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By

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Statement of Originality

The experimental work in this thesis has been carried out by the author in the Department of Chemistry at the University of Leicester between September 2004 and October 2007. The work has not been submitted, and is not presently submitted, for any other degree at this or any other university.

Signed..... Date.....

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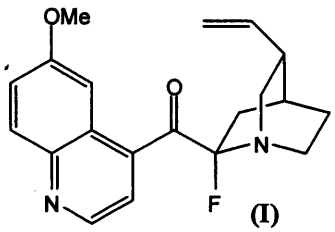
Structural Modification of Cinchona Alkaloids for the Synthesis of Novel Chiral Fluorinating Agents

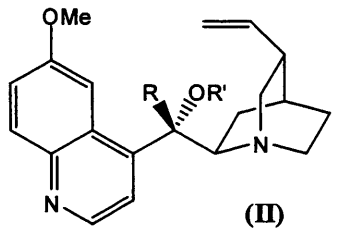
Carla M. Jones

Abstract

The diastereoisomers, 8-fluoroquinidinone **(I)** and 8-fluoroquininone, were synthesised, separated and their structures were determined by HOESY spectroscopy and X-ray crystallography. The addition of a methyl group to the carbonyl of 8-fluoroquinidinone led to a single diastereoisomer of 8-fluoro-9-methyl quinidine and NOESY spectroscopy strongly suggested the 8-(*S*), 9-(*S*) configuration. Although the introduction of fluorine at the C8 position prevented the mutarotation of the ketones in solution, the strong electron-withdrawing effect of the fluorine also reduced the nucleophilicity of the quinuclidine nitrogen.



(I)



(II)

R = Me, Et, Ph
R' = H, Ac, *p*-ClBz

A small library of new derivatised cinchona alkaloids containing a quaternary carbon at the C9 position **(II)** were synthesised in three steps. After oxidising quinine to quinidinone, the diastereoselective addition of methylmagnesium iodide, methylmagnesium bromide, ethylmagnesium bromide and phenylmagnesium bromide to the ketone was developed. The hydroxyl function was protected in the third step with an acetyl or *p*-chlorobezoyl group and finally, the quinuclidine nitrogen of the new quinidine analogues was fluorinated using Selectfluor and NFSI for the synthesis of novel asymmetric fluorinating agents.

The novel modified cinchona alkaloids were screened in the asymmetric fluorinations of the β-ketoesters, ethyl 1-indanone-2-carboxylate and *tert*-butyl 1-indanone-2-carboxylate, and the acyclic ester, ethyl α-cyano-*p*-tolylacetic acid. High isolated yields were obtained in most cases and both 9-methylquinidine and 9-phenylquinidine gave improved enantioselectivity of 38 % and 36 % ee compared to the 30 % ee obtained with quinidine in the fluorination of ethyl 1-indanone-2-carboxylate.

The ease at which the derivatised quinidines could be quaternised was also investigated leading to the synthesis of two novel quaternary ammonium salts, *N*-benzyl-9-methylquinidinium bromide and *N*-benzyl-*O*-acetyl-9-methylquinidinium bromide. This new class of chiral quaternary ammonium salts could potentially be used in asymmetric phase transfer catalysis.

Acknowledgments

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I must also thank my family for their love, support and for being there to listen when things go wrong or right. I appreciate that you probably did not understand half of what I said. A special thanks goes to my parents for providing free accommodation throughout my PhD (I will remember that when it comes to choosing your care home).

Finally, I have to thank some very special people, Pedro Villuendas, James Bennet, Jose Vidal, Dan Duncan, Andy West, Donna Palmer, Kiran Rakkar, Michal Fornalczyk and the rest of the Fluorine Group for providing excellent company during the long days in the lab and at the various social gatherings in order to make the past four years the most enjoyable so far.

Contents

Chapter Five

Experimental Procedures

List of Abbreviations

Ac	Acetyl fragment
Ad	Adamantyl fragment
AIBN	Azobisisobutyronitrile
Ar	Aryl fragment
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BMS	Bristol-Myers Squibb
Bn	Benzyl fragment
Boc	*tert*-Butyloxycarbonyl
BOX	Bisoxazoline
Bu	Butyl fragment
Bz	Benzoyl fragment
CA	Cinchona alkaloid
CD	Cinchonidine
CN	Cinchonine
Cy	Cyclohexyl fragment
d	Doublet
Dbfox	Dibenzofurandiyloxazoline
DCM	Dichloromethane
DHCD	Dihydrocinchonidine
DHCN	Dihydrocinchonine
$(DHQ)_2AQN$	Dihydroquinine (anthraquinone-1,4-diyl) diether
$(DHQD)_2AQN$	Dihydroquinidine (anthraquinone-1,4-diyl) diether
DHQD	Dihydroquinidine
DHQDA	Dihydroquinidine acetate
$(DHQD)_2PHAL$	Dihydroquinidine 1,4-phthalazinediyl diether
$(DHQD)_2PYR$	Dihydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether
DHQN	Dihydroquinine
DHQNB	Dihydroquinine *p*-Chlorobenzoate
$(DHQ)_2PHAL$	Dihydroquinine 1,4-phthalazinediyl diether
$(DHQ)_2PYR$	Dihydroquinine-2,5-diphenyl-4,6-pyrimidinediyl diether
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide

DNA	Deoxyribonucleic acid
DTBM-SEGPHOS	(*R*)-(−)-5,5′-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl) phosphino]-4,4′-bi-1,3-benzodioxole
E	General Electrophile
ee	Enantiomeric excess
EI	Electron impact
ES	Electrospray
Et	Ethyl fragment
ether	Diethyl ether
FAB	Fast Atom Bombardment
GABA	Gamma-aminobutyric acid
Hex	Hexyl fragment
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
hmim	1-Hexyl-3-methylimidazolium
HMQC	Heteronuclear Multiple Quantum Coherence
HOESY	Heteronuclear Overhauser Enhancement Spectroscopy
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	hertz
Im	Imidazole fragment
IPA	Isopropyl alcohol
J	Coupling Constant
LDA	Lithium diisopropylamide
m	Multiplet
M. p.	Melting point
*m*CPBA	*m*-Chloroperoxybenzoic acid
Me	Methyl fragment
MTBE	Methyl-*tert*-butyl ether
napht	Naphthalene fragment
NFSI	*N*-Fluorobenzenesulphonimide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser Enhancement Spectroscopy
OMs	Mesylate fragment
OTf	Triflate fragment
OTs	Tosylate fragment
Pent	Pentyl fragment

Ph	Phenyl fragment
ppm	Parts per million
Pr	Propyl fragment
q	Quartet
QD	Quinidine
QN	Quinine
R	General alkyl or aryl fragment
r.t.	Room Temperature
s	Singlet
SEGPHOS	5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
Selectfluor	1-Chloromethyl-4-Fluoro-1, 4-Diazoniabicyclo[2.2.2]Octane Bis-(Tetrafluoroborate)
t	Triplet
TADDOL	(-)-trans-α, α '-(Dimethyl-1,3-dioxolane-4,5-diyl) bis(diphenylmethanol)
TBME	Methyl-*tert*-butyl ether
TBS	*tert*-Butyldimethylsilyl fragment
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl fragment
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl fragment
X	General counterion

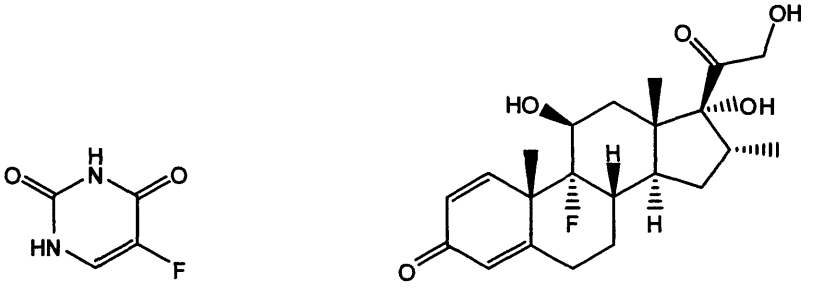
Chapter One

University of Leicester

Introduction

1.1 Fluoraza Reagents

The replacement of hydrogen or a hydroxyl group for fluorine is a common tool in medicinal chemistry, since compounds containing a fluorine atom have very different characteristics to their non-fluorine containing counterparts. The biological activity is greatly influenced as not only does the introduction of fluorine affect the pharmokinetic properties of a compound, but also its pharmodynamics and toxicology. These characteristics are also desirable in the agrochemical industry where the number of new fluorine containing compounds synthesised has increased 3-fold in the last 30 years.[1] The replacement of a hydroxyl group for fluorine is particularly interesting as the latter can only accept hydrogen bonds whereas the former can both accept and donate. The small size of fluorine combined with the fact that it is the most electronegative element means that is forms short, strong polarised bonds. The strength of the C-F bond is the main reason why the introduction of fluorine onto aromatic rings is common as it reduces the rate of oxidative metabolism.

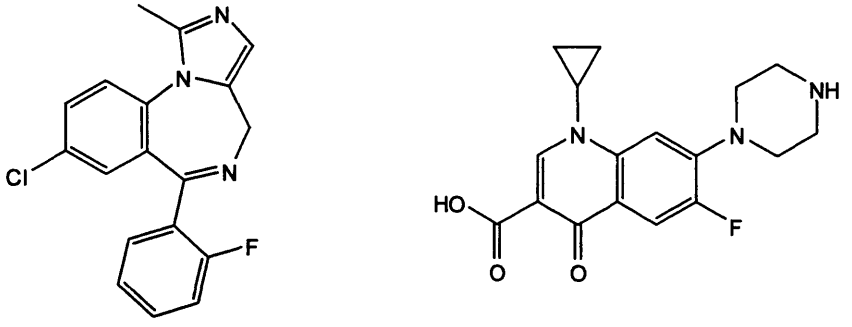


5-Fluorouracil Dexamethasone

Figure 1.1 *The Structures of 5-Fluorouracil and Dexamethasone*

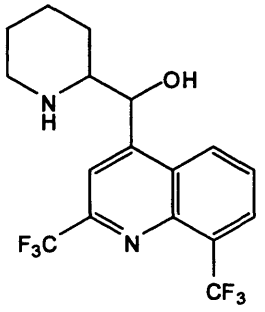
There are many fluorinated drugs on the market and the most successful are 5-fluorouracil and the range of fluorinated glucocorticoid steroids (Figure 1.1). 5-Fluorouracil is an anti-metabolite used in the treatment of cancer. It works by inhibiting the thymidylate synthase enzyme which synthesises pyrimidine thymidine, a nucleotide needed for DNA replication. Dexamethasone is an anti-inflammatory and immunosuppressant. It is used in the treatment for rheumatoid arthritis, but it is also given to patients after the removal of wisdom teeth and to cancer patients to counteract certain side effects of their treatment. Fluorinated steroids generally have a higher anti-inflammatory potency than the non-fluorinated counterparts and so the introduction of the fluorine means that Dexamethasone is 20-30 times more potent than hydrocortisone. Other fluorinated medicines include Midazolam, that has an inhibitory effect on the central nervous system by binding to the $GABA_A$ receptor making it a

useful general anaesthetic; Ciprofloxacin, an antibiotic, works by blocking the enzyme DNA gyrase thus preventing DNA replication; Linezolid, an antibiotic used to treat methicillin-resistant *Staphylococcus aureus* (MRSA); Mefloquine, an anti-malarial and a synthetic analogue of quinine and Haloperidol, a potent antipsychotic (Figure 1.2).

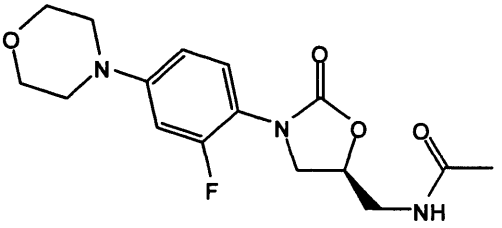


Midazolam
(general anesthetic)

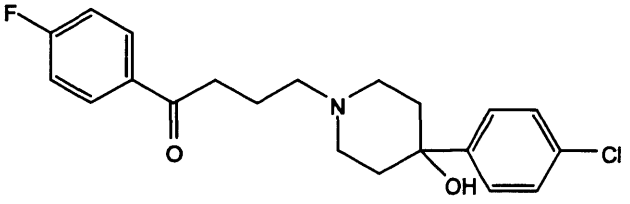
Ciprofloxacin
(antibiotic)



Mefloquine
(anti-malarial)



Linezolid
(antibiotic)

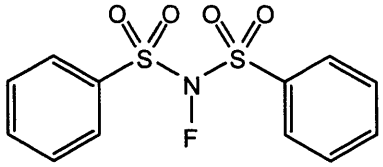


Haloperidol
(antipsychotic)

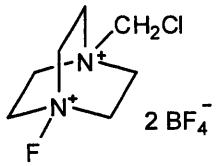
Figure 1.2 *A Range of Fluorinated Drugs Currently on the Market*

Organofluorine compounds occur very rarely in nature so virtually all fluorinated compounds have to be synthesised. There are many different types of fluorinating reagents and synthetic methods for the fluorination of organic molecules, but the most successful are the fluoraza reagents. The fluoraza reagents contain an N-F bond and are an electrophilic source of fluorine. They are much safer, easier to handle and more selective than the previous electrophilic fluorinating reagents, which include elemental fluorine[2] (highly toxic, very reactive), the hypofluorites[3] (potentially explosive), xenon difluoride[4] (expensive) and

perchloryl fluoride (toxic gas). There are two classes of fluoraza reagents, the neutral N-F type, represented by NFSI (*N*-fluorobenzenesulphonimide) **(1)** and the quaternary $[N\text{-}F]^+$ type represented by probably the most popular electrophilic fluorinating reagent, Selectfluor **(2)**[5] (Figure 1.3).



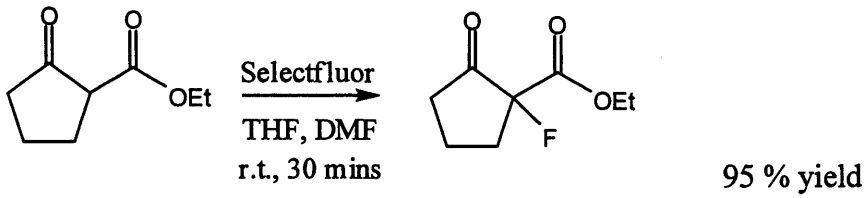
(1)



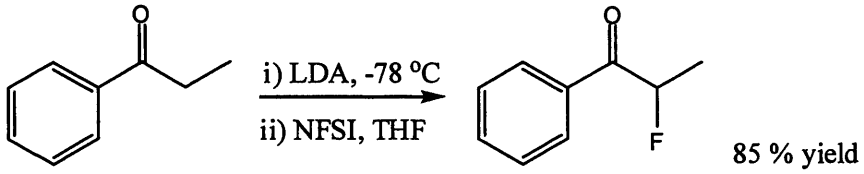
(2)

Figure 1.3 *The Structures of NFSI and Selectfluor*

Selectfluor and NFSI can be used to fluorinate a range of nucleophilic substrates such as activated aromatics, stabilised carbanions and activated olefins e.g. silyl enol ethers, enamines and enol acetates.[6] Overall, Selectfluor is a more powerful fluorinating reagent than NFSI and can be used to fluorinate activated aromatics. On the other hand, NFSI is normally the reagent of choice for the fluorination of reactive metal enolates, especially since it is soluble in many common organic solvents such as ether and THF, whilst Selectfluor is only soluble in polar organic solvents such as acetonitrile and methanol. For example, Selectfluor can fluorinate β-dicarbonyl compounds via their enol to give the fluorinated product in high yields (Scheme 1.1), whereas the fluorination of monocarbonyl compounds with Selectfluor was not so good, but the use of NFSI was much more effective (Scheme 1.2).[7]

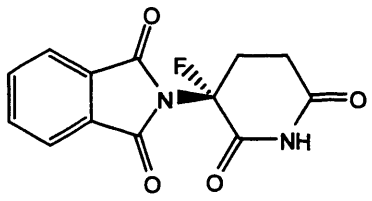


Scheme 1.1 *The Fluorination of a β-Dicarbonyl Compound with Selectfluor.*

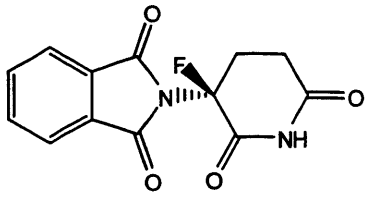


Scheme 1.2 *The Fluorination of a Monocarbonyl Compound with NFSI*

The fluorinations of organic compounds with Selectfluor and NFSI proceed with some regioselectivity, but as organofluorine compounds are widely used in medicinal chemistry, the development of an enantioselective fluorination reaction was the obvious next step. An example of where asymmetric fluorination is important is during the synthesis of 3-fluorothalidomide (Figure 1.4).[8] Thalidomide itself was marketed as a racemic mixture and the (*R*)-enantiomer was responsible for the sedative hypnotic effect of the drug whilst the (*S*)-enantiomer possessed the notorious teratogenic properties. The main problem with this compound was that under physiological conditions, it rapidly epimerises due to a very acidic hydrogen at the stereogenic centre. One method of preventing this epimerisation was to replace the hydrogen with a methyl group, but this led to a much weaker drug due to the steric alterations caused by its introduction.[9] More recently, (*R*)- and (*S*)-3-fluorothalidomide were synthesised as the fluorine atom is much smaller than a methyl group, so removing any steric effects and also a C-F bond is much stronger than a C-H bond thus preventing the possibility of epimerisation. These new compounds have led to a series of non-racemisable analogues of thalidomide which keep the benefits of the original drug but do not contain the terrible teratogenic effects.



(3*R*)-fluorothalidomide

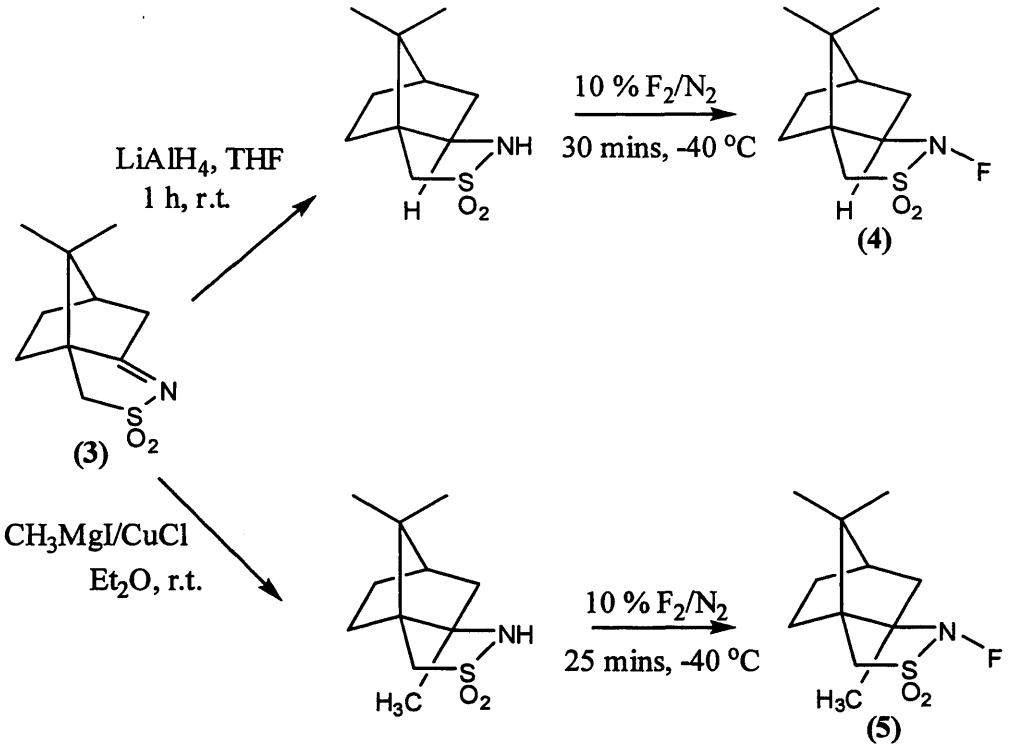


(3*S*)-fluorothalidomide

Figure 1.4 *The (R)- and (S)- Enantiomer of 3-Fluorothalidomide*

There are two main approaches to asymmetric fluorination under investigation in the literature.[10,11] The first involves the use of a chiral fluorinating reagent,[12] while the second uses Selectfluor or NFSI in combination with a chiral catalyst.[13,14] Both routes have their advantages and disadvantages. A stoichiometric amount of the chiral fluorinating reagent is required in the fluorination of a substrate, whereas only a catalytic amount of the chiral catalyst is needed, which at most is 30 mol %, but often the catalyst loadings are much lower. The major advantage of chiral fluorinating reagents is that they can fluorinate a wider range of substrates compared to the chiral catalysts, where the range of substrates is mainly restricted to β-ketoesters, β-ketophosphonates and oxindoles. Recent work, however, has demonstrated that by using a chiral secondary amine as an organocatalyst, aldehydes can also be fluorinated in good yields and enantioselectivities.

1.2 Chiral Fluorinating Reagents



Scheme 1.3 *The Synthesis of N-Fluorosultams (4) and (5)*

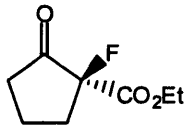
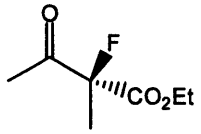
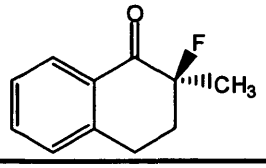
Entry	Product	Reaction Conditions	Yield (%)	ee (%)
1		NaH, Et_2O, 0 °C - r.t. **(4)**(1.5 equiv.)	63	70
2		LiH, Et_2O, r.t. **(4)** (1.3 equiv.)	31	≤10
3		LDA, THF, -78 °C - r.t. **(4)** (1.2 equiv.)	27	32
4		LDA, THF, -78 °C - r.t. **(4)** (1.2 equiv.)	≤5	35

Table 1.1 *The Fluorination of Metal Enolates with Reagent (4)*

In 1988, Differding and Lang[15] synthesised the first enantioselective fluorinating agents, **(4)** and **(5)** (Scheme 1.3). The *N*-fluorosultam **(4)** was synthesised from the imine **(3)**, which was easily prepared in two steps from commercially available (+)-camphor-10-

sulphonyl chloride. Various metal enolates were generated under standard conditions and fluorinated to their respective α-fluoro carbonyl compounds using the *N*-fluorosultam **(4)**. It was found that the enantiomeric excess was heavily dependant on the structure of the metal enolate (Table 1.1).

The fluorination of ethyl cyclopentanone-2-carboxylate gave the best result with 70 % ee and 63 % yield (Table 1.1, entry 1). The fluorination of other ester or ketone enolates gave low enantioselectivities and low yields that were generally below 30 % due to a competing secondary reaction. Under the reaction conditions, the enolate eliminates HF from the sultam to give the imine **(3)** and the starting carbonyl compound. To prevent HF elimination *N*-fluorosultam **(5)** was synthesised, but in the fluorination of metal enolates, poor enantioselectivities and yields ($\leq$ 10 %) were obtained.

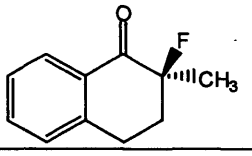
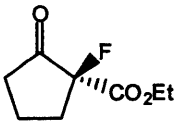
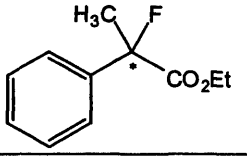
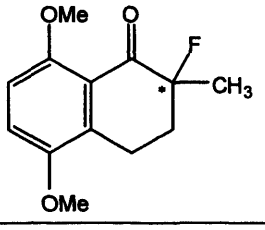
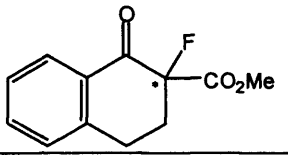
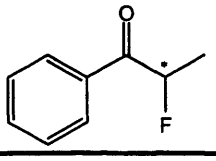
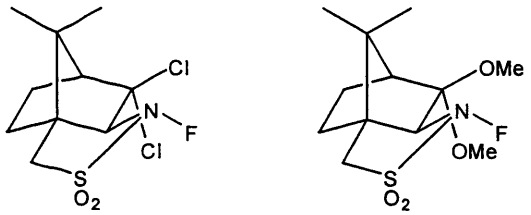
Entry	Product	Reaction Conditions	Yield (%)	ee (%)
1		NaHMDS, THF, -78 - 0 °C (+)-**(6)** (0.8 equiv.)	53	76
2		NaH, Et_2O, -78 - 0 °C (+)-**(6)** (0.8 equiv.)	59	34
3		LDA, THF, -78 °C (+)-**(6)** (1.5 equiv.)	29	62
4		NaH, THF, -78 °C (+)-**(6)** (1.5 equiv.)	95	46
5		KHMDS, THF, -78 °C (+)-**(6)** (1.5 equiv.)	90	41
6		NaHMDS, THF, -78 °C - r.t. (+)-**(6)** (1.5 equiv.)	41	0

Table 1.2 *The Fluorination of Metal Enolates with Reagent (6)*

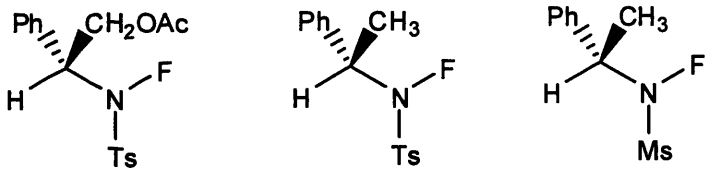


(6) (7)

Figure 1.5 *N-Fluorosultams Synthesised by Davis*

Davis[16,17] improved on this work by synthesising both enantiomers of *N*-fluoro-2, 10-(3,3-dichlorocamphorsultam) **(6)** (Figure 1.5). This compound gave generally better enantioselectivities and yields when reacted with metal enolates and the highest enantioselectivity obtained was 76 % ee in the formation of 2-fluoro-2-methyl tetralone (Table 1.2, entry 1). However, the fluorinations of β-keto ester enolates generally gave around 34 - 46 % ee (Table 1.2). *N*-Fluoro-2,10-(3,3-dimethoxycamphorsultam) **(7)** was also synthesised and used to fluorinate various metal enolates. While this compound gave good yields, it only gave very poor enantioselectivities (<5 % ee). The only secondary enolate to be fluorinated, the sodium enolate of propiophenone, gave a racemic product because it easily undergoes base catalysed epimerisation under the reaction conditions due to the increased acidity of the α-fluoro proton (Table 1.2, entry 6).

Takeuchi attempted to design new N-F reagents from readily available chiral amines that could easily be structurally modified. The new reagent must be stable and produce efficient enantioselective fluorination. The first reagents were based on the amino acid derivatives, *N*-tosyl and *N*-mesyl-D-phenylglycine ethyl esters **(8)**, **(9)** and **(10)** (Figure 1.6).[18]

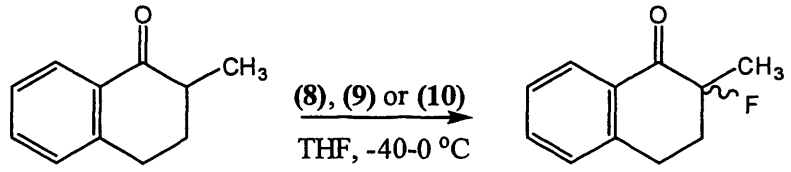


(8) **(9)** **(10)**

Figure 1.6 *The N-F Reagents Synthesised by Takeuchi*

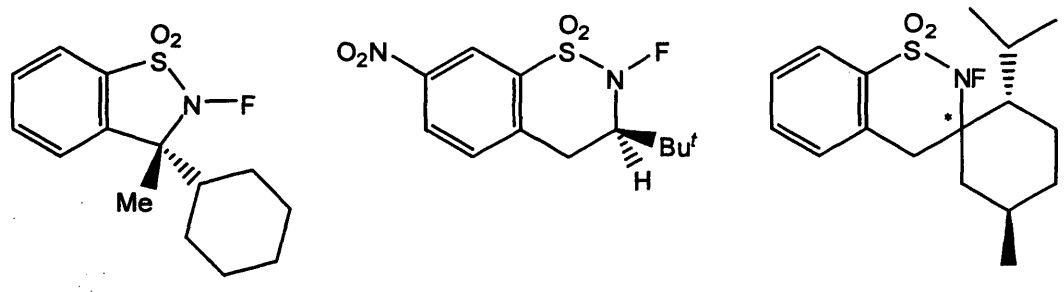
The new enantioselective fluorinating reagents were tested in the fluorination of the metal enolate of 2-methyl-1-tetralone (Table 1.3) but, unfortunately, the results in terms of both yield and enantioselectivity were poor. In an attempt to improve the reaction, other

substrates (2-benzyl-1-tetralone, ethyl 2-oxocyclopentanecarboxylate and ethyl 2-benzoyl-propionate) were fluorinated, but again poor yields and enantioselectivities were observed.



Entry	Fluorinating Reagent	Base	Yield (%)	ee (%)
1	**(8)** (1.1 equiv.)	LDA	12	2
2	**(8)** (1.1 equiv.)	KHMDS	8	8
3	**(9)** (1.1 equiv.)	LDA	16	46
4	**(9)** (2.0 equiv.)	LDA	37	32
5	**(9)** (1.1 equiv.)	NaH	0	0
6	**(9)** (1.1 equiv.)	KH	0	0
7	**(9)** (1.1 equiv.)	KHMDS	46	46
8	**(9)** (1.1 equiv.)	LHMDS	3	46
9	**(9)** (1.1 equiv.)	NaHMDS	16	32
10	**(10)** (0.9 equiv.)	LDA	11	20

Table 1.3 *The Fluorination of 2-Methyl-1-tetralone with Fluorinating Reagents (8), (9) and (10)*



(11) **(12)** **(13)**

Figure 1.7 *The Three N-Fluorosulfonamides Synthesised by Takeuchi and Shibata*

Undeterred by the initial results Takeuchi and Shibata synthesised three novel N-F sulfonamides **(11)**,[19] **(12)**,[20] and **(13)**[21] that were designed to have a stable but reactive N-F bond and also steric factors that would favour asymmetric induction (Figure 1.7). *N*-Fluoro-3-cyclohexyl-3-methyl-2,3-dihydrobenzo[1,2-*d*]-isothiazole 1,1-dioxide **(11)** was synthesised in five steps from saccharin and was used to fluorinate metal enolates of 1-tetralones, 1-

indanones and 1-benzosuberones with moderate yields and poor to moderate enantioselectivities (Table 1.4). The exception was the reaction of **(11)** with 2-benzyl-1-tetralone that gave 2-fluoro-2-benzyl-1-tetralone in 79 % yield and 88 % ee (Table 1.4, entry 1). One interesting finding was that the fluorination of 2-methyl-1-indanone with (*R*)-**(11)** gave the (*S*)-product in 54 % yield and 54 % ee, while the fluorination with (*S*)-**(11)** gave the (*R*)-product in 62 % yield and 48 % ee. This proves the theory that one enantiomer of the chiral reagent would lead to one enantiomer of the fluorinated product, while the other enantiomer of the chiral reagent would give the other enantiomer of the product.

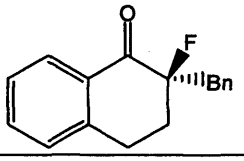
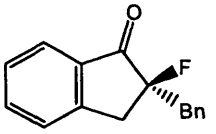
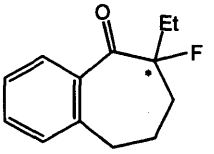
Entry	Product	Reaction Conditions	Yield (%)	ee (%)
1		LDA, THF, -78 °C (*R*)-**(11)** (1.1 equiv.)	79	88
2		LDA, THF, -78 °C (*R*)-**(11)** (1.1 equiv.)	63	54
3		LDA, THF, -78 °C (*R*)-**(11)** (1.1 equiv.)	48	43

Table 1.4 *The Fluorination of Metal Enolates with Reagent (11)*

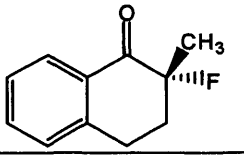
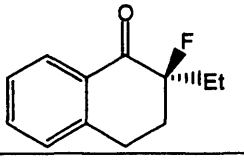
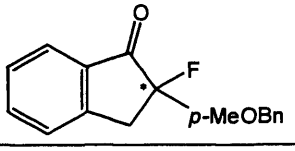
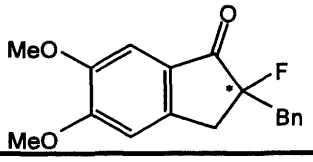
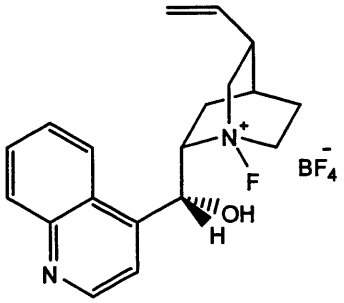
Entry	Product	Reaction Conditions	Yield (%)	ee (%)
1		LHMDS, THF, -78 °C (*R*)-**(12)** (1.2 equiv.)	79	62
2		LHMDS, THF, -78 °C (*S*)-**(12)** (1.2 equiv.)	70	69
3		LHMDS, THF, -78 °C (*R*)-**(12)** (1.2 equiv.)	76	44
4		LHMDS, THF, -78 °C (*S*)-**(12)** (1.2 equiv.)	56	60

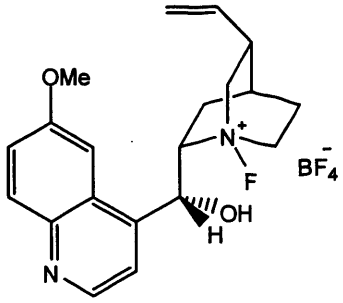
Table 1.5 *The Fluorination of Metal Enolates with Reagent (12)*

During the development of **(11)**, it was noted that the steric bulk of the R groups at the chiral centre α to the nitrogen affected the enantioselectivity of the fluorination reaction. With this in mind, *N*-fluoro-3-*tert*-butyl-7-nitro-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxide **(12)** was synthesised. When **(12)** was used to fluorinate metal enolates of 1-tetralones and 1-indanones the results were moderate (Table 1.5). All yields were between 40-79 % and enantiomeric excesses between 43-69 %. Although the 79 % yield and 88 % ee obtained by **(11)** wasn't exceeded, the results were generally better for **(12)** than **(11)**.

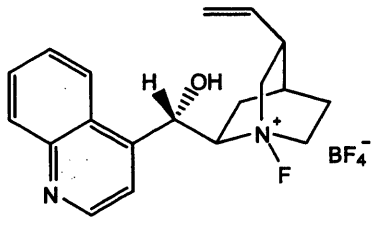
Takeuchi and Shibata synthesised both enantiomers of 2-fluoro-14-methyl-11-(methylethyl)-spiro[4*H*-benzo[e]-1,2-thiazine-3,2'-cyclohexane]-1,1-dione, **(13a)** [11*S*, 12*R*, 14*R*] and **(13b)** [11*S*, 12*S*, 14*R*] and used them to fluorinate pre-formed enolates of aryl ketones. Although **(13a)** exhibited much better enantioselectivity than **(13b)**, **(13a)** only gave modest results. The best result was the fluorination of the metal enolate of 2-methyl-1-tetralone that gave 65 % yield and 70 % ee, but the rest were comparable to the *N*-fluoro-camphorsultams developed by Differding, Lang and Davis.



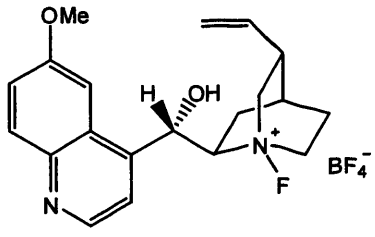
F-CD-BF_4 **(14)**



F-QN-BF_4 **(15)**



F-CN-BF_4 **(16)**

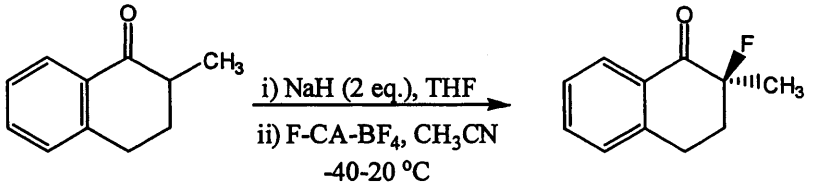


F-QD-BF_4 **(17)**

Figure 1.8 *The Four N-F Reagents Synthesised by Cahard*

The major breakthrough in reagent-controlled enantioselective fluorination happened in 2000 when Cahard[22] and Shibata[23] simultaneously, but independently, synthesised the *N*-fluoro ammonium salts of cinchona alkaloids. These compounds formed a new class of

charged $[N\text{-}F]^+$ enantioselective fluorinating agents. Cahard's group initially formed the *N*-fluoro ammonium salts of four naturally occurring cinchona alkaloids, quinidine, quinine, cinchonidine and cinchonine (Figure 1.8). Whereas the development of the previous reagents involved multi-step syntheses and the formation of the N-F bond by either elemental fluorine or $FClO_3$, these $[N\text{-}F]^+$ reagents were synthesised by a simple one step transfer fluorination of the cinchona alkaloid with Selectfluor. Transfer fluorination reactions were described by Banks using Selectfluor and the simpler but analogous quinuclidine tetrafluoroborate.[24] It was found that the thermodynamic driving force for the reaction was the relief from the dication state of Selectfluor to two mono cations of ammonium salts.[12]



Entry	$[N\text{-}F]^+$	Yield (%)	Ee (%)	Configuration
1	F-CD-BF_4 **(14)**	98	50	(*S*)
2	F-QN-BF_4 **(15)**	98	20	(*S*)
3	F-CN-BF_4 **(16)**	70	40	(*R*)
4	F-QD-BF_4 **(17)**	87	27	(*R*)

Table 1.6 *The Fluorination of an Aryl Ketone with $[N\text{-}F]^+$ Cinchona Alkaloid Reagents **(14)**, **(15)**, **(16)** and **(17)***

When the four reagents, *N*-fluorocinchonidinium tetrafluoroborate (F-CD-BF_4) **(14)**, *N*-fluoroquininium tetrafluoroborate (F-QN-BF_4) **(15)**, *N*-fluorocinchoninium tetrafluoroborate (F-CN-BF_4) **(16)** and *N*-fluoroquinidinium tetrafluoroborate (F-QD-BF_4) **(17)** were used to fluorinate metal enolates of aryl ketones, the yields of the α-fluoro carbonyl products were moderate (40-50 %). The reason for this was that the free hydroxyl group on the alkaloid was protonating the enolate and so 2 equivalents of the base were needed to circumvent this problem. The reactions were then repeated and the chemical yields obtained were much higher than previously reported (Table 1.6). This was probably due to the greater fluorinating power of the $[N\text{-}F]^+$ reagents compared to the neutral N-F compounds. The *N*-fluorocinchona alkaloid reagents were also less substrate dependant and it was possible to fluorinate silyl enol ethers which do not react with neutral N-F reagents. The trimethylsilyl enol ether of 2-methyl-1-tetralone was fluorinated in an excellent yield (93 %) and with a very promising enantioselectivity (61 % ee).

Cahard[25] carried out the first enantioselective fluorination of α-amino acid derivatives by reacting the preformed ester enolate or nitrile anion with an *N*-fluoro cinchona alkaloid. When the four naturally occurring cinchona alkaloids **(14)**, **(15)**, **(16)**, **(17)**, were used in this reaction though, the enantioselectivity was poor to moderate (7-48 % ee). The group then decided to examine the structure of the cinchona alkaloid to find out what factors affected the enantioselectivity in order to improve the results (Figure 1.9).

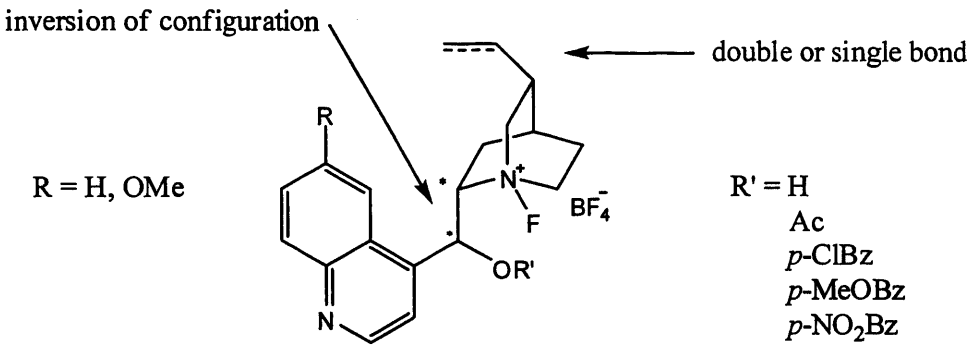
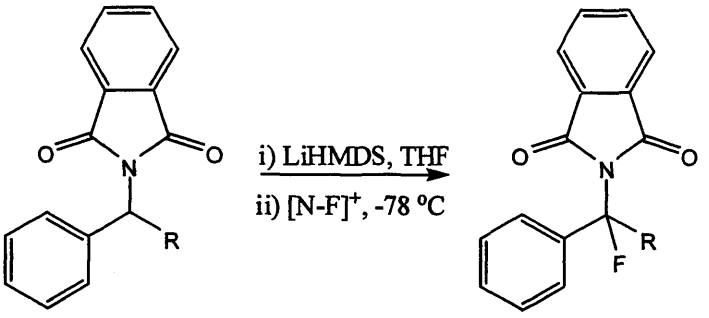


Figure 1.9 *Modifications of the Cinchona Alkaloid Structure*

Since, the free hydroxyl group on the alkaloid protonates the enolate, acetyl and benzoyl groups were used to protect the hydroxyl group on the cinchona alkaloid structure and a new range of $[N\text{-}F]^+$ reagents were formed. These were used to fluorinate various imido-protected (phthaloyl, tetrachlorophthaloyl, succinoyl, dimethylmaleoyl) phenylglycine esters (methyl, ethyl, benzyl), phenylglycinonitrile, and phenylglycine *N,N*-diethylamides to give the corresponding α-fluorinated products. It was observed that the phthaloyl protected compounds gave better enantioselectivity than the succinoyl and dimethylmaleoyl protected compounds, so for simplicity, work concentrated on two compounds, *N*-phthaloyl-α-aminophenylglycine ethyl ester **(18)** and phenylglycinonitrile **(19)** (Table 1.7).

Under the reaction conditions, *N*-phenylglycinonitrile **(19)** showed better enantiomeric excesses than *N*-phthaloyl phenylglycine ethyl ester **(18)**. Also, reagents based on cinchonidine (CD) and quinine (QN) gave better enantioselectivity than their psuedoenantiomers, cinchonine (CN) and quinidine (QD), that give the opposite enantiomer of the α-fluorinated product. Quinine type reagents gave higher enantioselectivities than cinchonidine types when forming one enantiomer and quinidine derivatives gave higher enantiomeric excesses than cinchonine derivatives when forming the other enantiomer. This suggests that the methoxy substituent on the quinoline ring, the only difference between quinine, cinchonidine and quinidine, cinchonine, plays a part in the enantioselectivity. The other important point was that the hydroxyl protection was essential for high enantioselectivity, though the nature of the protecting group was substrate dependant. In the

ester series, the acetyl protecting group led to higher enantioselectivities, while in the nitrile series, the benzoyl protecting group gave higher enantioselectivities though there was no significant improvement in changing the para substituents on the ring. The best result was the fluorination of *N*-phthaloylphenylglycinonitrile with *O*-(*p*-methoxybenzoyl)-*N*-fluoroquininium tetrafluoroborate (F-*p*MeOBzQN-BF_4) which gave 94 % ee.

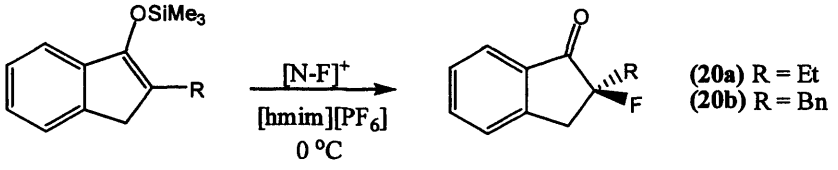


[N-F]$^+$ Reagent	R = CO_2Et (18)		R = CN (19)	
	Yield (%)	ee (%)	Yield (%)	ee (%)
F-CD-BF_4	65	8	48	36
F-AcCD-BF_4	87	42	91	52
F-AcQN-BF_4	79	76	88	80
F-*p*ClBzQN-BF_4	73	68	70	91
F-*p*ClBzDHQN-BF_4	86	76	65	92
F-*p*MeOBzQN-BF_4	64	66	56	94
F-*p*NO_2BzQN-BF_4	60	60	58	90
F-CN-BF_4	62	26	68	48
F-*p*ClBzCN-BF_4	67	28	70	66
F-AcDHQD-BF_4	60	50	72	75
F-*p*ClBzDHQD-BF_4	65	38	64	82

Table 1.7 *The Fluorination of N-phthaloyl-α-aminophenylglycine ethyl ester (18) and N-phenylglycinonitrile (19) with Cinchona Alkaloid Derivatives*

Cahard also investigated asymmetric fluorinations in ionic liquids since reagents having ionic character can be immobilised in these solvents.[26] Work concentrated mainly on [hmim][PF_6] (1-hexyl-3-methylimidazolium hexafluorophosphate) as the solvent due to its higher fluidity making stirring easier. Ionic liquids have many advantages over classical solvents and they are seen particularly as replacements for volatile solvents as they have no vapour pressure.[27-30] There are many examples in the literature where asymmetric syntheses have been carried out in this media, but they were usually transition metal catalysed [31-34]

though some involving biocatalysts have also been reported.[35-37] A range of benzoyl and naphthoyl protected quinine-based N-F reagents were used to fluorinate the trimethylsilyl enol ethers **(20a)** and **(20b)** since they gave higher enantioselectivities in acetonitrile than other types of reagent. This fluorination also provided the first example of an enantioselective C-F bond formation reaction not to involve a metal catalyst or biocatalyst in ionic liquids. For simplicity, the $[N\text{-}F]^+$ reagents were created *in situ* by stirring the cinchona alkaloid with either Selectfluor or NFSI prior to the addition of the substrate. Interestingly, the transfer fluorination was five time faster with NFSI than Selectfluor and the enantioselectivities were better or equal to that obtained in acetonitrile (Table 1.8). The main advantage of this method was that the reaction could be carried out at 0 °C instead of -40 °C which was required for the acetonitrile reaction. Also, as the product was removed from the ionic liquid by extraction with ether, the recovered ionic liquid, containing the cinchona alkaloid, could be reused after the addition of another equivalent of Selectfluor or NFSI making it possible to repeat the reaction in the same vessel with no effect on the enantiomeric excess.



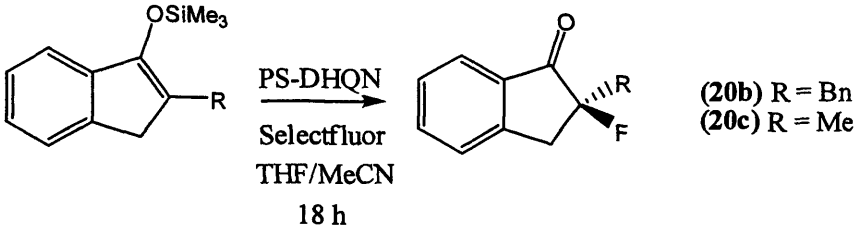
Entry	R	$[N\text{-}F]^+$ Reagent	Yield (%)	ee[a] (%)
1	Et	F-*p*ClBzQN-BF_4	82	82 (82)
2	Et	F-2NaphtQN-BF_4	98	83 (80)
3	Bn	F-*p*ClBzQN-BF_4	89	86 (82)
4	Bn	F-*p*ClBzCD-BF_4	61	73 (26)
5	Bn	F-*p*MeOBzQN-BF_4	74	84 (84)
6	Bn	F-1NaphtQN-BF_4	93	86 (75)
7	Bn	F-2NaphtQN-BF_4	87	84 (84)

[a] In brackets, the enantiomeric excess of the same reaction run in acetonitrile at -40 °C

Table 1.8 *The Fluorination of Silyl Enol Ethers in Ionic Liquids*

The use of polymer bound quaternary ammonium salts of cinchona alkaloids have been used with great effect in phase transfer catalysis.[38,39] It was thought that by anchoring the cinchona alkaloid onto a polystyrene support before or after the *N*-fluorination, could lead to easy physical separation from the product followed by subsequent reuse.[40] Therefore, *O*-(*p*-vinyl-benzoate) dihydroquinine was polymerised with a catalytic amount of AIBN (2,2'-azobisisobutyronitrile) in dry benzene to yield the supported catalyst (PS-QN). The supported

cinchona alkaloid was then fluorinated with Selectfluor (or NFSI) and the solution was added to the silyl enol ether **(20)** (Table 1.9). The results in terms of yield and enantioselectivity were good especially in the case of **(20b)** where a very respectable 86 % ee was achieved (Table 1.9, entry 4). During the recycling studies on this substrate, the same level of isolated yield and enantioselectivity could be obtained after four runs (Table 1.10).



Entry	R	Temp (°C)	Yield (%)	ee (%)`
1	Me	-40	95	48 (*R*)
2	Me	-78	68	59 (*R*)
3	Bn	-40	98	80 (*R*)
4	Bn	-78	72	86 (*R*)
5	Bn	-40	96	80 (*R*)[a]
6	Bn	-40	98	85 (*R*)[b]

[a] *NFSI was used as the fluorine source*
[b] *The PS-[QN-F]$^+$ reagent was isolated prior to the fluorination reaction*

Table 1.9 *The Fluorination of Silyl Enol Ethers with Polystyrene-Supported Quinine*

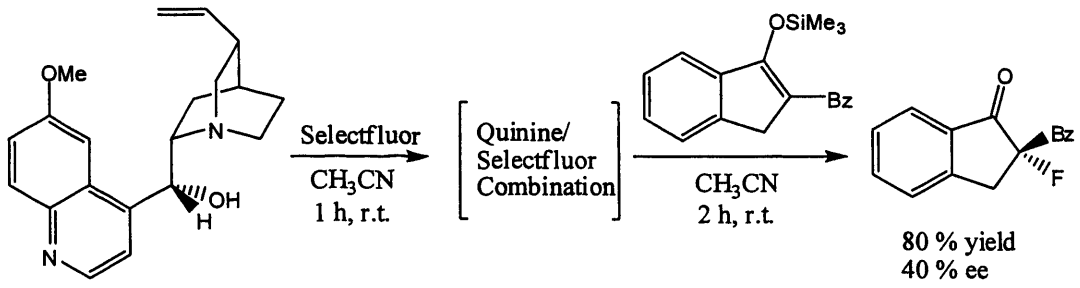
Run	Time (h)	Yield (%)	ee (%)
1	18	98	80
2	18	96	82
3	18	95	81
4	18	95	81

[a] *Reactions were run in THF/MeCN at -40 °C using NFSI as the fluorine source*

Table 1.10 *Recycling study of Poly [O-(4-vinylbenzoate) dihydroquinine] in the Enantioselective Fluorination of* ***(20b)***

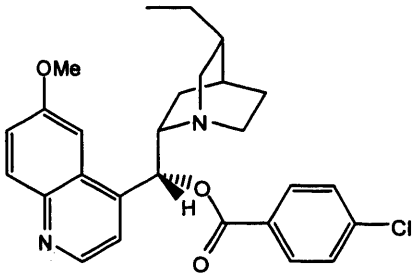
Shibata did not isolate any of the *N*-fluorocinchona alkaloids;[23,41,42] but instead preferred to make them *in situ* by stirring Selectfluor (1.2 equiv.) and the cinchona alkaloid hydrate (1.2 equiv.) in dry acetonitrile with 3Å molecular sieves (to remove water) for 1 h at room temperature. This combination was then added to the substrate without any further

purification. The first substrate to be fluorinated was (2-benzyl-3H-iden-1-yloxy)-trimethylsilane with a quinine/Selectfluor combination (Scheme 1.4).



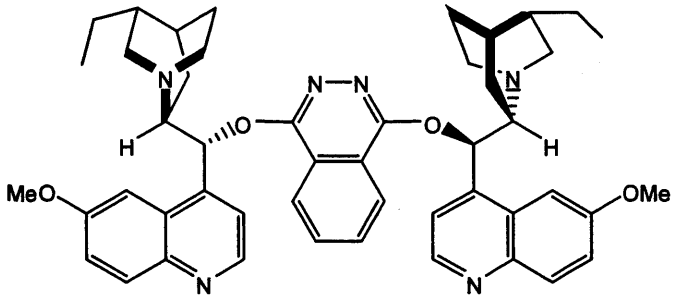
Scheme 1.4 *The Fluorination of (2-Benzyl-3H-inden-1-yloxy)trimethylsilane*

The good yield and promising enantioselectivity led to other cinchona alkaloid/Selectfluor combinations being investigated to try and improve on the initial result. After screening a range of combinations, dihydroquinine *p*-chlorobenzoate **(21)** (DHQNB)/Selectfluor and dihydroquinine 1,4-phthalazinediyl diether $(DHQ)_2PHAL$ **(22)**/Selectfluor proved to be the best reagents giving >80 % ee (Figure 1.10). As these two cinchona alkaloids gave similar results and dihydroquinine *p*-chlorobenzoate was cheaper than $(DHQ)_2PHAL$, dihydroquinine *p*-chlorobenzoate/Selectfluor was the combination that was used in further investigations.



Dihydroquinine *p*-Chlorobenzoate

(21)



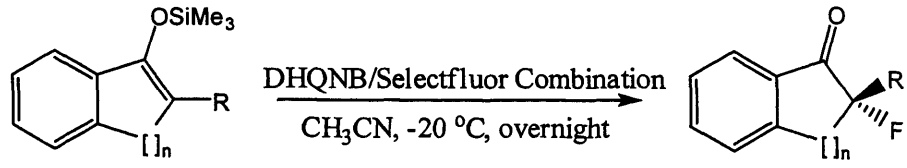
$(DHQ)_2PHAL$

(22)

Figure 1.10 *The Structures of Dihydroquinine p-Chlorobenzoate (DHQNB) (21) and $(DHQ)_2PHAL$ (22)*

When fluorinating indanones and tetralones, both dihydroquinine *p*-chlorobenzoate and $(DHQ)_2PHAL$ yielded the *(R)*-product. To obtain the *(S)*-product, either a quinidine/Selectfluor or a cinchonine/Selectfluor combination was used, but the enantioselectivity was lower. Other silyl enol ethers were fluorinated to investigate the generality of this combination and high yields and moderate to high enantioselectivities were

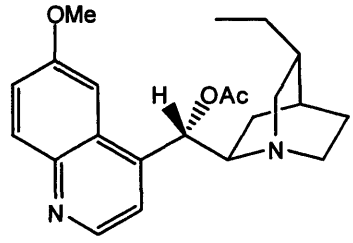
obtained (Table 1.11). To investigate whether the enantioselectivity of this reaction could be improved, Shibata, like Cahard, modified the cinchona alkaloid structure by esterification. A range of dihydroquinine derivatives were produced where benzoate (benzoate, *p*-nitrobenzoate, *p*-methoxybenzoate) or acetate (acetate, 1-naphthalenecarboxylate, anthraquinone-2-carboxylate, trifluoroacetate) groups replaced the *p*-chlorobenzoate group. These derivatives were just as effective as dihydroquinine *p*-chlorobenzoate **(21)**.



Entry	n	R	Yield (%)	ee (%)	Configuration
1	1	Bn	99	89	(*R*)
2	1[a]	Bn	86	91	(*R*)
3	1	Me	93	54	(*R*)
4	1	Et	99	73	(*R*)
5	2	Me	94	42	(*R*)
6	2[b]	Et	71	67	(*R*)
7	2	Bn	95	71	(*S*)

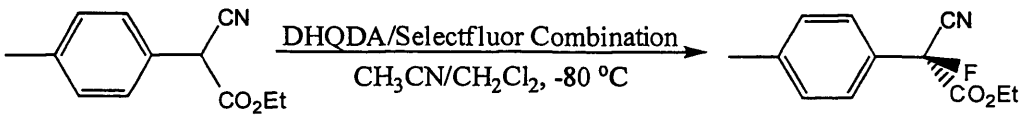
[a] Fluorination carried out at –80 °C in MeCN/CH_2Cl_2 (3/4) for 48 h. [b] Fluorination carried out at –50 °C in MeCN/CH_2Cl_2 (3/4) for 12 h.

Table 1.11 *The Fluorinations of Silyl Enol Ethers with Dihydroquinine p-Chlorobenzoate (DHQNB)/Selectfluor Combination*



Dihydroquinidine Acetate (DHQDA) **(23)**

Figure 1.11 *The Structure of Dihydroquinidine Acetate (DHQDA) (23)*



(24) 80 % yield
87 % ee

Scheme 1.5 *The Fluorination of Ethyl α–Cyano-tolyl Acetate with DHQDA/Selectfluor*

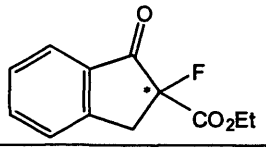
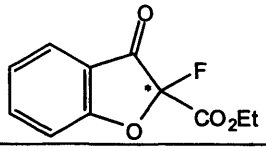
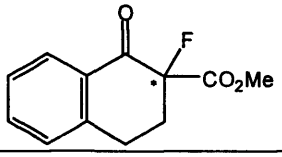
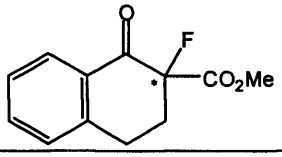
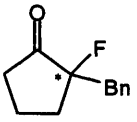
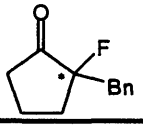
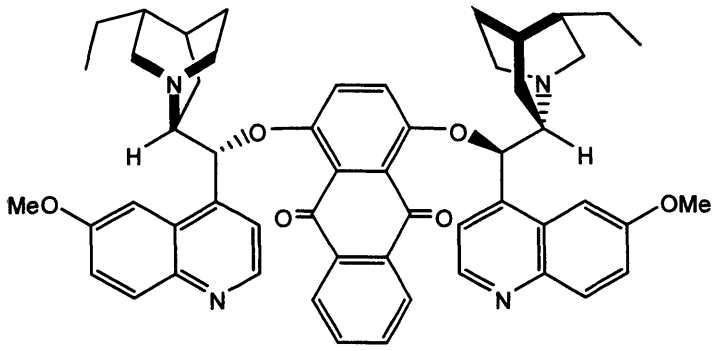
Entry	Product	Reaction Conditions	Yield (%)	ee (%)
1		DHQDA (2.0 equiv.) Selectfluor (1.5 equiv.) MeCN, –80 °C	89	78
2		DHQDA (2.0 equiv.) Selectfluor (1.5 equiv.) MeCN, –80 °C	92	80
3		DHQDA (2.0 equiv.) Selectfluor (1.5 equiv.) MeCN, –80 °C	26	2
4		DHQD (2.0 equiv.) Selectfluor (1.5 equiv.) MeCN, –80 °C	79	59
5		DHQDA (2.0 equiv.) Selectfluor (1.5 equiv.) MeCN, –80 °C	28	25
6		DHQN (2.0 equiv.) Selectfluor (1.5 equiv.) MeCN, –80 °C	55	43

Table 1.12 *The Fluorination of Cyclic β-Ketoesters*

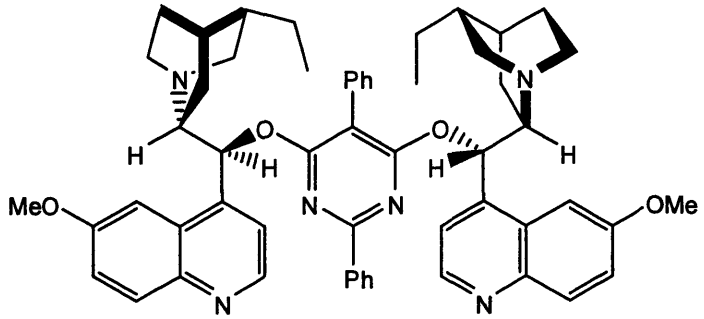
One challenge was to fluorinate acyclic esters that could be used as building blocks to synthesise larger chiral fluorinated compounds. The target compound ethyl α–cyano-α-fluoro-tolyl acetate **(24)** was chosen. When ethyl α–cyano-tolyl acetate was fluorinated with the dihydroquinine *p*-chlorobenzoate **(21)**/Selectfluor combination at -20 °C the enantioselectivity was poor (29 % ee), but when the reaction was carried out at -80 °C the enantioselectivity increased to 51 % ee. As the starting material has an acidic hydrogen at the reaction centre, there was no need to convert the compound to its silyl enol ether prior to the fluorination. Other cinchona alkaloid/Selectfluor combinations were screened and it was found that dihydroquinidine acetate (DHQDA) **(23)** (Figure 1.11)/Selectfluor gave the best

enantioselectivity (87 % ee, Scheme 1.5). After the fluorination, the cinchona alkaloid dihydroquinidine acetate **(25)** was recovered by a simple acidic/basic extraction. The recovered material was then used to fluorinate a second batch of ethyl α-cyano-tolyl acetate in 79 % yield and 85 % ee. The results showed that recycling the cinchona alkaloid has no effect on the enantioselectivity. This dihydroquinidine acetate/Selectfluor combination also produced high enantioselectivity when fluorinating other acyclic esters.

When the DHQDA **(23)**/Selectfluor combination was used to fluorinate cyclic β-ketoesters the enantioselectivity was high (78-80 % ee) for the fluorination of cyclic, active methylene compounds (Table 1.12, entries 1 and 2). As with the acyclic esters, the starting material was not converted to the silyl enol ether before fluorination, as there was an acidic hydrogen at the reactive centre. Table 1.12 shows that the enantioselectivity of the fluorination reaction of the esters (entries 3 and 5) resulted in poor enantioselectivity (2 % ee and 25 % ee respectively), but it could be improved to 59 % ee and 43 % ee respectively by using alternative combinations, dihydroquinidine (DHQD)/Selectfluor or dihydroquinine (DHQN)/Selectfluor. The reasons for this are not known, but it does emphasise the point that the steric influence of the hydroxyl-protecting group does affect the reaction.

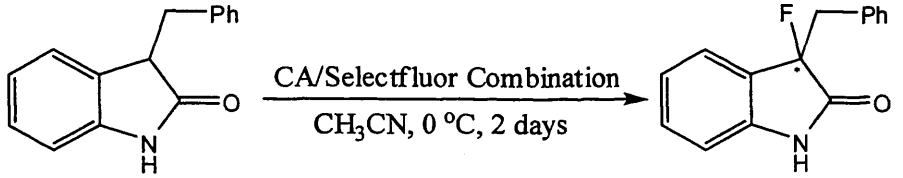


$(DHQ)_2AQN$ **(25)**



$(DHQD)_2PYR$ **(26)**

Figure 1.12 *The Bis-Cinchona Alkaloids, $(DHQ)_2AQN$ (25) and $(DHQD)_2PYR$ (26) Used in the Fluorinations of 3-Benzyl-oxindole*



(27) **(28)**

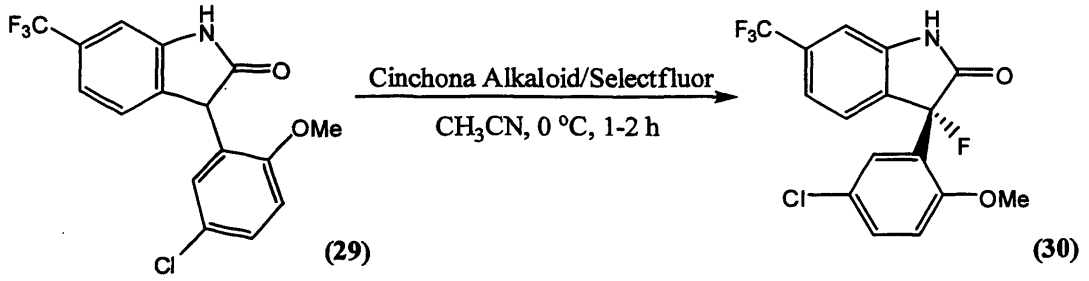
Entry	Alkaloid	Amount of Alkaloid/Selectfuor	Yield (%)	ee (%)
1	DHQDA	Cinchona alkaloid (1.5 equiv.) Selectfluor (1.5 equiv.)	27	37
2	DHQDA	Cinchona alkaloid (3 equiv.) Selectfluor (1.5 equiv.)	53	44
3	DHQNB	Cinchona alkaloid (3 equiv.) Selectfluor (3 equiv.)	60	7
4	DHQD	Cinchona alkaloid (1.5 equiv.) Selectfluor (1.5 equiv.)	17	18
5	$(DHQ)_2PHAL$	Cinchona alkaloid (1.5 equiv.) Selectfluor (1.5 equiv.)	74	23
6	$(DHQ)_2AQN$	Cinchona alkaloid (1.5 equiv.) Selectfluor (1.5 equiv.)	100	78
7	$(DHQ)_2AQN$	Cinchona alkaloid (1.5 equiv.) Selectfluor (3 equiv.)	50	64
8	$(DHQD)_2PYR$	Cinchona alkaloid (1.5 equiv.) Selectfluor (1.5 equiv.)	91	72

Table 1.13 *The Fluorination of (27) with Various Cinchona Alkaloid/Selectfluor Combinations*

3-Fluorooxindoles are important because not only are they potential mimics of oxindoles, but also 3-hydroxyoxindoles. There was no enantioselective synthesis of 3-benzyl-3-fluorooxindole **(28)** reported previously, but several racemic methods are known.[43,44] The dihydroquinidine acetate **(23)**/Selectfluor and dihydroquinine *p*-chlorobenzoate **(21)**/Selectfluor combinations that worked well in previous fluorinations failed giving 37 % and 7 % ee respectively when reacted with **(27)** (Table 1.13, entries 1 and 3). These reactions had to be done at 0 °C as lower temperatures led to incomplete reactions. Other cinchona alkaloid/Selectfluor combinations were screened, but none surpassed the 37 % ee obtained when dihydroquinidine acetate was used. However, good enantioselectivity could be obtained

from the bis-cinchona alkaloid combinations, dihydroquinine (anthraquinone-1,4-diyl) diether ((DHQ)$_2$AQN) **(25)**/Selectfluor and dihydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether ((DHQD)$_2$PYR) **(26)**/Selectfluor resulting in 78 % ee and 72 % ee respectively (Figure 1.12, Table 1.13).

One interesting point was that when the bis-cinchona alkaloids were used with 1 equivalent of Selectfluor, 100 % yield and 78 % ee were obtained (Table 1.13, entry 6), but when 2 equivalents of Selectfluor were used the yield decreased to 50 % and the enantioselectivity to 64 % ee (Table 1.13, entry 7). The same effect was observed when the mono-cinchona alkaloid dihydroquinidine acetate was used. DHQDA/Selectfluor in a 2:1 ratio gave 53 % yield and 44 % ee of 3-fluorooxindole (Table 1.13, entry 2), but DHQDA/Selectfluor in a 1:1 ratio gave only a 27 % yield and 37 % ee (Table 1.13, entry 1). This suggests that the additional equivalent of cinchona alkaloid was aiding the release of the acidic proton at the reaction centre which then forms an anion prior to the fluorination.



Entry	Alkaloid	Yield (%)	ee (%)	Configuration
1	(DHQD)$_2$PYR	93	7	(*S*)
2	DHQB	94	18	(*S*)
3	DHQDA	82	32	(*R*)
4	QD	98	52	(*R*)
5	QN	91	25	(*S*)
6	(DHQ)$_2$PYR	90	14	(*R*)
7	(DHQD)$_2$PHAL	98	54	(*R*)
8	(DHQ)$_2$PHAL	89	53	(*S*)
9	(DHQ)$_2$AQN	89	74	(*S*)

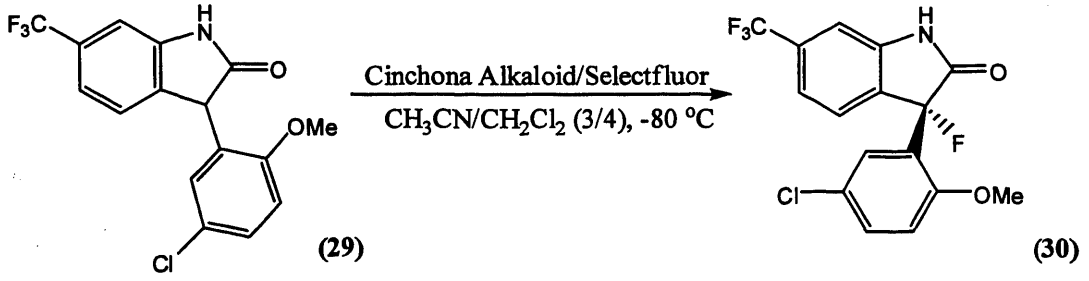
Table 1.14 *The Fluorination of (29) using Various Cinchona Alkaloid/Selectfluor Combinations*

Since Differding and Lang synthesised the *N*-fluorosultams, asymmetric fluorination by chiral reagents has progressed a long way. One example where these compounds have proved invaluable was in the synthesis of BMS-204352 (MaxiPost) **(30)**.[41] MaxiPost is an

effective opener of maxi-K channels and at present, is in worldwide phase III clinical trials for the treatment of acute ischemic stroke. Although both enantiomers of the compound are active, the (*S*)-isomer consistently gives a more robust response and so was the enantiomer being developed as BMS-204352. Previously, this enantiomer was separated out from the racemic mixture of **(30)** using chiral HPLC or through the formation and separation of diastereomeric salts of the corresponding ring-opened compound with (*S*)-α-methyl benzylamine.

The oxindole **(29)** was formed in five steps from commercially available 3-aminobenzotrifluoride. The hydrogen at the reactive centre has high acidity so conversion of **(29)** to its silyl enol ether was not necessary. As stated previously, the $(DHQD)_2PYR$ **(26)**/Selectfluor combination led to high yields and enantioselectivities in the fluorination of oxindoles. In this case, the yield was high (93 %), but the enantioselectivity was poor (7 % ee) (Table 1.14, entry 1). Other cinchona alkaloid/Selectfluor combinations were screened and selected results are shown in Table 1.14.

All the combinations gave high yields, but varied enantioselectivities. The QD, $(DHQD)_2PHAL$, $(DHQ)_2PHAL$ and $(DHQ)_2AQN$ combinations showed the most promising results which were optimised further. When the solvent was changed from CH_3CN to EtOH the enantioselectivity decreased, so the reactions were carried out at –80 °C in CH_3CN/CH_2Cl_2 (3/4) with the result that all enantioselectivities increased except $(DHQD)_2PHAL$ which decreased (Table 1.15).

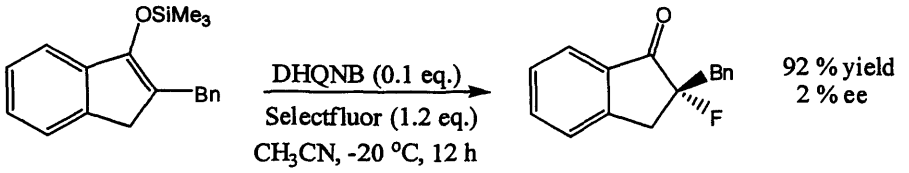


(29) **(30)**

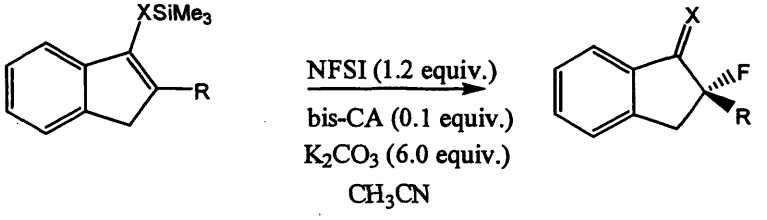
Entry	Alkaloid	Yield (%)	ee (%)	Configuration
1	$(DHQ)_2AQN$	94	84	(*S*)
2	$(DHQ)_2PHAL$	75	78	(*S*)
3	$(DHQD)_2PHAL$	93	38	(*R*)
4	QD	96	68	(*R*)

Table 1.15 *The Fluorination of (29) with Various Cinchona Alkaloid/Selectfluor Combinations under Optimised Conditions*

Under these optimised conditions, the (*S*)-enantiomer of BMS-204352 (MaxiPost) can be obtained in 94 % yield and 84 % ee by the use of the $(DHQ)_2AQN$ **(26)**/Selectfuor combination. The enantioselectivity was improved by a simple recrystallisation from DCM/hexane to give the enantiopure product in >99 % ee. The (*R*)-enantiomer can also be obtained by using the quinidine/Selectfluor combination to give 96 % yield and 68 % ee, which improved to 93 % ee after recrystallisation.



Scheme 1.6 *The Fluorination of the 2-Benzyl-1-Indanone Silyl Enol Ether Using a Catalytic Amount of Dihydroquinine p-Chlorobenzoate* ***(21)***



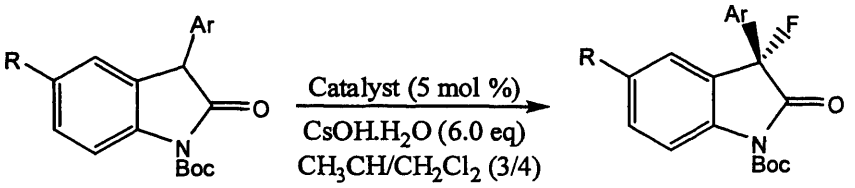
Entry	X	R	CA	Temp (°C)	Time	Yield (%)	ee (%)
1	CH_2	Bz	$(DHQ)_2PYR$	-40	3 d	75	94
2	CH_2	*p*-MeBz	$(DHQ)_2PYR$	-20	12 h	75	95
3	CH_2	*p*-ClBz	$(DHQ)_2PYR$	-20	18 h	81	94
4	CH_2	*p*-MeOBz	$(DHQ)_2PYR$	-20	34 h	65	90
5	CH_2	*o*-MeOBz	$(DHQ)_2PYR$	-20	9 h	58	93
6	O	Bz	$(DHQ)_2PHAL^a$	-40	10 d	82	82
7	O	*p*-MeBz	$(DHQ)_2PHAL^a$	-40	8 d	79	86
8	O	*p*-ClBz	$(DHQ)_2PHAL^a$	-40	8 d	74	86
9	O	*p*-MeOBz	$(DHQ)_2PHAL^a$	-40	6 d	84	85

[a] 20 mol % of the catalyst was used

Table 1.16 *The Fluorination of Allyl Silanes and Silyl Enol Ethers Using a Catalytic Amount of a Bis-Cinchona Alkaloid*

Following the success of the cinchona alkaloid/Selectfluor combinations, Shibata then turned his attention to developing a catalytic version of the reaction. Initially, the results were

poor to moderate as the fluorination of the enolate by Selectfluor was just as fast as the transfer fluorination of Selectfluor to the cinchona alkaloid.[45] By adapting the reaction conditions, a range of allyl silanes could be fluorinated in high yields and enantiomeric excesses with NFSI, 10 mol % of $(DHQ)_2PYR$ and a large excess of base (Table 1.16, entries 1-5).[46] Silyl enol ethers could also be fluorinated asymmetrically in high yields and enantioselectivities with $(DHQ)_2PHAL$ **(22)** (20 mol %), though much longer reaction times were needed (Table 1.16, entries 6-9). This methodology could be extended to the fluorination of oxindoles in good yields and enantiomeric excesses using 5 mol % of $(DHQD)_2AQN$ (Table 1.17, entries 1-3). The opposite enantiomer of product could be obtained with $(DHQ)_2AQN$ **(25)** as the catalyst with comparable results (Table 1.17. entries 4-6).

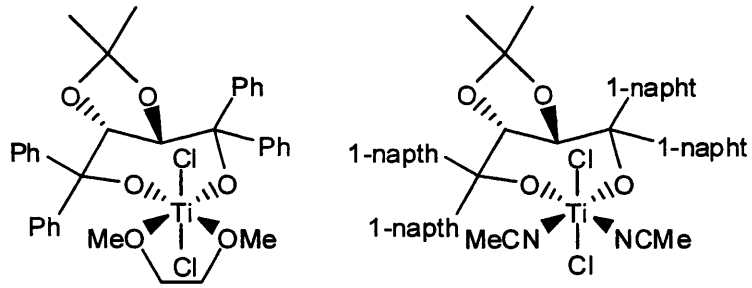


Entry	Ar	R	Catalyst	Time (d)	Yield (%)	ee (%)
1	*p*-Tol	H	$(DHQD)_2AQN$	5	86	83 (*S*)
2	Ph	OMe	$(DHQD)_2AQN$	5	92	84 (*S*)
3	*p*-FBz	OMe	$(DHQD)_2AQN$	5	86	81 (*S*)
4	Ph	H	$(DHQ)_2AQN$	5	99	85 (*R*)
5	*p*-Tol	Me	$(DHQ)_2AQN$	7	86	84 (*R*)
6	*p*-Tol	OMe	$(DHQ)_2AQN$	5	99	85 (*R*)

Table 1.17 *The Asymmetric Fluorination of Oxindoles Using a Catalytic Amount of a Bis-Cinchona Alkaloid*

1.3 Asymmetric Catalysis

Catalyst-controlled fluorination is an extremely attractive method for asymmetric fluorination and Togni published the first example of a catalytic enantioselective fluorination in 2000.[47,48] The work was based on an observation by Umemoto[49] where the fluorination of a β-ketoester with *N*-fluoropyridinium salts was accelerated by the addition of the Lewis acid catalyst $ZnCl_2$. The Lewis acid catalyst promoted enolisation to the enol form which was known to be much more reactive than the keto form in electrophilic fluorinations. Togni proposed that asymmetric induction should be possible by using a chiral Lewis acid catalyst if the fluorination occurs on the coordinated enolate.



(31) (32)

Figure 1.13 *The Structures of Ti Complexes Used by Togni*

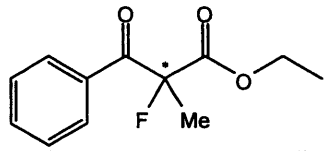
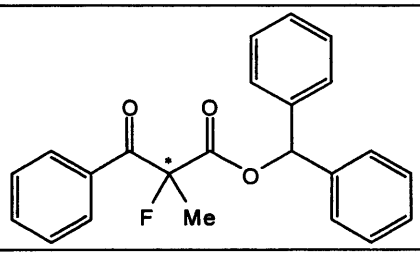
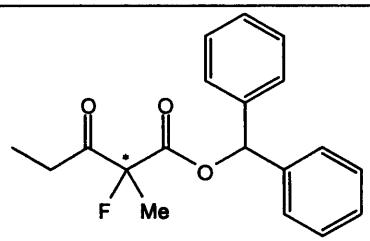
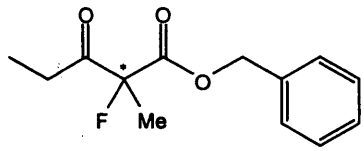
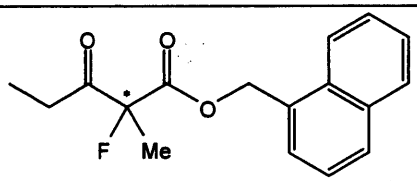
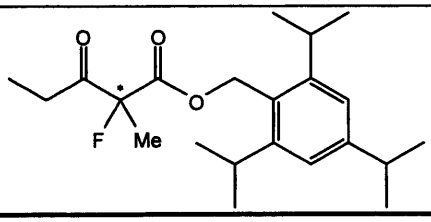
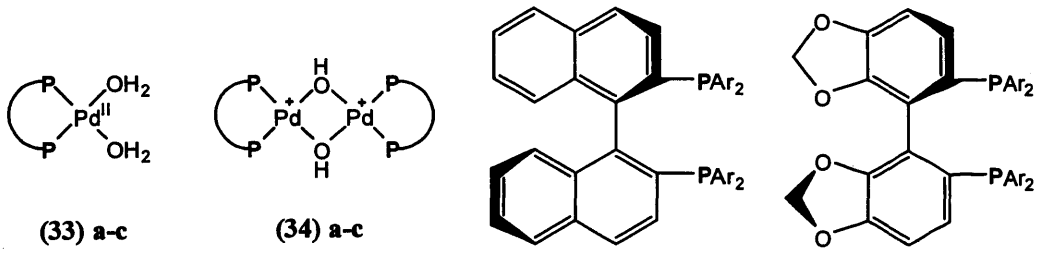
	Catalyst (35)		Catalyst (36)	
Product	**Reaction Time**	**ee (%)**	**Reaction Time**	**ee (%)**
	4 h	28	40 min	62
	1 d	59	1 d	82
	2 h	58	20 min	81
	15 min	48	< 7 min	71
	< 15 min	51	< 15 min	68
	1 h	55	< 15 min	90

Table 1.18 *The Catalytic Fluorination of β-Ketoesters*

Togni then isolated the Ti complexes **(31)** and **(32)** to yield crystalline, air-stable materials as adducts with DME (dimethoxyethane) and acetonitrile respectively (Figure 1.13), since Seebach[50] has used [$TiCl_2$(TADDOLato)] complexes *in situ* for a wide range of asymmetric reactions. These isolated forms were used to catalyse the fluorination of various β-ketoesters with Selectfluor (Table 1.18). All the yields were between 85-95 %, but substrates were restricted to those containing an α-methyl group to yield compounds with a quaternary stereogenic centre. It was found that the isolated forms of **(31)** and **(32)** gave much more reliable results in terms of both reproducibility and enantioselectivity than the ones prepared *in situ*.

One important finding was that the steric bulk of the catalyst was important for achieving high enantioselectivity. The Ti complex **(32)** contains bulky 1–naphthyl groups whilst **(31)** contains phenyl groups. The additional steric bulk on **(32)** led to better enantioselectivity than **(31)** in every fluorination reaction. The best result obtained using these Ti-complexes was the fluorination of a substituted benzyl ester to yield 90 % ee (Table 1.18, entry 6).

It was proposed that the enolate complexes to the catalyst through two-point binding, and then undergoes fluorination with the electrophilic fluorinating reagent, Selectfluor. The steric bulk of the catalyst means that a *si*-facial attack is preferred. This method was limited to branched keto esters due to the catalysts power to promote the enolisation of the products.



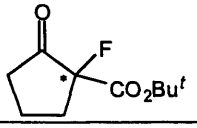
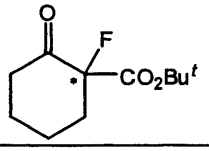
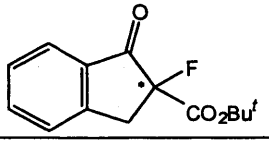
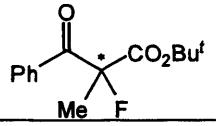
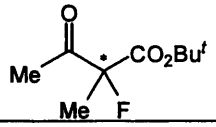
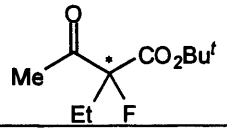
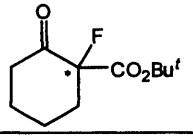
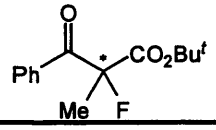
(33) a-c **(34) a-c** **a, b** **c,d**

a: Ar = Ph : ((*R*)-BINAP)
b: Ar = 3,5-dimethylphenyl : ((*R*)-DM-BINAP)
c: Ar = 3,5-di(tert-butyl)-4-methoxyphenyl : ((*R*)-DTBM-SEGPHOS)
d: Ar = 3,5-dimethylphenyl : ((*R*)-DM-SEGPHOS)
e: Ar = 3,5-dimethylphenyl : ((*S*)-DM-BINAP

Figure 1.14 *The Structures of Palladium Complexes (33) and (34)*

Since Sodeoka[51] found that a chiral palladium enolate was formed directly from the β-ketoester interacting with the palladium complexes **(33)** or **(34)**, the fluorination of various cyclic and acyclic substrates were carried out using 1.5 equivalents of NFSI and 2.5 mol % of Pd catalyst in EtOH. As Table 1.19 shows, the fluorinated products were all obtained in good yields and enantioselectivities, even when the catalyst loading was reduced to 1 mol %. All of these reactions were easily scaled up without any loss in efficiency. Catalysts **(34b)** and **(34c)**

proved to be the most effective, but the efficiency was dependant on the nature of the substrate. One important finding was that the reaction was not sensitive to air or moisture so the use of dried solvents and inert atmospheres are not required.

Entry	Product	Catalyst	Temp (°C)	Time (h)	Yield (%)	ee (%)
1		**(34c)** TfO^-	20	18	90	92
2		**(34b)** BF_4^-	-10	20	91	94
3		**(34b)** TfO^-	-20	36	85	83
4		**(34b)** BF_4^-	20	40	92	91
5		**(34c)** TfO^-	20	72	49	91
6		**(34b)** TfO^-	20	42	88	87
7		**(34b)**[a] BF_4^-	0	20	82	91
8		**(33b)** TfO^-	20	48	96	91

[a] 1 mol % **(34b)** was used.

Table 1.19 *The Fluorination of β-Ketoesters using NFSI (1.5 equiv.) and Pd Catalyst (2.5 mol %) in EtOH*

Since the key step to the reaction was the formation of a palladium enolate with the β-ketoester, Sodeoka suggested that other bidentate carbonyl compounds could react in a similar way.[52] β-Ketophosphonates were then chosen as substrates since the difluoro and monofluorophosphonates have been investigated as mimics of phosphates in drug design.[53] There are procedures in the literature for the achiral and diastereoselective syntheses of α-monofluorophosphonates,[54,55] but at that time there was no catalytic enantioselective synthesis

of chiral α-fluoro β-ketophosphonates. Various cyclic and acyclic β-ketophosphonates were fluorinated under the same conditions as described previously for the fluorination of β-ketoesters (Table 1.20). All of the fluorinated products were obtained in high enantioselectivities even when the catalyst loading was reduced to 1 mol %, although a longer reaction time was required. Compared to the cyclic substrates, the acyclic substrates were slow to react. In some cases the reaction had not gone to completion after 48 hours at 40 °C, hence the modest yields. Like the fluorination of β-ketoesters, this reaction was found not to be sensitive to air or moisture.

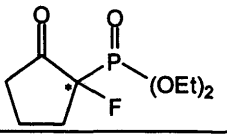
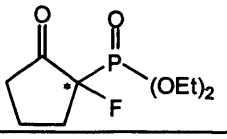
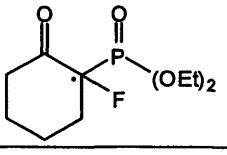
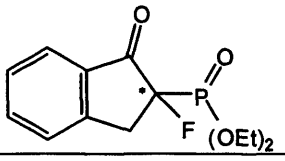
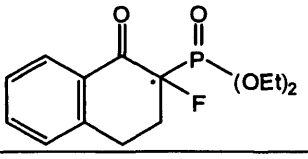
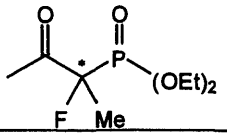
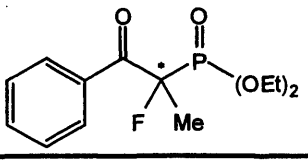
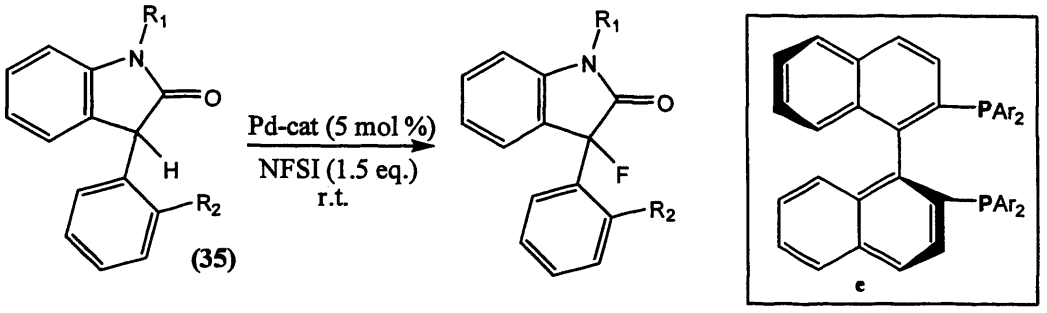
Entry	Product	Catalyst	mol (%)	Temp (°C)	Time (h)	Yield (%)	ee (%)
1		**33c**	5	r.t.	5	46	98
2		**33b**	5	r.t.	2	91	95
3		**33b**	5	r.t.	8	93	96
4		**33b**	5	r.t.	3	84	95
5		**33b**	5	r.t.	3	97	94
6		**33d**	10	40	48	57	94
7		**33d**	10	40	48	38	95

Table 1.20 *The Fluorination of β-Ketophosphonates with Chiral Palladium Complexes*

Sodeoka then looked at the fluorination of oxindoles[56] as these are common in natural products, and so fluorinated versions could be important in medicinal chemistry. The main aim was to synthesise MaxiPost **(30)** by the catalytic enantioselective fluorination of oxindole **(29)** with chiral palladium complexes. The fluorination of oxindole **(35)** was investigated

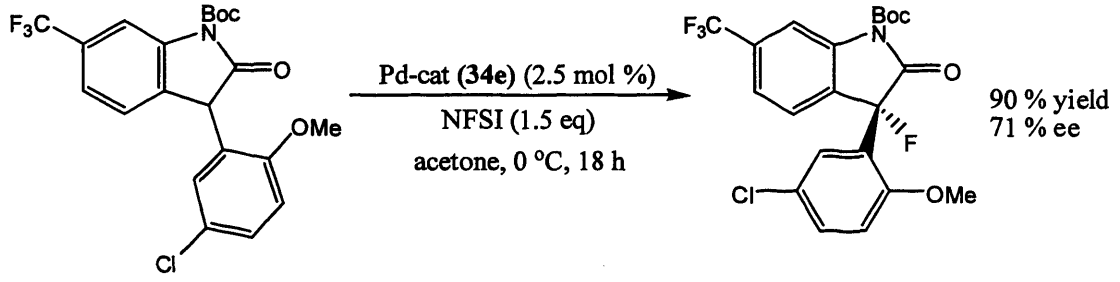
initially (Table 1.21), but the reaction with catalyst **(33e)** under the same conditions described previously gave the product in poor yield (20 %) and enantiomeric excess (5 %) (Table 1.21, entry 1). By simple Boc protection of the nitrogen moiety, the yield and enantioselectivity was improved to 53 % and 81 % respectively (Table 1.21, entry 2). The modest yields obtained were due to the deprotection of the nitrogen by the acidic nature of the catalyst **(33)**. This was easily overcome by the use of the less acidic catalyst **(34)**, which increased the yield of the reaction to 90 % with no loss in enantioselectivity (Table 1.21, entry 3). The influence of a methoxy group at R_2 was then investigated, but it had no real effect, though it was found that bulkier protecting groups led to better enantioselectivity (Table 1.21 entries 4 and 5).



Substrate	R_1/R_2	Catalyst	Solvent	Time (h)	Yield (%)	ee (%)
35a	H/H	**33e**	THF	60	20	5
35b	Boc/H	**33e**	THF	12	53	81
35b	Boc/H	**34e**	IPA	5	90	88
35c	Boc/OMe	**34e**	Acetone	18	89	76
35d	$OC(O)CHPh_2$/OMe	**34e**	Acetone	12	93	73

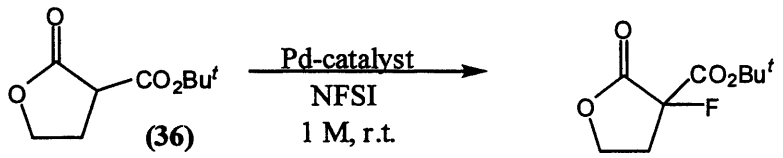
Table 1.21 *The Fluorination of Oxindole (35)*

With this information, the catalytic enantioselective synthesis of MaxiPost was carried out using Pd catalyst **(34e)** with 1.5 equivalents of NFSI in acetone at 0 °C for 18 hours (Scheme 1.7). The desired product was formed in 90 % yield and 71 % ee, but this was increased to >99 % ee after recrystallisation.



Scheme 1.7 *The Synthesis of MaxiPost Using Catalyst (34e)*

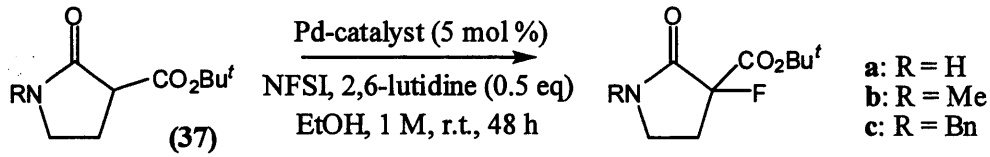
Sodeoka then developed a highly enantioselective catalytic fluorination of *tert*-butoxycarbonyl lactones and lactams.[57] Initially, lactone **(36)** was fluorinated in 96 % yield and 79 % ee, by the use of catalyst **(33b)** (Table 1.22, entry 1). These results could be improved significantly by the use of the bulkier catalyst **(33c)** to give the fluorinated product in a 74 % yield and an excellent 97 % ee (Table 1.22, entry 3). The use of another bulky catalyst **(34c)** also gave a comparable result (75 % yield, 98 % ee) (Table 1.22, entry 4). The less acidic lactams were also fluorinated using the same methodology in excellent enantiomeric excesses, though the use of 2,6-lutidine as a cocatalyst was required to aid the formation of the palladium enolate. Lactam **(37a)** was fluorinated using catalyst **(33c)** in 50 % yield and 99 % ee (Table 1.23, entry 1). The moderate yield was caused by a competing reaction which abstracted the amide proton. To counteract this, the fluorination of the *N*-substituted lactams **(37b)** and **(37c)** with **(34c)** was carried out to give excellent enantioselectivities and higher yields of 77 % and 89 % respectively (Table 1.23, entries 3 and 4).



Entry	Catalyst[a]	Solvent	Time (h)	Yield (%)	ee (%)
1	**(33b)** (5)	^{i}PrOH	6	96	79
2	**(33b)** (5)	^{t}BuOH	6	89	80
3	**(33c)** (5)	^{i}PrOH	24	74	97
4	**(34c)** (2.5)	^{i}PrOH	24	75	98

[a] mol % in parentheses

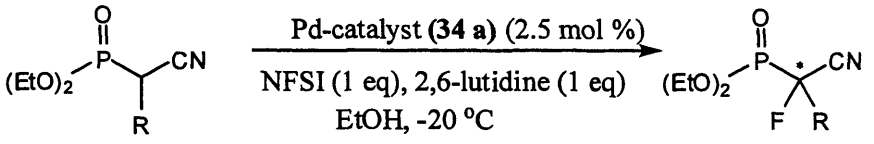
Table 1.22 *The Fluorination of tert-Butoxycarbonyl Lactone*



Entry	R	Catalyst	Yield (%)	ee (%)
1	H	**(33c)**	50	99
2	H	**(34c)**	58	> 99
3	Me	**(34c)**	77	99
4	Bn	**(34c)**	89	98

Table 1.23 *The Fluorination of tert-Butoxylcarbonyl Lactams*

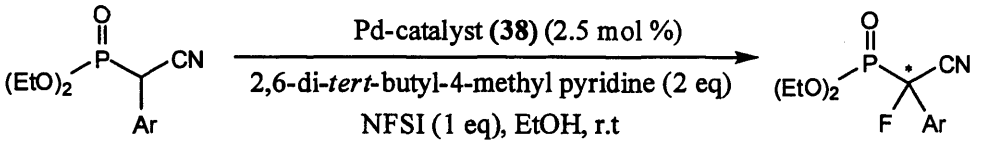
The same methodology was then extended to a range of α-aryl-α-cyanophosphonates to give generally good yields and moderate to good enantioselectivities (Table 1.24).[58] Unfortunately, this reaction could not be extended to α-alkyl-α-cyanophosphonates. Kim simultaneously worked on the same reaction (Table 1.25), but used catalyst **(38)** (Figure 1.15) and 2,6-di-*tert*-butyl-4-methyl pyridine as the base and gained much higher enantioselectivities.[59]



Entry	R	Time (h)	Yield (%)	ee (%)
1	*p*-MeC_6H_4	3	98	44
2	*p*-ClC_6H_4	1	95	24
3	*m*-ClC_6H_4	1	97	41
4	*m*-MeC_6H_4	48[a]	36	38
5	2-naphthalene	1	90	66
6	1-naphthalene	40	92	78

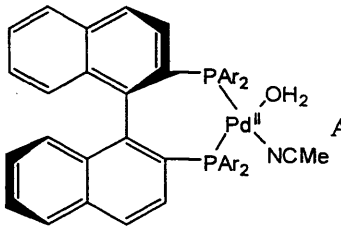
[a] Reaction carried out at 0 °C

Table 1.24 *The Fluorination of α-Aryl-α-Cyanophosphonates by Sodeoka*



Entry	Ar	Time (h)	Yield (%)	ee (%)
1	Ph	12	90	85
2	*p*-$OMeC_6H_4$	12	98	85
3	*p*-MeC_6H_4	12	96	80
4	*p*-ClC_6H_4	12	98	91
5	*p*-FC_6H_4	15	95	87
6	1-naphthalene	120	73	83
7	2-thienyl	18	94	81

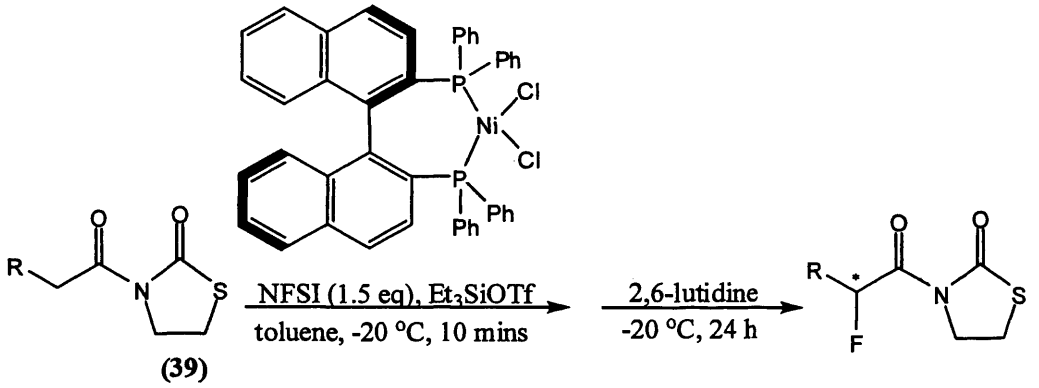
Table 1.25 *The Fluorination of α-Aryl-α-Cyanophosphonates by Kim*



Ar = 3,5-dimethylphenyl : ((*R*)-xylyl-BINAP **(38)**

Figure 1.15 *The Palladium Catalyst (38) Used by Kim*

Sodeoka has also fluorinated successfully a range of α-fluorothiazolidinones **(39)** in excellent yields and good enantioselectivities with a combination of Ni^{II}, (*R*)-BINAP, triethylsilyl triflate, 2,6-lutidine and NFSI (Table 1.26).[60] The fluorinated products were a precursor to α-monofluorinated aryl acetic acids which have applications in medicinal chemistry as they are a common subunit of non-steroidal anti-inflammatory treatments.

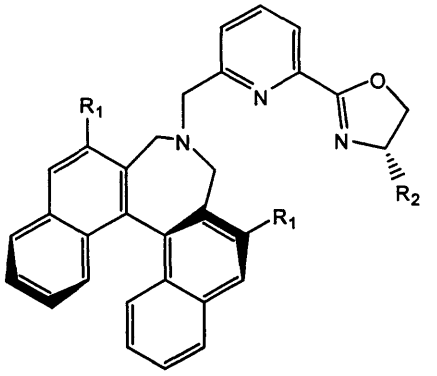


(39)

Entry	R	Mol (%)	Equiv. Of Et_3SiOTf	Yield (%)	ee (%)
1	Ph	5	0.75	99	88
2	*p*-FC_6H_4	5	0.75	90	83
3	*p*-$OMeC_6H_4$	5	0.75	92	81
4	*m*-$OMeC_6H_4$	5	0.75	56	69
5	*m*-$OMeC_6H_4$	10	1.5	95	82
6	*o*-$OMeC_6H_4$	5	0.75	73	61
7	*o*-$OMeC_6H_4$	10	1.5	87	78
8	2-naphthalene	10	1.5	99	83
9	1-naphthalene	5	0.75	94	87
10	*n*-propyl	10	1.5	15	11

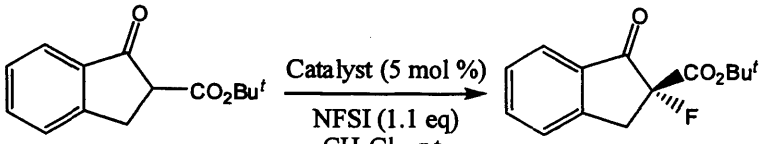
Table 1.26 *The Fluorination of Thiazolidinones*

Iwasa designed and synthesised the *N*, *N*, *N*-tridentate ligand (*S*, *S*)-**(40)** (Figure 1.16) and used it in combination with the Lewis acid catalyst $Ni(ClO_4)_2$ to fluorinate 2-*tert*-butoxycarbonyl-1-indanone **(41)** (Table 1.27).[61] Excellent yields of the fluorinated product were obtained for nearly all of the ligands and **(40a)** and **(40c)** proved to be particularly effective as 94 and 92 % ee was obtained (Table 1.27, entries 1 and 3).



(*S*, *S*)-**(40a)**: $R_1 = H$, $R_2 = {}^iPr$
(*S*, *S*)-**(40b)**: $R_1 = H$, $R_2 = Bn$
(*S*, *S*)-**(40c)**: $R_1 = H$, $R_2 = Ph$
(*S*, *S*)-**(40d)**: $R_1 = H$, $R_2 = {}^tBu$
(*S*, *S*)-**(40e)**: $R_1 = Ph$, $R_2 = Ph$

Figure 1.16 *The N, N, N-tridentate Ligands Synthesised by Iwasa*



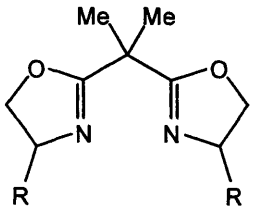
(41)

Entry	Ligand	Time (h)	Yield (%)	ee (%)
1	**40a**	0.5	99	94 (*R*)
2	**40b**	0.5	99	88 (*R*)
3	**40c**	0.5	98	92 (*R*)
4	**40d**	0.5	99	89 (*R*)
5	**40e**	3	68	20 (*R*)

Table 1.27 *The Fluorination of 2-tert-Butoxycarbonyl-1-indanone (41)*

Cahard[62] examined the catalytic applications of $[Cu(OTf)_2]$, $[Mg(ClO_4)_2]$ and $[Zn(OTf)_2]$ in combination with bisoxazolines **(42)** (Figure 1.17) for the asymmetric fluorination of the model substrate, *t*-butyl 2-oxo-cyclopentanecarboxylate. The best Lewis acid catalysts were the Cu(II) and Zn(II) bisoxazoline complexes that promoted the *in situ* generation of the enolate and gave good selectivity. NFSI was found to be a superior electrophilic fluorine donor and toluene or ether proved to be the better solvents. The use of the achiral additive, HFIP (1,1,1,3,3,3-hexafluoroisopropanol), led to a large increase in

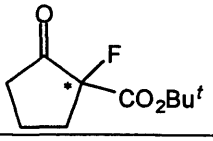
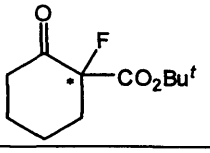
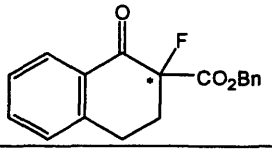
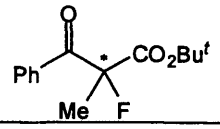
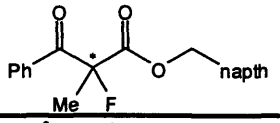
enantioselectivity by aiding the release of the fluorinated product from the catalyst and so increasing the catalyst turnover. After the conditions were optimised, various cyclic and acyclic β-ketoesters were fluorinated in good to excellent yields and with enantiomeric excesses up to 85 % for the cyclic substrates and up to 52 % for acyclic substrates (Table 1.28). The use of chiral ligands, (-)-sparteine, (+)-hydroquinine 4-methyl-2-quinoyl ether, (+)-hydroquinidine-2,5-diphenyl-4,6-pyrimidyldiyl diether, (*S*)-PyBox, Trost's ligand, (-)-quinine, (*S*)-BINOL and (-)-TADDOL lead to no improvement in the enantioselectivities.[63]



R = **a**: (*R*)-Ph-BOX
b: (*R*)-Bn-BOX
c: (*S*)-Bu^t-BOX
d: (*S*)-Ph-BOX

(42)

Figure 1.17 *Bisoxazolines Used by Cahard*

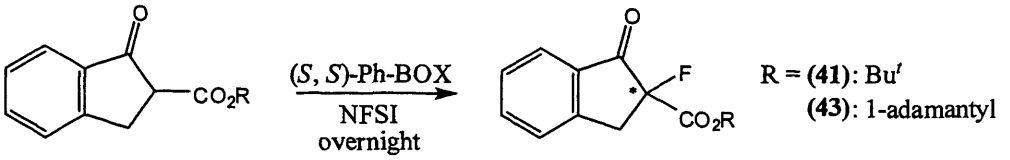
Entry	Product	Time (h)	Yield (%)	ee (%)
1		0.5	96	85
2		3	92	63
3		0.5	92	38
4		96	56	43
5		2	88	40

[a] 1 mol % Catalyst, 20 °C, Et_2O, HFIP (1 equiv.)

Table 1.28 *The Fluorination of β-Ketoesters with 1 mol % Cu(OTf)$_2$-(R)-Ph-BOX*[a]

The work on asymmetric catalysis described so far involves a chiral ligand coordinated to a metal, which was then used to fluorinate a β-ketoester to give one enantiomer in preference to the other. In order to get the minor enantiomer, the chirality of the ligand

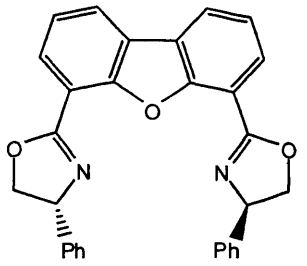
must be reversed. Therefore, both chiral ligands have to be available or synthesised, but that is not always possible. Shibata demonstrated recently that the same enantiomer of the chiral ligand, (*S*,*S*)-bis(oxazoline)-Ph **(42d)**, gave different enantiomers of the fluorinated product by changing the metal that it was coordinated to.[64]



Entry	Substrate	Catalyst	Solvent	Temp (°C)	Yield (%)	ee (%)
1	**41**	$Cu(OTf)_2$	THF	-10	89	46 (*S*)
2	**41**	$Cu(OTf)_2$	DCM	-10	50	39 (*S*)
3	**41**	$Ni(ClO_4)_2.6H_2O$	THF	-10	65	1 (*R*)
4	**41**	$Ni(ClO_4)_2.6H_2O$	DCM	-10	72	71 (*R*)
5	**43**	$Cu(OTf)_2$	TBME	20	79	84 (*S*)
6	**43**	$Cu(OTf)_2$	Ether	20	81	70 (*S*)
7	**41**	$Ni(ClO_4)_2.6H_2O$	DCM	20	87	93 (*R*)
8	**43**	$Ni(ClO_4)_2.6H_2O$	DCM	20	74	79 (*R*)

Table 1.29 *The Fluorination of (41) and (43) with (S,S)-Bis(oxazoline)-Ph*

The electrophilic fluorination of the model compounds, *t*-butyl 1-indanone-2-carboxylate **(41)** and 1-adamantyl 1-indanone-2-carboxylate **(43),** were examined using Cu(II) and Ni(II) bisoxazoline complexes and NFSI (Table 1.29). When the chiral ligand was coordinated to a Cu(II) centre, the configuration of the major product was (*S*), but when a Ni(II) centre was used, the configuration of the major product was (*R*). The solvent choice had a large effect on the selectivity of the reaction, especially in the case of the Ni(II) catalysed reactions (Table 1.29, entries 3 and 4). When the reaction was carried out in THF, the enantiomeric excess was extremely poor (1 % ee), but by using dichloromethane as the solvent, the enantioselectivity was greatly improved to 71 % ee. The enantioselectivity of the reaction could also be increased by the addition of 4 Å molecular sieves and increasing the reaction temperature. The best results were the fluorination of **(43)** with the Cu(II) catalysed reaction giving the (*S*) product in 79 % yield and 84 % ee (Table 1.29, entry 5) and the fluorination of **(41)** in the Ni(II) catalysed reaction giving the *(R)* product in 87 % yield and 93 % ee (Table 1.29, entry 7). These results were very promising and work by Shibata continued to improve the enantioselectivity of this reaction further.



(44)

Figure 1.18 *The Structure of the dbfox-Ph Ligand (44)*

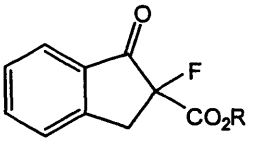
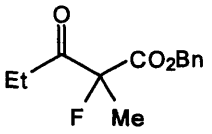
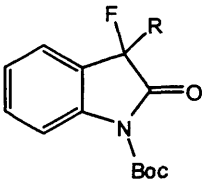
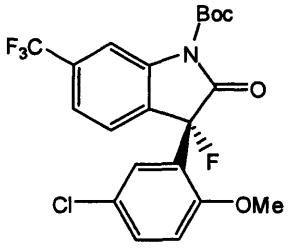
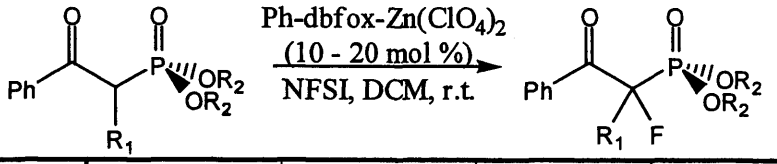
Entry	Product	R Group	Time (h)	Yield (%)	ee (%)
1		R = Bu^t R = Adamantyl R = L-Men	3 2 2	76 71 66	99 99 99
2			18	75	83
3		R = Me R = Ph	35 5	73 72	93 96
4			14	71	93

Table 1.30 *The Fluorination of β-Ketoesters and Oxindoles With Dbfox-Ph/Ni(II)*

Recently, Shibata used the dbfox-Ph ligand **(45)** coordinated to a Ni(II) centre to improve the asymmetric fluorination of carbonyl compounds capable of two-point binding (Figure 1.18).[65] Previously, this ligand has been used effectively for asymmetric Diels-Alder and Michael addition reactions.[66,67] Initially, β-ketoester **(41)** was fluorinated with NFSI in DCM at room temperature and catalyst dbfox-Ph/Ni(II) to give the fluorinated product in good yield (76 %) and excellent enantioselectivity (99 %). The reaction was extended to other β-ketoesters and under the same conditions all the fluorinated products were obtained in good yields and excellent enantioselectivities (Table 1.30, entries 1 and 2). The catalyst loading could be as low as 2 mol % without any loss in enantioselectivity. After the

successful asymmetric fluorinations of β-ketoesters, other carbonyl compounds capable of two-point binding were considered. A range of oxindoles (Table 1.30, entry 3), including MaxiPost (Table 1.30, entry 4), were fluorinated using the same method. The results were equally as good with the yields of fluorinated products ranging from 71-73 % and enantioselectivities of 93-96 % ee.

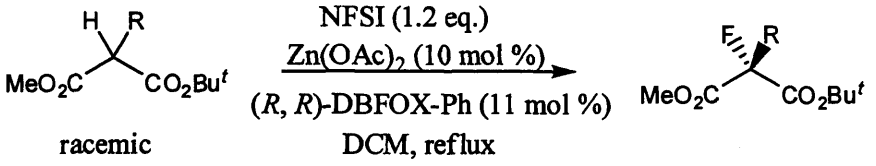
Jorgensen used the dbfox-Ph ligand **(44)** coordinated to a Zn(II) centre to fluorinate a range of β-ketophosphonates with NFSI in DCM at room temperature (Table 1.31).[68,69] The yields for this reaction can be significantly improved by performing the reaction at reflux with no loss in enantioselectivity.



Entry	R_1	R_2	Yield (%)	ee (%)
1	Me	Et	59 (86)[a]	89 (88)[a]
2	Me	Me	46 (77)[a]	70 (70)[a]
3	Allyl	Et	41 (91)[a]	91 (90)[a]

[a] *Results in parenthesis were performed at reflux*

Table 1.31 *The Fluorination of β-Ketophosphonates with Ph-dbfox-Zn(ClO4)2*

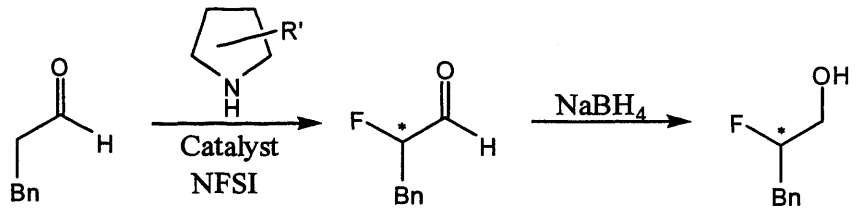


Entry	R	Time (h)	Yield (%)	ee (%)
1	Bn	15	90	98
2	Et	24	94	96
3	Me	24	90	99
4	Bu	36	93	99
5	Ph	24	95	99
6	OPh	15	85	98
7	SPh	24	81	90
8	Naphth	18	91	93

Table 1.32 *The Fluorination of a Range of Malonates Catalysed by DBFOX-Ph/Zn^{II}*

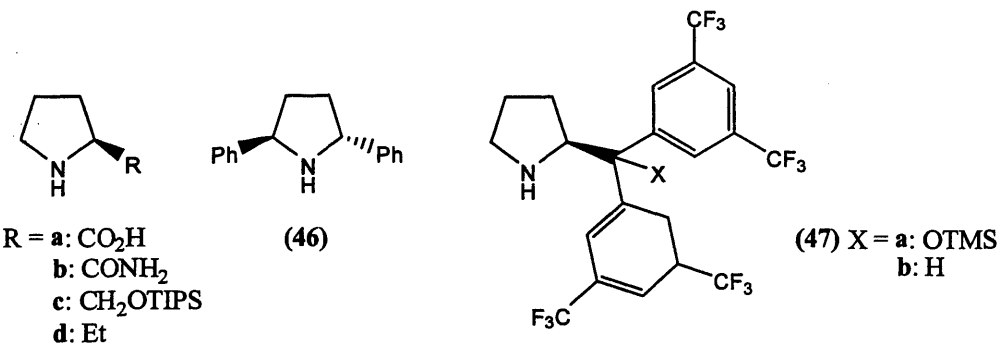
Shibata used the same methodology that was developed for the fluorination of β-ketoesters and oxindoles with BOX-Ph/$Cu(OTf)_2$ and DBFOX-Ph/$Ni(ClO_4)_2$ catalysts to fluorinate asymmetrically a range of malonates.[70] Since these compounds are less acidic than the previous substrates and are almost symmetrical, a different catalyst, DBFOX-Ph/Zn^{II}, was required to obtain the 2-fluorinated product in excellent yields and enantioselectivities (Table 1.32). The fluorinated products could be converted to their corresponding 2-fluorohydroxy esters to yield a range of synthetically useful compounds.

1.4 Enantioselective α-Fluorination of Aldehydes



Scheme 1.8 *The Fluorination of an Aldehyde Followed by Reduction to an Alcohol*

Recently, a new and easy method for the formation of stereogenic carbon-fluorine centres by the direct enantioselective α-fluorination of aldehydes has been developed. Chiral secondary amines can be used to catalyse carbon-heteroatom bond forming reactions via enamine intermediates and this process has now been applied to fluorination reactions. Since the resulting α-fluorinated aldehydes are known to decompose rapidly on silica making isolation impossible, they are converted to the optically active α-fluoroalcohols (Scheme 1.8).



(45) R = **a**: CO_2H
b: $CONH_2$
c: CH_2OTIPS
d: Et

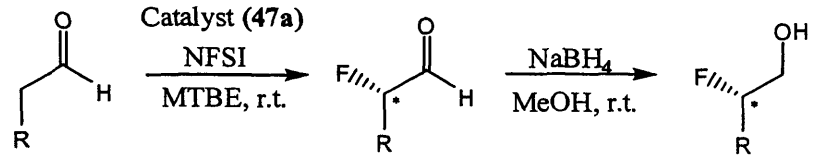
(46)

(47) X = **a**: OTMS
b: H

Figure 1.19 *The Structures of the Catalysts Screened*

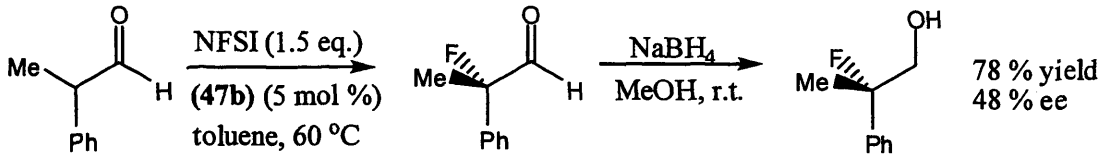
Jørgensen[71] used organocatalysts that have been used in the asymmetric synthesis of carbon-chlorine[72,73] and carbon-sulphur bonds,[74] to fluorinated a range of aldehydes (Figure 1.19). Amine **(47a)** quickly became the catalyst of choice and the fluorinated products were

obtained in good yields and excellent enantiomeric excesses, using only 1 mol % (Table 1.33). The reaction scope has been expanded to the formation of quaternary stereogenic centres, using the sterically hindered catalyst **(47b)** (Scheme 1.9).



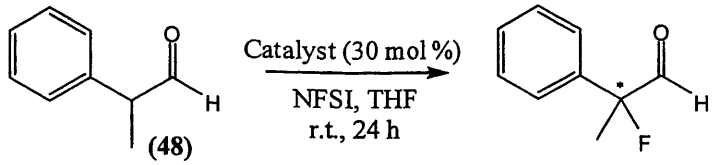
Entry	R Group	Time (h)	Yield (%)	ee (%)
1	Pr	6	>95	96
2	Bu	28	>90	91
3	Hex	4	55	96
4	$BnO(CH_2)_3$	2	64	91
5	Bn	2	74	93
6	Cy	5	69	96
7	*t*-Bu	2	>90	97
8	1-Ad	2	75	96

Table 1.33 *The Fluorination of Aldehydes*



Scheme 1.9 The Fluorination of Aldehyde

Barbas[75] carried out similar work using 2-phenylpropionaldehyde **(48)** as the model substrate since the fluorinated product would be unable to racemise. NFSI was found to be the best fluorine donor in THF at room temperature and by using L-proline as a catalyst the fluorinated product could be obtained in excellent yield (94 %), but poor enantioselectivity (28 % ee) (Table 1.34, entry 1). Various other L-proline derived organocatalysts were screened in this reaction (Table 1.34). The proline derived tetrazole catalyst **(49)** gave the best yield (98 %, 38 % ee) (Table 1.34, entry 5), but the silylated L-prolinol derivative **(45c)** gave the best enantioselectivity (44 % ee) (Table 1.34, entry 3).



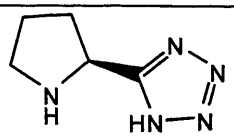
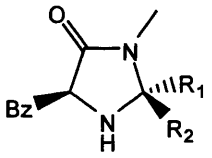
Entry	Catalyst	Yield (%)	ee (%)
1	**45a**	94	28
2	**45b**	99	12
3	**45c**	90	44
4	**45d**	83	24
5	 **49**	98	38

Table 1.34 *The Fluorination of 2-Phenylpropionaldehyde (48) Using Various Proline Based Organocatalysts*



(50) a: R_1 = H, R_2 = Bu^t
b: R_1 = Me, R_2 = Me

Figure 1.20 *The Structure of Catalyst (50)*

Barbas then examined the asymmetric fluorination of straight chain aldehydes which are known to self-react with organocatalysts to form aldol products. A range of aldehydes were then fluorinated using catalyst **(50b)** in DMF at 4 °C to prevent the formation of the α,α-difluoro product. All of the fluorinated products were obtained in moderate-excellent yields and with good-excellent enantioselectivities (Table 1.35, entries 1-4). Effective catalysts for branched aldehydes were **(45a)**, **(45c)** and **(49)**, and so they were used to fluorinate a range of substrates to give the fluorinated product in excellent yields, but poor-moderate enantioselectivity (Table 1.35, entries 5 and 6).

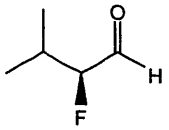
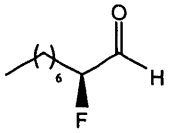
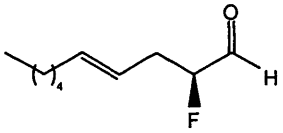
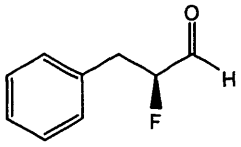
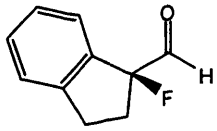
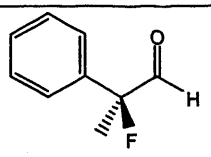
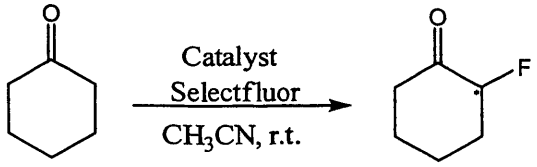
Entry	Product	Catalyst	Time (h)	Yield (%)	ee (%)
1		**50b**	2	74	96
2		**50b**	3	90	88
3		**50b**	3	59	93
4		**50b**	2	97	88
5		**45a** **45c** **49**	24 6 2	93 98 98	44 66 55
6		**45a** **45c** **49**	24 6 2	93 92 99	28 40 45

Table 1.35 *The Fluorination of Aldehydes Using Proline Based Organocatalysts*

Enders also carried out work in this area and investigated the proline-catalysed α-fluorination of aldehydes and ketones.[76] Initially, the fluorination of cyclohexanone **(51)** was investigated using (*S*)-proline **(45a)** as the catalyst, Selectfluor as the source of fluorine, acetonitrile as the solvent and one equivalent of trifluoroacetic acid. The addition of the acid not only promoted the formation of the enamine[77] and increased the reactivity of Selectfluor, but it also increased the solubility of the proline catalyst. Unfortunately, the enantioselectivity of this reaction was found to be low and only 29 % ee was observed (Table 1.36, entry 1). Therefore, various other organocatalysts were screened for their reactivity and selectivity in the asymmetric fluorination of cyclohexanone, but all led to moderate yields and poor enantiomeric excesses (Table 1.36).



(51)

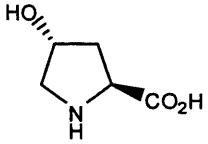
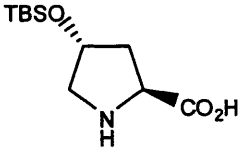
Entry	Catalyst	Time (h)	Yield (%)	ee (%)
1	**45a**	2.5	43	29
2	**45b**	21	42	17
3	**45d**	96	56	3
4		21	56	34
5		21	60	32

Table 1.36 *The Fluorination of Cyclohexanone with Selectfluor Using Various Organocatalysts*

1.5 Conclusions and Project Outline

Catalytic asymmetric fluorination, either with a transition metal catalyst or an organocatalyst, is an efficient way to selectively introduce fluorine into a compound. Although the range of substrates that can be fluorinated with high enantioselectivity by asymmetric catalysis has expanded significantly during my PhD studies, the transition metal catalysts require the enolate to be bound to the metal and so the substrates are limited to those capable of two-point binding. The organocatalysts only work for primary aldehydes. Reagent-controlled asymmetric fluorination requires the use of a stoichiometric quantity of the reagent and usually a number of reagents have to be screened to obtain the best results. The main advantage of this method is the wide range of substrates that can be fluorinated including silyl and acetyl enol ethers. The *N*-fluorocinchona alkaloids have proven to be the superior reagents for reagent controlled asymmetric fluorination as not only can they fluorinate the widest range of substrates, but they do so in high yields and high enantiomeric excesses. The cinchona alkaloids are relatively cheap starting materials and derivatisation is possible at various points on the structure due to the number of functional groups they contain. Therefore, work in this thesis has concentrated on synthesising a range of novel asymmetric

fluorinating reagents based on the cinchona alkaloids as these compounds show the most promise.

Cahard's group carried out some preliminary work to determine what structural factors of the cinchona alkaloid affect the selectivity of a particular reaction, but there was still far more to be explored. The main limiting factor displayed by all of the work so far was the use of commercially available cinchona alkaloids as reagents. Although this provides a simple route to the synthesis of effective $[N\text{-}F]^+$ reagents, a small amount of structural modification has the potential to increase enantioselectivity and provide a tool to allow the fine tuning of the fluorinating reagent to suit the substrate.

The aim of the work presented in this thesis was to synthesise a range of novel asymmetric fluorinating agents based on the cinchona alkaloid structure. Chapter Two focuses on the synthesis of a cinchona alkaloid-like compound from a commercially available source of the quinuclidine moiety and the investigation of quinidinone and ways of preventing its epimerisation to quininone. Chapter Three contains the addition of Grignard reagents to quinidinone to yield a new generation of cinchona alkaloids with an R group at the C9 position. The esterification of the hydroxyl function and the fluorination of the new and known cinchona alkaloids to the *N*-fluoro derivatives are also described. Chapter Four focuses on the synthesis of the model substrates that underwent preliminary testing of the new and known *N*-fluorocinchona alkaloids. A comparison is made between the efficiency of the pre-formed and *in situ* produced reagents and two different electrophilic sources of fluorine are also investigated. Finally, the potential for these reagents to be used in asymmetric phase transfer catalysis is discussed.

1.6 References

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Chapter Two

University *of*
Leicester

The Synthesis of and Reactions with 8-Fluoroquininone and 8-Fluoroquinidinone

2.1 Introduction

The total synthesis of cinchona alkaloids has been the subject of study for many years and various procedures are to be found in the literature.[1-3] Uskokovic[4-7] published one total synthesis which involved the formation of meroquinene (Figure 2.1). Meroquinene was synthesised in three steps followed by the separation of the enantiomers. To form the cinchona alkaloid, a meroquinene derivative was cyclised to form the quinuclidine ring and was then combined with the quinoline moiety (method A) or vice versa (method B). Method A involves the quinuclidine ring being formed first to give compounds like **(52)** which was reacted with 6-methoxy-4-quinolyllithium **(53)** to give quinine, quinidine and their two 9-epi isomers (Scheme 2.1). Notably, all four of these compounds contain the same 1*S*, 3*R*, 4*S* configuration and vary only at C8 and C9 with the assignments being quinine **(56)** (8*S*, 9*R*), quinidine **(57)** (8*R*, 9*S*), epi-quinine **(58)** (8*S*, 9*S*) and epi-quinidine **(59)** (8*R*, 9*R*). As the two 9-epi isomers were biologically inactive, they were converted to quinine and quinidine via oxidation to the epimers, quininone **(54)** and quinidinone **(55)**, and a stereoselective reduction with diisobutylaluminium hydride (DIBAL-H) (Scheme 2.2). The stereoselectivity of this reduction was due to the Lewis acidic DIBAL-H forming a complex with the quinuclidine nitrogen of quininone and quinidinone.[8] It was also possible to reduce quininone and quinidinone to predominately the two 9-epi isomers by the use of sodium borohydride (Scheme 2.2). In this case hydride attack occurred at the opposite face to that attacked by DIBAL-H so as to avoid the lone pair of electrons on the quinuclidine nitrogen. This method for the formation of cinchona alkaloids was not only used to synthesise quinoline type alkaloids but also to synthesise indole derivatives such as dihydrocinchonamine **(60)** (Figure 2.2).

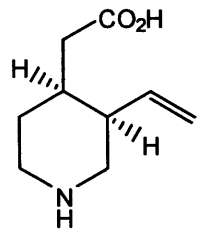
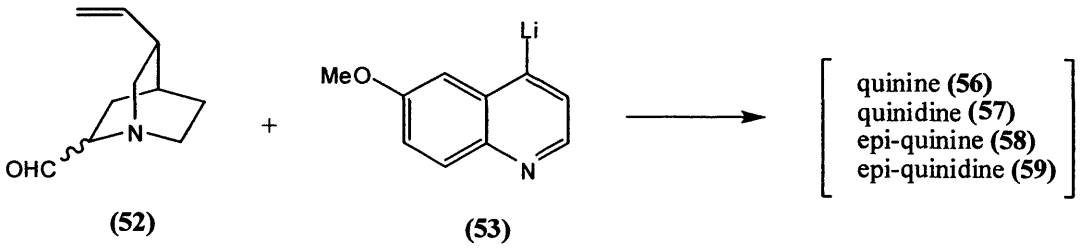
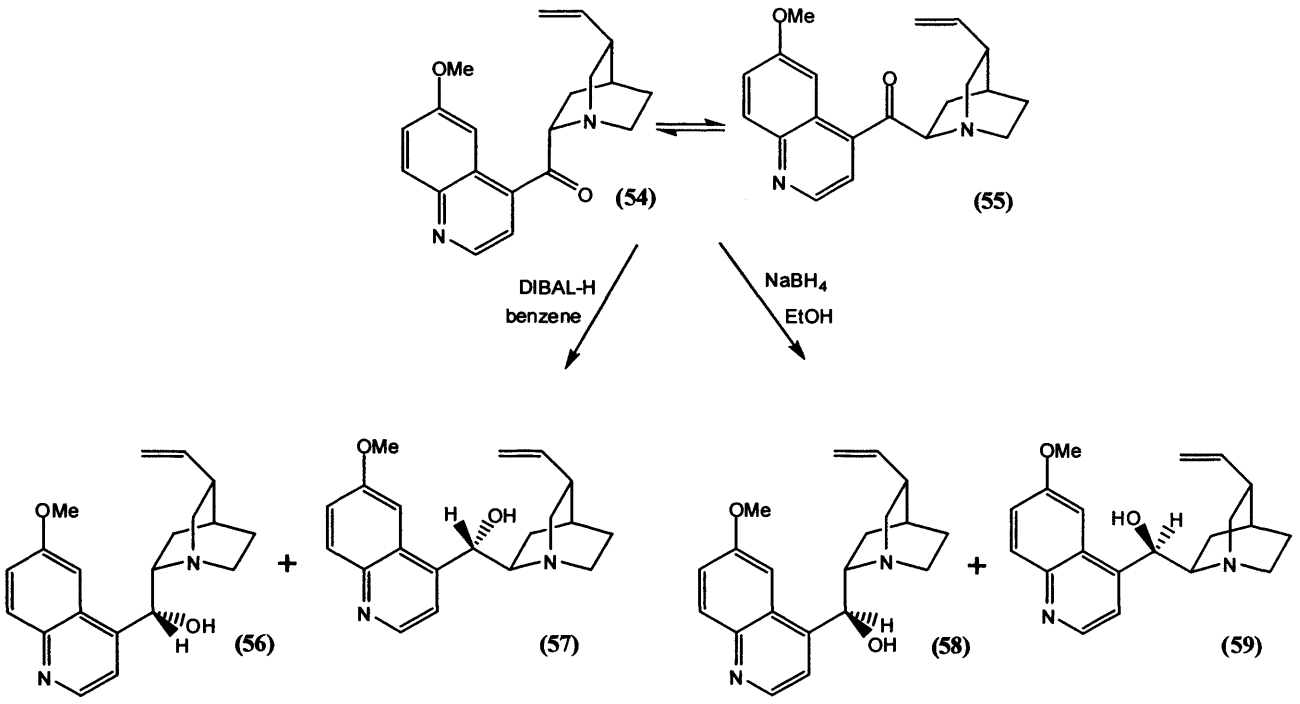


Figure 2.1 *The Structure of Meroquinene*



Scheme 2.1 *The Total Synthesis of Quinine (Method A)*



Scheme 2.2 *The Stereoselective Reduction of Quininone (54) and Quinidinone (55)*

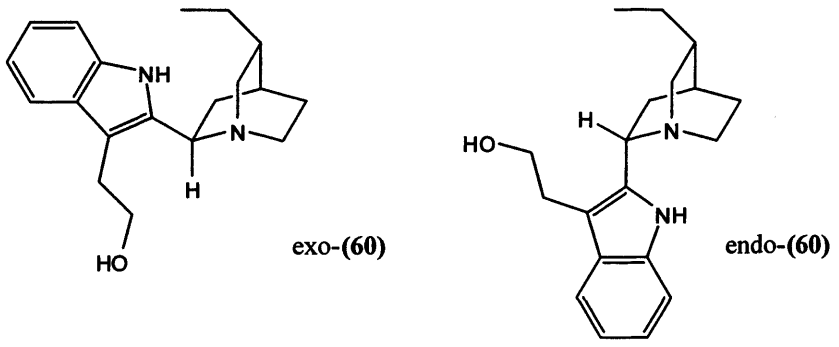
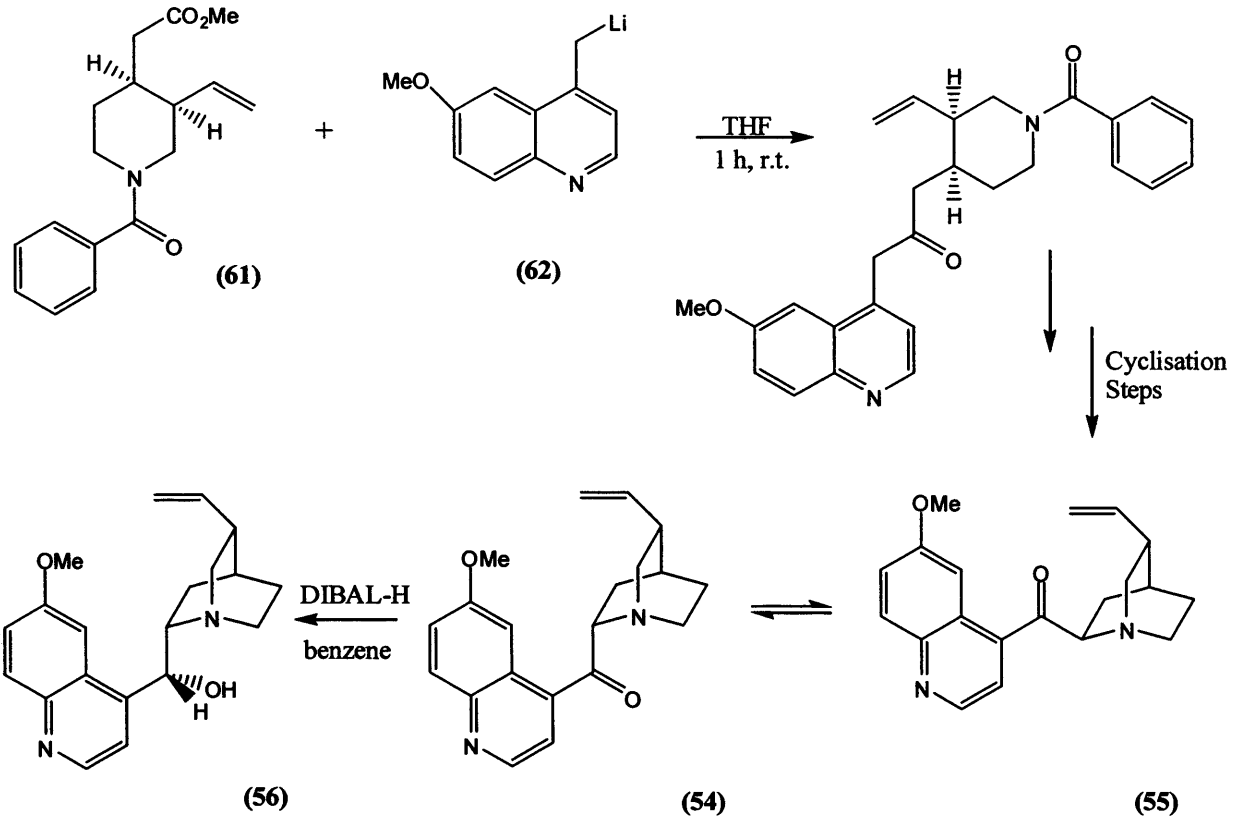


Figure 2.2 *The Two Diastereoisomers of Dihydrocinchonamine (60)*

In method B,[4,5] [(6-methoxyquinolin-4-yl)methyl] lithium **(62)** was added to a derivative of meroquinene **(61)**. After cyclisation to form the epimeric mixture of quininone and quinidinone, they were stereoselectively reduced with DIBAL-H as shown previously.

The products quinine **(56)** and quinidine **(57)** were obtained in an approximate 1:1 ratio and could be separated to yield both diastereoisomers pure in seven steps. One advantage of this synthesis was that different analogues could be formed by varying the substituents on the aromatic ring (Scheme 2.3).



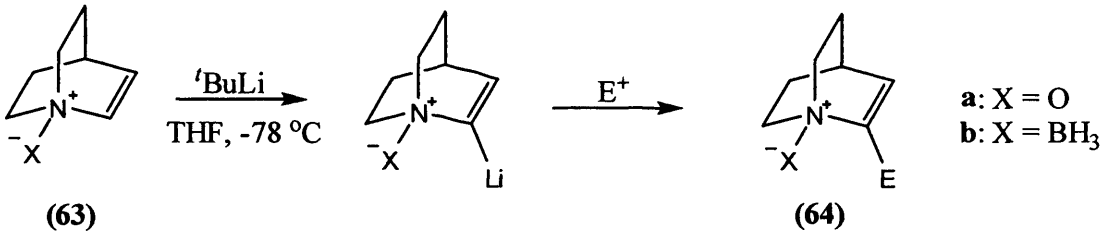
Scheme 2.3 *The Total Synthesis of Quinine (56) (Method B)*

The disadvantage of both of these methods is the long, multi-step syntheses particularly in the formation of the quinuclidine ring, as well as the poor yields obtained in many of the steps. There are other procedures in the literature for the formation of quinuclidine rings,[9,10] but all involve many steps. As there are many cheap, commercially available sources of the quinuclidine moiety, a synthesis which utilises this would be advantageous. Two different approaches using 3-quinuclidinol and 3-quinuclidinone hydrochloride as the starting materials were investigated.

2.2 Synthesis from 3-Quinuclidinol

O'Neil[11] synthesised the enamine *N*-oxide **(63a)** and the corresponding borane complex **(63b)** in good yields from 3-quinuclidinol (Scheme 2.4). Then **(63a)** and **(63b)** were lithiated and reacted with various electrophiles (Scheme 2.4, Table 2.1). The reaction with

aldehydes and ketones were of particular interest to us as the products from these reactions could potentially be used as precursors to modified cinchona alkaloid type compounds.

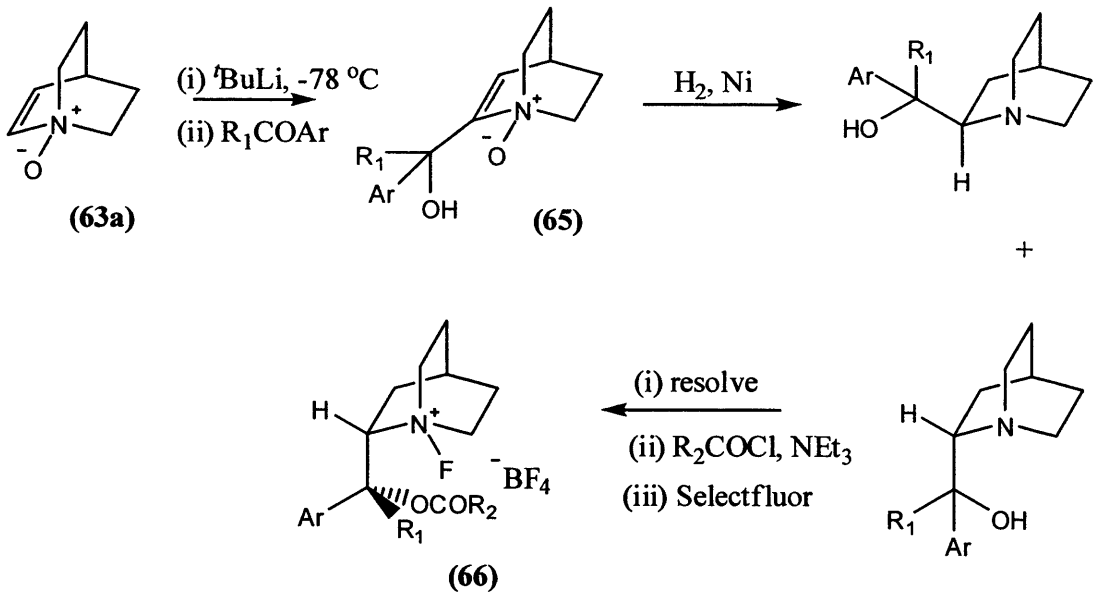


Scheme 2.4 *The Formation of* ***(64)*** *by Addition of Various Electrophiles*

Substrate	Electrophile	Yield (%)
X = O	Br_2	74
X = O	PhCHO	78
X = O	Bu_3SnCl	75
X = O	Ph_2CO	60
X = O	Fluorenone	85
X = O	$PhC(O)CH_3$	20
$X = BH_3$	Ph_2CO	81
$X = BH_3$	I_2	86
$X = BH_3$	Bu_3SnCl	56

Table 2.1 *The Reaction of* ***(63a)*** *and* ***(63b)*** *with Various Electrophiles*

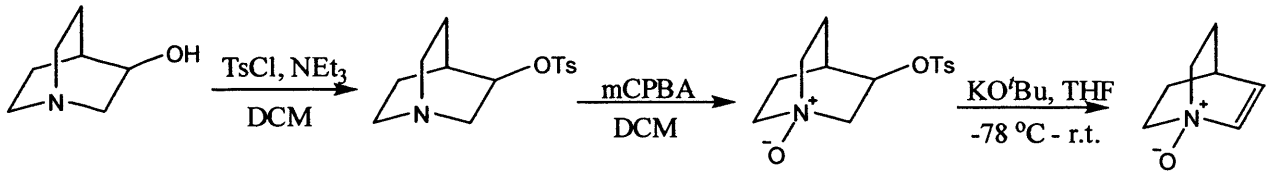
Scheme 2.5 outlines the proposed route to cinchona alkaloid type compounds using the enamine *N*-oxide **(63a)**. A suitable non-enolisable ketone or aldehyde would be used in the first step as competing enolisation of the electrophile lowers the reaction yield. The *N*-oxide **(65)** and the double bond would be reduced in one step to give two pairs of enantiomers that would each have to be separated. Finally, the –OH group would be protected and the quinuclidine ring fluorinated to give the N-F reagent **(66)**.



Scheme 2.5 *The Proposed Route to Cinchona Alkaloid Type Structures (66)*

One advantage of this method was the use of a pre-formed quinuclidine moiety as this reduces the number of steps in the synthesis compared to the total synthesis methods. This method also allows for more diversity to be introduced than previous attempts. The addition of an aldehyde to the enamine *N*-oxide, would lead to a secondary alcohol like that of quinine and quinidine, but the aromatic group could be varied to produce novel cinchona alkaloid-like compounds. There was also the possibility of synthesising a compound without any aromaticity by the addition of an aliphatic aldehyde. The addition of a ketone to the enamine *N*-oxide **(63a)** on the other hand would lead to a tertiary alcohol and a novel family of cinchona alkaloid-like structures as all previous examples are secondary alcohols. The number of novel compounds that could be produced would be vast as there would be two areas of diversity and that does not included the protection of the hydroxyl group. The addition of bulky groups should not cause a problem as O'Neil has proven in his work that large groups can be added to the enamine *N*-oxide in good yields. The ability to vary the structure in three places would be a major advantage when the compounds are tested in a fluorination reaction as certain groups could be added or removed from the novel N-F reagent as our understanding of the reaction improves. Another major advantage of this synthetic route was the access to quinine, quinidine, epi-quinine and epi-quinidine-like compounds. This would provide a method to yield both enantiomers of a fluorinated substrate in excess.

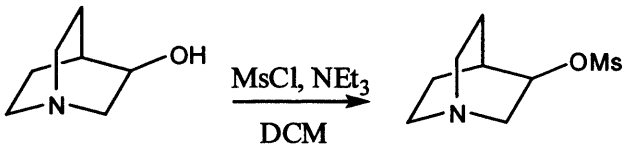
Synthesis of N-Oxide (63a)



(67) **(68)** **(69)** **(63a)**

Scheme 2.6 *The Synthesis of Enamine N-Oxide (63a)*

Initially, the *N*-oxide **(63a)** was synthesised from 3-quinuclidinol **(67)** as shown in Scheme 2.6. As there was no experimental procedure published, the quantities of reagents and reaction conditions had to be optimised. A procedure for the tosylation of a secondary alcohol by Kabalka[12] was used to develop a method for the first step. After attempting the reaction numerous times, it was found that using a slight excess of 3-quinuclidinol **(67)** gave the best results. Since the paper stated that the crude product was purified by column chromatography, a lot of work was put into finding a suitable eluting solvent. A suitable solvent or combination of solvents could not be found, but the crude product could be purified easily by washing with a dilute basic solution followed by brine. Washing with just brine was also attempted, but it was not as effective. Pure tosyl product **(68)** was synthesised in a 74 % yield and the key to obtaining the good yield is the reaction temperature. The whole reaction vessel must be kept at 0 °C, otherwise the reaction mixture turns orange. Not only was the yield of **(68)** lower, but reacting above 0 °C also lowers the purity. Alongside this experiment, the synthesis of the mesyl product **(70)** was attempted (Scheme 2.7), but failed to produce the desired product. This method was abandoned when **(68)** was obtained pure.



(67) **(70)**

Scheme 2.7 *The Attempted Synthesis of the Mesyl Product (70)*

A procedure for the formation of tertiary *N*-oxides was published by Craig[13] and a wide range of tertiary nitrogen containing compounds were oxidised and purified in the same way. This procedure was followed to produce the *N*-oxide **(69)**, but the purification was more complicated. According to Craig the crude product should be put through a column of basic alumina to give the pure product. The column should remove any unreacted starting material,

and as the *m*CBA residue "complexes" with the *N*-oxide, the basicity of the column holds onto the acid to give the pure *N*-oxide. After several attempts, the *N*-oxide **(69)** could not be obtained pure using this purification method. The basic column did remove the acid, as there was a definite highfield shift of at least seven protons in the ^{1}H NMR spectra of the crude and purified *N*-oxides. To obtain pure *N*-oxide **(69)**, however, it was necessary to carry out a second column using neutral alumina.

O'Neil stated that the reaction of the *N*-oxide **(69)** with potassium *t*-butoxide was carried out in THF, but the *N*-oxide **(69)** was not very soluble in THF and a large amount of solvent was required to dissolve a small quantity of solid. At the end of the reaction, water was added to destroy the potassium *t*-butoxide and the total volume of the solution was reduced before extracting with ether. The product was expected to be in the organic layer, but the ^{1}H NMR spectrum showed that this was not the case. The ^{1}H NMR spectrum of the aqueous layer showed the characteristic vinyl proton peaks at δ 6.44 and 6.65 ppm. Therefore, the aqueous layer was extracted with chloroform, but initially the ^{1}H NMR spectrum did not show any signals from the expected product. It was thought that the product formed dissolves in water in preference to all other solvents. Hence, the water was removed from the aqueous layer and a small amount of the residue was stirred in dichloromethane for ~ 30 mins. The ^{1}H NMR spectrum showed very clear peaks for the alkene protons, but there were still a few impurities present. The residue was re-dissolved in water and was then extracted with dichloromethane in order to remove the impurities. After removing the water from the aqueous phase, the product was finally obtained fairly pure by stirring with dichloromethane, but only a small amount of product was obtained. A second extraction with dichloromethane yielded slightly more product, but it still was not much. Small amounts of the residue were stirred in other solvents to try and obtain better results. Acetone and chloroform were chosen, and while no product was found in the acetone, the chloroform yielded a negligible amount.

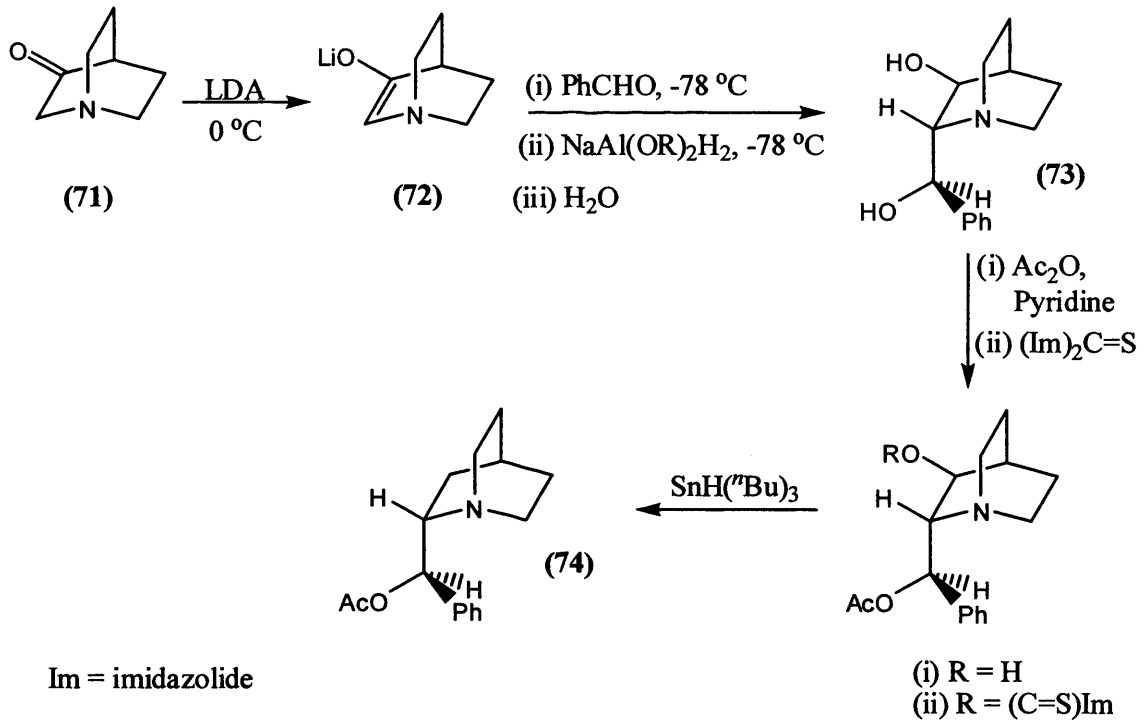
The reaction was repeated using one equivalent of potassium *t*-butoxide and the ^{1}H NMR spectrum of the crude product confirmed the presence of the double bond. A small sample of the solid was dissolved in chloroform and then ether was added to precipitate out the *N*-oxide **(63a)**. The small amount of solid obtained contained some product, but a lot of impurity according to its ^{1}H NMR spectrum. The product was finally purified using the same method as described above. After dissolving it in dichloromethane, it was extracted with water and the ^{1}H NMR spectra confirmed that there was no product in the dichloromethane layer, but there was a considerable amount in the aqueous layer along with a small amount of impurity. Finally, the oil obtained from the aqueous layer was extracted into dichloromethane. The resulting brown oil showed a clean ^{1}H NMR spectrum and the reaction was repeated on a larger scale to give the pure *N*-oxide **(63a)** in a poor yield (27%).

The overall yield for this three step synthesis was only 17 % which was very disappointing since compound **(63a)** is the key intermediate in Scheme 2.5 before diversity is introduced. The main problem was the low yield (27 %) in the third step due to the difficult purification of *N*-oxide **(63a)**. One solution would be to scale up the reaction but as the amount of solvent used in the elimination of *N*-oxide **(69)** was high, increasing the scale would be wasteful. Another solution was to repeat the reaction many times, but this would be very time consuming. Another concern about the proposed route in Scheme 2.5 was the lack of stereoselectivity in the hydrogenation of compound **(65)**. Not only would a pair of diastereoisomers have to be separated after this step, which can be difficult, but the next step would involve the resolution of enantiomers and this can be impossible. Alternatively, the enantiomers of **(65)** could be separated before reducing the double bond. However, due to all of these concerns, an alternative, more selective synthetic route that produces a single enantiomer or a pair of diastereoisomers that can easily be separated was sought.

2.3 Synthesis from 3-Quinuclidinone Hydrochloride (71)

In 1985 Stotter[14] published a new approach to the synthesis of quinine. The lithium enolate of 3-quinuclidinone hydrochloride **(72)** was reacted with benzaldehyde at low temperature in a stereoselective aldol condensation (Scheme 2.8). An *in situ* reduction with Red-Al formed predominately isomer **(73)** of the product and after recrystallisation only isomer **(73)** was obtained. In order to remove the hydroxyl group on C3, the benzylic hydroxyl group had to be protected first. The acetyl protecting group was chosen as the addition and subsequent removal would not involve the use of an acidic solution thus reducing the risk of epimerisation of **(73)**. After protecting, the C3 hydroxyl group it was removed by the addition of tri-*n*-butyltin hydride to yield compound **(74)**. It was not known whether exchanging the benzaldehyde for another aldehyde would affect the selectivity of the reaction or if a ketone could be used instead. The use of a ketone would be interesting as it would form a tertiary alcohol product and an extensive search of the literature has yet to yield a synthesis of such a compound. The reason that this method was examined for the synthesis of novel cinchona alkaloid-like compounds was that it utilised a cheap source of the quinuclidine moiety, but unlike the previous method, the reaction was more selective thus avoiding the separation of diastereoisomers or enantiomers. The proposed route leads to compounds of the quinine-type which have proven in the literature to generally give higher enantiomeric excesses in fluorination reactions. The relatively short route of six steps allows for two areas of diversity with the addition of various aldehydes and protecting groups. If the

addition of a ketone to **(72)** proves to be possible, then a third point of diversity would be created.



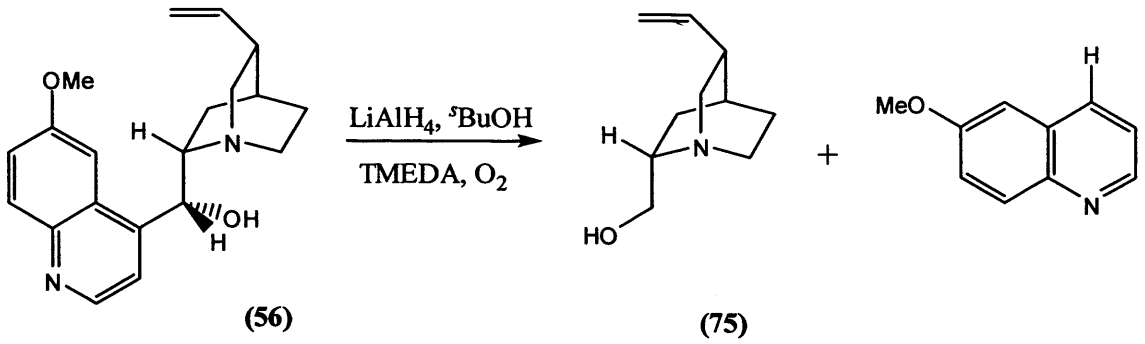
Scheme 2.8 *The Selective Formation of (74) from 3-Quinuclidinone Hydrochloride (71)*

Synthesis of Compound (73)

The first aim was to synthesise compound **(73)** using the procedure published by Stotter. The only small difference was instead of using ethereal CH_3Li and diisopropylamine to form lithium diisopropylamine (LDA) in the flask, a solution of commercial LDA was used. Also, the 3.5 M solution of sodium bis(2-methoxyethoxy)aluminum dihydride in THF was diluted to a 1.15 M solution by the addition of dry and degassed toluene to allow the solution to be transferred under nitrogen as it was a very viscous solution. The resulting crude product contained some impurities and was recrystallised from a THF/hexane (1/1) solvent mixture. The recrystallised product still contained some impurities, one of which could be 3-quinuclidinol. The impurity peaks are in the same region of the ^1H NMR spectrum as those of 3-quinuclidinol and also there was a parent ion peak in the mass spectrum at 128 that is consistent with 3-quinuclidinol. There was, however, no unreacted 3-quinuclidinone hydrochloride starting material remaining in the product. The amount of recrystallised product (only 13% yield) was very poor and includes some minor impurities. Also, the selectivity of this reaction was not as good as expected because the optical rotation showed that the product was racemic.

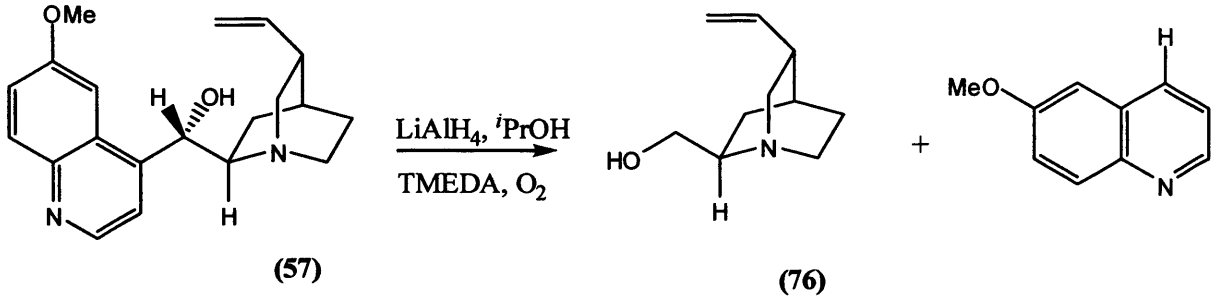
After these disappointing results, it became apparent that using these small quinuclidine starting materials was not the way forward. The yields and selectivity of the reactions are just not high enough and a more selective method was required.

2.4 Quincorine (75) and Quincoridine (76)



(56) (75)

Scheme 2.9 *The Synthesis of Quincorine (75) from Quinine (56)*

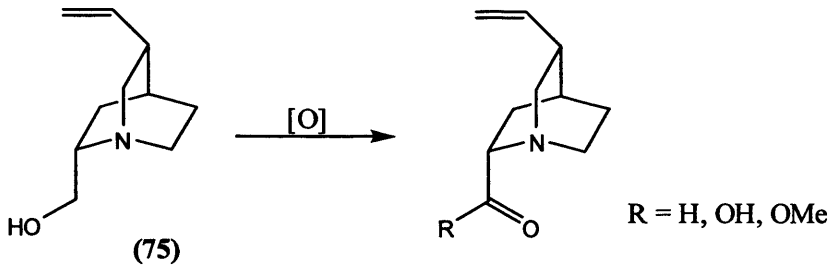


(57) (76)

Scheme 2.10 *The Synthesis of Quincoridine (76) from Quinidine (57)*

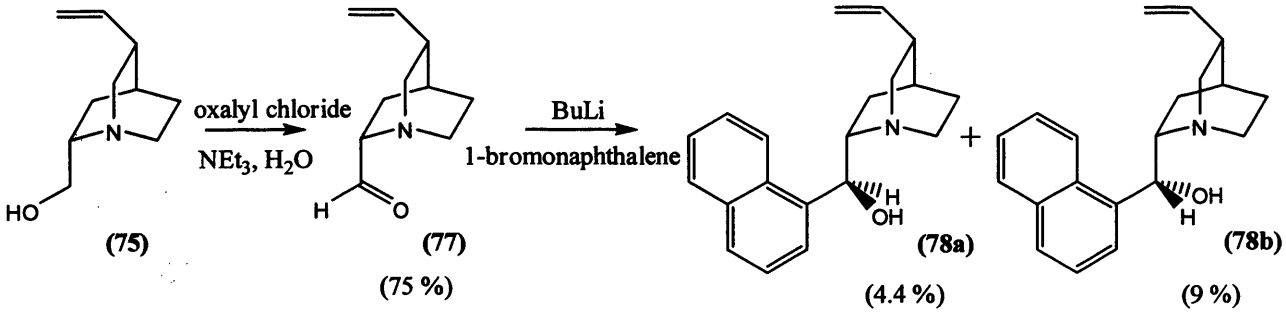
Hoffmann[15] synthesised quincorine **(75)** and quincoridine **(76)** from quinine and quinidine respectively (Schemes 2.9 and 2.10). He also oxidised these compounds to form the carboxylic acid, aldehyde or ester (Scheme 2.11).[16] The aldehydes and esters of these compounds had already been synthesised, but as epimeric mixtures and in poor yields. It is known that the oxidation of 1,2-amino alcohols to α-amino acids is difficult, especially if the nitrogen is unprotected. All standard methods for the oxidation of quincorine and quincoridine failed to yield the desired products. In some cases *N*-oxides or aldol-like coupling products were obtained. The only suitable method was Jones oxidation followed by esterification. In the first step, the Jones reagent had to be added slowly and carefully in order to achieve epimerically pure α-amino acid esters, as the carboxylic acid that was initially produced, forms a stable chromium chelate prior to epimerisation. Hoffmann found that the aldehyde was very unstable, so its synthesis and isolation was abandoned in favour of the

ester synthesis. Quincorine **(75)** and quincoridine **(76)** are extremely useful compounds as they are synthesised from cheap, commercially available starting materials, quinine **(56)** and quinidine **(57)** respectively, to yield useful chiral building blocks which each contain four chiral centres. There was also no loss in stereochemistry during the synthesis of these compounds, so providing ideal starting materials for introducing diversity into the cinchona alkaloid type structure.



Scheme 2.11 *The Oxidation of Quincorine (75) to the Aldehyde, Carboxylic Acid or Ester*

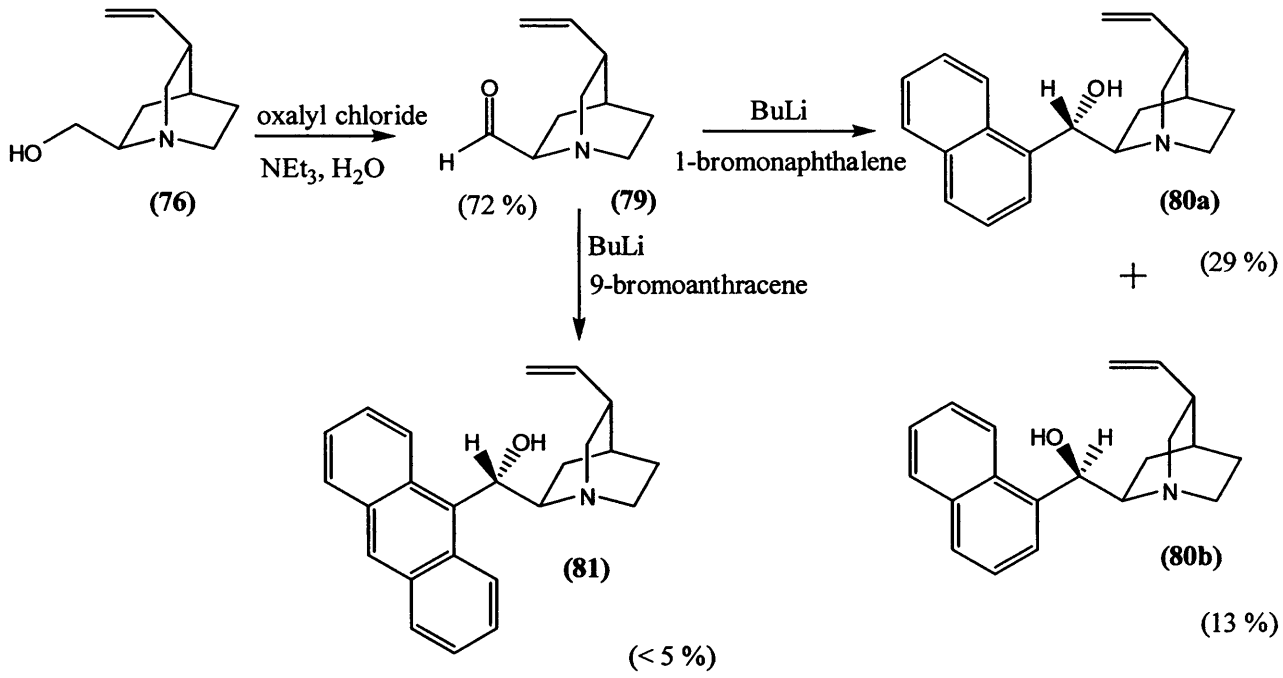
Recently, Dehmlow[17] oxidised quincorine **(75)** and quincoridine **(76)** to their corresponding aldehydes by Swern oxidation to give epimerically pure products. The aldehydes had to be used immediately indicating that these compounds epimerise over time. The organometallic coupling of the quincorine aldehyde **(77)** with 1-lithionaphthalene gave the diastereoisomers **(78a)** and **(78b)**, which could be separated by column chromatography (Scheme 2.12).



Scheme 2.12 *The Synthesis of Cinchona Alkaloid Type Structures (78a) and (78b)*

These compounds have very similar structures to the cinchona alkaloid derivatives that are the aim of this project. Unfortunately, the yields for these compounds were very poor. The oxidation of quincoridine **(76)** to aldehyde **(79)** and subsequent addition of 1-lithionaphthalene gave the two diastereoisomers **(80a)** and **(80b)** in better yields (Scheme 2.13). Aldehyde **(79)** was also reacted with 9-lithioanthracene to give a mixture of

diastereoisomers, but the overall yield was extremely poor and only the major diastereoisomer **(81)** could be isolated.



Scheme 2.13 *The Synthesis of Cinchona Alkaloid Type Structures* ***(80a), (80b) and (81)***

Although the reactions in Schemes 2.12 and 2.13 are low yielding, the ease in which the desired compounds can be synthesised and separated are advantageous. The separation of a pair of diastereoisomers is much easier than separating enantiomers, which would be required in the previous routes. Also, depending on the starting material used, quinine-like or quinidine-like products can be formed providing access to all four types of cinchona alkaloids (quinine **(56)**, quinidine **(57)**, epi-quinine **(58)** and epi-quinidine **(59)**). This would be extremely useful when the final fluorinating reagents are made as each pseudo-enantiomer should give the opposite configuration of the product. This route also has two areas of diversity which could be varied in order to produce a library of novel compounds.

Synthesis of Quincorine (75)

The synthesis of quincorine **(75)** was attempted over quincoridine **(76)** because quinine was slightly cheaper to buy and more importantly, it gives the better yield in this step (Scheme 2.9). Hoffmann does give a brief procedure for the synthesis of these two compounds, but no ^{1}H NMR data is available. The reaction was followed on the same scale as the procedure described. The first two attempts were carried out simultaneously. Both of the reaction vessels had a drying tube fitted after the addition of lithium aluminium hydride, s-

butanol, TMEDA and quinine and was left stirring for four days. In one of the reactions the hydroxyl group was Boc protected in order to isolate the protected alcohol. Unfortunately, the first, unprotected attempt at this reaction gave only starting material and even the Boc protected approach did not give the required product. The problem could be the $LiAlH_4$ since Hoffmann states that $LiAlH_4$ from a freshly opened bottle was used. The reaction was repeated using fresh $LiAlH_4$ under the same conditions. At the end of the reaction the ^1H NMR spectrum did not shown any clear signs of quincorine, but the mass spectrum did pick out a peak at 168 which could possibly be the parent ion peak of quincorine, so the reaction mixture was carried forward to the Boc protection step. Unfortunately, there was no evidence in the ^1H NMR spectrum or mass spectrum for the Boc protected quincorine. This could be because the amount of product was so small and the signals from the other products were masking the quincorine signals, but an attempted purification of the reaction mixture by column chromatography yielded no product. A reaction using ether as the solvent instead of THF was carried out using fresh $LiAlH_4$. This reaction also did not work, possibly because of the reactants poor solubility in ether. The results of this reaction were very disappointing so another method for the synthesis of novel cinchona alkaloid type compounds was required.

2.5 Quininone (54)/Quinidinone (55)

Similar to Hoffmann's work, it may be possible to adapt the cinchona alkaloid itself in order to synthesise new derivatives of the cinchona alkaloid structure. In the total synthesis of cinchona alkaloids (Scheme 2.3), the diastereoisomers quininone **(54)** and quinidinone **(55)** were synthesised. As these compounds contain a carbonyl group, they could be adapted to form new derivatives of cinchona alkaloids. The literature on these compounds proved to be rather confusing because the terms quininone and quinidinone were not used until 1947 to differentiate between the two diastereoisomers.[18] Previously, it was believed that the product formed from the oxidation of quinine **(56)** was quininone **(54)**, when it was in fact quinidinone **(55)**. Confusingly, the former name has stuck and even now some papers refer to quinidinone as quininone.[19] The synthesis of quininone/quinidinone has been known for almost 100 years when Rabe first oxidised quinine by chromic acid oxidation in 1909.[20] Since that time other methods of oxidation have been attempted with varying degrees of success. Woodward carried out the most thorough investigation of quinidinone, and not quininone as the title of his paper suggests, and its structure in 1945.[21] He attempted to oxidise quinine by utilising the Oppenauer oxidation method, but unfortunately this failed due to the Lewis acidic aluminium catalyst forming a complex with the basic nitrogen atom in the quinuclidine ring of quinine. It is commonplace to use aluminium catalysts in hydrogen transfer reactions

as the aluminium atom aids proton release from the alcohol and increases the acceptor capacity of the ketone. Woodward realised these driving forces were not unique and the same can be seen in any system containing primary or secondary alkoxide ions and carbonyl compounds. With this in mind he successfully oxidised quinine to yield quantitative amounts of quinidinone in the presence of a benzophenone H-acceptor **(82),** and potassium *tert*-butoxide (an alkali alkoxide). This method was also used to synthesise quinidinone from quinidine **(57)**, dihydroquinidinone from dihydroquinine and dihydrocinchoninone from dihydrocinchonine. It was determined that an equilibrium (Figure 2.3) occurs during the course of the reaction and by using an excess of benzophenone, the equilibrium gets pushed to the right leading to quantitative yields of quinidinone. The use of only one mole of benzophenone yields 80 % quinidinone as the equilibrium naturally favours product formation due to the stable potassium enolate **(83)** and the strongly acidic properties of the ketone. The fact that the formation of quinidinone goes via an enolate which eliminates the stereochemistry at both the C8 and C9 positions and that quinine and quinidine both gave the same single product after oxidation means that one diastereoisomer of the ketone was considerably more favoured than the other.

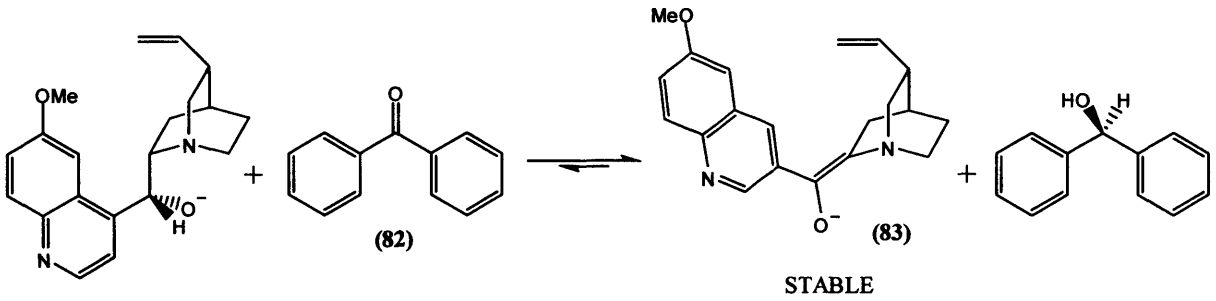


Figure 2.3 *The Equilibrium In The Oxidation of Quinine*

Woodward carried out many reactions in an attempt to determine the stereochemistry at the C8 position of the pure crystalline quinidinone. Initially, the reverse reaction was carried out by reducing the quinidinone with 10 moles of sodium diisopropoxide. Quinine **(56)** and quinidine **(57)** were the two products isolated in 30 % and 60 % yields respectively, implying that the product favours the quinidine type structure rather than the quinine type. Further evidence came from the catalytic hydrogenation of quinidinone, dihydroquinidinone and a derivative, 10,11-dibromoquinidinone, to which the sole product in all three cases was dihydroquinidine. Methyl and isobutyl Grignard reagents were also reacted with quinidinone to yield methylquinidine and isobutylquinidine, but the assignment of these structures was more hesitant and was based on the specific rotations. Quinidine is known to have a high positive specific rotation as does methylquinidine, isobutylquinidine and quinidinone itself, while quinine has a high negative specific rotation. Quinidinone does mutarotate in polar

solvents to gradually give a solution with a lower positive specific rotation due to the formation of the other stereoisomeric form, quininone **(54)**, via the enol **(84)** (Figure 2.4). In non-polar solvents though, this mutarotation does not occur.

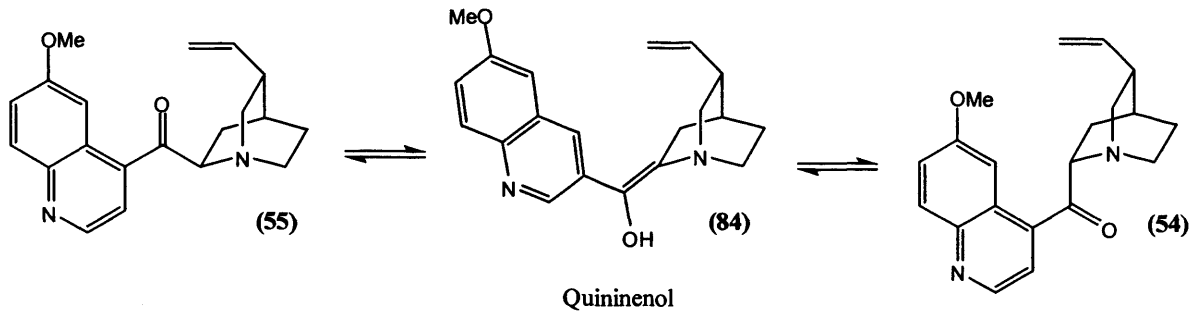
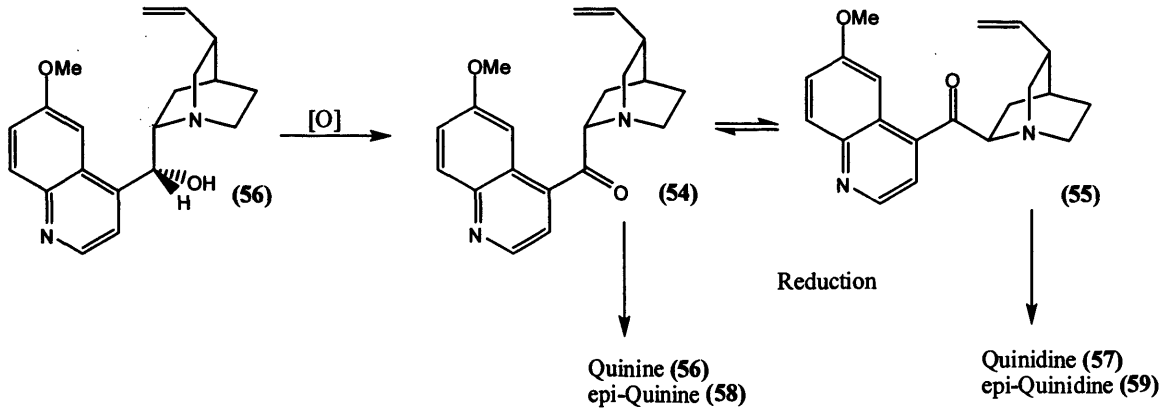
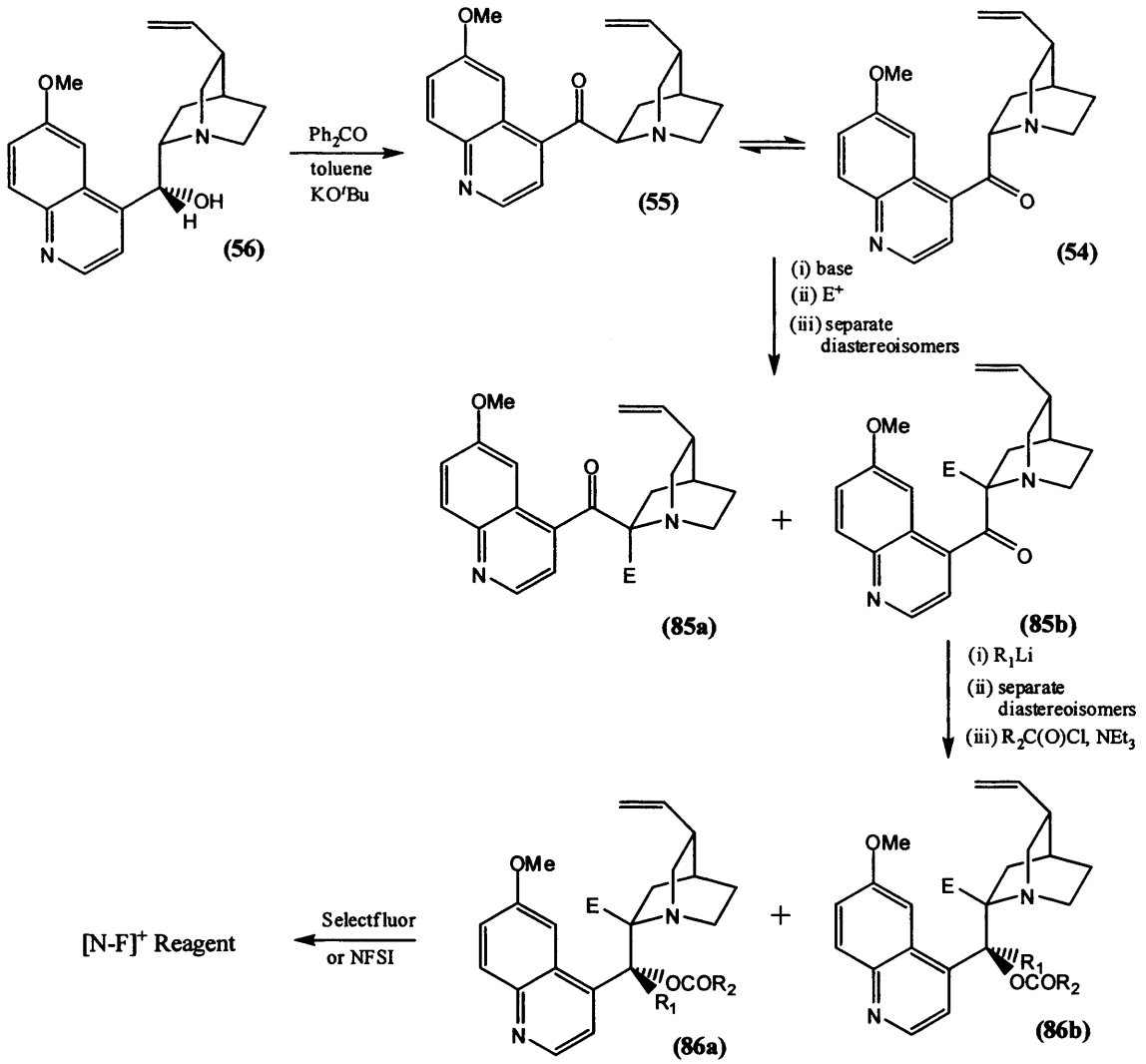


Figure 2.4 *The Mutarotation of Quinidinone to Quininone in Solution*

Doering supported the assignment of quinidinone during his investigation of the racemisation of quinine.[18] He observed that by boiling quinine in a solution of potassium hydroxide in amyl alcohol, a mixture of quinine (7 %), quinidine (10-15 %), epi-quinine (15-20 %) and epi-quinidine (15-20 %) was obtained and that the same ratio of products was obtained by boiling quinidine under identical conditions (Scheme 2.14). He proposed a two step mechanism to explain these results whereby the first step was the oxidation of quinine to quininone, thus removing the stereochemistry at the C9 position, and the stereochemistry at the C8 position once the base-catalysed equilibrium was established. The second step was the reduction of the two stereoisomeric forms, quininone **(54)** and quinidinone **(55)**. The reduction of quininone led to the formation of quinine **(56)** and epi-quinine **(58)** and the reduction of the more favoured quinidinone **(55)** resulted in quinidine **(57)** and epi-quinidine **(59)**.



Scheme 2.14 *The Formation of Quinine, Quinidine, epi-Quinidine and epi-Quinine from Quinine*



Scheme 2.15 *The Proposed Route to the Synthesis of Novel Asymmetric Fluorinating Reagents*

Since, quinidinone is the less soluble epimer, it can be obtained from a diastereomeric mixture by recrystallisation.[8] As quinidine type reagents lead to poorer enantioselectivity when used as a chiral fluorinating agents compared to quinine-type reagents,[22] a method for obtaining the unfavourable quininone was also required. It was known from ^{1}H and ^{13}C NMR spectroscopy studies on the tautomerisation of quinidinone that in equilibrium the quininone tautomer was favoured.[23] Therefore, reacting either quinidinone or a quininone/quinidinone mixture with a base, the same enolate would be formed and the aim was to introduce a small electrophile at the C8 position thus creating a pair of diastereoisomers with locked conformations whilst retaining the carbonyl functionality (Scheme 2.15). After separating the derivatised quininone **(85b),** from the derivatised quinidinone **(85a),** it could be subjected to a nucleophilic attack on the carbonyl by an alkyl or aryl lithiate (R_1Li) to yield a second pair of diastereoisomers. After the separation of these diastereoisomers, the hydroxyl group could then be protected by esterification with an acid chloride (R_2COCl) to give the diastereisomers

(86a) and **(86b)** (Scheme 2.15). The final step would be the fluorination of the quinuclidine nitrogen with an electrophilic source of fluorine like Selectfluor or NFSI to yield the new, chiral $(N\text{-}F)^+$ fluorinating agent.

This synthetic route has many advantages. One advantage was that the separation of diastereoisomers was required rather than the resolution or separation of enantiomers. The separation of diastereoisomers can usually be carried out by using standard laboratory techniques e.g. column chromatography whilst the separation of enantiomers involves the use of a chiral column, which is more difficult and more expensive to carry out or they could be resolved by the use of a chiral resolving agent thus adding an extra two steps to the synthesis. The synthesis of both diastereoisomers **(85a)** and **(85b)** is extremely useful for further derivatisation, as the reaction of diastereoisomer **(85b)** with a nucleophile would lead to quinine-like products, whereas the same reaction with diastereoisomer **(85a)** would give quinidine-like products. Finally, after the addition of the small electrophile (E), there are only three more steps two of which introduce diversity.

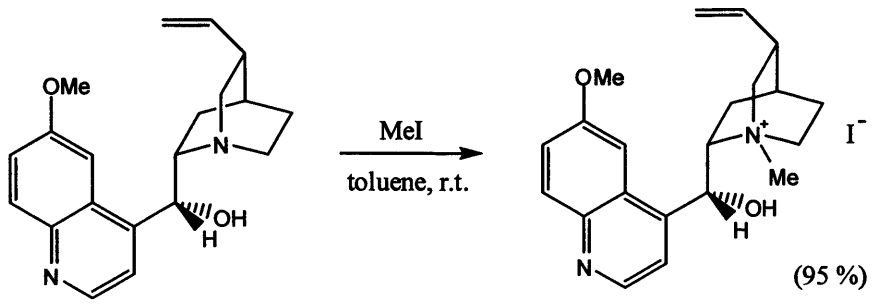
The synthesis of quinidinone **(55)** was carried out following the literature procedure using quinine, benzophenone and potassium *tert*-butoxide,[19] but on a small scale (Scheme 2.15). The first attempt at this reaction used a mechanical stirrer and a heating mantle to reflux the reaction mixture under a nitrogen atmosphere for 18 h. After leaving the reaction mixture overnight, a solid black mass was obtained since the solvent (a mixture of toluene and THF) had evaporated through a tiny gap where the mechanical stirrer inserts into the flask. The black solid was dissolved in dry toluene and worked up as stated in the paper. Surprisingly, the reaction had worked and gave fairly pure quinidinone (0.17 g) but in only an 8% yield. The ^{1}H NMR spectrum of the quinidinone in $CDCl_3$ showed the pure product along with some benzophenone impurity, but all of the product peaks had a smaller intensity peak alongside. It was concluded that these peaks were the diastereoisomer, quininone. A ^{1}H NMR spectrum was taken of the solid 24 h later, but there was no change in the ^{1}H NMR spectrum. Even after weeks in the sample tube, the NMR spectrum of the solid does not show any signs of epimerisation. A solution of the solid in $CDCl_3$ was then left overnight and the spectrum showed a mixture of the two diastereoisomers. As $CDCl_3$ contains a trace amount of HCl, it was most likely that this acid was causing the epimerisation as a solution of quinidinone in d^6-benzene showed no signs of the other epimer. The ^{13}C NMR spectrum of this solid also displays the peaks for both diastereoisomers, so the epimerisation must have occurred in the time taken for the ^{13}C NMR experiment to run, so the peaks in the carbon spectrum cannot be assigned to an individual diastereoisomer and the NMR data is reported as a mixture of diastereoisomers. It was possible to observe the quinidinone peaks as the major diastereoisomer in the spectrum by preparing the NMR sample in d^6-benzene immediately

prior to the ^{13}C NMR experiment being performed and the data for quinidinone is also reported.

All subsequent attempts at the quinidinone reaction led to a yellow-brown sticky mass containing both quinidinone and quininone in addition to some impurities. As a mixture of the two diastereoisomers was required, further crystallisation was not attempted. The reaction product was dried thoroughly under vacuum to give a yellow-brown solid, but further purification of the solid was needed. Column chromatography with eluting solvent of chloroform/methanol (9/1) failed to separate the quininone and quinidinone from the impurity, and so the solvent mixture chloroform/triethylamine/methanol (87.5/10/2.5) was used. The first fractions off the column had the solvent removed and the residue was dried under vacuum. The resulting solid was quinidinone as a diastereoisomeric mixture in 70% yield.

2.6 Addition of Electrophiles (E = Methyl)

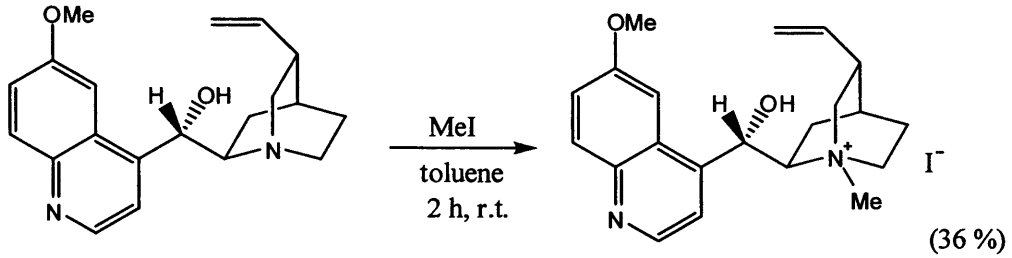
In the next step a small group, initially the methyl group, was to be introduced at the C8-position of quinidinone and quininone in order to prevent epimerisation of the ketone. It was proposed that the addition of base to the diastereomeric mixture of quinidinone and quininone would create the common enolate ion **(83)** and following the addition of methyl iodide would yield the desired product as a pair of diastereoisomers. The main concern with the addition of electrophiles to the cinchona alkaloid structure was the susceptibility of the alkaloid to form quaternary ammonium salts.[24] To test the ease at which an electrophile could add onto the quinuclidine nitrogen, quinine **(56)** was stirred with 1.1 equivalents of methyl iodide for 2 h at room temperature (Scheme 2.16). The ^{1}H NMR spectrum of the crude product was very clean, indicating that the reaction had gone to completion. The mass spectrum showed the parent ion peak (m/z 339) that was consistent with *N*-methylquininium iodide **(87)**.



(56) **(87)**

Scheme 2.16 *The Synthesis of N-Methylquininium Iodide (87)*

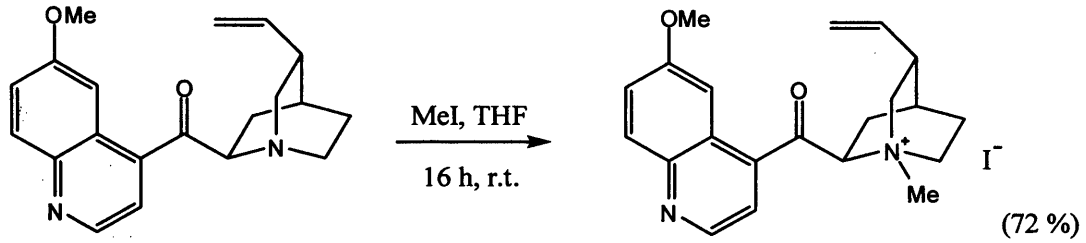
Quinidine **(57)** was also methylated using the same procedure (Scheme 2.17) and the resulting white solid was washed with chloroform. Although the yield (36 %) was not as high as expected, it proves that the quinuclidine nitrogen is very susceptible to forming quaternary ammonium salts with electrophiles such as alkyl iodides.



(57) **(88)**

Scheme 2.17 *The Synthesis of N-Methylquinidinium Iodide (88)*

Pure quinidinone was also methylated with methyl iodide in THF at room temperature. After 16 h, *N*-methylquinidinonium iodide **(89)** precipitated out of solution and was obtained pure in 72 % yield (Scheme 2.18). This compound epimerises in a $CDCl_3$ solution, but by preparing the NMR sample just prior to carrying out the experiment, a ^1H NMR spectrum of the pure *N*-methylquinidinonium iodide was obtained. Unfortunately, the epimerisation occurs too rapidly for a ^{13}C NMR spectrum to be gained in this solvent and due to its poor solubility in aprotic solvents, the ^{13}C NMR spectrum is quoted as a mixture of both diastereoisomers. The longer reaction time required to methylate quinidinone suggests that the quinuclidine nitrogen was less nucleophilic than in quinine and quinidine.



(55) **(89)**

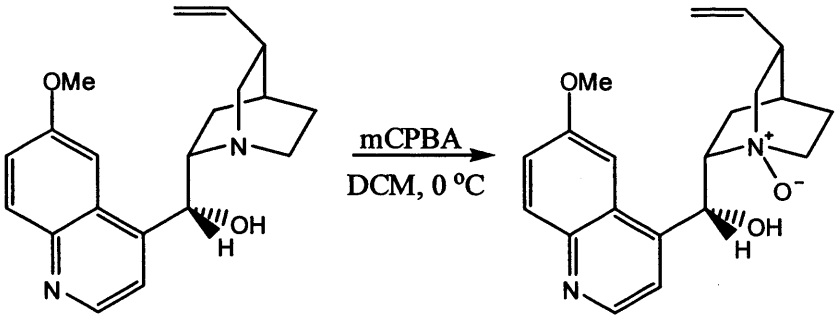
Scheme 2.18 *The Synthesis of N-Methylquinidinonium Iodide*

Consequently, if electrophiles are to be introduced to the cinchona alkaloid structure, then the quinuclidine nitrogen should first be protected. This is consistent with O'Neil's approach as the *N*-oxide was formed on the quinuclidine ring before electrophiles were introduced (Scheme 2.4). The formation of the *N*-oxide of quininone and quinidinone was the obvious next step and two routes were considered. In method A, the quinine *N*-oxide **(90)** would be formed first followed by the oxidation to quininone *N*-oxide **(92a)** and quinidinone

N-oxide **(92b)**. In method B the oxidation of quininone and quinidinone to quininone *N*-oxide and quinidinone *N*-oxide would be investigated. As there are procedures in the literature for the formation of quinine and quinidine *N*-oxides, method A was attempted first.

Method A

Synthesis of Quinine *N*-oxide (90)



(56) **(90)**

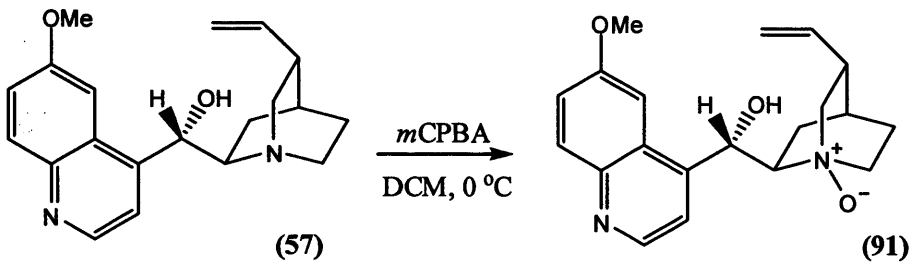
Scheme 2.19 *The Synthesis of Quinine N-Oxide (90)*

Following a procedure by Diaz-Arauzo[25] for the synthesis of quinine *N*-oxide **(90)**, a 5% solution of hydrogen peroxide was added to a solution of quinine in acetone and was stirred in the dark for four days. After the excess peroxide was destroyed with 10% Pd on charcoal, the reaction mixture was filtered and then extracted with chloroform. The ^{1}H NMR spectrum and mass spectrum of the organic layer showed that only starting material was recovered. In the second attempt the reaction mixture was left to stir for six days. After the same work-up, over half of the starting material was left unreacted in the organic layer. Previously, while synthesising enamine *N*-oxide **(63a)**, the main problem was removing the product from the aqueous layer, as it was water soluble. Contrary to the paper, the water was removed from the aqueous layer on the rotary evaporator to yield a brown oil. The mass spectrum showed peaks at 341, that was expected for quinine *N*-oxide **(90)**, and 325, that could be due to a fragment of quinine *N*-oxide or unreacted quinine. The ^{1}H NMR spectrum showed the presence of at least two products. TLC plates eluted with various solvents showed that the oil contained many different products and may be because the *N*-oxide thermally decomposed at the high temperatures used to remove the water. There are a few concerns about the published procedure. Firstly, the authors claim that the quinine *N*-oxide can be extracted from the aqueous layer with chloroform, even though this was not the case and previous work had shown that the *N*-oxides are very water soluble. Secondly, the good yield

reported in the paper could not be replicated and finally, the ^{1}H NMR data published contained 22 protons, but quinine *N*-oxide contains 24 protons.

Guentert[26] published two methods for synthesizing quinidine *N*-oxide **(91)**, but as quinine and quinidine react in very similar ways to each other, the same procedures were applied to quinine. The first method was exactly the same as that used by Diaz-Arauzo. This method was repeated except a 6% solution of hydrogen peroxide was used, as this is commercially available. The solvent from the organic layer was removed to give a small amount of white solid. The ^{1}H NMR spectrum showed only one main product and the aliphatic protons were shifted downfield as expected. The mass spectrum showed two peaks at 341 (M^+) and 325 $(M\text{-}O)^+$ and all the peaks in the ^{13}C NMR spectrum matched those published.[27] The only disappointing factor was the very poor yield. Jovanovic[28] also used the same procedure for synthesizing quinine *N*-oxide, but he used a different work-up. After destroying the peroxide, the solution was filtered and then saturated with sodium chloride before extracting with ether. The organic layer was dried, filtered and the solvent was removed. The ^{1}H NMR spectrum of the residue was messy and contained at least two compounds. Since each oxidation with hydrogen peroxide failed to give the quinine *N*-oxide **(90)** in a satisfactory yield, these methods were abandoned.

Guentert[26] also published a procedure using *m*CPBA to oxidise quinine. The quinine was dissolved in dichloromethane and cooled to 0 °C, then *m*CPBA was added as a solid in 20 mg portions over 30 mins and the reaction mixture was stirred for 30 mins at 0 °C. The resulting white solid was very pure but did contain some *m*CPBA residue. To remove this, the compound was eluted through a basic alumina column with chloroform/methanol (3/1) to yield the pure quinine *N*-oxide **(90)**. Quinidine *N*-oxide **(91)** was then synthesised using the same method (Scheme 2.20).



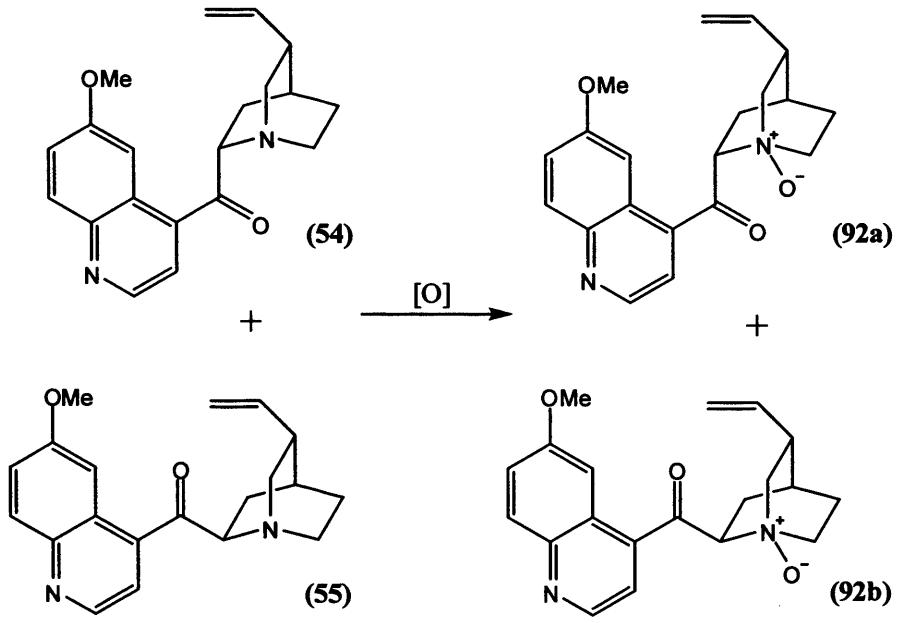
Scheme 2.20 *The Synthesis of Quinidine N-Oxide (91)*

The oxidation of quinine *N*-oxide to the quininone and quinidinone *N*-oxides with benzophenone and potassium *tert*-butoxide was then attempted using the same procedure described previously for the oxidation of quinine to quinidinone (Scheme 2.15, step 1). After

the addition of a 5 M sodium hydroxide solution, a brown sticky mass was formed. This was dried, but the ^{1}H NMR spectrum and mass spectra only showed peaks for the starting material. The ^{13}C NMR spectrum provided further proof that the desired products had not formed, as it showed no carbonyl peak. Since the oxidation of quinine *N*-oxide **(90)** may be more difficult than the oxidation of quinine **(56)**, the reaction was repeated. After refluxing the reaction for 24 h, a small sample of was removed, but the ^{1}H NMR spectrum and mass spectrum gave no sign that quininone *N*-oxide **(92a)** or quinidinone *N*-oxide **(92b)** had been formed.

Method B

Synthesis of Quininone and Quinidinone *N*-oxides (92)



Scheme 2.21 *The Attempted Oxidation of Quininone and Quinidinone to Quininone N-Oxide (92a) and Quinidinone N-Oxide (92b)*

The mixture of quininone and quinidinone prepared previously was oxidised with *m*CPBA in dichloromethane following the method used for the successful oxidation of both quinine and quinidine to their respective *N*-oxides (Scheme 2.21). The crude product showed two sets of peaks in the ^{1}H NMR spectrum, possibly quininone *N*-oxide **(92a)** and quinidinone *N*-oxide **(92b)** with a small amount of *m*CPBA residue. The mass spectrum showed the parent ion as being 339 that was consistent for quininone and quinidinone *N*-oxides. The *m*CPBA residue was removed by eluting the product through a column of basic alumina with chloroform/methanol (3/1). The resulting mixture showed three clear products

in the ^{1}H NMR spectrum, but the mass spectrum only gave one peak at 339. Since all attempts at separating the compounds by column chromatography failed, and since protecting and deprotecting the quinuclidine nitrogen would add at least two more steps to the synthetic route, work on this method was abandoned.

2.7 Addition at C8 with Electrophiles (E)

2.7.1 E = Methyl

The addition of an electrophile at the C8 position of quininone and quinidinone was attempted without protecting the quinuclidine nitrogen since the synthesis and isolation of the quininone/quinidinone *N*-oxide **(92)** was unsuccessful. It was thought that the protection may not be necessary as the enolate should be more reactive towards electrophiles than the quinuclidine nitrogen. Also, as the enolate was formed during the workup of quinidinone, it was proposed that the oxidation to the carbonyl and the addition of a methyl group at C8 and could occur in one step without isolating quinidinone **(55)** and quininone **(54)**. This would reduce the number of steps in the synthetic route. Therefore, the quinidinone reaction was carried out as before except methyl iodide was also added to the reaction mixture. The ^{1}H NMR spectrum of the crude product showed a mixture of three products. There are three possible sites where the methyl group could have added; at the C8 position on quinine **(93)** and quinidine, on the hydroxyl group of quinine **(94)** or on the quinuclidine nitrogen of quinine **(87)** (Figure 2.5).

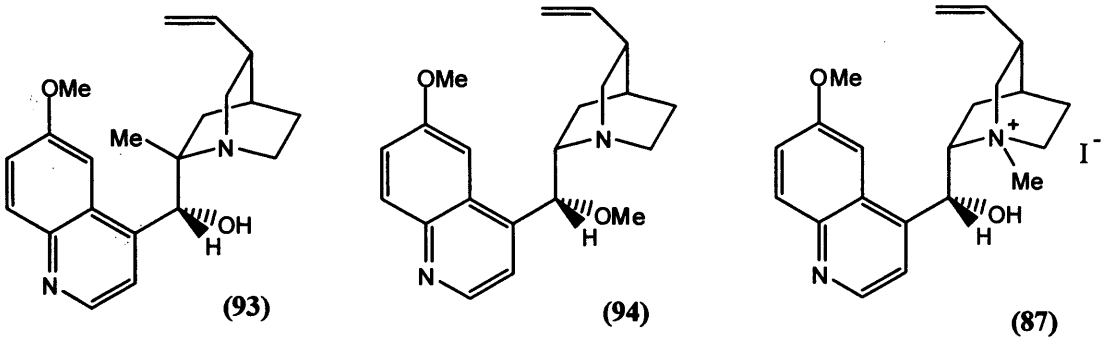
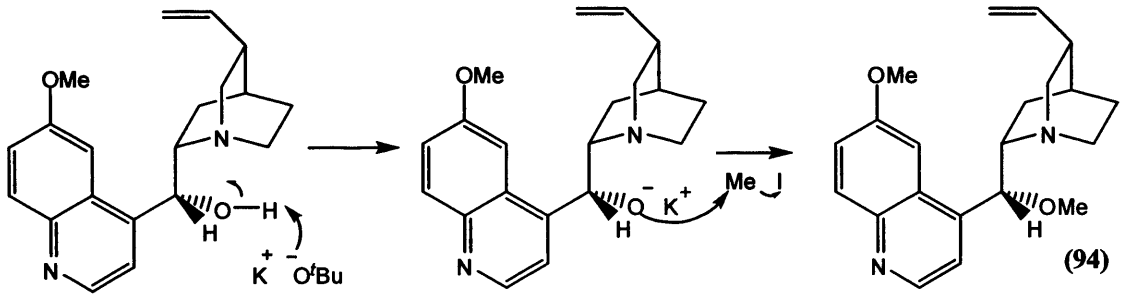


Figure 2.5 *Three Possible Reaction Products*

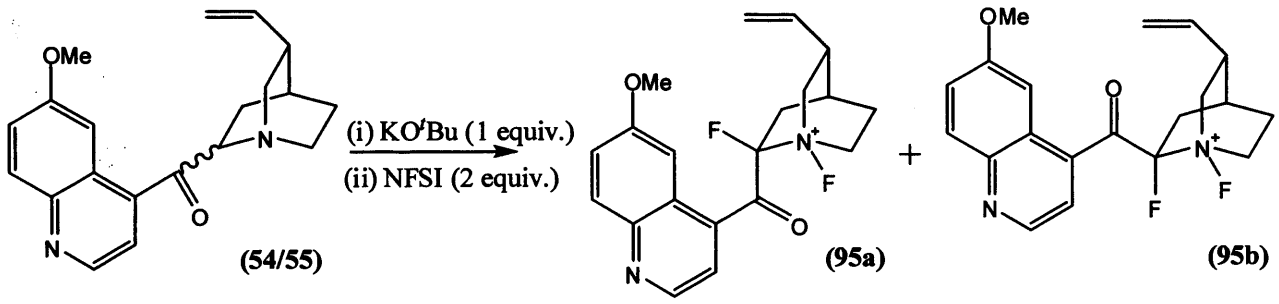
The ^{1}H NMR spectrum of the crude product was compared to the ^{1}H NMR spectra of *N*-methylquininium iodide **(87)**, *N*-methylquinidinium iodide **(88)** and *N*-methylquinidinonium iodide **(89)** synthesised previously. It was obvious that the products were neither *N*-methylquininium iodide **(87)** nor *N*-methylquinidinium iodide **(88)** due to the

characteristic proton signals at 6.44 ppm for the -OH group not being apparent. Also, the singlet of the *N*-methyl group occurs at 3.76 and 3.60 ppm for the *N*-methylated quinine and quinidinone respectively, but the product peaks are slightly lower at 3.26 and 3.29 ppm. The *N*-methyl group of *N*-methylquinidinium iodide occurs at 3.29 ppm like one of the product peaks, but the other peaks in the ^{1}H NMR spectrum did not match. However, the ^{1}H NMR spectrum of the product was identical to the ^{1}H NMR spectra of the derivatives of quinine and quinidine with a methyl group on the oxygen.[29] To explain the appearance of both the quinine and quinidine derivatives, the abstraction of the hydroxyl proton by the base must have occurred first followed by either the attack of methyl iodide to create the quinine derivative **(94)** (Scheme 2.22) or the base catalysed racemisation of quinine as described earlier (Scheme 2.14). Once the oxygen has been methylated then the oxidation reaction can not occur as the base cannot abstract a methyl group. As the desired C8 methylated compounds could not be synthesised this way, fluorine was considered as an alternative electrophile.



Scheme 2.22 *The Proposed Mechanism for the Synthesis of 9-O-Methylquinine (94)*

2.7.2 E = Fluorine

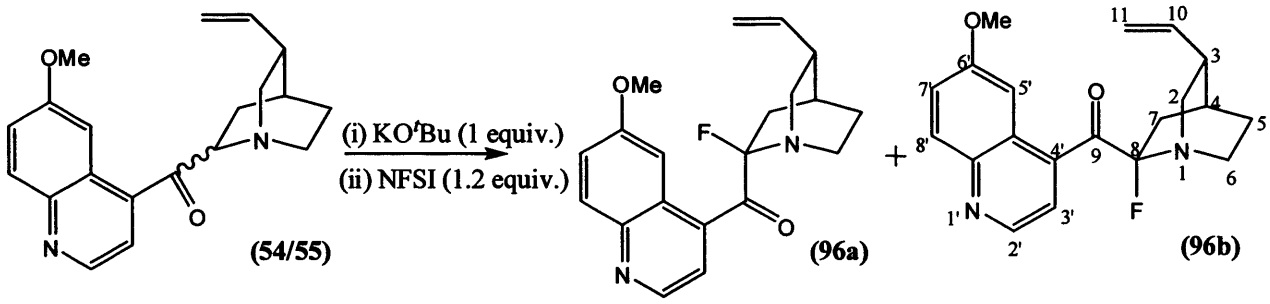


Scheme 2.23 *The Predicted Products of the Reaction of Quinidinone and Quininone with Base (1 equiv.) and NFSI (2 equiv.)*

It was decided to introduce a fluorine atom at the C8 position due to its much smaller size compared to a methyl group. One equivalent of base was added to the quinidinone/quininone mixture to form the enolate and two equivalents of the electrophilic

fluorinating agent, NFSI, was then added and the mixture stirred overnight at room temperature. It was thought that both the C8 site and the quinuclidine nitrogen would be fluorinated to give the products **(95a)** and **(95b)** since previous work had demonstrated the ease at which the quinuclidine nitrogen was fluorinated in quinine and similar structures (Scheme 2.23).[22,30]

A small sample of the reaction mixture was removed at intervals and the ^{19}F NMR spectrum revealed three peaks whose ratios changed over time. The peak at –39.9 ppm was due to excess NFSI, and so the other two peaks at –119 and –122 ppm must be due to the two diastereoisomers of the product. Since the ^{19}F NMR signals are in the wrong region for fluorine bonded to the quinuclidine nitrogen, these peaks must be for the fluorine at the α-position to the carbonyl. This suggests that the electron withdrawing effects of the fluorine α to the quinuclidine nitrogen prevents it from being fluorinated by NFSI.



Scheme 2.24 *The Fluorination of Quinidinone/Quininone with Base (1 equiv.) and NFSI (1.2 equiv.)*

The fluorination of the quinidinone/quininone mixture was repeated using one equivalent of base and 1.2 equivalents of NFSI. The ^1H NMR spectrum, ^{19}F NMR spectrum and mass spectra of the crude material showed the presence of the two diastereoisomers **(96a)** and **(96b)** and excess NFSI. The crude product was loaded onto a silica gel column and was eluted with chloroform to remove the excess NFSI. The two diastereoisomers **(96a)** and **(96b)** were then eluted with chloroform/methanol (92/8) leaving unreacted quinidinone and quininone on the column. After the two diastereoisomers were obtained pure, work then started on finding a suitable eluting solvent or combination of solvents to separate the two diastereoisomers by column chromatography. A large number of solvent systems were screened, but the best separation came from chloroform/ethyl acetate (4/1). The spots on the TLC plate were not separated completely, so some overlap of the compounds was expected. A long column was used to gain the maximum amount of separation thus allowing one of the diastereoisomers to be obtained pure, followed by the mixture of the two diastereoisomers, and then the other pure diastereoisomer. Both of the diastereoisomers were fully characterized

by ^{1}H, ^{19}F and ^{13}C NMR spectroscopy, mass spectrometry, optical rotation and in the case of 8-fluoroquinidinone **(96b)**, elemental analysis. Also, the ^{1}H NMR spectra of the diastereoisomers taken after being left in solution for days showed that no epimerisation had occured.

It was not possible to determine which diastereoisomer was which from the spectra obtained; so further NMR experiments were carried out. As the peaks on both ^{13}C NMR spectra were assigned with confidence, a HMQC experiment was performed which correlates the ^{13}C NMR spectrum to the ^{1}H NMR spectrum. This allowed the peaks on the ^{1}H NMR spectrum to be fully assigned. With this information, a HOESY experiment was performed, which correlated the ^{1}H NMR spectrum to the ^{19}F NMR spectrum. From the HOESY spectrum it was possible to determine which protons are close in space to the fluorine atom. The HOESY spectrum of the first diastereoisomer eluted from the column showed that protons on carbons 3', 2 and 7 are close to the fluorine atom (Figure 2.6), while the HOESY spectrum of the second diastereoisomer showed that its fluorine atom is close to protons on carbons 3', 6 and 7 (Figure 2.7). Both diastereoisomers were expected to be close in space to the proton on the aromatic carbon 3' as a small coupling was observed in the ^{1}H and ^{13}C NMR spectra and it is clear from the structures that both fluorine atoms are close in space to one of the protons on carbon 7. The fact that one fluorine atom was close to a proton on carbon 2 and the other was close to a proton on carbon 6 is the key piece of information. In order for this to occur, the first diastereoisomer eluted from the column must be 8-fluoroquininone **(96a)** and the second diastereoisomer must be 8-fluoroquinidinone **(96b)**. A crystal of **(96b)** was obtained by leaving a solution of **(96b)** in acetonitrile to evaporate slowly. The crystal structure confirmed that this diastereoisomer is **(96b)** and gave further proof to the NMR assignments (Figure 2.8). The crystal structure of 8-fluoroquinidinone **(96b)** when compared to the crystal structure data of quinidinone **(55)**[31] showed that the fluorine atom was affecting the shape of the quinuclidine ring. The C8-N1-C6 bond angle (represented by C12-N2-C17 on the 8-fluoroqinidinone structure) was 109.0(3)° compared to 107.95° for quinidinone. This in turn caused the C8-N1-C2 bond angle to become smaller at 107.2 (3)° compared to 108.90° for quinidinone (Table 2.2).

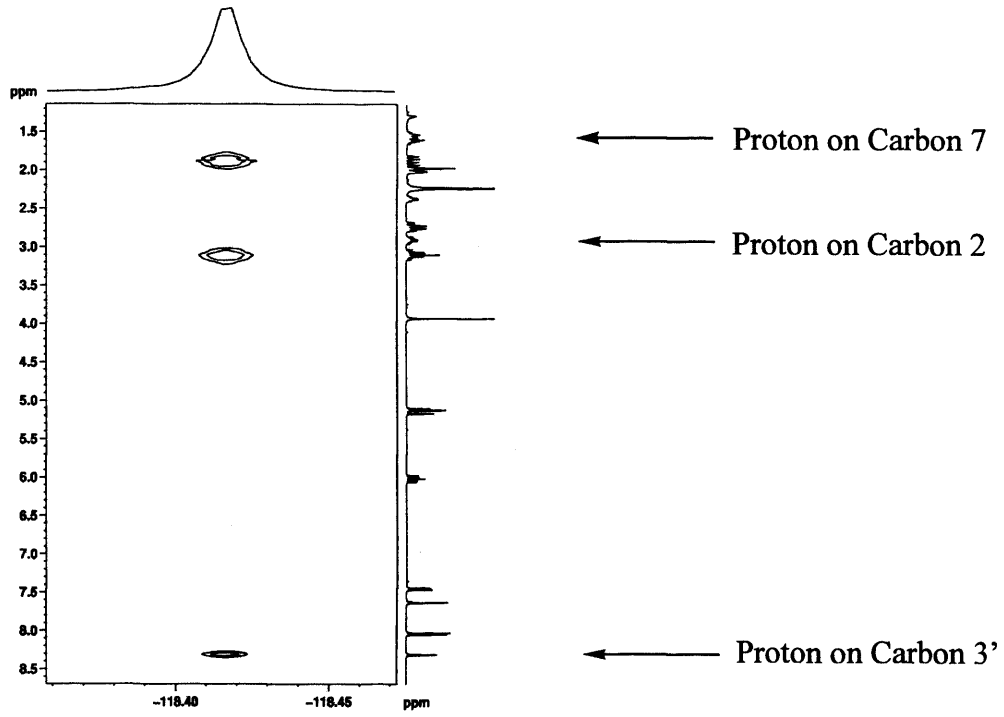


Figure 2.6 *The HOESY Spectrum of the First Diastereoisomer* ***(96a)***

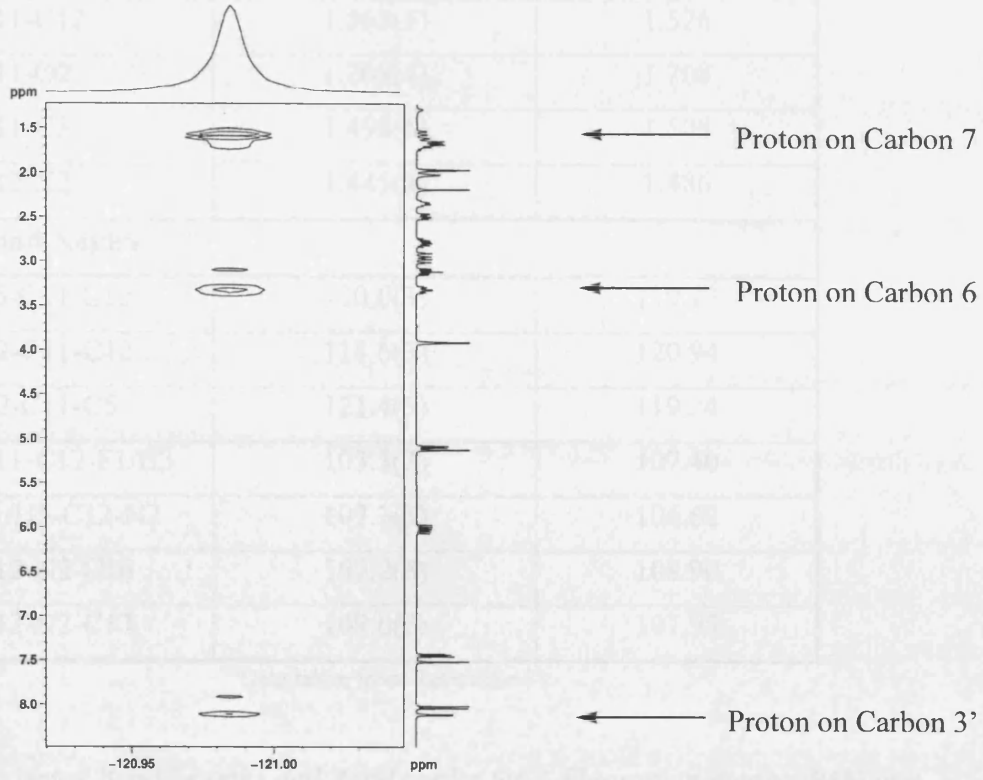


Figure 2.7 *The HOESY Spectrum of the Second Diastereoisomer* ***(96b)***

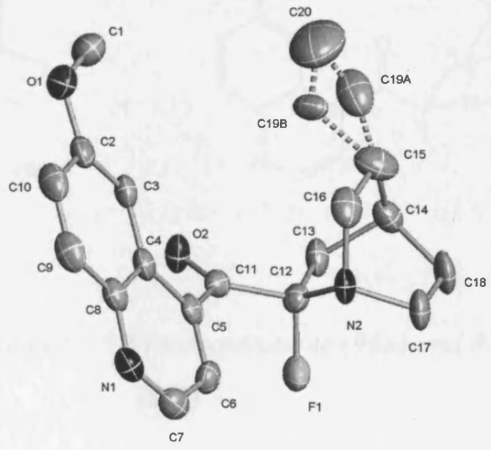


Figure 2.8 *The Crystal Structure of* ***(96b)***

Bond Lengths	8-Fluoroquinidinone	Quinidinone[a]
F1/H3-C12	1.408(4)	1.021
C11-C12	1.563(5)	1.526
C11-O2	1.207(4)	1.208
C11-C5	1.498(5)	1.508
C12-N2	1.445(4)	1.486
Bond Angles		
C5-C11-C12	120.0(3)	119.77
O2-C11-C12	118.6(3)	120.94
O2-C11-C5	121.4(3)	119.24
C11-C12-F1/H3	103.3(3)	107.40
F1/H3-C12-N2	107.3(3)	106.62
C12-N2-C16	107.2(3)	108.90
C12-N2-C17	109.0(3)	107.95

[a] Data taken from Reference 31

Table 2.2 *Selected Bond Lengths and Bond angles for 8-Fluoroquinidinone* ***(96b)*** *and Quinidinone* ***(55)***

Separation of Diastereoisomers (96a) and (96b)

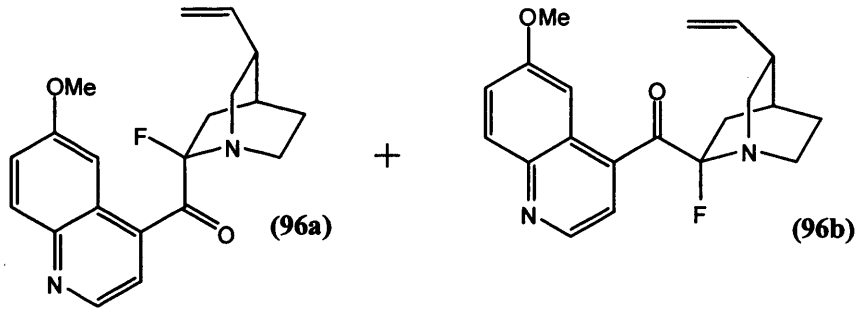


Figure 2.9 *The Two Diastereoisomers; 8-Fluoroquininone* ***(96a)*** *and 8-Fluoroquinidinone* ***(96b)***

Although samples of **(96a)** and **(96b)** were obtained pure by column chromatography, the separation was not complete, so the yields of pure **(96a)** and **(96b)** were very poor. Later it was found that by dissolving the mixture of isomers in acetonitrile and leaving in the fridge for ~2 weeks, **(96b)** crystallises out. The crystals were obtained by suction filtration and were washed with a little cold acetonitrile to yield pure **(96b)**.

Unfortunately, dissolving the filtrate in acetonitrile and leaving in a fridge as before, does not lead to a second crop of crystals. One important finding was that the mixture of diastereoisomers has to be very pure before crystallisation will take place. In one instance, the solid residue was dissolved in acetonitrile and left in the fridge, but no crystals formed. It was, therefore, necessary to purify the mixture of diastereoisomers by eluting through a silica gel column with chloroform/methanol (92/8) prior to crystallisation. Due to the length of time it takes **(96b)** to crystallise from acetonitrile, various other solvents were also investigated. The solvents used were methanol, acetone, ethyl acetate, ethyl acetate/hexane (1/1) and chloroform, but all failed to produce any crystals.

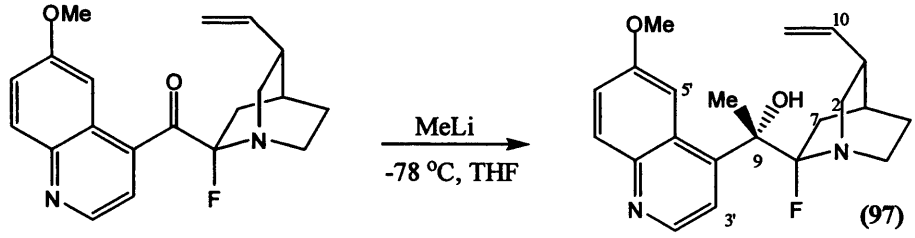
As only a small fraction of **(96b)** can be obtained by crystallisation, a lot of work was invested in finding an ideal solvent system for the separation of **(96a)** and **(96b)** by column chromatography. Verpoorte[32] published a list of solvent systems that have been used to separate various cinchona alkaloids. Tens of TLCs on both silica and alumina were carried out using most of the listed solvent systems, plus some novel ones, to determine whether the diastereoisomers can be fully separated. The two most promising solvent systems were toluene/ether/diethylamine (20/12/5) and toluene/ethyl acetate/diethylamine (7/2/1). A small amount of the mixture of **(96a)** and **(96b)** (252 mg) was purified by column chromatography using toluene/ether/diethylamine (20/12/5). The TLC analysis of the fractions showed three spots; the first being the mixture of the two isomers, the second being an unknown quinine like by-product and the third was unreacted quinidinone and quininone.

In an early paper by Doering[18] quinine and quinidine could be separated by treating with a solution of 0.5 equivalents of D-tartaric acid. The quinine tartrate crystals that formed were filtered and treatment of the filtrate with another 0.5 equivalents of D-tartaric acid allowed quinidine acid tartrate crystals to be obtained. As **(96a)** and **(96b)** are structurally similar to quinine **(56)** and quinidine **(57)**, this separation method was attempted. Unfortunately, on addition of the D-tartaric acid solution, no crystals formed. It is believed that the α-fluorine atom to the carbonyl group reduces the basicity of the quinuclidine nitrogen, thus preventing the formation of the tartrate. This was disappointing and a method for the complete separation of **(96a)** and **(96b)** has still not been found.

2.8 Addition of the Methyl Group at C9

The next step of the synthesis involved the addition of a nucleophile (R_1) to the carbonyl group (third step, Scheme 2.15) and was attempted initially with a methyl group. Following Dehmlow's procedure,[17] a solution of 8-fluoroquinidinone **(96b)** was added dropwise to a solution of methyl lithium at –78 °C under nitrogen. After working up the

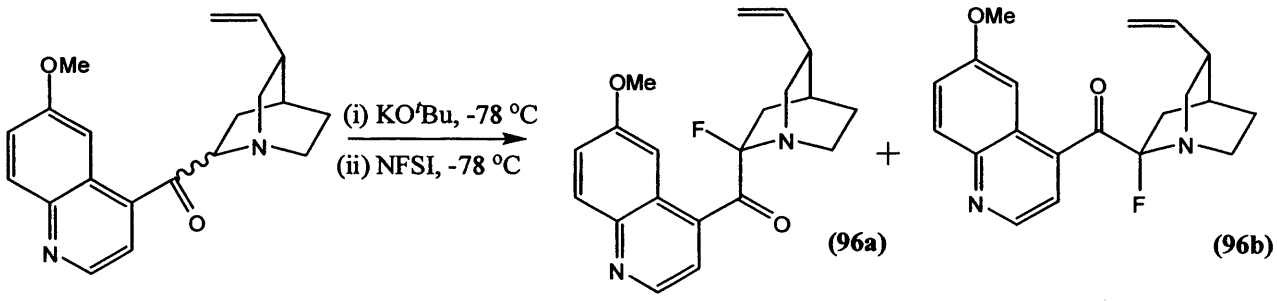
reaction, the crude reaction mixture was purified by column chromatography. A mixture of two diastereoisomers was expected as the product, but surprisingly, only one diastereoisomer was formed. It can not be said with certainty which isomer it was, as all attempts at growing a crystal for X-ray crystallography failed, but NMR analysis and the direction of optical rotation strongly suggest that it has the same configuration about C9 as the natural product. The main evidence came from the NOESY spectrum as the methyl group at C9 showed strong cross peaks with the proton at C3' and a proton on C2, and a weaker one with the proton at C5' (Scheme 2.25). These correlations would be expected with both orientations of the methyl group, but the fact that there was no cross peaks with either the proton on C7 or C10 made the epi-isomer unlikely. The ^{1}H NMR spectrum of the compound displays some unusually broad signals at 7.61 and 8.33 ppm. These peaks are due to the aromatic protons 3' and 5' respectively, but by performing the experiment at 328 K, the expected doublets, with the expected coupling constants, can be obtained. The same phenomenon is observed in the ^{19}F NMR spectrum and can similarly be resolved.



Scheme 2.25 *The Synthesis of 8-Fluoro-9-Methylquinidine (97)*

The unexpected stereoselectivity observed in the MeLi addition reaction, led to the possibility that adding methyl lithium to the mixture of **(96a)** and **(96b)** may give a mixture of just two diastereoisomers, which may be easier to separate. The reaction was carried out under exactly the same conditions, except that the methyl lithium solution was added to the 8-fluoroquininone and 8-fluoroquinidinone solution over 1 hour in order to maximise on any diastereoselectivity. After working up the reaction mixture, it was unclear how many compounds were obtained from the ^{1}H NMR spectrum. The ^{19}F NMR spectrum was also unclear due to the broad signals, but at least three sets of peaks were identified. After investigating a number of different solvent systems for TLC, the best resolution came from the toluene/ethyl acetate/diethylamine (7/2/1) and toluene/ether/diethylamine (20/12/5) solvent systems. Both of these systems showed four distinct spots indicating that four different products were present, but they could not be fully separated.

Addition of Fluorine at -78 °C



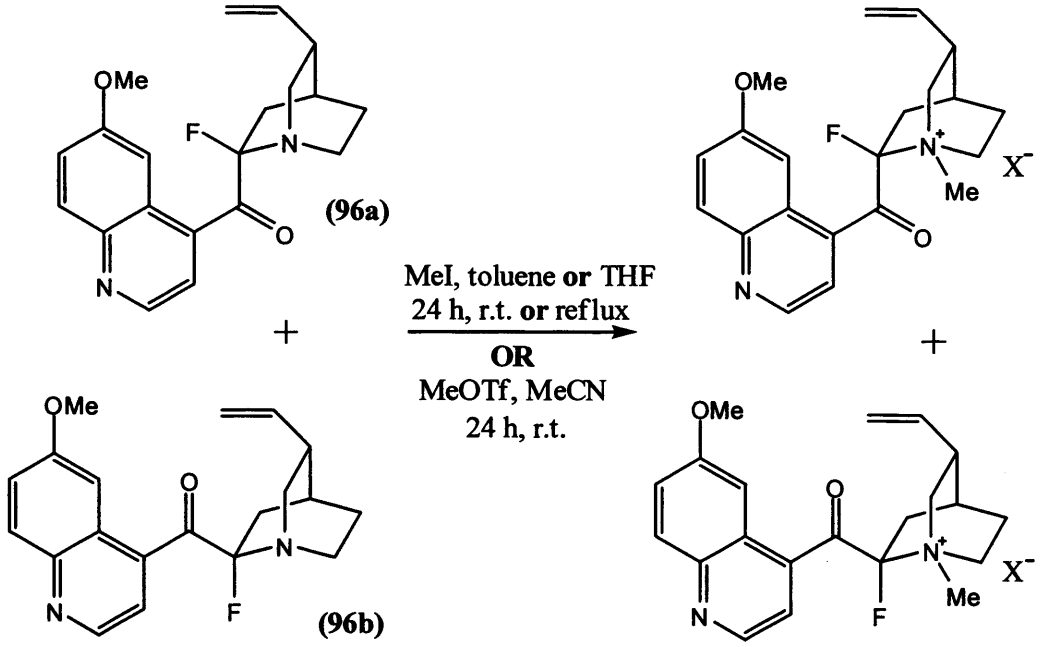
Scheme 2.26 *The Addition of Fluorine at Low Temperature*

After obtaining a diastereoselective addition of methyl lithium to 8-fluoroquinidinone at –78 °C (Scheme 2.25), the selectivity obtained in the addition of NFSI to the quininone/quinidinone enolate was investigated at this temperature (Scheme 2.26). A solution of quininone/ quinidinone was cooled to –78 °C and 1 equivalent of KO^{t}Bu was added and stirred for 10-15 mins before the addition of 1.2 equivalents of NFSI. The reaction was stirred at –78 °C under a nitrogen atmosphere for 12 h, after which it was allowed to warm to room temperature overnight. The solvent was then removed from the reaction mixture, to yield a solid yellow residue. The ^{1}H and ^{19}F NMR spectra both indicated that a near 50/50 mixture of **(96a)** and **(96b)** was obtained. Two possible reasons are that there was no diastereoselectivity in this reaction or that the reaction only took place after the reaction mixture had warmed. To determine which was the case, the reaction was carried out again, but the reaction was quenched after 6 h by the addition of a saturated solution of ammonium chloride at –78 °C. The reaction was then left to warm to room temperature overnight. The ^{1}H and ^{19}F NMR spectra of the crude product still showed a near 50/50 mixture of the two diastereoisomers. It was, therefore, concluded that there is no diastereoselectivity in the addition of NFSI at low temperature.

2.9 Formation of Quaternary Ammonium Salts

One concern with the proposed route (Scheme 2.15) was identified during the initial reaction of quininone and quinidinone with NFSI. Although 2 equivalents of the fluorinating agent was used, no species containing N-F$^+$ were observed probably due to the electron-withdrawing effect of the fluorine atom at C8 reducing the reactivity of the quinuclidine nitrogen. If this was the case, then the potential cinchona alkaloid derivatives produced could not be used as electrophilic fluorinating agents. To test the reactivity of the quinuclidine nitrogen, 8-fluoroquininone **(96a)** and 8-fluoroquinidinone **(96b)** were reacted with methyl

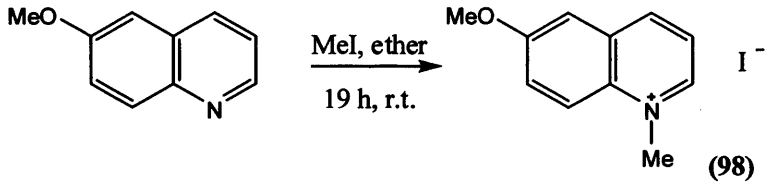
iodide to create the quaternary ammonium salts. The reason for making the quaternary ammonium salts rather than the N-F$^+$ compounds was that their synthesis and purification are generally easier. The reactions of **(96a)** and **(96b)** with methyl iodide were carried out initially in toluene (Scheme 2.27). After stirring at room temperature for 24 h, there was essentially no reaction. The ^{19}F NMR spectrum showed peaks at –117.65 ppm and –120.04 ppm which correspond to unreacted **(96a)** and **(96b)** respectively and the mass spectrum also showed only the starting material parent ion (m/z 341). The reaction was then repeated using the same conditions, but was refluxed for 24 h. The mass spectrum of the crude product showed a small peak for **(96a)** and **(96b)** plus a methyl group (m/z 355). The ^{19}F NMR spectrum showed two peaks for the starting material as well as two minor peaks at –119.13 ppm and –121.8 ppm. As only a trace amount of the methylated product had formed, the compounds could not be isolated.



Scheme 2.27 *The Methylations of 8-Fluoroquininone (96a) and 8-Fluoroquinidinone (96b)*

The poor conversion was thought to be because of the low solubility of **(96a)** and **(96b)** in toluene, so THF was used instead (Scheme 2.27). Initially, the reaction of **(96a)** and **(96b)** with MeI in THF was carried out at room temperature for 24 h, but this was unsuccessful. The obvious next step was to conduct the same experiment under reflux for 24 h. At the end of the reaction the ^{19}F NMR spectrum showed that there was a 10/1 mixture of starting material/product. The mass spectrum also showed two main peaks; m/z 341 (M^+) and 355 $(M+Me)^+$.

Since the choice of solvent was obviously not the main reason for the low conversions, methyltriflate was used as the triflate anion is a much better leaving group than iodide. A procedure by Denmark[33] that used MeOTf to methylate a tertiary amine to form a quaternary nitrogen was followed. The reaction was carried out using one equivalent of MeOTf in acetonitrile for 24 h at room temperature (Scheme 2.27). After work-up, two sets of peaks were observed in the ^{19}F NMR spectrum. The major peaks were at –119.39 ppm and –122.08 ppm and the minor peaks were at 130.15 ppm and 132.52 ppm, but neither set were starting material. The mass spectrum showed the main peak was the methylated parent ion (m/z 355), but there was no evidence of a 'doubly' methylated product. It is possible that the MeOTf was not selective and could have methylated both the quinuclidine nitrogen and the quinoline nitrogen. The ^{1}H NMR spectrum was examined to find the singlets that correspond to the methyl groups since the position of these peaks would provide a good indication of which nitrogen was methylated. The mixture of products showed larger peaks at 4.73 and 3.22 ppm and smaller ones at 4.62 and 3.28 ppm. It is known that the methyl group on *N*-methylquininium iodide **(87)**, *N*-methylquinidinium iodide **(88)** and *N*-methylquinidinonium iodide **(89)** occur at 3.76, 3.29 and 3.60 ppm respectively. Therefore, the peaks at ~3.2 ppm are possibly due to the methyl groups on the quinuclidine nitrogens, whilst the peaks at ~4.6 and ~4.7 ppm are expected to be due to the methyl groups on the quinoline nitrogens. To determine where a methyl peak would appear in a ^{1}H NMR spectrum when bonded to a quinoline nitrogen, *N*-methyl-6-methoxyquinolinium iodide **(98)** was synthesised.



(98)

Scheme 2.28 *The Synthesis of N-Methyl-6-Methoxyquinolinium Iodide (98)*

Geddes[34] described the synthesis of *N*-methyl-6-methoxyquinolinium iodide **(98)** and this procedure was followed (Scheme 2.28) giving the desired product as a bright yellow solid in good yield (78 %). More importantly, the ^{1}H NMR spectrum of the compound showed that the *N*-methyl peak appears at 4.61 ppm. This correlates to the singlets at 4.73 and 4.62 ppm observed for the methylated products of **(96a)** and **(96b)** with MeOTf. From this information, it seems that the α-fluorine atom reduces the reactivity of the quinuclidine nitrogen so much that it was allowing the quinoline nitrogen to compete in the methylation reaction. It is highly possible that this may also be the case for the fluorination reactions, which was not desired. A quinoline N-F reagent would probably induce very little, if any, enantioselectivity when used

to fluorinate a range of substrates. With this in mind, a new route to synthesising modified cinchona alkaloids was required and will be described in Chapter Three.

2.10 Conclusions

The novel compounds, 8-fluoroquininone **(96a)** and 8-fluoroquinidinone **(96b)**, have been synthesised and the diastereoisomers separated successfully by column chromatography and recrystallisation from acetonitrile. Their structures were determined by NMR spectroscopy and X-ray crystallography. The addition of the fluorine atom at the C8 position prevented the mutarotation of 8-fluoroquinidinone in solution. The addition of a methyl group to the carbonyl group of 8-fluoroquinidinone was also carried out successfully, leading unexpectedly to a single diastereoisomer of 8-fluoro-9-methylquinidine **(97)**. Unfortunately, the strong electron withdrawing effect of the α-fluorine atom prevented any further derivatisation on the quinuclidine nitrogen, so rendering the compounds useless as electrophilic fluorinating agents. Therefore, a new synthetic route for the synthesis of novel cinchona alkaloid derivatives will be investigated in Chapter Three.

2.11 References

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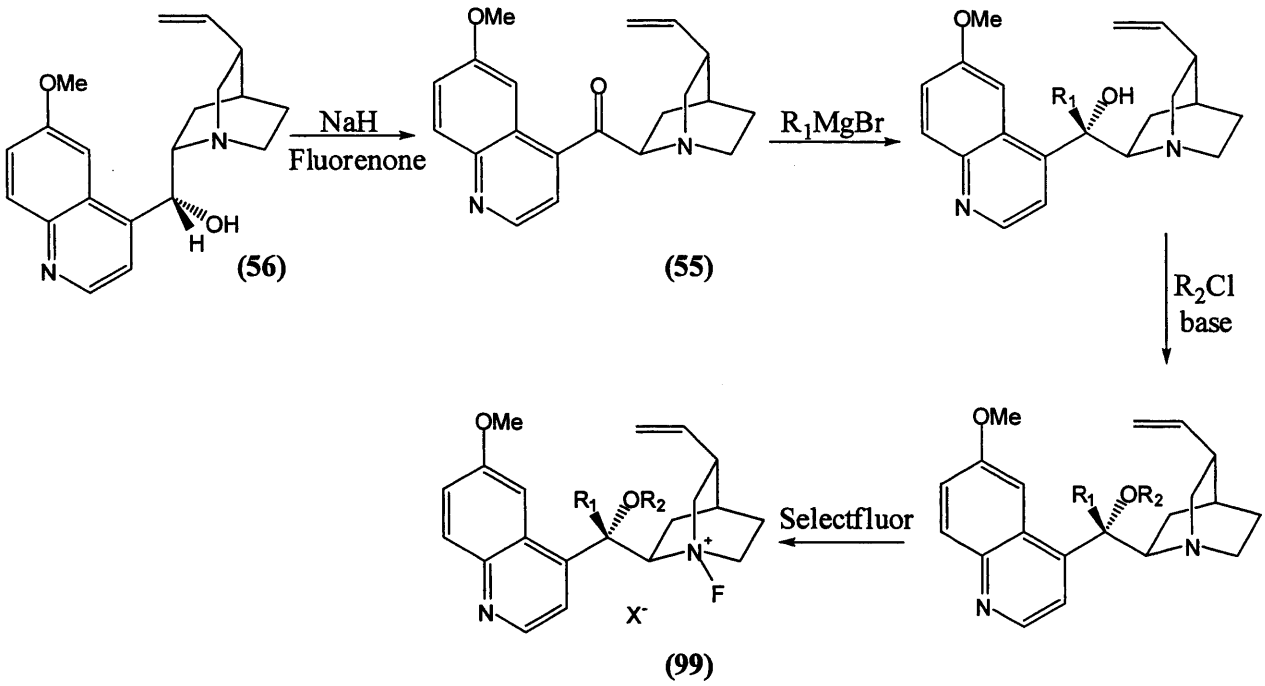
Chapter Three

University *of*
Leicester

Synthesis of a Novel Class of N-F Reagents

3.1 Introduction

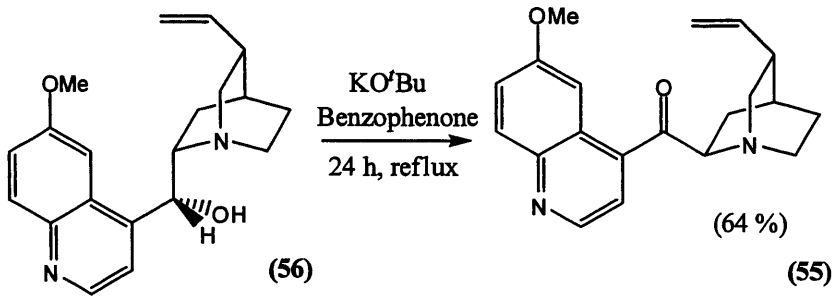


Scheme 3.1 *Proposed Synthetic Route for the Synthesis of Novel N-F Reagents*

A new synthetic approach for the structural modification of cinchona alkaloids was sought since the incorporation of a fluorine substituent on C8 led to a decrease in the basicity of the quinuclidine nitrogen. Although the synthesis of quinidinone **(55)** was known, previous attempts at synthesising this compound had led to a mixture of epimers. If a single epimer could be obtained, then a small library of novel *N*-F fluorinating agents could be obtained in three steps with diversity being introduced at the first two stages (Scheme 3.1). After oxidising quinine **(56)** to quinidinone **(55)**, the next step would be the addition of an R_1 group to the ketone. Once the method has been optimised, other R_1 groups could then be added to create a library of compounds. It would be interesting to have both aryl and alkyl derivatives as this may affect the fluorinating ability of the final N-F compound. The hydroxyl groups of the new derivatives would then be protected as the literature suggests that greater enantioselectivities can be obtained with the protected *N*-fluorocinchona alkaloids than with their unprotected counterparts. The final step would be to fluorinate the range of protected and unprotected derivatives to yield the novel N-F fluorinating reagents **(99)**. These new reagents will be screened in a model reaction to test their ability to selectively fluorinate the chosen substrates in Chapter Four and to compare their efficiency with known chiral fluorinating agents.

3.2 Quinidinone

It was essential that a single epimer of quinidinone was obtained in order to progress with the synthetic route. After examining all aspects of the oxidation procedure, a possible cause for the epimerisation of the product was found. According to the literature, quinidinone was known to mutarotate in alcoholic solvents[1] and as the potassium-*tert*-butoxide used in previous attempts was as a solution in THF, there would be a small amount of *tert*-butanol present. This small amount of alcohol could be the cause of the epimerisation and looking back at the procedures by Hutchison[2] and Woodward,[3] both used KO^{t}Bu in the solid form. Therefore, by simply replacing the form in which the base was used, may allow the pure quinidinone to be isolated.

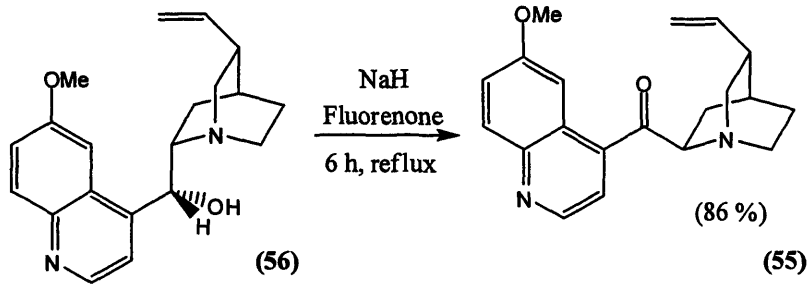


Scheme 3.2 *The Synthesis of Quinidinone (55) Using KO^{t}Bu and Benzophenone*

The synthesis of quinidinone was carried out again following the procedure by Hutchison and using solid KO^{t}Bu (Scheme 3.2).[2] The reaction was refluxed for 7 h and then worked-up to give a yellow oil, but it still contained a considerable amount of quinine. The reaction was carried out again, but this time it was refluxed for 24 h. The resulting yellow oil contained no quinine and on trituration with hexane gave quinidinone **(55)** as a white powder in 64 % yield. The ^{1}H NMR spectrum of quinidinone in $CDCl_3$ had to be carried out immediately after the solution had been made up, otherwise epimerisation occurs due to the small quantity of HCl often present in the solvent. Various other deuterated solvents were investigated to find a better solvent, but while none prevented the epimerisation completely, it did appear to be much slower in d^6-benzene.

Koenig modified this procedure and used sodium hydride as the base and fluorenone as the hydride acceptor.[4] This method had two advantages; the first was that the use of sodium hydride as the base prevented the mutarotation of quinidinone as there was no alcohol present and secondly, the hydride affinity of fluorenone was one hundred times that of benzophenone. Koenig carried out this reaction in DMF at room temperature, but then had trouble scaling up the reaction. Pratap carried out the same reaction in toluene under reflux and obtained a better

conversion.[1] Therefore, it was this procedure that was followed (Scheme 3.3). The reactants were added together and refluxed for 6 h (but usually left overnight). The work-up was similar to that by Hutchison, expect a 28 % ammonia solution was used in place of 5 M NaOH. The resulting yellow oil was made solid by trituration with hexane to give pure quinidinone in 86 % yield. This method not only gave an improved yield of product than the Hutchison method, but also the purity was better and the reaction time was much less (reaction complete in 6 h). This synthesis could be easily scaled-up without any loss in conversion. For conformation that the solid obtained was the pure quinidinone, a NOESY spectrum was obtained and showed correlation of the proton on C8 with a proton on C7, C5 and C6 (Figure 3.1). The latter two correlations would be impossible if the product had been quininone **(54)**. Also, the compound had a high negative specific rotation as observed by Woodward.[3]



Scheme 3.3 *The Synthesis of Quinidinone (55) Using NaH and Fluorenone*

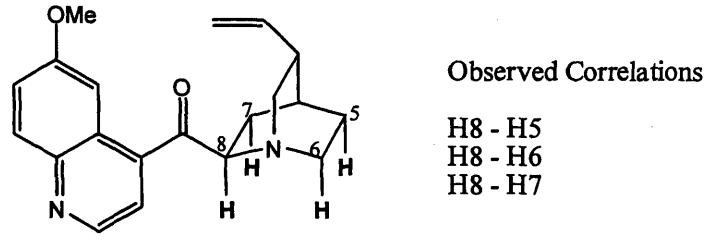


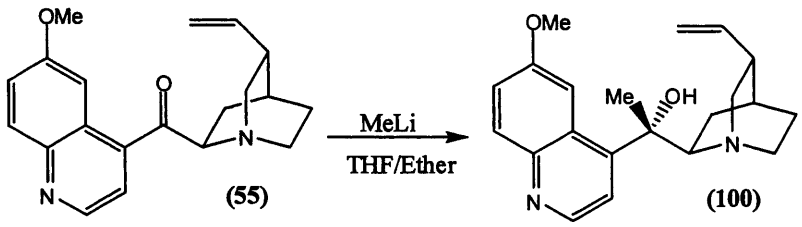
Figure 3.1 *The Structure of Quinidinone (55)*

3.3 Addition of R_1

3.3.1 R_1 = Methyl

The next step in the synthetic route was the addition of a methyl group to the ketone (Scheme 3.4). Previously, this reaction had been carried out successfully on 8-fluoroquinidinone **(96b)** using MeLi at –78 °C (Scheme 2.25), leading to only one diastereoisomer of the product being formed. The exact same conditions were then used for

the addition of a methyl group to quinidinone.[5] At the end of the reaction, the ^{1}H NMR spectrum showed that there was a mixture of starting material (as the two diastereoisomers) and two products. The presence of starting material was expected, as the conversion of **(96b)** to **(97)** was less than 50 %. The formation of two products was also not that surprising as a mixture of diastereoisomers was expected for this reaction, even though only one was produced earlier in the reaction with 8-fluoroquinidinone. Previously, the starting material and product were separated by column chromatography, so it was thought that the same purification technique could be applied here. A whole range of solvent systems were attempted on both silica and alumina TLC plates and surprisingly, not one could be found to separate the starting materials from the products.[5,6] Since the starting material could not be removed from the products, the reaction was carried out at 0 °C. It was thought that the higher temperature would allow the reaction to go to completion and hence, avoid any separation problems. Also, the main reason for carrying out the reaction at –78 °C initially was to maximise on any diastereoselectivity but there did not seem to be much in this case. At the end of the reaction, a large amount of starting material was still apparent along with the two products though the proportions of the two products had changed from a 1/0.5 ratio at -78 °C to a 1/1.3 ratio.



Scheme 3.4 *The Addition of a Methyl Group to Quinidinone (55)*

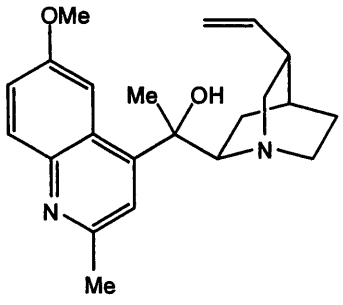
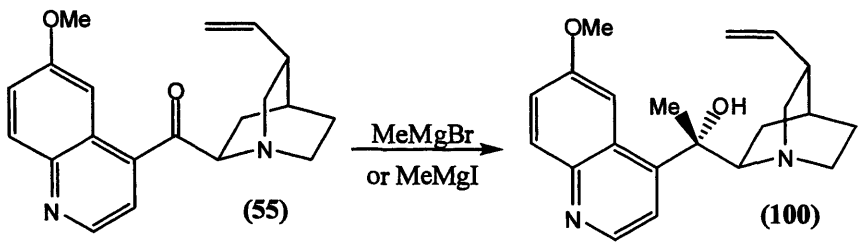


Figure 3.2 *The Addition of Methyl onto the 2-Position on the Quinoline Ring*

A thorough literature search did turn up procedures where MeMgI was used in place of MeLi as the source of Me^- to attack the carbonyl group on quinidinone,[3] but only one could

be found where MeLi was used.[7] In this paper the quinidinone was added to MeLi over a much longer period of time, the reaction time was longer and interestingly, the reaction mixture was refluxed. The literature procedure used a large excess of MeLi, but it was thought that this was unnecessary so only a small excess was used on the first attempt. The reaction was refluxed for 6 h, but there was a problem with the hotplate and the actual reflux time was probably slightly less. After work-up, the ^{1}H NMR spectrum clearly showed that there was still a small amount of starting material present, but only one major product. However, there was a small amount of a by-product, which was thought to be caused by the excess MeLi attacking the 2-position on the quinoline ring (Figure 3.2). In order to overcome the latter problem, it was decided to reduce the excess of MeLi. A solution of quinidinone was added slowly to the MeLi solution over 45 mins and then left refluxing overnight. After the work-up, there was still a considerable amount of starting material present. It was, therefore, decided to abandon this method in favour of another procedure.



Scheme 3.5 *The Addition of Methyl Using a Grignard Reagent*

Woodward described the addition of a methyl group onto quinidinone by using MeMgI at room temperature (Scheme 3.5).[3] Due to the lack of analytical data, it was unclear whether one or both diastereoisomers would be formed. On the first attempt, the reaction was carried out exactly as stated in the paper by slow addition of the quinidinone solution to the Grignard reagent and stirring for 2 h at room temperature. The ^{1}H NMR spectrum of the crude solid showed peaks for the two diastereoisomers of the starting quinidinone, but only one set of peaks for the product, implying that only one diastereoisomer had been formed. In the paper the product was purified by recrystallisation with 50 % aqueous ethanol, but the solid obtained would not completely dissolve even when heated. After decanting off some of the solution, it was cooled in ice and a solid did crash out but was found to be an impurity. It was concluded that in the attempt to dissolve the solid, the product was 'swamped' by the excess ethanol. Therefore, the solvent was removed and the residue was re-dissolved in the minimum volume of hot aqueous ethanol then filtered. The filtrate was left to cool in a fridge overnight and the ^{1}H NMR spectrum of the resulting solid showed that it was a single diastereoisomer of the desired product and interestingly, the peak for the proton at the C5' position was broad

due to the increased steric bulk caused by the addition of the methyl group. The peak could be resolved into a doublet by carrying out the NMR experiment at 331 K. The ^{1}H NMR spectrum of 9-methylquinidine **(100)** was found to match the major product obtained from the reaction of quinidinone and MeLi at -78 °C discussed previously. The yield for this reaction was only 21 % since most of the product was lost in the purification stage and so a better method was required. Trial recrystallisations of the crude solid were carried out using hot ether, ethanol and ethanol/water mixtures of which only the latter produced a crystalline product. 9-Methylquinidine could easily be obtained pure by dissolving the crude solid in the minimum volume of ethanol, filtering off the insoluble material (of which there could be a considerable amount), then adding water to crash out the product. Using this purification method, the yields of the diastereomerically pure product varied between 20-52 %.

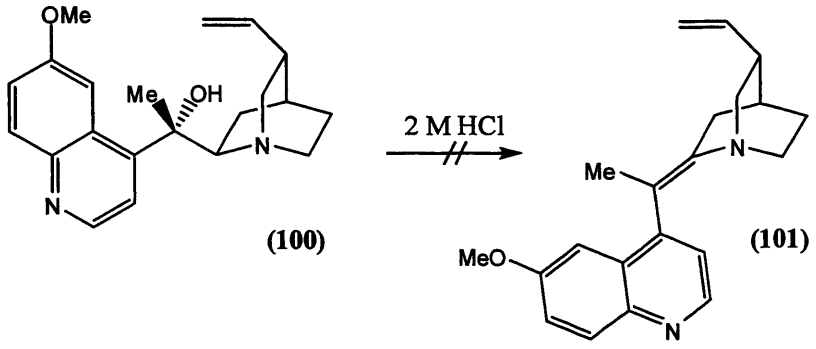
Entry	Grignard Reagent	Equiv. Used	Conc.	Addition Time (mins)	Reaction Time (h)	Conv.[a] (%)	Yield[b] (%)
1	MeMgI	10	1 M	40	2.5	71	**34**
2	MeMgI	10	1 M	15	18	82	**44**
3	MeMgI	10	3 M	90	15	84	**41**
4	MeMgBr	10	1 M	50	4	66	**32**
5	MeMgBr	10	3 M	50	4	69	**25**
6	MeMgBr	10	3 M	50	19.5	67	**47**
7	MeMgBr	10	1 M	30	19	--	**39**
8	MeMgBr[c]	10	1 M	30	21.5	54	**28**
9	MeMgBr	5	1 M	30	21	88	**60**
10	**MeMgBr**	**2**	**1 M**	**30**	**21**	**--**	**57**

[a] Conversion was determined by ^{1}H NMR spectroscopy; [b] Isolated yield; [c] Grignard reagent added to quinidinone

Table 3.1 *The Optimisation of the Methyl Grignard Addition*

Many attempts were made to improve the yield further (Table 3.1). The reaction was left to stir overnight at room temperature, but the final product was obtained in similar yields (23-57 %). Also, a 3 M solution of MeMgI was used instead of the usual 1 M solution, but comparable yields were again obtained (Table 3.1, entry 3). It is worth noting that the reaction never went to completion even though 10 equivalents of the Grignard reagent were used. The reaction could be scaled up from 0.5 g of quinidinone to 5 g of quinidinone with no effect on

the yield or conversion. One of the main problems with the reaction was the viscosity of the Grignard reagent. The syringes and needles had to be very dry because the slightest trace of moisture would cause the syringe barrel to stick. The transfer of the Grignard reagent was, therefore, a time consuming step. By using the less viscous MeMgBr, the transfer was a lot easier, but it had no effect on the yield (Table 3.1, entry 4). This could not be improved by increasing the reaction time or the concentration of the MeMgBr solution (Table 3.1, entries 5 and 6). The addition of the Grignard reagent to the quinidinone solution was attempted and led to a yield in the same range as already obtained but with poor conversion (Table 3.1 entry 8). One improvement in terms of ease of purification was observed when the amount of Grignard reagent was reduced from 10 equivalents to 5 equivalents (Table 3.1, entry 9). This obviously meant that there were less insoluble salts to remove from the crude solid, thus making the whole process faster. It was possible to decrease the amount of the Grignard reagent further to 2 equivalents to obtain comparable yields to those obtained with 5 equivalents (Table 3.1, entry 10).

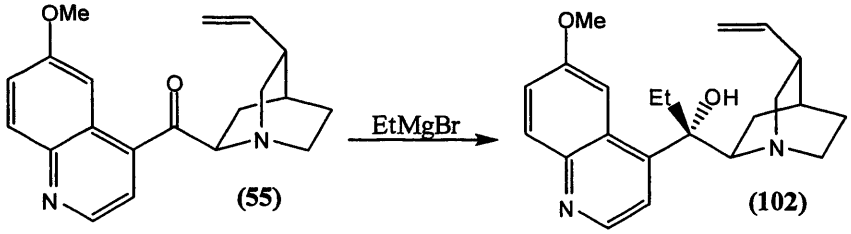


(100) **(101)**

Scheme 3.6 *The Dehydration of 9-Methylquinidine (100)*

More commonly, an aqueous ammonium chloride solution is used in the work up of tertiary alcohols instead of dilute acid as these compounds can easily be dehydrated under acidic conditions. This could possibly be a reason for the low yields for the reaction of quinidinone and the Grignard reagent. To test whether 9-methylquinidine **(100)** was stable in dilute acid, a small amount of this compound was stirred in 2 M hydrochloric acid for 1 h at room temperature and worked up using the same procedure as for the Grignard reaction with quinidinone. The ^{1}H NMR spectrum of the solid showed it to be pure 9-methylquinidine and no evidence of **(101)** or any other compound was observed (Scheme 3.6).

3.3.2 Addition of R_1 (R_1 = Ethyl)



Scheme 3.7 *The Addition of an Ethyl Group*

Equivalents of EtMgBr[a]	Addition time (mins)	Conversion[b] (%)	Isolated yield (%)
10	30	79	24
5	30	65	16
2	60	52	4

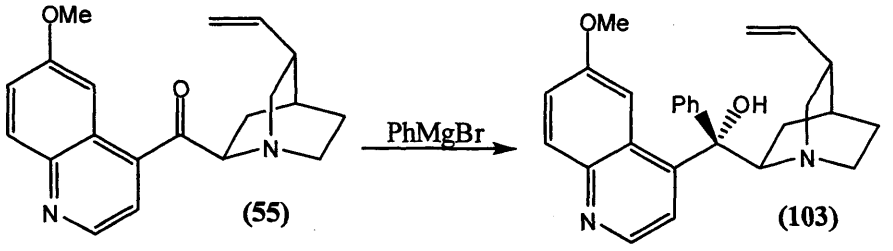
[a] Compared to quinidinone in moles; [b] Conversion was determined by ^{1}H NMR spectroscopy

Table 3.2 *The Conversions of Quinidinone to 9-Ethylquinidine (102) Compared to Isolated Yield*

As the nucleophilic addition of a methyl group worked, it was decided that the next group to add was an ethyl group, since there should be minimal steric differences (Scheme 3.7). The reaction was carried out using the same procedure as for 9-methylquinidine **(100)** (addition of quinidinone to the Grignard reagent and stirring overnight at room temperature) except for the purification step. The crystals did not precipitate out of solution on the addition of water, but instead they had to be left overnight in an aqueous ethanol solution. The ^{1}H NMR spectrum of the solid showed severe broadening of all the peaks and nothing could be seen clearly. It was necessary to carry out the ^{1}H NMR experiment at 347 K (74 °C) to resolve most of the peaks, though some remained broad, but it did prove that as in the 9-methylquinidine case that only one diastereoisomer of 9-ethylquinidine **(102)** had been obtained. The protons that displayed broad peaks in the high temperature ^{1}H NMR spectrum were all located close to the ethyl group at the C2, C7 and C8 positions on the quinuclidine ring and at the C3' and C5' positions on the quinoline ring. This indicated that even a relatively small group like an ethyl group was enough to cause steric problems. There was still some ethanol contained in the pure product which was removed by drying in the Kugelröhr oven at 50 °C for 6 h under oil pump vacuum. Initially, the reaction was carried out using 10 equivalents of the Grignard reagent, but subsequent attempts were carried out using

less Grignard reagent which affected the conversion (Table 3.2, entries 2 and 3). The purification of 9-ethylquinidine **(102)** proved to be temperamental as not every batch of crude material led to the pure product being obtained. Other methods were attempted, but none were successful.

3.3.3 Addition of R_1 (R_1 = Phenyl)



Scheme 3.8 *The Addition of a Phenyl Group*

Entry	Equivalents of PhMgBr[a]	Reaction time	Reaction Temperature	Conversion[b] (%)	Isolated Yield (%)
1	10	overnight	r. t.	47	6
2	5	overnight	r. t.	33	16
3	2	overnight	r. t.	33	22
4	2	3 d	r. t.	23	19
5	2	overnight	reflux	29	6

[a] Compared to quinidinone in moles; [b] Conversion was determined by ^{1}H NMR sopectroscopy

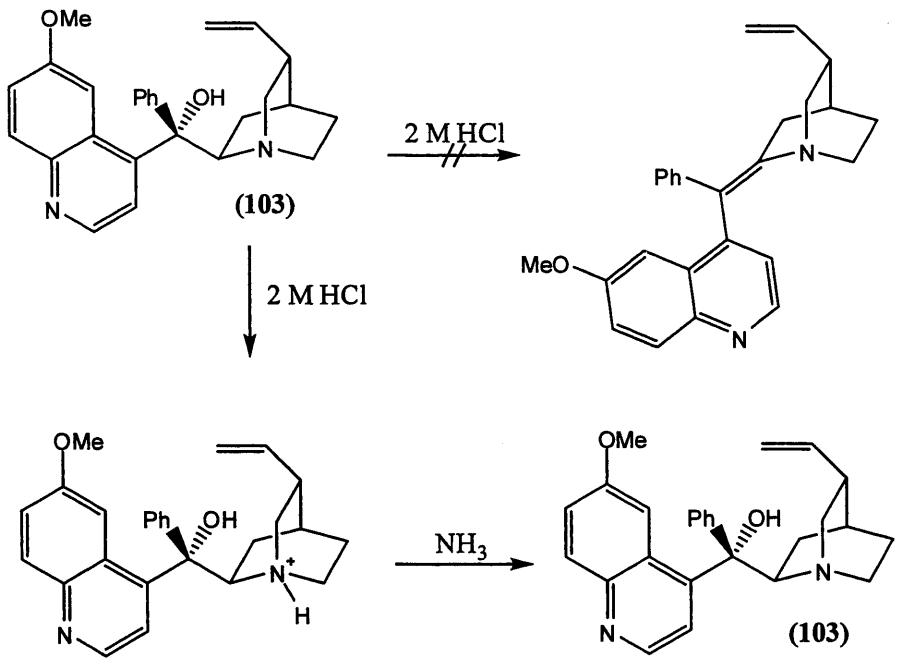
Table 3.3 *The Reaction of Quinidinone with PhMgBr Under Various Conditions*

After the successful synthesis of both 9-methylquinidine **(100)** and 9-ethylquinidine **(102)**, it was decided to attempt the synthesis of the bulkier 9-phenylquinidine **(103)** (Scheme 3.8). The conversions and yields for this reaction were expected to be lower due to steric hinderance. Initially, the reaction was carried out using 10 equivalents of phenylmagnesium bromide under the same reaction conditions for both of the previous Grignard reactions and the ^{1}H NMR spectrum of the crude product showed a moderate conversion of 47 % (Table 3.3, entry 1). To purify the crude product, the same method was attempted as that used for both 9-methylquinidine and 9-ethylquinidine. When the crude solid was dissolved in ethanol, an insoluble white solid was apparent, which was filtered off, dried under vacuum and the ^{1}H NMR spectrum showed that it was the pure 9-phenylquinidine **(103)**. Broadening of the

signals for the C3', C5' and C7 protons was apparent, but these could be resolved by performing the NMR experiment at 326 K. The spectrum also showed a significant amount of ethanol was still contained in the sample which could easily be removed by dissolving the 9-phenylquinidine in chloroform and washing with water as opposed to drying on the Kugelröhr distillation apparatus. Also, the spectrum showed no signs of any by-product, so although the extra bulk was decreasing the conversion and isolated yield it was improving the purity. In order to gain more 9-phenylquinidine, water was added to the filtrate until it turned cloudy and it was left overnight. Unfortunately, nothing came out of solution. The reaction was repeated under the same reaction conditions except 5 equivalents of the Grignard reagent were used. The ^{1}H NMR spectrum of the crude product showed that the conversion had decreased, but after purification the isolated yield had increased (Table 3.3, entry 2). By decreasing the amount of Grignard reagent to two equivalents, the conversion didn't decrease any further, but the isolated yield increased to 22 % (Table 3.3, entry 3). In an attempt to improve the conversion of the reaction, the mixture was left to stir for 3 days, but comparable conversions and yields were obtained (Table 3.3, entry 4). In a final attempt, the reaction mixture was refluxed overnight even though there were concerns that the higher temperature would start to yield both diastereoisomers of the product. The ^{1}H NMR spectrum of the crude product did appear to show a trace amount of a third compound, but this was removed during the purification. Disappointingly, the conversion and yield for this reaction were poor at 29 % and 6 % respectively. As all attempts to improve the yield of the reaction had failed, it was decided that the reaction would have to be carried out numerous times using the best conditions obtained. The overnight reaction of quinidinone and 2 equivalents of phenylmagnesium bromide at room temperature proved to give fairly consistent yields of between 19-22 %.

As with 9-methylquinidine **(100)**, the stability of 9-phenylquinidine **(103)** under acidic conditions was tested to eliminate dehydration of the tertiary alcohol as a possible reason for the low yields. A solution of pure 9-phenylquinidine in toluene was stirred with 2 M hydrochloric acid at room temperature for 1 h, the aqueous layer was separated and the solvent was removed. The mass spectrum of the resulting oil showed a peak at m/z 401, the same as the parent ion of 9-phenylquinidine and the ^{1}H NMR spectrum showed only one set of peaks, but the proton signals close to the quinuclidine nitrogen had shifted downfield whilst the aromatic protons remained close to their original positions. The oil was then redissolved in 2 M hydrochloric acid and after basification, the ^{1}H NMR spectrum showed only the pure 9-phenylquinidine. It was concluded that the acid had not dehydrated the alcohol, but instead had protonated the quinuclidine nitrogen which caused the downfield

shift in the ^1H NMR spectrum. On addition of the base (NH_3), the quinuclidine nitrogen was deprotonated to give the starting material, 9-phenylquinidine (Scheme 3.9).



Scheme 3.9 *The Reaction of 9-Phenylquinidine (103) with Aqueous Acid*

3.3.4 Mechanism of the Grignard Reaction

Equation 3.1 *The Schlenk Equilibrium*

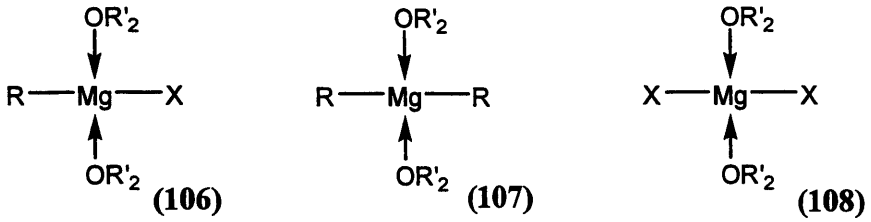
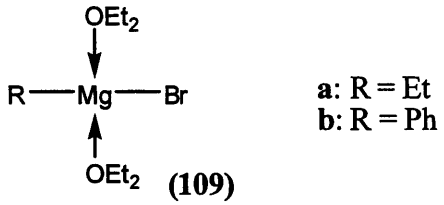


Figure 3.3 *The Three Structures of the Grignard Reagent in Solution*

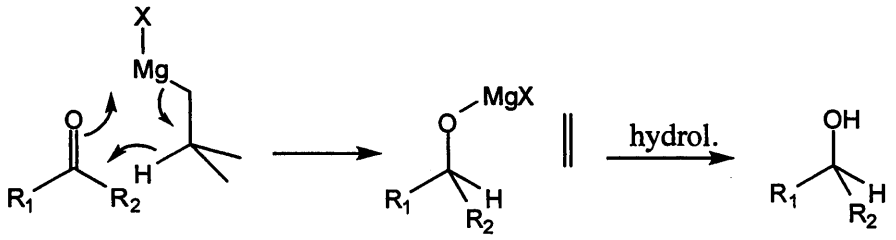
The mechanism of the Grignard reaction has been the subject of study for many years and is as complex as it is interesting. The uncertainty of the mechanism arises due to the fact that the reaction is difficult to reproduce as minor impurities in the magnesium can greatly affect the kinetics of the reaction.[13,14] More importantly, the species present in the Grignard solution are still a subject of controversy. The problems are best represented by the Schlenk

equilibrium (Equation 3.1), which describes the composition of the Grignard reagent in solution. Since both RMgX and R_2Mg can react with the ketone, and both of these species plus X_2Mg can all complex to the ketone,[15] the complication of determining the exact mechanism becomes apparent. This determination is further hampered as the position of the equilibrium is not only dependent on the nature of R and X, but also the concentration, solvent and temperature.[16,17] It is also known that the Grignard species, whatever the structure, can coordinate with two molecules of ether to form compounds **(106)**, **(107)** and **(108)** (Figure 3.3). In fact, crystal structures of ethylmagnesium bromide dietherate **(109a)** and phenylmagnesium bromide dietherate **(109b)** have been obtained from the corresponding Grignard reagent in ether (Figure 3.4).[18,19] The latter reagent has also crystallised out from THF and the structure was proved by X-ray diffraction.



(109)

Figure 3.4 *The Structure of Ethylmagnesium Bromide Dietherate (109a) and Phenylmagnesium Bromide Dietherate (109b)*

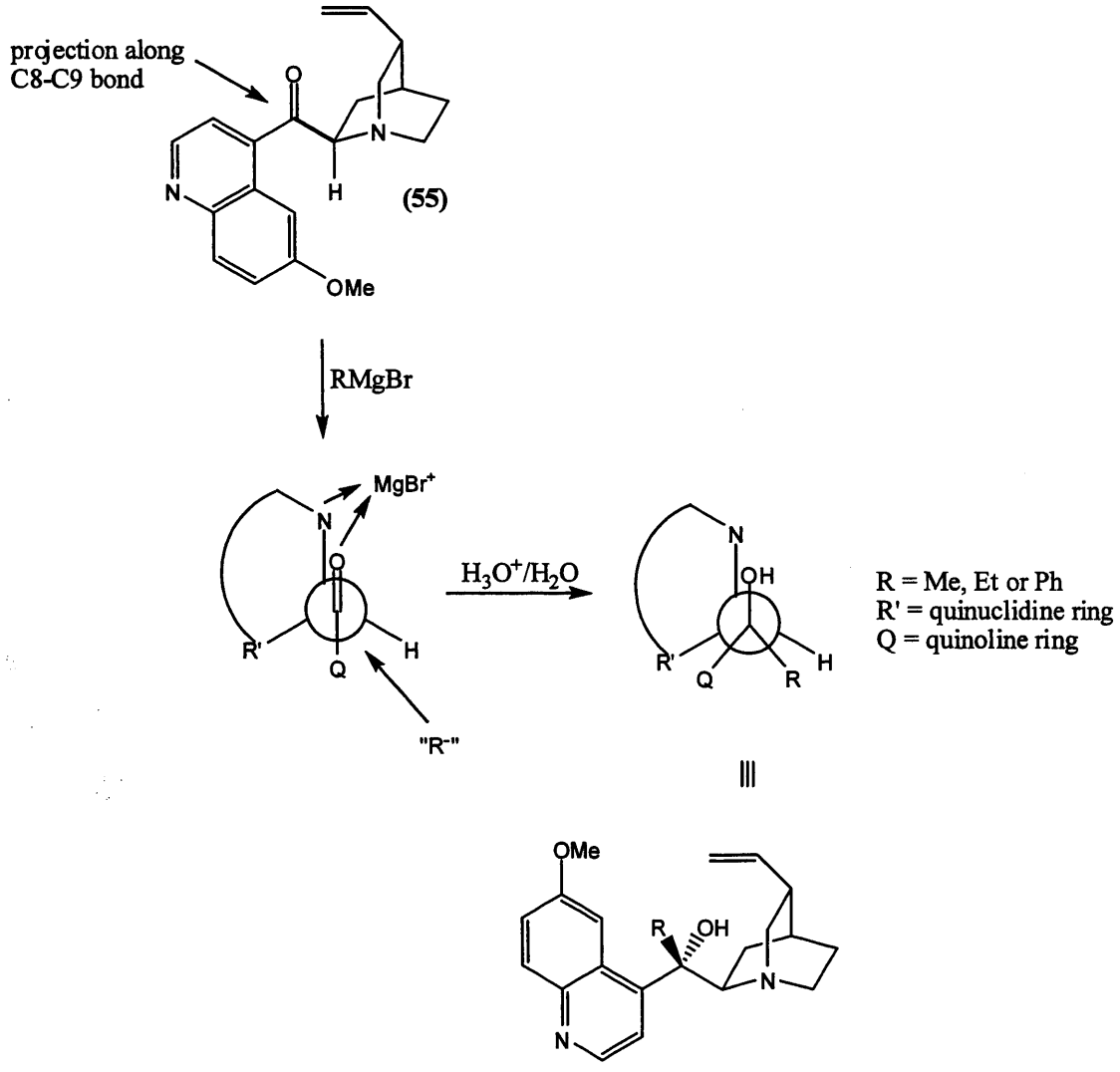


Scheme 3.10 *The Reduction of a Carbonyl Compound with a Grignard Reagent*

The use of bulky Grignard reagents or sterically hindered ketones are known to lead to competing reactions, particularly enolisation and reduction. If the Grignard reagent contains a β-hydrogen, then the reduction of the carbonyl group to an alcohol can occur (Scheme 3.10), which in our case would be the reduction of quinidinone **(55)** to quinidine **(57)** or possibly epi-quinidine **(59)**. The only Grignard reagent used which contained a β-hydrogen was ethylmagnesium bromide so this may explain the added complexity of obtaining the pure 9-ethylquinidine **(102)** though no quinidine was seen in the ^1H NMR spectra (but a small peak at m/z 325 in the mass spectrum of the crude material was observed). Since, enolisation is

generally associated with bulky Grignard reagents it would not be a concern with the use of methylmagnesium bromide, ethylmagnesium bromide or phenylmagnesium bromide.

The proposed mechanism for the diastereoselective addition of Grignard reagents to quinidinone **(55)** is shown in Scheme 3.11 and is rationalised by chelation controlled asymmetric induction. The lone pairs on the quinuclidine nitrogen and carbonyl oxygen coordinate with the Grignard reagent forming a 5-membered chelate ring. This fixes the structure into a *syn*-peri-planar conformation allowing the nucleophile ("R⁻") to attack from the less hindered side. In this case, the Grignard reagent attacks from the front which would lead to a product with the same stereochemistry at the C9 position as the natural product. The exact nature of the coordinating species is not known, but a likely candidate is the Lewis acid $MgBr_2$, which is known to coordinate to the electrophile making it more susceptible to attack from the Grignard reagent.



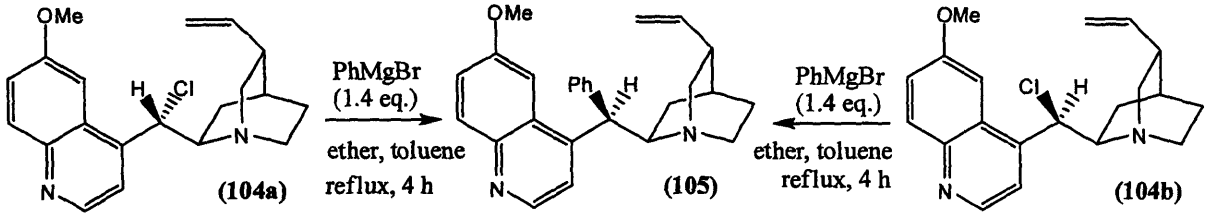
Scheme 3.11 *The Proposed Mechanism for the Diastereoselective Addition of a Grignard Reagent to Quinidinone (55)*

3.3.5 Stereochemistry at C9 in 9-Methylquinidine (100) and 9-Phenylquinidine (103)

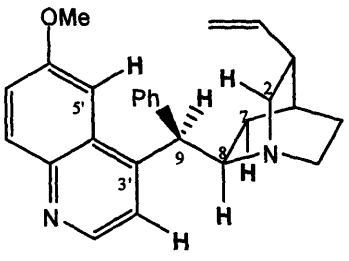
It would be very useful to know which diastereoisomer of 9-methylquinidine, 9-ethylquinidine and 9-phenylquinidine had been synthesised as this would greatly affect the outcome of the model reaction when the derivatives are tested. Since all attempts to grow a single crystal of these compounds and their derivatives have failed, X-ray crystallography could not be used to determine the stereochemistry at the C9 position.

The structures of 9-methylquinidine **(100)** and 9-phenylquinidine **(103)** rest on the following evidence:

1) According to the chelation controlled asymmetric induction mechanism proposed in Scheme 3.11, the product should have the 9(*S*) configuration, the same as that of quinidine.
2) Further evidence was obtained from the NOESY spectra of 9-methylquinidine **(100)** and 9-phenylquinidine **(103)** as NOESY spectroscopy has been used in the literature to aid the determination of stereochemistry for structurally similar compounds.



Scheme 3.12 *The Synthesis of 9(R)-phenylquinidine (105) from 9(R)-chloroquinidine (104a) and 9(S)-chloro quinidine (104b) by Skarzewski*



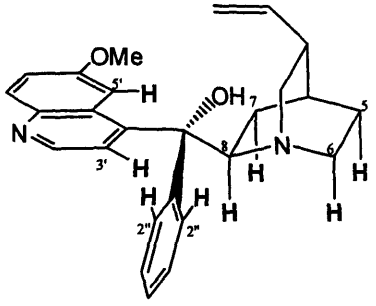
Correlations between:

H9 - H2 H3' - H7
H9 - H5' H3' - H8

Figure 3.5 *The NOE Correlations Observed by Skarzewski for 9(R)-Phenylquinidine (105)*

A recent paper by Skarzewski described the synthesis of a range of 9-aryl derivatives of quinine and quinidine by the reaction of the 9-chloro derivatives with a Grignard reagent.[12] When phenylmagnesium bromide was reacted with the 9(*S*)- and 9(*R*)-chloro derivatives of

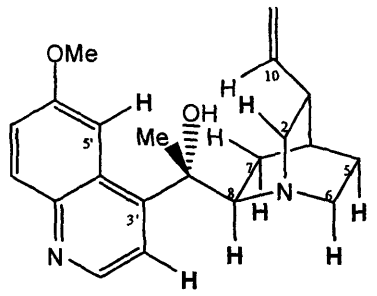
quinine, the only product observed was the 9(*S*)-phenylquinine regardless of which isomer was used. This configuration was proved by X-ray crystallography. The same stereoselectivity was observed in the reaction with the 9(*R*)- and 9(*S*)-chloro derivatives of quinidine **(104)** with the only product being 9(*R*)-phenylquinidine **(105)** (Scheme 3.12). In this case, the configuration was assigned by the use of NOESY spectroscopy as there were strong correlations between the proton on C9 with a proton on C2 and C5' and between the proton on C3' with a C7 proton and the one on C8 (Figure 3.5). As the 9-phenylquinidine synthesised in our work contains a hydroxyl group on C9 instead of a proton, the former correlation would not be apparent, but the latter correlation between the C3' and C8 protons can be seen. The main feature of the spectrum was the lack of correlations of any of the phenyl protons with the proton on C10 or C7 (Figure 3.6). The only correlation observed for the proton at the C3'' position of the phenyl ring was with the proton on C2''. The C2'' proton though did show correlations with the C8 proton, a proton on C6 and the aromatic proton at C5'. The proton on C8 also showed a correlation with the aromatic proton on C5' which indicates that there is some rotation about the C9-C4' bond. The quinidine assignment could be proven by the NOESY spectrum as the proton at C8 correlated to a proton on C7, C6 and C5, whereas a quinine type structure would show a correlation between the C8 proton with protons on C2 and C7. It is believed that 9-methylquinidine has the same configuration due to the strong correlation of the methyl group with the aromatic protons on carbons 3' and 5' and also with the proton on C8 and one of the protons on C2 (Figure 3.7). There was no correlation with either proton on C7 or the proton on C10 which would be expected if the stereochemistry was reversed. The quinidine-type structure was also proven as the proton on C8 correlates to the protons on C5, C6 and C7 whereas a quinine-type structure would show correlations of the C8 proton with protons on C2 and C7.



Correlations between:

H2'' - H6	H8 - H3'
H2'' - H8	H8 - H5'
H2'' - H3'	H8 - H5
H2'' - H5'	H8 - H6
	H8 - H7

Figure 3.6 *NOE Correlations of 9-Phenylquinidine (103)*



Observed Correlations

Me - H2	H8 - H5
Me - H8	H8 - H6
Me - H3'	H8 - H7
Me - H5'	

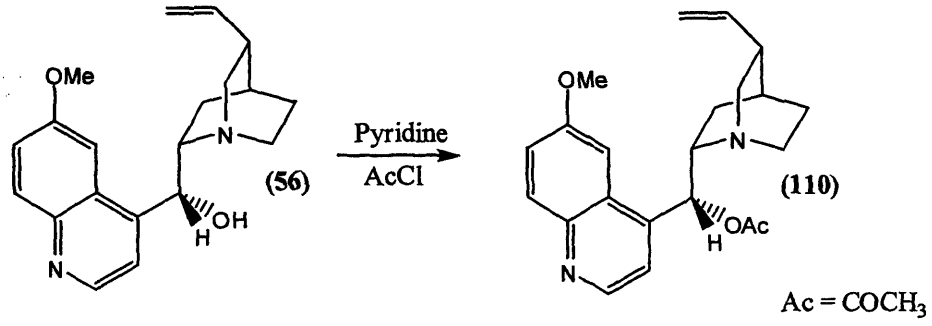
Figure 3.7 *NOE Correlations of 9-Methylquinidine (100)*

Although the stereochemistry at the C9 position could not be proved for any of the novel derivatised cinchona alkaloids, it was proposed that the products would most likely to have the 9(*S*) configuration. This was based on the combination of the proposed reaction mechanism, the literature data and the NOESY spectra which all strongly support this assignment.

3.4 Protection of the Quinidine Derivatives

With the successful synthesis of a number of quinidine derivatives, the next step was the protection of the hydroxyl group to hopefully maximise on any stereoselectivity obtained in the asymmetric fluorination with the new quinidine derivatives. The reaction was initially carried out on quinine **(56)** as it is the cheapest and most readily available cinchona alkaloid. Once the reaction conditions were optimised, then the procedure would be used with quinidine **(57)** and its derivatives.

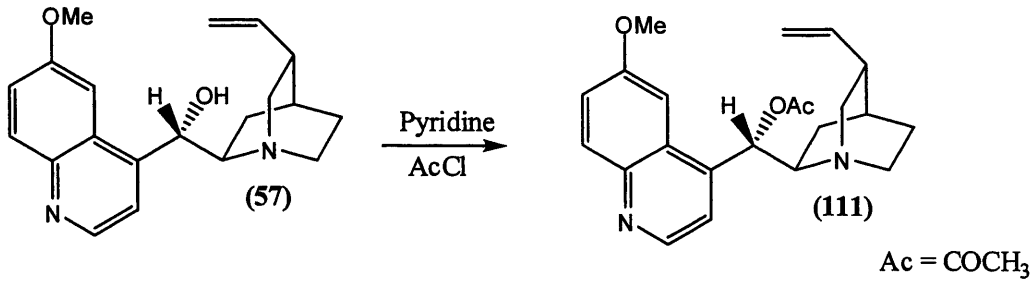
3.4.1 Protection with an Acetyl Group



Scheme 3.13 *The Synthesis of Quinine Acetate (110)*

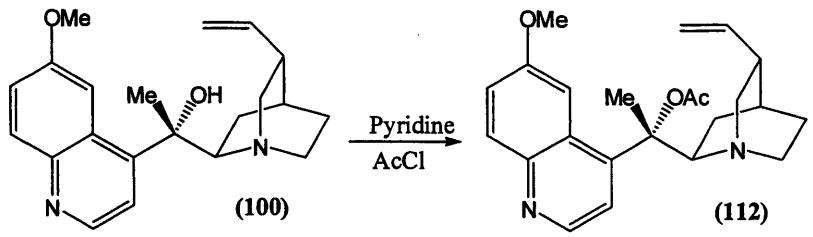
The first protecting group that was chosen was the acetyl group, partly because the synthesis of quinine acetate **(110)** has been described in the literature by Sharpless[21] and partly because it is a relatively small group that will minimise any steric problems associated

with the addition. Initially, the synthesis of quinine acetate was carried out following Sharpless's procedure (Scheme 3.13).[21] Pyridine and acetyl chloride were added to a solution of quinine in dichloromethane at room temperature and was stirred for 4 h. After work up, the crude quinine acetate was purified by column chromatography on a silica column and then dried under oil pump vacuum to remove the trace amount of water to give the pure product in 67 % yield.



Scheme 3.14 *The Synthesis of Quinidine Acetate (111)*

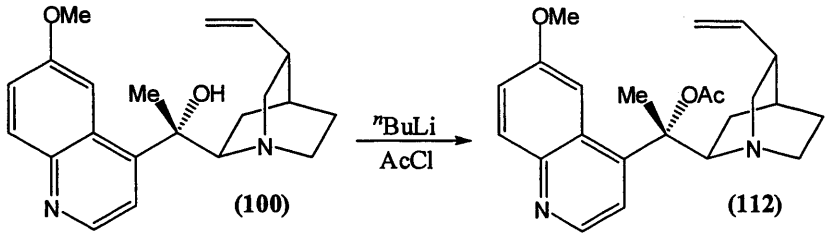
Quinidine acetate **(111)** was then synthesised using the same method except that the water was removed by a simple recrystallisation from ethyl acetate/hexane (1/1) to give the pure product in 69 % yield (Scheme 3.14).



Scheme 3.15 *The Synthesis of 9-Methylquinidine Acetate (112)*

The synthesis of 9-methylquinidine acetate **(112)** was attempted using the same procedure (Scheme 3.15). To a stirred solution of 9-methylquinidine **(100)** in dichloromethane, 1 equivalent of pyridine was added followed by 1.1 equivalents of acetyl chloride. After stirring at room temperature for 4 h, the ^{1}H NMR spectrum and mass spectrum showed that no reaction had occurred. Additional solvent, pyridine and acetyl chloride was therefore added to the residue which was then refluxed for 4 h. This time the ^{1}H NMR spectrum showed only a small amount of the product peaks and the mass spectrum gave a small peak at 381, which is the parent ion for 9-methylquinidine acetate **(112)**. As heating did not improve the reaction, another factor must be affecting the yield. In both of these attempts, a pale yellow solid formed instantly after the addition of the pyridine and acetyl chloride. It

was thought that water, which could be present in 9-methylquinidine as it was crystallised from aqueous ethanol, was affecting the reaction. Therefore, a sample of 9-methylquinidine was put through a column of anhydrous magnesium sulphate in an attempt to dry the starting material and the reaction was repeated at room temperature. Unfortunately, both the ^{1}H NMR spectrum and mass spectrum showed that no reaction had occurred and only starting material was apparent.



Scheme 3.16 *The Synthesis of 9-Methylquinidine Acetate (112)*

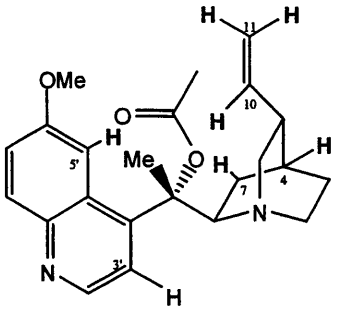
Since the esterification of a tertiary alcohol is more difficult than a secondary alcohol, Kaiser used ^{n}BuLi instead of pyridine. The ^{n}BuLi abstracts the proton of the tertiary alcohol and on addition of the desired chloride, the ester was formed.[22] It was, therefore, essential that 9-methylquinidine was dried completely as any water would destroy the lithium base. Woodward stated that 9-methylquinidine was obtained with 2 molecules of water and all attempts at drying the compound failed.[3] In the ^{1}H NMR spectrum of the starting material, a broad singlet at ~1.5 ppm was seen. Also, the first attempt at obtaining elemental analysis of the pure product came back with results close to what Woodward obtained. It was, therefore, necessary to find a suitable method for drying 9-methylquinidine especially since the use of magnesium sulphate had failed. The only method that worked was to dry 9-methylquinidine in a Kugelröhr oven at 50 °C for 1 day under oil pump vacuum.

Initially, the new esterification method was carried out exactly as the paper states (one equivalent ^{n}BuLi, one equivalent acetyl chloride, reflux, 1 h) (Scheme 3.16). After work-up, the ^{1}H NMR spectrum and mass spectrum showed that the residue was mainly starting material, but a small amount of a second compound with a parent ion of 381 could be seen. The reaction was repeated with a longer reflux time of 4.5 h. The ^{1}H NMR spectrum showed the best conversion to date, but all attempts at recrystallising the product failed. Therefore, various TLCs were carried out to find a suitable solvent system for separating the compounds by column chromatography. Initially, the best system was a chloroform/methanol (95/5) mixture, which gave a small amount of pure 9-methylquinidine acetate **(112)**, but further examination on the 400 MHz NMR spectrometer showed that there was still a fair amount of impurity in the sample. The reaction was carried out again, except it was refluxed for a longer

period of time in an attempt to improve the conversion. Small samples of the reaction mixture were intermittently removed to monitor its progress by ^{1}H NMR spectroscopy. After 17 h the desired product had formed but the conversion was only 29 %. The conversion did not improve over the next two days as samples taken after 24 h and 42 h showed conversions of 30 % and 32 % respectively. The latter spectrum also did not show a peak for the unreacted acetyl chloride. Therefore, additional acetyl chloride was added and the conversions increased to 40 % and 58 % after 65 h and 72 h respectively. After stirring for a total of 92 h, the reaction mixture was quenched. The reaction product was purified by column chromatography using chloroform/methanol (95/5) to yield a small amount of the pure product. The main reason for the low conversion was probably due to the acetyl chloride being used up in the reaction and so 1.5 equivalents were used in the next attempt. After just 21 h the conversion was 71 %, significantly better than previously gained and by exchanging the solvent from THF to ether and increasing the reaction time to 3 days, the highest conversion of 80 % was obtained. As the reaction could now be carried out in a reasonable conversion, the next task was to purify the product. Pure 9-methylquinidine acetate was initially gained by column chromatography, but the purity of the sample was not ideal, so therefore, it was necessary to look for a better eluting solvent or mixture of solvents. Various solvent systems were investigated, but the one that gave the best separation on the TLC plate was toluene/ethyl acetate/triethylamine (10/10/3). When this solvent system was used on a column, the product was obtained but it was contaminated with quinidinone **(55)**. This must have been an impurity in the 9-methylquinidine starting material which was then concentrated during the purification process. All attempts at separating the two compounds by column chromatography failed. As the initial solvent system of chloroform/methanol (95/5) led to a fairly pure product, it was thought that this could be improved by slowing down the column. Therefore, the crude product was loaded onto a silica gel column and eluted with chloroform/methanol (99/1) to give the pure 9-methylquinidine acetate as a colourless oil in 26 % yield. The ^{1}H NMR spectrum of the pure product again showed broadening of the signals for the C5' proton as well as for the C3', C8 and C7 protons and one C2 proton, which are all located close to the acetate. These could all be resolved by performing the NMR experiment at 337 K.

The stereochemistry of 9-methylquindine acetate **(112)** was examined by NOESY spectroscopy (Figure 3.8). The same correlations between the methyl group and the C2, C8, C3' and C5' protons were observed as for 9-methylquinidine **(100)** (Figure 3.3). In addition the spectrum also showed clear correlations between the acetyl protons and the protons on C4. C7, C10, C11, C3' and C5'. This provides further evidence for the 9-(*S*) assignment as the methyl group correlates to protons on one side of the molecule whilst the acetyl group

correlates to protons on the opposite side. The same correlations could be observed with the 9-(*R*) configuration, but correlations between H3' and H5' with H2 and H7 would be expected and none were observed. The 9-(*R*) configuration would also lead to massive steric interference of the protons on the quinoline ring with the protons on the quinuclidine ring thus making this configuration very unlikely.

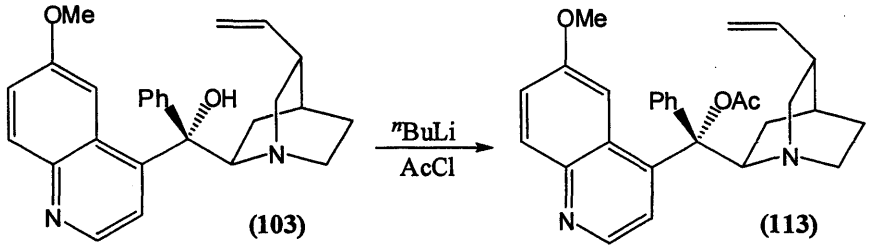


Correlations between:
$C(O)CH_3$ - H4
$C(O)CH_3$ - H7
$C(O)CH_3$ - H10
$C(O)CH_3$ - H11
$C(O)CH_3$ - H3'
$C(O)CH_3$ - H5'

Figure 3.8 *NOESY Correlations of 9-Methylquinidine Acetate (112)*

After the successful synthesis of 9-methylquinidine acetate **(112)**, the same optimised conditions were used to synthesise 9-phenylquinidine acetate **(113)** (the addition of 1 equivalent of ^{n}BuLi to a solution of 9-phenylquinidine **(103)** in ether followed by the addition of 1.5 equivalents of acetyl chloride) (Scheme 3.17). The reaction mixture was refluxed and small samples were removed periodically to monitor the reaction by ^{1}H NMR spectroscopy. After 17 h and 41 h, the ^{1}H NMR spectra showed no sign of any product being formed. After 3 days, a small sample was worked up but the ^{1}H NMR spectra of both the organic and aqueous phases showed that they contained no product. Finally, the reaction was refluxed for 1 week before being quenched and worked up. The ^{1}H NMR spectrum of the residue showed that it contained at least two compounds, one of them being unreacted 9-phenylquinidine, but the spectrum was not clear enough to determine the identity of the second compound. The reason that the reaction did not work could be because of the steric bulk around the C9 position making further addition impossible. It could also be due to the fact that the 9-phenylquinidine was not that soluble in ether or that on addition of the ^{n}BuLi, the solution turned cloudy. This insinuated that the ^{n}BuLi was being destroyed before the addition of the acetyl chloride, therefore making the protection impossible. To determine whether either of the two latter explanations was true, the reaction was carried out a second time using THF as the solvent. This time the 9-phenylquinidine was fully dissolved before the addition of the other reactants and no cloudiness was apparent after the addition of the ^{n}BuLi. After 17 h the ^{1}H NMR spectrum was promising as it showed that there were two distinct compounds in the sample. This was still true after 2 days, but on the third day there appeared to be mainly just the one compound, which importantly was not 9-phenylquinidine. The reaction was worked

up and the ^{1}H NMR spectrum of the small amount of solid material was shown to be mainly one unknown compound with some impurities. The mass spectrum showed that the parent ion of this compound had a mass of 443, which is consistent with 9-phenylquinidine acetate, but more importantly the other major peak at 383 corresponds to a loss of –OAc. This indicated that the acetyl group had added at the desired location and that the product was indeed 9-phenylquinidine acetate. To purify the sample further, it was recrystallised from ethyl acetate which led to the formation of colourless needles of the pure product. The filtrate still contained a substantial quantity of the product but it did not crystallise out. With this success the reaction was repeated on a larger scale. Strangely, after work-up, the organic phase showed no sign of the product so the solvent was removed from the aqueous layer, but again nothing could be seen in the ^{1}H NMR spectrum. It is known that THF can react with organolithium compounds which may be happening in this case, so the reaction was repeated except sodium hydride was used instead of ^{n}BuLi. This time after work-up the ^{1}H NMR spectrum showed that the desired product was formed, but it contained some impurities due to the residue of the excess acetyl chloride, solvent and some grease. The two former impurities could be removed simply by drying under vacuum and the grease was removed by washing the sample with petroleum ether. As with most of these types of compound, there was broadening of some of the peaks in the ^{1}H and ^{13}C NMR spectra, which could be resolved by carrying out the experiment at 272 K. As the reaction was proven to work for the second time, it was carried out on a large scale to yield enough 9-phenylquinidine acetate **(113)** to take forward to the next stage.

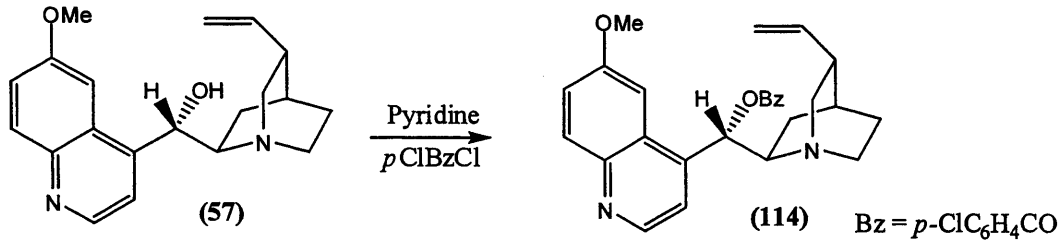


Scheme 3.17 *The Synthesis of 9-Phenylquinidine Acetate (113)*

3.4.2 Protection with a *p*-Chlorobenzoyl Group

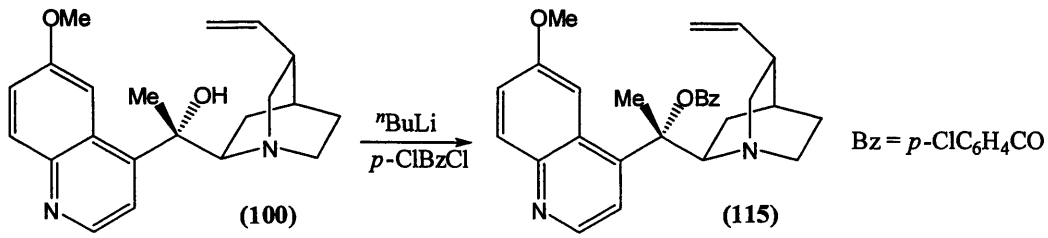
The synthesis of quinidine *p*-chlorobenzoate **(114)** was carried out in exactly the same way as the synthesis of quinidine acetate **(111)** except *p*-chlorobenzoyl chloride was used in place of acetyl chloride and the reaction was stirred for 4.5 h instead of 4 h (Scheme 3.18).[21] The purity after column chromatography was not as high as in the acetyl-protected compounds, so the recrystallisation of the compound from ethyl acetate/hexane (1/1) was

attempted but with no success. The crude compound was also dissolved in the minimum volume of ethyl acetate followed by the slow addition of hexane to encourage precipitation, which led to a sticky yellow solid forming. Due to the difficulty of recrystallising the compound, it was carried forward without any further purification.



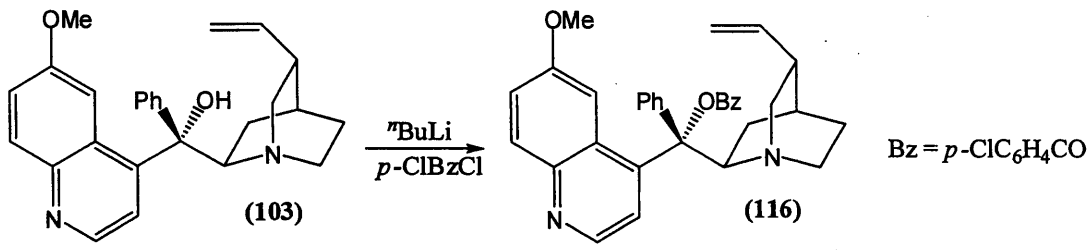
Scheme 3.18 *The Synthesis of Quinidine p-Chlorobenzoate (114)*

As it has been proven that 9-methylquinidine **(100)** can be protected with an acetyl group, the next task was to synthesise the *p*-chlorobenzoate **(115)** using the same procedure (1.5 equivalents of *p*-chlorobenzoyl chloride in THF at reflux) (Scheme 3.19). After 22 h the ^{1}H NMR spectrum of the reaction mixture did not show any evidence that a reaction had occurred, but after 47 h a 41 % conversion was obtained. The conversion was increased to 68 % by carrying out the reaction in ether for 3 days. The desired product was separated from the *p*-chlorobenzoyl residue by recrystallisation of the aromatic impurity from chloroform. This was not an ideal separation method, so the product also had to be purified by column chromatography. The crude product was loaded onto a silica gel column and was eluted initially with chloroform to remove the aromatic impurity, and then with chloroform/methanol (97/3) to yield the product. The product still contained a trace amount of impurity, but this could be avoided if the chloroform/methanol ratio was altered to 99/1. The ^{1}H NMR spectrum of the purified product showed broadening of all the peaks in the aliphatic region as well as the C5' aromatic proton, indicating that there was increased steric hinderance. All the peaks could be resolved by performing the ^{1}H NMR experiment at 326 K. This reaction was scaled up without any problems to yield pure 9-methylquinidine *p*-chlorobenzoate **(115)** in a 20 % yield.



Scheme 3.19 *The Synthesis of 9-Methylquinidine p-Chlorobenzoate (115)*

The final compound to be synthesised was 9-phenylquinidine *p*-chlorobenzoate **(116)**. It was expected to be a difficult synthesis as the formation of the acetate was troublesome and the increased steric bulk of the *p*-chlorobenzoate group would only add to these problems. In the first attempt at this reaction the same reaction conditions were used to that of 9-phenylquinidine acetate **(113)**, but initially using ^{n}BuLi as the base (Scheme 3.20). After work-up, the ^{1}H NMR spectrum showed that very little, if any, product had formed. It was difficult to determine as the spectrum was swamped by the aromatic peaks from the unreacted *p*-chlorobenzoyl chloride. As the synthesis of 9-phenylquinidine acetate **(113)** was more successful using NaH as the base, the same exchange was made here. The first attempt with the new base yielded a mixture of starting material and product in an approximate 1/1 ratio. Attempts were made to wash out the product using ethanol, but this failed. As the amount of crude product gained was very small, it was decided to repeat the reaction on a larger scale before a purification method was determined. Curiously, the ^{1}H NMR spectrum of the crude material from the next batch showed that it contained product and the residue from the excess *p*-chlorobenzoyl chloride, but no 9-phenylquinidine **(103)**. An attempt to remove the impurity by drying under vacuum as in the 9-phenylquinidine acetate case failed, so the sample was loaded onto a silica gel column and eluted with chloroform to remove the impurity followed by a mixture of chloroform/methanol 9/1 to obtain the pure product.

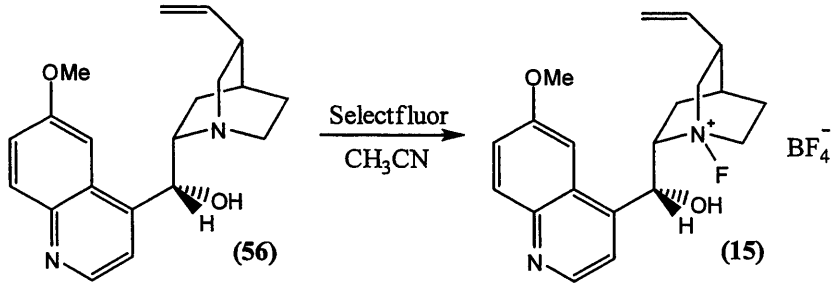


Scheme 3.20 *The Synthesis of 9-Phenylquinidine p-Chlorobenzoate (116)*

3.5 Fluorination of the Quinuclidine Nitrogen

After the successful synthesis of a small library of compounds based on quinidine, the next step was to fluorinate the quinuclidine nitrogen in order to create the new NF reagents that are to be tested in a model asymmetric fluorination. Two different methods were investigated. In the first method Selectfluor was used as the electrophilic source of fluorine whereas NFSI was used in the second method. In both approaches, the fluorination of quinine was attempted initially in order to optimise the reaction conditions as it was the cheapest and more readily available stereoisomer.

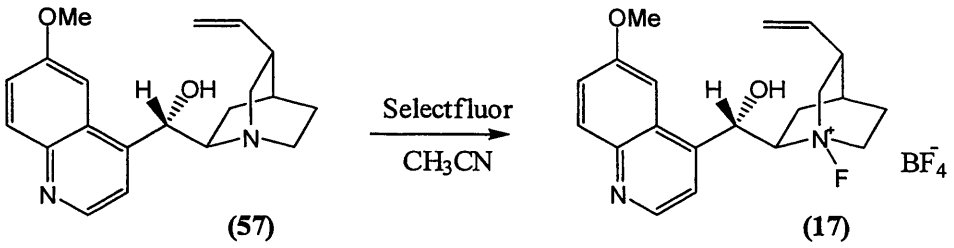
3.5.1 Using Selectfluor (2) as the Electrophilic Fluorine Source



Scheme 3.21 *The Fluorination of Quinine (56) with Selectfluor*

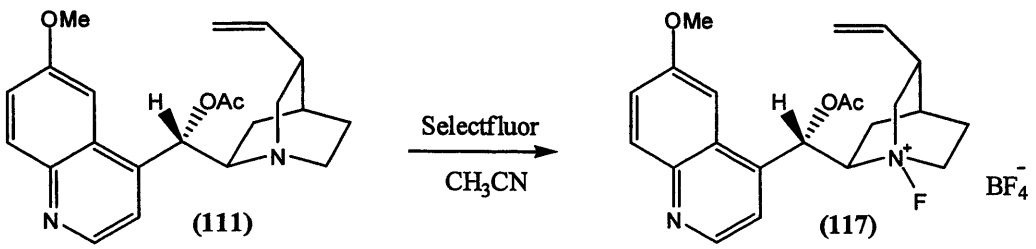
Cahard[23] published a procedure for the fluorination of cinchonine and used this method for the fluorination of a range of cinchona alkaloids. A solution of Selectfluor in acetonitrile was added to a solution of quinine **(56)** in acetonitrile dropwise (Scheme 3.21). The reaction mixture was stirred for 30 mins at room temperature, and then the solvent was removed. The residue was dissolved in acetone and a sulphuric acid solution in acetone was added to precipitate out the Selectfluor residue. The residue was filtered off and diethyl ether was added to the filtrate until precipitate stopped forming. The solid was filtered off and washed with a diethyl ether/acetone (1/1) solution and dried. The ^{1}H NMR spectrum of the crude product was quite messy, but the ^{19}F NMR spectrum showed clearly the two fluorine peaks at δ 42.82 and -151.10 ppm in an approximately 1/4 ratio. An attempt at recrystallising the product from acetone failed to purify it sufficiently. Selectfluor is not very soluble in acetonitrile, so not all of the fluorinating agent was being transferred into the reaction vessel at the start of the reaction. The added impurity of the unreacted starting material may be why the purification was not going as well as it should. As the purification of this product was proving difficult, this method was abandoned.

Shibata[24] also published a procedure for the synthesis of *N*-fluorocinchona alkaloids. In this case, solid Selectfluor was added to a suspension of quinine **(56)** in acetonitrile at room temperature. The mixture was stirred for a few minutes until homogeneous. After a few more minutes, a white powdery solid precipitated out of the solution. This solid was quickly filtered, washed with cold acetonitrile and dried. The ^{1}H and ^{19}F NMR spectra of the solid matched those in the literature for *N*-fluoroquininium tetrafluoroborate **(15)**.



Scheme 3.22 *The Fluorination of Quinidine (57) Using Selectfluor*

Shibata's method was then used to synthesise *N*-fluoroquinidinium tetrafluoroborate **(17)** (Scheme 3.22).[24] Selectfluor (1 equiv.) was added as a solid in one portion to a stirred suspension of quinidine **(57)** in acetonitrile and stirred at room temperature for 40 mins. The white solid apparent in the reaction vessel was filtered off and dried under vacuum. The ^{1}H and ^{19}F NMR spectra showed that the solid was the pure desired product and was obtained in 51 % yield. *N*-Fluoroquinidinium tetrafluoroborate **(17)** was also synthesised successfully using the procedure described by Cahard.[23] In this synthesis a solution of Selectfluor (1.2 equiv.) in acetonitrile was added dropwise to a suspension of quinidine **(57)** in acetonitrile and then stirred at room temperature for 30 mins. Again, a white precipitate was apparent at the end of the reaction which was filtered off and dried under vacuum. The ^{1}H and ^{19}F NMR spectra showed that it was the desired product, but the yield was poor (41 %). In order to obtain more product, a solution of sulphuric acid in acetone was added to the filtrate to precipitate out the Selectfluor residue which was then filtered off and ether was added to the filtrate. All attempts to recrystallise the resulting white sticky solid unfortunately failed. The best yield was obtained when Selectfluor (1.2 equiv.) was added as a solid in several portions to a suspension of quinidine in acetonitrile and stirred at room temperature for 1 h in the presence of 3 Å molecular sieves. The resulting white solid was filtered off and dried under vacuum to give the pure product in a 75 % yield. No melting point for *N*-fluoroquinidinium tetrafluoroborate **(17)** could be measured as it decomposed in the melting point tube at 152 °C.

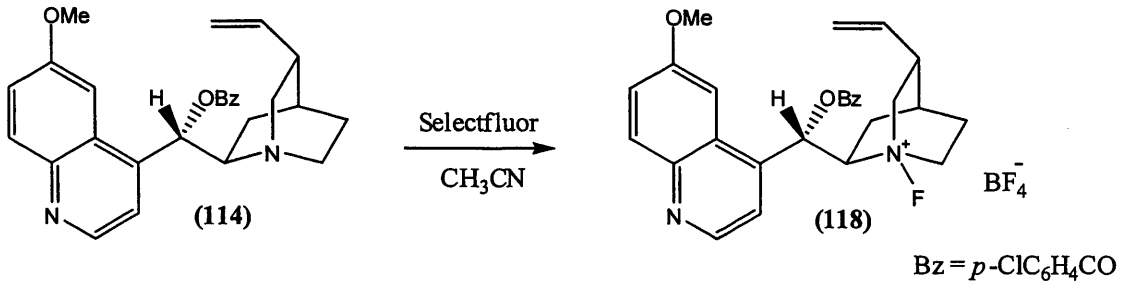


Scheme 3.23 *The Fluorination of Quinidine Acetate (111) Using Selectfluor*

The synthesis of the protected *N*-fluoroquinidinium salts was not as simple as the synthesis of *N*-fluoroquinidinium tetrfluoroborate **(17)** since they do not precipitate out during the reaction due to their higher solubility in acetonitrile. Initially, *N*-fluoro-*O*-acetylquinidinium tetrafluoroborate **(117)** was synthesised by the addition of solid Selectfluor (1 equiv.) in one portion to a solution of quinidine acetate **(111)** in acetonitrile and was stirred at room temperature for 40 mins (Scheme 3.23). As no solid precipitated out, the volume of solvent was reduced to yield a white solid which was filtered off and dried. The ^{1}H and ^{19}F NMR spectra showed that the solid was the pure desired product, but the yield was poor (22 %). In an attempt to retrieve more product from the solution, the residue was dissolved in the minimum volume of acetone and a dilute acidic acetone solution was added dropwise to precipitate out the Selectfluor residue, which was removed by filtration. According to the literature procedure, the dropwise addition of ether to the filtrate should cause the *N*-fluoro-*O*-acetylquinidinium tetrafluoroborate to precipitate out, but unfortunately every attempt led to a yellow sticky solid crashing out of solution. The ^{1}H and ^{19}F NMR spectra of the sticky solid showed that the desired compound was there, but it was impure as it contained traces of starting material. All attempts at recrystallising the solid failed. The reaction was repeated in exactly the same way except the solid obtained at the end of the reaction, though mainly product also contained traces of the starting material, quinidine acetate, as well as Selectfluor residue. An attempt was made to dissolve the product residue in the minimum volume of acetone, but it contained an insoluble white solid which was filtered off and dried under vacuum. ^{1}H and ^{19}F NMR spectroscopy revealed it to be the desired product which was obtained in a 22% yield. In an attempt to gain more product the method described above was implemented, but a trace amount of quinidine acetate could not be removed from the *N*-fluoro-*O*-acetylquinidinium tetrafluoroborate.

To improve the yield, the reaction was repeated using the minimum volume of solvent to dissolve the quinidine acetate **(111)**, in order to facilitate the precipitation of the product out of solution. Selectfluor (1.2 equiv.) was added as a solid in portions over a few minutes and the reaction was then stirred for 40 mins at room temperature. Unfortunately, the product did not precipitate out, but by removing most of the solvent under reduced pressure a solid did precipitate out and NMR spectroscopy showed it to be the desired product which was obtained in a 69 % yield. The reaction was repeated using the same reaction conditions but only one equivalent of Selectfluor was used. The ^{1}H NMR spectrum of the solid obtained at the end of the reaction showed that it was mainly product, but traces of the starting material, quinidine acetate, could be seen. These were removed successfully by dissolving the solid in the minimum volume of acetone, adding a small amount of water and leaving it to crystallise out overnight. The crystalline powder was washed with water and dried under vacuum to

yield the pure product in a 70 % yield. No melting point could be measured for *N*-fluoro-*O*-acetylquinidinium tetrafluoroborate **(117)** as it decomposed in the melting point tube at 212 °C.



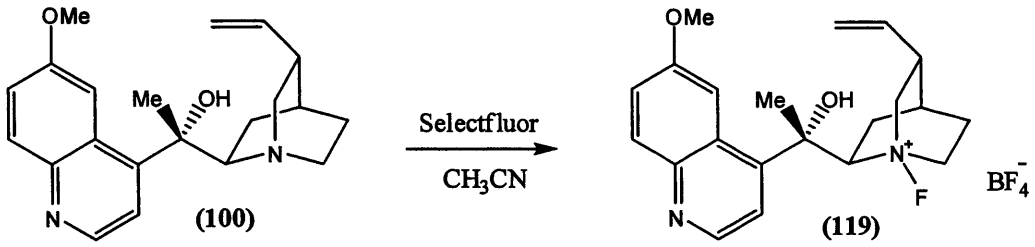
Scheme 3.24 *The Fluorination of Quinidine p-Chlorobenzoate (114) Using Selectfluor*

The synthesis of *N*-fluoro-*O*-*p*-chlorobenzoylquinidinium tetrafluoroborate **(118)** was attempted by following the procedure described by Shibata (Scheme 3.24).[24] Selectfluor (1 equiv.) was added as a solid in one portion to a solution of quinidine *p*-chlorobenzoate **(114)** and the reaction mixture was stirred at room temperature for 40 mins. At the end of the reaction, no precipitate was apparent so the solvent was removed under reduced pressure. The ^{1}H and ^{19}F NMR spectra showed that the residue was mainly the desired product, but it contained the starting material and Selectfluor residue. The product was dissolved in the minimum volume of ether and a dilute acidic solution was added to precipitate the Selectfluor residue out. The solid was filtered off and ether was added to the filtrate to enable the NF product to come out of solution. Unfortunately, on addition of diethyl ether a yellow oil was obtained which was mainly *N*-fluoro-*O*-*p*-chlorobenzoylquinidinium tetrafluoroborate **(118)**, but it still contained traces of the starting material. In an attempt to remove the quinidine *p*-chlorobenzoate, the oil was dissolved in acetone and a small amount of ether was added at 0 °C and left to cool for 3 days, but no precipitate formed.

In order to improve the reaction, it was repeated under anhydrous conditions using dry acetonitrile under a nitrogen atmosphere and in the presence of molecular sieves. Unfortunately, exactly the same problems were encountered and so the N-F derivative could not be obtained pure.

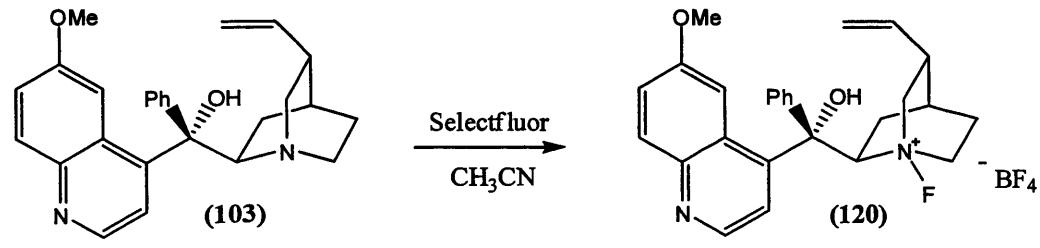
The procedure described by Shibata[24] was followed in the synthesis of *N*-fluoro-9-methylquinidinium tetrafluoroborate **(119)** (Scheme 3.25). Selectfluor (1.2 equiv.) was added as a solid in one portion to a suspension of 9-methylquinidine **(100)** in acetonitrile and after a few minutes the reaction mixture became a clear yellow solution which was stirred at room temperature for 1 h. As no solid precipitated out, the solvent was removed under reduced pressure to yield a yellow oil. The ^{1}H and ^{19}F NMR spectra showed that the desired product

had been formed, but traces of starting material, 9-methylquinidine, and the Selectfluor residue were also observed. The oil was dissolved in the minimum volume of acetone and a dilute solution of sulphuric acid in acetone was added to precipitate out the Selectfluor residue. The solid was filtered off and the filtrate turned cloudy on addition of ether, then a yellow oil collected at the bottom of the flask. The ^{1}H and ^{19}F NMR spectra of the yellow oil showed it to be the impure product. An attempt to triturate the oil with hexane failed to give the desired product, as did attempted recrystallisation from acetone, acetone/ether (1/1), acetonitrile and ethyl acetate.



Scheme 3.25 *The Fluorination of 9-Methylquinidine (100) Using Selectfluor*

The reaction was repeated using the same procedure except 1.3 equivalents of Selectfluor was used instead of 1.2 equivalents. A yellow oil was again apparent at the end of the reaction which was a mixture of desired product and Selectfluor residue. The oil was dissolved in the minimum volume of acetonitrile and cooled in an ice/water bath and the Selectfluor residue crystallised out. This was filtered off and ethyl acetate was added to the filtrate and left at room temperature to crystallise. The product obtained was mainly *N*-fluoro-9-methylquinidinium tetrafluoroborate **(119)**, but it still contained a small amount of the starting material, 9-methylquinidine. Finally, the product residue was washed with copious amounts of toluene in order to remove the 9-methylquinidine since the NF product is not soluble in it, but it failed to remove all of the impurity. NMR and mass spectroscopy characterisation of the product was obtained using this sample.



Scheme 3.26 *The Fluorination of 9-Phenylquinidine (103) Using Selectfluor*

Finally, the fluorination of 9-phenylquinidine **(103)** was attempted using the procedure by Shibata (Scheme 3.26).[24] Selectfluor (1 equiv.) was added as a solid in one portion to 9-phenylquinidine and the reaction mixture was stirred at room temperature for 1 h. As there was no precipitate at the end of the reaction, the solvent was removed under reduced pressure. The ^{1}H NMR spectrum was difficult to analyse as many of the peaks are broad, but it was clear that there was some Selectfluor residue present. Interestingly, the ^{19}F NMR spectrum only showed one peak at -151.6 ppm which corresponds to the BF_4 group. It is possible that the N-F bond has been made, but cannot be seen due to line broadening. The Selectfluor residue was removed by addition of a dilute acidic solution and the filtrate was re-examined. This time a small broad peak could be seen in the ^{19}F NMR spectrum at 40.3 ppm which was consistent for an N-F bond, but the ^{1}H NMR spectrum remained broad. The NMR experiments were therefore run at a higher temperature (336.6 K) and all the peaks were resolved in the ^{1}H NMR spectrum, but it was clear that there was still some 9-phenylquinidine in the sample. The ^{19}F NMR spectrum showed a broad peak at 40.8 ppm along with the sharp BF_4 peak. In an attempt to remove the starting material, the sample was washed with chloroform since 9-phenylquinidine is very soluble in this solvent, but the N-F product is not. Unfortunately, the starting material was not removed and remained in a 10/1 ratio of product to starting material. This led to the belief that there could possibly be some interaction between the fluorinated and non-fluorinated compounds. Attempts were made to recrystallise the sample by dissolving in acetonitrile and adding ethyl acetate, but all the attempts failed.

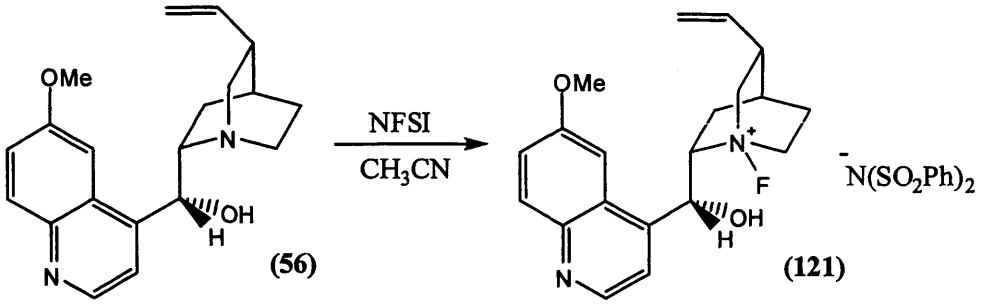
All of the *N*-fluorinated derivatives described above were characterised by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy as well as by mass spectrometry. Some of the derivatives were new compounds and in most cases, there was no literature data reported for the known derivatives. Hence, it is worth noting the key features of the spectra. The obvious difference between the fluorinated and non-fluorinated derivatives was the presence of two fluorine peaks in a 1/4 ratio in the ^{19}F NMR spectra. The smaller N-F peaks of the new *N*-fluorinated compounds were all in the same region (33.5 – 40.2 ppm), but were considerably more upfield than Selectfluor (Table 3.4). The larger peak, due to the BF_4 counter ion, was consistently at -151 ppm in all of the fluorinated compounds. In the ^{1}H NMR spectra, there was a downfield shift of all the proton peaks by varying degrees. The five aliphatic protons closest to the new N-F bond were the most affected and a downfield shift of ~1.5-2 ppm was observed. The other aliphatic protons were less affected but were still shifted downfield by ~0.5-1 ppm and the aromatic protons were shifted on average by 0.2 ppm. The obvious difference in the ^{13}C NMR of the fluorinated cinchona alkaloids compared to the non-fluorinated was the C-F coupling that was observed for most of the aliphatic carbons. The *N*-fluorocinchona alkaloids were also

characterised easily by mass spectrometry that showed a parent ion at $[M+F]^+$ under electrospray ionisation as well as $[BF_4]^-$ in the negative ion spectrum.

Compound	δ_F (NF)	δ_F (BF_4)
Selectfluor (**2**)	48.0	-151.3
NF-QD-BF_4 (**17**)	39.9	-151.8
NF-AcQD-BF_4 (**117**)	37.2	-151.7
NF-*p*ClBzQD-BF_4 (**118**)	37.0	-151.4
NF-MeQD-BF_4 (**119**)	33.5	-151.5
NF-PhQD-BF_4 (**120**)	40.2	-151.8

Table 3.4 *^{19}F NMR spectra of the N-Fluorocinchona Alkaloid Derivatives Compared With Selectfluor*

3.5.2 Using NFSI (1) as the Electrophilic Fluorine Source

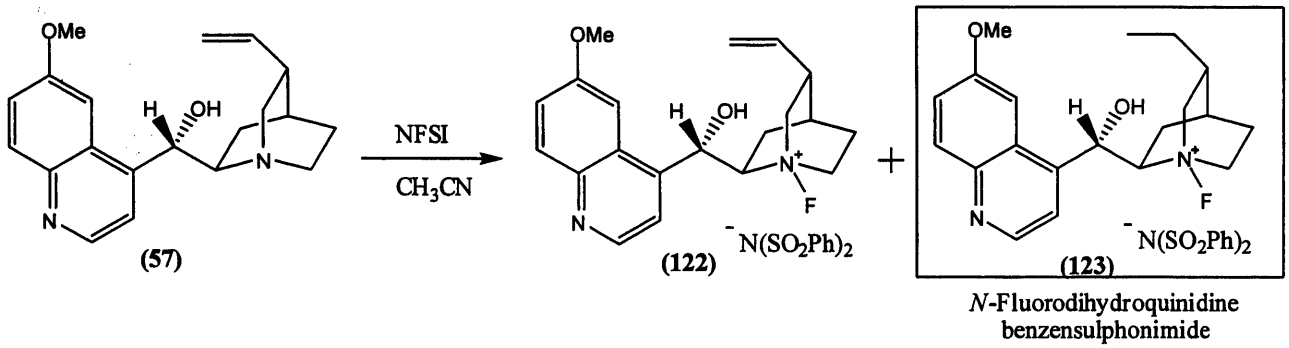


Scheme 3.27 *The Fluorination of Quinine (56) Using NFSI*

The syntheses of *N*-fluoroquininium benzenesulphonimide **(121)**, *N*-fluoroquinidinium benzenesulphonimide **(122)**, *N*-fluoro-*O*-acetylquinidinium benzenesulphonimide **(124)** and *N*-fluoro-*O*-*p*-chlorobenzoylquinidinium benzenesulphonimide **(126)** were carried out using NFSI as the electrophilic source of fluorine and a literature procedure by Cahard was followed (Scheme 3.27).[25] NFSI (*N*-fluorobenzenesulfonimide) can be a more useful reagent than Selectfluor due to its better solubility in a range of organic solvents. A solution of NFSI in acetonitrile was added slowly to an equimolar solution of quinine **(56)** in acetonitrile under a nitrogen atmosphere and the reaction mixture was stirred for 30 mins at room temperature. In the literature, the reaction gave a 100% yield, but this was not observed. The reaction gave a mixture of starting material and product. A second attempt was carried out with exactly one equivalent of NFSI to quinine. Again, a mixture of starting material and product was

obtained. It became obvious that a 100% conversion would not be achieved, so the crude product would have to be purified. The crude product was dissolved in the minimum volume of dichloromethane and the addition of diethyl ether caused the *N*-fluoroquininium benzenesulphonimide **(121)** to precipitate out. The solid was collected, dried and the ^{1}H and ^{19}F NMR spectra showed that it was pure product.

The fluorination of quinidine **(57)** was carried out using the same procedure (Scheme 3.28) and the ^{1}H NMR spectrum of the crude product showed two sets of peaks; the major set being the desired product and the minor set being starting material. Interestingly, the ^{19}F NMR spectrum showed two fluorine peaks at 36.7 ppm and 37.5 ppm in a ratio of 5/1. After recrystallisation from dichloromethane/ether, the ^{1}H NMR spectrum showed a clean product, but the ^{19}F NMR spectrum still displayed both peaks in a slightly increased ratio of 4/1. It was concluded that the smaller of the two peaks was due to the dihydroquinidine (an impurity in quinidine) being fluorinated and then concentrated in the purification stage. The commercial sources of quinidine contain up to 20 % dihydroquinidine which was roughly the same ratio that was seen before the purification of the NF reagent. Further proof for this can be found in the ^{1}H NMR spectrum of the pure product as there was a deficiency in the alkene protons because the integration of the aromatic protons and the alkene protons are in a ratio of 1/0.8. Also, a small triplet at 0.95 ppm was apparent which is consistent with the CH_3 group of dihydroquinidine. As dihydroquinidine and quinidine are so similar in structure, the other peaks in the ^{1}H NMR spectrum are probably lying on top of each other and so appear as a single product. The small amount of *N*-fluorodihydroquinidinium benzenesulphonimide **(123)** should not make much difference when it comes to the testing of these compounds as the results are expected to be similar to those for *N*-fluoroquinidinium benzenesulphonimide **(122)**.



Scheme 3.28 *The Fluorination of Quinidine (57) Using NFSI*

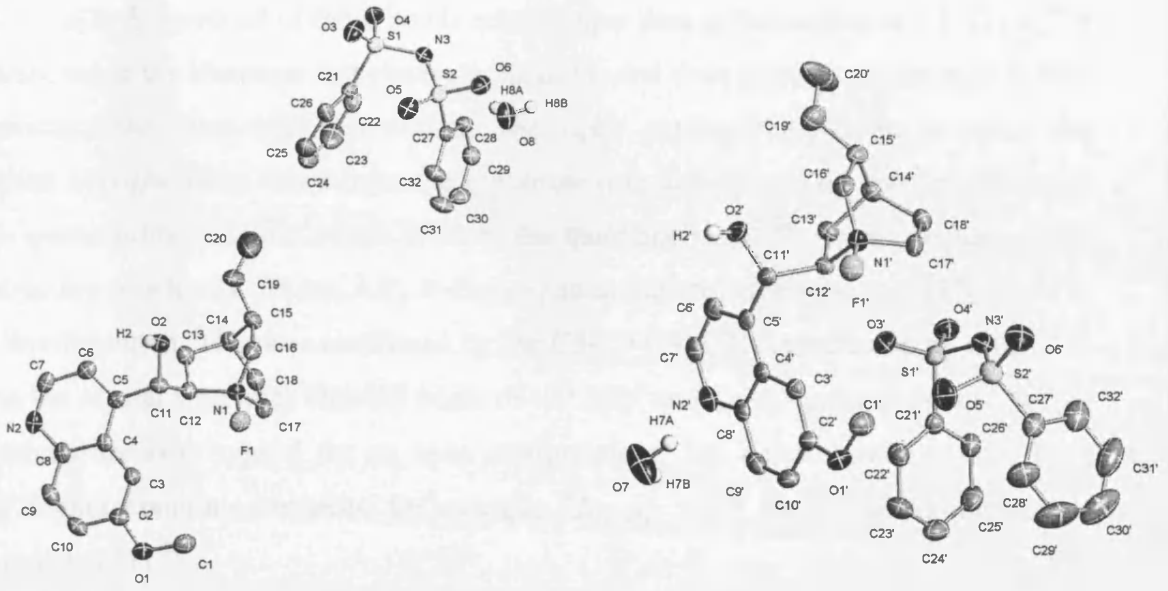


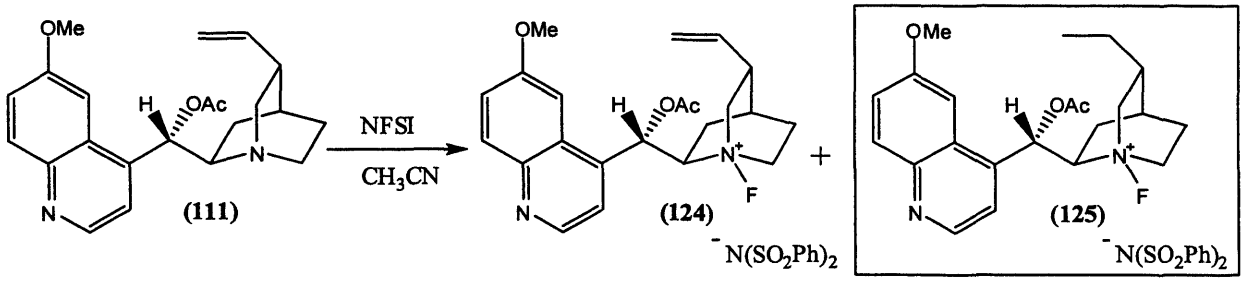
Figure 3.9 *The Crystal Structure of N-Fluoroquinidinium Benzenesulphonimide (122)*

	NF-QD-N(SO_2Ph)$_2$ (122)	**NF-QN-BF_4**[24] **(15)**	**NF-CD-BF_4**[27] **(14)**	**Selectfluor (2)**
Bond Lengths				
N(1)-F(1)	1.417(3) Å	1.4912(2) Å	1.409(7) Å	1.37(2) Å
Torsion Angles				
C2-C3-C9-C10	117.0(9)°	137.5(2)°		
C2a-C3a-C9a-C10a	156.3(6)°	-138.5(2)°		

Table 3.5 *Selected Bond Lengths and Torsion Angles For N-F Compounds*

A single crystal of *N*-fluoroquinidinium benzenesulphonimide **(122)** suitable for X-ray diffraction was produced by slow crystallisation from ethyl acetate and the crystal structure of this compound is shown in Figure 3.9. Selected bond lengths and torsion angles are shown in Table 3.5. As with the crystal structure of *N*-fluoroquininium tetrafluoroborate **(15)** obtained by Shibata,[24] *N*-fluoroquinidinium benzenesulphonimide exists as two molecules with the difference being the torsion angle of C2-C3-C10-C11 represented by C16-C15-C19-C20 and C16'-C15'-C19'-C20' on the crystal structure of 117.0(9)° and 156.3(6)° respectively. Also, a water molecule was bonded to one of the molecules of *N*-fluoroquinidinium benzenesulphonimide and so appears in the structural unit. From this crystal structure the N-F bond length was found to be 1.417(3) Å which was similar to the known N-F bond of *N*-fluoroquinuclidinium triflate at 1.407(6) Å[26] and *N*-fluorocinchonidinium tetrafluoroborate **(14)** at 1.409(7) Å,[27] but shorter than the N-F bond in *N*-fluoroquininium tetrafluoroborate

(15) at 1.4912(2) Å[24] with all of these bonds being longer than in Selectfluor at 1.37(2) Å.[28] It has been shown in the literature that cinchona alkaloids and their derivatives can exist in four conformations, two open and two closed. The open conformations refer to when the quinuclidine nitrogen point away from the quinoline ring and the closed conformations are when the quinuclidine nitrogen points towards the quinoline ring.[29,30] As can be seen in the crystal structure previously (Figure 3.9), *N*-fluoroquinidinium tetrafluoroborate **(122)** exists in an open conformation. This was confirmed by the C8-C9-C4'-C3' (represented by C12-C11-C5-C6 on the crystal structure) dihedral angle of -99.1(3)° and the coupling constant $^3J_{H11,H12}$ 2.0 Hz which are both typical for an open conformation. The closed conformations have generally higher coupling constants, for example $^3J_{H11,H12}$ = 7.8 Hz for dihydroquinine *p*-chlorobenzoate **(21)**.[24]

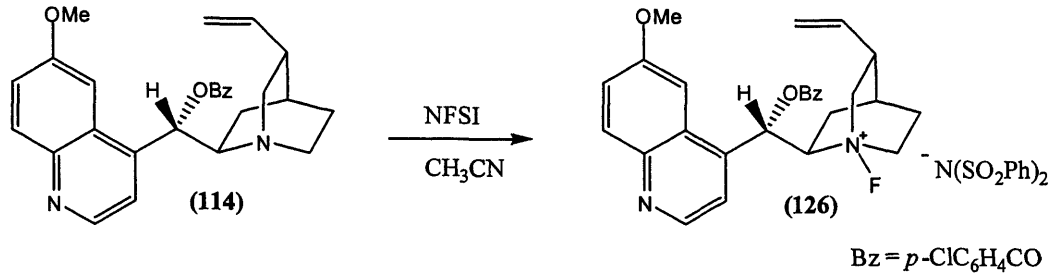


Scheme 3.29 *The Fluorination of Quinidine Acetate (111) Using NFSI*

The fluorination of quinidine acetate **(111)** proved to be more difficult (Scheme 3.29). The same procedure was followed and two peaks were observed in the ^{19}F NMR spectrum at 37.3 and 38.2 ppm with relative ratios of 4:1 after recrystallisation. The ^1H NMR spectrum showed that the vast majority of the product was the *N*-fluoro-*O*-acetylquinidinium benzenesulphonimide **(124)**, but it did show a trace of another compound. As with the *N*-fluoroquinidinium benzenesulphonimide **(122)**, the second compound is believed to be *N*-fluoro-*O*-acetyldihydroquinidinium benzenesulphonimide **(125)** as a characteristic triplet at 1.01 ppm caused by the protons on C11 was observed in the ^1H NMR spectrum. Further evidence for this assignment was provided by the mass spectrum, which shows a parent ion peak at 385, but also a smaller one at 387. This is consistent with *N*-fluoro-*O*-acetylquinidinium benzenesulphonimide **(124)** and *N*-fluoro-*O*-acetyldihydroquinidinium benzenesulphonimide **(125)** respectively. Attempts were made to purify the *N*-fluoro-*O*-acetylquinidinium benzenesulphonimide further by initially washing the solid with ether and then with cold chloroform. Unfortunately, this only leads to the product taking the form of an

oil and exhibiting a worse ^{1}H NMR spectrum. Unfortunately, the product could not be made solid again explaining why some analytical data is absent (see experimental section).

A second batch of *N*-fluoro-*O*-acetylquinidinium benzenesulphonimide **(124)** was synthesised, except the reaction was left to stir at room temperature overnight. The ^{1}H NMR spectrum showed two distinct compounds and the ^{19}F NMR spectrum showed the same two peaks in the same ratio. Unfortunately, all attempts to recrystallise this batch failed.

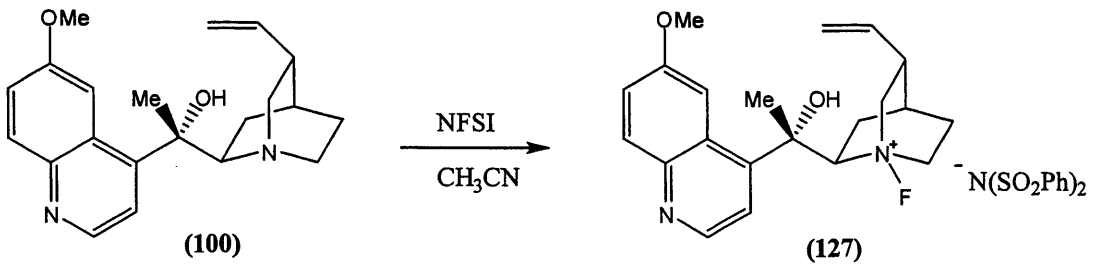


Scheme 3.30 *The Fluorination of Quinidine p-Chlorobenzoate (114) Using NFSI*

The synthesis of *N*-fluoro-*O*-*p*-chlorobenzoylquinidinium benzenesulphonimide **(126)** was carried out using the same procedure by Cahard,[25] except this time a white solid precipitated out at the end of the reaction (Scheme 3.30). The ^{1}H NMR spectrum taken in DMSO showed a fairly clean product, but the ^{19}F NMR spectrum showed just one peak at -167.0 ppm. This peak may be due to the N-F compound decomposing as it has been stated in the literature that Selectfluor (another quaternary N-F compound) decomposes in DMSO.[31] It was not possible to obtain a ^{1}H NMR spectrum in most other solvents (e.g. d^{6}-acetone, D_2O) as the solid is not particularly soluble in them, but weak ^{1}H and ^{19}F NMR spectra could be obtained in warm d^{3}-acetonitrile. Again two peaks could be seen in the ^{19}F NMR spectrum at 37.5 and 37.0 ppm in a 1:3 ratio suggesting that the solid is a mixture of both the quinidine and dihydroquinidine derivatives. It was not possible to see the characteristic triplet cause by the CH_3 group of the saturated quinidine derivative in the ^{1}H NMR spectrum due to the weak sample. The mass spectrum again showed the parent ion peak and another peak that was consistent for the fluorinated dihydroquinidine *p*-chlorobenzoate.

A solution of NFSI (1 equiv.) in acetonitrile was added dropwise to a stirred suspension of dry 9-methylquinidine **(100)** in acetonitrile under a nitrogen atmosphere and stirred at room temperature for 30 mins. After 10 mins, the solid in the reaction vessel had completely dissolved. After removing the solvent, the ^{1}H NMR spectrum of the resulting yellow foam showed at least two sets of peaks while the ^{19}F NMR spectrum showed a single peak at 35.8 ppm. Attempts were made to purify this sample by recrystallisation from hot acetonitrile, acetonitrile/ethyl acetate and acetone, but unfortunately, all attempts failed.

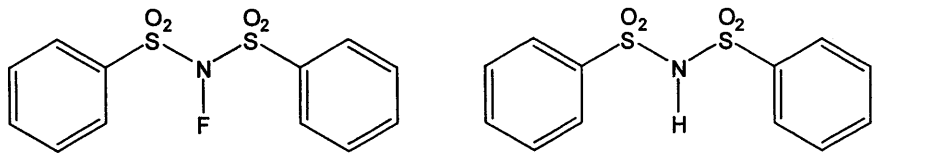
Additionally, the product residue was washed with ethyl acetate in an attempt to remove the impurities since 9-methylquinidine and NFSI are both soluble in ethyl acetate. Unfortunately, not all of the impurities were removed.



(100) (127)

Scheme 3.31 *The Fluorination of 9-Methylquinidine (100) Using NFSI*

The main concern with all of these fluorinations was that the reaction is not going to completion, yet there is no evidence of any excess NFSI (no peak in the ^{19}F NMR spectrum) even though one equivalent of reagent is used. In the attempt to fluorinate 9-methylquinidine **(100)**, there were too many aromatic protons in the ^{1}H NMR spectrum. This may mean that the NFSI is not entirely pure and is contaminated with a similar compound, such as *N*-(phenylsulphonyl)benzenesulphonamide **(128)** (Figure 3.10).



(1) (128)

Figure 3.10 *The Structures of NFSI (1) and N-(phenylsulphonyl)benzenesulphonamine (128)*

Since the purity of the NFSI was in doubt, an excess of the fluorinating agent was used. Therefore, the reaction was carried out for a second time and 1.2 equivalents of solid NFSI was added to the 9-methylquinidine **(100)** in acetonitrile, but not under dry conditions. After stirring at room temperature for 30 mins and removing the solvent, the ^{1}H NMR spectrum of the residue showed one major product with a trace amount of impurity and the excess NFSI. The ^{19}F NMR spectrum showed just two peaks at 35.9 ppm (N-F product) and at -39.9 ppm (excess NFSI). An attempt was made to remove the NFSI by washing with chloroform, but the *N*-fluoro-9-methylquinidiniuium salt **(127)** was also found to be soluble in chloroform. Ether was then added to the solution to precipitate out the product, but a yellow oil was deposited which still contained the excess fluorinating agent. The *N*-fluoro-9-

methylquinidinium salt was also found to be soluble in dichloromethane and as previous purifications used dichloromethane and ether to isolate the product, this was attempted, but again the excess NFSI was still apparent. Finally, the product residue was stirred in ether in order to remove the NFSI and leave behind the pure product. Unfortunately, after the solid was filtered, washed with copious amounts of ether and dried, some NFSI still remained. The solid was then washed with copious amounts of toluene and the ^{19}F NMR spectrum showed that all the NFSI had been removed, but now the ^{1}H NMR spectrum showed the presence of more than one product.

As it proved difficult to remove the excess NFSI at the end of the reaction, the fluorination was repeated using one equivalent of NFSI which was added to the 9-methylquinidine as a solid and stirred for 30 mins at room temperature. After the solvent was removed to give a yellow oil, ether was added to solidify the product, which was filtered off and dried under vacuum. The ^{1}H NMR spectrum showed the presence of two products, 9-methylquinidine **(100)** and *N*-fluoro-9-methylquinidinium benzenesulphononimide **(127)**, while the ^{19}F NMR showed only one singlet at 35.8 ppm for the fluorinated product.

3.6 Conclusions

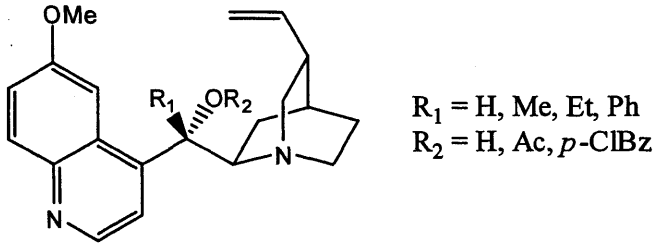


Figure 3.11 *General Structure of the Quinidine Derivatives*

A small library of quinidine derivatives of the type shown in Figure 3.11 have been synthesised successfully from quinine **(56)** in three steps. The oxidation of quinine gave quinidinone **(55)** which underwent the diastereoselective addition of three different Grignard reagents. The configuration at C9 was determined by 2D ^{1}H NMR experiments (NOESY) of 9-methyl and 9-phenylquinidine and the diastereoselectivity was rationalised by the chelation controlled addition of the Grignard reagent from the less hindered face. In the final step the hydroxyl group was protected with two different groups. The main advantage with this synthetic route was its very selective nature; at no point was there a need to separate diastereoisomers. This task had proved difficult in the previous chapter and many proposed routes failed solely on these grounds.

Some of the N-F derivatives were synthesised by transfer fluorination and the new compounds were fully characterised, though the purification was difficult. Other groups, notably Shibata's,[24] have also found the purification a difficult task, and consequently, the N-F compounds were made *in situ* in his work. Due to the relatively small quantities of, particularly, the protected 9-methylquinidines and 9-phenylquinidines, the fluorination and isolation of these compounds were not attempted. Instead the best course of action was to prepare the N-F compounds of these derivatives and the derivatives that were impossible to purify, *in situ*, so as not to give reduced enantiomeric excesses in the testing stage due to the presence of the achiral fluorinating agent impurity.

3.7 References

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Chapter Four

University *of*
Leicester

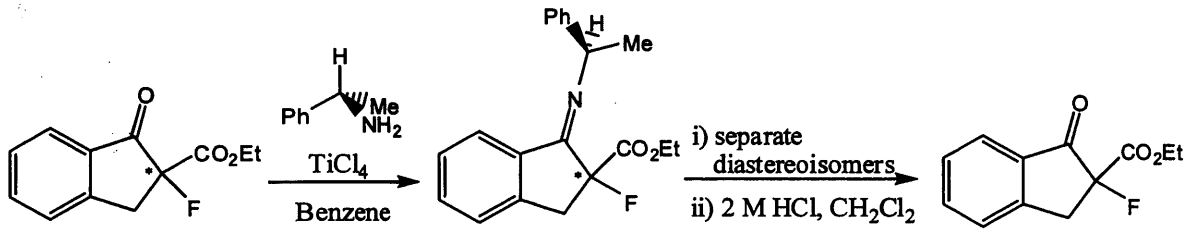
The Testing of Novel N-F Reagents

4.1 Introduction

After preparing successfully a small library of known and novel cinchona alkaloids, the final task was to test the derivatives in an asymmetric fluorination reaction. The *N*-fluorocinchona alkaloids had proven in the past to be rather substrate dependant in terms of enantioselectivity, so the choice of substrate for testing the novel derivatives was the key to obtaining good results. The *N*-fluorocinchona alkaloids have also been used to fluorinate the widest range of compounds so the choice of substrate was vast. It was logical to opt for a substrate that had given reasonable yields and enantiomeric excesses of the fluorinated product with *N*-fluorocinchona alkaloids. This would provide an ideal starting point using the optimised procedure that is reported in the literature, as well as a known procedure for determining the enantiomeric excess by chiral HPLC and would also allow a direct comparison between the novel compounds and other *N*-fluorocinchona alkaloids reported in the literature. A substrate that was easy to synthesise or purchase, yet be chemically or biologically important would be a major advantage. Many types of substrates were researched and most were eliminated due to the lack of access to the correct chiral column for HPLC or they had complex, time-consuming syntheses. Finally, two β-ketoesters were chosen, ethyl 1-indanone-2-carboxylate **(132)** and *tert*-butyl 1-indanone-2-carboxylate **(41)**, as well as the acyclic ester, ethyl α-cyano-*p*-tolylacetic acid **(135)**.

4.2 The Fluorination of Ethyl 1-indanone-2-carboxylate (132)

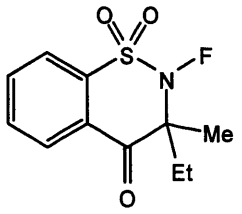
4.2.1 Background



Scheme 4.1 *The Separation of Enantiomers 2-Ethoxycarbonyl-2-Fluoro-1-Indanone (129) via an Imine Derivative*

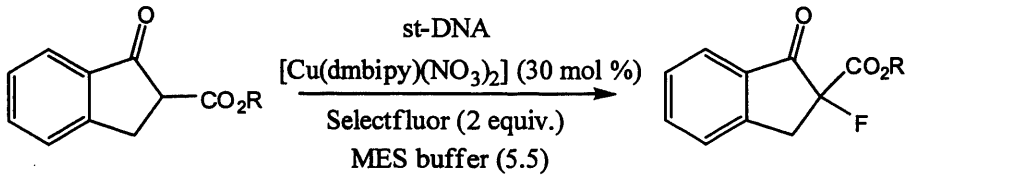
1-Indanones and 1-tetralones are common substrates for α-fluorination reactions due to their high susceptibility to α-substitutions. They are also important building blocks for the

syntheses of many natural products, medicines and agrochemicals.[1-4] Therefore, the first substrate chosen to test the asymmetric fluorinating ability of the novel cinchona alkaloid derivatives was ethyl 1-indanone-2-carboxylate **(132)**. Since it has been used to test a variety of asymmetric fluorinating strategies, it would provide an ideal comparison with many different approaches, not only other work involving cinchona alkaloids. Previously, (-)-2-ethoxycarbonyl-2-fluoro-1-indanone **(129)** was obtained pure by the separation of the (*R*)-(+)-α-methylbenzylimine derivatives **(130)** of the racemic mixture by flash column chromatography eluted with light petroleum ether/diethyl ether (9/1) (Scheme 4.1).[5] The resulting solid was found to have an enantiomeric excess of > 95 %, but as the actual fluorinating step was racemic, the overall yield was only 12 %. Takeuchi also synthesised 2-ethoxycarbonyl-2-fluoro-1-indanone as a racemic mixture using **(131)**, a novel achiral fluorinating agent based on saccharin (Figure 4.1).[6] The work was a precursor to the development of his asymmetric fluorinating agents **(11)**, **(12)** and **(13)** which were also based on saccharin (Figure 1.7).[7-9]



(131)

Figure 4.1 *The structure of N-Fluoro-3-ethyl-3-methyl-1,1-dioxo-2,3-dihydro-1H-1λ⁶-benzo[e]1,2-thiazin-4-one (131)*



(132) R = Et
(41) R = Bu^t

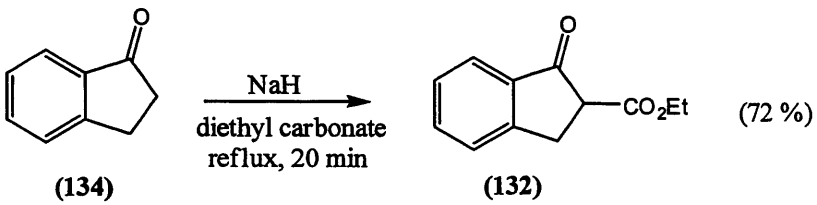
(129) R = Et, 72 % yield, 54 % ee
(133) R = ^{t}Bu, 75 % yield, 74 % ee

Scheme 4.2 *The DNA-Mediated Enantioselective Fluorination of (132) and (41)*

Ethyl 1-indanone-2-carboxylate **(132)** was fluorinated successfully by Shibata using a dihydroquinidine acetate **(23)**/Selectfluor combination to give the (+)-fluorinated product in 89 % yield and 78 % ee (Table 1.12, entry 1).[10] Recently, the same substrate was fluorinated using Selectfluor and the achiral catalyst [Cu(4-4'-dimethyl-2-2'-bipyridine)$(NO_3)_2$] in the presence of salmon testes DNA to obtain 2-ethoxycarbonyl-2-fluoro-1-indanone **(129)** in 72

% yield and 54 % ee (Scheme 4.2).[11] Finally, Kim and Park have also fluorinated asymmetrically ethyl 1-indanone-2-carboxylate using the phase transfer catalyst, *N*-(3,5-di-tert-butyl-4-methoxy)benzyl-*O*-propargyl cinchoninium bromide (**), NFSI and K_2CO_3 to give (+)-2-ethoxycarbonyl-2-fluoro-1-indanone in 92 % yield and 50 % ee.[12] By simply using Cs_2CO_3 as the base, the enantiomeric excess of the reaction could be improved to 63 % whilst still maintaining a high yield of 91 %. This work will be described in more detail at the end of this chapter.

4.2.2 The Fluorination of Ethyl 1-Indanone (132) Using the Novel Cinchona Alkaloid Derivatives



Scheme 4.3 *The Synthesis of Ethyl 1-indanone-2-carboxylate (132)*

Ethyl 1-indanone-2-carboxylate **(132)** was synthesised easily from 1-indanone **(134)** using sodium hydride and diethyl carbonate following a procedure by Brown (Scheme 4.3).[5] The ^1H and ^{13}C NMR spectra of the pure product showed the presence of both the keto and enol forms of this compound (Figure 4.2). Due to its high enol content, it was not necessary to convert ethyl 1-indanone-2-carboxylate into its silyl enol ether prior to fluorination, which had been required in many other examples by Cahard[13,14] and Shibata.[10,15]

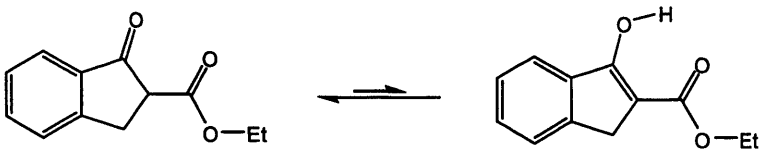
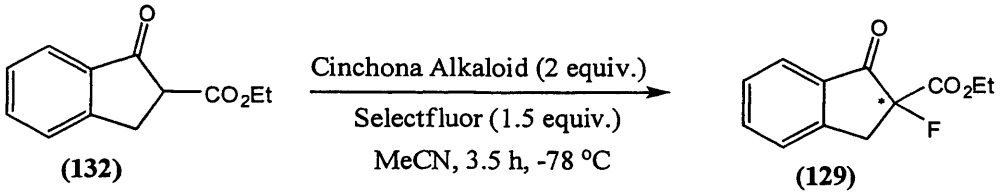


Figure 4.2 *The Keto and Enol Forms of Ethyl 1-indanone-2-carboxylate (132)*

During the many attempts to isolate the *N*-fluorocinchona alkaloids it was decided that the best course of action would be to produce them *in situ* prior to the addition of the substrate. This would lead to better enantioselectivities due to the main impurity being the achiral fluorinating agent (Selectfluor or NFSI) which would have an adverse effect on the enantioselectivity. Initially, ethyl 1–indanone-2-carboxylate **(132)** was fluorinated by the

addition of a pre-prepared solution consisting of 2 equivalents of the cinchona alkaloid and 1.5 equivalents of Selectfluor at -78 °C using the procedure described by Shibata.[10] Initially, the known reaction using quinine **(56)** was carried out on a larger scale than required for testing so that the fluorinated product could be isolated and fully characterised. The conversions for all of the fluorinations were excellent with no starting material observed in the ^{1}H NMR spectra of the crude products, the exception being the reaction with 9-ethylquinidine **(102)**. The isolated yields for all of the reactions were generally high, though mechanical losses were a problem as a small loss during the work up or purification process had a profound effect on the isolated yield due to the small scale on which the reactions were carried out. The fluorinations using the natural products, quinine **(56)** and quinidine **(57)**, led to good yields of the desired fluorinated product but low enantiomeric excesses of 24 % and 30 % respectively (Table 4.1, entries 1 and 2). These results are comparable to the 20 % ee and 27 % ee obtained by Cahard in the asymmetric fluorination of 2-methyl-1-tetralone (Table 1.6).[14] He found that by protecting the hydroxyl function on the natural cinchona alkaloids, he could increase the enantiomeric excesses of the reaction and here, the use of the protected quinidine acetate **(111)** and quinidine *p*-chlorobenzoate **(114)** led to increased enantioselectivities of 67 % and 42 % respectively (Table 4.1, entries 3 and 4). These were considerably lower than the 78 % ee obtained by Shibata with dihydroquinidine acetate in the same reaction (Table 1.12, entry 1). This shows that the group on C3 on the cinchona alkaloid was having a larger effect on the enantioselectivity than first thought. It appears that increasing the steric bulk at this position by using an ethyl group instead of a vinyl group increases the enantiomeric excess by ~10 %. The fluorination of ethyl 1-indanone-2-carboxylate was also carried out using the pre-formed *N*-fluoroquinidinium tetrafluoroborate **(17)** and *N*-fluoro-*O*-acetylquinidinium tetrafluoroborate **(117)** to give the desired product in good yields and 26 % ee and 48 % ee respectively (Table 4.1, entries 8 and 9). These turned out to be lower that the 30 % ee and 67 % ee observed for the equivalent cinchona alkaloid/Selectfluor combination (Table 4.1, entries 2 and 3). There is no reason why the pre-formed *N*-fluorocinchona alkaloids should give lower enantioselectivities compared to the ones made *in situ* because the same species was carrying out the fluorination in both cases. The only possible explanation was that the isolated *N*-fluorocinchona alkaloids were not completely pure and some of the residual achiral fluorinating agent had remained and was competing with the chiral fluorinating agent in the reaction, thus lowering the enantiomeric excess.



(132) (129)

Entry	Cinchona Alkaloid	Conversion[a] (%)	Yield[b] (%)	Ee[c] (%)	Major Isomer
1	QN (**56**)	100	74	24	(-)
2	QD (**57**)	100	82	30	(+)
3	QD-acetate (**111**)	100	94	67	(+)
4	QD-*p*-chlorobenzoate (**114**)	100	89	42	(+)
5	QD (**57**)	100	90	33	(+)
6	QD-acetate (**111**)	100	68	66	(+)
7	QD-*p*-chlorobenzoate (**114**)	100	66	41	(+)
8	*N*-fluoroQD- BF_4 (**17**)	100	63	26	(+)
9	*N*-fluoroQD-acetate- BF_4 (**117**)	100	70	48	(+)
10	9-MeQD (**100**)	100	75	38	(-)
11	9-EtQD (**102**)	incomplete	48	3	(+)
12	9-MeQD (**103**)	100	81	25	(-)
13	9-MeQD-acetate (**112**)	100	84	1	(-)
14	9-MeQD-*p*-chlorobenzoate (**115**)	100	82	5	(-)
15	9-PhQD (**103**)	100	79	36	(+)
16	9-PhQD-acetate (**113**)	100	80	13	(-)
17	9-PhQD-*p*-chlorobenzoate (**116**)	100	92	19	(-)

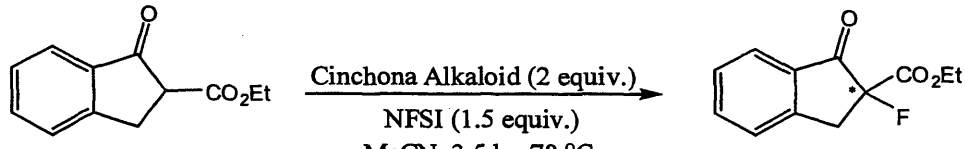
[a] Conversion based on lack of starting material observed in the ^1H NMR spectrum of the crude product.

[b] Isolated yield. [c] Determined by chiral HPLC.

Table 4.1 *The Synthesis of 2-Ethoxycarbonyl-2-fluoro-1-indanone (129) Using Selectfluor*

The results for the novel cinchona alkaloid derivatives were disappointing, but interesting. The use of 9-methylquinidine (**100**) gave a higher enantioselectivity of 38 % ee than quinidine (**57**), but surprisingly with reversed stereochemistry (Table 4.1, entry 10). 9-Phenylquinidine (**103**) gave a comparable enantioselectivity to that of 9-methylquindine (**100**), yet the favoured enantiomer was (+)-2-ethoxycarbonyl-2-fluoro-1-indanone the same as quinidine (**57**) (Table 4.1, entry 15). 9-Ethylquinidine (**102**) though turned out to be poor in terms of conversion, isolated yield and enantioselectivity (Table 4.1, entry 11). For this substrate the acetyl and *p*-chlorobenzoyl protection of both 9-methylquinidine and 9-

phenylquinidine lowered the enantioselectivity. Very poor enantiomeric excesses were obtained for 9-methylquinidine acetate **(112)** and 9-methylquinidine *p*-chlorobenzoate **(115)** and the same reversed stereochemistry as seen for 9-methylquinidine **(100)** was observed (Table 4.1, entries 13 and 14). 9-Phenylquinidine acetate **(113)** and 9-phenylquinidine *p*-chlorobenzoate **(116)** gave poor enantiomeric excesses but the opposite enantiomer to 9-phenylquidine **(103)** was obtained in excess (Table 4.1, entries 16 and 17). It appears that the hydroxyl protection of 9-methylquinidine and 9-phenylquinidine starts to shift the enantioselectivity towards the opposite enantiomer and so, has a detrimental effect with this substrate.



(132) **(129)**

Entry	Cinchona Alkaloid	Conversion[a] (%)	Yield[b] (%)	Ee[c] (%)	Major Isomer
1	QN **(56)**	100	73	19	(-)
2	QD **(57)**	100	42	40	(+)
3	QD-acetate **(111)**	100	48	61	(+)
4	QD-*p*-chlorobenzoate **(114)**	100	69	35	(+)
5	*N*-fluoroQD-N(SO_2Ph)$_2$ **(17)**	100	63	23	(+)
6	9-MeQD **(100)**	100	89	31	(-)
7	9-EtQD **(102)**	incomplete	18	7	(-)
8	9-PhQD **(103)**	100	51	38	(+)

[a] Conversion based on lack of starting material observed in the ^{1}H NMR spectrum of the crude product.
[b] Isolated yield. [c] Determined by chiral HPLC.

Table 4.2 *The Synthesis of 2-Ethoxycarbonyl-2-fluoro-1-indanone (129) Using NFSI*

The fluorination of ethyl 1-indanone-2-carboxylate **(132)** was also carried out using NFSI as the electrophilic source of fluorine. Using the same procedure as for the cinchona alkaloid/Selectfluor reaction, the conversions for all of the reactions (9-ethylquinidine excluded) were excellent and there was no starting material in the ^{1}H NMR spectra of the crude products. 2-Ethoxycarbonyl-2-fluoro-1-indanone **(129)** was isolated in moderate to good yields and lower isolated yields were due to the more difficult separation of the fluorinated product from the NFSI residue by column chromatography and some overlap was observed in some cases. With Selectfluor the residue was still a charged ammonium salt

which was retained by the column, whereas with NFSI the residue was a less polar, neutral compound which moved down the column. All attempts to slow the elution down failed as reducing the polarity of the solvent caused the product to remain on the column, so the original solvent system was used, but with a longer column. It was much better to obtain a lower isolated yield with a pure product than a higher yield and an impure product which could not be used for HPLC.

Although the fluorination using quinine **(56)**/NFSI gave a 19 % ee which was similar to the quinine/Selectfluor reaction (Table 4.2, entry 1), the quinidine **(57)**/NFSI combination gave a higher enantiomeric excess of 40 % compared to the 33 % achieved with the quinidine/Selectfluor combination (Table 4.2, entry 2). Quinidine acetate **(111)**/NFSI gave the highest enantiomeric excess of 61 % (Table 4.2, entry 3) and quinidine *p*-chlorobenzoate **(114)**/NFSI gave a similar result (35 % ee) to the analogous reaction with Selecfluor (42 % ee) (Table 4.1, entry 4). The product for all of these reactions was (+)-2-ethoxycarbonyl-2-fluoro-1-indanone. The fluorination of ethyl 1-indanone-2-carboxylate was also carried out using the pre-formed cinchona alkaloid derivative *N*-fluoroquinidinium benzenesulphonimide **(17)** to yield the desired product in 23 % ee (Table 4.2, entry 5). Once again this result was lower that the equivalent *N*-fluorocinchona alkaloid prepared *in situ* and for probably the same reason as in the previous cases where an achiral impurity capable of fluorinating the substrate remained in the sample after purification.

The use of the novel cinchona alkaloids, 9-methylquinidine **(100)**, 9-ethylquinidine **(102)** and 9-phenylquinidine **(103)**, were again disappointing, but comparable to the results obtained using Selectfluor. The 9-methylquinidine **(100)**/NFSI combination gave a similar 31 % ee to the 9-methylquinidine/Selectfluor combination and again the (-)-2-ethoxycarbonyl-2-fluoro-1-indanone was the favoured enantiomer (Table 4.2, entry 6). The combination of 9-phenylquinidine **(103)**/NFSI gave 38 % ee, very similar to that obtained by 9-phenylquinidine/Selectfluor, and the major enantiomer was (+)-2-ethoxycarbonyl-2-fluoro-1-indanone (Table 4.2, entry 8). Again, 9-ethylquinidine **(102)**/NFSI gave poor enantioselectivity but with an apparent reversal of stereochemistry compared to that of the 9-ethylquinidine/Selectfluor combination (Table 4.2, entry 7). It was in doubt whether this was true due to the low enantiomeric excesses observed.

The initial results for the enantioselective, electrophilic fluorination using novel cinchona alkaloid derivatives were highly surprising with the reversal of stereochemistry in the fluorinated product depending on whether 9-methylquinidine or 9-phenylquinidine was used as the chiral fluorinating agent. It was known that by exchanging the ester functionality to a *tert*-butyl ester, higher enantioselectivities can be obtained in catalytic asymmetric fluorination reactions. Therefore, this strategy was also investigated in this work in an attempt

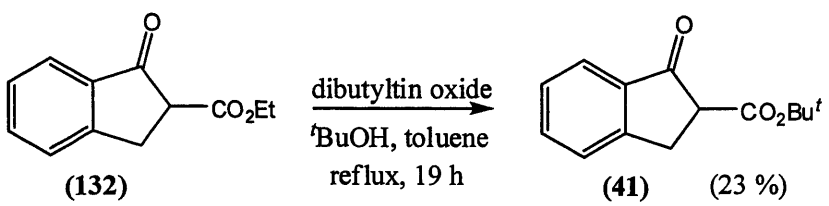
to improve on the results obtained for the fluorination of ethyl 1-indanone-2-carboxylate **(132)**.

4.3 The Fluorination of *tert*-Butyl 1-Indanone-2-carboxylate (41)

4.3.1 Background

The synthesis of 2-*tert*-butoxycarbonyl-2-fluoro-1-indanone **(133)** has been examined in many catalytic asymmetric carbon-fluorine bond forming systems, but no example could be found of it being used in a reagent controlled asymmetric fluorination. As described in Chapter One, Sodeoka fluorinated *tert*-butyl 1-indanone-2-carboxylate using the palladium catalyst **(34b)**, and 1.5 equivalents of NFSI in ethanol at – 20 °C to give the (*R*)-2-*tert*-butoxycarbonyl-2-fluoro-1-indanone **(133)** in 85 % yield and 83 % ee (Table 1.19).[16,17] Shibata used the same substrate for the optimisation of the enantioselective fluorinations using metal-bis(oxazoline) complexes (Table 1.29).[18] If Cu(II)$(OTf)_2$ was used as the catalyst with bis(oxazoline) and NFSI (1.2 equiv.) in the presence of 4 Å molecular sieves, 2-*tert*-butoxycarbonyl-2-fluoro-1-indanone was obtained in 81 % yield and up to 70 % ee favouring the (*S*)-enantiomer. Simply by exchanging the metal catalyst for Ni(II)$(ClO_4)_2.6H_2O$, then the (*R*)-enantiomer could be gained in 87 % yield and 93 % ee. A further improvement involved replacing the bis(oxazoline) with dbfox-Ph **(44)** to favour the (*S*)-enantiomer in an excellent 76 % yield and 99 % ee.[19] He also used this substrate for the DNA catalysed enantioselective electrophilic fluorination reactions, as well as ethyl 1-indanone-2-carboxylate **(132)**, to give an improved 75 % yield and 74 % ee of the fluorinated product (Scheme 4.2).[11] Iwasa produced some similar work in which *tert*-butyl 1-indanone-2-carboxylate **(41)** was fluorinated using the novel chiral *N,N,N*-tridentate ligand **(40)**, the Lewis acidic Ni$(ClO_4)_2$ and NFSI to yield the fluorinated product in 99 % yield and 94 % ee with the major enantiomer having the (*R*) configuration (Table 1.27).

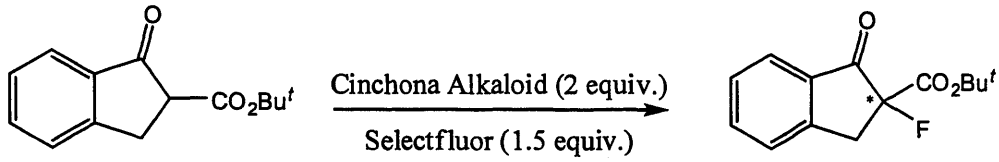
4.3.2 The Fluorination of *tert*-Butyl 1-indanone-2-carboxylate (41) Using the Novel Cinchona Alkaloid Derivatives



(132) **(41)** (23 %)

Scheme 4.4 *The Synthesis of tert-Butyl 1-Indanone-2-carboxylate (41)*

The substrate *tert*-butyl 1-indanone-2-carboxylate **(41)** was synthesised easily from ethyl 1-indanone-2-carboxylate **(132)** by a transesterification reaction based on a procedure by Nakajima (Scheme 4.4).[20] The literature preparation used methyl 1-indanone-2-carboxylate as the starting ester and involved a 2 h reflux of the reagents. Even though the reaction time was lengthened to 19 h in this case, the yield of the reaction was only 23 % compared to the literature value of 52 % most likely to be due to the different starting materials. Like ethyl 1-indanone-2-carboxylate, the ^{1}H and ^{13}C NMR spectra of the pure *tert*-butyl 1-indanone-2-carboxylate **(41)** did show the presence of the enol, but in a much smaller ratio.



(41) **(133)**

Entry	Cinchona Alkaloid	Conversion[a] (%)	Yield[b] (%)	Ee[c] (%)	Major Isomer
1	QN **(56)**	100	78[d]	6	(+)
2	QD **(57)**	100	70	12	(+)
3	QD-acetate **(111)**	100	75	61	(+)
4	QD-*p*-chlorobenzoate **(114)**	100	66	52	(+)
5	9-MeQD **(100)**	100	76	16	(+)
6	9-MeQD-acetate **(112)**	incomplete	68	2	(-)
7	9-MeQD-*p*-chlorobenzoate **(115)**	incomplete	95	3	(-)
8	9-PhQD **(103)**	100	85	35	(+)
9	9-PhQD-acetate **(113)**	100	90	13	(-)
10	9-PhQD-*p*-chlorobenzoate **(116)**	100	85	15	(-)
11	9-EtQD **(102)**	incomplete	85	2	(+)

[a] Conversion based on lack of starting material observed in the ^{1}H NMR spectrum of the crude product. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Reaction carried out on a large scale.

Table 4.3 *The Synthesis of 2-tert-Butoxycarbonyl-2-fluoro-1-indanone (133) Using Selectfluor*

The fluorination of *tert*-butyl 1-indanone-2-carboxylate **(41)** was carried out with Selectfluor using the same procedure as described for the fluorination of ethyl 1-indanone-2-carboxylate **(132)**. Selectfluor was preferred to NFSI as it had led to generally better yields and enantiomeric excesses, and a simpler purification of the crude product. The use of the

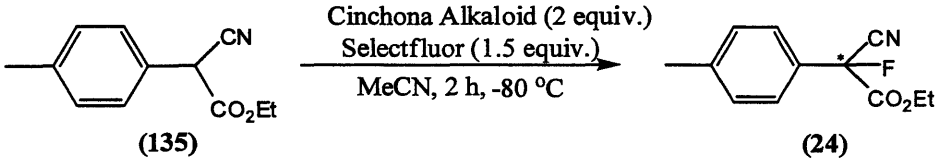
asymmetric fluorinating agents, *N*-fluoroquinidinium tetrafluoroborate **(17)** and *N*-fluoro-*O*-acetylquinidinium tetrafluoroborate **(117)**, were also excluded due to poor results obtained previously. The fluorination of *tert*-butyl 1-indanone-2-carboxylate using the natural products, quinine **(56)** and quinidine **(57)**, led to much lower enantiomeric excesses of 6 % and 12 % respectively (Table 4.3, entries 1 and 2) compared to using ethyl 1-indanone-2-carboxylate (Table 4.1, entries 1 and 2). In both of these cases, the (+)-enantiomer was obtained in excess which was surprising as usually quinine and quinidine act as pseudo-enantiomers. The protection of the hydroxyl function again led to an increased enantioselectivity and quinidine acetate **(111)** (61 % ee) and quinidine *p*-chlorobenzoate **(114)** (52 % ee) gave similar levels of enantiomeric excess to the analogous fluorination of ethyl 1-indanone-2-carboxylate (Table 4.3, entries 3 and 4).

The results with the novel cinchona alkaloids were again disappointing, especially the 9-methylquinidine series. The 9-methylquinidine **(100)**/Selectfluor combination only yielded a 16 % ee, but gave the same enantiomer in excess as quinidine, compared to the opposite enantiomer in the reaction with ethyl 1-indanone-2-carboxylate. 9-Methylquinidine acetate **(112)**/Selectfluor and 9-methylquinidine *p*-chlorobenzoate **(115)**/Selectfluor gave very poor results with only 2 % and 3 % ee respectively (Table 4.3, entries 5-7). The 9-ethylquinidine **(102)**/Selectfluor combination was again very poor and only a 2 % ee was observed (Table 4.3, entry 11). The 9-phenylquinidine **(103)**/Selecfluor combination gave one of the better results with 35 % ee observed with the major enantiomer having the (+) configuration (Table 4.3, entry 8). Again, protecting the hydroxyl group of 9-phenylquinidine with either acetyl or *p*-chlorobenzoyl group gave poorer enantiomeric excesses then their non-protected counterpart, and the opposite enantiomer was obtained in excess (Table 4.3, entries 9 and 10). 9-Phenylquinidine, 9-phenylquinidine acetate **(113)** and 9-phenylquinidine *p*-chlorobenzoate **(116)** all gave similar results in the fluorination of *tert*-butyl 1-indanone-2-carboxylate **(41)** compared to the fluorination of ethyl 1-indanone-2-carboxylate **(132)**. All of these fluorinations led to high isolated yields and complete conversion to 2-*tert*-butoxycarbonyl-2-fluoro-1-indanone **(133)**, except for the reactions involving 9-methylquinidine acetate **(112)**, 9-methylquinidine *p*-chlorobenzoate **(115)** and 9-ethylquinidine **(102)**. These reactions also had the poorest enantioselectivity which could indicate that the reaction centres have become too bulky and therefore, block the approach of the bulky substrate which effectively slowed the reaction down.

4.4 The Fluorination of Ethyl α-Cyano-*p*-tolylacetic Acid (135)

4.4.1 Background

The final substrate chosen to test the novel cinchona alkaloid derivatives was ethyl α-cyano-*p*-tolylacetic acid **(135)** because the product, ethyl α-cyano-α-fluoro-*p*-tolylacetic acid **(24)**, is a versitile chiral derivatising agent that has been used to determine the absolute configurations of chiral secondary alcohols.[21] This substrate provides a more challenging problem as the reagent controlled fluorinations of acyclic esters are much more problematic than the fluorination of cyclic esters. Unfortunately, ethyl α-cyano-α-fluoro-*p*-tolylacetic acid **(24)** is not in general use as a chiral deivatising agent due to its involved synthesis.[22] Previously, this compound was synthesised in two steps from *p*-xylyl cyanide **(136)** and diethyl carbonate to yield ethyl α-cyano-*p*-tolylacetic acid **(135)** which was then fluorinated using $FClO_3$. An enzymatic resolution using *Candida rugosa* lipase was used to obtain the optically pure forms in excellent yields and enantiomeric excesses ((*R*) - 99 %, (*S*) – 78 %).



(135) **(24)**

Scheme 4.5 *The Fluorination of Ethyl α-Cyano-α-fluoro-p-tolylacetic Acid (135)*

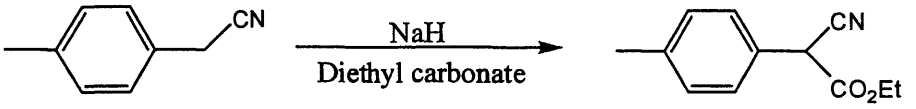
Shibata thoroughly examined the fluorination of ethyl α-cyano-*p*-tolylacetic acid **(135)** using a large number of cinchona alkaloid/Selectfluor combinations (Scheme 4.5).[10,15] There was no need to convert ethyl α-cyano-*p*-tolylacetic acid to its silyl enol ether due to the acidic hydrogen at the reaction centre, though an excess of the cinchona alkaloid was required to aid its release. From the large quantity of results shown in Table 4.4, some general trends were observed. It was found that quinine and quinidine gave higher enantioselectivities than cinchonine and cinchonidine and more importantly, quinidine based cinchona alkaloids were better than the quinine based ones. Hence, ethyl α-cyano-*p*-tolylacetic acid was thought to be a good substrate as all the novel cinchona alkaloid derivatives synthesisied in this work are based on quinidine. Again, dihydroquinidine gave a slightly better enantiomeric excess than quinidine at 29 % and 23 % respectively (Table 4.4, entries 7 and 6). A similar trend was observed with the previous substrates when the dihydrocinchona alkaloid derivatives induced a higher enantioselectivity than the ones containing a vinyl group. Initially, the reaction was carried out using dihydroquinine *p*-chlorobenzoate **(21)**/Selectfluor combination at -20 °C to give the desired ethyl α-cyano-α-fluoro-*p*-tolylacetic acid in 58 % yield and 29 % ee. These

results could be improved by performing the reaction at -80 °C to give the product in 100 % yield and 51 % ee (Table 4.4, entry 3). In both of these reactions, the (*R*)-ethyl α-cyano-α-fluoro-*p*-tolylacetic acid predominates. Attempts to improve the reaction further by varying the protecting group on the quinine led to no improvement in the yields or enantiomeric excesses. A considerable increase in enantioselectivitiy was observed when derivatives of quinidine were used especially in the case of dihydroquinidine acetate when an 80 % yield and 87 % ee was recorded (Table 4.4, entry 8).

Entry	Cinchona Alkaloid	Yield (%)	ee (%)
1	**QN (56)**	95	20 (*S*)
2	**DHQN**-acetate	89	31 (*R*)
3	**DHQN**-*p*-chlorobenzoate **(21)**	100	51 (*R*)
4	**(DHQ)$_2$**PHAL **(22)**	93	11 (*R*)
5	**(DHQ)$_2$**PYR	85	48 (*R*)
6	**QD (57)**	84	23 (*R*)
7	**DHQD**	55	29 (*R*)
8	**DHQD**-acetate **(23)**	80	87 (*S*)
9	**DHQD**-*p*-chlorobenzoate	97	73 (*S*)
10	**DHQD**-*p*-methoxybenzoate	27	79 (*S*)
11	**DHQD**-propionate	100	72 (*S*)
12	**(DHQD)$_2$**PHAL	76	58 (*S*)
13	**CN**	83	4 (*S*)
14	**DHCN**	93	1 (*S*)
15	**DHCN**-acetate	84	7 (*S*)
16	**CD**	87	9 (*R*)
17	**DHCD**	63	3 (*R*)
18	**DHCD**-acetate	90	12 (*S*)

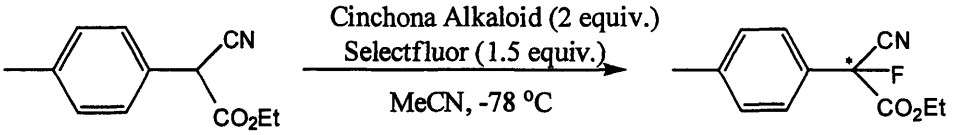
Table 4.4 *The Asymmetric Synthesis of Ethyl α-Cyano-α-fluoro-p-tolylacetic Acid* ***(24)***

4.4.2 The Fluorination of Ethyl α-Cyano-*p*-tolylacetic Acid (135) Using the Novel Cinchona Alkaloid Derivatives



(136) (135)

Scheme 4.6 *The Synthesis of Ethyl α-cyano-p-tolylacetic Acid (135)*



(135) (24)

Scheme 4.7 *The Synthesis of Ethyl α-Cyano-α-fluoro-p-tolylacetic Acid (24)*

Entry	Cinchona Alkaloid	Conversion[a] (%)	Yield[b] (%)	Ee[c] (%)	Major Isomer
1	QN (**56**)	100	29	24	*S*
2	QD (**57**)	100	58	24	*R*
3	QD-acetate (**111**)	100	66	67	*S*
4	QD-*p*-chlorobenzoate (**114**)	100	57	68	*S*
5	QD (**57**)	100	58	21	*R*
6	QD-acetate (**111**)	100	63	67	*S*
7	QD-*p*-chlorobenzoate (**114**)	100	73	68	*S*
8	9-MeQD (**100**)	100	83	8	*R*
9	9-EtQD (**102**)	100	64	6	*S*
10	9-PhQD (**103**)	100	84	25	*R*
11	9-MeQD (**100**)	100	69	9	*R*
12	9-MeQD-acetate (**112**)	100	65	16	*S*
13	9-MeQD-*p*-chlorobenzoate (**115**)	100	91	13	*S*
14	9-PhQD (**103**)	100	79	21	*R*
15	9-PhQD-*p*-chlorobenzoate (**116**)	100	78	15	*R*

[a] *Conversion based on lack of starting material observed in the ^{1}H NMR spectrum of the crude product* [b] *isolated yield* [c] *Determined by chiral HPLC*

Table 4.5 *The Synthesis of Ethyl α-Cyano-α-fluoro-p-tolylacetic Acid*

Ethyl α-cyano-*p*-tolylacetic acid **(135)** was synthesised from *p*-xylyl cyanide **(136)** as described by Takeuchi except a slightly longer reaction time of 6 h compared to the stated 2 h was used to allow for an improved conversion (Scheme 4.6).[23] The pure product was then fluorinated using Shibata's procedure in order to allow for a direct comparison of results.[10] A solution of 2 equivalents of the cinchona alkaloid and 1.5 equivalents of Selectfluor were added to the substrate at – 78 °C, initially, on a larger scale using quinine **(56)** in order to isolate and characterise the fluorinated product. Selectfluor was the fluorinating agent of choice as that was what Shibata used and it had also proven to be superior to NFSI in the fluorination of ethyl 1-indanone-2-carboxylate **(132)**. It was also decided to omit the use of the pre-formed *N*-fluoroquinidinium tetrafluoroborate **(17)** and *N*-fluoro-*O*-acetylquinidinium tetrafluoroborate **(117)** since these reagents led to poorer results.

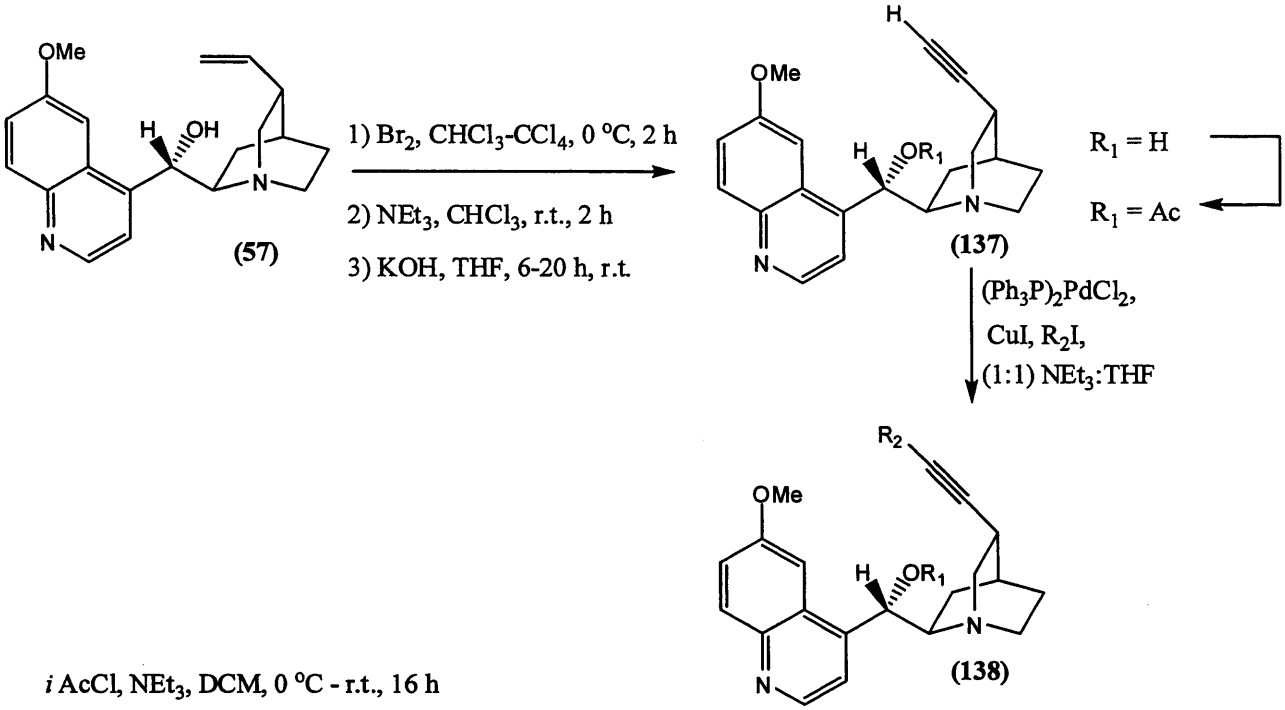
All the novel *N*-fluorocinchona alkaloids and their derivatives in Table 4.5 gave the desired product with 100 % conversion, which proves that they are effective fluorinating agents for the synthesis of ethyl α-cyano-α-fluoro-*p*-tolylacetic acid **(24)**. Unfortunately, the results in terms of enantioselectivity were poor and failed to come close to the 87 % reported by Shibata using the dihydroquinidine acetate **(23)**/Selectfluor combination (Table 4.4, entry 8). The reaction using quinine **(56)** gave a similar enantiomeric excess of 24 % (Table 4.5, entry 1) compared to the 20 % observed by Shibata with the (*S*) enantiomer predominating in both cases (Table 4.4, entry 1). The expected (*R*)-ethyl α-cyano-α-fluoro-*p*-tolylacetic acid preference was observed with 24 % ee when a quinidine **(57)**/Selectfluor combination was used (Table 4.5, entry 2), nearly identical to the literature value of 23 % ee (Table 4.4, entry 6). These results provide evidence that a reliable comparison can be made between this work and Shibata's. The fluorinations using quinidine acetate **(111)** and quinidine *p*-chlorobenzoate **(114)** showed the best enantioselectivities with 67 and 68 % ee respectively (Table 4.5, entries 3 and 4), but they were lower than the 87 and 73 % ee observed for Shibata's dihydroquinidine acetate and dihydroquinidine *p*-chlorobenzoate (Table 4.4, entries 8 and 9). This demonstrates that the ethyl group on C3, the only difference between the derivatised cinchona alkaloids, must be having a considerable effect on the enantioselectivity of the reaction compared to the vinyl group. The assumption that the group on C3 was too remote to affect the enantioselectivity was incorrect and the results suggest that the use of the dihydrocinchona alkaloids was a key factor to obtaining high enantiomeric excesses. The protected quinidines also led to a preference for the (*S*) enantiomer exactly as Shibata had observed. Disappointingly, the addition of aliphatic groups at the C9 position had a detrimental effect on the enantioselectivity of the reaction as the use of the novel 9-methylquinidine **(100)** and 9-ethylquinidine **(102)** lead to very poor results with 8 and 6 % ee respectively (Table 4.5, entries 8 and 9), though the addition of the phenyl group appeared to

have no effect on the enantioselectivity and gave comparable results to that obtained by quinidine (Table 4.5 entry 10). The protected 9-methylquinidines, 9-methylquinidine acetate **(112)** and 9-methylquinidine *p*-chlorobenzoate **(115)** gave slightly improved enantiomer excesses of 16 and 13 % ee than the non-protected counterpart and again the (*S*) enantiomer was preferred for the protected versions and the (*R*) enantiomer for the unprotected reagents (Table 4.5, entries 12 and 13). The protection of 9-phenylquinidine led to lower enantiomeric excess (15 %), but retention of the (*R*) configuration (Table 4.5, entry 15). Although the results in terms of enantioselectivity were disappointing, the results did highlight some key factors for obtaining high enantiomeric excesses.

4.5 Conclusions

The novel cinchona alkaloid derivatives synthesised in this work in combination with either Selectfluor or NFSI have proven to be effective asymmetric fluorinating agents for both cyclic and acyclic substrates. In most cases complete conversion of the substrate to the fluorinated product was observed which often led to high isolated yields. Unfortunately, the enantiomeric excesses failed to surpass those already in the literature. One reason for this is that previously dihydrocinchona alkaloid derivatives were used, which led to higher enantioselectivities than their unsaturated counterparts. Previous groups working in this area have used whichever cinchona alkaloids they could access commercially and so, a thorough examination of the effect of the cinchona alkaloid structure on asymmetric fluorination reactions has not been carried out. It is our belief that the group on C3 plays a major role in the enantioselectivity of the reaction by blocking the approach of the substrate from that side of the molecule. The increase in enantioselectivity by the use of a dihydroquinidine derivative instead of a quinidine derivative can be > 10 % ee. It may, therefore, be possible to create superior asymmetric fluorinating agents by increasing the steric bulk at the C3 position. Hoffmann has recently synthesised a novel class of cinchona alkaloids from the addition of various substituted aryl and vinyl iodides to the 10,11-didehydro-derivatives of quinine and quinidine.[24] The 10,11-didehydroderivative **(137)** could easily be obtained by an efficient two step synthesis from the natural product followed by the hydroxyl protection if required (Scheme 4.9). An optimised Sonogashira coupling[25,26,27] was then carried out on **(137)** using initially iodobenzene to give the desired product **(138)** in 80 % yield. The protected quinidine derivatives gave higher yields of up to 94 %. It was found that due to the strong basicity of the quinuclidine nitrogen and the presence of the quinoline nitrogen, the reaction could be carried out without the addition of the amine, though a lower yield of 44 % was observed. The optimised reaction was then used to synthesise a large number of novel cinchona alkaloids

with various R_2 groups including 3-quinoline, 2-naphthalene, *p*-iodobenzyl, *p*-methoybenzyl, *p*-nitrobenzyl, *o*-aminobenzyl and various sulphur and oxygen containing heterocycles. It would be simple to convert these derivatives into asymmetric fluorinating agents or use this methodology to synthesise another novel class of cinchona alkaloids.



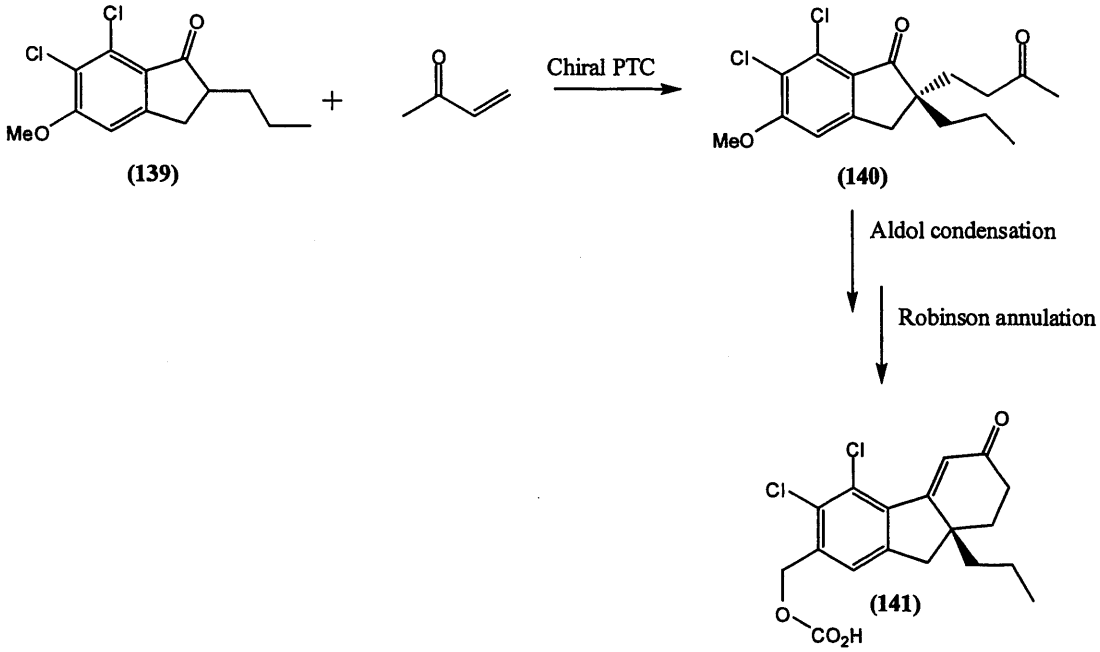
Scheme 4.9 *The Novel Quinidine Based Cinchona Alkaloid Derivatives Synthesised by Hoffmann*

The novel protected cinchona alkaloid derivatives were particularly disappointing in the asymmetric fluorination reactions as unlike the quinidine series where the protection of the hydroxyl function increased the enantiomeric excesses when used to fluorinate a substrate, the 9-methylquinidines and 9-phenylquinidines demonstrated the opposite trend. This could be because the reaction centre has become too crowded so instead of the fluorine preferring one face of the substrate over the other, neither is desirable. The poor conversions in some of these cases are partial evidence for that. 9-Methylquinidine **(100)** and 9-phenylquinidine **(103)** both gave comparable, though slightly improved results to that of quinidine **(57)**. The choice of the R group has been quite conservative in this work so in order to prove if the group at the C9 position really is affecting the enantioselectivity then a bulkier substituent like a naphthyl or adamantyl group could be used. 9-Ethylquinidine **(102)** turned out to be quite a poor fluorinating agent. Not only was it difficult to isolate and purify, but it also gave incomplete conversions and poor enantiomeric excesses in all of the fluorination reactions. This could be because the longer ethyl group is severely hindering the approach of the substrate. To prove this, another long chain could be added to the C9 position on the cinchona alkaloid to see if the same effect is observed. Due to the substrate-dependant nature of the *N*-fluorocinchona

alkaloids it is possible that the novel derivatives aren't ideal for the substrates chosen, but could be very effective in other systems. Therefore, it would be worth testing them in other asymmetric fluorination reactions using different substrates. There is also the potential to use the novel cinchona alkaloids in a completely different type of reaction.

4.6 Synthesis of Quaternary Ammonium Salts

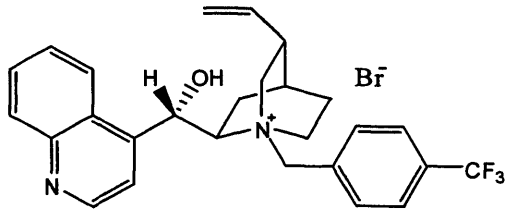
4.6.1 Introduction



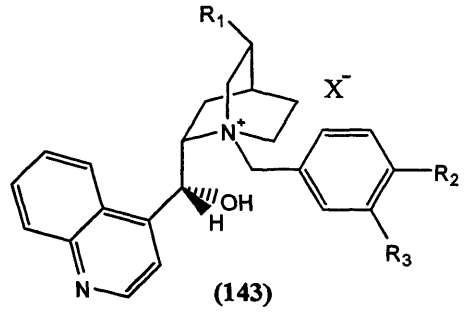
Scheme 4.9 *The Synthesis of (140) via a Chiral Michael Addition*

The focus of this work has been on using cinchona alkaloids as asymmetric fluorinating agents, but that is not their only application. The quaternary ammonium salts of various naturally occurring cinchona alkaloids have been used as efficient phase transfer catalysts and utilised in many catalytic asymmetric syntheses. Phase transfer catalysis has many advantages because it is generally a clean, efficient and simple process, leading to high yields under mild conditions. Conn used [*p*-trifluoromethyl)benzyl] cinchoninium bromide **(142)** and a range of *N*-substituted cinchonidinium salts **(143)** to catalyse the chiral Michael addition of methyl vinyl ketone to the 6,7-dichloro-5-methoxy-2-propyl-1-indanone **(139)** which was the first step in the synthesis of their target compound **(141)** (Scheme 4.9).[28] It was known that the free cinchona alkaloids were not basic enough to catalyse the reaction, but by converting to the quaternary ammonium salts, excellent yields of the desired product **(140)** were obtained by phase transfer catalysis. The reaction using [*p*-trifluoromethyl)benzyl]

cinchoninium bromide **(142)** as the catalyst gave the best result (95 % yield, 80 % ee) (Table 4.6, entry 1), but unfortunately the predominant enantiomer of the product had the (*S*) configuration and the (*R*) enantiomer was the desired product. The (*R*) enantiomer could easily be obtained in excess by using catalysts based on cinchonidine **(143)**, but this led to reduced enantiomeric excesses (Table 4.6, entries 2-6)). Unfortunately, the reaction was found to be insensitive to alterations in the conditions so no improvement in the yield or enantiomeric excess could be obtained by reaction optimisation.



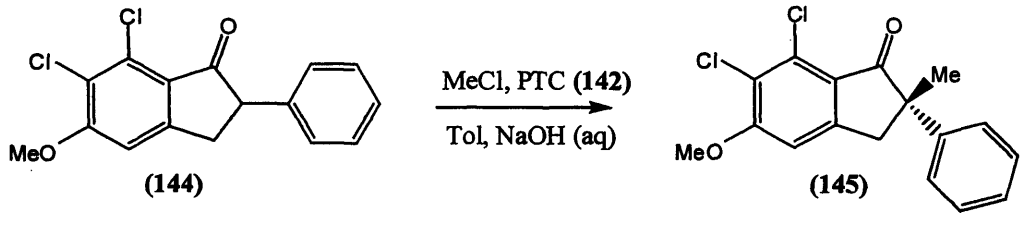
(142)



(143)

Entry	Catalyst	R_1	R_2	R_3	X	ee (%)
1	**(142)**	--	--	--	--	80 (*S*)
2	**(143a)**	CH_2=CH_2	Cl	Cl	Cl	20 (*R*)
3	**(143b)**	Et	Cl	Cl	Cl	40 (*R*)
4	**(143c)**	CH_2=CH_2	CF_3	H	Br	40 (*R*)
5	**(143d)**	Et	CF_3	H	Br	52 (*R*)
6	**(143e)**	CH_2=CH_2	CF_3	H	Cl	38 (*R*)

Table 4.6 *The Synthesis of (140) Using Various Phase Transfer Catalysts*



(144) **(145)**

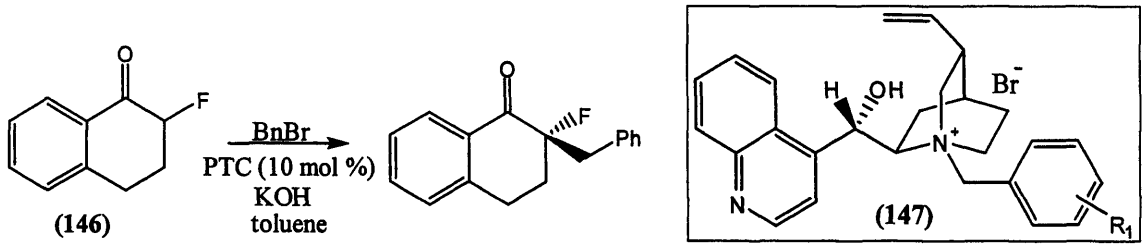
95 % yield
92 % ee

Scheme 4.10 *The Synthesis of (S)-6,7-Dichloro-5-methoxy-2-methyl-2-phenyl-1-indanone (145)*

Dolling also used cinchona alkaloid based phase transfer catalysts for asymmetric alkylation reactions.[29] He reacted 6,7-dichloro-5-methoxy-2-phenyl-1-indanone **(144)** with methyl chloride using [*p*-trifluoromethyl)benzyl] cinchoninium bromide **(142)** as the chiral catalyst to yield the desired product, (*S*)-6,7-dichloro-5-methoxy-2-methyl-2-phenyl-1-

indanone **(145)** in an excellent 95 % yield and 92 % ee (Scheme 4.10). The alkylation constituted the first step of the five step synthesis to the desired target molecule.

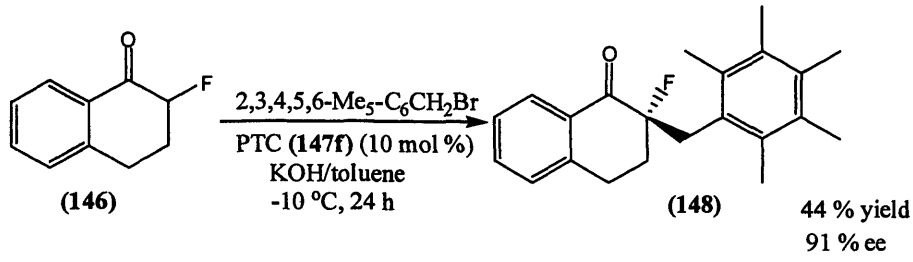
A more useful reaction was the asymmetric alkylation of α-fluorotetralone **(146)** due to the many advantages of fluorine containing compounds described in Chapter One.[30] For this reaction, Arai screened a range of quinidine quaternary ammonium salts **(147)** (Table 4.7) and found that electron withdrawing groups attached to the benzyl ring gave lower enantiomeric excesses compared to the benzyl group, while the incorporation of electron donating groups gave higher enantioselectivities. The best result was with the pentamethyl derivative leading to the substituted α-fluorotetralone in 71 % yield and 80 % ee (Table 4.7, entry 7).



Entry	R_1	Temp	Time (h)	Yield (%)	ee (%)
1	**a**: F_5	r.t.	48	72	29
2	**b**: 4-NO_2	r.t.	24	72	29
3	**c**: H_5	r.t.	24	75	32
4	**d**: 4-Me	r.t.	12	89	41
5	**e**: 3,5-Me_2	r.t.	12	78	46
6	**f**: Me_5	r.t.	24	71	76
7	**f**: Me_5	-10 °C	24	71	80

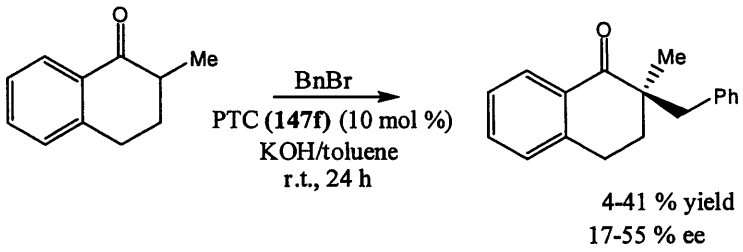
Table 4.7 *The Alkylation of α-Fluorotetralone (146) with Various Phase Transfer Catalysts*

Other aryl bromides were used as electrophiles in this reaction under the same conditions with equally good yields and enantiomeric excesses. Notably, the alkylation of α-fluorotetralone **(146)** with the sterically hindered, 2,3,4,5,6-pentamethylbenzyl bromide gave the corresponding substituted product **(148)** in a moderate 44 % yield, but with an excellent 91 % ee (Scheme 4.11).



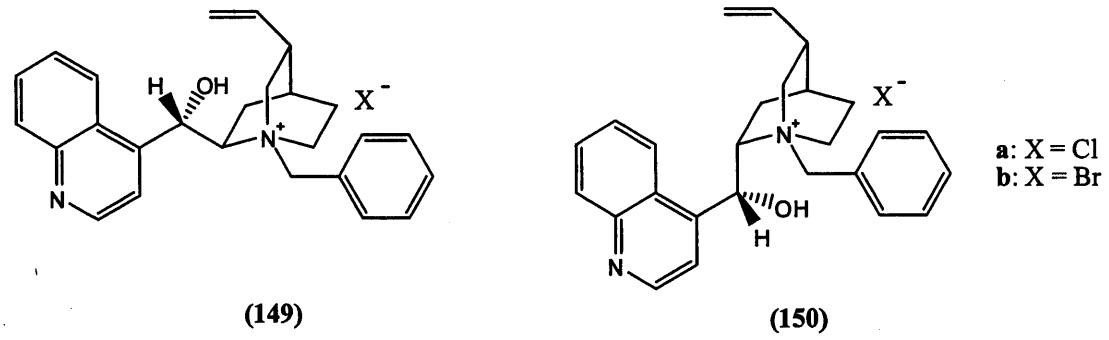
Scheme 4.11 *The Synthesis of α-(2,3,4,5,6-pentamethylbenzyl)-α-fluorotetralone (148)*

When α-methyltetralone was used as the substrate (Scheme 4.12), it proved to be quite ineffective and lower yields and enantioselectivities were observed for the whole range of phase transfer catalysts. The reason for this was believed to be that the enolate of α-methyltetralone was not as planar as that of α-fluorotetralone **(146)** so the bonding between that and the chiral catalysts was less efficient.



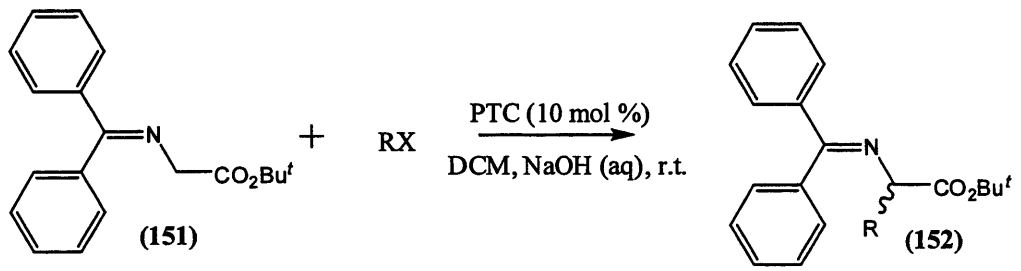
Scheme 4.12 *The Asymmetric Alkylation of α-Methyltetralone*

In O'Donnell's pioneering work, a range of protected α-amino acid derivatives were synthesised by reacting *N*-(diphenylmethylene) glycine ester **(151)** with various alkyl halides using phase transfer catalysts, **(149)** or **(150)** (Scheme 1.13).[31,32] He noted that the product with the opposite stereochemistry could be obtained by changing the catalyst from one based on cinchonine to one based on cinchonidine. O'Donnell obtained good to moderate yields and enantiomeric excesses in the range of 42–66 % (Table 4.8). In some cases this selectivity could be increased to > 99 % after a single recrystallisation.



(149) **(150)**

Figure 4.3 *The Chiral Catalysts Used by O'Donnell*



(151) **(152)**

Scheme 4.13 *The Alkylation of Glycine Imine (151)*

RX	Product	No. Equiv.	Catalyst	Time (h)	Yield (%)	ee (%)
CH_2=$CHCH_2Br$	**152a**	5	**(150a)**	5	75	66 (*R*)
CH_2=$CHCH_2Br$	**152a**	5	**(149a)**	5	78	62 (*S*)
$PhCH_2Br$	**152b**	1.2	**(150a)**	9	75	66 (*R*)
$PhCH_2Br$	**152b**	1.2	**(149a)**	9	85	64 (*S*)
MeBr	**152c**	5	**(150a)**	24	60	42 (*R*)
n-BuBr	**152d**	5	**(150a)**	14	61	52 (*R*)
4-Cl-$C_6H_4CH_2Br$	**152e**	1.2	**(150a)**	12	81	66 (*R*)
4-Cl-$C_6H_4CH_2Br$	**152e**	1.2	**(149a)**	12	82	62 (*S*)
2-naphthylCH_2Br	**152f**	1.2	**(150a)**	18	82	54 (*R*)
2-naphthylCH_2Br	**152f**	1.2	**(149a)**	18	81	48 (*S*)

Table 4.8 *Reaction of Various Alkyl Halides With N-(diphenylmethylene) glycine ester (151)*

O'Donnell then carried out various studies in an attempt to understand the reaction mechanism.[33] One very interesting observation was described during the racemisation studies on the substrate **(152b)**.[34] Under the normal phase transfer conditions (50 % aqueous NaOH, DCM, room temperature, 10 hours) in the absence of the alkyl halide, the pure (*S*)-benzophenone imine showed no racemisation with or without tetrabutylammonium bromide as the phase transfer catalyst. When the cinchonine or cinchonidine derived catalysts **(149)** and **(150)** were used under the same conditions, 36 % and 35 % respectively of the (*R*) isomer was observed, interestingly though, there was no (*R*) isomer detected when the alkyl halide was present during the reaction. These results were explained by a catalyst-degradation mechanism similar to that proposed by the Merck group.[35] Under the phase transfer conditions, the catalysts **(149)** and **(150)** could deprotonate to form the zwitterionic alkoxide **(153)** which in turn was capable of deprotonating the (*S*)-imine leading to the racemisation. There were two pathways in which the alkoxide could decompose. The first was the slow formation to the epoxide **(154)** and the second was the fast *O*-alkylation followed by Hoffmann elimination to yield the product **(156)** (Figure 4.4). When there was no alkyl halide present during the reaction, the epoxide was formed leading to the partial racemisation of the (*S*)-imine. When there was an alkyl halide present, rapid *O*-alkylation of the zwitterion occurred preventing the base-promoted racemisation. Therefore, it was concluded that the active species responsible for the asymmetric phase transfer catalysis was the *N*-alkyl-*O*-alkyl quaternary ammonium salts of cinchonine **(155)** and cinchonidine form *in situ* during the reaction and not **(149)** or **(150)**. In order to prove this statement, O'Donnell then synthesised *N*-benzyl-*O*-benzylcinchonidinium bromide and tested it in the model reaction. The results he

obtained were identical to that obtained with *N*-benzylcinchonidium bromide **(150b)** which strongly supported his claim.

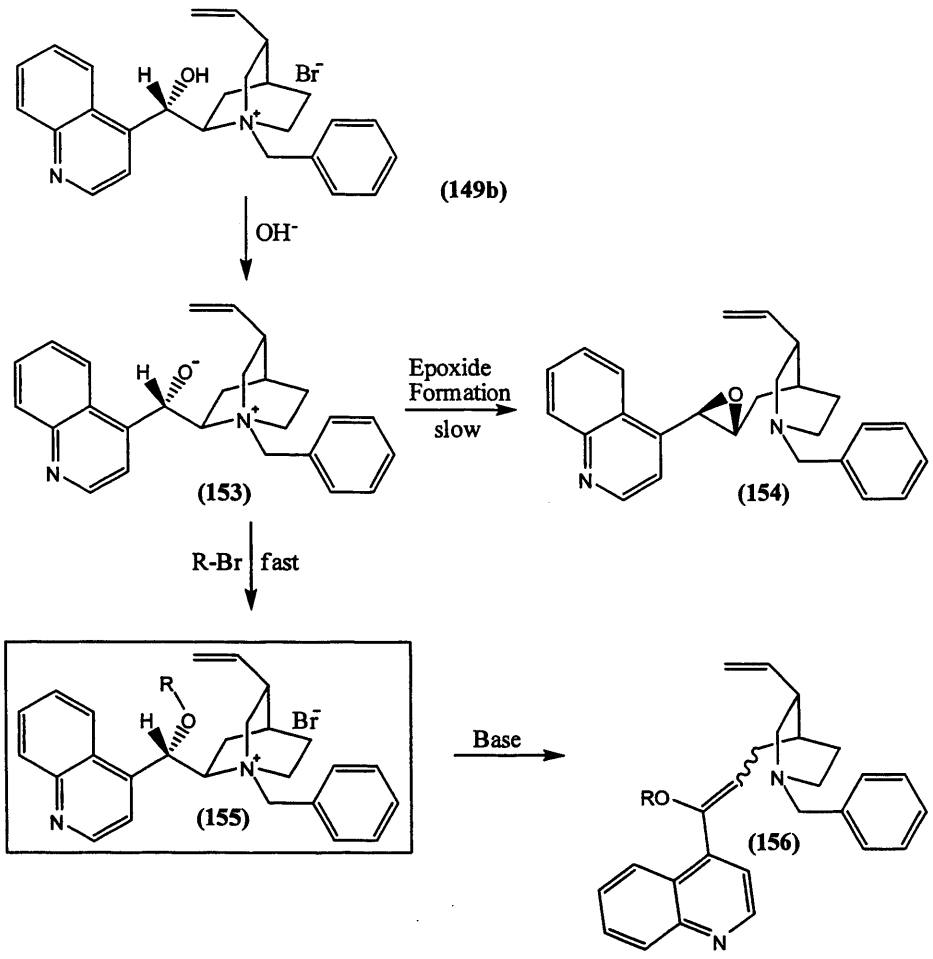


Figure 4.4 *The Identification of the Active Phase Transfer Catalyst via Catalyst Decomposition Studies*

Further studies were carried out on the model reaction and the group looked at the allylation of the substrate **(151)**. Initially, cinchonidine was used as the phase transfer catalyst and the (*S*)-product was obtained in 36 % ee. This was expected as the active catalyst formed *in situ* during the reaction would be *N*-allyl-*O*-allylcinchonidinium bromide and it was known that aromatic groups on the quinuclidine nitrogen lead to better enantiomeric excesses than alkyl groups. When the reaction was repeated using either *N*-benzylcinchonidinium bromide **(150b)** or pre-prepared *N*-benzyl-*O*-allylcinchonidinium bromide, a 59 % ee was observed. This was compared to the 54 % ee gained from the reaction using *N*-benzyl-*O*-benzylcinchonidinium bromide and lead to the conclusion that *O*-allyl catalysts are slightly better than *O*-benzyl ones.

A thorough investigation of the structure of the phase transfer catalyst and the effect it has on the enantioselectivity was carried out by Corey.[36] He stated simply that if the

quinuclidine nitrogen atom was at the centre of a tetrahedron, then the phase transfer catalyst needs to hinder three faces of the tetrahedron whilst leaving the fourth sufficiently open to allow the binding of the substrate. The quaternary ammonium salts of cinchona alkaloids are therefore ideal and the quinuclidine ring system blocks one face, a large bulky group on the quinuclidine nitrogen blocks a second and the third can be blocked by the conversion of the hydroxyl group to an ether (Figure 4.5). It was found that the best subunit to attach to the bridgehead nitrogen was the 9-anthracenyl group as steric hinderance forces this group into a fixed position.[37]

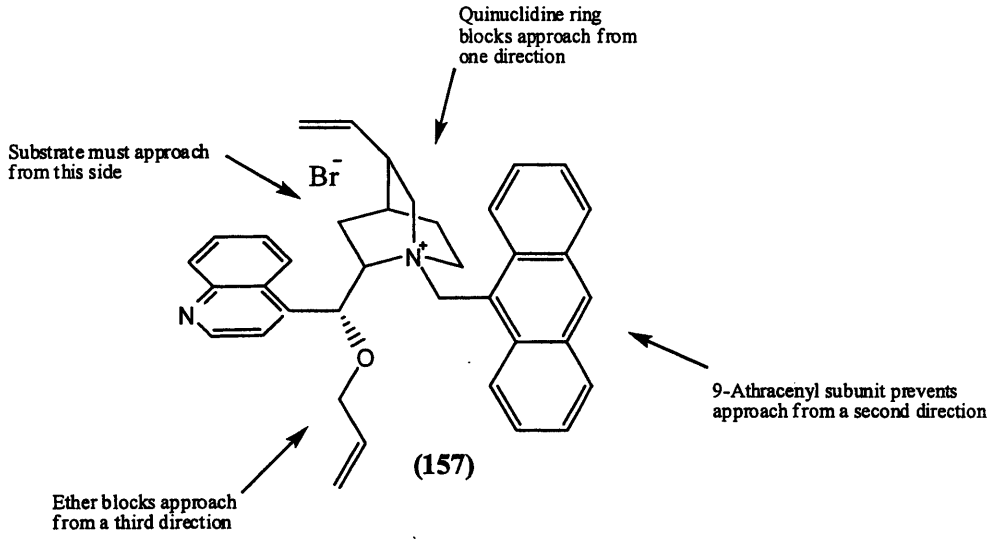
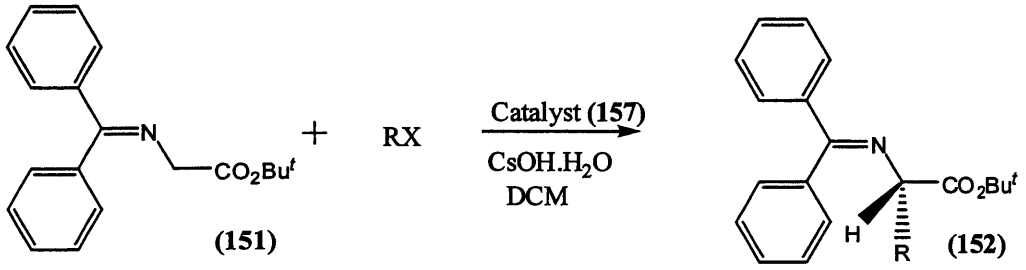


Figure 4.5 *The Structure of N-(9-anthracenylmethyl)-O(9)-allyl-cinchonidinium bromide (157)*

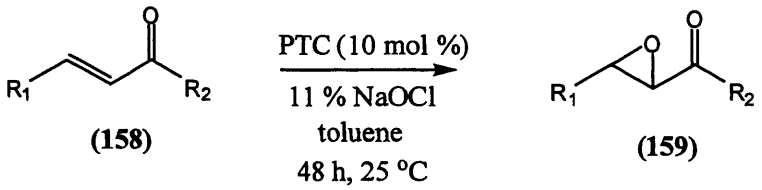
The chiral phase transfer catalyst was then tested in the alkylation of the *N*-(diphenylmethylene) glycine ester **(151)**, the same reaction studied by O'Donnell,[34] except solid cesium hydroxide monohydrate was used as the base in place of aqueous NaOH to allow for lower temperatures to be used (Scheme 4.14). The initial results were excellent as the desired products were obtained for a range of alkyl halides in high yields and very high enantiomeric excesses (Table 4.9). This method was then used in the synthesis of many biologically useful compounds.[38-42]



Scheme 4.14 *The Alkylation of Glycine Imine (151)*

RX	Temp (°C)	Time (h)	Yield (%)	ee (%)
CH_3I	-60	28	71	97
CH_3CH_2I	-60	30	82	98
$CH_3(CH_2)_4CH_2I$	-60	32	79	99.5
$(C_3H_5)CH_2Br$	-60	36	75	99
$CH_2{=}CH_2CH_2Br$	-78	22	89	97
$CH_2{=}CH(CH_3)CH_2Br$	-78	20	91	92
$PhCH_2Br$	-78	23	87	94
Ph_2CHBr	-78	22	73	99.5

Table 4.9 *The Alkylation of (151) Using N-(9-anthracenylmethyl)-O(9)-allyl-cinchonidinium bromide (157) as the Catalyst*



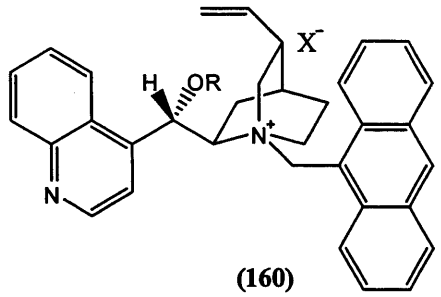
(158) **(159)**

Substrate	R_1	R_2	Catalyst	Yield (%)	ee (%)
158a	Ph	Ph	**(160a)**	65	39 (-)
158a	Ph	Ph	**(160b)**	90	81 (-)
158a	Ph	Ph	**(161b)**	90	86 (+)
158b	*p*-OMe(C_6H_4)	Ph	**(160b)**	86	81 (-)
158b	*p*-OMe(C_6H_4)	Ph	**(161b)**	87	82 (+)
158c	1-naphth	Ph	**(160b)**	92	82 (+)
158c	1-naphth	Ph	**(161b)**	86	82 (-)
158d	C_6H_{13}	Ph	**(160b)**	75	76 (-)
158d	C_6H_{13}	Ph	**(161b)**	92	77 (+)
158e	Ph	1-naphth	**(160b)**	75	69 (+)
158e	Ph	1-naphth	**(161b)**	77	71 (-)
158f	Ph	Bu^t	**(160b)**	42	87 (-)
158f	Ph	Bu^t	**(161b)**	40	85 (+)

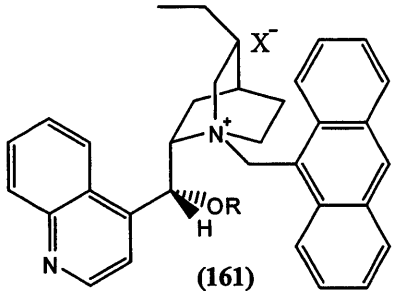
Table 4.10 *The Epoxidation of a Range of α-β Unsaturated Ketones (158)*

After the success of catalyst **(157)** in the alkylation of glycine imines, Lygo then used similar compounds to catalyse the asymmetric epoxidation of α,β-unsaturated ketones.[43,44]

During the initial epoxidation of chalcone **(158a)**, using catalyst **(160a)**, the enantioselectivities were low due to the free hydroxyl group on the catalyst interacting with the oxidant or the substrate. By simply protecting the hydroxyl group with a benzyl group leading to catalyst **(160b)**, the enantioselectivities were improved considerably (< 81 % ee). As the protection of the –OH seemed necessary for high enantioselectivities, catalyst **(160b)** and its pseudo-enantiomer **(161b)** were then used to test the generality of the reaction (Table 4.10). A range of enone substrates were epoxidised to yield the desired products in high yields and good enantioselectivities.



(160)

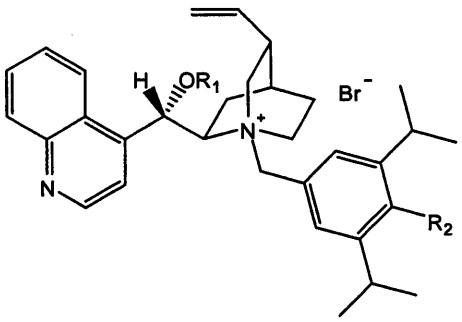


(161)

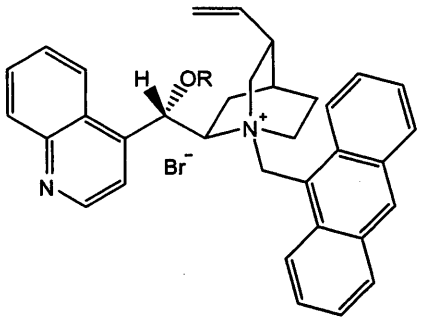
(a) R = H, X = Cl

(b) R = Bn, X = OH

Figure 4.6 *The Catalysts Used in the Epoxidation of α-β Unsaturated Ketones*



(162) **a**: R_1 = H, R_2 = OMe
b: R_1 = allyl, R_2 = OMe
c: R_1 = benzyl, R_2 = OMe
d: R_1 = propargyl, R_2 = OMe
e: R_1 = allyl, R_2 = H
f: R_1 = benzyl, R_2 = H

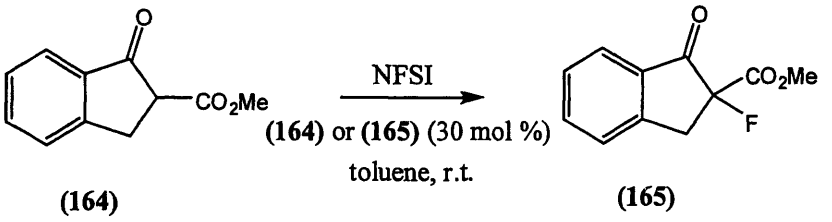


(163) **a**: R = H
b: R = allyl
c: R = benzyl
d: R = propargyl

Figure 4.7 *The Quaternary Ammonium Salts of Cinchona Alkaloids Synthesised by Kim and Park*

Kim and Park[12] synthesised a series of quaternary ammonium salts of cinchona alkaloids that contained a bulky subunit on the quinuclidine nitrogen to enhance the stereoselectivity in phase transfer catalysis (Figure 4.7). The fluorination of indanone

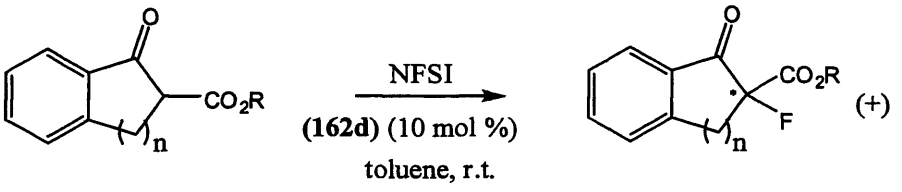
carboxylate **(164)** was examined using NFSI as the fluorine donor and either catalysts **(162)** or **(163)** (Scheme 4.15). The reaction of **(164)** with NFSI without base or phase transfer catalyst does occur, but the product obtained is racemic. Therefore, any enantioselectivity observed must be due to the phase transfer catalyst.



(164) (165)

Scheme 4.15 *The Fluorination of Indanone Carboxylate (164)*

The major isomer obtained was always the (+)-enantiomer, which is to be expected as all the catalysts have the same chirality. Catalysts **(162d)**, **(162e)** and the known compound **(163b)** proved to be the most effective catalysts in the presence of base giving good enantioselectivity. The most effective bases were found to be K_2CO_3 and Cs_2CO_3. Various cyclic and acyclic β-ketoesters were then fluorinated under these optimised conditions to give good yields of α-fluoro-β-ketoesters, but only moderate enantioselectivity (Table 4.11).



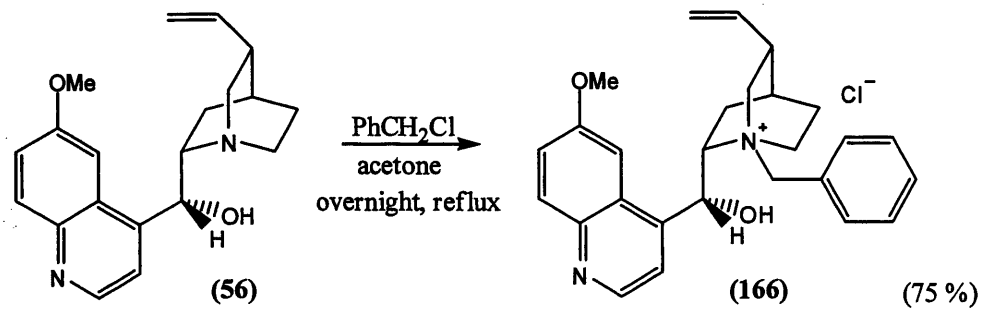
Entry	n	R	Base	Yield (%)	ee (%)
1	1	Me	K_2CO_3	92	69
2	1	Me	Cs_2CO_3	94	60
3	1	Et	K_2CO_3	92	5
4	1	Et	Cs_2CO_3	91	63
5	2	Me	Cs_2CO_3	88	48
6	2	Me	K_2CO_3	74	41
7	2	Et	CsOH	78	52

Table 4.11 The Fluorination of Cyclic and Acylic β-Ketoesters Using Phase-Transfer Catalyst **(162d)**

There are many applications for the quaternary ammonium salts of cinchona alkaloids in the literature, but as for the *N*-fluorocinchona alkaloids, there are no examples where groups had been added at the C9 position. Therefore, quaternary ammonium salts of the novel cinchona alkaloid derivatives would provide a new class of phase transfer catalysts, which could potentially overcome the catalyst decomposition problem by Hoffmann elimination.

4.6.2 The Synthesis of a Novel Class of Chiral Phase Transfer Catalysts

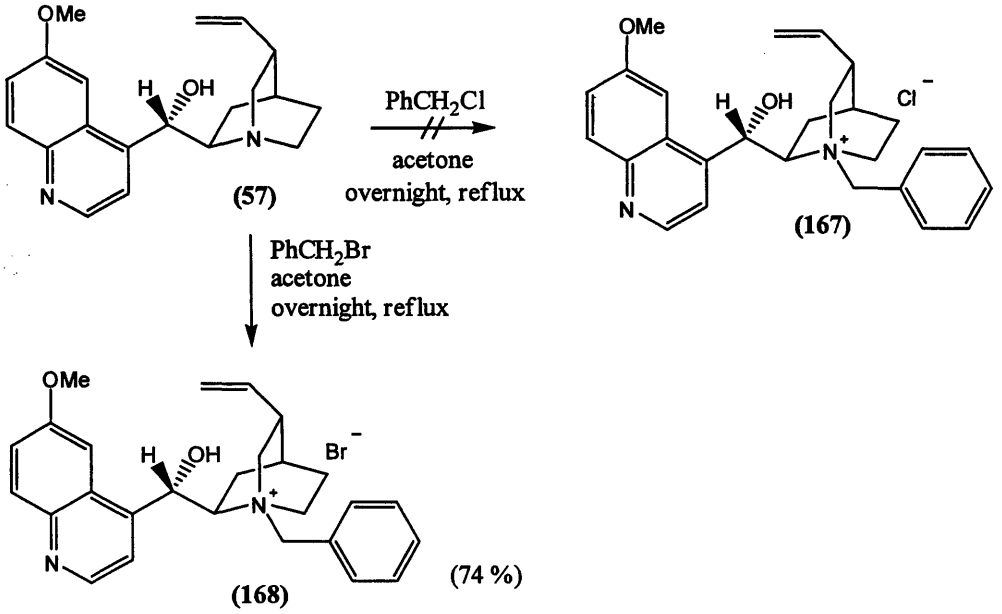
It was decided that the *N*-benzyl cinchona alkaloid derivatives would be synthesised as these are one of the simplest chiral phase transfer catalysts based on cinchona alkaloids. Even though a number of groups have investigated the use of cinchona alkaloids as chiral phase transfer catalysts, their synthesis and experimental data have been surprisingly difficult to find in the literature. The only procedure was from an old paper by Jacobs in which the synthesis of *N*-benzylquininium chloride **(166)** and *N*-benzylquinidinium chloride **(167)** was described and this procedure was adapted for the synthesis of all of the phase transfer catalysts presented in this work.[45] Initially, the synthesis of *N*-benzylquininium chloride **(166)** was carried out as quinine **(56)** is the most readily available cinchona alkaloid and so, it was used to adapt the literature procedure (Scheme 4.16). Jacobs synthesised *N*-benzylquininium chloride by allowing a solution of quinine and one equivalent of benzyl chloride in acetone to stand in a warm place for about one week. This reaction time was not acceptable, so to reduce it the reaction mixture was refluxed overnight. Following the same work up and purification procedure as Jacobs (remove solvent, dissolve in the minimum volume of ethanol, then add diethyl ether to precipitate out the product), *N*-benzylquininium chloride was obtained pure in 75 % yield.



Scheme 4.16 *The Synthesis of N-Benzylquininium Chloride (166)*

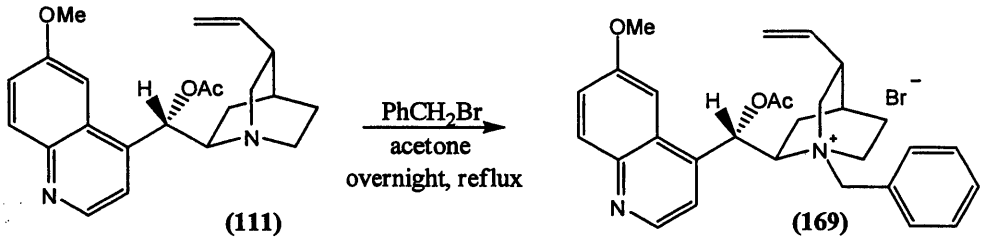
Jacobs also described the synthesis of *N*-benzylquinidinium chloride **(167)** by leaving a solution of quinidine **(57)** and benzyl chloride in acetone to stand in a warm place for 15-20 days, but used a different purification method to *N*-benzylquininium chloride **(166)**.[45] The majority of the acetone was removed at the end of the reaction time and *N*-benzylquinidinium

chloride **(167)** crystallised out of the remaining solvent. To reduce the length of the reaction, quinidine and one equivalent of benzyl chloride was refluxed overnight in acetone and Jacobs's purification method was employed (Scheme 4.17). Unfortunately, nothing came out of solution so the remaining acetone was removed and the ^{1}H NMR spectrum of the residue showed that no reaction had occurred. The reason for this was unclear so the reaction was repeated using benzyl bromide (Scheme 4.17). After refluxing overnight and removing most of the acetone, nothing came out of solution so the acetone was removed and the residue was dissolved in the minimum volume of ethanol and diethyl ether was added in an attempt to precipitate out the product. The result was a yellow/brown oil and its ^{1}H NMR spectrum showed that it contained two compounds in a 4/1 ratio. The major product was the desired *N*-benzylquinidinium bromide **(168)** and the minor product was identified as *N*-benzyldihydroquinidinium bromide. This was expected as the quinidine used contained approximately 20 % dihydroquinidine and, as previously described in Chapter Three, *N*-fluorodihydroquinidinium benzenesulphonimide was apparent in *N*-fluoroquinidinium benzenesulphonimide **(122)**. To provide further proof of this assignment, the integrations of an aromatic proton in the ^{1}H NMR spectrum, where the two compounds are known to overlap, and the ddd of the proton at C10 of quinidine were found to be 1/0.8. More prominently, the characteristic triplet for the CH_3 of the unsaturated compound was apparent at 0.81 ppm. The mass spectrum provided further proof as the major parent ion peak at m/z 415 was accompanied by a smaller peak at m/z 417. Previously, the dihydroquinidine impurity could not be removed from *N*-fluoroquinidinium benzenesulphonimide **(122)** due to the similar properties of the two compounds and unfortunately, the same was true here as all attempts to purify *N*-benzylquinidinium bromide **(168)** further by recrystallisation failed.



Scheme 4.17 *The Synthesis of N-Benzylquinidinium Bromide (168)*

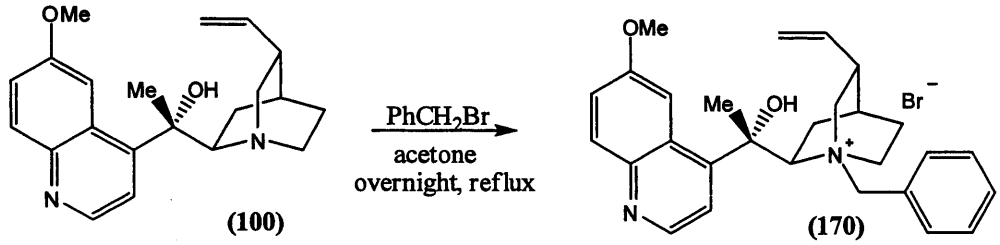
After the successful synthesis of both *N*-benzylquininium chloride **(166)** and *N*-benzylquinidinium bromide **(168)**, the next compound to be synthesised was *N*-benzyl-*O*-acetylquinidinium bromide **(169)** (Scheme 4.18). The procedure used was based on the synthesis of *N*-benzylquininium chloride.[45] Quinidine acetate **(111)** and one equivalent of benzyl bromide was refluxed in acetone overnight and after removing the acetone, the residue was dissolved in the minimum volume of ethanol and on addition of diethyl ether, an orange solid formed. The ^{1}H NMR spectrum was complicated and two compounds were identified. The major product was the desired *N*-benzyl-*O*-acetylquinidinium bromide **(169)** with the minor compound being *N*-benzyl-*O*-acetyldihydroquinidinium bromide. There was also some benzyl bromide residue in the solid as there were many additional protons in the aromatic region of the spectrum and an additional singlet at ~ 4.5 ppm. The mass spectrum supported these assignments with the parent ion peak at m/z 457, corresponding to *N*-benzyl-*O*-acetylquinidinium bromide **(169)**, and smaller peaks at m/z 459, for *N*-benzyl-*O*-acetyldihydroquinidinium bromide and m/z 91 for the benzyl group. The benzyl bromide impurity indicated that the reaction did not go to completion and so any residual starting material must have remained in the filtrate as there was no evidence of it in either the NMR spectra or the mass spectrum. To purify the product further, it was loaded onto a silica gel column and first eluted with chloroform to remove the benzyl bromide impurity and then chloroform/methanol 95/5 to remove the product as a mixture of *N*-benzyl-*O*-acetylquinidinium bromide **(169)** and *N*-benzyl-*O*-acetyldihydroquinidinium bromide. The ^{13}C NMR spectrum of *N*-benzyl–*O*-acetylquinidinium bromide had to be run in MeOD as the quaternary ammonium salts were not soluble enough in either chloroform or acetone at room temperature.



Scheme 4.18 *The Synthesis of N-Benzyl–O-Acetylquinidinium Bromide (111)*

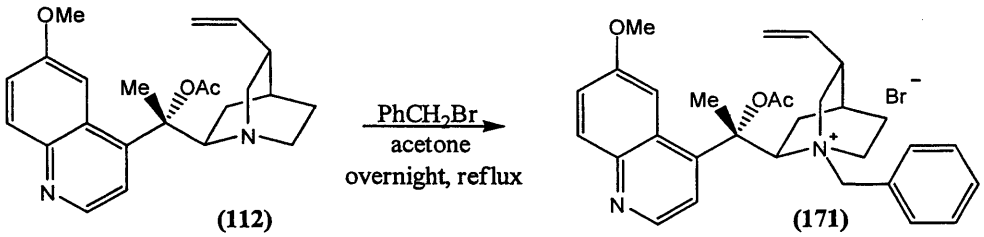
As the quinuclidine nitrogen of quinine **(56)**, quinidine **(57)** and quinidine acetate **(111)** was easily quaternised with benzyl chloride or benzyl bromide, the synthesis of two novel quaternary ammonium salts was performed. Unfortunately, at this stage the availability of most of the novel cinchona alkaloid derivatives were very low, so only the two most abundant derivatives, 9-methylquinidine **(100)** and 9-methylquinidine acetate **(112)** were

used. Initially, the synthesis of *N*-benzyl-9-methylquinidinium bromide **(170)** was carried out (Scheme 4.19). Using the same procedure, 9-methylquinidine **(100)** and one equivalent of benzyl bromide was refluxed in acetone overnight. After removing the acetone, the reside was dissolved in the minimum volume of ethanol and on the slow addition of diethyl ether a brown solid was obtained.[45] However, the reaction did not go to completion and the ^{1}H NMR spectrum of the solid showed the desired product, *N*-benzyl-9-methylquinidinium bromide **(170)**, as the major component with 9-methylquinidine and benzyl bromide impurities. The mass spectrum showed parent ion peaks at m/z 429, 339 and 91 which corresponded to the three compounds respectively. As described previously in the synthesis of *N*-benzyl-*O*-acetylquinidinium bromide **(169)**, further purification by column chromatography was required. Initially the column was eluted with chloroform to remove any benzyl bromide impurity and then chloroform/methanol (95/5) to remove the product. The ^{13}C NMR spectrum was carried out in MeOD as this compound also had a poor solubility in chloroform and acetone at room temperature.



Scheme 4.19 *The Synthesis of N-Benzyl-9-Methylquinidinium Bromide (170)*

Finally, *N*-benzyl-*O*-acetyl-9-methylquinidinium bromide **(171)**, was synthesised (Scheme 4.20). Following the same procedure as described for the previous *N*-benzyl cinchona alkaloid derivatives,[45] 9-methylquinidine acetate **(112)** and one equivalent of benzyl bromide was refluxed in acetone overnight. After removing the solvent, the residue was dissolved in the minimum volume of ethanol and on adding diethyl ether, an orange oil came out of solution. The ^{1}H NMR spectrum of the oil clearly showed the desired *N*-benzyl-*O*-acetyl-9-methylquinidinium bromide **(171)**, but with a trace amount of starting material (< 5 %). The mass spectrum showed the parent ion peak at m/z 471 and a smaller peak at m/z 381 which corresponds to the product and starting material respectively. As the reaction was done on such a small scale, the ^{13}C NMR experiment had to be performed overnight to give an adequate spectrum for analysis.



Scheme 4.20 *The Synthesis of N-Benzyl-O-Acetyl-9-Methylquinidinium Bromide (171)*

4.7 Conclusions

A small series of quaternary ammonium salts of cinchona alkaloids were synthesised successfully and could potentially be used as chiral phase transfer catalysts. Amonst this series were the two novel derivatives, *N*-benzyl-9-methylquinidinium bromide **(170)** and *N*-benzyl-*O*-acetyl-9-methylquinidinium bromide **(171)**. Unfortunately, like the *N*-fluoro counterparts, the purification of the *N*-benzylcinchona alkloids was not straightforward, so as yet they have not been tested in a model reaction, but there is scope to do so in the future. The main aim of these reactions was to demonstrate the ease at which the quinuclidine nitrogen of the novel cinchona alkaloid derivatives can be quaternised, which makes them extremely versatile reagents for many different types of asymmetric syntheses.

4.8 References

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Chapter Five

University *of* Leicester

Experimental Procedures

5.1 General

NMR Spectroscopy

The ^{1}H, ^{19}F and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a Bruker AM 300 spectrometer, a Bruker DRX 400 spectrometer or a Bruker AV 500 spectrometer at ambient temperature of the probe unless otherwise stated. The chemical shifts are quoted in ppm and are referenced to external $SiMe_4$ for ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra, and external $CFCl_3$ in the case of ^{19}F NMR spectroscopy using the high frequency positive convention. The coupling constants are in hertz (Hz). Deuterated chloroform was the solvent used unless otherwise stated. The following spectrometer frequencies are used:

Bruker AM 300 spectrometer:	^{1}H NMR spectra, 300.03 MHz
	^{13}C NMR spectra, 75.4426 MHz
	^{19}F NMR spectra, 282.3103 MHz
Bruker DRX 400 Spectrometer:	^{1}H NMR spectra, 400.13 MHz
	^{13}C NMR spectra, 100.6128 MHz
	^{19}F NMR spectra, 376.4984 MHz
Bruker AV 500 Spectrometer:	^{1}H NMR spectra, 500.13 MHz
	^{13}C NMR spectra, 125.758 MHz

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.

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.

High Pressure Liquid Chromatography

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

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.

Elemental Analysis

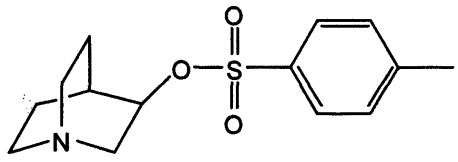
Elemental analyses were performed by the University of North London.

Starting Materials

Compounds were used as supplied from Sigma-Aldrich, Apollo, Fluorochem, Lancaster, Alfa Aesar or Acros Organics. Acetonitrile, diethyl ether, tetrahydrofuran and toluene were obtained dried from a distillation machine model Puresolve^{TM} and were stored in sealed ampoules over 4Å molecular sieves under an atmosphere of dry nitrogen. Where necessary, solvents were freeze-pump-thaw degassed at least three times prior to use.

5.2 Synthetic Procedures

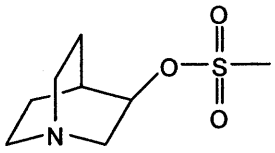
Synthesis of Quinuclidin-3-yl toluenesulfonate (68)



Compound **(68)** was synthesised by the procedure of O'Neil.[1] A solution of toluenesulphonyl chloride (1.75 g, 9 mmol) in dichloromethane (30 mL) was added over 30 mins to a stirred solution of 3-quinuclidinol (1.28 g, 10 mmol), triethylamine (1.1 mL, 15 mmol) and dichloromethane (30 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for a further 2 h, before washing with a 5% $NaHCO_3$ solution (2 × 20 mL) and then brine (20 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The tosyl product was obtained as a pale yellow oil (1.92 g, 74 %). δ_H ($CDCl_3$) 1.23-1.44 (2H, m, NCH_2CHH), 1.54-1.65 (1H, m, NCH_2CHH), 1.72-1.85 (1H, m, NCH_2CHH), 1.90-1.96 (1H, m, CH), 2.38 (3H, s, $ArCH_3$), 2.51-2.88 (5H, m, $NCHH$), 2.96-3.06 (1H, m, $NCHHCOTs$), 4.54 (1H, m, NCH_2CHOTs), 7.27 (2H, d, $^3J_{HH}$ 8.3 Hz, ArH), 7.72 (2H, d, $^3J_{HH}$ 8.3 Hz, ArH). δ_C ($CDCl_3$) 18.6 (CH_2), 21.6 (CH), 24.3 (CH_2), 26.1 (CH_3), 46.1 (CH_2), 47.2 (CH_2), 54.9

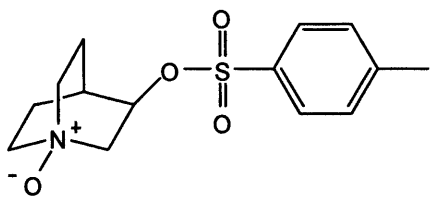
(CH_2), 79.2 (CH), 127.6 (CH), 129.0 (CH), 134.2 (C), 146.0 (C). m/z (ES^+) 282 ($[M+H]^+$, 100 %).

The Synthesis of Quinuclidin-3-yl methanesulfonate (70)



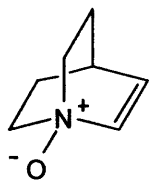
The synthesis of compound **(70)** was synthesised based on the procedure of O'Neil.[1] A solution of methanesulphonyl chloride (2.5 mL, 15 mmol) in dichloromethane (20 mL) was added over 30 mins to a stirred solution of 3-quinuclidinol (1.28 g, 10 mmol), triethylamine (1.5 mL, 20 mmol) and dichloromethane (20 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for a further 2 h, before washing with a 5 % $NaHCO_3$ solution (2 × 20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The ^1H NMR spectrum showed evidence that the mesyl product had formed, but no further purification was carried out.

Synthesis of 1-Azabicyclo[2.2.2]octan-3-ol, 4-methylbenzenesulfonate, 1-oxide (69)



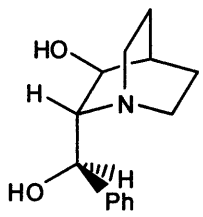
Compound **(69)** was synthesised by the procedure of O'Neil.[1] A 1.0 M solution of *m*-chloroperoxybenzoic acid (1.06 g, 4 mmol) in chloroform was added gradually over 30 mins to a stirred 1.0 M solution of 1-azabicyclo[2.2.2]octan-3-ol, 4-methylbenzenesulfonate (1.15 g, 4 mmol) in chloroform at 0 °C. The reaction mixture was stirred for 3 h and during this time it was allowed to warm to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in the minimum amount of chloroform (~5 mL). The solution was loaded onto a basic alumina column, eluted with chloroform/methanol (3/1) (~200 mL), the coloured band was collected and the solvent was removed. The solid residue was then dissolved in the minimum volume of chloroform (~5 mL), loaded onto a neutral alumina column and eluted with chloroform/methanol (92.5/7.5) (~150 mL). All fractions containing the product were combined and the solvent was removed to yield the tosyl *N*-oxide as a yellow solid (1.21 g, 86 %). M.p. 123 °C. δ_H ($CDCl_3$) 1.79-1.94 (2H, m, NCH_2CHH), 1.95-2.07 (1H, m, NCH_2CHH), 2.26 (2H, m, NCH_2CHH and CH), 2.40 (3H, s, $ArCH_3$), 3.13-3.36 (5H, m, $NCHH$), 3.50 (1H, m, $NCHHCOTs$), 4.83 (1H, m, NCH_2CHOTs), 7.31 (2H, d, $^3J_{HH}$ 8.5 Hz, ArH), 7.72 (2H, d, $^3J_{HH}$ 8.5 Hz, ArH). δ_C ($CDCl_3$) 20.6 (CH_2), 21.6 (CH), 22.8 (CH_2), 25.5 (CH_3), 62.0 (CH_2), 63.0 (CH_2), 69.1 (CH_2), 75.6 (CH), 127.6 (CH), 130.2 (CH), 133.1 (C), 145.7 (C). m/z (ES^+) 298 ($[M+H]^+$, 50 %). HRMS (FAB) 298.11122 ($C_{14}H_{20}NO_4S$ requires 298.11131).

Synthesis of 1-Azabicyclo[2.2.2]oct-2-ene, 1-oxide (63a)



Compound **(63a)** was synthesised by the procedure of O'Neil.[1] A 1.0 M solution of KO^{t}Bu (2.3 mL, 2.3 mmol) in THF was added to the *N*-oxide **(69)** (0.68 g, 2.3 mmol) stirring in dry and degassed THF (80 mL) at –78 °C under a nitrogen atmosphere. After stirring for 1 h at –78 °C, the reaction was allowed to warm to 0 °C where it was stirred for 3 h and then finally it was warmed to room temperature where it was stirred for 12 h. The solvent was removed by rotary evaporation and chloroform (50 mL) was added to the solid residue, stirred for 30 mins, filtered, then the solvent was removed. Dichloromethane (80 mL) was added to the residue and stirred for 15 mins. The organic layer was extracted with water (2 × 25 mL) and the water was removed from the aqueous layer on the rotary evaporator. The aqueous residue was then stirred with dichloromethane (30 mL) for 30 mins, dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. The product was obtained as a brown oil (0.08 g, 27 %). δ_H ($CDCl_3$) 1.70-1.83 (2H, m, NCH_2CH_2), 1.93-2.03 (2H, m, NCH_2CH_2), 2.81 (1H, m, NCH_2CH_2CH), 3.20-3.31 (2H, m, NCH_2CH_2), 3.57-3.68 (2H, m, NCH_2CH_2), 6.44 (1H, t, $^3J_{HH}$ 5.8 Hz, NCH=CH), 6.65 (1H, d, $^3J_{HH}$ 5.8 Hz, NCH=CH). δ_C ($CDCl_3$) 25.4 (CH), 26.3 (CH_2), 65.5 (CH_2), 130.4 (CH), 145.2 (CH). m/z (ES^+) 126 ($[M+H]^+$, 100 %). HRMS (EI) 125.08401 ($C_7H_{11}NO$ requires 125.08406).

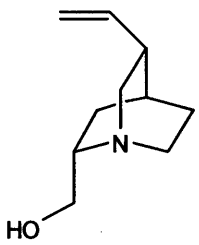
Synthesis of 1-Azabicyclo[2.2.2]octane-2-methanol, 3-hydroxy-α-phenyl-[2α, (S), 3β](73)



Compound **(73)** was synthesised using the procedure described by Stotter.[2] 3-Quinuclidinone hydrochloride (1.06 g, 6.2 mmol) was added in one portion to a stirred solution of lithium diisopropylamide (6.25 mL, 12.5 mmol) in dry and degassed THF (60 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred until homogeneous (20 mins) and then cooled to –78 °C. Benzaldehyde (0.65 mL, 6.4 mmol) was then added and the reaction mixture was stirred for 25 mins. After this time, a solution of sodium bis(2-methoxyethoxy)aluminum dihydride in toluene/THF (1/4) (1.15 M, 8.16 mL, 11.9 mmol) was added and the cooling bath was removed. The reaction mixture was left to warm to room temperature and was then stirred for a further 30 mins. Water (10 mL) was added slowly resulting in the precipitation of aluminium salts, which adhered to the sides of the glass vessel. The clear yellow organic solution was decanted off and dried over Na_2SO_4. Most of the solvent was removed by rotary evaporation and the solid was thoroughly dried under vacuum for 24 h. Recrystallisation of the crude product from THF/hexane (1/1) gave the desired product as a fine white powder (0.20 g, 13 %). M.p. 138 °C (lit.,[2] 146-147 °C). $[\alpha]_D$ (MeOH) 0.8 ° (*c* = 1). δ_H ($CDCl_3$) 1.18-1.32 (2H, m, NCH_2CHH), 1.46-1.64 (2H, m,

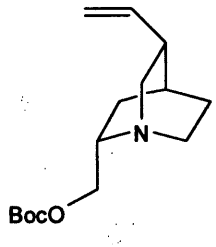
$NCH_2CH\mathit{H}$), 1.77 (1H, m, $NCH_2CH_2C\mathit{H}$), 1.84 (1H, m, $NCHC\mathit{H}OH$), 2.44-2.82 (4H, m, $NCH\mathit{H}$), 3.87 (1H, m, NCH), 4.61 (1H, d, $^3J_{HH}$ 9.1 Hz, PhCH), 7.20-7.31 (5H, m, PhH). δ_C ($CDCl_3$) 19.0 (CH_2), 25.9 (CH_2), 29.3 (CH), 42.6 (CH_2), 50.2 (CH_2), 71.4 (CH), 72.5 (CH), 75.4 (CH), 126.6 (CH), 128.0 (CH), 128.6 (CH), 143.1 (C). m/z (ES^+) 234 ($[M+H]^+$, 100 %). HRMS (FAB) 234.14933 ($C_{14}H_{20}NO_2$ requires 234.14940).

Attempted Synthesis of Quincorine (75)



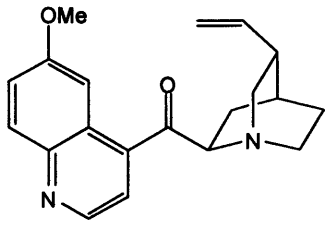
The synthesis of quincorine was attempted by following the procedure described by Hoffmann.[3] Lithium aluminium hydride (0.31 g, 8 mmol), from a freshly opened container, was added to dry and degassed THF (20 mL) in a vessel equipped with a calcium chloride drying tube. The reaction mixture was cooled to 0 °C and dry *s*-BuOH (1.3 mL, 14 mmol) and TMEDA (0.60 mL, 4 mmol) were added. Quinine (0.65 g, 2 mmol) was then added in several portions and the cooling bath was removed. The reaction mixture was stirred for 4 days at room temperature. Ethyl acetate (0.29 mL), water (0.30 mL) and 2 M NaOH (0.30 mL) was added to the reaction mixture. The precipitate that formed was filtered off and washed with dichloromethane (8 mL). The filtrate was then transferred to a round bottomed flask and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (25 mL), dried over Na_2SO_4, filtered and the solvent was removed to yield a yellow oil. The reaction was carried forward to the next step without any further purification or characterisation.

Attempted Synthesis of Boc Protected Quincorine



The synthesis of the Boc protected Quincorine was attempted by following the procedure described by Hoffmann.[3] The yellow oil obtained in the synthesis of quincorine was dissolved in dry dichloromethane (5 mL) under a nitrogen atmosphere. Dry triethylamine (0.85 mL, 6 mmol), di-*t*-butyl dicarbonate (1.31 g, 6 mmol) and DMAP (catalytic amount) were added and the reaction mixture was stirred overnight at room temperature. ^{1}H NMR spectroscopy revealed that none of the desired product was formed, so no further purification was undertaken.

Synthesis of Quinidinone (55)



Quinidinone was synthesised by following the procedure by Huchison.[4] A solution of benzophenone (2.25 g, 12.0 mmol) in dry and degassed toluene (20 mL) was charged in to a 3-necked

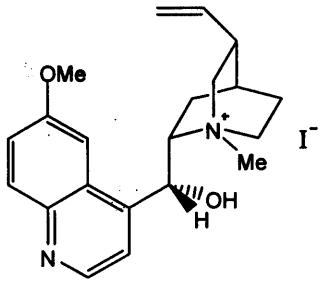
round bottomed flask equipped with a magnetic stirrer bar and condenser under a nitrogen atmosphere. Quinine (2.23 g, 6.0 mmol) was added to the stirred solution in one portion followed by a 1 M solution of potassium *tert*-butoxide in dry THF (15.6 mL, 16.0 mmol). The solution was refluxed for 8 h and then 2 M HCl (10 mL) was added slowly to the reaction mixture and then transferred to a separating funnel where more 2 M HCl (16 mL) was added. The aqueous layer was collected and the organic layer was washed with 2 M hydrochloric acid (2 ×10 mL). The combined aqueous layers were put into a round bottomed flask equipped with a magnetic stirrer bar and cooled to 0-5 °C in an ice-water bath. A 5 M sodium hydroxide solution was added dropwise to the stirred acidic solution until pH 9 (determined by pH paper). An oil was formed which became a yellow solid after vigorous stirring at 0-5 °C. The solid was then filtered off using a Buchner funnel to give the product as a yellow solid (0.17 g, 8 %). M.p. 91 °C (lit.,[5] 93-95 °C). $[\alpha]_D$ (MeOH) 52.4 ° (c = 1). δ_H ($CDCl_3$) 1.46-1.70 (4H, m, NCH_2CHH), 1.79-1.88 (1H, m, NCH_2CH_2CH), 2.18-2.29 (1H, m, NCH_2CH), 2.58-2.67 (1H, m, $NCHH$), 2.80-2.94 (2H, m, $NCHH$), 3.06-3.19 (1H, m, $NCHH$), 3.86 (3H, s, OCH_3), 4.26 (1H, m, NCH), 4.97 (1H, m, CH=C*H*H), 5.01 (1H, m, CH=C*H*H), 5.88 (1H, ddd, $^3J_{HH}$ 17.2, 10.5 and 7.3 Hz, C*H*=CH_2), 7.31 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.56 (1H, d, $^4J_{HH}$ 2.6 Hz, ArH(5')), 7.61 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(3')), 7.94 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.78 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(2')). δ_C ($CDCl_3$) 21.8 (CH_2), 22.1 (CH_2), 26.8 (CH_2), 27.2 (CH_2), 27.4 (CH), 27.6 (CH), 39.5 (CH), 39.7 (CH), 43.3 (CH_2), 48.8 (CH_2), 49.5 (CH_2), 55.5 (CH_2), 55.6 (CH_3), 55.6 (CH_3), 63.0 (CH), 63.1 (CH), 102.7 (CH), 102.9 (CH), 114.8 (CH_2), 114.9 (CH_2), 120.0 (CH), 120.6 (CH), 122.5 (CH), 122.6 (CH), 125.8 (C), 131.5 (CH), 131.5 (CH), 140.2 (CH), 140.4 (C), 140.9 (C), 141.4 (CH), 145.6 (C), 147.0 (CH), 147.1 (CH), 159.2 (C), 159.2 (C), 202.8 (C=O), 202.9 (C=O). m/z (ES^+) 323 ($[M+H]^+$, 100 %). HRMS (FAB) 323.17594 ($C_{20}H_{23}N_2O_2$ requires 323.17595).

Synthesis of the Two Diastereoisomers of Quininone (54) and (55)

Quininone was synthesised by following the procedure by Huchison[4] *et al.* A solution of benzophenone (2.25 g, 12.0 mmol) in dry and degassed toluene (20 mL) was charged in to a 3-necked round bottomed flask equipped with a magnetic stirrer bar and condenser under a nitrogen atmosphere. Quinine (2.23 g, 6.0 mmol) was added to the stirred solution in one portion followed by a 1 M solution of potassium *tert*-butoxide in dry THF (15.6 mL, 16.0 mmol). The solution was refluxed for 8 h and left to cool to room temperature overnight. After cooling to 5-10 °C, hydrochloric acid (2 M, 10 mL) was added slowly to the reaction mixture that was then transferred to a separating funnel where more hydrochloric acid (2 M, 16 mL) was added. The aqueous layer was collected and the organic layer was washed with 2 M hydrochloric acid (2 × 10 mL). The combined aqueous layers were put into a round

bottomed flask equipped with a magnetic stirrer bar and cooled to 0-5 °C in an ice-water bath. A 5 M sodium hydroxide solution was added dropwise to the stirred acidic solution until pH 9 (determined by pH paper) to form a pale brown sticky solid. The alkaline solution was decanted off and the solid was dried under vacuum (~ 30 mins) to yield a pale brown solid. The solid was then dissolved in the minimum volume of chloroform (~ 6 mL) and loaded onto a column of silica gel (85 g). The column was eluted with chloroform/triethylamine/methanol (87.5/10/2.5) (~600 mL) and the fractions containing the product were combined and the solvent was removed. Quininone was obtained as a yellow oil (1.55 g, 70 %). $[\alpha]_D$ (toluene) 87.9 ° (*c* = 1). δ_H ($CDCl_3$) 1.39-1.52 (2H, m, NCH_2CHH), 1.54-1.67 (4H, m, NCH_2CHH), 1.72-1.89 (2H, m, NCH_2CH_2CH), 2.04-2.34 (4H, m, NCH_2CHH, NCH_2CH), 2.55-2.63 (2H, m NC*H*H), 2.66-2.89 (4H, m, NC*H*H), 2.97-3.17 (2H, m, NC*H*H), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.06-4.20 (2H, m, NCH), 4.92-5.09 (4H, m, CH=CH*H*), 5.82-5.96 (2H, m, $CH=CH_2$), 7.32 (2H, dd, $^3J_{HH}$ 9.1 Hz, $^4J_{HH}$ 2.9 Hz, ArH(7')), 7.57 (1H, d, $^4J_{HH}$ 2.9 Hz, ArH(5')), 7.57 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(3')), 7.67 (1H, d, $^4J_{HH}$ 2.9 Hz, ArH(5')), 7.68 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(3')), 7.96 (1H, d, $^3J_{HH}$ 9.1 Hz, ArH(8')), 7.96 (1H, d, $^3J_{HH}$ 9.1 Hz, ArH(8')), 8.76 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(2')), 8.78 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(2')). δ_C ($CDCl_3$) 21.7 (CH_2), 22.0 (CH_2), 26.8 (CH_2), 27.2 (CH_2), 27.3 (CH), 27.6 (CH), 39.5 (CH), 39.7 (CH), 43.3 (CH_2), 48.8 (CH_2), 49.6 (CH_2), 55.5 (CH_2), 55.5 (CH_3), 55.6 (CH_3), 62.9 (CH), 63.0 (CH), 102.7 (CH), 102.8 (CH), 114.7 (CH_2), 114.8 (CH_2), 120.0 (CH), 120.6 (CH), 122.4 (CH), 122.6 (CH), 125.8 (C), 131.4 (CH), 131.5 (CH), 140.3 (CH), 140.4 (C), 141.0 (C), 141.4 (CH), 145.5 (C), 145.6 (C), 147.0 (CH), 147.1 (CH), 159.1 (C), 159.2 (C), 202.9 (C=O), 203.1 (C=O). m/z (ES^+) 323 ($[M+H]^+$, 100 %).

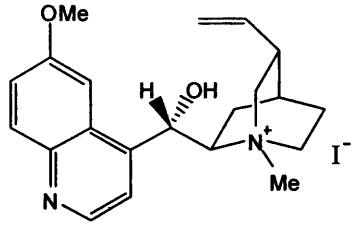
Synthesis of *N*-Methylquininium Iodide (87)



Methyl iodide (0.42 mL, 6.74 mmol) was added slowly to a stirred suspension of quinine (1.11 g, 3.42 mmol) in toluene (20 mL) at room temperature. The reaction mixture was allowed to stir for 2 h before the solid was filtered and washed with hexane. The known compound, *N*-methylquininium iodide, was obtained as a yellow powder (1.10 g, 95 %). M.p. 233 °C (lit.,[6] 233-236 °C). $[\alpha]_D$ (MeOH) -109.2 ° (*c* = 1). δ_H ($CDCl_3$) 1.29-1.42 (1H, m, NCH_2CHH), 1.89-2.01 (1H, m, NCH_2CH_2CH), 2.06 (1H, m, NCH_2CHH), 2.12-2.27 (2H, m, NCH_2CHH), 2.77-2.88 (1H, m, NCH_2CH), 3.08-3.17 (1H, m, NC*H*H), 3.33 (1H, m, NC*H*H), 3.60-3.73 (1H, m, NC*H*H), 3.76 (3H, s, CH_3), 3.91 (3H, s, OCH_3), 4.02 (1H, m, NC*H*H), 4.64-4.77 (1H, m, NCH), 5.03 (2H, m, CH=C*H*H), 5.44-5.59 (2H, m, $CH=CH_2$ and CHOH), 6.44 (1H, d, $^3J_{HH}$ 6.0 Hz, OH), 6.97 (1H, d, $^4J_{HH}$ 2.6 Hz, ArH(5')), 7.35 (1H, dd, $^3J_{HH}$ 8.9 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.69 (1H, d,

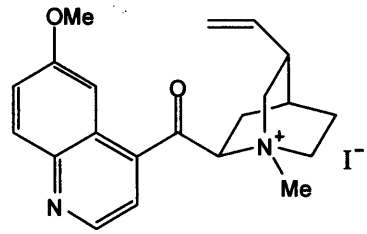
$^3J_{HH}$ 4.4 Hz, ArH(3')), 8.02 (1H, d, $^3J_{HH}$ 8.9 Hz, ArH(8')), 8.71 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(2')). δ_C (DMSO) 19.3 (CH_2), 24.6 (CH_2), 25.9 (CH), 37.5 (CH), 48.7 (CH_3), 54.1 (CH_2), 55.5 (CH_3), 63.8 (CH_2), 63.8 (CH), 66.7 (CH), 101.5 (CH), 116.5 (CH_2), 119.9 (CH), 121.6 (CH), 125.1 (C), 131.4 (CH), 138.0 (CH), 143.6 (C), 143.8 (C), 147.4 (CH), 157.3 (C). m/z (ES^+) 339 ($[M-I]^+$, 100 %). HRMS (FAB) 339.20721 ($C_{21}H_{27}N_2O_2$ requires 339.20725).

Synthesis of *N*-Methylquinidinium Iodide (88)



Methyl iodide (0.42 mL, 6.7 mmol) was added slowly to a stirred suspension of quinidine (1.11 g, 3.42 mmol) in toluene (20 mL) at room temperature. The reaction mixture was allowed to stir for 2 h before the solid was filtered and washed with chloroform. The known compound, *N*-methylquinidinium iodide, was obtained as a white powder (0.45 g, 36 %). M.p. 248 °C (lit.,[7] 248 °C). $[\alpha]_D$ (MeOH) 227.8 ° (*c* = 1). δ_H (DMSO) 0.96-1.07 (1H, m, NCH_2CHH), 1.75-1.97 (3H, m, NCH_2CHH, NCH_2CH_2CH), 2.21-2.32 (1H, m, NCH_2CHH), 2.70-2.82 (1H, m, NCH_2CH), 3.29 (3H, s, CH_3), 3.42-3.68 (3H, m, $NCHH$), 3.68-3.80 (1H, m, $NCHH$), 4.02 (3H, s, OCH_3), 4.15-4.25 (1H, m, NCH), 5.21-5.29 (2H, m, $CH=CHH$), 6.02 (1H, ddd, $^3J_{HH}$ 17.3 Hz, $^3J_{HH}$ 10.7 Hz, $^3J_{HH}$ 2.6 Hz, $CH=CH_2$), 6.21 (1H, d, $^3J_{HH}$ 6.3 Hz, CHOH), 6.44 (1H, d, $^3J_{HH}$ 6.3 Hz, CHO*H*), 6.97 (1H, d, $^4J_{HH}$ 2.6 Hz, ArH(5')), 7.35 (1H, dd, $^3J_{HH}$ 8.9 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.69 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(3')), 8.02 (1H, d, $^3J_{HH}$ 8.9 Hz, ArH(8')), 8.71 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(2')). δ_C (DMSO) 19.3 (CH_2), 24.6 (CH_2), 25.9 (CH), 37.5 (CH), 48.7 (CH_3), 54.1 (CH_2), 55.5 (CH_3), 63.8 (CH_2), 63.8 (CH), 66.7 (CH), 101.5 (CH), 116.5 (CH_2), 119.9 (CH), 121.6 (CH), 125.1 (C), 131.4 (CH), 138.0 (CH), 143.6 (C), 143.8 (C), 147.4 (CH), 157.3 (C). m/z (ES^+) 339 ($[M-I]^+$, 100 %). HRMS (FAB) 339.20717 ($C_{21}H_{27}N_2O_2$ requires 339.20725).

Synthesis of *N*-Methylquinidinonium Iodide (89)



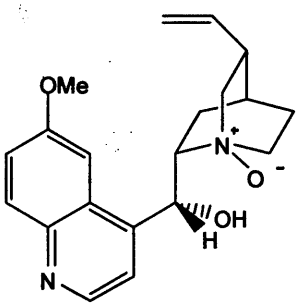
Methyl iodide (0.5 mL, 0.8 mmol) was added dropwise to a stirred suspension of quinidinone (0.26 g, 0.79 mmol) in THF (18 mL) at room temperature. The reaction mixture was allowed to stir for 16 h before the solid was filtered off and washed with hexane. The known compound, *N*-methylquinidinonium iodide, was obtained as a white powder (0.27 g, 72 %). M.p. 211-213 °C (lit.,[8] 213-214 °C). $[\alpha]_D$ (MeOH) 28.4 (*c* = 1). δ_H ($CDCl_3$) 1.52-1.62 (1H, m, NCH_2CHH), 1.82-1.93 (1H, m, NCH_2CHH), 2.01-2.17 (2H, m, NCH_2CHH, NCH_2CH_2CH), 2.48-2.60 (1H, m, NCH_2CHH), 2.91-3.01 (1H, m, NCH_2CH), 3.42-3.58 (2H, m, $NCHH$), 3.60 (3H, s,

N^+CH_3), 3.90 (3H, s, OCH_3), 4.61-4.73 (1H, m, NC*H*H), 4.87-4.96 (1H, m, NC*H*H), 5.24 (1H, ap. d, $^3J_{HH}$ 10.5 Hz, CH=C*H*H), 5.39 (1H, ap. d, $^3J_{HH}$ 17.2 Hz, CH=C*H*H), 6.06 (1H, ddd, $^3J_{HH}$ 17.2, 10.5 and 7.9 Hz, C*H*=CH_2), 6.90-6.97 (1H, m, NCH), 7.40 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.9 Hz, ArH(7')), 7.75 (1H, d, $^4J_{HH}$ 2.9 Hz, ArH(5')), 8.04 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.57 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(3')), 8.97 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_C ($CDCl_3$) 24.4 (CH_2), 25.1 (CH_2), 25.4 (CH_2), 25.9 (CH_2), 26.6 (CH), 27.4 (CH), 37.2 (CH), 38.0 (CH), 50.0 (CH_3), 50.2 (CH_3), 54.6 (CH_2), 55.6 (CH_3), 55.8 (CH_3), 57.7 (CH_2), 60.9 (CH_2), 64.4 (CH_2), 67.3 (CH), 67.9 (CH), 102.3 (CH), 102.5 (CH), 117.9 (CH_2), 119.4 (CH_2), 122.5 (CH), 122.7 (CH), 125.5 (C), 132.0 (CH), 132.1 (CH), 135.0 (C), 135.1 (CH), 135.3 (C), 135.7 (CH), 145.6 (C), 147.7 (CH), 160.2 (C), 196.4 (C=O), 197.3 (C=O). (NOTE: only one carbon peak for carbons 2', 3', 4', 6', 7', 10'). m/z (ES^+) 337 ($[M-I]^+$, 100 %). HRMS (FAB) 337.19161 ($C_{21}H_{25}N_2O_2$ requires 337.19160).

Synthesis of Quinine *N*-Oxide (90) (Method A)

The synthesis of quinine *N*-oxide was attempted by following the procedure described in the literature.[9,10] A 6 % aqueous solution of hydrogen peroxide (210 mL) was added to a stirred solution of quinine (0.51 g, 4.6 mmol) in acetone (67 mL). The reaction mixture was stirred in the dark for 64 h at room temperature. Excess hydrogen peroxide was destroyed by the addition of 10 % Pd on charcoal and left to stir for 1 h. The reaction mixture was filtered and sodium chloride was added to the filtrate until it was saturated. The solution was extracted with diethyl ether (2 × 50 mL) which was then dried over sodium sulphate, filtered and the solvent was removed. The mixture of products obtained was not purified or characterised further.

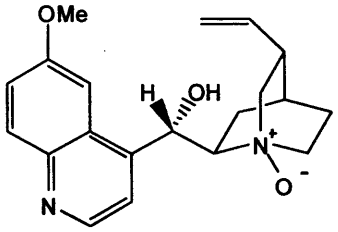
Synthesis of Quinine *N*-Oxide (90) (Method B)



Quinine *N*-oxide was synthesised by following the procedure described by Guentert.[9] *m*-Chloroperoxybenzoic acid (447 mg, 1.8 mmol) was added in 20 mg portions over 30 mins to a stirred solution of quinine (583 mg, 1.8 mmol) in dichloromethane (10 mL) at 0 °C. After stirring the reaction mixture for 30 mins at 0 °C, the solvent was removed. The resulting white solid was loaded onto a basic alumina column (32 g) in chloroform and eluted with $CHCl_3$/methanol (3/1) (~160 mL). All fractions containing the product were combined and the solvent was removed. The residue was dried under oil pump vacuum for 30 mins to give a white solid (0.52 g, 85 %). M.p. 95-97 °C (lit.,[10] 98 °C). $[\alpha]_D$ (MeOH) –153.4 ° (c = 1). δ_H ($CDCl_3$) 1.54 (1H, m, NCH_2CH_2CH), 1.92 (2H, m, NCH_2CHH), 2.34 (3H, m, NCH_2CHH), 2.77 (1H, m, NC*H*H), 2.93 (3H, s,

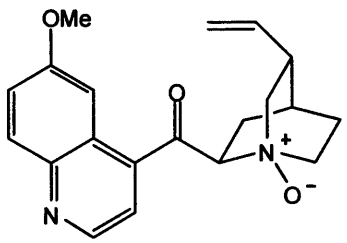
OCH_3), 3.00 (1H, m, NC*H*H), 3.22 (2H, m, NC*H*H), 3.60 (1H, m, NC*H*H), 4.67 (1H, m, C*H*(OH)), 4.93 (2H, m, CH=C*HH*), 5.54 (1H, m, C*H*=CH_2), 6.96 (1H, s, OH), 7.06 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.15 (1H, d, $^4J_{HH}$ 2.6 Hz, ArH(5')), 7.71 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(3')), 7.87 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.67 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(2')). δ_C ($CDCl_3$) 20.4 (CH_2), 27.2 (CH_2), 27.2 (CH), 41.1 (CH), 54.8 (CH_3), 58.9 (CH_2), 63.1 (CH), 70.9 (CH_2), 73.0 (CH), 100.1 (CH), 116.7 (CH_2), 119.2 (CH), 121.8 (CH), 125.8 (C), 131.2 (CH), 138.1 (CH), 143.8 (C), 146.9 (C), 147.6 (CH), 157.7 (C). m/z (ES^+) 341 ($[M+H]^+$, 100%). HRMS (FAB) 341.18660 ($C_{20}H_{25}N_2O_3$ requires 341.18652).

Synthesis of Quinidine *N*-oxide (91) (Method B)



Quinidine *N*-oxide was synthesised by following the procedure described by Guentert.[9] *m*-Chloroperoxybenzoic acid (164 mg, 0.6 mmol) was added in 20 mg portions over 30 mins to a stirred solution of quinidine (202 mg, 0.6 mmol) in dichloromethane (5 mL) at 0 °C. After stirring the reaction mixture for 30 mins at 0 °C, the solvent was removed. The resulting pink solid was loaded onto a basic alumina column (32 g) in chloroform and eluted with $CHCl_3$/methanol (3/1) (~160 mL). All fractions containing the product were combined and the solvent was removed. The residue was dried under oil pump vacuum for 30 mins to give a white solid (0.19 g, 87 %). M.p. 144 °C (lit.,[9] 148-150 °C). $[\alpha]_D$ (MeOH) 134.0 ° (c = 1). δ_H ($CDCl_3$) 1.28 (1H, m, NCH_2CH_2CH), 1.72-2.00 (3H, m, NCH_2CH), 2.67-2.76 (2H, m, NCH_2CHH), 2.78 (3H, s, OCH_3), 3.08-3.21 (2H, m, NC*H*H), 3.30 (1H, m, NC*H*H), 3.38-3.47 (2H, m, NC*H*H), 4.58 (1H, m, C*H*(OH)), 5.10-5.19 (2H, m, CH=C*HH*), 6.11 (1H, m, C*H*=CH_2), 7.04 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.08 (1H, br s, OH), 7.11 (1H, d, $^4J_{HH}$ 2.6 Hz, ArH(5')), 7.73 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(3')), 7.85 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.65 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(2')). δ_C ($CDCl_3$) 20.2 (CH_2), 26.7 (CH_2), 27.8 (CH), 41.3 (CH), 54.7 (CH_3), 62.9 (CH), 63.5 (CH_2), 65.4 (CH_2), 72.8 (CH), 100.1 (CH), 116.8 (CH_2), 119.2 (CH), 121.9 (CH), 125.8 (C), 131.2 (CH), 137.5 (CH), 143.8 (C), 147.5 (C), 147.6 (CH), 157.8 (C). m/z (ES^+) 341 ($[M+H]^+$, 100%). HRMS (FAB) 341.18642 ($C_{20}H_{25}N_2O_3$ requires 341.18652).

Attempted Synthesis of Quininone N-oxide and Quinidinone *N*-oxide (92) (Method A)



A 6 % solution of hydrogen peroxide (104 mL) was added to a stirred solution of quinidinone (0.24 g, 0.75 mmol) in acetone (33 mL). The reaction solution was stirred in the dark for 64 h at room temperature. Excess hydrogen peroxide was destroyed by the addition of 10 % Pd on charcoal and left to stir

for 1 h. The reaction mixture was filtered and the filtrate was extracted with chloroform (20 mL). The organic layer was dried over sodium sulphate, filtered and the solvent was removed. The reaction yielded very little product so no further purification or characterisation was undertaken.

Synthesis of Quininone *N*-oxide and Quinidinone N-oxide (92) (Method B)

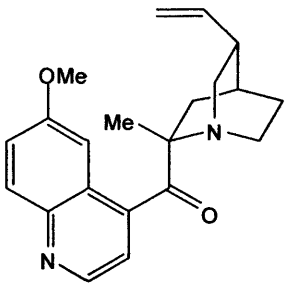
The synthesis of quininone *N*-oxide was attempted by following the procedure described by Guentert.[9] *m*-Chloroperoxybenzoic acid (168 mg, 0.6 mmol) was added in 20 mg portions over 30 mins to a stirred solution of quininone/quinidinone (194 mg, 0.6 mmol) in dichloromethane (5 mL) at 0 °C. After stirring the reaction mixture for 30 mins at 0 °C, the solvent was removed. The resulting oil was loaded onto a basic alumina column in chloroform and eluted with $CHCl_3$/methanol (3/1) (~150 mL) to remove the *m*-chloroperoxybenzoic acid residue. All fractions containing the product were combined and the solvent was removed. The two diastereoisomers of quininone *N*-oxide could not be obtained pure so no further characterisation was undertaken.

Attempted Synthesis of Quinidinone *N*-oxide (92b) (Method C)

A solution of benzophenone (0.28 g, 1.5 mmol) in dry and degassed toluene (6 mL) was charged in to a 3-necked round bottomed flask equipped with a magnetic stirrer bar and condenser under a nitrogen atmosphere. Quinine *N*-oxide (0.27 g, 0.78 mmol) was added to the stirred solution in one portion followed by a 1 M solution of potassium *tert*-butoxide in dry THF (1.95 mL, 1.95 mmol). The solution was refluxed for 8 h and left to cool to room temperature overnight. After cooling to 5-10 °C, hydrochloric acid (2 M, 2.5 mL) was added slowly to the reaction mixture that was then transferred to a separating funnel where more hydrochloric acid (2 M, 4 mL) was added. The aqueous layer was collected and the organic layer was washed with 2 M hydrochloric acid (2 × 2.5 mL). The combined aqueous layers were put into a round bottomed flask equipped with a magnetic stirrer bar and cooled to 0-5 °C in an ice-water bath. A 5 M sodium hydroxide solution was added dropwise to the stirred acidic solution until pH 9 (determined by pH paper) to form a brown sticky solid. The mixture was stirred rapidly for 1 h at 0-5 °C. This transformed the solid into a white powder, which was then filtered and dried under oil pump vacuum. The powder consisted of only starting material so no further characterisation or purification was undertaken.

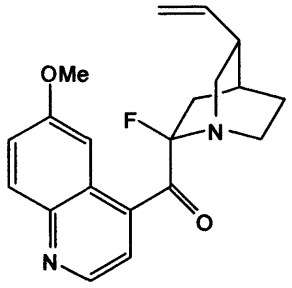
Attempted Synthesis of 8-Methylquininone (93)

A solution of benzophenone (1.51 g, 8.29 mmol) in dry and degassed toluene (20 mL) was charged in to a 3-necked round bottomed flask equipped with a magnetic stirrer bar and



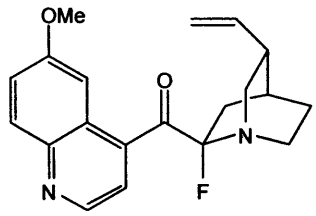
condenser under a nitrogen atmosphere. Quinine (1.48 g, 4.57 mmol) was added to the stirred solution in one portion followed by a 1 M solution of potassium *tert*-butoxide in dry THF (9.2 mL, 9.2 mmol) and methyl iodide (0.65 mL, 5.03 mmol). The solution refluxed for 8 h and left to cool to room temperature overnight. The reaction mixture was transferred to a separating funnel and washed with water (2 × 15 mL). The organic layer was dried over magnesium sulphate, filtered and the solvent was removed. The residue was loaded onto a silica (75 g) column using chloroform. The column was eluted with chloroform (~110 mL) and then chloroform/methanol (92/8) (~200 mL). The chloroform/methanol fractions containing product were combined and the solvent was removed to yield a mixture of products as a red oil. No further purification or characterisation was undertaken.

Synthesis of 8-Fluoroquininone (96a) and 8-Fluoroquinidinone (96b)



A 1 M solution of potassium *tert*-butoxide in dry THF (3.1 mL, 3.13 mmol) was added to a solution of quininone (1.01 g, 3.13 mmol) in dry THF (35 mL) under a nitrogen atmosphere. NFSI (0.99 g, 3.76 mmol) was then added in one portion. The reaction mixture was stirred for 20 h at room temperature before the solvent was removed. Chloroform (40 mL) was added to the residue, filtered and the solvent was removed from the filtrate. The resulting orange oil was loaded onto a silica gel column (35 g) in chloroform and eluted with $CHCl_3$/methanol (92/8) (~250 mL). All fractions containing the products were combined and the solvent was removed to give a pale yellow oil (0.56 g, 53 %). To separate the diastereoisomers, the resulting oil was loaded onto a silica gel column (400 g) in chloroform and eluted with $CHCl_3$/ethyl acetate (4/1) (~2 L). All fractions containing the top diastereoisomer **(96a)** were combined and the solvent was removed. The top diastereoisomer was obtained as a yellow oil (0.013 g, 1 %). δ_H (CD_3CN) 1.45 (2H, m, NCH_2CHH), 1.75 (1H, ddt, $^3J_{HF}$ 30.1 Hz, $^2J_{HH}$ 14.9 Hz, $^3J_{HH}$ 2.3 Hz, $^4J_{HH}$ 2.3 Hz, NCFC*H*H), 1.90 (1H, m, CH), 2.26 (1H, m, NCH_2CH), 2.62 (2H, m, NC*H*H, NCFC*H*H), 2.80 (1H, m, NC*H*H), 2.98 (2H, m, NC*H*H), 3.82 (3H, s, OCH_3), 5.02 (2H, m, CH=C*HH*), 5.91 (1H, m, $CH{=}CH_2$), 7.34 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.53 (1H, d, $^4J_{HH}$ 2.6 Hz, ArH(5')), 7.93 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.21 (1H, dd, $^3J_{HH}$ 4.7 Hz, $^5J_{HF}$ 0.9 Hz, ArH(3')), 8.73 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_C (CD_3CN) 24.1 (CH_2), 27.1 (d, $^2J_{CF}$ 28.7 Hz, CH_2), 27.9 (CH), 38.2 (CH), 42.3 (d, $^3J_{CF}$ 7.2 Hz, CH_2), 46.0 (CH_2), 55.0 (CH_3), 102.7 (CH), 106.2 (d, $^1J_{CF}$ 197.5 Hz, C), 114.2 (CH_2), 121.5 (d, $^4J_{CF}$ 4.8 Hz, CH), 121.7 (CH), 125.3 (C), 131.2 (CH), 137.9 (C), 140.0 (CH), 144.9 (C), 146.6 (CH), 158.7 (C), 198.3 (d, $^2J_{CF}$ 32.3 Hz,

C=O). δ_F (CD_3CN) –118.4 (1F, m, CF). m/z (ES^+) 341 ($[M+H]^+$, 100%). HRMS (FAB) 341.16649 ($C_{20}H_{22}FN_2O_2$ requires 341.16653).



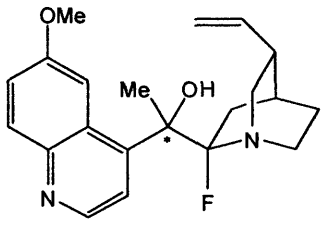
All fractions containing the bottom diastereoisomer **(96b)** were combined and the solvent was removed. The bottom diastereoisomer was obtained as a pale yellow solid (0.17 g, 16 %). 8-Fluoroquinidinone could also be obtained pure by dissolving the diastereomeric mixture in the minimum volume of acetonitrile and leaving to slowly recrystallise in the fridge for ~ 2 weeks. The crystals were then filtered, washed with a little cold acetonitrile and dried under oil pump vacuum. The crystals were of good enough quality for X-ray analysis. M.p. 105-106 °C. $[\alpha]_D$ (MeOH) 284.1 ° (*c* = 1.5). (Found: C, 70.48; H, 6.19; N, 8.22. $C_{20}H_{21}FN_2O_2$ requires C, 70.57; H, 6.22; N, 8.23). δ_H (CD_3CN) 1.39-1.67 (3H, m, NCFC*H*H, NCH_2CH_2) 1.93 (1H, m, CH), 2.25 (1H, m, NCH_2CH), 2.39 (1H, m, NC*H*H), 2.69 (1H, m, NC*H*H), 2.86 (1H, ddt, $^3J_{HF}$ 26.9 Hz, $^2J_{HH}$ 15.5 Hz, $^3J_{HH}$ 2.3 Hz, $^4J_{HH}$ 2.3 Hz, NCFC*H*H), 3.02 (1H, m, NC*H*H), 3.22 (1H, m, NC*H*H), 3.81 (3H, s, OCH_3), 5.00 (2H, m, CH=C*HH*), 5.92 (1H, m, C*H*=CH_2), 7.34 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.41 (1H, d, $^4J_{HH}$ 2.6 Hz, ArH(5')), 7.93 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.01 (1H, dd, $^3J_{HH}$ 4.4 Hz, $^5J_{HF}$ 1.2 Hz, ArH(3')), 8.72 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(2')). δ_C (CD_3CN) 25.1 (CH_2), 27.2 (d, $^2J_{CF}$ 26.3 Hz, CH_2), 28.0 (CH), 37.5 (CH), 40.0 (d, $^3J_{CF}$ 6.0 Hz, CH_2), 47.8 (d, $^3J_{CF}$ 6.0 Hz, CH_2), 55.0 (CH_3), 102.6 (CH), 105.9 (d, $^1J_{CF}$ 197.5 Hz, C), 114.3 (CH_2), 121.2 (d, $^4J_{CF}$ 4.8 Hz, CH), 121.8 (CH), 125.3 (C), 131.1 (CH), 138.7 (C), 140.0 (CH), 144.7 (C), 146.5 (CH), 158.5 (C), 198.3 (d, $^2J_{CF}$ 32.3 Hz, C=O). δ_F (CD_3CN) –120.9 (1F, ddt, $^3J_{FH}$ 32.2 Hz, $^3J_{FH}$ 25.8 Hz, $^4J_{FH}$ 6.4 Hz, CF). m/z (ES^+) 341 ($[M+H]^+$, 100%). HRMS (FAB) 341.16647 ($C_{20}H_{22}FN_2O_2$ requires 341.16653).

Attempted Separation of 8-Fluoroquininone (96a) and 8-Fluoroquinidinone (96b) with D-Tartaric Acid

The separation of 8-fluoroquininone and 8-fluoroquinidinone was attempted by following a procedure by Doering.[11] A hot solution of D-tartaric acid (0.28 g, 1.89 mmol) in ethanol (~ 3 mL) was added dropwise to a solution of 8-fluoroquininone and 8-fluoroquinidinone (1.22 g, 3.59 mmol) in hot ethanol (~5 mL). The reaction mixture was left in the fridge, but no crystals formed.

Synthesis of 8-Fluoro-9-MethylQuinidine (97)

The synthesis of 8-fluoro-9-methylquinidine was based on a procedure described by Dehmlow.[12] A 1.6 M solution of methyllithium in ether (1.4 mL, 2.22 mmol) was added to



dry and degassed ether (20 mL) at –78 °C under a nitrogen atmosphere. This was followed by the dropwise addition of 8-fluoroquinidinone (0.76 g, 2.22 mmol) in dry THF (40 mL) over 30 mins. The reaction was then stirred at –78 °C for 3 h. Water (20 mL) was then added and the reaction mixture was warmed to room temperature overnight. The organic layer was removed and the remaining aqueous layer was washed with ether (2 × 10 mL). The organic layers were combined, dried over sodium sulphate and the solvent was removed. The residue was then dissolved in the minimum volume of chloroform, loaded onto a silica gel column (55 g) and eluted with chloroform/ethyl acetate (4/1) (750 mL) to remove any starting material. The product was recovered by eluting with ethyl acetate (500 mL). All fractions containing the product were combined and the solvent was removed to give 8-fluoro-9-methylquinidine as a white foamy solid (0.38 g, 48 %). M.p. 181-182 °C. $[\alpha]_D$ (MeOH) 66.8 ° (c = 1). (Found: C, 70.85; H, 7.00; N, 7.75. $C_{21}H_{25}FN_2O_2$ requires C, 70.76; H, 7.07; N, 7.86). δ_H ($CDCl_3$, 400 MHz, 328 K) 1.54-1.57 (1H, m, NCH_2CHH), 1.66 (1H, ddd, $^3J_{HF}$ 14.9 Hz, $^2J_{HH}$ 4.3 Hz, $^3J_{HH}$ 1.6 Hz, NCFC*H*H), 1.71-1.78 (1H, m, NCH_2CHH), 1.98 (3H, d, $^4J_{HF}$ 2.3 Hz, CH_3), 2.00 (1H, m, NCH_2CH_2CH), 2.18-2.27 (1H, m, NCH_2CH), 2.46-2.61 (2H, m, NC*H*H, NCFC*H*H), 2.86-3.04 (2H, m, NC*H*H), 3.20-3.29 (1H, m, NC*H*H), 3.94 (3H, s, OCH_3), 4.94 (1H, dt, $^3J_{HH}$ 17.2 Hz, $^2J_{HH}$ = $^4J_{HH}$ 1.6 Hz, CH=CH*H*), 5.03 (1H, ddd, $^3J_{HH}$ 10.6 Hz, $^2J_{HH}$ 1.6 Hz, $^4J_{HH}$ 1.2 Hz, CH=CH*H*), 5.77 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^3J_{HH}$ 10.6 Hz, $^3J_{HH}$ 7.0 Hz, CH=CH_2), 7.36 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.7 Hz, ArH(7')), 7.61 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(3')), 8.06 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.33 (1H, d, $^4J_{HH}$ 2.7 Hz, ArH(5')), 8.69 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_H ($CDCl_3$, 400 MHz, 300 K) 1.46-1.55 (1H, m, NCH_2CHH), 1.61-1.76 (2H, m, NCFC*H*H, NCH_2CHH), 1.94 (3H, d, $^4J_{HF}$ 2.0 Hz, CH_3), 1.96-2.00 (1H, m, NCH_2CH_2CH), 2.17-2.25 (1H, m, NCH_2CH), 2.44-2.62 (2H, m, NC*H*H, NCFC*H*H), 2.84-2.93 (1H, m, NC*H*H), 3.01-3.09 (1H, m, NC*H*H), 3.15-3.24 (1H, m, NC*H*H), 3.92 (3H, s, OCH_3), 4.93 (1H, dt, $^3J_{HH}$ 17.2 Hz, $^2J_{HH}$ 1.6 Hz, $^4J_{HH}$ 1.6 Hz, CH=CH*H*), 5.00 (1H, ddd, $^3J_{HH}$ 10.6 Hz, $^2J_{HH}$ 1.6 Hz, $^4J_{HH}$ 1.2 Hz, CH=CH*H*), 5.80 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^3J_{HH}$ 10.6 Hz, $^3J_{HH}$ 7.0 Hz, CH=CH_2), 7.33 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.7 Hz, ArH(7')), 7.58 (1H, br s, ArH(3')), 8.00 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.32 (1H, br s, ArH(5')), 8.64 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_C ($CDCl_3$, 300 MHz) 24.8 (CH_2), 27.4 (d, $^3J_{CF}$ 4.8 Hz, CH_3), 28.1 (d, $^2J_{CF}$ 25.1 Hz, CH_2), 28.4 (CH), 37.2 (CH), 43.4 (d, $^3J_{CF}$ 12.0 Hz, CH_2), 48.6 (d, $^3J_{CF}$ 4.8 Hz, CH_2), 54.4 (CH_3), 80.3 (d, $^2J_{CF}$ 27.5 Hz, C), 105.7 (d, $^5J_{CF}$ 6.0 Hz, CH), 108.0 (d, $^1J_{CF}$ 197.5 Hz, C), 113.8 (CH_2), 119.9 (CH), 120.2 (CH), 127.6 (C), 130.1 (CH), 139.2 (CH), 144.3 (C), 145.7 (CH), 148.3 (C), 155.6 (C). δ_F ($CDCl_3$, 300 MHz) –121.3 (1F, br. m., CF). m/z (ES^+) 357 ($[M+H]^+$, 100%). HRMS (FAB) 357.19787 ($C_{21}H_{26}FN_2O_2$ requires 357.19783).

Attempted Methylation of 8-Fluoroquininone (96a) and 8-Fluoroquinidinone (96b) (Method A)

Methyl iodide (0.20 mL, 3.2 mmol) was added slowly to a stirred solution of 8-fluoroquininone and 8-fluoroquinidinone (0.55 g, 1.63 mmol) in toluene (20 mL). The reaction mixture was stirred at room temperature for 24 h before the solvent was removed. The ^{1}H and ^{19}F NMR spectra and mass spectrum, showed that no reaction had occurred.

Attempted Methylation of 8-Fluoroquininone (96a) and 8-Fluoroquinidinone (96b) (Method B)

Methyl iodide (0.20 mL, 3.2 mmol) was added slowly to a stirred solution of 8-fluoroquininone and 8-fluoroquinidinone (0.52 g, 1.54 mmol) in toluene (35 mL). The reaction mixture was refluxed for 24 h before cooling to room temperature and removing the solvent. The ^{1}H and ^{19}F NMR spectra and mass spectrum, showed that most of the residue was starting material with a trace of product. No attempt was made to isolate the products. δ_F ($CDCl_3$) **–117.60 (s)**, -119.13 (s), **-119.96 (s)**, -121.80 (s) (values in bold are starting material). m/z (ES^+) 341 ($[M+H]^+$, 100%), 355 ($[M+Me]^+$, 29%).

Attempted Methylation of 8-Fluoroquininone (96a) and 8-Fluoroquinidinone (96b) (Method C)

Methyl iodide (0.20 mL, 3.2 mmol) was added slowly to a stirred solution of 8-fluoroquininone and 8-fluoroquinidinone (0.50 g, 1.47 mmol) in THF (35 mL). The reaction mixture was stirred at room temperature for 24 h before the solvent was removed. The ^{1}H and ^{19}F NMR spectra and mass spectrum, showed that most of the residue was starting material with a trace of product. No attempt was made to isolate the products. δ_F ($CDCl_3$) –116.99 (s), **–117.64 (s)**, -119.41 (s), **-120.02 (s)** (values in bold are starting material). m/z (ES^+) 341 ($[M+H]^+$, 100%).

Attempted Methylation of 8-Fluoroquininone (96a) and 8-Fluoroquinidinone (96b) (Method D)

Methyl iodide (0.20 mL, 3.2 mmol) was added slowly to a stirred solution of 8-fluoroquininone and 8-fluoroquinidinone (0.51 g, 1.50 mmol) in THF (35 mL). The reaction mixture was refluxed for 24 h before cooling to room temperature and removing the solvent. The ^{1}H and ^{19}F NMR spectra and mass spectrum, showed a 20 % conversion to product, but the majority was still starting material. No attempt was made to isolate the products. δ_F ($CDCl_3$) **–117.63 (s)**, -119.13 (s), **-119.99 (s)**, -121.78 (s) (values in bold are starting material). m/z (ES^+) 341 ($[M+H]^+$, 100%), 355 ($[M+Me]^+$, 50%).

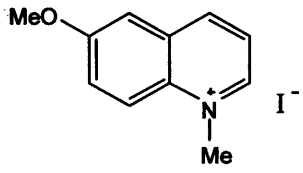
Attempted Methylation of 8-Fluoroquininone (96a) and 8-Fluoroquinidinone (96b) (Method E)

Methyl trifluoromethanesulphonate (0.20 mL, 1.8 mmol) was added slowly to a solution of 8-fluoroquininone and 8-fluoroquinidinone (0.61 g, 1.77 mmol) in dry acetonitrile (20 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 24 h before removing the solvent. The oily product residue was then washed with plenty of toluene and dried. The ^{1}H and ^{19}F NMR spectra and mass spectrum, showed that the reaction had gone to completion, but had formed two sets of diastereoisomers. The two sets were not separated. δ_F ($CDCl_3$) –119.38 (s), -122.06 (s), -130.15 (s), -132.52(s). m/z (ES^+) 341 ($[M+H]^+$, 100%), 355 ($[M+Me]^+$, 75%).

Attempted Synthesis of *N*-Methyl-6-Methoxyquinoline (98) (Method A)

Methyl trifluoromethanesulphonate (0.40 mL, 3.5 mmol) was added dropwise to a solution of 6-methoxyquinoline (0.56 g, 3.54 mmol) in dry acetonitrile (20 mL) at 0 °C under a nitrogen atmosphere. The reaction was left to stir at room temperature for 24 h, during which time the initial colourless solution turned pink. The solvent was removed and the ^{1}H NMR spectrum showed that at least three products had formed. No attempt was made to separate the reaction products.

Synthesis of *N*-Methyl-6-Methoxyquinoline (98) (Method B)



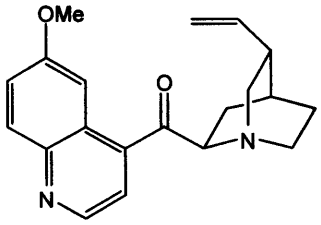
N-Methyl-6-Methoxyquinoline was synthesised by following a procedure by Geddes.[13] 6-Methoxyquinoline (0.90 g, 5.67 mmol) and methyl iodide (0.30 mL, 4.8 mmol) were heated at 75 °C for 40 mins. On cooling, ether (25 mL) was added and the reaction mixture was stirred at room temperature for 19 h. The resulting yellow precipitate was filtered and washed with ether. *N*-Methyl-6-methoxyquinoline was obtained as a yellow powder (1.08 g, 78 %). M.p. 243 °C (lit.,[14] 243-246 °C). δ_H (DMSO) 4.00 (3H, s, OCH_3), 4.61 (3H, s, CH_3), 7.90 (2H, m, ArH(5), ArH(7)), 8.10 (1H, dd, $^{3}J_{HH}$ 8.5 Hz and 5.8 Hz, ArH(3)), 8.43 (1H, d, $^{3}J_{HH}$ 8.5 Hz, ArH(4)), 9.11 (1H, d, $^{3}J_{HH}$ 8.2 Hz, ArH(8)), 9.32 (1H, d, $^{3}J_{HH}$ 5.8 Hz, ArH(2)). δ_C (DMSO) 45.4 (CH_3), 56.4 (CH_3), 107.9 (CH), 120.8 (CH), 122.4 (CH), 127.4 (CH), 131.2 (C), 134.0 (C), 145.1 (CH), 147.1 (CH), 159.2 (C). m/z (ES^+) 174 (M^+, 100%). HRMS (FAB) 174.09199 ($C_{11}H_{12}NO$ requires 174.09189).

Synthesis of Quinidinone (55) (Method A)

The synthesis of quinidinone was attempted by following the procedure described by Woodward.[15] A 1.0 M solution of potassium-*tert*-butoxide in THF (2.5 mL, 25 mmol), dry

toluene (50 mL), quinine (3.24 g, 10 mmol) and benzophenone (9.10 g, 50 mmol) were all added to a 100 mL round-bottomed flask under a nitrogen atmosphere. The reaction mixture was refluxed overnight, and then allowed to cool to room temperature. The reaction mixture was then cooled further to 0 °C and 2 M hydrochloric acid (20 mL) was added slowly. The aqueous layer was removed and the organic layer was extracted with 2 M hydrochloric acid (4 × 10 mL) until no colour was observed in the aqueous phase. The combined aqueous phases were washed with ether (2 × 30 mL) and were then added dropwise to a stirred 5 M sodium hydroxide solution (48 mL) containing crushed ice. A pale yellow precipitate formed, which was taken into ether (150 mL). The aqueous layer was saturated with sodium chloride and extracted with ether (3 × 50 mL). The organic phases were combined, washed with brine (50 mL), dried over magnesium sulphate and the solvent was removed. The resulting yellow oil contained mostly quinine so this method was abandoned.

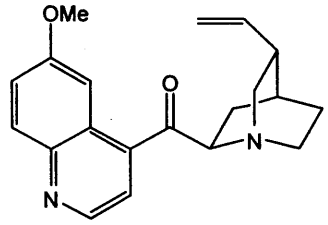
Synthesis of Quinidinone (55) Using Benzophenone and Solid KO^{t}Bu (Method B)



Quinidinone was synthesised by following the procedure by Huchison.[4] Quinine (0.51 g, 1.55 mmol) was added to a solution of benzophenone (0.55 g, 3.05 mmol) in dry and degassed toluene (5 mL) in one portion under a nitrogen atmosphere. Solid potassium *tert*-butoxide (0.44 g, 3.90 mmol) was then added to the reaction mixture and refluxed for 24 h before cooling to room temperature overnight. After cooling to 0 °C, hydrochloric acid (2 M, 4 mL) was added slowly to the reaction mixture then transferred to a separating funnel and the aqueous layer was removed. The organic layer was extracted with more hydrochloric acid (2 M, 4 × 4 mL) and the aqueous phases were combined. The combined aqueous phase was then added dropwise to a 28 % solution of ammonia/crushed ice mixture where a yellow sticky solid formed. This precipitate was taken into toluene (60 mL), dried over sodium sulphate, filtered and the solvent was removed to yield a yellow oil. Hexane (~2 mL) was added to the oil and the sides of the glass vessel were scratched until a precipitate formed. The solid was dried under oil pump vacuum to yield pure quinidinone as a white powder (0.32 g, 64 %). M.p. 91 °C (lit.,[5] 93-95 °C). $[\alpha]_D$ (MeOH) 59.7 (c = 1). δ_H ($CDCl_3$) 1.44-1.55 (1H, m, NCH_2CHH), 1.60-1.70 (2H, m, NCH_2CHH), 1.79-1.86 (1H, m, NCH_2CH_2CH), 2.17-2.31 (2H, m, NCH_2CHH, NCH_2CH), 2.56-2.65 (1H, m, $NCHH$), 2.79-2.93 (2H, m, $NCHH$), 3.04-3.15 (1H, m, $NCHH$), 3.86 (3H, s, OCH_3), 4.18-4.26 (1H, m, NCH), 4.93-5.03 (2H, m, $CH{=}CHH$), 5.88 (1H, ddd, $^3J_{HH}$ 17.2, 10.5 and 7.3 Hz, $CH{=}CH_2$), 7.32 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.9 Hz, ArH(7')), 7.57 (1H, d, $^4J_{HH}$ 2.9 Hz, ArH(5')), 7.60 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(3')), 7.95 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.77 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(2')). δ_H (C_6D_6) 1.19-1.37 (3H, m, NCH_2CHH, NCH_2CH_2CH), 1.69-1.75 (1H, m,

NCH_2CHH), 1.94-2.05 (1H, m, NCH_2CH), 2.50-2.62 (1H, m, NCH_2CHH), 2.67 (1H, br. s, $NCHH$), 2.69 (1H, br. s, $NCHH$), 2.71-2.82 (2H, m, $NCHH$), 3.54 (3H, s, OCH_3), 3.67-3.74 (1H, m, NCH), 5.04-5.15 (2H, m, $CH=CHH$), 6.15 (1H, ddd, $^3J_{HH}$ 17.2, 10.5 and 7.6 Hz, $CH=CH_2$), 7.36 (1H, dd, $^3J_{HH}$ 9.1 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.52 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(3')), 8.21 (1H, d, $^4J_{HH}$ 2.6 Hz, ArH(5')), 8.31 (1H, d, $^3J_{HH}$ 9.1 Hz, ArH(8')), 8.84 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(2')). m/z (ES^+) 323 ($[M+H]^+$, 100%). HRMS (FAB) 323.17532 ($C_{20}H_{23}N_2O_2$ requires 323.17538).

Synthesis of Quinidinone (55) using Fluorenone and Sodium Hydride (Method C)



Quinidinone was synthesised by following the procedure by Pratap.[16] Fluorenone (5.94 g, 33.0 mmol) was added to a suspension of quinine (4.87 g, 15.0 mmol) in dry toluene (60 mL) under a nitrogen atmosphere. The reaction mixture was refluxed until all of the solid had dissolved. Sodium hydride as a 60 % dispersion in mineral oil (2.80 g, 70.0 mmol) was added in portions over 30 mins, in which time the yellow solution turned dark green. The reaction mixture was refluxed for 18 h and left to cool to room temperature overnight. After cooling to 0 °C, water (30 mL) was added slowly. The two layers were transferred to a separating funnel and dilute hydrochloric acid (2 M, 40 mL) was added. The aqueous layers were removed and the organic layer was extracted with dilute hydrochloric acid (2 M, 4 × 30 mL). The aqueous layers were combined and poured into a 28 % ammonia solution/ice mixture with rapid stirring. A white precipitate formed which was taken into toluene (60 mL), dried over sodium sulphate, filtered and the solvent was removed to yield a yellow oil. Hexane (~8 mL) was added to the oil and the sides of the glass vessel were scratched until a precipitate formed. The solid was dried under oil pump vacuum to yield pure quinidinone as a brown powder (4.14 g, 86 %). M.p. 90-92 °C (lit.,[5] 93-95 °C). $[\alpha]_D$ (MeOH) 316.5 ° (c = 1). (Found: C, 74.39; H, 6.84; N, 8.58. $C_{20}H_{22}N_2O_2$ requires C, 74.51; H, 6.88; N, 8.69). δ_H ($CDCl_3$) 1.48-1.59 (1H, m, NCH_2CHH), 1.64-1.75 (2H, m, NCH_2CHH), 1.86-1.91 (1H, m, NCH_2CH_2CH), 2.22-2.41 (2H, m, NCH_2CHH, NCH_2CH), 2.58-2.67 (1H, m, $NCHH$), 2.84-2.96 (2H, m, $NCHH$), 3.06-3.17 (1H, m, $NCHH$), 3.93 (3H, s, OCH_3), 4.15-4.23 (1H, m, NCH), 5.00-5.10 (2H, m, $CH=CHH$), 5.90-6.03 (1H, m, $CH=CH_2$), 7.40 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.9 Hz, ArH(7')), 7.64 (1H, d, $^4J_{HH}$ 2.9 Hz, ArH(5')), 7.65 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(3')), 8.03 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.84 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(2')). δ_H (C_6D_6) 1.20-1.36 (3H, m, NCH_2CHH, NCH_2CH_2CH), 1.69-1.75 (1H, m, NCH_2CHH), 1.95-2.05 (1H, m, NCH_2CH), 2.50-2.62 (1H, m, NCH_2CHH), 2.66 (1H, br. s, $NCHH$), 2.69 (1H, br. s, $NCHH$), 2.70-2.83 (2H, m, $NCHH$), 3.54 (3H, s, OCH_3), 3.67-3.75 (1H, m, NCH), 5.05-5.15 (2H, m, $CH=CHH$), 6.15 (1H, ddd, $^3J_{HH}$ 17.5, 10.5 and 7.6 Hz,

C*H*=CH_2), 7.36 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.52 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(3')), 8.21 (1H, d, $^4J_{HH}$ 2.6 Hz, ArH(5')), 8.31 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.85 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(2')). δ_C (300 MHz, C_6D_6) 19.9 (CH_2), 20.1 (CH_2), 25.8 (CH_2), 26.0 (CH_2), 26.4 (CH), 26.6 (CH), 38.6 (CH), 39.0 (CH), 42.0 (CH_2), 47.3 (CH_2), 48.5 (CH_2), 53.6 (CH_3), 54.2 (CH_2), 61.6 (CH), 61.9 (CH), 102.1 (CH), 102.3 (CH), 113.0 (CH_2), 113.3 (CH_2), 120.0 (CH), 120.7 (CH), 121.0 (CH), 121.1 (CH), 124.9 (C), 131.0 (CH), 131.0 (CH), 139.0 (C), 139.5 (CH), 140.6 (CH), 145.2 (C), 146.0 (CH), 146.1 (CH), 158.3 (C), 158.4 (C), 201.3 (C=O), 201.6 (C=O). (NOTE: only one peak for carbons OMe, 4', 9' and 10'). δ_C (400 MHz, C_6D_6) 21.3 (CH_2), 26.9 (CH_2), 27.8 (CH), 40.2 (CH), 48.5 (CH_2), 49.7 (CH_2), 54.8 (CH_3), 62.8 (CH), 103.3 (CH), 114.5 (CH_2), 121.1 (CH), 122.3 (CH), 126.0 (C), 132.1 (CH), 140.3 (C), 140.7 (CH), 146.3 (C), 147.1 (CH), 159.4 (C), 202.7 (C=O). m/z (ES^+) 323 ($[M+H]^+$, 100%). HRMS (FAB) 323.17597 ($C_{20}H_{23}N_2O_2$ requires 323.17595).

5.3 Addition of R_1

Attempted Synthesis of 9-Methylquinidine (100) (Method A)

A solution of quinidinone (0.52 g, 1.6 mmol) in dry THF (25 mL) was added dropwise over 15 mins to a stirred 0.12 M solution of MeLi in ether (13 mL, 1.6 mmol) at -78 °C. After stirring the reaction at -78 °C for 3 h under a nitrogen atmosphere, the reaction was quenched by the addition of water (15 mL) and allowed to warm to room temperature. The solvent was then removed from the organic phase. The ^1H NMR spectrum of the reaction residue showed a mixture of starting material and at least two products. Separation of the compounds by thin layer chromatography could not be achieved.

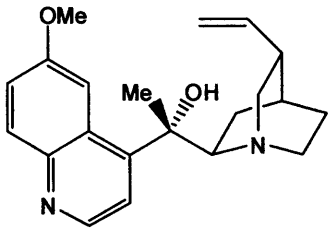
Attempted Synthesis of 9-Methylquinidine (100) (Method B)

A solution of quinidinone (1.00 g, 3.1 mmol) in dry THF (30 mL) was added dropwise over 15 mins to a stirred 1.6 M solution of MeLi in ether (1.9 mL, 3.1 mmol) and dry THF (25 mL) at 0 °C. After stirring the reaction mixture at 0 °C for 2 h under a nitrogen atmosphere, it was allowed to warm to room temperature and water (30 mL) was added to quench the reaction. After 2 h, the organic layer was separated and the solvent was removed to give a residue which was found to contain a mixture of products. No further purification or separation was performed.

Attempted Synthesis of 9-Methylquinidine (100) (Method C)

A solution of quinidinone (0.49 g, 1.52 mmol) in dry toluene (10 mL) was added dropwise over 45 mins to a stirred 1.6 M solution of MeLi in ether (1 mL, 1.6 mmol). The reaction was then refluxed for 15 h under a nitrogen atmosphere. After the reaction was cooled to room temperature, it was added to a saturated solution of ammonium chloride (25 mL) and ice. The organic layer was removed and the aqueous layer was extracted with ether (4 × 2 mL). The organic layers were combined, dried over $NaSO_4$ and the solvent was removed. The residue was found to contain a mixture of products so no further purification or separation was performed.

Synthesis of 9-Methylquinidine (100) Using 1 M Methylmagnesium Iodide (10 equiv.) (Method D)



The synthesis of 9-methylquinidine was carried out by following the procedure by Woodward.[15] A solution of quinidinone (1.89 g, 5.9 mmol) in dry toluene (60 mL) was added dropwise over 30 mins to a stirred 1 M solution of methylmagnesium iodide (60 mL, 0.06 mol) in diethyl ether. The reaction mixture was stirred for 2.5 h at room temperature under a nitrogen atmosphere. The reaction was hydrolysed by the very slow addition of 2 M hydrochloric (40 mL) and crushed ice mixture and the aqueous layer was removed. Any solid residue in the reaction vessel was taken into 2 M hydrochloric acid (20 mL). The acidic aqueous layers were combined, washed with ether (30 mL) and then poured into 35 % ammonia solution (80 mL) and crushed ice mixture. The white precipitate that forms was filtered off and dried under vacuum. The crude material was dissolved in the minimum volume of ethanol and water was added to precipitate out the product. The solid was filtered off and dried under oil pump vacuum. 9-Methylquinidine was obtained as fine white needles (1.01 g, 52 %). M.p. 115-117 °C. $[\alpha]_D$ (EtOH) 193.3° (c = 1). (Found: C, 74.40; H, 7.83; N, 8.15. $C_{21}H_{26}N_2O_2$ requires C, 74.52; H, 7.74; N, 8.28). δ_H ($CDCl_3$) 0.88-1.00 (1H, m, NCH_2CHH), 1.42-1.51 (2H, m, NCH_2CHH), 1.57-1.63 (1H, m, NCH_2CH_2CH), 1.67-1.77 (1H, m, NCH_2CHH), 1.89 (3H, s, CH_3), 2.02-2.13 (1H, m, NCH_2CH), 2.70-2.86 (2H, m, $NCHH$), 2.90-3.08 (2H, m, $NCHH$), 3.17-3.26 (1H, m, NCH), 3.85 (3H, s, OCH_3), 4.72 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^2J_{HH}$ 1.8 Hz, $^4J_{HH}$ 1.5 Hz, CH=C*H*H), 4.81 (1H, ddd, $^3J_{HH}$ 10.2 Hz, $^2J_{HH}$ 1.8 Hz, $^4J_{HH}$ 1.2 Hz, CH=C*H*H), 5.67 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^3J_{HH}$ 10.2 Hz, $^3J_{HH}$ 7.3 Hz, C*H*=CH_2), 7.28 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.60 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(3')), 7.65 (1H, br. s, ArH(5')), 7.97 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.63 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_H ($CDCl_3$, 400 MHz, 331 K) 1.04-1.12 (1H, m, NCH_2CHH), 1.53-1.61 (2H, m, NCH_2CHH), 1.69-1.73 (1H, m, NCH_2CH_2CH), 1.77-

1.85 (1H, m, NCH_2CHH), 1.98 (3H, s, CH_3), 2.12-2.20 (1H, m, NCH_2CH), 2.81-2.94 (2H, m, $NCHH$), 3.01-3.10 (2H, m, $NCHH$), 3.28-3.34 (1H, m, NCH), 3.95 (3H, s, OCH_3), 4.81 (1H, dt, $^3J_{HH}$ 17.2 Hz, $^2J_{HH}$ 1.6 Hz, $^4J_{HH}$ 1.6 Hz, CH=CHH), 4.90 (1H, ddd, $^3J_{HH}$ 10.6 Hz, $^2J_{HH}$ 1.6 Hz, $^4J_{HH}$ 1.2 Hz, CH=CHH), 5.74 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^3J_{HH}$ 10.6 Hz, $^3J_{HH}$ 7.0 Hz, $CH=CH_2$), 7.37 (1H, dd, $^3J_{HH}$ 9.0 Hz, $^4J_{HH}$ 2.7 Hz, ArH(7')), 7.67 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(3')), 7.79 (1H, d, $^4J_{HH}$ 2.7 Hz, ArH(5')), 8.07 (1H, d, $^3J_{HH}$ 9.0 Hz, ArH(8')), 8.75 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_C ($CDCl_3$) 22.0 (CH_2), 26.3 (CH_2), 28.7 (CH), 29.5 (CH_3), 39.8 (CH), 49.8 (CH_2), 51.2 (CH_2), 55.4 (CH_3), 63.3 (CH), 77.3 (C), 104.9 (CH), 114.3 (CH_2), 119.9 (CH), 120.6 (CH), 127.0 (C), 132.0 (CH), 140.3 (CH), 145.3 (C), 147.4 (CH), 150.8 (C), 156.7 (C). δ_C (Acetone-d^6) 22.5 (CH_2), 27.3 (CH_2), 28.8 (CH), 30.1 (CH_3), 41.5 (CH), 50.8 (CH_2), 51.8 (CH_2), 55.8 (CH_3), 62.9 (CH), 78.5 (C), 105.7 (CH), 114.2 (CH_2), 120.6 (CH), 121.2 (CH), 127.8 (C), 132.9 (CH), 142.3 (CH), 146.4 (C), 148.3 (CH), 152.6 (C), 157.5 (C). m/z (ES^+) 339 ($[M+H]^+$, 100%). HRMS (FAB) 339.20723 ($C_{21}H_{27}N_2O_2$ requires 339.20725).

Synthesis of 9-Methylquinidine (100) Using 3 M Methylmagnesium Iodide (10 equiv.) (Method E)

The synthesis of 9-methylquinidine was carried out by following the procedure by Woodward.[15] A solution of quinidinone (1.17 g, 3.63 mmol) in dry toluene (40 mL) was added dropwise over 90 mins to a stirred 3 M solution of methylmagnesium iodide (12.1 mL, 36.3 mmol) in diethyl ether. The reaction mixture was stirred overnight at room temperature under a nitrogen atmosphere. The reaction was hydrolysed by the very slow addition of 2 M hydrochloric (30 mL) and crushed ice mixture and the aqueous layer was removed. The organic layer was extracted with 2 M hydrochloric acid (2 × 10 mL) and the acidic aqueous layers were combined, washed with ether (20 mL) and then poured into 28 % ammonia solution (30 mL) and crushed ice mixture. The white precipitate that forms was filtered off and dried under vacuum. The crude material was dissolved in the minimum volume of ethanol and water was added to precipitate out the product. The solid was filtered off and dried on the Kugelrohr apparatus for 1 d at 50 °C. 9-Methylquinidine was obtained as a white powder (0.50 g, 41 %).

Synthesis of 9-Methylquinidine (100) Using 1 M Methylmagnesium Bromide (10 equiv.) (Method F)

The synthesis of 9-methylquinidine was carried out by following the procedure by Woodward.[15] A solution of quinidinone (1.90 g, 5.89 mmol) in dry toluene (60 mL) was added dropwise over 50 mins to a stirred 1 M solution of methylmagnesium bromide (60 mL, 0.06 mol) in diethyl ether. The reaction mixture was stirred for 4 h at room temperature under

a nitrogen atmosphere. The reaction was hydrolysed by the very slow addition of 2 M hydrochloric (40 mL) and crushed ice mixture and the aqueous layer was removed. Any solid residue in the reaction vessel was taken into 2 M hydrochloric acid (20 mL). The organic layer was extracted with 2 M hydrochloric acid (2 × 30 mL) and the acidic aqueous layers were combined, washed with ether (30 mL) and then poured into 28 % ammonia solution (50 mL) and crushed ice mixture. The white precipitate that forms was filtered off and dried under vacuum. The crude material was dissolved in the minimum volume of ethanol and water was added to precipitate out the product. The solid was filtered off and dried on the Kugelrohr apparatus for 1 d at 50 °C. 9-Methylquinidine was obtained as a white powder (0.64 g, 32 %).

Synthesis of 9-Methylquinidine (100) Using 3 M Methylmagnesium Bromide (10 equiv.) (Method G)

The synthesis of 9-methylquinidine was carried out by following the procedure by Woodward.[15] A solution of quinidinone (1.90 g, 5.90 mmol) in dry toluene (60 mL) was added dropwise over 50 mins to a stirred 3 M solution of methylmagnesium bromide (20 mL, 0.06 mol) in diethyl ether. The reaction mixture was stirred for 4 h at room temperature under a nitrogen atmosphere. The reaction was hydrolysed by the very slow addition of 2 M hydrochloric (40 mL) and crushed ice mixture and the aqueous layer was removed. Any solid residue in the reaction vessel was taken into 2 M hydrochloric acid (20 mL). The organic layer was extracted with 2 M hydrochloric acid (2 × 30 mL) and the acidic aqueous layers were combined, washed with ether (30 mL) and then poured into 28 % ammonia solution (50 mL) and crushed ice mixture. The white precipitate that forms was filtered off and dried under vacuum. The crude material was dissolved in the minimum volume of ethanol and water was added to precipitate out the product. The solid was filtered off and dried on the Kugelrohr apparatus for 1 d at 50 °C. 9-Methylquinidine was obtained as a white powder (0.50 g, 25 %).

Synthesis of 9-Methylquinidine (100) Using 1 M Methylmagnesium Bromide (10 equiv.) (Method H)

The synthesis of 9-methylquinidine was carried out by following the procedure by Woodward.[15] A 1 M solution of methylmagnesium bromide (15 mL, 0.015 mol) in diethyl ether was added dropwise over 50 mins to a stirred solution of quinidinone (0.49 g, 1.5 mmol) in dry toluene (15 mL). The reaction mixture was stirred overnight at room temperature under a nitrogen atmosphere. The reaction was hydrolysed by the very slow addition of 2 M hydrochloric (10 mL) and crushed ice mixture and the aqueous layer was removed. Any solid residue in the reaction vessel was taken into 2 M hydrochloric acid (10 mL). The acidic aqueous layers were combined, washed with ether (10 mL) and then poured into 28 %

ammonia solution (20 mL) and crushed ice mixture. The white precipitate that forms was filtered off and dried under vacuum. The crude material was dissolved in the minimum volume of ethanol and water was added to precipitate out the product. The solid was filtered off and dried on the Kugelrohr apparatus for 1 d at 50 °C. 9-Methylquinidine was obtained as a white powder (0.15 g, 28 %).

Synthesis of 9-Methylquinidine (100) Using 1 M Methylmagnesium Bromide (5 equiv.) (Method I)

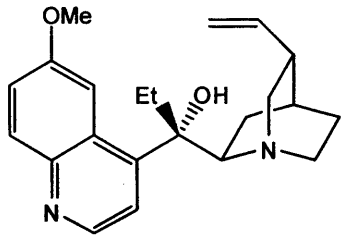
The synthesis of 9-methylquinidine was carried out by following the procedure by Woodward.[15] A solution of quinidinone (5.80 g, 0.018 mol) in dry toluene (120 mL) was added dropwise over 15 mins to a stirred 1 M solution of methylmagnesium bromide (90 mL, 0.09 mol) in diethyl ether. The reaction mixture was stirred overnight at room temperature under a nitrogen atmosphere. The reaction was hydrolysed by the very slow addition of 2 M hydrochloric (60 mL) and crushed ice mixture and the aqueous layer was removed. Any solid residue in the reaction vessel was taken into 2 M hydrochloric acid (30 mL). The organic layer was extracted with 2 M hydrochloric acid (3 × 30 mL) and the acidic aqueous layers were combined, washed with ether (30 mL) and then poured into 28 % ammonia solution (80 mL) and crushed ice mixture. The white precipitate that forms was filtered off and dried under vacuum. The crude material was dissolved in the minimum volume of ethanol and water was added to precipitate out the product. The solid was filtered off and dried on the Kugelrohr apparatus for 1 d at 50 °C. 9-Methylquinidine was obtained as a white powder (3.59 g, 60 %).

Synthesis of 9-Methylquinidine (100) Using 1 M Methylmagnesium Bromide (2 equiv.) (Method J)

The synthesis of 9-methylquinidine was carried out by following the procedure by Woodward.[15] A solution of quinidinone (5.80 g, 0.018 mol) in dry toluene (120 mL) was added dropwise over 15 mins to a stirred 1 M solution of methylmagnesium bromide (36 mL, 0.036 mol) in diethyl ether. The reaction mixture was stirred overnight at room temperature under a nitrogen atmosphere. The reaction was hydrolysed by the very slow addition of 2 M hydrochloric (60 mL) and crushed ice mixture and the aqueous layer was removed. Any solid residue in the reaction vessel was taken into 2 M hydrochloric acid (30 mL). The organic layer was extracted with 2 M hydrochloric acid (3 × 30 mL) and the acidic aqueous layers were combined, washed with ether (30 mL) and then poured into 28 % ammonia solution (80 mL) and crushed ice mixture. The white precipitate that forms was filtered off and dried under vacuum. The crude material was dissolved in the minimum volume of ethanol and water was

added to precipitate out the product. The solid was filtered off and dried on the Kugelrohr apparatus for 1 d at 50 °C. 9-Methylquinidine was obtained as a white powder (3.47 g, 57 %).

Synthesis of 9-Ethylquinidine (102) Using Ethylmagnesium Bromide (10 equiv.) (Method A)



The synthesis of 9-ethylquinidine was carried out using the procedure described by Woodward.[15] A solution of quinidinone (1.90 g, 6.0 mmol) in dry toluene (60 mL) was added dropwise over 30 mins to a stirred 1 M solution of ethylmagnesium bromide in diethyl ether (60 mL, 0.06 mol) at room temperature. The reaction was stirred at room temperature under a nitrogen atmosphere overnight. The reaction mixture was hydrolysed by the slow addition of 2 M hydrochloric acid (40 mL) and crushed ice mixture. The aqueous layer was removed and the organic layer was extracted with 2 M hydrochloric acid (2 × 30 mL). The aqueous layers were combined, washed with ether (20 mL) and poured into a 28 % ammonia solution (50 mL) and crushed ice mixture with rapid stirring. The yellow/white precipitate that forms on addition was filtered off and dried under oil pump vacuum. The crude solid was then dissolved in the minimum volume of ethanol and the insoluble material was filtered off. To the filtrate, a small amount of water was added until the solution turned cloudy. The solid that resulted was filtered off and dried under vacuum to yield 9-ethylquinidine as a pale brown solid (0.48 g, 24 %). M.p. 68-73 °C. $[\alpha]_D$ (MeOH) 108.7° (c = 1). (Found: C, 72.64; H, 8.42; N, 7.62. $C_{22}H_{28}N_2O_2.{}^1/_2H_2O$ requires C, 73.09; H, 8.10; N, 7.75). δ_H (C_6D_6, 400 MHz, 347 K) 0.92-1.01 (1H, m, NCH_2CHH), 1.26-1.41 (4H, m, NCH_2CHH, CH_2CH_3), 1.53-1.58 (1H, m, NCH_2CH_2CH), 1.79-1.87 (1H, m, NCH_2CHH), 1.98-2.07 (1H, m, NCH_2CHH), 2.30-2.41 (1H, m, NCH_2CH), 2.52-2.62 (1H, m, $NCHH$), 2.67-2.74 (1H, m, $NCHH$), 2.74-2.83 (2H, m, CH_2CH_3), 2.89-2.97 (1H, m, $NCHH$), 3.14-3.22 (1H, m, $NCHH$), 3.28-3.36 (1H, m, NCH), 3.64 (3H, s, OCH_3), 4.90 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^2J_{HH}$ 1.6 Hz, $^4J_{HH}$ 1.2 Hz, CH=C*H*H), 4.98 (1H, ddd, $^3J_{HH}$ 10.2 Hz, $^2J_{HH}$ 1.6 Hz, $^4J_{HH}$ 1.2 Hz, CH=C*H*H), 5.80 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^3J_{HH}$ 10.2 Hz, $^3J_{HH}$ 7.0 Hz, $CH{=}CH_2$), 7.35 (1H, dd, $^3J_{HH}$ 9.0 Hz, $^4J_{HH}$ 2.7 Hz, ArH(7')), 7.59 (1H, br. s, ArH(3')), 8.03 (1H, br. s, ArH(5')), 8.39 (1H, d, $^3J_{HH}$ 9.0 Hz, ArH(8')), 8.89 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_H (C_6D_6, 300 MHz) 0.88 (1H, br. s, NCH_2CHH), 1.15-1.19 (2H, br. m, NCH_2CHH), 1.20-1.28 (3H, br. m, CH_2CH_3), 1.47-1.54 (1H, br. m, NCH_2CH_2CH), 1.75-1.86 (1H, br. m, NCH_2CHH), 1.93-2.00 (1H, br. m, NCH_2CHH), 2.36 (1H, br. s, NCH_2CH), 2.60-2.92 (5H, m, $NCHH$, CH_2CH_3), 3.25 (1H, br. s, NCH), 3.52 (3H, br. s, OCH_3), 4.88-5.03 (2H, br. m, CH=C*H*H), 5.85 (1H, br. s, $CH{=}CH_2$), 7.31 (1H, br. s, ArH(7')), 7.57 (1H, br. s, ArH(3')), 7.88 (1H, br. s, ArH(5')), 8.44 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.89 (1H, br. s,

ArH(2')). δ_C (C_6D_6, 400 MHz, 347 K) 7.7 (CH_3), 22.3 (CH_2), 26.5 (CH_2), 29.1 (CH), 33.7 (CH_2), 40.1 (CH), 50.1 (CH_2), 51.3 (CH_2), 54.7 (CH_3), 63.5 (CH), 77.4 (C), 105.3 (CH), 113.8 (CH_2), 120.0 (CH), 121.1 (CH), 127.0 (C), 128.3 (C), 133.0 (CH), 140.4 (CH), 146.3 (C), 147.5 (CH), 157.2 (C). m/z (ES^+) 353 ($[M+H]^+$, 100%). HRMS (FAB) 353.22294 ($C_{22}H_{29}N_2O_2$ requires 353.22290).

Synthesis of 9-Ethylquinidine (102) Using Ethylmagnesium Bromide (5 equiv.) (Method B)

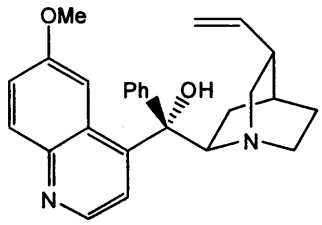
The synthesis of 9-ethylquinidine was carried using the procedure described by Woodward.[15] A solution of quinidinone (1.90 g, 6.0 mmol) in dry toluene (60 mL) was added dropwise over 30 mins to a stirred 1 M solution of ethylmagnesium bromide in diethyl ether (30 mL, 0.03 mol) at room temperature. The reaction mixture was stirred at room temperature under a nitrogen atmosphere overnight. The reaction mixture was hydrolysed by the slow addition of 2 M hydrochloric acid (40 mL) and crushed ice mixture. The aqueous layer was removed and the organic layer was extracted with 2 M hydrochloric acid (2 × 30 mL). The aqueous layers were combined, washed with ether (20 mL) and poured into a 28 % ammonia solution (50 mL) and crushed ice mixture with rapid stirring. The yellow/white precipitate that forms on addition was filtered off and dried under oil pump vacuum. The crude solid was then dissolved in the minimum volume of ethanol and the insoluble material was filtered off. To the filtrate, a small amount of water was added until the solution turned cloudy. The solid that resulted was filtered off and dried under vacuum to yield 9-ethylquinidine as a pale brown solid (0.31 g, 16 %).

Synthesis of 9-Ethylquinidine (102) Using Ethylmagnesium Bromide (2 equiv.) (Method C)

The synthesis of 9-ethylquinidine was carried out using the procedure described by Woodward.[15] A solution of quinidinone (4.83 g, 0.015 mmol) in dry toluene (100 mL) was added dropwise over 1 h to a stirred 1 M solution of ethylmagnesium bromide in ether (30 mL, 0.03 mol) at room temperature. The reaction mixture was stirred at room temperature under a nitrogen atmosphere overnight. The reaction mixture was hydrolysed by the slow addition of 2 M hydrochloric acid (40 mL) and crushed ice mixture. The aqueous layer was removed and the organic layer was extracted with 2 M hydrochloric acid (2 × 30 mL). The aqueous layers were combined, washed with ether (20 mL) and poured into a 28 % ammonia solution (50 mL) and crushed ice mixture with rapid stirring. The yellow/white precipitate that forms on addition was filtered off and dried under oil pump vacuum. The crude solid was then dissolved in the minimum volume of ethanol and the insoluble material was filtered off.

To the filtrate, a small amount of water was added until the solution turned cloudy. The solid that resulted was filtered off and dried under vacuum to yield 9-ethylquinidine as a pale brown solid (0.20 g, 4 %).

Synthesis of 9-Phenylquinidine (103) Using Phenylmagnesium Bromide (10 equiv.) (Method A)



The synthesis of 9-phenylquinidine was carried out based on the procedure described by Woodward.[15] A solution of quinidinone (1.90 g, 6.0 mmol) in dry toluene (60 mL) was added dropwise over 30 mins to a stirred 1 M solution of phenylmagnesium bromide in diethyl ether (60 mL, 0.06 mol) at room temperature. The reaction mixture was stirred at room temperature under a nitrogen atmosphere overnight. The reaction was hydrolysed by the slow addition of 2 M hydrochloric acid (40 mL) and crushed ice mixture. The aqueous layer was removed and the organic layer was extracted with 2 M hydrochloric acid (2 × 30 mL). The aqueous layers were combined, washed with ether (20 mL) and poured into a 28 % ammonia solution (50 mL) and crushed ice mixture with rapid stirring. The yellow/white precipitate that forms on addition was filtered off and dried under oil pump vacuum. The crude solid was then dissolved in the minimum volume of ethanol and a small amount of water was added until the solution turned cloudy. The solid that resulted was filtered off and dried under oil pump vacuum. To remove the ethanol, the solid was dissolved in chloroform (40 mL), washed with water (3 × 30 mL), dried over magnesium sulphate, filtered and dried under oil pump vacuum to yield the new compound 9-phenylquinidine as a white solid (0.58 g, 25 %). M.p. 184-186 °C. $[\alpha]_D$ (MeOH) 129.6° (c = 1). (Found: C, 78.04; H, 6.94; N, 7.04. $C_{26}H_{28}N_2O_2$ requires C, 77.97; H, 7.05; N, 6.99). δ_H ($CDCl_3$, 400 MHz, 326 K) 1.22-1.31 (1H, m, NCH_2CHH), 1.62-1.70 (2H, m, NCH_2CHH), 1.72-1.82 (2H, m, NCH_2CH_2CH, NCH_2CHH), 2.12-2.20 (1H, m, NCH_2CH), 2.79-2.88 (2H, m, $NCHH$), 2.90-2.99 (1H, m, $NCHH$), 3.26-3.34 (1H, m, $NCHH$), 3.51 (3H, s, OCH_3), 4.00-4.07 (1H, m, NCH), 4.72 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^2J_{HH}$ 1.6 Hz, $^4J_{HH}$ 1.2 Hz, CH=C*H*H), 4.84 (1H, ddd, $^3J_{HH}$ 10.6 Hz, $^2J_{HH}$ 1.6 Hz, $^4J_{HH}$ 1.2 Hz, CH=C*H*H), 5.51 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^3J_{HH}$ 10.6 Hz, $^3J_{HH}$ 7.0 Hz, C*H*=CH_2), 6.87 (1H, s, ArH(5')), 7.21 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.7 Hz, ArH(7')), 7.26-7.36 (3H, m, ArH(3"), ArH(4")), 7.52-7.55 (2H, m, ArH(2")), 7.99 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.10 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(3')), 8.86 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_H ($CDCl_3$, 300 MHz) 1.14-1.22 (1H, m, NCH_2CHH), 1.59-1.72 (2H, m, NCH_2CHH, NCH_2CH_2CH), 1.97-2.07 (1H, m, NCH_2CHH), 2.59-2.67 (2H, m, NCH_2CHH, NCH_2CH), 2.77-2.87 (1H, m, $NCHH$), 3.11-3.21 (1H, m, $NCHH$), 3.38 (3H, s, OCH_3), 3.61-3.70 (2H, m, $NCHH$), 3.85-3.93 (1H, m, NCH), 4.54 (1H, ddd, $^3J_{HH}$ 17.5 Hz, $^2J_{HH}$ 1.2 Hz,

$^4J_{HH}$ 0.9 Hz, CH=C*H*H), 4.68 (1H, ddd, $^3J_{HH}$ 10.5 Hz, $^2J_{HH}$ 1.2 Hz, $^4J_{HH}$ 0.9 Hz, CH=C*H*H), 5.34 (1H, ddd, $^3J_{HH}$ 17.5 Hz, $^3J_{HH}$ 10.5 Hz, $^3J_{HH}$ 7.3 Hz, C*H*=CH_2), 6.72 (1H, br. s, ArH(5')), 7.10 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.15-7.27 (3H, m, ArH(3"), ArH(4")), 7.39-7.43 (2H, m, ArH(2")), 7.87 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.01 (1H, br. s, ArH(3')), 8.77 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_C ($CDCl_3$, 400 MHz, 326 K) 23.7 (CH_2), 26.1 (CH_2), 29.0 (CH), 39.6 (CH), 49.7 (CH_2), 50.7 (CH_2), 55.1 (CH_3), 61.4 (CH), 79.5 (C), 105.0 (CH), 114.4 (CH_2), 120.4 (CH), 120.9 (CH), 127.2 (CH), 127.6 (CH), 128.4 (C), 128.5 (CH), 131.6 (CH), 139.4 (CH), 145.4 (C), 147.3 (C), 147.4 (CH), 149.1 (C), 156.6 (C). δ_C ($CDCl_3$, 300 MHz) 23.8 (CH_2), 26.2 (CH_2), 29.0 (CH), 39.7 (CH), 49.4 (CH_2), 50.8 (CH_2), 55.2 (CH_3), 61.3 (br.s, CH), 104.9 (CH), 114.3 (CH_2), 120.5 (CH), 121.0 (CH), 127.1 (CH), 127.6 (CH), 128.6 (CH), 131.4 (CH), 139.5 (CH), 147.4 (CH), 149.5 (C), 156.3 (C), three aromatic quaternary carbons and quaternary carbon 9 absent due to broadening. m/z (ES^+) 401 ($[M+H]^+$, 100%). HRMS (FAB) 401.22284 ($C_{26}H_{29}N_2O_2$ requires 401.22290).

Synthesis of 9-Phenylquinidine (103) Using Phenylmagnesium Bromide (5 equiv.) (Method B)

The synthesis of 9-phenylquinidine was carried out based on the procedure described by Woodward.[15] A solution of quinidinone (1.90 g, 6.0 mmol) in dry toluene (60 mL) was added dropwise over 30 mins to a stirred 1 M solution of phenylmagnesium bromide in diethyl ether (30 mL, 0.03 mol) at room temperature. The reaction mixture was stirred at room temperature under a nitrogen atmosphere overnight. The reaction was hydrolysed by the slow addition of 2 M hydrochloric acid (40 mL) and crushed ice mixture. The aqueous layer was removed and the organic layer was extracted with 2 M hydrochloric acid (2 × 30 mL). The aqueous layers were combined, washed with ether (20 mL) and poured into a 28 % ammonia solution (80 mL) and crushed ice mixture with rapid stirring. The yellow/white precipitate that forms on addition was filtered off and dried under oil pump vacuum. The crude solid was then dissolved in the minimum volume of ethanol and a small amount of water was added until the solution turned cloudy. The solid that resulted was filtered off and dried under oil pump vacuum. To remove the ethanol, the solid was dissolved in chloroform (40 mL), washed with water (3 × 30 mL), dried over magnesium sulphate, filtered and dried under oil pump vacuum to yield 9-phenylquinidine as a white solid (0.38 g, 16 %).

Synthesis of 9-Phenylquinidine (103) Using Phenylmagnesium Bromide (2 equiv.) (Method C)

The synthesis of 9-phenylquinidine was carried out based on the procedure described by Woodward.[15] A solution of quinidinone (4.84 g, 0.015 mol) in dry toluene (60 mL) was

added dropwise over 1 h to a stirred 1 M solution of phenylmagnesium bromide in diethyl ether (30 mL, 0.03 mol) at room temperature. The reaction mixture was stirred at room temperature under a nitrogen atmosphere overnight. The reaction was hydrolysed by the slow addition of 2 M hydrochloric acid (40 mL) and crushed ice mixture. The aqueous layer was removed and the organic layer was extracted with 2 M hydrochloric acid (2 × 30 mL). The aqueous layers were combined, washed with ether (20 mL) and poured into a 28 % ammonia solution (80 mL) and crushed ice mixture with rapid stirring. The yellow/white precipitate that forms on addition was filtered off and dried under oil pump vacuum. The crude solid was then dissolved in the minimum volume of ethanol and a small amount of water was added until the solution turned cloudy. The solid that resulted was filtered off and dried under oil pump vacuum. To remove the ethanol, the solid was dissolved in chloroform (40 mL), washed with water (3 × 30 mL), dried over magnesium sulphate, filtered and dried under oil pump vacuum to yield 9-phenylquinidine as a white solid (1.33 g, 22 %).

Synthesis of 9-Phenylquinidine (103) Using Phenylmagnesium Bromide (2 equiv.) for 3 Days (Method D)

The synthesis of 9-phenylquinidine was carried out based on the procedure described by Woodward.[15] A solution of quinidinone (4.84 g, 0.015 mol) in dry toluene (60 mL) was added dropwise over 30 mins to a stirred 1 M solution of phenylmagnesium bromide in diethyl ether (30 mL, 0.03 mol) at room temperature. The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 3 d. The reaction was hydrolysed by the slow addition of 2 M hydrochloric acid (40 mL) and crushed ice mixture. The aqueous layer was removed and the organic layer was extracted with 2 M hydrochloric acid (2 × 30 mL). The aqueous layers were combined, washed with ether (20 mL) and poured into a 28 % ammonia solution (80 mL) and crushed ice mixture with rapid stirring. The yellow/white precipitate that forms on addition was filtered off and dried under oil pump vacuum. The crude solid was then dissolved in the minimum volume of ethanol and a small amount of water was added until the solution turned cloudy. The solid that resulted was filtered off and dried under oil pump vacuum. To remove the ethanol, the solid was dissolved in chloroform (40 mL), washed with water (3 × 30 mL), dried over magnesium sulphate, filtered and dried under oil pump vacuum to yield 9-phenylquinidine as a white solid (1.16 g, 19 %).

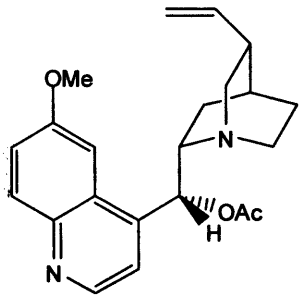
Synthesis of 9-Phenylquinidine (103) Using Phenylmagnesium Bromide (2 equiv.) at Reflux (Method E)

The synthesis of 9-phenylquinidine was carried out based on the procedure described by Woodward.[15] A solution of quinidinone (2.42 g, 7.50 mmol) in dry toluene (30 mL) was

added dropwise over 30 mins to a stirred 1 M solution of phenylmagnesium bromide in diethyl ether (15 mL, 0.015 mol) at room temperature. The reaction mixture was refluxed under a nitrogen atmosphere overnight. The reaction was hydrolysed by the slow addition of 2 M hydrochloric acid (20 mL) and crushed ice mixture. The aqueous layer was removed and the organic layer was extracted with 2 M hydrochloric acid (2 × 15 mL). The aqueous layers were combined, washed with ether (10 mL) and poured into a 28 % ammonia solution (40 mL) and crushed ice mixture with rapid stirring. The yellow/white precipitate that forms on addition was filtered off and dried under oil pump vacuum. The crude solid was then dissolved in the minimum volume of ethanol and a small amount of water was added until the solution turned cloudy. The solid that resulted was filtered off and dried under oil pump vacuum. To remove the ethanol, the solid was dissolved in chloroform (20 mL), washed with water (2 × 10 mL), dried over magnesium sulphate, filtered and dried under oil pump vacuum to yield 9-phenylquinidine as a white solid (0.19 g, 6 %).

5.4 Protection With an Acetyl Group

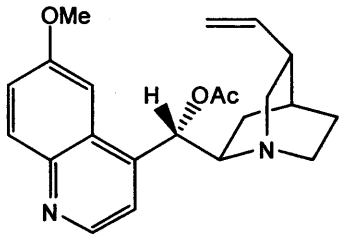
Synthesis of Quinine Acetate (110)



Quinine acetate was synthesised by following the procedure described by Sharpless.[17] Pyridine (0.12 mL, 1.50 mmol) and acetyl chloride (0.12 mL, 1.69 mmol) were added to a stirred solution of quinine (0.52 g, 1.54 mmol) in dichloromethane (10 mL) at room temperature. The solution was stirred at room temperature for 4 h. Water (0.5 mL) was added to the reaction mixture and then stirred for a further 30 mins. The reaction solution was then poured into a 2 M solution of potassium carbonate (15 mL) and extracted with dichloromethane (3 × 15 mL). The organic phases were combined, dried over potassium carbonate and the solvent was removed. The crude product was purified on a silica gel column (30 g) eluted with ethyl acetate/ethanol/triethylamine (90/8/2) (120 mL) and then ethyl acetate/ethanol/triethylamine (83/15/2) (150 mL). All fractions containing the product (as determined by TLC) were combined, the solvent was removed and the product was dried under oil pump vacuum to yield quinine acetate as a white powder (0.35 g, 67 %). M.p. 116 °C (lit.,[18] 116-117 °C). $[\alpha]_D$ (MeOH) –27.7 ° (c = 1). δ_H ($CDCl_3$) 1.46 (2H, m, NCH_2CHH), 1.65 (1H, m, NCH_2CH_2CH), 1.80 (2H, m, NCH_2CHH), 2.05 (3H, s, CH_3), 2.21 (1H, m, NCH_2CH), 2.56 (2H, m, $NCHH$), 2.98 (1H, m, $NCHH$), 3.03 (1H, m, NCH), 3.31 (1H, m, $NCHH$), 3.89 (3H, s, OCH_3), 4.93 (1H, ddd, $^3J_{HH}$ 10.2, $^2J_{HH}$ 1.6, $^4J_{HH}$ 1.2, CH=C*H*H), 4.95 (1H, dt, $^3J_{HH}$ 17.2, $^2J_{HH} = {}^4J_{HH}$ 1.5, CH=C*H*H), 5.77 (1H, ddd, $^3J_{HH}$ 17.2, $^3J_{HH}$ 10.5, $^3J_{HH}$ 7.3, C*H*=CH_2), 6.42 (1H, d, $^3J_{HH}$ 7.3 Hz, C*H*OC(O)CH_3), 7.28 (1H, d,

$^3J_{HH}$ 4.7 Hz, ArH(3')), 7.31 (1H, dd, $^3J_{HH}$ 9.1 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.37 (1H, d, $^4J_{HH}$ 2.6 Hz, ArH(5')), 7.92 (1H, d, $^3J_{HH}$ 9.1 Hz, ArH(8')), 8.67 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_C ($CDCl_3$) 21.1 (CH_3), 24.4 (CH_2), 27.6 (CH), 27.8 (CH_2), 39.7 (CH), 42.5 (CH_2), 55.7 (CH_3), 56.6 (CH_2), 59.1 (CH), 73.8 (CH), 101.5 (CH), 114.5 (CH_2), 118.9 (CH), 121.8 (CH), 127.1 (C), 131.8 (CH), 141.8 (CH), 143.6 (C), 144.8 (C), 147.5 (CH), 157.9 (C), 170.1 (C=O). m/z (ES^+) 367 ($[M+H]^+$, 100%). HRMS (FAB) 367.20224 ($C_{22}H_{27}N_2O_3$ requires 367.20217).

Synthesis of Quinidine Acetate (111)



Quinidine acetate was synthesised by following the procedure described by Sharpless.[17] Pyridine (0.6 mL, 7.45 mmol) and acetyl chloride (0.57 mL, 8.03 mmol) were added to a stirred solution of quinidine (2.42 g, 7.45 mmol) in dichloromethane (35 mL) at room temperature. The solution was stirred at room temperature for 4 h. Water (1 mL) was added to the reaction mixture and then stirred for a further 30 mins. The reaction solution was then poured into a 2 M solution of potassium carbonate (50 mL) and extracted with dichloromethane (2 × 60 mL). The organic phases were combined, dried over potassium carbonate and the solvent was removed. The crude product was purified on a silica gel column (30 g) eluted with ethyl acetate/ethanol/triethylamine (90/8/2) (120 mL) and then ethyl acetate/ethanol/triethylamine (83/15/2) (100 mL). All fractions containing the product (as determined by TLC) were combined, the solvent was removed and the product was dried under oil pump vacuum to yield quinidine acetate as a white powder (1.88 g, 69 %). M.p. 97 °C (lit.,[19] 97-99 °C). $[\alpha]_D$ (MeOH) 135.8 ° (c = 1). δ_H ($CDCl_3$) 1.46 (3H, m, NCH_2CHH), 1.75 (1H, m, NCH_2CHH), 1.79 (1H, m, NCH_2CH_2CH), 2.07 (3H, s, CH_3), 2.20 (1H, m, NCH_2CH), 2.70 (2H, m, $NCHH$), 2.85 (2H, m, $NCHH$), 3.22 (1H, m, NCH), 3.89 (3H, s, OCH_3), 5.03 (2H, m, $CH=CHH$), 5.96 (1H, ddd, $^3J_{HH}$ 17.0, $^3J_{HH}$ 10.5, $^3J_{HH}$ 7.3, $CH=CH_2$), 6.46 (1H, d, $^3J_{HH}$ 6.7 Hz, $CHOC(O)CH_3$), 7.27 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(3')), 7.30 (1H, dd, $^3J_{HH}$ 9.1 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.33 (1H, d, $^4J_{HH}$ 2.6 Hz, ArH(5')), 7.94 (1H, d, $^3J_{HH}$ 9.1 Hz, ArH(8')), 8.66 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_C ($CDCl_3$) 21.0 (CH_3), 23.3 (CH_2), 26.3 (CH_2), 27.8 (CH), 39.7 (CH), 49.1 (CH_2), 49.8 (CH_2), 55.5 (CH_3), 58.9 (CH), 73.5 (CH), 101.6 (CH), 114.8 (CH_2), 118.5 (CH), 121.8 (CH), 127.0 (C), 131.7 (CH), 140.3 (CH), 143.8 (C), 144.6 (C), 147.4 (CH), 157.9 (C), 169.9 (C=O). m/z (ES^+) 367 ($[M+H]^+$, 100%). HRMS (FAB) 367.20214 ($C_{22}H_{27}N_2O_3$ requires 367.20217).

Attempted Synthesis of 9-Methylquinidine Acetate (112) (Method A)

The synthesis of 9-methylquinidine acetate was attempted by following the procedure described by Sharpless.[17] Pyridine (0.08 mL, 0.95 mmol) and acetyl chloride (0.08 mL, 1.12 mmol) were added to a stirred solution of 9-methylquinidine (0.32 g, 0.95 mmol) in dichloromethane (15 mL) at room temperature. The reaction mixture was stirred at room temperature for 4 h then water (1 mL) was added and the reaction mixture was stirred for a further 30 mins. After pouring the reaction mixture into 2 M K_2CO_3 solution (15 mL), the organic layer was removed. The aqueous layer was then extracted with dichloromethane (2 × 15 mL). The organic layers were combined, dried over K_2CO_3 and the solvent was removed. The ^{1}H NMR spectrum of the reaction product showed that no reaction had occurred.

Attempted Synthesis of 9-Methylquinidine Acetate (112) (Method B)

The synthesis of 9-methylquinidine acetate was attempted by following the procedure described by Sharpless.[17] Pyridine (0.08 mL, 0.95 mmol) and acetyl chloride (0.08 mL, 1.12 mmol) were added to a stirred solution of 9-methylquinidine (0.32 g, 0.95 mmol) in dichloromethane (15 mL) at room temperature. The reaction mixture was refluxed for 4 h then water (1 mL) was added and the reaction was stirred for a further 30 mins in which time the reaction mixture was allowed to cool to room temperature. After pouring the reaction mixture into 2 M K_2CO_3 solution (15 mL), the organic layer was removed. The aqueous layer was then extracted with dichloromethane (2 × 15 mL). The organic layers were combined, dried over K_2CO_3 and the solvent was removed. The ^{1}H NMR spectrum of the reaction product showed that no reaction had occurred.

Attempted Synthesis of 9-Methylquinidine Acetate (112) (Method C)

The synthesis of 9-methylquinidine acetate was attempted by following the procedure described by Kaiser.[20] A 1.6 M solution of ^{n}BuLi in hexane (0.7 mL, 1.15 mmol) was added slowly over a few minutes to a stirred solution of 9-methylquinidine (0.38 g, 1.12 mmol) in dry THF (10 mL). The reaction was left to stir at room temperature for 30 mins under a nitrogen atmosphere. A solution of acetyl chloride (0.09 mL, 1.15 mmol) in dry THF (5 mL) was then added dropwise and the reaction mixture was refluxed for 1 h. After cooling the reaction mixture to 0 °C, water (10 mL) was added slowly. The organic layer was removed and the aqueous layer was extracted with ether (3 × 5 mL). The organic layers were combined, dried over $MgSO_4$ and the solvent was removed. The ^{1}H NMR spectrum showed that a trace amount of the desired product had formed, but it was not isolated.

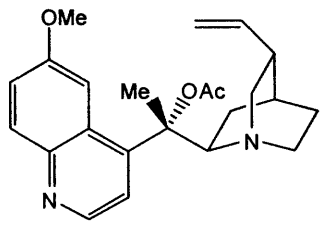
Synthesis of 9-Methylquinidine Acetate (112) (Method D)

The synthesis of 9-methylquinidine acetate was attempted by following the procedure described by Kaiser.[20] A 1.6 M solution of ^{n}BuLi in hexane (1.1 mL, 1.76 mmol) was added slowly over a few minutes to a stirred solution of 9-methylquinidine (0.58 g, 1.70 mmol) in dry THF (15 mL). The reaction mixture was stirred at room temperature for 30 mins under a nitrogen atmosphere. A solution of acetyl chloride (0.13 mL, 1.76 mmol) in dry THF (5 mL) was then added dropwise and the reaction mixture was refluxed for 4.5 h. After cooling the reaction mixture to 0 °C, water (15 mL) was added slowly. The organic layer was removed and the aqueous layer was extracted with ether (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$ and the solvent was removed. The sample was dissolved in the minimum volume of chloroform, loaded onto a silica gel (30 g) column and eluted with chloroform/methanol (95/5) (300 mL). All fractions containing the product were combined and the solvent was removed. The ^{1}H NMR spectrum showed that there was still an impurity present (possibly AcOH). So the sample was dissolved in ether (15 mL), washed with water (2 × 10 mL), dried over $MgSO_4$ and the solvent was removed to yield a trace amount of fairly pure 9-methylquinidine acetate.

Synthesis of 9-Methylquinidine Acetate (112) (Method E)

The synthesis of 9-methylquinidine acetate was attempted by adapting the procedure described by Kaiser.[20] A 1.6 M solution of ^{n}BuLi in hexane (4.2 mL, 6.72 mmol) was added slowly over a few minutes to a stirred solution of 9-methylquinidine (2.21 g, 6.54 mmol) in dry THF (60 mL). The reaction mixture was stirred at room temperature for 30 mins under a nitrogen atmosphere. A solution of acetyl chloride (0.72 mL, 10.08 mmol) in dry THF (20 mL) was then added dropwise and the reaction mixture was refluxed overnight. After cooling to 0 °C, water (60 mL) was added slowly to the reaction mixture, the organic layer was removed and the aqueous layer was extracted with ether (3 × 40 mL). The organic layers were combined, washed with water (40 mL), dried over $MgSO_4$ and the solvent was removed. The sample was then dissolved in the minimum volume of chloroform, loaded onto a silica gel (50 g) column and eluted with chloroform/ethyl acetate/triethylamine (10/10/3) (230 mL). All fractions containing the product were combined and the solvent was removed. The ^{1}H NMR spectrum showed that the sample contained 9-methylquinidine acetate and both diastereoisomers of quinidinone. No suitable solvent system could be found to separate the three compounds.

Synthesis of 9-Methylquinidine Acetate (112) (Method F)



The synthesis of 9-methylquinidine acetate was carried out by adapating the procedure described by Kaiser.[20] A 1.6 M solution of ^{n}BuLi in hexane (5.6 mL, 9.00 mmol) was added slowly over a few minutes to a stirred solution of 9-methylquinidine (3.00 g, 8.88 mmol) in dry ether (300 mL). The reaction was stirred at room temperature for 30 mins under a nitrogen atmosphere. A solution of acetyl chloride (0.95 mL, 13.3 mmol) in dry ether (20 mL) was then added dropwise and refluxed for 3 days. Since most of the ether evaporated off, additional ether was added (300 mL). The reaction mixture was left to cool to 0 °C then water (90 mL) was added slowly. The organic layer was removed and the aqueous layer was extracted with ether (3 × 50 mL). The organic layers were combined, washed with water (60 mL), dried over $MgSO_4$ and the solvent was removed. The sample was dissolved in the minimum volume of chloroform, loaded onto a silica gel (60 g) column and eluted with chloroform (150 mL) to remove one impurity. The column was then eluted with chloroform/methanol (99/1) (1 L) to remove the product. All fractions containing the product were combined and the solvent was removed to yield the new compound, 9-methylquinidine acetate, as a colourless oil (0.89 g, 26 %). $[\alpha]_D$ (MeOH) 108.0° (c = 1). δ_H (C_6D_6, 400 MHz, 337 K) 1.23-1.29 (2H, m, NCH_2CHH), 1.60-1.64 (1H, m, NCH_2CH_2CH), 1.93 (3H, s, $C(O)CH_3$), 2.00-2.07 (3H, m, NCH_2CHH, NCH_2CH), 2.29 (3H, s, CH_3), 2.59-2.68 (1H, m, $NCHH$), 2.76-2.90 (2H, m, $NCHH$), 3.02-3.09 (1H, m, $NCHH$), 3.23-3.32 (1H, m, NCH), 3.66 (3H, s, OCH_3), 4.98 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^3J_{HH}$ 1.6 Hz, $^3J_{HH}$ 1.6 Hz, CH=CHH), 5.08 (1H, ddd, $^3J_{HH}$ 10.2 Hz, $^2J_{HH}$ 1.6 Hz, $^4J_{HH}$ 1.6 Hz, CH=CHH), 5.93 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^3J_{HH}$ 10.2 Hz, $^3J_{HH}$ 7.0 Hz, $CH=CH_2$), 7.22 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(3')), 7.32 (1H, dd, $^3J_{HH}$ 9.0 Hz, $^4J_{HH}$ 2.7 Hz, ArH(7')), 7.99 (1H, d, $^4J_{HH}$ 2.7 Hz, ArH(5')), 8.34 (1H, d, $^3J_{HH}$ 9.0 Hz, ArH(8')), 8.82 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_H (C_6D_6, 300 MHz) 1.27-1.30 (2H, br. m, NCH_2CHH), 1.39-1.44 (1H, br. m, NCH_2CH_2CH), 1.72 (3H, s, $C(O)CH_3$), 1.78-1.87 (3H, br. m, NCH_2CHH, NCH_2CH), 2.12 (3H, br. s, CH_3), 2.38-2.50 (2H, m, $NCHH$), 2.58-2.72 (2H, br. m, $NCHH$), 2.84-2.94 (1H, br. m, NCH), 3.42 (3H, s, OCH_3), 4.82 (1H, d, $^3J_{HH}$ 17.2 Hz, CH=CHH), 4.91 (1H, ddd, $^3J_{HH}$ 10.5 Hz, $^2J_{HH}$ 1.5 Hz, $^4J_{HH}$ 0.9 Hz, CH=CHH), 5.75 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^3J_{HH}$ 10.5 Hz, $^3J_{HH}$ 7.0 Hz, $CH=CH_2$), 6.99 (1H, br. s, ArH(3')), 7.14 (1H, dd, $^3J_{HH}$ 9.1 Hz, $^4J_{HH}$ 2.9 Hz, ArH(7')), 7.81 (1H, br. s, ArH(5')), 8.21 (1H, d, $^3J_{HH}$ 9.1 Hz, ArH(8')), 8.67 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_C (C_6D_6, 400 MHz, 337 K) 21.3 (CH_3), 22.4 (CH_2), 25.9 (CH_3), 26.1 (CH_2), 28.9 (CH), 39.8 (CH), 49.9 (CH_2), 51.3 (CH_2), 54.8 (CH_3), 64.4 (CH), 87.1 (C), 105.0 (CH), 113.8 (CH_2), 119.7 (CH), 120.3 (CH), 127.1 (C), 132.9 (CH), 140.8 (CH), 146.1 (C), 146.9 (C), 147.3 (CH), 157.3 (C), 167.8 (C=O). δ_C (C_6D_6, 300 MHz) 20.1 (CH_3), 21.1 (CH_2), 24.8 (br. s, CH_3), 24.8 (CH_2), 27.6

(CH), 38.6 (CH), 48.6 (CH_2), 50.1 (CH_2), 53.6 (CH_3), 85.8 (C), 103.5 (CH), 112.8 (CH_2), 118.6 (CH), 119.4 (CH), 126.7 (C), 131.7 (CH), 139.6 (CH), 144.8 (C), 145.8 (C), 146.3 (CH), 156.1 (C), 166.8 (C=O) carbon 8 absent due to line broadening. m/z (ES^+) 381 ($[M+H]^+$, 100%). HRMS (FAB) 381.21792 ($C_{23}H_{29}N_2O_3$ requires 381.21792).

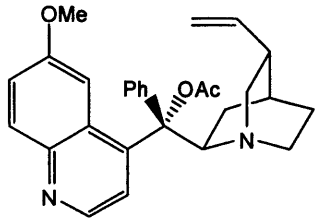
Attempted Synthesis of 9-Phenylquinidine Acetate (113) (Method A)

The synthesis of 9-phenylquinidine acetate was carried out by following the procedure described by Kaiser.[20] A 1.6 M solution of ^{n}BuLi in hexane (1.6 mL, 2.50 mmol) was added slowly over a few minutes to a stirred solution of 9-phenylquinidine (1.00 g, 2.50 mmol) in dry ether (70 mL). The reaction mixture was stirred at room temperature for 30 mins under a nitrogen atmosphere. Acetyl chloride (0.3 mL, 3.75 mmol) was then added dropwise and the reaction mixture was refluxed for 7 days. Since most of the ether had evaporated, additional ether was added (70 mL). The reaction mixture was left to cool to 0 °C then water (30 mL) was added slowly. The organic layer was removed and the aqueous layer was extracted with ether (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$ and the solvent was removed. The ^{1}H NMR spectrum of the residue showed a mixture of both 9-phenylquinidine acetate and 9-phenylquinidine with the majority being the latter compound. Unfortunately a suitable solvent system for the separation of the two compounds by column chromatography could not be found.

Attempted Synthesis of 9-Phenylquinidine Acetate (113) (Method B)

The synthesis of 9-phenylquinidine acetate was carried out by following the procedure described by Kaiser.[20] A 1.6 M solution of ^{n}BuLi in hexane (0.8 mL, 1.28 mmol) was added slowly over a few minutes to a stirred solution of 9-phenylquinidine (0.50 g, 1.25 mmol) in dry THF (30 mL). The reaction mixture was stirred at room temperature for 30 mins under a nitrogen atmosphere. Acetyl chloride (0.13 mL, 1.82 mmol) was then added dropwise and the reaction mixture was refluxed for 3 days. After cooling to 0 °C, water (15 mL) was added slowly. Ether (20 mL) was then added, the organic layer was removed and the aqueous layer was extracted with ether (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$ and the solvent was removed. The ^{1}H NMR spectrum of the trace amount of material showed it to be the desired 9-phenylquinidine acetate.

Synthesis of 9-Phenylquinidine Acetate (113) (Method C)

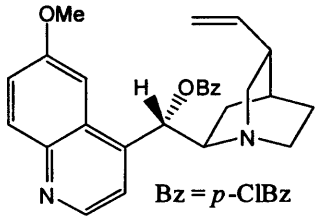


The synthesis of 9-phenylquinidine acetate was carried out by adapting the procedure described by Kaiser.[20] NaH (60 % dispersion in mineral oil) (0.05 g, 1.25 mmol) was added slowly to

a stirred solution of 9-phenylquinidine (0.51 g, 1.25 mmol) in dry THF (30 mL). The reaction mixture was stirred at room temperature for 1 h under a nitrogen atmosphere. Acetyl chloride (0.13 mL, 1.82 mmol) was then added dropwise and refluxed for 2 days. After cooling the reaction mixture to 0 °C, water (20 mL) was added slowly. Ether (20 mL) was then added, the organic layer was removed and the aqueous layer was extracted with ether (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$ and the solvent was removed to yield the new, desired 9-phenylquinidine acetate as a clear oil (0.37 g, 65 %). $[\alpha]_D$ (MeOH) 20.7 ° (c = 0.5). (Found: C, 75.87; H, 6.78; N, 6.36. $C_{28}H_{30}N_2O_3$ requires C, 75.99; H, 6.83; N, 6.33). δ_H ($CDCl_3$, 300 MHz) 0.95-1.05 (1H, m, NCH_2CHH), 1.37-1.58 (2H, m, NCH_2CHH, NCH_2CH_2CH), 1.67-1.81 (2H, m, NCH_2CHH), 1.86-1.96 (2H, m, NCH_2CH, $NCHH$), 1.97 (3H, s, CH_3), 2.15-2.25 (1H, m, $NCHH$), 2.68-2.80 (1H, m, $NCHH$), 3.30-3.41 (1H, m, $NCHH$), 3.42 (3H, s, OCH_3), 4.57 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^4J_{HH}$ 1.8 Hz, $^2J_{HH}$ 1.5 Hz, $CH=CHH$), 4.65-4.73 (1H, m, NCH), 4.77 (1H, ddd, $^3J_{HH}$ 10.2 Hz, $^2J_{HH}$ 1.5 Hz, $^4J_{HH}$ 1.2 Hz, $CH=CHH$), 5.40 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^3J_{HH}$ 10.2 Hz, $^3J_{HH}$ 7.0 Hz, $CH=CH_2$), 6.65 (1H, br. s, PhH), 6.94 (1H, d, $^4J_{HH}$ 2.6 Hz, ArH(5')), 6.98 (1H, br. s, PhH), 7.09 (1H, dd, $^3J_{HH}$ 9.1 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.21-7.25 (1H, m, PhH), 7.42 (1H, br. s, PhH), 7.87 (1H, d, $^3J_{HH}$ 9.1 Hz, ArH(8')), 7.93 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(3')), 7.99 (1H, br.s, PhH), 8.80 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_H ($CDCl_3$, 400 MHz, 223 K) 0.87-0.95 (1H, m, NCH_2CHH), 1.47-1.55 (1H, m, NCH_2CHH), 1.57-1.65 (1H, m, NCH_2CHH), 1.70-1.85 (2H, m, NCH_2CHH, NCH_2CH_2CH), 1.92-2.06 (2H, m, NCH_2CH, $NCHH$), 2.08 (3H, s, CH_3), 2.23-2.31 (1H, m, $NCHH$), 2.79-2.88 (1H, m, $NCHH$), 3.42-3.48 (1H, m, $NCHH$), 3.50 (3H, s, OCH_3), 4.68 (1H, d, $^3J_{HH}$ 17.2 Hz, $CH=CHH$), 4.76 (1H, t, $^3J_{HH}$ 9.3 Hz, NCH), 4.86 (1H, d, $^3J_{HH}$ 10.2 Hz, $CH=CHH$), 5.49 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^3J_{HH}$ 10.2 Hz, $^3J_{HH}$ 7.4 Hz, $CH=CH_2$), 6.64 (1H, d, $^3J_{HH}$ 7.4 Hz, PhH), 6.99 (1H, d, $^4J_{HH}$ 2.3 Hz, ArH(5')), 7.05 (1H, t, $^3J_{HH}$ 7.4 Hz, PhH), 7.20 (1H, dd, $^3J_{HH}$ 9.0 Hz, $^4J_{HH}$ 2.3 Hz, ArH(7')), 7.32 (1H, t, $^3J_{HH}$ 7.4 Hz, PhH), 7.56 (1H, t, $^3J_{HH}$ 7.4 Hz, PhH), 7.95 (1H, d, $^3J_{HH}$ 9.0 Hz, ArH(8')), 7.96 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(3')), 8.01 (1H, d, $^3J_{HH}$ 7.4 Hz, PhH), 8.91 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_C ($CDCl_3$, 300 MHz) 20.3 (CH_3), 20.4 (CH_2), 25.3 (CH_2), 27.9 (CH), 38.6 (CH), 47.5 (CH_2), 49.4 (CH_2), 54.0 (CH_3), 58.0 (CH), 85.8 (C), 103.7 (CH), 113.3 (CH_2), 119.6 (CH), 119.8 (CH), 124.9 (C), 125.4 (CH), 127.1 (CH), 127.9 (CH), 130.7 (CH), 138.5 (C), 138.9 (CH), 144.7 (C), 146.1 (C), 146.5 (CH), 155.7 (C), 167.5 (C=O). δ_C ($CDCl_3$, 400 MHz, 223 K) 21.2 (CH_2), 21.7 (CH_3), 26.0 (CH_2), 28.6 (CH), 39.6 (CH), 48.3 (CH_2), 50.3 (CH_2), 55.4 (CH_3), 58.8 (CH), 86.5 (C), 104.4 (CH), 114.9 (CH_2), 120.4 (CH), 121.3 (CH), 125.8 (CH), 126.3 (C), 128.2 (CH), 128.4 (CH), 128.5 (CH), 128.8 (CH), 131.8 (CH), 139.2 (C), 139.9 (CH), 145.5 (C), 147.1 (C), 147.9 (CH), 156.5 (C), 169.2 (C=O). m/z (FAB^+) 443 ($[M+H]^+$, 60 %), 383 ($[M-OAc]^+$, 100 %). HRMS (FAB) 443.23350 ($C_{28}H_{31}N_2O_3$ requires 443.23347).

5.5 Protection With a *p*-Chlorobenzoyl Group

Synthesis of Quinidine *p*-Chlorobenzoate (114)



Quinidine *p*-chlorobenzoate was synthesised by following the procedure described by Sharpless.[17] Pyridine (1.2 mL, 14.82 mmol) and *p*-chlorobenzoyl chloride (2.1 mL, 16.06 mmol) were added to a stirred solution of quinidine (4.82 g, 14.9 mmol) in dichloromethane (70 mL) at room temperature. The solution was stirred at room temperature for 4.5 h. Water (2 mL) was added to the reaction mixture and then stirred for a further 30 mins. The reaction solution was then poured into a 2 M solution of potassium carbonate (100 mL) and extracted with dichloromethane (2 × 100 mL). The organic phases were combined, dried over potassium carbonate and the solvent was removed. The crude product was purified on a silica gel column (50 g) eluted with ethyl acetate (150 mL), then ethyl acetate/ethanol/triethylamine (83/15/2) (400 mL). All fractions containing the product (as determined by TLC) were combined, the solvent was removed and the product was dried under oil pump vacuum to yield quinidine *p*-chlorobenzoate as a white solid (5.24 g, 76 %). M.p. 57-59 °C. $[\alpha]_D$ (MeOH) –64.2 ° (*c* = 1). δ_H ($CDCl_3$) 1.47-1.59 (3H, m, NCH_2CHH), 1.77-1.83 (1H, m, NCH_2CHH), 1.85-1.95 (1H, m, NCH_2CH_2CH), 2.18-2.28 (1H, m, NCH_2CH), 2.66-2.83 (2H, m, $NCHH$), 2.87-2.93 (2H, m, $NCHH$), 3.31-3.41 (1H, m, NCH), 3.90 (3H, s, OCH_3), 5.01 (1H, ddd, $^3J_{HH}$ 17.2, $^4J_{HH}$ 1.8, $^2J_{HH}$ 1.5, CHH=CH), 5.05 (1H, dt, $^3J_{HH}$ 10.5, $^4J_{HH}$ = $^2J_{HH}$ 1.5, CH=C*H*H), 5.94 (1H, ddd, $^3J_{HH}$ 17.2, $^3J_{HH}$ 10.5, $^3J_{HH}$ 7.0, CH=CH_2), 6.68 (1H, d, $^3J_{HH}$ 7.0 Hz, C*H*OC(O)ArCl), 7.31 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.9 Hz, ArH(7')), 7.32 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(3')), 7.35-7.40 (2H, m, ArH(2'')), 7.41 (1H, d, $^4J_{HH}$ 2.9 Hz, ArH(5')), 7.94-7.98 (2H, m, ArH(3'')), 7.95 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.66 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(2')). δ_C ($CDCl_3$) 23.5 (CH_2), 26.3 (CH_2), 27.6 (CH), 39.4 (CH), 49.2 (CH_2), 49.8 (CH_2), 55.7 (CH_3), 59.3 (CH), 74.3 (CH), 101.2 (CH), 115.0 (CH_2), 118.4 (CH), 122.0 (CH), 127.0 (C), 128.1 (C), 129.0 (CH), 131.1 (CH), 131.9 (CH), 140.0 (C), 140.1 (CH), 143.6 (C), 144.7 (C), 147.4 (CH), 158.0 (C), 164.7 (C=O). m/z (ES^+) 463 ($[M+H]^+$, 100 %). HRMS (FAB) 463.17897 ($C_{27}H_{27}ClN_2O_3$ requires 463.17885).

Synthesis of 9-Methylquinidine *p*-Chlorobenzoate (115) (Method A)

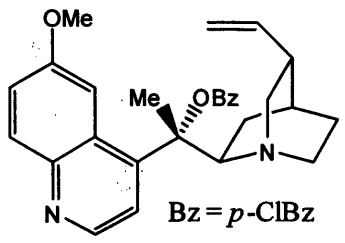
The synthesis of 9-methylquinidine *p*-chlorobenzoate was attempted based on the procedure described by Kaiser.[20] A 1.6 M solution of ^{n}BuLi in hexane (1.1 mL, 1.76 mmol) was added slowly over a few minutes to a stirred solution of 9-methylquinidine (0.58 g, 1.73 mmol) in dry THF (15 mL). The reaction mixture was stirred at room temperature for 30 mins under a nitrogen atmosphere. A solution of *p*-chlorobenzoyl chloride (0.3 mL, 2.34 mmol) in dry THF (5 mL) was then added dropwise and refluxed for 47 h. After cooling the reaction

mixture to 0 °C, water (15 mL) was added slowly. The organic layer was removed and the aqueous layer was extracted with ether (3 × 10 mL). The organic layers were combined, washed with water (10 mL), dried over $MgSO_4$ and the solvent was removed. The ^1H NMR spectrum showed that the desired product had been formed, but there was also an aromatic containing impurity in the sample. No further purification was undertaken.

Synthesis of 9-Methylquinidine *p*-Chlorobenzoate (115) (Method B)

The synthesis of 9-methylquinidine *p*-chlorobenzoate was attempted based on the procedure described by Kaiser.[20] A 1.6 M solution of ^{n}BuLi in hexane (1.2 mL, 1.92 mmol) was added slowly over a few minutes to a stirred solution of 9-methylquinidine (0.59 g, 1.82 mmol) in dry ether (45 mL). The reaction mixture was stirred at room temperature for 30 mins under a nitrogen atmosphere. A solution of *p*-chlorobenzoyl chloride (0.3 mL, 2.34 mmol) in dry ether (5 mL) was then added dropwise and refluxed for 3 days. After cooling the reaction mixture to 0 °C, water (15 mL) was added slowly. The organic layer was removed and the aqueous layer was extracted with ether (3 × 10 mL). The organic layers were combined, washed with water (10 mL), dried over $MgSO_4$ and the solvent was removed to yield a white solid. The ^1H NMR spectrum showed that the solid contained product and an unknown aromatic impurity. The crude material was dissolved in the minimum volume of chloroform and loaded onto a silica gel (30 g) column and eluted with chloroform (100 mL) to remove the unknown impurity. The column was then eluted with chloroform/methanol (97/3) (200 mL) to yield fairly pure product which contained a minor impurity.

Synthesis of 9-Methylquinidine *p*-Chlorobenzoate (115) (Method C)



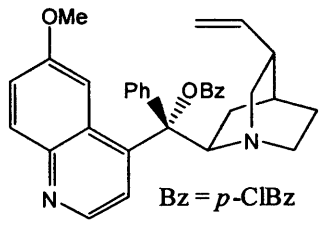
The synthesis of 9-methylquinidine *p*-chlorobenzoate was carried out based on the procedure described by Kaiser.[20] A 1.6 M solution of ^{n}BuLi in hexane (2.4 mL, 3.82 mmol) was added slowly over a few minutes to a stirred solution of 9-methylquinidine (1.30 g, 3.82 mmol) in dry ether (150 mL). The reaction mixture was stirred at room temperature for 30 mins under a nitrogen atmosphere. A solution of *p*-chlorobenzoyl chloride (0.73 mL, 5.73 mmol) in dry ether (10 mL) was then added dropwise and refluxed for 3 days. After cooling the reaction mixture to 0 °C, water (35 mL) was added slowly. The organic layer was removed and the aqueous layer was extracted with ether (3 × 35 mL). The organic layers were combined, washed with water (25 mL), dried over $MgSO_4$ and the solvent was removed. The crude material was dissolved in the minimum volume of chloroform and loaded onto a silica gel (80 g) column and eluted with chloroform (200 mL) to remove the aromatic impurity. The column was then eluted with

chloroform/methanol (99/1) (1 L) to obtain the new compound, 9-methylquinidine *p*-chlorobenzoate, as a white foamy solid (0.36 g, 20 %). M.p. 72-74 °C. $[\alpha]_D$ (MeOH) -43.7° (c = 1). δ_H ($CDCl_3$, 400 MHz, 326 K) 1.31-1.42 (1H, m, NCH_2CHH), 1.57-1.70 (2H, m, NCH_2CHH), 1.91-1.96 (1H, m, NCH_2CH_2CH), 2.14-2.22 (1H, m, NCH_2CHH), 2.27-2.33 (1H, m, NCH_2CH), 2.34 (3H, s, CH_3), 2.85-2.94 (1H, m, $NCHH$), 3.00-3.12 (3H, m, $NCHH$), 3.46-3.56 (1H, m, NCH), 3.60 (3H, s, OCH_3), 5.02 (1H, dt, $^3J_{HH}$ 17.2 Hz, $^2J_{HH}$ 1.6 Hz, $^4J_{HH}$ 1.6 Hz, CH=C*H*H), 5.15 (1H, dt, $^3J_{HH}$ 10.6 Hz, $^2J_{HH}$ 1.6 Hz, $^4J_{HH}$ 1.6 Hz, CH=C*H*H), 5.96 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^3J_{HH}$ 10.6 Hz, $^3J_{HH}$ 6.3 Hz, C*H*=CH_2), 7.31 (1H, dd, $^3J_{HH}$ 9.0 Hz, $^4J_{HH}$ 2.3 Hz, ArH(7')), 7.42-7.49 (2H, m, ArH(2")), 7.47 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(3')), 7.76 (1H, d, $^4J_{HH}$ 2.3 Hz, ArH(5')), 8.03-8.07 (2H, m, ArH(3")), 8.08 (1H, d, $^3J_{HH}$ 9.0 Hz, ArH(8')), 8.79 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_H ($CDCl_3$, 300 MHz) 1.24 (1H, br.s, NCH_2CHH), 1.44-1.55 (2H, br. m, NCH_2CHH), 1.82 (1H, br. s, NCH_2CH_2CH), 2.00-2.09 (1H, br. m, NCH_2CHH), 2.20 (4H, s, NCH_2CH, CH_3), 2.67-2.82 (1H, m, $NCHH$), 2.83-2.96 (3H, br. m, $NCHH$), 2.95-3.01 (1H, br. m, NCH), 3.47 (3H, br. s, OCH_3), 4.91 (1H, d, $^3J_{HH}$ 17.2 Hz, CH=C*H*H), 5.04 (1H, d, $^3J_{HH}$ 10.5 Hz, CH=C*H*H), 5.8 6 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^3J_{HH}$ 10.5 Hz, $^3J_{HH}$ 6.4 Hz, C*H*=CH_2), 7.19 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.9 Hz, ArH(7')), 7.31 (1H, br. s, ArH(3')), 7.36 (2H, d, $^3J_{HH}$ 8.8 Hz, ArH(2")), 7.63 (1H, br.s, ArH(5')), 7.94 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 7.95 (2H, d, $^3J_{HH}$ 8.8 Hz, ArH(3")), 8.67 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_C ($CDCl_3$, 400 MHz, 326 K) 22.8 (CH_2), 25.7 (CH_3), 25.8 (CH_2), 28.2 (CH), 39.1 (CH), 50.1 (CH_2), 51.1 (CH_2), 55.1 (CH_3), 64.9 (CH), 87.9 (C), 104.0 (CH), 114.6 (CH_2), 119.6 (CH), 121.4 (CH), 125.6 (C), 128.5 (CH), 128.8 (CH), 129.1 (C), 131.1 (CH), 131.3 (CH), 131.9 (CH), 139.0 (C), 139.8 (CH), 144.9 (C), 145.0 (C), 147.0 (CH), 157.3 (C), 163.6 (C=O). m/z (ES^+) 477 ($[M+H]^+$, 100%). HRMS (FAB) 477.19456 ($C_{28}H_{30}ClN_2O_3$ requires 477.19450).

Attempted Synthesis of 9-Phenylquinidine *p*-Chlorobenzoate (116) (Method A)

The synthesis of 9-phenylquinidine *p*-chlorobenzoate was carried out by following the procedure described by Kaiser.[20] A 1.6 M solution of ^{n}BuLi in hexane (0.8 mL, 1.28 mmol) was added slowly over a few minutes to a stirred solution of 9-phenylquinidine (0.50 g, 1.25 mmol) in dry THF (30 mL). The reaction mixture was stirred at room temperature for 30 mins under a nitrogen atmosphere. *p*-Chlorobenzoyl chloride (0.25 mL, 1.88 mmol) was then added dropwise and refluxed for 4 days. After cooling the reaction to 0 °C, 2 M hydrochloric acid (15 mL) was added slowly. Ether (20 mL) was then added, the organic layer was removed and the aqueous layer was extracted with ether (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$ and the solvent was removed. The ^{1}H NMR spectrum of the trace amount of material showed it to be the desired 9-phenylquinidine acetate.

Synthesis of 9-Phenylquinidine *p*-Chlorobenzoate (116) (Method B)



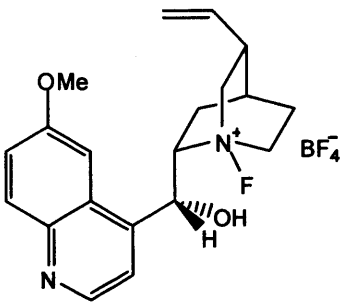
The synthesis of 9-phenylquinidine *p*-chlorobenzoate was carried out by adapting the procedure described by Kaiser.[20] NaH (60 % dispersion in mineral oil) (0.06 g, 1.37 mmol) was added slowly to a stirred solution of 9-phenylquinidine (0.55 g, 1.37 mmol) in dry THF (30 mL). The reaction mixture was stirred at room temperature for 1 h under a nitrogen atmosphere. *p*-Chlorobenzoyl chloride (0.26 mL, 2.05 mmol) was then added dropwise and the reaction mixture was refluxed for 4 days. After cooling the reaction mixture to 0 °C, water (15 mL) was added slowly. Ether (20 mL) was then added, the organic layer was removed and the aqueous layer was extracted with ether (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$ and the solvent was removed. The crude material was then loaded onto a silica gel column and eluted with chloroform (200 mL) to remove an aromatic impurity, then with chloroform/methanol 96/4 to remove the desired product. All fractions containing the product were combined to yield the new compound, 9-phenylquinidine *p*-chlorobenzoate as an orange oil (0.58 g, 79 %). $[\alpha]_D$ (MeOH) 3.7 ° (c = 1). δ_H ($CDCl_3$, 400 MHz) 1.01-1.09 (1H, m, NCH_2CHH), 1.37-1.45 (1H, m, NCH_2CHH), 1.49-1.58 (1H, m, NCH_2CHH), 1.68-1.81 (2H, NCH_2CHH, NCH_2CH_2CH), 1.89-2.01 (2H, m, NCHH, NCH_2CH), 2.22-2.32 (1H, m, NCHH), 2.74-2.83 (1H, m, NCHH), 3.27 (3H, s, OCH_3), 3.36-3.45 (1H, m, NCHH), 4.57 (1H, dt, $^3J_{HH}$ 17.2 Hz, $^2J_{HH}$ = $^4J_{HH}$ 1.6 Hz, CH=CHH), 4.77 (1H, ddd, $^3J_{HH}$ 10.6 Hz, $^2J_{HH}$ 1.6 Hz, $^4J_{HH}$ 1.2 Hz, CH=CHH), 4.82-4.89 (1H, m, NCH), 5.40 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^3J_{HH}$ 10.6 Hz, $^3J_{HH}$ 6.7 Hz, $CH{=}CH_2$), 6.70 (1H, br. s, PhH), 6.92 (1H, d, $^4J_{HH}$ 2.7 Hz, ArH(5')), 7.02 (1H, dd, $^3J_{HH}$ 9.0 Hz, $^4J_{HH}$ 2.7 Hz, ArH(7')), 7.25-7.30 (1H, br. m, PhH), 7.33-7.38 (3H, m, ClArH(3''), PhH), 7.53 (1H, br. s, PhH), 7.88-7.93 (2H, m, ClArH(2'')), 7.95 (1H, d, $^3J_{HH}$ 9.0 Hz, ArH(8')), 8.07 (1H, d, $^3J_{HH}$ 4.7 Hz. ArH(3')), 8.15 (1H, br. s, PhH), 8.88 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_C ($CDCl_3$, 400 MHz) 21.5 (CH_2), 26.2 (CH_2), 28.8 (CH), 39.4 (CH), 48.5 (CH_2), 50.5 (CH_2), 54.9 (CH_3), 77.3 (CH), 87.5 (C), 104.5 (CH), 114.5 (CH_2), 120.9 (CH), 121.3 (CH), 125.7 (C), 126.5 (C), 128.2 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 129.0 (CH), 130.9 (CH), 131.1 (CH), 131.3 (CH), 139.6 (C), 139.8 (CH), 140.0 (C), 145.1 (C), 147.0 (CH), 147.2 (C), 156.8 (C), 162.9 (C=O). m/z (FAB^+) 539 ($[M+H]^+$, 100 %). HRMS (FAB) 539.21010 ($C_{33}H_{32}ClN_2O_3$ requires 539.21015).

5.6 Fluorination of the Cinchona Alkaloid Derivatives Using Selectfluor

Synthesis of *N*-Fluoroquininium Tetrafluoroborate (15) (Method A)

The synthesis of *N*-fluoroquinininium tetrafluoroborate was attempted by following the procedure described by Cahard.[21] A solution of Selectfluor (0.508 g, 1.4 mmol) in dry acetonitrile (10 mL) was added dropwise over 10 mins to a solution of quinine (0.401 g, 1.4 mmol) in dry acetonitrile (10 mL) under a nitrogen atmosphere. The reaction mixture was stirred for 20 mins at room temperature before the solvent was removed under reduced pressure. The residue was dissolved in acetone and a solution of 98% H_2SO_4 (0.6 mL, 10.9 mmol) in acetone (100 mL) was added dropwise. The precipitate that forms (1-chloromethyl-4-hydro-1,4-diazoniabicyclo [2.2.2] octane hydrogen sulphate tetrafluoroborate) was filtered off. Diethyl ether (150 mL) was added to the filtrate and the precipitate that formed was collected and washed with diethyl ether/acetone (1/1). The ^1H and ^{19}F NMR spectra showed that the product had formed but contained traces of starting material. Attempts to recrystallise the product failed so this route was abandoned.

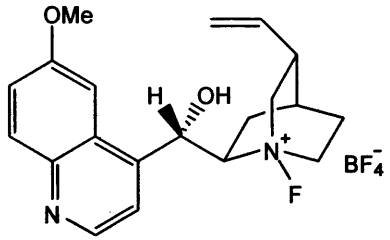
Synthesis of *N*-Fluoroquininium Tetrafluoroborate (15) (Method B)



N-Fluoroquininium tetrafluoroborate was synthesised by following the procedure described by Shibata.[22] Selectfluor (546 mg, 1.54 mmol) was added to a stirred suspension of quinine (500 mg, 1.54 mmol) in acetonitrile (3 mL) at room temperature in one portion. The reaction mixture was stirred for several minutes until homogeneous and then stirred for several minutes more until a white powdery solid precipitated out. The solid was quickly filtered off, washed with a little cold acetonitrile and dried under vacuum to yield *N*-fluoroquininium tetrafluoroborate as a white powder (0.27 g, 52%). M.p. 170 °C (dec. 136-138 °C) (lit.,[22]138-140 °C). $[\alpha]_D$ (MeOH) -141.1 ° (c = 1). δ_H (CD_3CN) 1.98-2.05 (1H, m, NCH_2CHH), 2.14-2.22 (1H, m, NCH_2CHH), 2.30-2.44 (1H, m, NCH_2CH_2CH), 2.53-2.73 (2H, m, NCH_2CHH), 3.28-3.39 (1H, m, NCH_2CH), 3.99 (3H, s, OCH_3), 4.04 (1H, m, $NCHH$), 4.10-4.23 (1H, m, $NCHH$), 4.34-4.52 (2H, m, $NCHH$), 4.81 (1H, dd, $^3J_{HH}$ 3.8 Hz, $^3J_{HH}$ 1.5 Hz, $CHOH$), 4.84-4.98 (1H, m, NCH), 5.13-5.25 (2H, m, $CH=CHH$), 5.80 (1H, m, $CH=CH_2$), 6.39 (1H, d, $^3J_{HH}$ 3.8 Hz, OH), 7.16 (1H, d, $^4J_{HH}$ 2.6 Hz, ArH(5')), 7.48 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.72 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(3')), 8.06 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.82 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(2')). δ_C (CD_3CN) 22.6 (CH_2), 26.5 (d, $^4J_{CF}$ 6.0 Hz, CH), 27.6 (d, $^3J_{CF}$ 4.8 Hz, CH_2), 42.6 (d, $^3J_{CF}$ 3.6 Hz, CH), 55.0 (CH_3), 58.3 (d, $^2J_{CF}$ 9.8 Hz, CH_2), 62.3 (d, $^3J_{CF}$ 3.4 Hz, CH), 67.3 (d, $^2J_{CF}$ 8.4 Hz, CH_2), 73.7 (d, $^2J_{CF}$ 9.8 Hz, CH), 100.2 (CH), 117.5 (CH_2),

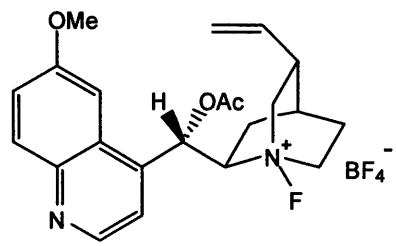
119.1 (CH), 121.6 (CH), 124.9 (C), 131.6 (CH), 135.3 (CH), 141.7 (C), 143.9 (C), 147.4 (CH), 158.0 (C). δ_F (CD_3CN) 41.8 (1F, s, NF), -151.8 (4F, s, BF_4). m/z (ES^+) 343 (M^+, 100%). m/z (ES^-) 87 ($[BF_4]^-$ 100 %). HRMS (FAB) 343.18230 ($C_{20}H_{24}FN_2O_2$ requires 343.18218).

Synthesis of *N*-Fluoroquinidinium Tetrafluoroborate (17)



N-Fluoroquinidinium tetrafluoroborate was synthesised by following the procedure described by Shibata.[22] Selectfluor (1.64 g, 4.63 mmol) was added to a stirred suspension of quinidine (1.50 g, 4.63 mmol) in acetonitrile (15 mL) at room temperature in one portion. The reaction mixture was stirred for several minutes until homogeneous and then stirred for several minutes more until a white powdery solid precipitated out. The solid was quickly filtered off, washed with a little cold acetonitrile and dried under vacuum to yield *N*-fluoroquinidinium tetrofloroborate as a white powder (0.65 g, 41 %). M.p. 192 °C. $[\alpha]_D$ (MeOH) 225.3 ° (c = 1). δ_H (CD_3CN) 1.63 (1H, m, NCH_2CHH), 2.11 (1H, m, NCH_2CHH), 2.33 (1H, m, NCH_2CHH), 2.86 (1H, m, NCH_2CH_2CH), 3.29 (1H, m, NCH_2CHH), 4.01 (3H, s, OCH_3), 4.24 (1H, m, NCH_2CH), 4.24 (2H, m, $NCHH$), 4.42 (1H, m, $NCHH$), 5.04 (2H, m, $NCHH$, NCH), 5.35 (2H, m, $CH{=}CHH$), 6.16 (1H, m, $CH{=}CH_2$), 6.44 (1H, br. s, $CH(OH)$), 7.16 (1H, d, $^4J_{HH}$ 2.6 Hz, ArH(5')), 7.48 (1H, dd, $^3J_{HH}$ 9.1 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.73 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(3')), 8.06 (1H, d, $^3J_{HH}$ 9.1 Hz, ArH(8')), 8.81 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(2')). δ_C (CD_3CN) 22.8 (CH_2), 26.5 (d, $^4J_{CF}$ 4.8 Hz, CH), 26.7 (d, $^3J_{CF}$ 4.8 Hz, CH_2), 42.1 (d, $^3J_{CF}$ 3.6 Hz, CH), 55.1 (CH_3), 62.1 (d, $^2J_{CF}$ 8.4 Hz, CH_2), 62.7 (d, $^3J_{CF}$ 8.4 Hz, CH), 63.3 (d, $^2J_{CF}$ 9.6 Hz, CH_2), 73.1 (d, $^2J_{CF}$ 9.6 Hz, CH), 100.3 (CH), 117.7 (CH_2), 119.2 (CH), 121.6 (CH), 124.9 (C), 131.5 (CH), 135.0 (CH), 141.5 (C), 143.8 (C), 147.4 (CH), 158.0 (C). δ_F (CD_3CN) 39.9 (1F, s, NF), -151.8 (4F, s, BF_4). m/z (ES^+) 343 (M^+, 100 %). m/z (ES^-) 87 ($[BF_4]^-$ 100 %). HRMS (FAB) 343.18219 ($C_{20}H_{24}FN_2O_2$ requires 343.18218).

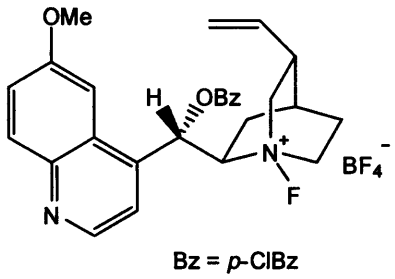
Synthesis of *N*-Fluoro-*O*-acetylquinidinium Tetrafluoroborate (117)`



N-Fluoro-*O*-acetylquinidinium tetrafluoroborate was synthesised by following the procedure described by Shibata.[22] Selectfluor (1.46 g, 4.10 mmol) was added to a stirred suspension of quinidine acetate (1.51 g, 4.10 mmol) in acetonitrile (15 mL) at room temperature in one portion. The reaction mixture was stirred for 40 minutes until homogeneous. The volume of solvent was then reduced to approximately 2 mL and the

resulting white solid was filtered and washed with a little cold acetonitrile and dried under vacuum to yield *N*-fluoro-*O*-acetylquinidinium tetrafluoroborate as a white powder (0.35 g, 22 %). M.p. 173 °C (dec. 138 °C). $[\alpha]_D$ (MeOH) 126.4 ° (*c* = 1). δ_H (CD_3CN) 1.89 (1H, m, NCH_2CHH), 2.20 (2H, m, NCH_2CHH), 2.32 (3H, s, CH_3), 2.35 (1H, m, NCH_2CH_2CH), 2.91 (1H, m, NCH_2CHH), 3.34 (1H, m, NCH_2CH), 4.02 (3H, s, OCH_3), 4.19-4.43 (3H, m, $NCHH$), 4.55 (2H, m, $NCHH$, NCH), 5.37 (1H, ddd, $^3J_{HH}$ 17.2, $^4J_{HH}$ 1.5, $^2J_{HH}$ 0.9, CH=C*H*H), 5.44 (1H, dt, $^3J_{HH}$ 10.5, $^2J_{HH}$ 0.9 Hz, $^4J_{HH}$ 1.2, CH=C*H*H), 6.17 (1H, dddd, $^3J_{HH}$ 17.2, $^3J_{HH}$ 10.5, $^3J_{HH}$ 6.7, $^4J_{HH}$ 1.2, $CH=CH_2$), 7.09 (1H, br. s, $CHOC(O)CH_3$), 7.19 (1H, d, $^4J_{HH}$ 2.6 Hz, ArH(5')), 7.51 (1H, dd, $^3J_{HH}$ 4.4 Hz, $^6J_{HF}$ 0.9 Hz, ArH(3')), 7.51 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 8.08 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.78 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_C (CD_3CN) 20.3 (CH_3), 24.2 (CH_2), 26.2 (d, $^4J_{CF}$ 4.8 Hz, CH), 26.4 (d, $^3J_{CF}$ 4.8 Hz, CH_2), 41.7 (d, $^3J_{CF}$ 3.6 Hz, CH), 55.2 (CH_3), 62.5 (d, $^2J_{CF}$ 9.6 Hz, CH_2), 63.7 (d, $^2J_{CF}$ 9.6 Hz, CH_2), 65.5 (d, $^2J_{CF}$ 8.4 Hz, CH), 71.6 (d, $^3J_{CF}$ 9.6 Hz, CH), 100.0 (CH), 118.0 (CH_2), 118.2 (CH), 122.0 (CH), 124.6 (C), 131.9 (CH), 134.8 (CH), 137.5 (C), 144.1 (C), 147.3 (CH), 158.4 (C), 168.4 (C=O). δ_F (CD_3CN) 37.2 (1F, s, NF), -151.7 (4F, s, BF_4). m/z (ES^+) 385 (M^+, 70 %). m/z (ES^-) 87 ($[BF_4]^-$, 100 %). HRMS (FAB) 385.19266 ($C_{22}H_{26}FN_2O_3$ requires 385.19275).

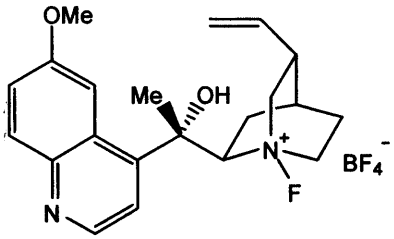
Synthesis of *N*-Fluoro-*O*- *p*-Chlorobenzoylquinidinium Tetrafluoroborate (118)



N-Fluoro-*O*-*p*-chlorobenzoylquinidinium tetrafluoroborate was synthesised by following the procedure described by Cahard.[23] Selectfluor (1.53 g, 4.32 mmol) was added to a stirred solution of quinidine *p*-chlorobenzoate (2.00 g, 4.32 mmol) in acetonitrile (12 mL) at room temperature in one portion. The reaction mixture was stirred at room temperature for 40 mins before removing the solvent. The residue was dissolved in the minimum volume of acetone and a solution of 98% H_2SO_4 (0.3 mL, 5.45 mmol) in acetone (50 mL) was added dropwise and the precipitate that formed (1-chloromethyl-4-hydro-1,4-diazoniabicyclo [2.2.2] octane hydrogen sulphate tetrafluoroborate) was filtered off. Diethyl ether (150 mL) was added to the filtrate which caused a yellow oil to crash out of solution. The ^1H and ^{19}F NMR spectra showed the oil to be mainly the desired *N*-fluoro-*O*-*p*-chlorobenzoylquinidinium tetrafluoroborate, but a trace of quinidine *p*-chlorobenzoate was apparent and all attempts to remove the starting material failed. δ_H (CD_3CN) 2.24-2.41 (2H, m, NCH_2CHH), 3.04-3.14 (2H, m, NCH_2CHH), 3.17-3.19 (1H, m, NCH_2CH_2CH), 3.36-3.41 (1H, m, NCH_2CH), 4.03 (3H, s, OCH_3), 4.29-4.46 (4H, m, $NCHH$), 4.68-4.77 (1H, m, NCH), 5.25 (1H, dddd, $^3J_{HH}$ 17.2 Hz, $^4J_{HH}$ 1.8 Hz, $^2J_{HH}$ 0.9 Hz, $^6J_{HF}$ 0.6 Hz, CH=C*H*H), 5.43 (1H, dddd, $^3J_{HH}$ 10.5 Hz, $^4J_{HH}$ 1.8 Hz, $^2J_{HH}$ 0.9 Hz, $^6J_{HF}$ 0.6 Hz, CH=C*H*H),

6.11 (1H, dddd, $^3J_{HH}$ 17.2 Hz, $^3J_{HH}$ 10.5 Hz, $^3J_{HH}$ 5.8 Hz, $^5J_{HF}$ 1.2 Hz, C*H*=CH$_2$), 7.28 (1H, d, $^4J_{HH}$ 2.6 Hz, ArH(5')), 7.44 (1H, br. s, C*H*(O*p*-ClBz), 7.52 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7'), 7.61 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(3')), 7.64 (2H, d, $^3J_{HH}$ 9.1 Hz, ArH(2'')), 8.08 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.16 (2H, d, $^3J_{HH}$ 9.1 Hz, ArH(3'')), 8.73 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_C (CD_3CN) 24.5 (CH_2), 25.6 (d, $^4J_{CF}$ 4.8 Hz, CH), 26.1 (d, $^3J_{CF}$ 4.8 Hz, CH_2), 41.2 (d, $^3J_{CF}$ 3.6 Hz, CH), 55.3 (CH_3), 62.6 (d, $^2J_{CF}$ 8.4 Hz, CH_2), 63.8 (d, $^2J_{CF}$ 9.6 Hz, CH_2), 66.0 (d, $^3J_{CF}$ 9.6 Hz, CH), 72.1 (d, $^2J_{CF}$ 8.4 Hz, CH), 100.0 (CH), 118.2 (CH_2), 118.4 (CH), 122.4 (CH), 124.8 (C), 126.9 (C), 128.9 (CH), 131.4 (CH), 131.5 (CH), 134.7 (CH), 138.0 (C), 140.0 (C), 143.8 (C), 147.1 (CH), 158.6 (C), 163.2 (C=O). δ_F (CD_3CN) 36.9 (1F, s, NF), -151.6 (4F, s, BF_4). m/z (ES^+) 481 (M^+, 90%) 463 ($[M+H-F]^+$, 90 %), 325 ($[M+H-p\text{ClBz}]^+$, 100 %). m/z (ES^-) 87 ($[BF_4]^-$ 100 %). HRMS (FAB) 481.16862 ($C_{27}H_{27}ClFN_2O_3$ requires 481.16875).

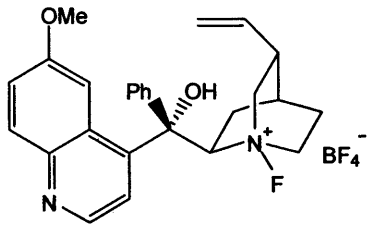
Synthesis of *N*-Fluoro-9-Methylquinidinium Tetrafluoroborate (119)



N-Fluoro-9-methylquinidinium tetrafluoroborate was synthesised by following the procedure described by Cahard.[23] Selectfluor (0.26 g, 0.74 mmol) was added to a stirred suspension of 9-methylquinidine (0.25 g, 0.74 mmol) in acetonitrile (5 mL) at room temperature in one portion. The reaction mixture was stirred at room temperature for 1 h before removing the solvent. The residue was dissolved in acetone and a solution of 98% H_2SO_4 (0.3 mL, 5.45 mmol) in acetone (50 mL) was added dropwise and the precipitate that formed (1-chloromethyl-4-hydro-1,4-diazoniabicyclo [2.2.2] octane hydrogen sulphate tetrafluoroborate) was filtered off. Diethyl ether (150 mL) was added to the filtrate which caused a brown oil to crash out of solution. The ^1H and ^{19}F NMR spectra showed the oil to be mainly the desired *N*-fluoro-9-methylquinidinium tetrafluoroborate, but a trace of 9-methylquinidine was apparent, and all attempts to remove the starting material failed. δ_H (CD_3CN) 1.32-1.44 (1H, m, NCH_2CHH), 1.90-2.01 (1H, m, NCH_2CH_2CH), 2.23 (3H, d, $^5J_{HF}$ 5.3 Hz, CH_3), 2.27-2.35 (2H, m, NCH_2CHH), 3.65-3.84 (2H, NCH_2CHH, NCH_2CH), 4.01 (3H, s, OCH_3), 4.12-4.34 (2H, m, $NCHH$), 4.46-4.60 (1H, m, $NCHH$), 4.80-4.89 (1H, m, $NCHH$), 5.26-5.35 (2H, m, CH=C*HH*), 5.49 (1H, br. s, NCH), 5.99 (1H, dddd, $^3J_{HH}$ 17.5 Hz, $^3J_{HH}$ 10.2 Hz, $^3J_{HH}$ 7.0 Hz, $^4J_{HH}$ 1.5 Hz, C*H*=CH$_2$), 7.80 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 8.19 (1H, br. s, ArH(5')), 8.23 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.26 (1H, br. s, ArH(3')), 8.90 (1H, d, $^3J_{HH}$ 5.8 Hz, ArH(2')). δ_C (CD_3CN) 26.3 (d, $^3J_{CF}$ 4.8 Hz, CH_2), 26.7 (d, $^4J_{CF}$ 4.8 Hz, CH), 27.2 (d, $^3J_{CF}$ 2.4 Hz, CH_2), 29.4 (CH_3), 41.6 (d, $^3J_{CF}$ 3.6 Hz, CH), 55.4 (CH_3), 63.2 (d, $^2J_{CF}$ 8.4 Hz, CH_2), 65.0 (d, $^2J_{CF}$ 10.8 Hz, CH_2), 75.4 (d, $^2J_{CF}$ 9.6 Hz, CH), 77.1 (C), 103.8 (CH), 117.3 (CH_2),

119.3 (CH), 120.6 (CH), 125.2 (C), 131.9 (CH), 134.9 (CH), 136.5 (C), 144.8 (C), 147.3 (CH), 157.6 (C). δ_F (CD_3CN) 33.5 (1F, s, NF), -151.5 (4F, s, BF_4). m/z (FAB^+) 339 ([M+1-F]$^+$, 100 %), 357 (M^+, 5 %). m/z (ES^-) 87 ([BF_4]$^-$ 100 %). HRMS (FAB) 357.19792 ($C_{21}H_{26}FN_2O_2$ requires 357.19783).

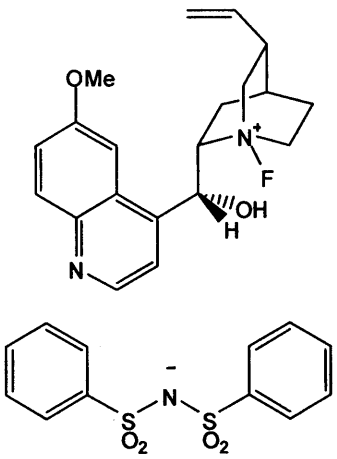
Synthesis of *N*-Fluoro-9-Phenylquinidinium Tetrafluoroborate (120)



N-Fluoro-9-phenylquinidinium tetrafluoroborate was synthesised by following the procedure described by Cahard.[23] Selectfluor (0.22 g, 0.63 mmol) was added to a stirred suspension of 9-phenylquinidine (0.25 g, 0.63 mmol) in acetonitrile (5 mL) at room temperature in one portion. The reaction mixture was stirred at room temperature for 1 h before removing the solvent. The residue was dissolved in acetone and a solution of 98% H_2SO_4 (0.3 mL, 5.45 mmol) in acetone (50 mL) was added dropwise and the precipitate that formed (1-chloromethyl-4-hydro-1,4-diazoniabicyclo [2.2.2] octane hydrogen sulphate tetrafluoroborate) was filtered off. Diethyl ether (150 mL) was added to the filtrate which caused a yellow oil to crash out of solution. The ^1H and ^{19}F NMR spectra showed the oil to be mainly the desired *N*-fluoro-9-phenylquinidinium tetrafluoroborate, but a trace of 9-phenylquinidine was apparent, and all attempts to remove the starting material failed. δ_H ($CDCl_3$, 500 MHz, 323 K) 2.25-2.41 (5H, m, NCH_2CHH, NCH_2CH_2CH), 2.74-2.80 (1H, m, NCH_2CH), 3.09-3.14 (1H, m, $NCHH$), 3.25-3.31 (2H, m, $NCHH$), 3.72 (3H, s, OCH_3), 4.14-4.18 (1H, m, $NCHH$), 4.48-4.52 (1H, m, NCH), 5.21 (1H, d, $^3J_{HH}$ 10.2 Hz, CH=C*H*H), 5.22 (1H, d, $^3J_{HH}$ 16.9 Hz, CH=C*H*H), 5.97 (1H, ddd, $^3J_{HH}$ 16.9 Hz, $^3J_{HH}$ 10.2 Hz, $^3J_{HH}$ 6.5 Hz, C*H*=CH_2), 7.28 (1H, dd, $^3J_{HH}$ 9.1 Hz, $^4J_{HH}$ 2.7 Hz, ArH(7')), 7.42-7.44 (1H, m, ArH(4")), 7.46-7.49 (2H, m, ArH(3")), 7.60 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(3')), 7.61 (1H, d, $^4J_{HH}$ 2.7 Hz, ArH(5')), 7.63-7.65 (2H, m, ArH(2")), 7.94 (1H, d, $^3J_{HH}$ 9.1 Hz, ArH(8')), 8.87 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(2')). δ_C (CD_3CN, 400 MHz, 336.6 K) 22.5 (d, $^3J_{CF}$ 4.6 Hz, CH_2), 26.9 (d, $^3J_{CF}$ 3.2 Hz, CH_2), 27.2 (d, $^4J_{CF}$ 4.6 Hz, CH), 41.8 (d, $^3J_{CF}$ 3.6 Hz, CH), 55.5 (CH_3), 64.1 (d, $^2J_{CF}$ 9.2 Hz, CH_2), 65.1 (d, $^3J_{CF}$ 7.6 Hz, CH), 65.9 (d, $^2J_{CF}$ 9.4 Hz, CH_2), 81.2 (C), 105.0 (CH), 117.9 (CH_2), 118.8 (CH), 121.2 (CH), 125.6 (CH), 125.8 (C), 126.3 (CH), 128.1 (CH), 129.1 (C), 129.9 (CH), 131.9 (CH), 134.9 (CH), 136.6 (CH), 142.7 (C), 145.2 (C), 147.0 (CH), 157.5 (C). δ_F (CD_3CN, 400 MHz, 336.6 K) 38.0 (1F, s, NF), -152.2 (4F, s, BF_4). δ_F (CD_3CN, 400 MHz) 36.1 (1F, s, NF), -151.8 (4F, s, BF_4). m/z (FAB^+) 419 ([M]$^+$, 30 %), 401 ([M+1-F]$^+$, 100 %). m/z (ES^-) 87 ([BF_4]$^-$ 100 %). HRMS (FAB) 419.21339 ($C_{26}H_{28}FN_2O_2$ requires 419.21348).

5.7 Fluorination of the Cinchona Alkaloid Derivatives Using NFSI

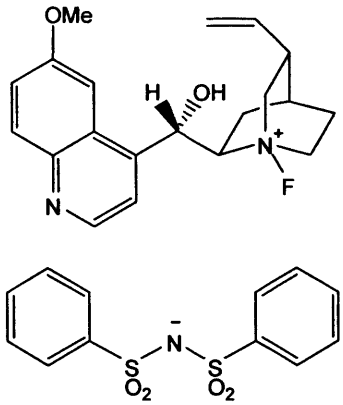
Synthesis of *N*-Fluoroquininium Benzenesulphonimide (121)



The synthesis of *N*-fluoroquininium benzenesulphonimide was carried out by following the procedure described by Cahard.[24] A solution of NFSI (0.502 g, 1.9 mmol) in dry acetonitrile (10 mL) was added slowly to a stirred solution of quinine (0.623 g, 1.9 mmol) in dry acetonitrile (10 mL) under a nitrogen atmosphere. The reaction mixture was stirred for 30 mins at room temperature before removing the solvent. The solid residue was dissolved in dichloromethane (~20 mL) and then ether (~20 mL) was added to precipitate out the product. The mixture was cooled in ice to allow the solid to form, which was then filtered, washed with a little ether and dried. *N*-Fluoroquininium benzenesulphonimide was obtained as a white powder (0.41 g, 62 %). M.p. 134 °C. $[\alpha]_D$ (MeOH) –64.2 ° (c = 1). δ_H (CD_3CN) 1.90-2.22 (2H, m, NCH_2CHH), 2.35 (1H, m, NCH_2CH_2CH), 2.54-2.75 (2H, m, NCH_2CHH), 3.33 (1H, m, NCH_2CH), 3.96 (3H, s, OCH_3), 4.01 (1H, m, $NCHH$), 4.15 (1H, m, $NCHH$), 4.34-4.52 (2H, m, $NCHH$), 4.98 (1H, m, NCH), 5.18 (2H, m, $CH{=}CHH$), 5.42 (1H, m, $CH(OH)$), 5.79 (1H, m, $CH{=}CH_2$), 6.50 (1H, br. s, OH), 7.17 (1H, d, $^4J_{HH}$ 2.6 Hz, ArH(5')), 7.27-7.34 (4H, m, ArH(3'')), 7.36-7.42 (2H, m, ArH(4'')), 7.47 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.68 (4H, m, ArH(2'')), 7.73 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(3')), 8.06 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 8.81 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_C (CD_3CN) 22.6 (CH_2), 26.4 (d, $^4J_{CF}$ 4.8 Hz, CH), 27.5 (d, $^3J_{CF}$ 3.6 Hz, CH_2), 42.5 (d, $^3J_{CF}$ 3.6 Hz, CH), 55.0 (CH_3), 58.1 (d, $^2J_{CF}$ 8.4 Hz, CH_2), 62.0 (d, $^2J_{CF}$ 4.8 Hz, CH), 67.1 (d, $^2J_{CF}$ 8.4 Hz, CH_2), 73.9 (d, $^3J_{CF}$ 9.6 Hz, CH), 100.3 (CH), 117.4 (CH_2), 119.2 (CH), 121.4 (CH), 125.0 (C), 125.9 (CH), 127.6 (CH), 129.9 (CH), 131.5 (CH), 135.4 (CH), 142.2 (C), 143.9 (C), 145.7 (C), 147.4 (CH), 157.8 (C). δ_F (CD_3CN) 42.3 (s, NF). m/z (ES^+) 343 (M^+, 100 %). m/z (ES^-) 296 ($[N(SO_2Ph)_2]^-$, 100 %). HRMS (FAB) 343.18215 ($C_{20}H_{24}FN_2O_2$ requires 343.18218).

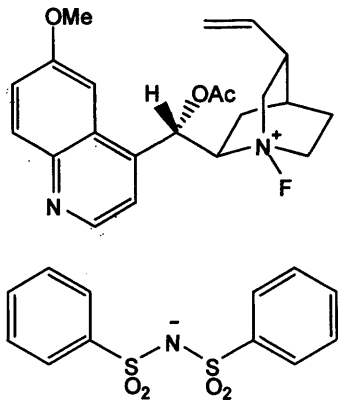
Synthesis of *N*-Fluoroquinidinium Benzenesulphonimide (122)

The synthesis of *N*-fluoroquinidinium benzenesulphonimide was carried out by following the procedure described by Cahard.[24] A solution of NFSI (0.50 g, 1.9 mmol) in dry acetonitrile (10 mL) was added slowly to a stirred suspension of quinidine (0.61 g, 1.9 mmol) in dry acetonitrile (10 mL) under a nitrogen atmosphere. The reaction mixture was stirred for 40 mins at room temperature before removing the solvent. The solid residue was dissolved in dichloromethane (~15 mL) and then ether (~15 mL) was added to precipitate out the product. After cooling the mixture in ice, the solid was filtered, washed with a little ether and dried



under oil pump vacuum. *N*-Fluoroquinidinium benzenesulphonimide was obtained as a white powder (0.62 g, 51 %). M. p. 112-114 °C. $[\alpha]_D$ (MeOH) 166.2 ° (c = 1). δ_H (Acetone-d^6) 1.78-1.91 (1H, m, NCH_2CHH), 2.15-2.23 (1H, m, NCH_2CH_2CH), 2.38-2.57 (2H, m, NCH_2CHH), 3.01-3.11 (1H, m, NCH_2CHH), 3.48-3.60 (1H, m, NCH_2CH), 3.96 (3H, s, OCH_3), 4.58-4.75 (3H, m, $NCHH$), 4.79-4.88 (1H, m, $NCHH$), 5.23-5.30 (1H, m, NCH), 5.33 (1H, dt, $^3J_{HH}$ 10.2 Hz, $^2J_{HH} = {}^4J_{HH}$ 1.2 Hz, CH=C*H*H), 5.39 (1H, dt, $^3J_{HH}$ 17.2 Hz, $^2J_{HH} = {}^4J_{HH}$ 1.2 Hz, CH=C*H*H), 6.28 (1H, ddd, $^3J_{HH}$ 17.2 Hz, 10.2 Hz and 7.9 Hz, $CH{=}CH_2$), 6.58 (1H, d, $^3J_{HH}$ 3.8 Hz, C*H*(OH)), 6.77-6.83 (1H, s, OH), 7.17-7.24 (4H, m, ArH(3'')), 7.26-7.33 (3H, m, ArH(4''), ArH(5')), 7.43 (1H, dd, $^3J_{HH}$ 9.1 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.62-7.68 (4H, m, ArH(2'')), 7.82 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(3')), 8.02 (1H, d, $^3J_{HH}$ 9.1 Hz, ArH(8')), 8.80 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_C (Acetone-d^6) 24.3 (CH_2), 28.2 (d, $^4J_{CF}$ 4.8 Hz, CH), 28.2 (d, $^3J_{CF}$ 4.8 Hz, CH_2), 43.7 (d, $^3J_{CF}$ 3.6 Hz, CH), 56.0 (CH_3), 63.1 (d, $^2J_{CF}$ 8.4 Hz, CH_2), 63.8 (d, $^3J_{CF}$ 9.6 Hz, CH), 64.4 (d, $^2J_{CF}$ 10.8 Hz, CH_2), 74.7 (d, $^2J_{CF}$ 9.6 Hz, CH), 101.7 (CH), 118.8 (CH_2), 120.5 (CH), 122.7 (CH), 126.4 (C), 127.3 (CH), 128.5 (CH), 130.8 (CH), 132.6 (CH), 136.9 (CH), 143.7 (C), 145.2 (C), 147.1 (C), 148.5 (CH), 159.0 (C). δ_F (Acetone-d^6) 37.0 (s, NF). m/z (ES^+) 343 (M^+, 100 %). m/z (ES^-) 296 ($[N(SO_2Ph)_2]^-$, 100 %). HRMS (FAB) 343.18217 ($C_{20}H_{24}FN_2O_2$ requires 343.18218).

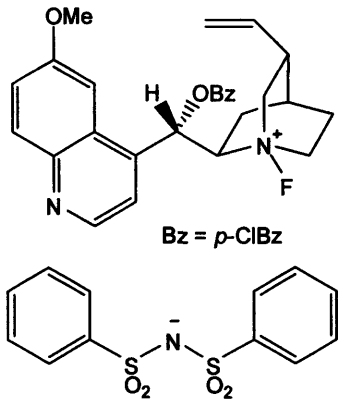
Synthesis of *N*-Fluoro-*O*-acetylquinidinium Benzenesulphonimide (124)



The synthesis of *N*-fluoro-*O*-acetylquinidine benzenesulphonimide was carried out by following the procedure described by Cahard.[24] A solution of NFSI (0.50 g, 1.9 mmol) in dry acetonitrile (10 mL) was added slowly to a stirred solution of quinidine acetate (0.70 g, 1.9 mmol) in dry acetonitrile (10 mL) under a nitrogen atmosphere. The reaction mixture was stirred for 40 mins at room temperature before removing the solvent. The solid residue was dissolved in dichloromethane (~15 mL) and then ether (~15 mL) was added to precipitate out the product. After cooling the mixture in ice, the solid was filtered, washed with a little ether and dried. *N*-Fluoro-*O*-acetylquinidinium benzenesulphonimide was obtained as a white powder (0.57 g, 44 %). Unfortunately, all subsequent attempts at this reaction failed and some characterisaton data is missing. δ_H (CD_3CN) 1.75-1.94 (3H, m, NCH_2CHH), 2.22-2.25 (1H, m, NCH_2CH_2CH), 2.31 (3H, s, CH_3), 2.84-2.95 (1H, m, NCH_2CHH), 3.32-3.42 (1H, m,

NCH_2CH), 4.01 (3H, s, OCH_3), 4.21-4.34 (2H, m, $NCHH$), 4.34-4.52 (1H, m, $NCHH$), 4.47-4.54 (1H, m, $NCHH$), 4.54-4.64 (1H, m, NCH), 5.36 (1H, dm, $^3J_{HH}$ 17.2 Hz, $CH=CHH$), 5.42 (1H, dm, $^3J_{HH}$ 10.5 Hz, $CH=CHH$), 6.16 (1H, dddd, $^3J_{HH}$ 17.2 Hz, $^3J_{HH}$ 10.5 Hz, $^3J_{HH}$ 6.7 Hz, $^4J_{HH}$ 0.9 Hz, $CH=CH_2$), 7.08 (1H, s, $CH(OAc)$), 7.18 (1H, d, $^4J_{HH}$ 2.6 Hz, ArH(5')), 7.32-7.45 (6H, m, ArH(3''), ArH(4'')), 7.50 (1H, dd, $^3J_{HH}$ 9.1 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.52 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(3')), 7.69-7.76 (4H, m, ArH(2'')), 8.08 (1H, d, $^3J_{HH}$ 9.1 Hz, ArH(8')), 8.77 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(2')). δ_F (CD_3CN) 37.3 (s, NF). m/z (ES^+) 385 (M^+, 100 %), (ES^-) 296 ($[N(SO_2Ph)_2]^-$, 100 %). HRMS (FAB) 385.19267 ($C_{22}H_{26}FN_2O_3$ requires 385.19275).

Synthesis of *N*-Fluoro-*O*-*p*-Chlorobenzoylquinidinium Benzenesulphonimide (126)



The synthesis of *N*-fluoro-*O*-*p*-chlorobenzoylquinidinium benzenesulphonimide was carried out by following the procedure described by Cahard.[24] A solution of NFSI (0.25 g, 0.95 mmol) in dry acetonitrile (5 mL) was added slowly to a stirred solution of quinidine *p*-chlorobenzoate (0.44 g, 0.95 mmol) in dry acetonitrile (5 mL) under a nitrogen atmosphere. The reaction mixture was stirred for 40 mins at room temperature in which time a white solid precipitated out. The solid was filtered, washed with a little ether and dried. *N*-Fluoro-*O*-*p*-chlorobenzoylquinidinium benzenesulphonimide was obtained as a white powder (0.45 g, 61 %). M. p. 186-188 °C. $[\alpha]_D$ (MeCN) -3.3 ° (c = 0.5). δ_H (CD_3CN) 2.25-2.27 (1H, m, NCH_2CHH), 2.28-2.43 (3H, m, NCH_2CHH), 3.02-3.13 (1H, m, NCH_2CH_2CH), 3.30-3.41 (1H, m, NCH_2CH), 4.05 (3H, s, OCH_3), 4.25-4.44 (4H, m, $NCHH$), 4.66-4.74 (1H, m, NCH), 5.25 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^4J_{HH}$ 1.8 Hz, $^2J_{HH}$ 0.6 Hz, $CH=CHH$), 5.44 (1H, ddd, $^3J_{HH}$ 10.5 Hz, $^4J_{HH}$ 1.5 Hz, $^2J_{HH}$ 0.6 Hz, $CH=CHH$), 6.04-6.17 (1H, m, $CH=CH_2$), 7.28 (1H, d, $^4J_{HH}$ 2.6 Hz, ArH(5')), 7.33-7.45 (7H, m, ArH(3''), ArH(3'''), CHOBz), 7.53 (1H, dd, $^3J_{HH}$ 9.1 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.58 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(3')), 7.63-7.68 (2H, m, ArH(4''')), 7.72-7.78 (4H, m, ArH(2''')), 8.01 (1H, d, $^3J_{HH}$ 9.1 Hz, ArH(8')), 8.15-8.21 (2H, m, ArH(2'')), 8.74 (1H, d, $^3J_{HH}$ 4.4 Hz, ArH(2')). δ_F (CD_3CN) 37.0 (s, NF). It was not possible to obtain a ^{13}C NMR spectrum due to the compounds low solubility in all solvents.

Synthesis of *N*-Fluoro-9-methylquinidinium Benzenesulphonimide (127) Method A

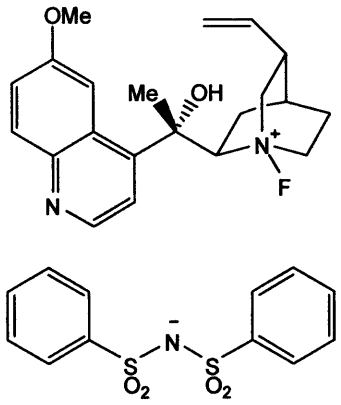
The synthesis of *N*-fluoro-9-methylquinidinium benzenesulphonimide was attempted by following the procedure described by Cahard.[24] A solution of NFSI (0.46 g, 1.45 mmol) in dry acetonitrile (5 mL) was added slowly to a stirred solution of 9-methylquinidine (0.49 g, 1.45 mmol) in dry acetonitrile (10 mL). The reaction mixture was stirred at room temperature

for 24 h under a nitrogen atmosphere before removing the solvent. The ^{1}H NMR spectrum showed a mixture of compounds while the ^{19}F NMR spectrum showed only one peak. No further purification was carried out. δ_F (CD_3CN) 35.8 (s, NF).

Synthesis of *N*-Fluoro-9-methylquinidinium Benzenesulphonimide (127) Method B

The synthesis of *N*-fluoro-9-methylquinidinium benzenesulphonimide was attempted by following the procedure described by Cahard.[24] A solution of NFSI (0.35 g, 1.12 mmol) in dry acetonitrile (2.5 mL) was added slowly to a stirred solution of 9-methylquinidine (0.38 g, 1.12 mmol) in dry acetonitrile (2.5 mL). The reaction mixture was stirred at room temperature for 30 mins under a nitrogen atmosphere before removing the solvent to give a yellow foam. The ^{1}H NMR spectrum showed a mixture of compounds, while the ^{19}F NMR spectrum showed one peak. All attempts to further purify the compound failed. δ_F (CD_3CN) 35.8 (s, NF).

Synthesis of *N*-Fluoro-9-Methylquinidinium Benzenesulphonimide (127)

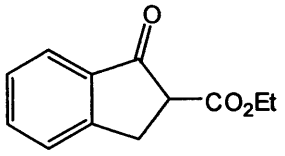


The synthesis of *N*-fluoro-9-methylquinidinium benzenesulphonimide was attempted by following the procedure described by Cahard.[24] NFSI (0.28 g, 0.89 mmol) was added as a solid in portions to a stirred solution of 9-methylquinidine (0.25 g, 0.89 mmol) in acetonitrile (5 mL). The reaction mixture was stirred at room temperature for 30 mins before removing the solvent to give a yellow foam. The ^{1}H NMR spectrum showed a mixture of *N*-fluoro-9-methylquinidinium benzenesulphonimide and NFSI residue, while the ^{19}F NMR spectrum showed one peak. All attempts to further purify the compound failed. δ_H (CD_3CN) 1.25-1.37 (1H, m, NCH_2CHH), 1.88-1.94 (2H, m, NCH_2CHH, NCH_2CH_2CH), 2.19 (3H, d, $^{5}J_{HF}$ 5.3 Hz, CH_3), 2.23-2.33 (2H, m, NCH_2CHH), 3.15-3.26 (1H, m, NCH_2CH), 4.02 (3H, s, OCH_3), 4.13-4.26 (2H, m, $NCHH$), 4.40-4.51 (1H, m, $NCHH$), 4.77-4.87 (1H, m, $NCHH$), 5.25-5.34 (3H, m, NCH, $CH{=}CHH$), 6.00 (1H, dddd, $^{3}J_{HH}$ 17.2 Hz, $^{3}J_{HH}$ 10.5 Hz, $^{3}J_{HH}$ 7.0 Hz, $^{4}J_{HH}$ 1.5 Hz, $CH{=}CH_2$), 7.33-7.43 (7H, m, ArH(3'), ArH(3''), ArH(4'')), 7.51 (1H, dd, $^{3}J_{HH}$ 9.4 Hz, $^{4}J_{HH}$ 2.6 Hz, ArH(7')), 7.72-7.78 (2H, m, ArH(2''), 7.83 (1H, br. s, ArH(5'), 8.13 (1H, d, $^{3}J_{HH}$ 9.4 Hz, ArH(8'), 8.82 (1H, d, $^{3}J_{HH}$ 4.7 Hz, ArH(2'). δ_C (CD_3CN) 26.3 (d, $^{3}J_{CF}$ 4.8 Hz, CH_2), 26.6 (d, $^{4}J_{CF}$ 4.8 Hz, CH), 27.3 (d, $^{3}J_{CF}$ 2.4 Hz, CH_2), 29.4 (CH_3) 41.6 (d, $^{3}J_{CF}$ 3.6 Hz, CH), 55.3 (CH_3), 63.1 (d, $^{2}J_{CF}$ 8.4 Hz, CH_2), 64.9 (d, $^{2}J_{CF}$ 10.8 Hz, CH_2), 75.4 (d, $^{3}J_{CF}$ 8.6 Hz, CH), 77.3 (C), 103.9 (CH), 117.3 (CH_2), 119.5 (CH), 120.7 (CH), 125.3 (C), 126.0 (CH), 127.7 (CH), 130.0 (CH), 131.8 (CH), 135.0 (CH), 144.2 (C), 145.6 (C), 147.0 (CH), 147.6 (C), 157.5 (C).

δ_F (CD_3CN) 35.8 (s, NF). m/z (FAB$^+$) 357 (M^+, 80 %), 339 ($[M-F+H]^+$, 100 %). (ES$^-$) 296 ($[N(SO_2Ph)_2]^-$, 100 %). HRMS (FAB) 357.19712 ($C_{21}H_{26}FN_2O_2$ requires 357.19718).

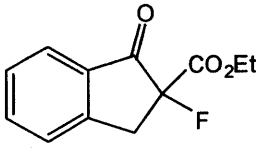
5.8 Substrate Synthesis

Synthesis of Ethyl 1-indanone-2-carboxylate (132)



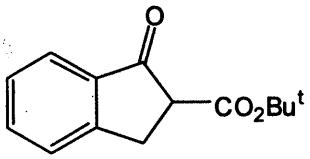
Ethyl 1-indanone-2-carboxylate was synthesised by following a procedure by Brown.[25] A solution of 1-indanone (2.01 g, 15.1 mmol) in dry diethyl carbonate (55 mL) was added via syringe to a stirred suspension of sodium hydride (60 % dispersion in mineral oil, 0.73 g, 18.2 mmol) in dry diethyl carbonate (55 mL). The solution was then refluxed for 20 mins during which time a green solid formed in the reaction vessel. TLC analysis of this solid (silica eluted with petroleum ether 40 - 60 °C/ethyl acetate, 9/2) showed that it contained none of the 1-indanone starting material so the reaction mixture was allowed to cool to room temperature. The solid was then dissolved in 2 M hydrochloric acid (100 mL) and the aqueous phase was extracted with ethyl acetate (4 × 100 mL). The combined organic phases were dried over magnesium sulphate, filtered and the solvent was removed to yield the crude product as a brown oil. The oil was loaded onto a column of silica gel and eluted with petroleum ether 40 - 60 °C/ethyl acetate (9/1, 300 mL) and all fractions containing the product were combined and the solvent was removed. Ethyl 1-indanone-2-carboxylate was obtained pure as a red oil (2.24 g, 72 %). δ_H ($CDCl_3$) 1.22 (3H, t, $^3J_{HH}$ 7.0 Hz, ketoester CH_2CH_3), 1.28 (3H, t, $^3J_{HH}$ 7.0 Hz, enol CH_2CH_3), 3.28 (1H, dd, $^2J_{HH}$ 17.2 Hz, $^3J_{HH}$ 8.5 Hz, ketoester CHH), 3.42 (2H, s, enol CH_2), 3.46 (1H, dd, $^2J_{HH}$ 17.2 Hz, $^3J_{HH}$ 4.1 Hz, ketoester CHH), 3.63 (1H, dd, $^3J_{HH}$ 8.5 Hz, $^3J_{HH}$ 4.1 Hz, ketoester CH), 4.16 (2H, qd, $^3J_{HH}$ 7.0 Hz, J_{HH} 0.6 Hz, ketoester CH_2CH_3), 4.24 (2H, q, $^3J_{HH}$ 7.0 Hz, enol CH_2CH_3), 7.25-7.34 (3H, m, ketoester ArH, enol ArH, enol ArH), 7.35-7.38 (1H, m, enol ArH), 7.39-7.44 (1H, m, ketoester ArH), 7.50-7.57 (2H, m, ketoester ArH, enol ArH), 7.66-7.70 (1H, m, ketoester ArH) 10.35 (1H, br. s, enol OH). δ_C ($CDCl_3$) 14.1 (ketoester CH_3), 14.3 (enol CH_3), 30.2 (ketoester CH_2), 32.4 (enol CH_2), 53.2 (ketoester CH), 60.0 (enol CH_2), 61.5 (ketoester CH_2), 102.4 (enol C), 120.5 (enol CH), 124.4 ketoester CH), 124.6 (enol CH), 126.5 (ketoester CH), 126.7 (enol CH), 127.6 (ketoester CH), 129.2 (enol CH), 135.1 (ketoester and enol C), 135.3 (ketoester CH), 143.1 (ketoester and enol C), 153.6 (enol C), 169.0 (ketoester and enol C=O), 199.5 (ketoester C=O). m/z (ES$^+$) 205 ($[M+H]^+$, 100 %). HRMS (FAB) 205.08648 ($C_{12}H_{13}O_3$ requires 205.08647).

Synthesis of 2-Ethoxycarbonyl-2-fluoro-1-indanone (129)



2-Ethoxycarbonyl-2-fluoro-1-indanone was synthesised by following the procedure described by Shibata.[22] Quinine (1.59 g, 4.90 mmol) and Selectfluor (1.30 g, 3.68 mmol) in dry acetonitrile (60 mL) were stirred at room temperature for one hour before cooling to – 78 °C in an dry ice/acetone bath. A solution of ethyl 1-indanone-2-carboxylate (0.50 g, 2.45 mmol) in dry dichloromethane (50 mL) was then added via syringe and the reaction mixture was stirred at -78 °C for 3 h. After quenching the reaction with water (50 mL), it was warmed to room temperature before being extracted with ethyl acetate (3 × 50 mL). The combined organic phases were then washed with a 5 % hydrochloric acid solution (50 mL), saturated $NaHCO_3$ (50 mL), brine (50 mL) and then dried over sodium sulphate and the solvent was removed. The crude oil was loaded onto a silica gel column and eluted with hexane/ethyl acetate (9/1) (600 mL). All fractions containing the product were combined and the solvent was removed to yield 2-ethoxycarbonyl-2-fluoro-1-indanone as a colourless oil (0.38 g, 69 %). δ_H ($CDCl_3$) 1.20 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 3.39 (1H, dd, $^3J_{HF}$ 23.4 Hz, $^2J_{HH}$ 17.8 Hz, C*H*H), 3.76 (1H, dd, $^2J_{HH}$ 17.8 Hz, $^3J_{HF}$ 12.3 Hz, C*H*H), 4.23 (2H, q, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 7.39-7.50 (2H, m, ArH), 7.64-7.70 (1H, m, ArH) 7.76-7.80 (1H, m, ArH). δ_C ($CDCl_3$) 13.8 (CH_3), 38.1 (d, $^2J_{CF}$ 23.9 Hz, CH_2), 62.4 (CH_2), 94.4 (d, $^1J_{CF}$ 201.1 Hz, C), 125.3 (CH), 126.7 (CH), 128.6 (CH), 133.1 (C), 136.8 (CH), 151.0 (d, $^3J_{CF}$ 4.8 Hz, C), 167.2 (d, $^2J_{CF}$ 28.7 Hz, ester C=O), 195.3 (d, $^2J_{CF}$ 18.0 Hz, C=O). δ_F ($CDCl_3$) -164.4 (dd, $^3J_{HF}$ 23.6 Hz, $^3J_{HF}$ 10.7 Hz). m/z (ES^+) 223 ($[M+H]^+$, 100 %). HRMS (FAB) 223.07712 ($C_{12}H_{12}FO_3$ requires 223.07705).

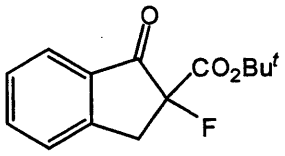
Synthesis of *tert*-Butyl 1-indanone-2-carboxylate (41)



The synthesis of *tert*-butyl 1-indanone-2-carboxylate was carried out following a procedure by Nakajima.[26] A solution of ethyl 1-indanone-2-carboxylate (0.51 g, 2.5 mmol), dibutyltin oxide (0.06 g, 0.25 mmol) and dry *tert*-butanol (1.4 mL, 25 mmol) in toluene (25 mL) was refluxed for 19 h under a nitrogen atmosphere. After cooling to room temperature, the solvent was removed under reduced pressure to yield the crude product as a brown oil. This was loaded onto a silica gel column and eluted with petroleum ether (40 – 60 °C)/ethyl acetate (9/1, 300 mL) to yield the pure product as a red oil (0.13 g, 23 %). δ_H ($CDCl_3$) 1.42 (9H, s, ketoester CH_3), 1.50 (9H, s, enol CH_3), 3.26 (1H, dd, $^2J_{HH}$ 17.3 Hz, $^3J_{HH}$ 8.2 Hz, ketoester C*H*H), 3.41 (2H, s, enol CH_2), 3.43 (1H, dd, $^2J_{HH}$ 17.3 Hz, $^3J_{HH}$ 4.1 Hz, ketoester C*H*H), 3.53 (1H, dd, $^3J_{HH}$ 8.2 Hz, $^3J_{HH}$ 4.1 Hz, ketoester CH), 7.28-7.35 (2H, m, ketoester ArH, enol ArH), 7.35-7.39 (1H, m, enol ArH), 7.40-7.45 (1H, m, ketoester ArH), 7.51-7.57 (2H, m, ketoester ArH, enol ArH), 7.67-7.72 (2H, m, ketoester ArH, enol ArH),

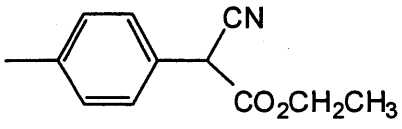
10.44 (1H, br. s, enol OH). δ_C ($CDCl_3$) 27.0 (ketoester CH_3), 27.5 (enol CH_3), 29.3 (ketoester CH_2), 31.8 (enol CH_2), 53.4 (ketoester CH), 80.0 (enol C), 81.0 (ketoester C), 103.0 (enol C), 119.5 (enol CH), 123.5 (ketoester CH), 125.5 (ketoester CH), 125.7 (enol CH), 126.3 (enol CH), 126.6 (ketoester CH), 128.0 (enol CH), 134.2 (ketoester CH), 134.4 (ketoester and enol C), 142.0 (ketoester and enol C), 152.7 (enol C), 167.3 (ketoester and enol C=O), 199.0 (ketoester C=O). m/z (ES^-) 231 ($[M-H]^-$, 55 %), 160 ($[M-OBu^t]^-$, 100 %). HRMS (FAB) 233.11785 ($C_{14}H_{16}O_3$ requires 233.11777).

Synthesis of 2-*tert*-Butoxycarbonyl-2-fluoro-1-indanone (133)



2-*tert*-Butoxycarbonyl-2-fluoro-1-indanone was synthesised by following the procedure described by Shibata.[22] Quinine (127 mg, 0.392 mmol) and Selectfluor (104 mg, 0.294 mmol) were stirred in acetonitrile (3 mL) at room temperature for one hour before cooling to – 78 °C in a dry ice/acetone bath. A solution of *tert*-butyl 1-indanone-2-carboxylate (45.9 mg, 0.196 mmol) in dichloromethane (4 mL) was then added via syringe and the reaction mixture was stirred at -78 °C for 3 h. After quenching the reaction with water (4 mL), it was warmed to room temperature and extracted with ethyl acetate (3 × 4 mL). The combined organic phases were washed with 5 % hydrochloric acid solution (4 mL), saturated $NaHCO_3$ (4 mL), brine (4 mL) and then dried over sodium sulphate and the solvent was removed. The crude oil was loaded onto a silica gel column and eluted with hexane/ethyl acetate (9/1) (50 mL). All fractions containing the product were combined and the solvent was removed to yield 2-ethoxycarbonyl-2-fluoro-1-indanone as a colourless oil (40.2 mg, 81 %). δ_H ($CDCl_3$) 1.36 (9H, s, CH_3), 3.33 (1H, dd, $^3J_{HF}$ 22.8 Hz, $^2J_{HH}$ 17.5 Hz, C*H*H), 3.66 (1H, dd, $^2J_{HH}$ 17.5 Hz, $^3J_{HF}$ 10.8 Hz, C*H*H), 7.35-7.45 (2H, m, ArH), 7.58-7.65 (1H, m, ArH), 7.74-7.80 (1H, m, ArH). δ_C ($CDCl_3$) 26.8 (CH_3), 37.3 (d, $^2J_{CF}$ 23.9 Hz, CH_2), 83.1 (C), 93.4 (d, $^1J_{CF}$ 202.3 Hz, C), 124.4 (CH), 125.4 (CH), 127.5 (CH), 132.6 (C), 135.4 (CH), 149.9 (C), 165.2 (d, $^2J_{CF}$ 27.5 Hz, ester C=O), 194.6 (d, $^2J_{CF}$ 23.9 Hz, C=O). δ_F ($CDCl_3$) -164.0 (dd, $^3J_{HF}$ 23.6 Hz, $^3J_{HF}$ 10.7 Hz). m/z (FAB^+) 251 ($[M]^+$, 100 %). HRMS (FAB) 251.10837 ($C_{14}H_{15}FO_3$ requires 251.10835).

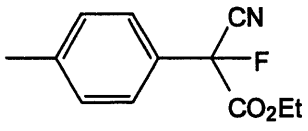
Synthesis of Ethyl α-cyano-*p*-tolylacetate (135)



Ethyl α-cyano-*p*-tolylacetate was synthesised following a procedure by Takeuchi.[27] Sodium hydride (60 % dispersion in mineral oil, 2.40 g, 60 mmol) and diethyl carbonate (7.3 mL, 60 mmol) was added to a stirred solution of *p*-tolylacetonitrile (4.85 mL, 37 mmol) in dry THF (80 mL). The mixture was refluxed for 2 h before quenching with water

(40 mL). The THF was removed from the mixture and the resulting solution was acidified to pH 1 with concentrated hydrochloric acid. The aqueous solution was extracted with ethyl acetate (3 × 40 mL) and the organic phases were combined, washed with brine (40 mL), dried over $MgSO_4$ and the solvent was removed. The resulting oil was purified by column chromatography on silica gel and eluted with hexane/ethyl acetate (10/1) (400 mL) to yield pure ethyl α-cyano-*p*-tolylacetate as a colourless oil (2.16 g, 29 %). δ_H ($CDCl_3$) 1.21 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 2.29 (3H, s, $ArCH_3$), 4.16 (2H, qd, $^3J_{HH}$ 7.0 Hz, $^5J_{HH}$ 1.2 Hz, CH_2CH_3), 4.60 (1H, s, CH), 7.15 (2H, d, $^3J_{HH}$ 8.2 Hz, ArH), 7.27 (2H, d, $^3J_{HH}$ 8.2 Hz, ArH). δ_C ($CDCl_3$) 13.9 (CH_3), 21.1 (CH_3) 43.3 (CH), 63.1 (CH_2), 116.0 (CN), 127.2 (C), 127.8 (CH), 130.0 (CH), 139.2 (C), 165.2 (C=O). m/z (ES^+) 204 ($[M+H]^+$, 100 %). HRMS (FAB) 204.10250 ($C_{12}H_{14}NO_2$ requires 204.10245).

Synthesis of Ethyl α-cyano-α-fluoro-α-tolylacetate (24)



Ethyl α-cyano-α-fluoro-α-tolylacetate was synthesised by following the procedure described by Shibata.[22] Quinine (1.60 g, 4.93 mmol) and Selectfluor (1.30 g, 3.70 mmol) were stirred in dry acetonitrile (30 mL) at room temperature for one hour before cooling to – 78 °C in a dry ice/acetone bath. A solution of ethyl α-cyano-*p*-tolylacetate (0.50 g, 2.46 mmol) in dry dichloromethane (40 mL) was then added via syringe and the reaction mixture was stirred at -78 °C for 2 h. After quenching the reaction with water (50 mL), it was warmed to room temperature and then extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with 5 % hydrochloric acid solution (50 mL), saturated $NaHCO_3$ (50 mL), brine (50 mL), dried over sodium sulphate and the solvent was removed. The crude oil was loaded onto a silica gel column and eluted with hexane/ethyl acetate (9/1) (250 mL). All fractions containing the product were combined and the solvent was removed to yield ethyl α-cyano-α-fluoro-α-tolylacetate as a colourless oil (0.49 g, 89 %). δ_H ($CDCl_3$) 1.21 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_2CH_3), 2.31 (3H, s, $ArCH_3$), 4.18-4.31 (2H, m, CH_2CH_3), 7.19 (2H, d, $^3J_{HH}$ 8.2 Hz, ArH), 7.44 (2H, d, $^3J_{HH}$ 8.2 Hz, ArH). δ_C ($CDCl_3$) 13.8 (CH_3), 21.3 (CH_3), 64.3 (CH_2), 87.1 (d, $^1J_{CF}$ 196.3 Hz, C), 114.1 (d, $^2J_{CF}$ 32.3 Hz, CN), 125.5 (d, $^3J_{CF}$ 4.8 Hz, CH), 128.6 (d, $^2J_{CF}$ 23.9, C), 129.9 (CH), 141.7 (d, $^5J_{CF}$ 2.4 Hz, C), 163.1 (d, $^2J_{CF}$ 29.9 Hz, C=O). δ_F ($CDCl_3$) -143.8 (s). m/z (ES^+) 221 ($[M]^+$, 10 %) 202 ($[M-F]^+$, 70 %), 195 ($[M-CN]^+$, 80 %). HRMS (FAB) 221.08519 ($C_{12}H_{12}FNO_2$ requires 221.08521).

5.9 Substrate Testing Procedures

Fluorination of Ethyl 1-indanone-2-carboxylate Using Selectfluor

The *N*-fluorocinchona alkaloid tetrafluoroborate was prepared *in situ* by stirring Selectfluor (104 mg, 0.294 mmol) with the corresponding cinchona alkaloid (0.392 mmol) in acetonitrile (3 mL) for 1 h at room temperature. The reaction was then cooled to – 78 °C and a solution of ethyl 1-indanone-2-carboxylate (40.0 mg, 0.196 mmol) in dichloromethane (4 mL) was added. After stirring for 3.5 h, the reaction was quenched by the addition of water (4 mL) and warmed to room temperature. The organic layer was removed and the aqueous layer was extracted with ethyl acetate (3 × 4 mL). The combined organic phases were then washed with a 5 % hydrochloric acid solution (4 mL), saturated $NaHCO_3$ (4 mL), brine (4 mL) and dried over sodium sulphate. The solvent was removed under reduced pressure to give the crude product, which was then loaded onto a silica gel column and eluted with hexane/ethyl acetate (10/1, 50 mL) to yield the pure 2-ethoxycarbonyl-2-fluoro-1-indanone as a colourless oil. The enantiomers were separated on a Chiralcel OJ column eluted with 10 % isopropanol in hexane. The flow rate of the mobile phase was set to 1 mL/min. R_t = 20.2 min (enantiomer 1), R_t = 29.5 min (enantiomer 2).

Fluorination of Ethyl 1-indanone-2-carboxylate Using NFSI

The *N*-fluorocinchona alkaloid benzenesulphonimide was prepared *in situ* by stirring NFSI (93 mg, 0.294 mmol) with the corresponding cinchona alkaloid (0.392 mmol) in acetonitrile (3 mL) for 1 h at room temperature. The reaction was then cooled to – 78 °C and a solution of ethyl 1-indanone-2-carboxylate (40.0 mg, 0.196 mmol) in dichloromethane (4 mL) was added. After stirring for 3.5 h, the reaction was quenched by the addition of water (4 mL) and warmed to room temperature. The organic layer was removed and the aqueous layer was extracted with ethyl acetate (3 × 4 mL). The combined organic phases were then washed with a 5 % hydrochloric acid solution (4 mL), saturated $NaHCO_3$ (4 mL), brine (4 mL) and dried over sodium sulphate. The solvent was removed under reduced pressure to give the crude product, which was then loaded onto a silica gel column and eluted with hexane/ethyl acetate (10/1, 50 mL) to yield the pure 2-ethoxycarbonyl-2-fluoro-1-indanone as a colourless oil. In some cases the product was not sufficiently pure so was purified further on a silica gel column and eluted with hexane/diethyl ether (10/1, 50 mL). The enantiomers were separated on a Chiralcel OJ column eluted with 10 % isopropanol in hexane. The flow rate of the mobile phase was set to 1 mL/min. R_t = 20.2 min (enantiomer 1), R_t = 29.5 min (enantiomer 2).

Fluorination of Ethyl 1-indanone-2-carboxylate Using Pre-Formed *N*-Fluorocinchona Alkaloid Reagents

A solution of the pre-formed *N*-fluorocinchona alkaloid reagent (0.392 mmol) in acetonitrile (3 mL) was cooled to – 78 °C and a solution of ethyl 1-indanone-2-carboxylate (40.0 mg, 0.196 mmol) in dichloromethane (4 mL) was added. After stirring for 3.5 h, the reaction was quenched by the addition of water (4 mL) and allowed to warm to room temperature. The organic layer was removed and the aqueous layer was extracted with ethyl acetate (3 × 4 mL). The combined organic phases were then washed with a 5 % hydrochloric acid solution (4 mL), saturated $NaHCO_3$ (4 mL), brine (4 mL) and dried over sodium sulphate. The solvent was removed under reduced pressure to give the crude product, which was loaded onto a silica gel column and eluted with hexane/ethyl acetate (10/1, 50 mL) to yield the pure 2-ethoxycarbonyl-2-fluoro-1-indanone as a colourless oil. The enantiomers were separated on a Chiralcel OJ column eluted with 10 % isopropanol in hexane. The flow rate of the mobile phase was set to 1 mL/min. R_t = 20.2 min (enantiomer 1), R_t = 29.5 min (enantiomer 2).

Fluorination of Ethyl α-cyano-*p*-tolylacetate Using Selectfluor

The *N*-fluorocinchona alkaloid tetrafluoroborate was prepared *in situ* by stirring Selectfluor (131 mg, 0.370 mmol) with the corresponding cinchona alkaloid (0.493 mmol) in acetonitrile (3 mL) for 1 h at room temperature. The reaction was then cooled to – 78 °C and a solution of ethyl α-cyano-*p*-tolylacetate (50.0 mg, 0.246 mmol) in dichloromethane (4 mL) was added. After stirring for 2 h, the reaction was quenched by the addition of water (4 mL) and allowed to warm to room temperature. The organic layer was removed and the aqueous layer was extracted with ethyl acetate (3 × 4 mL). The combined organic phases were then washed with a 5 % hydrochloric acid solution (4 mL), saturated $NaHCO_3$ (4 mL), brine (4 mL) and dried over sodium sulphate. The solvent was removed under reduced pressure to give the crude product, which was then loaded onto a silica gel column and eluted with hexane/ethyl acetate (9/1, 30 mL) to yield the pure ethyl α-cyano-α-fluoro-α-tolylacetate as a colourless oil. The enantiomers were separated on a Chiralcel OJ column eluted with 1 % isopropanol in hexane. The flow rate of the mobile phase was set to 1 mL/min. R_t = 19.4 min (enantiomer 1), R_t = 21.7 min (enantiomer 2).

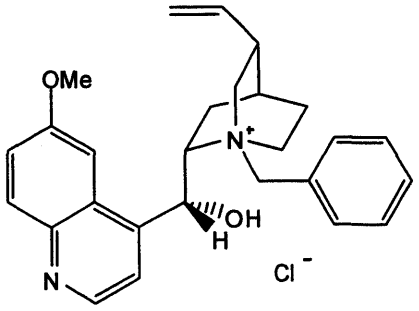
Fluorination of tert-Butyl 1-indanone-2-carboxylate Using Selectfluor

The *N*-fluorocinchona alkaloid tetrafluoroborate was prepared *in situ* by stirring Selectfluor (69 mg, 0.196 mmol) with the corresponding cinchona alkaloid (0.261 mmol) in acetonitrile (2 mL) for 1 h at room temperature. The reaction was then cooled to – 78 °C and a

solution of *tert*-butyl 1-indanone-2-carboxylate (30.3 mg, 0.131 mmol) in dichloromethane (3 mL) was added. After stirring for 3 h, the reaction was quenched by the addition of water (3 mL) and allowed to warm to room temperature. The organic layer was removed and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic phases were then washed with a 5 % hydrochloric acid solution (3 mL), saturated $NaHCO_3$ (3 mL), brine (3 mL) and dried over sodium sulphate. The solvent was removed under reduced pressure to give the crude product, which was then loaded onto a silica gel column and eluted with hexane/ethyl acetate (10/1, 30 mL) to yield the pure 2-tert-butoxycarbonyl-2-fluoro-1-indanone as a colourless oil. The enantiomers were separated on a Chiralcel OJ column eluted with 5 % isopropanol in hexane. The flow rate of the mobile phase was set to 1 mL/min. R_t = 10.9 min (enantiomer 1), R_t = 13.1 min (enantiomer 2).

5.10 Chiral Phase-Transfer Catalysts

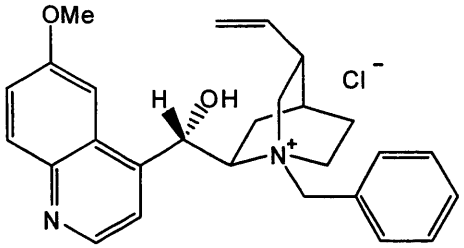
Synthesis of *N*-Benzylquininium Chloride (166)



The synthesis of *N*-benzylquininium chloride was carried out based on a procedure by Jacobs.[28] Benzyl chloride (0.18 mL, 1.57 mmol) was added slowly to a stirred solution of quinine (0.51 g, 1.57 mmol) in acetone (50 mL) at room temperature. The reaction mixture was refluxed overnight and was then cooled to room temperature. After removing the solvent, the residue was dissolved in the minimum volume of hot ethanol and diethyl ether was added until the solution turned cloudy and it was cooled in ice. The solid was then filtered and dried under oil pump vacuum. The known compound, *N*-benzylquininium chloride, was obtained as a white powder (0.49 g, 75 %). M.p. 182-184 °C (lit.,[28] 183-188 °C). $[\alpha]_D$ (MeOH) -320.0 ° (*c* = 1). δ_H ($CDCl_3$, 400 MHz) 1.48-1.57 (1H, m, NCH_2CHH), 1.70-1.78 (1H, m, NCH_2CHH), 2.02-2.06 (1H, m, NCH_2CH_2CH), 2.28-2.41 (2H, m, NCH_2CHH), 2.55-2.62 (1H, m, NCH_2CH), 3.05-3.14 (1H, m, $NCHH$), 3.19-3.27 (1H, m, $NCHH$), 3.48-3.56 (1H, m, $NCHH$), 3.77-3.83 (1H, m, $NCHH$), 3.99 (3H, s, OCH_3), 4.60-4.67 (1H, d, $^3J_{HH}$ 10.6 Hz, NCH), 5.06 (2H, d, $^2J_{HH}$ 11.7 Hz, $PhCHH$), 5.11 (1H, d, $^3J_{HH}$ 17.2 Hz, $CH=CHH$), 5.61 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^3J_{HH}$ 10.2 Hz, $^3J_{HH}$ 7.0 Hz, $CH=CH_2$), 6.26 (1H, d, $^3J_{HH}$ 10.2 Hz, $CH=CHH$), 7.00 (1H, s, $C(OH)H$), 7.31-7.49 (6H, m, PhH, ArH(7')), 7.75 (1H, d, $^4J_{HH}$ 2.7 Hz, ArH(5')), 7.77 (1H, d, $^3J_{HH}$ 4.3 Hz, ArH(3')), 8.04 (1H, d, $^3J_{HH}$ 9.0 Hz, ArH(8')), 8.75 (1H, d, $^3J_{HH}$ 4.3 Hz, ArH(2')). δ_C ($CDCl_3$, 400 MHz) 21.6 (CH_2), 24.9 (CH_2), 26.7 (CH), 38.2 (CH), 50.9 (CH_2), 56.2 (CH_3), 61.3 (CH_2), 63.9 (CH_2), 64.2 (CH), 70.4 (CH), 102.0 (CH), 118.1 (CH_2), 120.5 (CH), 120.8 (CH), 126.8 (C), 127.1 (C), 129.3 (CH), 130.7

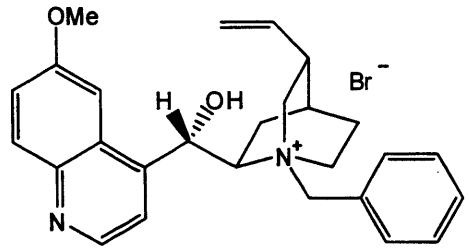
(CH), 132.2 (CH), 133.8 (CH), 136.4 (CH), 142.2 (C), 143.3 (C), 147.9 (CH), 159.4 (C). m/z (ES^+) 415 ($[M]^+$, 100 %). HRMS (FAB) 415.23780 ($C_{27}H_{31}N_2O_2$ requires 415.23778).

Attempted Synthesis of *N*-Benzylquinidinium Chloride (167)



The synthesis of *N*-benzylquinidinium chloride was carried out based on a procedure by Jacobs.[28] Benzyl chloride (0.35 mL, 3.09 mmol) was added slowly to a stirred solution of quinidine (1.01 g, 3.09 mmol) in acetone (50 mL) at room temperature. The reaction mixture was refluxed overnight and was then cooled to room temperature. After removing the solvent, the residue was dissolved in the minimum volume of hot ethanol and diethyl ether was added until the solution turned cloudy and it was cooled in ice. The solid was then filtered and dried under oil pump vacuum, but the ^{1}H NMR and mass spectrum showed that no reaction had occurred.

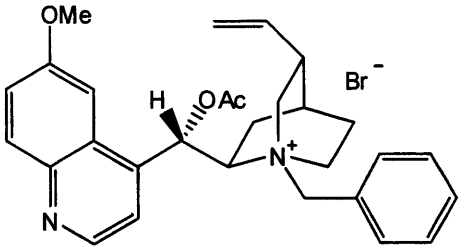
Synthesis of *N*-Benzylquinidinium Bromide (168)



The synthesis of *N*-benzylquinidinium bromide was carried out based on a procedure by Jacobs.[28] Benzyl bromide (0.37 mL, 3.09 mmol) was added slowly to a stirred solution of quinidine (1.00 g, 3.09 mmol) in acetone (50 mL) at room temperature. After refluxing the reaction mixture was refluxed overnight, it was cooled to room temperature and the solvent was removed. The residue was dissolved in the minimum volume of hot ethanol and diethyl ether was added. The ^{1}H NMR spectrum of the product showed it to be mainly the desired *N*-benzylquinidinium bromide and the data is reported, but due to the presence of the *N*-benzyldihydroquinidine bromide impurity, the product was obtained as a yellow oil. (0.94 g, 74 %). $[\alpha]_D$ (MeOH) 141.0 ° (c = 1). δ_H ($CDCl_3$, 400 MHz) 0.90-0.98 (1H, m, NCH_2CHH), 1.67-1.81 (2H, m, NCH_2CHH, NCH_2CH_2CH), 2.28-2.40 (2H, m, NCH_2CHH), 2.79-2.89 (1H, m, NCH_2CH), 3.29-3.37 (1H, m, NC*H*H), 3.83 (3H, s, OCH_3), 3.98-4.05 (1H, m, NC*H*H), 4.14-4.22 (1H, m, NC*H*H), 4.43-4.51 (1H, m, NC*H*H), 5.10-5.16 (1H, m, NCH), 5.14 (1H, d, $^3J_{HH}$ 17.2 Hz, CH=CHH), 5.15 (1H, d, $^3J_{HH}$ 10.2 Hz, CH=CHH), 5.20 (1H, d, $^2J_{HH}$ 11.7 Hz, PhCHH), 5.61 (1H, d, $^2J_{HH}$ 11.7 Hz, PhCHH), 5.86 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^3J_{HH}$ 10.2 Hz, $^3J_{HH}$ 7.0 Hz, $CH=CH_2$), 6.40 (1H, s, C(OH)*H*), 7.16 (1H, dd, $^3J_{HH}$ 9.0 Hz, $^4J_{HH}$ 2.3 Hz, ArH(7')), 7.23-7.32 (5H, m, PhH), 7.51 (1H, d, $^4J_{HH}$ 2.3 Hz, ArH(5')), 7.71 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(3')), 7.85 (1H, d, $^3J_{HH}$ 9.0 Hz, ArH(8')), 8.51 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_C ($CDCl_3$) 21.5 (CH_2), 23.9 (CH_2), 27.1 (CH), 38.1 (CH), 53.9 (CH_2), 56.3 (CH_3), 56.9 (CH_2),

62.8 (CH_2), 67.8 (CH), 77.4 (C), 102.7 (CH), 118.0 (CH_2), 120.7 (CH), 121.5 (CH), 126.3 (C), 127.2 (C), 129.4 (CH), 130.3 (CH), 130.9 (CH), 134.0 (CH), 135.8 (CH), 143.4 (C), 143.6 (C), 146.7 (CH), 157.9 (C). m/z (ES^+) 415 ($[M]^+$, 100 %). m/z (ES^-) 79/81 ($[Br]^-$, 100 %), 81 ($[Br]^-$, 100 %). HRMS (FAB) 415.23765 ($C_{27}H_{31}N_2O_2$ requires 415.23778).

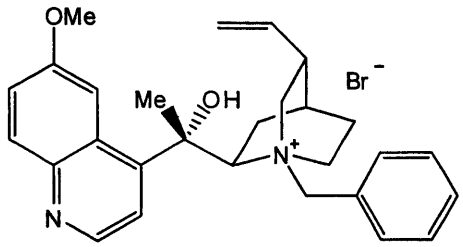
Synthesis of *N*-Benzyl-*O*-Acetylquinidinium Bromide (169)



The synthesis of *N*-Benzyl-*O*-acetylquinidinium bromide was carried out based on a procedure by Jacobs.[28] Benzyl bromide (0.08 mL, 0.68 mmol) was added slowly to a stirred solution of quinidine acetate (0.25 g, 0.68 mmol) in acetone (15 mL) at room temperature. After refluxing the reaction mixture overnight, it was cooled to room temperature and the solvent was removed. The residue was dissolved in the minimum volume of chloroform, loaded onto a silica gel column and eluted with chloroform (50 mL) to remove the benzyl bromide impurity, then chloroform/methanol (95/5, 100 mL) to remove the product. The ^1H NMR spectrum of the product showed it to be mainly the desired *N*-benzyl-*O*-acetylquinidinium bromide and the data is reported, but due to the presence of the *N*-benzyl-*O*-acetyldihydroquinidinium bromide impurity, the product was obtained as an orange oil (0.28 g, 88 %). $[\alpha]_D$ (MeOH) 67.0 ° (*c* = 1). δ_H ($CDCl_3$, 400 MHz) 1.57-1.93 (3H, m, NCH_2CHH, NCH_2CH_2CH), 2.16 (3H, s, CH_3), 2.38-2.55 (2H, m, NCH_2CHH), 3.35-3.49 (1H, m, NCH_2CH), 3.59-3.68 (1H, m, $NCHH$), 3.55 (3H, s, OCH_3), 4.72-4.80 (1H, m, $NCHH$), 4.92-4.98 (2H, m, $NCHH$), 5.03-5.13 (1H, m, NCH), 5.19 (1H, d, $^3J_{HH}$ 17.2 Hz, $CH=CHH$), 5.22 (1H, d, $^2J_{HH}$ 10.2 Hz, $PhCHH$), 5.28 (1H, d, $^2J_{HH}$ 10.2 Hz, $PhCHH$), 5.71 (1H, d, $^3J_{HH}$ 10.5 Hz, $CH=CHH$), 5.90 (1H, ddd, $^3J_{HH}$ 17.2, $^3J_{HH}$ 10.5, $^3J_{HH}$ 6.7, $CH=CH_2$), 6.35 (1H, d, $^3J_{HH}$ 8.2 Hz, $CHOC(O)CH_3$), 7.16-7.51 (5H, m, PhH), 7.87 (1H, dd, $^3J_{HH}$ 9.3 Hz, $^4J_{HH}$ 2.7 Hz, ArH(7')), 7.93 (1H, d, $^4J_{HH}$ 2.7 Hz, ArH(5')), 8.15 (1H, d, $^3J_{HH}$ 4.3 Hz, ArH(3')), 8.28 (1H, d, $^3J_{HH}$ 9.3 Hz, ArH(8')), 9.61 (1H, d, $^3J_{HH}$ 4.3 Hz, ArH(2')). δ_C (MeOD, 400 MHz) 21.9 (CH_3), 23.5 (CH_2), 24.5 (CH_2), 28.3 (CH), 38.7 (CH), 56.3 (CH_2), 57.2 (CH_3), 58.7 (CH_2), 62.6 (CH_2), 68.4 (CH), 69.8 (CH), 105.2 (CH), 118.4 (CH_2), 121.8 (CH), 123.0 (CH), 128.7 (C), 129.0 (CH), 129.6 (C), 130.2 (CH), 130.7 (CH), 132.0 (CH), 137.8.3 (CH), 137.9 (C), 148.1 (CH), 152.7 (C), 162.0 (C), 171.1 (C=O). m/z (ES^+) 457 ($[M]^+$, 100 %). m/z (ES^-) 79/81 ($[Br]^-$, 100 %). HRMS (FAB) 457.24819 ($C_{29}H_{33}N_2O_3$ requires 457.24829).

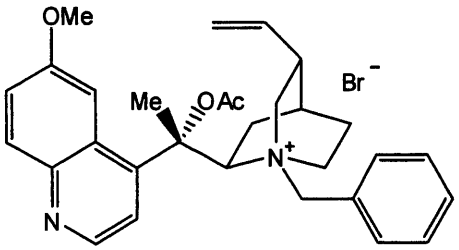
Synthesis of *N*-Benzyl-9-Methylquinidinium Bromide (170)

The synthesis of *N*-benzyl-9-methylquinidinium bromide was carried out based on a procedure by Jacobs.[28] Benzyl bromide (0.09 mL, 0.74 mmol) was added slowly to a stirred



solution of 9-methylquinidine (0.25 g, 0.74 mmol) in acetone (15 mL) at room temperature. After refluxing the reaction mixture overnight, it was cooled to room temperature and the solvent was removed. The residue was dissolved in the minimum volume of hot ethanol and diethyl ether was added until the solution turned cloudy when it was cooled in ice. The solid was then filtered and dried under oil pump vacuum. The ^{1}H NMR spectrum of the brown powder showed a mixture of *N*-benzyl-9-methylquinidinium bromide and 9-methylquinidine so the solid was dissolved in the minimum volume of chloroform and loaded onto a silica gel column. The column was eluted with chloroform (50 mL) to remove any benzyl bromide residue and then it was eluted with chloroform/methanol (95/5, 100 mL). All fractions containing the product were combined and *N*-benzyl-9-methylquinidinium bromide was obtained as a yellow oil (0.12 g, 38 %). $[\alpha]_D$ (MeOH) 7.9 ° (*c* = 0.5). δ_H ($CDCl_3$) 1.86-1.94 (1H, m, NCH_2CHH), 2.29 (3H, s, CH_3), 2.45-2.57 (1H, m, NCH_2CHH), 2.69-2.79 (1H, m, NCH_2CH_2CH), 3.20-3.28 (1H, m, NCH_2CHH), 3.43-3.57 (2H, m, NCH_2CHH, NCH_2CH), 3.94 (3H, s, OCH_3), 4.06-4.14 (1H, m, $NCHH$), 4.19-4.27 (1H, m, $NCHH$), 4.42-4.52 (1H, m, $NCHH$), 4.67-4.75 (1H, m, $NCHH$), 5.07-5.14 (1H, m, NCH), 5.21 (1H, d, $^3J_{HH}$ 17.6 Hz, $CH=CHH$), 5.47 (1H, d, $^2J_{HH}$ 11.0 Hz, $PhCHH$), 5.80 (1H, ddd, $^3J_{HH}$ 17.6 Hz, $^3J_{HH}$ 10.6 Hz, $^3J_{HH}$ 7.0 Hz, $CH=CH_2$), 6.20 (1H, d, $^3J_{HH}$ 10.6 Hz, $CH=CHH$), 6.35 (1H, d, $^2J_{HH}$ 11.0 Hz, $PhCHH$), 7.17-7.34 (5H, m, PhH), 7.57 (1H, dd, $^3J_{HH}$ 9.0 Hz, $^4J_{HH}$ 2.6 Hz, ArH(7')), 7.76 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(3')), 8.68 (1H, br. s, ArH(5')), 8.83 (1H, d, $^3J_{HH}$ 9.0 Hz, ArH(8')), 9.69 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_C (MeOD) 23.8 (CH_2), 28.8 (CH_2), 28.8 (CH), 31.8 (CH_3), 38.5 (CH), 58.7 (CH_3), 58.9 (CH_2), 62.6 (CH_2), 65.6 (CH_2), 71.2 (CH), 79.9 (C), 108.5 (CH), 118.0 (CH_2), 121.3 (CH), 123.8 (CH), 126.4 (C), 127.3 (C), 128.8 (CH), 130.5 (CH), 130.7 (CH), 135.3 (CH), 138.1 (CH), 147.0 (C), 147.6 (CH), 162.2 (C), 165.3 (C). m/z (ES^+) 429 ($[M]^+$, 100 %). m/z (ES^-) 79/81 ($[Br]^-$, 100 %). HRMS (FAB) 429.25330 ($C_{28}H_{33}N_2O_2$ requires 429.25338).

Synthesis of *N*-Benzyl-*O*-Acetyl-9-Methylquinidinium Bromide (171)



The synthesis of *N*-benzyl-*O*-acetyl-9-methylquinidinium bromide was carried out based on a procedure by Jacobs.[28] Benzyl bromide (0.10 mL, 0.84 mmol) was added slowly to a stirred solution of 9-methylquinidine acetate (0.32 g, 0.84 mmol) in acetone (20 mL) at room temperature. After refluxing the reaction mixture overnight, it was cooled to room temperature and the solvent was

removed. The residue was dissolved in the minimum volume of hot ethanol and diethyl ether was added when the reaction mixture was cooled in ice. The ^{1}H NMR spectrum of the orange oil showed the desired *N*-benzyl-*O*-acetyl-9-methylquinidinium bromide with a trace amount of 9-methylquinidine acetate. All attempts to the purify the product further failed. δ_H (MeOD, 400 MHz) 1.48-1.59 (1H, m, NCH_2CHH), 1.96-2.07 (1H, m, NCH_2CHH), 2.03 (3H, s, $C(O)CH_3$), 2.17-2.21 (1H, m, NCH_2CH_2CH), 2.37 (3H, s, CH_3), 2.39-2.47 (1H, m, NCH_2CHH), 2.52-2.58 (1H, m, NCH_2CHH), 2.79-2.90 (1H, m, NCH_2CH), 3.38-3.50 (1H, m, $NCHH$), 3.58-3.66 (1H, m, $NCHH$), 3.78-3.89 (2H, m, $NCHH$), 4.08 (3H, s, OCH_3), 4.15-4.34 (1H, m, NCH), 5.34 (1H, d, $^3J_{HH}$ 17.2 Hz, $CH=CH_2$), 5.37 (1H, d, $^2J_{HH}$ 11.0 Hz, $PhCHH$), 6.01 (1H, ddd, $^3J_{HH}$ 17.2 Hz, $^3J_{HH}$ 10.6 Hz, $^3J_{HH}$ 7.0 Hz, $CH=CHH$), 6.32 (1H, d, $^3J_{HH}$ 10.2 Hz, $CH=CHH$), 6.33 (1H, d, $^2J_{HH}$ 11.0 Hz, $PhCHH$), 7.37-7.57 (5H, m, PhH), 7.87 (1H, dd, $^3J_{HH}$ 9.4 Hz, $^3J_{HH}$ 2.7 Hz, ArH(7')), 8.05 (1H, d, $^4J_{HH}$ 2.7 Hz, ArH(5')), 8.30 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(3')), 8.54 (1H, d, $^3J_{HH}$ 9.4 Hz, ArH(8')), 9.54 (1H, d, $^3J_{HH}$ 4.7 Hz, ArH(2')). δ_C (MeOD, 500 MHz) 22.0 (CH_3), 23.4 (CH_2), 23.7 (CH_2), 28.5 (CH), 28.7. (CH_3), 37.8 (CH), 50.9 (CH_2), 51.9 (CH_2), 57.2 (CH_3), 62.6 (CH_2), 65.4 (CH), 66.7 (CH), 108.5 (CH), 117.5 (CH_2), 122.9 (CH), 123.5 (CH), 127.8 (C), 128.6 (CH), 129.5 (C), 130.5 (CH), 130.7 (CH), 132.6 (CH), 137.9 (C), 138.3 (CH), 146.9 (CH), 153.2 (C), 161.5 (C), 170.2 (C=O). m/z (ES^+) 471 ($[M]^+$, 100 %). m/z (ES^-) 79/81 ($[Br]^-$, 100 %). HRMS (FAB) 471.26400 ($C_{30}H_{35}N_2O_3$ requires 471.26389).

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Appendix

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Appendix

A1 Crystal Data and Structural Refinement for 8-Fluoroquinidinone

Empirical formula	C20 H21 F N2 O2	
Formula weight	340.39	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 8.511(2) Å	α= 90°.
	b = 8.112(2) Å	β= 95.658(5)°.
	c = 12.346(3) Å	γ = 90°.
Volume	848.3(4) $Å^3$	
Z	2	
Density (calculated)	1.333 Mg/m^3	
Absorption coefficient	0.094 mm^{-1}	
F(000)	360	
Crystal size	0.25 x 0.12 x 0.10 mm^3	
Theta range for data collection	2.40 to 25.00°.	
Index ranges	-10<=h<=10, -9<=k<=9, 0<=l<=14	
Reflections collected	2964	
Independent reflections	2964 [R(int) = 0.0000]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2964 / 1 / 237	
Goodness-of-fit on F^2	0.981	
Final R indices [I>2sigma(I)]	R1 = 0.0618, wR2 = 0.1139	
R indices (all data)	R1 = 0.0902, wR2 = 0.1243	
Absolute structure parameter	-1.1(15)	
Largest diff. peak and hole	0.189 and -0.186 $e.Å^{-3}$	

A2 Crystal Data and Structural Refinement for N-Fluoroquinidine Benzenesulphonimide

Empirical formula	C32 H36 F N3 O7 S2	
Formula weight	657.76	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 9.8630(17) Å	α= 100.664(3)°.
	b = 11.3944(19) Å	β= 103.523(3)°.
	c = 15.030(3) Å	γ = 90.807(3)°.
Volume	1611.0(5) $Å^3$	
Z	2	
Density (calculated)	1.356 Mg/m^3	
Absorption coefficient	0.223 mm^{-1}	
F(000)	692	
Crystal size	0.33 x 0.29 x 0.22 mm^3	
Theta range for data collection	1.82 to 26.00°.	
Index ranges	-12<=h<=12, -14<=k<=14, -18<=l<=18	
Reflections collected	12680	
Independent reflections	11221 [R(int) = 0.0195]	
Completeness to theta = 26.00°	98.9 %	
Absorption correction	Empirical	
Max. and min. transmission	0.928 and 0.804	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	11221 / 3 / 820	
Goodness-of-fit on F^2	0.971	
Final R indices [I>2sigma(I)]	R1 = 0.0426, wR2 = 0.0913	
R indices (all data)	R1 = 0.0494, wR2 = 0.0942	
Absolute structure parameter	0.05(4)	
Largest diff. peak and hole	0.403 and -0.286 $e.Å^{-3}$	

A3 Lecture Courses Attended

CH4001	Organofluorine Chemistry	Prof. J. Percy / Dr. A. Stuart
CH4003	Advanced Structure Determination	Dr. J. Malpass
CH4021	Green Chemistry	Prof. E. Hope

A4 Organic/Inorganic Seminar Programme (Autumn/Winter 2004)

4th October	*Templates and Tentacles* Dr. Stuart Warriner, University of Leeds
15th October	*The Chemistry of Interstellar Space* Prof. Eric Hebst, Ohio State University
18th October	*Continuous Flow Homogeneous Catalysis* Prof. David Cole-Hamilton, University of St. Andrews
25th October	*New Methods and Synthetic Applications of Asymmetric Heteroatom Transfer* Prof. Alan Armstrong, Imperial College London
8th November	*Chiral Lanthanide Complexes for Organic Synthesis* Dr. Helen Aspinall, University of Liverpool
15th November	*New Routes to Heterocyclic Systems from Vinylcyclopropanes* Dr. Gareth Pritchard, Loughborough University
29th November	*Polymer Imprinting: Metal Clusters That Make a Lasting Impression* Prof. Paul Walton, University of York

A5 Organic/Inorganic Seminar Programme (Spring/Summer 2005)

17th January	*Non Innocent N-Heterocyclic Carbene and Phosphine Ligands: Computational Studies* Dr. Stuart MacGregor, Heriot-Watt University, Edinburgh

7th February	*Molecular Catalysis with Group 2 Metals* Dr. Mike Hill, Imperial College, London
14th February	*Fiddling with Phosphorus* Dr. Simon Jones, University of Sheffield
7th March	*New Strategies for the Synthesis of Pyran Containing Natural Products* Dr. Paul Clark, University of Nottingham
4th April	*s-Electron Deficiency in Chemistry* Prof. P. P. Power, University of California
25th April	*Metal Helicates and Pacman Complexes – Topological Control of Bimetallic Reaction Sites Using Polypyrrolic Ligands* Dr. Jason Love, University of Nottingham
4th May	*The Synthesis of Marine Natural Products* Prof. Christine Willis, University of Bristol
6th June	*Fixed Configuration Macrocyclic Chelators: Chemokine Receptor Antagonists and Radiopharmaceuticals* Dr. Steve Archibald, University of Hull
13th June	*Combining Two-Directional Synthesis and Tandem Reactions: Developing Efficient Strategies for Synthesis* Dr. Robert Stockman, University of East Anglia
31st August	*Development of Enantioselective Fluorination Reaction and its Application to the Synthesis of Biologically Active Compounds* Prof. Norio Shibata, Nagoya Institute of Technology, Japan

A6 Organic/Inorganic Seminar Programme (Autumn/Winter 2005)

10th October	*Exploring New Strategies in Organic Synthesis via Catalytic Conjugate Addition Catalytic Organic Synthesis* Dr. Christopher Frost (University of Bath)
17th October	*Aspects of Chiral Surface Chemisty: an Electrochemical Perspective* Prof. Gary Attard (University of Cardiff)
26th October	*Structural and Functional Analogues of Molybdenum and Tungsten Oxotransferases/Hydroxylases: What can be Learned?* Prof. R. H. Holm (University of Harvard)
31st October	*Metal and Non-Metal Phenolates: Catalysts, Sensors and Surprises* Prof. Matthew Davidson (University of Bath)
7th November	*How Cells Survive - from Lipids to Liquid Crystals* Prof. Richard Templar (Imperial College London)
9th November	*Chemical Glycomics: Automated Synthesis of Carbohydrates as a Platform for Biological and Medical Research* Prof. Peter H. Seeberger (ETH, Zurich)
14th November	*Harnessing Reactive Intermediates for Organic Synthesis* Dr. Richard Grainger (University of Birmingham)
21st November	*Synergic Effects in Catalysis with Phosphorus (III) Ligands* Prof. Paul Pringle (University of Bristol)
29th November	*From Highly excited to Ultracold Molecules: Chemical Dynamics in the Extreme* Prof. Tim Softley (University of Oxford)

5th December — *Fungal Polyketides: Tales of the Unexpected*
Prof. Tom Simpson (University of Bristol)

7th December — *Studies on Solute-Solvent Interactions in Supercritical CO_2 by Using Raman Spectroscopy*
Dr Yasuhisa Ikeda

Applications of Ionic Liquids to Pyrochemical Reprocessing Methods
Dr Yasuhisa Ikeda

A7 Organic/Inorganic Seminar Programme (Spring/Summer 2006)

22nd February — Leicester Half-day Symposium

Chiral Water from Chiral Relays: Stereocontrol in the Oxy-Michael and Related Reactions
Dr. Darren Dixon (University of Manchester)

Novel Approaches for the Enantioselective Total Synthesis of Steroids
Dr. Bruno Linclau (University of Southampton)

Recent Advances in Methods for Parallel Synthesis
Prof. Tony Barrett (Imperial College)

6th March — *Enantioselective Catalysis Based on Palladium Enolate Chemistry*
Prof. M. Sodeoka (Tohoku University)

A8 Organic/Inorganic Seminar Programme (Autumn/Winter 2006)

22nd November — Leicester Green Chemistry Symposium

Green Chemistry and Ionic Liquids
Dr Neil Winterton (University of Liverpool)

Ionic Liquids In Vacuo
Dr Peter Licence (University of Nottingham)

Application of Micro-reactors for Improving Atom Efficient Chemical Reactions
Dr Paul Watts (University of Hull)

A9 Organic/Inorganic Seminar Programme (Spring/Summer 2007)

30th April — Metals In Medicine Symposium

Designing Small-Molecule Based Probes for in vitro Fluorescence Imaging
Dr Sofia I Pascu (University of Oxford)

Labelling of Bioactive Peptides with Organometallic Compounds: From Solid Phase Synthesis to Biomedical Applications
Prof. Nils Metzler-Nolte (Ruhr-Universitat Bochum)

Sensing and Imaging with Cells Permeable Luminescent Platinum Complexes
Dr Gareth Williams (University of Durham)

Carbohydrate Conjugates in Medicinal Inorganic Chemistry
Prof. Chris Orvig (University of British Columbia)

A10 Conferences Attended

October 2004, *Organic Synthesis Symposium*, Loughborough University

December 2004, *Modern Aspects of Stereochemistry*, University of Sheffield

April 2005, *26th RSC Organic Division East Midlands Regional Meeting*, Loughborough University

April 2005, *5th Bristol Synthesis Meeting*, University of Bristol

April 2005, *Fluorination Technologies – Applications and Challenges*, Syngenta, Jealott's Hill, Bracknell

October 2005, *Organic Division Half-day Symposium*, University of Loughborough

April 2006, *East Midlands Meeting of the Organic Division of the Royal Society of Chemistry*, University of Warwick

September 2006, *6th Annual Postgrad, Fluorine Subject Group Meeting*, University of Manchester

September 2006, *Organic Division: Heterocyclic and Synthesis Group*, AstraZeneca, Loughborough

March 2007, *Organic Division Half-day Symposium*, University of Loughborough

April 2007, *East Midlands Meeting of the Organic Division of the Royal Society of Chemistry*, University of Nottingham

September 2007, *7th Annual Postgrad. Fluorine Subject Group Meeting*, University of Leicester

A11 Presentations

Presentation – *'The Synthesis of Novel Electrophilic Enantioselective Fluorinating Agents'* University of Leicester, 2005

Presentation – *'The Synthesis of Novel Electrophilic Enantioselective Fluorinating Agents'* University of Leicester, 2006

Presentation – *'The Synthesis of Novel Electrophilic Enantioselective Fluorinating Agents'* University of Leicester, 2007

Poster – *'Structural Modification of Cinchona Alkaloids for the Synthesis of New Chiral Fluorinating Agents'*

6th Annual Postgrad, Fluorine Subject Group Meeting

Organic Division: Heterocyclic and Synthesis Group

East Midlands Meeting of the Organic Division of the Royal Society of Chemistry

Presentation - *'Structural Modification of Cinchona Alkaloids for the Synthesis of New Chiral Fluorinating Agents'*

7th Annual Postgrad. Fluorine Subject Group Meeting

A12 Awards

Runner-up Presentation Prize

'Structural Modification of Cinchona Alkaloids for the Synthesis of New Chiral Fluorinating Agents' - 7th Annual Postgrad. Fluorine Subject Group Meeting