-2-yl)-2,3-dihydroquinoxaline 105b



$NaBH_4$ (1.2 g, 31.2 mmol) was added to 2-(naphthalen-2-yl)quinoxaline **101b** (2.0 g, 7.8 mmol) in AcOH (40 mL) at 0 °C. The reaction was monitored by TLC (CH_2Cl_2/AcOH, 3:1). After 15 min, the starting material was completely consumed and the mixture was diluted with water (80 mL) and washed with CH_2Cl_2 (50 mL). The aqueous layer was treated with aqueous NaOH (50 mL, 5 M) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave tetrahydroquinoxaline **105b** (2.1 g, 85%) as an oil; R_f 0.63 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (ATR)/cm^{-1} 3056, 2982, 2979, 2830, 1592, 1475, 1346, 1129, 895, 784; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02–7.94 (3H, m, 3 × CH), 7.91 (1H, brs, CH), 7.69–7.55 (3H, m, 3 × CH), 7.02–6.83 (4H, m, 4 × CH), 4.89 (1H, t, *J* = 4.0 Hz, CH),

3.64 (1H, dq, *J* = 14.0, 7.0 Hz, CH), 3.55 (1H, dd, *J* = 11.0, 4.0 Hz, CH), 3.50–3.37 (3H, m, 3 × CH), 3.31 (1H, dq, *J* = 14.0, 7.0 Hz, CH), 1.25 (3H, t, *J* = 7.0 Hz, CH_3), 1.23 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.8 (C), 135.8 (C), 135.3 (C), 133.5 (C), 133.2 (C), 128.3 (CH), 128.1 (CH), 127.9 (CH), 126.3 (CH), 125.9 (CH), 125.9 (CH), 125.7 (CH), 118.7 (CH), 117.0 (CH), 111.5 (CH), 110.7 (CH), 61.0 (CH), 53.1 (CH_2), 45.3 (CH_2), 43.4 (CH_2), 11.2 (CH_3), 10.6 (CH_3); HRMS (ES) Found: MH^+, 317.2013, $C_{22}H_{25}N_2$ requires MH^+, 317.2012; LRMS *m/z* (ES) 316.2 (100%, MH^+), 302.2 (8%, MH^+-Me) 265.2 (5%), 209.1 (4%).

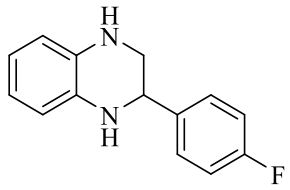
2-(4-Fluorophenyl)quinoxaline 102c



Pyridine (0.22 mL, 3.77mmol) was added to a solution of phenacyl bromide (3.0 g, 13.8 mmol) in THF (40 mL). The mixture was left to stir for 15 min and *o*-phenylenediamine (1.5 g, 13.83 mmol) was added in one portion. After 16 h, the solvent was evaporated. the mixture was extracted between CH_2Cl_2 (2 × 100 mL) and water (30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the quinoxaline **102c** (1.92 g, 62%) as a yellow solid; m.p. 129–131 °C; R_f 0.41 [petrol–EtOAc (80:20)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.32 (1H, s, CH), 8.26–8.20 (2H, m, 2 × CH), 8.18–8.11 (2H, m, 2 × CH), 7.81–7.74 (2H, m, 2 × CH), 7.32–7.23 (2H, m, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.5 (d, *J* = 251.5 Hz, C), 150.8 (C), 143.0 (CH), 142.2 (C), 141.5 (C), 133.0 (d, *J* = 3.0 Hz, C), 130.4 (CH), 130.0 (CH), 129.6 (CH), 129.5 (d, *J* = 8.0 Hz, CH), 129.2 (CH), 116.4 (d, *J* = 23.4 Hz, CH); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 110.55; HRMS (ES) Found: MH^+, 225.0824, $C_{14}H_{10}FN_2$ requires MH^+, 225.0823; LRMS *m/z* (ES) 225.1 (100%, MH^+). ^{1}H NMR data consistent with the literature.[118]

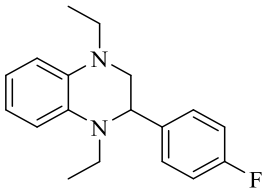
Alternatively, 2-bromo-4′-fluoroacetophenone (1.0 g, 4.61 mmol) was added to *o*-phenylenediamine (0.4 g, 4.61 mmol) in polyethylene glycol (PEG-400) (20 mL). The reaction mixture was heated at 80 °C for 3 h and then was cooled to room temperature. The reaction was quenched with H_2O (15 mL) and was extracted with EtOAc (3 ×30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the quinoxaline **102c** (0.39 g, 38%).

2-(4-Fluorophenyl)-1,2,3,4-tetrahydroquinoxaline 103c



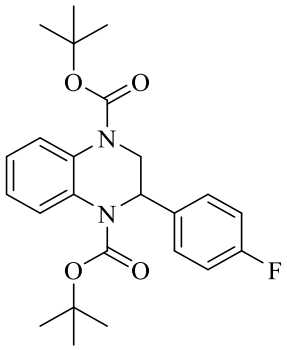
$NaBH_4$ (1.1 g, 28.4 mmol) was added a portion to quinoxaline **102c** (1.6 g, 7.14 mmol) in AcOH (40 mL) at 0 C. The reaction was monitored by TLC (CH_2Cl_2/AcOH, 3:1). After 10 min, the starting material was completely consumed and the mixture was diluted with water (80 mL) and washed with CH_2Cl_2 (1 × 50 mL). The aqueous layer was treated with aqueous NaOH (50 mL, 5 M) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), to give the tetrahydroquinoxaline **103c** (1.14 g, 4.99 mmol, 70%) as yellow solid m.p. 96–98 °C; R_f 0.16 [petrol–EtOAc (80:20)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42–7.34 (2H, m, 2 × CH), 7.14–7.04 (2H, m, 2 × CH), 6.71–6.57 (4H, m, 4 × CH), 4.50 (1H, dd, *J* = 8.0, 3.0 Hz, CH), 3.89 (2H, brs, 2 × NH), 3.46 (1H, dd, *J* = 11.0, 3.0 Hz, CH) 3.32 (1H, dd, *J* = 11.0, 8.0 Hz, CH); HRMS (ES) Found: MH^+, 229.1135, $C_{14}H_{14}FN_2$ requires MH^+, 229.1136; LRMS *m/z* (ES) 229.1 (100%, MH^+). Data consistent with the literature.[119] In addition, the side product **105c** (0.4 g, 20%) was isolated as an oil, data as below.

1,4-Diethyl-2-(4-fluorophenyl)-2,3-dihydroquinoxaline 105c



Side product **105c** (0.4 g, 20%) was prepared as described above, as oil; R_f 0.6 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (ATR)/cm^{-1} 3053, 2972, 2939, 2939, 2855, 1583, 1502, 1474, 1345, 1242, 1013, 843, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27–7.21 (2H, m, 2 × CH) 7.04–6.96 (2H, m, 2 × CH), 6.79–6.64 (4H, m, 4 × CH), 4.55 (1H, t, *J* = 4.0 Hz, CH), 3.42 (1H, dq, *J* = 14.0, 7.0 Hz, CH), 3.34 (1H, dd, *J* = 11.0, 4.0 Hz, CH), 3.31–3.19 (2H, m, 2 × CH), 3.19–3.05 (2H, m, 2 × CH), 1.07 (6H, t, *J* = 7.0 Hz, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.1 (d, *J* = 246.75 Hz, C), 139.1 (C), 135.4 (C), 135.0 (C), 128.0 (CH), 118.6 (CH), 116.8 (CH), 115.1 (d, *J* = 21.39 Hz, CH), 11.8 (CH), 110.5 (CH), 60.1 (CH), 52.9 (CH_2), 45.1 (CH_2), 43.4 (CH_2), 11.2 (CH_3), 10.5 (CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 115.7; HRMS (ES) Found: MH^+, 285.1760, $C_{18}H_{22}FN_2$ requires MH^+, 285.1762; LRMS *m/z* (ES) 285.2 (100%, MH^+).

1,4-Di-*tert*-butyl 2-(4-fluorophenyl)-2,3-dihydroquinoxaline-1,4-dicarboxylate 104c

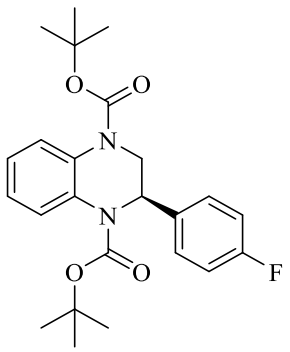


n-BuLi (4.21 mL, 9.68 mmol, 2.3 M) was added to a stirred solution of tetrahydroquinoxaline **103c** (1.0 g, 4.4 mmol) in THF (30 mL) at –78 °C. After 20 min, Boc_2O (2.1 g, 9.86 mmol) in THF (10 mL) was added over 5 min. After allowing the mixture to warm to room temperature gradually over 18 h, the reaction was quenched with a saturated $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were

dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the dicarbamate **104c** (1.13 g, 2.64 mmol, 60%) as white needles; m.p. 180–182 °C; R_f 0.43 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (ATR)/cm^{-1} 2971, 1710 (C=O), 1692 (C=O), 1499, 1390, 1139, 1014, 767; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.09 (1H, d, *J* = 8.0 Hz, CH), 7.51 (1H, brs, CH), 7.23–7.11 (3H, m, 3 × CH), 7.09–6.96 (3H, m, 3 × CH), 5.46 (1H, t, *J* = 5.0 Hz, CH), 3.99–3.57 (2H, brs, 2 × CH), 1.38 (9H, s, *t*-Bu), 1.30 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, one quaternary carbon could not be observed) δ = 160.8 (d, *J* = 259.0 Hz, C), 153.0 (C=O), 152.5 (C=O), 137.6 (C), 131.8 (C), 127.4 (d, *J* = 8.29 Hz, CH), 124.5 (CH), 124.1 (CH), 123.0 (CH), 122.8 (CH), 115.4 (d, *J* = 21.4 Hz, CH), 81.7 (C), 81.2 (C), 60.7 (CH), 49.3 (CH_2), 28.1 (CH_3), 27.9 (CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 115.45; HRMS (ES) Found: MNa^+, 451.2012 $C_{24}H_{29}FN_2O_4Na$ requires MNa^+, 451.2004; LRMS *m/z* (ES) 451.2 (36%, MNa^+), 317.1 (100%, MH^+-Boc^+H), 273.1 (23%), 229.1 (34%, MH^+-2×Boc^+H).

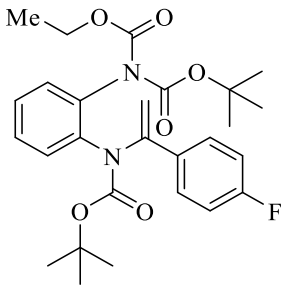
Resolution between the enantiomers of the carbamate **104c** was achieved using a Beckman system fitted with a Lux Cellulose-4 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99.2:0.8 v/v) as the mobile phase at a flow rate of 0.5 $mL \cdot min^{-1}$; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 μL of the sample prepared in a 2 $g \cdot L^{-1}$ solution of the eluent. Under these conditions, the components were eluted at 18.7 min and 23.0 min with an analysis time of 30 min.

1,4-Di-*tert*-Butyl (2*R*)-2-(4-Fluorophenyl)-2,3-dihydroquinoxaline-1,4-dicarboxylate (*R*)-104c



n-BuLi (90 µL, 0.21 mmol, 2.3 M in hexane) was added to a mixture of (+)-sparteine (70 mg, 0.28 mmol) and the racemic dicarbamate **104c** (100 mg, 0.23 mmol) in dry PhMe (8 mL) at –78 °C. After 60 min, EtOCOCl (60 µL, 0.72 mmol) was added and the reaction mixture was allowed to warm to room temperature over 16 h and then MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (95:5) to give recovered dicarbamate (*R*)-**103c** (48 mg, 48%) as white needles; mp 179–181 °C; data as above; the enantiomeric ratio was determined to be 96:4 by CSP-HPLC (major component eluted at 18.7 min); $[\alpha]_D^{21}$ –19.2 (1.3, $CHCl_3$). In addition, the dicarbamate **107** (50 mg, 43%) was isolated as an oil, data as below.

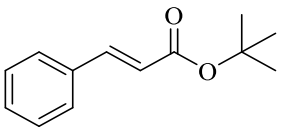
***tert*-Butyl N-{2-[(*tert*-butoxycarbonyl)(ethoxycarbonyl)amino]phenyl}-N-[1-(4-fluorophenyl)ethenyl]carbamate 107c**



Dicarbamate **107** (50 mg, 43%) was prepared as described above, as an oil; R_f 0.26 [petrol–EtOAc (80:20)]; FT-IR ν_{max} (ATR)/cm^{-1} 3073, 2992, 2916, 1793 (C=O), 1750 (C=O), 1695 (C=O), 1540, 1218, 842; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52–7.45 (2H, m, 2 × CH), 7.40–

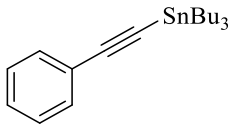
7.35 (2H, m, 2 × CH), 7.35–7.25 (2H, m, 2 × CH), 7.10–7.01 (2H, m, 2 × CH), 5.09 (1H, s, CH), 4.38 (1H, s, CH), 4.28–3.99 (2H, m, CH_2), 1.40 (9H, s, *t*-Bu), 1.19 (9H, s, *t*-Bu) 0.97–0.87 (3H, m, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, one aromatic carbon could not be observed) δ = 163.0 (d, *J* = 259.05 Hz, C), 153.1 (C=O), 152.6 (C=O), 151.1 (C=O), 147.2 (C), 140.3 (C), 134.8 (C), 130.9 (CH), 129.3 (CH), 128.0 (CH), 127.5 (d, *J* = 8.1 Hz, CH), 127.1 (CH), 115.0 (d, *J* = 21.0 Hz, CH), 109.0 (CH_2), 83.1 (C), 81.4 (C), 62.9 (CH_2), 27.8 (CH_3), 27.7 (CH_3), 14.1 (CH_3); HRMS (ES) Found: MNa^+, 523.2217, $C_{27}H_{33}FN_2O_6Na$ requires MNa^+, 523.2215; LRMS *m/z* (ES) 523.2 (14%, MNa^+), 401.2 (13%, MH^+-*t*-Bu) 301.1 (100%, MH^+-2 ×*t*-Bu).

tert-butyl cinnamate 116



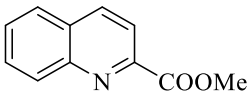
t-BuLi (1.93 mL, 3.28 mmol, 1.7 M in pentane) was added to *β*-bromostyrene in methyl *tert*-butyl ether (2 mL) at –78 ºC. After 30 min, quinoline in MTBE (2 mL) was slowly added at –78 ºC. After 1 h, Boc_2O in MTBE (1 mL) was added over 5 min. After allowing the mixture to warm to room temperature gradually over 16 h, the reaction was quenched with a saturated $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the cinnamate **116** (134 mg, 40%) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61 (1H, d, *J* = 16.0 Hz, CH), 7.56–7.50 (2H, m, 2 × CH) 7.42–7.34 (3H, m, 3 × CH), 6.39 (1H, d, *J* = 16.0 Hz, CH), 1.56 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.4 (C=O), 134.7 (CH), 134.7 (C), 130.0 (CH), 128.8 (CH), 128.0 (CH), 120.2 (CH), 80.5 (C), 28.2 (CH_3). Data consistent with the literature.[120]

Phenylethynyltributylstannane 121



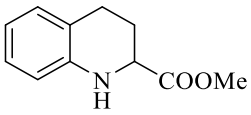
Freshly distilled phenylacetylene (4.1 g, 40 mmol) was added to Bu_3SnH (11.6 g, 40 mmol) and AIBN (0.2 g, 1.2 mmol) in toluene (80 mL). The reaction mixture was heated at 90 °C for 16 h and then was cooled to room temperature. The solvent was removed under reduced pressure. The crude mixture was extracted between CH_2Cl_2 (60 mL) and water (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give stannane **121** (14.1 g, 36.0 mmol, 95%) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39–7.38 (3H, m, 3 × CH) 7.23–7.14 (2H, m, 2 × CH), 1.59–1.47 (6H, m, 3 × CH), 1.34 (6H, sextet, *J* = 7.0 Hz, 3 × CH_2), 1.00–0.97 (6H, m, 3 × CH_2) 0.92 (9H, t, *J* = 7.0 Hz, 3 × CH_3); HRMS (ES) Found: MH^+, 392.1529, $^{120}SnC_{20}H_{33}$ requires MH^+, 392.1521; LRMS *m/z* (ES) 392.1 (8%, MH^+, ^{120}Sn), 364.1 (100%, ^{120}Sn), 362.1 (75%, ^{118}Sn). Data consistent with the literature.[121]

Methyl quinoline-2-carboxylate 129



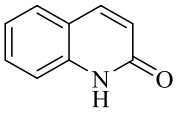
$SOCl_2$ (0.5 mL, 6.9 mmol) was added dropwise to quinoline-2-carboxylic acid (1.0 g, 5.8 mmol) in MeOH (30 mL) at 0 °C. The reaction mixture was refluxed for 16 h and then was cooled to room temperature. The reaction was quenched with saturated $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give ester **129** (1.0 g, 95%) as a needles; m.p. 81–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.37–8.31 (2H, m, 2 × CH) 8.24 (1H, d, *J* = 8.5 Hz, CH), 7.92 (1H, dd, *J* = 8.0, 1.5 Hz, CH), 7.83 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz, CH), 7.69 (1H, ddd, *J* = 8.0, 7.0, 1.1 Hz, CH) 4.12 (3H, s, OCH_3). Data consistent with the literature.[122]

Methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate 130



PtO_2 (363 mg, 1.6 mmol) was added to ester **129** (0.15 g. 0.80 mmol) in MeOH (5 mL) under a H_2 atmosphere at room temperature. After 16 h, the reaction was quenched with H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (90:10), gave ester **130** (0.14 g, 0.74 mmol, 92%) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.05–7.0 (1H, m, CH), 6.98 (1H, d, *J* = 7.5 Hz, CH), 6.67 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.61 (1H, d, *J* = 8.0 Hz, CH), 4.37 (1H, brs, NH), 4.07 (1H, ddd, *J* = 9.0, 4.0, 2.0 Hz, CH), 3.80 (3H, s, CH_3), 2.95–2.67 (2H, m, CH_2), 2.38–2.24 (1H, m, CH_2), 2.13–1.93 (1H, m, CH_2). Data consistent with the literature.[123]

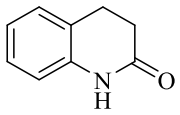
Quinoline-2(1H)-one 136



m-Chloroperoxybenzoic acid (2.0 g 116.1 mmol) was added to distilled quinoline (0.9 mL, 7.74 mmol) in CH_2Cl_2 (50 mL) at 0 ºC. The reaction mixture was allowed to stir at room temperature. After 24 h, the reaction was quenched with $NaHCO_3$ solution (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, to give quinoline *N*-oxide (1.1 g, 7.66 mmol, 99%). Methanesulfonyl chloride (1.0 mL, 12.98 mmol) was added to quinoline *N*-oxide (1.0 g, 6.49 mmol) in H_2O (60 mL) and the mixture was shaken at room temperature. After 8 min, the resulting solid was filtered, washed with H_2O and dried, to gave lactam **136** in (0.93 g, 6.42

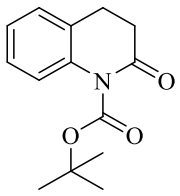
mmol, 99%) as a solid; m.p. 199–201 °C; ^{1}H NMR (400 MHz, d^6–DMSO) δ = 11.74 (1H, brs, NH), 7.90 (1H, d, *J* = 9.5 Hz, CH), 7.75–7.62 (1H, m, CH), 7.59–7.52 (1H, m, CH), 7.52–7.45 (1H, m, CH), 7.31 (1H, d, *J* = 8.0 Hz, CH), 6.50 (1H, d, *J* = 9.5 Hz, CH); HRMS (ES) Found: MH^+, 146.0601, C_9H_8NO requires MH^+, 146.0600; LRMS *m/z* (ES) 146.0 (100%, MH^+). Data consistent with the literature.[85]

3, 4-dihydroquinolin-2(1H)-one 140



Pd/C 10% (2.8 g, 12.4 mmol) was added to lactam **136** (0.9 g, 6.2 mmol) in MeOH (20 mL) under a H_2 atmosphere at room temperature. The reaction mixture was heated at 65 °C for 16 h and then was cooled to room temperature. The solvent was removed under reduced pressure. After 16 h, the mixture was filtered through Celite and the filtrate was washed with CH_2Cl_2 (7 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2–MeOH (98:2), gave lactam **140** (0.89 g, 6.08 mmol, 98%) as a solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.2–7.16 (2H, m, *2* × CH), 7.04–6.93 (1H, m, CH), 6.77–6.73 (1H, m, CH), 3.83 (1H, brs, NH), 3.00 (2H, t, *J* = 7.5 Hz, CH_2), 2.69–2.63 (2H, t, *J* = 7.5 Hz, CH_2); HRMS (ES) Found: MH^+, 148.0760, $C_9H_{10}NO$ requires MH^+, 148.0757; LRMS *m/z* (ES) 148.0 (100%, MH^+) 134.5 (6%), 114.0 (10%). Data consistent with the literature.[124]

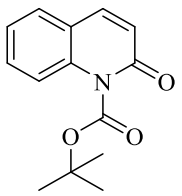
***tert*-Butyl 2-oxo-3,4-dihydroquinoline-1-carboxylate 141**



Lactam **140** (0.5 g, 3.40 mmol) was added to a suspension of NaH (0.33 g, 13.6 mmol) in THF (10 mL). The mixture was stirred for 3 h at 50 °C.[86] After cooling, Boc_2O (2.96 g, 13.6 mmol)

in THF (5 mL) was added and the mixture was heated at 50 °C for 16 h. After cooling to room temperature, the mixture was quenched with saturated aqueous NH_4Cl (50 mL) and was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the carbamate **141** (0.82 g, 3.33 mmol, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31–7.16 (2H, m, *2* × CH), 7.08 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.67 (1H, dd, *J* = 7.5, 1.0 Hz, CH), 3.02–2.94 (2H, m, CH_2), 2.73–2.65 (2H, m, CH_2), 1.63 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.3 (C=O), 151.8 (C=O), 137.1 (C), 128.0 (CH), 127.3 (CH), 125.9 (C), 124.1 (CH), 117.0 (CH), 85.0 (C), 32.2 (CH_2), 27.7 (CH_3), 25.5 (CH_2); HRMS (ES) Found: MNa^+, 270.1109, $C_{14}H_{17}NO_3Na$ requires MNa^+, 270.1101; LRMS *m/z* (ES) 270.1 (100%, MNa^+), 192.1 (42%, MNa^+) 170.1 (13% MNa^+-*t*-Bu+H^+). Data consistent with the literature.[125]

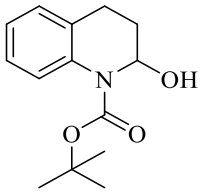
tert-Butyl 2-oxoquinoline-1-carboxylate 137



Lactam **136** (0.2 g, 1.4 mmol) was added to a suspension of NaH (0.13 g, 5.5 mmol) in THF (5 mL) at 0 °C. The mixture was stirred for 3 h at 50 °C.[86] After cooling, Boc_2O (1.2 g, 5.5 mmol) in THF (5 mL) was added and the mixture was heated at 50 °C for 16 h. After cooling to room temerature, the mixture was quenched with saturated aqueous NH_4Cl (30 mL) and was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), gave the carbamate **137** (0.32 g, 1.3 mmol, 95%) as an solid; ^{1}H NMR (400

MHz, $CDCl_3$) δ = 8.27 (1H, d, *J* = 8.5 Hz, CH), 8.04 (1H, d, *J* = 8.5 Hz, CH) 7.89–7.84 (1H, m, CH), 7.78–7.72 (1H, m, CH), 7.57 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz, CH), 7.29–7.26 (1H, m, CH), 1.61 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.1 (C=O), 151.1 (C=O), 146.5 (C), 140.1 (CH), 130.2 (CH), 128.8 (CH), 127.4 (CH), 127.1 (C), 126.5 (CH), 115.2 (CH_2), 84.2 (C), 27.7 (CH_3); HRMS (ES) Found: MNa^+, 268.0947, $C_{14}H_{15}NO_3Na$ requires MNa^+, 268.0944; LRMS *m/z* (ES) 146.1 (100%, MH^+-Boc^+H).

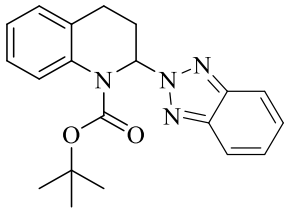
tert-Butyl 2-Hydroxy-3,4-dihydro-2H-quinoline-1-carboxylate 142



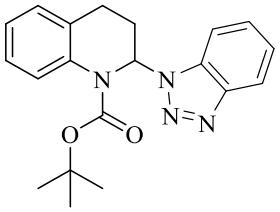
DIBAL-H (8.1 mL, 8.9 mmol, 1 M in cyclohexane) was added to carbamate **141** (1.1 g, 4.5 mmol) in THF (15 mL) at –78 ºC. The reaction mixture was stirred at –78 ºC for 1 h, and for 1 h at room temperature. The reaction was quenched with saturated aqueous potassium acetate solution (5 mL). The solids were filtered and were washed with EtOAc (5 × 15 mL). The combined organic layers were washed with saturated brine solution (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol– EtOAc (75:25), gave the carbamate **142** (0.9 g, 3.6 mmol, 80%) as a white solid; m.p. 57–60 °C; R_f 0.42 [petrol–EtOAc (60:40)]; FT-IR ν_{max} ATR/cm^{-1} 3395 (OH), 2973, 2929, 1700 (C=O), 1154; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 (1H, d, *J* = 8.0 Hz, CH), 7.22–7.16 (1H, m, CH), 7.12 (1H, d, *J* = 8.0 Hz, CH), 7.05–6.99 (1H, m, CH), 5.86–5.80 (1H, m, CH), 4.02 (1H, brs, OH), 2.74–2.65 (1H, m, CH), 2.61–2.51 (1H, m, CH), 2.31–2.22 (1H, m, CH) 1.86–1.76 (1H, m, CH) 1.58 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.7 (C=O), 136.3 (C), 132.0 (C), 127.2 (CH), 126.2 (CH), 123.9 (CH), 123.5 (CH), 82.1 (C), 79.0 (CH), 31.1 (CH_2), 28.1 (CH_3), 24.6 (CH_2); HRMS (ES) Found: MNa^+, 272.1263 $C_{14}H_{19}NO_3Na$

requires MNa^+, 272.1257; LRMS *m/z* (ES) 272.1 (81%, MNa^+), 188.1 (7%), 176.1 (39%), 132.1 (100%, MNa^+–*t*-Bu+H, OH).

tert-Butyl 2-(1,2,3-benzotriazol-2-yl)-3,4-dihydro-2H-quinoline-1-carboxylate 133a

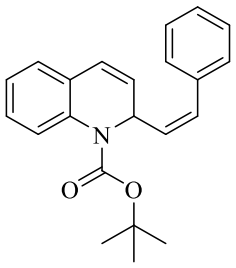


Benzotriazole (0.36 g, 3.0 mmol) and $MgSO_4$ (0.34 g, 2.4 mmol) were added to alcohol **142** (0.5 g, 2.0 mmol) in toluene (15 mL). The reaction mixture was refluxed for 14 h and then was cooled to room temperature. The reaction mixture was washed with saturated aqueous Na_2CO_3 (3 × 5 mL) and brine (3 × 5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (90:10), gave the carbamate **133a** (14.7 mg, 0.63 mmol 21%) as an oil; R_f 0.61 [petrol-EtOAc (80:20)]; FT-IR ν_{max} ATR/cm^{-1} 2975, 2901, 2863, 1689 (C=O), 1162, 1110; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90–7.79 (3H, m, 3 × CH), 7.41–7.35 (2H, m, 2 × CH), 7.32–7.25 (1H, m, CH), 7.20–7.14 (2H, m, 2 × CH), 7.13–7.06 (1H, m, CH), 2.81–2.68 (3H, m, 3 × CH), 2.52–2.42 (1H, m, CH_2), 1.36 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, one quaternary carbon could not be observed) δ = 153.1 (C=O), 144.0 (C), 136.6 (C), 131.2 (C), 127.4 (CH), 126.8 (CH) 126.2 (CH), 124.5 (CH), 124.2 (CH), 118.4 (CH), 82.4 (C), 74.4 (CH), 31.4 (CH_2), 28.0 (CH_3), 24.6 (CH_2); HRMS (ES) Found: MNa^+, 373.1638, $C_{20}H_{22}N_4O_2Na$ requires MNa^+, 373.1635; LRMS *m/z* (ES) 373.2 (100%, MNa^+). In addition, the benzotriazole isomer **133b** (385 mg, 1.1 mmol, 53%) was isolated as a solid, data as below.



Benzotriazole isomer **133b** (385 mg, 53%) was prepared as described above, as a solid; m.p. 57–60 °C; R_f 0.40 [petrol–EtOAc (80:20)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.05 (1H, dt, *J* = 7.5, 1.3 Hz, CH), 7.57 (1H, d, *J* = 8.0 Hz, CH), 7.41–7.31 (3H, m, 3 × CH), 7.30–7.21 (3H, m, 3 × CH), 7.14 (1H, dt, *J* = 7.5, 1.3 Hz, CH), 2.99–2.85 (2H, m, CH_2), 2.82–2.71 (1H, m, CH), 2.65–2.47 (1H, m, CH), 1.39 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.2 (C=O), 146.1 (C), 136.3 (C), 132.1 (C), 131.4 (C), 127.7 (CH), 127.3 (CH), 126.9 (CH), 125.2 (CH), 124.9 (CH), 123.9 (CH), 120.0 (CH), 110.5 (CH), 82.0 (C), 68.5 (CH), 30.7 (CH_2), 28.1 (CH_3), 25.1 (CH_2); HRMS (ES) Found: MNa^+, 373.1632, $C_{20}H_{22}N_4O_2Na$ requires MNa^+, 373.1635; LRMS *m/z* (ES) 373.2 (11%, MNa^+), 188.1 (7%), 176.1 (33%), 132.1 (100%, MNa^+-*t*-Bu-Bt+H).

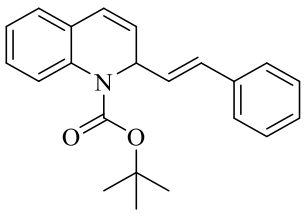
tert-Butyl 2-[(*Z*)-2-phenylethenyl]-2H-quinoline-1-carboxylate 127a



n-BuLi (6.26 mL, 14.4 mmol, 2.3 M) was added to stannane **121** (2.2 g, 12.0 mmol) in THF (20 mL) at –78 °C. After 30 min, the mixture was added to a solution of quinoline (1.4 mL, 12.0 mmol) in THF (5 mL) at room temperature over 10 min. After 60 min, the quinoline was

consumed as monitored by TLC and then Boc_2O (2.9g, 13.2 mmol) in THF (5 mL) was added over 5 min at 0 °C. After allowing the mixture to warm to room temperature gradually over 16 h, the reaction was quenched with a saturated aqueous NH_4Cl solution (20 mL). The aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), gave the DHQ-**127a** (49.7 mg, 0.15 mmol, 1%) as an oil; R_f 0.68 [petrol–EtOAc (97:3)]; FT-IR ν_{max} (ATR)/cm^{-1} 2926, 2872, 2854, 1736 (C=O), 1481,1250; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.68 (1H, d, *J* = 8.0, CH), 7.43–7.31 (3H, m, 3 × CH), 7.30–7.27 (1H, m, CH), 7.23–7.13 (2H, m, 2 × CH), 7.10–6.95 (2H, m, 2 × CH), 6.54–6.47 (1H, m, CH), 6.35 (1H, d, *J* = 11.5 Hz, CH), 6.08–5.91 (2H, m, 2 × CH), 5.61 (1H, dd, *J* = 11.5, 9.0 Hz, CH), 1.27 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, one quaternary carbon could not be observed) δ = 152.7 (C=O), 136.7 (C), 133.0 (C), 129.0 (CH), 128.5 (CH), 128.2 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 126.3 (CH), 125.4 (CH), 124.6 (CH), 123.8 (CH), 81.1 (C), 50.6 (CH), 28.0 (CH_3); HRMS (ES) Found: MNa^+, 356.1637, $C_{22}H_{23}NO_2Na$ requires MNa^+, 356.1621; LRMS *m/z* (ES) 356.2 (100%, MNa^+), 174.1 (63%), 130.1 (9%, MNa^+-Boc-styrene+H). In addition, the (*E*)-isomer DHQ-**127b** (119.1 mg, 0.36 mmol, 3%) was isolated as a solid, data as below.

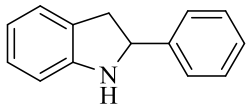
tert-Butyl 2-[(*E*)-2-phenylethenyl]-2H-quinoline-1-carboxylate 127b



(*E*)-isomer DHQ-**127b** (119.1 mg, 0.36 mmol, 3%), was prepared as described above, as a solid; m.p. 102–104 °C; R_f 0.45 [petrol–EtOAc (97:3)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.63 (1H, d, *J* = 8.0, CH), 7.33–7.25 (4H, m, 4 × CH), 7.24–7.18 (2H, m, 2 × CH), 7.11 (1H, dd, *J*

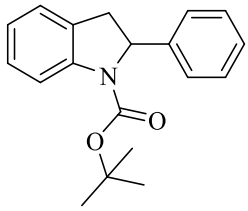
= 7.5, 1.5 Hz, CH), 7.05 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.58 (1H, d, *J* = 10.0 Hz, CH), 6.52 (1H, d, *J* = 16.0 Hz, CH), 6.12–6.02 (2H, m, 2 × CH), 5.67 (1H, d, *J* = 6.5 Hz, CH), 1.58 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.1 (C=O), 136.6 (C), 135.1 (C), 128.5 (CH), 127.7 (CH), 127.4 (CH), 127.4 (CH), 127.2 (CH), 126.9 (C), 126.6 (CH), 126.4 (CH), 126.0 (CH), 125.6 (CH), 124.4 (CH), 123.7 (CH), 81.5 (C), 54.2 (CH), 28.4 (CH_3); HRMS (ES) Found: MNa^+, 356.1631, $C_{22}H_{23}NO_2Na$ requires MNa^+, 356.1621; LRMS *m/z* (ES) 356.2 (100%, MNa^+), 278.1 (22%, MNa^+-styrene +H), 174.1 (63%), 130.1 (25%, MNa^+-Boc-styrene+H).

2-Phenylindoline 165a



Indole **164a** (5.0 g, 28.9 mmol) and Sn powder (15.0 g, 129.4 mmol) were added to a mixture of concentrated hydrochloric acid (25 mL) and EtOH (75 mL). The mixture was heated at 90 ℃ for 4 h and then was cooled to room temperature. The reaction was quenched by KOH (120 mL, 20%) at 0 °C. The organic product was extracted with Et_2O (3 × 100 mL). The combined organic layers were filtered through Celite and the filtrate was washed with brine (75 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), gave the amine **XX** (4.5 g, 23.1 mmol, 80%) as a solid; m.p. 185–186 °C; R_f *0.62* [petrol–EtOAc (80:20)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47–7.42 (2H, m, 2 × CH), 7.41–7.33 (2H, m, 2 × CH), 7.30–7.26 (1H, m, CH), 7.14–7.07 (2H, m, 2 × CH), 6.76 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.70 (1H, d, *J* = 7.5 Hz, CH), 4.98 (1H, t, *J* = 9.0 Hz, CH), 4.17 (1H, brs, *N*H), 3.48 (1H, dd, *J* = 16.0, 9.0 Hz, CH), 3.02 (1H, dd, *J* = 16.0, 9.0 Hz, CH), 1.58 (9H, s, *t*-Bu). Data consistent with the literature.[126]

***tert*-Butyl 2-phenyl-2,3-dihydroindole-1-carboxylate 166a**

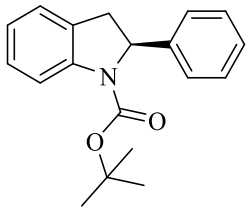


n-BuLi (12.26 mL, 28.2 mmol, 2.3 M in hexane) was added to a stirred solution of 2-phenyl-2,3-dihydro-1H-indole (5.0 g, 25.6 mmol) in THF (65 mL) at –78 °C. After 30 min, Boc_2O (5.59 g, 25.6 mmol) in THF (25 mL) was added over 10 min. After allowing the mixture to warm to room temperature gradually over 16 h, the reaction was quenched with aqueous saturated $NaHCO_3$ solution (60 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), gave the carbamate **166a** (6.05 g, 20.51 mmol, 80%) as needles; m.p. 119–120 °C; R_f 0.71 [petrol–EtOAc (90:10)]; FT-IR *ν*max (ATR)/cm-1 3011, 3029, 2980, 2938, 1708, 1696 (C=O), 1599, 1482, 1388, 1258, 1141, 1061, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 (1H, s, CH), 7.33–7.18 (6H, m, 6 × CH), 7.14 (1H, dd, *J* = 7.2 Hz, CH), 7.03 – 6.97 (1H, m, CH), 3.70 (1H, dd, *J* = 16.0, 10.5 Hz, CH), 2.98 (1H, dd, *J* = 16.0, 3.5 Hz, CH), 1.34 (9H, brs, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.4 (C=O), 144.7 (C), 143.2 (C), 129.2 (C), 128.5 (CH), 127.7 (CH), 127.2 (CH), 125.0 (CH), 122.6 (CH), 114.7 (CH), 80.8 (C), 62.6 (CH), 37.8 (CH_2), 28.2 (CH_3); HRMS (ES) Found: MK^+, 334.1201 $C_{19}H_{21}NO_2K$ requires MK^+, 334.1204; LRMS *m/z* (ES), 334.1 (6%), 240 (100%).

Resolution between the enantiomers of the carbamate **166a** was achieved using a Beckman system fitted with a Cellulose-1 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min–1; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 μL of the sample prepared in a 2 g·L–1 solution of the eluent. Under these conditions,

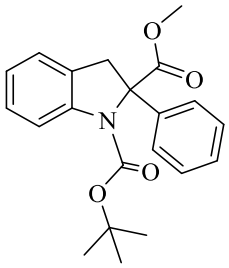
the faster running component and slower running component were eluted at 5.87 min and 6.97 min respectively with an analysis time of 15 min.

tert-Butyl (2*S*)-2-phenyl-2,3-dihydroindole-1-carboxylate (*S*)-166a



n-BuLi (80 µL, 0.2 mmol, 2.5 M in hexane) was added to a mixture of (+)-sparteine (80 mg, 0.34 mmol) and the racemic carbamate **166a** (100 mg, 0.34 mmol) in dry PhMe (8 mL) at –78 °C. After 60 min, EtOCOCl (0.1 mL, 1.0 mmol) was added and the reaction mixture was allowed to warm to room temperature over 16 h and then MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (98:2) to give recovered carbamate (S)-**166*a*** (44 mg, 44%) as needles; m.p. 115–116 °C; data as above; the enantiomeric ratio was determined to be 94:6 by CSP-HPLC (major component eluted at 6.27 min); $[\alpha]_D^{20}$ –25 (1.6, $CHCl_3$). In addition, the carbamate **167a** (45 mg, 36%) was isolated as a solid, data as below.

1-_tert_-Butyl 2-methyl 2-phenyl-3H-indole-1,2-dicarboxylate 167a

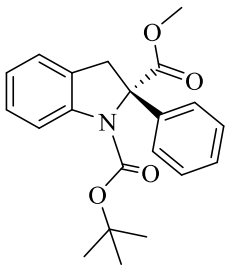


n-BuLi (0.2 mL, 0.41 mmol, 2.1 M in hexanes) was added to *N*-Boc-2-phenylindoline **166a** (100 mg, 0.34 mmol) in THF (4 mL) at –78 °C. After 20 min, MeOCOCl (0.1 mL, 0.68 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column

chromatography on silica gel, eluting with petrol–EtOAc (98:2), to give the carbamate **167a** (110 mg, 88%) as needles; m.p. 95–97 °C; R_f 0.41 [petrol–EtOAc (90:10)]; FT-IR ν_{max} (ATR)/cm^{-1} 2973, 2950, 1753 (C=O), 1706 (C=O), 1483, 1377, 1142, 1018, 755, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06 (1H, brs, CH), 7.54–7.45 (2H, m, 2 × CH), 7.37–7.31 (2H, m, 2 × CH), 7.31–7.22 (2H, m, 2 × CH), 7.10–7.04 (1H, m, CH), 6.97 (1H, t, *J* = 7.0 Hz, CH), 3.90 (1H, d, *J* = 16.0 Hz, CH), 3.82 (3H, s, CH_3), 3.43 (1H, d, *J* = 16.0 Hz CH), 1.30 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.4 (C=O), 151.9 (C=O), 142.5 (C), 141.4 (C), 131.5 (C), 128.0 (CH), 127.8 (CH), 127.3 (CH), 126.5 (CH), 126.3 (CH), 123.0 (CH), 115.0 (CH), 84.4 (C), 52.7 (CH_3), 46.4 (C), 40.9 (CH_2), 28.0 (CH_3); HRMS (ES) Found: MH^+, 376.1524, $C_{21}H_{23}NO_4Na$ requires MNa^+, 376.1519; LRMS *m/z* (ES) 376.2 (70%, $MHNa^+$), 298.1 (25%) 245.1 (100%).

Resolution between the enantiomers of the the carbamate **167a** was achieved using a Beckman system fitted with a Lux Cellulose–1 column (250 mm × 460 mm i.d.) as the stationary phase with a mixture of *n*-hexane–isopropanol (99.4:0.6 v/v) as the mobile phase at a flow rate of 0.5 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 µL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 20.9 min and 23.5 min with an analysis time of 30 min.

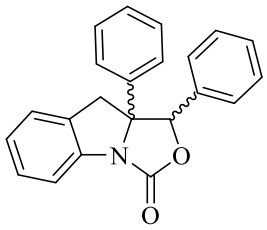
1-*tert*-Butyl 2-methyl (2*S*)-2-phenyl-3H-indole-1,2-dicarboxylate (*S*)-167a



n-BuLi (0.2 mL, 0.41 mmol, 2.1 M in hexane) was added to carbamate (*S*)-**167a** (100 mg, 0.34 mmol) in dry PhMe (8 mL) at –78 °C. After 20 min, MeOCOCl (0.1 mL, 0.68 mmol) was added and the reaction mixture was allowed to warm to room temperature over 16 h and then

MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), to give carbamate (*S*)-**167a** (83 mg, 83%) as needles; m.p. 96–98 °C; data as above; the enantiomeric ratio was determined to be 99.4:0.6 by CSP-HPLC (major component eluted at 23.3 min); $[\alpha]_D^{23}$ –6.0 (1.0, $CHCl_3$).

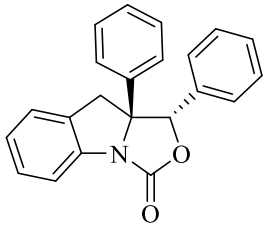
(*trans*)-1,9a-Diphenyl-1H,9H-[1,3]oxazolo[3,4-a]indol-3-one 167c



n-BuLi (0.4 mL, 0.82 mmol, 2.1 M) was added to a stirred solution of carbamate **166a** (200 mg, 0.68 mmol) in THF (8 mL) at –78 °C. After 20 min, benzaldehyde (0.14 mL, 1.36 mmol) was added. The mixture was allowed to warm to room temperature over 16 h, and MeOH (2 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), to give the carbamate **167c** (65.4 mg, 0.2 mmol, 29%) as an oil; R_f 0.31 [petrol–EtOAc (90:10)]; FT-IR ν_{max} (ATR)/cm^{-1} 3064, 3030, 2959, 1785 (C=O), 1594, 1483, 1376, 1038, 1022, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (1H, d, *J* 8.0 Hz, CH), 7.58–7.52 (2H, m, 2 × CH), 7.51–7.41 (4H, m, 4 × CH), 7.39–7.33 (4H, m, 4 × CH), 7.33–7.29 (1H, m, CH), 7.04 (1H, td, *J* = 7.5, 1.5 Hz, CH), 6.97 (1H, d, *J* 7.5 Hz, CH), 5.78 (1H, s, CH), 3.15 (1H, d, *J* 16.0 Hz, CH), 2.94 (1H, d, *J* 16.0 Hz, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.5 (C=O), 145.7 (C), 139.0 (C), 136.3 (C), 132.9 (CH), 131.9 (C), 129.3 (CH), 129.2 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.5 (CH), 126.0 (CH), 125.0 (CH), 125.2 (CH), 125.1 (CH), 124.6 (CH), 115.7 (CH), 88.0 (CH), 76.0 (C), 40.9 (CH_2); HRMS (ES) Found: $(M+H)^+$, 328.1341, $C_{22}H_{18}NO_2$ requires $M+H^+$, 328.1332; LRMS *m/z* (ES) 328.1 ($M+H^+$, 55%), 284.1 (8%), 182.1 (11%), 167.1 (100%).

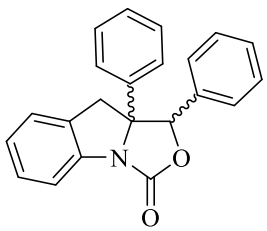
Resolution between the enantiomers of the **167c** was achieved using a Beckman system fitted with a Cellulose-1 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 0.5 mL·min–1; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 μL of the sample prepared in a 2 g·L–1 solution of the eluent. Under these conditions, the components were eluted at 44.8 min and 49.8 min with an analysis time of 60 min.

(1*S*,9a*S*)-1,9a-Diphenyl-1H,9H-[1,3]oxazolo[3,4-a]indol-3-one 167c



n-BuLi (0.16 mL, 0.41 mmol, 2.5 M in hexane) was added to carbamate (*S*)-**167c** (100 mg, 0.34 mmol) in dry PhMe (8 mL) at –78 °C. After 20 min, PhCHO (0.1 mL, 1.0 mmol) was added and the reaction mixture was allowed to warm to room temperature over 16 h and then MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), to give carbamate (1*R*,9a*S*)-**167c** (25 mg, 25%) as an oil; data as above; the enantiomeric ratio was determined to be 99.4:0.6 by CSP-HPLC (major component eluted at min); $[\alpha]_D^{21}$ –8.9 (1.35, $CHCl_3$).

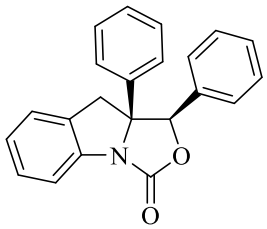
(*cis*)-1,9a-Diphenyl-1H,9H-[1,3]oxazolo[3,4-a]indol-3-one 167c



n-BuLi (0.4 mL, 0.82 mmol, 2.1 M) was added to a stirred solution carbamate **167b** (200 mg, 0.68 mmol) in THF (8 mL) was at –78 °C. After 20 min, benzaldehyde (0.14 mL, 1.36 mmol) was added. After allowing the mixture to warm to room temperature gradually over 16 h, the

reaction was quenched with MeOH (2 mL). The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), to give indoline **167c** (154 mg, 69%) as needles; m.p. 174–176 °C; R_f 0.25 [petrol–EtOAc (90:10)]; FT-IR ν_{max} (ATR)/cm^{-1} 3035, 3050, 2958, 1743 (C=O), 1594, 1389, 1133, 1043, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69 (1H, d, *J* 8.0 Hz, CH), 7.41–7.27 (2H, m, 2 × CH), 7.25–7.14 (4H, m, 4 × CH), 7.13–7.06 (3H, m, 3 × CH), 7.02–6.95 (4H, m, 4 × CH), 5.90 (1H, s, CH), 3.88 (1H, d, *J* 15.5 Hz, CH), 3.57 (1H, d, *J* 15.5 Hz, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.4 (C=O), 139.4 (C), 139.2 (C), 133.7 (C), 131.8 (C), 129.0 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 126.6 (CH), 126.4 (CH), 125.4 (CH), 124.8 (CH), 115.0 (CH), 90.7 (CH), 75.9 (C), 44.1 (CH_2); HRMS (ES) Found: (MH^+), 328.1330. $C_{22}H_{18}NO_2$ requires MH^+, 328.1332; LRMS *m/z* (ES) 350.1 (MNa^+, 100%) 328.1 (MH^+, 72%), 284.1 (10%), 182.1 (37%), 167.1 (83%).

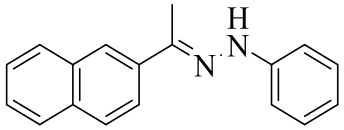
Resolution between the enantiomers of the carbamate **167c** was achieved using a Beckman system fitted with a Cellulose-1 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99.3:0.7 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 16.7 min and 29.3 min with an analysis time of 40 min.



n-BuLi (0.16 mL, 0.41 mmol, 2.5 M in hexane) was added to carbamate (*S*)-**166a** (100 mg, 0.34 mmol) in dry PhMe (8 mL) at –78 °C. After 20 min, PhCHO (0.1 mL, 1.0 mmol) was added and the reaction mixture was allowed to warm to room temperature over 16 h and then

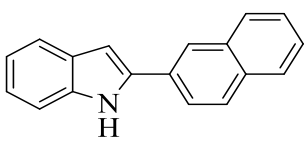
MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), to give carbamate (1*R*,9a*S*)-**167c** (63 mg, 63%) as an oil; data as above; the enantiomeric ratio was determined to be 99.4:0.6 by CSP-HPLC (major component eluted at min); m.p. 177–179 °C; $[\alpha]_D^{21}$ –159.55 (2.25, $CHCl_3$).

1-[1-(naphthalen-2-yl)ethylidene]-2-phenylhydrazine 169



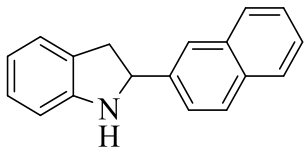
Phenylhydrazine (2.89 mL, 29.4 mmol) and 2-acetonaphthone (5.0 g, 29.4 mmol) in EtOH (50 mL) followed by addition of a few drops of AcOH.[107] The mixture was warmed to 50 °C for 15 min and was allowed to stir for 1 h at room temperature. The mixture was added to ice/water (50 mL) and after filtering was washed with cold water (5 × 30 mL) and dried to give hydrazine **169** (7.4 g, 99%) as a solid, which was used in next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.25 (1H, dd, *J* = 8.5, 2.0 Hz, CH), 8.05–8.01 (1H, m, CH), 7.91–7.84 (3H, m, 3 × CH) 7.53–7.49 (2H, s, 2 × CH), 7.40–7.33 (2H, m, 2 × CH), 7.31–7.25 (2H, m, 2 × CH), 6.95 (1H, tt, *J* = 7.0, 1.0 Hz, CH), 2.36 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.2 (C), 140.9 (C), 136.6 (C), 133.4 (C), 133.2 (C), 129.3 (CH), 128.3 (CH), 127.9 (CH), 127.7 (CH), 126.2 (CH), 126.1 (CH), 124.5 (CH), 123.7 (CH), 120.3 (CH), 113.3 (CH), 11.6 (CH_3); HRMS (ES) Found: MH^+, 261.1389, $C_{18}H_{17}N_2$ requires MH^+, 261.1386; LRMS m/z (ES) 261.1 (100%).

2-(Naphthalen-2-yl)-1H-indole 164b



Polyphosphoric acid (76.2 g) was heated at 50 °C, followed by adding hydrazine **169** (12.7 g, 48.85 mmol) in toluene (100 mL). The mixture was heated at 135 °C for 2 h and was added to ice/H_2O (200 mL) and after filtering was washed with cold MeOH (5 × 50 mL). The filtrate was recrystallized by dissolving in a hot ethanol (50 mL) and a small amount of charcoal was added. After filtration, the solution was reheated and then water (5 mL) until the cloudy point. Ethanol (2 mL) was added to give a clear solution that was allowed to cool to room temperature to give indole **164b** (7.2 g, 29.6 mmol, 61%), as needles; m.p. 203–205 °C, lit. ref. m.p. 200–202 °C;[127] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.52 (1H, brs, NH), 8.07–8.05 (1H, m, CH), 7.95–7.81 (4H, m, 4 × CH), 7.71 (1H, d, *J* = 7.8 Hz, CH), 7.59–7.49 (2H, m, 2 × CH), 7.46 (1H, d, *J* = 8.0 Hz, CH), 7.30–7.23 (1H, m, CH), 7.23–7.17 (1H, m, CH), 7.01–6.96 (1H, m, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 137.9 (C), 137.1 (C), 133.6 (C), 132.9 (C), 129.7 (C), 129.4 (C), 128.9 (CH), 128.0 (CH), 127.9 (CH), 126.7 (CH), 126.2 (CH), 123.8 (CH), 123.1 (CH), 122.6 (CH), 120.8 (CH), 120.4 (CH), 111.0 (CH), 100.7 (CH); HRMS (ES) Found: MH^+, 244.1122; $C_{18}H_{14}NO$ requires MH^+, 244.1121 LRMS *m*/*z* (ES) 244.4 (100%). Data consistent with the literature.[107,128]

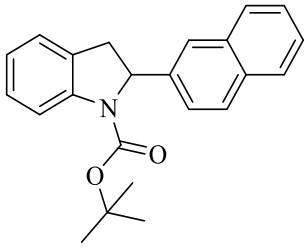
2-(Naphthalen-2-yl)-2,3-dihydro-1H-indole 165b



Indole **164b** (5 g, 21 mmol), and Tin powder (12 g, 103 mmol) was added to a mixture of concentrated hydrochloric acid (20 mL) and EtOH (60 mL). The mixture was heated at 90 °C for 4 h, and then was cooled to room temperature. The reaction was quenched by aqueous KOH (60 mL, 20%) at 0 °C. The organic product was extracted by Et_2O (3 × 100 mL). The combined organic layers were filtered through Celite and the filtrate was washed by brine (75 mL). The

organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), gave the amine **165b** (2.1 g, 8.57 mmol, 42%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04–7.94 (4H, m, 4 × CH), 7.74–7.61 (3H, m, 3 × CH), 7.35–7.26 (2H, m, 2 × CH), 6.98 (1H, t, *J* = 7.5 Hz, CH), 6.84 (1H, d, *J* = 7.6 Hz, CH), 5.16 (1H, t, *J* = 9.0 Hz, CH) 4.23 (1H, brs, NH), 3.62 (1H, dd, *J* = 15.5, 9.0 Hz, CH) 3.20 (1H, dd, *J* = 15.7, 9.0 Hz, CH);^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.2 (C), 142.1 (C), 133.6 (C), 133.1 (C), 128.7 (CH), 128.3 (C), 128.1 (CH), 128.0 (CH), 127.9 (CH), 126.4 (CH), 126.0 (CH), 125.0 (CH), 125.0 (CH), 124.9 (CH), 119.1 (CH), 109.1 (CH), 63.9 (CH), 39.8 (CH_2); HRMS (ES) Found: MH^+, 246.1279; $C_{18}H_{16}N$ requires MH^+, 246.1277; LRMS m/z (ES) 246.1 (100%). Data consistent with the literature.[129]

***tert*-Butyl 2-(naphthalen-2-yl)-2,3-dihydroindole-1-carboxylate 166a**

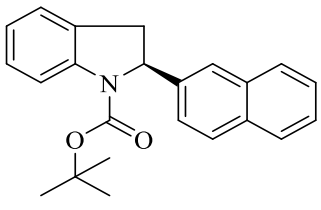


n-BuLi (3.92 mL, 9.79 mmol, 2.5 M in hexane) was added to a stirred solution of amine **165b** (2.0 g, 8.16 mmol) in THF (25 mL) at –78 °C. After 30 min, Boc_2O (1.78 g, 8.16 mmol) in THF (25 mL) was added over 5 min. After allowing the mixture to warm to room temperature gradually over 16 h, the reaction was quenched with aqueous saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), gave the carbamate **166b** (1.0 g, 2.9 mmol, 36%) as needles; R_f 0.58 [petrol–EtOAc (90:10)]; FT-IR ν_{max} (ATR)/cm^{-1} 2985, 2938, 1696 (C=O), 1258, 1141, 1061, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08 (1H, brs, CH), 7.92–7.80 (3H, m, 3 × CH), 7.74 (1H, s, CH), 7.55–7.46 (2H, m, 2 × CH), 7.42–7.32 (2H, m, 2 × CH), 7.20

(1H, d, *J* = 7.0 Hz, CH), 7.11–7.06 (1H, m, CH), 5.61 (1H, brs, CH), 3.83–7.73 (1H, m, CH), 3.09 (1H, dd, *J* = 16.0, 5.0 Hz, CH), 1.29 (9H, brs, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.5 (C=O), 143.3 (C), 142.0 (C), 136.2 (C), 133.4 (C), 132.4 (C), 128.8 (CH), 127.9 (CH), 127.8 (CH), 127.0 (CH), 126.3 (CH), 125.8 (CH), 125.0 (CH), 124.1 (CH), 123.7 (CH), 122.8 (CH), 114.9 (CH), 80.8 (C), 62.9 (CH), 37.9 (CH_2), 28.3 (CH_3); HRMS (ES) Found: MNa^+, 368.1626 $C_{19}H_{21}NO_2Na$ requires MNa^+, 368.1621; LRMS *m/z* (ES), 368.2 (100%), 280.1 (74%) 162 (84%).

Resolution between the enantiomers of the carbamate **166b** was achieved using a Beckman system fitted with a Cellulose-1 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99.4:0.6 v/v) as the mobile phase at a flow rate of 0.5 $mL \cdot min^{-1}$; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 μL of the sample prepared in a 2 $g \cdot L^{-1}$ solution of the eluent. Under these conditions, the components were eluted at 23.9 min and 26.0 min with an analysis time of 15 min.

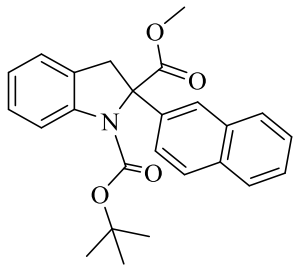
***tert*-Butyl (2*S*)-2-(naphthalen-2-yl)-2,3-dihydroindole-1-carboxylate** (*S*)-**166b**



n-BuLi (70 μL, 0.17 mmol, 2.5 M in hexane) was added to a mixture of (+)-sparteine (70 mg, 0.29 mmol) and the racemic carbamate **XX** (100 mg, 0.29 mmol) in dry PhMe (8 mL) at –78 °C. After 90 min, MeOCOCl (70 μL, 0.87 mmol) was added and the reaction mixture was

allowed to warm to room temperature over 16 h and then MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (98:2) to give recovered carbamate (*S*)-**166b** (31 mg, 31%) as an amorphous off-white solid; mp 110–111 °C; data as above; the enantiomeric ratio was determined to be 85:15 by CSP-HPLC (major component eluted at 25.5 min); $[\alpha]_D^{19}$ –28.2 (1.7, $CHCl_3$). In addition, the carbamate (*R*)-**169** (68 mg, 57%) was isolated as an oil and the indole (11 mg, 11%), data as below.

1-*tert*-Butyl 2-methyl 2-(naphthalen-2-yl)-3H-indole-1,2-dicarboxylate 168a

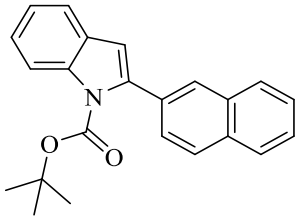


n-BuLi (0.14 mL, 0.35 mmol, 2.5 M in hexanes) 0.14 mL, 0.35 mmol, 2.5 M in hexanes in THF (4 mL) at –78 °C. After 20 min, MeOCOCl (70 µL, 0.87 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), to give the carbamate **128a** (108 mg, 94%) as solid; m.p. 109–111 °C; R_f 0.38 [petrol–EtOAc (90:10)]; FT-IR ν_{max} (ATR)/cm^{-1} 3065, 2970, 2920, 2850, 1745 (C=O), 1708 (C=O), 1490, 1365, 1245, 1150, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (1H, brs, CH), 7.92–7.75 (4H, m, 2 × CH), 7.66 (1H, dd, *J* = 8.8, 2.0 Hz, CH), 7.52–7.42 (2H, m, 2 × CH), 7.34–7.28 (1H, m, CH), 7.08 (1H, d, *J* = 7.0 Hz, CH), 7.01 (1H, t, *J* = 7.5 Hz, CH), 3.96 (1H, d, *J* = 16.0 Hz, CH), 3.86 (3H, s, OCH_3), 3.52 (1H, d, *J* = 16.0 Hz, CH), 1.29 (9H, s, t-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, one quaternary carbon could not be observed) δ = 172.5 (C=O), 152.9 (C=O), 138.0 (C), 136.9 (C), 132.6 (C), 132.5 (CH), 128.3 (CH), 128.1 (CH), 127.7 (CH), 127.4 (CH), 126.1 (CH), 126.0 (CH), 125.2 (CH), 124.9 (CH), 124.4 (CH), 123.1

(CH), 115.1 (CH), 82.9 (C), 56.9 (C), 52.7 (CH_3), 40.9 (CH_2), 28.0 (CH_3); HRMS (ES) Found: MNa^+, 426.1695, $C_{25}H_{25}NO_4Na$ requires MNa^+, 426.1676; LRMS *m/z* (ES) 426.2 (100%, $MHNa^+$), 348.1 (14%), 304.1 (73%, MNa^+-Boc+H) 272.1 (13%).

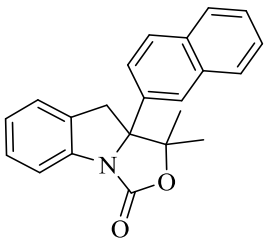
Resolution between the enantiomers of the the carbamate **168a** was achieved using a Beckman system fitted with a Lux Cellulose–2 column (250 mm × 460 mm i.d.) as the stationary phase with a mixture of *n*-hexane–isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 $mL \cdot min^{-1}$; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 µL of the sample prepared in a 2 $g \cdot L^{-1}$ solution of the eluent. Under these conditions, the components were eluted at 11.4 min and 14.9 min with an analysis time of 30 min.

tert-Butyl 2-(naphthalen-2-yl)indole-1-carboxylate 169



Carbamate **169** (11 mg, 11%) was prepared as described above, as solid; m.p. 132–135 °C, 134–135 °C;[130] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.27 (1H, dd, *J* = 8.0, 1.0 Hz, CH), 7.96–7.93 (1H, m, CH), 7.90–7.86 (3H, m, 3 × CH), 7.61 (1H, d, *J* = 7.5 Hz CH), 7.58–7.51 (3H, m, 3 × CH), 7.38 (1H, ddd, *J* = 8.5, 7.5, 1.3 Hz, CH), 7.31 (1H, dd, *J* = 7.5, 1.0 Hz, CH), 6.69 (1H, s, CH), 1.28 (9H, s, t-Bu).[130]

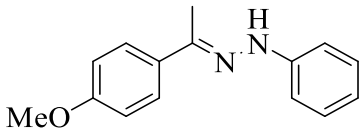
1,1-Dimethyl-9a-(naphthalen-2-yl)-9H-[1,3]oxazolo[3,4-a]indol-3-one 168b



n-BuLi (0.14 mL, 0.35 mmol, 2.5 M in hexanes) was added to carbamate **166b** (100 mg, 0.29 mmol) in THF (4 mL) at –78 °C. After 20 min, MeCOMe (60 µL, 0.68 mmol) was added. The

mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), to give the carbamate **168b** (56 mg, 60%) as white solid; m.p. 150–153 °C R_f 0.19 [petrol–EtOAc (90:10)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95–7.92 (1H, m, CH), 7.90–7.81 (3H, m, 3 × CH), 7.66 (1H, d, *J* = 8.0 Hz, CH), 7.55–7.45 (3H, m, 3 × CH), 7.32–7.29 (1H, m, CH), 7.13 (1H, t, *J* = 7.5 Hz, CH), 7.06 (1H, td, *J* = 7.5, 1.0 Hz, CH), 3.98 (1H, d, *J* = 16.0 Hz, CH), 3.45 (1H, d, *J* = 16.0 Hz, CH), 1.75 (3H, s, CH_3), 1.14 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, one quaternary carbon could not be observed) δ = 156.1 (C=O), 140.4 (C), 138.4 (C), 132.8 (C), 132.3 (C), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.5 (CH), 126.7 (CH), 126.5 (CH), 125.1 (CH), 125.0 (CH), 124.3 (CH), 124.2 (CH), 116.0 (CH), 86.7 (C), 54.2 (C), 39.9 (CH_2), 26.2 (CH_3), 26.0 (CH_3); HRMS (ES) Found: MH^+, 330.1488, $C_{22}H_{20}NO_4$ requires MH^+, 330.1489; LRMS *m*/*z* (ES) 330.1 (100%, MH^+), 286.2 (8%) 203.6 (34%).

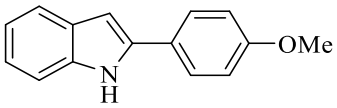
1-(4-Methoxyphenyl)ethanone phenylhydrazone 170



Phenylhydrazine (3.3 mL, 33.3 mmol) and 4′-methoxyacetophenone (5.0 g, 33.3 mmol) in EtOH (30 mL) followed by adding a few drops of AcOH.[107] The mixture was warmed to 50 °C for 15 min and was allowed to stir for 1 h at room temperature. The mixture was added to ice/water (50 mL) and after filtering was washed with cold water (5 × 30 mL) and dried to give hydrazine **170** (8.0 g, 99%) as a solid, which was used in next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69–7.59 (2H, m, 2 × CH), 7.24–7.04 (4H, m, 4 × CH), 6.86–6.74 (3H, m, 3 × CH) 3.74 (3H, s, OCH_3), 2.10 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.7 (C), 145.5 (C), 141.4 (C), 132.0 (C), 129.3 (CH), 126.9 (CH), 120.0 (CH), 113.7 (CH),

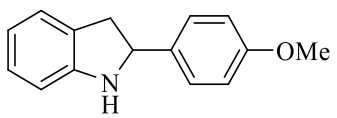
113.2 (CH), 55.4 (OCH_3) 11.9 (CH_3); HRMS (ES) Found: MH^+, 241.1342 $C_{15}H_{16}N_2O$ requires MH^+, 241.1335 LRMS *m/z* (ES) 241.1 (100%). Data consistent with the literature.[131]

2-(4-Methoxyphenyl)-1H-indene 164c



Polyphosphoric acid (6 g) was heated at 50 °C until followed by adding hydrazine **170** (3.0 g, 12.5 mmol) in toluene (30 mL). The mixture was heated at 135 °C for 2 h and was added to ice/H_2O (200 mL) and after filtering was washed with cold MeOH (5 × 50 mL). The filtrate was recrystallized by dissolving in a hot ethanol (50 mL) and a small amount of charcoal was added. After filtration, the solution was reheated and then water (5 mL) until cloudy point. Ethanol (2 mL) was added to give a clear solution that was allowed to cool to room temperature to give indole **164c** (1.98 g, 8.88 mmol, 71%), as white solid; m.p. 226–227 °C R_f 0.27 [petrol–EtOAc (90:10)]; ^{1} ^{1}H NMR (400 MHz, d_6-DMSO) δ = 11.41 (1H, brs, NH), 7.88 – 7.71 (2H, m, 2 × CH), 7.55–7.32 (2H, m, 2 × CH), 7.14–6.89 (4H, m, 4 × CH), 6.75 (1H, s, CH), 3.80 (3H, s, OCH_3); ^{13}C NMR (100 MHz, d_6-DMSO) δ = 158.8 (C), 137.8 (C), 137.0 (C), 128.9 (C), 126.4 (CH), 124.0 (C), 121.0 (CH), 1119.7 (CH), 1119.2 (CH), 114.4 (CH), 111.1 (CH), 97.3 (CH), 55.2 (OCH_3); HRMS (ES) Found: MH^+, 244.1070 $C_{15}H_{14}NO$ requires MH^+, 224.1070 LRMS m/z (ES) 244.1 (100%). Data consistent with the literature.[139]

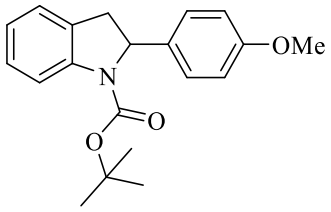
2-(4-Methoxyphenyl)-2,3-dihydro-1H-indole 165c



Indole **164c** (1.0 g, 4.5 mmol), and tin powder (3.0 g, 22.5 mmol) was added to a mixture of concentrated hydrochloric acid (10 mL) and EtOH (30 mL). The mixture was heated at 90 °C for 4 h, and then was cooled to room temperature. The reaction was quenched by aqueous KOH

(30 mL, 20%) at 0 °C. The organic product was extracted by Et_2O (3 × 100 mL). The combined organic layers were filtered through the Celite and the filtrate was washed by brine (40 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), gave the amine **165c** (832 mg, 3.7 mmol, 83%) as a solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42–7.32 (2H, m, 2 × CH), 7.14–7.05 (2H, m, 2 × CH), 6.94–6.84 (2H, m, 2 × CH), 6.81–6.71 (1H, m, CH), 6.69 (1H, d, *J* = 7.5 Hz, CH), 4.94 (1H, *J* = 9.0 Hz, CH), 4.12 (1H, brs, NH), 3.83 (3H, s, CH_3), 3.43 (1H, dd, *J* = 16.0, 9.0 Hz, CH), 2.99 (1H, dd, *J* = 16.0, 9.0 Hz, CH). Data consistent with the literature.[132]

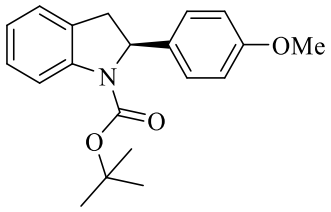
tert-Butyl 2-(4-methoxyphenyl)-2,3-dihydroindole-1-carboxylate 166c



n-BuLi (1.73 mL, 4.32 mmol, 2.5 M in hexane) was added to a stirred solution of indole **165c** (830 mg, 3.6 mmol) in THF (10 mL) at –78 °C. After 30 min, Boc_2O (780 mg, 3.6 mmol) in THF (5 mL) was added over 5 min. After allowing the mixture to warm to room temperature gradually over 16 h, the reaction was quenched with aqueous saturated $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), gave the carbamate **166c** (787 mg, 2.42 mmol, 67%) as needles; m.p. 81–82 °C; R_f 0.56 [petrol–EtOAc (90:10)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 (1H, br, CH), 7.25 (1H, t, *J* = 7.5 Hz, CH), 7.17–7.10 (3H, m, 3 × CH), 7.00 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.86–6.79 (2H, m, 2 × CH), 5.35 (1H, br, CH), 3.20 (3H, s, CH_3), 3.67 (1H, dd, *J* = 16.0, 11 Hz, CH), 2.96 (1H, dd, *J* = 16.0, 3.0 Hz, CH), 1.34 (9H, brs, *t*-Bu).[133]

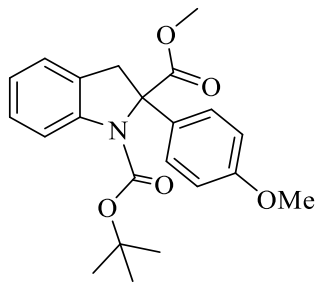
Resolution between the enantiomers of the carbamate **166c** was achieved using a Beckman system fitted with a Cellulose-1 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 $mL \cdot min^{-1}$; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 μL of the sample prepared in a 2 $g \cdot L^{-1}$ solution of the eluent. Under these conditions, the faster running component and slower running component were eluted at 19.4 min and 21.59 min respectively with an analysis time of 60 min.

***tert*-Butyl (2*S*)-2-phenyl-2,3-dihydroindole-1-carboxylate** (*S*)-**166c**



n-BuLi (0.24 mL, 0.55 mmol, 2.3 M in hexane) was added to a mixture of (+)-sparteine (220 mg, 0.92 mmol) and the racemic carbamate **166c** (300 mg, 0.92 mmol) in dry PhMe (21 mL) at –78 °C. After 190 min, MeOCOCl (0.21 mL, 2.76 mmol) was added and the reaction mixture was allowed to warm to room temperature over 16 h and then MeOH (3 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (98:2) to give recovered carbamate (*S*)-**166c** (150 mg, 50%) as an amorphous off-white solid; mp 83–84 °C; data as above; the enantiomeric ratio was determined to be 95:5 by CSP-HPLC (major component eluted at 21.85 min); $[\alpha]_D^{23}$ –42.4 (1.7, $CHCl_3$). In addition, the carbamate (*R*)-**170** (159 mg, 49%) was isolated as a solid data as below.

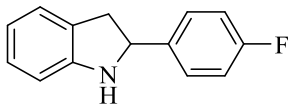
1-*tert*-Butyl 2-Methyl 2-phenyl-3H-indole-1,2-dicarboxylate 170



n-BuLi (0.2 mL, 0.37 mmol, 2.2 M in hexanes) was added to carbamate **166c** (100 mg, 0.31 mmol) in THF (4 mL) at –78 °C. After 35 min, MeOCOCl (0.1 mL, 0.93 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), to give the carbamate **170** (92 mg, 85%) as solid; m.p. 102–105 °C; R_f 0.25 [petrol–EtOAc (90:10)]; FT-IR ν_{max} (ATR)/cm^{-1} 2926, 2854, 1755 (C=O), 1710 (C=O), 1454, 1160, 1142, 1018, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06 (1H, brs, CH), 7.44–7.37 (2H, m, 2 × CH), 7.30–7.22 (1H, m, CH), 7.07 (1H, d, *J* = 7.0 Hz, CH), 7.02–6.96 (1H, m, CH), 6.91–6.81 (2H, m, 2 × CH), 3.87 (1H, d, *J* = 16 Hz, CH), 3.83–3.74 (6H, m, 2 × CH_3), 3.39 (1H, d, *J* = 16.0 Hz, CH), 1.29 (9H, brs, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, one quaternary carbon could not be observed) δ = 172.6 (C=O), 158.7 (C=O), 151.8 (C), 142.4 (C), 133.1 (C), 128.0 (CH), 127.8 (CH), 124.4 (CH), 123.0 (CH), 115.1 (CH), 113.1 (CH), 81.4 (C), 72.7 (C), 55.3 (CH_3), 52.6 (CH_3), 46.4 (C), 28.0 (CH_3); HRMS (ES) Found: MNa^+, 406.1645, $C_{22}H_{25}NO_5Na$ requires MNa^+, 406.1625; LRMS *m/z* (ES) 406.2 (100%, $MHNa^+$), 284 (11%) 204 (7%).

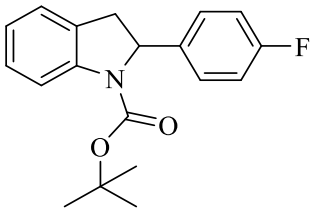
Resolution between the enantiomers of the the carbamate **170** was achieved using a Beckman system fitted with a Lux Cellulose–2 column (250 mm × 460 mm i.d.) as the stationary phase with a mixture of n-hexane–isopropanol (99.7:0.3 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 µL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the components were eluted at 46.1 min and 58.5 min with an analysis time of 100 min.

2-(4-Fluorophenyl)-2,3-dihydro-1H-indol 165d



Indole **164d** (1.0 g, 4.7 mmol), and tin powder (2.8 g, 23.7 mmol) was added to a mixture of concentrated hydrochloric acid (10 mL) and EtOH (30 mL). The mixture was heated at 90 °C for 4 h, and then was cooled to room temperature. The reaction was quenched by aqueous KOH (30 mL, 20%) at 0 °C. The organic product was extracted by Et_2O (3 × 100 mL). The combined organic layers were filtered through the Celite and the filtrate was washed by brine (40 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), gave the amine **165d** (3.7 g, 17.3 mmol, 91%) as a solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41–7.36 (2H, m, 2 × CH), 7.01–7.13 (4H, m, 4 × CH), 6.81–6.67 (2H, m, 2 × CH), 5.05 (1H,t, *J* = 9.0 Hz, CH), 4.15 (1H, br, NH), 3.54 (1H, dd, *J* = 16.0, 9 Hz, CH), 3.06 (1H, dd, *J* =16.0, 9 Hz, CH), Data consistent with the literature.[134]

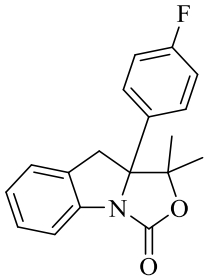
***tert*-Butyl 2-(4-fluorophenyl)-2,3-dihydroindole-1-carboxylate 166d**



n-BuLi (2.30 mL, 5.71 mmol, 2.5 M in hexane) was added to a stirred solution of indole **165d** (1.22 g, 5.71 mmol) in THF (20 mL) at –78 °C. After 30 min, Boc_2O (1.24 g, 5.71 mmol) in THF (5 mL) was added over 5 min. After allowing the mixture to warm to room temperature gradually over 16 h, the reaction was quenched with aqueous saturated $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), gave the carbamate **166d** (0.80 g, 45%) as white

cubic crystals; m.p. 105–110 °C; R_f 0.35 [petrol–EtOAc (90:10)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.26 (1H, br, CH), 7.24 (1H, t, *J* = 7.5 Hz, CH), 7.20–7.10 (3H, m, 3 × CH), 7.05–6.92 (3H, m, 3 × CH), 5.46 (1H, m, CH), (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.86–6.79 (2H, m, 2 × CH), 5.35 (1H, br, CH), 3.20 (3H, s, CH_3), 3.67 (1H, dd, *J* = 16.0, 10 Hz, CH), 2.95 (1H, dd, *J* = 16.0, 3.0 Hz, CH), 1.33 (9H, brs, *t*-Bu).[135]

9a-(4-Fluorophenyl)-1,1-dimethyl-9H-[1,3]oxazolo[3,4-a]indol-3-one 171



n-BuLi (0.15 mL, 0.38 mmol, 2.5 M in hexane) was added to carbamate **171** (100 mg, 0.34 mmol) in THF (4 mL) at –78 °C. After 35 min, acetone (0.07 mL, 0.96 mmol) was added. The mixture was allowed to warm to room temperature over 16 h and MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), to give the carbamate **166d** (67 mg, 70%) as solid; m.p. 170–172 °C; R_f 0.3 [petrol–EtOAc (90:10)]; FT-IR ν_{max} (ATR)/cm^{-1} 3048, 2982, 2935, 2866, 1748 (C=O), 1609, 1508, 1486; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 (1H, d, *J* = 8.0 Hz, CH), 7.39–7.35 (2H, m, 2 × CH), 7.30–7.22 (1H, m, CH), 7.05–6.88 (4H, m, 4 × CH), 3.88 (1H, d, *J* = 16 Hz, CH), 3.27 (1H, d, *J* = 16.0 Hz, CH), 1.64 (3H, s, CH_3), 1.06 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.3 (d, *J* = 248 Hz, C), 155.9 (C=O), 140.3 (C), 137.0 (C), 132.2 (C), 127.8 (C), 128.3 (C), 127.9 (d *J* = 8.0 Hz, CH), 125.2 (CH), 125.0 (CH), 116.1 (CH), 115.4 (d, *J* = 21.6 Hz, CH) 86.6 (C), 78.1 (C), 40.0 (CH_2), 26.1 (CH_3), 25.8 (CH_3).

Chapter 6 - Appendices

Appendices A: The absolute configuration of quinoxaline **(*R*)-103a** obtained by single crystal X-ray analysis.

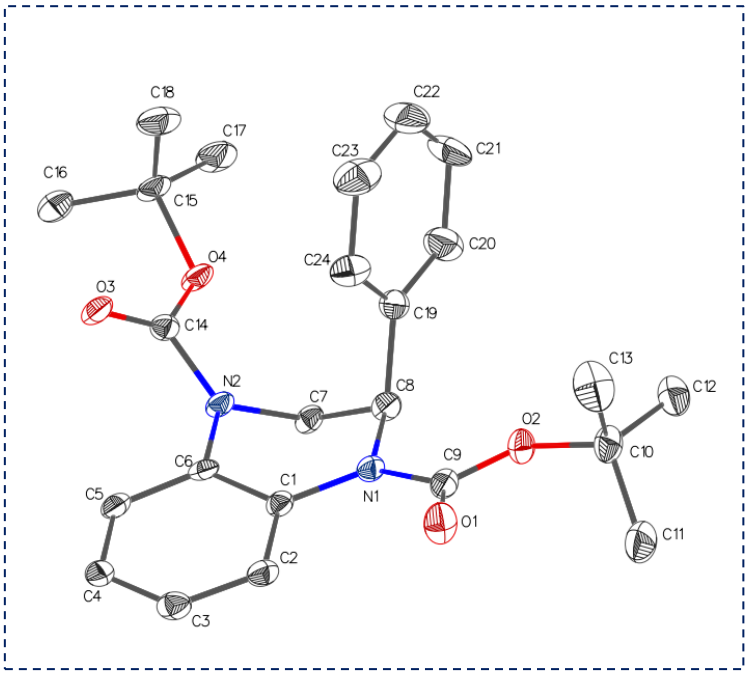


Table 1 Crystal data and structure refinement for oic295v_02_fs.

Identification code	oic295v_02_fs
Empirical formula	$C_{24}H_{30}N_2O_4$
Formula weight	410.50
Temperature/K	99.99
Crystal system	monoclinic
Space group	$P2_1$
a/Å	11.2883(10)
b/Å	6.3738(6)
c/Å	16.3030(14)
α/°	90
β/°	104.260(4)
γ/°	90
Volume/Å^3	1136.85(18)
Z	2
ρ_{calc}g/cm^3	1.199
μ/mm^{-1}	0.658
F(000)	440.0
Crystal size/mm^3	0.15 × 0.15 × 0.05
Radiation	CuKα (λ = 1.54178)

2Θ range for data collection/°	5.592 to 130.336
Index ranges	$-13 \leq h \leq 13, -7 \leq k \leq 6, -19 \leq l \leq 19$
Reflections collected	19490
Independent reflections	3800 [R_{int} = 0.0672, R_{sigma} = 0.0500]
Data/restraints/parameters	3800/1/278
Goodness-of-fit on F^2	1.109
Final R indexes [I>=2σ (I)]	R_1 = 0.0423, wR_2 = 0.0826
Final R indexes [all data]	R_1 = 0.0501, wR_2 = 0.0849
Largest diff. peak/hole / e $Å^{-3}$	0.19/-0.17
Flack parameter	0.04(13)

Appendices B: *N*-Boc-2-(4-methoxyphenyl)indoline (*S*)-166a

The absolute configuration of (***S***)-**22a** obtained by single crystal X-ray analysis. **ASH-473-RSM**

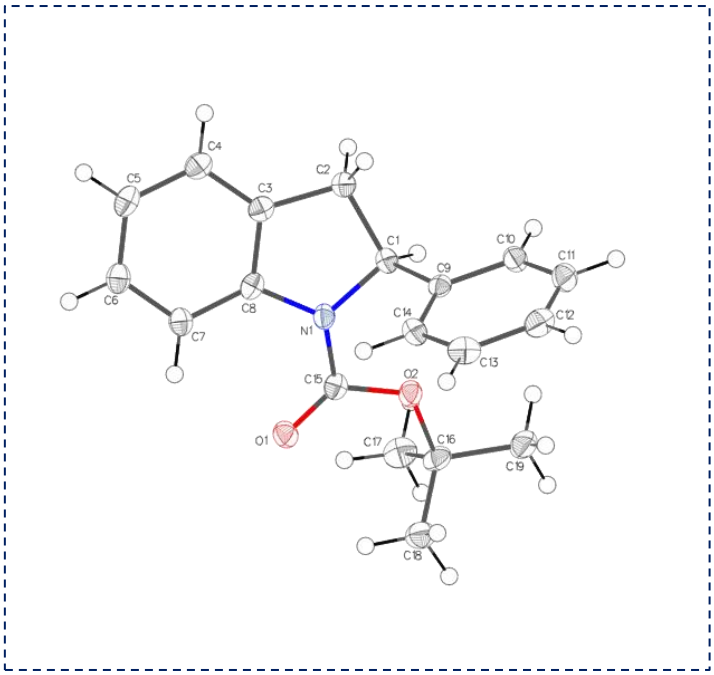


Table 1 Crystal data and structure refinement for OIC310v.

Identification code OIC310v

Empirical formula $C_{19}H_{21}NO_2$

Formula weight 295.37

Temperature/K 100.04

Crystal system orthorhombic

Space group P2 1 2 1 2 1

a/Å 5.8602(9)

b/Å 16.445(2)

c/Å 16.445

α/° 90

β/° 90

γ/° 90

Volume/Å 3 1584.7(3)

Z 4

ρ calc g/cm 3 1.238

μ/mm 1 0.632

F(000) 632.0

Crystal size/mm 3 0.25 × 0.23 × 0.19

Radiation CuKα (λ = 1.54178)

2Θ range for data collection/° 7.602 to 135.514

Index ranges -7 ≤ h ≤ 6, -19 ≤ k ≤ 19, -19 ≤ l ≤ 19

Reflections collected 59531

Independent reflections 2819 [R int = 0.0784, R sigma = 0.0230]

Data/restraints/parameters 2819/0/202

Goodness-of-fit on F 2 1.170

Final R indexes [I>=2σ (I)] R 1 = 0.0312, wR 2 = 0.0761

Final R indexes [all data] R 1 = 0.0321, wR 2 = 0.0775

Largest diff. peak/hole / e Å -3 0.18/-0.26

Flack parameter 0.15(6)

Appendices C: The absolute configuration of (*S*,*R*)-**166a** obtained by single crystal X-ray analysis.

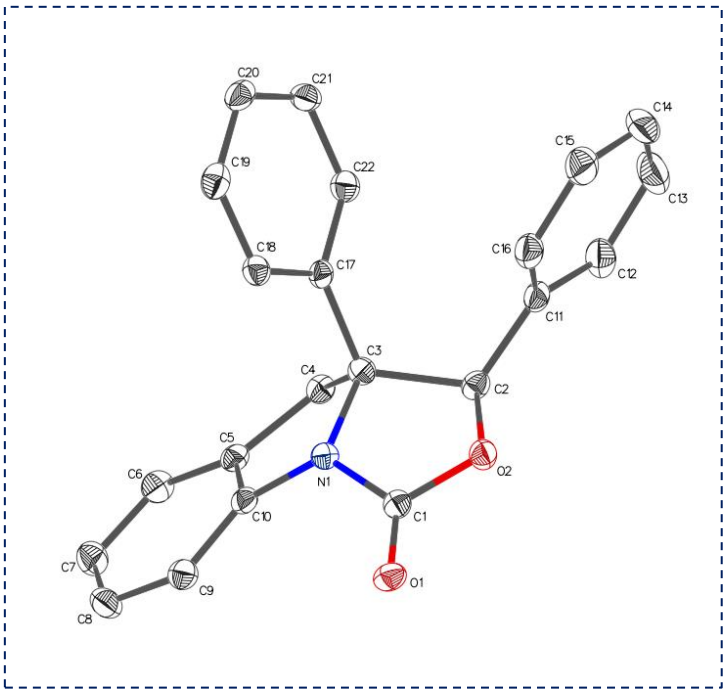


Table 1 Crystal data and structure refinement for OIC312v_0m.

Identification code OIC312v_0m

Empirical formula C 22 H 17 NO 2

Formula weight 327.36

Temperature/K 100.03

Crystal system monoclinic

Space group P2 1

a/Å 11.0623(10)

b/Å 6.2201(6)

c/Å 12.3625(11)

α/° 90

β/° 104.795(3)

γ/° 90

Volume/Å 3 822.44(13)

Z 2

ρ calc g/cm 3 1.322

μ/mm 1 0.674

F(000) 344.0

Crystal size/mm 3 0.3 × 0.25 × 0.23

Radiation CuKα (λ = 1.54178)

2Θ range for data collection/° 7.396 to 133.466

Index ranges -13 ≤ h ≤ 13, -7 ≤ k ≤ 7, -13 ≤ l ≤ 14

Reflections collected 19740

Independent reflections 2890 [R int = 0.0457, R sigma = 0.0274]

Data/restraints/parameters 2890/1/226

Goodness-of-fit on F 2 1.087

Final R indexes [I>=2σ (I)] R 1 = 0.0285, wR 2 = 0.0698

Final R indexes [all data] R 1 = 0.0292, wR 2 = 0.0703

Largest diff. peak/hole / e Å -3 0.15/-0.21

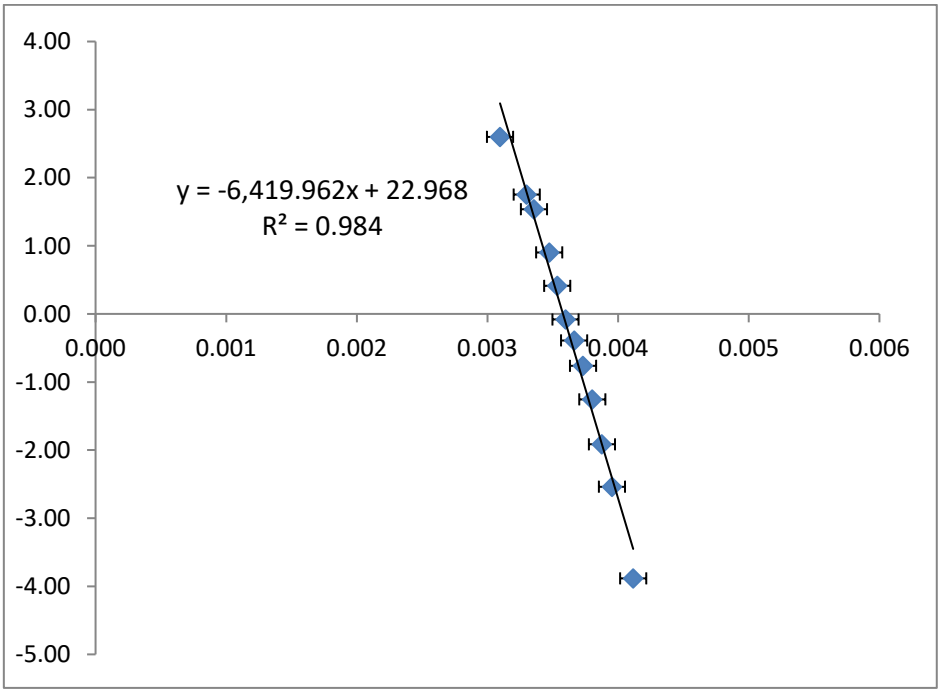
Flack parameter 0.01(7)

Appendices D: Variable Temperature of *tert*-Butyl 2-Phenyl-2,3-dihydroindole-1-carboxylate 166a

T/K	1/T	k1	In(k1/T)	lnk1	k-1	In(k-1/T)	lnk-1
223	0.004484	0	X	X	0	X	X
233	0.004292	0	X	X	0	X	X
243	0.004115	5	-3.88362	1.609438	0.833	-5.67538	-0.18232
253	0.003953	20	-2.53766	2.995732	3.333	-4.32942	1.203973
258	0.003876	38	-1.91537	3.637586	6.333	-3.70713	1.845827
263	0.003802	75	-1.25467	4.317488	12.500	-3.04643	2.525729
268	0.003731	125	-0.76267	4.828314	20.833	-2.55443	3.036554
273	0.003663	185	-0.38912	5.220356	30.833	-2.18088	3.428596
278	0.003597	256	-0.08244	5.545177	42.667	-1.87420	3.753418
283	0.003534	427	0.411337	6.056784	71.167	-1.38042	4.265025
288	0.003472	711	0.903712	6.566672	118.500	-0.88805	4.774913
298	0.003356	1387	1.537805	7.234898	231.167	-0.25395	5.443139
303	0.003300	1748	1.752495	7.466228	291.333	-0.03926	5.674468
323	0.003096	4347	2.599589	8.377241	724.500	0.80783	6.585482

Eyring plot for minor rotamer to major:

Eyring plot: A plot of ln(k/T) against 1/T will give a straight line of the form $y = mx + c$ with gradient $m = -\Delta H^{\ddagger}/R$ and intercept $c = \Delta S^{\ddagger}/R + \ln(kB/h)$.

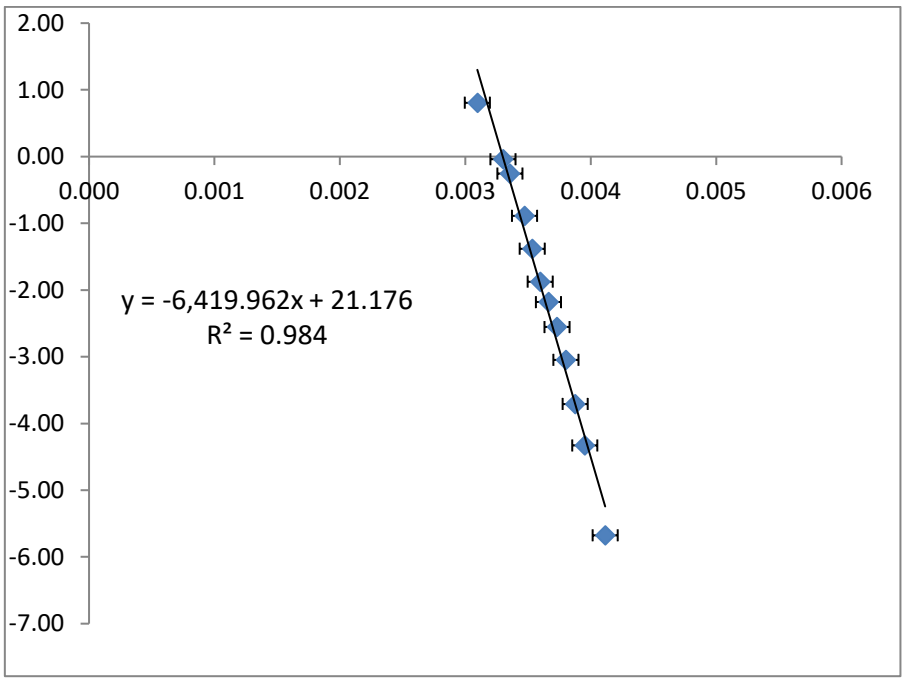


Forward direction (minor rotamer to major)

Slope	Intercept	ΔH (J/mol)	ΔH (kcal/mol)	ΔS (J/K.mol)
-6419.96	22.968	53378.76	12.76	-6.59

ΔG (kJ/mol)	ln k	k (s-1)	t(1/2) (sec)
54.66 at -78 C 13.1 kcal/mol	-4.68184	0.0093	74.84

Eyring plot for major rotamer to minor:



Reverse direction (major rotamer to minor):

Slope	Intercept	ΔH (J/mol)	ΔH (kcal/mol)	ΔS (J/K.mol)
-7063.3	23.651	58727.81	14.04	-0.91

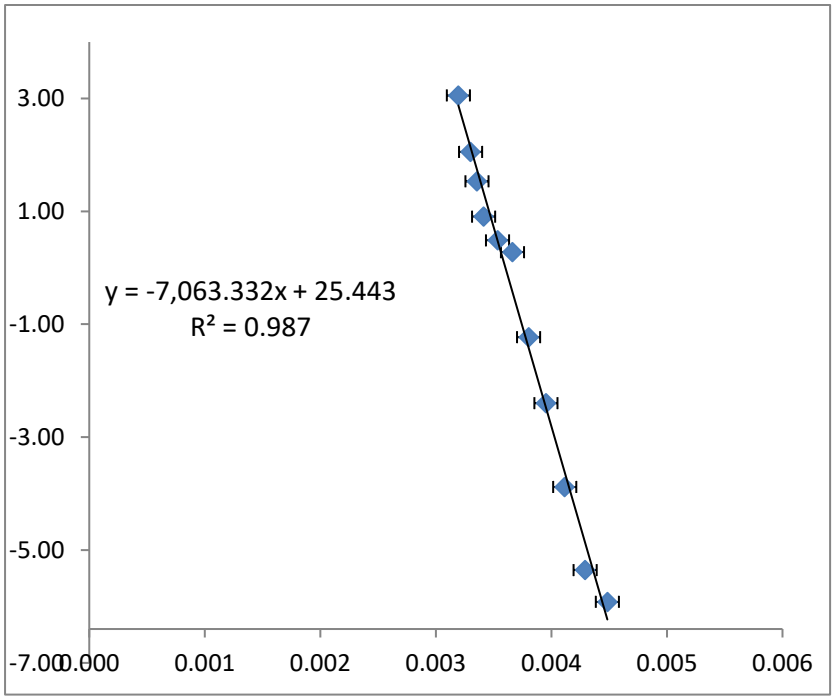
ΔG (kJ/mol)	ln k	k (s-1)	$t_{(1/2)}$ (sec)
58.90 at -78 C	-7.29802	0.0007	1024.03 17.07 min

Appendices D: *tert*-Butyl 2-(4-Methoxyphenyl)-2,3-dihydroindole-1-carboxylate

166c

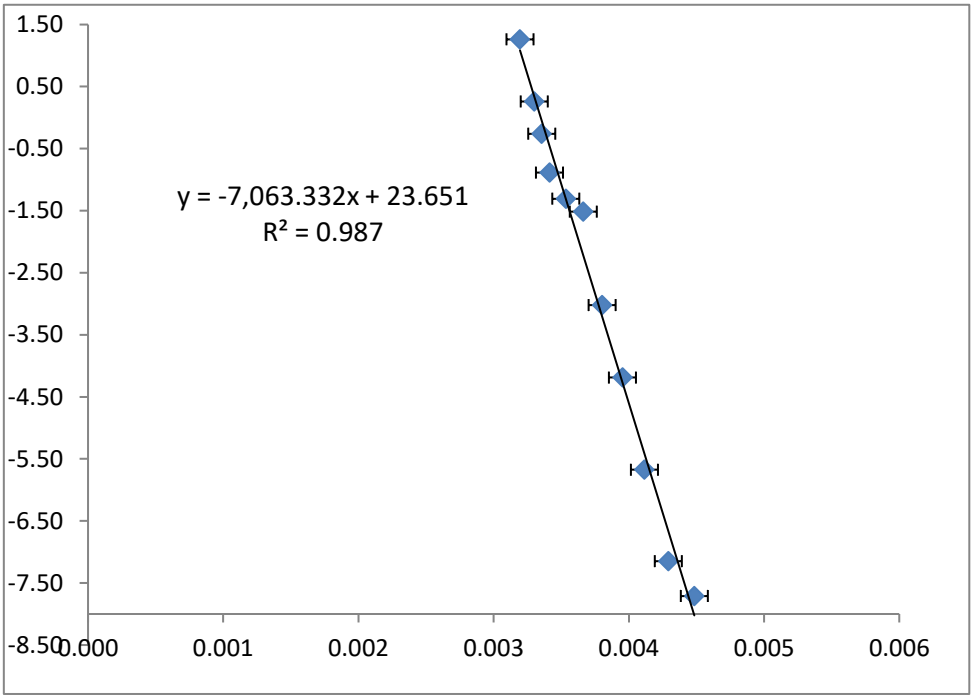
Here are data for forward and reverse direction based on iNMR D simulation done myself 24 Jun 2019:

T/K	1/T	k1	In(k1/T)	lnk1	k-1	In(k-1/T)	lnk-1
195	0.005128	0	#NUM!	#NUM!	0	#NUM!	#NUM!
203	0.004926	1	-5.31321	0	0.166667	-7.10497	-1.79176
213	0.004695	2	-4.89129	0.470004	0.266667	-6.68305	-1.32176
223	0.004484	1	-5.918	-0.51083	0.1	-7.70976	-2.30259
233	0.004292	1	-5.35573	0.09531	0.183333	-7.14749	-1.69645
243	0.004115	5	-3.88362	1.609438	0.833333	-5.67538	-0.18232
253	0.003953	23	-2.3979	3.135494	3.833333	-4.18965	1.343735
263	0.003802	77	-1.22835	4.343805	12.83333	-3.02011	2.552046
273	0.003663	360	0.276632	5.886104	60	-1.51513	4.094345
283	0.003534	460	0.48578	6.131226	76.66667	-1.30598	4.339467
293	0.003413	725	0.905999	6.586172	120.8333	-0.88576	4.794412
298	0.003356	1380	1.532745	7.229839	230	-0.25901	5.438079
303	0.003300	2360	2.052684	7.766417	393.3333	0.26092	5.974657
313	0.003195	6640	3.054664	8.800867	1106.667	1.26290	7.009108
323	0.003096		#NUM!	#NUM!	0	#NUM!	#NUM!



Forward direction (minor rotamer to major)

Slope	Intercept	ΔH (J/mol)	ΔH (kcal/mol)	ΔS (J/K.mol)	
-7063.3	25.443	58727.81	14.04	13.99	
		ΔG (kJ/mol)	ln k	k (s-1)	t(1/2) (sec)
		56.00 at -78 C 13.4 kcal/mol	-5.50602	0.0041	170.63



Reverse direction (major rotamer to minor):

Slope	Intercept	ΔH (J/mol)	ΔH (kcal/mol)	ΔS (J/K.mol)	
-7063.3	23.651	58727.81	14.04	-0.91	
		ΔG (kJ/mol)	ln k	k (s-1)	t(1/2) (sec)
		58.90 at -78 C 14.1 kcal/mol	-7.29802	0.0007	1024.03 17.07 min

Chapter 7 - References

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