Kinetic Resolution by Lithiation of Substituted 1,2-Dihydroquinolines and Dihydrobenzoxazines

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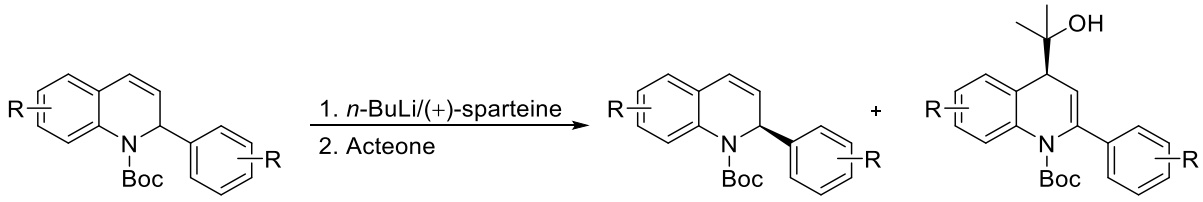
Abstract

The dihydroquinoline (DHQ) moiety is found in many compounds which have biological activity. This thesis discusses the lithiation-substitution reactions of 2-aryl DHQs with a variety of electrophiles, which react at the 4-position. The DHQ compounds synthesised in this thesis were fully deprotonated within a few minutes and the lithiated intermediates were configurationally stable at low temperature. Kinetic resolutions were attempted using *n*-BuLi/sparteine chiral base and the starting materials were recovered in good yield and excellent enantiomer ratios (ers). Lithiation-substitution of enantioenriched recovered starting material occurred with retention of configuration.



Lithiation-substitution of enantioenriched 4-methyl-2-phenyl-1,2-DHQ obtained by kinetic resolution gave enantioenriched 2,4,4-trisubstituted products. Both enantiomers of highly enantioenriched 2,4,4-trisubstituted-1,4-DHQs can be obtained from the same enantiomer of sparteine.

Hydrogenation by reduction of the 1,4-DHQ gave 2,4-disubstituted tetrahydroquinoline as *cis*- product. The Boc protecting group was removed under acidic conditions and by oxidation 2,4-disubstituted quinoline was prepared. This was applied to a short synthesis of the anti-malarial drug M5717.

Lithiation-electrophilic quench reactions and kinetic resolution of *N*-Boc-2-alkyl-DHQs were also attempted. However, poor results were obtained and was not studied further.

Enantioenriched 7,8-difluoro-3-phenyl-benzoxazine obtained by kinetic resolution was used to synthesise an analogue of antibiotic levofloxacin which was screened for its activity.

Acknowledgements

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Contents

Abbreviation

(–)-sp	(–)-sparteine
(+)-sp	(+)-sparteine
$\Delta G^{\ddagger}$	Gibbs free energy
Ac	acetyl
ADME	absorption, distribution, metabolism and excretion
aq.	aqueous
Ar	aryl
atm	atmospheric pressure
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
cat.	catalyst
COD	1,5-cyclooctadiene
conc.	concentration
Cy	cyclohexyl
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DHQ	dihydroquinoline
DIPEA	*N*,*N*-diisopropylethylamine
DIPT	diisopropyltartrate
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid

dr	diastereomeric ratio
E^+	electrophile
ee	enantiomeric excess
EI	electron impact
eq.	equivalent(s)
er	enantiomeric ratio
ES	electrospray
Et	ethyl
FT	fourier transform
g	gram(s)
GDH	glutamate dehydrogenase
h	hour(s)
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i.d.	internal diameter
^{i}Pr	isopropyl
IR	infrared
IRED	imine reductase
J	joule(s)
K	kelvin
kJ	kilojoule(s)
KR	kinetic resolution
L*	chiral ligand

LDA	lithium diisopropylamide
lit.	literature
LRMS	low resolution mass spectrometry
M	molar
m.p.	melting point
Me	methyl
mg	miligram(s)
MHz	megahertz
min	minute(s)
mL	mililitre(s)
mmol	milimole(s)
mol	mole(s)
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
n-Bu	normal butyl
$NADP^+$	nicotinamide adenine dinucleotide phosphate
nm	nanometre(s)
NMR	nuclear magnetic resonance
o-	*ortho*-
^oC	degree Celcius
p-	*para*-
Pe	pentyl
pH	potential of hydrogen
Ph	phenyl
pin	pinacol

PPE	polyphenylene ether
ppm	parts-per-million
PTSA	*p*-toluenesulfonic acid
rac-	racemic
R_f	retention factor
RSM	recovered starting material
rt	room temperature
s	selectivity factors
s-Bu	secondary butyl
SM	starting material
surr	surrogate
t	time
T	temperature
t-Bu	tertiary butyl
TBAB	tetrabutylammonium bromide
TBHP	*tert*-butyl hydroperoxide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THQ	tetrahydroquinoline
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TOF	time of flight
Ts	tosyl
UV	ultraviolet
µL	microlitre(s)

Chapter 1 – Introduction

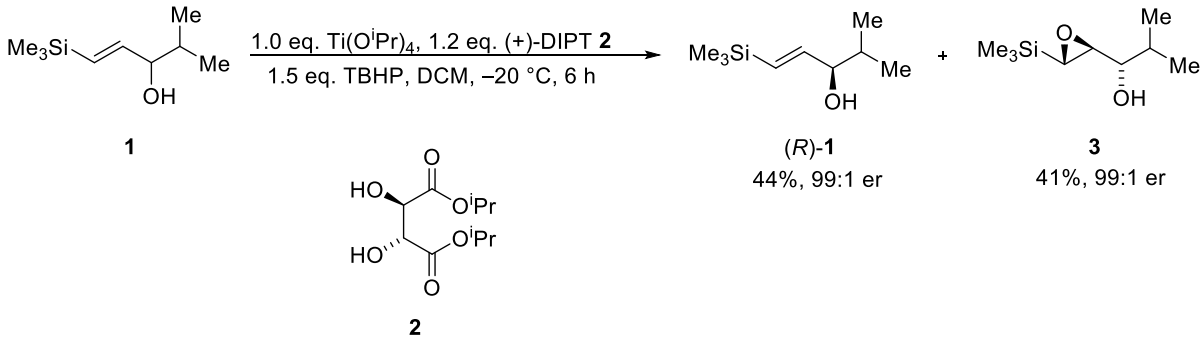
1.1 Kinetic resolution

Enantiomerically enriched compounds can be obtained by functional group interconversions of chiral pool compounds or by asymmetric synthesis, for example using chiral auxiliaries or catalysts. Kinetic resolution (KR) is one method to prepare chiral (non-racemic) molecules in organic synthesis. KR was first understood by Pasteur in 1890.[1] KR is a process leading to differentiation of two enantiomers in a racemic mixture normally in the presence of a chiral catalyst or ligand using chemical reactions. They are also known as kinetically controlled asymmetric transformations.[2] The enantiomers in a racemic mixture need to react at different rates, where both enantiomers have the same Gibbs free energy and the products of both enantiomers are also at equal energy levels. However, the transition state energies ($\Delta G^{\ddagger}$) are different due to the presence of the chiral ligand or reagent (L*). The enantiomer with lower $\Delta G^{\ddagger}$ reacts faster to produce the product compound. In comparison, the enantiomer with higher $\Delta G^{\ddagger}$ reacts slower and produces the recovered (unreacted) starting material (RSM). Enantiomeric ratio (er) is used as the ratio of the percentage of one enantiomer in a mixture to the other enantiomer. The er value of the product drops as the conversion approaches or exceeds 50%. Hence, the reaction has to be stopped before 50% conversion of the starting material to obtain a high enantiomer ratio of the product. However, high enantiomer ratio of the RSM is possible after 50% conversion and the er increases with conversion.

Kinetic resolution is a very useful method to form enantiomerically pure chiral substances and to improve the enantiomer ratio of a compound. KR can be applied to every class of chiral substrates and used in combination with all the methods of

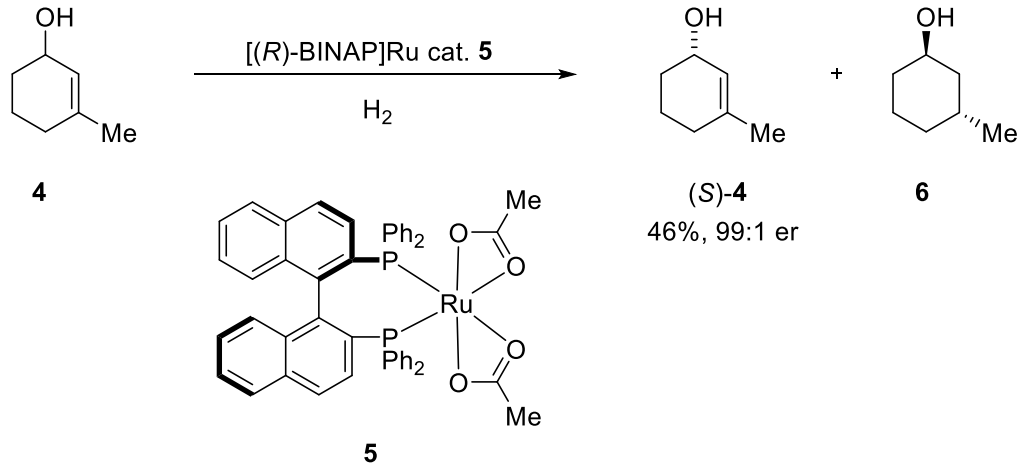
enantioselective synthesis.[2] However, KR has the downside of a maximum yield of 50% for both the product and the RSM for higher er. Furthermore, the product has to be separated from the RSM. If the product and the RSM have close retention factor (R_f) values, then it may be difficult to separate by column chromatography.

Kinetic resolution has become important for the synthesis of enantiopure organic compounds. In 1988, Sato and co-workers reported kinetic resolution of secondary allylic alcohols after the discovery of asymmetric epoxidation of allylic alcohols by Sharpless.[3] The kinetic resolution of allylic alcohol **1** was performed by 1.5 eq. *tert*-butyl hydroperoxide (TBHP) using 1.0 eq. $Ti(O^iPr)_4$ and 1.2 eq. (+)-diisopropyl tartrate ((+)-DIPT) **2** in dichloromethane (DCM) for 6 h at –20 °C (Scheme 1). An excellent result was obtained with alcohol (*R*)-**1** recovered in 44% yield and 99:1 er and product **3** in 41% yield and 99:1 er.



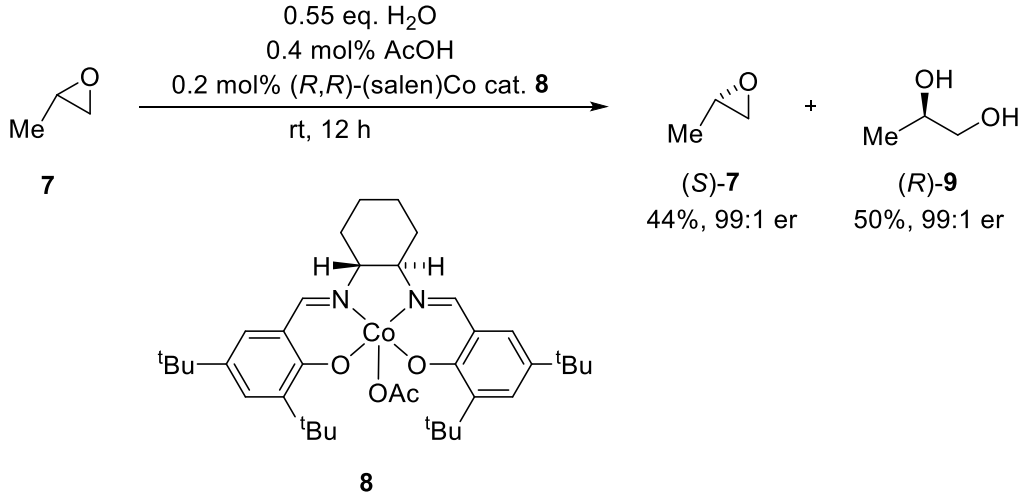
Scheme 1

Noyori and co-workers reported kinetic resolution of cyclic allylic alcohols by asymmetric hydrogenation.[4] The hydrogenation of alkene **4** was catalysed by (*R*)-BINAP-ruthenium(II) dicarboxylate catalyst **5** (Scheme 2). Enantioenriched alkene (*S*)-**4** was successfully obtained in 46% yield and 99:1 er.



Scheme 2

In 1997, Jacobsen and co-workers demonstrated hydrolytic kinetic resolution of epoxides using a chiral catalyst.[5] Terminal epoxide **7** was reacted with 0.55 eq. water in the presence of 0.2 mol% of (*R*,*R*)-(salen)Co catalyst **8** and 0.4 mol% of acetic acid (AcOH) at room temperature for 12 h (Scheme 3). A mixture of recovered starting material (*S*)-**7** and the product 1,2-diol (*R*)-**9** was obtained in 44% yield with 99:1 er and 50% yield with 99:1 er respectively.



Scheme 3

Recently there has been an increase in studies on kinetic resolutions, even though the theoretical maximum yield of highly enantioenriched compounds is 50%. There is one striking advantage that kinetic resolution has over other methods of asymmetric synthesis. In asymmetric synthesis, the enantiomeric ratio is simply a consequence of the difference in Gibbs free energy ($\Delta G^{\ddagger}$) between the two diastereomeric transition state energies. Hence, the only way to improve the er is by increasing the free energy difference, $\Delta\Delta G^{\ddagger}$. The kinetic resolution also depends on $\Delta\Delta G^{\ddagger}$. However, $\Delta\Delta G^{\ddagger}$ is expressed uniquely and represents a constant differential pressure upon the two enantiomers in kinetic resolution.[6] This continues until all molecules of the more reactive species are used up, and one is left with an absolute enantiomeric purity, that is the RSM. Likewise, at low conversions, highly enantioenriched product can be obtained. This project will explore KR using organolithium reagents that are introduced in the next section.

1.2 Asymmetric synthesis using organolithium reagents

Organolithium reagents were first synthesised in 1917 by Schlenk and Holtz.[7] Reactions with organolithium species as reagents, reactants or intermediates are so well recognised that organolithiums are the most widely used organometallics in organic chemistry.[8] In many cases, higher yields and increased rates have been obtained when reactions were performed with organolithium reagents instead of with organomagnesium reagents.[9] Organolithium reagents contain a carbon-lithium bond which is highly ionic in nature due to the significant difference in electronegativity between carbon and lithium atoms. The polarity of this bond effectively makes the organolithium compounds extraordinarily reactive as both a base and a nucleophile. Due to its reactivity, organolithium compounds are moisture-sensitive and air-sensitive. Organolithium reagents are reactive and therefore stored in solvents like hexane. Coordinating solvents act as Lewis bases to coordinate to the lithium ions, resulting in different structures and deaggregation. For example, *n*-butyllithium (*n*-BuLi) exist as hexamers in hexane, but deaggregates in tetrahydrofuran (THF) forming tetramers.[10] Many Lewis basic compounds like amines and ethers can also deaggregate organolithiums in the absence of coordinating solvents. An example of this is sparteine, which forms a dimeric structure with *n*-BuLi (Figure 1).[10]

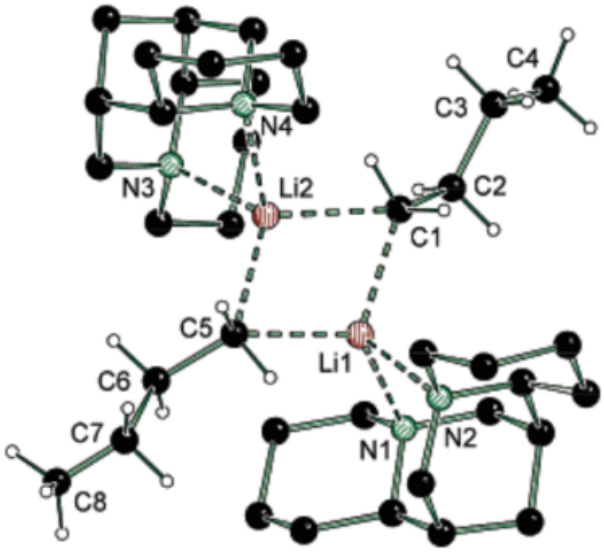
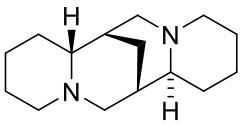
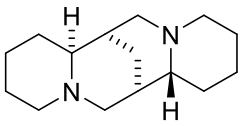


Figure 1 – A dimeric structure of sparteine with *n*-BuLi

Asymmetric synthesis using organolithiums involves the addition of a chiral ligand to introduce stereoselectivity into the reaction.[11] In 1987, Hoppe and co-workers discovered that enantioselective deprotonation could be carried out by using *n*-BuLi and a chiral amine, (–)-sparteine ((–)-sp) **10**.[12] Then not long after the discovery by Hoppe, in 1991, Beak and co-workers used (–)-sp **10** and *sec*-butyllithium (*s*-BuLi) to perform asymmetric lithiation on nitrogen heterocycles by deprotonating a prochiral hydrogen atom adjacent to a nitrogen atom.[13] The ligand (–)-sp **10** is a chiral diamine and is a naturally occurring alkaloid extracted from plants such as Scotch Broom (Figure 2).[8,14] It is commercially available, although the availability has varied over the last 20 years. The other enantiomer, (+)-sparteine ((+)-sp) **11** can be obtained by reduction of (–)-lupinine, which can be extracted from the seeds of *Lupinus albus* (Figure 2).[15]



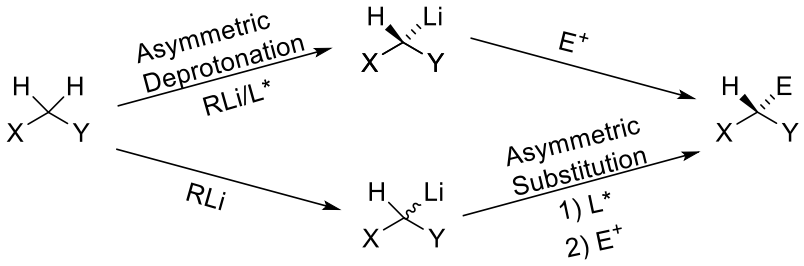
(–)-sparteine
10



(+)-sparteine
11

Figure 2 – Structures of sparteine

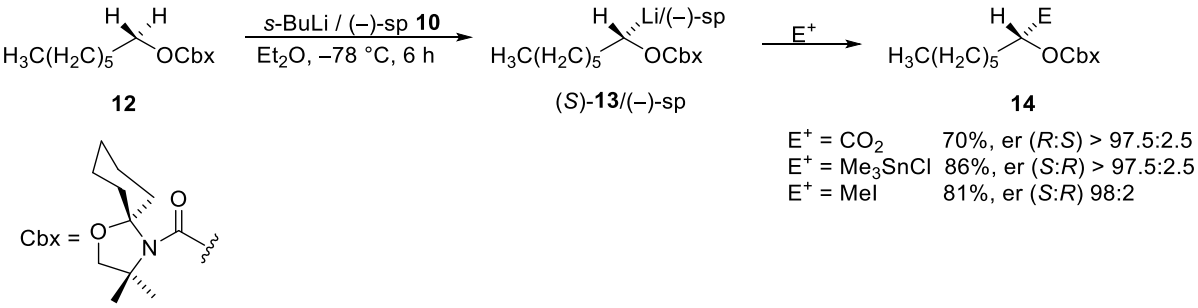
Asymmetric synthesis using organolithiums can occur either by asymmetric deprotonation or substitution (Scheme 4).[16] In the asymmetric deprotonation pathway, the stereochemical information is transferred to the products in the initial step, whereas in asymmetric substitution, the asymmetric induction occurs in a post deprotonation step.[17] Hoppe and co-workers reported asymmetric deprotonation in 1989.[18] Organolithium reagents with chiral ligands like (–)-sp **10** can remove an enantiotopic proton from a substrate. For asymmetric deprotonation, the sp^3 hybridized organolithium has to be configurationally stable and must react stereoselectively with an electrophile (E^+). Excellent selectivities have been obtained with asymmetric deprotonation. Hence configurationally stable organolithium compounds are valuable reagents for stereoselective synthesis.[19,20]



Scheme 4

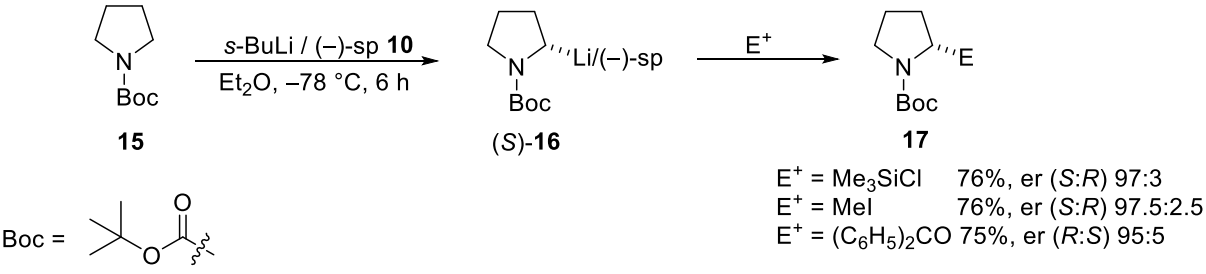
In 1990, Hoppe and co-workers reported asymmetric deprotonation in the presence of (–)-sp **10** using *s*-BuLi in diethyl ether (Et_2O) (Scheme 5).[21] The proton adjacent to the

oxygen of the carbamate **12** was deprotonated and formed the complex (*S*)-**13**/(–)-sp with high diastereomeric excess. The intermediate was then quenched with various electrophiles and the products **14** were obtained with an excellent enantiomeric ratio.



Scheme 5

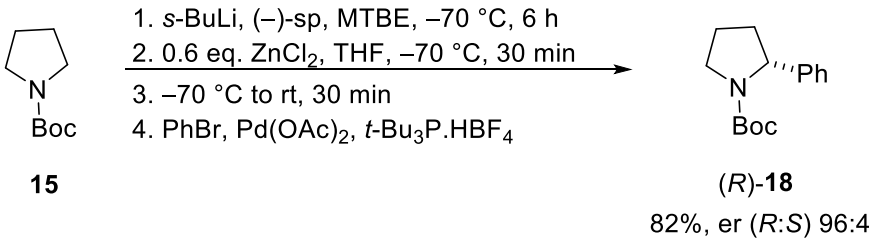
In 1991, Beak and Kerrick applied Hoppe's methods and reported the asymmetric deprotonation of *N*-Boc-pyrrolidine **15** (Scheme 6).[22] The *s*-BuLi/(–)-sp complex deprotonated one of the α-protons to give the chiral organolithium intermediate (*S*)-**16** which was quenched with variety of electrophiles to give the products **17** in good yields and excellent ers.



Scheme 6

In 2006, Campos and co-workers reported an enantioselective Negishi cross-coupling of pyrrolidine **15** (Scheme 7).[23] A substoichiometric amount of zinc(II) chloride ($ZnCl_2$) was added to enantioenriched organolithium which was then quenched with $Pd(OAc)_2$,

t-$Bu_3P.HBF_4$ and bromobenzene to give product (*R*)-**18** in excellent yield of 82% and er (*R*:*S*) of 96:4.

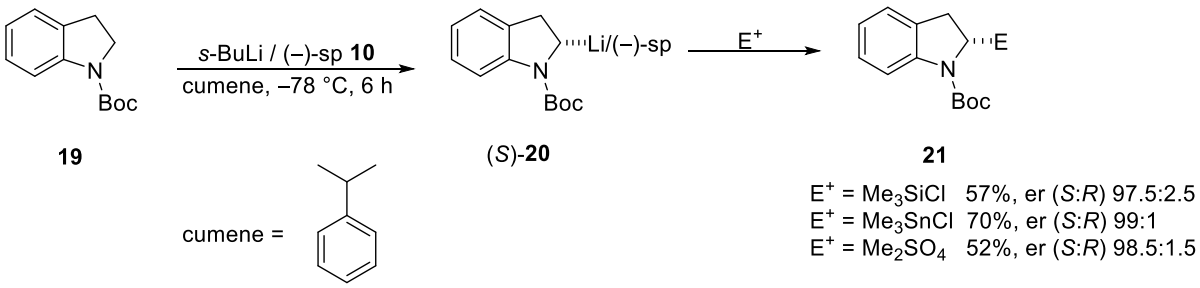


15 (*R*)-**18**

82%, er (*R*:*S*) 96:4

Scheme 7

In 1997, Beak and co-workers expanded this methodology to *N*-Boc-indoline **19** (Scheme 8).[24] Enantioenriched 2-substituted indoline products **21** were successfully obtained when the reaction was performed using *s*-BuLi and (–)-sp **10** in cumene as solvent.



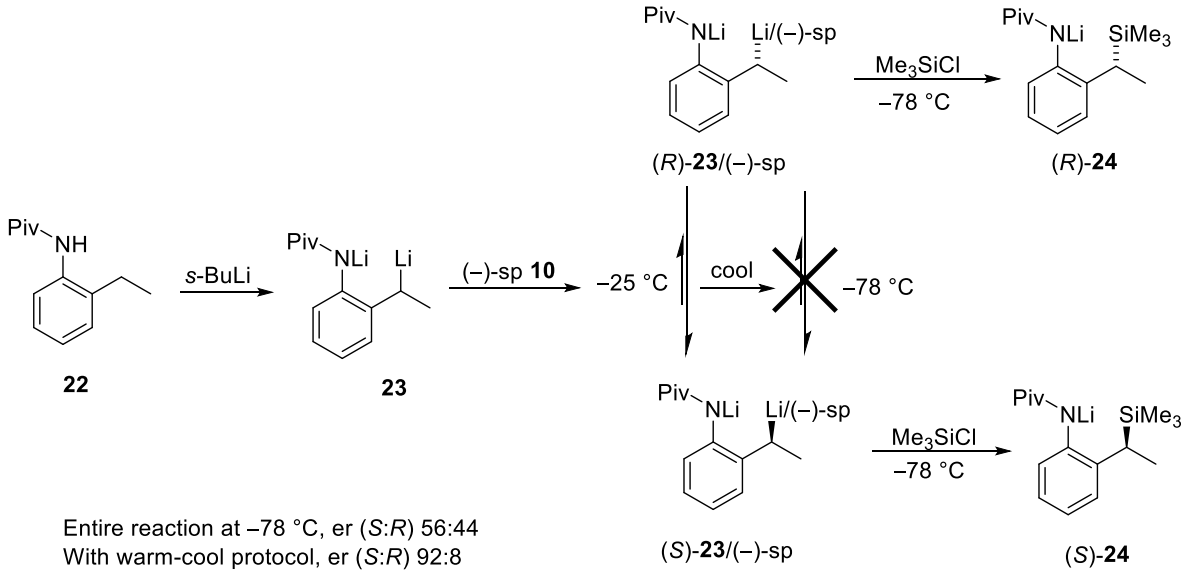
19 (*S*)-**20** **21**

$E^+ = Me_3SiCl$ 57%, er (*S*:*R*) 97.5:2.5
$E^+ = Me_3SnCl$ 70%, er (*S*:*R*) 99:1
$E^+ = Me_2SO_4$ 52%, er (*S*:*R*) 98.5:1.5

Scheme 8

Unlike asymmetric deprotonation, in asymmetric substitution, the enantiodetermining step is the selective reaction of one diastereomeric lithiated complex towards the electrophiles (as shown in Scheme 4). Dynamic thermodynamic resolution (DTR) is when asymmetric induction after quenching with an electrophile happens from a thermodynamic preference of one diastereomeric complex.[25] The rate of addition of

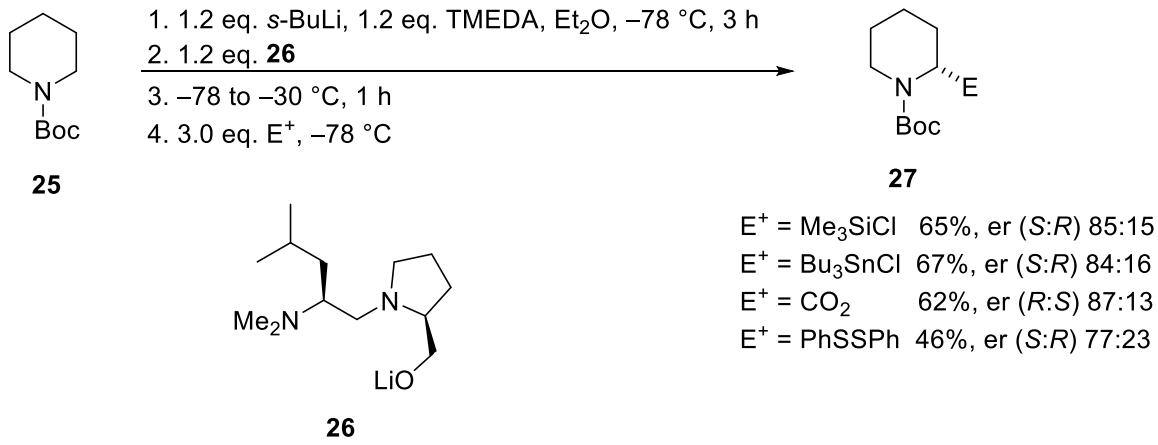
organolithium to the electrophile is faster than interconversion of the diastereomeric complexes. In 1996, Beak and Basu reported an example of DTR of amide **22** by employing a warm-cool protocol (Scheme 9).[26] Using *s*-BuLi, amide **22** was deprotonated and (–)-sp **10** was added to intermediate **23** to form the diastereomeric complexes. When organolithium intermediate **23** complexed with (–)-sp **10** at –78 °C, the product **24** was obtained with a poor er. However, when the reaction was stirred at –25 °C for 45 min and then cooled to –78 °C, (*S*)-**24** was obtained with excellent er. Leaving the mixture to stir at –25 °C allowed the complexes to equilibrate before quenching with the electrophile.



Scheme 9

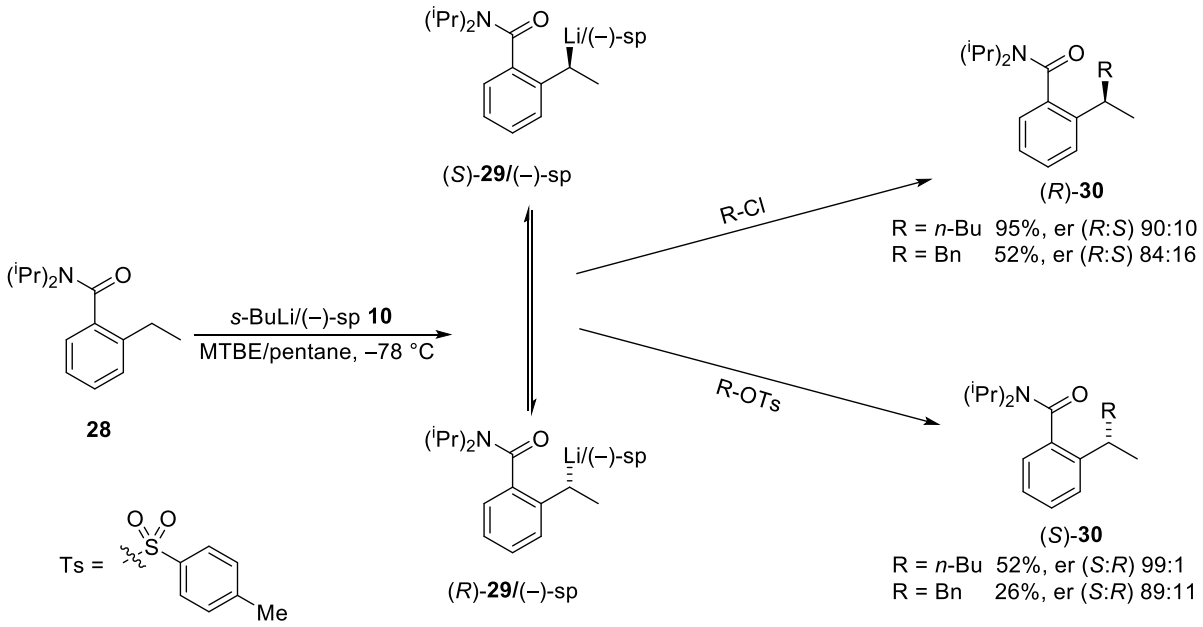
In 2010, Coldham and co-workers reported DTR of *N*-Boc-piperidine **25** with *s*-BuLi and TMEDA in the presence of the chiral ligand **26** (Scheme 10).[27] To a mixture of piperidine **25** and 1.2 eq. of TMEDA in Et_2O, 1.2 eq. of *s*-BuLi was added at –78 °C. After 3 h, 1.2 eq. of chiral ligand **26** was added and the mixture was warmed to –30 °C

and stirred for 1 h. Then the mixture was cooled to –78 °C and quenched with various electrophiles to give enantioenriched 2-substituted piperidines **27**.



Scheme 10

Dynamic Kinetic Resolution (DKR) is when the rate of interconversion of the two diastereomeric complexes is faster than the electrophilic quench and one diastereomer reacts with electrophile faster than the other .[8] In 1994, Beak and co-workers reported an example of a DKR (Scheme 11).[28] The amide **28** was lithiated using *s*-BuLi/(–)-sp at –78 °C to form intermediate complexes **29** which was then quenched with alkyl halides (RCl) to form the products (*R*)-**30** in good yields and enantiomer ratios. When alkyl tosylates (ROTs) were used, products (*S*)-**30** with the opposite configurations were obtained. It was hypothesised that (*S*)-**30**/(–)-sp is more reactive than (*R*)-**30**/(–)-sp **10** and reacts with retention with RCl but inversion with ROTs.



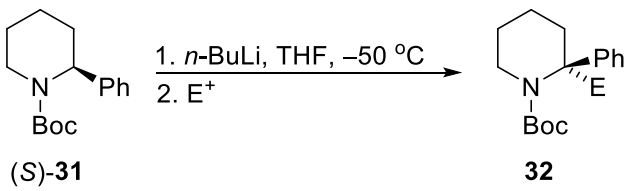
Scheme 11

In addition to the use of prochiral substrates (as shown in Scheme 4), asymmetric reaction can be achieved starting from chiral (racemic) substrates. This is possible by a kinetic resolution process.

1.3 Previous work in the group

Over the past decades, significant efforts have been made to develop the synthesis of novel nitrogen-containing heterocycles. Nitrogen heterocycles are one of the most fundamental compounds in organic and medicinal chemistry. The structures of nitrogen heterocycles are well represented among natural products, biologically active structures and medicinally relevant compounds.[29] Nearly 60% of small molecule drugs contain a nitrogen heterocycle with active roles as anti-bacterial, anti-viral, anti-fungal, anti-inflammatory and anti-tumour drugs, along with local anaesthetics.[30] The size of the ring structure and the substituent groups attached affect the physicochemical properties.[31] Moreover, different enantiomers of a molecule have different biological activity; one might be a useful drug while the other might be toxic. Hence, synthesis of chiral drugs has become an important subject to research by chemists.

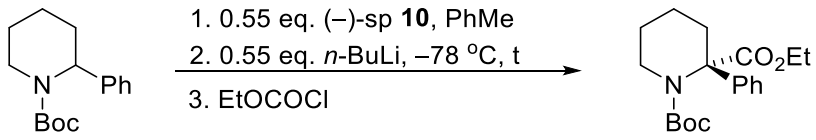
The Coldham group have been focusing on the synthesis of enantioenriched substituted nitrogen-containing compounds by kinetic resolution using an organolithium-chiral amine system. Previously, Coldham and O'Brien and co-workers reported that enantiomerically enriched 2,2-disubstituted piperidines **32** were successfully synthesised from enantiomerically enriched *N*-Boc-2-phenylpiperidine **31** (Scheme 12).[32] The success in the synthesis of enantiomerically enriched compound **32** led to a study of the kinetic resolution of *N*-Boc-2-arylpiperidines performed under different conditions and with different aryl groups by asymmetric deprotonation.[33]



(*S*)-**31** **32**

Scheme 12

Different conditions were studied to give compound **33** with good enantiomer ratios. Initially, the study showed that instead of pre-mixing the *n*-BuLi and the (–)-sp **10** in toluene (PhMe), adding the *n*-BuLi to a solution of piperidine **31** and (–)-sp **10** in PhMe gave better enantiomer ratios.[33] The reaction time was also studied to optimise the yields and enantiomer ratios of **33** (Scheme 13, Table 1). The optimum reaction time was determined to be 3 h which gave the product with an er 92:8 and a yield of 42% (Entry 5). With these optimum conditions, the kinetic resolution was studied with various electrophiles. However, lower yields and enantiomer ratios occurred due to the partial racemisation of the lithiated intermediate before the electrophilic quench. Therefore, instead of focusing on the products, the yield and er of the RSM was studied.[33]



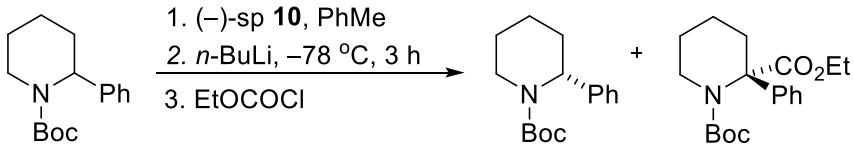
31 **33**

Scheme 13

Table 1

Entry	t/ min	33 yield %	33 er
1	10	16	95:5
2	30	27	95:5
3	60	33	93:7
4	120	36	93:7
5	180	42	92:8

By altering the equivalents of *n*-BuLi and (–)-sp **10**, the yields and enantiomer ratios of compounds **31** and **33** were studied (Scheme 14, Table 2). The best result with excellent yield (40-50% for a KR) and enantiomer ratio of the compound (*R*)-**31**, the RSM, was obtained when 0.77 eq. of *n*-BuLi and (–)-sp **10** were used (Entry 2).



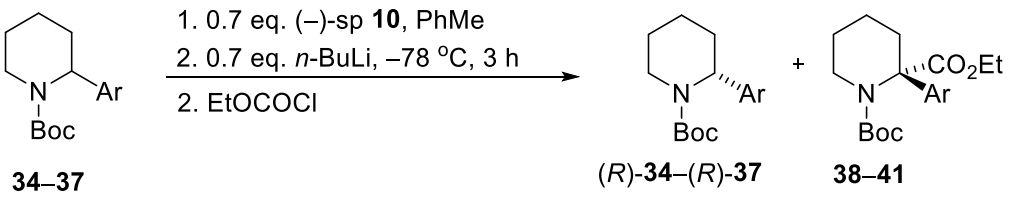
31 (*R*)-**31** **33**

Scheme 14

Table 2

Entry	eq. *n*-BuLi and (–)-sp	(*R*)-31 yield %	(*R*)-31 er	33 yield %	33 er
1	0.55	50	77:23	42	92:8
2	0.77	45	96:4	51	86:14
3	0.80	31	92:8	56	77:23
4	1.00	13	98:2	74	57:43

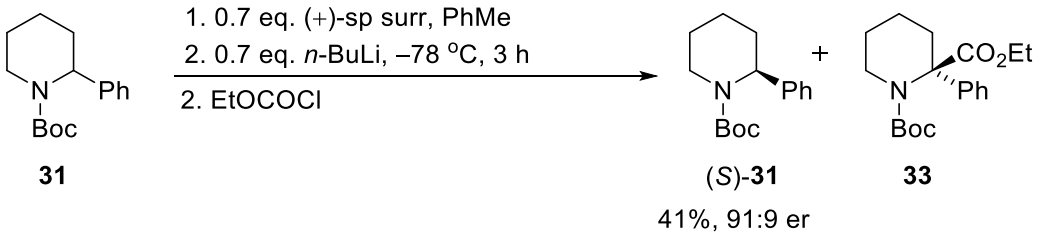
The kinetic resolution of *N*-Boc-2-arylpiperidines **34**–**37** was then studied by varying the aryl group (Scheme 15, Table 3). Most of the products gave high enantiomer ratios between 90:10 to 97:3 and yields of more than 40% of the RSM. When (–)-sp **10** was used, as expected based on asymmetric lithiation of *N*-Boc-piperidine,[34] the (*R*)-enantiomer of *N*-Boc-2-phenylpiperidine was obtained as the RSM. On the other hand, the (*S*)-enantiomer could be formed by changing the chiral ligand to O'Brien's (+)-sparteine surrogate ((+)-sp surr) instead of (–)-sp **10** (Scheme 16).[35]



Scheme 15

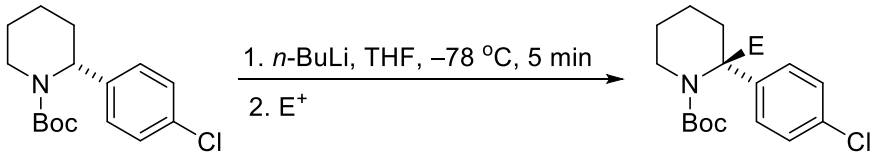
Table 3

Entry	Ar	RSM yield %	RSM er
1	4-Chlorophenyl **34**	41	96:4
2	4-Fluorophenyl **35**	48	94:6
3	Naphthalen-2-yl **36**	40	97:3
4	4-Methoxyphenyl **37**	49	90:10



Scheme 16

In addition, a THF mediated lithiation followed by substitution was performed on the enantiopure RSM. The (*R*)-enantiomer of *N*-Boc-2-(4-chlorophenyl)-piperidine (*R*)-**34** was deprotonated with *n*-BuLi in THF at –78 °C and followed by quenching with various electrophiles (methyl iodide, ethyl chloroformate or allyl bromide). The reactions gave products **42**–**44** with the same er 96:4 as the starting material and in good yields (Scheme 17, Table 4). Hence, highly enantiomerically enriched 2,2-disubstituted piperidine products were successfully formed without losing the enantiomeric ratio.



(*R*)-**34**
96:4 er

42–**44**

Scheme 17

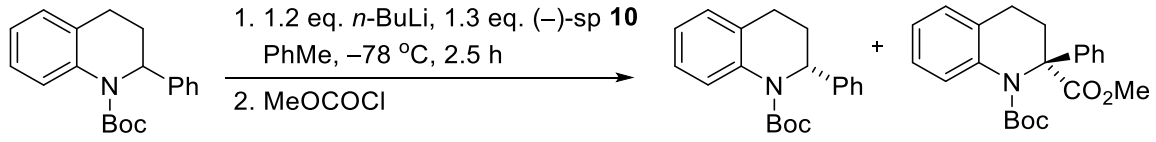
Table 4

Entry	E^+	Product	Product yield %	Product er
1	MeI	**42**	88	96:4
2	EtOCOCl	**43**	72	96:4
3	$BrCH_2CH{=}CH_2$	**44**	57	96:4

Recently, Coldham and co-workers studied the kinetic resolution of *N*-Boc-2-aryltetrahydroquinolines.[36] The kinetic resolution of *N*-Boc-2-aryltetrahydroquinolines followed by quenching with electrophiles was an efficient method to synthesise highly enantioenriched 2,2-disubstituted tetrahydroquinolines.

The kinetic resolution of compound **45** was studied using the chiral ligand (–)-sp **10** in PhMe followed by the addition of *n*-BuLi (Scheme 18). However, unlike the kinetic resolution of the corresponding *N*-Boc-2-arylpiperidine, pre-mixing the *n*-BuLi and (–)-sp **10** before adding compound **45** gave better results. Upon pre-mixing, the enantiomer ratio of compound (*R*)-**45** improved from 81:19 to 97:3. Also, as the deprotonation was slow under these conditions, 1.2 eq. of *n*-BuLi was used to attain a suitable rate. Kinetic resolution using (+)-sp **11** was also used in the study to obtain the other enantiomer of the RSM **45** (Scheme 19). The (*S*)-enantiomer of compound

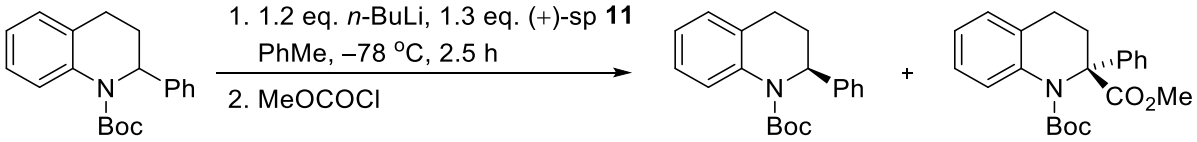
45 was obtained in er 92:8 with a yield of 45%, or er 98:2 with a yield of 43% on a second run.



45 (*R*)-**45** **46**

43%, 97:3 er 56%, 81:19 er

Scheme 18

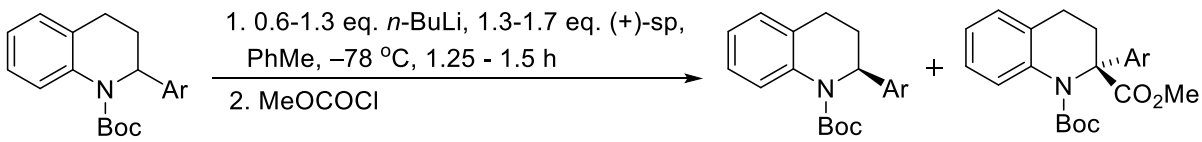


45 (*S*)-**45** **46**

Run 1 45 %, 92:8 er 42 %, 93:7 er
Run 2 43 %, 98:2 er 54 %, 82:18 er

Scheme 19

The kinetic resolutions of *N*-Boc-2-aryltetrahydroquinolines **47**–**48**, with various aromatic substituents attached were then studied using (+)-sp **11** (Scheme 20, Table 5). The (*S*)-enantiomer of compound **47** was obtained in reasonable yield and high enantiomer ratio (Entry 1). Likewise, good results were obtained with compound **48** (Entry 2).



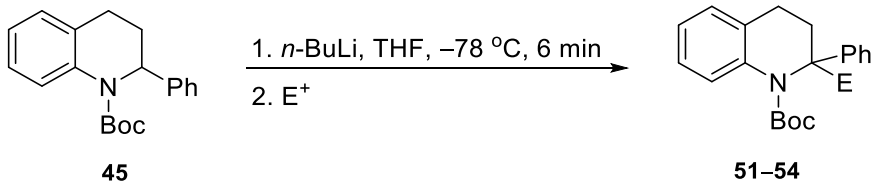
47–**48** (*S*)-**47**–(*S*)-**48** **49**–**50**

Scheme 20

Table 5

Entry	Ar	RSM yield %	RSM er	Product yield %	Product er
1	2-Fluorophenyl **47**	36	94:6	42	85:15
2	Naphthalen-2-yl **48**	39	96:4	12	78:22

Finally, the enantiomerically enriched tetrahydroquinoline **45** was lithiated and quenched with a variety of electrophiles towards the synthesis of enantioenriched 2,2-disubstituted tetrahydroquinolines **51**–**54**. The enantiopure recovered tetrahydroquinoline **45** was treated with *n*-BuLi in THF at –78 °C and quenched with various electrophiles (Scheme 21, Table 6). When compound (*R*)-**45** was treated with electrophiles like EtOCOCl and MeI, enantiomer ratios of 97:3 and 94:6 were obtained respectively with good yields (Entries 1,2). Compound (*S*)-**45** also gave products with good yields and enantiomer ratios (Entries 3,4).



45 **51–54**

Scheme 21

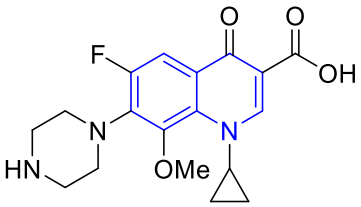
Table 6

Entry	Compound	E^+	Product	Product yield %	Product er
1	(*R*)-**45**	EtOCOCl	**51**	78	97:3
2	er 97:3	MeI	**52**	91	94:6
3	(S)-**45**	$BrCH_2CO_2Me$	**53**	71	92:8
4	er 92:8	MeI	**54**	69	87:13

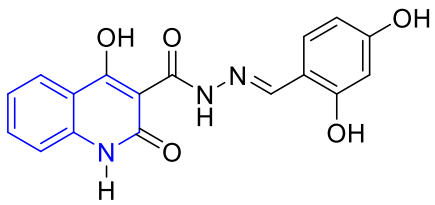
Chapter 2 – Synthesis and Kinetic Resolution of Substituted Dihydroquinolines

2.1 Introduction to dihydroquinoline chemistry

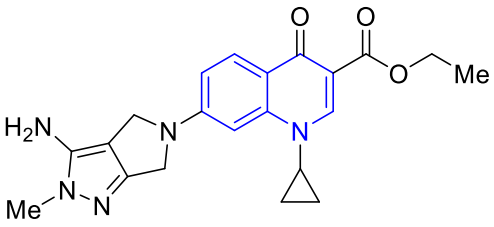
Quinolines are a well-known entity in the alkaloid class of natural products and are present in plants, pharmaceuticals, agrochemicals and dyes.[37] Organic compounds containing quinoline scaffolds have been studied extensively because of their significant application as biologically active molecules, exhibiting anti-tubercular, anti-bacterial, anti-oxidant, anti-proliferative and anti-plasmodial properties (Figure 3).[30,38] Furthermore, it has been identified that carbamate DQS1-02 is a prodrug of a potent acetylcholinesterase (AChE) inhibitor for Alzheimer's disease therapy (Figure 4).[39] Natural products containing the dihydroquinoline (DHQ) skeleton are used in medicine or usually employed as lead molecules for the development of new and potent molecules. Hence, development of new and efficient synthetic routes for DHQs is important to both synthetic organic and medicinal chemistry.



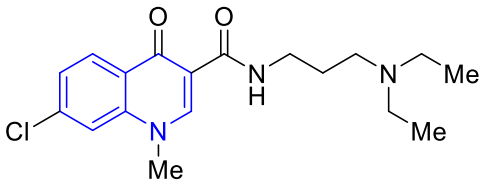
Anti-tubercular
56



Anti-oxidant
57

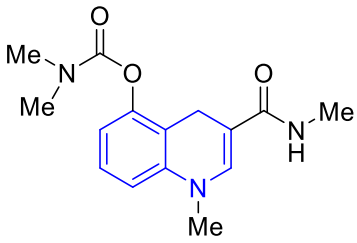


Anti-bacterial
58



Anti-proliferative
59

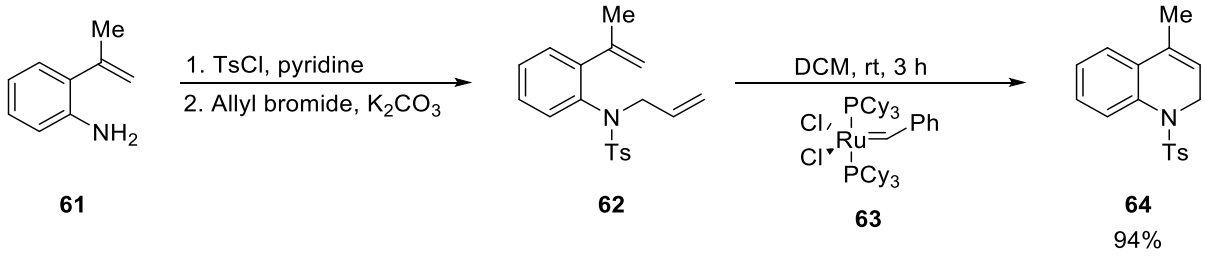
Figure 3 – Structures of biologically active molecules with quinoline scaffolds



DQS1-02
60

Figure 4 – Structure of carbamate DQS1-02

Various methods to synthesise 1,2-DHQ and 1,4-DHQ derivatives have been reported over the years. In 2001, Nakagawa and co-workers reported a synthesis of 4-substituted 1,2-DHQ by ring-closing olefin metathesis of dienes (Scheme 22).[40] From commercially available 2-isopropenylaniline **61**, the diene **62** was prepared. Diene **62** was then reacted in DCM at room temperature for 3 h using 30 mol% of Grubbs' catalyst **63** to give 1,2-DHQ **64** in 94% yield.

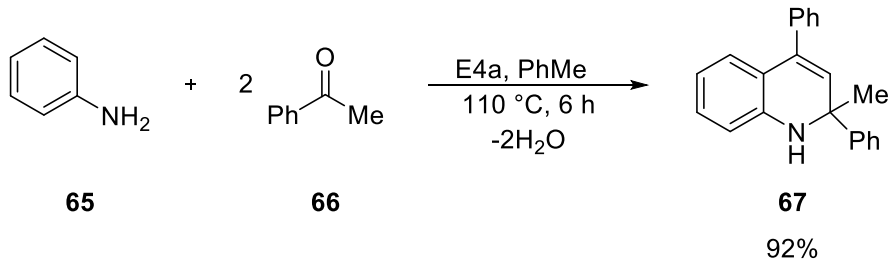


61 **62** **63** **64**
94%

Scheme 22

Hell and co-workers reported an environmentally friendly synthesis of trisubstituted 1,2-DHQ *via* simple cyclocondensation using zeolite absorbent (Scheme 23).[41] Ersorb-4 (E4a) was used and it is a weak acidic clinoptilolite-type zeolite absorbent. A mixture of aniline **65** and acetophenone **66** in PhMe was stirred with E4a at 110 °C for 6 h. This gave 2,4-diphenyl-2-methyl-1,2-DHQ **67** in excellent yield of 92%. In 2008, Harja and co-workers also reported a solvent free one pot synthesis of DHQ **69** using

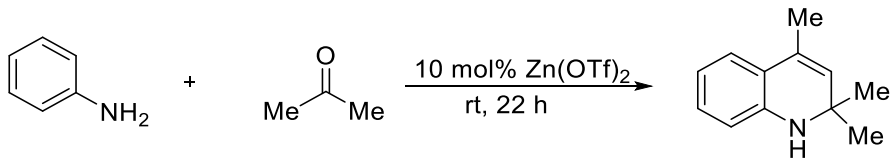
a zinc(II) catalyst (Scheme 24).[42] Condensation was performed between aniline **65** and acetone **68** using 10 mol% $Zn(OTf)_2$ for 22 h at room temperature and product **69** was obtained in a good yield of 78%.



65 **66** **67**

92%

Scheme 23

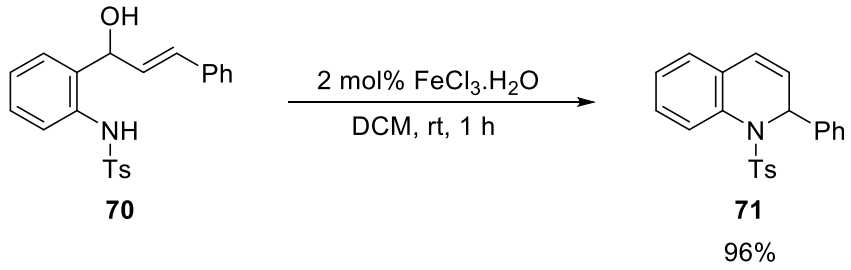


65 **68** **69**

78%

Scheme 24

In 2012, Wang and co-workers reported a synthesis of 2-substituted 1,2-DHQ by intramolecular allylic amination (Scheme 25).[43] Starting material alcohol **70** and catalyst, 2 mol% $FeCl_3.6H_2O$ in DCM, was stirred at room temperature for 1 h. The product, 2-phenyl-1,2-DHQ **71**, was successfully obtained in an excellent yield of 96%.

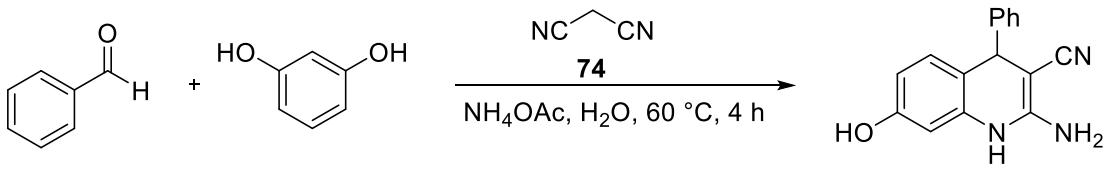


70 **71**

96%

Scheme 25

The 1,4-DHQ derivatives are as important as the 1,2-DHQ because they are scaffolds of medicinally significant compounds. In 2014, Jonnalagadda and co-workers reported synthesis of trisubstituted 1,4-DHQ under mild and catalyst free conditions (Scheme 26).[44] Benzaldehyde **72**, resorcinol **73**, malononitrile **74**, and ammonium acetate (NH_4OAc) in water were heated at 60 °C for 4 h gave 2,3,4-trisubstituted-1,4-DHQ **75** in an excellent yield of 80%.

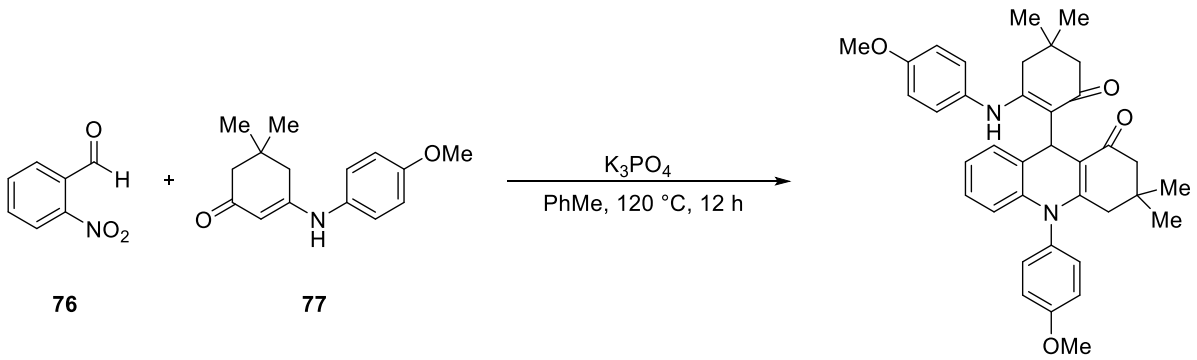


72 **73** **75**

80%

Scheme 26

Synthesis of 1,4-DHQ by transition metal-free cyclisation of enaminones and aldehydes was studied by Ji and co-workers (Scheme 27).[45] The reaction was performed between 2-nitrobenzaldehyde **76** and β-enaminone **77** in PhMe using tripotassium phosphate (K_3PO_4) as a base, stirred at 120 °C for 12 h. The one pot synthesis successfully gave substituted 1,4-DHQ product **78** in 79%.

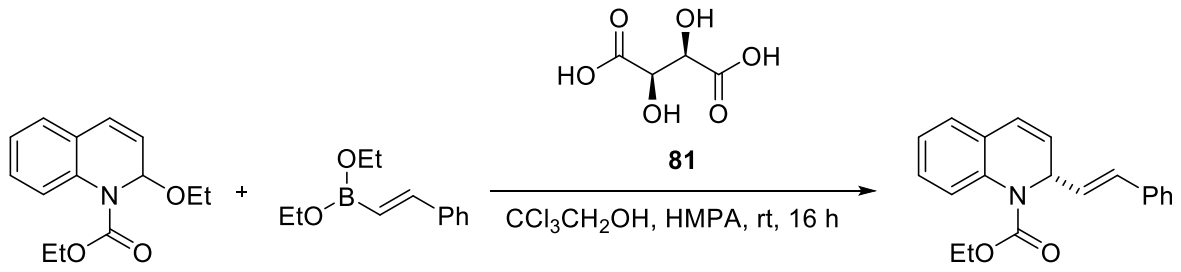


76 **77** **78**

79%

Scheme 27

Synthesis of chiral substituted DHQs has been studied. In 2011, Schaus and co-workers reported a synthesis of enantioenriched 2-substituted DHQ by a catalytic nucleophilic boronate addition reaction (Scheme 28).[46] Diethyl styrylboronate **80** was added to 2-ethoxy-1,2-DHQ **79** in hexamethylphosphoramide (HMPA) with 20 mol% (*R*,*R*)-tartaric acid **81** as a catalyst and 2,2,2-trichloroethanol (CCl_3CH_2OH) as an additive. The mixture was stirred at room temperature for 16 h and the desired chiral substituted DHQ (*R*)-**82** was obtained in 61% yield and 96:4 er.

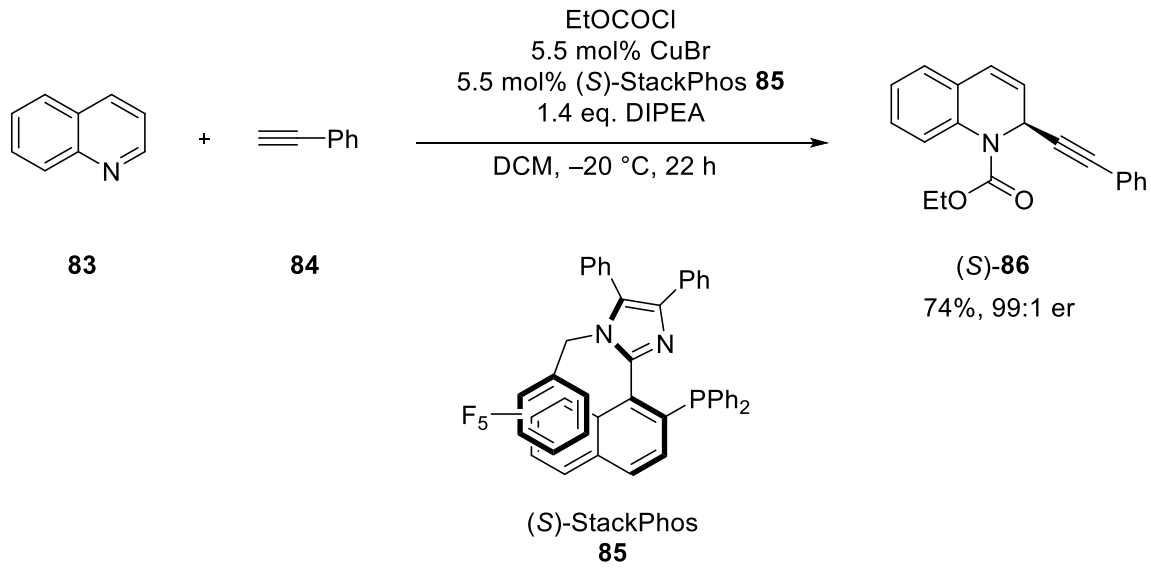


79 **80** **81** (*R*)-**82**

61%, 96:4 er

Scheme 28

In 2015, Aponick and co-workers reported a catalytic enantioselective synthesis for the dearomative alkynylation of quinolines (Scheme 29).[47] The ligand (5.5 mol% of (*S*)-StackPhos **85**), 5.5 mol% of copper(I) bromide (CuBr), 1.4 eq. of *N*,*N*-diisopropylamine (DIPEA) and ethyl chloroformate (EtOCOCl) were added to a mixture of quinoline **83** and phenyl acetylene **84** in DCM at –20 °C. Stirring the mixture for 22 h gave the desired product (*S*)-**86** in 74% yield and 99:1 er.

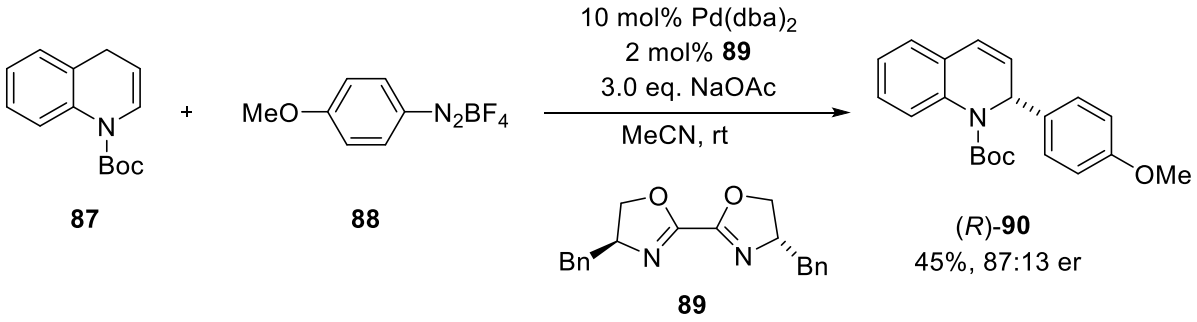


83 **84** (*S*)-**86** 74%, 99:1 er

(*S*)-StackPhos **85**

Scheme 29

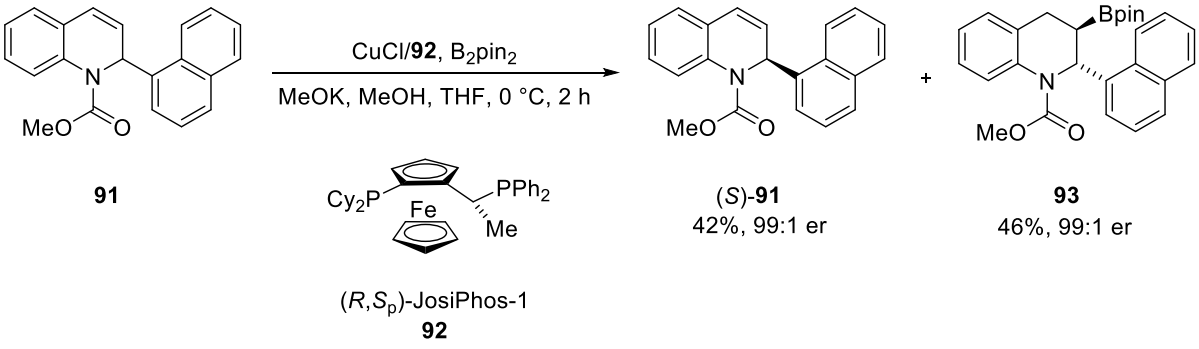
Ding and co-workers investigated the synthesis of chiral 2-aryl-1,2-DHQ by palladium-catalysed asymmetric Heck-Matsuda reaction (Scheme 30).[48] To 1,4-DHQ **87** and *p*-methoxybenzenediazonium tetrafluoroborate **88** in acetonitrile (MeCN), 10 mol% $Pd(dba)_2$ (as a palladium source) and 2 mol% benzyl substituted chiral ligand **89** were added at room temperature. The enantioenriched product, (*R*)-*N*-Boc-2-(4-methoxyphenyl)-1,2-DHQ (*R*)-**90** was obtained in 45% yield and 87:13 er.



87 **88** **89** (*R*)-**90** 45%, 87:13 er

Scheme 30

Transition metal catalysts have also been applied to kinetic resolution to synthesise chiral DHQ. In 2017, Hou and co-workers reported kinetic resolution of 2-substituted 1,2-DHQ *via* copper-catalysed borylation (Scheme 31).[49] The complex was formed from copper(I) chloride (CuCl) and (R,S_p)-JosiPhos-1 **92** in the presence of potassium methoxide (MeOK) and methanol (MeOH) as additives. This was then added to the 2-(naphthalene-1-yl)-1,2-DHQ **91** with bis(pinacolato)diborane (B_2pin_2) in THF at 0 °C for 2 h. The recovered starting material (*S*)-**91** and the THQ product **93** were both formed in 99:1 er with an excellent selectivity factor of 251.

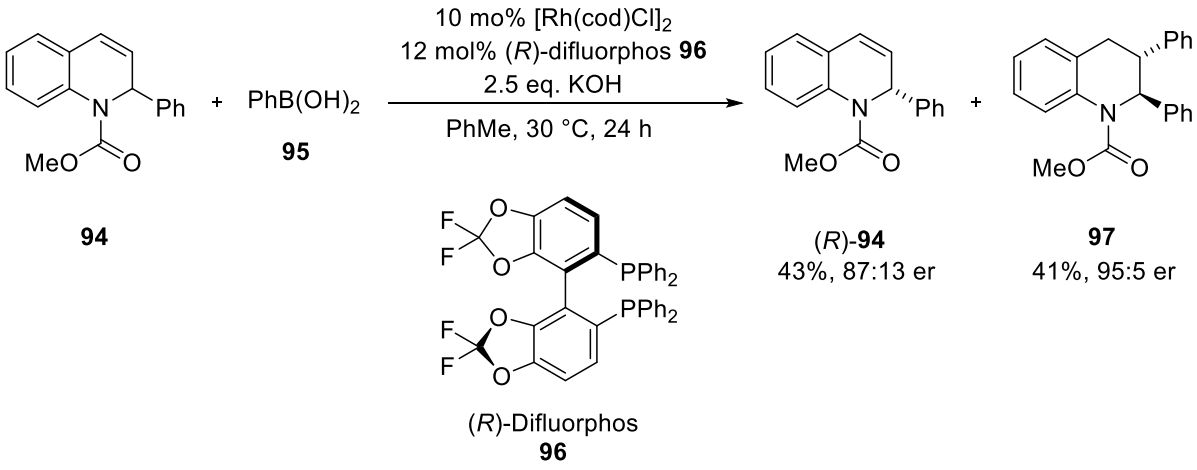


91 (*S*)-**91** 42%, 99:1 er **93** 46%, 99:1 er

(R,S_p)-JosiPhos-1 **92**

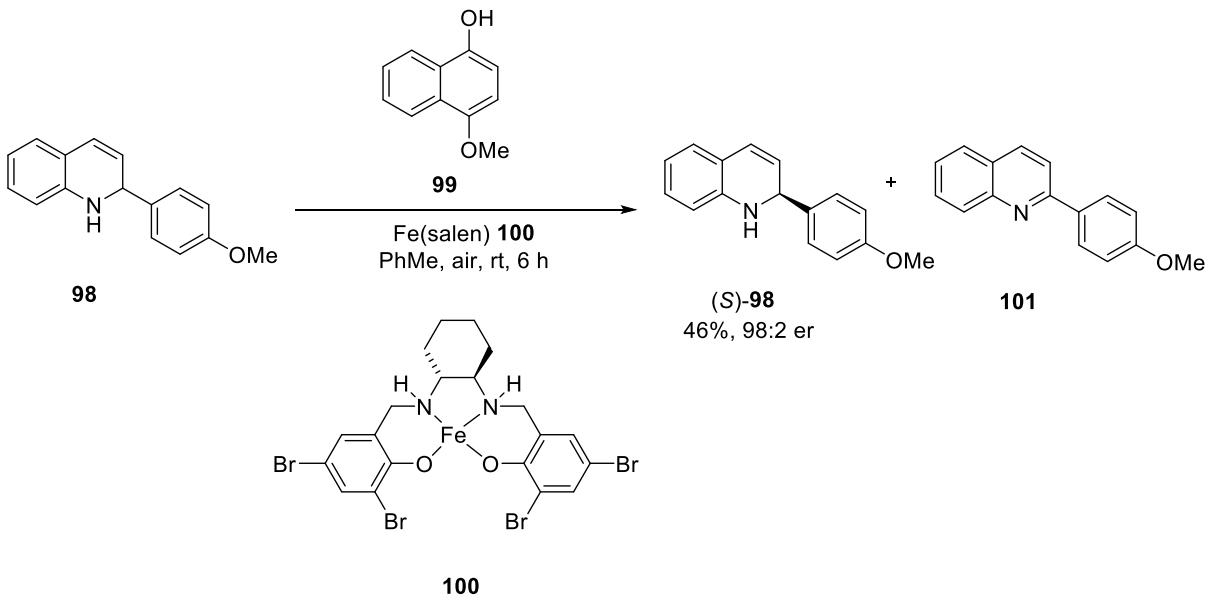
Scheme 31

More recently, Wang and co-workers reported similar work, but *via* rhodium catalysed kinetic resolution (Scheme 32).[50] The catalyst and base were added to a mixture of 2-phenyl-1,2-DHQ **94** and phenylboronic acid **95** in PhMe at 30 °C and the mixture was stirred for 24 h. In the reaction, 10 mol% $[Rh(cod)Cl]_2$ and 12 mol% (*R*)-difluorphos **96** were used as catalysts and 2.5 eq. of potassium hydroxide (KOH) as a base. The recovered starting material (*R*)-**94** and 2,3-disubstituted THQ product **97** were obtained in 43% yield with 87:13 er and 41% yield with 95:5 er respectively.



Scheme 32

Liu and co-workers reported an iron-catalysed dehydrogenative kinetic resolution using air as an oxidant (Scheme 33).[51] To the 1,2-DHQ **98** in PhMe, 4-methoxy-1-naphthol **99** and Fe(salen) **100** were added, as an additive and catalyst respectively. The mixture was stirred at room temperature for 6 h and an excellent result was obtained, giving (*S*)-**98** in 46% yield and 98:2 er.



Scheme 33

The 1,2-DHQ and 1,4-DHQ is a key intermediate for the synthesis of natural products and in the design of biologically active compounds. However, the preparation of chiral DHQs has not been extensively studied. The aim of this project was to synthesise chiral aryl and alkyl group substituted 1,2-DHQ and 1,4-DHQ using kinetic resolution by lithiation. This could allow synthesis of a natural product, (–)-angustureine **102**, and anti-malarial drug M5717 **103** in efficient, short routes (Figure 5).

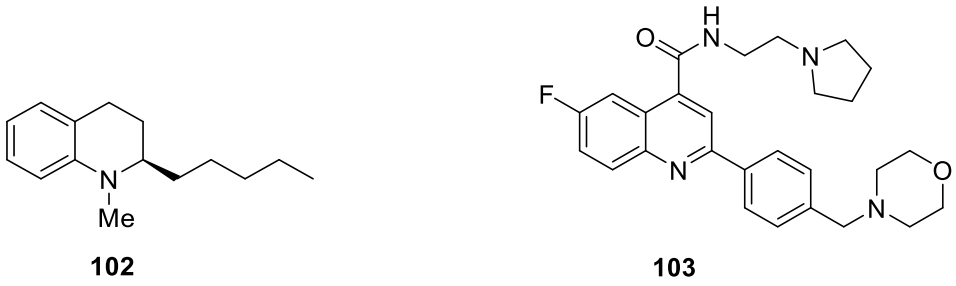
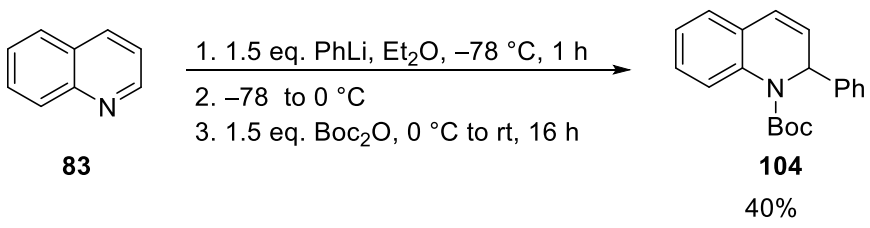


Figure 5 – Structures of (–)-angustureine and drug M5717

2.2 Previous work

The Coldham group have been working on the synthesis of enantiopure nitrogen heterocycles, such as substituted piperidine, tetrahydroisoquinoline and tetrahydroquinoline.[32,36,52] Recently, a study of the lithiation quench reaction and kinetic resolution of substituted DHQ was carried out using chiral organolithium chemistry. [53-55]

The aim of the postgraduate taught research project was to obtain the absolute configuration after lithiation quench of enantioenriched *N*-Boc-2-phenyl-1,2-DHQ **104** prepared by kinetic resolution.[55] The starting material was not available commercially and was synthesised readily in one pot from quinoline **83**. To quinoline **83** in Et_2O, phenyllithium (PhLi) and di-*tert*-butyldicarbonate (Boc_2O) were added and the mixture was left to warm to room temperature for 16 h (Scheme 34).[56]

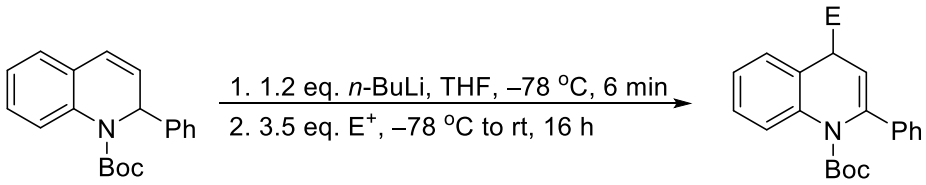


83 **104** 40%

Scheme 34

A study of lithiation of DHQ **104** was carried out using *in-situ* IR spectroscopy. It was found that within 6 min, the starting material was being fully deprotonated by the *n*-BuLi forming a stable lithiated species. Using these data, lithiation at –78 °C in THF with *n*-BuLi for 6 min was carried out (Scheme 35). The addition of a variety of

electrophiles gave the products **105** in good to excellent yields except for tributyltin chloride (Bu_3SnCl) (Table 7).[53]



104 **105**

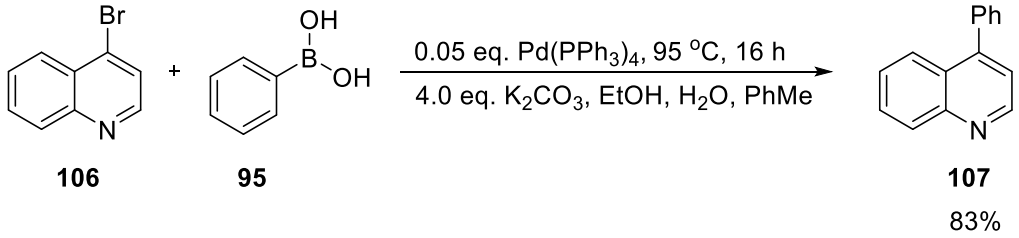
Scheme 35

Table 7

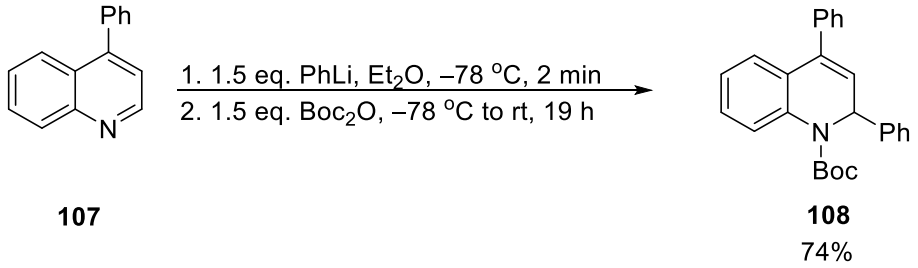
E^+	E	105 yield %
MeI	Me	92
$Br(CH_2)_4Br$	$Br(CH_2)_4$	79
$H_2C=CHCH_2Br$	$H_2C=CHCH_2$	51
$Me_2C=CHCH_2Br$	$Me_2C=CHCH_2$	61
MeCOMe	$Me_2C(OH)$	75
Bu_3SnCl	Bu_3Sn	0

Unlike the THQ compound **45**, the electrophiles were substituted at the 4-position rather than at the 2-position. The phenyl group at C-2 is sterically bulky and may hinder the electrophilic substitution from occurring at the 2-position. The presence of the double bond results in the formation of an allylic anion during lithiation, allowing conjugation into the phenyl ring and thereby stabilising the anion. Overall, the 4-position is more sterically and/or electronically favoured. To confirm what affected the electrophilic substitution to occur at the 4-position, *N*-Boc-2,4-diphenyl-1,2-DHQ **108** was synthesised and lithiation-quench reactions were performed.[55] Unlike *N*-Boc-2-phenyl-1,2-DHQ **104**, *N*-Boc-2,4-diphenyl-1,2-DHQ **108** could not be synthesised in one pot. First, 4-phenyl-quinoline **107** was synthesised from 4-bromoquinoline **106** by

a Suzuki-Miyaura coupling and PhLi and Boc_2O were then added to synthesise the desired compound **108** (Scheme 36 and 37).[55,57]

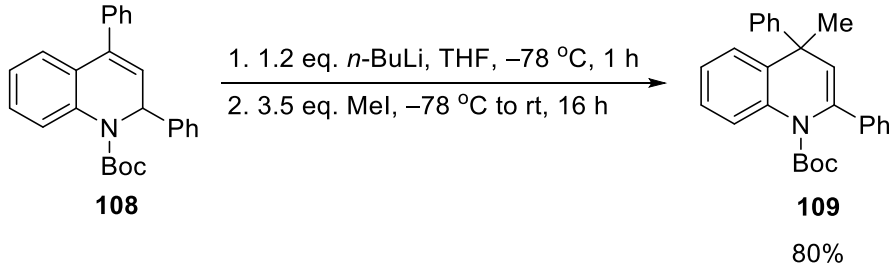


Scheme 36

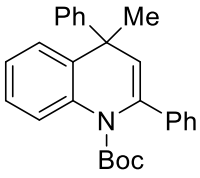


Scheme 37

The lithiation-quench reaction was then performed with methyl iodide as the electrophile (Scheme 38). However, despite the presence of an additional phenyl ring, the substitution still occurred in the 4-position as shown by single crystal X-ray analysis (Figure 6). Therefore, this indicated that substitution was mainly controlled by electronics rather than by sterics.



Scheme 38



109

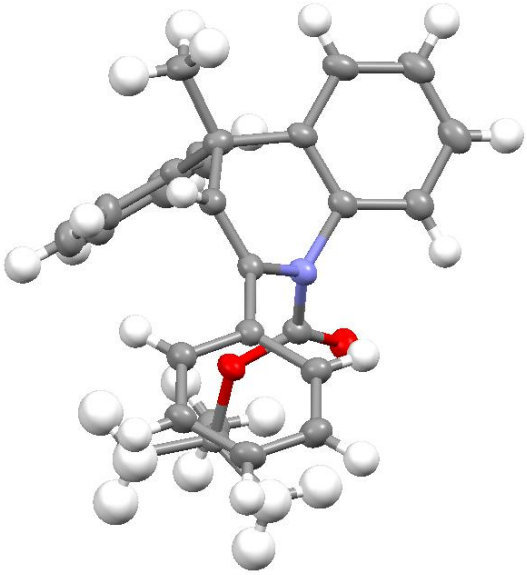
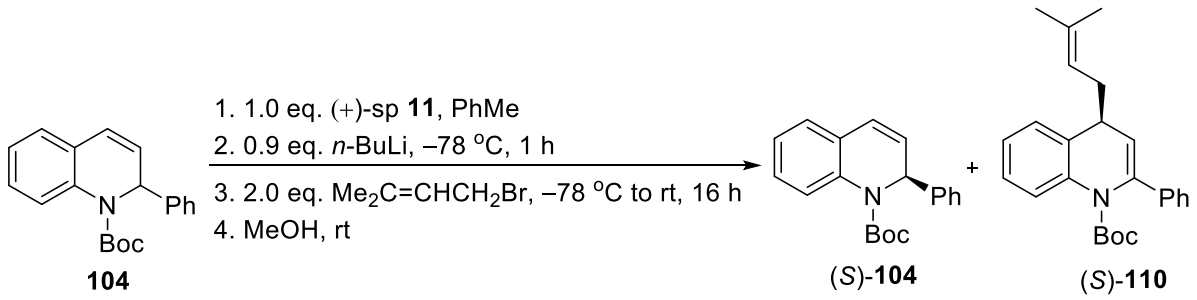


Figure 6 – Structure of 109 obtained by single crystal X-ray analysis

The kinetic resolutions of *N*-Boc-2-phenyl-1,2-DHQ **104** were carried out by using (+)-sp **11** and prenyl bromide as the chiral ligand and electrophile respectively (Scheme 39, Table 8).[55] Although poor yields were obtained for the recovered starting material (*S*)-**104**, high ers were obtained. There was a substantial mixture of the product (*S*)-**110** and the RSM (*S*)-**104** that co-eluted from the column, because of a small difference between the R_f values. Hence, in order to obtain better yields of the RSM (*S*)-**104**, a different electrophile was used instead of prenyl bromide.

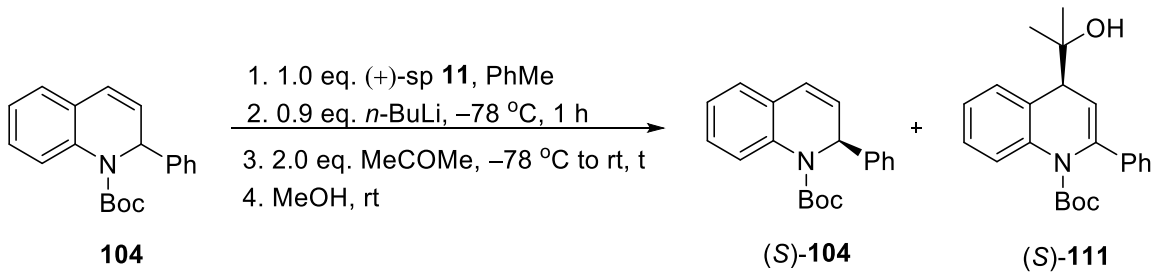


Scheme 39

Table 8

Entry	(*S*)-104 yield %	(*S*)-104 er	(*S*)-110 yield %	(*S*)-110 er	s
1	15	96:4	74	64:36	4
2	22	99:1	67	79:21	7

Among the many electrophiles that had been tested previously, acetone was the most suitable candidate to replace prenyl bromide. Using the optimum reaction conditions found previously, kinetic resolution with acetone was performed (Scheme 40, Table 9). However, a poor er was obtained for the RSM (*S*)-**104**, despite the yield being appropriate for a kinetic resolution (41%) (Entry 1). It was likely that the RSM (*S*)-**104** racemised when the mixture was left to warm to room temperature for a long time. Hence, instead of warming the reaction mixture to room temperature over 16 h, the mixture was warmed for 1 h after adding the acetone, which resulted in an excellent er and yield of RSM (*S*)-**104** (Entry 2).



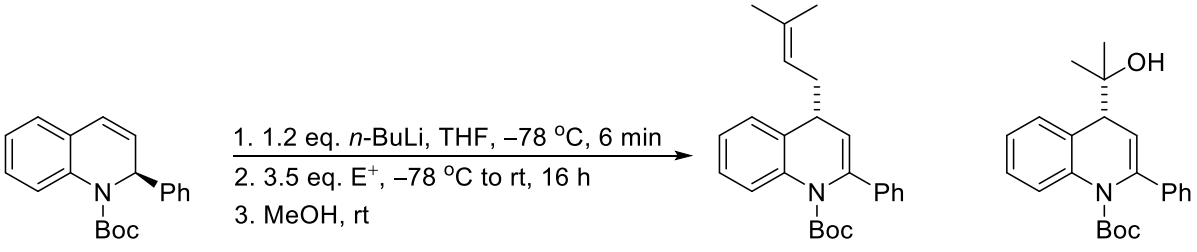
104 (*S*)-**104** (*S*)-**111**

Scheme 40

Table 9

Entry	t/ h	(*S*)-104 yield %	(*S*)-104 er	(*S*)-111 yield %	(*S*)-111 er	s
1	16	41	51:49	38	63:37	1
2	1	45	98:2	52	67:33	32

The lithiation-quench reaction on the enantioenriched starting material (*S*)-**104** was studied using both acetone and prenyl bromide as the electrophiles. The products (*R*)-**110** and (*R*)-**111** were isolated in reasonable yields while retaining the enantioenrichment (Scheme 41, Table 10). The er of (*R*)-**110** could be higher if the reaction was not left for 16 h, but this was not carried out. The absolute configuration of product (*R*)-**111** was confirmed by single crystal X-ray analysis and showed that the lithiation-electrophilic quench reaction occurred with retention of configuration (Figure 7).

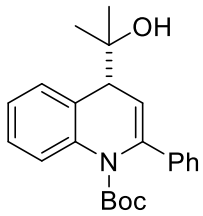


(*S*)-**104** (*R*)-**110** (*R*)-**111**

Scheme 41

Table 10

E^+	(*S*)-104 er	Product yield %	Product er	After crystallisation, product er
Acetone	95:5	54	94:6	99:1
Prenyl bromide	99:1	63	89:11	98:2



(*R*)-**111**

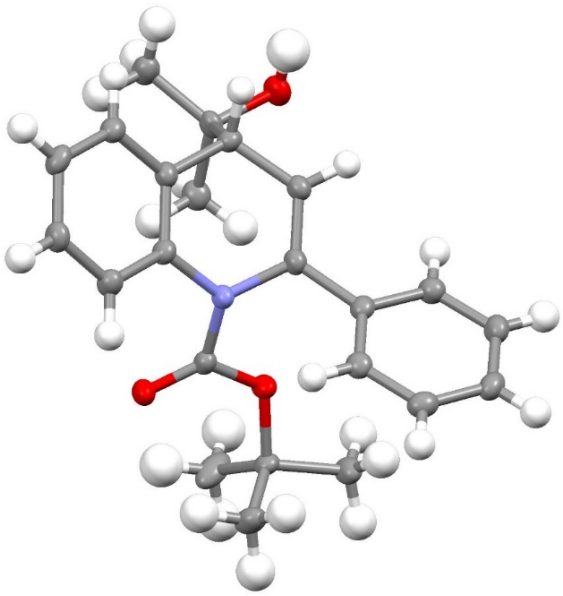
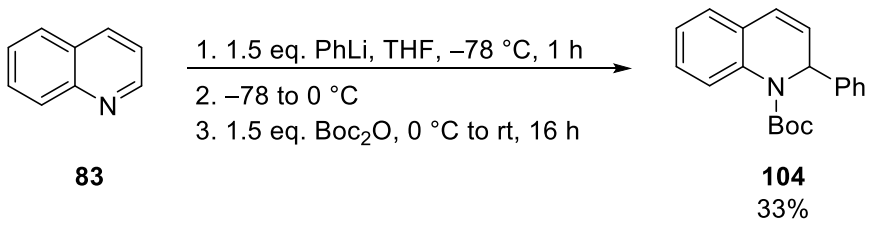


Figure 7 – The absolute configuration of (*R*)-111 obtained by single crystal X-ray analysis

2.3 Optimisation and further work on *N*-Boc-2-phenyldihydroquinoline

Continuing with successful previous work, the aim of this project was to optimise the chemistry of *N*-Boc-2-phenyl-1,2-DHQ **104** with better results and to obtain the absolute configuration after lithiation-quench of enantiopure starting material prepared with alkyl or allyl electrophiles. To expand the substrate further, lithiation-quench reactions were performed on racemic 2-substituted DHQ derivatives. If this was successful, kinetic resolution would then be undertaken in order to produce highly enantioenriched starting material and products. Lastly, the anti-malarial drug M5717 **103** would be synthesised using our methodology.

The *N*-Boc-2-phenyl-1,2-DHQ **104** was successfully synthesised in one pot, however the yield was poor at just 40% (Scheme 34). Instead of using Et_2O, quinoline **83** was dissolved in THF and PhLi was added at –78 °C followed by Boc_2O and the mixture was warmed to room temperature overnight (Scheme 42). Unfortunately, the product **104** was isolated in 33% yield, which is poorer than when the reaction was performed in Et_2O (40%).

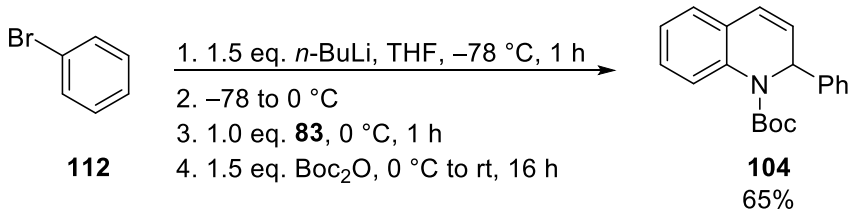


83 **104** 33%

Scheme 42

Considering the quality of the PhLi that had been bought, it was decided to make fresh PhLi by adding *n*-BuLi to 4-brombenzene **112** at –78 °C in THF to allow halogen-lithium exchange to take place (Scheme 43).[58] After stirring for 1 h, the dry ice bath

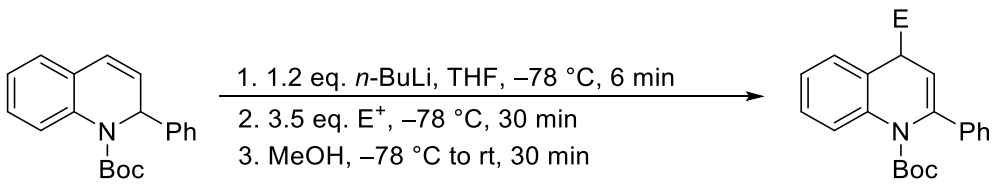
was changed to an ice bath and quinoline **83** was added into the same reaction pot, followed by the Boc_2O. The desired product **104** was successfully isolated in an improved yield of 65%.



112 **104** 65%

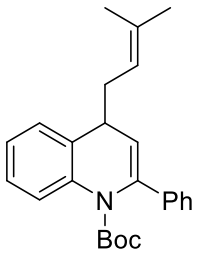
Scheme 43

The 2-phenyl-1,2-DHQ **104** was lithiated at –78 °C in THF using *n*-BuLi and after 6 min electrophiles were added (Scheme 44). The conditions for the lithiation-quench reaction were studied to improve yield of the product **105**. Previously, the mixture was left to warm to room temperature overnight after the addition of the electrophiles and quenched with MeOH at room temperature. So instead, MeOH was added at –78 °C, 30 min after the electrophiles were added, then the mixture was warmed to room temperature over 30 min (Figure 8). Overall, under these conditions, the yield of the product **105** was improved and was more efficient as the reaction was performed in a shorter period of time.

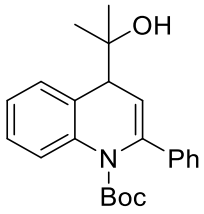


104 **105**

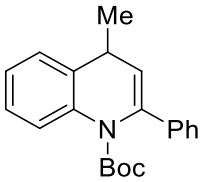
Scheme 44



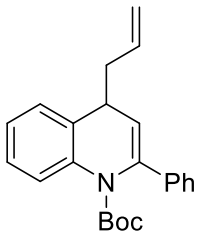
110
89%
$E^+ = Me_2C{=}CHCH_2Br$



111
92%
$E^+ = MeCOMe$



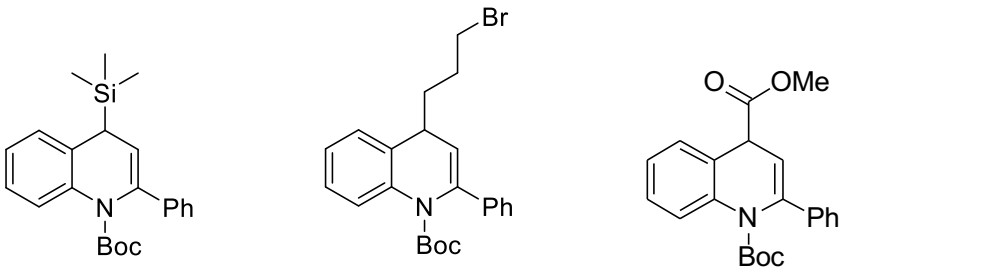
113
96%
$E^+ = MeI$



114
95%
$E^+ = CH_2{=}CHCH_2Br$

Figure 8 – Products of lithiation-electrophilic quench of 104 with various electrophiles

The lithiation-quench reaction was performed using a variety of electrophiles. Good to excellent yields of product **115**–**117** were obtained when trimethylsilyl chloride, methyl chloroformate, methyl cyanoformate and 1,4-dibromobutane were used (Figure 9). The same product **117** was obtained when methyl chloroformate and methyl cyanoformate were used as electrophiles.



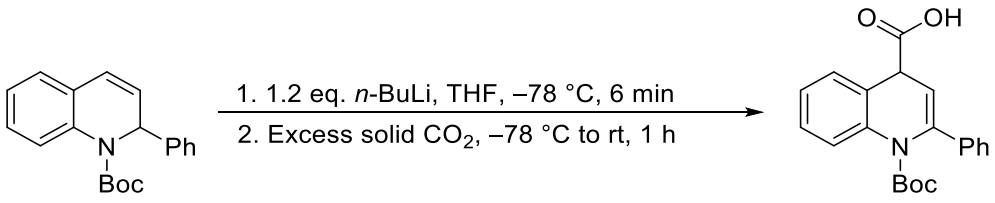
115
87%
$E^+ = Me_3SiCl$

116
78%
$E^+ = Br(CH_2)_3Br$

117
$E^+ = MeOCOCl$ 86%
$E^+ = MeOCOCN$ 50%

Figure 9 – Products of lithiation-electrophilic quench of 104 with various electrophiles

From a literature search, a methodology was found to use dry ice (CO_2) as an electrophile.[59] The carboxylic acid product **118** was successfully obtained using this method (Scheme 45). After 6 min addition of *n*-BuLi at –78 °C, excess dry ice milled using mortar and pestle was added to the reaction flask using a funnel. The mixture was left to warm to room temperature over 1 h to ensure all the CO_2 had reacted and excess CO_2 evaporated. The product **118** was obtained in a good yield of 61%.



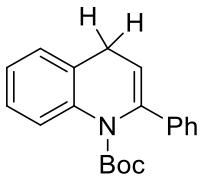
104

118
61%

Scheme 45

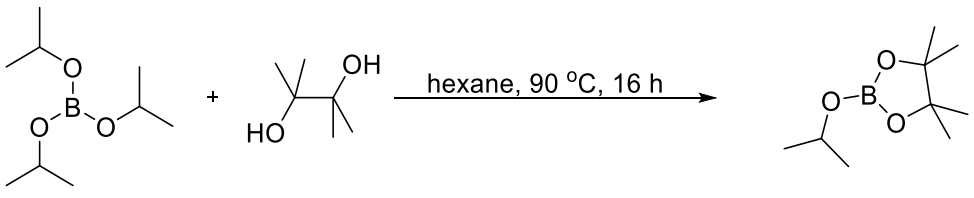
Previous work in the group attempted to use Bu_3SnCl as an electrophile, however no desired substituted product was obtained.[53] We thought that this may have been due to the steric bulk of Bu_3SnCl. Therefore, the reaction was repeated with trimethyltin chloride (Me_3SnCl). However, instead of obtaining the desired product, compound **119**

was isolated instead in 85% yield (Figure 10). This indicated that although the starting material **104** was undergoing lithiation, the lithiated intermediate was not reacting with the Me_3SnCl. As a result, upon quenching with MeOH, compound **119** was formed instead. In addition, reactions with other electrophiles, including (*S*)-phenyl benzenethiosulfonate, trimethyl borate and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **122**, gave no desired product. There was concern about the quality of the ^{i}PrOBPin used, therefore it was synthesised by refluxing triisopropyl borate **120** and pinacol **121** in hexane at 90 ^{o}C for 16 h (Scheme 46).[60] The lithiation-quench reaction was then repeated, but still no product was formed. Like Bu_3SnCl, this may have been due to the steric bulk of ^{i}PrOBPin.



119

Figure 10 – Proton quenched product on 4-position of 104



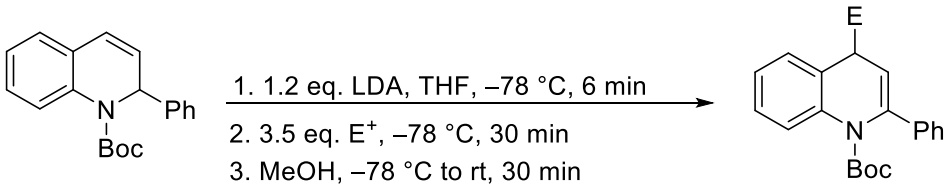
120 **121** **122**

68%

Scheme 46

The lithiation-electrophilic quench reaction was further investigated using a different organolithium base. Instead of using *n*-BuLi, lithium diisopropylamide (LDA) was

added to DHQ **104** in THF at –78 °C (Scheme 47). After 6 min, electrophiles acetone and methyl iodide were added and produced yields of 25% and 20%, respectively (Figure 11). The expected products were formed successfully but in a very poor yield and most of the compound was the unreacted starting material **104**.



104 **105**

Scheme 47

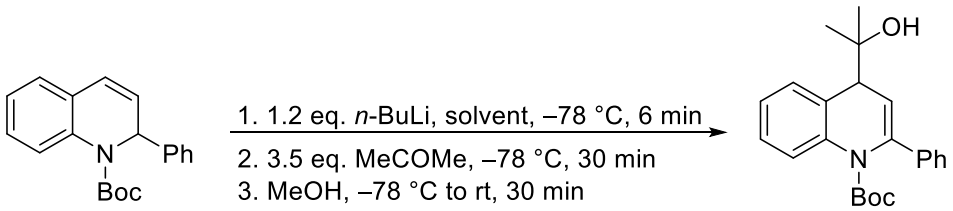
111
25%
E^+ = MeCOMe

113
20%
E^+ = MeI

Figure 11 – Products of lithiation-electrophilic quench of 104 with various electrophiles

After the investigation of a different organolithium base, solvent studies were then attempted. Instead of performing the reaction in THF, the lithiation-quench reaction was performed in a variety of solvents at –78 °C, followed by the addition of acetone as an electrophile (Scheme 48, Table 11). When the reaction was performed in Et_2O, the product **111** (24%) and the unreacted starting material **104** (74%) were obtained (Entry 1). Furthermore, 2-methyltetrahydrofuran (2-MeTHF) was used and the product **111** (87%) and the unreacted starting material **104** (11%) were obtained (Entry 2). Better results were obtained when the reaction was performed in 2-MeTHF, but still

the starting material **104** was not fully deprotonated. Hence, it was decided to perform the reaction in THF as it gave the highest yield, with 92% of the product **111**.



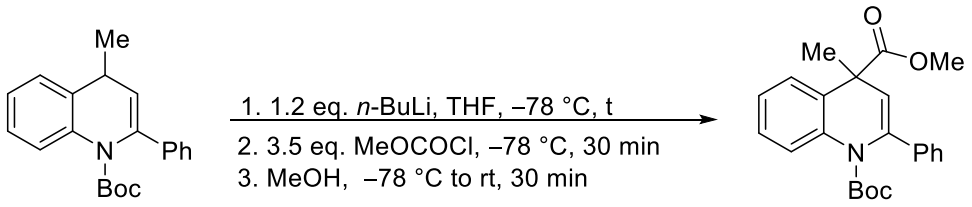
104 **111**

Scheme 48

Table 11

Entry	Solvent	111 yield %	104 yield %
1	Et_2O	24	74
2	2-MeTHF	87	11

We wondered if the product **113** from the lithiation-quench reaction could be lithiated and quenched to give 4,4-disubstituted compounds. *n*-BuLi was added to 1,4-DHQ product **113** in THF at –78 °C and methyl chloroformate (MeOCOCl) was added as an electrophile after 10 min (Scheme 49, Table 12). The intermediate organolithium was quenched at the 4-position to give 4,4,2-trisubstituted product **123**. The product **123** was obtained in 51%, and unreacted starting material obtained **113** in 48% (Entry 1). To ensure all starting material was deprotonated, the reaction was left longer, this time for 1 h, and this gave better results, with the product **123** being obtained in 77% yield (Entry 2).



113 **123**

Scheme 49

Table 12

Entry	t/ min	123 yield %	113 yield %
1	10	51	48
2	60	77	0

A study of Boc protecting group rotation was performed using variable temperature (VT) NMR. The VT NMR study was carried out in THF-d_8 and coalescence of C-8 hydrogen signal (ratio ~2:1) occurred between −38 °C and −28 °C (Figure 12). Since the ratio is not 1:1, dynamic NMR and Eyring plot was used to calculate the activation parameter. Using line-shape analysis, activation parameters $\Delta H^{\ddagger} \approx 46.8$ kJ mol^{-1} and $\Delta S^{\ddagger} \approx -12.7$ J K^{-1} mol^{-1} were obtained. These values were used to calculate a $\Delta G^{\ddagger}$ value about 49.3 kJ mol^{-1} at −78 °C and the half-life of the Boc group rotation was about 3 sec (Appendix 5). The value correlates to the experimental data that the Boc group was rotating quickly.

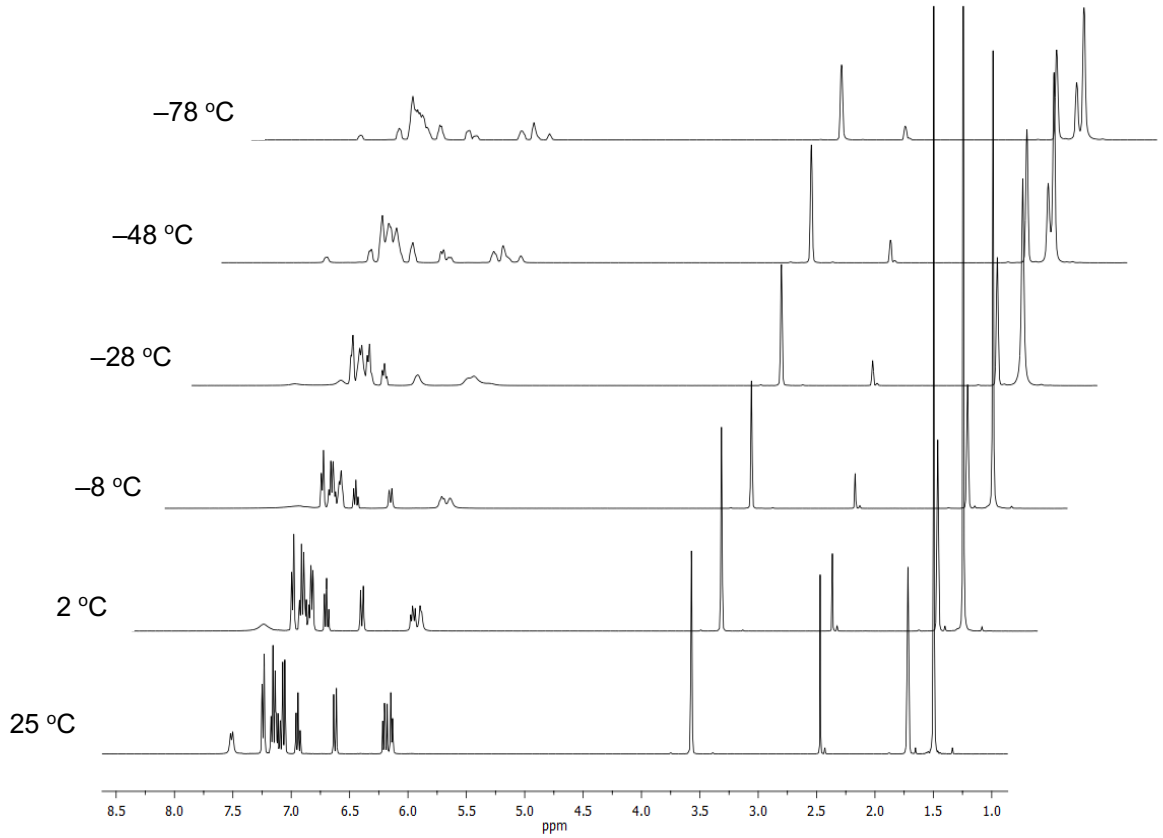
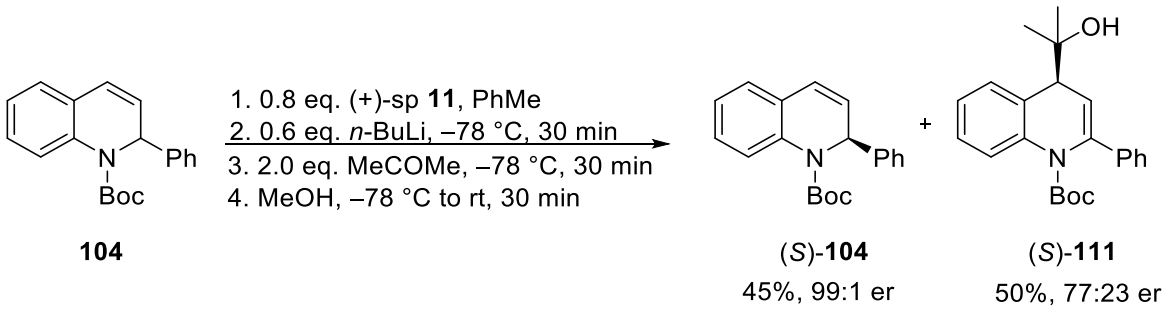


Figure 12 – ^{1}H NMR spectra obtained at various temperatures in THF-d$_8$, 500 MHz

The kinetic resolution of 2-phenyl-1,2-DHQ **104** was then investigated. Continuing with previous work done in the group, *n*-BuLi was added to a mixture of compound **104** and (+)-sp **11** in PhMe at –78 °C. The electrophile acetone was then added and after a further 30 min the reaction was quenched with MeOH at –78 °C, rather than at room temperature (Scheme 50). The product (*S*)-**111** was obtained in 50% yield with 77:23 er, while the RSM (*S*)-**104** was isolated in 45% yield with 99:1 er which has a selectivity factor of 41. Overall, this indicated that quenching the reaction with MeOH at –78 °C was beneficial for the er of both the RSM and substituted product (as shown in Scheme 39 and Table 8). Furthermore, this was in agreement with similar work done by Beak and co-workers.[61] However, it would be worth trying either to decrease the number of

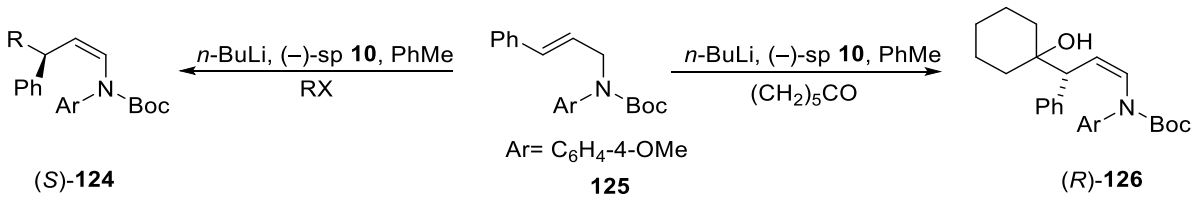
equivalents of *n*-BuLi or to decrease the time before the addition of MeOH to see whether it gives an even better result.



104 (*S*)-**104** 45%, 99:1 er (*S*)-**111** 50%, 77:23 er

Scheme 50

Previously, Weisenburger and Beak reported the enantioselective synthesis of allylamines.[62] This was achieved by reacting Boc protected amine **125** with *n*-BuLi/(–)-sp at –78 °C and quenching with different electrophiles (Scheme 51). An interesting observation was that when the reaction was quenched with cyclohexanone, (*R*)-**126** was isolated, whereas when alkyl halides such as methyl iodide and benzyl bromide were used, compound (*S*)-**124** was isolated. Therefore, the stereochemical course of the reaction was dependent on the choice of electrophile. Hence, it would be interesting to test whether this effect will still be observed with the DHQs.

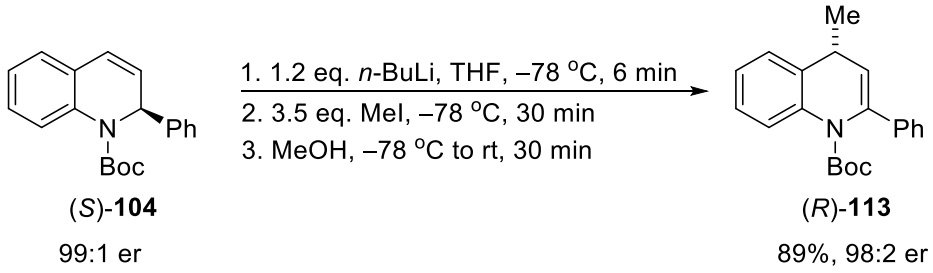


(*S*)-**124** **125** (*R*)-**126**

Scheme 51

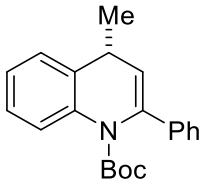
The absolute configuration of the lithiation-quench reaction product (*R*)-**111** (quenched with acetone) (see page 34) has been obtained, but not the configuration

after adding alkyl halides in the lithiation-quench reaction. A lithiation-quench reaction was performed using methyl iodide as an electrophile on the enantioenriched starting material (*S*)-**104** with 99:1 er (Scheme 52). Carbamate (*R*)-**113** was isolated in a good yield of 89%, retaining the enantioenrichment.



Scheme 52

The product was then crystallised and the absolute configuration of the carbamate (*R*)-**113** was confirmed by single crystal X-ray analysis (Figure 13, Appendix 1). The lithiation-electrophilic quench occurred with retention of configuration starting with enantiomerically enriched (*S*)-**104**. The Flack parameter of the sample was 0.02, suggesting that the absolute stereochemistry was obtained. The result obtained contrasts with Beak's research, as with DHQs the electrophilic-substitution for both carbonyl electrophiles and alkyl halide electrophiles gave the same configuration (retention). Therefore, the configuration of the reaction with DHQ was not affected by the choice of electrophile.



(*R*)-**113**

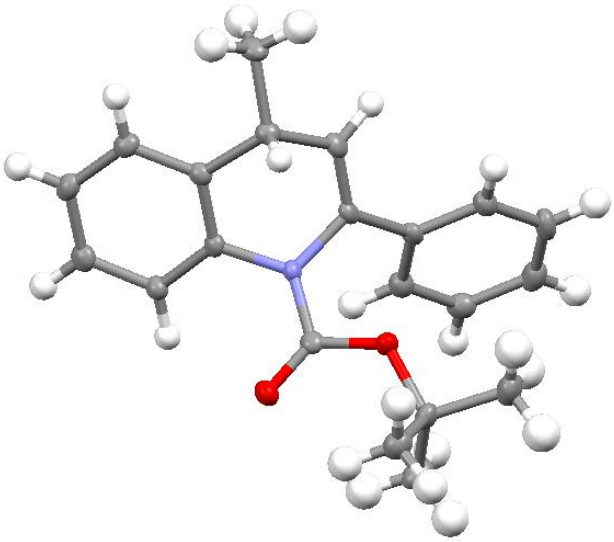
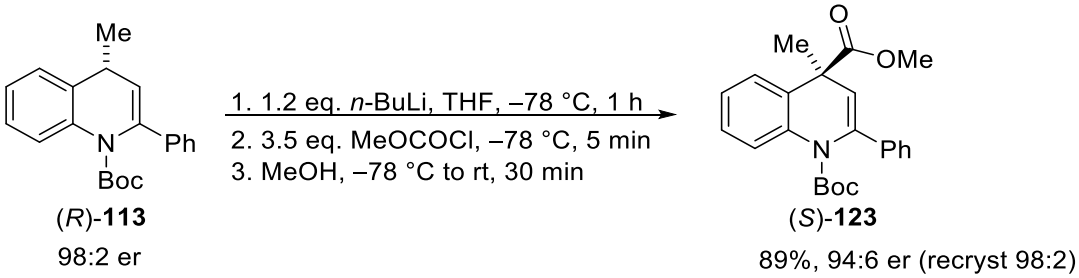


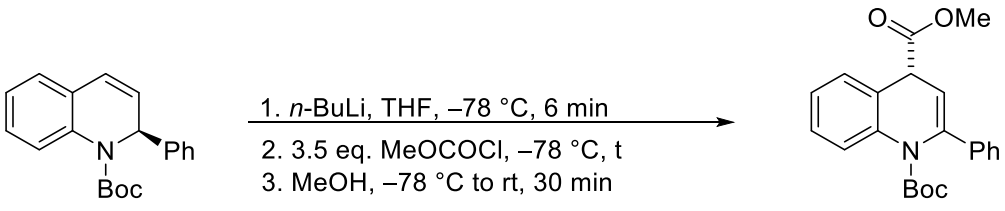
Figure 13 – The absolute configuration of (*R*)-113 obtained by single crystal X-ray analysis

A lithiation-electrophilic quench reaction was also performed on the enantioenriched 1,4-DHQ (*R*)-**113** with 98:2 er. The reaction was quenched with methyl chloroformate using the optimised conditions found above (Scheme 53). The reaction was quenched with MeOH 5 min after the addition of the electrophile. Promising results were obtained with an excellent yield of 89% and the er was only decreased from 98:2 to 94:6, which was recrystallised to improve the er to 98:2.



Scheme 53

The lithiation-electrophilic addition was then performed on the recovered starting material (*S*)-**104** obtained from the kinetic resolution by adding *n*-BuLi in THF at –78 °C and stirring for 6 min (Scheme 54, Table 13). Then 1.2 eq. of methyl chloroformate was added and after 30 min, the reaction was quenched with MeOH at –78 °C and warmed to room temperature over 30 min. However, unlike other electrophiles, the enantioenrichment was not retained and poor er was obtained. The yield of the product (*R*)-**117** obtained was great with 75%, but the er decreased to 75:25 er (Entry 1). When quenching with methyl chloroformate, the product is fairly acidic and if it deprotonates, it gives a planar enolate which is achiral. Hence, less eq. of *n*-BuLi were used to prevent excess base causing the product to racemise in the reaction (Entry 2). However, this did not give a better result and the er of the product (*R*)-**117** was 77:23. Lastly, instead of leaving the reaction for 30 min after the addition of methyl chloroformate, it was only left for 5 min (Entry 3). The er of the product (*R*)-**117** obtained has still decreased, but it was not as bad as the previous results. It seems like the ester product (*R*)-**117** is causing the loss of enantioenrichment as it is more prone to racemise as it can form an enolate.



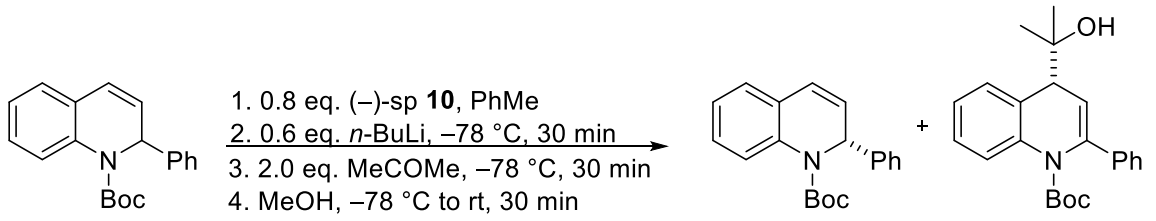
(*S*)-**104** (*R*)-**117**

Scheme 54

Table 13

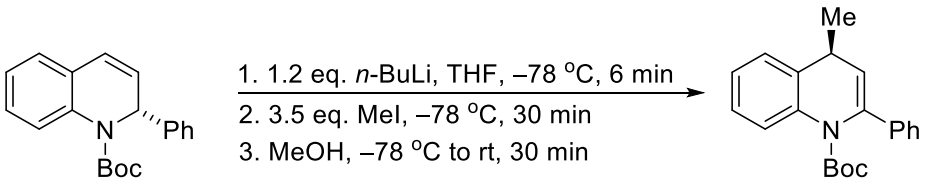
Entry	eq. *n*-BuLi	t/ min	(*S*)-104 er	(*R*)-117 yield %	(*R*)-117 er
1	1.2	30	99:1	75	75:25
2	1.0	30	99:1	63	77:23
3	1.2	5	99:1	80	88:12

The DHQ (*R*)-**104** can be easily synthesised by performing kinetic resolution using the opposite enantiomer of the chiral ligand, (–)-sp **10** (Scheme 55). The same conditions were applied and opposite enantiomer (*R*)-**104** was successfully obtained in a great result of 47% yield and 97:3 er with a selectivity factor of 39. The absolute configuration was not confirmed by single crystal X-ray analysis, but the opposite sign was observed by polarimetry and the opposite major peak was seen on the chiral HPLC spectra – both indications that the opposite configuration was formed. A lithiation-quench was then performed on (*R*)-**104** using methyl iodide as an electrophile (Scheme 56). As expected, the lithiation-electrophilic quench occurred with retention of configuration and the opposite enantiomer of the product *(S)*-**113** was obtained while mostly retaining its enantioenrichment. The methyl iodide may be quenching slowly and allowing a little racemisation.



104 (*R*)-**104** 47%, 97:3 er (*R*)-**111** 50%, 82:18 er

Scheme 55



(*R*)-**104**

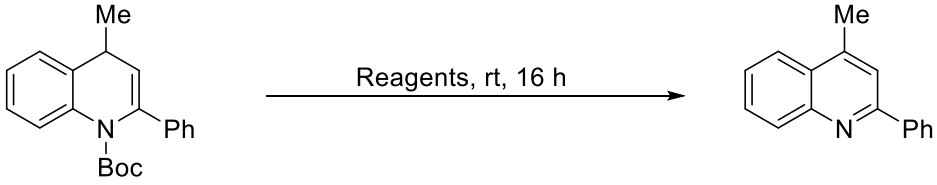
97:3 er

(*S*)-**113**

54%, 92:8 er

Scheme 56

Removal of the Boc protecting group would allow further functionalisation of the molecules. Racemic 4-methyl-2-phenyl-1,4-DHQ **113** was dissolved in DCM and trifluoroacetic acid (TFA) was added at room temperature (Scheme 57, Table 14). The mixture was left to stir overnight and 4-methyl-2-phenylquinoline **127** was successfully isolated in an excellent yield of 95% (Entry 1). A more environmentally friendly reagent, hydrochloric acid (HCl) in dioxane, was used in place of TFA to deprotect the Boc group (Entry 2). The Boc group was successfully removed and quinoline **127** is presumably being formed by oxidation of the intermediate *N*-H 1,4-DHQ. It would be desirable to remove the Boc group from enantioenriched compounds, however not on this 1,4-DHQ compound as it would give a substituted quinoline and lose its chirality.



113

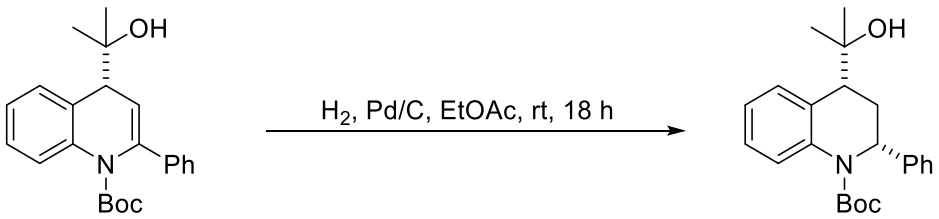
127

Scheme 57

Table 14

Entry	Reagents	127 yield %
1	TFA, DCM	95
2	HCl in dioxane	95

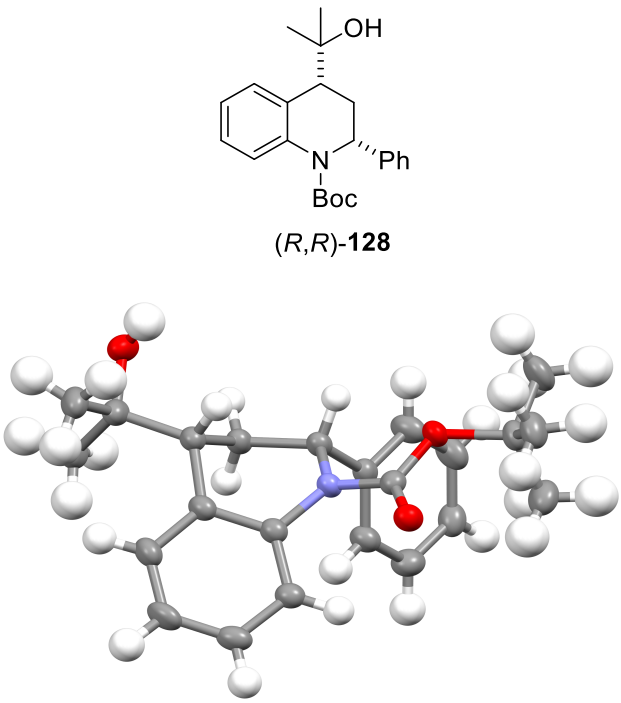
In contrast to oxidation, the substituted 1,4-DHQ can be converted to a THQ by reducing the double bond by hydrogenation. Racemic DHQ **111** was stirred with 10% palladium on carbon (Pd/C) in ethyl acetate (EtOAc), under a hydrogen gas atmosphere (1 atm) at room temperature. TLC was used to monitor the reaction and showed that the starting material was fully hydrogenated after 18 h. This gave 2,4-disubstituted THQ product **128** in an excellent yield of 85%. This was then applied to the enantioenriched (*R*)-**111** with 97:3 er and formed a single diastereomer without losing the enantiopurity (Scheme 58). Single crystal X-ray analysis of recrystallised **128** (er 96:4) was carried out (Figure 14, Appendix 2). The Flack parameter of the sample was 0.02, suggesting that the absolute stereochemistry was obtained and that reduction had given the *cis*- isomer.



(*R*)-**111**
97:3 er

(*R*,*R*)-**128**
99%, 96:4 er

Scheme 58

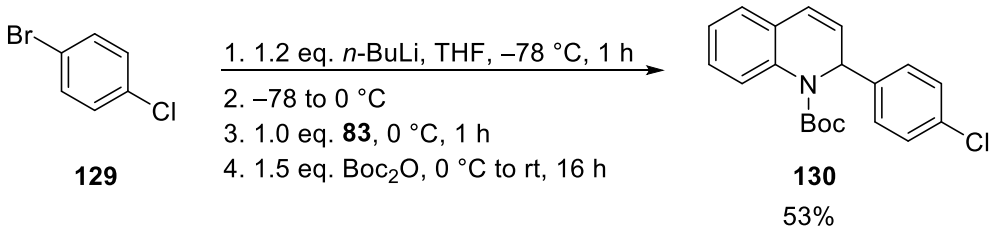


(*R*,*R*)-**128**

Figure 14 – The absolute configuration of (*R*,*R*)-128 obtained by single crystal X-ray analysis

2.4 Lithiation of *N*-Boc-2-aryldihydroquinolines

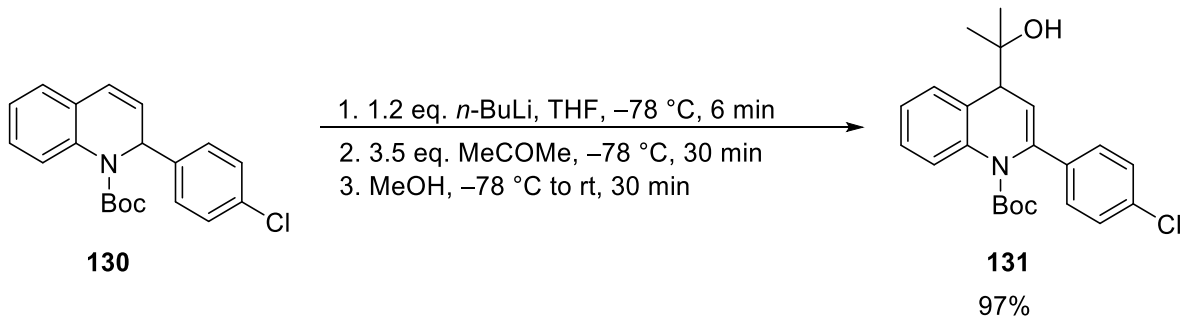
Continuing with the work, DHQ derivatives with different aryl groups in the 2-position were next investigated. Firstly, *N*-Boc-2-(4-chlorophenyl)-1,2-DHQ **130** was investigated. This aryl group was chosen as it would introduce an electron withdrawing chlorine atom onto the aromatic ring and decrease the pK_a of the benzylic proton, thus changing the reactivity. The compound **130** was synthesised in one pot and successfully isolated in a reasonable yield of 53% (Scheme 59). Before adding the quinoline **83**, *n*-BuLi was added to bromo-4-chlorobenzene **129** at –78 °C in THF to allow halogen-lithium exchange to take place.[63] The mixture was stirred for 1 h, after which time quinoline **83** was added at 0 °C. After a further 1 h, Boc_2O was added and the mixture was warmed to room temperature with stirring over 16 h.



129 **130** 53%

Scheme 59

With DHQ **130** in hand, a lithiation-quench reaction was then performed. Similar reaction conditions to those used on DHQ **104** were applied to DHQ **130** (Scheme 60). Quenching the reaction with acetone gave 2,4-disubstituted product **131** in an excellent yield of 97%.

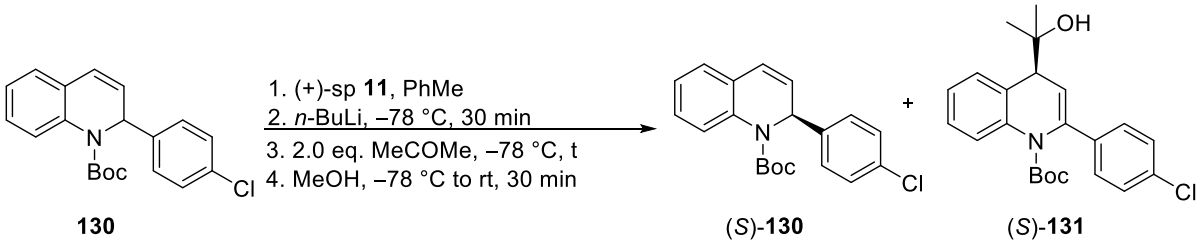


130 **131**

97%

Scheme 60

Kinetic resolution was then performed with the optimum conditions found for DHQ **104** (Scheme 61, Table 15). Initially, the recovered starting material (*S*)-**130** was obtained with a yield of 56% and an er of 88:12, whereas product (*S*)-**131** was obtained in 40% yield and 87:13 er (Entry 1). As the RSM (*S*)-**130** was obtained in a high yield, the equivalents of *n*-BuLi and (+)-sp **11** were increased and the reaction was repeated. Unfortunately, although the er of RSM (*S*)-**130** was excellent at 99:1, the yield was just 21% while the product (*S*)-**131** was obtained in 72% (Entry 2). As the product (*S*)-**131** was obtained in high yield, the time after the addition of electrophile was reduced which led to improved results with a selectivity factor of 30. The RSM (*S*)-**130** and product (*S*)-**131** were obtained in 43% yield with er of 99:1 and 56% yield with er of 73:27 respectively (Entry 3). The low er of product (*S*)-**131** was most likely because of partial racemisation of the allyllithium.



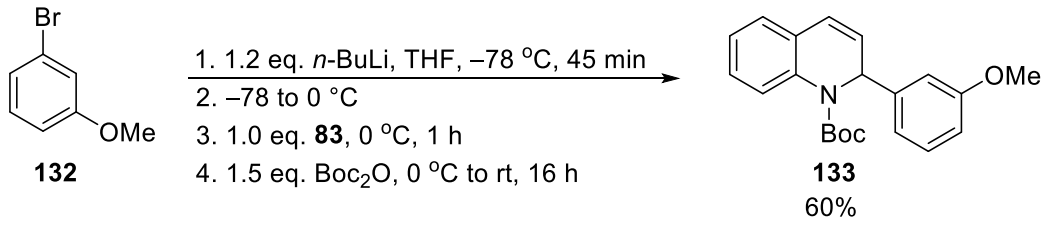
130 (*S*)-**130** (*S*)-**131**

Scheme 61

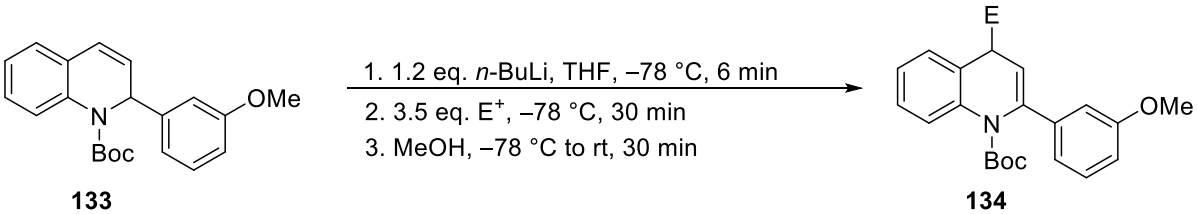
Table 15

Entry	t/ min	eq. *n*-BuLi	eq. (+)-sp	(*S*)-130 yield %	(*S*)-130 er	(*S*)-131 yield %	(*S*)-131 er	s
1	60	0.6	0.8	56	88:12	40	87:13	-
2	60	0.7	0.9	21	99:1	72	57:43	6
3	30	0.7	0.9	43	99:1	56	73:27	30

Moving forward, *N*-Boc-2-(3-methoxyphenyl)-1,2-DHQ **133** was then investigated. Using the same method as for compound **104**, compound **133** was obtained in 60% yield (Scheme 62).[64] Before proceeding to kinetic resolution, a racemic lithiation-quench was performed. Using acetone and prenyl bromide as the electrophiles, the desired products **135** and **136** were obtained in an excellent yield of 93% and 91% respectively (Scheme 63, Figure 15).



Scheme 62



Scheme 63

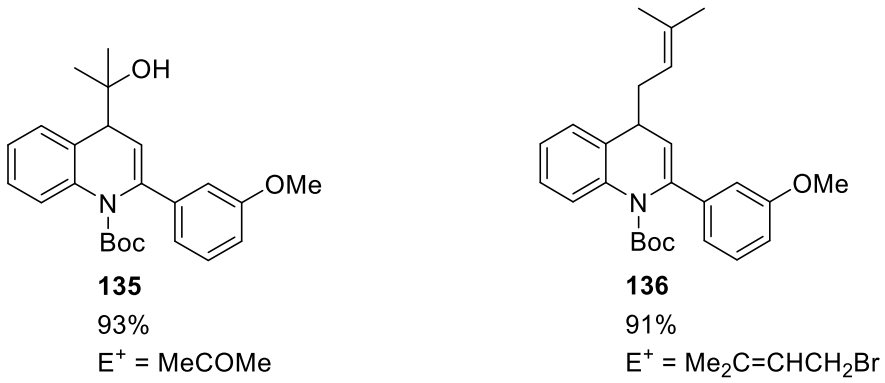
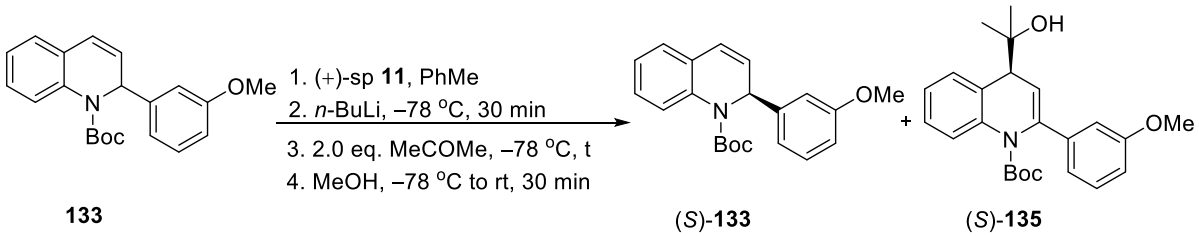


Figure 15 – Products of lithiation-electrophilic quench of 133 with various electrophiles

A kinetic resolution was then performed on 2-(3-methoxyphenyl)-1,2-DHQ **133** (Scheme 64, Table 16). Using 0.6 eq. of *n*-BuLi and 0.8 eq. of (+)-sp **11** gave high yield of RSM (*S*)-**133** and thus poor er (Entry 1). Hence, the reaction was left longer as it might help to give more of the lithiated product. Unfortunately, the result did not improve (Entry 2). Therefore, the equivalents of *n*-BuLi and (+)-sp **11** were increased to 0.7 eq. and 0.9 eq. respectively and this gave a better result (Entry 3). However, the best result was obtained when both the equivalents and lithiation time were increased (Entry 4). The RSM (*S*)-**133** was obtained in 41% yield with er of 98:2 and the product (*S*)-**135** was obtained in 57% yield with er of 77:23.

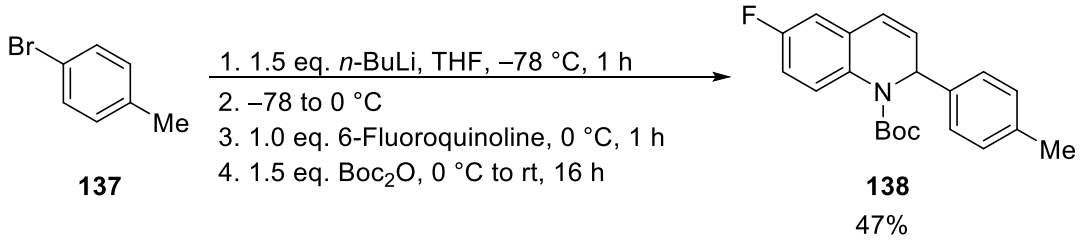


Scheme 64

Table 16

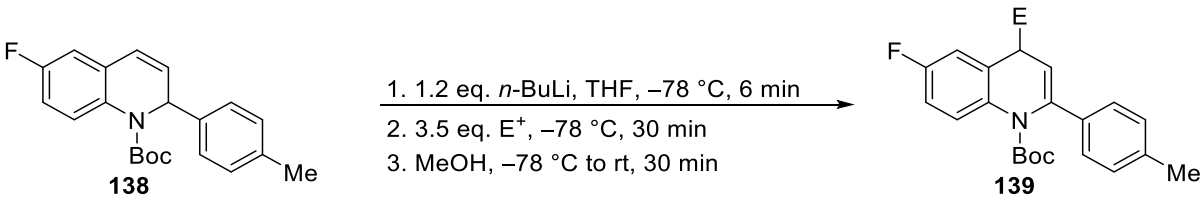
Entry	t/ min	eq. *n*-BuLi	eq. (+)-sp	(*S*)-133 yield %	(*S*)-133 er	(*S*)-135 yield %	(*S*)-135 er	s
1	30	0.6	0.8	66	76:24	30	90:10	-
2	60	0.6	0.8	67	71:29	30	86:14	-
3	30	0.7	0.9	59	79:21	40	80:20	20
4	60	0.7	0.9	41	98:2	57	77:23	19

Furthermore, the *N*-Boc-6-fluoro-2-(4-methylphenyl)-1,2-DHQ **138** was studied to see how the substituent on the other ring affects the chemistry. The compound **138** was synthesised in one pot by addition of *n*-BuLi to 4-bromotoluene **137** in THF and followed by 6-fluoroquinoline which was commercially available (Scheme 65).[65] The product **138** was successfully isolated in a reasonable yield of 47%.

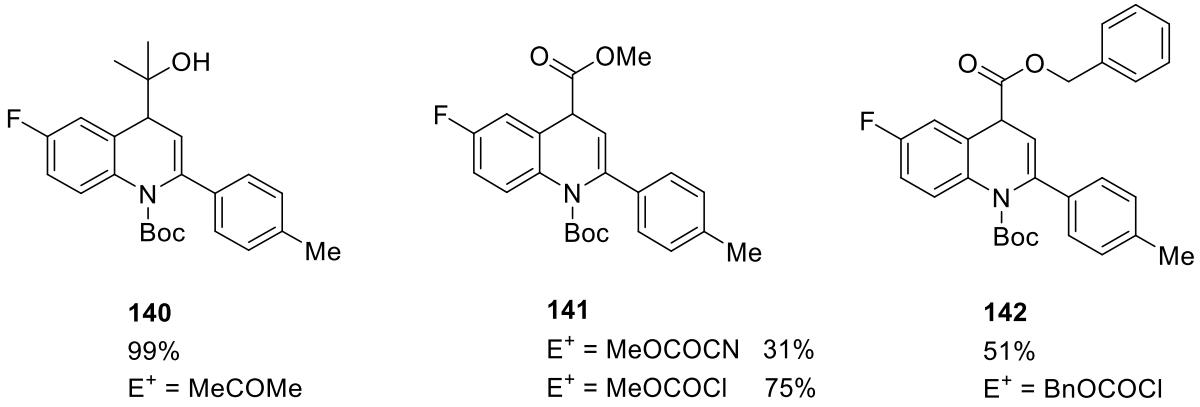


Scheme 65

Before kinetic resolution was studied, a racemic lithiation-quench reaction of DHQ **138** was investigated with various electrophiles. Using the same reaction conditions found above with lithiation time of 6 min, products **140**-**142** were successfully formed with good to excellent yield (Scheme 66, Figure 16). Like the 2-phenyl-1,2-DHQ **104**, using methyl cyanoformate and methyl chloroformate gave the same product. However, the yield was much better when methyl chloroformate was used (75%).



Scheme 66



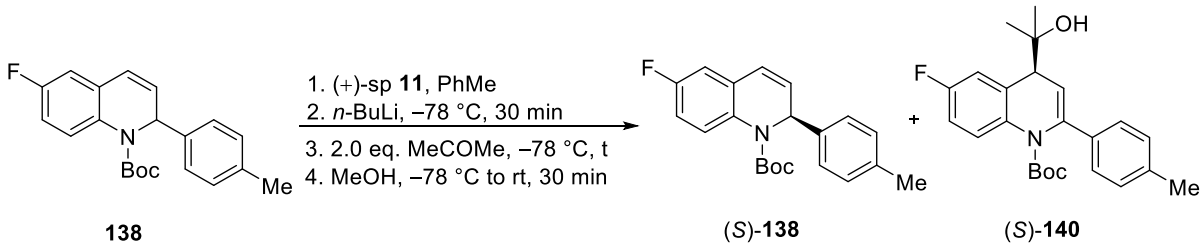
140
99%
E^+ = MeCOMe

141
E^+ = MeOCOCN 31%
E^+ = MeOCOCl 75%

142
51%
E^+ = BnOCOCl

Figure 16 – Products of lithiation-electrophilic quench of 138 with various electrophiles

Kinetic resolution was carried out in order to obtain enantioenriched compounds (Scheme 67, Table 17). More than 50% of enantioenriched starting material (*S*)-**138** was obtained when 0.6 eq. and 0.8 eq. of *n*-BuLi and (+)-sp **11** were used respectively, which gave poor er as a result (Entry 1). So the reaction was repeated, this time increasing the eq. of *n*-BuLi and this gave a better result of RSM (*S*)-**138** in 47% yield and 90:10 er (Entry 2). An even better result was obtained when the reaction was left longer, this time for 1 h, which gave more product (*S*)-**140** and hence, better er of RSM (*S*)-**138** (Entry 3). In summary, it can be said that the kinetic resolution of derivatives of *N*-Boc-2-aryl-1,2-DHQs has been successful, with remarkable yields and excellent er of (*S*)-**130**, (*S*)-**133** and (*S*)-**138.**



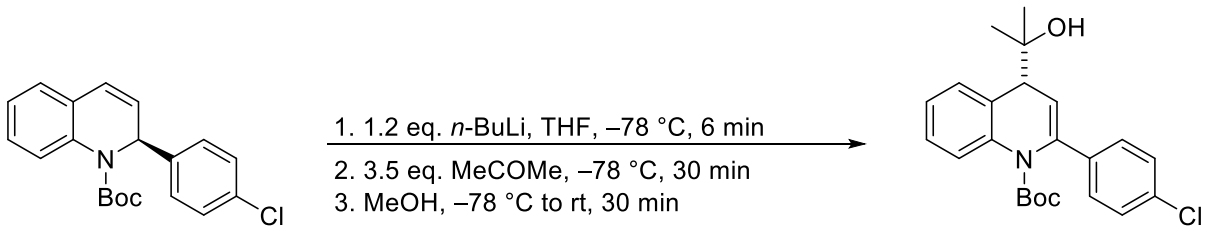
138 (*S*)-**138** (*S*)-**140**

Scheme 67

Table 17

Entry	t/ min	eq. *n*-BuLi	eq. (+)-sp	(*S*)-138 yield %	(*S*)-138 er	(*S*)-140 yield %	(*S*)-140 er	s
1	60	0.6	0.8	58	81:19	40	80:20	24
2	30	0.7	0.9	47	90:10	50	74:26	14
3	60	0.7	0.9	43	96:4	55	75:25	18

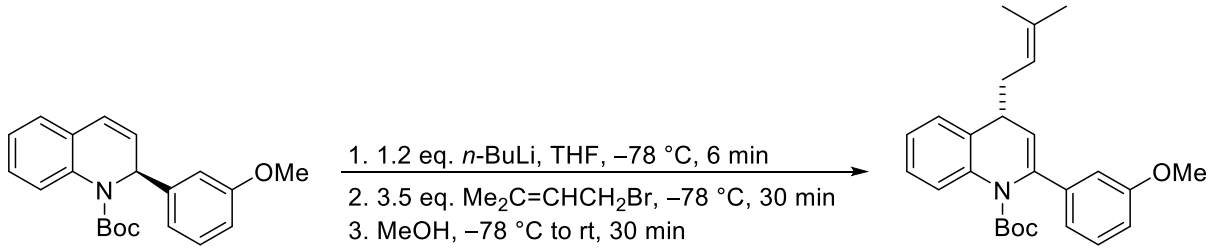
To conclude work on the DHQ, a lithiation-quench reaction was performed on the enantioenriched derivatives of *N*-Boc-2-aryl-1,2-DHQs obtained from kinetic resolution. On the starting material (*S*)-**130**, using acetone as the electrophile, alcohol (*R*)-**131** was isolated in an excellent yield of 77% with er of 96:4, retaining the enantioenrichment (Scheme 68). In addition, (*S*)-**133** was lithiated and quenched with prenyl bromide and an excellent result was obtained with 72% yield and 93:7 er (Scheme 69). The absolute configuration of (*R*)-**131** and (*R*)-**136** were assumed based on the absolute configuration of (*R*)-**111** that the lithiation-electrophilic quench reaction occurred with retention of configuration.



(*S*)-**130**
99:1 er

(*R*)-**131**
75%, 96:4 er

Scheme 68



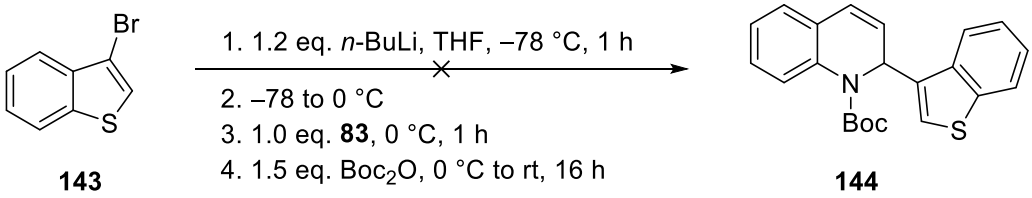
(*S*)-**133**
98:2 er

(*R*)-**136**
72%, 93:7 er

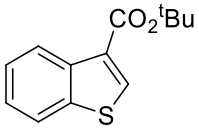
Scheme 69

After obtaining positive results from a study of substituted aryl groups at the 2-position of the DHQ, it was attempted to synthesise compounds containing a heteroaromatic ring. As a first example, synthesis of *N*-Boc-2-(3-benzothiophenyl)-1,2-DHQ **144** was attempted (Scheme 70). Using the previous method, *n*-BuLi was added to 3-bromobenzothiophene **143** in THF at 0 °C.[66] After 1 h, quinoline **83** was added followed by Boc_2O and the mixture was left to warm to room temperature overnight. Unfortunately, the desired product **144** was not obtained and instead compound **145** was obtained in 78% yield (as shown in Figure 17). This shows that halogen-lithium exchange took place, but it did not add to the quinoline. So, the reaction conditions were altered slightly. Instead of leaving the reaction at 0 °C after the addition of quinoline, the reaction was heated under refluxed overnight to help the addition of

lithiated benzothiophene to quinoline (Scheme 71). Unfortunately, this still did not give the desired DHQ **144**.



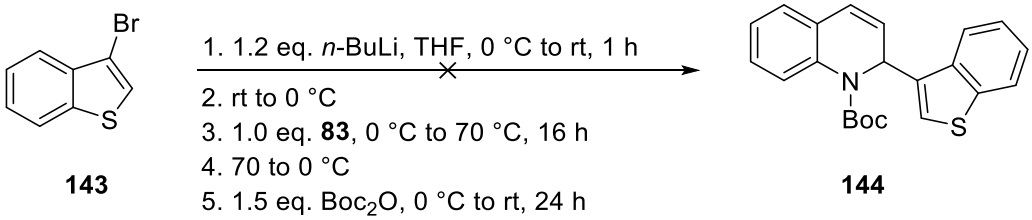
Scheme 70



145

78%

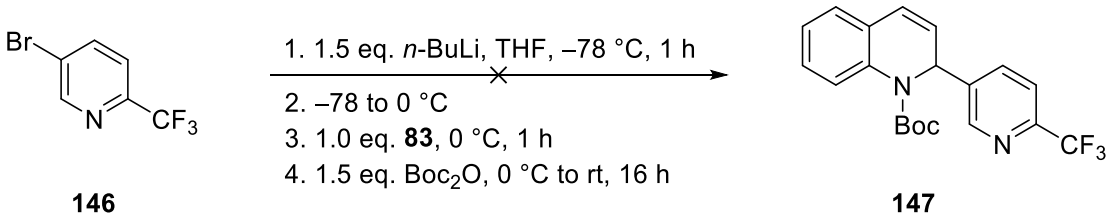
Figure 17 – Structure of compound 145



Scheme 71

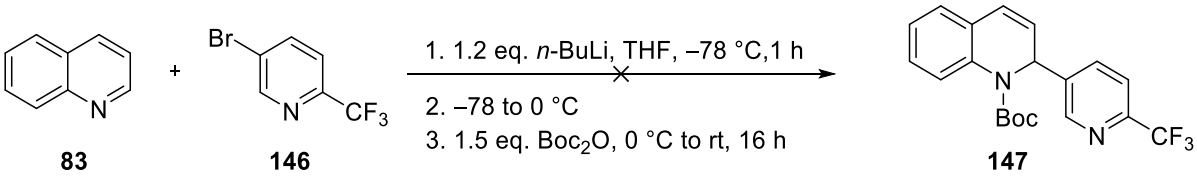
Moving on from the 2-(3-benzothiophene)-1,2-DHQ to synthesise compounds with different heteroaromatic groups on the 2-position, the synthesis of substituted pyridine-DHQ **147** was attempted. Lithium-halogen exchange was performed by adding *n*-BuLi to 5-bromo-2-(trifluoromethyl)pyridine **146** followed by quinoline **83** and Boc_2O (Scheme 72). Disappointingly, the desired DHQ **147** was not synthesised and unreacted quinoline was obtained. Unlike the benzothiophene, it appears that the

substituted pyridine was not lithiated during the first step. Most likely the *n*-BuLi was not carrying out lithium-halogen exchange on the pyridine. The synthesis was repeated by adding the *n*-BuLi to pre-mixed pyridine **146** and quinoline **83** in THF (Scheme 73). However, the DHQ **147** was still not obtained, instead unreacted quinoline **83** was obtained.



146 **147**

Scheme 72

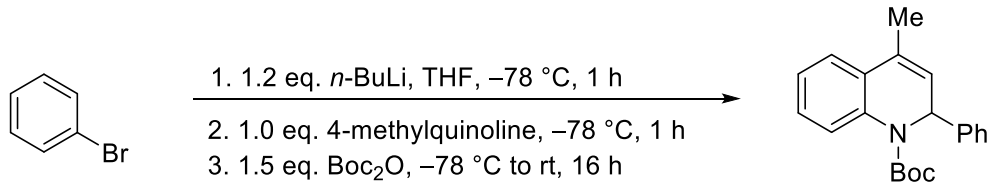


83 **146** **147**

Scheme 73

2.5 Use of *N*-Boc-2,4-disubstituted-dihydroquinolines

Previously, the lithiation-quench reaction of *N*-Boc-2,4-diphenyl-1,2-DHQ **108** was performed and it was confirmed that steric effects were negligible for the electrophilic substitution to occur on the 4-position (Scheme 38). However, lithiation-quench could not be studied further because when electrophiles other than methyl iodide were used, the reaction was unsuccessful. This was probably because of the bulky phenyl group in the 4-position which blocked the electrophiles, preventing lithiated species of **108** from being quenched. Hence, instead of having a bulky phenyl ring at the 4-position, *N*-Boc-4-methyl-2-phenyl-1,2-DHQ **148** was studied. Unlike *N*-Boc-2,4-diphenyl-1,2-DHQ **108**, *N*-Boc-4-methyl-2-phenyl-1,2-DHQ **148** could be synthesised in one pot as 4-methylquinoline is commercially available. Like with other DHQs, *n*-BuLi was added to 4-bromobenzene **112** at –78 °C and after 1 h, 4-methylquinoline was added followed by a protecting group, Boc_2O. The *N*-Boc-4-methyl-2-phenyl-1,2-DHQ **148** was isolated in good yield of 62% (Scheme 74).

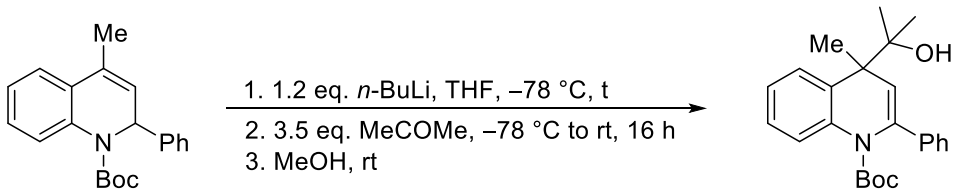


112 **148** 62%

Scheme 74

Lithiation-quench reactions were attempted with racemic DHQ **148** by using acetone as an electrophile (Scheme 75, Table 18). *n*-BuLi was added to a mixture of DHQ **148** in THF at –78 °C. After 10 min, acetone was added and the mixture was left to warm to room temperature overnight. The desired 4-position quenched product **149** was

obtained, but in a poor yield of 51% with unreacted DHQ **148** in 48% yield (Entry 1). As not all starting material had been lithiated, the reaction was left longer, to increase the lithiation time. Hence, the reaction was repeated with 1 h of lithiation time and a promising result was obtained, with product **149** in 90% yield and no unreacted DHQ **148** was obtained (Entry 2). The 4-methyl-2-phenyl-1,2-DHQ **148** takes longer to be lithiated than the 2-phenyl-1,2-DHQ **104**. It would be worth using *in situ* IR (ReactIR) or NMR to determine the exact time at which starting material is fully deprotonated to form a stable lithiated species in future studies, as well as studies looking at the rate of Boc rotation.



148 **149**

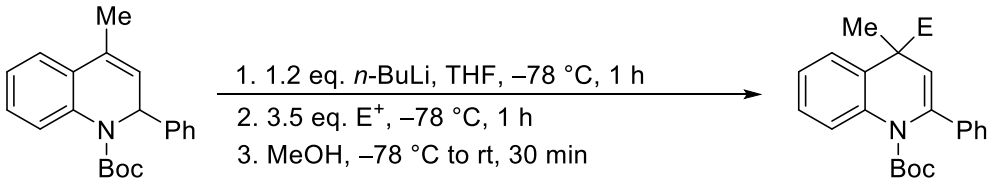
Scheme 75

Table 18

Entry	t/ min	149 yield %	148 yield %
1	10	51	48
2	60	90	0

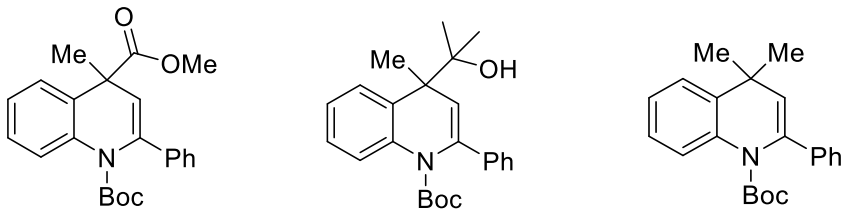
Like the lithiation-quench reaction of DHQ **104**, it would be beneficial to see if a better yield can be obtained when the reaction is quenched with MeOH at –78 ^{o}C instead of at room temperature. So 1 h after the addition of *n*-BuLi, the electrophile was added and the mixture was left to stir for 1 h before MeOH was added to quench the reaction (Scheme 76, Figure 18). When acetone was used as the electrophile, the yield of the

product **149** obtained was 90%, which is much better than the yield obtained when MeOH was added at room temperature (77%). Likewise, excellent yields of desired products **123** and **151** were obtained when methyl chloroformate and methyl iodide were used as electrophiles respectively.



148 **150**

Scheme 76



123
93%
E^+ = MeOCOCl

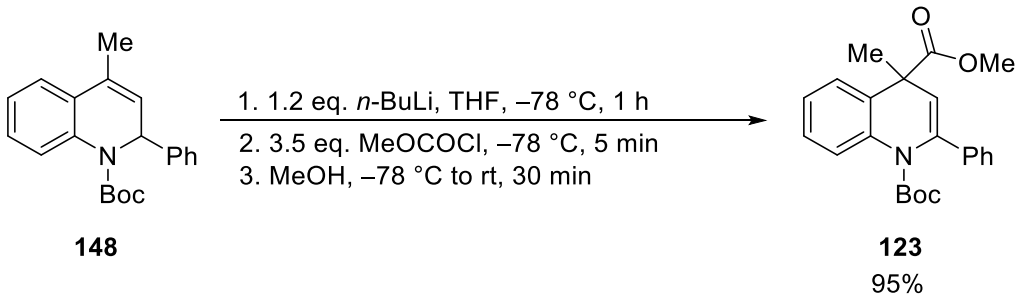
149
90%
E^+ = MeCOMe

151
81%
E^+ = MeI

Figure 18 – Products of lithiation-electrophilic quench of 148 with various electrophiles

In the lithiation-quench reaction, the mixture was left to stir for 30 min or 1 h before quenching the reaction with MeOH, assuming that this would allow the electrophile to be fully quenched by the lithiated species. It would be interesting to see how the yield of the product is affected if the reaction is left for shorter period of time which could be monitored by ReactIR or *in situ* NMR. Hence, the reaction was quenched with MeOH 5 min after the addition of electrophile, in this example with methyl chloroformate (Scheme 77). The yield of the product **123** obtained was 95%, which is similar to when

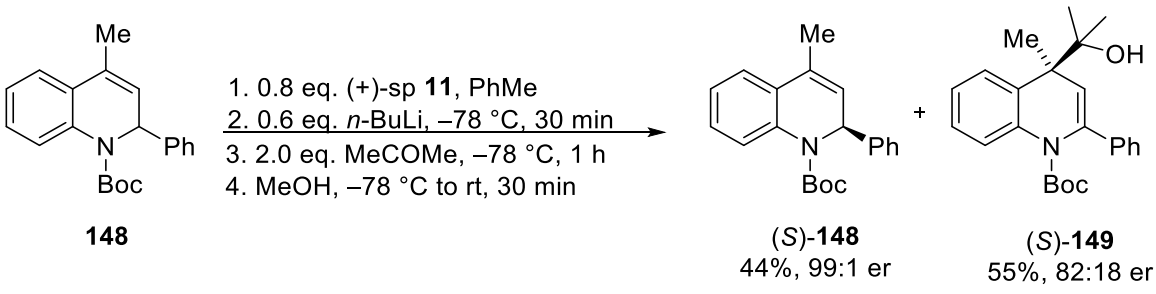
the reaction was left for 1 h. Hence, the time left to stir after the addition of electrophiles does not appear to affect the yield of product.



148 **123**
95%

Scheme 77

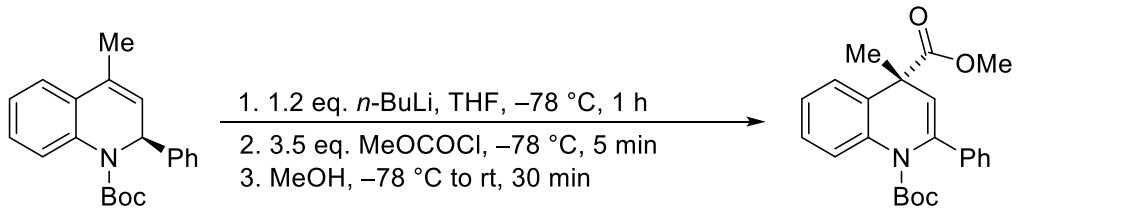
The kinetic resolution of 4-methyl-2-phenyl-1,2-DHQ **148** was then performed (Scheme 78). Using the optimum conditions found previously, 0.6 eq. of *n*-BuLi was added to a mixture of compound **148** and 0.8 eq. (+)-sp **11** in PhMe at –78 °C. The electrophile acetone was then added and after a further 30 min the reaction was quenched with MeOH at –78 °C. An excellent result was obtained with the product (*S*)-**149** in 55% yield with 82:18 er and RSM (*S*)-**148** was isolated in 44% yield with 99:1 er. This represents a selectivity factor of 34.



148
(*S*)-**148**
44%, 99:1 er
(*S*)-**149**
55%, 82:18 er

Scheme 78

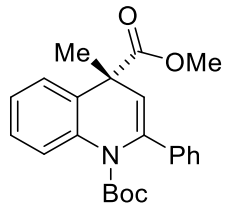
A lithiation-quench was then performed by adding *n*-BuLi to the recovered starting material (*S*)-**148** in THF and stirring for 1 h (Scheme 79). The electrophile methyl chloroformate was then added and the mixture was stirred for 5 min before the reaction was quenched with MeOH at –78 °C. The product (*R*)-**123** was obtained with good yield of 72% and enantioenrichment was retained. The product of the lithiation-quench of enantioenriched (*S*)-**148** gave the opposite enantiomer of the product of a lithiation-quench of enantioenriched (*R*)-**113**. The opposite sign was observed by polarimetry and the opposite major peak on HPLC was also observed. The product (*R*)-**123** was then crystallised to give 99:1 er and the absolute configuration was confirmed by single crystal X-ray analysis (Figure 19, Appendix 3). The lithiation-electrophilic quench occurred with retention of configuration starting with enantioenriched (*S*)-**148**. The Flack parameter of the sample was 0.03, suggesting that the absolute stereochemistry was obtained.



(*S*)-**148**
99:1 er

(*R*)-**123**
72%, 95:5 er (recryst 99:1)

Scheme 79



(*R*)-**123**

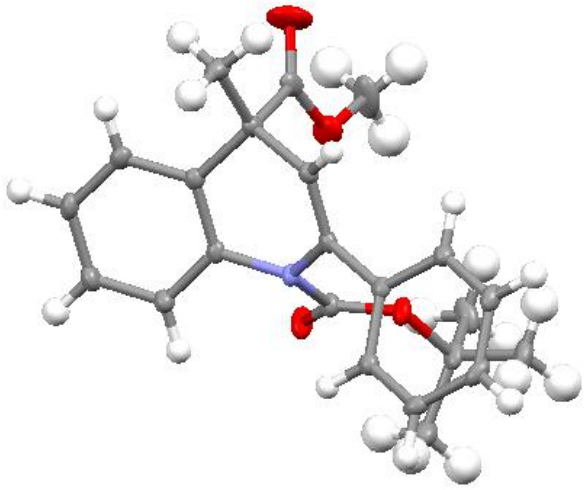
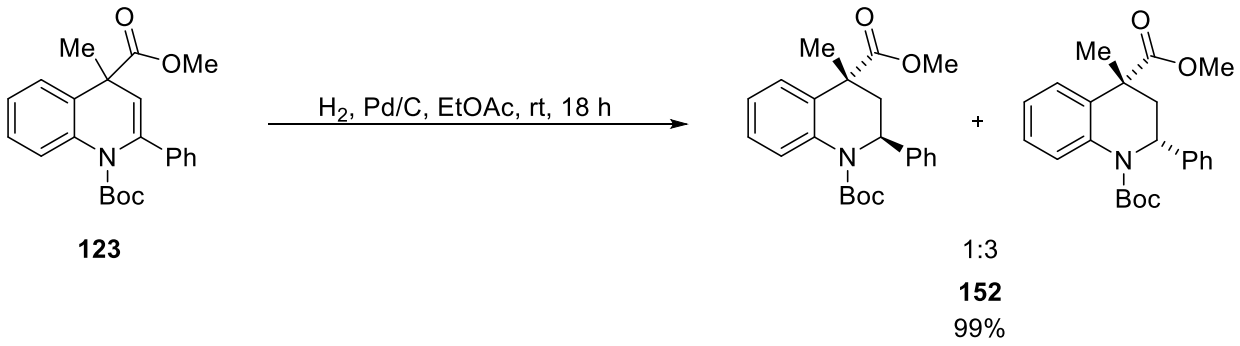


Figure 19 – The absolute configuration of (*R*)-123 obtained by single crystal X-ray analysis

Hydrogenation was then performed on the racemic **123** and enantioenriched (*R*)-**123** to give 4,4,2-trisubstituted THQ **152**. The starting material was stirred with 10% Pd/C in EtOAc under a hydrogen gas atmosphere (1 atm) at room temperature for 18 h. With racemic starting material **123**, the desired product was successfully obtained as a mixture of diastereomers with very high yield of 99% (Scheme 80). Without any purification, the NMR spectrum of the crude product was taken to measure the diastereomeric ratio (dr). From the crude NMR spectrum, the dr of the major to minor diastereomer was approximately 3:1. The diastereomers were not able to be separated by column chromatography, hence only the major product was extracted by recrystallisation from hexane and DCM. After the recrystallisation, only peaks resulting from the major diastereomer were observed in the NMR spectra. Hydrogenation is

preferred opposite to the methyl ester group, most likely to avoid the bulkier ester substituent, as determined from single crystal X-ray analysis as shown below.



123

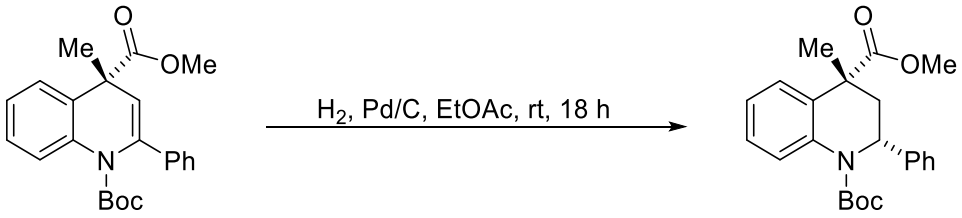
1:3

152

99%

Scheme 80

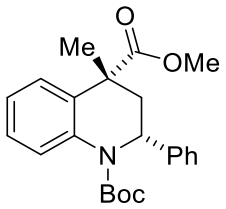
The hydrogenation of enantioenriched starting material (*R*)-**123** gave THQ **152** in a yield of 99% and retained the enantioenrichment (Scheme 81). The NMR spectrum of the crude product showed a mixture of diastereomers with a dr of approximately 4:1. After the recrystallisation, only a few small amount of crystals were isolated and the major diastereomer was observed from the NMR spectra. The solvent that was removed after the recrystallisation must have contained both diastereomers. To confirm the absolute configuration, a single crystal X-ray configuration was performed. However, the result indicated that the crystal was racemic (Figure 20, Appendix 4). The HPLC was repeated and it appears that the crystals were racemic while the gummy oil around the edges of the flask was the enantioenriched product, with an er of 98:2 and a specific rotation of $[\alpha]_D^{23}$ +136 (0.1, $CHCl_3$). Hence, the absolute configuration could not be confirmed, but nevertheless, the enantioenriched product **152** was successfully isolated.



(*R*)-**123**
99:1 er

152
99%, 98:2 er

Scheme 81



(±)-**152**

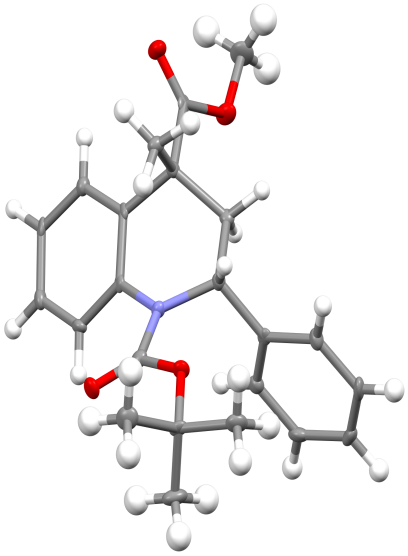
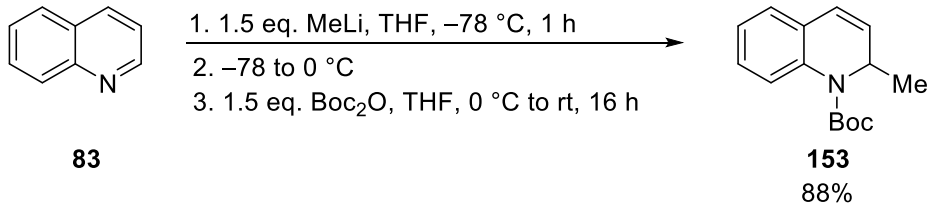


Figure 20 – Structure of (±)-152 obtained by single crystal X-ray analysis

2.6 Preparation of *N*-Boc-2-alkyldihydroquinolines

To extend the work on the 2-aryl-DHQ compounds, the focus turned to other DHQ compounds with various alkyl groups in the 2-position. Firstly, *N*-Boc-2-methyl-1,2-DHQ **153** was investigated. The DHQ **153** was easily synthesised in one pot from quinoline **83** (Scheme 82). To quinoline **83** in THF, methyllithium (MeLi) was added at –78 °C and Boc_2O was added.[67] The mixture was then warmed to room temperature overnight and the desired product **153** was successfully isolated in an excellent yield of 88%.

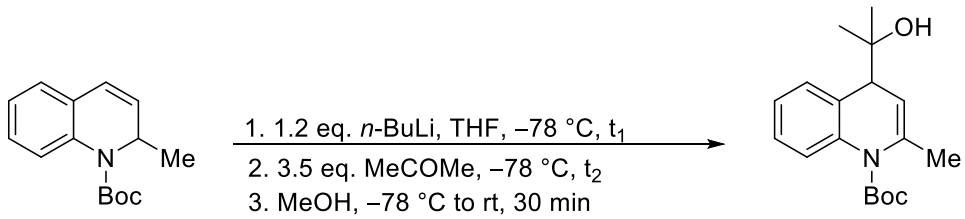


83 **153** 88%

Scheme 82

Racemic lithiation-electrophilic quench of 2-methyl-1,2-DHQ **153** was first investigated before performing kinetic resolution (Scheme 83, Table 19). The conditions that were optimised for 2-phenyl-1,2-DHQ **104** were used to test whether the same conditions were suitable for DHQ **153**. The starting material was dissolved in THF and *n*-BuLi was added at –78 °C. After 6 min, the organolithium intermediate was trapped with acetone, which was used as an electrophile. After 30 min, the reaction was quenched with MeOH and was warmed to room temperature over 30 min. The product **154** was obtained with the electrophile quenched on the 4-position as expected. However, the product **154** was obtained in 31% yield and the majority of compound obtained was the unreacted starting material **153** (Entry 1). To allow the starting material to be lithiated completely, the reaction was left longer before the addition of an electrophile.

A better yield of product **154** was obtained in 83% (Entry 2). The reaction was repeated and left for 1 h after the addition of electrophile to see if an even better result could be obtained. However, the yield of product **154** was 84% which shows little improvement from when the reaction was left for 30 min (Entry 3). Overall, 2-methyl-1,2-DHQ **153** needed a longer lithiation time and it is most likely because the proton is less acidic compared to having phenyl group on the 2-position.



153 **154**

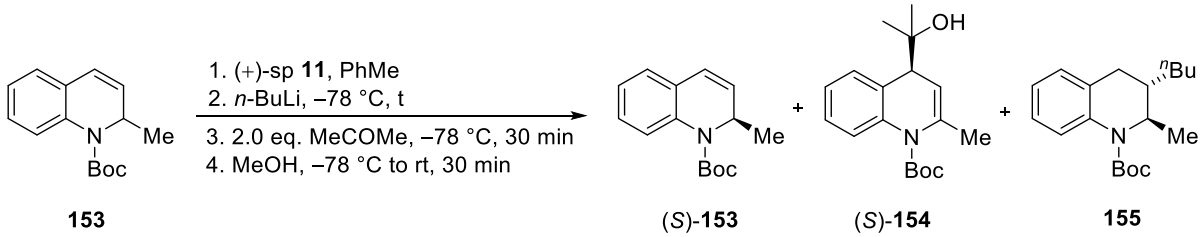
Scheme 83

Table 19

Entry	t_1/ min	t_2/ min	154 yield %	153 yield %
1	6	30	31	63
2	60	30	83	10
3	60	60	84	10

Kinetic resolutions with 2-methyl-1,2-DHQ **153** were attempted using (+)-sp **11** (Scheme 84, Table 20). Firstly, 0.8 eq. of *n*-BuLi was added to pre-mixed DHQ **153** and 1.0 eq. of (+)-sp **11** in PhMe and left to stir for 1 h. Acetone was then added and after 30 min, the reaction was quenched by MeOH at –78 °C then warmed to room temperature. The enantioenriched RSM (*S*)-**153** was obtained in 49% with 73:27 er and product (*S*)-**154** in 11% with 78:22 er (Entry 1). Unlike kinetic resolution of other DHQ compounds, kinetic resolution of *N*-Boc-2-methyl-1,2-DHQ **153** gave three

products: the RSM (*S*)-**153**, the acetone quenched product (*S*)-**154** and compound **155**. The products were isolated by column chromatography and from the NMR analysis, compound **155** was *N*-Boc-3-butyl-2-methyl-THQ. The compound **155** was obtained as one enantiomer and likely to be *trans*- isomer. This is most likely because the proton is less acidic, so the carbolithiation competes using the hindered *n*-BuLi/sparteine. The reaction was then repeated by increasing the eq. of chiral base to allow more starting material to be lithiated. However, a similar result was observed with poor er of RSM (*S*)-**153** (Entry 2). Hence, instead of altering the eq., the reaction was left longer before the addition of an electrophile. When the reaction was left for 2 h, less RSM (*S*)-**153** was obtained in 30% with better er of 87:13 (Entry 3). To improve the er, the reaction was repeated with 0.8 eq. of *n*-BuLi, 1.5 eq. of (+)-sp **11** and the reaction was left for 2 h. This resulted in a poorer result of more than 50% of RSM (*S*)-**153** with 65:35 er (Entry 4). When a low yield of RSM is obtained, it is expected that excellent er will be observed. However, for 2-methyl-1,2-DHQ **153**, despite having a low yield of 30%, the er was also not great (87:13 er). Overall, the selectivity of 2-methyl-1,2-DHQ **153** seems poor, so it was not studied further.



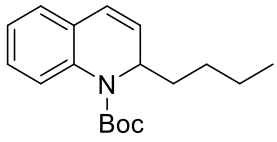
Scheme 84

Table 20

Entry	t/ h	eq. *n*-BuLi	eq. (+)-sp	(*S*)-153 yield %	(*S*)-153 er	(*S*)-154 yield %	(*S*)-154 er	155 yield %	155 er
1	1	0.8	1.0	49	73:27	11	78:22	35	-
2	1	1.0	1.2	45	77:23	30	69:31	23	-
3	2	1.0	1.2	30	87:13	30	69:31	34	59:41
4	2	0.8	1.5	55	65:35	31	60:40	12	60:40

(–)-Angustureine **102** is one of the Hancock alkaloids, a natural product found in the Angostura tree, that has been used to treat fever, chronic diarrhoea and dysentery (Figure 5).[68] It has also been reported to exhibit anti-malarial and cytotoxic activities.[69,70] Hence, synthesis of this motif has been studied and developed extensively by many chemists. Generally, the synthesis is achieved by asymmetric catalytic hydrogenation of quinolines or by rhodium-catalysed hydroamination.[71,72] (–)-Angustureine **102** is a 2-substituted tetrahydroquinoline and we envisaged that it could be synthesised by reduction of an enantioenriched DHQ obtained by kinetic resolution.

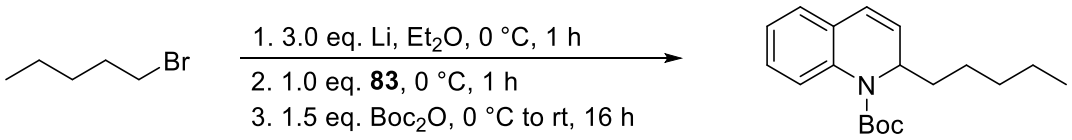
The synthesis of *N*-Boc-2-pentyl-1,2-DHQ **158** was attempted using the same methodology used for other DHQs by halogen lithium exchange with *n*-BuLi. To 1-bromopentane **157** in THF, *n*-BuLi was added followed by quinoline **83** and Boc_2O. Unfortunately, instead of the desired DHQ **158**, *N*-Boc-2-butyl-1,2-DHQ **156** was obtained in 88% yield (Figure 21). To prevent the addition of the butyl group, instead of using *n*-BuLi, lithium wire was used and this allowed successful synthesis of the *N*-Boc-2-pentyl-1,2-DHQ **158** in an excellent yield of 94% (Scheme 85).[73]



156

88%

Figure 21 – Structure of compound 156

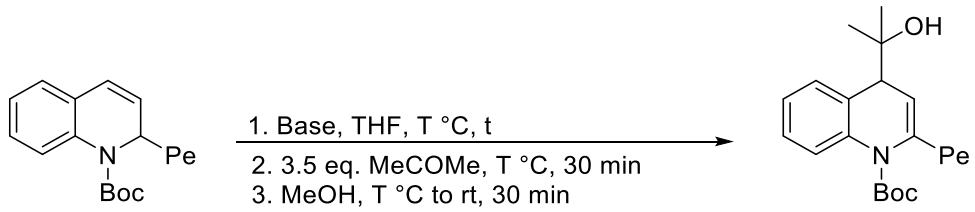


157 **158**

94%

Scheme 85

Racemic lithiation-electrophilic quench of *N*-Boc-2-pentyl-1,2-DHQ **158** was then studied (Scheme 86 and Table 21). DHQ **158** was lithiated at –78 °C in THF using *n*-BuLi, and electrophile acetone was added after 1 h. The desired product **159** was successfully obtained but in a poor yield of 51% alongside the unreacted DHQ **158** in 45% (Entry 1). To ensure more starting material was lithiated, the eq. of *n*-BuLi was increased to 2.0 eq., but the yield of the product **159** did not improve (Entry 2). The lithiation time was then studied by leaving it longer and a slightly better result was obtained (Entries 3, 4 and 5). The reaction was then performed at the higher temperature of –40 °C instead of –78 °C and poorer yield of product **159** was obtained (Entries 6, 7 and 8). Altering the eq. of *n*-BuLi, lithiation time and temperature did not improve the yield of product **159**. So the stronger base *s*-BuLi was used instead of *n*-BuLi, but this still did not give a better result (Entries 9 and 10).



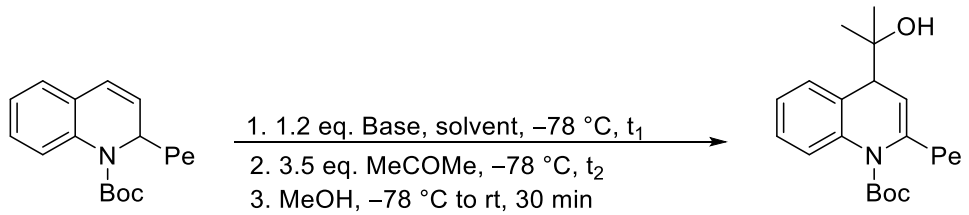
158 **159**

Scheme 86

Table 21

Entry	t/ h	T/ ºC	Base	eq. base	159 yield %	158 yield %
1	1	−78	*n*-BuLi	1.2	51	45
2	1	−78	*n*-BuLi	2.0	53	40
3	2	−78	*n*-BuLi	1.2	63	34
4	4	−78	*n*-BuLi	1.2	65	30
5	6	−78	*n*-BuLi	1.2	64	23
6	1	−40	*n*-BuLi	1.2	30	60
7	2	−40	*n*-BuLi	1.2	35	60
8	3	−40	*n*-BuLi	1.2	17	75
9	1	−78	*s*-BuLi	1.2	58	35
10	2	−78	*s*-BuLi	1.2	56	35

Finally, the reaction was left longer after the addition of the electrophile (Scheme 87, Table 22). Different bases were used: *n*-BuLi, *s*-BuLi with *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA) and *s*-BuLi alone (Entries 1, 2 and 3). The product **159** was obtained in the highest yield (74%) when the reaction was left for 1 h before and after the addition of 3.5 eq. of acetone (Entry 3). The reaction was then left longer to see if it would give even better yield, however this was not the case (Entries 4 and 5). Although the yield of 74% is not excellent, it was decided to move on to the next step.



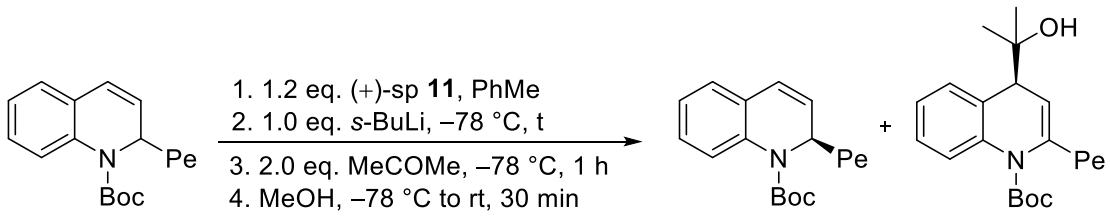
158 **159**

Scheme 87

Table 22

Entry	t_1/ h	t_2/ h	Base	Solvent	159 yield %	158 yield %
1	1	1	*n*-BuLi	THF	46	51
2	1	1	*s*-BuLi, TMEDA	Et_2O	31	67
3	1	1	*s*-BuLi	THF	74	20
4	2	1	*s*-BuLi	THF	68	29
5	2	2	*s*-BuLi	THF	66	30

A kinetic resolution was carried out to obtain enantioenriched starting material (Scheme 88, Table 23). A mixture of DHQ **158** and (+)-sp **11** in PhMe were deprotonated using *s*-BuLi and the mixture was stirred at –78 °C for 1 h. Acetone was added and the reaction was quenched using MeOH at –78 °C and warmed to room temperature over 30 min. This gave both the recovered starting material (*S*)-**158** and product (*S*)-**159** in poor yields and ers. The RSM (*S*)-**158** was isolated in 85% yield with 51:49 er and the product (*S*)-**159** was isolated in 14% yield with 53:47 er (Entry 1). The reaction was left longer for 2 h to be lithiated to ensure more products were obtained. However, the result obtained was similar to the previous result (Entry 2). Despite the low yield of product (*S*)-**159**, the er was also poor. From this, it is most likely that the selectivity of recovered starting material (*S*)-**158** will still be poor even when a yield below 50% is obtained. Hence, the kinetic resolution of 2-pentyl-1,2-DHQ **158** was not studied further.



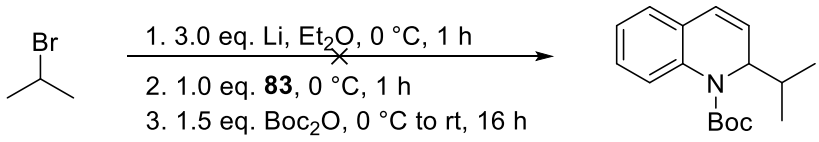
158 (*S*)-**158** (*S*)-**159**

Scheme 88

Table 23

Entry	t/ h	(*S*)-158 yield %	(*S*)-158 er	(*S*)-159 yield %	(*S*)-159 er
1	1	85	51:49	14	52:48
2	2	83	51:49	15	53:47

We thought it would be interesting to see how branched alkyl groups would affect the kinetic resolution. Hence, a synthesis of *N*-Boc-2-(*i*-propyl)-1,2-DHQ **161** was attempted. Thinly sliced lithium wire was added to 2-bromopropane **160** in Et_2O at 0 °C and after 1 h, quinoline **83** and Boc_2O were added (Scheme 89). Unfortunately, the desired DHQ **161** was not synthesised and unreacted quinoline **83** was recovered. The reaction was repeated by leaving it longer, however this still was unsuccessful.

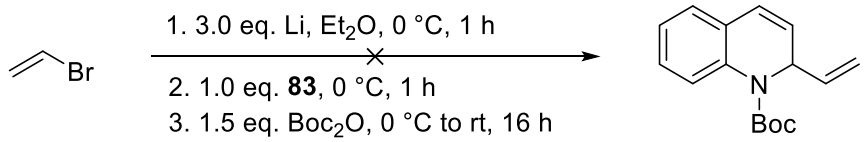


160 **161**

Scheme 89

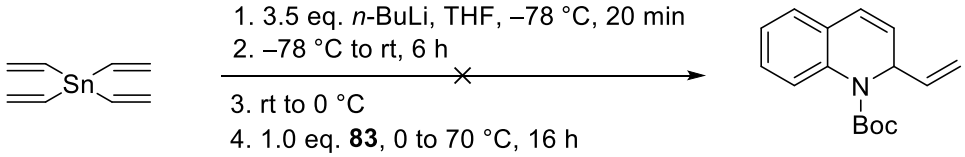
A synthesis of *N*-Boc-2-vinyl-1,2-DHQ **163** was also attempted. Firstly, vinyl bromide **162** and lithium wire were used but this did not give the product **163** and unreacted quinoline **83** was recovered (Scheme 90). A method had been reported in the literature

which involved adding *n*-BuLi to tetravinyltin **164** and stirring at –78 °C for 6 h to form the vinyl lithium.[74] This method was used to synthesise 2-vinyl-DHQ **163** (Scheme 91). However, the synthesis was unsuccessful and unreacted quinoline **83** was obtained.



162 **163**

Scheme 90

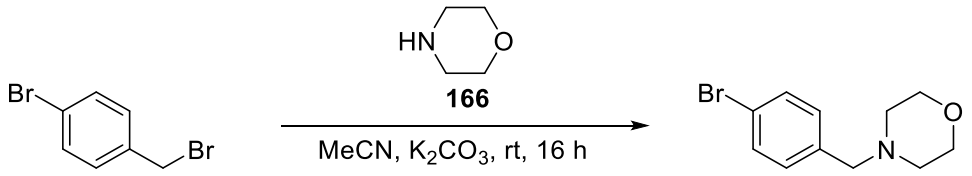


164 **163**

Scheme 91

2.7 Synthesis of the antimalarial drug M5717

Considering the ease of oxidation and reduction of the DHQ, a short route to the antimalarial drug M5717 **103**, which is in clinical trials, was developed (Figure 5).[75] The first step was the synthesis of 4-[(4-bromophenyl)methyl]morpholine **167** (Scheme 92).[76] Morpholine **166** and potassium carbonate (K_2CO_3) were added to 4-bromobenzyl bromide **165** in MeCN and stirred at room temperature overnight. This gave the desired product **167** in an excellent yield of 96%.

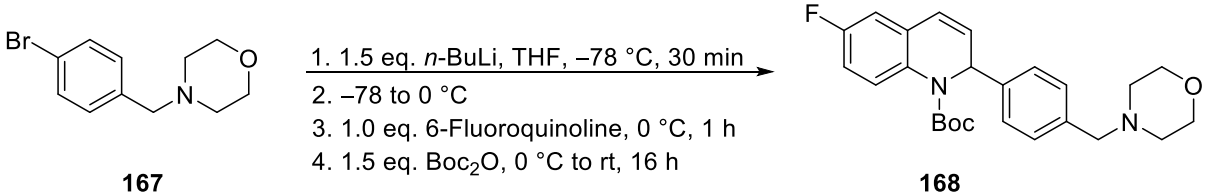


165 **167**

96%

Scheme 92

The second step was a synthesis of the corresponding DHQ **168** from 6-fluoroquinoline (Scheme 93). *n*-BuLi was added to bromide **167** in THF at –78 °C and after 30 min, 6-fluoroquinoline was added at 0 °C. The protecting group Boc_2O was then added and the mixture was left to warm to room temperature overnight. This gave the desired product, the *N*-Boc-6-fluoro-2-{4-[(morpholin-4-yl)methyl]phenyl}-1,2-DHQ **168** in a good yield of 67%.

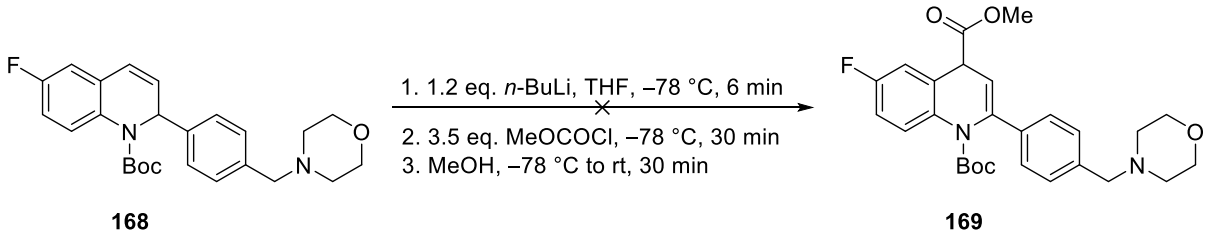


167 **168**

67%

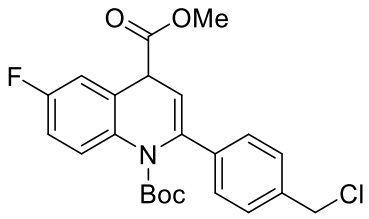
Scheme 93

The second step was a lithiation-electrophilic quench reaction to add the substituent at the 4-position. Using the optimum conditions found for 2-phenyl-1,2-DHQ **104**, DHQ **168** was deprotonated with *n*-BuLi in THF and stirred for 6 min before methyl chloroformate was added (Scheme 94). The desired product **169** was not obtained, and instead compound **170** was formed (Figure 22). It appears that after methyl chloroformate was quenched at the 4-position, the excess methyl chloroformate reacts with the morpholine group, resulting in the formation of an ammonium salt that loses the morpholine ring by displacement with chloride.



168 **169**

Scheme 94

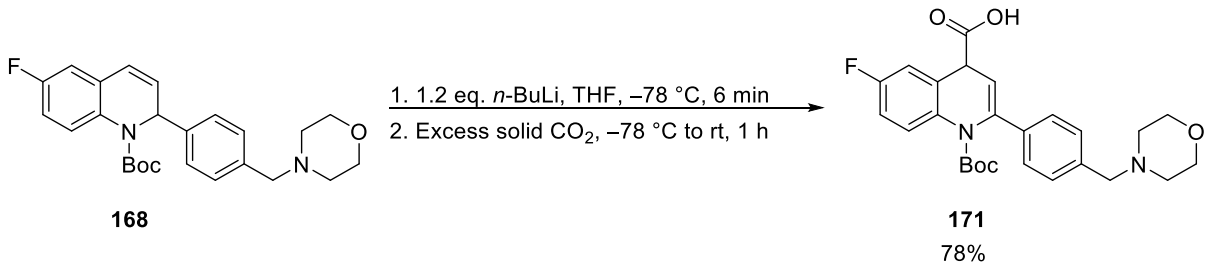


170
25%

Figure 22 – Structure of compound 170

Instead of using methyl chloroformate, a different electrophile had to be used to prevent the loss of the morpholine ring. In addition, one less step will be required if we introduced a carboxylic acid on the 4-position instead of a methyl ester group, as hydrolysis would not need to be done prior to amide formation. Hence, the lithiation-electrophilic quench was performed using solid CO_2 as an electrophile (Scheme 95).

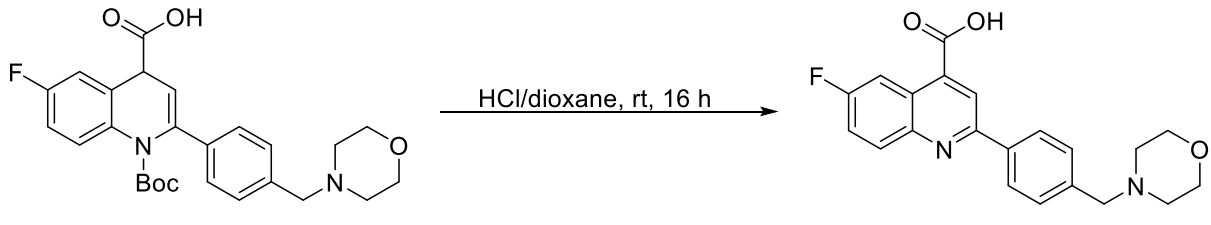
The *n*-BuLi was added to DHQ **168** in THF at –78 °C and after 6 min, milled dry ice was added and the mixture was warmed to room temperature without a suba seal to avoid build-up of pressure. This gave the desired carboxylic acid **171** in excellent yield of 78%.



168 **171** 78%

Scheme 95

With compound **171** in hand the next step involved a Boc deprotection reaction to form the quinoline in acidic conditions using HCl in dioxane (Scheme 96). The mixture was stirred at room temperature overnight. This successfully gave the reduced product, the 6-fluoro-2-{4-[(morpholin-4-yl)methyl]phenyl}-quinoline-4-carboxylic acid **172** in a good yield of 58%. The NMR spectra of product **172** matched the literature.[77] The quinoline **172** is a known compound that can be converted to M5717 drug in a single step by amide formation.[78]



171 **172** 58%

Scheme 96

2.8 Conclusions and Future work

In conclusion, a variety of *N*-Boc-2-aryl-1,2-DHQs have been synthesised successfully in one pot starting from commercially available compounds. These compounds were able to be lithiated by using *n*-BuLi and after quenching the intermediate with various electrophiles, a variety of 4-substituted products were formed. A variable temperature NMR study has been carried out and this supported the hypothesis that the Boc group was rotating quickly.

Kinetic resolutions were successfully carried out with *n*-BuLi/sparteine chiral base and using acetone as electrophile. These gave highly enantioenriched DHQ starting materials in excellent yield. Lithiation-electrophilic quench reactions were then performed and enantioenriched 4-substituted products were formed in good yield, retaining the enantioenrichment.

It was shown that the Boc protecting group was able to be removed under acidic conditions and by oxidation 2,4-disubstituted quinoline was formed. Hydrogenation of the alkene resulted in 2,4-disubstituted tetrahydroquinoline as *cis*- products with almost no loss in enantiopurity. This allowed the synthesis of anti-malarial drug M5717 in an efficient and shorter route than has been reported.

N-Boc-4-methyl-2-phenyl-1,2-DHQ was also successfully synthesised from 4-methylquinoline. The 2,4-disubstituted-1,2-DHQ was lithiated to give 2,4,4-trisubstituted-1,4-DHQ. Either enantiomer of highly enantioenriched 2,4,4-trisubstituted-1,4-DHQs can be obtained using the same enantiomer of sparteine.

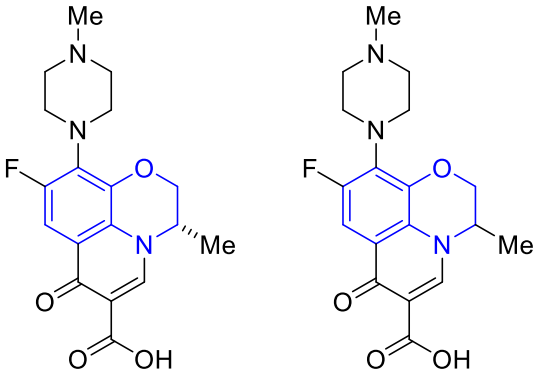
Unfortunately, lithiation-electrophilic quench reactions and kinetic resolution of *N*-Boc-2-alkyl-1,2-DHQ gave poor results.

Synthesis of 2-benzothiophene and 2-pyridine DHQs were attempted but were unsuccessful. In the future, DHQs with other heteroaromatic groups on the 2-position could be synthesised in order to see how this affects the selectivity during kinetic resolution. Likewise, synthesis of DHQ's with alkenyl or alkynyl groups on the 2-position could be tested and it would be interesting to determine where the electrophiles would be quenched.

Chapter 3 – Synthesis of Antibiotic Levofloxacin Analogue

3.1 Introduction to antibiotic levofloxacin

Levofloxacin **173** is one of the most potent antibacterial agents, and one of the most prescribed quinolone class of antibiotic worldwide (Figure 23). It has a broad spectrum activity including anti-fungal, anti-tumour, anti-inflammatory, anti-hypertensive, anti-cancer, anti-rheumatic, anti-allergic, vasorelaxant, anti-arrhythmic, neuroprotective, cytotoxic, and anti-HIV activities.[79] It is used to treat infections caused by either Gram-positive or Gram-negative bacteria, operating with superior pharmacokinetics, pharmacodynamics and ADME properties.[80] Hence, developing new quinolone antibacterial agents that are safer and more potent to deal with the resistant strains is desirable. Also, it is important to develop an efficient route to synthesise the drug, which has relevant medical applications.



173 **174**

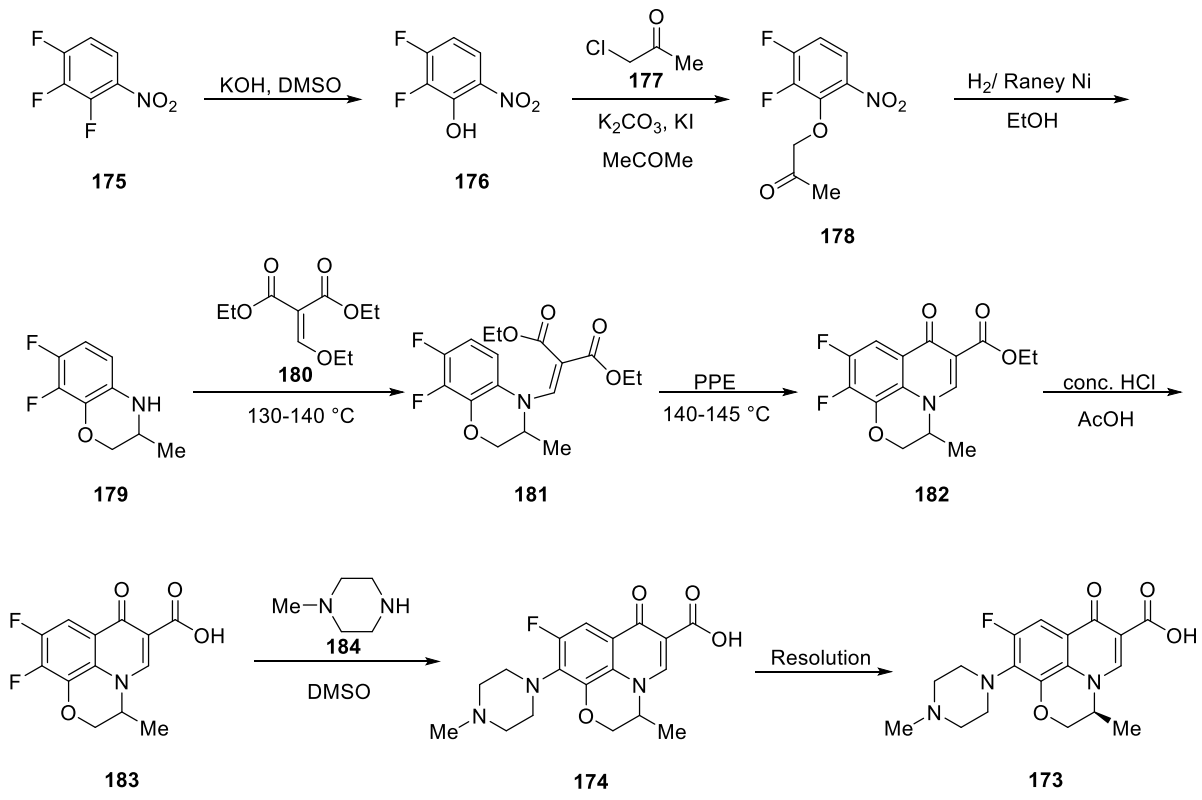
Figure 23 – Structures of levofloxacin and ofloxacin

Levofloxacin **173** is the (*S*)-enantiomer of racemate ofloxacin **174** and it is more selective and more water soluble. The (*S*)-enantiomer is superior to (*R*)-enantiomer as it is 8–128 fold more potent because of greater binding affinity to the DNA-DNA

gyrase complex, involved in the mode of action of this drug.[81-83] Levofloxacin interferes with critical processes, such as DNA replication, transcription, repair and recombination in bacterial cells. It binds effectively to both bacterial DNA gyrase and topoisomerase IV, which are responsible for regulating the DNA structure by forming a negative superhelix, and separating interlocked DNA, respectively. The DNA gyrase contain four subunits: two A subunits and two B subunits.[84] The A subunit is responsible for breaking chromosomal strands and resealing after it forms a superhelix, whilst the B subunit produces negative superhelixes which have been released by the A subunits. Topoisomerase IV is responsible for separating DNA that has been replicated. Hence, by inhibiting both of these enzymes, levofloxacin inhibits the separation of DNA and the action of the A subunit by interfering with the transcription and replication of bacterial DNA. Both mechanisms result in irreparable alteration to the geometry of the DNA strand which leads to cell death.[84]

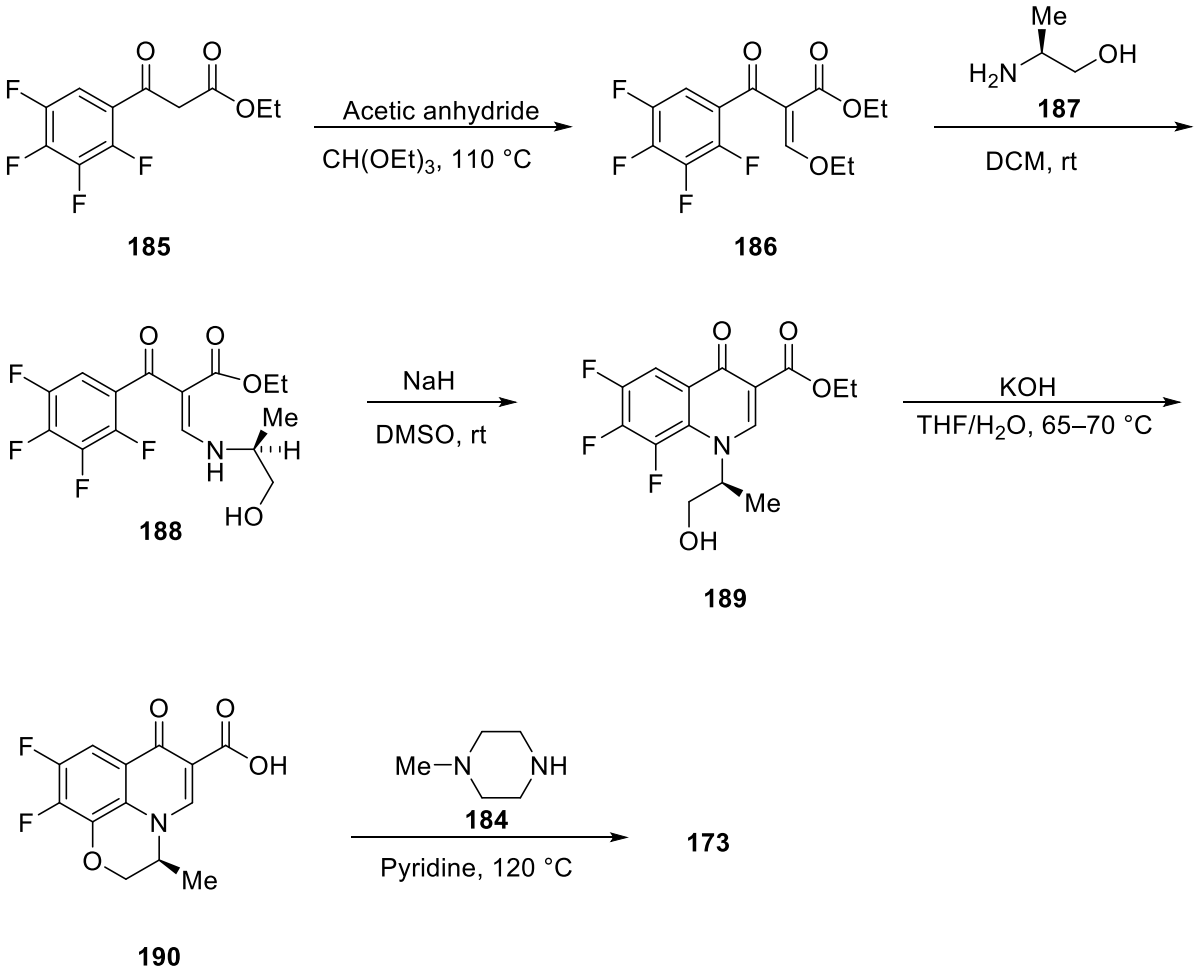
The structure of the antibiotic affects the drug's potency, spectrum activity, safety and distribution in the body. Levofloxacin is a bicyclic heteroaromatic compound with a third ring fused to 3,4-dihydro-*2H*-1,4-benzoxazine. The fluorine atom at the C-8 position and the piperazinyl group at the C-7 position increase potency against Gram-negative bacteria and improve the drug's pharmacokinetic properties by helping binding to the topoisomerase IV enzyme of the bacteria.[81] The methyl substituent on the piperazine ring improves the oral bioavailability of the antibiotic.[81] The carbonyl and carboxylic acid binds to the DNA by hydrogen bonding while the piperazinyl groups bind to the enzyme.

Numerous synthetic routes to levofloxacin have been developed over the last few decades and this is an ongoing interest. In 1984, Hayakawa and co-workers reported the synthesis of levofloxacin using 2,3,4-trifluoro-1-nitrobenzene **175** as starting material (Scheme 97).[85] Firstly, the fluorine atom ortho to the nitro group was displaced by a hydroxyl group using potassium hydroxide (KOH) in dimethyl sulfoxide (DMSO). This was followed by reacting **176** with chloroacetone **177** in the presence of potassium carbonate (K_2CO_3) and potassium iodide (KI) to give 1-(2,3-difluoro-6-nitrophenoxy)-propan-2-one **178**. Then the resulting compound **178** was hydrogenated using Raney nickel in ethanol (EtOH) and gave the cyclic product, 7,8-difluoro-3-methyl-3,4-*2H*-benzoxazine **179**. Using a Gould-Jacobs reaction, diethyl ethoxymethylenemalonate **180** was reacted with amine **179**, followed by a cyclisation using polyphosphoric ester (PPE) to give a tricyclic product **182**. Furthermore, compound **182** was hydrolysed in AcOH and conc. HCl, then the C-7 fluorine atom was displaced by a secondary amine, *N*-methylpiperazine **184**, activated by the carbonyl substituent to give ofloxacin **174**. The enantiomers were resolved by either optical or enzymatic resolution, or crystallization, to obtain more potent levofloxacin **173**.



Scheme 97

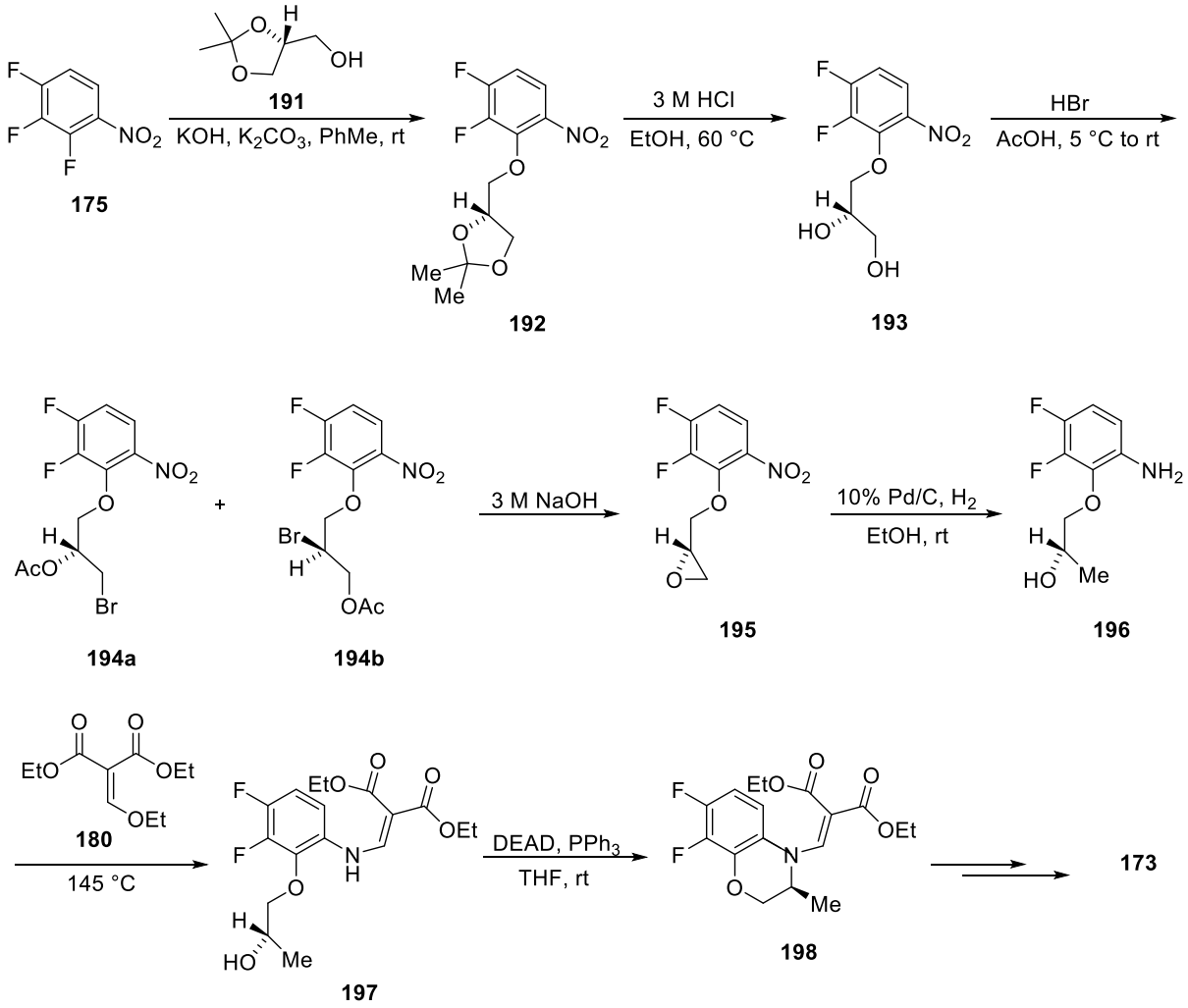
In 1987, the first asymmetric synthesis of levofloxacin **173** was reported by Mitscher and co-workers without having to synthesise Ofloxacin **174** first (Scheme 98).[86] The keto ester **185** and triethyl orthoformate ($CH(OEt)_3$) were heated under reflux in acetic anhydride to give condensation product **186**. Then compound **186** was reacted with (*S*)-2-amino-1-propanol **187** and gave enantioenriched propionate **188**, which was then treated with sodium hydride (NaH) in DMSO. The bicyclic compound **189** was treated with KOH, followed by substitution of the fluorine atom with *N*-methylpiperazine **184** to successfully give enantiomerically pure levofloxacin **173**.



Scheme 98

Chen and co-workers developed an efficient and practical method to synthesise levofloxacin **173** (Scheme 99).[87] The chirality was introduced by reacting 2,3,4-trifluoro-1-nitrobenzene **175** with (*S*)-glycerol acetonide **191**. Ether **192** was then deprotected and treated with hydrogen bromide (HBr) to give a mixture of acetoxy bromide **194a** and **194b** which was then carried forward for epoxidation with aqueous sodium hydroxide (NaOH). Under catalytic hydrogenation, the epoxide was ring-opened and the nitro group was reduced to an amino group. Malonate **180** was then added to amine **196** and cyclised *via* a Mitsunobu reaction to give bicycle **198** which

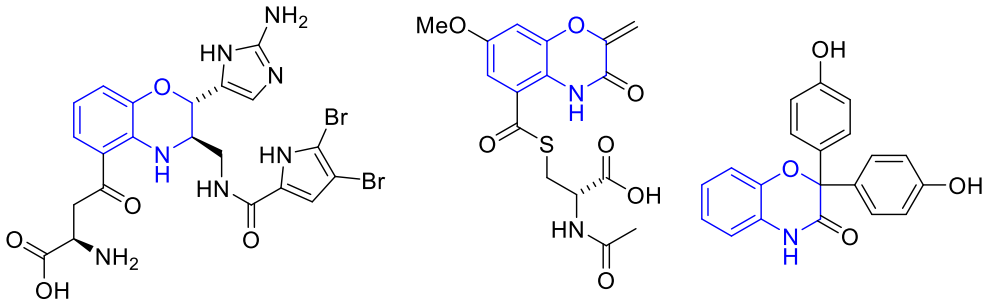
then can be converted to levofloxacin **173** in three steps: cyclisation, hydrolysis and substitution.



Scheme 99

3.2 Introduction to benzoxazine chemistry

Benzoxazines are cyclic subunits, the building blocks found in a wide range of biologically active compounds with relevant medicinal applications. The 1,4-benzoxazine framework is present in a variety of natural products, such as agelamadin C **199** and benzoxacystol **200** (Figure 24).[88,89] The moiety also forms an important part of a number of pharmaceutical compounds, including the laxative bisoxatin **201** and antibiotic levofloxacin **173** (Figure 24).[90,91]



Agelamadin C
199

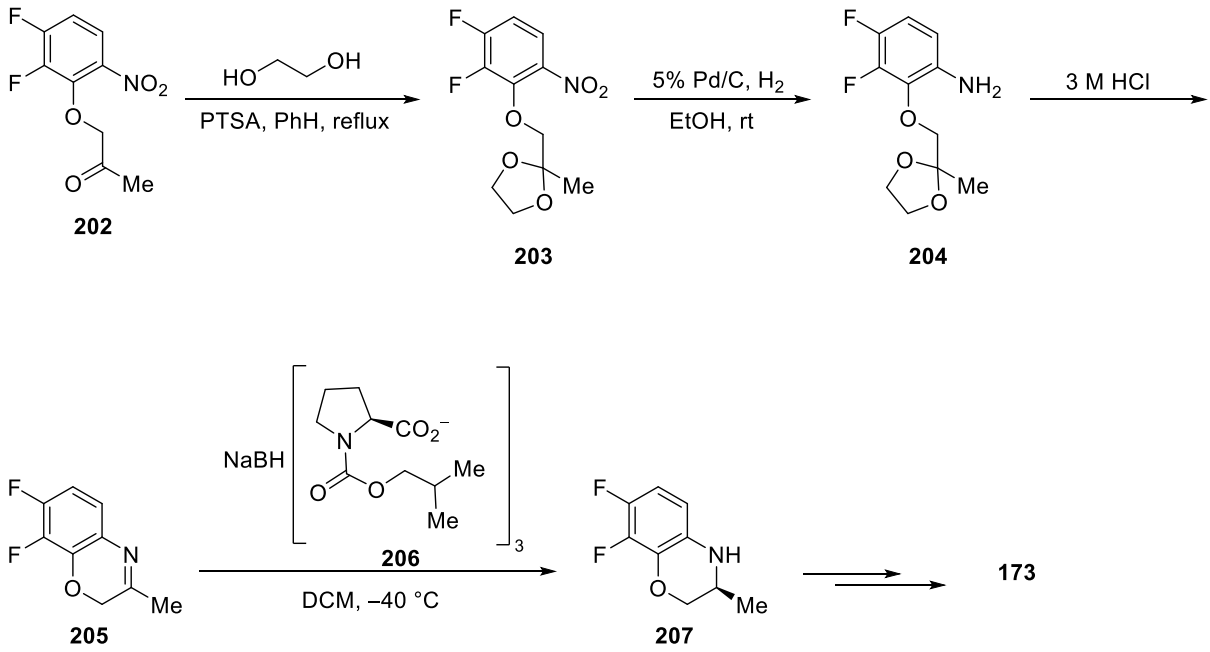
Benzoxacystol
200

Bisoxatin
201

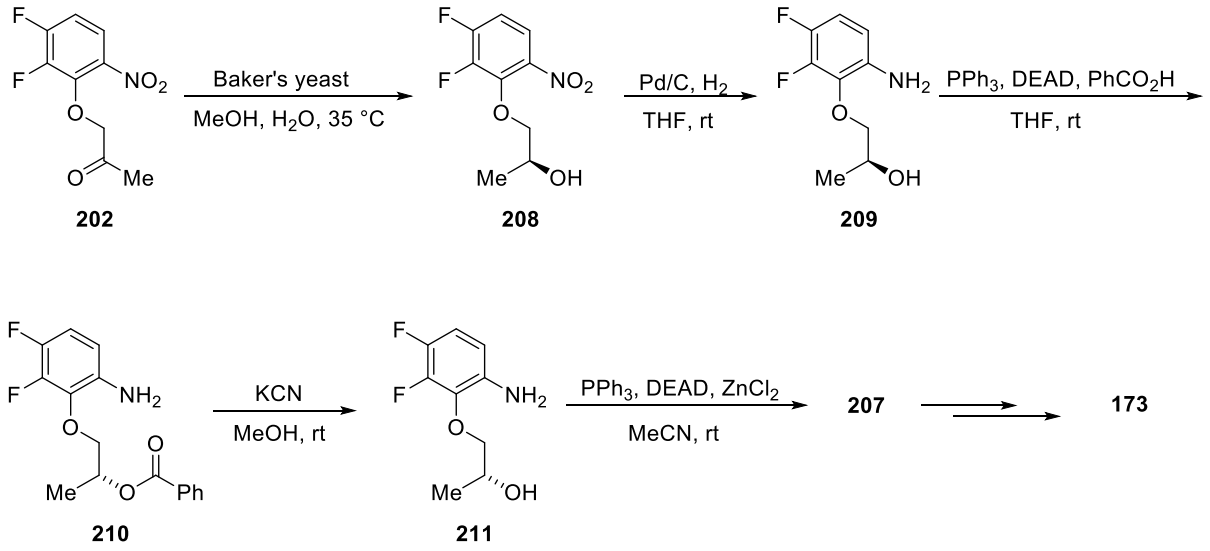
Figure 24 – Structures of compounds with 1,4-benzoxazine framework

Synthesis of racemic and enantioenriched 1,4-benzoxazines has been reported extensively. Hayakawa and co-workers reported asymmetric synthesis by reduction of a cyclic imine with a chiral reagent (Scheme 100).[92] The cyclic imine **205** was prepared in three steps from methyl ketone **202** and reduced enantioselectively using chiral borohydride **206,** to give enantioenriched 7,8-difluoro-3-methyl-1,4-benzoxazine **207**. Compound **207** can also be synthesised from methyl ketone **202** using a different route (Scheme 101).[93] The stereogenic centre can be formed *via* Baker's yeast reduction to give alcohol **208** with excellent er. This can then be followed by reduction of the nitro group to amine **209**. The enantiomer was then inverted under Mitsunobu conditions

and the alcohol group was deprotected using potassium cyanide (KCN). Finally, cyclisation of **211** using triphenylphosphine (PPh_3), diethyl azodicarboxylate (DEAD) and $ZnCl_2$ gave compound **207**.

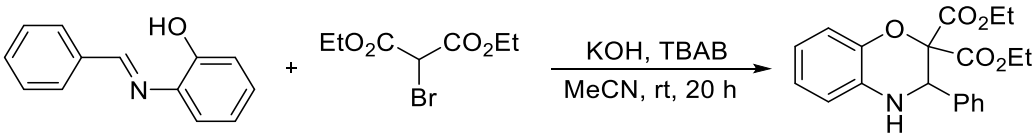


Scheme 100



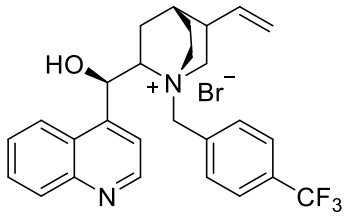
Scheme 101

In 2012, Zhu and co-workers reported a synthesis of 1,4-benzoxazine **214** *via* [5+1] annulation of imines **212** and diethyl α-bromomalonate **213** (Scheme 102).[94] The optimum result was obtained when KOH and tetrabutylammonium bromide (TBAB) were used as base and acetonitrile (MeCN) as solvent with the reaction performed at room temperature. The group have also successfully achieved enantioselective [5+1] annulation to synthesise enantiomerically pure 1,4-benzoxazine. Instead of using the above conditions, chiral quaternary ammonium salts **215** were used as organocatalysts (Figure 25). The base used was K_2CO_3 and the reaction was performed at 20 °C. This successfully afforded chiral 1,4-benzoxazines with good enantioselectivities. The absolute configuration was confirmed by single crystal X-ray analysis.



212 **213** **214**

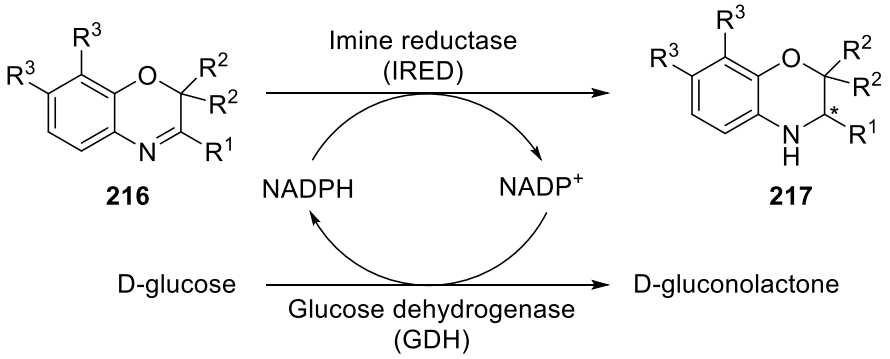
Scheme 102



215

Figure 25 – Structure of chiral quaternary ammonium salts 215

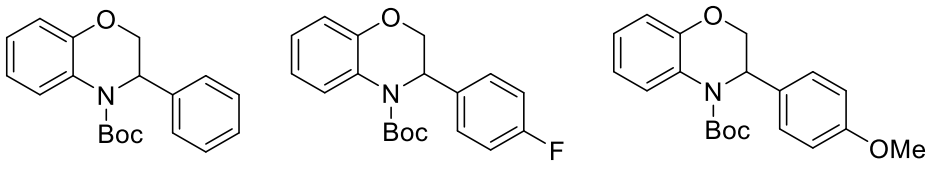
Chiral 1,4-benzoxazines can also be obtained by an enzyme catalysed process (Scheme 103).[95] The enantioselective biocatalytic reduction of cyclic imines **216** uses the reducing agent D-glucose and cofactor NAD(P)H which can be recycled using glucose dehygrogenase. Under these mild conditions and efficient method, enantioenriched 1,4-benzoxazine **217** was obtained with an excellent enantiomer ratio.



Scheme 103

3.3 Previous work

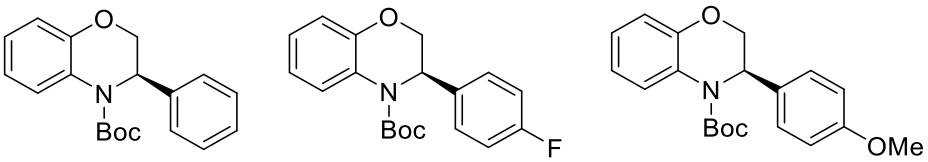
Previously, the Coldham group has been working on the kinetic resolution of three *N*-Boc-3-aryl-3,4-dihydro-*2H*-1,4-benzoxazine derivatives **218**–**220** (Figure 26).[96] The compounds were synthesised using an efficient two step method found in the literature, followed by Boc protection.



218 **219** **220**

Figure 26 – Structures of aryl-3,4-dihydro-*2H*-1,4-benzoxazine derivatives

Kinetic resolution was performed in the presence of base *n*-BuLi and the chiral ligand (+)-sp **11**. When methanol, acetic acid and sodium bicarbonate were used as electrophiles, it resulted in decomposition. It is assumed that the intermediate undergoes elimination to an unstable enaminophenol. However, with ethyl chloroformate, the quenched ring-opened product was obtained. Hence, good yield and excellent enantiomer ratio of recovered benzoxazine (*R*)-**218** were obtained when the optimised conditions of 1.0 eq. of *n*-BuLi, 1.0 eq. of (+)-sp **11** and ethyl chloroformate as electrophile were used. Even with electron-withdrawing or electron-donating substituents, [(*R*)-**219** and (*R*)-**220**] attached on the 3-aryl ring, excellent results of enantioenriched benzoxazines were obtained and the absolute configurations were confirmed by single crystal X-ray analysis (Figure 27).



(*R*)-**218**
39%, 98:2 er

(*R*)-**219**
40%, 97:3 er

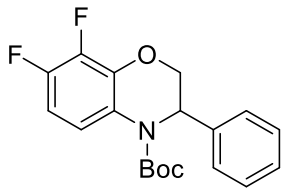
(*R*)-**220**
41%, 98:2 er

Figure 27 – Structures of enantioenriched benzoxazine derivatives

With the successful results already obtained, the focus of the project was now to synthesise and to carry out kinetic resolution reactions on *N*-Boc-7,8-difluoro-3-phenyl-3,4-dihydro-*2H*-1,4-benzoxazine **221** using this methodology. This would allow synthesis of the 3-phenyl derivative of antibiotic levofloxacin **173**, and its bioactivity can be tested and compared with the analogous 3-methyl analogues.

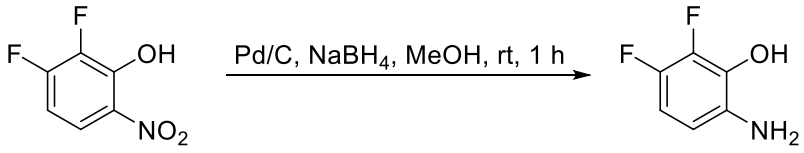
3.4 Synthesis and KR of *N*-Boc-7,8-difluoro-3-phenyl-3,4-dihydro-*2H*-1,4-benzoxazine

The target benzoxazine **221** was unavailable commercially and needed to be prepared from readily available starting materials (Figure 28). The first step was a reduction reaction of 2,3-difluoro-6-nitrophenol **222** (Scheme 104).[97] The starting material was added to 10% palladium on carbon in methanol, then $NaBH_4$ was added at 15 ^oC and the mixture was stirred at room temperature for 1 h. This gave the desired product, the 6-amino-2,3-difluorophenol **223** in a good yield of 83%.



221

Figure 28 – Structure of *N*-Boc-7,8-difluoro-3-phenyl-3,4-dihydro-*2H*-1,4-benzoxazine 221

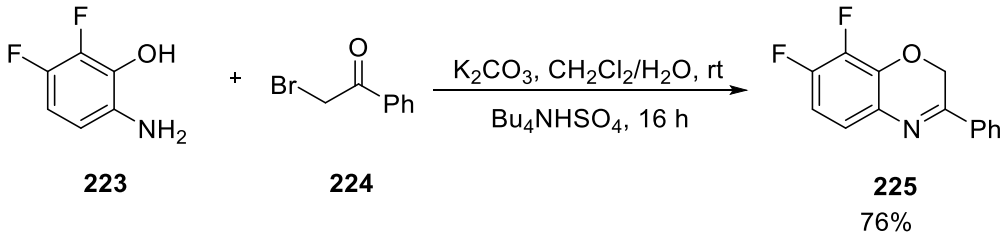


222 **223** 83%

Scheme 104

The second step was a condensation reaction between 6-amino-2,3-difluorophenol **223** and 2-bromoacetophenone **224** in a mixture of DCM and water (Scheme 105).[98] Potassium carbonate was used as a base and tetrabutyl ammonium hydrogen sulfate

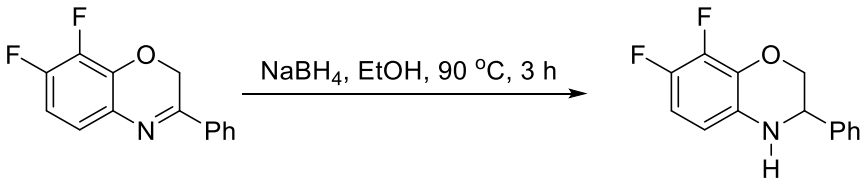
was used as a phase transfer reagent. The mixture was stirred at room temperature overnight. This gave the desired benzoxazine compound **225** in a good yield of 76%.



223 **224** **225**
76%

Scheme 105

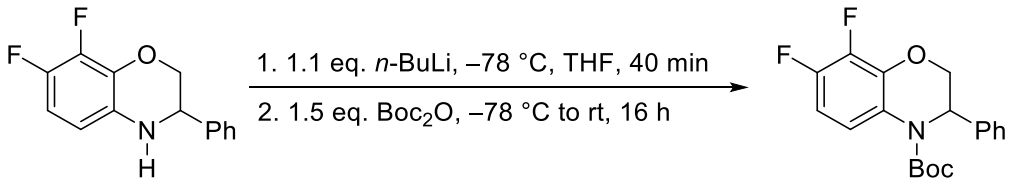
With compound **225** in hand the next step involved a reduction reaction using sodium borohydride ($NaBH_4$) (Scheme 106). The mixture was heated at 90 ^oC in an EtOH and water solvent mixture and stirred for 3 h. This gave the reduced product, the 3,4-dihydro-*2H*-1,4-benzoxazine **226**, in an excellent yield of 93%.



225 **226**
93%

Scheme 106

In the final step of the synthesis, the base *n*-BuLi was used to deprotonate benzoxazine **226** at –78 ^oC. After leaving the mixture to stir for 40 min, a solution of Boc_2O in THF was added. This gave the desired compound **221** in an excellent yield of 90% (Scheme 107).

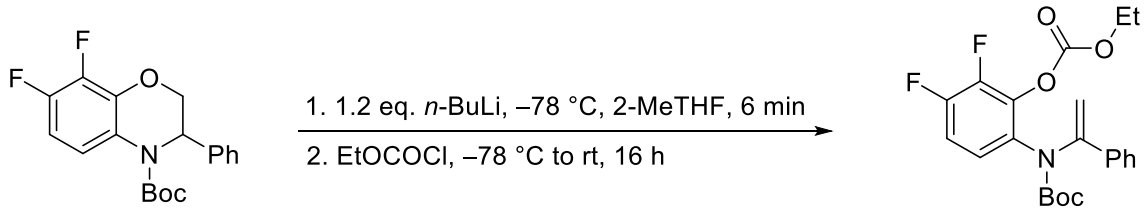


226 **221**

90%

Scheme 107

After successfully synthesising the racemic 3,4-dihydro-*2H*-1,4-benzoxazine **221**, the lithiation-electrophilic quench of the substrate could be tested with *n*-BuLi. The reaction was performed by addition of 1.2 eq. of *n*-BuLi in THF at –78 ºC and after 6 min the electrophile, ethyl chloroformate, was added and the mixture was left to warm up to room temperature overnight. However, it did not give the desired ethyl carbonate product **227**. Hence, the reaction was repeated using the same conditions but a different solvent. Instead of using THF, 2-MeTHF was used and product **227** was obtained in 68% yield (Scheme 108).



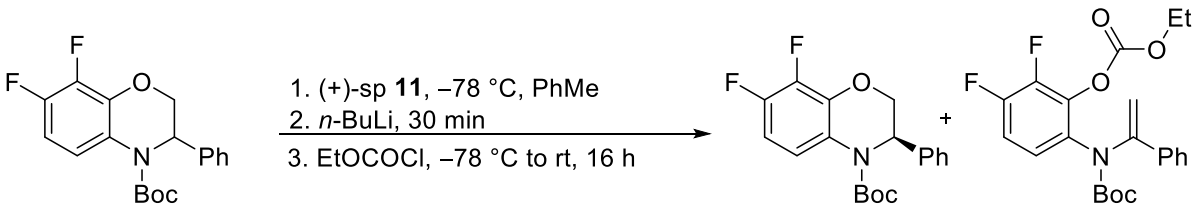
221 **227**

68%

Scheme 108

When synthesising the antibiotic levofloxacin **173**, the major issue is to produce the correct chiral form by identifying correct entries into the benzoxazine core. This issue can be resolved when it is synthesised by kinetic resolution using *n*-BuLi/sparteine. Kinetic resolution was then studied to obtain enantioenriched compound **221**. From

the previous study, it is known that the starting material can be recovered in high er despite forming the ring-opened product instead of the *α*-substituted product. The reaction was studied using different conditions to obtain the optimum result. To begin with, the same conditions from the previous result were used as this had given good yield with excellent er (Scheme 109, Table 24). Hence, 1.0 eq. of *n*-BuLi was added to a mixture of benzoxazine **221** and 1.0 eq. of (+)-sp **11** in PhMe at –78 °C. Then after 30 min, ethyl chloroformate was added as an electrophile. Disappointingly, the yield of recovered starting material (*R*)-**221** was only 13% but with a high er of 94:6 (Entry 1). Further kinetic resolutions were attempted with less *n*-BuLi and (+)-sp **11**. With addition of lower equivalents of the chiral base, a better result was obtained with slightly higher yield of the recovered starting material (*R*)-**221** with excellent er (Entries 2 and 3).



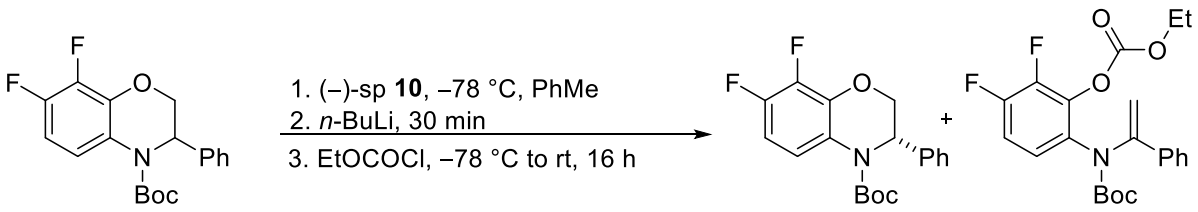
221 (*R*)-**221** **227**

Scheme 109

Table 24

Entry	eq. *n*-BuLi	eq. (+)-sp	(*R*)-221 yield %	(*R*)-221 er	227 yield %	s
1	1.0	1.0	13	94:6	80	3
2	0.9	1.2	20	95:5	73	4
3	0.6	0.8	24	96:4	51	5

Knowing that the (*S*)-enantiomer of ofloxacin is more potent than the (*R*)-enantiomer, it would be more relevant to synthesise the (*S*)-enantiomer of the levofloxacin analogue. This was easily achieved by performing kinetic resolution with (–)-sp **10** (Scheme 110, Table 25). For the first attempt, 0.6 eq. of *n*-BuLi and 0.8 eq. (–)-sp **10** were used and the yield of the recovered starting material was 51% (Entry 1). Therefore, equivalents of the chiral base were then increased and the result was improved, with a yield of 35% and er of 84:16 (Entry 3). When reactions were repeated using the same conditions, the yield of the recovered starting material increased resulting in a poorer enantiomer ratio. This may have been due to the fact that the reaction was performed on a small scale, and so even when the micro syringe was used, it was difficult to be precise about the amount of *n*-BuLi added.



221 (*S*)-**221** **227**

Scheme 110

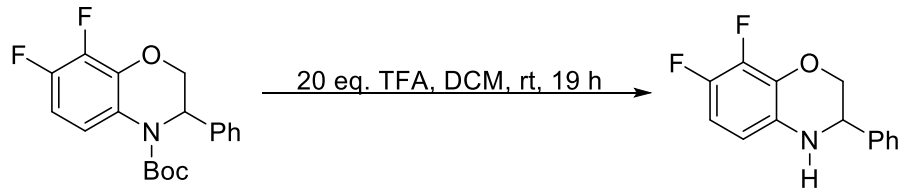
Table 25

Entry	eq. *n*-BuLi	eq. (–)-sp	(*S*)-221 yield %	(*S*)-221 er	(*S*)-221 er after recryst	227 yield %	s
1	0.6	0.8	51	77:23	-	32	6
2	0.6	0.9	47	77:23	95:5	52	5
3	0.7	0.9	35	84:16	98:2	56	4
4	0.7	0.9	45	78:22	98:2	54	4
5	0.7	0.9	49	75:25	94:6	50	5
6	0.7	1.2	28	98:2	-	67	7

There was an issue with the poor enantiomer ratio of some reactions (Entries 2–5). Fortunately, this can easily be improved by recrystallisation from DCM and hexane to give excellent er of the recovered starting material. Excellent er can also be achieved when 1.2 eq. of (–)-sp **10** was used. However, due to the shortage of (–)-sp **10**, slightly poor er of recovered starting material was recrystallised so that more (*S*)-**221** can be obtained for the next step.

3.5 Synthesis of derivative of antibiotic levofloxacin

Before trying to synthesise the derivative of antibiotic levofloxacin **173**, it was first attempted to synthesise the derivative of racemic ofloxacin **174**. The first step was to remove the protecting Boc group under acidic conditions (Scheme 111). This was easily done by adding TFA to compound **221** in DCM and leaving the mixture to stir overnight. The crude product was then purified by column chromatography and 3,4-dihydro-2*H*-1,4-benzoxazine **226** was obtained in excellent yield of 97%.

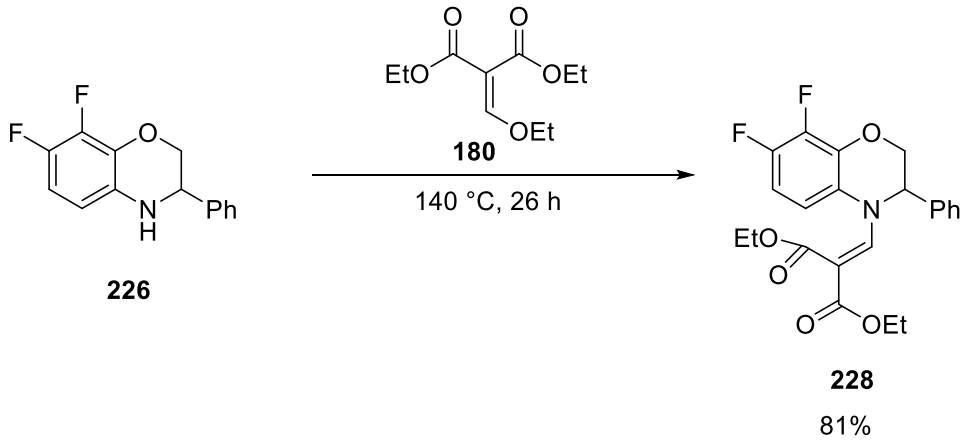


221 **226**

97%

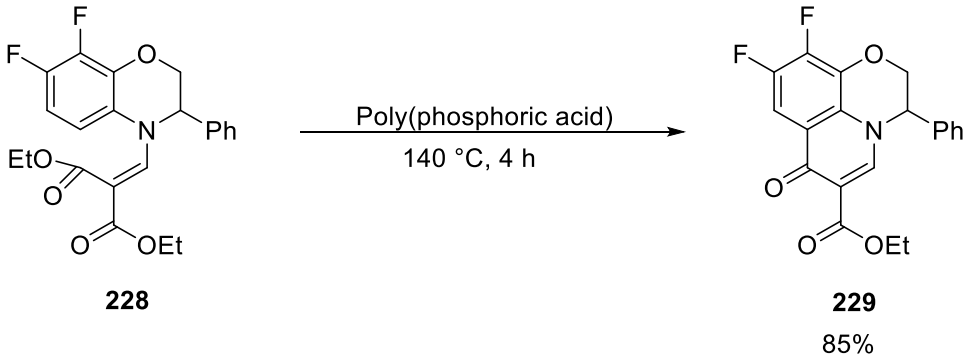
Scheme 111

From the literature search, the next step was the addition of diethyl ethoxymethylenemalonate **180** to amine **226** (Scheme 112).[99] The reaction was performed under neat Gould-Jacobs reaction conditions at 140 ^{o}C for 26 h, and recrystallisation in DCM and hexane successfully gave the desired diester **228** in good yield of 81%.



Scheme 112

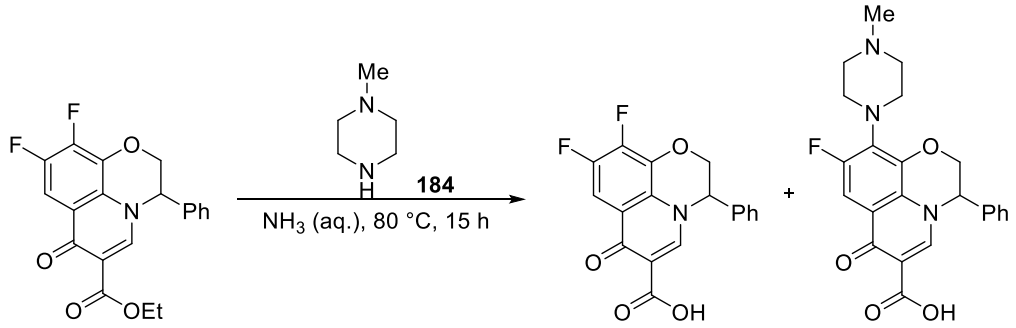
Then diester **228** was converted to ketone **229** by cyclisation (Scheme 113). Poly(phosphoric acid) was added to starting material **228** and the mixture was heated at 140 °C for 4 h.[100] This gave the cyclised product **229** in a good yield.



Scheme 113

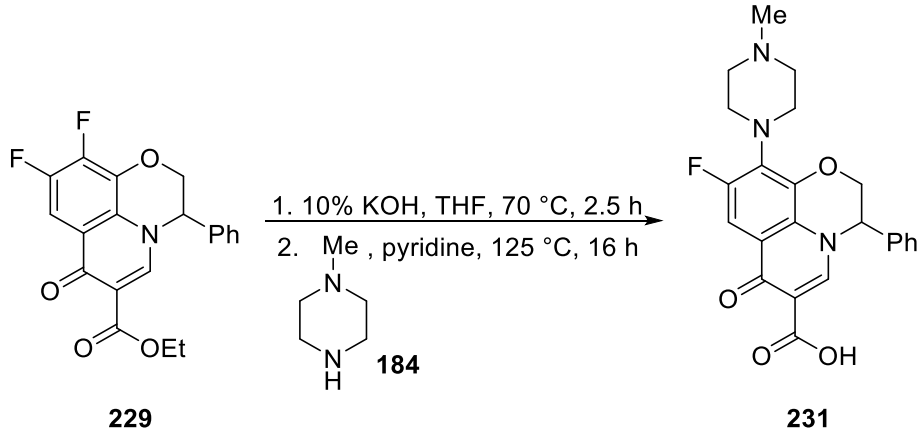
For the next step, it was attempted to perform hydrolysis and substitution in a one pot reaction. The *N*-methylpiperazine **184** was added to carbamate **229** in aq. ammonia (NH_3) and heated at 80 °C overnight (Scheme 114).[101] From the LC-MS chromatogram, it was found that the crude product was a mixture of three compounds: hydrolysed product **230**, desired product **231** and unreacted starting material **229**. Column

chromatography was performed to purify the product **231**, but only unreacted starting material **229** was isolated in 90% yield. The other two compounds were not able to be isolated from the column chromatography. To allow more product **231** to be formed, the reaction was repeated at higher temperature and left to react for longer. However, this did not improve the yield of the product **231**. Hence, different reaction conditions were attempted (Scheme 115). A 10% KOH solution was added to carbamate **229** in THF and heated at 70 °C. After 2.5 h, *N*-methylpiperazine **184** in pyridine was added to the reaction mixture and it was left to stir at 125 °C overnight. Unfortunately, these conditions still gave a mixture of compounds with the major product being the unreacted starting material **229** in 86% yield.



229 **230** **231**

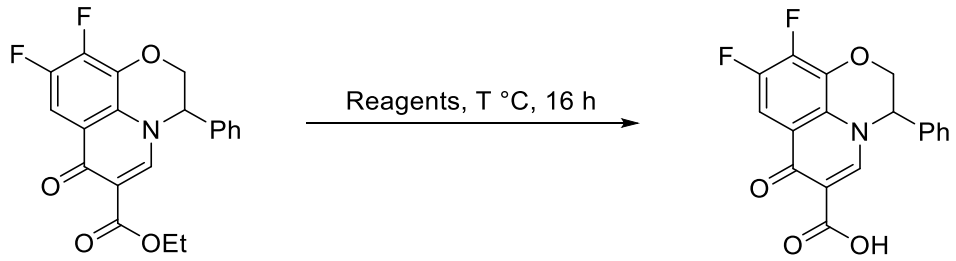
Scheme 114



229 **231**

Scheme 115

Due to poor conversion and inability to separate the compounds, it was decided to perform the hydrolysis step first to obtain the acid product **230** (Scheme 116, Table 26). The hydrolysis was carried out under basic conditions using 10% NaOH in MeOH and 10% KOH in THF, which gave compound **230** in 16% and 17% respectively (Entries 1 and 2). A pure product **230** was successfully obtained, but the yield was poor. So instead, the hydrolysis was performed with water, aq. sulfuric acid (H_2SO_4) and glacial acetic acid and the resulting yield was 32% (Entry 3). The yield of the product **230** was improved to 67% when conc. hydrochloric acid, which is more acidic than the previous acids, was used (Entry 4).



229 **230**

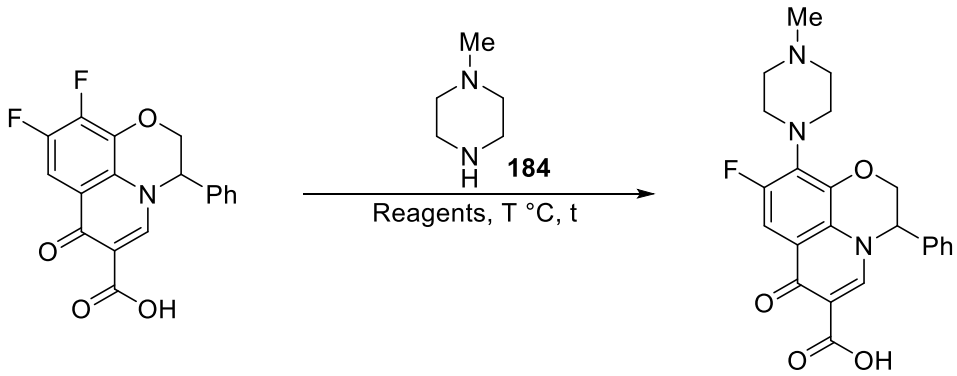
Scheme 116

Table 26

Entry	Reagents	T/ °C	230 yield %
1	10% NaOH	80	16
2	10% KOH	70	17
3	Acetic acid, H_2SO_4	125	32
4	Acetic acid, conc. HCl	90	67

In the final step of the synthesis, nucleophilic aromatic substitution (S_NAr) was performed to substitute the fluorine atom at C-7 with *N*-methylpiperazine **184** (Scheme

117, Table 27). As a first attempt, the reaction was performed under neat conditions and heated at 90 °C overnight (Entry 1). A mixture of products were obtained which were inseparable and could not be purified. So, the reaction was repeated with addition of *N*-methylpiperazine **184** to acid **230** in pyridine and pure product was obtained, though in a poor yield of 6% (Entry 2). When the reaction was performed in MeCN and triethylamine (Et_3N) and left to heat for longer, the yield of the product **231** was improved to 29% (Entries 3 and 4). Unfortunately, the yield of the final product **231** could not be improve any further. It was decided to focus on the synthesis of a derivative of enantioenriched levofloxacin **173**.



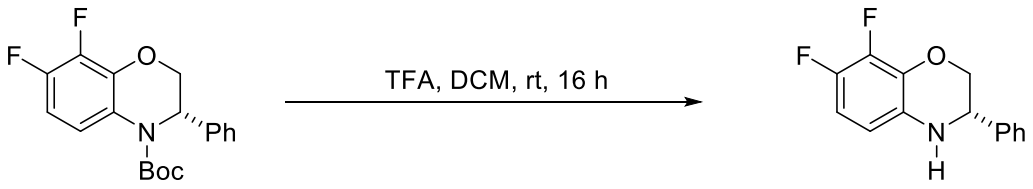
230 **231**

Scheme 117

Table 27

Entry	Reagents	T/ °C	t/ h	231 yield %
1	-	90	16	-
2	Pyridine	120	16	6
3	MeCN, Et_3N	90	16	7
4	MeCN, Et_3N	90	24	29

To synthesise the derivative of antibiotic levofloxacin, enantioenriched benzoxazine **221** obtained from kinetic resolution was used. Firstly, Boc deprotection was performed on (*S*)-**221** which had been recrystallised from DCM and hexane to improve the er (Scheme 118). Removal of the Boc group gave amine (*S*)-**226** with a small loss of enantiopurity.



(*S*)-**221**

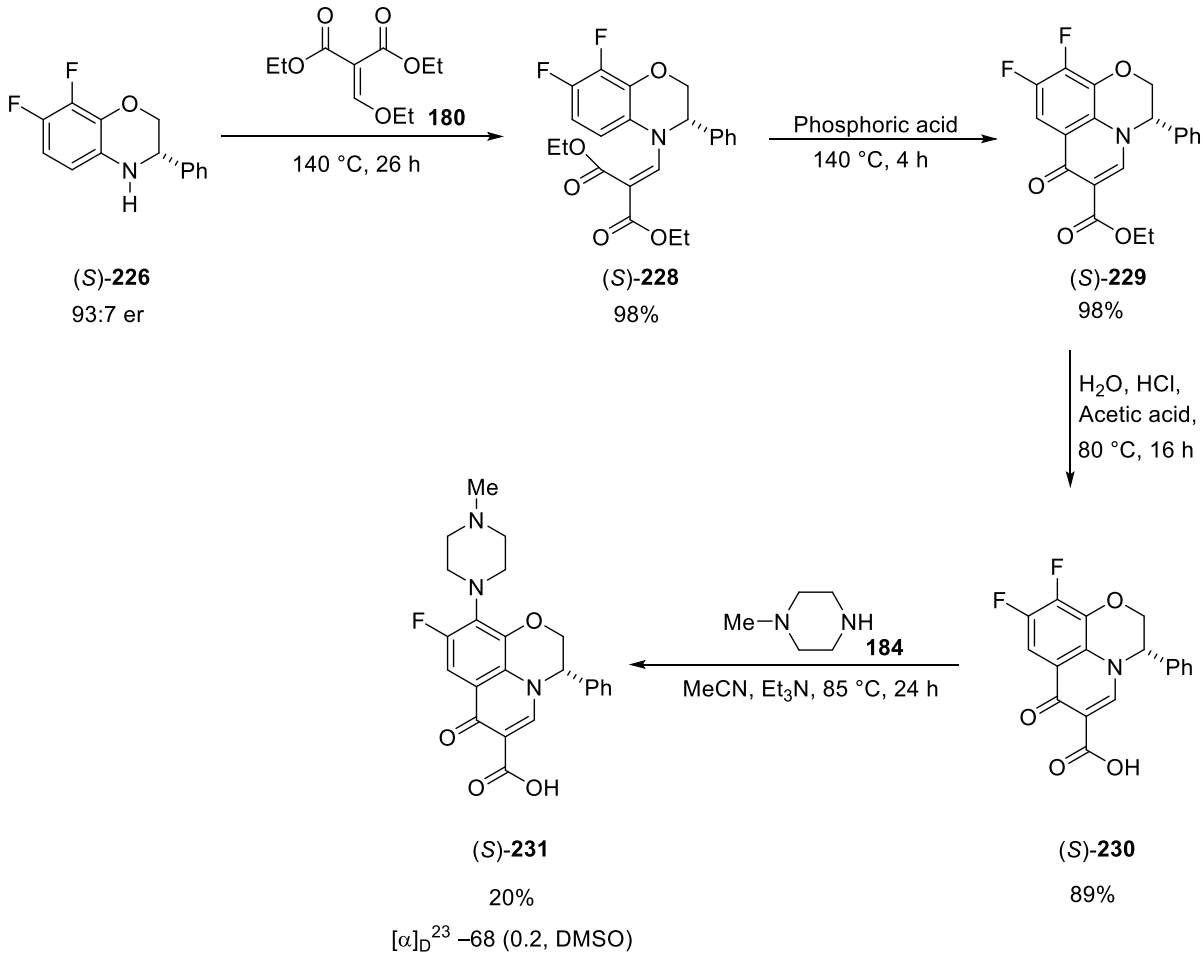
Run 1 80:20 er (recryst 98:2 er)
Run 2 85:15 er (recryst 98:2 er)
Run 3 85:15 er (recryst 98:2 er)

(*S*)-**226**

99% (92:8 er)
88% (95:5 er)
90% (92:8 er)

Scheme 118

To synthesise the derivative of levofloxacin **173**, there were four more steps to perform. Hence, three separate batches of amine (*S*)-**226** were combined and the er was confirmed to be 93:7 by chiral HPLC. With enantioenriched amine (*S*)-**226**, addition, cyclisation, hydrolysis and S_NAr were performed using conditions found from racemic amine **226** (Scheme 119). These four reactions successfully gave the analogue of levofloxacin (S)-**231**. It was not possible to determine the enantiomer ratio of products (*S*)-**228**−(*S*)-**231**, but the desired analogue (*S*)-**231** had a specific rotation of $[\alpha]_D^{23}$ −68 (0.2, DMSO) which proves the compound is not racemic.


F
F
O
N
H
Ph
(S)-226
93:7 er
O
O
EtO
OEt
OEt
180
140 °C, 26 h
F
F
O
N
Ph
EtO
O
O
OEt
(S)-228
98%
Phosphoric acid
140 °C, 4 h
F
F
O
N
Ph
O
O
OEt
(S)-229
98%
H2O, HCl,
Acetic acid,
80 °C, 16 h
F
F
O
N
Ph
O
O
OH
(S)-230
89%
Me–N
NH
184
MeCN, Et3N, 85 °C, 24 h
Me
N
N
F
O
N
Ph
O
O
OH
(S)-231
20%
[α]D23 –68 (0.2, DMSO)

Scheme 119

3.6 Bioactivity study

After successfully synthesising the 3-phenyl analogue of ofloxacin **231** and levofloxacin (*S*)-**231**, their bioactivity was tested and compared to the parent antibiotic levofloxacin **173**. The test was carried out by Carolin, a postdoc in the Fenton group from the Department of Molecular Biology and Biotechnology at the University of Sheffield. The three compounds were dissolved in DMSO (10 mg•mL^{-1}) and mixed with *Streptococcus pneumoniae* (D39 Δ*cps*).[102-107] The cultures were incubated at 37 ^{o}C and samples were taken at regular intervals (Figure 29, Appendix 6). The number of viable cells remaining were compared to a control, a DMSO solvent.

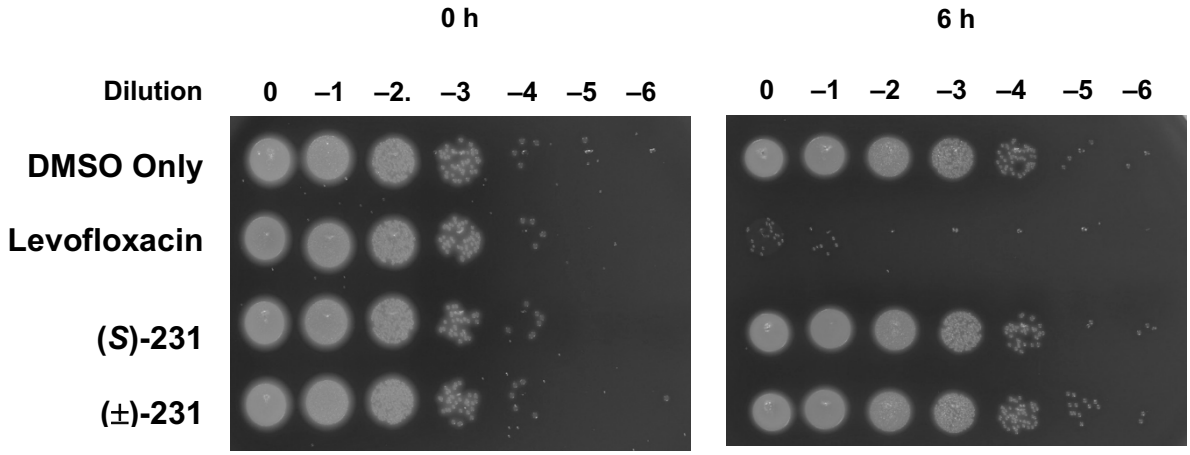


Figure 29 – Antibacterial activity spot assays

In this study, results showed a significant reduction of cell growth and eventually cell death after 6 h when incubated with the antibiotic levofloxacin **173**. In contrast, the synthesised analogues (*S*)-**231** and (±)-**231** had similar profile to the solvent only control and did not reduce cell viability even after 6 h. The test was repeated using a higher concentration of these compounds and similar results were observed. Disappointingly, this means that the analogues do not have any antimicrobial effect,

unlike levofloxacin **173**. Most likely, the presence of a phenyl group at C-3, instead of a methyl group, results in a poor fit in the active site of the target enzyme and hence, these compounds are unable to carry out the antibiotic activity.

3.7 Conclusions and Future work

N-Boc-7,8-difluoro-3-phenyl-3,4-dihydro-*2H*-1,4-benzoxazine was synthesised in four steps from readily available starting material. The kinetic resolution was performed using the chiral ligand sparteine and the base *n*-butyllithium, followed by an electrophilic quench with ethyl chloroformate. The recovered 3,4-dihydro-*2H*-1,4-benzoxazine showed reasonably poor selectivity. However, the enantiopurity can be improved by recrystallisation in DCM and hexane.

The Boc group was then removed and the enantioenriched recovered benzoxazine showed only a small loss of enantiopurity. This successfully led to the synthesis of an analogue of ofloxacin and antibiotic levofloxacin in four steps. Bioactivity was tested on the synthesised 3-phenyl racemic and enantioenriched analogues. Unfortunately, even after being incubated with bacterial cells for 6 h, the two analogues did not kill the cell. Hence, unlike ofloxacin and levofloxacin, they do not have any antimicrobial effect.

Future work will explore synthesis and kinetic resolution on a variety of smaller substituents at the 3-position of benzoxazine, which then can lead to synthesis of analogues of levofloxacin.

Chapter 4 – Experimental

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). Acetone, methyl chloroformate, ethyl chloroformate, trimethylsilyl chloride, allyl bromide and diisopropylamine were freshly distilled from CaH_2, *n*-BuLi was regularly titrated using L-menthol and *N*-(4-phenylbenzylidene)benzylamine in THF, quinoline, (−)-sparteine and (+)-sparteine were freshly distilled. Thin layer chromatography was performed on Merck silica gel 60 F_{254} plates and visualized by UV radiation at 254 nm or by staining with an alkaline $KMnO_4$ dip. Flash column chromatography was carried out on VWR silica gel (40-63 micron mesh). Petrol refers to petroleum ether, b.p. 40−60 ^oC. The ^1H proton 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, at 30 ^oC in deuterated chloroform, deuterated methanol, deuterated benzene or deuterated dimethyl sulfoxide. All chemical shifts are expressed in parts-per-million (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*) are given in Hertz (Hz) to the nearest 0.5 Hz and were corrected. Diastereotopic protons are assigned as CH unless otherwise stated. ^{13}C NMR were recorded on the above instruments at 100 MHz. ^{19}F NMR spectra were recorded on the above instruments at 377 MHz. Low and high resolution (accurate mass) mass spectra were recorded on a Micromass Autospec for Electron Impact (EI) and on a Walter LCT instrument for electrospray (ES) with Time of Flight (TOF) analysis. Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum RX Fourier

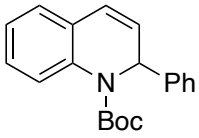
Transform IR system. Only selected peaks are reported and absorption maxima are given in cm^{-1}. Melting points were recorded using a Gallenkamp hot stage and were uncorrected. Specific rotations were calculated from optical rotations recorded on an AA-10 automatic polarimeter. Resolution between the 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 Daicel ChiralPak IA 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. 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.

The selectivity factors (s) in the manuscript were calculated using the formula

$$s = \ln[(1-c)(1-ee)] / \ln[(1-c)(1+ee)]$$

where c is the conversion based on the amount of recovered starting material and ee is the enantiomeric excess of the recovered starting material.

(±)-*tert*-Butyl 2-Phenyl-1,2-dihydroquinoline-1-carboxylate (104)



n-BuLi (25 mL, 58 mmol, 2.3 M in hexane) was added to a solution of bromobenzene **112** (6.1 mL, 58 mmol) in dry THF (20 mL) at −78 °C. After 1 h, a solution of quinoline **83** (4.6 mL, 39 mmol) in dry THF (20 mL) was added at 0 °C. After 1 h, a solution of Boc_2O (13 g, 58 mmol) in dry THF (5 mL) was added dropwise and the mixture was allowed to warm to room temperature over 16 h. The reaction was quenched with MeOH (5 mL) and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (98:2), gave carbamate **104** (7.7 g, 65%) as white needles; m.p. 67−69 °C (no lit. m.p. reported.[56]); R_f 0.45 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3055, 2987, 1695 (C=O), 1265; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63−7.49 (1H, m, ArH), 7.33−7.02 (8H, m, ArH), 6.67 (1H, d, *J* 9.0 Hz, C=CH), 6.26−6.12 (2H, m, C=CH and CH), 1.59 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.5 (C=O), 140.2 (C), 135.3 (C), 128.5 (CH), 128.3 (CH), 127.7 (CH), 127.5 (CH), 127.1 (C), 127.0 (CH), 126.3 (CH), 125.4 (CH), 124.8 (CH), 123.8 (CH), 81.6 (C), 55.3 (CH), 28.4 (CH_3); HRMS (ES) found MH^+, 330.1471. $C_{20}H_{22}NO_2$ requires MH^+, 330.1465; LRMS (ES) 252 (100%, $MH^+ - {}^t$Bu), 330 (60%, MNa^+), 208 (10%, MH^+ −Boc). Data consistent with the literature.[56]

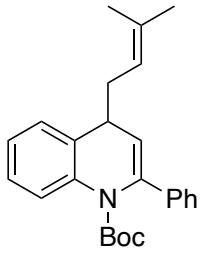
Alternatively,

PhLi (29 mL, 29 mmol) was added to a solution of quinoline **83** (4.6 mL, 39 mmol) in dry THF (50 mL) at −78 °C. After 1 h, a solution of Boc_2O (14.3 g, 65.5 mmol) in dry THF (25 mL) was added dropwise at 0 °C and the mixture was allowed to warm to

room temperature over 16 h. The reaction was quenched with MeOH (2 mL) and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (99:1 → 97:3), gave carbamate **104** (3.9 g, 33%) as a white crystalline solid; data as above.

Resolution between enantiomers of the carbamate **104** was achieved using a Beckman system fitted with a Lux Cellulose−1 column (250 mm × 4.6 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 5.6 min and 6.2 min respectively with an analysis time of 10 min.

(±)-*tert*-Butyl 4-(3-Methylbut-2-en-1-yl)-2-phenyl-1,4-dihydroquinoline-1-carboxylate (110)

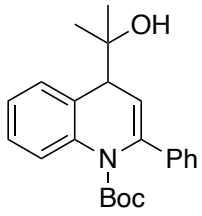


n-BuLi (0.17 mL, 0.40 mmol, 2.4 M in hexane) was added to carbamate **104** (102 mg, 0.330 mmol) in dry THF (4 mL) at −78 °C. After 6 min, prenyl bromide (0.13 mL, 1.2 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room

temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (97:3), gave carbamate **110** (110 mg, 89%) as a colourless oil; R_f 0.62 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3060, 3031, 2971, 2930, 2861, 1713 (C=O), 1601, 1447, 1367, 1316, 1272, 1236, 1160, 1135, 1016, 846, 754, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 (1H, d, *J* 8.0 Hz, ArH), 7.45−7.41 (2H, m, ArH), 7.38−7.29 (4H, m, ArH), 7.20−7.13 (2H, m, ArH), 5.87 (1H, d, *J* 6.5 Hz, C=CH), 5.33−5.22 (1H, m, C=CH), 3.44 (1H, dt, *J* 8.5 and 6.5 Hz, CH), 2.49−2.25 (2H, m, CH_2), 1.76 (3H, s, CH_3), 1.56 (3H, s, CH_3), 1.16 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.5 (C=O), 141.1 (C), 139.3 (C), 139.2 (C), 136.2 (C), 133.9 (C), 128.1 (CH), 127.3 (CH), 126.7 (CH), 125.7 (CH), 125.3 (CH), 124.9 (CH), 124.2 (CH), 121.4 (CH), 120.4 (CH), 81.3 (C), 39.9 (CH), 34.1 (CH_2), 27.7 (CH_3), 25.9 (CH_3), 17.8 (CH_3); HRMS (ES) found MNa^+, 398.2097. $C_{25}H_{29}NO_2Na$ requires MNa^+, 398.2091; LRMS (ES) found 320 (100%, $MH^+ - {}^t$Bu), 398 (50%, MNa^+), 276 (20%, $MH^+ - {}^t$Bu).

Resolution between enantiomers of the carbamate **110** was achieved using a Beckman system fitted with a Lux Cellulose−1 column (250 mm × 4.6 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·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 3.9 min and 4.2 min respectively with an analysis time of 10 min.

(±)-*tert*-Butyl 4-(2-Hydroxypropan-2-yl)-2-phenyl-1,4-dihydroquinoline-1-carboxylate (111)



n-BuLi (0.37 mL, 0.92 mmol, 2.5 M in hexane) was added to carbamate **104** (236 mg, 0.767 mmol) in dry THF (8 mL) at −78 °C. After 6 min, acetone (0.20 mL, 2.7 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (88:12), gave carbamate **111** (260 mg, 92%) as white needles; m.p. 118−120 °C; R_f 0.38 [petrol−EtOAc (6:4)]; FT-IR ν_{max} (film)/cm^{-1} 3058, 2975, 1713 (C=O), 1602, 1582, 1266, 1162; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 (1H, d, *J* 8.0 Hz, ArH), 7.52−7.18 (8H, m, ArH), 5.85 (1H, d, *J* 7.5 Hz, C=CH), 3.55 (1H, d, *J* 7.5 Hz, CH), 1.73 (1H, s, OH), 1.37 (3H, s, CH_3), 1.21 (3H, s, CH_3), 1.14 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.4 (C=O), 142.5 (C), 139.8 (C), 139.2 (C), 131.7 (C), 129.4 (CH), 128.1 (CH), 127.6 (CH), 126.6 (CH), 125.3 (CH), 124.9 (CH), 124.8 (CH), 116.9 (CH), 81.6 (C), 74.9 (C), 51.6 (CH), 27.6 (CH_3), 27.0 (CH_3), 25.9 (CH_3); HRMS (ES) found MNa^+, 388.1890. $C_{23}H_{27}NO_3Na$ requires MNa^+, 388.1883; LRMS (ES) found 266 (100%, MH^+ −Boc), 388 (80%, MNa^+), 292 (30%, MH^+ −^{t}Bu).

Alternatively,

n-BuLi (0.24 mL, 0.60 mmol, 2.5 M in hexane) was added to diisopropylamine (0.08 mL, 0.60 mmol) in dry THF (3 mL) at 0 °C. After 10 min, solution of carbamate **104** (154 mg, 0.502 mmol) in dry THF (3 mL) was added at −78 °C. After 6 min, acetone (0.13 mL, 1.8 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (88:12), gave carbamate **111** (45 mg, 25%) as white needles; data as above.

Alternatively,

n-BuLi (0.34 mL, 0.75 mmol, 2.2 M in hexane) was added to carbamate **104** (193 mg, 0.627 mmol) in dry Et_2O (8 mL) at −78 °C. After 6 min, acetone (0.16 mL, 2.2 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (88:12), gave carbamate **111** (55 mg, 24%) as white needles; data as above.

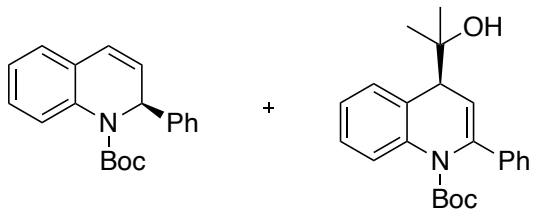
Alternatively,

n-BuLi (0.37 mL, 0.80 mmol, 2.2 M in hexane) was added to carbamate **104** (206 mg, 0.671 mmol) in dry 2-MeTHF (8 mL) at −78 °C. After 6 min, acetone (0.17 mL, 2.4 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure.

Purification by column chromatography on silica gel, eluting with petrol−EtOAc (88:12), gave carbamate **111** (214 mg, 87%) as white needles; data as above.

Resolution between enantiomers of the carbamate **111** was achieved using a Beckman system fitted with a Lux Cellulose−1 column (250 mm × 4.6 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 19.2 min and 22.5 min respectively with an analysis time of 30 min.

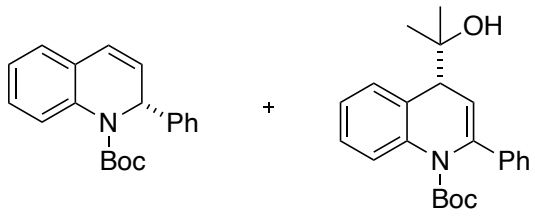
(*S*)-*tert*-Butyl 2-Phenyl-1,2-dihydroquinoline-1-carboxylate ((*S*)-104) and (*S*)-*tert*-butyl 4-(2-Hydroxypropan-2-yl)-2-phenyl-1,4-dihydroquinoline-1-carboxylate ((*S*)-111)



n-BuLi (0.27 mL, 0.62 mmol, 2.3 M in hexane) was added to carbamate **104** (319 mg, 1.04 mmol) and (+)-sparteine (209 mg, 0.893 mmol) in dry toluene (24 mL) at −78 °C. After 30 min, acetone (0.15 mL, 2.1 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with

petrol−EtOAc (88:12), gave carbamate (*S*)-**104** (150 mg, 45%) as white needles; m.p. 49−51 °C (no lit. m.p. reported.[56]); data as above; the enantiomeric ratio was determined to be 99:1 by CSP−HPLC (Cellulose−1, major component eluted at 5.4 min); $[\alpha]_D^{23}$ −609 (1.2, $CHCl_3$) (no lit. specific rotation reported); the carbamate (*S*)-**111** (180 mg, 50%) was also isolated as white needles; m.p. 109−112 °C; data as above; the enantiomeric ratio was determined to be 77:23 by CSP−HPLC (Cellulose−1, major component eluted at 20.8 min); $[\alpha]_D^{23}$ −41 (0.3, $CHCl_3$).

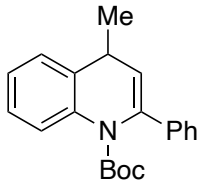
(*R*)-*tert*-Butyl 2-Phenyl-1,2-dihydroquinoline-1-carboxylate ((*R*)-104) and (*R*)-*tert*-butyl 4-(2-Hydroxypropan-2-yl)-2-phenyl-1,4-dihydroquinoline-1-carboxylate ((*R*)-111)



n-BuLi (0.25 mL, 0.58 mmol, 2.3 M in hexane) was added to carbamate **104** (300 mg, 0.975 mmol) and (−)-sparteine (200 mg, 0.854 mmol) in dry toluene (24 mL) at −78 °C. After 30 min, acetone (0.14 mL, 1.9 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (88:12), gave carbamate (*R*)-**104** (140 mg, 47%) as white needles; m.p. 50−52 °C (no lit. m.p. reported.[56]); data as above; the enantiomeric ratio was determined to be 97:3 by CSP−HPLC (Cellulose−1, major component eluted at 6.5 min); $[\alpha]_D^{23}$ +652 (1.2, $CHCl_3$) (no lit. specific rotation reported); the carbamate (*R*)-

111 (180 mg, 50%) was also isolated as white needles; m.p. 105−107 °C; data as above; the enantiomeric ratio was determined to be 82:18 by CSP−HPLC (Cellulose−1, major component eluted at 17.7 min); $[\alpha]_D^{23}$ +51 (0.3, $CHCl_3$).

(±)-*tert*-Butyl 4-Methyl-2-phenyl-1,4-dihydroquinoline-1-carboxylate (113)



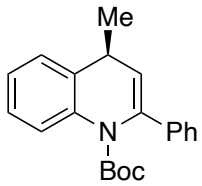
n-BuLi (0.17 mL, 0.42 mmol, 2.5 M in hexane) was added to carbamate **104** (108 mg, 0.350 mmol) in dry THF (4 mL) at −78 °C. After 6 min, methyl iodide (0.08 mL, 1.0 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (98:2), gave carbamate **113** (110 mg, 96%) as yellow needles; m.p. 89−91 °C; R_f 0.47 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3058, 2974, 1711 (C=O), 1486, 1349, 1316, 1134, 1269, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 (1H, d, *J* 8.0 Hz, ArH), 7.49−7.43 (2H, m, ArH), 7.38−7.26 (4H, m, ArH), 7.24−7.20 (2H, m, ArH), 5.83 (1H, d, *J* 5.0 Hz, C=CH), 3.57−3.48 (1H, m, CH), 1.44 (3H, d, *J* 7.0 Hz, CH_3), 1.19 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.5 (C=O), 140.9 (C), 139.1 (C), 139.0 (C), 137.8 (C), 130.1 (CH), 128.1 (CH), 127.3 (CH), 125.7 (CH), 125.3 (CH), 125.2 (CH), 124.2 (CH), 122.3 (CH), 81.4 (C), 33.3 (CH), 27.7 (CH_3), 19.9 (CH_3); HRMS (ES) found MNa^+, 344.1632. $C_{21}H_{23}NO_2Na$ requires MNa^+, 344.1621; LRMS (ES) found 266 (100%, $MH^+ - {}^t$Bu), 344 (16%, MNa^+), 222 (8%, MH^+ −Boc), 322 (2%, MH^+).

Alternatively,

n-BuLi (0.26 mL, 0.64 mmol, 2.5 M in hexane) was added to diisopropylamine (0.09 mL, 0.64 mmol) in dry THF (3 mL) at 0 °C. After 10 min, solution of carbamate **104** (164 mg, 533 mmol) in dry THF (3 mL) was added at −78 °C. After 6 min, methyl iodide (0.12 mL, 1.9 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (98:2), gave carbamate **113** (34 mg, 20%) as yellow needles; data as above.

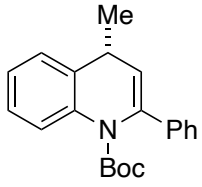
Resolution between enantiomers of the carbamate **113** was achieved using a Beckman system fitted with a Lux Cellulose−1 column (250 mm × 4.6 mm i.d.) as the stationary phase with a mixture of *n*-hexane−isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1.0 $mL \cdot min^{-1}$; ambient temperature, 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 4.8 min and 6.1 min respectively with an analysis time of 10 min.

(*S*)-*tert*-Butyl 4-Methyl-2-phenyl-1,4-dihydroquinoline-1-carboxylate ((*S*)-113)



n-BuLi (0.17 mL, 0.39 mmol, 2.3 M in hexane) was added to carbamate (*R*)-**104** (100 mg, 0.352 mmol, er 97:3) in dry THF (4 mL) at −78 °C. After 6 min, methyl iodide (0.07 mL, 1.0 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (98:2), gave carbamate (*S*)-**113** (56 mg, 54%) as yellow needles; m.p. 60−62 °C; data as above; the enantiomeric ratio was determined to be 92:8 by CSP−HPLC (Cellulose−1, major component eluted at 4.2 min); $[\alpha]_D^{23}$ +50 (0.8, $CHCl_3$).

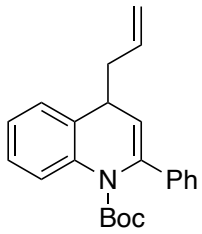
(*R*)-*tert*-Butyl 4-Methyl-2-phenyl-1,4-dihydroquinoline-1-carboxylate ((*R*)-113)



n-BuLi (0.15 mL, 0.36 mmol, 2.4 M in hexane) was added to carbamate (*S*)-**104** (92 mg, 0.30 mmol, er 99:1) in dry THF (4 mL) at −78 °C. After 6 min, methyl iodide (0.07 mL, 1.1 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure.

Purification by column chromatography on silica gel, eluting with petrol−EtOAc (98:2), gave carbamate (*R*)-**113** (85 mg, 89%) as yellow needles; m.p. 68−70 °C; data as above; the enantiomeric ratio was determined to be 98:2 by CSP−HPLC (Cellulose−1, major component eluted at 6.1 min); $[\alpha]_D^{23}$ −79 (0.2, $CHCl_3$).

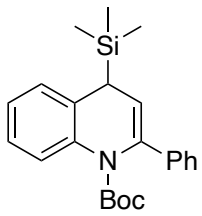
(±)-*tert*-Butyl 4-(Prop-2-en-1-yl)-2-phenyl-1,4-dihydroquinoline-1-carboxylate (114)



n-BuLi (0.19 mL, 0.44 mmol, 2.4 M in hexane) was added to carbamate **104** (114 mg, 0.371 mmol) in dry THF (4 mL) at −78 °C. After 6 min, allyl bromide (0.11 mL, 1.3 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (96:4), gave carbamate **114** (120 mg, 95%) as a white amorphous solid; m.p. 52−54 °C; R_f 0.50 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3077, 3031, 2999, 2972, 2937, 2905, 1710 (C=O), 1484, 1320, 1162, 1134, 918, 768, 754, 699, 634; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 (1H, d, *J* 8.0 Hz, ArH), 7.48−7.42 (2H, m, ArH), 7.38−7.28 (4H, m, ArH), 7.22−7.15 (2H, m, ArH), 5.94−5.82 (2H, m, C=CH), 5.10−5.02 (2H, m, $C=CH_2$), 3.53 (1H, dd, *J* 13.5 and 6.5 Hz, CH), 2.53−2.37 (2H, m, CH_2), 1.17 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.5 (C=O), 141.6 (C), 139.3 (C), 139.2 (C), 135.6 (C),

135.4 (CH), 128.1 (CH), 127.4 (CH), 126.6 (CH), 125.9 (CH), 125.3 (CH), 125.0 (CH), 124.3 (CH), 119.4 (CH), 117.1 (CH_2), 81.3 (C), 40.0 (CH_2), 39.2 (CH), 27.7 (CH_3); HRMS (ES) found MNa^+, 370.1790. $C_{23}H_{25}NO_2Na$ requires MNa^+, 370.1778; LRMS (ES) found 292 (100%, $MH^+ - {}^tBu$), 370 (56%, MNa^+), 348 (3%, MH^+).

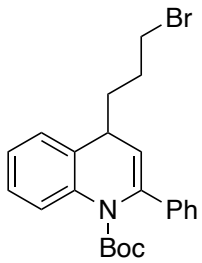
(±)-*tert*-Butyl 4-(Trimethylsilyl)-2-phenyl-1,4-dihydroquinoline-1-carboxylate (115)



n-BuLi (0.21 mL, 0.51 mmol, 2.4 M in hexane) was added to carbamate **104** (131 mg, 0.426 mmol) in dry THF (5 mL) at −78 °C. After 6 min, trimethylsilyl chloride (0.19 mL, 1.5 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (96:4), gave carbamate **115** (140 mg, 87%) as a white amorphous solid; m.p. 95−97 °C; R_f 0.58 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3058, 2996, 1709 (C=O), 1249, 840 (Si−C); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.83 (1H, d, *J* 8.0 Hz, ArH), 7.43−7.20 (6H, m, ArH), 7.13 (1H, t, *J* 7.5 Hz, ArH), 6.97−6.95 (1H, m, ArH), 5.89 (1H, d, *J* 7.5 Hz, C=CH), 3.06 (1H, d, *J* 7.5 Hz, CH), 1.15 (9H, s, ^tBu), 0.11 (9H, s, 3 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.4 (C=O), 139.8 (C), 137.7 (C), 137.2 (C), 135.2 (C), 128.0 (CH), 126.7 (CH), 126.4 (CH), 124.9 (CH), 124.8 (CH), 124.7 (CH), 124.6 (CH), 119.0 (CH), 81.0 (C), 36.1 (CH), 27.7 (CH_3), −3.0 (CH_3); HRMS (ES) found MNa^+, 402.1866.

$C_{23}H_{29}NO_2SiNa$ requires MNa^+, 480.1860; LRMS (ES) found 324 (100%, $MH^+ - {}^tBu$), 280 (2%, MH^+ −Boc), 380 (1%, MH^+).

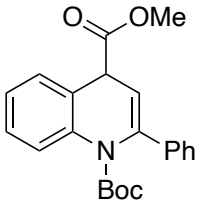
(±)-*tert*-Butyl 4-(3-Bromopropyl)-2-phenyl-1,4-dihydroquinoline-1-carboxylate (116)



n-BuLi (0.21 mL, 0.51 mmol, 2.4 M in hexane) was added to carbamate **104** (130 mg, 0.422 mmol) in dry THF (5 mL) at −78 °C. After 6 min, 1,3-dibromopropane (0.15 mL, 1.5 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (96:4), gave carbamate **116** (140 mg, 78%) as a white amorphous solid; m.p. 78−80 °C; R_f 0.45 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3037, 2987, 2970, 2923, 2911, 2841, 1709 (C=O), 1651, 1487, 1365, 1336, 1317, 1270, 1156, 1134, 1016, 840, 756, 699, 618; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 (1H, d, *J* 8.0 Hz, ArH), 7.49−7.42 (2H, m, ArH), 7.38−7.29 (4H, m, ArH), 7.23−7.13 (2H, m, ArH), 5.88 (1H, d, *J* 6.5 Hz, C=CH), 3.51−3.37 (3H, m, CH and CH_2), 2.06−1.93 (2H, m, CH_2), 1.90−1.73 (2H, m, CH_2), 1.17 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.5 (C=O), 141.9 (C), 139.2 (C), 139.1 (C), 135.5 (C), 128.1 (CH), 127.5 (CH), 126.8 (CH), 126.1 (CH), 125.3 (CH), 125.1 (CH), 124.5 (CH), 119.2 (CH), 81.6 (C), 38.9 (CH), 34.4 (CH_2), 33.7 (CH_2), 30.0

(CH_2), 27.7 (CH_3); HRMS (ES) found MNa^+, 452.1040. $C_{23}H_{26}{}^{81}BrNO_2Na$ requires MNa^+, 452.1022; LRMS (ES) found 370 (100%, $MH^+ - {}^tBu$ (^{79}Br)), 372 (99%, $MH^+ - {}^tBu$ (^{81}Br)), 452 (44%, MNa^+ (^{81}Br)), 450 (43%, MNa^+ (^{79}Br)).

(±)-1-*tert*-Butyl 4-Methyl 2-phenyl-1,4-dihydroquinoline-1,4-dicarboxylate (117)



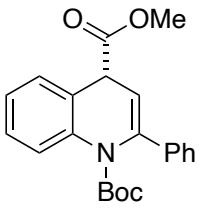
n-BuLi (0.34 mL, 0.85 mmol, 2.5 M in hexane) was added to carbamate **104** (218 mg, 0.710 mmol) in dry THF (8 mL) at −78 °C. After 6 min, methyl chloroformate (0.19 mL, 2.5 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (96:4), gave carbamate **117** (210 mg, 86%) as a yellow amorphous solid; m.p. 94−96 °C; R_f 0.37 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 2973, 2950, 1732 (C=O), 1713 (C=O), 1488, 1354, 1321, 1207, 1137, 1157, 1009, 846, 756, 700, 625, 566; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 (1H, d, *J* 8.0 Hz, ArH), 7.53−7.46 (2H, m, ArH), 7.42−7.31 (4H, m, ArH), 7.26−7.19 (2H, m, ArH), 5.90 (1H, d, *J* 6.5 Hz, C=CH), 4.45 (1H, d, *J* 6.5 Hz, CH), 3.70 (3H, s, CH_3), 1.18 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.3 (C=O), 152.3 (C=O), 143.4 (C), 139.0 (C), 138.5 (C), 130.3 (C), 128.2 (CH), 127.9 (CH), 127.2 (CH), 127.1 (CH), 125.5 (CH), 125.3 (CH), 124.9 (CH), 113.0 (CH), 81.6 (C), 52.6 (CH_3), 45.9 (CH), 27.7 (CH_3); HRMS (ES) found MNa^+, 388.1537. $C_{22}H_{23}NO_4Na$ requires MNa^+, 388.1519; LRMS (ES) found 388 (100%, MNa^+), 266 (59%, MH^+ −Boc).

Alternatively,

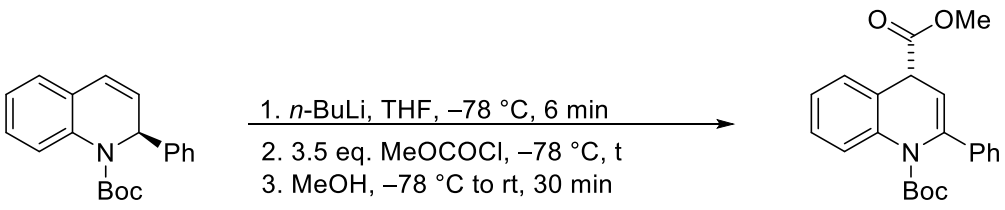
n-BuLi (0.32 mL, 0.70 mmol, 2.2 M in hexane) was added to carbamate **104** (181 mg, 0.587 mmol) in dry THF (7 mL) at −78 ^{o}C. After 6 min, methyl cyanoformate (0.16 mL, 2.1 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (96:4), gave carbamate **117** (110 mg, 50%) as a yellow amorphous solid; data as above.

Resolution between enantiomers of the carbamate **117** was achieved using a Beckman system fitted with a Lux Cellulose−1 column (250 mm × 4.6 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·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 10.4 min and 12.9 min respectively with an analysis time of 20 min.

(*R*)-1-*tert*-Butyl 4-Methyl 2-phenyl-1,4-dihydroquinoline-1,4-dicarboxylate ((*R*)-117)



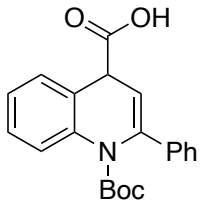
n-BuLi (0.16 mL, 0.40 mmol, 2.5 M in hexane) was added to carbamate (*S*)-**104** (102 mg, 0.332 mmol, 99:1 er) in dry THF (4 mL) at −78 °C. After 6 min, methyl chloroformate (0.09 mL, 1.0 mmol) was added and the mixture was stirred for a further 5 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (96:4), gave carbamate (*R*)-**117** (97 mg, 80%) as a yellow amorphous solid; m.p. 89−91 °C; data as above; the enantiomeric ratio was determined to be 88:12 by CSP−HPLC (Cellulose−1, major component eluted at 12.7 min); $[\alpha]_D^{23}$ −30 (0.3, $CHCl_3$).



(*S*)-**104** (*R*)-**117**

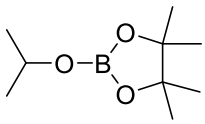
Entry	eq. *n*-BuLi	t/ min	(*S*)-104 er	(*R*)-117 yield %	(*R*)-117 er
1	1.2	30	99:1	75	75:25
2	1.0	30	99:1	63	77:23
3	1.2	5	99:1	80	88:12

(±)-1-[(*tert*-Butoxy)carbonyl]-2-phenyl-1,4-dihydroquinoline-4-carboxylic acid (118)



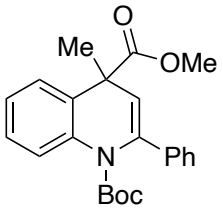
n-BuLi (0.36 mL, 0.87 mmol, 2.4 M in hexane) was added to carbamate **104** (223 mg, 0.725 mmol) in dry THF (9 mL) at −78 °C. After 6 min, milled dry ice[59] was added and the mixture was stirred for at room temperature. After 1 h, the solvent was removed under reduced pressure. The residue was dissolved in H_2O (25 mL) and DCM (25 mL) and the organic layers were removed. The aqueous layer was washed with DCM (3 x 25 mL) and acidified with 1 M aqueous HCl to pH 2. The mixture was then extracted with DCM (4 x 25 mL). The combined organic layers were dried using $MgSO_4$, filtered and the solvent was removed under reduced pressure to give carbamate **118** (160 mg, 61%) as a yellow amorphous solid; m.p. 136−138 °C; R_f 0.16 [petrol−EtOAc (5:5)]; FT-IR ν_{max} (film)/cm^{-1} 3073, 3031, 2981, 2930, 1711 (C=O), 1490, 1353, 1316, 1271, 1249, 1136, 1158, 1118, 1013, 755, 696, 666, 628, 600; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 (1H, d, *J* 8.0 Hz, ArH), 7.53−7.46 (2H, m, ArH), 7.43−7.30 (4H, m, ArH), 7.28−7.26 (2H, m, ArH), 5.88 (1H, d, *J* 7.0 Hz, C=CH), 4.42 (1H, d, *J* 7.0 Hz, CH), 1.16 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.5 (C=O), 152.3 (C=O), 143.8 (C), 139.0 (C), 138.4 (C), 129.7 (C), 128.2 (CH), 128.0 (CH), 127.4 (CH), 127.2 (CH), 125.6 (CH), 125.4 (CH), 125.0 (CH), 112.3 (CH), 81.8 (C), 45.4 (CH), 27.6 (CH_3); HRMS (ES) found MNa^+, 374.1360. $C_{21}H_{21}NO_4Na$ requires MNa^+, 374.1363; LRMS (ES) found 252 (100%, MH^+ −Boc), 374 (71%, MNa^+).

2-Isopropyloxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (122)



A mixture of triisopropyl borate **120** (9.8 g, 83 mmol) and pinacol **121** (6.7 g, 57 mmol) in *n*-hexane (50 mL) was heated under reflux for 16 h. The solvent was removed by distillation and the residue was distilled at 90 °C, 7 mbar to give product **122** (6.6 g, 68%) as a colourless oil; ν_{max}/cm^{-1} (thin film) 2975, 1504, 1473, 1441, 1371, 1346, 1316, 1149, 1121, 959, 853, 700, 675, 622; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.35 (1H, sept, *J* 6.1 Hz, CH), 1.27 (12H, s, 4 × CH_3), 1.22 (6H, d, *J* 6.1 Hz, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 82.5 (C), 67.4 (CH), 24.6 (CH_3), 24.4 (CH_3). Data consistent with the literature.[60]

(±)-1-*tert*-Butyl 4-Methyl 4-Methyl-2-phenyl-1,4-dihydroquinoline-1,4-dicarboxylate (123)

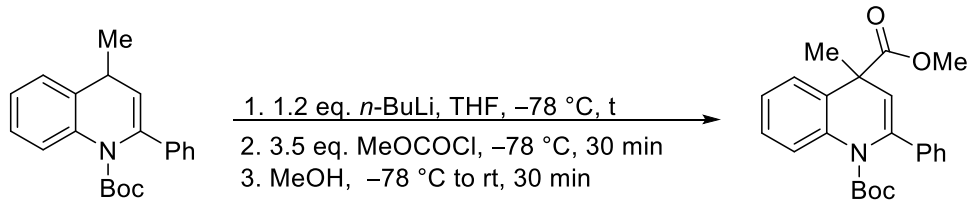


n-BuLi (0.21 mL, 0.53 mmol, 2.5 M in hexane) was added to carbamate **148** (143 mg, 0.445 mmol) in dry THF (6 mL) at −78 °C. After 1 h, methyl chloroformate (0.12 mL, 1.6 mmol) was added and the mixture was stirred for a further 1 h. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (96:4),

gave carbamate **123** (160 mg, 93%) as yellow needles; m.p. 104−106 °C; R_f 0.26 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3053, 2978, 2950, 2930, 2872, 1728 (C=O), 1717 (C=O), 1637, 1488, 1458, 1448, 1430, 1350, 1318, 1271, 1248, 1222, 1155, 1131, 1017, 827, 774, 757, 697, 628; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 (1H, dd, *J* 8.0 and 0.5 Hz, ArH), 7.52−7.47 (2H, m, ArH), 7.41−7.18 (6H, m, ArH), 5.70 (1H, s, C=CH), 3.66 (3H, s, CH_3), 1.76 (3H, s, CH_3), 1.17 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.0 (C=O), 152.4 (C=O), 141.8 (C), 138.6 (C), 138.5 (C), 135.4 (C), 128.2 (CH), 127.8 (CH), 126.9 (CH), 125.5 (CH), 125.3 (CH), 124.8 (CH), 124.4 (CH), 120.3 (CH), 81.5 (C), 52.8 (CH_3), 46.6 (C), 27.7 (CH_3), 23.7 (CH_3); HRMS (ES) found MNa^+, 402.1683. $C_{23}H_{25}NO_4Na$ requires MNa^+, 402.1676; LRMS (ES) found 280 (100%, MH^+ −Boc), 402 (98%, MNa^+).

Alternatively,

n-BuLi (0.26 mL, 0.65 mmol, 2.5 M in hexane) was added to carbamate **113** (175 mg, 0.544 mmol) in dry THF (7 mL) at −78 °C. After 1 h, methyl chloroformate (0.15 mL, 1.9 mmol) was added and the mixture was stirred for a further 1 h. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (96:4), gave carbamate **123** (160 mg, 77%) as yellow needles; data as above.



113 **123**

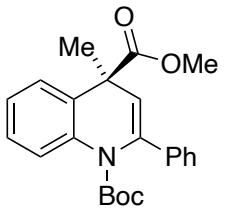
Entry	t/ min	123 yield %	113 yield %
1	10	51	48
2	60	77	0

Alternatively,

n-BuLi (0.17 mL, 0.41 mmol, 2.4 M in hexane) was added to carbamate **148** (111 mg, 0.345 mmol) in dry THF (5 mL) at −78 °C. After 1 h, methyl chloroformate (0.09 mL, 1.2 mmol) was added and the mixture was stirred for a further 5 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (96:4), gave carbamate **123** (120 mg, 95%) as yellow needles; data as above.

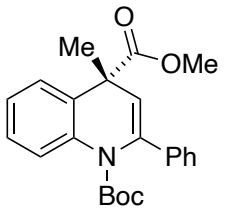
Resolution between enantiomers of the carbamate **123** was achieved using a Beckman system fitted with a Lux Cellulose−1 column (250 mm × 4.6 mm i.d.) as the stationary phase with a mixture of *n*-hexane−isopropanol (99:1 v/v) as the mobile phase at a flow rate of 0.5 $mL \cdot min^{-1}$; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 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 14.6 min and 15.9 min respectively with an analysis time of 20 min.

(*S*)-1-*tert*-Butyl 4-Methyl 4-Methyl-2-phenyl-1,4-dihydroquinoline-1,4-dicarboxylate ((*S*)-123)



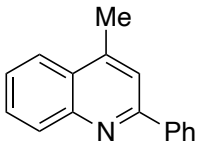
n-BuLi (0.27 mL, 0.63 mmol, 2.3 M in hexane) was added to enantioenriched carbamate (*R*)-**113** (177 mg, 0.550 mmol, er 98:2) in dry THF (6 mL) at −78 °C. After 1 h, methyl chloroformate (0.26 mL, 1.8 mmol) was added and the mixture was stirred for a further 5 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (96:4), gave carbamate (*S*)-**123** (190 mg, 89%) as yellow needles; m.p. 120−122 °C; data as above; the enantiomeric ratio was determined to be 94:6; recrystallisation (DCM−hexane) gave er 98:2 by CSP−HPLC (Cellulose−1, major component eluted at 13.2 min); $[\alpha]_D^{23}$ +23 (0.4, $CHCl_3$).

(*R*)-1-*tert*-Butyl 4-Methyl 4-Methyl-2-phenyl-1,4-dihydroquinoline-1,4-dicarboxylate ((*R*)-123)



n-BuLi (0.18 mL, 0.40 mmol, 2.2 M in hexane) was added to enantioenriched carbamate (*S*)-**148** (106 mg, 0.330 mmol, er 99:1) in dry THF (4 mL) at −78 °C. After 1 h, methyl chloroformate (0.09 mL, 1.0 mmol) was added and the mixture was stirred for a further 5 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (96:4), gave carbamate (*R*)-**123** (90 mg, 72%) as yellow needles; m.p. 122−124 °C; data as above; the enantiomeric ratio was determined to be 95:5; recrystallisation (DCM−hexane) gave er 99:1 by CSP−HPLC (Cellulose−1, major component eluted at 16.3 min); $[\alpha]_D^{23}$ −14 (0.4, $CHCl_3$).

4-Methyl-2-phenylquinoline (127)



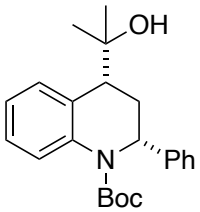
Trifluoroacetic acid (1.1 mL, 14 mmol) was added to a stirred solution of the carbamate **113** (230 mg, 0.749 mmol) in DCM (25 mL) at room temperature. After 1 day, the solvent was evaporated under reduced pressure and the crude product was purified

by column chromatography on silica gel, eluting with petrol−EtOAc (9:1), to give the product **127** (150 mg, 95%) as a yellow amorphous solid; m.p. 65−67 °C (lit. m.p. 61−62 °C.[108]); R_f 0.07 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3072, 3019, 2971, 2943, 1664, 1365, 1196, 1124, 824, 800, 717, 700, 520; ^{1}H NMR (400 MHz, CD_3OD) δ = 8.45 (1H, d, *J* 8.5 Hz, ArH), 8.34 (1H, d, *J* 8.5 Hz, ArH), 8.25 (1H, s, ArH), 8.18−8.09 (3H, m, ArH), 8.02−7.91 (1H, m, ArH), 7.82−7.67 (3H, m, ArH), 3.07 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 134.0 (CH), 132.4 (CH), 129.4 (CH), 129.0 (CH), 128.7 (CH), 125.2 (CH), 121.8 (CH), 121.6 (CH), 18.7 (CH_3); HRMS (ES) found MH$^+$, 220.1121. $C_{16}H_{14}N$ requires MH$^+$, 220.1121; LRMS (ES) found 220 (100%, MH$^+$). Data consistent with the literature.[108]

Alternatively,

Hydrochloric acid (1.8 mL, 7.0 mmol, 4 M in dioxane) was added to a stirred solution of the carbamate **113** (226 mg, 0.703 mmol) at room temperature. After 1 day, the solvent was evaporated under reduced pressure gave the product **127** (150 mg, 95%) as a yellow amorphous solid; data as above.

(*2R,* 4*R*)-*tert*-Butyl 4-(2-Hydroxypropan-2-yl)-2-phenyl-1,2,3,4-tetrahydroquinoline-1-carboxylate (128)



Carbamate **111** (208 mg, 0.568 mmol) was added to 10% Pd/C (747 mg, 0.0702 mmol) in EtOAc (5 mL). The reaction mixture was stirred at room temperature under H_2

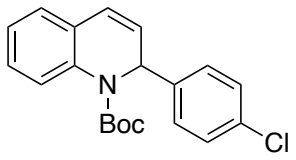
balloon. After 18 h, the mixture was filtered through a pad of celite and the solvent was removed under reduced pressure, to give the carbamate **128** (180 mg, 85%) as white needles; m.p. 108−110 °C; R_f 0.38 [petrol−EtOAc (6:4)]; FT-IR ν_{max} (film)/cm^{-1} 3476 (O−H), 3415, 3033, 2971, 2936, 2872, 1693, 1680 (C=O), 1486, 1453, 1334, 1143, 1022, 913, 864, 828, 774, 756, 738, 606; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 (1H, d, *J* 7.5 Hz, ArH), 7.65 (1H, d, *J* 8.0 Hz, ArH), 7.33−7.28 (2H, m, ArH), 7.28−7.26 (1H, m, ArH), 7.25−7.18 (3H, m, ArH), 7.16−7.11 (1H, m, ArH), 5.25 (1H, dd, *J* 11.5 and 8.0 Hz, CH), 2.78 (1H, br d, *J* 12.0 Hz, CH), 2.67−2.55 (1H, m, CH), 1.66−1.61 (1H, m, CH), 1.50 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.38 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.9 (C=O), 145.1 (C), 138.8 (C), 135.8 (C), 128.4 (CH), 126.7 (CH), 126.4 (CH), 125.9 (CH), 125.8 (CH), 125.6 (CH), 123.7 (CH), 80.8 (C), 72.4 (C), 59.7 (CH), 47.6 (CH_3), 39.8 (CH_2), 28.2 (CH_3); HRMS (ES) found MH^+, 368.2219. $C_{23}H_{30}NO_3$ requires MH^+, 368.2220; LRMS (ES) found 390 (100%, MNa^+), 312 (89%, $MH^+ - {}^t$Bu), 268 (78%, MH^+ −Boc), 368 (46%, $MH^+ - {}^t$Bu).

Alternatively,

Enantioenriched carbamate (*R*)-**111** (129 mg, 0.352 mmol, er 97:3) was added to 10% Pd/C (46 mg, 0.043 mmol) in EtOAc (12 mL). The reaction mixture was stirred at room temperature under H_2 balloon. After 18 h, the mixture was filtered through a pad of celite and the solvent was removed under reduced pressure, to give the carbamate (*R*,*R*)-**128** (130 mg, 99%) as white needles; data as above; the enantiomeric ratio was determined to be 96:4 by CSP−HPLC (ChiralPak IA, major component eluted at 30.2 min); $[\alpha]_D^{23}$ +118 (0.4, $CHCl_3$).

Resolution between enantiomers of the carbamate **128** was achieved using a Beckman system fitted with a Daicel ChiralPakIA column (250 mm × 4.6 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 1.5 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 μL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the faster running component and slower running component were eluted at 27.6 min and 30.5 min respectively with an analysis time of 35 min.

(±)-*tert*-Butyl 2-(4-Chlorophenyl)-1,2-dihydroquinoline-1-carboxylate (130)

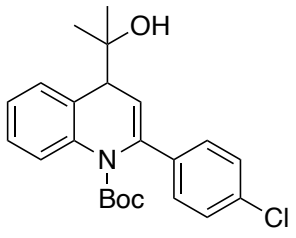


n-BuLi (12 mL, 28 mmol, 2.4 M in hexane) was added to a solution of 1-bromo-4-chlorobenzene **129** (5.3 g, 28 mmol) in dry THF (15 mL) at −78 °C. After 1 h, a solution of quinoline **83** (2.8 mL, 23 mmol) in dry THF (15 mL) at 0 °C. After 1 h, a solution of Boc_2O (7.6 g, 35 mmol) in dry THF (5 mL) was added dropwise and the mixture was allowed to warm to room temperature over 16 h. The reaction was quenched with MeOH (5 mL) and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (98:2), gave carbamate **130** (4.2 g, 53%) as yellow needles; m.p. 88−90 °C; R_f 0.29 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3042, 2975, 1691 (C=O), 1158, 872; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56−7.46 (1H, m, ArH), 7.24−7.02 (7H, m, ArH), 6.68 (1H, d, *J* 9.0 Hz, C=CH), 6.20−6.09 (2H, m, C=CH and CH), 1.56 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz,

$CDCl_3$) δ = 153.4 (C=O), 138.5 (C), 134.9 (C), 133.5 (C), 128.6 (CH), 128.5 (CH), 127.7 (CH), 126.9 (C), 126.3 (CH), 125.8 (CH), 124.7 (CH), 123.9 (CH), 118.6 (CH), 81.8 (C), 54.5 (CH), 28.4 (CH_3); HRMS (ES) found MNa^+, 364.1085. $C_{20}H_{20}NO_2{}^{35}ClNa$ requires MNa^+, 364.1080; Found MNa^+, 366.1060. $C_{20}H_{20}NO_2{}^{37}ClNa$ requires MNa^+, 366.1051; LRMS (ES) 364 (100%, MNa^+ for ^{35}Cl), 366 (33%, MNa^+ for ^{37}Cl).

Resolution between enantiomers of the carbamate **130** was achieved using a Beckman system fitted with a Lux Cellulose−2 column (250 mm × 4.6 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 1.0 $mL \cdot min^{-1}$; 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 4.5 min and 6.1 min respectively with an analysis time of 10 min.

(±)-*tert*-Butyl 4-(2-Hydroxypropan-2-yl)-2-(4-chlorophenyl)-1,4-dihydroquinoline-1-carboxylate (131)

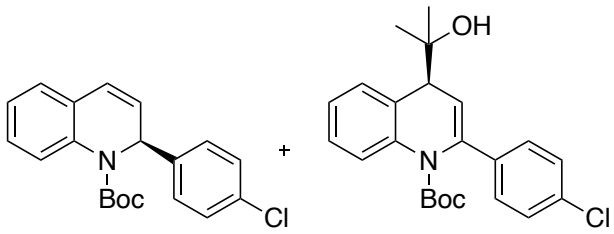


n-BuLi (0.17 mL, 0.41 mmol, 2.4 M in hexane) was added to carbamate **130** (117 mg, 0.341 mmol) in dry THF (5 mL) at −78 °C. After 6 min, acetone (0.09 mL, 1.2 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room

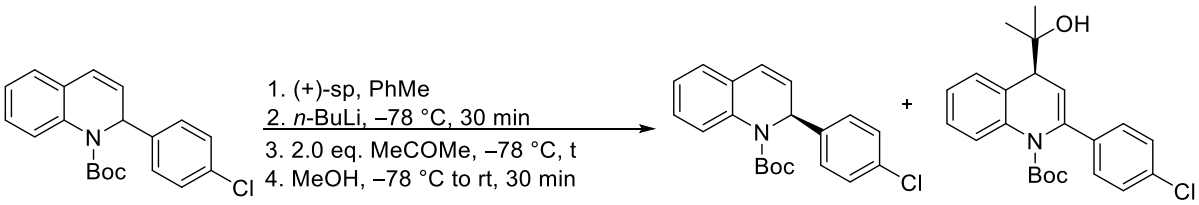
temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (88:12), gave carbamate **131** (130 mg, 97%) as a yellow oil; R_f 0.06 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3438 (O−H), 2973, 1712 (C=O), 1459, 1159, 825; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 (1H, d, *J* 8.0 Hz, ArH), 7.44−7.28 (5H, m, ArH), 7.24−7.13 (2H, m, ArH), 5.83 (1H, d, *J* 7.5 Hz, C=CH), 3.51 (1H, d, *J* 7.5 Hz, CH), 2.17 (1H, s, OH), 1.31 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.16 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.3 (C=O), 141.3 (C), 139.6 (C), 137.8 (C), 133.1 (C), 131.8 (C), 129.5 (CH), 128.3 (CH), 126.6 (CH), 126.5 (CH), 125.0 (CH), 124.9 (CH), 117.9 (CH), 81.8 (C), 74.8 (C), 51.6 (CH), 27.7 (CH_3), 27.0 (CH_3), 26.0 (CH_3); HRMS (ES) found MNa$^+$, 422.1500. $C_{23}H_{26}NO_3{}^{35}ClNa$ requires MNa$^+$, 422.1493; Found MNa$^+$, 424.1474. $C_{23}H_{26}NO_3{}^{37}ClNa$ requires MNa$^+$, 424.1469; LRMS (ES) found 422 (100%, MNa$^+$ for ^{35}Cl), 424 (36%, MNa$^+$ for ^{37}Cl).

Resolution between enantiomers of the carbamate **131** was achieved using a Beckman system fitted with a Lux Cellulose−2 column (250 mm × 4.6 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·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 21.3 min and 26.7 min respectively with an analysis time of 30 min.

(*S*)-*tert*-Butyl 2-(4-Chlorophenyl)-1,2-dihydroquinoline-1-carboxylate ((*S*)-130) and (*S*)-*tert*-Butyl 4-(2-Hydroxypropan-2-yl)-2-(4-chlorophenyl)-1,4-dihydroquinoline-1-carboxylate ((*S*)-131)



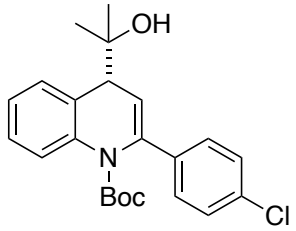
n-BuLi (0.27 mL, 0.60 mmol, 2.2 M in hexane) was added to carbamate **130** (295 mg, 0.862 mmol) and (+)-sparteine (182 mg, 0.777 mmol) in dry toluene (24 mL) at −78 °C. After 30 min, acetone (0.13 mL, 1.7 mmol) was added and the mixture was stirred for a further 1 h. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (88:12), gave carbamate (*S*)-**130** (130 mg, 43%) as yellow needles; m.p. 67−69 °C; data as above; the enantiomeric ratio was determined to be 99:1 by CSP−HPLC (Cellulose−2, major component eluted at 6.8 min); $[\alpha]_D^{23}$ −216 (1.0, $CHCl_3$); the carbamate (*S*)-**131** (190 mg, 56%) was also isolated as a yellow oil; data as above; the enantiomeric ratio was determined to be 73:27 by CSP−HPLC (Cellulose−2, major component eluted at 29.8 min); $[\alpha]_D^{23}$ −54 (0.4, $CHCl_3$).



130 (*S*)-**130** (*S*)-**131**

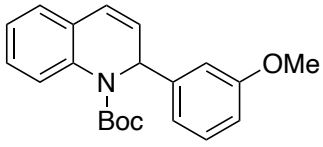
Entry	t/ min	eq. *n*-BuLi	eq. (+)-sp	(*S*)-130 yield %	(*S*)-130 er	(*S*)-131 yield %	(*S*)-131 er	s
1	60	0.6	0.8	56	88:12	40	87:13	-
2	60	0.7	0.9	21	99:1	72	57:43	6
3	30	0.7	0.9	43	99:1	56	73:27	30

(*R*)-*tert*-Butyl 4-(2-Hydroxypropan-2-yl)-2-(4-chlorophenyl)-1,4-dihydroquinoline-1-carboxylate ((*R*)-131)



n-BuLi (0.17 mL, 0.37 mmol, 2.2 M in hexane) was added to enantioenriched carbamate (*S*)-**130** (105 mg, 0.306 mmol, er 99:1) in dry THF (4 mL) at −78 °C. After 6 min, acetone (0.08 mL, 1.0 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (88:12), gave carbamate (*R*)-**131** (92 mg, 75%) as a yellow oil; data as above; the enantiomeric ratio was determined to be 96:4 by CSP−HPLC (Cellulose−2, major component eluted at 22.1 min); $[\alpha]_D^{23}$ +105 (0.4, $CHCl_3$).

(±)-*tert*-Butyl 2-(3-Methoxyphenyl)-1,2-dihydroquinoline-1-carboxylate (133)

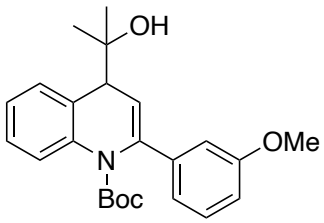


n-BuLi (11 mL, 28 mmol, 2.5 M in hexane) was added to a solution of 1-bromo-3-methoxybenzene **132** (3.5 mL, 28 mmol) in dry THF (15 mL) at −78 °C. After 1 h, a solution of quinoline **83** (2.8 mL, 23 mmol) in dry THF (15 mL) was added at 0 °C. After 1 h, a solution of Boc_2O (7.8 g, 35 mmol) in dry THF (5 mL) was added dropwise and the mixture was allowed to warm to room temperature over 16 h. The reaction was quenched with MeOH (5 mL) and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (98:2), gave carbamate **133** (4.7 g, 60%) as a yellow oil; R_f 0.65 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3006, 2973, 1695 (C=O), 1488, 1159; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 (1H, d, *J* 6.5 Hz, ArH), 7.17 (2H, m, ArH), 7.13−7.02 (2H, m, ArH), 6.90−6.75 (3H, m, ArH), 6.63 (1H, d, *J* 9.5 Hz, C=CH), 6.24−6.09 (2H, m, C=CH and CH), 3.73 (3H, s, CH_3), 1.57 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$, one CH_3 signal could not be observed) δ = 159.6 (C), 153.5 (C=O), 141.8 (C), 135.3 (C), 129.5 (CH), 128.2 (CH), 127.5 (CH), 127.0 (C), 126.3 (CH), 125.4 (CH), 124.7 (CH), 123.8 (CH), 119.3 (CH), 112.9 (CH), 112.8 (CH), 81.6 (C), 55.2 (CH), 28.4 (CH_3); HRMS (ES) found 360.1569. $C_{21}H_{23}NO_3Na$ requires MNa^+, 360.1570; LRMS (ES) 282 (100%, $MH^+ - {}^t$Bu), 360 (26%, MNa^+), 238 (9%, MH^+ −Boc).

Resolution between enantiomers of the carbamate **133** was achieved using a Beckman system fitted with a Lux Cellulose−1 column (250 mm × 4.6 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·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 7.6 min and 8.9 min respectively with an analysis time of 10 min.

(±)-*tert*-Butyl 4-(2-Hydroxypropan-2-yl)-2-(3-methoxyphenyl)-1,4-dihydroquinoline-1-carboxylate (135)

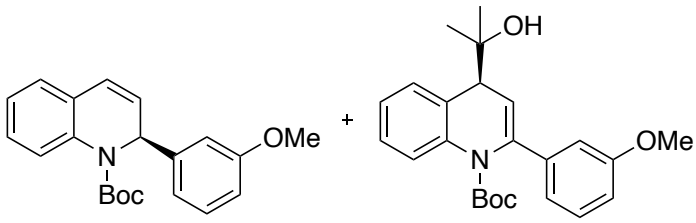


n-BuLi (0.23 mL, 0.54 mmol, 2.4 M in hexane) was added to carbamate **133** (153 mg, 0.453 mmol) in dry THF (6 mL) at −78 °C. After 6 min, acetone (0.12 mL, 1.6 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (88:12), gave carbamate **135** (170 mg, 93%) as a yellow oil; R_f 0.37 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3463 (O−H), 3006, 2975, 1711 (C=O), 1487, 1159; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (1H, d, *J* 8.0 Hz, ArH), 7.37−7.15 (4H, m, ArH), 7.09−6.97 (2H, m, ArH), 6.84 (1H, dd, *J* 8.0 and 1.5 Hz, ArH), 5.85 (1H, d, *J* 7.5 Hz, C=CH), 3.82 (3H, s, CH_3), 3.52 (1H, d, *J* 7.5 Hz, CH), 2.17 (1H, s, OH), 1.33 (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.16 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.5 (C), 152.4 (C=O), 142.2 (C), 140.7 (C), 139.7 (C), 131.8 (C), 129.5 (CH), 129.2 (CH), 126.5 (CH), 124.9 (CH),

124.8 (CH), 118.0 (CH), 117.2 (CH), 112.9 (CH), 111.1 (CH), 81.6 (C), 74.8 (C), 55.3 (CH_3), 51.6 (CH), 27.7 (CH_3), 27.0 (CH_3), 25.9 (CH_3); HRMS (ES) found MNa^+, 418.1997. $C_{24}H_{29}NO_4Na$ requires MNa^+, 418.1989; LRMS (ES) found 296 (100%, MH^+ −Boc), 418 (49%, MNa^+).

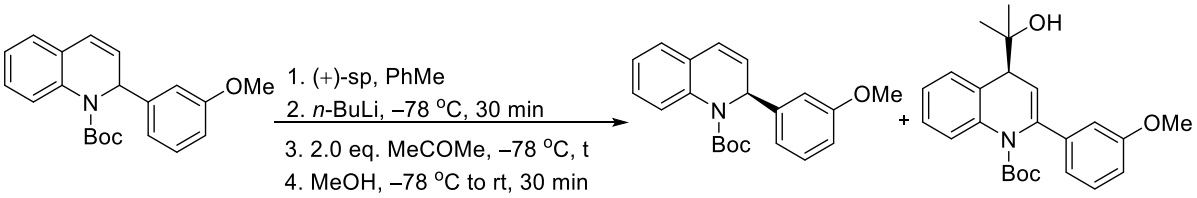
Resolution between enantiomers of the carbamate **135** was achieved using a Beckman system fitted with a Lux Cellulose−1 column (250 mm × 4.6 mm i.d.) as the stationary phase with a mixture of *n*-hexane−isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1.0 $mL \cdot min^{-1}$; ambient temperature, 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 26.8 min and 29.1 min respectively with an analysis time of 35 min.

(*S*)-*tert*-Butyl 2-(3-Methoxyphenyl)-1,2-dihydroquinoline-1-carboxylate ((*S*)-133) and (*S*)-*tert*-Butyl 4-(2-Hydroxypropan-2-yl)-2-(3-methoxyphenyl)-1,4-dihydroquinoline-1-carboxylate ((*S*)-135)



n-BuLi (0.32 mL, 0.70 mmol, 2.2 M in hexane) was added to carbamate **133** (337 mg, 0.999 mmol) and (+)-sparteine (211 mg, 0.899 mmol) in dry toluene (24 mL) at −78 °C. After 30 min, acetone (0.15 mL, 2.0 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture

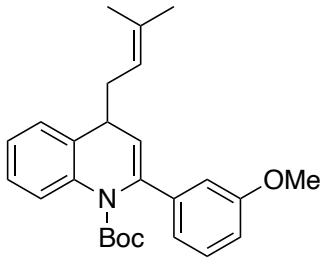
was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (88:12), gave carbamate (*S*)-**133** (140 mg, 41%) as a yellow oil; data as above; the enantiomeric ratio was determined to be 98:2 by CSP−HPLC (Cellulose−1, major component eluted at 7.4 min); $[\alpha]_D^{23}$ −440 (0.1, $CHCl_3$); the carbamate (*S*)-**135** (230 mg, 57%) was also isolated as a yellow oil; data as above; the enantiomeric ratio was determined to be 77:23 by CSP−HPLC (Cellulose−1, major component eluted at 28.4 min); $[\alpha]_D^{23}$ −36 (0.2, $CHCl_3$).



133 (*S*)-**133** (*S*)-**135**

Entry	t/ min	eq. *n*-BuLi	eq. (+)-sp	(*S*)-133 yield %	(*S*)-133 er	(*S*)-135 yield %	(*S*)-135 er	s
1	30	0.6	0.8	66	76:24	30	90:10	-
2	60	0.6	0.8	67	71:29	30	86:14	-
3	30	0.7	0.9	59	79:21	40	80:20	20
4	60	0.7	0.9	41	98:2	57	77:23	19

(±)-*tert*-Butyl 4-(3-Methylbut-2-en-1-yl)-2-(3-methoxyphenyl)-1,4-dihydroquinoline-1-carboxylate (136)

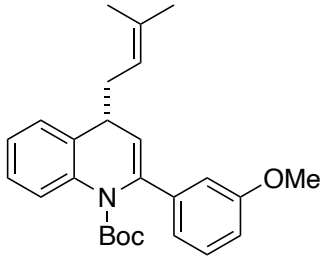


n-BuLi (0.33 mL, 0.80 mmol, 2.4 M in hexane) was added to carbamate **133** (226 mg, 0.669 mmol) in dry THF (9 mL) at −78 °C. After 6 min, prenyl bromide (0.27 mL, 2.4 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (97:3), gave carbamate **136** (250 mg, 91%) as a yellow oil; R_f 0.77 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3069, 2975, 2933, 2835, 1712 (C=O), 1600, 1486, 1313, 1159, 1131, 1044, 849, 770, 755, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 (1H, d, *J* 8.0 Hz, ArH), 7.34−7.29 (1H, m, ArH), 7.27−7.23 (1H, m, ArH), 7.20−7.13 (2H, m, ArH), 7.06−7.02 (1H, m, ArH), 7.00−6.97 (1H, m, ArH), 6.85 (1H, ddd, *J* 8.0, 2.5 and 0.5 Hz, ArH), 5.89 (1H, d, *J* 6.5 Hz, C=CH), 5.31−5.22 (1H, m, C=CH), 3.84 (3H, s, CH_3), 3.43 (1H, dt, *J* 8.0 and 6.5 Hz, CH), 2.48−2.23 (2H, m, CH_2), 1.76 (3H, s, CH_3), 1.56 (3H, s, CH_3), 1.20 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.5 (C), 152.5 (C=O), 140.9 (C), 140.8 (C), 139.2 (C), 136.1 (C), 133.9 (C), 129.1 (CH), 126.7 (CH), 125.7 (CH), 124.9 (CH), 124.2 (CH), 121.4 (CH), 120.5 (CH), 118.0 (CH), 112.7 (CH), 111.1 (CH), 81.4 (C), 55.3 (CH), 39.9 (CH_3), 34.1 (CH_2), 27.8 (CH_3), 25.9 (CH_3), 17.8 (CH_3); HRMS (ES)

found MNa^+, 428.2215. $C_{26}H_{31}NO_3$ requires MNa^+, 428.2196; LRMS (ES) found 350 (100%, $MH^+ - {}^tBu$), 428 (41%, MNa^+), 306 (22%, MH^+ −Boc).

Resolution between enantiomers of the carbamate **136** was achieved using a Beckman system fitted with a Lux Cellulose−1 column (250 mm × 4.6 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 4.5 min and 5.1 min respectively with an analysis time of 10 min.

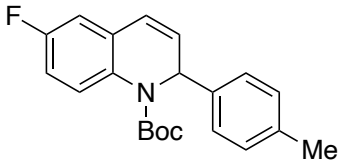
(*R*)-*tert*-Butyl 4-(3-Methylbut-2-en-1-yl)-2-(3-methoxyphenyl)-1,4-dihydroquinoline-1-carboxylate ((*R*)-136)



n-BuLi (0.21 mL, 0.47 mmol, 2.2 M in hexane) was added to carbamate (*S*)-**133** (131 mg, 0.389 mmol, er 98:2) in dry THF (5 mL) at −78 °C. After 6 min, prenyl bromide (0.16 mL, 1.4 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (97:3),

gave carbamate (*R*)-**136** (110 mg, 72%) as a yellow oil; data as above; the enantiomeric ratio was determined to be 93:7 by CSP−HPLC (Cellulose−1, major component eluted at 5.4 min); $[\alpha]_D^{23}$ +124 (0.1, $CHCl_3$).

(±)-*tert*-Butyl 6-Fluoro-2-(4-methylphenyl)-1,2-dihydroquinoline-1-carboxylate (138)

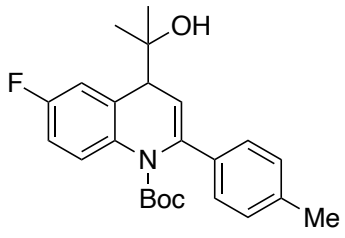


n-BuLi (22 mL, 52 mmol, 2.4 M in hexane) was added to a solution of 4-bromotoluene **137** (6.4 mL, 52 mmol) in dry THF (20 mL) at −78 °C. After 1 h, a solution of 6-fluoroquinoline (4.2 mL, 35 mmol) in dry THF (20 mL) was added at 0 °C. After 1 h, a solution of Boc_2O (11 g, 52 mmol) in dry THF (5 mL) was added dropwise and the mixture was allowed to warm to room temperature over 16 h. The reaction was quenched with MeOH (5 mL) and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (96:4), gave carbamate **138** (5.5 g, 47%) as white needles; m.p. 64−66 °C; R_f 0.60 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3053, 3005, 2981, 2930, 1698 (C=O), 1493, 1383, 1368, 1307, 1251, 1157, 1122, 1107, 1018, 872, 813, 785, 723, 697, 552, 484; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.49 (1H, br s, ArH), 7.15 (2H, d, *J* 8.0 Hz, ArH), 7.07 (2H, d, *J* 8.0 Hz, ArH), 6.85 (2H, ddd, *J* 17.5, 8.5 and 3.0 Hz, ArH), 6.61 (1H, d, *J* 9.5 Hz, C=CH), 6.25 (1H, dd, *J* 9.5 and 6.0 Hz, C=CH), 6.13 (1H, d, *J* 6.0 Hz, CH), 2.30 (3H, s, CH_3), 1.57 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.0 (d, *J* 242.5 Hz, C), 153.4 (C=O), 137.6 (C), 136.5 (C), 131.0 (d, *J* 2.5 Hz, C), 130.0 (CH), 129.2 (CH),

128.7 (d, *J* 9.5 Hz, C), 127.0 (CH), 126.4 (d, *J* 6.5 Hz, CH), 124.6 (CH), 113.9 (d, *J* 22.5 Hz, CH), 112.3 (d, *J* 23.0 Hz, CH), 81.7 (C), 55.0 (CH), 28.4 (CH_3), 21.1 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −119.4 (1F, s, CF); HRMS (ES) found MNa^+, 362.1536. $C_{21}H_{22}FNO_2Na$ requires MNa^+, 362.1527; LRMS (ES) found 284 (100%, $MH^+ - {}^tBu$), 362 (70%, MNa^+), 240 (8%, MH^+ −Boc).

Resolution between enantiomers of the carbamate **138** was achieved using a Beckman system fitted with a Lux Cellulose−2 column (250 mm × 4.6 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 4.3 min and 5.5 min respectively with an analysis time of 10 min.

(±)-*tert*-Butyl 6-Fluoro-4-(2-hydroxypropan-2-yl)-2-(4-methylphenyl)-1,4-dihydroquinoline-1-carboxylate (140)

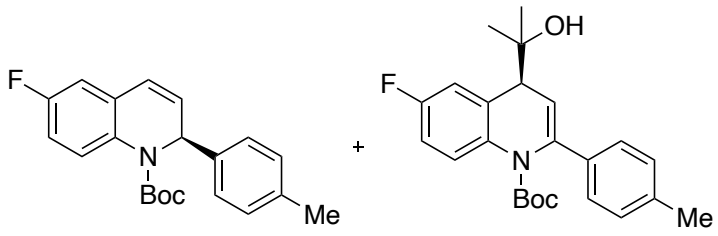


n-BuLi (0.31 mL, 0.75 mmol, 2.4 M in hexane) was added to carbamate **138** (212 mg, 0.626 mmol) in dry THF (8 mL) at −78 °C. After 6 min, acetone (0.17 mL, 2.2 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room

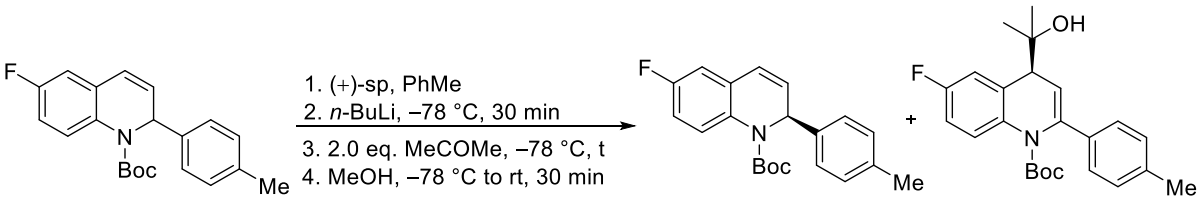
temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (88:12), gave carbamate **140** (250 mg, 99%) as a white amorphous solid; m.p. 55−57 ^{o}C; R_f 0.20 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 2975, 2933, 1714 (C=O), 1613, 1495, 1353, 1314, 1243, 1159, 1129, 1026, 849, 812, 764, 740, 489; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (1H, d, *J* 8.5 Hz, ArH), 7.34 (2H, d, *J* 8.0 Hz, ArH), 7.16 (2H, d, *J* 8.0 Hz, ArH), 7.05 (1H, td, *J* 8.5 and 3.0 Hz, ArH), 6.93 (1H, d, *J* 3.0 Hz, ArH), 5.78 (1H, d, *J* 7.5 Hz, C=CH), 3.48 (1H, d, *J* 7.5 Hz, CH), 2.39 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.21 (3H, s, CH_3), 1.15 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.8 (d, *J* 244.0 Hz, C), 152.5 (C=O), 142.7 (C), 137.5 (C), 136.0 (C), 135.9 (d, *J* 2.5 Hz, C), 134.1 (d, *J* 7.5 Hz, C), 128.8 (CH), 126.2 (d, *J* 8.5 Hz, CH), 125.2 (CH), 115.8 (CH), 115.6 (d, *J* 5.5 Hz, CH), 113.3 (d, *J* 22.5 Hz, CH), 81.7 (C), 74.8 (C), 51.6 (CH), 27.6 (CH_3), 27.1 (CH_3), 26.0 (CH_3), 21.2 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −118.4 (1F, s, CF); HRMS (ES) found MNa^+, 420.1965. $C_{24}H_{28}FNO_3Na$ requires MNa^+, 420.1945; LRMS (ES) found 420 (100%, MNa^+), 298 (45%, MH^+ −Boc).

Resolution between enantiomers of the carbamate **140** was achieved using a Beckman system fitted with a Lux Cellulose−2 column (250 mm × 4.6 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·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 20.4 min and 23.2 min respectively with an analysis time of 30 min.

(*S*)-*tert*-Butyl 6-Fluoro-2-(4-methylphenyl)-1,2-dihydroquinoline-1-carboxylate ((*S*)-138) and (*S*)-*tert*-Butyl 6-Fluoro-4-(2-hydroxypropan-2-yl)-2-(4-methylphenyl)-1,4-dihydroquinoline-1-carboxylate ((*S*)-140)



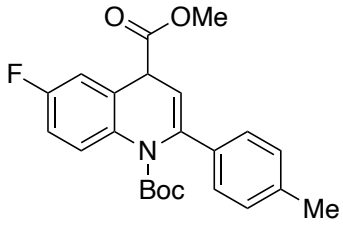
n-BuLi (0.26 mL, 0.61 mmol, 2.3 M in hexane) was added to carbamate **138** (295 mg, 0.870 mmol) and (+)-sparteine (192 mg, 0.818 mmol) in dry toluene (24 mL) at −78 °C. After 30 min, acetone (0.13 mL, 1.7 mmol) was added and the mixture was stirred for a further 1 h. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (88:12), gave carbamate (*S*)-**138** (130 mg, 43%) as white needles; m.p. 62−64 °C; data as above; the enantiomeric ratio was determined to be 96:4 by CSP−HPLC (Cellulose−2, major component eluted at 5.9 min); $[\alpha]_D^{23}$ −502 (0.3, $CHCl_3$); the carbamate (*S*)-**140** (190 mg, 55%) was also isolated as a white amorphous solid; m.p. 48−50 °C; data as above; the enantiomeric ratio was determined to be 75:25 by CSP−HPLC (Cellulose−1, major component eluted at 21.3 min); $[\alpha]_D^{23}$ −33 (0.3, $CHCl_3$).



138 (*S*)-**138** (*S*)-**140**

Entry	t/ min	eq. *n*-BuLi	eq. (+)-sp	(*S*)-138 yield %	(*S*)-138 er	(*S*)-140 yield %	(*S*)-140 er	s
1	60	0.6	0.8	58	81:19	40	80:20	24
2	30	0.7	0.9	47	90:10	50	74:26	14
3	60	0.7	0.9	43	96:4	55	75:25	18

(±)-1-*tert*-Butyl 4-Methyl 6-Fluoro-2-(4-methylphenyl)-1,4-dihydroquinoline-1,4-dicarboxylate (141)



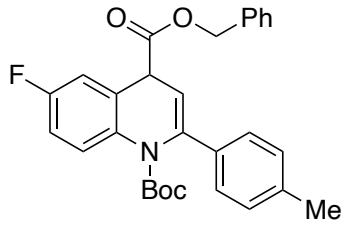
n-BuLi (0.28 mL, 0.65 mmol, 2.3 M in hexane) was added to carbamate **138** (185 mg, 0.544 mmol) in dry THF (6 mL) at −78 ºC. After 6 min, methyl chloroformate (0.15 mL, 1.9 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (96:4), gave carbamate **141** (160 mg, 75%) as a yellow oil; R_f 0.26 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3031, 3004, 2971, 2952, 2873, 1717 (C=O), 1494, 1350, 1315, 1233, 1217, 1156, 1128, 1109, 1026, 808, 768, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88

(1H, d, *J* 8.5 Hz, ArH), 7.36 (2H, d, *J* 8.0 Hz, ArH), 7.17 (2H, d, *J* 8.0 Hz, ArH), 7.07 (1H, td, *J* 8.5 and 3.0 Hz, ArH), 6.94 (1H, dd, *J* 8.5 and 3.0 Hz, ArH), 5.85 (1H, d, *J* 6.5 Hz, C=CH), 4.38 (1H, d, *J* 6.5 Hz, CH), 3.71 (3H, s, CH_3), 2.39 (3H, s, CH_3), 1.19 (9H, s, ^tBu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.8 (C=O), 160.0 (d, *J* 244.5 Hz, C), 152.4 (C=O), 143.5 (C), 137.9 (C), 135.3 (C), 135.2 (d, *J* 3.0 Hz, C), 132.3 (d, *J* 8.0 Hz, C), 128.9 (CH), 126.3 (d, *J* 8.5 Hz, CH), 125.4 (CH), 113.9 (d, *J* 22.5 Hz, CH), 113.6 (d, *J* 23.5 Hz, CH), 111.8 (CH), 81.7 (C), 52.7 (CH_3), 45.7 (CH), 27.7 (CH_3), 21.2 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −117.8 (1F, s, CF); HRMS (ES) found MNa^+, 420.1599. $C_{23}H_{24}NO_4Na$ requires MNa^+, 420.1582; LRMS (ES) found 298 (100%, MH^+ −Boc), 420 (77%, MNa^+).

Alternatively,

n-BuLi (0.29 mL, 0.67 mmol, 2.3 M in hexane) was added to carbamate **138** (191 mg, 0.562 mmol) in dry THF (7 mL) at −78 °C. After 6 min, methyl cyanoformate (0.16 mL, 2.0 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (96:4), gave carbamate **141** (70 mg, 31%) as a yellow oil; data as above.

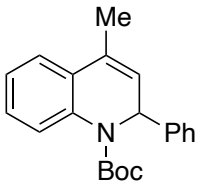
(±)-4-Benzyl 1-*tert*-Butyl 6-Fluoro-2-(4-methylphenyl)-1,4-dihydroquinoline-1,4-dicarboxylate (142)



n-BuLi (0.27 mL, 0.63 mmol, 2.3 M in hexane) was added to carbamate **138** (177 mg, 0.521 mmol) in dry THF (6 mL) at −78 °C. After 6 min, benzyl chloroformate (0.26 mL, 1.8 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (96:4), gave carbamate **142** (130 mg, 51%) as a white amorphous solid; m.p. 88−90 °C; R_f 0.39 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3028, 3010, 2971, 2940, 2873, 1741 (C=O), 1718 (C=O), 1493, 1366, 1348, 1230, 1217, 1158, 729; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (1H, d, *J* 8.5 Hz, ArH), 7.40−7.30 (7H, m, ArH), 7.18 (2H, d, *J* 8.0 Hz, ArH), 7.11−7.05 (1H, m, ArH), 6.93 (1H, dd, *J* 8.5 and 3.0 Hz, ArH), 5.83 (1H, d, *J* 6.5 Hz, C=CH), 5.22−5.12 (2H, m, CH_2), 4.41 (1H, d, *J* 6.5 Hz, CH), 2.40 (3H, s, CH_3), 1.13 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$, one C signal could not be observed) δ = 170.0 (C=O), 160.0 (d, *J* 244.0 Hz, C), 152.3 (C=O), 143.5 (C), 137.9 (C), 135.5 (C), 135.2 (d, *J* 2.0 Hz, C), 132.1 (d, *J* 8.0 Hz, C), 128.9 (CH), 128.6 (CH), 128.2 (CH), 127.7 (CH), 126.3 (d, *J* 8.5 Hz, CH), 125.5 (CH), 113.9 (d, *J* 22.5 Hz, CH), 113.6 (d, *J* 23.5 Hz, CH), 111.6 (CH), 81.8 (C), 67.0 (CH_2), 45.7 (CH), 27.6 (CH_3), 21.3 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −117.8 (1F, s, CF); HRMS (ES) found MNa^+, 496.1908.

$C_{29}H_{28}FNO_4Na$ requires MNa^+, 496.1895; LRMS (ES) found 374 (100%, MH^+ −Boc), 496 (50%, MNa^+).

(±)-*tert*-Butyl 4-Methyl-2-phenyl-1,2-dihydroquinoline-1-carboxylate (148)

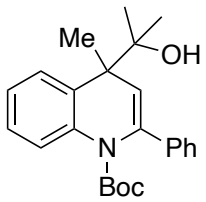


n-BuLi (13 mL, 31 mmol, 2.4 M in hexane) was added to a solution of 4-bromobenzene **112** (3.3 mL, 31 mmol) in dry THF (15 mL) at −78 °C. After 1 h, a solution of 4-methylquinoline (2.8 mL, 21 mmol) in dry THF (10 mL) was added at 0 °C. After 1 h, a solution of Boc_2O (7.6 g, 35 mmol) in dry THF (5 mL) was added dropwise and the mixture was allowed to warm to room temperature over 16 h. The reaction was quenched with MeOH (5 mL) and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (98:2), gave carbamate **148** (4.2 g, 62%) as white needles; m.p. 92−94 °C; R_f 0.52 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3064, 3036, 2976, 2930, 1689 (C=O), 1487, 1450, 1366, 1324, 1154, 1145, 1065, 876, 772, 757, 701, 501; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.55 (1H, d, *J* 7.5 Hz, ArH), 7.30 (1H, dd, *J* 7.5 and 1.0 Hz, ArH), 7.27−7.16 (6H, m, ArH), 7.09 (1H, td, *J* 7.5 and 1.0 Hz, ArH), 6.12−6.03 (2H, m, C=CH and CH), 2.19 (3H, s, CH_3), 1.58 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.5 (C=O), 140.6 (C), 135.2 (C), 130.5 (C), 128.8 (C), 128.4 (CH), 127.4 (CH), 127.3 (CH), 127.0 (CH), 125.1 (CH), 124.9 (CH), 123.7 (CH), 123.2 (CH), 81.4 (C), 54.9 (CH), 28.4 (CH_3), 18.6 (CH_3); HRMS (ES) found MNa^+, 344.1634. $C_{21}H_{23}NO_2Na$ requires MNa^+,

344.1621; LRMS (ES) found 266 (100%, $MH^+ - {}^tBu$), 344 (37%, MNa^+), 222 (11%, MH^+ −Boc).

Resolution between enantiomers of the carbamate **148** was achieved using a Beckman system fitted with a Lux Cellulose−2 column (250 mm × 4.6 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 4.7 min and 5.3 min respectively with an analysis time of 10 min.

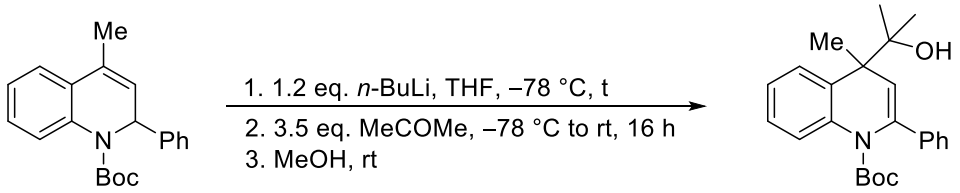
(±)-*tert*-Butyl 4-(2-Hydroxypropan-2-yl)-4-methyl-2-phenyl-1,4-dihydroquinoline-1-carboxylate (149)



n-BuLi (0.22 mL, 0.56 mmol, 2.5 M in hexane) was added to carbamate **148** (151 mg, 0.469 mmol) in dry THF (6 mL) at −78 °C. After 1 h, acetone (0.12 mL, 1.7 mmol) was added and the mixture was stirred for a further 1 h. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (88:12), gave carbamate **149** (160 mg, 90%) as white needles; m.p. 102−104 °C; R_f 0.28 [petrol−EtOAc (9:1)]; FT-

IR ν_{max} (film)/cm^{-1} 3511 (O−H), 3064, 3028, 2971, 2933, 1699 (C=O), 1667, 1485, 1446, 1368, 1349, 1318, 1275, 1159, 1138, 1087, 1018, 844, 754, 698, 637, 586, 497; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96−7.91 (1H, m, ArH), 7.50−7.45 (2H, m, ArH), 7.41−7.30 (5H, m, ArH), 7.27−7.21 (1H, m, ArH), 5.50 (1H, s, C=CH), 1.59 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.13 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.5 (C=O), 140.8 (C), 139.5 (C), 139.4 (C), 136.2 (C), 128.2 (CH), 127.5 (CH), 127.1 (CH), 126.4 (CH), 125.3 (CH), 124.9 (CH), 124.5 (CH), 123.9 (CH), 81.6 (C), 76.5 (C), 47.3 (C), 27.6 (CH_3), 26.0 (CH_3), 24.7 (CH_3), 24.1 (CH_3); HRMS (ES) found MNa^{+}, 402.2037. $C_{24}H_{29}NO_3Na$ requires MNa^{+}, 402.2040; LRMS (ES) found 280 (100%, MH^{+} −Boc), 402 (99%, MNa^{+}).

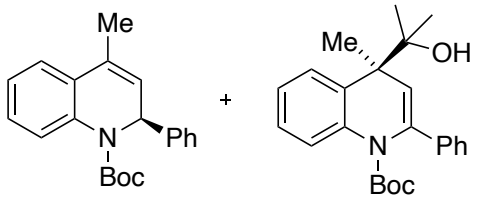
Resolution between enantiomers of the carbamate **149** was achieved using a Beckman system fitted with a Lux Cellulose−1 column (250 mm × 4.6 mm i.d.) as the stationary phase with a mixture of *n*-hexane−isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1.0 mL·min^{-1}; ambient temperature, 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 11.3 min and 16.2 min respectively with an analysis time of 20 min.



148 **149**

Entry	t/ min	149 yield %	148 yield %
1	10	51	48
2	60	90	0

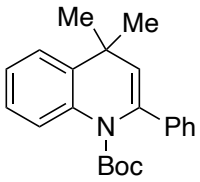
(*S*)-*tert*-Butyl 4-Methyl-2-phenyl-1,2-dihydroquinoline-1-carboxylate ((*S*)-148) and (*S*)-*tert*-Butyl 4-(2-Hydroxypropan-2-yl)-4-methyl-2-phenyl-1,4-dihydroquinoline-1-carboxylate ((*S*)-149)



n-BuLi (0.27 mL, 0.60 mmol, 2.2 M in hexane) was added to carbamate **148** (319 mg, 0.992 mmol) and (+)-sparteine (197 mg, 0.840 mmol) in dry toluene (24 mL) at −78 °C. After 30 min, acetone (0.15 mL, 2.0 mmol) was added and the mixture was stirred for a further 1 h. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (88:12), gave carbamate (*S*)-**148** (140 mg, 44%) as white needles; m.p. 82−84 °C; data as above; the enantiomeric ratio was determined to be 99:1 by CSP−HPLC (Cellulose−2, major component eluted at 5.1 min); $[\alpha]_D^{23}$ −299 (0.4, $CHCl_3$); the carbamate (*S*)-**149** (200 mg, 55%) was also isolated as white needles; m.p. 99−101 °C; data as above; the enantiomeric ratio was determined to be 82:18 by

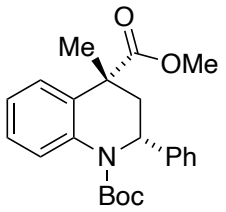
CSP−HPLC (Cellulose−1, major component eluted at 14.2 min); $[\alpha]_D^{23}$ −59 (0.8, $CHCl_3$).

(±)-*tert*-Butyl 4,4-Dimethyl-2-phenyl-1,4-dihydroquinoline-1-carboxylate (151)



n-BuLi (0.21 mL, 0.54 mmol, 2.5 M in hexane) was added to carbamate **148** (144 mg, 0.447 mmol) in dry THF (6 mL) at −78 °C. After 1 h, methyl iodide (0.10 mL, 1.6 mmol) was added and the mixture was stirred for a further 1 h. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (98:2), gave carbamate **151** (120 mg, 81%) as yellow needles; m.p. 123−125 °C; R_f 0.61 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 2972, 2927, 2869, 1705 (C=O), 1651, 1484, 1448, 1364, 1345, 1318, 1274, 1159, 1133, 1147, 1019, 843, 756, 701, 630, 505; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94−7.90 (1H, m, ArH), 7.48−7.44 (2H, m, ArH), 7.38−7.29 (5H, m, ArH), 7.25−7.20 (1H, m, ArH), 5.72 (1H, s, C=CH), 1.45 (6H, s, 2 x CH_3), 1.18 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$, one CH signal could not be observed) δ = 152.6 (C=O), 141.5 (C), 140.1 (C), 139.0 (C), 138.6 (C), 128.1 (CH), 127.4 (CH), 127.3 (CH), 125.6 (CH), 125.3 (CH), 124.4 (CH), 123.0 (CH), 81.3 (C), 35.5 (C), 28.4 (CH_3), 27.7 (CH_3); HRMS (ES) found MNa^+, 358.1794. $C_{22}H_{25}NO_2Na$ requires MNa^+, 358.1778; LRMS (ES) found 280 (100%, $MH^+ - {}^t$Bu), 358 (25%, MNa^+), 236 (6%, MH^+ −Boc).

1-*tert*-Butyl 4-Methyl 4-Methyl-2-phenyl-1.2.3,4-tetrahydroquinoline-1,4-dicarboxylate (152)



Carbamate **123** (55 mg, 0.14 mmol) was added to 10% Pd/C (15 mg, 0.014 mmol) in EtOAc (2 mL). The reaction mixture was stirred at room temperature under H_2 balloon. After 18 h, the mixture was filtered through a pad of celite and the solvent was removed under reduced pressure, to give the carbamate **152** (54 mg, 99%) as a white amorphous solid; m.p. 136−138 ^oC; R_f 0.26 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3028, 3010, 2971, 2949, 2873, 1728 (C=O), 1698 (C=O), 1366, 1329, 1231, 1207, 1145, 747, 706, 507; ^1H NMR (400 MHz, C_6D_6) δ = 8.05 (1H, d, *J* 8.0 Hz, ArH), 7.21−7.12 (3H, m, ArH), 7.10−7.04 (3H, m, ArH), 7.03−6.97 (1H, m, ArH), 6.90 (1H, td, *J* 7.5 and 1.0 Hz, ArH), 5.24 (1H, dd, *J* 11.5 and 7.0 Hz, CH), 3.25 (3H, s, CH_3), 2.49 (1H, dd, *J* 13.5 and 11.5 Hz, CH), 2.13 (1H, dd, *J* 13.5 and 7.0 Hz, CH), 1.55 (3H, s, CH_3), 1.24 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, C_6D_6) δ = 174.5 (C=O), 153.2 (C=O), 144.9 (C), 137.1 (C), 135.1 (C), 128.3 (CH), 127.0 (CH), 126.6 (CH), 126.3 (CH), 126.0 (CH), 124.7 (CH), 123.6 (CH), 80.4 (C), 56.3 (CH), 51.3 (CH_3), 46.2 (C), 43.3 (CH_2), 27.8 (CH_3), 20.5 (CH_3); HRMS (ES) found MNa^+, 404.1851. $C_{23}H_{27}NO_4Na$ requires MNa^+, 404.1832; LRMS (ES) found 404 (100%, MNa^+), 282 (31%, MH^+ −Boc).

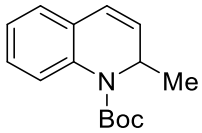
Alternatively,

Enantioenriched carbamate (*R*)-**123** (36 mg, 0.095 mmol, er 99:1) was added to 10% Pd/C (14 mg, 0.014 mmol) in EtOAc (5 mL). The reaction mixture was stirred at room

temperature under H_2 balloon. After 18 h, the mixture was filtered through a pad of celite and the solvent was removed under reduced pressure, gave the carbamate **152** (36 mg, 99%) as a colourless oil; data as above; the enantiomeric ratio was determined to be 98:2 by CSP−HPLC (ChiralPakIA, major component eluted at 6.9 min); $[\alpha]_D^{23}$ +136 (0.1, $CHCl_3$).

Resolution between enantiomers of the carbamate **152** was achieved using a Beckman system fitted with a Daicel ChiralPakIA column (250 mm × 4.6 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 7.0 min and 10.0 min respectively with an analysis time of 15 min.

(±)-*tert*-Butyl 2-Methyl-1,2-dihydroquinoline-1-carboxylate (153)

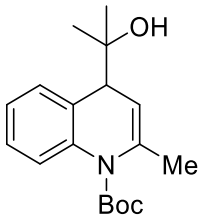


MeLi (22 mL, 35 mmol, 1.6 M in diethyl ether) was added to a solution of quinoline **83** (2.7 mL, 23 mmol) in dry THF (40 mL) at −78 °C. After 1 h, a solution of Boc_2O (7.6 g, 35 mmol) in dry THF (5 mL) was added dropwise at 0 °C and the mixture was allowed to warm to room temperature over 16 h. The reaction mixture was diluted with Et_2O (10 mL) and washed with water (3 x 5 mL). The organic layer was dried using $MgSO_4$, filtered, concentrated and purified by column chromatography on silica gel, eluting with

petrol−EtOAc (96:4), to give carbamate **153** (5.1 g, 88%) as white needles; m.p. 37−39 ^{o}C; R_f 0.68 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3004, 2979, 2930, 2867, 1691 (C=O), 1489, 1367, 1333, 1277, 1246, 1126, 1021, 755, 473; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (1H, d, *J* 7.5 Hz, ArH), 7.22−7.16 (1H, m, ArH), 7.09−7.01 (2H, m, ArH), 6.43 (1H, d, *J* 9.5 Hz, C=CH), 6.01 (1H, dd, *J* 9.5 and 6.5 Hz, C=CH), 5.08 (1H, p, *J* 6.5 Hz, CH), 1.55 (9H, s, ^{t}Bu), 1.11 (3H, d, *J* 6.5 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.1 (C=O), 134.7 (C), 130.8 (CH), 127.1 (CH), 126.9 (C), 126.1 (CH), 124.6 (CH), 124.2 (CH), 123.6 (CH), 81.1 (C), 48.7 (CH), 28.4 (CH_3), 18.6 (CH_3); HRMS (ES) found MNa^+, 268.1319. $C_{15}H_{19}NO_2$ requires MH^+, 268.1308; LRMS (ES) 190 (100%, $MH^+ - {}^{t}Bu$), 268 (34%, MNa^+).

Resolution between enantiomers of the carbamate **153** was achieved using a Beckman system fitted with a Lux Cellulose−2 column (250 mm × 4.6 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·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 4.2 min and 5.1 min respectively with an analysis time of 10 min.

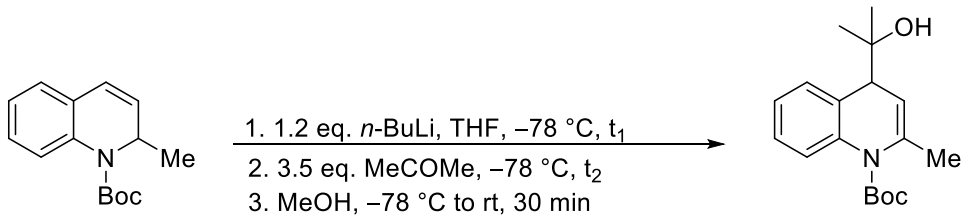
(±)-*tert*-Butyl 4-(2-Hydroxypropan-2-yl)-2-methyl-1,4-dihydroquinoline-1-carboxylate (154)



n-BuLi (0.45 mL, 1.1 mmol, 2.5 M in hexane) was added to carbamate **153** (231 mg, 0.940 mmol) in dry THF (9 mL) at −78 °C. After 1 h, acetone (0.24 mL, 3.3 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (9:1), gave carbamate **154** (240 mg, 83%) as a colourless oil; R_f 0.10 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3425 (O−H), 2974, 2931, 1708 (C=O), 1486, 1456, 1368, 1317, 1240, 1159, 1124, 1059, 848, 768, 652, 528, 487; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (1H, d, *J* 8.5 Hz, ArH), 7.36−7.24 (1H, m, ArH), 7.18−7.11 (2H, m, ArH), 5.48 (1H, dd, *J* 7.0 and 1.5 Hz, C=CH), 3.31 (1H, d, *J* 7.0 Hz, CH), 2.21 (3H, s, CH_3), 1.51 (9H, s, ^{t}Bu), 1.25 (3H, s, CH_3), 1.13 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.5 (C=O), 140.1 (C), 139.1 (C), 131.9 (C), 129.2 (CH), 126.0 (CH), 125.2 (CH), 124.5 (CH), 116.9 (CH), 81.7 (C), 74.6 (C), 51.4 (CH), 28.2 (CH_3), 26.8 (CH_3), 25.8 (CH_3), 21.0 (CH_3); HRMS (ES) found MNa^+, 326.1727. $C_{18}H_{25}NO_3Na$ requires MNa^+, 326.1752; LRMS (ES) found 204 (100%, MH^+ −Boc), 326 (87%, MNa^+).

Resolution between enantiomers of the carbamate **154** was achieved using a Beckman system fitted with a Lux Cellulose−2 column (250 mm × 4.6 mm i.d.) as the

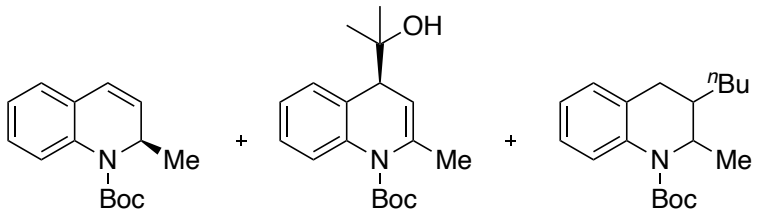
stationary phase with a mixture of *n*-hexane−isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1.0 mL·min^{-1}; ambient temperature, detection by UV absorbance at 254 nm. Injection volume 20 µL of the sample prepared in a 2 g·L^{-1} solution of the eluent. Under these conditions, the faster running component and slower running component were eluted at 16.3 min and 19.9 min respectively with an analysis time of 25 min.



153 **154**

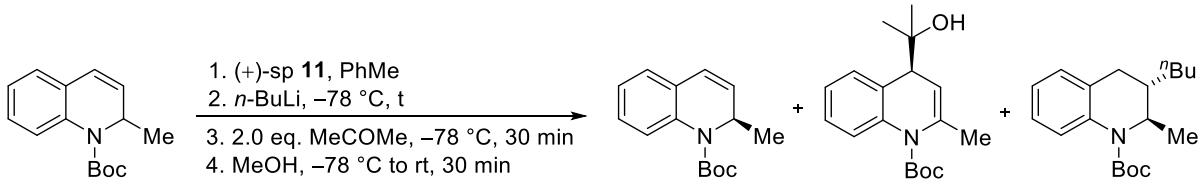
Entry	t_1/ min	t_2/ min	154 yield %	153 yield %
1	6	30	31	63
2	60	30	83	10
3	60	60	84	10

(*S*)-*tert*-Butyl 2-Methyl-1,2-dihydroquinoline-1-carboxylate ((*S*)-153) and (*S*)-*tert*-Butyl 4-(2-Hydroxypropan-2-yl)-2-methyl-1,4-dihydroquinoline-1-carboxylate ((*S*)-154) and (±)-*tert*-Butyl 3-Butyl-2-methyl-1,2,3,4-tetrahydroquinoline-1-carboxylate (155)



n-BuLi (0.35 mL, 0.87 mmol, 2.5 M in hexane) was added to carbamate **153** (214 mg, 0.872 mmol) and (+)-sparteine (248 mg, 1.06 mmol) in dry toluene (16 mL) at −78 °C. After 2 h, acetone (0.13 mL, 1.7 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with hexane−EtOAc (9:1), gave carbamate (*S*)-**153** (63 mg, 30%) as a colourless oil; data as above; the enantiomeric ratio was determined to be 87:13 by CSP−HPLC (Cellulose−2, major component eluted at 3.8 min); $[\alpha]_D^{23}$ +250 (0.2, $CHCl_3$); the carbamate (*S*)-**154** (110 mg, 30%) was also isolated as a single diastereomer as a colourless oil; data as above; the enantiomeric ratio was determined to be 69:31 by CSP−HPLC (Cellulose−2, major component eluted at 16.8 min); $[\alpha]_D^{23}$ +32 (0.1, $CHCl_3$); the carbamate **155** (90 mg, 34%) was also isolated as a colourless oil; R_f 0.79 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 2962, 2928, 2858, 1691 (C=O), 1492, 1366, 1329, 1251, 1168, 1125, 1020, 865, 754, 446; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44 (1H, br d, *J* 7.5 Hz, ArH), 7.06 (1H, td, *J* 7.5 and 1.5 Hz, ArH), 7.00 (1H, dd, *J* 7.5 and 1.5 Hz, ArH), 6.91 (1H, td, *J* 7.5 and 1.0 Hz, ArH), 4.17 (1H, p, *J* 6.5 Hz, CH), 2.69

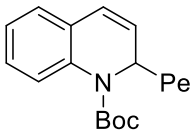
(1H, dd, *J* 15.5 and 5.0 Hz, CH), 2.27 (1H, dd, *J* 15.5 and 7.5 Hz, CH), 1.43 (9H, s, ^{t}Bu), 1.40−1.16 (7H, m, CH and CH_2 × 3), 1.06 (3H, d, *J* 6.5 Hz, CH_3), 0.83 (3H, t, *J* 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.0 (C=O), 136.9 (C), 130.9 (C), 127.8 (CH), 125.7 (CH), 125.2 (CH), 123.6 (CH), 80.3 (C), 53.8 (CH), 42.3 (CH), 33.9 (CH_2), 31.0 (CH_2), 29.5 (CH_2), 28.4 (CH_3), 22.9 (CH_2), 19.5 (CH_3), 14.1 (CH_3); HRMS (ES) found MNa^+, 326.2091. $C_{19}H_{29}NO_2Na$ requires MNa^+, 326.2107; LRMS (ES) found 248 (100%, $MH^+ - {}^{t}Bu$), 326 (28%, MNa^+), 204 (2%, MH^+ −Boc); the enantiomeric ratio was determined to be 59:41 by CSP−HPLC (Cellulose−2, major component eluted at 6.8 min); $[\alpha]_D^{23}$ +14 (0.1, $CHCl_3$);



153 (*S*)-**153** (*S*)-**154** **155**

Entry	t/ h	eq. *n*-BuLi	eq. (+)-sp	(*S*)-153 yield %	(*S*)-153 er	(*S*)-154 yield %	(*S*)-154 er	155 yield %	155 er
1	1	0.8	1.0	49	73:27	11	78:22	35	-
2	1	1.0	1.2	45	77:23	30	69:31	23	-
3	2	1.0	1.2	30	87:13	30	69:31	34	59:41
4	2	0.8	1.5	55	65:35	31	60:40	12	60:40

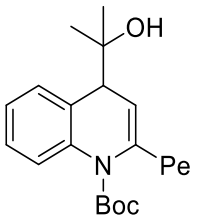
(±)-*tert*-Butyl 2-Pentyl-1,2-dihydroquinoline-1-carboxylate (158)



A portion (2 mL) of 1-bromopentane **157** (7.9 mL, 64 mmol) dissolved in dry Et_2O (10 mL) was added to a solution of Li (973 mg, 127 mmol) in dry Et_2O (50 mL) at room temperature. After 10 min, when the solution turns cloudy, the remaining 1-bromopentane (15.9 mL) solution was added at 0 °C. After 1 h, a solution of quinoline **83** (5.0 mL, 42 mmol) in dry Et_2O (20 mL) was added dropwise at 0 °C. After 1 h, a solution of Boc_2O (14 g, 64 mmol) in dry THF (5 mL) was added dropwise at 0 °C and the mixture was allowed to warm to room temperature over 16 h. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 16 h. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with hexane−EtOAc (95:5), gave carbamate **158** (12 g, 94%) as a colourless oil; R_f 0.88 [hexane−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 2958, 2929, 2857, 1694 (C=O), 1489, 1456, 1367, 1327, 1164, 1131, 1017, 764, 752, 660, 475, 419; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58 (1H, br s, ArH), 7.20 (1H, ddd, *J* 8.5, 6.5 and 2.5 Hz, ArH), 7.09−7.02 (2H, m, ArH), 6.45 (1H, d, *J* 9.5 Hz, C=CH), 6.06 (1H, dd, *J* 9.5 and 6.5 Hz, C=CH), 4.96 (1H, q, *J* 6.5 Hz, CH), 1.54 (9H, s, ^{t}Bu), 1.46−1.15 (8H, m, $CH_2 \times 4$), 0.87 (3H, t, *J* 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.4 (C=O), 135.0 (C), 130.3 (CH), 127.4 (C), 127.0 (CH), 126.0 (CH), 125.0 (CH), 124.6 (CH), 123.7 (CH), 80.9 (C), 52.3 (CH), 33.0 (CH_2), 31.5 (CH_2), 28.4 (CH_3), 25.0 (CH_2), 22.6 (CH_2), 14.0 (CH_3); HRMS (ES) found MNa^+, 324.1934. $C_{19}H_{27}NO_2Na$ requires MNa^+, 324.1949; LRMS (ES) found 246 (100%, $MH^+ - {}^t$Bu), 324 (26%, MNa^+).

Resolution between enantiomers of the carbamate **158** was achieved using a Beckman system fitted with a Lux Cellulose−2 column (250 mm × 4.6 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·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 3.7 min and 4.4 min respectively with an analysis time of 10 min.

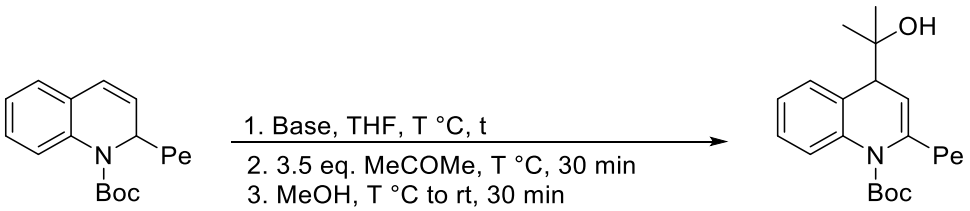
(±)-*tert*-Butyl 4-(2-Hydroxypropan-2-yl)-2-pentyl-1,4-dihydroquinoline-1-carboxylate (159)



s-BuLi (0.68 mL, 0.95 mmol, 1.4 M in cyclohexane) was added to carbamate **158** (239 mg, 0.791 mmol) in dry THF (9 mL) at −78 °C. After 1 h, acetone (0.20 mL, 2.8 mmol) was added and the mixture was stirred for a further 1 h. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with hexane−EtOAc (9:1), gave carbamate **159** (210 mg, 74%) as a colourless oil; R_f 0.09 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3425 (O−H), 2963, 2930, 2860, 1709 (C=O), 1487, 1456, 1367, 1321, 1243, 1162, 1124, 849, 768, 756, 502; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64−7.60 (1H, m, ArH), 7.27−7.23 (1H, m, ArH), 7.18−7.10 (2H, m, ArH), 5.52 (1H, dd, *J* 7.5 and 1.5 Hz,

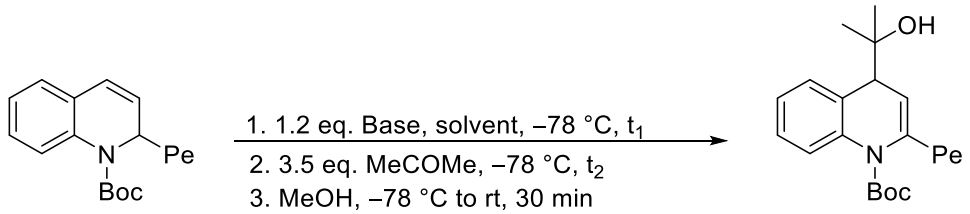
C=CH), 3.32 (1H, d, *J* 7.5 Hz, CH), 1.51 (9H, s, ^{t}Bu), 1.47−1.06 (11H, m, CH_3 and CH_2 × 4), 1.13 (3H, s, CH_3), 0.86 (3H, t, *J* 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.5 (C=O), 143.5 (C), 140.5 (C), 132.3 (C), 129.2 (CH), 126.0 (CH), 125.2 (CH), 124.5 (CH), 116.4 (CH), 81.5 (C), 74.6 (C), 51.5 (CH), 34.0 (CH_2), 31.3 (CH_2), 28.2 (CH_3), 27.2 (CH_2), 26.8 (CH_3), 25.9 (CH_3), 22.5 (CH_2), 14.0 (CH_3); HRMS (ES) found MNa^+, 382.2353. $C_{22}H_{33}NO_3Na$ requires MNa^+, 382.2381; LRMS (ES) found 260 (100%, MH^+ −Boc), 382 (91%, MNa^+).

Resolution between enantiomers of the carbamate **159** was achieved using a Beckman system fitted with a Lux Cellulose−2 column (250 mm × 4.6 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 12.8 min and 16.4 min respectively with an analysis time of 20 min.



158 **159**

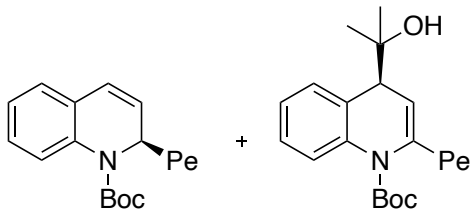
Entry	t/ h	T/ °C	Base	eq. base	159 yield %	158 yield %
1	1	−78	*n*-BuLi	1.2	51	45
2	1	−78	*n*-BuLi	2.0	53	40
3	2	−78	*n*-BuLi	1.2	63	34
4	4	−78	*n*-BuLi	1.2	65	30
5	6	−78	*n*-BuLi	1.2	64	23
6	1	−40	*n*-BuLi	1.2	30	60
7	2	−40	*n*-BuLi	1.2	35	60
8	3	−40	*n*-BuLi	1.2	17	75
9	1	−78	*s*-BuLi	1.2	58	35
10	2	−78	*s*-BuLi	1.2	56	35



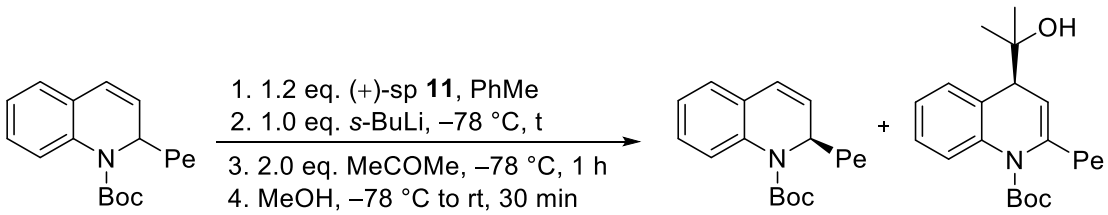
158 **159**

Entry	t_1/ h	t_2/ h	Base	Solvent	159 yield %	158 yield %
1	1	1	*n*-BuLi	THF	46	51
2	1	1	*s*-BuLi, TMEDA	Et_2O	31	67
3	1	1	*s*-BuLi	THF	74	20
4	2	1	*s*-BuLi	THF	68	29
5	2	2	*s*-BuLi	THF	66	30

(*S*)-*tert*-Butyl 2-Pentyl-1,2-dihydroquinoline-1-carboxylate ((*S*)-158) and (*S*)-*tert*-Butyl 4-(2-Hydroxypropan-2-yl)-2-pentyl-1,4-dihydroquinoline-1-carboxylate ((*S*)-159)



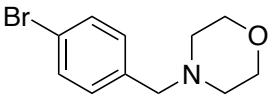
s-BuLi (0.50 mL, 0.70 mmol, 1.4 M in cyclohexane) was added to carbamate **158** (212 mg, 0.702 mmol) and (+)-sparteine (201 mg, 0.859 mmol) in dry toluene (16 mL) at −78 °C. After 2 h, acetone (0.10 mL, 1.4 mmol) was added and the mixture was stirred for a further 1 h. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with hexane−EtOAc (9:1), gave carbamate (*S*)-**158** (180 mg, 83%) as a colourless oil; data as above; the enantiomeric ratio was determined to be 51:49 by CSP−HPLC (Cellulose−2, major component eluted at 3.5 min); the carbamate (*S*)-**159** (38 mg, 15%) was also isolated as a colourless oil; data as above; the enantiomeric ratio was determined to be 53:47 by CSP−HPLC (Cellulose−2, major component eluted at 15.3 min).



158 (*S*)-**158** (*S*)-**159**

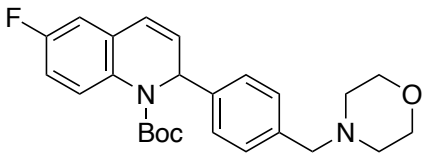
Entry	t/ h	(*S*)-158 yield %	(*S*)-158 er	(*S*)-159 yield %	(*S*)-159 er
1	1	85	51:49	14	52:48
2	2	83	51:49	15	53:47

4-[(4-Bromophenyl)methyl]morpholine (167)



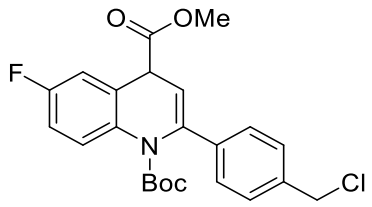
Morpholine **166** (10 mL, 110 mmol) and potassium carbonate (29 g, 200 mmol) were added to a solution of 4-bromobenzyl bromide **165** (25 g, 100 mmol) in acetonitrile (150 mL) and the solution was stirred for 16 h. The mixture was filtered through a pad of celite and the solvent was removed under reduced pressure to give the product **167** (25 g, 96%) as a white amorphous solid; m.p. 73−75 °C (lit. m.p. 82−83 °C.[76]); R_f 0.73 [DCM−MeOH (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3077, 3016, 2971, 2943, 2929, 1366, 1217, 1110, 1066, 516; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 (2H, d, *J* 8.5 Hz, ArH), 7.23 (2H, d, *J* 8.5 Hz, ArH), 3.72 (4H, t, *J* 4.5 Hz, 2 x CH_2), 3.46 (2H, s, CH_2), 2.44 (4H, t, 4.5 Hz, 2 x CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 137.0 (C), 131.4 (CH), 130.8 (CH), 121.0 (C), 67.0 (CH_2), 62.7 (CH_2), 53.6 (CH_2); HRMS (ES) found MH^+, 256.0342. $C_{11}H_{15}BrNO$ requires MH^+, 256.0332; LRMS (ES) found 256 (100%, MH^+). Data consistent with the literature.[76]

(±)-*tert*-Butyl 6-Fluoro-2-{4-[(morpholin-4-yl)methyl]phenyl}-1,2-dihydroquinoline-1-carboxylate (168)



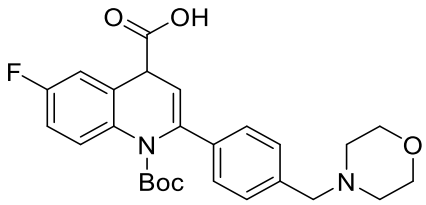
n-BuLi (28 mL, 62 mmol, 2.2 M in hexane) was added to a solution of 4-[(4-bromophenyl)methyl]morpholine **167** (17 g, 62 mmol) in dry THF (32 mL) at −78 °C. After 30 min, a solution of 6-fluoroquinoline (5.0 mL, 41 mmol) in dry THF (15 mL) at 0 °C. After 1 h, a solution of Boc_2O (15 g, 62 mmol) in dry THF (5 mL) was added dropwise and the mixture was allowed to warm to room temperature over 16 h. The reaction was quenched with MeOH (5 mL) and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with DCM−MeOH (98:2), gave carbamate **168** (12 g, 67%) as a red oil; R_f 0.73 [DCM−MeOH (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3007, 2971, 2931, 2855, 2806, 1698 (C=O), 1490, 1368, 1253, 1160, 1114, 1008, 866, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54−7.43 (1H, m, ArH), 7.23−7.18 (4H, m, ArH), 6.92−6.81 (2H, m, ArH), 6.61 (1H, d, *J* 9.5 Hz, C=CH), 6.26 (1H, dd, *J* 9.5 and 6.0 Hz, C=CH), 6.15 (1H, d, *J* 6.0 Hz, CH), 3.72−3.67 (4H, m, 2 x CH_2), 3.44 (2H, s, CH_2), 2.48−2.36 (4H, m, 2 x CH_2), 1.56 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.0 (d, *J* 242.5 Hz, C), 153.4 (C=O), 141.7 (C), 138.4 (C), 131.0 (d, *J* 2.5 Hz, C), 128.6 (d, *J* 8.5 Hz, C), 129.6 (CH), 129.3 (CH), 127.0 (CH), 126.3 (d, *J* 2.5 Hz, CH), 124.7 (CH), 114.0 (d, *J* 22.5 Hz, CH), 112.3 (d, *J* 23.0 Hz, CH), 81.7 (C), 67.0 (CH_2), 63.0 (CH_2), 54.9 (CH), 53.6 (CH_2), 28.4 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −119.3 (1F, s, CF); HRMS (ES) found MH$^+$, 425.2247. $C_{25}H_{30}FN_2O_3$ requires MH$^+$, 425.2235; LRMS (ES) found 425 (100%, MH$^+$).

(±)-1-*tert*-Butyl 4-Methyl 2-[4-(Chloromethyl)phenyl]-6-flouro-1,4-dihydroquinoline-1,4-dicarboxylate (170)



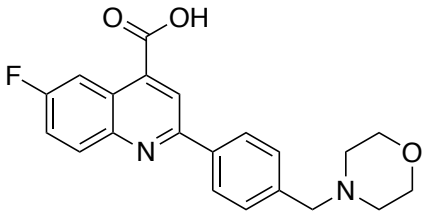
n-BuLi (0.28 mL, 0.66 mmol, 2.4 M in hexane) was added to carbamate **168** (235 mg, 0.554 mmol) in dry THF (9 mL) at −78 °C. After 6 min, methyl chloroformate (0.15 mL, 1.9 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with MeOH (2 mL) and the mixture was allowed to warm to room temperature over 30 min. The solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with DCM−MeOH (98:2), gave carbamate **170** (60 mg, 25%) as a yellow oil; R_f 0.26 [petrol−EtOAc (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 3005, 2977, 2927, 1713 (C=O), 1494, 1368, 1351, 1314, 1252, 11557, 1130, 1021, 817, 736, 674, 631, 449; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (1H, dd, *J* 8.5 and 5.0 Hz, ArH), 7.51−7.36 (4H, m, ArH), 7.08 (1H, td, *J* 8.5 and 3.0 Hz, ArH), 6.95 (1H, dd, *J* 8.5 and 3.0 Hz, ArH), 5.90 (1H, d, *J* 6.5 Hz, C=CH), 4.62 (2H, s, CH_2), 4.40 (1H, d, *J* 6.5 Hz, CH), 3.71 (3H, s, CH_3), 1.18 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.6 (C=O), 160.1 (d, *J* 245.0 Hz, C), 152.2 (C=O), 143.0 (C), 138.4 (C), 137.4 (C), 135.0 (d, *J* 2.5 Hz, C), 132.1 (d, *J* 7.5 Hz, C), 128.6 (CH), 126.4 (d, *J* 8.5 Hz, CH), 125.9 (CH), 114.1 (d, *J* 22.5 Hz, CH), 113.7 (d, *J* 22.5 Hz, CH), 113.0 (CH), 82.0 (C), 52.8 (CH_3), 45.9 (CH_2), 45.7 (CH), 27.7 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −117.5 (1F, s, CF); HRMS (ES) found MNa$^+$, 454.1184. $C_{23}H_{23}{}^{35}ClFNO_4Na$ requires MNa$^+$, 454.1192; LRMS (ES) found 332 (100%, MH$^+$ −Boc), 454 (92%, MNa$^+$).

(±)-1-[(*tert*-Butoxy)carbonyl]-6-fluoro-2-{4-[(morpholin-4-yl)methyl]phenyl}-1,4-dihydroquinoline-4-carboxylic acid (171)



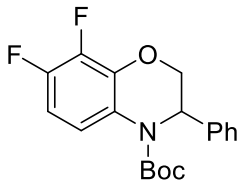
n-BuLi (2.6 mL, 6.5 mmol, 2.5 M in hexane) was added to carbamate **168** (2.3 g, 5.4 mmol) in dry THF (30 mL) at −78 °C. After 6 min, milled dry ice was added and the mixture was stirred for at room temperature. After 1 h, the solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with DCM−MeOH (9:1), gave carbamate **171** (1.97 g, 78%) as a red amorphous solid; m.p. 104−106 °C; R_f 0.17 [DCM−MeOH (9:1)]; FT-IR ν_{max} (film)/cm^{-1} 2974, 2935, 2873, 2810, 1710 (C=O), 1493, 1349, 1316, 1251, 1159, 1128, 1113, 1025, 865, 819, 768, 745, 452; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.80 (1H, dd, *J* 8.5 and 5.0 Hz, ArH), 7.39−7.27 (4H, m, ArH), 7.19−7.09 (2H, m, ArH), 6.01 (1H, d, *J* 6.5 Hz, C=CH), 4.35 (1H, d, *J* 6.5 Hz, CH), 3.62−3.52 (4H, m, 2 x CH_2), 3.47 (2H, s, CH_2), 2.42−2.27 (4H, m, 2 x CH_2), 1.06 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 164.6 (C=O), 159.8 (d, *J* 241.5 Hz, C), 151.9 (C=O), 141.3 (C), 137.5 (C), 136.0 (d, *J* 8.0 Hz, C), 135.8 (d, *J* 2.0 Hz, C), 135.2 (C), 129.4 (CH), 126.1 (d, *J* 8.5 Hz, CH), 125.2 (CH), 116.1 (CH), 113.8 (d, *J* 22.5 Hz, CH), 112.7 (d, *J* 22.5 Hz, CH), 81.4 (C), 71.8 (CH), 66.6 (CH_2), 62.5 (CH_2), 53.5 (CH_2), 27.7 (CH_3); ^{19}F NMR (376 MHz, DMSO-d_6) δ = −120.2 (1F, s, CF); HRMS (ES) found MH^+, 469.2133. $C_{26}H_{30}FN_2O_5$ requires MH^+, 469.2142; LRMS (ES) found 469 (100%, MH^+).

(±)-6-Fluoro-2-{4-[(morpholin-4-yl)methyl]phenyl}-quinoline-4-carboxylic acid (172)



Hydrochloric acid (2.4 mL, 9.6 mmol, 4.0 M in dioxane) was added to a stirred solution of the carbamate **171** (431 mg, 0.920 mmol) at room temperature. After 1 day, the solvent was evaporated under reduced pressure. The residue solution was adjusted to pH 7 to 8 with NaOH. The resulting precipitate was filtered and washed with water (5 mL) and ethyl acetate (5 mL) to give the product **172** (196 mg, 58%) as a white amorphous solid; m.p. 130−132 °C (lit. m.p. 132−134 °C.[77]); R_f 0.55 [DCM−MeOH (8:2)]; FT-IR ν_{max} (film)/cm^{-1} 3405, 3219, 1575, 1473, 1381, 1353, 1262, 1203, 1124, 969, 917, 869, 793, 740, 674, 533, 492; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.57−8.43 (2H, m, ArH), 8.30−8.18 (3H, m, ArH), 7.79 (1H, t, *J* 8.5 Hz, ArH), 7.53 (2H, d, *J* 8.0 Hz, ArH), 3.77−3.49 (6H, m, 3 x CH_2), 2.47−2.43 (4H, m, 2 x CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 173.4 (C=O), 160.7 (d, *J* 244.0 Hz, C), 141.1 (C), 140.8 (C), 138.8 (d, *J* 8.0 Hz, C), 137.5 (C), 137.0 (d, *J* 3.5 Hz, C), 135.4 (C), 129.5 (CH), 128.8 (d, *J* 8.5 Hz, CH), 127.3 (CH), 125.9 (CH), 115.8 (d, *J* 23.0 Hz, CH), 115.2 (d, *J* 22.5 Hz, CH), 66.6 (CH_2), 62.4 (CH_2), 53.6 (CH_2); ^{19}F NMR (376 MHz, DMSO-d_6) δ = −111.2 (1F, s, CF); HRMS (ES) found MH$^+$, 367.1453. $C_{21}H_{20}FN_2O_3$ requires MH$^+$, 367.1456; LRMS (ES) found 367 (100%, MH$^+$). Data consistent with the literature.[77]

(±)-1-*tert*-Butyl 7,8-Difluoro-3-phenyl-3,4-dihydro-*2H*-1,4-benzoxazine-1-carboxylate (221)

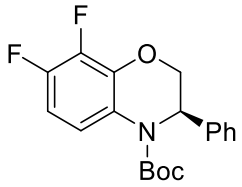


n-BuLi (6.2 mL, 15 mmol, 2.4 M in hexane) was added to a stirred solution of 7,8-difluoro-3-phenyl-1,2,3,4-tetrahydro-1,4-benzoxazine **226** (3.32 g, 13.4 mmol) in dry THF (34 mL) at −78 °C. After 40 min, a solution of Boc_2O (4.28 g, 19.6 mmol) in dry THF (5 mL) was added and the mixture was allowed to warm to room temperature over 16 h. The reaction mixture was diluted with 10% aqueous sodium hydrogencarbonate solution (20 mL) and was extracted with Et_2O (3 x 50 mL). The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel, eluting with petrol−EtOAc (98:2 → 95:5), to give the carbamate **221** (4.2 g, 90%) as a white amorphous solid; m.p. 56−58 °C; R_f 0.54 [petrol−EtOAc (8:2)]; FT-IR ν_{max}/cm^{-1} 3007, 2979, 2931, 2880, 1704 (C=O), 1509, 1492, 1368, 1302, 1260, 1230, 1160, 1090, 749; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82−7.74 (1H, m, ArH), 7.33−7.24 (5H, m, ArH), 6.77−6.68 (1H, m, ArH), 5.69 (1H, t, *J* 3.0 Hz, CH), 4.79 (1H, dd, *J* 11.0 and 3.0 Hz, CH), 4.41 (1H, dd, *J* 11.0 and 3.0 Hz, CH), 1.51 (9H, s, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.5 (C=O), 146.9 (dd, *J* 244.0 and 10.0 Hz, C), 140.1 (dd, *J* 245.5 and 15.5 Hz, C), 137.7 (C), 136.4 (dd, *J* 10.5 and 3.0 Hz, C), 128.7 (CH), 127.7 (CH), 126.4 (CH), 123.2 (br C), 117.2 (dd, *J* 7.0 and 4.0 Hz, CH), 107.8 (d, *J* 18.0 Hz, CH), 82.5 (C), 68.6 (CH_2), 53.9 (CH), 28.2 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −142.9 (1F, d, *J* 21.0 Hz, CF), −159.6 (1F, d, *J* 21.0 Hz,

CF); HRMS (ES) found MNa^+, 370.1225. $C_{19}H_{19}F_2NO_3Na$ requires MNa^+, 370.1225; LCMS (ES) 292.1 (100%, MH^+ -^{t}Bu), 370.1 (7%, MNa^+), 248.1 (7%, MH^+ −Boc).

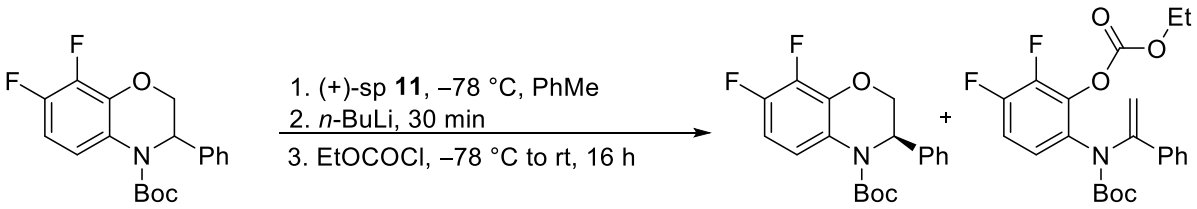
Resolution between enantiomers of the carbamate **221** was achieved using a Beckman system fitted with a Lux Cellulose−1 column (250 mm × 4.6 mm i.d.) as the stationary phase with a mixture of *n*-hexane−isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1.0 $mL \cdot min^{-1}$; ambient temperature, 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 8.3 min and 9.2 min respectively with an analysis time of 12 min.

(*R*)-1-*tert*-Butyl 7,8-Difluoro-3-phenyl-3,4-dihydro-*2H*-1,4-benzoxazine-1-carboxylate ((*R*)-221)



n-BuLi (73 μL, 0.18 mmol, 2.4 M in hexane) was added to carbamate **221** (103 mg, 297 mmol) and (+)-sparteine **11** (72 mg, 0.31 mmol) in dry toluene (8 mL) at −78 °C. After 30 min, ethyl chloroformate (60 μL, 0.58 mmol) was added and the mixture was allowed to warm to room temperature overnight. MeOH (2 mL) was added and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with petrol−EtOAc (95:5), to give recovered (*R*)-**221** (39 mg, 37%) as a white amorphous solid; m.p. 50−52 °C; data

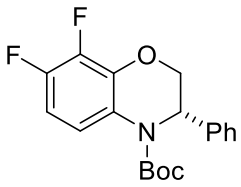
same as above; the enantiomeric ratio was determined to be 75:25 by CSP−HPLC (Cellulose−1, major component eluted at 8.1 min); recrystallisation (DCM−hexane) gave er 96:4 by CSP−HPLC; $[\alpha]_D^{23}$ −56 (0.1, $CHCl_3$); the carbamate **227** (64 mg, 51%) was also isolated as a yellow oil; data as above.



221 (*R*)-**221** **227**

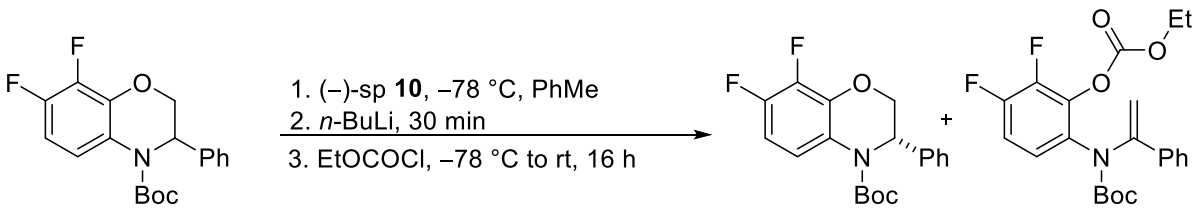
Entry	eq. *n*-BuLi	eq. (+)-sp	(*R*)-221 yield %	(*R*)-221 er	227 yield %	s
1	1.0	1.0	13	94:6	80	3
2	0.9	1.2	20	95:5	73	4
3	0.6	0.8	24	96:4	51	5

(*S*)-1-*tert*-Butyl 7,8-Difluoro-3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazine-1-carboxylate ((*S*)-221)



n-BuLi (0.30 mL, 0.70 mmol, 2.3 M in hexane) was added to carbamate **221** (350 mg, 1.0 mmol) and (−)-sparteine **10** (290 mg, 1.2 mmol) in dry toluene (28 mL) at −78 °C. After 30 min, ethyl chloroformate (0.2 mL, 2 mmol) was added and the mixture was allowed to warm to room temperature overnight. MeOH (5 mL) was added and the solvent was removed under reduced pressure. The crude product was purified by

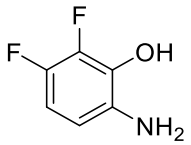
column chromatography, eluting with petrol−EtOAc (95:5), to give recovered (*S*)-**221** (96 mg, 28%) as a white amorphous solid; m.p. 50−52 °C; data as above; the enantiomeric ratio was determined to be 98:2 by CSP−HPLC (Cellulose−1, major component eluted at 8.5 min); $[\alpha]_D^{23}$ +91 (0.3, $CHCl_3$); the carbamate **227** (238 mg, 67%) was also isolated as a yellow oil; data as above.



221 (*S*)-**221** **227**

Entry	eq. *n*-BuLi	eq. (–)-sp	(*S*)-221 yield %	(*S*)-221 er	(*S*)-221 er after recryst	227 yield %	s
1	0.6	0.8	51	77:23	-	32	6
2	0.6	0.9	47	77:23	95:5	52	5
3	0.7	0.9	35	84:16	98:2	56	4
4	0.7	0.9	45	78:22	98:2	54	4
5	0.7	0.9	49	75:25	94:6	50	5
6	0.7	1.2	28	98:2	-	67	7

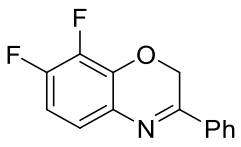
6-Amino-2,3-difluorophenol (223)



2,3-Difluoro-6-nitrophenol **222** (5.04 g, 28.8 mmol) was added to 10% Pd/C (1.55 g, 1.46 mmol) in MeOH (286 mL). The reaction mixture was cooled to 15 ºC and $NaBH_4$ (2.24 g, 59.1 mmol) was added slowly. After 1 h, the mixture was filtered through a

pad of celite and the solvent was removed under reduced pressure. Water (30 mL) was added and the mixture was basified using $NaHCO_3$ to pH 8. The organic product was extracted with Et_2O (20 mL) and was washed with water (3 × 10 mL). The combined organic layers were dried using $MgSO_4$, filtered and the solvent was removed under reduced pressure to give the product **223** (3.5 g, 83%) as a brown amorphous solid; m.p. 114−116 ºC (no lit. m.p. reported.[97]); R_f 0.09 [petrol−EtOAc (8:2)]; FT-IR ν_{max}/cm^{-1} 3267 (O−H), 3244, (N−H) 1597, 1505, 1345, 1261, 1035, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.65−6.41 (2H, m, ArH), 3.86 (2H, s, NH_2), 1.67 (1H, s, OH); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −149.5 (1F, d, *J* 21.5 Hz, CF), −162.9 (1F, d, *J* 21.5 Hz, CF); HRMS (ES) found MH$^+$, 146.0414. $C_6H_6F_2NO$ requires MH$^+$, 146.0412; LCMS (ES) 146.0 (100%, MH$^+$). Data consistent with the literature.[97]

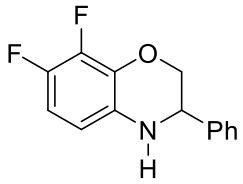
(±)-7,8-Difluoro-3-phenyl-*2H*-1,4-benzoxazine (225)



6-Amino-2,3-difluorophenol **223** (3.49 g, 24.0 mmol) and Bu_4NHSO_4 (277 mg, 0.814 mmol) were added to a solution of potassium carbonate (19.0 g, 138 mmol) in water (140 mL) and DCM (140 mL) and the solution was stirred vigorously. A solution of 2-bromoacetophenone **224** (4.84 g, 24.3 mmol) in DCM (50 mL) was slowly added to the reaction mixture and the mixture was left to stir for 16 h. The layers were separated and the aqueous phase was extracted with DCM (2 × 100 mL). The solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with petrol−EtOAc (95:5), to give product **225** (4.5 g, 76%) as a yellow amorphous solid; m.p. 114−116 ºC; R_f 0.54 [petrol−EtOAc

(8:2)]; FT-IR ν_{max}/cm^{-1} 3069, 3029, 2850, 1630, 1507, 1477, 1449, 1213, 1090, 809, 758; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97−7.90 (2H, m, ArH), 7.59−7.47 (3H, m, ArH), 7.20 (1H, ddd, *J* 8.5, 5.5 and 2.0 Hz, ArH), 6.83 (1H, ddd, *J* 10.0, 8.5 and 7.5 Hz, ArH), 5.15 (2H, s, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, one quaternary carbon could not be observed) δ = 158.2 (C), 150.4 (dd, *J* 248.5 and 10.5 Hz, C), 139.5 (dd, *J* 250.5 and 16.0 Hz, C), 134.9 (C), 131.6 (CH), 131.1 (dd, *J* 4.0 and 2.0 Hz, C), 128.9 (CH), 126.4 (CH), 122.1 (dd, *J* 8.0 and 3.5 Hz, CH), 109.1 (d, *J* 18.5 Hz, CH), 62.6 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −135.7 (1F, d, *J* 20.0 Hz, CF), −160.5 (1F, d, *J* 20.0 Hz, CF); HRMS (ES) found MH^+, 246.0716. $C_{14}H_{10}F_2NO$ requires MH^+, 246.0725; LCMS (ES) 246.1 (100%, MH^+).

(±)-7,8-Difluoro-3-phenyl-3,4-dihydro-*2H*-1,4-benzoxazine (226)



$NaBH_4$ (1.21 g, 31.9 mmol) was added to a solution of the benzoxazine **225** (3.59 g, 14.4 mmol) in ethanol (50 mL) and water (13 mL) and the mixture was heated at 90 °C for 3 h. After cooling to room temperature, DCM(100 mL) and H_2O (100 mL) were added. The aqueous phase was extracted with DCM (2 x 100 mL) and the solvent was removed under reduced pressure to give the product **226** (3.4 g, 93%) as a yellow amorphous solid; m.p. 54−56 °C; R_f 0.51 [petrol−EtOAc (8:2)]; FT-IR ν_{max}/cm^{-1} 3369 (N−H), 3064, 3029, 2956, 2921, 2851, 1612, 1500, 1324, 1255, 1223, 1055, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56−7.35 (5H, m, ArH), 6.63 (1H, dt, *J* 9.0 and 8.0 Hz, ArH), 6.37 (1H, ddd, *J* 9.0, 5.0 and 2.0 Hz, ArH), 4.50 (1H, dd, *J* 9.0 and 1.5 Hz, CH),

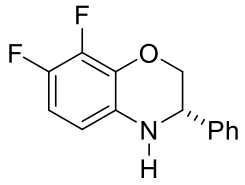
4.44−4.37 (1H, m, CH), 4.11−3.94 (2H, m, CH and NH); ^{13}C NMR (100 MHz, $CDCl_3$, one quaternary carbon could not be observed) δ = 144.5 (dd, *J* 237.5 and 10.5 Hz, C), 140.7 (dd, J 244.5 and 15.5 Hz, C), 138.2 (C), 131.5 (dd, *J* 6.0 and 3.5 Hz, C), 129.0 (CH), 128.7 (CH), 127.2 (CH), 108.4 (dd, *J* 7.5 and 4.0 Hz, CH), 108.0 (d, *J* 18.5 Hz, CH), 71.2 (CH_2), 53.8 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −149.7 (1F, d, *J* 21.0 Hz, CF), −160.4 (1F, d, *J* 21.0 Hz, CF); HRMS (ES) found MH^+, 248.0887. $C_{14}H_{12}F_2NO$ requires MH^+, 248.0881; LCMS (ES) 248.1 (100%, MH^+).

Alternatively,

Trifluoroacetic acid (0.22 mL, 2.9 mmol) was added to a stirred solution of the carbamate **221** (52 mg, 0.15 mmol) in DCM (5 mL) at room temperature. After 1 day, the solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel, eluting with petrol−EtOAc (96:4), to give the product **226** (36 mg, 97%) as a yellow amorphous solid; data as above.

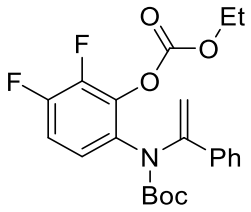
Resolution between enantiomers of the benzoxazine **226** was achieved using a Beckman system fitted with a Daicel ChiralPak IA column (250 mm × 4.6 mm i.d.) as the stationary phase with a mixture of *n*-hexane−isopropanol (99:1 v/v) as the mobile phase at a flow rate of 1.0 $mL \cdot min^{-1}$; ambient 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 18.2 min and 20.8 min respectively with an analysis time of 25 min.

(*S*)-7,8-Difluoro-3-phenyl-3,4-dihydro-*2H*-1,4-benzoxazine ((*S*)-226)



Trifluoroacetic acid (0.50 mL, 5.7 mmol) was added to a stirred solution of the carbamate (*S*)-**221** (100 mg, 287 mmol, 98:2 er) in DCM (10 mL) at room temperature. After 1 day, the solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel, eluting with petrol−EtOAc (96:4), to give the product (*S*)-**226** (63 mg, 88%) as a yellow amorphous solid; data as above; the enantiomeric ratio was determined to be 95:5 by CSP−HPLC (ChiralPak IA column, major component eluted at 18.7 min); $[\alpha]_D^{23}$ +110 (0.1, $CHCl_3$).

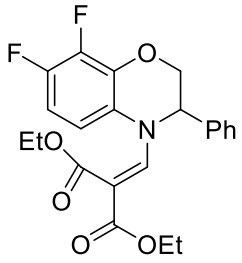
(±)-2-[(tert-Butoxycarbonyl)(1-phenylethenyl)amino]-5,6-difluorophenyl ethyl carbonate (227)



n-BuLi (0.15 mL, 0.346 mmol, 2.3 M in hexane) was added to carbamate **221** (103 mg, 0.297 mmol) in dry 2-MeTHF (8 mL) at −78 °C. After 6 min, ethyl chloroformate (0.1 mL, 1 mmol) was added and mixture was allowed to warm to room temperature over 16 h. MeOH (2 mL) was added and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (95:5), gave carbamate **227** (85 mg, 68%) as a yellow oil; R_f 0.46 [petrol−EtOAc (8:2)]; FT-IR

ν_{max}/cm^{-1} 2981, 1779 (C=O), 1714 (C=O), 1508, 1298, 1249, 1215, 1161, 1008, 775, 705; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 (2H, d, *J* 7.0 Hz, ArH), 7.42−7.30 (3H, m, ArH), 7.16−7.03 (2H, m, ArH), 5.30 (1H, s, CH), 4.93 (1H, s, CH), 4.40−4.15 (2H, m, CH_2), 1.36−1.17 (12H, m, CH_3 and ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.7 (C=O), 151.2 (C=O), 149.3 (dd, *J* 249.5 and 11.0 Hz, C), 148.5 (C), 144.2 (dd, *J* 253.0 and 15.0 Hz, C), 138.3 (C), 136.3 (dd, *J* 11.0 and 2.5 Hz, C), 133.0 (d, *J* 3.5 Hz, C), 128.4 (CH), 128.3 (CH), 125.8 (CH), 122.3 (dd, *J* 7.5 and 3.5 Hz, CH), 114.3 (d, *J* 18.0 Hz, CH), 110.4 (CH_2), 81.9 (C), 65.7 (CH_2), 27.6 (CH_3), 13.9 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −134.0 (1F, d, *J* 21.0 Hz, CF), −159.6 (1F, d, *J* 21.0 Hz, CF); HRMS (ES) found MNa^+, 442.1447. $C_{22}H_{23}F_2NO_5Na$ requires MNa^+, 442.1437; LCMS (ES) 320.1 (100%, MH^+), 442.1 (14%, MNa^+).

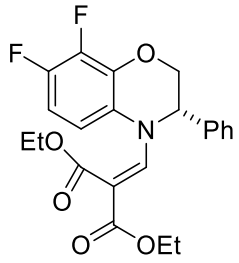
(±)-1,3-Diethyl 2-[(7,8-Difluoro-3-phenyl-3,4-dihydro-*2H*-1,4-benzoxazin-4-yl)methylidene]propanedioate (228)



Diethyl ethoxymethylenemalonate **180** (1.57 g, 7.28 mmol) was added to carbamate **226** (762 mg, 3.08 mmol) and the mixture was heated at 140 °C for 26 h. After cooling to room temperature, the solvent was removed under reduced pressure and the crude product was purified by recrystallisation in hexane−DCM, to give the product **228** (1.1 g, 81%) as a yellow amorphous solid; m.p. 108−110 °C; R_f 0.18 [petrol−EtOAc (8:2)]; FT-IR ν_{max}/cm^{-1} 3037, 2986, 1723 (C=O), 1594, 1564, 1480, 1304, 1250, 1170, 1084,

798, 699, 534; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 (1H, s, CH), 7.37−7.25 (3H, m, ArH), 7.15−7.13 (2H, m, ArH), 7.01−6.96 (1H, m, ArH), 6.89−6.82 (1H, m, ArH), 5.31 (1H, br s, CH), 4.71 (1H, dd, *J* 11.0 and 1.5 Hz, CH), 4.39 (1H, dd, *J* 11.0 and 1.5 Hz, CH), 4.33−4.16 (2H, m, CH_2), 3.98 (1H, dq, *J* 11.0 and 7.0 Hz, CH_2), 3.37 (1H, dq, *J* 11.0 and 7.0 Hz, CH_2), 1.28 (3H, t, *J* 7.0 Hz, CH_3), 0.93 (3H, t, *J* 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.6 (C=O), 166.2 (C=O), 147.6 (dd, *J* 245.0 and 10.5 Hz, C), 142.2 (CH), 140.4 (dd, *J* 248.5 and 15.5 Hz, C), 136.1 (dd, *J* 11.5 and 3.0 Hz, C), 135.7 (C), 128.8 (CH), 128.1 (CH), 126.2 (C), 126.1 (CH), 111.4 (dd, *J* 7.5 and 4.0 Hz, CH), 109.1 (d, *J* 19.0 Hz, CH), 103.1 (C), 69.3 (CH_2), 61.4 (CH_2), 61.0 (CH_2), 57.3 (CH), 14.3 (CH_3), 13.5 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −141.4 (1F, d, *J* 20.5 Hz, CF), −157.5 (1F, d, *J* 20.5 Hz, CF); HRMS (ES) found MH^+, 418.1475. $C_{22}H_{22}F_2NO_5$ requires MH^+, 418.1461; LCMS (ES) 418.1 (100%, MH^+), 440.1 (54%, MNa^+).

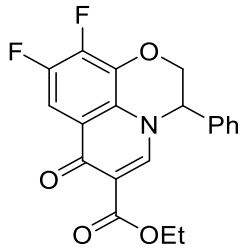
(*S*)-1,3-Diethyl 2-[(7,8-Difluoro-3-phenyl-3,4-dihydro-2H-1,4-benzoxazin-4-yl)methylidene]propanedioate ((*S*)-228)



Diethyl ethoxymethylenemalonate **180** (74 mg, 0.34 mmol) was added to carbamate (*S*)-**226** (44 mg, 0.17 mmol, 93:7 er) and the mixture was heated at 140 °C for 26 h. After cooling to room temperature, the solvent was removed under reduced pressure

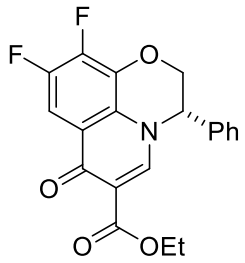
and the crude product was purified by recrystallisation in hexane−DCM, to give the product (*S*)-**228** (72 mg, 98%) as a yellow oil; data as above; $[\alpha]_D^{23}$ +75 (0.4, $CHCl_3$).

(±)-Ethyl 6,7-Difluoro-10-oxo-2-phenyl-4-oxa-1-azatricyclo[7.3.1.$0^{5,13}$]trideca-5,7,9(13),11-tetraene-11-carboxylate (229)



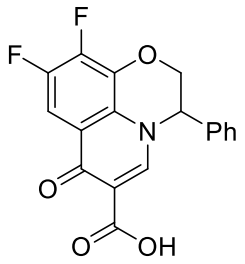
Poly(phosphoric acid) (928 mg, 9.47 mmol) was added to compound **228** (198 mg, 0.473 mmol) and the mixture was heated at 140 °C for 4 h. After cooling to room temperature, H_2O (20 mL) was added and the mixture was filtered to collect the crude product which was washed with H_2O (5 mL) to give compound **229** (150 mg, 85%) as a brown amorphous solid; m.p. 242−244 °C; R_f 0.72 [DCM−MeOH (9:1)]; FT-IR ν_{max}/cm^{-1} 1725 (C=O), 1595, 1565, 1483, 1305, 1252, 1172, 1086, 799, 751, 700; ^{19}F NMR (376 MHz, DMSO-d_6) δ = −138.6 (1F, d, *J* 23.0 Hz, CF), −153.6 (1F, d, *J* 23.0 Hz, CF); HRMS (ES) found MH^+, 372.1053. $C_{20}H_{16}F_2NO_4$ requires MH^+, 372.1042; LCMS (ES) 372.1 (100%, MH^+), 394.1 (8%, MNa^+).

(*S*)-Ethyl 6,7-Difluoro-10-oxo-2-phenyl-4-oxa-1-azatricyclo[7.3.1.0^{5,13}]trideca-5,7,9(13),11-tetraene-11-carboxylate ((*S*)-229)



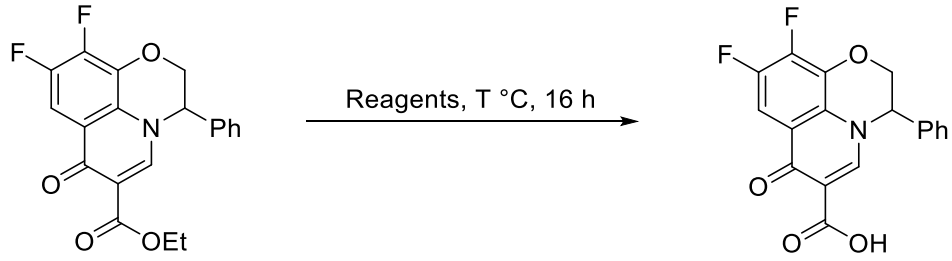
Poly(phosphoric acid) (339 mg, 3.46 mmol) was added to compound (*S*)-**228** (72 mg, 0.17 mmol) and the mixture was heated at 140 °C for 4 h. After cooling to room temperature, H_2O (10 mL) was added and the mixture was filtered to collect the crude product which was washed with H_2O (5 mL) to give compound (*S*)-**229** (63 mg, 98%) as a brown amorphous solid; data as above; m.p. 190−192 °C.

(±)-6,7-Difluoro-10-oxo-2-phenyl-4-oxa-1-azatricyclo[7.3.1.0^{5,13}]trideca-5,7,9(13),11-tetraene-11-carboxylate (230)



HCl (4 mL, 12 M) and glacial acetic acid (8 mL) were added to a solution of compound **229** (3.23 g, 9.40 mmol) in H_2O (4 mL) and the mixture was heated at 90 °C for 16 h. The reaction mixture was cooled to 0 °C for 1 h and was filtered to collect the crude product which was washed with H_2O (10 mL) to give compound **230** (2.0 g, 67%) as a brown amorphous solid; m.p. 288−290 °C; R_f 0.53 [DCM−MeOH (9:1)]; FT-IR ν_{max}/

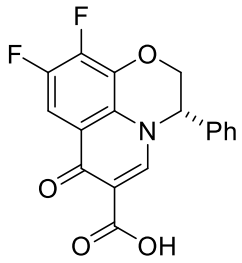
cm^{-1} 3067, 2953, 2919, 2852, 1724 (C=O), 1718 (C=O), 1621, 1567, 1490, 1470, 1302, 1102, 956, 807, 700; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 14.7 (1H, s, OH), 8.94 (1H, s, CH), 8.01−7.79 (1H, m, ArH), 7.45−7.36 (3H, m, ArH), 7.23−7.14 (2H, m, ArH), 6.17 (1H, br s, CH), 5.02 (1H, br d, *J* 11.5 Hz, CH), 4.81 (1H, br d, *J* 11.5 Hz, CH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 177.1 (C=O), 165.9 (C=O), 149.4 (dd, *J* 249.0 and 11.5 Hz, C), 148.0 (CH), 142.2 (dd, *J* 253.0 and 17.0 Hz, C), 136.7 (dd, *J* 11.5 and 3.0 Hz, C), 136.5 (C), 129.6 (CH), 129.3 (CH), 127.1 (CH), 126.9 (C), 121.7 (dd, *J* 8.0 and 2.0 Hz, C), 108.6 (C), 104.5 (d, *J* 19.5 Hz, CH), 69.7 (CH_2), 61.7 (CH); ^{19}F NMR (376 MHz, DMSO-d_6) δ = −135.6 (1F, d, *J* 22.5 Hz, CF), −150.6 (1F, d, *J* 22.5 Hz, CF); HRMS (ES) found MH^+, 344.0730. $C_{18}H_{12}F_2NO_4$ requires MH^+, 344.0729; LCMS (ES) 344.1 (100%, MH^+).



229 **230**

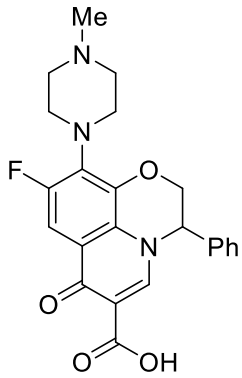
Entry	Reagents	T/ °C	230 yield %
1	10% NaOH	80	16
2	10% KOH	70	17
3	Acetic acid, H_2SO_4	125	32
4	Acetic acid, conc. HCl	90	67

(*S*)-6,7-Difluoro-10-oxo-2-phenyl-4-oxa-1-azatricyclo[7.3.1.0^{5,13}]trideca-5,7,9(13),11-tetraene-11-carboxylate ((*S*)-230)



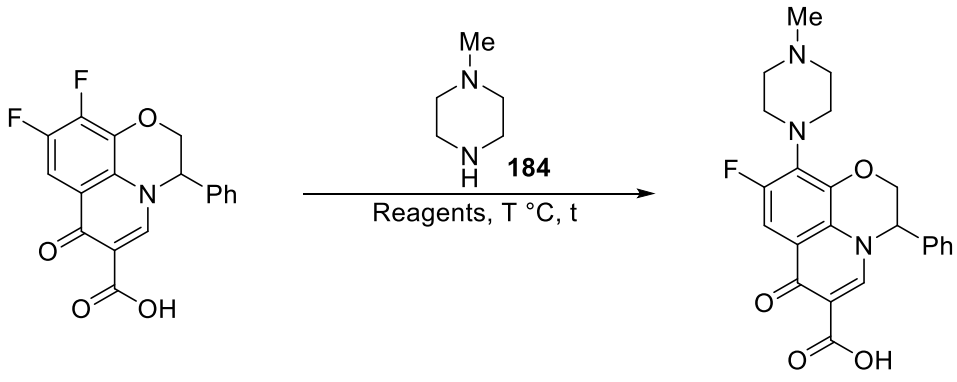
HCl (0.2 mL, 12 M) and glacial acetic acid (0.4 mL) were added to a solution of compound (*S*)-**229** (63 mg, 0.17 mmol) in H_2O (0.2 mL) and the mixture was heated at 90 °C for 16 h. The reaction mixture was cooled to 0 °C for 1 h and was filtered to collect the crude product which was washed with H_2O (2 mL) to give compound (*S*)-**230** (52 mg, 89%) as a brown amorphous solid; data as above; m.p. 274−276 °C.

(±)-7-Fluoro-6-(4-methylpiperazin-1-yl)-10-oxo-2-phenyl-4-oxa-1-azatricyclo[7.3.1.0^{5,13}]trideca-5,7,9(13),11-tetraene-11-carboxylic acid (231)



1-Methylpiperazine **184** (0.40 mL, 3.6 mmol) was added to a solution of compound **230** (208 mg, 0.606 mmol) in Et_3N (0.4 mL) and MeCN (1 mL) and the mixture was heated at 90 °C for 24 h. After cooling to room temperature, the mixture was filtered

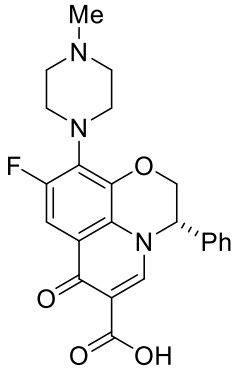
to collect the crude product which was washed with MeOH (5 mL) to give compound **231** (74 mg, 29%) as a yellow amorphous solid; m.p. 258−260 °C; R_f 0.44 [DCM−MeOH (9:1)]; FT-IR ν_{max}/cm^{-1} 3064, 3032, 2924, 2852, 2793, 1724 (C=O), 1619, 1520, 1448, 1374, 1291, 1238, 1089, 1005, 805, 744, 699, 449; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.80 (1H, s, CH), 7.66 (1H, d, *J* 12.5 Hz, ArH), 7.44−7.34 (3H, m, ArH), 7.17−7.10 (2H, m, ArH), 6.06 (1H, br s, CH), 4.88 (1H, br d, *J* 11.5 Hz, CH), 4.68 (1H, br d, *J* 11.5 Hz, CH), 3.26−3.21 (4H, m, 2 × CH_2), 2.43−2.33 (4H, m, 2 × CH_2), 2.20 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 177.1 (C=O), 166.3 (C=O), 155.9 (d, *J* 246.5 Hz, C), 147.2 (CH), 140.8 (C), 137.3 (C), 132.7 (C), 129.6 (CH), 129.1 (CH), 127.0 (CH), 126.6 (C), 119.8 (d, *J* 10.0 Hz, C), 107.5 (C), 104.1 (d, *J* 24.0 Hz, CH), 68.9 (CH_2), 61.6 (CH), 55.6 (CH_2), 50.5 (CH_2), 46.5 (CH_3); ^{19}F NMR (376 MHz, DMSO-d_6) δ = −120.0 (1F, s, CF); HRMS (ES) found MH$^+$, 424.1674. $C_{23}H_{23}FN_3O_4$ requires MH$^+$, 424.1667; LCMS (ES) 424.2 (100%, MH$^+$).



230 **231**

Entry	Reagents	T/ °C	t/ h	231 yield %
1	-	90	16	-
2	Pyridine	120	16	6
3	MeCN, Et_3N	90	16	7
4	MeCN, Et_3N	90	24	29

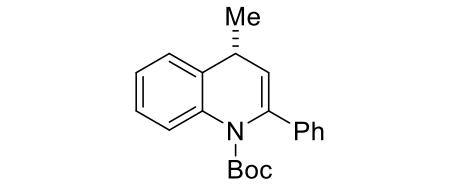
(*S*)-7-Fluoro-6-(4-methylpiperazin-1-yl)-10-oxo-2-phenyl-4-oxa-1-azatricyclo[7.3.1.0^{5,13}]trideca-5,7,9(13),11-tetraene-11-carboxylic acid ((*S*)-231)



1-Methylpiperazine **184** (0.75 mL, 6.8 mmol) was added to a solution of compound (*S*)-**230** (140 mg, 0.41 mmol) in Et_3N (0.3 mL) and MeCN (0.3 mL) and the mixture was heated at 90 °C for 24 h. After cooling to room temperature, the solvent was removed under reduced pressure. The mixture was filtered to collect the crude product which was washed with MeOH (2 mL) to give compound (*S*)-**231** (34 mg, 20%) as a yellow amorphous solid; data as above; m.p. 252−254 °C; $[\alpha]_D^{23}$ −68 (0.2, DMSO).

Appendices

Appendix 1 – X-ray crystal structure data for compound (*R*)-**113**



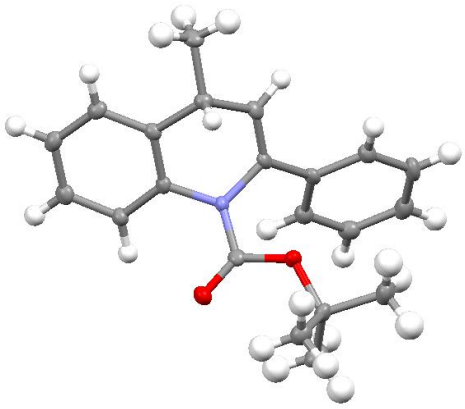


Table 1. Crystal data and structure refinement for oic318v_0m.

Identification code	OIC318v_0m
Empirical formula	$C_{21}H_{23}NO_2$
Formula weight	321.40
Temperature/K	100.01
Crystal system	monoclinic
Space group	$P2_1$
a/Å	9.8984(4)
b/Å	16.1478(6)
c/Å	11.9552(5)
α/°	90
β/°	112.850(2)
γ/°	90
Volume/Å^3	1760.93(12)
Z	4

ρ_{calc}g/cm^3	1.212
μ/mm^{-1}	0.610
F(000)	688.0
Crystal size/mm^3	0.3 × 0.25 × 0.14
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	8.024 to 133.27
Index ranges	-11 ≤ h ≤ 11, -19 ≤ k ≤ 19, -14 ≤ l ≤ 14
Reflections collected	87863
Independent reflections	6219 [R_{int} = 0.0463, R_{sigma} = 0.0172]
Data/restraints/parameters	6219/1/441
Goodness-of-fit on F^2	1.084
Final R indexes [I>=2σ (I)]	R_1 = 0.0420, wR_2 = 0.1080
Final R indexes [all data]	R_1 = 0.0429, wR_2 = 0.1085
Largest diff. peak/hole / e Å^{-3}	0.27/-0.21
Flack parameter	0.02(7)

Appendix 2 – X-ray crystal structure data for compound (*R*,*R*)-**128**

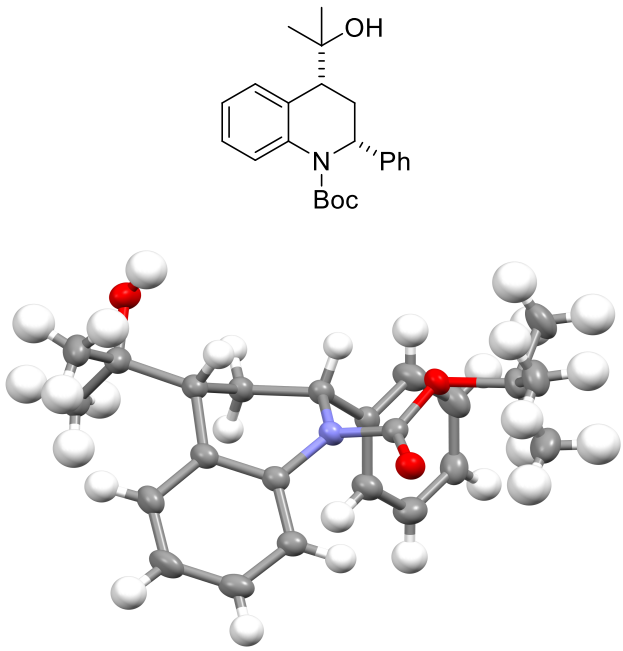
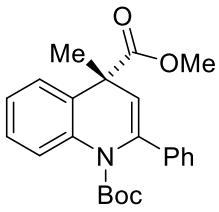


Table 1. Crystal data and structure refinement for oic325ncs_2022NCS0094r1.

Identification code	OIC325ncs_2022NCS0094r1
Empirical formula	$C_{23}H_{29}NO_3$
Formula weight	367.47
Temperature/K	100(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	10.1059(2)
b/Å	10.7256(2)
c/Å	37.6613(6)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	4082.18(13)
Z	8
ρ_{calc}g/cm^3	1.196
μ/mm^{-1}	0.622
F(000)	1584.0
Crystal size/mm^3	0.140 × 0.060 × 0.010
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	4.692 to 140.122
Index ranges	-12 ≤ h ≤ 12, -13 ≤ k ≤ 10, -45 ≤ l ≤ 45
Reflections collected	82266
Independent reflections	7726 [R_{int} = 0.0728, R_{sigma} = 0.0260]
Data/restraints/parameters	7726/0/499
Goodness-of-fit on F^2	1.041
Final R indexes [I>=2σ (I)]	R_1 = 0.0394, wR_2 = 0.0988
Final R indexes [all data]	R_1 = 0.0431, wR_2 = 0.1007
Largest diff. peak/hole / e Å^{-3}	0.20/-0.20
Flack parameter	0.02(7)

Appendix 3 – X-ray crystal structure data for compound (*R*)-**123**



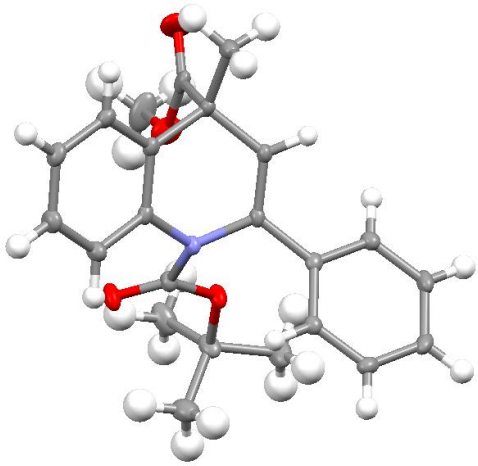
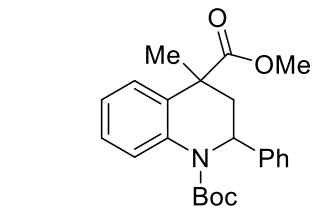


Table 1. Crystal data and structure refinement for oic321v_0m.

Identification code	OIC321v_0m
Empirical formula	$C_{23}H_{25}NO_4$
Formula weight	379.44
Temperature/K	100.01
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.6782(4)
b/Å	12.9220(6)
c/Å	20.5879(10)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2042.68(17)
Z	4
ρ_{calc}g/cm^3	1.234

μ/mm^{-1}	0.680
F(000)	808.0
Crystal size/mm^3	0.246 × 0.222 × 0.086
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	8.078 to 133.422
Index ranges	-9 ≤ h ≤ 9, -15 ≤ k ≤ 15, -24 ≤ l ≤ 24
Reflections collected	66030
Independent reflections	3604 [R_{int} = 0.0422, R_{sigma} = 0.0122]
Data/restraints/parameters	3604/0/258
Goodness-of-fit on F^2	1.130
Final R indexes [I>=2σ (I)]	R_1 = 0.0272, wR_2 = 0.0675
Final R indexes [all data]	R_1 = 0.0277, wR_2 = 0.0679
Largest diff. peak/hole / e Å^{-3}	0.15/-0.23
Flack parameter	0.03(4)

Appendix 4 – X-ray crystal structure data for compound (±)-**152**



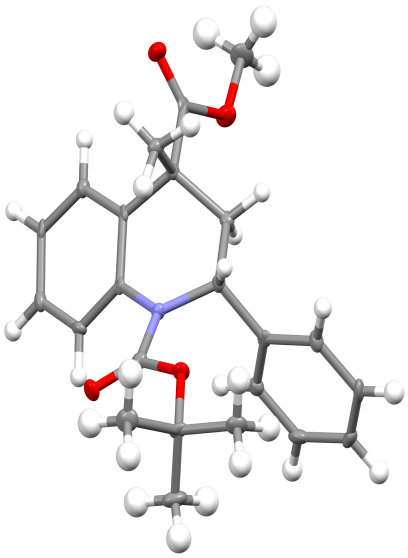
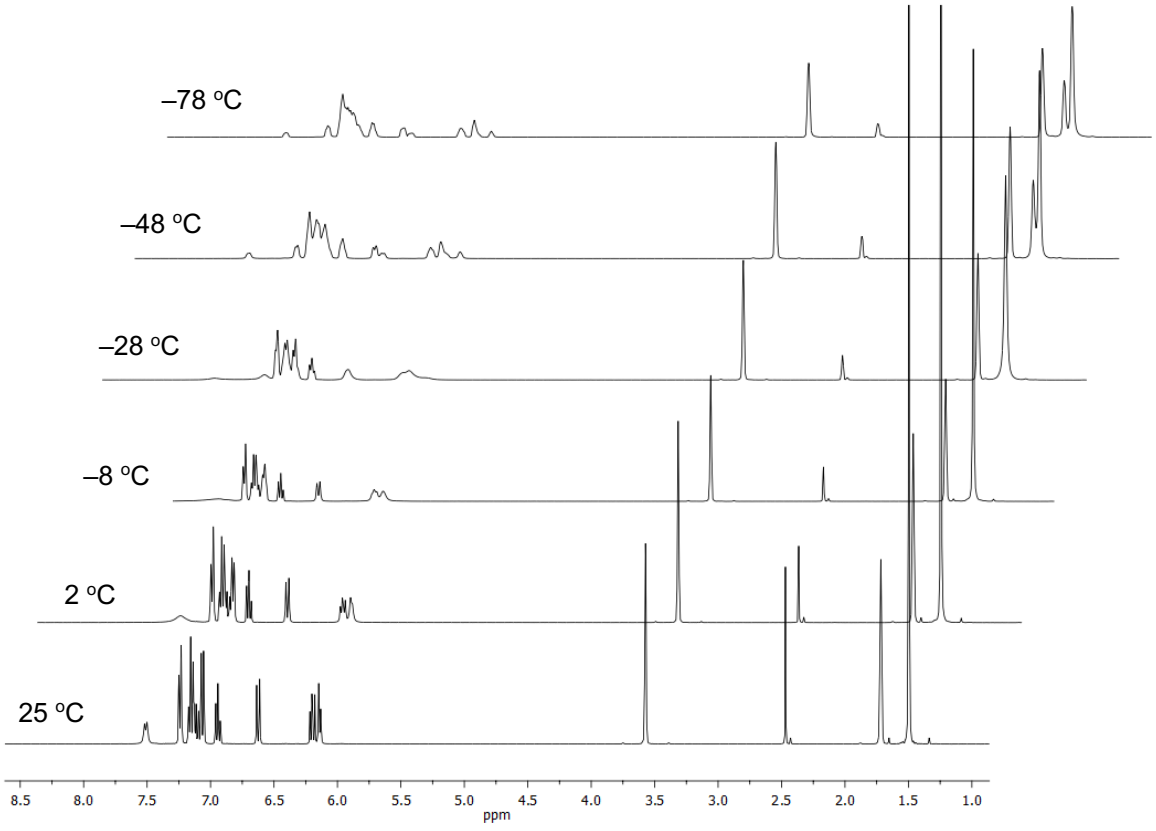


Table 1. Crystal data and structure refinement for OIC324ncs_2022NCS0093s.

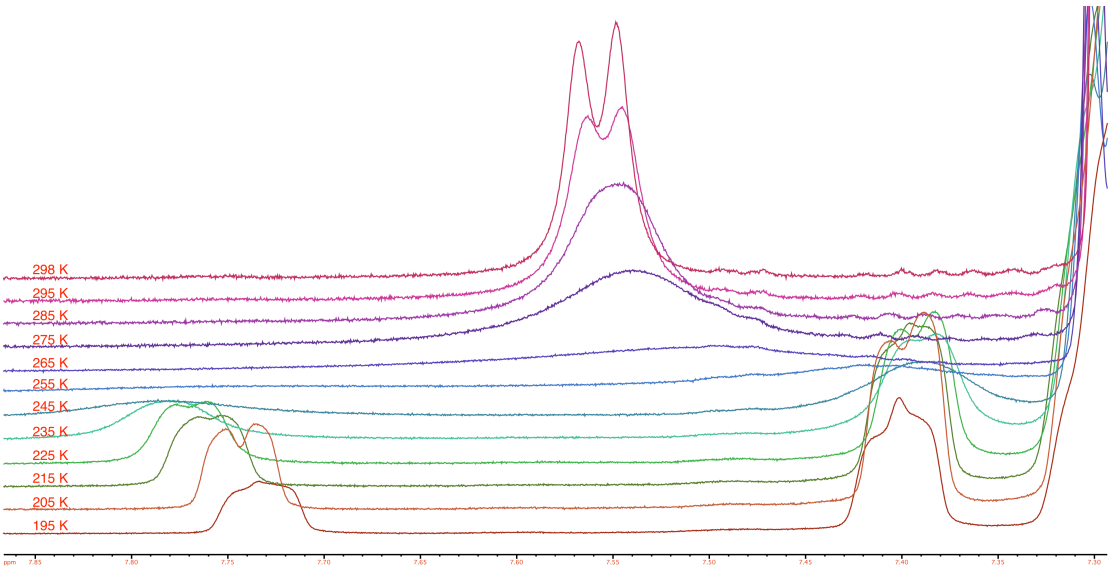
Identification code	OIC324ncs_2022NCS0093s
Empirical formula	$C_{23}H_{27}NO_4$
Formula weight	381.45
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	16.5540(2)
b/Å	10.47210(10)
c/Å	11.48900(10)
α/°	90
β/°	88.2370(10)
γ/°	90
Volume/Å^3	1990.73(4)
Z	4
ρ_{calc}g/cm^3	1.273
μ/mm^{-1}	0.698
F(000)	816.0
Crystal size/mm^3	0.19 × 0.02 × 0.015
Radiation	Cu Kα (λ = 1.54178)
2Θ range for data collection/°	5.34 to 140.068
Index ranges	-20 ≤ h ≤ 20, -12 ≤ k ≤ 12, -10 ≤ l ≤ 13
Reflections collected	44743
Independent reflections	3760 [R_{int} = 0.0281, R_{sigma} = 0.0133]
Data/restraints/parameters	3760/0/258
Goodness-of-fit on F^2	1.044
Final R indexes [I>=2σ (I)]	R_1 = 0.0319, wR_2 = 0.0835
Final R indexes [all data]	R_1 = 0.0350, wR_2 = 0.0859
Largest diff. peak/hole / e Å^{-3}	0.20/-0.21

Appendix 5 – Variable temperature ^{1}H NMR spectra for *N*-Boc-2-phenyldihydroquinoline **104**

A sample of dihydroquinoline **104** (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 and C-8 hydrogen atom, but coalescence of signal for C-8 hydrogen atom which occurred between −38 °C and −28 °C was better, so this was used in calculation. The ratio of the rotamers is ~ 2:1. By using line shape analysis by DNMR, the rate constants k_1 can be estimated.



The ^{1}H NMR spectra in the region 7.85−7.30 ppm are shown below:



Using line shape analysis[109,110] to determine $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$:

Pre-coalescence:

$k = [(\Delta v^{o}_{AB})^{2}–(\Delta v_{AB})^{2}]^{1/2} 202202\ \pi/\sqrt{2}$

Coalescence:

$k = (\Delta v^{o}_{AB})\ \pi/\sqrt{2}$

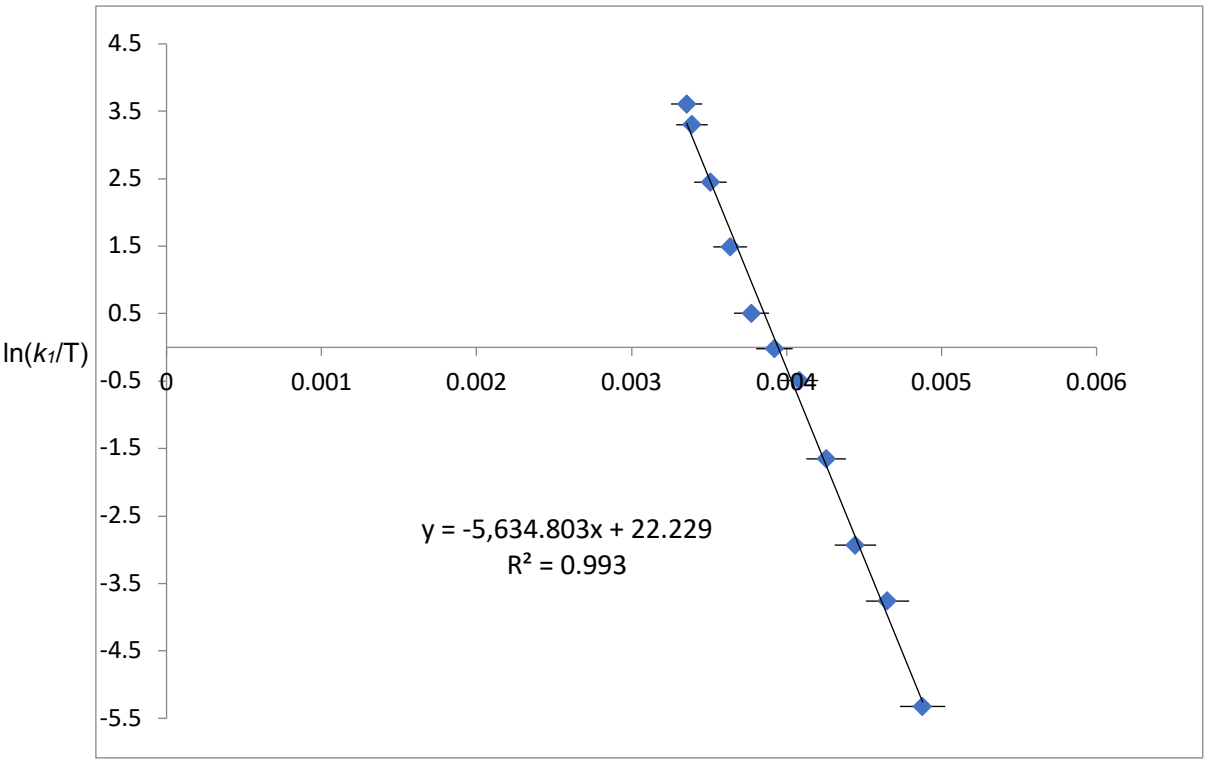
Post-coalescence:

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

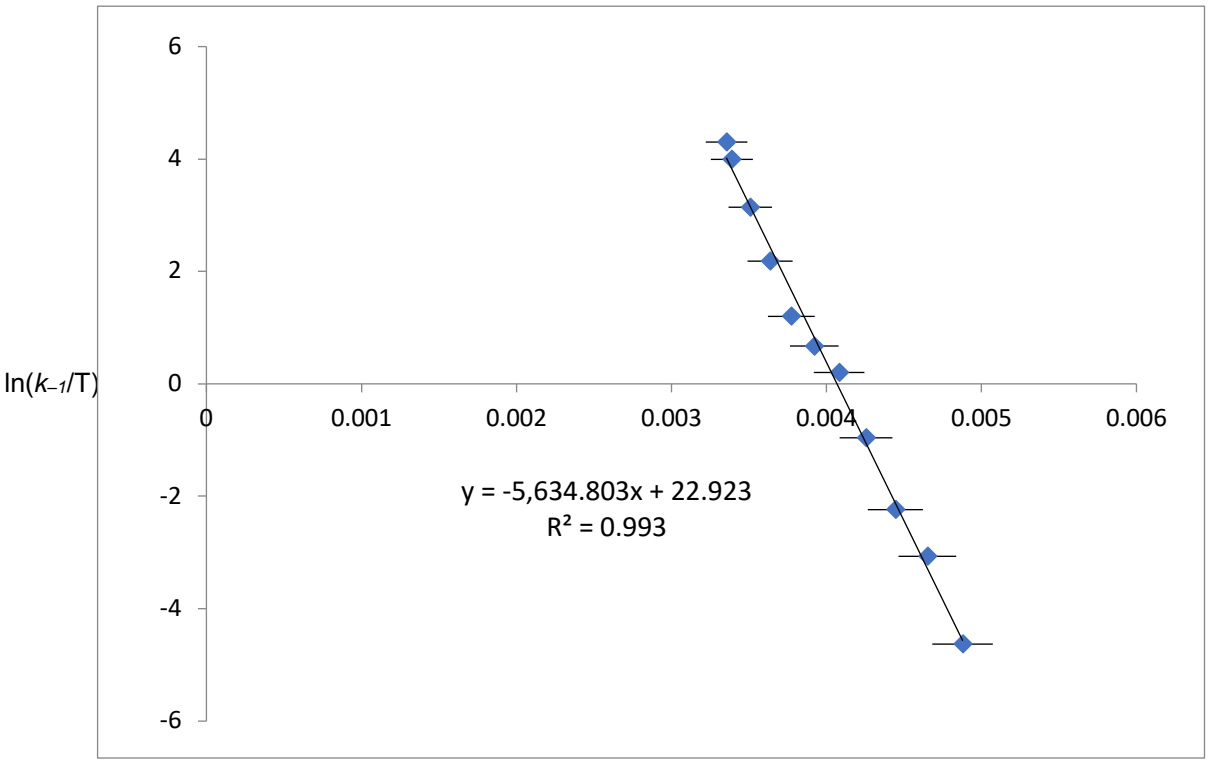
T/K	1/T	k_1	ln(k_1/T)	k_{-1}	ln(k_{-1}/T)
205	0.004878	1	-5.32301	2	-4.62986
215	0.004651	5	-3.7612	10	-3.06805
225	0.004444	12	-2.93119	24	-2.23805
235	0.004255	45	-1.65292	90	-0.95978
245	0.004082	150	-0.49062	300	0.202524
255	0.003922	250	-0.0198	500	0.673345
265	0.003774	440	0.507045	880	1.200192
275	0.003636	1220	1.489835	2440	2.182982
285	0.003509	3300	2.449189	6600	3.142336
295	0.00339	8000	3.300221	16000	3.993369
298	0.003356	11000	3.608557	22000	4.301704

The Eyring plot of 1/T against ln(k/T) for each of the forward and backward processes are shown below. It gives a straight line of the form $y = mx + c$ with gradient $m = -\Delta H^{\ddagger}/R$ and intercept $c = \Delta S^{\ddagger}/R + \ln(k_B/h)$.

Forward direction (k_1):



Reverse direction (k_{-1}):



From these Eyring plots:

Forward direction (major to minor rotamer, k_1):

slope –5634.8, intercept 22.23

Approximate activation parameters for Boc rotation in THF:

$\Delta H^{\ddagger}$ 46.8 kJ/mol

$\Delta S^{\ddagger}$ –12.7 J/K·mol.

Hence the barrier to rotation $\Delta G^{\ddagger} \approx 49.3$ kJ/mol at –78 °C.

The half-life for rotation is about 3 sec at –78 °C.

Reverse direction (minor to major rotamer, k_{-1}):

slope –5634.8, intercept 22.92

Approximate activation parameters for Boc rotation in THF:

$\Delta H^{\ddagger}$ 46.8 kJ/mol

$\Delta S^{\ddagger}$ –7 J/K·mol.

Hence the barrier to rotation $\Delta G^{\ddagger} \approx 48.2$ kJ/mol at –78 °C.

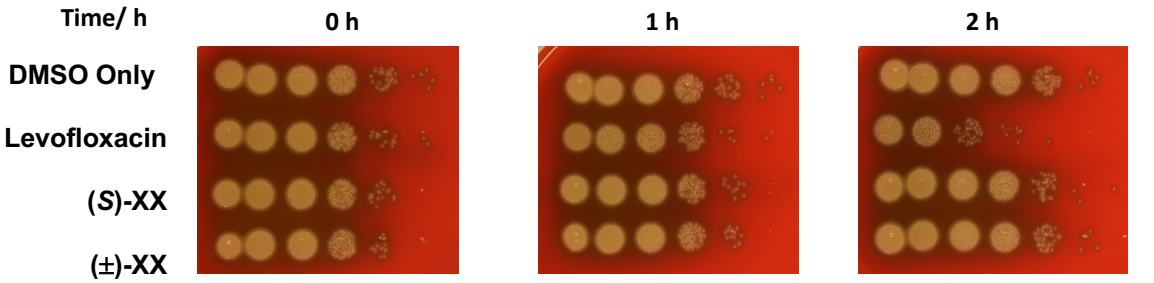
The half-life for rotation is about 1.5 sec at –78 °C.

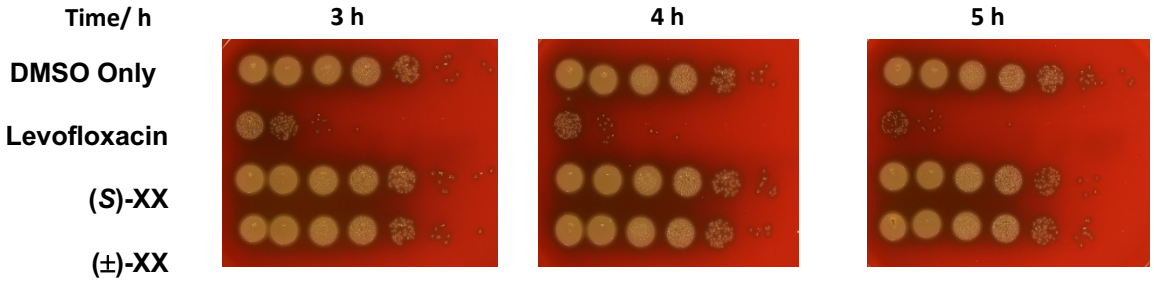
Appendix 6 – Biological data for Levofloxacin **173**, (±)-**231** and (*S*)-**231**

Antibiotic sensitivity assays using cell viability counts:

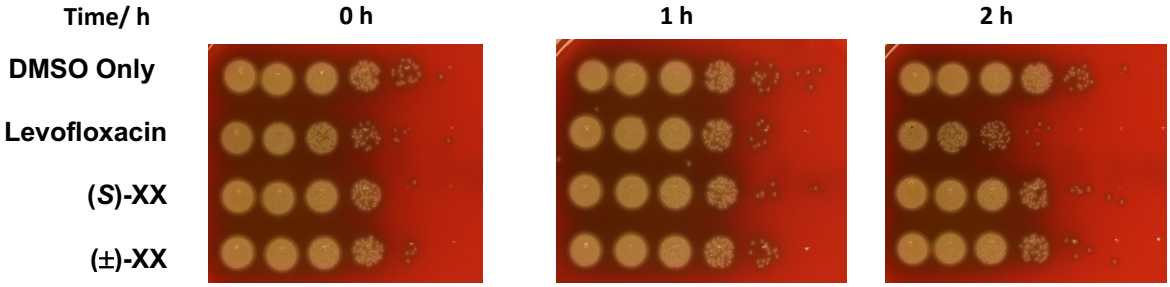
Streptococcus pneumoniae D39 Δ*cps* were grown in Todd-Hewitt broth and yeast extract (THY, Becton Dickinson) at 37 °C in an atmosphere containing 5% CO_2, until the cells reached exponential growth phase [Optical Density at 600 nm wavelength (OD_{600}) 0.2 – 0.8]. Cultures were diluted back to an OD_{600} of exactly 0.2 in pre-warmed THY. Levofloxacin **173**, or the phenyl analog (*S*)- **231** or (±)-**231**, was added to the culture to a final concentration of 10 μg ml^{-1} (stock concentration 10 mg ml^{-1} in DMSO). As a no-antibiotic control, the respective volume of DMSO solvent was used. Cultures were incubated at 37 °C in 5% CO_2 for t = 0, 1, 2, 3, 4 and 5 h. For spot-dilution assays, treated cell mixtures were serially diluted 1 in 10 to a final dilution of 10^{-6} and 5 μL of each diluted culture was spotted onto TSAIII agar plates containing 5% horse blood. Plates were incubated for 16–20 h at 37 °C, 5% CO_2, to allow growth before imaging. For more accurate quantification of cell viability at 5 h, 100 μL of diluted and treated cultures were spread onto TSAII agar plates containing 5% horse blood. Plates were incubated for 16–20 h at 37 °C, 5% CO_2, imaged and colony forming unit counts (CFU) recorded.

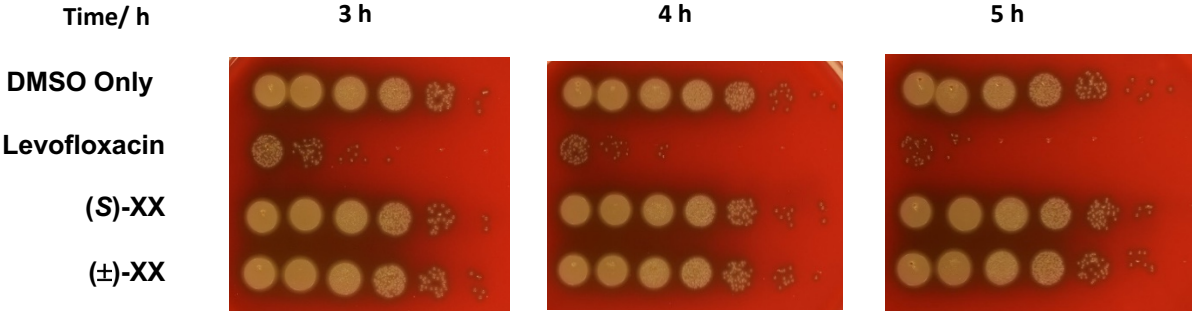
Levofloxacin **173** was shown to kill the cells within a few hours at 10 μg mL^{-1}, whereas the control, or using (*S*)-**231**, or (±)-**231** gave no activity.



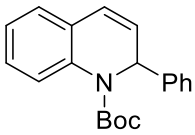


The experiment was repeated but using a final concentration of 100 μg mL^{-1} for (*S*)-**231**, or (±)-**231** with similar results.

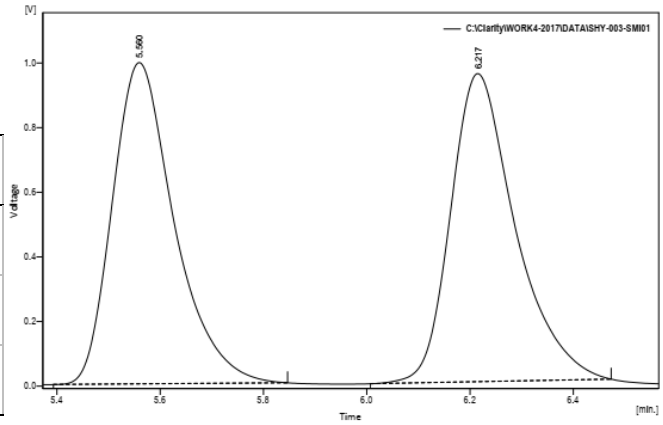


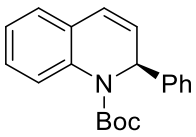


Appendix 7 – HPLC traces

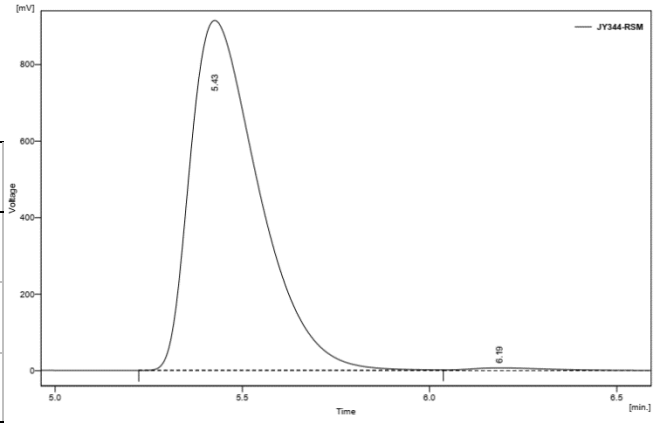


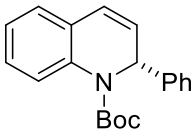
	R_t/ min	Area/ mV.s	Area/ %
1	5.560	8277.832	50
2	6.217	8286.300	50
	total	16564.132	100



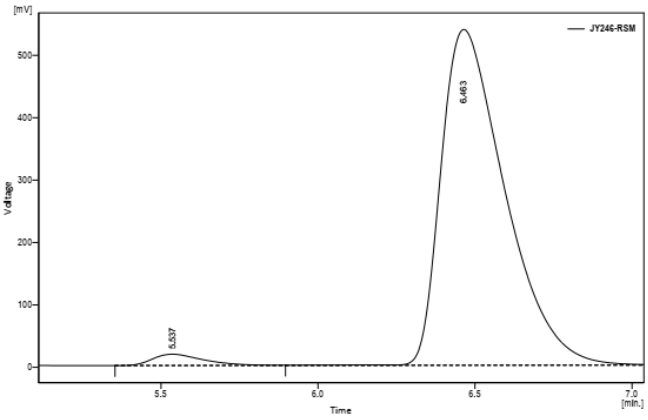


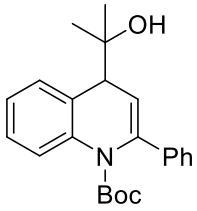
	R_t/ min	Area/ mV.s	Area/ %
1	5.427	11671.573	99
2	6.187	103.751	1
	total	11775.325	100



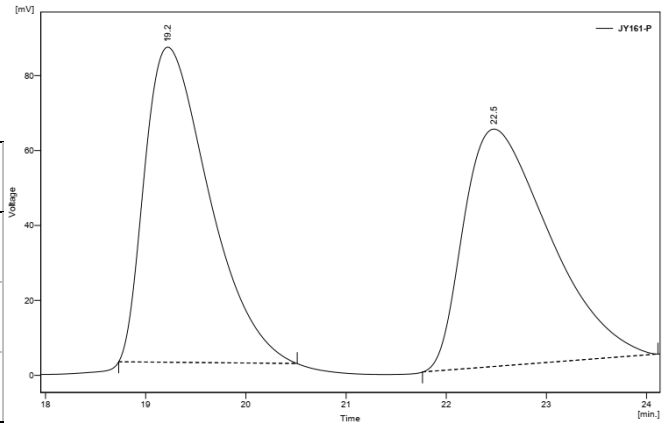


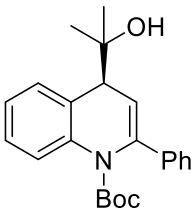
	R_t/ min	Area/ mV.s	Area/ %
1	5.537	205.387	3
2	6.463	7620.844	97
	total	10651.317	100



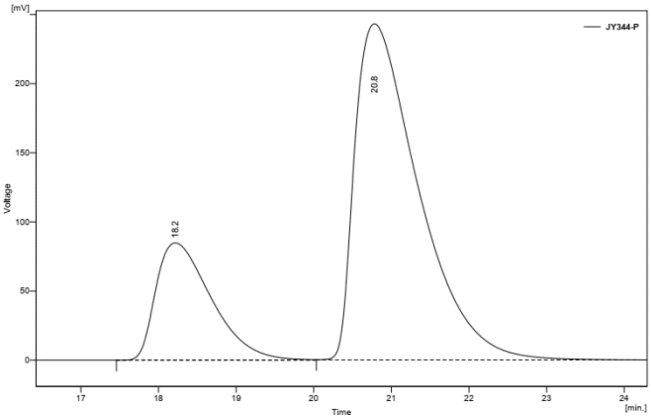


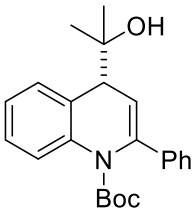
	R_t/ min	Area/ mV.s	Area/ %
1	19.220	7608.833	50
2	22.477	7600.755	50
	total	15209.588	100



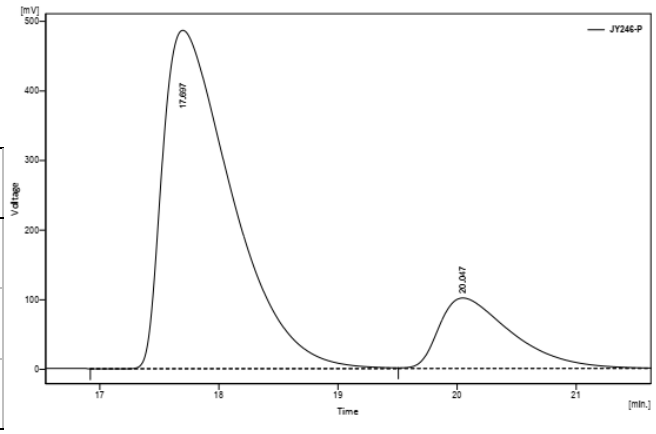


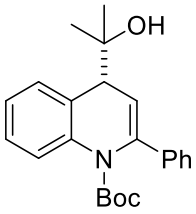
	R_t/ min	Area/ mV.s	Area/ %
1	18.217	4199.737	23
2	20.783	13890.980	77
	total	18090.717	100



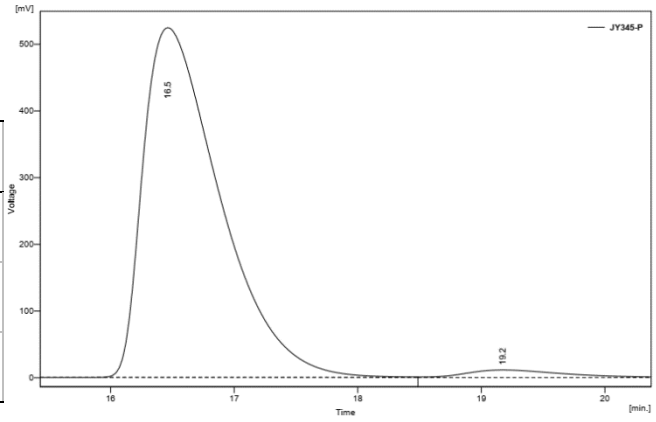


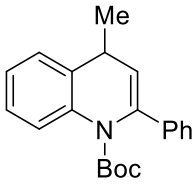
	R_t/ min	Area/ mV.s	Area/ %
1	17.697	19617.397	82
2	20.047	4322.045	18
	total	23939.442	100



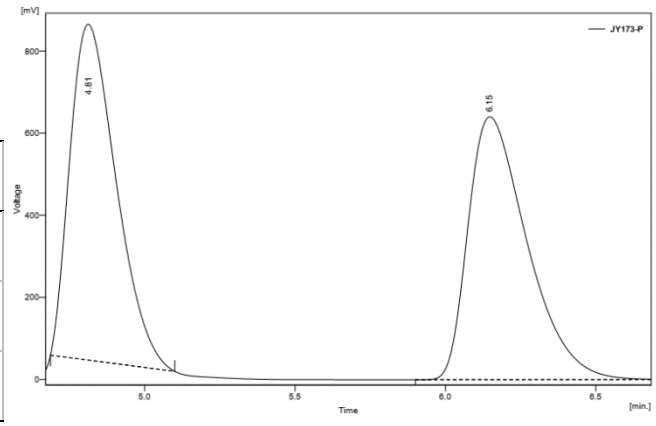


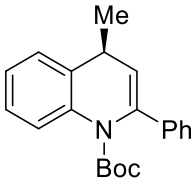
	R_t/ min	Area/ mV.s	Area/ %
1	16.463	22643.422	97
2	19.173	606.260	3
	total	23249.682	100



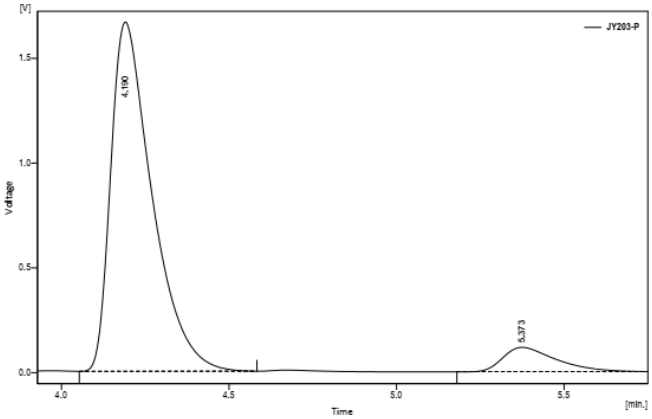


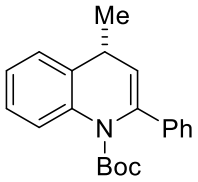
	R_t/ min	Area/ mV.s	Area/ %
1	4.813	701.793	50
2	6.147	701.934	50
	total	1403.727	100



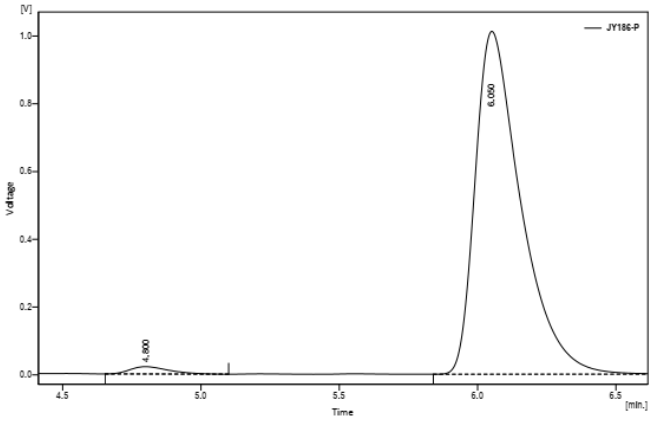


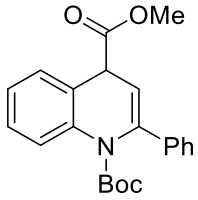
	R_t/ min	Area/ mV.s	Area/ %
1	4.190	14261.131	92
2	5.373	1287.246	8
	total	15548.377	100



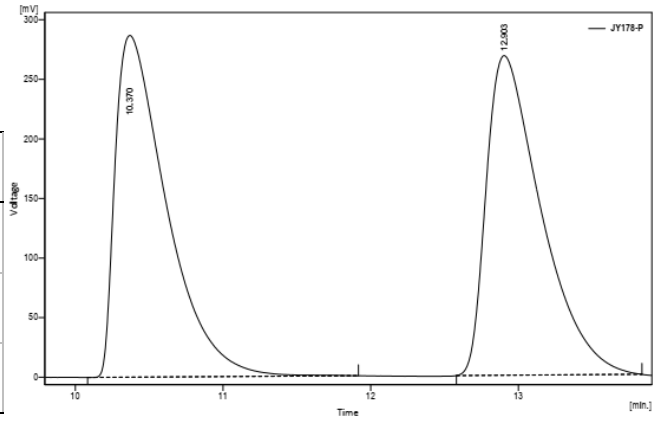


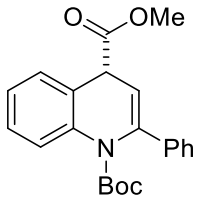
	R_t/ min	Area/ mV.s	Area/ %
1	4.800	213.242	2
2	6.050	11649.334	98
	total	11862.576	100



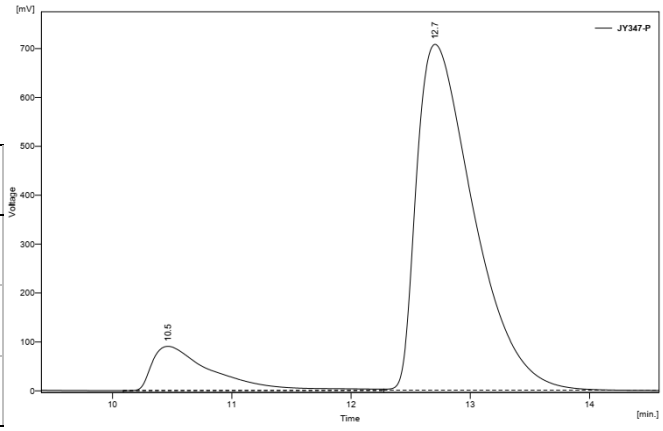


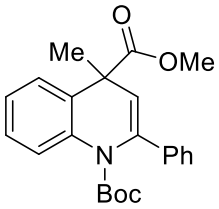
	R_t/ min	Area/ mV.s	Area/ %
1	10.370	6930.881	50
2	12.903	6933.940	50
	total	13864.821	100



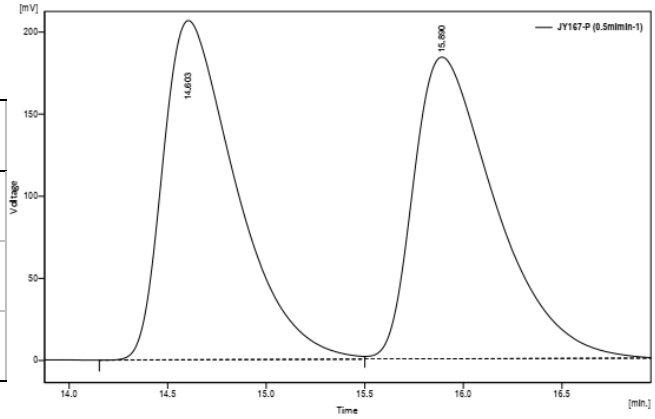


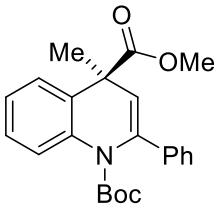
	R_t/ min	Area/ mV.s	Area/ %
1	10.463	3192.163	12
2	12.703	23509.716	88
	total	26701.878	100



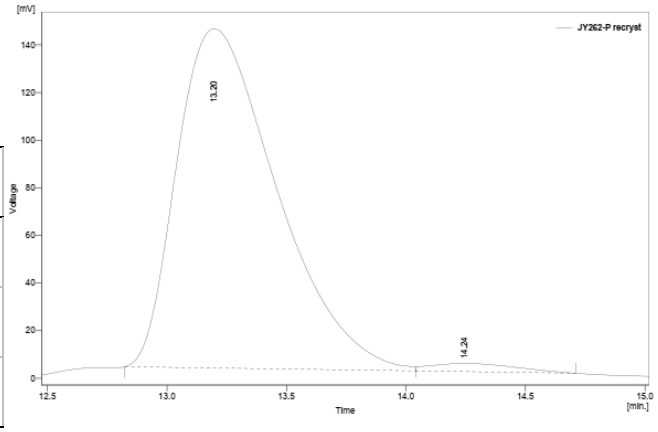


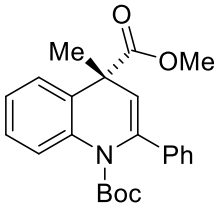
	R_t/ min	Area/ mV.s	Area/ %
1	14.603	5331.608	50
2	15.890	5323.549	50
	total	10655.157	100



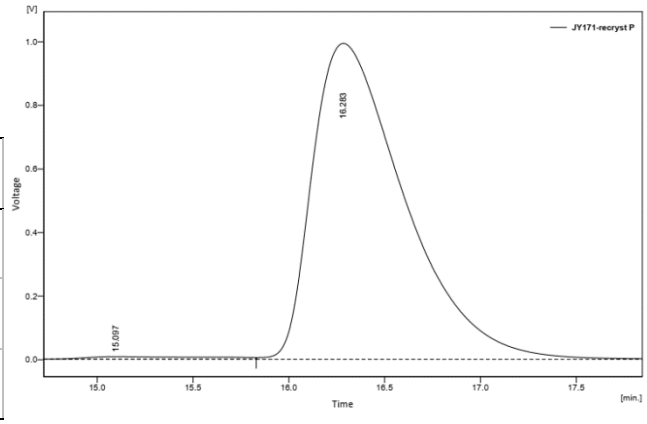


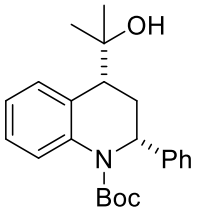
	R_t/ min	Area/ mV.s	Area/ %
1	13.197	4169.016	98
2	14.243	85.062	2
	total	4254.078	100



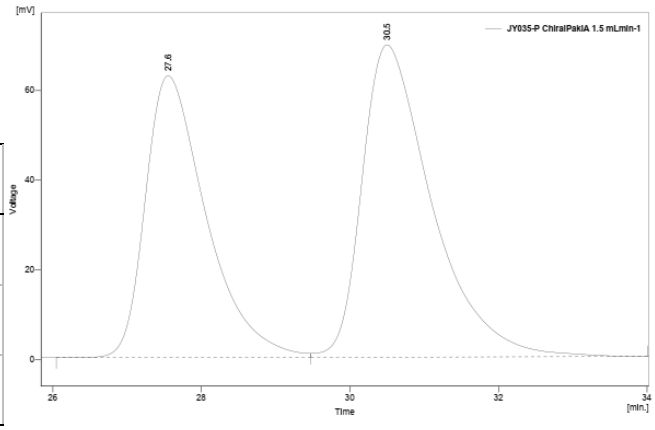


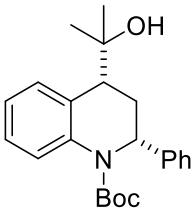
	R_t/ min	Area/ mV.s	Area/ %
1	15.097	382.368	1
2	16.283	33105.083	99
	total	33487.450	100



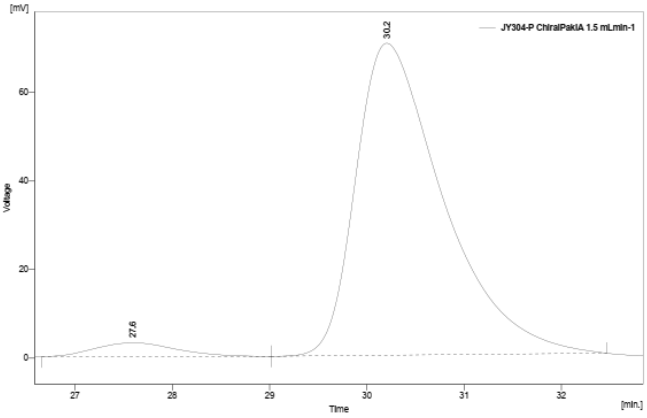


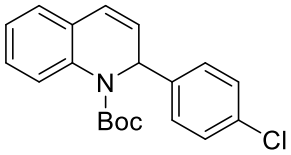
	R_t/ min	Area/ mV.s	Area/ %
1	27.553	3579.377	44
2	30.500	4559.316	56
	total	8138.693	100



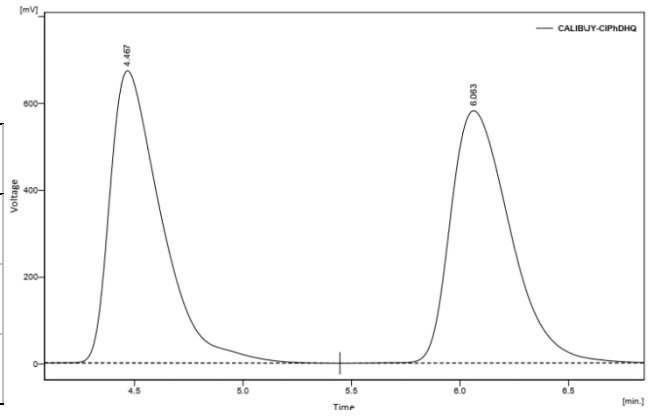


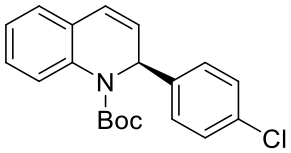
	R_t/ min	Area/ mV.s	Area/ %
1	27.593	181.525	4
2	30.207	4397.610	96
	total	4579.136	100



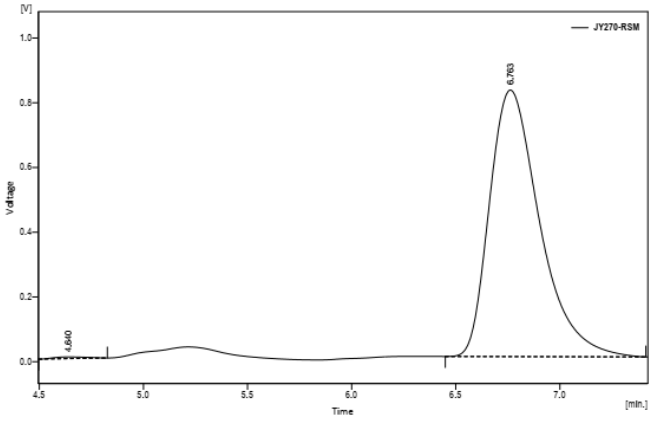


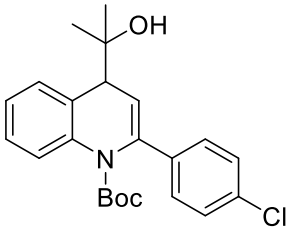
	R_t/ min	Area/ mV.s	Area/ %
1	4.467	11048.992	50
2	6.063	11053.724	50
	total	22102.716	100



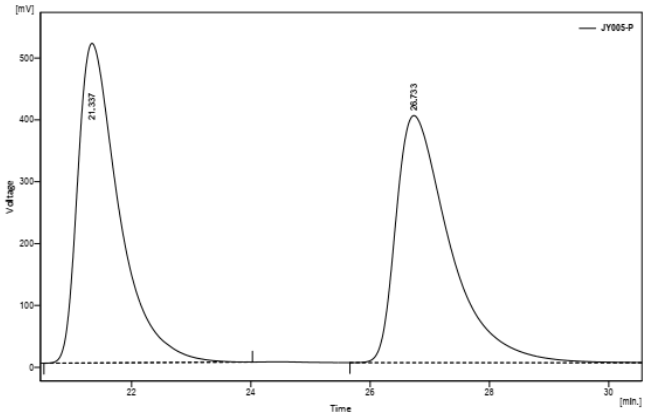


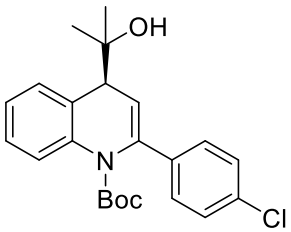
	R_t/ min	Area/ mV.s	Area/ %
1	4.640	59.715	1
2	6.763	13788.622	99
	total	13848.337	100



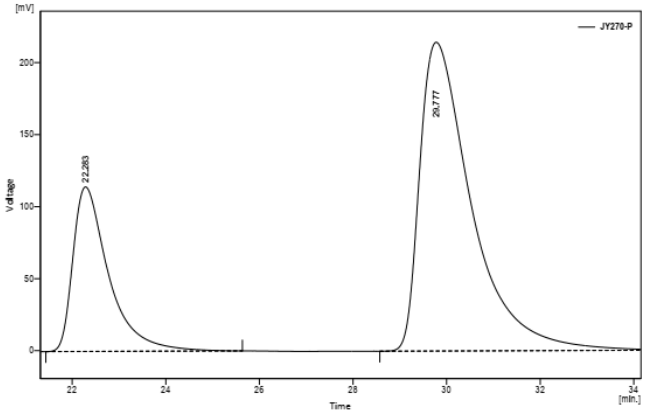


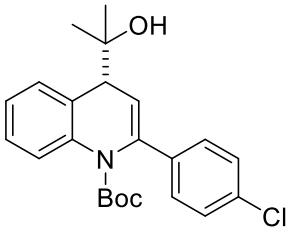
	R_t/ min	Area/ mV.s	Area/ %
1	21.337	24791.257	50
2	26.733	25023.517	50
	total	49814.775	100



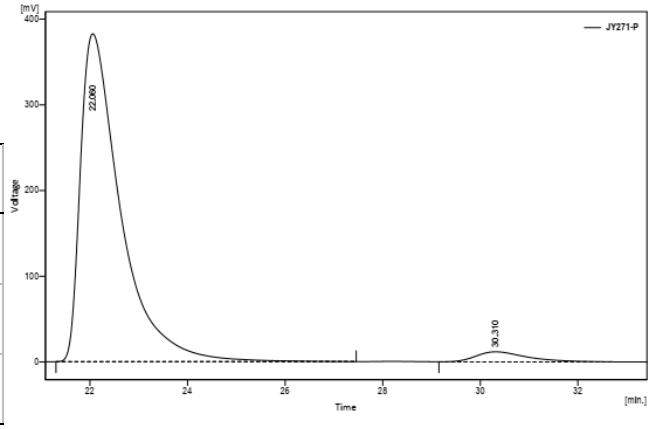


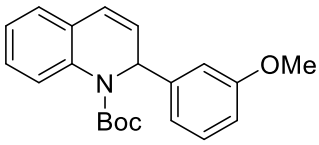
	R_t/ min	Area/ mV.s	Area/ %
1	22.283	6076.582	27
2	29.777	16516.750	73
	total	22593.332	100



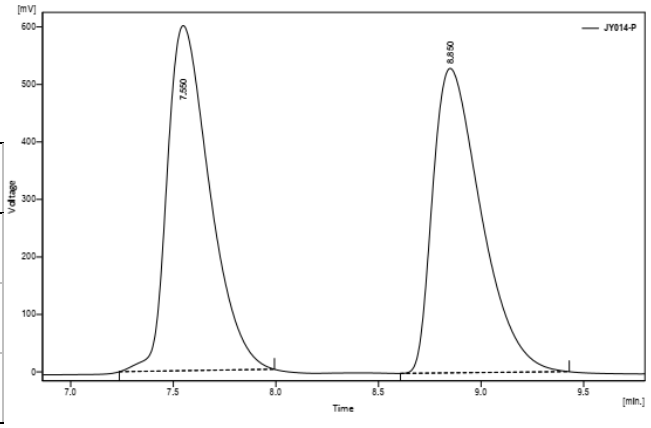


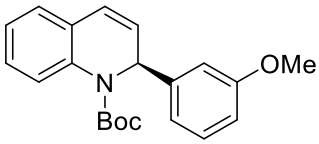
	R_t/ min	Area/ mV.s	Area/ %
1	22.060	21827.652	96
2	30.310	863.305	4
	total	22690.957	100



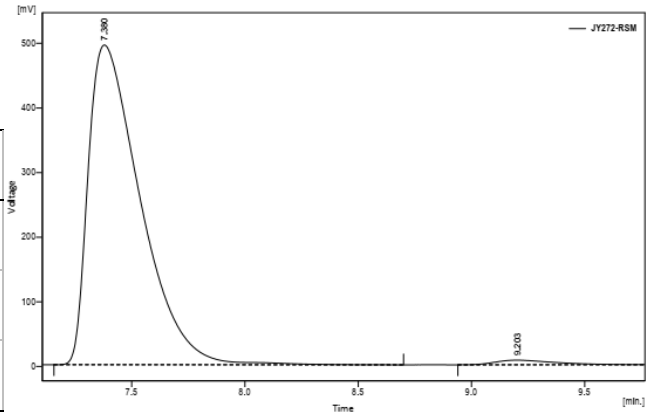


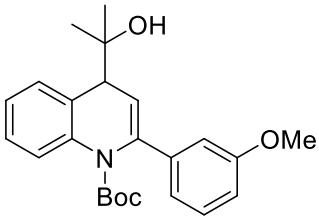
	R_t/ min	Area/ mV.s	Area/ %
1	7.550	8671.531	50
2	8.850	8681.147	50
	total	17352.678	100



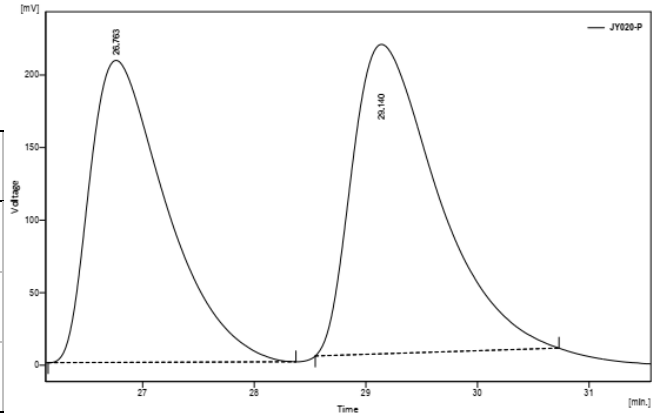


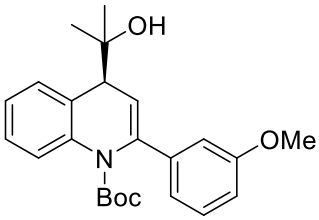
	R_t/ min	Area/ mV.s	Area/ %
1	7.380	7914.832	98
2	9.203	134.624	2
	total	8049.456	100



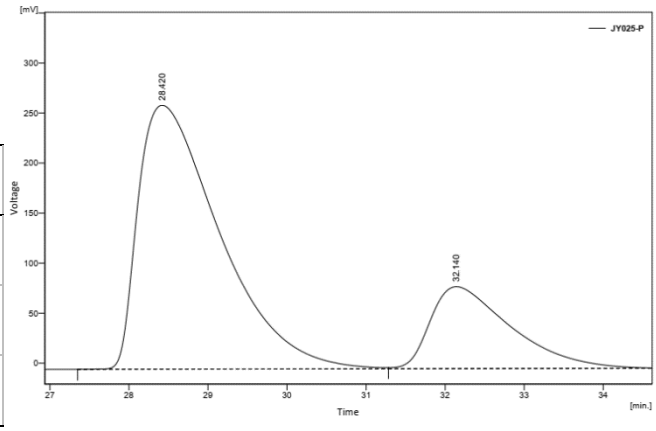


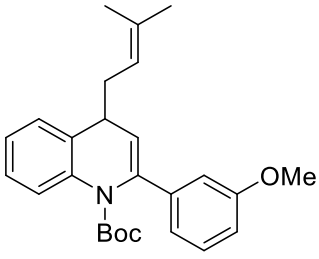
	R_t/ min	Area/ mV.s	Area/ %
1	26.763	10351.339	50
2	29.140	10345.496	50
	total	20696.835	100



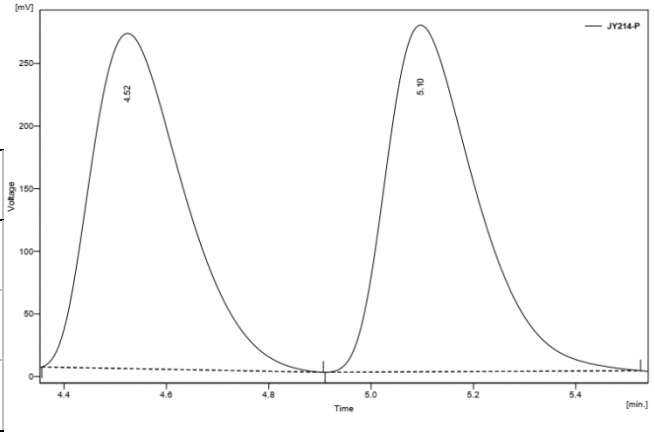


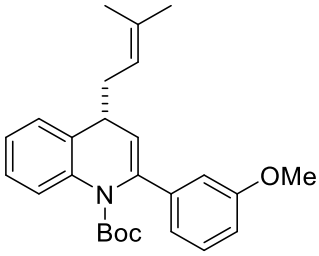
	R_t/ min	Area/ mV.s	Area/ %
1	28.420	18917.263	77
2	32.140	5777.444	23
	total	24694.708	100



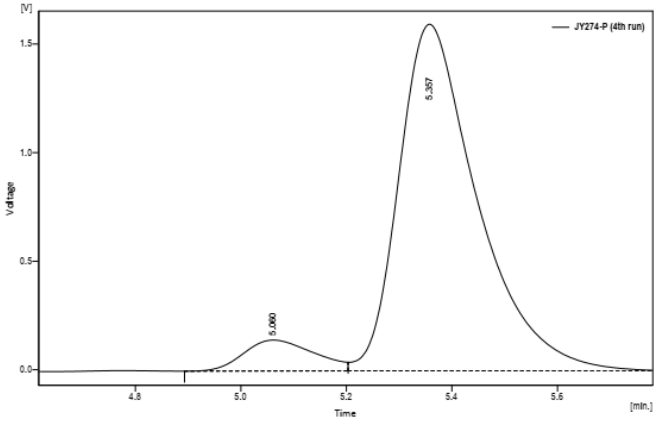


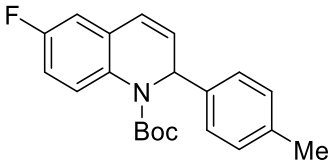
	R_t/ min	Area/ mV.s	Area/ %
1	4.523	3361.657	50
2	5.097	3363.636	50
	total	6725.293	100



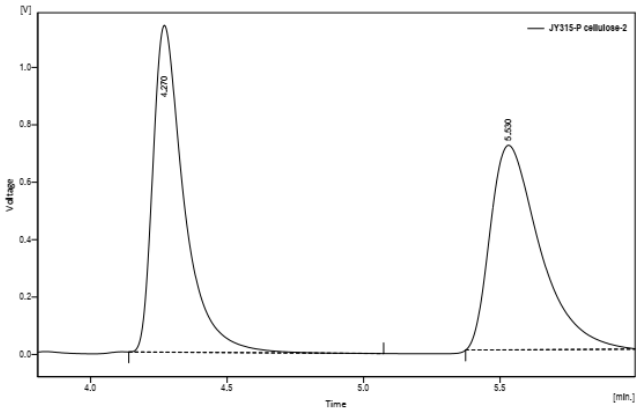


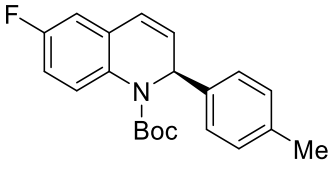
	R_t/ min	Area/ mV.s	Area/ %
1	5.060	1319.635	7
2	5.357	16461.287	93
	total	17780.922	100



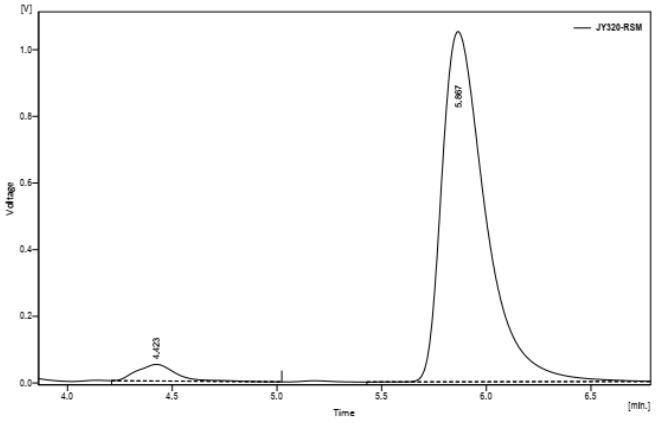


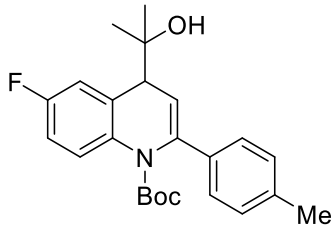
	R_t/ min	Area/ mV.s	Area/ %
1	4.270	9064.415	50
2	5.530	9054.962	50
	total	18119.376	100



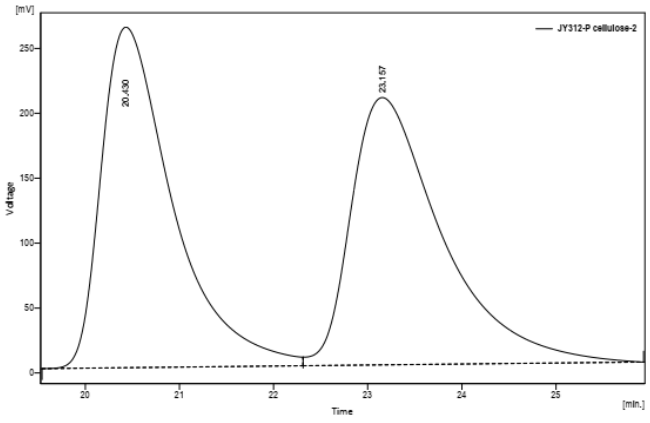


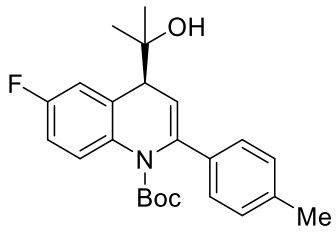
	R_t/ min	Area/ mV.s	Area/ %
1	4.423	644.842	4
2	5.867	15219.498	96
	total	15864.340	100



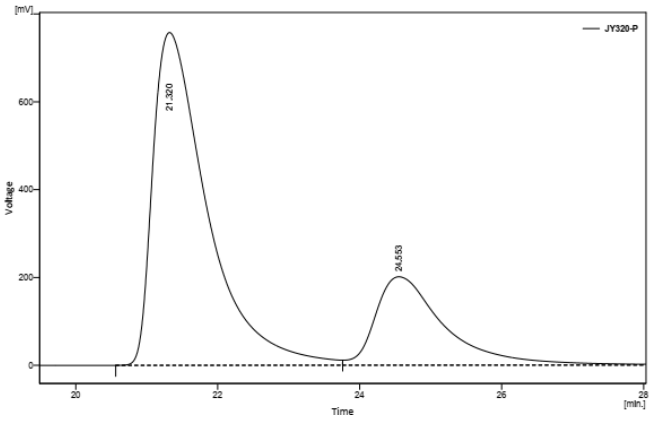


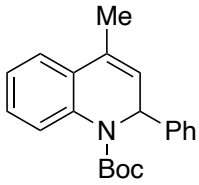
	R_t/ min	Area/ mV.s	Area/ %
1	20.430	13876.392	50
2	23.157	13866.089	50
	total	27742.481	100



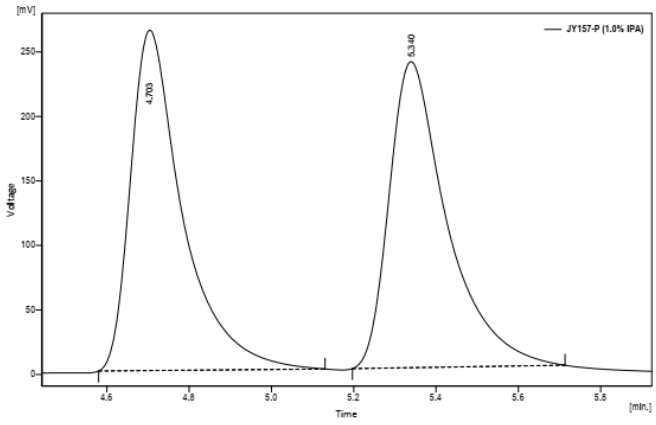


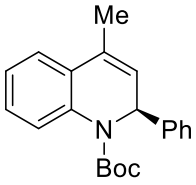
	R_t/ min	Area/ mV.s	Area/ %
1	21.320	40323.235	75
2	24.553	13777.611	25
	total	54100.846	100



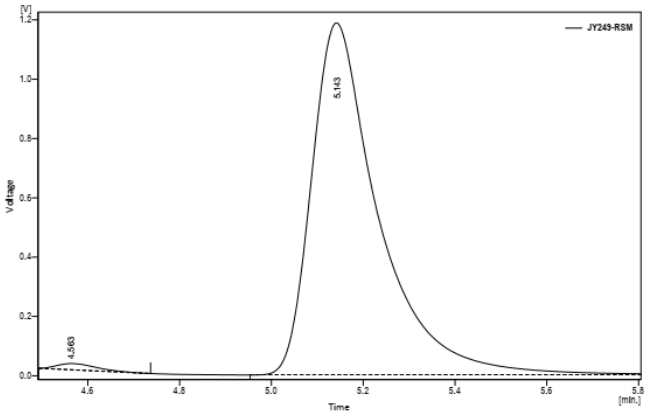


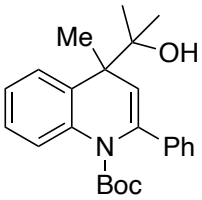
	R_t/ min	Area/ mV.s	Area/ %
1	4.703	2319.974	50
2	5.340	2315.800	50
	total	4635.774	100



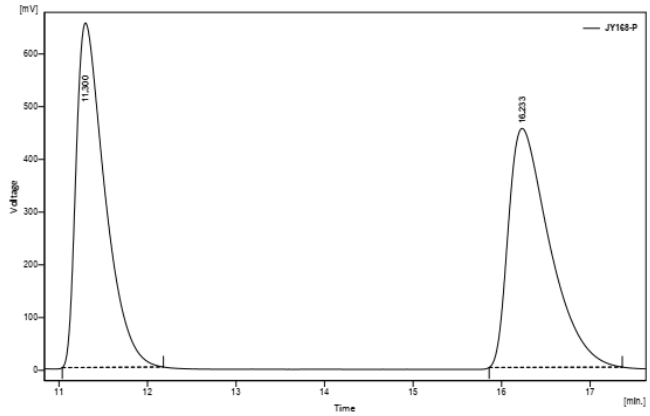


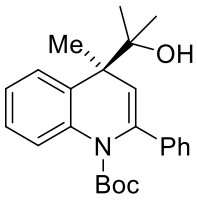
	R_t/ min	Area/ mV.s	Area/ %
1	4.563	128.597	1
2	5.143	12080.304	99
	total	12208.900	100



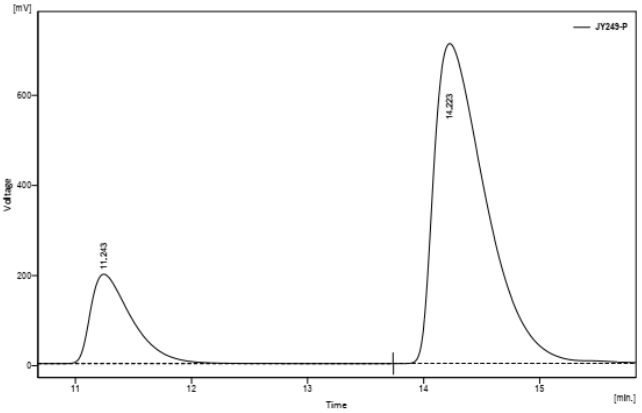


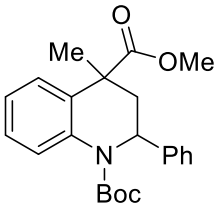
	R_t/ min	Area/ mV.s	Area/ %
1	11.300	14725.208	50
2	16.233	14668.849	50
	total	29394.057	100



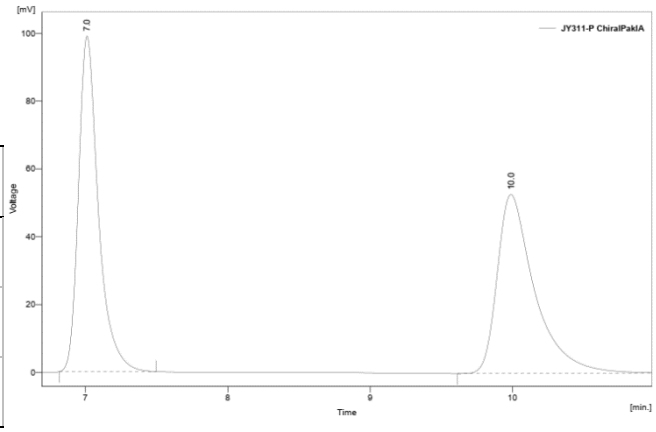


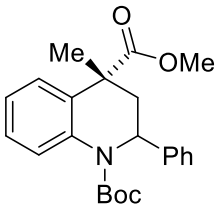
	R_t/ min	Area/ mV.s	Area/ %
1	11.243	4894.442	18
2	14.223	22084.322	82
	total	26978.763	100



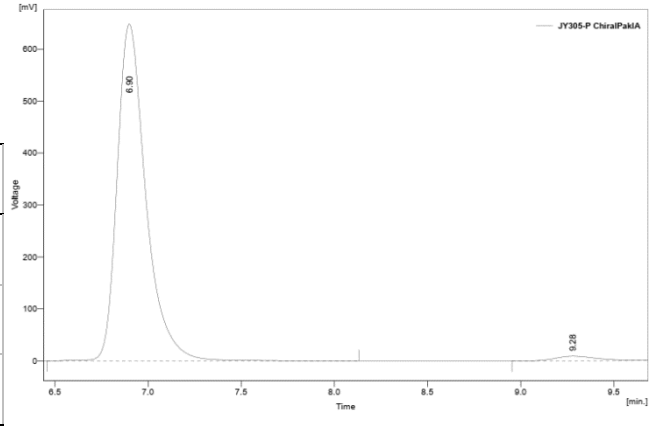


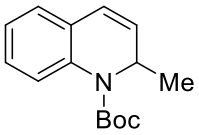
	R_t/ min	Area/ mV.s	Area/ %
1	7.010	961.828	50
2	9.990	962.453	50
	total	1924.281	100



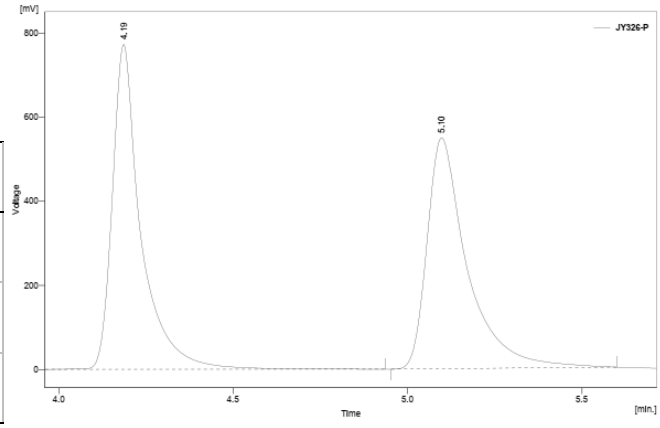


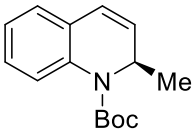
	R_t/ min	Area/ mV.s	Area/ %
1	6.900	6948.013	98
2	9.280	139.718	2
	total	7087.731	100



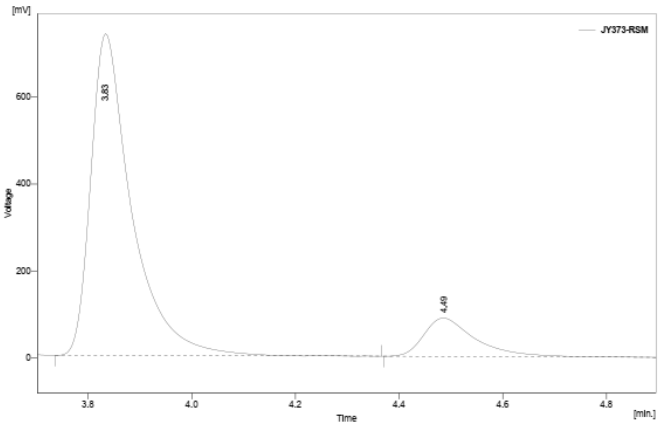


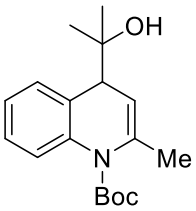
	R_t/ min	Area/ mV.s	Area/ %
1	4.187	4401.795	50
2	5.097	4393.899	50
	total	8795.694	100



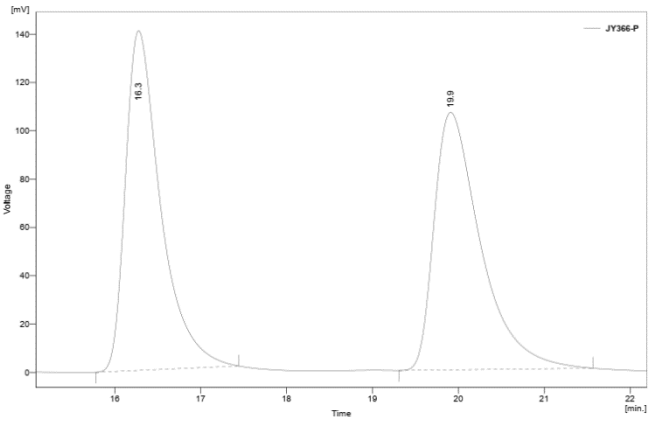


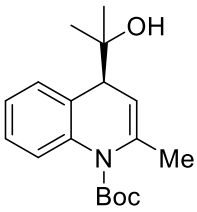
	R_t/ min	Area/ mV.s	Area/ %
1	3.833	4057.152	87
2	4.487	610.884	13
	total	4668.036	100



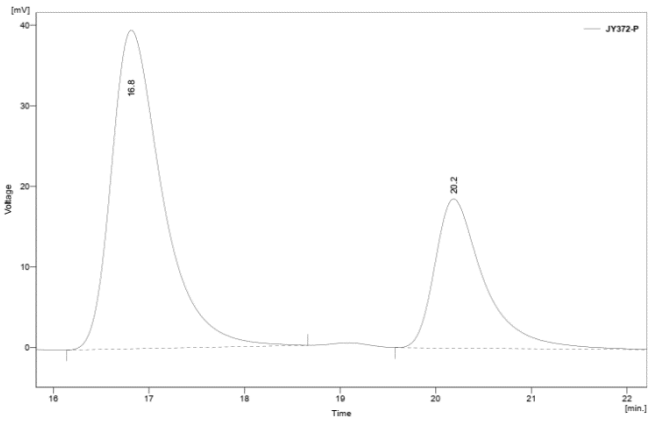


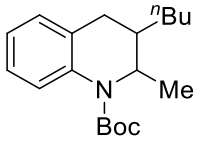
	R_t/ min	Area/ mV.s	Area/ %
1	16.277	4002.635	50
2	19.910	4008.227	50
	total	8010.862	100



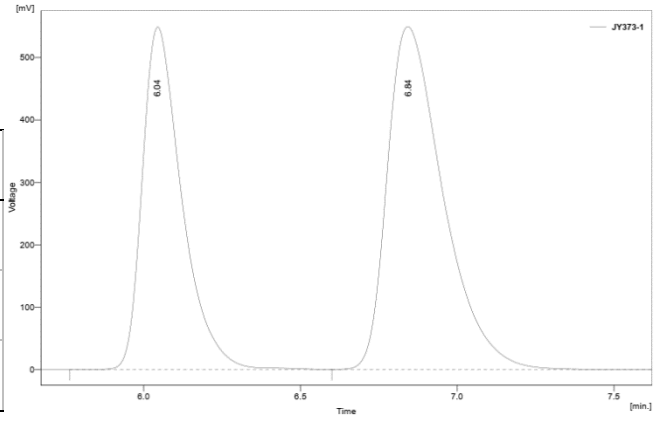


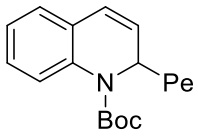
	R_t/ min	Area/ mV.s	Area/ %
1	16.817	1462.333	69
2	20.190	661.701	31
	total	2124.034	100



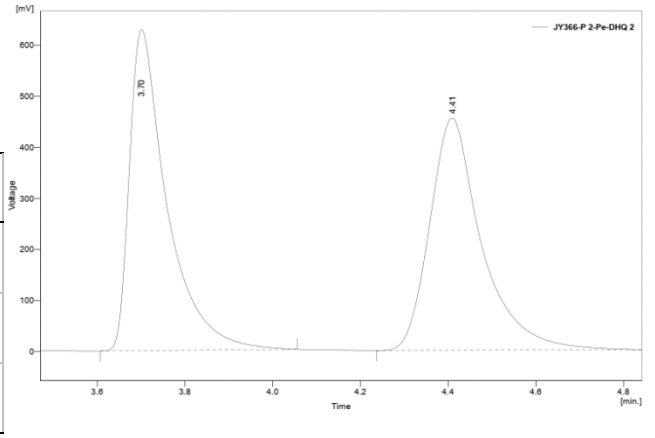


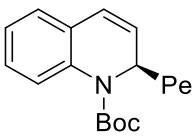
	R_t/ min	Area/ mV.s	Area/ %
1	6.043	4812.804	41
2	6.843	6797.764	59
	total	11610.588	100



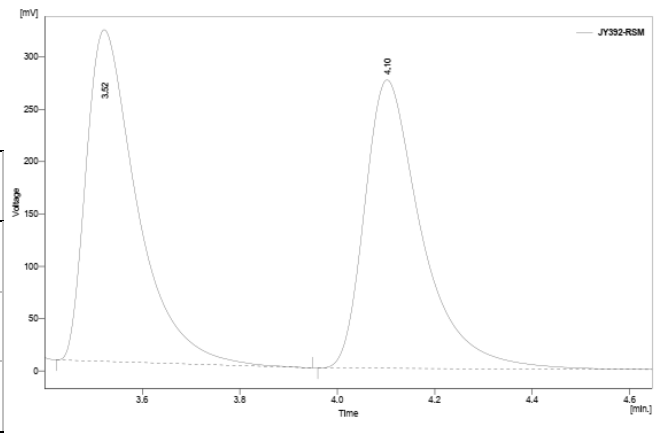


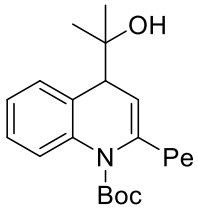
	R_t/ min	Area/ mV.s	Area/ %
1	3.700	3733.615	50
2	4.410	3730.201	50
	total	7463.817	100



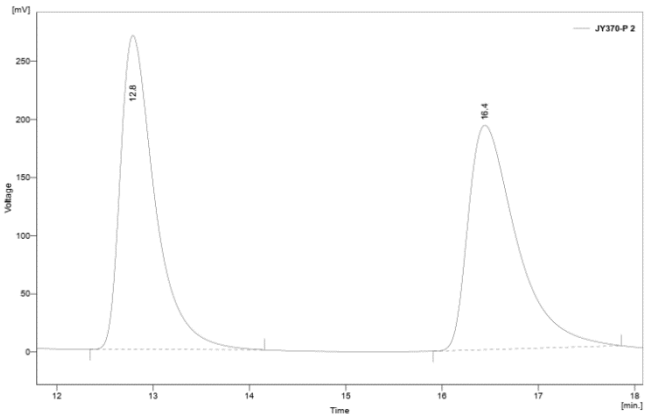


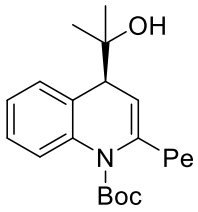
	R_t/ min	Area/ mV.s	Area/ %
1	3.523	2294.642	51
2	4.103	2239.986	49
	total	4534.628	100



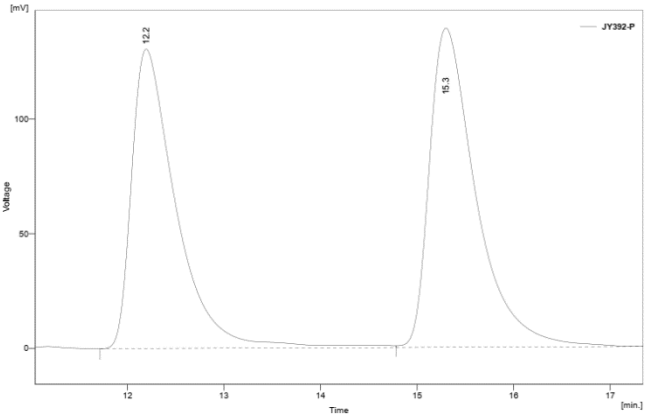


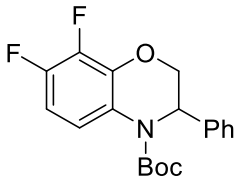
	R_t/ min	Area/ mV.s	Area/ %
1	12.790	6725.462	50
2	16.443	6714.010	50
	total	13439.472	100



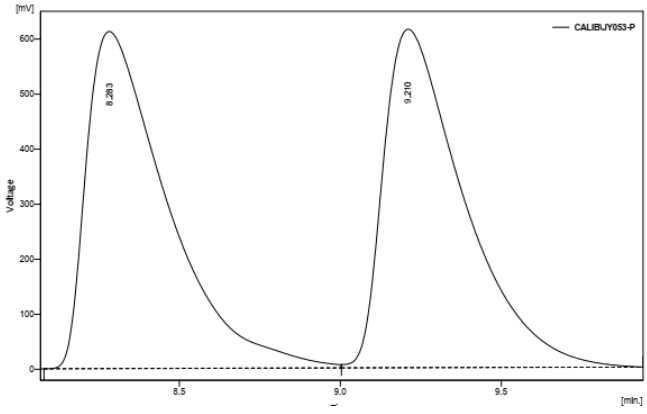


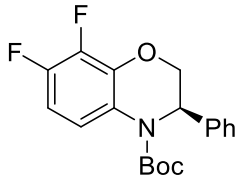
	R_t/ min	Area/ mV.s	Area/ %
1	12.193	4180.353	47
2	15.297	4641.503	53
	total	8821.856	100



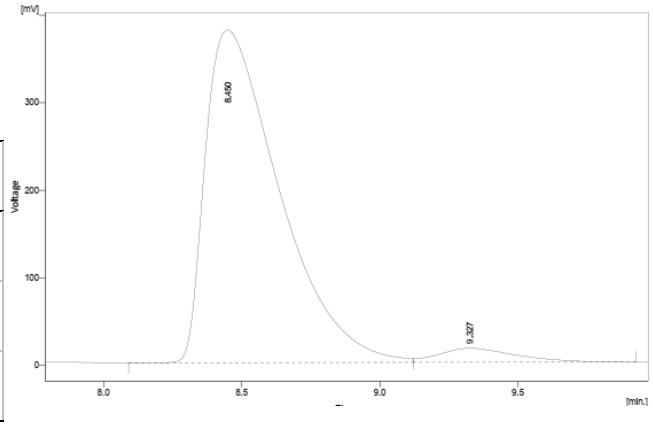


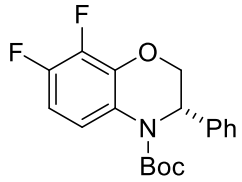
	R_t/ min	Area/ mV.s	Area/ %
1	8.283	10676.947	50
2	9.210	10669.981	50
	total	21346.928	100



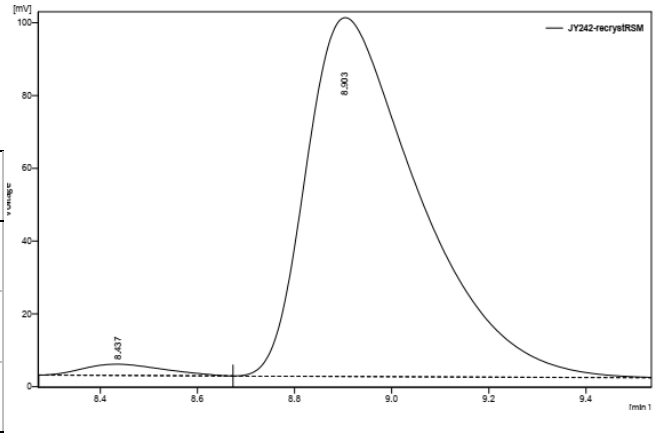


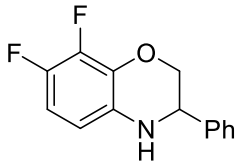
	R_t/ min	Area/ mV.s	Area/ %
1	8.450	7096.867	96
2	9.327	318.823	4
	total	7415.690	100



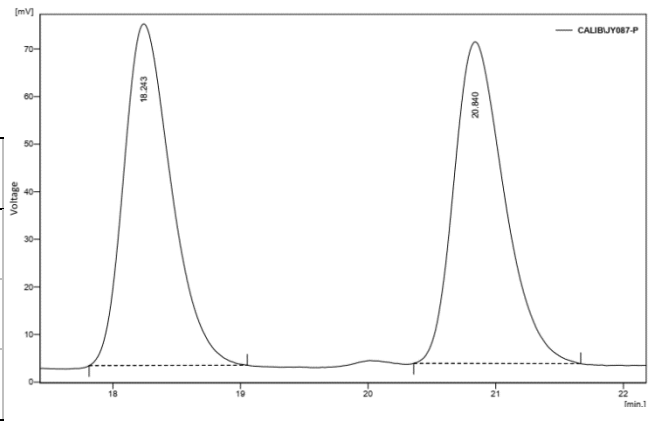


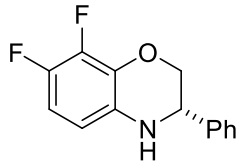
	R_t/ min	Area/ mV.s	Area/ %
1	8.437	35.784	2
2	8.903	1588.323	98
	total	1624.107	100



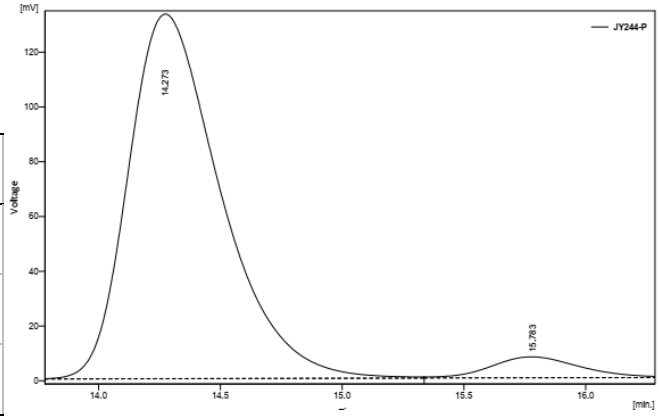


	R_t/ min	Area/ mV.s	Area/ %
1	18.243	1852.606	50
2	20.840	1852.858	50
	total	3706.464	100





	R_t/ min	Area/ mV.s	Area/ %
1	14.273	3507.105	95
2	15.783	199.967	5
	total	3707.072	100



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