

Synthesis and Applications of  
Structurally Modified *Cinchona*  
Alkaloid Derivatives

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# Synthesis and Applications of Structurally Modified *Cinchona* Alkaloid Derivatives

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Quinidinone was formed diastereoselectively from quinine and reacted with a variety of nucleophiles to produce a series of 9-substituted quinidine analogues. The configuration at the C9 position was determined to be (*S*) by X-ray crystallography, which supports the proposed chelation control mechanism of nucleophilic addition to quinidinone. Hydrogenation of the C10-C11 double bonds of the new compounds also allowed access to a series of 9-substituted-10,11-dihydroquinidine derivatives.

8-Fluoroquinidinone and 8-fluoroquininone were prepared from quinidinone, and both were reacted independently with nucleophiles to produce a series of 9-(*R*)-substituted-8-(*S*)-fluoro-*epi*-quinidines and 9-(*S*)-substituted-8-(*R*)-fluoro-*epi*-quinines, the configurations of which were confirmed by X-ray crystallography, supporting a Felkin-Ahn type mechanism for nucleophilic addition to 8-fluoroquinidinone and 8-fluoroquininone. A small series of 9-(*R*)-substituted-8-(*S*)-fluoro-10,11-dihydro-*epi*-quinidines were also synthesised by hydrogenation of the C10-C11 double bonds in the corresponding 9-(*R*)-substituted-8-(*S*)-fluoro-*epi*-quinidine derivatives.

All of the novel *Cinchona* alkaloid derivatives were screened as enantioselective electrophilic fluorinating reagents in the asymmetric fluorination of ethyl-1-indanone-2-carboxylate. Moderate enantioselectivities were achieved; the best, 64% enantiomeric excess, was obtained with 9-phenyl-8-fluoro-10,11-dihydro-*epi*-quinidine and was a significant improvement on the 30% enantiomeric excess obtained using quinidine.

Excellent enantioselectivities were obtained when the novel *Cinchona* derivatives were screened as chiral aminoalcohol ligands in the enantioselective addition of diethylzinc to benzaldehyde. The best enantiomeric excess achieved was 92%, using 9-(3,5-bis-trifluoromethylphenyl)-10,11-dihydroquinidine.

Preliminary screening of antimalarial activity has revealed that five of the novel *Cinchona* alkaloid derivatives possess antimalarial activity against the *Plasmodium falciparum* parasite. The active *Cinchona* alkaloid derivatives all contained either a fluorine atom at the C8 position or a trifluoromethyl group on the aromatic ring of the 9-aryl quinidine or 9-aryl-10,11-dihydroquinidine derivatives.

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## Abbreviations

pKa	Acid dissociation constant
PET	Positron Emission Tomography
Et	ethyl (-C <sub>2</sub> H <sub>5</sub> )
THF	Tetrahydrofuran
eq.	equivalent(s)
HMDS	Hexamethyldisilazide
LDA	Lithium diisopropylamide
Bn	benzyl (-CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> )
NFSI	<i>N</i> -fluorobenzenesulfonimide
h	hour(s)
Me	methyl (-CH <sub>3</sub> )
Ph	phenyl (-C <sub>6</sub> H <sub>5</sub> )
Bz	benzoyl (C <sub>6</sub> H <sub>5</sub> CO-)
Ac	acetyl (CH <sub>3</sub> CO-)
HPLC	High Performance Liquid Chromatography
DABCO	1,4-diazabicyclo[2.2.2]octane
TMEDA	Tetramethylethylenediamine
acac	acetyl acetone (pentane-1,4-dione)
bipy	2,2'-bipyridine
RT	room temperature
Tol	tolyl (CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> -)
DCE	Dichloroethane
hmim	1-hexyl-3-methylimidazolium
bmim	1-butyl-3-methylimidazolium
emim	1-ethyl-3-methylimidazolium
Naph	naphthyl (-C <sub>10</sub> H <sub>7</sub> )
TADDOL	$\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol
QM/MM	quantum mechanics/molecular mechanics
<sup>t</sup> Bu	<i>tert</i> -butyl
TBAF	tetra- <i>n</i> -butylammonium fluoride
DMF	dimethylformamide
DEAD	diethyl azodicarboxylate

DPPA	diphenylphosphoryl azide
Boc	<i>tert</i> -butoxycarbonyl
TFA	trifluoroacetic acid
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
OTf	triflate (trifluoromethanesulfonate) (CF <sub>3</sub> SO <sub>3</sub> <sup>-</sup> )
dppp	1,3-bis(diphenylphosphino)propane
Nu	nucleophile
CPME	cyclopentyl methyl ether
dr	diastereoisomeric ratio
ee	enantiomeric excess
DMAP	4-dimethylaminopyridine
MTBE	methyl <i>tert</i> -butyl ether
<sup><i>i</i></sup> Pr	<i>iso</i> -propyl
AD	asymmetric dihydroxylation
DCM	dichloromethane
Py	pyridyl
TFAA	trifluoroacetic anhydride
dichlorprop	2-(2,4-dichlorphenoxy)propionic acid
FMoc	Fluorenylmethyloxycarbonyl
Cbz	carboxybenzyl
<i>P.</i>	<i>Plasmodium</i>
FPPIX	ferriprotoporphyrin IX
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser effect
DMSO	dimethyl sulfoxide
TMS-	trimethylsilyl-
TBAT	tetrabutylammonium triphenyldifluorosilicate
HMQC	Heteronuclear multiple-quantum correlation spectroscopy
COSY	Correlation spectroscopy
NOESY	Nuclear Overhauser effect spectroscopy
DAST	diethylaminosulfur trifluoride
HOESY	Heteronuclear Nuclear Overhauser effect Spectroscopy
ppm	parts per million

DIBAL	diisobutylaluminium hydride
PTC	Phase Transfer Catalysis
(±)-DAIB	(±)-3- <i>exo</i> -(Dimethylamino)isoborneol
(±)-MIB	(±)-3- <i>exo</i> -Morpholinoisoborneol
DBNE	<i>N,N</i> -di- <i>n</i> -butylnorephedrine
2-MAP	( <i>1R,2S,3R,5R</i> )-6,6-dimethyl-2-morpholinobicyclo[3.1.1]heptan-3-ol
3-MAP	( <i>1R,2S,3R,5R</i> )-6,6-dimethyl-3-morpholinobicyclo[3.1.1]heptan-2-ol
GC	Gas chromatography
CYDEX-B	permethylated beta cyclodextrin
Rt	retention time
LDH	Lactate dehydrogenase
APAD	3-Acetylpyridine adenine dinucleotide
NBT	NitroBlue Tetrazolium
EI	electron impact
ES	Electrospray
FAB	Fast atom bombardment
OJ	cellulose tris 4-methylbenzoate
ODH	cellulose tris (3,5-dimethylphenylcarbamate)
Mp	melting point
d	doublet
t	triplet
q	quartet
m	multiplet
c	concentration

## 1. Introduction

### 1.1 Fluorine in medicinal chemistry

Fluorine is introduced into pharmaceutical compounds in order to alter the metabolic stability, basicity, lipophilicity and/or preferred molecular conformation, all of which will alter the activity of the molecule in the body. Consequently, fluorine is often introduced into drug candidates; more than 150 of the marketed pharmaceuticals in the world are fluorinated compounds (approximately 20%),<sup>1</sup> including four in the top ten best selling drugs,<sup>2</sup> and this is expected to continue to rise.

The metabolic stability of a drug molecule, and therefore the amount of unchanged drug molecule that reaches circulation (bioavailability), is often limited by the oxidation of CH bonds by cytochrome P450 enzymes, found mainly in the liver. To prevent this oxidation, the labile CH sites are substituted with a fluorine atom, which exerts only a minor steric change due to its similar van der Waals radius (F - 1.47 Å; H - 1.20 Å).<sup>3</sup>

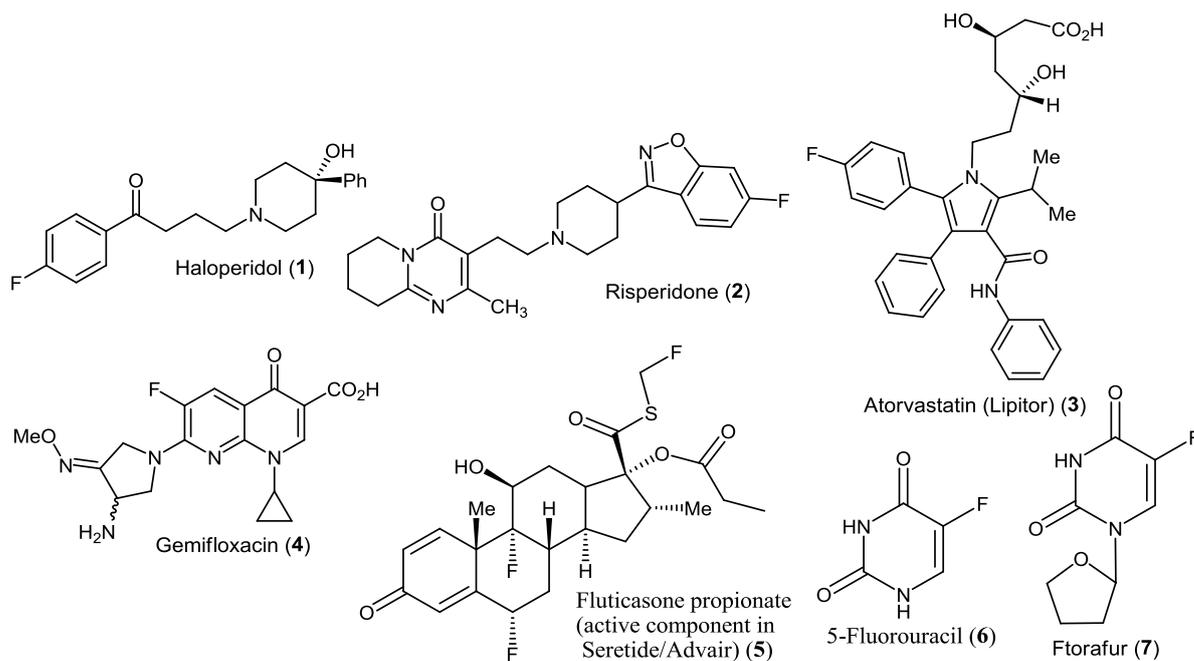
The proximity of the highly electronegative fluorine atom to a basic group on the molecule will decrease the basicity by altering the electron distribution in the molecule. A lower basicity will improve the membrane permeation of the molecule, which improves the bioavailability. Depending on the location of the fluorine relative to an acidic or basic group, changes of pKa can be significant; shifts of several log units have been observed. For example, the pKa of acetic acid (CH<sub>3</sub>CO<sub>2</sub>H) is 4.76, the pKa of CH<sub>2</sub>FCO<sub>2</sub>H is 2.59, the pKa of CHF<sub>2</sub>CO<sub>2</sub>H is 1.24, and the pKa of CF<sub>3</sub>CO<sub>2</sub>H is 0.23.<sup>4</sup>

Typically, a high lipophilicity is needed to bind to a target protein, but it can also lead to low solubility. A delicate balance is therefore required with the lipophilicity needed in order to pass into the lipid core of the cell membrane since too high a lipophilicity would cause the molecule to become trapped there. The introduction of single fluorine atoms and trifluoromethyl groups to saturated alkyl groups will lower the lipophilicity due to the electron withdrawing nature of the fluorine. Upon aromatic fluorination and fluorination next to atoms with  $\pi$  bonds, the lipophilicity increases due to the good overlap of the fluorine 2s and 2p orbitals with those of carbon. Changes in both the lipophilicity and the pKa will also affect the binding affinity of the molecule to the target enzyme.

The preferred molecular conformation of the molecule will be altered by the introduction of a fluorine atom. For example, 1,2-difluoroethane adopts a preferred gauche (rather than the expected anti) conformation so that the electronegative fluorine

atoms can both be positioned antiperiplanar to a CH bond, allowing beneficial double stabilising hyperconjugative ( $\sigma \rightarrow \sigma^*$ ) interactions. Therefore, the presence of fluorine on a stereogenic centre adjacent to another electronegative group may significantly influence the conformation in a similar way.

These alterations of biological processes by the presence of fluorine lead to fluorinated molecules being used as anaesthetics, anti-cancer, antibiotic and anti-inflammatory agents, as well as antidepressants and antipsychotics (Figure 1.1).<sup>5</sup>



**Figure 1.1:** Examples of fluorine containing drugs

Since the changes in lipophilicity due to fluorine substitution of a drug molecule lead to an increased blood brain barrier permeability, fluorinated drugs are especially important as central nervous system drugs.<sup>6</sup> Specific examples include haloperidol (1), a first generation antipsychotic in which the *para*-fluorine substituent on the phenyl ring increases the tranquilising activity compared to other butyrophenones; the 4-fluorobenzoyl group is therefore essential for optimum potency. Haloperidol (1) has a high binding affinity for the Dopamine D2 receptor, and is used in the treatment of schizophrenia, reducing the positive symptoms (delusions, hallucinations, disorganisation, grandiosity, hostility). Unfortunately, it has little effect on the negative symptoms (apathy, loss of attention, affective disorder, speech poverty). Risperidone (2), a second generation antipsychotic developed from haloperidol, reduces the positive symptoms of schizophrenia by acting on the dopaminergic pathway, but also reduces

the negative symptoms of schizophrenia by acting on serotonergic and adrenergic receptors.

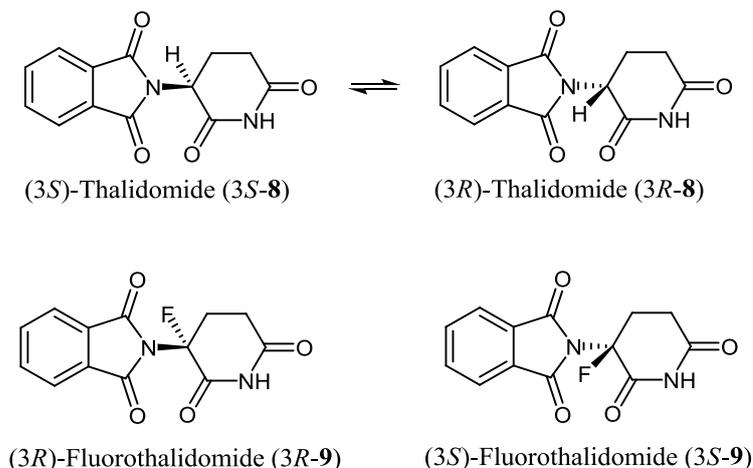
Fluorinated drugs are also used in the treatment of metabolic disorders linked to obesity such as type 2 diabetes and cardiovascular diseases such as hypercholesteremia (high cholesterol). Atorvastatin (Lipitor) (**3**) is a statin which inhibits the rate limiting step of cholesterol biosynthesis in the liver, thus lowering cholesterol. Lipitor, along with Seretide/Advair (medication for chronic obstructive pulmonary disorder) (**5**), were the major market sales leaders in 2007.<sup>7</sup>

Fluoroquinolones are highly active, safe, widely used antibacterials which overcome the problems of the first generation of quinolones, namely narrow antibacterial spectrum and comparatively weak activity. The fluorine substituent increases the binding affinity by a factor of 2-17, reduces plasma protein binding leading to a higher free fraction of the drug, and increases cell penetration by a factor of 1-70, all of which combine to give a dramatically improved antibacterial activity. Gemifloxacin (**4**) is one example, which retains activity against bacterial organisms that have developed resistance to earlier quinolones.<sup>8</sup>

Fluorinated drugs are also effective anti-cancer drugs. 5-Fluorouracil (**6**) is a mechanism based inhibitor of thymidylate synthase (TS), causing apoptotic cell death which affects rapidly dividing cells such as viral or cancer cells, and is used to treat gastrointestinal, breast, head and neck cancers. Due to its short biological half life and irregular absorption, it is administered by continuous infusion which is costly and inefficient. When it is used in combination therapy with other fluorinated drugs (such as Ftorafur (**7**)), the drug's bioavailability improves, and the undesirable cardiotoxic side effects decrease.<sup>9</sup>

It is well-recognised that one enantiomer of a molecule may have a property desirable in a drug molecule which is absent in the other enantiomer. In some cases the other enantiomer may even be harmful, such as in the tragic case of thalidomide (**8**) (Figure 1.2) where the *R*-enantiomer was effective against morning sickness in pregnant women whilst the *S*- enantiomer was teratogenic, causing many birth defects in babies whose mothers had been prescribed the drug. Since its withdrawal from the market in 1962, it has been discovered that replacement of the acidic hydrogen on the stereogenic centre adjacent to the carbonyl with a fluorine atom prevents the *in vivo* epimerisation of the drug. It has subsequently been discovered that 3-fluorothalidomide (**9**) has some anti-cancer activity, and that the (3*S*)-fluorothalidomide analogue is more active in

tumour inhibition than the (3*R*)-fluorothalidomide or than the racemic parent thalidomide.<sup>10</sup>

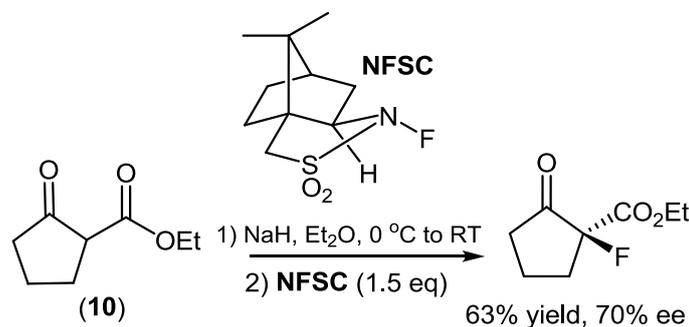


**Figure 1.2:** The two enantiomeric forms of thalidomide and 3-fluorothalidomide

Fluorine is also used in nuclear medicine, specifically as an  $^{18}\text{F}$  radiolabel for use in Positron Emission Tomography (PET), a nuclear medical imaging technology that shows biological processes rather than merely anatomical information. The use of  $^{18}\text{F}$  is advantageous since it has a significantly longer half life than other radionuclides used in medical imaging ( $^{18}\text{F}$ =110 mins, compared to  $^{11}\text{C}$ =20 mins,  $^{13}\text{N}$ =10 mins, and  $^{15}\text{O}$ =2 mins), which is important as radionuclides must be produced, incorporated into a radiotracer molecule, and used before they decay. The most frequently used radiotracer, described as ‘the workhorse of PET’,<sup>11</sup> is 2-deoxy-2- $^{18}\text{F}$ fluoro-D-glucose, which after intravenous injection is rapidly taken up in the body, particularly by cells that use a lot of glucose (i.e. cells of the brain, the kidneys, or cancer cells). It is phosphorylated in the same manner as glucose but due to the blocked C2 position it cannot undergo glycolysis before it decays, so it remains in the tissues under investigation, before the  $^{18}\text{F}$  decays into non radioactive  $^{18}\text{O}$  and is excreted. The use of 2-deoxy-2- $^{18}\text{F}$ fluoro-D-glucose in PET is particularly important in oncology, as tumours can be located and graded based on their 2-deoxy-2- $^{18}\text{F}$ fluoro-D-glucose uptake (invaluable for treatment planning), the response of the tumour to different therapies can be evaluated based on repeated measurements at different time points, and tumour recurrence can be detected.

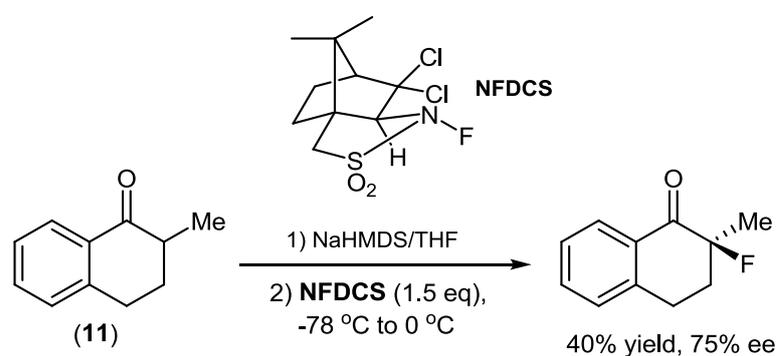
## 1.2 Enantioselective electrophilic fluorination

### 1.2.1 Reagent controlled enantioselective electrophilic fluorination



**Scheme 1.1**

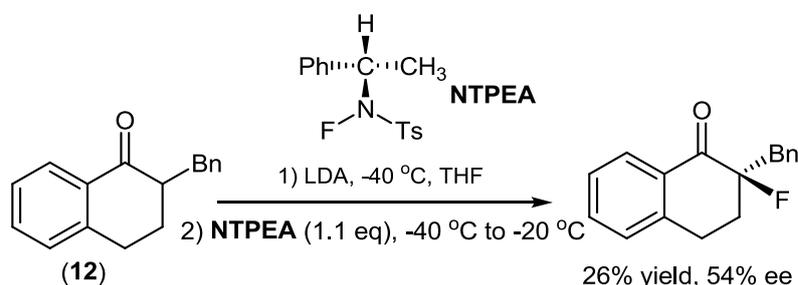
The first enantioselective electrophilic fluorination was carried out by Lang,<sup>12</sup> using optically pure *N*-fluorosultams derived from camphor. Lang fluorinated various prochiral metal enolates of  $\beta$ -ketoesters, obtaining the best result (63% yield, 70% ee) in the case of the sodium enolate of ethyl cyclopentanone-2-carboxylate (**10**) (Scheme 1.1). This good enantioselectivity was, however, difficult to extend to other  $\beta$ -ketoesters; for two of the reactions enantiomeric excesses of 35% were observed and enantiomeric excesses of  $\leq 10\%$  were observed for the remaining three  $\beta$ -ketoesters. Despite the generally low enantioselectivity obtained, the multistep synthesis involving the use of molecular fluorine in the final step, and the potential difficulty of structural modification to improve the efficiency due to the derivation of the reagent from a natural product, this reaction did demonstrate the potential of reagent controlled asymmetric fluorination.



**Scheme 1.2**

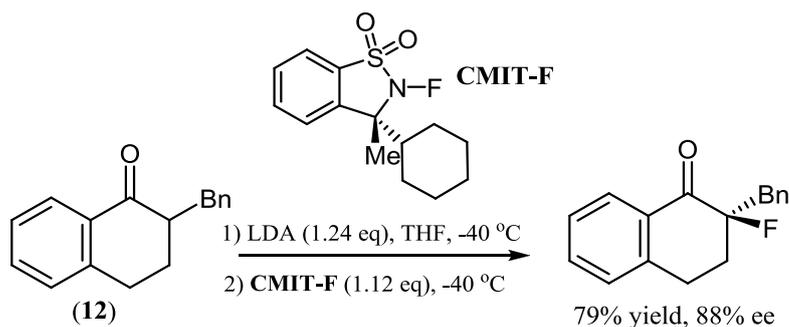
Davis<sup>13</sup> investigated the use of (-)-*N*-fluoro-2,10-(3,3-dichlorocamphor-sultam) **NFDCS** for similar enolates, obtaining generally higher yields and enantiomeric

excesses than those observed by Lang. The best result obtained was a 75% enantiomeric excess combined with a 40% isolated yield (Scheme 1.2).



**Scheme 1.3**

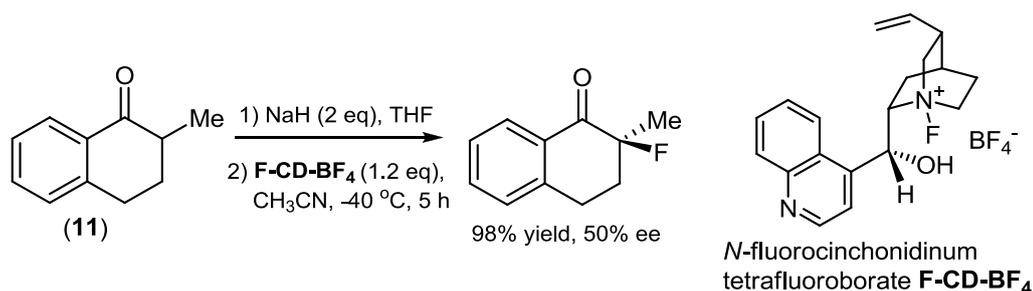
Takeuchi<sup>14</sup> investigated N-F reagents derived from readily available chiral amino acids, using the *N*-tosyl derivatives of D-phenylglycine and  $\alpha$ -phenethylamine as starting materials, and fluorinating them with  $\text{FCIO}_3$ . The fluorinations of four model substrates were carried out, with generally low yields and enantioselectivities; the best result obtained was a 54% enantiomeric excess together with a 26% yield (Scheme 1.3). Takeuchi considered this reagent neither sufficiently reactive towards carbanions nor stable enough to be useful under normal conditions, so he redesigned his chiral fluorinating reagents and reported<sup>15</sup> the synthesis of *N*-Fluoro-3-cyclohexyl-3-methyl-2,3-dihydrobenzo[1,2-*d*]-isothiazole 1,1-dioxide (**CMIT-F**), a reagent that promotes the asymmetric fluorinations of ketone metal enolates to give  $\alpha$ -fluoroketones in moderate to high yield with up to 88% enantiomeric excess (Scheme 1.4).



**Scheme 1.4**

The chiral fluorinating reagents described above all suffer from long complicated syntheses, some involving the handling of molecular fluorine, with limited scope and the achievement of only low to moderate yields and enantiomeric excesses in asymmetric fluorination. A major advance in the field was the introduction of a new

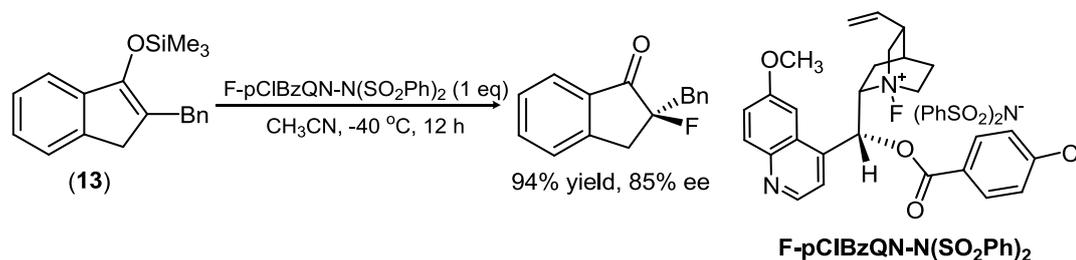
class of reagents derived from the *Cinchona* alkaloids. These reagents are *N*-fluoroammonium salts,  $[R_3N^+F^-]$  rather than  $[R_2NF]$ , and are therefore more reactive allowing access to a wider substrate scope. The commercially available *Cinchona* alkaloids diastereoisomeric forms (i.e. quinine/quinidine, cinchonidine/cinchonine) act as *pseudoenantiomers* in asymmetric synthesis. The fluorination of the quinuclidine nitrogen can also be performed under mild conditions via fluorine transfer from commercially available fluorinating agents such as Selectfluor or *N*-fluorobenzenesulfonimide (NFSI) rather than using molecular fluorine.



Scheme 1.5

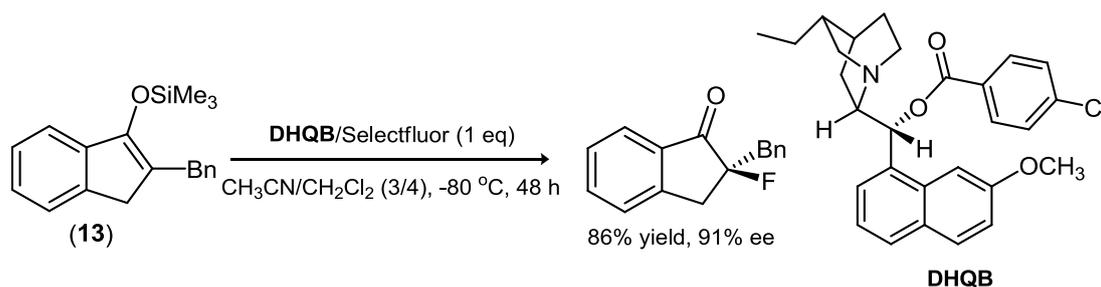
The synthesis of the *N*-fluoroammonium salts using a one step transfer fluorination of *Cinchona* alkaloids with Selectfluor was reported simultaneously but independently by two groups. Cahard<sup>16</sup> isolated the *N*-fluorocinchonium tetrafluoroborate salts of quinine, quinidine, cinchonidine and cinchonine, and then used them in the enantioselective fluorination of the enolate of 2-methyl-1-tetralone (**11**), in order to have a direct comparison with the results of previous studies which used neutral N-F reagents to fluorinate the same substrate. Initially, only one equivalent of base was used to generate the enolate, but the final fluorinated product was only isolated in moderate yield. When two equivalents of base were used to avoid protonation of the enolate by the free OH of the alkaloid, the yields were quantitative. Of the four *N*-fluorocinchonium salts, *N*-fluorocinchonidinium tetrafluoroborate gave the best enantioselectivity (98% yield, 50% ee), with the fluorinated stereocentre having the (*S*) configuration (Scheme 1.5). In a further paper<sup>17</sup> Cahard demonstrated that the transfer fluorination step can also be performed by other fluorinating agents such as NFSI (which is a cheaper reagent than Selectfluor, and is soluble in a range of non-polar solvents), Accufluor, and *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate. The *N*-fluorocinchonium salts thus prepared were used in the enantioselective electrophilic fluorination of silyl enol ethers. In this investigation the OH group on the alkaloid was

protected, contributing to the higher enantioselectivities observed, and the best result obtained was an 85% ee combined with a 94% yield (Scheme 1.6).



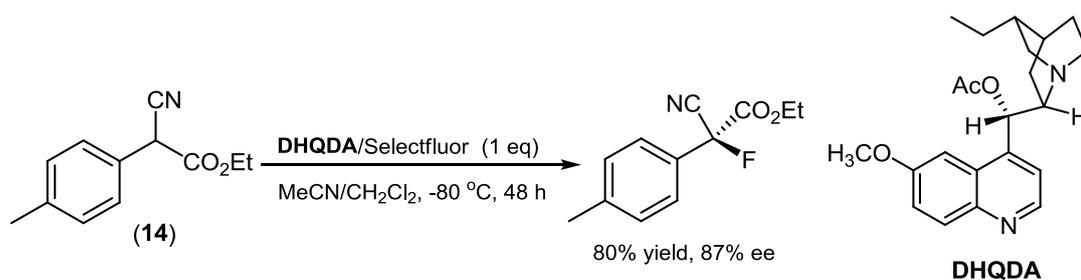
**Scheme 1.6**

Shibata<sup>18</sup> preferred to generate the *N*-fluoro ammonium salts *in situ* without isolation and purification. After screening several commercially available *Cinchona* alkaloids it was discovered that dihydroquinine 4-chlorobenzoate (DHQB) in combination with Selectfluor gave the best enantioselectivity for the fluorination of (2-benzyl-3H-inden-1-yloxy)-trimethylsilane (**13**) (86% yield, 91% ee) and for other silyl enol ethers (Scheme 1.7).



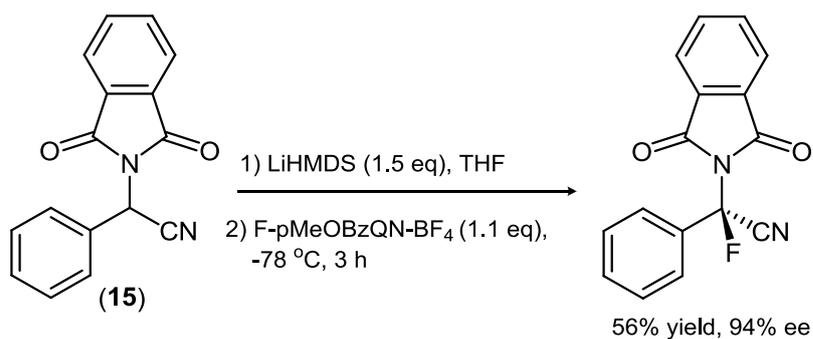
**Scheme 1.7**

In the same study Shibata investigated the enantioselective fluorination of acyclic esters using ethyl  $\alpha$ -cyano-tolyl acetate (**14**). Fluorination using the DHQB/Selectfluor combination only gave a 51% ee with a 99% yield. By screening other *Cinchona* alkaloids, the enantiomeric excess was improved to 87% with an 80% yield using dihydroquinidine acetate (DHQDA)/Selectfluor (Scheme 1.8). High enantiomeric excesses were also achieved in the fluorination of other acyclic esters, including the first asymmetric preparation of two chiral derivatising agents whose previous preparation involved enzymatic resolution or the separation of diastereoisomeric derivatives.



Scheme 1.8

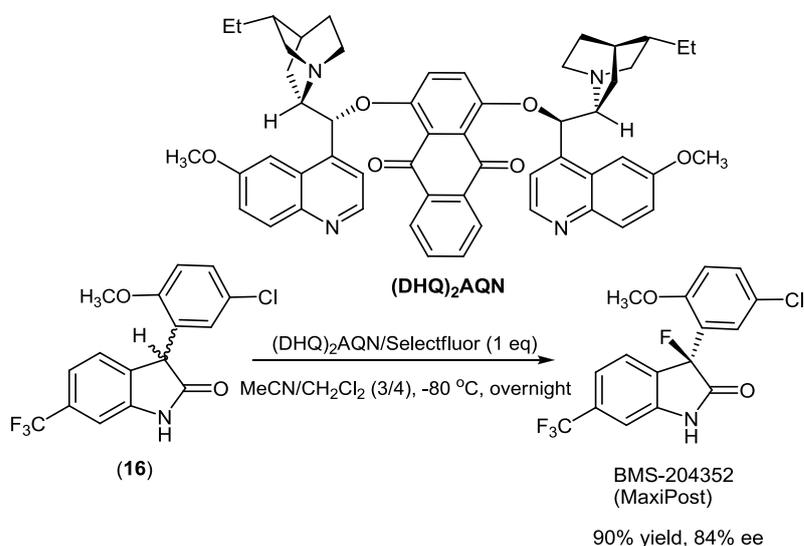
Cahard<sup>19</sup> then reported the first enantioselective synthesis of  $\alpha$ -fluoro- $\alpha$ -amino acids, molecules of special interest for the design of new fluorine containing peptides with unusual folding patterns. Work was focused on *N*-phthaloyl- $\alpha$ -aminophenylglycine and *N*-phthaloyl-phenylglycinonitrile (**15**). Higher enantioselectivities were obtained using *N*-fluoroquininium and *N*-fluoroquinidinium salts over *N*-fluorocinchonidinium and *N*-fluorocinchoninium salts, suggesting the participation of the quinoline methoxy group in the stereoselection. Protection of the hydroxyl group was essential for high enantioselectivity and enantiomeric excesses of up to 94% were achieved, further demonstrating the power of the method for generating chiral fluorinated centres (Scheme 1.9). In the ester series the enantioselectivity was higher with acetyl protection than with benzoyl protection, however, in the nitrile series this observation was reversed. Significantly higher enantiomeric excesses were observed for the nitrile derivatives compared to the ester derivatives, which could be explained by the different nature of the metalated intermediates.



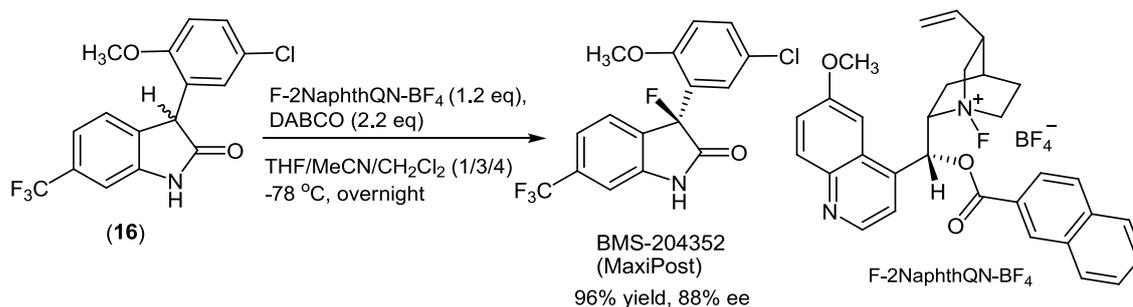
Scheme 1.9

Both Shibata<sup>20</sup> and Cahard<sup>21</sup> used enantioselective fluorination as the key step in the synthesis of a medically important target, BMS-204352 (Maxipost), a fluoroxindole in worldwide phase III clinical trials for the treatment of acute ischemic stroke. BMS-204352 is a chiral compound of which the major structural feature is a fluorine atom on the chiral centre, carbon three on the oxindole ring. BMS-204352 is the (*S*) enantiomer;

the (*R*) enantiomer is active but does not give a consistent robust response. Previously, the (*S*) enantiomer was separated by chiral HPLC resolution of the racemic mixture and no asymmetric syntheses had been carried out. Shibata examined the fluorination of the parent oxindole (**16**), which can be formed from commercially available 3-aminobenzotrifluoride in five steps, screening a variety of *Cinchona* alkaloids and obtaining the best results (84% ee with 90% yield) with the bis-*Cinchona* alkaloid (DHQ)<sub>2</sub>AQN in combination with Selectfluor (Scheme 1.10). Recrystallisation from CH<sub>2</sub>Cl<sub>2</sub>/hexane yielded enantiomerically pure BMS-204352 (ee > 99%).



Scheme 1.10

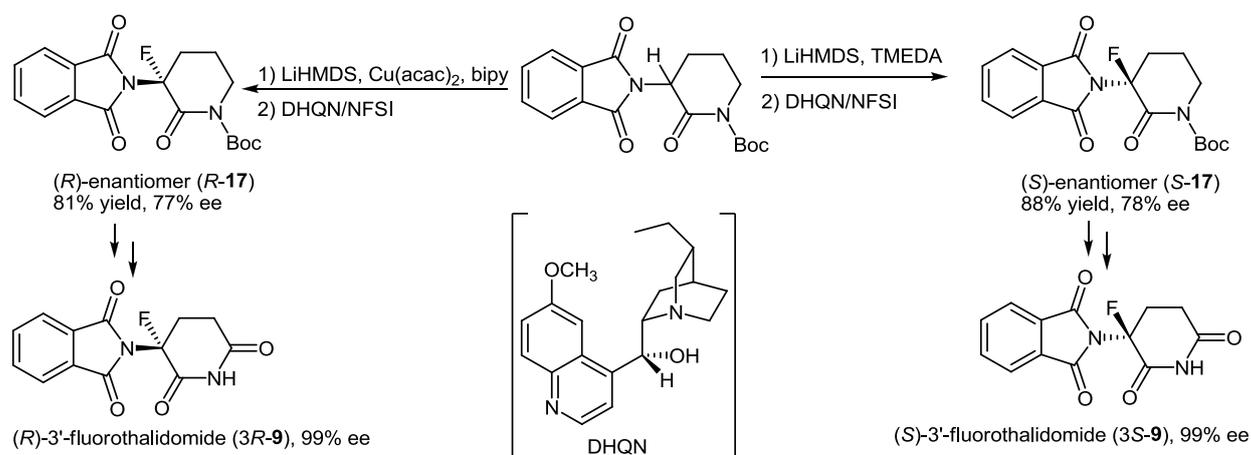


Scheme 1.11

Cahard's synthesis of BMS-204352 also involved the fluorination of the parent oxindole (**16**), and a series of *Cinchona* alkaloids were screened for the enantioselective fluorination. The best result (96% yield, 88% ee) was obtained using DABCO as the base and F-2NaphthQN-BF<sub>4</sub> (Scheme 1.11), which gave a slightly higher enantiomeric

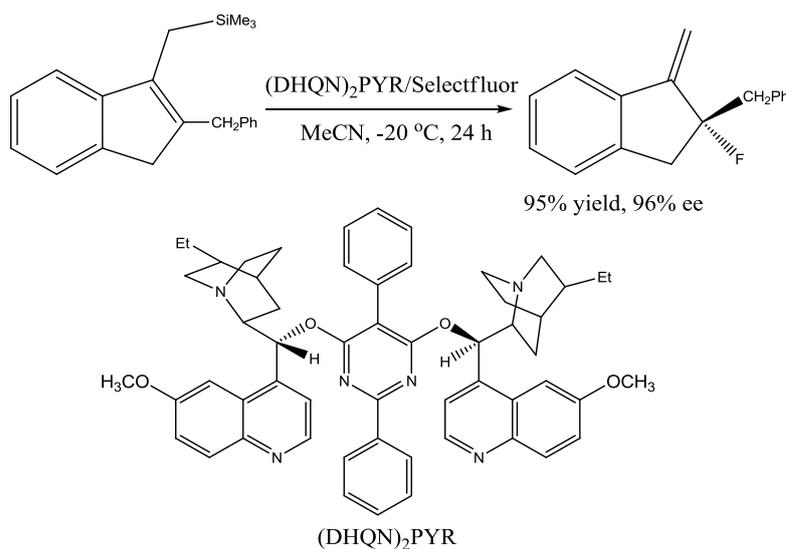
excess than Shibata's best result. Recrystallisation from  $\text{CH}_2\text{Cl}_2$ /hexane afforded enantiomerically pure BMS-204352.

Shibata<sup>22</sup> has also used a single *Cinchona* alkaloid, dihydroquinine (DHQN), in the enantioselective synthesis of both mirror images of 3-fluorothalidomide (**9**) by enantiodivergent fluorination. The rapid epimerisation between the two enantiomers of thalidomide makes determination of the differences in biological activity between the two enantiomers difficult. To answer the ambiguity as to whether thalidomide, which has been recently shown to be effective for the treatment of multiple myeloma, is in fact stereospecifically teratogenic, non-racemisable isosteric chiral analogues are required. 3-Fluorothalidomide (**9**) has been extensively studied for this purpose. Previously, the two enantiomers have been prepared by chiral HPLC separation, which could be an obstacle to *in vivo* studies into the teratogenicity. Dihydroquinine/NFSI allowed access to either mirror image form of the fluorothalidomide precursor (**17**), depending on the additives employed (Scheme 1.12). Thus, the use of TMEDA as an additive gave the (*S*)-enantiomer (88% yield, 78% ee), whilst the use of  $\text{Cu}(\text{acac})_2$  and 2,2'-bipyridine (bipy) gave the (*R*)-enantiomer (81% yield, 77% ee). The enantiomeric excesses of both enantiomers could be improved to >99% by a single recrystallisation. The synthesis of both enantiomers of 3-fluorothalidomide (**9**) was then completed in two steps from the precursor by deprotection and Ru catalysed oxidation, to give 3-(*S*)- and 3-(*R*)-fluorothalidomide (**9**) in enantiomeric excesses that were determined to be >99% by HPLC analysis.



Scheme 1.12

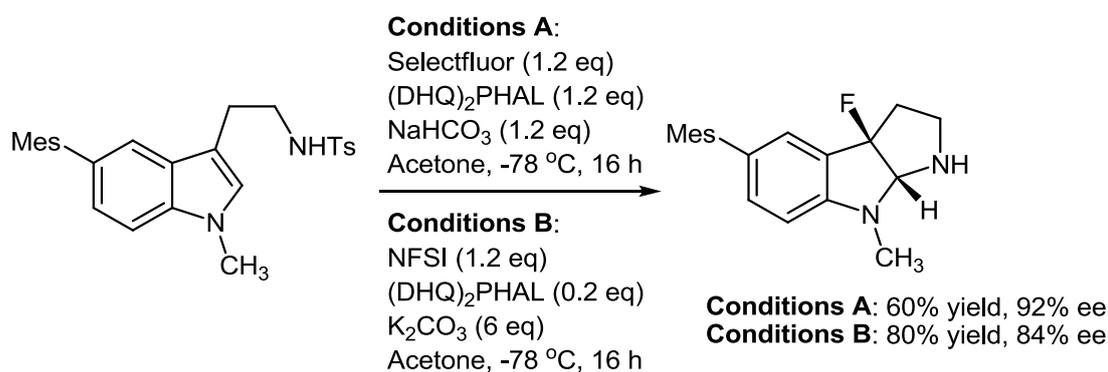
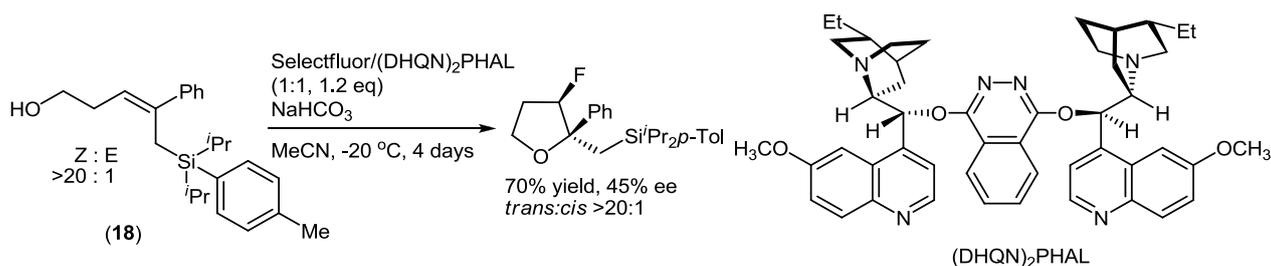
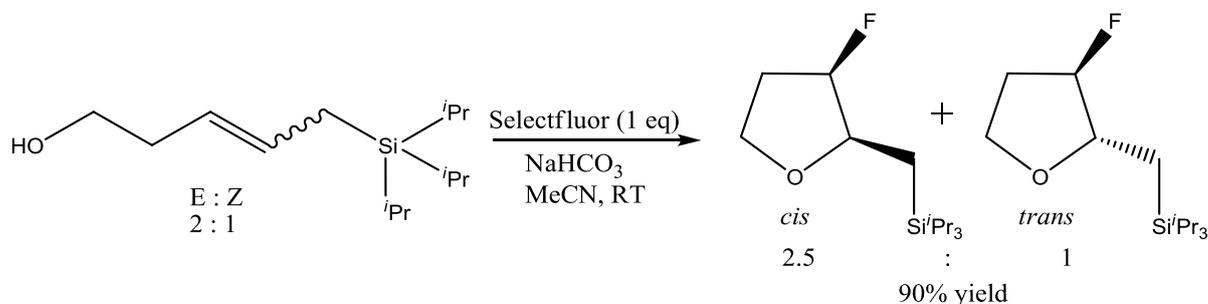
Gouverneur<sup>23</sup> reported the enantioselective preparation of allylic fluorides via the fluorodesilylation of allyl silanes. Selectfluor was found to be the best fluorine donor for the fluorodesilylations, and the *in situ* generation of the *N*-fluoroammonium salts from the *Cinchona* alkaloids was found to give better yields than using isolated *N*-fluoroammonium salts. Enantiomeric excesses of up to 96% were recorded, with yields greater than 95% (Scheme 1.13).



**Scheme 1.13**

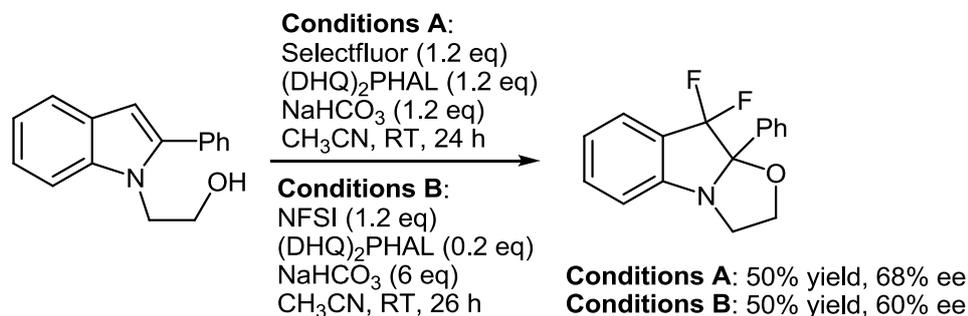
Gouverneur further extended this methodology by using silyl groups other than the trimethylsilyl group to bypass fluorodesilylation and instead enable the electrophilic fluorocyclisation of allyl silanes (Scheme 1.14).<sup>24</sup> The geometry of the alkene was found to influence the stereochemistry of the product, with *E*-allyl silanes leading to *cis*-substituted fluorinated tetrahydrofurans, and *Z*-allyl silanes leading to *trans*-substituted fluorinated tetrahydrofurans. *E*-Allyl silanes were found to be more diastereoselective than *Z*-allyl silanes, and the use of the single *E* isomer of allyl silane led to the *cis*-substituted product with no trace of the *trans*-substituted isomer. However, when the single *Z* isomer of the allyl silane was used traces of the *cis*-substituted isomer were observed in the product. A wide range of silyl-activated di- and tri-substituted alkenes were suitable substrates for the reaction and both *E*- and *Z*-allyl silanes underwent fluorocyclisation to give the desired fluorinated tetrahydrofurans in moderate to good yields (47-83%). The conditions also tolerated more functionalised allyl silanes, and the successful fluorocyclisation of a silylated carboxylic acid to make the fluorinated lactone in 80% yield demonstrates that the conditions are mild enough to prevent  $\beta$ -fluoride elimination after cyclisation. A preliminary study into reagent-

controlled asymmetric fluorocyclisation was carried out on the model substrate (*Z*)-5-(diisopropyl(*p*-tolyl)silyl)-4-phenylpent-3-en-1-ol (**18**), using a chiral N-F reagent prepared *in situ* from Selectfluor and the *Cinchona* alkaloid, (DHQN)<sub>2</sub>PHAL. In the presence of NaHCO<sub>3</sub> in acetonitrile at -20°C, the desired product was obtained as a single *trans*-diastereoisomer (70% yield, 45% ee) (Scheme 1.15).



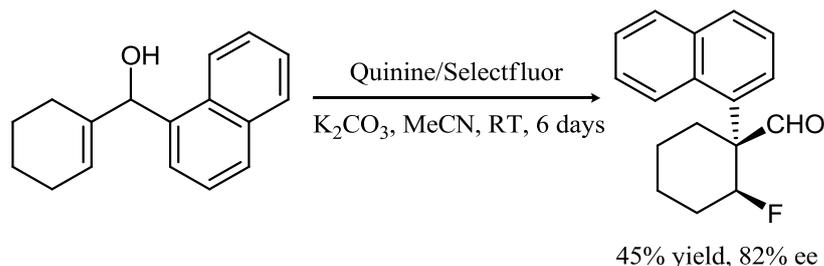
Gouverneur recently improved asymmetric fluorocyclisation reactions by making them catalytic in the chiral *Cinchona* alkaloid.<sup>25</sup> Slightly lower enantiomeric excesses were observed in the catalytic reactions (84% ee) compared to the stoichiometric

reactions (92% ee) (Scheme 1.16). The same enantiomer was formed preferentially under both sets of conditions. Asymmetric difluorocyclisation could also be achieved both stoichiometrically and catalytically (Scheme 1.17).



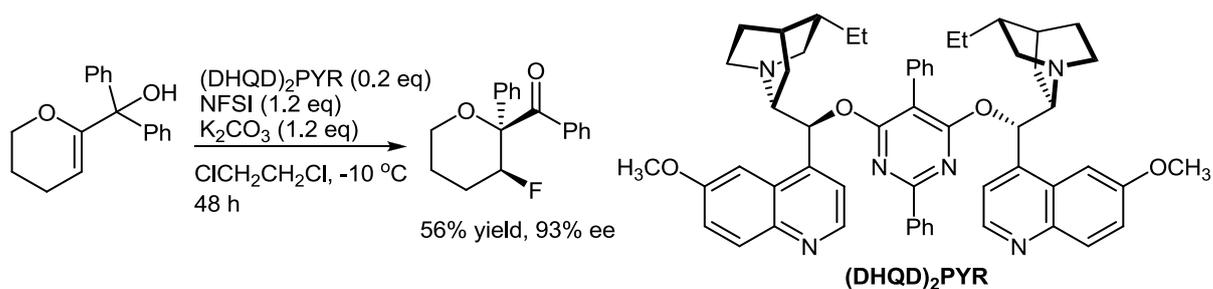
Scheme 1.17

An investigation by Tu<sup>26</sup> further increased the scope of *Cinchona* alkaloid/Selectfluor combination reactions to include the enantioselective formation of  $\alpha$ -quaternary  $\beta$ -fluoro aldehydes via a quinine/Selectfluor mediated semipinacol rearrangement of allylic alcohols with high enantioselectivity (Scheme 1.18).



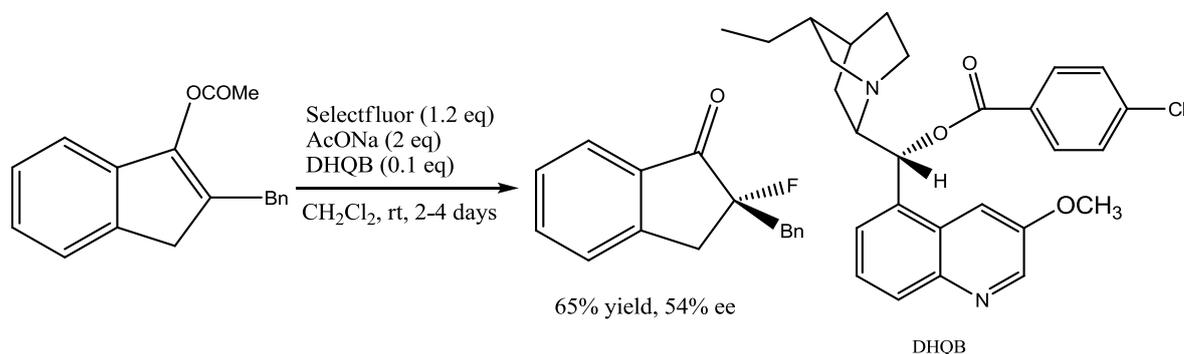
Scheme 1.18

Recently,<sup>27</sup> Tu developed a catalytic method for the asymmetric fluorination/semipinacol rearrangement for the formation of  $\beta$ -fluoroketones (Scheme 1.19). An examination of the enantiomeric excesses achieved with a series of chiral catalysts on one model substrate determined dihydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether ((DHQD)<sub>2</sub>PYR) to be the best catalyst for enantioselectivity. Solvent, additive and temperature investigations led to the establishment of the optimal conditions using DCE as the solvent and the inorganic base K<sub>2</sub>CO<sub>3</sub> as an additive, at a temperature of -10 °C. Various 2-oxa allylic alcohol substrates were tested, and moderate to good yields (34-76%) and moderate to excellent enantiomeric excesses (38-93%) were achieved. The use of dihydroquinine-2,5-diphenyl-4,6-pyrimidinediyl diether ((DHQ)<sub>2</sub>PYR) gave the opposite enantiomers of the products in moderate yields (29-73%) and moderate to excellent enantiomeric excesses (36-90%).



Scheme 1.19

Shibata also performed catalytic enantioselective fluorinations mediated by *Cinchona* alkaloids.<sup>28</sup> The fluorination of acyl enol ethers to give  $\alpha$ -fluorinated ketones using Selectfluor and a catalytic amount of *Cinchona* alkaloid, dihydroquinine benzoate (DHQB) or bis-dihydroquinine anthraquinone ((DHQ)<sub>2</sub>AQN), was carried out in high yield with up to 54% enantiomeric excess (Scheme 1.20). Acyl enol ethers were chosen because their reaction with Selectfluor is much slower than the reaction with silyl enol ethers used in previous work, and the high reactivity of silyl enol ethers towards Selectfluor would lead to racemic products in the catalytic reaction. Sodium acetate was added in order to help with the desired activation of the enolate.

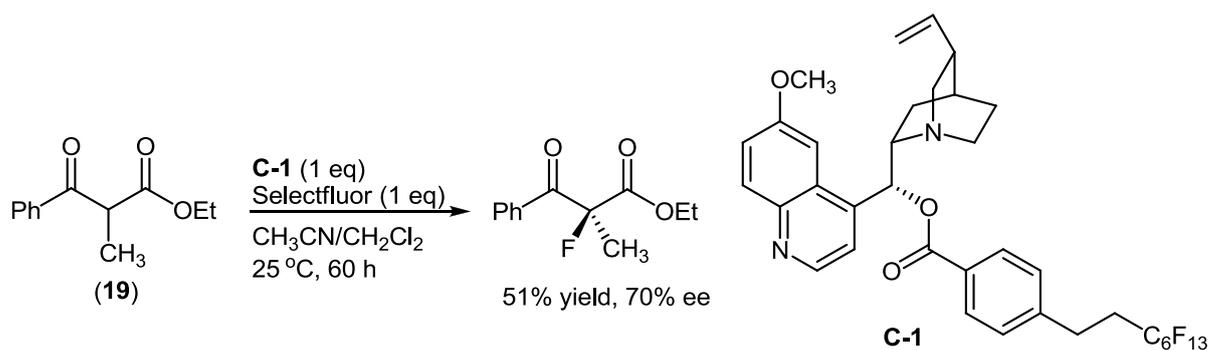


Scheme 1.20

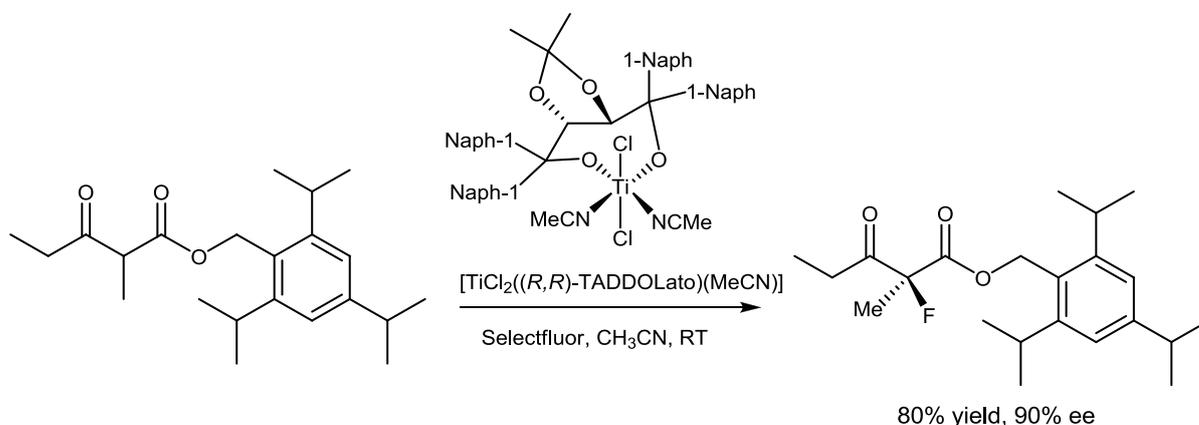
There are of course limitations to the applications of *Cinchona* alkaloid based [N-F<sup>+</sup>] reagents. The main drawbacks are the limited choice of possible solvents in which to perform the reactions (acetonitrile, acetone or DCM), the need for low temperatures to generate high enantiomeric excesses, and the difficult recovery of the *Cinchona* alkaloid after the reaction is complete. In order to address these problems Cahard<sup>29</sup> reported the first enantioselective reaction for the construction of carbon fluorine bonds in ionic liquids. The behaviour of several chiral [N-F<sup>+</sup>] reagents on silyl enol ethers in three different ionic liquids, [hmim][PF<sub>6</sub>], [bmim][PF<sub>6</sub>] and [emim][BF<sub>4</sub>], was explored. The [N-F<sup>+</sup>] reagents dissolved slowly in the ionic liquids at room temperature with the

aid of sonication, then the silyl enol ether was added at 0°C and the reaction was run at that temperature before the products were quantitatively isolated by extraction with diethyl ether. The enantiomeric excesses obtained were all observed to be equal to or greater than those obtained in acetonitrile, with the fluorinated stereocentre having the same absolute configuration in both solvents. The reaction was performed using *in situ* generation of the chiral [N-F<sup>+</sup>] reagent in order to simplify the system, and using NFSI the transfer fluorination step was found to be five times faster than with Selectfluor. Also, after isolation of the products by extraction with diethyl ether, the recovered ionic liquid containing the *Cinchona* alkaloid could be re-used by adding another equivalent of either Selectfluor or NFSI without significant alteration of the enantioselectivity.

Yi and Zhang<sup>30</sup> developed a fluorous *Cinchona* alkaloid ester derived from quinine (**C-1**) as a chiral promoter for the asymmetric fluorination of  $\beta$ -ketoesters (Scheme 1.21). The fluorination of the model compound, ethyl 2-methyl-3-oxo-3-phenyl propanoate (**19**), was carried out using **C-1**, and also with quinine, dihydroquinine, in addition to the benzoate and acetate esters of quinine, in order to allow a comparison with the performance of similar compounds. Compared with the other promoters, **C-1** gave slightly lower yield but improved stereoselectivity. Reducing the amount of **C-1** from 1 equivalent to 0.5 or 0.1 equivalents significantly decreased the enantioselectivity obtained from 65% ee to 26% and <5% ee respectively, suggesting a stoichiometric amount is required to minimise the formation of the achiral fluorination product by direct fluorination. The fluorous quinine ester could be easily recovered, in high yield (94%) and high purity (98%), by addition of base to the reaction mixture after fluorination to convert the *Cinchona* alkaloid/Selectfluor complex into free *Cinchona* alkaloid, and loading the organic phase onto a fluorous silica gel cartridge for fluorous solid phase extraction. The recovered fluorous quinine ester was recycled, and reused five times without significant change to the product yield or enantiomeric excess (cycle 1: 51% yield, 70% ee, cycle 5: 46% yield, 67% ee). The scope of asymmetric fluorination mediated by **C-1** was examined by carrying out reactions with a range of  $\alpha$ -substituted ethyl benzoyl acetates and with ethyl 2-cyclohexanonecarboxylate as substrates, generally achieving good yields (43-83%) and enantiomeric excesses (31-82%).

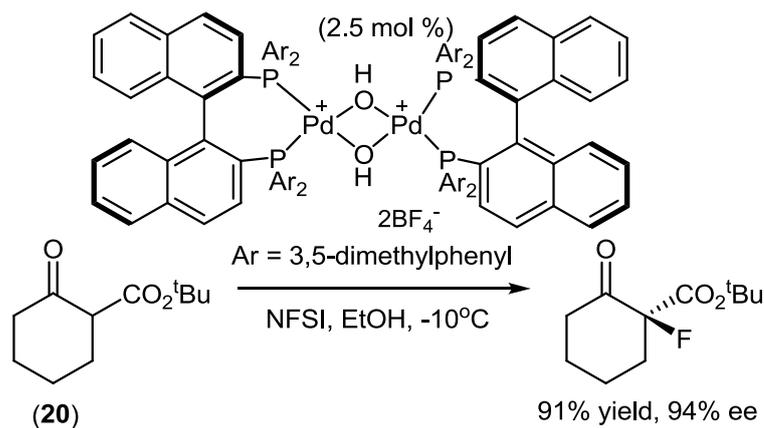


### 1.2.2 Transition metal catalysed enantioselective electrophilic fluorination



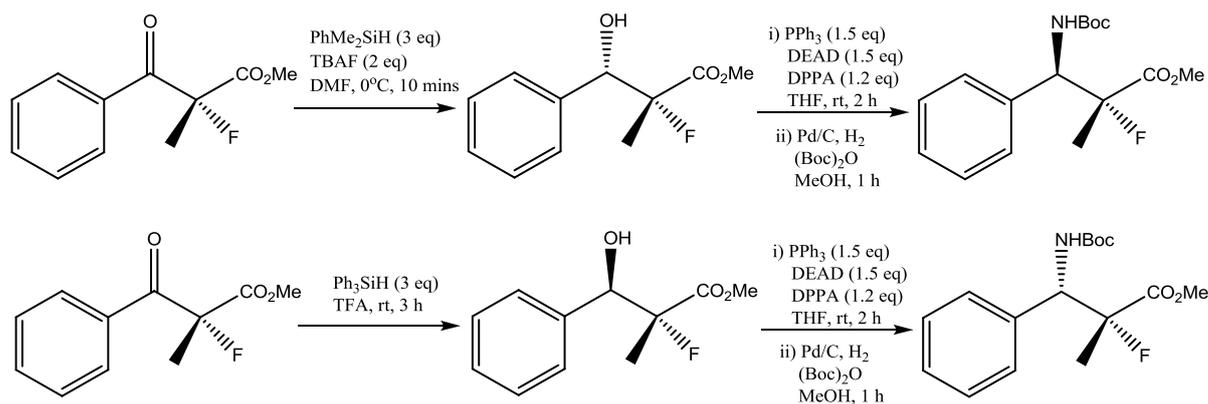
At the same time that the work on *Cinchona* alkaloids was being carried out, Togni<sup>31</sup> reported the catalytic enantioselective fluorination of  $\beta$ -keto esters. It was reasoned that since fluorination of these substrates proceeds via an enol form, the addition of a Lewis acid catalyst should accelerate the rate by catalysing the enolisation. A screen of Lewis acid catalysts for the fluorination of the model substrate, ethyl 2-methyl-3-oxo-3-phenylpropanoate (**19**), suggested that titanium based Lewis acid catalysts were the most potent, and since many chiral enantiopure Lewis acidic titanium complexes were known, there was the possibility of screening chiral catalysts for an enantioselective version of the reaction.  $[\text{TiCl}_2((R,R)\text{-TADDOLato})(\text{MeCN})]$  (TADDOL =  $\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol) was found to be the most effective chiral catalyst, and the results were more reliable in terms of reproducibility and enantioselectivity when the catalysts were isolated rather than prepared *in situ*. The fluorination of various  $\beta$ -keto esters were conducted at room temperature using 5 mol %

catalyst in a closed vessel with a slight excess of Selectfluor in acetonitrile. The yields after column chromatography were all greater than 80%, with enantiomeric excesses of up to 90% (Scheme 1.22). Further investigation<sup>32</sup> by Togni into the mechanism of this catalytic enantioselective fluorination, involving an extensive QM/MM first principle molecular dynamics study, strongly supported a single electron transfer mechanism as the pathway for halogen transfer in the reaction.



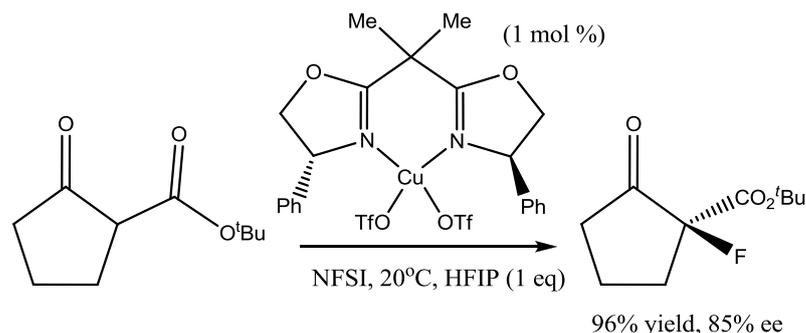
Scheme 1.23

Sodeoka,<sup>33</sup> inspired by the work of Togni, reported the catalytic enantioselective fluorination reaction of various  $\beta$ -keto esters using chiral palladium complexes, with excellent enantiomeric excesses of 83-94% ee. The best result (91% yield, 94% ee) was obtained for the fluorination of *tert*-butyl 2-oxocyclohexanecarboxylate (**20**) using a palladium  $\mu$ -hydroxo complex with chiral phosphine ligands that contained 3,5-dimethylphenyl groups (Scheme 1.23). The reaction proceeded well in alcoholic solvents (ethanol in particular), was not water sensitive, and could be scaled up and carried out on a 1 g scale. The fluorinated products could also be transformed into both diastereoisomers of  $\alpha$ -fluoro- $\beta$ -hydroxy- and  $\alpha$ -fluoro- $\beta$ -amino-acid derivatives by changing the reducing conditions (Scheme 1.24). Recently, Sodeoka<sup>34</sup> extended the scope of this work to report the enantioselective fluorination of *tert*-butoxycarbonyl lactones and lactams, achieving up to 99% enantiomeric excess.



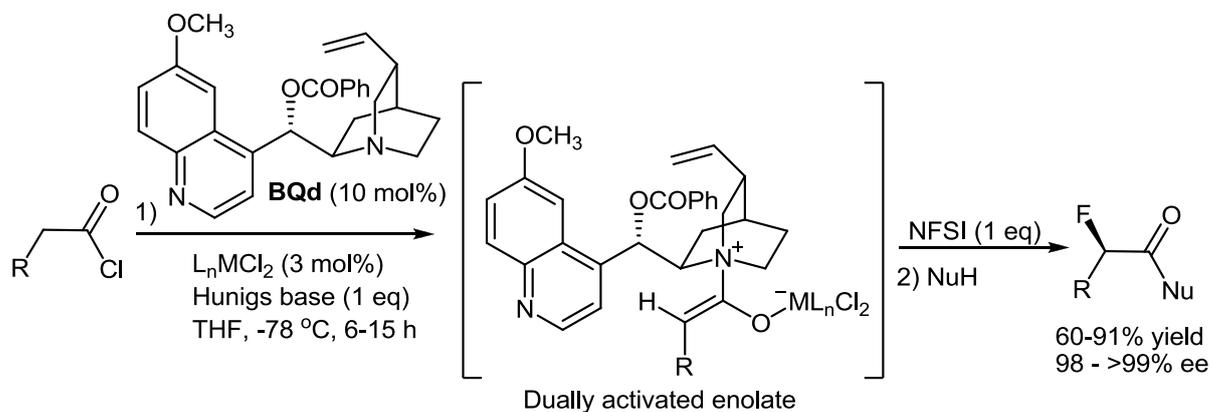
Scheme 1.24

Cahard<sup>35</sup> evaluated nitrogen containing ligands, which were considered complimentary to the oxygen and phosphorus containing ligands investigated by Togni and Sodeoka respectively, reporting a catalytic enantioselective fluorination of cyclic and acyclic  $\beta$ -keto esters by means of chiral bis(oxazoline)-copper complexes. Initially, 1-fluoro-2-oxo-cyclopentanecarboxylic acid *tert*-butyl ester was used as a model compound for the screening of different fluorinating reagents, Lewis acid catalysts, and chiral ligands. NFSI was found to be the best fluorine donor, giving a 10% higher enantiomeric excess than Selectfluor or *N*-fluoropyridinium triflate in dichloromethane. The solvent was found to have a major influence on the enantioselectivity, with diethyl ether and toluene giving higher enantiomeric excesses. The metal ion was also found to be crucial for the success of the reaction, with Cu(II) and Zn(II) having the properties necessary for the *in situ* generation of the enolate and good stereoselectivity in combination with the chiral ligands. The catalyst loading could be reduced to 0.1 mol % without significantly decreasing the catalytic activity or the enantioselectivity. A selection of additives were screened in order to improve the enantioselectivity; when one equivalent of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) was added a dramatic improvement in the enantioselectivity was observed. The HFIP promotes the release of the fluorinated product from the catalyst, therefore assisting the catalyst turnover. Under the optimised reaction conditions (NFSI, 1 mol % Cu(OTf)<sub>2</sub>/(*R*)-Ph-bis(oxazoline), 20 °C, HFIP (1 eq.), diethyl ether) the enantioselective fluorination was carried out on a range of cyclic  $\beta$ -ketoesters (35-85% ee) and acyclic  $\beta$ -ketoesters (43-52% ee), all in excellent yields. The best result is shown in Scheme 1.25.



Scheme 1.25

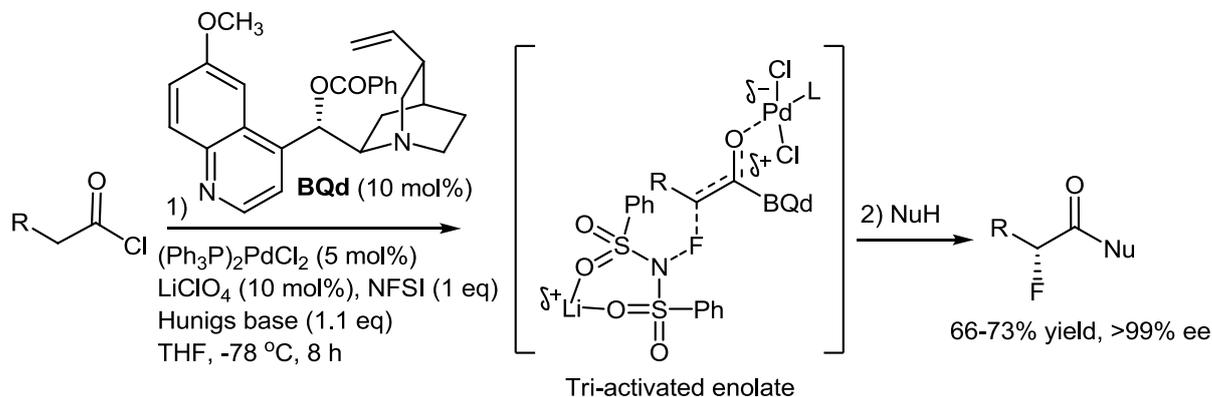
Lectka<sup>36</sup> significantly improved the modest yields achieved in the enantioselective  $\alpha$ -fluorination of acid chlorides catalysed by benzoylquinidine (BQd) alone by adding either *trans*-(Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub> or (1,3-dppp)-NiCl<sub>2</sub> as a co-catalyst, with no loss of enantioselectivity. In initial substrate screening, the products from the  $\alpha$ -fluorination of a range of aromatic acid chlorides were quenched with methanol to form  $\alpha$ -fluorinated methyl esters in 60-91% yield with 98->99% enantiomeric excess (Scheme 1.26). It was subsequently discovered that by varying the quench conditions, a variety of chiral  $\alpha$ -fluorinated carboxylic acid derivatives could be produced; esters, carboxylic acids, amides and thioesters were readily accessible. The reactions were low yielding when aliphatic substrates were used.



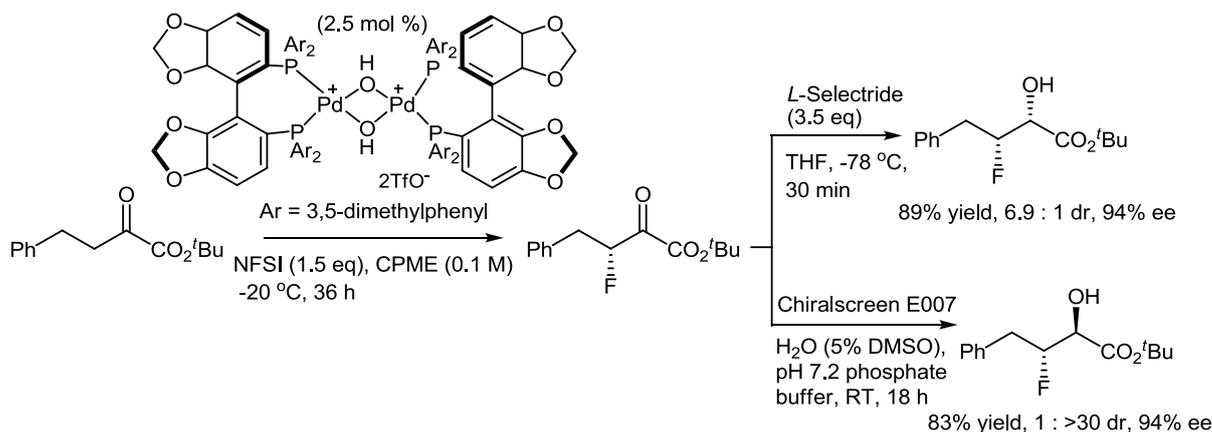
Scheme 1.26

Lectka<sup>37</sup> further improved the yield and scope of these reactions by using three catalysts cooperatively; a chiral nucleophile (BQd, 10 mol%), a transition metal catalyst (*trans*-(Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub>, 5 mol%), and an alkali metal Lewis acid (LiClO<sub>4</sub>, 10 mol%). The second Lewis acid specifically coordinates to the NFSI, increasing its electrophilicity.

The *trifunctional* catalytic system (Scheme 1.27) allowed access to a range of aliphatic carboxylic acid derivatives in 66-73% yield and >99% enantiomeric excess.



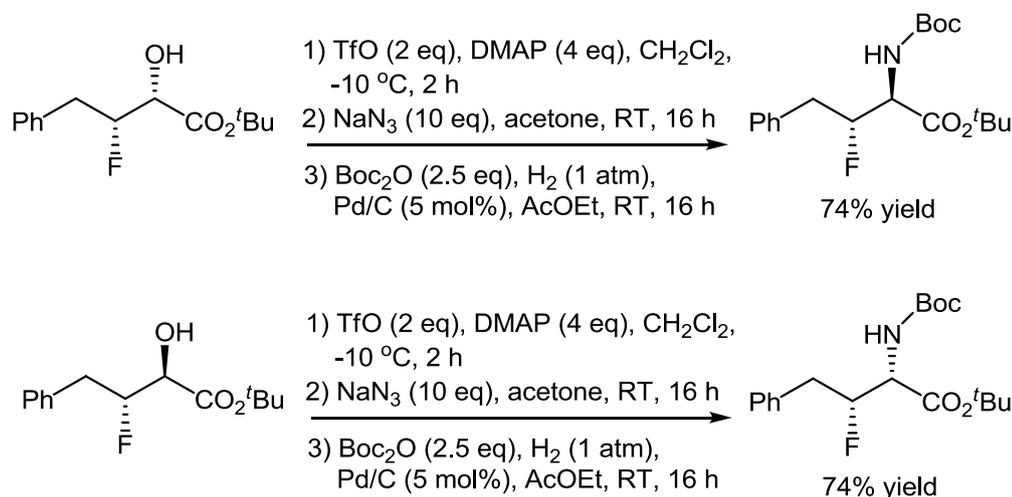
Scheme 1.27



Scheme 1.28

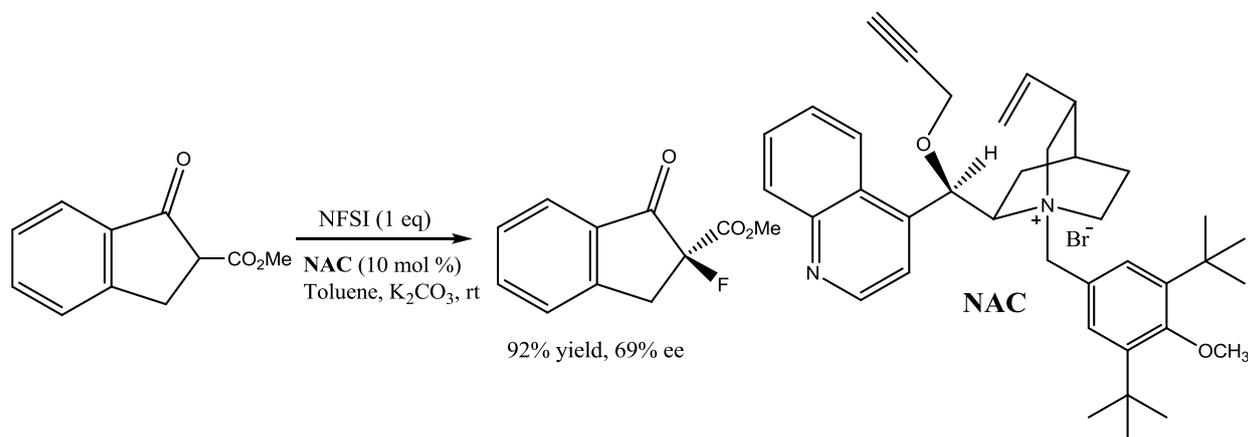
It was generally believed that an asymmetric route to medicinally important monofluorinated  $\beta$ -fluoro- $\alpha$ -hydroxy and  $\beta$ -fluoro- $\alpha$ -amino acid derivatives would not be possible due to facile enolisation leading to loss of optical purity. When Sodeoka<sup>38</sup> used Pd- $\mu$ -hydroxo complexes to catalyse the enantioselective monofluorination of  $\alpha$ -keto esters, the fluorinated  $\alpha$ -keto ester product (isolated in 79% yield with an excellent 94% enantiomeric excess, improved to >99% by recrystallisation) was stable under the reaction conditions, and racemisation was minimal. No undesired difluorinated product was observed. The  $\alpha$ -keto ester product was converted into both possible diastereoisomers of chiral  $\beta$ -fluoro- $\alpha$ -hydroxy ester by reduction with either *L*-Selectride (*syn* selective) or DAICEL ChiralScreen E007 (*anti* selective) with excellent diastereoselectivity and without any loss of enantioselectivity (Scheme 1.28). The chiral

$\beta$ -fluoro- $\alpha$ -hydroxy esters could also be converted into their corresponding  $\beta$ -fluoro- $\alpha$ -amino esters in three steps; conversion to the triflate, followed by nucleophilic substitution with sodium azide, and palladium catalysed reduction with *in situ* Boc protection; without any need for intermediate purification (Scheme 1.29).



Scheme 1.29

### 1.2.3 Organocatalysed enantioselective electrophilic fluorination

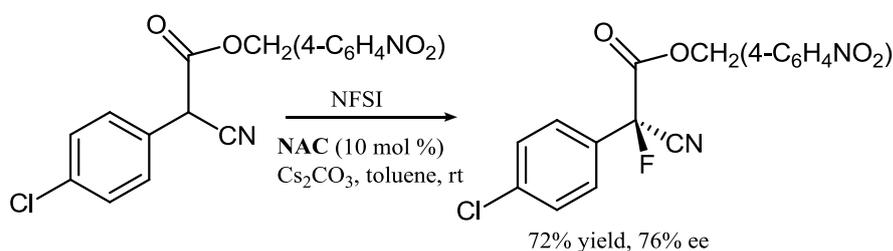


Scheme 1.30

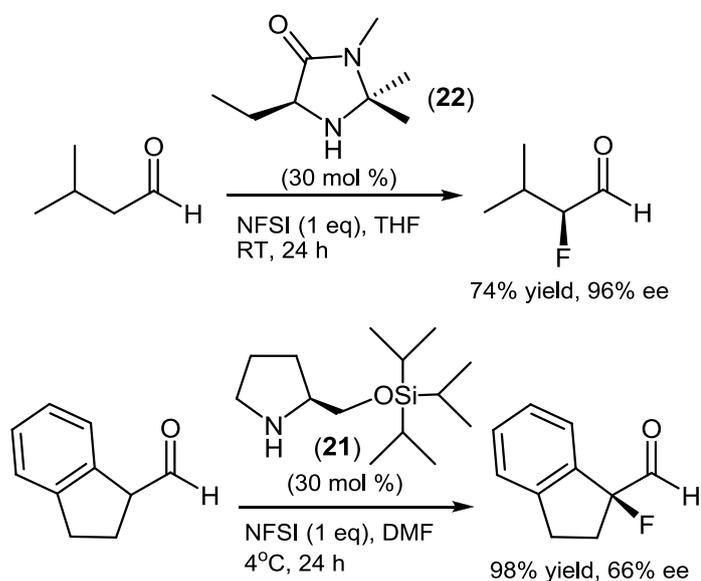
Kim<sup>39</sup> used a quaternary ammonium salt derived from cinchonine as a phase transfer catalyst for the catalytic enantioselective electrophilic fluorination of  $\beta$ -ketoesters. Using NFSI as the fluorine source in the presence of 10 mol % catalyst and potassium carbonate in toluene, the fluorination proceeded at room temperature to give the corresponding  $\alpha$ -fluorinated compounds in good yields and good enantioselectivities

under phase transfer conditions. The best result obtained was a 69% ee with a 92% yield (Scheme 1.30).

Further work by Kim<sup>40</sup> led to the development of a catalytic enantioselective fluorination of  $\alpha$ -cyano acetates using *Cinchona* alkaloid derived quaternary ammonium salts. The best results were achieved using the *para*-nitro benzyl esters of the substrates, with up to 76% enantiomeric excesses (Scheme 1.31). Caesium carbonate was also found to be a more effective base than potassium carbonate which was used in the previous study.



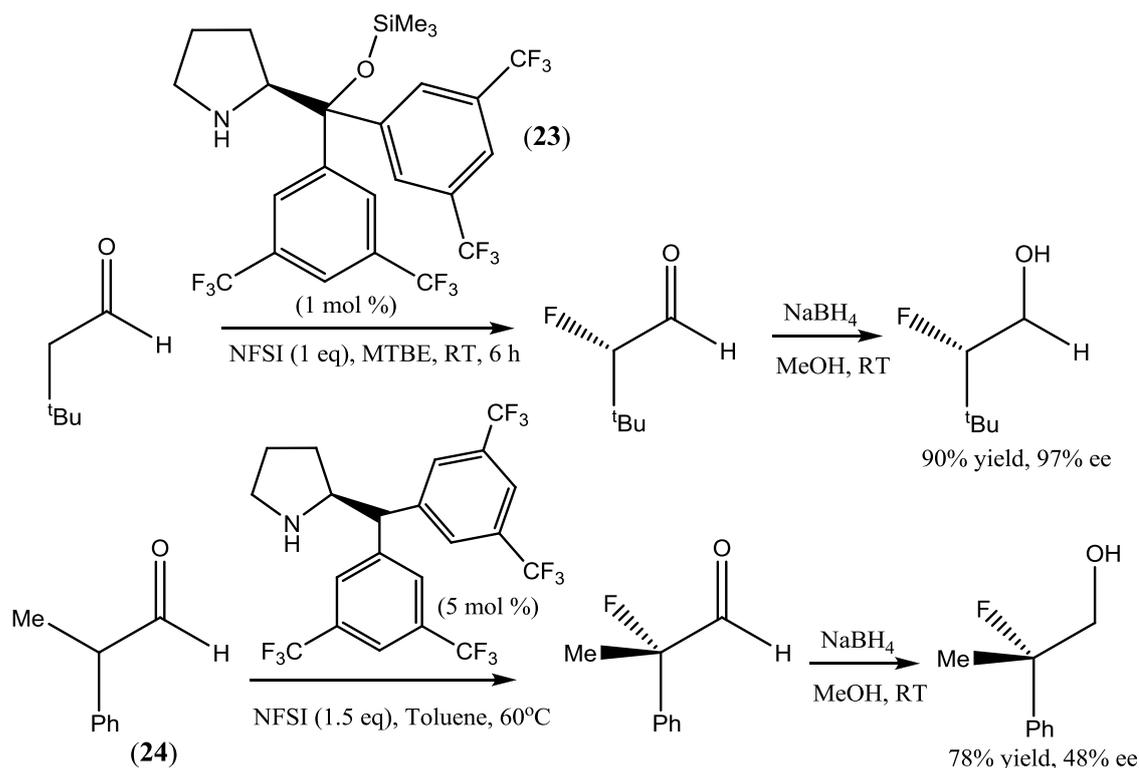
**Scheme 1.31**



**Scheme 1.32**

The enantioselective organocatalytic  $\alpha$ -fluorination of aldehydes was reported by three groups concurrently. Barbas<sup>41</sup> initially used the model substrate 2-phenylpropionaldehyde with L-proline as the catalyst to screen various fluorinating reagents and solvents, finding that NFSI was the only fluorinating reagent to give any enantioselectivity in a reasonable time period, and that THF afforded both the best

selectivity and the highest yield. In order to optimise the fluorination reaction with branched aldehydes, 2-phenylpropionaldehyde was then used in a catalyst screen with NFSI as the fluorinating reagent and THF as the solvent. The best enantioselectivity was obtained using the silylated L-prolinol derivative (*S*)-2-((triisopropylsilyloxy)methyl)pyrrolidine (**21**) (90% yield, 44% ee). Decanal was then chosen as the substrate for the optimisation of the organocatalytic asymmetric fluorination of straight chain aldehydes. It was found that DMF was the only solvent to inhibit the formation of  $\alpha,\alpha$ -difluoro products. The highest enantiomeric excesses were obtained using imidazolidinone based catalysts, the best of which was (*S*)-5-ethyl-2,2,3-trimethylimidazolidin-4-one (**22**) (30% yield, 88% ee). A series of aldehydes were then subjected to the optimised conditions; linear aldehydes were fluorinated in good to excellent yields (40-97%) and excellent enantioselectivities (86-96% ee), and the methodology was extended to branched aldehydes with excellent yields (92-98%) but only moderate enantioselectivities (up to 66% ee) (Scheme 1.32).

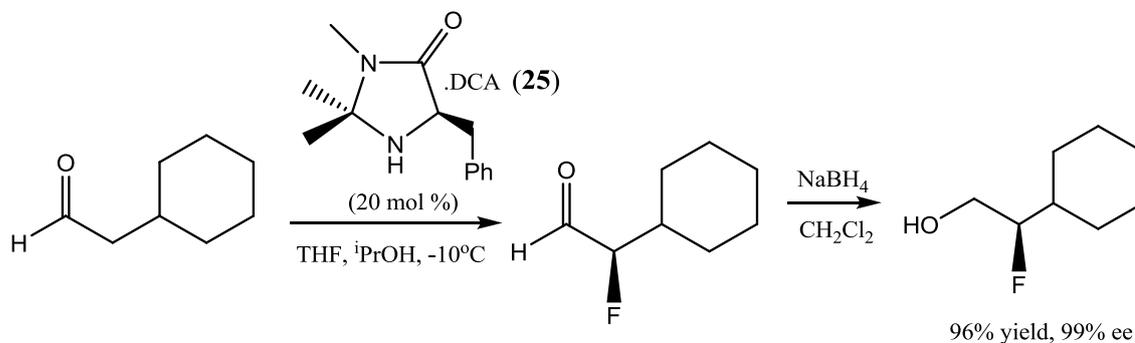


Scheme 1.33

Jørgensen<sup>42</sup> required only 1 mol % of the proline derived catalyst (*S*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)(trimethylsilyloxy)methyl)pyrrolidine (**23**) to fluorinate a range of straight chain aldehydes with high yields (55-95%) and excellent

enantioselectivities (91-97% ee). The  $\alpha$ -fluorinated aldehydes were reduced directly to the more stable  $\alpha$ -fluorinated alcohols, as  $\alpha$ -fluorinated aldehydes readily decompose on silica gel. The methodology was also extended to branched aldehydes. As the aldehydes themselves were more sterically encumbered, a less sterically demanding catalyst was required, and higher temperatures were necessary to maintain the reaction rate. A moderate enantiomeric excess of 48% ee was achieved in the  $\alpha$ -fluorination of 2-phenylpropanal (**24**) (Scheme 1.33).

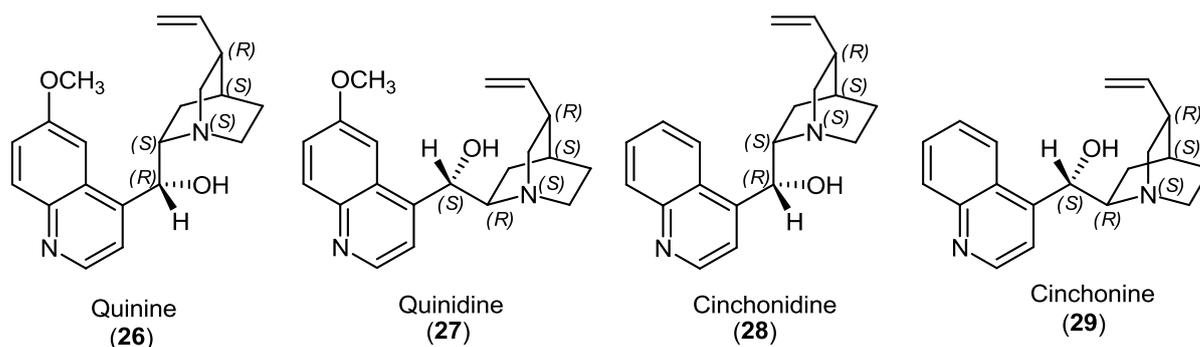
MacMillan<sup>43</sup> also used NFSI as the fluorine source, with 20 mol % (*R*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one (**25**) catalyst in THF/*i*PrOH at -10°C, to allow the  $\alpha$ -fluorination of a range of aldehydes (Scheme 1.34). A wide variety of functional groups on the aldehyde substrate were tolerated, including alkenes, esters, amines and carbamates, while maintaining high yield and enantioselectivity (77-85% yield, 91-99% ee). Increased steric demand of the substrate could also be tolerated without loss of enantioselectivity, even with benzyl (71% yield, 96% ee) and adamantyl (82% yield, 98% ee) groups. Catalyst loadings as low as 2.5 mol% could be used without a decrease in enantiomeric excess (79% yield, 99% ee for the  $\alpha$ -fluorination of 2-cyclohexylacetaldehyde).



Scheme 1.34

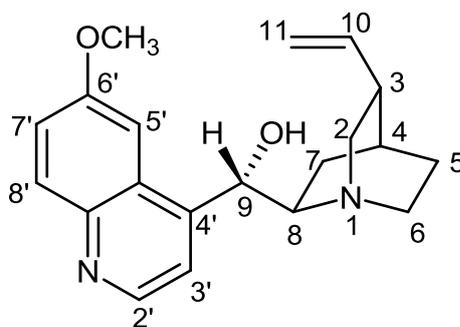
### 1.3 Cinchona alkaloids

Of the approximately forty alkaloids that can be isolated from the bark of the cinchona tree, the four major components are the diastereoisomeric pairs quinine (**26**) and quinidine (**27**), and cinchonidine (**28**) and cinchonine (**29**) (Figure 1.3), which account for over 50% of the alkaloid content.<sup>44</sup> The commonly used atom numbering system for *Cinchona* alkaloids is shown in Figure 1.4.



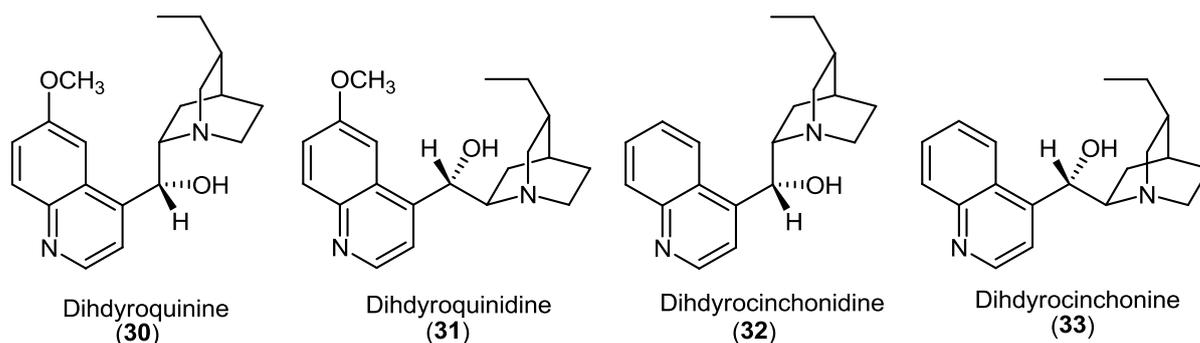
**Figure 1.3:** The four major *Cinchona* alkaloids

The configurations of the chiral centres around the quinuclidine ring remain constant in all four alkaloids, N1-*S*, 3-*R*, and 4-*S*. Quinine and quinidine differ in the configurations at C8 and C9; quinine has a 8*S*,9*R* configuration and quinidine has a 8*R*,9*S* configuration. The opposite configuration at these two stereocentres, with identical configurations at N1, C3 and C4, is the reason these diastereoisomers are described as *pseudo*-enantiomers. If the vinyl group was removed and replaced with a hydrogen atom, the chirality at N1, C3 and C4 would be erased and the two resulting compounds would be enantiomers. Cinchonidine and cinchonine share the structure and absolute configurations of quinine and quinidine respectively, although they lack the methoxy group at the C6' position of the quinoline ring.



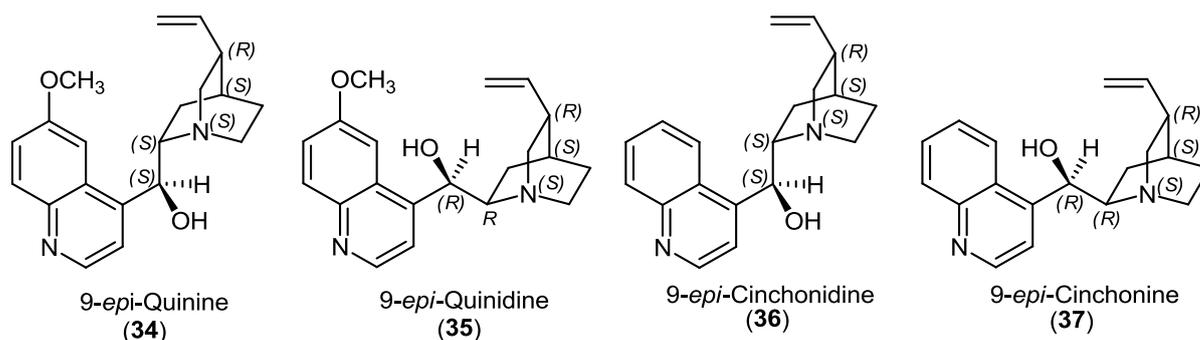
**Figure 1.4:** The atom numbering system used for *Cinchona* alkaloids

The 10,11-dihydro analogues of these four compounds, dihydroquinine (**30**), dihydroquinidine (**31**), dihydrocinchonidine (**32**) and dihydrocinchonine (**33**) (Figure 1.5), in which the vinyl group is replaced with an ethyl group, are also a large component of the alkaloids isolated from the bark.



**Figure 1.5:** The 10,11-dihydro-*Cinchona* alkaloids

The minor *epi-Cinchona* alkaloids (Figure 1.6), have the opposite configuration at C9 compared to their parent alkaloid. Thus, 9-*epi*-quinine (34) and 9-*epi*-cinchonidine (36) have 8*S*,9*S* configurations, and 9-*epi*-quinidine (35) and 9-*epi*-cinchonine (37) have 8*R*,9*R* configurations.

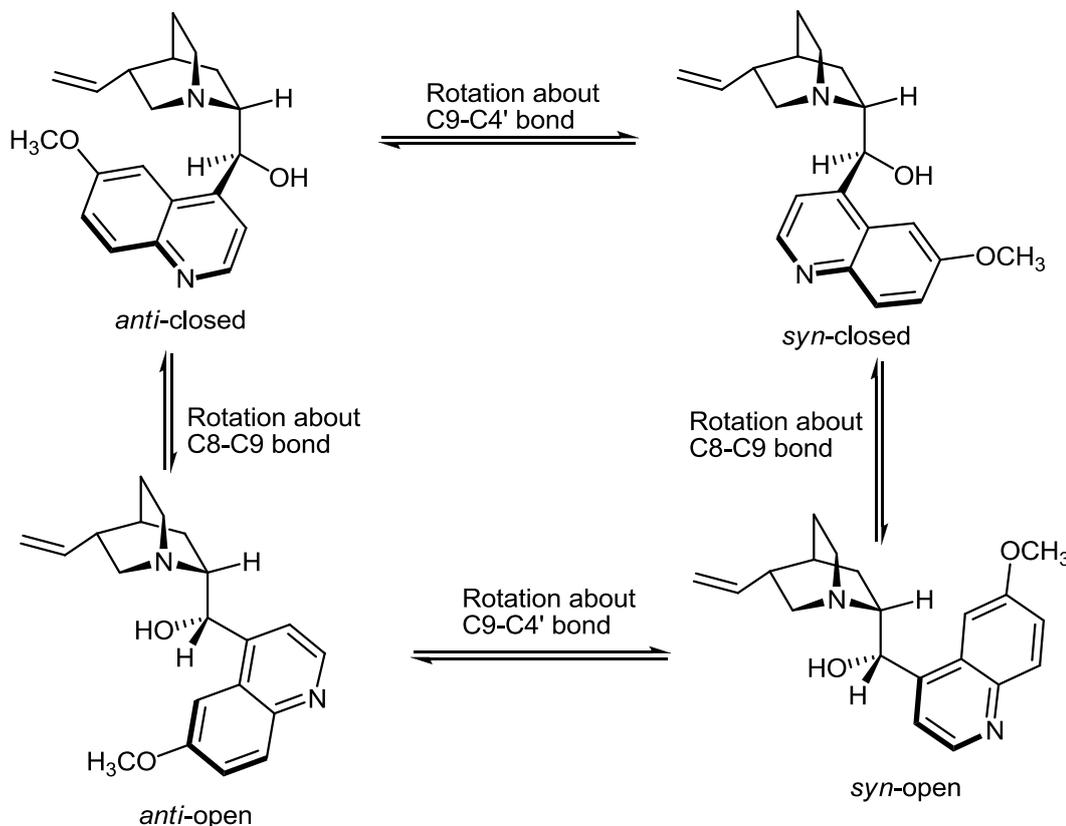


**Figure 1.6:** The 9-*epi*-*Cinchona* alkaloids

The commercially available, reasonably priced, *pseudo*-enantiomeric pairs behave as enantiomers in synthesis. The unique, densely functionalised structures contain five chiral centres and a diverse set of chemical subunits: a quinoline ring; a secondary alcohol; a terminal alkene; and a sterically hindered tertiary amine. *Cinchona* alkaloids are also very stable when exposed to air, light and/or moisture.

The most important degrees of freedom responsible for the conformational properties of *Cinchona* alkaloids are rotations about the C9-C8 bond, and rotations about the C9-C4' bond, leading to four main stable conformations which are shown, using quinidine as an example, in Figure 1.7. In closed conformers the quinoline ring sits in front of the quinuclidine nitrogen (N1), and H8 and H9 are in an almost *anti* orientation, whereas in open conformers there is reduced steric hindrance in front of

N1, and H8 and H9 are *gauche*. The *syn*- or *anti*- nomenclature relates to the C3'-C4'-C9-C8 torsion angle.<sup>45</sup>



**Figure 1.7:** The stable conformations of Cinchona alkaloids

### 1.3.1 Cinchona alkaloids in enantioselective reactions

Due to the ease of access to both diastereoisomers at a reasonable price, their stability, and the variety of possible functionalisations of the chemical groups present in the structures, *Cinchona* alkaloids are popular for use as chiral reagents and chiral auxiliaries. They are also considered privileged catalysts, due to their applications in a wide range of reactions. Some examples of the applications of *Cinchona* alkaloids in asymmetric processes are described below.

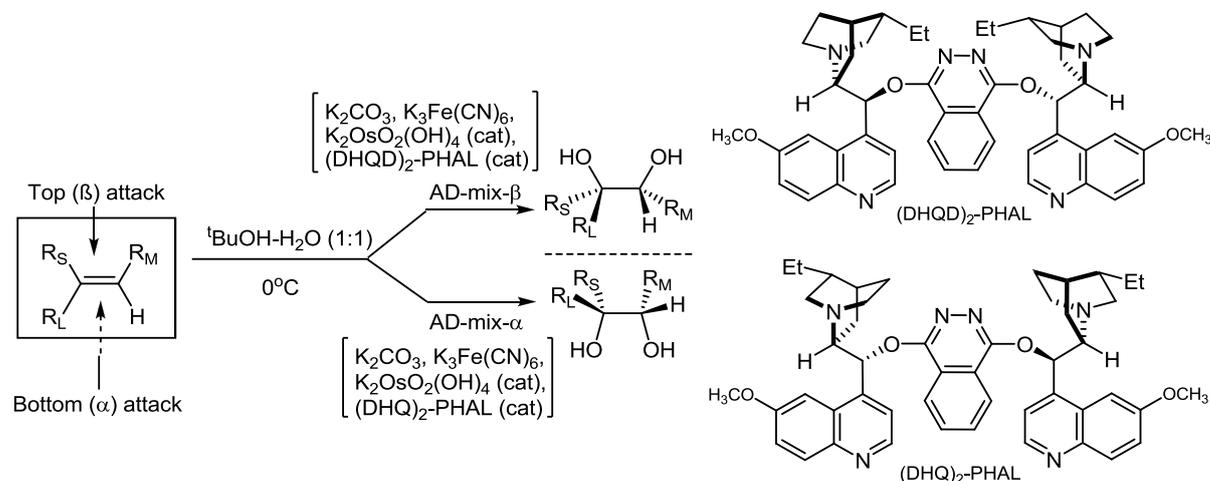
#### 1.3.1.1 Cinchona alkaloids in the Sharpless asymmetric dihydroxylation

One of the best known examples of the use of quinine and quinidine in asymmetric reactions is in the Sharpless asymmetric dihydroxylation, in which alkenes are converted into *syn*-diols through a reaction with osmium tetroxide, in the presence of a chiral ligand based on either quinine or quinidine. This application makes use of what Sharpless, in his 2001 Nobel lecture, described as “the perfect balance *Cinchona*

alkaloids achieve in ligating ability, binding well enough to accelerate the key step, but weakly enough to slip off allowing the hydrolysis and re-oxidation steps of the catalytic cycle to proceed.”

Ligands for asymmetric dihydroxylation were improved in effectiveness and scope by substitution of the OH group at C9. Initially, ester groups such as acetate were used, but these were superseded by aryl ether derivatives, ultimately resulting in the 9<sup>2</sup>-phenanthryl ether substituted dihydroquinidine and dihydroquinine monomer ligands, which gave enantiomeric excesses in the range 74-99% across all alkene substitution patterns.<sup>46</sup> Further improvements resulted from the development of dimeric ligands with a phthalazine core,<sup>47</sup> which gave excellent enantiomeric excesses (84 - >99.5%), and remain the best general ligands for asymmetric dihydroxylation.

The reaction is now so well established that AD-mix- $\alpha$  (containing potassium carbonate, potassium ferricyanide, potassium osmate dehydrate, and the quinine based dimeric chiral ligand (DHQ)<sub>2</sub>PHAL) and AD-mix- $\beta$  (containing potassium carbonate, potassium ferricyanide, potassium osmate dehydrate, and the quinidine based dimeric chiral ligand (DHQD)<sub>2</sub>PHAL) can be purchased and used to generate the desired single enantiomer of product (Figure 1.8).

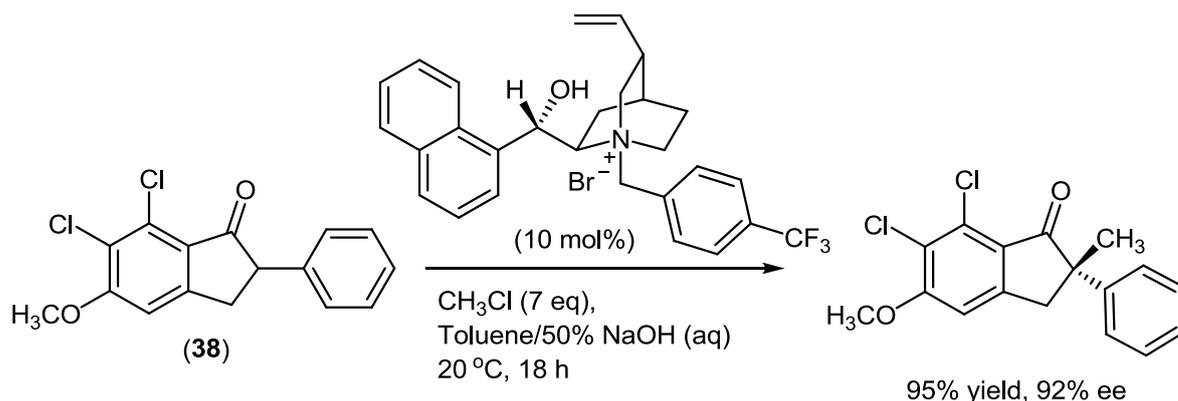


**Figure 1.8:** The Sharpless asymmetric dihydroxylation of alkenes

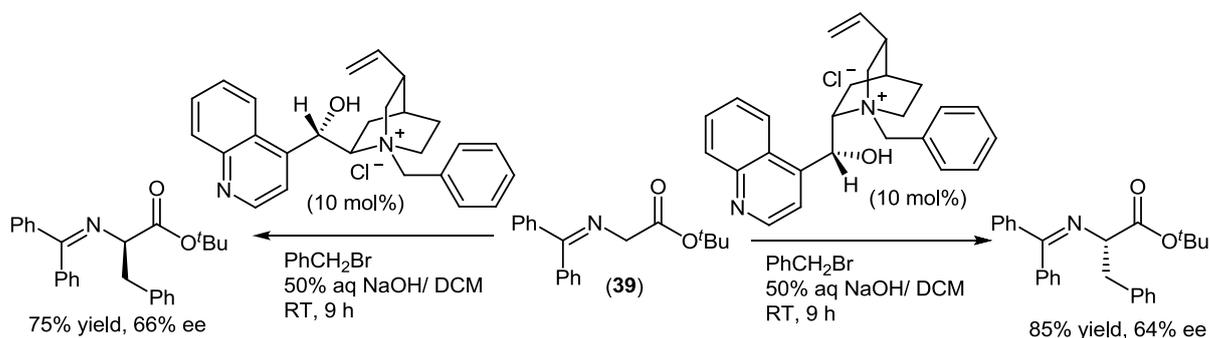
### 1.3.1.2 *Cinchona* alkaloids in asymmetric phase transfer catalysis

Alkylation of the quinuclidine nitrogen provided a series of quaternary ammonium salts that could be efficiently applied to chiral phase transfer catalysis, an area which has been described as mild, inexpensive and environmentally friendly.

In the phase transfer catalysis process an anion of the nucleophile is generated at the interface of the organic and inorganic phases by deprotonation with an alkali metal base such as sodium or potassium hydroxide. This nucleophile anion forms a chiral ionic complex with the quaternary ammonium cation, which reacts with the electrophile (which can only approach from the least sterically hindered face) to generate the chiral reaction product, allowing the quaternary ammonium salt to return to the interface for catalyst recycling.

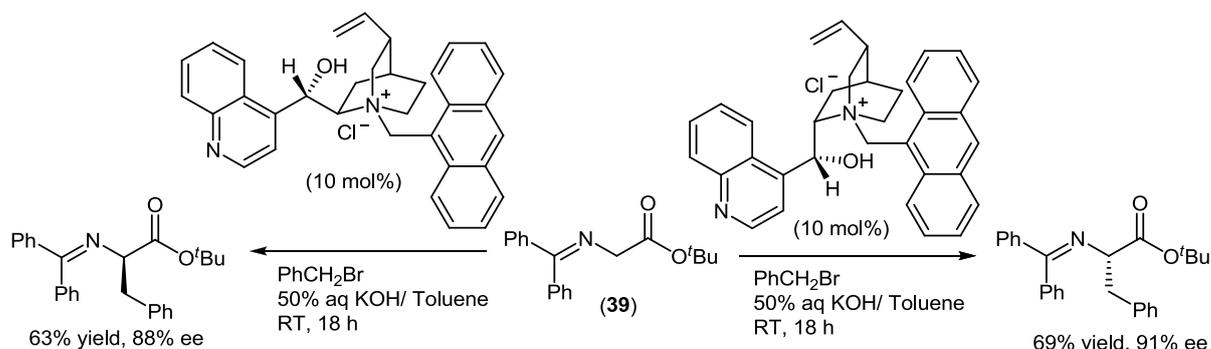


The first example of a *Cinchona* derived phase transfer catalyst was reported by Dolling.<sup>48</sup> As an initial stage in the synthesis of (+)-indacrinone, 6,7-dichloro-5-methoxy-2-phenyl-1-indanone (**38**) was methylated with  $\text{CH}_3\text{Cl}$  in toluene/50% NaOH using *N*-(*p*-trifluoromethylbenzyl)cinchonium bromide as the phase transfer catalyst, generating the desired product (*S*)-(+)-6,7-dichloro-5-methoxy-2-methyl-2-phenyl-1-indanone in 95% yield and 92% enantiomeric excess (Scheme 1.35).



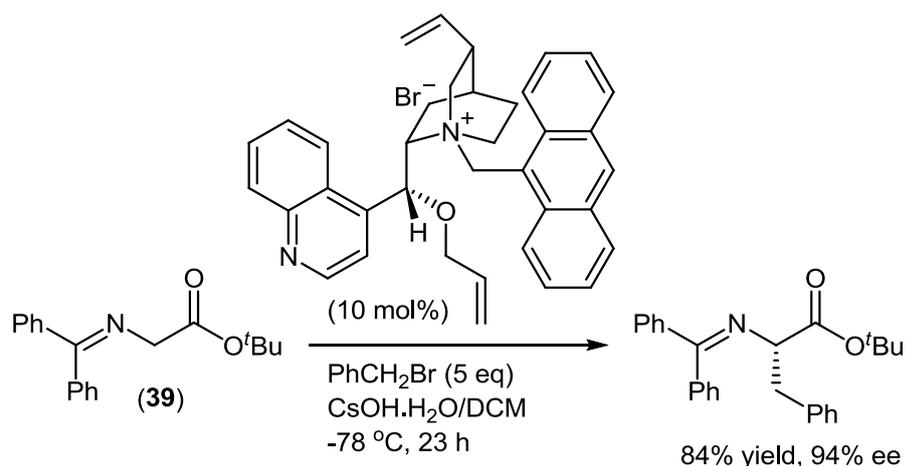
O'Donnell<sup>49</sup> also used first generation *N*-benzyl substituted *Cinchona* derivatives in the stereoselective synthesis of amino acids by phase transfer catalysis. The use of either *N*-benzylcinchonium or *N*-benzylcinchonidium chloride allowed the preparation

of both enantiomers of alkylated *N*-(diphenylmethylene)glycine *tert*-butyl ester in 64-66% enantiomeric excess (Scheme 1.36), which could then be hydrolysed to give the desired enantiomer of the  $\alpha$ -amino acid phenylalanine in high yield and good enantiomeric excess.



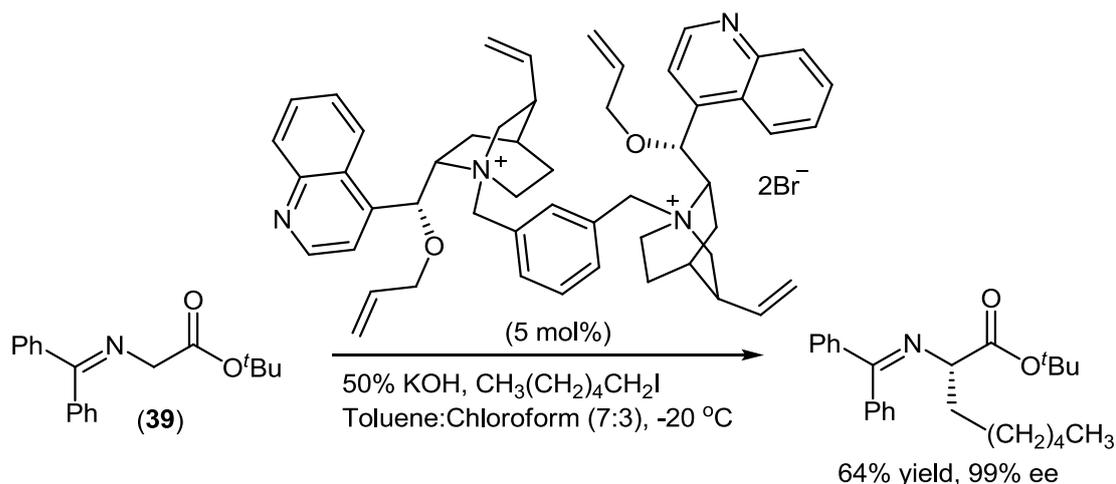
Scheme 1.37

The second generation of *Cinchona* derived phase transfer catalysts increased the steric bulk of the substituent on the quinuclidine nitrogen from a benzyl group to an anthracenylmethyl group, developed simultaneously but independently by the groups of Lygo and Corey, who also applied them to the asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**39**) in order to ultimately synthesise phenylalanine. Lygo<sup>50</sup> achieved enantiomeric excesses of 88-91% when *N*-9-anthracenylmethylcinchonidinium and *N*-9-anthracenylmethylcinchoninium chloride were used as the phase transfer catalysts (Scheme 1.37), a considerable improvement on those achieved by O'Donnell with the *N*-benzyl derivatives. Corey<sup>51</sup> used *O*-allyl-*N*-9-anthracenylmethylcinchonidinium bromide as the phase transfer catalyst for the same reaction, although at low temperature and using a different base, and achieved a slightly higher enantiomeric excess (94%, Scheme 1.38). In both cases the improvement in enantioselectivity was due to the increased steric hindrance caused by the anthracenyl compared with a benzyl group, forcing the electrophile to attack more specifically from one face.



Scheme 1.38

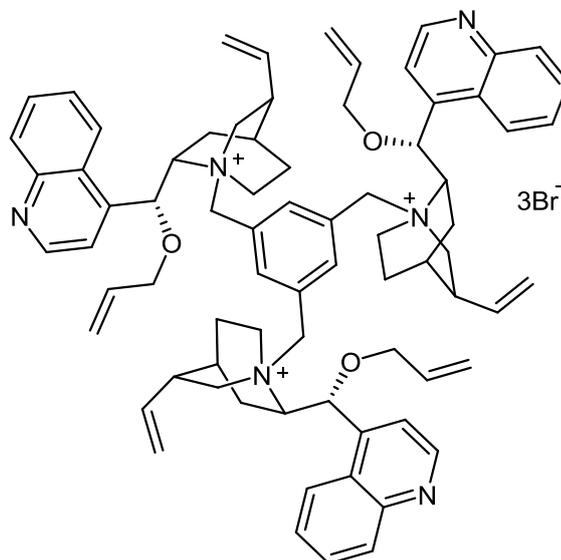
Park and Jew applied *O*-allyl-*N*-9-anthracenylmethyldihydrocinchonidinium bromide as the phase transfer catalyst for the alkylation of oxazoline<sup>52</sup> and thiazoline<sup>53</sup> substrates in order to ultimately produce enantioenriched  $\alpha$ -alkylserines (90-96% ee) and  $\alpha$ -alkylcysteines (75-88% ee) in very good yield (82-92%).



Scheme 1.39

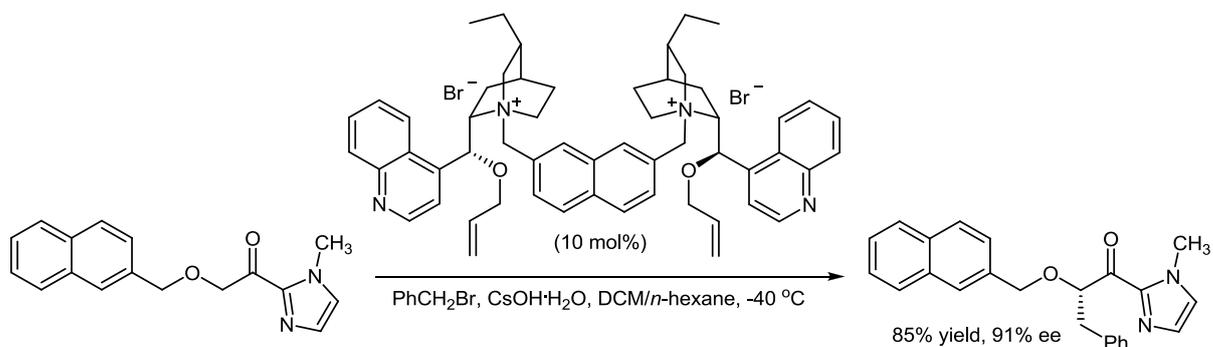
The third generation of *Cinchona* derived phase transfer catalysts were similar to the optimised dimers used in the Sharpless asymmetric dihydroxylation of alkenes. Jew and Park's investigation into the use of  $\alpha,\alpha'$ -bis[*O*(9)-allylcinchonidinium]-*o*-, *m*-, or *p*-xylene dibromide<sup>54</sup> dimeric phase transfer catalysts for the enantioselective benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**39**) yielded the following order of enantioselectivity: *meta*-dimer > *para*-dimer  $\approx$  monomer (*O*-allyl-*N*-benzylcinchonidinium bromide)  $\gg$  *ortho*-dimer. The *meta*-dimer was then used to catalyse the addition of various alkyl halides (Scheme 1.39) with excellent enantioselectivities (90-99% ee).

These catalysts were extended to include a *meta*-trimer (Figure 1.9) based on cinchonidinium bromide,<sup>55</sup> which also showed excellent enantioselectivity in the selective alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**39**) (90-97% enantiomeric excess).

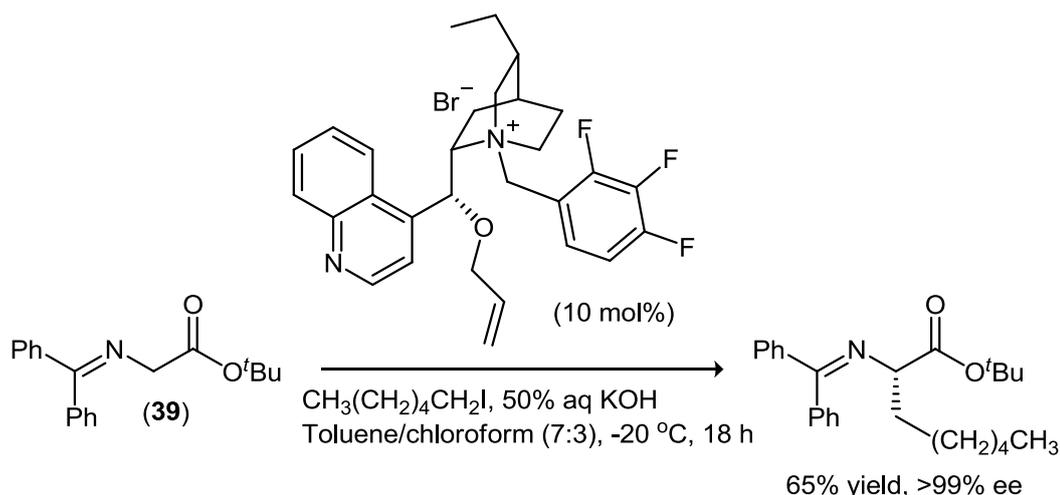


**Figure 1.9:** Jew and Parks *meta*-trimer phase transfer catalyst based on cinchonidinium bromide

Increasing the size of the spacer group between the *Cinchona* units of the dimer from a phenyl to a 2,7-naphthyl group further improved the scope of the catalysts and the enantioselectivity obtained in phase transfer catalysed alkylation reactions. Andrus<sup>56</sup> alkylated 2-acylimidazoles using a dihydrocinchonidinium dimer with a 2,7-naphthyl spacer as the phase transfer catalyst (Scheme 1.40), achieving excellent enantiomeric excesses (88- >99%), as part of a new synthesis of chiral  $\alpha$ -hydroxy carbonyl compounds. This new synthesis of chiral  $\alpha$ -hydroxy carbonyl compounds was later applied to the total synthesis of the hydroxy ketone natural product Kurasoin B.<sup>57</sup>



**Scheme 1.40**

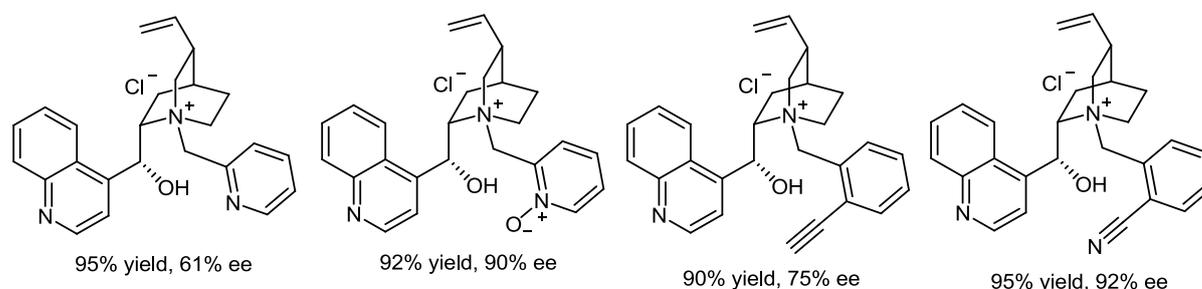


Scheme 1.41

The fourth generation of *Cinchona* derived phase transfer catalysts take into account electronic effects, which influence the chiral complex formed between the quinuclidine quaternary ammonium cation and the nucleophile anion. Jew and Park<sup>58</sup> prepared a series of *N*-benzylcinchonidinium salts with *ortho*-, *meta*- and *para*-substituents on the benzyl group with various functional groups (e.g. alkyl, methoxy, nitro, halides), and examined their catalytic efficiency in the standard asymmetric phase transfer benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester. It was expected that electron withdrawing substituents would lead to better enantioselectivity due to tighter binding between the ammonium cation and the nucleophile anion. Curiously, *meta*- and *para*-substituted derivatives, regardless of their electronic properties, did not produce any difference in the enantioselectivity. The strong improvement in enantioselectivity shown by *ortho*-fluorine substitution (89% ee, compared with 74% ee for unsubstituted benzyl), led to the development of a series of fluoro-substituted derivatives. An *ortho*-fluorine was required for improved enantioselectivity, and although the best performing catalysts were those with additional fluorine substituents at the *meta*- and/or *para*- positions, the number of fluoro groups on the ring was not directly linked to enantioselectivity. The role of the 2'-F in the enantioselectivity enhancement was speculated to be related to internal hydrogen bonding between the fluorine and the C9-O via a water molecule between the two, holding the molecule in a more rigid conformation. The best performing fluorinated catalyst, *O*-allyl-*N*-2',3',4'-F<sub>3</sub>-benzylidihydrocinchonidinium bromide gave an enantiomeric excess of 96% at 0 °C, which was improved to 98% at -20 °C. This catalyst was then further investigated using various alkyl halides for the alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester

(**39**), achieving excellent enantiomeric excesses in the range of 94- >99% (Scheme 1.41).

Other substituents capable of fixing a stable conformation via internal hydrogen bonding, such as *N*-oxypyridine and cyanobenzene groups, were also examined as catalysts for the phase transfer catalysed benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester.<sup>59</sup> *N*-1-oxopyridin-2-ylmethyl-cinchonidinium chloride (90% ee) and *N*-cyanobenzyl-cinchonidinium chloride (92% ee) led to much improved enantioselectivity compared with the standard catalysts containing a pyridyl group (61% ee) and an ethynyl benzene substituent (75% ee) (Figure 1.10), comparing favourably with the 2'-fluoro-substituted *Cinchona* derived phase transfer catalysts previously studied.

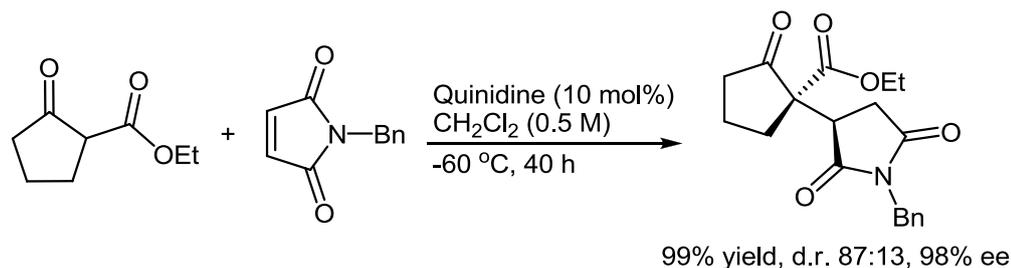


**Figure 1.10:** Comparison of *N*-oxypyridine and *N*-cyanobenzene substituents with *N*-pyridyl and *N*-ethynyl benzene substituents in the phase transfer catalysed benzylation of **39**

### 1.3.1.3 *Cinchona* alkaloids in enantioselective Michael additions

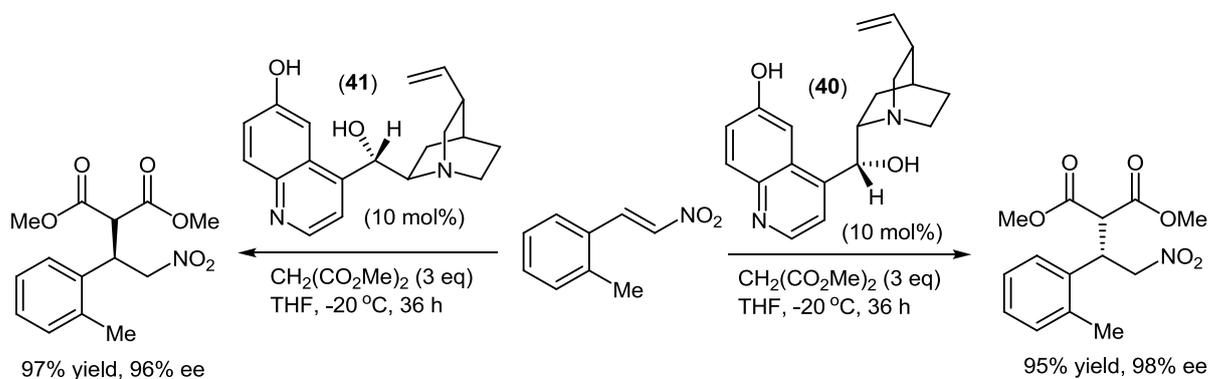
Michael addition reactions are among the most ubiquitous and most exploited for the formation of C-C bonds.<sup>60</sup> The wide variety of possible Michael donors and acceptors generates a need for different types of catalysts, and many different classes of functionalised *Cinchona* alkaloids have been developed and applied to these reactions.

Bartoli and Melchiorre<sup>61</sup> used the natural *Cinchona* alkaloids, quinine (**26**) and quinidine (**27**), as catalysts to promote the conjugate addition of 1,3-dicarbonyl compounds to maleimides, to form highly functionalised products containing two stereogenic centres (Scheme 1.42). The products were formed in excellent yield (80-99%), excellent diastereoselectivity (with a diastereoisomeric ratio up to >98:2), and excellent enantioselectivity (82-98% ee).



Scheme 1.42

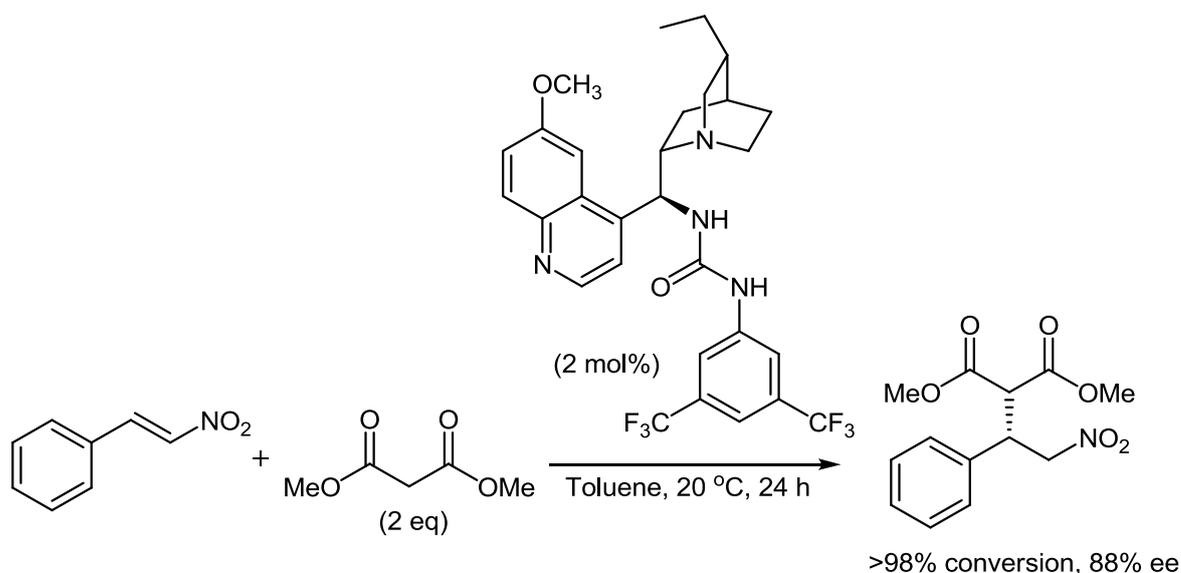
Replacement of the C6' methoxy group of quinine (**26**) and quinidine (**27**) with a hydroxyl group gives cupreine (**40**) and cupreidine (**41**) respectively, in which the C6' hydroxyl can be used for electrophilic activation, allowing additional functionalisation of the C9-OH to enhance the enantioselectivity of the reactions by tuning various properties such as molecular conformation or basicity. Deng<sup>62</sup> found that cupreine (**40**) was the most effective *Cinchona* derived catalyst for the addition of malonates to nitroalkenes, a substrate which had been challenging in previous studies. As higher conversions and enantioselectivities were achieved in initial catalyst screenings using dimethyl malonate than with diethyl malonate, dimethyl malonate was then employed in the nucleophilic addition to a wide range of nitroalkenes. Very high yields and enantioselectivities were achieved for heteroaryl and aryl nitroalkenes (88-99% yield, 92-98% ee), and although the yields were slightly lower for alkyl nitroalkenes the enantioselectivities achieved were still very high (80-86% yield, 91-94% ee). Cupreine (**40**) and cupreidine (**41**) gave similar yields and enantioselectivities, but opposite enantiomers (Scheme 1.43).



Scheme 1.43

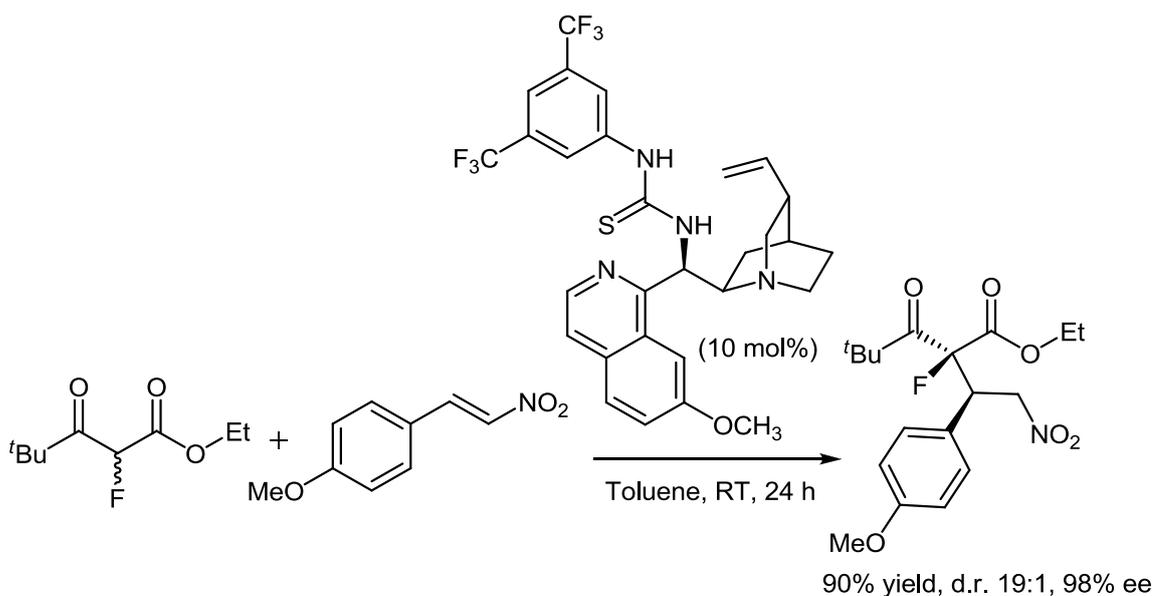
Substitution of the C9-OH with a thiourea or urea combines the catalytic and hydrogen bond donating abilities of these groups with the advantages of the *Cinchona* skeleton. The choice of thiourea or urea (S or O) allows tuneable Lewis acidity for activation of the electrophile, whilst their steric bulk and rigid structure further direct the conformation of transition states, leading to improved enantioselectivity.

Connon<sup>63</sup> applied both urea and thiourea *Cinchona* derivatives with both “natural” and *epi* configurations at C9 to the catalysis of the addition of dimethyl malonate to nitroalkenes. The catalysts with C9-*epi* configurations were found to be more efficient than those with the same C9 configurations as natural quinine and quinidine. Although the best performing catalyst was 9-*epi*-dihydroquinine thiourea, generating enantiomeric excesses of 86-99% in additions of dimethyl malonate to aryl and alkyl nitroalkenes, Scheme 1.44 demonstrates that urea derivatives were also effective.



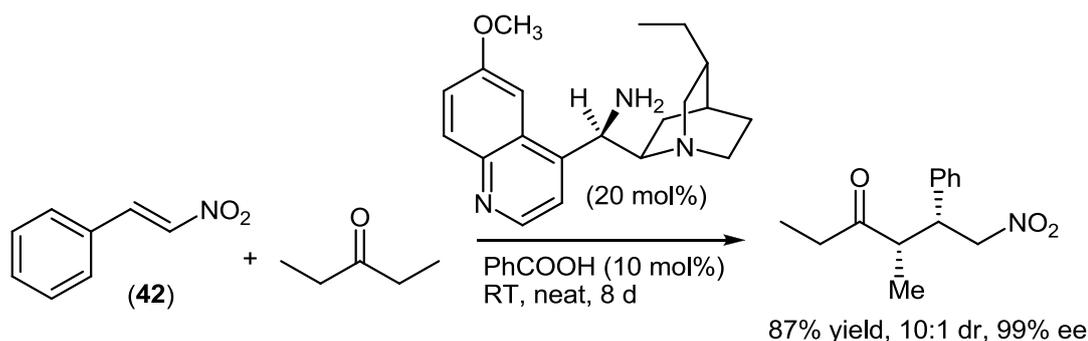
**Scheme 1.44**

Lu<sup>64</sup> screened various *Cinchona* thiourea derivatives before choosing the 9-*epi*-quinidine thiourea derivative with two trifluoromethyl substituents as the best catalyst for the addition of  $\alpha$ -fluorinated  $\beta$ -ketoester nucleophiles to aryl and alkyl nitroalkenes to form fluorinated quaternary stereocentres adjacent to tertiary stereocentres (Scheme 1.45), in an alternative to asymmetric fluorination. The products were formed in high to excellent yields (65-98%) with excellent diastereoselectivities (90% de) and enantioselectivities (95-98% ee).

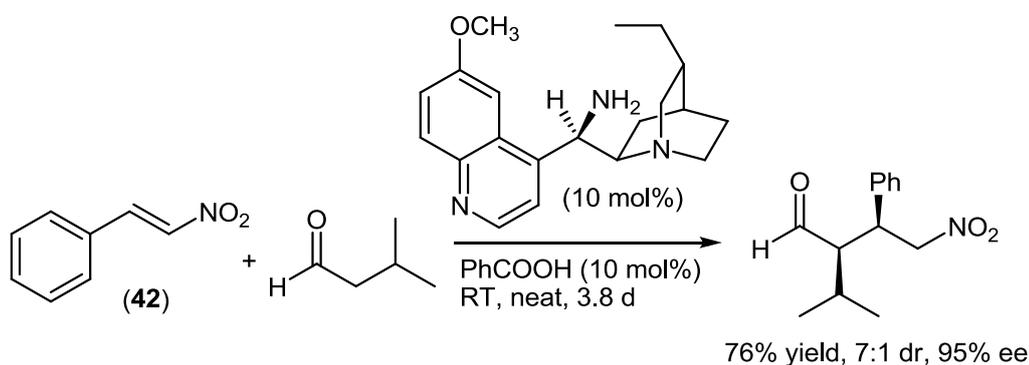


Scheme 1.45

*Cinchona* alkaloid derivatives replacing the C9-hydroxyl group with a primary amine have been used by Connon<sup>65</sup> to catalyse the addition of aldehydes and ketones to a wide range of nitroalkenes. As in previous examples, the 9-*epi* configuration led to more efficient catalysis than the “natural” configuration at C9, with 9-*epi*-amino-dihydroquinidine performing best in initial catalyst screens and used throughout the remainder of the investigation. In the addition of ketones to 2-nitrovinylbenzene (**42**) (Scheme 1.46), catalysed by 9-*epi*-amino-dihydroquinidine, acyclic ketone substrates (96-99% ee) were superior to cyclic substrates (69-84% ee), although both proceeded with very good *syn*-diastereoselectivity (d.r. up to 11:1). In the addition of both straight chain and  $\alpha,\alpha$ -disubstituted aldehydes (Scheme 1.47), the sense of stereoinduction was reversed compared with ketone substrates, but similar excellent *syn*-diastereoselectivities were achieved (d.r. up to >20:1), in addition to very good enantioselectivity (83-95% ee). The reaction scope was also examined with respect to the electrophile through addition of a range of nitroalkenes to *isobutryl*aldehyde, achieving the highest levels of enantioselectivity yet reported for that aldehyde substrate (82-94% ee). The mechanism proposed involved a transition state with an *in situ E*-enamine, where the bulkier substituent is directed away from the catalyst, leading to a single rotamer of which one face is shielded by the quinoline ring.

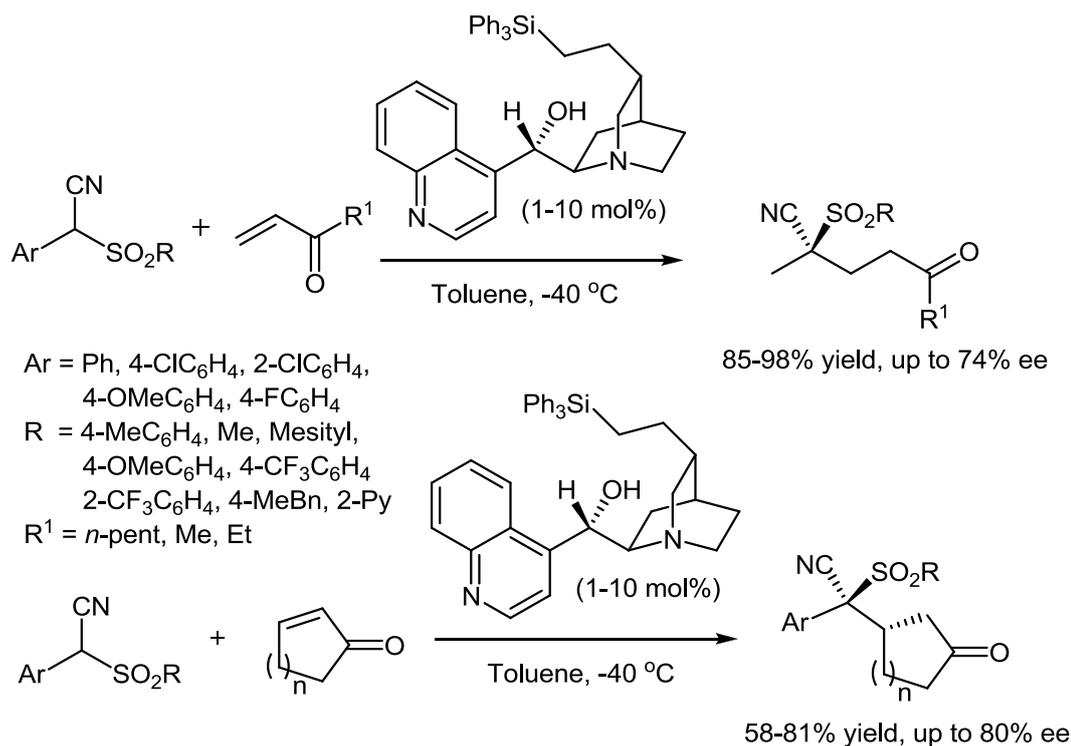


Scheme 1.46



Scheme 1.47

Chiral sulfonyl compounds are gaining importance in medicinal chemistry, and have shown activities against diseases such as glaucoma and Alzheimer's. Cid and Ruano<sup>66</sup> used silyl substituted *Cinchona* alkaloid derivatives to catalyse the Michael addition of  $\alpha$ -substituted- $\alpha$ -cyanosulfones to  $\alpha,\beta$ -unsaturated ketones to form  $\alpha,\alpha$ -disubstituted cyanosulfones in excellent yields with good enantioselectivity (up to 80% ee). In catalyst performance screening, in the reaction of  $\alpha$ -phenyl- $\alpha$ -cyano-*p*-tolylsulfone with methyl vinyl ketone, the C11-silyl substituted dihydrocinchonine derivative displayed enhanced performance compared with quinine, quinidine, cinchonine, cinchonidine, *O*-benzylated derivatives and dimeric catalysts such as (DHQ)<sub>2</sub>PYR or (DHQ)<sub>2</sub>PHAL, generating both higher conversion and higher enantioselectivity. This catalyst was then used to study the scope of the reaction. A wide range of substituents on both the sulfone and ketone reaction partners were tolerated without significant loss of conversion or enantioselectivity (Scheme 1.48). Crystalline products could be converted into enantiomerically pure compounds by a single crystallisation step.



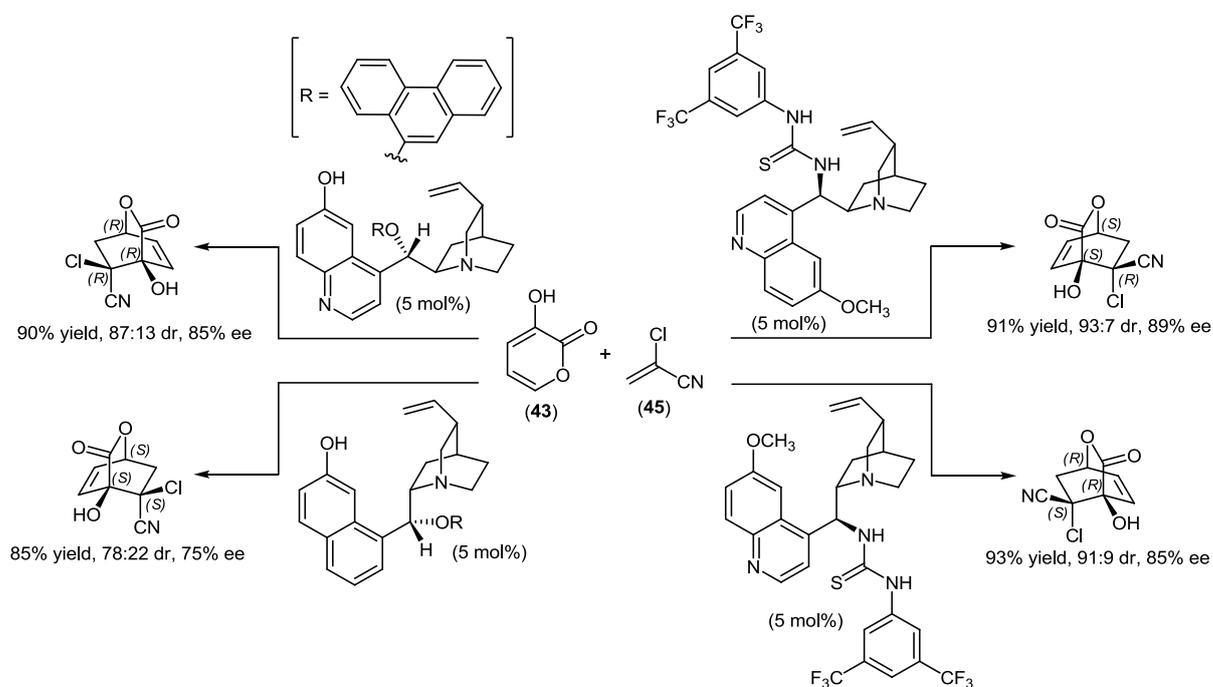
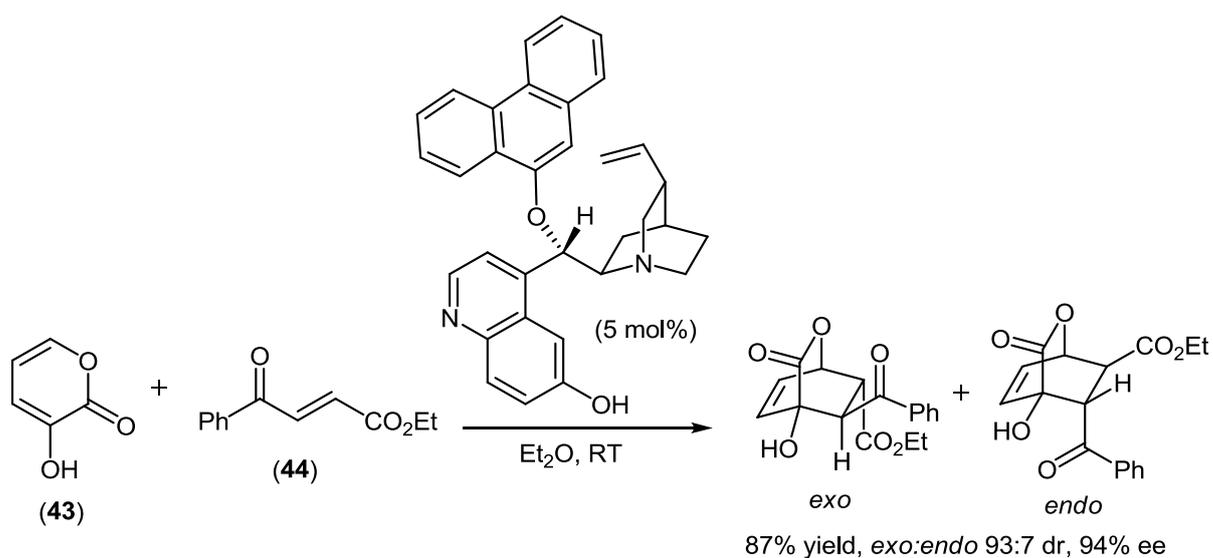
Scheme 1.48

### 1.3.1.4 *Cinchona* alkaloids in enantioselective Diels-Alder reactions

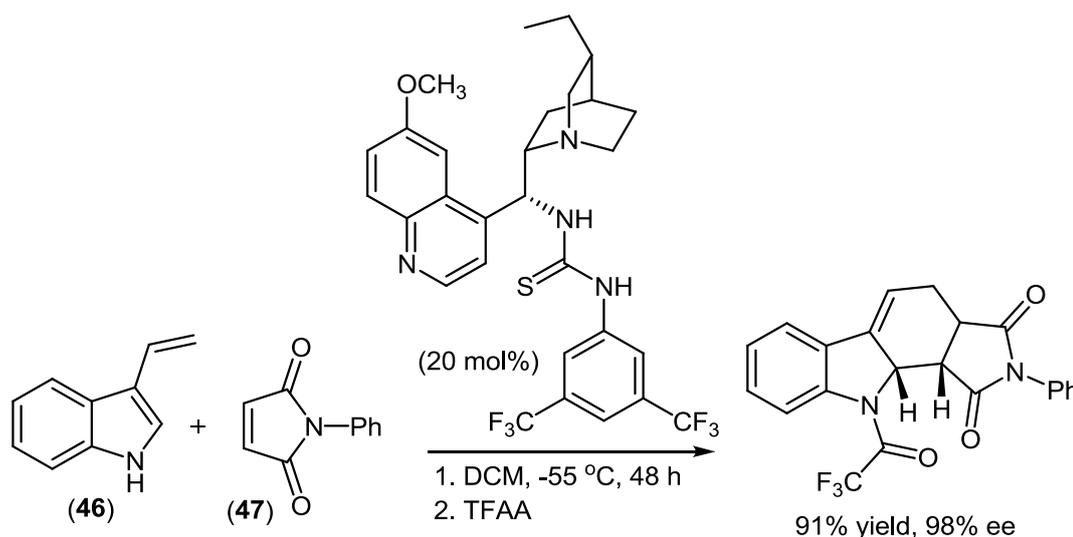
The Diels-Alder reaction is one of the most versatile reactions in organic synthesis given the wide scope of both dienes and dienophiles that can be used. The ability of asymmetric Diels-Alder reactions to transform achiral starting materials into stereochemically complex cyclic materials both diastereoselectively and enantioselectively is a highly desirable target for the development of new organocatalysts, some of which are based on *Cinchona* alkaloids.

Deng<sup>67</sup> investigated the enantioselective and diastereoselective Diels-Alder reaction of 2-pyrones with  $\alpha,\beta$ -unsaturated carbonyl compounds, catalysed by *Cinchona* alkaloid derivatives. In the model reaction of 3-hydroxy-2-pyrone (**43**) with *trans*-3-benzoylacrylic ester (**44**) (Scheme 1.49), the 6'-hydroxy-9-*O*-phenanthryl-quinidine derivative showed significantly better catalytic efficiency than the natural *Cinchona* alkaloids, generating an *exo:endo* diastereoisomeric ratio of 93:7, with a 94% enantiomeric excess. This catalyst was then used to examine the scope of the reaction, and was found to tolerate significant alterations in both the pyrone and the dienophile. Diastereoisomeric ratios were in the range 76:24 to 93:7, with the major isomer generated in 82-94% enantiomeric excess. Control of the *exo/endo* selectivity of the

Diels-Alder reaction was possible using either the 6'-hydroxy-9-*O*-phenanthryl-quinidine derivative for *endo* selectivity, or the C9-*epi*-thiourea-quinidine derivative for *exo* selectivity. Use of the corresponding quinine derivatives also allowed access to the opposite product enantiomers, ultimately allowing selective formation of the four possible stereoisomers from the reaction of 2-pyrone (43) with  $\alpha$ -chloroacrylonitrile (45) (Scheme 1.50).



Ricci<sup>68</sup> investigated the previously inaccessible catalytic asymmetric Diels-Alder reaction of 3-vinylindoles with a range of dienophiles, catalysed by *Cinchona* alkaloid derivatives. Initially, the reaction of 3-vinylindole (**46**) with *N*-phenylmaleimide (**47**) was used to screen reaction conditions and catalysts for optimum selectivity, which was achieved (98% ee) using the C9-thiourea derivative of dihydroquinine as the catalyst, in dichloromethane at -55 °C (Scheme 1.51). The *endo* product was obtained exclusively, and no isomerisation of the double bond was observed. The scope of the reaction was then investigated by varying the structure of the 3-vinylindole, with the reaction tolerating electron withdrawing or donating groups at the indole 5-position, in addition to a methyl substituent at the *exocyclic* double bond, with excellent enantioselectivity (90-98% ee). The dienophile was then varied to include various *N*-substituted maleimides, even including a bulky *tert*-butyl group, in addition to benzoquinone and naphthoquinone, also with excellent enantioselectivity (88 - >99% ee).

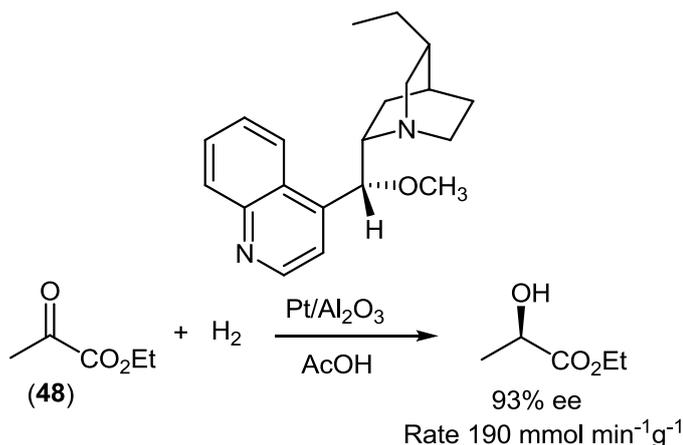


Scheme 1.51

### 1.3.1.5 *Cinchona* alkaloids in heterogeneous enantioselective hydrogenations

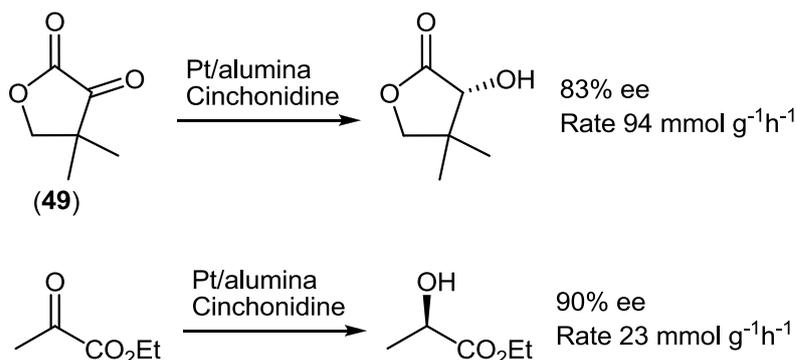
The addition of a strongly adsorbing chiral molecule to a (supported) metal catalyst is by far the simplest and most elegant approach to create a catalytically active chiral metal surface.<sup>69</sup> The most used catalyst for the hydrogenation of activated ketones is platinum modified by a *Cinchona* alkaloid, usually cinchonine or cinchonidine or derivatives thereof. *Cinchona* modified palladium is often used for the hydrogenation of C=C double bonds. The aromatic quinoline ring allows strong adsorption of the *Cinchona* alkaloid modifier onto the metal surface, the quinuclidine

nitrogen interacts with the ketone substrate, and the overall *Cinchona* framework provides conformational rigidity which induces enantioselectivity in the reaction, in addition to rate acceleration. Excellent enantioselectivities have been reported for a wide variety of ketone substrates. The reactions are typically performed under mild conditions, at room temperature using low hydrogen pressures, and the catalysts are recoverable, leading to a “green” reputation for heterogeneous *Cinchona* modified catalysts for asymmetric hydrogenation.



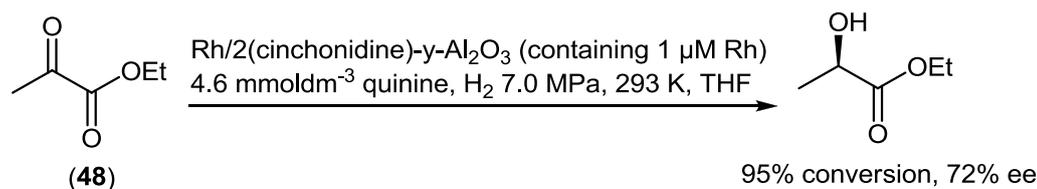
**Scheme 1.52**

Blaser<sup>70</sup> carried out an extensive study on the effect of the *Cinchona* alkaloid modifier structure on the rate and enantioselectivity of the asymmetric hydrogenation of ethyl pyruvate (48) catalysed by alumina supported platinum. Cinchonidine and quinine always gave ethyl-(*R*)-lactate preferentially, whereas cinchonine and quinidine always gave the (*S*) product preferentially, and this sense of induction was retained in the C10-C11 dihydro-derivatives. The cinchonidine and quinine derivatives induced higher enantioselectivity than the cinchonine and quinidine derivatives, although the enantiomeric excesses generated with cinchonine and cinchonidine were generally higher than with quinine and quinidine. Replacing the OH at C9 with any substituent other than a methoxy group caused a decrease in enantioselectivity, and hydrogenation of the quinoline ring caused a significant decrease in the observed enantiomeric excess (as the adsorption onto the surface was affected). The modifier was also no longer effective when the quinuclidine nitrogen was alkylated because it could no longer interact with the substrate. The best results were obtained using 1 mg *O*-methyl-10,11-dihydrocinchonidine in acetic acid (up to 93% ee, Scheme 1.52).



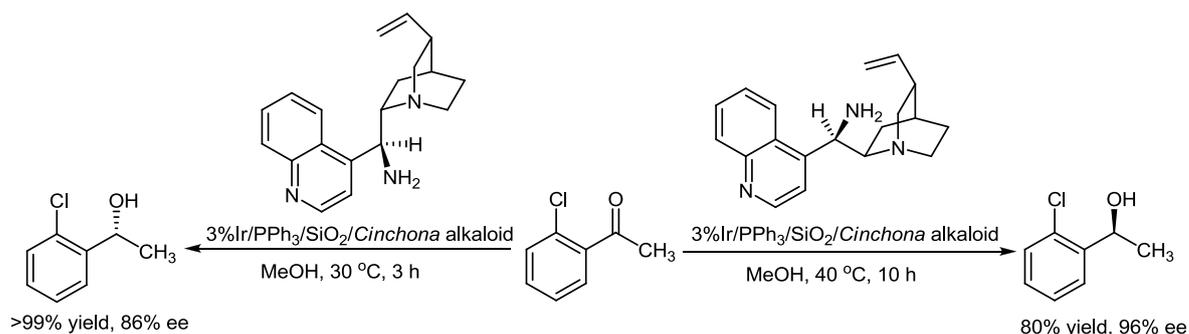
Scheme 1.53

Baiker<sup>71</sup> was the first to use a continuous flow reactor for the heterogeneous enantioselective hydrogenation of activated ketones over Pt/alumina modified by cinchonidine. In this system, very good enantiomeric excesses of 83% and 90% could be achieved in the hydrogenation of ketopantolactone (**49**) and ethyl pyruvate (**48**) respectively (Scheme 1.53).



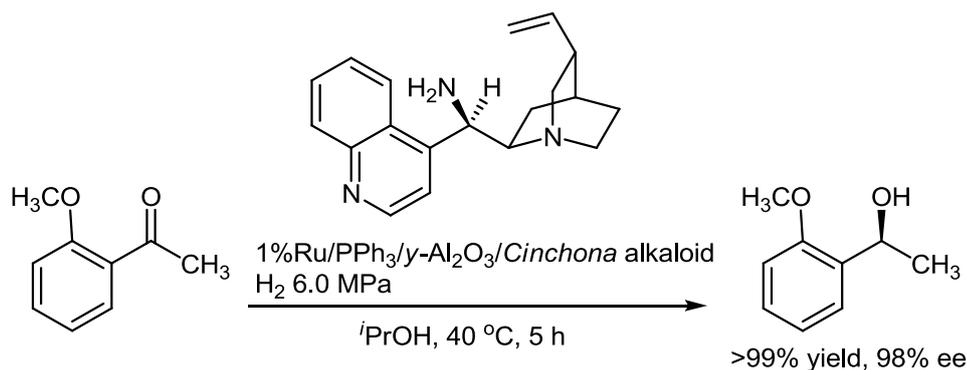
Scheme 1.54

In initial research into *Cinchona* modified heterogeneous catalysts for asymmetric hydrogenation, when transition metals other than platinum or palladium were used as the active element in the supported catalyst, the enantioselectivity decreased substantially. Work to extend the transition metal scope was carried out by Li,<sup>72</sup> who examined the enantioselective hydrogenation of ethyl pyruvate (**48**) using an alumina supported rhodium nanocluster catalyst, stabilised by cinchonidine and modified by quinine, which displayed both high activity and good enantioselectivity. The molar ratio of Rh:cinchonidine in the best performing catalyst, at which the optimum configuration of the active centre on the catalyst could form, was 2:1. Both quinine and cinchonidine could act as the catalyst stabiliser with similar results, but the enantioselectivity of the reactions was 5-6% better when quinine was used as the modifier rather than cinchonidine. A very high enantiomeric excess of 72% of (*R*)-ethyl lactate was achieved (Scheme 1.54).



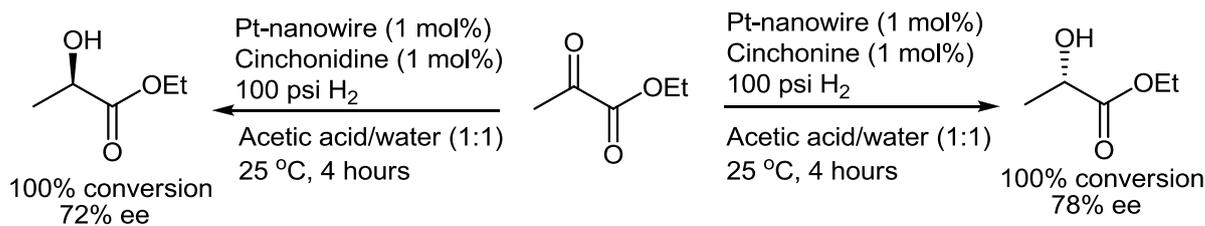
Scheme 1.55

Chen<sup>73</sup> reported the first successful example of asymmetric hydrogenation of simple aromatic ketones using iridium and hydrogen. A triphenylphosphine stabilised Ir/SiO<sub>2</sub> catalyst system, modified with both 9-amino-9-deoxy-*epi*-cinchonine and 9-amino-9-deoxy-*epi*-cinchonidine to generate both enantiomers of product (Scheme 1.55), was used to catalyse the asymmetric hydrogenation of a range of aromatic ketones with very good to excellent enantioselectivity (74-96% ee).



Scheme 1.56

Chen<sup>74</sup> also developed a triphenylphosphine stabilised alumina supported ruthenium catalyst system, modified by 9-amino-9-deoxy-*epi*-cinchonine. Up to 99% conversion and 83% enantiomeric excess were achieved in the hydrogenation of acetophenone, which was a significant improvement on results using the homogeneous ruthenium catalyst [RuCl<sub>2</sub>[P(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>]<sub>3</sub>]/9-amino-9-deoxy-*epi*-cinchonine system, which generated only 50% enantiomeric excess in the hydrogenation of acetophenone. High catalyst activity (97- >99% yields) and very good to excellent enantioselectivity (78-98% ee) were also achieved in the asymmetric hydrogenation of a series of aromatic ketones, with particularly impressive results for *ortho*-substituted aromatic ketones (Scheme 1.56).

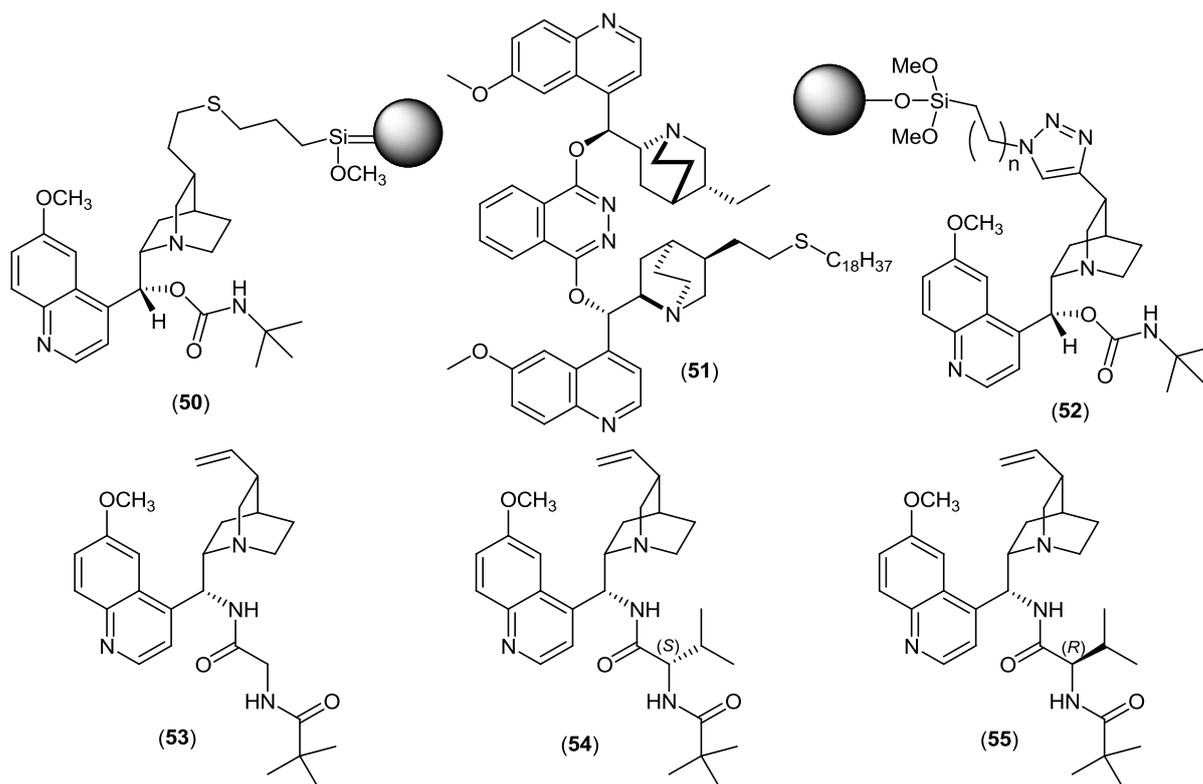


Scheme 1.57

Ying<sup>75</sup> performed the first enantioselective hydrogenation of  $\alpha$ -ketoesters using *Cinchona* alkaloid-modified platinum nanowires (Scheme 1.57). Initial studies focused on the hydrogenation of ethyl pyruvate, for which the catalyst modified with *Cinchona* alkaloids was not only enantioselective but also more active than the unmodified platinum nanowires alone, reducing the reaction time from 6 hours to 4 hours. Cinchonidine, dihydrocinchonidine, quinine and dihydroquinine all gave (*R*)-alcohols, whereas alkaloids with the opposite configuration at C8 and C9 (cinchonine, dihydrocinchonine, quinidine and dihydroquinidine) all gave (*S*)-alcohols. The best result was obtained using 1 mol% catalyst (with a 1:1 molar ratio of Pt to *Cinchona* modifier), in acetic acid/water (1:1), at a temperature of 25 °C, and a 100 psi pressure of hydrogen. The best enantioselectivity was achieved using cinchonine or cinchonidine (72-78% ee) to form either enantiomer of product. Moisture and air did not appear to affect the catalytic performance. The catalysts could be recovered by centrifugation, and were recycled 10 times without any loss in activity, and only a slight loss in selectivity (1-5%). The enantioselective hydrogenation of ethylbenzoyl formate was also carried out, and although the conversion remained quantitative the enantioselectivity was lower, at 54-57% enantiomeric excess.

### 1.3.1.6 *Cinchona* alkaloids as chiral stationary phases in chromatography

*Cinchona* alkaloids and their derivatives have also received considerable attention and gained popularity as highly enantioselective chiral selectors in chromatographic applications. One example is the availability of Chiralpak® QN-AX and QD-AX, commercially available enantioselective weak anion-exchange HPLC columns for the separation of chiral acids, *O*-9-*tert*-butylcarbamoylequinine (**50**) or quinidine immobilised on a 5  $\mu$ m silica support, developed by Professor Lindner's group.<sup>76</sup>



**Figure 1.11**

Maier<sup>77</sup> avoided the problems that can be associated with immobilised chiral stationary phases by using *Cinchona* derived chiral selectors in a support free liquid-liquid partition chromatographic technique, centrifugal partition chromatography (CPC), which uses immiscible solvents as stationary and mobile phases. The mobile phase is pumped through the liquid stationary phase, which is held in the column compartment by a centrifugal force generated by its fast rotation. For enantioselective separation the chiral selector is dissolved in the stationary phase. The enantiomers of the herbicidal agent 2-(2,4-dichlorphenoxy)propionic acid (dichlorprop) were separated using this technique with the (DHQD)<sub>2</sub>PHAL derived chiral stationary-phase additive **51**. Due to environmental issues, Maier used an organic stationary phase and a purely aqueous mobile phase. In order to make the chiral stationary phase additive (DHQD)<sub>2</sub>PHAL more hydrophobic, and thus insoluble in the mobile phase, a lipophilic moiety was attached. An octadecylthio group was chosen in order to both maintain the functional integrity of the (DHQD)<sub>2</sub>PHAL and to replicate the molecular microenvironment of the silica supported chiral stationary phase with which it was to be compared. The separation was found to have high enantioselectivity coupled with good system stability. In the comparison made with separation using HPLC with a silica

supported (DHQD)<sub>2</sub>PHAL derivative, the CPC method was found to have comparably high preparative loading and significantly reduced solvent consumption.

Kacprzak and Lindner<sup>78</sup> used *click* chemistry to immobilise various *Cinchona* alkaloid alkyne derivatives onto azido-modified silica gel to produce chiral stationary phases for HPLC enantiomer separations. This method was considered a milder and more broadly substrate compatible immobilisation strategy for *Cinchona* alkaloid derivatives than the conventional free radical addition of thiol modified silica gels to the C10-C11 double bond to form a thioether linkage, which requires thermal or photochemical activation over long periods of time. An additional advantage is the ability to control the surface coverage of the *Cinchona* alkaloid chiral selector on the silica gel. The triazole-linked *tert*-butylcarbamoylequinine derived chiral stationary phase (**52**) was compared with the corresponding thioether linked stationary phase for the separation of a set of six chiral model analytes under polar organic mobile phase conditions, and was found to elute the enantiomers in the same order with very similar enantioselectivities, suggesting similar chiral recognition capacities, although the retention times of some enantiomers were diminished on the triazole linked chiral stationary phase.

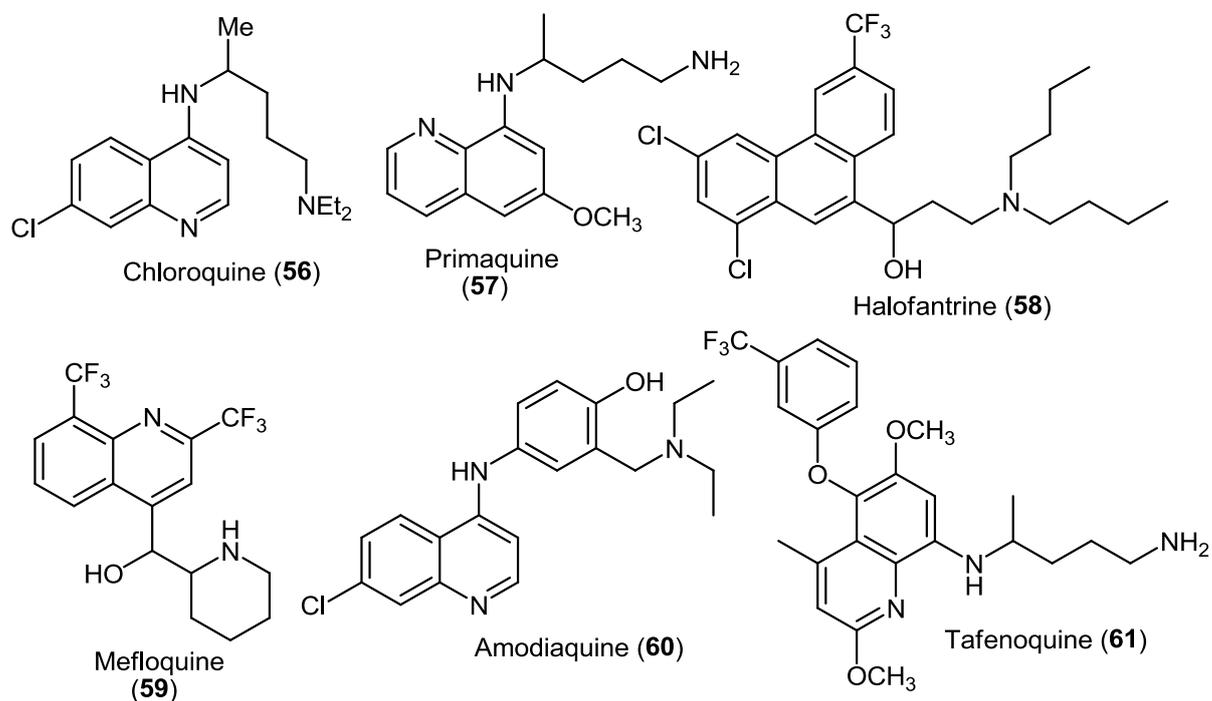
Maier<sup>79</sup> recently synthesised a new class of *epi-Cinchona* chiral selectors derived from 9-amino-9-deoxy-*epi*-quinine, with the sterically demanding amino acid groups *N*-pivaloyl-glycine (**53**), *N*-pivaloyl-(*S*)-valine (**54**), and *N*-pivaloyl-(*R*)-valine (**55**) attached to the C9 amino nitrogen. The chiral selectors were immobilised to silica to provide the corresponding chiral stationary phases, which were evaluated in the enantioseparation of a selection of nine amino acids bearing *N*-Fmoc-, *N*-Cbz- and *N*-Boc- protecting groups. The chiral recognition capabilities under polar organic mobile phase conditions were found to be modest. The enantioselective analyte binding was controlled by the absolute stereochemistry of the attached amino acid groups, with the (*S*)-valine derivative (**54**) binding *N*-protected-(*S*)-amino acids and the (*R*)-valine derivative (**55**) binding *N*-protected-(*R*)-amino acids, indicating that the chiral recognition properties of *epi-Cinchona* alkaloids can be altered and/or re-programmed by the incorporation of additional stereocentres remote from the *Cinchona* scaffold.

### 1.3.2 Introduction to malaria and its treatments

Malaria, a major public health concern in many regions of the globe, is caused in humans by five species of parasites of the genus *Plasmodium*: *Plasmodium falciparum*;

*P. vivax*; *P. ovale*; *P. malariae*; and *P. knowlesi*. *Plasmodium falciparum* and *P. vivax* account for 95% of all malaria infections, and almost all severe and fatal cases are caused by *Plasmodium falciparum*.<sup>80</sup> There were an estimated 655,000 deaths worldwide due to malaria in 2010, with approximately 86% of these deaths occurring in children under five.<sup>81</sup>

The name *Cinchona* alkaloid comes from the myth that in the early 17<sup>th</sup> Century Lady Chinchón, wife of the Spanish viceroy of Peru, was cured from malaria through use of the ancient herbal remedy “quinquina” bark.<sup>82</sup> Quinine has been used for the treatment of malaria ever since it was first brought to Europe from Peru in the early 17<sup>th</sup> century (at that time in the form of bark stripped from the *Cinchona* tree), until its replacement in the 1930s with the synthetic analogue Chloroquine (**56**). In 2004 the world’s consumption of Chloroquine (**56**) was 300-500 million courses of treatment per year, and due to a lack of an affordable alternative Chloroquine (**56**) (which costs approximately 6 pence per retail course) remains the most frequently used antimalarial in Africa.<sup>83</sup> Over time, resistance has developed, first appearing in Asia and then in Africa.



**Figure 1.12:** Examples of antimalarial drugs that are synthetic analogues of quinine

Further synthetic analogues have been introduced for the treatment of malaria,<sup>84</sup> examples of which can be seen in Figure 1.12. Primaquine (**57**), an 8-aminoquinoline

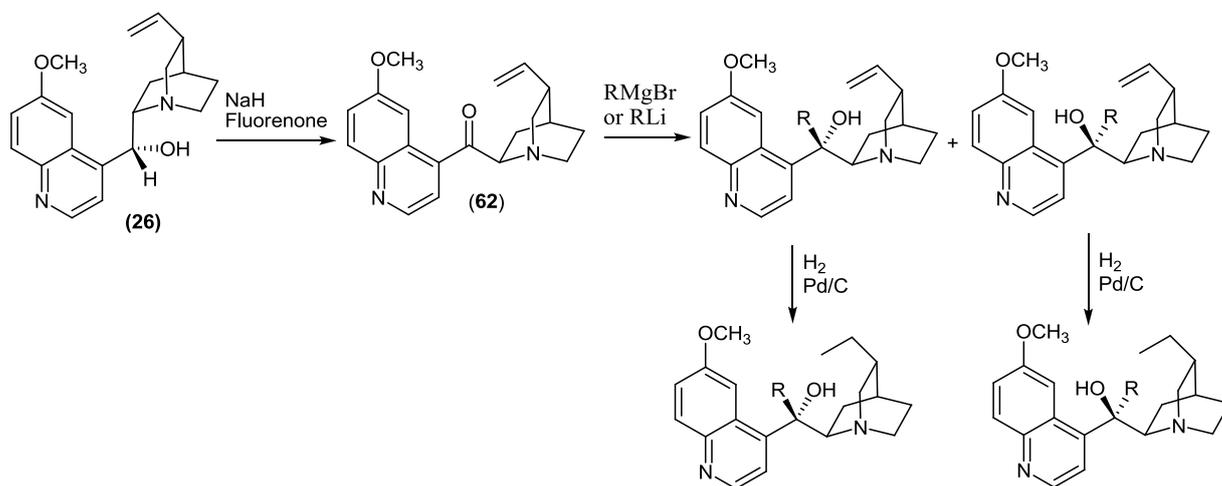
introduced in 1952, is the only drug licensed for the radical cure of *Plasmodium vivax* infections. The arylaminoalcohol Halofantrine (**58**), which was developed from 1965-1975, is active against Chloroquine resistant *Plasmodium* strains, but has been withdrawn from the market in many countries due to its association with a high risk of cardiac arrhythmias. Mefloquine (**59**), introduced in the 1970s, also displays high activity against Chloroquine resistant strains. Due to its widespread use resistance has become a problem, especially in Asia where in some areas monotherapy efficiency has dropped as low as 40%, although it is still >90% effective in Africa. Use of Mefloquine (**59**) has also been linked to psychiatric side effects such as insomnia, depression and panic attacks. The 4-aminoquinoline Amodiaquine (**60**), which was introduced in the 1980s, is effective against low level Chloroquine resistant parasites, but not against those with high Chloroquine resistance. Parasite resistance to Amodiaquine (**60**) is increasing, and if it is used for extended periods of time it can cause liver damage. The 8-aminoquinoline Tafenoquine (**61**), developed by GSK, is currently in phase IIb clinical trials for the treatment of *Plasmodium falciparum* and *Plasmodium vivax* strains of malaria. It potentially offers a shorter treatment course (single dose) than Primaquine (**57**) (which requires a 14 day treatment course), which should improve patient compliance.<sup>85</sup>

Inside a red blood cell the malaria parasite digests haemoglobin as a source of amino acids and iron. This digestion leads to the production of ferriprotoporphyrin IX (FPPIX) which is a byproduct toxic to the parasite. FPPIX polymerises and precipitates as crystals known as hemozoin, which are harmless to the parasite. Antimalarial compounds such as quinine and its structural analogues are known to interfere with the biocrystallisation of hemozoin, causing a build-up of FPPIX, and leading to parasite death.<sup>86</sup> However, the development of parasite resistance to commonly used antimalarials means new drugs are urgently needed.<sup>87</sup>

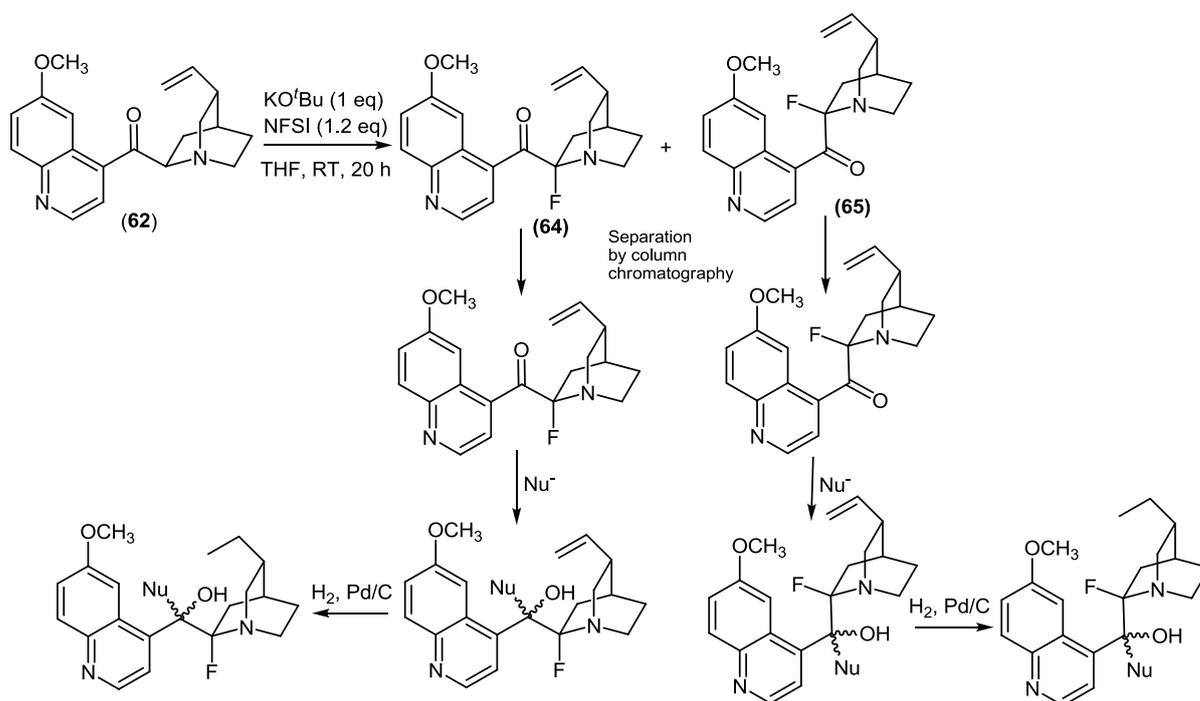
#### 1.4 Aims of the PhD

The research will first focus on the synthesis of novel quinidine derivatives containing a quaternary carbon at the C9 position. This will be achieved through nucleophilic addition to quinidinone (**62**) (Scheme 1.58), which can be diastereoselectively formed from quinine (**26**). The new *Cinchona* derived tertiary alcohols will feature a range of alkyl and aryl substituents, including bulky groups such as naphthyl which should improve the enantioselectivity obtained in asymmetric

fluorination reactions. As 10,11-dihydroquinidine derivatives have been shown to improve enantioselectivity in asymmetric fluorination reactions, the 9-substituted quinidine derivatives will also be converted to their 10,11-dihydroquinidine analogues by hydrogenation of the C10-C11 double bond.



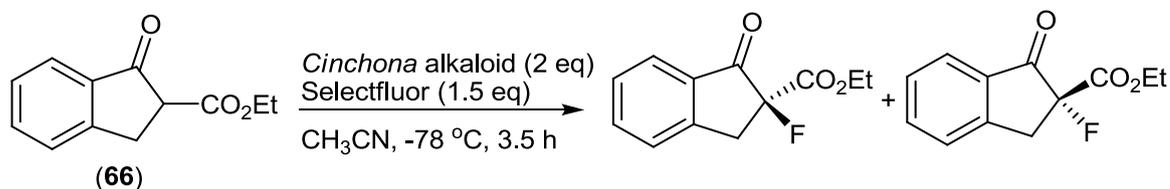
Scheme 1.58



Scheme 1.59

In order to prevent epimerisation between quinidinone (**62**) and quininone (**63**), the labile CH will be replaced *via* fluorination at the C8 position (Scheme 1.59). The 8-fluoroquinidinone (**64**) and 8-fluoroquininone (**65**) diastereoisomers will be separated

and isolated by column chromatography, and both will undergo nucleophilic addition reactions at the C9 carbonyl, to develop a series of 9-substituted-8-fluoroquinindine and 9-substituted-8-fluoroquinine derivatives. As in the case of quinidine analogues, the 9-substituted-8-fluoro derivatives will also be converted to their 10,11-dihydroquinidine/quinine analogues by hydrogenation of the C10-C11 double bond.



Scheme 1.60

The applications of the new *Cinchona* alkaloid derivatives will be investigated in the enantioselective electrophilic fluorination of model substrates such as ethyl-1-indanone-2-carboxylate (**66**) in order to directly compare with results from the literature (Scheme 1.60). The electrophilic fluorinating reagents will be formed *in situ* by a transfer fluorination from Selectfluor, rather than being isolated, to enable high throughput screening.

Resistance of malaria parasites to commonly used antimalarial drugs such as Chloroquine (**56**) and Mefloquine (**59**) has necessitated the development of novel antimalarial compounds. The new *Cinchona* alkaloid derivatives will have similar structures to quinine and quinidine, which are known to have antimalarial activity, and some derivatives will include a fluorine atom and/or a trifluoromethyl group, which are beneficial in medicinal chemistry. The new compounds will, therefore, be screened for antimalarial activity.

## 1.5 References for Chapter One

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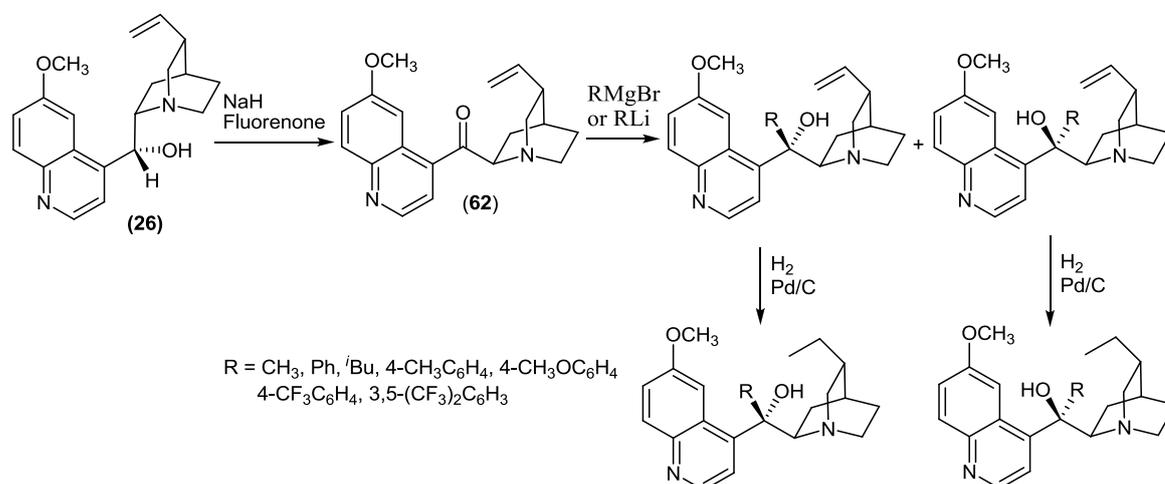
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## 2.1 Introduction

### 2.1.1 Aims of the chapter

This chapter will investigate the modification of the *Cinchona* alkaloid skeleton to form a small library of novel quinidine derivatives that contain a quaternary carbon at C9. This will be achieved by the diastereoselective formation of quinidinone (**62**) from quinine (**26**), followed by nucleophilic additions to the ketone (Scheme 2.1). Since 10,11-dihydroquinidine derivatives can increase the enantioselectivity in asymmetric fluorination by  $\geq 10\%$  compared to using quinidine derivatives, a small library of 9-substituted-10,11-dihydroquinidine derivatives will also be developed by selective hydrogenation of the C10-C11 double bond.

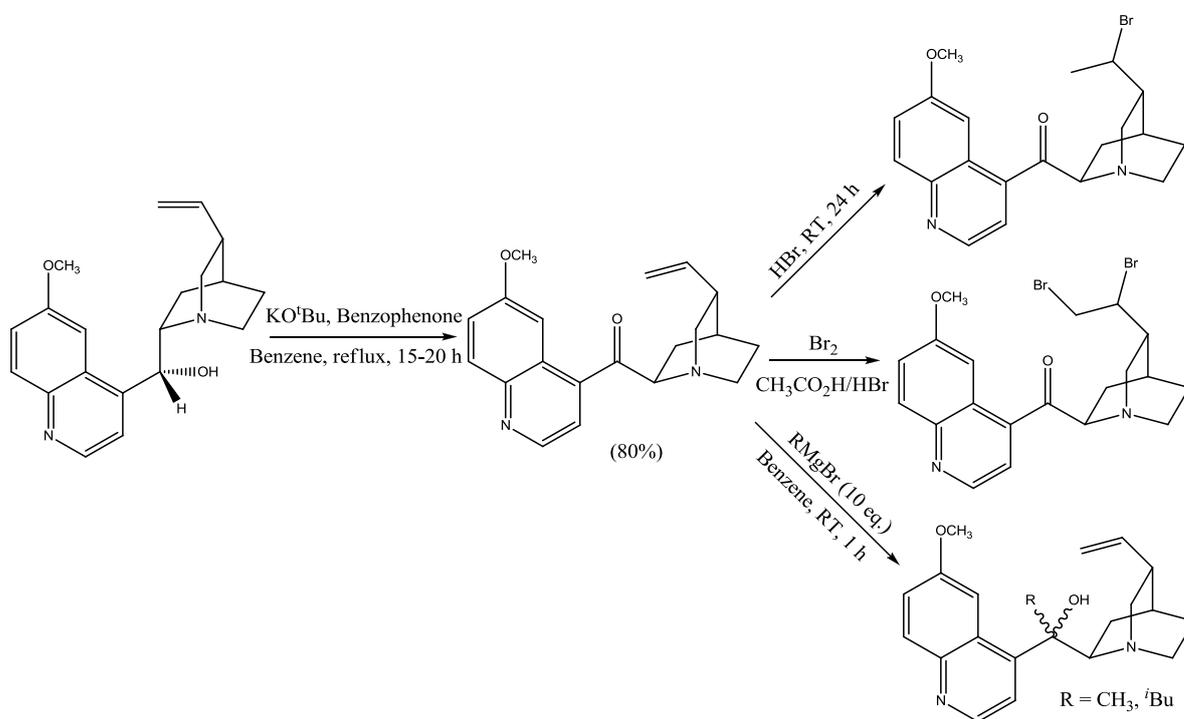


**Scheme 2.1**

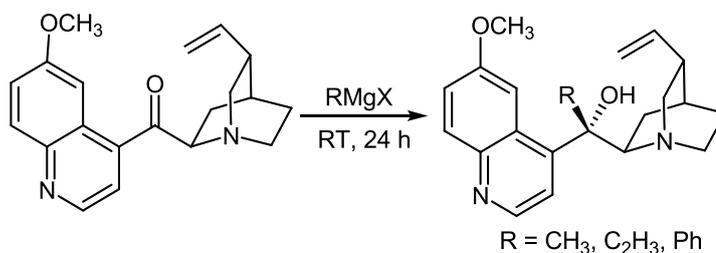
### 2.1.2 Examples of C9 derivatised *Cinchona* alkaloids

Woodward<sup>1</sup> formed quinidinone (**62**) from quinine (**26**) using the alkali alkoxide potassium *t*-butoxide as the oxidant in the presence of the hydrogen acceptor benzophenone. It is ironic that in order to avoid confusion Woodward referred to quinidinone as quinone throughout the paper, despite mentioning in a note that the compound should be called quinidinone, thus causing great confusion in modern searches for quinone/quinidinone. Several modifications were made to quinidinone (Scheme 2.2), including the addition of methylmagnesium bromide and *iso*-butylmagnesium bromide to the ketone (both additions used 10 equivalents of Grignard reagent). No isolated yields were reported for these transformations, although they were described as “smooth”. Woodward tentatively assigned the products as 9-

methylquinidine and 9-isobutylquinidine (rather than 9-methylquinine or 9-isobutylquinine) on the basis of their high positive specific rotations.



Scheme 2.2

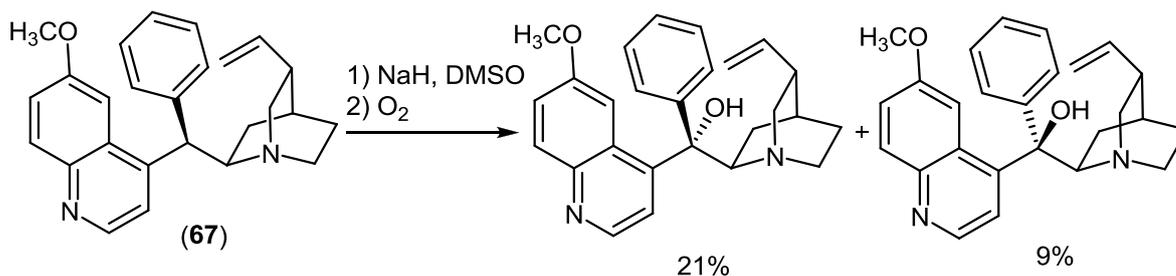
Table 2.1: Nucleophilic additions to quinidinone by Skarzewski<sup>2</sup>

Entry	RMgX	Solvent	Conversion (%)	Isolated yield (%)
1	CH <sub>3</sub> MgCl	THF/toluene	71	55
2	PhMgCl	THF/toluene	30	25
3	PhMgBr	DCM	50	48
4	C <sub>2</sub> H <sub>5</sub> MgBr	DCM	50	37

In work reported after completion of the synthesis described in this chapter, Skarzewski<sup>2</sup> also introduced a methyl group to C9 using methylmagnesium chloride (6.5 eq) in a THF/toluene mixture at room temperature over 24 hours, and expanded the

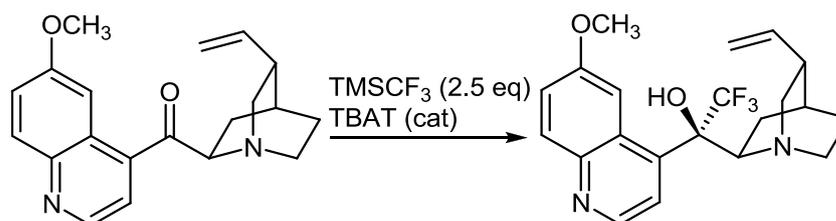
methodology to the addition of a phenyl group (Table 2.1). Initially, the nucleophilic addition to quinidinone was carried out using phenylmagnesium chloride (6.5 eq) in a THF/toluene mixture, but the yield was improved (from 25% to 48%) by using phenylmagnesium bromide (8.5 eq) and changing the solvent to dichloromethane. Vinylmagnesium bromide was also successfully added to the C9 position. Examination of the NMR NOE interactions and the X-ray crystallography data for 9-methylquinidine and 9-phenylquinidine confirmed that the Grignard additions were diastereoselective, giving the (8*R*,9*S*) configured products. The diastereoselectivity was proposed to be the result of coordination of the magnesium species to quinidinone through two metal atoms, forcing the *syn* orientation of the ketone oxygen and the quinuclidine nitrogen, which in turn caused nucleophilic attack from the *Re* face.

Surprisingly, the reaction did not proceed when phenyllithium was used, which, in addition to the moderate yields in the Grignard reactions, was attributed to concurrent enolate formation.



**Scheme 2.3**

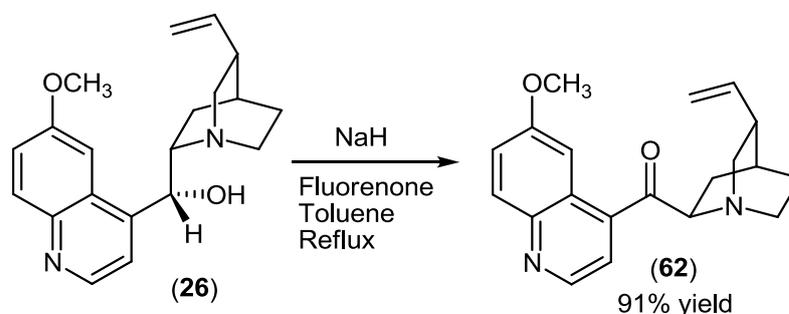
In a different approach (Scheme 2.3), Skarzewski<sup>2</sup> also hydroxylated 9-deoxy-9-phenyl-quinidine (67), forming 9-phenylquinidine with both configurations at C9, in a diastereomeric ratio of approximately 2:1 in favour of the (9*S*) configuration. The hydroxylation of 9-deoxy-9-phenyl-quinine was also carried out, thus achieving the formation of all four 8,9-diastereoisomers of the 9-phenyl-*Cinchona* alkaloids.



**Scheme 2.4**

Prakash and Olah<sup>3</sup> introduced a trifluoromethyl group at C9 (Scheme 2.4) as a steric barrier to rotation about the C9-C4' bond, in order to reduce interconversion between the *anti* and *syn* conformations to facilitate observation of their relative populations at room temperature. The trifluoromethyl group was chosen due to its increased steric size compared to a methyl group (it is isosteric with an isopropyl group), and due to the opportunity it provides to use <sup>19</sup>F NMR spectroscopy to observe the conformations, whilst still being small enough that the minimum energy conformations and their population distributions would resemble those of the parent molecule. Interestingly, the trifluoromethyl group adds from the back *Si* face, presumably because the Ruppert-Prakash reagent (TMSCF<sub>3</sub>) is non-coordinating.

## 2.2 The synthesis of quinidinone from quinine

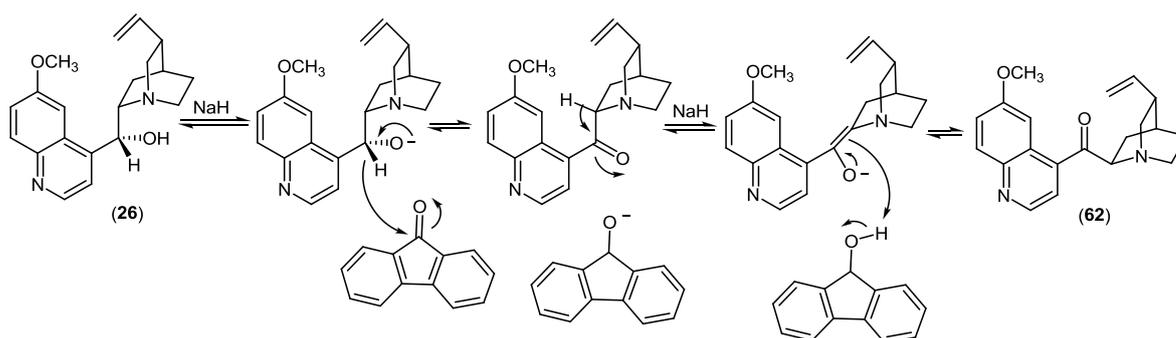


Scheme 2.5

Pratap's procedure was followed for the synthesis of quinidinone (**62**) from quinine (**26**),<sup>4</sup> using sodium hydride as the base and fluorenone as the hydride acceptor. After performing several reactions over two different reflux time periods (6 hours and overnight), refluxing overnight was considered preferable as it was more convenient to put the reaction on in the afternoon and work it up the next morning. The quinuclidine nitrogen was protonated in the workup by washing with HCl and the product was extracted into the aqueous layer. After deprotonation and precipitation by pouring into 28% ammonia/crushed ice mixture, the precipitate was taken into toluene, and the toluene was removed under vacuum. The resultant yellow oil was triturated with hexane to yield quinidinone as a brown solid in excellent isolated yield.

The mechanism for the synthesis of quinidinone is shown in Figure 2.1. First the quinine hydroxyl group is deprotonated by sodium hydride. The resulting negative charge on the oxygen then pushes in and causes a hydrogen transfer to the fluorenone hydride acceptor, forming quinone and fluorenol. As the sodium hydride base is in

excess, the hydrogen on C8, which is acidic due to its position alpha to a carbonyl, is removed from the quinone to form an enolate. Since the reaction is reversible the enolate can return to the ketone form, and does so, but because the enolate is planar it can return to either the quinone or quinidinone diastereoisomer. It returns to the quinidinone diastereoisomer because it is more stable to have the large group (the ketone and the attached quinoline ring) in the exo position at C8 on the quinuclidine ring, and to put the hydrogen at the endo position.

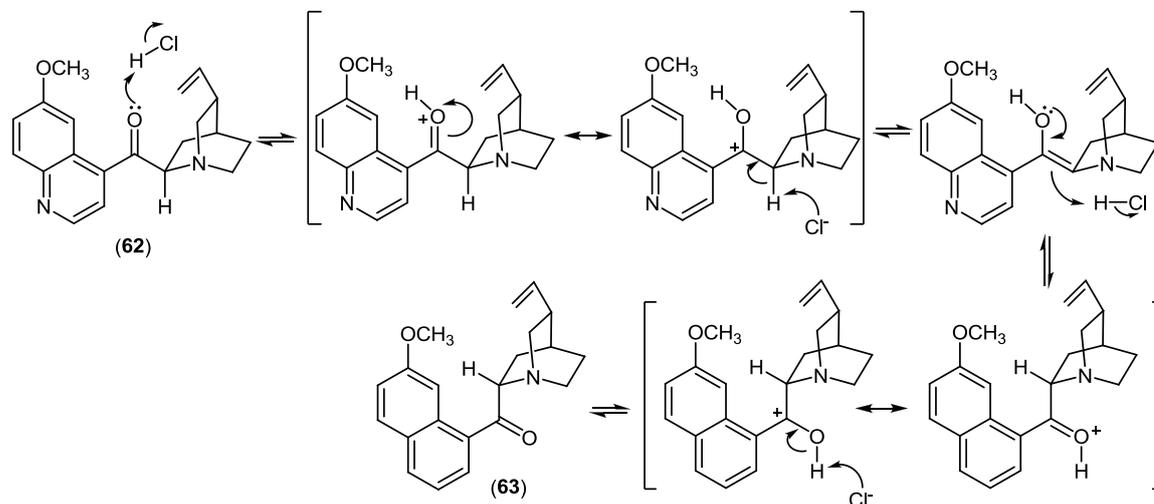


**Figure 2.1:** Mechanism for the conversion of quinine (**26**) to quinidinone (**62**)

When the reaction was performed using quinidine (**27**) rather than quinine (**26**), quinidinone (**62**) was still the major product formed. However, there also appeared to be another minor product present, and as quinidine is supplied in a lower purity than quinine and contains 15% dihydroquinidine, this by-product was thought to be dihydroquinidinone.

When the  $^1\text{H}$  NMR spectrum of quinidinone (**62**) was run in  $\text{CDCl}_3$  the presence of the quinone (**63**) diastereoisomer was detected. This was not observed in the  $^1\text{H}$  NMR spectra which were run almost immediately after preparation, but was seen to an increasing extent the longer the time interval was between sample preparation and the acquisition of the  $^1\text{H}$  NMR spectrum. The presence of quinone is due to epimerisation, catalysed by the presence of a small amount of hydrochloric acid in the  $\text{CDCl}_3$  solvent. The mechanism of this epimerisation is shown in Figure 2.2; an enol is formed, which can be reconverted into the ketone form, either to quinone (**63**) or to quinidinone (**62**), because it is a reversible reaction. The epimerisation in  $\text{CDCl}_3$  was found to be quite fast. After testing various solvents none were found to completely eliminate the epimerisation, but it was found to be slowest in  $\text{C}_6\text{D}_6$  and  $d_8$ -toluene. However, due to

the expensive nature of these solvents it was best to perform NMR analysis of the samples in  $\text{CDCl}_3$  with as little time as possible between the sample preparation and the acquisition of the  $^1\text{H}$  NMR spectrum.

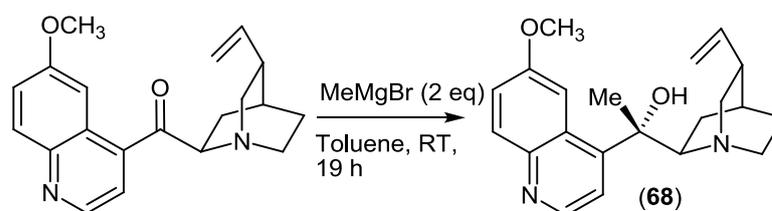


**Figure 2.2:** Mechanism for the epimerisation of quinidinone in  $\text{CDCl}_3$

## 2.3 Nucleophilic additions to quinidinone

### 2.3.1 Nucleophilic addition using $\text{MeMgBr}$ (Synthesis of 9-methylquinidine)

**Table 2.2:** Synthesis of 9-methylquinidine



Entry	Conversion <sup>a,b</sup> (%)
1	63 (29)
2	75 (40)
3	67 (56)

<sup>a</sup>determined by  $^1\text{H}$  NMR spectroscopy; <sup>b</sup>isolated yield in parenthesis

The next step was to add nucleophiles to the quinidinone ketone to form new quinidine analogues that contain a quaternary carbon at the C9 position. The first nucleophilic addition was attempted with methylmagnesium bromide. The reaction was

expected to proceed well due to the minimum steric hindrance caused by the small methyl group.<sup>5</sup>

Quinidinone, dissolved in toluene, was added slowly to the stirred Grignard reagent in a dropwise fashion at room temperature, and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with aqueous hydrochloric acid, the organic layer was washed with hydrochloric acid, and the combined aqueous layers were poured into 28% ammonia/crushed ice mixture. The resulting precipitate was filtered and dried, and the crude 9-methylquinidine (**68**) was recrystallised from ethanol.

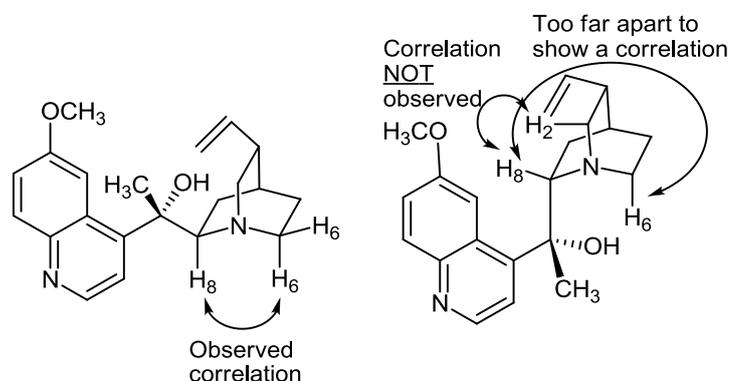
The conversion of the reaction was calculated from the integrations of the alkene CH signals for 9-methylquinidine (**68**) and quinidinone/quininone in the <sup>1</sup>H NMR spectrum of the crude solid. Since the <sup>1</sup>H NMR spectra of the crude products only contained quinidinone/quininone starting material and the 9-methylquinidine peaks, it was assumed that only one diastereoisomer of 9-methylquinidine was formed. The starting material was removed by recrystallisation from ethanol.

HMQC and <sup>1</sup>H<sup>1</sup>H-COSY NMR spectra were used to determine the exact identity of each peak on the hydrogen and carbon NMR spectra. The peaks were mostly as expected, although it was a surprise to see that the alkene CH<sub>2</sub> on the carbon spectrum was so far downfield, and that the aromatic 3'-carbon was so far upfield.

The signals in the room temperature <sup>1</sup>H NMR spectrum for H3' and H5' were merged into one broad singlet due to hindered rotation about the C9-C4' bond due to through space interactions with the C9 substituent. These signals could be resolved into two separate signals by high temperature <sup>1</sup>H NMR spectroscopy (at 328 K / 55 °C). Although the signal for H3' in the high temperature <sup>1</sup>H NMR was resolved into the expected doublet with a 4.6 Hz coupling constant from coupling to H2', the signal for H5' was still a broad singlet (rather than the expected doublet with a 2.7 Hz coupling constant from coupling to H7'), perhaps indicating that H5' experiences more steric interaction with the 9-CH<sub>3</sub> substituent than H3'.

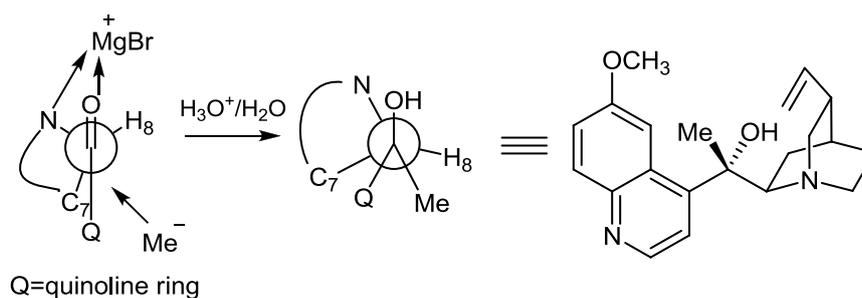
A NOESY spectrum was carried out to confirm that 9-methylquinidine (**68**) and not 9-methylquinine had been formed. The main correlation which suggested the 9-methylquinidine structure is the correlation observed between H8 and H6. In the quinine isomer, H8 would be in an *exo* position and would be too far away from H6 to show a through space correlation. The main correlation which would have suggested the

quinine isomer, but is absent, is a correlation between H8 and H2. This is illustrated in Figure 2.3. The correlations are also summarised in Table 2.6 (page 80).



**Figure 2.3:** 9-methylquinidine versus 9-methylquinine in the NOESY spectrum

Although the stereochemistry at the C9 position could not be proved by NOESY spectroscopy, the product formed was thought to be 9(*S*)-methylquinidine because of the proposed Chelation Control mechanism. The proposed mechanism involves chelation of the Grignard reagent to both the ketone oxygen and the quinuclidine nitrogen, fixing the molecule in a conformation that forces the nucleophile to attack from the less hindered front *Re* face in a diastereoselective manner. This is demonstrated in Figure 2.4, which shows a Newman projection down the C9-C8 bond.<sup>6</sup>

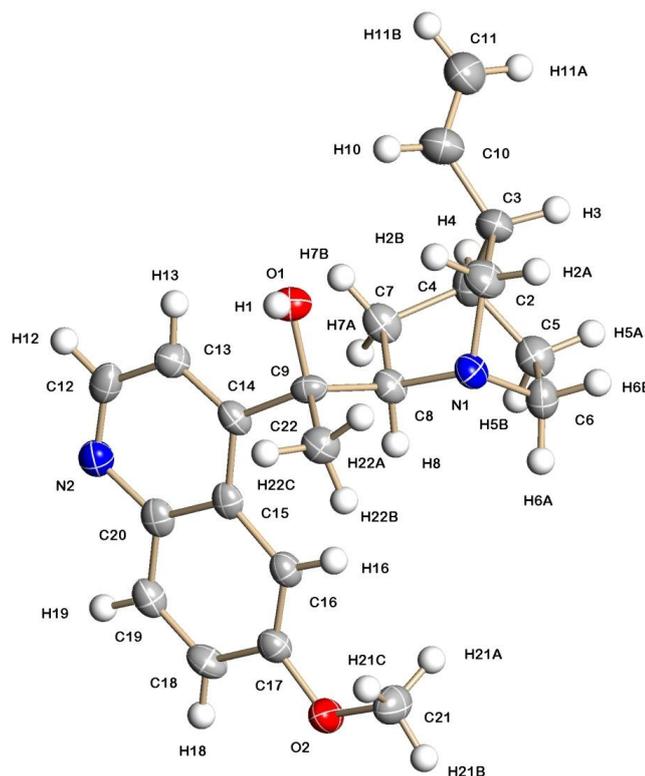


**Figure 2.4:** Proposed chelation control mechanism forming 9(*S*)-methylquinidine

The assignment of the product as 9(*S*)-methylquinidine is also in agreement with Skarzewski,<sup>2</sup> who reported very similar characterisation data for the product obtained in the reaction of quinidinone with 6.5 equivalents MeMgCl. It should be noted that similar conversion (67%) and isolated yield (56%) were achieved in this work to that of

Skarzewski (71% conversion, 55% isolated yield), although in this work only 2 equivalents of MeMgBr were used.

A crystal suitable for X-ray crystallography was grown by recrystallisation from diethyl ether/hexane. The crystal structure, shown in Figure 2.5, confirmed a quinidine (*R*) configuration at C8, and an (*S*) configuration at C9, as suggested by the proposed mechanism.



**Figure 2.5:** The molecular structure of 9(*S*)-methylquinidine

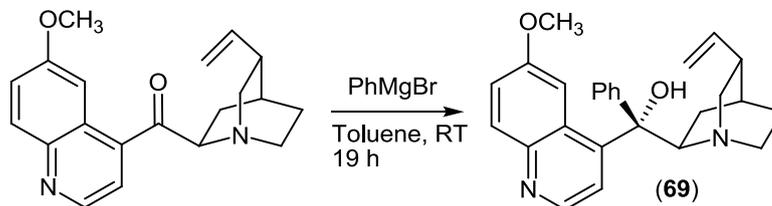
### 2.3.2 Synthesis of 9-phenylquinidine

After adding a methyl group to the C9 position successfully using methylmagnesium bromide, the next nucleophile attempted was a phenyl group. The reaction with phenylmagnesium bromide was expected to have a lower conversion than the methyl reaction due to the increased steric bulk of the large phenyl group (Table 2.3).

Although 9-phenylquinidine (**69**) could be purified by recrystallisation from ethanol, the co-crystallisation of ethanol with 9-phenylquinidine was a problem. However, the ethanol can be removed from the product by dissolving in chloroform and washing with water, before drying over magnesium sulphate and removing the solvent

by rotary evaporation. The isolated yield presented in Table 2.3 is after the ethanol has been washed out; some material may have been lost during this process.

**Table 2.3:** Synthesis of 9-phenylquinidine using PhMgBr

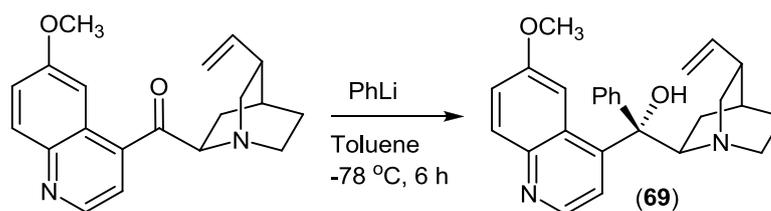


Entry	PhMgBr (no. equiv.)	Conversion <sup>a,b</sup> (%)
1	2.2	37 (10)
2	1.9	38 (10)

<sup>a</sup>determined by <sup>1</sup>H NMR spectroscopy; <sup>b</sup>isolated yield in parenthesis

Due to the low conversions and isolated yields obtained with the phenyl additions using phenylmagnesium bromide, the use of phenyllithium was investigated next. It was thought that phenyllithium should be more nucleophilic than phenylmagnesium bromide, and should therefore increase the conversion of the reaction. Rather than using the precipitation workup which had proved unpredictable when used in the Grignard reactions, the reaction was instead quenched with water and the organic layer was removed. The aqueous layer was then extracted with diethyl ether, and the combined organic layers were evaporated to give the crude product. The conversion was calculated from the <sup>1</sup>H NMR spectrum of the crude material by integrating the peaks representing the alkene CH of quinidinone/quininone and 9-phenylquinidine (**69**).

When the reaction was performed at 0 °C the <sup>1</sup>H NMR spectrum of the crude solid showed the peaks expected for 9-phenylquinidine and quinidinone/quininone, but also showed the presence of another unexpected material. The by-product could be a result of the addition of phenyllithium to the 2' position of the quinoline ring, as quinolines are susceptible to nucleophilic addition  $\alpha$  to the nitrogen. The conversion reported is the conversion to the desired product. The overall conversion of the reaction is higher, but as the by-product is unidentified it is unknown which peak correlates to an integration of one hydrogen in the by-product in order to have an accurate ratio.

**Table 2.4:** Synthesis of 9-phenylquinidine using PhLi

Entry	PhLi (no. equiv.)	Temperature (°C)	Conversion <sup>a,b</sup> (%)
1	2	0	48 <sup>c</sup>
2	2	-40	47
3	1	-78	31
4	2	-78	55 (38)
5	4	-78	55 (26)
6 <sup>d</sup>	2	-78	52
7 <sup>d,e</sup>	2	-78	44
8	4	-78	52

<sup>a</sup>determined by <sup>1</sup>H NMR spectroscopy; <sup>b</sup>isolated yield in parenthesis; <sup>c</sup>by-product formed; <sup>d</sup>inverse addition; <sup>e</sup>more concentrated reaction mixture.

The formation of the by-product was eliminated when the reaction was performed at lower temperatures; the only peaks observed in the crude <sup>1</sup>H NMR spectrum were those for 9-phenylquinidine (**69**), unreacted quinidinone/quininone, and for a biphenyl derivative caused by phenyllithium coupling with itself. Similar conversions were observed for the reactions using two equivalents of phenyllithium at both -40 °C and -78 °C (entries 2 and 4 in Table 2.4). Table 4 demonstrates clearly that at least two equivalents of phenyllithium are required to obtain a reasonable conversion to 9-phenylquinidine, but the conversion is not improved by increasing the excess of reagent to four equivalents (entries 3-5).

The moderate conversions observed in the nucleophilic additions to quinidinone using both organolithium and Grignard reagents could be due to the basic nature of these reagents. As the reagents can act as both nucleophiles and bases, they can not only add to the carbonyl at C9 but also deprotonate H8 to form a planar enolate, which is unreactive towards nucleophiles, and which under the reaction conditions is not protonated to re-form a ketone until the aqueous workup at the end of the reaction. This

also explains the presence of both quinidinone and quininone at the end of the reaction, and the fact that there is no evidence for a nucleophilic addition to quininone.

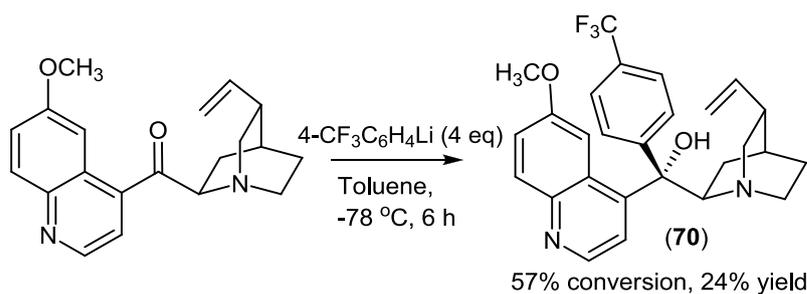
After a short column to remove the biphenyl derivative, the 9-phenylquinidine was isolated using a longer column and the solvent system: toluene/dichloromethane/diethyl ether/triethyl amine in the ratio 38/30/30/2. The 9-phenylquinidine is sandwiched between the quinidinone and the quininone, which makes the column difficult, and also makes some mixed fractions inevitable. Although the 9-phenylquinidine can be isolated if a long column is used initially, the best results were obtained when two columns were used.

In the room temperature  $^1\text{H}$  NMR spectrum, the signals for H3' and H5' were broad singlets. Although the signal for H3' could be resolved, into the expected doublet with a 4.6 Hz coupling constant from coupling to H2', by high temperature  $^1\text{H}$  NMR spectroscopy (at 328 K / 55 °C), the signal for H5' remained broad and was not resolved into the expected doublet with a 2.8 Hz coupling constant to H7'. This could indicate that H5' experiences more steric hindrance from the 9-phenyl substituent than H3'. Other peaks that were previously broad or merged together could also be resolved by high temperature  $^1\text{H}$  NMR spectroscopy, such as the 9-phenyl protons H2'', H3'' and H4'', which could be individually assigned.

A NOESY spectrum was recorded for the isolated 9-phenylquinidine. The correlations are summarised in Table 2.6 (page 80), and strongly suggest a quinidine configuration at C8. Unfortunately, the NOESY spectrum cannot assist with the determination of the configuration at C9.

Following the addition of quinidinone to a stirred solution of two equivalents of phenyllithium at -78 °C, 9-phenylquinidine was isolated successfully in 38% yield. This was a significant improvement on the isolated yield for the phenylmagnesium bromide reactions (only 10%), but was still lower than would generally be considered acceptable. Therefore, the conditions were altered to try and improve the conversion and isolated yield for the reaction. However, inverse addition by adding phenyllithium to a stirred solution of quinidinone in entry 6 (Table 2.4) gave a very similar conversion, and using a more concentrated solution of quinidinone (0.31 M rather than 0.16 M in toluene) in entry 7 decreased the conversion. Consequently, the reaction conditions were considered optimum.

### 2.3.3 Nucleophilic additions using aryllithiates



**Scheme 2.6**

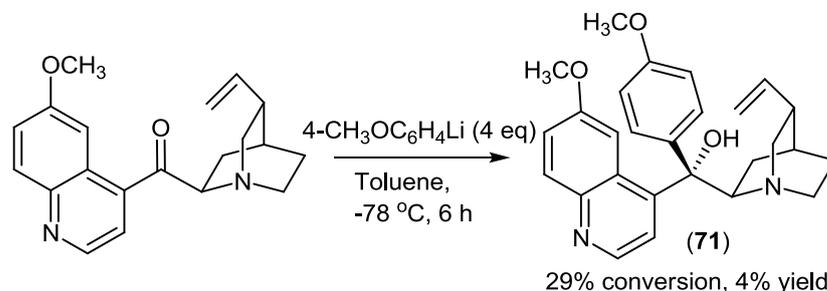
A small series of aryllithiates containing either electron withdrawing or electron donating substituents were reacted with quinidinone. The first nucleophile in this category was 4-trifluoromethylphenyllithium, a bulky nucleophile with an electron withdrawing group on the phenyl ring. The steric bulk is increased by the trifluoromethyl group, which is more comparable in size to an isopropyl group than to a methyl group (van der Waals volumes: CH<sub>3</sub> 16.8 Å<sup>3</sup>, CF<sub>3</sub> 42.6 Å<sup>3</sup>),<sup>7</sup> although with a different shape.

In order to check the lithiation conditions before the reaction with quinidinone, a test reaction with trimethylsilyl chloride was performed. The lithiate was formed by the addition of *n*-butyllithium over one hour to 4-bromobenzotrifluoride at 0 °C, followed by stirring at 0 °C for one hour. After cooling to -78 °C, trimethylsilyl chloride was added over one hour and the reaction mixture was stirred at -78 °C for six hours before being quenched with water and worked up. No further purification of the test reaction crude product was carried out. Since the lithiation was successful the reaction was repeated using the same conditions, but replacing the trimethylsilyl chloride with quinidinone.

It was expected that the electron withdrawing effect of the trifluoromethyl group might decrease the nucleophilicity of the phenyl group, leading to a lower conversion than that observed for phenyllithium. For this reason, in addition to a lithiation step that did not give 100% conversion, the number of equivalents of lithiate was increased to four (for phenyllithium the optimum number of equivalents was two), and from Scheme 2.6, it can be seen that a similar conversion (57%) was obtained to the reaction with phenyllithium (55%).

The crude solid was purified by column chromatography on silica gel; after an initial short column to remove unreacted 4-bromobenzotrifluoride, a longer column was used with the same solvent system as that used for the isolation of 9-phenylquinidine

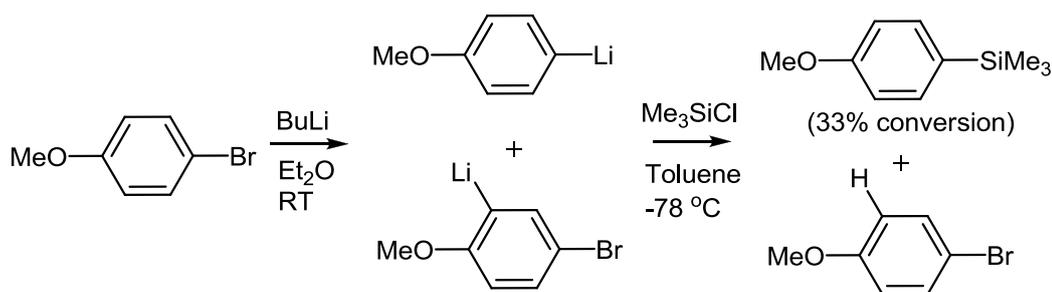
(toluene/diethyl ether/dichloromethane/triethylamine, 38/30/30/2). The 9-(4-trifluoromethylphenyl)quinidine (**70**) was also sandwiched between the quinidinone and quininone, which made mixed fractions inevitable, contributing to the moderate isolated yield.



**Scheme 2.7**

Following the successful addition of 4-trifluoromethylphenyllithium to the C9 position of quinidinone with higher than expected conversion, the next nucleophile to be investigated was 4-methoxyphenyllithium. The conversion was expected to be higher than that observed for the reaction with 4-trifluoromethylphenyllithium because the smaller size of methoxy compared with a trifluoromethyl group should lead to decreased steric hindrance, and the electron donating nature of the methoxy group would be expected to increase the nucleophilicity of the aryllithiate.

Initially, test reactions with trimethylsilyl chloride were performed to check that the lithiation step was working (Scheme 2.8). Test lithiations were carried out at -78 °C,<sup>8</sup> -40 °C, 0 °C,<sup>9</sup> and room temperature,<sup>10</sup> and the best results (highest conversion to desired *para*-lithiated product) were observed for the room temperature lithiation. The subsequent reaction with trimethylsilyl chloride was carried out at -78 °C as this temperature was to be used in the reaction with quinidinone. Since the reactions were only performed to test whether the lithiate could be formed under these conditions, and the compound formed was not new, no further purification of the product was carried out.

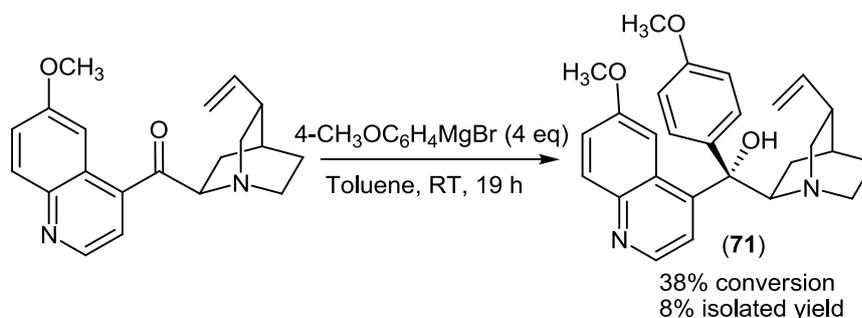


**Scheme 2.8**

The lithiate was formed by adding *n*-butyllithium over one hour to 4-bromoanisole at room temperature. The reaction mixture was stirred at room temperature for one hour to allow formation of the lithiate, before cooling to -78 °C and adding the quinidinone dropwise over one hour. After stirring the reaction mixture at -78 °C for six hours, it was quenched with water and worked up.

The conversion of the reaction was unexpectedly low. The crude <sup>1</sup>H NMR spectrum also showed the presence of 9-butylquinidine. An excess of 4-bromoanisole over butyllithium had been used to avoid the formation of 9-butylquinidine, suggesting that 4-bromoanisole did not lithiate as efficiently as 4-bromobenzotrifluoride. Consequently, when the reaction was repeated the first step was performed in toluene and heated to 50 °C to try to improve the lithiation,<sup>11</sup> but this was unsuccessful.

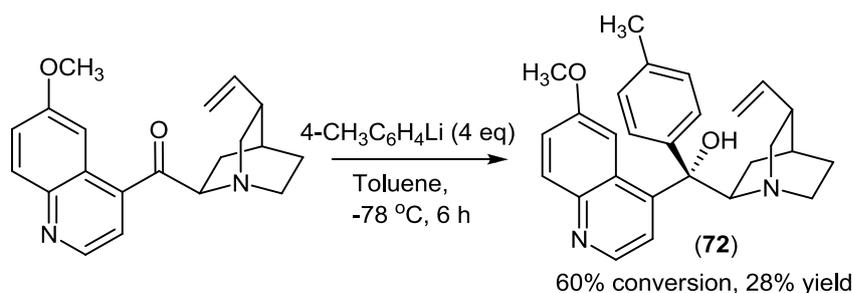
The low conversion of the reaction to desired product led to a difficult purification by column chromatography and a low isolated yield. The 9-(4-methoxyphenyl)quinidine (**71**) is eluted between the quinidinone and quininone fractions, and as there is only a very small amount present in the crude reaction mixture it is difficult to isolate the product without obtaining mixed fractions. Purification of the crude reaction mixture would possibly be easier if the conversion was improved, which could only be achieved by improving the efficiency of the lithiation step. As the directing effect of the methoxy group takes precedence over lithium-halogen exchange,<sup>12</sup> it is possible that *ortho*-lithiation is occurring faster than exchange with the bromine (demonstrated in Scheme 2.8 for the test reaction with trimethylsilyl chloride), and the resulting 5-bromo-2-methoxy-phenyllithium is too sterically hindered to add to the C9 carbonyl of quinidinone leading to a lower conversion. If this is the case, then optimisation of the lithiation step may not be possible, and so the reaction with the Grignard reagent, 4-methoxyphenylmagnesium bromide, was investigated.



Scheme 2.9

The Grignard reagent was formed by dropwise addition of 4-bromoanisole in diethyl ether to a flask containing magnesium turnings in diethyl ether, with vigorous stirring. After stirring for one hour at room temperature, the reaction mixture was refluxed until the magnesium turnings had been consumed. The reagent was then cooled to room temperature before the dropwise addition of quinidinone in toluene, after which the reaction mixture was stirred at room temperature overnight, quenched with water and worked up as usual.

Although the conversion was improved from 29% to 38%, the isolated yield of 9-(4-methoxyphenyl)quinidine (**71**) was not significantly improved (from 4% to 8%). It is unknown why the purification of 9-(4-methoxyphenyl)quinidine (**71**) by column chromatography on silica gel is more complicated than the purification of other 9-(4-substituted-phenyl)quinidines.



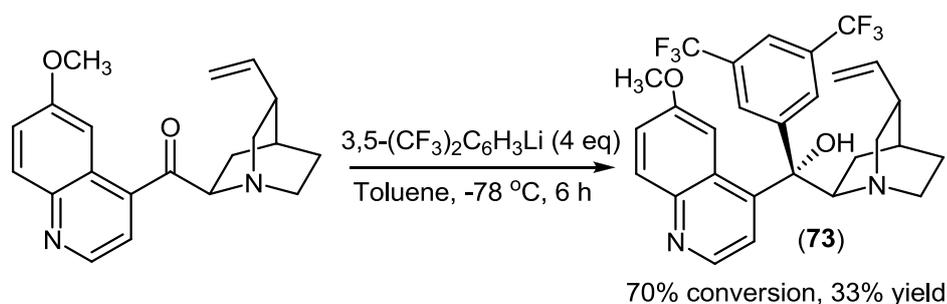
**Scheme 2.10**

The reaction of quinidinone with 4-methylphenyllithium was expected to proceed well due to the inductive electron donating effect of the methyl group increasing the nucleophilicity, and a methyl group having a lower steric effect than a trifluoromethyl group.

A test reaction with trimethylsilyl chloride was performed in order to check that the lithiation step was working. *n*-Butyllithium was added dropwise over 30 minutes to a stirred solution of 4-bromotoluene at room temperature (20 °C).<sup>13</sup> The reaction mixture was stirred at room temperature for 1.5 hours, before cooling to -78 °C. Trimethylsilyl chloride was then added dropwise over 40 minutes, and the reaction mixture was stirred at -78 °C for 6 hours before it was quenched and worked up as usual.

The test reaction with trimethylsilyl chloride was successful and so the reaction was repeated, replacing trimethylsilyl chloride with quinidinone. The conversion (60%)

was similar to that achieved with 4-trifluoromethylphenyllithium (57%). The crude product was successfully purified by column chromatography using the same solvent system used for the other 9-(4-substituted-phenyl)quinidines, toluene/dichloromethane/diethyl ether/triethylamine (38/30/30/2), and 9-(4-methylphenyl)quinidine (**72**) was isolated in 28% yield.



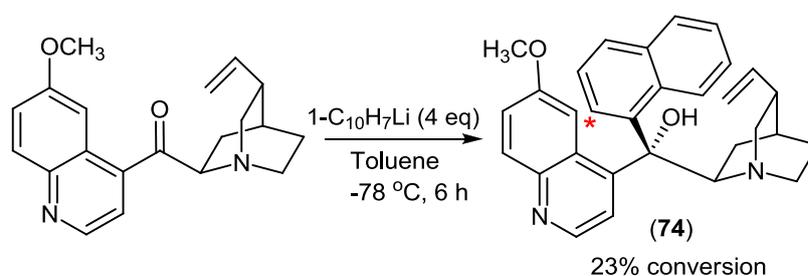
**Scheme 2.11**

To further increase the steric bulk, the next nucleophile to be added to the C9 position of quinidinone was 3,5-bis(trifluoromethyl)phenyllithium. The reaction was expected to have a low conversion due to the large increase in steric hindrance caused by the size of the two trifluoromethyl groups, in combination with their locations at the *meta* positions of the phenyl ring.

A test reaction was performed with trimethylsilyl chloride to ensure that the lithiation step was working before the reaction was attempted with quinidinone. An initial test reaction where the lithiation was performed at room temperature was unsuccessful, as the lithium exchanged with the acidic hydrogen *ortho* to the two CF<sub>3</sub> groups rather than with the bromine, and in the subsequent reaction there was too much steric hindrance to allow the trimethylsilyl group to react with the lithiate. The lithiation was therefore attempted at -78 °C. *n*-Butyllithium was added dropwise to a stirred solution of 3,5-bis(trifluoromethyl)bromobenzene at -78 °C and the reaction mixture was stirred at that temperature for 2 hours.<sup>14</sup> Trimethylsilyl chloride was then added dropwise at -78 °C, and the reaction mixture was stirred at -78 °C for 6 hours before being quenched with water and worked up as usual.

The reaction was then repeated, replacing trimethylsilyl chloride with quinidinone, and allowing the lithiation reaction mixture to stir for three hours rather than two to try and improve the conversion. The reaction conversion was 70%, which

was much better than expected for such a hindered nucleophile. The crude reaction mixture was purified by column chromatography using the same solvent system used for the other 4-substituted phenylquinidines, toluene/diethyl ether/dichloromethane/triethylamine (38/30/30/2), and 9-(3,5-bis(trifluoromethyl)phenyl)quinidine (**73**) was isolated in 33% yield.

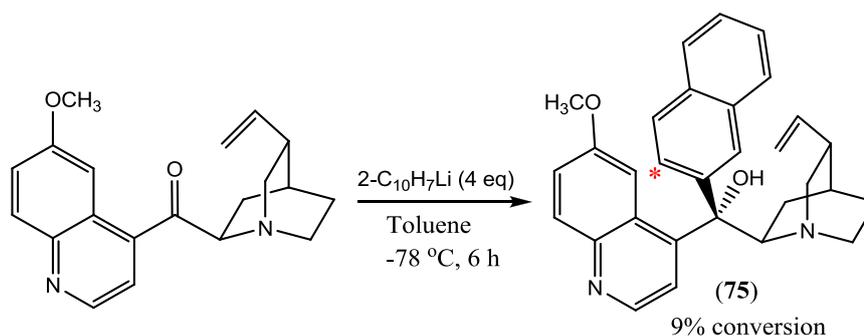


**Scheme 2.12**

To further increase the steric bulk of the substituent at the C9 position, the next nucleophile to be added was 1-naphthyllithium. The star in Scheme 2.12 indicates the hydrogen on the naphthyl ring which would experience steric congestion with H2, based on 3D models of the product. Due to this expected steric congestion, the conversion of the reaction was predicted to be lower than that observed for the other phenyllithium additions.

In order to pre-form the lithiate, *n*-butyllithium was added dropwise to a stirred solution of 1-bromonaphthalene in toluene at room temperature, before warming to approximately  $48\text{ }^\circ\text{C}$  and stirring at this temperature for one hour.<sup>15</sup> The lithiate was then cooled to  $-78\text{ }^\circ\text{C}$  before the dropwise addition of a solution of quinidinone in dry toluene. After stirring the reaction mixture at  $-78\text{ }^\circ\text{C}$  for six hours, it was quenched with water and worked up.

The conversion of the reaction was higher than expected (23%). However, it was not high enough to allow complete separation by column chromatography, and mixed fractions containing small amounts of quinidinone/quininone were obtained in addition to 9-(1-naphthyl)quinidine (**74**). Repeating the reaction at  $-40\text{ }^\circ\text{C}$  led to a similar conversion (21%). Performing the reaction at  $-40\text{ }^\circ\text{C}$  in diethyl ether/toluene (50/50) also led to no improvement in the conversion (22%).



Scheme 2.13

Based on the indications of 3D models that both 9-(1-naphthyl)quinidine and 9-(2-naphthyl)quinidine would have similar steric hindrance of H2 with the hydrogen at the position marked by a star in Scheme 2.13, the conversion of the reaction with 2-naphthyllithium was expected to be similar to the reaction with 1-naphthyllithium.

Due to the expectation that the reactions would be similar, no test reaction with trimethylsilyl chloride was carried out. This was a mistake, as the conversion of the reaction with quinidinone was only 9%, with the presence of 9-butylquinidine also observed in the crude  $^1\text{H}$  NMR spectrum, indicating a poor lithiation step. The 2-lithiated naphthalene should be more stable than the 1-lithiated naphthalene due to the absence of *peri*-interactions with the hydrogen at the 8 position.

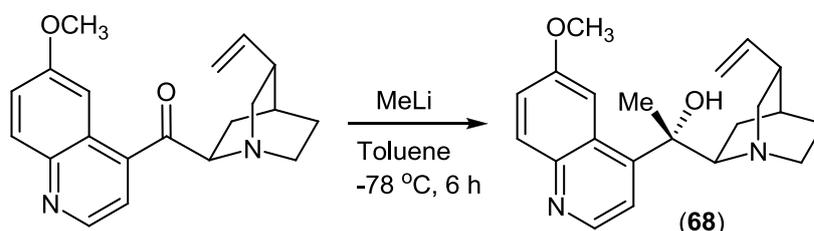
The conversion was considered too low to even attempt purification of 9-(2-naphthyl)quinidine (**75**) by column chromatography, and as further adjustments of the conditions for the lithiation step did not improve the conversion this reaction was not investigated further.

### 2.3.4 Nucleophilic additions of alkyl groups

Having successfully increased the conversion and isolated yield of the reaction to form 9-phenylquinidine by using the lithiate rather than the Grignard reagent, the methyl addition using the lithiate was also investigated to see whether similar improvements would be observed. The conversions were expected to be higher than those observed in the phenyllithium reactions because not only is the alkyl group expected to be more nucleophilic than the phenyl group, but also because conversions were higher for the methylmagnesium bromide reactions than for the phenylmagnesium bromide reactions.

However, as can be seen in Table 2.5, the conversions were lower than the reactions with methylmagnesium bromide (67-75%). In the phenyl additions the use of four equivalents of phenyllithium did not improve the conversion of the reaction, and was therefore a waste of the reagent. However, it was considered necessary to try using three equivalents of methyllithium to reach a balance where more equivalents had been tested without wasting too much of the reagent. Unfortunately, the conversion was not improved.

**Table 2.5:** The synthesis of 9-methylquinidine using MeLi



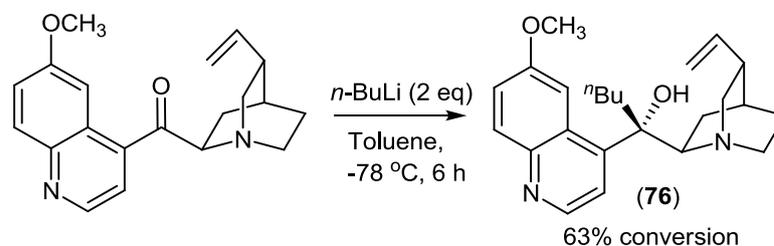
Entry	MeLi (no. equiv.)	Temperature (°C)	Conversion <sup>a</sup> (%)
1	2	-78	47 <sup>b</sup>
2	2	-78	50
3	3	-78	50

<sup>a</sup>determined by <sup>1</sup>H NMR spectroscopy; <sup>b</sup>inverse addition

The reaction with methyllithium at -78 °C was a less selective reaction compared to using methylmagnesium bromide and a by-product was formed which was either 9-(*R*)-methylquinidine, or possibly the result of methyl addition at the 2'-position of the quinoline ring. As the signals for the by-product appear to be similar to those of the major product, it is assumed that the by-product is more likely to be 9-(*R*)-methylquinidine, and that the addition of methyllithium is less diastereoselective than the addition of methylmagnesium bromide.

In addition to the reaction not being as selective, the conversion of the reaction was not improved and the product was not isolated. Recrystallisation of the crude oil from ethanol was unsuccessful. Attempts to triturate the crude oil to solidify it before recrystallisation failed, as did attempts to find an appropriate solvent system for purification using column chromatography. Therefore, it was concluded that although

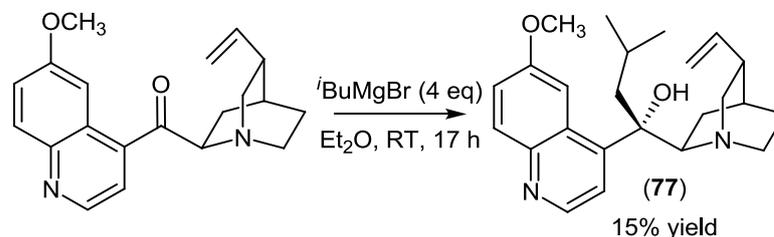
phenyllithium is a better reagent for the formation of 9-phenylquinidine (**69**) than phenylmagnesium bromide, methylmagnesium bromide is a better reagent for the formation of 9-methylquinidine (**68**) due to its higher selectivity and conversion to the desired product.



Scheme 2.14

To check that 9-*n*-butylquinidine (**74**) was the by-product formed in the nucleophilic addition of 4-methoxyphenyllithium to quinidinone due to an inefficient lithiation step, *n*-butyllithium was also reacted with quinidinone at  $-78\text{ }^\circ\text{C}$ .

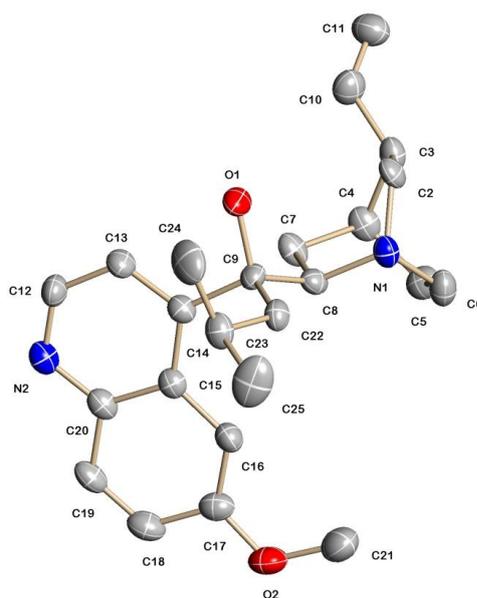
Quinidinone in toluene was added dropwise to a stirred solution of *n*-butyllithium at  $-78\text{ }^\circ\text{C}$ , and the reaction mixture was stirred for six hours at this temperature before being quenched with water and worked up as usual. Despite obtaining a reasonable conversion for the reaction (63%), it was not possible to completely isolate 9-*n*-butylquinidine by column chromatography, and mixed fractions containing mostly 9-*n*-butylquinidine with approximately 10% quinone/quinidinone contamination were obtained using the solvent system used for the 9-arylquinidines and similar solvent systems based upon this quaternary mixture.



Scheme 2.15

Since the pre-formation of lithiate reagents usually involves *n*-butyllithium, preparation of *i*-butyllithium and addition to quinidinone could have led to subsequent

mixtures of 9-*iso*-butyl-quinidine and 9-*n*-butylquinidine, which would further complicate an already complex purification and isolation procedure. Therefore, the Grignard reagent *iso*-butylmagnesium bromide was prepared in order to add a bulky aliphatic nucleophile to quinidinone. The Grignard reagent was prepared by dropwise addition of 1-bromo-2-methylpropane to a stirred suspension of oven dried magnesium turnings in diethyl ether, and subsequent stirring at room temperature for two hours. Quinidinone was added dropwise, and the reaction mixture was stirred at room temperature overnight before being quenched with water and worked up. The crude reaction mixture indicated the presence of a minor product that could have been either 9-(*R*)-*iso*-butylquinidine or a single diastereoisomer of 9-*iso*-butylquinine. The major product, 9-(*S*)-*iso*-butylquinidine (**77**), was isolated by recrystallisation from ethanol. The crystals were suitable for X-ray crystallography, and the molecular structure is shown in Figure 2.6.



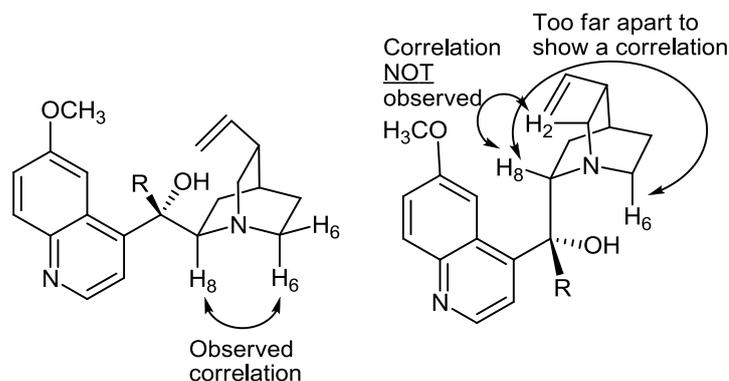
**Figure 2.6:** The molecular structure of 9(*S*)-*iso*-butylquinidine

### 2.3.5 NOESY spectra and optical rotations for 9-substituted quinidine derivatives

Table 2.6 shows the correlations observed in the NOESY spectra of 9-substituted-quinidine derivatives. All of the compounds show correlations of H8 with the *endo* H6 across the underside of the quinuclidine ring, which would be impossible in a quinine structure. Some compounds also show correlations of H8 with the *endo* H5, which would also be impossible in a quinine structure. These correlations strongly suggest a quinidine (*R*) configuration at C8, which is confirmed in the molecular structures of

9(*S*)-methylquinidine and 9(*S*)-*iso*-butylquinidine from X-ray crystallography. The absence of a correlation between H8 and H2, which would be expected in a quinine structure, also supports a quinidine structure.

**Table 2.6:** NOESY correlations for 9-substituted-quinidine derivatives



Compound	NOESY Correlations
9-Methylquinidine ( <b>68</b> )	H <sub>8</sub> →H <sub>6</sub> ( <i>endo</i> )
9-Phenylquinidine ( <b>69</b> )	H <sub>8</sub> →H <sub>6</sub> ( <i>endo</i> )
	H <sub>8</sub> →H <sub>5</sub> ( <i>endo</i> )
9-(4-Trifluoromethylphenyl)quinidine ( <b>70</b> )	H <sub>8</sub> →H <sub>6</sub> ( <i>endo</i> )
9-(4-Methoxyphenyl)quinidine ( <b>71</b> )	H <sub>8</sub> →H <sub>6</sub> ( <i>endo</i> )
	H <sub>8</sub> →H <sub>5</sub> ( <i>endo</i> )
9-(4-Methylphenyl)quinidine ( <b>72</b> )	H <sub>8</sub> →H <sub>6</sub> ( <i>endo</i> )
9-(3,5-Bis-trifluoromethylphenyl)quinidine ( <b>73</b> )	H <sub>8</sub> →H <sub>6</sub> ( <i>endo</i> )

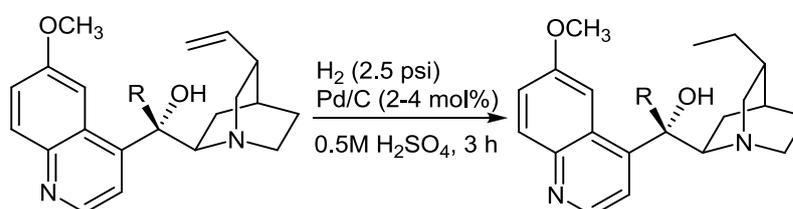
Table 2.7 shows the optical rotation values for the new 9-substituted quinidine derivatives. In contrast to quinine, which has a high negative optical rotation of  $-114.9^\circ$ , the new compounds all have high positive optical rotations more similar to quinidine, which has a high positive optical rotation of  $+194.8^\circ$ . This is further support for the quinidine (*R*) configuration at C8 for all of the compounds.

Although the NOESY spectra and optical rotation values do not help with the establishment of the configuration at C9 in the 9-substituted-quinidine derivatives, all of the new compounds are assumed to have an (*S*) configuration at C9 by analogy with the proposed Chelation Control mechanism, supported by the molecular structures of 9(*S*)-methylquinidine and 9(*S*)-*iso*-butylquinidine.

**Table 2.7:** Optical rotations of 9-substituted quinidine derivatives

Compound	Optical Rotation (°)
Quinine ( <b>26</b> )	-114.9
Quinidine ( <b>27</b> )	+194.8
Quinidinone ( <b>62</b> )	+182.5
9-MeQdine ( <b>68</b> )	+158.6
9- <i>Iso</i> -butylquinidine ( <b>77</b> )	+132.5
9-PhQdine ( <b>69</b> )	+226.4
9-(4OCH <sub>3</sub> )Qdine ( <b>71</b> )	+222.7
9-(4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )Qdine ( <b>72</b> )	+217.7
9-(4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )Qdine ( <b>70</b> )	+186.2
9-(3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> )Qdine ( <b>73</b> )	+119.0

## 2.4 Synthesis of 10,11-dihydro-quinidine derivatives

**Table 2.8:** Hydrogenation of C9-substituted quinidine derivatives

Entry	R group	Isolated Yield (%)
1	H ( <b>31</b> )	80
2	CH <sub>3</sub> ( <b>78</b> )	79
3	Ph ( <b>79</b> )	75
4	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>80</b> )	72
5	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>81</b> )	64
6	3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> ( <b>82</b> )	51

The literature on asymmetric fluorination suggests that the increased steric bulk resulting from the presence of an ethyl rather than a vinyl group at C10-C11 of *Cinchona* alkaloid derivatives can lead to an increase of approximately 10% in the enantiomeric excess achieved when they are used as enantioselective electrophilic fluorinating reagents. Using a method adapted from the literature procedure by Blaser,<sup>16</sup>

quinine (**26**), quinidine (**27**), 9-methylquinidine (**68**), 9-phenylquinidine (**69**), 9-(4-methylphenyl)quinidine (**72**), 9-(4-trifluoromethylphenyl)quinidine (**70**) and 9-(3,5-bis-trifluoromethylphenyl)quinidine (**73**) have been hydrogenated to their corresponding 10,11-dihydro derivatives. This was accomplished by dissolving the compound in sulphuric acid (0.5 M) and shaking under pressure of hydrogen (approximately 2.5 psi) in the presence of 2-4 mol% Pd/C catalyst for three hours. The solution was then filtered from the catalyst, neutralised with sodium hydroxide solution, and the precipitate collected and dried under vacuum to yield the hydrogenated product.

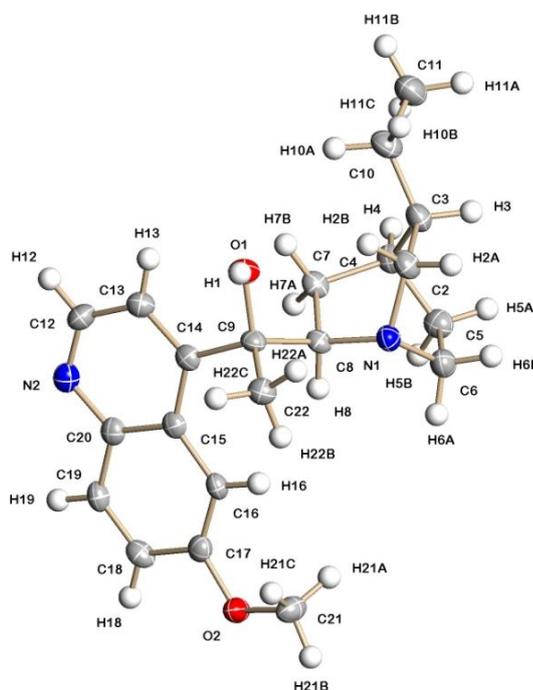
Quinine, quinidine, 9-methylquinidine and 9-phenylquinidine were completely hydrogenated using 2 mol% Pd/C. After several incomplete hydrogenations of the substituted phenyl quinidine derivatives which required a re-hydrogenation leading to decreased yield (due to two workups), the catalyst loading was increased to 4 mol% for the subsequent hydrogenations of 9-(4-methylphenyl)quinidine, 9-(4-trifluoromethylphenyl)quinidine and 9-(3,5-bis-trifluoromethylphenyl)quinidine. The hydrogenations of the bulkier quinidine derivatives using 4 mol% catalyst then proceeded with complete conversion. All of the products, dihydroquinine (**30**), dihydroquinidine (**31**), 9-methyl-10,11-dihydroquinidine (**78**), 9-phenyl-10,11-dihydroquinidine (**79**), 9-(4-methylphenyl)-10,11-dihydroquinidine (**80**), 9-(4-trifluoromethylphenyl)-10,11-dihydroquinidine (**81**) and 9-(3,5-bis-trifluoromethylphenyl)-10,11-dihydroquinidine (**82**), were isolated in good yield (51-80%) (Table 2.8).

**Table 2.9:** Optical rotations of 9-substituted-10,11-dihydroquinidine derivatives

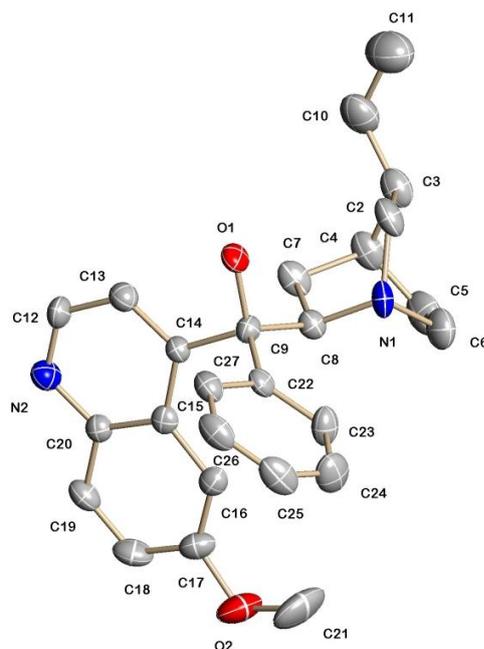
Compound	Optical Rotation (°)
Quinine ( <b>26</b> )	-114.9
10,11-Dihydroquinine ( <b>30</b> )	-91.1
Quinidine ( <b>27</b> )	+194.8
10,11-Dihydroquinidine ( <b>31</b> )	+173.1
9-Me-10,11-DHQdine ( <b>78</b> )	+122.1
9-Ph-10,11-DHQdine ( <b>79</b> )	+213.0
9-(4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )-10,11-DHQdine ( <b>80</b> )	+161.9
9-(4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )-10,11-DHQdine ( <b>81</b> )	+135.9
9-(3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> )-10,11-DHQdine ( <b>82</b> )	+120.9

The optical rotation values for the 10,11-dihydroquinidine derivatives are shown in Table 2.9. The high positive values, similar to those for quinidine and dihydroquinidine, and opposite to the high negative values for quinine and dihydroquinine, suggest that the configuration at the C8 position does not change during hydrogenation.

Crystals of 9(*S*)-methyl-10,11-dihydroquinidine (**78**) and 9(*S*)-phenyl-10,11-dihydroquinidine (**79**) suitable for X-ray crystallography were obtained by slow recrystallisation from ethanol. The molecular structures are shown in Figures 2.7 and 2.8.



**Figure 2.7:** The molecular structure of 9(*S*)-methyl-10,11-dihydroquinidine



**Figure 2.8:** The molecular structure of 9(*S*)-phenyl-10,11-dihydroquinidine

The (*S*) configuration at C9 and (*R*) configuration at C8 in 9(*S*)-methyl-10,11-dihydroquinidine confirm that the configuration of the molecule did not change during hydrogenation. Therefore, the (*S*) configuration at C9 and the (*R*) configuration at C8 in 9(*S*)-phenyl-10,11-dihydroquinidine strongly suggests that the same configuration existed in 9-phenylquinidine, which indicates that the chelation control mechanism does not just apply to the addition of alkylmagnesium bromides to quinidinone, but also to the addition of phenyllithium and aryllithiates to quinidinone.

## 2.5 Examination of molecular structures of 9-substituted quinidine derivatives

Table 2.10 shows some selected bond lengths in the molecular structures of the 9-substituted quinidine derivatives 9-methylquinidine (9MeQdine), 9-methyl-10,11-dihydroquinidine (9MeDHQdine), 9-phenyl-10,11-dihydroquinidine (9PhDHQdine) and 9-*iso*-butylquinidine (9<sup>*i*</sup>BuQdine). The literature data for quinidine<sup>17</sup> is given for comparison. It can be clearly seen that hydrogenation of the C10-C11 double bond, as expected, results in the lengthening of the bond (9-methylquinidine C10-C11 1.301 Å, 9-methyl-10,11-dihydroquinidine C10-C11 1.514 Å). Different substituents at C9 do not appear to have large effects on the bond lengths around the quaternary centre, although the bond between C9 and the quinoline ring (C9-C14) appears to be slightly

longer in the case of the smaller methyl substituent than for the bulkier *iso*-butyl and phenyl substituents.

**Table 2.10:** Selected bond lengths (Å) in the molecular structures of 9-substituted quinidine derivatives

Compound	Bond Length (Å)				
	C10-C11	C9-O1	C9-C22	C8-C9	C9-C14 (C4')
Quinidine <sup>a</sup> ( <b>27</b> )	1.260 (6)	1.423 (4)	-	1.534 (4)	1.525 (4)
9MeQdine ( <b>68</b> )	1.301(6)	1.440(4)	1.540(5)	1.538(5)	1.540(5)
9MeDHQdine ( <b>78</b> )	1.514(4)	1.426(3)	1.536(4)	1.546(4)	1.551(4)
9PhDHQdine ( <b>79</b> )	1.485(5)	1.427(3)	1.537(4)	1.546(4)	1.525(4)
9 <sup>i</sup> BuQdine ( <b>77</b> )	1.297(6)	1.423(4)	1.545(5)	1.541(5)	1.527(5)

<sup>a</sup>Data taken from reference 17

**Table 2.11:** Selected bond angles within the quinuclidine ring in the molecular structures of 9-substituted quinidine derivatives

Compound	Bond Angle (°)			
	C6-N1-C2	C8-N1-C2	C7-C4-C3	C5-C4-C3
Quinidine <sup>a</sup> ( <b>27</b> )	107.5 (2)	111.2 (2)	109.8 (2)	108.1 (2)
9MeQdine ( <b>68</b> )	106.8(3)	111.1(3)	108.8(3)	108.4(4)
9MeDHQdine ( <b>78</b> )	107.3(2)	111.2(2)	108.9(2)	108.4(2)
9PhDHQdine ( <b>79</b> )	106.1(3)	111.2(3)	108.9(3)	107.5(3)
9 <sup>i</sup> BuQdine ( <b>77</b> )	106.2(3)	111.7(3)	109.1(3)	107.6(3)

<sup>a</sup>Data taken from reference 17

Table 2.11 shows selected bond angles within the quinuclidine ring from the molecular structures of the 9-substituted quinidine derivatives. The differences in bond angles demonstrate the twist in the quinuclidine ring, which reduces excess ring strain allowing the CH<sub>2</sub> groups to approach staggered conformations.<sup>18</sup> Different substitution at C9 does not appear to cause a large alteration in this ring twist, as the angles are similar for all of the 9-substituted compounds, and for quinidine.

Table 2.12 shows selected bond angles around the C9 quaternary carbon in the molecular structures of the 9-substituted quinidine derivatives. Unusually, although the

bulky *iso*-butyl substituent appears to widen the angle between the hydroxyl oxygen, C9 and C22 (the *iso*-butyl carbon bonded to C9), the bulky phenyl substituent has a similar angle to that of the methyl substituent. This could be due to the possibility of rotation about the *iso*-butyl bonds making it a more flexible bulky substituent than the more rigid phenyl group. The bulkier phenyl and *iso*-butyl substituents appear to widen the angle between the quinuclidine and quinoline rings across C9 (C8-C9-C14), and also slightly increase the angle of C7-C8-C9, which indicates a small alteration in the conformation of the quinuclidine ring. As a result, the angle N1-C8-C9 is slightly decreased for the bulkier substituents *iso*-butyl and phenyl. Quinidine has a shallower N1-C8-C9 angle than the 9-substituted derivatives. It has a similar angle for C7-C8-C9, although its C8-C9-C14 angle is interestingly more similar to those of the bulkier substituted analogues 9-*iso*-butyl quinidine and 9-phenyl-quinidine than to those of the methyl substituted analogues.

**Table 2.12:** Selected bond angles around the quaternary carbon at C9 in the molecular structures of 9-substituted quinidine derivatives

Compound	Bond Angle (°)				
	C9-C8-H8	O1-C9-C22	C8-C9-C14	C7-C8-C9	N1-C8-C9
Quinidine <sup>a</sup> ( <b>27</b> )	-	-	109.2(2)	113.6(2)	112.6(2)
9MeQdine ( <b>68</b> )	106.0	107.6(3)	107.2(3)	112.4(3)	115.4(3)
9MeDHQdine ( <b>78</b> )	106.2	107.9(2)	106.6(2)	112.9(2)	114.5(2)
9PhDHQdine ( <b>79</b> )	106.1	107.2(3)	108.5(3)	114.4(3)	113.9(3)
9 <sup>i</sup> BuQdine ( <b>77</b> )	105.8	109.8(3)	109.6(3)	114.4(3)	113.9(3)

<sup>a</sup>Data taken from reference 17

Table 2.13 shows selected torsion angles in the molecular structures of 9-substituted quinidine derivatives. The variation in the torsion angle N1-C2-C3-C4 is a further indication of the ring twist in the quinuclidine ring, which must be affected more by substitution than can be seen by bond angles around the ring.

A comparison of the C8-C9-C14-C13 (C14 is C4' and C13 is C3') torsion angle in quinidine (-99.3°) with those of the 9-substituted quinidine derivatives (-107.9 to -118.2°) demonstrates the substantial difference made by the presence of a quaternary carbon at the C9 position to the preferred conformation of the molecule. This is also

demonstrated by comparison between the N1-C8-C9-O1 torsion angles of quinidine (75.9°), and the 9-substituted analogues, where methyl substitution at the C9 position does not lead to as large a bond rotation (9-methylquinidine 72.0°, 9-methyl-10,11-dihydroquinidine 74.2°) as the introduction of bulkier substituents such as phenyl (60.5°) or *iso*-butyl (65.2°) groups.

**Table 2.13:** Selected torsion angles in molecular structures of 9-substituted quinidine derivatives

Compound	Torsion Angle (°)					
	C8-C9-C14-C13	N1-C8-C9-C14	O1-C9-C14-C13	N1-C8-C9-O1	C22-C9-C14-C13	N1-C2-C3-C4
Quinidine <sup>a</sup> ( <b>27</b> )	-99.3 (3)			75.9 (3)		
9MeQdine ( <b>68</b> )	-109.3(4)	-171.9(3)	7.1(5)	72.0(4)	126.2(4)	11.3(5)
9MeDHQdine ( <b>78</b> )	-107.9(3)	-170.5(2)	8.5(3)	74.2(3)	127.7(3)	12.4(3)
9PhDHQdine ( <b>79</b> )	-109.0(3)	175.3(3)	8.5(4)	60.5(3)	124.2(3)	19.1(4)
9 <sup>i</sup> BuQdine ( <b>77</b> )	-118.2(4)	-179.7(3)	-0.7(4)	65.2(4)	118.7(4)	15.4(4)

<sup>a</sup>Data taken from reference 17

In all four examples the torsion angle of  $\pm 170.5$ -179.7 for N1-C8-C9-C14 indicates that the quinuclidine nitrogen is *anti/trans* to the quinoline ring, which indicates an open conformation.<sup>19</sup> The torsion angles of -107.9-118.2° for C8-C9-C14-C13 indicate an *anti* conformation.<sup>18</sup> This is supported by the torsion angles of 118.7-127.7° for C22-C9-C14-C13 (C22 is the substituent carbon that is bonded to C9) and  $\pm 0.7$ -8.5° for O1-C9-C14-C13.

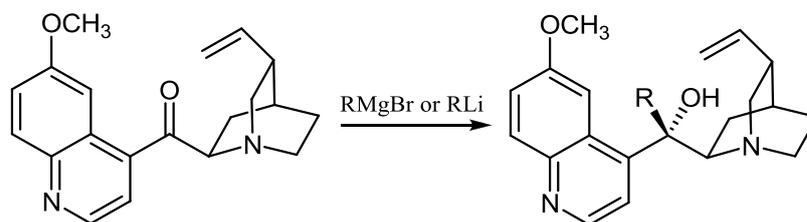
Therefore the preferred conformations, in the solid state, of 9(*S*)-methylquinidine, 9(*S*)-methyl-10,11-dihydroquinidine, 9(*S*)-phenyl-10,11-dihydroquinidine and 9(*S*)-*iso*-butylquinidine are *anti*-open. This is the same preferred conformation as quinidine in the solid state.

## 2.6 Conclusions

Table 2.14 summarises the results of the diastereoselective addition of Grignard reagents and aryllithiates to the carbonyl group of quinidinone in order to form a small library of 9-substituted quinidine analogues. Generally, aliphatic additions such as the

addition of a methyl group are best performed using a Grignard reagent, such as methylmagnesium bromide. When methyllithium was used, the reaction had a low conversion, a byproduct was formed even at  $-78^{\circ}\text{C}$ , and 9-methylquinidine could not be isolated. A good conversion was observed in the reaction with *n*-butyllithium but further investigation into chromatography conditions is needed in order to allow complete purification. 9-*Iso*-butylquinidine was formed successfully in the reaction with *iso*-butylmagnesium bromide, and was isolated in 15% yield by recrystallisation.

**Table 2.14:** Summary of nucleophilic additions to quinidinone



Entry	Nucleophile (R)	Conversion (%)	Isolated yield (%)
1	MeMgBr	67	56
2	PhLi	55	38
3	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> Li	57	24
4	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> Li	60	28
5	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> Li	29	4
6	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> MgBr	38	8
7	3,5- (CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> Li	70	33
8	<i>iso</i> -BuMgBr	60	15
9	<i>n</i> -BuLi	63	N/A
10	1-naphthyllithium	23	N/A
11	2-naphthyllithium	9	N/A

The addition of aromatic nucleophiles such as a phenyl group generally proceeds well using an aryl lithiate. The higher reactivity improves the conversion of the reaction significantly and allows the purification to be performed by column chromatography. However, the reaction must be performed at low temperature in order to avoid the formation of by-products, possibly due to the reaction of the nucleophile at the 2' position of the quinoline ring. 4-Methoxyphenyllithium appears to be an exception to the general rule; probably due to problems with the lithiation step. In this case, the

reaction with the Grignard reagent gave a better conversion (38%) but there were still problems with the purification of the product.

Even the reaction of quinidinone with 3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>Li gave a good conversion despite the increased steric hindrance caused by the two large trifluoromethyl groups, which would also be expected to decrease the nucleophilicity of the group due to the electron withdrawing effect of fluorine. Unfortunately, bulkier nucleophiles such as 1-naphthyl and 2-naphthyl groups led to a significant decrease in the reaction conversion, which in turn led to complicated purification. 9-(1-Naphthyl)quinidine was not isolated completely pure, the final product contained approximately 15% quinidinone/quininone, and the conversion to 9-(2-naphthyl)quinidine was so low (9%) that further purification was not attempted.

The generally moderate conversions of Grignard and lithiate reactions with quinidinone (55-70%) could be due to a competing deprotonation by the reagents, which can act as bases in addition to nucleophiles. The enolate which forms by deprotonation of H8 would not be re-protonated under the reaction conditions until the aqueous workup, and would not be reactive towards nucleophiles. This could also explain why increasing the number of equivalents of nucleophile did not significantly increase the conversion of the reaction, as some of the nucleophile is also acting as a base, and adding more is also facilitating the competing enolisation reaction.

A small library of 9-substituted-10,11-dihydroquinidine derivatives has also been developed by selective hydrogenation of the C10-C11 double bond of 9-substituted-quinidine derivatives, generating the hydrogenated compounds in good isolated yields (51-80%).

The evidence of the NOESY spectra strongly suggest that the quinidine, rather than the quinine, structures were being formed. This is supported by the molecular structures of 9(*S*)-methylquinidine and 9(*S*)-*iso*-butylquinidine, in addition to the molecular structures of 9(*S*)-methyl-10,11-dihydroquinidine and 9(*S*)-phenyl-10,11-dihydroquinidine, which all show a quinidine (*R*) configuration at C8. The molecular structures of these compounds also all show a (*S*) configuration at C9, which supports the proposed Chelation Control mechanism of nucleophilic addition to quinidinone.

An examination of the molecular structures of 9(*S*)-methylquinidine, 9(*S*)-methyl-10,11-dihydroquinidine, 9(*S*)-phenyl-10,11-dihydroquinidine and 9(*S*)-*iso*-butylquinidine indicates that all four compounds have a preferred *anti*-open conformation in the solid state.

**2.7 References for chapter two**

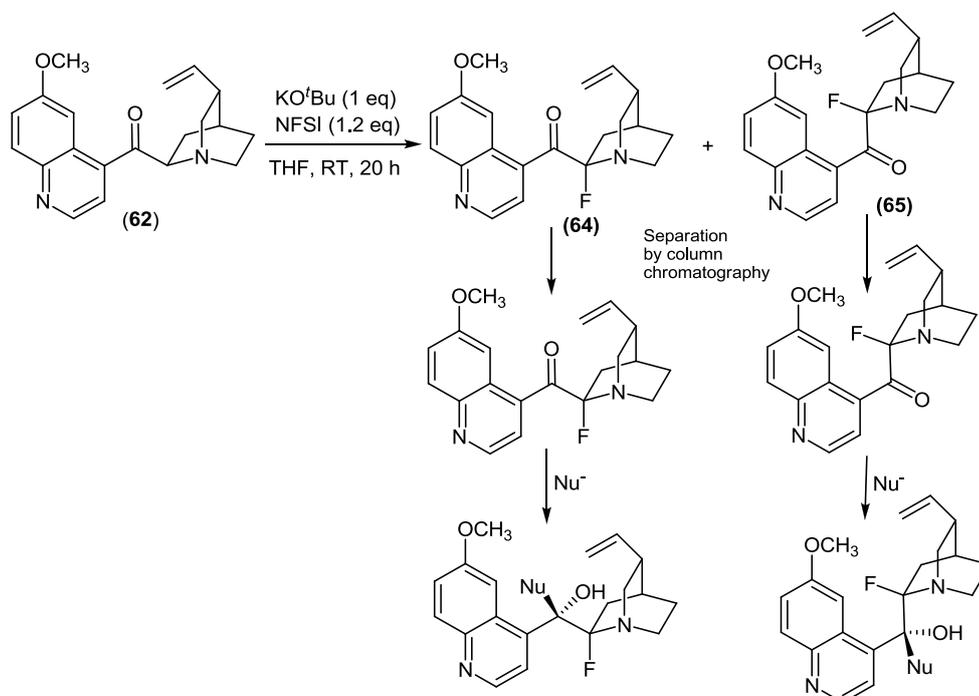
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### 3.1 Introduction

#### 3.1.1 Aims of the chapter

This chapter will investigate the fluorination of quinidinone (**62**) and quininine (**63**) at the C8 position. Fluorination at C8 will prevent the epimerisation between quinidinone and quininine, which in the nucleophilic additions to quinidinone led to complicated purification and low isolated yields. 8-Fluoroquinidinone (**64**) and 8-fluoroquininine (**65**) are diastereoisomers which should be able to be separated by column chromatography. After separation, both diastereoisomers will be used to undergo nucleophilic addition reactions at the C9 carbonyl as previously observed with quinidinone, to develop a series of 9-substituted-8-fluoroquinidine and 9-substituted-8-fluoroquinine analogues for use as enantioselective fluorinating reagents and anti-malarial compounds (Scheme 3.1).



**Scheme 3.1**

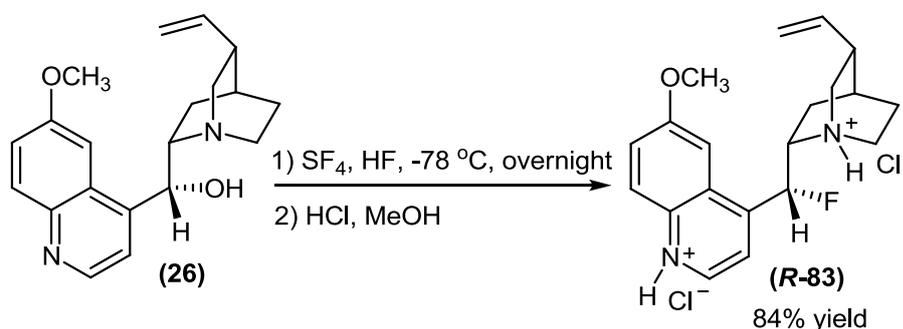
The major advantage of the 8-fluoro derivatives is that by reacting 8-fluoroquininine (**65**) with nucleophiles, 8-fluoroquinine analogues will be accessible, whereas the diastereoselective formation of quinidinone only allowed access to quinidine derivatives. Access to quinine derivatives is advantageous as a wider range of potential fluorinating reagents can be developed, and the quinine analogues should allow access to the opposite enantiomer of the product, or lead to improved enantiomeric excess compared to those of quinidine. It is also possible that a different

configuration could lead to different antimalarial activity depending on how the compounds interact with the malaria parasite. The aims of the chapter are summarised in Scheme 3.1.

### 3.1.2 Examples of fluorinated *Cinchona* alkaloids

Examples of fluorination of the *Cinchona* alkaloids in the literature are rare. Most examples appear to involve fluorination at the C9 position, with replacement of the C9 hydroxyl group with a fluorine atom being the most common example.

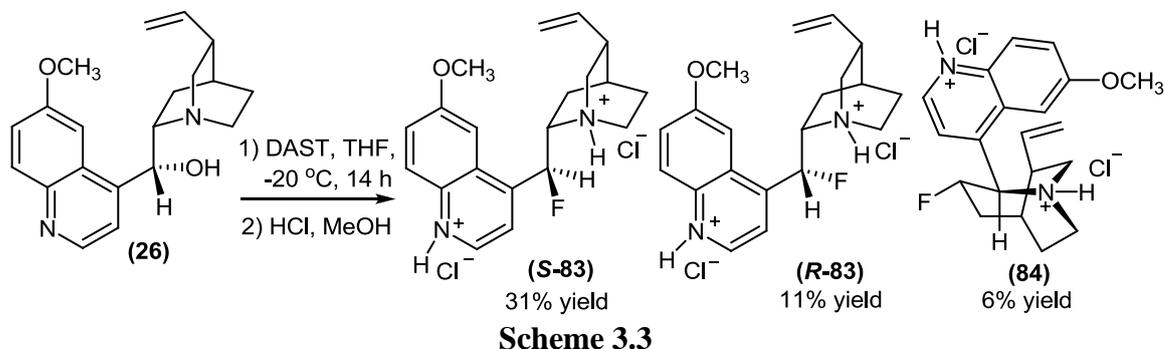
Kollonitsch<sup>1</sup> originally developed the method of fluorodehydroxylation, the process of transforming hydroxyamines and hydroxyamino acids into fluoroamines and fluoroamino acids, using sulphur tetrafluoride (SF<sub>4</sub>) in liquid HF at -78 °C at atmospheric pressure. Fluorinations using SF<sub>4</sub> were usually performed at 50-150 °C in a sealed container under pressure. Among various other examples of hydroxyamine fluorodehydroxylation, the C9 hydroxyl group of quinine (**26**) was replaced with fluorine to form a single diastereoisomer of deoxyfluoroquinine (**83**) in 84% isolated yield (Scheme 3.2).



**Scheme 3.2**

Gilmour,<sup>2</sup> using milder reaction conditions, fluorinated the C9 position of the *Cinchona* alkaloids using direct nucleophilic deoxyfluorination. After a screening process that identified THF as the best solvent for the reaction, the fluorination was carried out on quinine using DAST (diethylaminosulfur trifluoride) as the nucleophilic source of fluorine. Three distinct products were isolated; the inversion product (fluoroquinine **83** with an *S* configuration at C9), the retention product (fluoroquinine **83** with an *R* configuration at C9) and a ring-expanded 1-azabicyclo[3.2.2]nonane product with fluorine at the C3 position (**84**) (Scheme 3.3). The products were converted to their hydrochloride salts and analysed by X-ray crystallography, which showed that although the fluorine at C9 adopts a *gauche* configuration relative to the

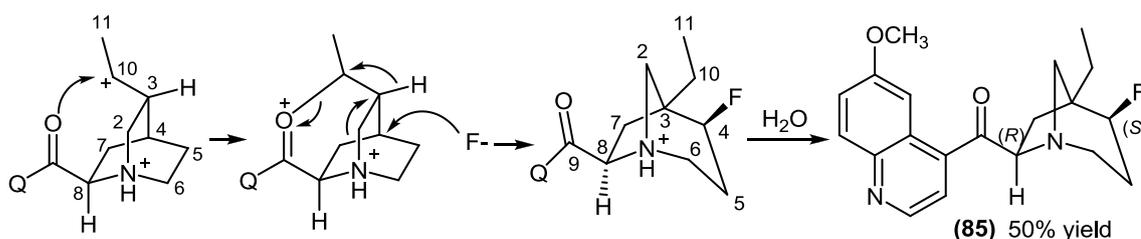
protonated quinuclidine nitrogen in both isomers of 9-fluoroquinine, in the ring expanded product the fluorine adopts an *anti* configuration relative to the protonated quinuclidine nitrogen, the first example of its kind to be observed.



The procedure was then expanded to include the rest of the *Cinchona* alkaloid series (10,11-dihydroquinine (**30**), quinidine (**27**), 10,11-dihydroquinidine (**31**), cinchonidine (**28**), 10,11-dihydrocinchonidine (**32**), cinchonine (**29**) and 10,11-dihydrocinchonine (**33**)). It was found that substrates lacking the 6'-methoxy group only gave the retention product rather than a mixture of 9-fluoroquinine diastereoisomers, and that cinchonidine gave the ring expanded product as the major component.

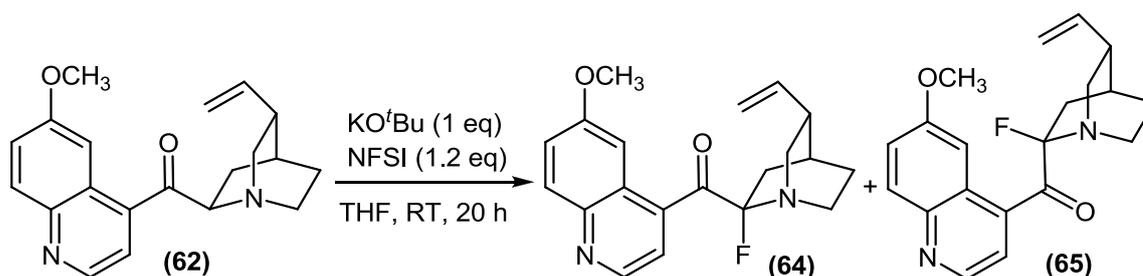
All of the deoxyfluorinated products were then tested for anti-malarial activity against the NF54 strain of malaria parasite *Plasmodium Falciparum* (which is sensitive to all known antimalarials). The results showed that the intact 1-azabicyclo[2.2.2]core is required for drug efficacy, as the ring expanded systems resulted in a substantial loss of antiplasmodial activity. It was also discovered that quinidine based structures showed an enhanced bioactivity relative to quinine based structures.

Jouannetaud<sup>3</sup> performed the fluorination of quinidinone in superacid, demonstrating that in HF/SbF<sub>5</sub> in a molar ratio of 25:1 at -78 °C quinidinone rearranges to an azabicyclo[3,2,1]octane, with fluorination at the C4 position (**85**). The mechanism is thought to involve protonation of the C10-C11 double bond, followed by a 1,2-hydride shift from C3 to C10 concerted with the migration of the C4-C7 carbon bond to C3, and nucleophilic attack of a fluoride ion at C4 leading to a precursor of the product (Scheme 3.4).



Scheme 3.4

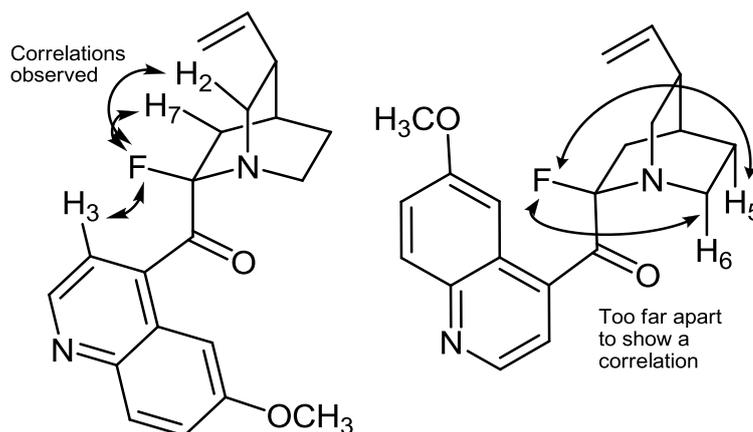
### 3.2 Synthesis of 8-fluoroquinidinone (**64**) and 8-fluoroquininone (**65**)



Scheme 3.5

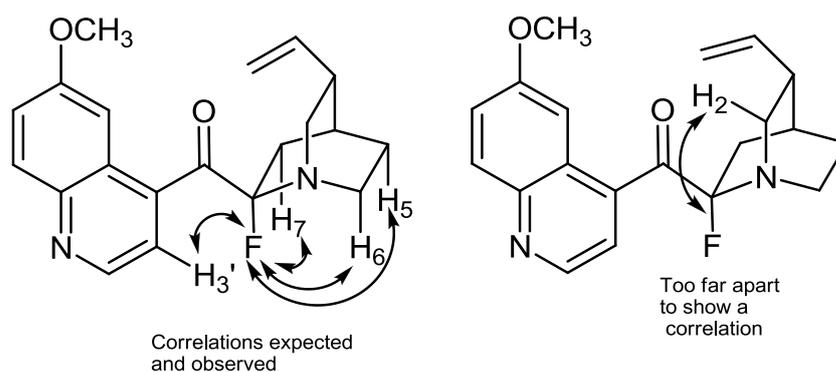
Quinidinone (**62**) was stirred in THF at room temperature, and the non-nucleophilic base, potassium *tert*-butoxide, was added in order to form the planar enolate without nucleophilic attack at the carbonyl group. *N*-Fluorobenzenesulfonimide (NFSI) was added, which acts as an electrophilic source of fluorine, and because the enolate is planar the fluorine added to the *endo* and *exo* position of C8, giving an approximately 50:50 mixture of 8-fluoroquinidinone and 8-fluoroquininone. The presence of fluorine at the C8 position stopped both diastereoisomers from being able to epimerise to the other diastereoisomer, as there was no hydrogen to remove. Consequently, the two diastereoisomers were separated by column chromatography using chloroform/ethyl acetate (80/20).

$^{19}\text{F}$ - $^1\text{H}$  HOESY spectroscopy was used to assign the two diastereoisomers as 8-fluoroquinidinone (**64**) or 8-fluoroquininone (**65**). The correlations are illustrated in Figures 3.1 and 3.2. The first diastereoisomer to elute from the column was assigned as 8-fluoroquininone (**65**), and the second diastereoisomer to elute was assigned as 8-fluoroquinidinone (**64**).



**Figure 3.1:** Correlations observed in the  $^{19}\text{F}$ - $^1\text{H}$  HOESY spectrum of 8-fluoroquininone (65)

The  $^{19}\text{F}$ - $^1\text{H}$  HOESY spectrum of 8-fluoroquininone showed a correlation between the fluorine and one of the H<sub>2</sub> protons and the *exo* H<sub>7</sub> proton. This HOESY also showed a correlation between the fluorine and H<sub>3</sub>' , which is possible due to rotation around the C<sub>9</sub>-C<sub>4</sub>' bond. The correlations are illustrated in Figure 3.1. The correlations of the fluorine atom to both H<sub>2</sub> and the *exo* H<sub>7</sub> strongly suggests a quinine configuration at C<sub>8</sub>.

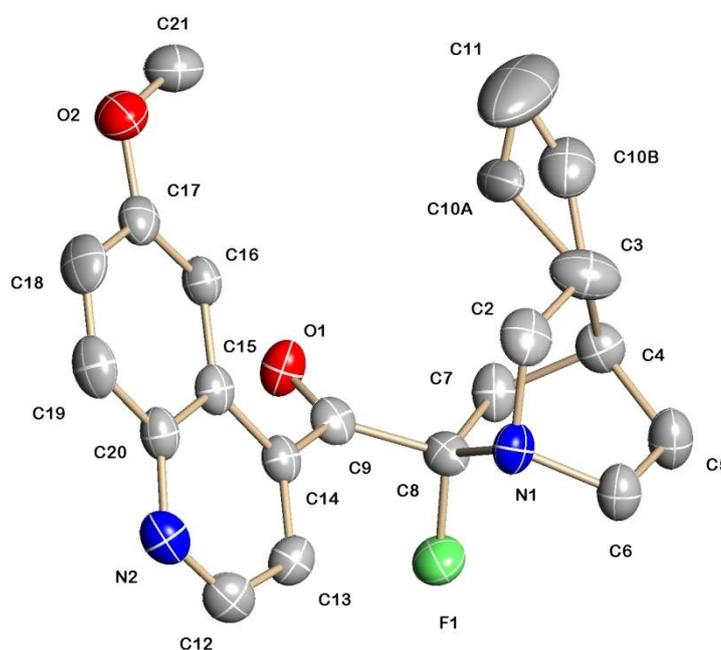


**Figure 3.2:** Correlations observed in the  $^{19}\text{F}$ - $^1\text{H}$  HOESY spectrum of 8-fluoroquinidinone (64)

The  $^{19}\text{F}$ - $^1\text{H}$  HOESY spectrum of 8-fluoroquinidinone (64) showed a correlation between the fluorine and the *endo* H<sub>5</sub> proton, the *endo* H<sub>6</sub> proton, and the *endo* H<sub>7</sub> proton. It also showed a correlation between the fluorine and H<sub>3</sub>' , possibly suggesting that the compound is not as free rotating as the non-fluorinated quinidine analogues

previously studied by NOESY spectroscopy (as were this the case a correlation would also be expected to H5'). The correlations are illustrated in Figure 3.2. The correlations of the fluorine atom to the *endo* protons under the quinuclidine ring strongly suggest a quinidine configuration at C8.

Usually the column gave more 8-fluoroquininone (**65**) than 8-fluoroquinidinone (**64**), but the mixed fractions obtained could be recrystallised from acetonitrile to yield more 8-fluoroquinidinone. Crystals suitable for X-ray crystallography were grown by slow evaporation from a solution of 8-fluoroquinidinone in acetonitrile and the molecular structure is shown in Figure 3.3. The solid state structure confirmed the initial assignment of the diastereoisomers by  $^{19}\text{F}$ - $^1\text{H}$  HOESY spectroscopy.

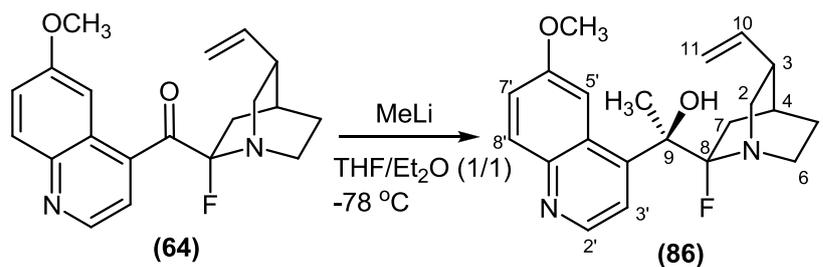


**Figure 3.3:** The molecular structure of 8-fluoroquinidinone (**64**)

### 3.3 Nucleophilic additions to 8-fluoroquinidinone (**64**)

#### 3.3.1 Synthesis of 9-methyl-8-fluoro-*epi*-quinidine (**86**)

The addition of a nucleophile to the carbonyl group in 8-fluoroquinidinone was initially attempted using two equivalents of methyllithium at  $-78\text{ }^{\circ}\text{C}$  for three hours (Table 3.1). This gave a good conversion (74%) to the desired product, 9-methyl-8-fluoro-*epi*-quinidine (**86**). The purification of the crude product by column chromatography was much easier than the purification of derivatives of quinidine, because any residual starting material was eluted using chloroform/ethyl acetate (80/20), and the product was then eluted using 100% ethyl acetate. A good isolated yield of 63% was obtained.

**Table 3.1:** The synthesis of 9-methyl-8-fluoro-*epi*-quinidine (**86**)

Entry	MeLi (no. equiv.)	Time (h)	Conversion (%)	Yield (%)
1	2.0	3	74	63
2	4.0	6	85	53

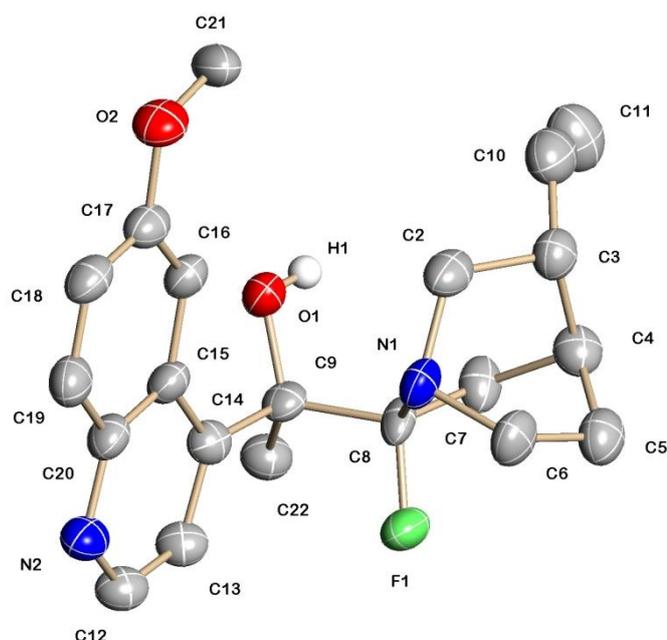
The conversion obtained in the nucleophilic addition of methyllithium to 8-fluoroquinidinone (**64**) (74%) was improved compared to the conversion obtained in the nucleophilic addition of methylmagnesium bromide to quinidinone (63%). This is most likely due to the electron withdrawing nature of the fluorine increasing the reactivity of the carbonyl carbon towards nucleophiles. In contrast to the nucleophilic additions to quinidinone, increasing the number of equivalents from two to four (Table 3.1, entry 2) resulted in an improved conversion. Replacing the hydrogen at the C8 position in quinidinone with a fluorine means that the nucleophile is no longer able to act as a base and form an enolate (which would be unreactive towards nucleophiles), so increasing the number of equivalents does not contribute to competing reactions.

The signals in the room temperature  $^1\text{H}$  NMR spectrum for H3' and H5' were broad singlets due to hindered rotation about the C9-C4' bond due to through space interactions with the C9 substituent. Although the signal for H3' in the high temperature  $^1\text{H}$  NMR was resolved into the expected doublet with a 4.5 Hz coupling constant from coupling to H2', the signal for H5' was still a broad singlet (rather than the expected doublet with a 2.7 Hz coupling constant from coupling to H7'), perhaps indicating that H5' experiences more steric interaction with the 9-CH<sub>3</sub> substituent than H3'. The broadness of the singlet in the  $^{19}\text{F}$  NMR spectrum was also reduced by high temperature NMR, but not eliminated completely.

An examination of the NOESY spectrum showed a correlation between H5' and both of the methyl groups. A correlation was also observed between H3' and the 9-methyl group. This was not highly suggestive of either a quinidine or a quinine structure

as the quinoline ring can rotate around the C4'-C9 bond. A correlation was also observed between H7' and the methoxy, which is as expected as they are next to each other. There appears to be a correlation between H2 and both H10 and H11. A correlation was also seen between H3 and one of the H5s (*exo*), and between one of the H7s (*endo*) and the other H5 (*endo*). Unfortunately, none of these correlations were very helpful in the determination of the configuration at either C8 or C9.

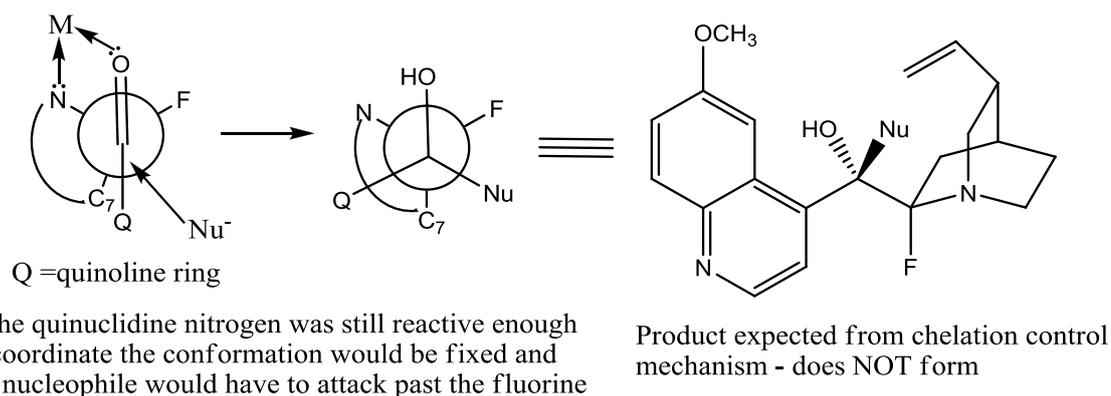
As most of the structurally suggestive NOESY correlations for quinidine analogues were related to H8, and H8 in this case has been replaced with fluorine, a heteronuclear H-F version of a NOESY, called a HOESY, is more useful. Correlations were observed between the fluorine and one of the H7 protons (*endo*), one of the H6 protons (*endo*), and the 9-methyl group, which can be explained by rotation around the C8-C9 bond. These correlations strongly suggested a quinidine configuration at C8, but could not be used to assign the configuration at the C9 position.



**Figure 3.4:** The molecular structure of 9(*R*)-methyl-8(*S*)-fluoro-*epi*-quinidine (**86**)

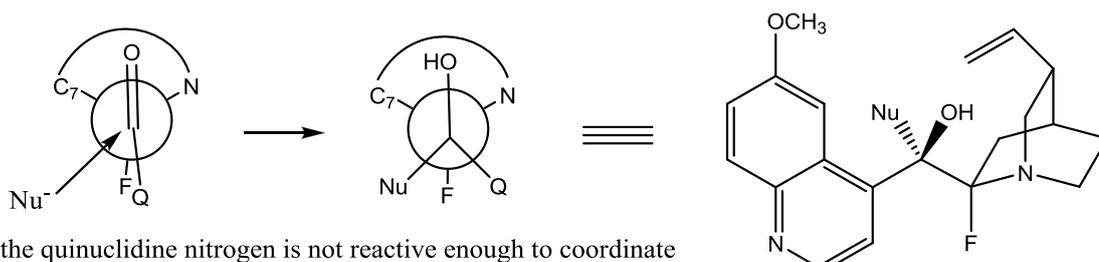
Figure 3.4 shows the molecular structure of 9-methyl-8-fluoro-*epi*-quinidine (**86**) from the X-ray crystallography of a suitable crystal grown by slow evaporation from acetonitrile. The configuration at C9 is (*R*) and the configuration at C8 is (*S*), confirming a quinidine-type structure (with fluorine *endo* and the large quinoline ring, bonded to C9, *exo*).

Figure 3.5, which shows a Newman projection down the C9-C8 bond of 8-fluoroquinidinone, demonstrates the product that would be expected if the nucleophilic addition to 8-fluoroquinidinone (**64**) proceeded by a Chelation Control mechanism as for nucleophilic additions to quinidinone. The Chelation Control product would have an (*S*) configuration at C9, which is opposite to the product actually isolated from this reaction.



**Figure 3.5:** The product that would be expected from a chelation control mechanism of nucleophilic addition to 8-fluoroquinidinone, which does not form

It appears that due to the electron withdrawing nature of the fluorine at C8, the lone pair of electrons on the quinuclidine nitrogen is less available for coordination to the lithiate, so Chelation Control is no longer possible, and the conformation is no longer fixed. Instead, the molecule is oriented in a favourable conformation which keeps the electronegative fluorine atom and carbonyl antiperiplanar to each other. As a result, the nucleophile is attacking from the least hindered back (*Si*) face in a Felkin Ahn type mechanism, rather than being directed to attack from the front (*Re* face) as in the chelation controlled reactions with quinidinone. The product would have a (*R*) configuration at the C9 position, as observed for isolated 9-methyl-8-fluoro-*epi*-quinidine. This is demonstrated in Figure 3.6, which shows a Newman projection down the C9-C8 bond of 8-fluoroquinidinone.

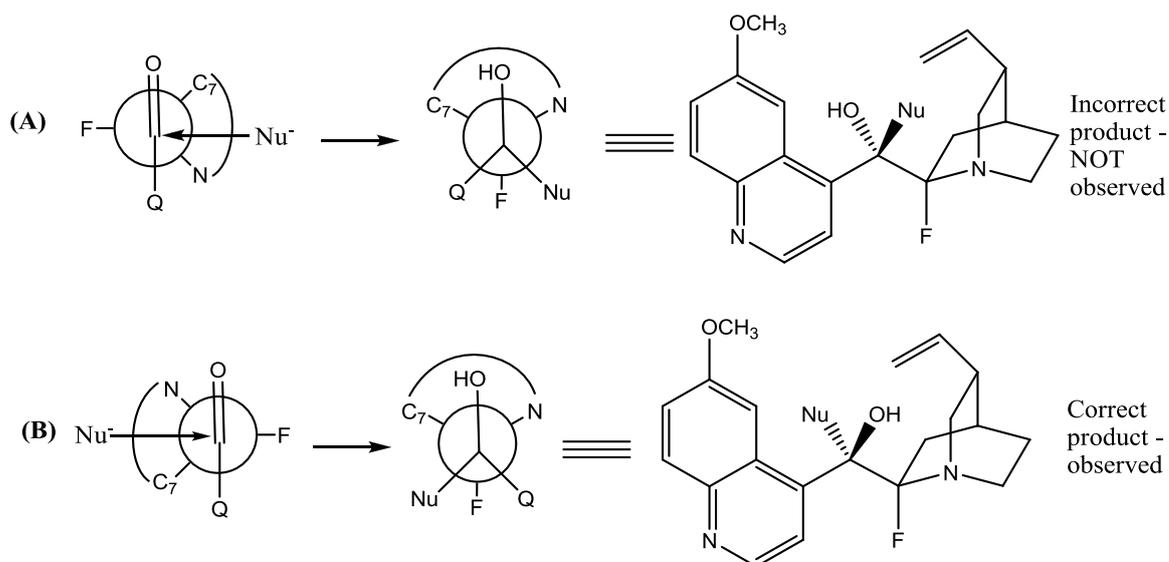


As the quinuclidine nitrogen is not reactive enough to coordinate the conformation is not fixed, and the molecule will rotate to keep the two most electronegative atoms (O and F) as far apart as possible. The nucleophile will then attack past the "small" substituent C7 in a Felkin Ahn addition.

Product expected from Felkin Ahn type mechanism - does form

**Figure 3.6:** The product that would be expected from a Felkin-Ahn type mechanism of nucleophilic addition to 8-fluoroquinidinone, which does form

The commonly accepted favoured transition state, proposed by O'Hagan,<sup>4</sup> involves a conformation where the fluorine is at  $90^\circ$  to the carbonyl, and the nucleophile tends to approach an  $\alpha$ -fluorocarbonyl compound in this conformation *via* a trajectory opposite to the fluorine atom, as shown in Figure 3.7. The problem with this mechanism is that in both situations **A** and **B** in Figure 3.7 a trajectory opposite to the fluorine atom would involve significant steric hindrance from the *exo* H7, H2, and the alkene at C10-C11 due to the rigid bicyclic structure of the quinuclidine ring. Therefore, the Felkin Ahn type mechanism shown in Figure 3.6 appears to be a better model, and accounts for the observed diastereoselectivity in the nucleophilic addition to 8-fluoroquinidinone.

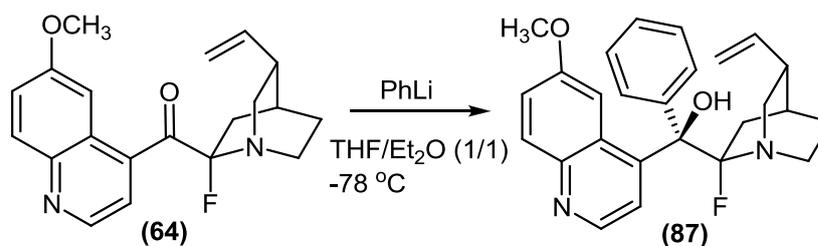


**Figure 3.7:** Nucleophilic attack from a trajectory opposite to the fluorine atom in nucleophilic addition to 8-fluoroquinidinone – either product could form

The same reaction with 8-fluoroquinidinone was also investigated with methylmagnesium bromide. The conversion (66%) and isolated yield (40%) were lower than the methyllithium reactions. As methylmagnesium bromide would usually be considered more coordinating than methyllithium, it was surprising that the  $^1\text{H}$  and  $^{19}\text{F}$  NMR spectra of the product obtained matched those of 9-methyl-8-fluoro-*epi*-quinidine (**86**) obtained from the reaction of 8-fluoroquinidinone with methyllithium. This indicates that even a more chelating Grignard nucleophile adds via the proposed Felkin Ahn type mechanism to give the *epi* configuration at the C9 position. The diastereoisomer with the opposite configuration at the C9 position has similar, but noticeably different  $^1\text{H}$ ,  $^{19}\text{F}$  and  $^{13}\text{C}$  NMR spectra (see section 3.7.1).

### 3.3.2 Synthesis of 9-phenyl-8-fluoro-*epi*-quinidine (**87**)

**Table 3.2:** The synthesis of 9-phenyl-8-fluoro-*epi*-quinidine (**87**)



Run	PhLi (no. equiv.)	Time (h)	Conversion (%)	Yield (%)
1	2.1	3	17	16
2	4.0	8	93	71

The next nucleophile to be introduced was a phenyl group. Initially, two equivalents of phenyllithium were used and the mixture was stirred for three hours at -78 °C before being quenched and worked up in the usual manner. Although the conversion for this reaction was poor (17%), it is a testament to the simplicity of the purification of the fluorinated products that a 16% isolated yield was still achieved by column chromatography, using the same solvent system as for 9-methyl-8-fluoro-*epi*-quinidine (**86**).

However, this low yield was not acceptable, and the conditions were altered in order to try to improve the conversion and the isolated yield. The number of equivalents of phenyllithium was increased to four, and the mixture was stirred for 8 hours at -78 °C before being quenched and worked up. Samples were taken after two, four and six

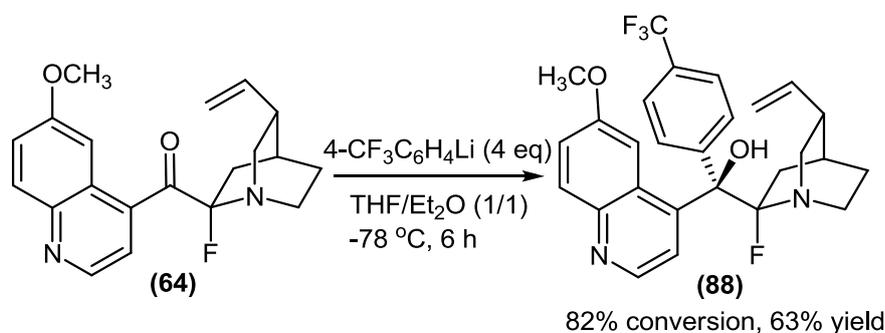
hours, and the conversion had reached 93% after two hours, with minor changes observed in the  $^{19}\text{F}$  NMR spectra of subsequent samples. The improved conversion also led to an improved isolated yield of 71%.

Using four equivalents of phenyllithium in the nucleophilic addition to 8-fluoroquinidinone (**64**) led to a 5.5 fold increase in the conversion compared to the addition using 2.1 equivalents. This is in contrast to observations in the nucleophilic addition of phenyllithium to quinidinone (**62**), where increasing the number of equivalents of phenyllithium from one to two increased the conversion from 31% to 55% (only a 1.8 fold increase), and further increasing the number of equivalents of phenyllithium to four still only led to a 55% conversion.

It is possible that in the nucleophilic additions to quinidinone (**62**) there is competing enolisation, with the nucleophile also acting as a base to deprotonate at the C8 position. Increasing the number of equivalents of nucleophile would not prevent this deprotonation, and would therefore not improve the conversion. In reactions with 8-fluoroquinidinone (**64**) there is no longer a hydrogen at C8 to be deprotonated, so competing enolisation is no longer a problem, resulting in an improvement in the conversion for the reaction, which can be further increased through the addition of a large excess of the nucleophile.

A NOESY spectrum was recorded and the correlations observed are summarised in Table 3.3 (page 104). Unfortunately, the correlations observed could not help with the determination of the configuration at either C8 or C9. A  $^{19}\text{F}$ - $^1\text{H}$  HOESY spectrum was also recorded and the correlations strongly suggest a quinidine configuration at C8, but cannot be used to assign the configuration at the C9 position (Table 3.3).

### 3.3.3 Synthesis of 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinidine (**88**)



**Scheme 3.6**

The next nucleophile to be added to 8-fluoroquinidinone was the sterically bulky and electron withdrawing 4-trifluoromethylphenyl group. The 4-trifluoromethylphenyllithium was pre-formed by stirring *n*-butyllithium with a slight excess of 4-bromobenzotrifluoride (to avoid any leftover butyllithium acting as a competing nucleophile) in diethyl ether at 0 °C for one hour. The reaction mixture was then cooled to -78 °C, 8-fluoroquinidinone (**64**) was added, and the mixture was stirred for six hours at -78 °C. 9-(4-Trifluoromethylphenyl)-8-fluoro-*epi*-quinidine (**88**) was purified by column chromatography using the standard solvent system for 8-fluoro-derivatives. A decreased yield was expected because of the combined effect of the steric bulk and the decreased nucleophilicity due to the electron withdrawing CF<sub>3</sub> group on the phenyl ring; however, the increased reactivity of the carbonyl group due to the nearby electron withdrawing fluorine on C8 cancelled out this effect, and a good isolated yield of 63% was obtained.

An examination of the NOESY spectrum did not help with the determination of the configuration at either C8 or C9, and the correlations observed are summarised in Table 3.3. The correlations observed in the <sup>19</sup>F-<sup>1</sup>H HOESY spectrum (Table 3.3) strongly suggest a quinidine configuration at C8, but do not help with the assignment of the configuration at the C9 position.

**Table 3.3:** NOESY and HOESY correlations of 9-substituted-8-fluoro-*epi*-quinidine derivatives

<b>9-R-8-fluoro-<i>epi</i>-quinidine</b>	<b>NOESY correlations</b>	<b>HOESY correlations</b>
<b>R = Me (86)</b>	Me – H5'	F – H7 ( <i>endo</i> )
	Me – H3'	F – H6 ( <i>endo</i> )
		F – 9Me
<b>R = Ph (87)</b>	H2'' – H3'	F – H7 ( <i>endo</i> )
	H2'' – H7 ( <i>exo</i> )	F – H6 ( <i>endo</i> )
	H2'' – H2	F – H3'
<b>R = 4-C<sub>6</sub>H<sub>4</sub>CF<sub>3</sub> (88)</b>		F – H7 ( <i>endo</i> )
		F – H6 ( <i>endo</i> )
	H2'' – H7 ( <i>exo</i> )	F – H5 ( <i>endo</i> )
		F – H3'

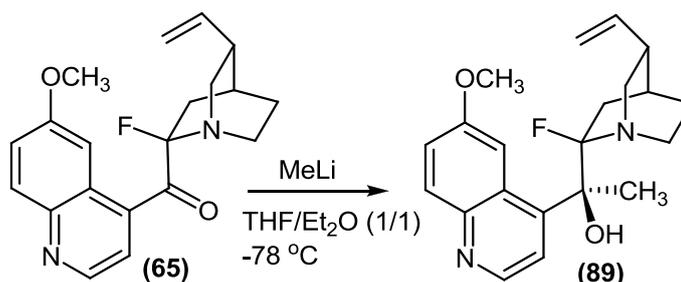
Table 3.3 shows the correlations observed in the NOESY and  $^{19}\text{F}$ - $^1\text{H}$  HOESY spectra of the 9-substituted-8-fluoro-*epi*-quinidine derivatives. Unlike for quinidine derivatives, the lack of a hydrogen at C8 in 8-fluoro derivatives means that the NOESY correlations are not useful in the determination of the configuration at C8 or C9. The correlations of the C8 fluorine across the underside of the quinuclidine ring to the *endo* H7, *endo* H6 and *endo* H5 protons confirms the quinidine configuration at C8, but cannot help with the determination of the configuration at the C9 position.

Although the configuration at C9 has not been established for 9-phenyl-8-fluoro-*epi*-quinidine (**87**) and 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinidine (**88**), it is assumed to be (*R*) by analogy with the mechanism proposed for 9-methyl-8-fluoro-*epi*-quinidine (**86**).

### 3.4 Nucleophilic additions to 8-fluoroquininone (**65**)

#### 3.4.1 Synthesis of 9-methyl-8-fluoro-*epi*-quinine (**89**)

**Table 3.4:** The synthesis of 9-methyl-8-fluoro-*epi*-quinine (**89**)



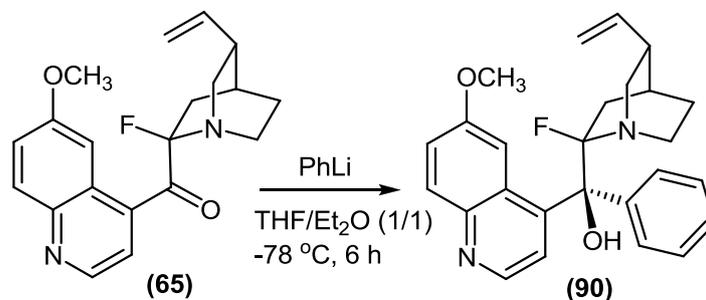
Entry	MeLi (no. equiv.)	Time (h)	Conversion (%)	Yield (%)
1	2.0	3	71	54
2	3.0	6	>90	68

Following the successful addition of alkyl and aryl nucleophiles to 8-fluoroquinidinone (**64**), the reaction with 8-fluoroquininone (**65**) was first attempted with methyllithium. Two equivalents of methyllithium were used at  $-78\text{ }^{\circ}\text{C}$  for 3 hours. The same purification conditions (column chromatography initially using chloroform/ ethyl acetate (80/20) to elute starting material, then using ethyl acetate to elute the product), were used for 9-methyl-8-fluoro-*epi*-quinine (**89**) to give an acceptable 54% isolated yield. Increasing the excess of methyllithium to three equivalents, and the time of the reaction to six hours, led to >90% conversion, and a good isolated yield of 68%.

Unfortunately, the singlet for the fluorine in the  $^{19}\text{F}$  NMR spectrum of 9-methyl-8-fluoro-*epi*-quinine (**89**) is too broad for a HOESY spectrum to be recorded.

### 3.4.2 Synthesis of 9-phenyl-8-fluoro-*epi*-quinine (**90**)

**Table 3.5:** The synthesis of 9-phenyl-8-fluoro-*epi*-quinine (**90**)

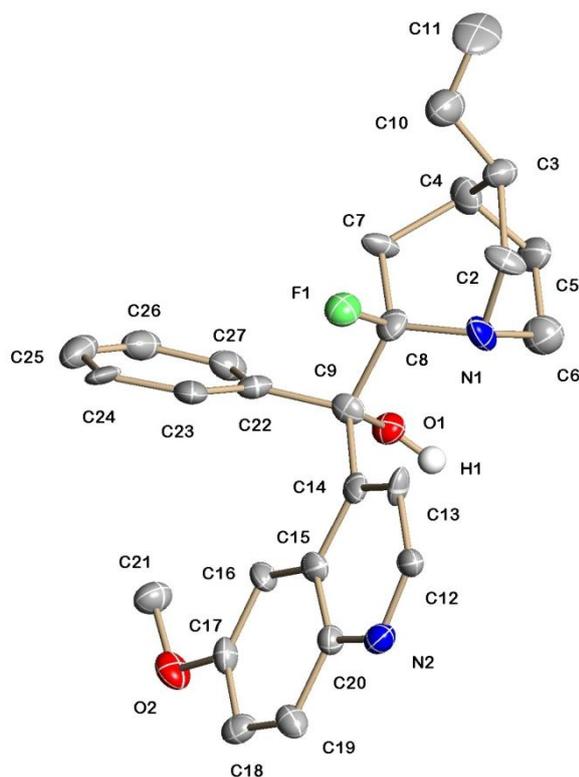


Entry	PhLi (no. equiv)	Time (h)	Conversion (%)	Yield (%)
1	2.0	6	36	22
2	4.1	6	60	49

A phenyl group was also successfully added to the carbonyl group of 8-fluoroquininone (**65**) using two equivalents of phenyllithium and stirring the reaction mixture at -78 °C for six hours (Table 3.5). The 36% conversion was not very good, but the isolated yield of 22% from this relatively poor conversion was acceptable. When the excess of phenyllithium was increased to four equivalents, the conversion of the reaction was improved significantly to 60%, and gave a good isolated yield of 49%.

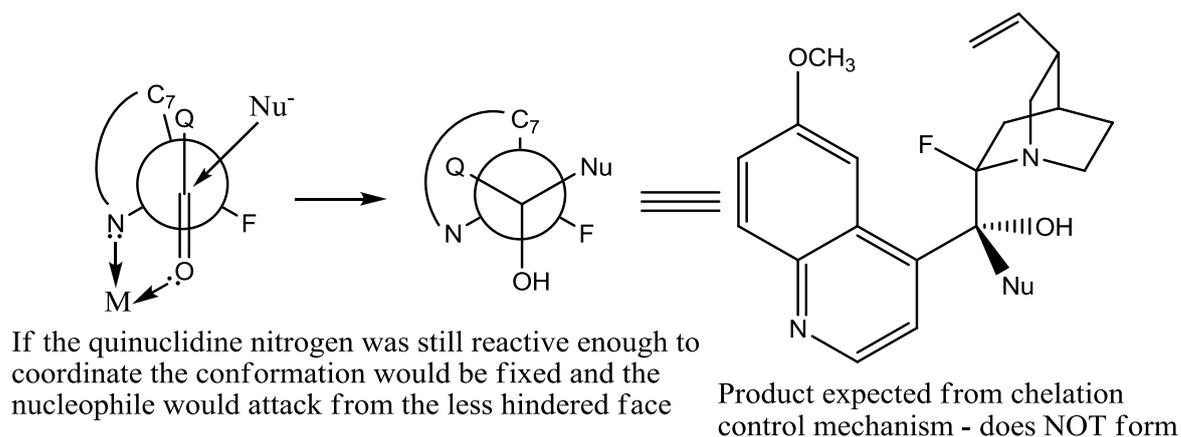
An examination of the NOESY spectrum did not help with the assignment of the configuration at the C8 or C9 positions, and the correlations are summarised in Table 3.6 (page 110). The correlations observed in the  $^{19}\text{F}$ - $^1\text{H}$  HOESY spectrum, which are also summarised in Table 3.6, strongly suggest a quinine configuration at C8, but cannot be used to assign the configuration at the C9 position.

A crystal suitable for X-ray crystallography was grown by slow evaporation from chloroform, and the molecular structure is shown in Figure 3.8. The configuration at C8 is (*R*) which confirms the quinine structure suggested by the HOESY spectrum, and the configuration at C9 is (*S*).



**Figure 3.8:** The molecular structure of 9(*S*)-phenyl-8(*R*)-fluoro-*epi*-quinine (**90**)

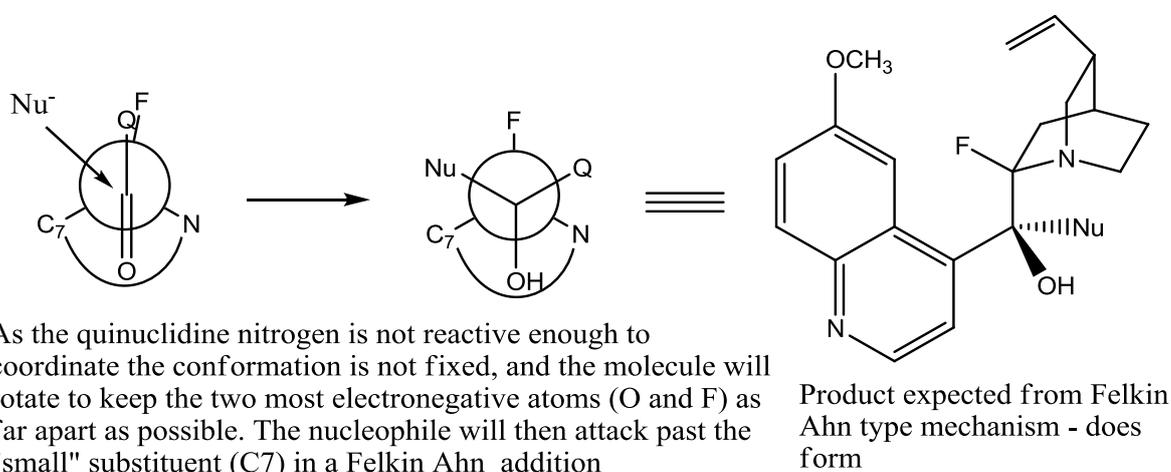
If the chelation control mechanism proposed for nucleophilic additions to quinidinone (**62**) had been followed the configuration at C9 would have been expected to have been (*R*), as shown in Figure 3.9 which shows a Newman projection down the C9-C8 bond.



**Figure 3.9:** The product expected from a chelation control mechanism of nucleophilic addition to 8-fluoroquininone does not form

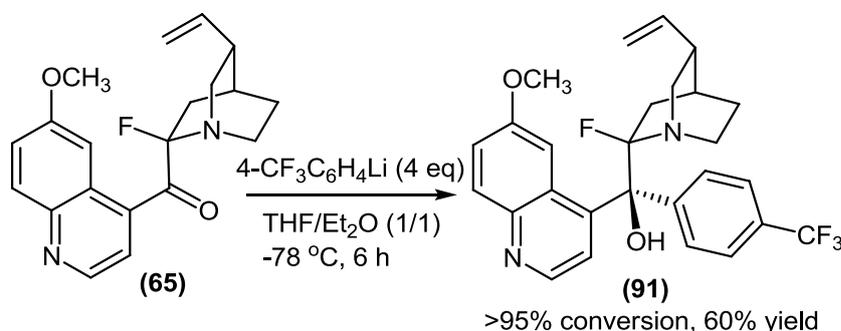
It is possible that the electron withdrawing nature of the fluorine is leading to decreased availability of the quinuclidine nitrogen lone pair for coordination to the nucleophile. Consequently, the nucleophile is attacking from the least hindered (*Re*) face, in a Felkin Ahn type mechanism, with the electrophilic fluorine atom and carbonyl oxygen antiperiplanar to each other, as described in Figure 3.10, and discussed on page 101, Figure 3.6 for the quinidine series of compounds.

In the Felkin Ahn type addition (Figure 3.10) there is only one possible conformation that keeps the fluorine atom and the carbonyl oxygen at 180° to each other, and hence only one favoured approach for the nucleophile, explaining the diastereoselectivity observed in the reaction.



**Figure 3.10:** The product that would be expected from a Felkin Ahn type mechanism for nucleophilic addition to 8-fluoroquininone

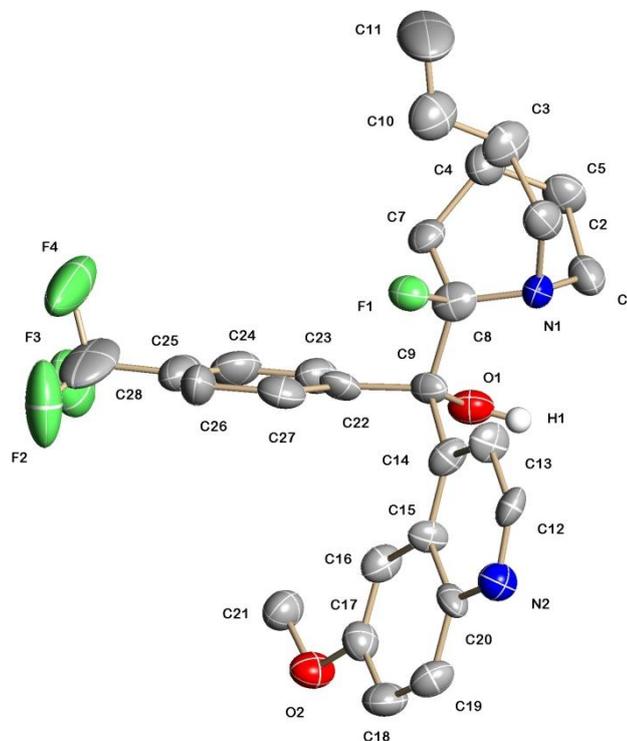
### 3.4.3 Synthesis of 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinine (91)



**Scheme 3.7**

A nucleophilic addition to the carbonyl group of 8-fluoroquininone was then carried out with four equivalents of 4-trifluoromethylphenyllithium at -78 °C. The

conversion was >95% and purification by column chromatography using the standard solvent system for 8-fluoro-derivatives, gave a good isolated yield of 60%. The  $^{19}\text{F}$ - $^1\text{H}$  HOESY spectrum was recorded, and the correlations are summarised in Table 3.6 (page 110). The correlations strongly suggest a quinine structure at the C8 position, but do not help with the determination of the configuration at the C9 position.



**Figure 3.11:** The molecular structure of 9(*S*)-(4-trifluoromethylphenyl)-8(*R*)-fluoro-*epi*-quinine (**91**)

A crystal suitable for X-ray structure determination was successfully grown by recrystallisation from acetonitrile. The molecular structure is shown in Figure 3.11, where it can be seen that the configurations are 8(*R*) and 9(*S*). An 8(*R*) configuration is a quinine-type structure. The (*S*) configuration at C9 further supports a Felkin Ahn type addition mechanism (Figure 3.10, page 108).

Table 3.6 shows the correlations observed in the NOESY and  $^{19}\text{F}$ - $^1\text{H}$  HOESY spectra of the 9-aryl-8-fluoro-*epi*-quinine derivatives. As with the 9-substituted-8-fluoro-*epi*-quinidine derivatives, the lack of a C8 hydrogen means that the NOESY correlations are not helpful in the determination of the configuration at C8 or at C9. The correlations of the C8 fluorine atom to H2 and to the *exo* H7 in the HOESY spectra strongly suggest a quinine configuration at the C8 position, but cannot help with the determination of the configuration at the C9 position.

**Table 3.6:** NOESY and HOESY correlations for 9-aryl-8-fluoro-*epi*-quinine derivatives

9-R-8-fluoro- <i>epi</i> -quinine	NOESY correlations	HOESY correlations
<b>R = Ph (90)</b>	H2'' – H7 ( <i>exo</i> )	F – H2
	H2'' – H5'	F – H7 ( <i>exo</i> )
		F – H3'
<b>R = 4-C<sub>6</sub>H<sub>4</sub>CF<sub>3</sub> (91)</b>	H2'' – H7 ( <i>exo</i> )	F – H2
	H2'' – H3'	F – H7 ( <i>exo</i> )
		F – H3'
		F – H2''

Although the configuration at C9 has not been established for 9-methyl-8-fluoro-*epi*-quinine (**89**), it is assumed to be (*S*) by analogy with the mechanism proposed for 9-phenyl-8-fluoro-*epi*-quinine (**90**) and 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinine (**91**).

### 3.5 Key characteristic NMR and optical rotation data for 9-substituted-8-fluoro-*epi*-quinidine and 9-substituted-8-fluoro-*epi*-quinine derivatives

**Table 3.7:** Trends in the chemical shifts of H10 in the 8-fluoro-*epi*-quinidine and 8-fluoro-*epi*-quinine derivatives

Cinchona Alkaloid	Chemical Shift H10 (ppm)	Cinchona Alkaloid	Chemical Shift H10 (ppm)
8-Fluoroquinidinone ( <b>64</b> )	5.91	8-Fluoroquininone ( <b>65</b> )	5.87
9-Me-8F- <i>epi</i> -quinidine ( <b>86</b> )	5.70	9-Me-8F- <i>epi</i> -quinine ( <b>89</b> )	5.91
9-Ph-8F- <i>epi</i> -quinidine ( <b>87</b> )	5.35	9-Ph-8F- <i>epi</i> -quinine ( <b>90</b> )	5.93
9-(4-Trifluoromethylphenyl)-8-fluoro- <i>epi</i> -quinidine ( <b>88</b> )	5.49	9-(4-Trifluoromethylphenyl)-8-fluoro- <i>epi</i> -quinine ( <b>91</b> )	5.89

There are some general trends within the NMR spectra of the 8-fluoro-*epi*-quinidine series and within the 8-fluoro-*epi*-quinine series. In the <sup>1</sup>H NMR spectra the chemical shifts of the alkene H10 proton for the 8-fluoro-*epi*-quinine series are usually further downfield than the H10 proton of the 8-fluoro-*epi*-quinidine series. Also in the 8-fluoro-*epi*-quinidine series the *cis* H11 proton signal is further downfield than the

*trans* H11 proton, whereas in the 8-fluoro-*epi*-quinine series the *trans* H11 proton signal is further downfield than the *cis* H11 proton signal. The two H11 signals are also closer together in the 8-fluoro-*epi*-quinine series than in the 8-fluoro-*epi*-quinidine series. These trends are illustrated in Tables 3.7 and 3.8.

**Table 3.8:** Trends in the chemical shifts of H11 in the 8-fluoro-*epi*-quinidine and 8-fluoro-*epi*-quinine derivatives

Cinchona Alkaloid	Chemical Shift H11 (ppm)	Cinchona Alkaloid	Chemical Shift H11 (ppm)
8-Fluoroquinidinone ( <b>64</b> )	4.99 <i>trans</i> , 5.00 <i>cis</i>	8-Fluoroquininone ( <b>65</b> )	5.02 <i>cis</i> , 5.03 <i>trans</i>
9-Me-8F- <i>epi</i> -quinidine ( <b>86</b> )	4.84 <i>trans</i> , 4.91 <i>cis</i>	9-Me-8F- <i>epi</i> -quinine ( <b>89</b> )	4.92 <i>cis</i> , 4.93 <i>trans</i>
9-Ph-8F- <i>epi</i> -quinidine ( <b>87</b> )	4.61 <i>trans</i> , 4.76 <i>cis</i>	9-Ph-8F- <i>epi</i> -quinine ( <b>90</b> )	4.95 <i>cis</i> , 4.98 <i>trans</i>
9-(4-Trifluoromethylphenyl)-8-fluoro- <i>epi</i> -quinidine ( <b>88</b> )	4.63 <i>trans</i> , 4.82 <i>cis</i>	9-(4-Trifluoromethylphenyl)-8-fluoro- <i>epi</i> -quinine ( <b>91</b> )	4.94 <i>cis</i> , 4.98 <i>trans</i>

The chemical shifts of the C8 fluorine atoms in the  $^{19}\text{F}$  NMR spectra are summarised in Table 3.9. In the 8-fluoro-*epi*-quinidine series the fluorine chemical shift is further downfield than in the 8-fluoro-*epi*-quinine series, typically approximately -123 ppm and -116 ppm respectively.

**Table 3.9:** Trends in the chemical shifts of the C8 fluorine atoms in 8-fluoro-*epi*-quinidine and 8-fluoro-*epi*-quinine derivatives

Cinchona Alkaloid	Chemical Shift 8F (ppm)	Cinchona Alkaloid	Chemical Shift 8F (ppm)
8-Fluoroquinidinone ( <b>64</b> )	-119.92	8-Fluoroquininone ( <b>65</b> )	-117.56
9-Me-8F- <i>epi</i> -quinidine ( <b>86</b> )	-121.25	9-Me-8F- <i>epi</i> -quinine ( <b>89</b> )	-115.07
9-Ph-8F- <i>epi</i> -quinidine ( <b>87</b> )	-123.62	9-Ph-8F- <i>epi</i> -quinine ( <b>90</b> )	-116.76
9-(4-Trifluoromethylphenyl)-8-fluoro- <i>epi</i> -quinidine ( <b>88</b> )	-123.39	9-(4-Trifluoromethylphenyl)-8-fluoro- <i>epi</i> -quinine ( <b>91</b> )	-116.85

Table 3.10 shows the trends in optical rotation values for the 8-fluoro-*epi*-quinidine and 8-fluoro-*epi*-quinine derivatives, in comparison with 8-fluoroquininone

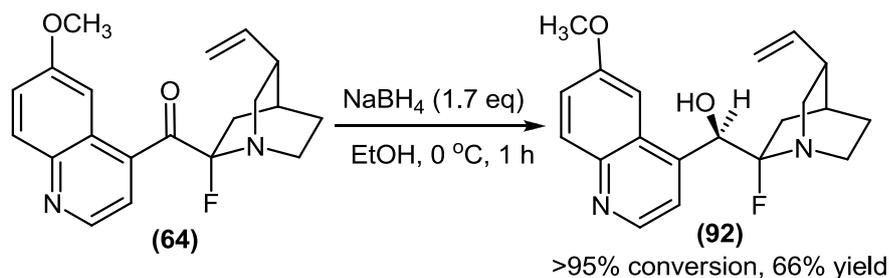
and 8-fluoroquinidinone. The 8-fluoro-*epi*-quinidine series generally have high positive optical rotations (ranging from +112.6 to +150.6°), although they are not as high as the value for 8-fluoroquinidinone (+306.1°). The high negative optical rotation of 8-fluoroquininone (-99.4°) was expected because it is a *pseudo*-enantiomer of 8-fluoroquinidinone. Although the optical rotations for the 8-fluoro-*epi*-quinine series are not completely opposite to those of the 8-fluoro-*epi*-quinidine series, they are all very low positive values (ranging from +5.6 to +8.7°).

**Table 3.10:** Trends in optical rotation for 8-fluoro-*epi*-quinine and 8-fluoro-*epi*-quinidine derivatives

Compound	Optical Rotation (°)	Compound	Optical Rotation (°)
8FQdone ( <b>64</b> )	+306.1	8FQnone ( <b>65</b> )	-99.4
9Me8 <i>Fepi</i> Qdine ( <b>86</b> )	+150.6	9Me8 <i>Fepi</i> Qnine ( <b>89</b> )	-16.3
9Ph8 <i>Fepi</i> Qdine ( <b>87</b> )	+112.6	9Ph8 <i>Fepi</i> Qnine ( <b>90</b> )	+8.7
9(4CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )8 <i>Fepi</i> Qdine ( <b>88</b> )	+147.3	9(4CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )Ph8 <i>Fepi</i> Qnine ( <b>91</b> )	+5.6

### 3.6 Reduction of 8-fluoroquinidinone (**64**) and 8-fluoroquininone (**65**)

#### 3.6.1 Synthesis of 8-fluoro-*epi*-quinidine (**92**) and 8-fluoro-*epi*-quinine (**93**)

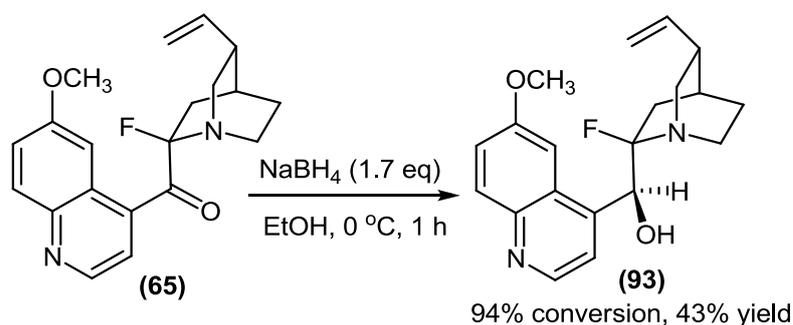


**Scheme 3.8**

A literature method<sup>5</sup> for the reduction of quinidinone (**62**) to *epi*-quinidine (**35**) was adapted for the formation of 8-fluoro-*epi*-quinidine (**92**) by reduction of 8-fluoroquinidinone (**64**). 8-Fluoroquinidinone was reacted with sodium borohydride for one hour at 0 °C in ethanol. After working up the reaction mixture, the <sup>1</sup>H NMR spectrum of the crude product showed that the conversion to the desired product was

>95%. The crude solid was purified by column chromatography using 100% ethyl acetate to give a good 66% isolated yield.

The correlations observed in the NOESY spectrum are summarised in Table 3.11 (page 114). Although the correlation between H9 and H2 is useful for assigning the configuration at the C8 position as a quinidine configuration, the correlations were not helpful in the determination of the configuration at the C9 position. The  $^{19}\text{F}$ - $^1\text{H}$  HOESY spectrum showed a correlation between the fluorine atom and the *endo* H7 and *endo* H6, strongly suggesting a quinidine configuration at C8, but it was not useful in determining the configuration at C9.



**Scheme 3.9**

The same literature method was used for the reduction of 8-fluoroquininone (65) to 8-fluoro-*epi*-quinine (93). According to the crude  $^1\text{H}$  NMR spectrum the conversion to the desired product was >90%. The crude material was purified by column chromatography using 100% ethyl acetate, but a lower isolated yield of 43% was obtained in comparison with that of 8-fluoro-*epi*-quinidine (92) (66%).

There are major differences in the chemical shifts of the alkene protons in the  $^1\text{H}$  NMR spectra for 8-fluoro-*epi*-quinidine (92) and 8-fluoro-*epi*-quinine (93). For 8-fluoro-*epi*-quinidine H10 (5.84 ppm) and both H11s (*trans* 5.10 ppm, *cis* 5.12 ppm) are slightly further downfield than H10 (5.73 ppm) and the H11s (*cis* 4.90, *trans* 4.92 ppm) for 8-fluoro-*epi*-quinine. The coupling constants between H9 and F are both very similar (24.3 Hz for the 8-fluoro-*epi*-quinidine and 24.6 Hz for the 8-fluoro-*epi*-quinine).

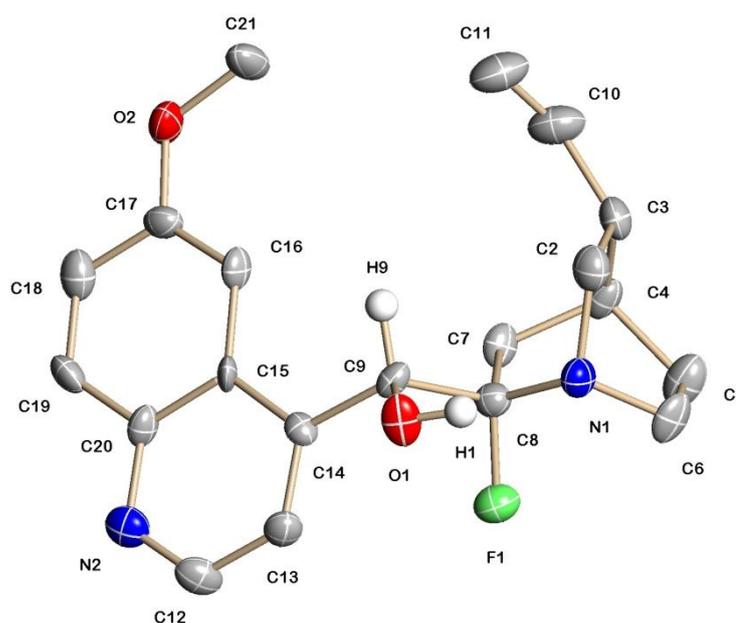
The correlations observed in the NOESY spectrum are shown in Table 3.11. The only correlation that helps with the assignment of configuration is that of H9 - H6 (*endo*), which would not be possible in a quinidine configuration at the C8 position. The correlation between the fluorine and H2 observed in the HOESY spectrum would also not be possible in a quinidine configuration, confirming the quinine configuration

at C8. The HOESY spectrum could not assist in the determination of the configuration at C9.

**Table 3.11:** NOESY and HOESY correlations observed for 8-fluoro-*epi*-quinidine and 8-fluoro-*epi*-quinine

Compound	NOESY Correlations	HOESY Correlations
8-fluoro- <i>epi</i> -quinidine ( <b>92</b> )	H3' – H9; H5' – H9;	
	H5' – OCH <sub>3</sub> ; H7' – OCH <sub>3</sub> ;	F – H7 ( <i>endo</i> )
	H9 – H2; H11 – H2; H3 – H5( <i>exo</i> );	F – H6 ( <i>endo</i> )
	H7( <i>endo</i> ) – H5( <i>endo</i> )	
	-----	
8-fluoro- <i>epi</i> -quinine ( <b>93</b> )	H3' – H9; H5' – OCH <sub>3</sub> ;	
	H5' – H9; H7' – OCH <sub>3</sub> ; H10 – H3; H9 – H6( <i>endo</i> ); H2 – H10, H3 – H2	F – H2 F – H3'

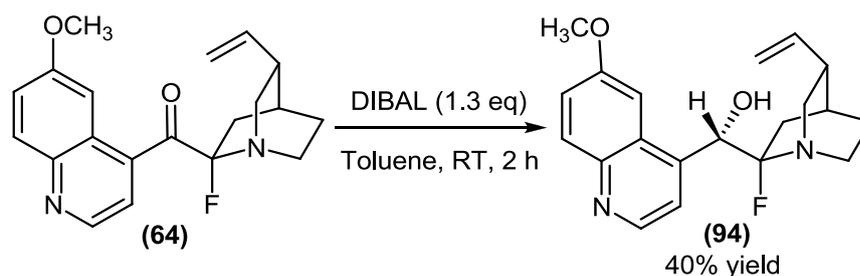
A crystal suitable for X-ray crystallography was grown by slow evaporation of a solution of 8-fluoro-*epi*-quinidine in chloroform. The molecular structure for 8(*S*)-fluoro-*epi*-quinidine is shown in Figure 3.12. The configuration at C8 is (*S*), confirming the quinidine-type structure, and the configuration at C9 is (*R*), confirming the *epi* configuration.



**Figure 3.12:** The molecular structure of 8(*S*)-fluoro-*epi*-quinidine (**92**)

Sodium borohydride is not a coordinating/chelating reducing agent, the hydride is therefore adding from the least hindered (*Si*) face in a Felkin Ahn mechanism, as for the addition of alkyl and aryl nucleophiles to 8-fluoroquinidinone and 8-fluoroquininone (Figure 3.6 page 101 for 8-fluoroquinidinone, and Figure 3.10 page 108 for 8-fluoroquininone).

### 3.6.2 Synthesis of 8-fluoroquinidine (**94**)



**Scheme 3.10**

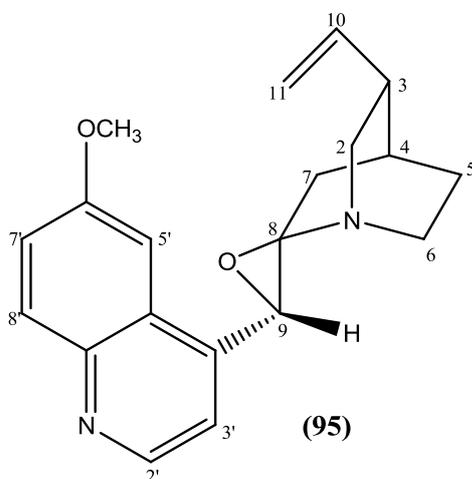
A literature procedure<sup>5</sup> for the reduction of quinidinone (**62**) to quinidine (**27**) was adapted for the stereoselective formation of 8-fluoroquinidine (**94**) by the reduction of 8-fluoroquinidinone (**64**). 8-Fluoroquinidinone was reacted with di-*iso*-butylaluminium hydride (DIBAL) in dry toluene at room temperature for two hours. After working up the reaction, the <sup>1</sup>H NMR spectrum of the crude product was not as clean as the reductions with sodium borohydride, although the desired product did appear to be the major component. The crude material was purified by column chromatography using 100% ethyl acetate to give 8-fluoroquinidine (**94**) in 40% isolated yield.

The reason for the stereoselectivity of the reduction is that DIBAL is a Lewis acid, which formed a complex with the quinuclidine nitrogen (which is reactive enough to hold a nucleophile on one face, if not to fix the conformation of the whole molecule), thus directing the hydride attack from the front (*Re*) face. Reduction with sodium borohydride formed the opposite configuration at C9 because the uncoordinated hydride attacks from the opposite less hindered (*Si*) face via a Felkin Ahn mechanism, therefore avoiding the lone pair of electrons on the quinuclidine nitrogen.

The coupling constants between H9 and F for 8-fluoro-*epi*-quinidine (**92**) and 8-fluoroquinidine (**94**) are very different; the coupling constant in 8-fluoro-*epi*-quinidine is 24 Hz, whereas the coupling constant in 8-fluoroquinidine is only 16 Hz. The chemical shifts for the alkene protons also differ; H10 (5.73 ppm) and both H11s (*cis*

4.94 ppm and *trans* 4.91 ppm) are further upfield in 8-fluoroquinidine than in 8-fluoro-*epi*-quinidine. The aromatic protons are also shifted further upfield in the  $^1\text{H}$  NMR spectrum of 8-fluoroquinidine, for example H2' is at 8.42 ppm in the  $^1\text{H}$  NMR spectrum of 8-fluoroquinidine, but at 8.71 ppm in the  $^1\text{H}$  NMR spectrum of 8-fluoro-*epi*-quinidine. Table 3.12 page 121 highlights the trends in the chemical shift and coupling constant values for the products from the successful reductions of 8-fluoroquinidinone and 8-fluoroquininone.

Another, non-fluorinated by-product (**95**) was also isolated from the column, eluting before the desired product. It is unclear whether this by-product is a reaction product, or the result of decomposition of the desired product. This by-product appears to be an epoxide formed by attack of the OH on C8, eliminating the fluorine. The proposed structure is shown in Figure 3.13. The mass spectrum of the by-product shows that its molecular mass is  $322\text{ gmol}^{-1}$ , but it cannot be quinidinone because the  $^1\text{H}$  NMR spectrum is distinctly different. The main peak of interest in the  $^1\text{H}$  NMR spectrum is a 1H singlet at 4.21 ppm, which does not connect to any other protons in the COSY spectrum. This is assigned as H9, which has no neighbouring protons because the adjacent carbons, C8 and C4', are now both quaternary.

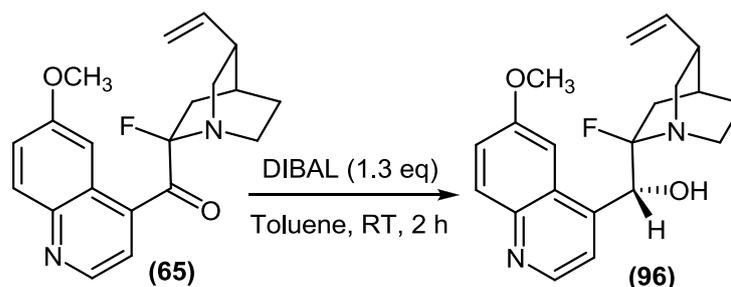


**Figure 3.13:** The proposed structure for the by-product (**95**) isolated after the reduction of 8-fluoroquinidinone (**64**) with DIBAL

The quaternary carbon signal for C8 in 8-fluoroquinidine (**94**) in the  $^{13}\text{C}$  NMR spectrum is a doublet with a  $^1J_{\text{CF}}$  coupling constant of 196.5 Hz at 107.1 ppm. In the  $^{13}\text{C}$  NMR spectrum of the by-product (**95**) there is no doublet corresponding to a fluorinated carbon, and the quaternary signal for C8 now appears at 77.55 ppm. The CH of C9

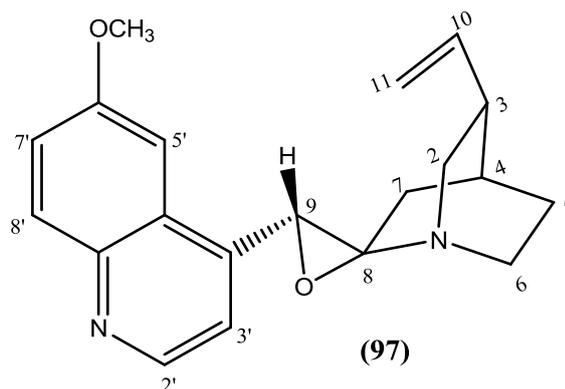
appears at 63.95 ppm. These signals are consistent with an epoxide adjacent to a nitrogen centre, for example in (1*S*,2*S*)-3-(3-methyl-3-phenyloxiranyl)oxazolidin-2-one,<sup>6</sup> the hydrogen that would be equivalent to H9 appears as a singlet at 4.97 ppm, and the carbon that would be equivalent to C9 appears at 69.6 ppm (the slight shift is because this example has a carbamate nitrogen rather than an amine).

### 3.6.3 Synthesis of 8-fluoroquinine (96)



**Scheme 3.11**

8-Fluoroquininone (**65**) was first reduced to 8-fluoroquinine (**96**) using DIBAL (1.3 eq) at room temperature, following the same literature procedure as for the reduction of 8-fluoroquinidinone (**64**) to 8-fluoroquinidine (**94**). The <sup>1</sup>H NMR spectrum of the crude product did not look as clean as for the reductions with sodium borohydride, and seemed to contain more compounds than the crude <sup>1</sup>H NMR spectrum of 8-fluoroquinidine. Similar to the reduction of 8-fluoroquinidinone to 8-fluoroquinidine, a non-fluorinated byproduct (**97**) was also formed. Unfortunately, the fluorinated desired product 8-fluoroquinine (**96**) was lost and only the non-fluorinated product (**97**) was isolated after purification by column chromatography. Initially, this was thought to be an isolated incident and that if the reaction was repeated the desired product could be isolated by column chromatography. However, the repeat reaction yielded the same result, and none of the desired product was isolated from the column. This led to the conclusion that the desired product (which could be observed in the crude <sup>1</sup>H NMR spectrum) was decomposing on the column to form an epoxide (**97**) with a similar structure to the epoxide (**95**) formed from the 8-fluoroquinidinone reduction with DIBAL to 8-fluoroquinidine. The proposed structure of the by-product (**97**) is shown in Figure 3.14.



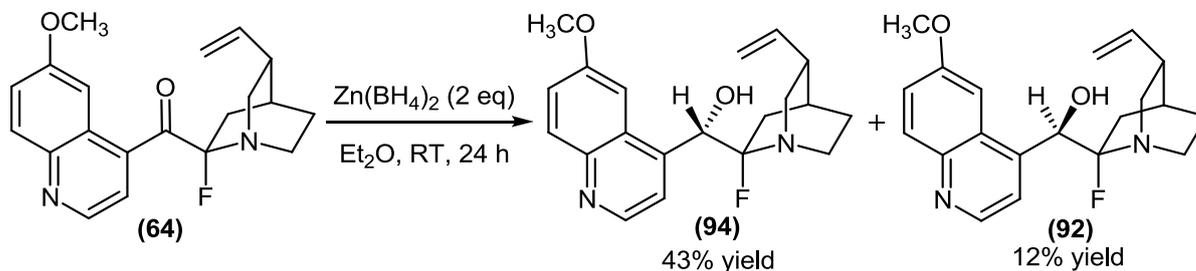
**Figure 3.14:** The proposed structure of the by-product (**97**) formed in the reduction of 8-fluoroquinine (**65**) with DIBAL

It seems strange that the hydroxyl group would attack the C8 carbon and cause the loss of fluorine in the case of 8-fluoroquinidine (**94**) and 8-fluoroquinine (**96**), but not decompose to form an epoxide in any of the other 9-substituted-8-fluoro-derivatives made so far, especially since fluorine is not a good leaving group. However, it could be a result of the configuration at C9, as all the crystal structures obtained for 8-fluoroproducts show an *epi* configuration at C9 (nucleophile coming from the back, OH pointing forward), whereas the configuration of 8-fluoroquinidine and 8-fluoroquinine has the OH at the back and the nucleophile, hydride, coming from the front (*Re* face for 8-fluoroquinidinone, *Si* face for 8-fluoroquininone). The only other difference is the presence of DIBAL; it is possible that aluminium is involved in coordination to fluorine, causing it to eliminate.

In order to test whether the formation of the epoxide was in some way related to the presence of aluminium, or was a result of the altered configuration at C9, the reduction of 8-fluoroquinidinone and 8-fluoroquininone was performed using zinc borohydride. Zinc borohydride is also a coordinating reducing agent, which should coordinate to the quinuclidine nitrogen and direct hydride attack from the front to form 8-fluoroquinidine (**94**) from 8-fluoroquinidinone (**64**) and 8-fluoroquinine (**96**) from 8-fluoroquininone (**65**). If the epoxides were the result of the configuration at C9 allowing hydroxyl attack at C8 and elimination of fluorine then they should still form when using zinc borohydride. If, however, the formation of the epoxide was related to aluminium then they should not form when using zinc borohydride.

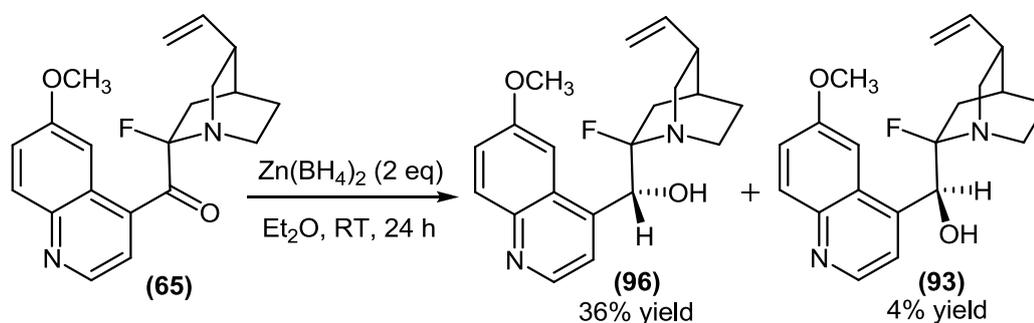
In order to form zinc borohydride, zinc chloride was dried thoroughly by repeated melting and cooling under vacuum, and then refluxed in dry diethyl ether until it dissolved. The cooled solution of zinc chloride in dry diethyl ether was added to a

stirred suspension of sodium borohydride in dry diethyl ether at room temperature, and stirred at room temperature overnight.<sup>7</sup> The supernatant fluid was then used for the reductions.



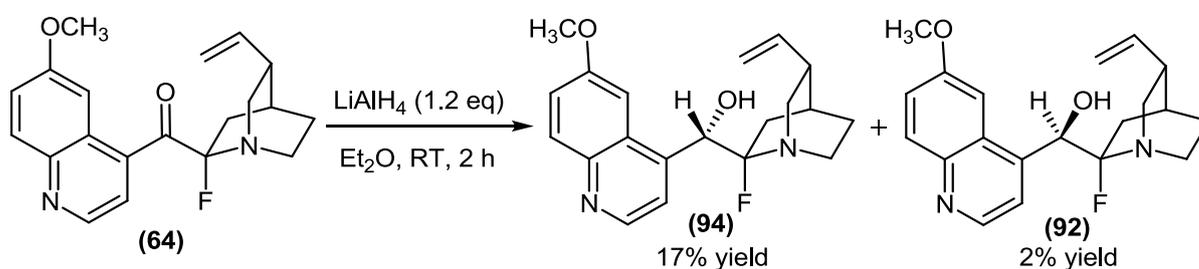
Scheme 3.12

The reduction of 8-fluoroquinidinone (Scheme 3.12) was carried out using two equivalents of zinc borohydride, stirring at room temperature for 24 hours. The conversion (taken from integration of the crude  $^{19}\text{F}$  NMR spectrum), was approximately 80%, with an approximately 5:1 ratio of 8-fluoroquinidine (**94**) to 8-fluoro-*epi*-quinidine (**92**) in the crude  $^{19}\text{F}$  NMR spectrum. The crude product was purified using column chromatography on silica gel using chloroform/ethyl acetate (80/20) to elute residual starting material (11% isolated yield), then 100% ethyl acetate to elute the products. Both products could be isolated pure; 8-fluoroquinidine (**94**) was isolated in 43% yield and 8-fluoro-*epi*-quinidine (**92**) was isolated in 12% yield, although some mixed fractions containing both were also obtained. Although the reaction was not as diastereoselective as that of 8-fluoroquinidinone (**64**) with DIBAL, no evidence of an epoxide by-product (**95**) was detected.



Scheme 3.13

The reduction of 8-fluoroquininone (**65**) (Scheme 3.13) was also carried out using two equivalents of zinc borohydride, stirring at room temperature for 24 hours. The approximate conversion (taken from integration of the crude  $^{19}\text{F}$  NMR spectrum) was 80%, with an approximate ratio of 8:1 8-fluoroquinine (**96**) to 8-fluoro-*epi*-quinine (**93**) in the crude  $^{19}\text{F}$  NMR spectrum. The reaction of 8-fluoroquininone (**65**) with zinc borohydride was more diastereoselective than that of 8-fluoroquinidinone (**64**) with zinc borohydride, as less 8-fluoro-*epi*-product was formed. The crude product was purified using column chromatography on silica gel using chloroform/ethyl acetate (80/20) to elute residual starting material (19% yield), then 100% ethyl acetate to elute the products. 8-Fluoroquinine (**96**) was successfully isolated in 36% yield, whilst 8-fluoro-*epi*-quinine (**93**) was isolated in 4% isolated yield, and there was a 15% isolated yield of mixed fractions containing mostly 8-fluoroquinine with traces of 8-fluoro-*epi*-quinine. As in the reduction of 8-fluoroquinidinone with zinc borohydride, there was no evidence of epoxide formation (**97**), which suggests that the epoxide formation in the DIBAL reactions is not due to the configuration at C9 of 8-fluoroquinidine (**94**) and 8-fluoroquinine (**96**) being ideal for hydroxyl attack on C8 to eliminate fluorine, and is more likely to be related to DIBAL.



Scheme 3.14

The reduction of 8-fluoroquinidinone (**64**) was also attempted with lithium aluminium hydride (Scheme 3.14), in order to investigate whether the epoxide formation would occur with other aluminium based coordinating reducing agents in addition to DIBAL, and if not whether the reaction would be more diastereoselective than the reductions using zinc borohydride. The reaction was carried out using 1.2 equivalents of lithium aluminium hydride, stirring at room temperature in dry diethyl ether for two hours. The crude product was purified by column chromatography on silica gel using chloroform/ethyl acetate (80/20) to elute residual starting material, followed by 100% ethyl acetate to elute the products. The conversion of the reaction

was only 30%, but with an approximately 12:1 ratio of 8-fluoroquinidine (**94**) to 8-fluoro-*epi*-quinidine (**92**). There was a 59% isolated yield of unreacted starting material (**64**) from the column. Despite 8-fluoroquinidine (**94**) being formed as the major product (17% yield), and the apparent increased diastereoselectivity in comparison with zinc borohydride reductions with only 2% of 8-fluoro-*epi*-quinidine (**92**) isolated, no further optimisation of this reaction was carried out. The absence of the epoxide by-product (**95**) in the lithium aluminium hydride reduction of 8-fluoroquinidinone suggests that the epoxide formation in the reduction of 8-fluoroquinidinone and 8-fluoroquininone with DIBAL is not generally due to aluminium containing reagents, but more specifically to DIBAL itself.

**Table 3.12:** Key NMR similarities and differences for 8-fluoro-reduction products

<b>8-fluoro-<i>epi</i>-quinidine (92)</b>	<b>8-fluoro-<i>epi</i>-quinine (93)</b>	<b>8-fluoroquinidine (94)</b>	<b>8-fluoroquinine (96)</b>
$\delta_{\text{H10}} = 5.84$	$\delta_{\text{H10}} = 5.73$	$\delta_{\text{H10}} = 5.73$	$\delta_{\text{H10}} = 5.82$
$\delta_{\text{H11}} = 5.10$ ( <i>trans</i> ) 5.12 ( <i>cis</i> )	$\delta_{\text{H11}} = 4.90$ ( <i>cis</i> ) 4.92 ( <i>trans</i> )	$\delta_{\text{H11}} = 4.91$ ( <i>trans</i> ) 4.94 ( <i>cis</i> )	$\delta_{\text{H11}} = 4.93$ ( <i>cis</i> ) 4.95 ( <i>trans</i> )
$\delta_{\text{H2}'} = 8.71$	$\delta_{\text{H2}'} = 8.68$	$\delta_{\text{H2}'} = 8.42$	$\delta_{\text{H2}'} = 8.37$
$\delta_{\text{F}} = -139.56$	$\delta_{\text{F}} = -137.44$	$\delta_{\text{F}} = -126.88$	$\delta_{\text{F}} = -125.23$
${}^3J_{\text{HF}} = 24.3$ Hz	${}^3J_{\text{HF}} = 24.6$ Hz	${}^3J_{\text{HF}} = 16.0$ Hz	${}^3J_{\text{HF}} = 14.5$ Hz

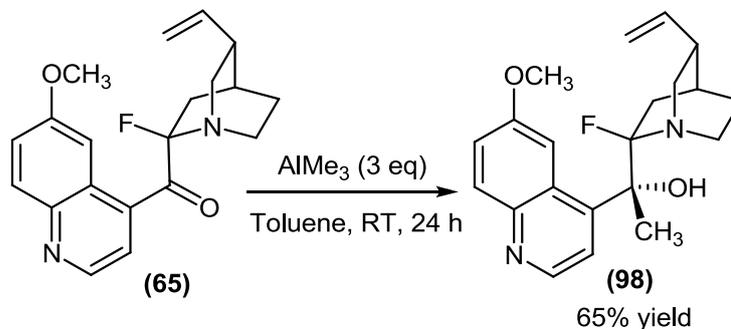
**Table 3.13:** Optical rotation data for the 8-fluoro-reduction products

<b>8-fluoro-<i>epi</i>-quinidine (92)</b>	<b>8-fluoro-<i>epi</i>-quinine (93)</b>	<b>8-fluoroquinidine (94)</b>	<b>8-fluoroquinine (96)</b>
+99.2°	+113.5°	+195.1°	-31.5°

Tables 3.12 and 3.13 highlight the similarities and differences in  ${}^1\text{H}$  NMR,  ${}^{19}\text{F}$  NMR and optical rotation data, for the products obtained from the successful reductions of 8-fluoroquinidinone and 8-fluoroquininone with various reducing agents.

### 3.7 Further nucleophilic additions to 8-fluoroquinidinone (64) and 8-fluoroquininone (65)

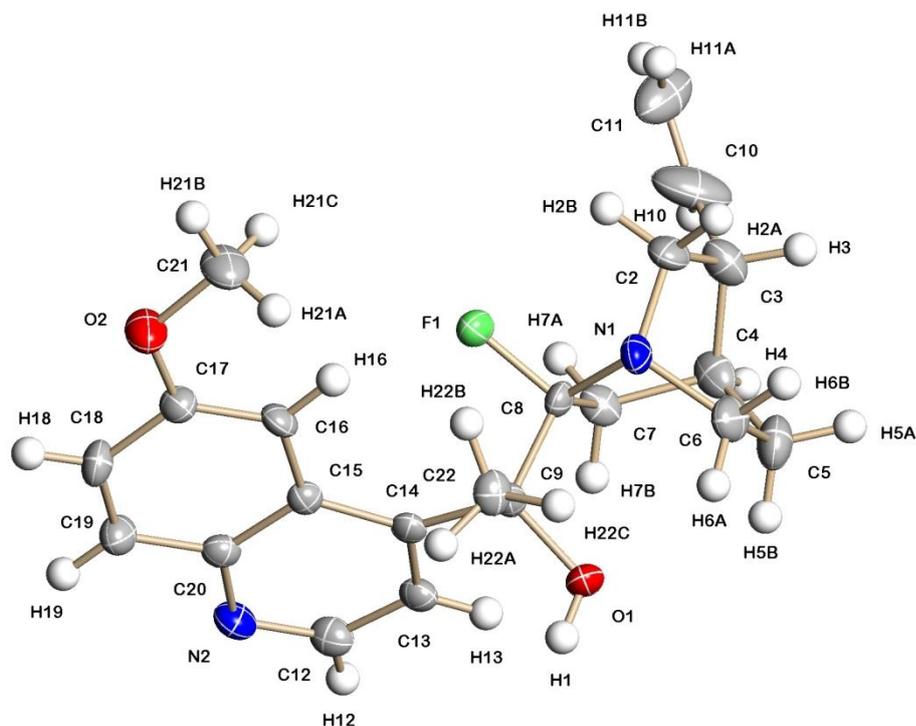
#### 3.7.1 Synthesis of 9-methyl-8-fluoroquinine (98)



**Scheme 3.15**

Following the successful reduction of 8-fluoroquinidinone (64) to 8-fluoroquinidine (94) using aluminium containing coordinating reducing agents such as DIBAL and lithium aluminium hydride, which coordinate to the quinuclidine nitrogen and deliver the hydride from the front, it was thought that perhaps other nucleophiles could be similarly delivered from the front using aluminium containing reagents. Trimethylaluminium (three equivalents) was added dropwise to a stirred solution of 8-fluoroquininone (65) in dry toluene at room temperature, and the reaction was stirred at room temperature for 24 hours before being quenched with water and worked up. The crude product was purified by column chromatography on silica gel using chloroform/ethyl acetate (80/20) to elute residual starting material (approximately 10%), followed by 100% ethyl acetate to elute the product, to give 9-methyl-8-fluoroquinine (98) in 65% yield.

A crystal suitable for X-ray crystallography was grown by slow recrystallisation from chloroform. The molecular structure of 9-methyl-8-fluoroquinine (98) is shown in Figure 3.15. The configuration at the C8 position is (*R*), confirming the quinine configuration, and the configuration at the C9 position is also (*R*), indicating that the methyl nucleophile has attacked from the front (*Si*) face.



**Figure 3.15:** The molecular structure of 9(*R*)-methyl-8(*R*)-fluoroquinine (**98**)

**Table 3.14:** Similarities and differences in the NMR Spectra of 9-Methyl-8-fluoro-*epi*-quinine (**89**) and 9-Methyl-8-fluoroquinine (**98**)

9-Methyl-8-fluoro- <i>epi</i> -quinine ( <b>89</b> )	9-Methyl-8-fluoroquinine ( <b>98</b> )
$\delta_{\text{H10}} = 5.99$	$\delta_{\text{H10}} = 5.76$
$\delta_{\text{H11}} = 5.02$ ( <i>cis</i> )	$\delta_{\text{H11}} = 4.82$ ( <i>cis</i> )
5.04 ( <i>trans</i> )	4.88 ( <i>trans</i> )
$\delta_{\text{H2}'} = 8.69$	$\delta_{\text{H2}'} = 8.39$
$\delta_{\text{F}} = -115.07$	$\delta_{\text{F}} = -118.41$
$\delta_{\text{C8}} = 108.88$ ( $^1J_{\text{CF}} 196.5$ Hz)	$\delta_{\text{C8}} = 105.75$ ( $^1J_{\text{CF}} 193.3$ Hz)

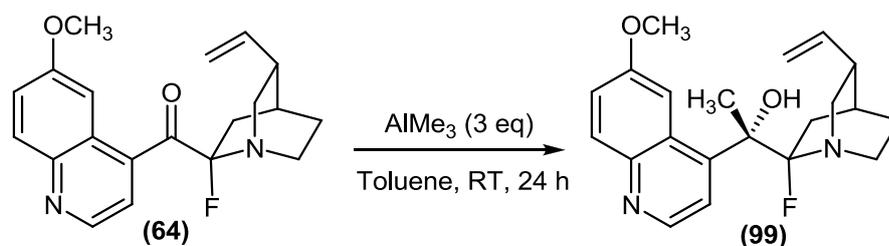
Table 3.14 shows the key differences (and similarities) in the  $^1\text{H}$ ,  $^{19}\text{F}$  and  $^{13}\text{C}$  NMR spectra of 9-methyl-8-fluoro-*epi*-quinine (**89**) and 9-methyl-8-fluoroquinine (**98**). The alkene H10 and both H11 peaks are shifted further upfield in 9-methyl-8-fluoroquinine (H10 5.76 ppm, H11 *cis* 4.82 ppm and *trans* 4.88 ppm) than in 9-methyl-8-fluoro-*epi*-quinine (H10 5.99 ppm, H11 *cis* 5.02 ppm and *trans* 5.04 ppm). The aromatic peaks are also shifted further upfield in 9-methyl-8-fluoroquinine. For example, H2' is located at 8.39 ppm, compared with 8.69 ppm in 9-methyl-8-fluoro-*epi*-quinine. The chemical shift of the fluorine peak for 9-methyl-8-fluoroquinine is also

shifted slightly upfield compared with that of 9-methyl-8-fluoro-*epi*-quinine (-118.41 ppm and -115.07 ppm respectively).

The success of this reaction indicates an ability to tune the configuration at C9 by using different reagents to give different diastereoselective methyl additions. Methyl lithium can be used to obtain 9-methyl-8-fluoro-*epi*-quinine (**89**) from 8-fluoroquininone (**65**), and trimethylaluminium can be used to obtain 9-methyl-8-fluoroquinine (**98**) from 8-fluoroquininone (**65**). As it is possible to purchase other similar aluminium reagents, such as triphenylaluminium and tri-*iso*-butylaluminium, other tuneable nucleophilic additions could possibly be carried out using these reagents and/or phenyllithium and *iso*-butyllithium.

Successful reductions of both 8-fluoroquinidinone (**64**) and 8-fluoroquininone (**65**) with hydride delivery from the front were also carried out with the coordinating reducing agent zinc borohydride. This suggests that further nucleophilic additions with nucleophiles delivered from the front could be achieved using reagents such as dimethylzinc, diethylzinc, or diphenylzinc. However, diethylzinc is not very reactive with carbonyl compounds and requires activation, for example by an amino alcohol. Moreover, organozinc reagents are considerably more expensive than organoaluminium reagents. Therefore, organoaluminium reagents seem preferable for these reactions.

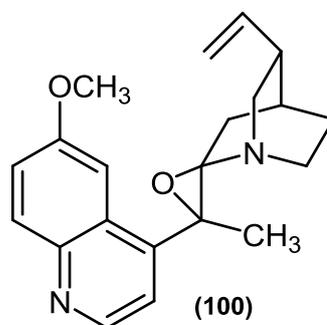
### 3.7.2 Synthesis of 9-methyl-8-fluoroquinidine (**99**)



**Scheme 3.16**

9-Methyl-8-fluoroquinidine (**99**) was also formed from the reaction of 8-fluoroquinidinone (**64**) with trimethylaluminium. Trimethylaluminium (3 equivalents) was added dropwise to a stirred solution of 8-fluoroquinidinone (**64**) at room temperature, and the reaction was stirred at room temperature for 24 hours before being quenched with water and worked up. The  $^1\text{H}$  NMR spectrum of the crude product contained multiple products. Initially the crude product was purified by column chromatography on silica gel using 100% ethyl acetate, which provided some mixed fractions containing multiple compounds, but also led to the isolation of the major

product. The major product (**100**) was not the desired 9-methyl-8-fluoroquinidine (**99**), but appears to be a similar epoxide to those observed in the reduction of 8-fluoroquininone and 8-fluoroquinidinone with DIBAL, although containing a methyl group at C9 instead of a hydrogen. The proposed structure of this product (**100**), which was isolated in 33% yield, is shown in Figure 3.16.



**Figure 3.16:** The proposed structure of the by-product (**100**) obtained in the reaction of 8-fluoroquinidinone (**64**) with  $\text{AlMe}_3$

Accurate mass spectrometry indicates that the molecular weight of the protonated compound (**100**) is  $337.1911 \text{ gmol}^{-1}$ ,  $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_2$  (the formula of **100** protonated) requires  $337.1916 \text{ gmol}^{-1}$ . The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are similar to those of the epoxides obtained previously, of course without the singlet for the hydrogen at C9 in the  $^1\text{H}$  NMR spectrum. Instead there is a singlet corresponding to the methyl group at C9, which appears at 1.59 ppm. In the  $^{13}\text{C}$  NMR spectrum, the quaternary carbon at C8 appears at 79.71 ppm, and the signal for C9, which is also quaternary in this case, appears at 68.01 ppm.

A second column, eluted with chloroform/ethyl acetate (80/20) was used to separate the compounds in the mixed fractions obtained from the first purification. 8-Fluoroquinidinone (**64**) starting material was recovered (30%), in addition to the desired product 9-methyl-8-fluoroquinidine (**99**), which was isolated in a disappointing 13% yield. Further mixed fractions containing unidentified compounds were obtained from this column, and it is possible that on the first column, and in the time between the two columns, the desired product (**99**) could have decomposed, and that if the reaction were to be repeated and a less polar solvent system used for purification in the first instance, the isolated yield of 9-methyl-8-fluoroquinidine (**99**) could be improved. The reaction of 8-fluoroquinidinone (**64**) with trimethylaluminium was a more concentrated reaction

mixture than that of the reaction of 8-fluoroquininone (**65**) with trimethylaluminium, and this could explain the difference in their reactions.

It is also possible that, as in the reactions of 8-fluoroquinidinone (**64**) and 8-fluoroquininone (**65**) with DIBAL, where 8-fluoroquinidinone (**64**) formed mostly 8-fluoroquinidine (**94**) with a small amount of epoxide by-product (**95**) whereas 8-fluoroquininone (**65**) formed only the epoxide (**97**) with no 8-fluoroquinine (**96**) isolated, that the reaction with trimethylaluminium only works well with one diastereoisomer. It is odd that in this case it is 8-fluoroquininone (**65**) that reacts as expected and forms the desired 9-methyl-8-fluoroquinine (**98**) product with no epoxide formed, and that 8-fluoroquinidinone (**64**) forms mostly epoxide (**100**) with a lower isolated yield of 9-methyl-8-fluoroquinidine (**99**), but at least some desired product can be formed in both cases.

Table 3.15 shows the similarities (and differences) in the  $^1\text{H}$ ,  $^{19}\text{F}$  and  $^{13}\text{C}$  NMR spectra of 9-methyl-8-fluoro-*epi*-quinidine (**86**) and 9-methyl-8-fluoro-quinidine (**99**). The alkene protons of 9-methyl-8-fluoroquinidine are shifted upfield (H10 at 5.61 ppm, H11(*trans*) at 4.73 ppm and H11(*cis*) at 4.81 pm) compared with those of 9-methyl-8-fluoro-*epi*-quinidine (H10 at 5.70 ppm, H11(*trans*) at 4.84 ppm and H11(*cis*) at 4.91 ppm). The fluorine signal is also shifted upfield in 9-methyl-8-fluoroquinidine (-123.78 ppm) compared to that of 9-methyl-8-fluoro-*epi*-quinidine (-121.25 ppm).

**Table 3.15:** Similarities and differences in the NMR spectra of 9-methyl-8-fluoro-*epi*-quinidine (**86**) and 9-methyl-8-fluoroquinidine (**99**)

9-Methyl-8-fluoro- <i>epi</i> -quinidine ( <b>86</b> )	9-Methyl-8-fluoroquinidine ( <b>99</b> )
$\delta_{\text{H10}} = 5.70$	$\delta_{\text{H10}} = 5.61$
$\delta_{\text{H11}} = 4.84$ ( <i>trans</i> )	$\delta_{\text{H11}} = 4.73$ ( <i>trans</i> )
4.91 ( <i>cis</i> )	4.81 ( <i>cis</i> )
$\delta_{\text{H2}'} = 8.56$	$\delta_{\text{H2}'} = 8.51$
$\delta_{\text{F}} = -121.25$	$\delta_{\text{F}} = -123.78$
$\delta_{\text{C8}} = 109.03$ ( $^1J_{\text{CF}} 199.7$ Hz)	$\delta_{\text{C8}} = 106.78$ ( $^1J_{\text{CF}} 198.1$ Hz)

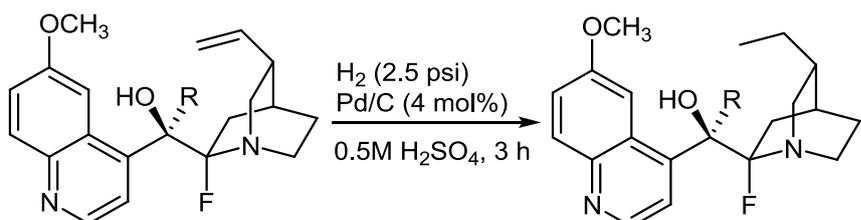
Unfortunately, the presence of the epoxide as the major product in the reaction of 8-fluoroquinidinone with trimethylaluminium means that the use of lithiate and aluminium based reagents to give different “tunable” diastereoselective methyl additions could not be applied in the nucleophilic addition to 8-fluoroquinidinone, as in

the approach suggested for reactions with 8-fluoroquininone. It may, however, be possible to optimise the reaction conditions to eliminate epoxide (**100**) formation, as some 9-methyl-8-fluoroquinidine (**99**) was isolated. Also, as the selective reduction of 8-fluoroquinidinone (**64**) was performed using zinc borohydride, with hydride delivery from the front (*Re*) face, it could still be possible to use zinc based reagents such as dimethylzinc to selectively form 9-methyl-8-fluoroquinidine (**99**). A balance would have to be made between the expense of zinc based reagents and of the purification to separate the epoxide (**100**) and 9-methyl-8-fluoroquinidine (**99**) if trimethylaluminium was used.

### 3.8 Hydrogenation of 9-substituted-8-fluoro-*epi*-quinidine derivatives

In the literature it is suggested that a single rather than a double bond between C10-C11, and the resulting increase in steric hindrance, can improve the enantiomeric excess achieved when using the *Cinchona* alkaloids as electrophilic enantioselective fluorination reagents. Therefore, the hydrogenations of 9-methyl-8-fluoro-*epi*-quinidine (**86**), 9-phenyl-8-fluoro-*epi*-quinidine (**87**) and 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinidine (**88**) to 9-methyl-8-fluoro-10,11-dihydro-*epi*-quinidine (**101**), 9-phenyl-8-fluoro-10,11-dihydro-*epi*-quinidine (**102**) and 9-(4-trifluoromethylphenyl)-8-fluoro-10,11-dihydro-*epi*-quinidine (**103**) respectively were carried out.

**Table 3.16:** Hydrogenation of 9-substituted-8-fluoro-*epi*-quinidine derivatives



Entry	R group	Isolated Yield (%)
1	Me ( <b>101</b> )	63
2	Ph ( <b>102</b> )	75
3	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>103</b> )	47

The procedure was adapted from a literature procedure by Blaser.<sup>8</sup> The 9-substituted-8-fluoro-*epi*-quinidine was dissolved in sulphuric acid (0.5 M) and shaken under pressure of hydrogen (approximately 2.5 psi) in the presence of 4 mol% Pd/C catalyst for three

hours. The product was filtered off the catalyst, neutralised with sodium hydroxide, and the resultant precipitate collected and dried under vacuum to give the pure 9-substituted-8-fluoro-10,11-dihydro-*epi*-quinidine product in good yield. The yield of 9-(4-trifluoromethylphenyl)-8-fluoro-10,11-dihydro-*epi*-quinidine (**103**) (Table 3.16, entry 3) is thought to have been lower due to the decreased solubility of 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinidine (**88**) in sulphuric acid.

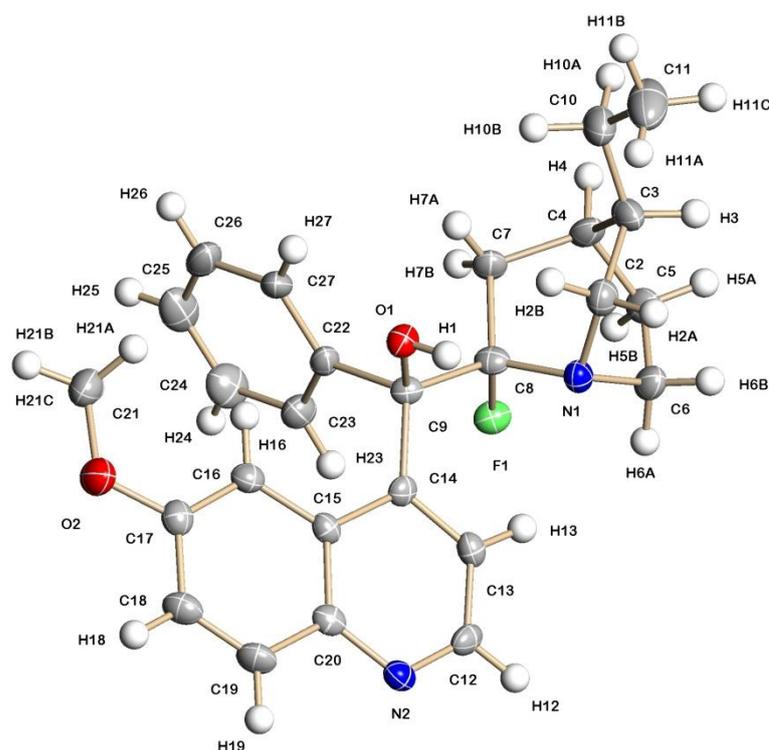
**Table 3.17:** Trends in optical rotations for 9-substituted-8-fluoro-*epi*-quinidine derivatives and 9-substituted-8-fluoro-*epi*-10,11-dihydroquinidine derivatives

Compound	Optical Rotation (°)	Compound	Optical Rotation (°)
9Me8 <i>Fepi</i> Qdine ( <b>86</b> )	+150.6	9Me8 <i>Fepi</i> DHQdine ( <b>101</b> )	+21.6
9Ph8 <i>Fepi</i> Qdine ( <b>87</b> )	+112.6	9Ph8 <i>Fepi</i> DHQdine ( <b>102</b> )	+46.7
9(4CF <sub>3</sub> )Ph8 <i>Fepi</i> Qdine ( <b>88</b> )	+147.3	9(4CF <sub>3</sub> )Ph8 <i>Fepi</i> DHQdine ( <b>103</b> )	+45.5

Table 3.17 shows the optical rotation values of the 9-substituted-8-fluoro-*epi*-10,11-dihydroquinidine derivatives, compared with those of their parent compounds. The unsaturated compounds all have high positive specific rotations (+112.6 to +150.6). The compounds resulting from the hydrogenation of the C10-C11 double bonds (9-methyl-8-fluoro-*epi*-10,11-dihydroquinidine (**101**), 9-phenyl-8-fluoro-*epi*-10,11-dihydroquinidine (**102**) and 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-10,11-dihydroquinidine (**103**)) all have low positive specific rotations (+21.6 to +46.7).

Recrystallisation of 9-phenyl-8-fluoro-10,11-dihydro-*epi*-quinidine (**102**) from chloroform gave a crystal suitable for X-ray crystallography, and the molecular structure is shown in Figure 3.17. The configuration at C9 is (*R*) (*epi*) and the configuration at C8 is (*S*) (quinidine structure). As the configuration of the molecule does not change during hydrogenation, this can be taken as proof that 9-phenyl-8-fluoro-*epi*-quinidine (**87**) shares this configuration, which is further support for the proposed Felkin Ahn type mechanism of nucleophilic addition to 8-fluoroquinidinone (**64**) using lithiate reagents.

The hydrogenations of this series of compounds were carried out to demonstrate that hydrogenations of 8-fluoro compounds could be achieved. It is believed that the hydrogenations of 9-substituted-8-fluoro-*epi*-quinidine derivatives could be performed under similar conditions, but these reactions were not attempted.



**Figure 3.17:** The molecular structure of 9(*R*)-phenyl-8(*S*)-fluoro-10,11-dihydro-*epi*-quinidine (**102**)

### 3.9 Examination of the molecular structures of 8-fluoro-*epi*-quinidine and 8-fluoro-*epi*-quinine derivatives

**Table 3.18:** Selected bond lengths in the molecular structures of 8-fluoro-*epi*-quinidine derivatives

Compound	Bond Length (Å)				
	C8-C9	C9-O1	C9-C14	C9-C22	C10-C11
Quinidine <sup>9</sup> ( <b>27</b> )	1.534(4)	1.423(4)	1.525(4)	-	1.260(6)
9MeQdine ( <b>68</b> )	1.538(5)	1.440(4)	1.540(5)	1.540(5)	1.301(6)
9PhDHQdine ( <b>79</b> )	1.546(4)	1.427(3)	1.525(4)	1.537(4)	1.485(5)
8FQdone ( <b>64</b> )	1.531(8)	1.217(6)	1.512(6)	-	1.201(15)
8FepiQdine ( <b>92</b> )	1.543(7)	1.429(5)	1.517(7)	1.000(0) <sup>a</sup>	1.275(8)
9Me8FepiQdine ( <b>86</b> )	1.560(8)	1.431(7)	1.549(9)	1.536(8)	1.284(10)
9Ph8FepiDHQdine ( <b>102</b> )	1.564(5)	1.429(4)	1.533(5)	1.547(5)	1.490(6)

<sup>a</sup>This is the C9-H9 bond length, equivalent to C9-C22 in 9-substituted derivatives

**Table 3.19:** Selected bond lengths in the molecular structures of 8-fluoro-*epi*-quinine and 8-fluoroquinine derivatives

Compound	Bond Length (Å)				
	C8-C9	C9-O1	C9-C14	C9-C22	C10-C11
9Ph8 <i>Fepi</i> Qnine ( <b>90</b> )	1.566(4)	1.431(4)	1.545(4)	1.529(4)	1.306(5)
9(4CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )8 <i>Fepi</i> Qnine ( <b>91</b> )	1.581(15)	1.427(11)	1.571(14)	1.515(14)	1.404(19)
9Me8 <i>FQ</i> nine ( <b>98</b> )	1.553(6)	1.448(5)	1.565(6)	1.514(5)	1.252(7)

Tables 3.18 and 3.19 show some selected bond lengths in the molecular structures of 8-fluoro-*epi*-quinidine and 8-fluoro-*epi*-quinine derivatives. It can be seen in Table 3.18 that a methyl or phenyl substituent at C9, rather than a hydrogen as in 8-fluoro-*epi*-quinidine (**92**), leads to a small increase in the length of the bonds between C9 and the quinuclidine ring (C8-C9) and C9 and the quinoline ring (C9-C14).

Tables 3.20 and 3.21 show selected bond angles around the quinuclidine ring in 8-fluoro-*epi*-quinidine and 8-fluoro-*epi*-quinine derivatives. Both Table 3.20 and Table 3.21 demonstrate the twist present in the quinuclidine ring to reduce excess ring strain.

**Table 3.20:** Selected bond angles within the quinuclidine ring in the molecular structures of 8-fluoro-*epi*-quinidine derivatives

Compound	Bond Angle (°)			
	C6-N1-C2	C8-N1-C2	C7-C4-C3	C5-C4-C3
Quinidine <sup>a</sup> ( <b>27</b> )	107.5(2)	111.2(2)	109.8(2)	108.1(2)
9MeQdine ( <b>68</b> )	106.8(3)	111.1(3)	108.8(3)	108.4(4)
9PhDHQdine ( <b>79</b> )	106.1(3)	111.2(3)	108.9(3)	107.5(3)
8 <i>FQ</i> dine ( <b>64</b> )	108.5(4)	107.1(4)	109.7(5)	108.6(5)
8 <i>Fepi</i> Qdine ( <b>92</b> )	107.5(5)	110.5(2)	109.9(5)	109.7(5)
9Me8 <i>Fepi</i> Qdine ( <b>86</b> )	106.1(5)	108.7(5)	109.9(5)	106.7(6)
9Ph8 <i>Fepi</i> DHQdine ( <b>102</b> )	105.5(3)	110.0(3)	109.0(3)	106.4(3)

<sup>a</sup>Data taken from reference 9

**Table 3.21:** Selected bond angles within the quinuclidine ring in the molecular structures of 8-fluoro-*epi*-quinine and 8-fluoroquinine derivatives

Compound	Bond Angle (°)			
	C6-N1-C2	C8-N1-C2	C7-C4-C3	C5-C4-C3
9Ph8 <i>Fepi</i> Qnine ( <b>90</b> )	105.9(3)	108.5(3)	111.7(3)	107.6(3)
9(4CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )8 <i>Fepi</i> Qnine ( <b>91</b> )	107.8(9)	107.7(8)	108.0(10)	105.1(10)
9Me8 <i>FQ</i> nine ( <b>98</b> )	106.4(4)	108.0(3)	109.1(4)	108.8(4)

**Table 3.22:** Selected bond angles around C9 in the molecular structures of 8-fluoro-*epi*-quinidine derivatives

Compound	Bond Angle (°)				
	C9-C8-F1	O1-C9-C22	C8-C9-C14	C7-C8-C9	N1-C8-C9
Quinidine <sup>a</sup> ( <b>27</b> )	-	-	109.2(2)	113.6(2)	112.6(2)
9MeQdine ( <b>68</b> )	106.0 <sup>b</sup>	107.6(3)	107.2(3)	112.4(3)	115.4(3)
9PhDHQdine ( <b>79</b> )	106.1 <sup>b</sup>	107.2(3)	108.5(3)	114.4(3)	113.9(3)
8 <i>FQ</i> done ( <b>64</b> )	104.5(4)	-	120.1(4)	113.5(4)	110.8(4)
8 <i>Fepi</i> Qdine ( <b>92</b> )	106.6(5)	109.1 <sup>c</sup>	113.3(5)	114.4(5)	109.3(5)
9Me8 <i>Fepi</i> Qdine ( <b>86</b> )	103.8(4)	106.9(5)	109.2(5)	114.6(5)	113.2(5)
9Ph8 <i>Fepi</i> DHQdine ( <b>102</b> )	104.0(3)	106.9(3)	114.8(3)	115.5(3)	114.4(3)

<sup>a</sup>Data taken from reference 9 <sup>b</sup>This is the C9-C8-H8 angle, equivalent to C9-C8-F1 <sup>c</sup>This is the O1-C9-H9 angle, equivalent to O1-C9-C22

**Table 3.23:** Selected bond angles around C9 in the molecular structures of 8-fluoro-*epi*-quinine and 8-fluoroquinine derivatives

Compound	Bond Angle (°)				
	C9-C8-F1	O1-C9-C22	C8-C9-C14	C7-C8-C9	N1-C8-C9
9Ph8 <i>Fepi</i> Qnine ( <b>90</b> )	103.3(2)	106.8(3)	114.4(3)	114.6(3)	115.7(3)
9(4CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )8 <i>Fepi</i> Qnine ( <b>91</b> )	101.4(8)	107.6(8)	114.9(9)	113.8(9)	116.4(9)
9Me8 <i>FQ</i> nine ( <b>98</b> )	103.1(3)	109.1(3)	110.6(4)	115.8(4)	112.6(4)

Tables 3.22 and 3.23 show selected bond angles around the C9 position in 8-fluoro-*epi*-quinidine and 8-fluoro-*epi*-quinine derivatives. The C8-C9-C14 bond angle

for 8-fluoroquinidinone (**64**) was expected to be wider than for 9-substituted-fluoro-derivatives due to the change in C9 from a  $sp^2$  hybridised carbonyl carbon to a tetrahedral  $sp^3$  hybridised carbon, where the bond angles would be expected to be  $109.5^\circ$ . For both 8-fluoro-*epi*-quinidine and 8-fluoro-*epi*-quinine derivatives, bulkier phenyl and 4-trifluoromethylphenyl substituents appear to widen the angle between the quinoline and quinuclidine rings to approximately  $115^\circ$  (C8-C9-C14), compared with methyl substitution, as 9-methyl-8-fluoro-*epi*-quinidine (**86**) and 9-methyl-8-fluoroquinine (**98**) have narrower angles of approximately  $110^\circ$ . Interestingly, the smaller C8-C9-C14 angles of 9-methyl-8-fluoro derivatives are more similar to quinidine (**27**) ( $109.2^\circ$ ) than to 8-fluoro-*epi*-quinidine (**92**) ( $113.3^\circ$ ), which shares the slightly wider angles of the bulkier aryl substituted 8-fluoro-compounds.

The O1-C9-C22 angle appears slightly wider in 9-methyl-8-fluoroquinine (**98**) than in the 9-substituted compounds with the *epi*-configuration at C9 (for both quinidine and quinine derivatives). It is closer to the O1-C9-H9 angle of 8-fluoro-*epi*-quinidine (**92**) ( $109.1^\circ$ ).

**Table 3.24:** Selected torsion angles in the molecular structures of 8-fluoro-*epi*-quinidine derivatives

Compound	Torsion Angle ( $^\circ$ )					
	C8-C9- C14-C13	N1-C8- C9-C14	O1-C9- C14-C13	N1-C8- C9-O1	C22- C9- C14- C13	N1- C2- C3-C4
Quinidine <sup>a</sup> ( <b>27</b> )	-99.3 (3)	-	-	75.9 (3)	-	-
9MeQdine ( <b>68</b> )	-109.3(4)	-171.9(3)	7.1(5)	72.0(4)	126.2(4)	11.3(5)
9PhDHQdine ( <b>79</b> )	-109.0(3)	175.3(3)	8.5(4)	60.5(3)	124.2(3)	19.1(4)
8FQdone ( <b>64</b> )	-43.3(7)	-42.5(6)	133.5(5)	140.8(4)	-	7.2(7)
8FepiQdine ( <b>92</b> )	77.6(7)	-163.0(5)	-43.0(7)	-43.9(7)	-	6.6(7)
9Me8FepiQdine ( <b>86</b> )	-86.5(7)	-50.7(7)	150.8(5)	70.2(7)	33.2(8)	18.6(7)
9Ph8FepiDHQdine ( <b>102</b> )	4.1(5)	-61.6(4)	-118.4(4)	60.8(4)	124.2(4)	20.2(4)

<sup>a</sup>Data taken from reference 9

**Table 3.25:** Selected torsion angles in the molecular structures of 8-fluoro-*epi*-quinine and 8-fluoroquinine derivatives

Compound	Torsion Angle (°)					
	C8-C9-C14-C13	N1-C8-C9-C14	O1-C9-C14-C13	N1-C8-C9-O1	C22-C9-C14-C13	N1-C2-C3-C4
9Ph8F <i>epi</i> Qnine ( <b>90</b> )	-3.3(4)	52.6(4)	118.2(3)	-69.4(3)	-124.6(3)	2.8(4)
9(4CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )8F- <i>epi</i> Qnine ( <b>91</b> )	-4.1(14)	55.7(12)	116.7(10)	-63.8(11)	-126.5(11)	-8.6(14)
9Me8FQnine ( <b>98</b> )	93.7(5)	164.7(3)	-20.6(5)	-80.1(4)	-140.7(4)	7.6(6)

Tables 3.24 and 3.25 show selected torsion angles in 8-fluoro-*epi*-quinidine and 8-fluoro-*epi*-quinine derivatives. The variation in the N1-C2-C3-C4 torsion angle is a further demonstration of the twist in the quinuclidine ring, which appears to be larger in substituted 8-fluoro-*epi*-quinidine derivatives (9-methyl-8-fluoro-*epi*-quinidine (**86**) 18.6°, 9-phenyl-8-fluoro-*epi*-10,11-dihydroquinidine (**102**) 20.2°) than in substituted 8-fluoro-*epi*-quinine and 8-fluoroquinine derivatives (9-phenyl-8-fluoro-*epi*-quinine (**90**) 2.8°, 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinine (**91**) -8.6°, 9-methyl-8-fluoroquinine (**98**) 7.6°). The large C9 and substituents must cause more distortion of the quinuclidine ring in the *exo* position at C8 than in the *endo* position.

An examination of the N1-C8-C9-C14 torsion angles of 8-fluoroquinidinone (**64**), 9-methyl-8-fluoro-*epi*-quinidine (**86**) and 9-phenyl-8-fluoro-*epi*-10,11-dihydroquinidine (**102**), which are in the range -42.5° to -61.6°, indicates that the quinoline ring is sat in front of the quinuclidine nitrogen, in a closed conformation. Conversely, the N1-C8-C9-C14 torsion angle of -163° for 8-fluoro-*epi*-quinidine (**92**) indicates the quinoline ring is *trans* to the quinuclidine nitrogen, in an open conformation. The C8-C9-C14-C13 torsion angles of these four compounds, in the range ±4.1-86.5°, indicate a *syn* conformation, although the value for 9-methyl-8-fluoro-*epi*-quinidine (**86**) is close to the borderline between *syn* and *anti* at -86.5°.

The preferred solid state conformation of 8-fluoro-*epi*-quinidine (**92**) is *syn*-open. This contrasts with the preferred solid state conformations of 8-fluoroquinidinone (**64**), 9-methyl-8-fluoro-*epi*-quinidine (**86**) and 9-phenyl-8-fluoro-*epi*-10,11-dihydroquinidine (**102**), which are *syn*-closed.

An examination of the N1-C8-C9-C14 torsion angles of 9-phenyl-8-fluoro-*epi*-quinine (**90**) (52.6°) and 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinine (**91**) (55.7°)

indicates that in both compounds the quinoline ring is sat in front of the quinuclidine nitrogen, in a closed conformation. In 9-methyl-8-fluoroquinine (**98**), however, the N1-C8-C9-C14 torsion angle of  $164.7^\circ$  indicates that the quinoline ring is *trans* to the quinuclidine nitrogen, in an open conformation. The C8-C9-C14-C13 torsion angles of  $-3.3^\circ$  and  $-4.1^\circ$  for 9-phenyl-8-fluoro-*epi*-quinine (**90**) and 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinine (**91**) respectively indicate a *syn* conformation, whereas the torsion angle of  $93.7^\circ$  for C8-C9-C14-C13 for 9-methyl-8-fluoroquinine (**98**) indicates an *anti* conformation (although it is very close to the borderline between *syn* and *anti*).

The preferred conformations in the solid state for 9-phenyl-8-fluoro-*epi*-quinine (**90**) and 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinine (**91**) are therefore *syn*-closed (the same preferred solid state conformation as for 8-fluoroquinidinone (**64**), 9-methyl-8-fluoro-*epi*-quinidine (**86**) and 9-phenyl-8-fluoro-*epi*-10,11-dihydroquinidine (**102**)). The preferred solid state conformation of 9-methyl-8-fluoroquinine (**98**) is *anti*-open (the same preferred solid state conformation as quinidine (**27**), 9-methylquinidine (**68**), 9-methyl-10,11-dihydroquinidine (**78**), 9-phenyl-10,11-dihydroquinidine (**79**) and 9-*iso*-butylquinidine (**77**)).

**Table 3.26:** Preferred solid state conformations of all compounds for which molecular structures have been obtained

<i>Syn</i> -open	<i>Syn</i> -closed	<i>Anti</i> -open
8 <i>Fepi</i> Qdine ( <b>92</b> )	8FQdone ( <b>64</b> )	9Me8FQnine ( <b>98</b> )
	9Me8 <i>Fepi</i> Qdine ( <b>86</b> )	Quinidine ( <b>27</b> )
	9Ph8 <i>Fepi</i> DHQdine ( <b>102</b> )	9MeQdine ( <b>68</b> )
	9Ph8 <i>Fepi</i> Qnine ( <b>90</b> )	9MeDHQdine ( <b>78</b> )
	9(4CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )8 <i>Fepi</i> Qnine ( <b>91</b> )	9PhDHQdine ( <b>79</b> )
		9-( <i>iso</i> -butyl)Qdine ( <b>77</b> )

### 3.10 Conclusions and future work

**Table 3.27:** Nucleophilic additions to 8-fluoroquinidinone (**64**)

Entry	Nucleophile	No. Equiv.	Time (h)	Conversion (%)	Yield (%)
<b>1</b>	MeLi	2	3	74	63
<b>2</b>	PhLi	4	8	93	71
<b>3</b>	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> Li	4	6	82	63

**Table 3.28:** Nucleophilic additions to 8-fluoroquininone (**65**)

Entry	Nucleophile	No. Equiv.	Time (h)	Conversion (%)	Yield (%)
1	MeLi	3	6	>90	68
2	PhLi	4.1	6	60	49
3	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> Li	4	6	>95	60

One important conclusion from the work with 8-fluoroquinidinone (**64**) and 8-fluoroquininone (**65**) is that it is easier to make and isolate analogues of 8-fluoro-*epi*-quinidine and 8-fluoro-*epi*-quinine than to make and isolate analogues of quinidine. The replacement of the hydrogen at C8 with a fluorine atom increases the polarity of the carbonyl carbon and hence, increases its reactivity towards nucleophiles, leading to increased conversions. The introduction of the fluorine also alters the polarity of the molecules; there is a greater difference in polarity between the starting materials (8-fluoroquinidinone and 8-fluoroquininone) and the products, making their separation by column chromatography easier. The improvement in the conversions, combined with the simpler purification, has led to much better isolated yields for the 8-fluoro-compounds compared to the non-fluorinated analogues of quinidine. It is also possible that in the nucleophilic additions to quinidinone there was competing enolisation in addition to nucleophilic attack, and that the lack of a hydrogen at C8 in 8-fluoroquinidinone and 8-fluoroquininone has eliminated this problem and may also contribute to increased conversions. As a result, a small library of both 8-fluoro-*epi*-quinine and 8-fluoro-*epi*-quinidine analogues substituted at C9 has been isolated (Tables 3.27 and 3.28).

It is very useful to have access to both the 8-fluoroquinidine and 8-fluoroquinine analogues, to give a wider range of potential enantioselective fluorinating reagents, and antimalarial agents, than the quinidine analogues alone. Quinine analogues could not be formed from quinidinone (**62**), which is formed diastereoselectively. The only potential route would be to allow quinidinone (**62**) to epimerise, then to add a nucleophile to the mixture of both quininone (**63**) and quinidinone (**62**), and to separate the resulting crude reaction mixture by column chromatography. The purification would be unlikely to be successful given the highly complicated purification following diastereoselective addition to quinidinone alone. Skarzewski<sup>10</sup> has performed this reaction, allowing quinidinone (**62**) to epimerise in solution over a period of several days before the

addition of phenylmagnesium chloride. Although it is mentioned that both 9(*S*)-phenylquinidine and 9(*R*)-phenylquinine (from addition to both quinidinone and quinone from the front) were observed as the reaction products, no mention is made of conversions, or of their separation/purification.

The mechanism for nucleophilic addition to 8-fluoroquinidinone (**64**) and 8-fluoroquininone (**65**) is different to that of nucleophilic addition to quinidinone (**62**). Addition to quinidinone (**62**) proceeded via a chelation control mechanism leading to the nucleophile attacking from the front (*Re*) face. From the evidence of molecular structures of 9-methyl-8-fluoro-*epi*-quinidine (**86**), 9-phenyl-8-fluoro-*epi*-quinine (**90**) and 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinine (**91**), (as well as 9-phenyl-8-fluoro-10,11-dihydro-*epi*-quinidine (**102**)), nucleophilic addition to 8-fluoroquinidinone (**64**) and 8-fluoroquininone (**65**) appears to go via a non-chelation-controlled Felkin Ahn type mechanism. Due to the electron withdrawing nature of the fluorine, the quinuclidine nitrogen of 8-fluoroquininone/8-fluoroquinidinone appears less able to coordinate to the nucleophile than that of quinidinone, leading to a non-fixed conformation. The molecule adopts a preferred conformation with the fluorine atom *anti* to the carbonyl oxygen. The nucleophile then attacks from the back (*Si* for 8-fluoroquinidinone and *Re* for 8-fluoroquininone) face (past the “small” C7 substituent) where there is less steric hindrance, and also avoiding electrostatic interactions with the nitrogen lone pair (see Figure 3.6 page 101 for addition to 8-fluoroquinidinone and Figure 3.10 page 108 for addition to 8-fluoroquininone). This is also true for reduction of 8-fluoroquinidinone (**64**) and 8-fluoroquininone (**65**) with sodium borohydride, which is a non-chelating reducing agent.

Interestingly, the quinuclidine nitrogen appears to be reactive enough to coordinate to DIBAL and  $\text{Zn}(\text{BH}_4)_2$  in order to direct the hydride attack from the front to give 8-fluoroquinidine (**94**) and 8-fluoroquinine (**96**). This coordination to the quinuclidine nitrogen and directed attack from the front also seems to apply to the addition of trimethylaluminium to 8-fluoroquininone (**65**) to form 9-(*R*)-methyl-8-(*R*)-fluoroquinine (**98**), rather than the *epi* configuration formed using lithiate nucleophiles. The ability to “tune” the configuration at C9 by using different nucleophilic reagents, *i.e.* using methyllithium to form 9-(*S*)-methyl-8-fluoro-*epi*-quinine (**89**), and trimethylaluminium to form 9-(*R*)-methyl-8-fluoroquinine (**98**), is very promising, as it should allow access to both diastereoisomers of the product. The availability of other organoaluminium reagents at moderate prices indicates that there is scope for further

“tuning” of configuration at C9 for other nucleophiles in addition to methyl groups. Unfortunately, the reaction of 8-fluoroquinidinone (**64**) with trimethylaluminium to form 9-(*S*)-methyl-8-fluoroquinidine (**99**) (rather than the 9-(*R*)-methyl-8-fluoro-*epi*-quinidine (**86**) formed in the addition of methyllithium or methylmagnesium bromide to 8-fluoroquinidinone), is not as selective as the reaction of 8-fluoroquininone (**82**) with trimethylaluminium. Instead, the major product formed is an epoxide (**100**), in a ratio of 2.5:1 with 9-methyl-8-fluoroquinidine (**99**). Therefore the conditions would need to be optimised to minimise epoxide (**100**) formation before such “tuneable” nucleophilic additions could be applied to 8-fluoroquinidinone.

9-Methyl-8-fluoro-10,11-dihydro-*epi*-quinidine (**101**), 9-phenyl-8-fluoro-10,11-dihydro-*epi*-quinidine (**102**) and 9-(4-trifluoromethylphenyl)-8-fluoro-10,11-dihydro-*epi*-quinidine (**103**) have also been formed in good isolated yield. The increased steric bulk caused by the hydrogenation of the C10-C11 double bond could lead to improved product enantiomeric excess when used in enantioselective electrophilic fluorination reactions. There is also potential to reduce the double bonds of 9-substituted-8-fluoro-*epi*-quinine derivatives by hydrogenation.

The preferred solid state conformations have been determined for the compounds of which molecular structures have been obtained. 8-Fluoroquinidinone (**64**), 9-methyl-8-fluoro-*epi*-quinidine (**86**), 9-phenyl-8-fluoro-*epi*-10,11-dihydroquinidine (**102**), 9-phenyl-8-fluoro-*epi*-quinine (**90**) and 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinine (**91**) all have *syn*-closed solid state conformations. 8-Fluoro-*epi*-quinidine (**92**) has a *syn*-open conformation in the solid state, and 9-methyl-8-fluoroquinine (**98**) is the only 8-fluoro-analogue to share the *anti*-open conformation in the solid state with the non fluorinated derivatives for which molecular structures were determined (9-methylquinidine, 9-methyl-10,11-dihydroquinidine, 9-phenyl-10,11-dihydroquinidine, and 9-*iso*-butylquinidine) in chapter two.

**3.11 References for chapter three**

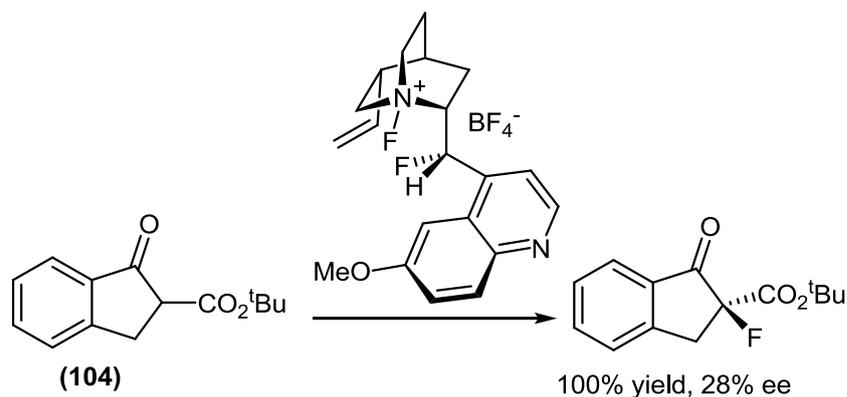
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#### 4.1 Aims of this chapter

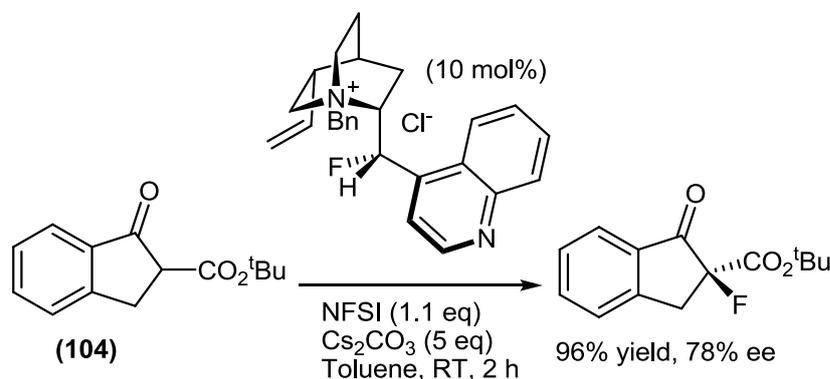
The quinidine, 8-fluoro-*epi*-quinidine and 8-fluoro-*epi*-quinine analogues synthesised in Chapters Two and Three will be tested in three different applications. These tests will include their application as asymmetric electrophilic fluorinating reagents and chiral aminoalcohol ligands in the asymmetric addition of diethylzinc to benzaldehyde, as well as examining their antimalarial activity.

#### 4.2 Enantioselective fluorination

Gilmour<sup>1</sup> replaced the C9 OH group of *Cinchona* alkaloids with a fluorine substituent in order to use a fluorine-ammonium *gauche* effect to limit rotation about the C8-C9 and C9-C4' bonds. As the antiperiplanar alignment of the C-F and C-N<sup>+</sup> is stereoelectronically disfavoured, *gauche* conformations would be favoured, and of the two possible *gauche* conformations the *syn*-clinical-*exo* conformation is disfavoured due to unfavourable non-bonding interactions between the quinoline and quinuclidine rings. *N*-Fluoro-9-(*S*)-fluoroquinidinium tetrafluoroborate was isolated and used in the stoichiometric asymmetric fluorination of *tert*-butyl-1-indanone-2-carboxylate (**104**) (Scheme 4.1), but only a poor enantiomeric excess was achieved (28%), precluding further investigation in this application. Instead, *N*-benzylated-9-fluoro-cinchonine was applied, in conjunction with NFSI, to the fluorination of *tert*-butyl-1-indanone-2-carboxylate (**104**) as a phase transfer catalyst. Initial investigations into optimum solvent, base and temperature conditions led to the best enantiomeric excesses being obtained using toluene, Cs<sub>2</sub>CO<sub>3</sub> and room temperature respectively (Scheme 4.2). These conditions were used in further studies investigating the effect of the *N*-substituent (*N*-benzyl gave a 78% ee, *N*-naphthyl was tolerated giving an ee of 74%, but increasing the bulk to *N*-anthracenyl decreased the ee to 55%), and counterion (five different counterions were investigated in the fluorination of 1-adamantyl-1-indanone-2-carboxylate; and all gave 81-82% ee). The ester substituent of the substrate was also varied, leading to the observation that more sterically demanding ester substituents led to higher enantiomeric excesses. *N*-Benzylated derivatives of 9-deoxycinchonine (10% ee), 9-methoxycinchonine (64% ee) and 9-(OTMS)cinchonine (57% ee) all showed decreased enantiomeric excess compared to that of 9-fluorocinchonine (78% ee).



Scheme 4.1



Scheme 4.2

#### 4.2.1 Screening of new *Cinchona* alkaloids as enantioselective electrophilic fluorinating reagents

##### 4.2.1.1 Confirming formation of *N*-fluoroammonium salt *in situ*

In order to avoid complicated purification and to facilitate high-throughput screening, the enantioselective electrophilic fluorinating reagents formed from the 9-substituted-quinidine, 9-substituted-8-fluoro-*epi*-quinidine and 9-substituted-8-fluoro-*epi*-quinine derivatives synthesised in Chapters Two and Three were generated *in situ* rather than isolated for use.

There was some concern about whether the quinuclidine nitrogen of the 8-fluoro derivatives would be reactive enough to form a *N*-fluoroammonium salt specifically at the quinuclidine nitrogen and not at the quinoline nitrogen due to the electronegativity of the adjacent fluorine atom, which decreases the availability of the quinuclidine nitrogen lone pair and thus prevents the chelation control mechanism from occurring in the nucleophilic addition to 8-fluoroquininone (**65**) and 8-fluoroquinidinone (**64**), leading to 9-substituted-8-fluoro-*epi*-quinine and 9-substituted-8-fluoro-*epi*-quinidine

products. Tests to determine whether the quinuclidine nitrogen would be fluorinated by Selectfluor to form the *N*-fluoroammonium transfer fluorinating reagent *in situ*, without fluorination of the quinoline nitrogen, were therefore carried out.

Initially, the formation of *N*-fluoroquinidinium tetrafluoroborate was carried out to determine the chemical shift at which the  $\text{N-F}^+$  was expected in the  $^{19}\text{F}$  NMR spectrum. Quinidine (**27**) was stirred at room temperature in the presence of Selectfluor (0.75 equivalents) in acetonitrile for one hour. The solvent was removed and the crude  $^{19}\text{F}$  NMR spectrum was recorded in  $\text{CD}_3\text{CN}$ . The  $\text{NF}^+$  fluorine peak was observed at 36.3 ppm. For comparison, in the  $^{19}\text{F}$  NMR spectrum of Selectfluor in  $\text{CD}_3\text{CN}$  the signal appears at 48 ppm for the  $\text{NF}^+$  fluorine atom, and this signal was absent in the  $^{19}\text{F}$  NMR spectrum of *N*-fluoroquinidinium tetrafluoroborate.

A similar test was carried out using 9-phenylquinidine (**69**), stirring in acetonitrile at room temperature for one hour in the presence of Selectfluor (0.75 equivalents), before removal of the solvent to record the  $^{19}\text{F}$  NMR spectrum in  $\text{CD}_3\text{CN}$ . The  $\text{NF}^+$  fluorine of *N*-fluoro-9-phenylquinidinium tetrafluoroborate was observed at 40.3 ppm. No signals related to Selectfluor were observed.

When 9-phenyl-8-fluoro-*epi*-quinidine (**87**) was stirred in acetonitrile for one hour at room temperature in the presence of Selectfluor (0.75 equivalents) before removal of the solvent and subsequent recording of the  $^{19}\text{F}$  NMR spectrum in  $\text{CD}_3\text{CN}$ , the  $\text{NF}^+$  peak was also observed, although shifted slightly upfield to 29.8 ppm. No signals related to Selectfluor were observed. This indicates that the 9-substituted-8-fluoro-*epi*-quinidine and 9-substituted-8-fluoro-*epi*-quinine derivatives do form the *N*-fluoroammonium salts necessary for them to act as enantioselective electrophilic fluorinating reagents.

**Table 4.1:** Chemical shifts of  $\text{NF}^+$  in  $^{19}\text{F}$  NMR spectra

Cinchona alkaloid	$\delta_{\text{F}}$ (ppm)
Selectfluor	48.0
Quinidine ( <b>27</b> )	36.3
9-phenylquinidine ( <b>69</b> )	40.3
9-phenyl-8-fluoro- <i>epi</i> -quinidine ( <b>87</b> )	29.8

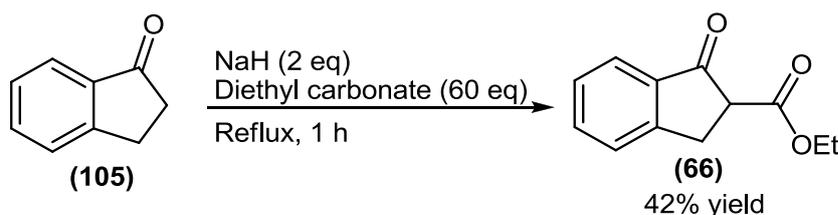
To be certain that the  $\text{NF}^+$  peak observed did not come from fluorination of the quinoline nitrogen, 6-methoxyquinoline was also stirred at room temperature in

acetonitrile for one hour in the presence of Selectfluor (0.75 equivalents). The only peaks observed in the  $^{19}\text{F}$  NMR spectrum (between 50 ppm and -180 ppm) were those of Selectfluor ( $\delta_{\text{F}}$  48.0 and -151.1 ppm), indicating that the quinoline nitrogen is not reactive towards Selectfluor and is not fluorinated under these conditions. Also, the  $\text{NF}^+$  peak in the  $^{19}\text{F}$  NMR spectrum of *N*-fluoropyridinium tetrafluoroborate has been recorded by Umemoto<sup>2</sup> at -48.8 ppm, which is very different from the  $\text{NF}^+$  peak observed for *N*-fluoro-9-phenyl-8-fluoro-*epi*-quinidinium tetrafluoroborate (+29.8 ppm).

Unfortunately, purification and isolation of the  $\text{NF}^+$  reagents generated in these tests was unsuccessful. However, as the intention was to use them *in situ*, the evidence of the formation of the  $\text{NF}^+$  reagents in the crude  $^{19}\text{F}$  NMR spectra was considered sufficient.

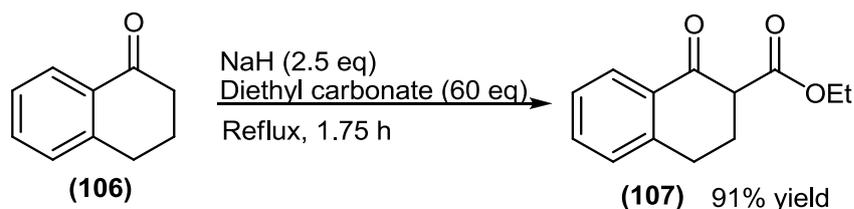
#### 4.2.1.2 Preparation of substrates for asymmetric fluorination

Ethyl-1-indanone-2-carboxylate (**66**) was prepared from indanone (**105**) and diethyl carbonate, using sodium hydride as the base (Scheme 4.3).<sup>3</sup> Diethyl carbonate acted as both a reagent and the solvent in the reaction. The moderate yield of the reaction is due to low conversion, which was not improved even when longer reaction times were used (up to four hours). As sufficient substrate was made for testing after two reactions, no further optimisation of the reaction was performed.



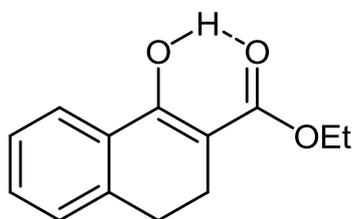
**Scheme 4.3**

Ethyl-1-tetralone-2-carboxylate (**107**) was prepared from tetralone (**106**) and diethyl carbonate in a similar reaction using sodium hydride as the base (Scheme 4.4). The formation of ethyl-1-tetralone-2-carboxylate (**107**) was much more efficient than the formation of ethyl-1-indanone-2-carboxylate (**66**), with a conversion of >95% leading to a good isolated yield (91%).



Scheme 4.4

Unlike ethyl-1-indanone-2-carboxylate (**66**), which was almost entirely in its keto form, the equilibrium for the keto-enol tautomerism of ethyl-1-tetralone-2-carboxylate (**107**) lies in favour of the enol, with the enol:ketone ratio approximately 4:1 (measured by integration of  $^1\text{H}$  NMR in  $\text{CDCl}_3$ ). This is due to the stability of the 6-membered ring shown in Figure 4.1.

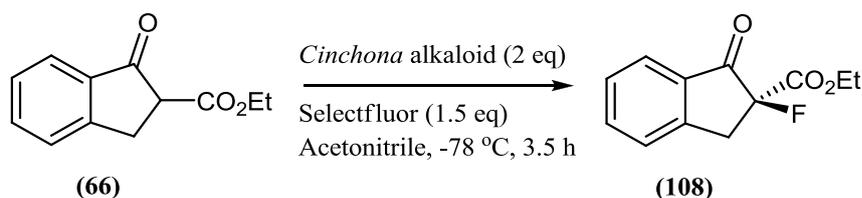
Figure 4.1: The stability of the enol form of ethyl-1-tetralone-2-carboxylate (**107**)

Both substrates were initially fluorinated on a larger scale than intended for testing, in order to fully characterise the fluorinated products, 2-ethoxycarbonyl-2-fluoro-1-indanone (**108**) and 2-ethoxycarbonyl-2-fluoro-1-tetralone (**109**), and also in order to optimise the separation of the enantiomers by chiral HPLC.

Following a literature procedure from Shibata,<sup>4</sup> quinine (2 eq) was stirred at room temperature with Selectfluor (1.5 eq) in acetonitrile to pre-form *N*-fluoroquininium tetrafluoroborate *in situ*, before cooling to 0 °C and slowly adding the substrate dissolved in dichloromethane. This temperature was chosen in order to make a racemic product more likely, to facilitate the development of appropriate HPLC conditions for the separation of the enantiomers. The reaction mixture was stirred at 0 °C for 3.5 hours before being quenched, worked up, and the products purified by column chromatography on silica gel. The products were used to develop the conditions necessary for the determination of the enantiomeric excesses by chiral HPLC. Shibata used the same HPLC column (Chiralcel OJ) for the determination of the enantiomeric excess of both 2-ethoxycarbonyl-2-fluoro-1-indanone and 2-fluoro-2-methoxycarbonyl-1-tetralone, eluted with 10% and 1% isopropanol in hexane respectively. In this case it

was found that the separation of the enantiomers of 2-ethoxycarbonyl-2-fluoro-1-indanone could be performed using 20% isopropanol in hexane with no loss of baseline separation. However, the enantiomers of 2-ethoxycarbonyl-2-fluoro-1-tetralone could not be separated using the Chiralcel OJ column. Following a screen of several possible chiral columns using 1% isopropanol in hexane, the enantiomers were separated using a Chiralcel OD-H column, although complete baseline separation was not achieved until the polarity was reduced by using 0.5% isopropanol in hexane.

#### 4.2.1.3 Enantioselective fluorination of ethyl-1-indanone-2-carboxylate (**66**)



**Scheme 4.5**

In order to test the compounds synthesised in chapters two and three as asymmetric electrophilic fluorinating reagents, the *Cinchona* alkaloid (2 eq) was stirred with Selectfluor (1.5 eq) at room temperature in acetonitrile for one hour to pre-form the *N*-fluoroammonium reagent *in situ*, before cooling to -78 °C and slowly adding ethyl-1-indanone-2-carboxylate (**66**) dissolved in dichloromethane (Scheme 4.5). The reaction mixture was then stirred at -78 °C for 3.5 hours before being quenched with water and worked up. The crude product was purified by column chromatography on silica gel, and the pure product was analysed by chiral HPLC to determine the enantiomeric excess.

Ethyl-1-indanone-2-carboxylate (**66**) was chosen as the substrate because it had previously been used for a number of asymmetric fluorinations in the literature and so a direct comparison could be made between the performance of the new *Cinchona* alkaloid derivatives and previously existing asymmetric fluorinating reagents. Also, the compound was synthesised efficiently using a known procedure,<sup>3</sup> and the HPLC conditions for the separation of the product enantiomers were already established,<sup>4</sup> allowing testing to be carried out without the need for time-consuming initial optimisation.

Each *Cinchona* alkaloid derivative was tested in duplicate in two simultaneous reactions; the conversion, isolated yield, and enantiomeric excess values are reported as

an average of the two tests. If the two reactions gave very different results they were repeated in duplicate in order to obtain consistent results. Some of the isolated yields are lower than might have been expected, probably due to the small scale of the reactions; a small loss in product during the workup or in loading onto the column would result in a significant decrease in isolated yield.

**Table 4.2:** Asymmetric fluorination of ethyl-1-indanone-2-carboxylate (**66**) with quinidine derivatives

Cinchona Alkaloid	Conversion	Yield	e.e.	Enantiomer
	(%) <sup>a</sup>	(%) <sup>b</sup>	(%) <sup>c</sup>	Ratio
Quinine ( <b>26</b> )	100	37	0	50:50
10,11-Dihydroquinine ( <b>30</b> )	50	8	14	43:57
Quinidine ( <b>27</b> )	100	69	30	65:35
10,11-Dihydroquinidine ( <b>31</b> )	100	67	36	68:32
9-Methylquinidine ( <b>68</b> )	100	64	18	41:59
9-Me-10,11-DH-Qdine ( <b>78</b> )	55	29	10	45:55
9-Phenylquinidine ( <b>69</b> )	80	54	22	61:39
9-Ph-10,11-DH-Qdine ( <b>79</b> )	80	37	52	76:24
9-(4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> )-quinidine ( <b>71</b> )	100	77	14	43:57
9-(4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )-quinidine ( <b>72</b> )	85	63	14	57:43
9-(4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )-quinidine ( <b>70</b> )	95	54	0	50:50
9-(3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> )-quinidine ( <b>73</b> )	100	67	42	29:71
9-(3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> )-10,11-DH-Qdine ( <b>82</b> )	90	31	40	30:70

<sup>a</sup>Conversion determined by integration of crude <sup>1</sup>H NMR spectra. <sup>b</sup>Isolated yield. <sup>c</sup>Determined by chiral HPLC.

The enantiomeric excesses obtained in the asymmetric fluorination of ethyl-1-indanone-2-carboxylate (**66**) using the quinidine derivatives synthesised in chapter two are shown in Table 4.2. Unfortunately, none of the quinidine analogues showed promising enantiomeric excess with this substrate, although they were an improvement on the racemic product obtained using quinine (**26**), and some offered an improvement on the enantiomeric excess achieved when using quinidine (**27**) (30%). The best enantiomeric excess (52%) was obtained with 9-phenyl-10,11-dihydroquinidine (**79**). Although increasing the steric bulk at the C9 position was expected to improve the

enantiomeric excess obtained, the sterically bulkier 9-(3,5-bis-trifluoromethylphenyl)quinidine (**73**) gave a lower enantiomeric excess (42%), and other sterically bulky compounds have given disappointing enantioselectivity, most notably 9-(4-trifluoromethylphenyl)quinidine (**70**) which generated a racemic product.

In general, the 10,11-dihydroquinidine derivatives have not met the expectations of improved enantiomeric excess based on evidence in the literature. Although 10,11-dihydroquinidine (**31**) offered improved enantiomeric excess over quinidine (**27**) (36% ee versus 30% ee respectively), 9-methyl-10,11-dihydroquinidine (**78**) (10% ee) led to a significant decrease in enantiomeric excess compared with 9-methylquinidine (**68**) (18% ee), and the enantiomeric excesses obtained with 9-(3,5-bis-trifluoromethylphenyl)quinidine (**73**) and 9-(3,5-bis-trifluoromethylphenyl)-10,11-dihydroquinidine (**82**) were essentially (within experimental error) the same (42% and 40% ee respectively). However, 9-phenyl-10,11-dihydroquinidine (**79**) (52% ee) did show a significant increase in enantiomeric excess, more than doubling the 22% ee generated by 9-phenylquinidine (**69**).

One of the more puzzling aspects of this work is that there does not seem to be a pattern in the enantiomer formed in excess in these reactions. It might have been expected that all of the quinidine derivatives would give the same enantiomer in excess, and that this would be the opposite enantiomer to that produced by quinine (**26**) and 10,11-dihydroquinine (**30**). However, this was not the case. Quinidine (**27**), 10,11-dihydroquinidine (**31**), 9-phenylquinidine (**69**), 9-phenyl-10,11-dihydroquinidine (**79**) and 9-(4-methylphenyl)quinidine (**72**) all gave one enantiomer in excess, whereas dihydroquinine (**30**), 9-methylquinidine (**68**), 9-methyl-10,11-dihydroquinidine (**78**), 9-(4-methoxyphenyl)quinidine (**71**), 9-(3,5-bis-trifluoromethylphenyl)quinidine (**73**) and 9-(3,5-bis-trifluoromethylphenyl)-10,11-dihydroquinidine (**82**) all gave the opposite enantiomer in excess. Interestingly, the three best results, 52% ee from 9-phenyl-10,11-dihydroquinidine (**79**) (enantiomer one in excess), 42% ee from 9-(3,5-bis-trifluoromethylphenyl)quinidine (**73**) (enantiomer two in excess), and 40% ee from 9-(3,5-bis-trifluoromethylphenyl)-10,11-dihydroquinidine (**82**) (enantiomer two in excess), indicated that the introduction of two trifluoromethyl groups on the aromatic ring resulted in the opposite enantiomer to that generated by 9-phenyl-10,11-dihydroquinidine (**79**). The absolute stereochemistry of the products was not determined.

**Table 4.3:** Asymmetric fluorination of ethyl-1-indanone-2-carboxylate (**66**) with 8-fluoro-*epi*-quinidine derivatives

Cinchona Alkaloid	Conversion	Yield	e.e.	Enantiomer
	(%) <sup>a</sup>	(%) <sup>b</sup>	(%) <sup>c</sup>	Ratio
Quinidine ( <b>27</b> )	100	69	30	65:35
10,11-Dihydroquinidine ( <b>31</b> )	100	67	36	68:32
9-Methyl-8-fluoro- <i>epi</i> -quinidine ( <b>86</b> )	85	59	12	56:44
9-Me-8F-10,11-DH- <i>epi</i> -quinidine ( <b>101</b> )	90	41	14	57:43
9-Phenyl-8F- <i>epi</i> -quinidine ( <b>87</b> )	93	66	46	73:27
9-Ph-8F-10,11-DH- <i>epi</i> -quinidine ( <b>102</b> )	95	80	64	82:18
9-(4CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )-8F- <i>epi</i> -quinidine ( <b>88</b> )	93	49	22	61:39
9-(4CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )-8F-10,11-DH- <i>epi</i> -quinidine ( <b>103</b> )	80	50	60	80:20

<sup>a</sup> Conversion determined by integration of crude <sup>1</sup>H NMR spectrum. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by chiral HPLC.

Table 4.3 shows the results obtained in the asymmetric fluorination of ethyl-1-indanone-2-carboxylate (**66**) using the 9-substituted-8-fluoro-*epi*-quinidine derivatives synthesised in chapter three. Three of the compounds surpassed the general level of enantiomeric excesses achieved with 9-substituted-quinidine derivatives (Table 4.2).

Generally, the 10,11-dihydro-8-fluoro-*epi*-quinidine derivatives led to improved enantiomeric excess compared to their unsaturated counterparts. With the exception of 9-methyl-8-fluoro-*epi*-quinidine (**86**) and 9-methyl-8-fluoro-10,11-dihydro-*epi*-quinidine (**101**), which gave the same enantiomeric excess (within experimental error, 12% and 14% ee respectively), a single bond at C10-C11 led to a significant increase in enantiomeric excess obtained. Replacing the vinyl group of 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinidine (**88**) with an ethyl group increased the enantiomeric excess almost threefold, from 22% to 60%, and hydrogenation of the C10-C11 double bond in 9-phenyl-8-fluoro-*epi*-quinidine (**87**) increased the enantiomeric excess from 46% ee to 64% ee, the best result obtained overall in the asymmetric fluorination tests.

The good enantiomeric excesses obtained with 9-phenyl-8-fluoro-10,11-dihydro-*epi*-quinidine (**102**) (64% ee) and with 9-(4-trifluoromethylphenyl)-8-fluoro-10,11-dihydro-*epi*-quinidine (**103**) (60% ee) were improvements on the best result obtained in the asymmetric fluorinations with 9-substituted-quinidine derivatives, that of 9-phenyl-

10,11-dihydroquinidine (**79**) (52%), although all three compounds gave the same enantiomer in excess. All three compounds offer a significant improvement on the results of using the quinine (**26**) (racemic, 0% ee) or quinidine (**27**) (30% ee) natural products.

In contrast to the asymmetric fluorinations with quinidine and 10,11-dihydroquinidine derivatives, where the enantiomer formed in excess did not seem to follow a pattern, all of the 9-substituted-8-fluoro-*epi*-quinidine derivatives gave the same enantiomer in excess.

**Table 4.4:** Asymmetric fluorination of ethyl-1-indanone-2-carboxylate (**66**) with 8-fluoro-*epi*-quinine derivatives

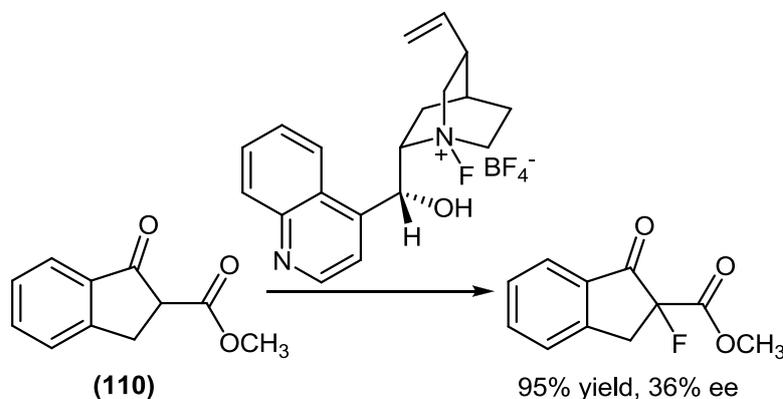
Cinchona Alkaloid	Conversion	Yield	e.e.	Enantiomer
	(%) <sup>a</sup>	(%) <sup>b</sup>	(%) <sup>c</sup>	Ratio
Quinine ( <b>26</b> )	100	37	0	50:50
10,11-Dihydroquinine ( <b>30</b> )	50	8	13	43:57
9-Methyl-8-fluoro- <i>epi</i> -quinine ( <b>89</b> )	78	34	28	36:64
9-Phenyl-8-fluoro- <i>epi</i> -quinine ( <b>90</b> )	90	59	16	42:58
9-(4CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )-8F- <i>epi</i> -quinine ( <b>91</b> )	80	16	30	35:65

<sup>a</sup>Conversion determined by integration of crude <sup>1</sup>H NMR spectrum. <sup>b</sup>Isolated yield. <sup>c</sup>Determined by chiral HPLC.

Table 4.4 shows the enantiomeric excesses obtained in the asymmetric fluorination of ethyl-1-indanone-2-carboxylate (**66**) using 9-substituted-8-fluoro-*epi*-quinine derivatives. 9-Methyl-8-fluoro-*epi*-quinine (**89**), 9-phenyl-8-fluoro-*epi*-quinine (**90**) and 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinine (**91**) all gave the same enantiomer in excess, which was the opposite enantiomer to that obtained in excess in reactions with 9-substituted-8-fluoro-*epi*-quinidine derivatives. All of the 9-substituted-8-fluoro-*epi*-quinine derivatives only gave moderate enantiomeric excesses.

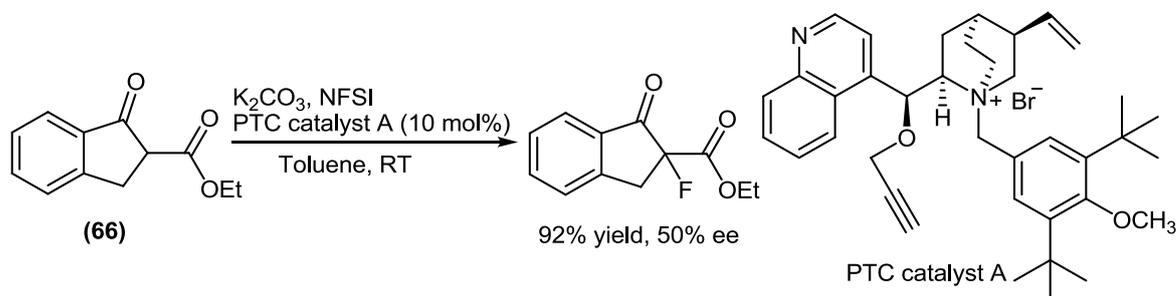
It is strange that the bulky 9-phenyl-8-fluoro-*epi*-quinine (**90**) gave a lower enantiomeric excess than that of 9-methyl-8-fluoro-*epi*-quinine (**89**) (16% ee and 28% ee respectively), and that even the best result for the 9-substituted-8-fluoro-*epi*-quinine derivatives, that of 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinine (**91**) (30% ee), was only slightly better than that of 9-methyl-8-fluoro-*epi*-quinine (**89**).

Despite the generally moderate enantiomeric excesses achieved in the asymmetric fluorination of ethyl-1-indanone-2-carboxylate (**66**), the best values (64% ee when using 9-phenyl-8-fluoro-10,11-dihydro-*epi*-quinidine (**102**), 60% ee when using 9-(4-trifluoromethylphenyl)-8-fluoro-10,11-dihydro-*epi*-quinidine (**103**), and 52% ee when using 9-phenyl-10,11-dihydroquinidine (**79**)) offer significant improvement over the enantioselectivity obtained using quinidine (**27**) or dihydroquinidine (**31**). These results can also be compared favourably with some examples from the literature on the asymmetric fluorination of this and similar substrates. Cahard<sup>5</sup> achieved a 95% yield but only 36% enantiomeric excess when using *N*-fluoro-cinchonidinium tetrafluoroborate to fluorinate the structurally similar methyl-1-indanone-2-carboxylate (**110**) (Scheme 4.6) at -40 °C.



Scheme 4.6

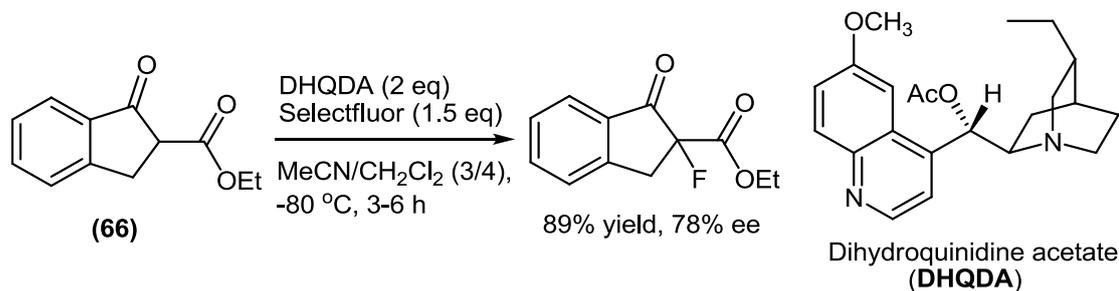
Kim,<sup>6</sup> using a *Cinchona* based phase transfer catalyst, was able to achieve 92% yield and 50% enantiomeric excess for the fluorination of ethyl-1-indanone-2-carboxylate (**66**), using NFSI as the fluorine source (Scheme 4.7). The enantiomeric excess could be improved to 63% by replacing the  $K_2CO_3$  base with  $Cs_2CO_3$ .



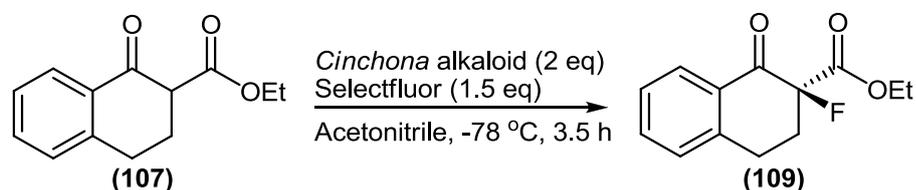
Scheme 4.7

The best literature result for the reagent controlled asymmetric fluorination of this substrate (**66**) was the 89% yield and 78% enantiomeric excess achieved by Shibata,<sup>4</sup>

using a dihydroquinidine acetate/Selectfluor combination (Scheme 4.8). This is only a 15% improvement in enantiomeric excess over the best achieved in this work.



#### 4.2.1.4 Enantioselective fluorination of ethyl-1-tetralone-2-carboxylate (**107**)



**Table 4.5:** Comparison of the performance of selected *Cinchona* alkaloids in the enantioselective fluorination of ethyl-1-indanone-2-carboxylate (**66**) and ethyl-1-tetralone-2-carboxylate (**107**)

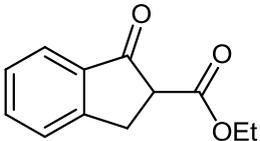
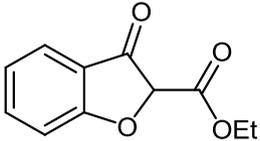
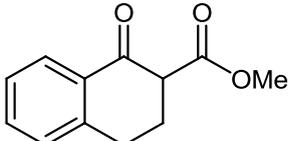
<b>Cinchona alkaloid</b>	<b>Ethyl-1-indanone-2-carboxylate ee (%)</b>	<b>Ethyl-1-tetralone-2-carboxylate ee (%)</b>
Quinine ( <b>26</b> )	Racemic	26
Quinidine ( <b>27</b> )	30	35
9-Ph-10,11-DHQdine ( <b>79</b> )	52	Racemic
9-(3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> )-Qdine ( <b>73</b> )	42	Racemic
9-(3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> )-10,11-DHQdine ( <b>82</b> )	40	6

The asymmetric fluorination of ethyl-1-tetralone-2-carboxylate (**107**) was also carried out (Scheme 4.9). Although there was a significant improvement in the enantiomeric excess obtained with quinine (**26**) (forming racemic 2-ethoxycarbonyl-2-fluoro-1-indanone (**108**), but forming 2-ethoxycarbonyl-2-fluoro-1-tetralone (**109**) in 26% enantiomeric excess with an enantiomeric ratio of 37:63), and a slight increase in enantiomeric excess in the reaction with quinidine (**27**) (30% ee when ethyl-1-indanone-

2-carboxylate (**66**) was the substrate, 35% ee when ethyl-1-tetralone-2-carboxylate (**107**) was the substrate), all of the novel quinidine derivatives led to racemic products or very low enantiomeric excesses. Even the best quinidine analogue from the ethyl-1-indanone-2-carboxylate (**66**) asymmetric fluorination tests, 9-phenyl-10,11-dihydroquinidine (**79**), which gave an enantiomeric excess of 52% for that substrate (**66**), only gave a racemic product in the asymmetric fluorination of ethyl-1-tetralone-2-carboxylate (**107**). Given the disappointing results for the quinidine derivatives, the 9-substituted-8-fluoro-*epi*-quinine and 9-substituted-8-fluoro-*epi*-quinidine derivatives were not tested with this substrate.

Substrate specificity can be a concern when developing compounds for asymmetric fluorination. As demonstrated by the loss of enantioselectivity encountered when the five membered ring of ethyl-1-indanone-2-carboxylate (**66**) was increased to a six membered ring in ethyl-1-tetralone-2-carboxylate (**107**) (Table 4.5), small changes in substrate structure can lead to significant alterations in the enantiomeric excesses achieved in their fluorination. This can be demonstrated by the results of Shibata,<sup>4</sup> summarised in Table 4.6, in which the combined use of dihydroquinidine acetate and Selectfluor in the asymmetric fluorination of three structurally similar substrates led to very different enantiomeric excesses under the same reaction conditions.

**Table 4.6:** Effect of substrate on enantiomeric excess with dihydroquinidine acetate/Selectfluor combination<sup>4</sup>

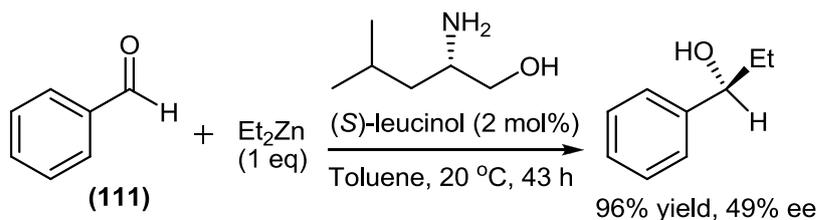
Entry	Substrate	Isolated Yield (%)	Enantiomeric Excess (%)
1		89	78
2		92	80
3		26	2

Although progress has been made in the development of novel asymmetric electrophilic fluorinating reagents through the synthesis and testing of the novel quinidine, 8-fluoro-*epi*-quinidine and 8-fluoro-*epi*-quinine derivatives, with results that compare favourably to some examples in the literature; the ideal substrate for their application has not been found. Substrates for which the enantioselectivity generated by these novel reagents would be excellent must certainly exist, but due to the problems of substrate specificity the search for an appropriate substrate could be time consuming and ultimately fruitless. The use of stoichiometric amounts of *Cinchona* alkaloid is also a problem; screening multiple substrates would be easier if the *Cinchona* alkaloids were used catalytically, as more reactions could be performed with the same amount of *Cinchona* alkaloid, reducing the need for time consuming re-synthesis and purification.

Instead, following the example of Ryan Gilmour<sup>1</sup> who, after receiving only 28% enantiomeric excess in the asymmetric fluorination of *tert*-butyl-1-indanone-2-carboxylate (**104**) using *N*-fluoro-9-(*S*)-fluoroquinidinium tetrafluoroborate, instead applied the compound to another application, in this case phase transfer catalysis, and achieved up to 78% enantiomeric excess with *N*-benzylated derivatives, the compounds will be tested in a different application. *Cinchona* based catalysts are known to be privileged catalysts, and this applicability to multiple types of catalysis will be utilised in the application of the compounds as chiral aminoalcohol ligands in the asymmetric addition of diethylzinc to benzaldehyde (**111**).

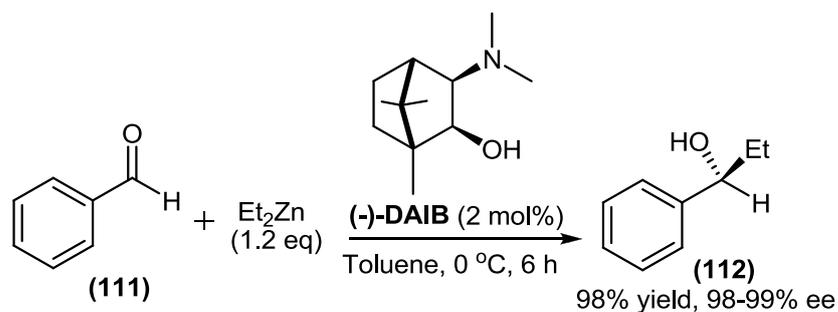
### **4.3 Introduction to the enantioselective addition of diethylzinc to benzaldehyde (111) using chiral aminoalcohols**

The reaction of diethylzinc with aldehydes has become a classical test in the design of new chiral ligands for asymmetric catalysis.<sup>7</sup> It allows the formation of chiral alcohols that are structurally common in natural products and drug compounds, as well as important precursors to other functional groups, with high enantioselectivity. Although dialkylzinc reagents in their *sp* hybridised linear form are unreactive towards carbonyl compounds, coordination to ligands converts the linear structure into a tetrahedral structure, which increases the polarity of the zinc-alkyl bond and increases the nucleophilicity of the alkyl groups.<sup>8</sup>



Scheme 4.10

The first report of an enantioselective diethylzinc addition to benzaldehyde (**111**), catalysed by chiral aminoalcohols, was made by Oguni (Scheme 4.10).<sup>9</sup> He investigated various 2-amino-1-alcohols which were prepared by reduction of chiral  $\alpha$ -amino acids. The yields obtained were excellent (95-100%), and although the enantiomeric excesses achieved were moderate (26-49%), they were a large improvement on those achieved with either a chiral amine or a chiral alcohol alone (2-4% ee), and demonstrated the potential of chiral aminoalcohols in asymmetric diethylzinc addition reactions.

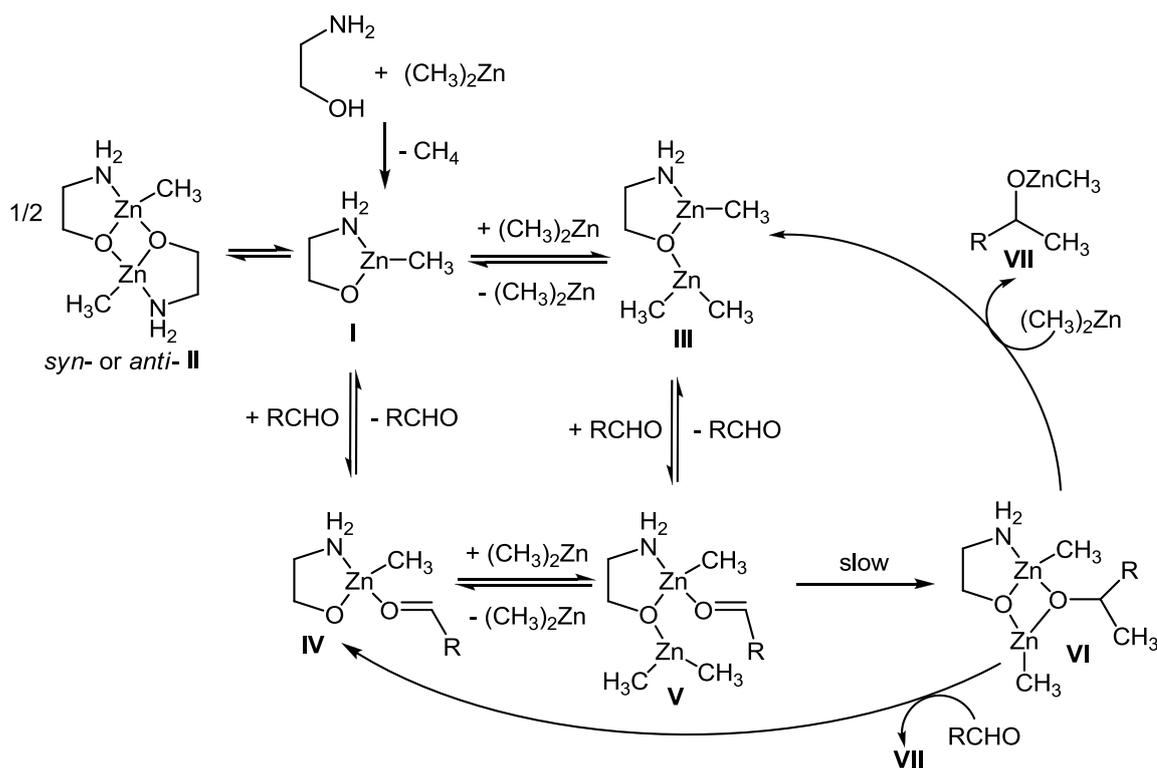


Scheme 4.11

The first highly enantioselective ligand for the catalysis of the alkylation of aldehydes by dialkylzinc reagents was reported by Noyori,<sup>10</sup> in the form of (-)-3-*exo*-(dimethylamino)isoborneol ((-)-DAIB). The reaction of benzaldehyde (**111**) with diethylzinc (1.2 eq.), catalysed by (-)-DAIB (2 mol%) in toluene at 0 °C gave (S)-1-phenyl-1-propanol (**112**) in 98% isolated yield and an excellent 98-99% enantiomeric excess (Scheme 4.11). *Para*-substituted benzaldehydes, as well as  $\alpha,\beta$ -unsaturated and aliphatic aldehydes could also be alkylated with high yield and enantioselectivity (81-96% yield, 61-96% ee). It was noted that two zinc species were required per alcohol for a successful alkylation reaction, a 1:1:1 or 1:2:2 mixture of benzaldehyde (**111**), diethylzinc and (-)-DAIB respectively led to the isolation of benzyl alcohol as the only product, with no evidence of ethylation.

Further investigation into the mechanism of the aminoalcohol promoted reaction of dialkylzincs with aldehydes was carried out by Noyori,<sup>11</sup> using the model system dimethylzinc (used because methylzinc intermediates are less fluxional than other alkyl

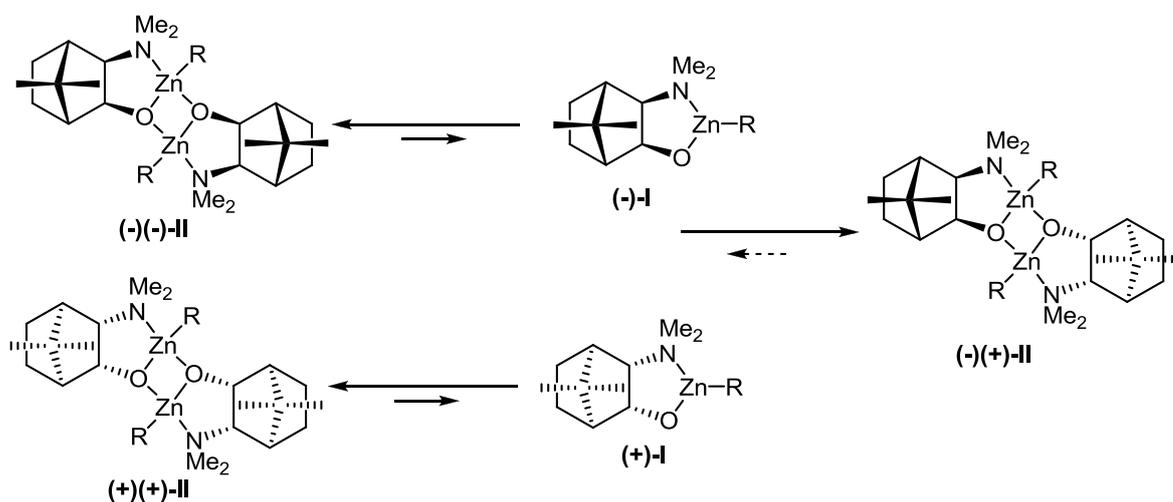
analogues and thus easier to monitor), formaldehyde and 2-aminoethanol, for which the catalytic cycle shown in Figure 4.2 was proposed. The reaction of the aminoalcohol with dimethylzinc forms zinc-amino alkoxide **I**, which is in equilibrium with dimer **II**. Reaction of **I** with dimethylzinc gives the dinuclear zinc compound **III**. When an aldehyde (RCHO) is added, the monoalkylated zinc becomes the Lewis acid activator for the carbonyl oxygen in complex **V**, which is also formed by introduction of an aldehyde into complex **I**, followed by dimethylzinc coordination. Compound **V** contains a nucleophilic methyl group, which transfers slowly to the carbonyl, leading to compound **VI**. The methyl group attached to the amine coordinated zinc interacts with the R group on the aldehyde, which often dictates the stereochemical outcome. Introduction of another aldehyde or dimethylzinc causes complex **VI** to collapse to compounds **III** or **IV**, or to product **VII** respectively, to continue the catalytic cycle. The actual catalyst for the dialkylzinc addition reaction is the zinc-amino alkoxide **I**, as this is regenerated.



**Figure 4.2:** Catalytic cycle for the asymmetric addition of dimethylzinc to aldehydes

Dialkylzinc reactions with aldehydes show a non-linear effect. For example, in the reaction of benzaldehyde (**111**) with diethylzinc catalysed by 8 mol% (-)-DAIB in only

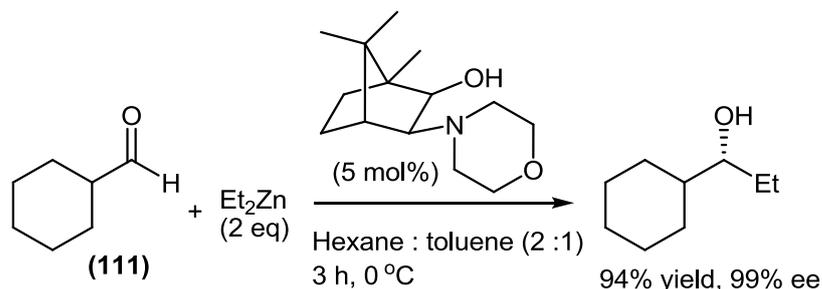
15% enantiomeric excess, (*S*)-1-phenyl-1-propanol (*S*-**112**) is generated in 95% enantiomeric excess.<sup>12</sup> When enantiomerically pure DAIB is used for the same reaction the enantiomeric excess of the product is 98%. This is due to the difference in reactivity between the different complexes of **II**. Homodimeric complexes (+)(+)-**II** and (-)(-)-**II** and their corresponding monomers (+)-**I** and (-)-**I** are in an equilibrium favouring the dimers. Whilst they are in monomeric form, (+)-**I** and (-)-**I** can combine to form the heterodimer (+)(-)-**II**, which is very stable, catalytically inactive and therefore does not participate in benzaldehyde alkylation. Therefore, (-)-DAIB dominates the catalytic cycle, as the homodimer dissociates more easily into the monomeric species responsible for the catalysis, and the minor (+)-DAIB is “tied up” in the heterodimer. This is demonstrated in Figure 4.3.



**Figure 4.3:** The dimers responsible for the nonlinear effect observed in dialkylzinc reactions with aldehydes

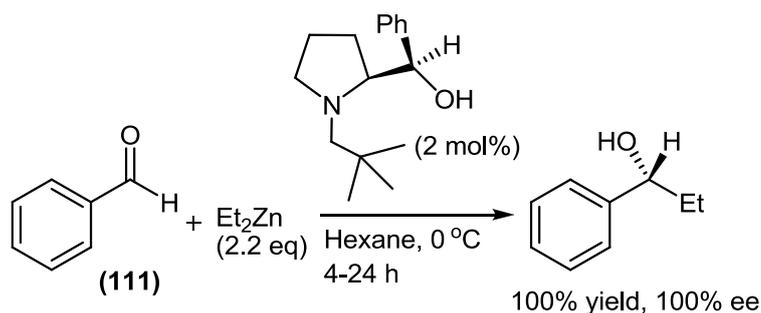
Derivatives of DAIB have been developed by Nugent,<sup>13</sup> in order to improve upon DAIB's air-sensitivity and lower enantioselectivity in the alkylation of aliphatic aldehydes. (2*R*)-(+)-3-*exo*-Morpholinoisoborneol ((+)-MIB), and the opposite enantiomer (-)-MIB, both promoted the asymmetric addition of diethylzinc to a series of aldehydes (Scheme 4.12). Addition to aromatic and substituted aliphatic aldehydes proceeded with excellent enantioselectivity (97-99% ee), and although the addition to straight chain aldehydes showed decreased enantioselectivity, the enantiomeric excess obtained was still excellent (91% ee in the reaction of *n*-hexanal with diethylzinc). It was also noted that MIB has improved air stability compared with DAIB. The crystals

of MIB showed no degradation of spectroscopic properties or catalytic performance after storage under air at ambient temperature for three months.



**Scheme 4.12**

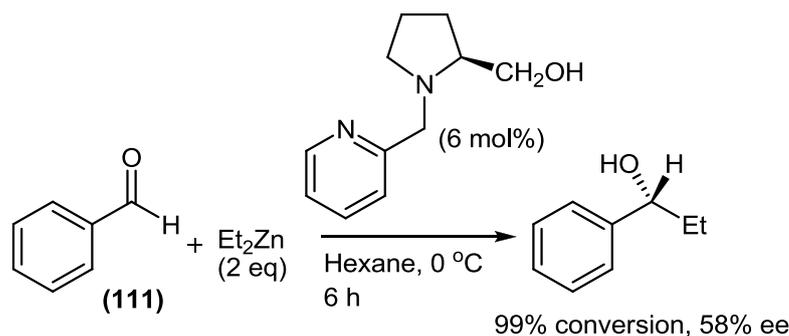
The first chiral catalysts to be specifically designed for the enantioselective addition of dialkylzinc reagents to aldehydes were chiral pyrrolidinylmethanols produced by stereospecific arylation of (*S*)-proline and subsequent reduction of the chiral  $\alpha$ -amino ketones, developed by Soai.<sup>14</sup> These catalysts, and their lithium alkoxide salts, were found to be efficient catalysts in the asymmetric addition of dimethyl and diethylzinc reagents to aryl,  $\alpha,\beta$ -unsaturated and aliphatic aldehydes, in excellent enantiomeric excess (up to 100%, Scheme 4.13).<sup>15</sup> Increasing the steric bulk of the alcohol moiety increased the asymmetric induction (the primary alcohol *N*-methylprolinol led to a racemic product, the secondary alcohol (1*R*,2'*S*)-(-)-phenyl(1-methylpyrrolidin-2-yl)methanol led to an enantiomeric excess of 72%, and the tertiary alcohol (*S*)-(+)-diphenyl(1-methylpyrrolidin-2-yl)methanol led to an enantiomeric excess of 97%). Increasing the steric bulk of the *N*-substituent led to the (*R*) enantiomer of the product alcohol being favoured.



**Scheme 4.13**

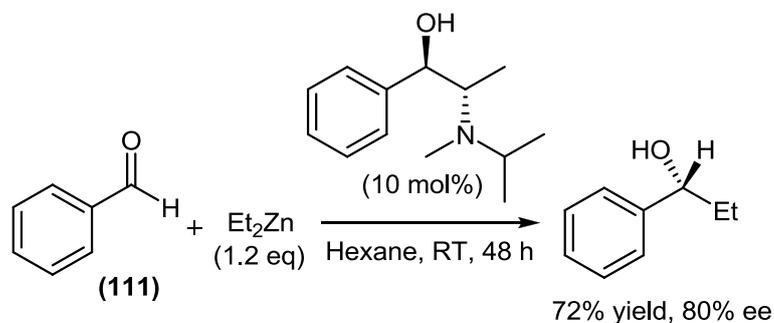
Chelucci<sup>16</sup> did not reach such impressive enantiomeric excesses when he used 2-substituted-1-(2-pyridylmethyl)pyrrolidines (Scheme 4.14). He observed the opposite effect to Soai whereby bulkier substituents on the nitrogen led to a decrease in the enantiomeric excess generated in the product ((*S*)-hydroxymethyl-1-(2-

pyridylmethyl)pyrrolidine gave an enantiomeric excess of 58%, whereas (*S*)-2-(1-hydroxy-1-methylethyl)-1-(2-pyridylmethyl)pyrrolidine gave an enantiomeric excess of 37% and (*S*)-2-(diphenylmethanol)-1-(2-pyridylmethyl)pyrrolidine only gave an enantiomeric excess of 3%). For the bulkier *N*-substituents, the lithium alkoxide of the catalyst led to better enantioselectivity than use of the catalyst without lithiation (e.g. the lithium alkoxide of (*S*)-2-(diphenylmethanol)-1-(2-pyridylmethyl)pyrrolidine increased the enantiomeric excess generated to 33%).



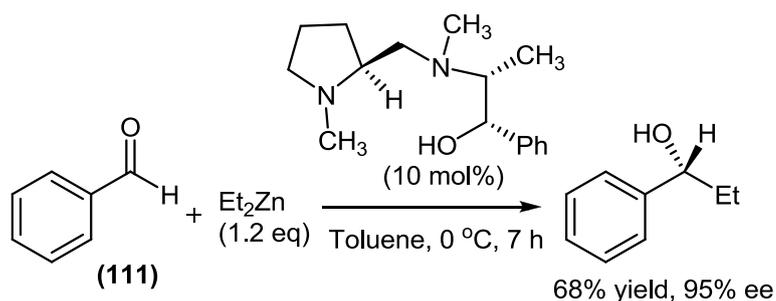
Scheme 4.14

Ephedrine and norephedrine derivatives have also been extensively investigated as catalysts for the asymmetric addition of dialkylzinc reagents to aldehydes. As both enantiomers are readily available, both enantiomers of chiral catalyst can be easily synthesised in the same yield and enantiopurity, leading to predictable access to both enantiomers of the product. Chaloner's *N*-alkylated ephedrine derivatives, when tested in the asymmetric addition of diethylzinc to benzaldehyde (**111**) (Scheme 4.15), gave good isolated yields (60-72%) and enantiomeric excesses (64-80%), with the enantioselectivity increasing with the size of the nitrogen substituent.<sup>17</sup> The catalysts were also successful for the asymmetric addition of diethylzinc to some substituted benzaldehydes such as 4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>CHO (52% ee), 4-MeC<sub>6</sub>H<sub>4</sub>CHO (75% ee), and 3-ClC<sub>6</sub>H<sub>4</sub>CHO (78% ee).



Scheme 4.15

Further investigation by Chaloner<sup>18</sup> into the alkylation of various aldehydes by diethylzinc, catalysed by *N*-*iso*-propylephedrine (the best catalyst in the initial screen of ephedrine derivatives) improved the yield and enantioselectivity of the reaction by using an excess of diethylzinc over benzaldehyde (**111**). In fact, the best enantiomeric excess (95%) was obtained when four equivalents of diethylzinc were used. The alkylations of heptanal (94% yield, 82% ee) and cyclohexane carbaldehyde (90% yield, 97% ee) also proceeded smoothly, with the use of four equivalents of diethylzinc consistently leading to much better enantioselectivity.

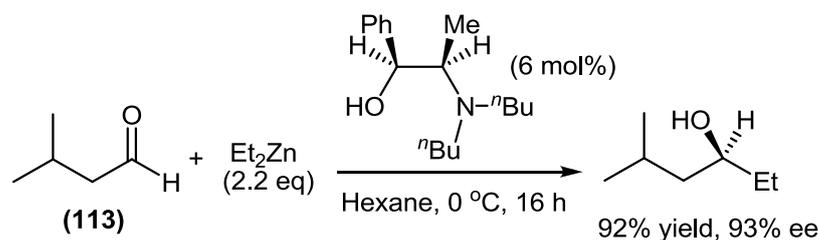


**Scheme 4.16**

Corey and Hannon<sup>19</sup> (Scheme 4.16) used the lithium salt of (1*R*,2*S*)-*N*-[2-(dimethylamino)ethyl]ephedrine to catalyse the addition of diethylzinc to benzaldehyde giving the (*R*) enantiomer in 90% enantiomeric excess. The use of (1*S*,2*S*)-*N*-[2-(dimethylamino)ethyl]ephedrine and (1*S*,2*R*)-*N*-[2-(dimethylamino)ethyl]ephedrine both gave the (*S*) enantiomer in 91% and 95% enantiomeric excess respectively, proving that the enantioselectivity is dependent on the configuration of the alcohol.

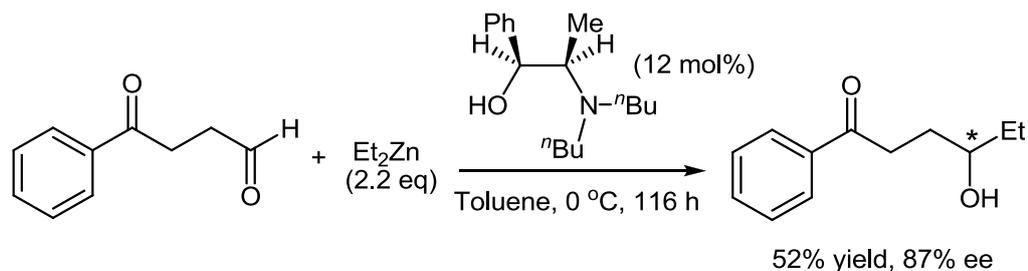
Soai<sup>20</sup> used *N,N*-dialkyl-norephedrine derivatives for the enantioselective addition of dialkylzinc reagents to aromatic and aliphatic aldehydes. In the reaction of diethylzinc with 3-methylbutanal (**113**) (Scheme 4.17), the enantioselectivity achieved increased with the number of carbons in the chain of the nitrogen substituent, peaking at four carbons, with *N,N*-di-*n*-butylnorephedrine (DBNE) giving the best enantiomeric excess (93%). The enantiopurity of the products decreased when the nitrogen substituent had a chain length of greater than four carbons (*n*-pentyl - 75% ee, *n*-octyl - 76% ee). *N,N*-Di-*n*-butylnorephedrine was also the most effective catalyst for the asymmetric addition of diethylzinc to nonanal (87% ee), where the use of bulky *N*-substituents such as *N*-*iso*-butyl and *N*-phenylethyl led to a complete disappearance of asymmetric induction. In the reaction of benzaldehyde (**111**) with diethylzinc, catalysed by DBNE, greater enantiomeric excess was achieved when the reaction was performed

at 0 °C (90% ee) compared with lower temperatures (running the reaction at -30 °C to -10 °C gave 78% enantiomeric excess). When the addition of diethylzinc to 3-methylbutanal (**113**) catalysed by 6 mol% DBNE was performed at 0 °C the enantiomeric excess was 93%, whereas at room temperature it was 91%, suggesting 0 °C as the optimum temperature. The optimum enantioselectivity was achieved when four equivalents of dialkylzinc were used in relation to aldehyde. DBNE was then used to catalyse the alkylation of several aliphatic aldehydes using various dialkylzinc reagents, generating chiral secondary aliphatic alcohols in very high enantiomeric excess (78-95%).



Scheme 4.17

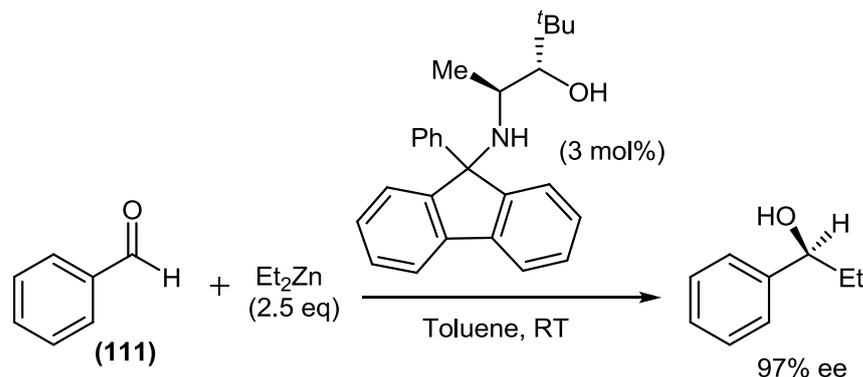
DBNE was later used by Soai to catalyse the formation of chiral  $\gamma$ -hydroxyketones without the need for an asymmetric aldol reaction, via the chemoselective asymmetric addition of dialkylzinc reagents to  $\gamma$ -keto aldehydes (Scheme 4.18).<sup>21</sup> The aliphatic  $\gamma$ -hydroxyketones were generated in high enantiomeric excess (81-87%), and the keto functionality remained unreacted.



Scheme 4.18

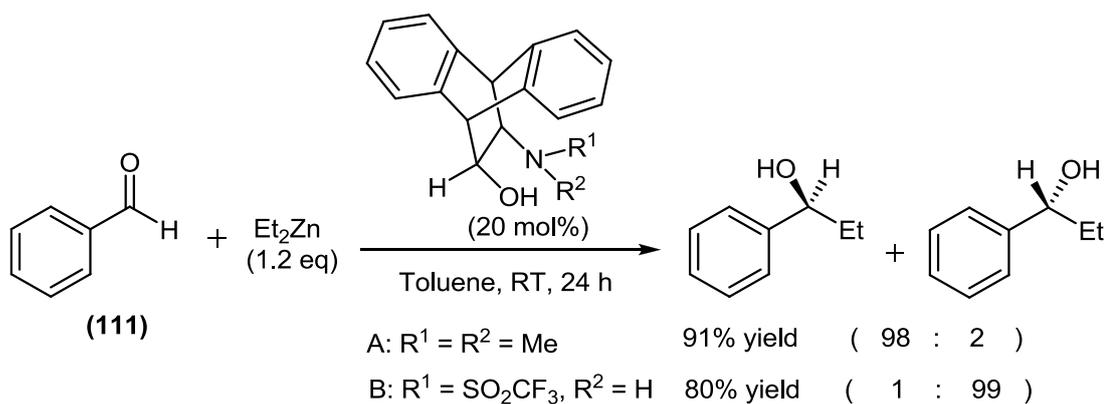
Sardina<sup>22</sup> used *N*-(9-phenylfluoren-9-yl)- $\beta$ -amino alcohols as catalysts for the asymmetric addition of diethylzinc to aldehydes. After screening various ligands in the addition of diethylzinc to benzaldehyde (**111**) using 3 mol% aminoalcohol in toluene at room temperature, (3*S*,4*S*)-2,2-dimethyl-4-[*N*-(9'-phenylfluoren-9'-yl)amino]pentan-3-ol was found to be the best catalyst, generating (*S*)-1-phenyl-1-propanol (*S*-**112**) in an excellent 97% enantiomeric excess (Scheme 4.19). The general applicability of this catalyst was then investigated in the asymmetric addition of diethylzinc to a series of

aromatic and aliphatic aldehydes, which all gave excellent enantiomeric excesses (83-98%). Steric hindrance in the substrate played an important role in the determination of enantioselectivity in the reaction. For example, *meta*- or *para*-substituted benzaldehydes generally underwent more enantioselective additions than *ortho*-substituted benzaldehydes, and 2-naphthaldehyde gave better enantiomeric excess (97%) than 1-naphthaldehyde (86% ee). Asymmetric alkylations of both linear and branched aliphatic aldehydes also proceeded with excellent enantioselectivity (97-98% ee).



Scheme 4.19

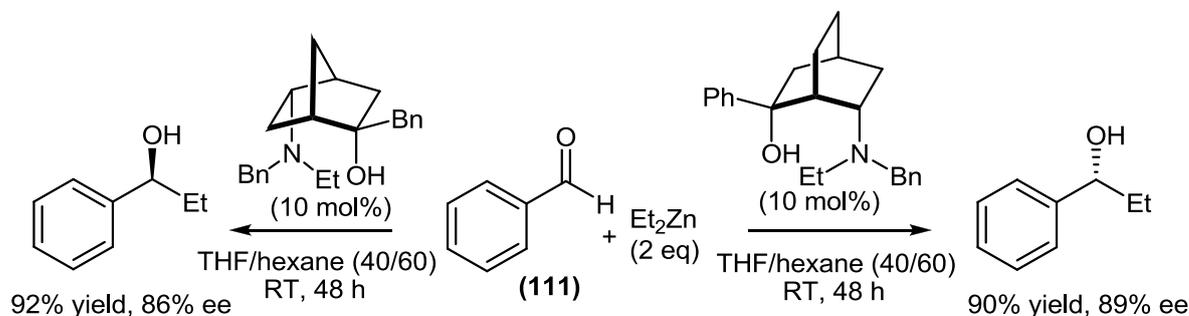
Kunieda<sup>23</sup> observed a dramatic reversal of stereoselectivity depending on the use of either *N,N*-dimethyl- or *N*-sulphonyl-substituted  $\beta$ -amino alcohols that were sterically constrained by a dibenzobicyclo[2.2.2] ring system (Scheme 4.20), both of which gave excellent enantiomeric excesses.



Scheme 4.20

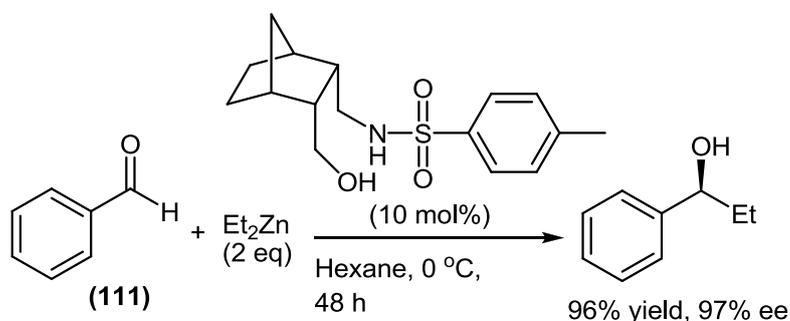
The rigid bicyclic structure of the  $\gamma$ - and  $\delta$ -amino alcohols based on bicyclo[2.2.1]heptane and bicyclo[2.2.2]octane was used by Frejd<sup>24</sup> to reduce the number of close energy diastereoisomeric transition states in the asymmetric diethylzinc addition to benzaldehyde (111). The very good enantiomeric excesses obtained (up to 89%) demonstrated that the formation of amino alcohol-zinc chelates was not

particularly sensitive to the distance between the nitrogen and oxygen. (*1R,2R,4S,6S*)-6-(*N*-benzyl-*N*-ethyl-amino)-2-phenyl-bicyclo[2.2.2]octan-2-ol (90% yield, 89% ee, (*R*)-1-phenyl-1-propanol (*R*-**112**) in excess) and (*1S,2R,4S,5S*)-2-benzyl-5-(*N*-benzyl-*N*-ethyl-amino)-bicyclo[2.2.1]heptan-2-ol (92% yield, 86% ee, (*S*)-1-phenyl-1-propanol (*S*-**112**) in excess) were the most promising ligands (Scheme 4.21).



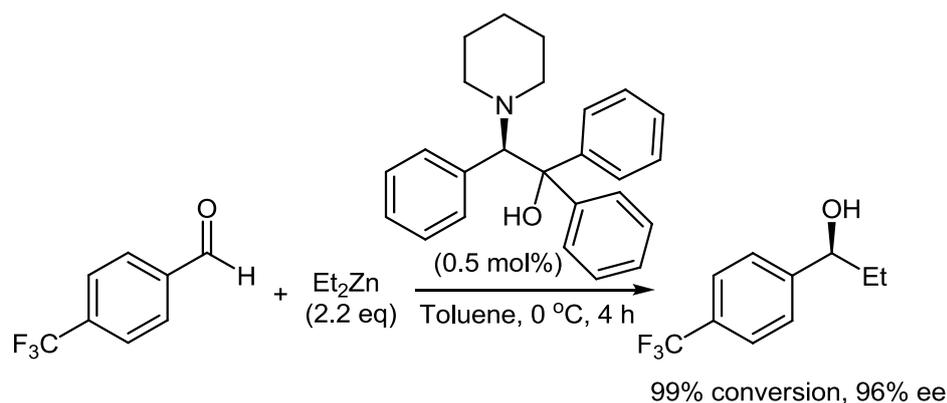
Scheme 4.21

Tanyeli<sup>25</sup> also made use of norbornane in designing *cis*-1,4-aminoalcohol ligands for diethylzinc addition to benzaldehyde (**111**). Of all the catalysts screened, *N*-(((2*S*,3*R*)-3-(hydroxymethyl)bicyclo[2.2.1]heptan-2-yl)methyl)-4-methylbenzenesulfonamide gave the best enantioselectivity, generating 1-phenyl-1-propanol (**112**) in 96% yield and 97% enantiomeric excess (Scheme 4.22).



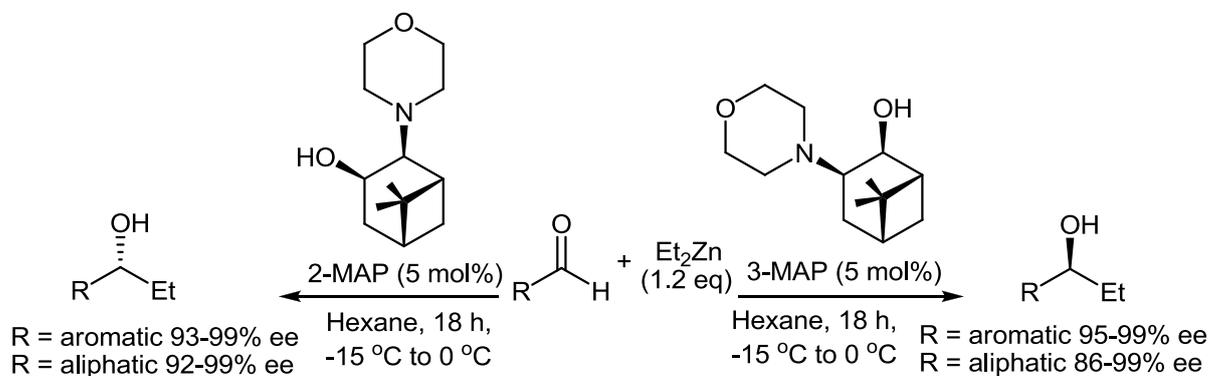
Scheme 4.22

Pericàs<sup>26</sup> synthesised a range of 2-aryl-1,1-diphenylethylene oxides with aryl groups with diverse structural and electronic properties. The optimum catalyst, (*R*)-2-piperidino-1,1,2-triphenylethanol, which out-performed all other catalysts in catalytic activity and enantioselectivity in the standard diethylzinc ethylation of benzaldehyde (**111**), in addition to the ethylation of a library of aromatic aldehydes, gave enantiomeric excesses of 95-96%, even when only 0.5 mol% (an order of magnitude below the usual amount of chiral ligand traditionally employed in this kind of reaction) was used (Scheme 4.23).



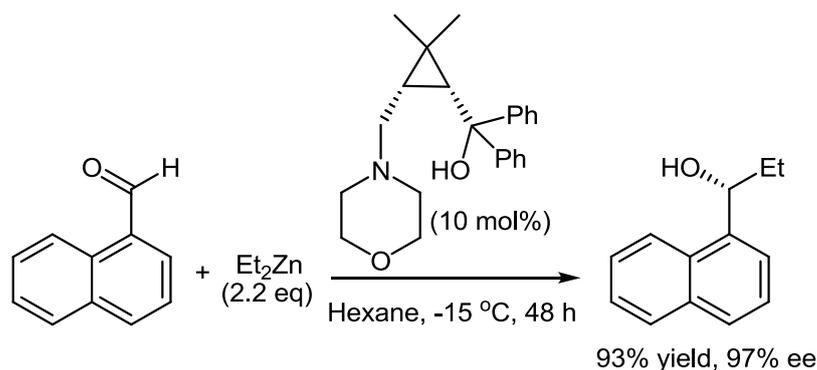
Scheme 4.23

Krzeminski and Singaram<sup>27</sup> synthesised the regioisomeric, *pseudo*-enantiomeric pair of amino alcohols (*1R,2S,3R,5R*)-6,6-dimethyl-2-morpholinobicyclo[3.1.1]heptan-3-ol (**2-MAP**) and (*1R,2S,3R,5R*)-6,6-dimethyl-3-morpholinobicyclo[3.1.1]heptan-2-ol (**3-MAP**) from naturally occurring (-)- $\beta$ -pinene. Switching the amino and alcohol positions led to opposite enantiofacial selectivity in the reaction of diethylzinc with aldehydes, which proceeded with near quantitative yield and excellent enantiomeric excess for both aromatic and aliphatic aldehydes (Scheme 4.24). The *pseudo*-enantiomeric behaviour of this aminoalcohol pair avoids the need for unnatural expensive (+)- $\beta$ -pinene for the synthesis of the opposite enantiomers of either 2-MAP or 3-MAP. These compounds therefore have an advantage over compounds such as DAIB or MIB which are based on camphor, as (-)-camphor is over 150 times more expensive than naturally occurring (+)-camphor, but both would be needed in order to access both enantiomers of product. This would be an advantage shared by chiral aminoalcohol catalysts derived from quinine and quinidine, as both *pseudo*-enantiomers are commercially available at similar prices and should give opposite enantiomers of the product.



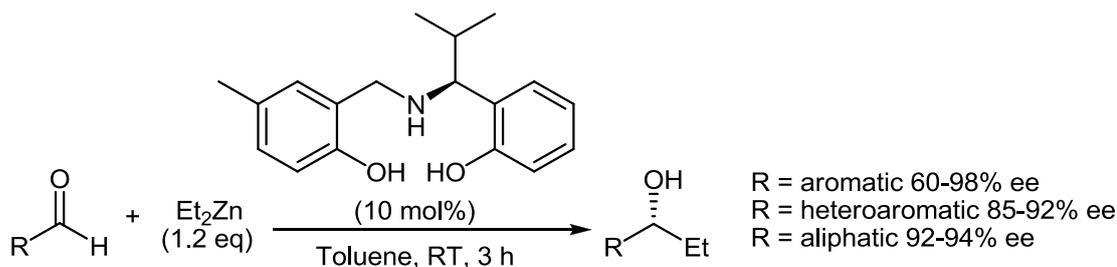
Scheme 4.24

Wang<sup>28</sup> designed and synthesised a new type of 1,4-aminoalcohol with *cis*-cyclopropane as a chiral backbone, for use in the asymmetric addition of diethylzinc to a range of aldehydes (Scheme 4.25). In the addition to aromatic aldehydes excellent enantiomeric excesses were achieved (95-97%). The addition to aliphatic and  $\alpha,\beta$ -unsaturated aldehydes gave, in general, lower enantioselectivity, with moderate enantiomeric excesses achieved in the addition to linear aldehydes (61-75%) and the best enantiomeric excess achieved for aliphatic aldehydes was an encouraging 93% for cyclohexanecarbaldehyde.



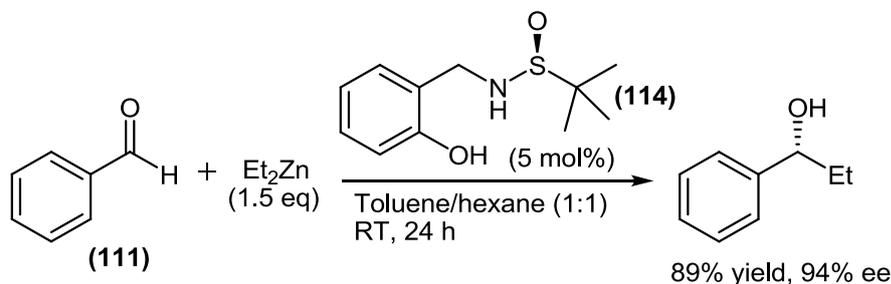
**Scheme 4.25**

Hirose<sup>29</sup> synthesised chiral tridentate aminophenol ligands for the catalytic asymmetric diethylzinc addition to aldehydes. Having established the optimal reaction conditions (toluene, room temperature, 1.2 eq  $\text{Et}_2\text{Zn}$ , 10 mol% catalyst, 3 hours) through the screening of temperature, solvent and catalysts in the standard reaction of diethylzinc with benzaldehyde (**111**), the catalyst generating the highest enantioselectivity, 2-((*S*)-1-(2-hydroxy-5-methylbenzylamino)-2-methylpropyl)phenol, was then used to catalyse the diethylzinc addition to a library of aromatic, heteroaromatic, aliphatic and  $\alpha,\beta$ -unsaturated aldehydes (Scheme 4.26). With the exception of the reactions with *ortho*-bromobenzaldehyde and *ortho*-chlorobenzaldehyde (60% ee and 80% ee respectively), excellent enantiomeric excesses were achieved in the addition to aromatic aldehydes (93-98% ee), with the decrease for *o*-chloro- and *o*-bromo- substituents attributed to the electrostatic influence on the coordination of diethylzinc to the carbonyl caused by the electronegative chloro- and bromo- in the *ortho* position. Addition to heteroaromatic aldehydes also proceeded smoothly, with excellent enantioselectivity obtained (85-92% ee). The addition of diethylzinc to the more challenging aliphatic and  $\alpha,\beta$ -unsaturated aldehydes also led to excellent enantioselectivity (92-94% ee).



Scheme 4.26

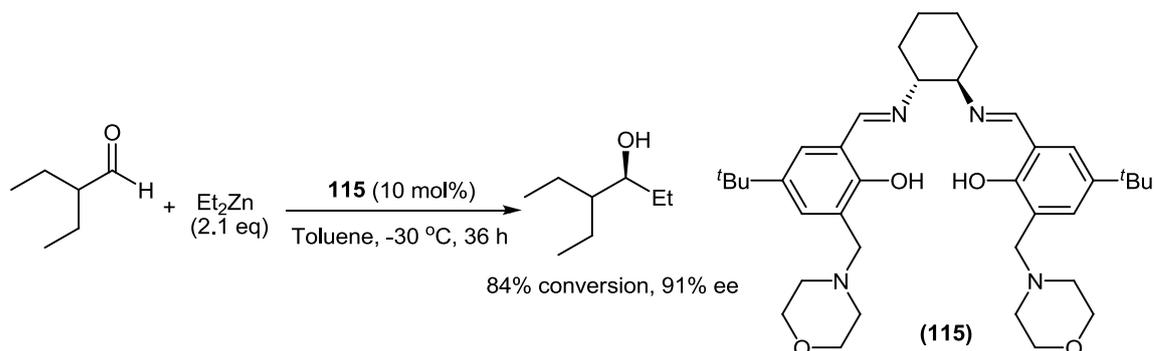
Tridentate ligands were also used by Qin,<sup>30</sup> who synthesised a series of new sulfinamido ligands from (*S*)-*tert*-butanesulfinamide. These ligands were screened for catalytic activity and enantioselectivity in the reaction of diethylzinc with benzaldehyde (**111**), and the best ligand (**114**, Scheme 4.27) was chosen for further reactions with other aldehydes. The addition of diethylzinc to aromatic aldehydes proceeded with excellent enantioselectivity (94-97% ee), as did the addition of diethylzinc to heteroaromatic aldehydes (93-94% ee). The addition of diethylzinc to aliphatic aldehydes proceeded with only moderate enantioselectivity (54-70% ee). The nitrogen and oxygen of the sulfinamido group, along with the oxygen of the hydroxyl group, are thought to coordinate with zinc to form *O,N,O* chelated transition states.



Scheme 4.27

Kozlowski<sup>31</sup> developed bifunctional salen complexes with Lewis acidic and Lewis basic appendages that could be modified independently to control activation of both the nucleophile and electrophile of a given reaction. These ligands were applied to the addition of diethylzinc to aldehydes, with the coordination on the salen metal centre acting as a Lewis acid to activate the aldehyde, and the tethered Lewis base activating the diethylzinc nucleophile. After an initial investigation into several Lewis basic appendages using the addition of diethylzinc to benzaldehyde as a standard reaction, the morpholine derivative **115** was chosen as the optimum catalyst precursor. This was then

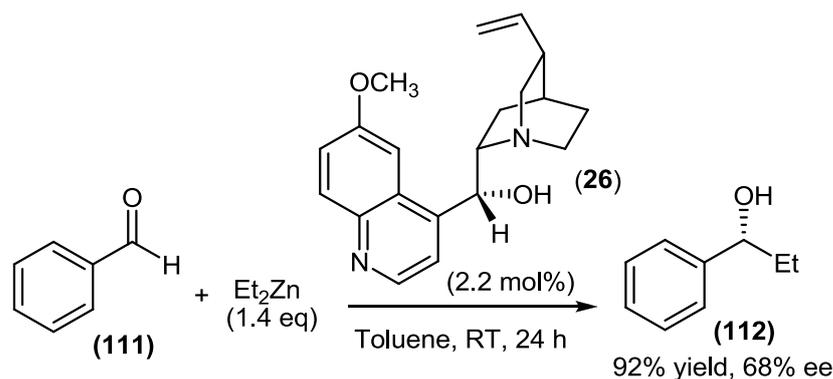
applied in the enantioselective addition of diethylzinc to a range of aromatic and aliphatic aldehydes, with very good enantioselectivity (69-91% ee, Scheme 4.28).



**Scheme 4.28**

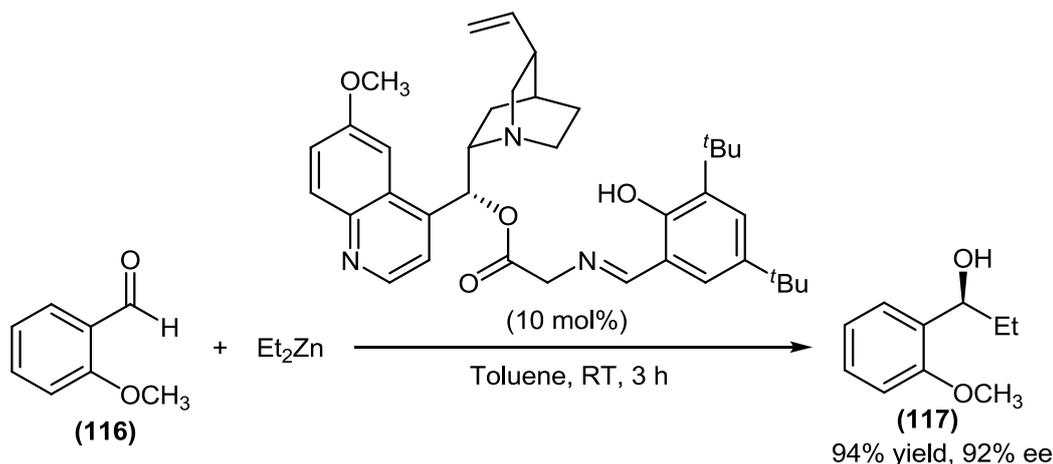
### 4.3.1 Introduction to *Cinchona* alkaloids as chiral aminoalcohols

Wynberg,<sup>32</sup> in using *Cinchona* alkaloids to catalyse the asymmetric addition of diethylzinc to benzaldehyde (**111**) (Scheme 4.29), found that the configuration of the product enantiomer in excess depended on the *Cinchona* alkaloid used. Quinine (**26**) gave (*R*)-1-phenyl-1-propanol (*R*-**112**) in excess, whilst quinidine (**27**) gave (*S*)-1-phenyl-1-propanol (*S*-**112**) in excess. In general, the use of quinine (**26**) led to the achievement of higher enantiomeric excesses (68%) than the use of quinidine (**27**) (48%). The presence or absence of the 6'-methoxy group (i.e. the use of quinidine (**27**) versus cinchonine (**29**), 48% and 46% ee respectively) did not seem to have a large effect on the enantiomeric excess obtained. The decrease in enantiomeric excess observed when dihydroquinine (**30**) (48% ee) was used in place of quinine (**26**) (68% ee) led to the suggestion that the vinyl group is directly involved in the reaction, either coordinating to the diethylzinc reagent in the transition state, or possibly directing the diethylzinc into the quinine molecule before the transition state is reached. An *ortho*-substituent on benzaldehyde (**111**) led to an improvement in enantiomeric excess, increasing the steric bulk of this substituent further improved the enantiomeric excess obtained (*o*-methoxybenzaldehyde 83% ee, *o*-ethoxybenzaldehyde 92% ee, both catalysed by quinine (**26**)). Altering the solvent from toluene to diethyl ether had only a minor effect on the enantioselectivity. The uncatalysed racemic reaction was slow but present; the conversion of the reaction of benzaldehyde (**111**) with diethylzinc with no catalyst present was 30% after 24 hours.



Scheme 4.29

Buono<sup>33</sup> also used *Cinchona* alkaloids as catalysts for the asymmetric addition of diethylzinc to benzaldehyde (**111**). The product enantiomer in excess depended on the *Cinchona* alkaloid used, with quinine (**26**) and cinchonidine (**28**) giving (*R*)-1-phenyl-1-propanol (*R*-**112**) in excess, and quinidine (**27**) and cinchonine (**29**) giving (*S*)-1-phenyl-1-propanol (*S*-**112**) in excess. Oddly, over shorter reaction times (15 minutes), better enantiomeric excesses were achieved at elevated temperatures, rather than at lower temperatures as would be expected. Thus, the reaction of diethylzinc (1.25 eq) with benzaldehyde (**111**) catalysed by quinine (**26**) had a 95% yield and 73% enantiomeric excess (the best obtained over all *Cinchona* alkaloids and temperatures) after 15 minutes at 100 °C, compared with a 97% yield and 64% enantiomeric excess after 16 hours at room temperature.

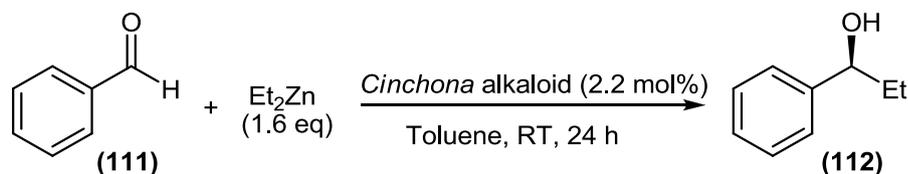


Scheme 4.30

More recently, Lin<sup>34</sup> used a quinine derived tridentate ligand to catalyse the addition of diethylzinc to 2-methoxybenzaldehyde (**116**) as a test reaction, generating the desired alcohol (**117**) in 94% yield with 92% enantiomeric excess (Scheme 4.30).

The substrate scope was then extended to a range of five other aromatic aldehydes, generating the benzyl alcohols in good to excellent yields (56-100%) and enantioselectivities (42-90%).

#### 4.3.2 Screening the new *Cinchona* alkaloid derivatives in the asymmetric addition of diethylzinc to benzaldehyde (**111**)



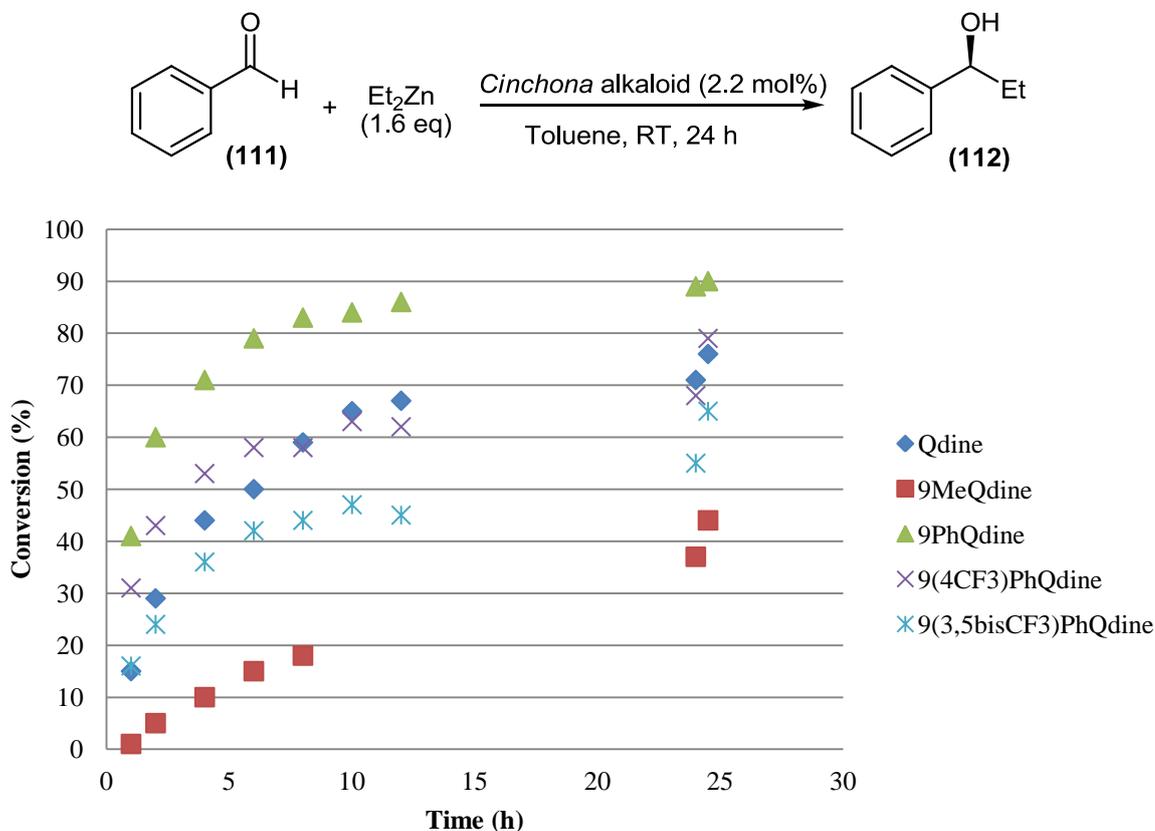
**Scheme 4.31**

It was proposed that the presence of a tertiary, rather than a secondary, alcohol at the C9 position in the new *Cinchona* alkaloid derivatives could improve the enantioselectivity obtained in the enantioselective addition of diethylzinc to benzaldehyde. The principle advantage of testing the compounds synthesised in chapters two and three as chiral aminoalcohols in the asymmetric addition of diethylzinc to benzaldehyde (**111**) is that in this reaction they are used catalytically, whereas in the asymmetric fluorination testing they were used stoichiometrically, which led to an increased requirement for time-consuming synthesis.

The reactions were initially performed following the literature procedure of Wynberg,<sup>32</sup> although on a smaller scale in order to avoid wasted reagents. However, the number of equivalents of diethylzinc was increased from the 1.4 equivalents used in Wynberg's work, to 1.6 equivalents in this work, in order to maximise the conversion in examples where the reaction was less efficient (for example in the case of 9-methylquinidine (**68**)). After screening reactions in toluene and diethyl ether, and at both room temperature and 0 °C, the optimum conditions were found to be toluene as the solvent, at room temperature for 24 hours.

Following Wynberg's procedure, initially the products were purified by Kugelrohr distillation, but this method was inefficient and often after several distillations some benzaldehyde (**111**) (or benzoic acid from its decomposition) was still present. Subsequent crude products were purified by column chromatography on silica gel using hexane/ethyl acetate (90/10). Some of the isolated yields were lower than might have been expected; as in the asymmetric fluorination tests, this is most likely due to the small scale upon which the reactions were performed. Similar to the asymmetric

fluorination testing, the reactions were performed in duplicate in two simultaneous reactions, and the conversion, isolated yield and enantiomeric excess values are reported as averages of the values from the two reactions.



**Figure 4.4:** Monitoring conversion of the addition of diethylzinc to benzaldehyde (**111**) by GC

The reactions catalysed by quinidine (**27**), 9-methylquinidine (**68**), 9-phenylquinidine (**69**), 9-(4-trifluoromethylphenyl)quinidine (**70**) and 9-(3,5-bis-trifluoromethylphenyl)quinidine (**73**) were monitored by GC, with samples taken after 1, 2, 4, 6, 8, 10, 12 and 24 hours (before quenching), as well as after the workup. Figure 4.4 shows the results of the monitoring reactions, with all of the reactions presented on one graph for a direct comparison. 9-Phenylquinidine (**69**) gave the best conversion, even at an early stage in the reaction, and the reaction seemed faster, than the reactions with some of the other ligands. 9-(4-Trifluoromethylphenyl)quinidine (**70**) gave higher conversions in the early stages of the reaction than quinidine (**27**), but since it plateaued earlier, the two ligands gave similar conversions at the end of the reaction. 9-

Methylquinidine (**68**) gave the lowest conversion and had the slowest rate of reaction. One concern with monitoring the reactions is that sampling could allow the entrance of air into the reaction, however briefly, and could therefore lead to a lower conversion than otherwise would have been recorded if the reaction had been undisturbed for 24 hours. The conversions do, however, appear to rise consistently until they reach a plateau, rather than stopping after the first sample, so these concerns may be unfounded.

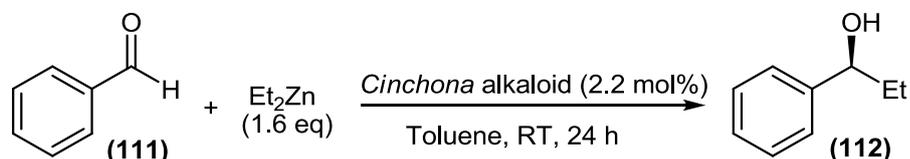
Table 4.7 summarises the results obtained in the asymmetric addition of diethylzinc to benzaldehyde (**111**), catalysed by the novel quinidine derivatives synthesised in chapter two. It is important to note that the background reaction, with no catalyst present (Table 4.7, entry 1), has a low conversion (13%) and gives a racemic product. This indicates that any enantioselectivity observed in the reactions with *Cinchona* alkaloids present are due to the chiral ligand.

Both quinine (**26**) and quinidine (**27**) gave good enantiomeric excesses (70% and 74% respectively), which is a small improvement on the results of Wynberg. The enantiomers obtained in excess are the same as those obtained by Wynberg and depend on the configuration of the *Cinchona* alkaloid, *R*-**112** for quinine (**26**) and *S*-**112** for quinidine (**27**). The *S* enantiomer is produced in excess for all of the quinidine derivatives. Presumably, if quinine derivatives could have been accessed they would have given the *R* enantiomer in excess. The *Cinchona* derived aminoalcohols therefore have an advantage over literature examples based on natural products such as DAIB or MIB, where the non-naturally occurring enantiomer of the catalyst precursor (needed to form the opposite enantiomer of the product) is much more expensive, as quinine (**26**) and quinidine (**27**) are both commercially available at reasonable prices and generate opposite product enantiomers.

Despite the initial disappointing results with 9-methylquinidine (**68**), which gave only 44% conversion and an essentially racemic product (4% ee), the bulkier phenyl substituted quinidine derivatives have yielded consistently very good results (Table 4.7, entries 6, 7, 9-11). 9-Phenylquinidine (**67**), 9-phenyl-10,11-dihydroquinidine (**79**), 9-(4-trifluoromethylphenyl)quinidine (**70**) and 9-(4-trifluoromethylphenyl)-10,11-dihydroquinidine (**81**) all gave enantiomeric excesses (82-86%) that were an improvement on the enantiomeric excess achieved with quinidine (**27**) (74%), combined with good conversions (approximately 80% for the 4-trifluoromethylphenyl derivatives and >90% for the phenyl derivatives).

In general, there does not seem to be a large difference in enantioselectivity between the 9-substituted-quinidine derivatives and the 9-substituted-10,11-dihydroquinidine derivatives. The only exceptions are the significant decrease in enantiomeric excess achieved with dihydroquinidine (**31**) (13% ee) compared with that obtained with quinidine (**27**) (74% ee), and the significant improvement in enantioselectivity displayed by 9-(3,5-bis-trifluoromethylphenyl)-10,11-dihydroquinidine (**82**) which gives an excellent enantiomeric excess of 92% combined with a conversion of 90% (Table 4.7, entry 12).

**Table 4.7:** Asymmetric addition of diethylzinc to benzaldehyde (**111**) catalysed by quinidine derivatives<sup>a</sup>



Entry	Cinchona Alkaloid	Conversion (%) <sup>b</sup>	Yield (%) <sup>c</sup>	e.e. (%) <sup>d</sup>	Enantiomer Ratio (R:S)
1	None	13	-	0	50:50
2	Quinine ( <b>26</b> )	93	-	70	85:15
3	Quinidine ( <b>27</b> )	76	47	74	13:87
4	10,11-Dihydroquinidine ( <b>31</b> )	38	23	14	43:57
5	9-Methylquinidine ( <b>68</b> )	44	30	4	48:52
6	9-Phenylquinidine ( <b>69</b> )	90	60	84	8:92
7	9-Ph-10,11-DH-Qdine ( <b>79</b> )	>95	86	84	8:92
8	9-(4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )-DH-Qdine ( <b>80</b> )	69	45	44	28:72
9	9-(4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )-quinidine ( <b>70</b> )	79	48	82	9:91
10	9-(4CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )-DH-Qdine ( <b>81</b> )	81	63	86	7:93
11	9-(3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> )-quinidine ( <b>73</b> )	65	31	76	12:88
12	9-(3,5-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> )-DHQdine ( <b>82</b> )	90	62	92	4:96

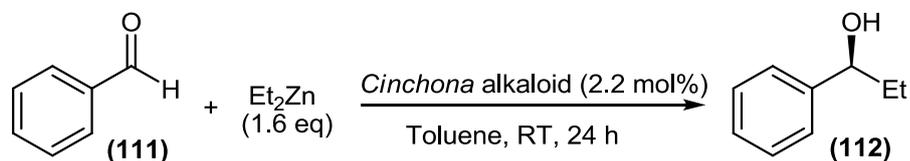
<sup>a</sup>Reaction performed using 0.4 mL PhCHO (3.9 mmol) in 8 mL dry toluene. <sup>b</sup>Conversion determined by GC. <sup>c</sup>Isolated yield. <sup>d</sup>Determined by chiral GC.

Table 4.8 shows the results obtained in the asymmetric addition of diethylzinc to benzaldehyde (**111**) catalysed by 8-fluoro-*epi*-quinidine and 8-fluoro-*epi*-quinine

derivatives. The enantiomeric excesses obtained in the reactions catalysed by 8-fluoro-*epi*-quinidine and 8-fluoro-*epi*-quinine derivatives are not as impressive as the reactions catalysed by quinidine derivatives. The 9-methyl-substituted-8-fluoro compounds gave much lower enantioselectivities compared to the 9-phenyl-8-fluoro compounds, a similar result to that observed with 9-methylquinidine (**68**) and 9-phenylquinidine (**69**). However, the enantiomeric excesses obtained using 9-phenyl-8-fluoro-*epi*-quinidine (**87**), 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinidine (**88**), and 9-phenyl-8-fluoro-*epi*-quinine (**90**) were all good (74%, 63%, 70% respectively), and gave similar enantioselectivity to that of quinidine (**27**) (74%).

Oddly, 9-methyl-8-fluoro-*epi*-quinidine (**86**) gave the opposite enantiomer in excess (*R*) to that observed with 9-phenyl-8-fluoro-*epi*-quinidine (**87**), 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinidine (**88**) and 9-(4-trifluoromethylphenyl)-8-fluoro-10,11-dihydro-*epi*-quinidine (**103**), which all gave the *S* enantiomer in excess. This is not the case with 9-methyl-8-fluoro-*epi*-quinine (**89**) and 9-phenyl-8-fluoro-*epi*-quinine (**90**), which both gave the *R* enantiomer in excess, as expected.

**Table 4.8:** Asymmetric addition of diethylzinc to benzaldehyde catalysed by 8-fluoro-*epi*-quinidine and 8-fluoro-*epi*-quinine derivatives<sup>a</sup>



Entry	Cinchona Alkaloid	Conversion (%) <sup>b</sup>	Yield (%) <sup>c</sup>	e.e. (%) <sup>d</sup>	Enantiomer Ratio ( <i>R</i> : <i>S</i> )
1	9-Me-8F- <i>epi</i> -quinidine ( <b>86</b> )	76	45	26	63:37
2	9-Ph-8F- <i>epi</i> -quinidine ( <b>87</b> )	81	57	74	13:87
3	9-(4CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )-8F- <i>epi</i> -qdine ( <b>88</b> )	70	44	63	18:82
4	9-(4CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> )-8FDH- <i>epi</i> -qdine ( <b>103</b> )	45	30	30	35:65
5	9-Me-8F- <i>epi</i> -quinine ( <b>89</b> )	56	54	8	54:46
6	9-Ph-8F- <i>epi</i> -quinine ( <b>90</b> )	73	54	70	85:15

<sup>a</sup>Reaction performed using 0.4 mL PhCHO (3.9 mmol) in 8 mL dry toluene. <sup>b</sup>Conversion determined by GC. <sup>c</sup>Isolated yield. <sup>d</sup>Determined by chiral GC.

Overall, the enantiomeric excesses obtained in the asymmetric addition of diethylzinc to benzaldehyde (**111**) catalysed by the quinidine, 8-fluoro-*epi*-quinidine and 8-fluoro-*epi*-quinine derivatives have been very good, especially when compared to those achieved in the asymmetric fluorinations. A favourable comparison with literature results can be made, especially considering that the majority of the examples in the literature use 3 mol% catalyst or higher, with a significant proportion using 10 mol%, whereas in this work consistently very good enantiomeric excesses have been achieved using a catalyst loading of 2.2 mol%. Also, typical literature examples use two or more equivalents of diethylzinc, whereas this work has successfully used 1.6 equivalents. The best result was obtained with 9-(3,5-bis-trifluoromethylphenyl)-10,11-dihydro-quinidine (**82**), which gave an excellent 92% enantiomeric excess, and demonstrates the promise of these compounds when used in an appropriate application.

#### 4.4 Modified *Cinchona* Alkaloids for the Treatment of Malaria

In 1973, Klayman<sup>35</sup> stated that all previously reported alterations at C9 in quinine (**26**) or quinidine (**27**), other than esterification of the carbinol function, had resulted in a decrease in or loss of antimalarial activity (Table 4.9). Klayman's replacement of the C9 hydroxyl group of quinine (**26**) with a thiosulphuric acid group resulted in a compound (9-deoxy*epi*quinine-9-thiosulphuric acid) that was equally effective against two strains of human malaria *Plasmodium falciparum*, a drug resistant strain from Vietnam and a drug sensitive strain from Uganda, with 1000 µg/L of blood required for inhibition of <50% of the parasites, and 2500 µg/L of blood required for inhibition of >90% of the parasites. Quinine (**26**) was also equally effective against both strains, requiring 1000 µg/L of blood for inhibition of >90% of the parasites.

Karle<sup>36</sup> investigated the difference in relative activity against *Plasmodium falciparum* malaria between various *Cinchona* alkaloids, and related this to their stereochemistry and three dimensional structure. Two different strains of *Plasmodium falciparum* were examined: D6, which originated in Sierra Leone (West Africa), was resistant to Mefloquine (**59**) but sensitive to Chloroquine (**56**), quinine (**26**), Sulfadoxine and Pyrimethamine; and W2, which originated in Vietnam (Southeast Asia) and was resistant to Chloroquine (**56**), quinine (**26**), Sulfadoxine and Pyrimethamine. It was found that against the D6 strain 9-*epi*-quinine (**34**) was 143 times weaker than quinine (**26**) and 334 times weaker than quinidine (**27**), and 9-*epi*-quinidine (**35**) was 107 times weaker than quinine (**26**) and 248 times weaker than quinidine (**27**). Both 9-*epi*

compounds were also less active against the W2 strain, although to a lesser extent, 9-*epi*-quinine (**34**) was 13.6 times less active than quinine (**26**) and 31.3 times less active than quinidine (**27**), and 9-*epi*-quinidine (**35**) was 11.3 times less active than quinine (**26**) and 26.5 times less active than quinidine (**27**). Quinidine (**27**) and dihydroquinidine (**31**) were found to be 1.9-2.8 times more active against both strains than quinine (**26**) and dihydroquinine (**30**). These differences in activity led to the conclusion that the direction of the N<sup>+</sup>-H and O-H bonds relative to each other is important for antimalarial activity, in order to form intermolecular hydrogen bonds within cells the molecule must be oriented correctly.

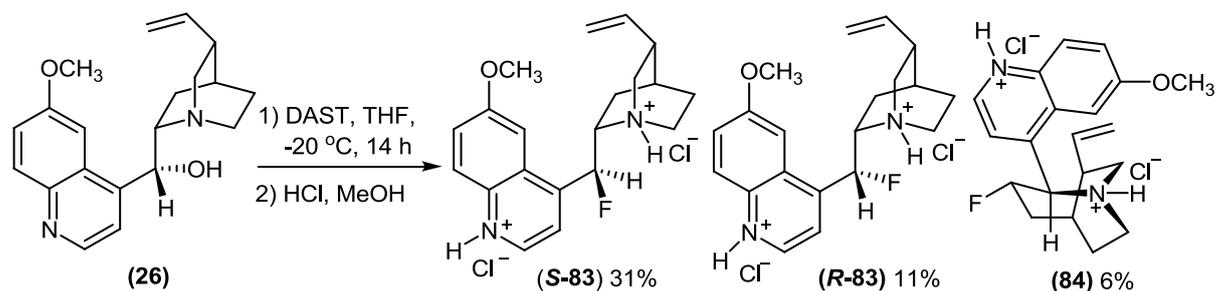
**Table 4.9:** Comparison by Klayman of antimalarial activities of quinine (**26**), quinidine (**27**) and their derivatives

	Dose, mg/kg (test minus control) <sup>a</sup>					
	640	320	160	80	40	20
9-Deoxy <i>epi</i> quinine-9-thiosulphuric acid	22.4 (c,3)	15.9 (c,3)	12.7 (a)	3.9	0.9	0.5
<i>N</i> -Quininium- <i>S</i> -thiosulphate	13.4 (c,3)	12.7 (a)	10.3 (a)	4.9	0.5	0.5
Quinine	7.1 (a)	6.1	4.7	2.3	1.5	0.5
Quinidine	7.7 (t, 1)	4.0	2.4	2.2	1.2	-
9-Deoxy-9-chloroquinine	0.5	0.5	0.3	0.3	0.3	0.1
9-Deoxy-9-hydroquinidine	-	0.3	-	0.1	-	0.1
Quinone <sup>b</sup>	0.9	-	0.7	-	0.7	-
Quinidinone <sup>b</sup>	0.2	-	0.2	-	0.0	-
9-Methylquinidine	0.2	-	0.2	-	0.2	-

The compounds were evaluated against *Plasmodium berghei* KBG 173 malaria by administration to 5 male mice per dilution in a single subcutaneous dose 72 hours after infection. <sup>a</sup>The mean survival time of the control animals was 6.1 days. Deaths from days 2-5 after drug administration are attributed to toxicity (t, number of dead mice). Compounds are classified as active (a) when the mean survival time of the treated mice is twice that of the controls i.e. test – control > 6.1 days, and curative (c, number of surviving mice) when one or more test animals live 60 days postinfection. <sup>b</sup>There is probable epimerisation of quinone to form quinidinone, the antimalarial activities of the two samples are not considered significantly different.

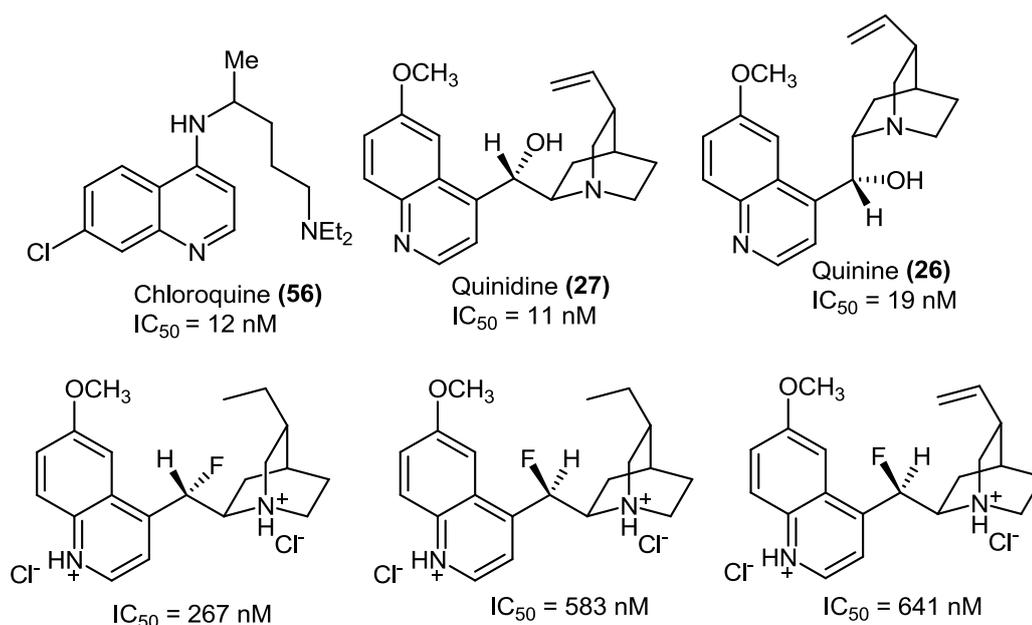
Gilmour,<sup>37</sup> on subjecting *Cinchona* alkaloids to direct nucleophilic deoxyfluorination using DAST, formed three distinct types of products, an inversion (*S*-

**83**) and retention product (**R-83**) with fluorination at C9, and a ring expanded product with fluorination at C3 (**84**) (Scheme 4.32).



**Scheme 4.32**

Twenty hydrochloride salts of deoxyfluorinated *Cinchona* alkaloid derivatives were then tested for anti-malarial activity against the NF54 strain of malaria parasite *Plasmodium falciparum* (which is sensitive to all known antimalarials). The results indicated that the intact 1-azabicyclo[2.2.2]core is required for drug efficacy, as the ring expanded systems resulted in a substantial loss of antiplasmodial activity. It was also discovered that quinidine based structures showed an enhanced bioactivity relative to quinine based structures. The configuration at C9 within the quinidine group did not seem to have a significant effect on the antimalarial activity.  $\text{IC}_{50}$  values of as low as 267 nM were observed (Figure 4.5), which, whilst not as impressive as that of Chloroquine (**56**), or of the parent alkaloids quinine (**26**) or quinidine (**27**), does show potential for these compounds in the development of novel antimalarial drugs.



**Figure 4.5**

#### 4.4.1 Testing novel *Cinchona* alkaloid derivatives as antimalarial agents

In order to determine the antimalarial activity of the quinidine, 8-fluoro-*epi*-quinidine and 8-fluoro-*epi*-quinine derivatives synthesised in Chapters Two and Three, two different biological assays were carried out. The first was a lactate dehydrogenase (LDH) assay (which is based on light absorbance), and the second a SYBR Green assay (which is based on fluorescence). For both assays the compounds (2  $\mu$ M concentration in DMSO) were incubated at body temperature (37 °C) for 48 hours with red blood cells infected with the malaria parasite *Plasmodium falciparum* in the trophozoite stage. This incubation was carried out in a 96 well plate, with each drug present in 3 wells, and in the presence of control wells consisting of un-infected red blood cells; red blood cells that were infected with malaria with no drug present; and red blood cells that were infected with malaria and in the presence of Chloroquine (**56**) (a standard malaria treatment). After the 48 hour incubation period the 96 well plates were frozen at -80 °C. The plates were then thawed and the reaction mix added in order to carry out the assay. For the SYBR Green assay the plate was shaken with the reaction mix and incubated in the dark for one hour before measurement of the fluorescence. For the LDH assay the reaction mix was added, the plate was shaken, and the absorbance at 650 nm was measured immediately.

Figures 4.6 and 4.7 show the absorbances in the LDH assay. The far left bar is a control containing red blood cells with no parasite present; the second bar in from the left is a control where the infected red blood cells were incubated in the presence of chloroquine, which is a standard drug for treating malaria. The third bar in from the left is a control containing red blood cells infected with the malaria parasite and untreated. The remaining bars are those in which the infected red blood cells were incubated with the new compounds synthesised in Chapters Two and Three.

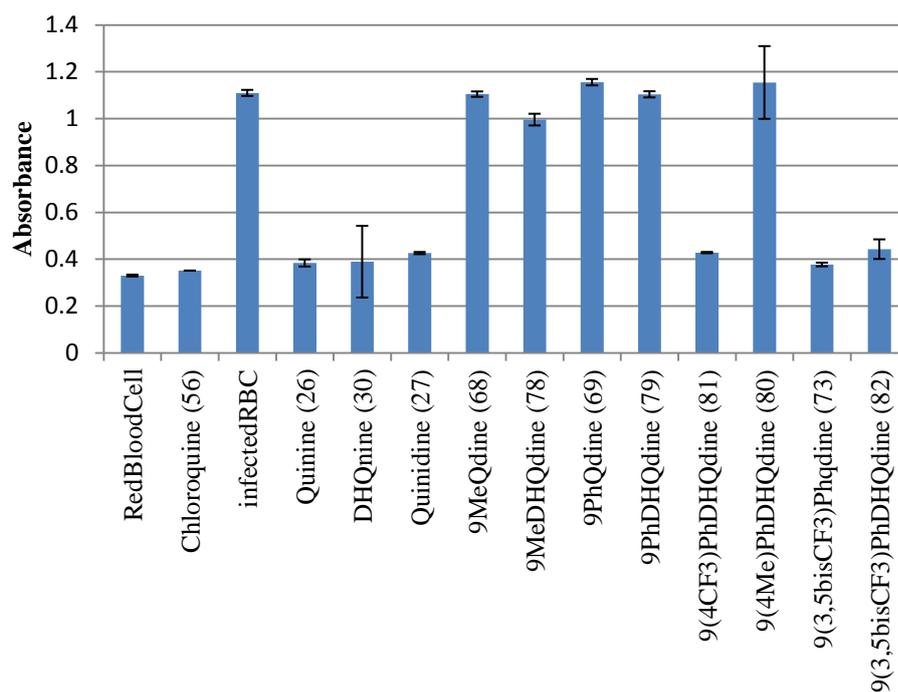
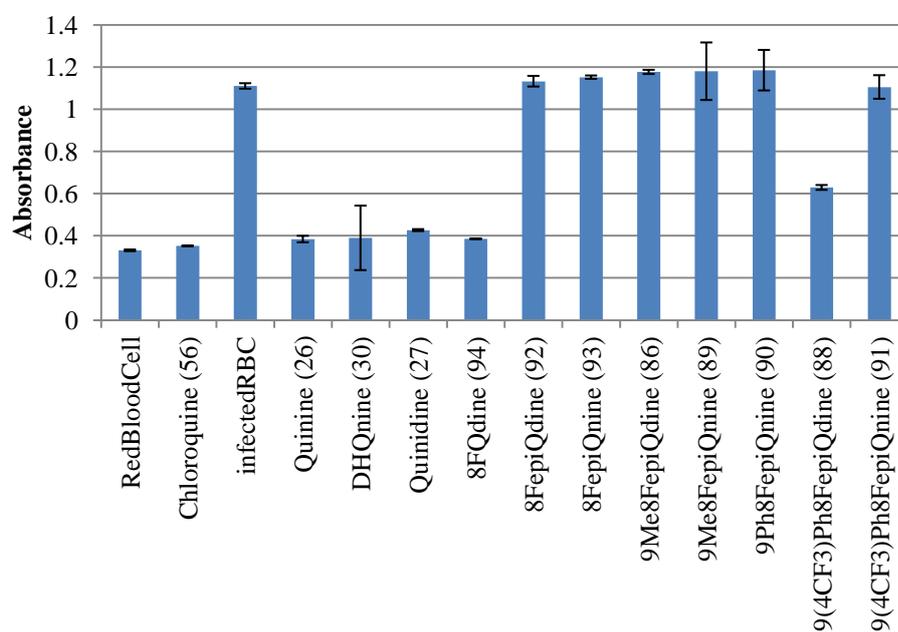
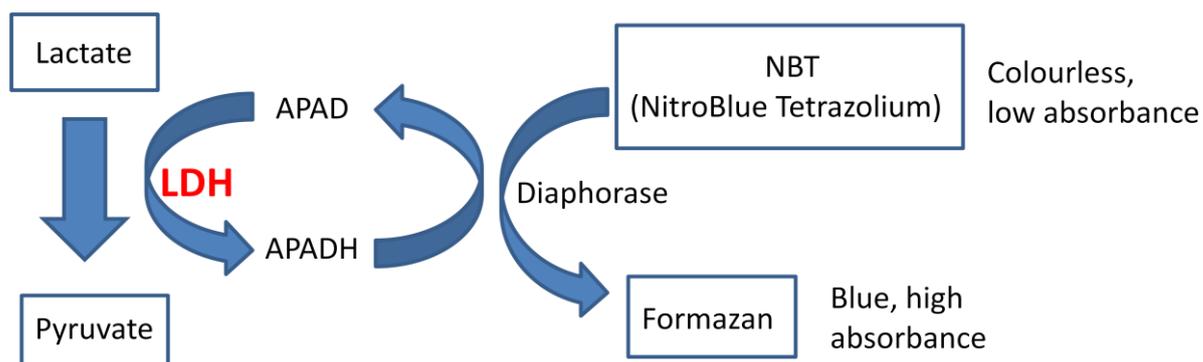
**Figure 4.6:** Absorbance in the Lactate Dehydrogenase Assay for quinidine derivatives**Figure 4.7:** Absorbance in the Lactate Dehydrogenase Assay for 8-fluoro-*epi*-quinine and 8-fluoro-*epi*-quinidine derivatives

Figure 4.8 shows the chemistry behind the LDH assay. During the normal metabolic processes of the parasite, lactate is converted to pyruvate by the lactate dehydrogenase enzyme present in the living parasite. In the LDH assay, APAD (3-Acetylpyridine adenine dinucleotide), diaphorase, and NitroBlue Tetrazolium dye are

added to cause a chain reaction whereby if the parasite is alive and using its lactate dehydrogenase to convert lactate to pyruvate the colourless NitroBlue Tetrazolium dye (which has low absorbance) is changed to Formazan, which is blue and therefore has a high absorbance. If, however, the parasite was killed by the drug with which it was incubated, it will not produce LDH for its normal metabolic processes, therefore the chain reaction will not occur and the NitroBlue Tetrazolium will remain colourless, and the absorbance will be low.



**Figure 4.8:** The Chemistry Behind the LDH Assay

The low absorbances recorded in Figures 4.6 and 4.7 are indications of compounds that have some antimalarial activity, as these are the compounds that have killed the parasite, preventing it from producing LDH. Quinine (**26**) and quinidine (**27**) were expected to show antimalarial activity as they are already used as antimalarial treatments. For this reason the antimalarial activity shown by 10,11-dihydroquinine (**30**) is also unsurprising. However, 9-(3,5-bis-trifluoromethylphenyl)quinidine (**73**), 9-(3,5-bis-trifluoromethylphenyl)-10,11-dihydroquinidine (**82**), 9-(4-trifluoromethylphenyl)-10,11-dihydroquinidine (**81**), and 8-fluoroquinidine (**94**) all show substantial decreases in absorbance indicative of antimalarial activity. 9-(4-Trifluoromethylphenyl)-8-fluoro-*epi*-quinidine (**88**) also shows a decrease in absorbance, although to a lesser extent, and may therefore also possess some antimalarial activity. This suggests that the introduction of one or more trifluoromethyl groups into the *Cinchona* alkaloid framework results in an enhancement of biological activity, and as a result any future testing should include 9-(4-trifluoromethylphenyl)quinidine.

The results in Figure 4.7 also support the conclusions of Karle,<sup>36</sup> that the configuration at the C9 position of *Cinchona* alkaloids is important for antimalarial activity. The only difference between 8-fluoroquinidine (**94**) (8*S*,9*S*) and 8-fluoro-*epi*-

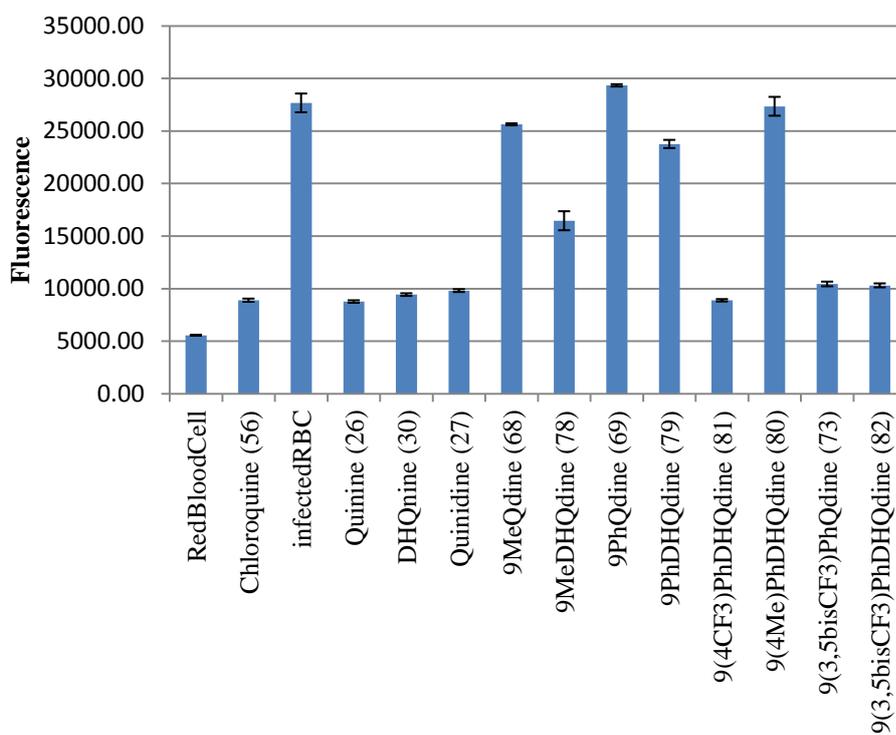
quinidine (**92**) (8*S*,9*R*) is the configuration at the C9 position, yet 8-fluoroquinidine has antimalarial activity and 8-fluoro-*epi*-quinidine does not. Future testing should include compounds with similar configurations; 8-fluoroquinine (**96**) (8*R*,9*R*), 8-fluoro-10,11-dihydroquinidine (8*S*,9*S*) and 8-fluoro-10,11-dihydroquinine (8*R*,9*R*). It would also have been interesting to test 9-methyl-8-fluoroquinidine (**99**) (8*S*,9*S*) and 9-methyl-8-fluoroquinine (**98**) (8*R*,9*R*) (from the reactions of 8-fluoroquinidinone (**64**) and 8-fluoroquininone (**65**) with trimethylaluminium) and compare with the results of 9-methyl-8-fluoro-*epi*-quinidine (**86**) (8*S*,9*R*) and 9-methyl-8-fluoro-*epi*-quinine (**89**) (8*R*,9*S*) (from the reactions of 8-fluoroquinidinone and 8-fluoroquininone with methyllithium), in order to discover if the alteration in the configuration at the C9 position in 9-substituted-8-fluoro derivatives would also lead to enhanced biological activity.

Figures 4.9 and 4.10 show the fluorescence in the SYBR Green assay. As in the LDH assay, the first three bars from the left are controls containing uninfected red blood cells, infected red blood cells incubated with Chloroquine (**56**), and infected red blood cells with no drug present. The remaining bars show the fluorescence obtained from infected red blood cells incubated with the new compounds synthesised in Chapters two and three. Unlike in the LDH assay, the SYBR Green assay does not necessarily indicate that the parasite is dead. SYBR Green binds to double stranded DNA, and the resulting DNA complex fluoresces at 520 nm. If the parasite was replicating normally, there would be more double stranded DNA present to which to bind after the incubation period and therefore the fluorescence would be high. A low fluorescence indicates that the replication of the parasite has been hindered, which could be a result of the parasite's death but could also be due to replication slowing rather than stopping completely. A low fluorescence in this assay is therefore still indicative of antimalarial activity. As in the LDH assay 9-(3,5-bis-trifluoromethylphenyl)quinidine (**71**), 9-(3,5-bis-trifluoromethylphenyl)-10,11-dihydroquinidine (**82**), 9-(4-trifluoromethylphenyl)-10,11-dihydroquinidine (**81**), and 8-fluoroquinidine (**94**) all show substantial decreases in fluorescence indicative of antimalarial activity. 9-(4-Trifluoromethylphenyl)-8-fluoro-*epi*-quinidine (**88**) shows a more substantial decrease in fluorescence in the SYBR Green assay than it showed in absorbance in the LDH assay, and this more obvious decrease more strongly suggests that it has antimalarial activity. In addition, 9-methyl-10,11-dihydroquinidine (**78**) shows a slight decrease in fluorescence which could suggest that it also has some antimalarial activity.

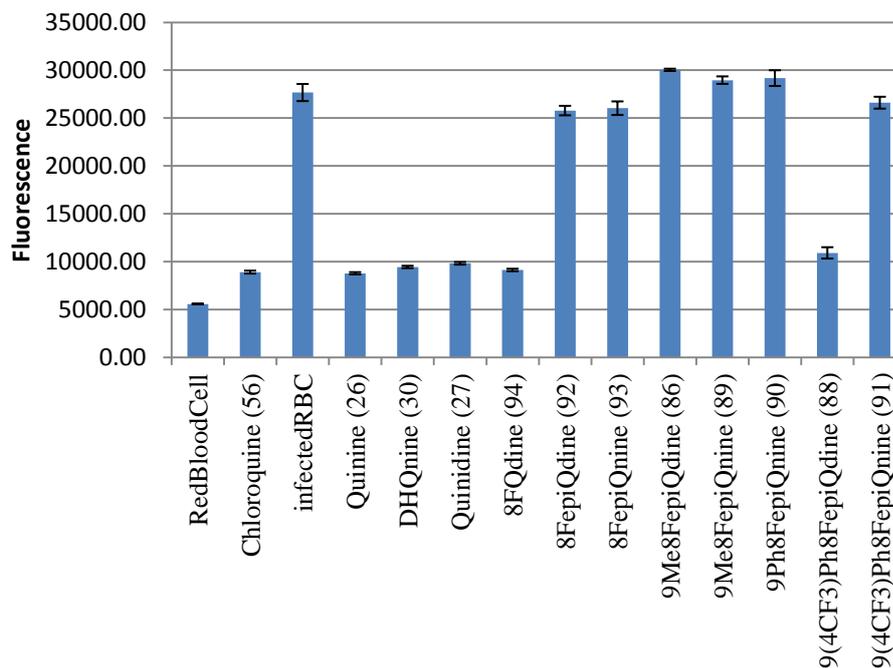
The SYBR Green assay results shown in Figures 4.9 and 4.10 further support the conclusion that the introduction of one or more trifluoromethyl groups leads to an enhancement of the biological activity.

The importance of the configuration at the C9 position is also supported by the SYBR Green assay results, as 8-fluoroquinidine (**94**) shows antimalarial activity but 8-fluoro-*epi*-quinidine (**92**), which differs only in the configuration at the C9 position, has none. Given the indicated antimalarial activity of 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinidine (**88**) in this assay, it is possible that the introduction of the trifluoromethyl group is more influential upon the biological activity than the configuration at the C9 position.

**Figure 4.9:** Fluorescence in the SYBR Green Assay for quinidine derivatives



**Figure 4.10:** Fluorescence in the SYBR Green Assay for 8-fluoro-*epi*-quinine and 8-fluoro-*epi*-quinidine derivatives



These assays are preliminary, qualitative, tests to indicate whether the compounds possess any antimalarial activity. Unfortunately, they are not quantitative. For example, the larger decrease in absorbance of 8-fluoroquinidine (**94**) compared with that of 9-(4-trifluoromethylphenyl)-10,11-dihydroquinidine (**81**) does not necessarily mean that 8-fluoroquinidine (**94**) is more active against the parasite. In order to determine how active the compounds are, more tests at different concentrations would have to be performed in order to determine the IC<sub>50</sub> values. Also, although these compounds are active against this parasite, they may also be active against human cells, and would therefore be less useful as antimalarial drugs for human consumption. For example, quinidine (**27**) is not used regularly as an antimalarial as it can cause abnormal heart rhythms. Furthermore, it would be interesting to test the compounds against a strain of malaria that is resistant to Chloroquine (**56**), in order to gauge how useful they are likely to be.

SYBR Green assays are usually performed using an incubation period of 72 hours. The fact that the assay was successful after 48 hours could suggest that the compounds are working on the malarial parasite in the trophozoite stage of the life cycle. No indication as to the mode of action of the compounds which show antimalarial activity can be gained from the assays. Quinine (**26**) is known to inhibit the biocrystallisation of hemozoin resulting in a build up of cytotoxic heme, and it is

possible that these compounds have similar modes of action, or they could be completely different.

#### 4.5 Conclusions and future work

The new *Cinchona* alkaloid derivatives synthesised in chapters two and three have been tested as enantioselective electrophilic fluorinating reagents in the enantioselective fluorination of ethyl-1-indanone-2-carboxylate. The enantioselectivities obtained were only moderate, and the best enantioselectivity (64%) was obtained with 9-phenyl-8-fluoro-10,11-dihydro-*epi*-quinidine. It would have been interesting to follow the example of Ryan Gilmour<sup>1</sup> and investigate the synthesis and applications of *N*-benzylated derivatives of the new *Cinchona* analogues as chiral phase transfer catalysts for enantioselective fluorinations.

The new *Cinchona* derivatives have also been applied as chiral aminoalcohol ligands in the enantioselective addition of diethylzinc to benzaldehyde, with excellent enantioselectivities obtained, the best of which (92%) was achieved using 9-(3,5-bis-trifluoromethylphenyl)-10,11-dihydroquinidine. Had time allowed, the scope of the work would have been expanded to include a range of aromatic and aliphatic aldehydes, and to include the addition of different nucleophiles through the use of dimethylzinc or diphenylzinc. It would also have been possible to investigate the applicability of the reaction to ketone substrates.

Preliminary screening of antimalarial activity has revealed that five of the new *Cinchona* alkaloid derivatives possess antimalarial activity. Had time allowed, the IC<sub>50</sub> values of the five biologically active compounds could have been determined in order to quantitatively establish how active they were, and to compare their activity against that of the parent alkaloids quinine, quinidine, dihydroquinine and dihydroquinidine. It would also have been interesting to investigate the activity of the compounds against a Chloroquine resistant parasite.

**4.6 References for chapter four**

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## 5.0 Experimental

### 5.1 General experimental procedures

#### 5.1.1 NMR spectroscopy

The  $^1\text{H}$ ,  $^{19}\text{F}$  and  $^{13}\text{C}\{^1\text{H}\}$  NMR spectra were recorded on Bruker DRX 400 and Bruker AM 300 spectrometers at the ambient temperature of the probe unless otherwise stated.  $^1\text{H}$  and  $^{13}\text{C}\{^1\text{H}\}$  NMR spectra were referenced internally using the residual protio solvent resonance relative to  $\text{SiMe}_4$  ( $\delta = 0$  ppm), whilst  $^{19}\text{F}\{^1\text{H}\}$  NMR spectra were referenced to external  $\text{CFCl}_3$  ( $\delta = 0$  ppm). All chemical shifts are quoted in  $\delta$  (ppm) and coupling constants in Hertz (Hz) using the high frequency positive convention. The following spectrometer frequencies were used:

Bruker AM 300 Spectrometer:  $^1\text{H}$  NMR spectra, 300.13 MHz,  
 $^{19}\text{F}\{^1\text{H}\}$  NMR spectra, 283.57 MHz,  
 $^{13}\text{C}\{^1\text{H}\}$  NMR spectra, 75.47 MHz.

Bruker DRX 400 Spectrometer:  $^1\text{H}$  NMR spectra, 400.13 MHz,  
 $^{19}\text{F}\{^1\text{H}\}$  NMR spectra, 376.46 MHz,  
 $^{13}\text{C}\{^1\text{H}\}$  NMR spectra, 100.62 MHz.

The solvent most frequently used was deuterated chloroform ( $\text{CDCl}_3$ ). However, if this was not possible due to solubility issues an alternative deuterio solvent was employed.

#### 5.1.2 Starting materials

Compounds were generally used as supplied from Sigma-Aldrich, Apollo Scientific or Acros Organics. Acetonitrile, THF, toluene, diethyl ether, hexane and dichloromethane were obtained dried from a solvent purification machine model Puresolve<sup>TM</sup>, and were stored in sealed ampoules over  $4\text{\AA}$  molecular sieves under an atmosphere of dry nitrogen.

#### 5.1.3 Mass spectrometry

Electron impact (EI) and fast atom bombardment (FAB) mass spectra were recorded on a Kratos concept 1 H, double focussing, forward geometry mass spectrometer. 3-Nitrobenzyl alcohol was used as the matrix for FAB spectra. Electrospray mass spectra were recorded on a Micromass Quatro LC.

#### **5.1.4 Optical rotation**

Optical rotation analyses were carried out using a Perkin Elmer 341 Polarimeter at 589 nm using a sodium/halogen lamp. Samples were dissolved in the solvent stated.

#### **5.1.5 Elemental analysis**

Elemental analyses were carried out at London Metropolitan University by Mr S. Boyer.

#### **5.1.6 X-ray crystallography**

X-ray crystallography data were collected on a Bruker Apex SMART 2000 diffractometer by Mr K. Singh. Crystal data and structure refinement can be found in the appendices.

#### **5.1.7 High Performance Liquid Chromatography**

Enantiomeric excesses were obtained by chiral HPLC performed on a Perkin Elmer Series 200 equipped with a Diacel Chiralcel OJ column or a Chiralcel ODH column, using hexane and isopropanol as eluents.

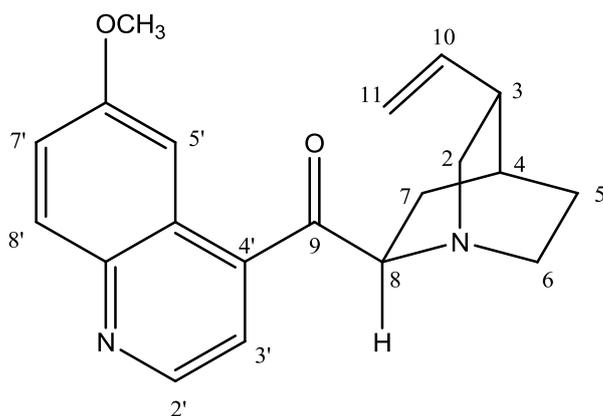
#### **5.1.8 Gas Chromatography**

Enantiomeric excesses were obtained by chiral GC performed on a PerkinElmer Autosystem XL equipped with a 30 m CYBEX-B column. The injector temperature was 220 °C, the detector temperature was 250 °C, the system was held at 110 °C for 30 minutes at a flow rate of 1mL/min. The samples were dissolved in dichloromethane.

### **5.2 Synthetic procedures for chapter two**

#### **5.2.1 Quinidinone<sup>1</sup> (62)**

Under a nitrogen atmosphere fluorenone (5.9 g, 33.0 mmol) was added to a suspension of quinine (4.9 g, 15.0 mmol) in dry toluene (60 mL) and the mixture was refluxed until all of the solid had dissolved. Sodium hydride (60% suspension in mineral oil, 2.8 g, 70.3 mmol) was then added in small portions over a period of 30 minutes at reflux, at which point the previously yellow solution became very dark green, almost black. The mixture was refluxed overnight (19 hours). After cooling to room temperature, the mixture was cooled to 0 °C using an ice bath and hydrolysed by slow addition of water

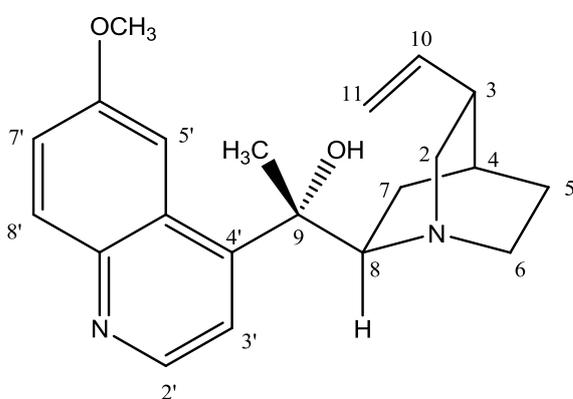


(30 mL). A colour change from very dark green to yellow was observed. The mixture was transferred to a separating funnel to which was added 2M hydrochloric acid (40 mL). The aqueous layer was removed, and the organic layer was extracted with 2M hydrochloric acid (4 x 30 mL). The aqueous layers were combined and

poured, with rapid stirring, into a mixture of 28% ammonia solution and crushed ice (approximately 50 mL of each). The white precipitate which was formed was taken into toluene, dried with sodium sulphate, filtered and the solvent was removed by rotary evaporation to give a yellow oil. Slow addition of hexane with scratching of the glass caused the formation of a brown precipitate, which was filtered and dried under vacuum to give quinidinone (4.4 g, 91% yield). Mp 87-90 °C (lit<sup>2</sup> 106-108 °C).  $[\alpha]_D^{20}$  182.5° (*c* 1.10 in toluene).  $\delta_H$  (C<sub>6</sub>D<sub>6</sub>) 1.20-1.38 (3H, m, NCHCH<sub>2</sub>, H7 and NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.68-1.74 (1H, m, NCHCH<sub>2</sub>, H7), 1.99 (1H, q, <sup>3</sup>*J*<sub>HH</sub> 7.9 Hz, CH<sub>2</sub>=CHCH, H3), 2.50-2.61 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 2.65 (1H, m, NCH<sub>2</sub>, H2), 2.69 (1H, m, NCH<sub>2</sub>, H2), 2.70-2.82 (2H, m, NCH<sub>2</sub>, H6), 3.54 (3H, s, OCH<sub>3</sub>), 3.71 (1H, t, <sup>3</sup>*J*<sub>HH</sub> 8.8 Hz, NCH, H8), 5.08 (1H, ddd, <sup>3</sup>*J*<sub>HH(trans)</sub> 17.4 Hz, <sup>2</sup>*J*<sub>HH</sub> 1.8 Hz, <sup>4</sup>*J*<sub>HH</sub> 1.2 Hz, CH<sub>2</sub>=CH, H11), 5.11 (1H, ddd, <sup>3</sup>*J*<sub>HH(cis)</sub> 10.2 Hz, <sup>2</sup>*J*<sub>HH</sub> 1.8 Hz, <sup>4</sup>*J*<sub>HH</sub> 1.2 Hz, CH<sub>2</sub>=CH, H11), 6.13 (1H, ddd, <sup>3</sup>*J*<sub>HH(trans)</sub> 17.4 Hz, <sup>3</sup>*J*<sub>HH(cis)</sub> 10.2 Hz, <sup>3</sup>*J*<sub>HH(vic)</sub> 7.9 Hz, CH<sub>2</sub>=CH, H10), 7.35 (1H, dd, <sup>3</sup>*J*<sub>HH</sub> 9.1 Hz, <sup>4</sup>*J*<sub>HH</sub> 2.9 Hz, ArH7'), 7.51 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 4.4 Hz, ArH3'), 8.19 (1H, d, <sup>4</sup>*J*<sub>HH</sub> 2.9 Hz, ArH5'), 8.30 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 9.1 Hz, ArH8'), 8.83 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 4.4 Hz, ArH2').  $\delta_H$  (CDCl<sub>3</sub>) 1.36-1.44 (1H, m, NCHCH<sub>2</sub>, H7), 1.50-1.59 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.72-1.76 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 2.09-2.15 (1H, m, CH<sub>2</sub>=CHCH, H3), 2.20 (1H, ddt, <sup>2</sup>*J*<sub>HH</sub> 13.7 Hz, <sup>3</sup>*J*<sub>HH</sub> 8.8 Hz, <sup>4</sup>*J*<sub>HH</sub> 2.0 Hz, NCHCH<sub>2</sub>, H7), 2.51 (1H, ddd, <sup>2</sup>*J*<sub>HH</sub> 14.1 Hz, <sup>3</sup>*J*<sub>HH</sub> 7.4 Hz, <sup>4</sup>*J*<sub>HH</sub> 2.0 Hz, NCH<sub>2</sub>, H2), 2.72-2.81 (2H, m, NCH<sub>2</sub>, H6), 2.95-3.03 (1H, m, NCH<sub>2</sub>, H2), 3.78 (3H, s, OCH<sub>3</sub>), 4.09 (1H, t, <sup>3</sup>*J*<sub>HH</sub> 8.8 Hz, NCH, H8), 4.89 (1H, dt, <sup>3</sup>*J*<sub>HH(trans)</sub> 17.2 Hz, <sup>2</sup>*J*<sub>HH</sub> = <sup>4</sup>*J*<sub>HH</sub> 1.6 Hz, CH=CH<sub>2</sub>, H11), 4.92 (1H, dt, <sup>3</sup>*J*<sub>HH(cis)</sub> 10.6 Hz, <sup>2</sup>*J*<sub>HH</sub> = <sup>4</sup>*J*<sub>HH</sub> 1.6 Hz, CH=CH<sub>2</sub>, H11), 5.81 (1H, ddd, <sup>3</sup>*J*<sub>HH(trans)</sub> 17.2 Hz, <sup>3</sup>*J*<sub>HH(cis)</sub> 10.6 Hz, <sup>3</sup>*J*<sub>HH(vic)</sub> 7.0 Hz, CH<sub>2</sub>=CH, H10), 7.24 (1H, dd, <sup>3</sup>*J*<sub>HH</sub> 9.4 Hz, <sup>4</sup>*J*<sub>HH</sub> 2.7 Hz, ArH7'), 7.50 (1H, d, <sup>4</sup>*J*<sub>HH</sub> 2.7 Hz, ArH5'), 7.51 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 4.7 Hz, Ar3') 7.88 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 9.4 Hz, ArH8'), 8.69 (1H,

d,  $^3J_{\text{HH}}$  4.7 Hz, ArH2').  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 22.12 ( $\text{CH}_2$ , C7), 26.83 ( $\text{CH}_2$ , C5), 27.66 ( $\text{CH}$ , C4), 39.71 ( $\text{CH}$ , C3), 48.81 ( $\text{CH}_2$ , C6), 49.58 ( $\text{CH}_2$ , C2), 55.55 ( $\text{OCH}_3$ ), 62.99 ( $\text{CH}$ , C8), 102.76 ( $\text{CH}$ , C3'), 114.89 ( $\text{CH}_2$ , C11), 120.59 ( $\text{CH}$ , C7'), 122.43 ( $\text{CH}$ , C5'), 125.77 (C), 131.45 ( $\text{CH}$ , C8'), 140.22 ( $\text{CH}$ , C10), 140.92 (C), 145.59 (C), 147.00 ( $\text{CH}$ , C2'), 159.15 (C, C6'), 202.89 (C=O).  $m/z$  (EI) 322.16736 ( $\text{M}^+$ .  $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2$  requires 322.16758, 10%), 182 (88), 181 (100), 180 (68), 170 (61), 152 (57), 136 ( $\text{C}_9\text{H}_{14}\text{N}^+$ , 35), 123 (35), 107 (42).

### 5.2.2 9-Methylquinidine (68) (MeMgBr)

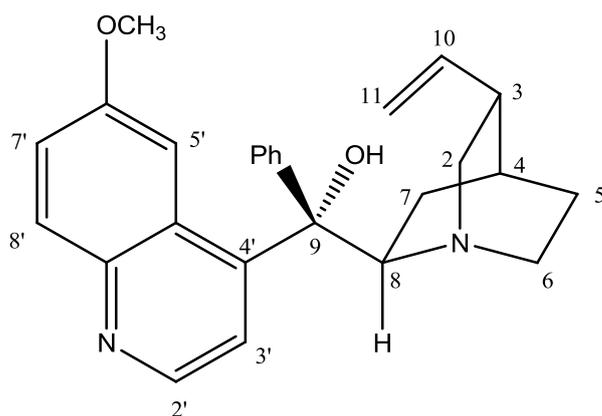


Under an argon atmosphere, a solution of quinidinone (2.0 g, 6.28 mmol) in dry toluene (20 mL) was added dropwise over 50 minutes to a stirred solution of methylmagnesium bromide (3 M in  $\text{Et}_2\text{O}$ , 4 mL, 12 mmol). The mixture was stirred at room temperature overnight and then hydrolysed by slow dropwise addition of

2 M hydrochloric acid / ice mixture (10 mL). The mixture was transferred to a separating funnel and the aqueous layer was removed. The solid residue in the flask was taken into 2 M hydrochloric acid (10 mL), and the organic layer was extracted with 2 M hydrochloric acid (3 x 10 mL). The aqueous layers were combined, washed with  $\text{Et}_2\text{O}$  (15 mL), and poured into 28% ammonia/ice mixture (25 mL). The white precipitate that formed was collected by filtration and dried under vacuum. The crude solid was dissolved in a minimum volume of ethanol, and water was added to precipitate the product, which was filtered and dried under vacuum. The white powder was 9-methylquinidine (1.2 g, 56% yield). Mp 91-95 °C (lit<sup>2</sup> 105-112 °C).  $[\alpha]_{\text{D}}^{20}$  158.6° ( $c$  0.98 in  $\text{CHCl}_3$ ).  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 0.93-1.01 (1H, m,  $\text{NCHCH}_2$ , H7), 1.49-1.55 (2H, m,  $\text{NCH}_2\text{CH}_2$ , H5), 1.64 (1H, br s,  $\text{NCH}_2\text{CH}_2\text{CH}$ , H4), 1.72 (1H, m,  $\text{NCHCH}_2$ , H7), 1.95 (3H, s, 9-Me), 2.12 (1H, q,  $^3J_{\text{HH}}$  8.0 Hz,  $\text{CH}_2=\text{CHCH}$ , H3), 2.73-2.85 (2H, m,  $\text{NCH}_2$ , H2 and  $\text{NCH}_2$ , H6), 2.92-3.07 (2H, m,  $\text{NCH}_2$ , H6 and  $\text{NCH}_2$ , H2), 3.23 (1H, t,  $^3J_{\text{HH}}$  9.2 Hz,  $\text{NCH}$ , H8), 3.86 (3H, s,  $\text{OCH}_3$ ), 4.76 (1H, d,  $^3J_{\text{HH}(\text{trans})}$  17.2 Hz,  $\text{CH}=\text{CH}_2$ , H11), 4.84 (1H, d,  $^3J_{\text{HH}(\text{cis})}$  10.2 Hz  $\text{CH}=\text{CH}_2$ , H11), 5.66 (1H, ddd,  $^3J_{\text{HH}(\text{trans})}$  17.2 Hz,  $^3J_{\text{HH}(\text{cis})}$  10.2 Hz,  $^3J_{\text{HH}(\text{vic})}$  7.0 Hz,  $\text{CH}=\text{CH}_2$ , H10), 7.29 (1H, dd,  $^3J_{\text{HH}}$  9.4 Hz,  $^4J_{\text{HH}}$  2.7 Hz, ArH7'),

7.62 (2H, br s, ArH5' and ArH3'), 7.98 (1H, d,  $^3J_{\text{HH}}$  9.4 Hz, ArH8'), 8.66 (1H, d,  $^3J_{\text{HH}}$  4.7 Hz, ArH2').  $\delta_{\text{H}}$  (CDCl<sub>3</sub>, 328 K) 1.08 (1H, ddd,  $^2J_{\text{HH}}$  13.6 Hz,  $^3J_{\text{HH}}$  9.5 Hz,  $^3J_{\text{HH}}$  5.6 Hz, NCHCH<sub>2</sub>, H7), 1.57-1.62 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.73 (1H, br s, NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 1.81 (1H, dd,  $^2J_{\text{HH}}$  13.1 Hz,  $^3J_{\text{HH}}$  10.3 Hz, NCHCH<sub>2</sub>, H7), 2.01 (3H, s, 9-CH<sub>3</sub>), 2.18 (1H, q,  $^3J_{\text{HH}}$  7.7 Hz, CH<sub>2</sub>=CHCH, H3), 2.86-2.96 (2H, m, NCH<sub>2</sub>, H2 and NCH<sub>2</sub>, H6), 3.05-3.17 (2H, m, NCH<sub>2</sub>, H2 and NCH<sub>2</sub>, H6), 3.35 (1H, t,  $^3J_{\text{HH}}$  9.5 Hz, NCH, H8), 3.96 (3H, s, OCH<sub>3</sub>), 4.84 (1H, d,  $^3J_{\text{HH}}$  17.3 Hz, CH=CH<sub>2</sub>, H11), 4.92 (1H, d,  $^3J_{\text{HH}}$  10.5 Hz, CH=CH<sub>2</sub>, H11), 5.74 (1H, ddd,  $^3J_{\text{HH}}$  17.3 Hz,  $^3J_{\text{HH}}$  10.5 Hz,  $^3J_{\text{HH}}$  7.7 Hz, CH=CH<sub>2</sub>, H10), 7.38 (1H, dd,  $^3J_{\text{HH}}$  9.2 Hz,  $^4J_{\text{HH}}$  2.7 Hz, ArH7'), 7.68 (1H, d,  $^3J_{\text{HH}}$  4.8 Hz, ArH3'), 7.77 (1H, br s, ArH5'), 8.07 (1H, d,  $^3J_{\text{HH}}$  9.2 Hz, ArH8'), 8.75 (1H, d,  $^3J_{\text{HH}}$  4.8 Hz, ArH2').  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 22.06 (CH<sub>2</sub>, C7), 26.24 (CH<sub>2</sub>, C5), 28.74 (CH, C4), 29.54 (CH<sub>3</sub>), 39.76 (CH, C3), 49.77 (CH<sub>2</sub>, C6), 51.18 (CH<sub>2</sub>, C2), 55.42 (OCH<sub>3</sub>), 63.42 (CH, C8), 77.83 (C, C9), 104.90 (CH, C3'), 114.34 (CH<sub>2</sub>, C11), 119.86 (CH, C7'), 120.62 (CH, C5'), 129.29 (C), 132.08 (CH, C8'), 140.19 (CH, C10), 145.30 (C), 147.45 (CH, C2'), 150.68 (C), 156.78 (C, C6'). *m/z* (EI) 338.19881 (M<sup>+</sup>. C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub> requires 338.19878, 70%), 323 (C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub><sup>+</sup>, 33), 202 (45), 160 (39), 158 (33), 136 (C<sub>9</sub>H<sub>14</sub>N<sup>+</sup>, 100), 108 (38). A single crystal suitable for X-ray crystallography was grown by slow evaporation from diethyl ether/hexane.

### 5.2.3 9-Phenylquinidine (69) (PhMgBr)



Under a nitrogen atmosphere, a solution of quinidinone (1.8 g, 5.51 mmol) in dry toluene (38 mL) was added dropwise over 30 minutes to a stirred solution of phenylmagnesium bromide (1 M in Et<sub>2</sub>O, 12 mL, 12.0 mmol). The mixture was stirred at room temperature overnight and then hydrolysed by slow dropwise addition of 2 M hydrochloric acid/ice mixture (20 mL). The mixture was transferred to a separating funnel and the aqueous layer was removed. The solid residue in the flask was taken into 2 M hydrochloric acid (20 mL), and the organic layer was extracted with 2 M hydrochloric acid (3 x 20 mL). The aqueous layers were combined, washed with Et<sub>2</sub>O

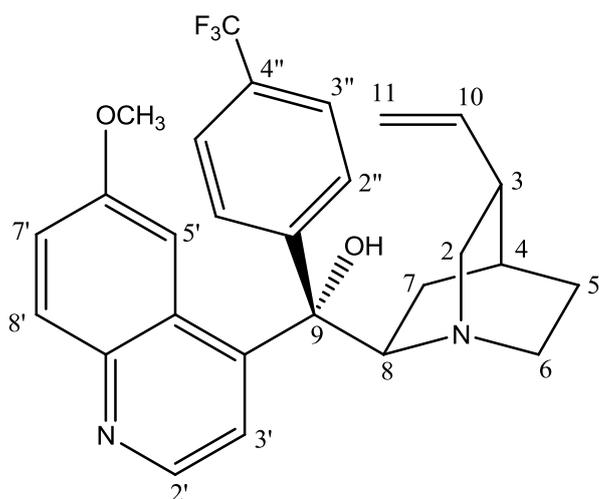
(30 mL), and poured into 28% ammonia/ice mixture (25 mL). The white precipitate that formed was collected by filtration and dried under vacuum. The crude solid was dissolved in a minimum volume of ethanol, and water was added to precipitate the product, which was filtered and dried under vacuum. The white powder was 9-phenylquinidine (1.0 g, 2.38 mmol). This solid was found to contain large amounts of ethanol, which were removed by dissolving the solid in chloroform (40 mL) and washing with water (3 x 30 mL), before drying over magnesium sulphate and removing the solvent under vacuum, to give 9-phenylquinidine without traces of ethanol (0.2 g, 10% yield). Mp 177-181 °C (lit<sup>3</sup> 182-186 °C).  $[\alpha]_D^{20}$  226.5° (*c* 0.99 in CHCl<sub>3</sub>).  $\delta_H$  (CDCl<sub>3</sub>) 1.18 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.45-1.53 (1H, m, NCHCH<sub>2</sub>, H7), 1.56-1.67 (3H, m, NCHCH<sub>2</sub>, H7, NCH<sub>2</sub>CH<sub>2</sub>, H5 and NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 1.98 (1H, q, <sup>3</sup>*J*<sub>HH</sub> 7.8 Hz, CH<sub>2</sub>=CHCH, H3), 2.50-2.63 (2H, m, NCH<sub>2</sub>, H6), 2.71-2.80 (1H, m, NCH<sub>2</sub>, H2), 3.11 (1H, m, NCH<sub>2</sub>, H2), 3.35 (3H, s, OCH<sub>3</sub>), 3.79-3.86 (1H, t, <sup>3</sup>*J*<sub>HH</sub> 11.3 Hz, NCH, H8), 4.54 (1H, dt, <sup>3</sup>*J*<sub>HH(trans)</sub> 17.2 Hz, <sup>2</sup>*J*<sub>HH</sub> = <sup>4</sup>*J*<sub>HH</sub> 1.6 Hz, CH<sub>2</sub>=CH, H11), 4.67 (1H, dt, <sup>3</sup>*J*<sub>HH(cis)</sub> 10.2 Hz, <sup>2</sup>*J*<sub>HH</sub> = <sup>4</sup>*J*<sub>HH</sub> 1.2 Hz, CH<sub>2</sub>=CH, H11), 5.37 (1H, ddd, <sup>3</sup>*J*<sub>HH(trans)</sub> 17.2 Hz, <sup>3</sup>*J*<sub>HH(cis)</sub> 10.2 Hz, <sup>3</sup>*J*<sub>HH(vic)</sub> 7.8 Hz, CH<sub>2</sub>=CH, H10), 6.76 (1H, br s, ArH5'), 7.06 (1H, dd, <sup>3</sup>*J*<sub>HH</sub> 9.4 Hz, <sup>4</sup>*J*<sub>HH</sub> 2.7 Hz, ArH7'), 7.12-7.22 (3H, m, ArH3'' and ArH4''), 7.40 (2H, d, <sup>3</sup>*J*<sub>HH</sub> 7.0 Hz, ArH2''), 7.81 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 9.4 Hz, ArH8'), 7.94 (1H, br s, ArH3'), 8.63 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 4.7 Hz, ArH2').  $\delta_H$  (CDCl<sub>3</sub>, 328 K) 1.21-1.30 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.59-1.66 (1H, m, NCHCH<sub>2</sub>, H7), 1.70-1.79 (3H, m, NCHCH<sub>2</sub>, H7, NCH<sub>2</sub>CH<sub>2</sub>, H5 and NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 2.13 (1H, q, <sup>3</sup>*J*<sub>HH</sub> 7.7 Hz, CH<sub>2</sub>=CHCH, H3), 2.73-2.81 (2H, m, NCH<sub>2</sub>, H6), 2.91 (1H, dt, <sup>2</sup>*J*<sub>HH</sub> 13.2 Hz, <sup>3</sup>*J*<sub>HH</sub> 8.9 Hz, NCH<sub>2</sub>, H2), 3.25 (1H, t, <sup>3</sup>*J*<sub>HH</sub> 11.4 Hz, NCH<sub>2</sub>, H2), 3.49 (3H, s, OCH<sub>3</sub>), 3.98 (1H, t, <sup>3</sup>*J*<sub>HH</sub> 9.9 Hz, NCH, H8), 4.70 (1H, dt, <sup>3</sup>*J*<sub>HH</sub> 17.2 Hz, <sup>2</sup>*J*<sub>HH</sub> = <sup>4</sup>*J*<sub>HH</sub> 1.5 Hz, CH<sub>2</sub>=CH, H11), 4.81 (1H, dt, <sup>3</sup>*J*<sub>HH</sub> 10.5 Hz, <sup>2</sup>*J*<sub>HH</sub> = <sup>4</sup>*J*<sub>HH</sub> 1.4 Hz, CH<sub>2</sub>=CH, H11), 5.50 (1H, ddd, <sup>3</sup>*J*<sub>HH</sub> 17.2 Hz, <sup>3</sup>*J*<sub>HH</sub> 10.5 Hz, <sup>3</sup>*J*<sub>HH</sub> 7.7 Hz, CH<sub>2</sub>=CH, H10), 6.87 (1H, br s, ArH5'), 7.20 (1H, dd, <sup>3</sup>*J*<sub>HH</sub> 9.2 Hz, <sup>4</sup>*J*<sub>HH</sub> 2.8 Hz, ArH7'), 7.26 (1H, tt, <sup>3</sup>*J*<sub>HH</sub> 7.3 Hz, <sup>4</sup>*J*<sub>HH</sub> 1.6 Hz, ArH4''), 7.32 (2H, tm, <sup>3</sup>*J*<sub>HH</sub> 7.3 Hz, ArH3''), 7.53 (2H, dd, <sup>3</sup>*J*<sub>HH</sub> 7.3 Hz, <sup>4</sup>*J*<sub>HH</sub> 1.6 Hz, ArH2''), 7.97 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 9.2 Hz, ArH8'), 8.09 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 4.7 Hz, ArH3'), 8.86 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 4.7 Hz, ArH2').  $\delta_C$  (CDCl<sub>3</sub>) 23.74 (CH<sub>2</sub>, C7), 26.17 (CH<sub>2</sub>, C5), 28.99 (CH, C4), 39.72 (CH, C3), 49.42 (CH<sub>2</sub>, C6), 50.76 (CH<sub>2</sub>, C2), 55.15 (OCH<sub>3</sub>), 61.33 (CH, C8), 79.21 (C, C9) 104.99 (CH, C3'), 114.33 (CH<sub>2</sub>, C11), 120.47 (CH, C5'), 121.03 (CH, C7'), 126.99 (C), 127.13 (CH, C4''), 127.61 (CH, C3''), 128.53 (CH, C2''), 131.41 (CH, C8'), 139.60 (CH, C10), 145.22 (C), 147.37

(CH, C2'), 149.53 (C), 156.35 (C, C6').  $m/z$  (FAB) 401.22198 ( $MH^+$ .  $C_{26}H_{29}N_2O_2$  requires 401.22218, 91%), 323 ( $C_{20}H_{23}N_2O_2^+$ , 18), 264 (26), 173 (18), 160 (20), 154 (80), 149 (36).

#### 5.2.4 9-Phenylquinidine (69) (PhLi)

Under a nitrogen atmosphere quinidinone (1.99 g, 6.2 mmol) dissolved in dry toluene (40 mL) was added dropwise over 20 minutes to a stirred solution of phenyllithium (1.8 M in  $nBu_2O$ , 7.0 mL, 12.6 mmol) at  $-78\text{ }^\circ\text{C}$ . The reaction mixture was stirred at  $-78\text{ }^\circ\text{C}$  for 6 hours and then quenched with water (30 mL), before warming to room temperature overnight. The mixture was transferred to a separating funnel and the organic layer was removed. The aqueous layer was extracted with diethyl ether (3 x 15 mL). The organic layers were then combined and dried over anhydrous sodium sulphate before the solvent was removed by rotary evaporation. The crude oil (3.85 g) was purified using column chromatography on silica gel, using the solvent system toluene/diethyl ether/dichloromethane/triethylamine (38/30/30/2) to give 9-phenylquinidine as a white powder (0.39 g, 38% yield). Mp  $184\text{--}188\text{ }^\circ\text{C}$  (lit<sup>3</sup>  $182\text{--}186\text{ }^\circ\text{C}$ ).  $[\alpha]_D^{20}$   $226.5^\circ$  ( $c$  0.99 in  $CHCl_3$ ).  $\delta_H$  ( $CDCl_3$ ) 1.18 (1H, m,  $NCH_2CH_2$ , H5), 1.50-1.58 (1H, m,  $NCHCH_2$ , H7), 1.60-1.71 (3H, m,  $NCHCH_2$ , H7,  $NCH_2CH_2$ , H5 and  $NCH_2CH_2CH$ , H4), 2.03 (1H, q,  $^3J_{HH}$  7.8 Hz,  $CH_2=CHCH$ , H3), 2.62-2.73 (2H, m,  $NCH_2$ , H6), 2.78-2.87 (1H, m,  $NCH_2$ , H2), 3.18 (1H, t,  $^3J_{HH}$  11.2 Hz,  $NCH_2$ , H2), 3.37 (3H, s,  $OCH_3$ ), 3.91 (1H, t,  $^3J_{HH}$  9.6 Hz,  $NCH$ , H8), 4.57 (1H, dt,  $^3J_{HH(trans)}$  17.2 Hz,  $^2J_{HH} = ^4J_{HH}$  1.6 Hz,  $CH_2=CH$ , H11), 4.70 (1H, dt,  $^3J_{HH(cis)}$  10.6 Hz,  $^2J_{HH} = ^4J_{HH}$  1.6 Hz,  $CH_2=CH$ , H11), 5.36 (1H, ddd,  $^3J_{HH(trans)}$  17.2 Hz,  $^3J_{HH(cis)}$  10.6 Hz,  $^3J_{HH(vic)}$  7.8 Hz,  $CH_2=CH$ , H10), 6.72 (1H, br s, ArH5'), 7.10 (1H, dd,  $^3J_{HH}$  9.3 Hz,  $^3J_{HH}$  2.9 Hz, ArH7'), 7.15-7.26 (3H, m, ArH3'' and ArH4''), 7.41 (2H, d,  $^3J_{HH}$  7.0 Hz, ArH2''), 7.86 (1H, d,  $^3J_{HH}$  9.3 Hz, ArH8'), 8.00 (1H, br s, ArH3'), 8.74 (1H, d,  $^3J_{HH}$  4.7 Hz, ArH2').  $\delta_C$  ( $CDCl_3$ ) 23.72 ( $CH_2$ , C7), 26.10 ( $CH_2$ , C5), 28.96 (CH, C4), 39.65 (CH, C3), 49.44 ( $CH_2$ , C6), 50.75 ( $CH_2$ , C2), 55.16 ( $OCH_3$ ), 61.33 (CH, C8), 79.22 (C, C9), 104.95 (CH, C3'), 114.40 ( $CH_2$ , C11), 120.46 (CH, C5'), 121.03 (CH, C7'), 126.96 (C), 127.12 (CH, C4''), 127.64 (CH, C3''), 128.55 (CH, C2''), 131.42 (CH, C8'), 139.50 (CH, C10), 145.21 (C), 147.38 (CH, C2'), 149.45 (C), 156.37 (C, C6').  $m/z$  (ESI) 401.2235 ( $MH^+$ .  $C_{26}H_{29}N_2O_2$  requires 401.2229, 90%), 201.1131 (100).

## 5.2.5 9-(4-Trifluoromethylphenyl)quinidine (70)

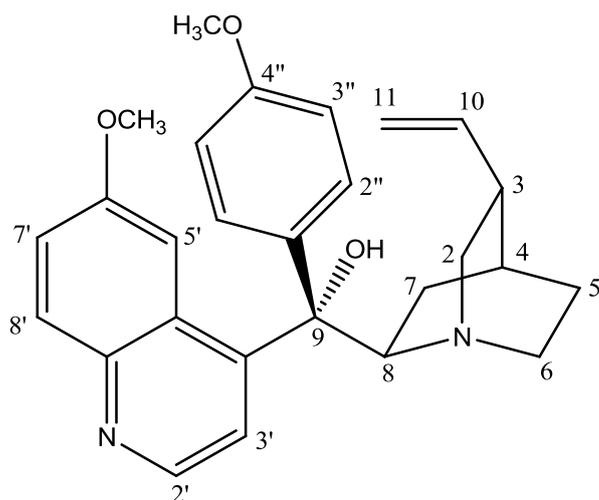


Under a nitrogen atmosphere *n*-butyllithium (1.6 M solution in hexanes, 15.4 mL, 24.6 mmol) in dry diethyl ether (10 mL) was added dropwise over a period of 50 minutes to a stirred solution of 4-bromobenzotrifluoride (3.8 mL, 27.1 mmol) in dry diethyl ether (10 mL) at 0 °C. The solution was stirred at 0 °C for a period of 1 hour 10 minutes, and

was then cooled to -78 °C. Quinidinone (2.0 g, 6.2 mmol) in dry toluene (40 mL) was added dropwise over a period of 36 minutes. The reaction was then stirred at -78 °C for 6 hours, quenched with water (30 mL), and allowed to warm to room temperature overnight. The crude reaction mixture was transferred to a separating funnel, the organic layer was removed and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over sodium sulphate and the solvent was removed to give the crude product as a reddish oil. The crude oil was dissolved in a minimum volume of chloroform and purified by column chromatography using the solvent system toluene/diethyl ether/dichloromethane/triethylamine (38/30/30/2) to give the desired product as a white solid (0.70 g, 24% yield). Mp 203-206 °C.  $[\alpha]_D^{20}$  186.2° (*c* 0.99 in CHCl<sub>3</sub>). Found: C, 69.38; H, 5.87; N, 5.84. C<sub>27</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub>F<sub>3</sub> requires C, 69.22; H, 5.81; N, 5.98%.  $\delta_H$  (CDCl<sub>3</sub>) 1.25 (1H, m, NCHCH<sub>2</sub>, H7), 1.48-1.59 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.60-1.70 (3H, m, NCHCH<sub>2</sub>, H7, NCH<sub>2</sub>CH<sub>2</sub>, H5 and NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 2.03 (1H, q, <sup>3</sup>J<sub>HH</sub> 7.7 Hz, CH<sub>2</sub>=CHCH, H3), 2.64 (2H, br d, <sup>3</sup>J<sub>HH</sub> 8.6 Hz, NCH<sub>2</sub>, H2), 2.78 (1H, m, NCH<sub>2</sub>, H6), 3.10 (1H, t, <sup>3</sup>J<sub>HH</sub> 10.6 Hz, NCH<sub>2</sub>, H6), 3.39 (3H, s, OCH<sub>3</sub>), 3.83 (1H, t, <sup>3</sup>J<sub>HH</sub> 9.4 Hz, NCH, H8), 4.10 (1H, br s, OH), 4.58 (1H, d, <sup>3</sup>J<sub>HH(trans)</sub> 17.2 Hz, CH<sub>2</sub>=CH, H11), 4.72 (1H, d, <sup>3</sup>J<sub>HH(cis)</sub> 10.6 Hz, CH<sub>2</sub>=CH, H11), 5.40 (1H, ddd, <sup>3</sup>J<sub>HH(trans)</sub> 17.2 Hz, <sup>3</sup>J<sub>HH(cis)</sub> 10.6 Hz, <sup>3</sup>J<sub>HH(vic)</sub> 7.7 Hz, CH<sub>2</sub>=CH, H10), 6.67 (1H, br s, ArH5'), 7.13 (1H, dd, <sup>3</sup>J<sub>HH</sub> 9.4 Hz, <sup>4</sup>J<sub>HH</sub> 2.7 Hz, ArH7'), 7.48 (2H, d, <sup>3</sup>J<sub>HH</sub> 8.6 Hz, ArH2''), 7.55 (2H, d, <sup>3</sup>J<sub>HH</sub> 8.2 Hz, ArH3''), 7.89 (1H, d, <sup>3</sup>J<sub>HH</sub> 9.4 Hz, ArH8'), 7.94 (1H, br s, ArH3'), 8.76 (1H, d, <sup>3</sup>J<sub>HH</sub> 4.7 Hz, ArH2').  $\delta_F$  (CDCl<sub>3</sub>) -62.62 (s, CF<sub>3</sub>).  $\delta_C$  (CDCl<sub>3</sub>) 23.64 (CH<sub>2</sub>, C7), 26.21 (CH<sub>2</sub>, C5), 28.85 (CH, C4), 39.52 (CH, C3), 49.40 (CH<sub>2</sub>, C2), 50.83 (CH<sub>2</sub>, C6), 55.10 (OCH<sub>3</sub>), 61.55 (CH, C8), 79.43 (C, C9), 104.75 (CH, C5'),

114.40 (CH<sub>2</sub>, C11), 120.32 (CH, C3'), 121.18 (CH, C7'), 123.69 (C, q, <sup>1</sup>J<sub>CF</sub> 270.6 Hz, CF<sub>3</sub>), 125.26 (CH, t, <sup>3</sup>J<sub>CF</sub> 3.2 Hz, C3''), 126.67 (C, C1''), 127.56 (CH, C2''), 129.63 (C, q, <sup>2</sup>J<sub>CF</sub> 32.5 Hz, C4''), 131.58 (CH, C8'), 139.61 (CH, C10), 145.27 (C), 147.26 (CH, C2'), 148.51 (C), 149.46 (C), 156.63 (C, C6'). m/z (ES<sup>+</sup>) 469.2127 (MH<sup>+</sup>). C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>F<sub>3</sub> requires 469.2103, 60%), 235.1060 (100).

### 5.2.6 9-(4-Methoxyphenyl)quinidine (71) (4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>Li)



Under a nitrogen atmosphere *n*-butyllithium (1.6 M solution in hexanes, 15.5 mL, 24.8 mmol) in dry diethyl ether (10 mL) was added dropwise over a period of 43 minutes to a stirred solution of 4-bromoanisole (3.4 mL, 27.2 mmol) in dry diethyl ether (10 mL) at room temperature (19 °C). The solution was stirred at room temperature for a period of 1 hour 15

minutes, and was then cooled to -78 °C. Quinidinone (2.00 g, 6.2 mmol) in dry toluene (40 mL) was added dropwise over a period of 28 minutes. The reaction was then stirred at -78 °C for 6 hours, quenched with water (30 mL), and allowed to warm to room temperature overnight. The crude reaction mixture was transferred to a separating funnel, the organic layer was removed and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over sodium sulphate and the solvent was removed to give the crude product as a yellow oil. The crude oil was dissolved in a minimum volume of chloroform and purified by column chromatography using toluene/diethyl ether/dichloromethane/triethylamine (38/30/30/2) to give the desired product as a pale yellow solid (0.12 g, 4% yield). Mp 185-190 °C. [ $\alpha$ ]<sub>D</sub><sup>20</sup> 222.7° (*c* 0.93 in CHCl<sub>3</sub>).  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 1.12 (1H, t, <sup>3</sup>J<sub>HH</sub> 7.0 Hz, NCHCH<sub>2</sub>, H7), 1.44-1.53 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.55-1.65 (3H, m, NCHCH<sub>2</sub>, H7, NCH<sub>2</sub>CH<sub>2</sub>, H5 and NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 1.99 (1H, q, <sup>3</sup>J<sub>HH</sub> 8.0 Hz, CH<sub>2</sub>=CHCH, H3), 2.56-2.67 (2H, m, NCH<sub>2</sub>, H2), 2.77 (1H, m, NCH<sub>2</sub>, H6), 3.12 (1H, t, <sup>3</sup>J<sub>HH</sub> 11.3 Hz, NCH<sub>2</sub>, H6), 3.41 (3H, s, OCH<sub>3</sub>, 6'), 3.66 (3H, s, OCH<sub>3</sub>, 4''), 3.81 (1H, t, <sup>3</sup>J<sub>HH</sub> 9.6 Hz, NCH, H8), 4.58 (1H, d, <sup>3</sup>J<sub>HH(trans)</sub> 17.4 Hz, CH<sub>2</sub>=CH, H11), 4.70 (1H, d, <sup>3</sup>J<sub>HH(cis)</sub> 10.4 Hz, CH<sub>2</sub>=CH, H11), 5.41 (1H, ddd, <sup>3</sup>J<sub>HH(trans)</sub> 17.4 Hz, <sup>3</sup>J<sub>HH(cis)</sub> 10.4 Hz, <sup>3</sup>J<sub>HH(vic)</sub> 8.0 Hz, CH<sub>2</sub>=CH, H10), 6.73 (2H, d, <sup>3</sup>J<sub>HH</sub> 8.8 Hz,

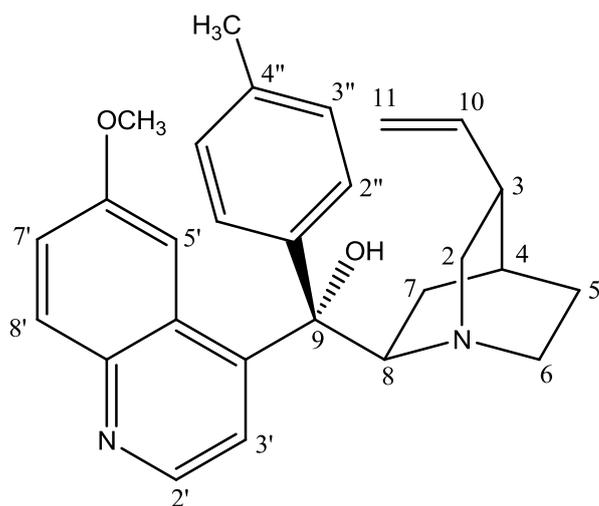
ArH3''), 6.79 (1H, br s, ArH5'), 7.07 (1H, dd,  $^3J_{\text{HH}}$  9.4 Hz,  $^4J_{\text{HH}}$  2.7 Hz, ArH7'), 7.32 (2H, d,  $^3J_{\text{HH}}$  8.8 Hz, ArH2''), 7.83 (1H, d,  $^3J_{\text{HH}}$  9.4 Hz, ArH8'), 7.94 (1H, br s, ArH3'), 8.66 (1H, d,  $^3J_{\text{HH}}$  4.7 Hz, ArH2').  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 23.62 (CH<sub>2</sub>, C7), 26.18 (CH<sub>2</sub>, C5), 28.97 (CH, C4), 39.82 (CH, C3), 49.48 (CH<sub>2</sub>, C6), 50.75 (CH<sub>2</sub>, C2), 55.18 (OCH<sub>3</sub>), 55.24 (OCH<sub>3</sub>), 61.17 (CH, C8), 78.96 (C, C9), 105.04 (CH, C5'), 113.78 (CH, C3''), 114.27 (CH<sub>2</sub>, C11), 120.35 (CH, C3'), 120.90 (CH, C7'), 127.00 (C), 128.47 (CH, C2''), 131.33 (CH, C8'), 137.83 (C), 139.79 (CH, C10), 145.12 (C), 147.32 (CH, C2'), 149.79 (C), 156.31 (C), 158.78 (C).  $m/z$  (ES<sup>+</sup>) 431.2334 (MH<sup>+</sup>. C<sub>27</sub>H<sub>31</sub>N<sub>2</sub>O<sub>3</sub> requires 431.2335, 67%), 216 (100), 207 (65).

### 5.2.7 9-(4-Methoxyphenyl)quinidine (71) (4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>MgBr)

Under a nitrogen atmosphere 4-bromoanisole (2.9 mL, 23.2 mmol) in dry diethyl ether (10 mL) was added dropwise over a period of 54 minutes to a flask containing oven dried magnesium turnings (0.54 g, 22.4 mmol) in dry diethyl ether (6 mL) at room temperature. The mixture was stirred at room temperature for one hour, and then refluxed until all of the magnesium had been consumed. The mixture was then cooled to room temperature and quinidinone (1.80 g, 5.6 mmol) in dry toluene (40 mL) was added dropwise over a period of 31 minutes. The mixture was then stirred at room temperature overnight (19 hours) before being quenched with water (30 mL). The crude reaction mixture was transferred to a separating funnel, the organic layer was removed and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over sodium sulphate and the solvent was removed to give the crude product as a yellow oil. The crude oil was dissolved in a minimum volume of chloroform and purified by column chromatography using toluene/diethyl ether/dichloromethane/triethylamine (38/30/30/2) to give the desired product as a pale yellow solid (0.19 g, 8% yield).

### 5.2.8 9-(4-Methylphenyl)quinidine (72)

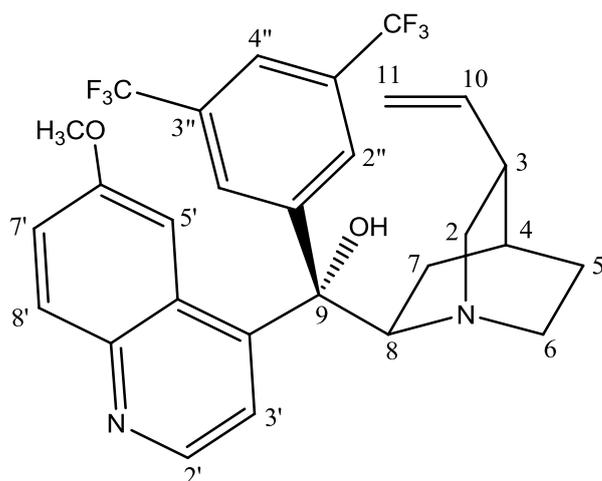
Under a nitrogen atmosphere *n*-butyllithium (1.6 M in hexanes, 7.8 mL, 12.5 mmol) in dry diethyl ether (10 mL) was added dropwise over 40 minutes to a stirred solution of 4-bromotoluene (1.7 mL, 13.8 mmol) in dry diethyl ether (10 mL) at room temperature (19 °C). After stirring at room temperature for one hour, the reaction mixture was cooled to -78 °C and quinidinone (1.02 g, 3.2 mmol) in dry toluene (40 mL) was added dropwise over 33 minutes. The reaction mixture was stirred at -78 °C for 6 hours, then



quenched with water (30 mL) and allowed to warm to room temperature overnight. The crude reaction mixture was transferred to a separating funnel, the organic layer was removed and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over sodium sulphate and the solvent

was removed to give the crude product as a brown oil. The crude product was purified by column chromatography using the solvent system toluene/dichloromethane/diethyl ether/triethylamine (38/30/30/2), to give pure 9-(4-methylphenyl)quinidine as a white solid (0.37 g, 28 % yield). Mp 208-212 °C.  $[\alpha]_D^{20}$  217.7° (*c* 0.99 in CHCl<sub>3</sub>). Found: C, 75.95; H, 7.24; N, 5.83. C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub> requires C, 78.23; H, 7.29; N, 6.76%.  $\delta_H$  (CDCl<sub>3</sub>) 1.09-1.20 (1H, m, NCHCH<sub>2</sub>, H7), 1.45-1.55 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.57-1.67 (3H, m, NCHCH<sub>2</sub>, H7, NCH<sub>2</sub>CH<sub>2</sub>, H5 and NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 2.00 (1H, q,  $^3J_{HH}$  7.8 Hz, CH<sub>2</sub>=CHCH, H3), 2.21 (3H, s, CH<sub>3</sub>), 2.57-2.66 (2H, m, NCH<sub>2</sub>, H2), 2.77 (1H, m, NCH<sub>2</sub>, H6), 3.12 (1H, t,  $^3J_{HH}$  11.2 Hz, NCH<sub>2</sub>, H6), 3.39 (3H, s, OCH<sub>3</sub>), 3.84 (1H, t,  $^3J_{HH}$  9.8 Hz, NCH, H8), 4.55 (1H, d,  $^3J_{HH(\text{trans})}$  17.2 Hz, CH=CH<sub>2</sub>, H11), 4.68 (1H, d,  $^3J_{HH(\text{cis})}$  10.2 Hz, CH=CH<sub>2</sub>, H11), 5.37 (1H, ddd,  $^3J_{HH(\text{trans})}$  17.2 Hz,  $^3J_{HH(\text{cis})}$  10.2 Hz,  $^3J_{HH(\text{vic})}$  7.8 Hz, CH=CH<sub>2</sub>, H10), 6.79 (1H, br s, ArH5'), 7.01 (2H, d,  $^3J_{HH}$  8.0 Hz, ArH3''), 7.08 (1H, dd,  $^3J_{HH}$  9.2 Hz,  $^4J_{HH}$  2.7 Hz, ArH7'), 7.28 (2H, d,  $^3J_{HH}$  8.0 Hz, ArH2''), 7.83 (1H, d,  $^3J_{HH}$  9.2 Hz, ArH8'), 7.96 (1H, br s, ArH3'), 8.68 (1H, d,  $^3J_{HH}$  4.7 Hz, ArH2').  $\delta_C$  (CDCl<sub>3</sub>) 21.02 (CH<sub>3</sub>), 23.59 (CH<sub>2</sub>, C7), 26.18 (CH<sub>2</sub>, C5), 28.98 (CH, C4), 39.79 (CH, C3), 49.40 (CH<sub>2</sub>, C2), 50.71 (CH<sub>2</sub>, C6), 55.13 (OCH<sub>3</sub>), 61.26 (CH, C8), 79.14 (C, C9), 105.14 (CH, C5'), 114.24 (CH<sub>2</sub>, C11), 120.31 (CH, C3'), 120.94 (CH, C7'), 127.07 (C), 127.10 (CH, C2''), 129.06 (CH, C3''), 131.20 (CH, C8'), 137.11 (C), 139.79 (CH, C10), 142.48 (C), 145.08 (C), 147.24 (CH, C2'), 149.92 (C), 156.26 (C, C6'). *m/z* (ES<sup>+</sup>) 415.2395 (MH<sup>+</sup>. C<sub>27</sub>H<sub>31</sub>N<sub>2</sub>O<sub>2</sub> requires 415.2386, 100%), 208.1206 (80).

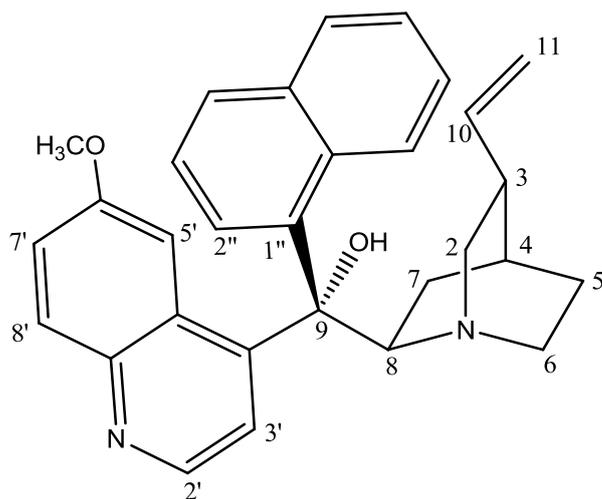
## 5.2.9 9-(3,5-Bis-trifluoromethylphenyl)quinidine (73)



Under a nitrogen atmosphere *n*-butyllithium (1.6 M in hexanes, 2.6 mL, 4.16 mmol) in dry diethyl ether (10 mL) was added dropwise over 16 minutes to a stirred solution of 3,5-bis-(trifluoromethyl)bromobenzene (0.8 mL, 4.6 mmol) in dry diethyl ether (10 mL) at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 3 hours, then quinidinone (0.3 g, 1.1 mmol) in dry toluene (30 mL) was added dropwise over 17 minutes at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 6 hours, then quenched with water (30 mL) and allowed to warm to room temperature overnight. The crude reaction mixture was transferred to a separating funnel, the organic layer was removed and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over sodium sulphate and the solvent was removed to give the crude product as a brown oil. The crude product was purified by column chromatography using the solvent system toluene/dichloromethane/diethyl ether/triethyl amine (38/30/30/2), to give pure 9-(3,5-bis-trifluoromethylphenyl)quinidine as a white solid (0.19 g, 33% yield). Mp  $198\text{--}201\text{ }^{\circ}\text{C}$ .  $[\alpha]_{\text{D}}^{20}$   $119.0^{\circ}$  (*c* 0.99 in  $\text{CHCl}_3$ ). Found: C, 62.58; H, 4.89; N, 5.25.  $\text{C}_{28}\text{H}_{26}\text{N}_2\text{O}_2\text{F}_6$  requires C, 62.68; H, 4.88; N, 5.22%.  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.29 (1H, t,  $^3J_{\text{HH}}$  7.2 Hz,  $\text{NCHCH}_2$ , H7), 1.50-1.59 (1H, m,  $\text{NCH}_2\text{CH}_2$ , H5), 1.63-1.73 (3H, m,  $\text{NCHCH}_2$ , H7,  $\text{NCH}_2\text{CH}_2$ , H5 and  $\text{NCH}_2\text{CH}_2\text{CH}$ , H4), 2.06 (1H, q,  $^3J_{\text{HH}}$  7.6 Hz,  $\text{CH}_2=\text{CHCH}$ , H3), 2.58-2.70 (2H, m,  $\text{NCH}_2$ , H2), 2.71-2.80 (1H, m,  $\text{NCH}_2$ , H6), 3.03 (1H, t,  $^3J_{\text{HH}}$  11.3 Hz,  $\text{NCH}_2$ , H6), 3.43 (3H, s,  $\text{OCH}_3$ ), 3.79 (1H, t,  $^3J_{\text{HH}}$  9.4 Hz,  $\text{NCH}$ , H8), 4.68 (1H, d,  $^3J_{\text{HH}(\text{trans})}$  17.2 Hz,  $\text{CH}=\text{CH}_2$ , H11), 4.79 (1H, d,  $^3J_{\text{HH}(\text{cis})}$  10.2 Hz,  $\text{CH}=\text{CH}_2$ , H11), 5.54 (1H, ddd,  $^3J_{\text{HH}(\text{trans})}$  17.2 Hz,  $^3J_{\text{HH}(\text{cis})}$  10.2 Hz,  $^3J_{\text{HH}(\text{vic})}$  7.6 Hz,  $\text{CH}_2=\text{CH}$ , H10), 6.80 (1H, br s,  $\text{ArH}5'$ ), 7.12 (1H, dd,  $^3J_{\text{HH}}$  9.4 Hz,  $^4J_{\text{HH}}$  2.7 Hz,  $\text{ArH}7'$ ), 7.68 (1H, br s,  $\text{ArH}8'$ ), 7.86 (1H, s,  $\text{ArH}4''$ ), 7.88 (1H, br s,  $\text{ArH}3''$ ), 7.89 (2H, br s,  $\text{ArH}2''$ ), 8.70 (1H, d,  $^3J_{\text{HH}}$  4.7 Hz,  $\text{ArH}2'$ ).  $\delta_{\text{F}}$  ( $\text{CDCl}_3$ )  $-62.78$  (s, 2 x  $\text{CF}_3$ ).  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 23.44 ( $\text{CH}_2$ , C7), 26.25 ( $\text{CH}_2$ , C5), 28.64 (CH, C4), 39.34 (CH, C3), 49.34 ( $\text{CH}_2$ , C2), 50.81 ( $\text{CH}_2$ , C6), 54.99 ( $\text{OCH}_3$ ), 61.54 (CH, C8), 79.83 (C, C9), 103.92 (CH, C3'), 114.47 ( $\text{CH}_2$ , C11), 119.97 (CH), 121.09 (CH, q,  $^3J_{\text{CF}}$  3.2 Hz, C2''), 121.59 (CH),

123.18 (C, q,  $^1J_{\text{CF}}$  272.2 Hz,  $\text{CF}_3$ ), 126.27 (C), 127.26 (CH, q,  $^3J_{\text{CF}}$  3.2 Hz,  $\text{C4}''$ ), 131.38 (C, q,  $^2J_{\text{CF}}$  33.6 Hz,  $\text{C3}''$ ) 131.74 (CH), 139.70 (CH,  $\text{C10}$ ), 145.41 (C), 147.21 (CH,  $\text{C2}'$ ), 148.27 (C), 156.99 (C,  $\text{C6}'$ ).  $m/z$  (ES) 537.1985 ( $\text{MH}^+$ .  $\text{C}_{28}\text{H}_{27}\text{N}_2\text{O}_2\text{F}_6$  requires 537.1977, 100%), 269 (80).

### 5.2.10 9-(1-Naphthyl)quinidine (74)

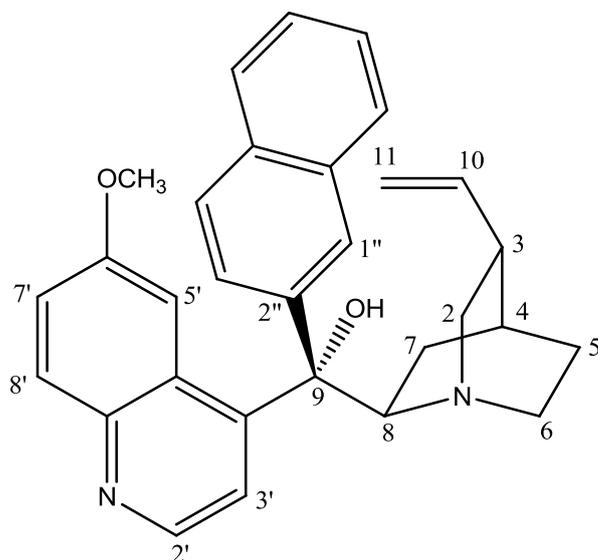


Under a nitrogen atmosphere *n*-butyllithium (1.6 M in hexanes, 8.2 mL, 13.1 mmol) in dry toluene (10 mL) was added dropwise over 32 minutes to a stirred solution of 1-bromonaphthalene (2 mL, 14.3 mmol) in dry toluene (10 mL) at room temperature. The reaction mixture was then warmed to approximately 48 °C and stirred at this temperature for one

hour. The mixture was then cooled to -78 °C and quinidinone (1.1 g, 3.3 mmol) dissolved in dry toluene (40 mL) was added dropwise over 31 minutes. The reaction mixture was stirred at -78 °C for 6 hours, then quenched with water (30 mL) and allowed to warm to room temperature overnight. The crude reaction mixture was transferred to a separating funnel, the organic layer was removed and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over sodium sulphate and the solvent was removed to give the crude product as a brown oil. The conversion to desired product was only 23%. Purification by column chromatography using the solvent system toluene/dichloromethane/diethyl ether/triethyl amine (38/30/30/2) yielded mixed fractions of 9-(1-naphthyl)quinidine with approximately 15% quinidinone present (by comparison of  $^1\text{H}$  NMR integrations of H10 and H11 peaks of each compound) as a brown oil, and no further separation could be achieved. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR assignments were taken from the NMR spectra of the mixed fractions.  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.20-1.30 (1H, m), 1.41-1.50 (1H, br t,  $^3J_{\text{HH}}$  11.0 Hz), 1.55-1.68 (3H, m), 1.94 (1H, q,  $^3J_{\text{HH}}$  8.2 Hz, H3), 2.52-2.68 (2H, m), 2.74 (1H, td,  $^2J_{\text{HH}}$  12.9 Hz,  $^3J_{\text{HH}}$  9.0 Hz), 3.09 (1H, br t,  $^2J_{\text{HH}}$  11.5 Hz), 3.22 (3H, br s,  $\text{OCH}_3$ ), 3.86-3.98 (1H, m), 4.36 (1H, d,  $^3J_{\text{HH}(\text{trans})}$  17.6 Hz,  $\text{CH}=\text{CH}_2$ , H11), 4.57 (1H, d,  $^3J_{\text{HH}(\text{cis})}$  10.6 Hz,  $\text{CH}=\text{CH}_2$ , H11), 5.18 (1H, m,  $\text{CH}_2=\text{CH}$ , H10), 6.68 (1H, br s), 6.94 (2H, ddd,  $^3J_{\text{HH}}$  8.6

Hz,  $^3J_{\text{HH}}$  7.0 Hz,  $^4J_{\text{HH}}$  1.6 Hz), 7.11 (1H, t,  $^3J_{\text{HH}}$  7.0 Hz), 7.43 (1H, t,  $^3J_{\text{HH}}$  7.8 Hz), 7.58 (1H, d,  $^3J_{\text{HH}}$  8.2 Hz), 7.70 (1H, d,  $^3J_{\text{HH}}$  8.2 Hz), 7.74 (1H, br d,  $^3J_{\text{HH}}$  8.6 Hz, ArH8'), 8.00 (1H, br s), 8.10 (1H, d,  $^3J_{\text{HH}}$  8.6 Hz), 8.31 (1H, m), 8.66 (1H, m, ArH2').  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 22.14 (CH<sub>2</sub>, C7), 25.92 (CH<sub>2</sub>, C5), 28.66 (CH, C4), 39.88 (CH, C3), 49.92 (CH<sub>2</sub>, C2), 51.10 (CH<sub>2</sub>, C6), 55.36 (OCH<sub>3</sub>), 62.99 (CH, C8), 79.22 (C, C9), 103.55 (CH, C5'), 114.32 (CH<sub>2</sub>, C11), 120.40 (CH), 121.20 (CH), 121.33 (CH), 124.15 (CH), 125.25 (CH), 126.53 (C), 128.17, (CH, C3'), 128.98 (CH, C7'), 131.23 (CH), 132.18 (CH, C8'), 134.83 (C), 137.77 (C), 140.22 (CH, C10), 144.74 (C), 147.72 (CH, C2'), 149.42 (C), 156.91 (C, C6'). As the carbon spectrum also contains quinidinone it is difficult to pick out the quaternary carbon signals relating to the desired product.

### 5.2.11 9-(2-Naphthyl)quinidine (75)



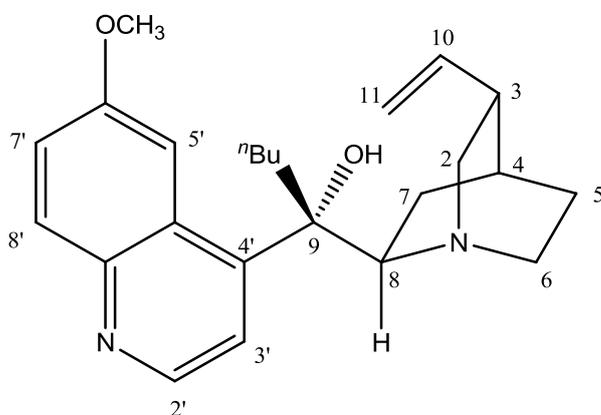
Under a nitrogen atmosphere *n*-butyllithium (1.6 M in hexanes, 7.8 mL, 12.5 mmol) in dry toluene (10 mL) was added dropwise over 12 minutes to a stirred solution of 2-bromonaphthalene (2.83 g, 13.7 mmol) in dry toluene (10 mL) at room temperature. The reaction mixture was then warmed to approximately 48 °C and stirred at this temperature for one hour. The mixture was then cooled to

-78 °C and quinidinone (1.00 g, 3.1 mmol) dissolved in dry toluene (40 mL) was added dropwise over 34 minutes. The reaction was stirred at -78 °C for 6 hours, then quenched with water (30 mL) and allowed to warm to room temperature overnight. The crude reaction mixture was transferred to a separating funnel, the organic layer was removed and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over sodium sulphate and the solvent was removed to give the crude product as a brown oil. The conversion of the reaction (9%) was considered too low to attempt purification.

### 5.2.12 9-Methylquinidine (68) (MeLi)

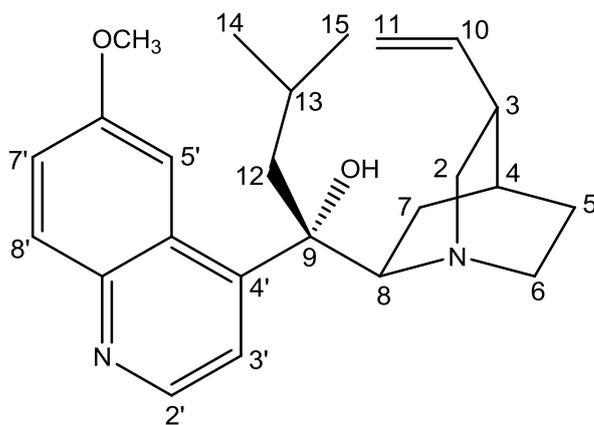
Under a nitrogen atmosphere quinidinone (1.99 g, 6.2 mmol) in dry toluene (40 mL) was added dropwise to a stirred solution of methyllithium (1.6 M in diethyl ether, 7.8 mL, 12.5 mmol) over a period of 44 minutes at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was then stirred for 6 hours at  $-78\text{ }^{\circ}\text{C}$  before being quenched with water (30 mL) and allowed to warm to room temperature overnight. The mixture was transferred to a separating funnel where the organic layer was removed. The aqueous layer was extracted with diethyl ether (3 x 15 mL), and the combined organic layers dried over sodium sulphate before the solvent was evaporated to give a yellow oil (1.01 g). Recrystallisation from ethanol/water was unsuccessful, as was trituration with hexane. The  $^1\text{H}$  NMR spectrum of the crude product showed that although some desired product was present (approximately 50% conversion), the reaction was not as selective as the reaction with methylmagnesium bromide, and at least one other product (most likely 9(*R*)-methylquinidine) was also present.

### 5.2.13 9-Butylquinidine (76)



Under a nitrogen atmosphere quinidinone (1.99 g, 6.2 mmol) dissolved in dry toluene (40 mL) was added dropwise over 25 minutes to a stirred solution of *n*-butyllithium (1.6 M in hexanes, 7.8 mL, 12.5 mmol) at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 6 hours and then quenched with water (30 mL), before

being warmed to room temperature overnight. The mixture was transferred to a separating funnel and the organic layer was removed. The aqueous layer was extracted with diethyl ether (3 x 15 mL). The organic layers were then combined and dried over anhydrous sodium sulphate before the solvent was removed by rotary evaporation. The product could not be completely separated from quinidinone by column chromatography using toluene/dichloromethane/diethyl ether/ triethylamine (38/30/30/2), and approximately 10% starting material remained in the purest fractions.

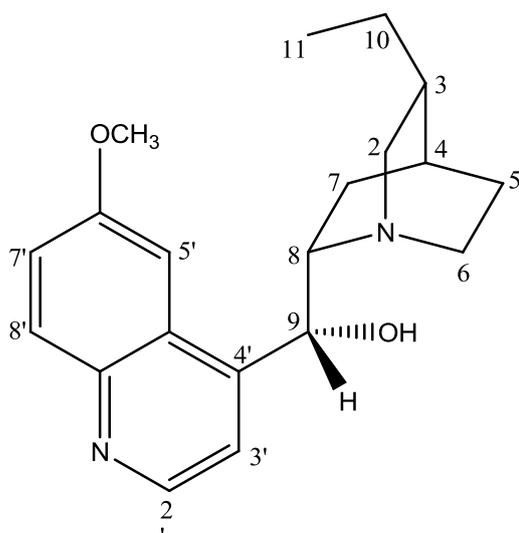
5.2.14 9-*Iso*-butylquinidine (77)

Under a nitrogen atmosphere 1-bromo-2-methylpropane (1.5 mL, 13.8 mmol) dissolved in dry diethyl ether (10 mL) was added dropwise over 20 minutes to a stirred suspension of oven dried magnesium turnings (0.30 g, 12.4 mmol) in dry diethyl ether (5 mL) at room temperature (23 °C). The reaction mixture was stirred at room

temperature for 2 hours to pre-form the Grignard reagent. A solution of quinidinone (1.00 g, 3.11 mmol) in dry toluene (35 mL) was then added dropwise over 17 minutes at room temperature. The reaction mixture was stirred at room temperature overnight (16 hours), before being quenched with water (30 mL). The organic layer was removed, and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic phases were dried over anhydrous sodium sulphate and the solvent was removed by rotary evaporation. The crude oil was dissolved in a minimum volume of ethanol, and water was added. Crystals of 9-*iso*-butylquinidine (co-crystallised with ethanol) were formed in this mixture after standing for several days (0.17 g, 15% yield). Mp 148-152 °C (lit<sup>2</sup> 146-147 °C).  $[\alpha]_D^{20}$  132.5° (*c* 1.01 in CHCl<sub>3</sub>). Found: C, 75.61; H, 8.58; N, 7.25. C<sub>24</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub> requires C, 75.75; H, 8.48; N, 7.36%.  $\delta_H$  (CDCl<sub>3</sub>) 0.61 (3H, d, <sup>3</sup>*J*<sub>HH</sub> 6.7 Hz, CH(CH<sub>3</sub>)<sub>2</sub>, H14 or H15), 0.72-0.80 (1H, m, (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>, H12), 0.77 (3H, d, <sup>3</sup>*J*<sub>HH</sub> 6.7 Hz, CH(CH<sub>3</sub>)<sub>2</sub>, H14 or H15), 1.17 (3H, t, <sup>3</sup>*J*<sub>HH</sub> 7.0 Hz, CH<sub>3</sub>CH<sub>2</sub>OH), 1.20-1.32 (1H, m, (CH<sub>3</sub>)<sub>2</sub>CH, H13), 1.39-1.44 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.51-1.55 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 1.58-1.65 (1H, m, (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>, H12), 1.97 (1H, dd, <sup>2</sup>*J*<sub>HH</sub> 15.3 Hz, <sup>3</sup>*J*<sub>HH</sub> 9.4 Hz, NCHCH<sub>2</sub>, H7), 2.03 (1H, m, CH<sub>2</sub>CH<sub>2</sub>CH, H3), 2.65 (1H, dd, <sup>2</sup>*J*<sub>HH</sub> 15.3 Hz, <sup>3</sup>*J*<sub>HH</sub> 3.9 Hz, NCHCH<sub>2</sub>, H7), 2.69-2.83 (2H, m, NCH<sub>2</sub> H2), 2.86-2.98 (2H, m, NCH<sub>2</sub> H6), 3.21 (1H, t, <sup>3</sup>*J*<sub>HH</sub> 9.4 Hz, NCH, H8), 3.65 (2H, q, <sup>3</sup>*J*<sub>HH</sub> 7.0 Hz, CH<sub>3</sub>CH<sub>2</sub>OH), 3.83 (3H, s, OCH<sub>3</sub>), 4.70 (1H, dt, <sup>3</sup>*J*<sub>HH(trans)</sub> 17.3 Hz, <sup>2</sup>*J*<sub>HH</sub> = <sup>4</sup>*J*<sub>HH</sub> 1.5 Hz, CH=CH<sub>2</sub>, H11), 4.77 (1H, dt, <sup>3</sup>*J*<sub>HH(cis)</sub> 10.5 Hz, <sup>2</sup>*J*<sub>HH</sub> = <sup>4</sup>*J*<sub>HH</sub> 1.2 Hz, CH=CH<sub>2</sub>, H11), 5.61 (1H, ddd, <sup>3</sup>*J*<sub>HH(trans)</sub> 17.3 Hz, <sup>3</sup>*J*<sub>HH(cis)</sub> 10.5 Hz, <sup>3</sup>*J*<sub>HH(vic)</sub> 7.3 Hz, CH=CH<sub>2</sub>, H10), 7.26-7.29 (2H, m, ArH8' and ArH5'), 7.85 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 4.7 Hz, ArH3'), 7.99 (1H, dd, <sup>3</sup>*J*<sub>HH</sub> 8.5 Hz, <sup>4</sup>*J*<sub>HH</sub> 1.2 Hz, ArH7'), 8.67 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 4.7 Hz, ArH2').  $\delta_C$  (CDCl<sub>3</sub>) 18.44 (CH<sub>3</sub>, CH<sub>3</sub>CH<sub>2</sub>OH), 22.14 (CH<sub>2</sub>, C12), 23.27 (CH, C13), 24.58 (CH<sub>3</sub>, C14 or C15), 24.78 (CH<sub>3</sub>, C14 or C15),

26.28 (CH<sub>2</sub>, C5), 28.73 (CH, C4), 39.87 (CH, C3), 49.70 (CH<sub>2</sub>, C7), 49.92 (CH<sub>2</sub>, C6), 51.22 (CH<sub>2</sub>, C2), 55.37 (CH<sub>3</sub>, OCH<sub>3</sub>), 58.22 (CH<sub>2</sub>, CH<sub>3</sub>CH<sub>2</sub>OH), 63.88 (CH, C8), 79.56 (C, C9), 103.99 (CH, C5'), 114.21 (CH<sub>2</sub>, C11), 120.57 (CH, C8'), 121.29 (CH, C3'), 126.84 (C), 132.23 (CH, C7'), 140.25 (CH, C10), 144.89 (C), 147.79 (CH, C2'), 149.34 (C), 156.84 (C, C6'). m/z (ES<sup>+</sup>) 381.2547 (MH<sup>+</sup>. C<sub>24</sub>H<sub>33</sub>N<sub>2</sub>O<sub>2</sub> requires 381.2542, 80%), 191.1277 (100).

### 5.2.15 10,11-Dihydroquinine (30)

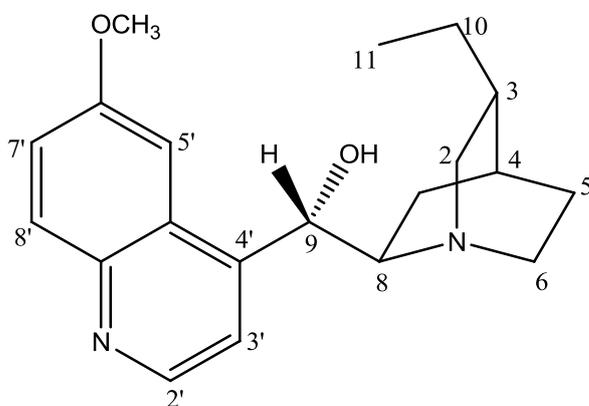


The procedure reported by Blaser to synthesise 10,11-dihydrocinchonidine from cinchonidine was adapted to synthesise 10,11-dihydroquinine from quinine.<sup>4</sup> Pd/C (5%, 0.52 g, 1.45 mol%) was added to a solution of quinine (5.50 g, 16.96 mmol) in 0.5 M sulphuric acid (36 mL). The mixture was shaken under pressure of hydrogen (approx 2.5 psi) for 2 hours. The clear solution was filtered from the catalyst and

neutralised with 2 M sodium hydroxide (20 mL). The white precipitate formed was collected and suspended twice in very cold ethanol, to give 10,11-dihydroquinine as a white solid (1.26 g, 23 % yield). Mp 168-171 °C (lit<sup>5</sup> 171-172 °C). [ $\alpha$ ]<sub>D</sub><sup>20</sup> -91.1° (*c* 1.07 in CHCl<sub>3</sub>).  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 0.73 (3H, t, <sup>3</sup>*J*<sub>HH</sub> 7.4 Hz, CH<sub>2</sub>CH<sub>3</sub>, H11), 1.07-1.16 (3H, m, CH<sub>2</sub>CH<sub>3</sub>, H10 and NCHCH<sub>2</sub>, H7), 1.42-1.52 (1H, m, NCH<sub>2</sub>CH<sub>2</sub> H5), 1.58-1.66 (1H, m, NCH<sub>2</sub>CH, H3), 1.86 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 1.90-1.99 (2H, m, NCHCH<sub>2</sub>, H7 and NCH<sub>2</sub>CH<sub>2</sub>, H5), 2.64 (1H, dm, <sup>2</sup>*J*<sub>HH</sub> 13.3 Hz, NCH<sub>2</sub>, H2), 3.05 (1H, td, <sup>2</sup>*J*<sub>HH</sub> 12.5 Hz, <sup>3</sup>*J*<sub>HH</sub> 5.1 Hz, NCH<sub>2</sub>, H6), 3.21 (1H, t, <sup>3</sup>*J*<sub>HH</sub> 9.0 Hz, NCH, H8), 3.38 (1H, dd, <sup>2</sup>*J*<sub>HH</sub> 13.3 Hz, <sup>3</sup>*J*<sub>HH</sub> 10.6 Hz, NCH<sub>2</sub>, H2), 3.92 (3H, s, OCH<sub>3</sub>), 4.35 (1H, br t, <sup>2</sup>*J*<sub>HH</sub> 12.5 Hz, NCH<sub>2</sub> H6), 6.36 (1H, s, CHOH, H9), 6.72 (1H, br s, OH), 7.13 (1H, dd, <sup>3</sup>*J*<sub>HH</sub> 9.0 Hz, <sup>4</sup>*J*<sub>HH</sub> 2.7 Hz, ArH7'), 7.23 (1H, d, <sup>4</sup>*J*<sub>HH</sub> 2.7 Hz, ArH5'), 7.54 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 4.7 Hz, ArH3'), 7.81 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 9.0 Hz, ArH8'), 8.62 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 4.7 Hz, ArH2').  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 11.48 (CH<sub>3</sub>, C11), 18.08 (CH<sub>2</sub>, C10), 24.58 (CH, C4), 25.06 (CH<sub>2</sub>, C5), 27.03 (CH<sub>2</sub>, C7), 35.71 (CH, C3), 43.72 (CH<sub>2</sub>, C6), 56.69 (CH<sub>2</sub>, C2), 56.85 (OCH<sub>3</sub>), 59.95 (CH, C8), 66.30 (CH, C9), 100.97 (CH, C5'), 118.62 (CH, C3'), 121.68 (CH, C7'), 125.59 (C), 131.36 (CH, C8'),

143.82 (C), 145.05 (C), 147.16 (CH, C2'), 158.16 (C, C6').  $m/z$  (ES<sup>+</sup>) 327.2071 (MH<sup>+</sup>). C<sub>20</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub> requires 327.2073, 80%), 164.1072 (100).

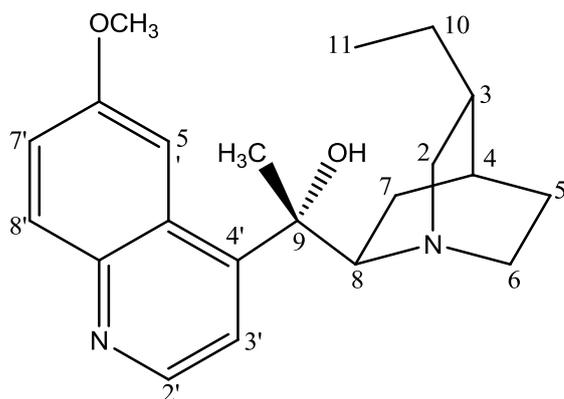
### 5.2.16 10,11-Dihydroquinidine (31)



The procedure reported by Blaser to synthesise 10,11-dihydrocinchonidine from cinchonidine was adapted to synthesise 10,11-dihydroquinidine from quinidine.<sup>4</sup> Pd/C (5%, 0.05 g, 1.5 mol%) was added to a solution of quinidine (0.50 g, 1.53 mmol) in 0.5 M sulphuric acid (5 mL). The mixture was

shaken under hydrogen (approx 2.5 psi) for 2 hours 15 minutes. The clear solution was filtered from the catalyst and neutralised with 2 M sodium hydroxide (approximately 6 mL). The white precipitate formed was collected and dried under vacuum at 50 °C to give 10,11-dihydroquinidine as a white solid (0.40 g, 80% yield). Mp 162-167 °C (lit<sup>6</sup> 165 °C).  $[\alpha]_D^{20}$  173.1° (*c* 0.99 in CHCl<sub>3</sub>).  $\delta_H$  (CDCl<sub>3</sub>) 0.86 (3H, t, <sup>3</sup>*J*<sub>HH</sub> 7.3 Hz, CH<sub>2</sub>CH<sub>3</sub>, H11), 1.10 (1H, ddd, <sup>2</sup>*J*<sub>HH</sub> 13.3 Hz, <sup>3</sup>*J*<sub>HH</sub> 9.3 Hz, <sup>3</sup>*J*<sub>HH</sub> 4.0 Hz, NCHCH<sub>2</sub>, H7), 1.33-1.42 (3H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5 and CH<sub>3</sub>CH<sub>2</sub>CH, H3), 1.43-1.50 (2H, m, CH<sub>3</sub>CH<sub>2</sub>, H10), 1.65-1.69 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 1.93 (1H, dd, <sup>2</sup>*J*<sub>HH</sub> 13.3 Hz, <sup>3</sup>*J*<sub>HH</sub> 9.2 Hz, NCHCH<sub>2</sub>, H7), 2.73 (1H, dd, <sup>2</sup>*J*<sub>HH</sub> 13.3 Hz, <sup>3</sup>*J*<sub>HH</sub> 9.2 Hz, NCH<sub>2</sub>, H2), 2.80-2.90 (2H, m, NCH<sub>2</sub>, H6), 3.00 (1H, td <sup>3</sup>*J*<sub>HH</sub> 9.3 Hz, <sup>3</sup>*J*<sub>HH</sub> 4.0 Hz, NCH, H8), 3.10 (1H, ddd, <sup>2</sup>*J*<sub>HH</sub> 13.3 Hz, <sup>3</sup>*J*<sub>HH</sub> 7.8 Hz, <sup>4</sup>*J*<sub>HH</sub> 1.6 Hz, NCH<sub>2</sub>, H2), 3.85 (3H, s, OCH<sub>3</sub>), 4.30 (1H, br s, OH), 5.60 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 4.0 Hz, CHOH, H9), 7.20 (1H, d, <sup>4</sup>*J*<sub>HH</sub> 2.7 Hz, ArH5'), 7.30 (1H, dd, <sup>3</sup>*J*<sub>HH</sub> 9.4 Hz, <sup>4</sup>*J*<sub>HH</sub> 2.7 Hz, ArH7'), 7.52 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 4.7 Hz, ArH3'), 7.96 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 9.4 Hz, ArH8'), 8.64 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 4.7 Hz, ArH2').  $\delta_C$  (CDCl<sub>3</sub>) 11.95 (CH<sub>3</sub>, C11), 20.69 (CH<sub>2</sub>, C10), 25.09 (CH<sub>2</sub>, C5), 26.26 (CH, C4), 27.04 (CH<sub>2</sub>, C7), 37.31 (CH, C3), 50.16 (CH<sub>2</sub>, C6), 51.12 (CH<sub>2</sub>, C2), 55.54 (OCH<sub>3</sub>), 59.82 (CH, C8), 71.56 (CH, C9), 101.34 (CH, C5'), 118.48 (CH, C3'), 121.37 (CH, C7'), 126.56 (C), 131.36 (CH, C8'), 144.02 (C), 147.43 (CH, C2'), 148.09 (C), 157.59 (C, C6').  $m/z$  (ES<sup>+</sup>) 327.2083 (MH<sup>+</sup>). C<sub>20</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub> requires 327.2073, 100%), 164.1057 (80%).

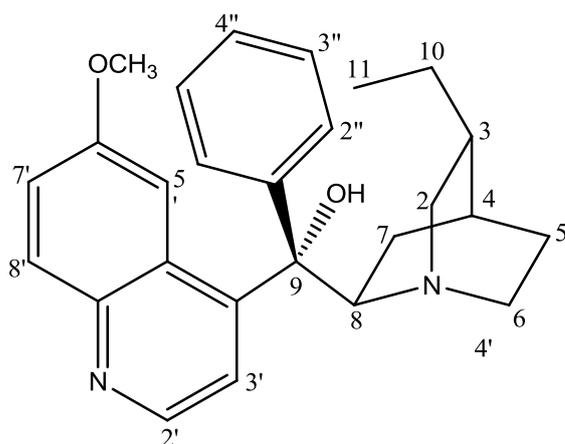
## 5.2.17 9-Methyl-10,11-dihydroquinidine (78)



The procedure reported by Blaser to synthesise 10,11-dihydrocinchonidine from cinchonidine was adapted to synthesise 9-methyl-10,11-dihydroquinidine from 9-methylquinidine.<sup>4</sup> Pd/C (5%, 0.04 g, 1.8 mol%) was added to a solution of 9-methylquinidine (0.40 g, 1.18 mmol) in

0.5 M sulphuric acid (5 mL). The mixture was shaken under pressure of hydrogen (approx 2.5 psi) for 2 hours. The clear solution was filtered from the catalyst and neutralised with 2 M sodium hydroxide (6 mL). The white precipitate formed was collected and dried under vacuum at 50 °C, to give 9-methyl-10,11-dihydroquinidine as a white solid (0.32 g, 79% yield). Mp 113-117 °C.  $[\alpha]_D^{20}$  122.1° (*c* 0.69 in CHCl<sub>3</sub>). Found: C, 65.32; H, 8.27; N, 7.61. C<sub>21</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>·2H<sub>2</sub>O requires C, 66.99; H, 8.57; N, 7.44%.  $\delta_H$  (CDCl<sub>3</sub>) 0.72 (3H, t,  $^3J_{HH}$  7.0 Hz, CH<sub>2</sub>CH<sub>3</sub>, H11), 0.96-1.04 (1H, m, NCHCH<sub>2</sub>, H7), 1.12 (2H, quintet of doublets,  $^3J_{HH}$  7.0 Hz,  $^4J_{HH}$  2.3 Hz, CH<sub>3</sub>CH<sub>2</sub>, H10), 1.30 (1H, q,  $^3J_{HH}$  8.2 Hz, CH<sub>3</sub>CH<sub>2</sub>CH, H3), 1.41-1.50 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.53 (1H, tm,  $^3J_{HH}$  9.8 Hz, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.58-1.61 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 1.70 (1H, t,  $^3J_{HH} = ^3J_{HH}$  10.7 Hz, NCHCH<sub>2</sub>, H7), 1.94 (3H, s, 9-CH<sub>3</sub>), 2.67-2.75 (1H, m, NCH<sub>2</sub>, H2), 2.77-2.88 (2H, m, NCH<sub>2</sub>, H2 and H6), 2.99 (1H, tm,  $^3J_{HH}$  10.2 Hz, NCH<sub>2</sub>, H6), 3.25 (1H, t,  $^3J_{HH}$  10.7 Hz, NCH, H8), 3.38 (1H, br s, OH), 3.92 (3H, s, OCH<sub>3</sub>), 7.35 (1H, dd,  $^3J_{HH}$  9.4 Hz,  $^4J_{HH}$  2.7 Hz, ArH7'), 7.68 (1H, d,  $^3J_{HH}$  4.7 Hz, ArH3'), 7.72 (1H, br s, ArH5'), 8.04 (1H, d,  $^3J_{HH}$  9.4 Hz, ArH8'), 8.71 (1H, d,  $^3J_{HH}$  4.7 Hz, ArH2').  $\delta_C$  (CDCl<sub>3</sub>) 11.85 (CH<sub>3</sub>, C11), 21.94 (CH<sub>2</sub>, C7), 24.81 (CH<sub>2</sub>, C10), 26.86 (CH, C4), 26.98 (CH<sub>2</sub>, C5), 29.70 (CH<sub>3</sub>, 9-CH<sub>3</sub>), 37.28 (CH, C3), 51.22 (CH<sub>2</sub>, C6), 51.62 (CH<sub>2</sub>, C2), 55.41 (CH<sub>3</sub>, OCH<sub>3</sub>), 63.73 (CH, C8), 77.17 (C, C9), 104.91 (CH, C5'), 119.94 (CH, C3'), 120.56 (CH, C7'), 127.01 (C), 132.13 (CH, C8'), 145.34 (C), 147.53 (CH, C2'), 150.69 (C), 156.73 (C, C6'). *m/z* (ESI) 341.2242 (MH<sup>+</sup>. C<sub>21</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub> requires 341.2229, 60%), 171.1129 (100). A single crystal suitable for X-ray crystallography was grown by slow evaporation of a solution of 9-methyl-10,11-dihydroquinidine in ethanol.

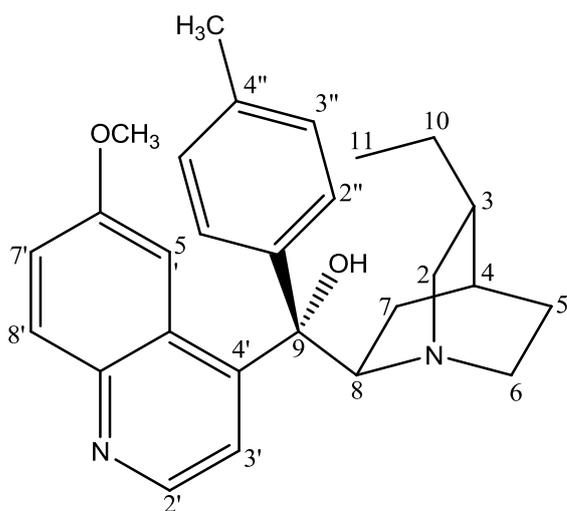
## 5.2.18 9-Phenyl-10,11-dihydroquinidine (79)



The procedure reported by Blaser to synthesise 10,11-dihydrocinchonidine from cinchonidine was adapted to synthesise 9-phenyl-10,11-dihydroquinidine from 9-phenylquinidine.<sup>4</sup> Pd/C (5%, 0.05 g, 3.0 mol%) was added to a solution of 9-phenylquinidine (0.29 g, 0.73 mmol) in 0.5 M sulphuric acid (5 mL). The mixture

was shaken under pressure of hydrogen (approx 2.5 psi) for 3 hours. The clear solution was filtered from the catalyst and neutralised with 2 M sodium hydroxide (7 mL). The white precipitate formed was collected and dried under vacuum at 50 °C, to give 9-phenyl-10,11-dihydroquinidine as a white solid (0.22 g, 75% yield). Mp 108-112 °C [ $\alpha$ ]<sub>D</sub><sup>20</sup> 213.0° (*c* 1.02 in CHCl<sub>3</sub>). Found: C, 77.64; H, 7.47; N, 7.02. C<sub>26</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub> requires C, 77.58; H, 7.51; N, 6.96%.  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 0.62 (3H, t, <sup>3</sup>J<sub>HH</sub> 7.0 Hz, CH<sub>2</sub>CH<sub>3</sub>, H11), 0.75-0.93 (2H, m, CH<sub>3</sub>CH<sub>2</sub>, H10), 1.24 (2H, m, NCH<sub>2</sub>CH, H3 and OH), 1.47-1.76 (5H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5, NCHCH<sub>2</sub>, H7, NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 2.29 (1H, m, NCH<sub>2</sub>, H2), 2.69 (1H, dd, <sup>2</sup>J<sub>HH</sub> 12.5 Hz, <sup>3</sup>J<sub>HH</sub> 9.8 Hz, NCH<sub>2</sub>, H2), 2.83 (1H, dt, <sup>2</sup>J<sub>HH</sub>, 13.1 Hz, <sup>3</sup>J<sub>HH</sub> 8.8 Hz, NCH<sub>2</sub>, H6), 3.18 (1H, ddt, <sup>2</sup>J<sub>HH</sub> 13.1 Hz, <sup>3</sup>J<sub>HH</sub> 9.8 Hz, <sup>3</sup>J<sub>HH</sub> 2.0 Hz, NCH<sub>2</sub>, H6), 3.44 (3H, s, OCH<sub>3</sub>), 3.93 (1H, t, <sup>3</sup>J<sub>HH</sub> 10.2 Hz, NCH, H8), 6.78 (1H, br s, ArH5'), 7.17 (1H, dd, <sup>3</sup>J<sub>HH</sub> 9.4 Hz, <sup>4</sup>J<sub>HH</sub> 2.7 Hz, ArH7'), 7.24-7.32 (3H, m, ArH3'' and ArH4''), 7.47 (2H, d, <sup>3</sup>J<sub>HH</sub> 7.0 Hz, ArH2''), 7.93 (1H, d, <sup>3</sup>J<sub>HH</sub> 9.4 Hz, ArH8'), 8.08 (1H, br s, ArH3') 8.81 (1H, d, <sup>3</sup>J<sub>HH</sub> 4.7 Hz, ArH2').  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 11.71 (CH<sub>3</sub>, C11), 23.66 (CH<sub>2</sub>, C7), 24.58 (CH<sub>2</sub>, C10), 26.99 (CH<sub>2</sub>, C5), 27.15 (CH, C4), 37.36 (CH, C3), 50.83 (CH<sub>2</sub>, C6), 51.46 (CH<sub>2</sub>, C2), 55.15 (OCH<sub>3</sub>), 61.42 (CH, C8), 79.13 (C, C9), 105.04 (CH, C5'), 120.59 (CH, C3'), 121.00 (CH, C7'), 127.02 (C), 127.13 (CH, C2''), 127.56 (CH, C4''), 128.52 (CH, C3''), 131.43 (CH, C8'), 145.17 (C), 145.73 (C), 147.40 (CH, C2'), 149.65 (C), 156.31 (C, C6'). *m/z* (ES<sup>+</sup>) 403.2402 (MH<sup>+</sup>. C<sub>26</sub>H<sub>31</sub>N<sub>2</sub>O<sub>2</sub> requires 403.2386, 85%), 202.1212 (100). A single crystal suitable for X-ray crystallography was grown by recrystallisation from ethanol.

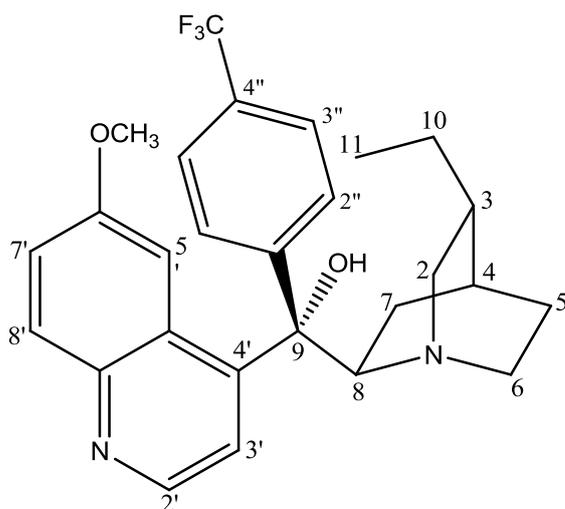
## 5.2.19 9-(4-Methylphenyl)-10,11-dihydroquinidine (80)



The procedure reported by Blaser to synthesise 10,11-dihydrocinchonidine from cinchonidine was adapted to synthesise 9-(4-methylphenyl)-10,11-dihydroquinidine from 9-(4-methylphenyl)quinidine.<sup>4</sup> Pd/C (5%, 0.03 g, 3.9 mol%) was added to a solution of 9-(4-methylphenyl)quinidine (0.15 g, 0.36 mmol) in 0.5 M sulphuric acid (5 mL). The mixture was shaken under

hydrogen (approx 2.5 psi) for 4 hours. The clear solution was filtered from the catalyst and neutralised with 2 M sodium hydroxide (~6 mL). The white precipitate formed was collected and dried under vacuum at 50 °C, to give 9-(4-methylphenyl)-10,11-dihydroquinidine as a white solid (0.11 g, 72% yield). Mp 110-114 °C.  $[\alpha]_D^{20}$  161.9° (*c* 1.06 in CHCl<sub>3</sub>). Found: C, 77.80; H, 7.78; N, 6.80. C<sub>27</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub> requires C, 77.85; H, 7.74; N, 6.73%.  $\delta_H$  (CDCl<sub>3</sub>) 0.65 (3H, t, <sup>3</sup>J<sub>HH</sub> 7.4 Hz, CH<sub>2</sub>CH<sub>3</sub>, H11), 0.79-0.98 (2H, m, CH<sub>2</sub>CH<sub>3</sub>, H10), 1.15-1.24 (1H, m, CH<sub>3</sub>CH<sub>2</sub>CH, H3), 1.28 (1H, t, <sup>3</sup>J<sub>HH</sub> 8.6 Hz, NCHCH<sub>2</sub>, H7), 1.55 (1H, t, <sup>3</sup>J<sub>HH</sub> 10.2 Hz, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.59-1.68 (2H, m, NCHCH<sub>2</sub>, H7 and NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 1.69-1.79 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5), 2.32 (3H, s, CH<sub>3</sub>), 2.34-2.48 (1H, m, NCH<sub>2</sub>, H2), 2.77 (1H, t, <sup>2</sup>J<sub>HH</sub> = <sup>3</sup>J<sub>HH</sub> 10.6 Hz, NCH<sub>2</sub>, H2), 2.83-2.92 (1H, m, NCH<sub>2</sub>, H6), 3.22 (1H, t, <sup>3</sup>J<sub>HH</sub> 10.2 Hz, NCH<sub>2</sub>, H6), 3.49 (3H, s, OCH<sub>3</sub>), 3.97 (1H, t, <sup>3</sup>J<sub>HH</sub> 8.6 Hz, NCH, H8), 6.81-6.90 (1H, br s, ArH5'), 7.12 (2H, d, <sup>3</sup>J<sub>HH</sub> 8.0 Hz, ArH3''), 7.19 (1H, dd, <sup>3</sup>J<sub>HH</sub> 9.4 Hz, <sup>4</sup>J<sub>HH</sub> 2.7 Hz, ArH7'), 7.37 (2H, d, <sup>3</sup>J<sub>HH</sub> 8.0 Hz, ArH2''), 7.96 (1H, d, <sup>3</sup>J<sub>HH</sub> 9.4 Hz, ArH8'), 8.07-8.13 (1H, br s, ArH3'), 8.83 (1H, d, <sup>3</sup>J<sub>HH</sub> 4.7 Hz, ArH2').  $\delta_C$  (CDCl<sub>3</sub>) 11.71 (CH<sub>3</sub>, C11), 21.01 (CH<sub>3</sub>), 23.69 (CH<sub>2</sub>, C7), 24.58 (CH<sub>2</sub>, C10), 26.96 (CH<sub>2</sub>, C5), 27.16 (CH, C4), 37.37 (CH, C3), 50.83 (CH<sub>2</sub>, C6), 51.49 (CH<sub>2</sub>, C2), 55.15 (OCH<sub>3</sub>), 61.34 (CH, C8), 77.21 (C, C9), 105.06 (CH, C5'), 120.57 (CH, C3'), 120.93 (CH, C7'), 126.99 (CH, C2''), 129.17 (CH, C3''), 131.44 (CH, C8'), 137.22 (C), 145.15 (C), 147.43 (CH, C2'), 149.73 (C), 156.24 (C, C6'). Unfortunately, some quaternary carbons were not detected. *m/z* (ES<sup>+</sup>) 417.2547 (MH<sup>+</sup>. C<sub>27</sub>H<sub>33</sub>N<sub>2</sub>O<sub>2</sub> requires 417.2542, 100%), 209.1287 (70).

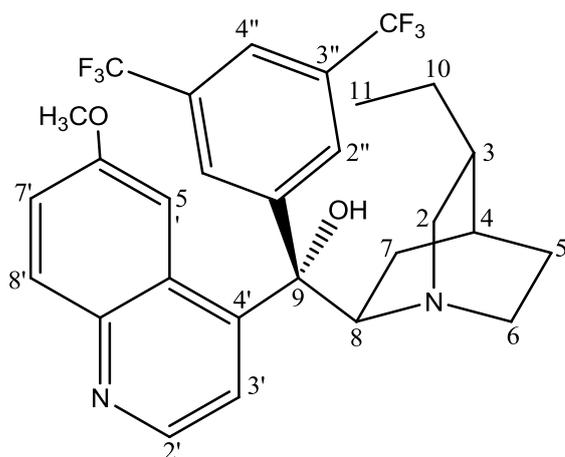
## 5.2.20 9-(4-Trifluoromethylphenyl)-10,11-dihydroquinidine (81)



The procedure reported by Blaser to synthesise 10,11-dihydrocinchonidine from cinchonidine was adapted to synthesise 9-(4-trifluoromethylphenyl)-10,11-dihydroquinidine from 9-(4-trifluoromethylphenyl)quinidine.<sup>4</sup> Pd/C (5%, 0.03 g, 3.5 mol%) was added to a solution of 9-(4-trifluoromethylphenyl)quinidine (0.19 g, 0.40 mmol) in 0.5 M sulphuric acid (6 mL). The mixture was

shaken under hydrogen (approx 2.5 psi) for 3 hours 45 minutes. The clear solution was filtered from the catalyst and neutralised with 2 M sodium hydroxide (~6 mL). The white precipitate formed was collected and dried under vacuum at 50 °C, to give 9-(4-trifluoromethylphenyl)-10,11-dihydroquinidine as a white solid (0.12 g, 64% yield). Mp 222-225 °C.  $[\alpha]_D^{20}$  135.9° (*c* 1.01 in CHCl<sub>3</sub>). Found: C, 68.86; H, 6.18; N, 6.02. C<sub>27</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub>F<sub>3</sub> requires C, 68.92; H, 6.21; N, 5.95%.  $\delta_H$  (CDCl<sub>3</sub>) 0.57 (3H, t,  $^3J_{HH}$  7.4 Hz, CH<sub>2</sub>CH<sub>3</sub>, H11), 0.75-0.92 (2H, m, CH<sub>2</sub>CH<sub>3</sub>, H10), 1.14-1.25 (1H, quintet,  $^3J_{HH}$  8.2 Hz, CH<sub>3</sub>CH<sub>2</sub>CH, H3), 1.43-1.50 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.53-1.58 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>, H7), 1.59-1.70 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5 and NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 2.20-2.33 (1H, m, NCH<sub>2</sub>, H2), 2.65 (1H, t,  $^2J_{HH} = ^3J_{HH}$  10.6 Hz, NCH<sub>2</sub>, H2), 2.72-2.81 (1H, m, NCH<sub>2</sub>, H6), 3.09 (1H, t,  $^3J_{HH}$  10.6 Hz, NCH<sub>2</sub>, H6), 3.38 (3H, s, OCH<sub>3</sub>), 3.84 (1H, t,  $^3J_{HH}$  9.8 Hz, NCH, H8), 6.59-6.70 (1H, br s, ArH5'), 7.12 (1H, dd,  $^3J_{HH}$  9.4 Hz,  $^4J_{HH}$  2.7 Hz, ArH7'), 7.48 (2H, d,  $^3J_{HH}$  8.6 Hz, ArH2''), 7.53 (2H, d,  $^3J_{HH}$  8.6 Hz, ArH3''), 7.88 (1H, d,  $^3J_{HH}$  9.4 Hz, ArH8'), 7.93-7.99 (1H, br s, ArH3'), 8.75 (1H, d,  $^3J_{HH}$  4.7 Hz, ArH2').  $\delta_F$  (CDCl<sub>3</sub>) -62.63 (3F, s, CF<sub>3</sub>).  $\delta_C$  (CDCl<sub>3</sub>) 11.67 (CH<sub>3</sub>, C11), 23.52 (CH<sub>2</sub>, C7), 24.65 (CH<sub>2</sub>, C10), 26.96 (CH<sub>2</sub>, C5), 27.09 (CH, C4), 37.25 (CH, C3), 50.85 (CH<sub>2</sub>, C6), 51.44 (CH<sub>2</sub>, C2), 55.11 (OCH<sub>3</sub>), 61.52 (CH, C8), 78.60 (C, C9), 104.73 (CH, C5'), 120.47 (CH, C3'), 121.14 (CH, C7'), 125.30 (CH, q,  $^3J_{CF}$  3.2 Hz, C3''), 126.65 (C), 127.58 (CH, C2''), 131.69 (CH, C8'), 134.87 (C), 145.22 (C), 147.38 (CH, C2'), 148.51 (C), 156.61 (C, C6'). Unfortunately, some quaternary carbons could not be detected. *m/z* (ES<sup>+</sup>) 471.2282 (MH<sup>+</sup>. C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>F<sub>3</sub> requires 471.2259, 60%), 236.1134 (100).

## 5.2.21 9-(3,5-Bis-trifluoromethylphenyl)-10,11-dihydroquinidine (82)



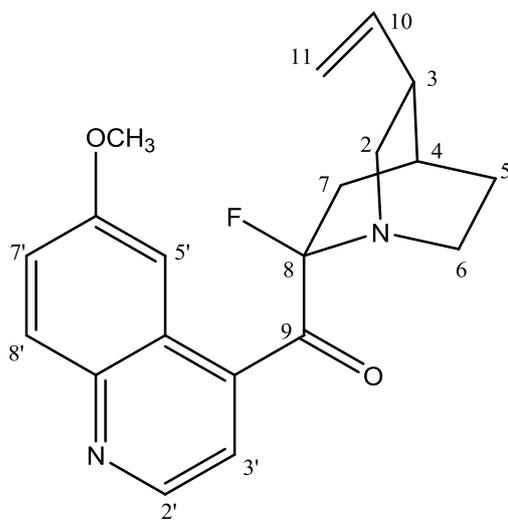
The procedure reported by Blaser to synthesise 10,11-dihydrocinchonidine from cinchonidine was adapted to synthesise 9-(3,5-bis-trifluoromethylphenyl)-10,11-dihydroquinidine from 9-(3,5-bis-trifluoromethylphenyl)quinidine.<sup>4</sup> Pd/C (5%, 0.03 g, 2.0 mol%) was added to a solution of 9-(3,5-bis-trifluoromethylphenyl)quinidine (0.37 g,

0.69 mmol) in 0.5 M sulphuric acid (5 mL). The mixture was shaken under hydrogen (approx 2.5 psi) for 4 hours 30 minutes. The clear solution was filtered from the catalyst and neutralised with 2 M sodium hydroxide (~6 mL). The white precipitate formed was collected and dried under vacuum at 50 °C, to give 9-(3,5-bis-trifluoromethylphenyl)-10,11-dihydroquinidine as a white solid (0.19 g, 51% yield). Mp 107-111°C.  $[\alpha]_D^{20}$  120.9° (*c* 0.98 in CHCl<sub>3</sub>). Found: C, 59.64; H, 5.14; N, 5.32. C<sub>28</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>F<sub>6</sub>·H<sub>2</sub>O requires C, 60.43; H, 5.43; N, 5.03%.  $\delta_H$  (CDCl<sub>3</sub>) 0.72 (3H, t,  $^3J_{HH}$  7.4 Hz, CH<sub>2</sub>CH<sub>3</sub>, H11), 0.97-1.13 (2H, m, CH<sub>2</sub>CH<sub>3</sub>, H10), 1.27-1.39 (1H, m, CH<sub>3</sub>CH<sub>2</sub>CH, H3), 1.51-1.62 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.60 (2H, br s, H<sub>2</sub>O), 1.63-1.79 (4H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5, NCH<sub>2</sub>CH<sub>2</sub>CH, H4, NCHCH<sub>2</sub>, H7), 2.41-2.52 (1H, m, NCH<sub>2</sub>, H2), 2.64-2.77 (1H, m, NCH<sub>2</sub>, H2), 2.78-2.88 (1H, m, NCH<sub>2</sub>, H6), 3.14 (1H, m, NCH<sub>2</sub>, H6), 3.53 (3H, s, OCH<sub>3</sub>), 3.87-3.97 (1H, m, H8), 4.14-4.43 (1H, br. s, OH), 6.74-6.87 (1H, br. s, ArH5'), 7.24 (1H, dd,  $^3J_{HH}$  9.0 Hz,  $^4J_{HH}$  2.7 Hz, ArH7'), 7.77 (1H, br. s, ArH3'), 7.94-7.96 (1H, br s, ArH8'), 7.97-8.03 (3H, s, ArH2'' and ArH4''), 8.85 (1H, d,  $^3J_{HH}$  4.7 Hz, ArH2').  $\delta_F$  (CDCl<sub>3</sub>) -62.80 (CF<sub>3</sub>).  $\delta_C$  (CDCl<sub>3</sub>) 11.70 (CH<sub>3</sub>, C11), 23.29 (CH<sub>2</sub>, C7), 24.74 (CH<sub>2</sub>, C10), 27.02 (CH<sub>2</sub>, C5), 28.66 (CH, C4), 37.22 (CH, C3), 50.84 (CH<sub>2</sub>, C6), 51.35 (CH<sub>2</sub>, C2), 54.98 (OCH<sub>3</sub>), 61.52 (CH, C8), 79.63 (C, C9), 103.80 (CH, C5'), 120.13 (CH, C3'), 121.14 (CH, q,  $^3J_{CF}$  3.2 Hz, C4''), 121.54 (CH, C7'), 125.93 (C, q,  $^1J_{CF}$  273.8 Hz, CF<sub>3</sub>), 126.20 (C), 127.40 (CH, q,  $^3J_{CF}$  3.2 Hz, C2''), 131.42 (C, d,  $^2J_{CF}$  33.6 Hz, C3''), 131.82 (CH, C8'), 139.72 (C), 145.35 (C), 147.25 (CH, C2'), 148.49 (C), 156.97 (C, C6'). *m/z* (ESI) 539.2150 (MH<sup>+</sup>. C<sub>28</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub>F<sub>6</sub> requires 539.2133, 80%), 270.1068 (100).

### 5.3 Experimental procedures for chapter three

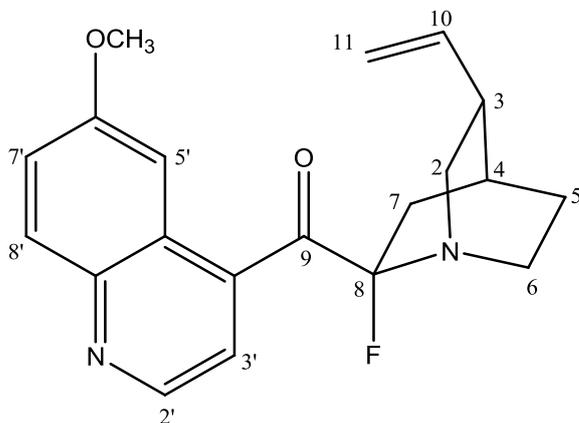
#### 5.3.1 8-Fluoroquinidinone (64) and 8-fluoroquininone (65)

Under an atmosphere of nitrogen, potassium *tert*-butoxide (6.2 mL, 1 M in THF, 6.2 mmol) was added to a stirred solution of quinidinone (2.00 g, 6.2 mmol) in dry THF (60 mL). NFSI (2.35 g, 7.5 mmol) was added in one portion and the mixture was stirred for 20 hours at room temperature. The solvent was removed by rotary evaporation, and the residue was extracted with chloroform (40 mL) and filtered. The solvent was removed from the filtrate by rotary evaporation to yield an orange oil. The crude oil was dissolved in a minimum volume of chloroform and purified by column chromatography on silica gel using chloroform/ethyl acetate (80/20), to give pure 8-fluoroquininone (first diastereoisomer off the column) and pure 8-fluoroquinidinone (second diastereoisomer off the column). Mixed fractions were dissolved in a minimum volume of acetonitrile and stored in the fridge to give crystals of pure 8-fluoroquinidinone suitable for X-ray crystallography.



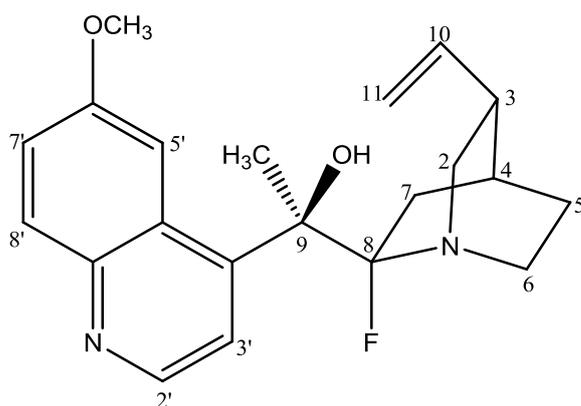
First diastereoisomer: 8-fluoroquininone is a yellow oil (0.56 g, 26 % yield).  $[\alpha]_D^{20}$  -99.4° (*c* 1.06 in  $\text{CHCl}_3$ ).  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.32-1.41 (1H, m,  $\text{NCH}_2\text{CH}_2$ , H5), 1.50-1.59 (1H, m,  $\text{NCH}_2\text{CH}_2$ , H5), 1.75 (1H, ddt,  $^3J_{\text{HF}}$  30.1 Hz,  $^2J_{\text{HH}}$  14.9 Hz,  $^3J_{\text{HH}} = ^4J_{\text{HH}}$  2.3 Hz,  $\text{NCFCH}_2$ , H7), 1.87-1.92 (1H, m,  $\text{NCFCH}_2$ , H7), 2.19 (1H, q,  $^3J_{\text{HH}}$  8.0 Hz,  $\text{CH}_2=\text{CHCH}$ , H3), 2.60-2.79 (3H, m,  $\text{NCH}_2$  6 and  $\text{CH}_2=\text{CHCHCH}$  H4), 2.93 (1H, ddd,  $^2J_{\text{HH}}$  14.3 Hz,  $^3J_{\text{HH}}$  10.2 Hz,  $^4J_{\text{HF}}$  6.7 Hz,  $\text{NCH}_2$ , H2), 3.14 (1H, ddd,  $^2J_{\text{HH}}$  14.3 Hz,  $^3J_{\text{HH}}$  7.0 Hz,  $^4J_{\text{HF}}$  2.3 Hz,  $\text{NCH}_2$ , H2), 3.85 (3H, s,  $\text{OCH}_3$ ), 5.02 (1H, dt,  $^3J_{\text{HH(cis)}}$  10.6 Hz,  $^2J_{\text{HH(gem)}} = ^4J_{\text{HH}}$  1.4 Hz,  $\text{CH}_2=\text{CH}$ , H11), 5.03 (1H, dt,  $^3J_{\text{HH(trans)}}$  17.2 Hz,  $^2J_{\text{HH(gem)}} = ^4J_{\text{HH}}$  1.4 Hz,  $\text{CH}_2=\text{CH}$ , H11), 5.87 (1H, ddd,  $^3J_{\text{HH(trans)}}$  17.2 Hz,  $^3J_{\text{HH(cis)}}$  10.6 Hz,  $^3J_{\text{HH(vic)}}$  8.0 Hz,  $\text{CH}_2=\text{CH}$ , H10), 7.31 (1H, dd,  $^3J_{\text{HH}}$  9.0 Hz,  $^4J_{\text{HH}}$  2.7 Hz, ArH7'), 7.65 (d,  $^4J_{\text{HH}}$  2.7 Hz, ArH5'), 7.96 (1H, d,  $^3J_{\text{HH}}$  9.0 Hz, ArH8'), 8.41 (1H, dd,  $^3J_{\text{HH}}$  4.6 Hz,  $^5J_{\text{HF}}$  1.4 Hz, ArH3'), 8.76 (1H, d,  $^3J_{\text{HH}}$  4.6 Hz, ArH2').  $\delta_{\text{F}}$  ( $\text{CDCl}_3$ ) -117.56 (s, CF).  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 23.69 ( $\text{CH}_2$ , C5), 26.70 ( $\text{CH}_2$ , d,  $^2J_{\text{CF}}$  27.2 Hz, C7), 27.43 (CH, C4), 37.96 (CH, C3), 41.94 ( $\text{CH}_2$ , d,  $^3J_{\text{CF}}$  6.4 Hz, C6),

45.68 (CH<sub>2</sub>, C2), 54.49 (OCH<sub>3</sub>), 101.92 (CH, C5'), 105.35 (C, d, <sup>1</sup>J<sub>CF</sub> 199.7 Hz, C8), 114.32 (CH<sub>2</sub>, C11), 121.12 (CH, C7'), 121.65 (CH, d, <sup>4</sup>J<sub>CF</sub> 4.8 Hz, C3'), 125.02 (C), 130.56 (CH, C8'), 136.02 (C), 138.86 (CH, C10), 144.47 (C), 145.92 (CH, C2'), 158.26 (C, C6'), 197.36 (C, d, <sup>2</sup>J<sub>CF</sub> 30.4 Hz, C=O). m/z (ES<sup>+</sup>) 341.1665 (MH<sup>+</sup>. C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>F requires 341.1665, 100%).



Second diastereoisomer: 8-fluoroquinidinone is a yellow solid (0.36 g, 17% yield). Mp 112-116 °C.  $[\alpha]_D^{20}$  306.1° (*c* 1.00 in CHCl<sub>3</sub>). Found: C, 70.67; H, 6.34; N, 8.16. C<sub>20</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub>F requires C, 70.57; H, 6.22; N, 8.23%.  $\delta_H$  (CDCl<sub>3</sub>) 1.43 (1H, ddd, <sup>2</sup>J<sub>HH</sub> 15.7 Hz, <sup>3</sup>J<sub>HH</sub> 3.5 Hz, <sup>4</sup>J<sub>HH</sub> 1.6 Hz, NCFCH<sub>2</sub>, H7),

1.50-1.57 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.60-1.68 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.93 (1H, br s, NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 2.19 (1H, q, <sup>3</sup>J<sub>HH</sub> 7.8 Hz, CH<sub>2</sub>=CHCH, H3), 2.41 (1H, ddd, <sup>2</sup>J<sub>HH</sub> 14.9 Hz, <sup>3</sup>J<sub>HH</sub> 7.0 Hz, <sup>4</sup>J<sub>HF</sub> 2.7 Hz, NCH<sub>2</sub>, H2), 2.62-2.72 (1H, m, NCH<sub>2</sub>, H6), 2.88-3.03 (2H, m, NCH<sub>2</sub>, H2 and NCFCH<sub>2</sub>, H7), 3.34 (1H, tdd, <sup>2</sup>J<sub>HH</sub> = <sup>4</sup>J<sub>HF</sub> 13.7 Hz, <sup>3</sup>J<sub>HH</sub> 10.6 Hz, <sup>3</sup>J<sub>HH</sub> 3.1 Hz, NCH<sub>2</sub>, H6), 3.84 (3H, s, OCH<sub>3</sub>), 4.99 (1H, dt, <sup>3</sup>J<sub>HH(trans)</sub> 17.2 Hz, <sup>2</sup>J<sub>HH(gem)</sub> = <sup>4</sup>J<sub>HH</sub> 1.6 Hz, CH<sub>2</sub>=CH, H11), 5.00 (1H, dt, <sup>3</sup>J<sub>HH(cis)</sub> 10.2 Hz, <sup>2</sup>J<sub>HH(gem)</sub> = <sup>4</sup>J<sub>HH</sub> 1.6 Hz, CH<sub>2</sub>=CH, H11), 5.91 (1H, ddd, <sup>3</sup>J<sub>HH(trans)</sub> 17.2 Hz, <sup>3</sup>J<sub>HH(cis)</sub> 10.2 Hz, <sup>3</sup>J<sub>HH(vic)</sub> 7.8 Hz, CH<sub>2</sub>=CH, H10), 7.30 (1H, dd, <sup>3</sup>J<sub>HH</sub> 9.4 Hz, <sup>4</sup>J<sub>HH</sub> 2.7 Hz, ArH7'), 7.51 (1H, d, <sup>4</sup>J<sub>HH</sub> 2.7 Hz, ArH5'), 7.95 (1H, <sup>3</sup>J<sub>HH</sub> 9.4 Hz, ArH8'), 8.19 (1H, dd, <sup>3</sup>J<sub>HH</sub> 4.3 Hz, <sup>5</sup>J<sub>HF</sub> 1.6 Hz, ArH3'), 8.75 (1H, d, <sup>3</sup>J<sub>HH</sub> 4.3 Hz, ArH2').  $\delta_F$  (CDCl<sub>3</sub>) -119.92 (s, CF).  $\delta_C$  (CDCl<sub>3</sub>) 25.90 (CH<sub>2</sub>, C5), 27.93 (CH<sub>2</sub>, d, <sup>2</sup>J<sub>CF</sub> 27.2 Hz, C7), 28.61 (CH, C4), 38.47 (CH, C3), 40.78 (CH<sub>2</sub>, d, <sup>3</sup>J<sub>CF</sub> 4.8 Hz, C6), 48.59 (CH<sub>2</sub>, d, <sup>3</sup>J<sub>CF</sub> 6.4 Hz, C2), 55.51 (OCH<sub>3</sub>), 102.85 (CH, C5'), 106.06 (C, d, <sup>1</sup>J<sub>CF</sub> 199.7 Hz, C8), 115.38 (CH<sub>2</sub>, C11), 122.20 (CH, C3'), 122.28 (CH, C7'), 126.10 (C), 131.53 (CH, C8'), 138.01 (C), 140.11 (CH, C10), 145.39 (C), 146.78 (CH, C2'), 159.10 (C, C6'), 198.19 (C, d, <sup>2</sup>J<sub>CF</sub> 30.4 Hz, C=O). m/z (ES<sup>+</sup>) 341.1663 (MH<sup>+</sup>. C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>F requires 341.1665, 100%).

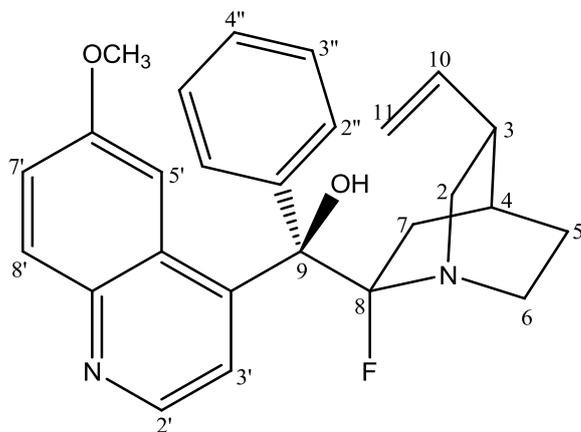
5.3.2 9-Methyl-8-fluoro-*epi*-quinidine (86)

Under an argon atmosphere, 8-fluoroquinidinone (0.47 g, 1.4 mmol) in dry THF (30 mL) was added dropwise over 35 minutes to a stirred solution of methyllithium (1.7 mL, 1.6 M in Et<sub>2</sub>O, 2.7 mmol) in dry diethyl ether (20 mL) at -78 °C. The mixture was stirred at -78 °C for three hours before being

quenched with water (30 mL) and allowed to warm to room temperature. The organic layer was removed and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over anhydrous sodium sulphate, and the solvent was removed to give the crude product. The yellow oil was dissolved in a minimum volume of chloroform and purified by column chromatography using chloroform/ethyl acetate (80/20) to elute residual starting material, then pure ethyl acetate to elute the product, to give 9-methyl-8-fluoro-*epi*-quinidine as a white solid (0.31 g, 63% yield). Mp 183-186 °C.  $[\alpha]_D^{20}$  150.6° (*c* 0.97 in CHCl<sub>3</sub>). Found: C, 70.83; H, 7.17; N, 7.77. C<sub>21</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub>F requires C, 70.76; H, 7.07; N, 7.86%.  $\delta_H$  (CDCl<sub>3</sub>, 298K) 1.41 (1H, t, <sup>3</sup>J<sub>HH</sub> 11.0 Hz, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.52-1.66 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5 and NCFCH<sub>2</sub>, H7), 1.85 (3H, d, <sup>4</sup>J<sub>HF</sub> 2.0 Hz, CH<sub>3</sub>), 1.88 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 2.12 (1H, q, <sup>3</sup>J<sub>HH</sub> 7.6 Hz, NCH<sub>2</sub>CH, H3), 2.37-2.44 (1H, m, NCH<sub>2</sub>, H6), 2.49 (1H, d, <sup>2</sup>J<sub>HH</sub> 14.9 Hz, NCFCH<sub>2</sub>, H7), 2.80 (1H, ddd, <sup>2</sup>J<sub>HH</sub> 13.9 Hz, <sup>3</sup>J<sub>HH</sub> 9.8 Hz, <sup>4</sup>J<sub>HF</sub> 5.5 Hz, NCH<sub>2</sub>, H2), 2.94 (1H, dd, <sup>2</sup>J<sub>HH</sub> 13.9 Hz, <sup>3</sup>J<sub>HH</sub> 7.6 Hz, NCH<sub>2</sub>, H2), 3.11 (1H, tm, <sup>2</sup>J<sub>HH</sub> = <sup>4</sup>J<sub>HF</sub> 11.5 Hz, NCH<sub>2</sub>, H6), 3.60 (1H, br s, OH), 3.83 (3H, s, OCH<sub>3</sub>), 4.84 (1H, dt, <sup>3</sup>J<sub>HH(trans)</sub> 17.2 Hz, <sup>2</sup>J<sub>HH(gem)</sub> = <sup>4</sup>J<sub>HH</sub> 1.4 Hz, CH<sub>2</sub>=CH, H11), 4.91 (1H, dt, <sup>3</sup>J<sub>HH(cis)</sub> 10.2 Hz, <sup>2</sup>J<sub>HH(gem)</sub> = <sup>4</sup>J<sub>HH</sub> 1.4 Hz, CH<sub>2</sub>=CH, H11), 5.70 (1H, ddd, <sup>3</sup>J<sub>HH(trans)</sub> 17.2 Hz, <sup>3</sup>J<sub>HH(cis)</sub> 10.2 Hz, <sup>3</sup>J<sub>HH(vic)</sub> 7.6 Hz, CH=CH<sub>2</sub>, H10), 7.24 (1H, dd, <sup>3</sup>J<sub>HH</sub> 9.4 Hz, <sup>4</sup>J<sub>HH</sub> 2.7 Hz, ArH7'), 7.49 (1H, br s, ArH3'), 7.91 (1H, d, <sup>3</sup>J<sub>HH</sub> 9.4 Hz, ArH8'), 8.22 (1H, br s, ArH5'), 8.56 (1H, d, <sup>3</sup>J<sub>HH</sub> 4.7 Hz, ArH2').  $\delta_H$  (CDCl<sub>3</sub>, 323K) 1.38 (1H, tm, <sup>3</sup>J<sub>HH</sub> 11.5 Hz, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.51-1.66 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5 and NCFCH<sub>2</sub>, H7), 1.82 (3H, d, <sup>4</sup>J<sub>HF</sub> 2.5 Hz, 9-CH<sub>3</sub>), 1.84-1.88 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 2.08 (1H, q, <sup>3</sup>J<sub>HH</sub> 7.6 Hz, NCH<sub>2</sub>CH, H3), 2.30-2.40 (1H, m, NCH<sub>2</sub>, H6), 2.47 (1H, ddt, <sup>3</sup>J<sub>HF</sub> 34.5 Hz, <sup>2</sup>J<sub>HH</sub> 14.9 Hz, <sup>3</sup>J<sub>HH</sub> 1.7 Hz, NCFCH<sub>2</sub>, H7), 2.74 (1H, ddd, <sup>2</sup>J<sub>HH</sub> 14.3 Hz, <sup>3</sup>J<sub>HH</sub> 9.8 Hz, <sup>4</sup>J<sub>HF</sub> 5.3 Hz, NCH<sub>2</sub>, H2), 2.96 (1H, ddm, <sup>2</sup>J<sub>HH</sub> 14.3 Hz, <sup>3</sup>J<sub>HH</sub> 7.3 Hz, NCH<sub>2</sub>, H2), 3.08 (1H, tm, <sup>2</sup>J<sub>HH</sub> = <sup>4</sup>J<sub>HF</sub> 12.1 Hz,

NCH<sub>2</sub>, H6), 3.79 (3H, s, OCH<sub>3</sub>), 4.82 (1H, dt, <sup>3</sup>J<sub>HH</sub> 17.1 Hz, <sup>2</sup>J<sub>HH</sub> = <sup>4</sup>J<sub>HH</sub> 1.4 Hz, CH=CH<sub>2</sub>, H11), 4.88 (1H, dt, <sup>3</sup>J<sub>HH</sub> 10.4 Hz, <sup>2</sup>J<sub>HH</sub> = <sup>4</sup>J<sub>HH</sub> 1.4 Hz, CH=CH<sub>2</sub>, H11), 5.69 (1H, ddd, <sup>3</sup>J<sub>HH</sub> 17.1 Hz, <sup>3</sup>J<sub>HH</sub> 10.4 Hz, <sup>3</sup>J<sub>HH</sub> 7.6 Hz, CH=CH<sub>2</sub>, H10), 7.20 (1H, dd, <sup>3</sup>J<sub>HH</sub> 9.3 Hz, <sup>4</sup>J<sub>HH</sub> 2.8 Hz, ArH7'), 7.48 (1H, br d, <sup>3</sup>J<sub>HH</sub> 5.0 Hz, ArH3'), 7.88 (1H, d, <sup>3</sup>J<sub>HH</sub> 9.3 Hz, ArH8'), 8.22 (1H, br s, ArH5'), 8.49 (1H, d, <sup>3</sup>J<sub>HH</sub> 5.0 Hz, ArH2'). δ<sub>F</sub> (CDCl<sub>3</sub>) -121.25 (br s, CF). δ<sub>C</sub> (CDCl<sub>3</sub>) 25.80 (CH<sub>2</sub>, C5), 28.52 (CH<sub>3</sub>), 29.11 (CH<sub>2</sub>, d, <sup>2</sup>J<sub>CF</sub> 36.7 Hz, C7), 29.39 (CH, C4), 38.14 (CH, C3), 44.40 (CH<sub>2</sub>, d, <sup>3</sup>J<sub>CF</sub> 12.8 Hz, C6), 49.72 (CH<sub>2</sub>, d, <sup>3</sup>J<sub>CF</sub> 4.8 Hz, C2), 55.39 (OCH<sub>3</sub>), 81.21 (C, C9), 106.76 (CH, d, <sup>5</sup>J<sub>CF</sub> 4.8 Hz, C5'), 109.03 (C, d, <sup>1</sup>J<sub>CF</sub> 199.7 Hz, C8), 114.82 (CH<sub>2</sub>, C11), 120.88 (CH, C7'), 121.20 (CH, C3'), 128.57 (C), 131.28 (CH, C8'), 140.19 (CH, C10), 145.52 (C), 146.79 (CH, C2'), 149.00 (C), 156.69 (C, C6'). m/z (ES<sup>+</sup>) 357.1980 (MH<sup>+</sup>). C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>F requires 357.1978, 100%. Crystals suitable for X-ray crystallography were grown by slow evaporation from acetonitrile.

### 5.3.3 9-Phenyl-8-fluoro-*epi*-quinidine (87)

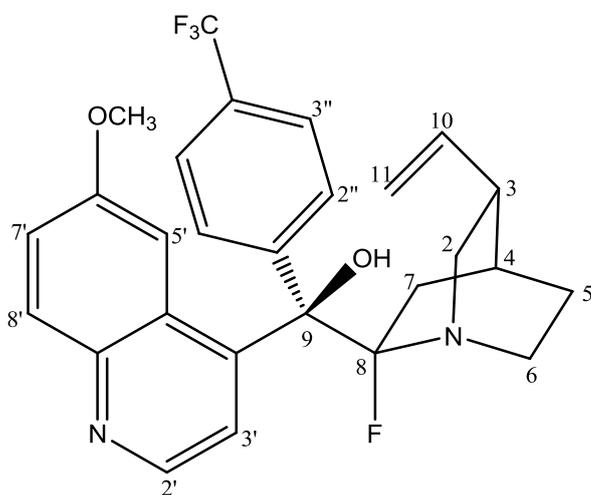


Under a nitrogen atmosphere, a solution of 8-fluoroquinidinone (0.27 g, 0.8 mmol) in dry THF (30 mL) was added dropwise over a period of 10 minutes to a stirred solution of phenyllithium (1.75 mL, 1.8 M in <sup>n</sup>Bu<sub>2</sub>O, 3.2 mmol) in dry diethyl ether (20 mL) at -78 °C. The mixture was stirred at -78 °C for 8 hours before being quenched with water

(30 mL) and allowed to warm to room temperature. The organic layer was removed and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over sodium sulphate, and the solvent was removed to give the crude product. The yellow oil was dissolved in a minimum volume of chloroform and purified by column chromatography using chloroform/ethyl acetate (80/20) to elute residual starting material, then pure ethyl acetate to elute the product, giving 9-phenyl-8-fluoro-*epi*-quinidine as a white solid (0.23 g, 71% yield). Mp 198-203 °C. [α]<sub>D</sub><sup>20</sup> 112.4° (c 1.00 in CHCl<sub>3</sub>). Found: C, 74.79; H, 6.40; N, 6.57. C<sub>26</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub>F requires C, 74.62; H, 6.50; N, 6.69%. δ<sub>H</sub> (CDCl<sub>3</sub>) 1.57 (1H, tm, <sup>3</sup>J<sub>HH</sub> 11.0 Hz, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.71 (1H, ddd, <sup>3</sup>J<sub>HF</sub> 27.0 Hz, <sup>2</sup>J<sub>HH</sub> 14.9 Hz, <sup>3</sup>J<sub>HH</sub> 3.9 Hz, NCFCH<sub>2</sub>, H7), 1.80-1.90 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5),

1.90-1.94 (1H, m, CH<sub>2</sub>=CHCHCH, H4), 2.14 (1H, m, CH<sub>2</sub>=CHCH, H3), 2.54-2.70 (2H, m, NCH<sub>2</sub>, H6 and NCFCH<sub>2</sub>, H7), 2.74-2.88 (2H, m, NCH<sub>2</sub>, H2), 3.49 (1H, tm, <sup>3</sup>J<sub>HH</sub> 10.6 Hz, NCH<sub>2</sub>, H6), 3.59 (3H, s, OCH<sub>3</sub>), 4.67 (1H, dm, <sup>3</sup>J<sub>HH(trans)</sub> 17.2 Hz, CH<sub>2</sub>=CH, H11), 4.83 (1H, dm, <sup>3</sup>J<sub>HH(cis)</sub> 10.2 Hz, CH<sub>2</sub>=CH, H11), 5.17 (1H, br s, OH), 5.40 (1H, ddd, <sup>3</sup>J<sub>HH(trans)</sub> 17.2 Hz, <sup>3</sup>J<sub>HH(cis)</sub> 10.2 Hz, <sup>3</sup>J<sub>HH(vic)</sub> 7.0 Hz, CH<sub>2</sub>=CH, H10), 7.13 (1H, dd, <sup>3</sup>J<sub>HH</sub> 9.0 Hz, <sup>4</sup>J<sub>HH</sub> 2.7 Hz, ArH7'), 7.18-7.27 (3H, m, ArH3'' and ArH4''), 7.48 (1H, d, <sup>4</sup>J<sub>HH</sub> 2.7 Hz, ArH5'), 7.56 (2H, d, <sup>3</sup>J<sub>HH</sub> 7.4 Hz, ArH2''), 7.88 (1H, d, <sup>3</sup>J<sub>HH</sub> 9.0 Hz, ArH8'), 8.02 (1H, dd, <sup>3</sup>J<sub>HH</sub> 4.7 Hz, <sup>5</sup>J<sub>HF</sub> 3.1 Hz, ArH3'), 8.75 (1H, d, <sup>3</sup>J<sub>HH</sub> 4.7 Hz, ArH2'). δ<sub>F</sub> (CDCl<sub>3</sub>) -123.62 (s, CF). δ<sub>C</sub> (CDCl<sub>3</sub>) 25.91 (CH<sub>2</sub>, C5), 29.61 (CH, C4), 30.69 (CH<sub>2</sub>, d, <sup>2</sup>J<sub>CF</sub> 22.6 Hz, C7), 38.25 (CH, C3), 44.50 (CH<sub>2</sub>, d, <sup>3</sup>J<sub>CF</sub> 13.8 Hz, C6), 49.98 (CH<sub>2</sub>, d, <sup>3</sup>J<sub>CF</sub> 2.9 Hz, C2), 55.23 (OCH<sub>3</sub>), 82.53 (C, d, <sup>2</sup>J<sub>CF</sub> 26.4 Hz, C9), 105.68 (CH, C5'), 108.98 (C, d, <sup>1</sup>J<sub>CF</sub> 203.8 Hz, C8), 114.91 (CH<sub>2</sub>, C11), 120.78 (C, C1''), 120.84 (CH, C3'), 121.06 (CH, C7'), 127.48 (CH, C4''), 127.63 (CH, C3''), 128.17 (CH, C2''), 131.41 (CH, C8'), 139.64 (CH, C10), 143.18 (C), 145.94 (C), 146.12 (C), 146.54 (CH, C2'), 156.60 (C, C6'). m/z (ES<sup>+</sup>) 419.2138 (MH<sup>+</sup>. C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>F requires 419.2135, 100%).

### 5.3.4 9-(4-Trifluoromethylphenyl)-8-fluoro-*epi*-quinidine (88)



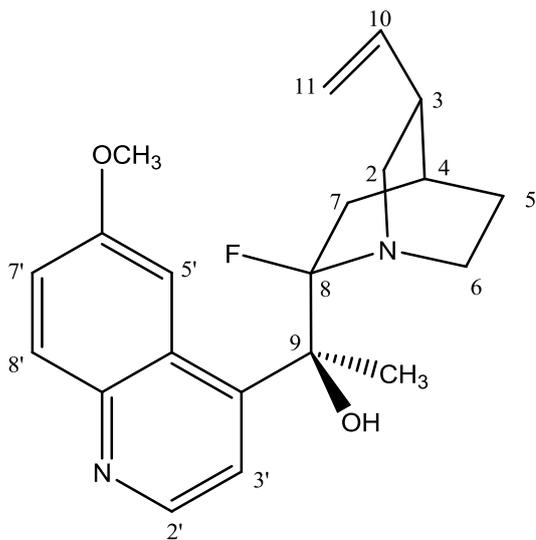
Under a nitrogen atmosphere, *n*-butyllithium (3.00 mL, 1.6 M in hexanes, 4.8 mmol) in dry diethyl ether (10 mL) was added dropwise over a period of 20 minutes to a stirred solution of 4-bromobenzotrifluoride (0.70 mL, 5.0 mmol) in dry diethyl ether (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for one hour and then cooled to -78 °C. A

solution of 8-fluoroquinidinone (0.26 g, 0.8 mmol) in dry THF (30 mL) was then added dropwise over a period of 10 minutes at -78 °C. The reaction mixture was stirred at -78 °C for 6 hours and then quenched with water (30 mL), before warming to room temperature overnight. After removing the organic layer, the aqueous layer was extracted with diethyl ether (3 x 15 mL). The organic layers were then combined and dried over anhydrous sodium sulphate before the solvent was removed by rotary

evaporation. The crude oil (1.32 g) was purified using column chromatography on silica gel, initially using the solvent system chloroform/ethyl acetate (80/20) to elute residual starting materials, then 100% ethyl acetate to elute the product, giving 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinidine as a white solid (0.23 g, 63% yield). Mp 277-279 °C.  $[\alpha]_D^{20}$  147.3° (*c* 0.76 in CHCl<sub>3</sub>). Found: C, 66.52; H, 5.35; N, 5.67. C<sub>27</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>F<sub>4</sub> requires C, 66.66; H, 5.39; N, 5.76%.  $\delta_H$  (CDCl<sub>3</sub>) 1.42 (1H, ddd,  $^3J_{HF}$  27.4 Hz,  $^2J_{HH}$  14.9 Hz,  $^3J_{HH}$  4.3 Hz, NCFCH<sub>2</sub>, H7), 1.50-1.56 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.75 (1H, qm,  $^3J_{HH}$  10.2 Hz, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.84-1.88 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 2.12 (1H, q,  $^3J_{HH}$  7.8 Hz, CH<sub>2</sub>=CHCH, H3), 2.44 (1H, ddt,  $^3J_{HF}$  36.8 Hz,  $^2J_{HH}$  14.9 Hz,  $^3J_{HH} = ^4J_{HH}$  1.6 Hz, NCFCH<sub>2</sub>, H7), 2.61 (1H, ddd,  $^2J_{HH}$  15.3 Hz,  $^3J_{HH}$  12.9 Hz,  $^4J_{HF}$  9.0 Hz, NCH<sub>2</sub>, H6), 2.78-2.86 (2H, m, NCH<sub>2</sub>, H2), 3.44 (1H, d,  $^2J_{HH}$  15.3 Hz, NCH<sub>2</sub>, H6), 3.49 (3H, s, OCH<sub>3</sub>), 4.63 (1H, d,  $^3J_{HH(\text{trans})}$  17.2 Hz, CH<sub>2</sub>=CH, H11), 4.70 (1H, br s, OH), 4.82 (1H, dt,  $^3J_{HH(\text{cis})}$  10.6 Hz,  $^2J_{HH(\text{vic})} = ^4J_{HH}$  1.2 Hz, CH<sub>2</sub>=CH, H11), 5.49 (1H, ddd,  $^3J_{HH(\text{trans})}$  17.2 Hz,  $^3J_{HH(\text{cis})}$  10.6 Hz,  $^3J_{HH(\text{vic})}$  7.8 Hz, CH<sub>2</sub>=CH, H10), 7.08 (1H, dd,  $^3J_{HH}$  9.0 Hz,  $^4J_{HH}$  2.7 Hz, ArH7'), 7.23 (1H, d,  $^4J_{HH}$  2.7 Hz, ArH5'), 7.45 (2H, d,  $^3J_{HH}$  8.0 Hz, ArH2''), 7.62 (2H, d,  $^3J_{HH}$  8.0 Hz, ArH3''), 7.83 (1H, d,  $^3J_{HH}$  9.0 Hz, ArH8'), 8.05 (1H, dd,  $^3J_{HH}$  4.7 Hz,  $^5J_{HF}$  2.7 Hz, ArH3'), 8.70 (1H, d,  $^3J_{HH}$  4.7 Hz, ArH2').  $\delta_F$  (CDCl<sub>3</sub>) -123.39 (1F, s, CF), -62.59 (3F, s, CF<sub>3</sub>).  $\delta_C$  (CDCl<sub>3</sub>) 25.74 (CH<sub>2</sub>, C5), 29.27 (CH, C4), 30.46 (CH<sub>2</sub>, d,  $^2J_{CF}$  22.6 Hz, C7), 38.02 (CH, C3), 44.60 (CH<sub>2</sub>, d,  $^3J_{CF}$  12.6 Hz, C6), 50.07 (CH<sub>2</sub>, C2), 55.21 (OCH<sub>3</sub>), 82.31 (C, d,  $^2J_{CF}$  26.4 Hz, C9), 105.10 (CH, C5'), 108.93 (C, d,  $^1J_{CF}$  208.0 Hz, C8), 114.99 (CH<sub>2</sub>, C11), 121.21 (CH, C7'), 121.48 (CH, C3'), 124.50 (CH, q,  $^3J_{CF}$  3.7 Hz, C3''), 127.14 (C, C1''), 128.58 (CH, C2''), 129.54 (C, q,  $^2J_{CF}$  31.1 Hz, C4''), 131.71 (CH, C8'), 139.48 (CH, C10), 144.78 (C), 146.02 (C), 146.61 (CH, C2'), 147.11 (C), 156.90 (C, C6'). Unfortunately, the CF<sub>3</sub> quaternary quartet could not be detected. *m/z* (ES<sup>+</sup>) 487.2018 (MH<sup>+</sup>. C<sub>27</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub>F<sub>4</sub> requires 487.2009, 100%).

### 5.3.5 9-Methyl-8-fluoro-*epi*-quinine (89)

Under an argon atmosphere, a solution of 8-fluoroquininone (0.52 g, 1.5 mmol) in dry THF (30 mL) was added dropwise over 25 minutes to a stirred solution of methyllithium (1.9 mL, 1.6 M in Et<sub>2</sub>O, 3.0 mmol) in dry diethyl ether (20 mL) at -78 °C. The mixture was stirred at -78 °C for 3 hours before being quenched with water (30 mL) and allowed to warm to room temperature. The organic layer was removed and

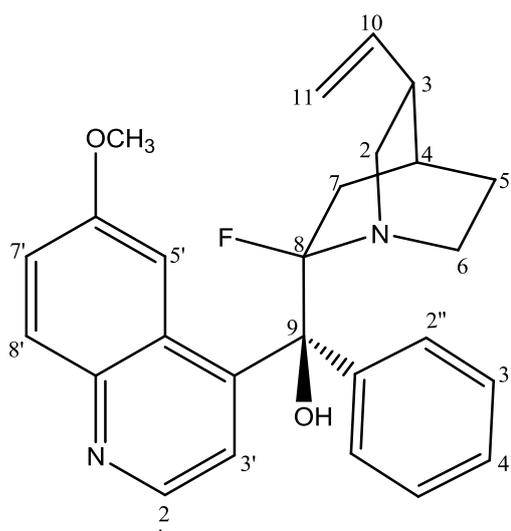


the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over sodium sulphate, and the solvent was removed to give the crude product. The yellow oil was dissolved in a minimum volume of chloroform and purified by column chromatography using chloroform/ethyl acetate (80/20) to elute residual starting material, then pure ethyl acetate to elute the product, giving 9-methyl-8-fluoro-*epi*-

quinine as a white solid (0.37 g, 68% yield). Mp 78-81 °C.  $[\alpha]_D^{20}$  -16.3° (*c* 1.00 in CHCl<sub>3</sub>). Found: C, 70.58; H, 6.85; N, 7.66. C<sub>21</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub>F requires C, 70.76; H, 7.07; N, 7.86%.  $\delta_H$  (CDCl<sub>3</sub>) 1.40-1.50 (1H, br t, <sup>3</sup>*J*<sub>HH</sub> 10.6 Hz, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.60-1.67 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.90 (3H, d, <sup>4</sup>*J*<sub>HF</sub> 2.3 Hz, 9-CH<sub>3</sub>), 1.96-1.99 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 2.05 (1H, ddt, <sup>3</sup>*J*<sub>HF</sub> 16.4 Hz, <sup>2</sup>*J*<sub>HH</sub> 14.9 Hz, <sup>3</sup>*J*<sub>HH</sub> = <sup>4</sup>*J*<sub>HH</sub> 2.7 Hz, NCFCH<sub>2</sub>, H7), 2.19-2.26 (1H, m, CH<sub>2</sub>=CHCH, H3), 2.37 (1H, ddm, <sup>3</sup>*J*<sub>HF</sub> 24.3 Hz, <sup>2</sup>*J*<sub>HH</sub> 14.9 Hz, NCFCH<sub>2</sub>, H7), 2.58-2.67 (1H, m, NCH<sub>2</sub>, H6), 2.71-2.81 (1H, dt, <sup>2</sup>*J*<sub>HH</sub> 14.1 Hz, <sup>3</sup>*J*<sub>HH</sub> 9.8 Hz, NCH<sub>2</sub>, H2), 3.08-3.14 (1H, dm, <sup>2</sup>*J*<sub>HH</sub> 14.1 Hz, NCH<sub>2</sub>, H2), 3.27-3.35 (1H, m, NCH<sub>2</sub>, H6), 3.91 (3H, s, OCH<sub>3</sub>), 5.02 (1H, dm, <sup>3</sup>*J*<sub>HH(cis)</sub> 10.6 Hz, CH=CH<sub>2</sub>, H11), 5.04 (1H, dm, <sup>3</sup>*J*<sub>HH(trans)</sub> 17.6 Hz, CH=CH<sub>2</sub>, H11), 5.99 (1H, ddd, <sup>3</sup>*J*<sub>HH(trans)</sub> 17.6 Hz, <sup>3</sup>*J*<sub>HH(cis)</sub> 10.6 Hz, <sup>3</sup>*J*<sub>HH(vic)</sub> 7.8 Hz, CH<sub>2</sub>=CH, H10), 7.32 (1H, dd, <sup>3</sup>*J*<sub>HH</sub> 9.4 Hz, <sup>4</sup>*J*<sub>HH</sub> 2.7 Hz, ArH7'), 7.74 (1H, br s, ArH3'), 8.00 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 9.4 Hz, ArH8'), 8.21 (1H, br. s, ArH5'), 8.69 (1H, d, <sup>3</sup>*J*<sub>HH</sub> 4.7 Hz, ArH2').  $\delta_F$  (CDCl<sub>3</sub>) -115.07 (br s, CF).  $\delta_C$  (CDCl<sub>3</sub>) 25.74 (CH<sub>2</sub>, C5), 27.76 (CH<sub>3</sub>), 29.69 (CH, C4), 29.89 (CH<sub>2</sub>, d, <sup>2</sup>*J*<sub>CF</sub> 4.8 Hz, C7), 39.39 (CH, C3), 43.34 (CH<sub>2</sub>, d, <sup>3</sup>*J*<sub>CF</sub> 6.4 Hz, C6), 49.53 (CH<sub>2</sub>, d, <sup>3</sup>*J*<sub>CF</sub> 8.0 Hz, C2), 55.37 (OCH<sub>3</sub>), 80.79 (C, d, <sup>2</sup>*J*<sub>CF</sub> 27.2 Hz, C9), 106.59 (CH, d, <sup>5</sup>*J*<sub>CF</sub> 12.8 Hz, C5'), 108.88 (C, d, <sup>1</sup>*J*<sub>CF</sub> 196.5 Hz, C8), 114.68 (CH<sub>2</sub>, C11), 120.80 (CH, C7'), 121.01 (CH, C3'), 128.42 (C), 130.95 (CH, C8'), 141.36 (CH, C10), 145.17 (C), 146.53 (CH, C2'), 150.38 (C), 156.73 (C, C6'). *m/z* (ESI) 357.1972 (MH<sup>+</sup>. C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>F requires 357.1978, 80%), 179.1001 (100).

### 5.3.6 9-Phenyl-8-fluoro-*epi*-quinine (90)

Under a nitrogen atmosphere, a solution of 8-fluoroquininone (0.54 g, 1.6 mmol) in dry THF (30 mL) was added dropwise over a period of 20 minutes to a stirred solution of

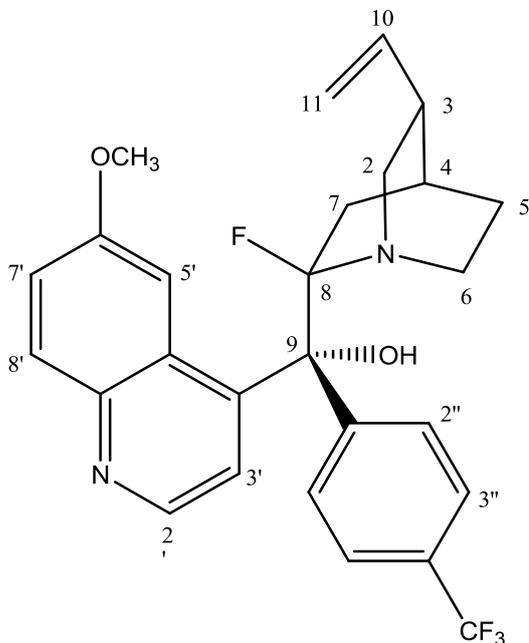


phenyllithium (1.75 mL, 1.8 M in  $n\text{Bu}_2\text{O}$ , 3.2 mmol) in dry diethyl ether (20 mL) at  $-78^\circ\text{C}$ . The mixture was stirred at  $-78^\circ\text{C}$  for 6 hours before being quenched with water (30 mL) and allowed to warm to room temperature. The organic layer was removed and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over sodium sulphate, and the solvent was removed to give the crude product. The yellow oil was

dissolved in a minimum volume of chloroform and purified by column chromatography using chloroform/ethyl acetate (80/20) to elute residual starting material, then pure ethyl acetate to elute the product, giving 9-phenyl-8-fluoro-*epi*-quinine as a white solid (0.33 g, 49% yield). Mp  $226\text{--}230^\circ\text{C}$ .  $[\alpha]_{\text{D}}^{20}$   $8.8^\circ$  ( $c$  0.63 in  $\text{CHCl}_3$ ). Found: C, 74.54; H, 6.56; N, 6.52.  $\text{C}_{26}\text{H}_{27}\text{N}_2\text{O}_2\text{F}$  requires C, 74.62; H, 6.50; N, 6.69%.  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.32 (2H, tm,  $^3J_{\text{HH}}$  7.8 Hz,  $\text{NCH}_2\text{CH}_2$ , H5), 1.75 (1H, ddm,  $^3J_{\text{HF}}$  28.2 Hz,  $^2J_{\text{HH}}$  14.9 Hz,  $\text{NCFCH}_2$ , H7), 1.82–1.86 (1H, m,  $\text{CH}_2=\text{CHCH}$ , H4), 2.16–2.24 (1H, m,  $\text{CH}_2=\text{CHCH}$ , H3), 2.42 (1H, ddm,  $^3J_{\text{HF}}$  28.2 Hz,  $^2J_{\text{HH}}$  14.9 Hz,  $\text{NCFCH}_2$ , H7), 2.54–2.64 (1H, m,  $\text{NCH}_2$ , H6), 2.85 (1H, dt,  $^2J_{\text{HH}}$  14.3 Hz,  $^3J_{\text{HH}} = ^4J_{\text{HF}}$  9.8 Hz,  $\text{NCH}_2$ , H2), 3.10–3.20 (1H, m,  $\text{NCH}_2$ , H6), 3.28 (1H, dm,  $^2J_{\text{HH}}$  14.3 Hz,  $\text{NCH}_2$ , H2), 3.49 (3H, s,  $\text{OCH}_3$ ), 4.05 (1H, br s, OH), 4.95 (1H, dm,  $^3J_{\text{HH(cis)}}$  10.4 Hz,  $\text{CH}_2=\text{CH}$ , H11), 4.98 (1H, dm,  $^3J_{\text{HH(trans)}}$  17.2 Hz,  $\text{CH}_2=\text{CH}$ , H11), 5.93 (1H, ddd,  $^3J_{\text{HH(trans)}}$  17.2 Hz,  $^3J_{\text{HH(cis)}}$  10.4 Hz,  $^3J_{\text{HH(vic)}}$  7.8 Hz,  $\text{CH}_2=\text{CH}$ , H10), 7.07 (1H, dd,  $^3J_{\text{HH}}$  9.0 Hz,  $^4J_{\text{HH}}$  2.7 Hz, ArH7'), 7.11–7.18 (3H, m, ArH3'' and ArH4''), 7.25 (1H, d,  $^4J_{\text{HH}}$  2.7 Hz, ArH5'), 7.49 (2H, dm,  $^3J_{\text{HH}}$  7.8 Hz, ArH2''), 7.83 (1H, d,  $^3J_{\text{HH}}$  9.0 Hz, ArH8'), 8.29 (1H, dd,  $^3J_{\text{HH}}$  4.7 Hz,  $^5J_{\text{HF}}$  2.3 Hz, ArH3'), 8.69 (1H, d,  $^3J_{\text{HH}}$  4.7 Hz, ArH2').  $\delta_{\text{F}}$  ( $\text{CDCl}_3$ )  $-116.76$  (s, CF).  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 25.84 ( $\text{CH}_2$ , C5), 29.53 (CH, C4), 31.28 ( $\text{CH}_2$ , d,  $^2J_{\text{CF}}$  25.6 Hz, C7), 39.32 (CH, C3), 44.12 ( $\text{CH}_2$ , d,  $^3J_{\text{CF}}$  4.8 Hz, C6), 50.00 ( $\text{CH}_2$ , d,  $^3J_{\text{CF}}$  9.6 Hz, C2), 55.20 ( $\text{OCH}_3$ ), 82.03 (C, d,  $^2J_{\text{CF}}$  28.8 Hz, C9), 105.20 (CH, C5'), 107.90 (C, d,  $^1J_{\text{CF}}$  199.7 Hz, C8), 114.87 ( $\text{CH}_2$ , C11), 120.89 (CH, C7'), 121.47 (CH, d,  $^4J_{\text{CF}}$  4.8 Hz, C3'), 127.25 (CH, C4''), 127.41 (CH, C3''), 128.44 (CH, C2''), 131.50 (CH, C8'), 131.61 (C), 141.11 (CH, C10), 142.95 (C), 145.78 (C), 146.64 (CH, C2'), 156.64 (C, C6'). Unfortunately a quaternary carbon is missing despite several re-runs of the spectrum.  $m/z$  ( $\text{ES}^+$ ) 419.2133 ( $\text{MH}^+$ ).

$C_{26}H_{28}N_2O_2F$  requires 419.2135, 100%). Crystals suitable for X-ray crystallography was grown by slow recrystallisation from chloroform.

### 5.3.7 9-(4-Trifluoromethylphenyl)-8-fluoro-*epi*-quinine (91)

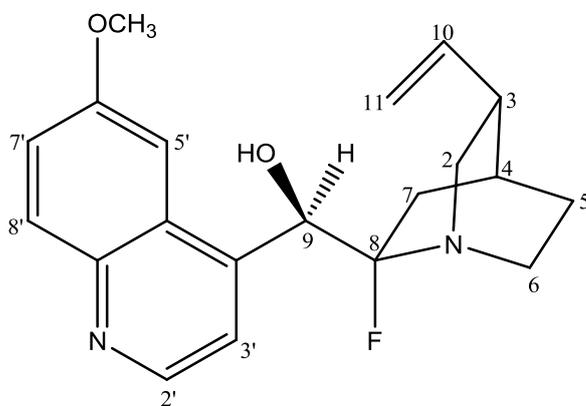


Under an atmosphere of nitrogen, *n*-butyllithium (3.75 mL, 1.6 M in hexanes, 6.0 mmol) in dry diethyl ether (10 mL) was added dropwise over 40 minutes to a solution of 4-bromobenzotrifluoride (0.9 mL, 6.4 mmol) in dry diethyl ether (10 mL) at 0 °C. The mixture was stirred at 0 °C for one hour, and then cooled to -78 °C. 8-Fluoroquininone (0.51 g, 1.5 mmol) in dry THF (30 mL) was then added dropwise over 10 minutes at -78 °C. The reaction mixture was stirred at -78 °C for 6 hours and then

quenched with water (30 mL), before warming to room temperature overnight. After removing the organic layer, the aqueous layer was extracted with diethyl ether (3 x 15 mL). The organic layers were then combined and dried over anhydrous sodium sulphate before the solvent was removed by rotary evaporation. The crude oil (1.25 g) was purified using column chromatography on silica gel, initially using the solvent system chloroform/ethyl acetate (80/20) to elute residual starting material, then 100% ethyl acetate to elute the product, and some mixed fractions were re-columned, giving 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinine as a white solid (0.45 g, 60% yield). Mp 252-254 °C.  $[\alpha]_D^{20}$  5.6° (*c* 0.98 in  $CHCl_3$ ). Found: C, 66.75; H, 5.23; N, 5.71.  $C_{27}H_{26}N_2O_2F_4$  requires C, 66.66; H, 5.39; N, 5.76%.  $\delta_H$  ( $CDCl_3$ ) 1.36-1.48 (2H, m,  $NCH_2CH_2$ , H5), 1.58 (1H, dd,  $^3J_{HF}$  30.3 Hz,  $^2J_{HH}$  14.9 Hz,  $NCFCH_2$ , H7), 1.85 (1H, m,  $NCH_2CH_2CH$ , H4), 2.18-2.24 (1H, m,  $CH_2=CHCH$ , H3), 2.30 (1H, dddd,  $^3J_{HF}$  28.2 Hz,  $^2J_{HH}$  14.9 Hz,  $^3J_{HH}$  2.7 Hz,  $^4J_{HH}$  1.2 Hz,  $NCFCH_2$ , H7), 2.66 (1H, ddd,  $^2J_{HH}$  15.3 Hz,  $^3J_{HH}$  10.6 Hz,  $^4J_{HF}$  5.5 Hz,  $NCH_2$ , H6), 2.88 (1H, dt,  $^2J_{HH}$  13.7 Hz,  $^3J_{HH} = ^4J_{HF}$  10.0 Hz,  $NCH_2$ , H2), 3.08-3.18 (1H, m,  $NCH_2$ , H6), 3.30 (1H, dm,  $^2J_{HH}$  13.7 Hz,  $NCH_2$ , H2), 3.48 (3H, s,  $OCH_3$ ), 3.70 (1H, br s, OH), 4.94 (1H, dt,  $^3J_{HH(cis)}$  10.2 Hz,  $^2J_{HH(germ)} = ^4J_{HH}$  1.4 Hz,  $CH_2=CH$ , H11), 4.98 (1H, dt,  $^3J_{HH(trans)}$  17.2 Hz,  $^2J_{HH(germ)} = ^4J_{HH}$  1.4 Hz,

$\text{CH}_2=\text{CH}$ , H11), 5.89 (1H, ddd,  $^3J_{\text{HH}(\text{trans})}$  17.2 Hz,  $^3J_{\text{HH}(\text{cis})}$  10.2 Hz,  $^3J_{\text{HH}(\text{vic})}$  7.8 Hz,  $\text{CH}_2=\text{CH}$ , H10), 7.09 (1H, d,  $^4J_{\text{HH}}$  2.6 Hz, ArH5'), 7.10 (1H, dd,  $^3J_{\text{HH}}$  9.8 Hz,  $^4J_{\text{HH}}$  2.6 Hz, ArH7'), 7.44 (2H, d,  $^3J_{\text{HH}}$  7.8 Hz, ArH3''), 7.62 (2H, d,  $^3J_{\text{HH}}$  7.8 Hz, ArH2''), 7.86 (1H, d,  $^3J_{\text{HH}}$  9.8 Hz, ArH8'), 8.43 (1H, dd,  $^3J_{\text{HH}}$  4.7 Hz,  $^5J_{\text{HF}}$  2.3 Hz, ArH3'), 8.71 (1H, d,  $^3J_{\text{HH}}$  4.7 Hz, ArH2').  $\delta_{\text{F}}$  ( $\text{CDCl}_3$ ) -116.85 (1F, s, CF), -62.52 (3F, s,  $\text{CF}_3$ ).  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 25.89 ( $\text{CH}_2$ , C5), 29.40 (CH, C4), 31.02 ( $\text{CH}_2$ , d,  $^2J_{\text{CF}}$  25.2 Hz, C7), 39.15 (CH, C3), 44.26 ( $\text{CH}_2$ , d,  $^3J_{\text{CF}}$  5.0 Hz, C6), 50.0 ( $\text{CH}_2$ , d,  $^3J_{\text{CF}}$  8.8 Hz, C2), 55.20 ( $\text{OCH}_3$ ), 81.60 (C, d,  $^2J_{\text{CF}}$  27.7 Hz, C9), 104.49 (CH, C5'), 107.62 (C, d,  $^1J_{\text{CF}}$  198.7 Hz, C8), 115.01 ( $\text{CH}_2$ , C11), 120.99 (CH, C7'), 122.16 (CH, C3'), 123.98 (C, q,  $^1J_{\text{CF}}$  269.9 Hz,  $\text{CF}_3$ ), 124.28 (CH, C2''), 126.79 (C, C1''), 128.88 (CH, C3''), 129.65 (C, q,  $^2J_{\text{CF}}$  32.7 Hz, C4''), 132.06 (CH, C8'), 140.91 (CH, C10), 144.25 (C), 146.01 (C), 146.82 (C), 146.90 (CH, C2'), 156.98 (C, C6').  $m/z$  ( $\text{ES}^+$ ) 487.2001 ( $\text{MH}^+$ ).  $\text{C}_{27}\text{H}_{27}\text{N}_2\text{O}_2\text{F}_4$  requires 487.2009, 100%). Crystals suitable for X-ray crystallography were grown by slow recrystallisation from acetonitrile.

### 5.3.8 8-Fluoro-*epi*-quinidine (92)

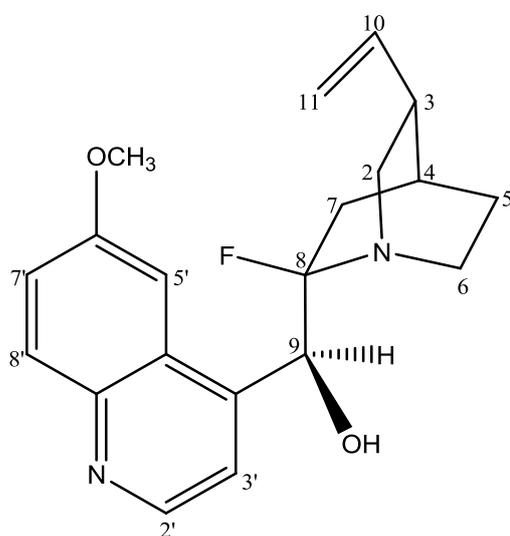


The procedure reported by Uskokovic for the reduction of quinidinone and quininone to *epi*-quinidine and *epi*-quinine respectively was used to reduce 8-fluoroquinidinone to 8-fluoro-*epi*-quinidine.<sup>7</sup> Sodium borohydride (0.18 g, 4.7 mmol) was added to a stirred solution of 8-fluoroquinidinone (0.94 g,

2.8 mmol) in ethanol (45 mL) at 0 °C. The mixture was stirred at 0 °C for one hour and then quenched with acetic acid (1 mL). A 2 M solution of sodium carbonate (10 mL) was added to the mixture and the solvent was evaporated. Water (30 mL) was added to the residue and the residue was extracted with dichloromethane (3 x 20 mL). The organic extracts were washed consecutively with 2 M sodium carbonate and water. After drying over anhydrous sodium sulphate, the solvent was removed by rotary evaporation. The crude solid (1.15 g) was dissolved in a minimum volume of chloroform and purified by column chromatography on silica gel using 100% ethyl acetate to give 8-fluoro-*epi*-quinidine as a white solid (0.65 g, 66% yield). Mp 120-124

$^{\circ}\text{C}$ .  $[\alpha]_{\text{D}}^{20}$  99.2 $^{\circ}$  ( $c$  0.97 in  $\text{CHCl}_3$ ). Found: C, 70.24; H, 6.58; N, 8.07.  $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_2\text{F}$  requires C, 70.15; H, 6.77; N, 8.18%.  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.14 (1H, dddd,  $^3J_{\text{HF}}$  28.5 Hz,  $^2J_{\text{HH}}$  15.6 Hz,  $^3J_{\text{HH}}$  4.2 Hz,  $^4J_{\text{HH}}$  1.7 Hz,  $\text{NCFCH}_2$ , H7), 1.47-1.65 (2H, m,  $\text{NCH}_2\text{CH}_2$ , H5), 1.75-1.89 (2H, m,  $\text{NCFCH}_2$ , H7 and  $\text{NCH}_2\text{CH}_2\text{CH}$ , H4), 2.32 (1H, q,  $^3J_{\text{HH}}$  7.4 Hz,  $\text{CH}_2=\text{CHCH}$ , H3), 2.63-2.74 (1H, m,  $\text{NCH}_2$ , H6), 2.93 (1H, ddt,  $^2J_{\text{HH}}$  14.6 Hz,  $^3J_{\text{HH}}$  7.2 Hz,  $^4J_{\text{HH}} = ^4J_{\text{HF}}$  2.0,  $\text{NCH}_2$ , H2), 3.21 (1H, ddd,  $^2J_{\text{HH}}$  14.6 Hz,  $^3J_{\text{HH}}$  10.2 Hz,  $^4J_{\text{HF}}$  4.3 Hz,  $\text{NCH}_2$ , H2), 3.30 (1H, ddt,  $^2J_{\text{HH}}$  13.3 Hz,  $^3J_{\text{HH}}$  10.2 Hz,  $^4J_{\text{HH}} = ^4J_{\text{HF}}$  2.6 Hz,  $\text{NCH}_2$ , H6), 3.86 (3H, s,  $\text{OCH}_3$ ), 4.37 (1H, br s, OH), 5.10 (1H, dt,  $^3J_{\text{HH}(\text{trans})}$  17.0 Hz,  $^2J_{\text{HH}(\text{gem})} = ^4J_{\text{HH}}$  1.6 Hz,  $\text{CH}_2=\text{CH}$ , H11), 5.12 (1H, dt,  $^3J_{\text{HH}(\text{cis})}$  10.6 Hz,  $^2J_{\text{HH}(\text{gem})} = ^4J_{\text{HH}}$  1.6 Hz,  $\text{CH}_2=\text{CH}$ , H11), 5.43 (1H, d,  $^3J_{\text{HF}}$  24.3 Hz,  $\text{CHOH}$ , H9), 5.84 (1H, ddd,  $^3J_{\text{HH}(\text{trans})}$  17.0 Hz,  $^3J_{\text{HH}(\text{cis})}$  10.6 Hz,  $^3J_{\text{HH}(\text{vic})}$  7.4 Hz,  $\text{CH}_2=\text{CH}$ , H10), 7.29 (1H, dd,  $^3J_{\text{HH}}$  9.4 Hz,  $^4J_{\text{HH}}$  2.3 Hz, ArH7'), 7.39 (1H, d,  $^4J_{\text{HH}}$  2.3 Hz, ArH5'), 7.57 (1H, dd,  $^3J_{\text{HH}}$  4.7 Hz,  $^5J_{\text{HF}}$  2.7 Hz, ArH3'), 7.96 (1H, d,  $^3J_{\text{HH}}$  9.4 Hz, ArH8'), 8.71 (1H, d,  $^3J_{\text{HH}}$  4.7 Hz, ArH2').  $\delta_{\text{F}}$  ( $\text{CDCl}_3$ ) -139.56 (s, CF).  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 25.80 ( $\text{CH}_2$ , C5), 28.23 (CH, C4), 30.57 ( $\text{CH}_2$ , d,  $^2J_{\text{CF}}$  25.6 Hz, C7), 37.13 (CH, C3), 42.47 ( $\text{CH}_2$ , d,  $^3J_{\text{CF}}$  9.6 Hz, C6), 48.97 ( $\text{CH}_2$ , d,  $^3J_{\text{CF}}$  6.4 Hz, C2), 55.49 ( $\text{OCH}_3$ ), 69.23 (CH, d,  $^2J_{\text{CF}}$  20.8 Hz, C9), 102.15 (CH, C5'), 105.0 (C, d,  $^1J_{\text{CF}}$  199.7 Hz, C8), 115.37 ( $\text{CH}_2$ , C11), 121.43 (CH, C7'), 122.82 (CH, d,  $^4J_{\text{CF}}$  3.2 Hz, C3'), 128.43 (C), 131.78 (CH, C8'), 140.32 (CH, C10), 141.37 (C), 144.79 (C), 147.36 (CH, C2'), 157.63 (C, C6').  $m/z$  ( $\text{ES}^+$ ) 343.1817 ( $\text{MH}^+$ ).  $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_2\text{F}$  requires 343.1822, 100%. Crystals suitable for X-ray crystallography were grown by slow recrystallisation from chloroform.

### 5.3.9 8-Fluoro-*epi*-quinine (93)

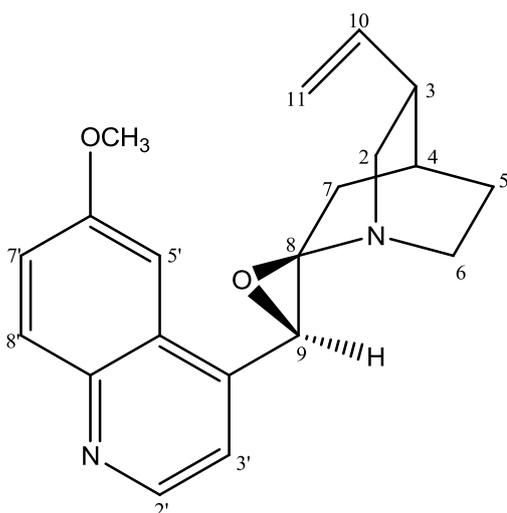


The procedure reported by Uskokovic for the reduction of quinidinone and quininone to *epi*-quinidine and *epi*-quinine respectively was used to reduce 8-fluoroquininone to 8-fluoro-*epi*-quinine.<sup>7</sup> Sodium borohydride (0.03 g, 0.7 mmol) was added to a stirred solution of 8-fluoroquininone (0.14 g, 0.4 mmol) in ethanol (30 mL) at 0  $^{\circ}\text{C}$ . The mixture was stirred at 0  $^{\circ}\text{C}$  for one hour and then quenched with acetic acid (1 mL). A 2



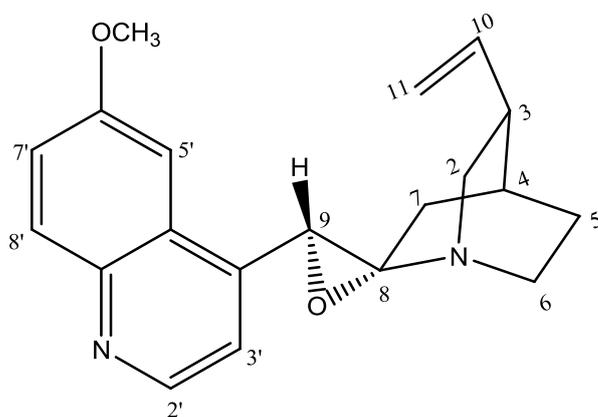
of nitrogen, diisobutylaluminium hydride (0.80 mL, 1 M in toluene, 0.8 mmol) was added slowly to a stirred solution of 8-fluoroquinidinone (0.21 g, 0.6 mmol) in dry toluene (25 mL) at room temperature (17 °C). The reaction mixture was stirred at room temperature for 2 hours, and then quenched with water/methanol (1:1, 2 mL). The solvent was evaporated, and the residue was dissolved in chloroform. This solution was washed consecutively with 1 M sodium hydroxide and brine. After drying over anhydrous sodium sulphate, the solvent was removed by rotary evaporation. The crude product (0.34 g) was dissolved in a minimum volume of chloroform and purified by column chromatography on silica gel using 100% ethyl acetate to give 8-fluoroquinidine as a white solid (0.09 g, 40% yield). Mp 170-173 °C.  $[\alpha]_D^{20}$  195.1° (*c* 0.90 in CHCl<sub>3</sub>). Found: C, 70.02; H, 6.76; N, 8.05. C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub>F requires C, 70.15; H, 6.77; N, 8.18%.  $\delta_H$  (CDCl<sub>3</sub>) 1.37-1.62 (3H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5 and NCFCH<sub>2</sub>, H7), 1.79-1.83 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 2.15 (1H, q, <sup>3</sup>J<sub>HH</sub> 7.8 Hz, CH<sub>2</sub>=CHCH, H3), 2.27 (1H, ddt, <sup>3</sup>J<sub>HF</sub> 30.1 Hz, <sup>2</sup>J<sub>HH</sub> 15.3 Hz, <sup>3</sup>J<sub>HH</sub> = <sup>4</sup>J<sub>HH</sub> 2.3 Hz, NCFCH<sub>2</sub>, H7), 2.40-2.51 (1H, m, NCH<sub>2</sub>, H6), 2.87-3.00 (2H, m, NCH<sub>2</sub>, H2), 3.15 (1H, dd, <sup>3</sup>J<sub>HH</sub> 12.9 Hz, <sup>4</sup>J<sub>HF</sub> 10.6 Hz, NCH<sub>2</sub>, H6), 3.78 (3H, s, OCH<sub>3</sub>), 4.60 (1H, br s, OH), 4.91 (1H, dt, <sup>3</sup>J<sub>HH(trans)</sub> 17.2 Hz, <sup>2</sup>J<sub>HH(gem)</sub> = <sup>4</sup>J<sub>HH</sub> 1.6 Hz, CH=CH<sub>2</sub>, H11), 4.94 (1H, dt, <sup>3</sup>J<sub>HH(cis)</sub> 10.6 Hz, <sup>2</sup>J<sub>HH(gem)</sub> = <sup>4</sup>J<sub>HH</sub> 1.6 Hz, CH=CH<sub>2</sub>, H11), 5.46 (1H, d, <sup>3</sup>J<sub>HF</sub> 16.0 Hz, CHOH, H9), 5.73 (1H, ddd, <sup>3</sup>J<sub>HH(trans)</sub> 17.2 Hz, <sup>3</sup>J<sub>HH(cis)</sub> 10.6 Hz, <sup>3</sup>J<sub>HH(vic)</sub> 7.8 Hz, CH<sub>2</sub>=CH, H10), 7.17 (1H, dd, <sup>3</sup>J<sub>HH</sub> 9.0 Hz, <sup>4</sup>J<sub>HH</sub> 2.7 Hz, ArH7'), 7.18 (1H, br s, ArH5'), 7.52 (1H, d, <sup>3</sup>J<sub>HH</sub> 4.7 Hz, ArH3'), 7.79 (1H, d, <sup>3</sup>J<sub>HH</sub> 9.0 Hz, ArH8'), 8.42 (1H, d, <sup>3</sup>J<sub>HH</sub> 4.7 Hz, ArH2').  $\delta_F$  (CDCl<sub>3</sub>) -126.88 (s, CF).  $\delta_C$  (CDCl<sub>3</sub>) 25.85 (CH<sub>2</sub>, C5), 28.80 (CH, C4), 30.71 (CH<sub>2</sub>, d, <sup>2</sup>J<sub>CF</sub> 25.6 Hz, C7), 37.90 (CH, C3), 42.81 (CH<sub>2</sub>, d, <sup>3</sup>J<sub>CF</sub> 9.6 Hz, C6), 49.45 (CH<sub>2</sub>, d, <sup>3</sup>J<sub>CF</sub> 4.8 Hz, C2), 55.50 (OCH<sub>3</sub>), 72.64 (CH, d, <sup>2</sup>J<sub>CF</sub> 28.8 Hz, C9), 102.13 (CH, C5'), 107.07 (C, d, <sup>1</sup>J<sub>CF</sub> 196.5 Hz, C8), 115.07 (CH<sub>2</sub>, C11), 120.29 (CH, d, <sup>4</sup>J<sub>CF</sub> 3.2 Hz, C3'), 121.54 (CH, C7'), 128.15 (C), 131.39 (CH, C8'), 140.14 (CH, C10), 144.34 (C, d, <sup>3</sup>J<sub>CF</sub> 6.4 Hz, C4'), 147.35 (CH, C2'), 147.43 (C), 157.64 (C, C6'). *m/z* (ES<sup>+</sup>) 343.1815 (MH<sup>+</sup>). C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>F requires 343.1822, 100%).

A second, non-fluorinated minor product was also isolated from the column as a yellow oil, believed to be an epoxide (**95**) (0.02 g, 11% yield).  $[\alpha]_D^{20}$  -37.5° (*c* 1.03 in CHCl<sub>3</sub>).  $\delta_H$  (CDCl<sub>3</sub>) 1.45-1.55 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.69-1.78 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.85 (1H, dm, <sup>2</sup>J<sub>HH</sub> 14.9 Hz, NCOCH<sub>2</sub>, H7), 1.94-1.99 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 2.09-2.22



(2H, m, CH<sub>2</sub>=CHCH, H3 and NCH<sub>2</sub>, H2), 2.39 (1H, dt, <sup>2</sup>J<sub>HH</sub> 14.9 Hz, <sup>3</sup>J<sub>HH</sub> = <sup>4</sup>J<sub>HH</sub> 2.7 Hz, NCOCH<sub>2</sub>, H7), 2.64-2.76 (2H, m, NCH<sub>2</sub>, H6 and NCH<sub>2</sub>, H2), 3.11-3.21 (1H, m, NCH<sub>2</sub>, H6), 3.89 (3H, s, OCH<sub>3</sub>), 4.21 (1H, s, H9), 4.93 (1H, d, <sup>3</sup>J<sub>HH(trans)</sub> 17.2 Hz, CH=CH<sub>2</sub>, H11), 5.00 (1H, d, <sup>3</sup>J<sub>HH(cis)</sub> 10.6 Hz, CH=CH<sub>2</sub>, H11), 5.84 (1H, ddd, <sup>3</sup>J<sub>HH(trans)</sub> 17.2 Hz, <sup>3</sup>J<sub>HH(cis)</sub> 10.6 Hz, <sup>3</sup>J<sub>HH(vic)</sub> 6.3 Hz, CH=CH<sub>2</sub>, H10), 7.14 (1H, d, <sup>4</sup>J<sub>HH</sub> 2.7 Hz, ArH5'), 7.29 (1H, d, <sup>3</sup>J<sub>HH</sub> 4.3 Hz, ArH3'), 7.32 (1H, dd, <sup>3</sup>J<sub>HH</sub> 9.4 Hz, <sup>4</sup>J<sub>HH</sub> 2.7 Hz, ArH7'), 7.98 (1H, d, <sup>3</sup>J<sub>HH</sub> 9.4 Hz, ArH8'), 8.67 (1H, d, <sup>3</sup>J<sub>HH</sub> 4.3 Hz, ArH2'). δ<sub>C</sub> (CDCl<sub>3</sub>) 27.01 (CH<sub>2</sub>, C5), 29.57 (CH, C4), 30.92 (CH<sub>2</sub>, C7), 38.09 (CH, C3), 43.60 (CH<sub>2</sub>, C6), 51.34 (CH<sub>2</sub>, C2), 55.43 (OCH<sub>3</sub>), 63.95 (CH, C9), 77.55 (C, C8), 100.98 (CH, C5'), 114.87 (CH<sub>2</sub>, C11), 119.59 (CH, C3'), 121.35 (CH, C7'), 127.42 (C), 131.84 (CH, C8'), 139.16 (C), 140.84 (CH, C10), 143.81 (C), 147.62 (CH, C2'), 157.72 (C, C6'). m/z (ESI) 323.1767 (MH<sup>+</sup>. C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub> requires 323.1760, 100%).

### 5.3.11 Failed Synthesis of 8-Fluoroquinine (DIBAL)



Under an atmosphere of nitrogen, diisobutylaluminium hydride (1.70 mL, 1 M in toluene, 1.7 mmol) was added slowly to a stirred solution of 8-fluoroquininone (0.40 g, 1.2 mmol) in dry toluene (25 mL) at room temperature (14 °C). The reaction mixture was stirred at room temperature for 2 hours, and then quenched with water/methanol (1:1, 2 mL). The solvent was evaporated, and the residue was dissolved in chloroform. This solution was washed consecutively with 1 M sodium hydroxide and brine. After drying over anhydrous sodium sulphate, the solvent was removed by rotary evaporation. The crude product was dissolved in a minimum volume of chloroform and purified by column chromatography on silica gel using ethyl acetate.

8-Fluoroquinine was not isolated from this column and a non fluorinated product believed to be the epoxide shown (**97**) was isolated as a yellow oil (0.12 g, 31% yield).  $[\alpha]_D^{20}$  74.6° (*c* 0.65 in CHCl<sub>3</sub>).  $\delta_H$  (CDCl<sub>3</sub>) 1.40-1.58 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.91-1.97 (2H, m, NCOCH<sub>2</sub>, H7), 2.19 (1H, q,  $^3J_{HH}$  7.8 Hz, CH<sub>2</sub>=CHCH, H3), 2.23-2.39 (3H, m, NCH<sub>2</sub>, H6 and NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 2.88-3.00 (2H, m, NCH<sub>2</sub>, H2), 3.88 (3H, s, OCH<sub>3</sub>), 4.19 (1H, s, H9), 5.04 (1H, dm,  $^3J_{HH(cis)}$  9.8 Hz, CH<sub>2</sub>=CH, H11), 5.05 (1H, dm,  $^3J_{HH(trans)}$  17.2 Hz, CH<sub>2</sub>=CH, H11), 5.91 (1H, ddd,  $^3J_{HH(trans)}$  17.2 Hz,  $^3J_{HH(cis)}$  9.8 Hz,  $^3J_{HH(vic)}$  7.8 Hz, CH<sub>2</sub>=CH, H10), 7.11 (1H, d,  $^4J_{HH}$  2.7 Hz, ArH5'), 7.31 (1H, dd,  $^3J_{HH}$  9.4 Hz,  $^4J_{HH}$  2.7 Hz, ArH7'), 7.33 (1H, d,  $^3J_{HH}$  4.7 Hz, ArH3'), 7.98 (1H, d,  $^3J_{HH}$  9.4 Hz, ArH8'), 8.67 (1H, d,  $^3J_{HH}$  4.7 Hz, ArH2').  $\delta_C$  (CDCl<sub>3</sub>) 25.79 (CH<sub>2</sub>, C5), 29.09 (CH, C4), 30.03 (CH<sub>2</sub>, C7), 38.09 (CH, C3), 43.62 (CH<sub>2</sub>, C6), 49.37 (CH<sub>2</sub>, C2), 54.52 (OCH<sub>3</sub>), 63.51 (CH, C9), 76.70 (C, C8), 99.84 (CH, C5'), 114.23 (CH<sub>2</sub>, C11), 118.44 (CH, C7'), 120.06 (CH, C3'), 126.49 (C), 130.87 (CH, C8'), 138.29 (C), 138.98 (CH, C10), 142.65 (C), 146.77 (CH, C2'), 156.72 (C, C6'). *m/z* (ESI) 323.1752 (MH<sup>+</sup>. C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub> requires 323.1760, 100%).

### 5.3.12 Formation of zinc borohydride<sup>8</sup>

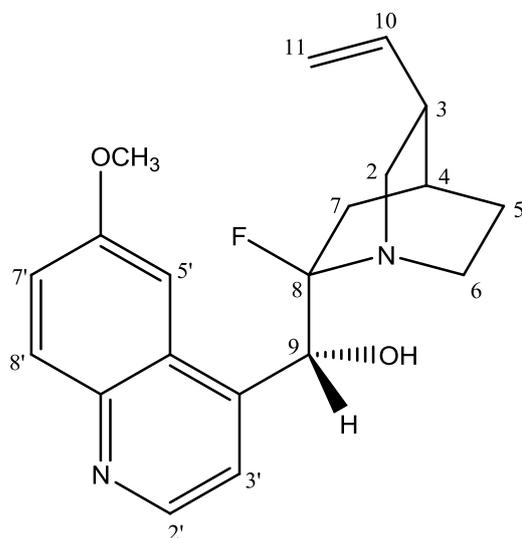
Under an argon atmosphere freshly fused zinc chloride (7.77 g, 0.057 moles) was refluxed in dry diethyl ether (55 mL) until all of the solid had dissolved. The solution was allowed to cool to room temperature and was then added to a suspension of sodium borohydride (4.32 g, 0.11 moles) in dry diethyl ether (150 mL). The mixture was stirred overnight at room temperature, and the supernatant fluid (zinc borohydride as a 0.278 M solution in diethyl ether) was used for reactions.

### 5.3.13 8-Fluoroquinidine (**94**) (Zn(BH<sub>4</sub>)<sub>2</sub>)

Under an argon atmosphere zinc borohydride (0.268 M in diethyl ether, 5 mL, 1.34 mmol) was added to a stirred solution of 8-fluoroquinidinone (0.23 g, 0.67 mmol) in dry diethyl ether (25 mL). The reaction mixture was stirred at room temperature for 24 hours before being quenched with water (20 mL). The organic phase was removed and the aqueous phase was extracted with diethyl ether (2 x 15 mL). The combined organic phases were dried over anhydrous sodium sulphate and the solvent was removed to give the crude product as a yellow oil. The crude oil was purified by column chromatography on silica gel using chloroform/ethyl acetate (80/20) to elute any residual starting

material, then 100% ethyl acetate to elute the products 8-fluoro-*epi*-quinidine (0.027 g, 0.08 mmol, 12% yield) and 8-fluoroquinidine (0.099 g, 0.29 mmol, 43% yield) as white solids.

### 5.3.14 8-Fluoroquinine (96) ( $\text{Zn}(\text{BH}_4)_2$ )



Under an argon atmosphere zinc borohydride (0.278 M in diethyl ether, 3.5 mL, 0.97 mmol) was added to a stirred solution of 8-fluoroquinone (0.17 g, 0.49 mmol) in dry diethyl ether (20 mL). The reaction mixture was stirred at room temperature for 24 hours before being quenched with water (20 mL). The organic phase was removed and the aqueous phase was extracted with diethyl ether (2 x 10 mL). The combined organic

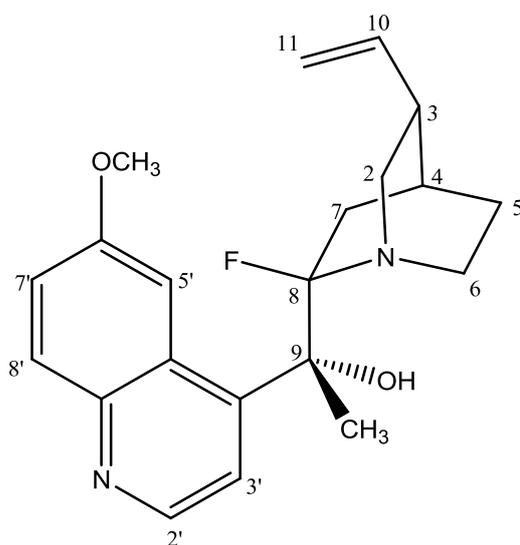
phases were dried over anhydrous sodium sulphate and the solvent was removed to give the crude product as a yellow oil. The crude oil was purified by column chromatography on silica gel using chloroform/ethyl acetate (80/20) to elute any residual starting material, then 100% ethyl acetate to elute the products 8-fluoro-*epi*-quinine (0.0071 g, 0.021 mmol, 4% yield) and 8-fluoroquinine (0.061 g, 0.18 mmol, 36% yield) as white solids. Mp 167-172 °C.  $[\alpha]_D^{20}$  -31.3° (*c* 1.08 in  $\text{CHCl}_3$ ). Found: C, 69.99; H, 6.75; N, 8.23.  $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_2\text{F}$  requires C, 70.15; H, 6.77; N, 8.18%.  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.36-1.45 (1H, m,  $\text{NCH}_2\text{CH}_2$ , H5), 1.49-1.58 (1H, m,  $\text{NCH}_2\text{CH}_2$ , H5), 1.74-1.87 (2H, m,  $\text{NCFCH}_2$ , H7 and  $\text{NCH}_2\text{CH}_2\text{CH}$ , H4), 2.10-2.28 (2H, m,  $\text{NCFCH}_2$ , H7 and  $\text{CH}_2=\text{CHCH}$ , H3), 2.53-2.64 (1H, m,  $\text{NCH}_2$ , H6), 2.71-2.80 (1H, ddd,  $^2J_{\text{HH}}$  14.1 Hz,  $^3J_{\text{HH}}$  10.2 Hz,  $^4J_{\text{HF}}$  7.0 Hz,  $\text{NCH}_2$ , H2), 2.94-3.07 (2H, m,  $\text{NCH}_2$ , H6 and  $\text{NCH}_2$ , H2), 3.81 (3H, s,  $\text{OCH}_3$ ), 4.93 (1H, dm,  $^3J_{\text{HH}}$  10.2 Hz,  $\text{CH}=\text{CH}_2$ , H11), 4.95 (1H, dm,  $^3J_{\text{HH}}$  17.2 Hz,  $\text{CH}=\text{CH}_2$ , H11), 5.32 (1H, d,  $^3J_{\text{HF}}$  14.5 Hz,  $\text{CHOH}$ , H9), 5.82 (1H, ddd,  $^3J_{\text{HH}(\text{trans})}$  17.2 Hz,  $^3J_{\text{HH}(\text{cis})}$  10.2 Hz,  $^3J_{\text{HH}(\text{vic})}$  7.4 Hz,  $\text{CH}_2=\text{CH}$ , H10), 7.16 (1H, dd,  $^3J_{\text{HH}}$  9.4 Hz,  $^4J_{\text{HH}}$  2.7 Hz, ArH7'), 7.25 (1H, br s, ArH5'), 7.61 (1H, d,  $^3J_{\text{HH}}$  4.7 Hz, ArH3'), 7.76 (1H, d,  $^3J_{\text{HH}}$  9.4 Hz, ArH8'), 8.37 (1H, d,  $^3J_{\text{HH}}$  4.7 Hz, ArH2').  $\delta_{\text{F}}$  ( $\text{CDCl}_3$ ) -125.23 (s, CF).  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 28.6 ( $\text{CH}_2$ , C5), 32.12 (CH, C4), 33.09 ( $\text{CH}_2$ , d,  $^2J_{\text{CF}}$  27.2 Hz, C7), 42.00 (CH, C3), 46.17 ( $\text{CH}_2$ , d,  $^3J_{\text{CF}}$  6.4 Hz, C6), 51.13 ( $\text{CH}_2$ , d,  $^3J_{\text{CF}}$  3.2 Hz, C2), 58.50 ( $\text{OCH}_3$ ), 74.95 (CH, d,  $^2J_{\text{CF}}$  25.6 Hz, C9), 105.25 (CH, C5'), 109.70 (C, d,  $^1J_{\text{CF}}$  194.9 Hz, C8), 117.89 ( $\text{CH}_2$ ,

C11), 123.32 (CH, C7'), 124.17 (CH, C3'), 131.13 (C), 133.87 (CH, C8'), 143.35 (CH, C10), 146.97 (C), 147.05 (C), 150.05 (CH, C2'), 160.57 (C, C6'). m/z (ESI) 343.1834 (MH<sup>+</sup>. C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>F requires 343.1822, 100%), 172.0947 (80).

### 5.3.15 8-Fluoroquinidine (94) (LiAlH<sub>4</sub>)

Under an argon atmosphere lithium aluminium hydride (0.03 g, 0.90 mmol) was added to a stirred solution of 8-fluoroquinidinone (0.25 g, 0.74 mmol) in dry diethyl ether (20 mL). The reaction mixture was stirred at room temperature for 2 hours before being quenched with water (20 mL). The organic phase was removed and the aqueous phase was extracted with diethyl ether (3 x 15 mL). The combined organic phases were dried over anhydrous sodium sulphate and the solvent was removed to give the crude product as a yellow oil. The crude oil was purified by column chromatography on silica gel using chloroform/ethyl acetate (80/20) to elute any residual starting material, then 100% ethyl acetate to elute the products 8-fluoro-*epi*-quinidine (0.0041 g, 0.012 mmol, 2% yield) and 8-fluoroquinidine (0.04 g, 0.13 mmol, 17% yield) as white solids. There was also a considerable recovery of 8-fluoroquinidinone starting material (0.15 g, 0.44 mmol, 59% yield), not unexpected from the low conversion of the reaction.

### 5.3.16 9-Methyl-8-fluoroquinine (98)

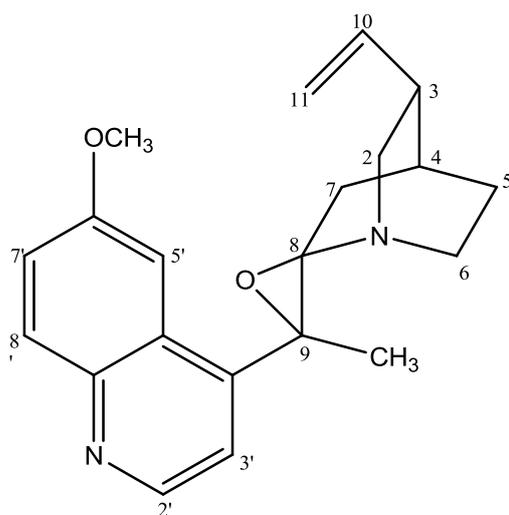


Under an argon atmosphere trimethylaluminium (2 M in toluene, 0.45 mL, 0.9 mmol) was added dropwise to a stirred solution of 8-fluoroquininone (0.10 g, 0.28 mmol) in dry toluene (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 24 hours before being cooled to 0 °C. The reaction was quenched by slow addition of water (10 mL) at 0 °C and allowed to warm to room temperature. The organic phase was removed

and the aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic phases were dried over anhydrous sodium sulphate, and the solvent was removed to give the crude product as a yellow oil. The crude product was purified by column chromatography on silica gel using 100% ethyl acetate, to give 9-methyl-8-

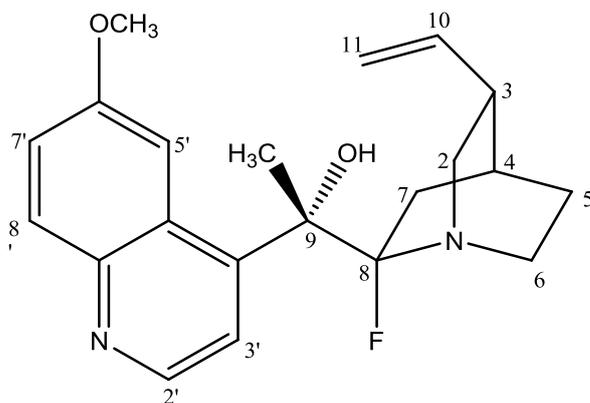
fluoroquinine as a yellow solid (0.06 g, 65% yield). Mp 203-205 °C.  $[\alpha]_D^{20}$  -13.0° (*c* 1.00 in CHCl<sub>3</sub>). Found: C, 70.58; H, 7.02; N, 7.60. C<sub>21</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub>F requires C, 70.76; H, 7.07; N, 7.86%.  $\delta_H$  (CDCl<sub>3</sub>) 1.33-1.47 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5 and NCFCH<sub>2</sub>, H7), 1.55-1.64 (1H, tm, <sup>3</sup>J<sub>HH</sub> 12.7 Hz, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.73-1.77 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 1.98 (3H, s, 9-CH<sub>3</sub>), 2.10-2.18 (1H, m, CH<sub>2</sub>=CHCH, H3), 2.18-2.28 (1H, m, NCFCH<sub>2</sub>, H7), 2.67-2.77 (1H, m, NCH<sub>2</sub>, H6), 2.84 (1H, dt, <sup>2</sup>J<sub>HH</sub> 14.1 Hz, <sup>3</sup>J<sub>HH</sub> 9.7 Hz, NCH<sub>2</sub>, H2), 3.13 (1H, dm, <sup>2</sup>J<sub>HH</sub> 14.1 Hz, NCH<sub>2</sub>, H2), 3.62-3.71 (1H, m, NCH<sub>2</sub>, H6), 3.79 (3H, s, OCH<sub>3</sub>), 4.30 (1H, br s, OH), 4.82 (1H, dm, <sup>3</sup>J<sub>HH</sub> 10.2 Hz, CH=CH<sub>2</sub>, H11), 4.88 (1H, dm, <sup>3</sup>J<sub>HH</sub> 17.2 Hz, CH=CH<sub>2</sub>, H11), 5.76 (1H, ddd, <sup>3</sup>J<sub>HH(trans)</sub> 17.2 Hz, <sup>3</sup>J<sub>HH(cis)</sub> 10.2 Hz, <sup>3</sup>J<sub>HH(vic)</sub> 7.8 Hz, CH<sub>2</sub>=CH, H10), 7.20 (1H, dd, <sup>3</sup>J<sub>HH</sub> 9.4 Hz, <sup>4</sup>J<sub>HH</sub> 2.7 Hz, ArH7'), 7.65 (1H, br s, ArH3'), 7.85 (1H, d, <sup>3</sup>J<sub>HH</sub> 9.4 Hz, ArH8'), 8.04 (1H, br s, ArH5'), 8.39 (1H, d, <sup>3</sup>J<sub>HH</sub> 5.1 Hz, ArH2').  $\delta_F$  (CDCl<sub>3</sub>) -118.41 (br s, CF).  $\delta_C$  (CDCl<sub>3</sub>) 24.94 (CH<sub>2</sub>, C5), 25.93 (CH<sub>3</sub>, 9-CH<sub>3</sub>), 28.14 (CH<sub>2</sub>, d, <sup>2</sup>J<sub>CF</sub> 25.6 Hz, C7), 28.36 (CH, C4), 38.19 (CH, C3), 43.21 (CH<sub>2</sub>, d, <sup>3</sup>J<sub>CF</sub> 6.4 Hz, C6), 49.00 (CH<sub>2</sub>, d, <sup>3</sup>J<sub>CF</sub> 8.0 Hz, C2), 54.36 (OCH<sub>3</sub>), 79.06 (C, br d, <sup>2</sup>J<sub>CF</sub> 24.0 Hz, C9), 105.75 (C, d, <sup>1</sup>J<sub>CF</sub> 193.3 Hz, C8), 105.87 (CH, d, <sup>4</sup>J<sub>CF</sub> 8.0 Hz, C5'), 113.56 (CH<sub>2</sub>, C11), 119.86 (CH, C7'), 121.18 (CH, C8'), 127.59 (C), 130.03 (CH, C3'), 140.16 (CH, C10), 144.26 (C), 145.42 (CH, C2'), 149.12 (C), 155.75 (C, C6'). *m/z* (ESI) 357.1977 (MH<sup>+</sup>. C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>F requires 357.1978, 100%). A crystal suitable for X-ray crystallography was grown by slow recrystallisation from chloroform.

### 5.3.17 Reaction of 8-Fluoroquinidinone with AlMe<sub>3</sub>



Under an argon atmosphere trimethylaluminium (2 M solution in toluene, 1.75 mL, 3.5 mmol) was added dropwise over two minutes to a stirred solution of 8-fluoroquinidinone (0.38 g, 1.12 mmol) in dry toluene (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 24 hours before being cooled to 0 °C and quenched by slow addition of water (10 mL). The organic phase was removed and the aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic phases were dried over anhydrous sodium sulphate and the solvent was removed to give the crude product as a yellow oil. The crude product was purified

by column chromatography on silica gel using ethyl acetate. The major product was obtained as a yellow solid, and is thought to be the epoxide (**100**) shown (0.12 g, 33% yield). Mp 107-109 °C.  $[\alpha]_D^{20}$  -86.9° (*c* 0.97 in CHCl<sub>3</sub>). Found: C, 69.74; H, 7.03; N, 7.94. C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub> requires C, 74.97; H, 7.19; N, 8.33%.  $\delta_H$  (CDCl<sub>3</sub>) 1.39-1.57 (3H, m, NCFCH<sub>2</sub>, H7 and NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.59 (3H, s, 9-CH<sub>3</sub>), 1.97-2.09 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>CH, H4 and NCFCH<sub>2</sub>, H7), 2.16 (1H, q, <sup>3</sup>J<sub>HH</sub> 7.8 Hz, CH<sub>2</sub>=CHCH, H3), 2.27-2.38 (1H, m, NCH<sub>2</sub>, H6), 2.64-2.73 (1H, m, NCH<sub>2</sub>, H6), 2.79 (1H, dd, <sup>2</sup>J<sub>HH</sub> 13.7 Hz, <sup>3</sup>J<sub>HH</sub> 9.8 Hz, NCH<sub>2</sub>, H2), 2.88 (1H, ddd, <sup>2</sup>J<sub>HH</sub> 13.7 Hz, <sup>3</sup>J<sub>HH</sub> 6.3 Hz, <sup>4</sup>J<sub>HH</sub> 2.0, NCH<sub>2</sub>, H2), 3.85 (3H, s, OCH<sub>3</sub>), 5.00 (1H, dm, <sup>3</sup>J<sub>HH</sub> 10.4 Hz, CH=CH<sub>2</sub>, H11), 5.01 (1H, dm, <sup>3</sup>J<sub>HH</sub> 17.2 Hz, CH=CH<sub>2</sub>, H11), 5.92 (1H, ddd, <sup>3</sup>J<sub>HH</sub> 17.2 Hz, <sup>3</sup>J<sub>HH</sub> 10.4 Hz, <sup>3</sup>J<sub>HH</sub> 7.8 Hz, CH<sub>2</sub>=CH, H10), 7.00 (1H, br s, ArH5'), 7.26 (1H, dd, <sup>3</sup>J<sub>HH</sub> 9.4 Hz, <sup>4</sup>J<sub>HH</sub> 2.3 Hz, ArH7'), 7.37 (1H, br d, <sup>3</sup>J<sub>HH</sub> 3.1 Hz, ArH3'), 7.93 (1H, d, <sup>3</sup>J<sub>HH</sub> 9.4 Hz, ArH8'), 8.64 (1H, br d, <sup>3</sup>J<sub>HH</sub> 3.1 Hz, ArH2').  $\delta_C$  (CDCl<sub>3</sub>) 19.65 (CH<sub>3</sub>, 9-CH<sub>3</sub>), 25.70 (CH<sub>2</sub>, C5), 27.59 (CH<sub>2</sub>, C7), 28.94 (CH, C4), 38.23 (CH, C3), 42.99 (CH<sub>2</sub>, C6), 49.46 (CH<sub>2</sub>, C2), 54.39 (OCH<sub>3</sub>), 67.03 (C, C9), 78.73 (C, C8), 102.12 (CH, C5'), 114.00 (CH<sub>2</sub>, C11), 118.70 (CH, C3'), 119.88 (CH, C7'), 125.25 (C), 130.88 (CH, C8'), 139.55 (CH, C10), 143.40 (C), 144.74 (C), 147.12 (CH, C2'), 155.93 (C, C6'). *m/z* (ES) 337.1911 (MH<sup>+</sup>. C<sub>21</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub> requires 337.1916, 100%).

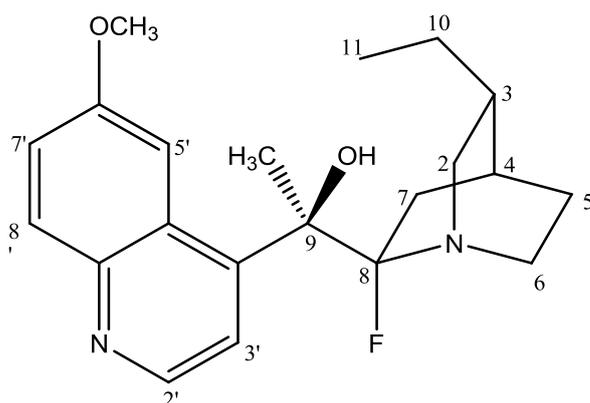


Some mixed fractions were also obtained and were purified on a second column, eluting with chloroform/ethyl acetate (80/20), to give 9-methyl-8-fluoroquinidine (**99**) as a white solid (0.05 g, 0.14 mmol, 13% yield). Mp 200-203 °C.  $[\alpha]_D^{20}$  73.7° (*c* 0.83 in CHCl<sub>3</sub>). Found: C, 70.67; H, 7.18; N,

7.82. C<sub>21</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub>F requires C, 70.76; H, 7.07; N, 7.86%.  $\delta_H$  (CDCl<sub>3</sub>) 1.08-1.21 (1H, dddd, <sup>3</sup>J<sub>HF</sub> 28.6 Hz, <sup>2</sup>J<sub>HH</sub> 14.9 Hz, <sup>3</sup>J<sub>HH</sub> 4.3 Hz, <sup>4</sup>J<sub>HH</sub> 1.2 Hz, NCFCH<sub>2</sub>, H7), 1.36-1.44 (1H, tm, <sup>3</sup>J<sub>HH</sub> 11.0 Hz, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.53-1.62 (1H, qm, <sup>3</sup>J<sub>HH</sub> 9.4 Hz, NCH<sub>2</sub>CH<sub>2</sub>, H5), 1.69-1.74 (1H, m, NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 1.91 (3H, br s, 9-CH<sub>3</sub>), 2.05-2.13 (1H, q, <sup>3</sup>J<sub>HH</sub> 7.6 Hz, NCH<sub>2</sub>CH, H3), 2.22-2.38 (1H, dd, <sup>3</sup>J<sub>HF</sub> 36.0 Hz, <sup>2</sup>J<sub>HH</sub> 14.9 Hz, NCFCH<sub>2</sub>, H7), 2.50-2.60 (1H, dq, <sup>2</sup>J<sub>HH</sub> 12.9 Hz, <sup>3</sup>J<sub>HH</sub> 9.4 Hz, NCH<sub>2</sub>, H6), 2.84-2.91 (1H, ddd, <sup>2</sup>J<sub>HH</sub> 14.5 Hz, <sup>3</sup>J<sub>HH</sub> 9.8 Hz, <sup>4</sup>J<sub>HF</sub> 5.1 Hz, NCH<sub>2</sub>, H2), 3.17-3.24 (1H, ddm, <sup>2</sup>J<sub>HH</sub> 14.5 Hz, <sup>3</sup>J<sub>HH</sub>

8.2 Hz,  $\text{NCH}_2$ , H2), 3.24-3.32 (1H, tm,  $^3J_{\text{HH}}$  11.0 Hz,  $\text{NCH}_2$ , H6), 3.82 (3H, s,  $\text{OCH}_3$ ), 4.26 (1H, br s, OH), 4.73 (1H, dt,  $^3J_{\text{HH}}$  17.2 Hz,  $^2J_{\text{HH}} = ^4J_{\text{HH}}$  1.4 Hz,  $\text{CH}=\text{CH}_2$ , H11), 4.81 (1H, dt,  $^3J_{\text{HH}}$  10.6 Hz,  $^2J_{\text{HH}} = ^4J_{\text{HH}}$  1.4 Hz,  $\text{CH}=\text{CH}_2$ , H11), 5.61 (1H, ddd,  $^3J_{\text{HH}}$  17.2 Hz,  $^3J_{\text{HH}}$  10.6 Hz,  $^3J_{\text{HH}}$  7.6 Hz,  $\text{CH}_2=\text{CH}$ , H10), 7.23 (1H, dd,  $^3J_{\text{HH}}$  9.4 Hz,  $^4J_{\text{HH}}$  2.7 Hz,  $\text{ArH}7'$ ), 7.58 (1H, br s,  $\text{ArH}3'$ ), 7.90 (1H, d,  $^3J_{\text{HH}}$  9.4 Hz,  $\text{ArH}8'$ ), 8.13 (1H, br s,  $\text{ArH}5'$ ), 8.51 (1H, d,  $^3J_{\text{HH}}$  4.7 Hz  $\text{ArH}2'$ ).  $\delta_{\text{F}}$  ( $\text{CDCl}_3$ ) -123.78 (br d, CF).  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 24.68 ( $\text{CH}_2$ , C5), 26.42 ( $\text{CH}_3$ , d,  $^3J_{\text{CF}}$  4.8 Hz, 9- $\text{CH}_3$ ), 28.16 ( $\text{CH}_2$ , d,  $^2J_{\text{CF}}$  24.0 Hz, C7), 28.31 (CH, C4), 37.24 (CH, C3), 43.58 ( $\text{CH}_2$ , d,  $^3J_{\text{CF}}$  11.2 Hz, C2), 48.75 ( $\text{CH}_2$ , d,  $^3J_{\text{CF}}$  4.8 Hz, C6), 54.35 ( $\text{OCH}_3$ ), 79.66 (C, C9), 105.51 (CH, C5'), 106.78 (C, d,  $^1J_{\text{CF}}$  198.1 Hz, C8), 113.61 ( $\text{CH}_2$ , C11), 120.02 (CH, C7'), 120.88 (CH, C3'), 127.44 (C), 130.37 (CH, C8'), 139.18 (CH, C10), 144.45 (C), 145.75 (CH, C2'), 148.18 (C), 155.79 (C, C6').  $m/z$  (ES) 357.1972 ( $\text{MH}^+$ .  $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_2\text{F}$  requires 357.1978, 100%).

### 5.3.18 9-Methyl-8-fluoro-10,11-dihydro-*epi*-quinidine (101)

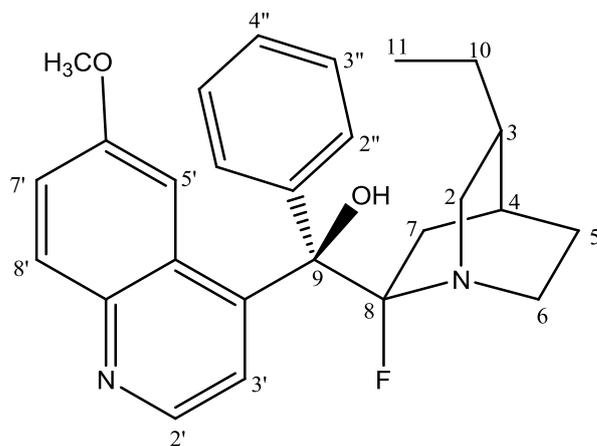


The procedure reported by Blaser to synthesise 10,11-dihydrocinchonidine from cinchonidine was adapted to synthesise 9-methyl-10,11-dihydro-8-fluoro-*epi*-quinidine from 9-methyl-8-fluoro-*epi*-quinidine.<sup>4</sup> Pd/C (5%, 0.034 g, 4 mol%) was added to a solution of 9-methyl-8-fluoro-*epi*-quinidine (0.14

g, 0.40 mmol) in sulphuric acid (0.5 M, 5 mL). The mixture was shaken under hydrogen (approx 2.5 psi) for 3 hours. The clear solution was filtered from the catalyst and neutralised with a 2 M solution of sodium hydroxide (~5 mL). The white precipitate formed was collected and dried under vacuum at 50 °C, to give 9-methyl-8-fluoro-10,11-dihydro-*epi*-quinidine as a white solid (0.090 g, 0.25 mmol, 63% yield). Mp 176-178 °C.  $[\alpha]_{\text{D}}^{20}$  21.6° ( $c$  0.87 in  $\text{CHCl}_3$ ). Found: C, 67.38; H, 7.68; N, 7.42.  $\text{C}_{21}\text{H}_{27}\text{N}_2\text{O}_2\text{F}$  requires C, 70.37; H, 7.59; N, 7.82%.  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 0.48 (3H, t,  $^3J_{\text{HH}}$  7.4 Hz,  $\text{CH}_2\text{CH}_3$ , H11), 0.72-0.87 (2H, m,  $\text{CH}_2\text{CH}_3$ , H10), 0.99-1.13 (2H, m,  $\text{NCFCH}_2$ , H7 and  $\text{NCH}_2\text{CH}_2\text{CH}$ , H4), 1.14-1.22 (1H, m,  $\text{NCH}_2\text{CH}_2$ , H5), 1.41-1.52 (2H, m,  $\text{NCH}_2\text{CH}_2$ , H5 and  $\text{CH}_3\text{CH}_2\text{CH}$ , H3), 1.76 (3H, d,  $^4J_{\text{HF}}$  2.3 Hz, 9- $\text{CH}_3$ ), 2.01 (1H, dd,  $^3J_{\text{HF}}$  36.0 Hz,  $^2J_{\text{HH}}$  14.9,  $\text{NCFCH}_2$ , H7), 2.38 (1H, dq,  $^2J_{\text{HH}}$  12.9 Hz,  $^3J_{\text{HH}}$  9.2 Hz,  $\text{NCH}_2$ , H2), 2.48-2.56 (1H, m,  $\text{NCH}_2$ , H6), 2.68 (1H, ddd,  $^2J_{\text{HH}}$  14.5 Hz,  $^3J_{\text{HH}}$  9.8 Hz,  $^3J_{\text{HH}}$  5.5 Hz,  $\text{NCH}_2$ ,

H6), 3.11 (1H, t,  $^3J_{\text{HH}}$  10.6 Hz,  $\text{NCH}_2$ , H2), 3.54 (1H, br s, OH), 3.70 (3H, s,  $\text{OCH}_3$ ), 7.11 (1H, dd,  $^3J_{\text{HH}}$  9.0 Hz,  $^4J_{\text{HH}}$  2.7 Hz, ArH7'), 7.48 (1H, br s, ArH5'), 7.78 (1H, d,  $^3J_{\text{HH}}$  9.0 Hz, ArH8'), 8.08 (1H, br s, ArH3'), 8.47 (1H, d,  $^3J_{\text{HH}}$  4.7 Hz, ArH2').  $\delta_{\text{F}}$  ( $\text{CDCl}_3$ ) -122.82 (br s, CF).  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 11.70 ( $\text{CH}_3$ , C11), 25.35 ( $\text{CH}_2$ , C10), 26.37 ( $\text{CH}_2$ , C5), 27.31 ( $\text{CH}$ , C4), 27.68 ( $\text{CH}_3$ , 9- $\text{CH}_3$ ), 29.19 ( $\text{CH}_2$ , d,  $^2J_{\text{CF}}$  23.9 Hz, C7), 35.85 ( $\text{CH}$ , C3), 44.56 ( $\text{CH}_2$ , d,  $^3J_{\text{CF}}$  12.8 Hz, C2), 51.54 ( $\text{CH}_2$ , d,  $^3J_{\text{CF}}$  4.8 Hz, C6), 55.37 ( $\text{OCH}_3$ ), 77.24 (C, C9), 106.36 ( $\text{CH}$ , d,  $^5J_{\text{CF}}$  6.4 Hz, C5'), 107.76 (C, d,  $^1J_{\text{CF}}$  201.3 Hz, C8), 120.98 ( $\text{CH}$ , C7'), 121.56 ( $\text{CH}$ , C3'), 131.67 ( $\text{CH}$ , C8'), 145.60 (C), 147.01 ( $\text{CH}$ , C2'), 156.80 (C, C6').  $m/z$  (ES) 359.2145 ( $\text{MH}^+$ ).  $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_2\text{F}$  requires 359.2135, 75%).

### 5.3.19 9-Phenyl-8-fluoro-10,11-dihydro-*epi*-quinidine (102)

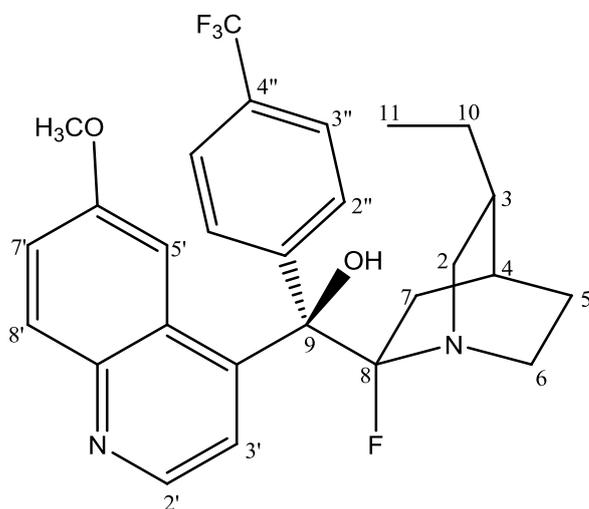


The procedure reported by Blaser to synthesise 10,11-dihydrocinchonidine from cinchonidine was adapted to synthesise 9-phenyl-10,11-dihydro-8-fluoro-*epi*-quinidine from 9-phenyl-8-fluoro-*epi*-quinidine.<sup>4</sup> Pd/C (5%, 0.040 g, 4.00 mol%) was added to a solution of 9-phenyl-8-fluoro-*epi*-quinidine (0.20 g, 0.47 mmol) in sulphuric acid

(0.5 M, 5 mL). The mixture was shaken under hydrogen (approx 2.5 psi) for 2 hours 50 minutes. The clear solution was filtered from the catalyst and neutralised with a 2 M solution of sodium hydroxide (~6 mL). The white precipitate formed was collected and dried under vacuum at 50 °C, to give 9-phenyl-8-fluoro-10,11-dihydro-*epi*-quinidine as a white solid (0.15 g, 75% yield). Mp 223-225 °C.  $[\alpha]_{\text{D}}^{20}$  46.7° ( $c$  1.08 in  $\text{CHCl}_3$ ). Found: C, 73.83; H, 6.83; N, 6.77.  $\text{C}_{26}\text{H}_{29}\text{N}_2\text{O}_2\text{F}$  requires: C, 74.26; H, 6.95; N, 6.66%.  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 0.55 (3H, t,  $^3J_{\text{HH}}$  7.4 Hz,  $\text{CH}_3\text{CH}_2$ , H11), 0.61-0.71 (1H, m,  $\text{CH}_3\text{CH}_2$ , H10), 0.80-0.92 (1H, m,  $\text{CH}_3\text{CH}_2$ , H10), 1.17-1.27 (1H, m,  $\text{CH}_3\text{CH}_2\text{CH}$ , H3), 1.42 (1H, t,  $^3J_{\text{HH}}$  9.4 Hz,  $\text{NCH}_2\text{CH}_2$ , H5), 1.63-1.83 (3H, m,  $\text{NCH}_2\text{CH}_2$ , H5,  $\text{NCFCH}_2$ , H7,  $\text{NCH}_2\text{CH}_2\text{CH}$ , H4), 2.29 (1H, dd,  $^2J_{\text{HH}}$  14.9 Hz,  $^3J_{\text{HH}}$  7.8 Hz,  $\text{NCH}_2$ , H2), 2.44-2.59 (2H, m,  $\text{NCH}_2$ , H6,  $\text{NCFCH}_2$ , H7), 2.71 (1H, ddd,  $^2J_{\text{HH}}$  14.9 Hz,  $^3J_{\text{HH}}$  9.8 Hz,  $^3J_{\text{HH}}$  5.5 Hz,  $\text{NCH}_2$ , H2), 3.38 (1H, t,  $^3J_{\text{HH}}$  10.6 Hz,  $\text{NCH}_2$ , H6), 3.54 (3H, s,  $\text{OCH}_3$ ), 5.49 (1H, br s, OH), 7.06 (1H, dd,  $^3J_{\text{HH}}$  9.4 Hz,  $^4J_{\text{HH}}$  2.7 Hz, ArH7'), 7.10-7.17 (3H, m, ArH3'' and ArH4''), 7.47-7.52 (3H,

m, ArH2'' and ArH5'), 7.80 (1H, d,  $^3J_{\text{HH}}$  9.4 Hz, ArH8'), 7.90 (1H, dd,  $^3J_{\text{HH}}$  4.7 Hz,  $^5J_{\text{HF}}$  3.1 Hz, ArH3'), 8.66 (1H, d,  $^3J_{\text{HH}}$  4.7 Hz, ArH2').  $\delta_{\text{F}}$  (CDCl<sub>3</sub>) -122.86 (s, CF).  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 11.59 (CH<sub>3</sub>, C11), 25.17 (CH<sub>2</sub>, C10), 26.60 (CH<sub>2</sub>, C5), 27.65 (CH, C4), 30.68 (CH<sub>2</sub>, d,  $^2J_{\text{CF}}$  24.0 Hz, C7), 35.61 (CH, C3), 44.44 (CH<sub>2</sub>, d,  $^3J_{\text{CF}}$  12.8 Hz, C6), 51.57 (CH<sub>2</sub>, d,  $^3J_{\text{CF}}$  3.2 Hz, C2), 55.21 (OCH<sub>3</sub>), 82.59 (C, d,  $^2J_{\text{CF}}$  27.2 Hz, C9), 105.90 (CH, C5'), 109.17 (C, d,  $^1J_{\text{CF}}$  204.5 Hz, C8), 120.59 (CH, d,  $^4J_{\text{CF}}$  6.4 Hz, C3'), 121.02 (CH, C7'), 127.42 (C, C1''), 127.50 (CH, C4''), 127.56 (CH, C3''), 128.15 (CH, C2''), 131.29 (CH, C8'), 143.34 (C), 145.64 (C), 146.15 (C), 146.46 (CH, C2'), 156.54 (C, C6'). m/z (ES) 421.2286 (MH<sup>+</sup>. C<sub>26</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>F requires 421.2291, 100%). Crystals suitable for X-ray crystallography were grown by slow recrystallisation from chloroform.

### 5.3.20 9-(4-Trifluoromethylphenyl)-8-fluoro-10,11-dihydro-*epi*-quinidine (103)



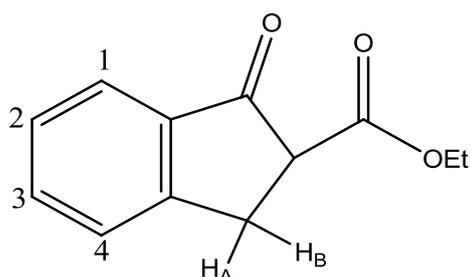
The procedure reported by Blaser to synthesise 10,11-dihydrocinchonidine from cinchonidine was adapted to synthesise 9-(4-trifluoromethylphenyl)-10,11-dihydro-8-fluoro-*epi*-quinidine from 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinidine.<sup>4</sup> Pd/C (5%, 0.041 g, 4.0 mol%) was added to a solution of 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinidine (0.24 g, 0.48 mmol) in

sulphuric acid (0.5 M, 20 mL). The mixture was shaken under hydrogen (approx 2.5 psi) for 3 hours 12 minutes. The clear solution was filtered from the catalyst and neutralised with a 2 M solution of sodium hydroxide (~15 mL). The white precipitate formed was collected and dried under vacuum at 50 °C, to give 9-(4-trifluoromethylphenyl)-8-fluoro-10,11-dihydro-*epi*-quinidine as a white solid (0.11 g, 0.23 mmol, 47% yield). Mp 263-266 °C.  $[\alpha]_{\text{D}}^{20}$  45.5° (c 1.25 in CHCl<sub>3</sub>). Found: C, 66.47; H, 5.86; N, 5.86. C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>F<sub>4</sub> requires C, 66.38; H, 5.78; N, 5.73%.  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 0.60 (3H, t,  $^3J_{\text{HH}}$  7.0 Hz, CH<sub>3</sub>CH<sub>2</sub>, H11), 0.74-0.87 (1H, m, CH<sub>3</sub>CH<sub>2</sub>, H10), 0.94-1.05 (1H, m, CH<sub>3</sub>CH<sub>2</sub>, H10), 1.23-1.32 (1H, m, NCFCH<sub>2</sub>, H7), 1.37-1.49 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5 and NCH<sub>2</sub>CH<sub>2</sub>CH, H4), 1.70-1.80 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>, H5 and CH<sub>3</sub>CH<sub>2</sub>CH, H3), 2.32-2.47 (2H, m, NCFCH<sub>2</sub>, H7 and NCH<sub>2</sub>, H2), 2.51-2.62 (1H, m, NCH<sub>2</sub>, H6), 2.73-2.82 (1H, m, NCH<sub>2</sub>, H2), 3.37-3.44 (1H, m, NCH<sub>2</sub>, H6), 3.49 (3H, s,

OCH<sub>3</sub>) 5.22 (1H, br s, OH), 7.05 (1H, d, <sup>3</sup>J<sub>HH</sub> 9.0 Hz, ArH7'), 7.27 (1H, br s, ArH5'), 7.43 (2H, d, <sup>3</sup>J<sub>HH</sub> 7.4 Hz, ArH2''), 7.62 (2H, d, <sup>3</sup>J<sub>HH</sub> 7.4 Hz, ArH3''), 7.78 (1H, d, <sup>3</sup>J<sub>HH</sub> 9.0 Hz, ArH8'), 8.01 (1H, br s, ArH3'), 8.63 (1H, d, <sup>3</sup>J<sub>HH</sub> 4.3 Hz, ArH2'). δ<sub>F</sub> (CDCl<sub>3</sub>) -122.60 (1F, CF), -62.58 (3F, CF<sub>3</sub>). δ<sub>C</sub> (CDCl<sub>3</sub>) 11.53 (CH<sub>3</sub>, C11), 25.29 (CH<sub>2</sub>, C10), 26.47 (CH<sub>2</sub>, C5), 27.51 (CH, C4), 30.43 (CH<sub>2</sub>, d, <sup>2</sup>J<sub>CF</sub> 22.7 Hz, C7), 35.60 (CH, C3), 44.51 (CH<sub>2</sub>, d, <sup>3</sup>J<sub>CF</sub> 14.4 Hz, C6), 51.65 (CH<sub>2</sub>, d, <sup>3</sup>J<sub>CF</sub> 3.6 Hz, C2), 55.18 (OCH<sub>3</sub>), 80.21 (C, d, <sup>2</sup>J<sub>CF</sub> 27.5 Hz, C9), 105.28 (CH, C5'), 106.19 (C, d, <sup>1</sup>J<sub>CF</sub> 208.2 Hz, C8), 121.11 (CH, C7'), 121.27 (CH, d, <sup>4</sup>J<sub>CF</sub> 7.2 Hz, C3'), 124.33 (CH, C3''), 127.20 (C), 128.56 (CH, C2''), 131.63 (CH, C8'), 144.95 (C), 146.09 (C), 146.61 (CH, C2'), 156.78 (C, C6'). Unfortunately, some quaternary carbons were not detected. m/z (ESI) 489.2157 (MH<sup>+</sup>. C<sub>27</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub>F<sub>4</sub> requires 489.2165, 75%), 245.1121 (100%).

## 5.4 Experimental procedures for chapter four

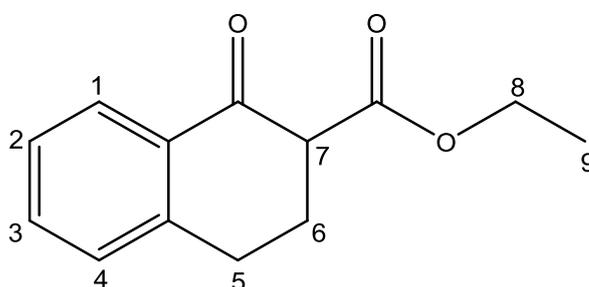
### 5.4.1 Ethyl-1-indanone-2-carboxylate<sup>9</sup> (66)



Under a nitrogen atmosphere 1-indanone (2.01 g, 15.20 mmol) dissolved in dry diethyl carbonate (55 mL), was added to a stirred suspension of sodium hydride (60% in mineral oil, 1.28 g, 32.1 mmol) in dry diethyl carbonate (55 mL). The reaction mixture was refluxed for one hour, and then allowed to cool to room temperature. The white solid formed in the reaction was filtered and dissolved in hydrochloric acid (2 M, 100 mL). The aqueous solution was extracted with ethyl acetate (4 x 100 mL). The organic phases were then combined and dried over magnesium sulphate, before the solvent was removed by rotary evaporation to give a crude oil (5.69 g). The crude oil was purified by column chromatography on silica gel using petroleum ether (40-60°C)/ethyl acetate (90/10), to give pure ethyl-1-indanone-2-carboxylate as a reddish oil (1.29 g, 42 % yield). δ<sub>H</sub> (CDCl<sub>3</sub>) 1.31 (3H, t, <sup>3</sup>J<sub>HH</sub> 7.0 Hz, keto OCH<sub>2</sub>CH<sub>3</sub>), 1.37 (3H, t, <sup>3</sup>J<sub>HH</sub> 7.0 Hz, enol OCH<sub>2</sub>CH<sub>3</sub>), 3.38 (1H, dd, <sup>2</sup>J<sub>HH</sub> 17.2 Hz, <sup>3</sup>J<sub>HH</sub> 8.6 Hz, keto CH<sub>A</sub>CH<sub>B</sub>), 3.53 (2H, s, enol CH<sub>2</sub>), 3.56 (1H, dd, <sup>2</sup>J<sub>HH</sub> 17.2 Hz, <sup>3</sup>J<sub>HH</sub> 4.1 Hz, keto CH<sub>A</sub>CH<sub>B</sub>), 3.71 (1H, dd, <sup>3</sup>J<sub>HH</sub> 8.6 Hz, <sup>3</sup>J<sub>HH</sub> 4.1 Hz, keto COCH), 4.25 (2H, qd, <sup>3</sup>J<sub>HH</sub> 7.0 Hz, <sup>5</sup>J<sub>HH</sub> 1.2 Hz, keto OCH<sub>2</sub>CH<sub>3</sub>), 4.33 (2H, q, <sup>3</sup>J<sub>HH</sub> 7.0 Hz, enol OCH<sub>2</sub>CH<sub>3</sub>), 7.37-7.42 (1H, m, keto ArH2), 7.42-7.49 (1H, m, enol ArH2), 7.51 (1H, dt, <sup>3</sup>J<sub>HH</sub> 4.7 Hz, <sup>4</sup>J<sub>HH</sub> 1.2 Hz and <sup>4</sup>J<sub>HH</sub> 0.8 Hz, keto ArH4), 7.63 (1H, td, <sup>3</sup>J<sub>HH</sub> 7.4 Hz, <sup>4</sup>J<sub>HH</sub> 1.2 Hz, keto ArH3), 7.63-7.66 (2H, m, enol

ArH4 and ArH3), 7.78 (1H, d,  $^3J_{\text{HH}}$  7.8 Hz, keto ArH1), 10.41 (1H, br. s, enol OH). One of the enol ArHs is located underneath the keto peaks.  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 14.20 (keto  $\text{CH}_3$ ), 14.47 (enol  $\text{CH}_3$ ), 30.31 (keto  $\text{CH}_2$ ), 32.57 (enol  $\text{CH}_2$ ), 53.34 (keto CH), 60.09 (enol  $\text{CH}_2$ ), 61.72 (keto  $\text{CH}_2$ ), 120.70 (enol CH), 123.73 (C), 124.67 (keto CH), 125.27 (enol CH), 126.45 (keto CH), 126.55 (enol CH), 126.80 (keto CH), 127.79 (C), 128.11 (C), 129.31 (enol CH), 135.31 (C), 135.38 (keto CH), 136.11 (C), 169.14 (keto and enol ester C=O), 199.55 (keto C=O).

#### 5.4.2 Ethyl-1-tetralone-2-carboxylate<sup>9</sup> (107)

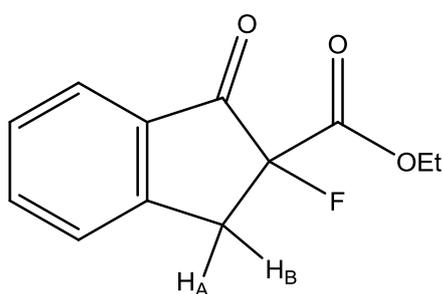


Under a nitrogen atmosphere  $\alpha$ -tetralone (2 mL, 15.04 mmol) dissolved in dry diethyl carbonate (55 mL), was added to a stirred suspension of sodium hydride (60% in mineral oil, 1.47 g, 36.85 mmol) in dry diethyl carbonate

(55 mL). The reaction mixture was refluxed for 1 hour 45 minutes, and then allowed to cool to room temperature. The solid formed in the reaction was filtered and dissolved in hydrochloric acid (2 M, 100 mL). The aqueous solution was extracted with ethyl acetate (4 x 100 mL). The organic phases were then combined and dried over magnesium sulphate, before the solvent was removed by rotary evaporation to give a crude oil (4.93 g). The crude oil was purified by column chromatography on silica gel using petroleum ether (40-60°C)/ethyl acetate (90/10), to give pure ethyl-1-tetralone-2-carboxylate as a reddish oil (2.99 g, 13.69 mmol, 91 % yield). The product appears to be predominately in its enol form (in a 4:1 ratio of enol:ketone) in both the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra.  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.26 (3H, t,  $^3J_{\text{HH}}$  7.0 Hz, keto  $\text{CH}_2\text{CH}_3$ , H9), 1.35 (3H, t,  $^3J_{\text{HH}}$  7.0 Hz, enol  $\text{CH}_2\text{CH}_3$ , H9), 2.36 (1H, ddt,  $^2J_{\text{HH}}$  13.3 Hz,  $^3J_{\text{HH}}$  5.9 Hz,  $^3J_{\text{HH}}$  4.7 Hz, keto ring  $\text{CH}_2$ , H6), 2.50 (1H, m, keto ring  $\text{CH}_2$ , H6), 2.57 (2H, dd,  $^3J_{\text{HH}}$  8.2 Hz,  $^3J_{\text{HH}}$  7.0 Hz, enol ring  $\text{CH}_2$ , H6), 2.81 (2H, dd,  $^3J_{\text{HH}}$  8.2 Hz,  $^3J_{\text{HH}}$  7.0 Hz, enol ring  $\text{CH}_2$ , H5), 2.95-3.11 (2H, m, keto ring  $\text{CH}_2$ , H5), 3.60 (1H, dd,  $^3J_{\text{HH}}$  10.6 Hz,  $^3J_{\text{HH}}$  4.7 Hz, keto CH, H7), 4.12 (2H, q,  $^3J_{\text{HH}}$  7.0 Hz, keto  $\text{OCH}_2\text{CH}_3$ , H8), 4.28 (2H, q,  $^3J_{\text{HH}}$  7.0 Hz, enol  $\text{OCH}_2\text{CH}_3$ , H8), 7.17 (1H, dm,  $^3J_{\text{HH}}$  7.0 Hz, enol ArH), 7.25 (1H, dm,  $^3J_{\text{HH}}$  7.4 Hz, keto ArH), 7.29 (1H, dd,  $^3J_{\text{HH}}$  7.4 Hz,  $^4J_{\text{HH}}$  1.6 Hz, enol ArH), 7.31 (1H, dd,  $^3J_{\text{HH}}$  7.0 Hz,  $^4J_{\text{HH}}$  1.6 Hz, enol ArH), 7.34 (1H, d,  $^4J_{\text{HH}}$  1.6 Hz, keto ArH), 7.49 (1H, td,  $^3J_{\text{HH}}$  7.4 Hz,  $^4J_{\text{HH}}$  1.6 Hz, keto ArH), 7.80 (1H, dd,  $^3J_{\text{HH}}$  7.0 Hz,  $^4J_{\text{HH}}$  1.6 Hz, enol ArH), 8.05 (1H, dd,  $^3J_{\text{HH}}$  7.8 Hz,  $^4J_{\text{HH}}$  1.2

Hz, keto ArH), 12.48 (1H, br. s, enol OH).  $\delta_C$  (CDCl<sub>3</sub>) 14.17 (keto CH<sub>3</sub>), 14.33 (enol CH<sub>3</sub>), 20.55 (enol CH<sub>2</sub>, C6), 26.39 (keto CH<sub>2</sub>, C6), 27.64 (keto CH<sub>2</sub>, C5), 27.79 (enol CH<sub>2</sub>, C5), 54.59 (keto CH, C7), 60.53 (enol CH<sub>2</sub>, C8), 61.27 (keto CH<sub>2</sub>, C8), 97.04 (enol C, C7), 124.31 (enol CH), 126.56 (enol CH), 126.90 (keto CH), 127.39 (enol CH), 127.76 (keto CH), 128.78 (keto CH), 130.08 (enol C), 130.45 (enol CH), 133.84 (keto CH), 139.41 (enol C), 165.01 (enol C-OH), 172.77 (enol C=O). Unfortunately, the keto quaternary carbons were not detected.

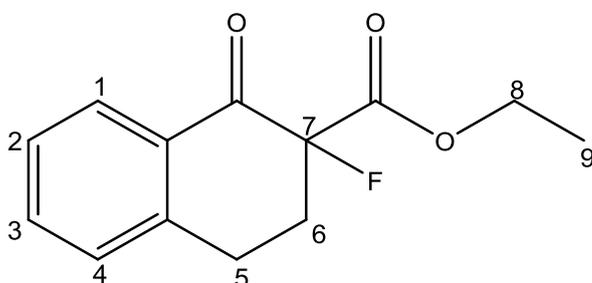
#### 5.4.3 2-Ethoxycarbonyl-2-fluoro-1-indanone (108) (large scale)



Under a nitrogen atmosphere quinine (1.59 g, 4.9 mmol) and Selectfluor (1.30 g, 3.7 mmol) were stirred for one hour in dry acetonitrile (60 mL) at room temperature (21°C). The reaction was then cooled to -78 °C. Ethyl-1-indanone-2-carboxylate (0.50 g, 2.5 mmol) dissolved in dry dichloromethane (50 mL) was then added, and the reaction mixture was stirred for three hours at -78 °C before being quenched with water (50 mL) and allowed to warm to room temperature overnight. The organic layer was removed and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were then washed successively with 5% hydrochloric acid solution (50 mL), saturated sodium hydrogen carbonate solution (50 mL), and saturated sodium chloride solution (50 mL). The organic phase was dried over sodium sulphate, and the solvent was removed by rotary evaporation to give the crude oil (0.98 g). The crude oil was purified by column chromatography on silica gel using hexane/ethyl acetate (90/10) to give pure 2-ethoxycarbonyl-2-fluoro-1-indanone as a colourless oil (0.32 g, 59% yield). The enantiomers were separated on a chiralcel OJ chiral HPLC column using 10% isopropanol in hexane, at a mobile phase flow rate of 1mL/min.  $R_t$  = 18.0 min (enantiomer 1),  $R_t$  = 24.1 min (enantiomer 2).  $\delta_H$  (CDCl<sub>3</sub>) 1.26 (3H, t,  $^3J_{HH}$  7.0 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.44 (1H, dd,  $^3J_{HF}$  23.5 Hz,  $^2J_{HH}$  17.6 Hz, CH<sub>A</sub>CH<sub>B</sub>), 3.79 (1H, dd,  $^2J_{HH}$  17.6 Hz,  $^3J_{HF}$  12.1 Hz, CH<sub>A</sub>CH<sub>B</sub>), 4.29 (2H, q,  $^3J_{HH}$  7.0 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 7.45-7.52 (2H, m, ArH), 7.70 (1H, td,  $^3J_{HH}$  7.4 Hz,  $^4J_{HH}$  1.2 Hz, ArH), 7.85 (1H, dm,  $^3J_{HH}$  8.2 Hz, ArH).  $\delta_F$  (CDCl<sub>3</sub>) -164.38 (s, CF).  $\delta_C$  (CDCl<sub>3</sub>) 13.98 (CH<sub>3</sub>), 38.26 (CH<sub>2</sub>, d,  $^2J_{CF}$  24.0 Hz, ring CH<sub>2</sub>), 62.54 (CH<sub>2</sub>, ethyl), 94.51 (C, d,  $^1J_{CF}$  201.3 Hz, CF), 125.53 (CH), 126.63

(CH), 128.61 (CH), 133.26 (C), 136.73 (CH), 150.93 (C, d,  $^3J_{CF}$  3.2 Hz), 167.29 (C, d,  $^2J_{CF}$  27.2 Hz, C=O ester), 195.28 (C, d,  $^2J_{CF}$  17.6 Hz, C=O ketone).

#### 5.4.4 2-Ethoxycarbonyl-2-fluoro-1-tetralone (109) (large scale)



Under a nitrogen atmosphere quinine (1.59 g, 4.90 mmol) and Selectfluor (1.30 g, 3.68 mmol) were stirred for one hour in dry acetonitrile (56 mL) at room temperature. The reaction was then cooled to 0 °C. Ethyl-1-tetralone-

2-carboxylate (0.53 g, 2.42 mmol) dissolved in dry dichloromethane (50 mL) was then added, and the reaction mixture was stirred at 0 °C for 3 hours before being quenched with water (50 mL) and allowed to warm to room temperature. The organic layer was removed and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were then washed successively with 5% hydrochloric acid solution (50 mL), saturated sodium hydrogen carbonate solution (50 mL), and saturated sodium chloride solution (50 mL). The organic phase was dried over sodium sulphate, and the solvent was removed by rotary evaporation to give the crude oil (1.95 g). The crude oil was purified by column chromatography on silica gel using hexane/ethyl acetate (90/10) to give pure 2-ethoxycarbonyl-2-fluoro-1-tetralone as a colourless oil (0.54 g, 2.29 mmol, 94% yield). The enantiomers were separated by chiral HPLC on an OD-H column using 1% isopropanol in hexane at a mobile phase flow rate of 1 mL/min.  $R_t$  = 8.22 min (enantiomer 1),  $R_t$  = 8.93 min (enantiomer 2).  $\delta_H$  (CDCl<sub>3</sub>) 1.28 (3H, t,  $^3J_{HH}$  7.0 Hz, OCH<sub>2</sub>CH<sub>3</sub>, H9), 2.55 (1H, dddd,  $^2J_{HH}$  14.1 Hz,  $^3J_{HF}$  11.3 Hz,  $^3J_{HH}$  7.8 Hz,  $^3J_{HH}$  5.1 Hz, CFCH<sub>2</sub>, H6a), 2.74 (1H, dddd,  $^3J_{HF}$  21.5 Hz,  $^2J_{HH}$  14.1 Hz,  $^3J_{HH}$  7.4 Hz,  $^3J_{HH}$  5.1 Hz, CFCH<sub>2</sub>, H6b), 3.08 (1H, ddd,  $^2J_{HH}$  17.2 Hz,  $^3J_{HH}$  7.8 Hz,  $^3J_{HH}$  5.1 Hz, CFCH<sub>2</sub>CH<sub>2</sub>, H5a), 3.20 (1H, ddd,  $^2J_{HH}$  17.2 Hz,  $^3J_{HH}$  7.4 Hz,  $^3J_{HH}$  5.1 Hz, CFCH<sub>2</sub>CH<sub>2</sub>, H5b), 4.30 (2H, q,  $^3J_{HH}$  7.0 Hz, CH<sub>3</sub>CH<sub>2</sub>O, H8), 7.29 (1H, d,  $^3J_{HH}$  7.8 Hz, ArH4), 7.37 (1H, td,  $^3J_{HH}$  7.8 Hz,  $^4J_{HH}$  1.4 Hz, ArH2), 7.55 (1H, td,  $^3J_{HH}$  7.8 Hz,  $^4J_{HH}$  1.4 Hz, ArH3), 8.08 (1H, dd,  $^3J_{HH}$  7.8 Hz,  $^4J_{HH}$  1.4 Hz, ArH1).  $\delta_C$  (CDCl<sub>3</sub>) 13.97 (CH<sub>3</sub>), 24.87 (CH<sub>2</sub>, d,  $^3J_{CF}$  6.4 Hz, C5), 31.85 (CH<sub>2</sub>,  $^2J_{CF}$  22.4 Hz, C6), 62.36 (CH<sub>2</sub>, ethyl), 93.18 (C, d,  $^1J_{CF}$  193.3 Hz, CF), 127.25 (CH), 128.35 (CH), 128.80 (CH), 130.57 (C), 134.57 (CH), 143.16 (C, d,  $^3J_{CF}$  1.6 Hz), 167.35 (C, d,  $^2J_{CF}$  27.2 Hz, C=O ester), 188.66 (C, d,  $^2J_{CF}$  19.2 Hz, C=O ketone).

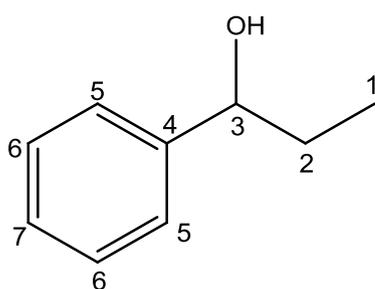
**5.4.5 2-Ethoxycarbonyl-2-fluoro-1-indanone (108) (testing scale)<sup>10</sup>**

Under a nitrogen atmosphere Selectfluor (0.104 g, 0.294 mmol) and a *Cinchona* alkaloid (0.392 mmol) were stirred for one hour in dry acetonitrile (3 mL) at room temperature. The reaction mixture was then cooled to -78 °C and a solution of ethyl-1-indanone-2-carboxylate (0.04 g, 0.196 mmol) in dry dichloromethane (4 mL) was added over approximately 5 minutes. The reaction was stirred at -78 °C for 3 ½ hours and was then quenched with water (4 mL) and allowed to warm to room temperature. The organic layer was removed and the aqueous phase was extracted with ethyl acetate (3 x 4 mL). The combined organic phases were washed successively with 5% hydrochloric acid (4 mL), saturated sodium hydrogen carbonate solution (4 mL), and saturated sodium chloride solution (4 mL). The organic phase was then dried over sodium sulphate and the solvent was removed by rotary evaporation to give a crude oil. The crude oil was purified by column chromatography on silica gel using hexane/ethyl acetate (10/1) to give the pure product. The enantiomers were separated on a chiralcel OJ chiral HPLC column using 20% isopropanol in hexane, at a mobile phase flow rate of 1mL/min.  $R_t = 13.25$  min (enantiomer 1),  $R_t = 18.25$  min (enantiomer 2).

**5.4.6 2-Ethoxycarbonyl-2-fluoro-1-tetralone (109) (testing scale)<sup>10</sup>**

Under a nitrogen atmosphere Selectfluor (0.104 g, 0.294 mmol) and a *Cinchona* alkaloid (0.392 mmol) were stirred for one hour in dry acetonitrile (3 mL) at room temperature. The reaction mixture was then cooled to -78 °C and a solution of ethyl-1-tetralone-2-carboxylate (0.04 g, 0.196 mmol) in dry dichloromethane (4 mL) was slowly added over approximately 5 minutes. The reaction was stirred at -78 °C for 3 ½ hours and was then quenched with water (4 mL) and allowed to warm to room temperature. The organic phase was removed and the aqueous phase was extracted with ethyl acetate (3 x 4 mL). The combined organic phases were washed successively with 5% hydrochloric acid (4 mL), saturated sodium hydrogen carbonate solution (4 mL), and saturated sodium chloride solution (4 mL). The organic phase was then dried over sodium sulphate and the solvent was removed by rotary evaporation to give a crude oil. The crude oil was purified by column chromatography on silica gel using hexane/ethyl acetate (10/1) to give the pure product. The enantiomers were separated on a chiralcel OD-H chiral HPLC column using 0.5% isopropanol in hexane, at a mobile phase flow rate of 1mL/min.  $R_t = 19.53$  (enantiomer 1),  $R_t = 20.62$  (enantiomer 2).

### 5.4.7 1-Phenyl-1-propanol (112) (testing scale)<sup>11</sup>



Under an argon atmosphere a *Cinchona* alkaloid (0.09 mmol, 2.2 mol%) was added to a stirred solution of benzaldehyde (0.4 mL, 3.94 mmol) in dry toluene (8 mL) at room temperature. The solution was stirred for 15 minutes before the dropwise addition of diethylzinc (1 M in hexane, 6.3 mL, 6.3 mmol) over a period of 6 minutes. The reaction mixture was then stirred at room temperature for 24 hours before being quenched by dropwise addition of hydrochloric acid (1 M, 10 mL) over approximately 10 minutes. The aqueous layer was removed, and the organic layer was washed with hydrochloric acid (1M, 2 x 8 mL) and dried over anhydrous sodium sulphate. The solvent was removed by rotary evaporation to leave a crude reaction mixture of benzaldehyde and 1-phenyl-1-propanol. A sample of the crude product (approximately 5 mg) was dissolved in dichloromethane (approximately 1 mL) and analysed by GC (CYDEX-B column, 30 m, 110 °C for 30 minutes, injector temperature 220 °C, detector temperature 250 °C, flow rate 1 mL/min,  $R_{t(\text{benzaldehyde})}$  6.06 min,  $R_{t(R \text{ enantiomer})}$  19.15 min,  $R_{t(S \text{ enantiomer})}$  19.57 min), to determine the enantiomeric excess of the 1-phenyl-1-propanol product, and to provide a second measurement of the conversion in addition to  $^1\text{H}$  NMR spectroscopy. The crude product was purified by column chromatography on silica gel eluted with hexane/ethyl acetate (90/10). The pure product was also analysed by chiral GC using identical conditions to those used for the crude product. Absolute configurations were assigned using optical rotation.  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 0.84 (3H, t,  $^3J_{\text{HH}}$  7.4 Hz,  $\text{CH}_2\text{CH}_3$ , H1), 1.62-1.81 (3H, m,  $\text{CH}_2\text{CH}_3$  H2 and OH), 4.52 (1H, t,  $^3J_{\text{HH}}$  6.5 Hz,  $\text{CHOH}$ , H3), 7.18-7.23 (1H, m, ArH), 7.25-7.30 (4H, m, ArH).  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 10.13 ( $\text{CH}_3$ , C1), 31.88 ( $\text{CH}_2$ , C2), 76.03 ( $\text{CH}$ , C3), 125.98 ( $\text{CH}$ , C7), 127.50 ( $\text{CH}$ , C5), 128.40 ( $\text{CH}$ , C6), 144.60 (C, C4).

### 5.4.8 Lactate Dehydrogenase (LDH) assay procedure

LDH Reaction buffer consists of sodium lactate (150 mM), APAD (150  $\mu\text{M}$ ), Nitro Blue (180  $\mu\text{M}$ ), diaphorase (0.5U per assay), Tween 20 surfactant (0.7%), tris-HCl buffer (pH 8.0, 100 mM), and water. Compounds (2  $\mu\text{M}$  in DMSO) to be tested for antimalarial activity were incubated for 48 hours at 37 °C with red blood cells infected with the malarial parasite *Plasmodium falciparum* in the trophozoite stage of development. The incubation took place on a 96 well plate, with each compound present

in three wells, in the presence of positive and negative controls (uninfected red blood cells, infected red blood cells with no drug present, infected red blood cells in the presence of the commonly used antimalarial drug Chloroquine). After the 48 hour incubation period the plates were frozen at  $-80\text{ }^{\circ}\text{C}$  and then allowed to warm to room temperature. LDH reaction buffer (150  $\mu\text{L}$ ) was added to the cultured parasites and the plate was shaken for 10 minutes at 900 rpm. The absorbance was then recorded at 650 nm.

#### **5.4.9 SYBR Green assay procedure**

Compounds (2  $\mu\text{M}$  in DMSO) to be tested for antimalarial activity were incubated for 48 hours at  $37\text{ }^{\circ}\text{C}$  with red blood cells infected with the malarial parasite *Plasmodium falciparum* in the trophozoite stage of development. The incubation took place on a 96 well plate, with each compound present in three wells, in the presence of positive and negative controls (uninfected red blood cells, infected red blood cells with no drug present, infected red blood cells in the presence of the commonly used antimalarial drug Chloroquine). After the 48 hour incubation period the plates were frozen at  $-80\text{ }^{\circ}\text{C}$  and then allowed to warm to room temperature. SYBR Green I (100  $\mu\text{L}$ ) in lysis buffer was added to the cultured parasites and the plate was shaken at 900 rpm until no visible erythrocyte sediment remained (10 minutes). The plate was incubated at room temperature in darkness for one hour before recording the fluorescence at 520 nm.

**5.5 References for chapter five**

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**Appendices****A1 Crystal data and structure refinement for 9-methylquinidine (68)**

Empirical formula	C <sub>21</sub> H <sub>30</sub> N <sub>2</sub> O <sub>4</sub>	
Formula weight	374.47	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.6018(13) Å	α = 90°.
	b = 14.075(3) Å	β = 90°.
	c = 18.390(3) Å	γ = 90°.
Volume	1967.7(6) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.264 Mg/m <sup>3</sup>	
Absorption coefficient	0.087 mm <sup>-1</sup>	
F(000)	808	
Crystal size	0.24 x 0.14 x 0.10 mm <sup>3</sup>	
Theta range for data collection	1.82 to 24.99°.	
Index ranges	-8 ≤ h ≤ 9, -16 ≤ k ≤ 16, -21 ≤ l ≤ 21	
Reflections collected	14210	
Independent reflections	1987 [R(int) = 0.1641]	
Completeness to theta = 24.99°	99.9 %	
Absorption correction	None	
Max. and min. transmission	0.9913 and 0.9794	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	1987 / 0 / 247	
Goodness-of-fit on F <sup>2</sup>	0.920	
Final R indices [I > 2σ(I)]	R1 = 0.0514, wR2 = 0.0877	
R indices (all data)	R1 = 0.0865, wR2 = 0.0973	
Largest diff. peak and hole	0.174 and -0.202 e.Å <sup>-3</sup>	

**A2 Crystal data and structure refinement for 9-(*iso*-butyl)quinidine (77)**

Empirical formula	C <sub>26</sub> H <sub>38</sub> N <sub>2</sub> O <sub>3</sub>	
Formula weight	426.58	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 9.0281(18) Å	α = 90°.
	b = 15.959(3) Å	β = 114.978(4)°.
	c = 9.3641(19) Å	γ = 90°.
Volume	1223.0(4) Å <sup>3</sup>	
Z	2	
Density (calculated)	1.158 Mg/m <sup>3</sup>	
Absorption coefficient	0.075 mm <sup>-1</sup>	
F(000)	464	
Crystal size	0.29 x 0.23 x 0.16 mm <sup>3</sup>	
Theta range for data collection	2.40 to 25.00°.	
Index ranges	-10 ≤ h ≤ 10, -18 ≤ k ≤ 18, -11 ≤ l ≤ 11	
Reflections collected	8898	
Independent reflections	2237 [R(int) = 0.0887]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Empirical	
Max. and min. transmission	0.969 and 0.709	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	2237 / 1 / 286	
Goodness-of-fit on F <sup>2</sup>	0.957	
Final R indices [I > 2σ(I)]	R1 = 0.0530, wR2 = 0.1015	
R indices (all data)	R1 = 0.0729, wR2 = 0.1096	
Largest diff. peak and hole	0.306 and -0.207 e.Å <sup>-3</sup>	

### A3 Crystal data and structure refinement for 9-methyl-10,11-dihydroquinidine (78)

Empirical formula	C <sub>21</sub> H <sub>32</sub> N <sub>2</sub> O <sub>4</sub>	
Formula weight	376.49	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.458(5) Å	α = 90°.
	b = 14.107(10) Å	β = 90°.
	c = 18.717(13) Å	γ = 90°.
Volume	1969(2) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.270 Mg/m <sup>3</sup>	
Absorption coefficient	0.087 mm <sup>-1</sup>	
F(000)	816	
Crystal size	0.25 x 0.20 x 0.11 mm <sup>3</sup>	
Theta range for data collection	1.81 to 25.00°.	
Index ranges	-8 ≤ h ≤ 8, -16 ≤ k ≤ 16, -21 ≤ l ≤ 22	
Reflections collected	14285	
Independent reflections	2001 [R(int) = 0.0784]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.969 and 0.657	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	2001 / 0 / 248	
Goodness-of-fit on F <sup>2</sup>	1.011	
Final R indices [I > 2σ(I)]	R1 = 0.0414, wR2 = 0.0846	
R indices (all data)	R1 = 0.0506, wR2 = 0.0879	
Largest diff. peak and hole	0.168 and -0.181 e.Å <sup>-3</sup>	

### A4 Crystal data and structure refinement for 9-phenyl-10,11-dihydroquinidine (79)

Empirical formula	C <sub>28</sub> H <sub>36</sub> N <sub>2</sub> O <sub>3</sub>	
Formula weight	448.59	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.7610(15) Å	α = 90°.
	b = 14.606(2) Å	β = 90°.
	c = 17.398(3) Å	γ = 90°.
Volume	2480.5(6) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.201 Mg/m <sup>3</sup>	
Absorption coefficient	0.078 mm <sup>-1</sup>	
F(000)	968	
Crystal size	0.27 x 0.21 x 0.19 mm <sup>3</sup>	
Theta range for data collection	1.82 to 24.99°.	
Index ranges	-11 ≤ h ≤ 11, -17 ≤ k ≤ 17, -20 ≤ l ≤ 20	
Reflections collected	18065	
Independent reflections	2487 [R(int) = 0.1378]	
Completeness to theta = 24.99°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	2487 / 0 / 302	
Goodness-of-fit on F <sup>2</sup>	0.958	
Final R indices [I > 2σ(I)]	R1 = 0.0492, wR2 = 0.0807	
R indices (all data)	R1 = 0.0773, wR2 = 0.0878	
Largest diff. peak and hole	0.183 and -0.158 e.Å <sup>-3</sup>	

**A5 Crystal data and structure refinement for 8-fluoroquinidinone (64)**

Empirical formula	C <sub>20</sub> H <sub>21</sub> F N <sub>2</sub> O <sub>2</sub>	
Formula weight	340.39	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 8.5049(19) Å	α = 90°.
	b = 8.1159(19) Å	β = 95.638(5)°.
	c = 12.344(3) Å	γ = 90°.
Volume	848.0(3) Å <sup>3</sup>	
Z	2	
Density (calculated)	1.333 Mg/m <sup>3</sup>	
Absorption coefficient	0.094 mm <sup>-1</sup>	
F(000)	360	
Crystal size	0.18 x 0.15 x 0.12 mm <sup>3</sup>	
Theta range for data collection	1.66 to 25.00°.	
Index ranges	-10 ≤ h ≤ 10, -9 ≤ k ≤ 9, -14 ≤ l ≤ 14	
Reflections collected	6189	
Independent reflections	1607 [R(int) = 0.1602]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.969 and 0.492	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	1607 / 1 / 236	
Goodness-of-fit on F <sup>2</sup>	0.957	
Final R indices [I > 2σ(I)]	R1 = 0.0641, wR2 = 0.1327	
R indices (all data)	R1 = 0.0901, wR2 = 0.1484	
Largest diff. peak and hole	0.275 and -0.301 e.Å <sup>-3</sup>	

**A6 Crystal data and structure refinement for 9-methyl-8-fluoro-*epi*-quinidine (86)**

Empirical formula	C <sub>21</sub> H <sub>25</sub> F N <sub>2</sub> O <sub>2</sub>	
Formula weight	356.43	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.825(3) Å	α = 90°.
	b = 14.484(6) Å	β = 90°.
	c = 15.833(7) Å	γ = 90°.
Volume	1794.4(12) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.319 Mg/m <sup>3</sup>	
Absorption coefficient	0.092 mm <sup>-1</sup>	
F(000)	760	
Crystal size	0.27 x 0.10 x 0.06 mm <sup>3</sup>	
Theta range for data collection	1.91 to 25.00°.	
Index ranges	-9 ≤ h ≤ 9, -17 ≤ k ≤ 17, -18 ≤ l ≤ 18	
Reflections collected	13057	
Independent reflections	1832 [R(int) = 0.2502]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.981 and 0.361	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	1832 / 0 / 237	
Goodness-of-fit on F <sup>2</sup>	0.915	
Final R indices [I > 2σ(I)]	R1 = 0.0701, wR2 = 0.1432	
R indices (all data)	R1 = 0.1258, wR2 = 0.1684	
Largest diff. peak and hole	0.245 and -0.278 e.Å <sup>-3</sup>	

**A7 Crystal data and structure refinement for 9-phenyl-8-fluoro-*epi*-quinine (90)**

Empirical formula	C <sub>26</sub> H <sub>27</sub> F N <sub>2</sub> O <sub>2</sub>
Formula weight	418.50
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	a = 6.6245(9) Å                      α = 90°. b = 10.1116(14) Å                     β = 90°. c = 30.606(5) Å                        γ = 90°.
Volume	2050.1(5) Å <sup>3</sup>
Z	4
Density (calculated)	1.356 Mg/m <sup>3</sup>
Absorption coefficient	0.092 mm <sup>-1</sup>
F(000)	888
Crystal size	0.24 x 0.20 x 0.05 mm <sup>3</sup>
Theta range for data collection	2.12 to 25.00°.
Index ranges	-7 ≤ h ≤ 7, -11 ≤ k ≤ 12, -36 ≤ l ≤ 35
Reflections collected	14985
Independent reflections	2112 [R(int) = 0.1061]
Completeness to theta = 25.00°	100.0 %
Absorption correction	Empirical
Max. and min. transmission	0.969 and 0.568
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	2112 / 0 / 282
Goodness-of-fit on F <sup>2</sup>	0.952
Final R indices [I > 2σ(I)]	R1 = 0.0455, wR2 = 0.0800
R indices (all data)	R1 = 0.0648, wR2 = 0.0854
Largest diff. peak and hole	0.186 and -0.196 e.Å <sup>-3</sup>

### A8 Crystal data and structure refinement for 9-(4-trifluoromethylphenyl)-8-fluoro-*epi*-quinine (91)

Empirical formula	C <sub>27</sub> H <sub>26</sub> F <sub>4</sub> N <sub>2</sub> O <sub>2</sub>	
Formula weight	486.50	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 10.419(11) Å	α = 90°.
	b = 6.506(7) Å	β = 98.16(2)°.
	c = 17.329(18) Å	γ = 90°.
Volume	1163(2) Å <sup>3</sup>	
Z	2	
Density (calculated)	1.390 Mg/m <sup>3</sup>	
Absorption coefficient	0.110 mm <sup>-1</sup>	
F(000)	508	
Crystal size	0.24 x 0.07 x 0.03 mm <sup>3</sup>	
Theta range for data collection	1.97 to 24.99°.	
Index ranges	-12 ≤ h ≤ 12, -7 ≤ k ≤ 7, -20 ≤ l ≤ 20	
Reflections collected	8476	
Independent reflections	2244 [R(int) = 0.3647]	
Completeness to theta = 24.99°	99.7 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9967 and 0.9742	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	2244 / 1 / 319	
Goodness-of-fit on F <sup>2</sup>	0.858	
Final R indices [I > 2σ(I)]	R1 = 0.0906, wR2 = 0.1799	
R indices (all data)	R1 = 0.1901, wR2 = 0.2294	
Extinction coefficient	0.010(4)	
Largest diff. peak and hole	0.307 and -0.403 e.Å <sup>-3</sup>	

**A9 Crystal data and structure refinement for 8-fluoro-*epi*-quinidine (92)**

Empirical formula	C <sub>20</sub> H <sub>23</sub> F N <sub>2</sub> O <sub>2</sub>	
Formula weight	342.40	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.041(4) Å	α = 90°.
	b = 13.007(6) Å	β = 90°.
	c = 18.173(9) Å	γ = 90°.
Volume	1664.3(14) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.367 Mg/m <sup>3</sup>	
Absorption coefficient	0.096 mm <sup>-1</sup>	
F(000)	728	
Crystal size	0.22 x 0.18 x 0.04 mm <sup>3</sup>	
Theta range for data collection	1.93 to 25.00°.	
Index ranges	-8 ≤ h ≤ 8, 0 ≤ k ≤ 15, 0 ≤ l ≤ 21	
Reflections collected	2938	
Independent reflections	1712 [R(int) = 0.1189]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.980 and 0.620	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	1712 / 0 / 228	
Goodness-of-fit on F <sup>2</sup>	0.814	
Final R indices [I > 2σ(I)]	R1 = 0.0559, wR2 = 0.0663	
R indices (all data)	R1 = 0.1394, wR2 = 0.0831	
Largest diff. peak and hole	0.200 and -0.214 e.Å <sup>-3</sup>	

**A10 Crystal data and structure refinement for 9-methyl-8-fluoroquinine (98)**

Empirical formula	C <sub>21</sub> H <sub>25</sub> F N <sub>2</sub> O <sub>2</sub>
Formula weight	356.43
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	a = 10.7828(17) Å      α = 90°. b = 11.4946(18) Å      β = 90°. c = 14.349(2) Å      γ = 90°.
Volume	1778.4(5) Å <sup>3</sup>
Z	4
Density (calculated)	1.331 Mg/m <sup>3</sup>
Absorption coefficient	0.093 mm <sup>-1</sup>
F(000)	760
Crystal size	0.27 x 0.17 x 0.10 mm <sup>3</sup>
Theta range for data collection	2.27 to 25.00°.
Index ranges	-12 ≤ h ≤ 12, -13 ≤ k ≤ 13, -17 ≤ l ≤ 17
Reflections collected	12974
Independent reflections	1802 [R(int) = 0.1485]
Completeness to theta = 25.00°	100.0 %
Absorption correction	Empirical
Max. and min. transmission	0.969 and 0.628
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	1802 / 0 / 237
Goodness-of-fit on F <sup>2</sup>	0.903
Final R indices [I > 2σ(I)]	R1 = 0.0525, wR2 = 0.0852
R indices (all data)	R1 = 0.0963, wR2 = 0.0972
Largest diff. peak and hole	0.273 and -0.225 e.Å <sup>-3</sup>

**A11 Crystal data and structure refinement for 9-phenyl-8-fluoro-10,11-dihydro-*epi*-quinidine (102)**

Empirical formula	C <sub>26</sub> H <sub>29</sub> F N <sub>2</sub> O <sub>2</sub>	
Formula weight	420.51	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.8536(18) Å	α = 90°.
	b = 14.593(4) Å	β = 90°.
	c = 21.104(6) Å	γ = 90°.
Volume	2110.7(10) Å <sup>3</sup>	
Z	4	
Density (calculated)	1.323 Mg/m <sup>3</sup>	
Absorption coefficient	0.090 mm <sup>-1</sup>	
F(000)	896	
Crystal size	0.27 x 0.16 x 0.08 mm <sup>3</sup>	
Theta range for data collection	1.70 to 25.00°.	
Index ranges	-8 ≤ h ≤ 8, -17 ≤ k ≤ 17, -25 ≤ l ≤ 25	
Reflections collected	15402	
Independent reflections	2152 [R(int) = 0.1359]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	Empirical	
Max. and min. transmission	0.981 and 0.757	
Refinement method	Full-matrix least-squares on F <sup>2</sup>	
Data / restraints / parameters	2152 / 0 / 282	
Goodness-of-fit on F <sup>2</sup>	0.889	
Final R indices [I > 2σ(I)]	R1 = 0.0495, wR2 = 0.0882	
R indices (all data)	R1 = 0.0771, wR2 = 0.0953	
Largest diff. peak and hole	0.218 and -0.231 e.Å <sup>-3</sup>	

**A12 Lecture courses attended**

CH4202 Advanced Synthetic Methods, 15 credits

Lecturers: Dr P. Jenkins and Dr S. Handa

**A13 Conferences attended**

Astra Zeneca Organic Chemistry Symposium, University of Loughborough, October 2009

East Midlands Meeting of the Organic Chemistry Division, University of Leicester, April 2010

10<sup>th</sup> Annual RSC Fluorine Subject Group Postgraduate Meeting, Durham University, September 2010

RSC Organic Chemistry Midlands Meeting, University of Loughborough, April 2011

11<sup>th</sup> Annual RSC Fluorine Subject Group Postgraduate Meeting, University of Aberdeen, September 2011

RSC Organic Chemistry Midlands Meeting, University of Warwick, April 2012

12<sup>th</sup> Annual RSC Fluorine Subject Group Postgraduate Meeting, University of St. Andrews, August 2012

**A14 Presentations**

Poster – “Synthesis of 8-Fluoroquinidine and 8-Fluoroquinine Analogues for Asymmetric Fluorination.” Presented at RSC Organic Chemistry Midlands Meeting, University of Loughborough, April 2011, and also at Annual Chemistry Department Postgraduate Research Day, University of Leicester, June 2011

Poster – “Syntheses of Asymmetric Transfer Fluorinating Reagents Based on *Cinchona* Alkaloids.” Presented at RSC Organic Chemistry Midlands Meeting, University of Warwick, April 2012

Presentation – “Synthesis and Applications of Structurally Modified *Cinchona* Alkaloids.” Presented at Annual Chemistry Department Postgraduate Research Day, University of Leicester, June 2012

Presentation – “Synthesis and Applications of Structurally Modified *Cinchona* Alkaloids.” (Updated) Presented at 12<sup>th</sup> Annual RSC Fluorine Subject Group Postgraduate Meeting, University of St. Andrews, August 2012