Synthesis of Substituted Tetrahydroquinolines Using Chiral Organolithium Chemistry

Submitted by

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to the University of Sheffield as a thesis for the degree of Doctor of Philosophy in Chemistry

August 2017

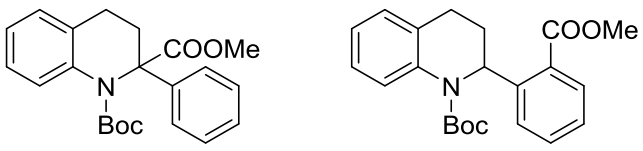
The University Of Sheffield.

Abstract

The tetrahydroquinoline (THQ) moiety is found in many natural products and compounds which have biological activity. This thesis describes the development of methodologies to carry out lithiation–substitution reactions of *N*-Boc-2-aryltetrahydroquinolines. Most of the THQ compounds fully deprotonated within a few minutes and the lithiated intermediates were configurationally stable at low temperature.

A variety of novel *α*-substituted products were obtained in good to excellent yields. Kinetic resolutions were attempted using the *n*-BuLi / (+)-sparteine 'chiral base' and a number of the starting materials were recovered in good yields and excellent enantiomer ratios (ers). The enantioenriched recovered starting materials were then used in lithiation-substitution reactions in order to give the *α*-substituted products in good to excellent yields and ers.

When cyanoformates were used as the electrophiles in the lithiation–substitution sequence, the *ortho*-substituted products were formed as opposed to the *α*-substituted products obtained when chloroformates were used as the electrophiles. This change in regioselectivity when different electrophiles were used was unprecedented in the area of organolithium chemistry.



When triethylborane was added to the lithiated intermediate, an N–C Boc migration was promoted. The secondary amine product was obtained in good yield and in high er when enantioenriched *N*-Boc-2-phenyl-THQ was used in the reaction.

Kinetic resolutions using the *n*-BuLi / (+)-sparteine 'chiral base' have also been attempted on a number of *N*-Boc-3-aryl-1,2,3,4-tetrahydro-1,4-benzoxazines. While no *α*-substituted products could be obtained due to *β*-elimination, the starting materials were recovered from these reactions in good to excellent yields and ers.

Contents

Acknowledgements

I would firstly like to thank my supervisor, Professor Iain Coldham, for giving me the opportunity to carry out a PhD in his research group. I have thoroughly enjoyed the experience and would do it all again if I could! I would also like to thank Iain for his invaluable help and guidance throughout my PhD, without which I would not be where I am today.

I would like to thank the EPSRC for funding the PhD.

I would like to thank all of the members of the Coldham group that I have shared D76 and E28 with over the last few years who have made the PhD a lot more enjoyable. Namely, these are Xiabing who introduced me to the techniques involved in carrying out organolithium chemistry, Graeme, Madeha, Melanie, Ed, Khalid, Rachel, Phil, Ryan, John, Karen, Ruaa (habibti!), Rungroj, Ziad, Tahani, Arghya, Ashraf and Anthony. I would also like to thank the Level 4 students that I have supervised during my PhD, Lewis, Anthony (again!) and Sophie for carrying out great work and all of the other Level 4 and summer students that have worked in the group. I really looked forward to coming into the lab' each day due to the friendliness and companionship of the group.

I would like to thank the support staff in the department for their help during my PhD. These are Keith, Rob in HPLC, Nick, Peter and Sharon in stores, Harry and Craig in X-ray, Brian, Sue and Sandra in NMR, Sharon and Simon in Mass Spec., Jenny in Elemental Analysis and Elaine for supervising my cyanoborohydride reactions.

I would finally like to thank my Mum and Dad for the massive amount of love and support they give me as without it, I wouldn't have been able to complete my PhD and I can't thank them enough.

Nil satis nisi optimum.

Gloria Patri, et Filio, et Spiritui Sancto, sicut erat in principio, et nunc, et semper, et in saecula saeculorum. Amen.

Abbreviations

Ac	acetyl
AIDS	Acquired Immune Deficiency Syndrome
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Boc-ON	2-(*tert*-Butoxycarbonyloxyimino)-2-phenylacetonitrile
CIPE	complex induced proximity effect
cm	centimetre(s)
COD	1,5-Cyclooctadiene
(–)-CSA	(–)-Camphorsulfonic acid
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
HIV	Human Immunodeficiency Virus
HMPA	Hexamethylphosphoramide
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/A	not available

n-Bu	normal butyl
nm	nanometre(s)
NMDA	*N*-Methyl-D-aspartate
NMR	nuclear magnetic resonance
Nos	nosyl / nitrobenzenesulfonyl
OTf	triflate
p-	*para*-
PARP	Poly (ADP-ribose) polymerase
pH	potential of hydrogen
Ph	phenyl
Piv	pivaloyl
PMDTA	*N*, *N*, *N*′, *N*′, *N*″-Pentamethyldiethylenetriamine
pro-	proton
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
surr	surrogate
t	time
^{t}Bu or *t*-Bu	tertiary butyl
TCE	1,1,2-Trichloroethane
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

Chapter 1 – Introduction

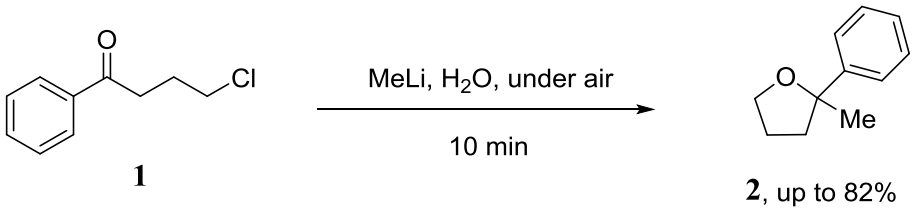
1.1 Organolithium chemistry

1.1.1 General introduction to organolithium chemistry

Organolithium chemistry is one of the most widely used and important areas of organic synthesis. Functionalisation by lithiation and electrophilic quench is among the most fundamental of synthetic transformations.[1] There are a wide variety of compounds that can be accessed via this, often simple, chemistry which makes it a very attractive technique. It is therefore broadly integrated and widely applied in studies that bridge inorganic, physical, organic, and theoretical chemistry.[2]

Organolithium reagents contain a strongly polarised carbon–lithium bond, thought to be largely ionic in nature, and it is this polarisation which is the key to their reactivity.[3] The difference between the electronegativity of the two atoms means that most of the electron density is on the carbon and so the bond can be thought of as having a similar type of reactivity to a carbanion which gives an organolithium reagent its strongly basic and nucleophilic properties.

The formation of new C–C σ bonds with a high degree of selectivity is still of great importance for researchers in a wide variety of fields. Therefore, the area of organolithium chemistry is very active with publications being reported on a regular basis. In 2016, Capriati and co-workers, demonstrated the progress made in this area of research over the years and showed that it was 'a land still worth exploring'.[4,5] They reported a remarkable reaction of 4-chloro-1-phenylbutan-1-one **1** with methyllithium which gave 2-methyl-2-phenyltetrahydrofuran **2** in good yield at room temperature, under air with water as the solvent (Scheme 1). This reaction would have been unthinkable a number of years ago as it had always been assumed that reactions employing organolithium reagents couldn't be successful unless they took place under anhydrous conditions and inert atmospheres.



1 **2**, up to 82%

Scheme 1

1.1.2 Organolithium reagents in solution – aggregation and reactivity

Organolithium reagents are typically highly reactive and are therefore usually stored in solvents in which they are soluble and stable, such as hydrocarbons. The electron-deficient lithium atom cannot be adequately stabilised by a single carbanionic ligand and with very little stabilisation provided by the hydrocarbon solvent, freezing-point measurements indicate that organolithiums are typically aggregated as hexamers, tetramers or dimers. This difference in aggregation state is mainly due to steric hindrance with bulky organolithiums such as benzyllithium primarily existing as dimers, whereas primary organolithiums such as *n*-butyllithium primarily exist as hexamers (Table 1).[1] These 'homo-aggregates', with a structure consisting of a core of alternating Li and C atoms, have a much lower reactivity than what is typically needed from an organolithium reagent.[6,7]

Hexameric	Tetrameric	Dimeric	Monomeric
EtLi	*i*-PrCH$_2$Li	PhCH$_2$Li	None
BuLi	*i*-PrLi		
	t-BuLi		

Table 1 – Typical aggregation state of organolithiums in hydrocarbon solution

The aggregation states need to be lowered in order to increase the reactivity of organolithiums to a suitable level and this can be done by introducing co-ordinating ligands or solvents to provide electron density for the electron-deficient lithium. In co-ordinating solvents such as diethyl ether or THF, tetramers and dimers become typical aggregation states for *n*-butyllithium which are much more reactive states than the hexamers found in hydrocarbon solutions. Other ligands, usually amines or ethers (Figure 1), can also be used to deaggregate the organolithiums, even in the absence of a co-ordinating solvent. These co-ordinating solvents and ligands form 'hetero-aggregates' which are typically much more reactive than the 'homo-aggregates'.[7,8]

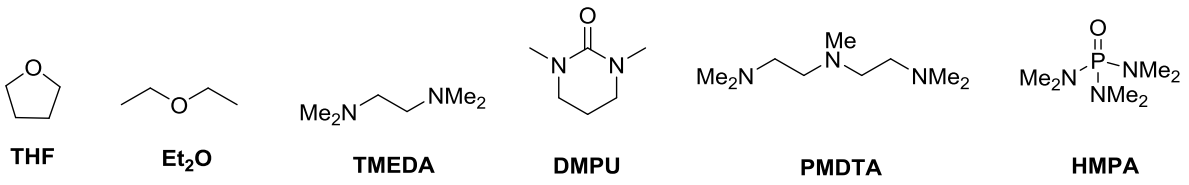
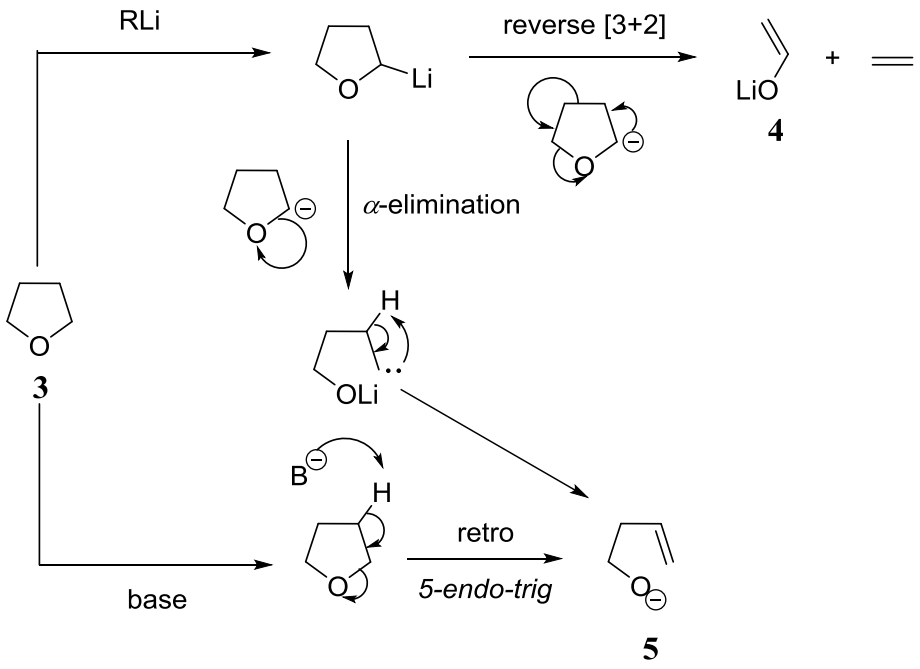


Figure 1

However, as the solvents and ligands in the figure above tend to react to some extent with organolithium reagents, reactions usually need to be carried out below ambient temperature.[1] THF readily decomposes in the presence of organolithium reagents at room temperature by one of two pathways (Scheme 2).[9,10]

The first pathway involves abstraction of an α-proton of THF **3**, followed by a reverse [3+2] cycloaddition of the anion to form ethylene and the lithium enolate of acetaldehyde **4**.[11] The second pathway, which was first reported in solution by Fleming and co-workers in 1998, only seems to be observed when very basic organolithiums are used.[12] It involves the formation of but-3-en-1-oxide **5** but it is not known whether this is formed *via* a disfavoured retro *5-endo-trig* reaction or as a result of the rearrangement of a carbene.[13]



Scheme 2

The half-lives of organolithium/solvent mixtures vary greatly depending both on the ability that an organolithium reagent has to react with the solvent it is dissolved in and also how fast the organolithium species can self-decompose (Table 2).[1,14,15] Changes in temperature can have a very large effect on an organolithium reagent's lifetime and as a general rule, a temperature increase of 20 °C shortens the lifetime of an organolithium by a factor of 10.[1]

Organolithium	Solvent	Temperature (°C)	Half-Life
MeLi	Et_2O	25	3 months
PhLi	Et_2O	35	12 d
n-BuLi	Bu_2O	150	35 min
	DME	0	<5 min
	Et_2O	35	31 h
	Et_2O	25	153 h
	Et_2O + TMEDA	20	10 h
	THF	35	10 min
	THF + TMEDA	20	30 min
	THF + TMEDA	0	5 h
	THF + TMEDA	–20	50 h
t-BuLi	Et_2O	0	1 h
	Et_2O	–20	8 h
	THF	–20	45 min

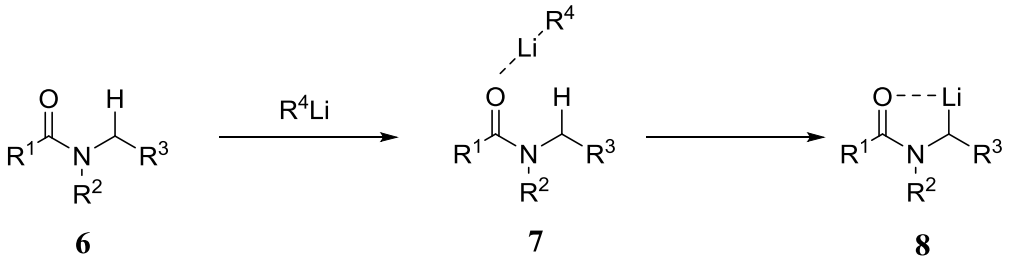
Table 2 – Stabilities of organolithium reagents in common solvents

1.1.3 *α*-Amino-organolithiums

Hydrocarbons lithiate very slowly under normal conditions and the organolithium intermediate species must be sufficiently stabilised for the deprotonation to occur at a reasonable rate.[1] There are two possible ways in which the intermediate can be stabilised. There can either be an intramolecular co-ordination of the electron-deficient lithium atom to a nearby heteroatom, such as oxygen or nitrogen, or the electron rich C–Li bond can be stabilised by a proximal empty orbital or electron-withdrawing group.

The co-ordination of organolithium reagents to nearby heteroatoms prior to lithiation was reviewed by Beak and Meyers in 1986.[16] The effect, which they called the 'complex induced proximity effect' (CIPE), involves complexation of the directing, Lewis basic moiety in a substrate **6** to the organolithium reagent to form a 'pre-lithiation complex' **7** (Scheme 3). This complex brings the reactive *α*-proton of the substrate into proximity of the reagent and this facilitates deprotonation to form the lithiated intermediate **8**.[17] Beak and Meyers postulated that

this effect could be as important as resonance, stereoelectronic, inductive and steric effects in determining the course of reactions involving these reagents.



Scheme 3

Lithiations adjacent to sulfur, phosphorus, oxygen and nitrogen based functional groups are favoured with the acidity of the proton being removed increasing if it is benzylic, allylic or attached to a small-ring saturated heterocycle. α-Amino-organolithium compounds are formed when lithiation takes place α to a nitrogen atom and these intermediates are important as they can readily react with electrophiles to form various substituted amines. There are three main classifications of these species: Unstabilised, dipole-stabilised and mesomerically-stabilised (Figure 2).[18]

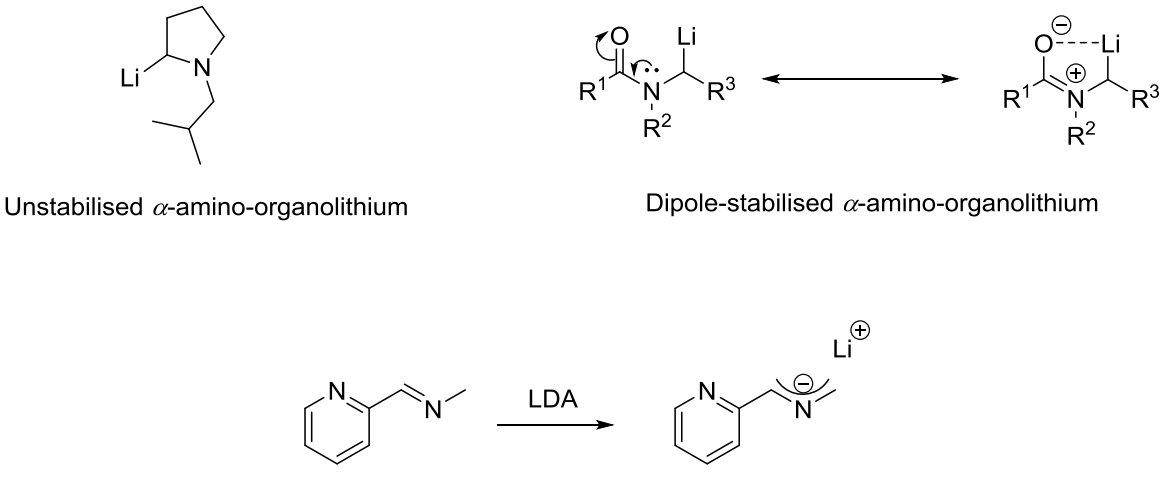
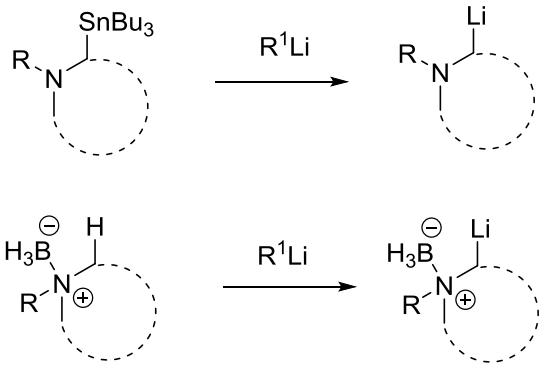


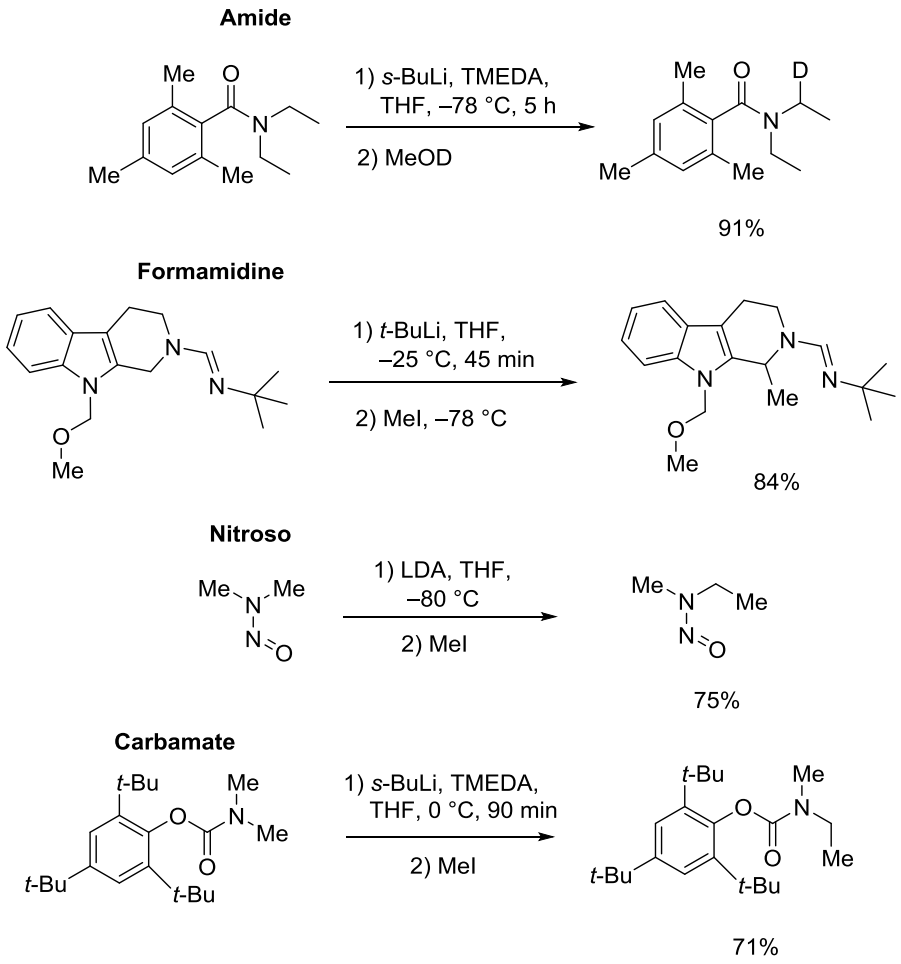
Figure 2

'Unstabilised' α-amino-organolithium compounds are derived from tertiary amines where the nitrogen atom is not acylated. The lone pair on the nitrogen can co-ordinate to and stabilise the incoming organolithium reagent. The lone pair also destabilises the adjacent carbon-lithium bond by an anti-bonding interaction but will stabilise the lithium by co-ordination, normally through a dimeric structure. The two main strategies of making these compounds are via either tin–lithium exchange reactions or deprotonation of quaternary ammonium complexes, although a degree of dipole stabilisation will be present in the latter to give some extra stability to the organolithium species (Scheme 4). The chemistry of these compounds has so far been less developed than stabilised α-amino organolithiums.[19]



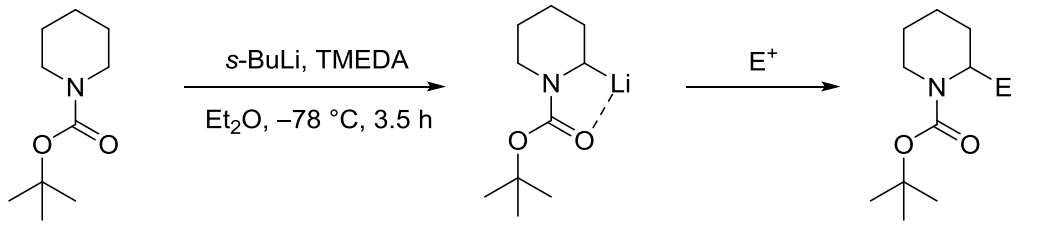
Scheme 4

If the nitrogen lone pair is in conjugation with a carbonyl group, the interaction between the lone pair and the C–Li bond is lessened. The delocalisation of the nitrogen atom's lone pair into the amide carbonyl, or similar functional group, gives a dipolar resonance form with a positively charged nitrogen atom adjacent to the carbanionic carbon atom. This is called a dipole-stabilised carbanion. Various groups have been used for this stabilisation, including amide,[20] formamidine,[21] nitroso[22] and carbamate[23] groups (Scheme 5).



Scheme 5

In 1989, Beak and Lee reported the first use of the *tert*-butoxycarbonyl (Boc) group as a convenient directing group for the α-lithiation of amines.[24] They showed that the α-lithiation of *N*-Boc-piperidine **9** with *s*-BuLi, followed by quenching with a range of electrophiles, proceeded smoothly to give the products **10** in good to excellent yields (Scheme 6). This group can usually be added using standard procedures and readily removed by mild acid treatment which has made it the most prevalent directing group for the α-lithiation of amines since this time.

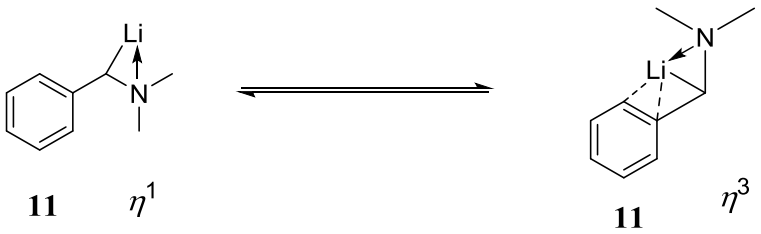


9 **10**

$E^+ = Me_3SiCl = 94\%$
$E^+ = PhSSPh = 61\%$
$E^+ = Me_2SO_4 = 53\%$

Scheme 6

There are two important structural types of mesomerically-stabilised *α*-amino-organolithium compounds; these are lithiated allylic or benzylic amines, and 2-azaallyl anions. Lithiated allylic or benzylic amines contain varying degrees of resonance stabilisation of the negative charge and the position of the lithium atom is not always clear. For example, *α*-lithio *N*,*N*-dimethylbenzylamine **11** shows a dynamic equilibrium, in solution, between η^1 and η^3 bonding.[25] The position of the equilibrium varies depending on the temperature, with η^1 bonding predominant at lower temperatures (Scheme 7).

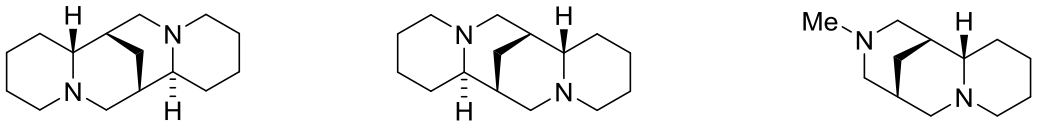


11 η^1 **11** η^3

Scheme 7

1.2 Asymmetric synthesis using organolithium reagents

In reactions involving organolithiums, chiral diamines can not only be used to stabilise the organolithium intermediate, but these ligands have also been shown to be remarkably efficient aids for enantioselective synthesis.[26] The most common chiral diamines in use are the lupine alkaloid (–)-sparteine **12** which can be obtained from Scotch Broom,[27] (+)-sparteine **13** which is a component of the shrub *Sophora pachycarpa C. A. Mey*,[28] or the (+)-sparteine surrogate **14**, developed by O'Brien and co-workers (Figure 3).[29]

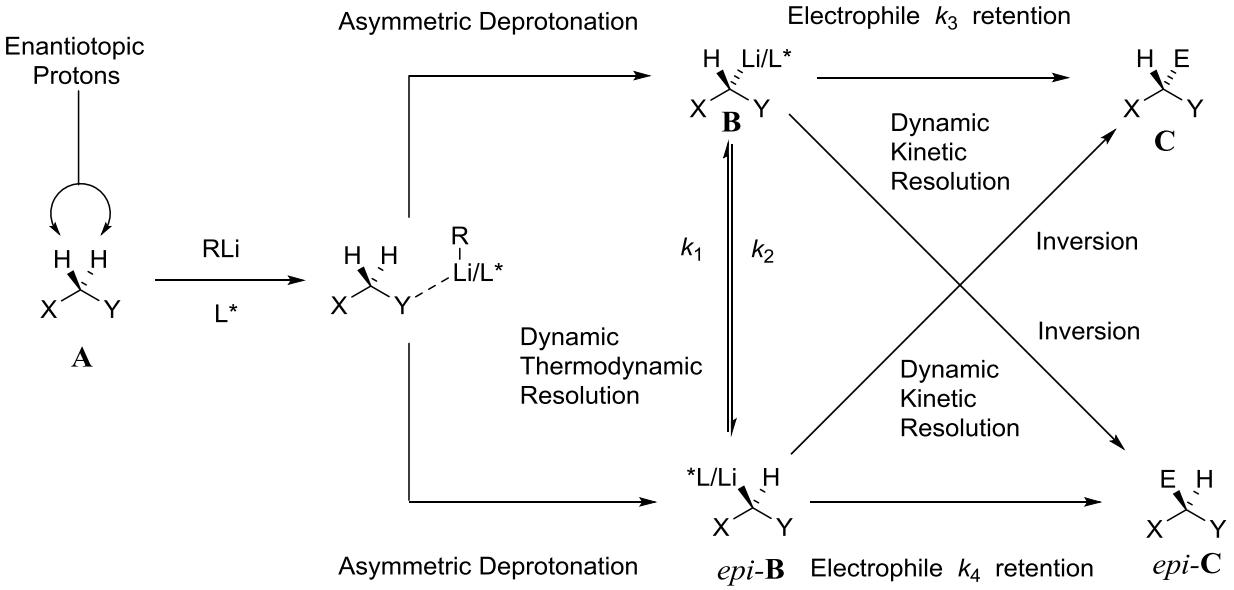


12 **13** **14**

Figure 3

When carrying out a reaction with a chiral organolithium species to induce asymmetry, there are three key factors which determine the stereoselectivity (Scheme 8).[2]

1) The selectivity of the proton abstraction of the substrate **A** to form **B** and *epi*-**B.**
2) The rate of epimerisation of **B** and *epi*-**B** relative to their rate of reaction with the electrophile.
3) The stereochemical course of the electrophile substitution (retention or inversion).



Scheme 8

Four pathways are possible for the transfer of stereochemical information:

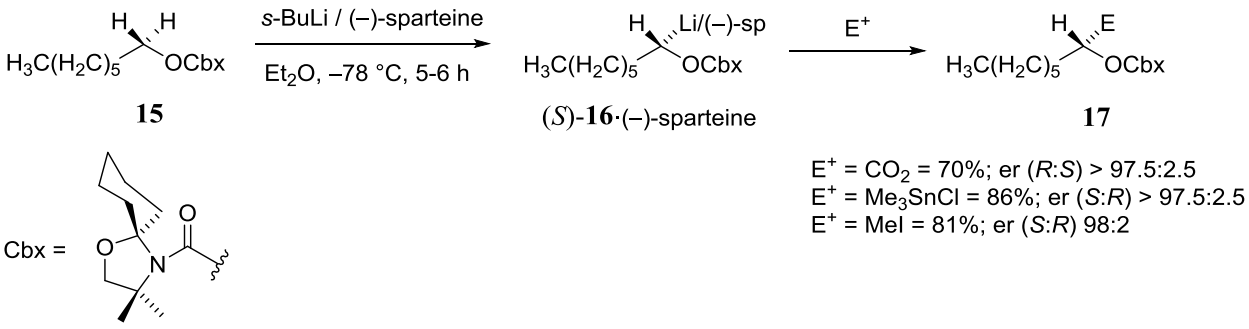
1) Asymmetric Deprotonation
2) Kinetic Resolution (KR)
3) Dynamic Thermodynamic Resolution (DTR)
4) Dynamic Kinetic Resolution (DKR)

1.2.1 Asymmetric deprotonation

Asymmetric deprotonation is the simplest method of asymmetric synthesis using organolithium reagents. It involves an organolithium reagent forming a complex with a chiral ligand, such as (–)-sparteine, to form a 'chiral base'. This can selectively remove an enantiotopic proton, via energetically non-equivalent diastereomeric transition states, from an achiral substrate.[26] After quenching the lithiated intermediate, which must be configurationally stable in order for this method to be viable, with an electrophile, products with a high enantiomeric ratio can be formed.

The work of Nozaki and co-workers, over 45 years ago, was pioneering in this field as they were the first to show that the use of an organolithium reagent in a complex with (–)-sparteine could induce asymmetry in a lithiation–substitution sequence.[30]

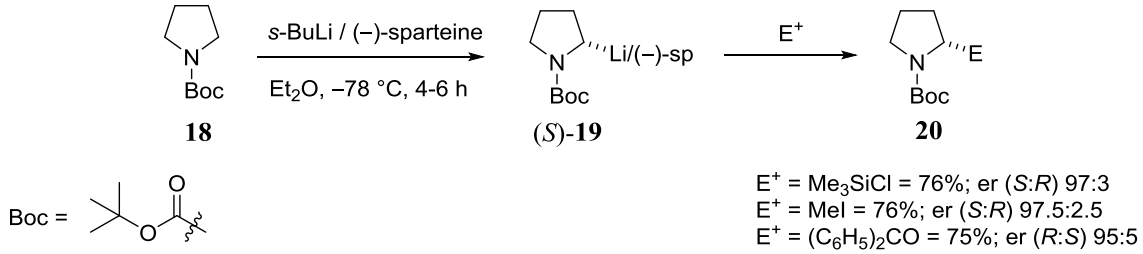
Hoppe and co-workers, over 25 years ago, re-stimulated interest in this area.[31] They found that deprotonation adjacent to the oxygen of the carbamate **15** using *s*-BuLi in Et_2O, in the presence of (–)-sparteine, formed the complex *(S)*-**16**·(–)-sparteine with high diastereomeric excess. This proved that the 'chiral base' can discriminate between the enantiotopic protons in **15** and can selectively abstract the *pro-S* proton. This was confirmed by quenching the intermediate with various electrophiles as excellent enantiomeric ratios of the products **17** were obtained in all reactions (Scheme 9).



Scheme 9

An excellent example of asymmetric deprotonation was reported by Beak and Kerrick in 1991.[32] They described the application of Hoppe's methods to the asymmetric deprotonation of *N*-Boc-pyrrolidine **18**. The *s*-BuLi/(–)-sparteine complex facilitated the asymmetric deprotonation of one of the *pro-S* α-protons to give the chiral organolithium intermediate

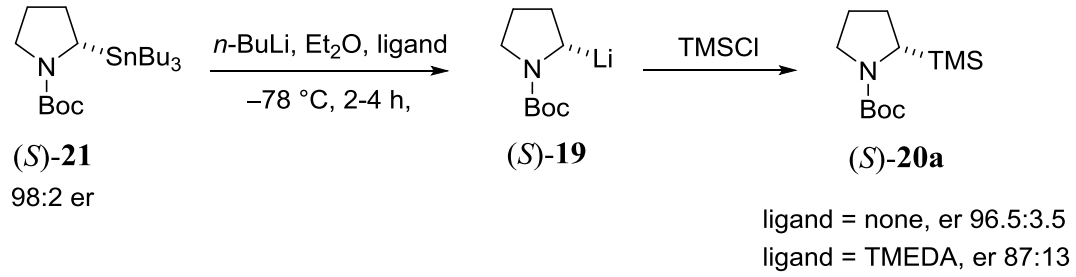
(*S*)-**19** which was quenched with a range of electrophiles to give the products **20** in good yields and excellent ers (Scheme 10).



Scheme 10

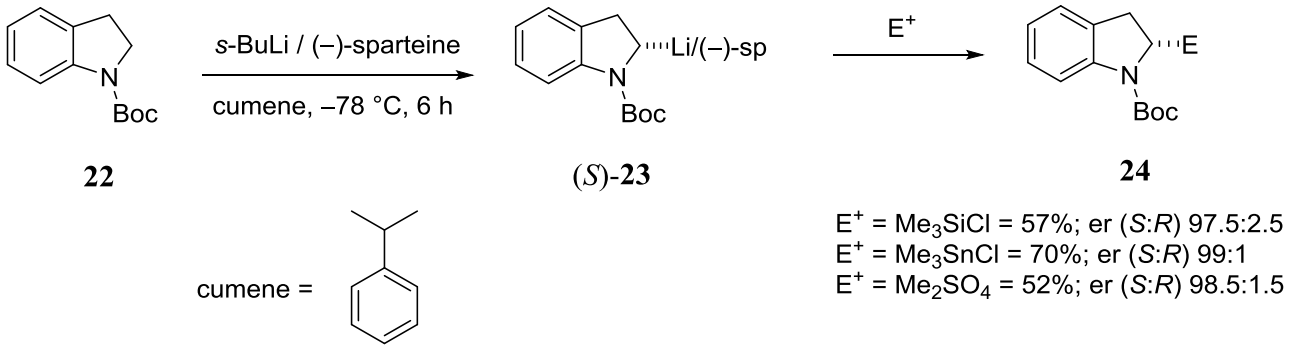
In order to confirm that this reaction was taking place via an asymmetric deprotonation pathway and not via asymmetric substitution, tin–lithium exchange reactions were carried out.[33] Firstly, the racemic organolithium intermediate **19** was formed both by deprotonation of **18** with *s*-BuLi and by tin–lithium exchange of the racemic stannane **21** (E = $SnBu_3$) with *n*-BuLi. Addition of TMSCl to this intermediate, followed by (–)-sparteine, yielded the product **20a** (E = $SiMe_3$) with very poor ers in both cases. These results supported their view that (–)-sparteine didn't induce the enantioselectivity in the reaction of the organolithium intermediate with the electrophile.

Furthermore, enantioenriched stannane (*S*)-**21** underwent tin–lithium exchange to give the organolithium intermediate (*S*)-**19**. This was quenched with TMSCl to give the product (*S*)-**20a** in good ers in both cases (Scheme 11). This confirmed that the organolithium intermediate (*S*)-**19** was configurationally stable under the reaction conditions which further supported the asymmetric deprotonation hypothesis.



Scheme 11

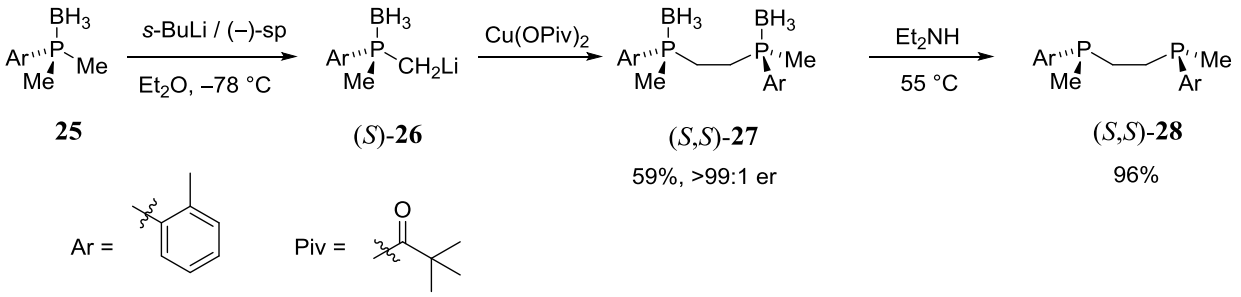
Beak and co-workers expanded this methodology to *N*-Boc-indoline **22** a few years later.[34] The *s*-BuLi/(–)-sparteine 'chiral base' was used to selectively remove the *pro-S* proton of *N*-Boc-indoline **22** to form the configurationally stable organolithium intermediate (*S*)-**23**. This was quenched with a range of electrophiles to obtain the enantioenriched products **24** in good yields and excellent ers (Scheme 12).



Scheme 12

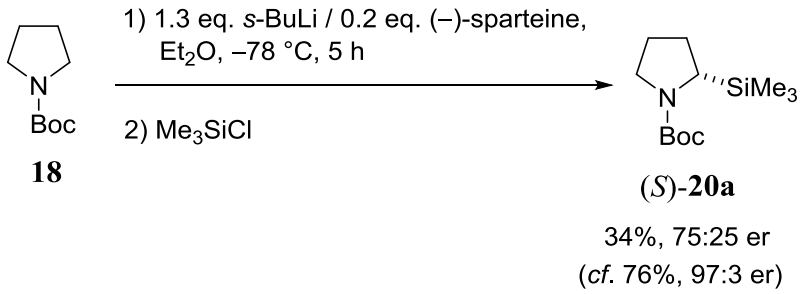
To support their asymmetric deprotonation hypothesis, the same tin–lithium exchange reactions used for *N*-Boc-pyrrolidine **18**, as described above, were carried out. A similar set of results were obtained, which confirmed the pathway followed in these reactions was also asymmetric deprotonation, not asymmetric substitution.

In 1995, Evans and co-workers reported the asymmetric deprotonation of aryldimethylphosphine-boranes, followed by oxidative coupling, to give diphosphine precursors.[35] Phosphine-borane **25** was deprotonated using the *s*-BuLi/(–)-sparteine 'chiral base' to give the chiral organolithium intermediate (*S*)-**26**. This underwent oxidative coupling with copper(II) pivalate to form the desired C_2-symmetric product (*S*,*S*)-**27** in good yield and excellent er (Scheme 13). The C_2-symmetric product was separated from the *meso*-diastereoisomer by column chromatography and this precursor was conveniently converted to the diphosphine (*S*,*S*)-**28** upon treatment with diethylamine.



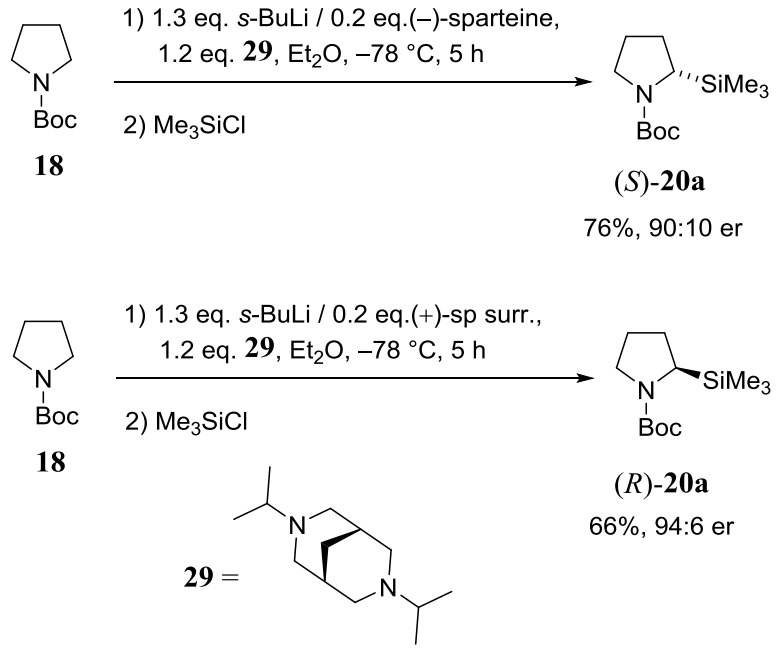
Scheme 13

As both enantiomers of sparteine are expensive, a method which uses the ligand in substoichiometric amounts is desirable. McGrath and O'Brien developed a method of catalytic asymmetric deprotonation which involved a ligand exchange process.[36] They found that using a substoichiometric amount of (–)-sparteine in the asymmetric deprotonation of *N*-Boc-pyrrolidine **18** led to a much poorer yield and er of the product (*S*)-**20a** when compared to the stoichiometric amounts used by Beak and co-workers (Scheme 14).



Scheme 14

This suggested that the chiral ligand did not readily dissociate from the lithiated intermediate formed in the reaction and so the reactive *s*-BuLi/(–)-sparteine complex could not be regenerated. However, they found that when they added an achiral diamine, such as bispidine **29**, to the reaction mixture, this formed product **20a** in a yield and er comparable to the one obtained by Beak and co-workers. An even better enantioselectivity was obtained when O'Brien's (+)-sparteine surrogate was used as the chiral ligand (Scheme 15).



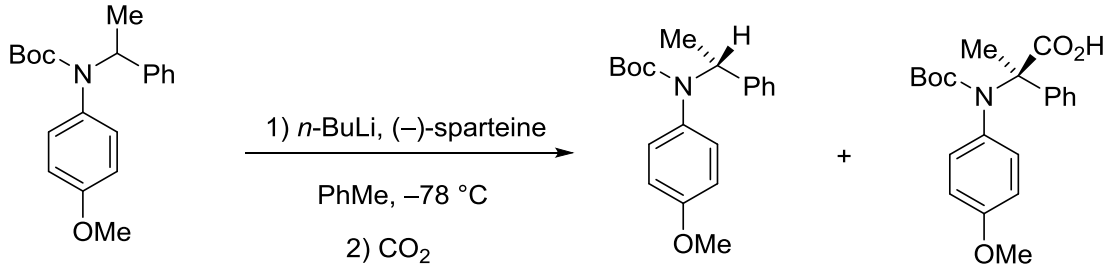
Scheme 15

These results implied that not only did ligand exchange take place but also, both organolithium species were configurationally stable under the conditions and the complex of *s*-BuLi/**29** deprotonated **18** slower than the 'chiral base' complex. This methodology was also shown to work with the asymmetric deprotonation of *O*-alkyl carbamates and phosphine boranes.[36]

1.2.2 Kinetic Resolution (KR)

Kinetic resolution is the achievement of partial or complete resolution of the enantiomers in a racemate, by virtue of unequal reaction rates with a chiral agent.[37] When using a 'chiral base', if no ligand exchange process is occurring, there needs to be more (or at least the same number of) equivalents of the chiral ligand present than of the organolithium reagent in order that the entire organolithium reagent is complexed with the ligand. This 'chiral base' can then preferentially deprotonate one enantiomer of starting material, allowing the other enantiomer to be recovered in good er. Using an electrophile to quench the reaction can give the product in high er as long as the organolithium intermediate that is formed is configurationally stable. A drawback of this procedure is that, theoretically, a maximum yield of only 50% of the recovered starting material and product are able to be obtained in good er.

In 1997, Beak and co-workers reported a moderate kinetic resolution of the carbamate **30** by deprotonation (Scheme 16).[38] This study showed that a kinetic resolution using the 'chiral base' of *n*-BuLi complexed with (–)-sparteine could be achieved albeit with limited success. Lithiation of **30** with 0.5 equivalents of the 'chiral base' followed by trapping with CO_2 gave the recovered starting material, (*R*)-**30**, in 55% yield and 75:25 er with the product (*R*)-**31** being formed in 22% yield and 87:13 er. Increasing the number of equivalents of the 'chiral base' used to 0.8 gave (*R*)-**30** and (*R*)-**31** in 12% and 66% yield with er 81:19 and 57:43 respectively. While these results didn't enable the starting material to be recovered in excellent er, it proved that this methodology had the potential to be extended to other substrates.

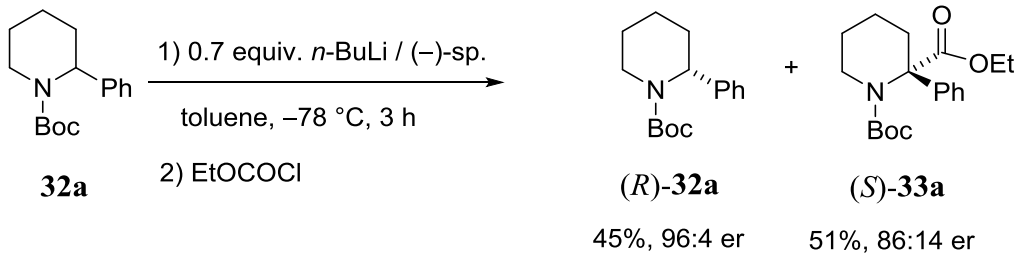


30 (*R*)-**30** (*R*)-**31**

0.5 eq. of (–)-sparteine:	55% 75:25 er	22% 87:13 er
0.8 eq. of (–)-sparteine:	12% 81:19 er	66% 57:43 er

Scheme 16

More recently, Coldham and co-workers reported the kinetic resolution of *N*-Boc-2-arylpiperidines.[39] They used 0.7 equivalents of *n*-BuLi and (–)-sparteine as a 'chiral base' to selectively deprotonate one enantiomer of *N*-Boc-2-phenylpiperidine **32a** in toluene at –78 °C before they quenched, after 3 hours, with ethyl chloroformate. This gave the recovered starting material (*R*)-**32a** in an excellent yield and er (Scheme 17). The organolithium reagent, *n*-BuLi, was added last to a mixture of the starting material and (–)-sparteine, as pre-mixing the *n*-BuLi with the (–)-sparteine resulted in lower ers.

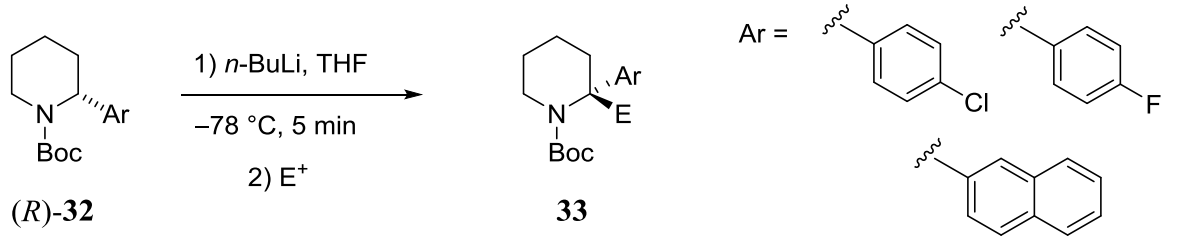


32a (*R*)-**32a** (*S*)-**33a**

45%, 96:4 er 51%, 86:14 er

Scheme 17

Ethyl chloroformate was used in this methodology as a sacrificial electrophile in order to consume the reactive enantiomer of starting material to form the product (*S*)-**33a**. The recovered starting material obtained from these kinetic resolutions was then used in lithiation–substitution reactions to form 2,2-disubstituted products **33** in excellent yields and with minimal or no loss in er (Scheme 18).



(*R*)-**32** **33**

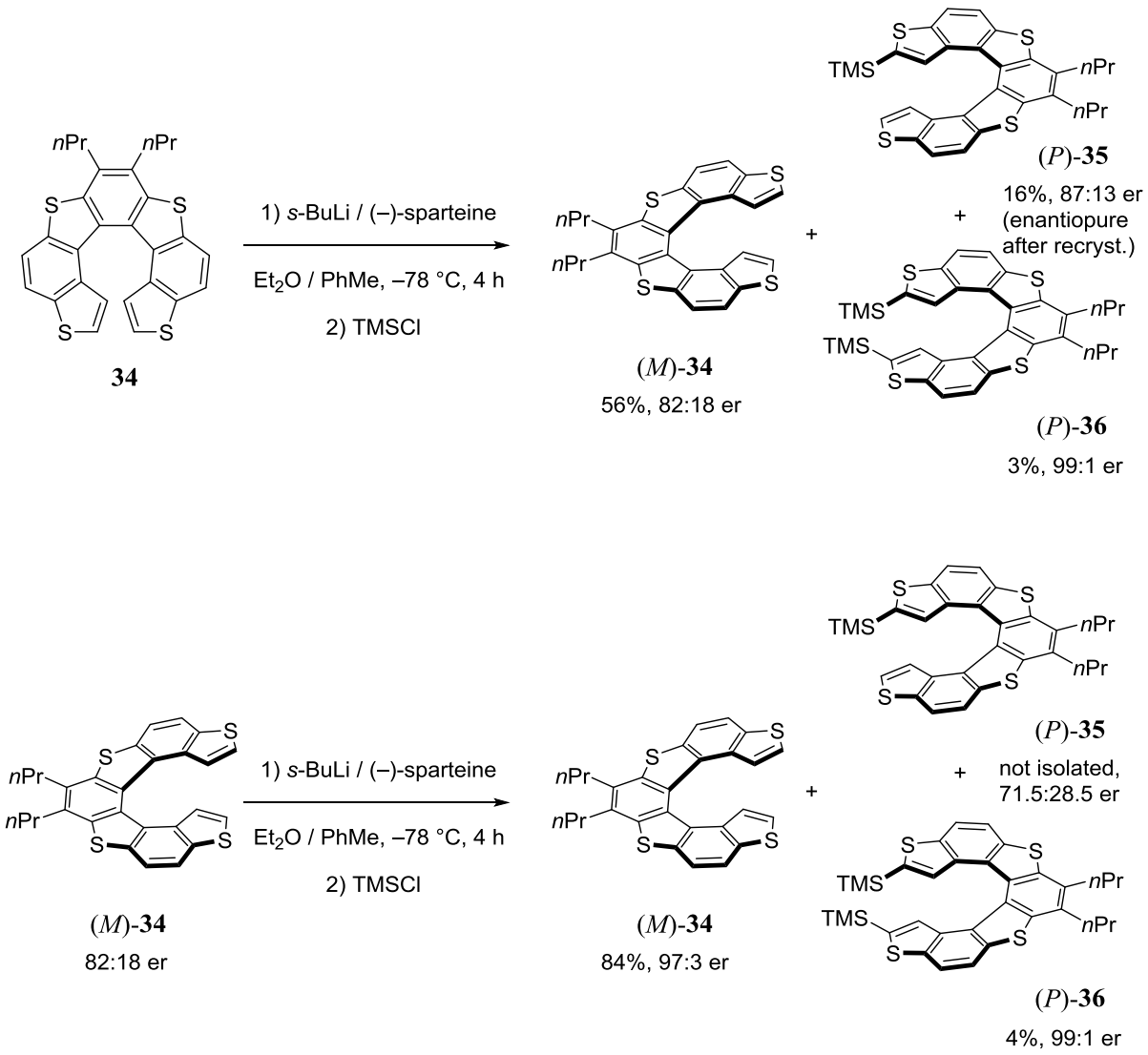
er > 94:6 67–88%, er > 91:9

E^+ = EtOCOCl, MeI, allyl bromide

Scheme 18

Reactions or reaction sequences that include two kinetic resolution processes are far less frequently encountered than those that include one, and yet can be very effective. In 2015, Doulcet and Stephenson reported a double kinetic resolution procedure of 7,8-dipropyltetrathia[7]helicene **34**.[40] The *s*-BuLi/(–)-sparteine 'chiral base' was used to deprotonate helicene **34** (Scheme 19). This gave, after they quenched with chlorotrimethylsilane, a mixture of enantioenriched recovered (*M*)-**34**, TMS-helicene (*P*)-**35** and di-TMS helicene (*P*)-**36**. The enantioenriched (*M*)-**34** was then subjected to the same reaction conditions in order to obtain (*M*)-**34** with a higher er than that obtained from the first kinetic resolution. Furthermore, (*P*)-**35** was able to be recrystallized to enantiomeric purity

from hexanes and so this procedure allowed the synthesis of 3 helicenes with ers greater than 97:3.



Scheme 19

In the methods described above, the enantioenrichment occurs in the initial deprotonation. If the enantioenrichment of the product arises after the initial deprotonation, it implies that the intermediate organolithium is configurationally unstable. This means that, in the presence of a chiral ligand, the two organolithium stereoisomers form interconverting diastereomeric complexes. There are two possibilities when this situation is present and these will be explained below.

1.2.3 Dynamic Thermodynamic Resolution (DTR)

If the rate of interconversion of the diastereomeric complexes is slow on the timescale of the addition of the organolithium to the electrophile, the product ratio in this case reflects the relative proportions of the complexes and so to obtain a good enantioselectivity, the equilibrium between them must lie heavily to one side. This reaction is under thermodynamic control and is called a Dynamic Thermodynamic Resolution or a Dynamic Resolution under Thermodynamic control (Figure 4).[41]

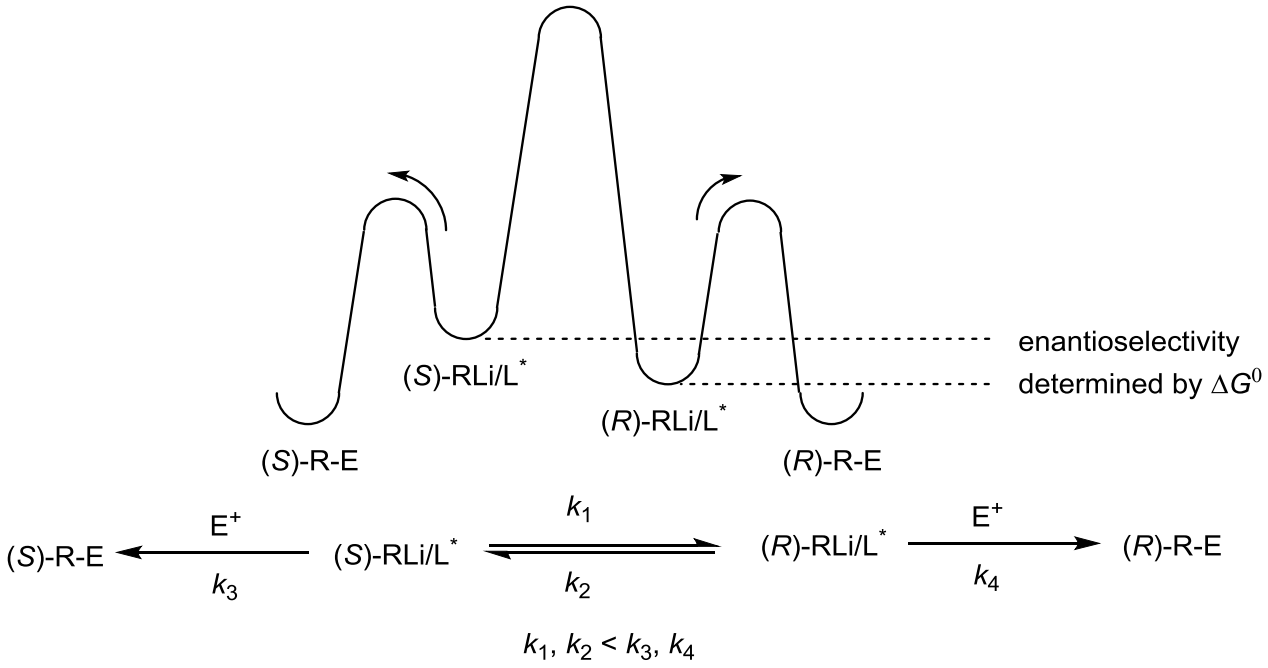
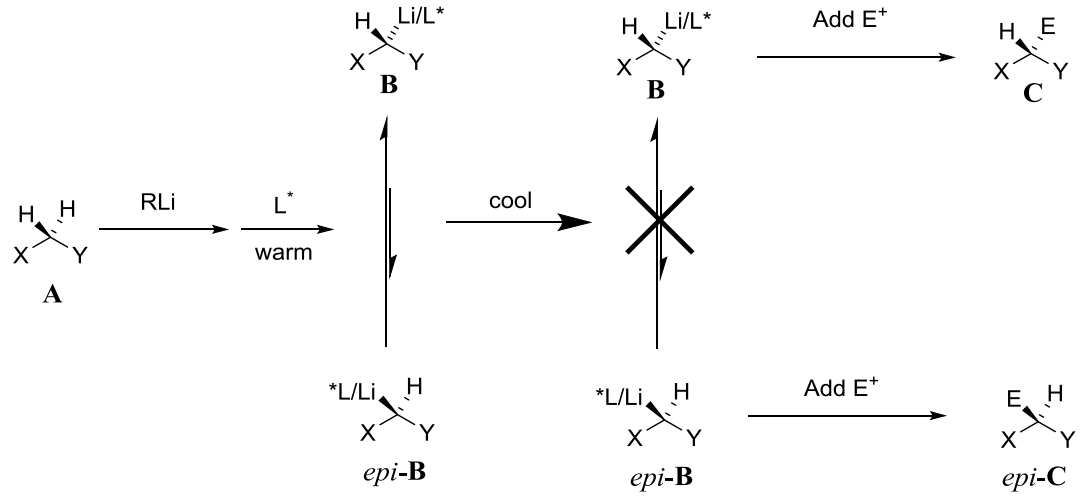


Figure 4

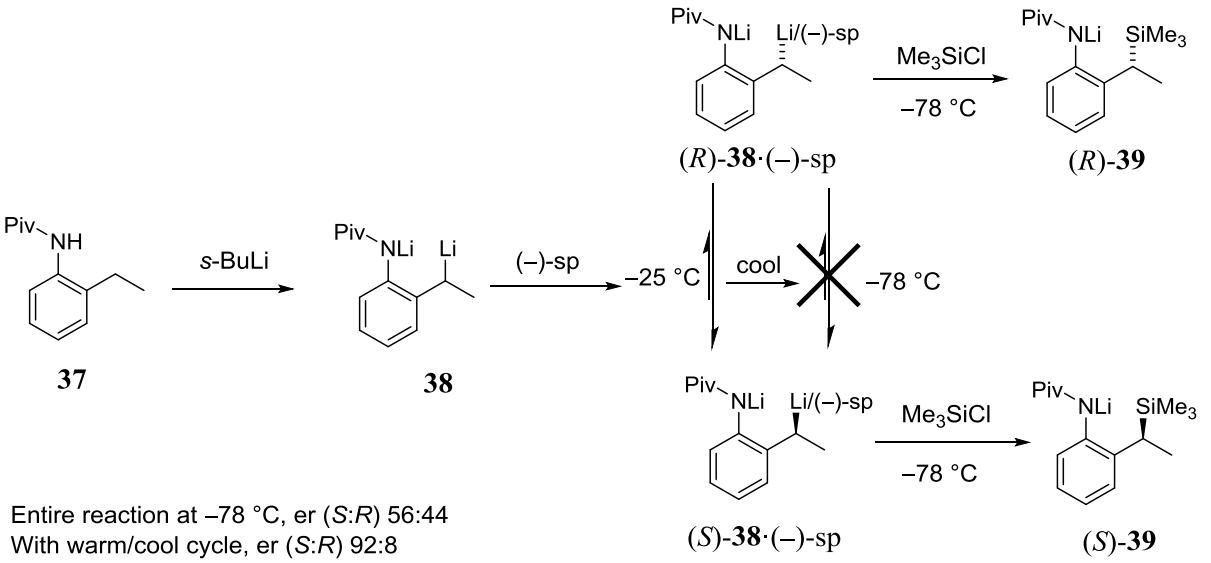
The DTR is a two-stage process. The first stage is reaching equilibrium between the two interconverting diastereomeric complexes and the second stage is locking this equilibrium at a lower temperature before the electrophile reacts to give the enantioenriched product (Scheme 20).[42] This procedure is known as a 'warm-cool' protocol.



Scheme 20

Beak and co-workers reported an excellent example of a DTR which involves the complexation-substitution of dilithio compound **38** (Scheme 21).[43,44]

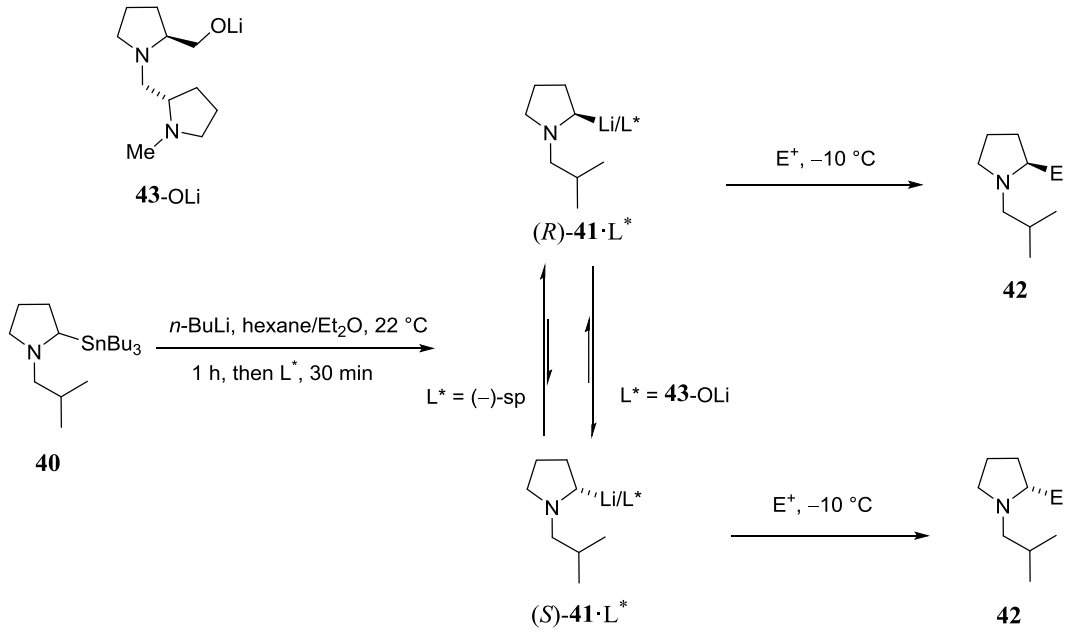
The amide **37** was deprotonated with *s*-BuLi and the intermediate **38** was complexed with (–)-sparteine in order to form the diastereomeric complexes. It was found that the reaction conditions used for complexation of compound **38** with (–)-sparteine were very important and had a large effect on the enantiomeric ratios of the product obtained. When the organolithium was complexed with (–)-sparteine at –78 °C, the product **39** was obtained after the addition of TMSCl with a poor enantiomeric ratio. However, if the complex of (–)-sparteine and **38** was allowed to stir for 45 minutes at –25 °C, before cooling to –78 °C, (*S*)-**39** was obtained with an excellent enantiomeric ratio. It was clear that this incubation period at –25 °C allowed the complexes to equilibrate prior to the reaction with the electrophile.



Scheme 21

Addition of 0.1 equiv. of Me_3SiCl after the warm/cool sequence provided the product (*S*)-**39** with a higher enantiomeric ratio (99:1) than addition of 2.4 equiv. of the same electrophile (91:9). This clearly showed that the two non-equilibrating complexes reacted with the electrophile at a different rate, with the more populated complex reacting faster. This suggests that it would be better to add TMSCl slowly at –25 °C and this example also illustrates the possibility that a DTR can be combined with a kinetic resolution in order to obtain more highly enantioenriched products.

In 2002, Coldham and co-workers reported the first ambient temperature DTR process of an unstabilised *α*-amino organolithium, *N*-isobutyl-2-lithiopyrrolidine **41**.[45,46] Tin–lithium exchange was carried out on the racemic stannane **40** using *n*-BuLi at room temperature. This organolithium species **41** was treated with the chiral ligand (–)-sparteine or diproline derivative **43** and the complexes were allowed to equilibrate. The mixture was then cooled and quenched with various electrophiles to give the 2-substituted pyrrolidines **42a-c** in good yields and good to excellent enantiomeric ratios (Scheme 22).



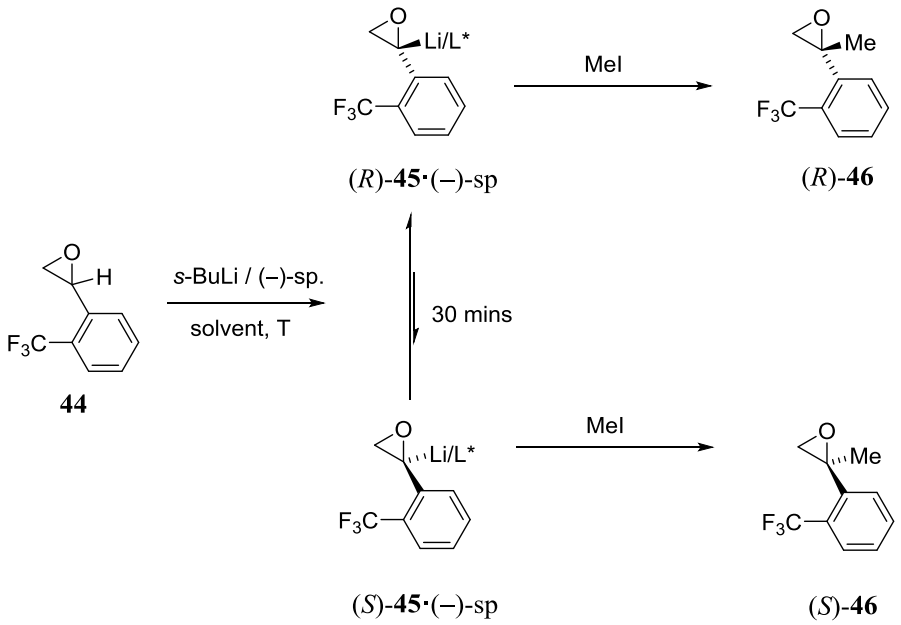
Resolution with (–)-sparteine
42a: E^+= Me_3SiCl; E= $SiMe_3$; Yield = 78%; er (*R*:*S*) 85:15
42b: E^+= PhNCO; E= C(O)NHPh; Yield = 57%; er (*S*:*R*) 82:18

Resolution with 43-OLi
42a: E^+= Me_3SiCl; E= $SiMe_3$; Yield = 75%; er (*S*:*R*) 96:4
42b: E^+= PhNCO; E= C(O)NHPh; Yield = 61%; er (*R*:*S*) 97:3
42c: E^+= acetone; E= $C(OH)Me_2$; Yield = 54%; er (*R*:*S*) 96:4

Scheme 22

It is interesting to note that the major enantiomer of the product **42a** obtained from the dynamic thermodynamic resolution with (–)-sparteine has the opposite configuration to the product **20a** obtained from the asymmetric deprotonation of *N*-Boc-pyrrolidine mentioned earlier.

Recently, Capriati and co-workers have reported the first DTR of a racemic oxiranyl-lithium species.[47] Using *s*-BuLi, lithiation was carried out on the racemic oxirane **44** which was pre-mixed with the chiral ligand (–)-sparteine (Scheme 23). The configurationally labile organolithium complexes **45** were allowed to equilibrate for 30 minutes before MeI was added to form the disubstituted oxirane **46**. When an excess of the electrophile was used, the product formed had a moderate 76:24 er. However, when a substoichiometric amount of the electrophile was used, the er of the product was 52:48. This difference in enantiomeric ratio provided evidence for a dynamic resolution under thermodynamic control. The essentially racemic product obtained when 0.1 eq. of the electrophile was used supported the view that the thermodynamically less populated diastereomeric complex reacted faster with the electrophile.



5 eq. of MeI (solvent = hexane, T = –78 °C) : 70%, er (*R*:*S*) 76:24
0.1 eq. of MeI (solvent = pentane, T = –120 °C to –78 °C) : 10%, er (*R*:*S*) 52:48

Scheme 23

1.2.4 Dynamic Kinetic Resolution (DKR)

Dynamic Kinetic Resolution is when the rate of interconversion of the two diastereomeric complexes is fast on the timescale of the addition of the organolithium to the electrophile. The product ratio in this case reflects the different rates of reaction that the complexes have with the electrophile, not the ratio of the complexes in the equilibrium. This reaction is under kinetic control and is called a Dynamic Kinetic Resolution (Figure 5 and Scheme 24).

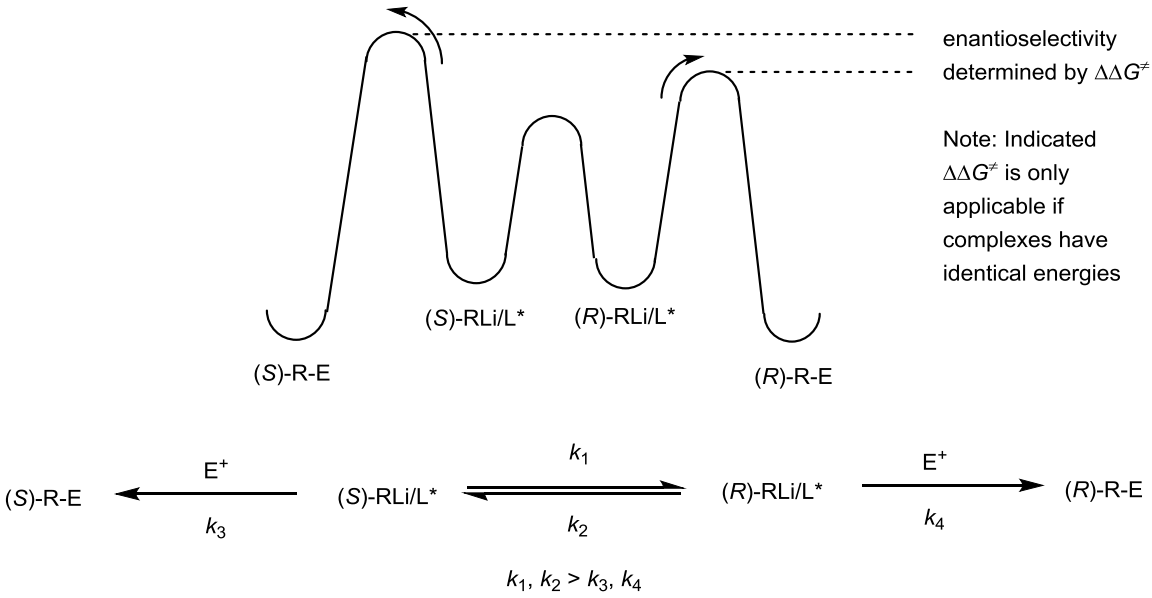
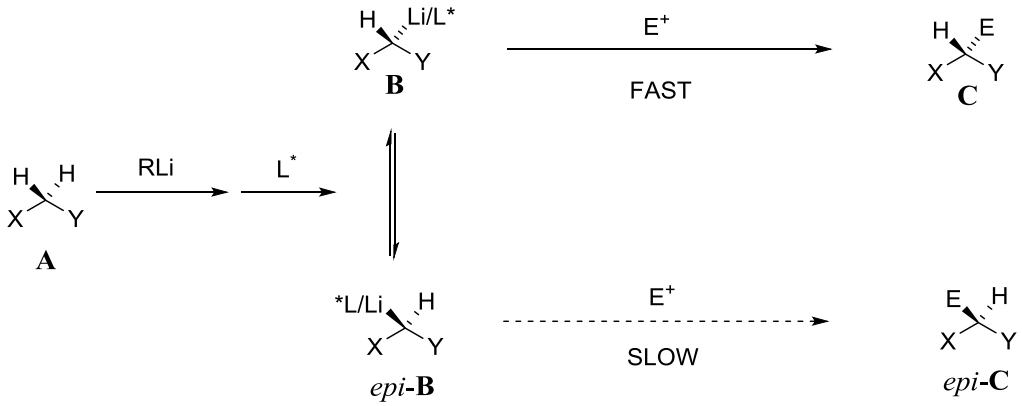
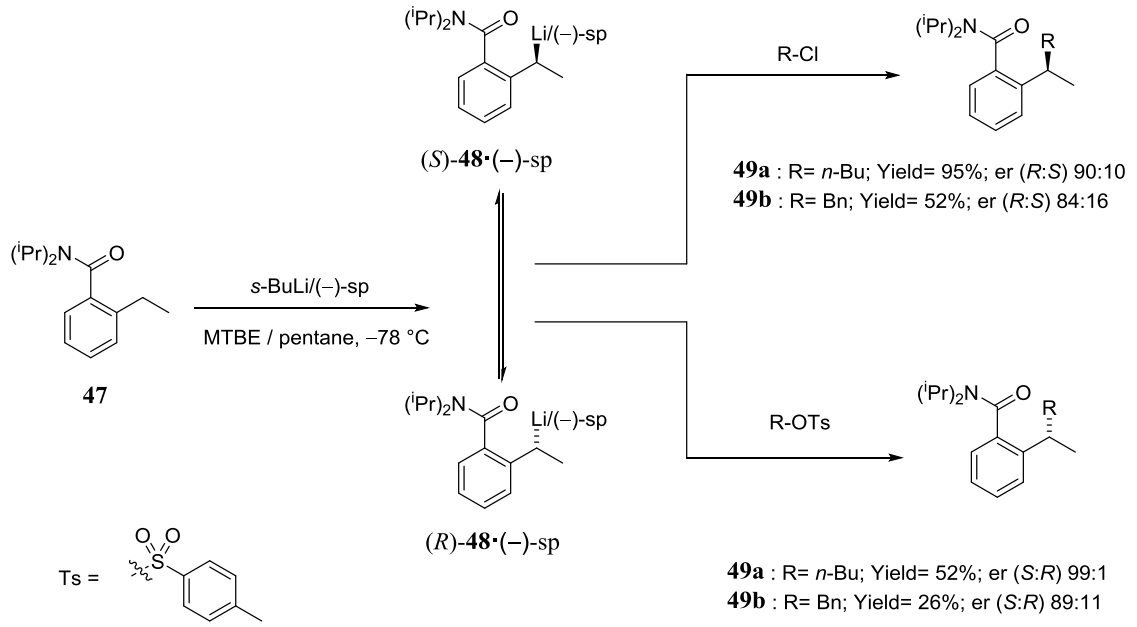


Figure 5



Scheme 24

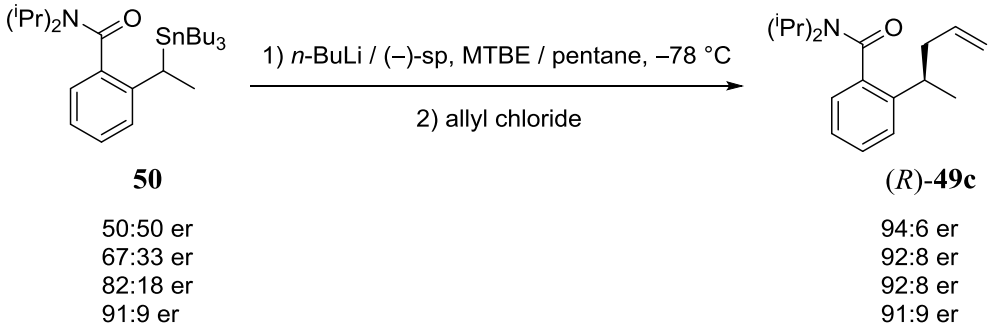
Beak and co-workers have reported an excellent example of a DKR.[44,48] The amide **47** was lithiated by the addition of *s*-BuLi/(–)-sparteine to form the rapidly interconverting intermediate complexes **48**. These were quenched with alkyl halides to form the products **49a** and **49b** in good yields and enantiomeric ratios (Scheme 25).



Scheme 25

Interestingly, when alkyl tosylates were used, the products with the opposite configurations were observed. They hypothesized that the non-complexing halide electrophiles approached the carbanion from the sterically less encumbered face resulting in an invertive substitution product. On the other hand, they postulated that slower reacting tosylates co-ordinated to the organolithium intermediate to form an ion-pair prior to C–C bond formation. This process could allow delivery of the alkyl group to the carbanionic centre on the same face as the lithium and result in a net retentive substitution

In order to confirm that the reaction was taking place via a DKR pathway, tin–lithium exchange reactions were carried out. Treatment of the stannyl compound **50**, of varying enantiomeric ratios, with *n*-BuLi in the presence of (–)-sparteine at –78 °C, followed by reaction with allyl chloride provided (*R*)-**49c** with high enantioenrichments, independent of the enantioenrichment of **50** (Scheme 26). They hypothesized that if the complexes were not equilibrating at the reaction temperature, the enantiomeric ratio of the product would have depended on the enantiomeric ratio of the stannane. They stated that as the two enantiomeric ratios were independent, the complexes were equilibrating faster than their reaction rate with the electrophile and therefore, the enantioselectivity was due to a dynamic kinetic resolution pathway.



50

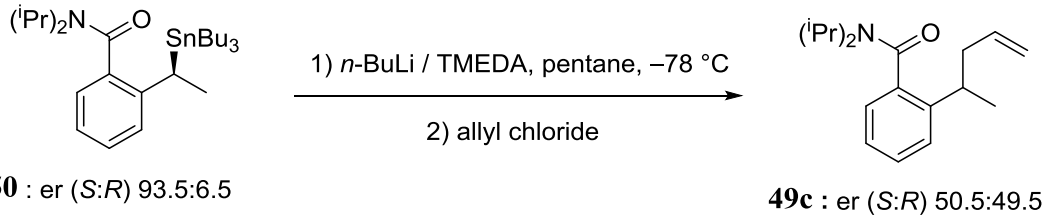
50:50 er
67:33 er
82:18 er
91:9 er

(*R*)-**49c**

94:6 er
92:8 er
92:8 er
91:9 er

Scheme 26

A tin–lithium exchange reaction in the absence of (–)-sparteine followed by electrophilic quench with allyl chloride generated virtually racemic product **49c** (Scheme 27). This showed the configurational instability of the intermediate organolithium with respect to the rates of reaction with the electrophile.

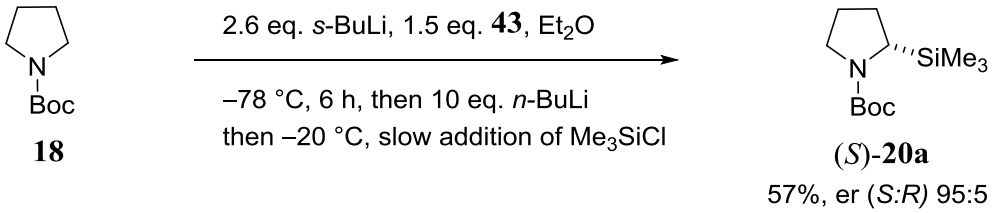


50 : er (*S*:*R*) 93.5:6.5

49c : er (*S*:*R*) 50.5:49.5

Scheme 27

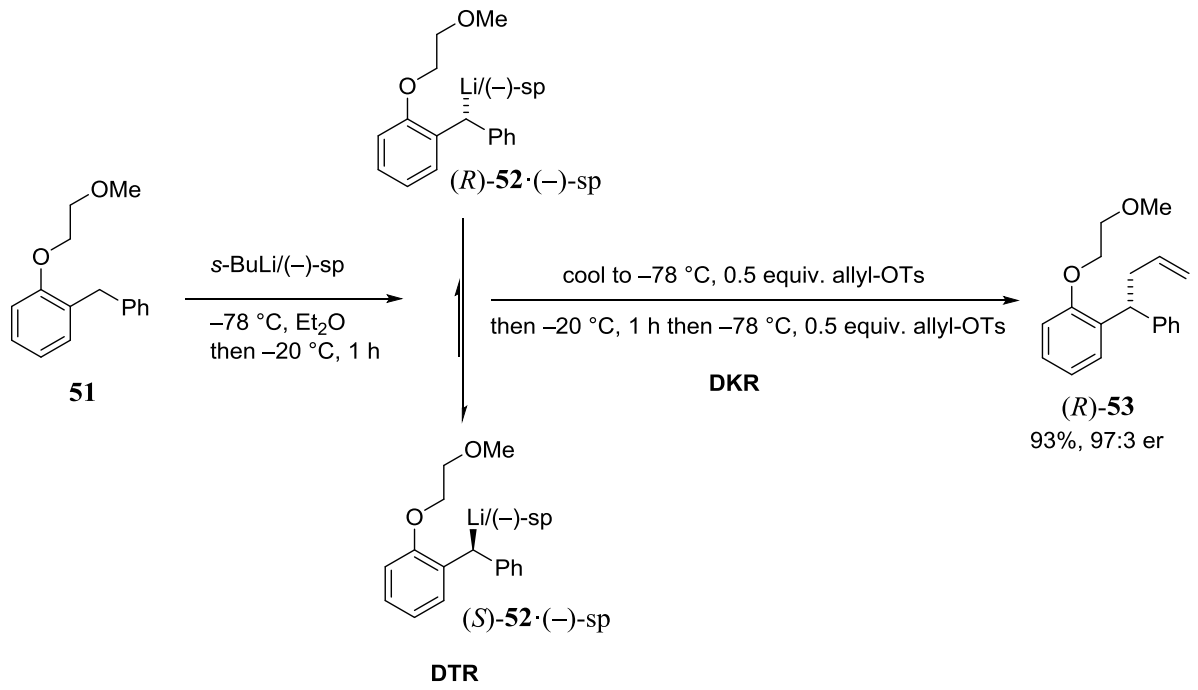
Coldham and co-workers have carried out DKR's of 2-lithiopyrrolidines using a variety of chiral ligands.[46] *N*-Boc-pyrrolidine **18** was treated with *s*-BuLi (2.6 eq.) and chiral ligand **43** (1.5 eq.) in Et_2O at –78 °C. After 6 h, a large excess of *n*-BuLi (10 eq.) was added and Me_3SiCl (5 eq.) was added slowly over 30 minutes to give the product (*S*)-**20a** with an excellent er (Scheme 28).



Scheme 28

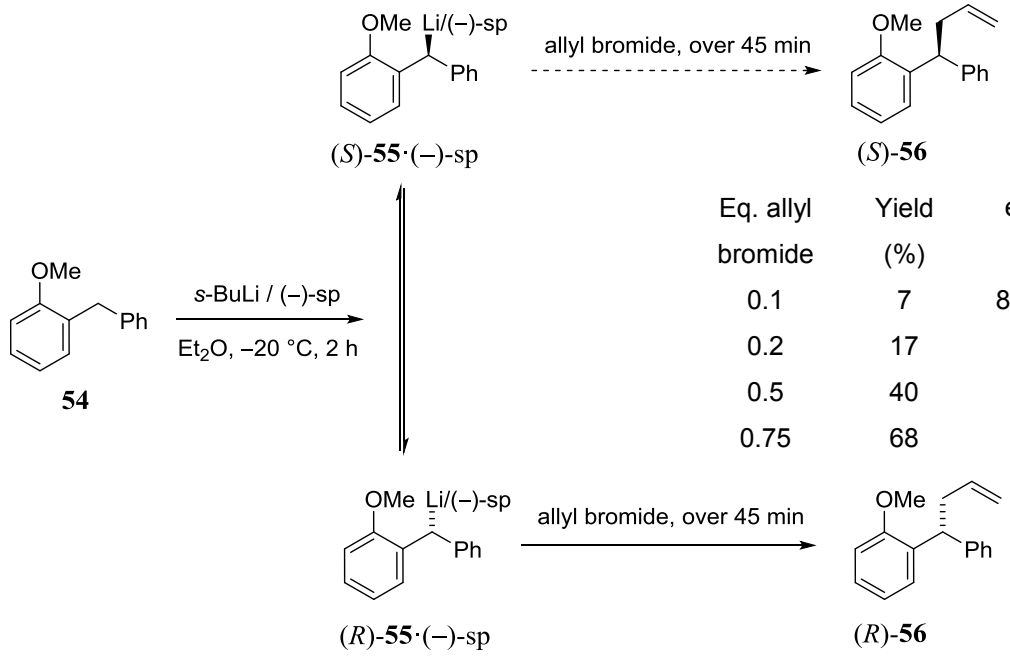
This procedure was actually an asymmetric deprotonation which took place at –78 °C (*vide supra*) followed by equilibration at –20 °C. They found that not only did a warm-cool protocol give lower selectivities but also different ers were obtained when different reaction conditions and different rates of addition of the electrophile were used, thereby supporting the view that the reaction took place via a DKR pathway.

In 2004, Wilkinson and co-workers reported a DKR combined with a DTR in order to enhance the enantioselectivity.[49,50] They used (–)-sparteine (1.1 eq.) complexed with *s*-BuLi (1.1 eq.) to deprotonate the diphenylmethane derivative **51** in Et_2O at –78 °C. This formed the organolithium species **52** that was configurationally stable at this low temperature. Warming the mixture to –20 °C promoted the equilibrium towards the more thermodynamically stable complex in 1 h. The mixture was re-cooled to –78 °C and a substoichiometric amount (0.5 eq.) of allyl tosylate was added. This reacted with the faster reacting, more stable complex and after another warm-cool cycle and addition of a further 0.5 equivalents of the electrophile, the product **53** was obtained with an excellent er (Scheme 29).



Scheme 29

Recently, Wilkinson has revisited this work and has provided evidence for a DKR pathway in the asymmetric allylation of 2-benzylanisole **54**.[51] Compound **54** was deprotonated using the complex of (–)-sparteine (1.2 eq.) with *s*-BuLi (1.2 eq.). Various substoichiometric amounts of allyl bromide were used to quench the organolithium intermediate **55** and they observed that the enantiomeric ratio of the product **56** remained approximately constant (Scheme 30) which suggested a dynamic kinetic resolution pathway.



Scheme 30

1.2.5 Hoffmann test

Hoffmann and co-workers developed a chemical test of the configurational stability of organolithium intermediates based on kinetic resolution during the electrophilic substitution step.[52–56] This test gives a qualitative guide to the stability of the organolithium on the timescale of its addition to the electrophile.[1]

The Hoffmann test includes two reactions. The first reaction is a control reaction where the racemic organolithium reacts with a racemic mixture of a chiral electrophile. The second reaction consists of the racemic organolithium being treated with an enantiopure sample of the electrophile (Figure 6).

In the control reaction, as both enantiomers of the electrophile are available, both enantiomers of the chiral organolithium species will react identically even if it is configurationally unstable. Therefore a racemic mixture of products will be formed, although the dr must not be 50:50 in order for the test to be successful; it is desirable that the diastereomeric ratio of the resulting products lies between 1.5 and 3.0. In the second reaction, if the organolithium intermediate is stable on the timescale of its addition to the electrophile, 50% of the product will arise from the *R*-enantiomer and 50% will arise from the *S*-enantiomer, with it being of no consequence that one product usually forms faster than the other. However, if the organolithium is configurationally unstable on the timescale of its addition to the electrophile, an imbalance in the obtained products can be obtained. If one enantiomer reacts faster than the other, the configurational instability will continually restore more of that enantiomer and more product arising from that enantiomer will be observed. It is critical that the reaction with the enantioenriched electrophile proceeds with high conversion to give a reliable result and so excess electrophile is usually used.[1,41,42]

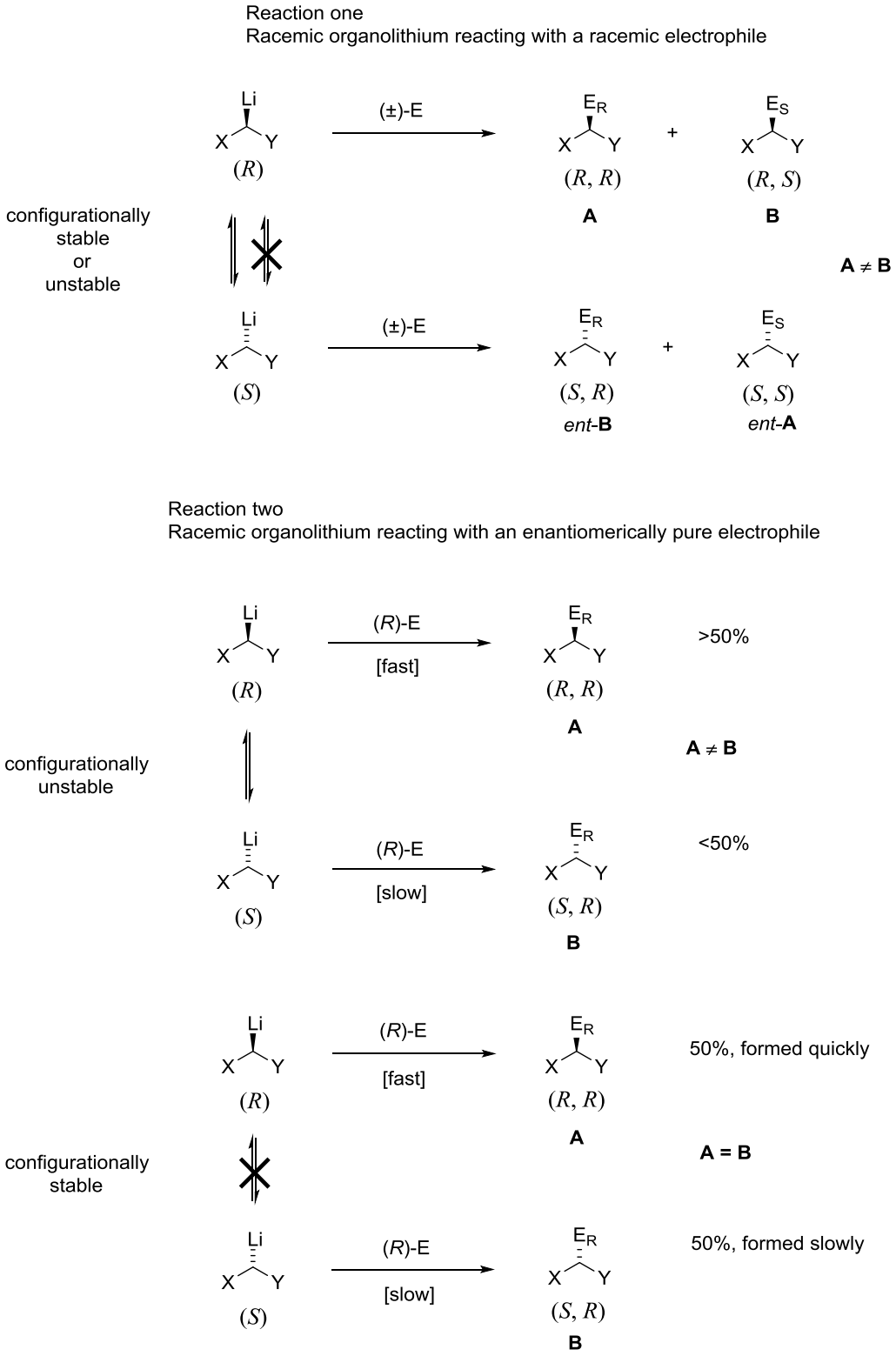


Figure 6

1.2.6 Poor man's Hoffmann test

As the Hoffmann test requires the use of a chiral electrophile which can be expensive, a modification of the test was carried out to allow the use of achiral electrophiles. Beak called

this the 'poor man's Hoffmann test' and it relies on a rate difference between diastereomeric transition states.[2,57–59] The test quantifies this rate difference by observing the outcome of a reaction in which enantiomeric organolithiums compete for a deficit of achiral electrophile in the presence of an enantiomerically pure chiral ligand, such as (–)-sparteine (Figure 7).[1] There is a different outcome for configurationally stable and unstable organolithiums. The latter should give the same er with either an excess or deficit of electrophile whereas the amount of **A** obtained will be the same as the amount of **B** obtained when using excess electrophile for a configurationally stable, racemic organolithium complexed with a chiral ligand.

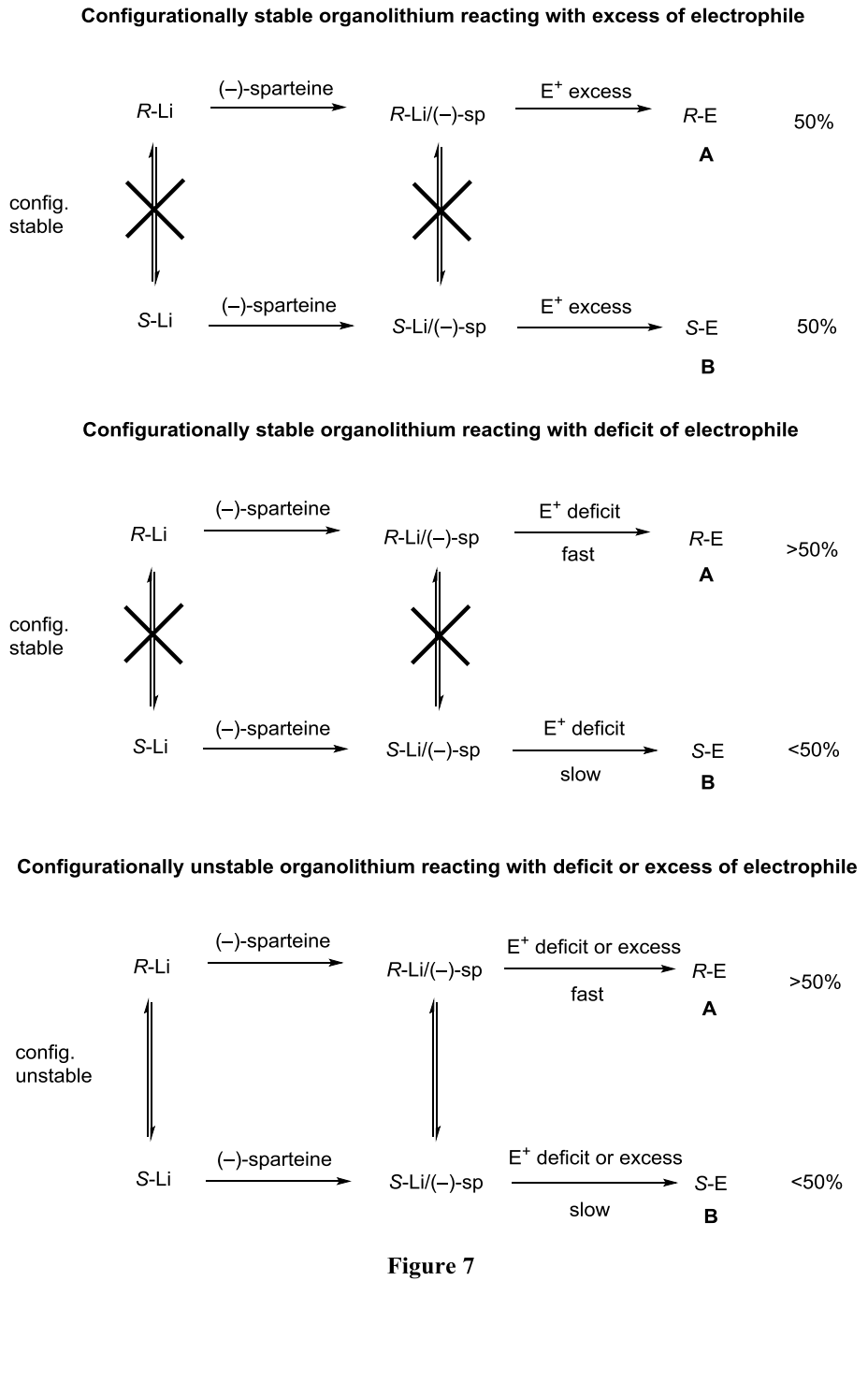
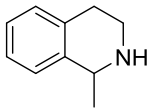


Figure 7

1.3 Previous work in the group

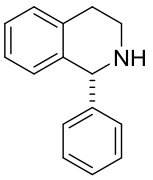
Recently, Coldham and co-workers have been investigating the synthesis of substituted tetrahydroisoquinoline (THIQ) derivatives using organolithium chemistry.[41,60–62] The lithiation of THIQ derivatives has previously also been studied in other research groups.[63–68]

Substituted tetrahydroisoquinolines are abundant in natural products and compounds that have medicinal properties (Figure 8).[69] Many derivatives of THIQs exhibit a wide range of antitumor, antimicrobial, anti-HIV and various other biological and pharmacological activities. 1-Methyl-1,2,3,4-tetrahydroisoquinoline **57** exists in the brains of mice, rats and humans and has been found to be related to the pathogenesis of Parkinson's Disease,[70] (*R*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline **58** has been developed as a general anaesthetic agent[71] while laudanosine **59** has been found to have an effect on the cardiovascular system.[72]



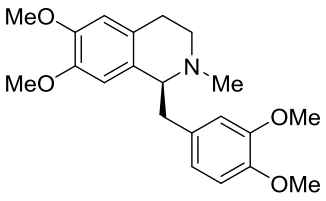
1-methyl-1,2,3,4-tetrahydroisoquinoline

57



(*R*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline

58



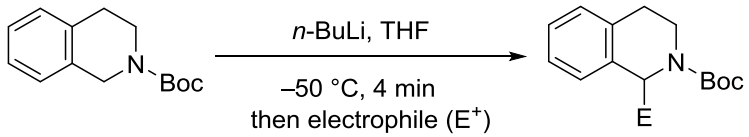
laudanosine

59

Figure 8

Coldham and co-workers carried out a study of the lithiation of *N*-Boc-1,2,3,4-tetrahydroisoquinoline **60** using *in-situ* IR spectroscopy and ^{1}H NMR spectroscopic monitoring.[60] It was found, by using *in-situ* IR spectroscopy, that there was slow rotation of the Boc group at –78 °C which limited the rate of lithiation. When the reaction temperature was increased to –50 °C, the lithiation was complete in a few minutes which meant that the Boc group must rotate more rapidly at this temperature. The half-life of the rotation at these temperatures was calculated using coalescence line shape analysis data from ^{1}H NMR spectra and it was found to be about 30 s at –50 °C and about 50 min at –78 °C. This data fitted well with the *in-situ* IR spectroscopic results.

Using this data, THIQ **60** was lithiated at –50 °C in THF using *n*-BuLi for 4 minutes. Addition of a variety of electrophiles gave the products **61a-g** in good to excellent yields (Scheme 31 and Table 3).[60]



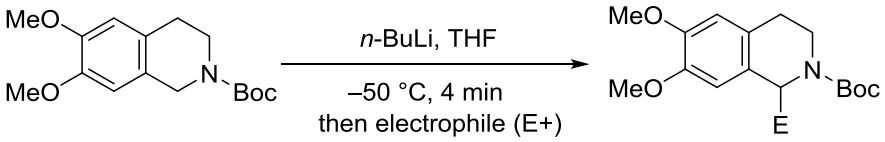
60 **61**

Scheme 31

Product	E^+	Yield (%)
61a	TMSCl	74
61b	BnBr	72
61c	allyl bromide	74
61d	MeI	78
61e	*n*-BuBr	62
61f	*n*-Bu_3SnCl	79
61g	PhCHO	90 (dr 1.7:1)

Table 3

Lithiation–substitutions of 6,7-dimethoxytetrahydroisoquinoline derivative **62** were also attempted and products **63a-f** were obtained in good to excellent yields (Scheme 32 and Table 4).[60]



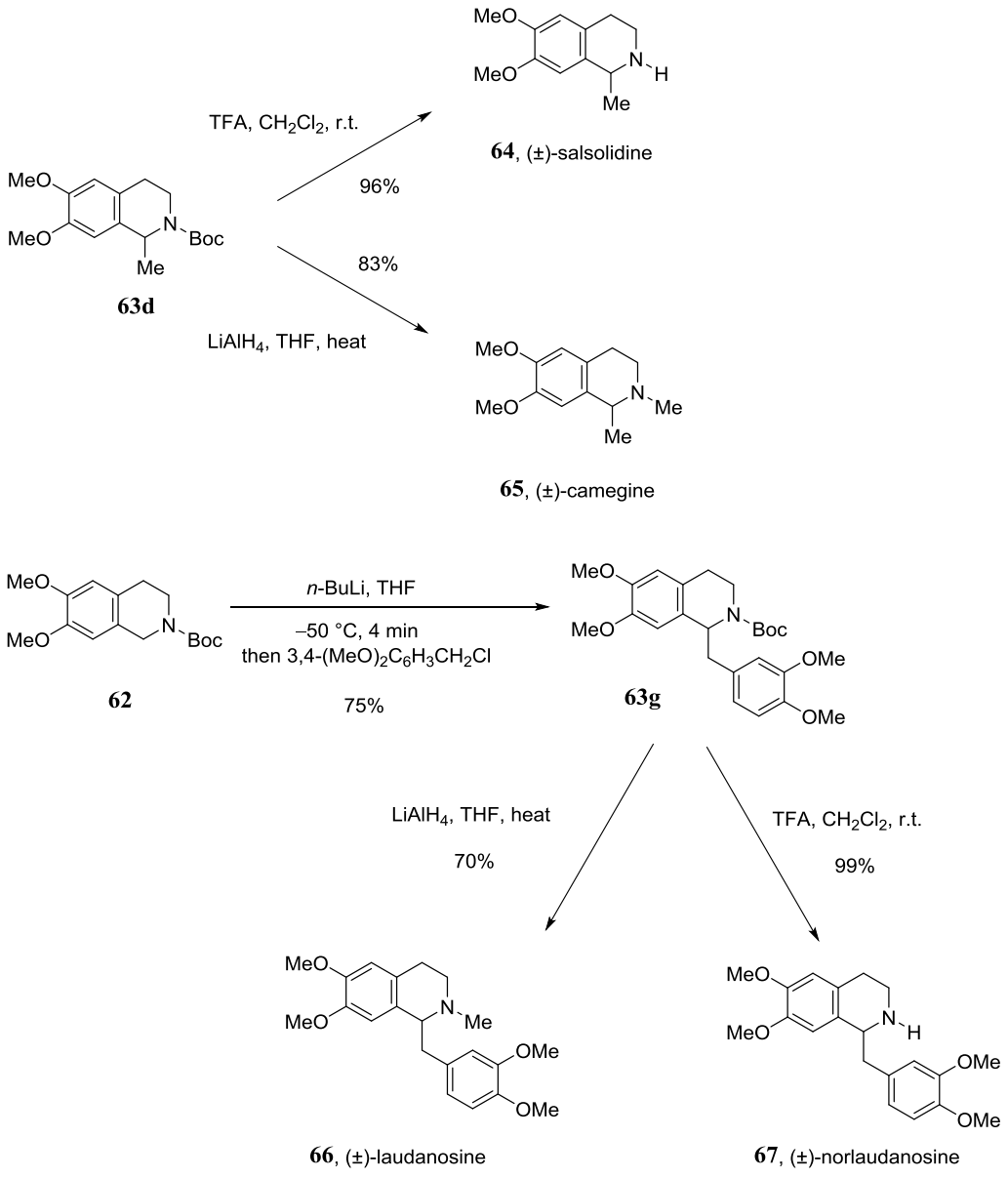
62 **63**

Scheme 32

Product	E^+	Yield (%)
63a	TMSCl	78
63b	BnBr	90
63c	allyl bromide	59
63d	MeI	64
63e	*n*-Bu_3SnCl	66
63f	PhCHO	61 (dr 1:1)

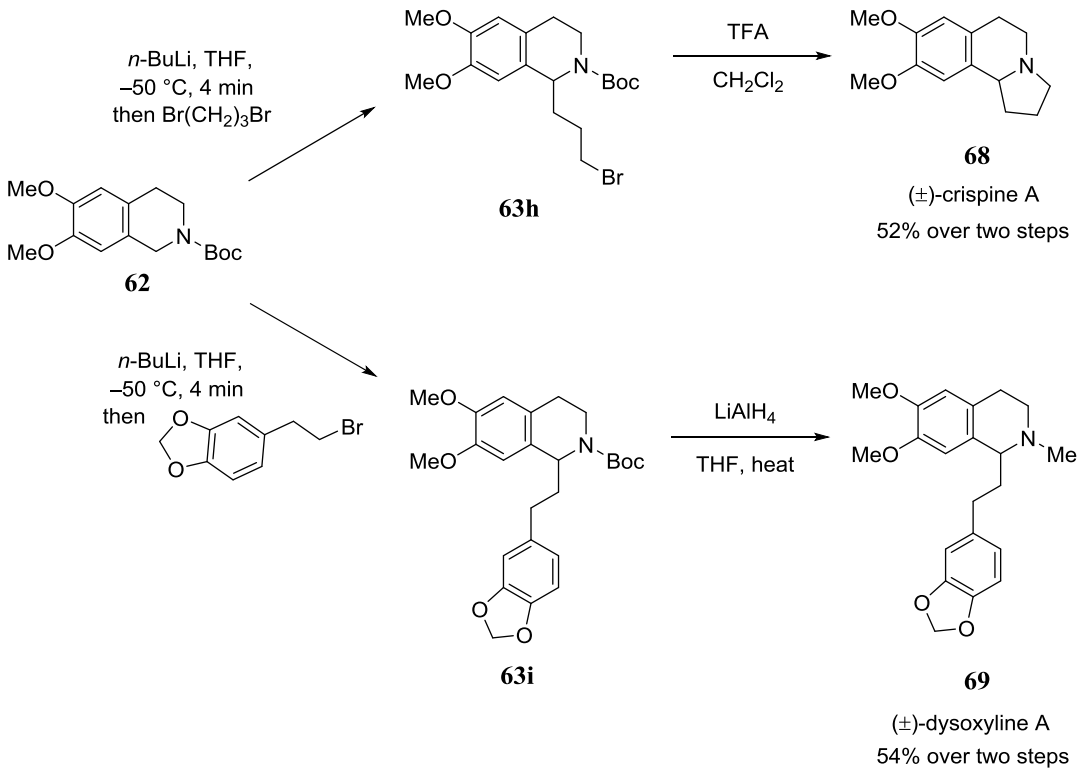
Table 4

Attempts at dynamic resolutions using these compounds were unsuccessful despite the poor-man's Hoffmann test indicating configurational instability, even at –100 °C. However, a number of racemic THIQ alkaloids (±)-salsolidine **64**, (±)-camegine **65**, (±)-laudanosine **66** and (±)-norlaudanosine **67** were successfully synthesised in just two steps from THIQ **62** (Scheme 33).



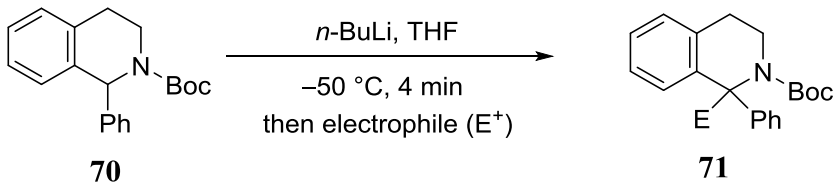
Scheme 33

Coldham and co-workers have more recently extended the chemistry with THIQ **62** and shown that this chemistry applies to a number of other THIQ derivatives.[62] Two more natural products, (±)-crispine A **68** and (±)-dysoxyline **69** were synthesised in good yields in two steps from THIQ **62** (Scheme 34).



Scheme 34

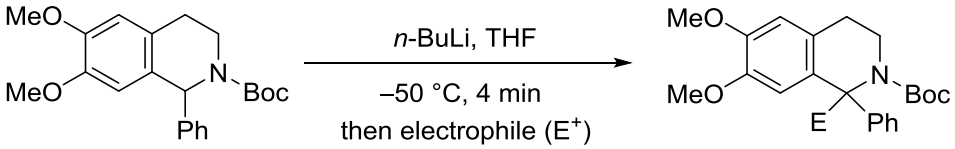
The lithiation of two *N*-Boc-1-phenyltetrahydroisoquinolines **70** and **72** have also been optimised recently by using *in-situ* IR spectroscopy.[61] The previously mentioned lithiation conditions of –50 °C in THF using *n*-BuLi for 4 minutes were also found to be suitable for these substrates. Lithiation–substitutions of these racemic substrates gave products **71a-i** and **73a-f** in excellent yields (Schemes 35 and 36, Tables 5 and 6).



Scheme 35

Product	E^+	Yield (%)
71a	BnBr	92
71b	MeI	92
71c	*n*-Bu_3SnCl	93
71d	*n*-BuBr	90
71e	MeOCOCN	91
71f	allyl bromide	98
71g	EtOCOCN	93
71h	BnOCOCN	94
71i	4-$BrC_6H_4CH_2Br$	90

Table 5



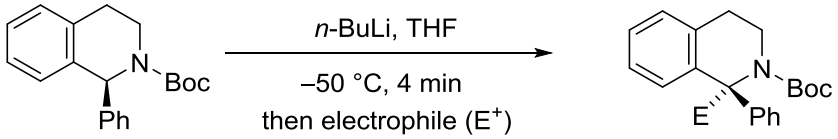
72 **73**

Scheme 36

Product	E^+	Yield (%)
73a	BnBr	88
73b	MeI	84
73c	*n*-Bu_3SnCl	88
73d	*n*-BuBr	91
73e	MeOCOCl	97
73f	allyl bromide	81

Table 6

Lithiation–substitution with enantiopure (*S*)-**70** led to products (*S*)-**71a, b, f-i** in good to excellent yields and excellent er (Scheme 37 and Table 7). This set of results implied that the organolithium intermediate was configurationally stable.



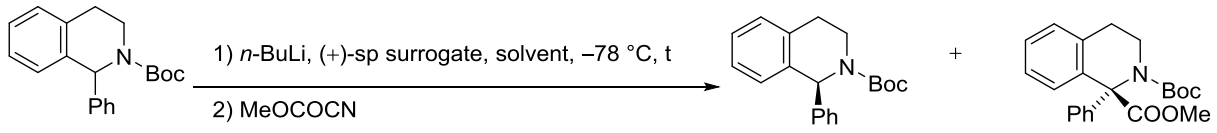
(*S*)-**70** (*S*)-**71**

Scheme 37

Product	E^+	Yield (%)	er
71a	BnBr	94	98:2
71b	MeI	90	97:3
71f	allyl bromide	92	97:3
71g	EtOCOCN	78	97:3
71h	BnOCOCN	60	98:2
71i	4-$BrC_6H_4CH_2Br$	82	99:1

Table 7

Kinetic resolutions, a dynamic kinetic resolution and a dynamic thermodynamic resolution using THIQ **70** have recently been attempted within the group with limited success.[73] Lithiation did not take place when using (–)-sparteine/*n*-BuLi and so the (+)-sparteine surrogate was used as the chiral ligand in the kinetic resolutions. Poor ers were obtained for both the product and the recovered starting material (Scheme 38 and Table 8). The yield of the product in each kinetic resolution was high and in three cases, higher than the theoretical maximum of 50% which indicates that the (+)-sparteine surrogate is not the best chiral ligand to use in these reactions. In reaction 1 of the table, inaccuracy may also be a factor as more of the product has been obtained than the theoretical maximum considering that only 0.5 equivalents of each component of the 'chiral base' were used.



70 (*S*)-**70** (*S*)-**71e**

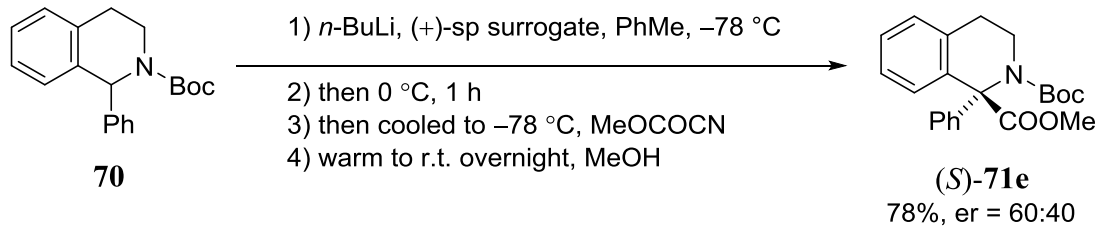
Scheme 38

Entry	Solvent	Equivalents of (+)-sparteine surrogate/*n*-BuLi	*t* (min)	Yield of RSM (%)	er of RSM	Yield of product (%)	er of product
1	PhMe	0.5	40	36	64:36	63	65:35
2	PhMe	0.7	45	43	62:38	48	61:39
3	PhMe	1.0	20	24	66:34	64	59:41
4	Et_2O	1.0	20	18	59:41	71	54:46

Table 8

Attempts at a dynamic kinetic resolution and a dynamic thermodynamic resolution yielded the product **71e** in good yields but with poor ers (Scheme 39).

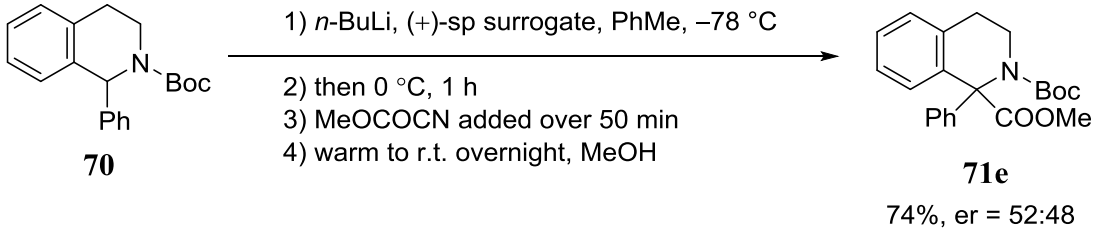
Dynamic Thermodynamic Resolution



70

(*S*)-**71e**
78%, er = 60:40

Dynamic Kinetic Resolution



70

71e
74%, er = 52:48

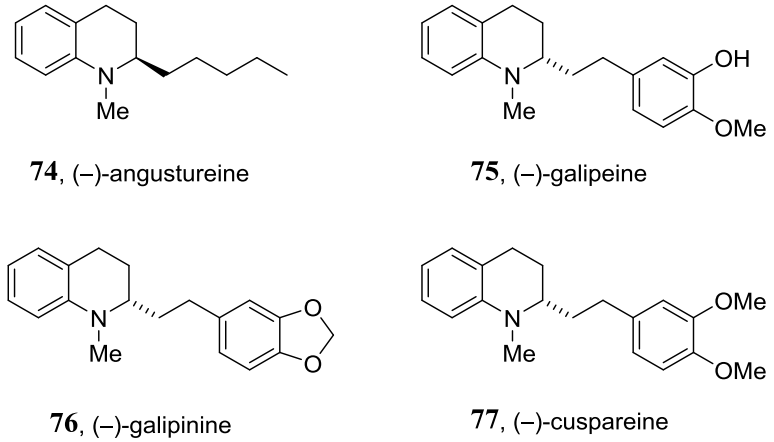
Scheme 39

As the THIQ work within the group gave some excellent results, it seemed natural for tetrahydroquinolines (THQs) to be investigated using the group's organolithium chemistry methodology. These are a similar class of compound to THIQs and synthesising them in enantioenriched form is just as important. Therefore, investigating the chemistry of THQs has been the basis of the majority of my PhD work and this work will be explained in detail in Chapter 2.

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

2.1 Tetrahydroquinolines in chemistry

Tetrahydroquinolines (THQs) are a class of compound whose derivatives are of great interest to synthetic organic chemists. They are ubiquitous moieties in natural products with many naturally occurring alkaloids containing the structure, such as (–)-angustureine **74**,[74] (–)-galipeine **75**,[74,75] (–)-galipinine **76**[76] and (–)-cuspareine **77**[77] (Figure 9).

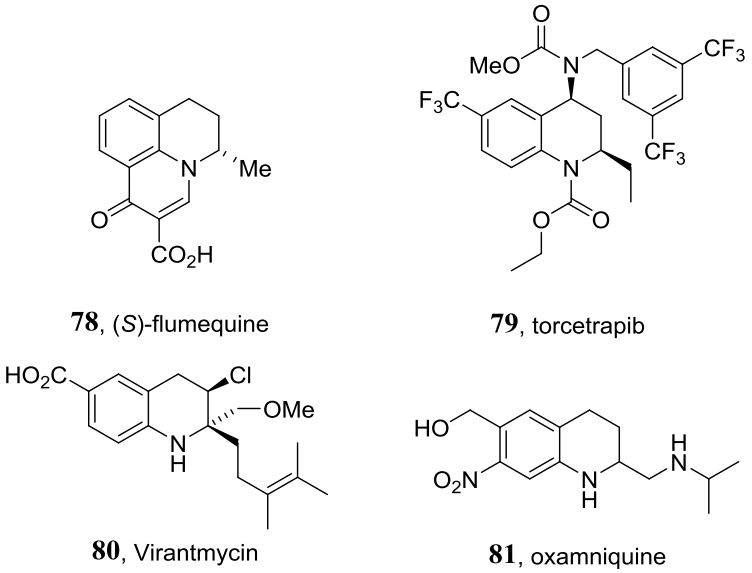


74, (–)-angustureine **75**, (–)-galipeine

76, (–)-galipinine **77**, (–)-cuspareine

Figure 9

Tetrahydroquinoline derivatives are also found in a wide variety of compounds that have medicinal properties. For example, (*S*)-flumequine **78**[78] is an antibacterial agent, torcetrapib **79**[79,80] is a potent inhibitor of the cholesteryl ester transfer protein, Virantmycin **80**[81] is an antiviral, antibiotic compound and oxamniquine **81**[82] is a schistosomicide (Figure 10).[83]

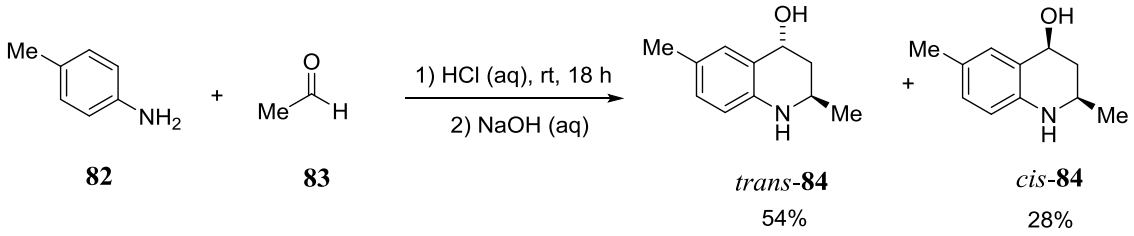


78, (*S*)-flumequine **79**, torcetrapib

80, Virantmycin **81**, oxamniquine

Figure 10

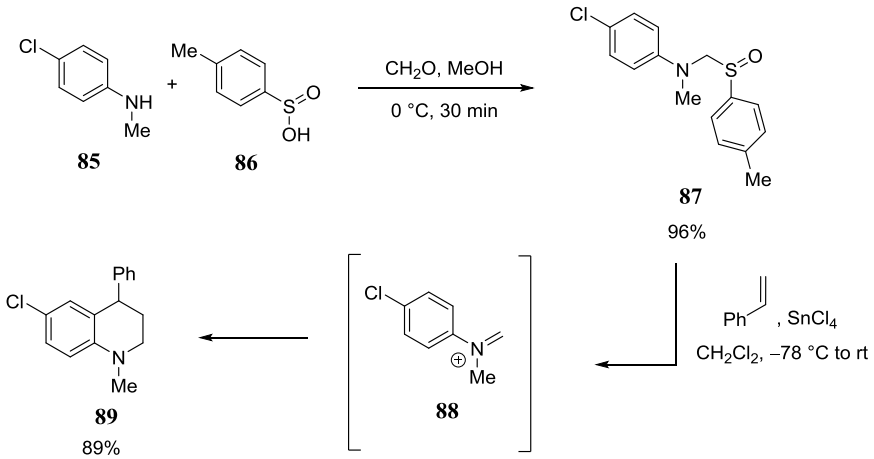
Various methods of synthesising THQ derivatives have been reported over the years as a result of their potential usage in pharmaceutical compounds. In 1994, Crabb and co-workers reported a synthesis of a mixture of THQs *cis*-**84** and *trans*-**84** by using chemistry over a century old (Scheme 40).[84–86] Reacting 1 mole of *p*-toluidine **82** with 2 moles of acetaldehyde **83** in the presence of excess hydrochloric acid formed the mixture of *cis*-**84** and *trans*-**84** in a 1:2 ratio as determined by NMR spectroscopy.



82 **83**

Scheme 40

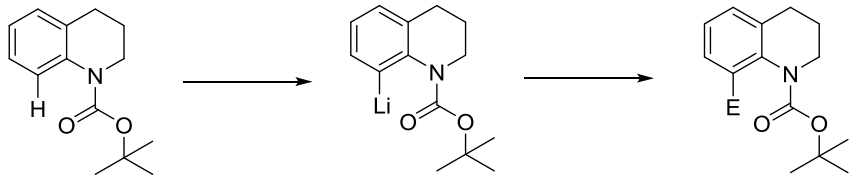
α-Arylaminosulfones are usually crystalline compounds and are therefore convenient reagents from which THQs can be prepared. In 1996, Beifuss and co-workers used this methodology to prepare a variety of THQ derivatives.[87] The *α*-arylaminosulfone **87** was easily prepared from the reaction of aniline **85** with aqueous formaldehyde and *p*-toluenesulfinic acid **86**. The *α*-arylaminosulfone was then cleaved upon treatment with $SnCl_4$ to form the cationic 2-azabutadiene intermediate **88** which underwent cycloaddition with styrene to form the desired THQ product **89** in excellent yield (Scheme 41).



85 **86** **87** 96% **88** **89** 89%

Scheme 41

Organolithium chemistry has been used a number of times to prepare substituted THQs. In 1989, Beak and Lee reported the lithiation–substitution of THQ **90** in their first reported use of the Boc group as a directing group for α-lithiation.[24] However, a mixture of *s*-BuLi and TMEDA in Et_2O at –78 °C lithiated the *ortho*-position of the aromatic ring to form the intermediate **91**. This was quenched with a small number of electrophiles to form the *ortho*-substituted products **92** in good to excellent yields (Scheme 42).

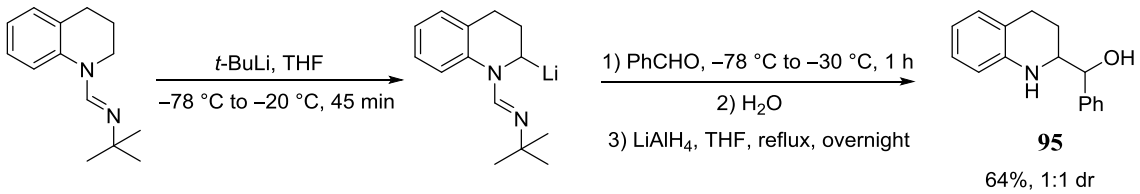


90 **91** **92**

$E^+ = Me_3SiCl = 82\%$
$E^+ = MeI = 78\%$
$E^+ = Br(CH_2)_3Cl = 60\%$

Scheme 42

Meyers and Hellring had previously investigated the lithiation of THQ **93**, with the formamidine directing group, using *t*-BuLi.[88] They had found that this gave the α-lithiated intermediate **94**. Quenching this intermediate with benzaldehyde gave, after cleavage of the directing group, the product **95** in good yield (Scheme 43).

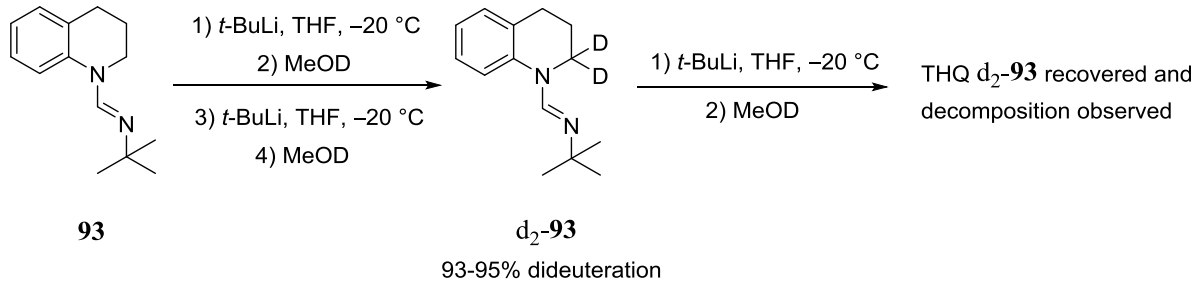


93 **94**

Scheme 43

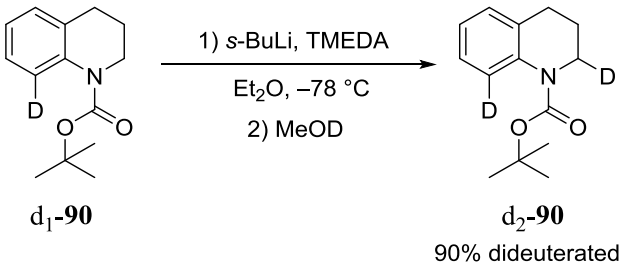
After Beak had reported the unexpected results using the Boc directing group, Meyers and Milot re-investigated the lithiation of THQs **90** and **93**.[89] They doubly deuterated THQ **93** in the α-position to give THQ d_2-**93**. Then, they attempted the lithiation of this compound to see whether the kinetic acidity of the *ortho*-aryl proton would compete with the stronger C–D

bonds. However, no *ortho*-lithiation was observed and only THQ d_2-**93** was recovered (Scheme 44).



Scheme 44

They also attempted the deuteration of *N*-Boc-THQ d_1-**90** which already had a deuterium in the *ortho*-position (Scheme 45). They found that there was high deuterium incorporation into the α-position which proved that the Boc group was capable of directing α-lithiation when the *ortho*-position was blocked.

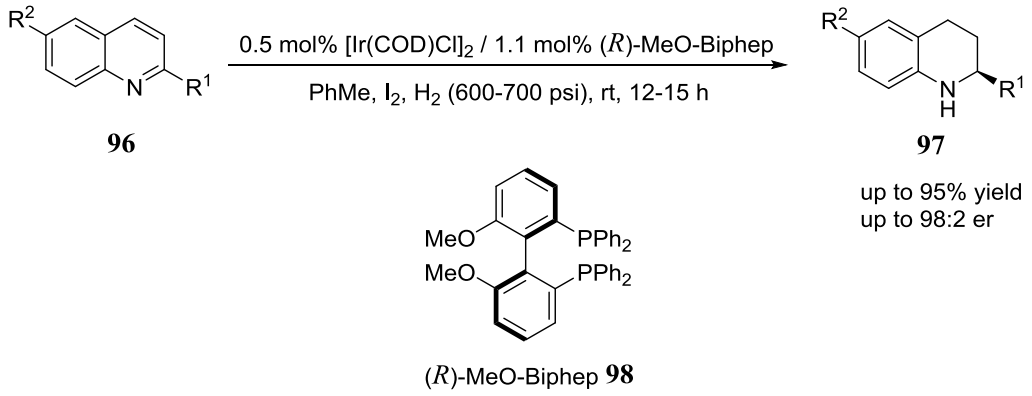


Scheme 45

While the examples above describe efficient methods of synthesising THQ derivatives, there is no enantioselectivity in any of the reactions. As reactions with high enantioselectivity are crucial in the pharmaceutical industry, methods which produce THQs with a high er are desirable.

In 2003, Zhou and co-workers reported the first example of highly enantioselective hydrogenation of quinoline derivatives using an iridium catalyst.[75,90] A wide variety of 2-substituted quinolines **96** were hydrogenated under high pressure with a chiral iridium complex

formed *in-situ* from $[Ir(COD)Cl]_2$ and (*R*)-MeO-BIPHEP **98,** with iodine additive, to form enantioenriched THQ derivatives **97** in excellent yields and ers (Scheme 46).



96

97

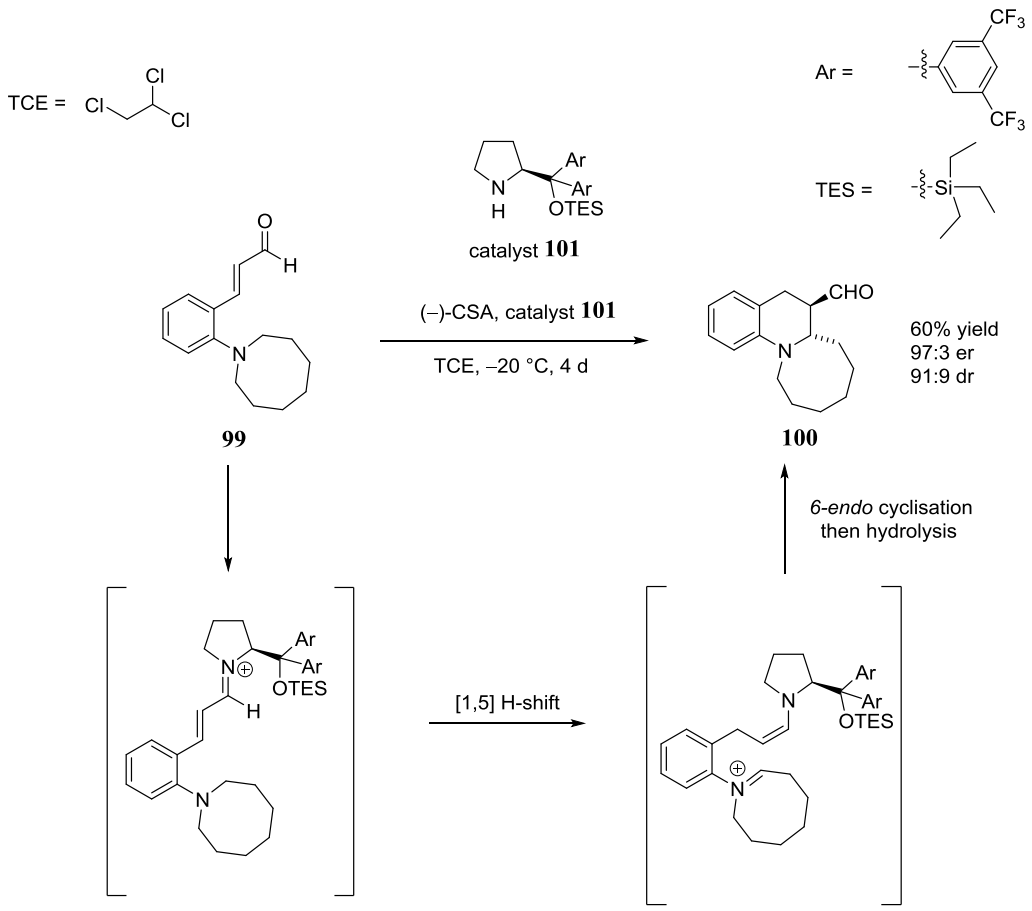
up to 95% yield
up to 98:2 er

(*R*)-MeO-Biphep **98**

Scheme 46

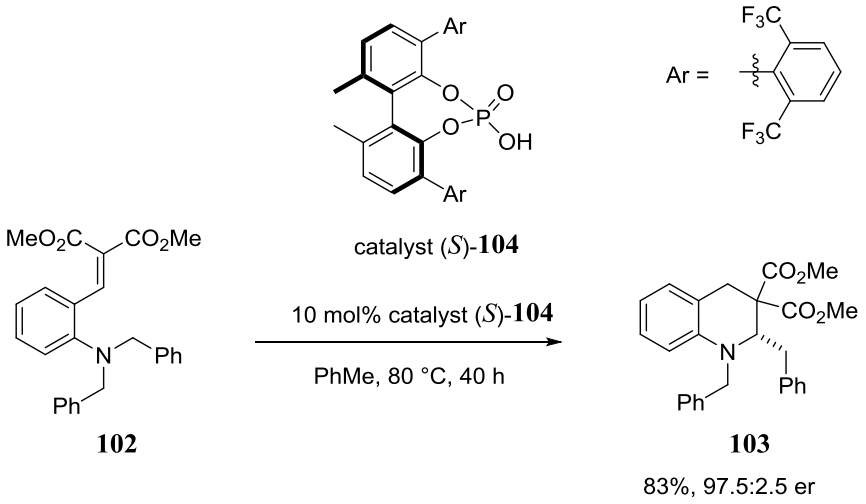
While this method is very useful, the high pressures and transition metal catalyst involved are drawbacks if the products need to be synthesised on a large scale. Therefore, methods which don't require such harsh conditions would be more desirable.

To this end, in 2010, Kim and co-workers reported the first organocatalytic, enantioselective, intramolecular 1,5-hydride transfer/ring closure reaction to form highly enantioenriched THQs with two contiguous stereocentres.[91] For example, cinnamaldehyde derivative **99** was treated with (–)-camphor sulfonic acid, in the presence of the chiral organocatalyst **101** and stirred at –20 °C for 4 days in 1,1,2-trichloroethane. This formed the ring-fused THQ **100**, *via* the pathway shown below, in good yield and excellent er (Scheme 47).



Scheme 47

In 2011, Akiyama and co-workers reported a chiral phosphoric acid-catalysed asymmetric C(sp^3)–H functionalization of a variety of benzylidene malonates *via* an internal redox process to form highly enantioenriched THQ derivatives.[92] For example, benzylidene malonate **102** was heated at 80 °C for 40 hours in toluene, in the presence of chiral phosphoric-acid **104**, in order to produce THQ **103** in excellent yield and er (Scheme 48).

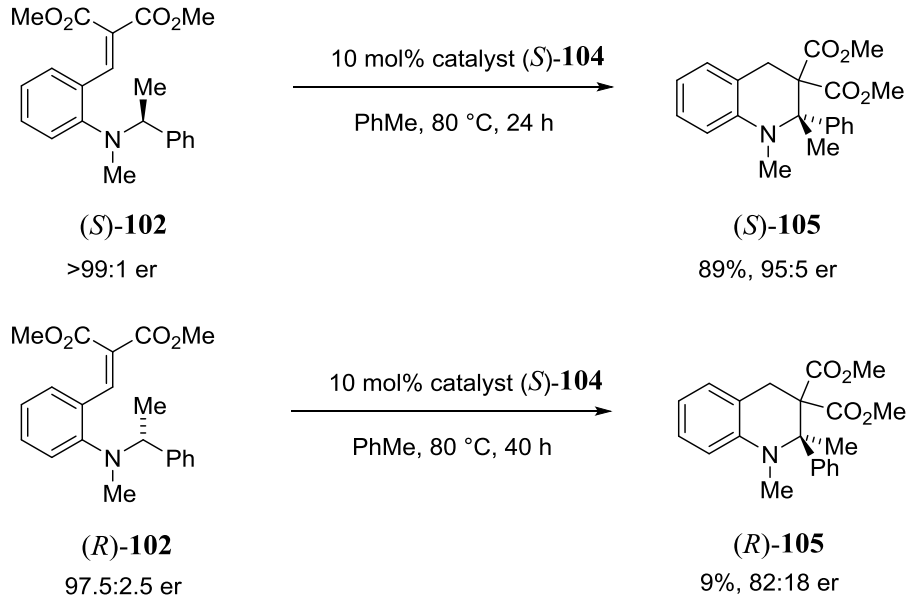


102 **103**

83%, 97.5:2.5 er

Scheme 48

They carried out some mechanistic studies using both enantiomers of benzylidene malonate **102** and found that the enantiomers exhibited totally different reactivities. While the reaction with (*S*)-**102** proceeded efficiently and gave the product with excellent er, the reaction with (*R*)-**102** was very slow in comparison and the product **105** had a much lower er (Scheme 49).



(*S*)-**102** (*S*)-**105**

>99:1 er 89%, 95:5 er

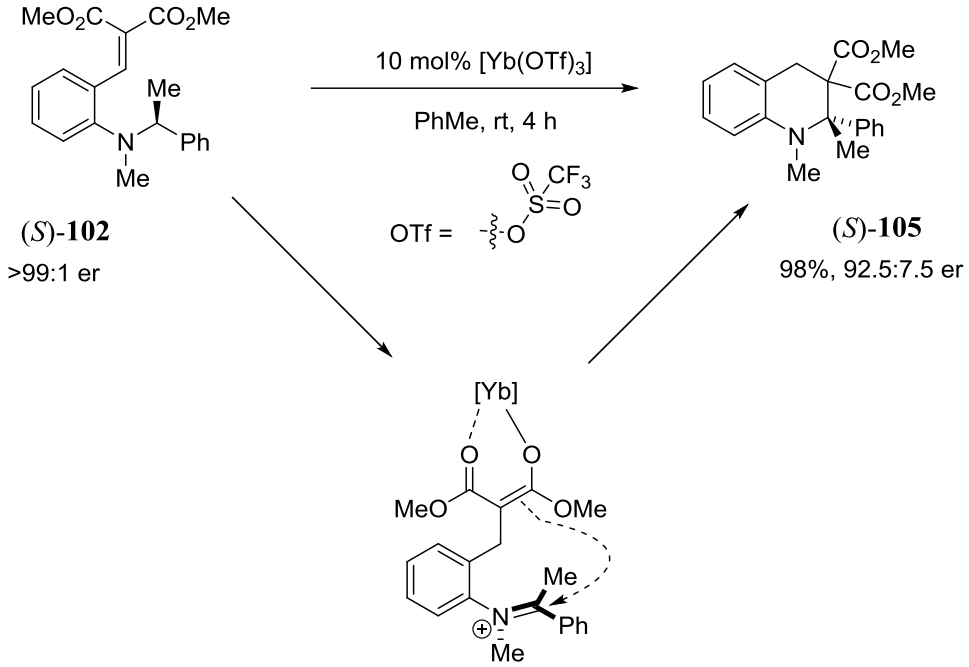
(*R*)-**102** (*R*)-**105**

97.5:2.5 er 9%, 82:18 er

Scheme 49

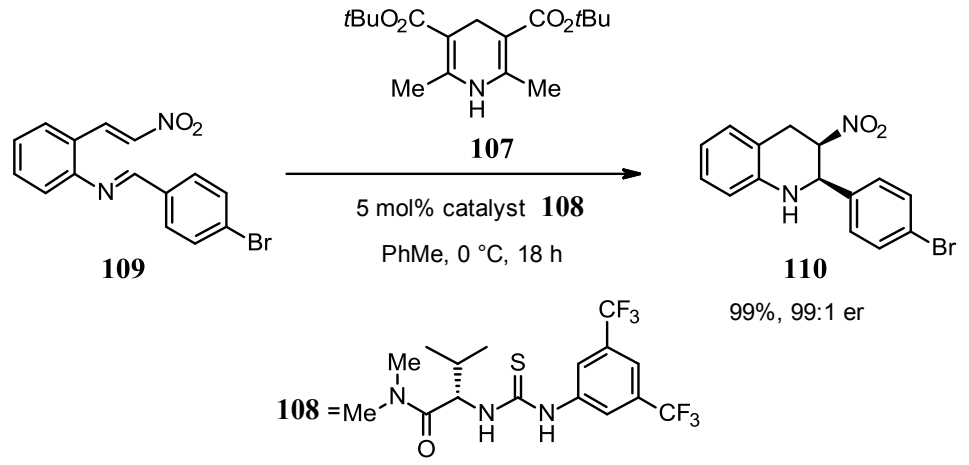
Interestingly, they found that treatment of (*S*)-**102** with an achiral acid, [$Yb(OTf)_3$], gave a product which retained most of the enantioenrichment. They postulated that these results supported their view that the reaction proceeded *via* a 'memory of chirality' pathway with the

chiral information being memorised as an axial chirality in the cationic intermediate **106** (Scheme 50).



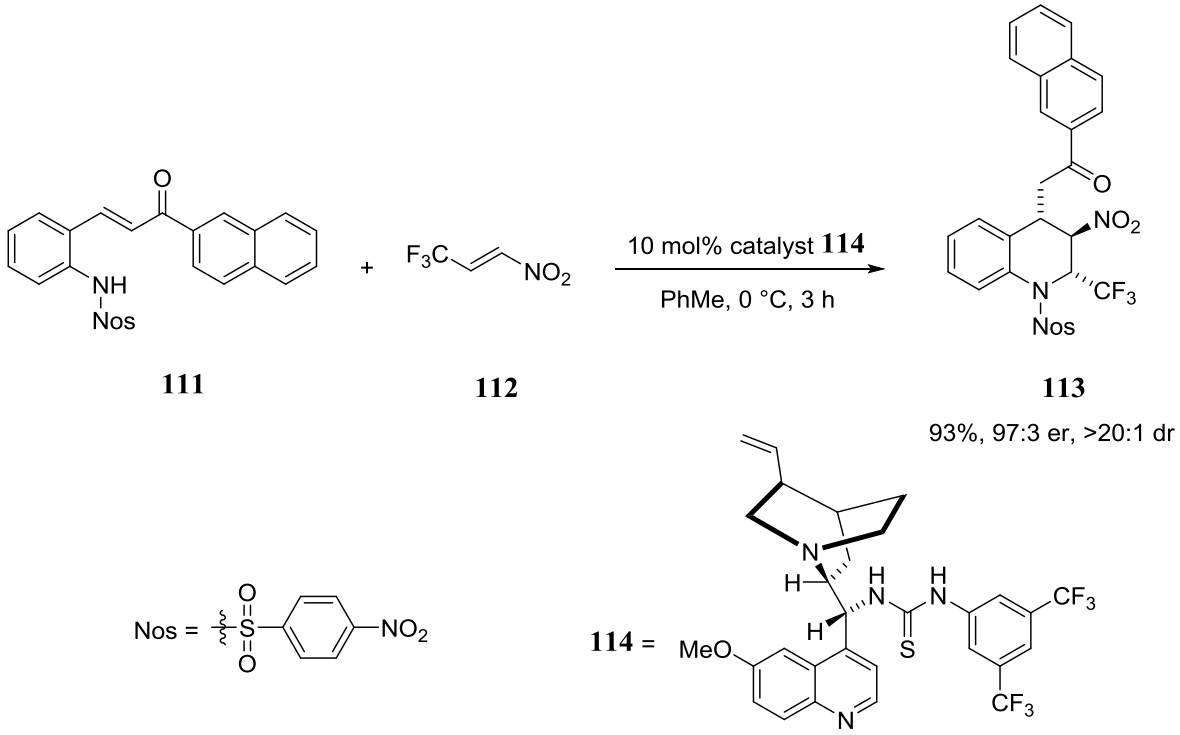
Scheme 50

More recently, in 2015, Anderson and co-workers reported an efficient asymmetric synthesis of *cis*-2-aryl-3-nitrotetrahydroquinolines *via* an enantioselective tandem reduction/nitro-Mannich reaction.[93] *tert*-Butyl Hantzsch ester **107** was used as a transfer hydrogenation reagent in the presence of thiourea catalyst **108** and stirred with the 2-iminonitrostyrene **109** in toluene for 18 hours at 0 °C. This formed the desired THQ product **110** as a single diastereoisomer in excellent yield and er (Scheme 51).



Scheme 51

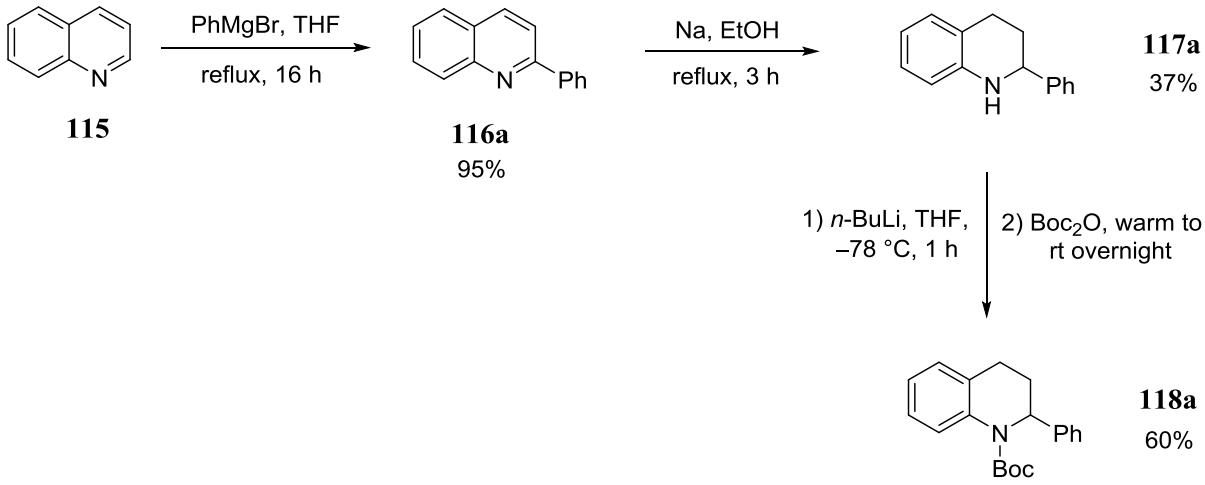
In early 2017, Yan, Wang and co-workers reported a similar thiourea catalysed cascade process to form a wide variety of 2-trifluoromethyl- and 2-perfluoroalkyl-THQ derivatives with three contiguous stereocentres.[94] The chalcone **111** with the nosyl protecting group on the nitrogen, in the presence of the cinchona alkaloid derivative **114**, was stirred with alkene **112** in toluene for 2 hours at 0 °C. The enantioenriched THQ **113** was formed in excellent yield with a high er and dr (Scheme 52).



Scheme 52

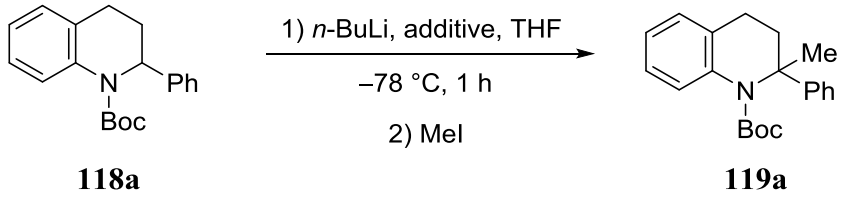
2.2 Previous THQ work in the group

Work on this project started in my fourth year undergraduate research project and the aim was to investigate the lithiation–substitution chemistry of *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **118a**.[95] The starting material was synthesised in 3 steps but the route was not ideal due to not only the use of excess Grignard reagent and sodium metal but also a moderate yield was obtained in the second step (Scheme 53).



Scheme 53

With *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **118a** in hand, the initial lithiation–substitutions were carried out using *n*-BuLi in THF at –78 °C, with a lithiation time of 1 hour. The reactions, both with and without the ligand TMEDA, yielded promising results with moderate to good yields of product **119a** being obtained (Scheme 54 and Table 9).



Scheme 54

Product	Additive	Yield (%)
119a	TMEDA	80
119a	None	53

Table 9

At this point, the work was continued by another member of the Coldham group.[41] The conditions of the lithiation were optimised by using *in-situ* IR spectroscopy and it was found that the Boc group rotation was rapid, even at –78 °C and that the lithiation was complete within a few minutes, with no decomposition observed (Figure 11). However, decomposition was detected at temperatures higher than –78 °C (Figure 12).[41]

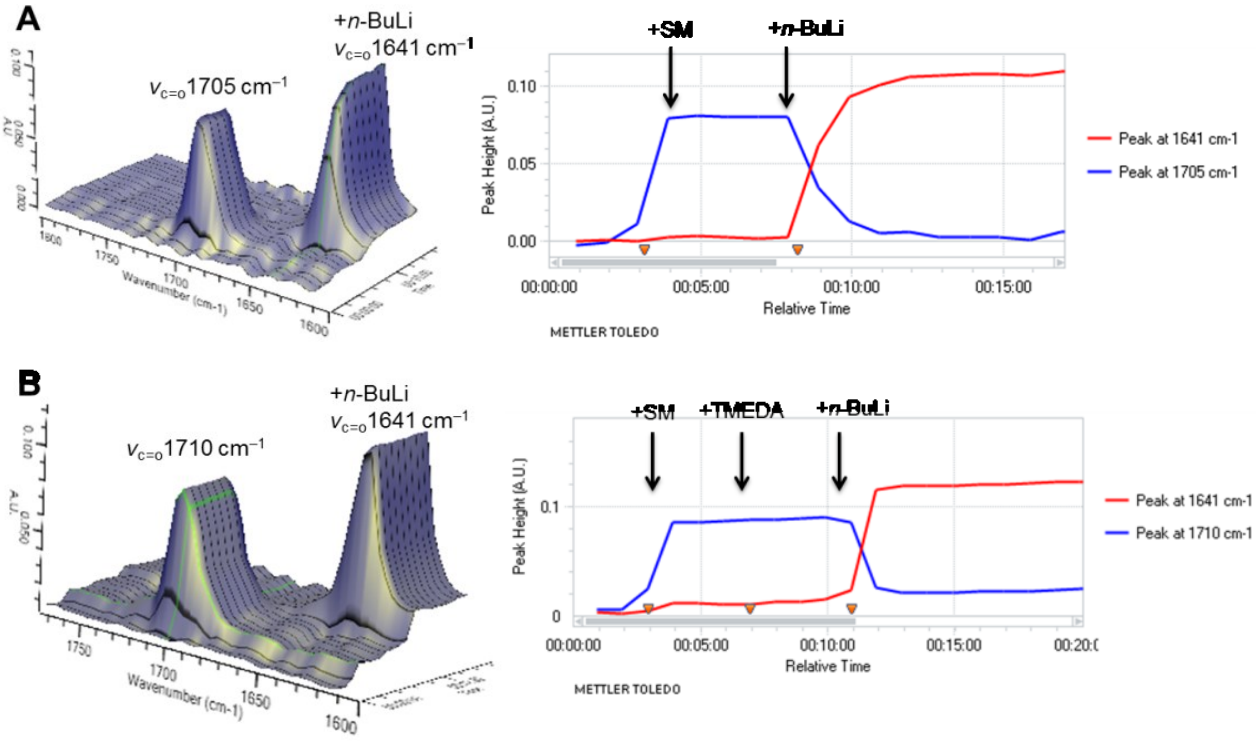


Figure 11. A). *In-situ* ReactIR™ 3D and 2D plots of the lithiation of *rac*-**118a** with *n*-BuLi at –78 °C in THF. Blue line represents intensity of C=O stretching frequency of *rac*-**118a** (1705 cm^{-1}) and red line of lithiated *rac*-**118a** (1641 cm^{-1}) over time. B). *In-situ* ReactIR™ 3D and 2D plots of the lithiation of *rac*-**118a** with *n*-BuLi/TMEDA at –78 °C in diethyl ether. Blue line represents intensity of C=O stretching frequency of *rac*-**118a** (1710 cm^{-1}) and red line of lithiated *rac*-**118a** (1641 cm^{-1}) over time.

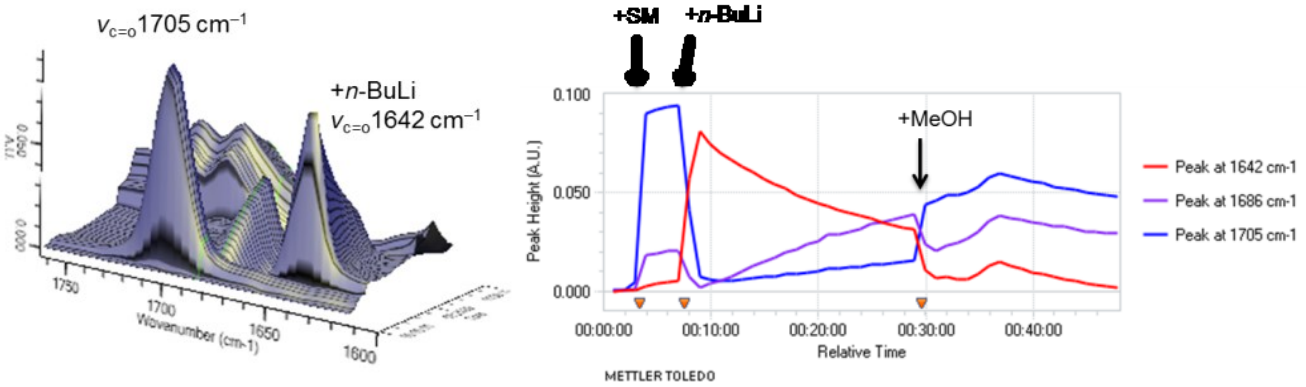
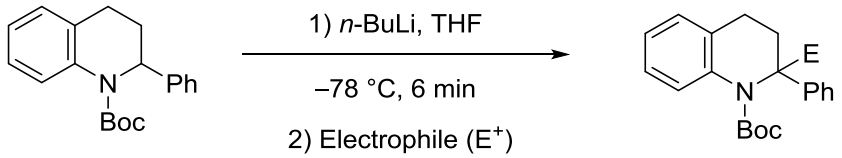


Figure 12. *In-situ* ReactIR™ 3D and 2D plots of the lithiation of *rac*-**118a** with *n*-BuLi at –50 °C in THF. Blue line represents intensity of C=O stretching frequency of *rac*-**118a** (1705 cm^{-1}); red line of lithiated *rac*-**118a** (1642 cm^{-1}) and purple line of decomposition (1682 cm^{-1}) over time.

On account of this data, THQ **118a** was lithiated at –78 °C in THF using *n*-BuLi. Addition of a variety of electrophiles after 6 minutes gave the majority of products **119a**–**k** in moderate to excellent yields but some reactions formed little to no product (Scheme 55 and Table 10).



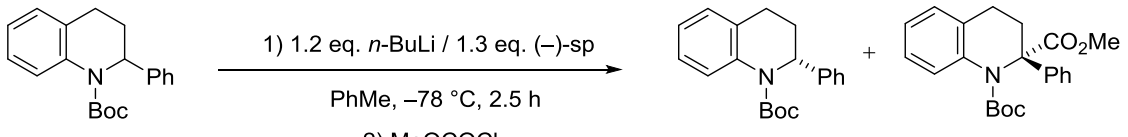
118a **119**

Scheme 55

Product	E^+	Yield (%)
119a	MeI	87
119b	MeOCOCl	90
119c	EtOCOCl	71
119d	allyl bromide	78
119e	BnBr	75
119f	4-$BrC_6H_4CH_2Br$	63
119g	*n*-Bu_3SnCl	53
119h	TMSCl	22
119i	*n*-BuBr	0
119j	PhNCO	0
119k	PhSSPh	0

Table 10

Kinetic resolutions were then attempted in order to try and recover enantioenriched starting material. After optimisation, it was found that pre-mixing 1.2 equivalents of *n*-BuLi and 1.3 equivalents of (–)-sparteine in toluene at –78 °C before adding the racemic THQ **118a**, stirring for 2.5 h and then adding the sacrificial electrophile, methyl chloroformate, gave the recovered starting material (*R*)-**118a** with excellent er (Scheme 56). The absolute configuration of (*R*)-**118a** was determined by removing the Boc group and then comparing the optical rotation with the known secondary amine.



rac-**118a** (*R*)-**118a** (*S*)-**119b**

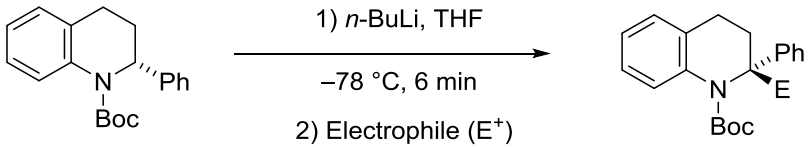
43%, 97:3 er

selectivity factor (s) (by RSM) = 20

56%, 81:19 er

Scheme 56

Using this enantioenriched starting material, lithiation–substitutions were attempted and these gave products **119a–f** in good to excellent yields**.** There was little to no loss of the enantioenrichment for **119a–c** (Scheme 57 and Table 11). However, products **119d–f** were virtually racemic and it was thought that this might be due to the electrophiles in these examples being converted to stabilised radicals, making a radical pathway most likely.



(*R*)-**118a**, 97:3 er **119**

Scheme 57

Product	E^+	Yield (%)	er
(*R*)-**119a**	MeI	91	94:6
(*R*)-**119b**	MeOCOCl	90	97:3
(*R*)-**119c**	EtOCOCl	78	97:3
119d	allyl bromide	74	54:46
119e	BnBr	70	52:48
119f	4-$BrC_6H_4CH_2Br$	58	52:48

Table 11

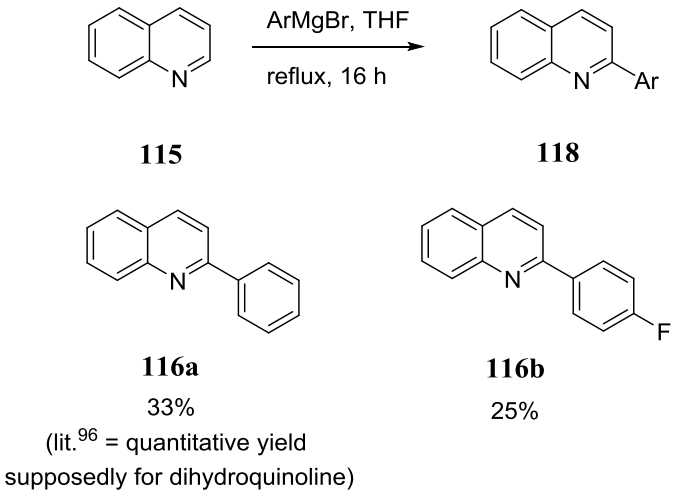
2.3 Results and Discussion

2.3.1 Synthesis of *N*-Boc-2-aryl-1,2,3,4-tetrahydroquinolines

The main aim of my PhD project has been to extend the successful results with *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **118a** to other 2-aryl-1,2,3,4-tetrahydroquinoline derivatives and to explore further the reactivity of these substrates.

The target *N*-Boc-2-aryl-1,2,3,4-tetrahydroquinolines were unavailable commercially and needed to be prepared from readily available starting materials. The first step of the synthesis involved the preparation of 2-arylquinolines. A method had been reported in the literature which involved adding a variety of Grignard reagents to quinoline **115** and heating under reflux for 16 hours to form the desired molecules.[96] This method was used in my fourth year research project to synthesise 2-phenylquinoline **116a** in excellent yield (*vide supra*). However, the method was quite hazardous with large amounts of the Grignard reagent required and poor

yields of products **116a** and **116b** were obtained when these reactions were attempted in my PhD project (Scheme 58).



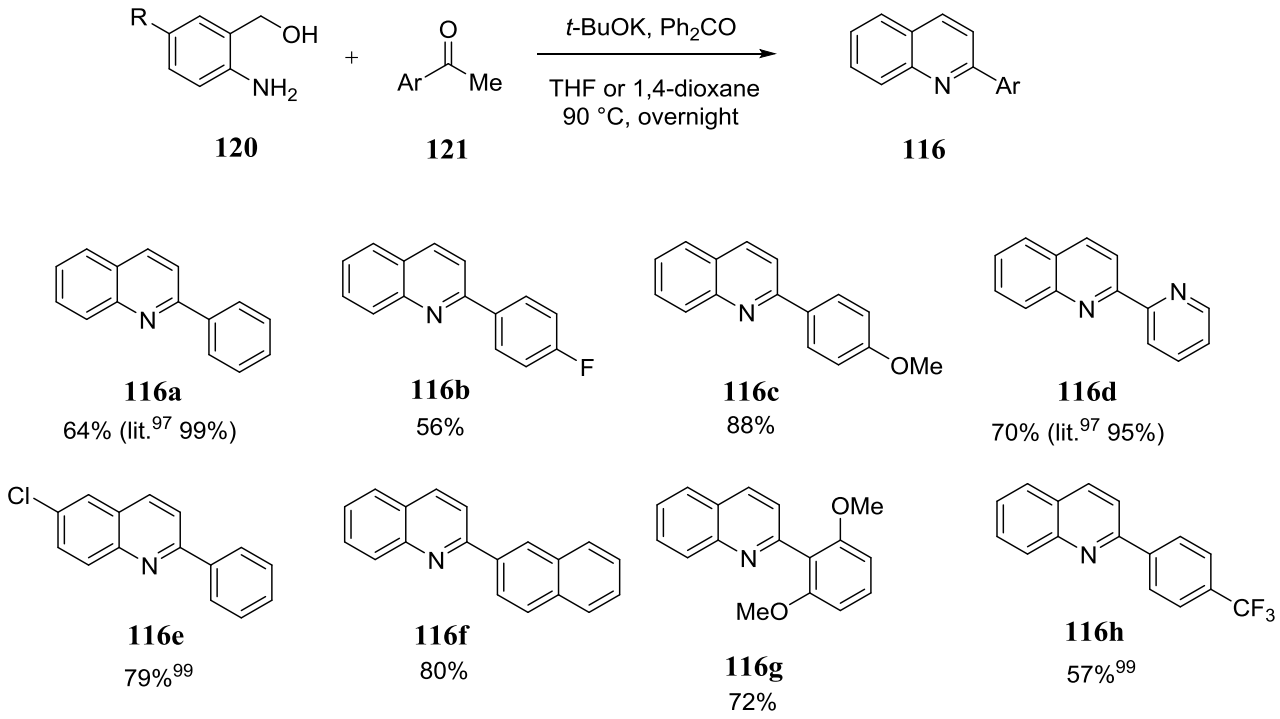
115 **118**

116a
33%
(lit.[96] = quantitative yield supposedly for dihydroquinoline)

116b
25%

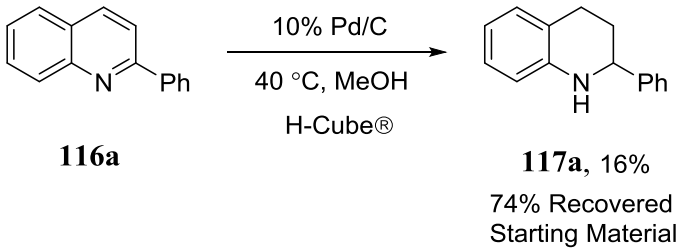
Scheme 58

A literature search was therefore carried out in order to find an alternative method of forming these compounds. In 2008, Martínez and co-workers reported a relatively simple, indirect Friedländer synthesis of 2-arylquinolines from readily available, inexpensive starting materials.[97] Therefore, 2-aminobenzyl alcohols **120**, acetophenones **121**, benzophenone and potassium *tert*-butoxide were stirred in THF or 1,4-dioxane and heated under reflux overnight. The benzophenone is required in this process for a Meerwein–Ponndorf–Verley (MPV) reduction which oxidises the alcohol to an aldehyde which then allows the Friedländer synthesis to proceed. This method produced the desired compounds **116a-h** in much improved yields (Scheme 59).



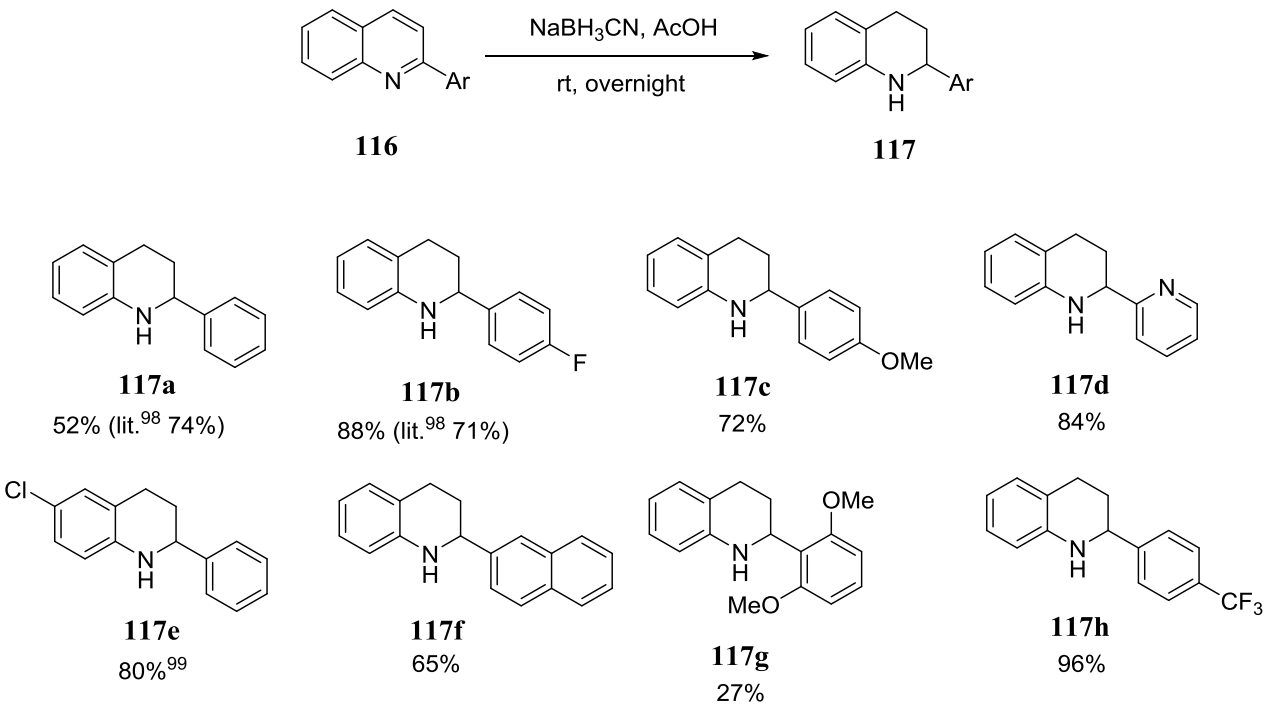
Scheme 59

With the 2-arylquinolines in hand, the second step of the synthesis required a reduction in order to form the 2-aryl-1,2,3,4-tetrahydroquinolines. As the reduction method used in my Level 4 project gave low yields and involved a hazardous, unpredictable procedure, an improved strategy was required. It was thought that the H-Cube® continuous flow hydrogenation reactor was a possibility to carry out this reduction at 40 °C, in methanol, using a 10% Pd/C cartridge.[41] However, when this procedure was attempted with 2-phenylquinoline **116a**, only a low yield of the desired product **117a** was obtained with 74% of the starting material being recovered (Scheme 60).



Scheme 60

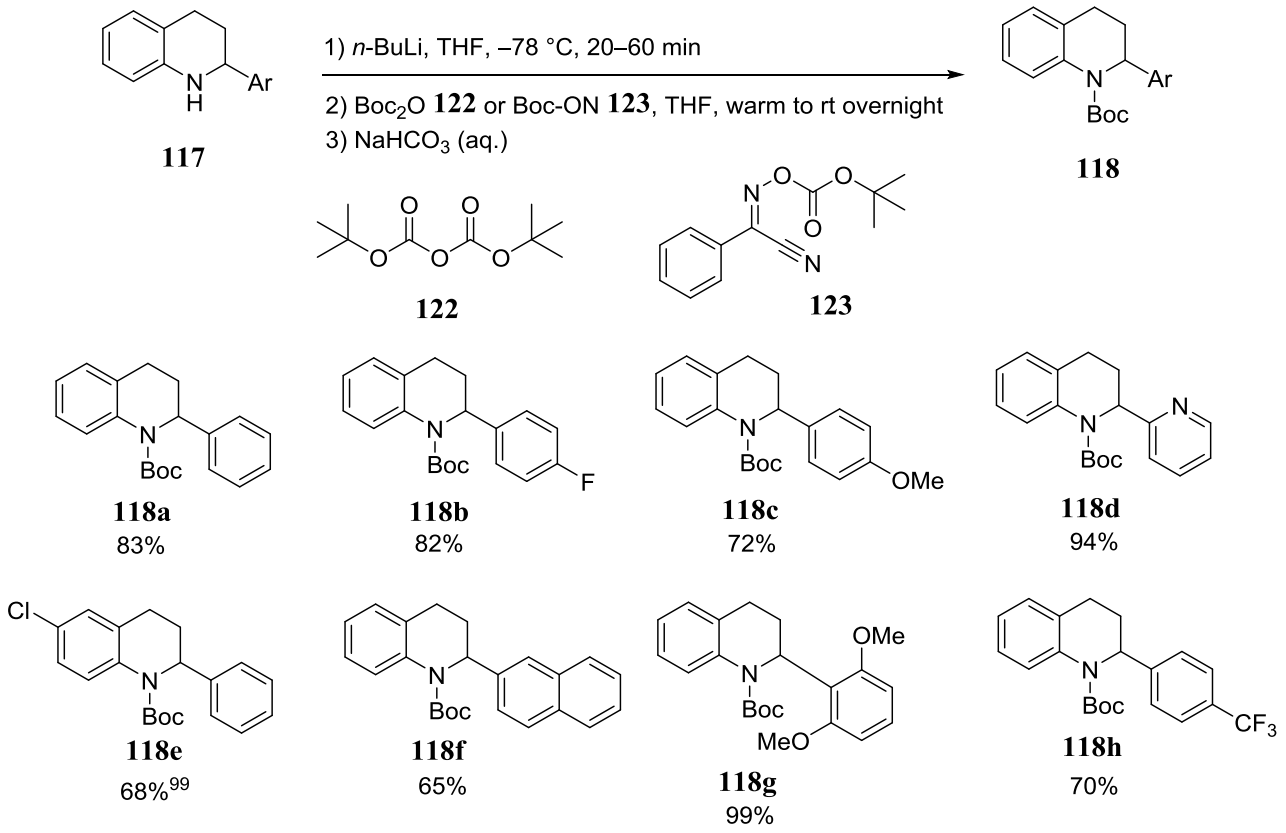
Another literature search was carried out and a simple method by Toste and co-workers involving the use of sodium cyanoborohydride was found.[41,98] Adding sodium cyanoborohydride in one portion to a solution of the 2-arylquinolines **116a-h** in acetic acid at room temperature, and stirring the solution under air overnight gave the desired 2-aryl-1,2,3,4-tetrahydroquinolines **117a-h** in mostly good to excellent yields (Scheme 61).



Scheme 61

With suitable conditions now in hand for the first two steps of the synthesis, the final step required was the Boc protection of the amine. It had been found in my fourth year research project that stirring the starting material with di-*tert*-butyl dicarbonate **122** (Boc_2O) in THF at 0 °C and then either warming to room temperature overnight or heating the mixture at reflux for 3 days yielded very little product.[95] This is likely due to the lone pair in the *p*-orbital of the sp^2-hybridised nitrogen being in conjugation with the aromatic ring which makes it much less nucleophilic than an alkylamine. To alleviate this problem, *n*-BuLi was used to deprotonate the 2-aryl-1,2,3,4-tetrahydroquinolines **117a-h** in THF at –78 °C. After 20–60 minutes, a solution of Boc_2O in THF was added to the mixture and the products **118a-d**, **f-h** were mostly obtained in good to excellent yields (Scheme 62**).** The R_f on silica of all of the products except **118d** were close to the R_f of the unreacted Boc_2O which made the separations difficult. In the case

of **118e**, the polarities were virtually identical. Therefore, an alternative reagent, 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile **123** (Boc-ON), was used in this case.[99]

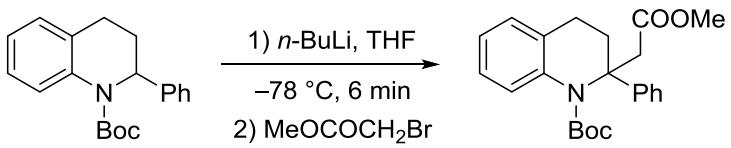


Scheme 62

2.3.2 Further work on *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline

While the organolithium chemistry carried out so far in this project had centred on *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **118a**, there were still multiple reactions that we wished to study on this parent compound in order to further explore its reactivity.

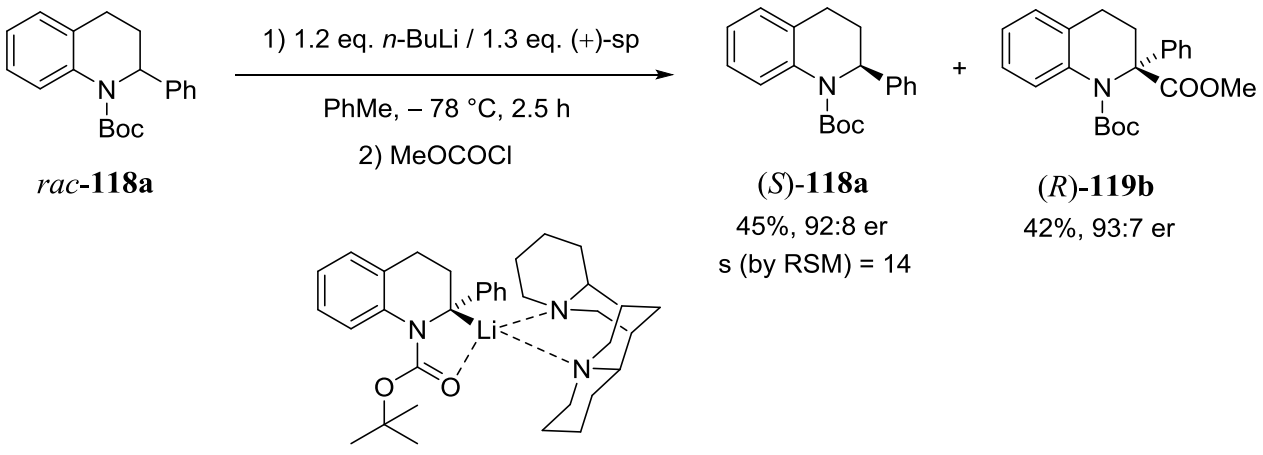
Firstly, a racemic lithiation-substitution was attempted using methyl bromoacetate as the electrophile. Using the optimum conditions found with *in-situ* IR spectroscopy (*vide supra*), THQ **118a** was deprotonated with *n*-BuLi in THF and stirred for 6 minutes before methyl bromoacetate was added. The product **119l** was obtained in good yield (Scheme 63).



118a **119l** 63%

Scheme 63

As the highly selective kinetic resolutions of THQ **118a** had only used (–)-sparteine as the chiral ligand so far, it was thought that by using the now more readily available (+)-sparteine as the chiral ligand instead, it would be a convenient way of obtaining the other enantiomers of the starting material and product in good er. To this end, THQ **118a** was deprotonated using the pre-mixed *n*-BuLi / (+)-sparteine complex in toluene and the mixture was stirred at –78 °C for 2.5 hours. Methyl chloroformate was added as the sacrificial electrophile and this gave both the recovered starting material and product in excellent yields and with good er's (Scheme 64). While the structure of the organolithium intermediate in these kinetic resolutions has not been determined, it is assumed that the organolithium is complexed to one sparteine molecule before addition of the electrophile forms the disubstituted product, as shown in the scheme below. Future spectroscopic studies or DFT calculations could be carried out in order to support this hypothesis.



rac-**118a** (*S*)-**118a** 45%, 92:8 er s (by RSM) = 14 (*R*)-**119b** 42%, 93:7 er

Scheme 64

Pleasingly, it was possible to obtain the X-ray crystal structure of product (*R*)-**119b** using a CuKα source in order to determine the absolute configuration. It was determined that the

electrophile added with retention of configuration to give the (*R*)-enantiomer as the major product (Figure 13 and Appendix 1a).

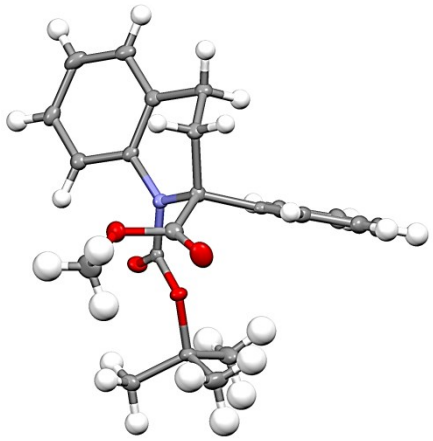
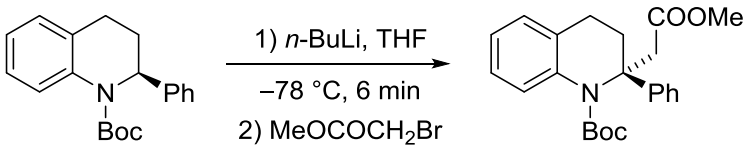


Figure 13

X-ray crystal absolute configuration determination of compound (*R*)-119b

Flack parameter = 0.03(6)

The enantioenriched starting material (*S*)-**118a** was then lithiated with *n*-BuLi in THF and stirred for 6 minutes. Methyl bromoacetate was added as the electrophile to give product (*R*)-**119l** in good yield with the enantioenrichment maintained (Scheme 65).



(*S*)-**118a**
92:8 er

(*R*)-**119l**
71%, 92:8 er

Scheme 65

It was pleasing that the X-ray crystal structure of this product could also be obtained on the CuKα source in order to determine the absolute configuration. This further confirmed that the electrophile added with retention of configuration as it was determined that the major product was the (*R*)-enantiomer (Figure 14 and Appendix 1b).

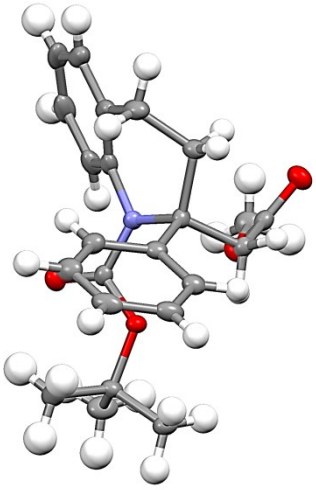


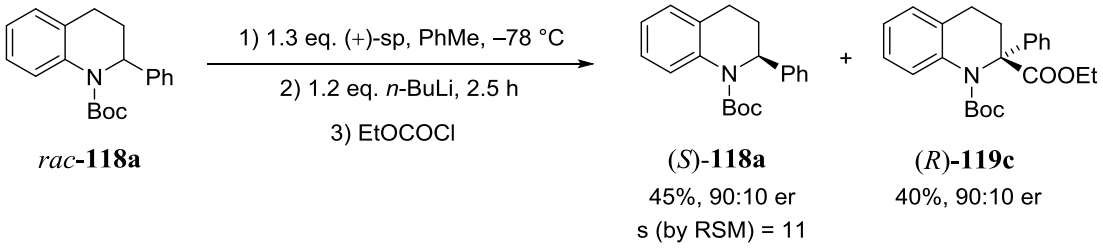
Figure 14

X-ray crystal absolute configuration determination of compound (*R*)-119l

Flack parameter = 0.11(12)

The kinetic resolutions that had been attempted with this substrate so far all involved pre-mixing the *n*-BuLi and (+)-sparteine in order to form the chiral base complex before the starting material was added, so-called 'inverse addition'. Li found that a kinetic resolution where the *n*-BuLi was added to a mixture of starting material and chiral ligand ('normal addition') only gave recovered starting material in a moderate 75:25 er.[41] However, the conversion was only 40% and so this procedure needed to be tested in order to confirm that 'inverse addition' was the best method to use for these kinetic resolutions.

Therefore, *n*-BuLi was added to a mixture of THQ **118a** and (+)-sparteine in toluene. The mixture was stirred at –78 °C for 2.5 hours and ethyl chloroformate was added to give both the recovered starting material (*S*)-**118a** and the product (*R*)-**119c** in good yields and ers (Scheme 66).



rac-**118a**

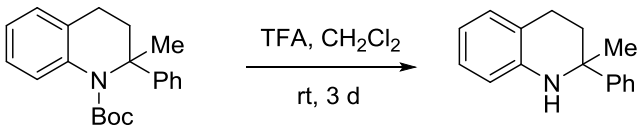
(*S*)-**118a**
45%, 90:10 er
s (by RSM) = 11

(*R*)-**119c**
40%, 90:10 er

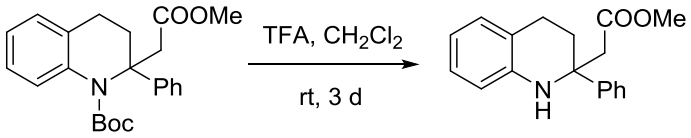
Scheme 66

This shows that both addition methods give good selectivity but for the remaining kinetic resolutions in this chapter, the 'inverse addition' method was used.

It would be very useful if it were possible to remove the Boc protecting group from these compounds as it would not only allow a wider variety of compounds to be accessed but it would also allow further functionalisation of the molecules. While Li was able to deprotect the enantioenriched starting material, none of the substituted products were deprotected.[41] Therefore, racemic THQs **119a** and **119l** were dissolved in CH_2Cl_2 and stirred in the presence of TFA under air at room temperature. The reactions proceeded slowly but pleasingly, after 3 days, the desired products **124a** and **124b** were obtained in excellent yields (Scheme 67).



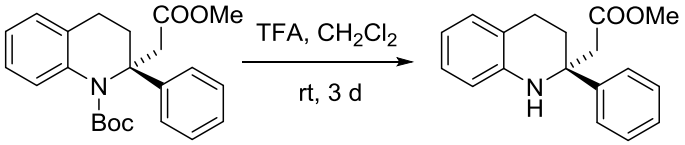
119a **124a**, 86%



119l **124b**, 86%

Scheme 67

It would be highly desirable to remove the Boc group from enantioenriched products and so the enantioenriched product (*R*)-**119l** was treated with TFA and the product (*R*)-**124b** was obtained in good yield and the product was still highly enantioenriched. This was pleasing as it proved that the Boc group could be removed without loss of the enantioenrichment (Scheme 68).



(*R*)-**119l**
92:8 er

(*R*)-**124b**
69%, 88:12 er

Scheme 68

As shown multiple times so far, chloroformate compounds have given good results when used as electrophiles in lithiation–substitution sequences. Therefore, it was assumed that a similar class of compounds, namely cyanoformates, would also be good electrophiles to use in these reactions. As the cyanoformates only had a different leaving group to the chloroformates, the products obtained from these reactions were predicted to be the same as the products obtained when chloroformates were used.

However, after multiple attempts at lithiation-substitution reactions with these electrophiles, it became clear that different products were being obtained.[99] For example, when methyl cyanoformate was used as the electrophile, the ^{1}H NMR spectrum of the expected product, THQ **119b**, had marked differences to the ^{1}H NMR spectrum of the compound obtained (Figure 15). The patterns for both the aromatic protons and the CH_2's were clearly different and most noticeably, the benzylic proton remained in the unknown product and there was one fewer aromatic proton.

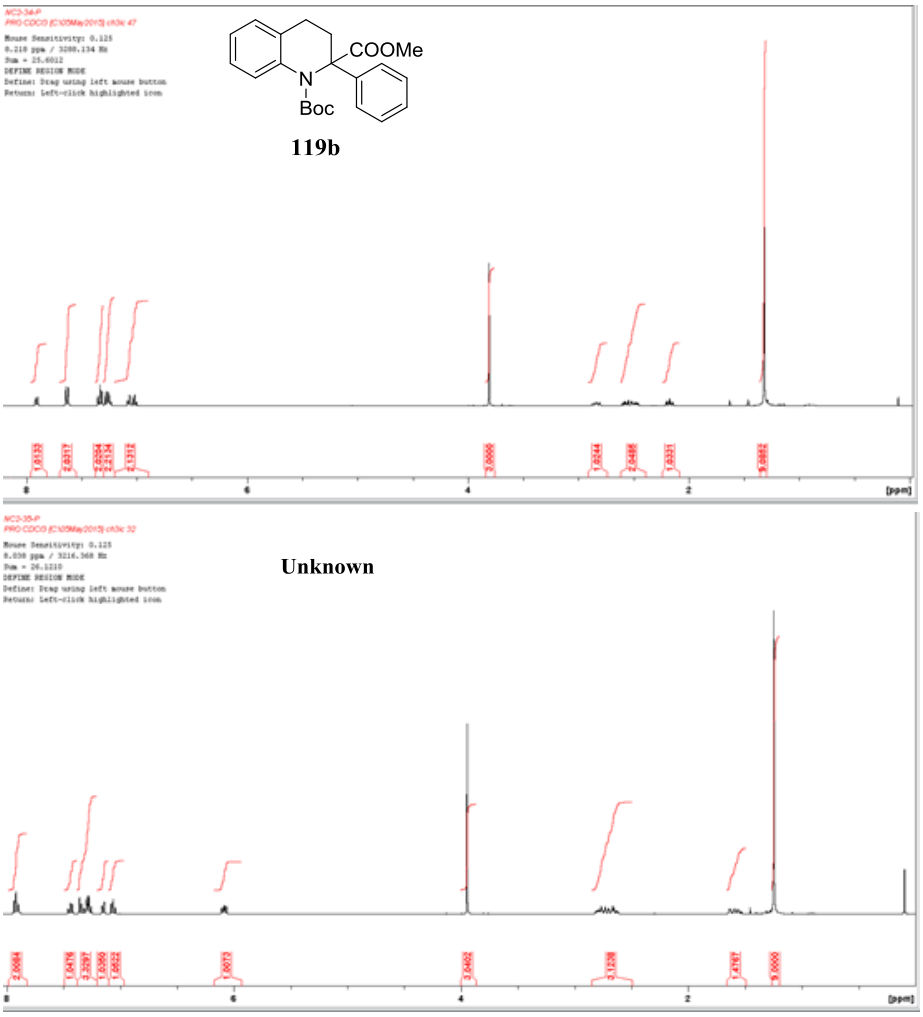
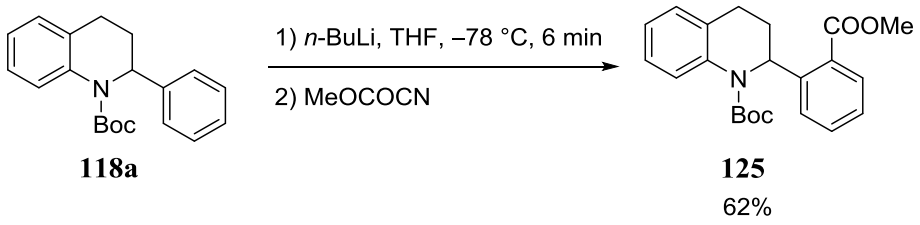


Figure 15

After careful analysis of the ^{1}H and ^{13}C NMR spectra of both compounds, it was postulated that the product obtained from the reaction with methyl cyanoformate was compound **125** where the substitution had taken place in the *ortho*-position of the aromatic ring in the 2-position (Scheme 69).

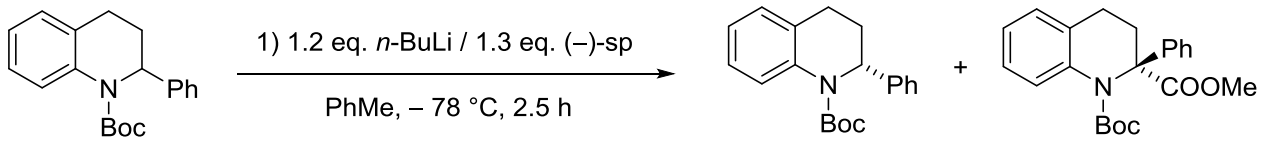


118a **125** 62%

Scheme 69

This difference in reactivity that was observed just by changing the electrophile was a remarkable result and as far as I could see, unprecedented in the area of organolithium chemistry. Therefore, more reactions needed to be carried out in order to explore potential mechanisms of this reaction.

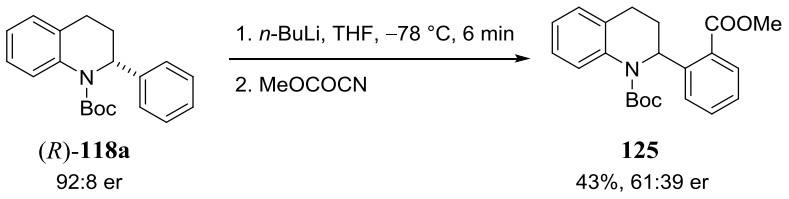
Firstly, a kinetic resolution was carried out in order to obtain enantioenriched starting material. Therefore, THQ **118a** was deprotonated using the pre-mixed *n*-BuLi / (–)-sparteine complex in toluene and the mixture was stirred at –78 °C for 2.5 hours. Methyl chloroformate was added and this gave both the recovered starting material (*R*)-**118a** and product (*S*)-**119b** in good yields and ers (Scheme 70).



rac-**118a** (*R*)-**118a** 43%, 92:8 er s (by RSM) = 11 (*S*)-**119b** 40%, 87:13 er

Scheme 70

The enantioenriched starting material (*R*)-**118a** obtained from this kinetic resolution was deprotonated with *n*-BuLi and stirred at –78 °C in THF for 6 minutes. The intermediate was quenched with methyl cyanoformate to give the product **125** (Scheme 71).

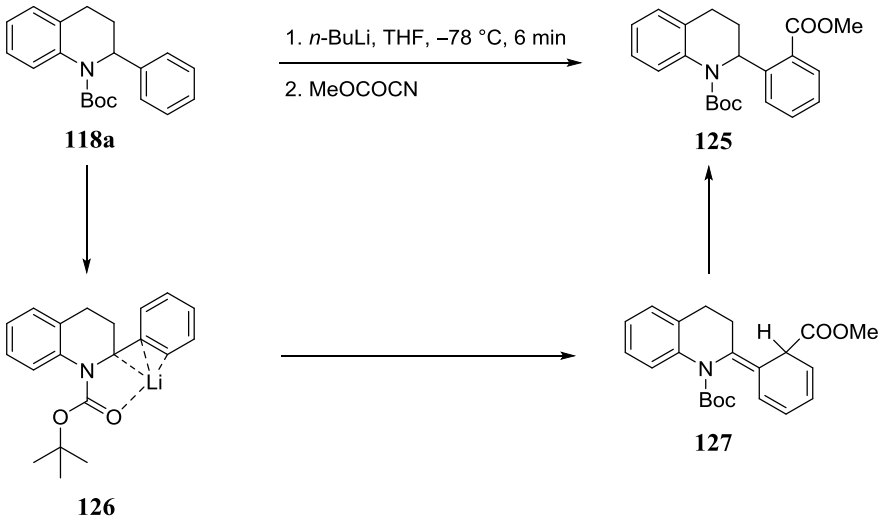


(*R*)-**118a**
92:8 er

125
43%, 61:39 er

Scheme 71

This product had a much lower er than the starting material and this supported the view that the reaction was taking place *via* a lithiation in the *α*-position and not simply in the *ortho*-position as the enantioenrichment was being lost. It was hypothesized that the organolithium species existed as an η^3 intermediate **126** with the lithium co-ordinated to the *α*-, *ipso*- and *ortho*- carbons as well as to the carbonyl oxygen of the Boc group.[100] On addition of a cyanoformate electrophile, the substitution could take place in the *ortho*-position to give the intermediate **127** which would explain the decrease in the enantioenrichment when enantioenriched starting material was used. Then, a deprotonation of the *ortho*-position and protonation of the *α*-position would give the product **125** but as concerted thermal 1,3-hydride shifts are not formally allowed by Woodward–Hoffmann rules, it is assumed that this proton transfer takes place in a stepwise, rather than concerted, manner (Scheme 72). The intermediates **126** and **127** are chiral and addition of methyl cyanoformate is likely to occur preferentially to one face and so it is anticipated that the intermediate ester **127** will have high er, although this could not be confirmed. Proton transfer occurs to give the product with a low er, but this is not completely racemic. Therefore the process is at least partially competitive with racemisation. One possibility is that as this proton is likely to be very acidic (being adjacent to an ester and alkenes), a mild base, possibly LiCN which is formed *in-situ*, promotes deprotonation and the resulting organolithium is chiral but racemises on warming.



Scheme 72

In order to support this hypothesis, computational DFT studies have been carried out by Dr. Anthony Meijer within the Department of Chemistry at the University of Sheffield. Density functional theory (DFT) calculations were performed using Gaussian09, version D.01. Gaussian was compiled with Gaussian-supplied versions of BLAS and ATLAS. The B3LYP functional was used throughout with the GD3-BJ correction to account for dispersion interactions, whereby it is noted that in this case this correction did not change the answers significantly compared to the bare B3LYP functional. The 6-311G** basis set was used throughout with the ultrafine setting for the integrals. All of the structures were fully optimized without any symmetry restrictions. All calculations were performed in THF solvent, as modelled through the polarizable continuum model (PCM) using the standard parameters as implemented in Gaussian.[101]

Frequency calculations in the harmonic approximation were carried out to characterize all stationary points obtained to confirm them as local minima. All minimum-energy structures were identified through the absence of imaginary frequencies.[101]

The calculations carried out so far have focussed on the lithiated intermediate, since this is clearly where the divergence between the different electrophiles takes place. α-deprotonation leads to an η^3 co-ordination of lithium to the deprotonated species. However, in such a case lithium is coordinationally unsaturated. The empty coordination sites will be taken up by the solvent (THF) or the electrophiles.

The calculations performed so far have shown that there is certainly a difference in the position of the lithium in the minimum energy structures when methyl chloroformate, methyl cyanoformate or THF are added to the lithiated intermediate of THQ **118a** (Figure 16). When methyl chloroformate or THF are added, the lithium is situated directly above the α-carbon whereas in the case of methyl cyanoformate, the lithium is situated closer to the *ortho*-position of the aromatic ring in more of an η^3 co-ordination. Thus, we can conclude that co-ordination of methyl cyanoformate to the lithiated compound changes the co-ordination of lithium, which rationalizes the experimental result. However, more calculations will be needed to further elucidate the mechanism of this transformation.

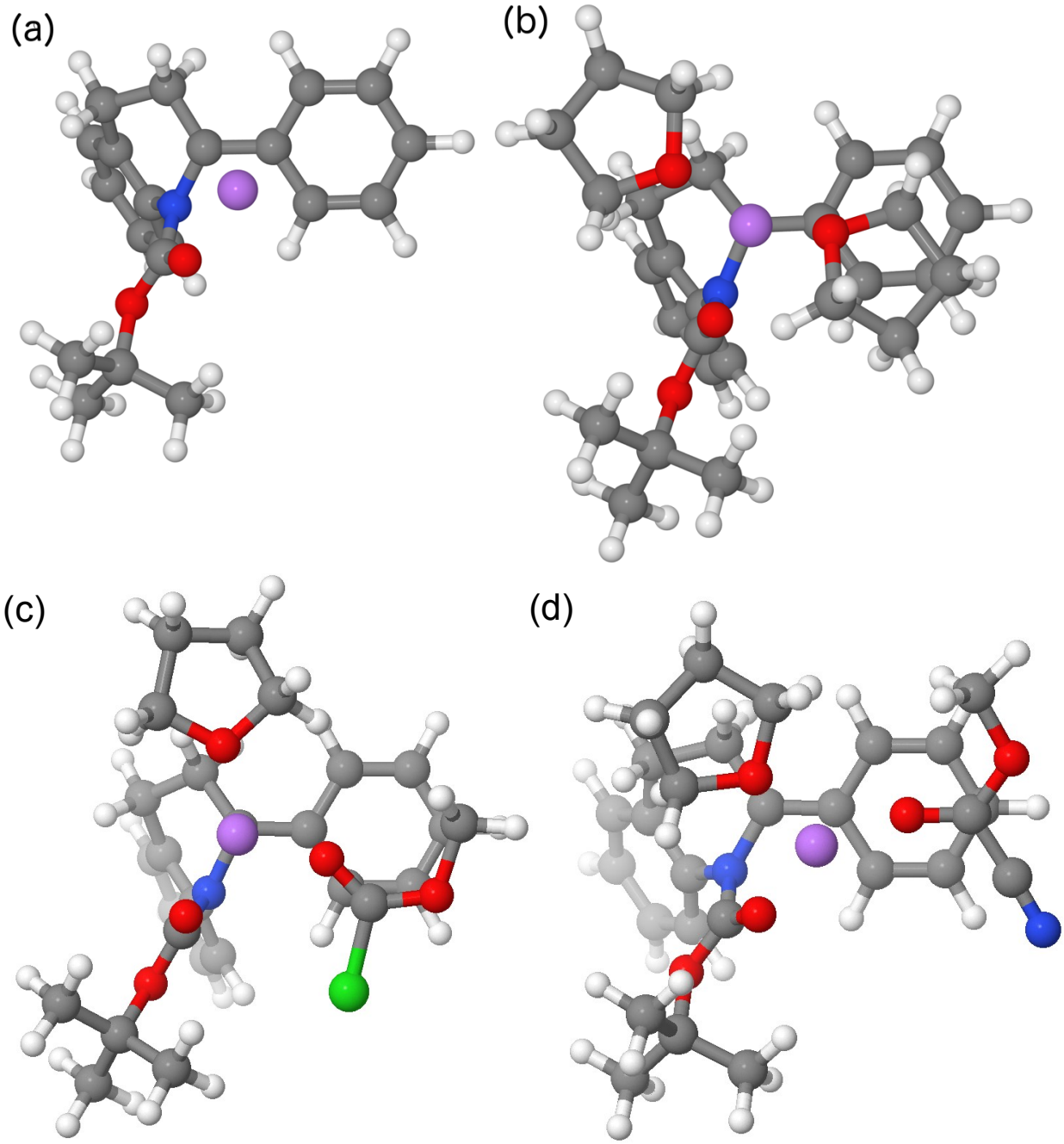
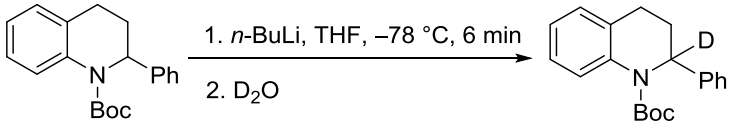


Figure 16: DFT structures of lithiated intermediate. Panel (a): bare lithiated structure. Panel (b): lithiated structure with coordinated THF. Panel (c): Lithiated structure with methyl chloroformate. Panel (d): Lithiated structure with methyl cyanoformate.

In order to further confirm this potential reaction mechanism and to eliminate the possibility of the reaction taking place *via* an *ortho*-lithiation pathway, reactions involving *N*-Boc-THQ **118a** with deuteriums incorporated into the structure were attempted.

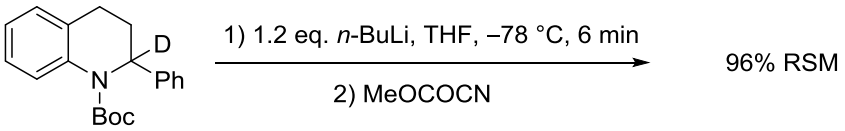
Firstly, THQ **118a** was deprotonated with *n*-BuLi and stirred at –78 °C in THF for 6 minutes. D_2O was added and this gave the deuterated THQ d_1-**118a** in good yield with around 95% deuterium incorporation in the *α*-position (Scheme 73).



118a d_1-**118a**
76%, 95% D

Scheme 73

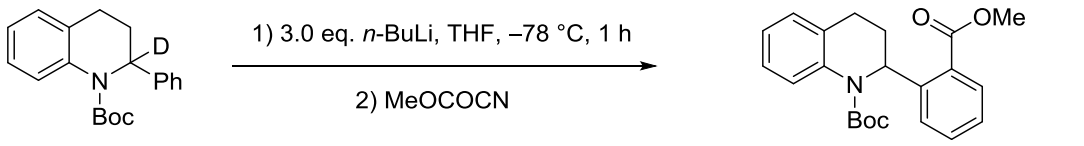
An attempt was then made to deprotonate THQ d_1-**118a** using the same conditions as had been used previously. Therefore, 1.2 equivalents of *n*-BuLi were added to THQ d_1-**118a** and the mixture was stirred at –78 °C for 6 minutes in THF before methyl cyanoformate was added. However, only the starting material was recovered in almost quantitative yield (Scheme 74).



d_1-**118a**

Scheme 74

Therefore, in a further attempt to lithiate this compound, a large excess (3.0 equivalents) of *n*-BuLi was added and the mixture was stirred at –78 °C for a longer reaction time of 1 hour in THF before methyl cyanoformate was added. Product **125** was obtained in a very poor yield with a large amount of starting material again being recovered. The product **125** was formed with a complete loss of the deuterium in the *α*-position (Scheme 75).



d_1-**118a**

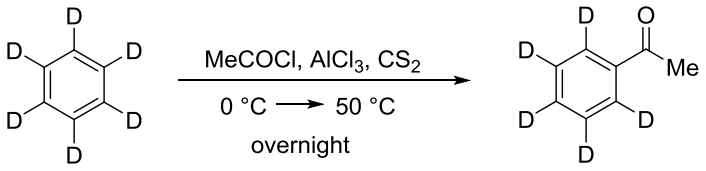
125

81% RSM, 8% **125** (100% H, 0% D)

Scheme 75

The large kinetic isotope effect in these reactions along with the loss of deuterium incorporation in the α-position of the product were very pleasing observations as they supported both the hypothesis that no *ortho*-lithiation was taking place and that the mechanism shown above in Scheme 72 was plausible.

Reactions were then attempted using another THQ compound with deuteriums incorporated in the aromatic ring. Using a literature method, benzene-d_6 **128**, was subjected to a Friedel–Crafts acylation reaction with acetyl chloride in the presence of aluminium trichloride in CS_2 to give the acetophenone d_5-**121a** (Scheme 76).[102]

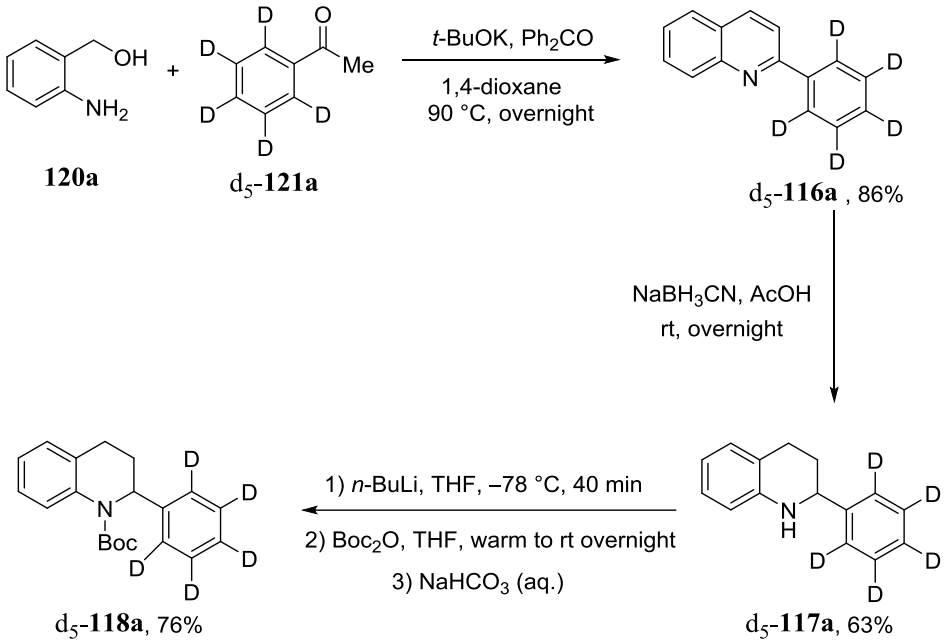


128

d_5-**121a**, 93%

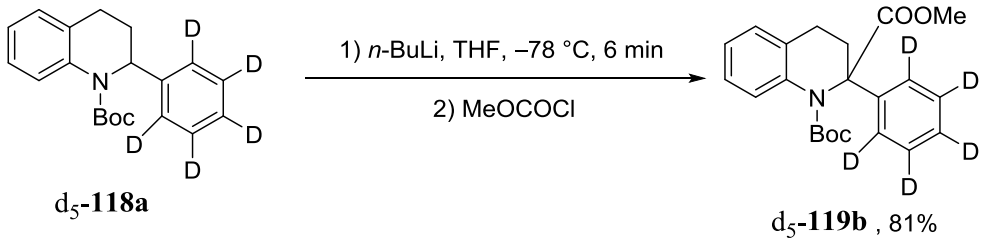
Scheme 76

Then, using the 3 steps outlined earlier in the chapter, THQ d_5-**118a** was made in a good overall yield, *via* compounds d_5-**116a** and d_5-**117a** (Scheme 77).



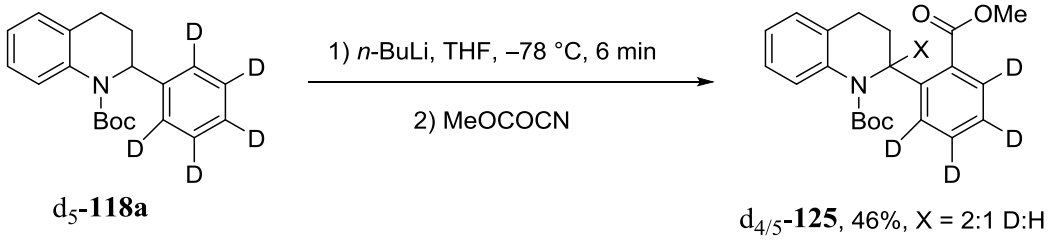
Scheme 77

With THQ d_5-**118a** in hand, two lithiation–substitution reactions were able to be carried out on this substrate. Firstly, 1.2 equivalents of *n*-BuLi were used to deprotonate the molecule using the same conditions as described earlier. Methyl chloroformate was then added as the electrophile to give, as expected, the *α*-substituted product d_5-**119b** in good yield (Scheme 78).



Scheme 78

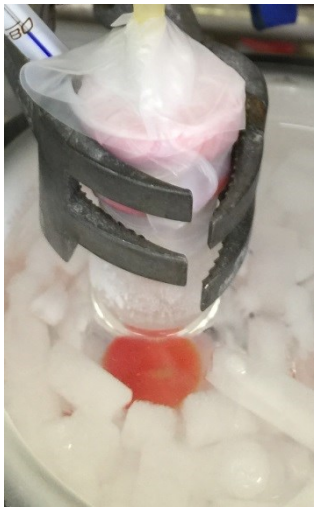
Then, the same reaction was attempted but this time, methyl cyanoformate was added as the electrophile. The *ortho*-substituted product $d_{4/5}$-**125** was obtained in moderate yield with a 2:1 ratio of deuterium:hydrogen in the *α*-position (Scheme 79).



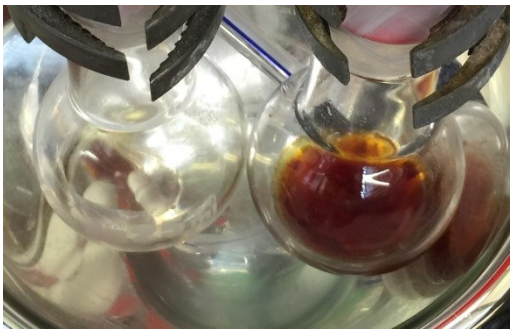
Scheme 79

This was a very pleasing result as it again clearly showed that the mechanism described in Scheme 72 was viable and supported the view that the deuterium lost from the *ortho*-position was not shifting to the α-position in a concerted manner.

It was noticeable that the yields of the products obtained from reactions using a cyanoformate as the electrophile were consistently lower than the yields obtained when chloroformates were used. Also, when a chloroformate (or other electrophile) was added, the mixture changed colour from the bright orange of the lithiated intermediate to colourless whereas it changed to a deep red colour when a cyanoformate was added (Figure 17). This potentially indicated the different mechanism that was taking place when a cyanoformate was added.



Lithiated intermediate of **118a**



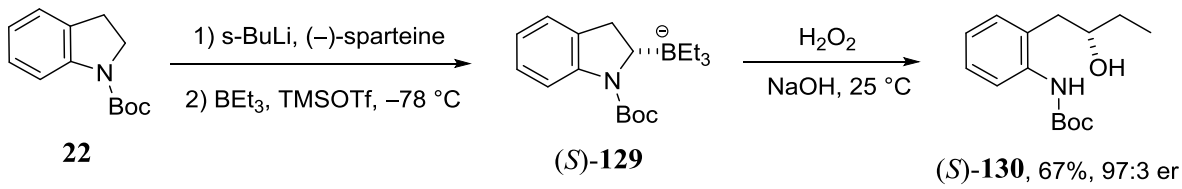
Left flask = Reaction of **118a** with MeOCOCl

Right flask = Reaction of **118a** with MeOCOCN

Figure 17

Satisfied with these results, the focus then shifted to another piece of chemistry that it was thought would yield good results with these substrates.

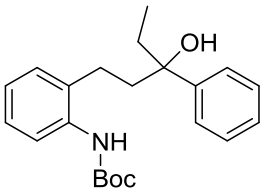
In 2008, Coldham, Aggarwal and co-workers reported the asymmetric–lithiation of amines, such as *N*-Boc-indoline **22**, followed by the addition of trialkylboranes.[103] The borane intermediate (*S*)-**129** underwent a rearrangement which, following oxidation, gave the chiral secondary alcohol (*S*)-**130** with a high er (Scheme 80).



22 (*S*)-**129** (*S*)-**130**, 67%, 97:3 er

Scheme 80

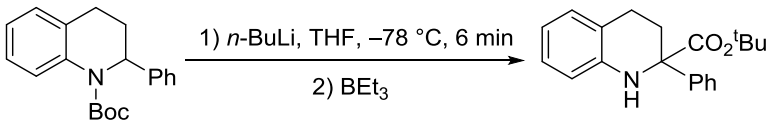
It was envisioned that carrying out similar reactions on 2-aryl THQ derivatives would yield chiral tertiary alcohols such as alcohol **131** (Figure 18).



131

Figure 18

To this end, THQ **118a** was deprotonated with *n*-BuLi and stirred at –78 °C in THF for 6 minutes. Triethylborane was added and after stirring for 16 hours, H_2O_2 and NaOH were added in order to oxidise the expected borane intermediate. However, it quickly became apparent that the expected chiral alcohol was not being formed and instead, an interesting reaction was taking place where the Boc protecting group migrated to the α-position to form the amine **132a** in good yield. It was shown that the reaction only needed to be quenched with MeOH as the H_2O_2/NaOH oxidation was not required (Scheme 81).



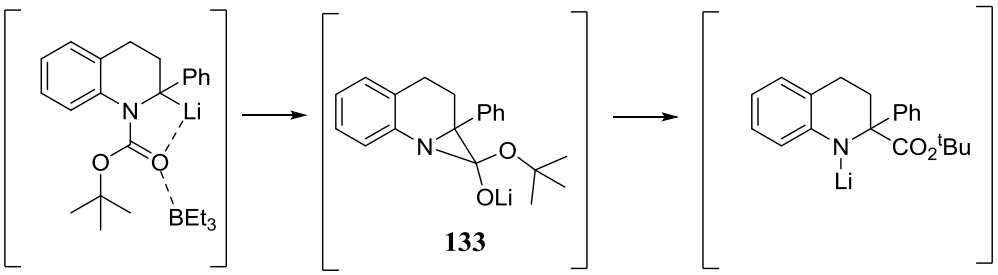
118a **132a**

H_2O_2 / NaOH quench: 69%

MeOH quench: 76%

Scheme 81

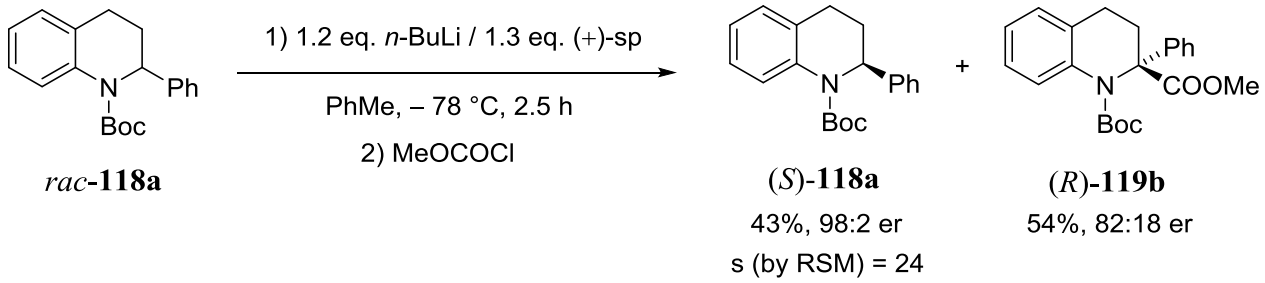
N to C migrations are known in the literature[104–106] and Boc group migrations specifically have been observed in aziridine, pyroglutamate and acyclic amine compounds.[107–111] It has been postulated that the mechanism of this reaction is a [1,2] aza-Wittig rearrangement which goes *via* the intermediate **133** (Scheme 82).[112]



Scheme 82

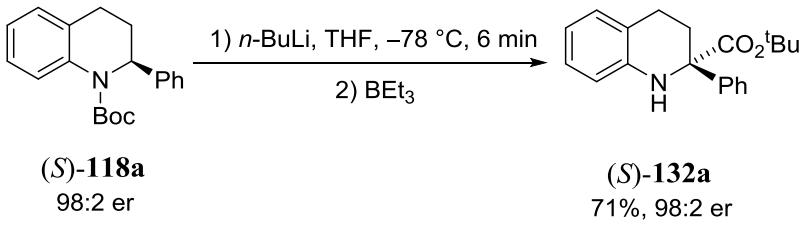
It was thought that a reaction with triethylborane using enantioenriched starting material would be very interesting as the amine **132a** could be formed with high enantioenrichment.

To this end, a kinetic resolution was attempted with THQ **118a** using the optimum conditions from earlier. The starting material (*S*)-**118a** was recovered in excellent yield and with the highest er obtained from this kinetic resolution procedure (Scheme 83).



Scheme 83

The enantioenriched starting material (*S*)-**118a** was deprotonated with *n*-BuLi and stirred at –78 °C in THF for 6 minutes before triethylborane was added. Delightfully, the product (*S*)-**132a** was obtained in good yield with the same enantioenrichment as the starting material (Scheme 84).



Scheme 84

It was also pleasing that the product was a solid and so after recrystallization, the absolute configuration was determined by X-ray crystallography using a CuKα source. From this, it was determined that the Boc group migrated with retention of configuration to give the (*S*)-enantiomer as the major product (Figure 19 and Appendix 1c).

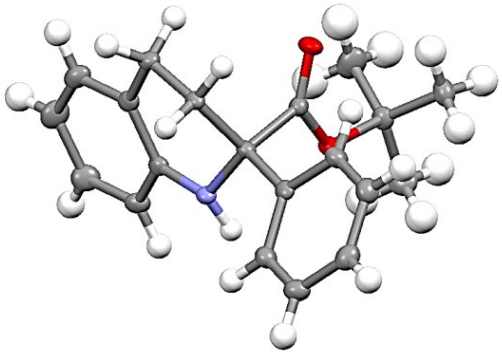
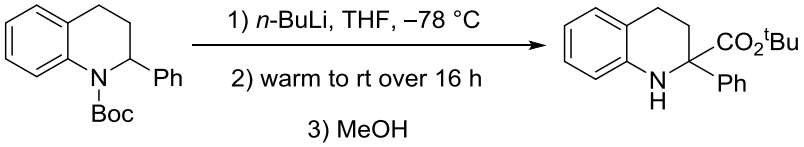


Figure 19

X-ray crystal absolute configuration determination of compound (*S*)-132a

Flack parameter = 0.08(7)

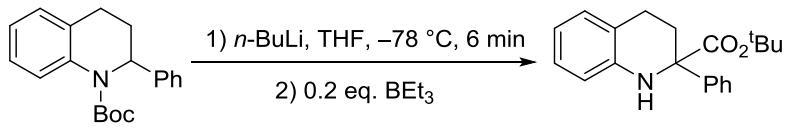
It was thought that the Boc group migration could potentially take place without the addition of triethylborane and so after deprotonating THQ **118a** with *n*-BuLi at –78 °C in THF, the mixture was left to warm to room temperature overnight before it was quenched with methanol. The product **132a** was obtained although the yield was only moderate and impurities could be seen in the crude mixture on the TLC plate which were not present when triethylborane was added (Scheme 85).



118a **132a**, 42%

Scheme 85

It was therefore hypothesized that the triethylborane didn't cause the Boc group to migrate but, due to its Lewis acidity, that it significantly accelerated the reaction. Due to its suspected catalytic activity, a reaction was then carried out using just 0.2 equivalents of triethylborane. While the yield of product **132a** wasn't as high as the yields obtained earlier, it was clearly higher than when no triethylborane was added (Scheme 86).



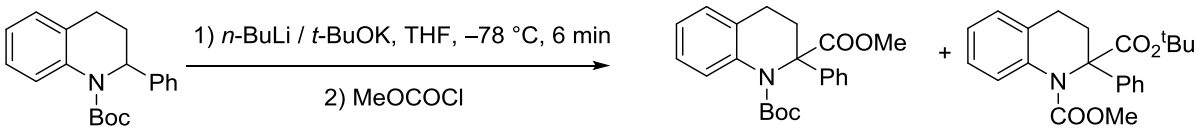
118a **132a**, 59%

Scheme 86

Finally, a reaction was carried out at the higher temperature of –50 °C. The product **132a** was obtained in 47% yield. It is possible that some of the decomposition that was observed in the ReactIR™ at this temperature could have been due to the Boc group migration taking place.

The super-basic Schlosser base mixture of *n*-BuLi / *t*-BuOK has been used for over 30 years to rapidly carry out reactions that are sluggish in either individual component.[113] Due to the changes in reactivity sometimes observed when Schlosser's base is used, we hypothesized that after carrying out a reaction of THQ **118a** using Schlosser's base with methyl chloroformate as the electrophile, the *ortho*-substituted product **125** could potentially be obtained.

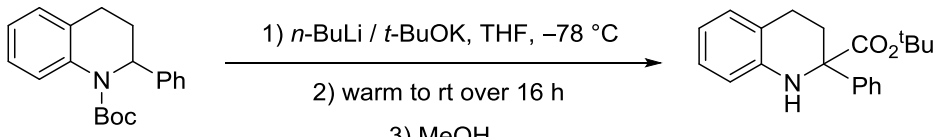
However, when this reaction was carried out, the α-substituted product **119b** was formed along with the product **134** where not only had the Boc group migrated but the CO_2Me was also now bonded to the nitrogen (Scheme 87).



118a **119b**, 21% **134**, 24%

Scheme 87

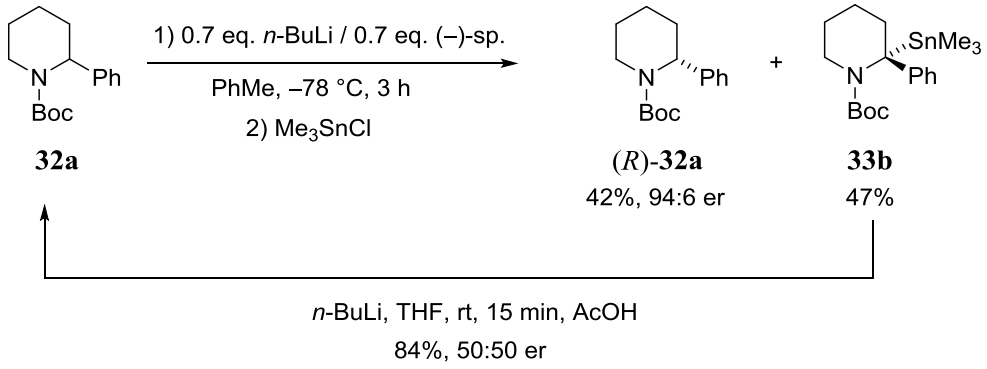
Both of these products were obtained in poor yield but the relatively substantial amount of the Boc migrated compound obtained after just 6 minutes indicated that the Schlosser base mixture also accelerated the migration. Therefore, a reaction was attempted without the addition of methyl chloroformate. THQ **118a** was deprotonated with the Schlosser base mixture at –78 °C in THF, the mixture was left to warm to room temperature overnight before it was quenched with methanol (Scheme 88). The yield of product **132a** was lower than expected and this might have been due to the super-base causing some components of the reaction mixture to decompose.



118a **132a**, 50%

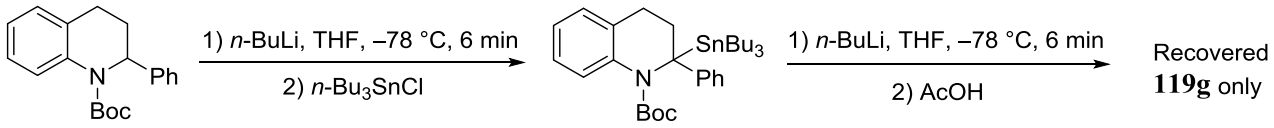
Scheme 88

Previous work in the group on *N*-Boc-2-phenylpiperidine **32a** has shown that by using a trialkyltin chloride as the electrophile in kinetic resolution reactions, the stannane product of the reactions **33b** could be recycled back to racemic starting material by carrying out a tin-lithium exchange at room temperature before quenching the lithiated intermediate with acetic acid (Scheme 89).[39] This racemic starting material can then be used in a further kinetic resolution and so this methodology allows a greater amount of enantioenriched (*R*)-**32a** to be obtained from the kinetic resolutions than would normally be possible which would be useful if the starting material was particularly valuable.



Scheme 89

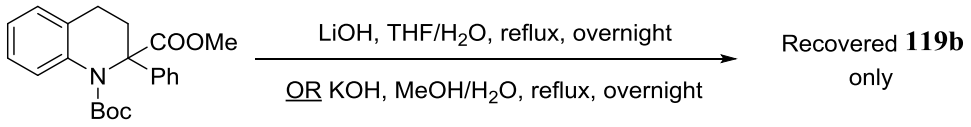
Therefore, in order to test whether this chemistry was viable with THQs, the stannane **119g** was prepared in a good yield by a lithiation-substitution reaction using the optimum conditions. *n*-BuLi was then added to stannane **119g** in THF and the reaction mixture was left to stir at –78 °C for 10 minutes before acetic acid was added to quench the reaction mixture. Disappointingly, the reaction was unsuccessful and only the stannane **119g** was recovered (Scheme 90).



118a **119g**

Scheme 90

Attempts were also made to hydrolyse the methyl ester product **119b** under basic conditions by using two different methods but in both cases, only the ester **119b** was recovered (Scheme 91).



119b

Scheme 91

The final work carried out on THQ **118a** was a NMR spectroscopic study in order to determine the kinetics of the rotation of the Boc group at the reaction temperature. This was assumed to be fast as the ReactIR™ study by Li, who worked on the project previously,[41] showed that the lithiation was complete within a few minutes and high yields were consistently obtained with a lithiation time of 6 minutes. Also, no rotamer peaks were observed in any of the ambient temperature NMR spectra of these compounds.

A variable temperature NMR study was carried out in THF-d_8 and coalescence of the *t*-butyl signal took place at around –38 °C (Figure 20). Line-shape analysis was carried out and this revealed activation parameters $\Delta H^{\ddagger} \approx 45$ kJ mol^{-1} and $\Delta S^{\ddagger} \approx -4$ J K^{-1} mol^{-1}. These values led to a $\Delta G^{\ddagger}$ value of around 45 kJ mol^{-1} at –78 °C and so the half-life of the Boc group rotation was calculated to be 0.25 sec (Appendix 2). This value corresponds well to the experimental data observed and supported the prediction that the Boc group was rotating quickly. However, these values assume an equal proportion (1:1) of each rotamer and therefore the values obtained would only be approximate. Dynamic NMR studies were also carried out due to the fact that the rotamers are actually present in approximately a 1.8:1 ratio. This study also supported the experimental data observed and an explanation of this method can be found in Appendix 2.

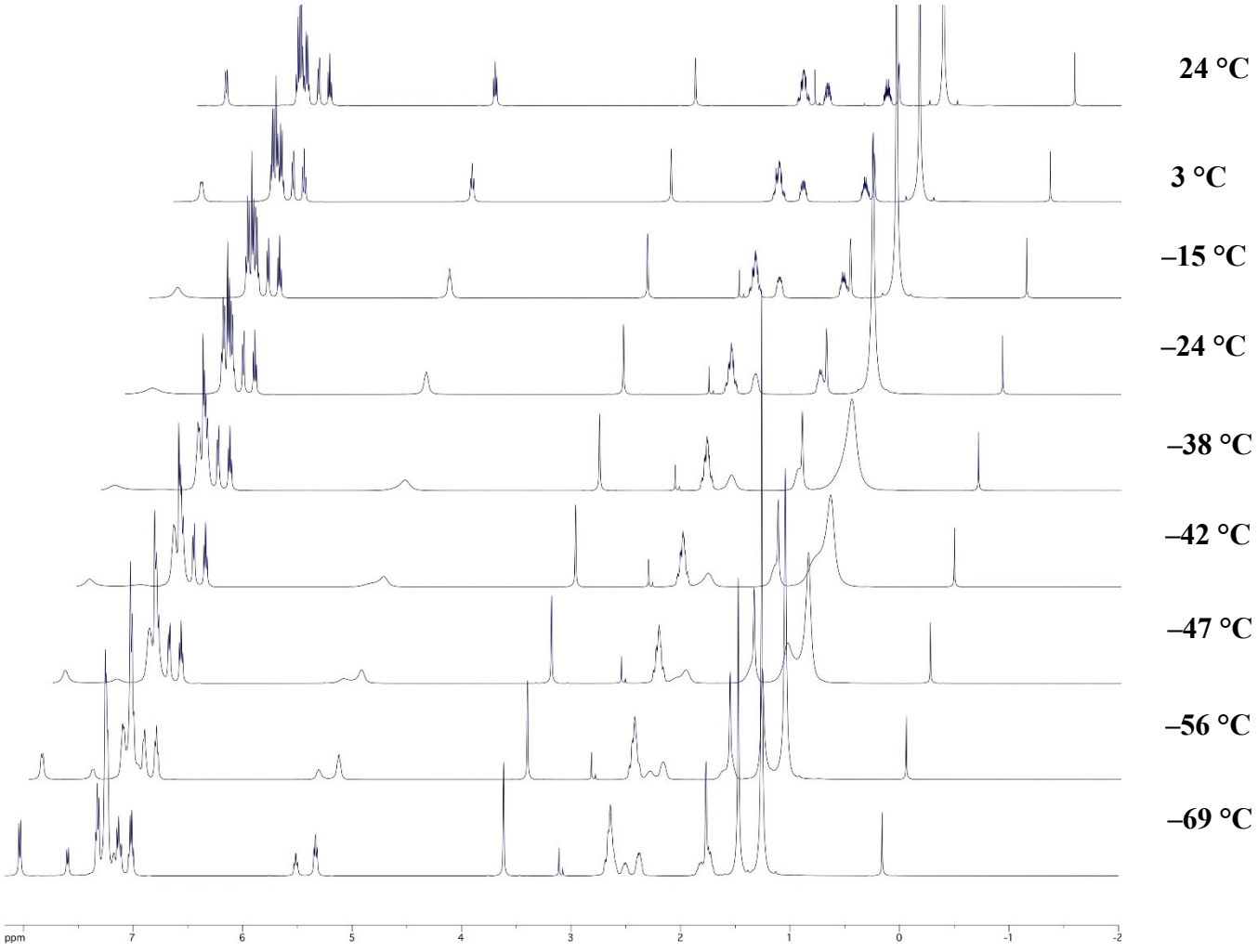


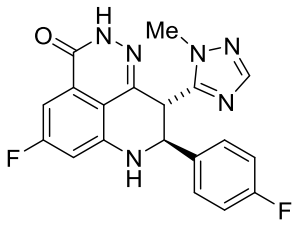
Figure 20

^{1}H NMR spectra obtained at various temperatures in THF-d_8, 500 MHz

2.3.3 Work on other *N*-Boc-2-aryl-1,2,3,4-tetrahydroquinolines

With work on the parent compound completed, the focus turned to other THQ compounds with various aryl groups in the 2-position.

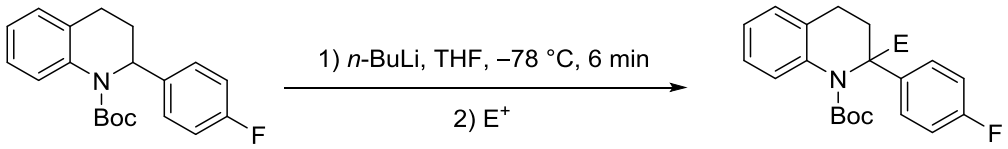
Firstly, *N*-Boc-2-(4-fluorophenyl)-1,2,3,4-tetrahydroquinoline **118b** was investigated. This compound was chosen as it was thought that introducing an electron-withdrawing fluorine atom onto the aromatic ring would decrease the pK_a of the benzylic proton and therefore the reactivity could change. Also, fluorine atoms are very important in a wide variety of medicinal compounds.[114] For example, compound **135**, Talazoparib (BMN-673), is a PARP-1/2 inhibitor which can be used in the treatment of human cancers with DNA repair deficiency (Figure 21).[115]



135, Talazoparib (BMN-673)

Figure 21

The conditions that were optimised for *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **118a** were used to test whether the same conditions were suitable for substrate **118b**. The starting material was dissolved in THF, cooled to –78 °C and *n*-BuLi was added. The mixture was left to stir for 6 minutes before the organolithium intermediate was trapped with a variety of electrophiles (Scheme 92 and Table 12). Good to excellent yields of the 2,2-disubstituted products were obtained when methyl chloroformate, ethyl chloroformate and methyl iodide were used as the electrophiles to give products **136a**–**c**. A moderate yield was obtained with allyl bromide to give product **136d**. No product was isolated when phenyl isocyanate was used.



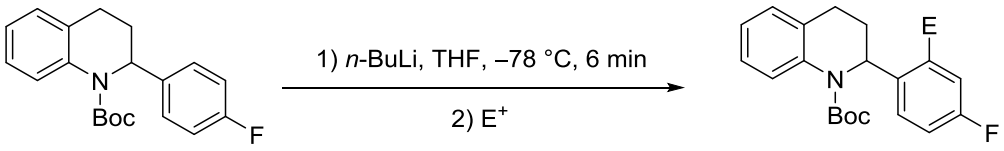
118b **136**

Scheme 92

Product	E^+	Yield (%)
136a	MeOCOCl	75
136b	EtOCOCl	86
136c	MeI	90
136d	allyl bromide	46
136e	PhNCO	0

Table 12

Ethyl and benzyl cyanoformate were also used as electrophiles and the *ortho*-substituted products **137a**–**b** were obtained in moderate to excellent yields (Scheme 93 and Table 13).



118b **137**

Scheme 93

Product	E^+	Yield (%)
137a	EtOCOCN	84
137b	BnOCOCN	50

Table 13

Pleasingly, product **137b** was crystalline and so the X-ray crystal structure was able to be obtained in order to completely confirm that the *ortho*-substituted product was being formed in these reactions (Figure 22 and Appendix 1d).

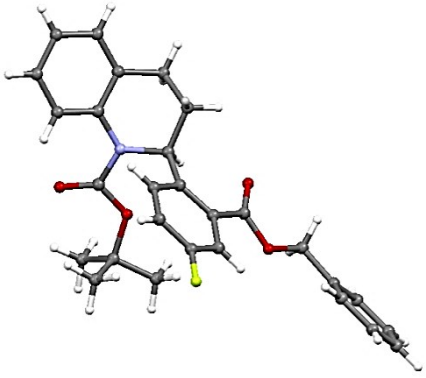
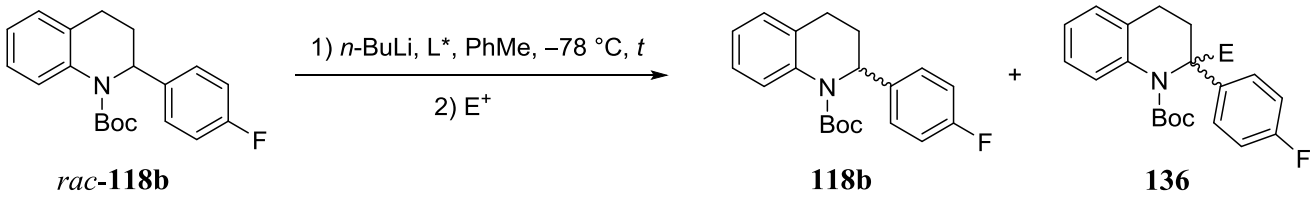


Figure 22

X-ray crystal structure determination of compound 137b

Kinetic resolutions with THQ **118b** were attempted using both enantiomers of sparteine (Scheme 94 and Table 14). Attempting to use the optimum conditions as used for THQ **118a** led to the starting material being recovered in only moderate er (Entry 1). Therefore, different conditions needed to be found in order to increase the enantioselectivity. Leaving the reaction for a longer time (Entry 2) or adding larger amounts of each component of the chiral base (Entry 3 and 4) didn't noticeably increase the selectivity and this also led to decomposition of the product. Interestingly, when methyl cyanoformate was used as the electrophile (Entry 5),

both the *ortho*-substituted product and the *α*-substituted product were obtained which showed that the different reaction conditions led to a different reactivity of the organolithium intermediate when the cyanoformate was added. While the selectivity increased when ethyl cyanoformate was used as the electrophile, the conversion was lower than required and no product was obtained (Entry 6). After further attempts with various amounts of *n*-BuLi and (+)-sparteine being used (Entries 7–11), it was clear that the enantioselectivity of the kinetic resolution with this derivative was lower than that of the parent compound. This may have been due to the predicted increased acidity of the benzylic proton in this substrate leading to a poorer selectivity in the deprotonation.



rac-**118b** **118b** **136**

Scheme 94

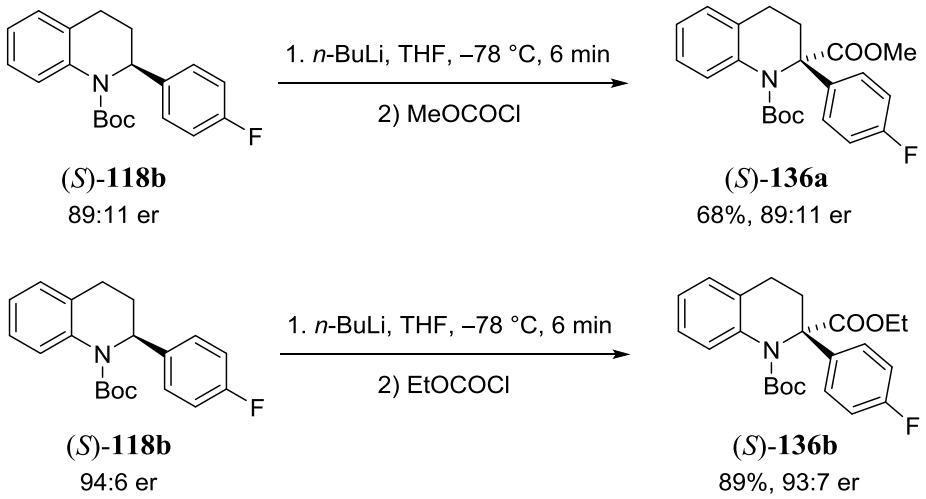
Entry	L*	time (h)	eq. *n*-BuLi	eq. L*	RSM		Product		s (by RSM)
					Yield (%)	er (*S*:*R*)	Yield (%)	er (*S*:*R*)	
1	(–)-sp	2.5	1.2	1.3	50	19:81	33	89:11	8
2	(–)-sp	4	1.2	1.3	40	22:78	13	89:11	4
3	(–)-sp	2.5	2.0	2.5	42	11:89	N/A	N/A	8
4*	(–)-sp	2.5	2.0	2.5	30	12:88	N/A	N/A	4
5**	(+)-sp	2.5	1.0	1.7	29	98:2	23	19:81	8
6***	(+)-sp	2.5	0.8	1.5	62	76:24	N/A	N/A	20
7	(+)-sp	2.5	0.9	1.6	36	85:15	16	12:88	5
8	(+)-sp	1	0.9	1.6	50	84:16	46	5:95	11
9	(+)-sp	1.5	1.0	1.7	45	89:11	43	7:93	10
10	(+)-sp	1.5	1.2	1.9	48	84:16	10	10:90	9
11	(+)-sp	1.5	1.0	1.7	36	94:6	42	15:85	8

Table 14

Electrophile used was MeOCOCl in all entries except entries 5 and 6. * = 1g scale. ** = MeOCOCN used, also obtained *ortho*-substituted product **137c** (28%, 56:44 er). *** = EtOCOCN used.

Lithiation-substitution reactions were then attempted on the enantioenriched starting material (*S*)-**118b** obtained from the kinetic resolutions outlined in entry 9 and 11 above and pleasingly, the products (*S*)-**136a** and (*S*)-**136b** were obtained with no loss of the enantioenrichment (Scheme 95). While the absolute configurations of these compounds have not been determined

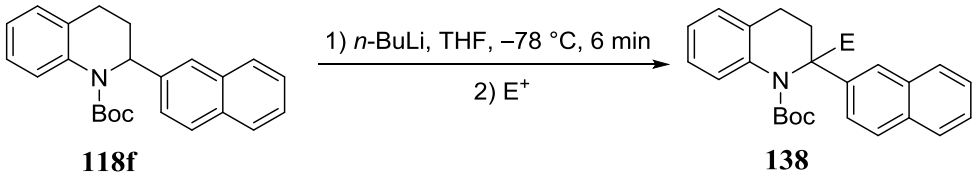
by X-ray crystallography, it has been assumed that the configurations are the same as the parent THQ **118a**.



Scheme 95

Another substrate investigated was *N*-Boc-2-(2-naphthyl)-1,2,3,4-tetrahydroquinoline **118f**. This was chosen as it was thought that the acidity of the benzylic proton would be similar to the parent compound and so there could be more selectivity in the kinetic resolutions. Naphthyl groups can also be found in pharmaceutical compounds such as Cinacalcet, one of the top 100 largest selling drugs in the world, which is used to treat secondary hyperparathyroidism.[116,117]

Lithiation–substitutions were attempted with racemic THQ **118f** using the same conditions found to be suitable for the previous substrates. The starting material was dissolved in THF, cooled to −78 °C and *n*-BuLi was added. The mixture was left to stir for 6 minutes before the organolithium intermediate was trapped with the electrophile. A good yield of the α-substituted product **138a** was obtained when methyl iodide was used while only a moderate yield of **138b** was obtained when methyl chloroformate was used (Scheme 96 and Table 15).



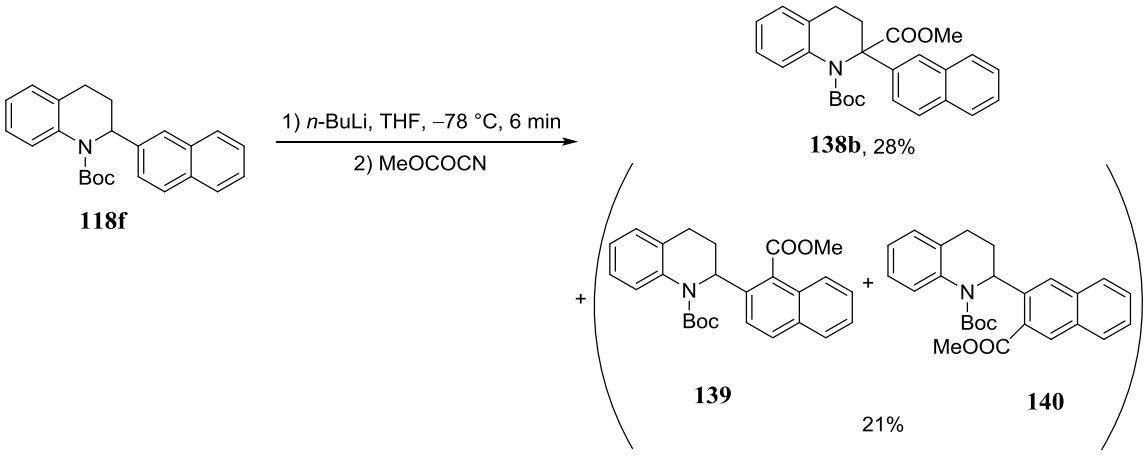
118f **138**

Scheme 96

Product	E^+	Yield (%)
138a	MeI	73
138b	MeOCOCl	47

Table 15

Interestingly, when methyl cyanoformate was used, the *α*-substituted product **138b** and the *ortho*-substituted products **139** and **140** were obtained in modest yields (Scheme 97). The R_f on silica of the *ortho*-substituted compounds were very similar and so a mixture of these products was obtained. Presumably, the energy differences associated with *α*-substitution and *ortho*-substitution when methyl cyanoformate is used in this case are approximately equal which leads to an approximate 1:1 mixture of the *α*- and *ortho*-substituted products.



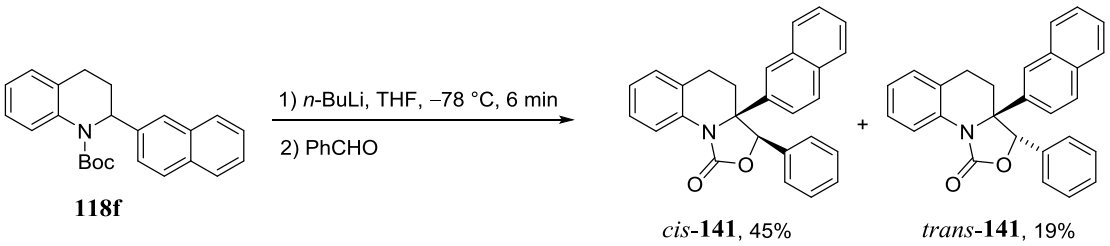
118f

138b, 28%

139 + **140**, 21%

Scheme 97

It was thought that if benzaldehyde was used as the electrophile, an alcohol would be produced which would quickly attack the Boc group in order to form a polycyclic molecule. This proved to be the case as the cyclic compound **141** was produced in good overall yield in just over a 2:1 dr (Scheme 98).



118f

cis-**141**, 45%

trans-**141**, 19%

Scheme 98

Pleasingly, the diastereoisomers were separable by column chromatography and both isomers were also solids which allowed, after recrystallization, the major diastereoisomer to be identified as the *cis*-isomer by X-ray crystallography (Figure 23 and Appendix 1e).

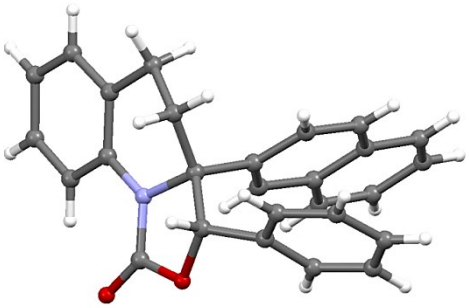
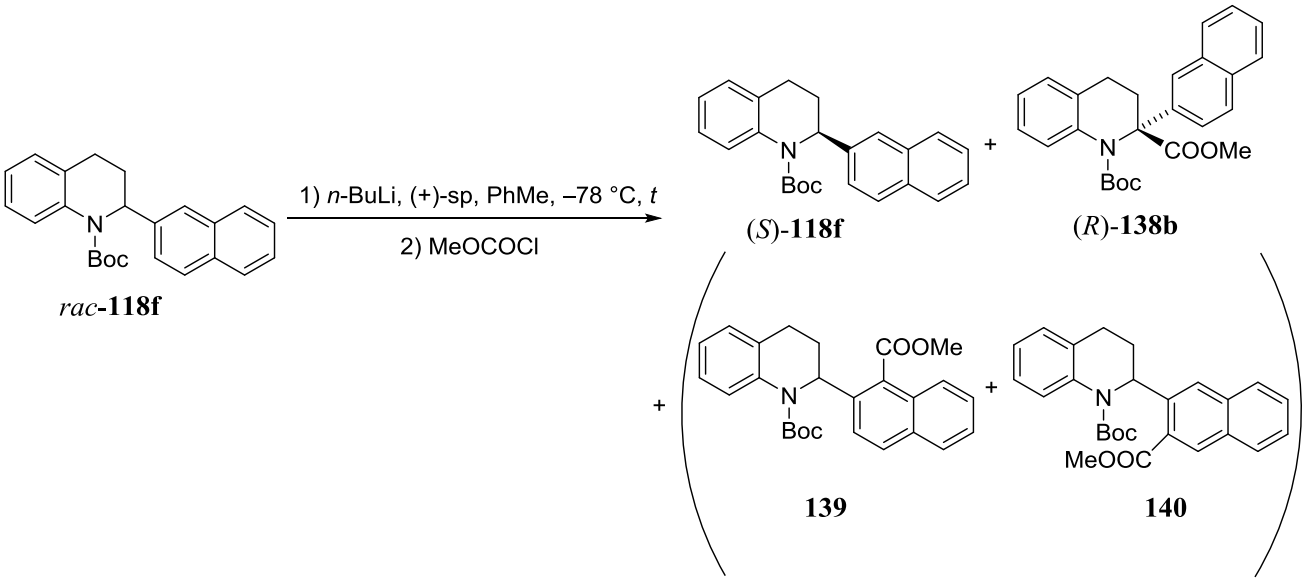


Figure 23

X-ray crystal structure determination of compound *cis*-141

Kinetic resolutions with THQ **118f** were then attempted using (+)-sparteine as the chiral ligand (Scheme 99 and Table 16). Attempting to use the optimum conditions as used for THQ **118a** led to the starting material (*S*)-**118f** being recovered in a very low yield with only a moderate er (Entry 1). Therefore, the reaction was left for a shorter time with the same *n*-BuLi / (+)-sparteine ratio found to be optimal for the kinetic resolution of THQ **118b** (Entry 2). While this improved the yield and the er also increased, the selectivity was still only moderate and so fewer equivalents of both components of the chiral base were used (Entry 3). This led to the starting material (*S*)-**118f** being recovered in good yield with an excellent er. Interestingly, high

yields of the *ortho*-substituted product mixture **139** and **140** were observed in each kinetic resolution even though methyl chloroformate was used as the electrophile. The small amounts of the *α*-substituted product (*R*)-**138b** that were obtained in each case had poor to moderate ers and the sticky nature of this compound may have been the reason why the total yield of the kinetic resolution in entry 3 came to be slightly over 100%. These results showed again the different reactivity of the organolithium intermediate under these kinetic resolution conditions compared to the racemic lithiation conditions. Also, when methyl chloroformate was used to quench the kinetic resolution, the solution turned deep red and so this showed that this colour was not just observed when methyl cyanoformate was used as the electrophile but rather it was observed when *ortho*-substitution took place.

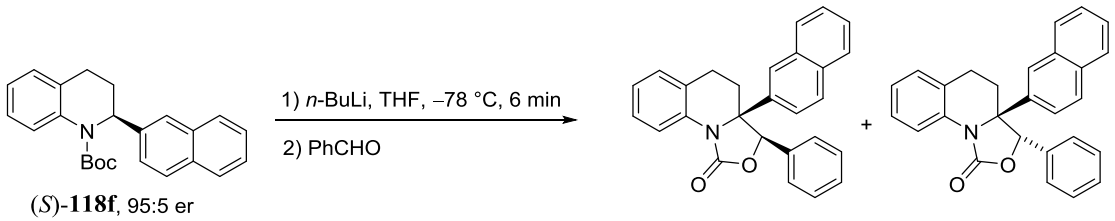


Scheme 99

Entry	time (h)	eq. *n*-BuLi	eq. (+)-sp	RSM		ORTHO-Product Mix		ALPHA-Product		s (by RSM
				Yield (%)	er (*S*:*R*)	Yield (%)	er	Yield (%)	er (*R*:*S*)	
1	2.5	1.2	1.3	19	82:18	55	N/A	15	64:36	2
2	1.5	1.0	1.7	30	92:8	50	N/A	14	71:29	5
3	1.5	0.8	1.3	39	95:5	49	N/A	14	78:22	11

Table 16

The recovered starting material (*S*)-**118f** from the reaction in entry 3 was deprotonated with *n*-BuLi using the optimal conditions and after addition of benzaldehyde as the electrophile the cyclic compounds (*R*,*S*)-**141** and (*S*,*S*)-**141** were formed in good yield, in just over a 2:1 dr. In both cases, the enantioenrichment was maintained to give er 95:5 (Scheme 100).



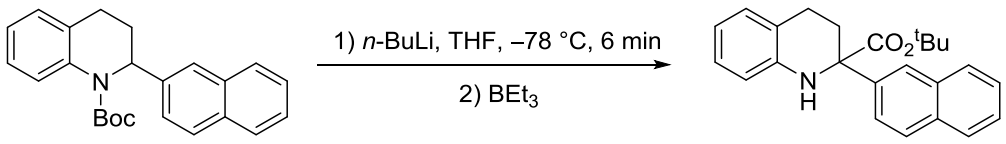
(*S*)-**118f**, 95:5 er

(*R*,*S*)-**141**, 42%, 95:5 er (*S*,*S*)-**141**, 20%, 95:5 er

Scheme 100

While the absolute configurations of these compounds have not been determined by X-ray crystallography, it has been assumed that the configurations are the same as the parent THQ **118a**.

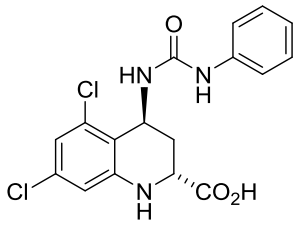
Finally with this substrate **118f**, triethylborane was added to the lithiated intermediate in order to try and effect the Boc rearrangement reaction and pleasingly, the amine **132b** was obtained in good yield (Scheme 101).



118f **132b**, 60%

Scheme 101

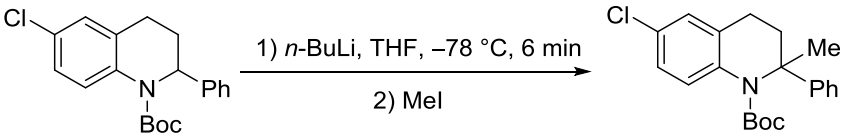
Another substrate investigated was *N*-Boc-6-chloro-2-phenyl-1,2,3,4-tetrahydroquinoline **118e**. Chlorine atoms can be found in a wide variety of pharmaceutical compounds, including L-689,560 **142** which is a potent antagonist of the NMDA receptor (Figure 24).[118]



142, L-689,560

Figure 24

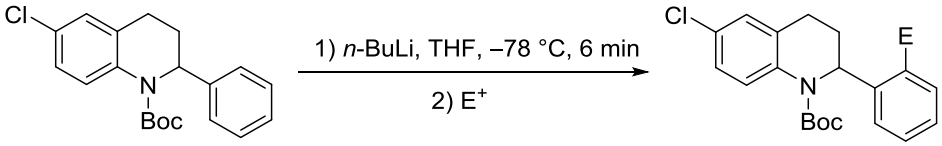
Some of the work on this substrate was carried out by a final year undergraduate student who worked in the group alongside me in a research project.[99] A racemic-lithiation substitution with methyl iodide yielded the *α*-substituted product **143a** in good yield (Scheme 102).



118e **143a**, 68%

Scheme 102

When cyanoformate electrophiles were used, the *ortho*-substituted products **144** were obtained exclusively in moderate yields (Scheme 103 and Table 17).



118e **144**

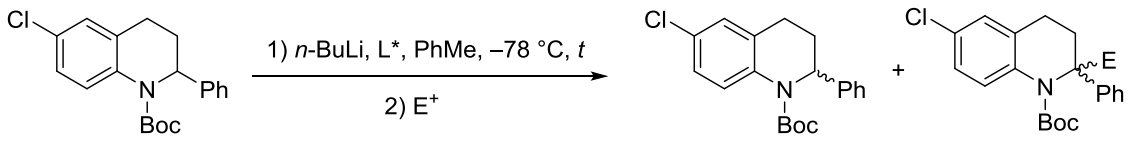
Scheme 103

Product	E^+	Yield (%)
144a	MeOCOCN	51
144b	BnOCOCN	50

Table 17

A couple of kinetic resolutions had been attempted in the undergraduate student's project with a better selectivity being obtained when the (+)-sparteine surrogate was used as the chiral ligand (Table 18, Entries 1 and 2). However, more kinetic resolutions needed to be carried out in my project and so various reactions were attempted in which both the number of equivalents

of each component of the chiral base and the reaction times were changed. Using a large excess of *n*-BuLi / (+)-sparteine gave the recovered starting material in only a moderate yield and er (Entry 3). The number of equivalents of each component of the chiral base was then lowered and the time of the reaction was shortened (Entry 4). This led to a reaction with high selectivity but with a low yield of product. Attempting to use the optimum kinetic resolution conditions for THQ **118a** led to the starting material being recovered in a good yield but with an er lower than that desired (Entry 5). Three further kinetic resolutions were then attempted varying both the time and number of equivalents of each component of the chiral base (Entries 6-8) but this gave no improvement in the selectivity. Finally, the optimum conditions were found (Entry 9) which gave the recovered starting material in excellent yield and er (Scheme 104 and Table 18). These conditions were a slight variation on the optimum conditions used for THQ **118b** (*vide supra*).



rac-**118e** **118e** **143**

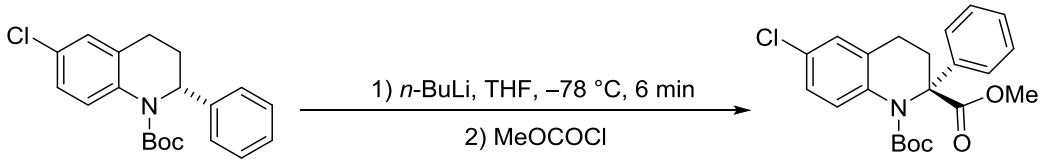
Scheme 104

Entry	L*	time (h)	eq. *n*-BuLi	eq. L*	RSM		Product		s (by RSM)
					Yield (%)	er (*S*:*R*)	Yield (%)	er (*S*:*R*)	
1[a]	(–)-sp	2.5	2.0	2.5	35	11:89	N/A	N/A	5
2[a]*	(+)-sp surr	2.5	1.2	1.3	33	98:2	N/A*	N/A*	10
3	(+)-sp	2.5	2.0	2.5	35	75:25	23	20:80	3
4	(+)-sp	1	0.7	1.0	53	87:13	16	9:91	24
5	(+)-sp	2.5	1.3	1.2	42	87:13	N/A	N/A	7
6	(+)-sp	2.5	0.8	1.5	30	88:12	34	22:78	4
7	(+)-sp	1	0.8	1.5	44	85:15	37	9:91	7
8	(+)-sp	1.5	1.1	1.8	36	93:7	49	13:87	7
9	(+)-sp	1.25	1.0	1.7	41	92:8	42	14:86	10

Table 18

Electrophile used was MeOCOCl in all entries except entry 2. [a] = Reaction carried out by undergraduate student. * = MeOCOCN used, mixture of *ortho*-substituted and *α*-substituted product obtained.

With enantioenriched starting material in hand, the undergraduate student carried out a lithiation-substitution reaction with methyl chloroformate using recovered starting material (*R*)-**118e** from the reaction outlined in entry 1. This reaction yielded product (*R*)-**143b** with no loss of enantioenrichment (Scheme 105).

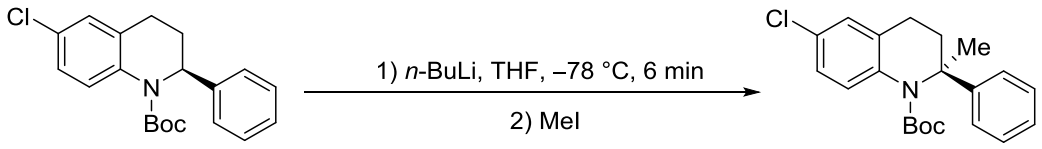


(*R*)-**118e**
89:11 er

(*R*)-**143b**
45%, 89:11 er

Scheme 105

A further reaction was then carried out in my project with the enantioenriched starting material (*S*)-**118e** obtained from the reaction outlined in entry 9. This starting material was deprotonated with *n*-BuLi using the optimal conditions and after addition of methyl iodide as the electrophile, the product (*S*)-**143a** was formed in good yield with a slight loss of enantioenrichment (Scheme 106). This was a similar observation to that found by Li with the parent compound THQ **118a** (Scheme 57).



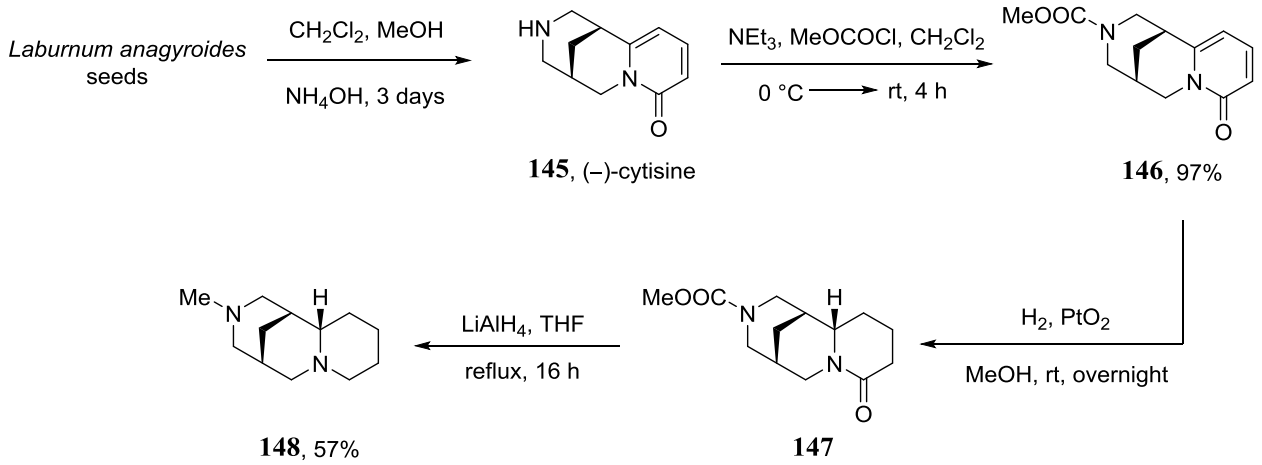
(*S*)-**118e**
92:8 er

(*S*)-**143a**
69%, 87:13 er

Scheme 106

Again, while the absolute configurations of these compounds have not been determined by X-ray crystallography, it has been assumed that the configurations are the same as the parent THQ **118a**.

The (+)-sparteine surrogate that was used in a small number of the kinetic resolutions was prepared in 4 steps from *Laburnum anagyroides* seeds using the method outlined in the literature by O'Brien and co-workers (Scheme 107).[119] Approximately 8 g of (–)-cytisine **145** was extracted from 700 g of the seeds and the amine was protected with methyl chloroformate to give the carbamate **146** in excellent yield. This was then hydrogenated in the presence of a platinum oxide catalyst to give compound **147** in excellent yield. Finally, compound **147** was reduced to the (+)-sparteine surrogate **148** in a moderate yield by using lithium aluminium hydride.



Scheme 107

The next substrate to be investigated was *N*-Boc-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline **118c**. It was thought that by introducing an electron-donating methoxy group onto the aromatic ring, the acidity of the benzylic proton would decrease which would influence the reactivity**.**

Initial lithiation–substitution reactions with this substrate used the optimum conditions that had worked well for all of the previous THQ substrates. However, these initial reactions gave inseparable mixtures of starting material and product with large amounts of starting material being recovered. Therefore, it was decided to carry out *in-situ* IR spectroscopy on this substrate in order to find suitable conditions for the lithiation. A solution of **118c** in THF at –78 °C exhibited a peak $\nu_{C=O}$ at 1703 cm^{-1} (Figure 25). Upon addition of 1.2 equivalents of *n*-BuLi, the intensity of the starting material peak slowly started to decrease with the gradual appearance of a peak $\nu_{C=O}$ at 1641 cm^{-1} which was assigned to the organolithium intermediate. Addition of another 1.2 equivalents of *n*-BuLi seemed to accelerate the lithiation but it still took approximately 1 hour for the lithiation to approach completion. This supported the hypothesis that the lithiation time for this substrate was considerably longer than the lithiation time for the other substrates investigated so far which was probably due to the decreased acidity of the benzylic proton.

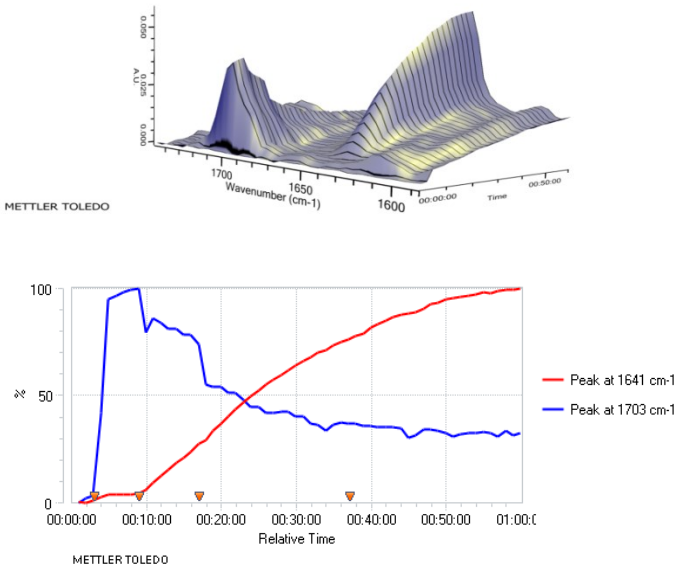
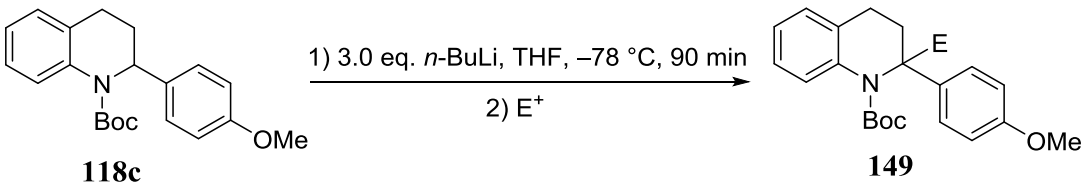


Figure 25. *In-situ* ReactIR™ 3D and 2D plots of the lithiation of *rac*-**118c** with *n*-BuLi at –78 °C in THF. Blue line represents intensity of C=O stretching frequency of *rac*-**118c** (1703 cm^{-1}) and red line of lithiated intermediate (1642 cm^{-1}) over time.

Therefore, with this data in hand, it was decided to use 3.0 equivalents of *n*-BuLi and to leave the reactions for 90 minutes before addition of the electrophile in order to ensure that the starting material was fully lithiated. Good to excellent yields of the 2,2-disubstituted products were obtained when methyl chloroformate, ethyl chloroformate or methyl iodide were used as the electrophiles to give products **149a**–**c** (Scheme 108 and Table 19).



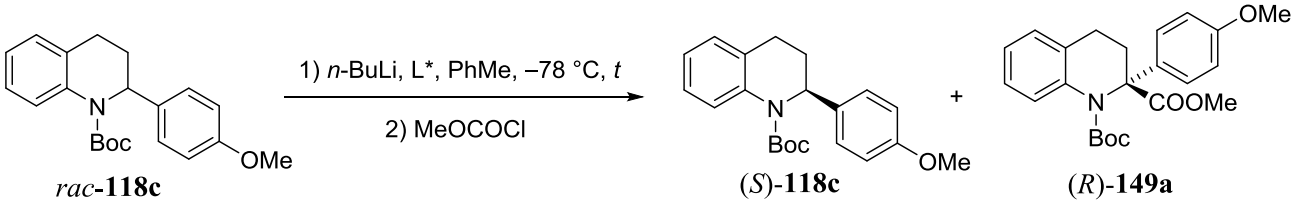
118c **149**

Scheme 108

Product	E^+	Yield (%)
149a	MeOCOCl	80
149b	EtOCOCl	79
149c	MeI	84

Table 19

Kinetic resolutions with this substrate were then attempted using either (+)-sparteine or the (+)-sparteine surrogate as the chiral ligand (Scheme 109 and Table 20). Poor conversions and/or selectivities were observed in all reactions, even when conditions that had worked well for other derivatives were used. Therefore, work on this substrate was discontinued.



rac-**118c** (*S*)-**118c** (*R*)-**149a**

Scheme 109

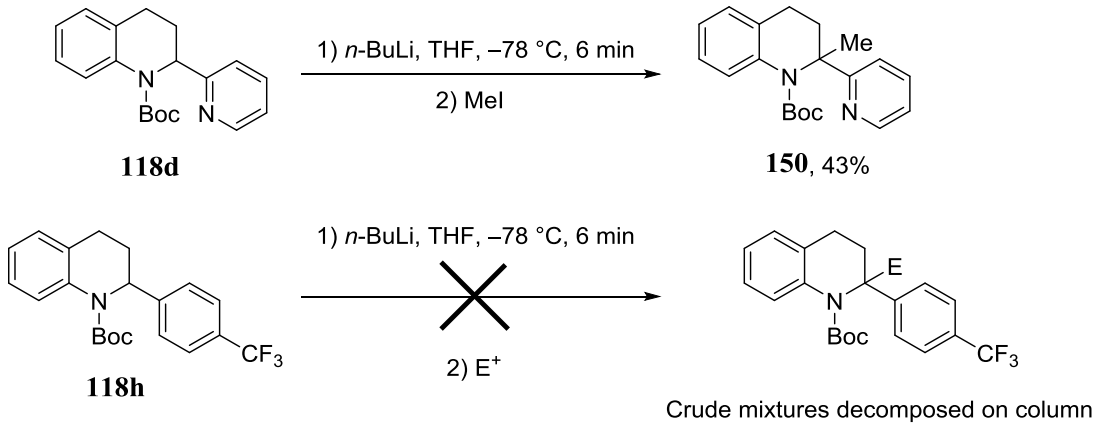
Entry	L*	Solvent	time (h)	eq. *n*-BuLi	eq. L*	RSM		Product		s (by RSM)
						Yield (%)	er (*S*:*R*)	Yield (%)	er (*R*:*S*)	
1	(+)-sp sur.	PhMe	2.5	1.2	1.3	80	59:41	8	97:3	7
2	(+)-sp sur.	PhMe	2.5	1.2	1.3	82	59:41	20	97:3	12
3	(+)-sp	Et_2O	2.5	1.2	1.3	56	64:36	26	88:12	3
4	(+)-sp	Et_2O	2.5	1.0	1.7	58	66:34	22	88:12	3
5	(+)-sp sur.	THF	1.5	2.0	2.5	83	54:46	15	85:15	2

Table 20

Again, while the absolute configurations of these compounds have not been determined by X-ray crystallography, it has been assumed that the configurations are the same as the parent THQ **118a**.

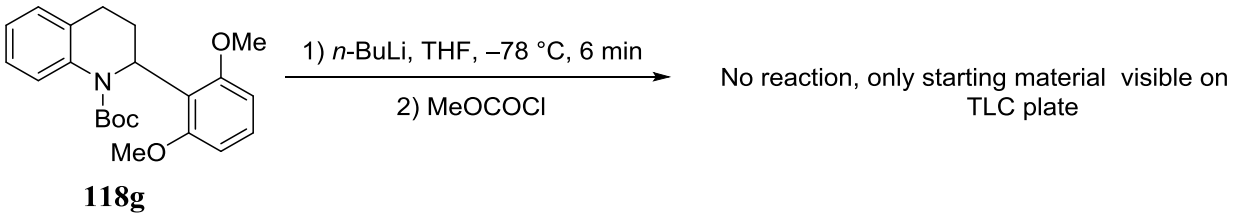
Unfortunately, lithiation-substitution reactions with three substrates, *N*-Boc-2-(2-pyridinyl)-THQ **118d**, *N*-Boc-2-(2,6-dimethoxyphenyl)-THQ **118g** and *N*-Boc-2-(4-trifluoromethyl)-THQ **118h** gave poor results.

While product **150** was obtained with THQ **118d**, the yield was only moderate and there was noticeable decomposition of the reaction mixtures of this substrate, even when attempts were made to shorten the reaction times considerably. This may have been due to an increase in the acidity of the benzylic proton predicted for this substrate. The crude reaction mixtures obtained from reactions with THQ **118h** were unstable to column chromatography (Scheme 110).



Scheme 110

The aim of using THQ **118g** was to see whether the α-substituted product would form when methyl cyanoformate was used as the electrophile due to the two *ortho*-positions being blocked. However, no lithiation was observed with only starting material being recovered which may have been due to the steric bulk of the *ortho*-methoxy groups hindering the deprotonation and/or the reduced acidity of this substrate (Scheme 111).



Scheme 111

Due to the disappointing results with these substrates, no kinetic resolutions were attempted with THQs **118d**, **118g** or **118h**.

Finally, the synthesis of the naphthyridine compound **151** was attempted as it was thought that the reactivity of this substrate could be interesting and the naphthyridine moiety is also found in pharmaceutical compounds such as Pagoclone **152**, which is used to treat anxiety (Figure 26).[120]

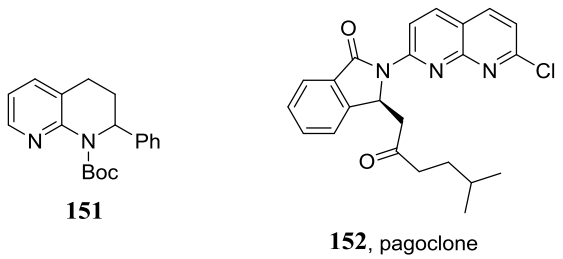
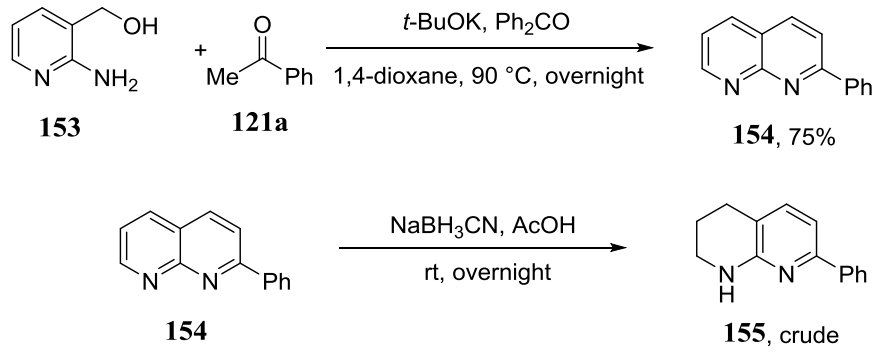


Figure 26

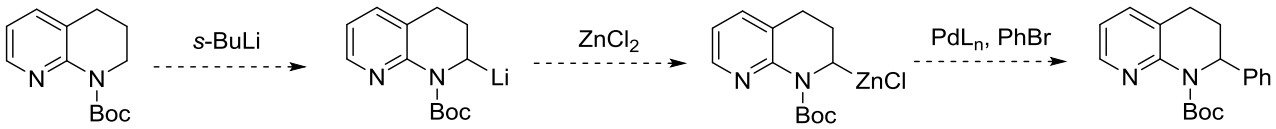
Firstly, by using the Friedländer synthesis, 2-phenyl-1,8-naphthyridine **154** was synthesised in good yield. However, while the reduction using sodium cyanoborohydride produced a mixture of products which was difficult to purify, it was clear to see by ^{1}H NMR spectroscopy that the major product was the undesired 5,6,7,8-tetrahydronaphthyridine **155**, presumably due to the less hindered aromatic ring being preferentially reduced (Scheme 112).



153 **121a** **154**, 75% **154** **155**, crude

Scheme 112

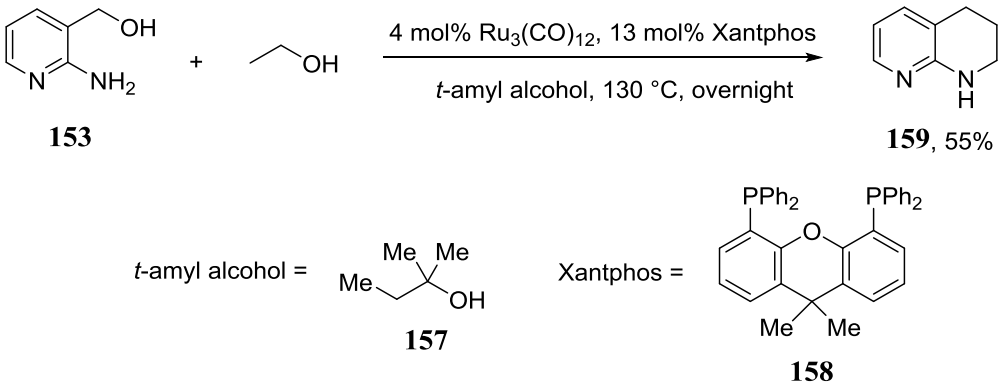
An alternative strategy for the synthesis of compound **151** was therefore required. It was thought that by firstly using *s*-BuLi to lithiate the *α*-position of the unsubstituted *N*-Boc-1,8-naphthyridine **156**, the intermediate formed could be transmetalated with $ZnCl_2$ before carrying out a Negishi cross-coupling reaction in order to obtain the desired compound **151** (Scheme 113).



156 **151**

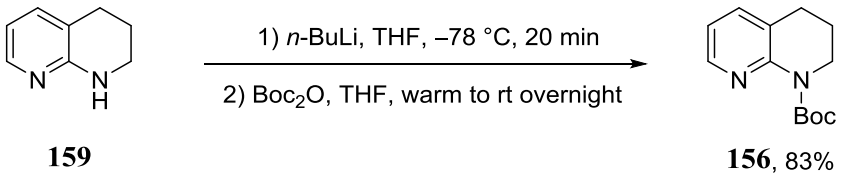
Scheme 113

Firstly, amino-alcohol **153** was stirred in *t*-amyl alcohol **157** at 130 °C overnight, in the presence of ethanol and substoichiometric amounts of $Ru_3(CO)_{12}$ and the ligand Xantphos **158**. This method followed a reported literature procedure and formed **159** in a moderate yield (Scheme 114).[121]



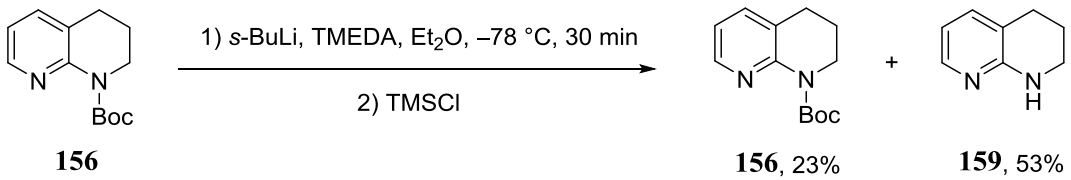
Scheme 114

Compound **159** was then subjected to the same Boc protection method used for the THQ compounds and this formed *N*-Boc-1,8-naphthyridine **156** in an excellent yield (Scheme 115).



Scheme 115

In order to test whether it was possible to lithiate compound **156**, *s*-BuLi was added to a solution of **156** in Et_2O in the presence of the ligand TMEDA. The reaction mixture was left to stir for 30 minutes before adding chlorotrimethylsilane as the electrophile (Scheme 116). Unfortunately, no product was obtained and in addition to a moderate amount of starting material being recovered, a substantial amount of compound **159** was obtained which showed that the Boc group was being lost under these conditions. Due to this unpromising result, work on compound **156** was discontinued.



Scheme 116

2.4 Conclusions and Future Work

In conclusion, a variety of *N*-Boc-2-aryltetrahydroquinolines have been synthesised by using an efficient 3-step method starting from cheap, commercially available compounds.

The majority of these compounds were able to be lithiated by using *n*-BuLi and after quenching the lithiated intermediate with electrophiles, a variety of *α*-substituted products were formed. However, *ortho*-substituted products were obtained when cyanoformate electrophiles were used and a range of experiments and DFT calculations have been carried out in order to elucidate the mechanism of this transformation. This is, as far as we are aware, a unique change in regioselectivity on changing the electrophile in an organolithium reaction. A variable temperature NMR spectroscopic study has been carried out and this supported the hypothesis that the Boc group was rotating quickly.

Kinetic resolutions were successfully carried out with the *n*-BuLi / sparteine chiral base and these gave a range of highly enantioenriched *N*-Boc-THQ starting materials in good yield. These were then subjected to lithiation–substitution reactions and a range of *α*-substituted products were formed in good yield with the enantioenrichment mostly being maintained which demonstrated the configurational stability of the intermediate.

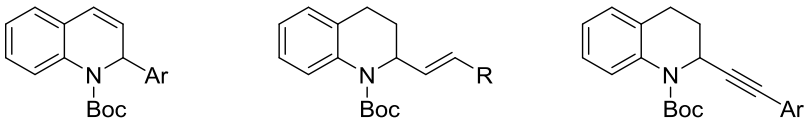
It was shown that the Boc protecting group of a small selection of these compounds was able to be removed under acid conditions and in one case the enantioenrichment was maintained when a compound with high er was deprotected.

When triethylborane was added to the lithiated intermediates, an N to C Boc group migration took place which had only rarely been noted in the literature. It was demonstrated that this migration could take place with no loss of enantioenrichment when highly enantioenriched starting material was used.

Unfortunately, lithiation–substitution reactions of three of the *N*-Boc-2-aryltetrahydroquinolines gave poor results and kinetic resolutions were not attempted on these substrates.

In future, other THQs with the *ortho*-positions blocked could be synthesised in order to see whether *α*-substituted products are obtained when methyl cyanoformate is used as the electrophile. Also, *in-situ* NMR or IR spectroscopic studies could be carried out in order to further confirm whether the proposed mechanism of *ortho*-substitution is plausible.

Finally, the chemistry of 2-aryldihydroquinolines (DHQ) **160** or various other 2-substituted THQ compounds (such as *N*-Boc-2-vinyl THQs **161** or *N*-Boc-2-arylethynyl THQs **162**) could be investigated and this methodology would then potentially allow the synthesis of a range of enantioenriched natural products, such as angustureine or galipinine (Figure 27).



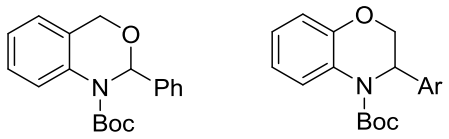
160 **161** **162**

Figure 27

Chapter 3 – Synthesis and Kinetic Resolutions of *N*-Boc-2-phenyl-1,2,3,4-tetrahydro-3,1-benzoxazine and *N*-Boc-3-aryl-1,2,3,4-tetrahydro-1,4-benzoxazines

3.1 Importance of tetrahydrobenzoxazines

A class of compound whose derivatives are of great importance in organic chemistry are tetrahydrobenzoxazines (THBs). Two varieties of this wide class of compound will be investigated in this chapter, *N*-Boc-2-phenyl-1,2,3,4-tetrahydro-3,1-benzoxazine **163** and *N*-Boc-3-aryl-1,2,3,4-tetrahydro-1,4-benzoxazines **164** (Figure 28).



163 **164**

Figure 28

The 3,1-benzoxazine moiety is found in a number of natural products, including terresoxazine **165**,[122] donaxanine **166**[123] and discoipyrrole A **167**[124]. It is also the framework of pharmaceutical compounds such as Efavirenz **168** which, as part of the World Health Organisation's list of essential medicines, is an antiretroviral medication used to treat and prevent HIV/AIDS.[125,126] Tanaproget **169**, a non-steroidal progestin, also contains the moiety (Figure 29).[127]

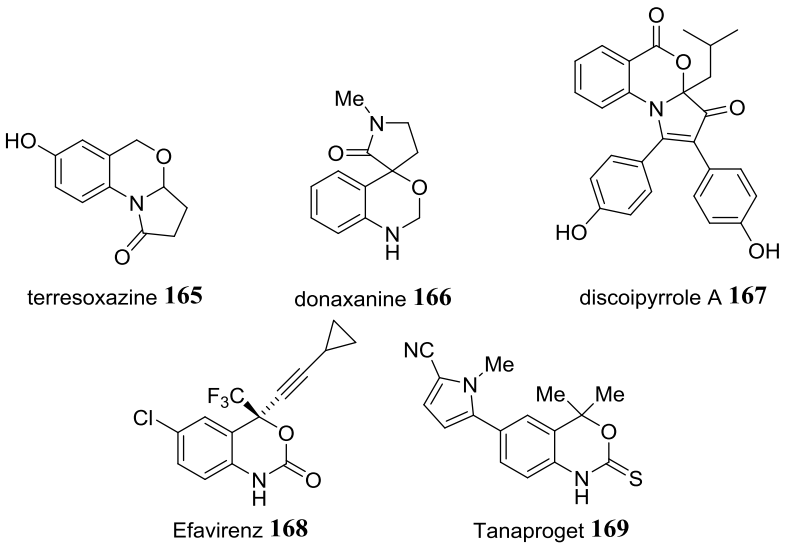


Figure 29

In the same way, the 1,4-benzoxazine framework is present in a variety of natural products, including agelamadin C **170**,[128] obscurinervidine **171**[129] and benzoxacystol **172**[130] with this latter compound exhibiting inhibition of glycogen synthase kinase 3β (Figure 30). The moiety also forms an important part of a number of pharmaceutical compounds, including the laxative Bisoxatin **173**[131] and the long-acting β_2 adrenergic receptor agonist Olodaterol **174**[132] (Figure 30).

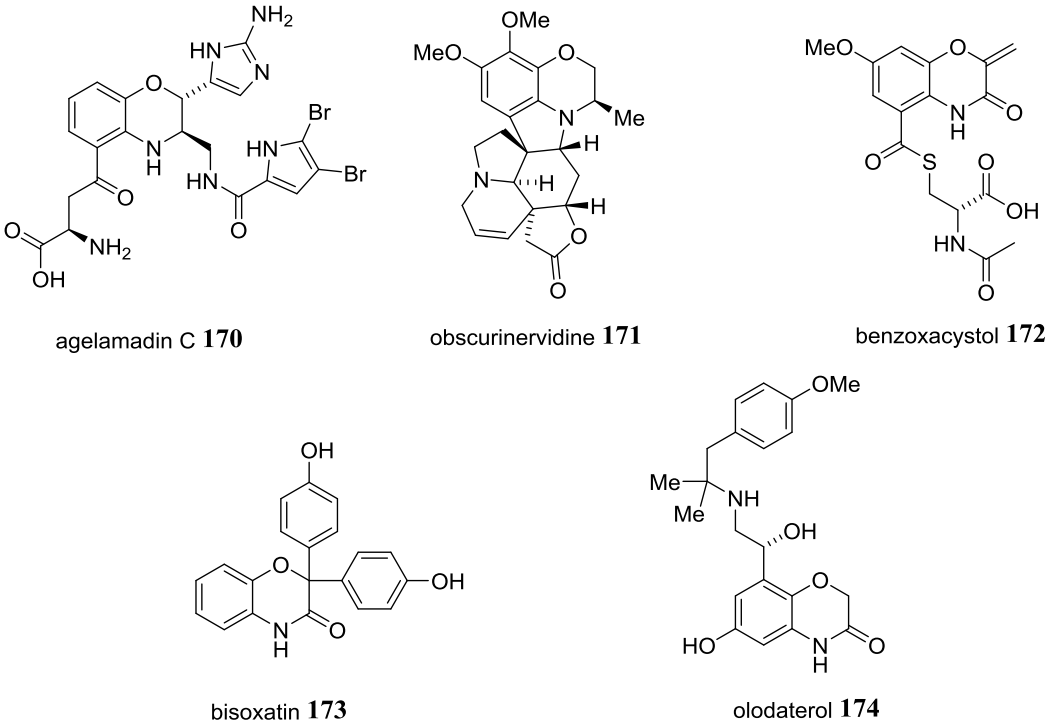


Figure 30

3.2 Previous work in the group

Due to their structural similarity to *N*-Boc-2-arylpiperidines which had yielded excellent results in the Coldham group,[39,133] work on the related compounds *N*-Boc-2-phenyl-1,3-oxazinane **175** and *N*-Boc-3-phenylmorpholine **176** was recently started by a final year undergraduate student within the group (Figure 31).[134]

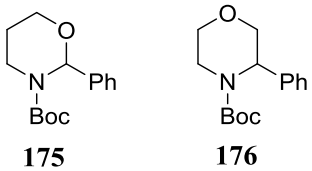
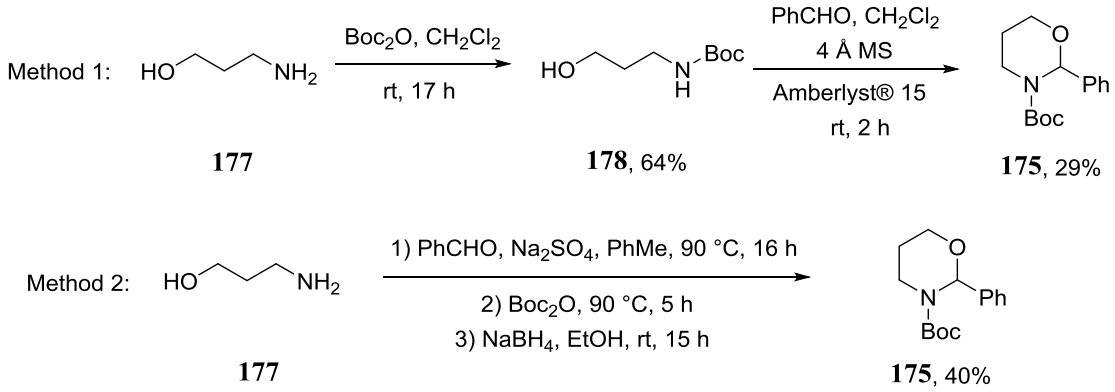


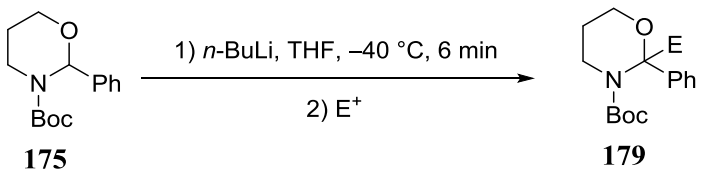
Figure 31

N-Boc-2-phenyl-1,3-oxazinane **175** was firstly synthesised over two steps, using a literature method, in a poor overall yield.[135] However, a one pot literature method was later found and the desired compound was able to be formed in moderate yield from readily available starting materials (Scheme 117).[136] In Method 2, the $NaBH_4$ was added to remove excess PhCHO that complicated the purification of the desired product.



Scheme 117

Using *in-situ* IR spectroscopy, it was found that the lithiation of this substrate took place quickly at –40 °C with no decomposition observed. Therefore, compound **175** was deprotonated with *n*-BuLi in THF at –40 °C and the reaction mixture was left to stir for 6 minutes. The lithiated intermediate was quenched with a variety of electrophiles to give the *α*-substituted products **179** in poor to good yields (Scheme 118 and Table 21).

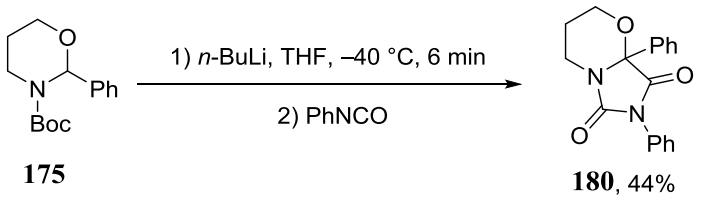


Scheme 118

Product	E^+	Yield (%)
179a	MeOCOCl	11
179a	MeOCOCN	11
179b	MeI	74
179c	Bu_3SnCl	56

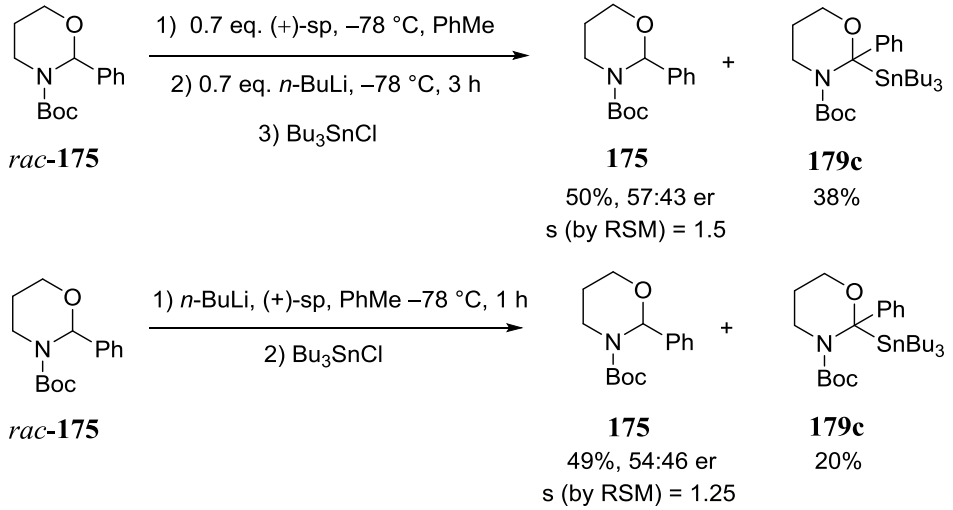
Table 21

When phenyl isocyanate was used as the electrophile, the interesting product **180** was formed in moderate yield (Scheme 119).



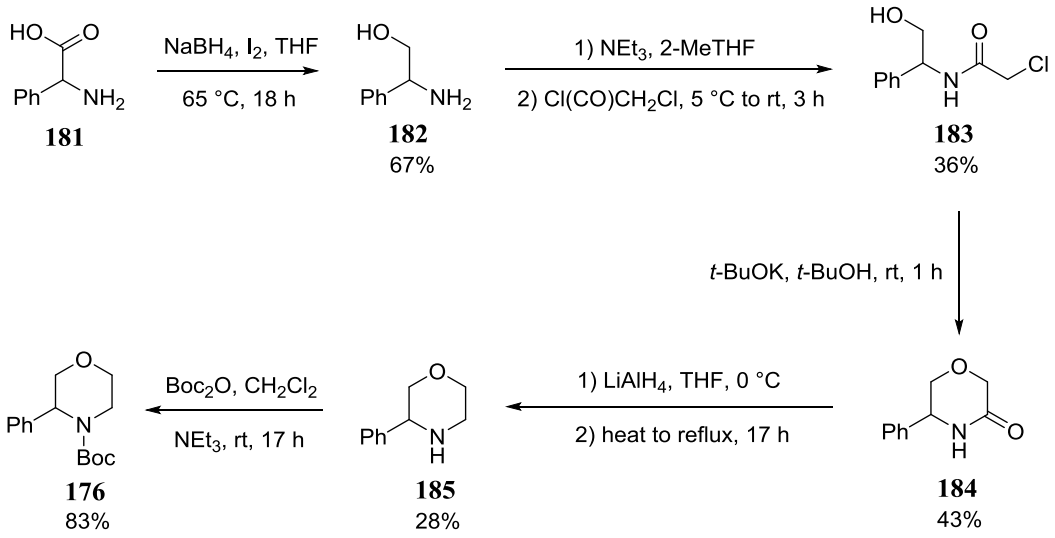
Scheme 119

Kinetic resolutions were then attempted with this substrate using *n*-BuLi / (+)-sparteine as the chiral base. While the reactivity of the 'chiral base' was acceptable, the enantioselectivity was very poor when both the 'normal' and 'inverse' addition methods were used (Scheme 120). This may have been due to the chiral base complex co-ordinating to the oxygen in the oxazinane ring, with this interaction potentially decreasing the enantioselectivity of the deprotonation.



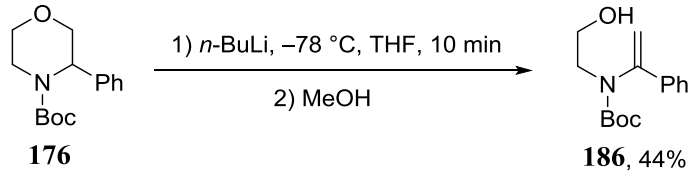
Scheme 120

The focus of the student's project therefore shifted to reactions with *N*-Boc-3-phenylmorpholine **176**. This substrate was synthesised in a poor overall yield in 5 steps and while enough of morpholine **176** was formed in order to carry out reactions, a shorter, more efficient route would need to be found if further work on this substrate was carried out (Scheme 121).[137,138]



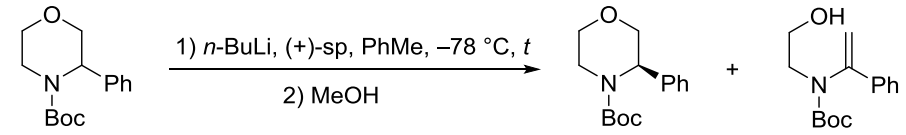
Scheme 121

A lithiation of this substrate was then carried out with *n*-BuLi in THF at –78 °C and the reaction mixture was left to stir for 10 minutes. Methanol was used to quench the reaction and, as expected, elimination had taken place to form the ring-opened product **186** in moderate yield (Scheme 122).



Scheme 122

Even though reactions of morpholine **176** with *n*-BuLi could not form α-substituted products, kinetic resolution reactions could still be attempted as the most important component of the group's kinetic resolutions is the er of the recovered starting material and this should not be affected by the product of the reaction. Therefore, kinetic resolutions were carried out using the pre-mixed *n*-BuLi / (+)-sparteine chiral base but the enantioselectivities were disappointing (Scheme 123 and Table 22).



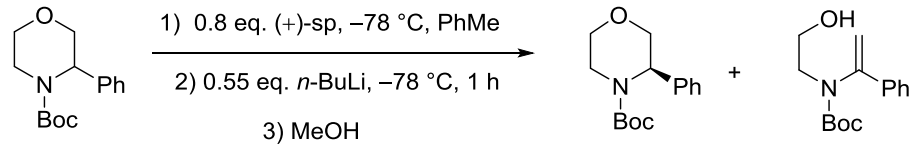
rac-**176** (*R*)-**176** **186**

Scheme 123

Entry	time (h)	eq. *n*-BuLi	eq. L*	RSM		Product Yield (%)	s (by RSM)
				Yield (%)	er (*R*:*S*)		
1	1	0.7	0.7	24	73:27	40	2
2	1	0.6	0.8	31	70:30	55	2
3	3	0.6	0.8	27	50:50	49	N/A
4	1	0.55	0.8	30	60:40	55	1.4

Table 22

In an attempt to improve these results, it was decided to add the *n*-BuLi last to a mixture of the starting material and (+)-sparteine as this gave improved results in the work with *N*-Boc-2-arylpiperidines.[39] While the results didn't improve to the desired level, there was a marked improvement in the selectivity when the 'normal addition' strategy was employed with this substrate (Scheme 124). The absolute stereochemistry of the recovered starting material was not determined but the stereochemistry shown above is what would be expected when (+)-sparteine is employed as the chiral ligand.



rac-**176** (*R*)-**176** **186**

53%, 72:28 er

s (by RSM) = 4.5

38%

Scheme 124

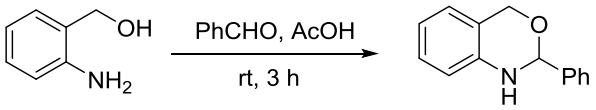
3.3 *N*-Boc-2-phenyl-1,2,3,4-tetrahydro-3,1-benzoxazine

Even though the work on the substrates discussed above gave mostly disappointing results, it was noted that the reactivities of the *N*-Boc-2-arylpiperidine substrates previously researched in the group were very different from those of the *N*-Boc-2-aryltetrahydroquinoline substrates

that have been the main focus of my project. For example, the lithiated intermediates of the *N*-Boc-2-arylpiperidine substrates were stable at –40 °C whereas the decomposition of the lithiated intermediate of the *N*-Boc-2-aryltetrahydroquinoline substrates was observed at temperatures above –78 °C.[133] Therefore, it was still considered to be worthwhile investigating the benzoxazine compounds related to the compounds described above as they might have different reactivities and give more promising results in the kinetic resolutions.

The first substrate that needed to be synthesised was *N*-Boc-2-phenyl-1,2,3,4-tetrahydro-3,1-benzoxazine **163**. A literature method was found in which 2-phenyl-1,2,3,4-tetrahydro-3,1-benzoxazine **187** was synthesised in one step from readily available starting materials without purification of the product.[139] It was envisioned that the product from this reaction could quickly be isolated and then, after subjecting it to a Boc protection, the desired compound **163** would be obtained.

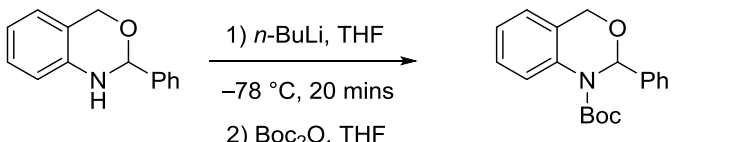
To this end, 2-aminobenzyl alcohol **120a** was stirred in acetic acid with benzaldehyde at room temperature for 3 hours. Product **187** was obtained in moderate yield without the need for purification (Scheme 125).



120a **187**, 46% (lit.[139] 98%)

Scheme 125

The Boc protection was then attempted on this compound using the conditions that were successfully used to protect the THQ substrates in the previous chapter. The amine **187** was deprotonated with *n*-BuLi in THF at –78 °C and the reaction mixture was left to stir for 20 minutes before a solution of Boc_2O in THF was added. Unfortunately, while some product **163** was formed, it was very difficult to purify by column chromatography as the polarities of the starting material, product and unreacted Boc_2O were all similar (Scheme 126).

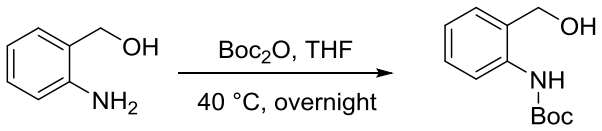


187 **163**, Inseparable mixture

Scheme 126

A different strategy was therefore required in order to access the desired substrate **163**. It was thought that by reversing the two steps above, such that the Boc protection was carried out before the cyclisation, it might be possible to access the desired compound more easily.

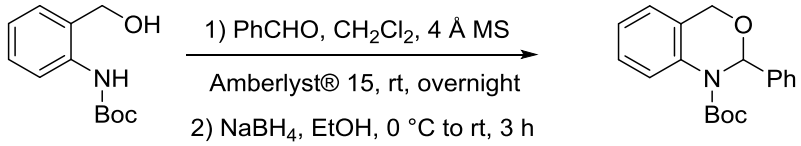
To this end, a *N*-Boc protection of 2-aminobenzyl alcohol **120a** was carried out using much gentler conditions than the conditions required for the Boc protection above which was an extra advantage of this method.[140] Gently heating 2-aminobenzyl alcohol in THF, in the presence of Boc_2O, overnight exclusively gave *N*-Boc protected compound **188** in excellent yield (Scheme 127).



120a **188**, 94%

Scheme 127

For the second step, elements of the two methods that had been carried out to form *N*-Boc-2-phenyl-1,3-oxazinane **175** were used to synthesise the desired compound **163**. The *N*-Boc protected alcohol **188** was stirred overnight, at reflux, in dichloromethane with benzaldehyde, Amberlyst® 15 acidic resin and 4 Å molecular sieves. After evaporating the solvent, the residue was dissolved in ethanol and $NaBH_4$ was added in order to reduce any excess benzaldehyde (Scheme 128). This made the separation much simpler and while the desired compound was only obtained in a moderate yield after column chromatography, it was pure and no further optimisation of this step was attempted.



188 **163**, 38%

Scheme 128

With THB **163** in hand, *in-situ* IR spectroscopy was carried out in order to determine the lithiation time of this substrate. A solution of THB **163** in THF at –78 °C exhibited a peak $\nu_{C=O}$ at 1709 cm^{-1} (Figure 32). Upon addition of 1.2 equivalents of *n*-BuLi, the intensity of the starting material peak slowly started to decrease with the gradual appearance of a peak $\nu_{C=O}$ at 1662 cm^{-1} which was assigned to $\nu_{C=O}$ of the organolithium intermediate. While the lithiated

intermediate showed no signs of decomposition under the conditions, it took approximately 2 hours for the starting material to fully lithiate.

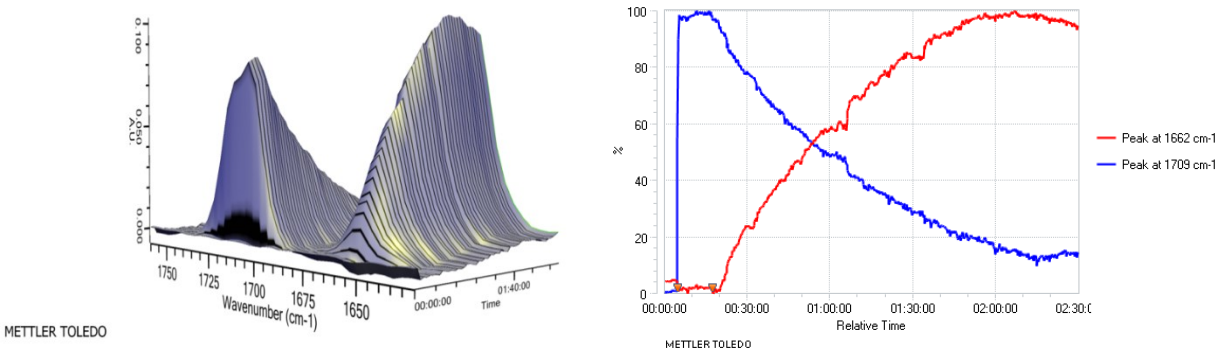
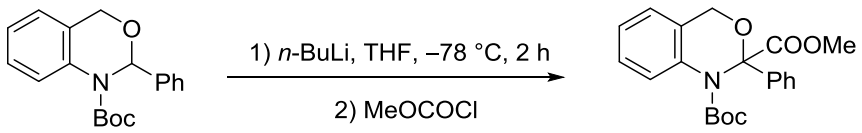


Figure 32. *In-situ* ReactIR 3D and 2D plots of the lithiation of *rac*-**163** with *n*-BuLi at –78 °C in THF. Blue line represents intensity of C=O stretching frequency of *rac*-**163** (1709 cm^{-1}) and red line of lithiated intermediate (1662 cm^{-1}) over time.

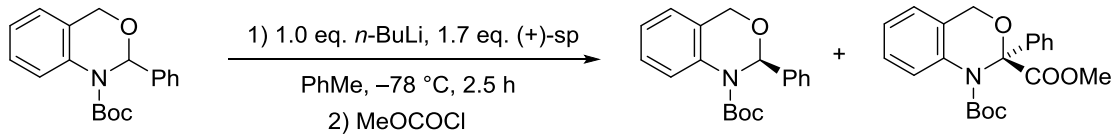
With this data in hand, THB **163** was deprotonated with *n*-BuLi in THF at –78 °C and the reaction mixture was left to stir for 2 hours before methyl chloroformate was added. Pleasingly, the desired *α*-substituted product **189** was obtained in good yield (Scheme 129).



163 **189**, 79%

Scheme 129

Due to the poor selectivities in the kinetic resolutions of *N*-Boc-2-phenyl-1,3-oxazinane **175**, it was decided at this point to attempt a kinetic resolution in order to see whether better selectivity could be observed with this substrate. Disappointingly, when substrate **163** was deprotonated with the pre-mixed *n*-BuLi / (+)-sparteine 'chiral base' and left to stir for 150 minutes before methyl chloroformate was added, the starting material was recovered in very low yield with only a moderate er (Scheme 130).



rac-**163** (*S*)-**163** 10%, 68:32 er (*S*)-**189** 46%, 77:23 er

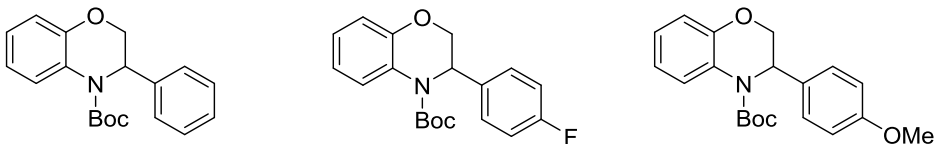
s (by RSM) = 1.4

Scheme 130

The absolute stereochemistries of the recovered starting material and product were not determined but the stereochemistries shown above are those that would be expected when (+)-sparteine is employed as the chiral ligand. As it looked like the selectivity with this substrate was no better than the selectivity with the oxazinane compound **175**, it was decided to stop work on this substrate and move on to *N*-Boc-3-aryl-1,2,3,4-tetrahydro-1,4-benzoxazines. A kinetic resolution in which the *n*-BuLi was added last to the reaction mixture ('normal addition') was not attempted with this substrate. While both addition methods did not give good selectivities for *N*-Boc-2-phenyl-1,3-oxazinane **175** (*vide supra*), the previous work within the group on *N*-Boc-2-arylpiperdines has shown that changing the method of addition can significantly improve the selectivity of the kinetic resolution.[39] A kinetic resolution which utilises this 'normal addition' method should therefore be attempted with THB **163** in order to see whether an improvement in selectivity is obtained.

3.4 *N*-Boc-3-aryl-1,2,3,4-tetrahydro-1,4-benzoxazines

The focus in this part of the project was to synthesise and carry out kinetic resolutions on three *N*-Boc-3-aryl-1,2,3,4-tetrahydro-1,4-benzoxazine derivatives, namely *N*-Boc-3-phenyl-1,2,3,4-tetrahydro-1,4-benzoxazine **164a**, the 4-fluorophenyl derivative **164b** and the 4-methoxyphenyl derivative **164c** (Figure 33).



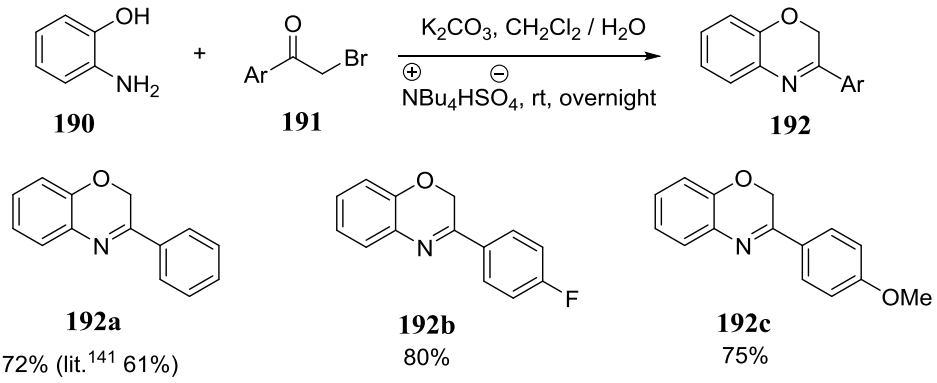
164a **164b** **164c**

Figure 33

The target *N*-Boc-3-aryl-1,2,3,4-tetrahydro-1,4-benzoxazines were unavailable commercially and needed to be prepared from readily available starting materials. A literature search revealed an efficient, patented two step method of gaining access to 3-aryl-1,2,3,4-tetrahydro-1,4-benzoxazine compounds which would then be able to be Boc protected to obtain the desired compounds.[141]

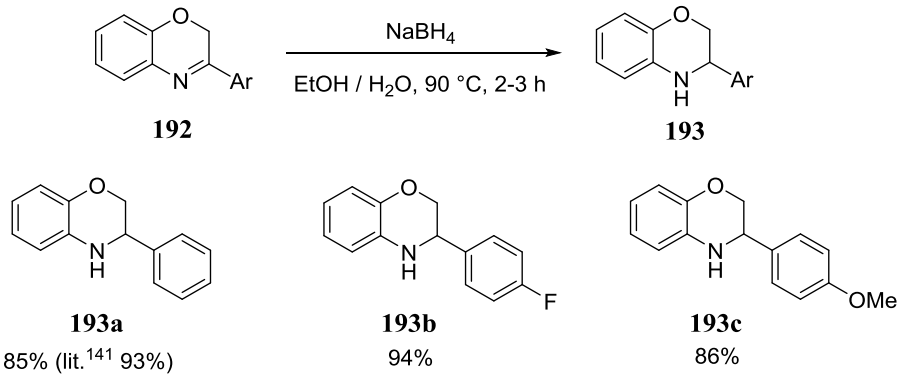
The first step was a condensation reaction between 2-aminophenol **190** and 2-bromoacetophenones **191** in a solvent mixture of dichloromethane and water. Potassium carbonate was used as a base, tetrabutyl ammonium hydrogen sulfate was used as a phase-

transfer reagent and the mixture was stirred at room temperature overnight. This gave the desired 3-aryl-1,4-benzoxazine compounds **192a–c** in good yields (Scheme 131).



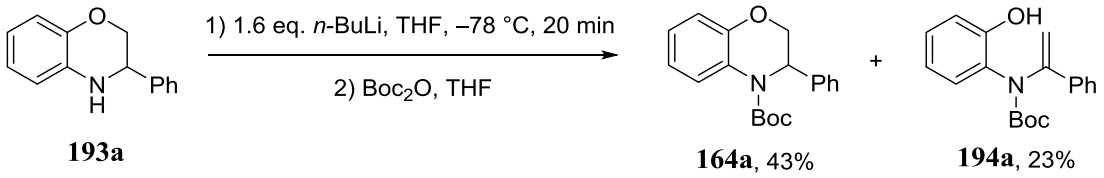
Scheme 131

The second step was a simple reduction reaction using sodium borohydride. The mixture was heated at 90 °C in an ethanol and water solvent mixture for between 2 and 3 hours and this yielded the 3-aryl-1,2,3,4-tetrahydro-1,4-benzoxazines **193a–c** in excellent yields (Scheme 132).



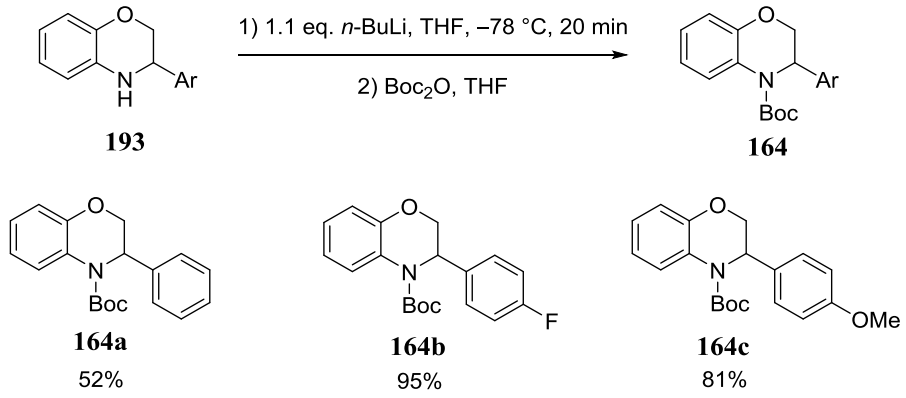
Scheme 132

The final step of the synthesis was the Boc protection reaction. The base *n*-BuLi (1.6 equiv.) was used to deprotonate benzoxazine **193a** at –78 °C. After leaving the mixture to stir for 20 minutes in THF, a solution of Boc_2O in THF was added. While this gave a moderate yield of the desired product **164a**, a substantial amount of alkene **194a** was obtained due to elimination of product **164a** by the excess *n*-BuLi that was present (Scheme 133).



Scheme 133

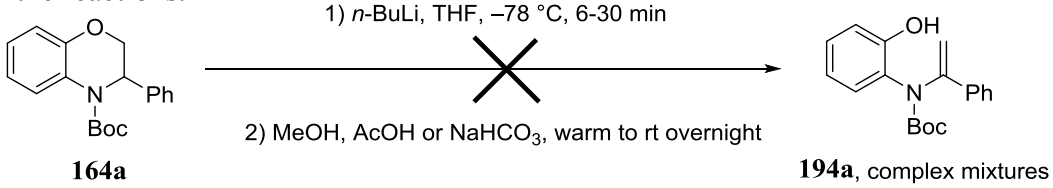
Therefore, it was decided to use just 1.1 equivalents of *n*-BuLi in the Boc protection reactions in order to limit the amount of elimination that could take place. Reactions using these conditions gave the desired compounds **164a–c** in moderate to excellent yields (Scheme 134).



Scheme 134

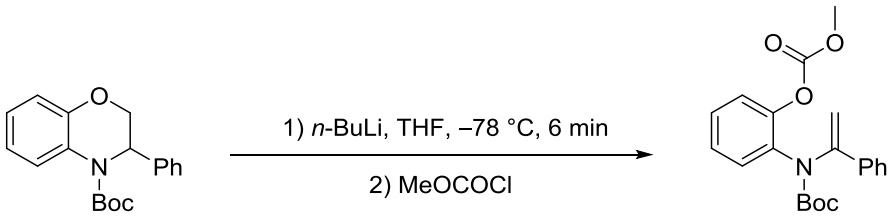
With the desired compounds in hand, the chemistry of the substrates could now be tested with *n*-BuLi. Firstly, even though *α*-substituted products could not be obtained from reactions with these compounds due to the preferred elimination, it was decided to attempt some reactions with substrate **164a** in THF in order to try and obtain the alkene products in good yields.

To this end, *n*-BuLi was added to substrate **164a** in THF and the reaction mixture was left to stir for between 6 and 30 minutes before either methanol, acetic acid or sodium hydrogen carbonate were added. In all cases, decomposition was observed and none of the desired alkene **194a** was obtained (Scheme 135). After warming the reaction mixtures overnight, the colour had changed from colourless to green and numerous spots were observed on the TLC plate. Potentially, the enamine could undergo hydrolysis in these conditions which would form the amine. However, no compounds were obtained that were able to be successfully identified from any of the reactions.



Scheme 135

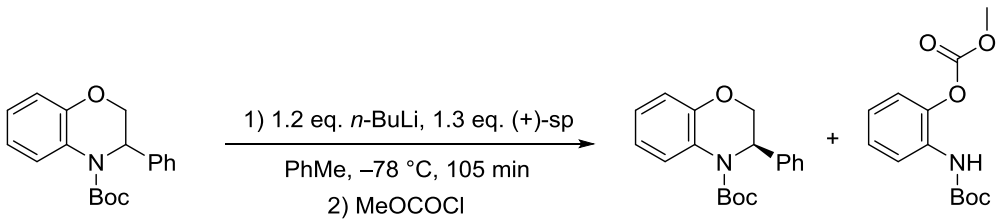
Methyl chloroformate was then used as an electrophile and a moderate yield of the desired alkene product **194b** was obtained which showed that this carbonate product was more stable under these conditions than the phenol and so this electrophile was used in the kinetic resolution reactions (Scheme 136).



164a **194b**, 39%

Scheme 136

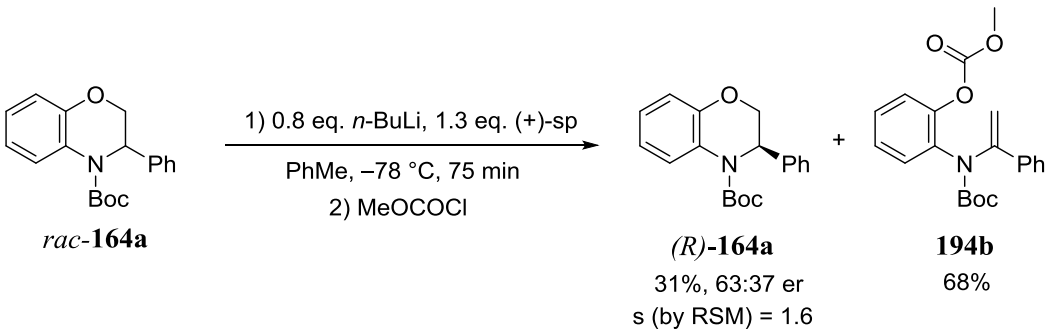
As these reactions in THF did not give promising results, it was decided to focus on kinetic resolution reactions as it was hoped that even though α-substituted products would not be obtained, the starting materials could be recovered in high er. It was decided that the 'inverse addition' method which had worked well for the tetrahydroquinoline substrates would be attempted first and so the *n*-BuLi / (+)-sparteine 'chiral base' was used to deprotonate THB **164a**. The reaction mixture was left to stir for 1 hour and 45 minutes before methyl chloroformate was added as the electrophile. The selectivity of the reaction was promising with the starting material being recovered in a lower than desired yield but with a high er. Interestingly, the product obtained from this reaction was carbonate **195** where the styrene fragment had been lost (Scheme 137). This product was not observed in any of the other reactions that were carried out. The absolute stereochemistry of the recovered starting material was not determined but the stereochemistry shown below is what would be expected when (+)-sparteine is used as the chiral ligand.



rac-**164a** *(R)*-**164a** 22%, 94:6 er s (by RSM) = 4.1 **195** 71%

Scheme 137

A further kinetic resolution was attempted with fewer equivalents of each of the 'chiral base' components. The reaction was also left for a shorter period of time but the yield of the recovered starting material was still lower than desired and the selectivity this time was poor (Scheme 138). This time, the product obtained was the expected alkene **194b**.



rac-**164a**

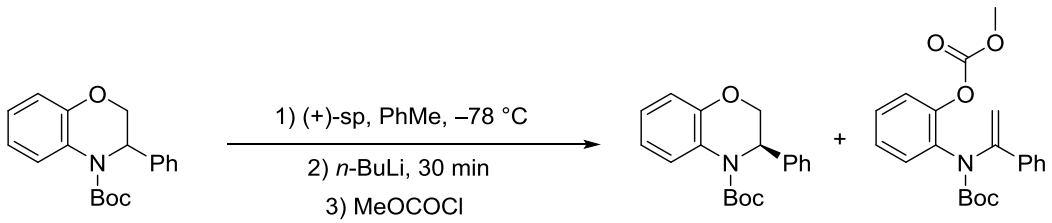
(R)-**164a**
31%, 63:37 er
s (by RSM) = 1.6

194b
68%

Scheme 138

On the basis of this disappointing result, it was decided to try further kinetic resolutions using the 'normal addition' method in which the *n*-BuLi was the final component added to the reaction mixture (Scheme 139 and Table 23). When 1.0 equivalent of *n*-BuLi and 1.7 equivalents of (+)-sparteine were used, only the alkene product **194b** was obtained (Table 23, Entry 1). This indicated that the starting material would be very sensitive to the amount of *n*-BuLi that was used in the reaction and so a further reaction was attempted which used fewer equivalents of each component of the 'chiral base'. The reaction was left for a shorter duration of time before the electrophile was added and delightfully, the starting material (*R*)-**164a** was recovered in a reasonable yield with an excellent er (Table 23, Entry 2). This showed that the 'normal addition' procedure was much more promising than the 'inverse addition' procedure. Further reactions were carried out in order to try to improve the yield and in most cases the reactions proceeded in a highly selective manner. (Table 23, Entries 3-11). It was found that by making the reaction mixtures more diluted, the selectivity increased further which may have been due to the reaction rate decreasing slightly in these more dilute conditions (Table 23,

Entries 9-11). The reaction outlined in entry 10 of Table 23 gave the ideal balance of good yield and excellent er of the recovered (*R*)-**164a**.



rac-**164a** (*R*)-**164a** **194b**

Scheme 139

Entry	*rac*-164a (mg)	PhMe (mL)	eq. *n*-BuLi	eq. L*	RSM		Product Yield (%)	s (by RSM)
					Yield (%)	er (*R*:*S*)		
1*	103	4	1.0	1.7	0	N/A	>100[a]	–
2	86	4	0.6	1.0	36	>99:1	76[a]	16
3	103	4	0.55	1.0	42	92:8	66[a]	10
4	60	2	0.55	1.0	15	>99:1	85	5
5	142	4	0.6	0.6	41	88:12	53	7
6	144	4	0.6	1.0	60	73:27	39	8.5
7	123	4	0.6	1.0	32	>99:1	66	12
8	401	4	0.6	1.0	57	60:40	43	2
9	115	8	0.6	0.6	39	>99:1	69[a]	20
10	102	8	0.55	0.55	41	>99:1	69[a]	25
11	113	8	0.58	0.58	42	94:6	62[a]	13

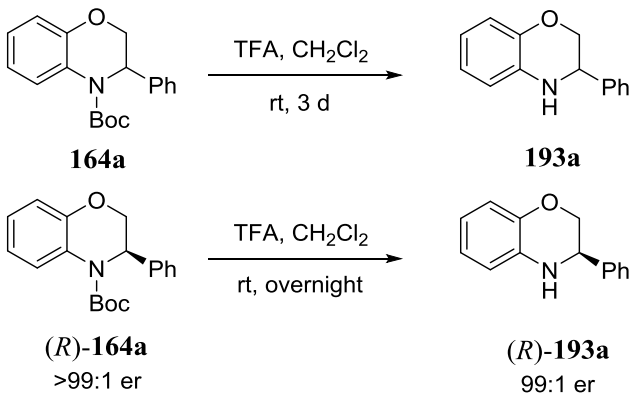
Table 23

* = 90 min reaction time, [a] = product yield more than theoretical maximum, see text.

Unfortunately, while the selectivities were excellent, there was an issue with the overall yield of some reactions (Table 23, Entries 1, 2, 3, 9, 10 and 11). This may have been due to the fact that when the alkene product **194b** was obtained from these reactions, its appearance was thick and sticky and so it was difficult to remove the solvent. Another possibility is that there may have been some impurities mixed with the recovered starting material or product although these were not visible by NMR spectroscopy and no substantial impurity peaks were detected in the chiral HPLC traces of the recovered starting material. In an effort to counteract the problem, *n*-BuLi was added between two non-zero marker points on the 1 mL syringe rather than from the zero point as it was easier to see how much *n*-BuLi was being added.

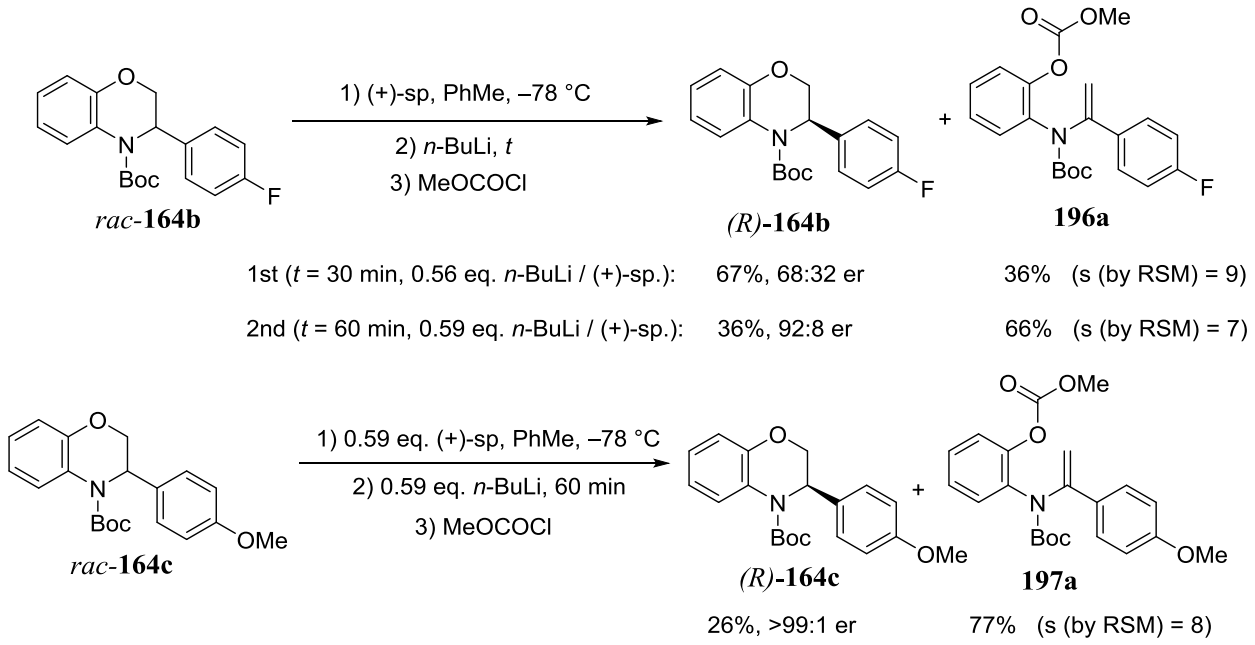
The Boc group of THB **164a** was able to be removed under acidic conditions to give amine **193a** and pleasingly the enantioenrichment was maintained when THB (*R*)-**164a** with an er of >99:1 was subjected to the same reaction conditions (Scheme 140). It was also found that the reaction using enantioenriched (*R*)-**164** was completed after leaving the mixture to stir

overnight, rather than the 3 days used for the racemic **164** and needed for the THQ compounds. While it was difficult to purify the amine **193a** after these reactions which meant that the products were still not pure after column chromatography, it was clear to see the enantioenrichment of the amine (*R*)-**193a** by CSP-HPLC.



Scheme 140

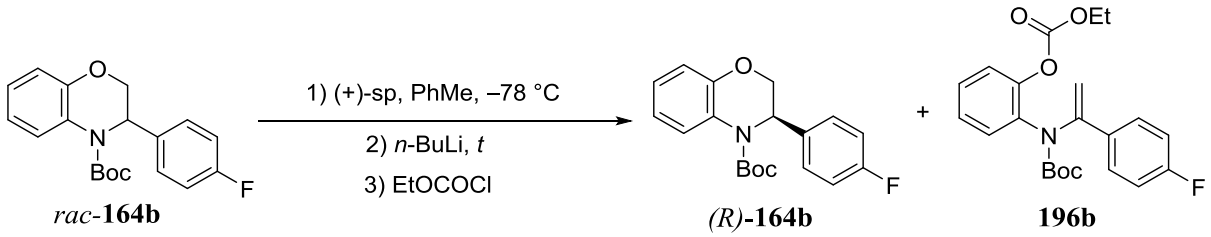
With good results obtained for the parent compound THB **164a**, it was decided to directly attempt kinetic resolution reactions with the 4-fluorophenyl and 4-methoxyphenyl derivatives **164b** and **164c**. Firstly, kinetic resolutions were attempted using methyl chloroformate as the electrophile but while the selectivities were promising, the issue with the overall yield of the reactions remained (Scheme 141).



Scheme 141

To try and get the overall yields below 100%, ethyl chloroformate was used as the electrophile for the remaining kinetic resolutions as this electrophile gave products that seemed to be less sticky when first isolated than those obtained when methyl chloroformate was used.

To this end, various kinetic resolution conditions were attempted using the 4-fluorophenyl derivative **164b** with the number of equivalents of the 'chiral base' components and the reaction times both being varied (Scheme 142 and Table 24). The selectivities of the kinetic resolutions with this derivative were lower than that of the parent compound but the starting material (*R*)-**164b** was still able to be obtained in good yield and reasonable er (Table 24, Entry 4). This observation corroborated with the results obtained in Chapter 2 when the 4-fluorophenyl THQ derivative **118b** was used in kinetic resolutions. It was interesting to observe that the use of ethyl chloroformate led to the total yield never being greater than 100% which showed that ethyl chloroformate was a more suitable electrophile in these reactions than methyl chloroformate.



rac-**164b** *(R)*-**164b** **196b**

Scheme 142

Entry	time (min)	*rac*-164b (mg)	PhMe (mL)	eq. *n*-BuLi	eq. L*	RSM		Product Yield (%)	s (by RSM)
						Yield (%)	er (*R*:*S*)		
1	45	101	8	0.57	0.57	23	>99:1	75	7
2	30	209	16	0.55	0.57	64	63:37	26	3.5
3	45	101	8	0.8	0.8	53	75:25	45	6
4	45	101	8	1.0	1.0	42	86:14	55	6.5

Table 24

Pleasingly, the absolute configuration of the starting material **164b** recovered from the kinetic resolution outlined in entry 3 of the table was able to be determined by performing X-ray crystallography using the CuKα source. This showed that the expected (*R*)-enantiomer was the major one recovered from these kinetic resolutions (Figure 34 and Appendix 1f).

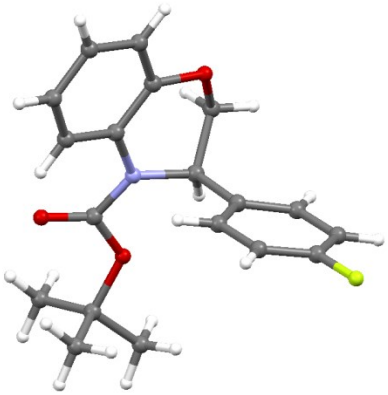
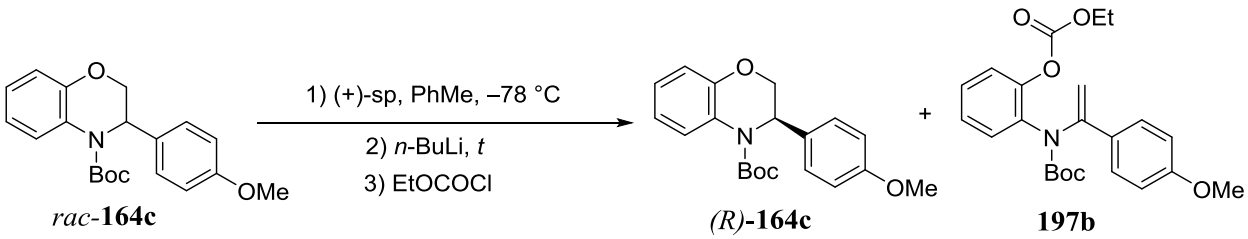


Figure 34

X-ray crystal absolute configuration determination of compound (*R*)-164b

Flack parameter = -0.07(10)

The final substrate used in kinetic resolution reactions was the 4-methoxyphenyl derivative **164c**. Again, various kinetic resolution conditions were attempted with the number of equivalents of the 'chiral base' components and the reaction times both being varied (Scheme 143 and Table 25). It was very pleasing to observe that the selectivities of the kinetic resolutions using this substrate were higher than that of the 4-fluorophenyl substrate **164b** and the starting material (*R*)-**164c** was able to be recovered in good yield and excellent er (Table 25, Entry 6).



rac-**164c** (*R*)-**164c** **197b**

Scheme 143

Entry	time (min)	*rac*-164c (mg)	PhMe (mL)	eq. *n*-BuLi	eq. L*	RSM		Product Yield (%)	s (by RSM)
						Yield (%)	er (*R*:*S*)		
1	30	102	8	0.57	0.57	25	>99:1	66	8
2	30	201	16	0.55	0.57	72	64:36	24	8
3	30	100	8	0.57	0.57	60	70:30	32	6
4	45	101	8	0.8	0.8	57	75:25	40	8
5	45	103	8	1.0	1.0	50	84:16	47	10.5
6	45	101	8	1.2	1.2	39	95:5	55	11

Table 25

The 4-methoxyphenyl THQ derivative **118c** was much less reactive compared to the other THQ derivatives, as shown in Chapter 2, and gave very poor selectivities. The increased reactivity and selectivity of the THB derivative **164c** may have been due to the increased reactivity of these substrates in general and the tendency they have to eliminate and form the alkene products.

Pleasingly, the X-ray crystal structure of the starting material **164c** recovered from the kinetic resolution outlined in entry 1 could be obtained on the CuKα source in order to determine the absolute configuration and this again showed that the major enantiomer obtained from these kinetic resolutions with (+)-sparteine was the (*R*)-enantiomer (Figure 35 and Appendix 1g).

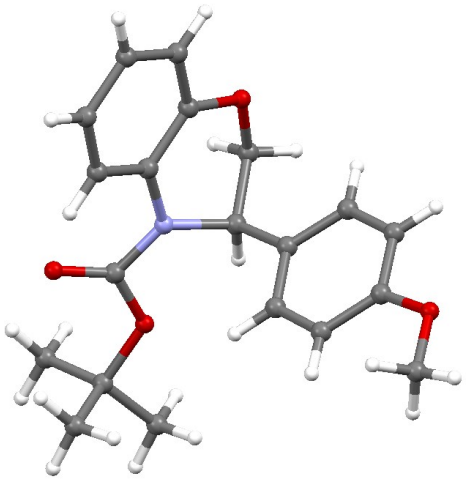


Figure 35

X-ray crystal absolute configuration determination of compound (*R*)-164c

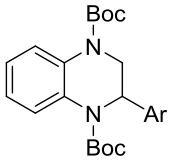
Flack parameter = 0.06(14)

3.5 Conclusions and Future Work

N-Boc-2-phenyl-1,2,3,4-tetrahydro-3,1-benzoxazine was synthesised in a 2 step procedure from readily available starting materials. However, while the racemic lithiation–substitution reaction gave the product in a good yield, the kinetic resolution reaction showed poor selectivity and so work on this substrate was discontinued. Future work with this substrate could test different chiral ligands and reaction conditions, such as the 'normal addition' method, in order to see whether the selectivity of the kinetic resolution reactions can be increased. DFT calculations could also be carried out in order to see whether the oxygen atom in the benzoxazine ring is co-ordinated to the chiral base complex during the kinetic resolutions.

The focus shifted to three *N*-Boc-3-aryl-1,2,3,4-tetrahydro-1,4-benzoxazines and these were able to be made efficiently, in 3 steps, from commercially available starting materials. While *α*-substituted products could not be obtained from reactions with these compounds, the starting material was able to be recovered from kinetic resolutions in good yields and excellent ers. A problem arose when the total yields of the reactions were consistently above 100% but this was rectified by changing the electrophile from methyl chloroformate to ethyl chloroformate.

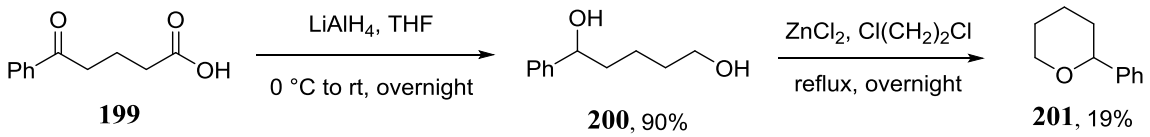
Further work will explore a variety of other derivatives to test the scope of the kinetic resolutions. In the future, in order not to waste the alkene products, further reactions on these could be attempted in order to convert them to more useful compounds. Reactions could also be attempted on other 2-aryl *N*-heterocycles such as N-Boc-2-arylquinoxalines **198** (Figure 36).



198

Figure 36

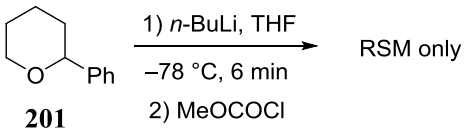
Kinetic resolutions using the BuLi / sparteine 'chiral base' could be attempted on 2-aryltetrahydropyrans such as 2-phenyltetrahydropyran **201**. This compound was synthesised in 2 steps using literature methods starting from readily available starting materials (Scheme 144).[142–144]



199 **200**, 90% **201**, 19%

Scheme 144

While the desired compound was obtained in a poor overall yield, the route used was 3 steps shorter than a route that has been recently used by Capriati and co-workers to obtain the same compound and the 2 step route also avoids the need to use highly toxic selenium containing compounds.[145] With compound **201** in hand, a lithiation was attempted. *n*-BuLi (1.2 equiv.) was used as the base and the mixture was stirred in THF at –78 °C for 6 minutes before methyl chloroformate was added as the electrophile. Unfortunately, only the starting material was recovered (Scheme 145).



201

Scheme 145

This is not surprising as Capriati and co-workers have since shown that 3.0 equiv. of *s*-BuLi is required to effectively deprotonate this substrate and so if any future kinetic resolutions are attempted, *s*-BuLi will probably be required.[145]

Chapter 4 – Experimental

4.1 General Experimental Details

All reagents were obtained from commercial suppliers and were used without further purification unless otherwise specified. Dry solvents were obtained from 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, (+)-sparteine and the (+)-sparteine surrogate were freshly distilled. 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 $KMnO_4$ 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 Walters LCT instrument for Electro–Spray (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.), a Phenomenex Lux Amylose-2 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. Only selected kinetic resolution reaction procedures are reported in this experimental, those not reported were carried out in the same way as those described below.

4.2 Experimental Procedures

General Procedure for the synthesis of 2-aryl quinolines – General Procedure A

2-Aminobenzyl alcohols **120** (1.0 equiv.), benzophenone (1.0 equiv.) and ketones **121** (1.0 equiv.) were dissolved in THF or 1,4-dioxane. Potassium *tert*-butoxide solution (1.0 equiv., 1.0 M in THF) or solid potassium *tert*-butoxide (2.0 equiv) was added and the resulting mixture was stirred at 90 °C for 16 h. The reaction mixture was filtered through Celite and was allowed to cool to room temperature. The resulting solution was added to a saturated solution of NH_4Cl (100 mL) and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried with $MgSO_4$, filtered, concentrated and the residue was purified by column chromatography on silica gel, as described below. An alternative purification method was to dissolve the residue in ethyl acetate (10 mL) and add aqueous HCl (50 mL, 2 M). The organic layer was extracted with aqueous HCl (2 × 50 mL) and the combined aqueous layers were basified with a solution of NaOH (2 M) until pH 13 to obtain a suspension that was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated to afford the near-pure 2-aryl quinolines **116.** A solid may be formed on the addition of acid. The remaining solution was decanted and the solid was subsequently basified with a solution of NaOH (2 M) until pH 13 to obtain a suspension that was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated to afford the near-pure 2-aryl quinolines **116.**

General Procedure for the reduction of 2-aryl quinolines – General Procedure B

2-Arylquinolines **116** (1.0 equiv.) were dissolved in glacial acetic acid and sodium cyanoborohydride (2.0 equiv.) was added in one portion to the stirred solution. The mixture was allowed to stir at room temperature for 16 h and was poured into saturated aqueous sodium carbonate. The mixture was allowed to stir for 15 min and was diluted with CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, concentrated and the residue was purified by column chromatography on silica gel, as described below, to give the 2-aryl-1,2,3,4-tetrahydroquinolines **117**. The alternative purification method described in General

Procedure A can also be carried out if there is no 2-substituted quinoline starting material in the mixture.

General Procedure for the *N*-Boc-protection of 2-aryl-1,2,3,4-tetrahydroquinolines and 3-aryl-1,2,3,4-tetrahydro-1,4-benzoxazines – General Procedure C

n-BuLi (1.1 or 1.6 equiv.) was added to a stirred solution of 2-substituted 1,2,3,4-tetrahydroquinolines **117** (1.0 equiv.) or 3-aryl-1,2,3,4-tetrahydro-1,4-benzoxazines **193** (1.0 equiv.) in THF at –78 °C. After the times described below, Boc_2O (1.0–3.0 equiv.) dissolved in THF was added. The mixture was allowed to warm to room temperature over 16 h, was diluted with 10% sodium hydrogencarbonate solution and was extracted with Et_2O (2 × 50 mL or 2 × 100 mL). The combined organic layers were dried with $MgSO_4$, filtered, concentrated and the residue was purified by column chromatography on silica gel, as described below, to give the *N*-Boc-2-aryl-1,2,3,4-tetrahydroquinolines **118** or the *N*-Boc-3-aryl-1,2,3,4-tetrahydro-1,4-benzoxazines **164**.

General Procedure for the deprotonation and electrophilic quench of *N*-Boc-2-substituted 1,2,3,4-tetrahydroquinolines – General Procedure D

n-BuLi (1.2 equiv.) was added to a stirred solution of *N*-Boc-2-aryl-1,2,3,4-tetrahydroquinolines **118** (1.0 equiv.) in THF at –78 °C. After the times described below, the electrophile (3.5 equiv.) 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, as described below.

General Procedure for the asymmetric deprotonation of *N*-Boc-2-substituted 1,2,3,4-tetrahydroquinolines or *N*-Boc-2-phenyl-1,2,3,4-tetrahydro-3,1-benzoxazine in the presence of (–)-sparteine, (+)-sparteine or the (+)-sparteine surrogate – General Procedure E

n-BuLi was added to a stirred solution of (–)-sparteine, (+)-sparteine or the (+)-sparteine surrogate in dry PhMe at –78 °C. After 30 min, *N*-Boc-2-substituted 1,2,3,4-tetrahydroquinolines **118** (1.0 equiv.) or *N*-Boc-2-phenyl-1,2,3,4-tetrahydro-3,1-benzoxazine **163** (1.0 equiv) dissolved in dry PhMe was added. After the times specified, methyl chloroformate (3.5 equiv.) was added. The mixture was allowed to warm to room temperature

over 16 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel, as described below.

General Procedure for the deprotonation and Boc group migration of *N*-Boc-2-substituted 1,2,3,4-tetrahydroquinoline – General Procedure F

n-BuLi (1.2 equiv.) was added to a stirred solution of *N*-Boc-2-substituted 1,2,3,4-tetrahydroquinolines **118** (1.0 equiv.) in THF (2 mL) at –78 °C. After 6 min, BEt_3 (0.2–3.5 equiv.) 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, as described below.

General Procedure for the Boc group deprotection of *N*-Boc-2,2-disubstituted 1,2,3,4-tetrahydroquinolines using TFA – General Procedure G

Trifluoroacetic acid (10.0 equiv.) was added to a stirred solution of the *N*-Boc-2,2-disubstituted 1,2,3,4-tetrahydroquinolines **119a** and **119l** (1.0 equiv.) in CH_2Cl_2 (5 mL) at room temperature. After 3 days, the solvent was evaporated and 1 M NaOH (2 mL) was added to basify the residue. The mixture was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, the solvent was evaporated and the residue was purified by column chromatography on silica gel, as described below, to give the 2,2-disubstituted 1,2,3,4-tetrahydroquinolines **124**.

General Procedure for the synthesis of 3-aryl 1,4-benzoxazines – General Procedure H

To a solution of potassium carbonate (6.0 equiv.) in water (200 mL) and CH_2Cl_2 (200 mL) was added 2-aminophenol (1.0 equiv.) and $NBu_4^+HSO_4^-$ (0.025 equiv.). The reaction mixture was stirred vigorously, a solution of the bromoacetophenones **191** in CH_2Cl_2 (100 mL) was slowly added and the reaction mixture was left to stir overnight. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give the crude product which was purified by column chromatography on silica gel, as described below, to give the 3-aryl 1,4-benzoxazines **192**.

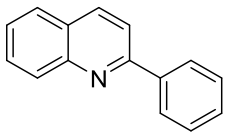
General Procedure for the reduction of 3-aryl 1,4-benzoxazines – General Procedure I

To a solution of the 3-aryl-1,4-benzoxazines **192** (1.0 equiv.) in ethanol (100 mL) and water (25 mL) was added sodium borohydride (2.0 equiv.). The mixture was heated at 90 °C for the time specified below and the reaction mixture was then cooled and the solvent was removed under reduced pressure. The crude mixture was partitioned between CH_2Cl_2 (200 mL) and water (200 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to give the crude product which was purified by column chromatography on silica gel, as described below, to give the 3-aryl-1,2,3,4-tetrahydro-1,4-benzoxazines **193**.

General Procedure for the asymmetric deprotonation of *N*-Boc-3-aryl-1,2,3,4-tetrahydro-1,4-benzoxazines in the presence of (+)-sparteine – General Procedure J

n-BuLi (0.55–1.2 equiv.) was added to a stirred solution of (+)-sparteine (0.55–1.3 equiv.) and the *N*-Boc-3-aryl-1,2,3,4-tetrahydro-1,4-benzoxazines **164** (1.0 equiv.) in dry PhMe (8 mL) at –78 °C. After the times specified below, the electrophile (3.5 equiv.) was added. The mixture was allowed to warm to room temperature over 16 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel, as described below.

2-Phenylquinoline (116a)[41,95,97,146]

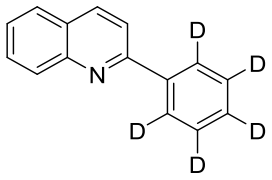


Using the general procedure A, 2-aminobenzyl alcohol **120a** (5.00 g, 40.6 mmol), benzophenone (7.40 g, 40.6 mmol), ketone **121a** (4.74 mL, 40.6 mmol), THF (20 mL) and solid *t*-BuOK (4.56 g, 40.6 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5) and then acid-base extraction, quinoline **116a** (5.31 g, 64%) as an amorphous brown solid; m.p. 81–82 °C (lit.[97] 80–82 °C); R_f 0.38 [petrol–EtOAc (95:5)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.26 (1H, d, *J* = 8.5 Hz, CH), 8.22–8.17 (3H, m, 3 × CH), 7.91 (1H, d, *J* = 8.5 Hz, CH), 7.87–7.85 (1H, m, CH), 7.78–7.74 (1H, m, CH), 7.58–7.54

(3H, m, 3 × CH), 7.52–7.47 (1H, m, CH). Data consistent with the literature.[97,146]

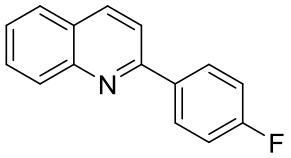
Alternatively, to a solution of quinoline **115** (5.49 mL, 47.0 mmol) in THF (20 mL) was added PhMgBr (47.0 mL, 47.0 mmol, 1.0 M in THF) at 0 °C. The reaction mixture was left to stir and heated under reflux for 16 h under an inert atmosphere. After cooling to room temperature, H_2O was added slowly at first before the reaction mixture was poured into H_2O (200 mL). The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated to give, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), quinoline **116a** (3.14 g, 33%); data as above.

2-Phenylquinoline (phenyl-d5) (d_5**-116a)**[147]



Using general procedure A, 2-aminobenzyl alcohol **120a** (5.04 g, 40.9 mmol), acetophenone(phenyl-d5) d_5-**121a** (4.77 mL, 40.9 mmol), benzophenone (7.46 g, 40.9 mmol), 1,4-dioxane (40 mL) and *t*-BuOK (40.9 mL, 40.9 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1) and then acid-base extraction, the quinoline d_5-**116a** (7.40 g, 86%) as an amorphous yellow solid; m.p. 69–71 °C (No melting point reported.[150]); R_f 0.58 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3390, 3060, 2960, 2895, 2845, 1615, 1595, 1500, 1425, 1315, 820, 775; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.25 (1H, d, *J* = 8.5 Hz, CH), 8.21 (1H, d, *J* = 8.5 Hz, CH), 7.88 (1H, d, *J* = 8.5 Hz, CH), 7.84 (1H, d, *J* = 8.5 Hz, CH), 7.81–7.73 (1H, m, CH), 7.59–7.52 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$, deuterated carbons could not be observed) δ = 157.4 (C), 148.3 (C), 139.5 (C), 136.8 (CH), 129.8 (CH), 129.7 (CH), 127.5 (CH), 127.2 (C), 126.3 (CH), 119.1 (CH); HRMS (ES) Found MH^+, 211.1278. $C_{15}H_7D_5N$ requires MH^+, 211.1278; LRMS *m/z* (ES) 211 (100%, MH^+). No data reported.[147]

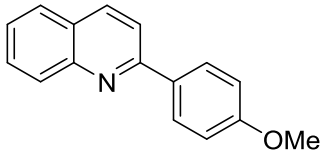
2-(4-Fluorophenyl)quinoline (116b)[148]



Using the general procedure A, 2-aminobenzyl alcohol **120a** (5.06 g, 41.1 mmol), benzophenone (7.49 g, 41.1 mmol), ketone **121b** (4.99 mL, 41.1 mmol), 1,4-dioxane (40 mL) and *t*-BuOK (41.1 mL, 41.1 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5) and then acid-base extraction, quinoline **116b** (5.14 g, 56%) as an amorphous brown solid, m.p. 84–85 °C (lit.[151] 92–93 °C); R_f 0.46 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3065, 3040, 1590, 1495, 1430, 1225, 1160, 815, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31–8.16 (4H, m, 4 × CH), 7.87 (2H, d, *J* = 8.5 Hz, 2 × CH), 7.80–7.75 (1H, m, CH), 7.60–7.55 (1H, m, CH), 7.27–7.21 (2H, m, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.8 (d, *J* = 249.0 Hz, C), 156.2 (C), 148.3 (C), 136.9 (CH), 135.8 (d, *J* = 3.0 Hz, C), 129.8 (CH), 129.7 (CH), 129.5 (d, *J* = 8.5 Hz, CH), 127.5 (CH), 127.1 (C), 126.4 (CH), 118.6 (CH), 115.8 (d, *J* = 21.5 Hz, CH); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 112.5; HRMS (ES) Found: MH^+, 224.0866. $C_{15}H_{11}NF$ requires MH^+, 224.0876; LRMS *m/z* (ES) 224 (100%, MH^+). Data consistent with the literature.[148]

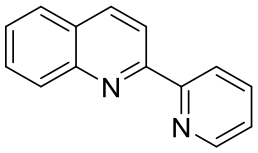
Alternatively, to a solution of quinoline **115** (5.49 mL, 47.0 mmol) in THF (20 mL) was added 4-fluorophenylmagnesiumbromide (47.0 mL, 47.0 mmol, 1.0 M in THF) at 0 °C. The reaction mixture was left to stir and heated under reflux for 16 h under an inert atmosphere. After cooling to room temperature, H_2O was added slowly at first before the reaction mixture was poured into H_2O (200 mL). The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated to give, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), quinoline **116b** (2.66 g, 25%); data as above.

2-(4-Methoxyphenyl)quinoline (116c)[149]



Using the general procedure A, 2-aminobenzyl alcohol **120a** (5.00 g, 40.6 mmol), benzophenone (7.40 g, 40.6 mmol), ketone **121c** (6.10 g, 40.6 mmol), 1,4-dioxane (40 mL) and *t*-BuOK (40.6 mL, 40.6 mmol, 1.0 M in THF) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5) and then acid-base extraction, the quinoline **116c** (8.40 g, 88%) as an amorphous yellow solid, m.p. 118–121 °C (lit.[152] 123 °C); R_f 0.45 [petrol–EtOAc (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 (1H, d, *J* = 8.5 Hz, CH), 8.19–8.14 (3H, m, 3 × CH), 7.86 (1H, d, *J* = 8.5 Hz, CH), 7.83 (1H, dd, *J* = 8.0, 1.0 Hz, CH), 7.76–7.71 (1H, m, CH), 7.55–7.49 (1H, m, CH), 7.10–7.05 (2H, m, 2 × CH), 3.92 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.8 (C), 156.9 (C), 148.3 (C), 136.7 (CH), 132.2 (C), 129.6 (CH), 129.5 (CH), 128.9 (CH), 127.5 (CH), 126.9 (C), 125.9 (CH), 118.6 (CH), 114.2 (CH), 55.4 (OCH_3); HRMS (ES) Found: MH^+, 236.1085. $C_{16}H_{14}NO$ requires MH^+, 236.1075; LRMS *m/z* (ES) 236 (100%, MH^+). Data consistent with the literature.[149]

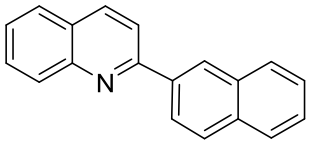
2-(Pyridin-2-yl)quinoline (116d)[97,150]



Using the general procedure A, 2-aminobenzyl alcohol **120a** (5.00 g, 40.6 mmol), benzophenone (7.40 g, 40.6 mmol), ketone **121d** (4.55 mL, 40.6 mmol), THF (30 mL) and *t*-BuOK (40.6 mL, 40.6 mmol, 1.0 M in THF) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1) and then acid-base extraction, the quinoline **116d** (5.90 g, 70%) as an amorphous yellow solid, m.p. 94–96 °C (lit.[97] 95–97 °C); R_f 0.64 [petrol–EtOAc (3:1)]; ^{1}H NMR (400 MHz, CDCl3) δ = 8.78–8.72 (1H, m, CH), 8.69–8.64 (1H, m, CH), 8.58 (1H, d, *J* = 8.5 Hz, CH), 8.27 (1H, d, *J* = 8.5 Hz, CH), 8.21 (1H, d, *J* = 8.5 Hz), 7.89–7.81 (2H, m, 2 × CH), 7.77–7.70 (1H, m, CH), 7.57–7.50 (1H, m, CH),

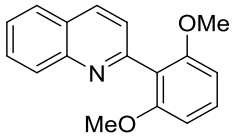
7.34 (1H, ddd, *J* = 7.5, 4.5, 1.0 Hz, CH); ^{13}C NMR (100 MHz, CDCl3) δ = 156.3 (C), 156.1 (C), 149.2 (CH), 147.9 (C), 137.0 (CH), 136.8 (CH), 129.8 (CH), 129.6 (CH), 128.3 (C), 127.6 (CH), 126.8 (CH), 124.1 (CH), 121.8 (CH), 119.0 (CH); HRMS (ES) Found: MH^+, 207.0930. $C_{14}H_{11}N_2$ requires MH^+, 207.0922; LRMS *m/z* (ES) 207 (100%, MH^+). Data consistent with the literature.[97,150]

2-(Naphthalen-2-yl)quinoline (116f)[149]



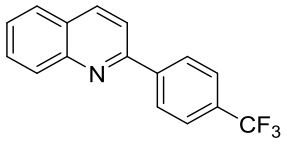
Using general procedure A, 2-aminobenzyl alcohol **120a** (5.05 g, 41.0 mmol), ketone **121f** (6.98 g, 41.0 mmol), benzophenone (7.48 g, 41.0 mmol), 1,4-dioxane (40 mL) and *t*-BuOK (41.00 mL, 41.0 mmol, 1.0 M in THF) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1) and then acid-base extraction, the quinoline **116f** (8.43 g, 80%) as an amorphous brown solid; m.p. 143–145 °C (lit.[152] 150 °C); R_f 0.49 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3055, 1595, 1555, 1495, 1420, 1360, 1290, 1200, 1130, 1005, 950, 820, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.65 (1H, s, CH), 8.45–8.38 (1H, m, CH), 8.29 (1H, d, *J* = 8.5 Hz, CH), 8.25 (1H, d, *J* = 8.5 Hz, CH), 8.07–7.99 (3H, m, 3 × CH), 7.97–7.90 (1H, m, CH), 7.86 (1H, d, *J* = 8.0 Hz, CH), 7.79 (1H, t, *J* = 8.0 Hz, CH), 7.61–7.53 (3H, m, 3 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.2 (C), 148.4 (C), 137.0 (C), 136.8 (CH), 133.9 (C), 133.5 (C), 129.8 (2 × CH), 128.9 (CH), 128.6 (CH), 127.8 (CH), 127.6 (CH), 127.3 (C), 127.2 (CH), 126.8 (CH), 126.4 (2 × CH), 125.1 (CH), 119.2 (CH); HRMS (ES) Found MH^+, 256.1125. $C_{19}H_{14}N$ requires MH^+, 256.1121; LRMS *m/z* (ES) 256 (100%, MH^+). Data consistent with the literature.[149]

2-(2,6-Dimethoxyphenyl)quinoline (116g)



Using general procedure A, 2-aminobenzyl alcohol **120a** (3.57 g, 29.0 mmol), ketone **121g** (5.22 g, 29.0 mmol), benzophenone (5.28 g, 29.0 mmol), 1,4-dioxane (40 mL) and *t*-BuOK (29.0 mL, 29.0 mmol, 1.0 M in THF) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1) and then acid-base extraction, the quinoline **116g** (5.60 g, 72%) as an amorphous brown solid; m.p. 110–111 °C; R_f 0.05 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3005, 2960, 2935, 2835, 1600, 1585, 1470, 1245, 1105, 1030, 825, 765; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.25 (1H, d, *J* = 8.5 Hz, CH), 8.18 (1H, d, *J* = 8.5 Hz, CH), 7.88–7.82 (1H, m, CH), 7.76–7.68 (1H, m, CH), 7.58–7.50 (1H, m, CH), 7.45 (1H, d, *J* = 8.5 Hz, CH), 7.37 (1H, t, *J* = 8.5 Hz, CH), 6.70 (2H, d, *J* = 8.5 Hz, 2 × CH), 3.72 (6H, s, 2 × OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.2 (C), 155.5 (C), 148.3 (C), 135.5 (CH), 129.9 (CH), 129.7 (CH), 129.1 (CH), 127.6 (CH), 127.1 (C), 126.2 (CH), 124. 4 (CH), 119.5 (C), 104.3 (CH), 56.0 (CH_3); HRMS (ES) Found MH^+, 266.1180. $C_{17}H_{16}NO_2$ requires MH^+, 266.1176; LRMS *m/z* (ES) 266 (100%, MH^+).

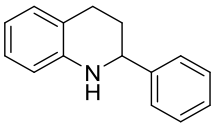
2-[4-(Trifluoromethyl)phenyl]quinoline (116h)[99,147]



Using general procedure A, 2-aminobenzyl alcohol **120a** (3.93 g, 31.9 mmol), ketone **121h** (6.00 g, 31.9 mmol), benzophenone (5.81 g, 31.9 mmol) and *t*-BuOK (31.9 mL, 31.9 mmol, 1.0 M in THF) gave the quinoline **116h** (4.95 g, 57%) as an amorphous orange solid; m.p. 119–120 °C (lit.[150] 125–126 °C); R_f 0.38 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3105, 3070, 3060, 1615, 1595, 1555, 1500, 1320, 1120, 1105, 1010, 815, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.35–8.27 (3H, m, 3 × CH), 8.21 (1H, d, *J* = 8.5 Hz, CH), 7.93 (1H, d, *J* = 8.5 Hz, CH), 7.90–7.87 (1H, m, CH), 7.85–7.75 (3H, m, 3 × CH), 7.63–7.57 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$, one extra quaternary carbon observed) δ = 155.7 (C), 148.3 (C), 142.7 (C), 137.2, (CH), 131.1 (q, *J* 32.0 Hz, C), 130.0 (CH), 129.9 (CH), 127.9 (CH), 127.5 (CH), 127.4 (C), 126.9 (CH), 125.8 (q, *J* 3.5 Hz, CH), 125.5 (C), 122.9 (C), 118.8 (CH); ^{19}F NMR (377 MHz,

$CDCl_3$) δ = 62.6; HRMS (ES) Found MH^+, 274.0833. $C_{16}H_{11}F_3N$ requires MH^+, 274.0844; LRMS *m/z* (ES) 274 (100%, MH^+). Data consistent with the literature.[147]

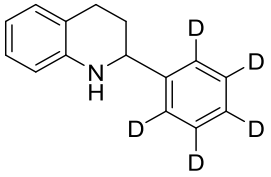
2-Phenyl-1,2,3,4-tetrahydroquinoline (117a)[41,95,98,151]



Using the general procedure B, quinoline **116a** (5.30 g, 25.8 mmol), acetic acid (30 mL) and sodium cyanoborohydride (3.25 g, 51.7 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the 1,2,3,4-tetrahydroquinoline **117a** (2.80 g, 52%) as an amorphous white solid; m.p. 37–38 °C (lit.[98] oil); R_f 0.51 [petrol–EtOAc (95:5)]; ν_{max} (ATR)/cm^{-1} 3390, 3380, 3020, 2920, 2840, 1610; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.44–7.35 (4H, m, 4 × CH), 7.34–7.29 (1H, m, CH), 7.06 (2H, t, *J* = 7.0 Hz , 2 × CH), 6.68 (1H, t, *J* = 7.0 Hz, CH), 6.58 (1H, d, *J* = 8.0 Hz, CH), 4.47 (1H, dd, *J* = 9.0, 3.0 Hz, CH), 4.10 (1H, s, NH), 2.99–2.89 (1H, m, CH), 2.77 (1H, dt, *J* = 16.0, 5.0 Hz, CH), 2.19–2.12 (1H, m, CH), 2.07–1.98 (1H, m, CH); HRMS (ES) Found: MH^+, 210.1281. $C_{15}H_{16}NO$ requires MH^+, 210.1283; LRMS *m/z* (ES) 210 (100%, MH^+). Data consistent with the literature.[98,151]

Alternatively, a solution of quinoline **116a** (5.14 g, 25.1 mmol) was dissolved in MeOH (250 mL). This solution was hydrogenated at 40 °C using the H-Cube® continuous flow reactor loaded with a 10% Pd/C catalyst cartridge. This gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the 1,2,3,4-tetrahydroquinoline **117a** (0.84 g, 16%); data as above.

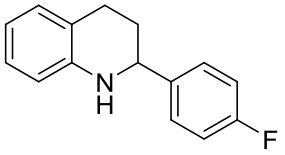
2-Phenyl-1,2,3,4-tetrahydroquinoline (phenyl-d5) (d_5**-117a)**



Using the general procedure B, quinoline d_5-**116a** (7.23 g, 34.4 mmol), acetic acid (100 mL) and sodium cyanoborohydride (4.33 g, 68.9 mmol) gave, after purification by column

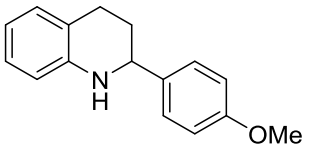
chromatography on silica gel, eluting with petrol–EtOAc (9:1), the 1,2,3,4-tetrahydroquinoline d_5-**117a** (4.67 g, 63%) as an oil; R_f 0.80 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3390 (N–H), 3050, 3015, 2920, 2840, 1605, 1585, 1480, 1310, 1270, 1250, 1110, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.13–7.05 (2H, m, 2 × CH), 6.74 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.64–6.58 (1H, m, CH), 4.51 (1H, dd, *J* = 9.5, 3.0 Hz, CH), 4.10 (1H, s, NH), 3.06–2.94 (1H, m, CH), 2.81 (1H, dt, *J* = 16.5, 5.0 Hz, CH), 2.25–2.15 (1H, m, CH), 2.14–2.00 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$, deuterated carbons could not all be observed) δ = 144.8 (C), 144.7 (C), 129.4 (CH), 128.1 (t, *J* = 24.0 Hz, CD), 127.0 (CH), 126.2 (t, *J* = 24.0 Hz, CD), 120.9 (C), 117.2 (CH), 114.0 (CH), 56.2 (CH), 31.1 (CH_2), 26.4 (CH_2); HRMS (ES) Found MH^+, 215.1595. $C_{15}H_{11}D_5N$ requires MH^+, 215.1591; LRMS *m/z* (ES) 215 (100%, MH^+).

2-(4-Fluorophenyl)-1,2,3,4-tetrahydroquinoline (117b)[98]



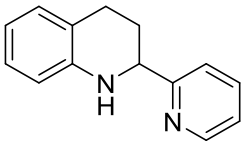
Using the general procedure B, quinoline **116b** (1.00 g, 4.48 mmol), acetic acid (15 mL) and sodium cyanoborohydride (0.60 g, 9.6 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the 1,2,3,4-tetrahydroquinoline **117b** (0.89 g, 88%) as an oil; R_f 0.45 [petrol–EtOAc (95:5)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43–7.36 (2H, m, 2 × CH), 7.11–7.02 (4H, m, 4 × CH), 6.71 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.58 (1H, d, *J* = 7.5 Hz, CH), 4.46 (1H, dd, *J* = 9.5, 3.0 Hz, CH), 4.05 (1H, s, NH), 3.02–2.91 (1H, m, CH), 2.77 (1H, dt, *J* = 16.5, 4.5 Hz, CH), 2.17–2.09 (1H, m, CH), 2.05–1.94 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.2 (d, *J* = 245.0 Hz, C), 144.6 (C), 140.5 (d, *J* = 3.0 Hz, C), 129.3 (CH), 128.1 (d, *J* = 8.5 Hz, CH), 127.0 (CH), 120.9 (C), 117.4 (CH), 115.4 (d, *J* = 21.5 Hz, CH), 114.1 (CH), 55.7 (CH), 31.1 (CH_2), 26.3 (CH_2); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 115.4; HRMS (ES) Found: MH^+, 228.1178. $C_{15}H_{15}NF$ requires MH^+, 228.1189; LRMS *m/z* (ES) 228 (100%, MH^+). Data consistent with the literature.[98]

2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroquinoline (117c)[152]



Using the general procedure B, quinoline **116c** (5.93 g, 25.2 mmol), acetic acid (100 mL) and sodium cyanoborohydride (3.17 g, 50.5 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the 1,2,3,4-tetrahydroquinoline **117c** (4.34 g, 72%) as an amorphous white solid, m.p. 65–67 °C (lit.[153] 77–80 °C); R_f 0.35 [petrol–EtOAc (95:5)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.32 (2H, m, 2 × CH), 7.08–7.01 (2H, m, 2 × CH), 6.96–6.90 (2H, m, 2 × CH), 6.69 (1H, t, *J* = 7.5 Hz, CH), 6.56 (1H, d, *J* = 8.5 Hz, CH), 4.42 (1H, dd, *J* = 9.5, 3.0 Hz, CH), 4.03 (1H, s, NH), 3.85 (3H, s, OCH_3), 3.02–2.91 (1H, m, CH), 2.78 (1H, dt, *J* = 16.5, 4.5 Hz, CH), 2.22–1.93 (2H, m, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.9 (C), 144.8 (C), 136.9 (C), 129.3 (CH), 127.7 (CH), 126.9 (CH), 120.9 (C), 117.1 (CH), 114.0 (CH), 113.9 (CH), 55.7 (CH), 55.3 (OCH_3), 31.1 (CH_2), 26.6 (CH_2); HRMS (ES) Found: MH^+, 240.1398. $C_{16}H_{18}NO$ requires MH^+, 240.1388; LRMS *m/z* (ES) 240 (100%, MH^+). Data consistent with the literature.[152]

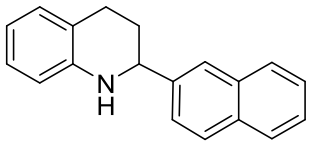
2-(Pyridin-2-yl)-1,2,3,4-tetrahydroquinoline (117d)[153,154]



Using the general procedure B, quinoline **116d** (5.90 g, 28.6 mmol), acetic acid (100 mL) and sodium cyanoborohydride (3.60 g, 57.3 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the 1,2,3,4-tetrahydroquinoline **117d** (5.10 g, 84%) as an amorphous brown solid; m.p. 59–61 °C (No melting point reported.[155,156]); R_f 0.27 [petrol–EtOAc (3:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3275 (N–H), 3100, 3015, 2975, 2960, 2920, 2845, 1610, 1590; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.61 (1H, d, *J* = 4.5 Hz, CH), 7.74–7.66 (1H, m, CH), 7.45 (1H, d, *J* = 8.0 Hz, CH), 7.25–7.18 (1H, m, CH), 7.10–6.99 (2H, m, 2 × CH), 6.73–6.62 (2H, m, 2 × CH), 4.62 (1H, dd, *J* = 9.0, 3.5 Hz, CH), 4.57 (1H, s, NH), 3.00–2.88 (1H, m, CH), 2.71 (1H, dt, *J* = 16.0, 5.5 Hz, CH), 2.34–2.24 (1H, m, CH), 2.12–2.00 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.1 (C), 149.1 (CH),

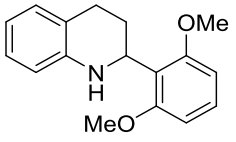
144.2 (C), 136.8 (CH), 129.3 (CH), 127.0 (CH), 122.2 (CH), 121.0 (C), 120.6 (CH), 117.2 (CH), 114.5 (CH), 56.8 (CH), 28.8 (CH_2), 26.0 (CH_2); HRMS (ES) Found: MH^+, 211.1235. $C_{14}H_{15}N_2$ requires MH^+, 211.1235; LRMS *m/z* (ES) 211 (100%, MH^+). Data consistent with literature.[153]

2-(Naphthalen-2-yl)-1,2,3,4-tetrahydroquinoline (117f)[151]



Using the general procedure B, quinoline **116f** (8.26 g, 32.4 mmol), acetic acid (300 mL) and sodium cyanoborohydride (4.07 g, 64.8 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the 1,2,3,4-tetrahydroquinoline **117f** (5.48 g, 65%) as an amorphous white solid; m.p. 79–81 °C (No melting point reported); R_f 0.65 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3365 (N–H), 3050, 3025, 2970, 2915, 2855, 1605, 1580, 1500, 1480, 1310, 1250, 1165, 1110, 860, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93–7.85 (4H, m, 4 × CH), 7.60–7.50 (3H, m, 3 × CH), 7.14–7.06 (2H, m, 2 × CH), 6.75 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.66–6.62 (1H, m, CH), 4.65 (1H, dd, *J* = 9.5, 3.0 Hz, CH), 4.18 (1H, s, NH), 3.07–2.96 (1H, m, CH), 2.82 (1H, dt, *J* = 16.5, 5.0 Hz, CH), 2.29–2.20 (1H, m, CH), 2.20–2.08 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.7 (C), 142.3 (C), 133.5 (C), 133.0 (C), 129.4 (CH), 128.4 (CH), 127.9 (CH), 127.7 (CH), 127.0 (CH), 126.2 (CH), 125.8 (CH), 125.1 (CH), 124.9 (CH), 121.0 (C), 117.3 (CH), 114.1 (CH), 56.4 (CH), 31.0 (CH_2), 26.5 (CH_2); HRMS (ES) Found MH^+, 260.1434. $C_{19}H_{18}N$ requires MH^+, 260.1434; LRMS *m/z* (ES) 260 (100%, MH^+). Data consistent with the literature.[151]

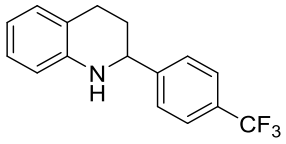
2-(2,6-Dimethoxyphenyl)-1,2,3,4-tetrahydroquinoline (117g)



Using the general procedure B, quinoline **116g** (5.37 g, 20.3 mmol), acetic acid (100 mL) and sodium cyanoborohydride (2.55 g, 40.5 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the 1,2,3,4-tetrahydroquinoline **117g** (1.50 g, 27%) as an amorphous yellow solid; m.p. 78–79 °C; R_f 0.38 [petrol–EtOAc (9:1)];

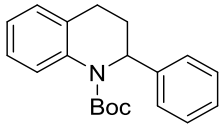
FT-IR ν_{max} (ATR)/cm^{-1} 3415 (N–H), 3000, 2965, 2930, 2840, 1590, 1470, 1310, 1245, 1100, 1035, 780, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24 (1H, t, *J* = 8.5 Hz, CH), 7.09–6.98 (2H, m, 2 × CH), 6.68 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.64–6.56 (3H, m, 3 × CH), 5.04 (1H, dd, *J* = 11.0, 3.0 Hz, CH), 3.81 (6H, s, 2 × OCH_3), 3.04–2.91 (1H, m, CH), 2.87–2.77 (1H, m, CH), 2.51–2.38 (1H, m, CH), 1.93–1.84 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.0 (C), 145.7 (C), 129.2 (CH), 128.6 (CH), 126.5 (CH), 122.8 (C), 118.8 (C), 117.1 (CH), 115.6 (CH), 104.4 (CH), 55.8 (CH_3), 48.5 (CH), 28.4 (CH_2), 25.6 (CH_2); HRMS (ES) Found MH^+, 270.1488. $C_{17}H_{20}NO_2$ requires MH^+, 270.1489; LRMS *m/z* (ES) 270 (100%, MH^+).

2-[4-(Trifluoromethyl)phenyl]-1,2,3,4-tetrahydroquinoline (117h)[151]



Using the general procedure B, quinoline **116h** (4.39 g, 16.1 mmol), acetic acid (100 mL) and sodium cyanoborohydride (2.02 g, 32.2 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the 1,2,3,4-tetrahydroquinoline **117h** (4.31 g, 96%) as an oil; R_f 0.69 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3401 (N–H), 3020, 2925, 2845, 1605, 1480, 1320, 1065, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (2H, d, *J* = 8.0 Hz, 2 × CH), 7.54 (2H, d, *J* = 8.0 Hz, 2 × CH), 7.10–7.01 (2H, m, 2 × CH), 6.71 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.60 (1H, dd, *J* = 8.0, 1.0 Hz, CH), 4.55 (1H, dd, *J* 9.0, 3.5 Hz, CH), 4.08 (1H, s, NH), 3.00–2.89 (1H, m, CH), 2.74 (1H, dt, *J* 16.5, 5.0 Hz, CH), 2.21–2.12 (1H, m, CH), 2.07–1.96 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.1 (C), 144.4 (C), 129.7 (q, *J* = 33.0 Hz, C), 129.5 (CH), 127.2 (CH), 127.0 (CH), 125.6 (q, *J* = 4.0 Hz, CH), 123.0 (C), 120.9 (C), 117.7 (CH), 114.3 (CH), 55.8 (CH), 30.9 (CH_2), 26.0 (CH_2); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 62.4; HRMS (ES) Found MH^+, 278.1144. $C_{16}H_{15}F_3N$ requires MH^+, 278.1151; LRMS *m/z* (ES) 278 (100%, MH^+). Data consistent with the literature.[151]

***tert*-Butyl 2-Phenyl-1,2,3,4-tetrahydroquinoline-1-carboxylate (118a)**[41,95]



Using the general procedure C, 1,2,3,4-tetrahydroquinoline **117a** (1.51 g, 7.2 mmol), *n*-BuLi (4.80 mL, 11.5 mmol, 2.4 M in hexanes), THF (30 mL) and Boc_2O (4.72 g, 21.6 mmol) with a reaction time of 1 h, gave, after purification by column chromatography on silica gel, eluting with petrol–Et_2O (98:2), the carbamate **118a** (1.85 g, 83%) as an amorphous white solid; m.p. 55–57 °C; R_f 0.27 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 2970, 1705 (C=O), 1490, 1325, 1150, 1010, 750, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 (1H, d, *J* = 8.0 Hz, CH), 7.32–7.24 (3H, m, 3 × CH), 7.24–7.18 (3H, m, 3 × CH), 7.10 (1H, d, *J* = 6.5 Hz, CH), 7.06–7.00 (1H, m, CH), 5.37 (1H, t, *J* = 8.0 Hz, CH), 2.74–2.59 (2H, m, 2 × CH), 2.50–2.41 (1H, m, CH), 1.91–1.80 (1H, m, CH), 1.37 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.0 (C=O), 144.5 (C), 138.2 (C), 132.5 (C), 128.3 (CH), 127.5 (CH), 126.5 (CH), 126.3 (CH), 125.8 (CH), 124.7 (CH), 123.4 (CH), 80.9 (C), 58.7 (CH), 33.5 (CH_2), 28.2 (CH_3), 26.3 (CH_2); HRMS (ES) Found: MH^+, 310.1815. $C_{20}H_{24}NO_2$ requires MH^+, 310.1807; LRMS *m*/*z* (ES) 310 (20%, MH^+), 295 (100), 254 (90, MH^+–*t*-Bu+H).

Resolution between the enantiomers of the carbamate **118a** 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 (99:1 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 faster running component and slower running component were eluted at 5.3 min and 6.2 min respectively with an analysis time of 10 min.

Using the general procedure E, *n*-BuLi (0.16 mL, 0.39 mmol, 2.45 M in hexanes), (+)-sparteine (100 mg, 0.43 mmol), toluene (4 mL), carbamate **118a** (101 mg, 0.33 mmol) and methyl chloroformate (0.09 mL, 1.15 mmol) with a reaction time of 2.5 h, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), recovered carbamate (*S*)-**118a** (46 mg, 45%) as an amorphous yellow solid; m.p. 51–54 °C; data as above; the enantiomeric ratio was determined to be 92:8 by CSP-HPLC (Cellulose-2, major component eluted at 6.6 min); $[\alpha]_D^{25}$ –85.5 (0.8, $CHCl_3$), the carbamate (*R*)-**119b** (51 mg, 42%) was also

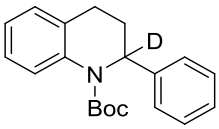
isolated; m.p. 71–74 °C; data as below; the enantiomeric ratio was determined to be 93:7 by CSP-HPLC (major component eluted at 22.5 min); $[\alpha]_D^{25}$ +76.6 (0.9, $CHCl_3$).

Also using the general procedure E, *n*-BuLi (0.16 mL, 0.39 mmol, 2.5 M in hexanes), (+)-sparteine (106 mg, 0.45 mmol), toluene (4 mL), carbamate **118a** (101 mg, 0.33 mmol) and methyl chloroformate (0.09 mL, 1.14 mmol) with a reaction time of 2.5 h, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), recovered carbamate (*S*)-**118a** (44 mg, 43%); data as above; the enantiomeric ratio was determined to be 98:2 by CSP-HPLC (major component eluted at 6.1 min); $[\alpha]_D^{23}$ –103.9 (0.6, $CHCl_3$), the carbamate (*R*)-**119b** (65 mg, 54%) was also isolated; data as below; the enantiomeric ratio was determined to be 82:18 by CSP-HPLC (major component eluted at 23.1 min); $[\alpha]_D^{24}$ +67.5 (1.0, $CHCl_3$).

Also using the general procedure E, *n*-BuLi (0.18 mL, 0.42 mmol, 2.4 M in hexanes), (–)-sparteine (108 mg, 0.46 mmol), toluene (5 mL), carbamate **118a** (110 mg, 0.35 mmol) and methyl chloroformate (0.10 mL, 1.24 mmol) with a reaction time of 2.5 h, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), recovered carbamate (*R*)-**118a** (44 mg, 43%); data as above; the enantiomeric ratio was determined to be 92:8 by CSP-HPLC (major component eluted at 5.2 min); $[\alpha]_D$ not obtained; the carbamate (*S*)-**119b** (52 mg, 40%) was also isolated; data as below; the enantiomeric ratio was determined to be 87:13 by CSP-HPLC (major component eluted at 12.5 min); $[\alpha]_D^{24}$ –75.2 (0.9, $CHCl_3$).

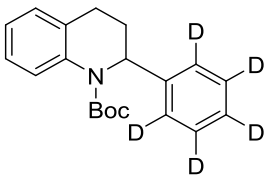
(+)-sparteine (106 mg, 0.45 mmol) and the carbamate **118a** (108 mg, 0.35 mmol) were dissolved in toluene (8 mL). The reaction mixture was cooled to –78 °C and *n*-BuLi (0.17 mL, 0.42 mmol, 2.5 M in hexanes) was added. The reaction mixture was left to stir for 2.5 h and ethyl chloroformate (0.12 mL, 1.22 mmol) was added to give, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the recovered carbamate (*S*)-**118a** (49 mg, 45%); data as above; the enantiomeric ratio was determined to be 90:10 by CSP-HPLC (major component eluted at 6.0 min); $[\alpha]_D$ not obtained; the carbamate (*R*)-**119c** (53 mg, 40%) was also isolated; data as below; the enantiomeric ratio was determined to be 90:10 by CSP-HPLC (major component eluted at 9.4 min); $[\alpha]_D^{24}$ +67.5 (1.0, $CHCl_3$).

***tert*-Butyl 2-Phenyl-1,2,3,4-tetrahydro(2-^{2}H)quinoline-1-carboxylate (d$_1$-118a)**



Using the general procedure D with a reaction time of 6 min, *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **118a** (53 mg, 0.17 mmol), *n*-BuLi (0.09 mL, 0.21 mmol, 2.4 M in hexanes) and deuterium oxide (0.3 mL) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate d$_1$-**118a** (41 mg, 76%, ~95% D) as a white amorphous solid; m.p. 56–58 °C; R_f 0.33 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3060, 3025, 2975, 2930, 1695 (C=O), 1605, 1320, 1145; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 (1H, d, *J* = 8.0 Hz, CH), 7.33–7.19 (6H, m, 6 × CH), 7.11 (1H, d, *J* = 6.5 Hz, CH), 7.05 (1H, td, *J* = 7.5, 1.0 Hz, CH), 5.38 (0.05H for compound **118a**, t, *J* = 8.0 Hz, CH), 2.75–2.59 (2H, m, 2 × CH), 2.50–2.41 (1H, m, CH), 1.91–1.81 (1H, m, CH), 1.38 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.0 (C=O), 144.5 (C), 138.2 (C), 132.5 (C), 128.3 (CH), 127.5 (CH), 126.5 (CH), 126.3 (CH), 125.8 (CH), 124.7 (CH), 123.4 (CH), 80.9 (C), 58.3 (t, *J* = 23.5 Hz, CD), 33.4 (CH_2), 28.2 (CH_3), 26.3 (CH_2); HRMS (ES) Found: MNa$^+$, 333.1699. $C_{20}H_{22}DNO_2Na$ requires MNa$^+$, 333.1689; LRMS *m*/*z* (ES) 333 (100%, MNa$^+$), 277 (40, MNa$^+$–*t*-Bu+H), 233 (30, MNa$^+$–Boc+H).

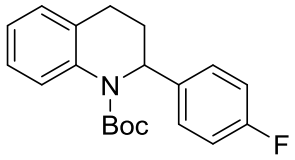
***tert*-Butyl 2-Phenyl-1,2,3,4-tetrahydroquinoline-1-carboxylate (phenyl-d5) (d$_5$-118a)**



Using the general procedure C, 1,2,3,4-tetrahydroquinoline d$_5$-**117a** (0.50 g, 2.35 mmol), *n*-BuLi (1.57 mL, 3.77 mmol, 2.4 M in hexanes), THF (10 mL) and Boc_2O (0.61 g, 2.82 mmol) with a reaction time of 40 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the carbamate d$_5$-**118a** (0.56 g, 76%) as an amorphous white solid; m.p. 57–58 °C; R_f 0.59 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3025, 3000, 2985, 2970, 2845, 1700 (C=O), 1490, 1350, 1320, 1240, 1150, 1130, 1010, 770, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (1H, d, *J* = 8.0 Hz, CH), 7.32–7.21 (1H, m, CH), 7.15–7.09 (1H, m, CH), 7.05 (1H, td, *J* = 7.5, 1.0 Hz, CH), 5.44–5.37 (1H, m, CH), 2.76–2.60 (2H, m, 2 ×

CH), 2.52–2.42 (1H, m, CH), 1.93–1.82 (1H, m, CH), 1.40 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, deuterated carbons could not all be observed) δ = 154.1 (C=O), 144.4 (C), 138.2 (C), 132.5 (C), 127.8 (t, *J* = 24.0 Hz, CD), 127.5 (CH), 126.3 (CH), 125.4 (t, *J* = 24.0 Hz, CD), 124.7 (CH), 123.4 (CH), 80.9 (C), 58.6 (CH), 33.5 (CH_2), 28.2 (CH_3), 26.3 (CH_2); HRMS (ES) Found: MNa^+, 337.1935. $C_{20}H_{18}D_5NO_2Na$ requires MNa^+, 337.1935; LRMS *m/z* (ES) 337 (5%, MNa^+), 259 (100, MH^+-*t*-Bu+H).

tert-Butyl 2-(4-Fluorophenyl)-1,2,3,4-tetrahydroquinoline-1-carboxylate (118b)



Using the general procedure C, 1,2,3,4-tetrahydroquinoline **117b** (0.90 g, 3.96 mmol), *n*-BuLi (2.64 mL, 6.34 mmol, 2.4 M in hexanes), THF (15 mL) and Boc_2O (2.59 g, 11.9 mmol) with a reaction time of 1 h, gave, after purification by column chromatography on silica gel, eluting with petrol–Et_2O (95:5), the carbamate **118b** (1.06 g, 82%) as an amorphous white solid; m.p. 79–80 °C; R_f 0.36 [petrol–Et_2O (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3075, 3040, 3005, 2975, 2930, 1700 (C=O), 1510, 1485, 1320, 1155; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 (1H, d, *J* = 7.5 Hz, CH), 7.30 (1H, t, *J* = 7.5 Hz, CH), 7.27–7.19 (2H, m, 2 × CH), 7.17–7.11 (1H, m, CH), 7.10–7.04 (1H, m, CH), 7.04–6.93 (2H, m, 2 × CH), 5.42 (1H, t, *J* = 7.5 Hz, CH), 2.77–2.58 (2H, m, 2 × CH), 2.52–2.40 (1H, m, CH), 1.91–1.77 (1H, m, CH), 1.45 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.6 (d, *J* = 244.0 Hz, C), 154.0 (C=O), 140.4 (d, *J* = 2.5 Hz, C), 138.0 (C), 132.4 (C), 127.6 (CH), 127.4 (d, *J* = 8.0 Hz, CH), 126.4 (CH), 124.8 (CH), 123.6 (CH), 115.2 (d, *J* = 21.5 Hz, CH), 81.0 (C), 58.1 (CH), 33.6 (CH_2), 28.2 (CH_3), 26.2 (CH_2); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 116.6; HRMS (ES) Found: MH^+, 328.1713. $C_{20}H_{23}NO_2F$ requires MH^+, 328.1713; LRMS *m/z* (ES) 328 (5%, MH^+), 313 (90, MH^+–CH_3), 272 (100, MH^+–*t*-Bu+H); Found: C, 73.62; H, 6.99; N, 4.11. $C_{20}H_{22}FNO_2$ requires C, 73.37; H, 6.77; N, 4.28.

7

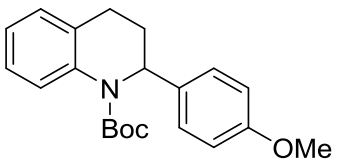
Resolution between the enantiomers of the carbamate **118b** was achieved using a Beckman system fitted with a Lux Cellulose-2 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was

20 μL of the sample prepared in a 2 $g \cdot L^{-1}$ solution of the eluent. Under these conditions, the faster running component and slower running component were eluted at 4.8 min and 5.8 min respectively with an analysis time of 10 min.

Using the general procedure E, *n*-BuLi (0.13 mL, 0.32 mmol, 2.4 M in hexanes), (+)-sparteine (129 mg, 0.55 mmol), toluene (4 mL), carbamate **118b** (105 mg, 0.32 mmol) and methyl chloroformate (0.09 mL, 1.03 mmol) with a reaction time of 1.5 h, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), recovered carbamate (*S*)-**118b** (47 mg, 45%) as an amorphous yellow solid; m.p. 52–54 °C; data as above; the enantiomeric ratio was determined to be 89:11 by CSP-HPLC (major component eluted at 6.2 min); $[\alpha]_D^{25}$ –71.7 (0.6, $CHCl_3$), the carbamate (*R*)-**136a** (53 mg, 43%) was also isolated; m.p. 38–40 °C; data as below; the enantiomeric ratio was determined to be 93:7 by CSP-HPLC (ChiralPak IA, major component eluted at 17.5 min), $[\alpha]_D^{23}$ +79.9 (0.7, $CHCl_3$).

Also, using the general procedure E, *n*-BuLi (0.13 mL, 0.32 mmol, 2.5 M in hexanes), (+)-sparteine (133 mg, 0.57 mmol), toluene (4 mL), carbamate **118b** (106 mg, 0.32 mmol) and methyl chloroformate (0.09 mL, 1.13 mmol) with a reaction time of 1.5 h, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), recovered carbamate (*S*)-**118b** (39 mg, 36%) as an amorphous yellow solid; data as above; the enantiomeric ratio was determined to be 94:6 by CSP-HPLC (major component eluted at 6.2 min); $[\alpha]_D^{24}$ –77.7 (0.1, $CHCl_3$), the carbamate (*R*)-**136a** (53 mg, 42%) was also isolated; data as below; the enantiomeric ratio was determined to be 85:15 by CSP-HPLC (ChiralPak IA, major component eluted at 18.0 min), $[\alpha]_D^{23}$ +59.8 (2.1, $CHCl_3$).

***tert*-Butyl 2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroquinoline-1-carboxylate (118c)**

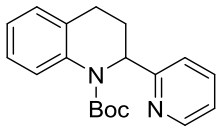


Using the general procedure C, 1,2,3,4-tetrahydroquinoline **117c** (1.04 g, 4.37 mmol), *n*-BuLi (2.91 mL, 6.99 mmol, 2.4 M in hexanes), THF (20 mL) and Boc_2O (1.62 g, 7.43 mmol) with a reaction time of 40 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (99.5:0.5), the carbamate **118c** (1.06 g, 72%) as an amorphous white solid; m.p. 74–77 °C; R_f 0.44 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3060, 3010, 2960,

2940, 2930, 2890, 2840, 1695 (C=O), 1510, 1490, 1320, 1245, 1230, 1140, 1010, 825, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 (1H, d, *J* = 8.0 Hz, CH), 7.27–7.21 (1H, m, CH), 7.16–7.07 (3H, m, 3 × CH), 7.03 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.86–6.79 (2H, m, 2 × CH), 5.39–5.32 (1H, m, CH), 3.79 (3H, s, OCH_3), 2.73–2.58 (2H, m, 2 × CH), 2.48–2.37 (1H, m, CH), 1.90–1.80 (1H, m, CH), 1.39 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.2 (C), 154.1 (C=O), 138.1 (C), 136.5 (C), 132.5 (C), 127.5 (CH), 127.0 (CH), 126.4 (CH), 124.8 (CH), 123.4 (CH), 113.7 (CH), 81.0 (C), 57.9 (CH), 53.2 (OCH_3), 33.4 (CH_2), 28.2 (CH_3), 26.2 (CH_2); HRMS (ES) Found: MNa^+, 362.1713. $C_{21}H_{25}NO_3Na$ requires MNa^+, 362.1732; LRMS *m/z* (ES) 378 (100%, MK^+), 362 (50, MNa^+).

Resolution between the enantiomers of the carbamate **118c** 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 (99:1 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 6.6 min and 11.2 min respectively with an analysis time of 15 min.

tert-Butyl 2-(Pyridin-2-yl)-1,2,3,4-tetrahydroquinoline-1-carboxylate (118d)

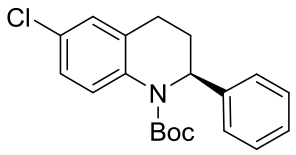


Using the general procedure C, 1,2,3,4-tetrahydroquinoline **117d** (2.02 g, 9.65 mmol), *n*-BuLi (6.44 mL, 15.45 mmol, 2.4 M in hexanes), THF (30 mL) and Boc_2O (4.21 g, 19.31 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the carbamate **118d** (2.82 g, 94%) as an amorphous white solid; m.p. 85–88 °C; R_f 0.41 [petrol–EtOAc (3:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3080, 3070, 3005, 2985, 2970, 2945, 2935, 2845, 1700 (C=O), 1590, 1490, 1365, 1325, 1155, 1145, 765, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.54 (1H, d, *J* = 4.5 Hz, CH), 7.88 (1H, d, *J* = 8.0 Hz, CH), 7.60 (1H, t, *J* = 8.0 Hz, CH), 7.27–7.17 (2H, m, 2 × CH), 7.17–7.11 (1H, m, CH), 7.09 (1H, d, *J* = 7.5 Hz, CH), 7.02 (1H, t, *J* = 7.5 Hz, CH), 5.50 (1H, t, *J* = 7.5 Hz, CH), 2.78–2.56 (2H, m, 2 × CH), 2.56–2.44 (1H, m, CH),

2.13–2.00 (1H, m, CH), 1.37 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.1 (C), 154.0 (C=O), 148.9 (CH), 137.7 (C), 136.6 (CH), 131.7 (C), 127.8 (CH), 126.3 (CH), 124.4 (CH), 123.4 (CH), 121.5 (CH), 119.7 (CH), 81.1 (C), 60.1 (CH), 30.8 (CH_2), 28.1 (CH_3), 25.9 (CH_2); HRMS (ES) Found: MH^+, 311.1758. $C_{19}H_{23}N_2O_2$ requires MH^+, 311.1760; LRMS *m/z* (ES) 311 (100%, MH^+), 255 (5, MH^+–*t*-Bu+H), 211 (5, MH^+–Boc+H).

Resolution between the enantiomers of the carbamate **118d** 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 (99.7:0.3 v/v) as the mobile phase at a flow rate of 1.65 $mL \cdot min^{-1}$; 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 33.6 min and 37.7 min respectively with an analysis time of 60 min.

***(S)-tert*-Butyl 6-Chloro-2-phenyl-1,2,3,4-tetrahydroquinoline-1-carboxylate (118e)**[99]

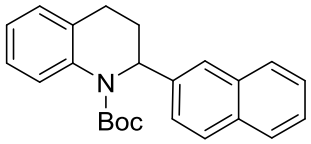


Using the general procedure E, carbamate **118e** (101 mg, 0.29 mmol), *n*-BuLi (0.12 mL, 0.29 mmol, 2.4 M in hexanes), (+)-sparteine (119 mg, 0.51 mmol) and methyl chloroformate (0.08 mL, 1.03 mmol) with a reaction time of 75 mins, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), recovered carbamate (*S*)-**118e** (0.04 g, 41%) as an off-white sticky solid; R_f 0.55 [petrol–Et_2O (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3025, 3005, 2975, 2955, 1705 (C=O), 1490, 1325, 1155, 1135, 755, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (1H, d, *J* = 9.0 Hz, CH), 7.33–7.26 (2H, m, 2 × CH), 7.25–7.15 (4H, m, 4 × CH), 7.09 (1H, d, *J* = 2.5 Hz, CH), 5.38 (1H, t, *J* = 7.0 Hz, CH), 2.70–2.57 (2H, m, 2 × CH), 2.46–2.38 (1H, m, CH), 1.92–1.83 (1H, m, CH), 1.36 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.0 (C=O), 143.9 (C), 136.8 (C), 133.8 (C), 128.4 (CH), 128.3 (C), 127.4 (CH), 126.7 (CH), 126.3 (CH), 125.8 (CH), 125.7 (CH), 81.3 (C), 58.4 (CH), 32.8 (CH_2), 28.1 (CH_3), 26.0 (CH_2); HRMS (ES) Found MNa^+, 366.1233. $C_{20}H_{22}{}^{35}ClNaNO_2$ requires MNa^+, 366.1231; Found MNa^+, 368.1207. $C_{20}H_{22}{}^{37}ClNaNO_2$ requires MNa^+, 368.1209; LRMS *m/z* (ES) 368

(<5%, MNa^+), 366 (5, MNa^+) 290 (30, MH^+–*t*-Bu), 288 (100, MH^+–*t*-Bu); the enantiomeric ratio was determined to be 92:8 by CSP-HPLC (major component eluted at 5.4 min); $[\alpha]_D^{23}$ – 98.9 (0.1, $CHCl_3$). The carbamate (*R*)-**143b** (54 mg, 42%) was also isolated; data as below.

Resolution between the enantiomers of the THQ **118e** 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 (99:1 v/v) as the mobile phase at a flow rate of 1 $mL \cdot min^{-1}$; ambient temperature and detection by UV absorbance at 254 nm. Under these conditions, the faster running component and slower running component were eluted at 4.6 min and 5.6 min respectively with an analysis time of 10 min.

***tert*-Butyl 2-(Naphthalen-2-yl)-1,2,3,4-tetrahydroquinoline-1-carboxylate (118f)**



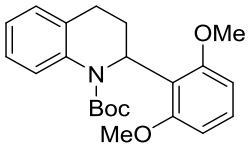
Using the general procedure C, 1,2,3,4-tetrahydroquinoline **117f** (1.02 g, 3.92 mmol), *n*-BuLi (2.73 mL, 6.27 mmol, 2.3 M in hexanes), THF (20 mL) and Boc_2O (1.45 g, 6.66 mmol) with a reaction time of 20 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the carbamate **118f** (0.92 g, 65%) as an amorphous white solid; m.p. 93–94 °C; R_f 0.49 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3055, 3005, 2975, 2930, 2870, 2845, 1695 (C=O), 1490, 1320, 1250, 1155, 1010, 815, 750; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.90 (1H, d, *J* = 8.0 Hz, CH), 7.85–7.74 (3H, m, 3 × CH), 7.68 (1H, s, CH), 7.51–7.42 (2H, m, 2 × CH), 7.35 (1H, dd, *J* = 8.5, 2.0 Hz, CH), 7.33–7.28 (1H, m, CH), 7.13 (1H, m, CH), 7.13 (1H, dd, *J* = 7.5, 1.0 Hz, CH), 7.07 (1H, td, *J* = 7.5, 1.0 Hz, CH), 5.59–5.52 (1H, m, CH), 2.80–2.62 (2H, m, 2 × CH), 2.58–2.46 (1H, m, CH), 2.03–1.90 (1H, m, CH), 1.36 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.1 (C=O), 141.9 (C), 138.2 (C), 133.3 (C), 132.5 (C), 132.4 (C), 128.2 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 126.4 (CH), 126.0 (CH), 125.5 (CH), 124.8 (CH), 124.4 (CH), 124.3 (CH), 123.5 (CH), 81.0 (C), 58.8 (CH), 33.5 (CH_2), 28.2 (CH_3), 26.4 (CH_2); HRMS (ES) Found: MNa^+, 382.1785. $C_{24}H_{25}NO_2Na$ requires MNa^+, 382.1778; LRMS *m/z* (ES) 382 (25%, MNa^+), 304 (90, MH^+-*t*-Bu+H), 176 (100).

Resolution between the enantiomers of the carbamate **118f** 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 (99:1 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 5.8 min and 8.8 min respectively with an analysis time of 15 min.

Using the general procedure E, *n*-BuLi (0.09 mL, 0.23 mmol, 2.5 M in hexanes), (+)-sparteine (0.09 g, 0.37 mmol), toluene (4 mL), carbamate **118f** (0.1 g, 0.29 mmol) and methyl chloroformate (0.08 mL, 1.00 mmol) with a reaction time of 1.5 h, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), recovered carbamate (*S*)-**118f** (0.04 g, 39%) as a sticky white solid; data as above; the enantiomeric ratio was determined to be 95:5 by CSP-HPLC (major component eluted at 9.1 min); $[\alpha]_D^{20}$ –61.8 (0.1, $CHCl_3$). The carbamate (*R*)-**138b** (0.02 g, 14%) was also isolated as a sticky white solid; data as below and the mixture of carbamates **139** and **140** (0.06 g, 49%) was also isolated as an amorphous white solid; data as below. For carbamate (*R*)-**138b**, the enantiomeric ratio was determined to be 78:22 by CSP-HPLC (major component eluted at 13.1 min); $[\alpha]_D^{24}$ +30.5 (0.6, $CHCl_3$).

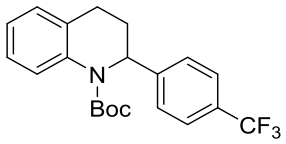
***tert*-Butyl 2-(2,6-Dimethoxyphenyl)-1,2,3,4-tetrahydroquinoline-1-carboxylate (118g)**



Using the general procedure C, 1,2,3,4-tetrahydroquinoline **117g** (0.50 g, 1.87 mmol), *n*-BuLi (1.30 mL, 3.00 mmol, 2.3 M in hexanes), THF (20 mL) and Boc_2O (0.70 g, 3.18 mmol) with a reaction time of 40 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the carbamate **118g** (0.69 g, 99%) as an amorphous white solid; m.p. 89–91 °C; R_f 0.41 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3065, 3030, 2955, 2935, 2840, 1695 (C=O), 1595, 1475, 1330, 1245, 1160, 1105, 1005, 770, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 (1H, d, *J* = 7.5 Hz, CH), 7.27–7.20 (1H, m, CH), 7.16 (1H, t, *J* = 8.5 Hz, CH), 7.12–7.06 (1H, m, CH), 7.01 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.51 (2H, d, *J* = 8.5 Hz, 2 × CH), 5.66 (1H, dd, *J* = 12.0, 7.5 Hz, CH), 3.66 (6H, s, 2 × OCH_3) 2.74–2.58 (2H, m, 2 × CH), 2.35–2.26 (1H, m, CH), 1.71 (1H, qd, *J* = 12.0, 4.0 Hz, CH), 1.30 (9H, s, *t*-Bu); ^{13}C NMR

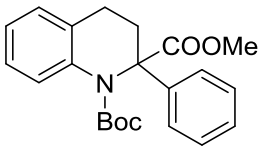
(100 MHz, $CDCl_3$) δ = 157.7 (C), 154.3 (C=O), 140.0 (C), 133.8 (C), 127.5 (CH), 126.5 (CH), 125.6 (CH), 125.5 (CH), 122.7 (CH), 120.2 (C), 103.5 (CH), 79.8 (C), 55.2 (CH_3), 52.1 (CH), 30.8 (CH_2), 28.4 (CH_2), 28.2 (CH_3); HRMS (ES) Found: MH^+, 370.2013. $C_{22}H_{28}NO_4$ requires MH^+, 370.2013; LRMS *m/z* (ES) 392 (20%, MNa^+), 370 (20%, MH^+), 270 (100, MH^+-Boc+H), 176 (40), 132 (95).

***tert*-Butyl 2-[4-(Trifluoromethyl)phenyl]-1,2,3,4-tetrahydroquinoline-1-carboxylate (118h)**



Using the general procedure C, 1,2,3,4-tetrahydroquinoline **117h** (1.37 g, 4.93 mmol), *n*-BuLi (3.29 mL, 7.90 mmol, 2.4 M in hexanes), THF (20 mL) and Boc_2O (2.36 g, 10.81 mmol) with a reaction time of 20 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the carbamate **118h** (1.30 g, 70%) as an amorphous white solid; m.p. 113–115 °C; R_f 0.60 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3040, 3010, 2975, 2935, 2900, 2875, 2850, 1680 (C=O), 1490, 1335, 1320, 1255, 1155, 1010, 840, 760; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.79 (1H, d, *J* = 8.0 Hz, CH), 7.55 (2H, d, *J* = 8.0 Hz, 2 × CH), 7.34 (2H, d, *J* = 8.0 Hz, 2 × CH), 7.30–7.23 (1H, m, CH), 7.14–7.09 (1H, m, CH), 7.09–7.03 (1H, m, CH), 5.42 (1H, t, *J* = 8.5 Hz, CH), 2.77–2.67 (1H, m, CH), 2.67–2.58 (1H, m, CH), 2.54–2.43 (1H, m, CH), 1.87–1.75 (1H, m, CH), 1.38 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.9 (C=O), 148.7 (C), 137.8 (C), 132.4 (C), 128.9 (q, *J* = 32.0 Hz, C), 127.5 (CH), 126.5 (CH), 126.0 (CH), 125.4 (q, *J* = 4.0 Hz, CH), 124.8 (CH), 123.7 (CH), 122.8 (C), 81.3 (C), 58.4 (CH), 33.5 (CH_2), 28.2 (CH_3), 26.3 (CH_2); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 62.4; HRMS (ES) Found: MNa^+, 400.1488. $C_{21}H_{22}NO_2F_3Na$ requires MNa^+, 400.1495; LRMS *m/z* (ES) 400 (<5%, MNa^+), 322 (100%, MH^+-*t*-Bu+H).

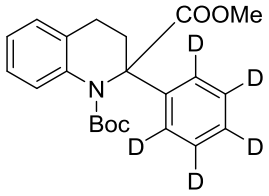
***tert*-Butyl 2-Methyl 2-Phenyl-1,2,3,4-tetrahydroquinoline-1,2-dicarboxylate (119b)**[41]



t-BuOK (0.38 mL, 0.38 mmol, 1.0 M in THF) was added to *n*-BuLi (0.15 mL, 0.38 mmol, 2.5 M in hexanes) in THF (2 mL) and left to stir for 15 min at –78 °C. *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **118a** (99 mg, 0.32 mmol) in THF (2 mL) was added and the reaction mixture was left to stir for 6 min. Methyl chloroformate (0.09 mL, 1.12 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 (97:3) to give the compound **119b** (25 mg, 21%) as an amorphous white solid; m.p. 104–106 °C; R_f 0.12 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3030, 2975, 2945, 2930, 1750 (C=O), 1700 (C=O), 1490, 1325, 1160, 1140, 755, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 (1H, d, *J* = 8.0 Hz, CH), 7.65–7.59 (2H, m, 2 × CH), 7.36–7.30 (2H, m, 2 × CH), 7.28–7.21 (2H, m, 2 × CH), 7.09–7.04 (1H, m, CH), 7.01 (1H, td, *J* = 7.5, 1.0 Hz, CH), 3.80 (3H, s, CH_3), 2.88–2.79 (1H, m, CH), 2.60–2.53 (1H, m, CH), 2.52–2.44 (1H, m, CH), 2.21–2.12 (1H, m, CH), 1.31 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.5 (C=O), 153.8 (C=O), 142.3 (C), 137.7 (C), 131.7 (C), 127.7 (CH), 127.6 (CH), 126.8 (CH), 126.7 (CH), 126.5 (CH), 124.4 (CH), 123.4 (CH), 82.1 (C), 68.7 (C), 52.4 (CH_3), 39.4 (CH_2), 27.9 (CH_3), 25.2 (CH_2); HRMS (ES) Found: MH^+, 368.1865. $C_{22}H_{26}NO_4$ requires MH^+, 368.1862; LRMS *m*/*z* (ES) 368 (20%, MH^+), 312 (20), 268 (100, MH^+–Boc+H); Found: C, 72.02; H, 6.74; N, 3.66. $C_{22}H_{25}NO_4$ requires C, 71.91; H, 6.86; N, 3.81. The carbamate **134** (29 mg, 24%) was also obtained; data as below.

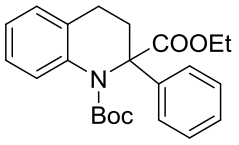
Resolution between the enantiomers of the tetrahydroquinoline **119b** was achieved using a Beckman system fitted with a Daicel Chiralpak IA column (250 mm × 460 mm i.d.) as the stationary phase with a mixture of *n*-hexane–isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient 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 faster running component and slower running component were eluted at 12.3 min and 17.9 min respectively with an analysis time of 30 min.

***tert*-Butyl 2-Methyl 2-Phenyl-1,2,3,4-tetrahydroquinoline-1,2-dicarboxylate (phenyl-d5) (d$_5$-119b)**



Using the general procedure D with a reaction time of 6 min, carbamate d$_5$-**118a** (102 mg, 0.33 mmol), *n*-BuLi (0.17 mL, 0.39 mmol, 2.3 M in hexanes) and methyl chloroformate (0.09 mL, 1.14 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate d$_5$-**119b** (98 mg, 81%) as an amorphous yellow solid; m.p. 107–108 °C; R_f 0.38 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3020, 3005, 2975, 2955, 2890, 2835, 1735 (C=O), 1690 (C=O), 1430, 1315, 1240, 1120, 1005, 790, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 (1H, d, *J* = 8.0 Hz, CH), 7.33–7.24 (1H, m, CH), 7.13–6.99 (2H, m, 2 × CH), 3.82 (3H, s, OCH_3), 2.93–2.77 (1H, m, CH), 2.66–2.44 (2H, m, 2 × CH), 2.26–2.12 (1H, m, CH), 1.33 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, deuterated carbons could not be observed) δ = 173.5 (C=O), 153.8 (C=O), 142.2 (C), 137.8 (C), 131.6 (C), 127.6 (CH), 126.5 (CH), 124.3 (CH), 123.4 (CH), 82.1 (C), 68.7 (C), 52.4 (CH_3), 39.5 (CH_2), 27.9 (CH_3), 25.2 (CH_2); HRMS (ES) Found: MNa^+, 395.1993. $C_{22}H_{20}D_5NO_4Na$ requires MNa^+, 395.1990; LRMS *m*/*z* (ES) 395 (10%, MNa^+), 273 (100, MH^+-Boc+H).

***tert*-Butyl 2-Ethyl 2-Phenyl-1,2,3,4-tetrahydroquinoline-1,2-dicarboxylate (119c)**[41]

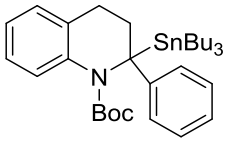


Using the general procedure D with a reaction time of 6 min, *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **118a** (81 mg, 0.32 mmol), *n*-BuLi (0.13 mL, 0.32 mmol, 2.4 M in hexanes) and ethyl chloroformate (0.09 mL, 0.92 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **119c** (64 mg, 64%) as an oil; R_f 0.25 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 2975, 2920, 2850, 1740 (C=O), 1710 (C=O), 1490, 1325, 1155, 1140, 1015, 755, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 (1H, d, *J* = 8.0 Hz, CH), 7.64–7.59 (2H, m, 2 × CH), 7.35–7.21 (4H, m, 4 × CH), 7.10–

6.99 (2H, m, 2 × CH), 4.34–4.19 (2H, m, CH_2), 2.90–2.81 (1H, m, CH), 2.61–2.53 (1H, m, CH), 2.53–2.44 (1H, m, CH), 2.20–2.12 (1H, m, CH), 1.32 (9H, s, *t*-Bu), 1.32 (3H, t, *J* = 7.0 Hz, CH_3, partially merged with *t*-Bu peak); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.8 (C=O), 153.8 (C=O), 142.4 (C), 137.8 (C), 131.9 (C), 127.7 (CH), 127.5 (CH), 126.8 (CH), 126.4 (CH), 124.4 (CH), 123.4 (CH), 82.0 (C), 68.6 (C), 61.5 (CH_2), 39.6 (CH_2), 27.9 (CH_3), 25.2 (CH_2), 14.2 (CH_3); HRMS (ES) Found: MH^+, 382.2001. $C_{23}H_{28}NO_4$ requires MH^+, 382.2018. LRMS *m*/*z* (ES) 382 (35%, MH^+), 282 (100).

Resolution between the enantiomers of the tetrahydroquinoline **119c** 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 (99.5:0.5 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 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 11.7 min and 12.8 min respectively with an analysis time of 30 min.

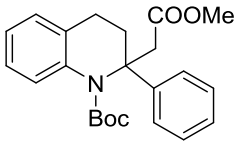
tert-Butyl 2-Phenyl-2-(tributylstannyl)-1,2,3,4-tetrahydroquinoline-1-carboxylate (119g)[41]



Using the general procedure D with a reaction time of 6 min, *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **118a** (101 mg, 0.33 mmol), *n*-BuLi (0.16 mL, 0.39 mmol, 2.4 M in hexane) and *n*-Bu_3SnCl (0.31 mL, 1.15 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the carbamate **119g** (141 mg, 72%) as an amorphous white solid; m.p. 52–54 °C; R_f 0.75 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 2955, 2920, 2870, 1670 (C=O), 1490, 1355, 1160, 1135, 1020, 1010, 755, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40–7.35 (1H, m, CH), 7.20–7.14 (2H, m, 2 × CH), 7.09–7.01 (3H, m, 3 × CH), 6.99–6.92 (2H, m, 2 × CH), 6.92–6.86 (1H, m, CH), 2.85–2.74 (1H, m, CH), 2.70–2.51 (3H, m, 3 × CH), 1.54 (9H, s, *t*-Bu), 1.47–1.33 (6H, m, 3 × CH_2), 1.33–1.20 (6H, m, 3 × CH_2), 0.87 (9H, t, *J* = 7.0 Hz, 3 × CH_3), 0.82–0.69 (6H, m, 3 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.1 (C=O), 146.3 (C), 139.0 (C), 131.7 (C), 128.1 (CH), 127.9 (CH), 126.5 (CH), 124.9

(CH), 124.6 (CH), 123.8 (CH), 123.4 (CH), 81.2 (C), 60.5 (C), 33.4 (CH_2), 29.1 (CH_2), 28.4 (CH_3), 27.7 (CH_2), 25.2 (CH_2), 13.7 (CH_3), 13.4 (CH_2); HRMS (ES) Found: MNa^+, 622.2706. $C_{32}H_{49}NO_2Na^{120}Sn$ requires MNa^+, 622.2683; LRMS *m*/*z* (ES) 622 (100%, MNa^+), 486 (25), 412 (90).

***tert*-Butyl 2-(2-Methoxy-2-oxoethyl)-2-phenyl-1,2,3,4-tetrahydroquinoline-1-carboxylate (119l)**

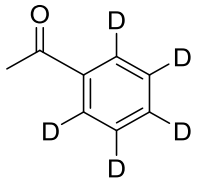


Using the general procedure D with a reaction time of 6 min, *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **118a** (97 mg, 0.31 mmol), *n*-BuLi (0.16 mL, 0.38 mmol, 2.4 M in hexanes) and methyl bromoacetate (0.1 mL, 1.10 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the carbamate **119l** (76 mg, 63%) as an amorphous white solid; m.p. 93–95 °C; R_f 0.37 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3060, 3030, 3000, 2950, 2920, 1735 (C=O), 1700 (C=O), 1490, 1315, 1155, 1130, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61–7.56 (1H, m, CH), 7.40–7.25 (5H, m, 5 × CH), 7.23–7.16 (1H, m, CH) , 7.09–7.03 (1H, m, CH), 6.98 (1H, td, *J* = 7.5, 1.0 Hz, CH), 3.83 (1H, d, *J* = 12.5 Hz, CH), 3.56 (3H, s, OCH_3), 3.23 (1H, d, *J* = 12.5 Hz, CH), 2.83–2.72 (1H, m, CH), 2.62 (1H, td, *J* = 13.0, 3.0 Hz, CH), 2.31 (1H, dt, *J* = 15.0, 3.0 Hz, CH), 2.00 (1H, dt, *J* = 13.0, 3.0 Hz, CH), 1.21 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.9 (C=O), 154.1 (C=O), 148.2 (C), 138.9 (C), 132.5 (C), 128.2 (CH), 127.3 (CH), 126.3 (CH), 125.9 (CH), 124.8 (CH), 124.5 (CH), 123.0 (CH), 81.2 (C), 63.7 (C), 51.6 (CH_3), 44.1 (CH_2), 40.7 (CH_2), 27.8 (CH_3), 24.0 (CH_2); HRMS (ES) Found: MH^+, 382.2008. $C_{23}H_{28}NO_4$ requires MH^+, 382.2013; LRMS *m*/*z* (ES) 382 (5%, MH^+), 282 (100, MH^+–Boc+H).

Resolution between the enantiomers of the tetrahydroquinoline **119l** 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 (99.2:0.8 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 faster running component and slower running component were eluted at 18.1 min and 20.0 min respectively with an analysis time of 30 min.

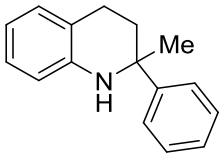
Using the general procedure D with a reaction time of 6 min, tetrahydroquinoline (*S*)-**118a** (30 mg, 0.01 mmol) with an enantiomeric ratio of 92:8, *n*-BuLi (48 μL, 0.11 mmol, 2.4 M in hexanes) and methyl bromoacetate (32 μL, 0.33 mmol) with a reaction time of 6 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the carbamate (*S*)-**119l** (26 mg, 71%) as an amorphous white solid; m.p. 96–98 °C; the enantiomeric ratio was determined to be 92:8 by CSP HPLC (major component eluted at 18.1 min); $[\alpha]_D^{25}$ +50.6 (1.7, $CHCl_3$).

Acetophenone (phenyl-d5) (d_5-**121a)**[102,155]



A solution of acetyl chloride (6.02 mL, 84.7 mmol) in anhydrous CS_2 (5 mL) was added dropwise to a solution of d_6-benzene **120** (6.0 mL, 67.7 mmol) and $AlCl_3$ (11.3 g, 84.7 mmol) in anhydrous CS_2 (15 mL) at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 5 h. The mixture was heated to 50 °C and was left to stir overnight. After cooling to room temperature, the mixture was poured into ice water (100 mL) and was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with saturated Na_2CO_3 (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The mixture was purified using column chromatography on silica gel, eluting with petrol–EtOAc (95:5), to give the ketone d_5-**121a** (7.91g, 93%) as a clear liquid; R_f 0.50 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3010, 3005, 3000, 1675 (C=O), 1565, 1380, 1225, 1020, 950, 815; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.64 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, one quaternary carbon and five deuterated carbons not observed) δ = 198.2 (C=O), 26.6 (CH_3); HRMS (GC/MS) Found: M^+, 125.0883. $C_8H_3D_5O$ requires M^+, 125.0884; LRMS *m*/*z* (GC/MS) 125 (5%, M^+), 110 (100), 82 (55). Data consistent with the literature.[155]

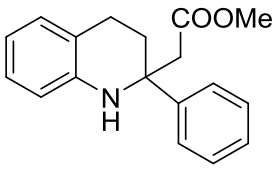
2-Methyl-2-phenyl-1,2,3,4-tetrahydroquinoline (124a)[156]



Using the general procedure G, carbamate **119a** (52 mg, 0.16 mmol) and TFA (0.12 mL, 1.62 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the amine **124a** (31 mg, 86%) as a yellow solid; m.p. 65–67 °C (lit.[148] oil); R_f 0.44 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3400 (N–H), 3055, 3020, 2920, 2845, 1605, 1480, 1310, 1260, 1130, 745, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47–7.41 (2H, m, 2 × CH), 7.34 (2H, t, *J* = 7.5 Hz, 2 × CH), 7.30–7.21 (1H, m, CH) , 7.08 (1H, t, *J* = 7.5 Hz, CH), 6.96 (1H, d, *J* = 7.5 Hz, CH), 6.70–6.61 (2H, m, 2 × CH), 4.16 (1H, s, NH), 2.65 (1H, dt, *J* = 16.5, 4.5 Hz, CH), 2.43–2.31 (1H, m, CH), 2.30–2.21 (1H, m, CH), 2.01–1.91 (1H, m, CH), 1.62 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.3 (C), 143.9 (C), 129.3 (CH), 128.4 (CH), 127.0 (CH), 126.4 (CH), 125.5 (CH), 120.4 (C), 116.7 (CH), 113.5 (CH), 55.5 (C), 35.4 (CH_2), 30.7 (CH_3), 24.4 (CH_2); HRMS (ES) Found: MH^+, 224.1438. $C_{16}H_{18}N$ requires MH^+, 224.1434; LRMS *m*/*z* (ES) 224 (100%, MH^+). Data consistent with the literature.[156]

Resolution between the enantiomers of the carbamate **124a** was achieved using a Beckman system fitted with a Daicel 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 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 6.6 min and 7.6 min respectively with an analysis time of 10 min.

Methyl 2-(2-Phenyl-1,2,3,4-tetrahydroquinolin-2-yl)acetate (124b)

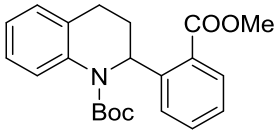


Using the general procedure G, carbamate **119l** (64 mg, 0.17 mmol) and TFA (0.13 mL, 1.67 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the amine **124b** (40 mg, 86%) as an amorphous brown solid; m.p. 81–83 °C; R_f 0.55 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3405 (N–H), 3050, 3020, 2955, 2910, 2840, 1715 (C=O), 1605, 1480, 1430, 1350, 1230, 1170, 1130, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43–7.37 (2H, m, 2 × CH), 7.32 (2H, t, *J* = 7.0 Hz, 2 × CH), 7.27–7.20 (1H, m, CH) , 7.09 (1H, t, *J* = 7.5 Hz, CH), 6.92 (1H, d, *J* = 7.5 Hz, CH), 6.74 (1H, d, *J* = 8.0 Hz, CH), 6.69–6.61 (1H, m, CH), 5.64 (1H, s, NH), 3.53 (3H, s, OCH_3), 3.14 (1H, d, *J* = 15.5 Hz, CH), 2.90 (1H, d, *J* = 15.5 Hz, CH), 2.61 (1H, dt, *J* = 16.5, 4.5 Hz, CH), 2.41–2.29 (1H, m, CH), 2.28–2.17 (1H, m, CH), 2.06 (1H, td, *J* = 12.0, 4.5 Hz, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.9 (C=O), 145.0 (C), 143.5 (C), 129.1 (CH), 128.4 (CH), 127.2 (CH), 126.7 (CH), 125.7 (CH), 120.2 (C), 116.9 (CH), 114.0 (CH), 56.8 (C), 51.6 (CH_3), 46.3 (CH_2), 35.2 (CH_2), 23.7 (CH_2); HRMS (ES) Found: MH^+, 282.1489. $C_{18}H_{20}NO_2$ requires MH^+, 282.1489; LRMS *m*/*z* (ES) 282 (100%, MH^+), 208 (5).

Resolution between the enantiomers of the carbamate **124b** was achieved using a Beckman system fitted with a Daicel ChiralCel OJ 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 24.8 min and 36.4 min respectively with an analysis time of 60 min.

Using the general procedure G, carbamate (*R*)-**119l** (14 mg, 0.0375 mmol) with an enantiomeric ratio of 92:8 and TFA (0.03 mL, 0.375 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the amine (*R*)-**124b** (7 mg, 69%) as an oil; the enantiomeric ratio was determined to be 88:12 by CSP HPLC (major component eluted at 24.6 min); $[\alpha]_D^{20}$ = –92.8 (0.3, $CHCl_3$).

***tert*-Butyl 2-[2-(Methoxycarbonyl)phenyl]-1,2,3,4-tetrahydroquinoline-1-carboxylate (125)**



Using the general procedure D with a reaction time of 6 min, with the addition of methanol taking place 1 h after the addition of methyl cyanoformate, *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **118a** (101 mg, 0.33 mmol), *n*-BuLi (0.16 mL, 0.39 mmol, 2.4 M in hexanes) and methyl cyanoformate (0.09 mL, 1.14 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **125** (74 mg, 62%) as an amorphous white solid; m.p. 73–75 °C; R_f 0.46 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3070, 3030, 3005, 2975, 2950, 2930, 1715 (C=O), 1700 (C=O), 1600, 1490, 1325, 1155, 1075, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95–7.88 (2H, m, 2 × CH), 7.47–7.41 (1H, m, CH), 7.37–7.24 (3H, m, 3 × CH) , 7.17–7.12 (1H, m, CH), 7.06 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.09 (1H, dd, *J* = 10.5, 7.0 Hz, CH), 3.95 (3H, s, OCH_3), 2.83–2.60 (3H, m, 3 × CH), 1.63–1.51 (1H, m, CH), 1.25 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.5 (C=O), 153.8 (C=O), 148.8 (C), 138.7 (C), 133.9 (C), 132.7 (CH), 130.2 (CH), 127.7 (C), 127.2 (CH), 126.5 (CH), 126.2 (CH), 125.9 (CH), 124.4 (CH), 123.4 (CH), 80.7 (C), 56.7 (CH), 52.0 (CH_3), 33.8 (CH_2), 27.9 (CH_3), 27.3 (CH_2); HRMS (ES) Found: MNa^+, 390.1681. $C_{22}H_{25}NO_4Na$ requires MNa^+, 390.1676; LRMS *m*/*z* (ES) 390 (15%, MNa^+), 268 (100, MH^+–Boc+H).

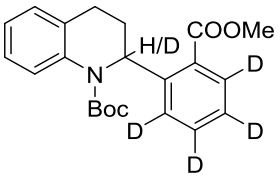
Also, using the general procedure D with a reaction time of 6 min, *N*-Boc-2-phenyl-1,2,3,4-tetrahydro(2-^{2}H)quinoline d$_1$-**118a** (27 mg, 0.09 mmol), *n*-BuLi (0.11 mL, 0.26 mmol, 2.4 M in hexanes) and methyl cyanoformate (25 μL, 0.30 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **125** (2.7 mg, 8%, 100% H); data as above. Compound d$_1$-**118a** (22 mg, 81%) was also recovered, data as above.

Resolution between the enantiomers of the tetrahydroquinoline **125** 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 (99.2:0.8 v/v) as the mobile phase at a flow rate of 0.8 mL·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 faster running component and slower running component were eluted at 11.1 min and 12.3 min respectively with an analysis time of 20 min.

Using the general procedure D with a reaction time of 6 min, tetrahydroquinoline (*R*)-**118a** (40 mg, 0.13 mmol) with an enantiomeric ratio of 92:8, *n*-BuLi (64 μL, 0.15 mmol, 2.4 M in hexanes) and methyl cyanoformate (36 μL, 0.45 mmol) with a reaction time of 6 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **125** (20 mg, 43%) as an amorphous white solid; the enantiomeric ratio was determined to be 61:39 by CSP HPLC (major component eluted at 12.5 min); data as above.

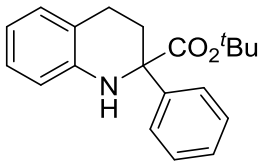
***tert*-Butyl 2-[2-(Methoxycarbonyl)phenyl]-1,2,3,4-tetrahydroquinoline-1-carboxylate (phenyl-d4) (**d_4**-125) and *tert*-Butyl 2-[2-(Methoxycarbonyl)phenyl]-1,2,3,4-tetrahydro(2-^{2}H) quinoline-1-carboxylate (phenyl-d4) (**d_5**-125)**



Using the general procedure D with a reaction time of 6 min, *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline d_4-**118a** (102 mg, 0.33 mmol), *n*-BuLi (0.17 mL, 0.39 mmol, 2.3 M in hexanes) and methyl cyanoformate (0.09 mL, 1.14 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate $d_{4/5}$-**125** (58 mg, 46%) as a white amorphous solid; ratio H:D = 1:2; m.p. 69–71 °C; R_f 0.19 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3025, 3005, 2970, 2950, 2845, 1710 (C=O), 1695 (C=O), 1490, 1350, 1325, 1235, 1145, 1075, 1010, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (1H, d, *J* = 8.5 Hz, CH), 7.34–7.25 (1H, m, CH), 7.15 (1H, d, *J* = 7.5 Hz, CH), 7.10–7.04 (1H, m, CH), 6.10 (0.33H, dd, *J* = 10.0, 7.0 Hz, CH), 3.95 (3H, s, OCH_3), 2.84–2.59 (3H, m, 3 × CH), 1.64–1.51 (1H, m, CH), 1.25 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, deuterated carbons could not be observed) δ = 167.5 (C=O), 153.9 (C=O), 148.8 and 148.7 (C), 138.7 (C), 133.9 (C), 127.6 (C), 127.2 (CH), 126.5 (CH), 124.4 (CH), 123.4 (CH), 80.7 (C), 56.6 (CH), 52.0 (CH_3), 33.7 and 33.6 (CH_2), 27.9 (CH_3), 27.2 (CH_2); HRMS (ES) Found: MNa^+, 394.1931. $C_{22}H_{21}D_4NO_4Na$ requires MNa^+, 394.1927 for α-H; Found: MNa^+, 395.1985. $C_{22}H_{20}D_5NO_4Na$ requires MNa^+, 395.1990 for α-D; LRMS *m*/*z* (ES) 395 (15%, MNa^+), 394 (20, MNa^+), 273 (80, MH^+–Boc+H),

272 (100, MH^+–Boc+H).

***tert*-Butyl 2-Phenyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (132a)**



Using the general procedure F, *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **118a** (101 mg, 0.33 mmol), *n*-BuLi (0.16 mL, 0.39 mmol, 2.4 M in hexanes) and BEt_3 (0.65 mL, 0.65 mmol, 1.0 M in hexanes), gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the compound **132a** (77 mg, 76%) as as an amorphous yellow solid; m.p. 54–56 °C; R_f 0.71 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3400 (N–H), 3055, 2980, 2930, 1720 (C=O), 1480, 1370, 1150, 1120, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60–7.54 (2H, m, 2 × CH), 7.40–7.33 (2H, m, 2 × CH), 7.33–7.27 (1H, m, CH), 7.11–7.05 (1H, m, CH), 6.96 (1H, d, *J* = 7.5 Hz, CH), 6.77–6.72 (1H, m, CH), 6.68 (1H, td, *J* = 7.5, 1.0 Hz, CH), 4.95 (1H, s, NH), 2.78–2.69 (1H, m, CH), 2.56–2.43 (2H, m, 2 × CH), 2.41–2.31 (1H, m, CH), 1.46 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.5 (C=O), 143.0 (C), 142.7 (C), 129.0 (CH), 128.5 (CH), 127.5 (CH), 127.0 (CH), 125.7 (CH), 120.4 (C), 117.4 (CH), 114.3 (CH), 82.2 (C), 63.5 (C), 31.2 (CH_2), 27.9 (CH_3), 24.0 (CH_2); HRMS (ES) Found: MH^+, 310.1800. $C_{20}H_{24}NO_2$ requires MH^+, 310.1802; LRMS *m*/*z* (ES) 310 (100%, MH^+), 254 (80, MH^+–*t*-Bu+H); Found: C, 77.57; H, 7.65; N, 4.28. $C_{20}H_{23}NO_2$ requires C, 77.64; H, 7.49; N, 4.53.

Alternatively, using the general procedure F without the addition of BEt_3, *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **118a** (107 mg, 0.35 mmol) and *n*-BuLi (0.17 mL, 0.42 mmol, 2.4 M in hexanes), after warming to room temperature over 16 h, gave after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the compound **132a** (45 mg, 42%); data as above.

Alternatively, also using the general procedure F at a temperature of –50 °C, *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **118a** (101 mg, 0.33 mmol), *n*-BuLi (0.16 mL, 0.39 mmol, 2.4 M in hexanes) and BEt_3 (0.49 mL, 0.49 mmol, 1.0 M in hexanes), gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the compound **132a** (48 mg, 47%); data as above.

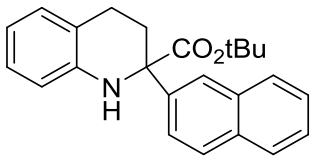
Alternatively, also using the general procedure F, *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **118a** (105 mg, 0.34 mmol), *n*-BuLi (0.17 mL, 0.41 mmol, 2.4 M in hexanes) and BEt_3 (0.07 mL, 0.07 mmol, 1.0 M in hexanes), gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the compound **132a** (63 mg, 59%); data as above.

Alternatively, *t*-BuOK (0.40 mL, 0.40 mmol, 1.0 M in THF) was added to *n*-BuLi (0.16 mL, 0.40 mmol, 2.5 M in hexanes) in THF (2 mL) and left to stir for 15 min at –78 °C. *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **118a** (102 mg, 0.33 mmol) in THF (2 mL) was added and the reaction mixture was left warm to room temperature over 16 h. 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 the compound **132a** (51 mg, 50%); data as above.

Resolution between the enantiomers of the carbamate **132a** was achieved using a Beckman system fitted with a Daicel 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 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 10.3 min and 12.2 min respectively with an analysis time of 15 min.

Using the general procedure F, tetrahydroquinoline (*S*)-**118a** (26 mg, 0.09 mmol) with an enantiomeric ratio of 98:2, *n*-BuLi (43 μL, 0.10 mmol, 2.4 M in hexanes) and BEt_3 (0.171 mL, 0.171 mmol, 1.0 M in hexanes) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the compound (*S*)-**132a** (19 mg, 71%) as an amorphous white solid; m.p. 78–80 °C; the enantiomeric ratio was determined to be 98:2 by CSP HPLC (major component eluted at 11.8 min); $[\alpha]_D^{24} = -94.2$ (0.4, $CHCl_3$).

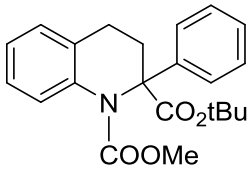
***tert*-Butyl 2-(Naphthalen-2-yl)-1,2,3,4-tetrahydro-quinoline-2-carboxylate (132b)**



Using the general procedure F, carbamate **118f** (101 mg, 0.28 mmol), *n*-BuLi (0.14 mL, 0.34 mmol, 2.4 M in hexanes) and BEt_3 (0.42 mL, 0.42 mmol, 1.0 M in hexanes), quenching with MeOH, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the compound **132b** (61 mg, 60%) as an amorphous white solid; m.p. 60–62 °C; R_f 0.64 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3425 (NH), 3060, 3010, 2975, 2970, 1720 (C=O), 1605, 1585, 1475, 1365, 1150, 1120, 845, 815, 745; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.04 (1H, d, *J* = 1.5 Hz, CH), 7.91–7.83 (3H, m, 3 × CH), 7.73 (1H, dd, *J* = 8.5, 2.0 Hz, CH), 7.54–7.48 (2H, m, 2 × CH), 7.17–7.10 (1H, m, CH), 6.98 (1H, d, *J* = 7.5 Hz, CH), 6.84 (1H, dd, *J* = 8.0, 1.0 Hz, CH), 6.71 (1H, td, *J* = 7.5, 1.0 Hz, CH), 5.10 (1H, s, NH), 2.78 (1H, dt, *J* = 16.0, 5.0 Hz, CH), 2.66–2.39 (3H, m, 3 × CH), 1.48 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.5 (C=O), 143.0 (C), 140.1 (C), 133.3 (C), 132.8 (C), 129.0 (CH), 128.4 (2 × CH), 127.5 (CH), 127.1 (CH), 126.2 (CH), 126.1 (CH), 125.2 (CH), 123.7 (CH), 120.5 (C), 117.5 (CH), 114.4 (CH), 82.4 (C), 63.7 (C), 31.1 (CH_2), 27.9 (CH_3), 24.0 (CH_2); HRMS (ES) Found: MH^+, 360.1965. $C_{24}H_{26}NO_2$ requires MH^+, 360.1958; LRMS *m*/*z* (ES) 360 (100%, MH^+), 304 (40, MH^+–*t*-Bu+H).

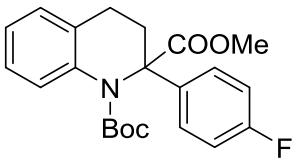
Resolution between the enantiomers of the carbamate **132b** was achieved using a Beckman system fitted with a Lux Cellulose–1 column (250 mm × 460 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 $mL \cdot min^{-1}$; ambient 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 8.0 min and 10.1 min respectively with an analysis time of 15 min.

2-*tert*-Butyl 1-Methyl-2-Phenyl-1,2,3,4-tetrahydroquinoline-1,2-dicarboxylate (134)



t-BuOK (0.38 mL, 0.38 mmol, 1.0 M in THF) was added to *n*-BuLi (0.15 mL, 0.38 mmol, 2.5 M in hexanes) in THF (2 mL) and left to stir for 15 min at –78 °C. *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **118a** (99 mg, 0.32 mmol) in THF (2 mL) was added and the reaction mixture was left to stir for 6 min. Methyl chloroformate (0.09 mL, 1.12 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 (97:3) to give the compound **134** (29 mg, 24%) as an amorphous white solid; m.p. 46–48 °C; R_f 0.11 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3010, 2985, 2975, 2965, 2955, 2930, 1710 (C=O), 1490, 1435, 1325, 1255, 1140, 750, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 (1H, d, *J* = 8.0 Hz, CH), 7.57–7.50 (2H, m, 2 × CH), 7.37–7.29 (2H, m, 2 × CH), 7.27–7.20 (2H, m, 2 × CH), 7.12–6.99 (2H, m, 2 × CH), 3.70 (3H, s, CH_3), 3.03–2.90 (1H, m, CH), 2.68 (1H, ddd, *J* = 13.5, 6.5, 3.5 Hz, CH), 2.56–2.44 (1H, m, CH), 2.22–2.12 (1H, m, CH), 1.51 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.0 (C=O), 155.8 (C=O), 141.8 (C), 137.7 (C), 132.5 (C), 127.8 (CH), 127.4 (CH), 126.8 (CH), 126.8 (CH), 126.6 (CH), 124.7 (CH), 124.0 (CH), 81.9 (C), 69.3 (C), 52.8 (CH_3), 39.7 (CH_2), 27.9 (CH_3), 25.3 (CH_2); HRMS (ES) Found: MNa^+, 390.1682. $C_{22}H_{25}NO_4Na$ requires MNa^+, 390.1676; LRMS *m*/*z* (ES) 390 (10%, MNa^+), 312 (100, MH^+–*t*-Bu+H), 294 (50), 266 (90, MH^+–Boc+H). The carbamate **119b** (25 mg, 21%) was also obtained; data as above.

1-*tert*-Butyl 2-Methyl-2-(4-fluorophenyl)-1,2,3,4-tetrahydroquinoline-1,2-dicarboxylate (136a)



Using the general procedure D with a reaction time of 6 min, carbamate **118b** (109 mg, 0.33 mmol), *n*-BuLi (0.17 mL, 0.40 mmol, 2.4 M in hexanes), THF (2 mL) and methyl chloroformate (0.09 mL, 1.17 mmol) gave, after purification by column chromatography on

silica gel, eluting with petrol–EtOAc (95:5), the carbamate **136a** (96 mg, 75%) as an amorphous white solid; m.p. 42–44 °C; R_f 0.25 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3080, 3070, 3030, 3005, 2980, 1745 (C=O), 1710 (C=O), 1320, 1230, 1155, 1135; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (1H, d, *J* = 8.0 Hz, CH), 7.65–7.58 (2H, m, 2 × CH), 7.30–7.24 (1H, m, CH), 7.10–7.06 (1H, m, CH), 7.06–6.98 (3H, m, 3 × CH), 3.81 (3H, s, OCH_3), 2.89–2.80 (1H, m, CH), 2.60–2.43 (2H, m, 2 × CH), 2.17–2.08 (1H, m, CH), 1.34 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.4 (C=O), 161.7 (d, *J* = 246.0 Hz, C), 153.7 (C=O), 138.1 (d, *J* = 3.0 Hz, C), 137.6 (C), 131.5 (C), 128.5 (d, *J* = 8.5 Hz, CH), 127.6 (CH), 126.5 (CH), 124.3 (CH), 123.5 (CH), 114.5 (d, *J* = 21.5 Hz, CH), 82.2 (C), 68.3 (C), 52.5 (CH_3), 39.5 (CH_2), 27.9 (CH_3), 25.1 (CH_2); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 116.5; HRMS (ES) Found: MH^+, 386.1754. $C_{22}H_{25}NO_4F$ requires MH^+, 386.1768; LRMS *m/z* (ES) 386 (85%, MH^+), 371 (20, MH^+–CH_3), 330 (100, MH^+–*t*-Bu+H), 286 (75, MH^+–Boc+H).

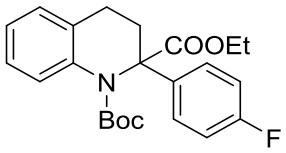
Resolution between the enantiomers of the carbamate **136a** was achieved using a Beckman system fitted with a Lux Cellulose-2 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99.6:0.4 v/v) as the mobile phase at a flow rate of 1.65 mL·min^{-1}; ambient 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 9.3 min and 10.6 min respectively with an analysis time of 20 min.

Resolution between the enantiomers of the tetrahydroquinoline **136a** was also achieved using a Beckman system fitted with a Daicel Chiralpak IA 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·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 faster running component and slower running component were eluted at 13.7 min and 16.2 min respectively with an analysis time of 20 min.

Using the general procedure D with a reaction time of 6 min, carbamate (*S*)-**118b** (34 mg, 0.10 mmol) with an enantiomeric ratio of 89:11, *n*-BuLi (54 μL, 0.13 mmol, 2.3 M in hexanes) and methyl chloroformate (30 μL, 0.36 mmol) with a reaction time of 6 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the carbamate (*S*)-

136a (27 mg, 68%) as an amorphous white solid; m.p. 42–44 °C; the enantiomeric ratio was determined to be 89:11 by CSP HPLC (major component eluted at 14.7 min); $[\alpha]_D^{25} = -59.3$ (0.78, $CHCl_3$).

***tert*-Butyl 2-Ethyl-2-(4-fluorophenyl)-1,2,3,4-tetrahydroquinoline-1,2-dicarboxylate (136b)**

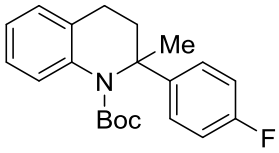


Using the general procedure D with a reaction time of 6 min, carbamate **118b** (100 mg, 0.31 mmol), *n*-BuLi (0.15 mL, 0.37 mmol, 2.5 M in hexanes), THF (2 mL) and ethyl chloroformate (0.10 mL, 1.07 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **136b** (106 mg, 86%) as a white gum; R_f 0.22 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3030, 2980, 2855, 1740 (C=O), 1710 (C=O), 1700, 1510, 1490, 1325, 1230, 1155, 1140, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 (1H, d, *J* = 8.5 Hz, CH), 7.64–7.55 (2H, m, 2 × CH), 7.31–7.22 (1H, m, CH), 7.11–7.06 (1H, m, CH), 7.06–6.96 (3H, m, 3 × CH), 4.36–4.17 (2H, m, O*CH*$_2$CH$_3$), 2.93–2.80 (1H, m, CH), 2.61–2.42 (2H, m, 2 × CH), 2.19–2.06 (1H, m, CH), 1.34 (9H, s, *t*-Bu), 1.32 (3H, t, *J* = 7.0 Hz, OCH$_2$*CH*$_3$, partially merged with *t*-Bu peak); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.8 (C=O), 161.6 (d, *J* = 245.5 Hz, C), 153.5 (C=O), 138.1 (d, *J* = 3.0 Hz, C), 137.7 (C), 131.8 (C), 128.5 (d, *J* = 7.5 Hz, CH), 127.5 (CH), 126.5 (CH), 124.4 (CH), 123.5 (CH), 114.4 (d, *J* = 21.5 Hz, CH), 82.2 (C), 68.2 (C), 61.6 (OCH$_2$), 39.6 (CH$_2$), 27.9 (CH$_3$), 25.1 (CH$_2$), 14.2 (CH$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 116.6; HRMS (ES) Found: MNa$^+$, 422.1742. $C_{23}H_{26}NO_4FNa$ requires MNa$^+$, 422.1738; LRMS *m/z* (ES) 422 (10%, MNa$^+$), 300 (100, MH$^+$–Boc+H).

Resolution between the enantiomers of the carbamate **136b** was achieved using a Beckman system fitted with a Lux Cellulose-1 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99.5:0.5 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 faster running component and slower running component were eluted at 9.5 min and 11.1 min with an analysis time of 15 min.

Using the general procedure D with a reaction time of 6 min, carbamate (*S*)-**118b** (25 mg, 0.08 mmol) with an enantiomeric ratio of 94:6, *n*-BuLi (36 μL, 0.09 mmol, 2.5 M in hexanes) and ethyl chloroformate (25 μL, 0.26 mmol) with a reaction time of 6 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the carbamate (*S*)-**136b** (26 mg, 89%) as a sticky white solid; m.p. 34–36 °C; the enantiomeric ratio was determined to be 93:7 by CSP HPLC (major component eluted at 11.0 min); $[\alpha]_D^{23} = -75.3$ (1.0, $CHCl_3$).

***tert*-Butyl 2-(4-Fluorophenyl)-2-methyl-1,2,3,4-tetrahydroquinoline-1-carboxylate (136c)**

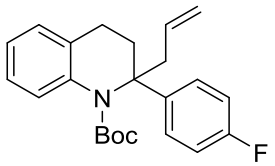


Using the general procedure D with a reaction time of 6 min, carbamate **118b** (101 mg, 0.31 mmol), *n*-BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexanes), THF (2 mL) and methyl iodide (0.06 mL, 1.08 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **136c** (96 mg, 90%) as an amorphous white solid; m.p. 75–77 °C; R_f 0.43 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3070, 3005, 2975, 2935, 1700 (C=O), 1505, 1485, 1315, 1150; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 (1H, d, *J* = 8.0 Hz, CH), 7.38–7.32 (2H, m, 2 × CH), 7.27–7.21 (1H, m, CH), 7.14–7.09 (1H, m, CH), 7.07–6.98 (3H, m, 3 × CH), 2.76–2.66 (1H, m, CH), 2.54 (1H, ddd, *J* = 15.0, 7.0, 3.5 Hz, CH), 2.05 (3H, s, CH_3), 2.04–1.96 (1H, m, CH), 1.92 (1H, ddd, *J* = 13.0, 7.0, 3.5 Hz, CH), 1.26 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.2 (d, *J* = 244.0 Hz, C), 154.4 (C=O), 145.2 (d, *J* = 3.5 Hz, C), 138.9 (C), 132.8 (C), 127.4 (CH), 126.3 (d, *J* = 8.5 Hz, CH), 126.1 (CH), 124.8 (CH), 122.8 (CH), 114.8 (d, *J* = 21.0 Hz, CH), 81.0 (C), 62.3 (C), 44.5 (CH_2), 28.0 (CH_3), 27.5 (CH_3), 25.0 (CH_2); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 117.9; HRMS (ES) Found: MH^+, 342.1872. $C_{21}H_{25}NO_2F$ requires MH^+, 342.1869; LRMS *m/z* (ES) 342 (5%, MH^+), 327 (55, MH^+–CH_3), 286 (100, MH^+–*t*-Bu+H).

Resolution between the enantiomers of the carbamate **136c** was achieved using a Beckman system fitted with a Lux Amylose-2 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 9.9 min and 11.4 min respectively with an analysis time of 15 min.

tert-Butyl 2-(4-Fluorophenyl)-2-(prop-2-en-1-yl)-1,2,3,4-tetrahydroquinoline-1-carboxylate (136d)

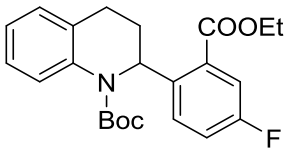


Using the general procedure D with a reaction time of 6 min, carbamate **118b** (103 mg, 0.31 mmol), *n*-BuLi (0.19 mL, 0.38 mmol, 2.0 M in hexanes), THF (2 mL) and allyl bromide (0.09 mL, 1.11 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **136d** (53 mg, 46%) as an amorphous white solid; m.p. 118–120 °C; R_f 0.47 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3070, 3045, 3000, 2980, 2960, 2920, 2860, 1690 (C=O), 1510, 1490, 1345, 1160, 770; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62–7.56 (1H, m, CH), 7.37–7.30 (2H, m, 2 × CH), 7.23–7.17 (1H, m, CH), 7.09–7.02 (3H, m, 3 × CH), 6.98 (1H, td, *J* = 7.5, 1.0 Hz, CH), 5.90–5.77 (1H, m, C*H*=CH$_2$), 5.23–5.07 (2H, m, CH=C*H*$_2$), 3.57 (1H, dd, *J* = 13.0, 7.0 Hz, CH), 2.93 (1H, dd, *J* = 13.0, 7.0 Hz, CH), 2.78–2.67 (1H, m, CH), 2.32 (1H, dt, *J* = 15.0, 3.0 Hz, CH), 2.16 (1H, td, *J* = 13.0, 3.0 Hz, CH), 1.85 (1H, dt, *J* = 13.0, 3.0 Hz, CH), 1.23 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.3 (d, *J* = 245.0 Hz, C), 154.3 (C=O), 144.9 (d, *J* = 3.5 Hz, C), 139.5 (C), 133.3 (*C*H=CH$_2$), 132.5 (C), 127.3 (CH), 126.5 (d, *J* = 8.0 Hz, CH), 126.1 (CH), 124.9 (CH), 122.8 (CH), 118.8 (CH=*C*H$_2$), 114.8 (d, *J* = 21.0 Hz, CH), 81.1 (C), 64.4 (C), 44.3 (CH$_2$), 40.8 (CH$_2$), 28.0 (CH$_3$), 24.0 (CH$_2$); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 117.6; HRMS (ES) Found: MNa$^+$, 390.1863. $C_{23}H_{26}NO_2FNa$ requires MNa$^+$, 390.1843; LRMS *m/z* (ES) 390 (100%, MNa$^+$), 334 (15, MNa$^+$–*t*-Bu+H).

Resolution between the enantiomers of the carbamate **136d** was achieved using a Beckman system fitted with a Lux Cellulose-1 column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99.65:0.35 v/v) as the mobile phase at a flow rate of 2 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume

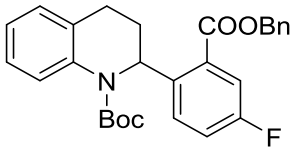
was 20 μL of the sample prepared in a 2 $g \cdot L^{-1}$ solution of the eluent. Under these conditions, the faster running component and slower running component were eluted at 5.1 min and 6.5 min respectively with an analysis time of 10 min.

tert-Butyl 2-[2-(Ethoxycarbonyl)-4-fluorophenyl]-1,2,3,4-tetrahydroquinoline-1-carboxylate (137a)



Using the general procedure D with a reaction time of 6 min, carbamate **118b** (28 mg, 0.08 mmol), *n*-BuLi (0.04 mL, 0.10 mmol, 2.4 M in hexanes) and ethyl cyanoformate (0.03 mL, 0.30 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the carbamate **137a** (28 mg, 84%) as a white amorphous solid; m.p. 64–66 °C; R_f 0.53 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3010, 2975, 2960, 2935, 2865, 1725 (C=O), 1700 (C=O), 1585, 1490, 1325, 1195, 1155, 1065, 765; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 (1H, d, *J* = 8.0 Hz, CH), 7.63 (1H, dd, *J* = 9.5, 2.5 Hz, CH), 7.35–7.26 (2H, m, 2 × CH), 7.18–7.11 (2H, m, 2 × CH), 7.07 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.06 (1H, dd, *J* = 10.0, 7.0 Hz, CH), 4.47–4.35 (2H, m, CH_2), 2.81–2.59 (3H, m, 3 × CH), 1.60–1.49 (1H, m, CH), 1.44 (3H, t, *J* = 7.0 Hz, CH_3), 1.27 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.9 (d, *J* = 2.5 Hz, C=O), 160.5 (d, *J* = 245.5 Hz, C), 153.8 (C=O), 144.7 (d, *J* = 3.0 Hz, C), 138.5 (C), 133.9 (C), 129.6 (d, *J* = 7.0 Hz, C), 127.8 (d, *J* = 8.5 Hz, CH), 127.2 (CH), 126.5 (CH), 124.4 (CH), 123.6 (CH), 119.6 (d, *J* = 20.5 Hz, CH), 116.7 (d, *J* = 23.0 Hz, CH), 80.8 (C), 61.3 (CH_2), 56.2 (CH), 33.9 (CH_2), 28.0 (CH_3), 27.2 (CH_2), 14.3 (CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 116.1; HRMS (ES) Found: MNa^+, 422.1746. $C_{23}H_{26}FNO_4Na$ requires MNa^+, 422.1738; LRMS *m*/*z* (ES) 422 (10%, MNa^+), 300 (100, MH^+–Boc+H).

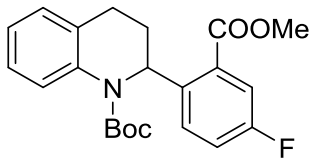
***tert*-Butyl 2-{2-[(Benzyloxy)carbonyl]-4-fluorophenyl}-1,2,3,4-tetrahydroquinoline-1-carboxylate (137b)**



Using the general procedure D with a reaction time of 6 min, carbamate **118b** (100 mg, 0.31 mmol), *n*-BuLi (0.15 mL, 0.37 mmol, 2.4 M in hexanes) and benzyl cyanoformate (0.16 mL, 1.08 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the carbamate **137b** (71 mg, 50%) as a white amorphous solid; m.p. 96–97 °C; R_f 0.42 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3070, 3040, 2960, 2930, 2875, 1705 (C=O), 1585, 1490, 1325, 1240, 1195, 1155, 1060, 750, 735, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 (1H, d, *J* = 8.0 Hz, CH), 7.67 (1H, dd, *J* = 9.5, 3.0 Hz, CH), 7.53–7.37 (5H, m, 5 × CH), 7.37–7.26 (2H, m, 2 × CH), 7.19–7.11 (2H, m, 2 × CH), 7.07 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.06 (1H, dd, *J* = 10.5, 7.0 Hz, CH), 5.44 (1H, d, *J* = 12.0 Hz, CH), 5.35 (1H, d, *J* = 12.0 Hz, CH), 2.77–2.56 (3H, m, 3 × CH), 1.58–1.46 (1H, m, CH), 1.24 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.6 (d, *J* = 2.5 Hz, C=O), 160.5 (d, *J* = 245.5 Hz, C), 153.8 (C=O), 144.8 (d, *J* = 3.0 Hz, C), 138.4 (C), 135.5 (C), 133.9 (C), 129.3 (d, *J* = 7.0 Hz, C), 128.7 (CH), 128.6 (CH), 128.5 (CH), 127.9 (d, *J* = 7.5 Hz, CH), 127.2 (CH), 126.5 (CH), 124.5 (CH), 123.6 (CH), 119.9 (d, *J* = 20.5 Hz, CH), 116.8 (d, *J* = 24.0 Hz, CH), 80.8 (C), 67.2 (CH_2), 56.2 (CH), 33.9 (CH_2), 28.0 (CH_3), 27.2 (CH_2); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 115.9; HRMS (ES) Found: MH^+, 462.2078. $C_{28}H_{29}FNO_4$ requires MH^+, 462.2081; LRMS *m*/*z* (ES) 484 (25%, MNa^+), 462 (100, MH^+), 362 (10, MH^+–Boc+H).

Resolution between the enantiomers of the carbamate **137b** 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 (99:1 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 8.8 min and 9.8 min respectively with an analysis time of 15 min.

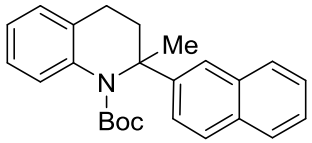
***tert*-Butyl 2-[4-Fluoro-2-(methoxycarbonyl)phenyl]-1,2,3,4-tetrahydroquinoline-1-carboxylate (137c)**



Using the general procedure E, carbamate **118b** (189 mg, 0.58 mmol), (+)-sparteine (230 mg, 0.98 mmol), *n*-BuLi (0.24 mL, 0.58 mmol, 2.4 M in hexanes) and methyl cyanoformate (0.16 mL, 2.02 mmol) with a reaction time of 2.5 h, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the carbamate **137c** (63 mg, 28%) as a white amorphous solid; m.p. 64–66 °C; R_f 0.63 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3020, 3005, 2980, 2955, 2930, 1725 (C=O), 1700 (C=O), 1585, 1490, 1325, 1205, 1155, 1070, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (1H, d, *J* = 8.0 Hz, CH), 7.62 (1H, dd, *J* = 9.5, 3.0 Hz, CH), 7.36–7.25 (2H, m, 2 × CH), 7.18–7.11 (2H, m, 2 × CH), 7.07 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.07 (1H, dd, *J* = 10.5, 7.0 Hz, CH), 3.95 (3H, s, OCH_3), 2.81–2.59 (3H, m, 3 × CH), 1.59–1.47 (1H, m, CH), 1.27 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.3 (d, *J* = 2.5 Hz, C=O), 160.5 (d, *J* = 245.5 Hz, C), 153.8 (C=O), 144.8 (d, *J* = 4.0 Hz, C), 138.5 (C), 134.0 (C), 129.2 (d, *J* = 7.0 Hz, C), 127.9 (d, *J* = 7.5 Hz, CH), 127.2 (CH), 126.5 (CH), 124.5 (CH), 123.6 (CH), 119.8 (d, *J* = 21.5 Hz, CH), 116.7 (d, *J* = 24.0 Hz, CH), 80.8 (C), 56.2 (CH), 52.3 (CH_3), 33.9 (CH_2), 28.0 (CH_3), 27.3 (CH_2); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 115.9; HRMS (ES) Found: MNa^+, 408.1586. $C_{22}H_{24}FNO_4Na$ requires MNa^+, 408.1582; LRMS *m*/*z* (ES) 408 (15%, MNa^+), 286 (100, MH^+–Boc+H). The carbamates (*S*)-**118b** (56 mg, 29%) and (*R*)-**X** (53 mg, 23%) were also recovered, data as above.

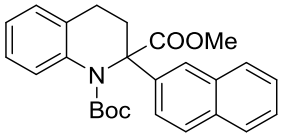
Resolution between the enantiomers of the carbamate **137c** was achieved using a Beckman system fitted with a Daicel ChiralPak IA column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, 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 9.2 min and 9.8 min respectively with an analysis time of 15 min.

***tert*-Butyl 2-Methyl-2-(naphthalen-2-yl)-1,2,3,4-tetrahydroquinoline-1-carboxylate (138a)**



Using the general procedure D with a reaction time of 6 min, carbamate **118f** (91 mg, 0.25 mmol), *n*-BuLi (0.13 mL, 0.31 mmol, 2.4 M in hexanes), THF (2 mL) and methyl iodide (0.06 mL, 0.89 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **138a** (70 mg, 73%) as an oil; R_f 0.61 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3065, 3055, 2970, 2965, 1695 (C=O), 1490, 1315, 1260, 1150, 1015, 800, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90–7.80 (4H, m, 4 × CH), 7.77 (1H, d, *J* = 8.0 Hz, CH), 7.60–7.53 (1H, m, CH), 7.53–7.43 (2H, m, 2 × CH), 7.32–7.24 (1H, m, CH), 7.14 (1H, d, *J* = 7.5 Hz, CH), 7.08–7.00 (1H, m, CH), 2.86–2.72 (1H, m, CH), 2.54 (1H, dt, *J* = 15.0, 4.5 Hz, CH), 2.17 (3H, s, CH_3), 2.11–2.00 (2H, m, CH_2), 1.15 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.5 (C=O), 146.8 (C), 139.1 (C), 133.3 (C), 133.0 (C), 131.9 (C), 128.0 (CH), 127.8 (CH), 127.4 (2 × CH), 126.1 (CH), 126.0 (CH), 125.4 (CH), 124.8 (CH), 123.7 (CH), 123.0 (CH), 122.8 (CH), 80.9 (C), 62.9 (C), 44.4 (CH_2), 27.9 (CH_3), 27.6 (CH_3), 25.1 (CH_2); HRMS (ES) Found: MNa^+, 396.1938. $C_{25}H_{27}NO_2Na$ requires MNa^+, 396.1934; LRMS *m/z* (ES) 396 (10%, MNa^+), 318 (100, MH^+–*t*-Bu+H), 190 (80).

***tert*-Butyl 2-Methyl 2-(Naphthalen-2-yl)-1,2,3,4-tetrahydroquinoline-1,2-dicarboxylate (138b)**

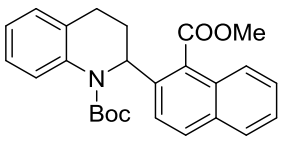


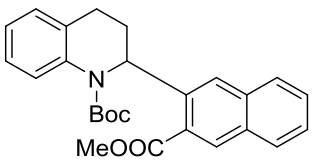
Using the general procedure D with a reaction time of 6 min, carbamate **118f** (60 mg, 0.17 mmol), *n*-BuLi (0.09 mL, 0.20 mmol, 2.4 M in hexanes) and methyl chloroformate (0.05 mL, 0.59 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **138b** (33 mg, 47%) as an amorphous white solid; m.p. 47–

49 °C; R_f 0.40 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3065, 2975, 2925, 2850, 1745 (C=O), 1710 (C=O), 1320, 1245, 1140, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08 (1H, d, *J* = 1.5 Hz, CH), 7.99 (1H, d, *J* = 8.0 Hz, CH), 7.86–7.76 (4H, m, 4 × CH), 7.51–7.45 (2H, m, 2 × CH), 7.33–7.27 (1H, m, CH), 7.08 (1H, dd, *J* = 7.5, 1.5 Hz, CH), 7.03 (1H, td, *J* = 7.5, 1.5 Hz, CH), 3.84 (3H, s, OCH_3), 2.84 (1H, ddd, *J* = 14.5, 9.0, 3.0 Hz, CH), 2.63 (1H, ddd, *J* = 13.5, 8.0, 3.0 Hz, CH), 2.51 (1H, ddd, *J* = 14.5, 8.0, 3.0 Hz, CH), 2.36–2.26 (1H, m, CH), 1.29 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.5 (C=O), 153.9 (C=O), 139.6 (C), 137.8 (C), 132.8 (C), 132.2 (C), 131.5 (C), 128.4 (CH), 127.6 (CH), 127.3 (CH), 127.3 (CH), 126.5 (CH), 125.9 (CH), 125.9 (CH), 125.4 (CH), 125.3 (CH), 124.4 (CH), 123.5 (CH), 82.2 (C), 68.9 (C), 52.5 (CH_3), 39.0 (CH_2), 27.9 (CH_3), 25.2 (CH_2); HRMS (ES) Found: MNa^+, 440.1835. $C_{26}H_{27}NO_4Na$ requires MNa^+, 440.1832; LRMS *m*/*z* (ES) 456 (5%, MK^+), 440 (15, MNa^+), 318 (100, MH^+–Boc+H).

Resolution between the enantiomers of the carbamate **138b** 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 (99:1 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 13.4 min and 17.0 min respectively with an analysis time of 20 min.

tert-Butyl 2-[1-(Methoxycarbonyl)naphthalen-2-yl]-1,2,3,4-tetrahydroquinoline-1-carboxylate (139) and _tert_-Butyl 2-[3-(Methoxycarbonyl)naphthalen-2-yl]-1,2,3,4-tetrahydroquinoline-1-carboxylate (140)



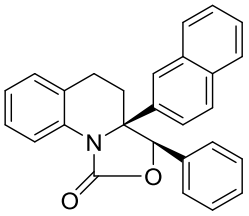


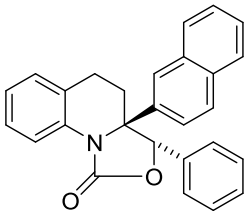
Using the general procedure D with a reaction time of 6 min, carbamate **118f** (103 mg, 0.29 mmol), *n*-BuLi (0.09 mL, 0.23 mmol, 2.5 M in hexanes) and methyl cyanoformate (0.08 mL, 1.00 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the mixture of carbamates **139** and **140** (25 mg, 21%) in a ratio of

approximately 1:2 or 2:1 as an amorphous white solid; R_f 0.26 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3025, 2970, 2920, 2845, 1700 (C=O), 1490, 1365, 1245, 1150, 1005, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44 (1H, d, *J* = 8.0 Hz, CH), 7.40–7.36 (1H, m, CH), 7.25–7.03 (6H, m, 7 × CH), 6.69–6.38 (2H, m, 2 × CH), 5.20 (0.67H, br s, CH), 4.78 (0.33H, br s, CH), 3.65 (1H, s, CH_3), 3.28 (2H, s, CH_3), 3.13–2.66 (4H, m, 2 × CH_2), 1.49 (9H, s, *t*-Bu); ^{13}C NMR (126 MHz, $CDCl_3$, some carbons could not be observed) δ = 171.9 (C=O), 151.7 (C=O), 139.5 (C), 135.1 (C), 132.3 (C), 131.9 (C), 131.2 (C), 127.9 (CH), 127.7 (CH), 127.5 (CH), 127.2 (CH), 125.9 (CH), 125.4 (CH), 125.0 (CH), 123.0 (CH), 81.6 (C), 52.0 (CH_3), 47.5 (CH), 47.1 (CH), 30.3 (CH_2), 29.7 (CH_2), 28.2 (CH_3), 27.5 (CH_2), 27.3 (CH_2); HRMS (ES) Found: MNa^+, 440.1840 and 440.1846. $C_{26}H_{27}NO_4Na$ requires MNa^+, 440.1832 (for both components); LRMS of 440.1840 component *m*/*z* (ES) 440 (20%, MNa^+), 318 (100, MH^+–Boc+H); LRMS of 440.1846 component *m*/*z* (ES) 440 (50%, MNa^+), 362 (40, MH^+-*t*-Bu+H), 318 (100, MH^+–Boc+H), 286 (30). The carbamate **138b** (33 mg, 28%) was also isolated, data as above.

Alternatively, using the general procedure E, carbamate **118f** (102 mg, 0.29 mmol), *n*-BuLi (0.09 mL, 0.23 mmol, 2.5 M in hexanes), (+)-sparteine (87 mg, 0.37 mmol) and methyl chloroformate (0.08 mL, 1.00 mmol) with a reaction time of 90 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the mixture of carbamates **139** and **140** in a ratio of approximately 2.5:1 or 1:2.5 (59 mg, 49%) as an amorphous white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48–7.36 (1H, m, CH), 7.31–7.05 (7H, m, 7 × CH), 6.64–6.42 (2H, m, 2 × CH), 5.21 (0.3H, br s, CH), 4.83 (0.7H, s, CH), 3.60 (2.1H, s, CH_3), 3.29 (0.9H, s, CH_3), 3.12–2.70 (4H, m, 2 × CH_2), 1.52–1.36 (9H, m, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, some carbons could not be observed) δ = 171.5 (C=O), 152.7 (C=O), 139.7 (C), 135.1 (C), 133.0 (C), 131.3 (C), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 127.2 (CH), 126.2 (CH), 125.9 (CH), 125.1 (CH), 124.9 (CH), 81.6 (C), 81.2 (C), 52.6 (CH_3), 52.0 (CH_3), 47.5 (CH), 29.7 (2 × CH_2), 28.2 (CH_3), 28.1 (CH_3), 27.5 (CH_2), 27.3 (CH_2); data as above. The carbamates (*S*)-**118f** (40 mg, 39%, 95:5 er) and (*R*)-**138b** (17 mg, 14%, 78:22 er) were also obtained; data as above.

***cis*-3a-(Naphthalen-2-yl)-3-phenyl-3H,4H,5H-[1,3]oxazolo[3,4-a]quinolin-1-one (*cis*-141) and *trans*-3a-(Naphthalen-2-yl)-3-phenyl-3H,4H,5H-[1,3]oxazolo[3,4-a]quinolin-1-one (*trans*-141)**





Using the general procedure D with a reaction time of 6 min, carbamate **118f** (80 mg, 0.22 mmol), *n*-BuLi (0.11 mL, 0.27 mmol, 2.4 M in hexanes) and benzaldehyde (0.05 mL, 0.44 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the carbamate *cis*-**141** (40 mg, 45%) and the carbamate *trans*-**141** (17 mg, 19%).

Carbamate *cis*-**141** was isolated as an amorphous white solid; m.p. 160–162 °C; R_f 0.15 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3060, 2970, 2885, 2880, 1745 (C=O), 1575, 1490, 1455, 1365, 1205, 1150, 1010, 820, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.80 (1H, d, *J* = 8.5 Hz, CH), 7.73–7.60 (2H, m, 2 × CH), 7.48–7.31 (5H, m, 5 × CH), 7.23–7.14 (1H, m, CH), 7.14–7.05 (2H, m, 2 × CH), 7.05–6.94 (4H, m, 4 × CH), 6.62 (1H, d, *J* = 7.0 Hz, CH), 5.61 (1H, s, CH), 3.06–2.93 (1H, m, CH), 2.91–2.74 (1H, m, CH), 2.52–2.34 (2H, m, 2 × CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.4 (C=O), 134.9 (C), 133.4 (C), 133.4 (C), 132.7 (C), 132.3 (C), 129.2 (CH), 128.8 (CH), 128.3 (CH), 128.1 (2 × CH), 127.8 (CH), 127.5 (CH), 127.3 (CH), 126.7 (3 × CH), 126.4 (CH), 126.2 (CH), 124.5 (C), 123.6 (CH), 123.5 (CH), 118.0 (CH), 86.9 (CH), 68.8 (C), 30.8 (CH_2), 24.5 (CH_2); HRMS (ES) Found: MH^+, 392.1649. $C_{27}H_{22}NO_2$ requires MH^+, 392.1645; LRMS *m*/*z* (ES) 414 (10%, MNa^+), 392 (100, MH^+).

Resolution between the enantiomers of the carbamate *cis*-**141** was achieved using a Beckman system fitted with a Daicel ChiralPak IA (250 mm × 460 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (95:5 v/v) as the mobile phase at a flow rate of 0.7 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 32.5 min and 49.9 min respectively with an analysis time of 120 min.

Using the general procedure D with a reaction time of 6 min, carbamate (*S*)-**118f** (35 mg, 0.10 mmol) with an enantiomeric ratio of 95:5, *n*-BuLi (50 μL, 0.12 mmol, 2.4 M in hexanes) and benzaldehyde (20 μL, 0.2 mmol) with a reaction time of 6 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate (3*R*,3a*S*)-**141** (16 mg, 42%) as an amorphous white solid; m.p. 172–174 °C; the enantiomeric ratio was determined to be 95:5 by CSP HPLC (major component eluted at 35.6 min); $[\alpha]_D^{24}$ = –228.9 (0.6, $CHCl_3$).

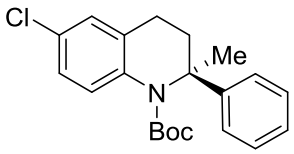
Carbamate *trans*-**141** was isolated as an amorphous white solid; m.p. 176–178 °C; R_f 0.14 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3060, 3035, 2965, 2955, 2930, 2845, 1745 (C=O), 1600, 1580, 1490, 1370, 1230, 1020, 745; ^{1}H NMR (400 MHz, $CDCl_3$) 8.43 (1H, dd, *J* = 8.5, 1.0 Hz, CH), 7.93 (1H, d, *J* = 8.5 Hz, CH), 7.89–7.83 (1H, m, CH), 7.82–7.76 (1H, m, CH), 7.73 (1H, d, *J* = 1.5 Hz, CH), 7.56–7.44 (6H, m, 6 × CH), 7.42–7.30 (3H, m, 3 × CH), 7.02 (1H, td, *J* = 7.5, 1.0 Hz CH), 6.93 (1H, d, *J* = 7.5 Hz, CH), 5.59 (1H, s, CH), 2.72–2.62 (1H, m, CH), 2.47–2.34 (1H, m, CH), 2.12 (1H, ddd, *J* = 13.5, 5.5, 1.5 Hz, CH), 1.73 (1H, td, *J* = 13.5, 5.5 Hz, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.2 (C=O), 138.8 (C), 135.1 (C), 134.8 (C), 133.2 (C), 132.8 (C), 129.7 (CH), 129.1 (CH), 129.0 (CH), 128.7 (CH), 128.3 (CH), 127.6 (CH), 127.2 (CH), 126.7 (CH), 126.7 (CH), 126.5 (CH), 125.4 (C), 125.0 (CH), 124.1 (CH), 122.5 (CH), 120.4 (CH), 85.3 (CH), 67.6 (C), 27.8 (CH_2), 24.3 (CH_2); HRMS (ES) Found: MH^+, 392.1657. $C_{27}H_{22}NO_2$ requires MH^+, 392.1645; LRMS *m*/*z* (ES) 414 (5%, MNa^+), 392 (100, MH^+), 348 (10).

Resolution between the enantiomers of the carbamate *trans*-**141** was achieved using a Beckman system fitted with a Daicel ChiralPak IA (250 mm × 460 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (95:5 v/v) as the mobile phase at a flow rate of 0.7 $mL \cdot min^{-1}$; 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 37.4 min and 95.8 min respectively with an analysis time of 120 min.

Using the general procedure D with a reaction time of 6 min, carbamate (*S*)-**118f** (35 mg, 0.10 mmol) with an enantiomeric ratio of 95:5, *n*-BuLi (50 μL, 0.12 mmol, 2.4 M in hexanes) and benzaldehyde (20 μL, 0.2 mmol) with a reaction time of 6 min, gave, after purification by

column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate (3*S*,3a*S*)-**141** (8 mg, 20%) as an off-white gum; the enantiomeric ratio was determined to be 95:5 by CSP HPLC (major component eluted at 38.7 min); $[\alpha]_D^{24} = -17.2$ (0.2, $CHCl_3$).

(*S*)-*tert*-Butyl 6-Chloro-2-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline-1-carboxylate (143a)[99]

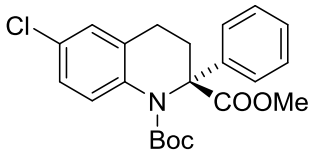


Using the general procedure D with a reaction time of 6 min, carbamate (*S*)-**118e** (34 mg, 0.10 mmol) with an enantiomeric ratio of 92:8, *n*-BuLi (50 μL, 0.12 mmol, 2.4 M in hexanes) and methyl iodide (21 μL, 0.34 mmol) with a reaction time of 6 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the carbamate (*S*)-**143a** (24 mg, 69%) as an oil; the enantiomeric ratio was determined to be 87:13 by CSP HPLC (major component eluted at 9.1 min); $[\alpha]_D^{25} = -18.9$ (1.1, $CHCl_3$); R_f 0.63 [petrol–EtOAc (94:6)]; FT-IR ν_{max} (ATR)/cm^{-1} 3065, 2975, 1700 (C=O), 1600, 1480, 1315, 1245, 1155, 1095, 910, 850, 730, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (1H, d, *J* = 9.0 Hz, CH), 7.38–7.31 (4H, m, 4 × CH), 7.27–7.21 (1H, m, CH), 7.18 (1H, dd, *J* = 9.0, 2.5 Hz, CH), 7.09 (1H, d, *J* = 2.5 Hz, CH), 2.78–2.64 (1H, m, CH), 2.53–2.41 (1H, m, CH), 2.02 (3H, s, CH_3), 1.99–1.92 (2H, m, 2 × CH), 1.18 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.3 (C=O), 148.9 (C), 137.7 (C), 134.5 (C), 128.2 (CH), 127.6 (C), 127.1 (CH), 126.0 (2 × CH), 124.6 (2 × CH), 81.2 (C), 62.8 (C), 44.0 (CH_2), 27.9 (CH_3), 27.5 (CH_3), 24.8 (CH_2); HRMS (ES) Found MH^+, 380.1394. $C_{21}H_{24}{}^{35}ClNaNO_2$ requires MH^+, 380.1388; Found MH^+, 382.1369. $C_{21}H_{24}{}^{37}ClNaNO_2$ requires MH^+, 382.1366; LRMS *m/z* (ES) 382 (<5%, MNa^+), 380 (5, MNa^+), 304 (30, MH^+–*t*-Bu), 302 (100, MH^+–*t*-Bu).

Resolution between the enantiomers of the tetrahydroquinoline **143a** was achieved using a Beckman system fitted with a Daicel Chiralpak IA 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 faster running component and slower running component were eluted at 7.2 min and 9.1 min respectively with an analysis time of 10 min.

(*R*)-1-*tert*-Butyl 2-Methyl 6-Chloro-2-phenyl-1,2,3,4-tetrahydroquinoline-1,2-dicarboxylate (143b)[99]

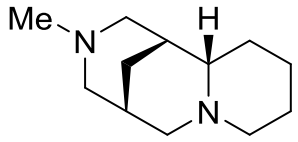


Using the general procedure E, carbamate (*S*)-**118e** (101 mg, 0.29 mmol), *n*-BuLi (0.12 mL, 0.29 mmol, 2.4 M in hexanes), (+)-sparteine (119 mg, 0.51 mmol) and methyl chloroformate (0.08 mL, 1.03 mmol) with a reaction time of 75 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the carbamate (*R*)-**143b** (54 mg, 42%) as an amorphous white solid; m.p. 41–43 °C; R_f 0.17 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3065, 3025, 2975, 2970, 1745 (C=O), 1705 (C=O), 1485, 1320, 1140, 815, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (1H, d, *J* = 9.0 Hz, CH), 7.62–7.56 (2H, m, 2 × CH), 7.37–7.30 (2H, m, 2 × CH), 7.28–7.19 (2H, m, 2 × CH), 7.06 (1H, d, *J* = 2.5 Hz, CH), 3.80 (3H, s, OCH_3), 2.78 (1H, ddd, *J* = 15.5, 8.5, 2.5 Hz, CH), 2.58–2.41 (2H, m, 2 × CH), 2.23–2.14 (1H, m, CH), 1.30 (9H, m, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.1 (C=O), 153.6 (C=O), 141.9 (C), 136.4 (C), 133.2 (C), 128.4 (C), 127.8 (CH), 127.3 (CH), 127.0 (CH), 126.6 CH), 126.5 (CH), 125.6 (CH), 82.5 (C), 68.7 (C), 52.5 (OCH_3), 38.8 (CH_2), 27.8 (CH_3), 25.0 (CH_2); HRMS (ES) Found MH$^+$, 424.1305. $C_{24}H_{23}{}^{35}ClNO_4$ requires MH$^+$, 424.1310; Found MH$^+$, 426.1284. $C_{24}H_{23}{}^{37}ClNO_4$ requires MH$^+$, 426.1291; LRMS *m/z* (ES) 426 (5%, MH$^+$), 424 (10, MH$^+$), 304 (30, MH$^+$–Boc), 302 (100, MH$^+$–Boc); the enantiomeric ratio was determined to be 86:14 by CSP-HPLC (major component eluted at 7.3 min), $[\alpha]_D^{25}$ +51.2 (1.2, $CHCl_3$). The carbamate (*S*)-**118e** (42 mg, 41%) was also recovered; data as above.

Resolution between the enantiomers of the THQ **143b** 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 (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature and detection by UV absorbance at 254 nm. Under these conditions, the

faster running component and slower running component were eluted at 7.3 min and 8.3 min respectively with an analysis time of 10 min.

(+)-Sparteine surrogate (148)[119]



A 2 L, three-necked round-bottomed flask equipped with an overhead mechanical stirrer with large Teflon-coated blades and two glass stoppers was charged with finely ground *Laburnum anagyroides* seeds (700 g), dichloromethane (1 L), methanol (250 mL) and aqueous 25% w/v ammonium hydroxide (100 mL). The resulting mixture was stirred vigorously at room temperature for 3 days. The mixture was then filtered in three separate batches and the filter cake was washed with CH_2Cl_2 until the filtrate was colourless. 3.3 M HCl was added to the filtrate until the organic layer was acidic. After 2 h, the two layers were separated and the aqueous layer was transferred to a 2 L conical flask equipped with a magnetic stirring bar. The stirred aqueous solution was basified to pH 9-10 by the careful, portionwise addition of aqueous 25% w/v ammonium hydroxide over 1 h, followed by stirring for an additional 2 h. The resulting solution was extracted with CH_2Cl_2 (7 × 400 mL then 3 × 200 mL). The CH_2Cl_2 extracts were combined, dried ($MgSO_4$), filtered and evaporated under reduced pressure to give crude (−)-cytisine **145** (11.92 g) as a yellow-brown solid. The crude (−)-cytisine **145** was purified by recrystallization from toluene (25-30 mL) to afford pure (−)-cytisine **145** (7.87 g, 1.1% mass yield) as a yellow-brown solid.

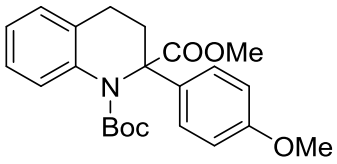
A flame-dried, 250 mL, two-necked round-bottomed flask equipped with a Teflon-coated magnetic stir bar, a glass stopper and a vacuum take-off adapter attached to the argon line was charged with (−)-cytisine **145** (7.87 g, 41.37 mmol), CH_2Cl_2 (120 mL) and triethylamine (6.34 mL, 45.51 mmol). The resulting stirred solution was immersed in an ice bath and methyl chloroformate (3.50 mL, 45.51 mmol) was added dropwise via syringe over 10 min at 0 °C. The resulting mixture was stirred for 1 h at 0 °C and then for 3 h at room temperature before the solvent was evaporated under reduced pressure. Ethyl acetate (60 mL) was added to the residue and the solids were removed by filtration through Celite. The filter cake was washed

with EtOAc (3 × 20 mL) and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography over a short plug of silica with CH_2Cl_2:MeOH (9:1) as eluent. The fractions containing the product (R_f = 0.51; 9:1, CH_2Cl_2:MeOH) were combined and evaporated under reduced pressure followed by removal of the last traces of solvent by high vacuum drying (10^{-3} mbar) for 2 h to afford pure cytisine methyl carbamate **146** (9.94 g, 40.07 mmol) as a thick oil.

A flame-dried, 250 mL, three-necked round-bottomed flask equipped with a magnetic stir bar, a glass stopper, and a vacuum take-off adapter that can be attached either to the argon line or to the H_2 supply was charged with cytisine methyl carbamate **146** (9.88 g, 39.83 mmol), MeOH (100 mL) and platinum(IV) oxide (0.90 g, 4.0 mmol). The resulting magnetically-stirred suspension was carefully evacuated and backfilled with nitrogen (three times) before evacuating and backfilling with hydrogen (*via* hydrogen balloons attached to the two-tap adaptor). The cloudy black mixture was stirred vigorously under a hydrogen atmosphere for 18 h. The solids were removed by filtration through Celite and the filter cake was washed with MeOH (50 mL). The filtrate was evaporated under reduced pressure followed by removal of the last traces of solvent by high vacuum drying (10^{-3} mbar) to afford the crude hydrogenation product **147** (9.61 g) as an off-white solid.

A flame-dried, 500 mL, two-necked round-bottomed flask equipped with a magnetic stir bar, a reflux condenser attached to the argon line, and a glass stopper, was charged with lithium aluminium hydride (4.14 g, 109.07 mmol) and THF (150 mL). The resulting magnetically-stirred suspension was immersed in an ice bath and a solution of the crude hydrogenation product **147** (4.80 g, 19.04 mmol) in THF (100 mL) was added dropwise over 10 min, at 0 °C. The mixture was allowed to warm to room temperature and then refluxed under nitrogen for 16 h. 1 M NaOH (aq) solution was added until the grey/silver colour disappeared and a clear solution with a white precipitate remained. The white precipitate was filtered off and the filter cake was washed with Et_2O. The filtrate was dried ($MgSO_4$), filtered and evaporated under reduced pressure to give crude diamine **148**. The crude diamine **148** was purified by Kugelrohr distillation to afford pure diamine **148** (2.13 g, 57%) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.04–2.91 (2H, m, 2 × CH), 2.89–2.76 (2H, m, 2 × CH), 2.25–2.18 (1H, m, CH), 2.17–2.08 (4H, m, 4 × CH), 1.96 (1H, dd, *J* = 11.5, 3.0 Hz), 1.90 (1H, d, *J* = 11.0 Hz), 1.82–1.46 (9H, m, 9 × CH), 1.37–1.19 (2H, m, 2 × CH); $[\alpha]_D$ not obtained. Data consistent with the literature.[119]

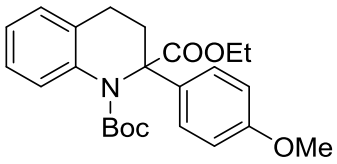
1-*tert*-Butyl 2-Methyl 2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroquinoline-1,2-dicarboxylate (149a)



Using the general procedure D with a reaction time of 90 min, carbamate **118c** (76 mg, 0.22 mmol), *n*-BuLi (0.28 mL, 0.68 mmol, 2.4 M in hexanes), THF (2 mL) and methyl chloroformate (0.06 mL, 0.79 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), carbamate **149a** (71 mg, 80%) as an oil; R_f 0.25 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3065, 3040, 2950, 2930, 2855, 2840, 1740 (C=O), 1705 (C=O), 1605, 1510, 1490, 1320, 1250, 1155, 1140, 1030, 825, 750, 745; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 (1H, d, *J* = 8.0 Hz, CH), 7.55–7.49 (2H, m, 2 × CH), 7.28–7.22 (1H, m, CH), 7.06 (1H, dd, *J* = 7.5, 1.0 Hz, CH), 7.01 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.88–6.83 (2H, m, 2 × CH), 3.81 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 2.88–2.76 (1H, m, CH), 2.58–2.43 (2H, m, 2 × CH), 2.21–2.11 (1H, m, CH), 1.33 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.7 (C=O), 158.3 (C), 153.8 (C=O), 137.8 (C), 134.3 (C), 131.6 (C), 127.9 (CH), 127.6 (CH), 126.4 (CH), 124.4 (CH), 123.4 (CH), 113.0 (CH), 82.0 (C), 68.3 (C), 55.2 (OCH_3), 52.4 (OCH_3), 39.2 (CH_2), 27.9 (CH_3), 25.1 (CH_2); HRMS (ES) Found: MNa^+, 420.1777. $C_{23}H_{27}NO_5Na$ requires MNa^+, 420.1787; LRMS *m/z* (ES) 436 (5%, MK^+), 421 (15, MK^+–CH_3), 420 (100, MNa^+).

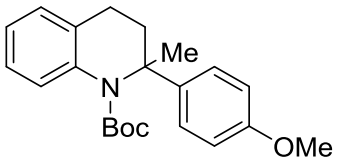
Resolution between the enantiomers of the carbamate **149a** was achieved using a Beckman system fitted with a Daicel ChiralPak IA column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 mL·min^{-1}; ambient temperature, 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 39.5 min and 43.4 min respectively with an analysis time of 60 min.

1-*tert*-Butyl 2-Ethyl 2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroquinoline-1,2-dicarboxylate (149b)



Using the general procedure D with a reaction time of 90 min, carbamate **118c** (89 mg, 0.26 mmol), *n*-BuLi (0.33 mL, 0.79 mmol, 2.4 M in hexanes), THF (2 mL) and ethyl chloroformate (0.09 mL, 0.92 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), carbamate **149b** (86 mg, 79%) as an oil; R_f 0.13 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3045, 3005, 2975, 2930, 2855, 1740 (C=O), 1705 (C=O), 1610, 1585, 1510, 1455, 1325, 1250, 1160, 1030, 910, 830, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (1H, d, *J* = 8.0 Hz, CH), 7.56–7.49 (2H, m, 2 × CH), 7.28–7.22 (1H, m, CH), 7.07 (1H, dd, *J* = 7.5, 1.0 Hz, CH), 7.01 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.89–6.83 (2H, m, 2 × CH), 4.33–4.18 (2H, m, OCH_2), 3.81 (3H, s, OCH_3), 2.90–2.79 (1H, m, CH), 2.58–2.44 (2H, m, 2 × CH), 2.21–2.11 (1H, m, CH), 1.35 (9H, s, *t*-Bu), 1.32 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.0 (C=O), 158.3 (C), 153.8 (C=O), 137.9 (C), 134.4 (C), 131.9 (C), 128.0 (CH), 127.5 (CH), 126.4 (CH), 124.4 (CH), 123.4 (CH), 113.0 (CH), 82.0 (C), 68.2 (C), 61.4 (CH_2), 55.2 (OCH_3), 39.4 (CH_2), 28.0 (CH_3), 25.2 (CH_2), 14.2 (CH_3); HRMS (ES) Found: MH^+, 412.2137. $C_{24}H_{30}NO_5$ requires MH^+, 412.2124; LRMS *m/z* (ES) 434 (10%, MNa^+), 412 (75, MH^+), 356 (60, MH^+–*t*-Bu+H), 312 (100, MH^+–Boc+H).

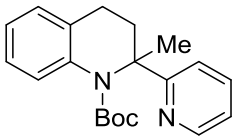
***tert*-Butyl 2-(4-Methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroquinoline-1-carboxylate (149c)**



Using the general procedure D with a reaction time of 90 min, carbamate **118c** (73 mg, 0.22 mmol), *n*-BuLi (0.27 mL, 0.65 mmol, 2.4 M in hexanes), THF (2 mL) and methyl iodide (0.05 mL, 0.76 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), carbamate **149c** (64 mg, 84%) as an amorphous orange solid; m.p. 80–82 °C; R_f 0.57 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3065, 3035, 3005, 2970, 2930,

2855, 2835, 1695 (C=O), 1610, 1585, 1510, 1490, 1315, 1245, 1155, 1030, 825, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70–7.65 (1H, m, CH), 7.32–7.26 (2H, m, 2 × CH), 7.25–7.19 (1H, m, CH), 7.10 (1H, dd, *J* = 7.5, 1.0 Hz, CH), 7.00 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.91–6.85 (2H, m, 2 × CH), 3.83 (3H, s, OCH_3), 2.78–2.68 (1H, m, CH), 2.50 (1H, ddd, *J* = 15.0, 6.0, 3.5 Hz, CH), 2.03 (CH_3), 2.00–1.89 (2H, m, 2 × CH), 1.25 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.7 (C), 154.6 (C=O), 141.6 (C), 139.1 (C), 132.9 (C), 127.4 (CH), 126.0 (CH), 125.8 (CH), 124.8 (CH), 122.6 (CH), 113.4 (CH), 80.7 (C), 62.4 (C), 55.3 (OCH_3), 44.6 (CH_2), 28.0 (CH_3), 27.6 (CH_3), 25.0 (CH_2); HRMS (ES) Found: MNa^+, 376.1877. $C_{22}H_{27}NO_3Na$ requires MNa^+, 376.1889; LRMS *m/z* (ES) 376 (100, MNa^+), 236 (10).

***tert*-Butyl 2-Methyl-2-(pyridin-2-yl)-1,2,3,4-tetrahydroquinoline-1-carboxylate (150)**

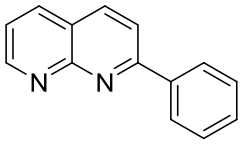


Using the general procedure D with a reaction time of 6 min, carbamate **118d** (103 mg, 0.33 mmol), *n*-BuLi (0.17 mL, 0.40 mmol, 2.4 M in hexanes), THF (2 mL) and methyl iodide (0.07 mL, 1.16 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), carbamate **150** (46 mg, 43%) as an oil; R_f 0.66 [petrol–EtOAc (3:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3065, 3005, 2975, 2930, 2855, 1700 (C=O), 1590, 1570, 1490, 1365, 1320, 1150, 1120, 1050, 850, 765, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.61–8.57 (1H, m, CH), 7.70 (1H, d, *J* = 8.0 Hz, CH), 7.65 (1H, td, *J* = 8.0, 2.0 Hz, CH), 7.42–7.37 (1H, m, CH), 7.25–7.19 (1H, m, CH), 7.17 (1H, ddd, *J* = 7.5, 5.0, 1.0 Hz, CH), 7.10 (1H, dd, *J* = 7.5, 1.0 Hz, CH), 7.00 (1H, td, *J* = 7.5, 1.0 Hz, CH), 2.83–2.72 (1H, m, CH), 2.51 (1H, dt, *J* = 15.0, 5.0 Hz, CH), 2.06 (CH_3), 2.04–1.99 (2H, m, 2 × CH), 1.22 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.9 (C), 154.3 (C=O), 148.4 (CH), 138.6 (C), 136.0 (CH), 132.9 (C), 127.4 (CH), 126.1 (CH), 124.8 (CH), 122.8 (CH), 121.0 (CH), 119.5 (CH), 80.8 (C), 64.3 (C), 42.6 (CH_2), 28.0 (CH_3), 26.6 (CH_3), 24.9 (CH_2); HRMS (ES) Found: MH^+, 325.1925. $C_{20}H_{25}N_2O_2$ requires MH^+, 325.1916; LRMS *m/z* (ES) 325 (100, MH^+), 225 (5, MH^+–Boc+H).

Resolution between the enantiomers of the carbamate **150** was achieved using a Beckman system fitted with a Daicel Chiralpak IA 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

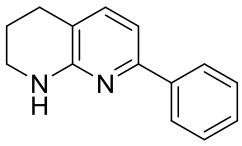
of 0.7 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume was 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the faster running component and slower running component were eluted at 15.4 min and 18.4 min respectively with an analysis time of 30 min.

2-Phenyl-1,8-naphthyridine (154)[121]



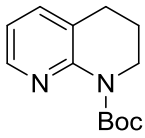
Using general procedure A, (2-aminopyridin-3-yl)methanol **153** (1.01 g, 8.11 mmol), acetophenone **121a** (0.95 mL, 8.11 mmol), benzophenone (1.48 g, 8.11 mmol), 1,4-dioxane (20 mL) and *t*-BuOK (8.11 mL, 8.11 mmol, 1.0 M in THF) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1) and then acid-base extraction, the naphthyridine **154** (1.27 g, 75%) as an amorphous white solid; m.p. 109–111 °C (lit.[121] 120–121 °C); R_f 0.24 [petrol–EtOAc (1:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.18–9.13 (1H, m, CH), 8.38–8.32 (2H, m, 2 × CH), 8.28 (1H, d, *J* = 8.5 Hz, CH), 8.22 (1H, dd, *J* = 8.0, 2.0 Hz, CH), 8.05 (1H, d, *J* = 8.5 Hz, CH), 7.59–7.46 (4H, m, 4 × CH). Data consistent with the literature.[121]

2-phenyl-5,6,7,8-tetrahydro-1,8-naphthyridine (155)[157]



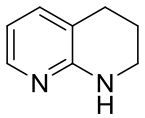
Using the general procedure B, naphthyridine **154** (1.27 g, 6.13 mmol), acetic acid (50 mL) and sodium cyanoborohydride (0.77 g, 12.26 mmol) gave, after partial purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the crude 5,6,7,8-tetrahydronaphthyridine **155**; ^{1}H NMR (400 MHz, $CDCl_3$, only selected peaks reported) δ = 3.47 (2H, t, *J* = 5.5 Hz, CH_2), 2.79 (2H, t, *J* = 6.5 Hz, CH_2), 2.00–1.92 (2H, m, CH_2). Data consistent with the literature.[157]

***tert*-Butyl 1,2,3,4-Tetrahydro-1,8-naphthyridine-1-carboxylate (156)**[158]



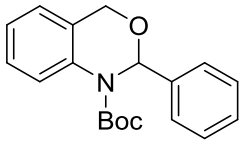
Using the general procedure C, 1,2,3,4-tetrahydroquinoline **159** (0.25 g, 1.88 mmol), *n*-BuLi (1.31 mL, 3.01 mmol, 2.3 M in hexanes), THF (20 mL) and Boc_2O (0.70 g, 3.20 mmol) with a reaction time of 20 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the carbamate **156** (0.37 g, 83%) as an amorphous off-white solid; m.p. 50–52 °C (No melting point reported.[158]); R_f 0.30 [petrol–EtOAc (3:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.37–8.32 (1H, m, CH), 7.42–7.37 (1H, m, CH), 6.96 (1H, dd, *J* = 7.5, 5.0 Hz, CH), 3.81–3.75 (2H, m, CH_2), 2.77 (2H, t, *J* = 6.5 Hz, CH_2), 1.98–1.90 (2H, m, CH_2), 1.55 (9H, s, *t*-Bu). Data consistent with the literature.[158]

1,2,3,4-Tetrahydro-1,8-naphthyridine (159)[157]



To a solution of (2-amino-pyridin-3-yl)-methanol **153** (0.529 g, 4.26 mmol) in *t*-amyl alcohol **157** (15 mL) was added ethanol (0.747 mL, 12.8 mmol), *t*-BuOK (2.13 mL, 2.13 mmol, 1.0 M in THF), Xantphos **158** (0.074 g, 0.13 mmol) and $Ru_3(CO)_{12}$ (0.027 g, 0.043 mmol). The reaction mixture was left to stir for 16 h at 130 °C under an inert atmosphere. After cooling to room temperature, the solvent was removed under reduced pressure and this gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (3:1), the 1,2,3,4-tetrahydronaphthyridine **159** (0.318 g, 55%) as a sticky brown solid; R_f 0.15 [petrol–EtOAc (1:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89–7.80 (1H, m, CH), 7.16–7.10 (1H, m, CH), 6.48 (1H, dd, *J* = 7.0, 5.0 Hz, CH), 5.08 (1H, s, NH), 3.42 (2H, t, *J* = 5.5 Hz, CH_2), 2.72 (2H, t, *J* = 6.5 Hz, CH_2), 1.96–1.87 (2H, m, CH_2). Data consistent with the literature.[157]

***tert*-Butyl 2-Phenyl-1,2,3,4-tetrahydro-3,1-benzoxazine-1-carboxylate (163)**

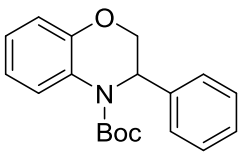


Dichloromethane (20 mL) was added to a mixture of carbamate **188** (1.02 g, 4.6 mmol), Amberlyst® 15 (0.5 g) and 4Å molecular sieves (5 g). Benzaldehyde (0.93 mL, 9.2 mmol) was added and the reaction mixture was left to stir overnight under reflux. The mixture was filtered and the solvent was removed under reduced pressure. The residue was re-dissolved in ethanol (45 mL), $NaBH_4$ (0.35 g, 9.2 mmol) was added at 0 °C and the mixture was left to stir for 3 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate (20 mL) and water (20 mL). The aqueous layer was extracted and the organic layer was washed with water (20 mL) and brine (20 mL). The organic layer was dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure to give the crude product which gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the carbamate **163** (0.54 g, 38%) as an amorphous white solid; m.p. 68–70 °C; R_f 0.66 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3065, 3035, 3005, 2975, 2930, 2855, 1700 (C=O), 1590, 1495, 1320, 1155, 1005, 735, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (1H, d, *J* = 8.5 Hz, CH), 7.38–7.21 (6H, m, 6 × CH), 7.01 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.97 (1H, s, CH), 6.85 (1H, dd, *J* = 7.5, 1.0 Hz, CH), 4.79 (1H, d, *J* = 15.0 Hz, CH), 4.66 (1H, d, *J* = 15.0 Hz, CH), 1.55 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.1 (C=O), 137.3 (C), 135.1 (C), 128.5 (CH), 128.1 (CH), 127.0 (CH), 126.8 (CH), 126.3 (C), 124.2 (CH), 123.9 (CH), 123.5 (CH), 82.8 (CH), 82.0 (C), 62.3 (CH_2) 28.3 (CH_3); HRMS (ES) Found MNa^+, 334.1404. $C_{19}H_{21}NO_3Na$ requires MNa^+, 334.1419; LRMS *m/z* (ES) 334 (70%, MNa^+), 234 (100, MNa^+-Boc+H).

Resolution between the enantiomers of the carbamate **163** 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 (99:1 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 13.3 min and 19.6 min respectively with an analysis time of 30 min.

Using the general procedure E, *n*-BuLi (0.36 mL, 0.91 mmol, 2.5 M in hexanes), (+)-sparteine (361 mg, 1.54 mmol), toluene (4 mL), carbamate **163** (282 mg, 0.91 mmol) and methyl chloroformate (0.24 mL, 3.17 mmol) with a reaction time of 2.5 h, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), recovered carbamate (*S*)-**163** (28 mg, 10%) as an amorphous white solid; data as above; the enantiomeric ratio was determined to be 89:11 by CSP-HPLC (major component eluted at 14.1 min); the carbamate (*S*)-**189** (155 mg, 46%) was also isolated; data as below; the enantiomeric ratio was determined to be 77:23 by CSP-HPLC (major component eluted at 65.8 min).

***tert*-Butyl 3-Phenyl-1,2,3,4-tetrahydro-1,4-benzoxazine-4-carboxylate (164a)**[159]



Using the general procedure C, tetrahydrobenzoxazine **193a** (0.73 g, 3.44 mmol), *n*-BuLi (1.51 mL, 3.78 mmol, 2.5 M in hexanes) and Boc_2O (0.75 g, 3.44 mmol) with a reaction time of 20 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **164a** (0.56g, 52%) as an amorphous white solid; m.p. 81–83 °C (No melting point reported.[164]); R_f 0.32 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3000, 2975, 2930, 2880, 1705 (C=O), 1585, 1490, 1365, 1250, 1140, 1065, 745; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.16–8.03 (1H, m, CH), 7.35–7.22 (5H, m, 5 × CH), 7.01–6.93 (2H, m, 2 × CH), 6.92–6.85 (1H, m, CH), 5.63 (1H, t, *J* = 2.5 Hz, CH), 4.57 (1H, dd, *J* = 11.0, 2.5 Hz, CH), 4.39 (1H, dd, *J* = 11.0, 3.0 Hz, CH), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.7 (C=O), 146.1 (C), 139.0 (C), 128.5 (CH), 127.4 (CH), 126.4 (CH), 126.2 (C), 123.8 (CH), 123.0 (CH), 121.2 (CH), 117.1 (CH), 81.9 (C), 68.5 (CH_2), 55.0 (CH), 28.2 (CH_3); HRMS (ES) Found: MNa^+, 334.1413. $C_{19}H_{21}NO_3Na$ requires MNa^+, 334.1414; LRMS *m/z* (ES) 334 (5%, MNa^+), 256 (100, MH^+-*t*-Bu+H), 212 (10, MH^+-Boc+H); Found: C, 73.29; H, 6.85; N, 4.39. $C_{19}H_{21}NO_3$ requires C, 73.29; H, 6.80; N, 4.50. Data consistent with the literature.[159]

Resolution between the enantiomers of the carbamate **164a** 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 (99.5:0.5 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 8.9 min and 10.0 min respectively with an analysis time of 15 min.

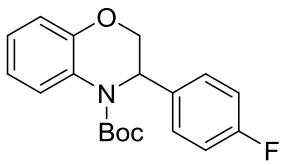
Alternatively, resolution between the enantiomers of the carbamate **164a** was also achieved using a Beckman system fitted with a Daicel ChiralCel OJ column (250 mm × 4.60 mm i.d.) as the stationary phase with a mixture of *n*-hexane:isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1 $mL \cdot min^{-1}$; 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 10.9 min and 14.5 min respectively with an analysis time of 20 min.

Using the general procedure J, *n*-BuLi (0.09 mL, 0.21 mmol, 2.5 M in hexanes), (+)-sparteine (50 mg, 0.21 mmol), carbamate **164a** (113 mg, 0.36 mmol) and methyl chloroformate (0.10 mL, 1.28 mmol) with a reaction time of 30 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), recovered carbamate (*R*)-**164a** (48 mg, 42%) as an amorphous off-white solid; m.p. 90–92 °C; data as above; the enantiomeric ratio was determined to be 94:6 by CSP-HPLC (major component eluted at 8.9 min); $[\alpha]_D^{23}$ –66.1 (0.8, $CHCl_3$). The carbonate **194b** (83 mg, 62%) was also isolated; data as below.

Also using the general procedure J, *n*-BuLi (0.09 mL, 0.22 mmol, 2.5 M in hexanes), (+)-sparteine (52 mg, 0.22 mmol), carbamate **164a** (115 mg, 0.37 mmol) and methyl chloroformate (0.10 mL, 1.29 mmol) with a reaction time of 30 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), recovered carbamate (*R*)-**164a** (44 mg, 39%); data as above; the enantiomeric ratio was determined to be >99:1 by CSP-HPLC (major component eluted at 8.8 min); $[\alpha]_D^{23}$ –63.7 (1.1, $CHCl_3$). The carbonate **194b** (94 mg, 69%) was also isolated; data as below.

Also using the general procedure J, *n*-BuLi (0.07 mL, 0.18 mmol, 2.5 M in hexanes), (+)-sparteine (42 mg, 0.18 mmol), carbamate **164a** (102 mg, 0.33 mmol) and methyl chloroformate (0.09 mL, 1.15 mmol) with a reaction time of 30 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), recovered carbamate (*R*)-**164a** (42 mg, 41%); data as above; the enantiomeric ratio was determined to be >99:1 by CSP-HPLC (major component eluted at 8.8 min); $[\alpha]_D^{23}$ –45.3 (0.3, $CHCl_3$). The carbonate **194b** (84 mg, 69%) was also isolated; data as below.

***tert*-Butyl 3-(4-Fluorophenyl)-1,2,3,4-tetrahydro-1,4-benzoxazine-4-carboxylate (164b)**



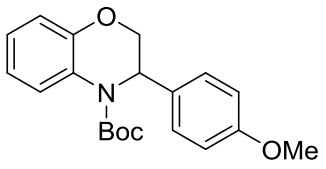
Using the general procedure C, tetrahydrobenzoxazine **193b** (1.07 g, 4.66 mmol), *n*-BuLi (2.05 mL, 5.12 mmol, 2.5 M in hexanes) and Boc_2O (1.02 g, 4.66 mmol) with a reaction time of 20 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **164b** (1.47 g, 95%) as an amorphous orange solid; m.p. 85–87 °C; R_f 0.26 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3130, 3045, 2990, 2980, 2880, 1700 (C=O), 1605, 1585, 1510, 1490, 1330, 1215, 1140, 1000, 830, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04 (1H, d, *J* = 7.0 Hz, CH), 7.30–7.22 (2H, m, 2 × CH), 7.02–6.92 (4H, m, 4 × CH), 6.91–6.86 (1H, m, CH), 5.61 (1H, t, *J* = 2.5 Hz, CH), 4.54 (1H, dd, *J* = 11.5, 2.0 Hz, CH), 4.37 (1H, dd, *J* = 11.5, 3.0 Hz, CH), 1.50 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.0 (d, *J* = 245.5 Hz, C), 152.7 (C=O), 145.8 (C), 134.6 (d, *J* = 3.0 Hz, C), 128.2 (d, *J* = 8.0 Hz, CH), 125.8 (C), 124.0 (CH), 123.0 (CH), 121.2 (CH), 117.1 (CH), 115.4 (d, *J* = 21.5 Hz, CH), 82.1 (C), 68.3 (CH_2), 54.2 (CH), 28.2 (CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 115.1; HRMS (ES) Found: MNa^+, 352.1325. $C_{19}H_{20}FNO_3Na$ requires MNa^+, 352.1319; LRMS *m/z* (ES) 352 (5%, MNa^+), 274 (100, MH^+-*t*-Bu+H), 230 (5, MH^+-Boc+H), 178 (30).

Resolution between the enantiomers of the carbamate **164b** was achieved using a Beckman system fitted with a Daicel 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·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 9.1 min and 12.4 min respectively with an analysis time of 15 min.

Using the general procedure J, *n*-BuLi (0.12 mL, 0.31 mmol, 2.5 M in hexanes), (+)-sparteine (71 mg, 0.31 mmol), carbamate **164b** (101 mg, 0.31 mmol) and ethyl chloroformate (0.10 mL, 1.07 mmol) with a reaction time of 45 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), recovered carbamate (*R*)-**164b** (43 mg, 42%) as an amorphous white solid; m.p. 99–101 °C; data as above; the enantiomeric ratio was determined to be 86:14 by CSP-HPLC (major component eluted at 12.8 min); $[\alpha]_D^{24}$ –56.0 (0.2, $CHCl_3$). The carbonate **196b** (68 mg, 55%) was also isolated, data as below.

***tert*-Butyl 3-(4-Methoxyphenyl)-1,2,3,4-tetrahydro-1,4-benzoxazine-4-carboxylate (164c)**



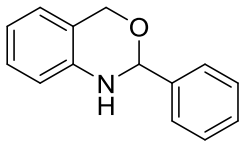
Using the general procedure C, tetrahydrobenzoxazine **193c** (1.00 g, 4.18 mmol), *n*-BuLi (1.84 mL, 4.60 mmol, 2.5 M in hexanes) and Boc_2O (0.91 g, 4.18 mmol) with a reaction time of 20 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **164c** (1.16 g, 81%) as an amorphous white solid; m.p. 95–96 °C; R_f 0.20 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3125, 3015, 3000, 2985, 2975, 2840, 1705 (C=O), 1610, 1585, 1510, 1490, 1330, 1245, 1140, 1030, 830, 770; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.05 (1H, d, *J* = 7.5 Hz, CH), 7.25–7.19 (2H, m, 2 × CH), 7.01–6.91 (2H, m, 2 × CH), 6.91–6.86 (1H, m, CH), 6.86–6.80 (2H, m, 2 × CH), 5.60 (1H, t, *J* = 2.5 Hz, CH), 4.56 (1H, dd, *J* = 11.0, 2.0 Hz, CH), 4.37 (1H, dd, *J* = 11.0, 3.0 Hz, CH), 3.77 (3H, s, OCH_3), 1.52 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.8 (C), 152.7 (C=O), 146.0 (C), 130.9 (C), 127.7 (CH), 125.9 (C), 123.9 (CH), 123.1 (CH), 121.1 (CH), 117.0 (CH), 113.9 (CH), 81.8 (C), 68.5 (CH_2), 55.2 (CH), 54.1 (OCH_3), 28.3 (CH_3); HRMS (ES) Found: MNa^+, 364.1521.

$C_{20}H_{23}NO_4Na$ requires MNa^+, 364.1519; LRMS *m/z* (ES) 364 (10%, MNa^+), 242 (15, MH^+-Boc+H), 134 (100).

Resolution between the enantiomers of the carbamate **164c** was achieved using a Beckman system fitted with a Daicel 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·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 14.4 min and 20.5 min respectively with an analysis time of 30 min.

Using the general procedure J, *n*-BuLi (0.14 mL, 0.36 mmol, 2.5 M in hexanes), (+)-sparteine (84 mg, 0.36 mmol), carbamate **164c** (101 mg, 0.30 mmol) and ethyl chloroformate (0.10 mL, 1.04 mmol) with a reaction time of 45 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), recovered carbamate (*R*)-**164c** (40 mg, 39%) as an amorphous white solid; m.p. 81–83 °C; data as above; the enantiomeric ratio was determined to be 95:5 by CSP-HPLC (major component eluted at 20.0 min); $[\alpha]_D^{24}$ –90.7 (0.2, $CHCl_3$). The carbonate **196b** (68 mg, 55%) was also isolated, data as below.

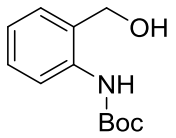
2-Phenyl-1,2,3,4-tetrahydro-3,1-benzoxazine (187)[139]



A mixture of 2-aminobenzyl alcohol **120a** (5.03 g, 40.8 mmol), benzaldehyde (4.15 mL, 40.8 mmol) and acetic acid (100 mL) was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and the tetrahydrobenzoxazine **187** (4.0 g, 46%) was obtained without further purification as an amorphous yellow solid; m.p. 103–105 °C (lit.[139] 94–96 °C); R_f 0.59 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3330 (N–H), 3035, 3015, 2975, 1610, 1590, 1485, 1365, 1020, 740, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67–7.59 (2H, m, 2 × CH), 7.52–7.41 (3H, m, 3 × CH), 7.16 (1H, t, *J* = 7.5 Hz, CH), 7.02 (1H, d, *J* = 7.5 Hz, CH), 6.95–6.87 (1H, m, CH), 6.80–6.72 (1H, m, CH), 5.63 (1H, s, CH), 5.17 (1H, d, *J* = 14.5 Hz, CH), 4.99 (1H, d, *J* = 14.5 Hz, CH), 4.21 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$)

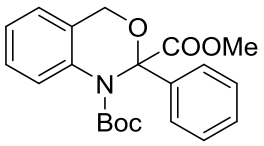
δ = 141.7 (C), 139.2 (C), 129.2 (CH), 128.7 (CH), 127.5 (CH), 126.6 (CH), 125.1 (CH), 122.2 (C), 119.9 (CH), 117.1 (CH), 85.3 (CH), 67.8 (CH_2); HRMS (ES) Found MNa^+, 234.0887. $C_{14}H_{13}NONa$ requires MNa^+, 234.0895; LRMS *m/z* (ES) 315 (100%), 234 (15, MNa^+), 212 (5, MH^+). Data consistent with the literature.[139]

***tert*-Butyl *N*-[2-(Hydroxymethyl)phenyl]carbamate (188)**[140]



Boc_2O (3.94 g, 18.1 mmol) in THF (10 mL) was added to a solution of 2-aminobenzyl alcohol **120a** (2.12 g, 17.2 mmol) in THF (10 mL). The reaction mixture was stirred at 40 °C overnight, the solvent was removed under reduced pressure and the mixture was purified by column chromatography on silica gel, eluting with petrol–EtOAc (9:1) to give the carbamate **188** (3.61 g, 94%) as an oil; R_f 0.17 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3345 (N–H), 3005, 2980, 2930, 1730, 1700 (C=O), 1590, 1520, 1450, 1235, 1150, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (1H, d, *J* = 8.5 Hz, CH), 7.68 (1H, s, NH), 7.36–7.29 (1H, m, CH), 7.18 (1H, dd, *J* = 7.5, 1.0 Hz, CH), 7.04 (1H, td, *J* = 7.5, 1.0 Hz, CH), 4.69 (2H, d, *J* = 6.0 Hz, CH_2), 2.31 (1H, t, *J* = 6.0 Hz, OH), 1.54 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.5 (C=O), 138.0 (C), 129.2 (CH), 129.0 (C), 129.0 (CH), 123.2 (CH), 121.1 (CH), 80.5 (C), 64.3 (CH_2), 28.4 (CH_3); HRMS (ES) Found MNa^+, 246.1102. $C_{12}H_{17}NO_3Na$ requires MNa^+, 246.1101; LRMS *m/z* (ES) 246 (5%, MNa^+), 150 (100), 132 (25). Data consistent with the literature.[140]

1-*tert*-Butyl 2-Methyl 2-Phenyl-4H-3,1-benzoxazine-1,2-dicarboxylate (189)

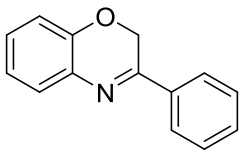


n-BuLi (0.17 mL, 0.40 mmol, 2.4 M in hexanes) was added to a solution of carbamate **163** (104 mg, 0.33 mmol) in THF (2 mL) at –78 °C. The reaction mixture was left to stir for 2 h and methyl chloroformate (0.09 mL, 1.17 mmol) was added before leaving the reaction mixture to stir overnight. Methanol (1 mL) was added, the solvent was removed under reduced pressure

to give the crude product which gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the carbamate **189** (97 mg, 79%) as an amorphous white solid; m.p. 120–122 °C; R_f 0.30 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3050, 3010, 3000, 2985, 2970, 2960, 2935, 2870, 1760 (C=O), 1710 (C=O), 1610, 1585, 1490, 1315, 1235, 1155, 1085, 760, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69 (1H, d, *J* = 8.0 Hz, CH), 7.56–7.51 (2H, m, 2 × CH), 7.32–7.20 (4H, m, 4 × CH), 7.03 (1H, td, *J* = 7.5, 1.0 Hz, CH), 6.92–6.86 (1H, m, CH), 5.06 (1H, d, *J* = 14.5 Hz, CH), 4.67 (1H, d, *J* = 14.5 Hz, CH), 3.79 (3H, s, OCH_3), 1.48 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.3 (C=O), 153.4 (C=O), 137.0 (C), 136.3 (C), 128.5 (CH), 128.4 (C), 127.9 (CH), 127.8 (CH), 127.2 (CH), 125.3 (CH), 124.4 (CH), 124.2 (CH), 89.5 (C), 83.1 (C), 64.1 (CH_2), 52.8 (OCH_3), 28.0 (CH_3); HRMS (ES) Found MNa^+, 392.1469. $C_{21}H_{23}NO_5Na$ requires MNa^+, 392.1468; LRMS *m/z* (ES) 392 (20%, MNa^+), 270 (100, MH^+-Boc+H), 252 (20), 150 (50).

Resolution between the enantiomers of the carbamate **189** 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 (99:1 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 37.5 min and 63.3 min respectively with an analysis time of 90 min.

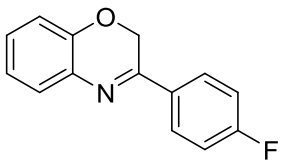
3-Phenyl-2H-1,4-benzoxazine (192a)[160,161]



Using the general procedure H, potassium carbonate (38 g, 275 mmol), 2-aminophenol **190** (5.0 g, 45.8 mmol), ketone **191a** (9.1 g, 45.8 mmol) and $NBu_4^+HSO_4^-$ (0.4 g, 1.1 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the benzoxazine **192a** (7.0 g, 72%) as an amorphous yellow solid; m.p. 106–108 °C (lit.[161] 113 °C); R_f 0.63 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3105, 3055, 3035, 2850, 1610, 1565, 1480, 1445, 1215, 1060, 880, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98–7.92 (2H, m, 2 × CH), 7.54–7.45 (4H, m, 4 × CH), 7.19 (1H, td, *J* = 7.5, 1.5 Hz, CH), 7.07 (1H, td, *J* = 7.5, 1.5

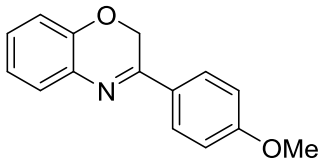
Hz, CH), 6.96 (1H, dd, J = 8.0, 1.5 Hz, CH), 5.10 (2H, s, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.7 (C), 146.4 (C), 135.5 (C), 133.8 (C), 131.2 (CH), 128.8 (CH), 128.7 (CH), 127.9 (CH), 126.5 (CH), 122.4 (CH), 115.6 (CH), 62.9 (CH_2); HRMS (ES) Found: MH^+, 210.0911. $C_{14}H_{12}NO$ requires MH^+, 210.0913; LRMS *m/z* (ES) 210 (100%, MH^+). Data consistent with the literature.[160,161]

3-(4-Fluorophenyl)-2H-1,4-benzoxazine (192b)[161]



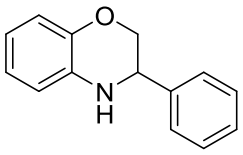
Using the general procedure H, potassium carbonate (30 g, 220 mmol), 2-aminophenol **190** (4.0 g, 36.7 mmol), ketone **191b** (8.0 g, 36.7 mmol), and $NBu_4^+HSO_4^-$ (0.3 g, 0.9 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the benzoxazine **192b** (6.7g, 80%) as an amorphous off-white solid; m.p. 130–131 °C (No melting point reported.[162]); R_f 0.37 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3065, 3050, 2995, 1600, 1585, 1570, 1480, 1385, 1210, 1110, 1005, 835, 750; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.00–7.92 (2H, m, 2 × CH), 7.45 (1H, dd, J = 7.5, 1.5 Hz, CH), 7.22–7.14 (3H, m, 3 × CH), 7.06 (1H, td, J = 7.5, 1.5 Hz, CH), 6.95 (1H, dd, J = 8.0, 1.5 Hz, CH), 5.06 (2H, s, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.6 (d, J = 252.5 Hz, C), 157.4 (C), 146.2 (C), 133.7 (C), 131.7 (d, J = 3.0 Hz, C), 128.7 (CH), 128.6 (d, J = 8.5 Hz, CH), 127.8 (CH), 122.5 (CH), 116.0 (CH), 115.7 (d, J = 22.0 Hz, CH), 62.7 (CH_2); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 108.4; HRMS (ES) Found: MH^+, 228.0819. $C_{14}H_{11}FNO$ requires MH^+, 228.0819; LRMS *m/z* (ES) 228 (100%, MH^+). Data consistent with the literature.[161]

3-(4-Methoxyphenyl)-2H-1,4-benzoxazine (192c)[161,162]



Using the general procedure H, potassium carbonate (30 g, 220 mmol), 2-aminophenol **190** (4.0 g, 36.7 mmol), ketone **191c** (8.4 g, 36.7 mmol), and $NBu_4^+HSO_4^-$ (0.3 g, 0.9 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the benzoxazine **192c** (6.6 g, 75%) as an amorphous yellow solid; m.p. 124–125 °C (lit.[166] 131 °C); R_f 0.18 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3080, 3065, 3050, 3000, 2960, 1605, 1560, 1480, 1420, 1315, 1255, 1110, 1025, 830, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95–7.89 (2H, m, 2 × CH), 7.44 (1H, dd, *J* = 8.0, 1.5 Hz, CH), 7.15 (1H, td, *J* = 8.0, 1.5 Hz, CH), 7.08–6.98 (3H, m, 3 × CH), 6.94 (1H, dd, *J* = 8.0, 1.5 Hz, CH), 5.06 (2H, s, CH_2), 3.89 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.1 (C), 158.2 (C), 146.3 (C), 134.0 (C), 128.2 (CH), 128.1 (CH), 128.1 (C), 127.5 (CH), 122.3 (CH), 115.5 (CH), 114.1 (CH), 62.7 (CH_2), 55.5 (OCH_3); HRMS (ES) Found: MH^+, 240.0911. $C_{15}H_{14}NO_2$ requires MH^+, 240.1019; LRMS *m/z* (ES) 240 (100%, MH^+). Data consistent with the literature.[161]

3-Phenyl-1,2,3,4-tetrahydro-1,4-benzoxazine (193a)[163]



Using the general procedure I, benzoxazine **192a** (6.8 g, 32.4 mmol) and sodium borohydride (2.5 g, 64.9 mmol) with a reaction time of 3 h gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the tetrahydrobenzoxazine **193a** (5.9 g, 85%) as an oil; R_f 0.58 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3360 (N–H), 3060, 3030, 2975, 2920, 2870, 1610, 1590, 1495, 1310, 1275, 1210, 1055, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49–7.36 (5H, m, 5 × CH), 6.94–6.90 (1H, m, CH), 6.88 (1H, td, *J* = 7.5, 1.5 Hz, CH), 6.76 (1H, td, *J* = 7.5, 1.5 Hz, CH), 6.72 (1H, dd, *J* = 7.5, 1.5 Hz, CH), 4.55

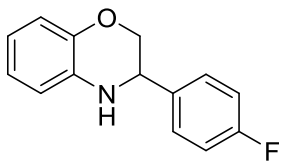
(1H, ddd, J = 8.5, 3.0, 1.0 Hz, CH), 4.37–4.30 (1H, m, CH), 4.08–4.00 (2H, m, CH + NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.6 (C), 139.2 (C), 134.0 (C), 128.9 (CH), 128.4 (CH), 127.2 (CH), 121.5 (CH), 119.0 (CH), 116.6 (CH), 115.4 (CH), 71.0 (CH_2), 54.2 (CH); HRMS (ES) Found: MH^+, 212.1073. $C_{14}H_{14}NO$ requires MH^+, 212.1070; LRMS *m/z* (ES) 212 (100%, MH^+). Data consistent with the literature.[163]

Resolution between the enantiomers of the carbamate **193a** was achieved using a Beckman system fitted with a Daicel 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·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 21.0 min and 24.8 min respectively with an analysis time of 30 min.

Trifluoroacetic acid (0.13 mL, 1.64 mmol) was added to a stirred solution of carbamate **164a** (51 mg, 0.164 mmol) in CH_2Cl_2 (5 mL) at room temperature. After 3 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 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated to give, after partial purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the crude amine **193a** as an oil.

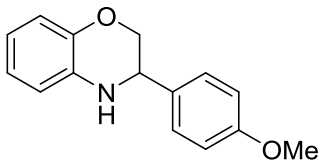
Trifluoroacetic acid (0.08 mL, 1.03 mmol) was added to a stirred solution of carbamate (*R*)-**164a** (32 mg, 0.103 mmol) with an enantiomeric ratio of >99:1, in CH_2Cl_2 (5 mL) at room temperature. After 16 h, the solvent was evaporated and NaOH (2 mL, 1 M) was added to basify the residue. The mixture was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated to give, after partial purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the crude amine (*R*)-**193a** as an oil; the enantiomeric ratio was determined to be >99:1 by CSP-HPLC (major component eluted at 20.8 min); $[\alpha]_D^{24}$ –93.2 (1.3, $CHCl_3$).

3-(4-Fluorophenyl)-1,2,3,4-tetrahydro-1,4-benzoxazine (193b)[163]



Using the general procedure I, benzoxazine **192b** (6.6 g, 29.1 mmol) and sodium borohydride (2.2 g, 59.0 mmol) with a reaction time of 3 h gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the tetrahydrobenzoxazine **193b** (6.3 g, 94%) as an amorphous yellow solid; m.p. 61–63 °C (lit.[163] 70–72 °C for 94:6 er compound); R_f 0.29 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3380 (N–H), 3340 (N–H), 3065, 3045, 2920, 2875, 2835, 1605, 1590, 1495, 1310, 1280, 1200, 1125, 1010, 835, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45–7.38 (2H, m, 2 × CH), 7.17–7.09 (2H, m, 2 × CH), 6.94–6.84 (2H, m, 2 × CH), 6.77 (1H, td, *J* = 7.5, 1.5 Hz, CH), 6.73 (1H, dd, *J* = 8.0, 1.5 Hz, CH), 4.52 (1H, dd, *J* = 8.5, 1.5 Hz, CH), 4.33–4.26 (1H, m, CH), 4.06–3.96 (2H, m, CH + NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.7 (d, *J* = 246.5 Hz, C), 143.5 (C), 135.0 (d, *J* = 3.0 Hz, C), 133.8 (C), 128.9 (d, *J* = 8.0 Hz, CH), 121.6 (CH), 119.1 (CH), 116.7 (CH), 115.8 (d, *J* = 21.5 Hz, CH), 115.5 (CH), 70.9 (d, *J* = 1.0 Hz, CH_2), 53.5 (CH); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 113.8; HRMS (ES) Found: MH^+, 230.0978. $C_{14}H_{13}FNO$ requires MH^+, 230.0976; LRMS *m/z* (ES) 230 (100%, MH^+). Data consistent with the literature.[163]

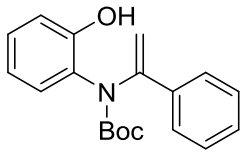
3-(4-Methoxyphenyl)-1,2,3,4-tetrahydro-1,4-benzoxazine (193c)[164]



Using the general procedure I, benzoxazine **192c** (6.5 g, 27.3 mmol) and sodium borohydride (2.1 g, 54.6 mmol) with a reaction time of 2 h gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (95:5), the tetrahydrobenzoxazine **193c** (5.7 g, 86%) as an amorphous yellow solid; m.p. 91–93 °C (No melting point reported.[167]); R_f 0.20 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3350 (N–H), 3045, 3000, 2990, 2920, 2880, 2840, 1610, 1585, 1515, 1500, 1425, 1310, 1245, 1205, 1170, 1030, 830,

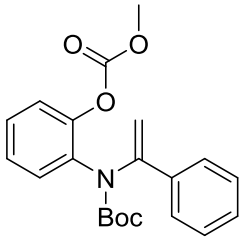
740; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39–7.32 (2H, m, 2 × CH), 6.99–6.93 (2H, m, 2 × CH), 6.89 (1H, dd, *J* = 7.5, 1.5 Hz, CH), 6.84 (1H, td, *J* = 7.5, 1.5 Hz, CH), 6.74 (1H, td, *J* = 7.5, 1.5 Hz, CH), 6.70 (1H, dd, *J* = 7.5, 1.5 Hz, CH), 4.48 (1H, dd, *J* = 8.5, 2.5 Hz, CH), 4.32–4.25 (1H, m, CH), 4.04–3.96 (2H, m, CH + NH), 3.85 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.6 (C), 143.5 (C), 134.0 (C), 131.2 (C), 128.4 (CH), 121.5 (CH), 118.9 (CH), 116.6 (CH), 115.4 (CH), 114.2 (CH), 71.1 (CH_2), 55.4 (OCH_3) 53.6 (CH); HRMS (ES) Found: MH^+, 242.1178. $C_{15}H_{16}NO_2$ requires MH^+, 242.1176; LRMS *m/z* (ES) 242 (100%, MH^+). Data consistent with the literature.[164]

tert-Butyl _N_-(2-Hydroxyphenyl)-_N_-(1-phenylethenyl)carbamate (194a)



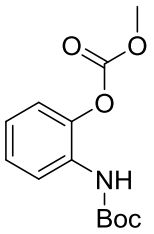
Using the general procedure C, tetrahydrobenzoxazine **193a** (1.50 g, 7.09 mmol), *n*-BuLi (4.73 mL, 11.35 mmol, 2.4 M in hexanes) and Boc_2O (1.70 g, 7.80 mmol) with a reaction time of 20 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the phenol **194a** (0.50 g, 23%) as an amorphous white solid; m.p. 123–125 °C; R_f 0.19 [petrol–EtOAc (9:1)]; FT-IR ν_{max} (ATR)/cm^{-1} 3250 (O–H), 3065, 2980, 2930, 1665 (C=O), 1510, 1360, 1265, 1165, 1075, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59–7.52 (2H, m, 2 × CH), 7.42–7.31 (3H, m, 3 × CH), 7.22 (1H, dd, *J* = 8.0, 1.5 Hz, CH), 7.18–7.11 (1H, m, CH), 7.06 (1H, dd, *J* = 8.0, 1.5 Hz, CH), 6.92–6.85 (2H, m, CH + OH), 5.59 (1H, s, C=CH), 5.16 (1H, s, C=CH), 1.31 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.4 (C=O), 150.5 (C), 148.1 (C), 138.0 (C), 131.3 (C), 128.5 (CH), 128.4 (CH), 127.6 (CH), 125.9 (CH), 125.5 (CH), 121.4 (CH), 120.1 (CH), 112.5 (CH_2), 82.7 (C), 27.9 (CH_3); HRMS (ES) Found: MNa^+, 334.1415. $C_{19}H_{21}NO_3Na$ requires MNa^+, 334.1414; LRMS *m/z* (ES) 334 (5%, MNa^+), 256 (5, MH^+-*t*-Bu+H), 212 (100, MH^+-Boc+H); Found: C, 73.15; H, 6.94; N, 4.31. $C_{19}H_{21}NO_3$ requires C, 73.29; H, 6.80; N, 4.50. The desired carbamate **164a** (0.96 g, 43%) was also isolated, data as above.

2-[(*tert*-Butoxycarbonyl)(1-phenylethenyl)amino]phenyl methyl carbonate (194b)



Using the general procedure J, carbamate **164a** (102 mg, 0.33 mmol), *n*-BuLi (0.07 mL, 0.18 mmol, 2.5 M in hexanes), (+)-sparteine (42 mg, 0.18 mmol) and methyl chloroformate (0.09 mL, 1.15 mmol) with a reaction time of 30 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the carbonate **194b** (84 mg, 69%) as an amorphous white solid; m.p. 62–64 °C; R_f 0.09 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3060, 3005, 2975, 2955, 2930, 1770 (C=O), 1700 (C=O), 1495, 1350, 1240, 1205, 765; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62–7.57 (2H, m, 2 × CH), 7.42–7.21 (7H, m, 7 × CH), 5.29 (1H, s, C=CH), 4.95 (1H, s, C=CH), 3.86 (3H, s, OCH_3), 1.24 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.7 (C=O), 152.9 (C=O), 148.9 (C), 146.3 (C), 138.9 (C), 135.3 (C), 128.3 (CH), 128.2 (CH), 128.0 (CH), 127.3 (CH), 126.6 (CH), 125.8 (CH), 123.3 (CH), 110.1 (CH_2), 81.3 (C), 55.3 (OCH_3), 27.7 (CH_3); HRMS (ES) Found: MNa^+, 392.1471. $C_{21}H_{23}NO_5Na$ requires MNa^+, 392.1468; LRMS *m/z* (ES) 392 (5%, MNa^+), 270 (100, MH^+-Boc+H). The carbamate (*R*)-**164a** (42 mg, 41%) was also recovered with an enantiomeric ratio of >99:1, data as above.

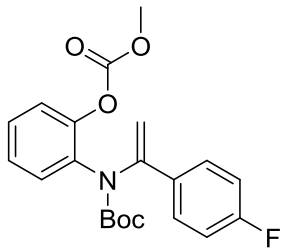
2-[(*tert*-Butoxycarbonyl)amino]phenyl methyl carbonate (195)[165]



Using the general procedure J, tetrahydrobenzoxazine **193a** (105 mg, 0.34 mmol), *n*-BuLi (0.16 mL, 0.41 mmol, 2.5 M in hexanes), (+)-sparteine (103 mg, 0.44 mmol) and methyl chloroformate (0.09 mL, 1.18 mmol) with a reaction time of 105 min, gave, after purification

by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the carbonate **195** (64 mg, 71%) as an amorphous yellow solid; m.p. 76–78 °C (lit.[165] oil); R_f 0.12 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3350 (N–H), 3010, 2980, 2965, 2930, 2850, 1760 (C=O), 1705 (C=O), 1520, 1450, 1230, 1150, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (1H, d, *J* = 7.5 Hz, CH), 7.26–7.18 (2H, m, 2 × CH), 7.08–7.02 (1H, m, CH), 6.74 (1H, s, NH), 3.95 (3H, s, OCH_3), 1.54 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.5 (C=O), 152.4 (C=O), 139.7 (C), 130.3 (C), 126.6 (CH), 122.9 (CH), 121.3 (CH), 120.2 (CH), 81.0 (C), 55.8 (OCH_3), 28.3 (CH_3); HRMS (ES) Found: MNa^+, 290.1002. $C_{13}H_{17}NO_5Na$ requires MNa^+, 290.0999; LRMS *m/z* (ES) 290 (25%, MNa^+), 212 (100, MH^+-*t*-Bu+H). Data consistent with the literature.[165] The carbamate (*R*)-**164a** (24 mg, 22%) was also recovered with an enantiomeric ratio of 94:6, data as above.

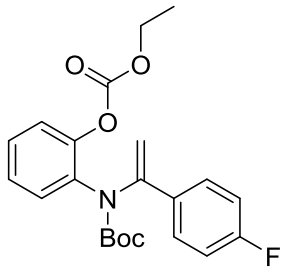
2-[(*tert*-Butoxycarbonyl)[1-(4-fluorophenyl)ethenyl]amino]phenyl methyl carbonate (196a)



Using the general procedure J, carbamate **164b** (112 mg, 0.34 mmol), *n*-BuLi (0.08 mL, 0.21 mmol, 2.5 M in hexanes), (+)-sparteine (48 mg, 0.21 mmol) and methyl chloroformate (0.09 mL, 1.19 mmol) with a reaction time of 1 h, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the carbonate **196a** (87 mg, 66%) as an amorphous white solid; m.p. 95–97 °C; R_f 0.07 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3000, 2985, 2965, 1770 (C=O), 1705 (C=O), 1630, 1600, 1505, 1440, 1350, 1250, 1205, 1160, 1135, 1075, 1000, 935, 845, 770, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60–7.53 (2H, m, 2 × CH), 7.36–7.21 (4H, m, 4 × CH), 7.11–7.03 (2H, m, 2 × CH), 5.23 (1H, s, CH), 4.92 (1H, s, CH), 3.85 (3H, s, OCH_3), 1.27 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$, one quaternary carbon could not be observed) δ = 162.7 (d, *J* = 247.0 Hz, C), 153.6 (C=O), 152.9

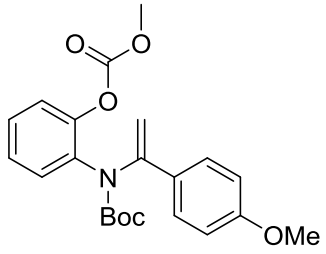
(C=O), 147.8 (C), 146.3 (C), 135.0 (C), 128.0 (CH), 127.6 (d, J = 8.0 Hz, CH), 127.5 (CH), 126.6 (CH), 123.3 (CH), 115.2 (d, J = 21.5 Hz, CH), 110.0 (CH_2), 81.5 (C), 55.3 (CH_3), 27.7 (CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 113.9; HRMS (ES) Found: MNa^+, 410.1383. $C_{21}H_{22}FNO_5Na$ requires MNa^+, 410.1374; LRMS *m/z* (ES) 410 (5%, MNa^+), 288 (100, MH^+-Boc+H). The carbamate (*R*)-**164b** (41 mg, 36%) was also recovered with an enantiomeric ratio of 92:8, data as above.

2-[(*tert*-Butoxycarbonyl)[1-(4-fluorophenyl)ethenyl]amino]phenyl ethyl carbonate (196b)



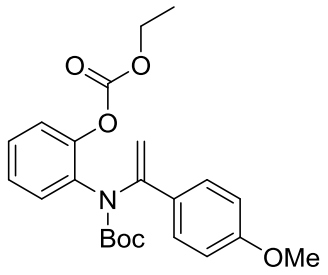
Using the general procedure J, carbamate **164b** (101 mg, 0.31 mmol), *n*-BuLi (0.12 mL, 0.31 mmol, 2.5 M in hexanes), (+)-sparteine (72 mg, 0.31 mmol) and ethyl chloroformate (0.10 mL, 1.07 mmol) with a reaction time of 45 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the carbonate **196b** (68 mg, 55%) as an amorphous white solid; m.p. 73–75 °C; R_f 0.09 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3010, 2995, 2985, 1755 (C=O), 1720, 1705 (C=O), 1630, 1600, 1500, 1350, 1245, 1160, 1075, 900, 845, 770, 725; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.62–7.54 (2H, m, 2 × CH), 7.38–7.21 (4H, m, 4 × CH), 7.11–7.03 (2H, m, 2 × CH), 5.22–5.18 (1H, m, CH), 4.92–4.88 (1H, m, CH), 4.29–4.20 (2H, m, CH_2), 1.31–1.21 (12H, m, *t*-Bu and CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, one quaternary carbon could not be observed) δ = 162.0 (d, J = 245.5 Hz, C), 153.0 (C=O), 152.8 (C=O), 147.8 (C), 146.1 (C), 135.1 (C), 128.2 (CH), 128.2 (d, J = 8.0 Hz, CH), 127.4 (CH), 126.5 (CH), 123.4 (CH), 115.4 (d, J = 21.5 Hz, CH), 109.8 (CH_2), 81.5 (C), 64.8 (CH_2), 27.7 (CH_3), 14.1 (CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ = 114.0; HRMS (ES) Found: MNa^+, 424.1539. $C_{22}H_{24}FNO_5Na$ requires MNa^+, 424.1531; LRMS *m/z* (ES) 424 (30%, MNa^+), 302 (100, MH^+-Boc+H). The carbamate (*R*)-**164b** (43 mg, 42%) was also recovered with an enantiomeric ratio of 86:14, data as above.

2-[(*tert*-Butoxycarbonyl)[1-(4-methoxyphenyl)ethenyl]amino]phenyl methyl carbonate (197a)



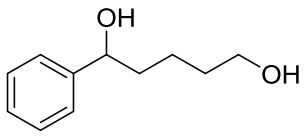
Using the general procedure J, carbamate **164c** (105 mg, 0.31 mmol), *n*-BuLi (0.07 mL, 0.18 mmol, 2.5 M in hexanes), (+)-sparteine (43 mg, 0.18 mmol) and methyl chloroformate (0.08 mL, 1.08 mmol) with a reaction time of 1 h, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the carbonate **196a** (94 mg, 77%) as an amorphous white solid; m.p. 97–99 °C; R_f 0.03 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3070, 3040, 3005, 2980, 2930, 2840, 1770 (C=O), 1700 (C=O), 1625, 1605, 1510, 1500, 1440, 1350, 1300, 1250, 1210, 1165, 1025, 935, 835, 770, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54–7.48 (2H, m, 2 × CH), 7.36–7.19 (4H, m, 4 × CH), 6.94–6.88 (2H, m, 2 × CH), 5.23 (1H, s, CH), 4.89 (1H, s, CH), 3.86 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 1.28 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.7 (C), 153.7 (C=O), 153.0 (C=O), 148.3 (C), 146.3 (C), 135.3 (C), 131.4 (C), 127.9 (CH), 127.2 (CH), 127.1 (CH), 126.5 (CH), 123.2 (CH), 113.6 (CH), 108.9 (CH_2), 81.2 (C), 55.3 (OCH_3), 55.3 (OCH_3), 27.8 (CH_3); HRMS (ES) Found: MH^+, 400.1759. $C_{22}H_{26}NO_6$ requires MH^+, 400.1755; LRMS *m/z* (ES) 400 (5%, MH^+), 300 (100, MH^+-Boc+H). The carbamate (*R*)-**164c** (28 mg, 26%) was also recovered with an enantiomeric ratio of >99:1, data as above.

2-[(*tert*-Butoxycarbonyl)[1-(4-methoxyphenyl)ethenyl]amino]phenyl ethyl carbonate (197b)



Using the general procedure J, carbamate **164c** (101 mg, 0.30 mmol), *n*-BuLi (0.14 mL, 0.36 mmol, 2.5 M in hexanes), (+)-sparteine (84 mg, 0.36 mmol) and ethyl chloroformate (0.10 mL, 1.04 mmol) with a reaction time of 45 min, gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the carbonate **196b** (68 mg, 55%) as an amorphous white solid; m.p. 90–92 °C; R_f 0.04 [petrol–EtOAc (95:5)]; FT-IR ν_{max} (ATR)/cm^{-1} 3070, 3005, 2980, 2935, 2835, 1765 (C=O), 1700 (C=O), 1625, 1605, 1505, 1455, 1350, 1300, 1245, 1165, 1025, 975, 885, 770, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55–7.50 (2H, m, 2 × CH), 7.37–7.18 (4H, m, 4 × CH), 6.94–6.88 (2H, m, 2 × CH), 5.21 (1H, s, CH), 4.88 (1H, s, CH), 4.27 (2H, q, *J* = 7.0 Hz, CH), 3.84 (3H, s, OCH_3), 1.33–1.25 (12H, m, CH_3 + *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.7 (C), 153.0 (C=O), 153.0 (C=O), 148.4 (C), 146.2 (C), 135.4 (C), 131.4 (C), 128.0 (CH), 127.2 (2 × CH), 126.4 (CH), 123.3 (CH), 113.6 (CH), 108.8 (CH_2), 81.2 (C), 64.7 (CH_2), 55.3 (OCH_3), 27.8 (CH_3), 14.1 (CH_3); HRMS (ES) Found: MNa^+, 436.1735. $C_{23}H_{27}NO_6Na$ requires MNa^+, 436.1731; LRMS *m/z* (ES) 436 (25%, MNa^+), 414 (5, MH^+), 314 (100, MH^+-Boc+H). The carbamate (*R*)-**164c** (40 mg, 39%) was also recovered with an enantiomeric ratio of 95:5, data as above.

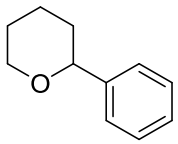
1-Phenylpentane-1,5-diol (200)[166]



4-benzoylbutyric acid **199** (5.05 g, 26.3 mmol) dissolved in THF (20 mL) was slowly added to a suspension of $LiAlH_4$ (2.99 g, 78.9 mmol) in THF (30 mL) at 0 °C. The reaction mixture was left to stir at rt overnight, re-cooled to 0 °C and H_2O (15 mL) was carefully added to quench the reaction. NaOH (6 mL, 2 M) and more H_2O (10 mL) was added and the reaction mixture

was filtered through Celite which was washed with EtOAc (20 mL). The filtrate was dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure to give, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the diol **200** (4.29 g, 90%) as an oil; R_f 0.24 [petrol–EtOAc (1:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37–7.32 (4H, m, 4 × CH), 7.31–7.25 (1H, m, CH), 4.71–4.62 (1H, m, CH), 3.61 (2H, t, *J* = 5.5 Hz, 2 × CH), 2.65 (1H, d, *J* = 2.5 Hz, OH), 2.15–2.09 (1H, m, OH), 1.89–1.66 (2H, m, 2 × CH), 1.64–1.44 (3H, m, 3 × CH), 1.44–1.32 (1H, m, CH). Data consistent with the literature.[166]

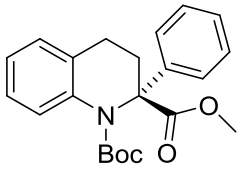
2-Phenyl-tetrahydropyran (201)[167]



Anhydrous zinc chloride (3.22 g, 23.6 mmol) was added at rt to a stirred solution of diol **200** (4.25 g, 23.6 mmol) in 1,2-dichloroethane (50 mL). The reaction mixture was stirred at reflux for 16 h, cooled to rt and diluted with CH_2Cl_2 (50 mL). The mixture was washed with H_2O (50 mL) and brine (50 mL), the combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (97:3), the tetrahydropyran **201** (0.72 g, 19%) as a clear liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44–7.36 (4H, m, 4 × CH), 7.34–7.27 (1H, m, CH), 4.41–4.34 (1H, m, CH), 4.24–4.17 (1H, m, CH), 3.72–3.62 (1H, m, CH), 2.03–1.97 (1H, m, CH), 1.92–1.84 (1H, m, CH), 1.80–1.60 (4H, m, 4 × CH). Data consistent with the literature.[167]

Chapter 5 – Appendices

Appendix 1a: X-ray crystal absolute configuration determination data of compound (*R*)-**119b**



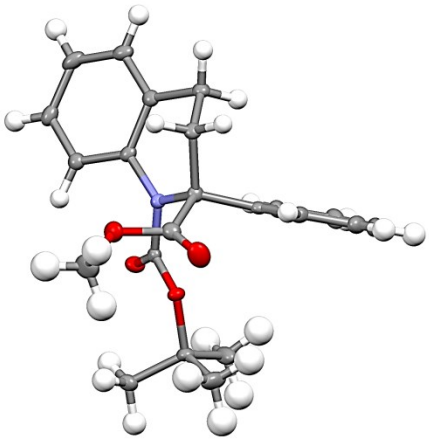
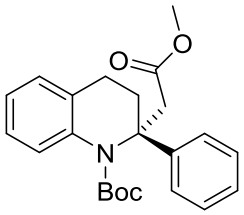


Table 1. Crystal data and structure refinement for carter1_0m.

Identification code	carter1_0m	
Empirical formula	C22 H25 N O4	
Formula weight	367.43	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 10.3192(3) Å	α= 90°.
	b = 11.0867(4) Å	β= 90°.
	c = 17.4057(6) Å	γ = 90°.
Volume	1991.31(12) $Å^3$	
Z	4	
Density (calculated)	1.226 Mg/m^3	
Absorption coefficient	0.680 mm^{-1}	
F(000)	784	

Crystal size	0.300 x 0.200 x 0.200 mm^3
Theta range for data collection	4.729 to 66.627°.
Index ranges	-12<=h<=12, -13<=k<=13, -20<=l<=20
Reflections collected	25795
Independent reflections	3512 [R(int) = 0.0414]
Completeness to theta = 66.627°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.89 and 0.79
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3512 / 0 / 248
Goodness-of-fit on F^2	1.095
Final R indices [I>2sigma(I)]	R1 = 0.0280, wR2 = 0.0682
R indices (all data)	R1 = 0.0296, wR2 = 0.0691
Absolute structure parameter	0.03(6)
Extinction coefficient	n/a
Largest diff. peak and hole	0.138 and -0.193 $e.Å^{-3}$

Appendix 1b: X-ray crystal absolute configuration determination data of compound (*S*)-**119l**



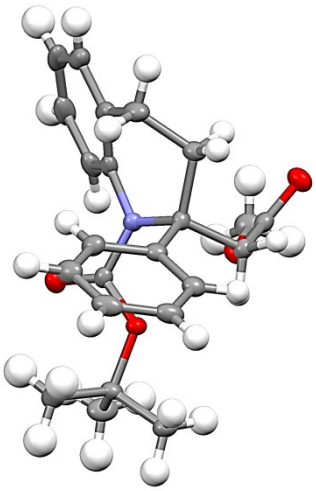
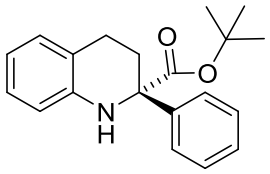


Table 1. Crystal data and structure refinement for CARTERN2_0m.

Identification code	CARTERN2_0m
Empirical formula	C23 H27 N O4

Formula weight	381.45	
Temperature	97(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 9.4950(3) Å	α= 90°.
	b = 8.8357(3) Å	β= 90.258(2)°.
	c = 12.0617(4) Å	γ = 90°.
Volume	1011.91(6) $Å^3$	
Z	2	
Density (calculated)	1.252 Mg/m^3	
Absorption coefficient	0.687 mm^{-1}	
F(000)	408	
Crystal size	0.320 x 0.120 x 0.090 mm^3	
Theta range for data collection	3.664 to 66.614°.	
Index ranges	-11<=h<=11, -10<=k<=9, -14<=l<=14	
Reflections collected	14554	
Independent reflections	3491 [R(int) = 0.0511]	
Completeness to theta = 66.614°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.91 and 0.87	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3491 / 1 / 258	
Goodness-of-fit on F^2	1.016	
Final R indices [I>2sigma(I)]	R1 = 0.0337, wR2 = 0.0753	
R indices (all data)	R1 = 0.0418, wR2 = 0.0786	
Absolute structure parameter	0.11(12)	
Extinction coefficient	0.0107(11)	
Largest diff. peak and hole	0.161 and -0.141 $e.Å^{-3}$	

Appendix 1c: X-ray crystal absolute configuration determination data of compound (*S*)-**132a**



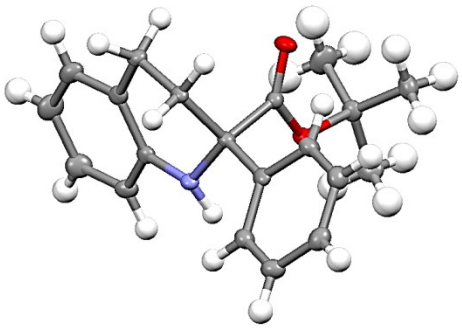
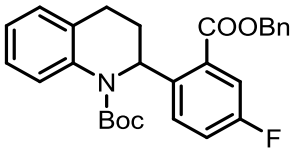


Table 1. Crystal data and structure refinement for OIC270A.

Identification code	OIC270A	
Empirical formula	C20 H23 N O2	
Formula weight	309.39	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.1094(3) Å	α= 90°.
	b = 14.2823(6) Å	β= 90°.
	c = 19.8409(8) Å	γ = 90°.
Volume	1731.24(13) $Å^3$	
Z	4	
Density (calculated)	1.187 Mg/m^3	
Absorption coefficient	0.599 mm^{-1}	
F(000)	664	
Crystal size	0.200 x 0.200 x 0.180 mm^3	
Theta range for data collection	3.813 to 66.624°.	
Index ranges	-6<=h<=7, -17<=k<=15, -23<=l<=21	
Reflections collected	11998	
Independent reflections	3043 [R(int) = 0.0313]	
Completeness to theta = 66.624°	99.4 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.92 and 0.82
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3043 / 0 / 211
Goodness-of-fit on F^2	1.091
Final R indices [I>2sigma(I)]	R1 = 0.0285, wR2 = 0.0687
R indices (all data)	R1 = 0.0303, wR2 = 0.0698
Absolute structure parameter	0.08(7)
Extinction coefficient	n/a
Largest diff. peak and hole	0.152 and -0.169 e.Å^{-3}

Appendix 1d: X-ray crystal structure determination data of compound **137b**



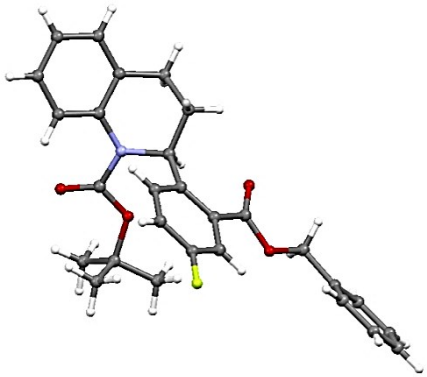


Table 1. Crystal data and structure refinement for OIC277v_0m.

Identification code	OIC277v_0m	
Empirical formula	C28 H28 F N O4	
Formula weight	461.51	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.1134(3) Å	α= 76.3096(12)°.
	b = 10.9832(3) Å	β= 85.4641(12)°.

	c = 11.2564(3) Å γ = 73.5894(13)°.
Volume	1165.22(6) $Å^3$
Z	2
Density (calculated)	1.315 Mg/m^3
Absorption coefficient	0.759 mm^{-1}
F(000)	488
Crystal size	0.180 x 0.120 x 0.050 mm^3
Theta range for data collection	4.042 to 66.668°.
Index ranges	-12<=h<=12, -12<=k<=13, -13<=l<=13
Reflections collected	34249
Independent reflections	4081 [R(int) = 0.0404]
Completeness to theta = 66.668°	99.1 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4081 / 0 / 310
Goodness-of-fit on F^2	1.076
Final R indices [I>2sigma(I)]	R1 = 0.0342, wR2 = 0.0827
R indices (all data)	R1 = 0.0401, wR2 = 0.0862
Extinction coefficient	n/a
Largest diff. peak and hole	0.231 and -0.247 $e.Å^{-3}$

Appendix 1e: X-ray crystal structure determination data of compound *cis*-**141**

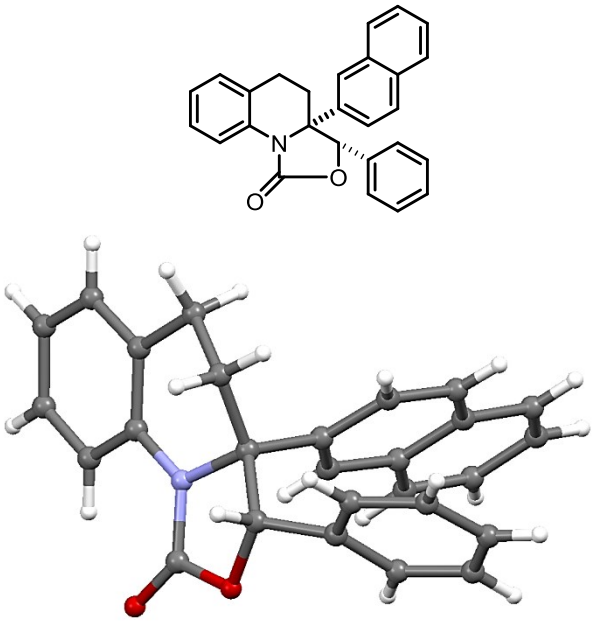
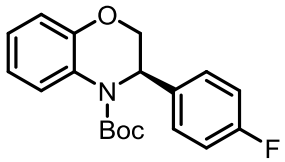


Table 1. Crystal data and structure refinement for OIC276v_0m.

Identification code	OIC276v_0m	
Empirical formula	C27 H21 N O2	
Formula weight	391.45	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.9717(3) Å	α= 95.3798(16)°.
	b = 9.2791(4) Å	β= 105.3362(17)°.
	c = 14.2492(6) Å	γ = 98.2795(16)°.
Volume	996.24(7) Å^3	
Z	2	
Density (calculated)	1.305 Mg/m^3	
Absorption coefficient	0.647 mm^{-1}	
F(000)	412	
Crystal size	0.180 x 0.080 x 0.050 mm^3	
Theta range for data collection	3.247 to 66.736°.	
Index ranges	-9<=h<=9, -11<=k<=11, -16<=l<=16	
Reflections collected	29236	
Independent reflections	3496 [R(int) = 0.0356]	

Completeness to theta = 66.736°	99.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7528 and 0.6965
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3496 / 0 / 272
Goodness-of-fit on F^2	1.038
Final R indices [I>2sigma(I)]	R1 = 0.0321, wR2 = 0.0768
R indices (all data)	R1 = 0.0387, wR2 = 0.0805
Extinction coefficient	0.0114(8)
Largest diff. peak and hole	0.250 and -0.186 e.$Å^{-3}$

Appendix 1f: X-ray crystal absolute configuration determination data of compound (*S*)-**164b**



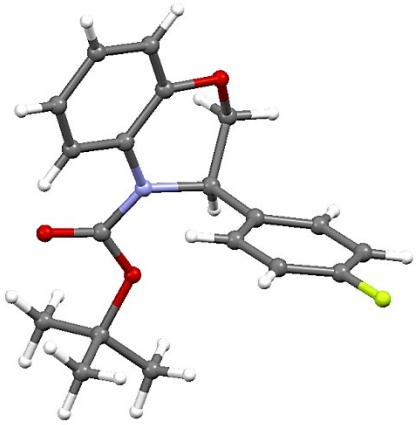
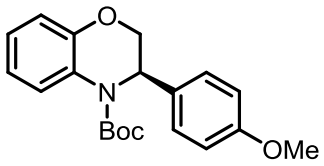


Table 1 Crystal data and structure refinement for oic282-v-t_0m.

Identification code	oic282-v-t_0m
Empirical formula	C19H20FNO3
Formula weight	329.36
Temperature/K	99.99
Crystal system	monoclinic
Space group	P21
a/Å	6.0760(3)

b/Å	10.0565(4)
c/Å	13.3334(5)
α/°	90
β/°	95.030(2)
γ/°	90
Volume/Å3	811.58(6)
Z	2
ρcalcg/cm3	1.348
μ/mm 1	0.814
F(000)	348.0
Crystal size/mm3	0.34 × 0.12 × 0.06
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	6.654 to 144.754
Index ranges	-7 ⩽ h ⩽ 6, -12 ⩽ k ⩽ 12, -16 ⩽ l ⩽ 16
Reflections collected	25124
Independent reflections	3190 [Rint = 0.0488, Rsigma = 0.0297]
Data/restraints/parameters	3190/1/220
Goodness-of-fit on F2	1.045
Final R indexes [I>=2σ (I)]	R1 = 0.0355, wR2 = 0.0783
Final R indexes [all data]	R1 = 0.0421, wR2 = 0.0814
Largest diff. peak/hole / e Å-3	0.14/-0.19
Flack parameter	-0.07(10)

Appendix 1g: X-ray crystal absolute configuration determination data of compound (*S*)-**164c**



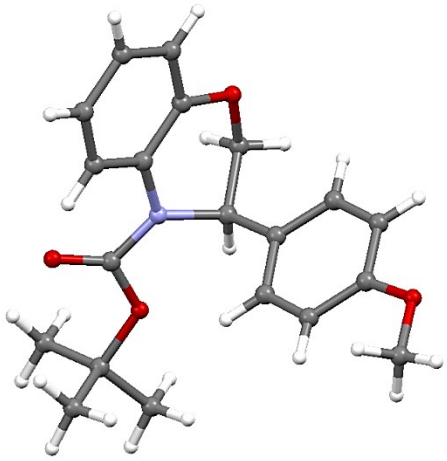


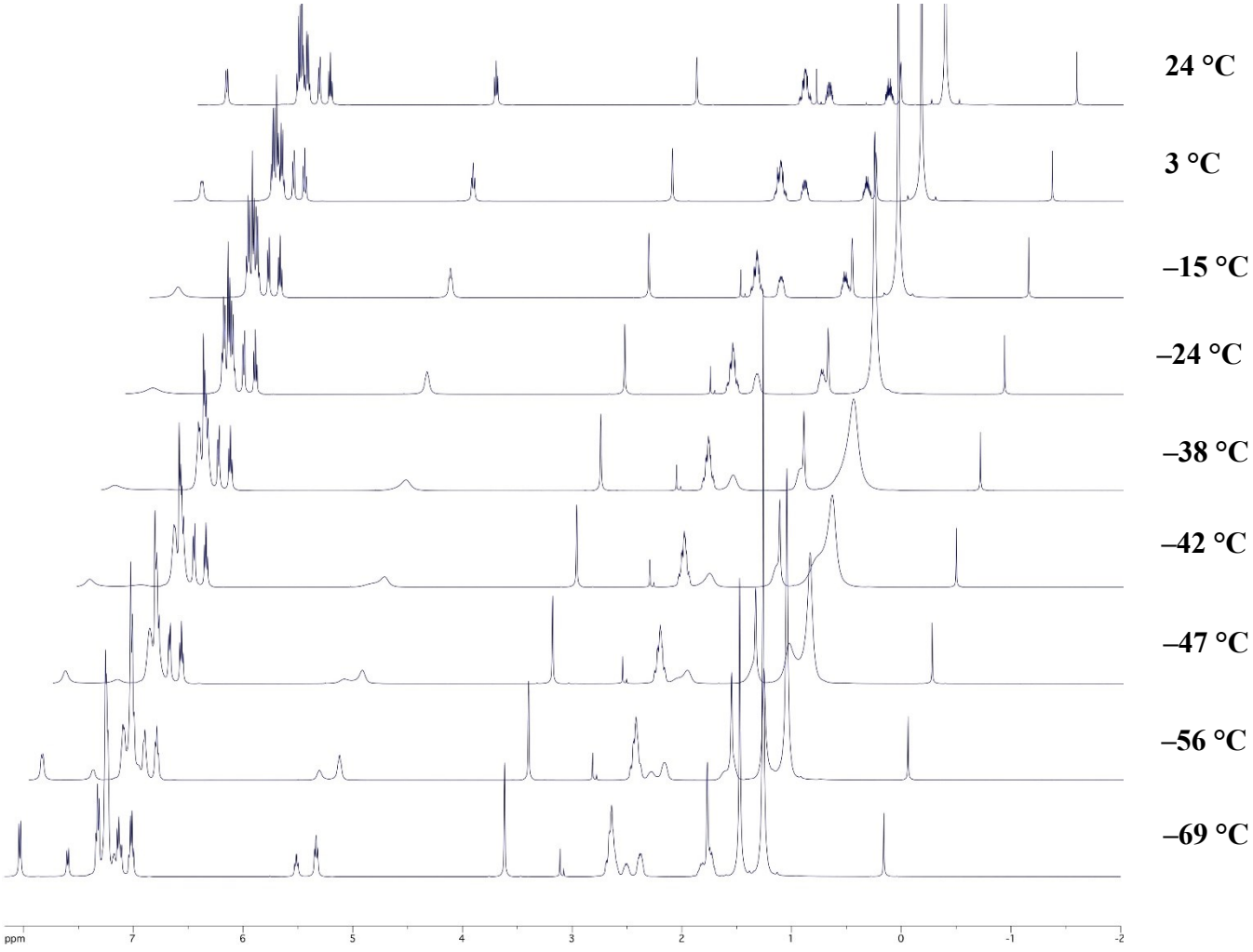
Table 1 Crystal data and structure refinement for OIC283_v_0m.

Identification code	OIC283_v_0m
Empirical formula	C20H23NO4
Formula weight	341.39
Temperature/K	100.01
Crystal system	orthorhombic
Space group	P212121
a/Å	5.5695(2)
b/Å	17.7764(6)
c/Å	17.7803(6)
α/°	90
β/°	90
γ/°	90
Volume/Å3	1760.35(11)
Z	4
ρcalcg/cm3	1.288
μ/mm 1	0.728
F(000)	728.0
Crystal size/mm3	0.31 × 0.05 × 0.05

Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	7.032 to 133.132
Index ranges	-6 ⩽ h ⩽ 6, -20 ⩽ k ⩽ 21, -21 ⩽ l ⩽ 21
Reflections collected	39230
Independent reflections	3094 [Rint = 0.0852, Rsigma = 0.0382]
Data/restraints/parameters	3094/0/230
Goodness-of-fit on F2	1.085
Final R indexes [I>=2σ (I)]	R1 = 0.0385, wR2 = 0.0772
Final R indexes [all data]	R1 = 0.0508, wR2 = 0.0815
Largest diff. peak/hole / e Å-3	0.16/-0.21
Flack parameter	0.06(14)

Appendix 2: Variable temperature ^{1}H NMR spectra for *N*-Boc-2-phenyl-1,2,3,4-tetrahydroquinoline **118a**

A sample of tetrahydroquinoline **118a** (40 mg, 0.13 mmol) in d_8-THF (0.7 mL) was placed in an NMR tube and the NMR spectrometer was warmed gradually from –78 °C. Warming allowed coalescence of the signals for the *t*-butyl protons, which occurred at approximately –38 °C as shown below.



From the coalescence spectra, $T_c \sim -38$ °C.

The difference in chemical shift ($\Delta\nu^o_{AB}$) between the rotamers at low temp. was ~107 Hz.

So, at –38 °C, $k = (\pi \times 107.0)/\sqrt{2} = 237.7\ s^{-1}$

So, at –38 °C, $t_{1/2} = (\ln 2)/k = 2.92 \times 10^{-3}$ s

And, at –38 °C, 235 K, $\Delta G^{\ddagger} = RT[\ln(k_B T/h) - \ln k] = 46.4$ kJ/mol

Alternatively, using line shape analysis[168,169] to determine $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$:

Pre-coalescence:

$k = [(\Delta\nu^o_{AB})^2 - (\Delta\nu_{AB})^2]^{1/2}\pi/\sqrt{2}$

Coalescence:

$k = (\Delta\nu^o_{AB})\pi/\sqrt{2}$

Post-coalescence:

$k = (\Delta\nu^{o}_{AB})^2\pi/2[(1/2\Delta\nu_{AB})–(1/2\Delta\nu^{o}_{AB})]$

The Eyring plot of 1/T against ln(k/T) is shown below, although there was a considerable margin of error in these data and so the following extrapolation of activation parameters is very tentative and should be treated with caution.

$\Delta H^{‡} \approx 44.6$ kJ mol^{-1}

$\Delta S^{‡} \approx –4.4$ J K^{-1} mol^{-1}

These values provide:

$\Delta G^{‡} \approx 45.9$ kJ/mol at 25 °C, that equates to $k = 56{,}457$ s$^{–1}$, $t_{1/2} = 1.23 \times 10^{-5}$ s

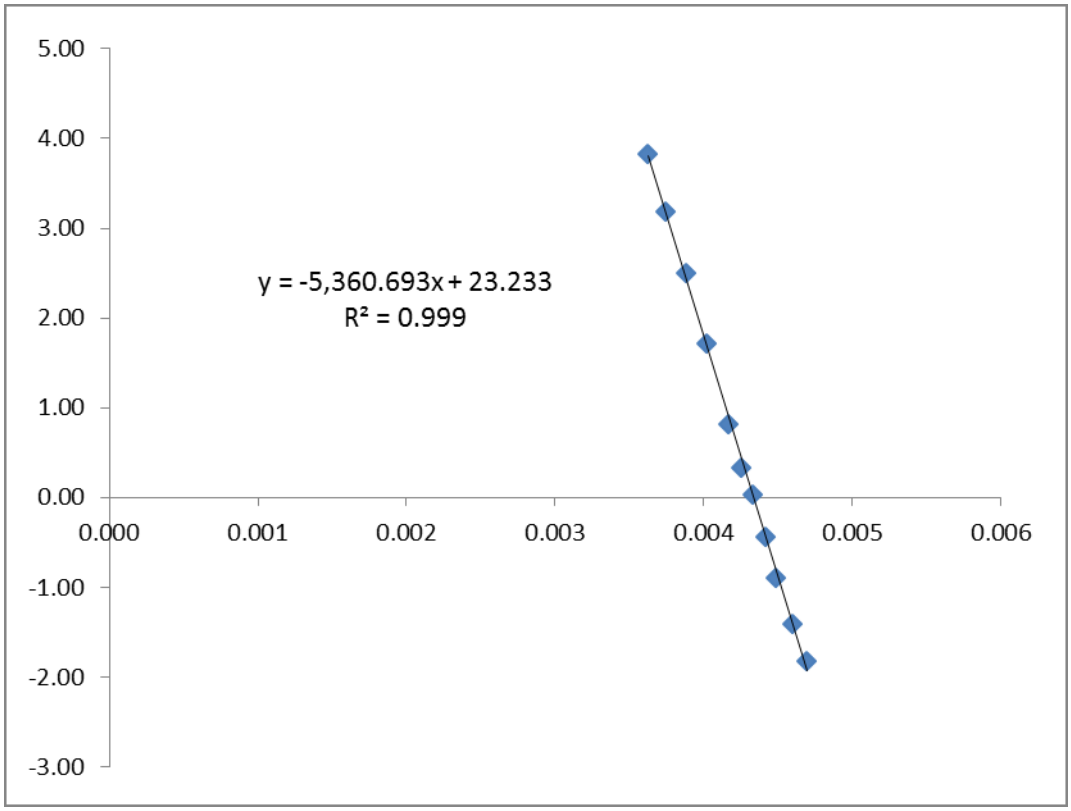
$\Delta G^{‡} \approx 45.6$ kJ/mol at –38 °C, that equates to $k = 358.2$ s$^{–1}$, $t_{1/2} = 1.94 \times 10^{-3}$ s

$\Delta G^{‡} \approx 45.4$ kJ/mol at –78 °C, that equates to $k = 2.76$ s$^{–1}$, $t_{1/2} = 0.25$ s

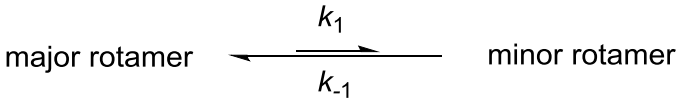
T/K	1/T	delta ν^{o}_{AB}	delta ν_{AB}	delta $\nu_{1/2}$	k (s$^{–1}$)	ln(k/T)
204.5	0.004890	107	107		-	-
213	0.004695	107	105.86		34.605	–1.81731
217.4	0.004600	107	104.29		53.157	–1.40849
223	0.004484	107	98.9		90.720	–0.89939
226.3	0.004419	107	84.22		146.615	–0.43405
231	0.004329	107	50.2		209.911	0.02857
235	0.004255	107			237.694	0.33643
240	0.004167	107		35.45	542.096	0.81480
249	0.004016	107		15.224	1388.836	1.71877
257.9	0.003877	107		8.028	3126.027	2.49495
267	0.003745	107		5.08	6411.420	3.17859
276	0.003623	107		3.687	12736.567	3.83183
297.3	0.003364	107			-	-

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

1/T



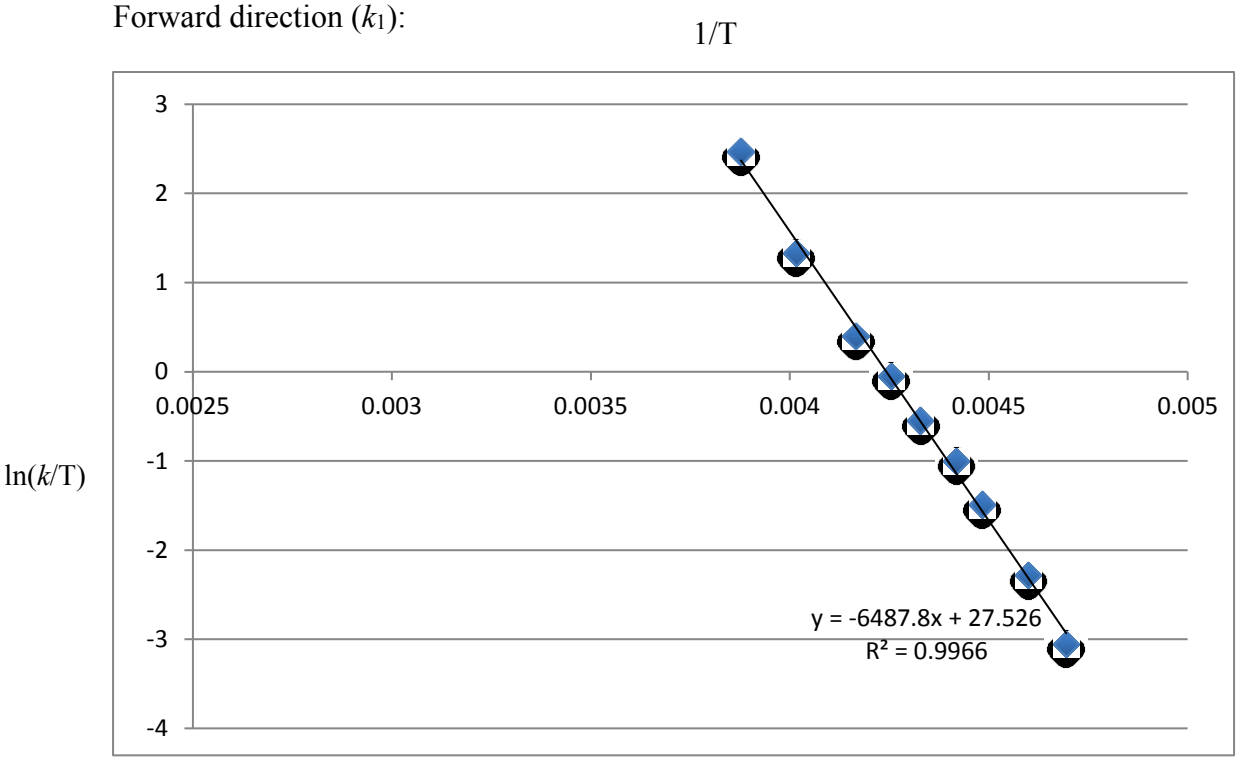
A better approach is to carry out dynamic NMR studies and to determine rate constants from best fit spectra. This was carried out using the software iNMR. The major:minor rotamers from integration are in a 1.8:1 ratio. The major rotamer was assigned a rate constant k_1 (determined from dynamic NMR) as it converts to the minor rotamer and the reverse rate constant k_{-1} (1.8 × k_1) according to the following equation and data:



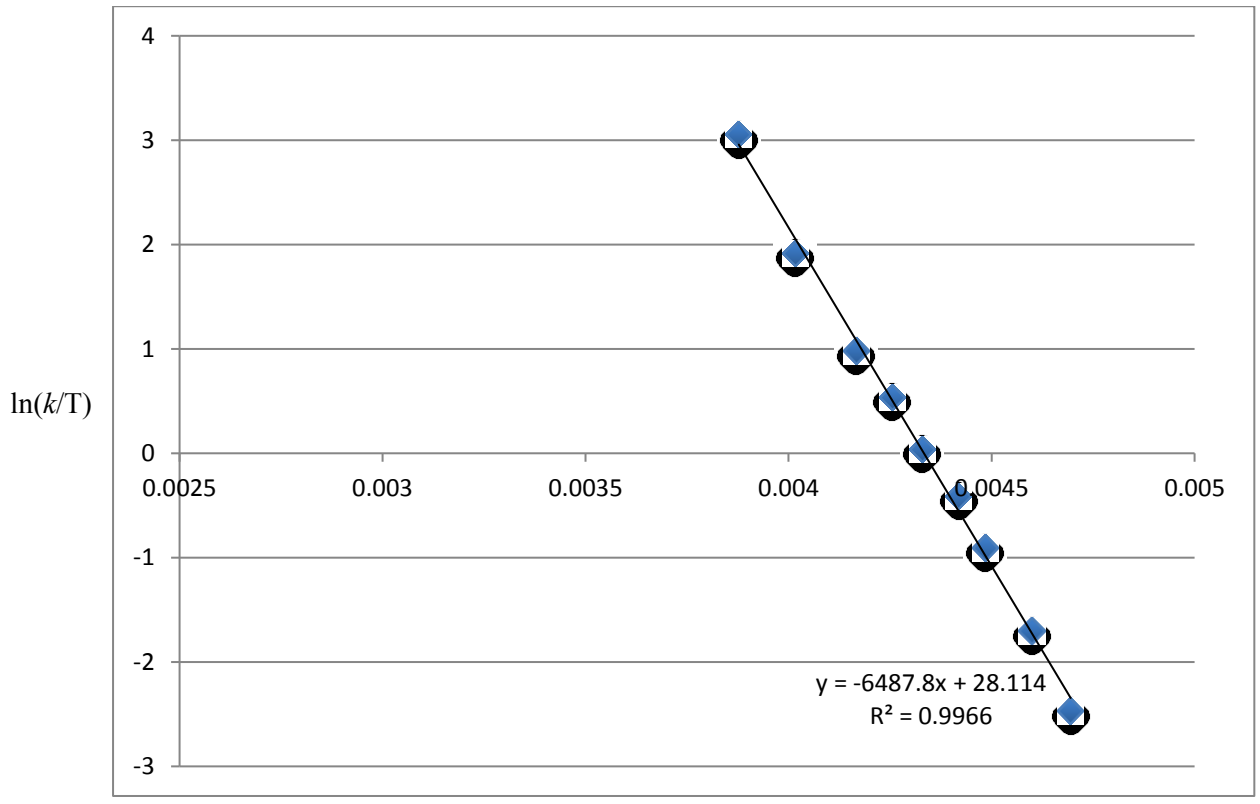
T/K	1/T	k_1	ln(k_1/T)	k_{-1}	ln(k_{-1}/T)
213	0.004695	10	–3.05871	18	–2.47092
217.4	0.004600	22	–2.29070	39.6	–1.70291
223	0.004484	50	–1.49515	90	–0.90736
226.3	0.004419	83	–1.00302	149.4	–0.41523
231	0.004329	133	–0.55207	239.4	0.03572
235	0.004255	223	–0.05241	401.4	0.53537
240	0.004167	356	0.39429	640.8	0.98208
249	0.004016	941	1.32949	1693.8	1.91728
257.9	0.003877	3034	2.46507	5461.2	3.05285

Eyring plots of 1/T against ln(k/T) for each of the forward and backward processes are shown below:

Forward direction (k_1):



Reverse direction (k_{-1}):



From these Eyring plots:

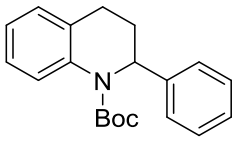
Forward direction $\Delta H^{\ddagger} \approx 54$ kJ/mol and $\Delta S^{\ddagger} \approx 31$ J/K·mol

$\Delta G^{\ddagger} \approx 47.8$ kJ/mol at –78 °C, that equates to $k = 0.6\ s^{-1}$, $t_{1/2} = 1.1$ s

Reverse direction $\Delta H^{\ddagger} \approx 54$ kJ/mol and $\Delta S^{\ddagger} \approx 36$ J/K·mol

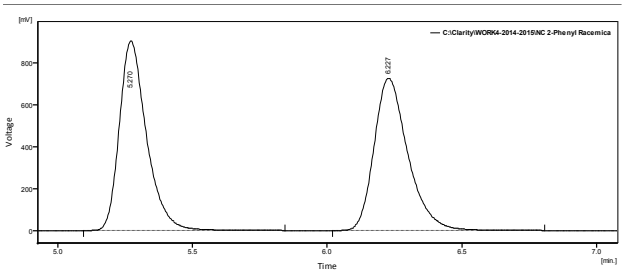
$\Delta G^{\ddagger} \approx 46.9$ kJ/mol at –78 °C, that equates to $k = 1.1\ s^{-1}$, $t_{1/2} = 0.6$ s

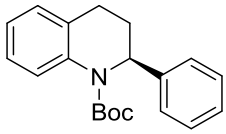
Appendix 3: HPLC traces



rac-**118a**

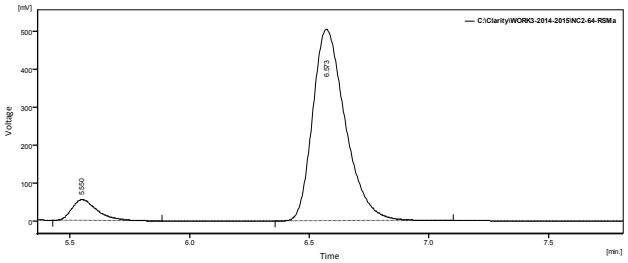
	R_t/min	Area/ mV.s	Area/%
1	5.270	6339.820	50.0
2	6.227	6336.386	50.0
	total	12676.206	100.0

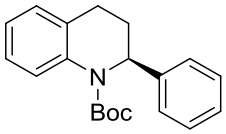




(S)-**118a**

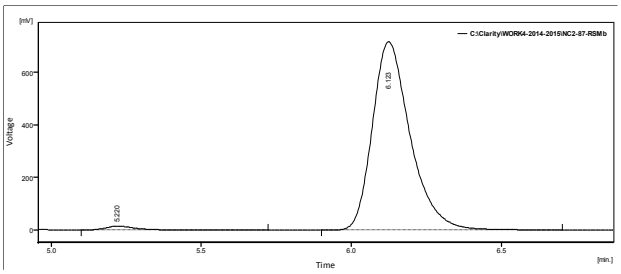
	R_t/min	Area/ mV.s	Area/%
1	5.550	409.294	7.8
2	6.573	4806.346	92.2
	total	5215.640	100.0

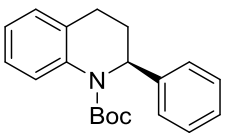




(S)-**118a**

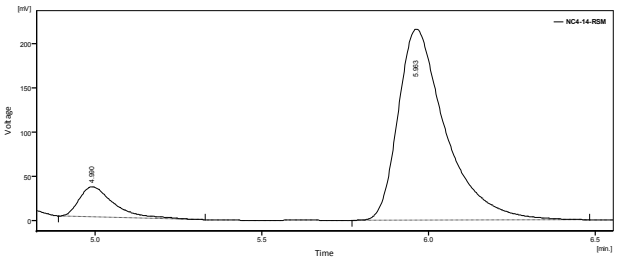
	R_t/min	Area/ mV.s	Area/%
1	5.220	104.217	1.6
2	6.123	6285.032	98.4
	total	6389.349	100.0

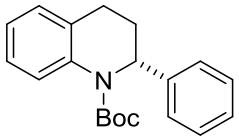




(S)-**118a**

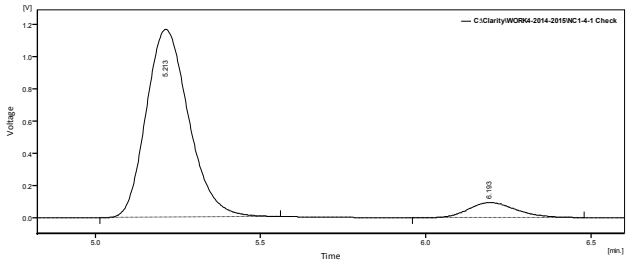
	R_t/min	Area/ mV.s	Area/%
1	4.990	246.445	10.3
2	5.963	2140.202	89.7
	total	2386.647	100.0

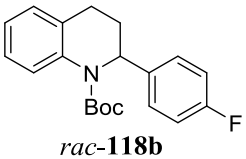




(R)-**118a**

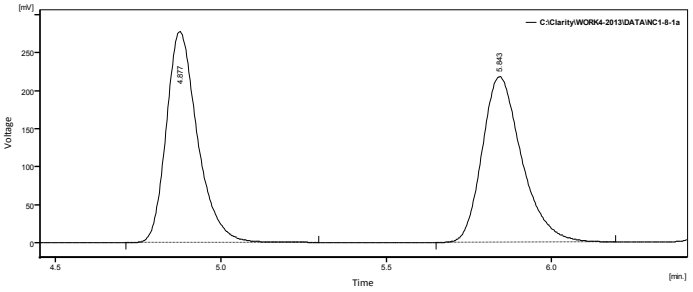
	R_t/min	Area/ mV.s	Area/%
1	5.213	10426.161	91.7
2	6.193	947.665	8.3
	total	11373.826	100.0

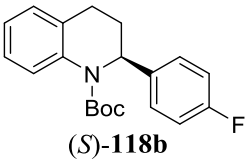




rac-**118b**

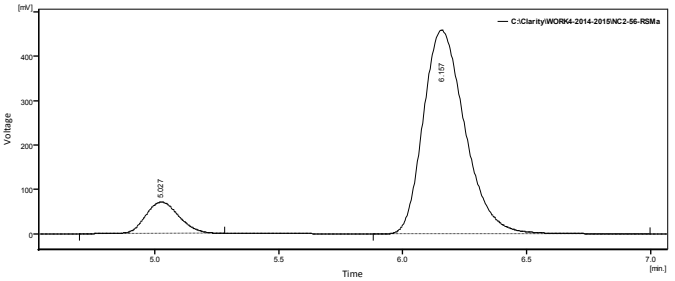
	R_t/min	Area/ mV.s	Area/%
1	4.877	1816.571	50.0
2	5.843	1814.579	50.0
	total	3631.150	100.0

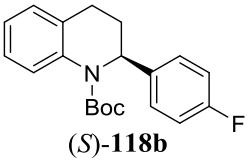




(*S*)-**118b**

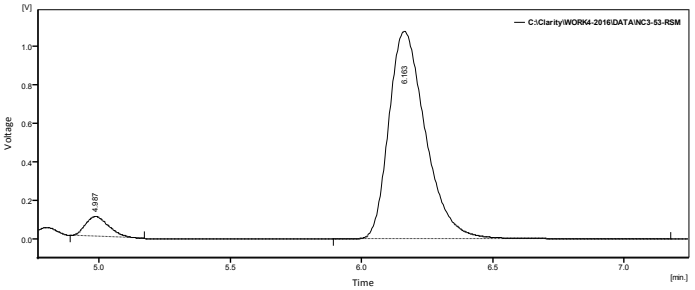
	R_t/min	Area/ mV.s	Area/%
1	5.027	679.797	11.2
2	6.157	5385.042	88.8
	total	6064.839	100.0

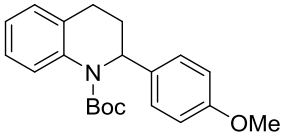




(*S*)-**118b**

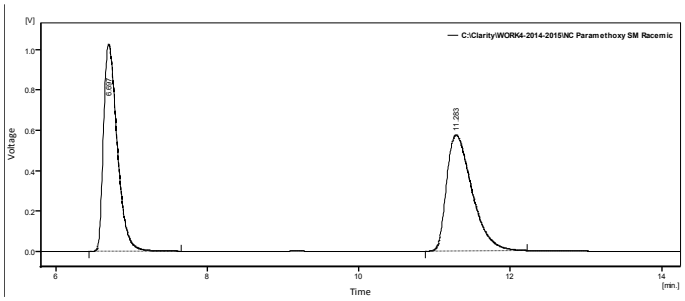
	R_t/min	Area/ mV.s	Area/%
1	4.987	650.361	5.8
2	6.163	10519.737	94.2
	total	11170.098	100.0

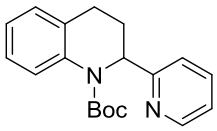




rac-**118c**

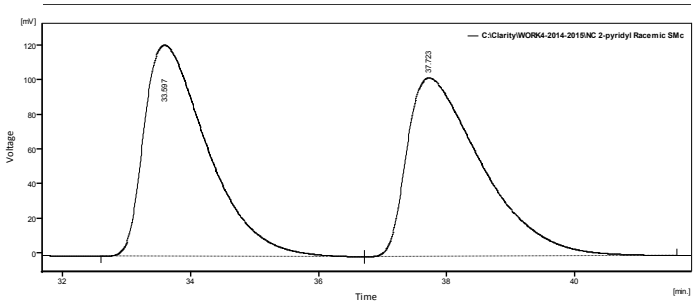
	R_t/min	Area/ mV.s	Area/%
1	6.697	12898.720	49.1
2	11.283	13380.703	50.9
	total	26729.423	100.0

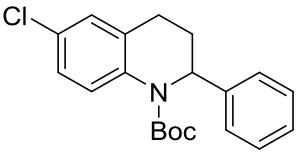




rac-**118d**

	R_t/min	Area/ mV.s	Area/%
1	33.597	8429.775	50.1
2	37.723	8389.066	49.9
	total	16818.841	100.0

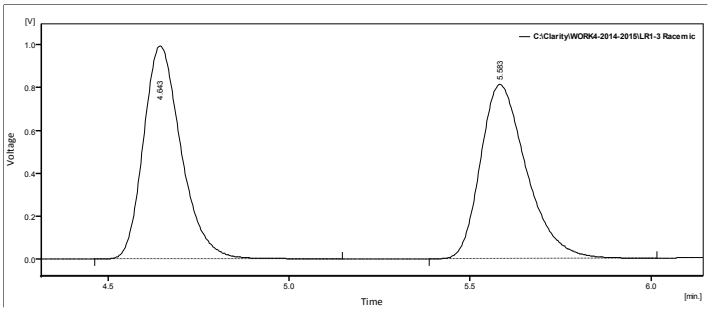


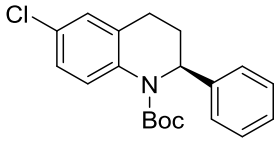


rac-**118e**

99

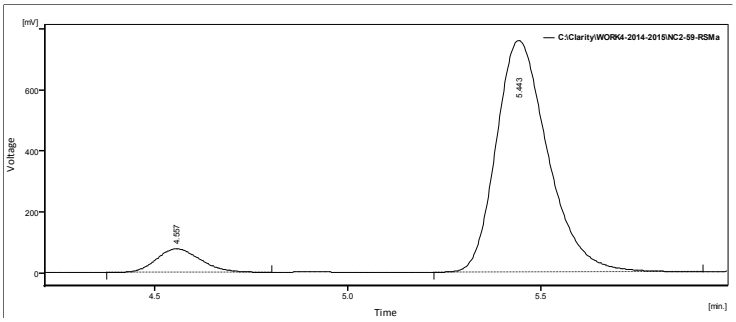
	R_t/min	Area/ mV.s	Area/%
1	4.643	7182.967	50.0
2	5.583	7184.082	50.0
	total	14367.049	100.0

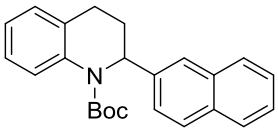




(*S*)-**118e**

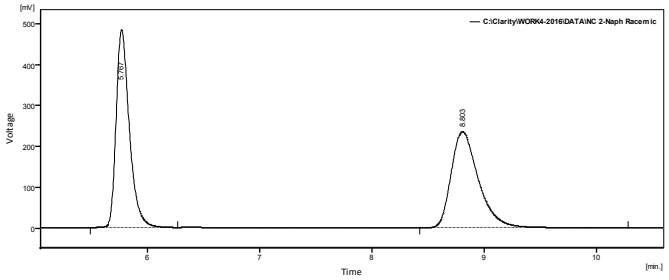
	R_t/min	Area/ mV.s	Area/%
1	4.557	617.958	8.0
2	5.443	7068.310	92.0
	total	7686.268	100.0

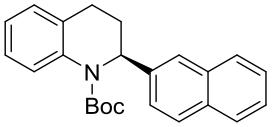




rac-**118f**

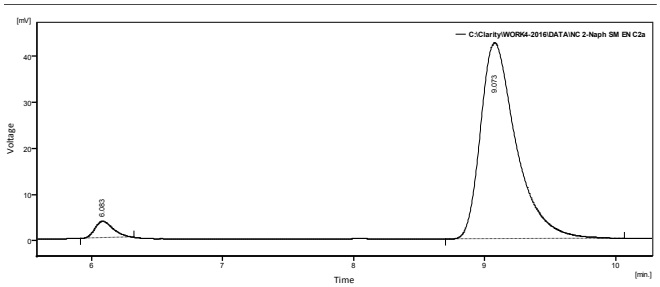
	R_t/min	Area/ mV.s	Area/%
1	5.767	3967.360	49.8
2	8.803	3996.123	50.2
	total	7963.483	100.0

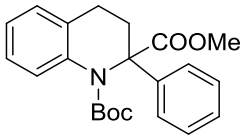




(*S*)-**118f**

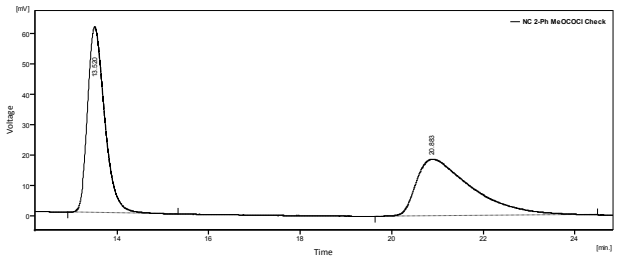
	R_t/min	Area/ mV.s	Area/%
1	6.083	36.225	4.3
2	9.073	805.644	95.7
	total	841.869	100.0

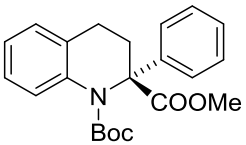




rac-**119b**

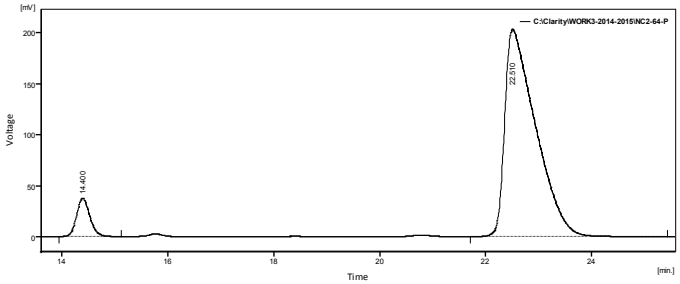
	R_t/min	Area/ mV.s	Area/%
1	13.520	1580.772	50.0
2	20.883	1580.230	50.0
	total	3161.002	100.0

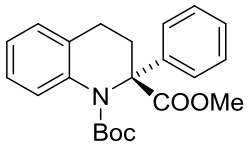




(*R*)-**119b**

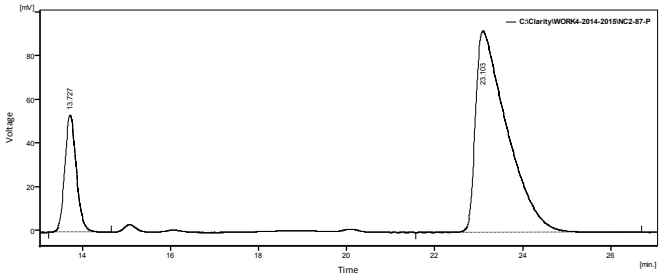
	R_t/min	Area/ mV.s	Area/%
1	14.400	655.600	7.4
2	22.510	8206.801	92.6
	total	8862.401	100.0

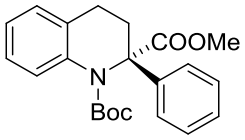




(*R*)-**119b**

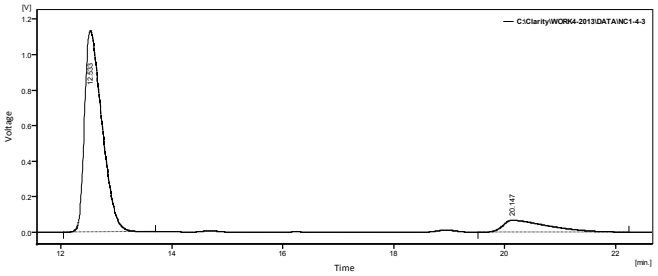
	R_t/min	Area/ mV.s	Area/%
1	13.727	984.514	17.7
2	23.103	4579.832	82.3
	total	5564.346	100.0

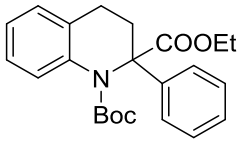




(*S*)-**119b**

	R_t/min	Area/ mV.s	Area/%
1	12.533	24914.729	86.7
2	20.147	3831.567	13.3
	total	28746.295	100.0

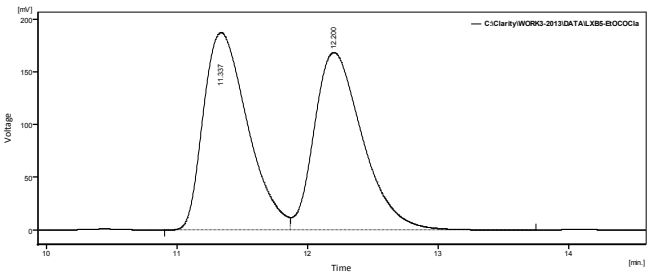


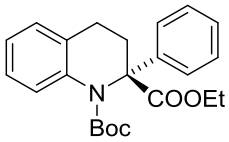


41

rac-**119c**

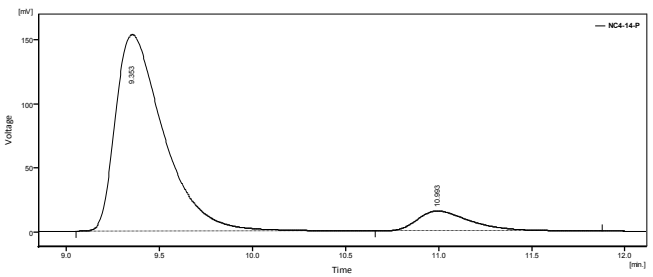
	R_t/min	Area/ mV.s	Area/%
1	11.337	4417.325	50.4
2	12.200	4340.606	49.6
	total	8757.931	100.0

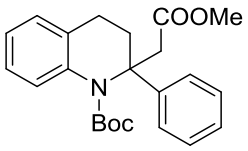




(*R*)-**119c**

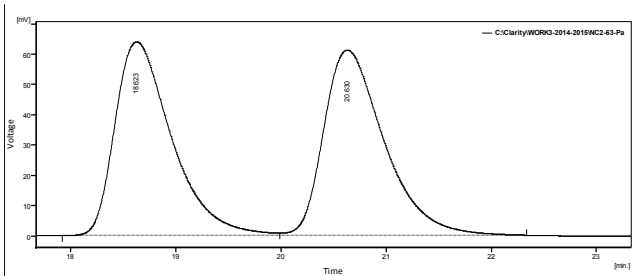
	R_t/min	Area/ mV.s	Area/%
1	9.353	2764.936	89.7
2	10.993	318.650	10.3
	total	3083.586	100.0

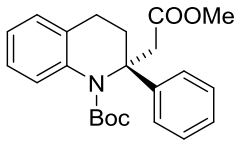




rac-**119l**

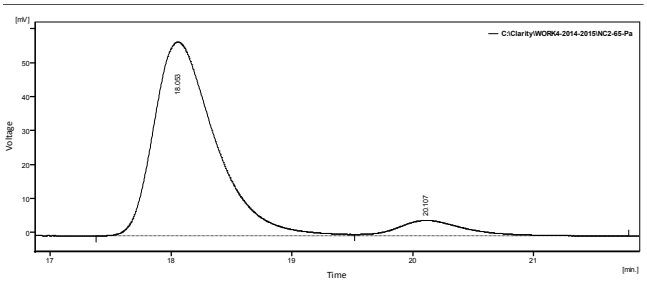
	R_t/min	Area/ mV.s	Area/%
1	18.623	2395.425	49.5
2	20.630	2441.602	50.5
	total	4837.026	100.0

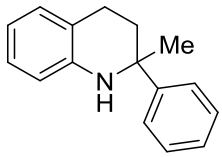




(*R*)-**119l**

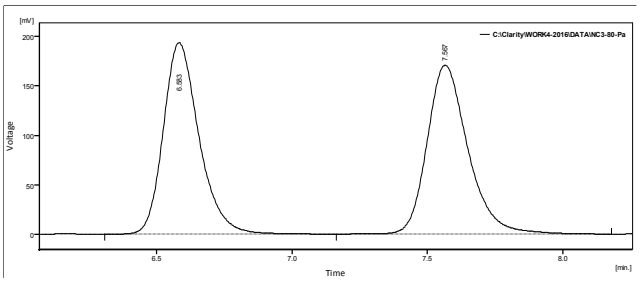
	R_t/min	Area/ mV.s	Area/%
1	18.053	2011.905	91.7
2	20.107	182.430	8.3
	total	2194.335	100.0

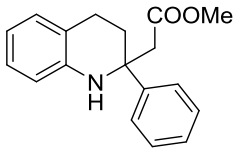




rac-**124a**

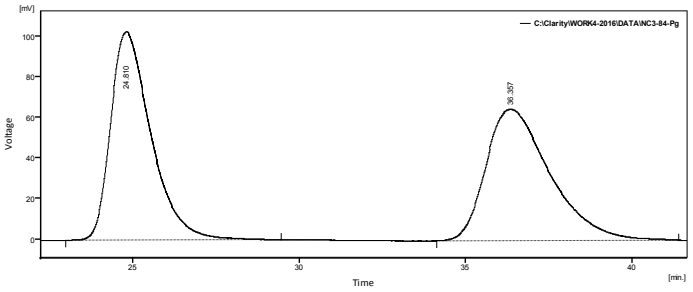
	R_t/min	Area/ mV.s	Area/%
1	6.583	1778.151	49.7
2	7.567	1797.606	50.3
	total	3575.757	100.0

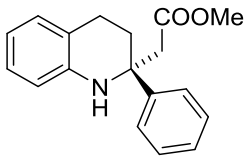




rac-**124b**

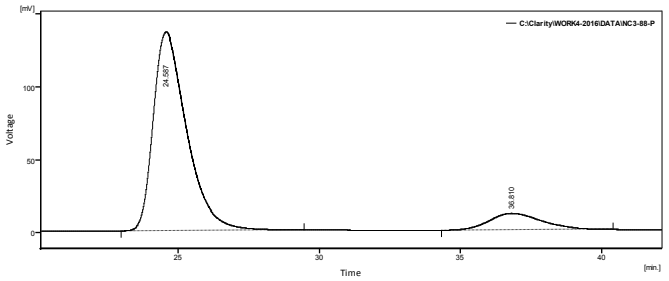
	R_t/min	Area/ mV.s	Area/%
1	24.810	8661.403	50.0
2	36.357	8669.377	50.0
	total	17330.780	100.0

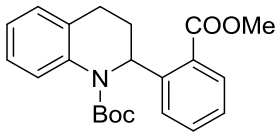




(*S*)-**124b**

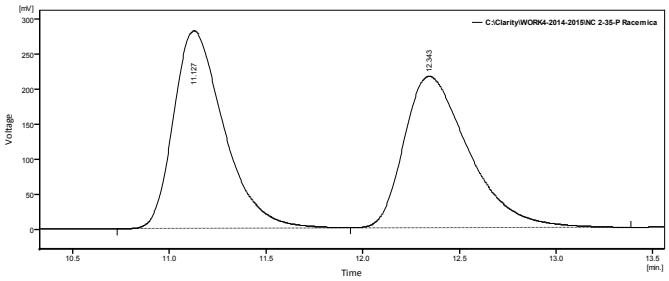
	R_t/min	Area/ mV.s	Area/%
1	24.587	11195.814	88.3
2	36.810	1486.358	11.7
	total	12682.171	100.0

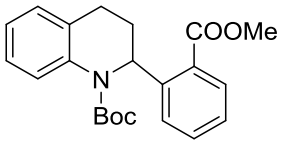




rac-**125**

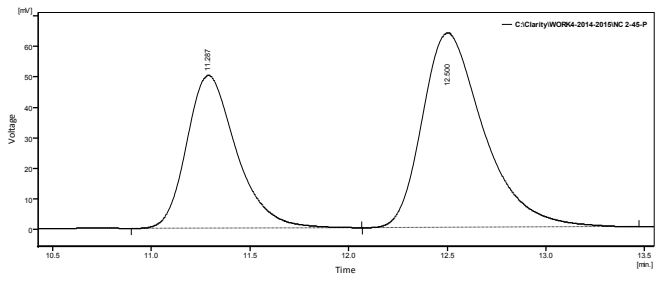
	R_t/min	Area/ mV.s	Area/%
1	11.127	5120.007	50.4
2	12.343	5030.621	49.6
	total	10150.628	100.0

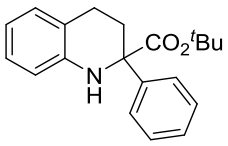




125

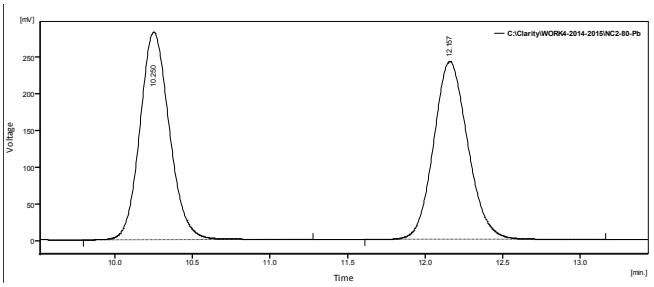
	R_t/min	Area/ mV.s	Area/%
1	11.287	876.156	38.7
2	12.500	1386.777	61.3
	total	2262.933	100.0

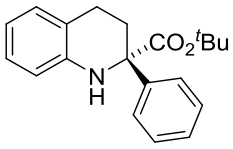




rac-**132a**

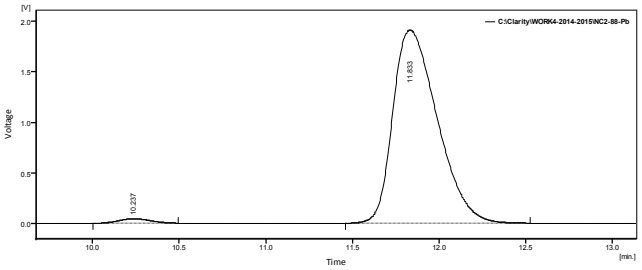
	R_t/min	Area/ mV.s	Area/%
1	10.250	3740.048	50.1
2	12.157	3726.581	49.9
	total	7466.628	100.0

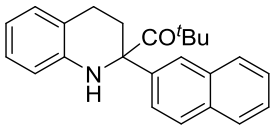




(*S*)-**132a**

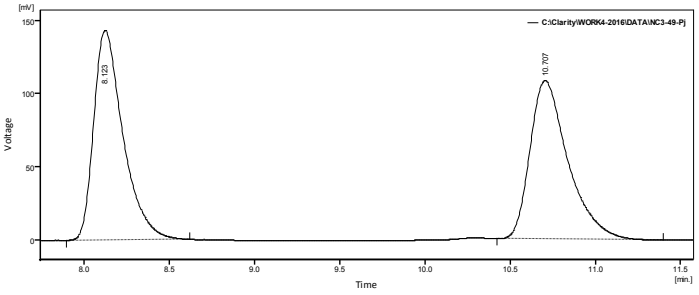
	R_t/min	Area/ mV.s	Area/%
1	10.237	592.441	1.7
2	11.833	34053.421	98.3
	total	34645.862	100.0

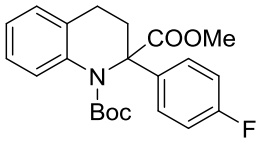




rac-**132b**

	R_t/min	Area/ mV.s	Area/%
1	8.123	1717.216	50.4
2	10.707	1689.407	49.6
	total	3406.623	100.0

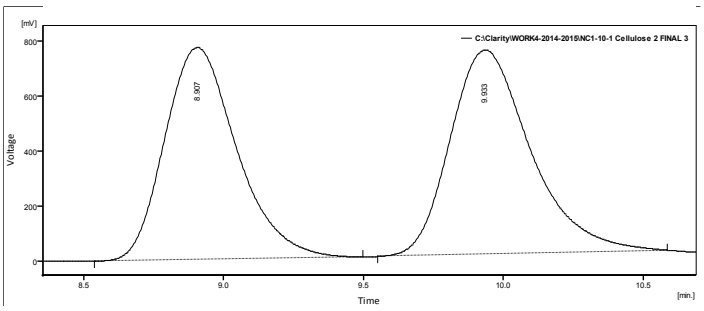


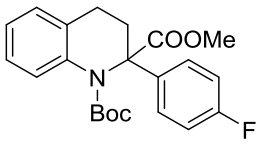


(Cellulose-2)

rac-**136a**

	R_t/min	Area/ mV.s	Area/%
1	8.907	13823.781	48.2
2	9.933	14866.677	51.8
	total	28690.459	100.0

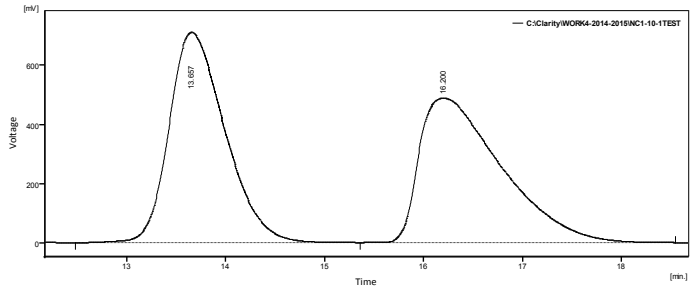


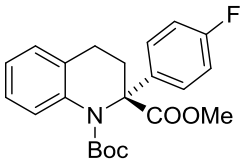


(ChiralPak IA)

rac-**136a**

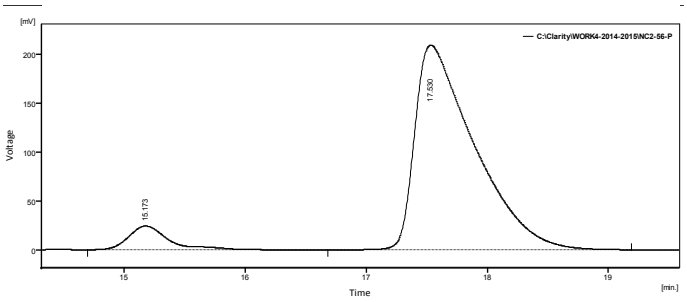
	R_t/min	Area/ mV.s	Area/%
1	13.657	27882.573	49.9
2	16.200	28018.519	50.1
	total	55901.093	100.0

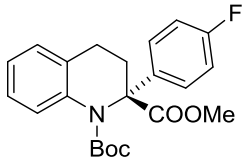




(*R*)-**136a**

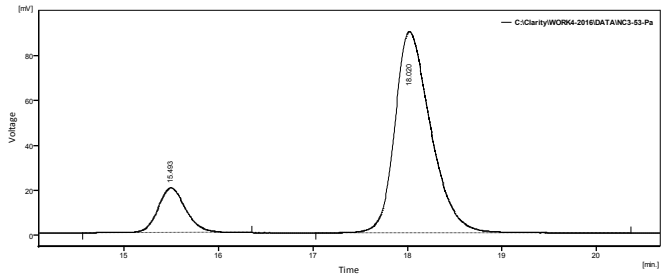
	R_t/min	Area/ mV.s	Area/%
1	15.173	562.149	7.3
2	17.530	7131.856	92.7
	total	7694.005	100.0

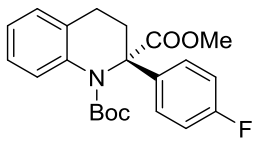




(*R*)-**136a**

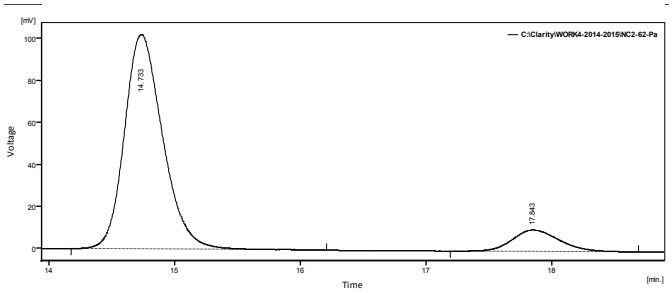
	R_t/min	Area/ mV.s	Area/%
1	15.493	415.147	14.9
2	18.020	2375.856	85.1
	total	2791.003	100.0

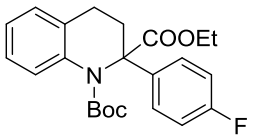




(*S*)-**136a**

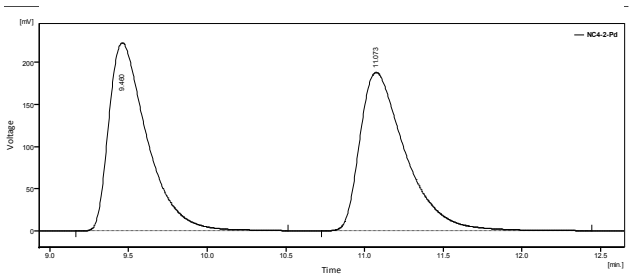
	R_t/min	Area/ mV.s	Area/%
1	14.733	2163.532	89.0
2	17.843	267.922	11.0
	total	2431.454	100.0

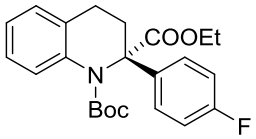




rac-**136b**

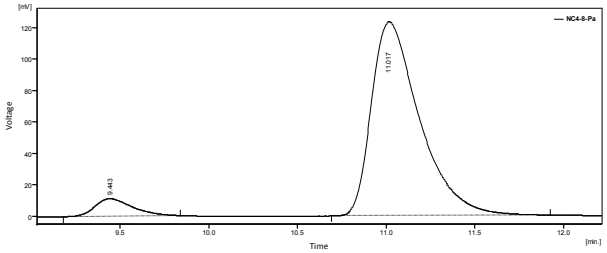
	R_t/min	Area/ mV.s	Area/%
1	9.460	3773.802	50.0
2	11.073	3778.984	50.0
	total	7552.786	100.0

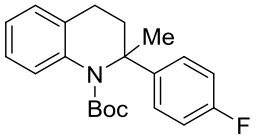




(*S*)-**136b**

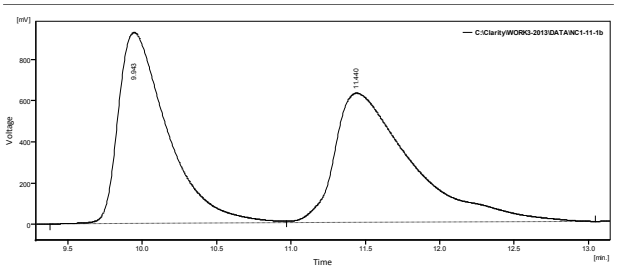
	R_t/min	Area/ mV.s	Area/%
1	9.443	164.690	6.6
2	11.017	2330.459	93.4
	total	2495.150	100.0

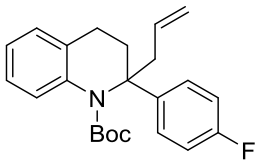




rac-**136c**

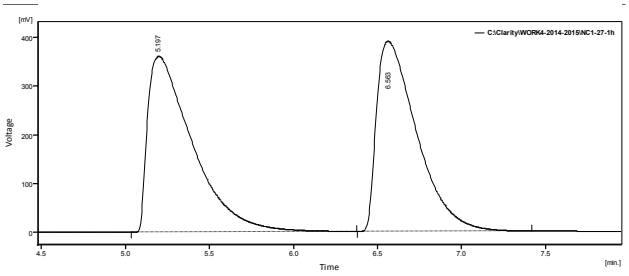
	R_t/min	Area/ mV.s	Area/%
1	9.943	21316.212	48.6
2	11.440	22507.259	51.4
	total	43823.471	100.0

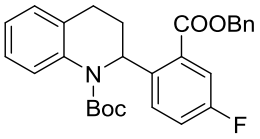




rac-**136d**

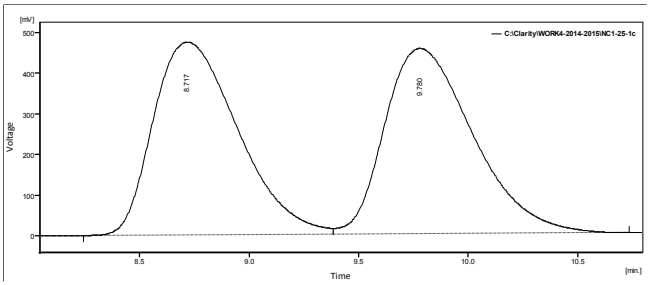
	R_t/min	Area/ mV.s	Area/%
1	5.197	6686.795	50.7
2	6.563	6494.606	49.3
	total	13181.401	100.0

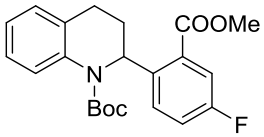




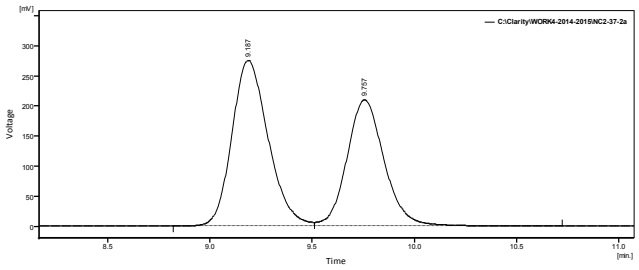
rac-**137b**

	R_t/min	Area/ mV.s	Area/%
1	8.717	12756.464	49.9
2	9.780	12806.035	50.1
	total	25562.498	100.0

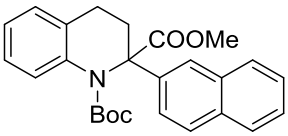




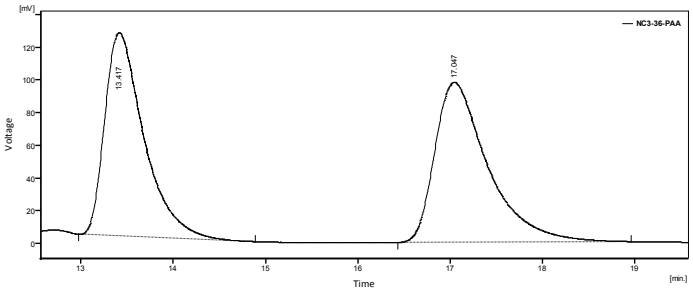
137c



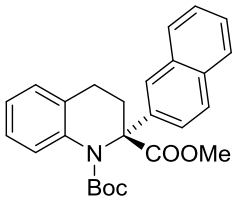
	R_t/min	Area/ mV.s	Area/%
1	9.187	3400.001	56.1
2	9.757	2665.093	43.9
	total	6065.094	100.0



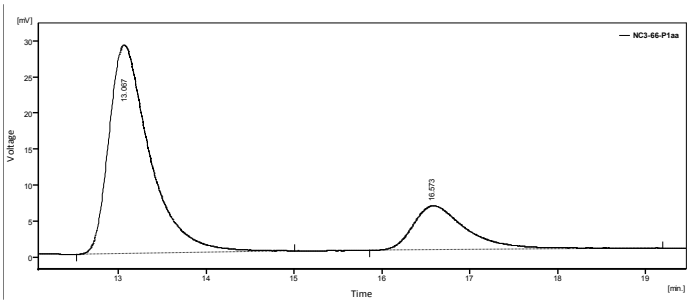
rac-**138b**



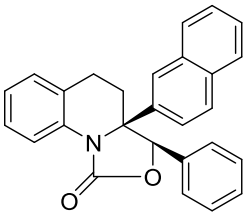
	R_t/min	Area/ mV.s	Area/%
1	13.417	3674.870	48.5
2	17.047	3906.137	51.5
	total	7581.007	100.0



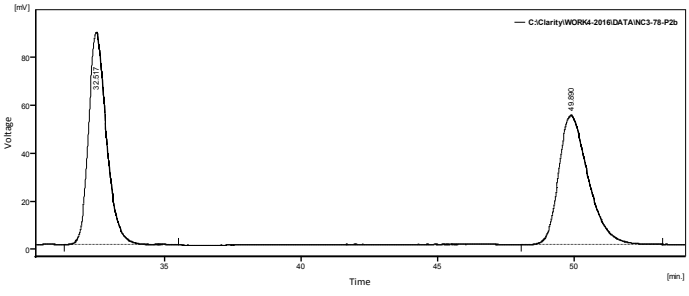
(*R*)-**138b**



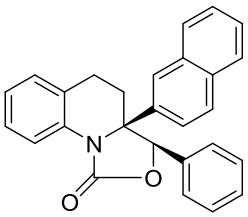
	R_t/min	Area/ mV.s	Area/%
1	13.067	933.164	78.0
2	16.573	262.472	22.0
	total	1195.636	100.0



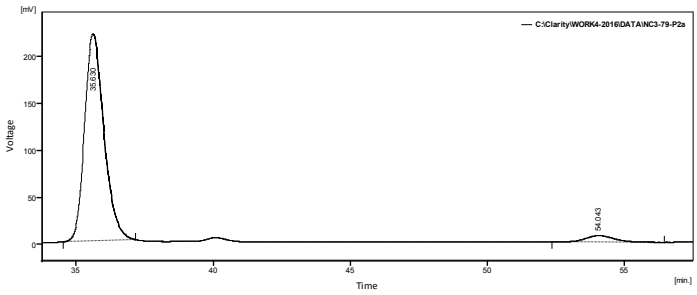
cis-**141**



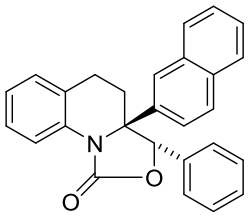
	R_t/min	Area/ mV.s	Area/%
1	32.517	4074.749	50.0
2	49.890	4073.760	50.0
	total	8148.509	100.0



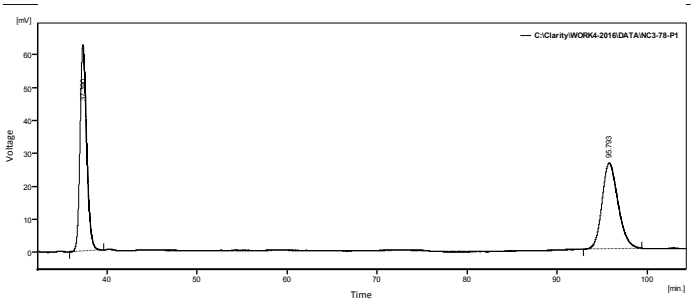
(*R*,*S*)-**141**



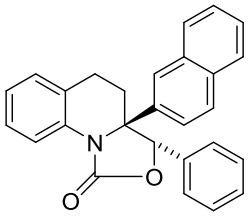
	R_t/min	Area/ mV.s	Area/%
1	35.630	10875.569	95.4
2	54.043	529.066	4.6
	total	11404.635	100.0



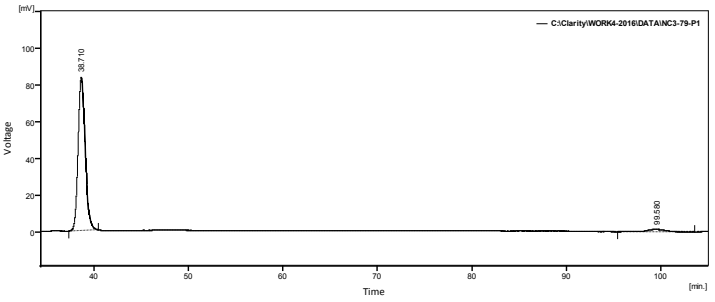
trans-**141**



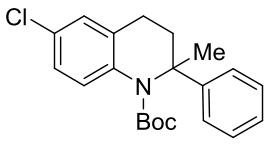
	R_t/min	Area/ mV.s	Area/%
1	37.390	3203.117	50.0
2	95.793	3199.154	50.0
	total	6402.271	100.0



(*S*,*S*)-**141**



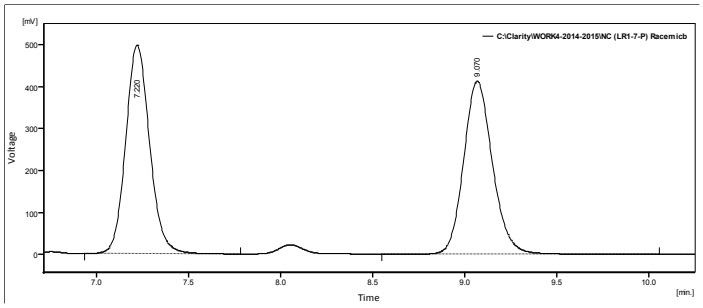
	R_t/min	Area/ mV.s	Area/%
1	38.710	4307.014	95.6
2	99.580	196.538	4.4
	total	4503.553	100.0

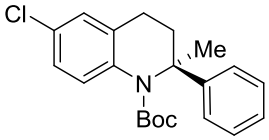


99

rac-**143a**

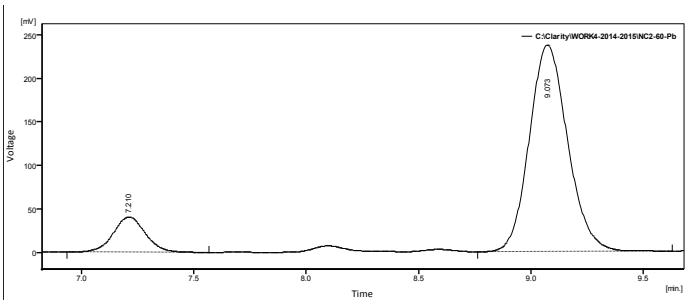
	R_t/min	Area/ mV.s	Area/%
1	7.220	4517.211	50.0
2	9.070	4517.369	50.0
	total	9034.579	100.0

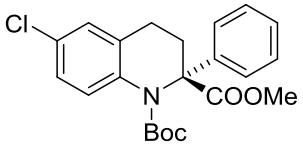




(*S*)-**143a**

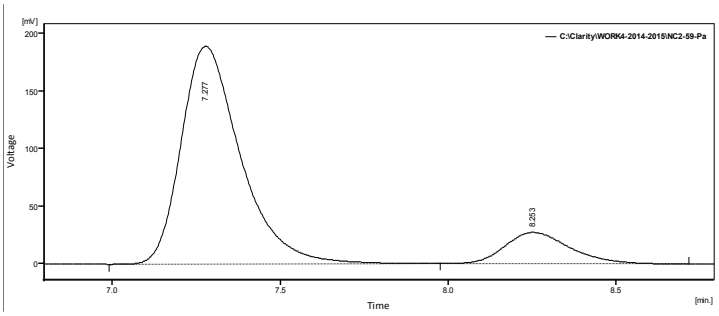
	R_t/min	Area/ mV.s	Area/%
1	7.210	407.746	12.6
2	9.073	2817.216	87.4
	total	3224.962	100.0

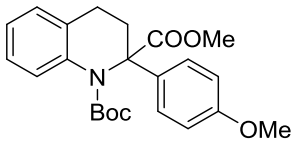




(*R*)-**143b**

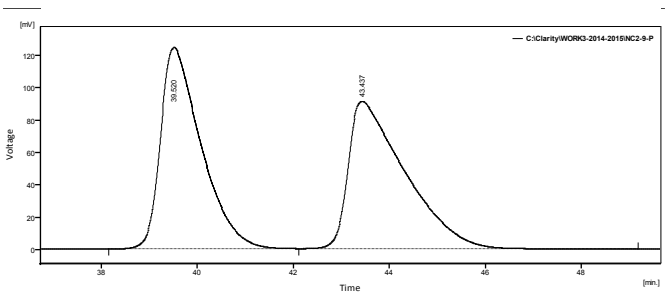
	R_t/min	Area/ mV.s	Area/%
1	7.277	2347.940	86.0
2	8.253	382.531	14.0
	total	2730.471	100.0

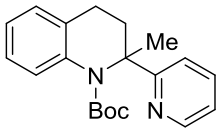




rac-**149a**

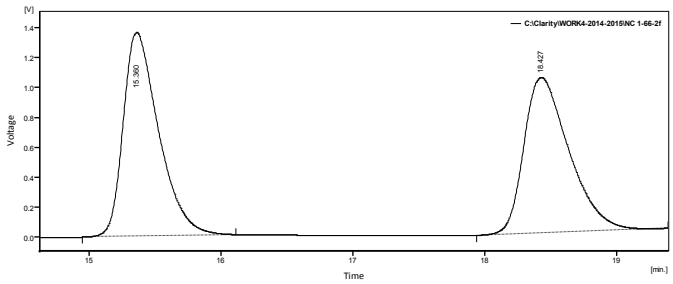
	R_t/min	Area/ mV.s	Area/%
1	39.520	7356.997	49.5
2	43.437	7515.139	50.5
	total	14872.136	100.0

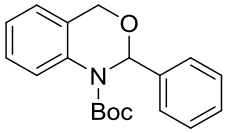




rac-**150**

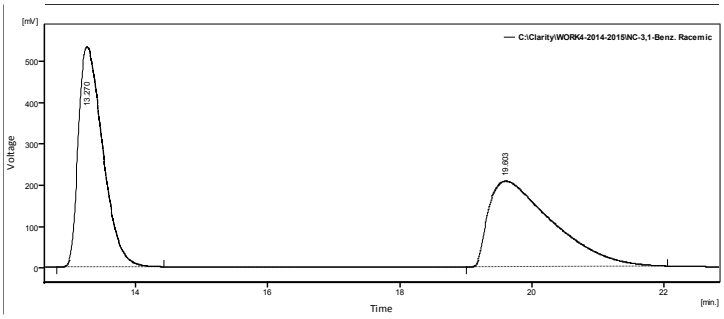
	R_t/min	Area/ mV.s	Area/%
1	15.360	25514.061	50.8
2	18.427	24718.722	49.2
	total	50232.783	100.0

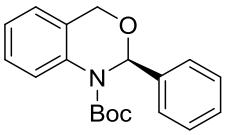




rac-**163**

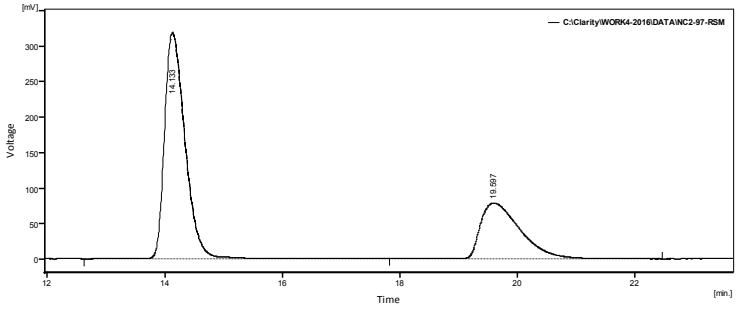
	R_t/min	Area/ mV.s	Area/%
1	13.270	13687.855	49.5
2	19.603	13960.598	50.5
	total	27648.452	100.0

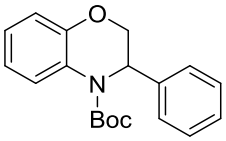




(*S*)-**163**

	R_t/min	Area/ mV.s	Area/%
1	14.133	7705.396	67.7
2	19.597	3676.159	32.3
	total	11381.554	100.0

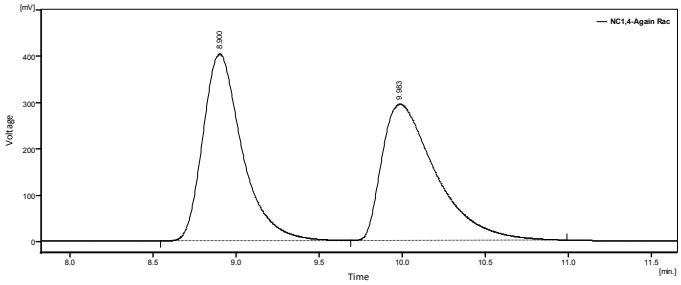


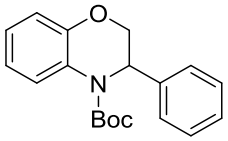


(Cellulose-2)

rac-**164a**

	R_t/min	Area/ mV.s	Area/%
1	8.900	6626.051	50.0
2	9.983	6627.480	50.0
	total	13253.531	100.0

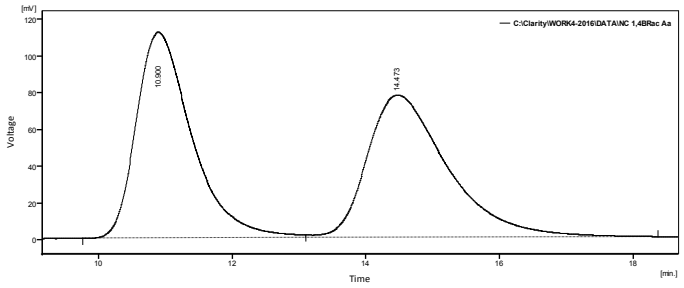


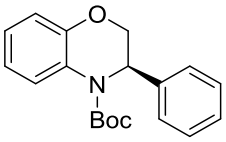


(ChiralCel OJ)

rac-**164a**

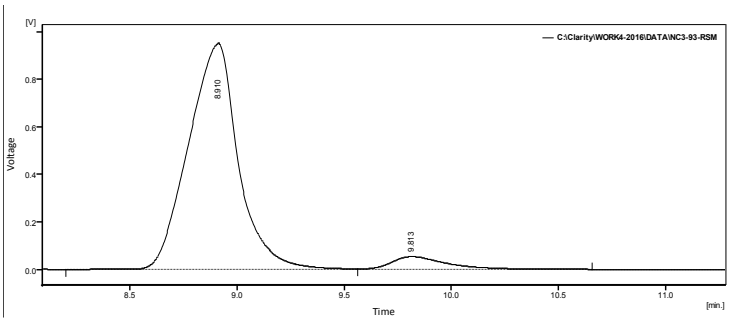
	R_t/min	Area/ mV.s	Area/%
1	10.900	6489.120	50.0
2	14.473	6489.237	50.0
	total	12978.357	100.0

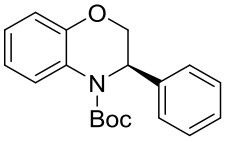




(*R*)-**164a**

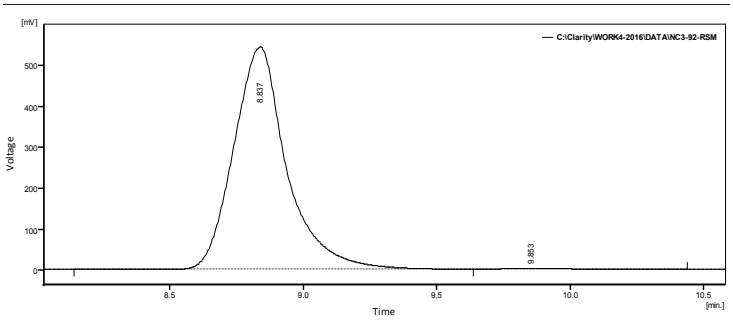
	R_t/min	Area/ mV.s	Area/%
1	8.910	15352.604	94.1
2	9.813	957.788	5.9
	total	16310.392	100.0

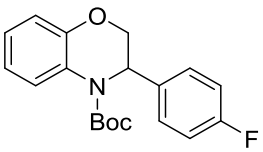




(*R*)-**164a**

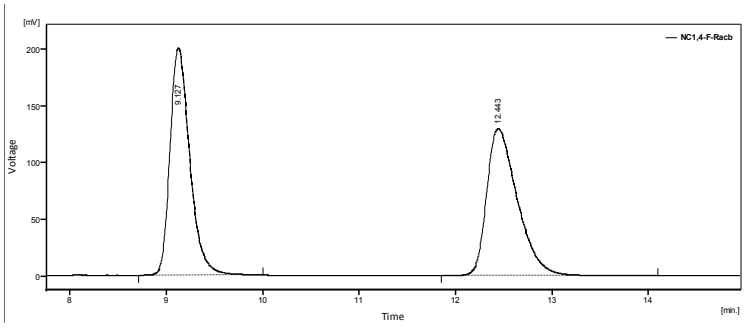
	R_t/min	Area/ mV.s	Area/%
1	8.837	7547.055	99.2
2	9.853	59.139	0.8
	total	7606.194	100.0

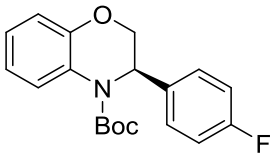




rac-**164b**

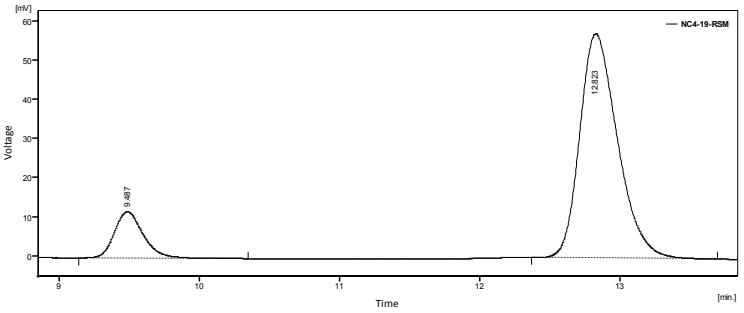
	R_t/min	Area/ mV.s	Area/%
1	9.127	2865.032	50.0
2	12.443	2866.016	50.0
	total	5731.048	100.0

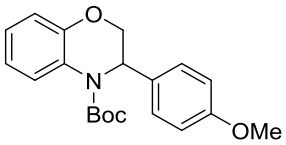




(*R*)-**164b**

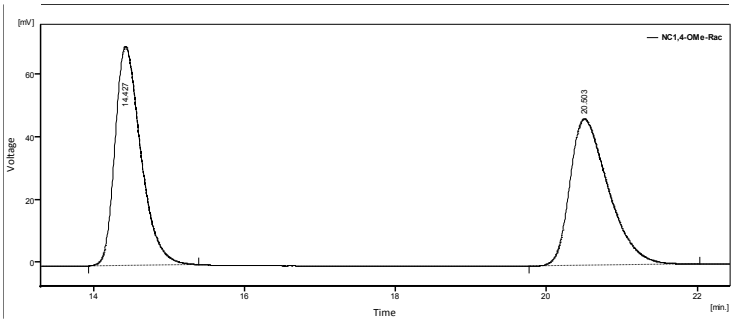
	R_t/min	Area/ mV.s	Area/%
1	9.487	170.139	13.7
2	12.823	1075.252	86.3
	total	1245.391	100.0

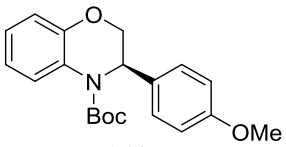




rac-**164c**

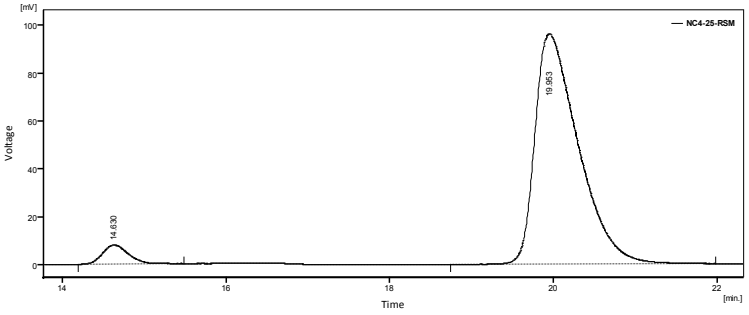
	R_t/min	Area/ mV.s	Area/%
1	14.427	1663.891	50.0
2	20.503	1664.593	50.0
	total	3328.485	100.0

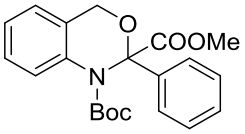




(*R*)-**164c**

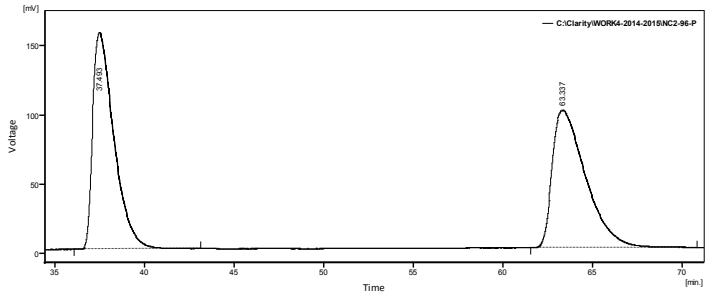
	R_t/min	Area/ mV.s	Area/%
1	14.630	177.497	4.8
2	19.953	3528.867	95.2
	total	3706.364	100.0

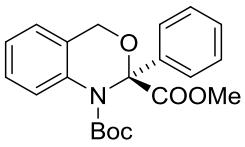




rac-**189**

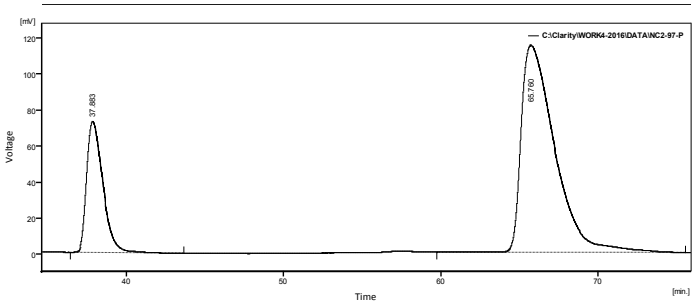
	R_t/min	Area/ mV.s	Area/%
1	37.493	12881.136	50.0
2	63.337	12871.413	50.0
	total	25752.549	100.0

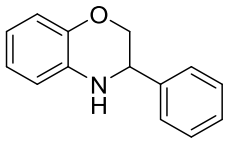




(*S*)-**189**

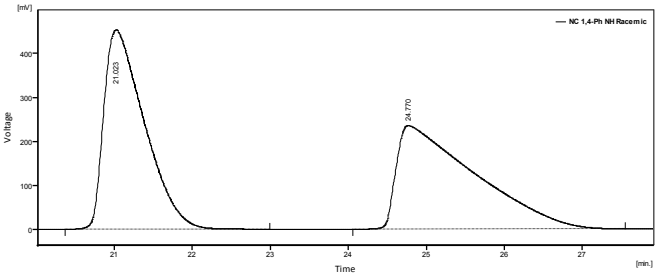
	R_t/min	Area/ mV.s	Area/%
1	37.883	5192.919	23.3
2	65.760	17121.811	76.7
	total	22314.730	100.0

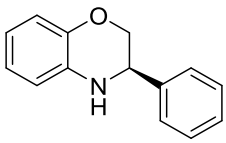




rac-**193a**

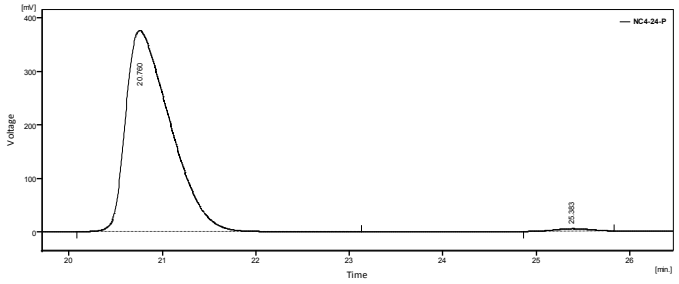
	R_t/min	Area/ mV.s	Area/%
1	21.023	16345.379	50.0
2	24.770	16370.111	50.0
	total	32715.490	100.0





(*R*)-**193a**

	R_t/min	Area/ mV.s	Area/%
1	20.760	12382.264	99.0
2	25.383	124.021	1.0
	total	12506.286	100.0



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