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Contents

1.0	Introduction.....	1
1.1	Organocatalysis	1
1.1.1	Hydrogen bond donor mediated organocatalysis.....	2
1.1.2	Hydrogen bond acceptors	4
1.2	Bifunctional catalysis	5
1.3	Quinine: a brief history	7
1.3.1	Nomenclature for the description of cinchona alkaloid based compounds ..	9
1.3.2	Quinine: selected chemical transformations	10
1.3.3	Modification of quinine at C10-11	11
1.3.4	Modification of quinine at C-9	12
1.3.5	Modification of quinine at C-2' (and C-3')	14
1.3.6	Modification of quinine at C-5'	17
1.3.7	Modification of quinine at the C-6' position	17
1.4	Quinine derivatives as catalysts	18
1.4.1	Quinine as a hydrogen bonds donor and acceptor	18
1.4.2	Catalysts with hydrogen bond donors at C-9	19
1.4.3	Catalysts with hydrogen bond donors at C-6'	28
1.4.4	Catalysts with hydrogen bond donors at C-5'	32
1.4.5	The importance of C-10 and C-11	33
1.5	Conformational analysis of cinchona alkaloid derivatives	34
1.5.1	Available methods for obtaining conformational information	35
1.5.2	Nuclear magnetic resonance techniques for conformational studies	35
1.5.3	The conformation of quinine: associated nomenclature	38

1.5.4	Conformatinal studies on quinine, related cinchona alkaloids and their major derivatives	40
1.6	Kinetic resolution (KR) and dynamic kinetic resolution (DKR)	44
1.6.1	General requirements for efficient DKR.....	44
1.6.2	Racemisation, a crucial step for DKR.....	46
1.6.3	DKR of azlactones by alcoholysis	48
1.6.4	Non-organocatalytic methodologies for the DKR of azlactones	49
1.6.5	Nucleophilic organocatalytic methodologies for the DKR of azlactones...	51
1.6.6	Specific acid mediated DKR.....	53
1.6.7	Bifunctional hydrogen bond mediated DKR	53
1.6.8	Conclusions.....	56
2.0	Generating a library of tuneable novel organocatalysts.....	57
2.1	Synthesis of initial catalysts	57
2.1.1	Synthesis of other simple C-9 aryl quinines	59
2.2	Initial catalyst testing	64
2.2.1	Michael addition of malonates to nitrostyrene.....	66
2.2.2	The addition of 2-cyanoindanone to 2-chloroacrylonitrile	68
2.2.3	The Henry reaction	70
2.2.4	The addition of 2-methylindole to nitrostyrene	73
2.3	Synthesis of -9- <i>epi</i> -deoxyaniline quinine derivatives	80
2.4	Catalyst conformation: A preliminary analysis.....	83
2.4.1	Establishing a nomenclature for conformations of 9- <i>epi</i> -aryl-quinine derivatives.....	83
2.4.2	NMR experiments towards conformational analysis	87
2.4.3	NMR analysis of novel catalysts.....	89

2.5	Conclusions	94
3.0	The Dynamic Kinetic resolution of azlactones	95
3.1	Optimisation of reaction conditions	108
3.1.1	Examination of nucleophile loading	108
3.1.2	Optimisation of catalysts loading and concentration	110
3.1.3	Optimisation of solvent and temperature	111
3.2	DKR of azlactones by 147; and examination of substrate scope	114
3.3	DKR of azlactones by thiolysis	117
3.4	Conclusions	120
4.0	Further development of novel 9- <i>epi</i> -aryldeoxyquinine derivatives	121
4.1	Investigation of the influence of hydrogen bond donor pK_a on catalytic activity 121	
4.1.1	Evaluation of catalysts with varied pK_a	126
4.2	The effect of saturation of C-10 C-11 on catalyst performance	128
4.3	The synthesis of catalysts exploring increased steric size at C-5''	129
4.3.1	Evaluation of 303 in the DKR of <i>N</i> -benzoyl valine	132
4.4	Modification of the catalyst skeleton at C-3''	132
4.4.1	Testing of 312 and 314 in the DKR of <i>N</i> -benzoyl valine	134
4.5	Modification of the catalyst skeleton at C-6''	134
4.5.1	Testing of 327 and 340 in the DKR of azlactones	139
4.6	Modification of the catalyst skeleton at C-6'	140
4.6.1	Evaluation of C-6' modified catalysts	142
4.7	Modification of the catalyst skeleton at C-5'	143
4.8	Modification of the catalyst skeleton at C-2'	146

4.8.1	Testing of C-2'-ethyl-9- <i>epi</i> -deoxy(2-hydroxyphenyl)quinine.....	147
4.8.2	Synthesis of further catalysts modified at C-2'	147
4.8.3	Evaluation of C-2'-modified catalysts as catalysts for the DKR of 110...	150
4.9	Synthesis of an optimised catalyst	152
4.9.1	Evaluation of the optimised catalyst in the DKR of azlactones.....	152
4.10	Application of the optimised catalyst to the DKR of more activated azlactones 153	
4.11	Further investigations into the behaviour of C-9 arylated quinine derivatives	155
4.12	Conclusions	161
5.0	Experimental: General	162

5.1	Experimental data for chapter 2	163
5.2	Procedure A: General procedure for the benzylation of aromatic alcohols .	163
5.2.1	1-(benzyloxy)-2-bromobenzene (124)	163
5.2.2	1-(benzyloxy)-3-bromobenzene (125)	164
5.2.3	1-(benzyloxy)-4-bromobenzene (126)	164
5.2.4	2-(benzyloxy)-1-bromonaphthalene (149a)	165
5.2.5	2-(benzyloxy)-3-bromonaphthalene (151a)	165
5.2.6	2-(benzyloxy)-7-bromonaphthalene (143)	166
5.2.7	2-(benzyloxy)-8-bromonaphthalene (141)	166
5.2.8	1-(benzyloxy)-8-bromonaphthalene (142)	167
5.2.9	8-bromonaphthalen-2-ol (137)	168
5.2.10	8-bromo-1-aminonaphthalene (139)	169
5.2.11	8-bromonaphthalen-1-ol (140)	170
5.2.12	9-epi-chloro(deoxy)quinine (Q22a)	171
5.2.13	Procedure B: General procedure for the formation of Grignard reagents	171
5.2.15	(2 <i>S</i>)-2-((<i>R</i>)-(2-(benzyloxy)phenyl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (127)	173
5.2.16	(2 <i>S</i>)-2-((<i>S</i>)-(3-(benzyloxy)phenyl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (128)	174
5.2.17	(2 <i>S</i>)-2-((<i>S</i>)-(4-(benzyloxy)phenyl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (129)	175
5.2.18	(2 <i>S</i>)-2-((<i>R</i>)-(2-(benzyloxy)naphthalen-1-yl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (150)	176
5.2.19	(2 <i>S</i>)-2-((<i>R</i>)-(2-(benzyloxy)naphthalen-3-yl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (152)	178

5.2.20	(2 <i>S</i>)-2-((<i>S</i>)-(2-(benzyloxy)naphthalen-8-yl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (144)	179
5.2.21	(2 <i>S</i>)-2-((<i>S</i>)-(2-(benzyloxy)naphthalen-7-yl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (146)	180
5.2.22	Procedure C: General procedure for the deprotection of catalysts by hydrogenation	181
5.2.23	(8 <i>S</i> ,9 <i>S</i>)-9-(3-hydroxyphenyl)-6'-methoxy-10,11-dihydro-cinchonan (131) 182	
5.2.24	(8 <i>S</i> ,9 <i>S</i>)-9-(4-hydroxyphenyl)-6'-methoxy-10,11-dihydro-cinchonan (132) 183	
5.2.25	(8 <i>S</i> ,9 <i>S</i>)-6'-methoxy-9-(7-hydroxynaphtalen-1-yl)-cinchonan (134)	184
5.2.26	(8 <i>S</i> ,9 <i>S</i>)-6'-methoxy-9-(7-hydroxynaphtalen-2-yl)-cinchonan (135)	185
5.2.27	(8 <i>S</i> ,9 <i>R</i>)-6'-methoxy-9-(1-hydroxynaphtalen-2-yl)-cinchonan (147).....	186
5.2.28	(8 <i>S</i> ,9 <i>R</i>)-6'-methoxy-9-(2-hydroxynaphtalen-3-yl)-cinchonan (148).....	187
5.2.29	dimethyl 2-(2-nitro-1-phenylethyl)malonate (18a).....	187
5.2.30	2-bromo-indan-1-one (157)	188
5.2.31	2-cyano-indan-1-one (158)	189
5.2.32	2-(2-chloro-2-cyanoethyl)-2-cyano-indan-1-one (161)	190
5.2.33	Ethyl 2-hydroxy-2-methyl-3-nitropropanoate (164).....	191
5.2.34	Ethyl 2-hydroxy-3-nitro-2-phenylpropanoate (166).....	191
5.2.35	2-methyl-3-(2-nitro-1-phenylethyl)-1 <i>H</i> -indole (170).....	192
5.2.36	2-Phenyl-4-isopropylloxazolone (110)	192
5.2.37	<i>N</i> -Benzoylvaline, allyl ester (114)	193
5.2.38	3-Phenylglutaric anhydride (173)	194
5.2.39	5-Methoxy-3-phenyl-5-oxopentanoic acid (174).....	194

5.2.40	Representative NMR experiments for the determination of conformations in C-9 arylated quinine derivative 131 and 132.....	195
5.3	Experimental data for chapter 3	197
5.3.1	Procedure D: General procedure for the strecker synthesis of amino acids. ²⁴⁷	197
5.3.2	2-amino-2-cyclohexylacetic acid 242.HCl	198
5.3.3	2-amino-3-ethylpentanoic acid methyl ester (241a)	198
5.3.4	2,4,6-Tribromobenzoic acid (227)	199
5.3.5	2,4,6-Tribromobenzoyl chloride (228)	199
5.3.6	2,6- <i>bis</i> -(trifluoromethyl)benzoyl chloride (233).....	200
5.3.7	Procedure E: General procedure for the synthesis of racemic <i>N</i> -benzoyl amino acids	200
5.3.8	Procedure F: General procedure for the synthesis of racemic <i>N</i> -benzoyl amino acids	201
5.3.9	<i>N</i> -2-Furoylvaline (206).....	202
5.3.10	<i>N</i> -Tritoyl Valine (210).....	204
5.3.11	Conversion of <i>N</i> -protected amino acids to azlactones.....	209
5.3.12	Cyclization procedure using DCC:	209
5.3.13	Cyclization procedure using EDCI:	210
5.3.14	Dynamic kinetic resolution of azlactones	210
5.3.15	Procedure G: General procedure for the dynamic kinetic resolution of racemic azlactones	210
5.3.16	General procedure H for the dynamic kinetic resolution of racemic azlactones.....	218
5.3.17	Sample preparation for CSP-HPLC analysis: Procedure for hydrogenolysis	219

5.3.18	N-2-furoylnorleucine (277a).....	223
5.3.19	N-2-furoylnorleucine 4- <i>t</i> -butylbenzyl thioester (278)	223
5.4	Experimental data for chapter 4	225
5.4.1	Procedure I: procedure for the deprotection of catalysts by acetal cleavage. 225	
5.4.2	(1S,2S,4S,5R)-2-((R)-(2-(methoxymethoxy)-5-(trifluoromethyl)phenyl)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (294).....	228
5.4.3	-2-((R)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)-4-(trifluoromethyl)phenol (281)	231
5.4.4	2-bromo-4-(tert-butyl)-1-(methoxymethoxy)benzene (298)	232
5.4.5	(1S,2S,4S,5R)-2-((R)-(5-(tert-butyl)-2-(methoxymethoxy)phenyl)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (302).....	233
5.4.6	4-(tert-butyl)-2-((R)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)phenol (303).....	235
5.4.7	1,3-dichloro-2-iodobenzene (305)	236
5.4.8	2'-iodo-1,1':3',1''-terphenyl (306)	237
5.4.9	4''-(benzyloxy)-3'-phenyl-1,1':2',1''-terphenyl (308).....	237
5.4.10	4-(benzyloxy)-3-bromo-6'-phenyl-1,1':2',1''-terphenyl (309)	238
5.4.11	(1S,2S,4S,5R)-2-((R)-(4-(benzyloxy)-6'-phenyl-[1,1':3',1''-terphenyl]-3-yl)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (309).....	239
5.4.12	3-((R)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)-[1,1'-biphenyl]-2-ol (314)	241
5.4.13	(1S,2S,4S,5R)-2-((R)-(2-(benzyloxy)-[1,1'-biphenyl]-3-yl)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (314a)	242
5.4.14	2-bromo-6-phenylphenol (316).....	243
5.4.15	1-bromo-2-benzyloxy-3-phenylbenzene (313)	243

5.4.16	(1S,2S,4S,5R)-2-((R)-(1-(benzyloxy)naphthalen-2-yl)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (312a).....	244
5.4.17	2-((R)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)naphthalen-1-ol (312)	246
5.4.18	2-iodoresorcinol (324)	247
5.4.19	2,6-Benzyloxy-1-iodobenzene (325)	247
5.4.20	(1S,2S,4S,5R)-2-((R)-(2,6-bis(benzyloxy)phenyl)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (326).....	248
5.4.21	2-((R)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)benzene-1,3-diol (327).....	249
5.4.22	1-(benzyloxy)-3-methoxybenzene (338)	250
5.4.23	1-(benzyloxy)-2-iodo-3-methoxybenzene (333).....	251
5.4.24	(1S,2S,4S,5R)-2-((R)-(2-(benzyloxy)-6-methoxyphenyl)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (335).....	252
5.4.25	3-methoxy-2-((R)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)phenol (339).....	254
5.4.26	Cupreine (341)	255
5.4.27	6'-isopropylquinine (342)	256
5.4.28	(1S,2S,4S,5R)-2-((R)-(6-isopropoxyquinolin-4-yl)(2-(methoxymethoxy)phenyl)methyl)-5-vinylquinuclidine (344a).....	258
5.4.29	2-((R)-(6-isopropoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)phenol (344).....	259
5.4.30	1-((R)-(6-isopropoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)naphthalen-2-ol (345)	260
5.4.31	5'-nitroquinine (346).....	262
5.4.32	5'-aminoquinine (347)	262

5.4.33	5'-Chloroquinine (348)	263
5.4.34	5-bromo-1,3-di-tert-butyl-2-methoxybenzene (362)	265
5.4.35	(1S,2S,4S,5R)-2-((R)-(2-(3,5-di-tert-butyl-4-methoxyphenyl)-6-methoxyquinolin-4-yl)(2-(methoxymethoxy)naphthalen-1-yl)methyl)-5-vinylquinuclidine (361a).....	266
5.4.36	1-((R)-(2-(3,5-di-tert-butyl-4-methoxyphenyl)-6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)naphthalen-2-ol	267
5.4.37	1-((R)-(2-([1,1':3',1''-terphenyl]-5'-yl)-6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)naphthalen-2-ol (360).....	268
5.4.38	1-((R)-(2-(tert-butyl)-6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)naphthalen-2-ol (359)	270
5.4.39	(1S,2S,4S,5R)-2-((R)-(2-(benzyloxy)naphthalen-1-yl)(6-methoxy-2-phenylquinolin-4-yl)methyl)-5-vinylquinuclidine (351a)	272
5.4.40	1-((R)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxy-2-phenylquinolin-4-yl)methyl)naphthalen-2-ol (351)	273
5.4.41	(1S,2S,4S,5R)-2-((R)-(2-(benzyloxy)-6-methoxyphenyl)(6-methoxy-2-phenylquinolin-4-yl)methyl)-5-ethylquinuclidine (363)	274
5.4.42	2-((R)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxy-2-phenylquinolin-4-yl)methyl)-3-methoxyphenol (364)	276

Abstract

This thesis reports the synthesis of a novel class of quinine derived catalyst and its application to the field of organocatalysis. Initially, a suite of seven novel C-9 phenol and naphthol substituted quinine derivatives were synthesised. The activity of this suite of catalysts has been explored in a range of reactions. The nature of these catalysts allowed for unprecedented tuneability, indeed it was possible to discriminate between 1,2 and 1,4-addition reactions based on iterative changes to the catalyst structure, which allowed alteration to the distances between hydrogen bond donors and acceptors within the catalyst. It was also possible to identify the conformation of the catalyst as a key component in determining their selectivity. Analysis of the solution phase conformations for several of the catalysts is shown. Efforts towards making C-9 aniline-substituted derivatives have also been attempted; however this was not successful, despite the investigation of a variety of synthetic pathways.

The application of the catalysts which proved to be active in 1,2-addition reactions to the dynamic kinetic resolution of azlactones was undertaken. It was possible, based on the choice of C-9 substituent, to select for either product enantiomer without changing the stereochemistry within the catalyst. By optimisation of the azlactone substrate it was possible to increase both the reactivity and selectivity observed. The most suitable of these catalysts was shown to promote the room temperature DKR of azlactones, affording the products derived from hindered α -amino acids in up to 95% *ee*. Unfortunately for less hindered substrates enantioselectivity observed was uniformly more modest.

Further investigation of modifications to the catalyst structure aimed at improving the overall efficiency of this catalytic system has been made, with large improvements in activity and selectivity achieved. The generation of a library of novel catalysts with significantly enhanced activity profiles compared to earlier catalysts of the same class has been described. Key considerations in the synthesis of quinine derivatives modified at several positions have been considered, with the scope of C-9 arylation reactions explored in depth. Furthermore it has been possible, through systematic modification of

the catalyst to identify features in the catalyst structure which are key to both the activity and selectivity profile of these systems.

The systematic modification of the catalyst structure has been used to optimise catalyst performance in the DKR of azlactones. This has allowed for the DKR of 2,4,6-trichlorobenzene substituted azlactones with enantioselectivity in excess of 90% *ee*, even using azlactones derived from unhindered amino acids. In the case of hindered azlactones exceptional enantioselectivity could be achieved with *ee* of up to 97% possible. Interestingly it was also possible to examine the mode of action of the catalyst. It was possible to discount nucleophilic catalysis as a catalyst role despite circumstantial evidence initially favouring it as a possibility. Furthermore, it was possible to observe that the catalysts synthesised were active in more than one conformation, which could favour the promotion of the formation of different product enantiomers. The alteration of the relative populations of these conformations by changes in temperature was shown to be possible and it was even possible, in one case, to demonstrate a temperature dependent change in the sense of enantiocontrol.

Abbreviations

Å	Angstrom
Ac	Acetyl
Ar	Aryl
atm	atmosphere
BINAP	(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
Bn	Benzyl
BOC	<i>tert</i> -Butoxycarbonyl
Bu	Butyl
Bz	Benzoyl
cat.	Catalyst
Conv.	Conversion
COSY	Correlation spectroscopy
CSP	Chiral stationary phase
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
<i>de</i>	Diastereomeric excess
DEPT	Distortionless Enhancement by Polarization Transfer
DIPA	Diisopropylamine
DIPEA	Diisopropylethylamine
DKR	Dynamic Kinetic Resolution
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
EAS	Electrophilic aromatic substitution
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide)
EDG	Electron donating group
<i>ee</i>	Enantiomeric excess
<i>ent</i>	Enantiomer
eq.	Equivalent
Et	Ethyl
EWG	Electron withdrawing group
EXSY	Exchange spectroscopy
FC	Friedel-Crafts
FGI	Functional group interconversion
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HPLC	High Performance Liquid Chromatography
HSQC	Heteronuclear single-quantum correlation spectroscopy
IPA	<i>Iso</i> -propyl alcohol
IR	Infra red
KR	Kinetic Resolution
k	Rate constant

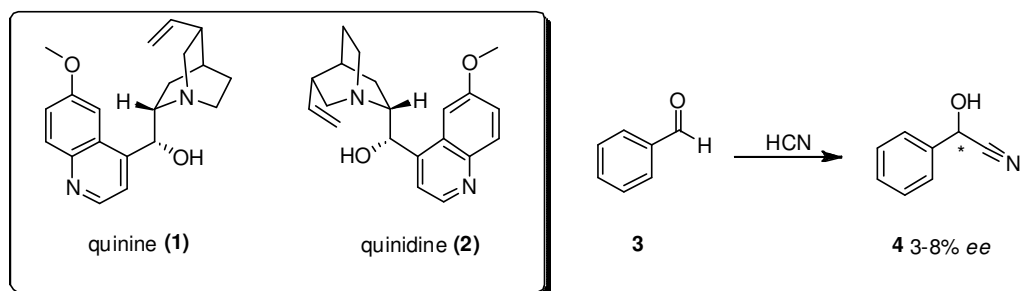
<i>m</i>	<i>meta</i>
MBH	Morita-Baylis-Hillman
Me	Methyl
MeCN	Acetonitrile
MOM	Methoxymethyl
MS	Molecular sieves
MTBE	Methyl- <i>tert</i> -butyl ether
Nap	Naphthyl
NAS	Nucleophilic aromatic substitution
NBS	N-bromosuccinimide
Nd	Not determined
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
Nu	Nucleophile
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
Ph	Phenyl
P	Product
<i>rac</i>	Racemic
ROESY	Rotating frame nuclear Overhauser effect spectroscopy
rt	Room temperature
S	Starting material
<i>sec</i>	Secondary
Taddol	$\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-1,3-dioxolane-4,5-dimethanol
TBDMS	<i>tert</i> -Butyldimethylsilyl
Tf	Triflate
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
TOCSY	Total correlation spectroscopy

1.1 Organocatalysis

The term organocatalysis is a recently coined term used to describe a long known phenomenon; the alteration of the rate of reactions by small metal free organic molecules.¹ The first organocatalyst could be considered to be acetaldehyde, observed in the promotion of the formation of oxamide from cyanogens, reported in 1860.² While organocatalytic reactions have continued to appear since this time, in the last 15 years organocatalysis has been transformed from an esoteric collection of isolated examples to a well defined area of research with many classes of reactions and catalysts.³ It is now a field of research which continues to advance at an exceptional pace.⁴⁻⁶

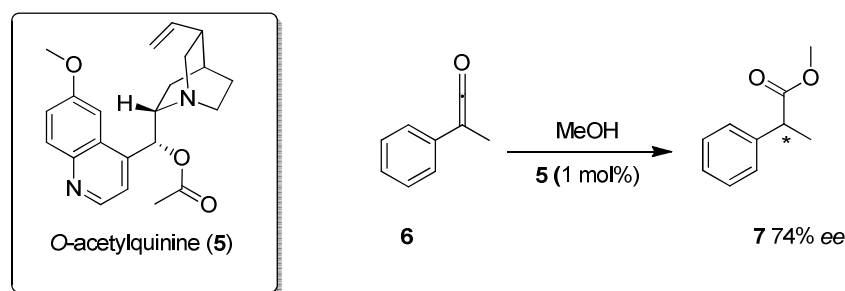
Organocatalysis offers the practitioner many obvious advantages over other methods of asymmetric synthesis.^{7,8} It is by definition, likely to be more atom economical than methods which require the use of chiral auxiliaries.⁹ It also compares favourably to other catalytic methods, being generally far simpler and more robust in execution than enzymatic methods.¹⁰ When compared to transition metal based catalysts, once the unassailable gold standard for asymmetric catalysis, it can offer several advantages.¹¹ The absence of metals removes a possible source of toxicity and the need for expensive and difficult purifications, reducing overall environmental impact,¹² while providing, in nearly all cases, much higher functional group tolerance through milder, more accessible reaction conditions.¹³

The first asymmetric organocatalytic reaction reported was the addition of hydrogen cyanide to benzaldehyde to afford mandelonitrile (Scheme 1.1).¹⁴ Reported in 1912 by G. Bredig and P. S. Fiske, they accomplished this using quinine and *pseudoenantiomeric* quinidine to afford the product with a modest 3-8% *ee*. However the conceptual importance of this reaction far outweighs any synthetic utility the reaction might have.



Scheme 1.1 The first asymmetric organocatalytic reaction

Nearly 50 years later Pracejus *et al.* demonstrated the enantioselective addition of methanol to phenylmethylketene using *O*-acetyl quinine (Scheme 1.2).¹⁵ This represents the first organocatalytic reaction to deliver synthetically useful enantioselectivity.



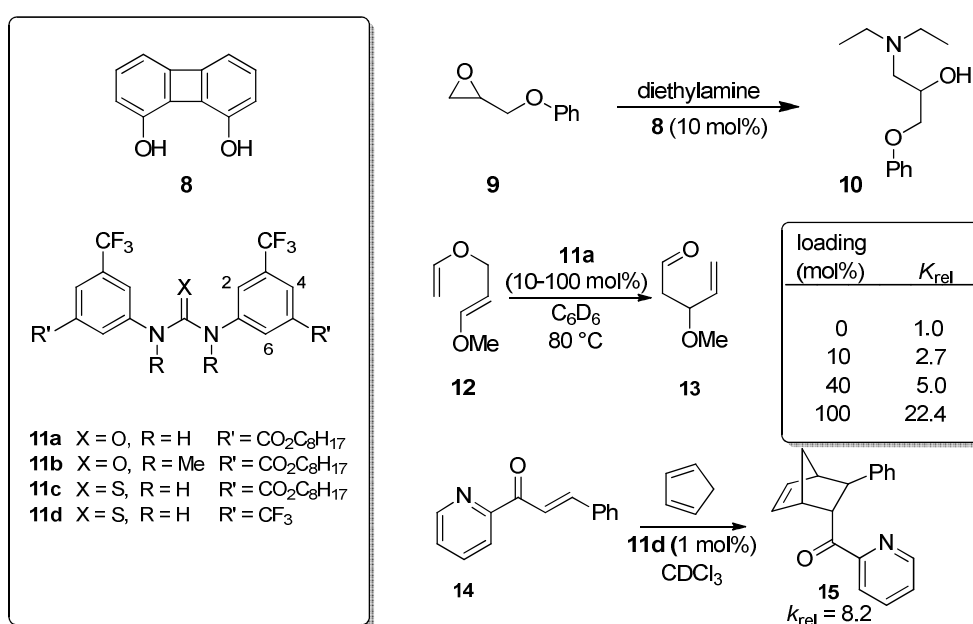
Scheme 1.2 The asymmetric addition of methanol to phenyl(methyl)ketene

From this point organocatalysis rapidly diverges into several categories such as covalent bond mediated catalysis,^{16,17} ion pair mediated catalysis^{18,19} and those that achieve catalysis through hydrogen bonding.²⁰ Each of these groups now encompasses vast areas of chemistry; catalysts that operate through hydrogen bond mediated pathways shall be the focus of this thesis.

1.1.1 Hydrogen bond donor mediated organocatalysis

Organocatalysis, mediated by hydrogen bonding can occur through either hydrogen bond acceptors, donors, or a combination of both.²¹ Seminal work in the area of catalysis

through hydrogen bond donation was reported by Hine *et al.*²² In this work, the idea that it was possible to donate two simultaneous hydrogen bonds from a rigid donor such as **8** (Scheme 1.3) to a single oxygen atom (such as that in oxirane **9**) was demonstrated. Subsequently, it was shown that this mode of action involving bifurcated hydrogen bonds conferred significant advantage in the catalysis of an epoxide opening when compared to equivalent monodentate catalysts.²³



Scheme 1.3 Bidentate rigid hydrogen bond donors

This development led to further study in the area, which in turn yielded more active catalysts bearing the now highly familiar urea functional group. Etter *et al.*, demonstrated the interactions (in the solid state) of this functional group with various Lewis bases, and showed that both hydrogens in a given urea molecule were engaged in hydrogen bonds to the same atom and that these resulted in greatly increased bond strength compared to those compounds in which one or both hydrogens had been replaced.^{24,25} This functional group was then applied, as an organocatalyst, (Scheme 1.3) by Curran *et al.*, who reported urea **11a** (but not **11b**) was capable of acting as a Lewis acid to increase the rate of the Claisen rearrangement of **12** to **13**.²⁶ Further improvement upon this catalyst by Schreiner *et al.* demonstrated that thioureas (such as **11c** and **11d**) were capable of forming stronger

hydrogen bonds, (as stronger Lewis acids) and thus act as more efficient catalysts for the promotion of the Diels-Alder reaction of **14** with cyclopentadiene (Scheme 1.3).²⁷

The application of (thio)urea based hydrogen bond donors to asymmetric catalysis was first achieved by Jacobsen *et al.* in 1998.²⁸ Originally hoping to find a chiral ligand for a Lewis acidic metal, his research focused on the Strecker reaction. It was observed that, even in the absence of any metal, the ligands were capable of functioning as efficient catalysts in their own right.

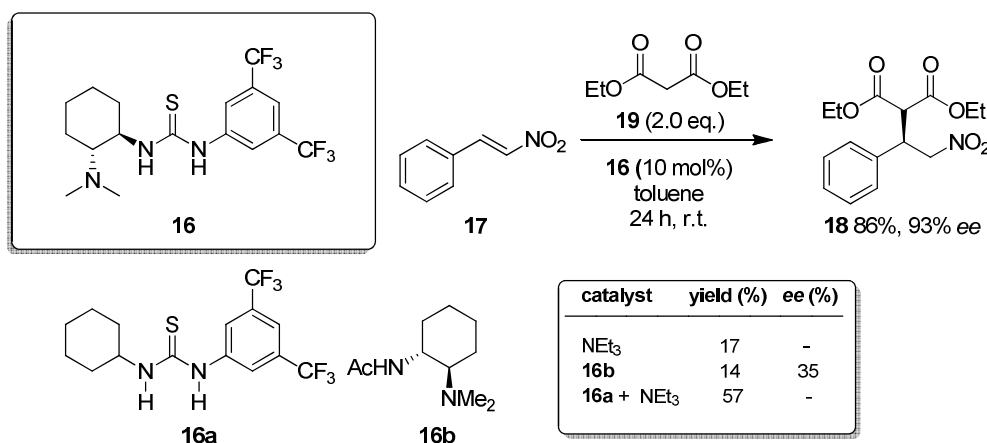
Since this development many catalysts have been developed bearing a huge variety of hydrogen bond donors, some bidentate, such as various (thio)ureas,^{13,29} diols,³⁰ and more recently squaramides.³¹ There has also been a large array of monodentate donors reported such as alcohols,^{32,33} amides,³⁴ sulfonamides³⁵ and (thio)carbamates.³⁶ The range of available hydrogen bond donors, in part, can be attributed to the need for different strengths of hydrogen bond required in each specific reaction, however it will become clear that much of the variety comes from blind exploitation of the subtle differences in bond geometry and has little to do with pure pK_a .

1.1.2 Hydrogen bond acceptors

General base catalysis (mediated by an amino functionality incorporated into the catalyst structure) is another well known strategy in organocatalysis: whether (more rarely) as a feature associated with monofunctional catalysts^{37,38} or (more usually) as part of a bifunctional catalytic system.^{39,40} This functionality is typically provided by an amine because this functional group can provide good control over several parameters. The basicity of amines is tuneable, by varying the nature of the substituents on the nitrogen atom, the pK_a of the protonated amine salt may be varied from below 8 to higher than 12.⁴¹ The steric environment also allows control over the nucleophilicity of the nitrogen, as well as affecting its basicity, thus general base catalysis is an important organocatalytic strategy.⁴²

1.2 Bifunctional catalysis

It is unsurprising, given the widespread use of both hydrogen bond donors and acceptors in organocatalysis that bifunctional catalysis featuring the synergistic use of hydrogen bond donating and accepting moieties has become a reliable strategy.⁴³ This strategy was initially demonstrated to be highly effective by Takemoto *et al.*, who achieved the asymmetric addition of malonates to nitroolefins in high yield with high enantioselectivity (Scheme 1.4).⁴⁰ By conclusively proving that both functionalities were necessary for efficient catalysis, it was shown experimentally that the simultaneous activation of both the electrophile and nucleophile was a highly effective means of asymmetric catalysis.



Scheme 1.4 Takemoto's bifunctional thiourea catalyst

It was postulated by Takemoto that the observed product configuration could be rationalised by the pre transition state assembly **16c** shown in Scheme 1.4.⁴⁴ Simultaneously activating the substrates in an ordered environment which conveys stereochemical information causes them to react in a stereo-controlled manner. In this case, the Michael acceptor which is planar forms a hydrogen bond to the catalyst. The phenyl ring which is bulky is oriented in only one direction meaning that the selectivity arises from the face that is attacked. (While the single sigma bond in the conjugated 1,4 system is free to rotate, in order for the system to react in a conjugated manner, the two double bonds must become co-planar.) The catalyst directs the attack using the amine

functionality to direct the incoming nucleophile, thus causing a stereoselective reaction to occur.

Furthermore it was shown that each molecule of catalyst acts alone, without interaction with other catalyst molecules.⁴⁴ This allows for the conclusion that since each molecule acts separately both functionalities on each molecule are indeed active in the catalytic process.

While this conceptually remains an acceptable model, further research has expanded upon this concept. Soós *et al.*, by way of computational study questioned some important features of the enantioselective process.⁴⁵ Firstly, it was noted that while in solid state the catalyst can be thought of as conformationally rigid, this was likely not to be the case in solution and that several conformations were sufficiently low in energy that the catalyst could occupy any of them. It was also found (computationally) that there was more than one possible mode of binding, and while Takemoto's binding model **16c** (Figure 1.1, **A**) was possible, another pathway computed to be marginally lower in energy (Figure 1.1, **B**) was available for the reaction to pass through. It was, on this basis, likely that both pathways were occurring during the course of the reaction. Fortuitously, both pathways lead to the same product enantiomer, however unlike the original proposed assembly, Soós' model also allowed for the possibility that the electrophile could bind to the already protonated amine of the catalyst.

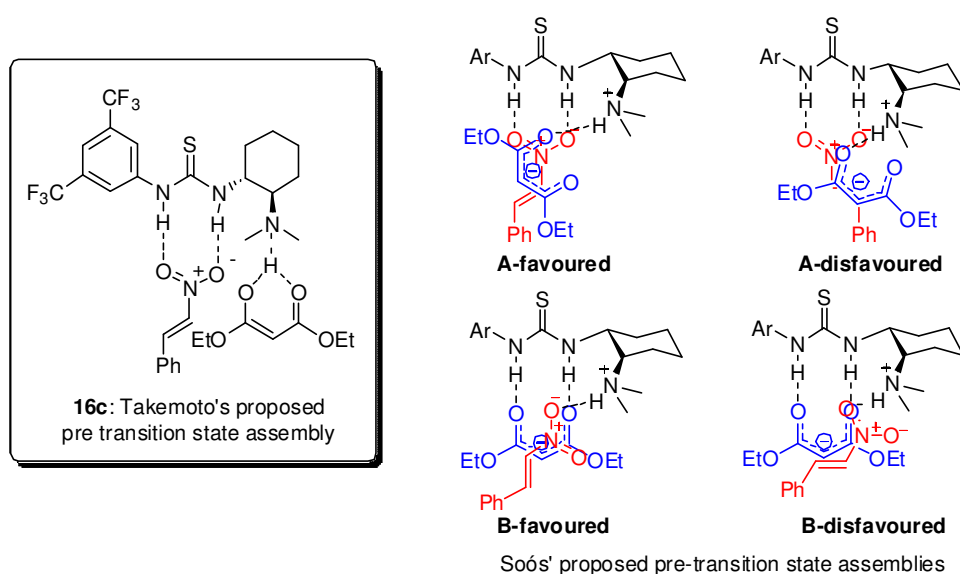


Figure 1.1 Possible pretransition state assemblies for the addition of nitroolefins to malonates catalysed by **16**

While Soós' model provides compelling reasons to suspect that the mechanisms of this and indeed most organocatalytic reactions are far from simple, in the absence of any complementary experimental results, it would be unwise to accept this as a definitive model of the reaction.

1.3 Quinine: a brief history

Quinine (**1**), known in Europe since its arrival in the 17th century, was the active constituent of the only known cure for malaria, “Jesuit’s bark”, which was the bark of several related plants from the genus *Cinchona*.⁴⁶ First isolated in 1820,⁴⁷ it is now isolated primarily from the species *Cinchona ledgeriana*, the bark of which may contain up to 8% quinine, (the rest consisting of related alkaloids, fiber, starch, gum, minerals, pigments, wax, fat, traces of volatile oils, and oxalic and quinic acids) as one of a family of related alkaloids (**1**, **2**, **19** and **20**, Figure 1.2) on a scale of roughly 700 tons per annum.^{48,49}

Quinine has had a diverse and important history. It remains a trusted treatment for many forms of malaria.⁵⁰ It has also been of huge geopolitical significance, allowing the first sustainable forays into Africa by Europeans unmolested by malaria,⁵¹ its absence during the second world war condemning tens of thousands to death.⁵²

More relevant is its long standing impact on chemistry, in particular asymmetric synthesis. In 1853 Louis Pasteur identified quinine as a potential agent for chiral resolution which was to be the beginning of its immeasurable impact on asymmetric synthesis.⁵³ In the century that followed, quinine was the ‘catalyst’ for discoveries such as Perkin’s synthetic dyes,⁵⁴ vast improvements in the areas of understanding and deciphering the nature of molecular structures⁵⁵ and great advances in chemical synthesis.⁵⁶ Indeed efforts towards the complete total synthesis of quinine, only achieved in 2001,⁵⁷ is something that has impacted nearly every generation of chemists.⁵⁸

As we have seen, in 1912 quinine and quinidine made their debut in asymmetric organocatalysis, furnishing the adduct of hydrogen cyanide and benzaldehyde.¹⁴ Since then, quinine and the related cinchona alkaloids have proved exceptionally important as a ‘privileged’ structure in organocatalysis.

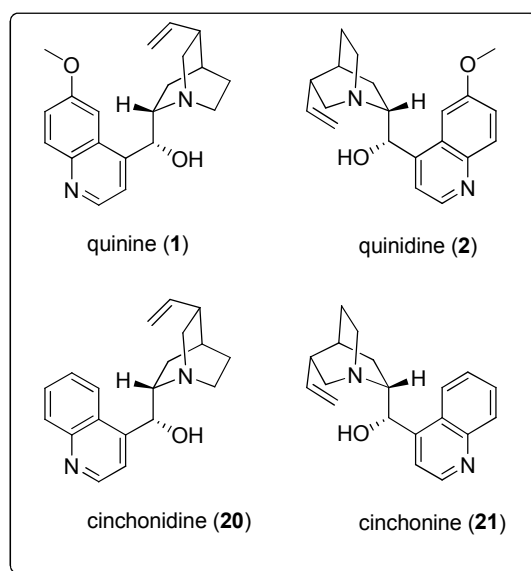


Figure 1.2 The cinchona alkaloids

It is worth noting the relationship between the four cinchona alkaloids shown in Figure 1.2; cinchonidine (**20**) is a des-methoxy analogue of quinine (which is otherwise identical) while quinidine (**2**) and its des-methoxy analogue cinchonine (**21**) are best described as pseudoenantiomeric with respect to **1** and **20**. They have the opposite configuration but have a different position of the vinyl group within the molecule, thus they behave almost as enantiomers. Alkaloids **1**, **2**, **20** and **21** are also referred to by the abbreviations Q, QD, CD and CN respectively; where the vinyl group is saturated DH may be prefixed to this name, *e.g.* DHQ for dihydroquinine.

1.3.1 Nomenclature for the description of cinchona alkaloid based compounds

Before beginning to discuss the methods and means for modifying quinine, it is first important to establish nomenclature. Figure 1.3 shows the numbering system used throughout this thesis which is in agreement with the system used in the contemporary literature.⁵⁷

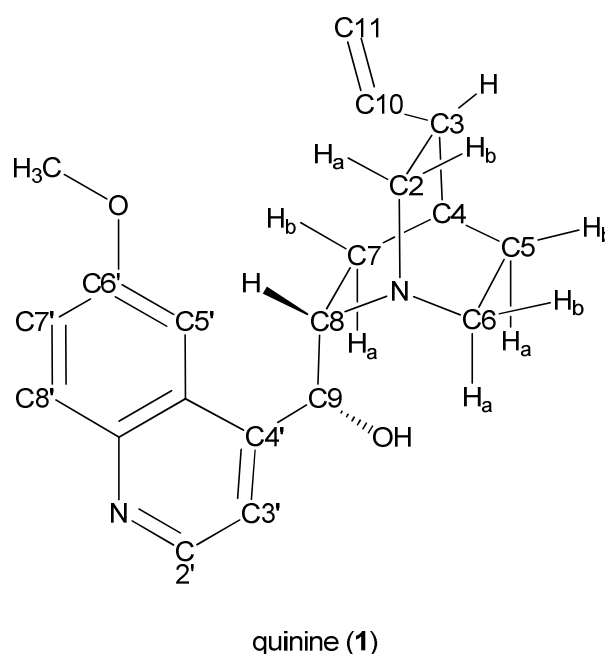
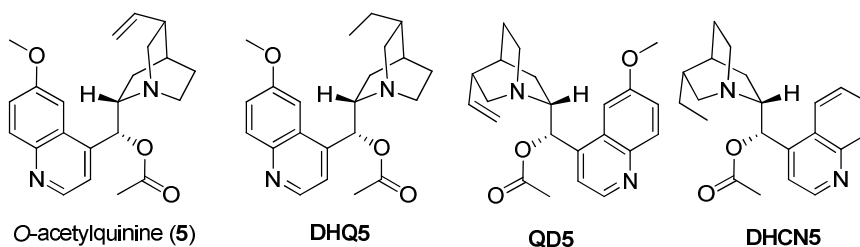


Figure 1.3 Systematic numbering of quinine

Furthermore, where a molecule resulting from the modification of a cinchona alkaloid is described, the modification, for the sake of clarity, it will be shown on a quinine skeleton and assigned a number. For brevity, the use of this modification on the related cinchona alkaloids will be referred to by prefixing the number of this compound with the description of the alkaloid which is used in the specific case at hand.



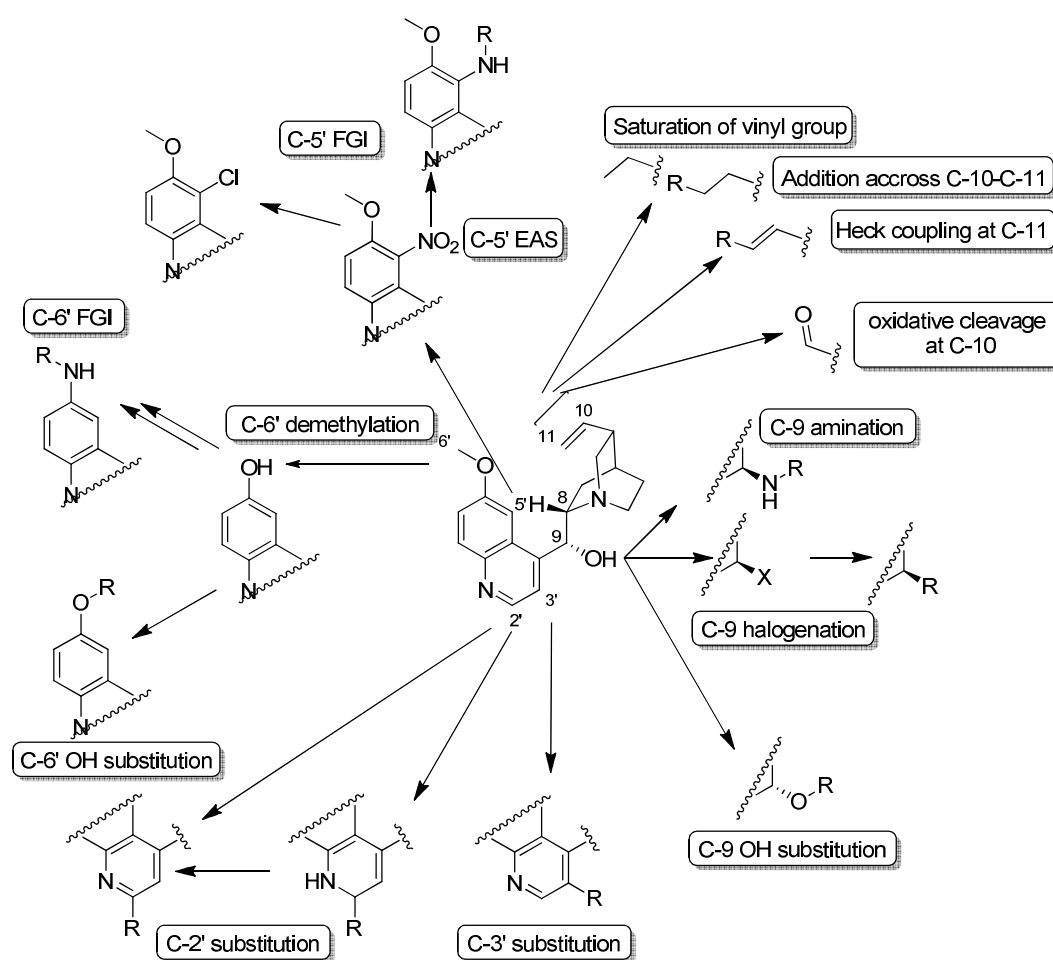


Figure 1.5 A selection of quinine modifications

1.3.3 Modification of quinine at C10-11

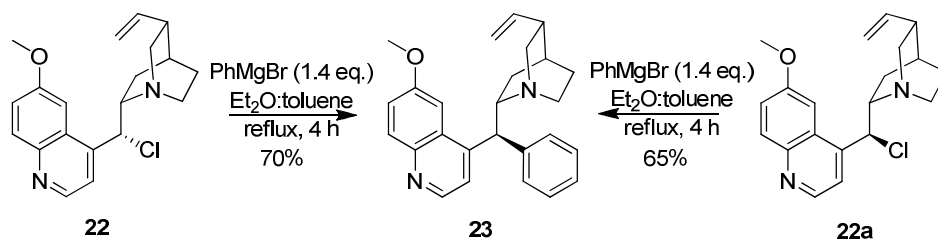
The vinyl bond present in quinine is highly amenable to modification. Saturation of this bond is easily achieved by catalytic hydrogenation,⁵⁹ while addition across the double bond has also been achieved with a variety of reagents.⁶⁰⁻⁶³ Other modifications have included Heck couplings,⁶⁴ oxidative cleavage,⁶⁵ hydroformylations⁶⁶ and dehydrogenation to the corresponding alkyne,^{67,68} each allowing different possibilities for the transformation of the vinyl group. In short it is possible to either reduce or expand the steric bulk of this moiety, in addition to using it as a point of attachment for appending quinine to other chemical entities.⁶⁹

1.3.4 Modification of quinine at C-9

The secondary alcohol positioned at C-9 is easily modified by a number of classic chemical reactions: it is easily either acylated or alkylated by careful use of the appropriate base and electrophile.^{65,70,71} Inversion at C-9 to afford 9-*epi*-quinine can be achieved either by hydrolysis of the corresponding mesylate, or by Mitsunobu reaction followed by hydrolysis of the intermediate ester.^{72,73} It should be noted however that hydrolysis of the 9-*epi*-mesylate proceeds with complete retention of configuration such that quinine of a natural configuration cannot be reached by this route from 9-*epi*-quinine.⁷⁴ (While this is not a practically desirable transformation, it does speak to the potential for aspects of quinine based chemistry to be less than straight forward.)

Use of the Mitsunobu reaction with hydrazoic acid, followed by a Staudinger reduction of the resultant azide allows the installation of an amine.⁷⁵ It is worth noting that quinine is prone to rearrange under acidic conditions and that an earlier report of synthesis of C-9 amino-(deoxy)-quinine may be called into question.^{75,76}

It is possible to convert the alcohol to the corresponding alkyl chloride or bromide by treatment with thionyl chloride or phosphorus tribromide.⁷³ These 9-(*epi*)-haloquinine compounds (e.g. **Q22**, **QD22**, **Q22a** and **QD22a**) have been shown to undergo chemistry that is highly influenced by both the presence of the quinuclidine amine (which is located β to the alkyl chloride) and the benzylic nature of the α position.^{73,74}



Scheme 1.5 The stereoconvergent reaction of **22** and **22a** with Grignard reagents

Reactions of these molecules with Grignard reagents have been known for more than 50 years however, it is only relatively recently that the stereochemical outcome of this reaction has been clearly elucidated.^{77,78} Reported in 2008, the reaction of Grignard reagents with 9-(*epi*)-chloroquinine (**Q22(a)**) gives the same product regardless of the stereochemical configuration of the starting material at C-9 (Scheme 1.5).

In explanation of this observation it was postulated⁷⁸ that the two different epimers react *via* mechanistically distinct pathways (Figure 1.6). In the case of the conversion of 9-chloroquinine; the authors contend that reaction proceeds by an unremarkable S_N2 pathway, with promotion of the reaction by the coordination of the Lewis acidic magnesium to the quinuclidine nitrogen. On the other hand, 9-*epi*-chloroquinine undergoes the same initial coordination step to one Grignard molecule, which can then coordinate, *via* the bromine to a second magnesium to allow for removal of the chlorine with concomitant delivery of the aryl group. (This mechanism can be described by the label S_Ni, or internal nucleophilic substitution.)⁷⁹

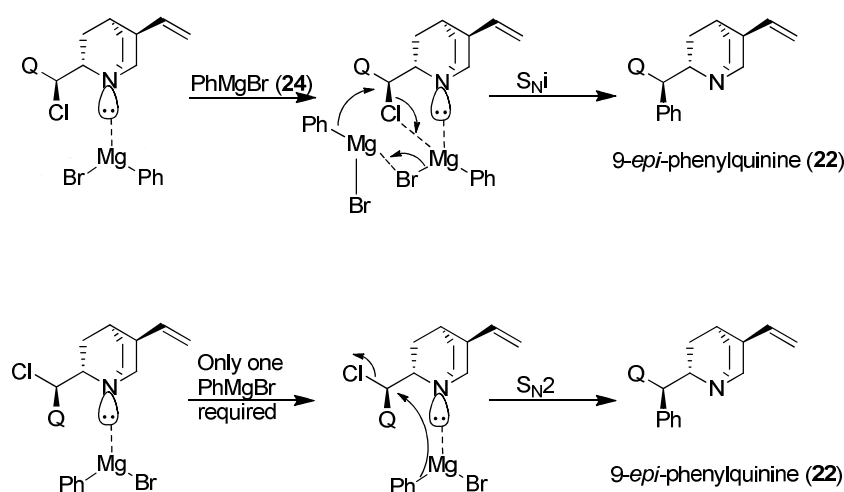


Figure 1.6 Mechanistic explanation of the outcome of the addition of PhMgBr to chloroquinine

While this explanation seems plausible, it seems unlikely that the above mechanistic explanation would result in the perfect selectivity observed experimentally. It would seem likely that, at the elevated temperatures at which the reaction occurs, the possibility of the molecule reacting while in a different conformation would be great enough to allow observation of the other product diastereoisomer. Furthermore, in the case of the

postulated S_Ni pathway, it has been observed that even in the presence of highly hindered Grignard reagents the same outcome is observed. It would seem that such a sterically congested transition state is unlikely.

Instead it is possible to postulate a mechanistic pathway whereby the initial coordination of quinuclidine and Grignard reagent occurs, however this is then followed by an S_N1 type formation of a transient planar carbocation which reacts with the bound Grignard reagent. In this case, all the stereochemistry is provided by the face of attack of the nucleophile which is controlled by the quinuclidine moiety, which has identical stereochemistry in both cases leading to identical products.

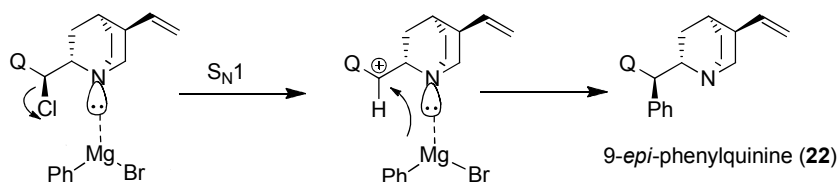


Figure 1.7 Mechanistic explanation of the outcome of the addition of PhMgBr to chloroquinine

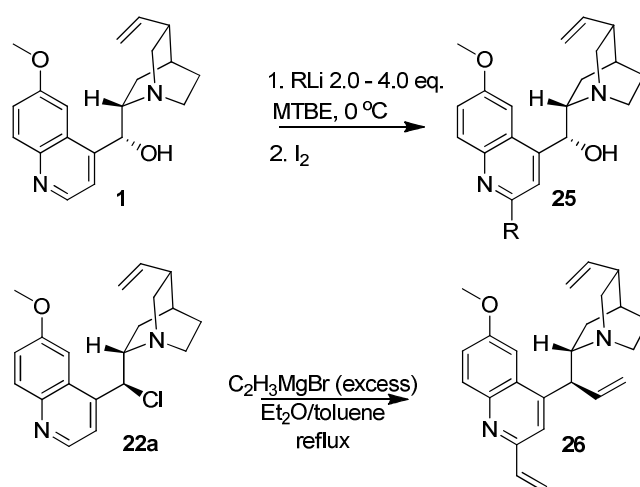
While the formation of a carbocation adjacent to a bicyclic ring structure such as quinuclidine might usually be expected to result in a variety of products (none of which is observed in more than trace amounts), it is possible that the coordination of the lone pair on the quinuclidine amine prevents this from readily occurring allowing the attack of the carbon nucleophile to happen preferentially.

In any case, it has been observed experimentally that this reaction results in the formation of a single diastereoisomer with none of the product epimer observed in either case.

1.3.5 Modification of quinine at C-2' (and C-3')

The C-2' position of quinine, activated by the pyridyl nature of the quinoline ring, is amenable to several different reactions. Early efforts at functionalisation of quinine in pursuit of novel antimalarials demonstrated the possibility of such a modification.^{80,81} Later reports by the groups of Knochel, Skarzewski, Hintermann, Ley, Kelly and Baran have more recently demonstrated, with various levels of success, methodologies allowing the functionalisation of quinine at the C-2' position.^{78,82-86}

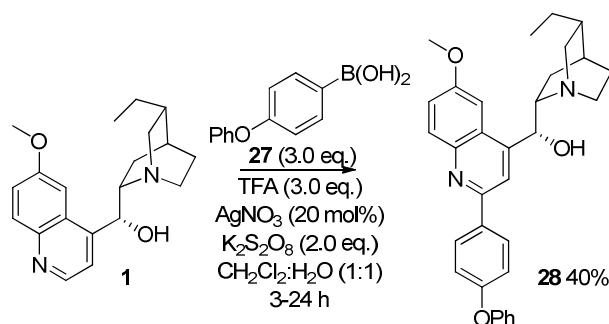
Addition of strong carbon nucleophiles, in a mechanism similar to the classic Chichibabin reaction, were shown by Mead *et al.*, to be a viable method of C-2' substitution.⁸¹ Gaunt and Skarzewski also took advantage of this type of reactivity (Scheme 1.6).^{85,87} In the case of the addition of aryl/alkyl lithium reagents, *i.e.* the transformation of **1** into **25**, the resulting dihydroquinoline is oxidised on workup (using iodine as the oxidising agent); while the addition of Grignard reagents (such as in the transformation of **22a** into **26**) appears to proceed with elimination of hydride in a complete nucleophilic aromatic substitution (NAS) type reaction to afford the C-2' substituted product.



Scheme 1.6 Nucleophilic addition to the C-2' position of quinine type molecules

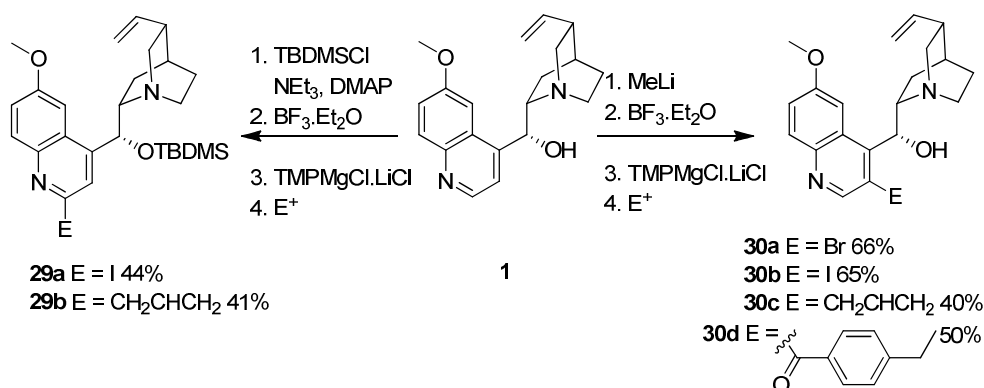
Yardley *et al.* demonstrated that quinine *N*-oxide was also reactive at C-2', reacting readily with primary Grignard reagents and aryl/alkyl lithium reagents, both primary, secondary and tertiary, also giving the same C-2' substitution.⁸⁰

Baran *et al.*, demonstrated the possibility of using radical chemistry based on the Minisci reaction to afford C-2' arylation under milder conditions (Scheme 1.7), building on the earlier reported C-2' alkylation by Kelly.⁴⁹ Only modest yield can be achieved, and the resulting mix of products results in challenging purifications, thereby limiting the scalability of the reaction.^{82,86}



Scheme 1.7 Radical addition to the C-2' position of quinine

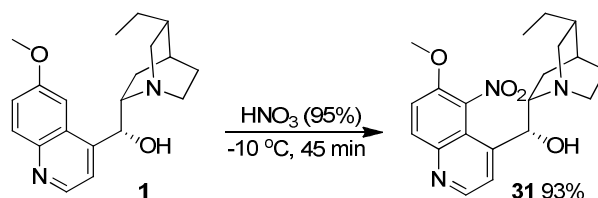
At this position, there also exists the possibility of controlled selective deprotonation, reported by Knochel *et al.*,⁸³ again adapted from pyridine chemistry.⁸⁸ The reported reactions allow for selective metalation at either C-2' or C-3' and the addition of the resultant metalate to a range of electrophiles (Scheme 1.8), again with modest to good yields. This represents another possibility for the functionalisation of quinine at the C2' position.



Scheme 1.8 Metalation of quinine, possible at both C-2' and C-3'

1.3.6 Modification of quinine at C-5'

The C-5' position on the quinoline ring in quinine, as the most activated site, is the position at which electrophilic aromatic substitution (EAS) reactions occur (after saturation of the vinyl group which would otherwise be highly reactive). Unfortunately however, the range of compatible electrophiles which have successfully been added at this position is limited to a single example. Nitration was first tentatively reported in 1881 by Rennie.⁸⁹ Subsequently preparation of the corresponding dihydrocompound was used as a starting point for the synthesis of other limited examples of quinine derivatives functionalised at the C-5' position.^{90,91}

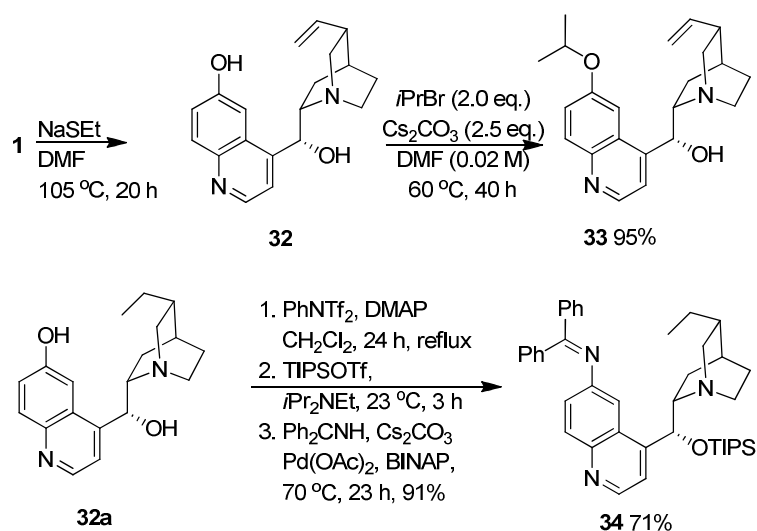


Scheme 1.9 Nitration of dihydroquinine at C-5'

Further examples of EAS at this position have also been reported where the methyl group at 6' has been removed.^{92,93}

1.3.7 Modification of quinine at the C-6' position

The methyl ether occupying the C-6' position can readily be converted to the corresponding alcohol.⁹⁴ This phenol can then react with electrophiles, allowing for the replacement of the natural methyl group with more bulky substituents such as that shown in the transformation of **32** into **33** (Scheme 1.10).⁹⁵ It can also be converted into an aniline using the Buchwald amination having first converted the phenol into a triflate.⁹⁶ This transformation, exemplified by the transformation of **32a** into **34** (Scheme 1.10), allows for the synthesis of an aromatic amine with substantial potential for further synthetic development.⁹⁷



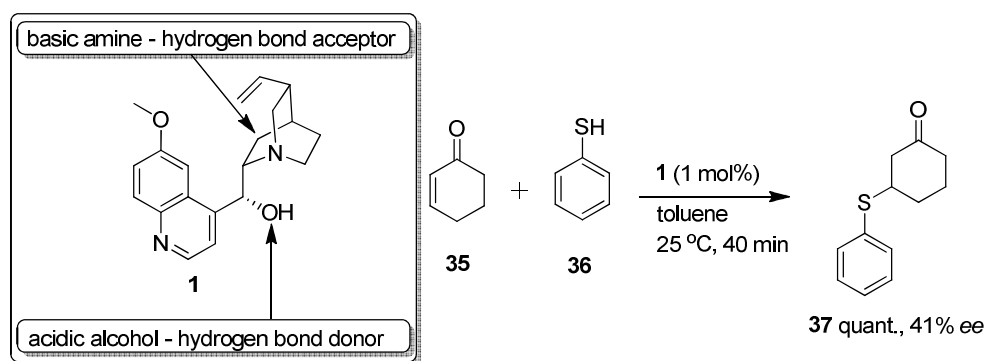
Scheme 1.10 Synthetic possibilities for quinine at C-6'

1.4 Quinine derivatives as catalysts

Given quinine's position as a 'privileged' structure in organic chemistry, it is unsurprising that there are an extensive number of derivatives which have been shown to be effective and capable organocatalysts.⁹⁸ In order to classify the reported catalysts, extensive as they are, they can be divided up by location of the relevant hydrogen bond donor and acceptors within the catalyst.

1.4.1 Quinine as a hydrogen bond donor and acceptor

Before examining the plethora of artificial analogues that modern chemistry has provided it is worth examining the catalytic capabilities of quinine itself. It has been shown to be a highly effective organocatalyst. A detailed study by Wynberg *et al.*⁹⁹ of the Michael addition of thiophenol to cyclohexenone (Scheme 1.11) made clear that the catalytic competence of quinine was based on a bifunctional mode of action.



Scheme 1.11 Quinine bifunctionally promotes Michael addition of thiols to cyclohexenone

1.4.2 Catalysts with hydrogen bond donors at C-9

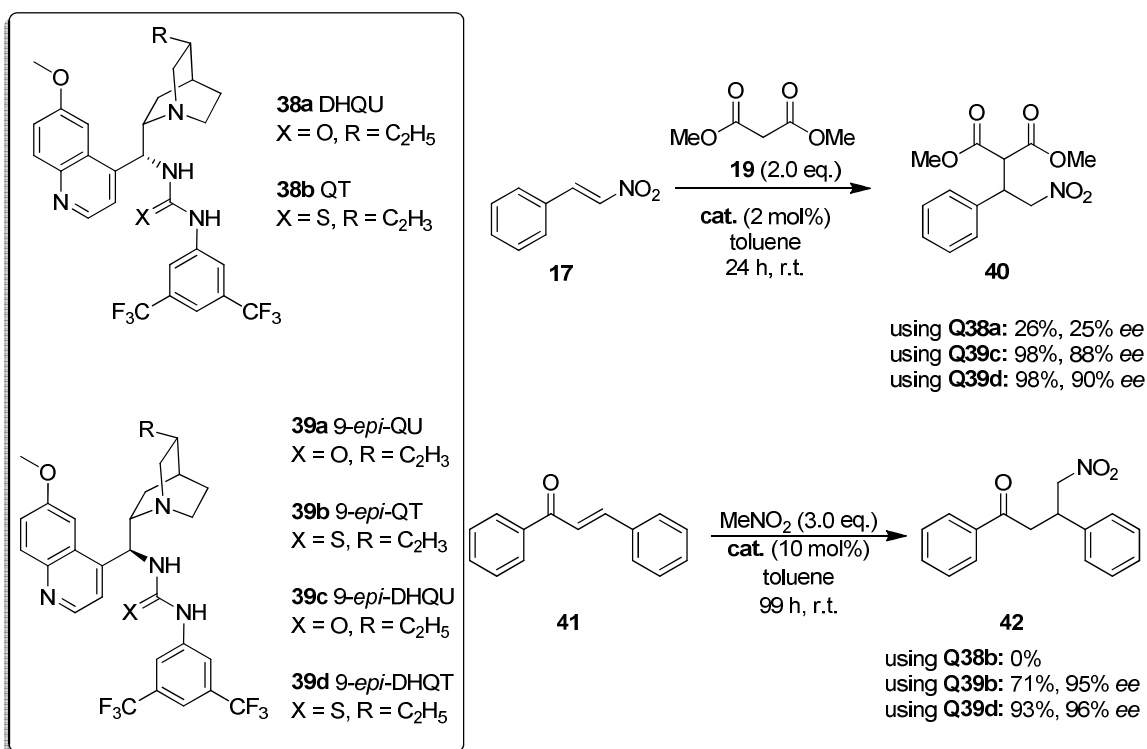
It is unsurprising then that extensive research into functionalising quinine at C-9 for the purposes of creating more effective organocatalysts has been undertaken. Early examples involving the acylation of the secondary alcohol, proved more effective promoters of [2+2] cycloadditions than quinine, and several examples of this catalyst and reaction type exist.^{100–101} These however proceed through monofunctional nucleophilic catalysis; thus are of less interest than the subsequent class of catalysts which involve replacement of the C-9 oxygen with an amine.

While such derivatives have been applied to diverse types of catalysis we will confine ourselves to those which function through hydrogen bond mediated processes. Brunner *et al.* reported the synthesis of 9-*epi*-amino(deoxy)quinine in 1995 and evaluated a range of catalysts based on this functionality in the years that followed.⁷⁵ While his organocatalytic work appears largely to have been ignored, it is worth noting that his studies produced the first examples of several classes of catalyst that remain popular today.^{102,103}

Replacing the alcohol at the C-9 position with an amine and subsequently installing a (thio)urea, for the purposes of organocatalysis, was first reported nearly simultaneously by four research groups.^{59,104–106} McCooey *et al.*, demonstrated that this type of catalyst could function analogously to (and more efficiently than) Takemoto's cyclohexane based catalyst (**16**) in promoting the addition of malonates to nitroolefins (Scheme 1.12).⁵⁹ Figure 1.8 shows the correlation between 9-*epi*-substituted quinines and Takemoto's

catalyst, both based around a 1,2 diamine structural motif, both of which contain a tertiary amine and a primary amine which has been converted into a thiourea moiety.

Of interest is the importance of the inversion of the natural C-9 stereochemistry to the ability of the catalysts to promote reactions. While its importance is noted in these reports little detail is provided. A similar observation was made by Lindner *et al.*,¹⁰⁷ when using quinine derivatives as a receptor for chromatic separation of racemic materials. They observed that while the 9-urea functionalised quinine was a poor receptor its corresponding epimer proved highly effective. They rationalised this observation by comparing the likely conformation of their materials to the reported conformations of unaltered quinine and C-9 *epi*-quinine.¹⁰⁸ Similar studies by several groups have shown that the conformation of quinine, its related alkaloids and their derivatives is highly dependent on a number of factors and defies a facile explanation.^{108,109} This topic will be dealt with in greater detail further into this thesis.



Scheme 1.12 Michael additions with C-9 modified quinine derivatives

Soós *et al.* demonstrated the addition of a different, base activated, pronucleophile to a Michael acceptor, in this case pairing nitromethane with chalcone (Scheme 1.12). With the advantage that this catalyst was readily synthesised from an economically available natural product which was easily transformed into the desired catalyst without need for chiral resolution, it became clear that C-9 modified quinine analogues were highly valuable structures in organocatalysis. It is thus unsurprising that in the years that followed a diverse array of permutations on the initial catalysts and reactions promoted by these catalysts have been reported.

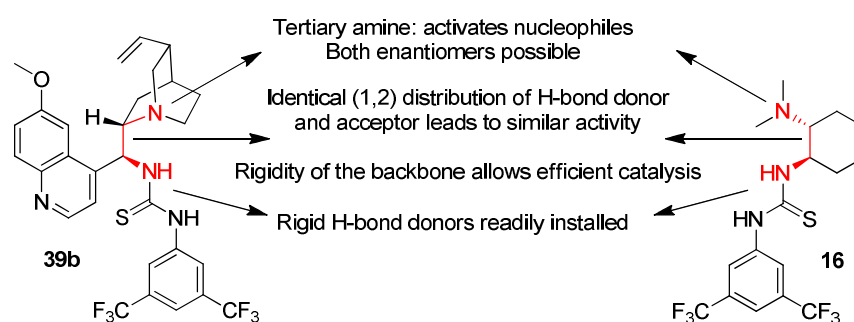
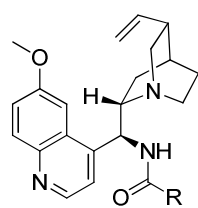
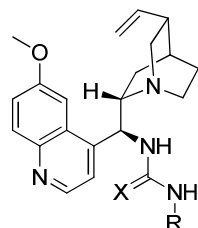


Figure 1.8 A comparison of Takemoto's catalyst and quinine based **Q39b**

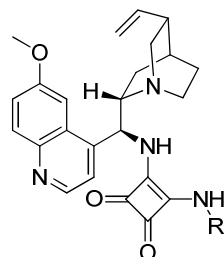
A review of the literature reveals immense numbers of derivatives which have been based on the combination of Takemoto's and Brunner's work. It is worth observing however that nearly all of the resulting catalysts, while representing significant contributions to the field rely on the same fundamental 1,2-diamino relationship between hydrogen bond donor and acceptor. Figure 1.8 shows a selection of these catalysts, the similarity becomes immediately apparent. Each contains a different hydrogen bond donor but is fundamentally based on the 1,2 diamine structure of Takemoto's 2003 catalyst.



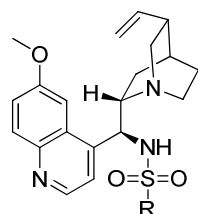
- 43a** R = C₆H₅
43b R = 2-OEt-C₆H₄
43c R = 1-naphthyl
43d R = furoyl
43e R = cyclohexyl
43f R = ferrocynyl
43g R = (1*S*)-(2)-camphyl
43h R = 3,5-(C(CH₃)₃)₂C₆H₃



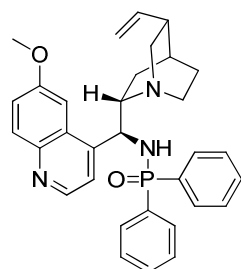
- 39a** X = O, R = 3,5-(CF₃)₂C₆H₃
39b X = S, R = 3,5-(CF₃)₂C₆H₃
39e X = O, R = C₆H₅
39f X = S, R = *N,N*-di-*i*-isobutyl-*t*-leucinamide
39g X = S, R = trityl



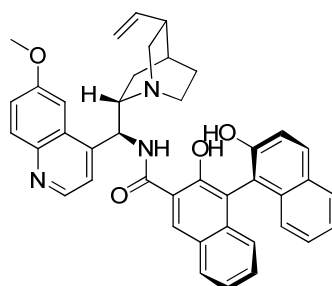
- 44a** R = 4-F-C₆H₄
44b R = 3,5-(CF₃)₂C₆H₃
44c R = 4-(CF₃)C₆H₄
44d R = 3,5-(CF₃)₂C₆H₃
44e R = quinine



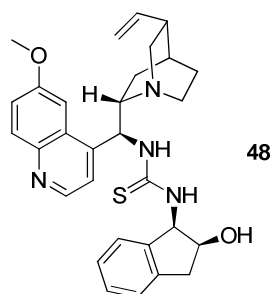
- 45a** R = 4-CH₃-C₆H₄
45b R = 3,5-(C(CH₃)₃)₂C₆H₃
45c R = 3,5-(CF₃)₂C₆H₃
45d R = 2,4,6-(CH₃)₃-C₆H₂
45e R = 4-F-C₆H₄
45f R = C₆F₅



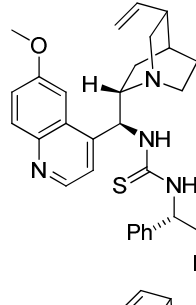
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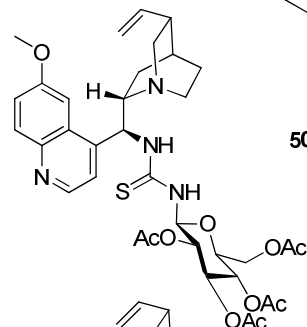
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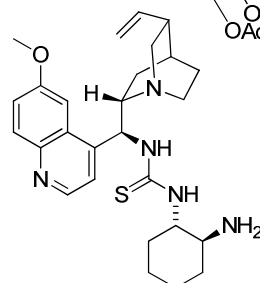
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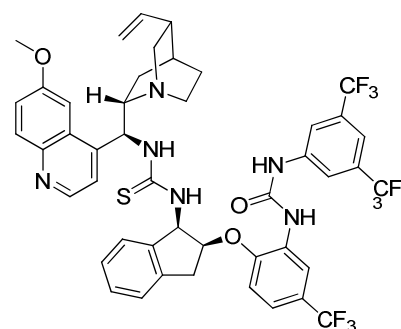
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50



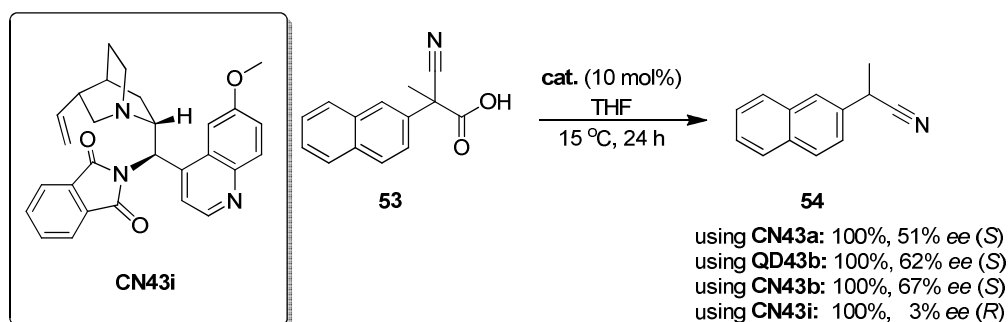
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52

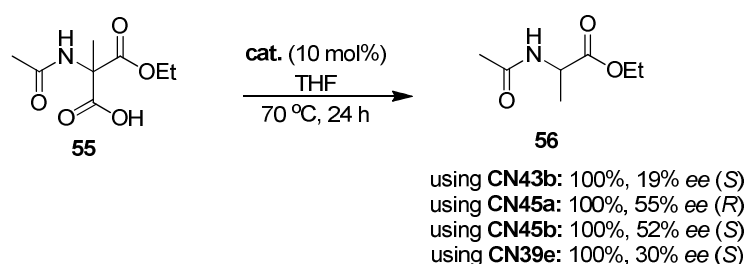
Figure 1.9 A selection of C-9 modified quinine based catalysts

The first reported class of these catalysts was a selection of amides, first put to organocatalytic use in 2000.¹⁰² These were shown to be effective in the enantioselective decarboxylation of quaternary malonoheminitriles (Scheme 1.13). At the time, a bifunctional mode of action was not considered despite the observation that the amide proton was necessary for enantioselectivity.



Scheme 1.13 Enantioselective decarboxylation of malonoheminitriles

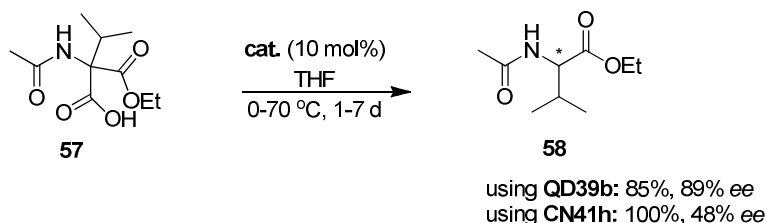
Further work by Brunner *et al.* on enantioselective decarboxylation led to the synthesis of several more first in class catalysts including the first urea, sulfonamide and carbamate and an expansion of substrate scope to allow the enantioselective formation of amino acids.¹⁰³ Again however, despite the abundance of evidence for a bifunctional mechanism involving hydrogen bond donation/general acid catalysis it was not specifically noted as the likely mode of action



Scheme 1.14 Organocatalytic enantioselective formation of protected aminoacids

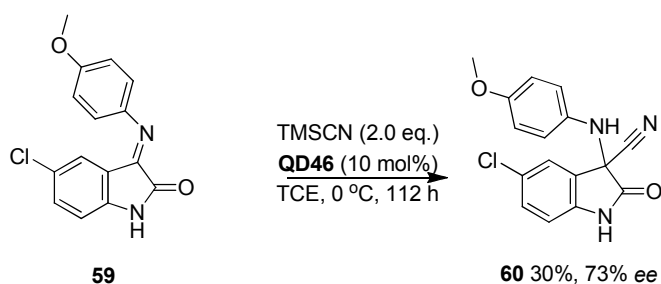
In 2007 Rouden *et al.* reported that a large increase in enantioselectivity was possible using **Q39b** to promote the same reaction, in place of the catalysts used by Brunner *et al.*,

highlighting the bifunctional role these catalysts have in promoting the reaction shown in Scheme 1.15.¹¹⁰



Scheme 1.15 Improvements on the work of Brunner *et al.* by Rouden *et al.*

The many other examples of catalysts shown above each serve to promote reactions in high yield and with excellent enantioselectivity, indeed sulfonamides such as **45a-f** have been shown to be effective promoters of the desymetrisation of *meso* anhydrides both with simple alcohols and with concomitant kinetic resolution of thiols. They have also proven effective in the addition of malonates to Michael acceptors though little credit is given to the original creator of this class of catalyst.^{35,103,111,112} Phosphamides have also been shown to be effective monodentate hydrogen bond donors, capable of promoting the Strecker addition of cyanide to ketimines as part of a bifunctional catalytic system (Scheme 1.16).¹¹³



Scheme 1.16 Organocatalytic enantioselective Strecker reaction

Squaramides have also recently been applied as highly effective bidentate H-bond donors. Squaramides have been demonstrated to bind efficiently in a bifurcate manner to hydrogen bond acceptors.¹¹⁴ This property of squaramides led to their use as anion receptors prior to their application in the field of organocatalysis.^{115,116} First reported as effective

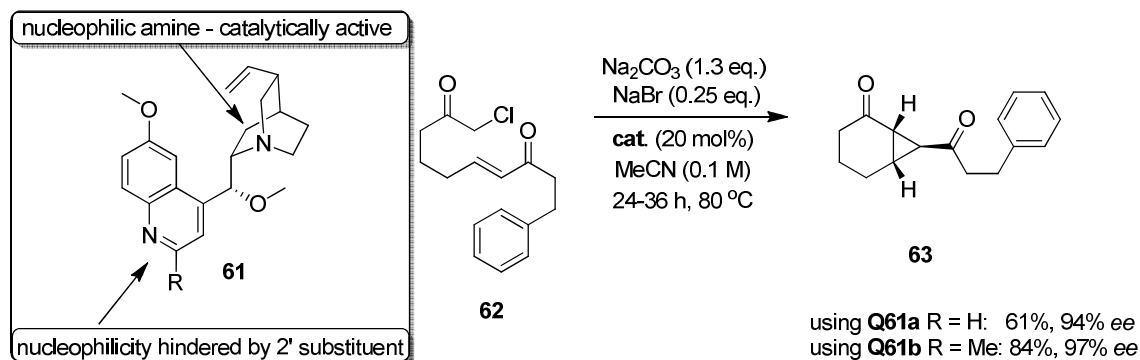
organocatalysts by Rawal *et al.*, **CN44d** was shown to operate analogously but more efficiently and selectively than both Takemoto's catalyst and **DHQ39b**.³¹ It has since been shown to offer superior results to the corresponding thiourea in some (but not all), classes of reaction.^{115,117,118} Other more exotic systems have also been devised for example the self activated thiourea, **QD52** has been used in the addition of malonates to aldimines,¹¹⁹ giving an improvement in both activity and selectivity when compared to Dixon's original application of **CN39b** to the same reaction.

The strategy of including more than one hydrogen bond donating group in the catalyst design has also been explored. Catalysts **47**, **48** and **49** are representative of these efforts, which have met with various degrees of success, again in the promotion of Michael additions.¹²⁰⁻¹²² In the case of **50**, the inclusion of additional steric bulk with stereochemical significance improved the outcome for the addition of TMS-CN to α -ketophosphonates,¹²³ while **51** represents an amalgamation of general acid/base catalysis and promotion of reactions through nucleophilic catalysis.¹²⁴

1.4.2.1 Catalysts with hydrogen bond donors at C-9 modified at C-2'

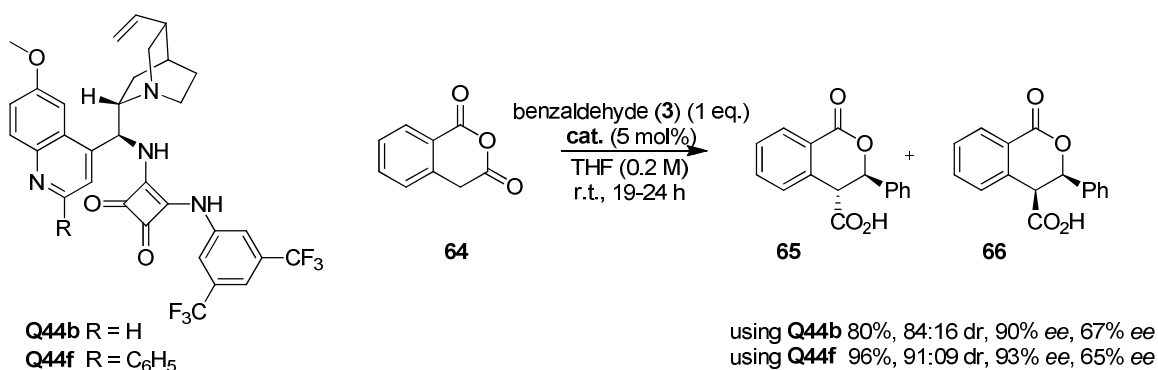
The catalysts above make clear that a strategy of adding additional steric bulk or stereochemical information to a catalyst can be advantageous, it (unsurprisingly) has also been shown to be advantageous to effect such modifications directly on the cinchona alkaloid skeleton. Modification of quinine at C-2' has been shown to be one such strategy. The advantage of such a modification comes from two possible sources, firstly, while the quinuclidine amine is responsible for the catalytic activity demonstrated in all the examples so far, the nitrogen present in the quinoline ring has also been shown to be capable of acting as a base and nucleophile.¹²⁵ This unwanted activity can promote reactions through non-stereoselective pathways but is significantly decreased by the steric hinderance provided by *ortho* substitution, increasing the selectivity of a potential catalyst.^{85,126} Secondly, and more nebulously, as larger, more bulky substituents are added they can affect the conformation and binding availability of the catalyst, however the effect of such modifications, while certain, is far less clear.¹²⁷

This modification was first applied to organocatalysis by Gaunt *et al.* using catalyst **Q61b**, to promote intramolecular cyclopropanation through nucleophilic catalysis, which proved to be more effective than **Q61a** in which no C-2' modification had taken place (Scheme 1.17).



Scheme 1.17 Intramolecular cyclopropanation *via* a catalytic nucleophilic pathway

The first example of this in a catalyst functioning purely through hydrogen bonding was recently reported by Cornaggia *et al.*¹²⁷ They showed that a modification at C-2' of **Q44b** (giving **Q44f**) also led to more satisfactory results when compared to unmodified **Q44b** in the addition of enolisable anhydride **64** to benzaldehyde (**3**) (Scheme 1.18).

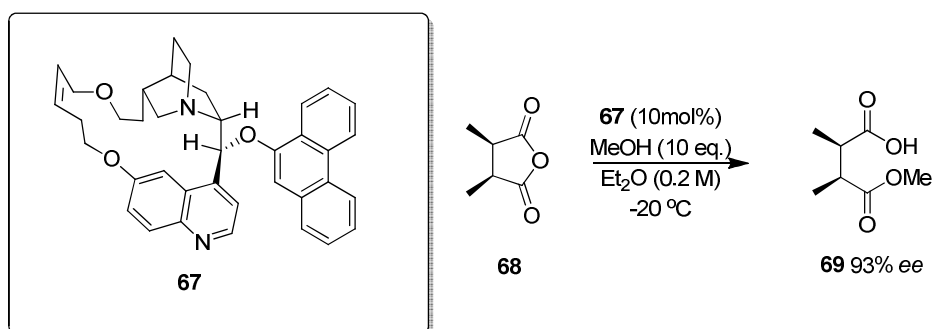


Scheme 1.18 Improved catalytic activity is observed when a C'-2 substituent is present

1.4.2.2 Catalysts with hydrogen bond donors at C-9 modified at C-6'

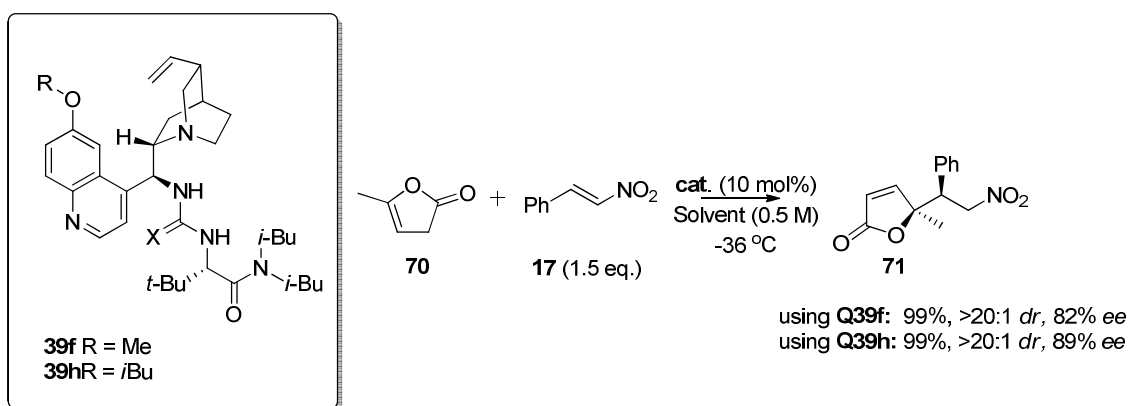
The C-6' site offers another position at which modifications to the quinine skeleton may easily be achieved. Modifications at this site have been shown to provide greater conformational control over each quinine molecule, thereby (on occasion) conferring selectivity and activity onto catalysts thus modified. Such modifications have been used for purposes beyond the scope of bifunctional organocatalysis (such as creation of stationary phases for chromatography and the synthesis of ligands for inorganic catalysis) with many positive results.^{128,129}

An excellent study on the use of C-6' position was completed by Deng *et al.*, showing that catalyst **QD67** (Scheme 1.19) acted in a similar manner as the untethered **QD72b**. They were able to demonstrate unequivocally the active conformation of this catalyst during the reaction, albeit in a reaction involving monofunctional, general base catalysis.¹³⁰ It should also be noted that his results made clear the deficiencies of other methods of conformational analysis such as analysis of solid state structures through X-ray crystallography.



Scheme 1.19 Desymmetrisation of *meso* prochiral cyclic anhydrides

Within hydrogen bond mediated organocatalysis there are also several examples of this modification being used in diverse reactions.^{36,131-133}



Scheme 1.20 Enhanced enantioselectivity observed with C-6' substitution

The modification of catalyst **Q39f** at this position by replacing the methyl with an *isobutyl* was capable of enhancing the enantioselectivity observed in the Michael addition of lactone **70** to nitroalkene **17** (Scheme 1.20). It has been shown that such modifications can affect the catalyst in two ways, firstly it can provide alterations to the binding site by (using steric hinderance) closing off more of the catalytically active site, alternatively or additionally the added bulk at this position can affect the type and relative populations of the conformations the catalyst molecule may adopt.¹³⁴

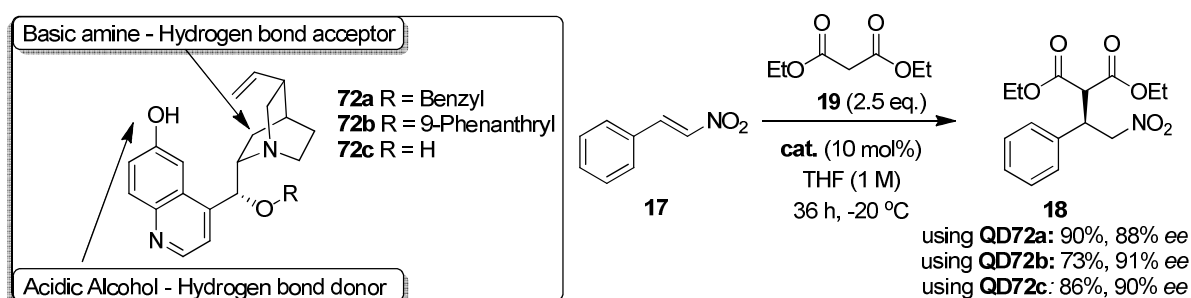
It is clear, that while a large variety of catalysts have been investigated, the basic structure of C-9 aminated cinchona alkaloids is present in all cases and fundamentally dictates the possible reactions which can be successfully promoted with this class of catalyst.

1.4.3 Catalysts with hydrogen bond donors at C-6'

By examining the available modifications readily made to quinine, it is apparent that C-6' offers a site in which catalytically active functionalities can be installed. It is thus unsurprising, that many novel organocatalysts which promote reactions through general acid/base catalysis characterised by this modification have been developed. These can be divided up into 3 categories, those at which C-6' has been demethylated, those at which C-6' has been demethylated and further functional group interconversions (FGI) have been

used to install other catalytically active moieties and those in which modification has taken place at C-6' as well as other overall alteration of the cinchona alkaloid skeleton.

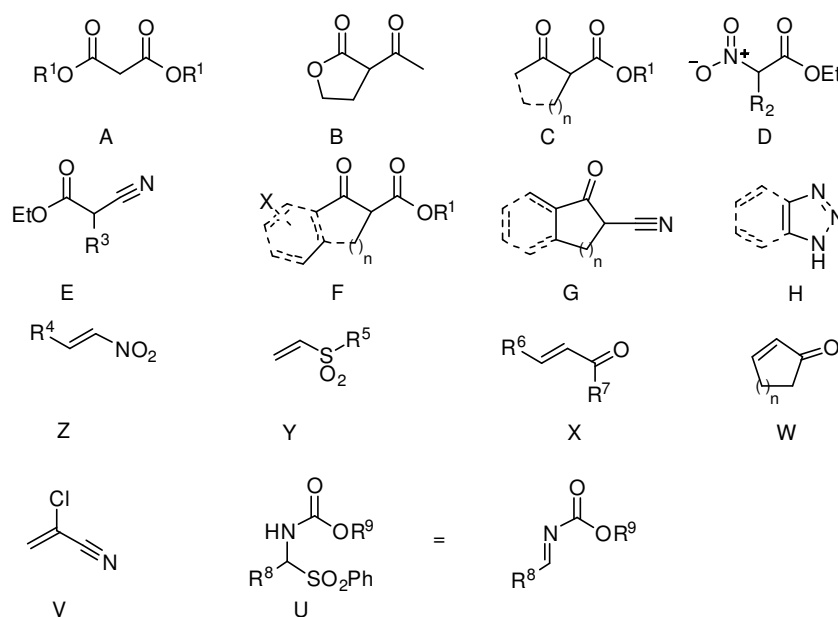
Catalysts of the first type were first reported by Deng *et al.*, and were shown to act as a highly efficient catalysts again in the addition of malonates to nitroolefins (Scheme 1.21).⁹⁴ It was also shown to be capable of promoting this reaction between nitroolefins and cyclic malonate type molecules, creating two stereocentres simultaneously with excellent yield and diastereoselectivity.¹³⁵



Scheme 1.21 The addition of diethylmalonate to nitrostyrene

It was shown that these catalysts operated through bifunctional means, and that the size of the substituent on the C-9 oxygen dictated conformational stability and thus optimisation of this substituent led to optimal catalytic performance.⁹⁴ This class of catalysts was later shown to be capable of promoting a range of other reactions including the asymmetric Henry reaction between nitromethane and benzaldehyde¹³⁶ (albeit with poor activity and selectivity, Scheme 1.22) or β -ketoesters (with excellent activity and enantioselectivity),¹³⁷ and other Michael additions generally consisting of a malonate and various Michael acceptors; an outline of the possibilities is given in (Table 1.1).^{39,138}

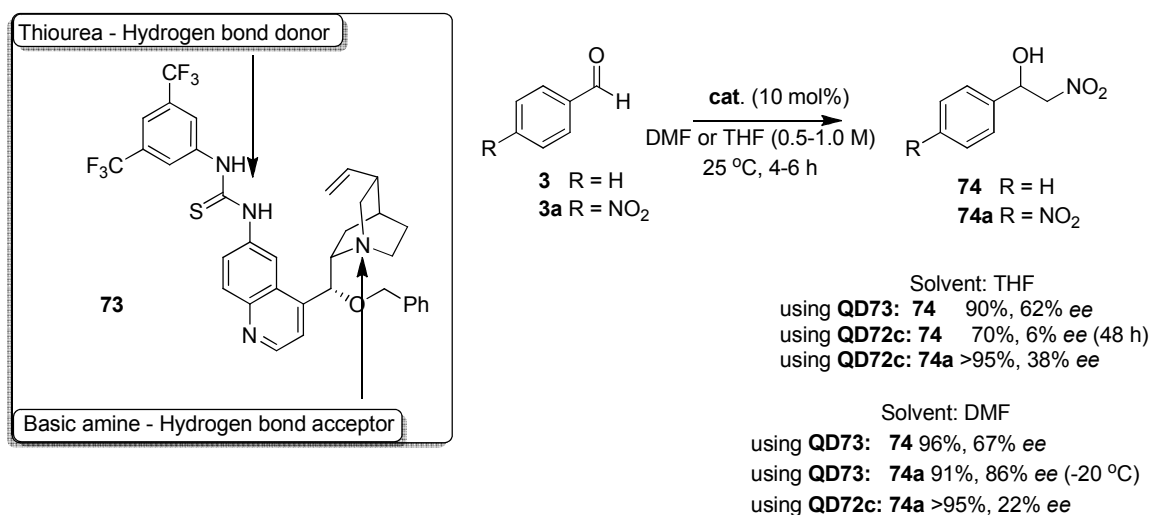
Table 1.1 An outline of the catalytic capabilities of **QD66b** and related catalysts



Entry	Nucleophile	Electrophile	Catalysts	Solv.	Temp.	Yield (%)	ee (%)	de (%)	Ref
1	A $\text{R}^1 = \text{Et, Me}$	Z: $\text{R}^4 = \text{ar, alk}$	CN72b	THF	-20 °C	>70	>94	-	94
2	B	Z: $\text{R}^4 = \text{ar, alk}$	CN72a	THF	-20 °C	>82	99	96	135
			CN72b						
3	C: $n = 1,2$ R = Me, Et	Z: $\text{R}^4 = \text{ar, alk}$	CN72a	THF	-60 °C to r.t.	>83	99	>96 90	135
			CN72b						
			CN72c						
4	D: $\text{R}^2 = \text{Me, Et}$	Z: $\text{R}^4 = \text{Ph, C}_5\text{H}_{11}$	CN72c	THF	-20 °C	>77	92- 96	>84	135
5	E: $\text{R}^3 = \text{Me}$	Z: $\text{R}^4 = \text{Ph, C}_5\text{H}_{11}$	CN72a	THF	-50 to - 20 °C	> 77	>96	>86	135
			CN72b						
			CN72c						
6	E: $\text{R}^3 = \text{Aryl}$ $\text{R}^3 = \text{Me/Allyl}$	Y: $\text{R}^5 = \text{Ph, 3,5-}$ $(\text{CF}_3)_2\text{C}_6\text{H}_3$	CN72b	toluene	-25 0 °C	80-99	>93 >92	- -	138
7	F: X = H, $n = 1,2$	X: $\text{R}^6 = \text{H, Me, Et, Hex}$ $\text{R}^7 = \text{H}$	CN72a	CH_2Cl_2	r.t.	>97	>90	>89	139
			CN72b						
8	F: X = Cl, OMe, $n = 1,2$	X: $\text{R}^6 = \text{H, R}^7 = \text{Me, Et, Ph}$	CN72b	CH_2Cl_2	-27 to 23 °C	>90	>94	-	140
9	C: $n = 1$, R = $\text{CH}(\text{CF}_3)_2$	W: $n = 1,2$	CN72b	CH_2Cl_2	23 °C	>83	>95	>72	140
10	G: Ar - $n = 1-3$, Alk: $n = 3$	V	CN72b	toluene	r.t.	>94	>94	>80	141
11	E: $\text{R}^3 = \text{Aryl}$	V	CN72b	toluene	r.t.	>98	>94	>80	141
12	H	Z: $\text{R}^4 = \text{aryl, alkyl}$	CN72c	CH_2Cl_2	-25 °C	64-90	57-94	-	142

It can be seen that while there are many reactions available, for those that require bifunctional catalysis, it appears that nearly all successful examples entail Michael addition to a conjugated system, similar to that which Takemoto's catalyst (**16**) and C-9 modified cinchona alkaloid catalysts have been shown to promote (Scheme 1.12).

Catalysts of the second type, that is, with other hydrogen bond donors at C-6' were first reported by Hiemstra *et al.* in 2006, as effective catalysts for the enantioselective catalysis of the Henry reaction (Scheme 1.22).⁹⁷

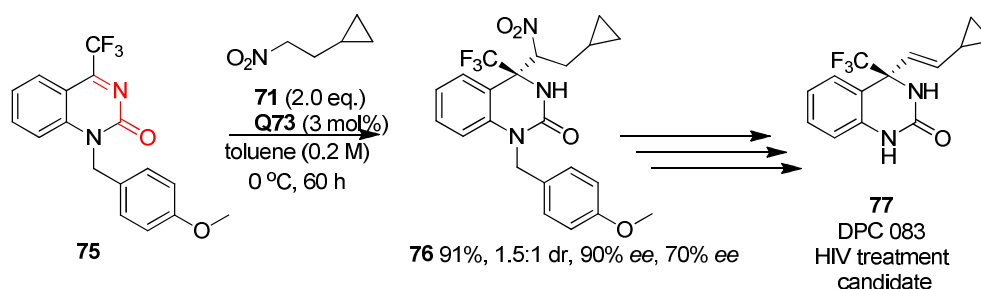


Scheme 1.22 The Henry reaction catalysed by C-6' substituted cinchona alkaloids

In this paper he noted that, (in contrast to trends reported in processes catalysed by thiourea catalysts)^{13,40,59,104} the solvent that gave optimal enantioselectivity was not one which best supported catalyst-substrate hydrogen bonding (*i.e.* toluene or dichloromethane), but rather DMF. Methanol was also shown to be surprisingly effective as a solvent; this was attributed to the fact that the conformation of the catalyst was dictated by the solvent and in non-polar solvents the most catalytically effective conformation of the catalyst was not present.⁹⁷

This catalyst has also been shown capable of synthetically useful asymmetric addition of nitroalkanes to α -CF₃-aza-Michael systems (Scheme 1.23).¹⁴³ Interestingly the catalysts

promoted the reaction optimally in toluene in contrast to Hiemstra's earlier findings, indicating that the transition state is probably reliant on a 1,4 interaction similar to those seen in Deng's earlier catalysts (Scheme 1.21) despite the ostensibly 1,2 nature of the reaction that might be imagined from the "aza-Henry" title given.

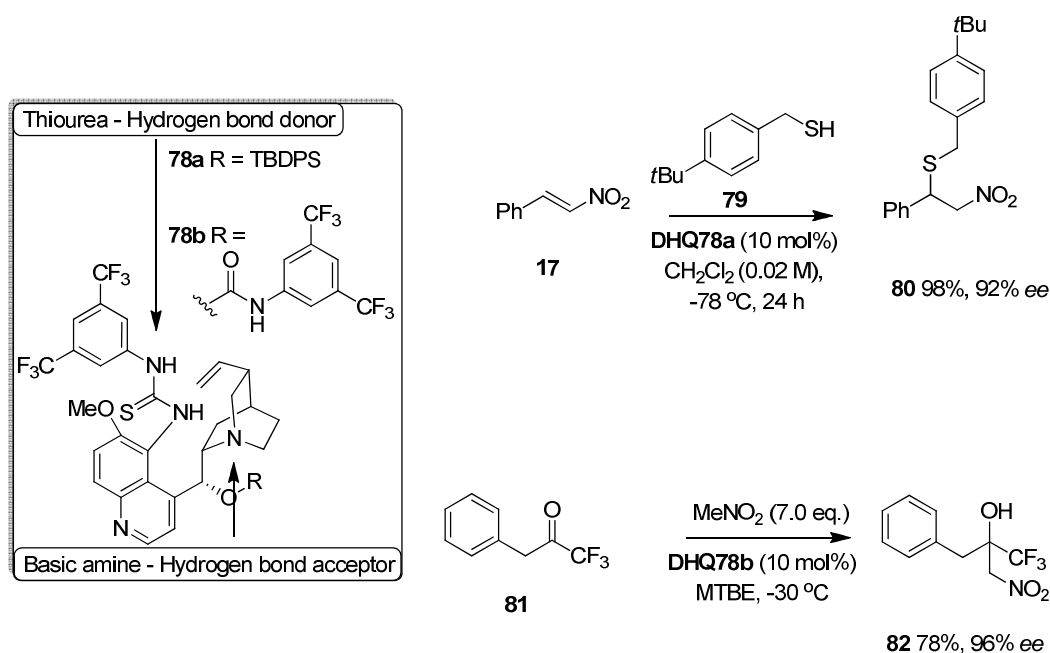


Scheme 1.23 Enantioselective aza-Henry reaction

1.4.4 Catalysts with hydrogen bond donors at C-5'

Given that the possibly utility of any catalyst system is limited by the potential transition states it can efficiently accommodate, and that this is limited by the orientation of the catalytically relevant functional groups, it is reasonable to expect that further positions on the cinchona alkaloid skeleton have been accessed. Examples of a catalyst bearing a hydrogen bond donor at C-5' have been reported by Palacio *et al.*^{144,145} They have been shown to be an efficient catalyst class in two reactions, however one might imagine that given how recently they have been reported further examples will come to light (Scheme 1.24).

Interestingly, catalyst **DHQ78a** catalyses the Michael addition of thiol **79** to β -nitrostyrene (**17**), while catalyst **DHQ78b** promotes the addition of nitromethane to activated α -CF₃ ketone **81**, a 1,2-addition. It would seem likely that in the case of **DHQ78b** the C-9 carbamate is either catalytically active or confers significant conformational change in comparison to **DHQ78a**.



Scheme 1.24 Applications of C-5' substituted cinchona alkaloid based catalysts

1.4.5 The importance of C-10 and C-11

While the quinuclidine substructure in quinine is essentially rigid, a description which is for most intents and purposes acceptable, this overlooks the ability of bicyclic ring systems such as this to twist. Such a twisting motion has been shown to affect the basicity of the quinuclidine nitrogen, a factor which could easily affect the performance of a given catalytic system.^{67,146} Figure 1.10 shows the twisting modes available to the quinuclidine ring system, it may be either left or right handed, *e.g.* counter clockwise or clockwise, but must go through an eclipsed conformation in order to change between these conformations. The extent to which it is twisted is dependent on the size and orientation of the substituents attached to the ring. The larger a substituent the greater the desire to avoid an eclipsed conformation, the greater the torsion angles and the lower the basicity of the quinuclidine nitrogen.¹⁴⁷

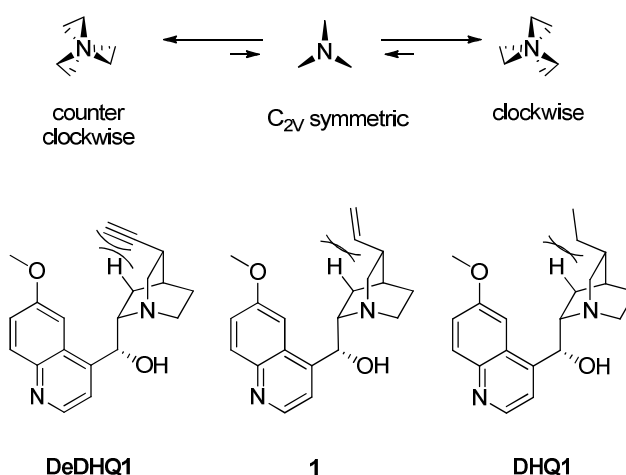


Figure 1.10 Twisting of the quinuclidine ring

Synthesis of the didehydro analogues of the cinchona alkaloids demonstrated this to be the case, with dedihydroquinine and dedihydroquinidine both showing increased basicity compared to the parent compounds (Figure 1.10 shows the relative bulk of these 3 substituents). X-ray crystal structures of both DeHQD and DHQD revealed that the sum of the 3 torsion angles (in the solid state) was nearly doubled from 36.9° in DeHQD to 65° in DHQD.⁶⁷

Thus it is unsurprising that despite being substantially distant from the catalytically active site, the saturation of this double bond is, in many cases seen to have some effect on the performance of a given catalytic system.^{59,148,149}

1.5 Conformational analysis of cinchona alkaloid derivatives

Quinine and its related analogues have been of great importance to chemistry throughout most of its existence.⁵⁶ Many studies have been made into the behaviour of quinine and related analogues at the molecular level with the aim of elucidating the structural characteristics that cause it to behave in the manner it does.^{99,108,109,149-157}

1.5.1 Available methods for obtaining conformational information

There are a variety of methods by which the conformation of a molecule can be deduced. These include purely theoretical means such as computational simulations or even more simply, using basic knowledge of the bonds within a molecule to build a model by manual inspection. While computational simulations allow the user to create a solid theoretical basis for the likely conformations a molecule may have, and their respective energies, without experimental verification they are subject to doubt. On the other hand, building a model by manual inspection of a particular system allows for the construction of a set of qualitative models which can be confirmed or dismissed by way of experimental analysis.

There are a number of means by which experimental data can be obtained. The most common and easily accessible are X-ray crystallography and nuclear magnetic resonance spectroscopy (for which an array of possible experiments is available). Others include techniques less frequently used by the organic chemist such as circular dichroism spectroscopy, fluorescence spectroscopy and exotic forms of mass spectrometry such as resonance-enhanced multiphoton ionization or vapor-phase osmometry. While techniques such as these can provide exquisitely accurate detail of conformations in many environments, they are beyond the necessary and practical scope of this thesis.

1.5.2 Nuclear magnetic resonance techniques for conformational studies

Nuclear magnetic resonance spectroscopy can provide excellent solution phase structural and conformational information.¹⁵⁸ It is possible, owing to the range of deuterated solvents available, to examine the molecule of interest in an environment which very closely matches that which it may experience during its application as a catalyst (or any other chemical application). Two main techniques allow for conformational analysis, those which rely on through-bond coupling, and those which operate through space.

1.5.2.1 Through-space techniques

Through space techniques in NMR spectroscopy rely on the nuclear Overhauser effect (NOE), and consist of one-dimensional and two-dimensional techniques based on this effect. In its simplest form NOE spectroscopy operates by excitation of a particular frequency which corresponds to a known proton. This excited proton can, *via* the Overhauser effect, excite other protons which are close in space, that is to say polarisation transfer can occur by cross relaxation. This polarisation transfer can then be observed in the recipient protons at their respective frequencies allowing for identification of protons which are close in space.

Use of these techniques can allow the approximate conformation of a given molecule to be obtained, however, this is only possible provided two conditions are fulfilled. Firstly, the molecule must have a sufficiently stable conformation such that it is not switching between conformations on a timescale shorter than the NMR experiment which attempts to observe it, (although it is possible that two (or more) stable conformations may exist, in such a case, signals for both conformations may be observed.) In cases where more than one conformation exists but they are separated by a sufficiently high barrier, they may be examined individually to give information about both conformations. Secondly, for a conformation to be observed, it must be present in sufficient quantity relative to other conformations that may be present such that it is present in sufficient concentration as to be above the detection limit of the instrument.

1.5.2.2 Through bond techniques

Bond angles may be established in systems for which vicinal (*i.e.* ^3J or H-C-C-H) coupling between sp^3 hybridised carbons can be quantified. In such a case, the relationship between the dihedral angle of the coupled protons and the coupling constant is given by the Karplus equations and subsequent refinements of these.¹⁵⁸⁻¹⁶⁰ For systems where the dihedral angle

is less than 90° the equation [$^3J_{ab} = J^0 \cos^2 \theta - 0.28$] is used, where the dihedral angle is greater than 90° the equation [$^3J_{ab} = J^{180} \cos^2 \theta - 0.28$] where J^0 and J^{180} are constants that depend on the other substituents present and θ is the dihedral angle.

The use of such an equation is obviously contingent on other basic structural information as each J value is consistent with four possible solutions (equations and orientations) and the requirement for an empirical constant, based on the other substituents, limits the accuracy for any calculation. Even still it remains a qualitatively useful tool. Use of this simple equation also assumes that the resolved NMR spectrum only correlates to a single conformation. In the case that there are several conformations divided by small barriers, they will be able to interconvert on a timescale which is much smaller than that over which the NMR experiment is carried out, thus what will be observed is a weighted average of the various conformations. If however each of the bond angles is known (or estimated by computational means) it will be possible to estimate the average populations of the different conformations.¹⁶¹

The use of any of these techniques however is predicated on the assumption that a clear spectrum of the molecule being analysed with resolved coupling constants can be obtained. Also useful in identifying conformations which undergo slow exchange where the timescale is seconds to minutes (or any other exchange) is EXSY or exchange correlation spectroscopy. Operating on a similar pulse sequence to NOESY experiments, the experiment identifies molecules engaged in slow interchange as they will appear excited despite excitation occurring at a different frequency. However (for molecules of a molecular weight of below 1000 u) the resultant signal will be of opposite phase to any excitation due to NOE transfer thus clearly identifying them.

1.5.2.3 X-ray crystallography

X-ray crystal structures provide exceptionally precise structural information, however their use as means of conformational elucidation is limited as X-ray crystal structures can only be obtained from a crystalline solid. Assuming such a state is tractable, the conformation of the molecules in the solid state may still differ greatly from those of the same molecule

in the solvated state and indeed it would even be unjustified to assume that similar conformations would predominate in different solvents. Accordingly, the contribution of X-ray crystallography is limited, however it can provide important structural information.

1.5.3 The conformation of quinine: associated nomenclature

Quinine is composed of two essentially rigid ring systems, a quinoline and a (vinyl substituted) quinuclidine joined by a benzylic sp^3 hybridised carbon, further substituted with, in the case of the natural derivatives, a hydroxyl moiety. The result is that quinine can, with an acceptable degree of accuracy, be described simply in a two-dimensional manner; the dimensions being the angle along the C-8 to C-9 bond and the angle of the C-4' to C-9 bond.^{108,155} (While the level of twist in the quinuclidine, orientation of the C-9 hydroxyl proton, orientation of the methyl and vinyl groups are other factors, they do not play a large role in the overall conformation.)¹⁴⁹

While *a priori*, a molecule such as quinine may adopt any combination of angles along C-8-C-9 and C9-C-4', it has been shown by a combination of methods that there are four principal minimum energy positions along these bonds that it may adopt.^{108,109}

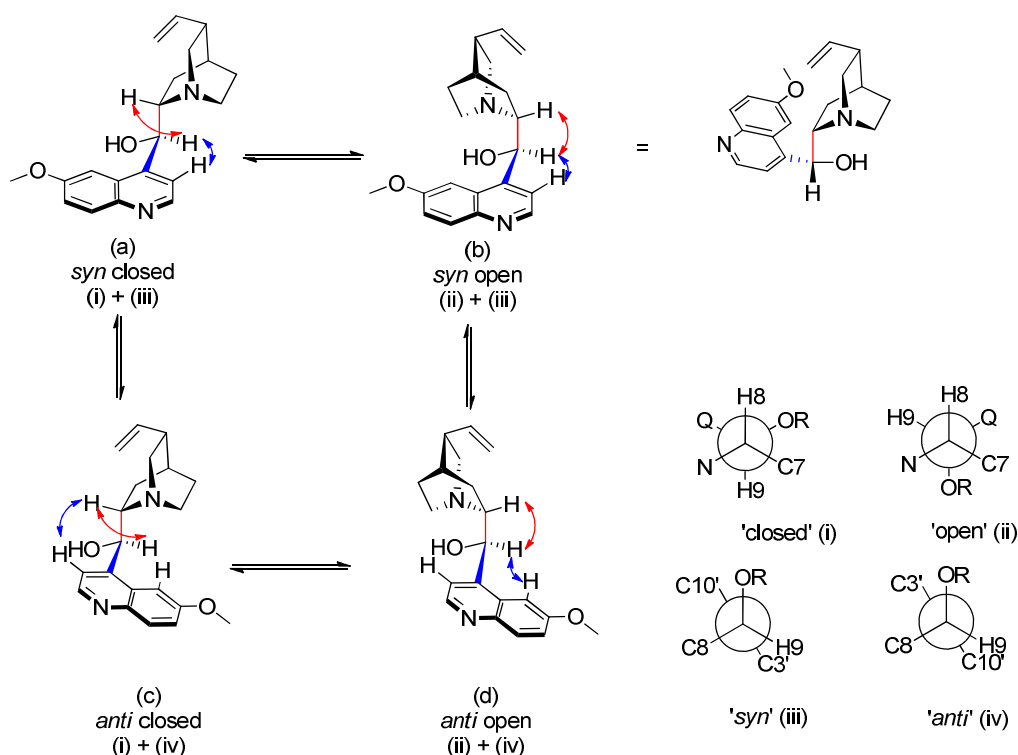


Figure 1.11 Minimum energy conformations of the cinchona skeleton and their associated Newman projections

These conformations are given the labels 'open' and 'closed', which describes the orientation along the C-8-C-9 axis. The label closed is applied where H-8 and H-9 are approximately antiperiplanar and the large quinoline ring is directed in front of the nitrogen containing bridgehead of the quinuclidine ring. Alternatively an open conformation may be adopted whereby this bond is rotated approximately 120° and the quinoline is directed away from the face of the quinuclidine. Importantly, in cases where C-9 has been epimerised, *e.g.* 9-*epi*-quinine the open conformation refers to the position of the quinoline ring in front of the quinuclidine nitrogen and the relative orientation of the diagnostic protons changes accordingly.

In either case the quinoline ring is also able to rotate and may occupy one of two positions where H-3 is close to H-9 or alternatively where it is pointing in the opposite direction,

described as either '*syn*' or '*anti*' (from the point of view of protons H-9 and H-3'). The elucidation of these conformations has been achieved by a combination of methods including X-ray, NMR spectroscopy and *in silico* modelling.^{99,108,152}

1.5.4 Conformational studies on quinine, related cinchona alkaloids and their major derivatives

Having discussed how the conformations of quinine may be described, and by which methods these conformations are identified, we shall now examine the conformations of some of the cinchona alkaloids and their derivatives which are relevant to the studies undertaken in this thesis.

Studies by Sharpless *et al.*, demonstrated effectively the major conformations of the cinchona alkaloids and some of their derivatives.^{108,109} Although earlier studies exist these represent the earliest practically useful report on the topic.^{155,162}

These studies revealed that quinine in its lowest energy conformation exists in an open *anti* conformation (Figure 1.12). This behaviour is exhibited by all four of the naturally occurring cinchona alkaloids and the related dihydro compounds, and is consistent across all solvents (although the levels of the minor conformers vary). Modification of the alcohol at C-9 however, results in conformational change. Methylation of the alcohol results in a compound which exists in both a closed *anti* and open *anti* conformation. While in CDCl₃ the open conformation is in excess, in CD₂Cl₂ the closed conformation is in excess. Furthermore, if the C-9 alcohol is esterified (acetyl or benzoyl), the closed *anti* conformation predominates, except in methanol-d₄ where open *anti* predominates. Protonation of any of the C-9 substituted derivatives resulted in a reversion to the open *anti* conformation. Inversion of the C-9 stereocentre to give -9-*epi*-quin(id)ine results in a conformational change to give open *syn* conformation (Figure 1.12).

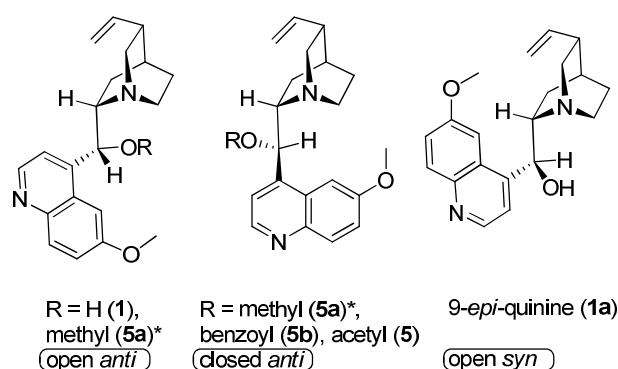


Figure 1.12 Conformations of quinine and selected derivatives

In each of these examples, all of the ^1H -NMR spectra yielded sharp well resolved peaks, indicating that the barriers to interconversion between the conformers were low, however this was shown not to be the case for chloroquine (Figure 1.13).

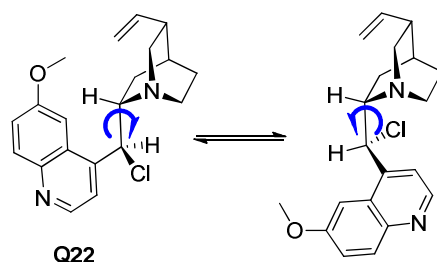


Figure 1.13 Chloroquine (22) exhibits a large barrier to rotation around C-8 C-9

This derivative adopts the closed *anti* conformation in the main (~90%) with small amounts of open *anti*, however unlike the other C-9 substituted derivatives this does not change upon protonation. Furthermore, the NMR spectra of this compound exhibited significant line broadening of the signals (in both CDCl_3 and C_6D_6) for protons H-8, H-9, H-3' and H-5', caused by coalescence, which was not seen in any of the other derivatives analysed in Sharpless' study. This indicated that the barrier to rotation for this compound was no longer sufficiently low to allow an average signal at room temperature. Heating to 70 °C in C_6D_6 resulted in significant sharpening, however even significant cooling of the

other cinchona alkaloids did not allow observation of this phenomenon. This would seem to indicate a substantial change in the nature of the barrier to rotation for cinchona alkaloid derivatives for which the C-9 oxygen is substituted by a larger substituent.

Further investigation of 9-*epi*-amino(deoxy)quinine (**Q43a**) derivatives was undertaken by Brunner *et al.*¹⁵⁶ In this study he showed that these molecules preferred an open-*anti* conformation shown in Figure 1.14.

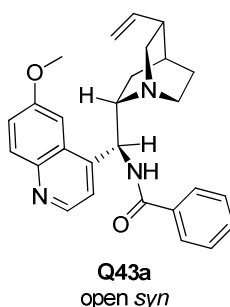


Figure 1.14 The preferred conformation of **Q43a**

These studies have shown that minor adjustments to the cinchona alkaloids can result in large differences to the relative population of conformations and that importantly, while one conformation may predominate, many conformations are sufficiently prevalent (*i.e.* low in energy) to be detected by ¹H NMR spectroscopy at room temperature.

1.5.4.1 Conformational studies on C-9 arylated cinchona alkaloid derivatives

Studies by Skarżewski *et al.* on the solution state conformation of basic 9-vinyl and 9-aryl derivatives of quinine and quinidine have been undertaken. Having synthesised 9-*epi*-phenyl(deoxy)quinidine by reaction of the corresponding quinidine chloride and Grignard reagent, its absolute structure was confirmed by X-ray crystallography, crystallising the material as a thiocyanate salt.

The resulting structure confirmed all aspects of the stereochemical outcome of the reaction and the same molecule (9-*epi*-phenyl(deoxy)quinidine) was analysed (as the free base) by NMR spectroscopy using benzene- d_6 as the solvent.

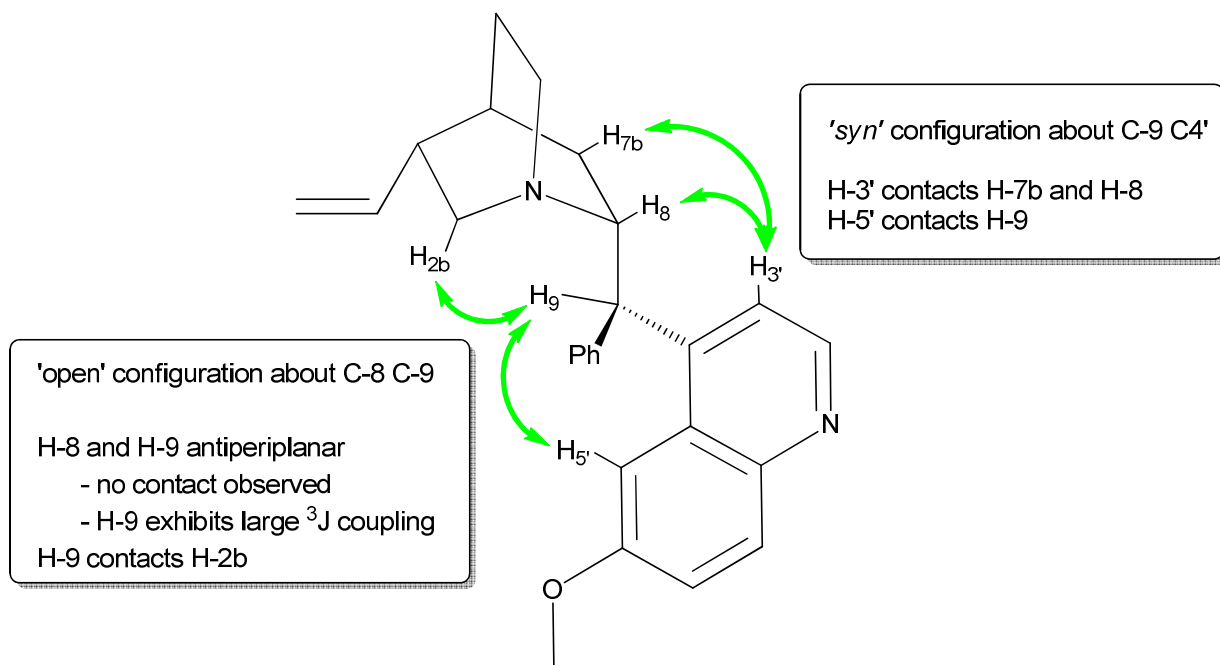


Figure 1.15 9-*epi*-phenyl(deoxy)quinidine (**QD23**) with observed NOE contacts

Based on the structure determined by X-ray crystallography, the NOE contacts were fit to the model giving a conformation approximate to that shown in Figure 1.15 (NOE contacts marked in green). While this presentation gives the impression of a single stable conformation, a closer examination of the ^1H NMR spectra of this molecule shows that several of the peaks are poorly resolved, indicating that there may be interconversion between a number of conformations, with observation of the major only in the NOE experiments. Furthermore the orientation of the phenyl ring is not addressed however on the basis that the two *ortho* protons (H-2'') are equivalent by NMR and well resolved, it is likely that this ring is in free rotation.

1.6 Kinetic resolution (KR) and dynamic kinetic resolution (DKR)

In order to obtain enantioenriched material from a racemic mixture, *i.e.* chiral resolution, it is possible to employ a process whereby one enantiomer reacts more rapidly than the other in the presence of a chiral catalyst (or reagent). Such a process is termed kinetic resolution and is a widely used approach to the preparation of enantiopure materials. It is however limited, in the same way as other forms of chiral resolution, by the limitation that a yield of no more than 50% is possible.¹⁶³

One possible means of overcoming this lack of efficiency is by effecting a kinetic resolution in which there is also racemisation or epimerisation of the starting material occurring, thus allowing for complete conversion to the desired enantiomer or diastereoisomer.¹⁶⁴ This type of process is described as a dynamic kinetic resolution.^{165,166}

1.6.1 General requirements for efficient DKR

In a standard kinetic resolution, the level of enantiopurity obtained is directly dependant on the different rates at which the two enantiomers react, k_R and k_S . In DKR it is important that the enantiomers react at sufficiently different rates for efficient formation of the desired enantiomer, however there is also the requirement that the racemisation that is occurring take place at a rate (k_{rac}) that is much faster than the rate of reaction of the slow reacting enantiomer.^{167,168}

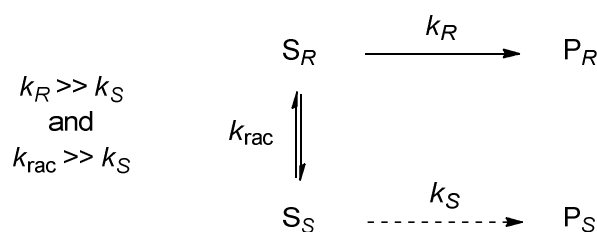


Figure 1.16 The kinetic requirements for efficient DKR

Without this condition being fulfilled, it is clear that the enantioselectivity of the product would be less than that which was possible on the basis of the difference of k_R and k_S while fast racemisation means that the complete conversion of starting material to a product of very high *ee* is possible.¹⁶⁹ Such a process may be represented diagrammatically (Figure 1.16) where in this case the *R* enantiomer is the desired enantiomer.

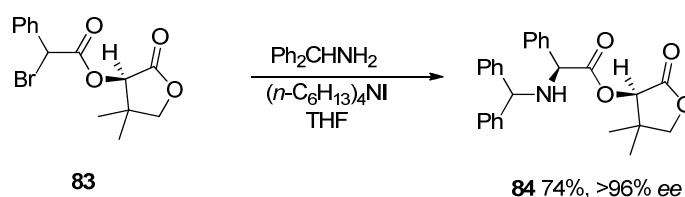
It is also important to note that any racemisation process must not affect the product as this would clearly reduce the utility of any such process making the racemisation a crucial component of any effective dynamic kinetic resolution protocol.¹⁷⁰

Using this process it is theoretically possible to obtain 100% yield of the desired enantiomer from a racemic starting material. There have been a large range of reports detailing a variety of methods by which this reaction may be achieved.^{166,171}

Interestingly, when considering processes in which catalytic DKR is occurring, it should be noted that the racemisation is usually dependent on two components (*i.e.* the molecule being racemised and the agent causing the racemisation), while the reaction itself is dependent on three components, *i.e.* the substrate pair (assuming the reaction is intermolecular) and the catalyst. Since this is the case, it follows that the entropic requirement could be significantly larger than that of the racemisation and that lowering the temperature of the reaction will cause a relative increase in the rate of reaction in comparison to that of racemisation. Therefore (possibly counter intuitively), while in a simple case of asymmetric catalysis, the change in the Boltzmann distribution of molecular energies would imply that a lower temperature would yield greater selectivity; this may not be the case for DKR.

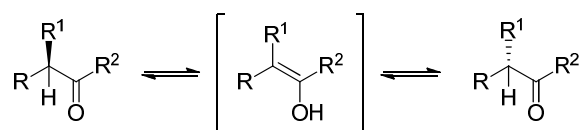
1.6.2 Racemisation, a crucial step for DKR

There are a large number of examples of reactions which employ DKR, with various racemisation protocols.¹⁶⁴ Many of these use chiral auxiliaries to provide the stereochemical information (such as that shown in Scheme 1.25), however such protocols lack the atom efficiency of purely catalytic methods.¹⁷² They do however reveal various methods available of effecting DKR, in particular the crucial racemisation step. All methods rely on a configurationally labile stereocentre and examples of these have been shown to include halides (Scheme 1.25),¹⁷³ anions (*e.g.* benzyl lithiums),^{174,175} and stereocentres capable of undergoing sp^3 to sp^2 interconversion.^{172,176-178}



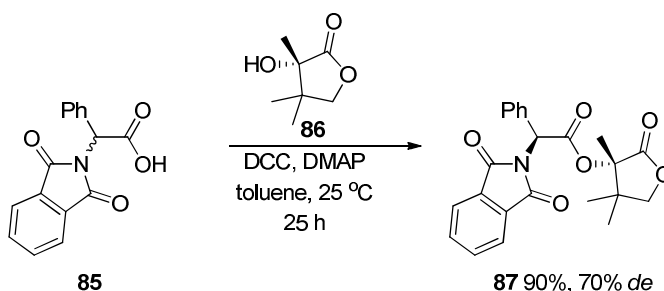
Scheme 1.25 DKR like halide mediated epimerisation to provide protected α -amino acids

Of greatest interest to us are methods which involve the deprotonation and reprotonation of a stereogenic centre adjacent to a functional group (such as a carbonyl) leading to sp^3 to sp^2 interconversion, (such systems may be susceptible to both base and acid catalysed racemisation *e.g.* Scheme 1.26) and those which yield amino acid like products. α -Amino acids are of great economic importance¹⁷⁹ and while biosynthesis of enantiopure natural amino acids is a highly efficient means of synthesising those for which there is substantial demand,¹⁰ DKR represents an excellent methodology for the asymmetric synthesis of orthogonally protected α -amino acids with unnatural or unusual substituents.



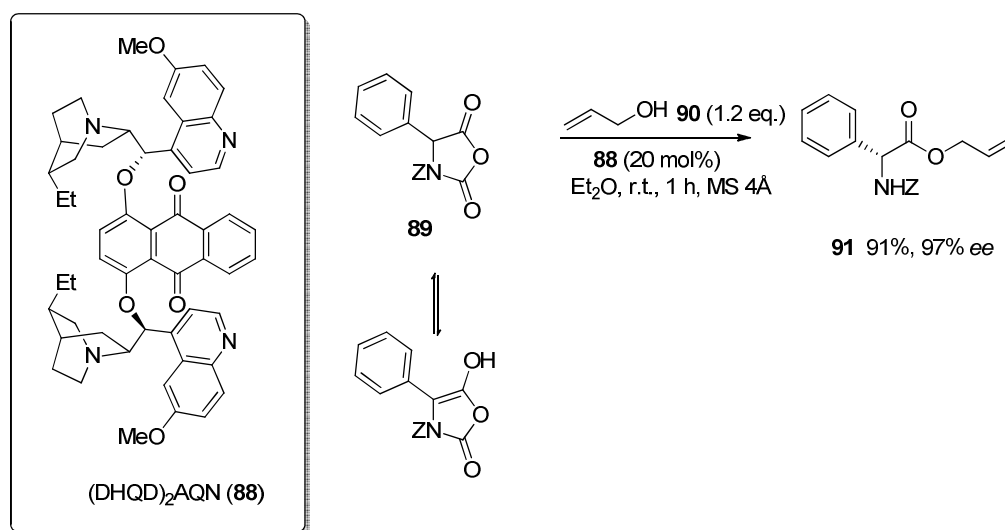
Scheme 1.26 Enolisation and racemisation of α -carbonyls

A large number of protocols based on this interconversion have been reported.¹⁸⁰ As well as the DKR of azlactones, which shall be treated in some detail, it is first worthwhile looking at other examples of organocatalytic DKR which lead to similar products. Scheme 1.25 is an example of generation of α -amino acid like products using chiral auxiliaries as the source of stereochemical information. It is also possible to use a chiral nucleophile as the source of stereochemical information as demonstrated in Scheme 1.27.¹⁸¹ In this case, the intermediate formed between acid **85** and DCC is the rapidly racemised intermediate which reacts selectively with alcohol **86**.



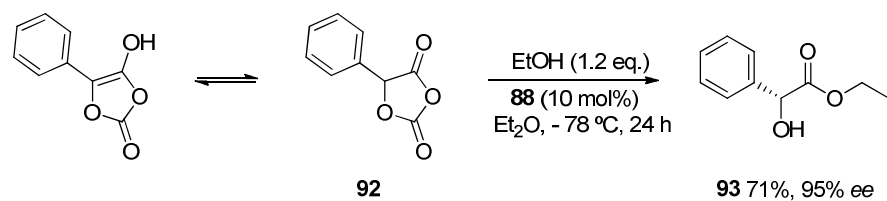
Scheme 1.27 DKR by alcoholysis with chiral alcohols

Other examples of DKR by enolisation include those of Deng *et al.* involving the production of orthogonally protected enantioenriched α -aryl α -amino acids and α -aryl α -hydroxy acids from racemic, racemisable starting materials.^{182,183}



Scheme 1.28 The DKR of *N*-carboxyanhydrides to produce protected enantioenriched α -aryl α -amino acids

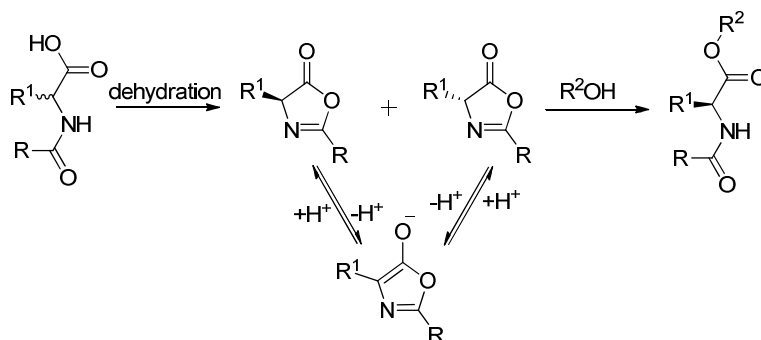
Scheme 1.28 shows this reaction and the catalyst that it was achieved with, a monofunctional cinchona alkaloid derivative, with the base serving to promote both racemisation and preferential attack of the achiral nucleophile on one enantiomer of starting material. Scheme 1.29 shows the DKR of 5-substituted 1,3-dioxolane-2,4-diones a similar reaction which produces protected enantioenriched α -aryl α -hydroxy acids.



Scheme 1.29 The DKR of 5-substituted 1,3-dioxolane-2,4-diones

1.6.3 DKR of azlactones by alcoholysis

Another strategy for the preparation of orthogonally protected α -amino acids by DKR is the opening of azlactones (oxazol-5-(4*H*)ones).^{184,185} This methodology also allows for the enantioselective production of orthogonally protected α -aminoacids *via* simple reactions under mild conditions.¹⁸⁶



Scheme 1.30 The DKR of azlactones

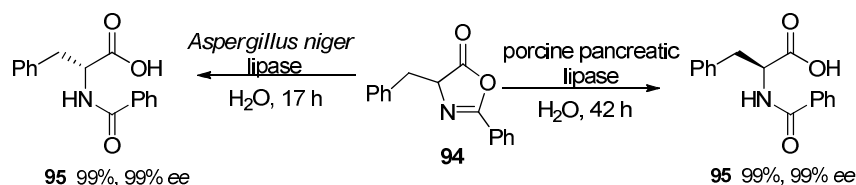
This process occurs in the same manner as other DKR reactions, involving a fast racemisation. Owing to the relatively low pK_a of azlactones ($pK_a = ca. 9$, H_2O , $25\text{ }^\circ C$),¹⁸⁷ enolisation occurs rapidly and is easily catalysed by both acids and bases.¹⁸⁸ Infact the racemisation of azlactones, a phenomenon that has bedevilled peptide synthesis, can even be autocatalytic.¹⁸⁹

(It is worth noting that pK_a may vary considerably and shows great dependence on solvent and steric changes in ostensibly similar systems, as such, these number may be used as a general guide to relative acidity only.)¹⁹⁰

1.6.4 Non-organocatalytic methodologies for the DKR of azlactones

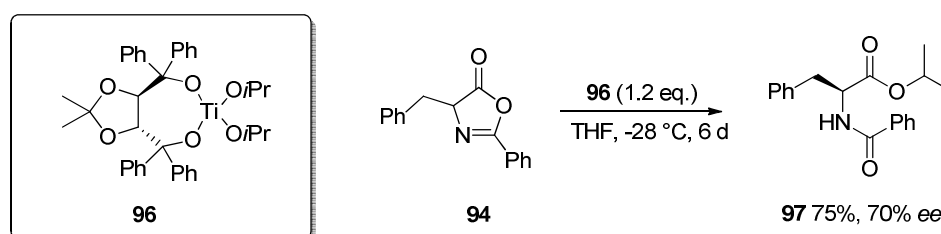
Non-organocatalytic methodologies reported have consisted of either those involving a chiral Lewis acidic metal-ligand complex or those that involve the use of enzymes as catalysts.

Several enzymatic methodologies have been reported for the DKR of azlactones involving a variety of different enzymes, since there is no natural ‘azlactonase’.^{187,191,192} These methods, while effective for certain substrate combinations, also suffer from the shortcomings for which enzyme based reactions are known; a lack of substrate scope, the high cost of enzymes and the poor availability of matched pairs of enzymes which can deliver opposite enantiomers.¹⁹¹ Despite these shortcomings, Sih and co-workers reported the enantioselective DKR of **94** (Scheme 1.31) with 99% *ee* and quantitative conversion however results using azlactones derived from other aminoacids were significantly less impressive.¹⁹²



Scheme 1.31 The lipase promoted DKR of azlactones

The use of Lewis acidic Ti-TADDOLate complexes as promoters of the DKR of azlactones was reported by Seebach *et al.*^{193,194} Testing of a variety of tartaric acid derived Ti-TADDOLate complexes allowed the optimisation of the reaction to give the results shown in Scheme 1.32, furnishing product **99** in 75% yield and 70% *ee*.¹⁹⁴ It was found that complete conversion could be obtained with longer reaction times of up to 20 days.



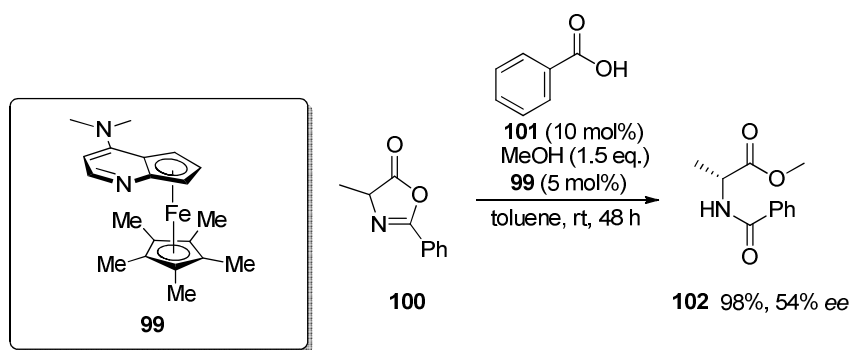
Scheme 1.32 The DKR of azlactones promoted by bis-isopropoxy- Ti-TADDOLate

Further investigation into this methodology found that similar results could be obtained for a variety of compounds where the phenyl group was either substituted or replaced with other aromatic rings, however substrates containing aliphatic side chains were found to result in almost racemic products. The reaction also required more than one equivalent of chiral reagent which, despite its readily available nature, represents poor atom economy. This methodology also suffers a lack of ability to furnish esters other than the isopropyl one shown (Scheme 1.32) with ethyl esters providing greatly reduced enantioselectivity and the use of titanium *t*-butoxides resulting in little reactivity.

1.6.5 Nucleophilic organocatalytic methodologies for the DKR of azlactones

The opening of azlactones involves the acylation of an alcohol (or other suitable nucleophile) and is thus amenable to nucleophilic acyl transfer catalysis. Dialkylaminopyridine derivatives are known to be effective nucleophilic catalysts.¹⁹⁵ Such an approach was investigated by Fu *et al.*, who demonstrated that planar chiral dimethylaminopyridine (DMAP) derivatives are effective as agents of asymmetric nucleophilic catalysis.¹⁹⁶ While there is a metal present in the DMAP derivatives described, the metal does not play an active catalytic role, thus the catalyst can reasonably be described as acting in an organocatalytic manner even if it itself is not an organocatalyst.

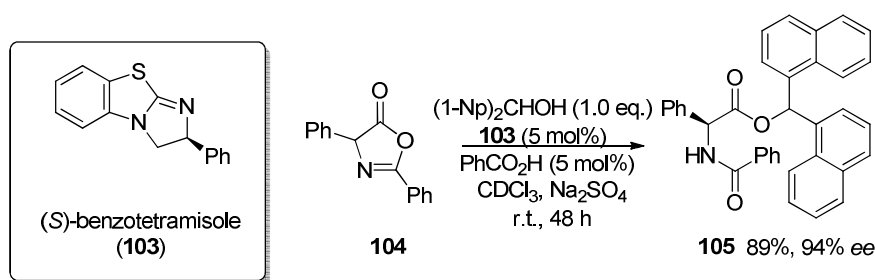
Research into this methodology demonstrated that using DMAP derivative **99** and benzoic acid as an additive, a range of *N*-benzoyl amino acid derived azlactones could be opened to furnish orthogonally protected amino acids in excellent yield and modest to good enantioselectivity.



Scheme 1.33 DKR of azlactones promoted by DMAP analogue **99**

During this study they noted that use of more sterically demanding alcohols resulted in greater levels of enantiomeric excess at the expense of reaction rate (up to 78% *ee* in the case of isopropanol).¹⁹⁷ This made clear that enantioselectivity did not result from discrimination of enantiomers during the initial nucleophilic DMAP attack, and that (in keeping with known amino acid chemistry)¹⁹⁸ the addition of DMAP was a reversible process. (The Curtin–Hammett principle can be applied to this process.)¹⁶⁹

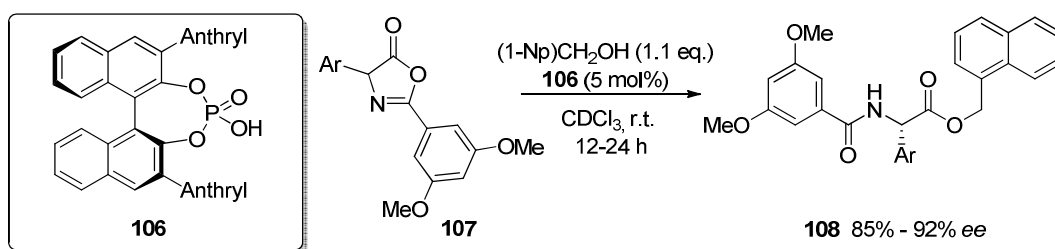
The approach of nucleophilic catalysis was re-examined by Birman *et al.* who used a benzotetramisole catalyst in a similar role to Fu's DMAP derivative.¹⁹⁹ Again it was shown (by the dependence of enantioselectivity on the alcohol nucleophile) that the selectivity did not occur at the nucleophilic attack step (Scheme 1.34). This catalyst, while capable of furnishing the product with excellent conversion and enantioselectivity for phenyl glycine derived azlactone and related analogues fell short when applied to those derived from aliphatic amino acids and in particular hindered amino acids. It also required the use of the very bulky alcohol di(1-naphthyl)methanol to provide high selectivity, with the use of other (less hindered) alcohols such as methanol and benzyl alcohol giving greatly reduced enantioselectivity.



Scheme 1.34 Benzotetramisole, an effective acyl transfer catalyst for the DKR of selected azlactones

1.6.6 Specific acid mediated DKR

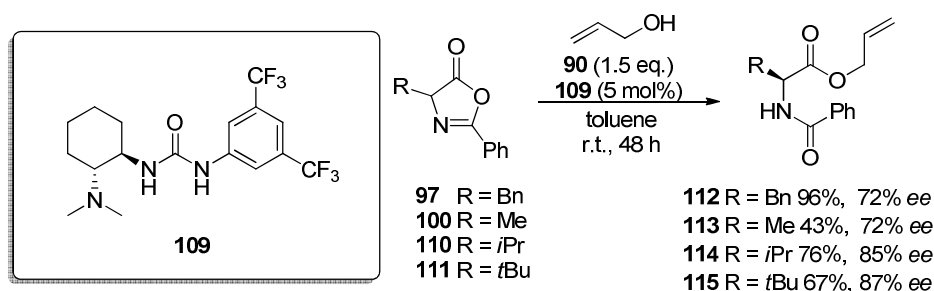
Specific acid mediated organocatalysis has also been shown to be an effective catalytic strategy in a diverse array of reactions.¹⁸ It has been shown to be useful in the promotion of the DKR of azlactones. Brønsted acid **106** reported by Birman *et al.* was demonstrated to be capable of promoting the DKR of azlactones with a scope very similar to that of the nucleophilic catalyst **103** (Scheme 1.34), also reported by his research group (Scheme 1.35). Here however there is no nucleophile present other than the alcohol so in this case enantiodiscrimination takes place during the attack of the nucleophile.²⁰⁰



Scheme 1.35 Brønsted acids are also capable of promoting the DKR of azlactones

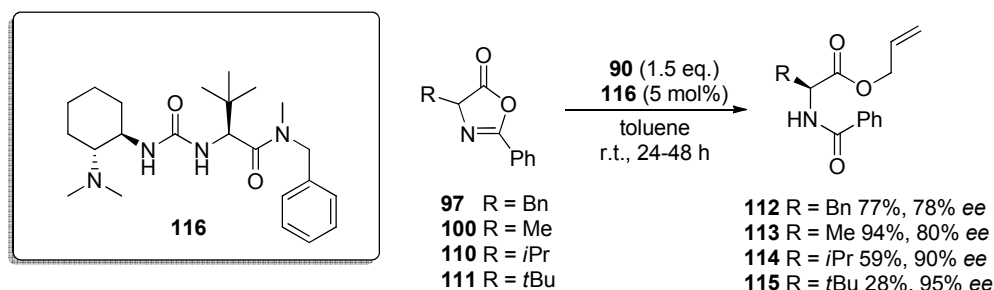
1.6.7 Bifunctional hydrogen bond mediated DKR

The catalysis of the DKR of azlactones by hydrogen bond donors and acceptors (*i.e.* general acid/base mechanisms) has proven to be the most generally effective means of achieving high yield and selectivity combined with high substrate tolerance.¹⁸⁵ The first example of such catalysts was reported by Berkessel *et al.* who applied Takemoto type catalysts to the reaction, resulting in acceptable levels of enantioselectivity as well as in some cases excellent conversion (Scheme 1.36).²⁰¹



Scheme 1.36 DKR of azlactones mediated by **109** through general acid/base interactions

This was improved upon in two subsequent reports from the same group in which a wide variety of catalysts operating through the same mode were screened.^{202,203} It was shown that addition of further elements with matched stereochemical information could be beneficial to both selectivity and activity leading to excellent enantioselectivity for bulky amino acids and good enantioselectivity for others (Scheme 1.37).

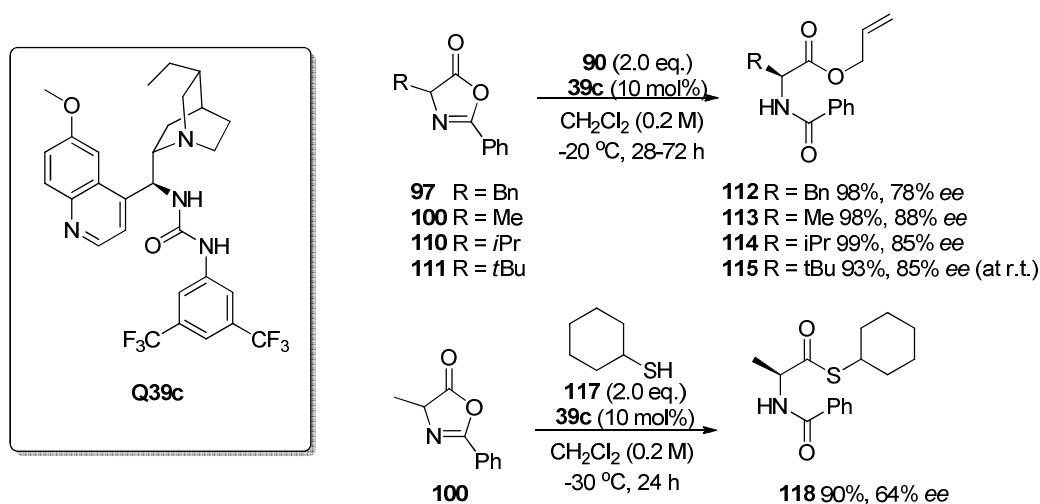


Scheme 1.37 DKR of azlactones by urea **116**, an optimised bifunctional catalyst based on urea **109**

Also made clear in these studies was the dependence of catalytic efficiency on the 1,2 relationship of the catalytic functionalities. Other catalysts not containing this substitution pattern failed to deliver either in terms of selectivity and/or rate.

Given the propensity for catalysts analogous to Takemoto's catalyst (**16**) to be effective as promoters of the DKR of azlactones, it is unsurprising that 9-*epi*-deoxyamino cinchona alkaloid derivatives were also shown to be successful as catalysts (Scheme 1.38). A report by Pesciulli and co-workers demonstrated that **DHQ39c** was an excellent catalyst for this reaction, furnishing products with greater selectivity than that available using **116** for substrates that were less sterically hindered, such as alanine derived azlactones.¹⁴⁸

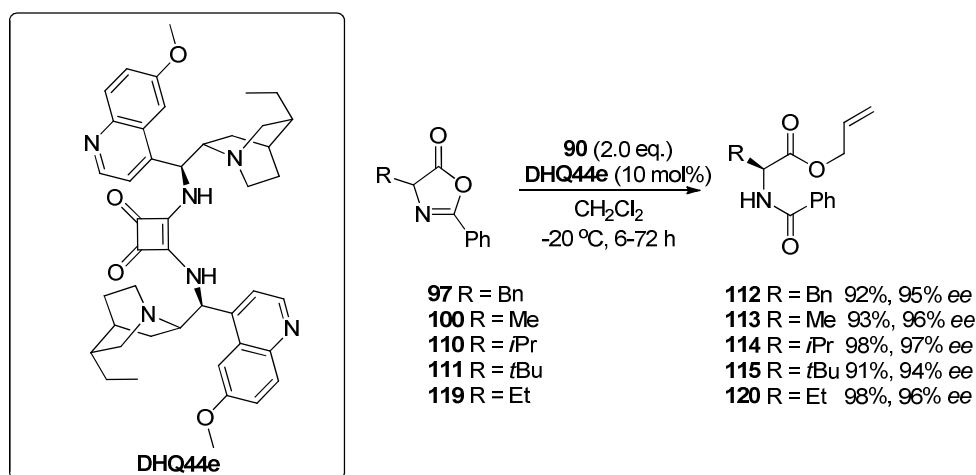
Also in this report (for the first time) the use of thiols as nucleophiles was investigated with moderate success (Scheme 1.38). While thiols are ostensibly similar to alcohols, the different bond angles and much greater bond lengths combined with a significantly higher acidity means that they are far more challenging substrates. Thiols do not experience the same level of hydrogen bonding as alcohols (in fact it is not even described as such) and so ultimately are far more difficult substrates for hydrogen bond mediated catalysis,²⁰⁴ however, the resultant thioesters offer synthetic opportunities not available from esters.²⁰⁵



Scheme 1.38 The DKR of azlactones by thiolysis

Mentioned earlier, C-9 squaramide derivatives reported by Rawal *et al.* have been shown to be more capable catalysts in many reactions where (thio)ureas have proven effective.³¹

In the case of the DKR of azlactones by alcoholysis with allyl alcohol, this was definitely shown to be the case (Scheme 1.39).¹¹⁸ Song *et al.* demonstrated that catalyst **DHQ44e** was exceptionally effective for this purpose, delivering a range of amino acids, both hindered and unhindered, with excellent enantioselectivity (91-97%) in excellent yield (91-99% in <72 h and <24 h for all but the most hindered substrates). In this report the use of thiols as nucleophiles is not explored and subsequent reports on the matter have not yet been made.



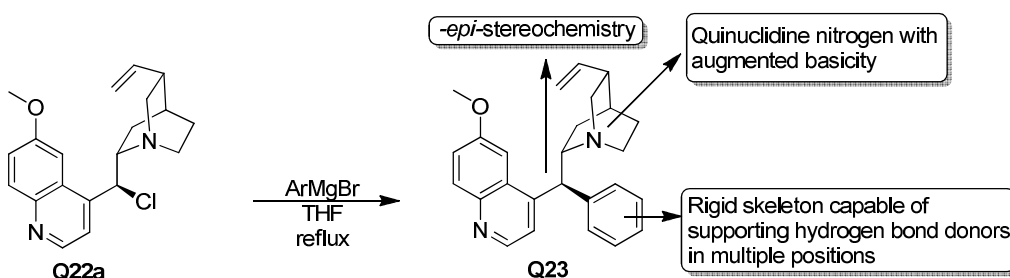
Scheme 1.39 DKR of azlactones promoted by a squaramide based catalyst

1.6.8 Conclusions

The DKR of azlactones by alcoholysis is a reaction for which a broad scope of solutions have been shown effective and indeed, use of squaramide catalyst **DHQ42e** in particular would appear to be an excellent solution providing both high yield and exceptional enantioselectivity across a broad scope of substrates. Nonetheless, it is clear that the large range of variables available in this reaction mean that it is ideal for examining any potential novel catalytic system. Furthermore, while excellent selectivity and yield have been achieved, the requirement for extended reaction times at low temperatures is less than ideal and in the ideal case would not be necessary.

2.0 Generating a library of tuneable novel organocatalysts

As discussed (1.4.2), the arylation of quinine at the C-9 position by reaction of the C-9 chloride with sp^2 hybridised Grignard reagents has been known for over 60 years.²⁰⁶ Its stereochemical outcome is now well understood and thus it was decided that such a reaction would be ideal for providing the synthetic pathway to a novel library of quinine derived organocatalysts which possessed a high degree of tuneability (Scheme 2.1).

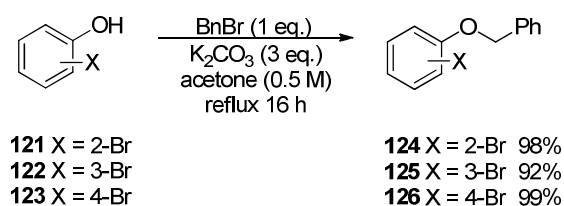


Scheme 2.1 The synthetic potential of C-9 arylation of quinine

Scheme 2.1 shows how the presence of an aromatic ring at C-9 allows for the installation of a catalytically relevant functionality at several positions, each of which would provide a unique set of distances between hydrogen bond forming functionalities.

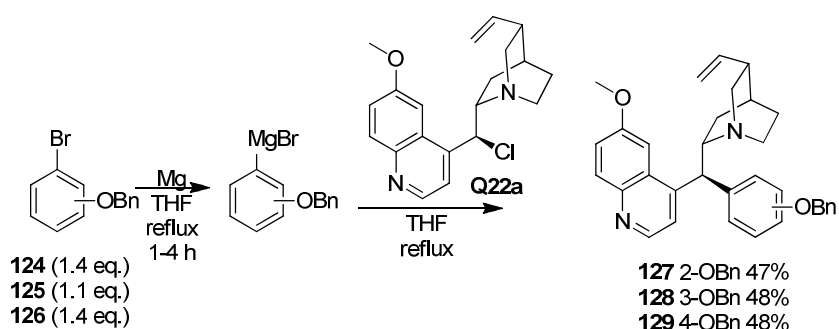
2.1 Synthesis of initial catalysts

Starting with the simplest aryl derivative, **Q23**, it is clear that the installation of a hydroxyl moiety is possible in one of 3 positions, giving rise to a simple set of organocatalysts with defined and (at least in some dimensions) rigid architecture in which the distance between the catalytically active moieties is subject to control. In order to achieve this reaction, the relevant *O*-benzylated bromophenols (**124-126**) were readily synthesised from commercially available starting materials **121-123** (Scheme 2.2).



Scheme 2.2 The synthesis of simple *O*-benzylated bromophenols

These arylbromides could then be quantitatively transformed into the corresponding Grignard reagents by reaction with freshly ground magnesium metal in THF under reflux until all of the magnesium had reacted (and no solid remained). The addition of a solution of chloroquinine in THF allowed for its reaction with the freshly generated Grignard reagent to afford the desired *O*-benzylated 9-*epi*-(deoxy)arylquinine. In the case of these three analogues (**127**, **128** and **129**) this reaction proceeded in moderate yield (Scheme 2.3).

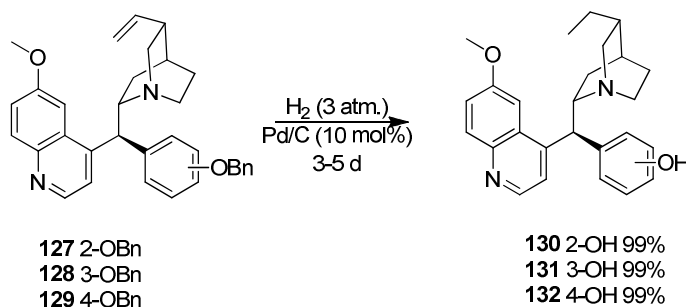


Scheme 2.3 The synthesis of *O*-benzylated 9-*epi*-(deoxy)arylquinine derivatives

Several factors were found necessary to achieve optimal yield over the course of synthesising the suite of catalysts. Firstly, any excess of magnesium remaining after the complete formation of Grignard from the aryl bromide would react with the 9-*epi*-chlorodeoxyquinine resulting in the (temporary) formation of the corresponding Grignard reagent which could then react with another equivalent of the chloroquinine, thereby reducing overall yield. Furthermore, this resulted in the creation of by products which resulted in a dramatic increase in difficulty associated with the purification step. Secondly, any remaining chloroquinine in the final crude material would result in additional

difficulty in purification, thus the use of a slight excess in Grignard reagent was advisable. However in cases where the Grignard reagent was not excessively hindered, the use of excess Grignard reagent would result in additional undesired attack at C-2' leading to reduced overall yield of the desired product, and so a very small excess of Grignard reagent was used. Thirdly, the exclusion of water, while obviously a necessity for all reactions involving highly reactive organometallic species, was quite imperative in this case as adventitious water appeared to impede the reaction to an extent greater than its stoichiometric quantity would suggest. An explanation for this is may be that the formation of relatively Lewis acidic magnesium salts could interfere with the necessary coordination which must occur between the Grignard reagent and the quinuclidine in the reaction. Taking all these factors into account it was later possible to achieve synthesis of 9-*epi*-aryldeoxyquinine derivatives in good to excellent yields.

The benzyl protecting group could subsequently be removed by hydrogenolysis after installation of the phenyl ring at the C-9 position by treatment with catalytic palladium on charcoal under a hydrogen atmosphere. This also led to the saturation of the C-10-C-11 vinyl bond to afford the corresponding dihydroquinine analogue. This allowed for the synthesis of catalyst candidates **130**, **131** and **132** (Scheme 2.4).



Scheme 2.4 Deprotection of **127-129** under catalytic hydrogenation conditions

2.1.1 Synthesis of other simple C-9 aryl quinines

While the three positions for the installation of a hydrogen bond donating functionality offered by the 9-*epi*-(deoxy)phenylquinine architecture allow distinctly different intramolecular distances between the hydrogen bond accepting quinuclidine amine and the

hydrogen donating phenol, in order to obtain a more expansive library, a greater number of derivatives which would allow a greater variety of distances was desired. In order to achieve this, it was envisioned that the installation of a naphthyl ring would provide a suitable architecture, thus derivatives **133**, **134** and **135** were targeted.

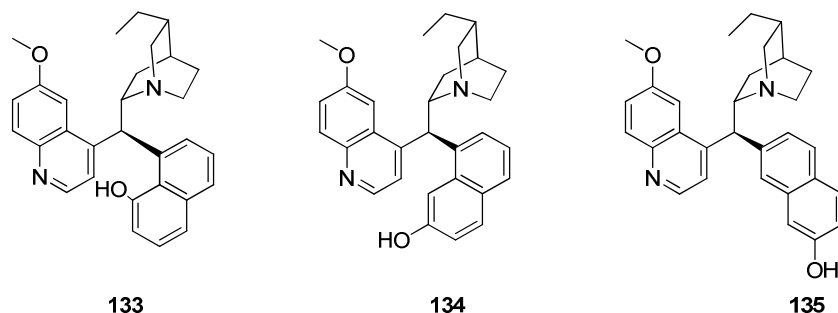
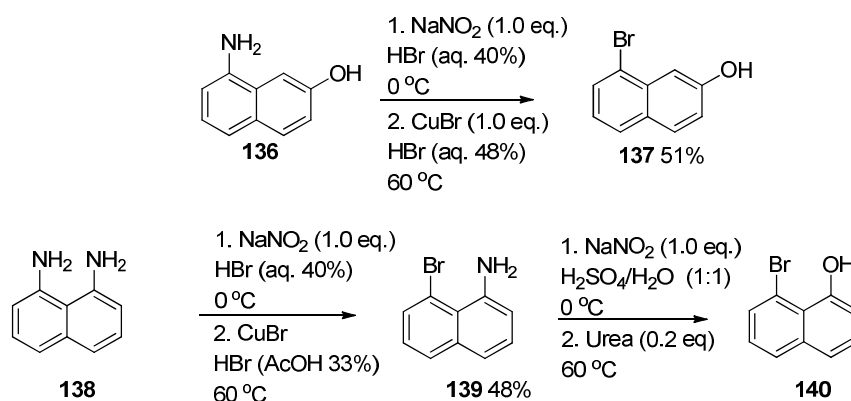


Figure 2.1 Potential catalysts with augmented distances between catalytically active functional groups

2.1.1.1 Synthesis of bromophenol derivatives by Sandmeyer reaction

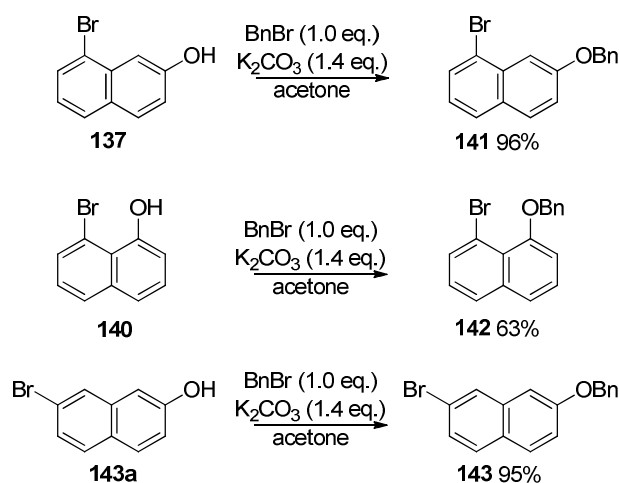
While the bromonaphthol required for the synthesis of **135** was commercially available, the halonaphthol precursors required for the synthesis of the 1,7 and 1,8 substituted derivatives (**137** and **140** respectively) were not, necessitating their synthesis from 1,8-diaminonaphthalene and 8-amino-2-naphthol (Scheme 2.5).



Scheme 2.5 Synthesis of bromonaphthols by Sandmeyer reaction

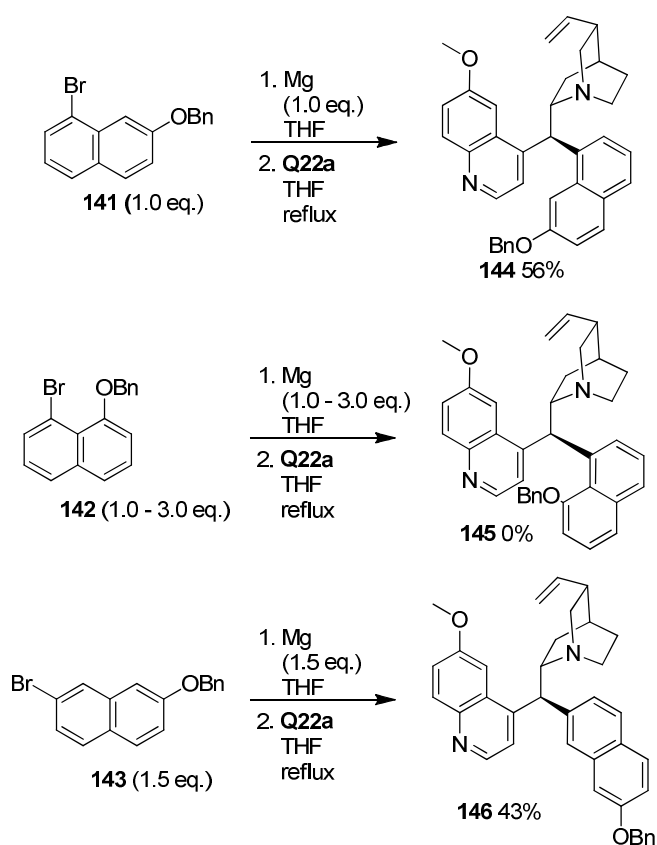
The transformation of these compounds into the corresponding bromo naphthols was achieved by Sandmeyer reaction,²⁰⁷ allowing for the FGI of the aniline into a bromide or phenol as required. Pleasingly, compound **138** behaves in a manner similar to proton sponge allowing the selective reaction of a single amine without considerable difficulty.²⁰⁸

Having synthesised bromonaphthols **137** and **140** the three required bromonaphthols were benzylated under conditions identical to those in Scheme 2.2 to afford the products **141**, **142** and **143** in 96%, 63% and 95% yield respectively (Scheme 2.6).

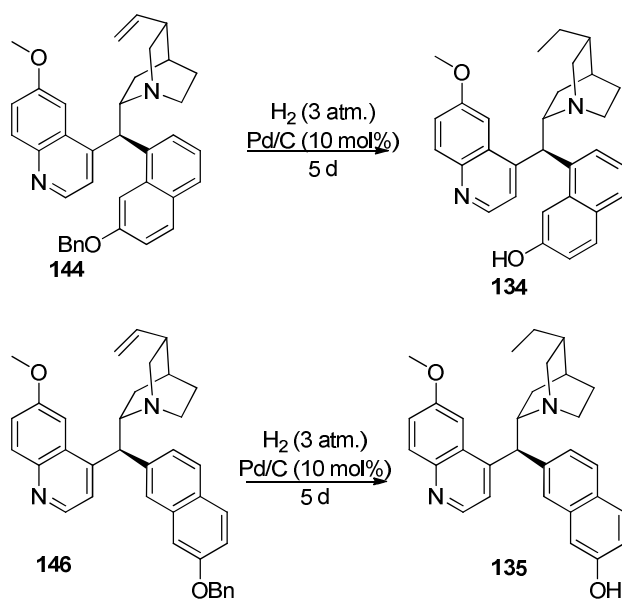


Scheme 2.6 Benzylation of bromonaphthols

Having now synthesised the required precursors, the Grignard reagents were formed and reaction with chloroquine (**Q22a**) was undertaken (Scheme 2.7). While the reaction of chloroquine with 8-bromo-2-benzyloxynaphthalene (**141**) proceeded smoothly to give the desired product in 56% yield, 1-bromo-8-benzyloxynaphthalene proved incapable of undergoing the reaction, with the exposure of chloroquine to between 1.0 and 3.0 equivalents of Grignard reagent failing to produce any of the desired product. Treatment of products **144** and **146** with conditions identical those in Scheme 2.4 gave catalysts **134** and **135** with hydrogenolysis again proceeding quantitatively (Scheme 2.8).



Scheme 2.7 The synthesis of *O*-benzylated 9-epi-(deoxy)arylquinine derivatives



Scheme 2.8 The formation of catalyst candidates **134** and **135**

Before testing our initial library of catalysts, two final derivatives, **147** and **148** were prepared based on the C-9 naphthyl skeleton. It was anticipated that while analogues **147** and **148** (Figure 2.2) would possess an identical *ortho* relationship between the hydroxyl and the quinine as in catalyst **130** the addition of the second ring could cause overall changes to the conformation of the resultant molecule.

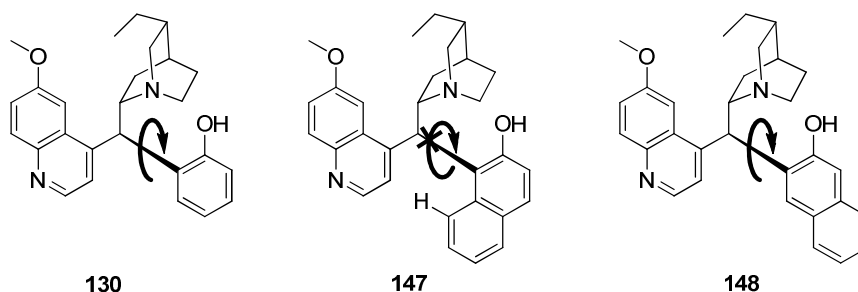
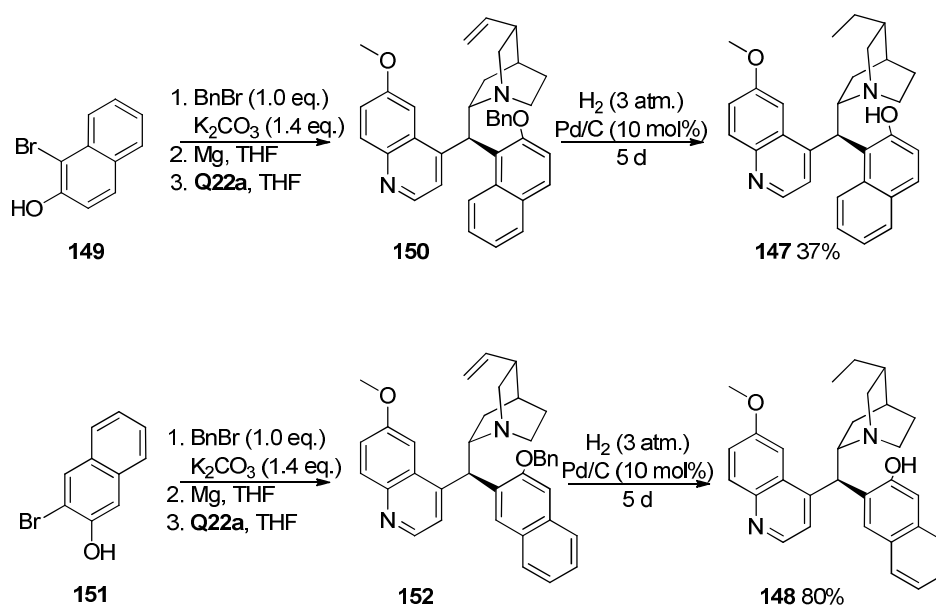


Figure 2.2 Comparison of catalysts **130**, **147** and **148**

It was postulated that such an addition would both increase steric hinderance at a potential binding site in comparison to the C-9 phenyl derivative and also likely impede free rotation about the C-9 – C-1'' bond. Highlighted in Figure 2.2, it is clear that the barrier to rotation about this bond will be significantly higher in the case of **147** in comparison to either **130** or **148**.

The fact that phenol, and 2-naphthol have sufficiently different pK_a s that their efficacy as catalysts could be affected was also noted,¹⁹⁰ however this was not seen as being of primary importance. The pK_a values for these two molecules are 18 and 17.2 respectively in DMSO. (A fuller exploration of the effect of pK_a would be undertaken later in a manner which would minimise simultaneous steric changes.)

These catalysts were readily synthesised in four steps from commercially available 2-bromo-1-naphthol and 3-bromo-2-naphthol in 37% and 80% yield respectively, as shown in Scheme 2.9.



Scheme 2.9 Synthesis of catalyst candidates **147** and **148** from the corresponding commercially available bromonaphthols

2.2 Initial catalyst testing

Having synthesised a library of eight different catalysts, assessment of their catalytic potential was undertaken. By testing their efficacy in a number of well known reactions which had been shown to be highly amenable to organocatalysis, it was envisaged that an understanding of their potential as organocatalysts could be obtained.

Our initial expectation was that it would be possible to discriminate between the requirements for reactions that occurred *via* a 1,2 addition pathway and those which occurred through a 1,4 Michael type addition pathway. Indeed a quick examination of the transition states of these two distinct mechanisms shows that the relative positions of the nucleophile and the destination of the electron density (*i.e.* the point at which the hydrogen bond donor is most likely to interact favourably to promote the reaction) are very different, and accordingly the spatial arrangement required of the catalytically active moieties should be similarly different.

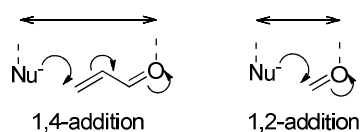
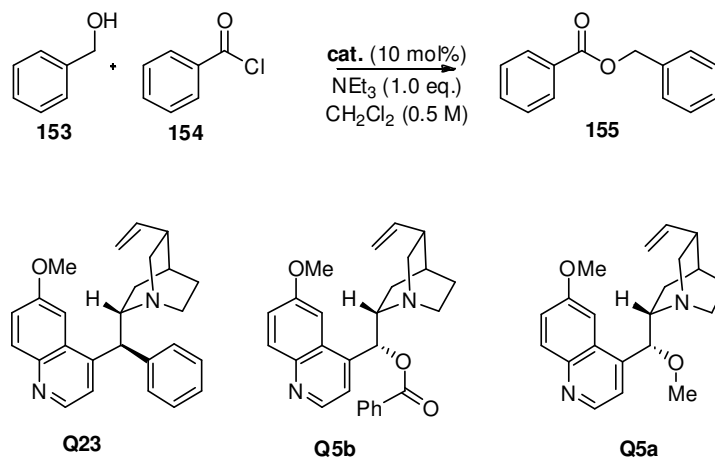


Figure 2.3 The interatomic distances required to support reactions occurring through 1,4 and 1,2 addition pathways

It is worth noting at this point, experiments carried out by Dr. Marine Peuchmaur which compared the efficacy of **Q23** with *O*-benzoyl quinine and *O*-methyl quinine as nucleophilic catalysts for the acylation of benzyl alcohol with benzoyl chloride. It is clear from the results given in Table 2.1 that the presence of a phenyl ring at the C-9 position prevents the quinuclidine from acting as an effective nucleophile. While quinine readily promotes the reaction, the quinine derivative **Q23** is only marginally faster than the reaction in the absence of any catalyst (entries 1-3). It is clear that the hindrance of the quinuclidine in **Q23** is far greater than that resulting from substituting the C-9 hydroxyl even with bulky groups (entries 4-5). This is an important piece of information was used to inform our choice of test reactions. It is obvious that our new library of catalysts will be incapable of catalysing reactions such as the Mortia-Baylis-Hillman where the catalyst is required to act as a nucleophile.²⁰⁹ At the same time, it was postulated that the reduction in nucleophilicity could allow our catalysts to function more effectively than other currently available catalysts in situations where competing undesired pathways involving nucleophilic catalysis were potentially problematic.

Table 2.1 Selected quinine derivatives as acyl transfer catalysts



entry	catalyst	time to completion ^a
1	-	3 h
2	1	20 min
3	Q23	2.5 h
4	Q5b	40 min
5	Q5a	30 min

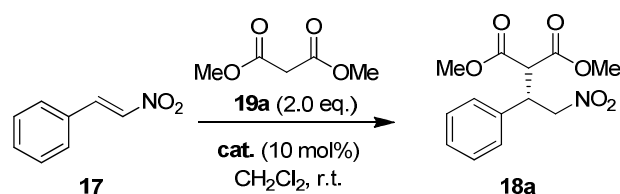
^a As determined by TLC.

2.2.1 Michael addition of malonates to nitrostyrene

Given the success of other quinine derived catalysts in promoting the Michael addition of malonates to nitrostyrene and its place in seminal papers on the topic of organocatalysis, it was decided to test the ability of the novel suite of potential catalysts to promote this reaction.^{40,59,94} Using conditions identical to those used by McCooey *et al.* the performance of the newly synthesised catalysts was evaluated.⁵⁹

The results obtained, summarised in Table 2.2, were not encouraging, with the catalyst failing to promote the reaction effectively. Low enantioselectivity was observed and the correlation between the overall architecture and orientation in which the catalytically relevant functionalities were present was unclear. Nonetheless the results did show that the molecules were capable of promoting reactions in an organocatalytic manner, the reaction fails to proceed in the absence of a suitable catalyst (entry 1).

Table 2.2 Addition of dimethylmalonate to β -nitrostyrene



entry	catalyst	time (h)	conversion ^a (%)	ee ^b (%)	enantiomer
1	-	20	0	-	-
2	130	20	18	6	<i>S</i>
3	131	20	12	10	<i>S</i>
4	132	20	11	10	<i>S</i>
5	147	20	24	3	<i>S</i>
6	148	20	23	15	<i>S</i>
7	134	20	0	-	-
8	135	20	18	7	<i>S</i>

^a As determined by ^1H NMR spectroscopy. ^b As determined by CSP-HPLC.

It was clear that change in catalyst layout affected the efficacy of the catalysts in promoting the reaction however not to the extent that was hoped (entries 2-4). Interestingly catalysts **130**, **147** and **148** in which the hydrogen bond donor was located in the *ortho*

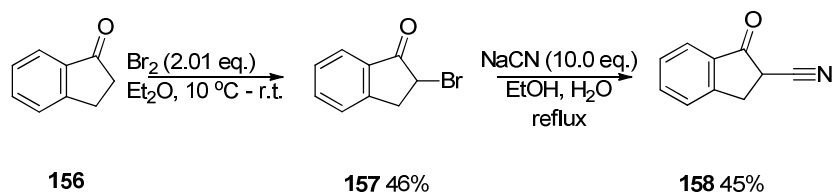
position on the aromatic ring (entires 2, 5 and 6) all displayed greater activity than either **131** or **132** (entries 3 and 4) however it is clear that the position of the hydroxyl moiety relative to the quinuclidine is not the only factor affecting catalyst performance. Catalyst **134** (entry 7) failed to promote the reaction as it failed to dissolve under the reaction conditions, but catalyst **135** (entry 8) (having a significantly greater distance between hydrogen bond acceptor and donor) was also capable of similar levels of activity to **130**.

During the undertaking of these experiments, the solubility of the range of catalysts in a variety of solvents was qualitatively evaluated. It was noted that all of the catalysts, with the exception of **134**, were soluble in a broad range of solvents, polar such as methanol, DMF and ethyl acetate, less polar such as benzene and toluene, and chlorinated solvents such as CH₂Cl₂ and chloroform. They were also soluble in non polar mixtures of hexane with small amounts of chlorinated solvents added. The notable exception **134** failed to dissolve in appreciable quantities in any solvent combination except methanol and chloroform.

2.2.2 The addition of 2-cyanoindanone to 2-chloroacrylonitrile

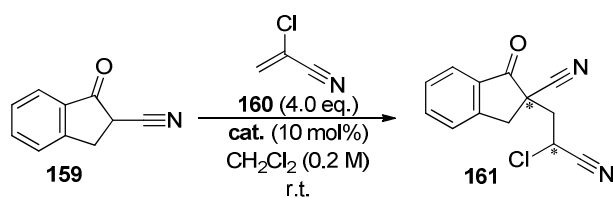
In order to further investigate the behaviour of the catalyst suite in this class of reaction the addition of 2-cyanoindanone to 2-chloroacrylonitrile was undertaken. This reaction was chosen because it had been shown to be amenable to catalysis by organocatalysts bearing a phenolic hydrogen bond donor.¹⁴¹ 2-Chloroacrylonitrile was commercially available, while 2-cyanoindanone necessitated synthesis from 1-indanone. This was achieved by α -bromination of the ketone with bromine in diethyl ether, followed by substitution with cyanide using a large excess of sodium cyanide, the pathway being shown in Scheme 2.10 (taking all due precautions).

Having synthesised the required substrate the reaction was undertaken under conditions used by Deng *et al.*,¹⁴¹ and the results are given in Table 2.3. In this case it is clear that the highly reactive substrates react readily in the presence of nearly all of the catalysts regardless of the distances between catalytically active functionalities.



Scheme 2.10 Synthesis of **158** from indanone

Table 2.3 Addition of 2-cyanoindanone to 2-chloroacrylonitrile



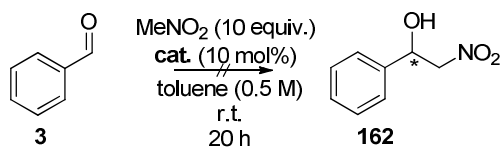
entry	catalyst	conversion ^a (%)	dr	<i>ee</i> ^b (%)	<i>ee</i> ^b (%)
			(<i>SR:RR</i>)		<i>RS</i>
1	-	0	-	-	-
2	23	32	1:0.67	-14	10
3	130	100	1:0.9	34	6
4	131	100	1:0.72	14	15
5	132	88	1:0.79	3	17
6	147	85	1:1.18	-43	26
7	148	98	1:0.97	31	-12
8	134	51	1:0.98	2	16
9	135	100	1:0.78	-4	0

^a As determined by ¹H NMR spectroscopy. ^b As determined by CSP-HPLC.

The reaction fails to proceed in the absence of a suitable catalyst (entry 1), but monofunctional promotion of the reaction is possible (entry 2). There is however, a clear advantage to bifunctional catalysis (entries 3-9). Whilst none of the catalysts promote the reaction with high diastereoselectivity, it is noticeable that, for the three catalysts that contain an *ortho* hydroxyl functionality **130**, **147** and **148** (entries 3, 6 and 7), the resulting diastereoselectivity and enantioselectivity observed differs with catalyst **147** showing selectivity for the opposite enantiomers and diastereomer to **130** and **148**. This clearly indicates that the steric nature of the C-9 attachment is of key importance.

2.2.3 The Henry reaction

The next type of reaction chosen was the Henry reaction, having previously been shown to be amenable to organocatalysis.^{97,136,210,211} The new set of catalysts was evaluated for its ability to promote the addition of nitromethane to benzaldehyde (**3**) (Scheme 2.11) using conditions found effective by Marcelli *et al.* in earlier studies using organocatalysts bearing phenolic hydrogen bond donors.¹³⁶

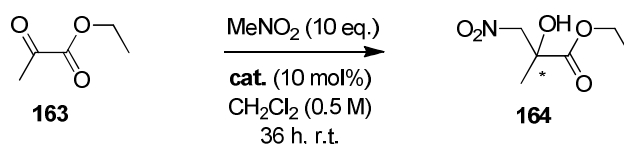


Scheme 2.11 The addition of nitromethane to benzaldehyde

Unfortunately the catalysts proved entirely inactive as promoters of this reaction, failing to promote the reactions even at a low rate. After 20 hours no trace of product was observed and on this basis it was decided that a more active substrate pair would be appropriate. Benzaldehyde (**3**) was replaced with ethyl pyruvate (**164**) and the reaction was repeated; the results are summarised in Table 2.4.

Again, as was the case with the Michael addition of dimethylmalonate (**19a**) to nitrostyrene (**17**), there was no clear trend matching the arrangement of the catalytically active functionalities in the catalysts with their ability to promote the reaction in question. Despite this, these results provided important clues as to the activity of our catalysts. Again, the reaction requires the aid of a catalyst to proceed under the reaction conditions (entry 1). Each of the catalysts containing a phenol substituent at C-9 promoted the reaction with those with a closer distance between hydrogen bonding moieties (**130** and **131**) functioning more efficiently than **132** (entries 2-4) and also more effectively than **134** and **135** (entries 7 and 8).

Table 2.4 The addition of nitromethane to ethyl pyruvate



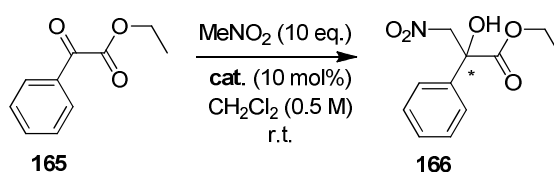
entry	Catalyst	conversion ^a (%)	ee ^b (%)
1	-	0	-
2	130	96	36
3	131	99	0
4	132	74	32
5	147	63	-5
6	148	98	41
7	134	28	11
8	135	87	30

^a As determined by ¹H NMR spectroscopy. ^b As determined by CSP-HPLC.

Interestingly, **147** (entry 5) despite having identical distances between the quinuclidine nitrogen and the hydroxyl as measured by the number of bonds (as opposed to actually

measured distances based on the actual conformations present in the molecules) when compared to **130** and **148** gave very different results both in terms of activity and enantioselectivity (entries 2, 5 and 6 Table 2.4) indicating that activity and selectivity of the catalyst was not solely driven by the number of bonds between the quinuclidine nitrogen and the hydroxyl moieties.

Table 2.5 The addition of nitromethane to ethyl benzoylformate



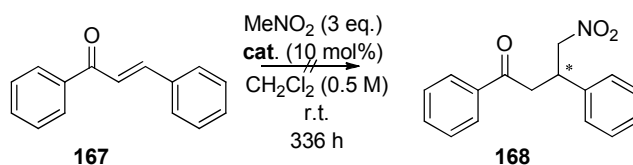
entry	catalyst	time (h)	conversion ^a (%)
1	Q23	80	0
2	130	80	41
3	131	80	38
4	132	80	15
5	147	80	27
6	148	80	28
7	134	80	9
8	135	80	17

^a As determined by ¹H NMR spectroscopy.

Examination of this reaction with a further change in substrate was undertaken, this time replacing the ethyl pyruvate with the more hindered ethyl benzoylformate. These results are outlined in Table 2.5. Entry 1 shows that the inactivity of **Q23** which clearly indicates that the catalysis is occurring through bifunctional means. In the remaining entries 2-8 it

can be seen that the addition of increased steric bulk causes a large reduction in the activity exhibited by the catalysts however, the reactivity shown broadly correlates to that observed in Table 2.4.

Having shown that our new catalysts were capable of promoting 1,2 additions of nitromethane to α -ketoesters, it was also decided to examine their ability to promote the addition of nitromethane to chalcone (Scheme 2.12); a 1,4 addition reaction. Unfortunately, all of the catalysts synthesised proved to be incapable of promoting this reaction even after extended reaction times. This is however, somewhat unsurprising given the much lower reactivity of chalcone.



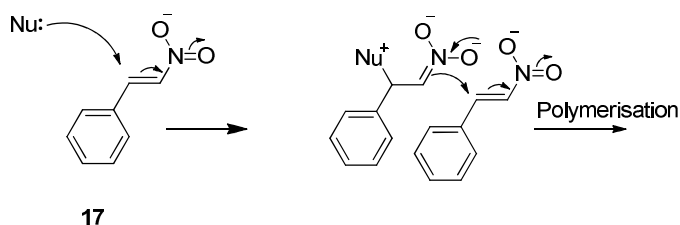
Scheme 2.12 The addition of nitromethane to chalcone catalysed by **130-132**, **134**, **135**, **147** and **148**

2.2.4 The addition of 2-methylindole to nitrostyrene

With the aim of finding a suitable reaction to take full advantage of the properties of our new array of catalysts, it was decided to continue evaluating the library in known organocatalytic reactions with the hope of achieving a fuller understanding of the capabilities of the catalysts. With this in mind, two further reactions were explored.

To further assess the capability of the catalysts to promote 1,4 reactions, the Friedel-Crafts type reaction of nitrostyrene (**17**) and 2-methylindole (**169**) was chosen. This reaction having previously been reported by Ricci *et al.*,²¹² was clearly amenable to organocatalysis. Previous attempts by Dr. S. McCooey and Ms. A. Cullen to use organocatalysts in which a base was present resulted in unacceptable levels of a side reaction in which polymerisation of the nitrostyrene was postulated to occur. Given that

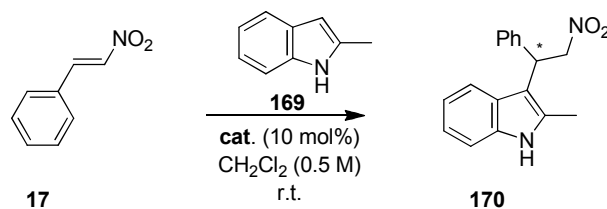
nucleophile promoted polymerisation of nitrostyrene (Scheme 2.13) is a well known phenomenon,²¹³ it was thought that this was likely to be promoted by the quinuclidine nitrogen.



Scheme 2.13 Nucleophilic polymerisation of β -nitrostyrene

Since our catalyst library had been shown to be significantly less able to promote reactions through nucleophilic catalysis due to the steric congestion around the quinuclidine nitrogen it was thought that it would be an excellent candidate for this reaction. Furthermore, hydrogen bonding between the nucleophile and the catalysts would likely only occur at one point which would allow a clearer assessment of the relationship between the orientation of the catalytically relevant functional groups and the efficacy of a given catalyst in promoting a reaction proceeding through a specified transition state, associated with either 1,4 or 1,2.addition reactions. On this basis the reaction was assessed.

These results shown in Table 2.6 represented somewhat of a vindication of our hypothesis that the transition states of a 1,4 addition reaction would require a greater distance between catalytically active functional groups. The reaction is capable of occurring in the absence of a catalyst (entry 1) and little improvement over this rate is shown by any of the catalysts **130-132**, **134**, **147** or **148** (entries 2-8). However, catalyst **135**, shows noticeably greater activity than any other catalyst (entry 9). This difference in activity is further highlighted by an increase in catalyst loading and extended reaction time (entries 10 and 11).

Table 2.6 Addition of 2-methylindole to β -nitrostyrene

entry	catalyst	loading (mol%)	time (h)	conversion (%) ^a	ee (%) ^b
1	-	-	44	8	<5
2	Q23	10	44	9	<5
3	130	10	44	10	<5
4	131	10	44	13	<5
5	132	10	44	12	<5
6	147	10	44	8	<5
7	148	10	44	17	<5
8	134	10	44	9	<5
9	135	10	44	27	<5
10	130	20	168	35	<5
11	135	20	168	61	<5

^a As determined by NMR.

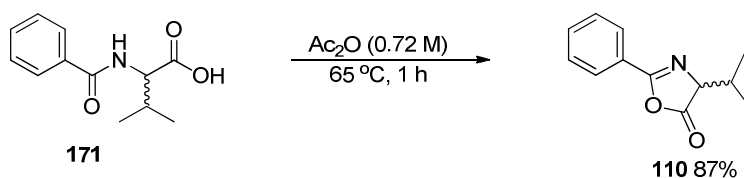
Unfortunately, all of the catalysts evaluated gave a product with almost no enantiomeric excess, thus while clearly demonstrating our initial premise, it was clear that in order to provide enantioselectivity, greater control over the space in which the transition state occurred would be required, something which was unlikely to be possible when using

catalyst **135** since the reaction is being catalysed at such a significant distance from the region of the catalyst which contains stereochemical information.

Having demonstrated that our catalysts were indeed capable of discriminating between reactions based on transition state type, it was decided that placing further efforts into examining the catalysis of 1,2 reactions would (hopefully) prove more fruitful.

The next reaction we examined was the DKR of azlactones. This reaction seemed like an excellent choice for several reasons. Firstly, both substrates are readily available or easily synthesised from readily available materials. Secondly, both substrates can be modified in several different aspects without reducing the overall synthetic utility of the reaction which would allow (at least in theory) for an in depth examination of the nature and potential of our catalysts.

On this basis, it was decided to examine the ability of our catalyst library to promote the opening of *N*-benzoyl valine derived azlactone **110** with allyl alcohol. The azlactone was easily prepared by the dehydration of the readily available *N*-benzoyl valine (**171**) using acetic anhydride, furnishing the azlactone in high yield (Scheme 2.14).

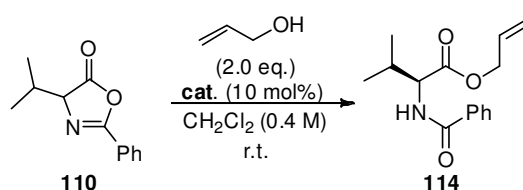


Scheme 2.14 Formation of azlactone **110** by dehydration of *N*-benzoylvaline

Having prepared the substrate, the reaction was examined under suitable conditions matching those which had been found in the literature. Under these conditions the reaction was shown to progress at a moderate but acceptable rate and the results are summarised in Table 2.7.

In this case, where both nucleophile and electrophile appeared to have only one likely effective mode of hydrogen bonding, it became very apparent that the catalysts showing *o*-phenolic substitution fit the transition state assembly (entries 2, 5 and 6), while all the others were more or less inactive: even after extended reaction times, only very small levels of conversion were observed in these cases.

Table 2.7 Initial examination of the DKR of azlactones



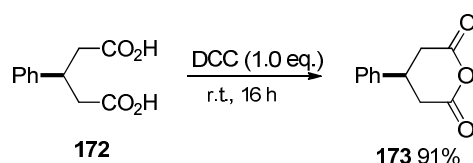
entry	catalyst	time (h)	conversion ^a (%)	ee ^b (%)	enantiomer
1	Q23	88	0	-	
2	130	88	67	40	<i>S</i>
3	131	88	2	Nd	
4	132	88	8	Nd	
5	147	69	39	40	<i>R</i>
6	148	69	40	12	<i>R</i>
7	134	69	5	Nd	
8	135	69	10	Nd	

^a As determined by ¹H NMR spectroscopy. ^b As determined by CSP-HPLC.

Most interestingly, the enantioselectivity was dependent on the substitution present on the phenyl ring of the catalyst, with the *ortho* phenol based catalyst (entry 2) furnishing the

same level of product enantiomeric excess as the 1,2 substituted naphthol based catalyst (entry 5) but selecting for the opposite enantiomer. While it is entirely coincidental that the reaction promoted by these two catalysts furnish the same levels of enantioselectivity, the fact that they select preferentially for different enantiomers strongly indicates that catalyst's conformation ultimately dictates the stereochemical outcome of the reaction and that our catalytic system is clearly capable of being tuned into conformations which can select for either enantiomer. Ideally this would allow for selection of either product enantiomer from a single source of stereochemistry.

On the basis of the modest but encouraging result in the DKR of azlactones it was also decided to evaluate the closely related desymmetrisation of *meso*glutaric anhydrides since it would seem likely that this reaction would require a similar catalyst architecture. The methanolysis of 3-phenylglutaric anhydride was chosen as a representative example of this reaction and optimised conditions found in previous studies were used.¹⁴⁸ 3-Phenylglutaric anhydride was synthesised from the readily available 3-phenylglutaric acid by dehydration with DCC (Scheme 2.15).



Scheme 2.15 Synthesis of 3-phenylglutaric anhydride

This was then treated with methanol in MTBE and 10 mol% of the catalysts which had been shown to be active in 1,2 type reactions, since this involves a 1,2 activation mode. The choice of an ethereal solvent, while likely to diminish the ability of the catalyst to form hydrogen bonds to the substrates, was necessary to prevent quantitative protonation (and deactivation) of the quinuclidine amine by the carboxylic acid produced in the reaction.

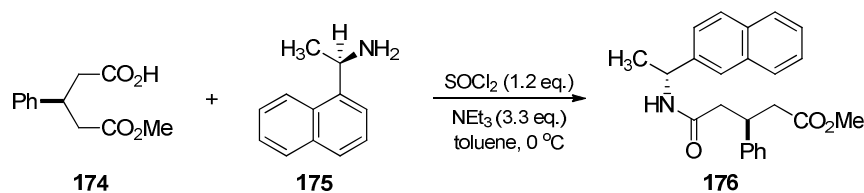
Table 2.8 The desymmetrisation of 3-phenylglutaric anhydride by methanolysis

Ph-CH2-CH2-CO-O-CO-CH2-CH2-Ph (173)
 $\xrightarrow[\text{cat. (10 mol\%), MTBE, r.t., 40 h}]{\text{MeOH (10 eq.)}}$
Ph-CH2-CH2-CO2H (174)

entry	catalyst	yield ^a (%)	<i>ee</i> ^b (%)
1	-	0	
2	130	70	3%
3	147	77	-31%
4	148	52	14%

^a Isolated yield ^b As determined by CSP-HPLC

Following desymmetrisation, the enantioselectivity was determined by ¹H NMR spectroscopy after formation of diastereomers by coupling the resultant monoprotected *bis*-acid with an enantiopure sample of 1-amino-1-(1-naphthyl)ethane (Scheme 2.16).



Scheme 2.16 Analysis of the stereochemistry of 3-phenylglutaric acid monomethyl ester

2.3 Synthesis of -9-*epi*-deoxyaniline quinine derivatives

As described, while aromatic alcohols have been shown to be competent hydrogen bond donors, those derived from anilines are capable of more effective hydrogen bonding and are more diverse in nature. Hence, it was thought that the synthesis of aniline analogues of the phenol catalysts thus far synthesised would be highly valuable.

In an attempt to synthesise these molecules, an identical route to that which furnished catalyst **130** (and the other catalysts) was undertaken with the substrates shown in Figure 2.4, which were readily synthesised from the corresponding commercially available anilines.

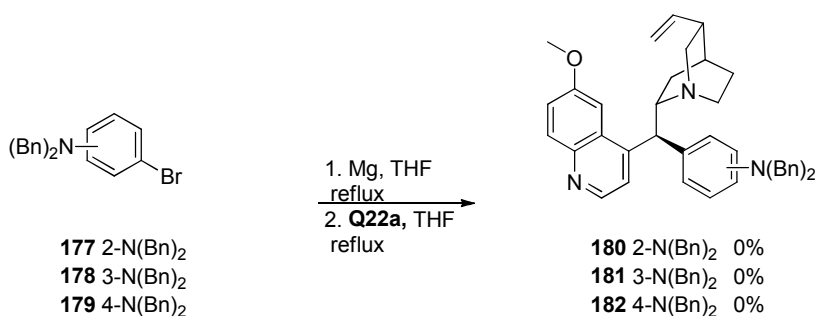
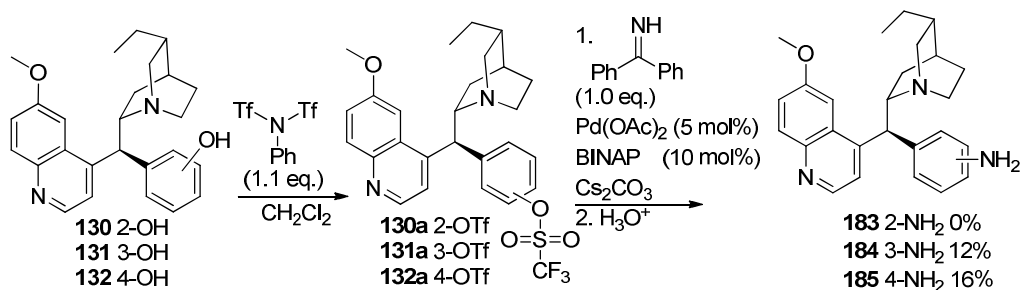


Figure 2.4 *N,N*-dibenzyl-bromoanilines

Unfortunately while each of these substrates reacted readily with magnesium to form the required Grignard reagent, the Grignard reagents failed to react with chloroquine to give the desired products. It was clear that the presence of the additional amine resulted in disruption of the S_Ni pathway. It was later shown by Skarzewski *et al.*²¹⁴ that the reaction involving the corresponding iodoanilines (in the cases of **178** and **179**) proceeded in moderate yield, giving **181** and **182**, however, the *ortho* iodo analogue of **177** failed to undergo the reaction. Furthermore Skarzewski reported that the removal of the benzyl groups from the resulting compound was not possible by hydrogenation, meaning that such a route would be unable furnish catalytically useful molecules.

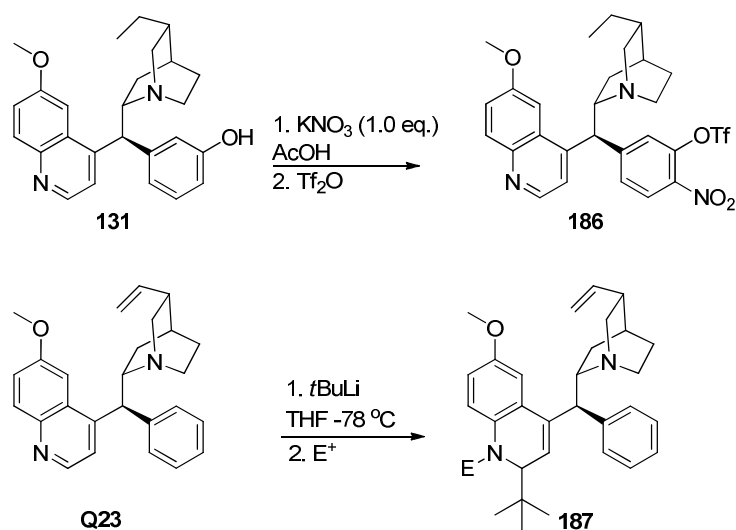
In light of the relative ease with which the phenol derivatives had been synthesised, it was decided that a literature preceded functional group interconversion should, hopefully, be a practical means of reaching the desired targets.⁹⁷



Scheme 2.17 Synthesis of C-9 aniline substituted derivatives of quinine

Following the route outlined in Scheme 2.17, it was possible to synthesise both the *para* and *meta* substituted derivatives **184** and **185** in their unprotected aniline forms however yields were less than ideal and purification of the aniline proved quite challenging. Unfortunately the Buchwald amination involving **130a** failed to proceed. It is likely that the site is too sterically encumbered to allow the reaction to occur.

In light of the initial results obtained from the catalytic evaluation of the phenol based catalysts, the *ortho* aniline derivative (**183**) was seen as a high value target. Thus, further synthetic efforts were invested and the synthetic paths in Scheme 2.18 were investigated.



Scheme 2.18 Potential synthetic routes to **183**

The nitration of **Q23** was attempted however it was found the both aromatic rings (the quinoline and the phenyl) were similarly activated towards EAS preventing selective reaction at the desired position. Attempts at selective nitration of **Q23** resulted in substitution at multiple positions giving an inseparable mixture of products. Instead, after optimisation of conditions and substrate, it was found that by using the appropriate phenol, **131**, EAS could be restricted to the desired ring. It was expected that since the hydroxyl should function as an *ortho/para* directing group that at least some portion of the product would be that resulting from the substitution at one of the two possible positions that would lead to the desired product (*i.e.* position 2'' or 6''). Furthermore it was envisaged that the phenol could then be transformed into the corresponding triflate allowing for simultaneous removal of this, now extraneous, functional group and conversion of the installed nitro group into the desired amine. Edifyingly, this was found not to be the case, and upon purification the undesired isomer **186**, shown in Scheme 2.18 was isolated as the exclusive product resulting from EAS.

Further synthetic effort was then invested in attempting to *ortho*-lithiate **Q23**. It was expected that the quinuclidine nitrogen would be able to act as a directing group, however the resulting reaction was C-2' addition which occurred even with use of the sterically hindered *t*-BuLi. It was at this point decided to refocus our efforts on the catalysts containing a phenolic hydrogen bond donor.

2.4 Catalyst conformation: A preliminary analysis

Clearly from the results obtained, the ability of the new library to catalyse reactions is highly dependent on more than just the absolute configuration at each chiral centre of the catalysts. It was decided that an examination of the solvent phase conformations of the catalysts might yield important clues that would inform further design decisions when making new catalysts based on this platform.

Our first port of call was to examine the NMR spectra obtained from these molecules. Using NMR spectroscopy it should, at least in theory, be possible to determine the predominant conformations of our new catalysts in solution. While the merits of determining the most prevalent conformations may be questionable, given that the lowest energy conformations may or may not be the catalytically important conformations, it is certainly a necessary first step in understanding the activity of these catalysts.

An analysis of the NMR spectra of 9-*epi*-phenyldeoxyquinine (**Q23**) was undertaken as a starting point for these studies. Its *pseudoenantiomer* had already been fully elucidated by Boratynski *et al.*⁷⁸ Using this study as a basis for our own, the predominant conformation of this molecule was examined.

2.4.1 Establishing a nomenclature for conformations of 9-*epi*-aryl-quinine derivatives

Taking 9-*epi*-phenyldeoxyquinine, it is clear that like quinine, it has two key conformational features. The relative orientations of substituents along the C-8 to C-9 bond and the orientation of the quinoline ring would for the most part describe the overall conformation of the molecule. However, unlike quinine, in the case of the novel catalytic system the orientation of a third ring must be described. Furthermore where quinine can be described as ‘open’ or ‘closed’, this description cannot sensibly be applied to the new class of molecules as both of the C-9 substituents are now aromatic rings meaning that the quinuclidine amine is no longer more substantially ‘open’ or ‘closed’ in either of the

orientations that would be analogous to that found in the natural alkaloid. On this basis, it is pertinent to set forth a new nomenclature to accurately describe the conformations which are possible.

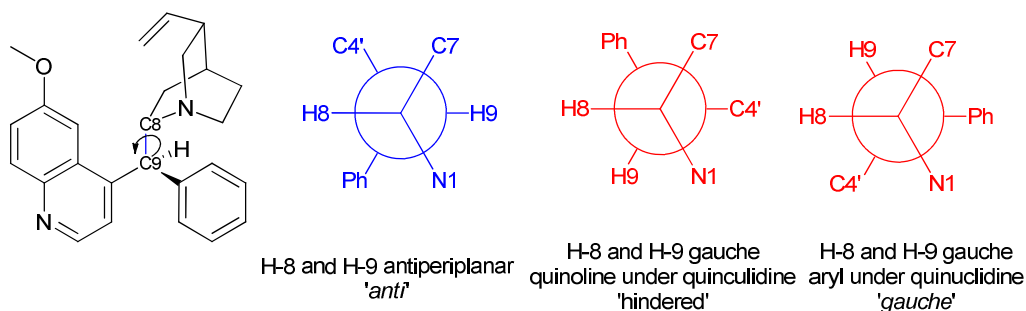


Figure 2.5 Conformations about the bond between C-8 and C-9

Figure 2.6 shows Newman projections of the three possible conformations about the bond between C-8 and C-9; the steric bulk of the substituents means that an eclipsed conformation is highly unlikely. It is also worth noting that since the steric size of both C-9 substituents is now comparable, it would also seem unlikely that either hindered or *gauche* would be favourable, since the corresponding conformation is not observed in the natural cinchona alkaloids and their derivatives (for which conformational information exists).¹⁰⁹ Furthermore this is congruent with the experimental observations in Table 2.1; were the molecule present in an “open” conformation *i.e.* were it in the ‘hindered’ conformation it should be capable of nucleophilic catalysis however this is not the case.

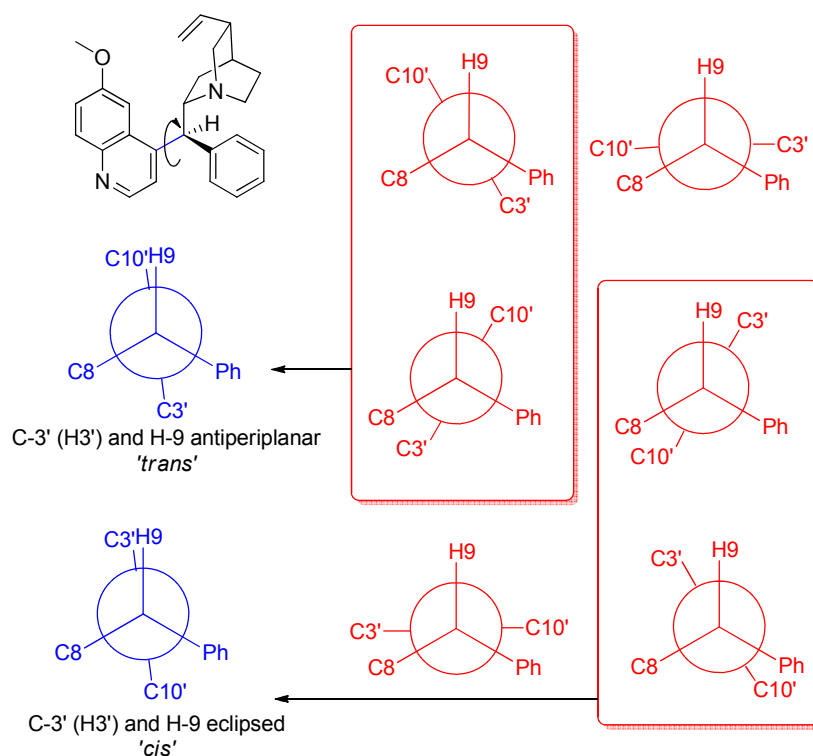


Figure 2.6 Newman projections of the possible orientations of the quinoline ring

The next bond described is the C-9 to C-4' bond controlling the orientation of the quinoline ring. Figure 2.6 shows Newman projections for the possible orientations this may have. Shown in red are the six possible conformations in which quinoline ring avoids eclipsing any of the substituents however, even a trivial analysis of the molecules in question implies that the barrier to rotation though the angle in which H-9 is eclipsed is much less than that involving eclipsing any other substituent, meaning that these can be averaged. It also shows that the other two Newman projections in red describe the molecule in a state which is highly sterically congested. This is unlikely to occur in practice and therefore naming these is not necessary. Hence, the labels for the orientation of the quinoline ring can be described by the labels, *cis* and *trans* to avoid confusion with the *anti* and *gauche* labels used for H-8 and H-9.

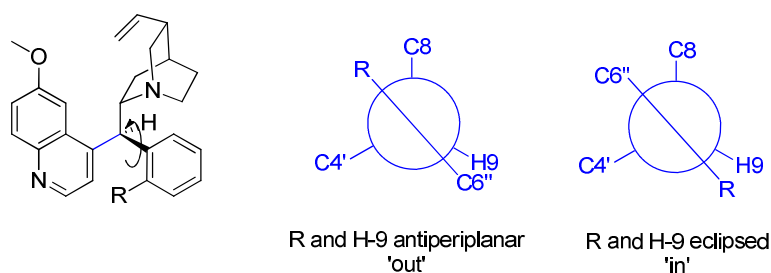


Figure 2.7 Newman projections of the possible orientations of the phenyl ring

The final bond which controls the conformation of the catalyst is that between C-9 and C-1'. The orientation of this bond is very important as it controls the orientation of the hydrogen bond donation moiety. Figure 2.7 shows Newman projections for the two possible orientations of this ring. (Without drawing out a full set of projections it is again apparent that the six possible non eclipsed conformations can be replaced by two in which H-9 is eclipsed.) These can be described as either in, where the hydrogen bond donor (represented by R) points (approximately) in towards the quinuclidine nitrogen, or out, where it points in the opposite direction. A summary of the conformations used and associated structures and names is given Figure 2.8.

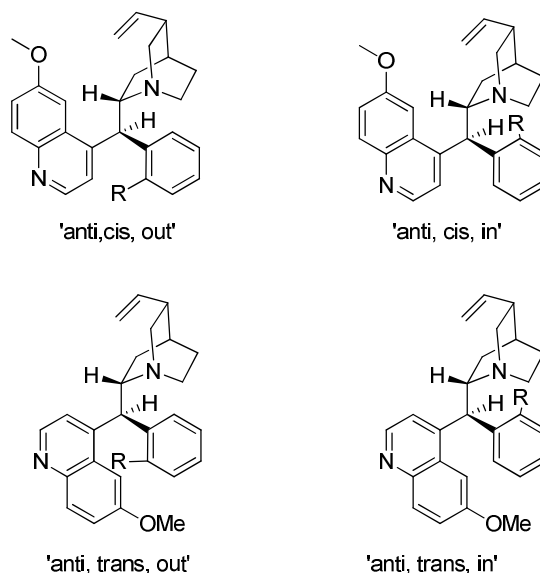


Figure 2.8 A selection of named conformations of C-9 arylated quinine derivatives

2.4.2 NMR experiments towards conformational analysis

In seeking to determine the predominant conformation for 9-*epi*-phenyldeoxyquinine, the through space interactions between protons were determined by either NOE or ROE experiments. On the basis that the conformation might exhibit solvent dependent behaviour, C₆D₆ was chosen as the initial solvent in which to investigate the conformation as this solvent was used in the previous literature study on 9-*epi*-phenyldeoxyquinidine.⁷⁸

The orientation of the C-8-C-9 bond was examined by analysing protons H-8 and H-9, their interactions with each other and the rest of the molecule. In the case of this molecule there was no through space interaction observed, an indication that H-8 and H-9 must be in an antiperiplanar configuration given their proximity of three bonds. Further evidence for the orientation of C-9 was obtained by observing interactions of H-9 with H-7 α and H-6 α , indicating that it must be positioned underneath the quinuclidine ring.

The next step was to analyse the orientation of the quinoline ring. The NOE and ROE contacts were examined and two clear interactions were determined, allowing for an assignment, C-3' was seen to be proximate to C-8 (but not C-9) and C-5' was seen to be near to C-9. Thus, it was possible to assign *trans* orientation about this bond.

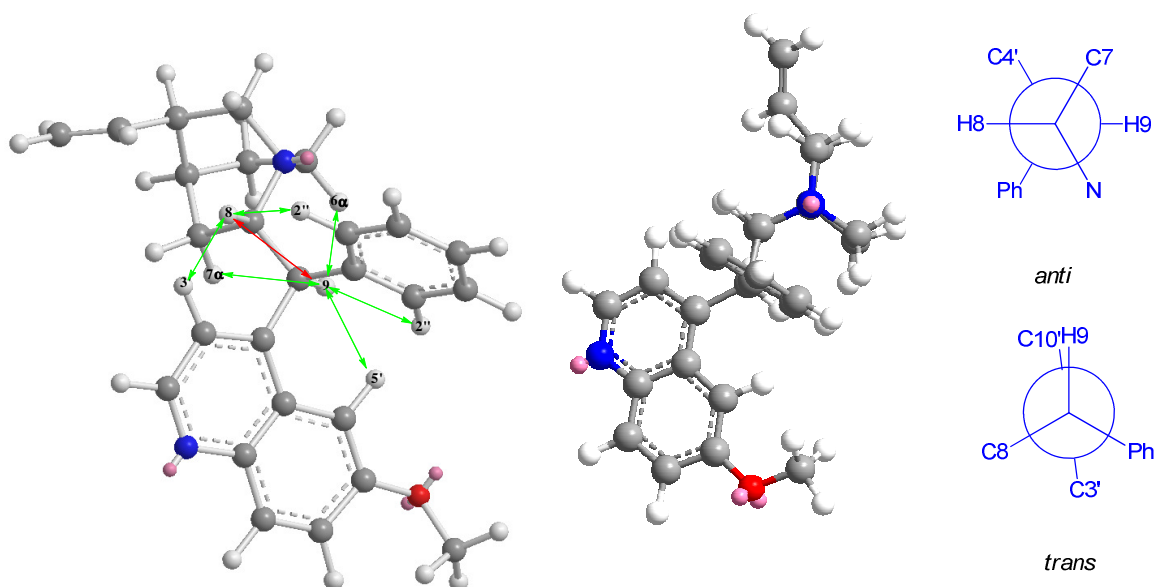


Figure 2.9 Through space interactions in **Q23** by 2D NOE and ROE in C₆D₆

The last piece for which orientational evidence was needed was the phenyl ring, it was however clear in this case that the phenyl ring was free to rotate, as both protons on C-2'' *ortho* to the quinine substitution appeared degenerate when interrogated by NMR spectroscopy, with the resultant doublet showing through space interactions with both H-8 and H-9. This is only possible if the ring is able to freely rotate within the timescale of the NMR experiments. When each of these pieces of structural information is put together the model seen in Figure 2.9 is obtained. The NOE contacts seen are marked in green with the numbers of the relevant protons indicated while the conspicuously absent H-8 H-9 contact is noted in red.

This is in agreement with the conformation assigned to the corresponding quinidine derivative described in the literature.⁷⁸ It was however clear that while this represented a lowest energy conformation, peaks for H-9, H-5' and several of the protons on the quinuclidine ring gave broad signals, implying that the molecule was not existing in one constant conformer and that interchange through a relatively small barrier was occurring.

The next step was to assess any solvent dependency that the conformation of 9-*epi*-phenyldeoxyquinine may have. Three solvents were chosen, CDCl₃, DMSO-d₆ and Methanol-d₄. Chloroform is a slightly more polar solvent than benzene, while DMSO and methanol are both significantly more polar. Dielectric constants (ϵ_r) for these solvents are 2.28, 4.81, 47 and 32.6 respectively.²¹⁵ DMSO has a capacity to accept hydrogen bonds but cannot donate them while methanol possesses hydrogen bond donating ability, thus, this selection of solvents would seem ideal to examine the potential effects solvents on conformation.

The spectra obtained from the compound dissolved in CDCl₃ were broad and the resultant signals were not well separated making further analysis impossible. In both methanol and DMSO these peaks were, in the main, sharper, however no significant alterations in conformation were observed. In both of these solvents the ³J coupling constant for H-9 was also sufficiently large to support assignment of the *anti* conformation as the major species. Satisfied that we had a reasonable method for assigning conformations, we continued our investigations.

2.4.3 ^1H NMR spectroscopic analysis of novel catalysts

Results matching those obtained by the interrogation of 9-*epi*-phenyldeoxyquinine (**Q23**) by ^1H NMR spectroscopy were found for both of the phenol derivatives **131** and **132** (in which the hydrogen bond donating hydroxyl was positioned either *meta* or *para* to C-1”) when these were examined in DMSO-d_6 . Thus these molecules were assigned an ‘anti-trans’ conformation with the phenyl ring appearing to rotate freely. Representations of these molecules can be seen in Figure 2.10.

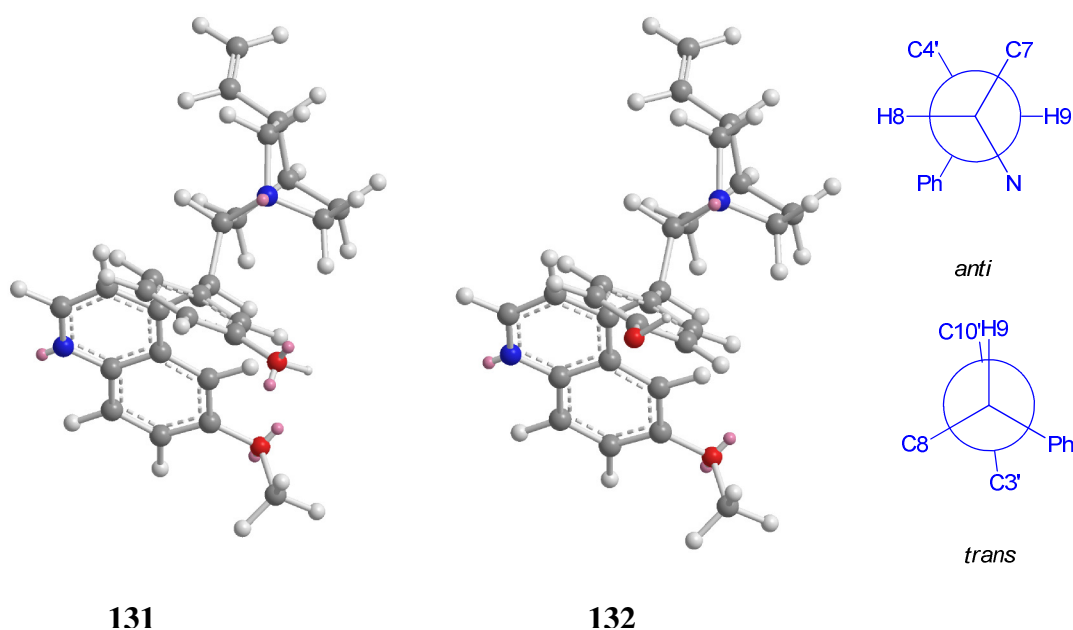


Figure 2.10 Solution state conformations for **131** and **132** in DMSO d_6 as determined by ^1H NMR spectroscopy

DMSO-d_6 was chosen for use as the solvent as it provided sufficient separation of signals to allow analysis, which unfortunately was not the case for CDCl_3 (which would otherwise be preferred since it is similar in polarity and nature to many of the solvents used for organocatalytic reactions). What is worth noting is that, since in the case of **131**, the phenyl ring is in free rotation, there is a large range of positions which the hydrogen bond donating phenol can occupy. It is thus unlikely to function in a highly selective manner, it is also further removed from the chiral information contained in the catalyst than the hydrogen bond donor contained in **130**, another factor which reduces its likely ability to

promote reactions with high selectivity. While in **132**, the hydrogen bond donor is in a position that is rotationally symmetric, it is likely that is too distant from the region of the molecule containing stereochemical information to function as an effective asymmetric catalyst, a hypothesis which also applies to **135**. Conformational analysis of this molecule again in DMSO yielded a similar result to that of **131** and **132** and the resulting molecule is shown in Figure 2.11.

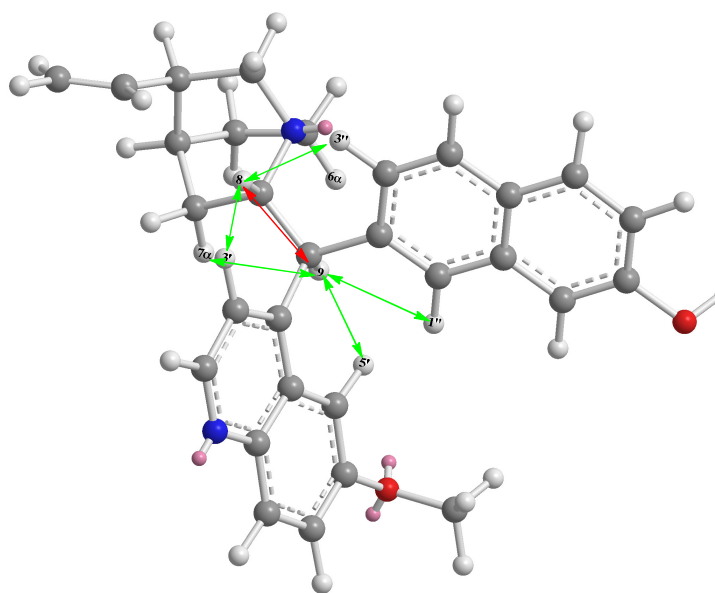


Figure 2.11 Proposed major solution phase conformation of **135** in DMSO- d_6 with NOE shown contacts in green.

The introduction of an *ortho* substituent on the 9-aryl ring however raised the possibility that this ring would be unable to freely rotate. While it was initially hoped that both **130** and **147** could be examined in $CDCl_3$, a solvent which was relatively non polar and possessed no hydrogen bond acceptors, it was immediately apparent that this would not be possible. While **147** gave a clear and readily assigned NMR spectrum when examined in $CDCl_3$, **130** did not. In fact, this catalyst gave only broad signals implying that it was slowly interconverting between conformations (which were separated by a suitably sized barrier) on the NMR timescale. Instead, an examination of this catalyst (**130**) in DMSO- d_6 gave a spectrum with clear signals although, strangely, when analysed in DMSO **147** gave broad signals. This markedly different behaviour from the closely related analogues **130**

and **147** clearly showed that these molecules were likely to possess different conformational preferences.

It also suggested that there might be a crucial role played by an intramolecular hydrogen bond between the hydroxyl and the quinuclidine nitrogen since CDCl_3 was likely to favour the presence of such a bond while DMSO was not. In order to investigate this, it was decided to investigate the effect of the addition of a competing hydrogen bond donor. For this purpose, pentafluorophenol was chosen since it would be an excellent hydrogen bond donor but would not provide complete protonation of the quinuclidine, (the reported $\text{p}K_{\text{a}}$ for pentafluorophenol is 9.5 in DMSO and 19.5 in MeCN).²¹⁶

The effect of the addition of a hydrogen bond donor can be seen in Figure 2.12. This shows the aromatic region of the ^1H NMR spectrum of **130**, shown in red. The spectrum shown in blue is that which results from the addition of 1 equivalent of pentafluorophenol. To ensure that this was not an effect resulting from quantitative protonation, an excess of strong acid (D_2SO_4) was added. The spectrum in green shows the effect of this.

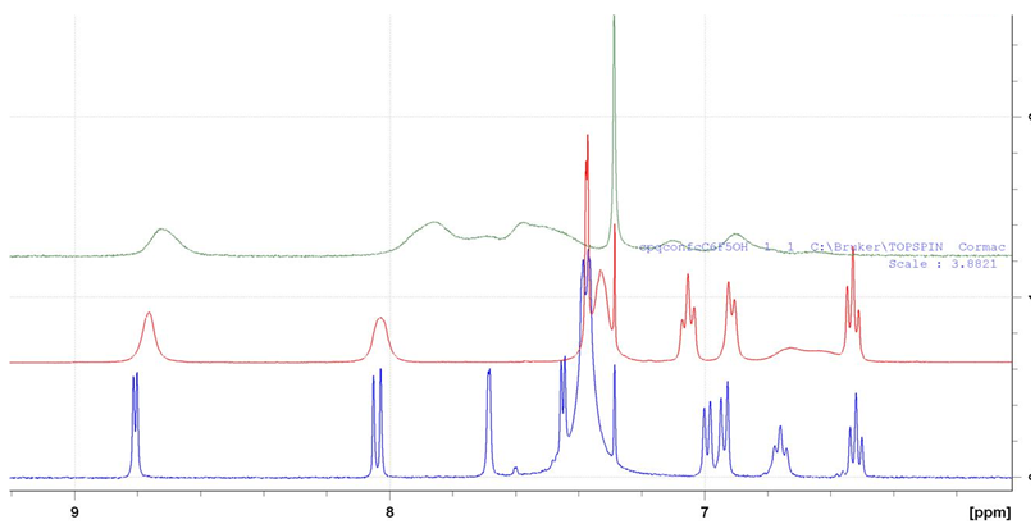


Figure 2.12 ^1H NMR spectra for **130** (red) in CDCl_3 with added pentafluorophenol (blue) and D_2SO_4 (green)

This dramatic change in behaviour on addition of a hydrogen bond donor implies a number of things, importantly it suggests the presence of an intramolecular hydrogen bond (an intermolecular hydrogen bond is unlikely to occur given the hindered nature of the

hydrogen bond acceptor and the orientation of the hydrogen bond donor) and that a significant change in the catalyst conformation occurs when the catalyst interacts with a hydrogen bond donor. Since this is the same type of interaction that is postulated to occur during organocatalytic reactions (albeit in a weaker fashion), this change in behaviour casts doubt on the relevance of solution phase conformations of the free molecules.

Nonetheless, it was felt that even if the solution phase conformations for the molecules did not relate directly to their active conformations it was hoped that comparisons between different catalysts might reveal characteristics which would still correlate with their reactivity and selectivity. With this in mind, the solution phase conformation of **130** in DMSO- d_6 was analysed. The result is shown in Figure 2.13. The structure shown accounts for NOE contacts seen between H-3' and H-8 and also those between H-9 and H-5' while there is no H-8 H-9 contact observed. The phenol ring, as in **131** and **132** appears to be free to rotate.

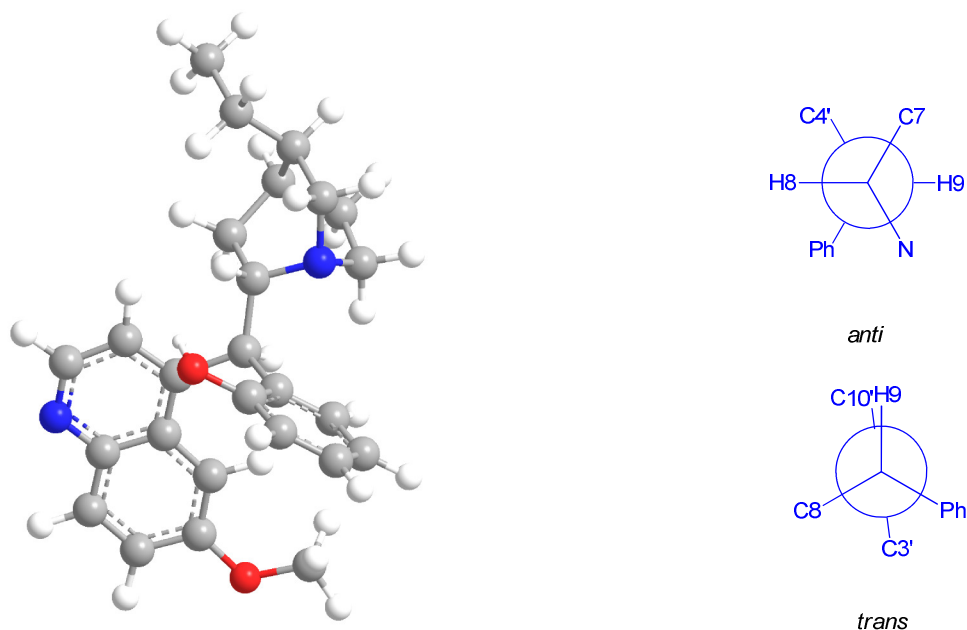


Figure 2.13 Solution phase conformation of **130** in DMSO- d_6 observed by ^1H NMR spectroscopy.

Interestingly, for catalyst **147**, spectra obtained in DMSO- d_6 contained broad signals while those obtained in $CDCl_3$ contained well resolved, sharp signals. In this case it would seem that rotation about the C-9-C-1'' bond, which is likely to be significantly more difficult than in the case of **130**, is impeded sufficiently by the presence of the intramolecular hydrogen bond that the molecule is sufficiently stable in this conformation to result in a clear ^1H NMR spectra. An experiment similar to that shown in Figure 2.12 showed significant broadening of the signals in the spectra of **147** in $CDCl_3$ on the addition of pentafluorophenol; strongly implying the possibility of the presence of an intramolecular hydrogen bond. The solution phase conformation for **147** is shown in Figure 2.14.

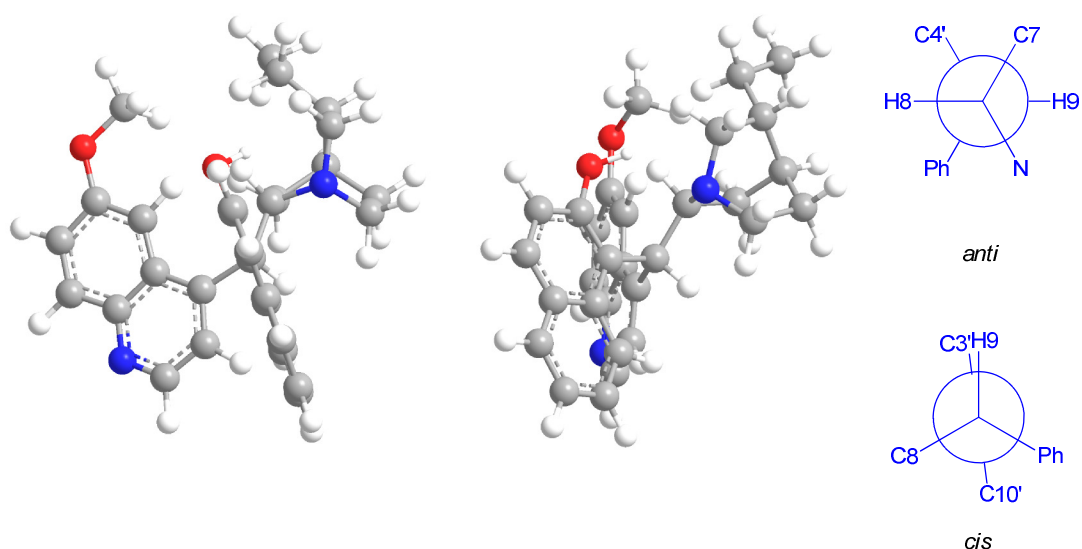


Figure 2.14 Solution phase conformation for **147** in $CDCl_3$ observed by ^1H NMR spectroscopy

Interestingly, it would appear that the orientation of the quinoline ring in this molecule is the opposite of that found in **130**, the added bulk of the naphthyl ring results in large conformational changes throughout the molecule. Furthermore, while in the case of **130** the phenyl ring was in free rotation, in this case the naphthol ring appears to have a more defined orientation with the phenolic proton forming an intramolecular hydrogen bond resulting in a definite orientation for this ring.

2.5 Conclusions

The synthesis of a novel suite of quinine derived catalysts containing C-9 hydroxyaryl substituents with systematically altered distances between hydrogen bond donor and acceptor has been described. These have been tested in a range of reactions known to be amenable to organocatalysis. It has been shown that they are capable of catalysing a range of reactions, albeit without high levels of enantioselectivity. The synthesis of C-9 aniline derivatives has also been investigated. Unfortunately this has been found to be impractical.

Importantly however, it has been demonstrated that it is possible to selectively catalyse 1,2-addition reactions and 1,4-addition reactions by systematically altering the distances between the hydrogen bond forming moieties within the catalyst structures. It was possible, based on the choice of C-9 substituent, to select for either product enantiomer without changing the stereochemistry within the catalyst. Furthermore the catalysts have been analysed to establish differences in solution phase conformations with the hope of using trends observed to inform future catalyst design.

3.0 The Dynamic Kinetic resolution of azlactones

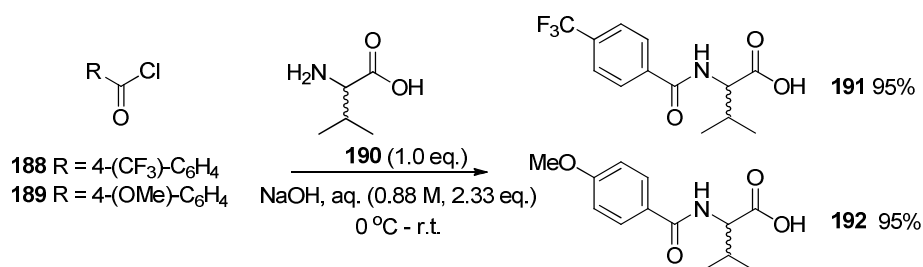
Having shown that catalysis of the DKR of azlactones was readily promoted by quinine derivatives **130**, **147** and **148**, it was decided that it would be valuable to assess the full potential of these novel catalysts by fully optimising a particular reaction in order to showcase the catalysts' utility. The reaction that we chose was the DKR of azlactones, because, as mentioned earlier, there are a large number of variables which can be modified in this reaction without prejudicing its overall synthetic value.

Having shown in our initial assessment of the catalyst library that each of the *ortho* substituted catalysts resulted in a different level of enantioselectivity, it was expected that each catalyst would react differently to changes in substrate. It was anticipated that the enantioselectivity achieved with at least one catalyst could be improved to a synthetically useful degree even if the same alterations might result in the attenuation of the enantioselectivity afforded by the other catalysts. With this in mind, the most easily examined variable was that of nucleophile. Experiments in which alcohols which were not primary were used as nucleophiles failed to proceed. On the other hand, methanol and benzyl alcohol were viable substrates, but in both cases the *ee* obtained was less than that obtained in the case of allyl alcohol. On this basis, it was decided to use allyl alcohol as the nucleophile in all further studies.

The next variable which was easily altered in the substrates was the *N*-protecting group. While we had used *N*-benzoyl, many other possibilities were suitable for this purpose. In altering this, there were several factors to be considered. Firstly, the inclusion of an electron withdrawing or donating group would have two important effects. In the case of an electron withdrawing group, the electron density of the five membered ring would decrease, decreasing the pK_a of the most labile proton, thus increasing rates of racemisation. It would also increase the electrophilicity of the acyl group, increasing the reactivity of the azlactone.

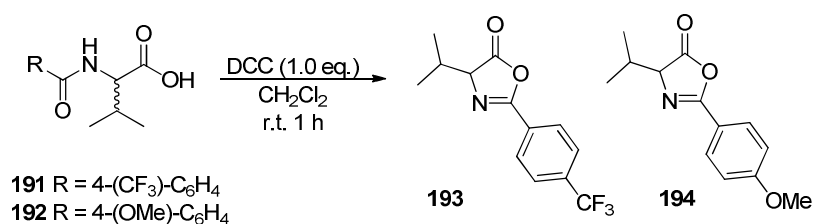
In order to test this theory, initially, two additional substrates were assessed. These were, *p*-trifluoromethylbenzoyl valine (**191**) and *p*-methoxybenzoyl valine (**192**), representing examples of both an electron withdrawing and electron donating group, respectively.

Neither would significantly change the steric properties of the protecting group, since the *para* position of the group is distant from the site of reactivity. These were synthesised by the acylation of valine under Schotten–Baumann conditions to afford the *N*-protected amino acids in excellent yields (Scheme 3.1).²¹⁵



Scheme 3.1 Synthesis of *N*-Benzoyl amino acids

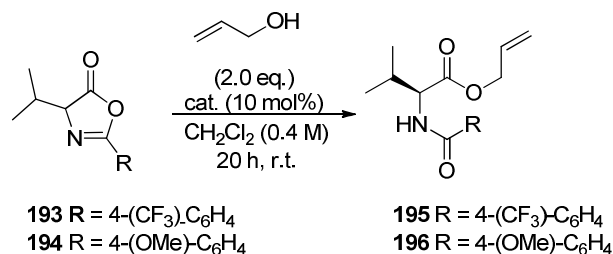
Amides **191** and **192** were then cyclised by dehydration using dicyclohexycarbodiimide (DCC), as shown in Scheme 3.2. While the use of acetic anhydride, as shown in Scheme 2.14, was a highly economical method for cyclization, the harsher conditions resulted in formation of side products which were not easily removed, while the possibility of the presence of acetic acid in the final product could also cast doubt upon the veracity of any catalyst testing done. On this basis, DCC was chosen as a superior reagent, the byproduct, dicyclohexylurea (DCU), being removed by filtration before the product was rapidly eluted through a short layer of silica to ensure removal of any residual DCC or starting material. Since both were significantly more polar than the desired product, elution could be carried out rapidly before excessive decomposition of the product which is unstable on silica. In all cases the reaction was observed to go to completion by TLC however, isolation of product resulted in low isolated yields.



Scheme 3.2 Synthesis of azlactones by dehydration with DCC

Table 3.1 shows details for the DKR of azlactones **193** and **194** catalysed by catalysts **130**, **147** and **148** which confirmed our hypothesis that the catalysts might react differently to changes in the substrate. The DKR of the EDG bearing substrate **194** resulted in poorer rates and lower selectivity in all cases (entries 1-3), while the inclusion of the EWG in substrate **193**, (entries 4-6), resulted in an improvement in the rate of reaction in all cases. Improved enantioselectivity was seen in the reaction catalysed by **147** (entry 5), while reduced enantioselectivity was observed in the other two cases.

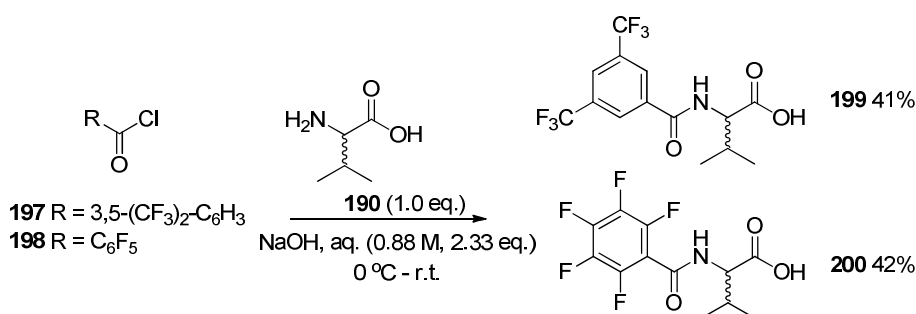
Table 3.1 Testing the effect of changes to the nature of the *N*-protecting group



entry	catalyst	substrate (R=)	product	enantiomer	conversion ^a (%)	ee ^b (%)
1	130	4-MeO-C ₆ H ₄	196	<i>S</i>	19	20
2	147	4-MeO-C ₆ H ₄	196	<i>R</i>	11	17
3	148	4-MeO-C ₆ H ₄	196	<i>R</i>	20	34
4	130	4-CF ₃ -C ₆ H ₄	195	<i>S</i>	32	27
5	147	4-CF ₃ -C ₆ H ₄	195	<i>R</i>	36	60
6	148	4-CF ₃ -C ₆ H ₄	195	<i>S</i>	38	4

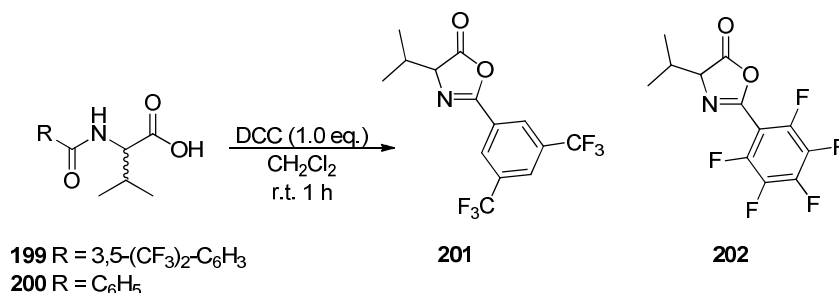
^a Determined by ¹H-NMR spectroscopy ^b Determined by CSP-HPLC

On this basis, two further, more electron deficient substrates were synthesised (**199** and **200**). These were again synthesised under Schotten–Baumann conditions followed by dehydration with DCC, however the first part of this synthetic route shown in Scheme 3.3 proved less suitable for highly reactive substrates with formation of significant amounts of the corresponding benzoic acid, which was not readily separated, resulting in significantly reduced yield.



Scheme 3.3 Synthesis of N-acylated valine derivative **199** and **200**

The formation of the azlactones however proceeded smoothly again with both giving complete conversion to the desired product, Scheme 3.4.

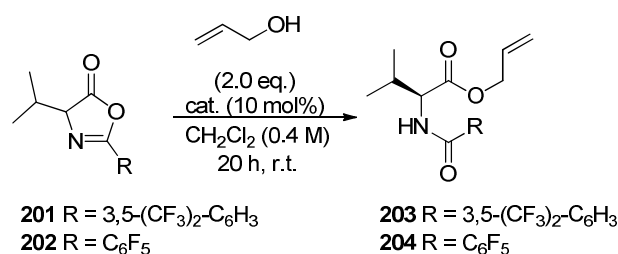


Scheme 3.4 Formation of substrates **201** and **202**

These substrates were evaluated for their behaviour as substrates for DKR with allyl alcohol catalysed by catalysts **130**, **147** and **148** with results shown in Table 3.2. The large increase in electron withdrawing power of the protecting group in **201** leads to a large increase in rate of the reaction, and, matching the trend seen in Table 3.1, results in a increase in enantioselectivity furnished by **147** and a reduction in enantioselectivity for **130** while that catalysed by **148** fails to deliver significant *ee* (Entries 1-3). The veracity of this trend is further substantiated by the results obtained using the even more electron deficient substrate **202** with both rates and enantioselectivity observed in these experiments again following the same pattern (Entries 4-6).

It was clear from these results that each increase in the power of the EWG was leading to a further increase in reactivity and selectivity for reactions catalysed by **147**, however as the azlactones became more and more electron deficient they became drastically less stable, becoming highly moisture sensitive, as well as decomposing rapidly on silica and in the presence of air. It was clear then that other avenues would need to be explored in order for optimal enantioselectivity to be obtained.

Table 3.2 Testing the effect of changes to the nature of the *N*-protecting group



entry	catalyst	substrate (R=)	product	enantiomer	conversion ^a (%)	ee ^b (%)
1	130	3,5-(CF ₃) ₂ -C ₆ H ₃	203	<i>S</i>	56	20
2	147	3,5-(CF ₃) ₂ -C ₆ H ₃	203	<i>R</i>	86	67
3	148	3,5-(CF ₃) ₂ -C ₆ H ₃	203	<i>S</i>	nd	4
4	130	C ₆ F ₅	204	<i>S</i>	>95	21
5	147	C ₆ F ₅	204	<i>R</i>	>95	71
6	148	C ₆ F ₅	204	<i>S</i>	>95	12

^a Determined by ¹H-NMR spectroscopy ^b Determined by CSP-HPLC

With this in mind, a number of further azlactones were synthesised in which the steric bulk of the *N*-protecting group was varied significantly. Figure 3.1 shows the *N*-protected amino acids which were synthesised for this purpose.

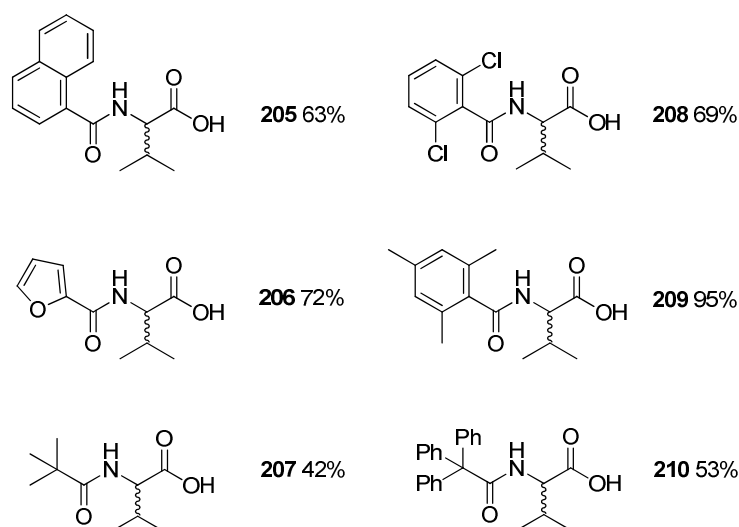
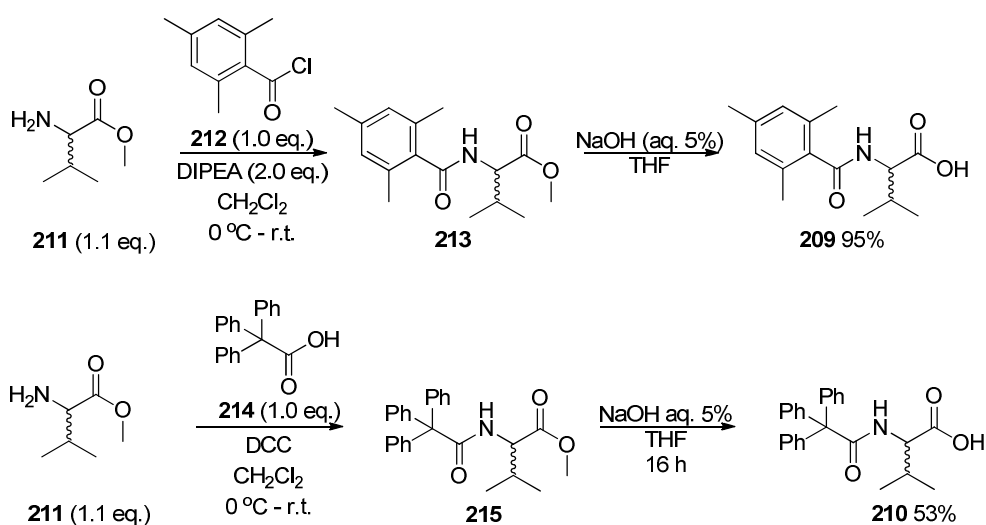


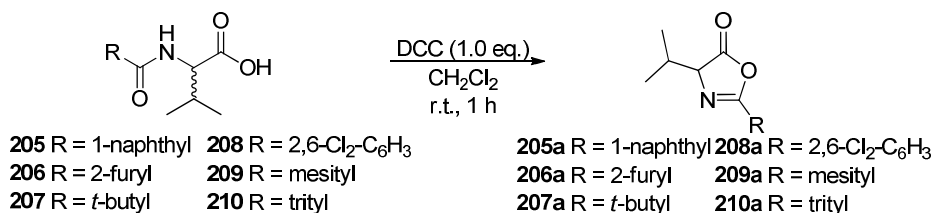
Figure 3.1 A selection of substrates with varied *N*-protecting groups

Of these, amides **205**, **206** and **207** were synthesized using the same Schotten–Baumann type conditions, however **208** required the addition of DMAP (5 mol%) in order for this reaction to proceed. The remaining *N*-protected amino acids could not be synthesised in this manner. In the case of **209** the required acid chloride **212** was found to react readily with the amino acid methyl ester **211** in the presence of DIPEA (Scheme 3.5). This was then readily deprotected in the presence of aqueous sodium hydroxide. Amide **210** was also synthesised according to the route shown in Scheme 3.5, coupling the amino acid methyl ester to the acid using DCC, followed by an identical hydrolysis step to afford the desired product in acceptable yield.



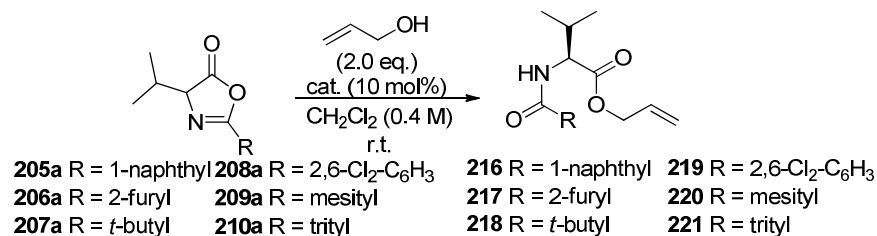
Scheme 3.5 Synthesis of *N*-mesityl valine

These amides were then cyclised using DCC, in all cases the complete conversion to product was observed by TLC however due to the unstable nature of the products only the amount required for the next step was isolated (the remainder left to decompose on the silica column).



Scheme 3.6 Cyclisation of *N*-acyl amino acids to generate azlactones using DCC

The results obtained for the DKR of each of these substrates catalysed by the three active catalysts (**130**, **147** and **148**) are summarised in Table 3.3. It is clear from entries 1-6 that increasing the steric bulk of the *N*-protecting group favours the formation of the *R* product enantiomer in all cases relative to the same reaction with the less bulky benzoyl protecting group. Since catalyst **147** naturally selects for this enantiomer increasing the steric bulk of the protecting group will allow for this catalyst to achieve high levels of enantioselectivity. This improvement however came with concomitant reduction of the reaction rate.

Table 3.3 Further investigation of *N*-protecting group effects

entry	catalyst	R	product	enantiomer	time (h)	conversion ^a (%)	ee ^b (%)
1	130	1-naphthyl	216	<i>S</i>	20	21	30
2	147	1-naphthyl	216	<i>R</i>	20	20	53
3	148	1-naphthyl	216	<i>R</i>	20	27	22
4	130	mesityl	220	<i>S</i>	20	11	22
5	147	mesityl	220	<i>R</i>	20	19	74
6	148	mesityl	220	<i>R</i>	20	25	56
7	130	furyl	217	<i>S</i>	24	37	18
8	147	furyl	217	<i>R</i>	24	59	75
9	148	furyl	217	<i>R</i>	24	48	23
10	130	trityl	221	<i>S</i>	500	>95	52
11	147	trityl	221	<i>R</i>	500	>95	53
12	148	trityl	221	<i>S</i>	500	>95	3
13	130	<i>t</i> -butyl	218	<i>R</i>	500	>95	16
14	147	<i>t</i> -butyl	218	<i>R</i>	500	>95	41
15	148	<i>t</i> -butyl	218	<i>R</i>	500	>95	28
16	130	2,6-Cl ₂ C ₆ H ₃	219	<i>R</i>	21	16	16
17	147	2,6-Cl ₂ C ₆ H ₃	219	<i>R</i>	21	69	76
18	148	2,6-Cl ₂ C ₆ H ₃	219	<i>R</i>	21	26	23

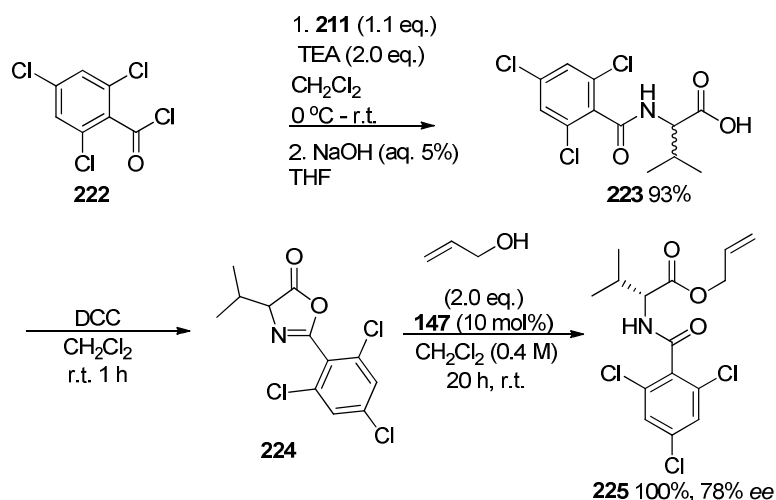
^a Determined by ¹H-NMR spectroscopy ^b Determined by CSP-HPLC

Strangely, results for the DKR of the N-furoyl valine derived azlactone **206a** (entries 7-9), also showed significant relative bias towards the R enantiomer. This cannot be explained by steric interactions as a furan ring occupies less space than a benzene ring. It is also not congruent with the other results (Table 3.1, entries 1-6) which showed an improvement in rate and enantioselectivity with the use of more electron deficient substrates with catalyst **147**; furan, containing a 5 membered 6 electron system is far more electron rich than benzene. It was instead postulated that the lone pair on the oxygen (not involved in the aromatic system), may act as a hydrogen bond acceptor allowing further catalyst-substrate and substrate-substrate interactions. The use of the bulky aliphatic protecting groups featured in **218** and **221** was explored in Entries 10-15. It was clear that aliphatic protecting groups were unsuitable as they resulted in poor reactivity with full conversion only achieved after more than 3 weeks.

Detailed in entries 16-18, the use of the 2,6-dichlorophenyl substituted azlactone **208a**, a substrate which combined an increase in steric bulk with increased electron deficiency, pleasingly resulted in both greatly improved conversion and selectivity for the reaction catalysed by **147**.

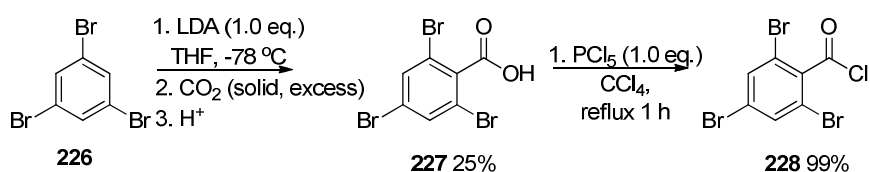
Having shown that a strategy of increasing electron deficiency and steric bulk of the *N*-protecting group allowed for increased selectivity and reactivity for reactions catalysed by **147**, three further protecting groups were examined.

The first to be examined was the 2,4,6-trichlorobenzoyl protecting group shown in **223**. This was chosen as the corresponding acid chloride, **222**, was commercially available and the additional chlorine atom would hopefully provide increased selectivity and rate due to its electron withdrawing effect. The required azlactone **224** was easily synthesised and evaluated, pleasingly both improved rate and selectivity were observed (Scheme 3.7).



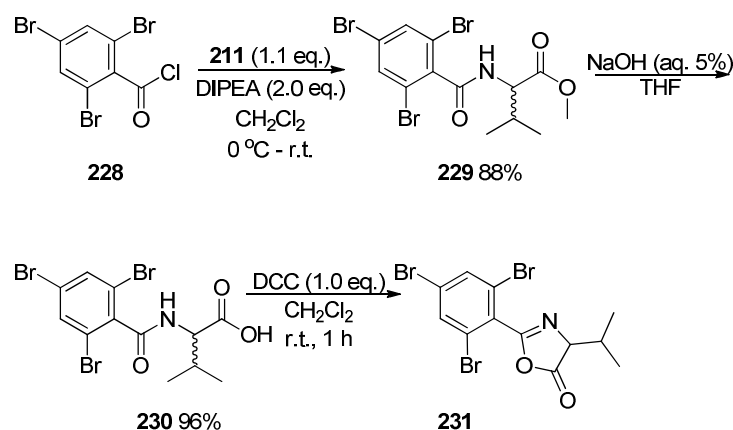
Scheme 3.7 Synthesis and testing with the 2,4,6-trichlorobenzoyl protecting group

Secondly, the use of a 2,4,6-tribromophenyl substituted azlactone was investigated. Neither the corresponding acid chloride nor carboxylic acid was available, so it was necessary to synthesise the required material. This was achieved in sufficient yield by deprotonation of 1,3,5-tribromobenzene (**226**) at -78 °C followed by reaction with solid carbon dioxide and an acidic workup to afford **227**. Attempts to perform this reaction using CO₂ gas met with failure. Having synthesised the necessary carboxylic acid, this was transformed into acid chloride **228** using PCl₅ at elevated temperature (Scheme 3.8).



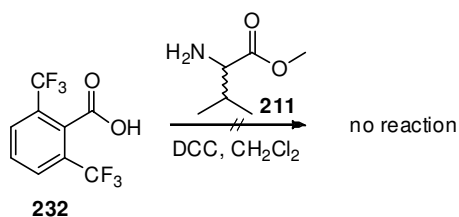
Scheme 3.8 Synthesis of 2,4,6-tribromobenzoyl chloride

This acid chloride could then be coupled with valine methyl ester (**211**) followed by deprotection to give the required protected amino acid. This was then cyclised using DCC. The alcoholysis of this substrate unfortunately resulted in a poorer outcome for the reaction in terms of reactivity and selectivity (Table 3.4, entry 4).



Scheme 3.9 Formation of 2,4,6-tribromophenyl substituted azlactone **231**

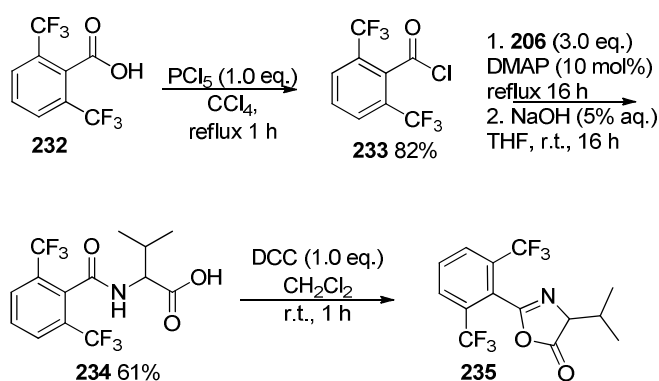
The final protecting group to be examined was 2,6-*bis*(trifluoromethyl)benzoyl. This group was of particular interest because would confer the greatest electron deficiency on the azlactone substrate of all the materials evaluated thus far. It would also be exceptionally hindered, indeed previous reports describing the reactivity of this and similar compounds noted that it had highly unusual properties for an electron poor acid chloride.^{217,218} Since the commercially available material was the carboxylic acid **232**, an attempt was made to couple this to the required amino acid methyl ester **211** (Scheme 3.10) – a strategy that had proven effective for the very hindered triphenylacetic acid (**214**).



Scheme 3.10 2,6-*bis*(trifluoromethyl)benzoic acid fails to react with DCC

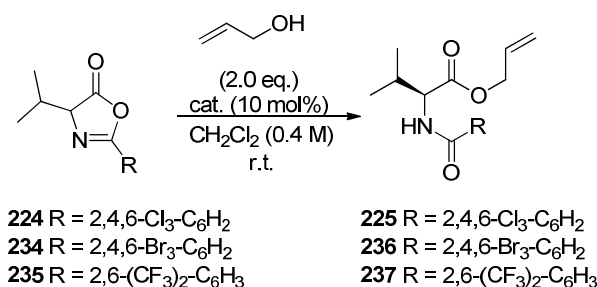
That this reaction failed was testament to the extremely hindered nature of the carboxylic acid. Instead, it was decided to transform the acid into the acid chloride and then attack this with the corresponding amine. The carboxylic acid was reported (and observed) to be resistant to chlorination by thionyl chloride, however reflux in carbon tetrachloride with PCl_5 was reported to be effective. The resulting acid chloride was then stirred with DMAP,

valine methyl ester (3.0 equivalents *in lieu* of a base) and CH₂Cl₂. Even after 5 days stirring at room temperature, only traces of product were observed. The reaction was then heated to reflux for 16 hours which gave the required amide **234** in a relatively poor 61% yield after workup and purification and deprotection. This could be cyclised under standard conditions to give a surprisingly (relatively) stable azlactone.



Scheme 3.11 An alternative route to **233**

Table 3.4 shows a summary of the results for the DKR of this substrate (**235**) and the two previous substrates (**224** and **231**). Unfortunately, the results obtained with **235** (entries 1-3) were disappointing with the rate of the reaction being far slower while also resulting in products with lower *ee* than that in comparable reactions (such as those in Table 3.3, entries 16-18). A comparison with entries 4 and 5 shows 2,4,6-trichlorobenzoyl to be the optimal choice of protecting group for the *N*-protected precursor.

Table 3.4 Further investigation of *N*-protecting group effects

entry	catalyst	substrate (R =)	product	enantiomer	conversion ^a (%)	ee ^b (%)
1	130	2,6-(CF ₃) ₂ -C ₆ H ₃	226	<i>R</i>	9	9
2	147	2,6-(CF ₃) ₂ -C ₆ H ₃	226	<i>R</i>	30	53
3	148	2,6-(CF ₃) ₂ -C ₆ H ₃	226	<i>R</i>	10	8
4	147	2,4,6-Br ₃ -C ₆ H ₂	227	<i>R</i>	69	67
5	147	2,4,6-Cl ₃ -C ₆ H ₂	222	<i>R</i>	100	78

^a Determined by ¹H-NMR spectroscopy ^b Determined by CSP-HPLC

3.1 Optimisation of reaction conditions

Having optimised both the nucleophile and *N*-protecting group the effect of reaction conditions was next examined. Five variables were examined, catalyst loading, solvent, concentration, temperature and quantity of nucleophile.

3.1.1 Examination of nucleophile loading

The reaction was set up under identical conditions to the earlier experiments however nucleophile loading was varied from 2.0 equivalents to 1.0 equivalents, summarised in Table 3.5. Pleasingly this resulted in an appreciable gain in enantioselectivity; however

this came at the expense of increased reaction times on account of the greatly diminished rate at lower loadings. These results led to the use of 1.2 equivalents as optimal loading of alcohol since it was apparent that below this the increase in enantioselectivity was marginal while the rate of reaction continued to diminish.

Table 3.5 Investigation of the effect of nucleophile loading

entry	nucleophile loading (eq.)	time (h)	conversion ^a (%)	ee ^b (%)
1	2.0	20	100	76
2	1.5	16	52	81
3	1.2	16	45	84
4	1.0	16	36	86

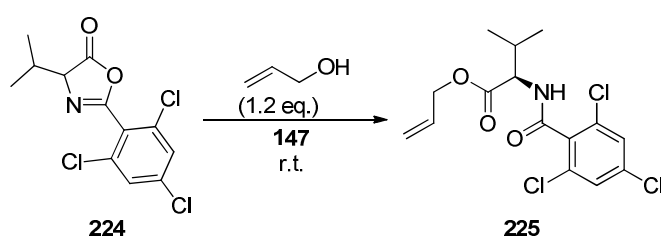
^a Determined by ¹H-NMR spectroscopy ^b Determined by CSP-HPLC

As had been shown in previous studies,¹⁴⁸ the increase in enantioselectivity observed by lowering the concentration of the reaction could be attributed to both an overall decrease in solvent polarity (due to the lower concentration of alcohol), and a reduction in concentration of extraneous hydrogen bond donors (*i.e.* the alcohol) which could cause unselective catalysis to occur.

3.1.2 Optimisation of catalyst loading and concentration

The influence of catalyst loading was next examined by varying the catalyst loading from 5% -20% and it was found that while the rate of reaction was dependent on catalyst loading, stereoselectivity was not (Table 3.6, entries 1-3).

Table 3.6 Examination of catalyst loading and concentration



entry	solvent	concentration (M)	catalyst loading (%)	time (h)	conversion ^a (%)	ee ^b (%)
1	CH ₂ Cl ₂	0.4	5	44	61	84
2	CH ₂ Cl ₂	0.4	10	44	100	84
3	CH ₂ Cl ₂	0.4	20	44	100	84
4	CH ₂ Cl ₂	0.2	10	44	58	85
5	CH ₂ Cl ₂	0.05	20	44	45	93

^a Determined by ¹H-NMR spectroscopy ^b Determined by CSP-HPLC

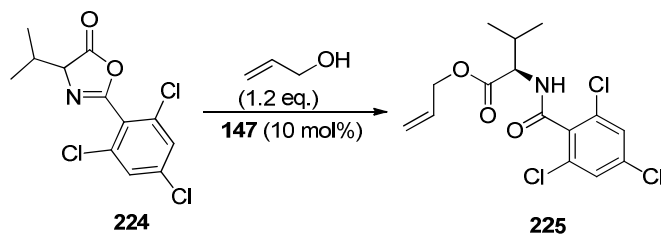
A set of experiments to outline the effect of concentration were then also undertaken which made it clear that a reduction in concentration resulted in an increase in enantioselectivity at the expense of the overall rate of the reaction (Table 3.6, entries 4 and 5). On this basis, an optimum set of conditions balancing catalyst loading and

concentration was chosen to maximise selectivity while still maintaining a practical rate of reaction and catalyst loading.

3.1.3 Optimisation of solvent and temperature

The reaction was performed in several solvents in order to assess both the optimal solvent and also to assess the behaviour of the catalyst in different solvents and solvent mixtures. Solvent screening, shown in Table 3.7, revealed that the reaction slowed dramatically in polar solvents (entries 1-3; MTBE, acetonitrile and sulfolane) while less polar solvents such as toluene, dichloromethane and chloroform (entries 4-6) gave excellent results.

On this basis, further experiments were undertaken at greater dilution and CH₂Cl₂/Hexane mixtures were also examined (entries 7-11). Pleasingly, levels of product enantiomeric excess of up to 95% *ee* were obtained in 1:1 CH₂Cl₂/hexane giving the highest conversion and near optimum *ee* (entry 9, Table 3.7). However this solvent system was eschewed in favour of CDCl₃ on the basis that mixed solvent systems might be seen as impractical. (CDCl₃ was chosen in place of CHCl₃ as it readily allowed monitoring of the reaction by NMR spectroscopy.)

Table 3.7 Solvent optimisation for the DKR of azlactones catalysed by **147**

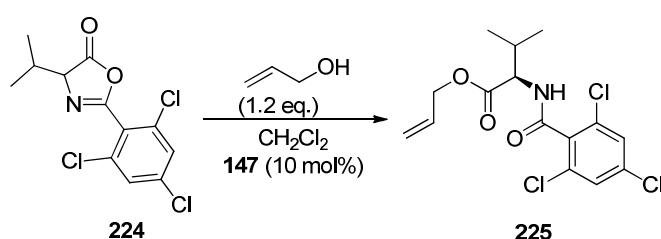
entry	solvent	concentration (M)	temperature (°C)	time (h)	conversion ^a (%)	ee ^b (%)
1	MeCN	0.4	Rt	16	14	-
2	MTBE	0.4	Rt	16	14	-
3	sulfolane	0.4	30	16	41	33
4	toluene	0.4	Rt	16	72	85
5	CDCl ₃	0.4	Rt	16	57	87
6	CH ₂ Cl ₂	0.4	Rt	16	45	84
7	CH ₂ Cl ₂	0.05	Rt	64	31	93
8	CH ₂ Cl ₂ :hexane 3:1	0.05	Rt	64	32	94
9	CH ₂ Cl ₂ :hexane 1:1	0.05	Rt	64	37	94
10	toluene	0.05	Rt	64	30	92
11	CDCl ₃	0.05	Rt	64	24	95

^a Determined by ¹H-NMR spectroscopy ^b Determined by CSP-HPLC

At this point the effect of temperature on the outcome of the reaction was examined. In order to fully evaluate these reaction parameters, a series of experiments were carried out examining the effects of both increasing the temperature and decreasing the temperature at different concentrations. The results shown in Table 3.8 make it apparent that either

heating the reaction or cooling it by as little as 10 °C resulted in an appreciable loss of enantioselectivity. The loss in selectivity on increasing temperature (entries 1 and 2) is readily explained by examining the basic processes of enantioselective catalysis (see section 1.6.1 General requirements for efficient DKR). The loss of selectivity on reducing the temperature (entries 3 and 4) was, however, a surprising result.

Table 3.8 The examination of the effect of temperature on enantioselectivity



entry	solvent	concentration (M)	temperature	time (h)	conversion ^a (%)	ee ^b (%)
1	CH ₂ Cl ₂	0.1	30 °C	20	41	85
2	CH ₂ Cl ₂	0.4	30 °C	16	83	78
3	CH ₂ Cl ₂	0.4	10 °C	44	69	80
4	CH ₂ Cl ₂	0.4	0 °C	44	34	79

^aDetermined by ¹H-NMR spectroscopy ^bDetermined by CSP-HPLC

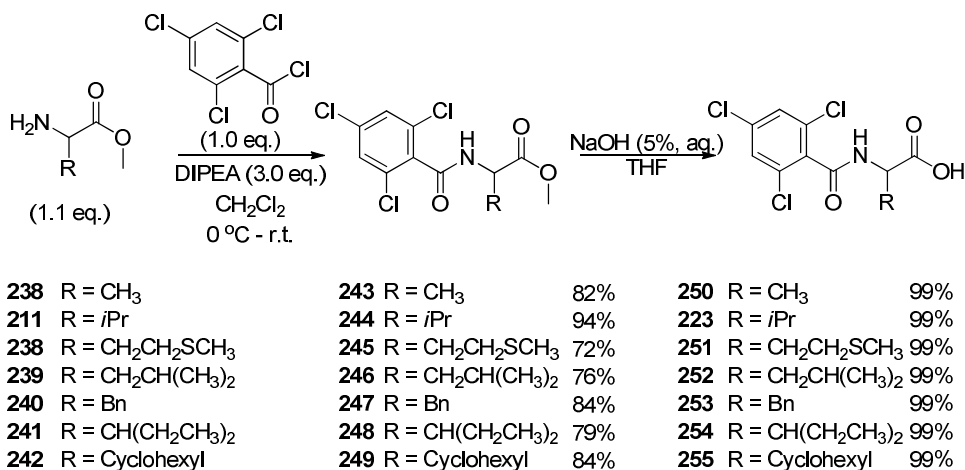
Two explanations were postulated. Firstly it is possible, though unlikely, that since elevated temperatures favour racemisation over the desired reaction, that upon cooling, racemisation becomes too slow to allow the DKR to proceed efficiently. This however was discounted on the basis that azlactones have been widely reported to undergo rapid racemisation under similar conditions. The second possibility was that the catalyst (for which the active conformation is uncertain), was only active and selective in a conformation which was not the lowest energy conformation, thus upon lowering the

temperature of the reaction, the level of catalyst available in the desired conformation is diminished and replaced with catalyst which may be promoting the reaction unselectively.

Regardless of the actual causes behind the changes in enantioselectivity, it was realised that in order for optimal reaction outcome, careful control over the temperature would be necessary, thus further reactions were performed in an oil bath equilibrated at 19 °C since ambient temperature in the laboratory could vary by as much as 15 °C.

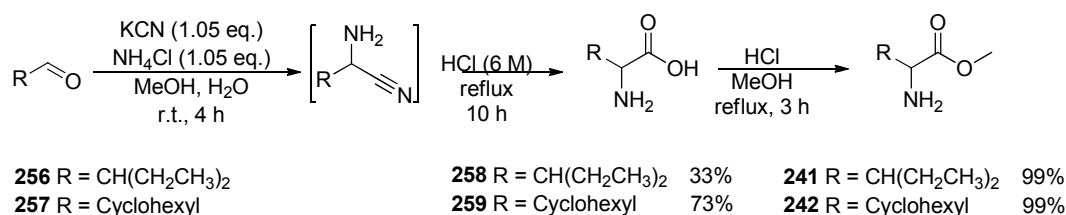
3.2 DKR of azlactones promoted by **147**; and examination of substrate scope

Having established the optimum conditions for this reaction, an examination of the substrate scope was undertaken. With this aim, a number of substrates were prepared (Scheme 3.12). Substrates for which amino acids were commercially available were synthesised according to the established procedure shown in Scheme 3.5 earlier.



Scheme 3.12 Synthesis of *N*-(2,4,6-trichlorobenzoyl) protected amino acids

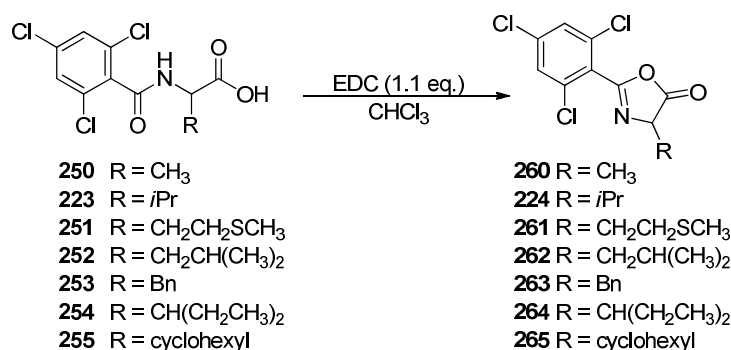
The amino acid esters **241** and **242** required synthesis from the corresponding aldehydes **256** and **257** as the amino acids were not economically available. Amino acids **258** and **259** were synthesised with due care *via* the Strecker reaction from the corresponding readily available aldehydes and subsequently esterified according to the procedure shown in Scheme 3.13.



Scheme 3.13 The Strecker synthesis of amino acids **258** and **259**

Having synthesised the required *N*-protected amino acids, their transformation to azlactones was undertaken. While DCC had proven effective for achieving this transformation with *N*-(2,4,6-trichlorobenzoyl) valine (**223**), when identical conditions were applied to less hindered substrates such as **250** and **253** the results were unsatisfactory. The resulting azlactone was not sufficiently stable to allow for separation of the azlactone from the DCU by-product.

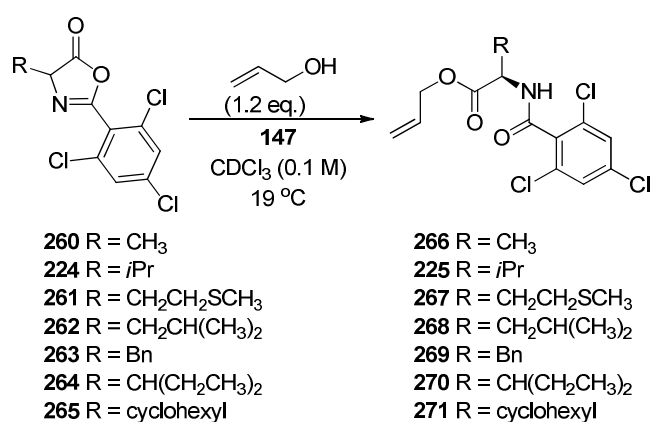
The coupling agent 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) was used. Available as a water soluble hydrochloride, the resultant urea could be easily removed by rapid aqueous work up and the resulting azlactone purified by expedient filtration through a short layer of silica. This strategy allowed for the efficient synthesis of all of the required azlactones, **224** and **260-265**.



Scheme 3.14: Synthesis of azlactones with EDC

The DKR of these azlactones was then undertaken, with high levels of selectivity achieved in all cases. The experiment shown in Table 3.9 entry 1 was carried out by Dr. Zaida Rodriguez-Docampo. In the case of the amino acids with unbranched sidechains and those with less bulky side chains, (entries 1-5), levels of enantioselectivity obtained were moderate to good, and the reaction proceeded rapidly with a reduction in catalyst loading possible in some cases. In the cases where a large substituent was present *ee* exceeding 90% was achieved with yields above 90% in all cases (entries 6-8).

Table 3.9 DKR of azlactones under optimised conditions



entry	R	product	catalyst loading (mol%)	concentration (M)	time (h)	yield ^a (%)	<i>ee</i> ^b (%)
*1	CH ₃	266	20	0.1	44	96	74
2	Bn	269	20	0.1	20	85	73
3	CH ₂ CH ₂ SCH ₃	267	20	0.1	20	96	84
4	CH ₂ CH ₂ SCH ₃	267	10	0.05	20	95	84
5	CH ₂ CH(CH ₃) ₂	268	20	0.1	115	96	83
6	<i>i</i> Pr	225	20	0.1	120	92	90
7	CH(CH ₂ CH ₃) ₂	270	20	0.1	120	91	90
8	cyclohexyl	271	20	0.1	120	92	92

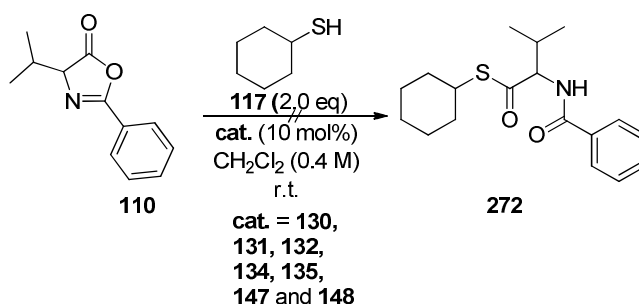
^a Isolated yield. ^b Determined by CSP-HPLC.

This highly enantioselective process demonstrates the potential utility of this novel class of catalyst. Interestingly amino acid **241** is one of the extraterrestrial amino acids isolated

from the Murchison meteorite and entry 7 Table 3.9 shows the first asymmetric, organocatalytic synthesis of a derivative of this amino acid.²¹⁹

3.3 DKR of azlactones by thiolysis

As discussed (in section 1.6.7) the DKR of azlactones by thiolysis is a potentially useful methodology for furnishing orthogonally protected amino acids for which there is excellent synthetic potential. On this basis, the DKR by thiolysis of azlactones was also examined. In this case our initial study used cyclohexane thiol as the nucleophile since it had been shown to be optimal in earlier studies involving catalysts such as **Q39a**.¹⁴⁸ We also began to examine this reaction by returning to the simple *N*-benzoyl valine derived azlactone **110**.



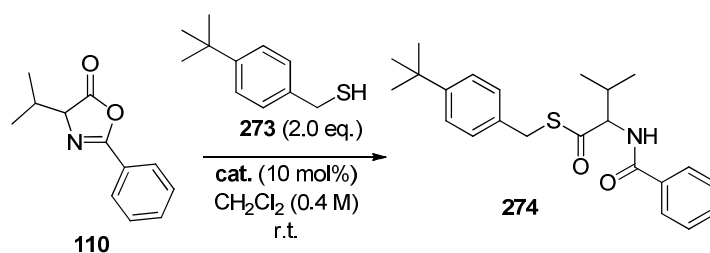
Scheme 3.15 DKR of azlactones with cyclohexyl thiol

In this case, the reaction did not proceed in the presence of any of the suite of catalysts tested. This however was not especially surprising since these catalysts also failed to promote the DKR of azlactones when challenged with more hindered alcohols under the same conditions. Thus, it was decided to substitute cyclohexane thiol with *t*-butyl benzyl thiol (**273**). The results of these experiments are outlined in Table 3.10.

These results were compatible with the theory that control over the intracatalytic distances would lead to control over activity. Entries 1 and 2 make clear that a bifunctional catalyst is necessary for efficient catalysis. Entries 3-9 show broadly similar trends to the behaviour seen in the alcoholysis of the same substrate, that is to say catalyst **130** (entry 3)

in which the hydrogen bond donating hydroxyl is located in the *ortho* position on the C-9 phenyl, is active while **131**, and **132** (entries 4-5) are relatively inactive. Similarly, **147** and **148** (entries 6-7) possessing similar substitution pattern to **130** are relatively active while catalysts **134** and **135** (entries 8-9) are much less active since they do not possess the correct layout of hydrogen bond donors and acceptors to catalyse a 1,2-addition reaction.

Table 3.10 Preliminary investigation into DKR of azlactones by thiolysis



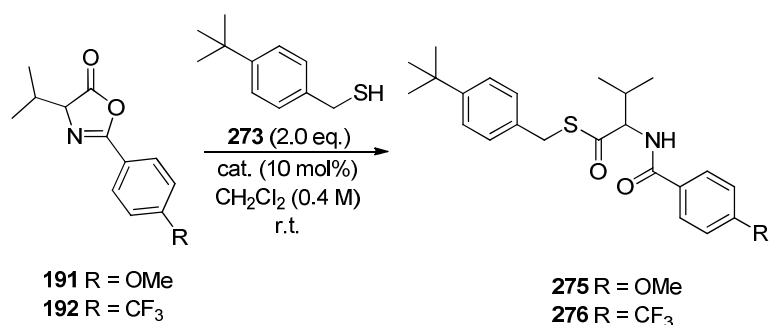
entry	catalyst	time (h)	conversion ^a (%)	ee ^b (%)	enantiomer
1	-	20	0	-	
2	Q23	20	7	-	
3	130	20	60	23	<i>S</i>
4	131	20	46	-	
5	132	20	23	-	
6	147	20	100	0	-
7	148	20	54	19	<i>S</i>
8	134	20	5	-	
9	135	20	12	-	

^a Determined by ^1H -NMR spectroscopy ^b Determined by CSP-HPLC

On this basis, it was decided to investigate further the behaviour of the catalysts in this reaction by examining the effect of adding an electron donating or withdrawing group to the aryl azlactone substituent. These results, given in Table 3.11, made clear that the protecting group was definitely able to affect the level of stereocontrol possible in the reaction, though these initial results were less than promising. Entries 1-4 show that the

addition of an EWG results in greater rate of reaction however the trend in enantioselectivity does not match that seen in the DKR of **110** with allyl alcohol. In this case it appears that **147** does not catalyse the reaction selectively. Entry 5 shows that the installation of an EDG on the aryl substituent of the azlactone reduces the rate of reaction however is also lowers the *ee* of the product.

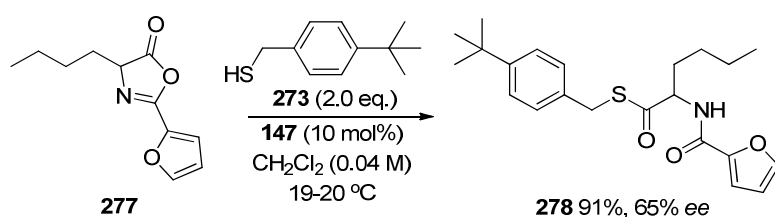
Table 3.11 Preliminary investigation into DKR of azlactones by thiolysis



entry	catalyst	R	product	time (h)	conversion ^a (%)	<i>ee</i> ^b (%)
1	Q23	CF ₃	276	44	<5	-
2	130	CF ₃	276	44	60	20
3	147	CF ₃	276	44	59	-4
4	148	CF ₃	276	44	73	17
5	130	OMe	275	44	44	10

^a Determined by ¹H-NMR spectroscopy ^b Determined by CSP-HPLC

Having shown that this reaction was worth further consideration, a full optimisation was undertaken by Dr. Zaida Rodríguez-Docampo and optimised conditions were found which allowed for the DKR of azlactones by thiolysis with primary thiols delivering unprecedented levels of enantioselectivity for this reaction. Based on these optimisations, a representative example of this reaction was carried out by the author and is shown in Scheme 3.16.



Scheme 3.16: Optimised DKR of azlactones by thiolysis

3.4 Conclusions

Pleasingly, it has been possible to demonstrate that the novel suite of catalysts which we have synthesised is capable of promoting reactions in an organocatalytic fashion with unprecedented levels of selectivity. In the case of DKR by alcoholysis, it has been possible to achieve high enantioselectivity, at ambient temperature, particularly in the case of more hindered substrates. While in the case of less hindered substrates it has still been possible to achieve lesser, but still notable, selectivity.

In the case of DKR by thiolysis, the results achieved represent unprecedented levels of selectivity, again providing an excellent showcase of the potential utility of this novel class of catalysts. In this case, catalyst **147** promotes the DKR of unhindered azlactones such as **277** with primary thiols, both of which under previous methodologies would have been considered more challenging substrates.

While there is clearly scope for improvement, the results presented in this chapter represent the first use of this novel class of quinine derived catalyst in the promotion of an asymmetric reaction with high levels of selectivity. These results pleasingly demonstrate that readily synthesised C-9 arylated quinine derivatives have the potential to become synthetically useful catalysts.

4.0 Further development of novel 9-*epi*-aryldeoxyquinine derivatives

Having shown that the initial library of catalysts, synthesised as described in Chapter 2, in particular catalyst **147**, was capable of promoting reactions with excellent enantioselectivity it was clear that further exploration of the catalytic space and investigation into the ‘tuneability’ of the catalysts should be the next objective.

4.1 Investigation of the influence of hydrogen bond donor pK_a on catalytic activity

The first parameter chosen for investigation was the effect of the pK_a of the hydrogen bond donor on the activity of the catalyst. In order to evaluate this it was decided to synthesise a number of catalysts based on the phenol derivative **130** in which the pK_a of the aryl alcohol had been modified, without causing any undue difference in the steric properties of the ring. It was thus hoped that the effect of pK_a could be examined in isolation from any other effects that might be caused by increased substitution of the phenyl ring.

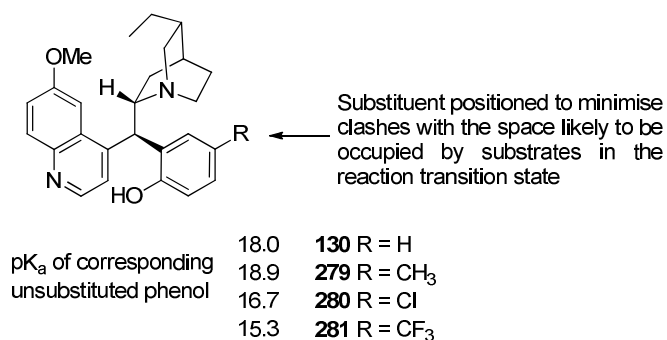


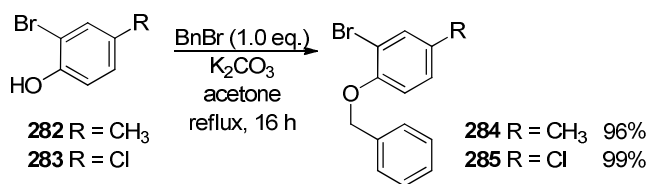
Figure 4.1 Proposed synthetic targets for the investigation of the response of the catalyst to changes in pK_a

The position *para* to the hydroxyl group was chosen as the ideal position in which to place a substituent to affect the group's pK_a , on the basis that it was furthest removed from the catalytically active site of the molecule and also unlikely to interact with (and cause conformational changes in) the rest of the molecule. The groups chosen, *i.e.* methyl, chloro

and trifluoromethyl; giving catalysts **279**, **280** and **281**, were chosen (Figure 4.1) to allow maximum return on information for minimum synthetic effort. Methyl and chloro were ideal since they had very similar steric sizes thus any effect due to their size would be approximately the same in both cases thus allowing us to interpret the result without undue consideration of conformational issues. They would also allow for a definite, but not excessive, alteration of the pK_a such that the effect could be examined without expectation of wholesale change in the catalyst's mode of action.

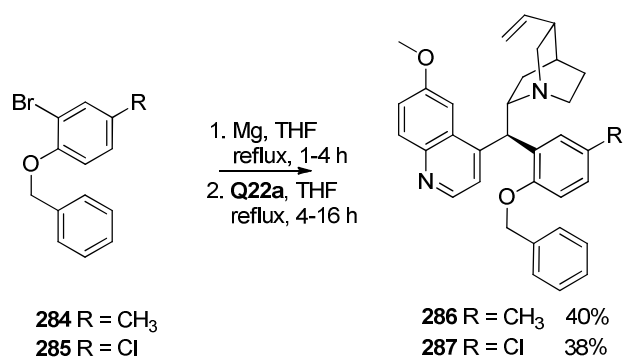
The pK_a data shown in Figure 4.1 are those for the corresponding unsubstituted phenol as measured in DMSO.¹⁹⁰ While the pK_a of phenol is greatly dependent on the solvent varying from 10 in water^{220,221} to approximately 29 in acetonitrile,^{222,223} values obtained in DMSO are available for a range of substitution patterns. It is expected that the corresponding hydroxyl moieties incorporated into the catalysts' structures, while having slightly altered pK_a due to the further substitution of the ring, would still show strong correlation to the unsubstituted analogues. Thus by making the modifications outlined, we will have catalysts with a pK_a of approximately one unit higher than that associated with catalyst **130** (*i.e.* catalyst **279**) in the case of the methyl, and in the case of the chloro substituted catalyst **280** one unit lower. Trifluoromethyl substitution (*i.e.* catalyst **281**) would then provide a much more marked drop in pK_a of nearly three units. Interestingly the pK_a of 4-fluorophenol in DMSO is identical to that of phenol thus precluding it as a synthetic target.²²⁴

Having identified the required targets, it was envisaged that they could be synthesised in a manner identical to that used to prepare the other catalysts previously. Bromophenols **282** and **283** were commercially available. These were then readily protected *via* benzylation using the same method as was used for earlier bromophenols, to give the required compounds **284** and **285** (Scheme 4.1).



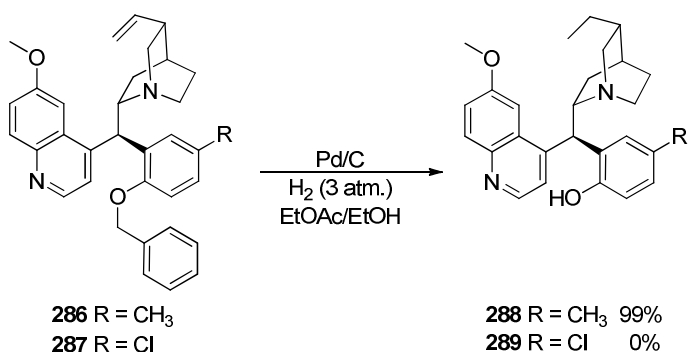
Scheme 4.1 Protection of bromophenols

The resulting aryl bromides, **284** and **285** were readily transformed into their corresponding Grignard reagents allowing the synthesis of the corresponding protected catalysts.



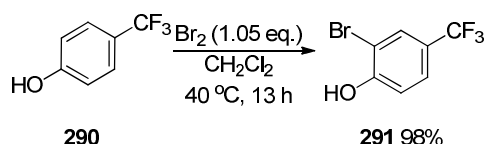
Scheme 4.2 C-9 arylation of quinine with Grignard reagents.

The reaction proceeded adequately in both cases (Scheme 4.2). In the case of bromobenzene **285**, as expected, no magnesiation of the aryl chloride bond was seen and Grignard formation occurred solely at the aryl bromide, allowing selective formation of the desired product. The next step, deprotection, was also undertaken using conditions identical to those used for the earlier catalysts, as shown in Scheme 4.3.



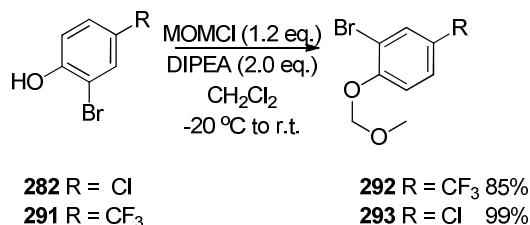
Scheme 4.3 Debenzylation of protected catalysts **288** and **289**

While the reaction proceeded smoothly in the case of **286** giving a quantitative yield, in the case of **287** the reaction conditions also resulted in the complete hydrogenolysis of the aryl chloride resulting in the synthesis of **130**. In order to overcome this difficulty, an alternative protecting group was used, the phenol was converted into a methoxymethyl acetal, which would be capable of withstanding the harsh reaction conditions involved in the other synthetic steps and could also be easily removed to afford the desired catalysts. This protecting group was also chosen for use with 4-trifluoromethylbromophenol (**291**) as it was envisaged that the MOM protecting group would increase the rate at which Grignard formation occurred and also allow for a more expedient deprotection. It was first necessary to synthesise the required 2-bromo-4-trifluoromethylphenol (**291**) from the commercially available 4-trifluoromethylphenol (**290**).



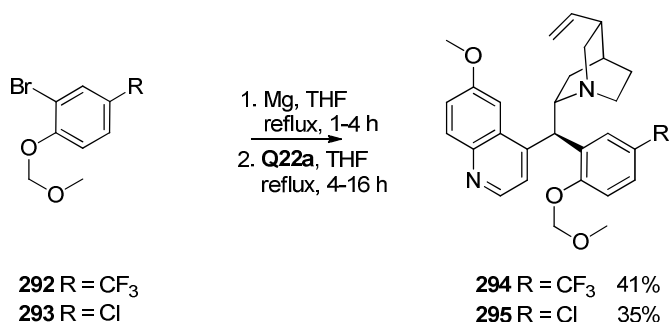
Scheme 4.4 Synthesis of 2-bromo-4-trifluoromethylphenol

This was readily accomplished by the addition of bromine to a solution of 4-trifluoromethylphenol (**290**) under literature conditions giving the desired product in excellent yield (Scheme 4.4).²²⁵ Bromophenols **282** and **291** were then transformed into the corresponding MOM protected derivatives **292** and **293** by reaction with chloromethyl methyl ether (MOMCl) in the presence of DIPEA (Scheme 4.5).



Scheme 4.5 MOM protection of bromophenols **282** and **291**

With the necessary substrates in hand, the Grignard reaction was undertaken (Scheme 4.6).



Scheme 4.6 Formation of protected catalysts **294** and **295**

Both substrates underwent the reaction with modest but adequate yield, to afford catalyst precursors **294** and **295**. These were then deprotected by treatment with aqueous HCl to afford the corresponding phenols (Scheme 4.7) and subjected to hydrogenation in order to saturate the remaining vinyl group so as to provide **280** and **281**; analogues of the previously synthesised catalysts (such as **130**) varying only at the desired position – *para* to the hydroxy group.



Scheme 4.7 Removal of MOM protecting group and saturation of the vinyl bond

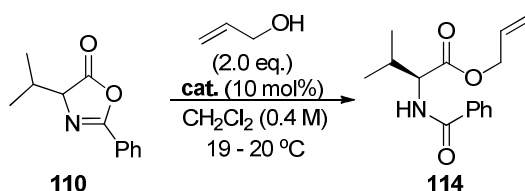
In this case hydrogenation was sufficiently rapid compared to hydrogenolysis, thereby avoiding significant dechlorination of **295** and allowing the desired product to be isolated after careful flash chromatography.

4.1.1 Evaluation of catalysts with varied pK_a

Having synthesised the necessary catalysts, it was then decided to examine their efficacy in promoting the DKR of azlactones. Specifically, the reaction of the *N*-benzoyl valine-derived azlactone **110** and allyl alcohol was chosen as it had provided an ideal distribution of product *ee* amongst the different catalysts tested so far (*e.g.* **130**, **147** and **148**), which would likely allow for the observation of even small changes in catalyst selectivity. It was also a reaction which was easily executed using a robust reproducible protocol. These reactions also occurred on a convenient timescale.

The results are shown in Table 4.1. Entry 1, detailing the DKR as catalysed by **130** is provided for reference. Understandably, the introduction of the methyl group in catalyst **288** (entry 2) reduces the relative strength of the hydrogen bond donating ability of the catalyst and results in a small but significant decrease in the enantioselectivity, with no attendant decrease in rate compared to the unaltered catalyst **130**. Conversely the increase in hydrogen bond donating strength due to the presence of the chlorine atom in catalyst **280** results in a slight increase in enantioselectivity and a marked increase in rate (entry 3).

Table 4.1 Evaluation of catalysts with varied hydrogen bond donor strength



entry	catalyst	R	enantiomer	time (h)	conversion ^a (%)	<i>ee</i> ^b (%)
1	130	H	<i>S</i>	20	20	40
2	279	CH ₃	<i>S</i>	20	20	35
3	280	Cl	<i>S</i>	20	32	43
4	281	CF ₃	<i>R</i>	20	27	3

^a Determined by ^1H -NMR spectroscopy. ^b Determined by CSP-HPLC.

When the pK_a of the phenol is significantly reduced as in the case of the trifluoromethyl substituted catalyst **281**, the reaction is no longer promoted selectively (entry 4). This would seem to indicate that there is an optimum catalyst acidity. It is also worth noting at this point that the pK_a of 4-chlorophenol is almost identical to that of 2-naphthol reported at 16.7 and 17.1 respectively.^{190,224} Thus it would appear that catalyst **147**, serendipitously, possesses a near optimal pK_a .

While it was assumed that the loss of selectivity in the case of reactions catalysed by **281** was due to the change in pK_a of the hydroxyl moiety, it was noted that the size of the CF_3 group in **281** was larger than either the methyl group in **279** or chlorine atom in **280** and that in a similar fashion to catalyst **148** it might be the case that this steric bulk was causing differences in the conformational preferences of the catalyst, **281** and **148** are shown in Figure 4.2 for comparison.

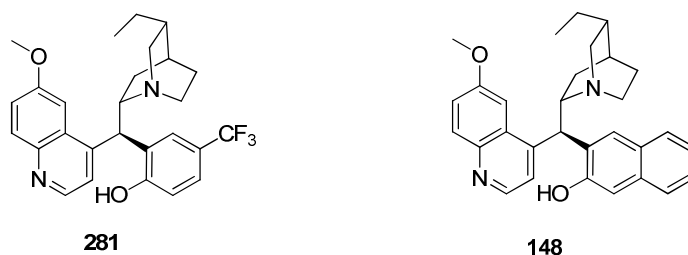
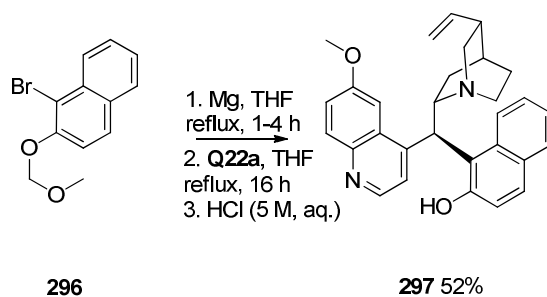


Figure 4.2 A comparison of **281** and **148** shows that they both possess larger substituents at C-3'' than either **279** or **280**

Conformational analysis of **279-281** also suggested that they all existed in the same solution phase conformation again indicating that it was likely to be that change in pK_a which altered the catalytic profile of **281** rather than any other possibility, it was however felt that exploration of this fact by synthesis would give a more definitive answer. Thus to investigate this possibility a further pair of catalysts was later designed.

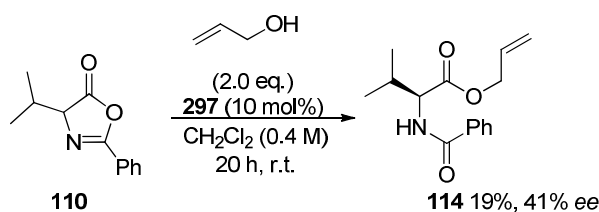
4.2 The effect of saturation of C-10 C-11 on catalyst performance

Since, depending on synthetic route, the vinyl bond contained in the quinine structure would be saturated or not, it was decided to examine the effect of this modification. It was hoped, that the effects of this modification would be negligible, allowing the hydrogenation step to be neglected where the synthetic route did not otherwise require it. With this in mind, the synthetic route shown in Scheme 4.8 was undertaken using the MOM group in place of the previously used benzyl protecting group.



Scheme 4.8 Synthesis of an analogue of **147** which is not saturated at C-10 and C-11

This catalyst, **297**, was then evaluated in the DKR of **110** as shown in Scheme 4.9. The catalyst performed identically to within experimental error when compared to its saturated analogue **147**, promoting the formation of **114** with essentially identical yield and product enantioselectivity.



Scheme 4.9 DKR of **110** catalysed by **297**

On this basis, it was decided that since the effect of saturation of C-10–C-11 was virtually undetectable, that it would be unnecessary to wilfully modify this moiety in future catalysts. The lack of effect seen as a result of this modification is likely due to the greater steric bulk at C-9, in C-9 arylated quinine derivatives, meaning that the relative effect of the ethyl or vinyl group on the quinuclidine ring system is comparatively minor when compared to its effect in quinine derivatives with smaller C-9 substituents.

4.3 The synthesis of catalysts exploring increased steric size at C-5''

On the basis of the outcome of the DKR of **110** catalysed by the trifluoromethyl substituted catalyst **281**, it was decided to synthesise two further catalysts with large substituents at C-5'' to investigate the possible effect that large substituents at this position may have. For this, two catalysts were devised, based on the substitution of protected bromophenols **298** and **299** (Figure 4.3).

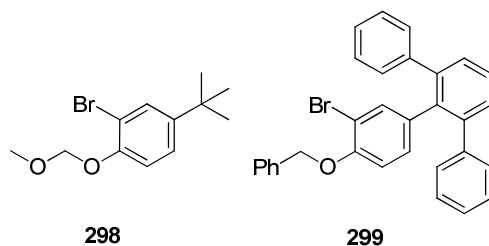
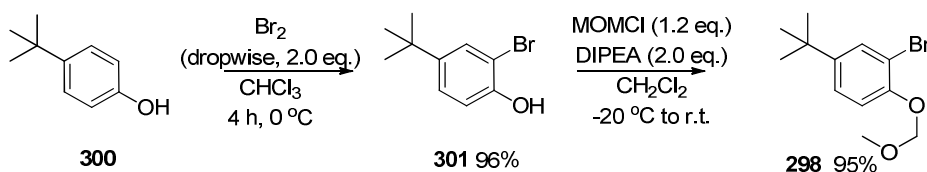


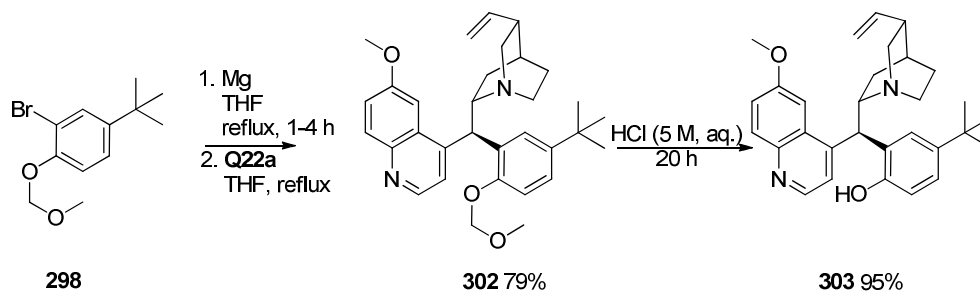
Figure 4.3 Bromophenols for the exploration of C-5'' substitution

Aryl bromide **298** was readily synthesised from commercially available 4-*t*-butyl phenol (**300**) by bromination to give **301** and subsequent acetylation using MOMCl to furnish **298** as shown in Scheme 4.10.



Scheme 4.10 Synthesis of **298**

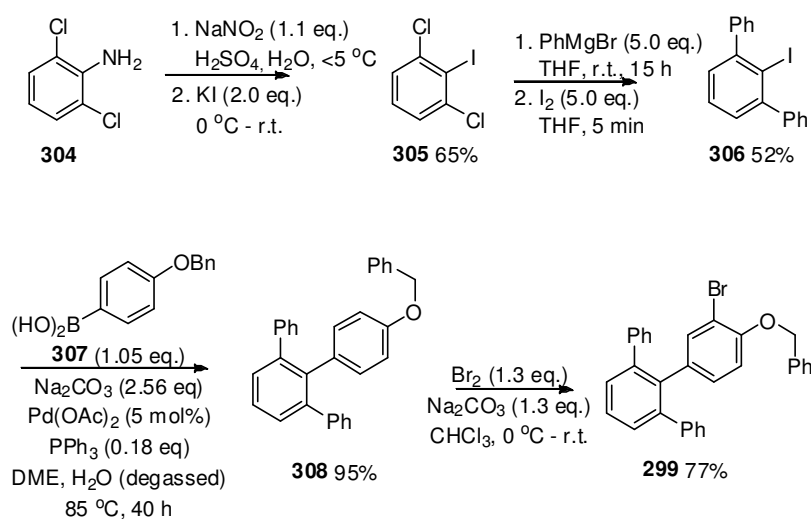
The resulting protected bromophenol **298** was transformed into a Grignard reagent and the resulting reaction with 9-*epi*-chloroquinine (**Q22a**) provided catalyst precursor **302**.



Scheme 4.11 Synthesis of **302** and subsequent deprotection to give **303**

The deprotection proceeded smoothly to afford the desired compound **303** in excellent yield over the two steps (Scheme 4.11).

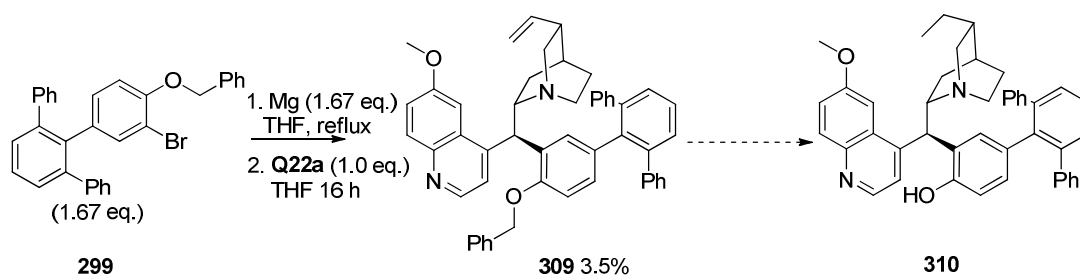
The synthesis of the second target was a more challenging proposition since no precursors resembling this structure were economically available. The synthetic route outlined in Scheme 4.12 was undertaken.



Scheme 4.12 Synthesis of the protected bromophenol **299**

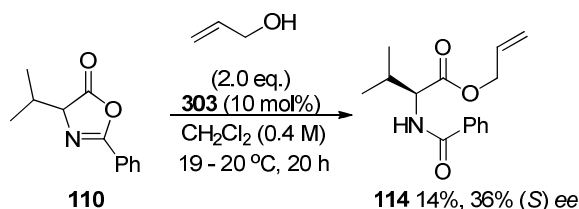
The route outlined in Scheme 4.12 afforded the required protected bromophenol **299** in acceptable yield in four steps. Diazotisation of amine **304** followed by addition of potassium iodide gave aryl iodide **305**. Reaction of this material with excess phenylmagnesium bromide generated the intermediate *m*-terphenylmagnesium bromide after a double elimination addition.²²⁶ This was quenched with excess molecular iodine to give aryl iodide **306**. Boronic acid **307** was commercially available and coupled with **306** under standard Suzuki coupling conditions in excellent yield.²²⁷ It should be noted that an attempted shorter route involving synthesis of the corresponding aryl triflate in place of phenyl iodide **306** failed at the Suzuki coupling stage, necessitating this longer, but previously described synthesis of **308**.^{226,228} Finally **308** was brominated in the desired position to give **299**.

Bromide **299** was then transformed into the corresponding Grignard reagent and allowed to react with 9-*epi*-deoxychloroquinine (**Q22a**) as shown in Scheme 4.13.



4.3.1 Evaluation of **303** in the DKR of *N*-benzoyl valine (**110**)

The ability of catalyst **303** to promote the DKR of *N*-benzoyl valine (**110**) by alcoholysis with allyl alcohol was assessed.

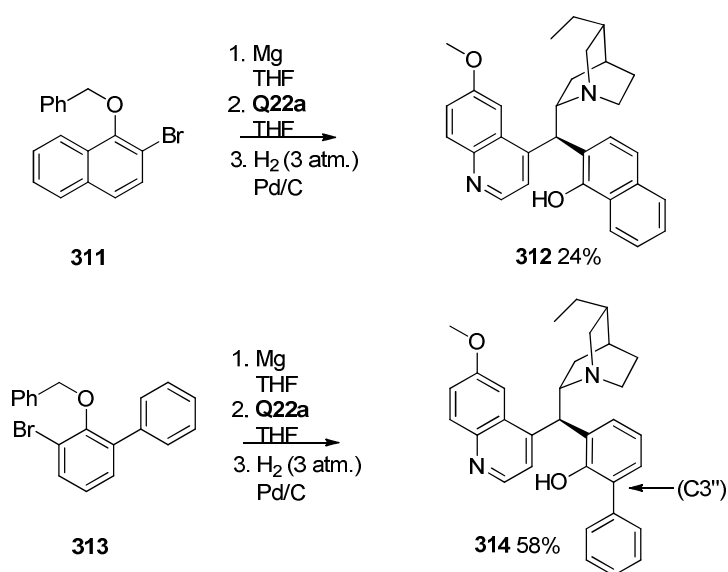


Scheme 4.14 DKR of **110** promoted by **303**

The result obtained clearly demonstrated that it was highly unlikely to be the steric nature of the trifluoromethyl substituent in **296** which caused the dramatic loss in stereoselectivity and instead validated our theory that the reduction in $\text{p}K_{\text{a}}$ was so great that the catalyst no longer promoted the reaction selectively.

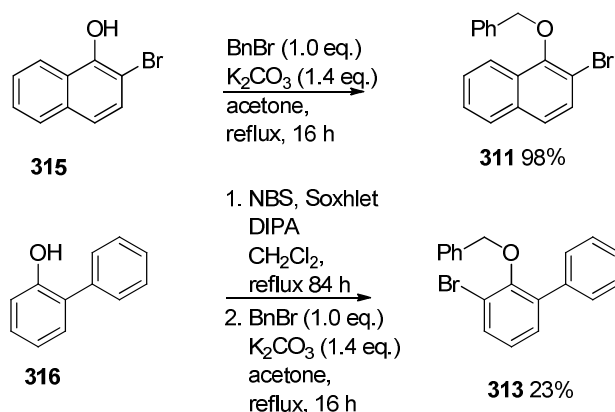
4.4 Modification of the catalyst skeleton at C-3''

Having modified the phenol ring extensively at C-5'' and found that the steric properties of substituents at this position were of little consequence, it was decided to quickly examine the consequences of modifications at C-3''. The two molecules **312** and **314**, (Scheme 4.15), were proposed to evaluate this.



Scheme 4.15 Synthesis of **312** and **314** with C-3'' indicated

The desired molecules **312** and **314** were readily synthesised from the required aryl bromides. These were synthesized from the commercially available starting materials **315** and **316** (Scheme 4.16). 2-Phenylphenol (**316**) was brominated by with slow addition of *N*-bromosuccinimide by use of a Soxhlet apparatus. Benzylation of both alcohols gave the required aryl bromides, **311** and **313** in acceptable yield.



Scheme 4.16 Synthesis of protected bromophenols **311** and **313**

4.4.1 Testing of 312 and 314 in the DKR of *N*-benzoyl valine

It was found that both of the new molecules were inactive and failed to promote the DKR of azlactone **110** with allyl alcohol to any observable extent. Clearly adding further steric impediment to the interaction of the phenol with substrates results in complete deactivation of the catalyst and is not a viable strategy.

4.5 Modification of the catalyst skeleton at C-6''

Having shown that substitution at the C-5'' position had little influence over selectivity, and yet with evidence in hand that catalysts **130** and **147** perhaps adopted different conformations and possessed very different selectivity profiles, it was decided that investigating substitution at 6'' would allow us to clarify that this effect was in fact due to difference in conformation and not any other unspecified reason.

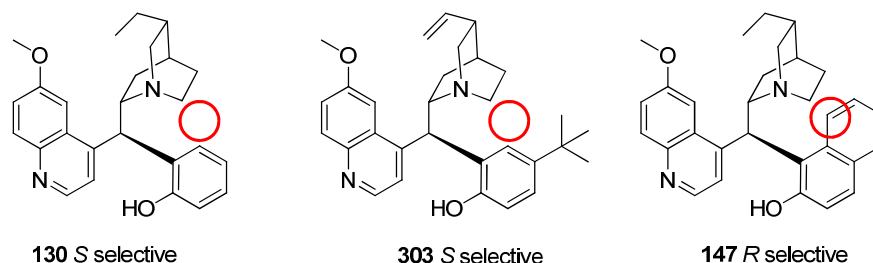


Figure 4.4 The difference in demand at C-6'' is shown for **130**, **147** and **148**.

Figure 4.4 highlights the differences and similarities of catalysts **130**, **147** and **303**, showing that steric bulk at C-6'' (highlighted in red) appears to confer significant change in the selectivity and activity profiles of otherwise similar catalysts. To investigate this, a number of potential catalysts were proposed. These are shown in Figure 4.5 .

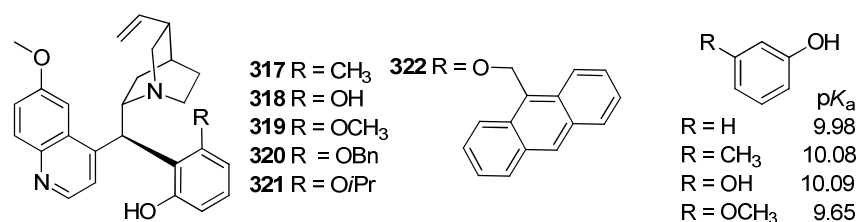
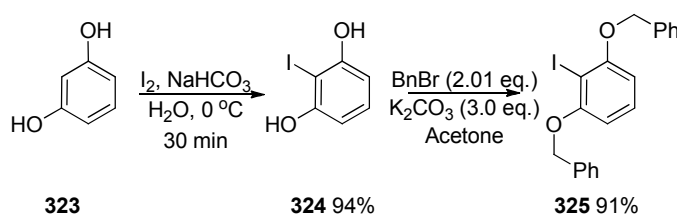


Figure 4.5 Proposed C-6'' substituted catalyst candidates

The range of catalysts was chosen such as to give as wide an array of size of substituent as possible while also allowing for practical synthesis. It was also envisaged that the meta-substitution pattern of the oxygen atoms on the C-9 phenyl ring would lower the pK_a of the phenol in a manner that would increase reactivity. Some pK_a data for meta substituted phenols related to **130**, **317**, **318** and **319** are provided for reference, these data refers to pK_a in water as data for these molecules in DMSO were unavailable.^{221,229}

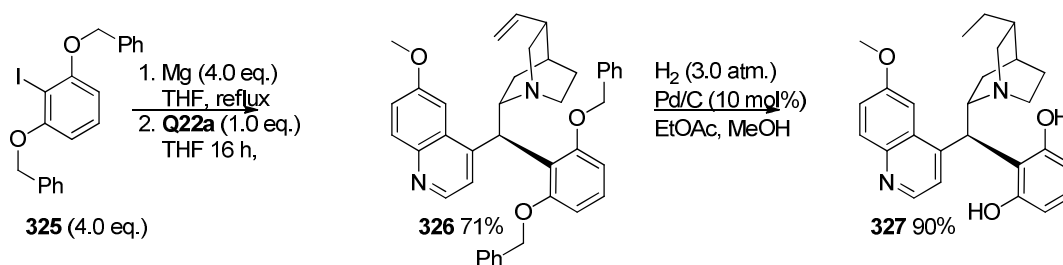
It was envisaged from the outset that the S_Ni reaction might prove highly challenging given the difficulty experienced thus far with other highly hindered substrates in this reaction. As a result it was decided to approach the reaction by attempting the synthesis of the most structurally simple member of this group *i.e.* **318**.

In order to achieve the required 2,6-dihydroxy substitution pattern, the synthetic route began with resorcinol (**323**) with the *ortho*-directing *meta* distributed hydroxyl groups providing the necessary directing effect to allow facile, regioselective iodination. In this case iodine was used as the halogen in place of bromine as the resulting Grignard reagent was shown to give superior results in the S_Ni reaction when compared to the equivalent aryl magnesium bromide.²¹⁴



Scheme 4.17 Iodination and benzylation of resorcinol

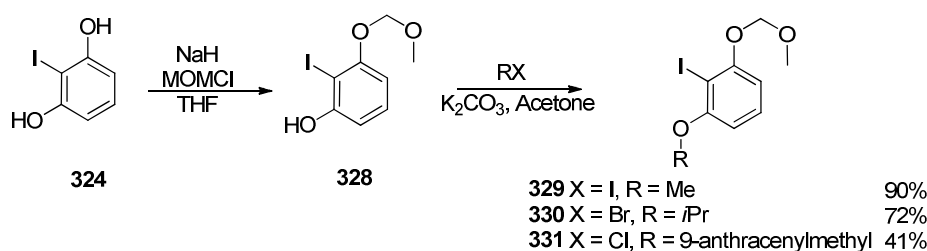
Reaction of **323** with molecular iodine at reduced temperature gave rapid and selective formation of **324**. The iodoresorcinol **324** was benzylated using the standard procedure (Scheme 4.17) and the resulting aryl halide was transformed into the corresponding Grignard reagent and allowed to react with **Q22a** as shown in Scheme 4.18.



Scheme 4.18 Synthesis of 9-*epi*-deoxy(2,6-dihydroxy)phenylquinine (**327**)

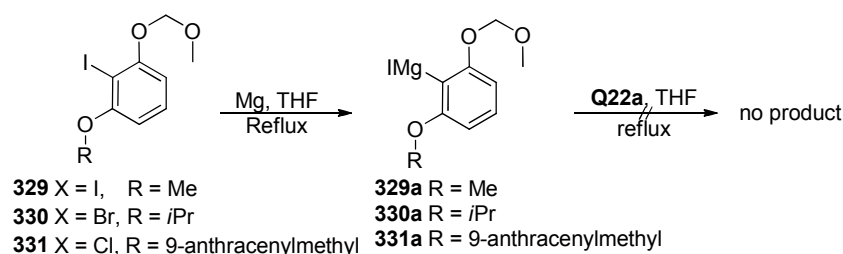
Pleasingly (with use of sufficient excess of Grignard reagent) it was possible to obtain a reasonable yield of the protected catalyst **326**. Deprotection proceeded smoothly under catalytic hydrogenation conditions to give **327**. The resulting product was however unstable, slowly oxidising over time requiring it to be used promptly after synthesis.

With the other synthetic objectives now seemingly more tractable it was decided to attempt the synthesis of other analogues. Precursors **329**, **330** and **331** were synthesised *via* acetalisation, as shown in Scheme 4.19 with the MOM protecting group chosen both for synthetic ease (as it was expected to provide higher yields in the desymmetrisation of **324**) and because its (marginally) lower steric bulk when compared to a benzyl group was expected to provide a Grignard reagent which would more readily undergo the required S_Ni reaction.



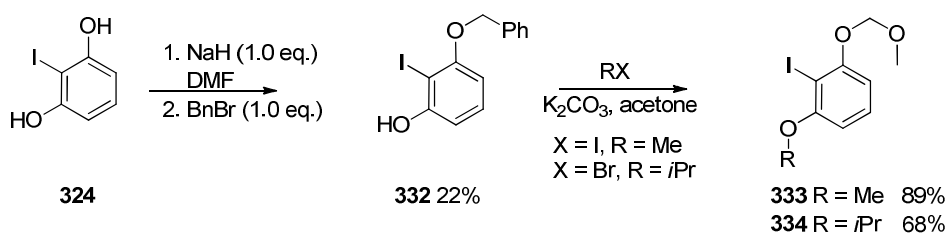
Scheme 4.19 Synthesis of precursors required for **319**, **321** and **322**

Unfortunately the subsequent reaction failed in all three cases, despite clear formation of the Grignard reagent in all three cases. Even trace product formation was not observed. It was thus speculated (since the steric demand of the methyl derivative was definitely lower than the already successful benzyl analogue) that the MOM protecting group may be incompatible with the $\text{S}_{\text{N}}\text{i}$ reaction mechanism in these cases (where two oxygen atoms are situated *ortho* to the carbon-magnesium bond) as it may result in over coordination of the magnesium atom preventing its participation in the coordination steps required for the $\text{S}_{\text{N}}\text{i}$ mechanism.



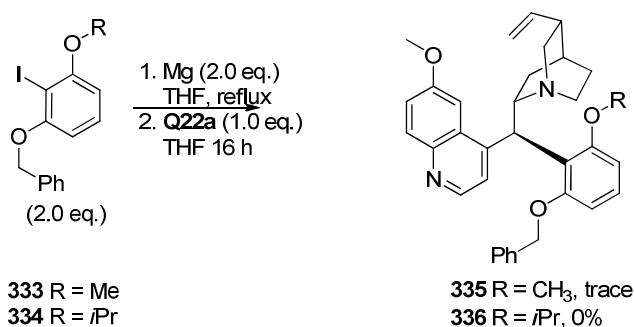
Scheme 4.20 Substrates **329-331** were incapable of undergoing the required $\text{S}_{\text{N}}\text{i}$ reaction

With this in mind, precursors **333** and **334** were synthesised with benzyl protecting groups by the desymmetrisation of **324** by a single deprotonation step followed by addition of benzyl bromide and subsequent alkylation with the required alkylation reagent to provide **333** and **334**.



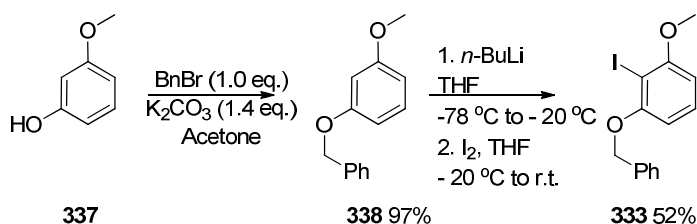
Scheme 4.21 Formation of the benzyl protected iodoresorcinol derivatives **333** and **334**

The resulting Grignard formation and reaction with chloroquinine (Scheme 4.22) gave only small amounts of product not readily isolated in the case of the methyl derivative **333**, and no product in the case of the *isopropyl* derivative **334**.



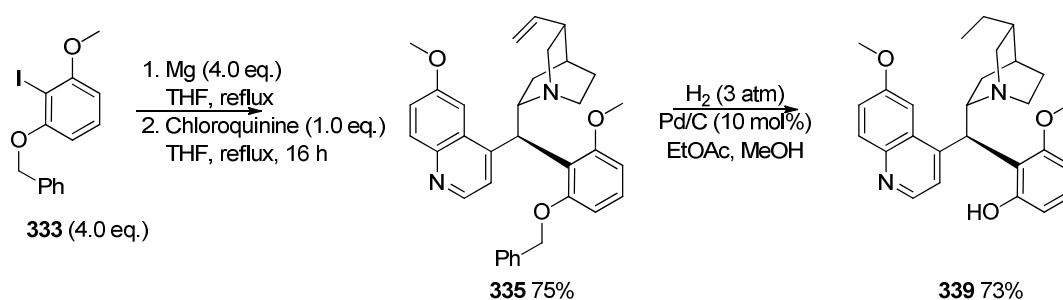
Scheme 4.22 Attempts at synthesis of C-6'' substituted catalysts **335** and **336**

Having shown that synthesis of the methyl derivative **335** was possible, it was decided to approach the synthesis of this catalyst by a more efficient route that would more easily allow for a large excess of the required 2-iodo-methylbenzylresorcinol to be synthesised. Precursor **337** was cheaply available and obviated the need for the desymmetrisation step shown in Scheme 4.21, which had given a poor yield. The synthetic route outlined in Scheme 4.23 was thus undertaken.



Scheme 4.23 A more efficient route to **333**

Benzylation of the commercially available *m*-hydroxyanisole (**337**) to give **338** was followed by *ortho*-lithiation with *n*-BuLi. The *ortho*-directing nature of both substituents provides regiospecific deprotonation at the desired position. Reaction of the aryllithium with a solution of iodine yielded the desired product **333** in 50% yield over the two steps. With this in hand, the Grignard reaction in Scheme 4.22 was re-evaluated this time using a large excess of Grignard.

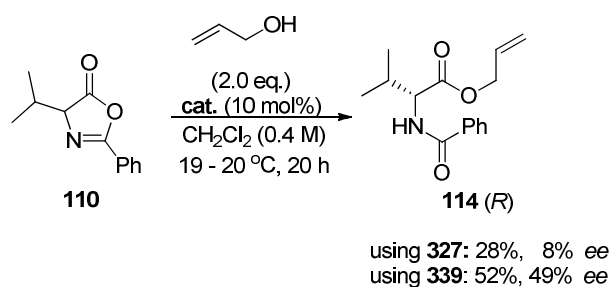


Scheme 4.24 A more efficient route to **335** and subsequent deprotection to give **339**

The reaction resulted in the formation of the desired product **336** in high yield, with the subsequent deprotection also proceeding smoothly to give **319**. With two of the desired products in hand, and a high yielding route to the remaining targets (*i.e.* **317** and **320-322**) difficult to identify, it was decided to test our hypothesis regarding the importance of substitution at C-6'' by evaluating the performance of these two catalysts **327** and **339** (*i.e.* the C-10-C-11 dihydro analogues of **318** and **319**).

4.5.1 Testing of **327** and **340** in the DKR of azlactones

Catalysts **327** and **339** were tested in the DKR of azlactone **110** under standard conditions giving the results shown in Scheme 4.25.

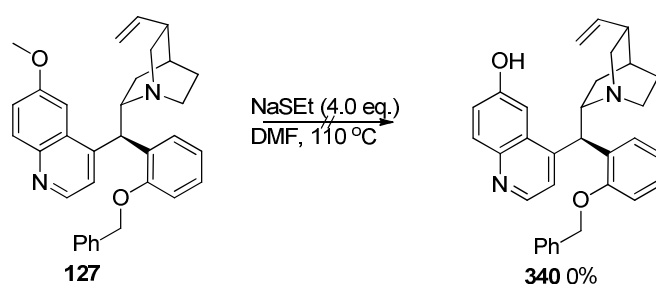


Scheme 4.25 Testing of **327** and **340** in the DKR of azlactone **110**

It was clear that substitution at C-6'' was highly important to determining the stereochemical outcome of this reaction with both **327** and **339** exhibiting markedly different behaviour to **130**. Catalyst **339**, selecting for the opposite enantiomer of **110** to that preferentially ring opened in the presence of **130**, demonstrated that substitution of this position was key to controlling the sense of enantiodiscrimination in these reactions. Perhaps of equal interest is the excellent selectivity profile exhibited by catalyst **339**, which promoted more efficient and more enantioselective DKR of **110** than any catalyst previously designed and synthesised in this work.

4.6 Modification of the catalyst skeleton at C-6'

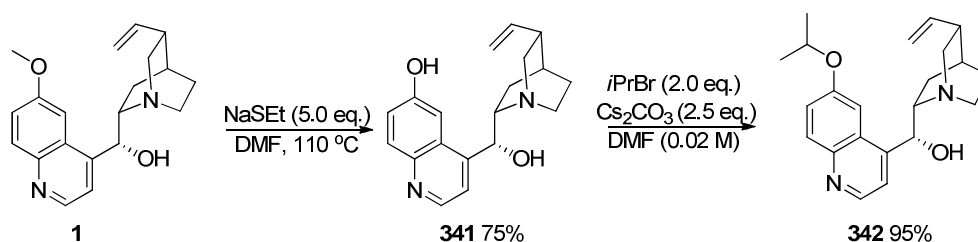
With the strategy of modification at C-6'' having proven fruitful, it was speculated that modification at the C-6' position of the catalysts could exaggerate any steric clashes between the two aromatic rings present in the catalyst; thereby potentially improving overall conformational stability and improving catalyst performance. With this in mind, demethylation of catalyst precursor **127** was attempted using conditions known to allow the reaction to proceed smoothly in the case of quinine.



Scheme 4.26 The attempted demethylation of **127**

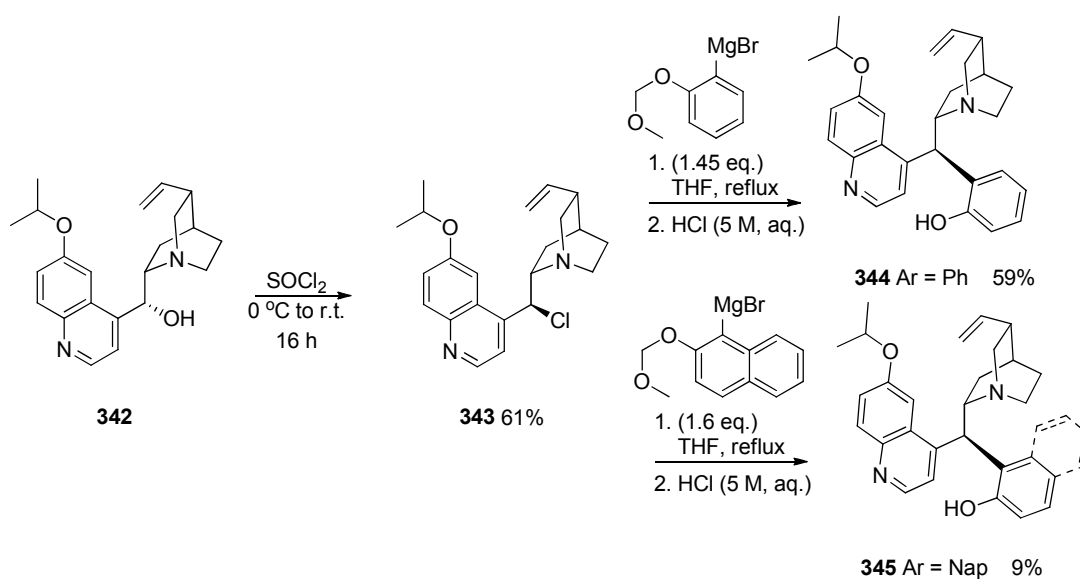
Unfortunately, these conditions were not compatible with **127** and the reaction resulted in a mixture of a large array of products in which the desired material could not be observed.

This route being unfeasible it was decided that modification of quinine at C-6' according to literature procedures to allow the replacement of the methyl group with a more bulky isopropyl one, followed by a synthetic route analogous to the one yielding **130** would be a suitable, if cumbersome, path to the desired materials.



Scheme 4.27 Demethylation and subsequent alkylation of the C-6' oxygen of quinine

The required quinine derivative **342** was readily synthesised (Scheme 4.27) following literature procedures.⁹⁴

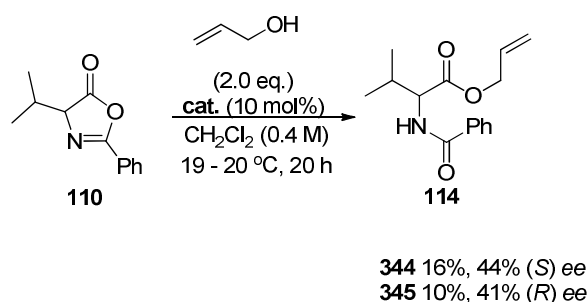


Scheme 4.28 Generation of novel catalyst candidates from quinine derivative **342**

This underwent chlorination smoothly to give **343** and in the case of **344** the Grignard reaction and subsequent deprotection provided the desired product in good yield. Unfortunately the same reaction with the naphthyl derivative to generate **345** was far less efficient providing the desired product in only 9% yield. However this provided sufficient material to evaluate **345** as a catalyst in the DKR of **110**.

4.6.1 Evaluation of C-6' modified catalysts

Having successfully synthesised catalysts **344** and **345**, these were evaluated as catalysts for the DKR of azlactone **110** under standard conditions giving the results shown in Scheme 4.29.



Scheme 4.29 Testing catalysts **344** and **345** in the DKR of **110**

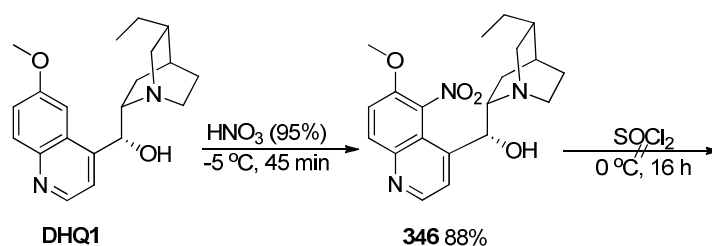
While the effect of this modification on the ability of alkaloid derivatives of this type to act as catalysts in this reaction can be seen to be minimal, it clearly causes a loss in activity in the reaction catalysed by phenol derivative **344** when compared to the results obtained with use of **130** and only a slight increase in *ee*. In the case of the naphthol derivative **345** a more severe fall off in rate is observed and the change in product *ee* is almost indiscernable relative to the results obtained with used of closely related analogue **147**.

On this basis, while it has been shown that it is possible to incorporate modifications at this position into the catalyst structure, it appears not to have significant benefit from an activity stand point. Given the level of synthetic effort required to make this modification, it would not seem to be worthwhile incorporating it into an optimised catalyst structure.

4.7 Modification of the catalyst skeleton at C-5'

Having shown that the effect of increased steric bulk at C-6' was minimal, it was thought that the addition of a substituent at C-5' on the quinoline ring would be capable of producing a far stronger clash between the two aromatic rings in the catalyst.

On this basis, the substitution at C-5' was attempted. Firstly, since it was known that nitration of the C-5' position on dihydroquinine by EAS was easily accomplished by following literature procedures, this was seen as an excellent starting point.

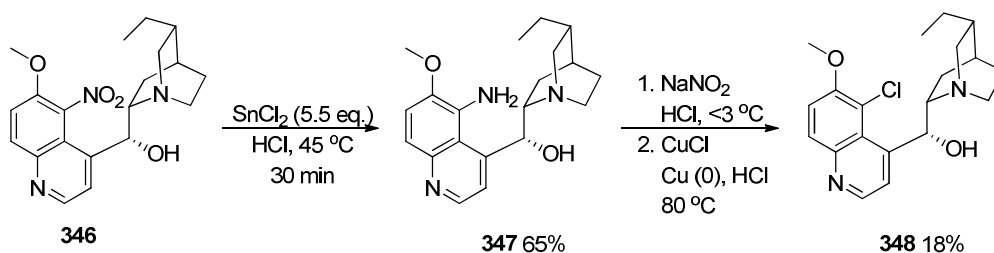


Scheme 4.30 Nitration of dihydroquinine by EAS

While the nitro group would likely have proven reactive in the presence of Grignard reagents at elevated temperature,^{230,231} it was hoped that the resulting product would still have been of interest. Unfortunately, such speculation was obviated by the failure of the chlorination of the C-9 position to result in a stable product. It seemed that the nitro group was capable of interacting with the resultant alkyl chloride, resulting in decomposition of the desired product. On this basis, it was decided that installing a different functional group at C-5' would deliver more satisfactory results.

It was clear that given the lack of a successful report of EAS of (dihydro)quinine (or its related alkaloids) with another electrophile in the literature, it was likely that such a reaction was likely to prove difficult. Indeed, after systematic attempts at bromination of dihydroquinine, the desired C-5' substituted product was not forthcoming.

Instead, it was decided to attempt FGI of the nitro group, for which a literature precedent was available.⁹¹ The reduction of 5'-nitro-DHQ (**346**), could be achieved by catalytic hydrogenation in the presence of palladium on carbon to afford the corresponding amine **347**, however this reaction was less than ideal since the desired product was also reactive under the reaction conditions meaning that slight differences in gas pressure or catalyst activity could result in sub-optimal yields. Instead, reduction by tin (II) chloride was preferred (Scheme 4.31), resulting in a clean transformation with no side reactions. In either case, the resultant bright yellow solid was highly susceptible to oxidation, decomposing in the presence of air, which required immediate use after synthesis.

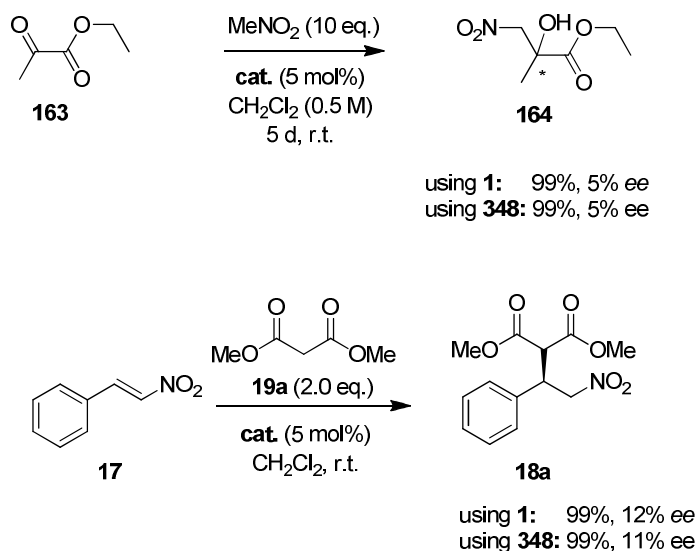


Scheme 4.31 Synthesis of the chloroquinine derivative **348**

The following Sandmeyer reaction was capricious, with the single example in the literature (1948), describing a procedure in a less than clear manner. However it was possible to isolate the desired aryl chloride **348**, albeit in poor yield.⁹¹

Since further manipulation at this position would require significant investment of time, it was decided to first evaluate C-5' chloro quinine to see if it exhibited significantly different behaviour to its parent compound.

To achieve this, two readily accessible reactions, known to be catalysed by quinine were undertaken: the addition of dimethylmalonate (**19a**) to nitrostyrene (**17**) and the addition of nitromethane to ethyl pyruvate (**163**). The results for these are shown in Scheme 4.32.



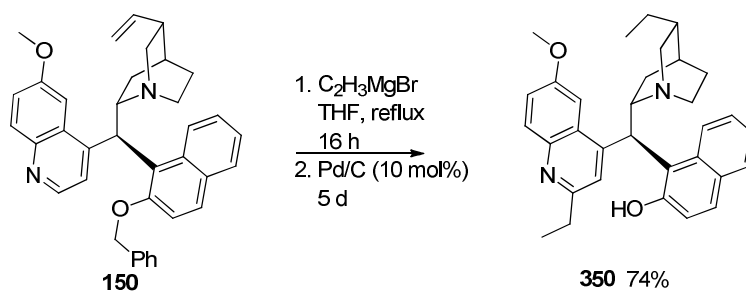
Scheme 4.32 The evaluation of differences in catalytic ability of **1** and **348**

Unfortunately the differences in reaction outcome were minor, and while it is not clear how this would translate into our catalyst system, it was chosen not to pursue it further due to the high level of synthetic effort that would need to be invested.

4.8 Modification of the catalyst skeleton at C-2'

The possibility of modification of the quinine skeleton by substitution at C-2', was of interest to us as a possible means of improving the performance exhibited by C-9 arylated quinine derivatives in the promotion of the DKR of azlactones. While C-2' is somewhat removed from the bonds which control the conformation of quinine and its derivatives, it is also known that quinoline is capable of acting as a nucleophile and that despite the excellent *ees* which had been obtained using **147** as a catalyst for the DKR of **110**, it remained possible that some losses in selectivity may be due to the quinoline functioning as a nucleophile. On this basis, substitution at C-2' was explored.

Initially on the basis of the reactions reported by Jacek *et al.*,⁷⁸ the protected catalyst **150** was exposed to vinyl magnesium bromide according to the conditions outlined in Scheme 4.33.



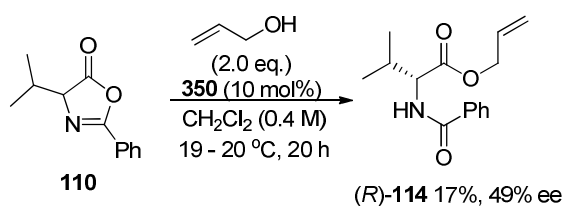
Scheme 4.33 C-2' substitution of protected catalyst **150**

While this reaction failed to progress at room temperature, even after prolonged reaction times, at reflux the reaction proceeded to afford the desired product in good yield. This was then deprotected under standard hydrogenation conditions giving simultaneous saturation of the two vinyl groups resulting in a C-2' ethylated catalyst which was

evaluated promptly in the DKR of **110**, to establish if this modification was worth further investigation.

4.8.1 Testing of C-2'-ethyl-9-*epi*-deoxy(2-hydroxyphenyl)quinine

Results for the evaluation of **350** as a promoter of the DKR of **110** under standard conditions are shown in Scheme 4.34.



Scheme 4.34 DKR of azlactone **110** promoted by **350**

The new catalyst promoted the reaction with increased enantioselectivity under standard conditions, prompting us to investigate further. The results however did not allow us to determine whether this modification was due to prevention of a theoretical nucleophilic role of the adjacent quinoline nitrogen atom or due to other alterations to the shape of the reaction site or overall conformation of the catalyst.

4.8.2 Synthesis of further catalysts modified at C-2'

In order to answer the question raised by the strong performance of **350**, the molecules outlined in Figure 4.6 were targeted. Targets **351**, **352** and **353** were chosen as it was hoped that a variety of different sizes of substituents would allow discovery of the optimal size of the installed moiety at C-2'. Catalyst **355** on the other hand should allow us to determine if the role of this group is solely in preventing non selective nucleophilic pathways to occur.

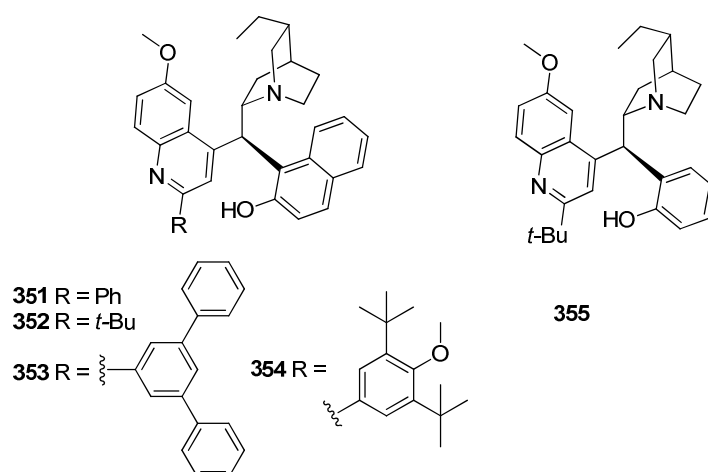
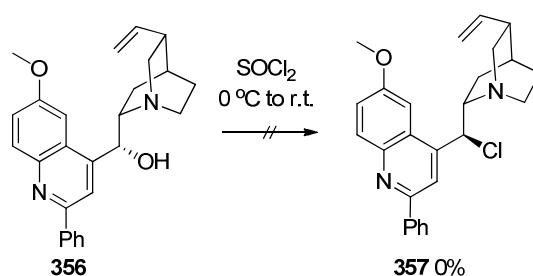


Figure 4.6 Synthetic targets towards evaluating the effect of C-2' substitution

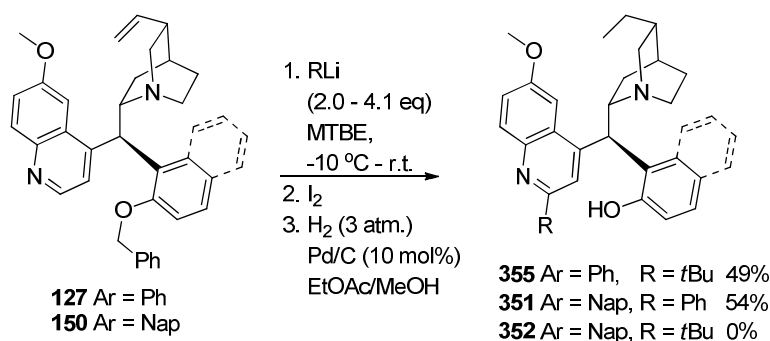
If it is the case that C-2' substitution only causes the deactivation of a non selective nucleophilic pathway then we would expect the enantioselectivity of reactions promoted by **349** and **355** to improve relative to **130** and **147** respectively. In the event that this is not the case, and improvement is not seen in both cases, (while the deactivation of the quinoline nitrogen atom as a nucleophile may be a contributing factor) it will be clear that other factors are more important.

In order to synthesise the targets **351** it was envisaged that a synthesis starting at quinine functionalised at C-2' would lead to the desired product. The 2'-phenyl derivative **356** was graciously made available by Seán Tallon.



Scheme 4.35 C-2' phenyl derivative of quinine fails to undergo chlorination at C-9

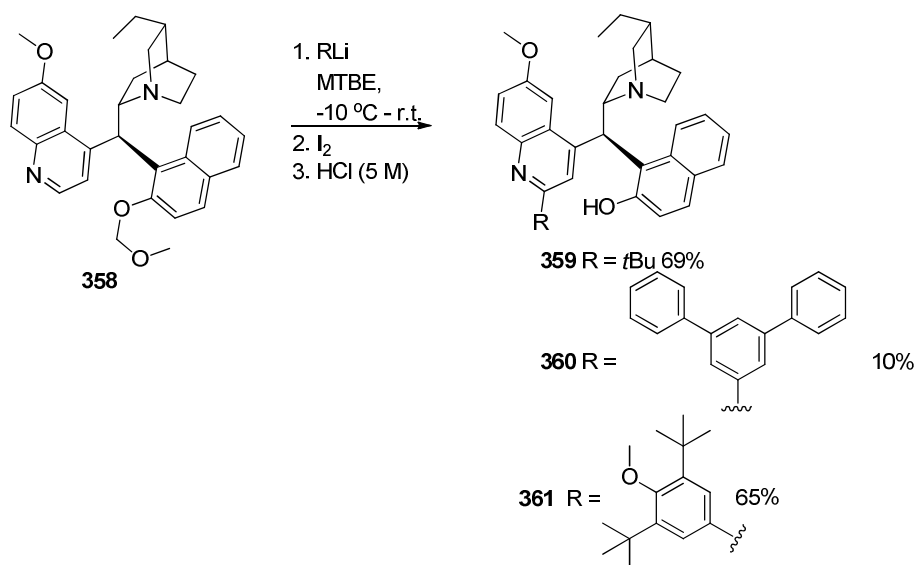
Unfortunately, the chlorination was unsuccessful (Scheme 4.35) with the starting material **356** breaking down into a number of products. This, while tedious, did not represent an insurmountable hurdle and interestingly confirmed that C-2' substituted quinines behave quite differently to the parent compound. Since this was not a viable synthetic pathway, the earlier method of nucleophilic attack at C-2' was revisited, however the use of Grignard reagents was replaced with more reactive alkyl/aryl lithium reagents which were expected to provide a more efficient reaction which could proceed at lower temperatures.



Scheme 4.36 C-2' functionalisation of quinine derivatives **127** and **150**

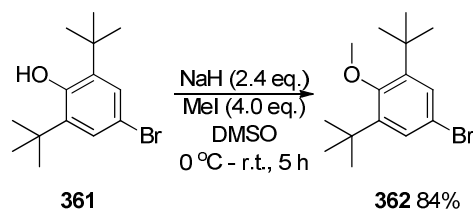
The use of lithium reagents allowed the reaction to proceed at lower temperatures however the required re-aromatisation did not occur spontaneously, so the reaction mixture was treated with iodine on workup in order to fully re-aromatise the quinoline ring. In all cases this step was successful, however the subsequent deprotection was only successful for **355** and **351** with deprotection of the corresponding *t*-butyl substituted analogue of **150** occurring at an impractically slow rate (<2% after 3d).

In order to circumvent this, MOM protected catalyst **358** was substituted for **150** in the organolithium addition reaction, allowing for deprotection in aqueous HCl. This was used to allow synthesis of the remaining targets.



Scheme 4.37 Generation of further novel C-2' substituted catalyst candidates **359-361**

The required lithium reagents (where not commercially available) were generated from the corresponding bromides by lithium halogen exchange. The bromide required for **362** was kindly provided by Francesco Manoni, having been synthesised by a method analogous to that shown in Scheme 4.12. The bromide required for **361** was synthesised by careful methylation of the easily oxidised 4-bromo-2,6-di-*t*-butylphenol as shown in Scheme 4.38.



Scheme 4.38 Generation of aryl bromide **362**

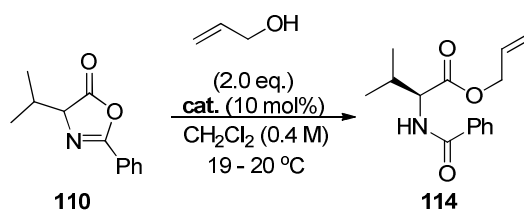
4.8.3 Evaluation of C-2'-modified catalysts as catalysts for the DKR of **110**

The results for the evaluation of the ability of catalysts modified at C-2' to promote the DKR of azlactones are summarised in Table 4.2. The results presented in entry 1, for the reaction promoted by **355**, describes the effect of C-2' substitution on the ability of C-9

phenol type catalysts to promote the DKR of **110**. A comparison of this result with the same reaction catalysed by **130**, shows that the C-2' substitution results in diminished rate and selectivity. It is thus clear that the role of this group is not solely that of lowering the ability of the quinoline ring to act as a nucleophile.

As the size of the substituent at C-2' was increased, it began to impinge further on the activity of the catalysts without increase in selectivity (entries 2-5). This allowed us to identify the ideal substituent. The phenyl group in catalyst **351** is shown to be the optimum substituent at this position (entry 2), with higher product *ee* resulting from the use of this catalyst compared to the use of the other catalysts with more bulky C-2' substituents (entries 3-5, catalysts **359-361**).

Table 4.2 Evaluation of C-2' substituted catalysts in the DKR of **110**



entry	catalyst	enantiomer	time (h)	conversion ^a (%)	<i>ee</i> ^b (%)
1	355	<i>S</i>	20	25	22
2	351	<i>R</i>	20	26	53
3	359	<i>R</i>	20	9	49
4	360	<i>R</i>	20	20	39
5	361	<i>R</i>	20	10	33

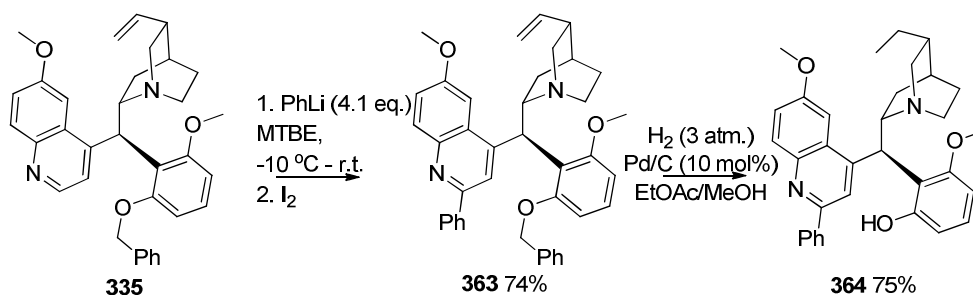
^a Determined by ¹H-NMR spectroscopy ^b Determined by CSP-HPLC

It is also clear from these results that both the behaviour of the quinoline ring, and its orientation, are key to the overall success of a given catalyst. Thus careful observation of this might yield further clues as to the important features of the catalysts conformation.

4.9 Synthesis of an optimised catalyst

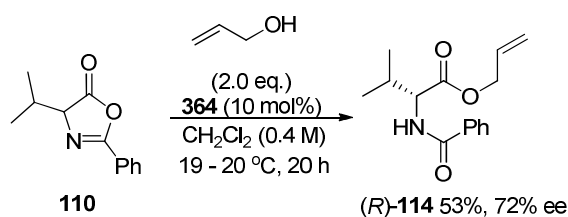
Having shown that appropriate substitution at C-2' was capable of increasing the enantioselectivity of a given catalyst which selected for the *R* isomer in the DKR of azlactone **110**, and that replacing the second ring of the naphthalene ring found in **147** with a C-6'' methoxy substituent (giving catalyst **339**) also gave catalysts possessing significantly increased selectivity and reactivity profiles, it was decided to combine both of these design features, with the expectation that they would act synergistically to produce an even more selective catalyst.

This was readily accomplished by reaction of **335** with phenyl lithium to give **363** followed by deprotection to afford the desired compound **364** in acceptable yield.



Scheme 4.39 Synthesis of a C-2' phenyl derivative of **340**

4.9.1 Evaluation of the optimised catalyst in the DKR of azlactones



Scheme 4.40 DKR of N-benzoyl valine derived azlactone promoted by **364**

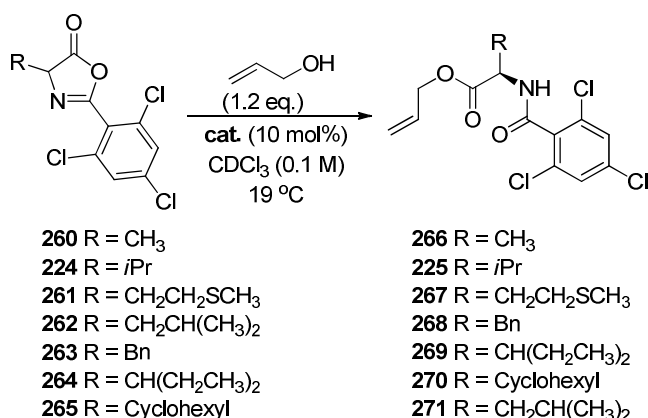
Scheme 4.40 describes the evaluation of catalyst **364**, which, pleasingly, proved to be more active than all catalysts previously synthesised in this work while simultaneously delivering the product with higher selectivity than the other catalysts tested.

4.10 Application of the optimised catalyst to the DKR of more activated azlactones

Having clearly synthesised catalysts with significantly improved activity and selectivity profiles compared to the first generation of catalysts described in chapter 2, it was decided that an exploration of their full potential was warranted. In the absence of another reaction which could readily be promoted with excellent enantioselectivity by this catalytic system, it was decided that a re-examination of the DKR of azlactones would allow for the synthetic utility of these catalysts to be shown to best advantage. Table 4.3 shows the results obtained from the evaluation of catalysts **364** and **350**.

Pleasingly, in the case of catalyst **364** it was possible to achieve results equal to those achieved with **147** at half the catalyst loading (entry 1). Unfortunately the large increase in enantioselectivity seen in the DKR of **110** did not translate into greater selectivity when more activated substrates were used. It was decided, because of this, to also evaluate **350** in the DKR of more activated azlactones since it had been shown to deliver greater product enantioselectivity without a large increase in rate.

Pleasingly, the use of catalyst **350** gave exceptional levels of enantioselectivity as exemplified in the DKR of **224** (entry 2). Catalysts **350** and **364** were then tested for a range of substrates.

Table 4.3 Evaluation of the performance of optimised catalysts **350** and **364**

entry	substrate (R =)	catalyst	time (h)	yield ^a (%)	ee ^b (%)
1	<i>i</i> Pr	364	120	92	90
2	<i>i</i> Pr	350	44	50	96
3	CH ₂ CH ₂ SCH ₃	364	20	97	76
4	CH ₂ CH ₂ SCH ₃	350	20	97	91
5	CH ₂ CH ₂ CH(CH ₃) ₂	350	60	98	90
6	benzyl	350	44	93	82
7	CH ₃	350	44	95	83
8	cyclohexyl	364	120	91	87
9	cyclohexyl	350	120	68	95
10	CH(CH ₂ CH ₃) ₂	364	120	91	88
11	CH(CH ₂ CH ₃) ₂	350	120	63	97

^aIsolated yield. ^bDetermined by CSP-HPLC

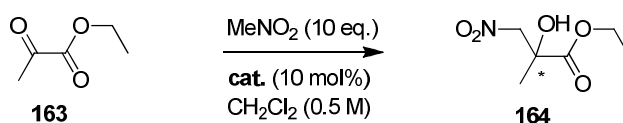
It was clear when challenged with less bulky substituents that catalyst **350** represented a significant improvement over **147**. In the case of the DKR of methionine derivative **261**, selectivity was significantly improved compared to the comparable result when **147** was used to catalyse the reaction (entry 3). Unfortunately, **364** which was capable of promoting

the reaction a much greater rate than **350**, resulted in lower enantioselectivity when challenged with unhindered substrates such as **261** (entry 4). In the case of further unhindered azlactones, (entries 5-7), only catalyst **350** was evaluated since the use of **364** offered no advantage. It was shown that the use of **350** provided the products with excellent enantioselectivity, >90% *ee* in the case of methionine derivative **261** and isoleucine derivative **262** (entries 4 and 5) and >80% *ee* in the case of **260** and **263** (entries 6 and 7).

In the case of hindered substrates **264** and **265**, the use of catalyst **364** was shown to be advantageous, delivering high enantioselectivity and product yield even at lower loadings of 10 mol%. Alternatively, the use of **350** to promote the reaction of these substrates resulted in exceptional product enantioselectivity of up to 97% *ee* (entries 8-11).

4.11 Further investigations into the behaviour of C-9 arylated quinine derivatives

Having optimised our catalyst on the basis of empirical data garnered from evaluating the effect of modifications to different parts of the overall structure, it was decided to more closely examine the behaviour of our synthesised catalysts. It was shown earlier (Section 2.4.3) that the preferred conformations of catalysts **130** and **147** were quite different, when analysed by ¹H NMR. It was speculated that the failure of these catalysts to promote the DKR of **110** more selectively at reduced temperature was a result of the change in relative populations of different conformations in which the various catalysts were present. In order to test this postulate, it was decided to evaluate the response of the ability of **130** and **147** to promote a more simple reaction to temperature. For this purpose the addition of nitromethane to ethyl pyruvate was chosen as the test reaction.

Table 4.4 The addition of nitromethane to ethyl pyruvate catalysed by **130** and **147**

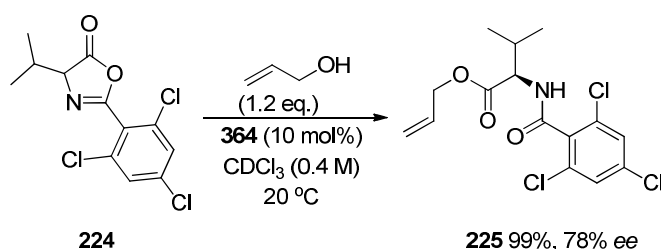
entry	catalyst	time (h)	temperature (°C)	conversion ^a (%)	ee ^b (%)
1	-	36	rt	0	-
2	130	36	rt	96	36
3	147	36	rt	63	-5
4	130	72	-10	100	61
5	147	72	-10	100	28

^a As determined by ¹H-NMR spectroscopy (entries 1-3), determined by TLC (entries 4-5). ^b As determined by CSP-HPLC.

Table 4.4 shows the evaluation of the effect of temperature on addition of nitromethane to **163**. The reaction fails to proceed in the absence of catalyst (entry 1). As shown before (Table 2.4), the reaction catalysed by **130** at room temperature delivers **164** with modest enantioselectivity (entry 2). In the presence of **147**, the product *ee* is marginal, however the opposite enantiomer is preferred (entry 3). Upon cooling, catalyst **130** furnishes the product with much higher selectivity (entry 4). Catalyst **147** also furnishes **164** with greater enantioselectivity at lower temperature however, a change in the preferred enantiomer is observed (entry 5). This strongly implies that the catalyst has (at least) two active conformations, which select for opposite enantiomers. In the case of the use of **147** the relative populations change upon lowering temperature, implying that the conformation of **147** which promotes the enantiomer favoured by **130**, is lower in energy.

It would appear that to fully capitalise on the full potential of the C-9 arylated quinine structure, modifications that confer complete rigidity would be necessary. Unfortunately,

increasing steric bulk around C-9 is a fundamentally limited strategy since we have shown that the synthetic route used to obtain these molecules has a limited tolerance for hindrance at the positions which would require bulky substituents to create increase rigidity. To further examine the behaviour of catalyst **364** while promoting the DKR of azlactones the reaction detailed in Scheme 4.41 was undertaken under observation by NMR at 10 minute intervals.



Scheme 4.41 The DKR of **224** promoted by **364**

It was found that upon addition of **224**, the catalyst appeared to open the azlactone by attack of the phenol generating two intermediates not present at the end of the reaction. Figure 4.7 shows this behaviour. The lowest spectrum (in blue) shows the catalyst with no other additives at room temperature. Minor changes can be seen upon addition of allyl alcohol (spectrum 2 - red). Once the azlactone is added, signals for the catalyst are progressively reduced and two further sets of related signals are observed (spectra 3 & 4). Once all of the azlactone is consumed the catalyst begins to revert to a form (more) closely resembling its original form before the addition of azlactone (spectra 5). *In situ* HSQC and HMBC analysis of these transient compounds (which could not be isolated) indicated the presence of corresponding amide N-H signals leading to speculation that catalysis could be occurring through a nucleophilic pathway.

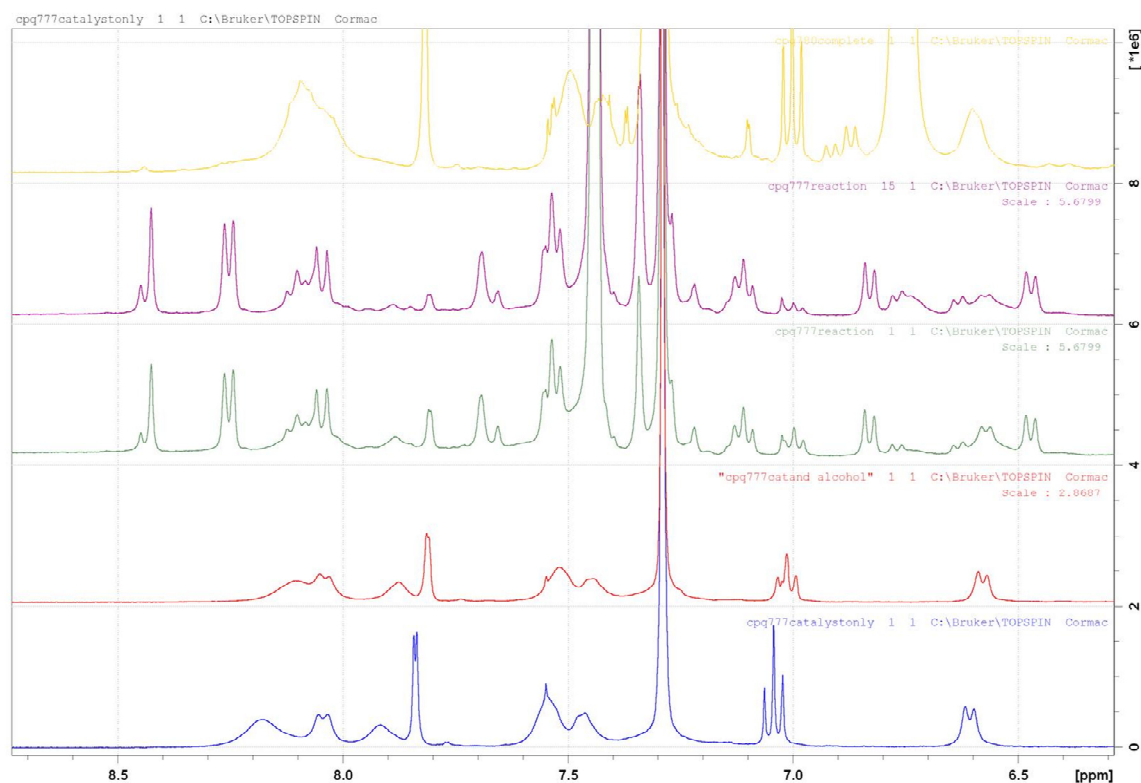
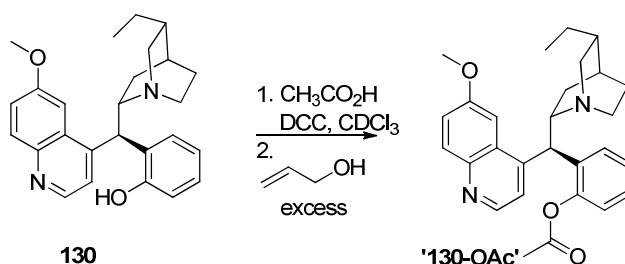


Figure 4.7 ^1H NMR spectra for the reaction detailed in **Scheme 4.41**

It was decided to investigate the possibility that the catalyst was operating as an acyl transfer catalyst rather than through the envisaged hydrogen bond donor acceptor mechanism. It was however not possible to isolate the intermediates which were observed by NMR. In order to examine the ability of catalysts of this type to act as acyl transfer agents the experiment shown in Scheme 4.42 was undertaken.



Scheme 4.42 Acetylation of **130** and subsequent exposure to allyl alcohol

It was observed that acetylation of **130** occurred however upon exposure to allyl alcohol no trans-esterification was shown to occur. This experiment was also repeated using *N*-(2,4,6-trichlorobenzoyl)sarcosine to allow for the possibility that the inclusion of an amide would result in significantly different reactivity. The resulting ester was also found to be unreactive in the presence of allyl alcohol.

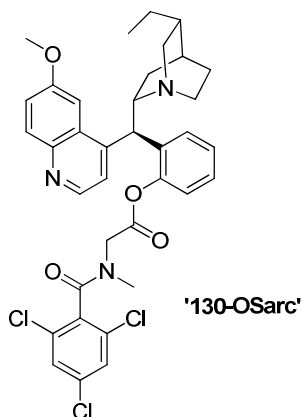


Figure 4.8 Catalyst **130** coupled to *N*-(2,4,6-trichlorobenzoyl)sarcosine

This allowed us to preclude an acyl transfer mechanism and allowed us to continue to consider only hydrogen bond mediated mechanisms.

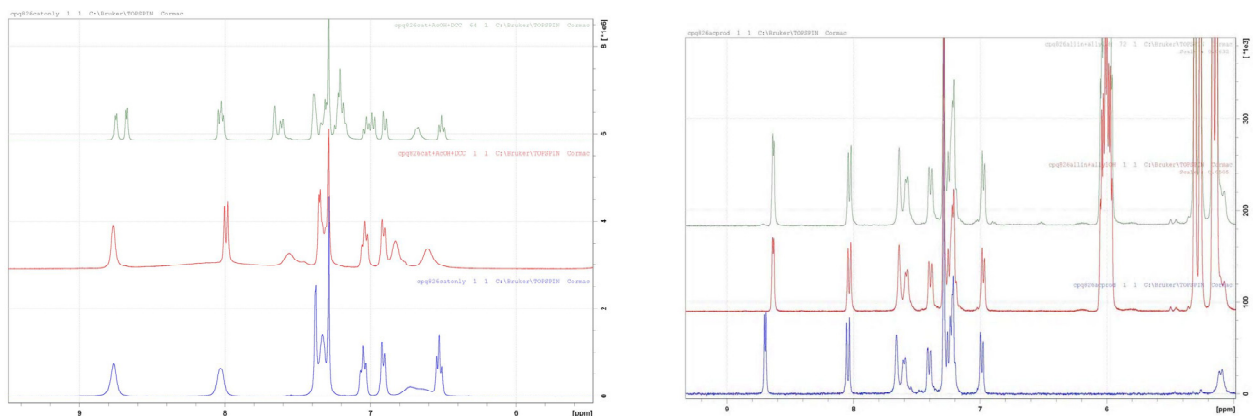


Figure 4.9 ^1H NMR spectra associated with the experiment detailed in **Scheme 4.42**.

The on the left are spectra for catalyst **130** in CDCl_3 (bottom), **130** after the addition of acetic acid (middle), followed by the addition of DCC (top) (Figure 4.9). Coupling between the phenol and acetic acid takes place. On the right, acetylated **130** is seen in isolation in the lower spectrum. The two upper spectra show that exposure to allyl alcohol does not result in transesterification even after prolonged exposure (48 h).

Interestingly though, it is not now clear which of the species present during the course of the DKR observed by NMR shown in Scheme 4.41 is in fact acting as a catalyst, as it may be the case that intermediates formed by the catalyst are also catalytically active. On this basis, given the complexity, it would seem unwise to offer a definitive mode of action for the catalysts. However it has still been possible to identify the importance of conformation to the behaviour exhibited by this class of catalyst.

4.12 Conclusions

The generation of a library of novel catalysts with significantly enhanced activity profiles compared to earlier catalysts of the same class has been described. Key considerations in the synthesis of quinine derivatives modified at several positions have been considered, with the synthetic scope of C-9 arylation explored in depth. Furthermore it has been possible, through systematic modification to identify features in the catalyst structure which are key to both the activity and selectivity profile of these catalysts. The importance of C-6'' and C-2' substitution and the relative unimportance of C-5'' substitution have been shown.

Detailed examination of the mode of action of the catalysts has allowed us to rule out acyl transfer as a catalyst mode of action and while it has not been possible to identify the catalytic mode of action beyond doubt, it has been shown that certain aspects of their free solution phase conformation correlate with changes in catalytic activity.

The systematic modification of the catalyst structure has been used to optimise catalyst performance in the DKR of azlactones. This has allowed for the DKR of even unhindered 2,4,6-trichlorophenyl substituted azlactones, with enantioselectivity in excess of 90% *ee*. In the case of hindered azlactones exceptional enantioselectivity could be achieved, with *ee* of up to 97% possible. While the scope of the catalysts described is not as tolerant of alternatives to the 2,4,6-trichlorophenyl group as other reported catalysts which can give comparable *ee* over a broader range of substrates, it should be noted that many of these require low temperatures to give optimal performance while the novel C-9 arylated quinine derived catalysts deliver the experienced *ee* at or very near ambient temperature.

5.0 Experimental: General

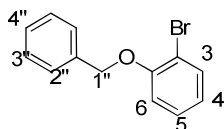
Proton Nuclear Magnetic Resonance spectra were recorded on a Bruker Avance 400 or 600 MHz spectrometer in CDCl_3 , C_6D_6 , MeOD or DMSO-d_6 . Chemical shifts were referenced relative to residual solvent chemical shifts and are reported in ppm and coupling constants in Hertz. Proton assignments were made using 1D and 2D TOCSY, COSY, NOESY, ROESY, EXSY HMBC and HSQC experiments as necessary. All spectra were recorded at 20 °C unless otherwise noted. Carbon NMR spectra were recorded on the same instruments (100 or 150 MHz) with total proton decoupling. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum One spectrophotometer. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated 60F254 slides, and visualised by UV irradiation, KMnO_4 , phosphomolybdic acid or anisaldehyde staining. Specific rotation measurements were made on a Rudolph research analytical Autopol IV instrument, and are quoted in units of $10^{-1}\text{degcm}^2\text{g}^{-1}$. Anhydrous THF was distilled over sodium-benzophenone ketyl radical before use. Methylene chloride, toluene and triethylamine were distilled from calcium hydride. Commercially available anhydrous *t*-butyl methyl ether was used. Methanol and allyl alcohol were distilled and stored of molecular sieves (3 Å). All reactions were carried out under a protective argon atmosphere unless otherwise stated. Analytical CSP-HPLC was performed on Daicel CHIRALCEL OD-H (4.6 mm x 25 cm), CHIRALPAK AD-H (4.6 mm x 25 cm) and AS (4.6 mm x 25 cm) columns. For all known compounds the spectral characteristics were in agreement with those reported in the literature.

5.1 Experimental data for chapter 2

5.2 Procedure A: General procedure for the benzylation of aromatic alcohols

A round bottom flask was charged with K_2CO_3 (1.6-3.0 eq.), acetone (0.33 M), benzylbromide (1.0 eq.) and the appropriate naphthol or phenol (1.0 eq.). This was heated under reflux overnight, protected by a CaCl_2 trap to exclude moisture. The mixture was cooled and partitioned between H_2O and CH_2Cl_2 . The aqueous layer was extracted with one further portion of CH_2Cl_2 and then the organic extracts were combined and washed with NaOH (aq. 5% w/v) and the solvent was removed *in vacuo*. The resulting compound was purified by flash chromatography using gradient elution (0-10% CH_2Cl_2 in hexane).

5.2.1 1-(Benzyloxy)-2-bromobenzene (**124**)

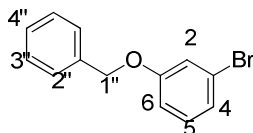


Procedure A was followed using 2-bromophenol (**121**, 5.00 g, 28.9 mmol), K_2CO_3 (11.75 g, 50 mmol), benzyl bromide (3.37 mL, 28.3 mmol) and acetone (55 mL) to give 1-(benzyloxy)-2-bromobenzene (**124**, 7.4 g, 98%) as a clear oil.²³²

δ_{H} (400 MHz, CDCl_3): 7.61 (1H, d, J 8.0 Hz, H-3), 7.53 (2H, d, J 7.2 Hz, H-2''), 7.44 (2H, app. t, H-3''), 7.36 (1H, t, J 7.2 Hz, H-4''), 7.27 (1H, app. t, H-5), 6.98 (1H, d, J 8.0 Hz, H-6), 6.88 (1H, app. t, J 7.6 Hz, H-4), 5.20 (2H, s, H-1'').

HRMS (TOF MS EI+): Found: 261.9993 (M^+ , $C_{13}H_{11}OBr$ Requires: 261.9993).

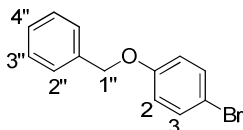
5.2.2 1-(Benzyloxy)-3-bromobenzene (**125**)



Procedure A was followed using 3-bromophenol (**122**, 5.10 g, 29.5 mmol), K_2CO_3 (6.80 g, 50.0 mmol), benzyl bromide (3.50 mL, 29.5 mmol) and acetone (55 mL) to give 1-(benzyloxy)-3-bromobenzene (**125**, 7.1 g, 92%) as an off-white solid. M.p. 60-61 °C. (Lit. m.p. 61-62 °C).²³³

δ_H (400 MHz, $CDCl_3$): 7.38-7.47 (m, 5H, H-2'', H-3'' and H-4''), 7.20-7.09 (m, 3H, H-2, H-4 and H-5), 6.91-6.95 (m, 1H, H-6), 5.07 (s, 2H, H-1'').

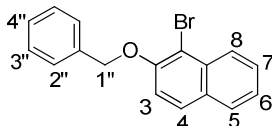
5.2.3 1-(Benzyloxy)-4-bromobenzene (**126**)



Procedure A was followed using 4-bromophenol (**123**, 2.00g 11.6mmol), K_2CO_3 (2.56 g, 18.5 mmol), benzyl bromide (1.37 mL, 11.6 mmol) and acetone (23 mL) used to give 1-(benzyloxy)-4-bromobenzene (**126**, 3.02 g, 99%) as an off-white solid. M.p. 59-60 °C. (Lit. m.p. 58-60 °C.)^{234,235}

δ_H (400 MHz, $CDCl_3$): 7.33-7.47 (m, 7H, H-3, H-2'', H-3'' and H-4''), 6.85-6.91 (m, 2H, H-2), 5.06 (s, 2H, H-1'').

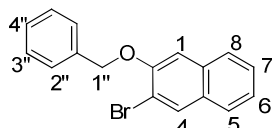
5.2.4 2-(Benzyloxy)-1-bromonaphthalene (**149a**)



Procedure A was followed using 1-bromo-2-naphthol (**149**, 4.46 g, 20.0 mmol), K_2CO_3 (8.29 g, 60.0 mmol), benzyl bromide (2.38 mL, 20.0 mmol) and acetone (40 mL) to give 2-(benzyloxy)-1-bromonaphthalene (**149a**, 6.20 g, 99%) as an off-white solid. M.p. 103-105 °C. (Lit. m.p. 104-106 °C).²³⁶

δ_H (400 MHz, $CDCl_3$): 8.28 (d, J 8.4, 1H, H-8), 7.76-7.84 (m, 2H, H-4 and H-5), 7.53-7.65 (m, 3H, H-7 and H-2''), 7.39-7.47 (m, 3H, H-3'' and H-6) 7.33-7.39 (m, 1H, H-4''), 7.31 (d, J 8.8, 1H, H-3) 5.35 (s, 2H, H-1').

5.2.5 2-(Benzyloxy)-3-bromonaphthalene (**151a**)



Procedure A was followed using 3-bromo-2-naphthol (**151**, 1.30 g, 5.83 mmol), K_2CO_3 (2.41 g, 17.48 mmol), benzyl bromide (686 μ L, 5.83 mmol) and acetone (19 mL) to give 2-(benzyloxy)-3-bromonaphthalene (**151a**, 1.79 g, 98%) as an off-white solid. M.p. 136-138 °C.

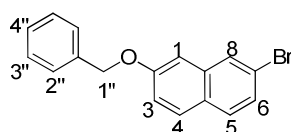
δ_H (400 MHz, $CDCl_3$): 8.12 (s, 1H, H-4), 7.73 (app. d, 2H, H-5 and H-8), 7.58 (d, J 7.2, 2H, H-2''), 7.50-7.35 (m, 5H, H-7, H-6, H-3'' and H-4''), 7.25 (s, 1H, H-1), 5.30 (s, 2H, H-1').

δ_{C} (100 MHz, CDCl_3): 152.1 (q), 135.9 (q), 133.0 (q), 131.9, 129.1 (q), 128.2, 128.0, 127.5, 126.5, 126.3, 126.2, 124.1, 113.4 (q), 107.8, 70.2.

ν_{max} (solid)/ cm^{-1} : 3031, 2871, 1620, 1585, 1499, 1454, 1379, 1326, 1245, 1216, 1181, 1019, 891, 858, 826, 753, 727, 697

HRMS (m/z +ES): Found: 335.0044 (M^+ + Na. $\text{C}_{17}\text{H}_{13}\text{OBrNa}$ Requires: 335.0047).

5.2.6 2-(Benzyloxy)-7-bromonaphthalene (**143**)



Procedure A was followed using 7-bromo-2-naphthol (**143a**, 1.00 g, 4.48 mmol), K_2CO_3 (1.86 g, 13.44 mmol), benzyl bromide (533 μL , 4.48 mmol) and acetone (15 mL) to give 2-(benzyloxy)-7-bromonaphthalene (**143**, 1.35 g, 96%) as an off-white solid. M.p. 102-103 $^{\circ}\text{C}$.

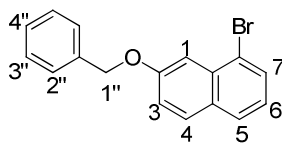
δ_{H} (400 MHz, CDCl_3): 7.90 (s, 1H, H-8), 7.74 (d J 8.8, 1H, H-4), 7.65 (d J 8.8, 1H, H-5), 7.51 (d J 7.6, 2H, H-2''), 7.47-7.41 (m, 3H, H-3'' and H-6), 7.41-7.36 (m, 1H, H-4''), 7.26 (dd J 2.6, 9.2, 1H, H-3), 7.14 (d J 2.6, 1H, H-1), 5.20 (2H, s, H-1'').

δ_{C} (100 MHz, CDCl_3): 157.3 (q), 136.5 (q), 135.6 (q), 129.3, 129.1, 128.6, 128.5, 128.0, 127.4, 127.3 (q), 126.9, 120.4 (q), 119.4, 106.2, 70.0.

ν_{max} (solid)/ cm^{-1} : 3052, 2881, 1621, 1589, 1500, 1448, 1388, 1357, 1243, 1199, 1169, 1001, 885, 844, 733, 696.

HRMS (m/z ES+): Found: 335.0049 (M^+ + Na. $\text{C}_{17}\text{H}_{13}\text{OBrNa}$ Requires: 335.0047).

5.2.7 2-(Benzyloxy)-8-bromonaphthalene (**141**)



Procedure A was followed using 8-bromo-2-naphthol (**137**, 1.20 g, 5.38 mmol), K_2CO_3 (2.23 g, 16.14 mmol), benzyl bromide (639 μ L, 5.38 mmol) and acetone (16 mL) to give 2-(benzyloxy)-8-bromonaphthalene (**141**, 1.03 g, 63%) as an off-white solid after a repeat purification by column chromatography (0-10% CH_2Cl_2 in hexane). M.p. 74-76 $^{\circ}C$.

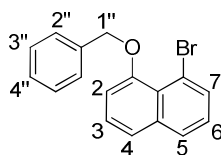
δ_H (400 MHz, $CDCl_3$): 7.80-7.75 (m, 3H, H-4, H-5 and H-7), 7.65 (d, 1H, J 2.4, H-1), 7.56 (d, 2H, J 7.6, H-2''), 7.45 (app. t, 2H, H-3''), 7.39 (t, 1H, J 7.6, H-4''), 7.29 (dd, J 2.4, 8.8, 1H, H-3), 7.22 (app. t, 1H, H-6), 5.26 (s, 2H, H-1'').

δ_C (100 MHz, $CDCl_3$): 157.6 (q), 136.1 (q), 132.8 (q), 129.9, 129.7 (q), 129.6, 128.2, 127.7, 127.4, 127.2, 123.6, 121.1 (q), 119.5, 106.3, 69.8.

ν_{max} (solid)/ cm^{-1} : 3029, 2938, 2878, 1624, 1596, 1505, 1446, 1377, 1323, 1261, 1232, 1169, 1125, 1013, 919, 901, 825, 772, 758, 719, 690, 656.

HRMS (TOF MS EI⁺): Found: 312.0149 (M^+ . $C_{17}H_{13}OBr$ Requires: 312.0150).

5.2.8 1-(Benzyloxy)-8-bromonaphthalene (**142**)



Procedure A was followed using 8-bromo-1-naphthol (**140**, 2.43 g, 10.95 mmol), K_2CO_3 (4.50 g, 32.8 mmol), benzyl bromide (1.56 mL, 13.14 mmol) and acetone (33 mL) to give 1-(benzyloxy)-8-bromonaphthalene (**142**, 0.82 g, 24%) as an off-white solid after a repeat purification by column chromatography (2-20% CH_2Cl_2 in hexane). M.p. 40-41 $^{\circ}C$.

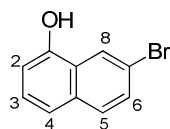
δ_{H} (400 MHz, CDCl_3): 7.83-7.75 (m, 2H, H-7 and H-5), 7.65 (d, 2H, J 8.0, H-2''), 7.50-7.33 (m, 5H, H-3, H-3'', H-4 and H-4''), 7.26 (app. t, J 8.0, 1H, H-6), 7.01 (d, J 9.2, 1H, H-2), 5.29 (2H, s, H-1'').

δ_{C} (100 MHz, CDCl_3): 154.2 (q), 136.7 (q), 136.3 (q), 132.6, 128.1, 127.6, 127.5, 127.4, 126.1, 126.0, 123.6 (q), 121.4, 116.3 (q), 108.4, 70.9.

ν_{max} (solid)/ cm^{-1} : 3055, 2930, 2878, 1617, 1556, 1447, 1362, 1260, 1236, 1193, 1103, 1046, 986, 896, 807, 762, 744, 694.

HRMS (m/z –ES): Found: 335.0053 ($\text{M}^+ + \text{Na}$. $\text{C}_{17}\text{H}_{13}\text{OBrNa}$ Requires: 335.0047).

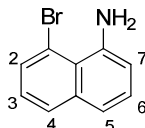
5.2.9 8-Bromo-2-naphthol (137)



8-Amino-2-naphthol (**136**, 1097 mg, 6.9 mmol) was added to a round bottom flask containing HBr (aq. 40%, w/w 40 mL) and cooled to 0 °C. To this a solution of NaNO_2 (476 mg, 6.9 mmol) in H_2O (20 mL), was added drop wise maintaining an internal temperature of less than 3 °C. This was stirred for a further 30 min and then added portion-wise to a solution of CuBr (900 mg) in HBr (aq. 48%, w/w 40 mL) at 60 °C and then was stirred for a further 30 min after the last addition. The solution was then allowed to cool and extracted with Et_2O (2 x 150 mL). The organic extracts were combined, dried over MgSO_4 and filtered and the solvent was removed *in vacuo*. The resulting brown solid was purified by column chromatography (1:1 to 1.6:1 CH_2Cl_2 -hexane) to give the title compound **137** (712 mg, 44%) as a light brown solid. M.p. 112-113 °C. (Lit. m.p. 113-114 °C).²³⁷

δ_{H} (400 MHz, CDCl_3): 7.79 -7.75 (m, 3H, H-5, H-6 and H-3), 7.58 (d J 2.4, 1H, H-8), 7.16-7.22 (m, 2H, H-4 and H-2) 5.38 (br s, 1H, OH)

5.2.10 1-Amino-8-bromonaphthalene (**139**)

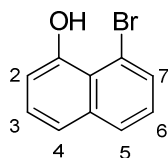


1,8 Diaminonaphthalene (**138**, 8.00 g, 50.6 mmol) was dissolved in a solution of H₂O (528 mL) and HCl (19.2 mL, aq. 37% w/w) at 90 °C and cooled to 0 °C. To this, a solution of NaNO₂ (3.58 g, 51.8 mmol), in H₂O (96 mL), cooled to 0 °C, was added drop wise, while maintaining a reaction temperature below 3 °C. This was stirred for 15 min after the final addition and then filtered to give a dark brown solid. This was washed with Et₂O and once dry immediately added portion wise to a round bottom flask containing CuBr (8.70 g, 60.6 mmol) in HBr (56 mL, AcOH 33% w/w) heated 100 °C, stirring rapidly. This was left to stand for 14 h at ambient temperature after the last addition and then NaOH (aq. 5N) was added until pH 10 was reached. The resulting mixture was extracted with CH₂Cl₂ (2 x 400 mL), the organic extracts were then combined and solvent was removed *in vacuo*. The residue was purified by column chromatography (30-50% CH₂Cl₂ in hexane) to give the title compound **139** (5.37 g, 48%) as a dark brown amorphous solid.^{208,238}

δ_{H} (400 MHz, CDCl₃): 7.72 (dd, 1H, J 1.2, 8.0, H-7), 7.65 (dd, J 1.2, 8.0, 1H, H-5), 7.25-7.31 (m, 2H, H-3 and H-4), 7.17 (app. t, 1H, H-6), 6.74-6.80 (m, 1H, H-2), 4.80-5.60 (br s, 2H, H-NH₂).

HRMS (m/z +ES): Found: 221.9915 (M⁺ + H. C₁₀H₉NBr Requires: 221.9918).

5.2.11 8-Bromo-1-naphthol (**140**)

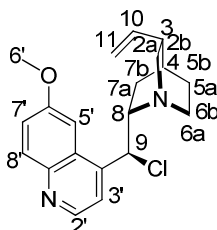


A round bottom flask was charged with 8-bromo-1-aminonaphthalene (**139**, 3.35 g, 15.15 mmol), H₂O (16.8 mL) and H₂SO₄ (16.8 mL conc.) and stirred at room temperature until a solution was obtained. This was cooled to 0 °C, and a solution of NaNO₂ (1.05 g, 15.91 mmol) in H₂O (10 mL) at 0 °C was added drop wise. This was stirred for a further 15 min and urea was added in small portions until no further effervescence was observed. The resulting solution was then added portion wise to a round bottom flask containing H₂SO₄ (141 mL aq. 52% v/v) at 60 °C and heated for a further h after the last addition. The resulting solution was allowed to cool to room temperature, and extracted with Et₂O (2 x 200 mL). The organic extracts were combined, washed with brine (100 mL), dried over MgSO₄ and filtered and the solvent was removed *in vacuo* to give **140** (2.70g, 80%) as a light blue solid. M.p. 58-59 °C. (Lit. m.p.56 °C)^{239 240}

δ_{H} (400 MHz, CDCl₃): 8.10 (br s, 1H, H-OH), 7.81 (d, J 8.0, 1H, H-7), 7.66 (d, J 8.0, 1H, H-5), 7.40-7.50 (m, 2H, H-2 and H-3), 7.25 (app. t, J 8.0, 1H, H-6), 7.10 (dd, J 0.4, 8.0, 1H, H-4).

HRMS (TOF MS EI⁺): Found: 221.9675 (M⁺. C₁₀H₇OBr Requires: 221.9680).

5.2.12 9-Epi-chloro(deoxy)quinine (Q22a)



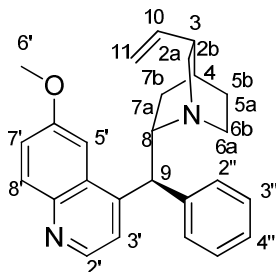
Quinine (**1**, 10.60 g, 32.7 mmol) was added portion-wise to a round bottom flask containing SOCl_2 (20.0 mL, 276 mmol) at 0 °C. This was allowed to warm to room temperature and stirred overnight. The solution was then quenched by adding it carefully to a saturated aqueous solution of Na_2CO_3 (500 mL), adding solid Na_2CO_3 as necessary to maintain a pH >8. This solution was then extracted with CH_2Cl_2 (3 x 200 mL) and the combined organics dried over MgSO_4 . Solvent was removed *in vacuo* and the resulting solid purified by flash chromatography (98:2 EtOAc- NH_3 (aq.) 35% w/v) giving **Q22a** (9.3 g, 83%) as a white solid. M.p. 149-150 °C. (Lit. m.p. 151 °C).¹⁰⁹

δ_{H} (400 MHz, DMSO-d_6): 8.77 (d, J 4.8, 1H, H-2'), 7.99 (d, J 9.2, 1H, H-8'), 7.66-7.73 (m, 2H, H-3' and H-5'), 7.48 (dd, J 2.4, 9.2, 1H, H-7'), 5.75-6.02 (br s, 2H, H-10 and H-9), 4.93-5.09 (m, 2H, H-11), 3.98 (s, 1H, H-6'), 3.48-3.60 (br s, 1H, H-8), 3.27-3.36 (br s, 1H, H-6 α), 3.14-3.23 (m, 1H, H-2 β), 2.61-2.79 (m, 2H, H-2 α and H-6 β), 2.20-2.29 (br s, 1H, H-3), 1.40-1.62 (m, 4H, H-4, H-5 α , H-5 β and H-7 β), 0.53-0.67 (br s, 1H, H-7 α).

5.2.13 Procedure B: General procedure for the formation of Grignard reagents

A suspension of freshly ground magnesium turnings in dry THF (1.01 eq., 0.25 M) under argon atmosphere was placed in a round bottomed flask. Aryl bromide (1.0 equiv.) was added and the reaction was heated under reflux until all magnesium dissolved (30- 240 minutes). 1,2-dibromoethane (4-5 drops) was added to the mixture if Grignard formation failed to occur spontaneously after 1 hour. The resulting solution was used immediately. Phenylmagnesiumbromide solution in (2.0 M in THF) was purchased from Aldrich.

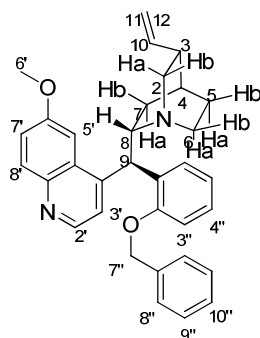
5.2.14 (8*S*,9*S*)-6'-methoxy-9-phenyl-cinchonan (**Q23**)



Phenylmagnesiumbromide in THF (3.0 mL, 2.0 M, 6.0 mmol) was added to a solution of **Q22a** (2.0 mmol, 686 mg) in THF (10 mL) and heated under reflux for 4 h. The solution was cooled and a saturated solution of NH₄Cl ((aq.), 30 mL) was added. This was extracted with CH₂Cl₂ (2 x 100 mL), organics were combined, dried over MgSO₄ and solvent was removed at reduced pressure. This was purified by column chromatography (30:20:1 hexane-EtOAc-NEt₃) to give **Q23** (500 mg, 65%) as an off-white solid. M.p. 147-149 °C. (Lit. m.p. 145-152°C).¹⁰⁹

δ_{H} (600 MHz, C₆D₆): 8.73 (1H, d, J 4.8, H-2'), 7.90 (1H, d, J 9.2, H-8'), 7.72-7.69 (2H, m, H-5', H-3'), 7.47 (2H, d, J 7.8, H-2''), 7.37 (1H, dd, J 9.0, 1.8, H-7'), 7.19 (2H, t, J 7.2, H-3''), 7.07, (1H, t, J 7.2, H-4''), 6.00-6.11 (1H, m, H-10), 5.04 (2H, app. dd, J 17.4, 29.4, H-11), 4.85 (1H, d, J 10.8, H-9), 3.97 (3H, s, 6'), 3.81 (1H, s, H-8), 3.42 (1H, s, H-6 α), 3.00 (1H, app. t, H-2 β), 2.59 (1H, br d, J 10.2, H-2 α), 2.47 (1H, app. t, H-6 β), 2.23 (1H, s, H-3), 1.89 (1H, s, 7 β), 1.54-1.65 (2H, m, H-4,5 α), 1.46 (1H, s, H-5 β), 0.70 (1H, s, H-7 α).

5.2.15 (2*S*)-2-((*R*)-(2-(benzyloxy)phenyl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (127)



A solution of 9-*epi*-chloroquinine (**Q22a**, 3.13 g, 9.12 mmol) in dry THF (36.5 mL) was added to a round bottom flask containing a solution of 1-((2-bromomagnesiumphenoxy)methyl)benzene (2.62 g, 9.12 mmol) in dry THF (36.5 mL) (prepared using general procedure B), and heated under reflux overnight under a protective argon atmosphere. The resulting solution was cooled and a saturated aqueous solution of NH₄Cl (50 mL) was added. The resulting mixture was then extracted with CH₂Cl₂ (2 x 200 mL), and the organic extracts were combined, dried over MgSO₄ and solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (25:25:1 hexane-EtOAc-NEt₃) to give **127** (3.25 g, 88%) as an off-white solid. $[\alpha]_D^{20} = -44.1$ (c 0.085, CHCl₃). M.p. 63-65 °C.

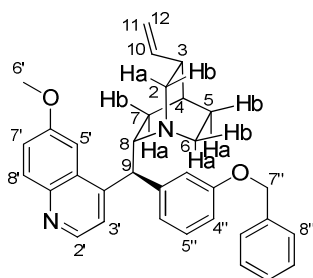
δ_H (400 MHz, CDCl₃): 8.70 (d, *J* = 4.0, 1H, H-2'), 7.97 (d, *J* = 9.2, 1H, H-8'), 7.59 (s, 1H, H-5') 7.10-7.46 (m, 9-H, H-7', H-3', H-3'', H-5'', H-8'', H-9'', H-10''), 6.88-6.99 (m, 2H, H-6'', H-4''), 5.87-5.99 (m, 1H, H-10), 5.27-5.39 (br d, 1H, H-9), 5.00-5.13 (m, 4H, H-11, H-12, H-7''), 3.78-3.66 (br s, 1H, H-8), 3.61 (s, 3H, H-6'), 3.39-3.53 (br s, 1H, H-6a), 3.16-3.32 (br s, 1H, H-2b), 2.64-2.84 (m, 2H, H-2a, H-6b), 2.24-2.33 (br s, 1H, H-3), 1.74-1.88 (br s, 1H, H-7b), 1.63-1.73 (br s, 1H, H-4), 1.47-1.64 (m, 2H, H-5a, H-5b), 0.98-0.84 (m, 1H, H-7a).

δ_C (100 MHz, CDCl₃): 158.4 (q), 157.3 (q), 147.2, 146.1 (q), 144.3 (q), 143.3 (q), 141.5, 136.5 (q), 131.5, 129.0, 128.4 (q), 128.1, 127.5, 127.2, 120.5, 120.3, 119.2, 114.9, 113.9, 111.8, 101.6, 76.8, 69.5, 59.1, 56.1,

$\nu_{\max}$ (solid)/cm⁻¹: 2928, 2860, 1620, 1586, 1507, 1450, 1225, 1031, 916, 850, 747, 696.

HRMS (ES⁺): calcd. for [C₃₃H₃₄N₂O₂ + H]⁺ requires: 491.2699; found: 491.2693

5.2.16 (2S)-2-((S)-3-(benzyloxy)phenyl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (**128**)



A solution of 9-*epi*-chloroquinine (**Q22a**, 1.71 g, 5.00 mmol) in dry THF (20 mL) was added to a round bottom flask containing a solution of 1-((3-bromomagnesiumphenoxy)methyl)benzene (1.58 g, 5.50 mmol) in dry THF (20 mL) (prepared using general procedure B), and heated under reflux for 4 h under a protective argon atmosphere. The resulting solution was cooled and a saturated aqueous solution of NH₄Cl (25 mL) was added. The resulting mixture was extracted twice with CH₂Cl₂ (2 x 150 mL), the organic extracts were combined, dried over MgSO₄ and solvent was removed under reduced pressure. The resulting material was purified by column chromatography (98:2 EtOAc-NH₃ (aq. 35% w/w)) to give **128** (1.14 g, 48%) as an off-white solid. M.p. 122-123 °C. [α]_D²⁰ = -10.80 (c 0.136, CHCl₃).

δ_{H} (600 MHz, CDCl₃): 8.77 (d, *J* = 4.8, 1H, H-2'), 8.03 (d, *J* = 9.0, 1H, H-8'), 7.55 (br s, 1H, H-5'), 7.46-7.31 (m, 7H, H-8'', H-9'', H-10'', H-3', H-7'), 7.21 (app. t, 1H, H-5''), 7.03 (d, *J* = 7.8, 1H, H-6''), 6.98 (s, 1H, H-2''), 6.79 (d, *J* = 8.4, 1H, H-4''), 6.02-5.91 (d, *J* = 11.2, 1H, H-9), 5.14-5.06 (m, 2H, H-11, H-12), 5.00 (s, 2H, H-6'), 4.76 (br s, 1H, H-9), 3.99 (s, 3H, H-6'), 3.71 (br s, 1H, H-8), 3.34 (br s, 1H, H-6a), 3.30-3.23 (m, 1H, H-2b), 2.86-2.73 (m, 2H, H-2a, H-6b), 2.37-2.28 (m,

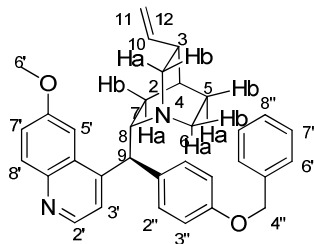
1H, H-3), 1.98-1.86 (br s, 1H, H-7b), 1.76-1.71 (s, 1H, H-4), 1.67-1.55 (m, 2H, H-5a, H-5b), 0.89-0.82 (m, 1H, H-7a).

δ_C (100 MHz, $CDCl_3$): 157.1 (q), 155.6 (q), 147.0, 144.1 (q), 141.7, 136.2 (q), 132.7, 131.1 (q), 130.1 (q), 129.0, 128.1, 128.1, 127.6, 127.2, 120.8, 120.7, 119.9, 119.9, 113.8, 111.4, 102.1, 76.8, 69.9, 59.5, 56.0, 54.7, 40.9, 39.2, 27.9, 27.5, 27.5.

ν_{max} (solid)/ cm^{-1} : 2946, 2831, 1619, 1581, 1485, 1249, 1224, 1023, 916, 837, 771, 750, 698.

HRMS (ES⁺): calcd. for: $[C_{33}H_{34}N_2O_2 + H]^+$ requires: 491.2699; found 491.2708.

5.2.17 (2*S*)-2-((*S*)-(4-(benzyloxy)phenyl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (**129**)



A solution of 9-*epi*-chloroquinine (**Q22a**, 5.14 g, 15.0 mmol) in dry THF (60 mL) was added to a round bottom flask containing a solution of 1-((4-bromomagnesiumphenoxy)methyl)benzene (5.62 g, 19.5 mmol) in dry THF (60 mL) (prepared using general procedure E), and heated under reflux over night under a protective argon atmosphere. The resulting solution was cooled and a saturated aqueous solution of NH_4Cl (100 mL) was added. The resulting mixture was extracted twice with CH_2Cl_2 (2 x 200 mL), the organic extracts were combined, dried over $MgSO_4$ and solvent was removed under reduced pressure. The resulting material was purified by column chromatography (40:10:1 hexane-EtOAc- NEt_3) to give **129** (6.33 g, 86%) as an off-white solid. M.p. 50-52 °C. $[\alpha]_D^{20} = -128.5$ (c 0.071, $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 8.79 (d, $J = 4.8$, 1H, H-2'), 8.04 (d, $J = 9.6$, 1H, H-8'), 7.54 (s, 1H, H-5'), 7.46-7.26 (m, 9H, H-3', H-7', H-2'', H-6'', H-7'', H-8''), 6.90

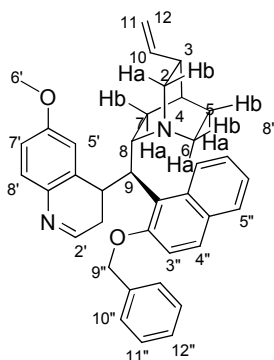
(d, $J = 8.4$, 2H, H-3''), 6.06-5.89 (m, 1H, H-10), 5.16-5.06 (m, 2H, H-11, H-12), 4.98 (s, 2H, H-4''), 4.76 (d, $J = 10$, 1H, H-9), 3.99 (s, 3H, H-6'), 3.80-3.64 (br s, 1H, H-8), 3.43-3.23 (m, 2H, H-6a, H-2b), 2.88-2.73 (m, 2H, H-6b, H-2a), 2.38-2.28 (br s, 1H, H-3), 2.01-1.89 (br s, 1H, H-7b), 1.73 (br s, 1H, H-4), 1.69-1.52 (br s, 2H, H-5a, H-5b), 0.93-0.81 (m, 1H, H-7a).

δ_{C} (100 MHz, CDCl_3): 157.3 (q), 157.0 (q), 147.2, 146.6 (q), 144.4 (q), 141.5, 136.6 (q), 134.0 (q), 131.5, 128.4, 128.1, 127.5, 127.1, 120.5, 119.1, 114.4, 113.9, 101.7, 76.8 (q), 69.4, 59.2, 56.2, 55.1, 48.2, 40.5, 39.1, 28.4, 27.7, 27.6.

ν_{max} (solid)/ cm^{-1} : 2936, 2202, 1620, 1586, 1507, 1471, 1228, 1027, 907, 826, 726, 696, 675.

HRMS (ESI⁺): Calcd. for $[\text{C}_{33}\text{H}_{34}\text{N}_2\text{O}_2 + \text{H}]^+$ requires 491.2699; found 491.2682.

5.2.18 (2*S*)-2-((*R*)-(2-(benzyloxy)naphthalen-1-yl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (**150**)



A solution of 2-(benzyloxy)-1-bromomagnesiumnaphthalene (1.68 g, 5.00 mmol) in THF (9.0 mL) was added to **Q22a** (686 mg, 2.00 mmol) in THF (9 mL) to give **150** (895 mg, 82%) after workup and purification by flash chromatography (40:10:1 to 50:50:1 hexane-EtOAc- NEt_3). M.p. 103-104 °C. $[\alpha]_{\text{D}}^{20} = +198.5$ (c 0.125, CHCl_3).

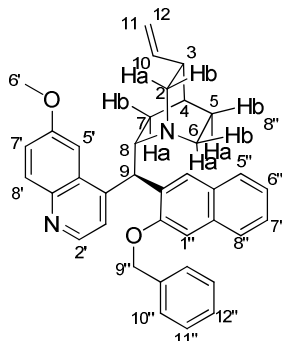
δ_{H} (600 MHz, CDCl_3): 8.83-8.90 (br s, 0.24H, H-8''), 8.72 (d, $J = 7.8$, 0.76H, H-8''), 8.42 (d, $J = 4.8$, 0.76H, H-2'), 8.32 (d, $J = 8.4$, 0.24H, H-2'), 7.91 (d, $J = 9.0$, 1H, H-8'), 7.80-7.87 (m, 1H, H-5''), 7.69-7.79 (m, 1H, H-4''), 7.61-7.68 (m, 1H, H-7''), 7.35-7.55 (m, 6H, H-6'', H-10'', H-11'', H-12''), 7.28-7.34 (m, 1H, H-5'), 7.15-7.26 (m, H-3', 3H, H-3'', H-7'), 6.06-6.17 (m, 0.24H, H-10), 5.85-6.01 (m, 0.76H, H-10), 5.54-5.63 (m, 0.24H, H-9), 5.37 (d, $J = 11.4$, 0.76H, H-9), 5.04-5.22 (m, 3H, H-9'', H-12), 4.76-4.89 (m, 1H, H-11), 4.36-4.59 (m, 1H, H-8), 3.72 (s, 0.76H, H-6'), 3.29-3.57 (m, 3.28H, H-6a, H-6'), 3.03-3.23 (m, 1H, H-2b), 2.78-2.88 (m, 0.76H, H-3), 2.56-2.74 (m, 1H, H-3, H-6b), 2.41-2.52 (m, 0.24H, H-6b), 2.23-2.34 (m, 1H, H-2a), 2.08-2.16 (m, 1H, H-7b), 1.65-1.88 (m, 2H, H-4, H-5a), 1.47-1.60 (m, 0.76H, H-5b), 1.34-1.46 (m, 0.24H, H-5b), 1.13-1.22 (m, 0.24H, H-7b), 0.91-1.02 (m, 0.76H, H-7b).

δ_{C} (100 MHz, CDCl_3): 157.3 (q), 155.1 (q), 146.8, 144.6 (q), 144.4 (q), 142.5, 136.6 (q), 133.3 (q), 131.6, 130.0, 129.6 (q), 129.5, 128.7, 128.6, 128.5, 127.3, 126.9, 123.5, 123.0, 122.8, 121.2, 114.6, 114.3, 102.2, 77.3, 70.6 (q), 56.8 (q), 56.4, 55.7, 44.6, 42.3, 40.1, 30.5, 28.3, 28.0. (^{13}C resonances associated with the major rotamer only)

ν_{max} (solid)/ cm^{-1} : 2924, 2860, 1620, 1508, 1453, 1430, 1237, 1088, 1024, 907, 803, 729, 696.

HRMS (ESI⁺): Calcd. for $[\text{C}_{37}\text{H}_{36}\text{N}_2\text{O}_2 + \text{H}]^+$ requires 541.2855; found 541.2855.

5.2.19 (2*S*)-2-((*R*)-(2-(benzyloxy)naphthalen-3-yl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (152**)**



Procedure as for **150** using a solution of 2-(benzyloxy)-3-bromomagnesiumnaphthalene (739 mg, 2.19 mmol) in THF (6.0 mL) and 9-*epi*-chloroquinine (500 mg, 1.46 mmol) in THF (6.0 mL) to give **152** (310 mg, 39%).

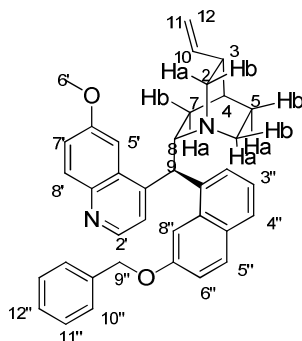
δ_{H} (400 MHz, CDCl_3): 8.71 (d, $J = 3.6$, 1H, H-2'), 7.98 (d, $J = 8.8$, 1H, H-8'), 7.79-7.85 (br s, 1H, H-5'), 7.66 (d, $J = 8.0$, 1H, H-5''), 7.73 (d, $J = 8.0$, 1H, H-8''), 7.57 (d, $J = 2.4$, 1H, H-4''), 7.27-7.41 (m, 9H, H-3', H-7', H-6'', H-7'', H-10'', H-11'', H-12''), 7.23 (s, 1H, H-1''), 5.89-6.01 (m, 1H, H-10), 5.37-5.50 (br s, 1H, H-9), 5.05-5.27 (m, 4H, H-11, H-12, H-9''), 3.80-3.95 (br s, 1H, H-8), 3.66 (s, 3H, H-6'), 3.42-3.56 (br s, 1H, H-6a), 3.21-3.36 (br s, 1H, H-2b), 2.69-2.93 (m, 2H, H-6b, H-2a), 2.27-2.41 (br s, 1H, H-3), 1.81-1.96 (br s, 1H, H-7b), 1.49-1.79 (m, 3H, H-4, H-5a, H-5b), 0.96-1.10 (br s, 1H, H-7a).

δ_{C} (100 MHz, CDCl_3): 157.1 (q), 154.5 (q), 147.0, 144.2 (q), 141.8, 135.8 (q), 132.9 (q), 132.0 (q), 131.1, 129.0 (q), 128.6 (q), 128.4 (q), 128.1, 127.8, 127.7, 127.5, 127.2, 125.9, 125.5, 123.3, 120.8, 120.1, 113.8, 106.14, 102.0, 76.8, 70.0, 59.7, 56.2, 54.7, 41.0, 39.3, 27.8, 27.6, 27.5.

ν_{max} (solid)/ cm^{-1} : 2934, 2863, 1617, 1505, 1359, 1240, 1183, 1080, 1035, 915, 851, 739, 712.

HRMS (ESI⁺): Calcd. for $[\text{C}_{37}\text{H}_{36}\text{N}_2\text{O}_2 + \text{H}]^+$ requires 541.2855; found 541.2858.

5.2.20 (2*S*)-2-((*S*)-(2-(benzyloxy)naphthalen-8-yl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (144)



Procedure as for **150** using a solution of 2-(benzyloxy)-8-bromomagnesiumnaphthalene (739 mg, 2.19 mmol) in THF (6.0 mL), 9-*epi*-chloroquinine (500 mg, 1.46 mmol) and THF (6.0 mL) to give **144** (895 mg, 39%). M.p. 62-64 °C. $[\alpha]_D^{20} = -124.5$ (c 0.068, CHCl₃).

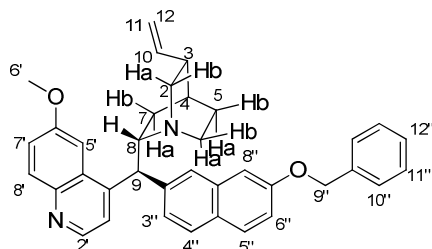
δ_H (400 MHz, CDCl₃): 8.62 (d, *J* = 4.4, 1H, H-2'), 8.09 (d, *J* = 9.6, 1H, H-8'), 7.95-8.02 (br s, 1H, H-5'), 7.80 (d, *J* = 6.8, 1H, H-7''), 7.70 (app. t, 2H, H-11''), 7.23-7.52 (m, 9H, H-3', H-7', H-1'', H-4'', H-5'', H-6'', H-10'', H-12''), 7.11 (d, *J* = 8.4, 1H, H-3''), 5.89-6.04 (m, 1H, H-10), 5.56 (d, *J* = 9.6, 1H, H-9), 4.91-5.18 (m, 4H, H-9'', H-11, H-12), 4.33 (app. d, 1H, H-8), 3.84-3.99 (m, 4H, H-6', H-6a), 3.18-3.36 (m, 3H, H-2a, H-2b, H-6b), 2.90-3.02 (m, 1H, H-3), 2.69-2.82 (m, 1H, H-6b), 2.28-2.41 (m, 1H, H-7b), 1.53-1.83 (m, 3H, H-4, H-5a, H-5b), 1.24-1.37 (m, 1H, H-7a).

δ_C (100 MHz, CDCl₃): 152.9 (q), 151.6 (q), 142.7, 139.3 (q), 136.7, 131.4 (q), 128.1 (q), 127.4, 125.5, 124.5 (q), 123.8 (q), 123.4, 123.3 (q), 122.8, 122.3, 122.1 (q), 122.0, 120.6, 118.3, 116.1, 115.3, 112.9, 109.3, 98.3, 97.2, 64.6, 54.4, 50.9, 50.5, 50.4, 36.3, 34.4, 23.1, 22.7, 21.8.

$\nu_{\max}$ (solid)/cm⁻¹: 2937, 2862, 1621, 1508, 1449, 1361, 1245, 1214, 1027, 908, 827, 727, 695.

HRMS (ESI⁺): Calcd. for [C₃₇H₃₆N₂O₂ + H]⁺ requires 541.2855; found 541.2848.

5.2.21 (2*S*)-2-((*S*)-(2-(benzyloxy)naphthalen-7-yl)(6-methoxyquinolin-4-yl)methyl)-8-ethylquinuclidine (146)



Procedure as for **150** using a solution of 2-(benzyloxy)-7-bromomagnesiumnaphthalene (1.01 g, 3.00 mmol) in THF (9.0 mL) and 9-*epi*-chloroquinine (686 mg, 2.00 mmol) in THF (9.0 mL) to give **146** (460 mg, 43%). M.p. 162-163 °C. $[\alpha]_D^{20} = -168.8$ (c 0.201, CHCl₃).

δ_H (400 MHz, CDCl₃): 8.80 (d, *J* = 4.4, 1H, H-2'), 8.02 (d, *J* = 9.2, 1H, H-8'), 7.63-7.71 (m, 3H, H-3'', H-4'', H-8''), 7.56-7.62 (br s, 1H, H-5'), 7.46-7.51 (m, 3H, H-3', H-10''), 7.31-7.45 (m, 5H, H-7', H-5'', H-11'', H-12''), 7.09-7.18 (m, 2H, H-1'', H-6''), 5.93-6.05 (m, 1H, H-12), 5.07-5.22 (m, 4H, H-9'', H-11), 4.93 (d, *J* = 10.8, 1H, H-9), 3.80-4.08 (m, 4H, H-6', H-8), 3.36-3.51 (br s, 1H, H-6a), 3.21-3.33 (m, 1H, H-2b), 2.74-2.90 (m, 2H, H-2a, H-6b), 2.29-2.41 (br s, 1H, H-3), 1.89-2.07 (br s, 1H, H-7b), 1.74-1.82 (br s, 1H, H-4), 1.56-1.73 (m, 2H, H-5a, H-5b), 0.89-1.03 (m, 1H, H-7a).

δ_C (100 MHz, CDCl₃): 157.3 (q), 156.5 (q), 147.2, 146.0 (q), 144.4 (q), 141.4, 139.7 (q), 136.5 (q), 134.1 (q), 131.5, 128.7, 128.4 (q), 128.1, 127.6 (q), 127.5, 127.0, 125.3, 123.6, 120.5, 118.3, 114.0, 106.7, 101.8, 85.0, 76.8, 69.5, 59.2, 56.1, 55.1, 49.3, 40.6, 39.0, 28.4, 27.6, 27.5.

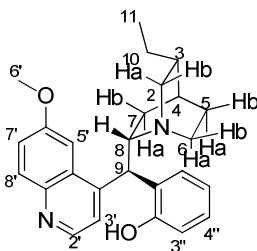
$\nu_{\max}$ (solid)/cm⁻¹: 2944, 2859, 1628, 1508, 1452, 1377, 1256, 1184, 1025, 1008, 827, 728.

HRMS (ESI⁺): Calcd. for [C₃₇H₃₆N₂O₂ + H]⁺ requires 541.2855; found 541.2859.

5.2.22 Procedure C: General procedure for the deprotection of catalysts by hydrogenation

The benzylated catalyst precursors were placed in a round bottom flask with solvent and the flask was flushed with argon. Pd/C (10 mol%) was added, the flask was evacuated, placed under an atmosphere of hydrogen gas at 1-3 atmospheres and stirred for 2-5 d. The flask was then evacuated and filled with an inert atmosphere. The mixture was filtered through a layer of Celite with CH₂Cl₂ and/or MeOH or EtOH as the eluent. The solvent was removed *in vacuo* to afford the product.

5.2.22.1 (8*S*,9*R*)-9-(2-hydroxyphenyl)-6'-methoxy-10,11-dihydro-cinchonan (130)



Procedure C was followed using **127** (3.20 g, 6.71 mmol), 10% Pd/C (752 mg, 10 mol%), and EtOH (160 mL) to give **130** (2.66 g, 99%). M.p. 121-122 °C. $[\alpha]_D^{20} = -43.0$ (c 0.123, CHCl₃).

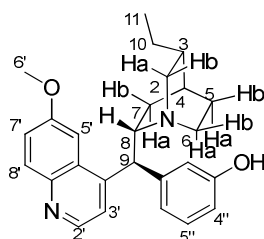
δ_H (600 MHz, DMSO-d₆): 9.92 (br s, 1H, OH), 8.70 (d, J = 4.8, 1H, H-2'), 7.96 (br s, 1H, H-5'), 7.87 (d, J = 9.6, 1H, H-8'), 7.69 (d, J = 4.8, 1H, H-3'), 7.34 (dd, J = 2.4, 9.0, 1H, H-7'), 7.13 (d, J = 7.2, 1H, H-6''), 6.87 (t, J = 7.2, 1H, H-4''), 6.76 (d, J = 8.4, 1H, H-3''), 6.60 (t, J = 7.2, 1H, H-5''), 3.93 (s, 3H, H-6'), 3.71 (d, J = 7.8, 1H, H-8), 3.46 (br s, 1H, H-6a), 2.96 (app. t, 1H, H-2b), 2.47 (br s, 1H, H-6b), 2.29 (app. d, 1H, H-2b), 1.89 (br s, 1H, H-7b), 1.49-1.54 (m, 2H, H-5b, H-4), 1.3-1.48 (m, 4H, H-3, H-5a, H-10), 0.86 (t, J = 7.2, 3H, H-11), 0.65 (1H, br s, H-7a).

δ_C (150 MHz, DMSO- d_6): 157.5 (q), 154.7 (q), 148.1 (q), 147.9, 144.3 (q), 131.4, 129.7 (q), 129.4 (q), 128.6, 126.8, 121.3, 120.3, 119.3, 115.2, 103.3, 59.3, 58.0, 55.8, 41.9, 41.1, 37.1, 29.2, 28.6, 27.3, 26.0, 12.4.

$\nu_{\max}$ (neat) cm^{-1} : 2928, 2969, 1621, 1586, 1508, 1454, 1237, 1029, 844, 827, 750, 711, 678.

HRMS (ESI+): Calcd. for $[\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_2 + \text{H}]^+$ requires 403.2386; found 403.2378.

5.2.23 (8*S*,9*S*)-9-(3-hydroxyphenyl)-6'-methoxy-10,11-dihydro-cinchonan (**131**)



Procedure C was followed using **128** (800 mg, 1.68 mmol), 10% Pd/C (188 mg, 10 mol%), and EtOH (40 mL) to give **131** (673 mg, 99%). M.p. 111-112 °C $[\alpha]_D^{20} = -148.8$ (c 0.088, CHCl_3).

δ_H (600 MHz, DMSO- d_6): 9.11 (s, 1H, OH), 8.72 (d, $J = 4.8$, 1H, H-2'), 7.90 (d, $J = 9.6$, 1H, H-8'), 7.68 (s, 1H, H-5), 7.64 (d, $J = 4.2$, 1H, H-3'), 7.37 (d, $J = 9.0$, 1H, H-7'), 6.97 (t, $J = 7.2$, 1H, H-5''), 6.88 (d, $J = 7.2$, 1H, H-6''), 6.78 (s, 1H, H-2''), 6.47 (d, $J = 7.2$, 1H, H-4''), 4.73 (d, $J = 10.8$, 1H, H-9), 3.96 (s, 3H, H-6'), 3.68 (br s, 1H, H-8), 3.38 (br s, 1H, H-6a), 2.98 (app. t, 1H, H-2b), 2.48 (br s, 1H, H-6b), 2.33 (app. d, 1H, H-2a), 1.82 (br s, 1H, H-7b), 1.58 (br s, 2H, H-4, H-5a), 1.3-1.5 (m, 4H, H-3, H-5b, H-10), 0.86 (t, $J = 7.2$, 3H, H-11), 0.64 (br s, 1H, H-7a).

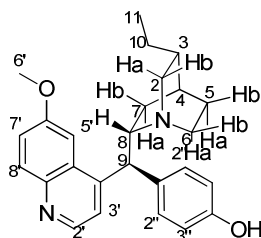
δ_C (100 MHz, DMSO- d_6): 157.1 (q), 156.9 (q), 147.7, 146.8 (q), 144.6 (q), 144.1 (q), 131.3, 128.7, 120.8, 119.8, 119.1, 115.2, 112.8, 102.9, 79.2

(q), 58.4, 57.6, 55.6, 49.0, 40.4, 36.9, 28.6, 28.4, 27.1, 25.7, 12.1.

$\nu_{\max}$ (neat) cm^{-1} : 2929, 2862, 1621, 1586, 1509, 1454, 1364, 1230, 1030, 828, 756, 714, 697.

HRMS (ESI⁺): Calcd. for $[\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_2 + \text{H}]^+$ requires 403.2386; found 403.2394.

5.2.24 (8*S*,9*S*)-9-(4-hydroxyphenyl)-6'-methoxy-10,11-dihydro-cinchonan (**132**)



Procedure C was followed using **129** (100 mg, 0.21 mmol), 10% Pd/C (23.5 mg, 10 mol%), and EtOH (5 mL) to give **132** (81 mg, 99%). M.p. 177-178 °C. $[\alpha]_{\text{D}}^{20} = -187.7$ (c 0.089, CHCl_3).

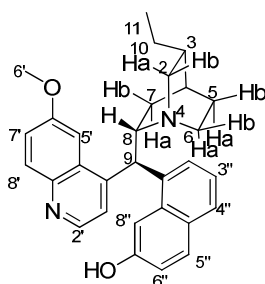
δ_{H} (600 MHz, DMSO-d_6): 9.07 (s, 1H, OH), 8.70 (d, $J = 4.2$, 1H, H-2'), 7.89 (d, $J = 9.0$, 1H, H-8'), 7.67 (br s, 1H, H-5'), 7.63 (d, $J = 4.8$, 1H, H-3'), 7.37 (dd, $J = 2.4, 9.0$, 1H, H-7'), 7.21 (d, $J = 8.4$, 2H, H-2''), 6.57 (d, $J = 8.4$, 2H, H-3''), 4.71 (d, $J = 10.8$, 1H, H-9), 3.95(s, 3H, H-6'), 3.65 (br s, 1H, H-8), 3.35 (H-6a under DMSO residual peak), 2.98 (app. t, 1H, H-2b), 2.46 (br s, 1H, H-6b), 2.34 (br s, 1H, H-2a), 1.80 (br s, 1H, H-7b), 1.58 (app. br s, 2H, H-4, H-5a), 1.32-1.49 (m, 4H, H-10, H-3, H-5b), 0.85 (t, $J = 7.2$, 3H, H-11), 0.63 (br s, 1H, H-7a).

δ_{C} (150 MHz, DMSO-d_6): 157.5 (q), 155.7 (q), 148.0, 147.7 (q), 144.4 (q), 131.6, 129.3, 129.3 (q), 128.7, 121.0, 120.0, 115.0, 103.2, 58.8, 57.9, 55.9, 48.9, 48.5, 37.2, 31.0 (q), 28.9, 27.3, 26.1, 12.4.

$\nu_{\max}$ (neat) cm^{-1} : 2928, 2864, 1619, 1588, 1508, 1455, 1431, 1364, 1235, 1172, 1030, 824.

HRMS (ESI⁺): Calcd. for $[\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_2 + \text{H}]^+$ requires 403.2386; found 403.2367.

5.2.25 (8*S*,9*S*)-6'-methoxy-9-(7-hydroxynaphthalen-1-yl)-cinchonan (**134**)



Procedure C was followed using **144** (1800 mg, 3.32 mmol), 10% Pd/C (360 mg, 10 mol%), and EtOAc (90 mL). The resulting product was purified by column chromatography (2:5:93 NEt_3 :MeOH:EtOAc) to give **134** (986 mg, 66%). M.p. 256 °C (dec.). $[\alpha]_{\text{D}}^{20} = +103.1$ (c 0.012, CHCl_3).

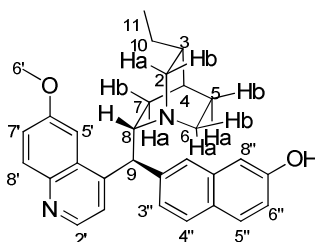
δ_{H} (600 MHz, DMSO-d_6): 9.90 (s, 1H, H-2''), 8.71 (d, $J = 4.8$, 1H, H-2'), 7.91-7.98 (br s, 1H, H-5'), 7.86 (d, $J = 8.4$, 1H, H-8'), 7.80-7.43 (m, 5H, H-3', H-4'', H-5'', H-6'' and H-7''), 7.30 (d, $J = 8.4$, 1H, H-7'), 7.00-7.20 (m, 2H, H-1'', H-3''), 5.33-5.53 (br s, 1H, H-9), 4.08-4.26 (br s, 1H, H-8), 3.80 (s, 3H, 6'), 3.59-3.31 (br m, 1H, H-2b) (partly obscured by residual H_2O peak), 2.82-3.01 (br s, 1H, H-6a), 2.20-2.58 (partly obscured by residual solvent peak), (m, 2H, H-6b, H-2a), 1.84-2.04 (br s, 1H, H-7b), 1.56-1.80 (m, 2H, H-4, H-5a), 1.21-1.55 (m, 4H, H-10, H-3, H-5b), 0.93-1.09 (br s, 1H, H-7a), 0.76-0.91 (t, $J = 7.2$, 3H, H-11).

δ_{C} (100 MHz, DMSO-d_6): 157.2 (q), 155.8 (q), 147.7, 144.0 (q), 133.1 (q), 131.4, 130.6, 128.6 (q), 128.5 (q), 128.2 (q), 126.5, 126.1, 122.2, 121.4, 120.5, 117.7, 105.4, 102.4, 60.8 (q), 57.2, 55.6, 54.9, 48.6, 43.1, 41.3, 36.7, 28.1, 27.0, 25.3, 12.1.

$\nu_{\max}$ (neat) cm^{-1} : 2948, 2868, 1619, 1585, 1508, 1452, 1359, 1221, 1026, 836, 748, 712.

HRMS (ESI⁺): Calcd. for $[\text{C}_{30}\text{H}_{32}\text{N}_2\text{O}_2 + \text{H}]^+$ requires 453.2542; found 453.2541.

5.2.26 (8*S*,9*S*)-6'-methoxy-9-(7-hydroxynaphtalen-2-yl)-cinchonan (**135**)



Procedure C was followed using **146** (360 mg, 0.66 mmol), 10% Pd/C (71 mg, 10 mol%), and EtOH (17.5 mL) to give **135** (295 mg, 99%). M.p. 99-101 °C.

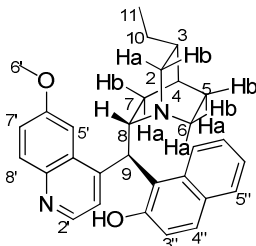
δ_{H} (600 MHz, DMSO- d_6): 9.59 (s, 1H, H-OH), 8.74 (d, $J = 4.2$, 1H, H-2'), 7.88 (d, $J = 9.6$, 1H, H-8'), 7.79 (br s, 1H, H-5'), 7.77 (d, $J = 4.2$, 1H, H-3'), 7.59 (d, $J = 9.0$, 1H, H-5''), 7.56 (d, $J = 8.4$, 1H, H-3''), 7.31-7.37 (m, 2H, H-4, H-7'), 7.00 (s, 1H, H-8''), 6.96 (d, $J = 8.4$, 1H, H-6''), 4.95 (d, $J = 9.6$, 1H, H-9), 3.98 (s, 3H, H-6'), 3.85 (br s, 1H, H-8), 3.48 (br s, 1H, H-6a), 2.94 (br s, 1H, H-2b), 2.39 (br s, 1H, H-6b), 2.35 (br s, 1H, H-2a), 1.89 (br s, 1H, H-7b), 1.62 (br s, 2H, H-4, H-5a), 1.31-1.50 (m, 4H, H-3, H-5b, H-10), 0.97 (br s, 3H, H-11), 0.74 (br s, 1H, H-7a).

δ_{C} (150 MHz, DMSO- d_6): 157.1 (q), 155.2 (q), 147.7, 144.1 (q), 134.4 (q), 131.3, 128.7, 127.0, 126.3 (q), 125.0, 123.2, 120.8, 119.8, 117.9, 108.3, 102.8, 67.0 (q), 59.7, 58.3, 57.5, 55.6, 49.4, 45.7 (q), 36.8, 30.6, 28.3, 27.0, 25.7, 25.1 (q), 12.0.

$\nu_{\max}$ (neat) cm^{-1} : 2928, 2862, 1621, 1586, 1509, 1454, 1364, 1216, 1174, 1028, 830, 712.

HRMS (ESI+): Calcd. for $[C_{30}H_{32}N_2O_2 + H]^+$ requires 453.2542; found 453.2540.

5.2.27 (8*S*,9*R*)-6'-methoxy-9-(1-hydroxynaphthalen-2-yl)-cinchonan (147)



Procedure C was followed using **150** (420 mg, 0.78 mmol), 10% Pd/C (83 mg, 10 mol%), and EtOH (20 mL) to give **147** (352 mg, 99%). M.p. 121-122 °C. $[\alpha]_D^{20} = -203.8$ (c 0.067, $CHCl_3$).

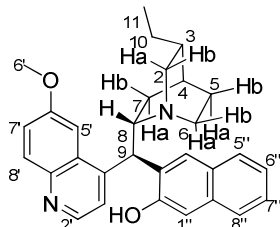
δ_H (400 MHz, $CDCl_3$): 8.70 (d, $J = 4.0$, 1H, H-2'), 8.03 (d, $J = 8.8$, 1H, H-5''), 7.94-7.99 (br s, 1H, H-5'), 7.91 (d, $J = 8.8$, 1H, H-8''), 7.58-7.69 (m, 3H, H-3', H-7'', H-6''), 7.21-7.32 (m, 2H, H-3'', H-7'), 7.12-7.20 (m, 2H, H-8'', H-8), 4.97-5.25 (br s, 1H, H-9), 3.85-4.04 (m, 4H, H-6', H-8), 3.31-3.42 (m, 1H, H-6a), 3.18-3.30 (m, 1H, H-2b), 2.79-2.92 (m, 1H, H-2a), 2.56-2.67 (m, 1H, H-6b), 1.87-2.00 (m, 2H, H-4, H-7b), 1.52-1.76 (m, 4H, H-3, H-5a, H-5b, H-7a), 1.22-1.38 (m, 2H, H-10), 0.86 (t, $J = 7.6$, 3H, H-11).

δ_C (100 MHz, $CDCl_3$): 157.1 (q), 154.9 (q), 146.3, 144.9 (q), 133.5 (q), 131.3, 129.4, 129.0 (q), 128.4, 127.5 (q), 125.5, 123.8 (q), 122.9, 122.3, 121.7, 121.3, 117.2 (q), 102.3, 76.8, 57.7, 55.4, 55.1, 41.0, 35.8, 29.2, 27.4, 26.4, 25.6, 25.4, 11.3.

ν_{max} (neat) cm^{-1} : 2829, 2870, 1619, 1507, 1455, 1314, 1236, 1029, 1006, 857, 818, 740.

HRMS (ESI+): Calcd. for $[C_{30}H_{32}N_2O_2 + H]^+$ requires 453.2542; found 453.2535

5.2.28 (8*S*,9*R*)-6'-methoxy-9-(2-hydroxynaphthalen-3-yl)-cinchonan (148)



Procedure C was followed using **152** (210 mg, 0.39 mmol), 10% Pd/C (42 mg, 10 mol%), and Toluene (11.0 mL) to give **148** which was purified by flash chromatography (49:1 CH₂Cl₂-NEt₃) to give **148** (165 mg, 95%) as a white solid.

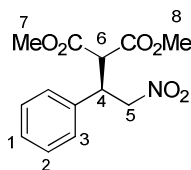
δ_{H} (400 MHz, CDCl₃): 8.79-8.90 (br s, 1H, H-2'), 8.05 (d, *J* = 9.2, 1H, H-8'), 7.61 (d, *J* = 8.0, 1H, H-5''), 7.25-7.44 (m, 6H, H-3', H-5', H-7', H-4'', H-7'', H-8''), 7.06-7.22 (m, 2H, H-1'', H-6''), 4.57-5.58 (br m, 2H, H-OH, H-9), 3.83 (app. br s, 4H, H-6', H-8), 3.34-3.60 (br s, 1H, H-6a), 3.18-3.33 (m, 1H, H-2b), 2.87-3.01 (m, 1H, H-6b), 2.62-2.74 (app. d, 1H, H-2a), 1.66-1.81 (m, 3H, H-3, H-4, H-7b), 1.50-1.64 (m, 2H, H-5a, H-5b), 1.33-1.46 (m, 2H, H-10), 0.94-1.06 (br s, 1H, H-7a), 0.81-0.93 (m, 3H, H-11).

δ_{C} (100 MHz, CDCl₃): 157.5 (q), 155.1 (q), 146.7, 144.8 (q), 133.8 (q), 131.5, 131.1 (q), 128.1 (q), 127.2 (q), 127.1, 125.5, 125.0, 122.7 (q), 122.2, 121.5, 112.9, 102.1, 76.8, 59.9, 55.3, 55.2, 40.1, 36.6, 28.4, 27.2, 27.1, 25.1, 20.6, 13.7, 11.6.

ν_{max} (neat) cm⁻¹: 2934, 2873, 1618, 1580, 1506, 1463, 1241, 1225, 1183, 1085, 1035, 1016, 999, 979, 853, 827, 757, 741, 713, 702.

HRMS (ESI⁺): Calcd. for [C₃₀H₃₂N₂O₂ + H]⁺ requires 453.2542; found 453.2540.

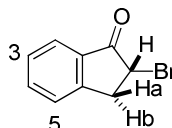
5.2.29 Dimethyl 2-(2-nitro-1-phenylethyl)malonate (18a)



β -nitrostyrene (32.8 mg, 0.25 mmol), styrene (28.6 μ l, 0.25 mmol), CH_2Cl_2 (414 μ l) and catalyst (10 mol%), were placed in a reaction vial and placed under a protective argon atmosphere. To this (37.3 mg, 2.5 mmol), was added and stirring continued for 36 h. The resulting solution was then purified by column chromatography (1:9 EtOAc-hexane) without removal of solvent to afford **18a** (7 mg, 15%). CSP-HPLC analysis. Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 20.7 min (major enantiomer) and 34.6 (minor enantiomer).²⁴¹

δ_{H} (400 MHz, CDCl_3): 7.30-7.38 (3H, m, H-1 and H-2), 7.25 (2H, d, J 6.8 Hz, H-3), 4.86-4.99 (2H, m, H-5), 4.23-4.31 (1H, m, H-4), 3.89 (1H, d, J 8.8 Hz, H-6), 3.79 (3H, s, H-7), 3.59 (3H, s, H-8).

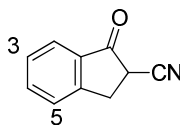
5.2.30 2-Bromo-indan-1-one (**157**)



Indanone (**156**, 5.48 g, 41.5 mmol) and Et_2O (80 ml) were placed in a flask under argon, cooled to 10 $^{\circ}\text{C}$ and bromine (2.4 ml, 93.7 mmol) was added dropwise. Stirring was continued at ambient temperature for 16 hours, before the mixture was washed with ice water (2x100 ml), NaHCO_3 soln. (conc. aq., 2 x 50 ml), and NaS_2O_3 soln. (conc. aq., 2 x 80 ml). The organic layer was dried over MgSO_4 and filtered and the solvent was removed under reduced pressure. The resulting oil was purified by flash chromatography eluting with 20-100% DCM in hexanes to afford **157** as a white solid (4.21 g, 46%). M.p. 38 $^{\circ}\text{C}$. Litt. M.p. 37-38.5 $^{\circ}\text{C}$ ^{242,243}

δ_{H} (400 MHz, CDCl_3): 7.88 (d, J 7.8, 1H, H-2), 7.70 (app t, J 7.8, 1H, H-4), 7.51-7.44 (m, 2H, H-3, H-5), 4.69 (dd, J 3.2, 7.4, 1H, H-CH), 3.87 (dd, J 7.4, 18.0, 1H, H-H_b), 3.45 (dd, J 3.2, 18.0, 1H, H-H_a).

5.2.31 2-Cyano-indan-1-one (158)

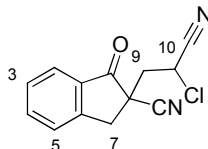


The following procedure was carried out in an efficient fume hood take all necessary precautions.

2-Bromoindanone (**157**, 2.11 g, 10.0 mmol), NaCN (4.90 g, 100 mmol) CARE! And EtOH (70 ml) were placed in a RBF fitted with a condenser under an argon atmosphere. Water (a few ml) was slowly added until all solids had dissolved and the solution was kept a reflux for 25 minutes. After the reaction had cooled water (200 ml) was added and this was extracted with Et₂O (2 x 100 ml). The aqueous portion was then placed in an icebath and slowly very cautiously acidified with cold hydrochloric acid (5 M). The resulting two phase mixture was extracted with chloroform (2 x 100 ml), and the organics were combined, dried over MgSO₄ and filtered. This was then extracted with NaOH in 25 ml portions until test portions of the extract no longer gave a precipitate on acidification. The combined organics were again acidified and the resulting oil separated. The aqueous layer was further extracted with DCM (100 ml), and the combined organics were dried over MgSO₄ and filtered and the solvent was removed under reduced pressure to afford the desired compound. **158** (707 mg, 45%). M.p. 70.5-71.2 °C. Litt m.p. 70-71 °C.²⁴⁴

δ_{H} (400 MHz, CDCl_3): 7.87 (d, J 7.8, 1H, H-2), 7.73 (app t, 1H, H-4), 7.59-7.47 (m, 2H, H-3, H-5), 3.78-3.62 (m, 2H, H-CH, H-CH₂), 3.50 (dd, J 5.0, 16.4, 1H, H-CH₂).

5.2.32 2-(2-Chloro-2-cyanoethyl)-2-cyano-indan-1-one (**161**)



2-Cyano-1-indanone (**159**, 31.4 mg, 0.20 mmol), DCM (1 ml) and catalyst (10 mol%) were placed in a sealed vial under argon and chloroacrylonitrile (**160**, 63.9 μ l, 0.80 mmol) were added. This was stirred for 6 hours. The reaction was then directly loaded onto a column and purified by flash chromatography to afford the title compound **161** as a white solid (48 mg, 98%).

Obtained as an inseparable mix of diastereoisomers. Major diastereomer – *RS/SR*

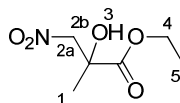
CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 8/2, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times:

Major diastereoisomer: 11.9 min (major enantiomer) and 22.9 min (minor enantiomer).

Minor diastereoisomer: 10.1 min (minor enantiomer) and 13.9 min (major enantiomer).

δ_{H} (400 MHz, CDCl₃): 7.92 (d, J 7.6, 1H, H-2_{maj&min}), 7.75-7.84 (app t, 1H, H-4_{maj&min}), 7.61-7.51 (m, 2H, H-3_{maj&min} H-5_{maj&min}), 5.03 (dd, J 3.2, 10.0, 0.5H, H-10_{maj}), 4.96 (dd, J 4.0, 10.2, 0.5H, H-10_{min}), 3.93-3.84 (m, 1H, H-7_{maj&min}), 3.72-3.58 (m, 1H, H-7_{maj&min}), 3.03 (dd, J 3.2, 16.0, 0.5H, H-9_{maj}), 2.93 (dd, J 4.0, 14.4, 0.5H, H-9_{min}), 2.54-2.41 (m, 1H, H-9_{maj&min}).

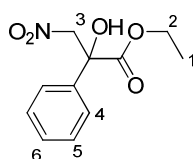
5.2.33 Ethyl 2-hydroxy-2-methyl-3-nitropropanoate (**164**)



Ethyl pyruvate (**163**, 27.8 μL , 0.25 mmol), styrene (28.6 μL , 0.25 mmol), CH_2Cl_2 (308 μL) and catalyst (10 mol%), were placed in a reaction vial and placed under a protective argon atmosphere. To this nitromethane (135.4 μL , 2.5 mmol), was added and stirring continued for 36 h. The resulting solution was then purified by column chromatography (1:9 EtOAc-hexane) without removal of solvent to afford **164** (27 mg, 61%). Chiralcel AS (4.6 mm x 25 cm), hexane/IPA, 96/4, 1.0 mL min⁻¹, RT, UV detection at 215 nm, retention times: 23.3 min (major enantiomer) and 27.3 min (minor enantiomer).¹³⁷

δ_{H} (400 MHz, CDCl_3): 4.87 (d, J 14.0, 1H, H-2a), 4.58 (d, J 14.0, 1H, H-2b), 4.30-4.44 (m, 2H, H-4), 3.71-3.81 (br s, 1H, H-3), 1.48 (s, 3H, H-1), 1.35 (t, J 6.8, 3H, H-5).

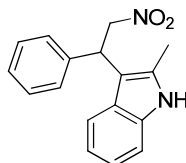
5.2.34 Ethyl 2-hydroxy-3-nitro-2-phenylpropanoate (**166**)



A vial was charged with benzoylethylformate (**165**, 39.7 μL , 0.25mmol), styrene (28.6 μL , 0.25 mmol), nitromethane (135.4 μL , 2.5 mmol), CH_2Cl_2 (308 μL) and catalyst (10 mol%) and stirred for 88 h. The resulting solution was then purified by column chromatography (1:9 EtOAc-hexane) without removal of solvent to afford **166** (25 mg, 42%). Chiralcel AD-H (4.6 mm x 25 cm), hexane/IPA, 90/10, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 8.6 min (minor enantiomer) and 10.9 min (major enantiomer).¹³⁷

δ_{H} (400 MHz, CDCl_3): 7.66-7.62 (m, 2H, H-4), 7.47-7.39 (m, 3H, H-5 and H-6), 5.29 (d, J 14.0, 1H, H-3), 4.71 (d, J 14.0, 1H, H-3), 4.46-4.34 (m, 2H, H-2), 4.26 (s, 1H, H-OH), 1.36 (t, J 7.2, 3H).

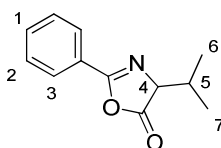
5.2.35 2-Methyl-3-(2-nitro-1-phenylethyl)-1H-indole (170)



2-methylindole (**169**, 32.8 mg, 0.25 mmol), styrene (28.6 μl , 0.25 mmol), CH_2Cl_2 (500 μl) and catalyst (10 mol%), were placed in a reaction vial and placed under a protective argon atmosphere. To this β -nitrostyrene (**17**, 37.3 mg, 2.50 mmol), was added and stirring continued for the time indicated in Table 2.6. The resulting solution was then purified by column chromatography (1:9 EtOAc-hexane) without prior removal of solvent to afford **170**, (34 mg, 61%), M.p. 102-104 $^{\circ}\text{C}$ (lit. m.p. 104-105 $^{\circ}\text{C}$).²⁴⁵

δ_{H} (400 MHz, CDCl_3): 7.83-7.97 (1H, br s, H-NH), 7.40 (1H, d, J = 8.0, H-7), 7.23-7.38 (6H, m, H-1, H-2, H-3, H-10), 7.14 (1H, app. t, H-8), 7.06 (1H, app. t, H-9), 5.09-5.33 (3H, m, H-4 and H-5), 2.43 (3H, s, H-6).

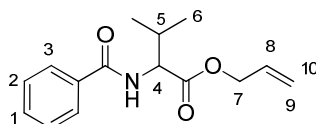
5.2.36 2-Phenyl-4-isopropylloxazolone (110)



Racemic *N*-Benzoylvaline (**171**, 1.00 g) and acetic anhydride (2.50 mL) were placed in a round bottom flask under a protective argon atmosphere and heated to 65 $^{\circ}\text{C}$ for 30 mins. The flask was allowed to cool and then the resulting mixture was purified by column chromatography (0-5% EtOAc:hexane). The desired product was obtained as a white solid (800 mg, 84%). M.p. 50-51 $^{\circ}\text{C}$. (Lit. m.p. 50-52 $^{\circ}\text{C}$).¹⁴⁸

δ_{H} (400 MHz, CDCl_3): 8.03(m, 2H, H-3), 7.60 (m, 1H, H-1), 7.51(m, 2H, H-2), 4.31 (d, J 4.5, 1H, H-4), 2.41(m, 1H, H-5), 1.17 (d, J 7.0, 3H H-6), 1.04 (d, J 6.8, 3H, H-7).

5.2.37 *N*-Benzoylvaline, allyl ester (**114**)

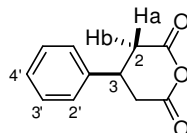


2-Phenyl-4-isopropylloxazolone (**114**, 40.6 mg, 0.2 mmol) was placed in a vial with the appropriate catalyst (0.02 mmol), CH_2Cl_2 (450 μL), styrene (20.8 μL , 0.2 mmol) (as an internal standard for ^1H -NMR analysis) and allyl alcohol (27.0 μL , 0.4 mmol), under a protective argon atmosphere and stirred for the time indicated in Table **2.7**. The product was purified by column chromatography (5:1 EtOAc-hexane) without prior removal of solvent. The desired product, **114**, was obtained as a white solid (26 mg, 50%). M.p. 43-45 $^{\circ}\text{C}$.¹⁴⁸

CSP-HPLC analysis. Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 8.4 min (*R*) and 11.7 (*S*).

δ_{H} (400 MHz, CDCl_3): 1.04 (m, 6H, H-6), 2.34 (m, 1H, H-5), 4.70 (m, 2H, H-7), 4.85 (dd, 1H, H-4), 5.31 (d, 1H, J 10.6, H-9), 5.39 (d, 1H, J 16.0, H-10), 5.95 (m, 1H, H-8), 6.66 (d, 1H, J 8.5, H-NH), 7.38 (m, 2H, H-2), 7.45 (m, 1H, H-1), 7.74 (2H, m, H-3)

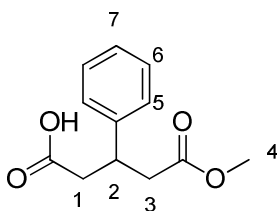
5.2.38 3-Phenylglutaric anhydride (173)



3-Phenylglutaric acid (**172**, 1,041 mg, 5.00 mmol) and DCC (1032 mg, 5.00 mmol) were placed in a round bottom flask with CH_2Cl_2 (30 ml). This mixture was stirred overnight and filtered to remove the resulting white precipitate. The reaction was concentrated *in vacuo* and the resulting oil was rapidly purified by flash chromatography (0-10% EtOAc in Hexanes) to afford the title compound as a white solid (741 mg, 78% yield). M.p. 101-102 °C; (lit., 103-104 °C).²⁴⁶

δ_{H} (400 MHz, CDCl_3): 2.90 (dd, J 17.0, 11.2, 2H, H-2a), 3.15 (dd, J 17.0, 4.5, 2H, H-2b), 3.40-3.50 (m, 1H, H-3), 7.23 (d, J 7.0, 2H, H-2'), 7.33-7.47 (m, 3H, H-3' and H-4').

5.2.39 5-Methoxy-3-phenyl-5-oxopentanoic acid (174)



A flask was flushed with argon and charged with MTBE (13.3 ml), 3-phenylglutaric anhydride (38 mg, 0.2 mmol), MeOH (81.3 μl , 2.0 mmol), and catalyst (0.02 mmol). Stirring was continued for 40 hours. The solution was then washed with HCl (0.1 M, 10 ml) and the aqueous layer further extracted with EtOAc (2 x 10 ml). The organics were combined and the solvent was removed under reduced pressure. The resulting mixture was

purified by flash chromatography eluting with 10-50% EtOAc in Hexanes to provide the title compound as a white solid. (34 mg, 77%), M.p. 91-92 °C; (lit., 93-95 °C, rac.).²⁴⁶

δ_{H} (400 MHz, CDCl_3): 7.20-7.35 (m, 5H, H-2', H-3' and H-4'), 3.55-3.70 (m, 4H, H-3 and -OCH₃), 2.65-2.85 (m, 4H, H-2a, H-2b, H-4a and H-4b).

Determination of the enantiomeric excess of 174

A flask was charged with dry toluene (2 ml), and 3-phenylsuccinic acid monomethyl ester (22 mg, 0.1 mmol), flushed with argon and cooled to 0 °C. To this a solution of SOCl_2 (9 μl , 0.12 mmol) in dry toluene (1 ml) was added and the reaction mixture was stirred for 10 minutes. Triethylamine (46 μl , 0.33 mmol) was added followed by (R)-1-(1-naphthyl)ethylamine (18 μl , 0.11 mmol) and the reaction mixture was stirred at 0 °C for one hour followed by a further hour at ambient temperature. The reaction mixture was then diluted with EtOAc (15 ml) and washed with HCl (1 M aq., 10 ml), NaHCO_3 (sat. aq., 10 ml) and brine (10 ml) before drying over MgSO_4 . This was then filtered and the solvent was removed under reduced pressure to give a diastereomeric mixture which allowed determination of enantiomeric excess by NMR.¹⁴⁸

5.2.40 Representative NMR experiments for the determination of conformations in C-9 arylated quinine derivative 131 and 132

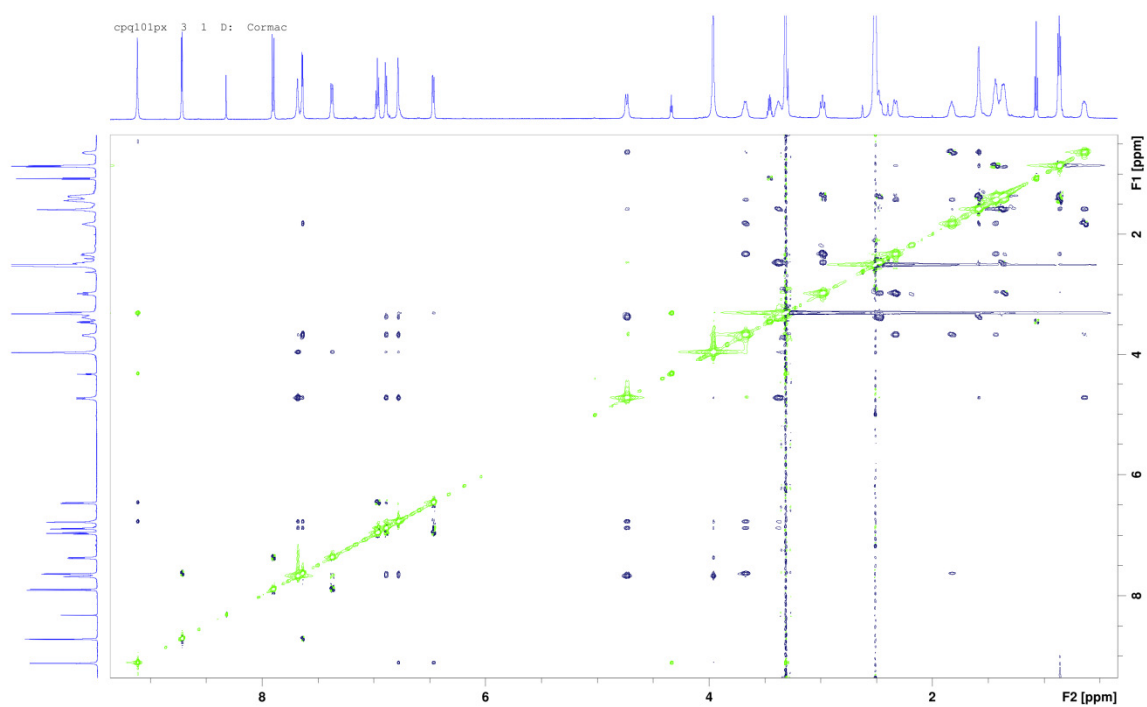


Figure 5.1: 2D NMR spectra showing a ROESY experiment used to analyse the conformation of 131

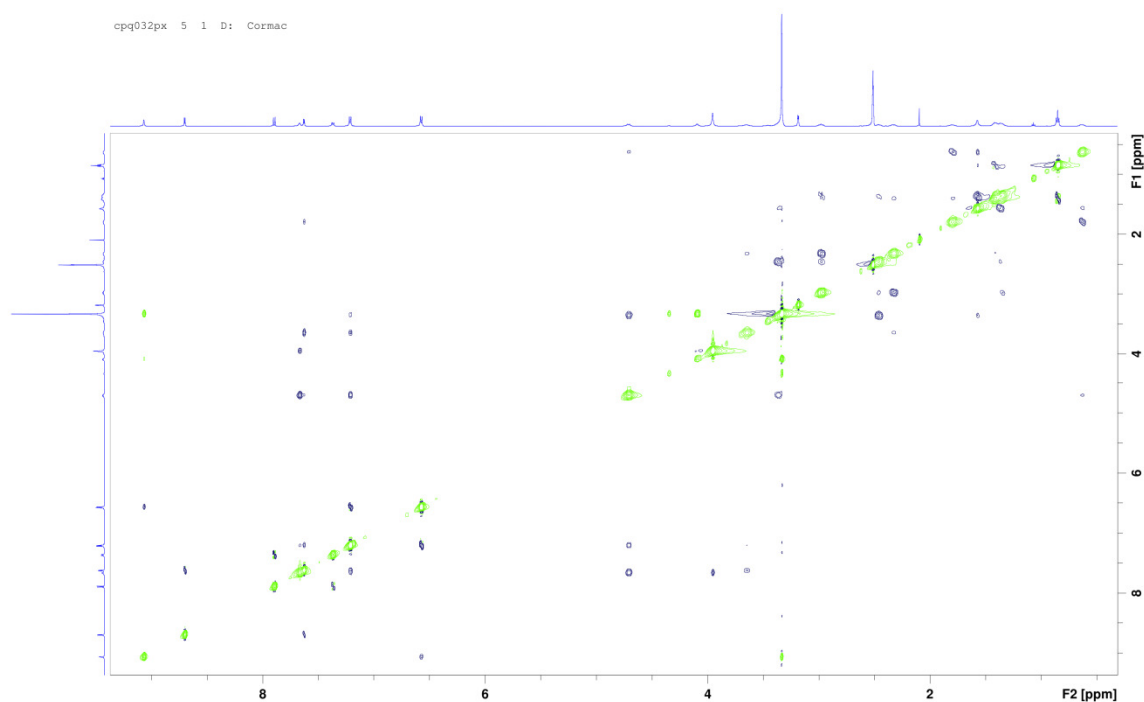


Figure 5.2: 2D NMR spectra showing a ROESY experiment used to analyse the conformation of 132

5.3 Experimental data for chapter 3

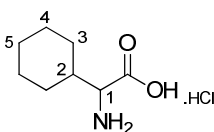
5.3.1 Procedure D: General procedure for the Strecker synthesis of amino acids.²⁴⁷

Reaction was carried out in an efficient fume hood with all necessary precautions.

Potassium cyanide (1.05 equiv.) was placed in a RBF with deionised water (3.81 M) and an equal volume of MeOH. CARE! To this NH_4Cl (1.05 equiv.) was added followed by the rapid addition of aldehyde (1.0 equiv.). This was stirred at ambient temperature for 4 hours. The reaction was then diluted with water (to 2.5 times initial volume) and extracted with an equal volume of toluene. The organic layer was then extracted with HCl (6 M x 3), to give an approximately 1.27 M solution. This was heated to reflux for 10 h. After cooling

to room temperature, the reaction mixture was washed with Et₂O, and the solvent (water) was removed under reduced pressure. The resulting white solid was washed with a portion of cold brine and then a very small portion of cold acetone. The solid was then dried under vacuum to afford the amino acid as the hydrochloride salt.

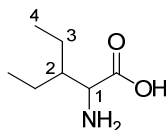
5.3.2 2-Amino-2-cyclohexylacetic acid **242**.HCl



Procedure D was followed using potassium cyanide (3.05 g, 46.8 mmol), cyclohexane carbaldehyde (5.00 g, 44.6 mmol), ammonium chloride (2.51 g, 46.8 mmol), MeOH (12.7 ml) and water (12.7 ml). This was diluted with water (38 ml) and extracted with toluene (38 ml) which was then extracted with HCl (6 M, aq., 3 x 13 ml). After reflux and purification the product **242**.HCl was obtained as a white solid. (5.10 g, 59%). M.p. 268 °C. (Lit. m.p.267-269 °C).²⁴⁸

δ_{H} (400 MHz, D₂O): 3.74 (d, J 4.2, 1H, H-1), 1.87 (m, 1H, H-2), 1.73-1.59 (m, 3H, H-3 and H-5), 1.59-1.47 (m, 2H, H-4), 1.25-0.93 (m, 5H, H-3, H-4 and H-5).

5.3.3 2-Amino-3-ethylpentanoic acid(**241**)

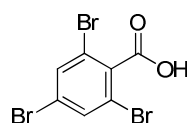


Procedure D was followed using potassium cyanide (6.84 g, 105 mmol), 2-ethyl butyraldehyde (12.3 ml, 100 mmol), ammonium chloride (5.62 g, 105 mmol), MeOH (28.5 ml) and water (28.5 ml). This was diluted with water (85 ml) and extracted with toluene

(85 ml) which was then extracted with HCl (6 M, aq., 3 x 29 ml). (4.83 g, 27%). M.p. 278 °C.

δ_{H} (400 MHz, DMSO- d_6): 3.25 (m, 1H, H-1), 1.92 (m, 1H, H-2) , 1.47-1.21 (m, 4H, H-3), 0.70-1.03 (m, 6H, H-4).

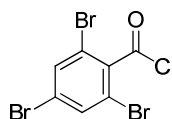
5.3.4 2,4,6-Tribromobenzoic acid (**227**)



226 (12.0 g, 37.5 mmol) was added to a flask containing freshly prepared LDA (37.5 mmol) in THF (60 ml) stirred at -78 °C. Stirring was continued for 2 hours and the solution was then transferred to a flask containing a large excess of solid CO₂ and stirred for a further 2 hours. Saturated NaHCO₃ solution (60 ml) was added and the reaction was allowed to warm to ambient temperature. THF was removed under reduced pressure and NaOH (aq. 5%, 10 ml) was added. This solution was washed with CH₂Cl₂ (2 x 60ml). The aqueous layer was then acidified with HCl (2 M) and the resulting precipitate extracted with CH₂Cl₂ (2 x 100 ml). The combined organics were dried over MgSO₄, and filtered and the solvent was removed at reduced pressure to afford the crude product, which could be recrystallized from chloroform to afford **227** (3.30 g, 25%). M.p. 188-190 °C. (Lit. m.p. 189-190 °C)²⁴⁹

δ_{H} (400 MHz, CDCl₃): 7.92 (s, 2H) .Signal for CO₂H not observed.

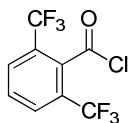
5.3.5 2,4,6-Tribromobenzoyl chloride (**228**)



Acid **227** (2.00 g, 5.57 mmol) was placed in a round bottom flask with carbon tetrachloride (1.11 ml) and PCl₅ (762 mg, 3.66 mmol). This was heated at reflux for 1 hour and solvent was removed at reduced pressure. CARE! The remaining oil was then added to NaHCO₃ solution (50 ml) and ice, which was then extracted with CH₂Cl₂ (50 ml). The organic layer was dried over MgSO₄ and filtered and solvent was removed at reduced pressure to afford the desired compound **228** (2.17 g, 99%) as a clear oil which slowly solidified. M.p. 48 °C. (Lit. m.p. 47-49 °C).²⁵⁰

δ_H (400 MHz, CDCl₃): 7.78 (s, 2H)

5.3.6 2,6-Bis-(Trifluoromethyl)benzoyl chloride (**233**)



Acid **232** (2.00 g, 7.75 mmol) was placed in a round bottom flask with carbon tetrachloride (1.5 ml) and PCl₅ (2.00 g, 9.60 mmol). This solution was heated at reflux for 1 hour and the solvent was removed at reduced pressure. CARE! The remaining oil was then added to NaHCO₃ solution (50 ml) and ice, which was then extracted with CH₂Cl₂ (50 ml). The organic layer was dried over MgSO₄ and filtered and the solvent was removed at reduced pressure to afford the desired compound **228** (2.12 g, 99%) as a clear oil.²¹⁷

δ_H (400 MHz, CDCl₃): 8.00 (app. d, 2H), 7.83 (app. t, 1H).

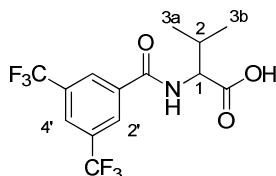
5.3.7 Procedure E: General procedure for the synthesis of racemic *N*-benzoyl amino acids

The appropriate amino acid (1.0 eq) was added to a round bottomed flask containing NaOH (aq. 0.875 M, 2.33 eq.). The resulting solution was cooled to 0 °C and the appropriate benzoyl chloride (1.0 - 1.05 eq.) was slowly added *via* syringe. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred until one phase was obtained. The mixture was then acidified to approximately pH 2 by addition of HCl (1 N) and a white precipitate formed. The solid was isolated by filtration and dried to give the desired *N*-benzoyl amino acid.

5.3.8 Procedure F: General procedure for the synthesis of racemic *N*-benzoyl amino acids

Methanol (0.6 M) was placed in a round bottom flask under argon and cooled to 0 °C. Thionyl chloride (2.0 eq.) slowly added over 5 minutes and then the reaction was stirred for a further 5 minutes. The desired amino acid (or amino acid hydrochloride salt) (1.0 eq.) was then added in one portion and the solution heated at reflux for 3 hours. The reaction mixture was then cooled to ambient temperature and solvent was completely removed under reduced pressure. In the case that the methyl ester was readily available the initial steps of this procedure are not necessary. CH₂Cl₂ (0.45 M) was then added and the reaction was cooled to 0 °C, diisopropylethylamine or triethylamine (3.0 eq.) was added followed by the appropriate acyl chloride (1.0 eq.) which was slowly added *via* syringe. After the addition was complete, the reaction was allowed to warm up to room temperature and stirred for 16 h. The solution was then diluted with further CH₂Cl₂ and washed with HCl (1 N), NaOH (aq. 5% w/v) and brine. The organic layer was dried over MgSO₄ and filtered, and the solvent was removed *in vacuo*. The resulting material was then placed in a round bottom flask with THF (10 mL/g) and NaOH (aq. 5% w/v, 10 mL/g) and stirred for a further 16 h. THF was then removed *in vacuo* and the solution acidified by addition of HCl (6 N) and extracted using CHCl₃ (x3). The organic layers were combined, dried over MgSO₄ and filtered and the solvent was removed *in vacuo* to give the desired *N*-benzoyl amino acid.

5.3.8.1 3,5-Bis(trifluoromethyl)-N-benzoyl valine (**199**)



Procedure E was followed using DL-valine (2,000 mg, 17.07 mmol) and 3,5-bis(trifluoromethyl)benzoyl chloride (3.09 mL, 17.07 mmol) to give the desired product as a white solid **199** (2.53 g, 42%) M.p. 120-122 °C

δ_{H} (400 MHz, DMSO- d_6): 9.08 (d, J = 8.0, 1H, NH), 8.55 (s, 2H, H-2'), 8.34 (s, 1H, H-4'), 4.38 (dd, J = 6.8, 8.0, 1H, H-1) 2.27-2.16 (m, 1H, H-2), 1.02-0.95 (m, 6H, H-3a).

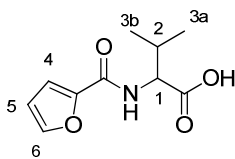
δ_{C} (100 MHz, DMSO- d_6): 172.7 (q), 164.0 (q), 136.1 (q), 130.4 (q, J = 32.9, $\underline{\text{C}}\text{CF}_3$), 128.5, 125.1, 123.1 (q, J = 273.2, CF_3), 58.6, 29.7, 19.3, 18.8.

δ_{F} (376 MHz, DMSO- d_6): -61.7 (s, 6F).

ν_{max} (neat) cm^{-1} : 3310, 2974, 1706, 1653, 1543, 1272, 1179, 1128, 907, 847, 701, 681, 659.

HRMS (ESI-) calcd. for $[\text{C}_{14}\text{H}_{13}\text{NO}_3\text{F}_6 - \text{H}]^-$ requires 356.0721; found 356.0722.

5.3.9 N-2-Furoylvaline (**206**)



Procedure E was followed using furoyl chloride and DL-valine to give the desired compound **206** as a bright white solid (0.61 g, 58%). M.p. 113–114 °C.

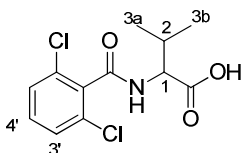
δ_{H} (400 MHz, DMSO- d_6): 12.78 (bs, 1H, CO₂H); 8.21 (d, J 8.3, 1H, NH), 7.89 (m, 1H, H-5), 7.28 (d, J 3.5, 1H, H-6), 6.67 (dd, J 3.5, 1.8, 1H, H-4), 4.31–4.25 (m, 1H, H-1), 2.26–2.15 (m, 1H, H-2), 0.97 (d, J 2.9, 3H, H-3a), 0.96 (d, J 2.9, 3H, H-3b)

δ_{C} (100 MHz, DMSO- d_6): 173.0 (q), 158.0 (q), 147.3 (q), 145.3, 114.0, 111.8, 57.5, 29.6, 19.3, 18.6

ν_{max} (neat) cm^{-1} : 3363, 2961, 1708, 1618, 1593, 1532, 1478, 1394, 1328, 1295, 1228, 1196, 1020, 926, 885, 803, 770, 758, 740

HRMS (ESI+) calcd. for [C₁₀H₁₃NO₄ + Na]⁺ requires 234.0742; found 234.0740

5.3.9.1 2,6-Dichloro-*N*-benzoyl valine (**208**)



Procedure E was followed using DL-valine (2,000 mg, 17.07 mmol) and 2,6-dichlorobenzoyl chloride (2.45 mL, 17.07 mmol) followed by the addition of DMAP (20 mg) to give the desired product, **208** (3.44 g, 69%) as a white solid: M.p. 113–115 °C.

δ_{H} (400 MHz, DMSO- d_6): 8.96 (d, J = 8.8, 1H, NH), 7.51–7.46 (m, 2H, H-3'), 7.45–7.39 (m, 1H, H-4'), 4.34 (dd, J = 6.4, 8.8, 1H, H-1), 2.18–2.07 (m,

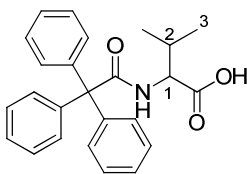
1H, H-2), 0.98 (d, J = 6.8, 3H, H-3a), 0.94 (d, J = 6.8, 3H, H-3b).

δ_C (100 MHz, DMSO- d_6): 172.4 (q), 163.7 (q), 136.5 (q), 131.2 (q), 130.8, 128.0, 57.6, 30.1, 19.3, 18.1.

$\nu_{\max}$ (neat) cm^{-1} : 3552, 2970, 2647, 1717, 1635, 1565, 1264, 1196, 1155, 880, 801, 778, 736, 679.

HRMS (ESI+): calcd. for : $[\text{C}_{12}\text{H}_{13}\text{Cl}_2\text{NO}_3 + \text{Na}]^+$ requires 312.0170; found 312.0161.

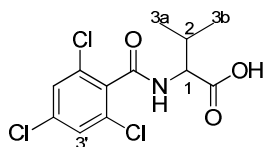
5.3.10 N-Triphenylacetyl valine (210)



Triphenylacetic acid (1.44 g, 5.0 mmol), valine methyl ester (656 mg, 5.0 mmol) and CH_2Cl_2 (10 ml) were placed in a round bottom flask and a solution of DCC (1238 mg, 6.0 mmol) in CH_2Cl_2 (5 ml) was added. This mixture was stirred for 3 hours and then the mixture was filtered, washing through with additional CH_2Cl_2 (50 ml). This was then washed with NaOH (aq., 5%, 50 ml), HCl (aq., 1 M, 50 ml) and brine (25 ml). The organic layer was dried over MgSO_4 and filtered, and solvent was removed under reduced pressure. The resulting oil was dissolved in THF (20 ml) and NaOH (aq., 5%, 80 ml) was added and stirring continued for 16 h. THF was then removed at reduced pressure and the aqueous layer was washed with an equal volume of CH_2Cl_2 . The aqueous layer was then acidified (HCl, conc.) and extracted with chloroform (2 x 50 ml). The organic layers were combined, dried over MgSO_4 and filtered and the solvent was removed at reduced pressure to afford the desired compound as a white solid (1.02 g, 53%). M.p. 125 °C. Lit m.p. 126-128 °C.²⁵¹

^1H NMR (400 MHz, CDCl_3): 7.35-7.29 (m, 15H, Ar-H), 6.21 (d, $J = 8.0$, 1H, NH) 4.60 (dd, $J = 4.4$, 8.0, 1H, H-1), 2.28-2.17 (m, 1H, H-2), 0.89 (d, $J = 6.8$, 3H, H-3), 0.72 (d, $J = 6.8$, 3H, H-3).

5.3.10.1 N-(2,4,6-Trichlorobenzoyl) valine (**223**)



Procedure F was followed using valine methyl ester (1.18 g, 9.02 mmol), 2,4,6-trichlorobenzoyl chloride (**222**), (1.28 mL, 8.20 mmol) and triethylamine, to give the title compound **223** (2.46 g, 93%) as a white solid. M.p. 162-164 °C.

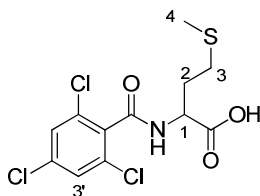
δ_{H} (400 MHz, CDCl_3): 7.40 (s, 2H, H-3'), 6.32 (br d, $J = 8.8$, 1H, NH), 4.88 (dd, $J = 4.4$, 8.8, 1H, H-1), 2.47-2.37 (m, 1H, H-2), 1.15 (d, $J = 6.8$, 3H, H-3a), 1.05 (d, $J = 6.8$, 3H, H-3b).

δ_{C} (100 MHz, CDCl_3): 174.7 (q), 163.3 (q), 135.7 (q), 133.6 (q), 132.6 (q), 127.8, 56.8, 31.0, 18.7, 17.2.

ν_{max} (neat) cm^{-1} : 3301, 2964, 2523, 1723, 1615, 1581, 1547, 1371, 1212, 1143, 1034, 856, 820, 801, 717, 688.

HRMS (ESI⁺): calcd. for $[\text{C}_{12}\text{H}_{12}\text{NO}_3\text{Cl}_3 + \text{Na}]^+$ requires 345.9780; found 345.9793

5.3.10.2 N-(2,4,6-Trichlorobenzoyl) methionine (**251**)



Procedure F was followed using DL-methionine methyl ester (816 mg, 5.00 mmol), 2,4,6-trichlorobenzoyl chloride (781 μ l, 5.00 mmol) and diisopropylethylamine (2.61 mL, 15.0 mmol) to give the desired product (1265 mg, 71%) as a white solid: M.p. 141-143 $^{\circ}$ C.

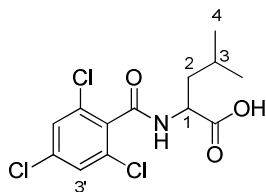
δ_{H} (400 MHz, CDCl_3): 7.39 (s, 2H, H-3'), 6.63 (br d, $J = 7.6$, 1H, NH), 5.05-4.98 (m, 1H, H-1), 2.70 (app. t, 2H, H-3), 2.46-2.35 (m, 1H, H-2a), 2.25-2.12 (m, 4H, H-2b, H-4).

δ_{C} (100 MHz, CDCl_3): 173.8 (q), 163.2 (q), 135.8 (q), 133.3 (q), 132.5 (q), 127.8, 51.3, 30.8, 29.3, 15.0.

ν_{max} (neat) cm^{-1} : 3254, 3083, 2921, 1709, 1650, 1549, 1432, 1300, 1250, 1184, 1133, 956, 875, 851, 818, 802, 708, 679.

HRMS (ESI⁺): calcd. for $[\text{C}_{12}\text{H}_{12}\text{NO}_3\text{SCl}_3 + \text{Na}]^+$ requires 377.9501; found 377.9499.

5.3.10.3 N-(2,4,6-Trichlorobenzoyl) leucine (**252**)



Procedure F was followed using DL-leucine methyl ester (871 mg, 6.00 mmol), 2,4,6-trichlorobenzoyl chloride (0.78 mL, 5.00 mmol), and diisopropylethylamine (2.61 mL, 15.0 mmol), to give 2,4,6 trichloro-*N*-benzoyl leucine (**252**, 1276 mg, 75%) as an off white crystalline solid. M.p. 162-164 $^{\circ}$ C.

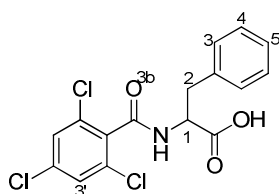
δ_{H} (400 MHz, CDCl_3): 7.37 (s, 2H, H-3'), 6.29 (br d, $J = 7.2$, 1H, NH), 4.93-4.85 (m, 1H, H-1), 1.96-1.69 (m, 3H, H-2, H-3), 1.08-.99 (m, 6H, H-4).

δ_{C} (100 MHz, CDCl_3): 176.4 (q), 163.3 (q), 135.6 (q), 133.3 (q), 132.6 (q), 127.7, 50.5, 40.8, 24.3, 22.4, 21.2.

ν_{max} (neat) cm^{-1} : 3206, 3068, 2962, 1715, 1644, 1581, 1548, 1421, 1369, 1257, 1153, 1063, 933, 860, 820, 731.

HRMS (ESI+) cald. for $[\text{C}_{16}\text{H}_{18}\text{NO}_3\text{Cl}_3 + \text{Na}]^+$ requires 400.0250; found 400.0268.

5.3.10.4 N-(2,4,6-Trichlorobenzoyl)phenyl alanine (**253**)



Procedure F was followed using DL-phenyl alanine methyl ester (1075 mg, 6.0 mmol), 2,4,6-trichlorobenzoyl chloride (0.78 mL, 5.0 mmol) and diisopropylethylamine (2.61 mL, 15.0 mmol) to give **253** (1.57 g, 84%). M.p. 162-164 °C.

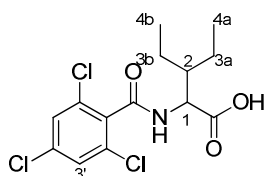
δ_{H} (400 MHz, CDCl_3): 7.37-7.22 (m, 7 H, H-Ar), 6.35 (d, J 7.8, 1H, H-NH), 5.21 (m, 1H, H-1), 3.36 (dd, J 5.4, 14.0, 1H, H-2), 3.27 (dd, J 5.4, 14.0, 1H, H-2)

δ_{C} (100 MHz, CDCl_3): 174.3, 178.3, 133.6, 133.0, 129.5, 129.4, 128.7, 128.6, 128.2, 127.3

ν_{max} (neat) cm^{-1} : 3262, 3065, 1721, 1653, 1582, 1547, 1247, 1137, 876, 850, 690.

HRMS (ESI+) cald. for $[\text{C}_{16}\text{H}_{12}\text{NO}_3\text{Cl}_3 + \text{Na}]^+$ requires 393.9780; found 393.9780.

5.3.10.5 2-(2,4,6-trichlorobenzamido)-3-ethylpentanoic acid (254)



Procedure F was followed using DL-2-amino-3-ethylpentanoic acid (796 mg, 5.0 mmol), 2,4,6-trichlorobenzoyl chloride (0.78 mL, 5.0 mmol) and diisopropylethylamine (2.61 mL, 15.0 mmol) to give 2-(2,4,6-trichlorobenzamido)-3-ethylpentanoic acid (1372 mg, 78%). M.p. 183-185 °C.

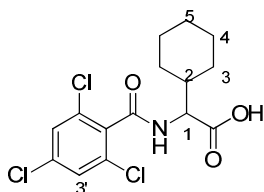
δ_{H} (400 MHz, CDCl_3): 7.38 (s, 2H, H-3'), 6.24 (d, $J = 8.8$, 1H, NH), 5.08 (dd, $J = 3.6, 8.8$, 1H, H-1), 1.98-1.87 (m, 1H, H-2), 1.56-1.29 (m, 4H, H-3a,b), 1.07 (t, $J = 7.2$, 3H, H-4a), 1.01 (t, $J = 7.2$, 3H, H-4b).

δ_{C} (100 MHz, CDCl_3): 175.2 (q), 163.2 (q), 135.6 (q), 133.7 (q), 132.6 (q), 127.8, 53.2, 44.2, 22.5, 22.3, 11.4, 11.3.

ν_{max} (neat) cm^{-1} : 3283, 3088, 2095, 2878, 2480, 1721, 1615, 1582, 1547, 1459, 1368, 1344, 1208, 1138, 966, 857, 820, 804, 710.

HRMS (ESI⁺): calcd. for $\text{C}_{14}\text{H}_{16}\text{Cl}_3\text{NO}_3$ requires 374.0093; found 374.0087.

5.3.10.6 N-(2,4,6-Trichlorobenzoyl) cyclohexylglycine (255)



Procedure F was followed using DL-cyclohexylglycine methyl ester (1.10 g, 6.4 mmol), 2,4,6 trichlorobenzoyl chloride (1.00 mL, 6.4 mmol) and diisopropylethylamine (3.35 mL, 19.2 mmol) to give 2,4,6 trichloro-*N*-benzoyl cyclohexylglycine (1.91 g, 83%) as an off-white solid. M.p. 166-168 °C.

δ_{H} (400 MHz, CDCl_3): 7.37 (s, 2H, H-3'), 6.46 (d, $J = 8.4$, 1H, NH), 4.83 (dd, 4.4, 8.4, 1H, H-1), 2.02 (m, 1H, H-2), 1.89-1.76 (m, 3H, H-3, H-5), 1.75-1.65 (m, 2H, H-4), 1.37-1.24 (m, 3H, H-3, H-5), 1.24-1.10 (m, 2H, H-4).

δ_{C} (100 MHz, CDCl_3): 175.0 (q), 163.3 (q), 135.6 (q), 133.6 (q), 132.6 (q), 127.7, 56.6, 40.5, 29.1, 27.5, 25.6, 25.5 (2C).

ν_{max} (neat) cm^{-1} : 3269, 3077, 2929, 2855, 1713, 1649, 1547, 1449, 1368, 1305, 1270, 1137, 908, 856, 820, 806, 729, 698.

HRMS (ESI⁺): calcd. for $[\text{C}_{15}\text{H}_{16}\text{NO}_3\text{Cl}_3 + \text{Na}]^+$ requires 386.0093; found 386.0098.

5.3.11 Conversion of *N*-protected amino acids to azlactones.

5.3.12 Cyclization procedure using DCC:

A round bottom flask was flushed with nitrogen, charged with a stirring bar and a solution of the appropriate *N*-benzoylated amino acid in CH_2Cl_2 (1.0 eq., 0.11 M). To this, a solution of DCC in CH_2Cl_2 (1.0-1.2 eq., 0.33 M) was added and stirring continued at room temperature for 1-4 h. The resulting suspension was filtered to remove the white precipitate and concentrated *in vacuo*. The crude product was eluted on a column of silica

gel (19:1 hexane-EtOAc), dried as necessary under high vacuum and used immediately without further purification.

5.3.13 Cyclization procedure using EDCI:

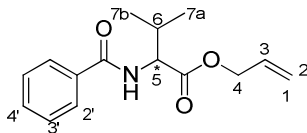
A round bottom flask was flushed with nitrogen, charged with a stirring bar and the appropriate *N*-benzoylated amino acid (1.0 equiv.), fitted with a septum and CHCl_3 added *via* syringe. To this 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) (1.1 equiv.) was added and stirring continued at room temperature for 1-4 h. The reaction mixture was then diluted with CH_2Cl_2 washed twice with saturated NaHCO_3 solution at 0 °C, followed by washing with water. The organic layer was then dried over MgSO_4 and filtered and the solvent was removed *in vacuo*. The crude product was then filtered through a pad of silica gel using CH_2Cl_2 as the eluents. The solvent was then removed *in vacuo* and the product dried as necessary under high vacuum and used immediately without further purification.

5.3.14 Dynamic kinetic resolution of azlactones

5.3.15 Procedure G: General procedure for the dynamic kinetic resolution of racemic azlactones

A 3 mL reaction vial containing a stirring bar was charged with the appropriate catalyst (0.02 mmol). The reaction vial was flushed with argon and fitted with a stopper. CH_2Cl_2 (0.5 mL), Styrene (23 μL , 0.20 mmol) and allyl alcohol (27 μL , 0.40 mmol) were added *via* syringe followed by the appropriate azlactone (0.20 mmol). The resulting reaction mixture was stirred at room temperature for the time indicated in Table 1. The solution was then poured directly onto a column of silica gel and the product purified by flash chromatography (2-10% EtOAc in hexane).

5.3.15.1 *N*-Benzoylvaline allyl ester (**114**)

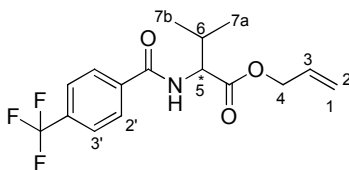


The desired product was synthesized as per general procedure G as a white waxy solid (7.8 mg, 15%) 40% *ee*. M.p. 43-45 °C (litt. M.p. 43-45°C).¹⁴⁸ CSP-HPLC analysis: Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 8.4 min (*R*) and 11.7 (*S*).

δ_{H} (400 MHz, CDCl₃): 7.84 (d, *J* = 7.0, 2H, H-2'), 7.55 (t, *J* = 7.3, 1H, H-4'), 7.48 (app. t, 2H, H-3'), 6.67 (br d, *J* = 8.5, NH), 5.91-6.02 (m, 1H, H-3), 5.40 (dd, *J* = 17.2, 1.2, H-1), 5.31 (dd, *J* = 10.4, 1.2, 1H, H-2), 4.85 (dd, *J* = 8.4, 4.4, 1H, H-5), 4.65-4.76 (m, 2H, H-4), 2.28-2.40 (m, 1H, H-6), 1.05 (d, *J* = 6.8, 3H, H-7a), 1.02 (d, *J* = 6.8, 3H, H-7b).

The absolute configuration of **114** was established by comparing the retention times with those published in the literature.

5.3.15.2 *N*-(4-(Trifluoromethyl)benzoyl) valine allyl ester (**195**)

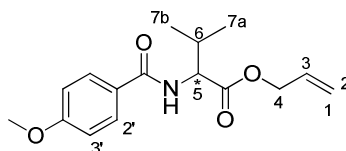


The desired product was synthesized as per general procedure G (24 mg, 36%) 60% *ee* was obtained as a colourless oil. CSP-HPLC analysis: Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 10.7 min (*R*) and 19.9 min (*S*).

δ_{H} (400 MHz, CDCl₃): 7.95 (d, *J* = 8.0, 2H, H-3'), 7.75 (d, *J* = 8.0, 2H, H-2'), 6.68 (br d, *J* = 8.4, 1H, NH), 5.96 (m, 1H, H-3), 5.44-5.29 (m, 2H, H-1, H-2),

4.85 (dd, $J = 4.4, 8.4$, 1H, H-5), 4.77-4.66 (m, 2H, H-4), 2.41-2.29 (m, 1H, H-6), 1.08-1.00 (m, 6H, H-7a,b).¹⁴⁸

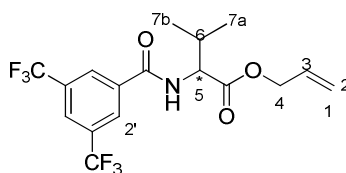
5.3.15.3 *N*-(4-(methoxy)-benzoyl) valine allyl ester (196)



The desired product was synthesized as per general procedure G (6.4 mg, 11%) 34% *ee* obtained as a colourless oil. CSP-HPLC analysis: Chiralpak OD-H (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 7.8 min (major enantiomer) and 25.3 (minor enantiomer).¹⁴⁸

δ_H (400 MHz, CDCl₃): 7.81 (d, $J = 8.8$, 2H, H-2'), 6.97 (d, $J = 8.8$, 2H, H-3'), 6.57 (br d, $J = 8.0$, 1H, NH), 5.96 (m, 1H, H-3), 5.43-5.26 (m, 2H, H-1, H-2), 4.84 (dd, $J = 4.8, 8.4$, H-5), 4.76-4.62 (m, 2H, H-4), 3.89 (s, 3H, H-4'), 2.39-2.24 (m, 1H, H-6), 1.05 (d, $J = 6.8$, 3H, H-7a), 1.02 (d, $J = 6.8$, 3H, H-7b).¹⁴⁸

5.3.15.4 *N*-(3,5-Bis-(trifluoromethyl)benzoyl) valine allyl ester (203)



The desired product was synthesized as per general procedure G to give **203** (68 mg, 86%) 67% *ee* as a white solid. M.p. 59-60 °C. CSP-HPLC analysis: Chiralpak OD-H (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 3.7 min (*R*) and 4.7 min (*S*).

δ_{H} (400 MHz, CDCl_3): 8.25 (s, 2H, H-2'), 8.04 (s, 1H, H-4'), 6.88 (br d, $J = 8.4$, 1H, NH), 6.02-5.89 (m, 1H, H-3), 5.40 (dd, $J = 1.2, 17.2$, 1H, H-1), 5.33 (dd, $J = 1.2, 10.4$, 1H, H-2), 4.85 (dd, $J = 4.8, 8.4$, 1H, H-5), 4.78-4.66 (m, 2H, H-4), 2.29-2.43 (m, 1H, H-6), 1.07-1.02 (app. t, 6H, H-7a,b).

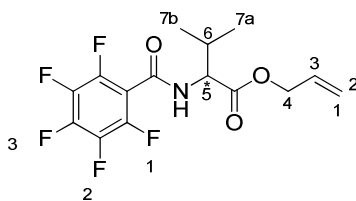
δ_{C} (100 MHz, CDCl_3): 171.3 (q), 164.5 (q), 135.7 (q), 131.7 (q, $J = 33.7$, C- CCF_3), 130.8, 127.0, 124.8 (sept, $J = 3.8$), 122.4 (q, $J = 273.0$, C- CF_3), 119.0, 65.8, 57.4, 31.1, 18.5, 17.5.

δ_{F} (376 MHz, CDCl_3): -63.5 (s, 6F).

ν_{max} (neat) cm^{-1} : 3301, 3088, 2964, 1735, 1649, 1556, 1276, 1168, 1122, 906, 847, 700, 681.

HRMS (ESI+) calcd. for $[\text{C}_{17}\text{H}_{17}\text{NO}_3\text{F}_6 + \text{Na}]^+$ requires 420.1010; found 420.1030.

5.3.15.5 *N*-pentafluorobenzoylvaline allyl ester (204)



The desired product was synthesized as per general procedure G (67 mg, 95%) 71% *ee* as a white solid. M.p. 90-91 °C. CSP-HPLC analysis: Chiralpak OD-H (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 7.0 min (*R*) and 9.8 min (*S*).

δ_{H} (400 MHz, CDCl_3): 6.53 (br d, $J = 8.0$, 1H, NH), 6.01-5.89 (m, 1H, H-3), 5.39 (dd, $J = 1.2, 17.2$, 1H, H-1), 5.32 (dd, $J = 0.8, 10.4$, 1H, H-2), 4.83 (dd, $J = 4.4, 8.8$, 1H, H-5), 4.76-4.64 (m, 2H, H-4), 2.42-2.29 (m, 1H, H-6), 1.06 (d, $J = 6.8$, 3H, H-7a), 0.98 (d, $J = 6.8$, 3H, H-7b).

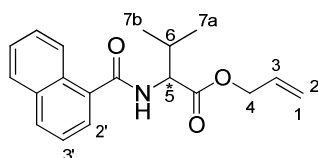
δ_{C} (100 MHz, CDCl_3): 170.4 (q), 156.7 (q), 143.8 (d, $J = 248.7$, CF), 142.0 (d, $J = 251.0$, CF), 137.2 (d, $J = 255.5$, CF), 130.8, 119.0, 110.8 (q), 65.8, 57.3, 18.5, 17.1.

δ_{F} (376 MHz, CDCl_3): -140.6 (m, 2F, F-1), -150.8 (t, $J = 20.6$, 1F, F-3), -160.4 (dt, $J = 9.3$, 22.9, 2F, F-2).

ν_{max} (neat) cm^{-1} : 3277, 3095, 2969, 1734, 1656, 1501, 1217, 1106, 987, 754.

HRMS (ESI⁺): calcd. for $[\text{C}_{15}\text{H}_{14}\text{F}_5\text{NO}_3 + \text{Na}]^+$ requires 374.0792; found 374.0803.

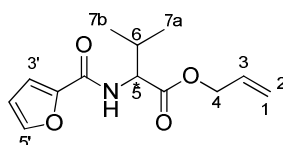
5.3.15.6 *N*-Naphthoylvaline allyl ester (**216**)



The desired product was synthesized as per general procedure G (12.5 mg, 20%) 53% *ee* as a white solid. M.p. 53-54 °C. CSP-HPLC analysis: Chiralpak OD-H (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 10.2 min (*R*) and 13.2 (*S*).¹¹⁸

δ_{H} (400 MHz, CDCl_3): 8.37 (d, $J = 8.4$, 1H, H-8'), 7.97 (d, $J = 8.4$, 1H, H-2'), 7.91 (d, 1H, H-5'), 7.71 (dd, $J = 1.2, 7.2$, 1H, H-4'), 7.63-7.54 (m, 2H, H-6, H-7), 7.51 (dd, $J = 7.2, 8.0$, 1H, H-3), 6.51 (d, $J = 8.8$, 1H, NH), 6.05-5.94 (m, 1H, H-3), 5.42 (dd, $J = 1.2, 17.2$, 1H, H-1), 5.33 (dd, $J = 1.2, 10.4$, 1H, H-2), 4.97 (dd, $J = 4.4, 8.8$, 1H, H-5), 2.47-2.34 (m, 1H, H-6), 1.14 (d, $J = 6.8$, 3H, H-7a), 1.02 (d, $J = 6.8$, 3H, H-7b).

5.3.15.7 *N*-Furoylvaline allyl ester (**217**)



The desired product was synthesized as per general procedure G to give **217** (30 mg, 59%) 75% *ee* as a colourless oil. CSP-HPLC analysis: Chiralpak AD-H (4.6 mm x 25 cm),

hexane/IPA: 9/1, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 7.9 min (*R*) and 10.4 min (*S*).

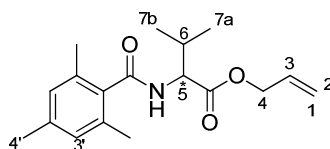
δ_{H} (400 MHz, CDCl₃): 7.49 (d, *J* = 1.6, 1H, H-5'), 7.14 (d, *J* = 3.6, 1H, H-3'), 6.85 (d, *J* = 8.8, 1H, NH), 6.52 (dd, *J* = 1.6, 3.6, 1H, H-4), 6.00-5.88 (m, 1H, H-3), 5.37 (dd, *J* = 1.2, 17.2, 1H, H-1), 5.29 (dd, *J* = 1.2, 10.4, 1H, H-2), 4.77 (dd, *J* = 4.8, 8.8, 1H, H-5), 4.73-4.63 (m, 2H, H-4), 2.37-2.24 (m, 1H, H-6), 1.05-0.97 (m, 6H, H-7a,b).

δ_{C} (100 MHz, CDCl₃): 171.1 (q), 157.7 (q), 147.1 (q), 143.7, 131.1, 118.6, 114.3, 111.8, 65.5, 56.2, 31.2, 18.6, 17.3.

ν_{max} (neat) cm⁻¹: 3321, 2966, 1736, 1659, 1592, 1514, 1473, 1311, 1184, 1148, 1009, 934, 758.

HRMS (ESI⁺): Calcd. for [C₁₃H₁₇NO₄ + Na]⁺ requires 274.1055, found 274.1055.

5.3.15.8 *N*-Mesitylvaline allyl ester (220)



The desired product was synthesized as per general procedure G (12 mg, 19%) 74% *ee* as a white solid. M.p. 74 °C. CSP-HPLC analysis: Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 7.0 min (*S*) and 8.9 min (*R*).

δ_{H} (400 MHz, CDCl₃): 6.88 (s, 2H, H-3'), 6.13 (d, *J* = 8.8, 1H, NH), 6.01-5.89 (m, 1H, H-3), 5.39 (dd, *J* = 1.2, 17.2, 1H, H-1), 5.30 (dd, *J* = 1.2, 10.4, 1H, H-2), 4.85 (dd, *J* = 4.4, 8.8, 1H, H-5), 4.75-4.64 (m, 2H, H-4), 2.33 (s,

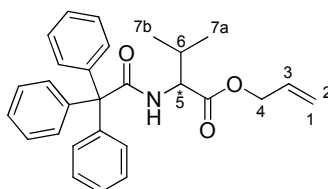
6H, H-2'), 2.31 (s, 3H, H-4'), 1.08 (d, $J = 6.8$, 3H, H-7a), 0.96 (d, $J = 6.8$, 3H, H-7b).

δ_C (100 MHz, $CDCl_3$): 171.1 (q), 170.1 (q), 138.2 (q), 134.1 (q), 133.9 (q), 131.1, 127.8, 118.7, 65.5, 56.5, 30.7, 20.6, 18.9, 18.8, 17.3.

ν_{max} (neat) cm^{-1} : 3268, 2964, 2923, 1744, 1637, 1532, 1186, 1149, 1032, 992, 848, 658.

HRMS (ESI⁺): calcd. for $[C_{18}H_{25}NO_3 + Na]^+$ requires 326.1732; found 326.1741.

5.3.15.9 N-Tritoyl valine allyl ester (221)



The desired product was synthesized as per general procedure G (84.6 mg, 99%) 53% *ee* as a colourless oil. CSP-HPLC analysis: Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 19/1, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 13.4 min (minor enantiomer) and 23.7 min (major enantiomer).

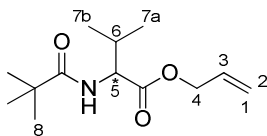
δ_H (400 MHz, $CDCl_3$): 7.35-7.26 (m, 15H, Ar-H), 6.21 (d, $J = 8.4$, 1H, NH), 5.97-5.86 (m, 1H, H-3), 5.34 (dd, $J = 1.2, 16.8$, 1H, H-1), 5.27 (dd, $J = 1.2, 10.4$, 1H, H-2), 4.70-4.58 (m, 3H, H-4, H-5), 2.26-2.11 (m, 1H, H-6), 0.86 (d, $J = 6.8$, 3H, H-7), 0.70 (d, $J = 6.8$, 3H, H-7).

δ_C (100 MHz, $CDCl_3$): 172.9 (q), 170.9 (q), 142.8 (q), 131.2, 130.1, 127.5, 126.6, 118.5, 67.4, 65.4, 57.4, 30.4, 18.7, 17.0.

ν_{max} (neat) cm^{-1} : 3437, 3059, 2963, 1736, 1674, 1490, 1446, 1188, 1146, 987, 742, 699.

HRMS (ESI⁺): Calcd. for $[C_{28}H_{29}NO_3 + H]^+$ requires 428.2226; found 428.2227.

5.3.15.10 *N*-*t*-Butyroyl valine allyl ester (218)



The desired product was synthesized as per general procedure G (48 mg, 99%) 41% *ee* as a clear oil. CSP-HPLC analysis: Chiralpak OD-H (4.6 mm x 25 cm), hexane/IPA: 19/1, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 5.4 min (major enantiomer) and 6.3 min (minor enantiomer).

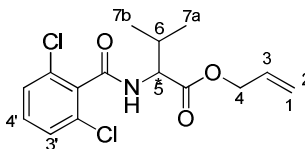
δ_{H} (400 MHz, CDCl₃): 6.15 (d, *J* = 7.2, 1H, NH), 5.97-5.87 (m, 1H, H-3), 5.36 (dd, *J* = 1.2, 17.2, 1H, H-1), 5.28 (dd, *J* = 1.2, 10.4, 1H, H-2), 4.72-4.57 (m, 3H, H-4, H-5), 2.28-2.14 (m, 1H, H-6), 1.25 (s, 9H, H-8), 0.98-0.90 (m, 6H, H-7a,b).

δ_{C} (100 MHz, CDCl₃): 177.9 (q), 171.6 (q), 131.1, 118.5, 65.4, 56.2, 38.4 (q), 31.0, 27.1, 18.5, 17.2.

ν_{max} (neat) cm⁻¹: 3362, 2964, 2875, 1737, 1650, 1507, 1188, 1143, 990, 932.

HRMS (ESI⁺): calcd. for [C₁₃H₂₃NO₃ + Na]⁺ requires 264.1576; found 264.1571.

5.3.15.11 *N*-(2,6 Dichlorobenzoyl) valine allyl ester (219)



The desired product was synthesized as per general procedure G (46 mg, 69%), 76% *ee*, as a white solid. M.p. 73 °C. CSP-HPLC analysis: Chiralpak AS (4.6 mm x 25 cm),

hexane/IPA: 9/1, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 7.0 min (*S*) and 13.2 min (*R*).

δ_{H} (400 MHz, CDCl₃): 7.39-7.34 (m, 2H, H-3'), 7.33-7.27 (m, 1H, H-4), 6.34 (d, *J* = 8.8, 1H, NH), 6.02-5.90 (m, 1H, H-3), 5.39 (dd, *J* = 1.2, 17.2, 1H, H-1), 5.31 (dd, *J* = 1.2, 10.4, 1H, H-2), 4.88 (dd, *J* = 4.4, 8.8, 1H, H-5), 4.77-4.65 (m, 2H, H-4), 2.44-2.32 (m, 1H, H-6), 1.12 (d, *J* = 6.8, 3H, H-7a,b), 1.01 (d, *J* = 6.8, 3H, H-7).

δ_{C} (100 MHz, CDCl₃): 171.0 (q), 164.2 (q), 135.8 (q), 132.3, 131.5 (q), 130.7, 128.1, 119.2, 66.0, 57.4, 31.7, 19.1, 17.8.

ν_{max} (neat) cm⁻¹: 3281, 2964, 1749, 1649, 1539, 1430, 1314, 1186, 989, 776, 682.

HRMS (ESI⁺): calcd. for [C₁₅H₁₇NO₃Cl₂ + Na]⁺ requires 352.0483; found 352.0472.

Further CSP-HPLC analysis was carried out after hydrogenolysis by placing the compound (33 mg, 0.10 mmol) in a round bottomed flask with EtOAc (1 mL), diisopropylethylamine (52.3 μ l, 0.30 mmol) and 10% Pd/C (10.6 mg, 10mol%). The flask was evacuated and filled with an atmosphere of H₂ (1 atm) for 4 h to afford the dechlorinated propyl ester upon purification by flash chromatography (2-10% EtOAc in hexane). Chiralpak ADH (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: min (minor enantiomer) and min (major enantiomer).

5.3.16 General procedure H for the dynamic kinetic resolution of racemic azlactones

A 5 mL reaction vial containing a stirring bar was charged with the appropriate catalyst (0.04 mmol). The reaction vial was flushed with argon and fitted with a stopper. CDCl₃ (2-4 mL) and allyl alcohol (16 μ L, 0.24 mmol) were added *via* syringe followed by the appropriate azlactone (0.20 mmol). The resulting reaction was stirred at 19 °C for the time indicated in Table 2. The solution was filtered through a thin pad of silica gel to remove

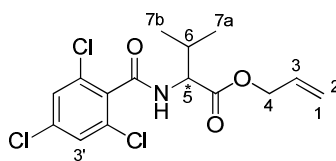
the catalyst, concentrated *in vacuo* and then purified by flash chromatography (49:1-9:1 hexane-EtOAc).

5.3.17 Sample preparation for CSP-HPLC analysis: Procedure for hydrogenolysis

The amide products following ring-opening of trichloroaryl azlactones are difficult to resolve using CSP-HPLC due to significant peak-tailing. To circumvent this difficulty the purified ring-opened products were reduced and dechlorinated by hydrogenolysis using the following procedure.

The compound (0.10 mmol) was placed in a round bottomed flask with EtOAc (1 mL), diisopropylethylamine (70 μ l, 0.40 mmol) and 10% Pd/C (10.6 mg, 10mol%). The flask was evacuated and filled with an atmosphere of H₂ (1 atm) for 4 h to afford the dechlorinated propyl ester upon purification by flash chromatography (2-10% EtOAc in hexane).

5.3.17.1 *N*-(2,4,6-Trichlorobenzoyl) valine allyl ester (225)



Procedure H was followed, stirring was continued for 72 h, to give the desired product (67 mg, 92%), 90% *ee*, as a white solid. M.p. 56-58 °C.

CSP-HPLC analysis (using hydrogenolysis procedure): Chiralpak ADH (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 7.0 min (*S*) and 13.2 min (*R*).

δ_{H} (400 MHz, CDCl₃): 7.38 (s, 2H, H-3'), 6.36 (d, *J* = 8.8, 1H, NH), 6.01-5.89 (m, 1H, H-3), 5.39 (dd, *J* 1.2, 17.2, 1H, H-1), 5.31 (dd, *J* = 1.2, 10.4, 1H, H-2), 4.85 (dd, *J* = 4.4, 8.8, 1H, H-5), 4.76-4.64 (m, 2H, H-4), 2.43-2.30

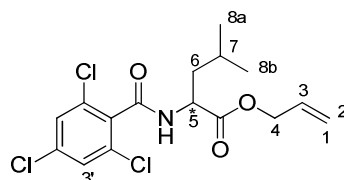
(m, 1H, H-6), 1.10 (d, $J = 6.8$, 3H, H-7a), 1.00 (d, $J = 6.8$, 3H, H-7b).

δ_C (100 MHz, $CDCl_3$): 170.5 (q), 163.0 (q), 135.5 (q), 133.9 (q), 132.6 (q), 130.9, 127.8, 118.9, 65.7, 57.0, 31.2, 18.7, 17.3.

ν_{max} (neat) cm^{-1} : 3283, 3077, 2963, 1731, 1651, 1569, 1536, 1246, 990, 939, 867, 736.

HRMS (ESI⁺): calcd for $[C_{15}H_{16}NO_3Cl_3 + Na]^+$ requires 386.0093; found 386.0103.

5.3.17.2 *N*-(2,4,6-Trichlorobenzoyl) leucine allyl ester (268)



Procedure H was followed, stirring was continued for 115 h, to give the desired product (73 mg, 96%), 83% *ee*, as a colourless oil. CSP-HPLC analysis (using hydrogenolysis procedure): Chiralpak ADH (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 7.8 min (*R*) and 12.8 min (*S*).

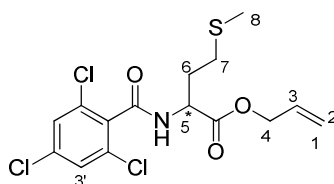
δ_H (400 MHz, $CDCl_3$): 7.37 (s, 2H, H-3'), 6.21 (br d, $J = 8.4$, 1H, NH), 6.01-5.89 (s, 1H, H-3), 5.38 (dd, $J = 1.2, 17.2$, 1H, H-1), 5.30 (dd, $J = 1.2, 10.4$, 1H, H-2), 4.96-4.88 (m, 1H, H-5), 4.75-4.61 (m, 2H, H-4), 1.92-1.65 (m, 3H, H-6, H-7), 1.04 (d, $J = 6.4$, 3H, H-8a), 1.00 (d, $J = 6.4$, 3H, H-8b).

δ_C (100 MHz, $CDCl_3$): 171.4 (q), 162.7 (q), 135.5 (q), 133.7 (q), 132.6 (q), 131.0, 127.7, 118.7, 65.7, 50.6, 41.3, 24.3, 22.4, 21.4.

ν_{max} (neat) cm^{-1} : 3315, 2960, 1741, 1641, 1536, 1197, 1164, 693.

HRMS (ESI⁺): calcd for $[C_{15}H_{16}NO_3Cl_3 + Na]^+$ requires 386.0093; found 386.0103.

5.3.17.3 *N*-(2,4,6-Trichlorobenzoyl) methionine allyl ester (267)



Procedure H was followed to give **45** as a white solid (76 mg, 96%). M.p. 76-78 °C. CSP-HPLC analysis: Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 10.0 min (*S*) and 12.3 min (*R*).

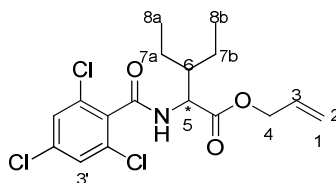
δ_{H} (400 MHz, CDCl₃): 7.39 (s, 2H, H-3'), 6.53 (d, *J* = 7.6, 1H, NH), 6.02-5.90 (m, 1H, H-3), 5.40 (dd, *J* = 1.2, 17.2, 1H, H-1), 5.33 (dd, *J* = 1.2, 10.4, 1H, H-2), 5.00 (td, *J* = 5.2, 7.6, 1H, H-5), 4.78-4.67 (m, 2H, H-4), 2.37-2.59 (m, 2H, H-7), 2.45-2.33 (m, 1H, H-6), 2.23-2.10 (m, 4H, H-6, H-8).

δ_{H} (400 MHz, CDCl₃): 170.5 (q), 162.8 (q), 135.7 (q), 133.5 (q), 132.5 (q), 130.7, 127.8, 119.1, 66.1, 51.5, 31.3, 29.3, 15.0.

ν_{max} (neat) cm⁻¹: 3247, 3081, 2917, 1731, 1644, 1582, 1548, 1427, 1296, 988, 819, 690.

HRMS (ESI+) calcd. For [C₁₅H₁₆NO₃Cl₃S + H]⁺ requires 395.9995; found 395.9990.

5.3.17.4 Allyl 2-(2,4,6-trichlorobenzamido)-3-ethylpentanoate (270)



Procedure H was followed, stirring was continued for 5 d, to give the desired product (71 mg, 91%), 90% *ee*, as a white solid. M.p. 70-71 °C. CSP-HPLC analysis (using hydrogenolysis procedure): Chiralpak ADH (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 5.0 min (*R*) and 8.3 min (*S*).

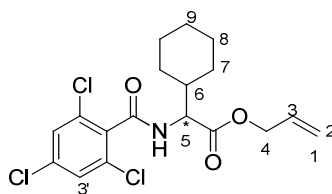
δ_{H} (400 MHz, CDCl_3): 7.38 (s, 2H, H-3'), 6.26 (d, $J = 9.2$, 1H, H-NH), 6.01-5.89 (m, 1H, H-3), 5.38 (dd, $J = 1.2, 17.2$, 1H, H-1), 5.31 (dd, $J = 1.2, 10.4$, 1H, H-2), 5.05 (dd, $J = 4.0, 8.8$, 1H, H-5), 4.76-4.63 (m, 2H, H-4), 1.94-1.84 (m, 1H, H-6), 1.50-1.34 (m, 4H, H-7a,b), 1.06 (t, $J = 7.2$, 3H, H-8a), .99 (t, $J = 7.2$, 3H, H-8b).

δ_{C} (100 MHz, CDCl_3): 171.1 (q), 162.9 (q), 135.5 (q), 133.9 (q), 132.6, 131.0 (q), 127.7, 118.7, 65.7, 53.5, 44.4, 22.5, 22.2, 11.4, 11.3.

ν_{max} (neat) cm^{-1} : 3262, 3083, 2956, 2876, 1740, 1651, 1583, 1549, 1339, 1203, 1139, 984, 932, 850, 814, 699.

HRMS (ESI+): calcd. for $[\text{C}_{17}\text{H}_{20}\text{Cl}_3\text{NO}_3 + \text{Na}]^+$ requires 414.0406; found 414.0418.

5.3.17.5 Allyl 2-(2,4,6-trichlorobenzamido)-2-cyclohexylacetate (271)



Procedure H was followed, stirring was continued for 5 d, to give the desired product (74.5 mg, 92%), 92% *ee*, as a white solid. M.p. 70-71 °C. CSP-HPLC analysis (using hydrogenolysis procedure): Chiralpak ADH (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min^{-1} , RT, UV detection at 220 nm, retention times: 5.2 min (*R*) and 8.5 min (*S*).

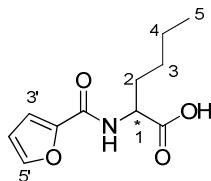
δ_{H} (400 MHz, CDCl_3): 7.38 (s, 2H, H-3'), 6.32 (d, $J = 8.8$, 1H, NH), 6.00-5.89 (m, 1H, H-3), 5.39 (dd, $J = 1.2, 17.2$, 1H, H-1), 5.31 (dd, $J = 1.2, 10.4$, 1H, H-2), 4.82 (dd, $J = 4.8, 8.8$, 1H, H-5), 4.75-4.65 (m, 2H, H-4), 2.04-1.93 (m, 1H, H-6), 1.88-1.75 (m, 3H, H-7, H-9), 1.75-1.66 (m, 2H, H-8), 1.35-1.10 (m, 5H, H-7, H-8, H-9).

δ_{C} (100 MHz, CDCl_3): 170.4 (q), 162.9 (q), 135.5 (q), 133.9 (q), 132.6 (q), 130.97, 127.75, 118.76, 65.6, 56.7, 40.8, 29.1, 27.7, 25.6, 25.5.

ν_{max} (neat) cm^{-1} : 3255, 3079, 2928, 2854, 1736, 1644, 1580, 1545, 1449, 1368, 1252, 1135, 991, 818, 715.

HRMS (ESI+): calcd. for $[\text{C}_{18}\text{H}_{20}\text{Cl}_3\text{NO}_3 + \text{Na}]^+$ requires 426.0406; found 426.0403.

5.3.18 N-(2-Furoyl)norleucine (**277a**)



Procedure E was followed using DL-norleucine, and furoyl chloride to afford **277a** as an off-white solid (0.95 g, 83%), mp 94–96 °C;

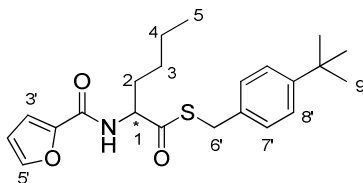
δ_{H} (400 MHz, DMSO- d_6): 8.44 (d, J 8.2, 1H, H-NH), 7.86 (dd, J 1.8, 0.8, 1H, H-5'), 7.19 (dd, J 3.5, 0.8, 1H, H-3'), 6.64 (dd, J 1.8, 3.5, 1H, H-4'), 4.27–4.35 (m, 1H, H-1), 1.69–1.85 (m, 2H, H-2), 1.22–1.39 (m, 4H, H-3 and H-4), 0.86 (t, 3H, J 7.2, H-5).

δ_{C} (100 MHz, DMSO- d_6): 173.7 (q), 157.9 (q), 147.4 (q), 145.2, 113.8, 111.8, 51.8, 30.2, 27.9, 21.7, 13.8

ν_{max} (neat) cm^{-1} : 3370, 2952, 2870, 1734, 1715, 1625, 1596, 1530, 1479, 1416, 1288, 1200, 1151, 1007, 870, 790, 748;

HRMS (ESI+) calcd for $[\text{C}_{11}\text{H}_{15}\text{NO}_4 + \text{Na}]^+$ requires 248.0899; found, 248.0905.

5.3.19 N-(2-Furoyl)norleucine 4-*t*-butylbenzyl thioester (**278**)



Procedure G was followed using **277** (0.2 mmol), 4-*t*-butylbenzyl thiol (75 μl) catalyst **147** (9.1 mg, 10 mol%) and CH_2Cl_2 . After purification **278** was obtained as a yellow oil (136.0 mg, 91%, 65% ee). CSP-HPLC analysis: Chiralcel OD-H (4.6 mm $\times$ 25 cm), 90:10 hexane/IPA, 1 mL/min, 254 nm; tR = 7.74 min (major enantiomer) and 9.19 min (minor enantiomer).

δ_{H} (400 MHz, CDCl_3): 0.91 (t, J 7.2, 3H, H-5), 1.30–1.43 (m, 13H, H-3, H-4 and H-9'), 1.71–1.82 (m, 1H, H-2), 1.98–2.08 (m, 1H, H-2), 4.14 (s, 2H, H-6'), 4.91 (dt, J = 4.8, 8.4, 1H, H-1), 6.54 (dd, J 1.8, 3.6, 1H, H-4'), 6.76 (d, J 8.4, 1H, H-NH), 7.18 (d, J 3.6, 1H, H-3'), 7.23 (d, J 8.4, 2H-7'), 7.33 (d, J 8.4, 2H, H-8'), 7.49 (d, J 1.8 Hz, 1H, H-5').

δ_{C} (100 MHz, CDCl_3): 199.5 (q), 157.6 (q), 149.4 (c), 143.9, 133.3 (q), 128.1, 125.2, 114.7, 111.9, 58.2, 34.1 (q), 32.5, 32.2, 30.9, 26.9, 21.9, 13.4.

ν_{max} (neat) cm^{-1} : 3289, 2958, 1865, 1651, 1591, 1568, 1515, 1473, 1302, 1180, 1009, 934, 884, 756

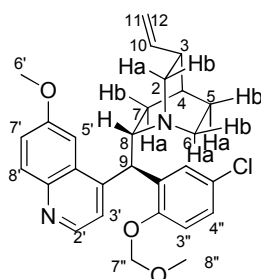
HRMS (ESI+) calcd for $[\text{C}_{22}\text{H}_{29}\text{NO}_3\text{S}_4\text{Na}]^+$ requires 410.1766; found, 410.1773.

5.4 Experimental data for chapter 4

5.4.1 Procedure I: procedure for the deprotection of catalysts by acetal cleavage.

Protected catalyst (1.0 eq.) was placed in a flask and HCl (5 M, aq.) was added. Stirring was continued for the time specified or until complete conversion was observed by TLC. The solution was then slowly neutralised with NaHCO₃ (conc. aq.) and extracted twice with CH₂Cl₂. Removal of solvent after, drying over MgSO₄, typically afforded the desired compound without need for further purification.

5.4.1.1 (2*S*)-2-((*R*)-(5-chloro-2-(methoxymethoxy)phenyl)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (**295**)



A solution of **Q22a** (2.06 g, 6.0 mmol) in dry THF (24.0 mL) was added to a round bottom flask containing a solution of 2-bromomagnesium-4-chloro-methoxymethylphenol (1.58 g, 6.3 mmol) in dry THF (24 mL) (prepared using general procedure C), and heated under reflux overnight under a protective argon atmosphere. The resulting solution was cooled and a saturated aqueous solution of NH₄Cl (30 mL) was added. The resulting mixture was then extracted with CH₂Cl₂ (2 x 120 mL), and the organic extracts were combined, dried over MgSO₄ and filtered and solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (25:25:1 hexane-EtOAc-NEt₃) to give **295** (1008 mg, 35%) as an off-white solid. M.p. 136-137 °C. [α]_D²⁰ = -151.03 (c 1.00, CHCl₃).

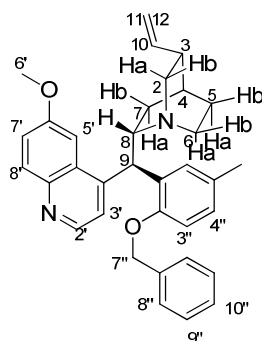
δ_{H} (400 MHz, CDCl_3): 8.75 (d, $J = 4.4$, 1H, H-2'), 8.01 (d, $J = 9.2$, 1H, H-8'), 7.72 (br d, $J = 2.0$, 1H, H-5'), 7.39 (dd, $J = 2.4$, 9.2, 1H, H-7'), 7.36-7.32 (m, 2H, H-3', H-6''), 7.07 (dd, $J = 2.4$, 8.8, 1H, H-4''), 6.99 (d, $J = 8.8$, 1H, H-3''), 6.00-5.89 (m, 1H, H-10), 5.26 (br d, $J = 10.8$, H-9), 5.30-5.04 (m, 4H, H-11, H-12, H-7'') 4.00 (s, 3H, H-6'(OCH₃)), 3.63 (br d, $J = 8.0$, H-8), 3.36 (br s, 1H, H-6a), 3.28-3.16 (m, 4H, H-8'', H-2b), 2.84-2.64 (m, 2H, H-2a, H-6b), 2.30 (br s, 1H, H-3), 1.81 (br s, 1H, H-7b), 1.71 (br s, 1H, H-4), 1.68-1.50 (m, 2H, H-5a, H-5b), 0.88 (app. dd, 1H, H-7a).

δ_{C} (100 MHz, CDCl_3): 157.3 (q), 153.0 (q), 147.2, 146.4 (q), 144.2 (q), 141.6, 132.6 (q), 131.3, 128.8 (q), 127.7, 127.0, 126.5 (q), 120.3, 119.9, 114.7, 113.9, 102.3, 94.2, 59.2, 56.1, 55.5, 55.1, 40.8, 39.2, 27.8, 27.7, 27.4.

ν_{max} (solid)/ cm^{-1} : 2935, 2859, 1621, 1586, 1508, 1473, 1232, 1153, 1075, 985, 851, 813, 681.

HRMS (ESI⁺): calcd. for $[\text{C}_{28}\text{H}_{31}\text{N}_2\text{O}_3 + \text{H}]^+$ requires: 479.2101 found: 479.2100

5.4.1.2 (2*S*)-2-((*R*)-(5-methyl-2-(methoxymethoxy)phenyl)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (286)



A solution of 9-*epi*-chloroquinine (2.60 g, 7.58 mmol) in dry THF (24.0 mL) was added to a round bottom flask containing a solution of 1-((2-bromomagnesium-4-methylphenoxy)methyl)benzene (2.29 g, 7.58 mmol) in dry THF (24.0 mL) (prepared using general procedure E), and heated under reflux overnight under a protective argon atmosphere. The resulting solution was cooled and a saturated aqueous solution of NH₄Cl (30 mL) was added. The resulting mixture was then extracted with CH₂Cl₂ (2 x 120 mL), and the organic extracts were combined, dried over MgSO₄ and filtered and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (25:25:1 hexane-EtOAc-NEt₃) to give **286** (1.54 g, 40%) as an off-white solid. M.p. 157-158 °C. $[\alpha]_D^{20} = -45.21$ (c 1.00, CHCl₃).

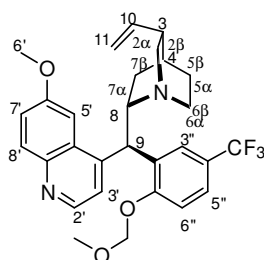
δ_H (400 MHz, CDCl₃): 8.74 (d, J = 4.4, 1H, H-2'), 7.97 (d, J = 9.2, 1H, H-8'), 7.63 (d, J = 2.4, 1H, H-5'), 7.44-7.33 (m, 6H, H-8'', H-9'', H-10'', H-3'), 7.29 (dd, J = 2.4, 9.2, 1H, H-7' (partly obscured by residual CHCl₃ peak)), 7.15 (br s, 1H, H-6''), 6.93 (d, J = 8.4, 1H, H-4''), 6.83 (d, J = 8.4, 1H, H-3''), 6.03-5.91 (m, 1H, H-10), 5.33 (br s, 1H, H-9), 5.14-5.05 (m, 4H, H-11, H-12, H-7''), 3.72 (br s, 1H, H-8), 3.62 (s, 3H, H-6'), 3.49 (br s, H-6a), 3.24 (m, 1H, H-2b), 2.83-2.65 (m, 2H, H-6b, H-2a), 2.35-2.22 (m, 4H, H-5'', H-3), 1.86 (br m, 1H, H-7b), 1.70 (br s, 1H, H-4), 1.64-1.46 (m, 2H, H-5a, H-5b), 0.89 (m, 1H, H-7a).

δ_C (100 MHz, CDCl₃): 157.1 (q), 153.4 (q), 147.2 (q), 147.0, 144.16 (q), 141.8, 136.4 (q), 131.0, 129.9 (q), 129.7 (q), 129.0 (q), 128.6, 128.5, 128.1, 127.8, 127.5, 127.1, 120.8, 119.8, 113.8, 111.3, 102.0, 70.0, 59.7, 56.2, 54.8, 41.0, 39.3, 30.5, 28.2, 27.6, 20.4.

$\nu_{\max}$ (solid)/cm⁻¹: 3031, 2927, 2855, 1621, 1502, 1324, 1234, 1036, 1020, 853, 797, 734, 699.

HRMS (ESI⁺): calcd. for [C₃₄H₃₆N₂O₂ + H]⁺ requires 505.2855; found 505.2864.

5.4.2 (1S,2S,4S,5R)-2-((R)-(2-(methoxymethoxy)-5-(trifluoromethyl)phenyl)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (294)



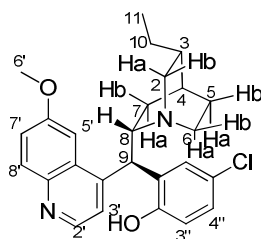
Procedure B was followed using 2-bromo-4-(trifluoromethyl)-methoxymethylphenol (1.70g, 5.96 mmol), magnesium (151mg, 6.20 mmol), THF (27ml) and chloroquine (2.04 g, 5.96 mmol) in THF (27 ml). An eluent of 30-50% EtOAc in Hex with 2% TEA added was used to furnish the title compound **294** (1.26 g, 41%) as an offwhite solid.

δ_{H} (400 MHz, CDCl_3): 8.74 (d, J 4.6, 1H, H-2'), 8.02 (d, J 9.2, 1H, H-8), 7.76-7.64 (m, 2H, H-5' & H-3''), 7.42-7.36 (m, 2H, H-7' & H-6''), 7.34 (d, J 4.6, 1H, H-3'), 7.11 (d, J 8.8, 1H, H-5'), 5.95 (m, 1H, H-10), 5.29 (d, J 10.4, 1H, H-9), 5.24-5.04 (m, 4H, H-11, H-12 & H- OCH_2), 3.99 (s, 3H, H-ArOCH₃), 3.69 (m, 1H, H-8), 3.33 (m, 1H, H-6 α), 3.25-3.13 (m, 4H, H-2 β & H-CH₂OCH₃), 2.81-2.67 (m, 2H, H-2 α & H-6 β), 2.23 (br s, 1H, H-3), 1.85-1.50 (m, 4H, H-4, H-5 α , H-5 β & H-7 β), 0.90 (m, 1H, H-7 α).

δ_{C} (100 MHz, CDCl_3): 157.3 (q), 156.7 (q), 147.2, 146.1, 144.2 (q), 141.6, 131.4, 128.8 (q), 125.0, 124.9, 124.6, 124.5, 123.9 (q, J 270.2, CF_3), 123.3 (q, J 31.4, CCF_3), 120.3, 120.1 (q), 113.9, 113.1, 102.2, 93.8, 59.0, 56.0, 55.6, 55.0, 40.8, 39.2, 27.7, 27.6, 27.4.

 δ_F (376 MHz, CDCl₃): -61.9 (s, 3F)

**5.4.2.2 (8*S*,9*R*)-9-(5-2-chlorohydroxyphenyl)-6'-methoxy-10,11-dihydro-cinchonan
(280)**



A round bottom flask was charged with **287** (500 mg, 1.04 mmol) and HCl (aq. 5 M, 10 mL), and stirred for 16 h. The resulting solution was neutralised using a saturated aqueous solution of NaHCO₃ and extracted three times with CH₂Cl₂ (3 x 35 mL). The organic extracts were combined, dried over MgSO₄ and the solvent was removed under reduced pressure. The resulting material was then placed in a round bottom flask, dissolved in EtOAc (10 mL) and methanol (5 mL) and placed under a protective argon atmosphere. 10% Pd/C (70 mg) was added, and the flask was evacuated and filled with an atmosphere of H₂ at 1 atm. This was stirred for 30 minutes before the flask was evacuated and refilled with argon. The resulting mixture was filtered through a pad of celite with EtOAc as the eluens. The solvent was removed under reduced pressure and the resulting material was purified by flash chromatography (30:20:1 hexane-EtOAc-NEt₃) to give **12** (377 mg, 83%) as a white solid. M.p. 204-205 °C. [α]_D²⁰ = -24.8 (c 0.165, CHCl₃).

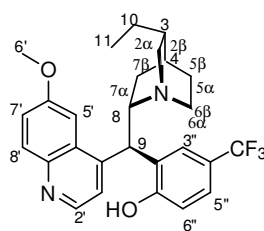
δ_H (400 MHz, MeOD-*d*₄): 8.70 (d, *J* = 4.8, 1H, H-2'), 7.97 (br s, 1H, H-5'), 7.90 (d, *J* = 9.2, 1H, H-8'), 7.74 (d, *J* = 4.8, 1H, H-3'), 7.37 (dd, *J* = 2.8, 9.2, 1H, H-7'), 7.17 (br s, 1H, H-6''), 6.95 (dd, *J* = 2.4, 8.4, 1H, H-4''), 6.78 (d, *J* = 8.4, 1H, H-3''), 5.35 (d, *J* = 10.4, 1H, H-9), 3.99 (s, 3H, H-6'), 3.90 (m, 1H, H-8), 3.71 (m, 1H, H-6a), 3.15 (m, 1H, H-2b), 2.65 (m, 1H, H-2a), 2.49 (m, 1H, H-6b), 2.09 (m, 1H, H-7b), 1.75-1.64 (m, 2H, H-3, H-5b), 1.62-1.47 (m, 4H, H-4, H-5a, H-10), 0.95 (t, *J* = 6.8, 3H, H-11), 0.84 (m, 1H, H-7a).

δ_C (100 MHz, MeOD- d_4): 159.3 (q), 154.3 (q), 148.8 (q), 146.8, 144.0 (q), 130.3 (q), 129.8, 128.4 (q), 128.1, 127.2, 124.6 (q), 122.3, 119.8, 116.6, 102.2, 60.1, 57.6, 55.0, 42.2, 40.9, 36.9, 28.7, 27.6, 27.1, 25.7, 11.0.

$\nu_{\max}$ (solid)/ cm^{-1} : 2926, 2860, 2581, 1622, 1584, 1513, 1477, 1432, 1264, 1242, 1018, 813, 727, 653.

HRMS (ESI+): Calcd. for $[\text{C}_{26}\text{H}_{29}\text{N}_2\text{O}_2\text{Cl} + \text{H}]^+$ requires 437.1996; found 437.2106.

5.4.3 -2-((R)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)-4-(trifluoromethyl)phenol (281)



294 (666 mg, 1.3 mmol) was treated according to procedure 1 with HCl (aq., 5 M, 15 ml) and stirred for 20 hours. The resulting white solid was placed in a RBF with 10% Pd/C (136 mg, 0.128 mmol), EtOAc (5 ml) and EtOH (5 ml) and stirred under Hydrogen (1 atm.) for 45 min. The solids were then removed by filtration through a layer of celite, and solvent was removed under reduced pressure to give the desired compound as a near-white solid (600 mg, 98%). $[\alpha]_D^{20} = -18$ (c 1.24, CHCl_3).

δ_H (400 MHz, DMSO- d_6): 10.95 (br s, 1H, H-OH), 8.73 (d, J 4.6, 1H, H-2'), 7.92-7.84 (m, 2H, H-5' and H-8'), 7.79 (d, J 4.6, 1H, H-3'), 7.45 (br s, 1H, H-3''), 7.36 (dd, J 2.0, 9.2, 1H, H-7'), 7.25 (d, J 8.6, 1H, H-5''), 6.92 (d, J 8.6, 1H, H-6''), 5.21 (d, J 11.4, 1H, H-

9), 3.92 (s, 3H, H-OCH₃), 3.82 (m, 1H, H-8), 3.45 (m, 1H, H-6 α)*, 2.95 (m, 1H, H-2 β), 2.47 (m, 1H, H-6 β)**, 2.30 (m, 1H, H-2 α), 1.88 (m, 1H, H-7 β), 1.60-1.27 (m, 6H, H-CH₂, H-3, H-4, H-5 α & H-5 β), 0.85 (t, J 7.0, 3H, H-CH₃), 0.65 (m, 1H, H-7 α).

*obscured by residual water signal

**obscured by residual solvent signal

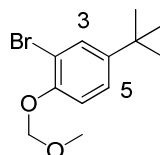
δ_C (100 MHz, DMSO-d₆): 158.2 (q), 157.3 (q), 147.7, 146.8 (q), 144.0 (q), 131.21, 130.3 (q), 128.9 (q), 125.39, 124.8 (q, J 270.4, C-CF₃), 124.1, 121.1, 120.2, 119.3 (q, J 33.7, C-CCF₃), 115.4, 102.61, 58.8, 57.5, 55.4, 41.6, 40.8, 36.7, 28.7, 28.1, 26.9, 25.5, 12.1.

δ_F (376 MHz, CDCl₃): -61.2 (s, 3F)

$\nu_{\max}$ (solid)/cm⁻¹: 2932, 1621, 1589, 1510, 1455, 1322, 1282, 1236, 1106, 825, 715.

HRMS (ESI-): calcd. for [C₂₇H₂₈N₂O₂F₃]⁻ requires: 469.2103; found: 469.2109.

5.4.4 2-bromo-4-(tert-butyl)-1-(methoxymethoxy)benzene (298)



4-*t*-Butylphenol (**300**, 10 g, 66.6 mmol) and chloroform (80 ml), were placed in a RBF and cooled to 0°C. To this a solution of bromine (3.5ml, 137.0 mmol) in chloroform (18 ml) was added dropwise over 60 min maintaining a reaction temperature close to 0 °C. The resulting solution was stirred for a further 3 hours. A concentrated solution of Na₂S₂O₃ (50

ml) was then added and stirring continued for 15 min while warming to room temperature. The organic layer was then separated, washed with water (50 ml) and brine (50 ml), dried over Na₂SO₄ and filtered and solvent was removed under reduced pressure to give crude 2-bromo-4-*t*-butylphenol as a yellow oil (15 g). 4.6g of crude material was then placed in a RBF with DCM (80 ml) and DIPEA (6.97 ml, 40 mmol) and cooled to -20 °C. To this MOMCl (1.82 ml, 24 mmol) was slowly added and the resulting solution was stirred at ambient temperature for 16 hours. The solution was taken and washed with HCl solution (80 ml, 1 M) and brine (40 ml), dried over MgSO₄ and filtered and solvent was removed under reduced pressure. The resulting oil was purified by flash chromatography to give the title compound **298** as a clear oil (4.34 g, 79%).

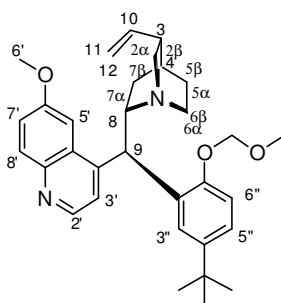
δ_{H} (400 MHz, CDCl₃): 7.57 (d, J 2.4, 1H, H-3) 7.27 (dd, J 2.4, 8.6 1H, H-5), 7.10 (d, J 8.6, 1H, H-6), 5.25 (s, 2H, H-CH₂), 3.55 (s, 3H, H-OCH₃), 1.31 (s, 9H, H-CCH₃).

δ_{C} (100 MHz, CDCl₃): 150.9 (q), 146.0 (q), 130.0, 124.9, 115.4, 112.0 (q), 94.7, 55.9, 33.8 (q), 30.9.

ν_{max} (solid)/cm⁻¹: 2960, 1498, 1259, 1244, 1148, 1084, 1042, 989, 922, 815, 690.

HRMS (EI⁺): calcd. for [C₁₂H₁₇BrO₂]⁺ requires: 272.0420; found: 272.0412

5.4.5 (1S,2S,4S,5R)-2-((R)-5-(tert-butyl)-2-(methoxymethoxy)phenyl)(6-methoxyquinolin-4-yl)methyl-5-vinylquinuclidine (302)



Procedure B was followed using 2-bromo-4-(tert-butyl)-1-(methoxymethoxy)benzene (3844 mg, 14.07 mmol), Magnesium (340 mg, 14.0 mmol), THF (31.5 ml) and chloroquine (2.40 g, 7.0 mmol) in THF (31.5 mg) refluxing for 5 hours. Purification by flash chromatography with EtOAc (50%) and TEA (2%) in Hexanes gave the product **302** as a beige solid (2.76 g, 79%). M.p. 165-167 °C. $[\alpha]_D^{20} = -105.3$ (c 0.48, CHCl₃).

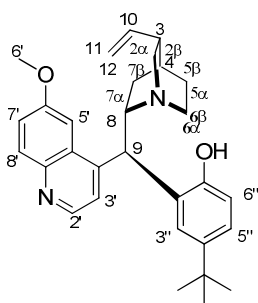
δ_H (400 MHz, CDCl₃): 8.76 (d, J 4.6, 1H, H-2'), 8.01 (d, J 9.2, 1H, H-8'), 7.82 (br s, 1H, H-5'), 7.46 (s, 1H, H-3''), 7.42 (d, J 4.6, 1H, H-3'), 7.37 (dd, J 2.4, 7.2, 1H, H-7'), 7.13 (d, J 8.8, 1H, H-5''), 6.99 (d, J 8.8, 1H, H-6''), 5.99 (ddd, J 7.6, 9.8, 17.6, 1H, H-10), 5.30 (d, J 10.6, 1H, H-9), 5.23-5.14 (m, 2H, H-OCH₂), 5.13-5.05 (m, 2H, H-11 & H-12), 4.00 (s, 3H, H-6'), 3.73 (m, 1H, H-8), 3.43 (m, 1H, H-6 α), 3.32 (s, 3H, H-CH₂OCH₃), 3.20 (m, 1H, H-2 β), 2.79-2.68 (m, 2H, H-2 α & H-6 β), 2.29 (m, 1H, H-3), 1.87 (m, 1H, H-7 β), 1.71 (br s, 1H, H-4), 1.62 (m, 1H, H-5 α), 1.54 (m, 1H, H-5 β), 1.28 (s, 9H, C(CH₃)₃), 0.88 (m, 1H, H-7 α).

δ_C (100 MHz, CDCl₃): 157.2 (q), 152.2 (q), 147.3 (q), 147.1, 144.2 (q), 143.6 (q), 141.8, 131.1, 129.6 (q), 129.0 (q), 125.0, 123.9, 120.3, 119.8, 113.8, 112.7, 102.6, 94.3, 59.5, 56.2, 55.6, 55.1, 41.2, 40.8, 39.3, 33.7, 31.0, 28.1, 27.7, 27.5.

$\nu_{\max}$ (solid)/cm⁻¹: 2930, 1499, 1261, 1235, 1155, 1129, 1069, 1040, 1009, 923, 966, 817, 716.

HRMS (ESI-): calcd. for [C₃₂H₃₉N₂O₃]⁻ requires: 499.2961; found: 499.2955.

5.4.6 4-(tert-butyl)-2-((R)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)phenol (303)



302 (560 mg, 1.12 mmol) was stirred in HCl (aq., 5 M, 20 ml) for 20 hours. DCM (50 ml) and NaHCO₃ solution (sat. aq., 30 ml) were added, followed by additional solid NaHCO₃ until no further effervescence was observed. The organic layer was removed and the aqueous layer was washed with DCM (50 ml). Ammonium Hydroxide (conc., 10 ml) was then added to the aqueous layer and it was further extracted with DCM (2 x 50 ml). All the organics were combined, dried over MgSO₄ and filtered and solvent was removed under reduced pressure to give the title compound as a yellow solid. M.p. 120-121 °C. $[\alpha]_D^{20} = -164$ (c 0.24, CHCl₃).

δ_H (400 MHz, DMSO-d₆): 9.68 (br s, 1H, H-OH), 8.72 (d, J 4.4, 1H, H-2'), 7.99 (br s, 1H, H-5'), 7.87 (d, J 9.2, 1H, H-8'), 7.75 (d, J 4.4, 1H, H-3'), 7.34 (dd, J 2.4, 9.2, 1H, H-7'), 7.21 (br s, 1H, H-3''), 6.87 (dd, J 1.8, 8.2, 1H, H-5''), 6.66 (d, J 8.2, 1H, H-6''), 6.11 (m, 1H, H-10), 5.17 (d, J 11.2, 1H, H-9), 5.08-4.98 (m, 2H, H-11 & H-12), 3.93 (s, 3H, H-6'), 3.81 (m, 1H, H-8), 3.47 (m, 1H, H-6 α), 3.00 (m, 1H, H-2 β), 2.57-2.41 (m, 2H, H-2 α & H-6 β)*, 2.21 (m, 1H, H-

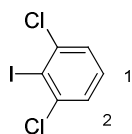
3), 1.95 (m, 1H, H-7 β), 1.56 (br s, H-4), 1.53-1.37 (m, 2H, H-5 α & H-5 β), 1.10 (s, 9H, H-C(CH₃)₃), 0.65 (m, 1H, H-7 α).

δ_C (100 MHz, DMSO-d₆): 161.9 (q), 156.8 (q), 152.7 (q), 152.3, 148.7 (q), 147.6, 145.5 (q), 135.8, 133.8 (q), 132.9 (q), 129.8, 127.8, 125.8, 124.6, 119.0, 118.8, 107.8, 63.9, 60.9, 60.2, 46.4, 45.3, 44.3*, 38.4, 36.1, 33.9, 32.7, 32.3.

$\nu_{\max}$ (solid)/cm⁻¹: 2951, 1621, 1586, 1508, 1432, 1361, 1270, 1231, 1030, 852, 820, 713.

HRMS (ESI-): calcd. for [C₃₀H₃₅N₂O₂]⁻ requires: 455.2699; found: 455.2697.

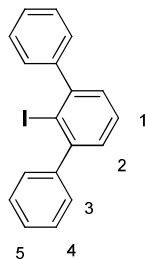
5.4.7 1,3-dichloro-2-iodobenzene (**305**)



2,6-dichloroaniline (**304**, 8.81 g, 54.3 mmol) was placed in an RBF containing deionised water (55 ml) and stirred rapidly. Conc. sulfuric acid (17.1 ml) was added slowly and then the solution was cooled to 0 °C, and a solution of NaNO₂ (4.14 g, 60 mmol) in water (110 ml) was slowly added over 20 minutes maintaining a reaction temperature of less than 5°C, and stirring continued for a further 10 minutes. A solution of potassium iodide (18.3 g, 108.6 mmol) in water was added to the reaction and stirring continued for a further 15 minutes before allowing the reaction to warm to ambient temperature and allowing it to stir for a further hour. This was then poured into a flask containing hexanes (350 ml) and stirred for a further 20 min. The organic layer was separated, washed with 5% NaHSO₄ (150 ml) and Na₂S₂O₃ solution (100 ml). The organic layer was then dried over MgSO₄ and filtered and evaporated to give a yellow solid. This was purified by flash chromatography eluting with hexanes (100%) to give the title compound **305** as a white solid (9.63, 65%). M.p. 67-68 °C.²²⁸

δ_H (400 MHz, CDCl₃): 7.37 (d, J 8.4, 2H, H-2), 7.24 (t, J 8.4, 1H, H-1)

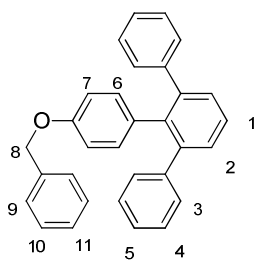
5.4.8 2'-iodo-1,1':3',1''-terphenyl (306)



Magnesium (2.23 g, 91.61 mmol) and dry THF (90 ml) were placed in a RBF under an argon atmosphere and a small portion of the bromobenzene (1 ml) was added. This was heated to reflux until the formation of grignard was observed to begin (solution turns yellow). Heating was then reduced and bromobenzene (total 9.84 ml, 93.44 mmol) added portionwise at such a rate as to maintain the reaction at reflux until all the bromobenzene had been added. Reflux was continued until all of the magnesium had been consumed. The resulting solution was then cooled to room temperature and 2,6 dichlorobenzene (5.00 g, 18.32 mmol), in THF (20 ml) was added. This was stirred for a further 15 hours before Iodine (23.25 g, 91.61 mmol) in the minimum amount of THF was added and the reaction stirred for 5 minutes. The reaction was then washed with a saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ (100 ml) and solid $\text{Na}_2\text{S}_2\text{O}_3$ added as necessary to quench any remaining iodine. The organic layer was separated, and the aqueous layer further washed with DCM (2 x 100 ml). The organics were combined, dried over MgSO_4 and solvent was removed under reduced pressure to afford a brown oil. This was purified by flash chromatography EtOAc (0-5%) in hexanes to afford the title compound as a white solid. 52% M.p. 113-115 °C. (Lit. m.p. 114-115 °C)²²⁶

δ_{H} (400 MHz, CDCl_3): 7.52-7.38 (m, 11H, H-1, H-3, H-4, H-5), 7.29 (d, J 8.0, 2H, H-2).

5.4.9 4''-(benzyloxy)-3'-phenyl-1,1':2',1''-terphenyl (308)



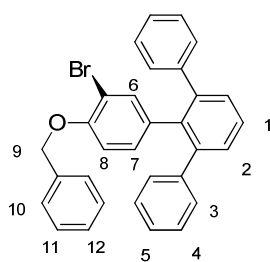
A flask was charged with 2'-iodo-1,1':3,1''-terphenyl (356 mg, 1 mmol), 4-benzyloxybenzeneboronic acid (240 mg, 1.05 eq.), Na₂CO₃ (271 mg, 2.56 mmol), Pd(OAc)₂ (11 mg, 0.05mol) and triphenyl phosphine (47 mg, 0.18 mmol). This was flushed with argon and sealed. Degassed, deionised water (2.6 ml) and then degassed DME (7.8 ml) were added and the reaction was stirred at 85 °C for 40 hours. This was partitioned between water (10 ml) and DCM (2 x 20 ml). The organic layers were combined, washed with brine (10 ml), dried over MgSO₄ and filtered and the solvent was removed under reduced pressure. The resulting solid was purified by flash chromatography with EtOAc (0-5%) in Hexanes as the eluent to give the product as a white solid. (391 mg, 95%). M.p. 143-145 °C.

δ_{H} (400 MHz, CDCl₃): 7.53-7.44 (m, 3H, H-1 & H-2), 7.44 (7.33 (m, 5H, H-9, H-10 & H-11), 7.26-7.19 (m, 6H, H-4 & H-5), 7.18-7.12 (m, 4H, H-3), 6.79 (d, J 8.8, 2H, H-6), 6.66 (d, J 8.8, 2H, H-7), 4.97 (s, 2H, H-8).

δ_{C} (100 MHz, CDCl₃): 156.5 (q), 141.7 (q), 141.6 (q), 138.3 (q), 136.6 (q), 132.3, 131.7 (q), 129.5, 129.2, 128.0, 127.4, 127.2, 127.1, 126.7, 125.7, 113.3, 69.3.

ν_{max} (solid)/cm⁻¹: 1608, 1510, 1494, 1454, 1295, 1223, 1175, 1027, 752, 696.

5.4.10 4-(benzyloxy)-3-bromo-6'-phenyl-1,1':2,1''-terphenyl (309)



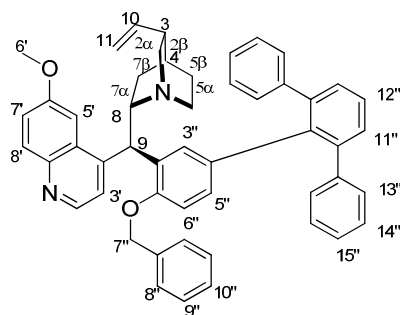
4''-(benzyloxy)-3'-phenyl-1,1':2',1''-terphenyl (1.13 g, 2.74 mmol), chloroform (27.4 ml) and Na_2CO_3 (377 mg, 3.56 mmol) were placed in a RBF, cooled to 0 °C and bromine (183 μl , 3.56 mmol), was added dropwise. This was allowed to warm to ambient temperature and stirred for a further hour. The reaction was washed with Conc. $\text{Na}_2\text{S}_2\text{O}_3$ solution (50 ml), which was further extracted with DCM (50 ml), the organics were combined, washed with brine (20 ml), dried over MgSO_4 and filtered and solvent was removed under reduced pressure. The resulting solid was purified by flash chromatography eluting with EtOAc (0-10%) in hexanes to give the title compound as a white solid, (1033 mg, 77%). M.p. 134-135 °C.

δ_{H} (400 MHz, CDCl_3): 7.52-7.30 (m, 8H, H-1, H-2, H-10, H-11 & H-12), 7.25-7.15 (m, 6H, H-3 & H-5), 7.12-7.07 (m, 4H, H-4), 7.04 (d, J 2.0, 1H, H-6), 6.69 (dd, J 2.0, 8.6, 1H, H-7), 6.58 (d, J 8.6, 1H, H-8), 5.04 (s, 2H, H-9).

δ_{C} (100 MHz, CDCl_3): 152.6 (q), 141.6 (q), 141.2 (q), 136.8 (q), 136.0 (q), 135.9, 133.2 (q), 131.1, 129.4, 129.2, 128.0, 127.4, 127.3, 127.1, 126.6, 125.9, 112.1, 110.7, 70.1.

ν_{max} (solid)/ cm^{-1} : 3056, 1600, 1496, 1454, 1421, 1379, 1279, 1240, 1049, 989, 920, 855, 759, 697.

5.4.11 (1S,2S,4S,5R)-2-((R)-(4-(benzyloxy)-6'-phenyl-[1,1':3',1''-terphenyl]-3-yl)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (309)



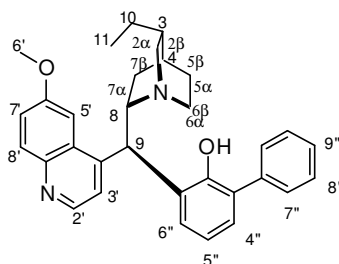
δ_{H} (600 MHz, CDCl_3): 8.61 (d, J 4.4, 1H, H-2'), 8.00 (d, J 9.2, 1H, H-8'), 7.51-7.42 (m, 2H, H-8'' & H-12''), 7.42-7.30 (m, 6H, H-5', H-7', H-3'', H-9'', H-15''), 7.28-7.13 (m, 7H, H-10'', H-11'' & H-13''), 6.86 (m, 7H, H-3', H-5'' & H-14''), 6.63-6.57 (m, 2H, H-3'' & H-6''), 5.90 (m, 1H, H-10), 5.11 (d, J 10.8, 1H, H-9), 5.08-5.02 (m, 2H, H-11 & H-12), 5.02-4.91 (m, 2H, H-7''), 3.58 (s, 3H, H-6'), 3.27 (m, 1H, H-6 α), 3.19 (m, 1H, H-8), 3.10 (m, 1H, H-2 β), 2.64-2.53 (m, 2H, H-2 α & H-6 β), 2.23 (m, 1H, H-3), 1.77 (m, 1H, H-7 β), 1.65 (m, 1H, H-4), 1.54-1.42 (m, 2H, H-5 α & H-5 β), 0.87 (m, 1H, H-7 α).

δ_{C} (150 MHz, CDCl_3): 157.2 (q), 154.1 (q), 147.3 (q), 147.2, 144.3 (q), 142.3, 141.9 (q), 139.0 (q), 136.5 (q), 132.4, 131.8 (q), 131.2, 130.1 (q), 130.0, 129.8, 129.7 (q), 129.2, 129.1 (q), 128.3, 127.7, 127.5, 127.4, 127.0, 125.9, 121.0, 120.0, 113.9, 110.3, 102.2, 69.9, 60.5, 56.3, 55.0, 41.4, 40.8, 39.9, 28.2, 28.1, 28.0.

ν_{max} (solid)/ cm^{-1} : 2930, 1621, 1504, 1454, 1228, 1028, 908, 852, 816, 760, 733, 698.

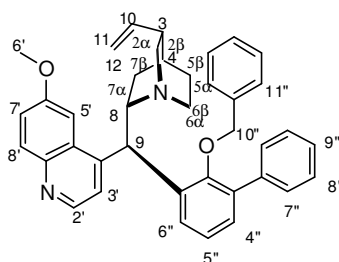
HRMS (EI+): calcd. for $[\text{C}_{51}\text{H}_{47}\text{N}_2\text{O}_2]^+$ requires: 719.3638; found: 719.3641

5.4.12 3-((R)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)-[1,1'-biphenyl]-2-ol (314)



Procedure B was followed using **313** (300 mg, 0.53 mmol), Pd/C 10% (56 mg, 0.053 mmol) and EtOH (10 ml). Hydrogenation was continued at atmospheric pressure for 5 days. The crude material was purified by flash chromatography eluting with EtOAc (30-50%) and TEA (2%) in hexanes to give the title compound as a pale brown solid (225 mg, 89%). M.p.

5.4.13 (1S,2S,4S,5R)-2-((R)-(2-(benzyloxy)-[1,1'-biphenyl]-3-yl)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (314a)



Procedure B was followed using 1-bromo-2-benzyloxy-3-phenylbenzene (1.19 g, 3.5 mmol), magnesium (89.3 mg, 3.68 mmol), THF (14 ml), 1,2 dibromoethane (a few drops) and chloroquine (1.20 g, 3.5 mmol) in THF (14 ml). Reflux was continued overnight and the crude product was purified by flash chromatography eluting with EtOAc (30-50%) and TEA (2%) in hexanes to give the title compound as a yellow solid (1.27g, 65%). M.p. 106-107 °C.

δ_{H} (400 MHz, CDCl_3): 8.74 (d, J 4.0, 1H, H-2'), 8.02 (d, J 9.2, 1H, H-8'), 7.73 (br s, 1H, H-5'), 7.66 (d, J 7.2, 1H, H-6''), 7.56 (d, J 7.2, 2H, H-11''), 7.46-7.37 (m, 4H, H-3', H-12'', H-13''), 7.36-7.20 (m, 6H, H-7', H-4'', H-5'', H-8'' & H-9''), 6.85 (d, J 6.8, 2H, H-7''), 5.99 (ddd, J 7.6, 10.4, 17.2, 1H, H-10), 5.55 (d, J 9.8, 1H, H-9), 5.16-5.06 (m, 2H, H-11 & H-12), 4.45 (d, J 10.0, 1H, H-10''), 4.00 (d, J 10.0, 1H, H-10''), 3.80 (m, 1H, H-8), 3.49-3.34 (m, 4H, H-6 α & H-6'), 3.28 (dd, J 10.4, 13.4, 1H, H-2 β), 2.95-2.79 (m, 2H, H-2 α & H-6 β), 2.32 (m, 1H, H-3), 1.78-1.50 (m, 4H, H-4, H-5 α , H-5 β & H-7 β), 0.99 (m, 1H, H-7 α).

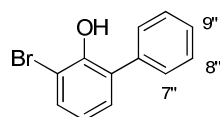
δ_{C} (100 MHz, CDCl_3): 157.3 (q), 153.8 (q), 147.4 (q), 147.0, 144.2 (q), 141.8, 138.7 (q), 136.7 (q), 135.4 (q), 135.0 (q), 131.1, 129.7, 128.8 (q), 128.6,

128.0, 127.6, 127.3, 127.3, 127.2, 126.9, 124.0, 121.4, 120.2, 113.9, 101.9, 74.1, 59.7, 55.9, 44.6, 41.1, 40.4, 39.4, 27.8, 27.5, 27.2.

ν_{max} (solid)/ cm^{-1} : 2940, 1620, 1508, 1430, 1228, 1027, 977, 907, 762, 728, 697.

HRMS (ESI⁺): Calcd. for $[\text{C}_{39}\text{H}_{38}\text{N}_2\text{O}_2 + \text{H}]^+$ requires 567.3012; found 567.3000.

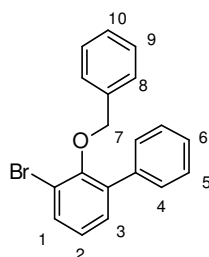
5.4.14 2-bromo-6-phenylphenol (316)



2-phenylphenol (10.5 g, 61.7 mmol) was placed in a RBF with DCM (200 ml) and diisopropylamine (0.83 ml, 5.92 mmol) were placed in a round bottomed flask under argon to which a Soxhlet apparatus containing NBS (10.46 g, 58.8 mmol) was attached. The solution was kept at reflux for 84 hours at a rate that allowed addition of all of the NBS over this time. The resulting mixture was washed with Na_2SO_3 (conc. aq., 50 ml) and brine (50 ml), dried over MgSO_4 and filtered and solvent was removed under reduced pressure. This was then separated by flash chromatography eluting in EtOAc (2.5%) in Hexane to afford the title compound as a yellow as a low melting point solid (3.38 g, 23%). M.p. 37-38 °C (Lit. m.p. 38-39 °C)²⁵²

δ_{H} (400 MHz, CDCl_3): 7.60-7.38 (m, 6H, H-5, H-7'', H-8'' & H-9''), 7.29 (d, J 7.8, 1H, H-3), 6.92 (t, J 7.8, 1H, H-4), 5.73 (br s, 1H, H-OH).

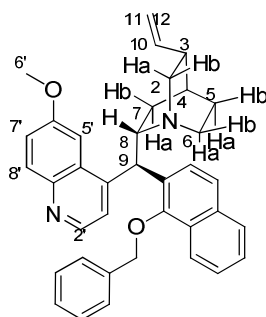
5.4.15 1-bromo-2-benzyloxy-3-phenylbenzene (313)



Procedure A was followed using 2-bromo-6-phenylphenol (1,984 mg, 8.00 mmol), benzyl bromide (950 μ l, 8.00 mmol) K_2CO_3 (3317 mg, 24.0 mmol) and acetone (16 ml) to afford the desired compound as a clear oil (2.65 g, 97%).

δ_H (400 MHz, $CDCl_3$): 7.64-7.57 (m, 3H, H-3 & H-4), 7.50-7.39 (m, 3H, H-5 & H-6), 7.36 (d, J 7.6, 1H, H-3), 7.33-7.26 (m, 3H, H-9 & H-10), 7.12 (app t, J 7.8, 1H, H-2), 4.55 (s, 2H, H-7).

5.4.16 (1S,2S,4S,5R)-2-((R)-(1-(benzyloxy)naphthalen-2-yl)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (312a)



Procedure B was followed using 1-benzyloxy-2-bromonaphthalene (3.29 g, 10.5 mmol), magnesium (255 mg, 10.5 mmol), THF (40 ml) and chloroquine (3.43 g, 10.0 mmol) in THF (40 ml) refluxing for 16 hours. The product was isolated using flash chromatography using EtOAc (20-50%) and TEA (2%) in hexanes to afford the desired product as a pale brown solid (1.42 g, 26%). M.p. 87-89 $^{\circ}C$.

δ_H (600 MHz, $CDCl_3$): 8.71 (d, J 4.8, 1H, H-2'), 8.06 (d, J 7.8, 1H, H-8''), 7.98 (d, J 9.2, 1H, H-8'), 7.82 (dd, J 1.6, 6.8, 1H, H-5''), 7.81-7.76 (m, 2H, H-5')

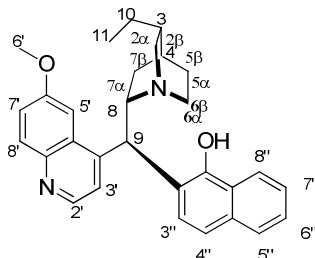
& H-3''), 7.71 (d, J 8.7, 1H, H-4''), 7.49-7.40 (m, 8H, H-3', H-6'', H-7'', H-10'', H-11'' & H-12''), 7.30 (dd, J 2.5, 9.2, 1H, H-7'')*, 6.00 (ddd, 7.4, 10.5, 17.4, 1H, H-10), 5.66 (br d, J 11.0, 1H, H-9), 5.14-5.08 (m, 2H, H-11 & H-12), 5.06 (d, J 11.8, 1H, H-9''), 4.75 (d, J 11.8, 1H, H-9''), 3.86 (m, 1H, H-8), 3.55 (s, 3H, H-6'), 3.37 (m, 1H, H-6 α), 3.23 (dd, J 10.2, 13.6, 1H, H-2 β), 2.88 (br d, J 13.6, 1H, H-2 α), 2.77 (m, 1H, H-6 β), 2.31 (m, 1H, H-3), 1.80 (m, 1H, H-7 β), 1.76 (br s, 1H, H-4), 1.67 (m, 1H, H-5 α), 1.56 (m, 1H, H-5 β), 1.05 (br dd, J 7.9, 13.4, 1H, H-7 α).

δ_{C} (150 MHz, CDCl₃): 157.8 (q), 152.1 (q), 147.4 (q), 147.3, 144.6 (q), 142.2, 137.6 (q), 134.0 (q), 131.6, 131.1 (q), 129.1 (q), 128.5, 128.2, 127.9, 127.7 (q), 126.8, 125.9, 125.7, 125.7, 124.6, 121.9, 121.8, 120.7, 114.3, 102.1, 75.6, 59.9, 56.3, 55.1, 41.6, 41.0, 39.8, 28.3, 27.9, 27.6.

ν_{max} (solid)/cm⁻¹: 2932, 1620, 1506, 1453, 1361, 1226, 1029, 807, 726, 696.

HRMS (ESI+): Calcd. for [C₃₇H₃₆N₂O₂ + H]⁺ requires 541.2855; found 541.2848.

5.4.17 2-((R)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)naphthalen-1-ol (312)



Procedure B was followed using 2-bromo-1-benzoyloxynaphthalene (650 mg, 1.20 mmol), 10% Pd/C (128 mg, 0.12 mmol) and EtOH (12.5 ml), to afford the title compound as a brown solid (529 mg, 97%). $[\alpha]_D^{20} = -228.6$ (c 0.106, CHCl_3).

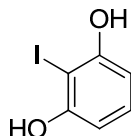
The NMR signals observed for this compound are broad in all solvents and all peaks could not be unambiguously assigned. M.p. 99-101 °C.

δ_H (400 MHz, MeOD-d_4): 8.66 (d, J 4.5, 1H, H-2'), 8.29 (br d, J 6.9 1H, H-Ar), 7.94-7.80 (m, 2H, H-Ar), 7.64 (d, J 4.5, 1H, H-3'), 7.59 (br d, 1H, H-Ar), 7.46-7.21 (m, 3H, H-Ar), 7.16-6.93 (m, 2H, H-Ar), 5.89-5.23 (br m, 1H, H-9), 4.03-3.59 (m, 5H), 3.26 (br s, 1H), 2.78 (br m, 1H), 2.57 (br m, 1H), 1.89-1.17 (m, 9H), 0.95-0.75 (m, 3H)

δ_C (150 MHz, MeOD-d_4): 158.4, 156.7, 151.9, 149.37, 146.9, 144.0, 134.2, 134.1, 130.3, 128.1, 127.2, 125.8, 124.7, 122.5, 122.2, 118.5, 102.9, 78.5, 78.2, 60.7, 56.6, 55.3, 44.1, 40.9, 36.8, 28.8, 27.5, 27.2, 26.0.

HRMS (ESI⁺): Calcd. for $[\text{C}_{30}\text{H}_{32}\text{N}_2\text{O}_2 + \text{H}]^+$ requires 453.2542; found 453.2541

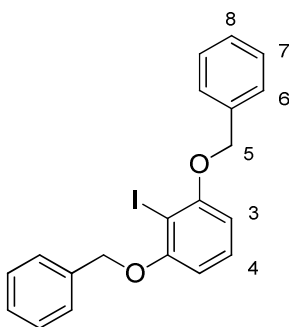
5.4.18 2-iodoresorcinol (**324**)



Resorcinol (**323**, 16.50 g, 150.0 mmol) was placed in a large conical flask with an ice/water mix (40 ml) and stirred rapidly. A crushed mixture of iodine (40.2 g, 158.4 mmol), and NaHCO₃ (13.8 g, 164.4 mmol) were added carefully and the resulting mixture stirred for 30 min. The resulting mixture was filtered, and the filtrate was dissolved in ether (approx. 300ml). This was washed with brine (75 ml), dried over MgSO₄ and filtered and evaporated to give a pale brown solid. This was then dissolved in a minimum amount of hot chloroform and left to stand at -20 °C for 24 hours. The solid was separated by filtration to afford the title compound **324** as a white solid in 94% yield (33.41 g, 141.6 mmol). M.p. 101-102 °C. Litt m.p. 101-104 °C.²⁵³

δ_{H} (400 MHz, CDCl₃): 7.14 (t, J 8.0, 1H, H-4), 6.58 (d, J 8.0, 1H, H-3), 5.29 (br s, 2 H, H-OH).

5.4.19 2,6-Benzyloxy-1-iodobenzene (**325**)

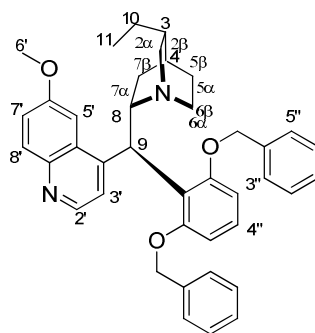


2-Iodoresorcinol (2.70 g, 11.4 mmol), potassium carbonate (4.74 g, 34.3 mmol) and acetonitrile (44 ml), were placed in an RBF under argon and benzyl bromide (2.71ml,

22.88 mmol) was added. The reaction was stirred for 20 h, and then solvent was removed under reduced pressure. The resulting solid was partitioned between water (75 ml) and DCM (75 ml) and the aqueous layer was further washed with DCM (75ml). The organic layers were combined, washed with brine, dried over magnesium sulphate and filtered and solvent was removed under reduced pressure to give a brown oil which was purified by flash chromatography with EtOAc (10-20%) in Hexanes as the eluent. The desired product was obtained as a pale yellow solid (**325**, 4.32 g, 91%) with spectra in accordance with those previously reported. M.p. 89-91 °C. Litt. M.p. 90-91 °C.²⁵⁴

δ_{H} (400 MHz, CDCl_3): 7.56 (d, J 7.6, 4H, H-6), 7.43 (app t, J 7.6, 4H, H-7), 7.35 (t, J 7.6, 2H, H-8), 7.23 (t, J 8.4, 1H, H-4), 6.58 (d, J 8.4, 2H, H-3), 5.21 (s, 4H, H-5).

5.4.20 (1S,2S,4S,5R)-2-((R)-(2,6-bis(benzyloxy)phenyl)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (**326**)



Procedure B was followed using **325** (1.90 g, 4.56 mmol), magnesium (113 mg, 4.66 mmol), THF (21 ml) and **Q22a** (1.56 g, 4.56 mmol) in THF. Reflux was continued for 16 hours. **326** (1.93 g, 71%) was obtained as an off-white solid, M.p. 109-111 °C. $[\alpha]_{\text{D}}^{20} = -53.5$ (c 1.34, CHCl_3).

δ_{H} (400 MHz, CDCl_3): 8.35 (d, J 4.2, 1H, H-2'), 7.94 (d, J 9.2, 1H, H-8'), 7.82 (br s, 1H, H-5'), 7.57 (d, J 7.4, 2H, H-12''), 7.53-7.34 (m, 8H, H-8'', H-9'', H-10'', H-13'', H-14''), 7.25 (br d, J 9.2, 1H, H-7), 7.15-7.07 (m, 2H, H-3' & H-5''), 6.73 (d, J 8.4, 1H, H-6''), 6.53 (d, J 8.4, 1H, H-4''),

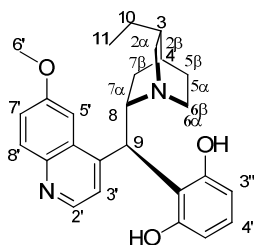
5.86 (ddd, J 7.8, 11.0, 18.4, 1H, H-10), 5.38-5.30 (m, 2H, H-9 & H-7''), 5.23 (d, J 11.8, 1H, H-7''), 5.08-5.01 (m, 2H, H-11 & H-12), 4.98 (d, J 10.6, 1H, H-11''), 4.74 (d, J 10.6, 1H, H-11''), 4.26 (m, 1H, H-8), 3.66 (s, 3H, H-6'), 3.47 (m, 1H, H-6 α), 3.22 (dd, 10.2 & 13.6, 1H, H-2 β), 2.80 (m, 1H, H-2 α), 2.60 (m, 1H, H-6 β), 2.24 (m, 1H, H-3), 1.90 (m, 1H, H-7 β), 1.78 (br s, 1H, H-4), 1.56-1.36 (m, 2H, H-5 α & H-5 β), 0.77 (m, 1H, H-7 α).

δ_C (100 MHz, CDCl₃): 158.0 (q), 157.0 (q), 156.3 (q), 146.5, 144.4 (q), 144.1 (q), 142.1 (q), 140.8, 136.2 (q), 136.0 (q), 131.7, 131.0, 129.8 (q), 128.4, 128.2, 128.0, 127.8, 127.6, 126.8, 122.9, 119.8, 113.6, 105.4, 104.9, 103.0, 70.6, 69.9, 56.1, 55.5, 54.9, 41.1, 40.9, 39.5, 29.7, 27.7, 27.3.

$\nu_{\max}$ (solid)/cm⁻¹: 2941, 1619, 1586, 1508, 1451, 1233, 1068, 1028, 854, 832, 735, 697.

HRMS (ESI⁺): calcd. for [C₄₀H₄₁N₂O₃]⁺ requires: 597.3117; found: 597.3120.

5.4.21 2-((R)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)benzene-1,3-diol (327)



Procedure C was followed using **326** (597 mg, 1.0 mmol) and Pd/C (106 mg, 10 mol%) to give the desired compound **327** as a pale solid (409 mg, 98%). $[\alpha]_{\text{D}}^{20} = -76.6$ (c 0.223, CHCl_3).

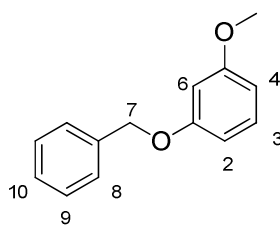
δ_{H} (400 MHz, CDCl_3): 8.41 (d, J 4.6, 1H, H-2'), 7.89 (br s, 1H, H-5'), 7.66 (d, J 9.2, 1H, H-8'), 7.49 (br s, 1H, H-3'), 7.15 (br d, J 9.2, 1H, H-7'), 6.81 (t, J 8.0, 1H, H-4''), 6.30 (br s, 2H, H-3''), 5.25 (br s, 0.34H, H-9), 4.66 (br s, 0.66H, H-9), 3.92 (s, 3H, H-6'), 3.73 (m, 1H, H-8), 3.33-3.05 (m, 2H, H-2 β & H-6 α), 2.68 (m, 1H, H-6 β), 2.41 (m, 1H, H-2 α), 1.88-1.69 (m, 2H, H-4 & H-5 α), 1.62-1.42 (m, 3H, H-3, H-5 β & H-7 β), 1.31-1.15 (m, 3H, H-7 α & H-10), 0.79 (t, J 7.4, 3H, H-11).

δ_{C} (100 MHz, CDCl_3): 157.0 (q, br), 156.9 (q), 146.0 (q, br), 145.4 (br), 143.9 (q, br), 129.9, 127.9, 125.4 (q, br), 121.4 (br), 115.4 (br), 109.5 (q, br), 109.0 (br), 102.7, 55.3, 55.1, 52.9 (br), 45.0, 40.8, 35.6, 29.3 (br), 27.1, 26.4, 25.2, 11.3.

ν_{max} (solid)/ cm^{-1} : 2929, 1586, 1509, 1453, 1237, 1024, 790.

HRMS (ESI⁺): calcd. for $[\text{C}_{26}\text{H}_{31}\text{N}_2\text{O}_3]^+$ requires: 419.2335; found: 419.

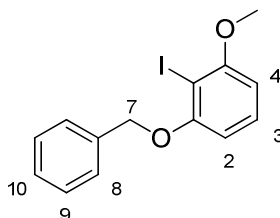
5.4.22 1-(benzyloxy)-3-methoxybenzene (**338**)



Procedure A was followed using 3-methoxyphenol (5.00 g, 40.3 mmol), benzyl bromide (4.78 ml, 40.3 mmol), K_2CO_3 (11.13 g, 80.6 mmol) and acetone (80 ml), reflux was continued overnight and the crude product was purified by flash chromatography eluting with EtOAc (0-10%) in hexanes to afford the desired compound as a clear oil (8.38 g, 97%).

δ_{H} (400 MHz, CDCl_3): 7.47 (d, J 7.6, 2H, H-8), 7.43 (app t, J 7.6, 2H, H-9), 7.36 (m, 1H, H-10), 7.22 (app t, J 8.0, 1H, H-3), 6.65-6.54 (m, 3H, H-2, H-4 & H-6), 5.08 (s, 2H, H-7), 3.82 (s, 3H, H- CH_3).

5.4.23 1-(benzyloxy)-2-iodo-3-methoxybenzene (333)



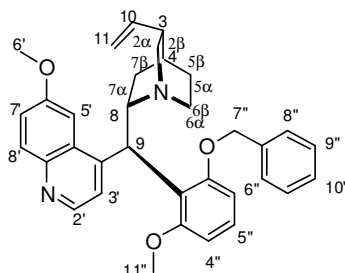
1-(benzyloxy)-3-methoxybenzene (7.05 g, 32.9 mmol) was placed in a round bottom flask with dry THF (165 ml) under an argon atmosphere. This was cooled to $-78\text{ }^{\circ}\text{C}$, and *n*BuLi in Hexanes (13.4 ml, 2.5M, 33.6 mmol) was added carefully over 10 min. The resulting solution was allowed to warm to $-20\text{ }^{\circ}\text{C}$, and stirred for 1 h. To this a solution of Iodine (8.53g, 33.56 mmol) was carefully but quickly added and the solution then allowed to warm to ambient temperature. The resulting solution was washed with a saturated solution of sodium thiosulphate (120 ml). The aqueous layer was washed with DCM (2 x 150 ml). The organic layers were then washed with brine (80 ml), combined, dried over MgSO_4 and filtered and solvent was removed under reduced pressure. The resulting yellow oil was purified by flash chromatography with EtOAc (5-7.5%) in Hexanes as the eluent to give an off-white solid (5.82 g, 52%). M.p $55\text{--}56\text{ }^{\circ}\text{C}$.

δ_{H} (400 MHz, CDCl_3): 7.54 (d, J 7.6, 2H, H- 8), 7.42 (m, 2H, H-9), 7.34 (app t, 1H, H-10), 7.26 (app t, J 8.4, 1H, H-3), 6.58-6.52 (m, 2H, H-2 & H-4), 5.20 (s, 2H, H-7), 3.93 (s, 3H, H- CH_3).

δ_{C} (100 MHz, CDCl_3): 159.2 (q), 158.2 (q), 136.2 (q), 129.3, 128.1, 127.4, 126.5, 105.3, 103.9, 78.1 (q), 70.5, 56.1.

ν_{max} (solid)/ cm^{-1} : 1586, 1466, 1431, 1379, 1250, 1093, 1018, 761, 733, 695.

5.4.24 (1S,2S,4S,5R)-2-((R)-2-(benzyloxy)-6-methoxyphenyl)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (335)



Procedure C was followed using 1-(benzyloxy)-2-iodo-3-methoxybenzene (3.40 g, 10.0 mmol), Magnesium (243 mg, 10.0 mmol), THF (22.5 ml) and chloroquinine (857 mg, 2.5 mmol) in THF (11.25 ml). Reflux was continued overnight and the product was purified using flash chromatography eluting with EtOAc (20-50%) and TEA (2%) in Hexanes to give a yellow solid (690 mg, 53%). M.p. 115-119 °C.

The interchange of rotamers was observed by EXSY experiment at 20 °C.

δ_H (400 MHz, $CDCl_3$): 8.76 (d, J 4.8, 0.26H, H-2' min), 8.35 (d, J 4.8, 0.74H, H-2' maj), 7.97 (d, J 9.0, 0.26H, H-8' min), 7.94 (d, J 9.0, 0.74H, H-8' maj), 7.85-7.82 (m, 1H, H-5' maj & H-5' min), 7.69 (d, J 4.8, 0.26H, H-3' min), 7.56-7.34 (m, 5H, H-8'' maj, H-8'' min, H-9'' maj, H-9'' min, H-10'' maj & H-10'' min), 7.29-7.25 (m, 1H, H-7' maj & H-7' min), 7.13-7.07 (m, 1.74H, H-3' maj, H-5'' maj & H-5'' min), 6.70 (d, J 8.0, 0.26H, H-6'' min), 6.63 (d, J 8.4, 0.76H, H-4' maj), 6.53-6.48 (m, 1H, H-4' min & H-6' maj), 6.03 (m, 0.26H, H-10), 5.89 (m, 0.74H, H-10), 5.39 (d, J 11.4, 0.26H, H-9 min), 5.31 (d, J 12.0, 0.26H, 1H, H-7''), 5.27 (d, J 11.2, 0.74H, H-9 maj), 5.22 (d, J 12.0, 0.26H, H-7'' min), 5.13-5.04 (m, 2H, H-11 maj, H-11 min, H-12 maj & H-12 min), 4.97 (d, J 10.4, 0.74H, H-7''), 4.74 (d, J 10.4,

0.74H, H-7''), 4.34 (m, 0.26H, H-8 min), 4.23 (m, 0.74H, H-8 maj), 4.03 (s, 2.22H, H-11'' maj), 3.95 (s, 2.22H, H-6' maj), 3.67 (s, 0.78H, H-11'' min), 3.65 (s, 0.78H, H-6'), 3.54-3.41 (m, 1H, H-6 α maj & H-6 α min), 3.27-3.15 (m, 1H, H-2 β maj & H-2 β min), 2.83-2.76 (m, 1H, H-2 α maj & H-2 β min), 2.72-2.57 (m, 1H, H-6 β maj & H-6 β min), 2.31-2.23 (m, 1H, H-3 maj & H-3 min), 2.07-1.99 (m, 0.26H, H-7 β min), 1.94-1.87 (m, 0.74H, H-7 β maj), 1.74-1.64 (m, 1H, H-4 maj & H-4 min), 1.64-1.55 (m, 1H, H-5 α maj & H-5 α min), 1.54-1.42 (m, 1H, H-5 β maj & H-5 β min), 0.89-0.82 (m, 0.26H, H-7 α), 0.76-0.66 (m, 0.74H, H-7 α min).

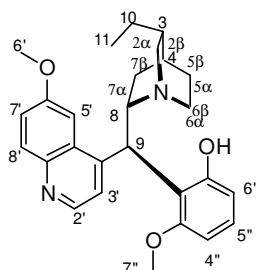
δ_C (100 MHz, CDCl₃): peaks for major rotamer: 158.3 (q), 157.4 (q), 157.4 (q), 146.8, 144.9 (q), 144.5 (q), 142.7, 136.5 (q), 131.3, 130.2 (q), 128.7, 128.6, 128.4, 128.1, 123.3, 120.7, 118.0 (q), 113.9, 105.6, 104.0, 102.7, 70.3, 56.7, 56.0, 55.8, 55.4, 41.1, 40.9, 40.0, 30.1, 28.2, 28.0.

δ_C (100 MHz, CDCl₃): peaks for minor rotamer 159.5 (q), 157.4 (q), 156.7 (q), 146.9, 146.0 (q), 144.7 (q), 142.6, 136.7 (q), 131.4, 130.2 (q), 128.7, 128.6, 128.0, 127.3, 122.6, 120.3, 118.9 (q), 113.9, 106.1, 105.3, 103.4, 70.9, 56.7, 56.5, 55.3, 55.2, 41.6, 41.3, 39.9, 30.0, 28.2, 27.9.

$\nu_{\max}$ (solid)/cm⁻¹: 2939, 1620, 1590, 1508, 1462, 1235, 1083, 1020, 911, 857, 826, 751, 696, 672.

HRMS (ESI⁺): calcd. for [C₃₄H₃₇N₂O₃]⁺ requires: 521.2804; found: 521.2804.

5.4.25 3-methoxy-2-((R)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)phenol (339)



Procedure C was followed using **335** (500 mg, 0.96 mmol), Pd/C 10% (100 mg, 0.096 mmol), EtOAc (10 ml) and MeOH (10 ml). Reaction was continued for 48 hours under H₂ at 3 atm. Purification by flash chromatography eluting with 2% TEA and 30-50% EtOAc in hexanes to provide the title compound as a near white solid. (351 mg, 85%). M.p. 99-101 °C. $[\alpha]_D^{20} = -119.0$ (c 0.33, CHCl₃).

δ_H (400 MHz, 50 °C, CDCl₃): 13.88 (br s, 1H, H-OH), 8.67 (d, J 4.4, 1H, H-2'), 7.97 (d, J 9.2, 1H, H-8'), 7.84 (d, J 2.6, 1H, H-5'), 7.39 (d, J 4.4, 1H, H-3'), 7.29 (m, 1H, H-7')*, 7.03 (app t, J 8.1, 1H, H-5''), 6.60 (dd, J 1.0, 8.1, 1H, H-4''), 6.22 (dd, J 1.0, 8.1, 1H, H-5''), 4.87 (br s, 1H, H-9), 4.00 (s, 3H, H-6'), 3.76 (m, 1H, H-8), 3.40 (s, 3H, H-7''), 3.35-3.20 (m, 2H, H-2β & H-6α), 2.83 (m, 1H, H-6β), 2.54 (ddd, J 2.4, 6.2, 13.9, 1H, H-2α), 1.89 (dddd, J 2.4, 2.8, 9.1, 13.1, 1H, H-5α), 1.79 (m, 1H, H-4), 1.71-1.49 (m, 2H, H-3 & H-5β), 1.37-1.22 (m, 3H, H-7β & H-10), 0.85 (t, J 7.5, 3H, H-11).

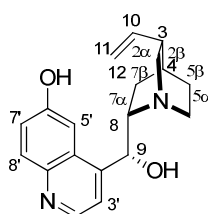
δ_C (100 MHz, 50 °C, CDCl₃): 159.1 (q), 157.6 (q), 157.4 (q), 147.0, 145.1 (q), 131.6, 128.2, 123.8, 121.4, 117.6 (q), 113.5, 103.0, 102.3, 58.2 (br), 55.8, 55.7, 54.9, 41.4, 36.4, 28.9 (br), 27.9, 26.8, 25.9, 11.6.

Signals corresponding to Carbons for C-9, C-4' and C-10' are not observed.

$\nu_{\max}$ (solid)/ cm^{-1} : 2929, 1621, 1509, 1466, 1368, 1235, 1073, 1030, 827, 789, 710.

HRMS (ESI+): calcd. for $[\text{C}_{27}\text{H}_{31}\text{N}_2\text{O}_3]^+$ requires: 431.2335; found: 431.2323

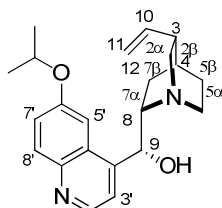
5.4.26 Cupreine (341)



Quinine (3.6 g, 11.46 mmol), NaSEt (5.0 g, 59.4 mmol) and dry DMF (60 ml) were placed in a RBF under argon and heated to 105 °C for 16 hours. The mixture was cooled to room temperature and saturated aqueous NH_4Cl (100 ml) was added. This was then washed with EtOAc (2 x 200 ml) and the organics were combined and washed with HCl (aq., 2 M, 4 x 25 ml), the aqueous layers were combined, ammonia (conc. aq., 20 ml) was added and the mixture was extracted with EtOAc (2 x 250 ml). The combined organic layers were washed with brine (100 ml), dried over Na_2SO_4 and filtered and solvent was removed under reduced pressure. The resulting solid was triturated with Et_2O to afford the title compound as a white solid (2.65 g, 75%). M.p. (Lit. m.p. 203 - 206 °C) ⁹⁹

δ_{H} (400 MHz, MeOD): 8.61 (d, J 4.6, 1H, H-2'), 7.92 (d, J 9.0, 1H, H-8'), 7.65 (d, J 4.6, 1H, H-3'), 7.35 (dd, J 2.4, 9.0, 1H, H-7'), 7.30 (d, J 2.4, 1H, H-5'), 5.78 (ddd, J 7.6, 10.4, 17.4, 1H, H-10), 5.54 (d, J 2.8, 1H, H-9), 4.99 (d, J 17.4, 1H, H-12), 4.93 (d, J 10.4, 1H, H-11)*, 3.73 (m, 1H, H-6 α), 3.18-3.08 (m, 2H, H-2 β & H-8), 2.80-2.66 (m, 2H, H-2 α & H-6 β), 2.39 (m, 1H, H-3), 1.95-1.79 (m, 3H, H-4, H-5 α & H-7 α), 1.61 (m, 1H, H-5 β), 1.46 (m, 1H, H-7 β).

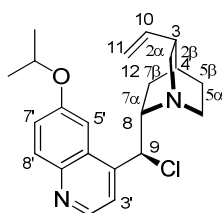
5.4.27 6'-isopropylquinine (342)



Cupreine (2.60 g, 8.38 mmol) and Cs_2CO_3 (6.83 g, 21.0 mmol) were placed in a RBF with dry DMF (420 ml, 0.02 M). Isopropyl bromide (1.57 ml, 16.8 mmol) was added and the reaction was stirred at 60 °C for 40 hours. Solvent was removed under reduced pressure and the resulting solid was purified by flash chromatography, eluting with 5% MeOH in chloroform to afford the title compound as a white solid (2.80 g, 95%). M.p. 160-161 °C. Litt m.p. 166 °C. ⁹⁵

δ_{H} (400 MHz, CDCl_3): 8.54 (d, J 4.4, 1H, H-2'), 7.91 (d, J 10.0, 1H, H-8'), 7.48 (d, J 4.4, 1H, H-3'), 7.27-7.23 (m, 2H, H-5' & H-7'), 5.72 (ddd, J 7.8, 10.4, 17.6, 1H, H-10), 5.58 (d, J 2.8, 1H, H-9), 5.00-4.89 (m, 2H, H-11 & H-12), 4.76-4.61 (m, 2H, H-OH & H-OCH(CH_3)₂), 3.54 (m, 1H, H-6 α), 3.17-3.05 (m, 2H, H-2 β & H-8), 2.73-2.63 (m, 2H, H-2 α & H-6 β), 2.30 (m, 1H, H-3), 1.86-1.72 (m, 3H, H-4, H-5 β & H-7 β), 1.57-1.44 (m, 2H, H-5 α & H-7 α), 1.40-1.34 (m, 6H, H-OCH(CH_3)₂).

-9-*epi*-chloro(deoxy)-6'-isopropylquinine (343)



6'-isopropylquinine (2.40 g, 6.8 mmol) was added to rapidly stirred SOCl_2 (8.0 ml) at 0 °C and then allowed to warm to ambient temperature and stirred for a further 16 hours. The resulting solution was carefully added to ice and Na_2CO_3 (sat. aq., 200 ml) adding further solid Na_2CO_3 as necessary to maintain a pH of >7. This was extracted with chloroform (150 ml). The aqueous layer was treated with NH_3 (aq. conc., 20 ml) and further extracted with chloroform (150 ml). This organic layer was washed with brine (50 ml) and the organic layers were combined, dried over MgSO_4 and filtered and the solvent was removed under reduced pressure. The resulting brown solid was purified by flash chromatography eluting with 2% .880 NH_3 in EtOAc to afford the title compound as a near white solid (1537 mg, 61%). M.p. 72.1-74.0 °C.

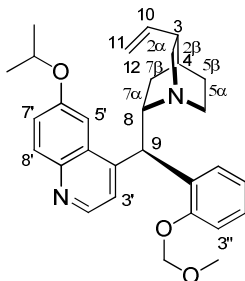
δ_{H} (400 MHz, CDCl_3): 8.78 (br s, 1H), 8.07 (d, J 9.2, 1H), 7.56-7.30 (m, 3H), 5.49 (br s, 1H), 5.08 (br s, 1H), 5.12-4.93 (m, 2H), 4.81-4.69 (m, 1H), 3.55 (br s, 1H), 3.42 (dd, J 10.1, 13.8, 1H), 3.24 (br s, 1H) 3.00-2.84 (m, 2H), 2.33 (br s, 1H), 1.73-1.49 (m, 4H), 1.45 (t, J 5.6, 6H)

δ_{C} (100 MHz, DMSO-d_6): 157.2, 155.4, 147.6, 144.4, 142.0, 131.5, 122.5, 120.0, 114.3, 104.3, 78.9, 69.5, 59.8, 56.8, 55.25, 49.6, 27.6, 27.1, 24.1, 21.6, 21.5.

ν_{max} (solid)/ cm^{-1} : 2934, 1618, 1504, 1462, 1218, 1111, 969, 828, 741.

HRMS (ESI+): calcd. for $[\text{C}_{22}\text{H}_{28}\text{N}_2\text{OCl}]^+$ requires: 371.1890; found: 371.1893.

5.4.28 (1S,2S,4S,5R)-2-((R)-(6-isopropoxyquinolin-4-yl)(2-(methoxymethoxy)phenyl)methyl)-5-vinylquinuclidine (344a)



Procedure B was followed using 2-bromo-methoxymethylphenol (439 mg, 2.02 mmol), magnesium (47.5 mg, 1.95 mmol), THF (6 ml) and 6'-isopropyl-9-epi-chloroquinine (500 mg, 1.35 mmol) in THF (6 ml). Reflux was continued for 4 hours and flash chromatography was carried out with 40-50% EtOAc in Hexanes with 2% TEA to afford the desired compound as an off white solid (394 mg, 62%).

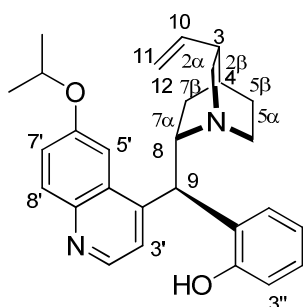
δ_{H} (600 MHz, CDCl_3): 8.71 (d, J 4.6, 1H, H-2'), 8.00 (d, J 9.2, 1H, H-8'), 7.83 (br s, 1H, H-5'), 7.44 (d, J 7.4, 1H, H-3''), 7.37-7.33 (m, 2H, H-3' & H-7'), 7.13 (m, 1H, H-5''), 7.06 (d, J 8.2, 1H, H-6''), 6.99 (m, 1H, H-4''), 5.95 (ddd, J 7.4, 10.6, 17.2, 1H, H-10), 5.31 (d, J 11.2, 1H, H-9), 5.25-5.20 (m, 1H, H- OCH_2), 5.13-5.05 (m, 3H, H-11, H-12 & H- OCH_2), 4.79 (m, 1H, H- $\text{OCH}(\text{CH}_3)_2$), 3.71 (m, 1H, H-8), 3.39 (m, 1H, H-6 α), 3.29-3.21 (m, 4H, H-2 β & H- OCH_3), 2.83-2.71 (m, 2H, H-2 β & H-6 α), 2.31 (m, 1H, H-3), 1.82 (m, 1H, H-7 β), 1.72 (m, 1H, H-4), 1.65 (m, 1H, H-5 α), 1.56 (m, 1H, H-5 β), 1.48-1.41 (m, 6H, H- $\text{C}(\text{CH}_3)_2$), 0.93 (m, 1H, H-7 α).

δ_{C} (100 MHz, CDCl_3): 155.7 (q), 154.7 (q), 147.4 (2C, 1q), 144.2 (q), 141.9, 131.5, 130.8 (q), 129.3 (q), 128.0, 127.5, 121.8, 121.4, 120.2, 114.2, 113.8, 105.7, 94.4, 70.0, 70.0, 59.6, 56.3, 55.8, 41.1 (2C), 39.5, 28.1, 27.9, 27.8, 22.0, 21.8.

$\nu_{\max}$ (solid)/ cm^{-1} : 2935, 1616, 1490, 1455, 1213, 1152, 1076, 1000, 912, 855, 855, 826, 751.

HRMS (ESI⁺): calcd. for $[\text{C}_{30}\text{H}_{37}\text{N}_2\text{O}_3]^+$ requires: 473.2804; found: 473.2803

5.4.29 2-((R)-(6-isopropoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)phenol (344)



Procedure I was followed using the protected starting material **344a** (350 mg, 0.74 mmol), stirring in HCl (20 ml, aq., 5 M) for 16 h to afford the desired compound **344** on workup as a near white solid, (302 mg, 95%). M.p. 206-208 °C.

δ_{H} (400 MHz, DMSO- d_6): 9.90 (br s, 1H, H-OH), 8.70 (d, J 4.4, H-2'), 7.89-7.83 (m, 2H, H-5' & H-8'), 7.68 (d, J 4.4, 1H, H-3'), 7.28 (dd, J 2.0, 8.8, 1H, H-7'), 7.16 (d, J 7.6, 1H, H-3''), 6.89 (app t, J 7.6, 1H, H-5''), 6.76 (d, J 7.6, 1H, H-6''), 6.62 (app t, J 7.6, 1H, H-4''), 6.08 (m, 1H, H-10), 5.15 (d, J 11.2, 1H, H-9), 5.10-4.99 (m, 2H, H-11 & H-12), 4.82 (m, 1H, H-OCH(CH₃)₂), 3.74 (m, 1H, H-8), 3.51 (m, 1H, H-6 α), 3.00 (m, 1H, H-2 β), 2.50 (m, 2H, H-2 α & H-6 β)*, 2.22 (m, 1H, H-3), 1.94 (m, 1H, H-7 β), 1.58 (m, 1H, H-4), 1.53-1.38 (m, 5H, H-5 α , H-5 β & H-OCH(CH₃)₂), 1.27 (d, J 6.0, 3H, H-OCH(CH₃)₂), .067 (m, 1H, H-7 α).

*obscured by residual DMSO peak

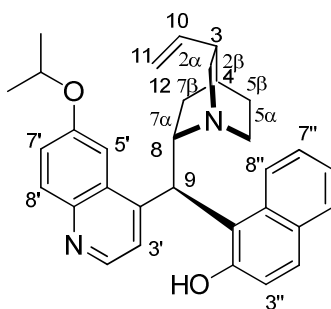
δ_{C} (100 MHz, DMSO- d_6): 155.7 (q), 154.7 (q), 147.9, 147.8 (q), 144.1 (q), 143.2, 131.6, 129.7 (q), 129.5 (q), 128.7, 127.0, 122.6, 120.4, 119.4, 115.3, 114.6, 104.6, 69.9, 59.7, 56.6, 41.9, 41.1, 40*, 29.6, 28.4, 28.0, 22.2, 22.0.

*obscured by residual DMSO peak

ν_{max} (solid)/ cm^{-1} : 2923, 1619, 1585, 1503, 1454, 1231, 1105, 966, 847, 827, 750.

HRMS (ESI+): calcd. for $[\text{C}_{28}\text{H}_{33}\text{N}_2\text{O}_2]^+$ requires: 429.2542; found: 429.2546

5.4.30 1-((R)-(6-isopropoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)naphthalen-2-ol (345)



Procedure B was followed using 1-bromo-2-methoxymethylnaphthol (625 mg, 2.34 mmol), magnesium (51 mg), THF (6 ml) and THF (6 ml) and 6'-isopropyl-9-epi-chloroquinine (500 mg, 1.35 mmol). Reflux was continued for 14 hours and flash chromatography was carried out with 30-50% EtOAc in Hexanes with 2% TEA to remove non-quinineoid compounds from the mixture. This crude material was dissolved in a minimum amount of dioxane and then placed in a RBF with HCl (5 M, 20 ml) and stirred for 20 hours. This was then worked up as for procedure I and the desired product was obtained by careful elution on neutral alumina with EtOAc (20-50%) and TEA (2%) in Hexanes as a brown solid (58 mg, 9%).

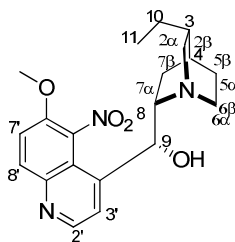
δ_{H} (600 MHz, CDCl_3): 8.67 (d, J 2.4, 1H, H-2'), 8.06 (d, J 8.0, 1H, H-8''), 7.96-7.86 (m, 2H, H-5' & H-8'), 7.66 (d, J 8.0, 1H, H-5''), 7.64-7.60 (m, 2H, H-3' & H-4''), 7.30-7.16 (m, 4H, H-7', H-3'', H-6'', H-7''), 5.75 (ddd, J 7.5, 10.4, 17.7, 1H, H-10), 5.17 (br s, 1H, H-9), 5.11-5.01 (m, 2H, H-11 & H-12), 4.83 (br s, 1H, H-OCH(CH_3)₂), 4.05 (br s, 1H, H-8), 3.41 (dd, J 10.8, 13.4, 1H, H-2 β), 3.26 (m, 1H, H-6 α), 2.97-2.84 (m, 2H, H-2 α & H-6 β), 2.48 (m, 1H, H-3), 1.99-1.90 (m, 2H, H-4 & H-5 α), 1.82-1.71 (m, 2H, H-5 β & H-7 β), 1.65 (m, 1H, H-7 α), 1.48 (d, J 6.0, 3H, H-OCH(CH_3)₂), 1.35 (br s, 3H, H-OCH(CH_3)₂).

δ_{C} (100 MHz, CDCl_3): 155.3 (q), 154.5 (q), 146.7 (q), 146.2, 144.6 (q), 139.3, 133.4 (q), 131.5, 129.3, 129.1 (q), 128.5, 127.5 (q), 125.6, 123.9 (q), 123.0, 122.8, 122.2, 121.8, 117.6, 115.2, 103.7, 76.8, 69.6, 57.5, 53.4, 41.0, 38.0, 29.3, 27.5, 26.8, 21.7, 21.6.

ν_{max} (solid)/ cm^{-1} : 2934, 1618, 1503, 1457, 1382, 1315, 1233, 1111, 967, 908, 819, 726.

HRMS (ESI-): calcd. for $[\text{C}_{32}\text{H}_{33}\text{N}_2\text{O}_2]^-$ requires: 477.2542; found: 477.2553.

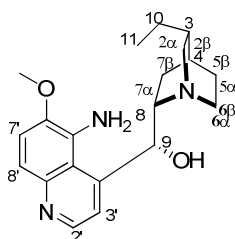
5.4.31 5'-nitroquinine (346)



Dihydroquinine (12.46 g, 38.22 mmol) was slowly added to a flask containing rapidly stirred nitric acid (95% fuming, 50 ml) at -10 °C maintaining a temperature below -5 °C. After the completion of addition the solution was stirred for a further 30 minutes at -10 °C then added cautiously to ice water (250 ml) to which NaOH solution (25% in ice water, 210 ml) was then slowly added followed by ammonia (33% aq, 100 ml). This was then extracted with DCM (4 x 150 ml), and the organics were combined, washed with water (2 x 150 ml) and brine (150 ml), dried over MgSO₄ and filtered. Solvent was removed under reduced pressure and the resulting yellow-brown solid was triturated with EtOAc to give a cream solid. (12.46 g, 88%). M.p. 220-221 °C. (Lit. m.p. 219-221 °C).¹⁴⁵

δ_H (400 MHz, CDCl₃): 8.89 (d, J 4.6, 1H, H-2'), 8.31 (d, J 9.4, 1H, H-8'), 7.77 (d, J 4.6, 1H, H-3'), 7.59 (d, J 9.4, 1H, H-7'), 5.06 (d, J 7.8, 1H, H-9), 4.08 (s, 3H, H-OCH₃),

5.4.32 5'-aminoquinine (347)

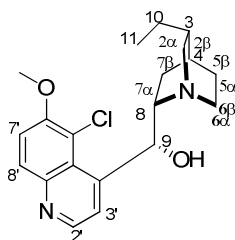


SnCl₂·2H₂O (6.67 g, 29.5 mmol) was dissolved in HCl (conc. aq., 16 ml) and then water (4 ml) was added. In a separate flask 5'-nitroquinine (2.00 g, 5.38 mmol) was dissolved in H₂O (10.7 ml) and HCl (conc. aq., 2.67 ml) and this solution was slowly added to the

solution of SnCl_2 allowing the temperature to rise 40-45 °C. After addition was completed the temperature was held at 45 °C for a further 30 mins. The bright red mixture obtained is diluted with water until a solution is obtained and then neutralised with excess NaOH (25% aq.). The resulting bright yellow solid was removed by filtration and dried under vacuum. The solid can be recrystallised from EtOH or stored for short amounts of time at -20 °C but quickly oxidises to form a brown solid. After drying the product was obtained as a yellow solid (1.20 g, 65%). M.p. 220 °C, dec. (Lit. m.p. 223 °C).⁹¹

δ_{H} (400 MHz, CDCl_3): 8.48 (d, J 3.9 1H, H-2'), 7.56 (d, J 9.0, 1H, H-8'), 7.36 (d, J 9.0, 1H, H-7'), 7.17 (d, J 3.9, 1H, H-3'), 5.87 (br s, H-NH₂), 5.30 (br s, 1H, H-9), 3.97 (s, 3H, H-OCH₃), 3.39-3.45 (m, 1H, H-8), 2.99 (dd, 9.0, 13.1, 1H, H-2 β), 2.73-2.91 (m, 1H, H-6 α), 2.39-2.53 (m, 2H, H-2 α and H-6 β), 1.77-1.91 (m, 2H, H-4 and H-5 α), 1.52-1.72 (m, 2H, H-3 & H-7 α), 1.26-1.48 (m, 4H, H-5 β , H-7 β and H-10), 0.87 (app. t, 3H, H-11).

5.4.33 5'-Chloroquinine (348)



5'-aminoquinine (3.41 g, 10.0 mmol) was dissolved in a solution of HCl (conc. aq., 6.67 ml) and water (13.33 ml) and cooled to 0 °C. To this a solution of NaNO₂ (1 M, 10 ml) was added dropwise maintaining the temperature below 3 °C. This was stirred for a further 15 mins. In a separate flask a solution of CuCl which was freshly prepared by the reduction of CuCl₂ with sodium sulphite and dried under high vacuum (4.00 g, 40 mmol) was added to HCl (conc., 30 ml) and heated to 80 °C. A small amount of fresh copper shavings (approx 100 mg) were added and then the prepared solution of diazonium salt was added quickly

but in a controlled fashion (with vigorous evolution of nitrogen). The resulting solution was stirred for a further 15 mins. This was cooled to room temperature and poured into HCl (2% aq., 100 ml). This was then treated with excess NH₃ (35%) and extracted with Et₂O (3 x 150 ml). The organics were combined, washed with brine (100 ml), dried over MgSO₄ and filtered and solvent was removed under reduced pressure to afford a brown solid. This was triturated with EtOAc to afford the title compound as a pale brown solid (657 mg, 18%).

M.p. 205-206 °C. Litt. m.p. 206 °C.⁹¹

δ_H (400 MHz, CD₃OD): 8.73 (d, J 4.6, 1H, H-2'), 8.09 (d, J 9.4, 1H, H-8'), 8.06 (d, J 4.6, 1H, H-3'), 7.76 (d, J 9.4, 1H, H-7'), 6.75 (d, J 2.0, 1H, H-9), 4.08 (s, 3H, H-OCH₃), 3.79 (m, 1H, H-6α), 3.24 (m, 1H, H-8), 3.08 (dd, J 10.2, 13.4, 1H, H-2β), 2.67 (m, 1H, H-6β), 2.48 (m, 1H, H-2α), 1.84-1.73 (m, 3H, H-4, H-5α & H-7β), 1.51-1.44 (m, 2H, H-3 & H-5β), 1.19 (m, 2H, H-CH₂), 1.07 (m, 1H, H-7α), 0.80 (t, J 7.4, 1H, H-CH₃).

δ_C (100 MHz, CD₃OD): 154.4 (q), 150.3 (q), 147.3, 144.0 (q), 129.5, 124.9 (q), 120.8, 115.9, 114.8 (q), 70.8, 59.3, 58.1, 56.0, 43.0, 37.1, 27.4, 27.2, 25.3, 18.9, 10.8.

HRMS (ESI⁺): calcd. for [C₂₀H₂₆N₂O₂Cl]⁺ requires: 361.1683; found: 361.1696.

Procedure J: Procedure for the C-2' substitution of quinine derivatives

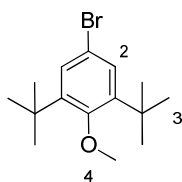
Protected catalyst was placed in a RBF under argon with dry MTBE (0.15 M) and cooled to -10 °C. To this a solution of lithiate in hexanes (1.5-4 eq.) was added and stirring continued for 20 minutes, the reaction was allowed to warm to ambient temperature and stirred for a further 1-20 hours. An equal volume of saturated NH₄Cl solution was added followed by a concentrated solution of iodine in DCM until iodine was clearly remaining.

After 5 minutes a concentrated solution of $\text{Na}_2\text{S}_2\text{O}_3$ was added to quench remaining iodine and the organic layer separated and washed with brine. The combined aqueous layers were further washed with DCM (2 x equivalent volume), and all organics were combined, dried over MgSO_4 and filtered and the solvent was removed under reduced pressure. The crude produce was then purified by flash chromatography.

Procedure K: Procedure for the C-2' substitution of quinine derivatives

Aryl bromide (2-3 eq.) was placed in a RBF under argon and dry MTBE (0.5 M) was added. This was cooled to $-10\text{ }^\circ\text{C}$ and *n*-butyl lithium (3.8-5.7 eq.) was added slowly. This was stirred at $-10\text{ }^\circ\text{C}$ for 30 minutes and then a room temperature for 1 hour. The reaction was then cooled to $-10\text{ }^\circ\text{C}$ and a solution of protected catalyst (1 eq.) in dry MTBE (0.167 M) was added. Stirring was continued for 20 minutes at $-10\text{ }^\circ\text{C}$ and then 1 hour at ambient temperature. . An equal volume of saturated NH_4Cl solution was added followed by a concentrated solution of iodine in DCM until iodine was clearly remaining. After 5 minutes a concentrated solution of $\text{Na}_2\text{S}_2\text{O}_3$ was added to quench remaining iodine and the organic layer separated and washed with brine. The combined aqueous layers were further washed with DCM (2 x equivalent volume), and all organics were combined, dried over MgSO_4 and filtered and the solvent was removed under reduced pressure. The crude produce was then purified by flash chromatography.

5.4.34 5-bromo-1,3-di-*tert*-butyl-2-methoxybenzene (362)

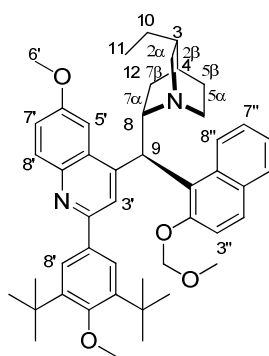


To a dry round bottom flask dry DMSO (24 ml) was added under argon. To this NaH 60% in mineral oil (571mg, 23.8 mmol) was added and the reaction was stirred vigorously. The reaction was cooled in an icebath at $0\text{ }^\circ\text{C}$ with care taken to avoid freezing the mixture. 2,6-di-*t*-butyl-4-bromophenol (2.85 g, 10 mmol) was added in portions over 20 mins and stirring was continued for a 15 minutes. Methyl Iodide (2.43 ml, 39.1 mmol) was

added and stirring was continued for a further 15 minutes before removing the flask from the ice bath and stirring for a further 5 hours. The flask was then cooled to 0 °C and hexanes (50 ml) was added followed by the slow addition of water until two phases were apparent. The organic layer was collected and the aqueous layer was extracted with hexanes (3 x 50 ml). The organics were combined and washed with water (4 x 100 ml). The organics were then dried over MgSO₄ and filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography eluting with 100% hexanes to afford the title product **328** as a white solid (2.51 g, 84%). M.p. 59-60 °C. (Lit. m.p. 49-50 °C).²⁵⁵

δ_C (100 MHz, CDCl₃): 158.3 (q), 145.6 (q), 129.1, 115.9 (q), 64.0, 35.5 (q), 31.4.²⁵⁶

5.4.35 (1S,2S,4S,5R)-2-((R)-(2-(3,5-di-tert-butyl-4-methoxyphenyl)-6-methoxyquinolin-4-yl)(2-(methoxymethoxy)naphthalen-1-yl)methyl)-5-vinylquinuclidine (361a)



Procedure K was followed using 5-bromo-1,3-di-tert-butyl-2-methoxybenzene, *s*-BuLi in hexanes, (5.57 ml, 7.8 mmol), (2S,4S,5R)-2-((R)-(2-(methoxymethoxy)naphthalen-1-yl)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (993 mg, 2 mmol) and MTBE (32 ml). The product was obtained after purification by flash chromatography, using 30-

50% EtOAc and 2% TEA in Hexanes as the eluent to afford the product **361a** as a beige solid (1032 mg, 72%). M.p. 124 °C. $[\alpha]_D^{20} = 229.4$ (c 0.05, CHCl₃).

The NMR spectra of this molecule contain small levels other conformers however these can be found to disappear on warming to 70 °C in DMSO. The signals reported are at 20 °C as the spectra is otherwise sharper. The carbon spectra contains several broad peaks.

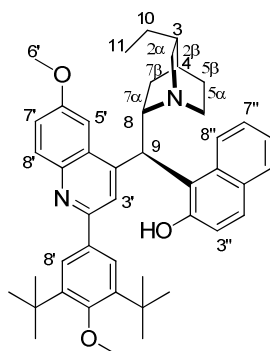
δ_H (400 MHz, CDCl₃): 9.10 (d, J 8.6, 1H) , 8.23 (br s, 1H), 8.17 (br s, 2H), 7.91-7.82 (m, 2H), 7.77-7.62 (m, 2H), 7.45-7.38 (m, 1H), 7.34 (br s, 1H), 7.24-7.13 (m, 2H), 5.65-5.56 (m, 1H), 5.05-4.92 (m, 2H), 4.57-4.46 (m, 1H), 3.73 (s, 3H) , 3.48-3.29* (m, 4H), 3.03 (s, 3H), 2.88-2.78 (m, 1H), 2.41-2.14 (m, 2H), 1.78- 1.45 (m, 24H), 1.4-1.19 (m, 3H), 1.16-1.07 (m, 1H), 0.95-0.84 (m, 3H)

δ_C (100 MHz, CDCl₃): 160.3, 156.4, 152.8, 152.0, 145.3, 144.0, 143.5, 133.3, 131.2, 129.4, 129.1, 128.6, 128.22, 126.7, 124.5, 124.3, 124.1, 123.1, 121.1, 120.0, 119.9, 116.0, 102.9, 93.7, 64.3, 57.6, 55.7, 55.4, 55.3, 43.5, 41.7, 37.3, 35.6, 31.9, 29.6, 28.3, 28.1, 25.5, 12.3.

$\nu_{\max}$ (solid)/cm⁻¹: 2955, 1622, 1345, 1221, 1151, 1008, 830, 744.

HRMS (ESI+): calcd. for [C₄₇H₅₉N₂O₄]⁺ requires: 715.4475; found: 715.4484.

5.4.36 1-((R)-(2-(3,5-di-tert-butyl-4-methoxyphenyl)-6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)naphthalen-2-ol (361)



Procedure I was followed using **361a** (950 mg, 1.42 mmol), dioxane (5 ml) and HCl (5 M, aq, 15 ml). Stirring was continued for 20 hours. The **361** was obtained on workup as a near white solid (857 mg, 90 %). M.p. 110 °C. $[\alpha]_{\text{D}}^{20} = 180.3$ (c 0.15, CHCl₃).

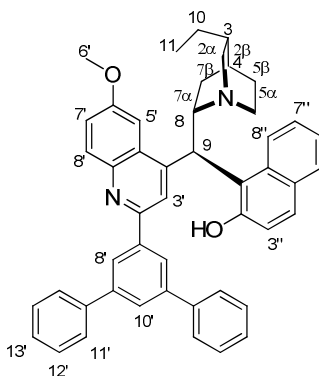
δ_{H} (400 MHz, CDCl₃): 8.25-8.11 (m, 1H), 8.06-7.82 (m, 5H), 7.70-7.60 (m, 2 H), 7.36-7.13 (m, 4H), 5.18 (br s, 1H), 4.06-3.93 (m, 4H), 3.78 (s, 3H), 3.37 (dd, J 10.0, 13.4, 1H), 3.32-3.21 (m, 1H), 2.86 (m, 1H), 2.69-2.59 (m, 1H), 2.01-1.86 (m, 2H), 1.78-1.48 (m, 22H), 1.34-1.35 (m, 3H), 0.86 (t, J 7.6, 3H)

δ_{C} (100 MHz, CDCl₃): 160.3, 158.7, 156.7, 156.6, 154.9, 154.4, 144.9, 143.5, 134.0, 133.5, 131.6, 129.4, 129.1, 128.5, 126.0, 125.6, 125.4, 122.8, 122.4, 122.2, 121.7, 121.1, 102.2, 64.0, 60.0, 55.4, 55.2, 41.0, 35.8, 35.5, 31.65, 27.5, 26.5, 25.4, 20.6, 13.8, 13.4.

ν_{max} (solid)/cm⁻¹: 2956, 1621, 1593, 1454, 1347, 1223, 1114, 1007, 876, 832, 743.

HRMS (ESI⁻): calcd. for [C₄₅H₅₃N₂O₃]⁻ requires: 669.4056; found: 669.4060.

5.4.37 1-((R)-2-([1,1':3',1''-terphenyl]-5'-yl)-6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methylnaphthalen-2-ol (360)



Procedure K was followed using 3,5-diphenylbromobenzene (1.24 g, 4.00 mmol), *n*BuLi (2.5 M in Hexanes, 3.12 ml, 7.8 mmol), MtBE (32 ml) and MOM protected **147** (993 mg,

2.00 mmol). The resulting crude material was then deprotected according procedure I. The product was purified by careful elution using EtOAc (20-60%) and TEA (2%) in Hexanes as the eluent to give the desired product as a near white solid (141mg, 10%) M.p. 98 °C. $[\alpha]_D^{20} = 140.0$ (c 0.10, CHCl_3).

NMR analysis showed that the room temperature spectra of this molecule consisted of several broad sets of signals for different conformations present in solution. On warming to 40 °C, two sets of signals appeared to become more clear and the resulting HSQC clearly shows signals diagnostic of the quinuclidine section. Spectra are shown below the lower spectra shows the effect of warming to 40 °C. The signal for H-9 can be seen to become two distinct peaks.

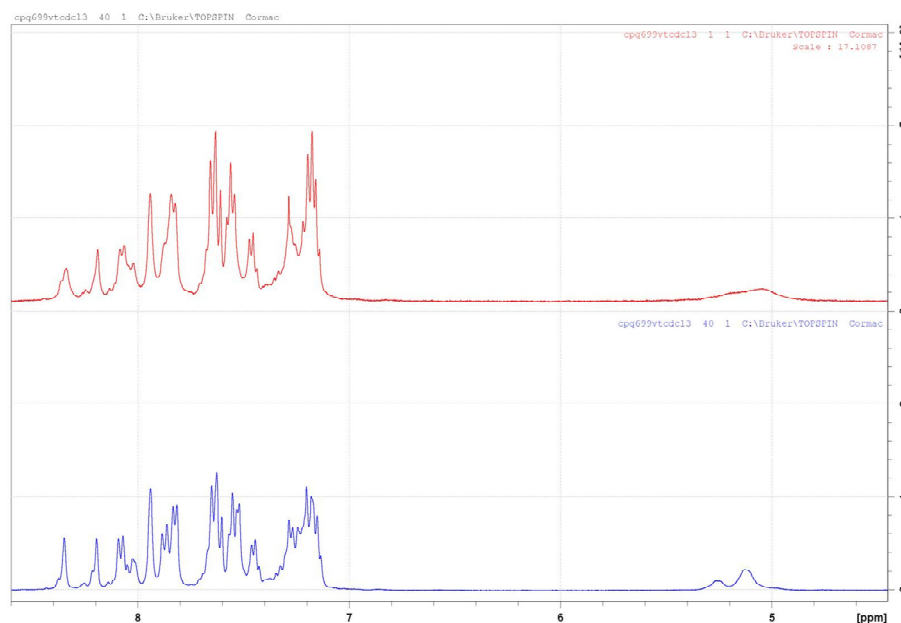
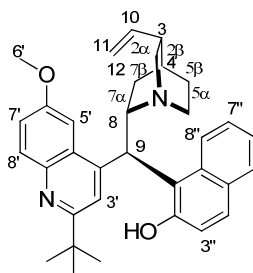


Figure 5.3 Aromatic section (and H-9) of a VT experiment. All of the peaks can be seen to sharpen significantly however it was not possible to obtain a clear spectra.

ν_{max} (solid)/ cm^{-1} : 2929, 1620, 1594, 1504, 1454, 1230, 1030, 877, 832, 820, 742, 698.

HRMS (ESI+): calcd. for $[C_{48}H_{45}N_2O_2]^+$ requires: 681.3481; found: 681.3492

5.4.38 1-((R)-(2-(tert-butyl)-6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)naphthalen-2-ol (359)



Procedure J was followed using the required protected catalyst (495 mg, 1.0 mmol), *t*Buli in Hexanes (1.7 ml, 3.0 mmol) and *Mt*BE (6 ml) to give the desired product as an off white solid (423 mg, 77%).

Procedure I was then followed using this material (400 mg, 0.73 mmol) to afford the desired product as a white solid in quantitative yield. M.p. 210-212°C. $[\alpha]_D^{20} = -144.8$ (c 0.21, $CHCl_3$).

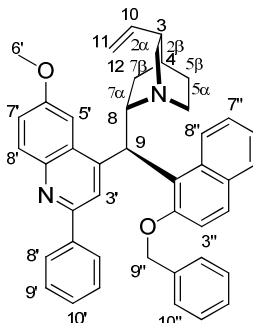
δ_H (600 MHz, $CDCl_3$): 14.8 (br s, 1H, H-OH), 8.10 (d, J 8.7, 1H, H-8''), 7.90-7.82 (m, 2H, H-5' & H-8'), 7.75 (s, 1H, H-3'), 7.65 (d, J 8.0, 1H, H-5''), 7.61 (8.8), 7.27 (m, 1H, H-7''), 7.19-7.14 (m, 3H, H-7', H-3'' & H-6''), 5.77 (ddd, J 7.6, 10.5, 17.4, 1H, H-10), 5.11-5.00 (m, 3H, H-9, H-11 & H-12), 4.03 (m, 1H, H-8), 3.91 (s, 3H, H- OCH_3), 3.39 (dd, J 10.4, 13.6, 1H, H-2 β), 3.26 (m, 1H, H-6 α), 2.98-2.84 (m, 2H, H-2 α & H-6 β), 2.48 (m, 1H, H-3), 2.00-1.92 (m, 2H, H-4 & H-5 α), 1.83-1.73 (m, 2H, H-5 β & H-7 β), 1.64-1.44 (m, 10H, H-7 α & H- $C(CH_3)_3$).

δ_C (150 MHz, $CDCl_3$): 165.2 (q), 156.9 (q), 154.9 (q), 145.4 (q), 145.3 (q), 139.9, 133.8 (q), 131.7, 129.8, 129.6 (q), 128.9, 125.9, 125.7, 123.1, 123.0, 122.1, 121.9 (q), 121.1, 117.7 (q), 115.6, 102.6, 57.8, 55.8, 55.5, 53.9, 41.4, 38.6, 37.5, 30.1, 29.9, 28.1, 27.3.

ν_{max} (solid)/ cm^{-1} : 2958, 1620, 1593, 1505, 1456, 1232, 1030, 922, 880, 821, 755, 743

HRMS (ESI-): calcd. for $[\text{C}_{34}\text{H}_{37}\text{N}_2\text{O}_2]^-$ requires: 505.2855; found: 505.2838.

5.4.39 (1S,2S,4S,5R)-2-((R)-2-(benzyloxy)naphthalen-1-yl)(6-methoxy-2-phenylquinolin-4-yl)methyl)-5-vinylquinuclidine (351a)



Procedure J was followed using **150** (1622 mg, 3.00 mmol), phenyl lithium in dibutyl ether (6.7 ml, 12.0 mmol), and *Mt*BE (20 ml). The desired compound was obtained after purification by flash chromatography, eluting in EtOAc (10-40%) and TEA (2%) in hexanes to give the title compound as a brown solid.

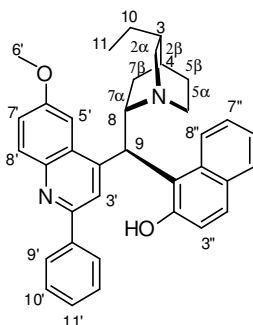
despite analysis in a range of solvents, the resultant spectra were unclear, thus an assigned proton could not be obtained.

δ_C (100 MHz, $CDCl_3$): 157.1 (q), 155.3 (q), 153.7 (q), 145.5 (q), 143.7 (q), 141.2, 141.1 (q), 139.6 (q), 135.8 (q), 133.0 (q), 129.8, 129.4 (q), 129.2 (q), 129.0, 128.2, 128.1, 128.0, 127.9, 127.6, 127.4, 126.9, 126.7, 122.8, 122.3, 121.2, 121.0, 114.2, 113.3, 101.9, 70.0, 56.1, 55.2, 54.4, 45.6, 44.1, 38.6, 29.4, 26.2, 28.9.

ν_{max} (solid)/ cm^{-1} : 3288, 2927, 1742, 1652, 1582, 1548, 1370, 1186, 821

HRMS (ESI⁺): calcd. for $[C_{43}H_{41}N_2O_2]^+$ requires: 617.3168; found: 617.3160.

5.4.40 1-((R)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxy-2-phenylquinolin-4-yl)methyl)naphthalen-2-ol (351)



Procedure C was followed using **351a** (800 mg, 1.30 mmol), Pd/C 10% (150 mg, 0.13 mmol Pd) in EtOAc:MeOH 1:1 (25 ml). The desired product was obtained after flash chromatography EtOAc (20-50%) and TEA (2%) in Hexanes as a beige solid (547 mg, 80%). M.p. 151-153 °C. $[\alpha]_D^{20} = -228.6$ (c 0.11, CHCl₃).

δ_H (400 MHz, 50 °C, CDCl₃): 14.65 (br s, 1H, H-OH), 8.16 (d, J 7.5, 2H, H-9'), 8.13 (d, J 9.2, H-8''), 8.08 (s, 1H, H-3'), 8.01 (d, J 2.1, 1H, H-5'), 7.99 (d, J 4.2, 1H, H-8'), 7.65 (d, J 8.5, 1H, H-5''), 7.63 (d, J 8.9, 1H, H-3''), 7.56 (app. t, 2H, H-10'), 7.47 (t, J 7.4, 1H, H-11'), 7.28 (m, 1H, H-7'')*, 7.21 (d, J 8.9, 1H, H-4''), 7.15 (app t, 1H, H-6''), 5.22 (m, 1H, H-9), 4.04-3.95 (m, 4H, H-8 & H-6'), 3.37 (dd, J 10.1, 13.4, 1H, H-2 β), 3.29 (m, 1H, H-6 α), 2.86 (m, 1H, H-6 β), 2.65 (dd, J 6.0, 13.4, 1H, H-2 α), 1.98 (m, 1H, H-5 α), 1.91 (m, 1H, H-4), 1.81-1.57 (m, 4H, H-3, H-5 β , H-7 α & H-7 β), 1.33 (m, 2H, H-10), 0.85 (t, J 7.35, 3H, H-11).

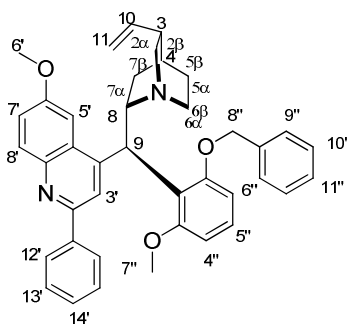
δ_C (100 MHz, 50 °C, CDCl₃): 157.6 (q), 155.4 (q), 153.9 (q), 147.2 (q), 145.6 (q), 140.0 (q), 134.1 (q), 132.2, 129.8, 129.6 (q), 128.9, 128.8, 128.7, 128.5, 127.3, 126.8 (q), 125.9, 123.4, 122.8, 122.1, 121.8,

118.0 (q), 102.9, 58.6, 55.9, 55.7, 41.5, 36.5, 29.8, 28.1, 27.8, 26.9, 26.0, 11.7.

$\nu_{\max}$ (solid)/ cm^{-1} : 2929, 1620, 1590, 1497, 1450, 1349, 1231, 1029, 820, 742, 694.

HRMS (ESI-): calcd. for $[\text{C}_{36}\text{H}_{35}\text{N}_2\text{O}_2]^-$ requires: 527.2699; found: 527.2717.

5.4.41 (1S,2S,4S,5R)-2-((R)-(2-(benzyloxy)-6-methoxyphenyl)(6-methoxy-2-phenylquinolin-4-yl)methyl)-5-ethylquinuclidine (363)



Procedure J was followed using **335** (500 mg, 0.96 mmol), phenyl lithium in dibutyl ether (2.2 ml, 4.0 mmol) and *Mt*BE (10 ml). The resulting product was purified by flash chromatography to afford the title compound as a pale beige solid. (432 mg, 75%). M.p. 103-105 °C.

δ_{H} (400 MHz, CDCl_3): 8.27 (s, 0.26H, H-3'min), 8.19 (d, J 7.8, 0.52H, H-12'), 8.06-8.00 (m, 1H, H-8'maj & H-8'min), 7.88 (d, J 2.4, 0.74H, H-5'maj), 7.85-7.81 (m, 1H, H-3'maj & H-5' min), 7.79-7.74 (m, 1.48H, H-12'maj), 7.61-7.52 (m, 1.04H, H-13'min & H-9''min), 7.51-7.36 (m, 3.74H, H-13'maj, H-13'min, H-14'maj, H-14'min & H-10''min), 7.33-7.26 (m, 3.48H, H-7'maj, H-7'min, H-9''maj, H-11''maj & H-11''min), 7.22 (m, 1.48H, H-10''maj), 7.14-7.07 (m, 1H, H-5''maj & H-5''min), 6.70 (d, J 8.2, 0.26H, H-6''min), 6.65 (d, J 8.4, 0.74H, H-4''maj), 6.54-6.49 (m, 1H, H-4''min & H-6''maj),

6.04 (ddd, J 7.8, 10.6, 17.6, 0.26H, H-10min), 5.95 (ddd, J 7.8, 10.6, 17.4, 0.74H, H-10maj), 5.46 (d, J 11.3, 0.26H, H-9min), 5.37 (d, J 11.3, 0.74H, H-9maj), 5.32 (d, J 12.0, 0.26H, H-8''min), 5.22 (d, J 12.0, 0.26H, H-8''min), 5.15-5.03 (m, 2H, H-11maj, H-11min, H-12maj & H-12min), 4.98 (d, J 11.0, 0.74H, H-8''maj), 4.78 (d, J 11.0, 0.74H, H-8''maj), 4.49-4.38 (m, 1H, H-8maj & H-8min), 4.04 (s, 2.22H, H-7''maj), 3.96 (s, 2.22H, H-6'maj), 3.70 (s, 0.78H, H-7''min), 3.65 (s, 0.78H, H-6'min), 3.57-3.44 (m, 1H, H-6 α maj & H-6 α min), 3.31-3.20 (m, 1H, H-2 β maj & H-2 β min), 2.91-2.79 (m, 1H, H-2 α maj & H-2 α min), 2.75-2.55 (m, 1H, H-6 β maj & H-6 β min), 2.34-2.24 (m, 1H, H-3maj & H-3min), 2.07-1.98 (m, 1H, H-7 β maj & H-7 β min), 1.74-1.59 (m, 2H, H-4maj, H-4min, H-5 α maj & H-5 α min), 1.57-1.42 (m, 1H, H-5 β maj & H-5 β min), 0.92-0.78 (m, 1H, H-7 α maj & H-7 α min).

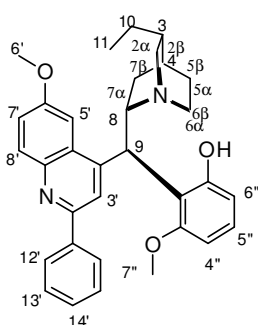
δ_C (150 MHz, CDCl₃): peaks for major rotamer: 159.5 (q), 158.5 (q), 157.4 (q), 157.3 (q), 156.7 (q), 153.9 (q), 145.9 (q), 144.6 (q), 142.4, 140.4 (q), 136.3 (q), 131.6, 128.7, 128.6, 128.5, 127.9, 127.9, 127.2, 127.1, 120.7, 120.7, 113.8, 105.9, 104.0, 102.7, 70.4, 56.5, 56.0, 55.9, 55.3, 41.2, 40.8, 39.8, 30.1, 28.0, 27.9.

δ_C (150 MHz, CDCl₃): peaks for minor rotamer: 159.5 (q), 158.5 (q), 157.4 (q), 157.3 (q), 156.7 (q), 153.7 (q), 145.8 (q), 144.6 (q), 142.4, 140.4 (q), 136.7 (q), 131.7, 129.0, 128.6, 128.5, 128.1, 128.0, 127.1, 127.0, 120.4, 120.3, 113.8, 106.0, 105.3, 103.3, 70.9, 56.6, 55.9, 55.4, 55.2, 41.4, 41.2, 39.8, 29.8, 28.0, 27.9.

$\nu_{\max}$ (solid)/cm⁻¹: 2926, 1621, 1593, 1497, 1461, 1348, 1230, 1098, 1029, 830, 779, 695.

HRMS (ESI⁺): calcd. for [C₄₀H₄₁N₂O₃]⁺ requires: 597.3117; found: 597.3112.

5.4.42 2-((R)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxy-2-phenylquinolin-4-yl)methyl)-3-methoxyphenol (364)



Procedure C was followed using **363** (250 mg, 0.48 mmol), Pd/C 10% (50 mg, 0.048 mmol), and EtOH (20 ml). Hydrogenation was continued for 4 days at a pressure of 3 atmospheres. The desired compound was purified by flash chromatography on neutral alumina (approx. grade 2) eluting with 2% TEA and 50% EtOAc in Hexanes to afford a pale yellow solid (179 mg, 73%). M.p. 111-112 °C. $[\alpha]_D^{20} = -29.4$ (c 0.102, CHCl₃).

δ_H (400 MHz, 50 °C, CDCl₃): 8.17 (br d, J 7.1, 2H, H-12'), 8.05 (d, J 9.2, 1H, H-8'), 7.93 (s, 1H, H-3'), 7.86 (d, J 2.7, 1H, H-5'), 7.53 (m, 2H, H-13'), 7.45 (m, 1H, H-14'), 7.31 (br d, J 9.2, 1H, H-7'), 7.04 (app t, J 8.1, 1H, H-5''), 6.63 (d, J 8.1, 1H, H-4''), 6.24 (d, J 8.1, 1H, H-6''), 4.93 (br s, 1H, H-9), 4.01 (s, 3H, H-6'), 3.86 (m, 1H, H-8), 3.44 (br s, 3H, H-7''), 3.38-3.24 (m, 2H, H-2β & H-6α), 2.85 (m, 1H, H-6β), 2.57 (dd, J 5.5, 13.4, 1H, H-2α), 1.93 (m, 1H, H-5α), 1.80 (m, 1H, H-4), 1.73-1.51 (m, 3H, H-3, H-5β & H-7β), 1.40 – 1.23 (m, 3H, H-7α & H-10), 0.84 (t, J 7.3, 3H, H-11).

δ_{C} (150 MHz, 20 °C, CDCl_3): 157.6 (q), 157.3 (q), 153.5 (q), 146.5 (q, br), 145.5 (q, br), 144.9 (q, br), 140.1 (q, br), 131.8, 128.7, 128.7, 128.3, 127.2, 123.2 (br), 121.9 (br), 119.6 (q, br), 116.7 (q, br), 113.4, 102.8, 102.2, 61.1 (br), 55.8, 55.7, 55.1, 53.6 (br), 41.4, 36.2, 30.0, 27.7, 26.8, 25.7, 11.7.

ν_{max} (solid)/ cm^{-1} : 2929, 1591, 1497, 1456, 1351, 1231, 1074, 1030, 780, 695.

HRMS (ESI-): calcd. for $[\text{C}_{33}\text{H}_{35}\text{N}_2\text{O}_3]^-$ requires: 507.2648; found: 507.2647.

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