An Organocatalytic Oxidative Coupling Strategy for the Synthesis of Arylated Quaternary Stereocentres and its Application in the Total Synthesis of Powelline and Buphanidrine

A thesis submitted to The University of Manchester for the degree of Doctor of Philosophy in the Faculty of Engineering and Physical Sciences

2010

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School of Chemistry
# Contents

Abstract ............................................................................................................................ 4  
Declaration .......................................................................................................................... 5  
Copyright Statement ........................................................................................................ 6  
Acknowledgments ............................................................................................................... 7  
Abbreviations ..................................................................................................................... 8  
Stereochemistry ................................................................................................................... 9  
1 Introduction ...................................................................................................................... 12  
   1.1 Significance of α-arylated quaternary stereocentres .............................................. 12  
   1.2 Methods for synthesising α-arylated quaternary carbon centres ....................... 13  
   1.3 Aims of this thesis................................................................................................. 23  
2 Methodology Development ................................................................................................. 24  
   2.1 Introduction to quinone chemistry ....................................................................... 24  
   2.2 Proof of Principle studies: Organocatalytic Michael addition to isolable ortho-quinones ............................................................................................. 31  
   2.3 Enantioselective Michael addition to stable ortho-quinones .................................. 36  
3 Oxidative coupling strategy – Michael addition to in situ generated ortho-benzoquinones .................................................................................................................................. 42  
   3.1 Racemic method ...................................................................................................... 42  
   3.2 Asymmetric Michael addition to in situ generated ortho-benzoquinones ............. 50  
4 Total Synthesis of (±)-powelline & (±)-buphanidrine ......................................................... 55  
   4.1 Amaryllidaceae Alkaloids ....................................................................................... 55  
   4.2 Retrosynthetic analysis ......................................................................................... 57  
   4.3 Initial Approach to Buphanamine .......................................................................... 58  
   4.4 Alternative approach to powelline, buphanidrine, undulatine, crinamidine and buphanamine ................................................................................................. 62  
5 Enantioselective total synthesis studies ................................................................................ 78  
   5.1 Initial organocatalyst screen .................................................................................... 78  
   5.2 Phase transfer catalysis ......................................................................................... 81  
   5.3 Pro-nucleophile screen ......................................................................................... 83  
   5.4 Conditions screen ................................................................................................... 86  
   5.5 Screen of novel cinchona alkaloid derived organocatalysts ..................................... 87
Abstract

The synthesis of compounds containing α-arylated quaternary stereogenic centres is a significant synthetic challenge. This thesis describes the development of an organocatalytic methodology for the direct construction of this motif through the Michael addition of carbon-centered pro-nucleophiles to highly reactive and unstable ortho-benzoquinones.

Proof-of-principle for the base catalysed Michael addition to ortho-quinones was established with stable 1,2-naphthoquinone (Chapter 2), however typical ortho-benzoquinones were found to be too unstable to use in this process. Accordingly an oxidative coupling strategy was developed for *in-situ* generation of the o-benzoquinone electrophile (Chapter 3.1). The base catalysed Michael addition followed by aromatisation allows for the direct construction of arylated quaternary stereocentres. An asymmetric variant was also developed by replacing the base catalyst with a cinchona alkaloid derived organocatalyst, up to 82% ee was achieved (Chapter 3.2).

The methodology was then applied to the racemic total synthesis of the amaryllidaceae alkaloids powelline and buphanidr ine (Chapter 4). The oxidative coupling methodology allowed rapid construction of the sterically congested arylated quaternary stereocentre in the key step of the syntheses, which were then completed in 13 and 14 steps respectively in 6% overall yield. Employing quinidine derived organocatalyst **QD-265** in the oxidative coupling step gave arylated product **208** in 57% yield (3 steps) and 70% ee (Chapter 5). However, the enantioselective total synthesis was thwarted by racemisation during the Dieckmann-type cyclisation for the formation of enol ether **212** and an alternative synthetic strategy will be required to synthesise the enantiopure alkaloid.
Declaration

I declare that no portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning. A preliminary proof-of-principle reaction of 1,2-naphthoquinone with methyl cyclopentanone-2-carboxylate conducted by Dr Kevin Greenaway is referenced in the text. All novel compounds synthesised by myself are shown in Chapter 7.

Katherine Bogle                July 2010
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Katherine Bogle              July 2010
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## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>Å</td>
<td>ångström</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Anh</td>
<td>anhydrous</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aromatic group</td>
</tr>
<tr>
<td>BEMP</td>
<td>2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthyl</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1'-bi-2,2'-naphthol</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>br.</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>c</td>
<td>concentration</td>
</tr>
<tr>
<td>calcd.</td>
<td>calculated</td>
</tr>
<tr>
<td>cat.</td>
<td>catalyst</td>
</tr>
<tr>
<td>Cbz</td>
<td>benzylxycarbonyl</td>
</tr>
<tr>
<td>Cl (+/-)</td>
<td>chemical ionisation (positive/negative)</td>
</tr>
<tr>
<td>cm</td>
<td>centimetre</td>
</tr>
<tr>
<td>COD</td>
<td>1,5-cyclooctadiene</td>
</tr>
<tr>
<td>conv.</td>
<td>conversion</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>d</td>
<td>day/doublet (NMR)</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DEPT</td>
<td>distortionless enhancement by polarization transfer</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>dtpf</td>
<td>1,1'-bis(di-tert-butyolphosphino)ferrocene</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI (+/-)</td>
<td>electron ionisation (positive/negative)</td>
</tr>
<tr>
<td>epi</td>
<td>epimer</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalents</td>
</tr>
</tbody>
</table>
ES (+/-) electrospray (positive/negative)
ESI electrospray ionisation
Et ethyl
EWG electron withdrawing group
g gram
h hour
HMBC heteronuclear multiple bond correlation
HMDS hexamethyldisilazane
HMQC heteronuclear multiple-quantum coherence
HPLC high performance liquid chromatography
HRMS high resolution mass spectroscopy
HSQC heteronuclear Single Quantum Coherence
Hz hertz
i iso
IR infra-red
L/K/N-Selectride® lithium/potassium/sodium tri-sec-butylborohydride
LHMDS lithium hexamethyldisilazane
m multiplet
m meta
M molar
m/z mass-to-charge ratio
max maximum
Me methyl
mg milligram
MHz megahertz
min minute
mL millilitre
mmol millimole
mol mole
MP melting point
MS mass spectroscopy
Ms mesyl (methanesulfonyl)
n normal, straight chain
NMR nuclear magnetic resonance
NOE/NOESY nuclear Overhauser effect
Nu nucleophile
o ortho
p para
Pg Protecting group
Ph phenyl
PIFA phenyliodonium bis(trifluoracetate)
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMP</td>
<td>1,2,2,6,6-pentamethylpiperidine</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>ps</td>
<td>polymer-supported</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>Q</td>
<td>quinine</td>
</tr>
<tr>
<td>QD</td>
<td>quinidine</td>
</tr>
<tr>
<td>Red-Al®</td>
<td>sodium bis(2-methoxyethoxy)aluminium hydride</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>sec</td>
<td>secondary</td>
</tr>
<tr>
<td>SNAr</td>
<td>nucleophilic aromatic substitution</td>
</tr>
<tr>
<td>Super-hydride®</td>
<td>lithium triethylborohydride</td>
</tr>
<tr>
<td>T</td>
<td>temperature</td>
</tr>
<tr>
<td>t</td>
<td>time or triplet (NMR)</td>
</tr>
<tr>
<td>t/tert</td>
<td>tertiary</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBME</td>
<td>tert-butyl methyl ether</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>trifluoroacetic anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>tri-isopropyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMG</td>
<td>1,1,3,3-tetramethylguanidine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Tr</td>
<td>trityl</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl (p-toluenesulfonyl)</td>
</tr>
<tr>
<td>vs</td>
<td>versus</td>
</tr>
</tbody>
</table>
Stereochemistry

Stereochemistry is drawn in accord with the conventions proposed by Maehr. Normal bond thickness is used for racemic compounds or enantioenriched compounds where stereochemistry is unknown. Enantioenriched compounds are identifiable by a (+) or (-) compound number prefix indicating the sign of the optical rotation. Solid and broken wedges are used to indicate absolute configuration when known (or inferred from other results) in enantioenriched or enantiopure compounds. Solid and broken lines are used to indicate the relative stereochemistry (when known) of diastereopure or diastereoenriched racemates (or diastereopure/diastereoenriched, enantioenriched compounds with known relative but unknown absolute stereochemistry).

1 Introduction

1.1 Significance of \( \alpha \)-arylated quaternary stereocentres

A significant number of pharmaceutically important compounds and biologically active natural products contain substituted catechol (1,2-dihydroxylated benzene) derivatives covalently bonded to all-carbon quaternary stereocentres. Typical examples include: the calcium channel antagonists verapamil (1);\(^1\) the phosphodiesterase IV inhibitor cilomilast (2);\(^2\) the paraherquamide family of anti-parasitic alkaloids (3);\(^3\) several members of the \textit{amaryllidaceae} alkaloid family, including haemanthidine (4), and tazettine (5) that exhibit analgesic and anti-cancer properties;\(^4\) and the galanthamine type \textit{amaryllidaceae} alkaloids that exhibit significant and diverse biological activities.\(^5\) Galanthamine (6) has been shown to be effective in the symptomatic treatment of senile dementia of the Alzheimer’s type,\(^6\) and further analogues of galanthamine with increased blood-brain barrier permeability have recently been reported as treatments for human brain diseases associated with a cholinergic deficit including Alzheimer’s disease, Parkinson’s disease, vascular dementia, schizophrenia and epilepsy.\(^7,8\)

![Scheme 1.1: A selection of pharmaceuticals and biologically active natural products containing catechol derivatives bonded to all carbon quaternary stereocentres.](image-url)
1.2 Methods for synthesising α-arylated quaternary carbon centres

The construction of α-arylated all-carbon quaternary stereogenic centres is still a significant synthetic challenge. Several approaches have been investigated and are detailed below.

1.2.1 Friedel-Crafts Alkylation

The synthesis of simple tri-alkyl substituted quaternary arylated carbon centres through Friedel-Crafts chemistry (e.g. introduction of a tert-butyl substituent) is a well established transformation. More recently enantioselective Friedel-Crafts reactions have been developed; however this chemistry is yet to find significant application in the synthesis of all-carbon arylated quaternary stereocentres. Examples of the diastereoselective synthesis of this motif have been reported, these include the intramolecular Friedel-Crafts-type cyclisation of tertiary benzylic cations generated through protonation of styrene precursors such as 7, reported by Bach to give α-arylated quaternary centres with high levels of facial selectivity (Scheme 1.2).

![Scheme 1.2: Intramolecular Friedel-Crafts alkylation for the synthesis of α-arylated quaternary stereocentres](image)

During studies towards the total synthesis of the hauoamines, Trauner developed an intramolecular Friedel-Crafts alkylation to generate α-arylated quaternary centres with simultaneous formation of enol triflates. Triflic anhydride activates enones such as 9 to generate a stabilised cation that is trapped by the pendant electron-rich arene (Scheme 1.3).
1.2.2 Stoichiometric Organometallic Reagents

The reaction of enolate nucleophiles with electrophiles including alkyl halides, carbonyls and α,β-unsaturated carbonyl compounds is one of the most widespread methods for the construction of carbon – carbon bonds. However the reaction of enolate nucleophiles with aromatic species for the construction of carbon – aryl bonds is far less common.

Pinhey has demonstrated the ability of aryllead tricarboxylates to react with β-ketoesters, cyanoacetates and malononitriles to give arylated quaternary carbon centres in modest to good yields.\(^1\) For example cyanoacetate 11 was reacted with p-methoxyphenyllead triacetate 12 to give arylated adduct 13 in 72% yield (Scheme 1.4). The involvement of free radicals in the reaction mechanism has been excluded and a ligand coupling mechanism proposed.\(^2\) Diastereoselective examples have also been reported (Scheme 1.5).\(^3\)

\[ \text{EtO}_2\text{C} = \text{CN} + \text{Pb(OAc)}_3 \rightarrow \text{EtO}_2\text{C} = \text{CN} \]

Scheme 1.4: Arylation of cyano acetate 11 with aryllead triacetate 12.

\[ \text{CO}_2\text{Me} \text{OTBDMS} + \text{p-MeOC}_6\text{H}_4\text{Pb(OAc)}_3 \rightarrow \text{CO}_2\text{Me} \text{OTBDMS} \]

Scheme 1.5: Diastereoselective arylation with aryllead triacetate.
Whilst these aryllead reagents allow the construction of sterically congested quaternary centres and are readily prepared, given the toxicity of lead compounds the stoichiometric use of these reagents is not desirable.

Organobismuth reagents have also been reported for the α-arylation of ketones, diketones and β-keto-esters (Scheme 1.6). Whilst these reagents do not have the toxicity liabilities associated with the aryllead reagents, in these cases only one of three aryl groups is transferred from the bismuth reagent.\textsuperscript{15}

\begin{center}
\begin{tikzpicture}
\begin{scope}[scale=0.7]
\node at (0,0) {16};
\node at (2,0) {$\text{Et}_2\text{O}$};
\node at (2,-0.5) {Ph$_3$BiOCOCF$_3$ (2 equiv)};
\node at (2,-1) {C$_6$H$_6$, 60 ºC, 24 h};
\node at (4,0) {17, 90\%};
\node at (5.5,0) {2-tert-Butyl-1,1,3,3-tetramethylguanidine};
\node at (0,-1) {O};
\node at (2,-1) {O};
\node at (4,-1) {O};
\node at (6,-1) {Ph};
\node at (0.5,-1.5) {$\text{CO}_2\text{Et}$};
\node at (2.5,-1.5) {$\text{CO}_2\text{Et}$};
\node at (4.5,-1.5) {$\text{CO}_2\text{Et}$};
\end{scope}
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.6:} α-Arylation of β-keto-ester with organobismuth reagent.

1.2.3 Asymmetric conjugate additions

A few isolated examples of quaternary carbon – aryl bond formation through the copper catalysed conjugate addition of Grignard or aryl zinc reagents to α,β-unsaturated ketones have been reported. For example the chiral imidazolidinium salt (ImH\textsuperscript{+}) assisted copper catalysed addition of phenylmagnesium bromide to 3-methyl-2-cyclohexen-1-one \textsuperscript{18} gave arylated adduct \textsuperscript{19} in modest yield and enantioselectivity (Scheme 1.7).\textsuperscript{16} Alternatively, the use of copper triflate in combination with a silver/N-heterocyclic carbene complex has been reported to catalyse the addition of diphenyl zinc to methyl-3-oxocyclohex-1-ene-1-carboxylate \textsuperscript{21} to give arylated adduct \textsuperscript{22} in good yield and with high levels of stereocontrol (Scheme 1.8).\textsuperscript{17}

\begin{center}
\begin{tikzpicture}
\begin{scope}[scale=0.7]
\node at (0,0) {18};
\node at (2,0) {3\% Cu(OTf)$_2$, 4\% ImH\textsuperscript{+}};
\node at (2,-0.5) {-30 ºC, 30 min};
\node at (4,0) {19};
\node at (5.5,0) {61\% yield, 66\% ee};
\node at (0,-1) {O};
\node at (2,-1) {O};
\node at (4,-1) {Ph};
\node at (0.5,-1.5) {$\text{CO}_2\text{Et}$};
\node at (2.5,-1.5) {$\text{CO}_2\text{Et}$};
\node at (4.5,-1.5) {$\text{CO}_2\text{Et}$};
\end{scope}
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.7:} Chiral imidazolidinium salt (ImH\textsuperscript{+}) assisted Cu catalysed conjugate addition of PhMgBr to generate an α-aryl quaternary carbon centre in modest yield and enantioselectivity.
Scheme 1.8: N-heterocyclic carbene silver complex assisted copper catalysed conjugate addition of an aryl-zinc reagent to generate an α-aryl quaternary stereocentre in high yield and enantioselectivity.

Whilst excellent enantioselectivities can be achieved (up to 93% ee) the aromatic group is limited and this approach has more generally been applied to the construction of tertiary arylated carbon centres.18

1.2.4 Transition metal catalysed arylation of carbon acids

The α-arylation of enolates has become more attractive since the introduction of the transition metal catalysed processes, which now represent the most general approach to arylated quaternary stereocentres.19

The first direct arylation of a ketone enolate was reported by Hartwig in 1997 (Scheme 1.9), employing 10 mol% Pd(db)2 catalyst. Only one example of the formation of a quaternary centre was presented and it is not stereogenic.20

Scheme 1.9: First example of transition metal catalysed arylation of ketone enolate for the synthesis of α-arylated quaternary centres.

Following from this, the first asymmetric example of a palladium catalysed arylation of a ketone enolate was reported by Buchwald in 1998. A typical example is illustrated in Scheme 1.10, the absolute stereochemistry was not reported. Isolated yields ranged from 40 – 74% and enantioselectivities ranged from 61 – 88%.21
Scheme 1.10: Pd catalyzed asymmetric arylation of a ketone enolate.

When \( \alpha'- \) blocked \( \alpha \)-methylcyclopentanones (e.g. 29) were employed as substrates excellent enantioselectivities were observed in the products (Scheme 1.11)

Scheme 1.11: Pd catalyzed asymmetric arylation of \( \alpha'- \) blocked ketone enolates. The absolute stereochemistry was not reported.

Subsequently an improved catalyst system has been reported employing Pd\(_2\)(dba)_3 and the bulky (\(R\))-2-(diisopropylphosphino)-2'-(1-naphthylmethoxy)-1,1'-binaphthyl ligand to give greater reactivity (reactions could be performed at room temperature with 2 mol% catalyst) giving high yields and enantioselectivities of up to 94\%.\(^\text{22}\) This system, in addition to allowing broad functional group tolerance, was highly selective for the less substituted position of ketones with 2 enolizable positions. The scope of these reactions was more recently expanded with the palladium or nickel catalysed coupling of aryl triflates reported by Hartwig.\(^\text{23}\) Buchwald\(^\text{24}\) and Hartwig\(^\text{25}\) both reported the \( \alpha \)-arylation of esters in 2001, containing isolated examples of the formation of quaternary centres. Expansion of this work allowed the coupling of a broad range of aryl halides to \( \alpha,\alpha \)-disubstituted esters in consistently high yield (for example, Scheme 1.12).\(^\text{26}\)

Scheme 1.12: \( \alpha \)-Arylation of \( \alpha,\alpha \)-disubstituted ester
The strongly basic conditions required to generate the enolate coupling partners, particularly in the cases of esters and amides, can result in low reaction yields for substrates with functionalities that are sensitive to basic or strongly nucleophilic reaction conditions. Coupling of the more hindered enolizable position is also not possible with the above chemistry. To allow more neutral conditions to be employed, Hartwig has reported the use of zinc enolates and silyl ketene or silyl ketimine acetals in the presence of zinc fluoride (for example, Scheme 1.13) for the arylation of esters and amides.27 Whilst this method requires pre-formed enolate equivalents and the use of stoichiometric metal reagents, it does allow the scope of the arylation to be increased, with many examples synthesised here that failed with the palladium catalysed alkali metal enolate chemistry.

![Scheme 1.13: Arylation of pre-formed ester and amide enolate equivalents under more neutral conditions](image)

The palladium catalysed intramolecular α-arylation of amides has also been reported for the synthesis of oxindoles.28 Particular attention was paid to α-methyl, α-aryl systems not accessible via the intramolecular Heck reactions described in chapter 1.2.5. In both racemic and asymmetric (assisted with chiral carbene ligands) cases, yields are typically excellent; however enantioselectivities are variable, ranging from 33 – 76%. A typical example is illustrated in Scheme 1.14.
The α-arylation of ketones, esters and amides can therefore be accomplished with the appropriate transition metal catalyst and base. Extension of these methodologies to the α-arylation of aldehydes is hindered by the aldol condensation of the aldehydes under the basic reaction conditions. In 2002 Miura developed a protocol for the α-arylation of aldehydes however isolated yields were modest and 2 equivalents of aldehyde were needed. An improved procedure was reported in 2007, with increased substrate scope and significantly improved isolated yields of α-arylated aldehydes (for example, Scheme 1.15). An enantioselective nickel-BINAP catalysed α-arylation of α-substituted γ-butyrolactones has also been reported by Buchwald in which the products are obtained in consistently high enantiomeric excess (90 – 99% ee); a representative example is shown in Scheme 1.16. Bicyclic lactones were also arylated under microwave irradiation catalysed by Pd(dba)₂.
α,α-Disubstituted nitriles have also been arylated under palladium catalysis. A range of arylated products were obtained in good yield (for example, Scheme 1.17).

\[
\begin{align*}
\text{PhCN} & \quad \text{Ph} \\
\text{CHCl}_3, 100 \, ^\circ\text{C} & \quad \text{NaN(SiMe}_3\text{)}_2 (1.3 \text{ equiv})
\end{align*}
\]

Scheme 1.17: Pd catalysed α-arylation of nitrile 52.

Copper catalysis has also been reported for the arylation of 2-methylacetoacetates, assisted by chiral L-proline ligands. The isolated yields are again consistently good and the enantiomeric excesses are typically >80%. A representative example is illustrated in Scheme 1.18.

\[
\begin{align*}
\text{NHCOCF}_3 & \quad \text{Cul} \\
\text{NaOH, DMF, H}_2\text{O} & \quad (2S,4R)-4\text{-hydroxyproline}
\end{align*}
\]

Scheme 1.18: Cu catalysed arylation of 2-methylacetoacetate 55.

Transition metal catalysis therefore allows for the α-arylation of a broad range of carbonyl compounds, generating arylated quaternary stereocentres, often with high levels of stereocontrol and in excellent yield whilst employing low catalyst loadings.

1.2.5 Asymmetric intramolecular Heck coupling

The first asymmetric Heck couplings were reported concurrently by Overman and Shibasaki in 1989 for the formation of cis-decalin derivatives and 2-dienyl-1,3-cyclohexandiones respectively. Subsequently intramolecular Heck reactions have been reported in which an arylated quaternary stereogenic carbon centre is created. This work has been pioneered by Overman, who reported the Pd-BINAP catalysed synthesis of oxindole derivatives in enantiomeric excesses up to 95% ee (Scheme 1.19). The stereoselectivity is reversed depending on whether cationic Heck conditions (employing silver salts as additives) or neutral Heck conditions
employing 1,2,2,6,6-pentamethylpiperidine (PMP) as the acid scavenging additive) are utilised.

**Scheme 1.19:** Intramolecular asymmetric Heck coupling for the synthesis of oxindole derivatives.

Wide variation to the alkene substituents in the substrate has been reported, and both $E$ and $Z$ isomers can give excellent enantioselectivities.$^{38}$ The methodology has been applied to the synthesis of the Calabar alkaloids physostigmine and physovenine$^{39}$ and has recently been expanded to include the creation of quaternary stereogenic centres bearing 2 aryl substituents (Scheme 1.20).$^{40}$

**Scheme 1.20:** Intramolecular Heck coupling to produce a quaternary carbon centre bearing 2 aryl substituents.

The intramolecular Heck reaction has also been applied by Shibasaki to carbocyclic systems for the synthesis of the analgesic (-)-eptazocine. In this case the $Z$ geometry of the alkene (62) was found to be essential for high enantioselectivity (Scheme 1.21).$^{41}$

**Scheme 1.21:** Intramolecular Heck coupling for the creation of a carbocyclic system containing an $\alpha$-arylated quaternary stereocentre.
1.2.6 Organocatalysis

Over the past decades the field of organocatalysis has grown significantly and continues to be an intensely researched field. The advantages of organocatalysis over transition metal catalysis have been well documented and include the reduced toxicity and environmental impact of the catalysts and the ability of the reactions to tolerate air and moisture. The field is broad, encompassing: covalent catalysis such as proline (64) and MacMillan’s imidazolidinone catalyst (65); non-covalent Brønsted acid catalysis such as BINOL phosphoric acids (66a, b); non-covalent hydrogen bonding catalysts such as Jacobsen’s Schiff base derived ureas/thioures (67), Takamoto’s bifunctional urea/thiourea catalysts (68) and cinchona alkaloid derived bifunctional organocatalysts developed by Chen, Connon, Dixon, Deng and others (69, 70, QD-71) (see chapter 2.3.1); and phase transfer catalysts (for example 72) (Figure 1.1).

![Figure 1.1: Selection of organocatalysts](image)

Whilst the synthesis of α-arylated quaternary stereocentres is dominated by transition metal catalysis, an organocatalytic approach is described below.
1.2.6.1 Nucleophilic Aromatic Substitution

In 2002 the S_NAr reaction of β-ketoesters and p-nitro-o-cyano chlorobenzenes was reported for the synthesis of racemic isoquinolones. Subsequently Jørgensen has reported the enantioselective S_NAr reaction of 1,3-dicarbonyl compounds with para-fluoronitrobenzenes, catalysed by cinchona alkaloid derived phase transfer catalyst 72, the most successful result is illustrated in Scheme 1.22.

![Scheme 1.22: Organocatalytic construction of products containing α-aryl quaternary carbon centre via an S_NAr reaction of β-ketoester 73 and para-fluoro nitrobenzene 74 catalysed by cinchona alkaloid derived phase transfer catalyst 72.](image)

The arylated products are generally obtained in good yield with, in some cases, excellent enantioselectivities, however due to the nature of the S_NAr reaction substitution patterns around the aromatic ring are restricted. This approach therefore only allows access to electron poor aromatic systems, and in all examples a para-nitro group is present. At the start of our research this was the only example of an organocatalytic arylation methodology for the creation of all-carbon quaternary stereocentres.

1.3 Aims of this thesis

We believed an effective strategy for the direct synthesis of catechols bearing all carbon quaternary stereocentres could be based on the Michael addition of a suitably acidic carbon-centred pro-nucleophile (77) to an ortho-benzoquinone (76) reagent in the presence of a basic catalyst, Scheme 1.23. Michael addition to the highly reactive o-quinone followed by aromatisation generates the substituted catechol product 79, containing the desired arylated quaternary stereogenic centre.
Scheme 1.23: Concept: Michael addition to o-benzoquinone electrophiles for the creation of products containing α-arylated quaternary stereocentres.

Due to their instability, ortho-Benzooquinones are rarely used as reagents in organic synthesis; however we believed that harnessing their reactivity could allow rapid access to this challenging motif. The aims of this research were to probe the reactivity of a range of ortho-benzoquinones towards carbon-centred pronucleophiles and to investigate the use of organocatalysts to give asymmetric induction in the reaction products. In addition we hoped to apply the methodology in the total synthesis of one of the many natural products bearing the target motif.

2 Methodology Development

2.1 Introduction to quinone chemistry

2.1.1 Para-quinones

para-Quinones are stable, often commercially available reagents that are known to act as dienophiles and Michael acceptors. The quinine (see chapter 2.3.1) catalysed Michael addition of β-keto esters (e.g. 80) to commercially available para-quinones was reported during the course of this work to give products containing arylated quaternary stereogenic centres, with high yields and enantioselectivities (Scheme 2.1).

Scheme 2.1: Organocatalytic Michael addition of β-ketoester 80 to para-quinone 81 to generate 82 containing an α-aryl quaternary stereocentre in high enantiomeric excesses. The absolute stereochemistry was not reported.
The $\alpha$-arylation of aldehydes and vinylogous addition of dicyanoalkylidenes to $p$-quinones for the formation of arylated tertiary centres was also reported by Jørgensen.\textsuperscript{57, 58}

### 2.1.2 Synthesis of ortho-quinones

In contrast to para-quinones, ortho-benzoquinones are notoriously difficult to handle due to rapid decomposition through dimerisations, polymerisations and isomerisations. Since ortho-quinones are known to act as carbodienes, heterodienes and dienophiles in Diels-Alder reactions a suggested mechanism for the dimerisation of ortho-quinone 83 is the Diels-Alder reaction to give dimer 84.\textsuperscript{59}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {O} node (b) at (0,1) {O} node (c) at (0,2) {O} node (d) at (1,1) {O} node (e) at (1,0) {O} node (f) at (1,2) {O};
  \draw (a) -- (b) -- (c) -- (d) -- (e) -- (f);
  \node [above] at (0.5,1) {2 x 83};
  \node [above] at (1.5,1) {84};
\end{tikzpicture}
\end{center}

**Scheme 2.2:** Dimerisation of $o$-benzoquinone reported to be responsible for the instability of this reagent.

As a result of this instability many ortho-benzoquinones cannot be isolated or stored. An increased number of substituents around the quinone ring increases stability, for example, 3,5-di-tert-butyl-$o$-benzoquinone 88 is stable and commercially available (Figure 2.1). In particular substituents in the 4-position appear to confer stability, for example 4-tert-butyl-$o$-benzoquinone 89 can be isolated in quantitative yields through conventional methods whereas we have found 3-tert-butyl-$o$-benzoquinone to be unstable (see chapter 3.1, Figure 3.1).\textsuperscript{60}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {O} node (b) at (0,1) {O} node (c) at (0,2) {Cl} node (d) at (1,1) {Cl} node (e) at (1,2) {Cl} node (f) at (2,1) {Cl} node (g) at (2,2) {Cl};
  \draw (a) -- (b) -- (c) -- (d) -- (e) -- (f) -- (g);
  \node [above] at (1.5,1) {86};
\end{tikzpicture}
\begin{tikzpicture}
  \node (a) at (0,0) {O} node (b) at (0,1) {Cl} node (c) at (0,2) {Br} node (d) at (1,1) {Br} node (e) at (1,2) {Br} node (f) at (2,1) {Br} node (g) at (2,2) {Br};
  \draw (a) -- (b) -- (c) -- (d) -- (e) -- (f) -- (g);
  \node [above] at (1.5,1) {87};
\end{tikzpicture}
\begin{tikzpicture}
  \node (a) at (0,0) {O} node (b) at (0,1) {Cl} node (c) at (0,2) {Br} node (d) at (1,1) {Br} node (e) at (1,2) {Br} node (f) at (2,1) {Cl} node (g) at (2,2) {Cl};
  \draw (a) -- (b) -- (c) -- (d) -- (e) -- (f) -- (g);
  \node [above] at (1.5,1) {88};
\end{tikzpicture}
\begin{tikzpicture}
  \node (a) at (0,0) {O} node (b) at (0,1) {Cl} node (c) at (0,2) {Cl};
  \draw (a) -- (b) -- (c);
  \node [above] at (1,1) {89};
\end{tikzpicture}
\end{center}

**Figure 2.1:** Selection of stable $o$-benzoquinones.

Isolable ortho-quinones are generally synthesised through oxidation of the parent catechol. Many oxidising agents have been reported for this, including manganese dioxide,\textsuperscript{61} silver oxide,\textsuperscript{62} hypervalent iodine reagents\textsuperscript{63} and diphenylselenide.\textsuperscript{64} There are conflicting reports in the literature on the isolation of unsubstituted ortho-benzoquinone 83 through various oxidation techniques, however experimental details and spectral data are rarely given. In 1952 silver oxide was reported to
oxidise catechol 90 to ortho-benzoquinone in a 15% yield and it is claimed that the red crystals can be kept unchanged for several days in the dark at -70 °C.\textsuperscript{62} Subsequently in 1998 ortho-benzoquinone was reported to be isolated in a 97% yield after refluxing catechol in acetone with manganese dioxide.\textsuperscript{61} In neither case is spectral data given to confirm the synthesis. Recently it has been reported that treatment of catechol with silver oxide in acetone affords ortho-benzoquinone, which is claimed to be stable for 3-4 hours at room temperature, a yield was not given but a proton NMR spectrum supports the structure (Scheme 2.3).\textsuperscript{65} We were unable to isolate o-benzoquinone following any of the reported procedures and found this reagent to be highly unstable.

![Scheme 2.3](image)

**Scheme 2.3:** Oxidation of catechol with silver oxide to give ortho-benzoquinone, a yield was not reported.

### 2.1.3 Reactions of ortho-quinones

Owing to the electron deficient nature of the olefinic carbons and the energy gained from aromatisation, ortho-benzoquinones are powerful electrophiles; reactive towards a range of carbon and heteroatom nucleophiles at every carbon atom in the ring.\textsuperscript{53} They can also act as carbodienes, heterodienes and dienophiles in Diels-Alder reactions (Figure 2.2).

![Figure 2.2](image)

**Figure 2.2:** Reactive positions of ortho-benzoquinones.

Despite this reactivity, reports of their use in synthesis as Michael acceptors are rare due to their rapid decomposition under attempted reaction conditions. Attempted additions to sparsely substituted ortho-benzoquinones generally suffer from low
yields and a lack of regiocontrol. The few reported examples of the addition of carbon-based nucleophiles are discussed below.

### 2.1.3.1 Nucleophilic additions of carbon-centred nucleophiles to o-quinones

The Lewis acid catalysed addition of allyl stannanes to 1,2-naphthoquinone 85, 4-methyl-o-benzoquinone 92, 4-\textit{tert}-butyl-o-benzoquinone 89 and 3,5-dimethyl-o-benzoquinone 93 gave the allylated products 94 – 97 in excellent yields (Scheme 2.4).\textsuperscript{66,67} In the case of sterically hindered 3,5-di-\textit{tert}-butyl-o-benzoquinone 88 the 1,2-addition products 98a and 98b were isolated in a 93% combined yield (Scheme 2.5). Some of the allylated hydroquinone products were found to be air sensitive and were therefore protected as the di-acetate.

![Scheme 2.4](attachment:image.png)

\textbf{Scheme 2.4:} The addition of allyl stannane 91 to a range of ortho-quinones to give 1,4-addition products 94 – 97.
Scheme 2.5: The addition of allyl stannanes \(91\) to sterically hindered 3,5-di-tert-butyl-\(\alpha\)-benzoquinone \(88\), to give the 1,2-addition products \(98a\) and \(98b\).

In 1986 the addition of pre-formed sodium enolates of malonic and cyanoacetic esters to 1,2-naphthoquinones to give 4-substituted 1,2-napthalenediols such as \(100\) in high yields was reported, a typical example is illustrated in Scheme 2.6.\(^{68}\) The reaction was not reported with the use of catalytic base.

Scheme 2.6: The addition of the pre-formed sodium enolate of diethyl malonate to 4-unsubstituted 1,2-naphthoquinone \(99\).

In 1988 the addition of silyl enol ethers to \(ortho\)-benzoquinones, promoted by catalytic trityl perchlorate, was reported. 1,4-Addition was found in the case of unsubstituted \(ortho\)-benzoquinone and 4-methyl-\(\alpha\)-benzoquinone \(92\), whereas 1,6-addition was found in the case of 4-\(tert\)-butylbenzoquinone \(89\) which resulted in further cyclisation to the benzofuran derivative \(104\) (Scheme 2.7).\(^{69}\)
Scheme 2.7: The addition of silyl enol ethers 101 and 103 to 4-methyl-o-benzoquinone (92) and 4-tert-butyl-o-benzoquinone (89) giving 1,4 and 1,6 additions respectively.

More recently the FeCl₃ mediated vinylogous Michael addition to 1,2-naphthoquinone 85 has been reported (Scheme 2.8). Due to the redox ability of the quinone starting materials and hydroquinone addition products, the oxidation state of the products obtained from Michael additions to quinones often depends on the reaction conditions and the particular substrates involved. In this case an excess of 1,2-naphthoquinone is used and the product 106 is obtained in the quinone oxidation state with oxidation of the cyclohexenone ring to the phenol moiety also occurring. Subsequent reduction with sodium hydrosulfite (Na₂S₂O₄) gives the biaryl product 107.

Scheme 2.8: The vinylogous Michael addition to 1,2-naphthoquinone.

These examples clearly demonstrate the ability of ortho-benzoquinones to act as Michael acceptors. At the start of this research no examples existed of a base catalysed Michael addition to o-quinones. The lack of exploitation of this reactivity reflects the difficulty in handling ortho-benzoquinone reagents.

An isolated example of the organocatalytic addition of a carbon-centred pronucleophile to an isolable ortho-naphthoquinone (Scheme 2.9) was reported during
the course of this work alongside the para-quinone examples discussed in section 2.1.1.56. In this case the quinone and β-ketoester are reacted in a 1:1 ratio and the 1,4-addition product (108) is obtained at the quinone oxidation level following column chromatography. It is proposed that the hydroquinone adduct is oxidised catalytically by the quinone starting material which is continually re-oxidised by atmospheric oxygen.

Within our group the organocatalytic addition of β-ketoesters to heavily substituted ortho-benzoquinones has been investigated. An aryloxylation reaction results to give tricyclic products such as 110, illustrated in Scheme 2.10.71

In order to act as electrophiles at carbon, and to avoid the aryloxylation reaction, the quinone substrate must not be too heavily substituted and is therefore likely to be unstable. A general method for the Michael addition to ortho-benzoquinones must accommodate this instability.
2.1.3.2 Nucleophilic additions to o-quinones generated in-situ

The addition of sulphur nucleophile 112 to ortho-benzoquinone and 4-methyl-o-benzoquinone generated in situ from the parent catechols 90 and 111 respectively through oxidation with hydrogen peroxide has been reported, however the products 113 and 114 are isolated in a disappointing 9 and 23% yield respectively (Scheme 2.11).^72

![Scheme 2.11: Addition of triazolium thiolate 28 to in situ generated ortho-benzoquinones to give the 1,4-addition products 29a and 29b.](image)

Electrochemical methods for additions of carbon-based nucleophiles to unstable o-quinones have also been reported in which electrochemical oxidation of catechols in the presence of β-dicarbonyl pro-nucleophiles (e.g. 116) in a buffered solution gives the addition products in high yields (Scheme 2.12).^73 In the case of 3-substituted catechols (e.g. 115), the addition products were obtained as mixtures or regioisomers (the ratio was not reported).

![Scheme 2.12: Electrochemical oxidation of catechol 115 in the presence of β-diketone 116 to give a regioisomeric mixture of addition products 117 and 118.](image)

2.2 Proof of Principle studies: Organocatalytic Michael addition to isolable ortho-quinones

To establish the feasibility of the base catalysed Michael addition to ortho-quinone reagents initial proof of principle studies were conducted with 1,2-naphthoquinone 85. 1,2-Naphthoquinone is one of the few stable, commercially available, ortho-quinone reagents and is therefore not a representative ortho-benzoquinone; but was chosen since no examples of base-catalysed Michael additions to ortho-quinones
had been reported when this work was begun. Methyl cyclopentanone-2-carboxylate 109 was chosen as a representative pro-nucleophile (Scheme 2.13).§

Scheme 2.13: The addition of β-ketoester 109 to 1,2-naphthoquinone 85 to give hydroquinone adduct 119 that can be oxidised to quinone 120 or protected to the diacylated product 121a.

Preliminary experiments were conducted with 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP) as the catalytic base, in CH₂Cl₂ at room temperature. When 1,2-naphthoquinone (added portion-wise) was reacted with 1 equivalent of pro-nucleophile 109 in the presence of BEMP (10 mol%) and the resulting mixture subjected to column chromatography on silica gel, the product was identified as the oxidised addition product 120, and could only be isolated in disappointing yields of 40-50%. The presence of a singlet in the aromatic region of the crude proton NMR spectrum and the appearance of a new methyl ester signal provided clear indication of a reaction. Whilst 1,4-addition was expected on the basis of reactivity and previous literature examples, the regioselectivity of addition was confirmed by COSY, HSQC and HMBC NMR analysis. This product could be quantitatively reduced back to the desired naphthalenediol addition product 119 using Na₂S₂O₄.⁷⁰ Crude proton NMR of the reaction mixtures in CDCl₃ identified a mixture of naphthalenediol 119 and naphthoquinone 120 addition products that was found to shift towards the quinone with time. Crude NMR in d₆-DMSO however showed good conversion to only the

---

§ The reaction of 1,2-naphthoquinone and methyl cyclopentanone-2-carboxylate was initially conducted by Dr Kevin Greenaway. Quinone adduct 120 was isolated in poor yield and was not fully characterised.
naphthalenediol adduct 119. It was therefore concluded that the reaction proceeds to the naphthalenediol addition product 119, which is oxidised by air in chloroform solution and during chromatography on silica gel. Several by-products were observed in the crude 1H NMR spectrum which we believed may have been a result of decomposition of 1,2-naphthoquinone. In an effort to decrease the probability of 1,2-naphthoquinone reacting with itself the reaction solvent was changed from CH₂Cl₂ to tert-butylmethylether (TBME) in which 1,2-naphthoquinone is sparingly soluble. Pleasingly the reaction in TBME gave significantly cleaner conversion to the desired naphthalenediol product, with few by-products visible in the crude 1H NMR spectrum. The crude reaction mixtures could be deliberately oxidised using aqueous sodium periodate, however the naphthoquinone product was found to be unsuitable for column chromatography; decomposition on silica gel was observed and the isolated yields did not reflect conversion. A method for protecting the naphthalenediol adduct was therefore investigated. Accordingly, the reaction was repeated and the crude reaction mixture treated with acetic anhydride in pyridine at room temperature overnight. Complete conversion to the di-acetylated product 121a was observed which could be purified by column chromatography on silica gel with no noticeable decomposition. With the ability to isolate the protected product, a screen of bases and temperatures was conducted to optimise the yield of product 121a (Table 2.1).

The optimised reaction conditions are illustrated by entry 8. Two equivalents of nucleophile were required however increasing the number of equivalents further than this had little effect on the reaction yield (entries 7, 8 and 9). The reaction proceeded well at room temperature, although starting the reaction at -20 °C for 1 h then warming to room temperature resulted in slightly improved yields (entry 8 vs. 6). Holding the reaction at -20 °C for 5 h gave a lower yield of arylated product (entry 10 vs. 8). The reaction also proceeded with triethylamine, 1,1,3,3-tetramethylguanidine (TMG) and 1,4-diazabicyclo-[2.2.2]octane (DABCO) (entries 1, 2 and 3) although the BEMP catalysed process was the highest yielding. The desired product was not identifiable by crude 1H NMR when no base was added (entry 11). The optimal loading of base was found to be 10%; lowering the amount of base resulted in a reduction in yield (entries 4 and 5 vs. 6). With the optimal reaction conditions the protected arylated adduct 121a could be isolated in a pleasing 83% yield over 2 steps.
Table 2.1: Optimisation of the reaction of 1,2-naphthoquinone 85 with methyl cyclopentanone-2-carboxylate 109. \(^a\)isolated yield following column chromatography on silica gel; \(^b\)conversion by NMR

The scope of this reaction with respect to the pro-nucleophile was then investigated. A series of pro-nucleophiles 122 – 134 and 73 (Chart 2.1) were chosen and reacted with 1,2-naphthoquinone 85. Lactones, indanones, oxindoles, \(\alpha\)-cyano ketones and \(\alpha\)-cyano acetates all performed well to give adducts 121b - 121h in consistently high yields (Chart 2.2).
Chart 2.1: Pro-nucleophiles screened in the reaction with 1,2-naphthoquinone.

Chart 2.2: Naphthalene-1,2-diol adducts 121b – 121h synthesised from the base catalysed Michael addition of a range of pro-nucleophiles to 1,2-naphthoquinone.

Whilst 1,2-naphthoquinone can be isolated and stored and is stable in solution, it is still believed to decompose under the reaction conditions. Therefore, to obtain the desired arylation product in high yield the rate of Michael addition to the quinone must be fast with respect to the rate of decomposition. Pro-nucleophiles 128 - 134 were found to give unsatisfactory conversion to the hydroquinone product. In these cases crude proton NMR spectra showed un-reacted pro-nucleophile and a complex mixture of quinone decomposition products. It is interesting to note the contrast in reactivity between the 5-membered cyclic β-ketoester 109 and its 6- and 7-
membered analogues. Particularly in the case of methyl- or ethyl-cyclohexanone-2-carboxylate (131, 132) the desired product could not be identified in the crude NMR spectra even when stoichiometric base was employed with 4 equivalents of nucleophile. We believe the low reactivity of the cyclohexanone derived pronucleophiles in comparison to methyl cyclopentanone-2-carboxylate 109 could be attributed to a possible increase in stability of the 6-membered cyclic enolate.

2.3 Enantioselective Michael addition to stable ortho-quinones

With a racemic method for the base catalysed Michael addition to stable ortho-quinones developed an enantioselective approach was desired. The fact that triethylamine and DABCO were able to catalyse the reaction led us to investigate the use of cinchona derived bifunctional organocatalysts to give asymmetric induction in the arylated products.

2.3.1 Cinchona Alkaloids

The parent cinchona alkaloids quinidine (135), quinine (136), cinchonine (137) and cinchonidine (138) are small, yet complex, natural products, isolated from the bark of *cinchona officinalis*. Their use in medicine and in organic synthesis has been well documented. The stereogenic centres at C8 and C9 are inverted in quinidine and quinine (and cinchonine and cinchonidine) and so the pairs of alkaloids are referred to as pseudo enantiomers, and when employed as catalysts normally give rise to opposite enantiomers of products with very similar levels of enantioselectivity.

![Figure 2.3: Structures of the parent cinchona alkaloids](image)

Figure 2.3: Structures of the parent cinchona alkaloids
Whilst the parent alkaloids are catalysts in their own right, significant effort has gone into developing modified cinchona alkaloid catalysts that offer improved levels of stereoselectivity. Those which have found particular use in conjugate additions will be discussed in more detail here.

### 2.3.2 C9-Epi-amino cinchonine/cinchonidine derived catalysts

Bifunctional organocatalysts 69 derived from 9-amino(9-deoxy) epi-cinchonine were developed by Chen\textsuperscript{75} and Dixon\textsuperscript{76} and, for example, have been shown to induce high levels of stereocontrol in the addition of dimethyl malonates and 5-aryl-1,3-dioxolan-4-ones to nitroolefins (Scheme 2.14).

![Scheme 2.14: Application of cat 69 in conjugate addition reaction to nitro olefins.](image-url)

The postulated mode of action of the catalyst involves activation of the pronucleophile by the bridge-head nitrogen to give a hydrogen bonded ammonium enolate, and concurrent activation of the electrophile through co-planar bidentate hydrogen bonding interactions with the thiourea moiety of the catalyst. The predicted transition state is stabilised by the complete hydrogen bonding network with the catalyst and positions the nucleophile and electrophile so that there is a favourable staggered arrangement around the newly formed C-C bond.\textsuperscript{77}
Figure 2.4: Postulated transition state and mode of action of bifunctional organocatalyst of type 69 in the reaction of malonates with nitro olefins, the catalyst vinyl group has been omitted for clarity.

Subsequently the urea analogue 70 was found within the Dixon group to offer equal levels of stereocontrol with significantly improved reaction rates, and was employed, for example, in the Michael addition step in the elegant synthesis of nakadomarin A (Scheme 2.15).78, 79

Scheme 2.15: Application of urea catalyst 70 in the Michael addition step in the synthesis of nakadomarin A.

2.3.3 Quinidine/Quinine Derived organocatalysts

Deng and co-workers have developed a series of quinidine/quinine-derived organocatalysts (Chart 2.3) that have been employed in highly enantioselective conjugate additions with a range of pro-nucleophiles and electrophiles including, for example, methyl vinyl ketone (Scheme 2.16) and nitro olefins (Scheme 2.17).80, 81
Chart 2.3: Examples of quinidine (QD) and quinine (Q) derived organocatalysts developed by Deng.

Scheme 2.16: Example of the use of Deng catalysts Q-148 in the conjugate addition of β-keto ester 80 to methyl vinyl ketone. The absolute stereochemistry was determined by comparison of optical rotation data with literature values.

Deng has proposed that in these systems the bridge head nitrogen of the quinuclidine ring of the catalyst activates the pro-nucleophile to give a hydrogen bonded ammonium enolate (as in the case of catalysts 69 and 70) with the hydroxyl on the quinoline acting as a monodentate hydrogen bond donor able to activate the electrophile and deliver it selectively to one face of the pro-nucleophile (Scheme 2.17). A second hydrogen bond from the quinoline hydroxyl is believed to aid positioning of the pro-nucleophile, bonding to the ring oxygen in the case of lactone 154 or the ester in the case of ethyl 2-oxocyclohexanecarboxylate 132. The relative stereochemistry of the product 153 and the absolute stereochemistry of product (-)-155 were proven by single crystal X-ray diffraction and support the transition state model proposed. Replacing catalyst Q-71 with QD-148 in the
synthesis of (-)-155 gave the opposite enantiomer (+)-155 with increased yield and almost identical levels of enantiomeric excess (92% yield, 97:3 dr, 98% ee).

**Scheme 2.17:** Postulated mode of action of Deng catalysts in the synthesis of adducts 153 and 155.

Of the low energy conformers of quinidine-derived catalysts of type QD-148, the postulated mode of action requires the catalyst to bind the reactants in its ‘gauche-open’ conformer (Figure 2.5). Due to the constraints of the additional ring, cupreidine catalyst 15183 is held in such a conformation and when employed in the synthesis of (+)-155 gave identical levels of enantiocontrol compared to catalyst
**QD-148** (Scheme 2.17). This further supports Deng’s postulated mode of action for catalysts Q/QD-71 and Q/QD-148.

![Catalysts QD-71 and QD-148](chart)

**Figure 2.5:** Cat. QD-71/QD-148 in the ‘gauche-open’ conformation and cupreidine catalyst 151.

### 2.3.4 Catalyst Screen

A range of known organocatalysts (Chart 2.4) were examined in the reaction of 1,2-naphthoquinone with tert-butyl 1-oxindane-2-carboxylate pro-nucleophile 80. The reactions were performed in an identical fashion to the racemic examples, replacing BEMP with the required organocatalyst. The enantioselectivities were determined by chiral HPLC analysis in comparison to a racemic sample prepared with BEMP catalysis (Table 2.2). The absolute stereochemistry was not proven and is drawn by analogy to the work of Deng whereby for quinidine derived catalysts the electrophile is delivered to the bottom face of the pro-nucleophile as drawn in Table 2.2.

![Chart 2.4: Catalysts screened in the reaction of tert-butyl 1-oxindane-2-carboxylate 80 and 1,2-naphthoquinone 85.](chart)

**Chart 2.4:** Catalysts screened in the reaction of tert-butyl 1-oxindane-2-carboxylate 80 and 1,2-naphthoquinone 85.
Catalyst **70** can be seen to give a slightly increased yield compared to the BEMP catalysed process (entry 2 vs. 1), however a disappointing enantiomeric excess of 11% was obtained. The Deng-catalysts **QD-71**, **QD-147** and **QD-148** gave more successful results, with the phenanthryl derived catalyst **QD-148** giving 70% ee (entry 5), albeit in lower yield.

Having developed a method for the organocatalysed Michael addition of a range of pro-nucleophiles to 1,2-naphthoquinone, expansion of the scope of the reaction with regard to the quinone electrophile was investigated.

### 3 Oxidative coupling strategy – Michael addition to *in situ* generated *ortho*-benzoquinones

#### 3.1 Racemic method

In order to expand the arylation methodology developed for 1,2-naphthoquinone to a range of *ortho*-benzoquinones, the synthesis of a range of 3-substituted *ortho*-benzoquinones was attempted through oxidation of the parent 3-substituted catechols. 3-Substituted *ortho*-benzoquinones were chosen in the belief that the 3-substituent would aid the regioselectivity of the Michael addition and increase the stability of the quinone relative to the unsubstituted reagent. A range of 3-substituted catechols were prepared through a one-pot formylation and Dakin oxidation of the appropriate 2-substituted phenol (Scheme 3.1).[^84]

For larger scale preparation of catechols, the dihydroxylation of substituted benzenes using a bacterial dioxygenase enzyme followed by oxidation with either palladium on carbon or a cis-dioldehydrogenase enzyme has also been reported. Accordingly 3-tert-butylicatechol 160 was synthesised from 2-tert-butylyphenol 157 and subject to aqueous sodium periodate oxidation (Scheme 3.2). Separation of the organic phase and evaporation of the solvent gave a highly coloured residue (often indicative of a quinone), however ¹H NMR of the residue showed a complex mixture.

Scheme 3.2: Attempted oxidation of 3-tert-butylicatehol (160) to the ortho-benzoquinone with NaIO₄.

Similarly, treatment of catechol, 3-phenyl-, 3-ethyl-, and 3-methoxycatechol with aqueous sodium periodate also lead to complex mixtures after attempted isolation. Attempts to obtain a cold solution of quinone reagent and react this directly with a solution of pro-nucleophile and base showed no conversion to the desired arylated products. It was rapidly concluded that these reagents were too unstable to be isolated and stored. To demonstrate the instability of the 3-substituted ortho-benzoquinones, 3-methoxycatechol 163 and 3-tert-butylicatechol 160 were oxidised with polymer-supported periodate (ps-IO₄⁻) in deuterated chloroform, filtered and the decomposition followed by ¹H NMR. The amount of o-benzoquinone with respect to an internal standard (methyl-3,4,5-trimethoxybenzoate) was recorded at various time intervals. The decomposition rate is illustrated in Figure 3.1. The half life of 3-methoxy and 3-tert-butyl ortho-benzoquinone was calculated from the plot to be approximately 8 hours and 1 hour respectively. The decomposition of o-
quinone, 3-ethyl- and 3-phenyl-o-quinone was found to be too rapid to measure in this way.

\[
\begin{align*}
&\text{OH} & \text{OH} & \text{ps-IO}_4^- & \text{CDCl}_3 & \text{decomposition} \\
&163, R = \text{OMe} & 160, R = \text{tBu} & & & \\
&164, R = \text{OMe} & 165, R = \text{tBu} & & & \\
\end{align*}
\]

**Figure 3.1**: Plot showing the decomposition rate of 3-methoxy-164 and 3-tert-butyl-o-quinone 165 in CDCl₃ (calculated with respect to an internal standard – methyl-3,4,5-trimethoxybenzoate) in comparison with stable 1,2-naphthoquinone.

Accordingly a method for *in-situ* generation of the reactive o-quinone intermediate from the catechol precursor was envisaged based on an ‘oxidative coupling’ strategy (Scheme 3.3). The catechol is oxidised in the presence of the protonucleophile and base catalyst to the highly electrophilic and unstable o-benzoquinone species 76; Michael addition followed by aromatisation regenerates the substituted catechol product 79, containing the desired arylated quaternary stereogenic centre.
Scheme 3.3: Concept: an oxidative coupling strategy for the synthesis of α-arylated all-carbon quaternary stereocentres.

Since this strategy does not rely on the ability to isolate (and store) the reactive o-benzoquinone reagent, and the 3-substituted catechols are either commercially available or readily prepared, it has the potential to provide a powerful and general route to compounds containing arylated quaternary stereogenic centres either where the aromatic ring contains the 1,2-dihydroxyl functionality, or where this has been further functionalised.

This strategy relies on the compatibility of the pro-nucleophile and base catalyst with the oxidising conditions. Periodate is known to be an effective and selective oxidising agent for catechols; however the aqueous conditions prevent low temperatures being employed which are desirable for decreasing the rate of decomposition of the o-quinone reagents. Therefore polymer-supported periodate (ps-IO₄⁻), reported to be very effective for the oxidation of catechols to stable quinones, was chosen for initial studies and prepared from the anion exchange resin Amberlite® IRA-900. This reagent allows the oxidation to be performed in purely organic solvents and at temperatures below 0 ºC, and was therefore believed to be ideal for the oxidative coupling strategy. The loading of periodate on the resin was determined by oxidising an excess of 3,5-di-tert-butylcatechol to the stable 3,5-di-tert-butyl-o-benzoquinone in deuterated chloroform and determining the ratio of catechol (167):quinone (88) (Scheme 3.4).
3.1.1 **Proof-of-principle for oxidative coupling methodology**

Initial experiments were conducted with 3-tert-butylcatechol 160 and 1 equivalent of ethyl phenylcyanoacetate 125 as a representative pro-nucleophile (Scheme 3.5) with 1 equivalent of ps-IO$_4^-$ in dichloromethane at -20 °C. Polymer-supported BEMP was used in place of liquid BEMP since this would be removed from the reaction mixture during the filtration to remove the oxidant.

The reaction mixture was subjected to aqueous Na$_2$S$_2$O$_4$ reductive work-up to ensure all products were at the catechol oxidation level. Under these conditions the desired arylated product could be isolated in 68% yield following column chromatography. The catechol product was not found to be oxidatively unstable in air and therefore protection as the di-acetate was not required. It was noted that not all of the starting catechol was consumed in this reaction, this was attributed to competing oxidation of the product by the periodate resin. The reaction was therefore repeated with 2 equivalents of oxidant to achieve complete consumption of the starting catechol and give the arylated product in a pleasing 85% yield. In this case the direct product of the reaction is at the quinone oxidation level and the reductive work-up is required to obtain the catechol product (the distinctive bright red quinone colour fades rapidly during the reductive work-up). In contrast to the
1,2-naphthoquinone examples, 2 equivalents of pro-nucleophile were not required to give satisfactory yields in this case.

Michael addition to the 5-position of the quinone (1,4-addition) was anticipated due to the 3-substituent hindering attack at the 4-position. The $^1$H NMR spectrum of the arylated product 169a shows 2 doublets for the aromatic protons with a coupling constant of 2.0 Hz indicating a meta relationship and confirming the anticipated regiochemistry of the Michael addition.

3.1.2 Scope of in-situ methodology

The scope of the reaction with respect to the catechol substrate and pro-nucleophile was then investigated. In addition to 3-tert-butylcatechol 160, 3-methoxy- 163, 3-phenyl- 162 and 3-ethylcatechol 161 were found to be successful substrates with a range of pro-nucleophiles to give arylated products 169b – 169p (Chart 3.1). In all cases the reaction was found to be highly regioselective; none of the other possible addition products could be detected in the crude $^1$H NMR spectra. In the case of 3-phenylcatechol, 2 equivalents of pro-nucleophile were required to give satisfactory isolated yields. For example, the yield of 169f decreased from 72% to 60% when one equivalent of pro-nucleophile was employed. The yield of the reaction of 3-tert-butylcatechol with methyl cyclopentanone-2-carboxylate to give adduct 169b was also improved through the use of 2 equivalents of pro-nucleophile. In most cases, however, using an excess of pro-nucleophile resulted in no appreciable increase in reaction yield. In all cases where an excess of the catechol substrate was used the $^1$H NMR spectra of the crude reaction mixtures showed many by-products. The reaction times varied from 30 min to 6 h. Unfortunately 3-bromocatechol was a poor substrate in this reaction.
Chart 3.1: α-Arylated addition products 169b – 169p synthesised via an oxidative coupling of the appropriately substituted catechol and carbon based pro-nucleophile. * 2 equiv of pro-nucleophile were required, ** 2 equiv pro-nucleophile, 1 equiv oxidant.

This represents the first general organocatalytic method for the addition of a carbon-based pro-nucleophile to ortho-benzoquinones generated in situ. The
method is practically simple and the addition is rapid, high yielding, and highly regioselective giving access to a broad range of arylated products. Alkyl, aryl, tert-butyl and methoxy substituted catechols are tolerated and the scope of the pro-nucleophile is large. In addition to the lactones, indanones, oxindoles, α-cyano ketones and α-cyano acetates already encountered (chapter 2.2), β-diketones, β-diketoamides and 7-membered cyclic pro-nucleophiles were also successful substrates. Furthermore the coupling substrates do not require extensive synthesis as they are either commercially available or are readily prepared in one-step from commercial materials (see chapters 7.2.1 and 7.3.1).

Catechols with different substitution patterns were also investigated. When 4-methylcatechol was reacted with 1 equivalent of methyl cyclopentanone-2-carboxylate no arylated products could be identified in the crude NMR, increasing the number of equivalents of pro-nucleophile to 2 gave 169p in a 10% yield (Chart 3.1). No other addition products (regioisomers) could be isolated from the reaction mixture or identified in the crude 1H NMR spectra, therefore, in this case 1,4-addition is still preferable, but occurs with significantly decreased efficiency. When the reaction was repeated with 4-tert-butylcatehol no desired arylated product could be identified in the crude 1H NMR. The steric effect of a substituent at the 4-position clearly has a considerable impact on the Michael addition at the adjacent position.

Catechol 90 was also investigated in the oxidative coupling reaction, generating unsubstituted o-benzoquinone following oxidation. Methyl cyclopentanone-2-carboxylate 109 was again chosen as the pro-nucleophile, and gave the 1,4-addition product 169q in a modest 17% yield when reacted with catechol, 10 mol % ps-BEMP and 2 equivalents of oxidant (Table 3.1, entry 1). Alternative conditions were screened to increase the isolated yield (Table 3.1); up to 21% was achieved with portion-wise addition of 1 equivalent of oxidant. Despite the poor yield, no other addition products could be isolated from the reaction mixture.
The 3-substituent on the catechol/o-quinone is therefore required to obtain the arylated products in high yield. A substituent at the 3 position appears to be important for increasing the stability of the o-benzoquinone compared to the unsubstituted reagent without hindering the preferred 1,4-addition, and so is also important for aiding the regioselectivity.

3.2 Asymmetric Michael addition to \textit{in situ} generated ortho-benzoquinones

In an analogous fashion to the work with 1,2-naphthoquinone an enantioselective oxidative coupling was investigated by replacing ps-BEMP with cinchona alkaloid derived organocatalysts. A range of known catalysts (Chart 3.2) were tested in the reaction of 3-methoxycatechol 163 with \textit{tert}-butyl 1-oxoindane-2-carboxylate 80.\textsuperscript{86,87} Gratifyingly the organocatalysts screened were compatible with the oxidising reaction conditions and were all able to catalyse the reaction. The results of the initial catalyst screen are illustrated in Table 3.2 entries 1 – 7.
Table 3.2: Results of the catalyst screen on the reaction of 3-methoxycatechol 163 with tert-butyl-1-oxoindane-2-carboxylate 80. Enantiomeric excesses were determined by HPLC analysis in comparison to a racemic sample prepared with ps-BEMP catalysis.

The tertiary amine bifunctional catalysts all efficiently catalysed the reaction with no appreciable loss in rate compared with ps-BEMP catalysis. In the case of catalyst QD-71, the enantiomeric excess appears to be independent of catalyst loading (entries 2-4) and at 10 mol% gave the arylated product in a moderate 58%
ee. From a comparison of the results of the reaction with catalyst QD-71 and catalyst QD-148/ QD-170 (entry 3 vs. 5-6) it appears that a bulky substituent at the C9 hydroxyl increases the asymmetric induction and that the proximity of the substituent to the C9 hydroxyl is also important. From these two results alone it is unclear whether it is the overall size of this group or the local bulk around the C9 hydroxyl that is important for asymmetric induction. Comparing the result with catalyst QD-171 and QD-71 (entry 7 vs. 3) it appears that the nature of the hydrogen bond donor substituent on the quinoline ring has little effect on enantiocontrol. A series of novel catalysts were synthesised from quinidine (Scheme 3.6) and screened in the oxidative coupling reaction to begin to investigate the effect of changing the O-substituent on the enantioselectivity (Table 3.2, entries 8 – 11).

Scheme 3.6: Synthesis of novel bifunctional organocatalysts QD-172, QD-173 and QD-174 tested for their ability to catalyse the reaction of 3-methoxycatechol and tert-butyl 1-oxoindane-2-carboxylate 80.

A comparison of the result of known catalyst QD-71 with novel catalyst QD-172 (Table 3.2, entries 3 vs. 8) suggests that local bulk around the C9 hydroxyl is important for organising the quinoline ring to enhance the asymmetric induction, however changing the phenyl group to trimethylphenyl (catalyst QD-173) results in a drop in enantiomeric excess (entries 8 vs. 9). The most successful catalyst identified was catalyst QD-174 with the large adamantyl group attached via an ester linkage to the C9 hydroxyl. This catalyst allowed arylated adduct (-)-169r to be isolated in 84% yield and 81% ee (entry 10). Unlike catalyst QD-71, decreasing the
catalyst loading to 1 mol % resulted in a significant decrease in enantiomeric excess with catalyst QD-174 (entries 10 vs. 11). Encouragingly, similarly high levels of enantiocontrol were achieved with 3-tert-butylcatechol to give adduct (+)-169s in 74% yield and 82% ee (Scheme 3.7). The absolute stereochemistry of the major enantiomer of (-)-169r and (+)-169s has been inferred from the results of Deng and co-workers (see chapter 2.3.3) but has not been proven.\textsuperscript{88}

\begin{center}
\begin{tikzpicture}

\node (a) at (0,0) {\textbf{OH}};
\node (b) at (1,0) {OH};
\node (c) at (2,0) {\textbf{OH}};
\node (d) at (3,0) {\textbf{CO}_2}\textbf{Bu}.

\draw[->] (a) -- (b);
\draw[->] (b) -- (c);
\draw[->] (c) -- (d);

\node (e) at (4,0) {1)};
\node (f) at (5,0) {\textbf{CO}_2}\textbf{Bu}.
\node (g) at (6,0) {80};

\node (h) at (7,0) {1 (equiv)};
\node (i) at (8,0) {\textbf{ps-IO}_4^-(2 equiv)};
\node (j) at (9,0) {catalyst QD-174};
\node (k) at (10,0) {CH}_2\text{Cl}_2, -20 ^\circ \text{C};
\node (l) at (11,0) {2) Na_2S_2O_4 (aq)};

\node (m) at (12,0) {\textbf{OH}};
\node (n) at (13,0) {OH};
\node (o) at (14,0) {\textbf{CO}_2}\textbf{Bu}.

\draw[->] (m) -- (n);
\draw[->] (n) -- (o);

\node (p) at (15,0) {(+)-169s};
\node (q) at (16,0) {74\% yield};
\node (r) at (17,0) {82\% ee}.

\end{tikzpicture}
\end{center}

\textbf{Scheme 3.7}: Addition of tert-butyl 1-oxoindane-2-carboxylate 80 to 3-tert-butylcatechol 160 with catalyst QD-174 to give arylated product (+)-169s in good enantiomeric excess.

To investigate the effect of changing the pro-nucleophile on the enantiomeric excess a small screen of pro-nucleophiles was conducted. Pro-nucleophiles tert-butyl 2-oxocyclopentanecarboxylate and 2,2,2-trifluoro-1-(trifluoromethyl)ethyl 2-oxocyclopentanecarboxylate (see chapter 7.3.1), reported to give high enantiomeric excesses with cinchona alkaloid derived catalysts, were chosen and screened, along with methyl 2-oxocyclopentanecarboxylate 109, in the oxidative coupling reaction with 3-methoxy 163 and 3-tert-butyl- 160 catechols giving arylated adducts 169t – 169w (Chart 3.3, Table 3.3).\textsuperscript{89}
Chart 3.3: Enantioselective coupling examples

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Catalyst (mol %)</th>
<th>T /ºC</th>
<th>solvent</th>
<th>% Yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(+)-169t</td>
<td>QD-148</td>
<td>-20</td>
<td>CH2Cl2</td>
<td>62</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>(+)-169t</td>
<td>QD-148</td>
<td>-45</td>
<td>CH2Cl2</td>
<td>66</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>(+)-169t</td>
<td>QD-148</td>
<td>-20</td>
<td>toluene</td>
<td>31</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>(+)-169t</td>
<td>QD-174</td>
<td>-20</td>
<td>CH2Cl2</td>
<td>72</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>(+)-169t</td>
<td>QD-70</td>
<td>-20</td>
<td>CH2Cl2</td>
<td>84</td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>169u</td>
<td>QD-174</td>
<td>-20</td>
<td>CH2Cl2</td>
<td>79</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>(-)-169v</td>
<td>QD-174</td>
<td>-20</td>
<td>CH2Cl2</td>
<td>62</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>(-)-169w</td>
<td>QD-174</td>
<td>-20</td>
<td>CH2Cl2</td>
<td>85</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 3.3: Screen of alternative pro-nucleophiles in the enantioselective oxidative coupling giving arylated adducts 169t – 169w.

The arylated products 169r – 169w were obtained with widely varying degrees of enantiocontrol (Table 3.3). The pro-nucleophile therefore has a significant effect on enantioselectivity. This could be expected if, (in accordance with the postulated mode of action for quinidine-derived organocatalysts) the deprotonated nucleophile is held through a hydrogen bonding network to the bridge-head nitrogen of the quinuclidine ring and the quinoline hydroxyl (see chapter 2.3.3). The quinone electrophile appears to have less influence on enantioselectivity, with 16% difference in ee between 169u and (+)-169v (entries 6 and 7) and only 1% difference between adducts (-)-169r and (+)-169s. In the postulated mode of enantiomeric induction, the electrophile is delivered to one face of the pro-nucleophile through a second hydrogen bond to the quinoline hydroxyl, with the
catalyst acting in a bifunctional manner. From these results it is clear that the interaction of the pro-nucleophile and catalyst is key for achieving high levels of stereocontrol. It is unclear, however, to what extent the quinone interacts with the catalyst. Changing the solvent and reaction temperature (entries 1 – 3) did not significantly change the enantiomeric excess of the product. In order to achieve high levels of enantiocontrol it is clear that the catalyst and pro-nucleophile must be matched. It was therefore decided to exemplify the methodology in total synthesis and optimise the catalyst for the pro-nucleophile required for the chosen target.

4 Total Synthesis of (±)-powelline & (±)-buphanidrine

4.1 Amaryllidaceae alkaloids

Over 500 structurally diverse alkaloids have been isolated from the plants of the amaryllidaceae family.\textsuperscript{90} The alkaloids exhibit a wide range of biological activities including antibacterial, antimalarial, antiviral, antiparasitic and immunostimulatory properties and several members of the family are cytotoxic. The alkaloid galanthamine is a competitive, reversible, inhibitor of acetylcholine esterase and is used to treat Alzheimer’s disease.\textsuperscript{91} Several of the alkaloids have been the subject many synthetic investigations, but many still have no reported syntheses. The alkaloids can be grouped into 15 structural classes according to their core skeleton, of these 7 contain arylated quaternary stereocentres (Figure 4.1).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.1.png}
\caption{Amaryllidaceae alkaloid structural classes containing arylated quaternary stereocentres}
\end{figure}
We decided to target the crinine-type *amaryllidaceae* alkaloids buphanamine 183, buphanidrine 184, powelline 185, undulatine 186 and crinamidine 187 (Figure 4.2) since these contain an aromatic methoxy substituent which would aid the key oxidative coupling step of the planned syntheses. Characterised by the 5,10\(\beta\)-ethanophenanthridine skeleton they differ in their substitution of ring E. Initial efforts concentrated on buphanamine, buphanidrine and powelline, all of which contain 6 fused rings and 3 stereocentres, one of which is quaternary. They have been isolated from several *amaryllidaceae* species and have been shown to bind to the selective serotonin re-uptake inhibitor site on the serotonin transporter in radioligand ([\(^3\)H]-citalopram) binding assays.\(^{92,93}\) Buphanamine and buphanidrine have been isolated from the bulbs and leaves of *Boophane disticha* which are used in South African herbal medicine for numerous purposes including the treatment of headaches and hysteria.\(^{94}\)

Crinine 194 (Scheme 4.1), the simplest member of this structural class, has been synthesised several times.\(^{95,96}\) Two of the main strategies involve either formation of 3\(\alpha\)-arylhydroxyindoles as key intermediates and formation of the C ring typically through a Pictet-Spengler cyclisation, or in a biomimetic approach, through simultaneous synthesis of the C and D rings in an oxidative phenol coupling and Michael addition sequence (191 → 192).\(^{98}\) The later approach has recently been applied to the racemic total synthesis of powelline 185 (reported during the course of this work). The synthesis follows an established route to crinine 194 and is shown in Scheme 4.1.\(^{97}\) Currently no syntheses of buphanidrine, buphanamine, undulatine or crinamidine have been reported.
The construction of the sterically congested arylated quaternary stereocentre is pivotal to the synthesis of this class of alkaloid. Accordingly we considered our oxidative coupling methodology to be ideally suited to the synthesis of these alkaloids.

4.2 Retrosynthetic analysis

Many reported syntheses of crinine-type amaryllidaceae alkaloids construct the B ring in the final stages through a Pictet-Spengler cyclisation. Whilst this strategy has not been applied to amaryllidaceae alkaloids with a substituent ortho to the catechol moiety, regioselective cyclisation could be expected due to the reduced electron donating nature of the methylene acetal group relative to the methoxy substituent. We planned to adopt a similar strategy (Scheme 4.2) so that the key disconnection is then that of the quaternary carbon of the 5,6-bicyclic ring system and the aromatic ring. Two retrosynthetic strategies were envisaged, however since 5,6-bicyclic nucleophiles such as 197 (strategy A) are untested in the oxidative coupling reaction and 6-membered ring nucleophiles are known not to perform well; a more tested approach to the key step would be to employ a 5-membered ring
nucleophile such as lactam 198 and build in the 6-membered ring in subsequent steps (strategy B).

Scheme 4.2: Retrosynthetic analysis of buphanamine/buphanidrine/powelline revealing alternative oxidative coupling substrates

4.3 Initial approach to buphanamine

Initially Buphanamine was targeted; the retrosynthetic analysis is shown in Scheme 4.3. Oxidative coupling of pro-nucleophile 205 with 3-methoxycatechol 163 in the key quaternary carbon-to-aryl bond forming step followed by methylene acetal protection should provide adduct 203. Reduction of the lactam followed by acylation could allow introduction of the allyl group through reaction with allyl silane in the presence of a Lewis acid to give 201. This sets up a ring closing metathesis to give the 5,6-bicyclic system 200. Removal of the Boc protecting group, 1,2-reduction of the α,β-unsaturated ketone and Pictet - Spengler cyclisation could provide rapid access to buphanamine 183.
Scheme 4.3 Retrosynthetic analysis of buphanamine 183 via a ring-closing-metathesis

The synthesis of pro-nucleophile 205 was initially attempted by adding LHMDS to a 1:1 mixture of N-boc-2-pyrrolidinone 206 and crotonoyl chloride. This gave the desired product but in a meagre 4% yield. Optimisation of the reaction conditions gave up to 41% yield when the lactam was added dropwise to 2.1 equivalents of base, followed by dropwise addition of freshly distilled electrophile (Scheme 4.4).

Scheme 4.4: Synthesis of pro-nucleophile 205.

Pro-nucleophile 205 (1 equiv) was reacted with 3-methoxycatechol according to the standard oxidative coupling conditions (Scheme 4.5) and gave the desired arylated product 204 in 53% yield following column chromatography on a 2 mmol scale. Increasing the quantity of pro-nucleophile to 2 equivalents increased the yield following chromatography to 56%, but was not practical due to the low yields for the synthesis of the pro-nucleophile.
Scheme 4.5: Oxidative coupling of pro-nucleophile 205 with 3-methoxycatechol 163.

The next step in the planned synthesis was to introduce the methylene acetal capping group. A series of reported conditions were tried and in all cases none of the desired product could be isolated (Table 4.1, entries 1-3). Acid and base catalysed reactions with formaldehyde and triethyl orthoformate were also investigated, but also gave no conversion to the desired product.

<table>
<thead>
<tr>
<th>Entry</th>
<th>CH₂X₂</th>
<th>Base</th>
<th>Solvent</th>
<th>T / °C</th>
<th>time</th>
<th>heating</th>
<th>% conv.</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Br₂ 1.5 equiv</td>
<td>Cs₂CO₃ 1.5 equiv</td>
<td>DMF</td>
<td>90</td>
<td>18 h</td>
<td>thermal</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>CH₂ClBr 10 equiv</td>
<td>K₂CO₃ 10 equiv</td>
<td>DMF</td>
<td>110</td>
<td>18 h</td>
<td>thermal</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>CH₂Br₂ 1.2 equiv</td>
<td>K₂CO₃ 10 equiv</td>
<td>DMF</td>
<td>90</td>
<td>1h</td>
<td>MW</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>CH₂ClBr 10 equiv</td>
<td>KF 17 equiv</td>
<td>DMF</td>
<td>110</td>
<td>18 h</td>
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<td>33</td>
</tr>
<tr>
<td>5</td>
<td>CH₂ClBr 5 equiv</td>
<td>KF 10 equiv</td>
<td>DMF</td>
<td>120</td>
<td>15 min</td>
<td>MW</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>CH₂ClBr</td>
<td>KF 10 eq</td>
<td>CH₂ClBr</td>
<td>70</td>
<td>15 min</td>
<td>MW</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>CH₂ClBr 5 equiv</td>
<td>KF 10 equiv</td>
<td>DMF</td>
<td>120</td>
<td>5 min</td>
<td>MW</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>CH₂ClBr 5 equiv</td>
<td>KF 17 equiv</td>
<td>DMF</td>
<td>120</td>
<td>5x5 min</td>
<td>MW</td>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>CH₂ClBr 20 equiv</td>
<td>KF 34 equiv</td>
<td>DMF</td>
<td>80</td>
<td>1 h</td>
<td>MW</td>
<td>-</td>
<td>50*</td>
</tr>
</tbody>
</table>

Table 4.1: Optimisation of methylene acetal protection. *75% based on recovered starting material.
Changing the base from caesium/potassium carbonate to potassium fluoride and heating with CH$_2$ClBr at 110 ºC in DMF for 15 h gave a 33% yield of the desired methylene acetal protected catechol 203 (entry 4). The efficiency of this reaction was increased using microwave heating. Heating to 120 ºC for 15 min gave 48% conversion by NMR (measured against remaining starting material) (entry 5). Conversion by NMR of 80% was achieved by heating to 120 ºC for 5 min 5 times, adding additional CH$_2$ClBr and base each time (entry 8), however the isolated yield was a poor 10%. Since the conversion by NMR was measured against remaining starting material, this implies that the starting material, product, or both are decomposing under the reaction conditions. Improved isolated yields (50%) were achieved by lowering the temperature to 80 ºC and heating for 1 h (entry 9).

The oxidative coupling and methylene acetal protection were combined into a telescoped procedure, using the crude product from the oxidative coupling directly in the acetal protection reaction. Yields up to 44% were achieved on a 1 mmol scale over the 3 steps (Scheme 4.6)

Scheme 4.6: One pot oxidative coupling – methylene acetal protection

Further optimisation (Table 4.2) showed that the reaction time for the acetal protection could be reduced to 30 min without decreasing the reaction yield (entry 4 vs 2) and that increasing the concentration or using hydrated KF decreased the yield of 203 (entry 3 vs 2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>CH$_2$ClBr equiv</th>
<th>KF equiv</th>
<th>Concentration /M</th>
<th>T/°C</th>
<th>t/min</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>34 (KF.2H$_2$O)</td>
<td>0.125</td>
<td>80</td>
<td>60</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>34</td>
<td>0.125</td>
<td>80</td>
<td>60</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>17</td>
<td>0.333</td>
<td>80</td>
<td>60</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>34</td>
<td>0.125</td>
<td>80</td>
<td>30</td>
<td>44</td>
</tr>
</tbody>
</table>

Table 4.2: Optimisation of the telescoped oxidative coupling and methylene acetal protection (Scheme 4.6) for the synthesis of 203.
The next step involved selective reduction of the N-Boc lactam carbonyl over the α,β-unsaturated ketone to give N-Boc aminol 202 (Scheme 4.7). To ensure the α,β-unsaturated ketone was not reduced it was protected as its enolate through treatment of lactam 203 with 1.1 equivalents of LHMDS before adding the DIBAL reductant.\textsuperscript{101}

\[ \text{Scheme 4.7: Selective reduction of N-Boc lactam 203 to 202.} \]

Whilst the reduction appeared to proceed smoothly with no starting material present in the crude \textsuperscript{1}H NMR and the correct mass ion for the reduced product present as the only major peak in the mass spectrum of the reaction mixture, varying diastereomeric mixtures of conjugated and non-conjugated enones (presumably resulting from competing γ− and α−reprotonation) were observed in the complex crude \textsuperscript{1}H NMR spectra obtained following work-up. These inconsistent results, combined with the poor yields obtained in the pro-nucleophile synthesis, hampered this approach to the target alkaloid. An alternative approach via a more readily prepared pro-nucleophile was sought.

4.4 Alternative approach to powelline, buphanidrine, undulatine, crinamidine and buphanamine

Since the high reactivity of the crotonoyl side chain of pro-nucleophile 205 was believed to be causing difficulties throughout the original synthesis, an alternative strategy utilising a less reactive pro-nucleophile was desired. As such the α,β-unsaturated ketone was replaced with a methyl ester in a new synthetic plan (Scheme 4.8). Instead of a ring closing metathesis to form the key 5,6-bicyclic intermediate, a Dieckmann-type cyclisation of keto-ester intermediate 210 was envisaged to give diketone 211. Formation of the methyl enol ether 212 could then give access to the 5 alkaloids buphanamine, buphanidrine, undulatine, powelline and crinamidine from this common intermediate. Thus in addition to the anticipated
advantages of removing the crotonoyl side chain this route also provides a more
general strategy to this family of alkaloids.

Scheme 4.8: Alternative retrosynthetic analysis avoiding highly reactive
crotonoyl pro-nucleophile 205.

Pleasingly, synthesis of the methyl ester pro-nucleophile 207 proceeded smoothly in
up to 96% yield on a 5 g scale, following the same procedure used previously for
the synthesis of 205 (Scheme 4.9), but replacing crotonoyl chloride with methyl
chloroformate. The increased yield in the pro-nucleophile synthesis compared to
crotonoyl pro-nucleophile 205 facilitated the synthesis of multi-gram quantities of
synthetic intermediates.

Scheme 4.9: Synthesis of pro-nucleophile 207.

The oxidative coupling (Scheme 4.10) of 207 with 3-methoxycatechol 163 gave
reasonable conversion to the desired arylated product under the established
conditions. The crude product was used directly in the reaction with CH₂ClBr to
form the methylene acetal protecting group. This was unsuccessful with KF as base
giving 208 in a poor 10% yield. Changing the base to Cs₂CO₃ and irradiating at 85
°C in a microwave for 1 hour gave 208 in 38% yield (Table 4.3, entry 1). A
temperature, solvent, and concentration screen showed that increasing or decreasing
the reaction temperature from -20 °C had a detrimental effect on the yield of 208
(entry 1 vs. 2, 3). Increasing the number of equivalents of pro-nucleophile also
decreased the isolated yield (entry 4), although this was mainly due to difficulties in
separating the arylated product from the excess of pro-nucleophile during column
chromatography and did not reflect a decrease in conversion. Increasing the
dilution of the reaction mixture also had a detrimental effect on reaction yield (entry
5). The reaction in acetonitrile was equivalent to CH₂Cl₂ however the isolated yield
was increased to 52% on a 10 mmol scale by running the oxidative coupling
reaction in acetone (entries 6 and 7). The methylene acetal capping reaction was
initially conducted under microwave irradiation; however conventional heating in a
sealed vessel was later shown to give the same result.

\[
\begin{align*}
\text{Scheme 4.10: One pot oxidative coupling and methylene acetal} \\
\text{protection of 207 and 3-methoxycatechol 163.}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv Pro-Nu</th>
<th>Solvent</th>
<th>Equiv base</th>
<th>Concentration /M</th>
<th>T/°C</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>CH₂Cl₂</td>
<td>0.1</td>
<td>0.1</td>
<td>-20</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>CH₂Cl₂</td>
<td>0.1</td>
<td>0.1</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>CH₂Cl₂</td>
<td>0.1</td>
<td>0.1</td>
<td>-30</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>CH₂Cl₂</td>
<td>0.2</td>
<td>0.1</td>
<td>-20</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>CH₂Cl₂</td>
<td>0.1</td>
<td>0.05</td>
<td>-20</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>MeCN</td>
<td>0.1</td>
<td>0.1</td>
<td>-20</td>
<td>37</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>acetone</td>
<td>0.1</td>
<td>0.1</td>
<td>-20</td>
<td>52 b</td>
</tr>
</tbody>
</table>

Table 4.3: Optimisation of oxidative coupling of 163 and 207 (Scheme 4.10). a isolated yield of
208 after methylene acetal protection with CH₂ClBr and Cs₂CO₃, b methylene acetal protection
conducted with conventional heating in a sealed vessel or under microwave irradiation gave
identical product yields.

Subsequent reduction of the ketonic N-Boc lactam carbonyl (the most reactive
carbonyl) with 1 equivalent of Super-hydride® was highly chemoselective and gave
quantitative conversion to N-Boc aminol 209 as a 1:1 diastereomeric mixture.
Isolated yields of 93% following simple filtration through a plug of silica gel were
achieved (Scheme 4.11).
Scheme 4.11: N-Boc lactam reduction to give 209.

Although signals indicative of the open form aldehyde 213 were not observed in the \(^1\)H NMR in d\(_6\) DMSO of this N-Boc aminol, the two forms were expected to exist in dynamic equilibrium (Scheme 4.12). As such 209 was treated with Horner-Wadsworth-Emmons reagent dimethyl 2-oxopropylphosphonate and potassium tert-butoxide and heated to reflux. The only products obtained from the reaction mixture were identified as formamide 214 and de-formylated product 215 (Scheme 4.13).

Scheme 4.12: Anticipated equilibrium of aminol 209 and open form aldehyde 213.


The desired product was not isolated.

Treatment of N-Boc aminol 209 with strong base resulted in apparent complete conversion to the formamide 214 and subsequent conversion to de-formylated product 215 after extended heating. This process destroys the quaternary centre created in the key step. Introduction of the ketonic side chain of 210 was therefore
deemed to be impossible using Wittig or Horner-Wadsworth-Emmons chemistry and an \(N\)-acyliminium ion approach was investigated instead.

Acylation of \(N\)-Boc aminol 209 with acetic anhydride in pyridine gave quantitative conversion to 216, which was used crude in the Lewis acid mediated reaction with (isopropenyloxy)trimethylsilane (Scheme 4.14).\(^{103}\)

![Scheme 4.14: Acylation of \(N\)-Boc aminol 209 and Lewis-acid mediated displacement with (isopropenyloxy)trimethylsilane to give 210.](image)

Pleasingly treatment of 216 with \(BF_3\cdot Et_2O\) in \(CH_2Cl_2\) with an excess of (isopropenyloxy)trimethylsilane gave the desired product in 91% yield (over 2 steps), although in a moderate 3:1 dr (Table 4.4, entry 1). A series of solvents and Lewis/Bronsted acids were screened in order to increase the dr (Table 4.4). The highest dr was achieved in acetone (entry 6), which also gave smooth conversion and an isolated yield of 76%. Both the minor and major diastereomers show an NOE interaction between proton \(H_A\) and the protons of the aromatic ring (Figure 4.3), so the relative stereochemistry of the major diastereomer could not be determined by \(^1\)H NMR analysis at this stage.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis/Brønsted Acid</th>
<th>Solvent</th>
<th>dr (isolated yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF(_3), Et(_2)O</td>
<td>CH(_2)Cl(_2)</td>
<td>3:1 (91%)</td>
</tr>
<tr>
<td>2</td>
<td>BF(_3), Et(_2)O</td>
<td>THF</td>
<td>4:1</td>
</tr>
<tr>
<td>3</td>
<td>BF(_3), Et(_2)O</td>
<td>TBME</td>
<td>5:2</td>
</tr>
<tr>
<td>4</td>
<td>BF(_3), Et(_2)O</td>
<td>Et(_2)O</td>
<td>5:2</td>
</tr>
<tr>
<td>5</td>
<td>BF(_3), Et(_2)O</td>
<td>MeCN</td>
<td>No conversion</td>
</tr>
<tr>
<td>6</td>
<td>BF(_3), Et(_2)O</td>
<td>Acetone</td>
<td>7:1 (76%)</td>
</tr>
</tbody>
</table>
Table 4.4: Screen of solvents and Lewis/Brønsted acids for the reaction of acylated aminol 216 and (isopropenylxy)trimethylsilane to give 210.

<table>
<thead>
<tr>
<th>Solvent/Reagent</th>
<th>Solvent</th>
<th>Acid</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 BF₃·Et₂O</td>
<td>EtOAc</td>
<td>4:1</td>
<td></td>
</tr>
<tr>
<td>8 TMSOTf</td>
<td>CH₂Cl₂</td>
<td>3:2</td>
<td></td>
</tr>
<tr>
<td>9 SnCl₄</td>
<td>CH₂Cl₂</td>
<td>2:1</td>
<td></td>
</tr>
<tr>
<td>10 CSA</td>
<td>CH₂Cl₂</td>
<td>No conversion</td>
<td></td>
</tr>
<tr>
<td>11 BF₃·THF</td>
<td>CH₂Cl₂</td>
<td>No conversion</td>
<td></td>
</tr>
</tbody>
</table>

Figure 4.3: NOE interactions (average values) observed for the major and minor diastereomer of 210. The relative stereochemistry could not be determined from these results.

Treatment of keto-ester 210 with potassium tert-butoxide (2 equivalents) in THF gave smooth conversion to the cyclic diketone 211 (Scheme 4.15), identifiable by mass-spectrometry. No conversion was observed with the alternative bases, NaH or KH in THF or with NaOMe/KOMe in methanol or NaOEt in ethanol. Adding keto-ester 210 to a warm (40 °C) solution of KOtBu in THF gave smooth conversion to the cyclic product, complete in 10 min. ⁱH NMR of the crude reaction mixture was broad with no sharpening of the peaks upon heating to 90 °C. This is possibly due to the presence of rotamers and meant that an accurate measure of conversion (or dr) could not be determined at this stage. Since the diketone was extremely polar the crude reaction mixture was reacted directly under various conditions to form the methyl enol ether 212 which was easier to handle and purify. Treatment of the crude mixture with 10 mol% CSA in methanol resulted in slow conversion to the methyl enol ether and a low isolated yield of 28%. This was increased to 46% with 20 mol% HCl in methanol. Quenching the cyclisation reaction with dimethylsulfate gave the desired enol ether in 29% yield and Mitsunobu conditions (1 equiv each of PPh₃ and DEAD, 5 equiv of methanol in THF) gave 42% (all yields over 2 steps).¹⁰⁴ Alternatively, treating the crude diketone with 5 mol % TiCl₄ in methanol gave good conversion to the desired methyl enol ether 212 and pleasing isolated yields of
64 % over 2 steps (Scheme 4.15).\textsuperscript{105} The methyl enol ether formation was highly regioselective; no minor regioisomer was identifiable in the crude \textsuperscript{1}H NMR of the reaction mixture. The structure of methyl enol ether \textsuperscript{212} was assigned through analysis of the \textsuperscript{13}C, HSQC and HMBC NMR spectra. Cross peaks between the protons of the pyrrolidine ring and the carbonyl carbon in the HMBC spectra confirmed that the desired regioisomer had been formed.

Scheme 4.15: Dieckmann-type cyclisation of keto ester \textsuperscript{210} and subsequent formation of enol ether \textsuperscript{212}.

Only one diastereomer of the methyl enol ether was isolated from the reaction and a minor diastereomer could not be identified in the NMR of the crude reaction mixture. Furthermore the isolated yield of methyl enol ether was consistent irrespective of the diastereomeric ratio of keto-ester \textsuperscript{210} cyclisation substrate. This implies the Dieckmann step is reversible and gives only the thermodynamic product under these conditions. Subsequent scaled-up batches of keto-ester \textsuperscript{210} were therefore prepared in CH\textsubscript{2}Cl\textsubscript{2} to give optimised yield and not dr.

To access the allylic alcohol system present in the target alkaloids, reductive manipulation of the enol ether moiety was required. The DIBAL reduction of enol ether systems to their corresponding enones is well documented in the literature,\textsuperscript{106} however there are few examples where the ketone is adjacent to a sterically congested quaternary centre. Treatment of methyl enol ether \textsuperscript{212} with DIBAL in toluene gave, following hydrolysis in aqueous HCl/diethyl ether, disappointing yields of the desired enone \textsuperscript{217} and significant quantities of saturated ketone by-product \textsuperscript{217b} resulting from competing 1,4-reduction, elimination of methanol and a second 1,4-reduction (Table 4.5, entry 6). Whilst 1,2-reduction would be expected with DIBAL, the adjacent quaternary centre is believed to hinder 1,2 reduction so that the 1,4-reduction process becomes competitive. Altering the temperature and rate of addition of DIBAL gave no significant improvement in result (entries 6 – 9). Treatment of enol ether \textsuperscript{212} under Luche reduction
conditions, or with LiAlH₄ or Red-Al® gave no conversion to the desired enone (entries 1 – 4). Changing the reducing agent to Super-hydride® resulted in saturated alcohol products 217c in a 1:1 diastereomeric ratio (separable by column chromatography) (entry 5). The isolated yield of enone 217 and the ratio of 217:217b:217c was improved by changing the solvent for the DIBAL reduction to CH₂Cl₂. With the optimal conditions (entry 12), enone 217 could be isolated in 58% yield over the 2 steps (reduction and hydrolysis). Increasing the reaction temperature from -20 to 0 ºC improved the ratio of 217:217b but decreased the isolated yield of 217; decreasing the reaction temperature had a detrimental effect on both the product ratio and yield (entries 11, 12 and 13). Changing the equivalents of DIBAL had little effect on the product ratio or isolated yield (entry 10 vs. 11).

![Chemical structures](image)

Table 4.5: Screen of reducing agents and conditions for reduction of methyl enol ether 212. *Starting material was recovered, *decomposition of starting material, 217 could not be detected in crude NMR, 6% unreacted starting material also recovered.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reductant (equiv)</th>
<th>Solvent</th>
<th>T /°C</th>
<th>Ratio 217:217b:217c</th>
<th>% Yield 217</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH₄/CeCl₃ (1)</td>
<td>MeOH</td>
<td>0</td>
<td>-</td>
<td>0a</td>
</tr>
<tr>
<td>2</td>
<td>LiAlH₄ (1)</td>
<td>THF</td>
<td>0</td>
<td>0:1:0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>LiAlH₄ (1)</td>
<td>toluene</td>
<td>0</td>
<td>0:1:0</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Red-Al® (2)</td>
<td>toluene</td>
<td>0</td>
<td>-</td>
<td>0b</td>
</tr>
<tr>
<td>5</td>
<td>Super-hydride® (2.2)</td>
<td>THF</td>
<td>-78</td>
<td>0:0:1</td>
<td>217c 52% (1:1 ratio of diastereomers)</td>
</tr>
<tr>
<td>6</td>
<td>DIBAL (2)</td>
<td>toluene</td>
<td>-78</td>
<td>1:1:0</td>
<td>217 33%, 217b 33%</td>
</tr>
<tr>
<td>7</td>
<td>DIBAL (2)</td>
<td>toluene</td>
<td>-85</td>
<td>1:1:0</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>DIBAL (2)</td>
<td>toluene</td>
<td>-20</td>
<td>1.2:1:0</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>DIBAL (2, dropwise)</td>
<td>toluene</td>
<td>-78</td>
<td>1.3:1:0</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>DIBAL (2)</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>7:1:0</td>
<td>217 28%, 217b 4%</td>
</tr>
<tr>
<td>11</td>
<td>DIBAL (4)</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>7.5:1:0</td>
<td>217 32%, 217b 4%</td>
</tr>
<tr>
<td>12</td>
<td>DIBAL (2.5)</td>
<td>CH₂Cl₂</td>
<td>-20</td>
<td>5.3:1:0</td>
<td>217 58%, 217b 11%</td>
</tr>
<tr>
<td>13</td>
<td>DIBAL (2)</td>
<td>CH₂Cl₂</td>
<td>-78</td>
<td>2:1:0</td>
<td>217 44%, 217b 21%</td>
</tr>
</tbody>
</table>
In an attempt to increase the ratio of $217:217b:217c$ in favour of the desired enone, ethyl-enol ether $218$ was synthesised in 38% yield from $210$ following the established procedure for the preparation of $212$ but replacing methanol with ethanol (Scheme 4.16). It was hoped that the small increase in bulk of the ether substituent would decrease the propensity for 1,4-reduction. Treatment of $218$ with DIBAL in toluene gave enone $217$ and ketone $217b$ in 36% and 18% yield respectively. The isolated yield is comparable to the analogous reduction of $212$, and the ratio is improved, however the low yield for the synthesis of the ethyl enol ether (38% vs. 64%) rendered this approach unattractive.

![Scheme 4.16: synthesis of enone $217$ via ethyl enol ether $218$.](image)

The enone product $217$ was found to be highly crystalline; therefore the relative stereochemistry at the ring-junction was proven to be cis (as desired) by single-crystal X-ray crystallography (Figure 4.4).

![Figure 4.4: X-ray crystal structure of enone $217$, confirming relative stereochemistry of ring junction.](image)
Reduction of enone 217 was initially attempted under standard Luche conditions (NaBH₄, CeCl₃·7H₂O) and gave the desired allylic alcohol as the minor component of a 5.5:1 diastereomeric mixture (overall yield 95%) (Scheme 4.17). The diastereomers were separable by silica gel chromatography although complete separation was difficult and the minor diastereomer was typically isolated containing varying degrees of major diastereomer. NOE studies on pure samples of both diastereomers confirmed the relative stereochemistry of the major and minor components (Figure 4.5).

Scheme 4.17: Luche reduction of enone 217

Figure 4.5: NOE studies (average values) on both diastereomers of allylic alcohol 219/219b.

Mesylation and inversion of the undesired allylic alcohol has been reported on similar systems to be an effective, but lengthy, strategy to obtain the desired allylic alcohol.107 Accordingly 219b (dr >99:1 219b:219) was treated with methanesulfonic anhydride followed by CsOAc and hydrolysis of the resulting ester with K₂CO₃ in methanol (Scheme 4.18). The desired diastereomer was obtained in 75% yield as the major component of a 3.1:1 diastereomeric mixture.
Scheme 4.18: Inversion of 219b to 219.

Whilst this approach allowed the desired diastereomer to be obtained as the major product, it is lengthy and the loss of stereochemical integrity meant that isolating the desired diastereomer in good yield would be difficult, with a theoretical maximum yield of 46% attainable assuming complete separation of diastereomers after the initial reduction and the inversion. Consequently a screen of reducing reagents/conditions was undertaken to try and alter the diastereomeric ratio (Table 4.6). Since the aim of the screen was to optimise dr, which was determined from the crude ¹H NMR, in most cases isolated yields were not determined.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reductant</th>
<th>T °C</th>
<th>Solvent</th>
<th>dr (219:219b)</th>
<th>Yield (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Superhydride(^a)</td>
<td>-20</td>
<td>THF</td>
<td>1:2</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>N-Selectride(^a)</td>
<td>-20</td>
<td>THF</td>
<td>2:1</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>N-Selectride(^a)</td>
<td>-20</td>
<td>CH(_2)Cl(_2)</td>
<td>1:1</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>N-Selectride(^a)</td>
<td>-20</td>
<td>toluene</td>
<td>1:1.3</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>N-Selectride(^a)</td>
<td>-78</td>
<td>THF</td>
<td>2:1</td>
<td>77%</td>
</tr>
<tr>
<td>6</td>
<td>N-Selectride(^a)</td>
<td>rt</td>
<td>THF</td>
<td>2:1</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>K-Selectride(^a)</td>
<td>-20</td>
<td>THF</td>
<td>1.7:1</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>L-Selectride(^a)</td>
<td>-20</td>
<td>THF</td>
<td>3.5:1</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>L-Selectride(^a)</td>
<td>-78</td>
<td>THF</td>
<td>3.5:1</td>
<td>78%</td>
</tr>
</tbody>
</table>

Table 4.6: Screen of reducing conditions for synthesis of allylic alcohol 219. \(^a\)Calculated from crude NMR at 90 °C, \(^b\)overall yield of both diastereomers
Whilst Superhydride® was found to give the undesired diastereomer 219b as the major product (entry 1), pleasingly N-, K- and L-Selectride® reversed the stereoselectivity and gave the desired allylic alcohol 219 as the major diastereomer. With N-Selectride® up to 2:1 dr and 77% overall yield was obtained in THF (entries 2, 5 and 6). Changing the temperature had no effect on the diastereomeric ratio however the crude spectra were noticeably cleaner at lower temperature; changing the reaction solvent had a detrimental effect on the stereoselectivity. L-Selectride® was found to be the optimal reagent, allowing the desired allylic alcohol to be synthesised as the major component of a 3.5:1 diastereomeric mixture, in an overall yield of 78%.

The difference in stereoselectivity between NaBH₄ and the Selectride® reducing agents could be expected based on the differing sizes of these reducing agents. For the reduction of rigid cyclohexanone systems with small reducing agents (such as NaBH₄) torsional effects dominate and so axial attack is expected (giving an equatorial hydroxyl group) to avoid the development of eclipsing interactions in the transition state. In contrast larger reducing agents (such as L-Selectride®) are more influenced by steric effects which are greater for axial attack and therefore these reagents prefer equatorial attack to give an axial hydroxyl. Whilst the reduction of 217 is significantly more complicated than simple cyclohexanone systems, this rationale can explain the experimental outcome of the reduction reactions if enone 217 reacts through the pseudo-chair conformations shown in Figure 4.6.

For the synthesis of (±)-powelline, allylic alcohol 219 was treated with neat TFA to remove the Boc protecting group (Scheme 4.19). The crude secondary amine (identifiable by mass spectrometry) was free-based and used directly without purification in the Pictet-Spengler cyclisation. Accordingly the crude amine was treated with aqueous formaldehyde in methanol for 15 min before adding 6 M HCl.
For crinine systems the analogous Pictet-Spengler cyclisation required heating to 40 °C, however with the additional electron donating methoxy group on the aromatic ring heating was not required on this system, with the reaction complete in 10 min after the addition of acid at room temperature. Pleasingly the two possible regioisomers in the Pictet-Spengler reaction were formed with ~7:1 selectivity for the desired product (Scheme 4.19) to give (±)-powelline 185 in 49% yield over 2 steps. Whilst (±)-powelline could be isolated free from the minor regioisomer, it was not possible to isolate the minor regioisomer from (±)-powelline and a further 35% of a 2.5:1 mixture of 185:185b was isolated. The minor regioisomer 185b was characterised from this mixture.

![Scheme 4.19: Synthesis of (±)-powelline 185 from 219.](image)

The spectral data for (±)-powelline (Figure 4.7) were consistent with the published data, and in addition the structure of synthetic powelline was confirmed with 2D and NOE NMR experiments (Figure 4.8). An NOE interaction between the NCH2Ar protons and the protons of the methoxy group confirmed the regioselectivity of the Pictet-Spengler cyclisation. Furthermore NOE experiments on the minor regioisomers 185b showed an interaction between the protons of the aromatic methoxy group and the proton of the aromatic ring that was absent in the major component.
The synthesis of C3-epi-powelline (C3-epi-185) was also accomplished from allylic alcohol 219b, following the same deprotection Pictet-Spengler sequence (Scheme 4.20). The major product was identified by 2D NMR and NOESY analysis as C3-epi-powelline. Sufficient quantities of the minor component of the crude reaction mixture could not be obtained for full characterisation, however identical mass-spectra and proton and NOESY spectra suggest this minor component is, as expected, the other regioisomer C3-epi-185b. The products obtained from this reaction sequence could not be identified in the crude reaction mixture in the synthesis of powelline, indicating that epimerisation of the allylic alcohol does not occur during the deprotection or Pictet-Spengler reactions.
Scheme 4.20: Synthesis of C3-epi-powelline (C3-epi-185) from 219b.

For the synthesis of (±)-buphanidrine 184 allylic alcohol 219 was O-methylated under standard conditions (NaH, MeI) to give methyl ether 221 in excellent yield (Scheme 4.21). Following the same deprotection/Pictet-Spengler sequence provided (±)-buphanidrine, again as the major component of a separable ~10:1 regioisomeric mixture in 51% yield (over 2 steps). Again the minor regioisomer 184b could not be completely separated from (±)-buphanidrine and a further 32% of a 2.8:1 184:184b mixture was isolated. The minor regioisomer was characterised from this mixture.


The spectral data (Figure 4.9) were in excellent agreement with the published data,\textsuperscript{110} and again NOE studies also confirmed the reported structure (Figure 4.10).
Thus the total syntheses of (±)-powelline 185 and (±)-buphanidrine 184 were accomplished in 13 and 14 linear steps respectively and in 6% overall yield in both cases (Scheme 4.22). This route represents a novel approach to the crinine skeleton with the quaternary carbon to aryl bond constructed directly through an oxidative coupling to allow rapid construction of the target alkaloids. No attempt was made to synthesise the remaining target alkaloids at this time as an enantioselective approach to powelline and buphanidrine was investigated. The synthesis of (±)-undulatine and (±)-crinamidine would require diastereoselective epoxidation of the allylic alcohol, and the synthesis of buphanamine would require an alternative reduction sequence or rearrangement of the allylic alcohol.
Scheme 4.22: Total synthesis of (±)-powelline 185 and (±)-buphanidrine 184.

5 Enantioselective total synthesis studies

5.1 Initial organocatalyst screen

With proof of concept for an organocatalysed enantioselective oxidative coupling established with 3-methoxycatechol and 3-tert-butylcatechol during methodology development (chapter 3.2), it was believed that an enantioselective synthesis of the target alkaloids could be achieved by employing similar organocatalysts in the key oxidative coupling step. However since the enantioselectivity was found to vary widely with the pro-nucleophile employed it was anticipated that a significant
degree of optimisation would be required to obtain high levels of stereocontrol with pro-nucleophile 207.

An initial screen of organocatalysts (Chart 5.1) was undertaken under the standard oxidative coupling procedure (Table 5.1) and the enantioselectivity determined by chiral HPLC analysis compared to a racemic sample. The methylene acetal protected product was initially used for HPLC analysis since the catechol product was found to ‘streak’ on silica. To increase the ease of catalyst screening the methylene acetal protecting group was later replaced with diacetate protection, following the established protocol described in chapter 2.2. The enantioselectivity obtained with catalyst QD-71 was identical from either method (entries 5 and 5b).

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Scale/mmol</th>
<th>Product</th>
<th>% ee</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>135</td>
<td>0.1</td>
<td>(-)-223</td>
<td>15</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>QD-147</td>
<td>0.2</td>
<td>(+)-223</td>
<td>11</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>137</td>
<td>0.1</td>
<td>(-)-223</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>0.1</td>
<td>(+)-208</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
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<td>QD-71</td>
<td>0.1</td>
<td>(+)-208</td>
<td>50</td>
<td>35</td>
</tr>
<tr>
<td>5b</td>
<td>QD-71</td>
<td>0.5</td>
<td>(+)-223</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>QD-148</td>
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<td>49</td>
<td>20</td>
</tr>
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<td>QD-172</td>
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<td>(+)-208</td>
<td>42</td>
<td>28</td>
</tr>
<tr>
<td>8</td>
<td>QD-173</td>
<td>0.1</td>
<td>(+)-208</td>
<td>31</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>QD-174</td>
<td>0.1</td>
<td>(+)-208</td>
<td>42</td>
<td>28</td>
</tr>
<tr>
<td>10</td>
<td>QD-170</td>
<td>0.1</td>
<td>(+)-208</td>
<td>55</td>
<td>25</td>
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<tr>
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<td>(-)-208</td>
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<td>18</td>
</tr>
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<td>(±)-208</td>
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<td>(+)-223</td>
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<td>43</td>
</tr>
<tr>
<td>16</td>
<td>228</td>
<td>0.1</td>
<td>(+)-223</td>
<td>12</td>
<td>43</td>
</tr>
<tr>
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<td>229</td>
<td>0.1</td>
<td>(-)-223</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
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<td>230</td>
<td>0.1</td>
<td>(+)-223</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>19</td>
<td>231</td>
<td>0.1</td>
<td>(-)-223</td>
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<td>232</td>
<td>0.1</td>
<td>(-)-223</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>21</td>
<td>233</td>
<td>0.1</td>
<td>(+)-223</td>
<td>4</td>
<td>33</td>
</tr>
</tbody>
</table>

**Table 5.1:** Initial organocatalyst screen in the reaction of 3-methoxycatechol 163 and 207.
Whilst all enantioselectivities were modest, the quinidine-derived benzyl series (entries 5 and 10) gave the highest levels of stereocontrol. Linking the aryl group directly to the C9-hydroxyl resulted in a loss in enantioselectivity (entry 5 vs. 7) and adding a carbonyl into the linker reduced the enantiomeric excess dramatically (entry 5 vs. 11). The effect of changing the pro-nucleophile on the enantioselectivity is clear from entry 9, catalyst QD-174 gave the arylated product in only 11% ee, considerably decreased from the enantiomeric excess achieved with tert-butyl 1-oxoindane-2-carboxylate pro-nucleophile 80. Takamoto’s catalyst\(^{47}\) (entry 13), Hiemstra’s catalyst\(^{87}\) (entry 14), Jacobsen’s catalysts\(^{46}\) (entries 19 – 21) and a range of commercially available primary chiral amines all gave the arylated product in disappointing enantiomeric excesses.

### 5.2 Phase transfer catalysis

Although phase transfer catalysis has been reported to be incompatible with quinone reagents, phase transfer catalyst 72 has been shown to induce high levels of enantiocontrol in the S\(_{\text{N}}\)Ar reaction of fluoro-nitrobenzenes and pro-nucleophile 236.\(^{51}\)

**Scheme 5.1:** Phase transfer catalysed S\(_{\text{N}}\)Ar reaction of N-Boc lactam pro-nucleophile 236.
Phase transfer catalyst 72 was screened in the oxidative coupling reaction with a range of stoichiometric bases (Table 5.2). Whilst the phase transfer catalyst was able to catalyse the reaction, both yields and enantioselectivities were disappointing (entries 1 – 4). When K3PO4 was employed as the stoichiometric base no conversion to the desired product was obtained. Control experiments without phase transfer catalyst 72 did result in conversion to the arylated product 223 (entries 5 – 7), so for high levels of enantiocontrol the rate of the phase transfer catalysed reaction must be greater than the background reaction rate. Decreasing the amount of inorganic base to match the molar percentage of the catalyst (entry 8) increased the enantiomeric excess of the product, as did employing stoichiometric phase transfer reagent, however the values obtained were still significantly lower than with the non-phase transfer cinchona alkaloid derived catalysts.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat. (mol %)</th>
<th>Base (equiv)</th>
<th>% Yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72 (20 mol %)</td>
<td>KOH (1.5)</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>72 (20 mol %)</td>
<td>CsOH.H2O (1.5)</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>72 (20 mol %)</td>
<td>K3PO4 (1.5)</td>
<td>-a</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>72 (20 mol %)</td>
<td>K2CO3 (1.5)</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>KOH (1.5)</td>
<td>complete conversion in 7 h.</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>K3PO4 (1.5)</td>
<td>trace product in 3 days</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>K2CO3 (1.5)</td>
<td>50% conversion in 3 days</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>72 (20 mol%)</td>
<td>KOH (0.2)</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>72 (1 equiv)</td>
<td>KOH (1.0)</td>
<td>11</td>
<td>22</td>
</tr>
</tbody>
</table>

Table 5.2: Screen of bases and conditions in the phase transfer catalysed oxidative coupling. a no conversion to arylated product after 3 days.

The low levels of enantiocontrol in the phase transfer catalysed oxidative coupling could be attributed to competition from the background reaction or to poor interactions between the phase transfer catalyst and pro-nucleophile 207. Since the analogous ethyl ester pro-nucleophile 236 is known to work well with catalyst 72, this pro-nucleophile was synthesised from tert-butyl 2-oxopyrrolidine-1-
carboxylate 206 and ethylchloroformate (following the procedure for the synthesis of pro-nucleophile 207), and screened in the oxidative coupling reaction (Scheme 5.2). The yield and enantiomeric excess of the arylated product were still low, and as a result phase transfer catalysis was not investigated further.

![Scheme 5.2: Phase transfer catalysed oxidative coupling with pro-nucleophile 236.](image)

### 5.3 Pro-nucleophile screen

Since the benzyl-derived quinidine catalysts gave the best results so far, catalyst QD-71 (readily prepared on scale) was used for further screening. A range of pro-nucleophiles that could be suitable replacements for 207 with esters and carbamate protecting groups were synthesised following the established procedure for the synthesis of pro-nucleophile 207 (Scheme 5.3). Benzyl and tosyl protected pro-nucleophiles 248 and 247 were prepared in an analogous fashion from commercially available 1-benzyl-2-pyrrolidinone 245 and 1-(p-toluenesulfonyl)-2-pyrrolidinone 244 respectively. Pro-nucleophile 249 was synthesised through deprotection of 207 with 4 M HCl in dioxane.
Scheme 5.3: Synthesis of alternative pro-nucleophiles.

The range of pro-nucleophiles was screened in the oxidative coupling with catalyst QD-71 and the enantiomeric excess determined by chiral HPLC analysis (Table 5.3). In many cases protection of the catechol was not required for HPLC analysis, otherwise the catechol was protected as the diacetate or methylene acetal as before.
Screen of alternative pro-nucleophiles with cat **QD-71**. After 24 h reaction time no arylated product was detectable by crude NMR.

Changing the bulk of the protecting group, or adding π-stacking ability to the ester group (entries 1 and 3) had no positive effect on the enantiomeric excess of the arylated product. When the carbamate protecting group and ester are of equal steric bulk racemic product was obtained, implying there is either no preference for the orientation in which this pro-nucleophile is held by the catalyst or that there is no (or very little) interaction between the catalyst and this pro-nucleophile. Cbz and tosyl protected pro-nucleophiles 246, 247 (entries 4 and 5) also gave disappointing enantioselectivities. According to the postulated mode of action of quinidine-derived catalysts such as **QD-71**, the deprotonated nucleophile is held by the bridgehead nitrogen with an additional hydrogen bond from the quinoline hydroxyl to the ester of the pro-nucleophile (see Scheme 2.17, chapter 2.3.3). In the case of pro-nucleophiles such as 207 this additional hydrogen bond could be formed with the ester or carbamate protecting group (Figure 5.1). These two arrangements lead to opposite enantiomers of the arylated product (assuming attack from one face by the quinone electrophile) and therefore, whilst these two arrangements may have transition states of significantly different energies, could be a cause for the lower enantioselectivities observed with pro-nucleophiles 207, 238, 239, 242, 246, 247 compared to tert-butyl 1-oxoindane-2-carboxylate pro-nucleophile 80.

**Figure 5.1**: Alternative catalyst (of type 71) – pro-nucleophile (of type 207) interactions leading to opposite enantiomers of product (assuming attack from one face by the electrophilic quinone).

Pro-nucleophiles 240, 248 - 249 (Scheme 5.3) were synthesised to alter this hydrogen bonding pattern since the additional hydrogen bond can only be formed to
either the ester or the protecting group in these cases. Pro-nucleophiles 248 and 249 did not react successfully under the oxidative coupling procedures and no arylated product could be detected by crude $^1$H NMR (following reductive work-up) after 24 h reaction time. This is presumably due to the decreased acidity of these pro-nucleophiles. Pro-nucleophile 240 (not a direct replacement for 207) gave a poor 6% ee. Of the pro-nucleophiles tested the originally chosen Boc-protected methyl ester lactam 207 gave the highest level of enantioselectivity and was therefore used in further studies.

### 5.4 Conditions screen

A screen of solvents (Table 5.4, entries 1 – 15), temperature (entries 20 – 22) and concentration (entries 18 – 19) was undertaken with the optimal pro-nucleophile, 207, and catalyst QD-71. The conditions were screened for their effect on enantioselectivity, and accordingly yields (where recorded) are unoptimised. In cases where yields are not reported the enantioselectivity was determined from a sample obtained from analytical TLC of the reaction mixture.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>mol % cat QD-71</th>
<th>T/°C</th>
<th>Conc./M</th>
<th>Product</th>
<th>% ee</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_2$Cl$_2$</td>
<td>10</td>
<td>-20</td>
<td>0.1</td>
<td>(+)-208</td>
<td>50</td>
<td>35</td>
</tr>
<tr>
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<td>CHCl$_3$</td>
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<td>-20</td>
<td>0.1</td>
<td>(+)-208</td>
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<td>25</td>
</tr>
<tr>
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<td>0.1</td>
<td>(+)-208</td>
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<td>33</td>
</tr>
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<td>toluene</td>
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<td>(+)-208</td>
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<td>8</td>
</tr>
<tr>
<td>5</td>
<td>MeCN</td>
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<td>0.1</td>
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<td>38</td>
</tr>
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<td>0.1</td>
<td>(+)-208</td>
<td>36</td>
<td>38</td>
</tr>
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<td>7</td>
<td>1,2-DCE</td>
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<td>-20</td>
<td>0.1</td>
<td>(+)-223</td>
<td>38</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>chlorobenzene</td>
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<tr>
<td>9</td>
<td>1,1,2,2-tetrachloroethane</td>
<td>10</td>
<td>-20</td>
<td>0.1</td>
<td>(+)-223</td>
<td>37</td>
<td>-</td>
</tr>
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<td>-20</td>
<td>0.1</td>
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<td>-</td>
</tr>
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<td>0.1</td>
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<td>-</td>
</tr>
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<td>0.1</td>
<td>(+)-223</td>
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<td>-</td>
</tr>
<tr>
<td>13</td>
<td>CH$_2$ClBr</td>
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<td>-20</td>
<td>0.1</td>
<td>(+)-223</td>
<td>50</td>
<td>-</td>
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</table>
Table 5.4: Conditions screen for the synthesis of (+)-223 with cat. QD-71.

From the initial screen of solvents it was clear that chlorinated solvents offer significantly higher enantiomeric excess compared to non chlorinated solvents (entries 1 and 2 vs. 3 – 5, 10 – 12). However, testing further halogenated solvents (entries 7 – 9, 13, 14) did not result in improved enantioselectivities. A relationship between solvent polarity and enantiomeric excess is difficult to establish as both polar and non-polar solvents resulted in decreased enantiomeric excesses compared with dichloromethane. Increasing or decreasing the reaction temperature (entries 21 – 22) decreased the enantiomeric excess, implying that -20 °C is near optimal. A very small increase in enantiomeric excess was observed on increasing the catalyst loading (entry 17), however decreasing the catalyst loading did not result in a corresponding decrease in enantiomeric excess (entry 18). Increasing the dilution of the reaction mixture had a positive effect, increasing the enantiomeric excess from 50 to 56% with a 5-fold dilution (entries 1 vs. 19). This was further increased to 62% by increasing the catalyst loading to 30 mol% at a concentration of 0.01 M (entry 20).

5.5 Screen of novel cinchona alkaloid derived organocatalysts

With optimal reaction conditions established, a range of benzyl substituted catalysts were synthesised (Scheme 5.4) in attempt to increase the enantioselectivities. A range of benzyl bromides/chlorides were selected and benzylation of the C9-hydroxy of quinidine appeared to proceed smoothly in all cases, however attempted demethylation of the crude benzylated intermediates with BBr₃ was unsuccessful. In most cases cleavage of the benzyl groups occurred faster than the demethylation.
(QD-258, QD-259, QD-262, QD-263). In some cases (QD-260, QD-261) a very small amount of product was obtained following mass-guided HPLC purification.

Scheme 5.4: Original synthetic approach to benzyl-substituted quinidine-derived catalysts QD-258 – QD-263.

Additional examples were synthesised following the above procedure with thiolate demethylation to give trifluoromethyl derivatives QD-265 and QD-267 (Scheme 5.5). For the halogenated example QD-269, the thiolate demethylation was also unsuccessful. A range of reported demethylation conditions including treatment with L-Selectride® in refluxing THF\textsuperscript{112} were tested with intermediate 268 however none of the desired catalyst could be isolated in any case. This was true for all halogenated benzyl substituents tested, including bromo-, chloro- and fluorobenzenes.
In a further attempt to synthesise halogenated benzyl catalysts an alternative protecting group for the phenolic hydroxyl group was investigated. Accordingly, quinidine 135 was demethylated and protected as the triisopropylsilyl ether 270.\textsuperscript{111(a)} Benzylolation with o-bromobenzylbromide and treatment of the crude reaction mixture with TBAF did not give the desired benzylated catalyst, but resulted in a mixture of QD-271 and doubly benzylated QD-272 (Scheme 5.6).

**Scheme 5.5:** Alternative demethylation for the synthesis of trifluoromethylated quinidine derived catalysts QD-265 and QD-267 and further attempted synthesis of brominated quinidine derived catalyst QD-269.

**Scheme 5.6:** Synthesis of bromobenzyl quinidine-derived catalysts QD-271, QD-272.
The benzyl substituted catalysts were screened in the oxidative coupling step under standard conditions (Table 5.5). The bromobenzene substituted catalyst QD-271 afforded the arylated product in a moderate enantiomeric excess, with the opposite sense of stereocontrol compared to the C9-benzylated analogues (entry 5). The doubly benzylated catalyst QD-272 resulted in a poor enantiomeric excess (entry 6).

![Chemical structure](image)

Table 5.5: Screen of novel benzyl-substituted organocatalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (loading)</th>
<th>Product</th>
<th>Conc./M</th>
<th>% ee</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>QD-260 (10 mol %)</td>
<td>(+)-223</td>
<td>0.1</td>
<td>43</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>QD-261 (10 mol %)</td>
<td>(+)-223</td>
<td>0.1</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>QD-267 (10 mol %)</td>
<td>(+)-223</td>
<td>0.1</td>
<td>43</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>QD-265 (10 mol %)</td>
<td>(+)-223</td>
<td>0.1</td>
<td>64</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>QD-271 (10 mol %)</td>
<td>(-)-223</td>
<td>0.1</td>
<td>44</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>QD-272 (10 mol %)</td>
<td>(+)-223</td>
<td>0.1</td>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td>QD-265 (20 mol %)</td>
<td>(+)-223</td>
<td>0.0125</td>
<td>73</td>
<td>54</td>
</tr>
<tr>
<td>8</td>
<td>QD-265 (20 mol %)</td>
<td>(+)-223</td>
<td>0.025</td>
<td>72</td>
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<td>9</td>
<td>QD-265 (20 mol %)</td>
<td>(+)-208</td>
<td>0.025</td>
<td>70</td>
<td>57</td>
</tr>
<tr>
<td>10</td>
<td>Q-265 (20 mol %)</td>
<td>(-)-208</td>
<td>0.025</td>
<td>70</td>
<td>55</td>
</tr>
</tbody>
</table>

Pleasingly catalyst QD-265 afforded the arylated product in 64% ee, a significant improvement on the unsubstituted benzyl catalyst QD-71 (entry 4). This catalyst was then tested at increased dilution with increased catalyst loading. Running the reaction at 0.025 M with 20 mol % catalyst gave the arylated product in 57% yield and 70% ee (entry 9). Further increases in dilution (entry 7) or catalyst loading (entry 8) did not improve the enantiomeric excess of the product sufficiently to justify the increased consumption of solvent/catalyst. It was hoped that this would be sufficient for obtaining enantiomerically pure alkaloid following recrystallisation at the enone stage (known to be highly crystalline as a racemate).
Ethyl ester pro-nucleophile 236 was also screened with the optimal catalyst QD-265, however the enantiomeric excess of the arylated product was significantly decreased compared to methyl ester analogue (Scheme 5.7).

Since the absolute stereochemistry of the major enantiomer is unknown, and difficult to predict, the pseudo enantiomer of catalyst QD-265 was prepared from quinine 136 (Scheme 5.8). When catalyst Q-265 was employed in the oxidative coupling, the opposite enantiomer of the arylated product (-)-208 was obtained in 70% ee (Table 5.5, entry 10).

5.6 Enantioselective total synthesis

In order to synthesise enantiomerically pure alkaloid, the catalyst synthesis was repeated on a 10 mmol scale to give 3.8 g of catalyst. The oxidative coupling was then repeated on a 10 mmol scale to provide 2.2 g of arylated product (+)-208 in 70% ee with the methylene acetal protecting group in place (Scheme 5.9). Reduction of the arylated product with Super-hydride® gave aminol (+)-209 as a 1:1 mixture of diastereomers with no loss of stereochemical integrity. Acylation and BF₃.OEt₂ mediated reaction with (isopropenylxy)trimethylsilane gave keto ester (-)-210 in 92 % yield (over 2 steps) as a 3:1 mixture of diastereomers in 69% ee (relative stereochemistry of the major diastereomer is unknown).
Scheme 5.9: Attempted enantioselective total synthesis, halted due to reduction in enantiomeric excess of (-)-212.

The Dieckmann-type cyclisation was then repeated in identical fashion to the racemic synthesis; reacting the crude reaction mixture with TiCl₄ in MeOH to give the methyl enol ether (-)-212 in 54% yield but with a significantly compromised enantiomeric excess. The enol ether was obtained in 24% ee. This points to a fast racemisation process probably through retro-Michael, Michael addition (Scheme 5.10); although it is interesting that the product is not completely racemised in this process. This rapid epimerisation process could also explain the formation of a single diastereomer from the Dieckmann-type cyclisation.

Scheme 5.10: Possible racemisation mechanism during Dieckmann-type cyclisation

To investigate the partial racemisation during the Dieckmann-type cyclisation, the reaction was repeated, removing an aliquot after 1, 5, 10 and 20 min and quenching each with 1 M HCl immediately. After methyl enol ether formation of each aliquot, HPLC analysis of the product (-)-212 showed the enantiomeric excess to be 26%
±1% in each case (sufficient product could not be obtained after 1 min for analysis). Since the enantiomeric excess of the product does not change with time, this implies that the epimerisation process occurs before cyclisation. To investigate the rate of epimerisation of the starting material (−)-210, the reaction was repeated and quenched after 1 min then purified to recover the starting material. HPLC analysis showed a 1.7:1 dr and enantiomeric excess of 26% for the major diastereomer and 21% for the minor. This supports rapid epimerisation of the starting material. Reducing the temperature of the Dieckmann-type cyclisation did not prevent racemisation. Changing the reaction solvent to toluene gave no product and did not prevent racemisation of the starting material (although this was slower than in THF).

This rapid racemisation of the keto-ester 210 under the Dieckmann-type cyclisation reaction conditions prevented the enantioselective total synthesis of powelline and buphanidrine being complete via this route. To obtain optically pure alkaloid, alternative conditions for the cyclisation step, or alterations to the route would be required in future studies.

6 Summary

In summary, a novel oxidative coupling methodology for the synthesis of arylated quaternary stereocentres has been developed and applied to the synthesis of 2 amaryllidaceae alkaloids.113-115 Proof-of-principle studies with stable 1,2-naphthoquinone established the ability of ortho-quinones to act as Michael acceptors towards carbon-centred pro-nucleophiles with organocatalytic base. In situ formation of reactive and unstable ortho-benzoquinones through oxidation of the parent catechols allows extension of the methodology to a wide range of quinone electrophiles. The scope of the method is also broad with respect to the pro-nucleophile, it is high yielding and provides remarkably simple access to a challenging motif. Replacement of ps-BEMP with cinchona alkaloid derived organocatalyst allowed formation of the arylated adducts in up to 81% ee. Catechol derivatives covalently bonded to all-carbon quaternary stereocentres are prevalent in nature, and the oxidative coupling methodology was successfully applied to the synthesis of 2 amaryllidaceae alkaloids (±)-powelline and (±)-buphanidrine. In studies towards an enantioselective synthesis of the target alkaloids, screening
known and novel organocatalysts in the oxidative coupling step afforded the arylated product in 70% ee. Unfortunately during the Dieckmann-type cyclisation rapid epimerisation of the quaternary carbon centre reduced the enantiomeric excess to 24%. Alternative conditions or an alternative route will be required to access optically pure alkaloid utilising the oxidative coupling methodology.

7 Experimental

7.1 General Experimental

7.1.1 General Techniques
Reactions were conducted under an air atmosphere with no effort to exclude moisture unless otherwise stated. For all reactions conducted under anhydrous conditions glassware was dried in an oven at 100 °C and cooled under a nitrogen atmosphere.

7.1.2 Solvents
Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. Solvents were obtained from commercial suppliers and used as supplied. Anhydrous solvents were either purchased from commercial suppliers or purified according to standard procedures. Petroleum ether refers to distilled light petroleum of fraction 40–65 °C.

7.1.3 Chromatography
Flash column chromatography was carried out using Merck Kieselgel 60 silica gel (200–400 mesh) and commercial solvents. Thin layer chromatography (TLC) was performed on aluminium plates pre-coated with Merck Kieselgel 60 F254 and visualised by ultra-violet radiation or by staining with aqueous basic potassium permanganate as appropriate. Enantiomeric excesses were determined using high performance liquid chromatography (HPLC) performed on a Hewlett-Packard Series 1050 series system and an Agilent Technologies 1200 series machine (column and solvent conditions are given with the compound).
7.1.4 Spectroscopy

All $^1$H and $^{13}$C NMR spectra were recorded using a Bruker AVII 500 MHz, Bruker DPX 400, DPX 500, Bruker DRX 500 MHz, and Varian 300 MHz spectrometers. Chemical shifts ($\delta$) are given in ppm downfield of tetramethylsilane relative to the residual protiosolvent, and coupling constants (J) are given in Hertz (Hz). The $^1$H NMR spectra are reported as follows: $\delta$/ppm [number of protons, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), coupling constants J/Hz (where appropriate) and assignment]. DEPT135, two-dimensional (COSY, HSQC, HMQC, HMBC) and NOE/NOESY NMR spectroscopy were used where appropriate to assist the assignment of signals in the $^1$H and $^{13}$C NMR spectra. Low resolution mass spectrometry was recorded on a Micromass Trio 2000 quadrupole (EI/Cl), a Micromass Platform II spectrometer, and a Micromass LCT premier (electrospray). High resolution mass spectra (accurate mass) were recorded on a Thermo Finnigan Mat95XP mass spectrometer and a Bruker MicroTof spectrometer. Infrared spectra were recorded on a Perkin Elmer Spectrum RX1 FTIR and a Bruker Tensor FT-IR spectrometer (solid state or thin film deposited onto a sodium chloride plate), only selected maximum absorbances are reported. Melting points were recorded using a Gallenkamp and a Leica Galen II melting point apparatus and are uncorrected. Optical rotations were recorded using an Optical Activity AA-1000 polarimeter and a Perkin-Elmer 241 polarimeter; $[\alpha]_D$ values are reported in $10^{-1}$degcm$^2$g$^{-1}$; concentration (c) is given in g/100 ml at 589 nm, T is given in ºC. (+) and (-) compound number prefixes indicate the sign of the optical rotation.

7.1.5 X-ray Crystallographic Data

7.2 Chapter 2 Experimental

7.2.1 Reagents

1,2-naphthoquinone was purchased from Fluka and used without further purification. All other commercially available reagents were used as received unless otherwise stated. Pro-nucleophiles 109, 125, 73, 128 – 132 and 134 are commercially available and were used as received, the following pro-nucleophiles were prepared according to literature procedures: tetrahydro-2-oxo-3-furancarboxylic acid methyl ester (122),116 2-(Methoxycarbonyl)indan-1-one (127),117 2-oxo-3-indolinecarboxylic acid methyl ester (126),118 tert-butyl 1-oxoindane-2-carboxylate (80),119 2-oxocyclohexanecarbonitrile (123) and 2-oxocyclopentanecarbonitrile (124).120 Catalysts 70, QD-147, QD-71, and QD-148 were prepared according to literature procedures.75-77,111

7.2.2 Synthesis and characterisation of methyl 1-(3,4-dioxo-3,4-dihydronaphthalen-1-yl)-2-oxocyclopentanecarboxylate, 120

![Chemical Structure](attachment:image.png)

To a stirred solution of methyl 2-oxocyclopentanecarboxylate 109 (284 mg, 4.00 mmol) and 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP) (59 μL, 0.20 mmol) in dichloromethane (20 mL) at room temperature was added, portion wise over 10 min, 1,2-naphthoquinone 85 (316 mg, 2.00 mmol). The resulting brown suspension was stirred at this temperature for 1 h then the solvent was removed by rotary evaporation. The residue was purified by column chromatography on silica gel, eluting with petroleum ether containing 40 – 50% diethyl ether to give 120 (250 mg, 42%) as a dark red solid. $^1$H NMR (500 MHz, CDCl$_3$) δH 8.20 (1H, dd, $J = 7.5$, 1.5 Hz, ArH), 7.63 (1H, dt, $J = 7.5$, 1.5 Hz, ArH), 7.54 (1H, t, $J = 7.5$ Hz, ArH), 7.25 (1H, d, $J = 7.5$ Hz, ArH), 6.23 (1H, s, ArH), 3.73 (3H, s, OCH$_3$), 3.14 (1H, ddd, $J = 13.5$, 9.0, 7.0, O(O)CH$_2$CH$_2$CH$_2$), 2.59 – 2.55 (2H, m, O(O)CH$_2$CH$_2$CH$_2$), 2.50 – 2.45 (1H, m, O(O)CH$_2$CH$_2$CH$_2$), 2.24 – 2.19 (1H, m, O(O)CH$_2$CH$_2$CH$_2$), 1.99 – 1.93 (1H, m,
7.2.3 Synthesis and characterisation of methyl 1-(3,4-dihydroxy-1-naphthyl)-2-oxocyclopentanecarboxylate, 119

To a solution of 121 (20 mg, 0.07 mmol) in CH₂Cl₂ (2 mL) was added a saturated aqueous solution of Na₂S₂O₄ (2 mL) and the resulting biphasic mixture stirred vigorously at room temperature for 3 hours by which time the orange quinone solution had turned pale yellow. The organic phase was separated and the aqueous extracted with CH₂Cl₂ (2 x 1 mL). The combined organic portions were dried over Na₂SO₄, filtered and evaporated to give 119 (20 mg, 99%) as a pale yellow oil.¹H NMR (500 MHz, d₆-DMSO) δH 9.29 (1H, s, OH), 8.99 (1H, s, OH), 8.09 (1H, d, J = 8.0 Hz, ArH), 7.43 (1H, d, J = 8.5 Hz, ArH), 7.38 (1H, t, J = 7.5 Hz, ArH), 7.27 (1H, ddd, J = 8.5, 7.0, 1.0 Hz, ArH), 6.85 (1H, s, ArH), 3.56 (3H, s, OCH₃), 2.96 (1H, ddd, J = 13.0, 10.0, 7.0 Hz, C(O)CH₂CH₂CH₂), 2.57 – 2.53 (2H, m, C(O)CH₂CH₂CH₂), 2.48 – 2.43 (1H, m, C(O)CH₂CH₂CH₂), 2.03 – 1.96 (1H, m, C(O)CH₂CH₂CH₂), 1.67 – 1.58 (1H, m, C(O)CH₂CH₂CH₂); ¹³C NMR (75 MHz, d₆-DMSO) δC 213.9 (C(O)), 171.7 (C(O)OCH₃), 138.3 (4º ArC), 137.2 (4º ArC), 127.0 (4º ArC), 125.4 (4º ArC), 125.0 (4º ArC), 124.3 (ArCH), 123.8 (ArCH), 123.0 (ArCH), 121.9 (ArCH), 118.2 (ArCH), 65.2 (4º C), 52.6 (C(O)OCH₃), 38.1 (C(O)CH₂CH₂CH₂), 35.8 (C(O)CH₂CH₂CH₂), 19.1 (C(O)CH₂CH₂CH₂); IR νmax/cm⁻¹ 3419, 2953, 1748, 1716, 1637, 1609, 1437, 1361, 1238, 762; MS (ES-)

C(O)CH₂CH₂CH₂; ¹³C NMR (75 MHz, CDCl₃) δC 210.7 (C(O)), 180.4 (C(O)OCH₃), 178.6 (quinone C(O)), 169.9 (quinone C(O)), 152.2 (4º ArC), 135.2 (ArCH), 133.5 (4º ArC), 132.0 (4º ArC), 130.9 (ArCH), 130.7 (ArCH), 127.0 (ArCH), 126.8 (ArCH), 65.5 (4º C), 53.7 (C(O)OCH₃), 38.3 (C(O)CH₂CH₂CH₂), 35.1 (C(O)CH₂CH₂), 19.5 (C(O)CH₂CH₂CH₂); IR νmax/cm⁻¹ 1753, 1724, 1667, 1605, 1587, 1450, 1261, 1238; MP 155 – 159 ºC; MS (ES+) m/z (relative intensity %) 321 (M + Na⁺, 100%), 619 (2M + Na⁺); HRMS (ES+): calcd. for C₁₇H₁₄O₅Na (M + Na⁺) 321.0733, found 321.0739.
m/z (relative intensity %) 299 (M − H+, 100%), 599 (2M − H+); HRMS (ES+): calcd. for C_{17}H_{15}O_{5} (M − H+) 299.0925, found 299.0930.

### 7.2.4 General Procedure A: Michael addition to 1,2-Naphthoquinone

![Diagram](image)

To a stirred solution of pro-nucleophile (2 equivalents) and 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP) (10 mol%) in tert-butyl methyl ether (5 mL/mmol) at -20 °C was added, portion wise over 10 min, 1,2-naphthoquinone 85 (1 equivalent). The resulting brown suspension was stirred at this temperature for 1 h then allowed to warm to room temperature and stirred for a further 1 h. The solvent was removed by rotary evaporation and the residue dissolved in pyridine (3 mL/mmol) and acetic anhydride (3.3 equivalents) was added. The mixture was stirred at room temperature overnight then diluted with Et_{2}O (6 mL/mmol) and washed with sat. aq. CuSO_{4} (4 x 6 mL/mmol). The aqueous washings were re-extracted with CH_{2}Cl_{2} (2 x 3 mL/mmol) and the combined organic portions washed with water (3 mL/mmol), brine (3 mL/mmol), dried over sodium sulfate, filtered and concentrated by rotary evaporation. The crude residue was purified by column chromatography on silica gel to give the arylated products 121a – h.

The optimal reaction conditions were identified following general procedure A, employing the bases and reaction temperatures detailed in Table 2.1, Chapter 2.2.

#### 7.2.4.1 Synthesis and characterization of methyl 1-(3,4-diacetoxy-1-naphthyl)-2-oxocyclopentanecarboxylate, 121a

![Diagram](image)

According to general procedure A, 1,2-naphthoquinone 85 (300 mg, 1.71 mmol) was reacted with methyl 2-oxocyclopentanecarboxylate 109 (501 mg, 3.42 mmol).
Purification by column chromatography on silica gel, eluting with petroleum ether containing 30% ethyl acetate, gave compound 121a (546 mg, 83%) as an off-white solid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 7.89 (1H, d, $J = 8.0$ Hz, Ar-H), 7.70 (1H, d, $J = 8.0$ Hz, Ar-H), 7.55 – 7.48 (2H, m, Ar-H), 7.02 (1H, s, Ar-H), 3.65 (3H, s, C(O)OCH$_3$), 3.23 (1H, ddd, $J = 13.0$, 9.5, 7.0 Hz, C(O)CH$_2$CH$_2$CH$_2$), 2.61 – 2.52 (3H, m, C(O)CH$_2$CH$_2$CH$_2$ and C(O)CH$_2$CH$_2$CH$_2$), 2.46 (3H, s, OC(O)CH$_3$), 2.31 (3H, s, OC(O)CH$_3$), 2.16 – 2.09 (1H, m, C(O)CH$_2$CH$_2$CH$_2$), 1.89 - 1.79 (1H, m, C(O)CH$_2$CH$_2$CH$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 213.6 (O), 171.6 (C(O)OCH$_3$), 168.2 (OC(O)CH$_3$), 167.9 (OC(O)CH$_3$), 137.9 (4º ArC), 136.7 (4º ArC), 133.7 (4º ArC), 129.9 (4º ArC), 128.9 (4º ArC), 128.9 (4º ArC), 126.7 (ArCH), 126.5 (ArCH), 124.5 (ArCH), 122.4 (ArCH), 121.3 (ArCH), 66.5, (4º C) 53.3 (C(O)OCH$_3$), 38.9 (C(O)CH$_2$CH$_2$CH$_2$), 36.4 (C(O)CH$_2$CH$_2$CH$_2$), 20.7 (OC(O)CH$_3$), 20.5 (OC(O)CH$_3$), 19.5 (C(O)CH$_2$CH$_2$CH$_2$); IR $\nu_{max}$/cm$^{-1}$ 1765, 1754, 1716, 1371, 1240, 1212, 1199, 770; MP 151-153 ºC (decomposed); MS (Cl+) m/z (relative intensity %) 402 (M + NH$_4^+$, 100%); HRMS (ES+): calcd. for C$_{21}$H$_{24}$O$_7$N$_1$ (M + NH$_4^+$) 402.1547, found 402.1548.

7.2.4.2 Synthesis and characterization of methyl 3-(3,4-diacetoxy-1-naphthyl)-2-oxotetrahydrofuran-3-carboxylate, 121b

According to general procedure A, 1,2-naphthoquinone 85 (300 mg, 1.71 mmol) was reacted with methyl 2-oxotetrahydrofuran-3-carboxylate 122 (493 mg, 3.42 mmol) to give compound 121b (488 mg, 74%) as cream solid after column chromatography on silica gel, eluting with petroleum ether containing 30% ethyl acetate; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 7.93 (1H, dd, $J = 8.0$, 1.5 Hz, Ar-H), 7.61-7.51 (3H, m, 3 of Ar-H), 7.31 (1H, s, Ar-H), 4.54 (1H, dt, $J = 9.0$, 3.0 Hz, OCH$_2$CH$_2$), 4.19 (1H, dt, $J = 9.0$, 6.5 Hz, OCH$_2$CH$_2$), 3.73 – 3.66 (4H, m, OCH$_2$CH$_2$ and C(O)OCH$_3$), 2.67 (1H, ddd, $J = 13.0$, 6.5, 3.0 Hz, OCH$_2$CH$_2$), 2.47 (3H, s, OC(O)CH$_3$), 2.33 (3H, s, OC(O)CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 173.3 (C(O)OCH$_3$), 170.1 (C(O)OCH$_3$), 168.1 (OC(O)CH$_3$), 167.9 (OC(O)CH$_3$),
138.1 (4° ArC), 137.5 (4° ArC), 131.1 (4° ArC), 129.3 (4° ArC), 129.0 (4° ArC), 127.1 (ArCH), 126.9 (ArCH), 123.5 (ArCH), 122.8 (ArCH), 122.0 (ArCH), 66.4 (OCH₂), 60.1 (4° C), 54.0 (C(O)OCH₃), 35.1 (OCH₂CH₂), 20.7 (OC(O)CH₃), 20.5 (OC(O)CH₃); IR νmax/cm⁻¹ 1768, 1763, 1758, 1737, 1609, 1369, 1204, 1168, 1156, 772; MP 141-143 ºC; MS (Cl⁺) m/z (relative intensity %) 404 (M + NH₄⁺, 100%); HRMS (ES⁺) calcd. for C₂₀H₂₂O₈N (M + NH₄⁺) 404.1340, found 404.1331.

7.2.4.3 Synthesis and characterization of 4-(1-cyano-2-oxocyclohexyl)naphthalene-1,2-diyldiacetate, 121c

According to general procedure A, 1,2-naphthoquinone 85 (90 mg, 0.57 mmol) was reacted with 2-oxocyclohexanecarbonitrile 123 (140 mg, 1.14 mmol) to give compound 121c (167 mg, 80%) as a colourless solid after column chromatography on silica gel, eluting with petroleum ether containing 30% ethyl acetate; ¹H NMR (500 MHz, CDCl₃) δH 7.96 – 7.93 (1H, m, ArH), 7.85 – 7.82 (1H, m, ArH), 7.59 – 7.54 (2H, m, ArH), 7.49 (1H, s, ArH), 2.94 (1H, ddd, J = 13.0, 10.0, 5.0 Hz, CH₂), 2.84 – 2.73 (2H, m, CH₂), 2.53 – 2.48 (4H, m, CH₂ and OC(O)CH₃), 2.36 (3H, s, OC(O)CH₃), 2.29 – 2.18 (3H, m, CH₂), 2.04 – 1.96 (1H, m, CH₂); ¹³C NMR (125 MHz, CDCl₃) δC 202.6 (C(O)), 168.2 (OC(O)CH₃), 167.7 (OC(O)CH₃), 138.2 (4° ArC), 137.9 (4° ArC), 129.7 (4° ArC), 128.7 (4° ArC), 128.4 (4° ArC), 127.1 (ArCH), 127.0 (ArCH), 124.9 (ArCH), 122.4 (ArCH), 121.8 (ArCH), 119.1 (CN), 54.8 (4° C), 39.1 (CH₂), 38.5 (CH₂), 28.7 (CH₂), 21.9 (CH₂), 20.8 (OC(O)CH₃), 20.5 (OC(O)CH₃); IR νmax/cm⁻¹ 1769, 1764, 1754, 1749, 1608, 1369, 1195, 1164, 1095, 1015, 765; MP 142-144 ºC; MS (ES⁺) m/z (relative intensity %) 383 (M + NH₄⁺, 15%), 388 (M + Na⁺, 100%); HRMS (ES⁺) calcd. for C₂₁H₁₉O₅NNa (M + Na⁺) 388.1155, found 388.1155.
7.2.4.4 Synthesis and characterization of 4-(1-cyano-2-oxocyclopentyl)naphthalene-1,2-diyl diacetate, 121d

According to general procedure A, 1,2-naphthoquinone 85 (158 mg, 1.0 mmol) was reacted with 2-oxocyclopentanecarbonitrile 124 (218 mg, 2.0 mmol) to give compound 121d (283 mg, 81%) as a pale cream solid after column chromatography on silica gel, eluting with petroleum ether containing 50 – 70% diethyl ether; \[^{1}H\text{NMR}\] (500 MHz, CDCl\textsubscript{3}) δ\textsubscript{H} 8.21 (1H, d, J = 7.5 Hz, ArH), 7.94 (1H, d, J = 7.5 Hz, ArH), 7.65 – 6.57 (2H, m, ArH), 7.25 (1H, s, ArH), 2.90 – 2.80 (2H, m, C(O)CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 2.66 (2H, t, J = 8.0 Hz, C(O)CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 2.45 (3H, s, OC(O)CH\textsubscript{3}), 2.32 (3H, s, OC(O)CH\textsubscript{3}), 2.26 – 2.18 (1H, m, C(O)CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}), 2.08 – 1.99 (1H, m, C(O)CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}); \[^{13}C\text{NMR}\] (125 MHz, CDCl\textsubscript{3}) δ\textsubscript{C} 207.7 (C(O)), 168.1 (OC(O)CH\textsubscript{3}), 167.7 (OC(O)CH\textsubscript{3}), 137.9 (4º ArC), 137.8 (4º ArC), 129.0 (4º ArC), 128.7 (4º ArC), 127.9 (4º ArC), 127.2 (ArCH), 127.0 (ArCH), 124.7 (ArCH), 122.5 (ArCH), 122.0 (ArCH), 118.5 (CN), 52.7 (4º C), 37.4 (CH\textsubscript{2}), 36.7 (CH\textsubscript{2}), 20.6 (OC(O)CH\textsubscript{3}), 20.3 (OC(O)CH\textsubscript{3}), 19.3 (CH\textsubscript{2}); IR \(\nu_{\text{max}}/\text{cm}^{-1}\) 1769, 1766, 1758, 1608, 1369, 1200, 1015, 1068; MP 70-71 °C (decomposed); MS (ES+) m/z (relative intensity %) 406 (M + Na\textsuperscript{+} + MeOH, 100%), 374 (M + Na\textsuperscript{+}, 85%); HRMS (ES+): calcd. for C\textsubscript{20}H\textsubscript{18}O\textsubscript{5}N (M+H\textsuperscript{+}) 352.1179, found 352.1178.

7.2.4.5 Synthesis and characterization of ethyl cyano(3,4-diacetoxy-1-naphthyl)phenylacetate, 121e

According to general procedure A, 1,2-naphthoquinone 85 (300 mg, 1.71 mmol) was reacted with ethyl phenylcyanoacetate 125 (647 mg, 3.42 mmol) to give compound 121e (565 mg, 77%) as a yellow solid after column chromatography on silica gel, eluting with petroleum ether containing 30% ethyl acetate; \[^{1}H\text{NMR}\] (500
MHz, CDCl₃) δH 7.98 (1H, d, J = 8.0 Hz, ArH), 7.94 (1H, d, J = 8.0 Hz, ArH), 7.64 – 7.63 (2H, m, ArH), 7.59 – 7.53 (2H, m, ArH), 7.51 – 7.47 (3H, m, ArH), 6.91 (1H, s, ArH), 4.43 – 4.31 (2H, m, OCH₂CH₃), 2.46 (3H, s, OCH₃), 2.26 (3H, s, OC(O)CH₃), 1.29 (3H, t, J = 7.0 Hz, OCH₂CH₃); 

δC 167.8 (C(O)O), 167.6 (C(O)O), 167.0 (C(O)O), 138.2 (4º ArC), 137.9 (4º ArC), 133.3 (4º ArC), 130.8 (4º ArC), 129.4 (ArCH), 129.4 (ArCH), 129.3 (4º ArC), 128.6 (4º ArC), 128.2 (ArCH), 127.1 (ArCH), 127.1 (ArCH), 124.4 (ArCH), 124.1 (ArCH), 122.4 (ArCH), 118.0 (CN), 64.0 (OCH₂), 57.6 (4º C), 20.6 (OC(O)CH₃), 20.4 (OC(O)CH₃), 13.7 (OCH₂CH₃); IR νmax/cm⁻¹ 1787, 1761, 1750, 1608, 1373, 1216, 1166, 1156, 895, 744, 734; MP 126-128 °C; MS (Cl⁺) m/z (relative intensity %) 449 (M + NH₄⁺, 100%); HRMS (ES+) calcd. for C₂₅H₂₅O₆N₂ (M + NH₄⁺) 449.1707, found 449.1698.

7.2.4.6 Synthesis and characterization of methyl 2-(3,4-diacetoxy-1-naphthyl)-1-oxoindane-2-carboxylate, 121f

![121f](image)

According to general procedure A, 1,2-naphthoquinone 85 (300 mg, 1.71 mmol) was reacted with methyl 1-oxoindane-2-carboxylate 127 (650 mg, 3.42 mmol) to give compound 121f (639 mg, 86%) as a yellow solid after column chromatography on silica gel, eluting with petroleum ether containing 30% ethyl acetate; 

δH 7.92 – 7.89 (2H, m, ArH), 7.76 – 7.74 (1H, m, ArH), 7.65 (1H, t, J = 7.5, ArH), 7.58 – 7.53 (2H, m, ArH), 7.45 – 7.42 (2H, m, ArH), 7.27 (1H, s, ArH), 4.69 (1H, d, J = 17.0 Hz, CH₂), 3.67 (3H, s, C(O)OCH₃), 3.49 (1H, d, J = 17.0 Hz, CH₂), 2.44 (3H, s, OCH₃), 2.28 (3H, s, OCH₃), 13C NMR (125 MHz, CDCl₃) δC 200.4 (C(O)), 171.2 (C(O)OCH₃), 168.1 (OC(O)CH₃), 168.0 (OC(O)CH₃), 153.1 (4º ArC), 138.1 (4º ArC), 136.8 (4º ArC), 136.3 (ArCH), 135.2 (4º ArC), 134.4 (4º ArC), 130.6 (4º ArC), 128.8 (4º ArC), 128.1 (ArCH), 126.8 (ArCH), 126.7 (ArCH), 126.5 (ArCH), 125.3 (ArCH), 124.1 (ArCH), 122.6 (ArCH), 121.4 (ArCH), 65.3 (4º C), 53.7 (C(O)OCH₃), 41.6 (CH₂), 20.7
(OC(O)CH₃), 20.5 (OC(O)CH₃); IR $\nu_{\text{max}}$/cm⁻¹ 1765, 1760, 1748, 1733, 1610, 1426, 1368, 1199, 1170, 763; MP 187-189 °C; MS (Cl⁺) m/z (relative intensity %) 450 (M + NH₄⁺, 100%); HRMS (ES⁺) calcd. for C₂₅H₂₄O₇N (M + NH₄⁺) 450.1547, found 450.1537.

7.2.4.7 Synthesis and characterization of methyl 3-(3,4-diacetoxy-1-naphthyl)-2-oxoindoline-3-carboxylate, 121g

According to general procedure A, 1,2-naphthoquinone 85 (47 mg, 0.30 mmol) was reacted with methyl 2-oxoindoline-3-carboxylate 126 (114 mg, 0.60 mmol) to give compound 121g (112 mg, 86%) as an off-white solid after column chromatography on silica gel eluting with diethyl ether; $^1$H NMR (500 MHz, d₆-DMSO) $\delta_{\text{H}}$ 11.0 (1H, s, NH), 8.17 – 8.15 (1H, m, ArH), 8.01 – 7.98 (1H, m, ArH), 7.68 – 7.64 (2H, m, ArH), 7.43 (1H, dt, $J = 7.5, 1.0$ Hz, ArH), 7.29 (1H, d, $J = 7.5$ Hz, ArH), 7.17 (1H, t, $J = 7.5$ Hz, ArH), 7.04 (1H, d, $J = 7.5$ Hz, ArH), 6.85 (1H, s, ArH), 3.69 (3H, s, C(O)OCH₃), 2.48 (3H, s, OC(O)CH₃), 2.25 (3H, s, OC(O)CH₃); $^{13}$C NMR (75 MHz, d₆-DMSO) $\delta$C 172.4 (C(O)), 169.8 (C(O)), 168.3 (C(O)), 168.2 (C(O)), 142.5 (ArC), 137.8 (ArC), 137.1 (ArC), 131.9 (ArC), 130.4 (ArC), 130.0 (ArC), 128.2 (ArC), 127.1 (ArC), 126.9 (ArC), 126.7 (ArC), 126.1 (ArC), 125.6 (ArC), 122.7 (ArC), 121.8 (ArC), 121.7 (ArC), 110.5 (ArC), 63.5 (OC(O)CH₃), 53.5 (OC(O)CH₃), 20.3 (OC(O)CH₃), 20.2 (OC(O)CH₃); IR $\nu_{\text{max}}$/cm⁻¹ 3361, 1769, 1755, 1738, 1729, 1474, 1370, 1212, 1193, 1165, 767, 750; MP 242 – 246 °C (decomposed); MS (Cl⁺) m/z (relative intensity %) 451 (M + NH₄⁺, 100%); HRMS (ES⁺) calcd. for C₂₅H₂₅O₇N₂ (M + NH₄⁺) 451.1500, found 451.1495.
7.2.4.8 Synthesis and characterization of ethyl 1-(3,4-diacetoxy-1-naphthyl)-2-oxocyclopentanecarboxylate, 121h

According to general procedure A, 1,2-naphthoquinone 85 (270 mg, 1.71 mmol) was reacted with ethyl 2-oxocyclopentanecarboxylate 73 (534 mg, 3.42 mmol) to give compound 121h (444 mg, 65%) as an pale brown solid after column chromatography on silica gel eluting with petroleum ether containing 30% ethyl acetate; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 7.89 (1H, dd, $J = 8.0$, 1.0 Hz, ArH), 7.73 (1H, d, $J = 8.5$ Hz, ArH), 7.54 – 7.46 (2H, m, ArH), 7.03 (1H, s, ArH), 4.15 (2H, q, $J = 7.0$ Hz, OCH$_2$CH$_3$), 3.21 (1H, ddd, $J = 13.0$, 9.5, 7.0 Hz, C(O)CH$_2$CH$_2$CH$_2$), 2.60 – 2.52 (3H, m, C(O)CH$_2$CH$_2$CH$_2$ and C(O)CH$_2$CH$_2$CH$_2$), 2.45 (3H, s, OC(O)CH$_3$), 2.31 (3H, s, OC(O)CH$_3$), 2.15 – 2.09 (1H, m, C(O)CH$_2$CH$_2$CH$_2$), 1.89 – 1.80 (1H, m, C(O)CH$_2$CH$_2$CH$_2$), 1.07 (3H, t, $J = 7.0$ Hz, OCH$_2$CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C 213.6 (C(O)), 171.0 (C(O)OCH$_3$), 168.2 (OC(O)CH$_3$), 167.9 (OC(O)CH$_3$), 137.8 (4º ArC), 136.6 (4º ArC), 133.9 (4º ArC), 129.9 (4º ArC), 128.8 (4º ArC), 126.7 (ArCH), 126.3 (ArCH), 124.8 (ArCH), 122.3 (ArCH), 121.3 (ArCH), 65.6 (4º C), 62.2 (OCH$_2$CH$_3$), 38.9 (C(O)CH$_2$CH$_2$CH$_2$), 36.4 (C(O)CH$_2$CH$_2$CH$_2$), 20.8 (O(CO)CH$_3$), 20.5 (OC(O)CH$_3$), 19.5 (C(O)CH$_2$CH$_2$CH$_2$), 13.8 (OCH$_2$CH$_3$); IR $\nu_{max}$/cm$^{-1}$ 1774, 1736, 1718, 1609, 1514, 1462, 1370, 1206, 1162, 769; MP 156 – 157 ºC; MS (Cl+) m/z (relative intensity %) 416 (M + NH$_4$$^+$, 100%); HRMS (ES+): calcd. for C$_{22}$H$_{26}$O$_7$N$_1$ (M + NH$_4$$^+$) 416.1704, found 416.1708.
7.2.5 Enantioselective Michael addition to 1,2-naphthoquinone.

7.2.5.1 Synthesis and characterisation of tert-butyl (2R)-2-(3,4-diaceotoy-1-naphthyl)-1-oxindane-2-carboxylate, (+)-156

According to general procedure A replacing BEMP with catalyst QD-148 (10 mol %), 1,2-naphthoquinone 85 (16 mg, 0.10 mmol) was reacted with tert-butyl 1-oxindane-2-carboxylate 80 (46 mg, 0.20 mmol) to give compound (+)-156 (26 mg, 55%) as an off-white solid after column chromatography on silica gel eluting with petroleum ether containing 30 – 40% diethyl ether in 70% ee determined by HPLC analysis [Chiralpaks AD, hexane/iso-propanol, 4:1, 1 mL.min⁻¹, λ = 230 nm, t (minor) = 7.26 min, t (major) = 11.19 min] by comparison to a racemic sample prepared according to general procedure A; \([\alpha]_D^{22} = + 123.7 \, (c \, 0.8, \, CHCl_3)\);

**1H NMR** (500 MHz, CDCl₃) δH 7.92 – 7.89 (2H, m, ArH), 7.84 – 7.82 (1H, m, ArH), 7.64 (1H, t, J = 7.0 Hz, ArH), 7.57 – 7.53 (2H, m, ArH), 7.44 – 7.42 (2H, m, ArH), 7.24 (1H, s, ArH), 4.62 (1H, d, J = 17.0 Hz, CH₂), 3.48 (1H, d, J = 17.0 Hz, CH₂), 2.44 (3H, s, OC(O)C₃H₃), 2.28 (3H, s, OC(O)C₃H₃), 1.28 (9H, s, C(C₃H₃)₃);

**13C NMR** (75 MHz, CDCl₃) δC 200.9 (C(O)), 169.2 (C(O)OC(CH₃)₃), 168.1 (OC(O)CH₃), 168.0 (OC(O)CH₃), 153.1 (4º ArC), 138.1 (4º ArC), 136.5 (4º ArC), 136.0 (4º ArC), 136.0 (4º ArC), 134.7 (4º ArC), 134.7 (4º ArC), 128.7 (4º ArC), 127.9 (ArCH), 126.5 (ArCH), 126.4 (ArCH), 126.3 (ArCH), 125.1 (ArCH), 124.7 (ArCH), 122.4 (ArCH), 121.2 (ArCH), 82.8 (C(CH₃)₃), 66.2 (4º C), 41.4 (CH₂), 27.4 (C(CH₃)₃), 20.7 (OC(O)CH₃), 20.4 (OC(O)CH₃); **IR** νmax/cm⁻¹ 1773, 1742, 1704, 1606, 1467, 1368, 1205, 1149, 748; **MP** 60 – 64 °C (69 – 73 °C for racemate); **MS** (ES+) m/z (relative intensity %) 576 (M + NEt₃ + H⁺, 100%), 497 (M + Na, 90%), 971 (2M + H⁺, 80%); **HRMS** (ES+): calcd. for C₂₈H₃₀O₇N₁ (M + NH₄⁺) 492.2017, found 492.2013.
Similarly replacing ps-BEMP with catalysts 70, QD-71 and QD-147 gave arylated adduct (+)-156 in the yields and enantioselectivities shown in Table 7.1 (below).

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<th>% Yield</th>
<th>t (minor) (min)</th>
<th>t (major) /min</th>
<th>% ee</th>
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<td>7.42</td>
<td>11.61</td>
<td>26</td>
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<tr>
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<td>53</td>
<td>7.45</td>
<td>11.76</td>
<td>40</td>
</tr>
</tbody>
</table>

Table 7.1: Screen of organocatalysts in the Michael addition of 80 to 1,2-naphthoquinone 85.

7.3 Chapter 3 Experimental

7.3.1 Reagents

Catechol, 3-Methoxy-, and 3-bromocatechol are commercially available and were used as received. Pro-nucleophiles (Chart 7.1) methyl 6-methoxy-1-oxoindane-2-carboxylate 77j,\textsuperscript{121} tert-butyl 5-bromo-1-oxoindane-2-carboxylate 77k,\textsuperscript{122} 2-oxo-N-propylcyclopentanecarboxamide 77o,\textsuperscript{123} 2-oxocycloheptanecarbonitrile 77n,\textsuperscript{120} tert-Butyl 2-oxocyclopentanecarboxylate 77t,\textsuperscript{89} 2,2,2-trifluoro-1-(trifluoromethyl)ethyl 2-oxocyclopentanecarboxylate 77u,\textsuperscript{81(b)} were synthesised according to literature procedures. Pro-nucleophile 2-acetylcyclopentanone (77l) is commercially available.

![Chart 7.1: Pro-nucleophiles synthesised according to literature procedures](image)

Amberlite® IRA-900 was purchased from Aldrich. Polymer bound 2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (polymer supported-BEMP or ps-BEMP) was purchased from Fluka and contains 2.2 mmol/g of base.
7.3.2 General procedure B for the synthesis of 3-substituted catechols

To a stirred mixture of 2-substituted phenol 157 – 159 (1 equiv), MgCl₂ (2 equiv) and para-formaldehyde (3 equiv) in anhydrous THF (1.5 mL/mmol) under N₂ was added triethylamine (2 equiv) dropwise. The reaction mixture was heated to reflux for 3 h then allowed to cool to room temperature before adding NaOH (0.1 M, 60 mL) dropwise. Once all components had dissolved H₂O₂ (30%, 0.4 mL/mmol) was added dropwise and the reaction mixture stirred vigorously for 2 h before adding a further portion of H₂O₂ (30% 0.4 mL/mmol). The reaction mixture was stirred at room temperature for 12 h then acidified with HCl (aq) (1 M, 2.5 mL/mmol) and extracted with CH₂Cl₂ (3 x 1 mL/mmol). The organic extracts were combined, dried over sodium sulfate and evaporated. The dark brown residue was purified by column chromatography to afford the corresponding 3-substituted catechol 160 – 162.

7.3.2.1 Synthesis of 3-tert-butylbenzene-1,2-diol (3-tert-butylcatechol), 160

According to general procedure B, 2-tert-butylphenol 157 (6.01 g, 40.0 mmol) was formylated and oxidised to give, following column chromatography on silica gel eluting with CH₂Cl₂, 3-tert-butylcatechol 160 as a brown oil (2.13 g, 32%); NMR (500 MHz, CD₃OD) δH 6.70 (1H, d, J = 8.0 Hz, ArH), 6.65 (1H, d, J = 8.0 Hz, ArH), 6.55 (1H, t, J = 8.0 Hz, ArH), 1.38 (9H, s, C(CH₃)₃); MS (ES-) m/z (relative intensity %) 165 (M – H⁺, 100%). Data is consistent with literature values.

7.3.2.2 Synthesis of 3-ethylbenzene-1,2-diol (3-ethylcatechol), 161

According to general procedure B, 2-ethylphenol 158 (4.88 g, 40.0 mmol) was formylated and oxidised to give 3-ethylcatechol 161 (1.99 g, 36% yield) as a yellow oil following column chromatography on silica gel, eluting with CH₂Cl₂; NMR (500 MHz, CDCl₃) δH 6.67 – 6.63 (3H, m, ArH), 5.09 (2H, br. s, OH), 2.57 (2H, q, J = 7.5 Hz, CH₂CH₃), 1.16 (3H, t, J = 7.5 Hz, CH₂CH₃); MS (Cl-) m/z (relative intensity %) 137 (M – H⁺, 100%). Data consistent with literature values.
7.3.2.3 Synthesis of biphenyl-2,3-diol (3-phenylcatechol), 162

According to general procedure B, 1,1’-biphenyl-2-ol 159 (3.40 g, 20.0 mmol) was formylated and oxidised to give 3-phenylcatechol 162 (2.11 g, 57% yield) as a yellow solid following column chromatography on silica gel, eluting with CH₂Cl₂; NMR (500 MHz, CDCl₃) δH 7.60 (2H, d, J = 8.0 Hz, ArH), 7.39 (2H, t, J = 8.0 Hz, ArH), 7.31 – 7.28 (1H, m, ArH), 6.86 (1H, d, J = 7.5 Hz, ArH), 6.82 (1H, d, J = 7.5 Hz, ArH), 6.78 (1H, t, J = 7.5 Hz, ArH); MS (ES-) m/z (relative intensity %) 185 (M – H⁺, 100%). Data is consistent with literature values.

7.3.3 Attempted synthesis of 3-substituted ortho-benzoquinones

Several oxidising agents have been reported for the synthesis of ortho-quinones from catechols. Attempted syntheses of o-benzoquinone and 3-substituted-o-benzoquinones following literature procedures led to complex mixtures in all cases. For example sodium periodate has been reported for the synthesis of stable o-benzoquinones from catechols in quantitative yields. Applying the same procedure to 3-tert-butylcatechol resulted in a complex mixture:

NaIO₄ (139 mg, 0.65 mmol) was added to a vigorously stirred solution of 3-tert-butylcatechol 160 (100 mg, 0.65 mmol) in CH₂Cl₂ (3 mL) and water (1 mL). The biphasic mixture was stirred at room temperature for 30 min, after which TLC analysis showed complete conversion. The organic phase was separated and the aqueous extracted with CH₂Cl₂ (2 x 1 mL). The combined organic extracts were dried over MgSO₄, filtered and the solvent evaporated under a flow of N₂. NMR analysis of the resulting residue showed a complex mixture of products.

7.3.4 Preparation of polymer-supported periodate resin (ps-IO₄⁻)

Polymer-supported periodate was prepared from Amberlite® IRA-900 according to the method of Hodge. The periodate loading was determined through oxidation of an excess of 3,5-di-tert-butylcatechol 167 (known to give a stable quinone) and calculation of the ratio of catechol:quinone products and was found to vary between batches but is typically 4 – 6 mmol/g. For example:
Amberlite® IRA-900 resin (40 g) was stirred in a solution of NaIO₄⁻ (32 g) in H₂O (240 mL) at room temperature of 10 h. The solution was decanted from the resin and the resin stirred in a fresh solution of NaIO₄⁻ (32 g) in H₂O (240 mL) for a further 18 h. The resin was filtered, ground with a pestle and mortar and dried under vacuum.

3,5-di-tert-butylcatechol 167 (52 mg, 0.23 mmol) was dissolved in CDCl₃ (0.5 mL) and ps-IO₄⁻ (29 mg) was added. The reaction mixture was stirred vigorously at room temperature for 2 h then filtered, washing the resin with CDCl₃ (2 x 0.2 mL). The NMR spectrum of the filtrate was recorded and showed 70% oxidation of starting material, corresponding to a periodate loading of 5.7 mmol/g.

7.3.5 Procedure for determining the decomposition rate of 3-substituted quinones by ¹H NMR

To a stirred solution of 3-substituted catechol (160, 163) (0.2 mmol) in CDCl₃ (2 mL) at -20 ºC in a flask wrapped in tin foil was added polymer-supported periodate (ps-IO₄⁻) (0.4 mmol) and the resulting mixture stirred at this temperature for 20 min. The cold solution was rapidly filtered into an NMR tube and an internal standard (methyl-3,4,5-trimethoxy benzoate) (approx. 10 mg accurately weighed) was added and NMR spectra recorded immediately (assumed to be t = 0) and at various time intervals over 24 h. The distinctive o-quinone doublet at ca. 6 - 6.5 ppm was integrated with respect to the internal standard and the data plotted using Microcal Origin software. Smooth curves were fitted to the data points (except for stable 1,2-naphthoquinone where a linear plot was appropriate) and approximate half-lives calculated as 8 hours for 3-methoxy-o-benzoquinone 164 and 1 hour for 3-tert-butyl-o-benzoquinone 165. No decomposition of 1,2-naphthoquinone could be detected over the time period measured.
7.3.6 General procedure C: Michael addition to in-situ generated o-benzoquinones

To a stirred solution of substituted catechol 160 – 163 (1 equivalent), pronucleophile (1 or 2 equivalents) and ps-BEMP (10 mol %) in dichloromethane (10 mL/mmol) at -20 °C, in a flask wrapped in aluminium foil, was added ps-IO₄⁻ (2 equivalents). The resulting suspension was stirred at this temperature until TLC analysis showed complete consumption of starting materials. The reaction mixture was filtered to remove the polymer supported reagents, and the resin washed on the sinter with CH₂Cl₂ (10 mL/mmol). The typically deep red filtrate was stirred vigorously with saturated aqueous Na₂S₂O₄ (20 mL/mmol) for 10 min (the colour typically fades to pale yellow). The organic layer was separated and the aqueous extracted with CH₂Cl₂ (2 x 5 mL/mmol). The combined organic portions were dried over sodium sulfate, filtered and concentrated by rotary evaporation. The
residue was purified by column chromatography on silica gel to give arylated products 169a-q.

7.3.6.1 Synthesis and characterization of ethyl (3-tert-butyl-4,5-dihydroxyphenyl)(cyano)phenylacetate, 169a

According to general procedure C, 3-tert-butylcatechol 160 (166 mg, 1.00 mmol) was reacted with ethyl phenylcyanoacetate 125 (189 mg, 1.00 mmol) to give, after 30 min reaction time, compound 169a (302 mg, 85%) as a cream solid following column chromatography on silica gel eluting with petroleum ether containing 50-70% diethyl ether. $^1$H NMR (500 MHz, CDCl$_3$) $\delta_H$ 7.38 – 7.33 (5H, m, ArH), 6.86 (1H, d, $J = 2.5$ Hz, ArH), 6.82 (1H, d, $J = 2.5$ Hz, ArH), 6.09 (1H, s, OH), 5.89 (1H, s, OH), 4.33 (2H, dq, $J = 7.0$, 1.0 Hz, OCH$_2$CH$_3$), 1.36 (9H, s, C(CH$_3$)$_3$), 1.31 (3H, t, $J = 7.0$, OCH$_2$CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta_C$ 167.7 (C(O)OCH$_2$CH$_3$), 144.1 (4º ArC), 143.2 (4º ArC), 136.5 (4º ArC), 136.0 (4º ArC), 128.9 (ArCH), 128.8 (ArCH), 127.9 (ArCH), 124.9 (4º ArC), 118.9 (CN), 118.6 (ArCH), 112.4 (ArCH), 63.8 (OCH$_2$CH$_3$), 58.6 (4º C), 34.9 (C(CH$_3$)$_3$), 29.2 (C(CH$_3$)$_3$), 13.9 (OCH$_2$CH$_3$); IR $\nu_{\text{max}}$/cm$^{-1}$ 3366, 2964, 2257, 1744, 1594, 1433, 1300, 1233, 851, 744; MP 167-169 ºC; MS (Cl+) m/z (relative intensity %) 371 (M + NH$_4^+$, 100%), HRMS (ES+): calcd. for C$_{21}$H$_{27}$O$_4$N$_2$ (M + NH$_4^+$) 371.1965, found 371.1962.

7.3.6.2 Synthesis and characterization of methyl 1-(3-tert-butyl-4,5-dihydroxyphenyl)-2-oxocyclopentanecarboxylate, 169b

According to general procedure C, 3-tert-butylcatechol 160 (83 mg, 0.50 mmol) was reacted with methyl 2-oxocyclopentanecarboxylate 109 (142 mg, 1.00 mmol)
to give, after 4 h reaction time, compound 169b (119 mg, 78%) as a cream solid after column chromatography on silica gel, eluting with petroleum ether containing 50% diethyl ether; \[^1H\text{NMR}\] (500 MHz, CDCl\(_3\)) \(\delta_{H} 6.85 (1H, d, J = 2.0, \text{ArH}), 6.77 (1H, d, J = 2.0 \text{ Hz, ArH}), 6.39 (1H, br. s, OH), 5.77 (1H, br. s, OH), 3.72 (3H, s, OCH\(_3\)), 2.81 (1H, td, \(J = 13.0, 6.5 \text{ Hz, CH}_2\)), 2.56 (1H, td, \(J = 13.0, 6.5 \text{ Hz, CH}_2\)), 2.51 – 2.35 (2H, m, CH\(_2\)), 2.01 – 1.90 (2H, m, CH\(_2\)), 1.32 (9H, s, C(CH\(_3\))\(_3\)); \[^13C\text{NMR}\] (125 MHz, CDCl\(_3\)) \(\delta_{C} 214.0 (\text{C(O)}), 171.9 (\text{C(O)OCH}_3), 143.3 (4^\circ \text{ArC}), 143.0 (4^\circ \text{ArC}), 136.0 (4^\circ \text{ArC}), 125.3 (4^\circ \text{ArC}), 117.2 (\text{ArCH}), 112.6 (\text{ArCH}), 64.6 (4^\circ \text{C}), 53.1 (\text{OCH}_3), 37.8 (\text{C(O)CH}_2\text{CH}_2\text{CH}_2), 34.9 (\text{C(CH}_3)_3), 34.8 (\text{C(O)CH}_2\text{CH}_2\text{CH}_2), 29.4 (\text{C(CH}_3)_3), 19.3 (\text{C(O)CH}_2\text{CH}_2\text{CH}_2); \[^\text{IR}\] \(\nu_{\text{max/cm}^{-1}} 3261, 2952, 1744, 1715, 1424, 1384, 1253\); \[^\text{MP}\] 156-158 °C; \[^\text{MS}\] (Cl\(^+\) m/z (relative intensity %) 324 (M + NH\(_4^+\), 100%), 307 (M + H\(^+\), 20%), \[^\text{HRMS}\] (ES\(^+\)): calcd. for C\(_{17}\)H\(_{26}\)O\(_5\)N (M + NH\(_4^+\)) 324.1805, found 324.1805.

7.3.6.3 Synthesis and characterization of methyl 2-(3-tert-butyl-4,5-dihydroxyphenyl)-1-oxoindane-2-carboxylate, 169c

According to general procedure C, 3-tert-butylcatechol 160 (166 mg, 1.00 mmol) was reacted with methyl 1-oxoindane-2-carboxylate 127 (190 mg, 1.00 mmol) to give, after 3 h reaction time, compound 169c (299 mg, 84%) as a pale orange solid after column chromatography on silica gel, eluting with petroleum ether containing 50-70% diethyl ether; \[^1H\text{NMR}\] (500 MHz, CDCl\(_3\)) \(\delta_{H} 7.80 (1H, d, J = 7.5 \text{ Hz, ArH}), 7.65 (1H, dt, J = 7.5, 1.0 \text{ Hz, ArH}), 7.50 (1H, d, J = 7.5 \text{ Hz, ArH}), 7.40 (1H, t, J = 7.5 \text{ Hz, ArH}), 7.03 (1H, d, J = 2.0 \text{ Hz, ArH}), 6.95 (1H, br. s, OH), 6.77 (1H, d, J = 2.0 \text{ Hz, ArH}), 5.82 (1H, br. s, OH), 4.20 (1H, d, J = 17.5 \text{ Hz, CH}_2), 3.71 (3H, s, OCH\(_3\)), 3.61 (1H, d, J = 17.5 \text{ Hz, CH}_2), 1.37 (9H, s, C(CH\(_3\))\(_3\)); \[^13C\text{NMR}\] (125 MHz, CDCl\(_3\)) \(\delta_{C} 202.1 (\text{C(O)}), 171.5 (\text{C(O)OCH}_3), 152.6 (4^\circ \text{ArC}), 143.2 (4^\circ \text{ArC}), 143.1 (4^\circ \text{ArC}), 136.1 (4^\circ \text{ArC}), 136.0 (\text{ArCH}), 134.8 (4^\circ \text{ArC}), 128.1 (4^\circ \text{ArC}), 128.0 (\text{ArCH}), 126.2 (\text{ArCH}), 125.2 (\text{ArCH}), 117.5 (\text{ArCH}), 112.1 (\text{ArCH}), 65.1 (4^\circ \text{C}), 53.4 (\text{OCH}_3), 40.8 (\text{CH}_2), 34.8 (\text{C(CH}_3)_3), 29.3 (\text{C(CH}_3)_3); \[^\text{IR}\] \(\nu_{\text{max/cm}^{-1}} 3261, 2952, 1744, 1715, 1424, 1384, 1253; \[^\text{MS}\] (Cl\(^+\) m/z (relative intensity %) 324 (M + NH\(_4^+\), 100%), 307 (M + H\(^+\), 20%), \[^\text{HRMS}\] (ES\(^+\)): calcd. for C\(_{17}\)H\(_{26}\)O\(_5\)N (M + NH\(_4^+\)) 324.1805, found 324.1805.
According to general procedure C, 3-tert-butylcatechol 160 (83 mg, 0.50 mmol) was reacted with 2-oxocyclohexanecarbonitrile 123 (123 mg, 1.00 mmol) to give, after 4 h reaction time, compound 169d (84 mg, 58%) as a peach coloured solid after column chromatography on silica gel, eluting with petroleum ether containing 50-70% diethyl ether; $^1$H NMR (400 MHz, CDCl$_3$) $\delta_H$ 7.03 (1H, br. s, OH), 6.80 (1H, d, $J = 2.5$ Hz, ArH), 6.71 (1H, d, $J = 2.5$ Hz, ArH), 5.99 (1H, br. s, OH), 2.79 – 2.74 (1H, m, CH$_2$), 2.68 – 2.61 (1H, m, CH$_2$), 2.54 – 2.47 (1H, m, CH$_2$), 2.44 – 2.37 (1H, m, CH$_2$), 2.00 – 1.93 (4H, m, CH$_2$), 1.39 (9H, s, C(CH$_3$)$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta_C$ 203.6 (C(O)), 144.3 (4º ArC), 143.8 (4º ArC), 136.8 (4º ArC), 122.5 (4º ArC), 119.8 (CN), 116.9 (ArCH), 111.8 (ArCH), 55.7 (4º C), 38.6 (CH$_2$), 36.8 (CH$_2$), 34.9 (C(CH$_3$)$_3$), 29.3 (C(CH$_3$)$_3$), 27.3 (CH$_2$), 21.3 (CH$_2$); MP 89 – 91 ºC; IR $\nu_{\text{max}}$/cm$^{-1}$: 3435, 2955, 2870, 2250, 1719, 1644, 1430, 1362, 1304, 1252; MS (ES+) m/z (relative intensity %) 310 (M + Na$^+$, 100%), 342 (M + Na$^+$ + MeOH, 50%); HRMS: calcd. for C$_{17}$H$_{21}$N$_2$O$_3$Na (M + Na$^+$) 310.1414, found 310.1414.
7.3.6.5 Synthesis and characterization of methyl 2-(5,6-dihydroxybiphenyl-3-yl)-1-oxoindane-2-carboxylate, 169e

According to general procedure C, 3-phenylcatechol 162 (93 mg, 0.50 mmol) was reacted with methyl 1-oxoindane-2-carboxylate 127 (190 mg, 1.00 mmol) to give, after 5 h reaction time, compound 169e (145 mg, 77%) as a pale yellow solid after column chromatography on silica gel, eluting with petroleum ether containing 40-60% diethyl ether; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta_h 7.82 (1H, d, J = 7.5 \text{ Hz}, \text{ArH}), 7.64 (1H, dt, J = 7.5, 1.0 \text{ Hz}, \text{ArH}), 7.49 – 7.35 (7H, m, ArH), 7.06 (1H, d, J = 2.5 \text{ Hz}, \text{ArH}), 6.85 (1H, d, J = 2.5 \text{ Hz}, \text{ArH}), 4.19 (1H, d, J = 17.5 \text{ Hz}, \text{CH}_2), 3.74 (3H, s, \text{OCH}_3), 3.62 (1H, d, J = 17.5 \text{ Hz}, \text{CH}_2); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta_c 200.8 \text{ (C(O))}, 171.2 \text{ (C(O)OCH}_3), 152.2 \text{ (4º ArC)}, 144.1 \text{ (4º ArC)}, 140.1 \text{ (4º ArC)}, 136.8 \text{ (4º ArC)}, 135.8 \text{ (ArCH)}, 134.8 \text{ (4º ArC)}, 130.5 \text{ (4º ArC)}, 129.0 \text{ (ArCH)}, 128.9 \text{ (ArCH)}, 128.2 \text{ (4º ArC)}, 128.0 \text{ (ArCH)}, 127.8 \text{ (ArCH)}, 126.2 \text{ (ArCH)}, 125.2 \text{ (ArCH)}, 120.6 \text{ (ArCH)}, 113.9 \text{ (ArCH)}, 64.7 \text{ (4º C)}, 53.4 \text{ (OCH}_3), 40.7 \text{ (CH}_2); \text{ IR } \nu_{\text{max/cm}^{-1}} 3403, 2963, 1702, 1700, 1603, 1430, 1300, 1274, 1212, 1178, 799, 850, 754; \text{ MP 164-166 °C}; \text{ MS (Cl+) m/z (relative intensity %) 392 (M + NH}_4^+\text{, 100%), 375 (M + H}^+, 20%); \text{ HRMS (ES+): calcd. for C}_{23}\text{H}_{22}\text{O}_5\text{N (M + NH}_4^+) 392.1492, found 392.1491.\)

7.3.6.6 Synthesis and characterization of ethyl cyano(5,6-dihydroxybiphenyl-3-yl)phenylacetate, 169f

According to general procedure C, 3-phenylcatechol 162 (61 mg, 0.33 mmol) was reacted with ethyl phenylcyanoacetate 125 (125 mg, 0.66 mmol) to give, after 4 h reaction time, compound 169f (89 mg, 72%) as a colourless solid after column
chromatography on silica gel, eluting with petroleum ether containing 40-60% diethyl ether; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta_H 7.47 - 7.38\) (10H, m, Ar\(H\)), 6.92 - 6.91 (2H, m, Ar\(H\)), 4.35 (2H, q, \(J = 7.0 \text{ Hz, OCH}_2\text{CH}_3\)), 1.25 (3H, t, \(J = 7.0 \text{ Hz, OCH}_2\text{CH}_3\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta_C 167.3\) (C(O)OCH\(_2\)CH\(_3\)), 144.3 (4º Ar\(C\)), 140.9 (4º Ar\(C\)), 136.1 (4º Ar\(C\)), 135.7 (4º Ar\(C\)), 129.2 (Ar\(CH\)), 128.9 (Ar\(CH\)), 128.4 (4º Ar\(C\)), 128.2 (Ar\(CH\)), 128.0 (Ar\(CH\)), 127.9 (Ar\(CH\)), 127.9 (4º Ar\(C\)), 121.3 (Ar\(CH\)), 118.8 (CN), 114.3 (Ar\(CH\)), 63.7 (OCH\(_2\)CH\(_3\)), 13.9 (OCH\(_2\)CH\(_3\)); IR \(\nu_{\text{max}}/\text{cm}^{-1}\) 3438, 3370, 2360, 2338, 1737, 1598, 1425, 1308, 1241, 1006, 852; MP 126-130 °C; MS (CI+) m/z (relative intensity %) 391 (M + NH\(_4^+\), 100%); HRMS (ES+): calcd. for C\(_{23}\)H\(_{23}\)O\(_4\)N\(_2\) (M + NH\(_4^+\)) 391.1652, found 391.1652.

7.3.6.7 Synthesis and characterization of methyl 2-(3-ethyl-4,5-dihydroxyphenyl)-1-oxoindane-2-carboxylate, 169g

![169g](image)

According to general procedure C, 3-ethylcatechol 161 (138 mg, 1.00 mmol) was reacted with methyl 1-oxoindane-2-carboxylate 127 (190 mg, 1.00 mmol) to give, after 6 h reaction time, compound 169g (234 mg, 72%) as an orange oil after column chromatography on silica gel, eluting with petroleum ether containing 50% diethyl ether; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta_H 7.79\) (1H, d, \(J = 7.5 \text{ Hz, ArH}\)), 7.63 (1H, dt, \(J = 7.5, 1.0 \text{ Hz, ArH}\)), 7.47 (1H, d, \(J = 7.5 \text{ Hz, ArH}\)), 7.36 (1H, t, \(J = 7.5 \text{ Hz, ArH}\)), 7.15 (1H, br. s, OH), 6.94 (1H, d, \(J = 2.5 \text{ Hz, ArH}\)), 6.65 (1H, d, \(J = 2.5 \text{ Hz, ArH}\)), 5.72 (1H, br. s, OH), 4.16 (1H, d, \(J = 17.5 \text{ Hz, CH}_2\)), 3.70 (3H, s, OCH\(_3\)), 3.59 (1H, d, \(J = 7.5 \text{ Hz, CH}_2\)), 2.60 (2H, q, \(J = 7.5 \text{ Hz, CH}_2\)), 1.17 (3H, t, \(J = 7.5 \text{ Hz, CH}_2\)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta_C 201.7\) (C(O)), 171.5 (C(O)OCH\(_3\)), 152.5 (4º Ar\(C\)), 143.1 (4º Ar\(C\)), 142.0 (4º Ar\(C\)), 135.9 (Ar\(CH\)), 134.7 (4º Ar\(C\)), 130.7 (4º Ar\(C\)), 129.2 (4º Ar\(C\)), 128.0 (Ar\(CH\)), 126.2 (Ar\(CH\)), 125.2 (Ar\(CH\)), 119.6 (Ar\(CH\)), 112.1 (Ar\(CH\)), 64.8 (4º C), 53.4 (C(O)OCH\(_3\)), 40.7 (CH\(_2\)), 23.1 (CH\(_2\)CH\(_3\)), 14.0 (CH\(_2\)CH\(_3\)); IR \(\nu_{\text{max}}/\text{cm}^{-1}\) 3415, 1700, 1696, 1603, 1430, 1300, 1274, 1212, 1178, 799; MS (CI+) m/z (relative intensity %) 344 (M + NH\(_4^+\), 100%); HRMS (ES+): calcd. for C\(_{23}\)H\(_{23}\)O\(_4\)N\(_2\) (M + NH\(_4^+\)) 391.1652, found 391.1652.
100%), 327 (M + H⁺, 50%); **HRMS (ES+):** calcd. for C₁₉H₁₉O₅ (M + H⁺) 327.1277, found 327.1230.

7.3.6.8 **Synthesis and characterization of methyl 1-(3,4-dihydroxy-5-methoxyphenyl)-2-oxocyclopentanecarboxylate, 169h**

![Structure 169h](image)

According to general procedure C, 3-methoxycatechol 163 (140 mg, 1.00 mmol) was reacted with methyl 2-oxocyclopentanecarboxylate 109 (142 mg, 1.00 mmol) to give, after 30 min reaction time, compound 169h (199 mg, 71%) as a pale brown solid after column chromatography on silica gel, eluting with petroleum ether containing 30 – 50% diethyl ether; **¹H NMR** (500 MHz, CDCl₃) δH 6.61 (1H, d, J = 2.0 Hz, ArH), 6.56 (1H, d, J = 2.0 Hz, ArH), 5.54 (2H, br. s, OH) 3.85 (3H, s, OCH₃), 3.70 (3H, s, OCH₃), 2.79 (1H, td, J = 13.5, 7.0 Hz, CH₂), 2.53 – 2.42 (2H, m, CH₂), 2.39 – 2.32 (1H, m, CH₂), 2.01 – 1.86 (2H, m, CH₂); **¹³C NMR** (125 MHz, CDCl₃) δC 212.3 (C(O)), 171.4 (C(O)OCH₃), 146.8 (4º ArC), 143.7 (4º ArC), 132.1 (4º ArC), 127.2 (4º ArC), 107.9 (ArCH), 102.9 (ArCH), 64.3 (4º C), 56.2 (OCH₃), 53.0 (OCH₃), 37.7 (C(O)CH₂CH₂CH₂), 34.9 (C(O)CH₂CH₂CH₂), 19.2 (C(O)CH₂CH₂CH₂); **IR** νmax/cm⁻¹ 3436, 2953, 1720, 1700, 1601, 1426, 1301, 1252; **MP** 114-116 ºC; **MS** (Cl⁺) m/z (relative intensity %) 298 (M + NH₄⁺, 100%), 281 (M + H⁺, 25%); **HRMS (ES+):** calcd. for C₁₄H₂₀O₆N (M + NH₄⁺) 298.1285, found 298.1283.

7.3.6.9 **Synthesis and characterization of methyl 2-(3,4-dihydroxy-5-methoxyphenyl)-1-oxoindane-2-carboxylate, 169i**

![Structure 169i](image)

According to general procedure C, 3-methoxycatechol 163 (140 mg, 1.00 mmol) was reacted with methyl 1-oxoindane-2-carboxylate 127 (190 mg, 1.00 mmol) to
give, after 2 h reaction time, compound 169i (289 mg, 88%) as a viscous orange oil after column chromatography on silica gel, eluting with diethyl ether; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 7.82 (1H, d, $J$ = 7.5 Hz, ArH), 7.64 (1H, t, $J$ = 7.5 Hz, ArH), 7.49 (1H, d, $J$ = 7.5 Hz, ArH), 7.41 (1H, t, $J$ = 7.5 Hz, ArH), 6.65 (1H, d, $J$ = 2.0 Hz, ArH), 6.59 (1H, d, $J$ = 2.0 Hz, ArH), 5.35 (1H, s, OH), 5.25 (1H, s, OH), 4.18 (1H, d, $J$ = 15.7 Hz, CH$_2$), 3.87 (3H, s, OCH$_3$), 3.74 (3H, s, OCH$_3$), 3.55 (1H, d, $J$ = 17.5 Hz, CH$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 200.2 (C(O)), 171.1 (C(O)OCH$_3$), 152.1 (4º ArC), 146.8 (4º ArC), 143.7 (4º ArC), 135.7 (ArCH), 134.9 (4º ArC), 131.9 (4º ArC), 130.1 (4º ArC), 128.0 (ArCH), 126.2 (ArCH), 125.1 (ArCH), 108.0 (ArCH), 102.7 (ArCH), 64.8 (4º C), 56.2 (OCH$_3$), 53.3 (OCH$_3$), 40.2 (CH$_2$); IR $\nu_{max}$/cm$^{-1}$ 3415, 2952, 1742, 1701, 1604, 1518, 1251, 1200, 1176, 1091, 754; MS (Cl+) m/z (relative intensity %) 346 (M + NH$_4^+$, 100%), 329 (M + H$^+$, 60%); HRMS (ES+): calcd. for C$_{18}$H$_{17}$O$_6$ (M + H$^+$) 329.1020, found 329.1016.

7.3.6.10 Synthesis and characterization of methyl 2-(3,4-dihydroxy-5-methoxyphenyl)-6-methoxy-1-oxoindane-2-carboxylate, 169j

According to general procedure C, 3-methoxycatechol 163 (54 mg, 0.39 mmol) was reacted with methyl 6-methoxy-1-oxoindane-2-carboxylate 77j (56 mg, 0.39 mmol) to give, after 2 h reaction time, compound 169j (117 mg, 84%) as a cream solid after filtering through a small plug of silica gel, eluting with diethyl ether; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 7.37 (1H, d, $J$ = 9.0 Hz, ArH), 7.24 – 7.22 (2H, m, ArH), 6.62 (1H, d, $J$ = 2.0 Hz, ArH), 6.58 (1H, d, $J$ = 2.0 Hz, ArH), 5.39 (1H, s, OH), 5.31 (1H, s, OH), 4.08 (1H, d, $J$ = 17.0 Hz, CH$_2$), 3.86 (3H, s, OCH$_3$), 3.84 (3H, s, OCH$_3$), 3.74 (3H, s, OCH$_3$), 3.46 (1H, d, $J$ = 17.0 Hz, CH$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 200.2 (C(O)), 171.1 (C(O)OCH$_3$), 159.8 (4º ArC), 146.8 (4º ArC), 145.0 (4º ArC), 143.7 (4º ArC), 136.0 (4º ArC), 131.9 (4º ArC), 130.1 (4º ArC), 126.9 (ArCH), 125.2 (ArCH), 108.0 (ArCH), 106.0 (ArCH), 102.7 (ArCH), 65.6 (4º C), 56.9 (OCH$_3$), 55.6 (OCH$_3$), 53.3 (OCH$_3$), 40.2 (CH$_2$); IR $\nu_{max}$/cm$^{-1}$ 3444, 3221, 1705, 1615, 1517, 1495, 1432, 1307, 1275, 1195, 1173, 1107, 815; MP 143-145 ºC;
MS (CI+) m/z (relative intensity %) 359 (M + H+, 100%); HRMS (EI+): calcd. for C_{19}H_{18}O_{7} (M+) 358.1047, found 358.1052.

7.3.6.11 Synthesis and characterization of tert-butyl 5-bromo-2-(3,4-dihydroxy-5-methoxyphenyl)-1-oxoindane-2-carboxylate, 169k

![Chemical Structure](image)

According to general procedure C, 3-methoxycatechol 163 (14 mg, 0.10 mmol) was reacted with methyl 5-bromo-2,3-dihydro-1-oxo-1H-indene-2-carboxylate 77k (31 mg, 0.10 mmol) to give, after 2 h reaction time, compound 169k (36 mg, 80 %) as a pale yellow oil after column chromatography on silica gel, eluting with petroleum ether containing 50-70% diethyl ether; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta_{H}\) 7.66 (1H, s, ArH), 7.65 (1H, d, \(J = 8.5\) Hz, ArH), 7.54 (1H, d, \(J = 8.5\) Hz, ArH), 6.68 (1H, d, \(J = 2.0\) Hz, ArH), 6.57 (1H, d, \(J = 2.0\) Hz, ArH), 5.37 (1H, s, OH), 5.28 (1H, s, OH), 4.04 (1H, d, \(J = 17.5\) Hz, CH\(_2\)), 3.87 (3H, s, OCH\(_3\)), 3.52 (1H, d, \(J = 17.5\) Hz, CH\(_2\)), 1.39 (9H, s, C(CH\(_3\))\(_3\)); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta_C\) 199.3 (C(O)), 169.0 (C(O)OC(CH\(_3\))\(_3\)), 153.5 (4\(^\circ\) ArC), 146.7 (4\(^\circ\) ArC), 143.6 (4\(^\circ\) ArC), 134.0 (4\(^\circ\) ArC), 131.9 (4\(^\circ\) ArC), 131.5 (ArCH), 130.7 (4\(^\circ\) ArC), 129.8 (4\(^\circ\) ArC), 129.4 (ArCH), 126.1 (ArCH), 108.0 (ArCH), 102.9 (ArCH), 82.7 (C(CH\(_3\))\(_3\)), 65.5 (4\(^\circ\) C), 56.2 (OCH\(_3\)), 40.0 (CH\(_2\)), 27.7 (C(CH\(_3\))\(_3\)); IR \(\nu_{max}/cm^{-1}\) 3422, 2976, 2930, 1735, 1716, 1596, 1521, 1459, 1368, 1314, 1255, 1151; MS (ES+) m/z (relative intensity %) 471 (M + Na\(^+\), 100%), 473 (M + Na\(^+\), 100%); HRMS (EI+): calcd. for C\(_{25}\)H\(_{25}\)O\(_6\)NBr (M+ NH\(_4^+\)) 466.0860, found 466.0863.
7.3.6.12 Synthesis and characterization of 2-acetyl-2-(3,4-dihydroxy-5-methoxyphenyl)cyclopentanone, 169l

According to general procedure C, 3-methoxycatechol 163 (140 mg, 1.00 mmol) was reacted with 2-acetylcyclopentanone 77l (126 mg, 1.00 mmol) to give, after 4 h reaction time, compound 169l (191 mg, 72%) as a viscous yellow oil after column chromatography on silica gel, eluting with petroleum ether containing 60-80% diethyl ether; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta_H\) 6.54 (1H, d, \(J = 2.0\) Hz, ArH), 6.43 (1H, d, \(J = 2.0\) Hz, ArH), 5.62 (2H, br. s, OH), 3.85 (3H, s, OCH\(_3\)), 2.86 (1H, td, \(J = 13.5, 7.0\) Hz, CH\(_2\)), 2.38 (2H, dt, \(J = 7.0, 3.5\) Hz, CH\(_2\)), 2.21 (1H, m, CH\(_2\)), 2.07 (3H, s, C(O)CH\(_3\)), 1.90-1.81 (2H, m, CH\(_2\)); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)) \(\delta_C\) 213.9 (C(O)), 204.2 (C(O)), 147.2 (4º ArC), 144.1 (4º ArC), 132.1 (4º ArC), 129.5 (4º ArC), 107.6 (ArCH), 102.0 (ArCH), 71.9 (4º C), 56.3 (OCH\(_3\)), 39.2 (C(O)CH\(_2\)CH\(_2\)CH\(_2\)), 34.2 (C(O)CH\(_2\)CH\(_2\)CH\(_2\)), 26.6 (C(O)CH\(_3\)), 19.0 (C(O)CH\(_2\)CH\(_2\)CH\(_2\)); IR \(\nu_{\text{max}}/\text{cm}^{-1}\) 3426, 1729, 1698, 1613, 1204, 1091; MS (Cl+) m/z (relative intensity %) 282 (M + NH\(_4^+\), 100%), 265 (M + H\(^+\), 20%); HRMS (ES+): calcd. for C\(_{14}\)H\(_{20}\)O\(_5\)N (M + NH\(_4^+\)) 282.1336, 282.1335.

7.3.6.13 Synthesis and characterization of ethyl cyano(3,4-dihydroxy-5-methoxyphenyl)phenylacetate, 169m

According to general procedure C, 3-methoxycatechol 163 (140 mg, 1.00 mmol) was reacted with ethyl phenylcyanoacetate 125 (189 mg, 1.00 mmol) to give, after 30 min reaction time, compound 169m (311 mg, 95%) as a brown oil after filtering through a small plug of silica gel, eluting with diethyl ether; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta_H\) 7.40 – 7.38 (5H, m, ArH), 6.62 (1H, d, \(J = 2.0\) Hz, ArH), 6.55 (1H, d, \(J = 2.0\) Hz, ArH), 5.52 (1H, s, OH), 5.39 (1H, s, OH), 4.34 (2H, q, \(J = 7.0\) Hz,
OCH<sub>2</sub>CH<sub>3</sub>), 3.82 (3H, s, OCH<sub>3</sub>), 1.32 (3H, t, J = 7.0 Hz, OCH<sub>2</sub>CH<sub>3</sub>); ¹³C NMR (125 MHz, CDCl<sub>3</sub>) δ<sub>C</sub> 167.2 (C(O)OCH<sub>2</sub>CH<sub>3</sub>), 147.0 (4º ArC), 143.8 (4º ArC), 135.7 (4º ArC), 132.8 (4º ArC), 128.9 (ArCH), 128.8 (ArCH), 127.9 (ArCH), 127.2 (4º ArC), 118.8 (CN), 109.2 (ArCH), 103.2 (ArCH), 63.7 (C(O)OCH<sub>2</sub>CH<sub>3</sub>), 58.5 (4º C), 56.2 (OCH<sub>3</sub>), 13.9 (C(O)OCH<sub>2</sub>CH<sub>3</sub>); IR υ<sub>max</sub>/cm⁻¹ 3431, 2895, 1747, 1615, 1517, 1452, 1305, 1223, 1096; MS (Cl+) m/z (relative intensity %) 345 (M + NH<sub>4</sub>⁺, 100%); HRMS (ES+): calcd. for C<sub>18</sub>H<sub>21</sub>O<sub>5</sub>N<sub>2</sub> (M + NH<sub>4</sub>⁺) 345.1445, found 345.1436.

7.3.6.14 Synthesis and characterization of 1-(3,4-dihydroxy-5-methoxyphenyl)-2-oxocycloheptanecarbonitrile, 169n

According to general procedure C, 3-methoxycatechol 163 (70 mg, 0.50 mmol) was reacted with 2-oxocycloheptanecarbonitrile 77n (69 mg, 0.50 mmol) to give, after 4 h reaction time, compound 169n (107 mg, 78%) as an off-white solid after filtering through a small plug of silica gel, eluting with diethyl ether; ¹H NMR (500 MHz, d<sub>6</sub>-DMSO) δ<sub>H</sub> 9.28 (1H, s, OH), 8.66 (1H, s, OH), 6.54 (2H, m, ArH), 3.78 (3H, s, OCH<sub>3</sub>), 2.87 – 2.81 (1H, m, CH<sub>2</sub>), 2.55 – 2.43 (2H, m, CH<sub>2</sub>), 2.32 – 2.28 (1H, m, CH<sub>2</sub>), 2.12 – 2.09 (1H, m, CH<sub>2</sub>), 1.99 – 1.95 (1H, m, CH<sub>2</sub>), 1.83 (1H, d, J = 14 Hz, CH<sub>2</sub>), 1.61 – 1.52 (1H, m, CH<sub>2</sub>), 1.40 – 1.28 (2H, m, CH<sub>2</sub>); ¹³C NMR (75 MHz, d<sub>6</sub>-DMSO) δ<sub>C</sub> 204.6 (C(O)), 148.7 (4º ArC), 146.1 (4º ArC), 134.8 (4º ArC), 124.2 (4º ArC), 120.9 (CN), 107.5 (ArCH), 101.7 (ArCH), 59.5 (4º C), 56.1 (OCH<sub>3</sub>), 38.9 (CH<sub>2</sub>), 33.0 (CH<sub>2</sub>), 28.7 (CH<sub>2</sub>), 26.6 (CH<sub>2</sub>), 25.0 (CH<sub>2</sub>); IR υ<sub>max</sub>/cm⁻¹ 3333, 2936, 1720, 1700, 1612, 1519, 1302, 1107; MP 155 – 158 ºC; MS (Cl+) m/z (relative intensity %) 293 (M + NH<sub>4</sub>⁺, 100%); HRMS (ES+): calcd. for C<sub>18</sub>H<sub>21</sub>O<sub>4</sub>N (M + NH<sub>4</sub>⁺) 293.1496, found 293.1496.
7.3.6.15 Synthesis and characterization of 1-(3,4-dihydroxy-5-methoxyphenyl)-2-oxo-N-propylcyclopentanecarboxamide, 169o

According to general procedure C, 3-methoxycatechol 163 (28 mg, 0.20 mmol) was reacted with 2-oxo-N-propylcyclopentanecarboxamide 77o (34 mg, 0.20 mmol) to give, after 6 h reaction time, compound 169o (48 mg, 78%) as a colourless oil after column chromatography on silica gel, eluting with petroleum ether containing 50-70% diethyl ether; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 6.61 (1H, d, $J = 1.0$ Hz ArH), 6.58 (1H, s, NH), 6.48 (1H, d, $J = 1.0$ Hz, ArH), 6.03 (1H, s, OH), 5.53 (1H, s, OH), 3.86 (3H, s, OCH$_3$), 3.17 (2H, q, $J = 7.5$ Hz, NCH$_2$CH$_2$CH$_3$), 2.88 (1H, ddd, $J = 13.5$, 8.5, 6.5 Hz, CH$_2$), 2.46 – 2.40 (3H, m, CH$_3$), 1.95 (1H qd, $J = 13.0$, 6.5 Hz, CH$_2$), 1.84 – 1.75 (1H, m, CH$_2$), 1.46 (2H, sextet, $J = 7.5$ Hz, NCH$_2$CH$_2$CH$_3$), 0.83 (3H, t, $J = 7.5$ Hz, NCH$_2$CH$_2$CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C 217.9 (C(O)), 169.6 (C(O)NCH$_2$CH$_2$CH$_3$), 147.3 (4º ArC), 144.2 (4º ArC), 132.3 (4º ArC), 130.0 (4º ArC), 107.4 (ArCH), 101.7 (ArCH), 64.5 (4º C), 56.2 (OCH$_3$), 41.5 (CH$_2$), 39.2 (CH$_2$), 35.8 (CH$_2$), 22.5 (CH$_2$), 18.8 (CH$_2$), 11.2 (CH$_3$); IR $\nu_{max}$/cm$^{-1}$ 3369, 2963, 2935, 2877, 1726, 1652, 1520, 1460, 1206, 1094; MS (ES-) m/z (relative intensity %) 306 (M - H$^+$, 100%); HRMS (El+): calcd. for C$_{16}$H$_{21}$O$_5$N (M$^+$) 307.1414, found 307.1429.

7.3.6.16 Synthesis and characterisation of methyl 1-(4,5-dihydroxy-2-methylphenyl)-2-oxocyclopentanecarboxylate, 169p

According to general procedure C coupling procedure, 4-methylcatechol 111 (124 mg, 1.00 mmol) was reacted with methyl cyclopentanone-2-carboxylate 109 (284 mg, 2.00 mmol) to give, after 5 h reaction time, compound 169p (27 mg, 10%) as a
yellow oil after column chromatography on silica gel, eluting with petroleum ether containing 50-70% diethyl ether; \( ^1H \text{ NMR} \) (400 MHz, CDCl\(_3\)) \( \delta_H \) 6.70 (1H, s, ArH), 6.46 (1H, s, ArH), 5.37 (1H, br. s, OH), 5.28 (1H, br. s, OH), 3.75 (3H, s, OCH\(_3\)), 2.99 (1H, ddd, \( J = 13.0, 9.0, 7.0 \text{ Hz}, \text{CH}_2 \)), 2.52 – 2.48 (2H, m, CH\(_2\)), 2.30 – 2.24 (1H, m, CH\(_2\)), 2.09 – 2.01 (1H, m, CH\(_2\)), 2.07 (3H, s, CH\(_3\)) 1.89 – 1.77 (1H, m, CH\(_2\)); \( ^{13}C \text{ NMR} \) (100 MHz, CDCl\(_3\)) \( \delta_C \) 215.2 (C(O)), 171.8 (C(O)O), 142.9 (4º ArC), 140.9 (4º ArC), 129.2 (4º ArC), 128.8 (4º ArC), 119.1 (ArCH), 114.6 (ArCH), 65.9 (4º C), 53.2 (OCH\(_3\)), 39.0 (CH\(_2\)), 35.7 (CH\(_2\)), 19.5 (CH\(_2\)), 19.3 (CH\(_3\)); \( \text{IR} \) \( \nu_{\text{max}}/\text{cm}^{-1} \) 3417, 2955, 1748, 1720, 1518, 1436, 1280, 1233; \( \text{MS} \) (ES+) m/z (relative intensity %) 282 (M + NH\(_4^+\), 100%), 287 (M + Na\(^+\), 80%), 319 (M + Na\(^+\) + MeOH, 20%); \( \text{HRMS} \) (ES+): calc. for C\(_{14}\)H\(_{20}\)O\(_5\)N (M + NH\(_4^+\)) 282.1336, found 282.1327.

7.3.6.17 Synthesis and characterisation of methyl 1-(3,4-dihydroxyphenyl)-2-oxocyclopentanecarboxylate, 169q

According to general procedure C, except that ps-IO\(_4^-\) oxidant was added portion-wise over 75 min, catechol 90 (110 mg, 0.50 mmol) was reacted with methyl cyclopentanone-2-carboxylate 109 (142 mg, 1.00 mmol) to give, after 2 h reaction time, compound 169q (27 mg, 21%) as a yellow oil after column chromatography on silica gel, eluting with petroleum ether containing 50-70% diethyl ether; \( ^1H \text{ NMR} \) (500 MHz, CDCl\(_3\)) \( \delta_H \) 6.95 (1H, d, \( J = 2.0 \text{ Hz}, \text{ArH} \)), 6.80 – 6.74 (2H, m, ArH), 3.71 (3H, s, OCH\(_3\)), 2.79 (1H, td, \( J = 13.5, 7.0 \text{ Hz}, \text{CH}_2 \)), 2.55 – 2.43 (2H, m, CH\(_2\)), 2.40 – 2.34 (1H, m, CH\(_2\)), 2.02 – 1.86 (2H, m, CH\(_2\)); \( ^{13}C \text{ NMR} \) (75 MHz, CDCl\(_3\)) \( \delta_C \) 212.9 (C(O)), 171.6 (C(O)O), 143.6 (4º ArC), 143.5 (4º ArC), 128.0 (4º ArC), 119.8 (ArCH), 115.3 (ArCH), 114.9 (ArCH), 64.3 (4º C), 53.1 (OCH\(_3\)), 37.7 (CH\(_2\)), 34.8 (CH\(_2\)), 19.2 (CH\(_2\)); \( \text{IR} \) \( \nu_{\text{max}}/\text{cm}^{-1} \) 3430, 2955, 1748, 1720, 1518, 1436, 1261; \( \text{MS} \) (ES+) m/z (relative intensity %) 282 (M + Na\(^+\), 100%), 523 (dimer + Na\(^+\), 45%); \( \text{HRMS} \) (ES+): calc. for C\(_{14}\)H\(_{20}\)O\(_5\)Na (M + Na\(^+\)) 273.0733, found 273.0731.
7.3.7 Enantioselective Examples

7.3.7.1 Synthesis and characterisation of (-)-tert-butyl (2R)-2-(3,4-dihydroxy-5-methoxyphenyl)-1-oxoindane-2-carboxylate, (-)-169r

According to general procedure C, where ps-BEMP is replaced by catalyst QD-174 (4.8 mg, 10 mol%), 3-methoxycatechol 163 (14 mg, 0.10 mmol) was reacted with tert-butyl 1-oxindane-2-carboxylate 80 (23 mg, 0.10 mmol) to give, after 2 h reaction time, compound (-)-169r (31 mg, 84%) as an off-white solid after column chromatography on silica gel eluting with petroleum ether containing 50 – 70% diethyl ether, in 81% ee, determined by HPLC analysis [Chiralpak AD, hexane/iso-propanol, 4:1, 1.0 mL.min⁻¹, λ = 230 nm, t (minor) = 19.82 min, t (major) = 25.83 min] by comparison to a racemic sample prepared in 68% yield on 0.5 mmol scale according to general procedure C; [α]D²⁴ = -1.61 (c 0.87, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δH 7.80 (1H, d, J = 7.5 Hz, ArH), 7.61 (1H, t, J = 7.5 Hz, ArH), 7.48 (1H, d, J = 7.5 Hz, ArH), 7.39 (1H, t, J = 7.5, ArH), 6.71 (1H, d, J = 2.0 Hz, ArH), 6.61 (1H, d, J = 2.0, Hz, ArH), 5.45 (1H, s, OH), 5.41 (1H, s, OH), 4.05 (1H, d, J = 17.0 Hz, CH₂), 3.85 (3H, s, OCH₃), 3.56 (1H, d, J = 17.0 Hz, CH₂), 1.39 (9H, s, C(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃) δC 200.6 (C(O)), 169.6 (C(O)OC(CH₃)₃), 152.0 (4º ArC), 146.7 (4º ArC), 143.6 (4º ArC), 135.3 (ArCH), 135.1 (4º ArC), 131.9 (4º ArC), 130.1 (4º ArC), 127.7 (ArCH), 126.0 (ArCH), 124.9 (ArCH), 108.0 (ArCH), 103.1 (ArCH), 82.4 (C(O)OC(CH₃)₃), 65.4 (4º C), 56.1 (OCH₃), 40.4 (CH₂), 27.7 (C(O)OC(CH₃)₃); IR νmax/cm⁻¹ 3416, 2966, 1729, 1713, 1607, 1517, 1463, 1370, 1254, 1153, 1096, 842; MP 66 – 68 °C (144-147 °C for racemate); MS (CI⁺) m/z (relative intensity %) 332 (M - ¹Bu + NH₄⁺, 100%), 388 (M + NH₄⁺, 15%); HRMS (ES⁺): calcd. for C₂₁H₂₀O₅N (M + NH₄⁺) 388.1755, found 388.1763.

Similarly replacing ps-BEMP with catalysts 70, QD-71, QD-148, QD-170 – QD-174 gave arylated adduct (-)-169r in the yields and enantioselectivities shown in Table 7.2 (below).
<table>
<thead>
<tr>
<th>Catalyst (mol %)</th>
<th>Scale (mmol)</th>
<th>% Yield</th>
<th>t(minor) (min)</th>
<th>t(major) (min)</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 (10 mol %)</td>
<td>0.1</td>
<td>62%</td>
<td>19.75</td>
<td>25.80</td>
<td>40%</td>
</tr>
<tr>
<td>QD-71 (10 mol %)</td>
<td>0.1</td>
<td>86%</td>
<td>19.97</td>
<td>26.00</td>
<td>61%</td>
</tr>
<tr>
<td>QD-71 (1 mol %)</td>
<td>0.1</td>
<td>78%</td>
<td>19.82</td>
<td>26.17</td>
<td>58%</td>
</tr>
<tr>
<td>QD-71 (1 equiv)</td>
<td>0.1</td>
<td>78%</td>
<td>20.14</td>
<td>26.39</td>
<td>58%</td>
</tr>
<tr>
<td>QD-148 (10 mol %)</td>
<td>0.1</td>
<td>81%</td>
<td>20.16</td>
<td>26.56</td>
<td>74%</td>
</tr>
<tr>
<td>QD-170 (10 mol %)</td>
<td>0.1</td>
<td>76%</td>
<td>19.83</td>
<td>26.17</td>
<td>67%</td>
</tr>
<tr>
<td>QD-171 (10 mol %)</td>
<td>0.1</td>
<td>50%</td>
<td>19.80</td>
<td>26.22</td>
<td>58%</td>
</tr>
<tr>
<td>QD-172 (10 mol %)</td>
<td>0.1</td>
<td>78%</td>
<td>19.96</td>
<td>26.33</td>
<td>70%</td>
</tr>
<tr>
<td>QD-173 (10 mol %)</td>
<td>0.1</td>
<td>75%</td>
<td>19.07</td>
<td>24.73</td>
<td>50%</td>
</tr>
<tr>
<td>QD-174 (1 mol %)</td>
<td>0.1</td>
<td>71%</td>
<td>19.12</td>
<td>24.81</td>
<td>43%</td>
</tr>
</tbody>
</table>

Table 7.2: Screen of organocatalysts for the synthesis of (-)-169r.

7.3.7.2 Synthesis and characterisation of (+)-tert-butyl (2R)-2-(3-tert-butyl-4,5-dihydroxyphenyl)-1-oxoindane-2-carboxylate, (+)-169s

![Image of (+)-169s]

According to general procedure C, replacing ps-BEMP with catalyst QD-174, 3-tert-butylcatechol 160 (16 mg, 0.10 mmol) was reacted with tert-butyl 1-oxindane-2-carboxylate 80 (23 mg, 0.10 mmol) to give, after 2 h reaction time, (+)-169s (29 mg, 74%) as a yellow solid after column chromatography on silica gel, eluting with petroleum ether containing 50-70% diethyl ether, in 82% ee, determined by HPLC analysis [Chiralpak AD, hexane/isopropanol 95:5, 1.0 mL.min⁻¹, λ = 230 nm, t (minor) = 37.62 min, t (major) = 40.96 min] by comparison to a racemic sample prepared in 50 % yield on a 0.2 mmol scale according to the general procedure C; [α]D 24 = + 5.3 (c 3.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δH 7.78 (1H, d, J = 7.5 Hz, ArH), 7.63 (1H, t, J = 7.5 Hz, ArH), 7.48 (1H, d, J = 7.5 Hz, ArH), 7.39 (1H, t, J = 7.5 Hz, ArH), 6.91 (1H, d, J = 2.0 Hz ArH), 6.83 (1H, d, J = 2.0 Hz, ArH), 4.09 (1H, d, J = 17.0 Hz, CH₂), 3.54 (1H, d, J = 17.0 Hz, CH₂), 1.37 (18H, s, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δC 202.7 (CO), 170.0 (C(O)O), 152.7 (4º ArC), 143.2 (4º ArC), 143.0 (4º ArC), 135.7 (4º ArC), 135.6 (ArCH), 135.1 (4º ArC).
ArC), 128.6 (4° ArC), 127.8 (ArCH), 126.1 (ArCH), 125.0 (ArCH), 117.6 (ArCH), 112.1 (ArCH), 82.7 (C(O)OC(CH₃)₃), 66.1 (4° C), 40.8 (CH₂), 34.8 (C(CH₃)₃), 29.4 ((CH₃)₂), 27.7 ((CH₃)₂); MP: 124 – 126 °C (142 – 144 °C for racemate); IR υmax/cm⁻¹ 3388, 2953, 1708, 1693, 1601, 1426, 1368, 1250, 1150; MS (ES+) m/z (relative intensity %) 419 (M + Na⁺, 100%); HRMS (ES+): calcd. for C₂₄H₃₂O₅N (M + NH₄⁺) 414.2275, found 414.2276.

7.3.7.3 Synthesis and characterisation of (+)-tert-butyl (1R)-1-(3,4-dihydroxy-5-methoxyphenyl)-2-oxocyclopentanecarboxylate, (+)-169t

![Chemical Structure](image)

According to general procedure C, replacing ps-BEMP with catalyst QD-148, 3-methoxycatechol 163 (14 mg, 0.10 mmol) was reacted with pro-nucleophile 77t (18 mg, 0.10 mmol) to give, after 2 h reaction time, compound (+)-169t (21 mg, 62%) as a pale pink oil after column chromatography on silica gel, eluting with petroleum ether containing 50-70% diethyl ether, in 65% ee, determined by HPLC analysis [Chiralpak AD, hexane/isopropanol 4:1, 1.0 mL min⁻¹, λ = 230 nm, t (minor) = 18.67 min, t (major) = 21.97 min] by comparison to a racemic sample prepared, in 69% yield on a 0.1 mmol scale, according to general procedure C; [α]D²⁴ = + 20.0 (c 0.9, CHCl₃); ¦H NMR (500 MHz, CDCl₃) δH 6.62 (2H, s, ArH), 5.35 (1H, s, OH), 5.25 (1H, s, OH), 3.87 (3H, s, OCH₃), 2.76 (1H, td, J = 12.0, 6.5 Hz, CH₂), 2.50 – 2.41 (2H, m, CH₂), 2.31 (1H, td, J = 19.0, 8.5 Hz, CH₂), 1.98 – 1.93 (2H, m, CH₂), 1.42 (9H, s, C(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃) δC 212.1 (CO), 169.8 (C(O)O), 146.6 (4° ArC), 143.5 (4° ArC), 131.9 (4° ArC), 128.0 (4° ArC), 107.9 (ArCH), 103.1 (ArCH), 82.2 (OC(CH₃)₃), 65.1 (4° C), 56.2 (OCH₃), 37.6 (CH₂), 34.7 (CH₂), 27.8 (C(CH₃)₃), 19.3 (CH₃); IR υmax/cm⁻¹ 3436, 2979, 2938, 1747, 1725, 1613, 1520, 1455, 1369, 1255, 1152; MS (ES+) m/z (relative intensity %) 345 (M + Na⁺, 100%); HRMS (ES+): calcd. for C₁₇H₂₂O₇Na (M + Na⁺) 345.1309, found 345.1303.
Similarly replacing ps-BEMP with catalyst **QD-148**, **QD-174** or **QD-71** in the following solvents gave (+)-**169t** in the following enantiomeric excesses:

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Temp/°C</th>
<th>Solvent</th>
<th>Scale/mmol</th>
<th>Yield</th>
<th>t(minor)/min</th>
<th>t(major)/min</th>
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**7.3.7.4 Synthesis and characterization of 1,1,1,3,3,3-hexafluoropropan-2-yl )-1-(3-tert-butyl-4,5-dihydroxyphenyl)-2-oxocyclopentanecarboxylate, 169u**

![Image of molecule 169u]

According to general procedure C, replacing ps-BEMP with **QD-174**, 3-tert-butylcatechol **160** (17 mg, 0.10 mmol) was reacted with 1,1,1,3,3,3-hexafluoropropan-2-yl 2-oxocyclopentanecarboxylate **77u** (28 mg, 0.10 mmol) to give, after 3 h reaction time, compound **169u** (35 mg, 79%) as an off-white solid after column chromatography on silica gel, eluting with petroleum ether containing 50% diethyl ether; in 0% ee, determined by HPLC analysis [Chiralpak AD, hexane/iso-propanol 4:1, 1.0 mL.min⁻¹, λ = 230 nm, t = 12.51 min, t = 14.66 min] by comparison to a racemic sample prepared, in 80% yield on a 0.1 mmol scale, according to general procedure C; **¹H NMR** (500 MHz, CDCl₃) δH 6.85 (1H, d, J = 2.1 Hz, ArH), 6.82 (1H, d, J = 2.1 Hz, ArH), 5.81 (1H, s, OH), 5.79 (1H, s, OH), 5.71 (1H, h, J = 6.0 Hz CH(CF₃)₂), 2.81 – 2.75 (1H, m, CH₂), 2.72 – 2.67 (1H, m, CH₂), 2.53 – 2.40 (2H, m, CH₂), 2.08 – 1.92 (2H, m, CH₂), 1.38 (9H, s, C(CH₃)₃; **¹³C NMR** (75 MHz, CD₃OD) δC 211.9 (C(O)), 169.7 (C(O)O), 146.2 (4º ArC), 145.6 (4º ArC), 137.4 (4º ArC), 124.8 (4º ArC), 123.9 (m, CF₃), 120.2 (m, CF₃), 118.1 (ArCH), 112.7 (ArCH), 68.1 (h, ²J_C,F = 34.5 Hz, CH(CF₃)₂), 65.3 (4º C), 38.1 (CH₂), 35.8 (CH₂), 35.5 (C(CH₃)₃), 29.9 (C(CH₃)₃), 20.1 (CH₂); **IR** ν_max/cm⁻¹ 3488,

**Measured on different instrument resulting in shift in retention times, matches racemic sample run on same instrument**
7.3.7.5 Synthesis and characterisation of (+)-1,1,1,3,3,3-hexafluoropropan-2-yl (1R)-1-(3,4-dihydroxy-5-methoxyphenyl)-2-oxocyclopentanecarboxylate, (+)-169v

According to the general procedure C, replacing ps-BEMP with cat QD-174, 3-methoxycatechol 163 (14 mg, 0.10 mmol) was reacted with 1,1,1,3,3,3-hexafluoropropan-2-yl 2-oxocyclopentanecarboxylate 77u (28 mg, 0.10 mmol) to give, after 2 h reaction time, compound (+)-169v (26 mg, 62%) as an off-white solid after column chromatography on silica gel, eluting with petroleum ether containing 50% diethyl ether in 16% ee, determined by HPLC analysis [Chiralpak AD, hexane/iso-propanol 4:1, 1.0 mL.min⁻¹, λ = 230 nm, t (minor) = 27.07 min, t (major) = 31.70 min] by comparison to a racemic sample prepared, in 54% yield on a 0.1 mmol scale, according to general procedure C; [α]D²⁴ = +12.0 (c 0.5, CHCl₃); 

¹H NMR (500 MHz, CDCl₃) δH 6.63 (1H, d, J = 1.5 Hz, ArH), 6.57 (1H, d, J = 1.5 Hz, ArH), 5.72 (1H, h, J = 1.5 Hz, CH₂), 5.72 (1H, h, J = 1.5 Hz, CH₂), 3.86 (3H, s, OCH₃), 2.79 – 2.73 (1H, m, CH₂), 2.70 – 2.65 (1H, m, CH₂), 2.52 – 2.38 (2H, m, CH₂), 2.08 – 1.92 (2H, m, CH₂); 

¹³C NMR (75 MHz, CDCl₃) δC 209.5 (CO), 168.1 (C(O)O), 147.0 (4º ArC), 143.9 (4º ArC), 132.5 (4º ArC), 125.1 (4º ArC), 121.3 (m, CF₃), 119.1 (m, CF₃), 107.8 (ArCH), 103.1 (ArCH), 61.7 (h, JCEF = 35 Hz, CH(CF₃)₂), 63.6 (4º C), 56.2 (OCH₃), 37.2 (CH₂), 34.1 (CH₂), 19.2 (CH₂); 

MP 104 – 105 ºC (108 – 110 ºC for racemate); IR νmax/cm⁻¹ 3460, 2973, 2854, 2370, 1775, 1747, 1618, 1521, 1466, 1386, 1359, 1291, 1235, 1202, 1110; MS (EI-) m/z (relative intensity %) 415 (M - H⁺, 100%); HRMS (EI+): calcd. for C₁₆H₁₄O₆F₆ (M⁺) 416.0689, found 416.0709.
7.3.7.6 Synthesis and characterisation of (-)-methyl (1R)-1-(3,4-dihydroxy-5-methoxyphenyl)-2-oxocyclopentanecarboxylate, (-)-169w

According to general procedure C, replacing ps-BEMP with cat. QD-174, 3-methoxycatechol 163 (14 mg, 0.10 mmol) was reacted with methyl 2-oxocyclopentanecarboxylate 109 (14 mg, 0.10 mmol) to give, after 30 min reaction time, compound (-)-169w (24 mg, 85%) as a yellow oil after column chromatography on silica gel, eluting with petroleum ether containing 30 – 50% diethyl ether in 8% ee, determined by HPLC analysis [Chiralpak AD, hexane/isopropanol 4:1, 1.0 mL.min\(^{-1}\), \(\lambda = 230\) nm, \(t\) (minor) = 36.90 min, \(t\) (major) = 43.63 min] by comparison to a racemic sample prepared according to general procedure C; [\(\alpha\)]\(_D^{24}\) = -38.0 (c 1.0, CHCl\(_3\)); other data matches racemic example (section 7.3.6.8).

7.3.8 Preparation of catalysts

Catalyst 70 was prepared according to published procedures.\(^{75,76}\) Catalysts QD-71, QD-148, QD-170 were prepared according to the method of Deng and co-workers.\(^{80-82,86}\) Catalyst QD-171 was prepared according to the method of Hiemstra and co-workers.\(^{87}\) The synthesis and characterization of the novel cinchona alkaloid derived organocatalysts QD-172 – QD-174 is described below.

7.3.8.1 Synthesis and characterisation of (9S)-9-phenoxychonan-6′-ol, catalyst 172

To a solution of quinidine 135 (500 mg, 1.54 mmol) in anhydrous dimethylsulfoxide (10 mL) at room temperature was added sodium hydride (60% dispersion in mineral oil, (77 mg, 1.92 mmol)) in small portions to give an orange
solution. Pyridine (0.30 mL, 3.70 mmol) and copper(I) iodide (37 mg, 1.54 mmol) were added (reaction mixture turned dark green) and reaction mixture was stirred at room temperature for 30 min. Iodobenzene (0.14 mL, 1.28 mmol) was added and the reaction mixture was heated to 113 ºC for 70 h then cooled to room temperature. Water (4 mL), CH$_2$Cl$_2$ (4 mL) and diethyl ether (4 mL) were added followed by ethylenediaminetetraacetate disodium salt decahydrate (78 mg) and concentrated ammonia solution (0.8 mL, 20% w/w). The reaction mixture was stirred vigorously for 1 h then the aqueous layer was separated and re-extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic portions were extracted 3 times with aqueous ammonia solution (10 mL), then with HCl (1 M, 2 x 5 mL) and with water (3 x 5 mL). The organic layer was washed with NH$_4$OH and dried over Na$_2$SO$_4$ and evaporated. The residue was dissolved in diethyl ether (20 mL) and treated with HCl (1 M in diethyl ether) until no further precipitate was generated. The precipitates were collected and dissolved in CH$_2$Cl$_2$ (10 mL), basified with saturated aqueous NH$_4$OH, washed with brine (5 mL) and dried over sodium sulfate. The solvent was removed in vacuo to give intermediate 172b as a yellow solid which was used crude without purification or characterisation.

The crude residue was dissolved in DMF (10 mL) and NaSEt (430 mg, 5.12 mmol) was added. The reaction mixture was heated to 110 ºC for 12 h then cooled to room temperature and poured into a mixture of saturated aqueous NH$_4$Cl solution (8 mL) and water (10 mL). The resulting mixture was extracted with ethyl acetate (2 x 40 mL). The combined organic portions were washed with brine (2 x 10 mL), dried over sodium sulfate and evaporated. The residue was purified by column chromatography on silica gel eluting with ethyl acetate containing 10% methanol and 1% triethylamine to give catalyst QD-172 (68 mg, 14% over 2 steps) as a pale yellow solid; $[\alpha]_D^{24} = - 10.09$ (c 0.77, CHCl$_3$); $^1$H NMR (500 MHz, CD$_3$OD) $\delta$H 8.58 (1H, d, $J = 4.5$ Hz, ArH), 8.16 (1H, d, $J = 2.0$ Hz, ArH), 7.82 (1H, d, $J = 9.0$ Hz, ArH), 7.30 (1H, d, $J = 4.5$ Hz, ArH), 7.22 (1H, dd, $J = 9.0, 2.0$ Hz, ArH), 6.74 – 6.68 (3H, m, ArH), 6.43 (2H, d, $J = 6.5$ Hz, ArH), 6.29 (1H, ddd, $J = 17.5, 10.0, 7.5$ Hz, CH=CH$_2$), 6.15 (1H, s, OCH), 5.25 – 5.20 (2H, m, CH=CH$_2$), 3.58 (1H, dd, $J = 13.5, 7.5$ Hz, aliphatic CH), 3.24 (1H, t, $J = 9.5$ Hz, aliphatic CH), 3.19 – 3.08 (2H, m, aliphatic CH), 2.94 – 2.89 (1H, m, aliphatic CH), 2.60 – 2.56 (1H, m, aliphatic CH), 2.46 – 2.41 (1H, m, aliphatic CH), 1.93 (1H, s, aliphatic CH), 1.72 –
According to the above procedure for the preparation of catalyst 172, quinidine 135 (0.14 mmol) was reacted with 2-iodo-1,3,5-trimethylbenzene (0.34 mmol) to give a crude residue containing intermediate 173b. The crude residue was dissolved in dry CH₂Cl₂ (7 mL), cooled to -78 °C and a solution of BBr₃ in CH₂Cl₂ (1.36 mL of a 1 M solution in CH₂Cl₂, 1.36 mmol) added dropwise. The reaction mixture was allowed to warm slowly to room temperature and subsequently refluxed for 1 h. The reaction mixture was then cooled to 0 °C and a solution of 40% NH₄OH added slowly. After 30 min of vigorous stirring water (10 mL) and CH₂Cl₂ (10 mL) were added. The organic phase was separated and the aqueous extracted with CH₂Cl₂. The combined organics were dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with ethyl acetate containing 10% methanol and 1% triethylamine to give catalyst QD-173 as an orange viscous oil (45 mg, 31% over two steps); [α]D²⁴ = - 7.31 (c 0.29, CHCl₃); ¹H NMR (500 MHz, CD₃OD) δH 8.59 (1H, d, J = 4.5 Hz, ArH), 7.92 (1H, d, J = 9.0 Hz, ArH), 7.87 (1H, s, ArH), 7.38 (1H, d, J = 4.5 Hz, ArH), 7.26 (1H, d, J = 9.0 Hz, ArH), 6.64 (1H, br. s, OCH), 6.58 (2H, s, ArH), 6.02 (1H, ddd, J = 17.5, 8.0,
9.5 Hz, CH=CH2), 5.09 – 5.02 (2H, m, CH=CH2), 3.47 – 3.31 (1H, aliphatic CH), 3.20-3.07 (1H, s, aliphatic CH), 3.05 (1H, t, J = 11.5 Hz, aliphatic CH), 2.94 – 2.90 (1H, m, aliphatic CH), 2.84 – 2.80 (1H, m, aliphatic CH), 2.65 (1H, q, J = 7.0 Hz, aliphatic CH), 2.53 – 2.39 (1H, m, aliphatic CH), 2.32 (6H, s, ArCH3), 2.06 (3H, s, ArCH3), 1.90 (1H, s, aliphatic CH), 1.63 – 1.46 (3H, m, aliphatic CH); δC 156.7 (4º ArC), 151.2 (4º ArC), 146.4 (ArCH), 144.0 (4º ArC), 143.1 (4º ArC), 139.8 (CH=CH2), 132.2 (4º ArC), 131.7 (ArCH), 130.7 (ArCH), 128.8 (4º ArC), 127.9 (4º ArC), 122.9 (ArCH), 119.7 (ArCH), 115.7 (CH=CH2), 105.8 (ArCH), 60.5 (NCH), 50.0 (NCH2), 49.6 (NCH2), 39.7 (CH), 28.3 (CH), 27.3 (CH), 26.0 (CH2), 21.3 (CH2), 20.5 (CH3), 19.2 (CH3); IR νmax/cm⁻¹ 3070, 2925, 2869, 1617, 1509, 1479, 1403, 1209, 1151, 755; MS (ES+) m/z (relative intensity %) 429 (M + H⁺, 100%); HRMS (ES+): calcd. for C28H33O2N2 429.2537 (M + H⁺), found 429.2531.

7.3.8.3 Synthesis and characterisation of (9S)-6'-hydroxycinchonan-9-yl adamantane-1-carboxylate, catalyst 174

To a stirred solution of quinidine 135 (648 mg, 2.00 mmol) in CH₂Cl₂ (12 mL) was added triethylamine (0.55 mL, 4.00 mmol), 1-adamantylcarbonyl chloride (437 mg, 2.20 mmol) and 4-(dimethylamino)pyridine (24 mg, 0.20 mmol). The reaction mixture was stirred at room temperature overnight then the solvent removed by rotary evaporation.

The crude residue containing 174b was dissolved in anhydrous CH₂Cl₂ (20 mL) and cooled to -78 ºC under nitrogen. BBr₃ (6.6 mL of a 1 M solution in CH₂Cl₂, 6.60 mmol) was added dropwise. The reaction mixture was allowed to warm slowly to room temperature and stirred overnight. The reaction mixture was cooled to 0 ºC and NH₄OH (16 mL of a 40% aq. solution) was added slowly. The biphasic mixture was stirred vigorously for 30 min then diluted with water (10 mL) and CH₂Cl₂ (10 mL). The organic phase was separated and the aqueous extracted with CH₂Cl₂ (3 x 10 mL). The combined organic portions were dried over MgSO₄, filtered and
concentrated. The residue was purified by column chromatography on silica gel eluting with EtOAc containing 2 – 10% MeOH and 1% triethylamine to give catalyst QD-174 (426 mg, 47% over 2 steps) as an off-white solid following purification by column chromatography eluting with ethyl acetate containing 10% methanol and 1% triethylamine: $[\alpha]_D^{24} = +27.03$ (c 1.45, CHCl$_3$); $^1$H NMR (500 MHz, CD$_3$OD) $\delta$H 8.60 (1H, d, $J = 4.5$ Hz, ArH), 7.93 (1H, d, $J = 9.0$ Hz, ArH) 7.41 – 7.40 (2H, m, ArH), 7.37 (1H, d, $J = 9.0$ Hz, ArH), 6.46 (1H, d, $J = 4.0$ Hz, OCH), 6.12 (1H, ddd, $J = 17.5$, 10.5, 7.5 Hz, CH=CH$_2$), 5.17 – 5.14 (2H, m, CH$_2$=CH), 3.33 (1H, br. s, NH), 3.14 – 3.09 (1H, m, NCH), 3.02 – 2.97 (1H, m, NCH), 2.89 – 2.86 (1H, m, NCH), 2.81 – 2.74 (1H, m, NCH), 2.39 (1H, dd, $J = 16.5$, 8.0 Hz, aliphatic CH), 2.03 (4H, br. s, aliphatic CH), 1.97 (6H, br. s, aliphatic CH), 1.84 (1H, br. s, aliphatic CH), 1.77 (6H, q, $J = 12.0$ Hz, aliphatic CH), 1.61 (2H, t, $J = 6.5$ Hz, aliphatic CH), 1.49 (1H, s, aliphatic CH); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C 176.0 (C(O)O), 156.0 (4º ArC), 146.3 (ArCH), 143.7 (4º ArC), 143.4 (4º ArC), 139.3 (CH=CH$_2$), 131.3 (ArCH), 127.0 (4º ArC), 122.4 (ArCH), 118.0 (ArCH), 115.4 (CH=CH$_2$), 105.2 (ArCH), 73.1 (4º C), 58.7 (NCH), 49.5 (NCH$_2$), 49.0 (NCH$_2$), 40.8 (OCH), 39.3 (CH), 38.8 (CH$_2$), 36.4 (CH$_2$), 27.8 (CH), 27.4 (CH), 25.7 (CH$_2$), 22.6 (CH$_2$); IR $\nu_{max}$/cm$^{-1}$ 2907, 2850, 1730, 1618, 1468, 1454, 1226, 1182; MP 182 – 185 ºC MS (ES+) m/z (relative intensity %); 473 (M + H$^+$, 100%), 495 (M + Na$^+$, 70%), 427 (M + Na$^+$ + MeOH, 70%); HRMS (ES+): calcd. for C$_{30}$H$_{37}$O$_3$N$_2$ (M + H$^+$) 473.2789, found 473.2799.

7.4 Chapter 4 Experimental

7.4.1.1 Synthesis and characterisation of tert-butyl 3-[(2E)-but-2-enoyl]-2-oxopyrrolidine-1-carboxylate, 205

![Synthesis of tert-butyl 3-[(2E)-but-2-enoyl]-2-oxopyrrolidine-1-carboxylate](image)

To a stirred solution of HMDS (13.2 mL, 57.0 mmol), in THF (20 mL) at -78 ºC, was added n-BuLi (35.4 mL, 62.0 mmol) and the reaction mixture warmed to 0 ºC for 10 min, then cooled back to -78 ºC. *tert*-Butyl 2-oxopyrrolidine-1-carboxylate 206 (5.00 g, 27.0 mmol) was added dropwise as a solution in THF (30 mL) (cooled to -78 ºC) followed immediately by freshly distilled crotonoyl chloride (2.6 mL,
27.0 mmol) also as a solution in THF (20 ml) (cooled to -78 °C). The resulting bright yellow solution was stirred at -78 °C for 5 min then quenched with 1 M HCl (~70 ml, to pH 1) and allowed to warm to room temperature. The now almost colourless biphasic mixture was extracted with ethyl acetate (3 x 40 mL). The combined organic portions were dried, filtered and concentrated and the residue purified by column chromatography on silica gel, eluting with petroleum ether containing 30-50% ethyl acetate to give 205 (2.40 g, 41%) as a colourless solid.

$^1$H NMR (500 MHz, CDCl$_3$, 1:1 ratio of enol:keto forms) $\delta$H 11.73 (1H, d, $J = 1.5$ Hz, OH enol), 7.04 (1H, qd, $J = 15.5, 7.0$ Hz, CH=CH$_3$ keto), 6.67 (1H, qd, $J = 15.5, 7.0$ Hz, CH=CH$_3$ enol), 6.44 (1H, td, $J = 15.5, 1.5$ Hz, CH=CH$_3$ keto), 5.87 (1H, td, $J = 15.5, 1.5$ Hz, CH=CH$_3$ enol), 3.87 (1H, dd, $J = 9.0, 5.5$ Hz, CH keto), 3.84 – 3.68 (4H, m, CH$_2$ keto and CH$_2$ enol), 2.68 (2H, t, $J = 7.5$ Hz, CH$_2$ enol), 2.51 (1H, tdd, $J = 13.5, 8.0, 5.0$ Hz, CH$_2$ keto), 2.06 (1H, dt, $J = 13.0, 9.0, 7.0$ Hz, CH$_2$ keto), 1.94 (3H, dd, $J = 7.0, 1.5$ Hz, CH=CHCH$_3$ keto), 1.90 (3H, dd, $J = 7.0, 1.5$ Hz, CH=CHCH$_3$ enol), 1.53 (s, 9H, C(CH$_3$)$_3$ keto), 1.50 (s, 9H, C(CH$_3$)$_3$ enol); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 192.8 (C=O), 173.1 (C=O)N, 169.5 (C(O)N), 161.7 (C(O)N), 150.4 (OC(O)N), 150.0 (OC(O)N), 146.3 (C=C), 136.8 (C=C), 130.2 (C=C), 123.1 (C=C), 99.9 (C=C-O), 83.2 (C(CH$_3$)$_3$), 82.8 (C(CH$_3$)$_3$), 54.5 (CH), 45.1 (CH$_2$), 44.1 (CH$_2$), 28.0 (C(CH$_3$)$_3$), 27.9 (C(CH$_3$)$_3$), 19.6 (CH$_2$), 19.2 (CH$_2$), 18.6 (CH$_3$), 18.6 (CH$_3$); IR $\nu_{max}$/cm$^{-1}$ 2979, 2934, 1781, 1716, 1369, 1309, 1257, 1153; MP 121 – 124 ºC; MS (ES-) m/z (relative intensity %) 252 (M - H$^+$, 100%); HRMS (ES+): calcd. for C$_{13}$H$_{20}$O$_4$N$_1$ (M + H$^+$) 254.1387, found 254.1387.

7.4.1.2 Synthesis and characterisation of tert-butyl 3-[(2E)-but-2-enoyl]-3-(3,4-dihydroxy-5-methoxyphenyl)-2-oxopyrrolidine-1-carboxylate, 204

To a stirred solution of 3-methoxycatechol 163 (280 mg, 2.00 mmol) and 205 (506 mg, 2.00 mmol) in CH$_2$Cl$_2$ (20 mL) at -20 ºC in a flask wrapped in aluminium foil
was added ps-BEMP (91 mg, 0.20 mmol) followed by ps-IO₄ (800 mg, 4.00 mmol). The reaction mixture was stirred at this temperature for 2 h then filtered and the resin on the filter washed with CH₂Cl₂ (30 mL). The deep red filtrate was stirred with saturated aqueous Na₂S₂O₄ (20 mL) for 5 min then the now pale yellow organic phase separated and the aqueous extracted with CH₂Cl₂ (2 x 10 mL). The combined organic portions were dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with petroleum ether containing 70 to 90% ethyl acetate to give the arylated product 204 (413 mg, 53%) as a colourless solid. 

**¹H NMR** (500 MHz, CDCl₃) δH 6.97 (1H, qd, J = 15.5, 7.0 Hz, CH=CHCH₃), 6.61 (1H, d, J = 2.0 Hz, ArH), 6.53 (1H, d, J = 2.0 Hz, ArH), 6.46 (1H, qd, J = 15.5, 1.5 Hz, CH=CHCH₃), 5.39 (1H, s, OH), 5.30 (1H, s, OH), 3.87 (3H, s, OCH₃), 3.64 (2H, dd, J = 8.0, 5.5 Hz, CH₂), 3.03 (1H, td, J = 13.0, 5.5 Hz, CH₂), 2.07 (1H, td, J = 13.0, 8.0 Hz, CH₂), 1.79 (3H, dd, J = 7.0, 1.5 Hz, CH=CHCH₃), 1.53 (s, 9H, C(CH₃)₃); 

**¹³C NMR** (125 MHz, CDCl₃) δC 191.7 (C O), 171.6 (C(O)N), 150.0 (NC(O)O)), 147.3 (C=C), 144.9 (4º ArC), 144.2 (4º ArC), 132.2 (4º ArC), 129.3 (4º ArC), 127.0 (C=C)), 108.0 (ArCH), 102.3 (ArCH), 83.3 (C(CH₃)₃), 66.5 (4º C), 56.3 (OCH₃), 43.4 (CH₂), 29.3 (CH₂), 28.0 (C(CH₃)₃), 18.4 (CH₃); IR νmax/cm⁻¹ 3411, 1710, 1686, 1624, 1519, 1370, 1316; MP 162 – 164 ºC.; MS (ES-) m/z (relative intensity %) 390 (M - H⁺, 100%); HRMS (ES-): calcd. for C₂₀H₂₄O₇N₁ (M - H⁺) 390.1562, found 390.1558.

**7.4.1.3 Synthesis and characterisation of tert-butyl 3-[(2E)-but-2-enoyl]-3-(7-methoxy-1,3-benzodioxol-5-yl)-2-oxopyrrolidine-1-carboxylate, 203**

To a solution of 204 (39 mg, 0.10 mmol) in DMF (1 mL) in a microwave vial was added KF (197 mg, 3.40 mmol), and CH₂ClBr (130 μL, 2.00 mmol) and the mixture irradiated at 80 ºC for 1 h. The resulting purple/brown solution was evaporated to dryness and the residue purified by column chromatography on silica gel eluting with petroleum ether containing 70% diethyl ether to give the methylene acetal protected product 203 as a pale yellow solid (20 mg, 50%) along with
recovered starting material 204 (10 mg, 25%). $^1$H NMR (500 MHz, CDCl$_3$) δ$_H$ 6.98 (1H, qd, $J = 15.5, 7.0$ Hz, CH=CHCH$_3$), 6.58 (1H, d, $J = 1.5$ Hz, ArH), 6.53 (1H, d, $J = 1.5$ Hz, ArH), 6.46 (1H, dd, $J = 15.5, 1.5$ Hz, CH=CHCH$_3$), 5.96 (2H, s, OCH$_2$O), 3.87 (3H, s, OCH$_3$), 3.64 – 3.61 (2H, m, CH$_2$), 3.03 (1H, ddd, $J = 12.5, 6.5, 4.5$ Hz, CH$_3$), 2.04 (1H, td, $J = 12.5, 8.5$ Hz, CH$_3$), 1.80 (3H, dd, $J = 7.0, 1.5$ Hz, CH=CHCH$_3$), 1.52 (9H, s, C(CH$_3$)$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) δ$_C$ 191.4 (CO), 170.4 (C(O)N), 149.9 (OC(O)N), 149.3 (C=C), 145.2 (4º ArC), 143.8 (4º ArC), 134.9 (4º ArC), 132.1 (4º ArC), 126.9 (C=C), 107.0 (ArCH), 101.6 (ArCH), 101.6 (OCH$_2$O), 83.3 (C(CH$_3$)$_3$), 66.7 (4º C), 56.8 (OCH$_3$), 43.3 (CH$_2$), 29.4 (CH$_2$), 28.0 (C(CH$_3$)$_3$), 18.4 (CH$_3$); IR $\nu_{max}$/cm$^{-1}$ 3417, 2981, 1775, 1711, 1687, 1622, 1519, 1371, 1318, 1262, 1154, 1097; MP 165 – 168 ºC.; MS (ES+) m/z (relative intensity %) 426 (M + Na$^+$, 100%), 458 (M + Na$^+$ + MeOH, 15%), 829 (dimer + Na$^+$, 40%); HRMS (ES+): calcd. for C$_{21}$H$_{25}$O$_7$NNa (M + Na$^+$) 426.1527, found 426.1523.

A screen of alternative alkylating agents/bases was conducted following the above procedure under the conditions indicated in Table 7.3 (except for entries 1, 2 and 4 where conventional heating in a round bottom flask equipped with reflux condenser was employed). Conversions were measured with respect to remaining starting material, however this was found to be unreliable since conversion did not reflect isolated yield (entry 8), presumable due to decomposition of starting material/product under the reaction conditions.

<table>
<thead>
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<th>Entry</th>
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<th>Base</th>
<th>Solvent</th>
<th>T / ºC</th>
<th>Time</th>
<th>Heating</th>
<th>% Conv.</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
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<td>Cs$_2$CO$_3$</td>
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<td>O/N</td>
<td>thermal</td>
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<td>-</td>
</tr>
<tr>
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<td>K$_2$CO$_3$</td>
<td>DMF</td>
<td>110</td>
<td>O/N</td>
<td>thermal</td>
<td>0</td>
<td>-</td>
</tr>
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<td>3</td>
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<td>K$_2$CO$_3$</td>
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<td>90</td>
<td>1h</td>
<td>MW</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>CH$_2$ClBr</td>
<td>KF</td>
<td>DMF</td>
<td>110</td>
<td>O/N</td>
<td>thermal</td>
<td>-</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>CH$_2$ClBr</td>
<td>KF</td>
<td>DMF</td>
<td>120</td>
<td>15 min</td>
<td>MW</td>
<td>48</td>
<td>-</td>
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<td>6</td>
<td>CH$_2$ClBr</td>
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<td>CH$_2$ClBr</td>
<td>70</td>
<td>15 min</td>
<td>MW</td>
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<td>-</td>
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<tr>
<td>7</td>
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<td>DMF</td>
<td>120</td>
<td>5 min</td>
<td>MW</td>
<td>30</td>
<td>-</td>
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<td>8</td>
<td>CH$_2$ClBr</td>
<td>KF</td>
<td>DMF</td>
<td>120</td>
<td>5x5 min</td>
<td>MW</td>
<td>80</td>
<td>10</td>
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</tbody>
</table>
Table 7.3: Optimisation of methylene acetal protection. * 75% based on recovered starting material.

Alternatively tert-butyl 3-[(2E)-but-2-enoyl]-3-(7-methoxy-1,3-benzodioxol-5-yl)-2-oxopyrrolidine-1-carboxylate 203 was prepared by an oxidative coupling – methylene acetal protection sequence following the above procedures for the syntheses of compounds 204 and 203 without purification of the catechol to give 203 in 44% yield on a 1 mmol scale.

To a stirred solution of 3-methoxycatechol 163 (140 mg, 1.00 mmol) and pronucleophile 205 (278 mg, 1.10 mmol) in CH₂Cl₂ (10 mL) at -20 °C in a flask wrapped in aluminium foil was added ps-BEMP (46 mg, 0.10 mmol) followed by ps-IO₄⁻ (505 mg, 2.00 mmol). The reaction mixture was stirred at this temperature for 2 h then filtered and the resin on the filter washed with CH₂Cl₂ (30 mL). The deep red filtrate was stirred with saturated aqueous Na₂S₂O₄ for 5 min then the (now pale yellow) organic phase separated and the aqueous extracted with CH₂Cl₂ (2 x 10 mL). The combined organic portions were dried over Na₂SO₄, filtered and concentrated. The residue was dissolved in DMF (1 mL) in a microwave vial and KF (197 mg, 3.4 mmol) and CH₂ClBr (130 μL, 2 mmol) were added. The reaction mixture was irradiated at 80 °C for 1 h. The resulting purple/brown solution was evaporated to dryness and the residue purified by column chromatography on silica gel eluting with petroleum ether containing 70% diethyl ether to give the methylene acetal protected product 203 as a pale yellow solid (176 mg, 44%). All data identical to product obtained from the 2 step procedure.
7.4.2 Attempted reduction of 203

To a stirred solution of 203 (135 mg, 0.33 mmol) in THF (4 mL) at -78 ºC was added, dropwise, LHMDS (0.50 mL of a 1 M solution in cyclohexane, 0.50 mmol). The reaction mixture was stirred at this temperature for 10 min before added DIBALH (0.66 mL of a 1 M solution, 0.66 mmol). The reaction mixture was allowed to warm slowly to -20 ºC and stirred at this temperature for a further 14 h. The reaction mixture was quenched with sat. aq. NH₄Cl (2 mL) then sat. aq potassium sodium tartrate (3 mL). The reaction mixture was warmed to room temperature and extracted with ethyl acetate (3 x 5 mL) and the organic extracts dried over Na₂SO₄, filtered and concentrated. Crude ¹H NMR showed a mixture of several compounds, MS (ES+) m/z (relative intensity %) 428 (M + Na⁺, 100%); HRMS (ES+): calcd. for C₂₁H₂₇O₇NNa (M + Na⁺) 428.1680, found 428.1677. No further attempts were made to characterise the crude reactions products as an alternative synthetic strategy was sought.

7.4.3 Alternative Approach to Buphanidrine and Powelline

7.4.3.1 Synthesis and characterisation of 1-tert-butyl 3-methyl 2-oxopyrrolidine-1,3-dicarboxylate, 207

To a stirred solution of LHMDS (57 mL of a 1 M solution in cyclohexane, 57.0 mmol) in THF (20 mL) at -78 ºC was added 206 (5.00 g, 27.0 mmol) dropwise as a solution in THF (20 mL) followed by methylchloroformate (2.09 mL, 27.0 mmol) also dropwise as a solution in THF (20 mL). The resulting bright yellow reaction mixture was stirred at this temperature for 10 min then quenched with 1 M HCl (to pH 1, approx 70 mL) and allowed to warm to RT. The biphasic mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic portions dried
over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with cyclohexane containing 20 – 60% ethyl acetate to give pro-nucleophile 207 (6.30 g, 96% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 3.90 – 3.84 (1H, m, NCH$_2$), 3.77 (3H, s, OCH$_3$), 3.72 – 3.66 (1H, m, NCH$_2$), 3.54 (1H, dd, $J = 9.0, 7.5$ Hz, CH), 2.43 – 2.34 (1H, m, NCH$_2$CH$_2$), 2.26 – 2.17 (1H, m, NCH$_2$CH$_2$), 1.51 (9H, s, C(CH$_3$)$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C 169.1 (C(O)N), 168.6 (C(O)O), 149.9 (NC(O)O), 83.4 (C(CH$_3$)$_3$), 52.8 (OCH$_3$), 50.1 (CH), 44.8 (NCH$_2$), 27.9 (C(CH$_3$)$_3$), 21.4 (CH$_2$); IR $\nu_{max}/$cm$^{-1}$ 2981, 1789, 1737, 1370, 1297, 1258, 1153; MP 65 – 67 ºC; MS (ES+) m/z (relative intensity %) 266 (M + Na$^+$, 100%), 59 (dimer + Na$^+$, 70%); HRMS (ES+): calcd. for C$_{11}$H$_{17}$O$_5$NNa (M + Na$^+$) 266.0999, found 266.0991.

7.4.3.2 Synthesis and characterisation of 1-tert-butyl 3-methyl 3-(7-methoxy-1,3-benzodioxol-5-yl)-2-oxopyrrolidine-1,3-dicarboxylate, 208

![Chemical structure of 208](image)

To a stirred solution of 3-methoxycatechol 163 (1.40 g, 10.0 mmol) and 207 (2.43 g, 10.0 mmol) in acetone (100 mL) at -20 ºC was added ps-BEMP (450 mg, 1.00 mmol) followed by ps-IO$_4$ (2.50 g 20.0 mmol). The reaction mixture was stirred at this temperature for 7 h then filtered and the resin on the filter washed with CH$_2$Cl$_2$ (3 x 100 mL). The filtrate was stirred with saturated aqueous Na$_2$S$_2$O$_4$ (200 mL), the organic phase separated and the aqueous extracted with CH$_2$Cl$_2$ (2 x 50 mL). The combined organic portions were dried over Na$_2$SO$_4$, filtered and concentrated. The residue was dissolved in DMF and divided equally between 5 sealable vials. To each vial was added CH$_2$ClBr (0.19 mL, 3.00 mmol) and Cs$_2$CO$_3$ (977 mg, 3.00 mmol). The vials were sealed and heated at 85 ºC for 1 h then cooled to room temperature. The resulting purple-brown solution was concentrated and purified by column chromatography on silica gel, eluting with petroleum ether containing 30 – 60% diethyl ether to give the arylated product 208 (2.03 g, 52% yield) as a cream solid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 6.70 (1H, d, $J = 1.5$ Hz, ArH), 6.63 (1H, d, $J = 1.5$ Hz, ArH), 5.94 (2H, s, OCH$_2$O), 3.88 (3H, s, ArOCH$_3$), 3.75 – 3.70 (1H, m,
CH₂N), 3.74 (3H, s, OCH₃), 3.65 (1H, ddd, J = 11.0, 7.0, 5.5 Hz, CH₂N), 2.91 (1H, ddd, J = 13.0, 7.0, 5.5, CH₂CH₂N), 2.38 (1H, ddd, J = 13.0, 7.0, 5.5 Hz, CH₂CH₂N), 1.52 (9H, s, C(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃) δC 170.0 (NC(O)), 169.3 (OC(O)), 149.9 (NC(O)O), 149.0 (4º ArC), 143.3 (4º ArC), 135.0 (4º ArC), 130.1 (4º ArC), 107.3 (ArCH), 101.6 (OCH₂O), 101.6 (ArCH), 83.5 (C(CH₃)₃), 61.3 (4º C), 56.7 (ArOCH₃), 53.4 (OCH₃), 43.2 (NCH₂), 30.4 (NCH₂CH₂), 27.9 (C(CH₃)₃); IR νmax/cm⁻¹ 2980, 1784, 1726, 1643, 1368, 1311, 1255, 1152, 1100; MP 86 – 89 ºC MS (ES+) m/z (relative intensity %) 416 (M + Na⁺, 100%), 448 (M + Na⁺ + MeOH, 20%); HRMS (ES+): calcd. for C₁₀H₂₃O₈NNa (M + Na⁺) 416.1316, found 416.1309.

Alternatively following the same procedure with the conditions detailed in Table 7.4 gave arylated product 208 in the yields shown.

<table>
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<th>Scale /mmol</th>
<th>Equiv Pro-Nu</th>
<th>Solvent</th>
<th>Equiv base</th>
<th>Concentration /M</th>
<th>T/°C</th>
<th>% Yielda</th>
</tr>
</thead>
<tbody>
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<td>0.1</td>
<td>-20</td>
<td>37</td>
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</table>

Table 7.4: Optimisation of oxidative coupling. a isolated yield of 208 after methylene acetal protection.

7.4.3.3 Synthesis and characterisation of 1-tert-butyl 3-methyl 2-hydroxy-3-(7-methoxy-1,3-benzodioxol-5-yl)pyrrolidine-1,3-dicarboxylate, 209

To a stirred solution of 208 (4.30 g, 10.9 mmol) in anhydrous THF (100 mL) at -78 ºC was added, dropwise, Super-hydride® (13.1 mL of a 1 M solution in THF, 13.1 mmol). The reaction mixture was stirred at this temperature for 2 h then quenched
with sat. aq. NaHCO₃ (150 mL) and allowed to warm to room temperature. The biphasic mixture was extracted with EtOAc (3 x 50 mL), and the combined organic extracts dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with diethyl ether containing 30% petroleum ether to give aminol 209 (4.00 g, 93%) as a colourless solid. 

**1H NMR**

(500 MHz, d₆-DMsol, 90 °C, 1:1 ratio of diastereomers) δH 6.53 (1H, d, J = 1.5 Hz, ArH diastereomer A), 6.52 (1H, d, J = 1.5 Hz, ArH diastereomer A), 6.43 (1H, d, J = 1.5 Hz, ArH of diastereomer B), 6.42 (1H, d, J = 1.5 Hz, ArH of diastereomer B), 5.97 (2H, d, J = 1.5 Hz, OCH₂O), 5.95 (2H, s, OCH₂O), 5.85 (1H, br. s, CHOH of diastereomer A), 5.71 (1H, br. s, CHOH of diastereomer B), 3.86 (3H, s, ArOCH₃ of diastereomer A), 3.83 (3H, s, ArOCH₃ of diastereomer B), 3.59 (3H, s, OCH₃), 3.59 (3H, s, OCH₃), 3.42 (1H, t, J = 11.0 Hz, NCH₂ diastereomer A), 3.34 (1H, t, J = 11.0 Hz, NCH₂ diastereomer B), 3.18 (1H, ddd, J = 17.5, 11.0, 7.0 Hz, NCH₂ diastereomer A), 2.91 (1H, ddd, J = 17.5, 11.0, 7.0 Hz, NCH₂ diastereomer B), 2.78 (1H, m, NCH₂CH₂ diastereomer B), 2.68 (1H, dd, J = 11.0, 7.0 Hz, NCH₂CH₂ diastereomer A), 2.42 (1H, m, NCH₂CH₂ diastereomer A), 2.16 (1H, dd, J = 11.0, 7.0 Hz, NCH₂CH₂ diastereomer B), 1.45 (9H, s, C(CH₃)₃), 1.43 (9H, br. s, C(CH₃)₃), 13C NMR (125 MHz, d₆-DMsol, 90 °C, 1:1 mixture of diastereomers) δC 172.0 (O(C)(O)), 170.8 (OC(O)), 153.1 (NC(O)O from HMBC, 2 peaks visible in RT spectrum at 153.2, 153.0), 152.7 (NC(O)O), 148.5 (4º ArC), 147.9 (4º ArC), 142.6 (4º ArC), 142.3 (4º ArC), 133.8 (4º ArC), 133.8 (4º ArC), 133.0 (4º ArC), 131.7 (4º ArC), 108.6 (ArCH diastereomer A), 106.3 (ArCH diastereomer B), 101.8 (ArCH diastereomer A), 100.8 (OCH₂O), 100.6 (OCH₂O), 99.6 (ArCH diastereomer B), 82.9 (CHOH diastereomer B), 82.5 (CHOH diastereomer A), 78.7 (C(CH₃)₃), 78.4 (C(CH₃)₃), 61.9 (4º C diastereomer A, from HMBC), 61.2 (4º C diastereomer B, from HMBC), 56.4 (ArOCH₃), 56.3 (ArOCH₃), 51.7 (OCH₃), 51.2 (OCH₃), 42.5 (NCH₂ diastereomer A), 42.1 (NCH₂ diastereomer B), 30.0 (NCH₂CH₂ diastereomer B, from HSQC), 27.7 (C(CH₃)₃), 27.6 (C(CH₃)₃), 27.2 (NCH₂CH₂ diastereomer A, from HSQC); IR νmax/cm⁻¹ 3428, 2978, 2897, 1732, 1681, 1652, 1643, 1513, 1428, 1397, 1368, 1260, 1173, 1146, 1099, 1056; MP 71 – 74 °C; MS (ES+) m/z (relative intensity %) 418 (M + Na⁺, 100%), 450 (M + Na⁺ + MeOH, 20%); HRMS (ES+): calcd. for C₁₉H₂₅O₈NNa (M + Na⁺) 418.1472, found 418.1484.
7.4.3.4 Synthesis and characterisation of methyl 4-[(tert-butoxycarbonyl)(formyl)amino]-2-(7-methoxy-1,3-benzodioxol-5-yl)butanoate, 214 and methyl 4-[(tert-butoxycarbonyl)amino]-2-(7-methoxy-1,3-benzodioxol-5-yl)butanoate, 215

To a stirred solution dimethyl 2-oxopropylphosphonate (15 mg, 0.09 mmol) in THF (2 mL) was added KOt-Bu (22 mg, 0.22 mmol) and the reaction mixture stirred at room temperature for 10 min before adding 209 (35 mg, 0.09 mmol) and heating to reflux for 24 h. The reaction mixture was cooled to room temperature, diluted with sat. aq. NH₄Cl (10 mL) and extracted with ethyl acetate (3 x 5 mL). The desired product 210 was not isolated from the reaction mixture, instead formamide 214 (27 mg, 71%) as a colourless solid and de-formylated product 215 (2 mg, 5%) as a colourless oil were obtained. Formamide product 214: ¹H NMR (500 MHz, CDCl₃) 9.13 (1H, s, C(O)H), 6.49 (1H, d, J = 1.5 Hz, ArH), 6.46 (1H, d, J = 1.5 Hz, ArH), 5.94 (2H, s, OCH₂O), 3.90 (3H, s, OCH₃), 3.66 (3H, s, OCH₃), 3.62 – 3.48 (2H, m, CH₂N), 3.45 (1H, t, J = 7.5 Hz, CH), 2.28 – 2.19 (1H, m, CH₂CH₂N), 2.02 – 1.95 (1H, m, CH₂CH₂N), 1.53 (9H, s, C(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃) δC 173.5 (C(O)O), 163.0 (N(C(O)H), 152.2 (OC(O)N), 149.0 (4º ArC), 143.6 (4º ArC), 134.6 (4º ArC), 132.5 (4º ArC), 107.5 (ArCH), 101.8 (OCH₂O), 101.5 (ArCH), 84.2 (C(CH₃)₃), 56.6 (OCH₃), 52.2 (OCH₃), 49.0 (CH), 38.8 (CH₂), 31.5 (CH₂), 28.0 (C(CH₃)₃); MP 88 – 90 ºC; IR νmax/cm⁻¹ 2953, 1737, 1688, 1635, 1510, 1452, 1434, 1370, 1341, 1195, 1151, 1094; MS (ES+) m/z (relative intensity %) 418 (M + Na⁺, 100%), 450 (M + Na⁺ + MeOH 20%); HRMS (ES?): calcd. for C₁₉H₂₉O₈N₂ (M + NH₄⁺) 413.1915, found 413.1918.

De-formylated product 215: ¹H NMR (500 MHz, CDCl₃) 6.49 (1H, d, J = 1.5 Hz, ArH), 6.44 (1H, d, J = 1.5 Hz, ArH), 5.94 (2H, s, OCH₂O), 3.89 (3H, s, OCH₃), 3.66 (3H, s, OCH₃), 3.49 (1H, t, J = 7.5 Hz, CH), 3.08 (2H, dd, J = 13.0, 7.0 Hz, CH₂N), 2.21 (1H, qd, J = 14.5, 7.0 Hz, CH₂CH₂N), 1.91 (1H, dt, J = 14.5, 7.0 Hz,
CH₂CH₂N), 1.43 (9H, s, C(CH₃)₃); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta\) C 174.0 (C(O)O), 155.8 (OC(N)O), 149.0 (4° ArC), 143.5 (4° ArC), 134.5 (4° ArC), 132.7 (4° ArC), 107.5 (ArCH), 101.8 (OCH₂O), 101.5 (ArCH), 79.3 (C(CH₃)₃), 56.6 (OCH₃), 52.2 (OCH₃), 48.9 (CH), 38.7 (CH₂), 33.6 (CH₂), 28.4 (C(CH₃)₃). IR \(\nu_{\text{max}}/\text{cm}^{-1}\) 2976, 1732, 1711, 1634, 1510, 1452, 1433, 1366, 1167; MS (ES+) m/z (relative intensity %) 390 (M + Na⁺, 100%), 757 (dimer + Na⁺, 30); HRMS (ES+): calcd. for C₁₈H₂₅O₇NNa (M + Na⁺) 390.1523, found 390.1535.

7.4.3.5 Synthesis and characterisation of 1-tert-butyl 3-methyl 3-(7-methoxy-1,3-benzodioxol-5-yl)-2-(2-oxopropyl)pyrrolidine-1,3-dicarboxylate, 210

Aminol 209 (4.00 g, 10.1 mmol) was dissolved in pyridine (20 mL) and cooled to 0 °C before adding acetic anhydride (4 mL). The reaction mixture was allowed to warm to room temperature and stirred for 20 h then diluted with ethyl acetate (100 mL) and washed with saturated copper sulfate (until no darkening of the copper sulfate solution was noticeable). The organic phase was dried over Na₂SO₄, filtered and concentrated. The residue containing intermediate 216 (MS (ES+): 539 (M + HNEt₃⁺, 100%), 460 (M + Na⁺, 50%), 897 (2M + Na⁺) was used directly in the next step without purification or characterisation.

To a solution of crude 1-tert-butyl 3-methyl-2-acetoxy-3-(7-methoxy-1,3-benzodioxol-5-yl)pyrrolidine-1,3-dicarboxylate, 216 (4.40 g, 10.1 mmol) and (isopropenyloxy)trimethylsilane (16.7 mL, 100 mmol) in anhydrous CH₂Cl₂ (50 mL) at –78 °C was added, dropwise, BF₃·Et₂O (2.8 mL, 22.2 mmol). The reaction mixture was stirred at –78 °C for 5 h then diluted with water, warmed to RT and extracted with CH₂Cl₂. The organic extracts were dried over Na₂SO₄, filtered and concentrated and the residue purified by column chromatography on silica gel, eluting with petroleum ether containing 60 – 80% diethyl ether, to give keto-ester
210 (4.0 g, 91 %) as a colourless oil. \(^1\)H NMR (500 MHz, d\(_6\)-DMSO, 90 °C, 3:1 ratio of diastereomers, relative stereochemistry of major diastereomer (A) unknown) \(\delta\)\(_H\) 6.53 (2H, s, Ar\(H\) diastereomer B), 6.50 (1H, d, \(J = 1.5\) Hz, Ar\(H\) diastereomer A), 6.47 (1H, d, \(J = 1.5\) Hz, Ar\(H\) diastereomer A), 5.97 (4H, s, OCH\(_2\)O diastereomer A and B), 5.14 (1H, t, \(J = 6.0\) Hz, CHCH\(_2\)C(O)CH\(_3\) diastereomer A), 4.87 (1H, t, \(J = 6.0\) Hz, CHCH\(_2\)C(O)CH\(_3\) diastereomer B), 3.85 (3H, s, ArOCH\(_3\) diastereomer B), 3.84 (3H, s, ArOCH\(_3\) diastereomer A), 3.62 (3H, s, OCH\(_3\) diastereomer A), 3.55 (3H, s, OCH\(_3\) diastereomer B), 3.40 (1H, t, \(J = 10.0\) Hz, NCH\(_2\) diastereomer A), 3.31 (1H, t, \(J = 10.0\) Hz, NCH\(_2\) diastereomer B), 3.17 (1H, ddd, \(J = 18.0, 10.0, 7.0\) Hz, NCH\(_2\) diastereomer A), 3.02 – 2.97 (1H, m, NCH\(_2\) diastereomer B), 2.67 – 2.55 (4H, m, NCH\(_2\)CH\(_2\) diastereomer A and B and CHCH\(_2\)C(O)CH\(_3\) diastereomer B), 2.41 (1H, m, NCH\(_2\)CH\(_2\) diastereomer A), 2.32 (1H, dd, \(J = 13.5, 7.0\) Hz, NCH\(_2\)CH\(_2\) diastereomer B), 2.23 (2H, d, \(J = 6.0\) Hz, CHCH\(_2\)C(O)CH\(_3\) diastereomer A), 2.14 (3H, s, CHCH\(_2\)C(O)CH\(_3\) diastereomer B), 1.86 (3H, s, CHCH\(_2\)C(O)CH\(_3\) diastereomer A), 1.40 (9H, s, C(CH\(_3\))\(_3\) diastereomer A), 1.38 (9H, s, C(CH\(_3\))\(_3\) diastereomer B); \(^{13}\)C NMR (125 MHz, d\(_6\)-DMSO, 90 °C, 3:1 mixture of diastereomers) \(\delta\)\(_C\) 207.3 (C(O)CH\(_3\) diastereomer B), 204.4 (C(O)CH\(_3\) diastereomer A), 172.8 (C(O)OCH\(_3\) diastereomer A), 171.3 (C(O)OCH\(_3\) diastereomer B), 152.7 (NC(O)OC(CH\(_3\))\(_3\) diastereomer A and B), 148.5 (4º ArC diastereomer B), 148.3 (4º ArC diastereomer A), 142.5 (4º ArC diastereomer A), 142.2 (4º ArC diastereomer B), 134.2 (4º ArC diastereomer A), 133.9 (4º ArC diastereomer B), 133.9 (4º ArC diastereomer B), 130.5 (4º ArC diastereomer A), 108.2 (ArCH diastereomer A), 106.6 (ArCH diastereomer B), 101.4 (ArCH diastereomer A), 100.9 (OCH\(_2\)O diastereomer A), 100.8 (OCH\(_2\)O diastereomer B), 99.8 (ArCH diastereomer B), 78.7 (NC(O)OC(CH\(_3\))\(_3\) diastereomer A), 78.4 (NC(O)OC(CH\(_3\))\(_3\) diastereomer B), 60.3 (4º C diastereomer A), 58.2 (CHCH\(_2\)C(O)CH\(_3\) diastereomer B), 58.1 (CHCH\(_2\)C(O)CH\(_3\) diastereomer A), 56.2 (ArOCH\(_3\) diastereomer A), 55.4 (ArOCH\(_3\) diastereomer B), 52.1 (C(O)OCH\(_3\) diastereomer A), 51.4 (C(O)OCH\(_3\) diastereomer B), 46.1 (CHCH\(_2\)C(O)CH\(_3\) diastereomer B), 45.1 (CHCH\(_2\)C(O)CH\(_3\) diastereomer A), 42.6 (NCH\(_2\) diastereomer A), 42.2 (NCH\(_2\) diastereomer B), 31.2 (CHCH\(_2\)COCH\(_3\) diastereomer B), 29.3 (NCH\(_2\)CH\(_2\) diastereomer A), 29.1 (CHCH\(_2\)COCH\(_3\) diastereomer A), 27.6 (NC(O)OC(CH\(_3\))\(_3\) diastereomer A), 27.5
(NC(O)OC(CH₃)₃ diastereomer B); **IR** υₘₐₓ/cm⁻¹ 2977, 1732, 1693, 1633, 1396; **MS** (ES+) m/z (relative intensity %) 458 (M + Na⁺, 100%), 893 (2M + Na⁺60%); **HRMS** (ES+): calcd. for C₂₂H₂₉O₈NNa (M + Na⁺) 458.1785, found 458.1780.

NOE interactions were found between proton Hₐ and the aromatic protons in both diastereomers of 210 (Figure 7.2). The relative stereochemistry of the major diastereomer could therefore not be determined by NMR analysis.

![Figure 7.2: NOE interactions observed for the major and minor diastereomer of 210](image)

A solvent and Lewis/Brønsted acid screen was conducted following the above procedure with the conditions detailed in Table 7.5 (equivalents of reagents are unchanged). The dr was calculated from the crude NMR (at 90 ºC).

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<td>THF</td>
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<td>BF₃.THF</td>
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</table>

*Table 7.5:* Optimisation of synthesis of ketoester 210.
7.4.3.6 Synthesis and characterisation of tert-butyl rel-(3aS,7aR)-6-methoxy-3a-(7-methoxy-1,3-benzodioxol-5-yl)-4-oxo-2,3,3a,4,7,7a-hexahydro-1H-indole-1-carboxylate, 212

![Chemical structure](image)

A solution of keto-ester 210 (3.55 g, 8.16 mmol, 3:1 dr) in anh THF (20 mL) was added rapidly dropwise to a stirred solution of KOtBu (17.1 mL of a 1 M solution in THF, 17.1 mmol) in anh THF (130 mL) at 40 ºC. The resulting bright orange solution was stirred at this temperature for 10 min then quenched with 1 M HCl (20 mL, to pH ~1) and allowed to cool to room temperature. The reaction mixture was diluted with ethyl acetate (50 mL), the organic phase separated and the aqueous phase extracted with ethyl acetate (2 x 50 mL). The combined organic portions were dried and concentrated to give crude tert-butyl rel-(3aR,7aS)-3a-(7-methoxy-1,3-benzodioxol-5-yl)4,6-dioxooctahydro-1H-indole-1-carboxylate 211 (MS (ES-): 402 (M - H+, 100%) as a yellow solid which was used directly without purification or characterisation.

Diketone 211 (1.0 g of crude residue, 2.48 mmol) was dissolved in MeOH (10 mL) and TiCl₄ (0.12 mL of a 1 M solution in CH₂Cl₂, 0.12 mmol) was added in one portion at RT. The reaction mixture was stirred at RT for 30 min then quenched with sat. aq. NaHCO₃ (10 mL). The biphasic mixture was extracted with CH₂Cl₂ (2 x 10 mL) then with chloroform:isopropyl alcohol (4:1, 10 mL). The combined organic portions were dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with petroleum ether containing 50 – 95 % diethyl ether to give methylenol ether 212 as a single diastereomer (665 mg, 64%) as a colourless solid. 

\(^1\)H NMR (500 MHz, d₆-DMSO, 90 ºC) δH: 6.57 (1H, d, J = 1.5 Hz, ArH), 6.56 (1H, d, J = 1.5 Hz, ArH), 5.95 (2H, s, OCH₂O), 5.53 (1H, s, CH=COCH₃), 4.27 (1H, t, J = 4.5 Hz, CHCH₂), 3.84 (3H, s, ArOCH₃), 3.75 (3H, s, OCH₃), 3.35 (1H, ddd, J = 10.5, 8.5, 2.5 Hz, NCH₂), 3.16 (1H, br. d, J = 18.5 Hz, CHCH₂), 3.04 – 2.99 (1H, m, NCH₂), 2.76 (1H, dd, J =
18.5, 4.5 Hz, CHCH₂), 2.54 (1H, ddd, J = 10.5, 8.5, 2.5 NCH₂CH₂), 2.21 – 2.15 (1H, m, NCH₂CH₂), 1.42 (9H, s, C(CH₃)₃), ¹³C NMR (125 MHz, d₆-DMSO, 90 ºC) δC 196.5 (C=CH₂C(O)), 174.1 (CH=COCH₃), 153.5 (NC(O)OC(CH₃)₃), 148.3 (ArC), 142.5 (ArC), 133.7 (ArC), 133.6 (ArC), 107.3 (ArCH), 101.0 (ArCH), 100.6 (CH=COCH₃), 100.6 (OCH₂O), 78.6 (C(CH₃)₃), 60.5 (CHCH₂), 57.8 (ArC), 56.4 (ArOCH₃), 55.5 (OCH₃), 45.0 (NCH₂), 33.5 (NCH₂CH₂), 28.9 (CHCH₂), 27.6 (C(CH₃)₃); IR $\nu_{max}$/cm⁻¹ 2976, 2894, 1691, 1650, 1617, 1392, 1201, 1166, 1118; MP 109 - 113 ºC; MS (ES+) m/z (relative intensity %) 476 (M + NH₄⁺ + MeCN, 100%); HRMS (ES+): calcd. for C₂₂H₂₇O₇NNa (M + Na⁺) 440.1680, found 440.1668.

In order to determine the effect of the dr of the starting keto-ester 210 on the yield of enol ether 212 2 experiments were conducted in parallel on a 0.5 mmol scale using keto-ester 210 with 3:1 dr (prepared according to the above procedure in CH₂Cl₂) and 7:1 (prepared according to the above procedure in acetone) to give enol ether 212 as a single diastereomer in 53% and 55% yields respectively.

Alternatively enol ether 212 was prepared in 28% yield on a 0.87 mmol scale following the above procedure replacing TiCl₄ with CSA (10 mol%), and in a 46% yield on a 0.12 mmol scale replacing TiCl₄ with 0.5 M HCl in methanol (20 mol%).

Alternatively, crude diketone 211 was prepared on a 0.1 mmol scale according to the above procedure and the reaction mixture treated, at room temperature, with dimethylsulfate (3 equivalents) for 1 h. The reaction mixture was concentrated and purified by column chromatography on silica gel, eluting with petroleum ether containing 50 – 95 % diethyl ether, giving enol ether 212 (12 mg, 29%).

Alternatively crude diketone 211 was prepared on a 0.23 mmol scale and the residue dissolved in THF (5 mL) and treated with methanol (47 μL, 1.15 mmol), triphenylphosphine (60 mg, 0.23 mmol) and DIAD (46 mg, 0.23 mmol). The reaction mixture was stirred at room temperature overnight then concentrated and
purified by column chromatography on silica gel, eluting with petroleum ether containing 50 – 95 % diethyl ether, giving 212 (40 mg, 42%).

7.4.3.7 Synthesis and characterisation of tert-butyl rel-(3aR,7aS)-6-ethoxy-3a-(7-methoxy-1,3-benzodioxol-5-yl)-4-oxo-2,3,3a,4,7,7a-hexahydro-1H-indole-1-carboxylate, 218

Alternatively, following the above procedure for the synthesis of methyl enol ether 212, crude diketone 211 (200 mg of crude residue, 0.50 mmol) was dissolved in ethanol (2 mL) and treated with TiCl₄ (25 μL of a 1 M solution in CH₂Cl₂), 0.025 mmol) to give ethyl enol ether 218 (81 mg, 38% over 2 steps) following column chromatography on silica gel, eluting with petroleum ether containing 50 – 80% diethyl ether. ¹H NMR (500 MHz, d₆-DMSO, 90 ºC) δH 6.57 (1H, br. s, ArH), 6.55 (1H, br. s, ArH), 5.95 (2H, s, OCH₂O), 5.50 (1H, s, CH=COEt), 4.26 (1H, t, J = 4.5 Hz, CHCH₂), 4.06 – 3.99 (2H, m, OCH₂CH₃), 3.84 (3H, s, ArOCH₃), 3.55 – 3.51 (1H, m, NCH₂), 3.16 (1H, br. d, J = 18.5 Hz, CHCH₂), 3.04 – 2.99 (1H, m, NCH₂), 2.74 (1H, dd, J = 18.5, 4.5 Hz, CHCH₂), 2.56 – 2.53 (1H, m, NCH₂CH₂), 2.20 – 2.14 (1H, m, NCH₂CH₂), 1.42 (9H, s, C(CH₃)₃), 1.30 (3H, t, J = 7.0 Hz, OCH₂CH₂); ¹³C NMR (125 MHz, d₆-DMSO, 90 ºC) δC 196.5 (C=CHC(O)), 173.1 (CH=COEt), 153.5 (NC(O)OC(CH₃)₃), 148.3 (4º ArC), 142.5 (4º ArC), 133.7 (4º ArC), 133.6 (4º ArC), 107.3 (ArCH), 101.4 (CH=COEt), 100.6 (ArCH), 100.6 (OCH₂O), 78.6 (C(CH₃)₃), 63.9 (OCH₂CH₃), 60.5 (CHCH₂), 57.8 (4º C), 56.4 (ArOCH₃), 45.0 (NCH₂), 33.5 (NCH₂CH₂), 29.0 (CHCH₂), 27.6 (C(CH₃)₃), 13.3 (OCH₂CH₂); IR νmax/cm⁻¹ 2979, 1691, 1649, 1613, 1392, 1199, 1165; MP 129 - 134 ºC; MS (ES+) m/z (relative intensity %) 863 (2M + H⁺, 100%), 490 (M + NH₄⁺ + MeCN, 80%), 432 (M + H⁺, 40%); HRMS (ES+): calcd. for C₂₃H₂₉O₇NNa (M + Na⁺) 454.1836, found 454.1835.

7.4.3.8 Synthesis and characterisation of tert-butyl rel-(3aR,7aS)-3a-(7-methoxy-1,3-benzodioxol-5-yl)-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-indole-1-
carboxylate, 217 and tert-butyl rel-(3aR,7aS)-3a-(7-methoxy-1,3-benzodioxol-5-yl)-4-oxooctahydro-1H-indole-1-carboxylate, 217b

To a stirred solution of 212 (300 mg, 0.72 mmol) in CH$_2$Cl$_2$ (25 mL) at -20 ºC was added diisobutylaluminium hydride (1.80 mL of a 1 M solution in hexane, 1.80 mmol). The reaction mixture was stirred at -20 ºC for 15 min then quenched with methanol (0.5 mL), diluted with saturated aqueous potassium sodium tartrate tetrahydrate (30 mL) and stirred vigorously for 30 min (until clean phase separation was achieved). The biphasic mixture was extracted with CH$_2$Cl$_2$ (3 x 10 mL) and the combined organic portions were dried over Na$_2$SO$_4$, filtered and concentrated. The residue was dissolved in diethyl ether (10 mL) and HCl(aq) (2 mL of a 2 M solution) was added and the mixture stirred vigorously for 1 h. The organic phase was separated and the aqueous extracted with ethyl acetate (2 x 5 mL). The combined organic portions were dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with petroleum ether containing 50 – 70% diethyl ether to give enone 217 (161 mg, 58%) as a colourless crystalline solid: $^1$H NMR (500 MHz,d$_6$-DMSO, 90 ºC) $\delta$H 6.84 (1H, d, $J = 10.0$ Hz, CH=CHC(O)), 6.74 (1H, d, $J = 1.5$ Hz, ArH), 6.68 (1H, d, $J = 1.5$ Hz, ArH), 6.09 (1H, d, $J = 10$ Hz, CH=CHC(O)), 5.98 (2H, s, OCH$_2$O), 4.17 (1H, t, $J = 3.5$ Hz, CHCH$_2$CO), 3.88 (3H, s, OCH$_3$), 3.62 (1H, ddd, $J = 10.5$, 8.0, 2.5 Hz, NCH$_2$), 3.13 (1H, td, $J = 10.5$, 6.5 Hz, NCH$_2$), 2.99 (1H, dd, $J = 16.5$, 3.5 Hz, CHCH$_2$C(O)), 2.57 (1H, dd, $J = 16.5$, 3.5 Hz, CHCH$_2$C(O)), 2.54 – 2.47 (1H, m, NCH$_2$CH$_2$), 2.12 (1H, ddd, $J = 12.5$, 6.5, 2.5 Hz, NCH$_2$CH$_2$), 0.90 (9H, s, C(CH$_3$)$_3$); $^{13}$C NMR (125 MHz, d$_6$-DMSO, 90 ºC) $\delta$C 195.9 (C(O)), 153.1 (NC(O)O), 150.7 (CH=CHC(O)), 148.6 (4º ArC), 142.8 (4º ArC), 134.5 (4º ArC), 133.9 (4º ArC), 128.2 (CH=CHC(O)), 107.3 (ArCH), 100.8 (OCH$_2$O), 100.4 (ArCH), 78.5 (C(CH$_3$)$_3$), 61.9 (CHCH$_2$C(O)), 56.4 (OCH$_3$), 50.5 (4º C), 45.2 (NCH$_2$), 37.2 (CHCH$_2$C(O)), 35.4 (NCH$_2$CH$_2$), 27.6 (C(CH$_3$)$_3$); IR $\nu_{max}$/cm$^{-1}$ 2975,
The by-product 217b (30 mg, 11%) was also isolated as a colourless solid: $^1$H NMR (500 MHz, d$_6$-DMSO, 90 ºC) $\delta_H$ 6.51 (1H, br. d. $J = 1.5$ Hz, ArH), 6.47 (1H, s, ArH), 5.96 (2H, s, OCH$_2$O), 4.42 (1H, t, $J = 5.5$ Hz, CHCH$_2$CH$_2$CH$_2$(O)), 3.85 (3H, s, OCH$_3$), 3.36 (1H, ddd, $J = 10.5$, 7.5, 5.5 Hz, NCH$_2$), 3.16 (1H, td, $J = 10.5$, 7.5, NCH$_2$), 2.57 (1H, ddd, $J = 13.0$, 7.5, 5.5 Hz, NCH$_2$CH$_2$), 2.41 – 2.30 (2H, m, CHCH$_2$CH$_2$C(O)), 2.14 – 2.06 (2H, m, CHCH$_2$CH$_2$C(O)), 1.92 (1H, td, $J = 7.5$, 13.0, NCH$_2$CH$_2$), 1.88 – 1.83 (1H, m, CHCH$_2$CH$_2$CH$_2$(O)), 1.81 – 1.74 (1H, m, CHCH$_2$CH$_2$CH$_2$(O)), 1.41 (9H, s, C(CH$_3$)$_3$); $^{13}$C NMR (125 MHz, d$_6$-DMSO, 90 ºC) $\delta_C$ 209.3 (C(O)), 153.2 (NC(O)O), 148.5 (4º ArC), 142.6 (4º ArC), 133.7 (4º ArC), 133.6 (4º ArC), 107.2 (ArCH), 100.8 (OCH$_2$O), 100.5 (ArCH), 78.3 (C(CH$_3$)$_3$), 63.1 (CHCH$_2$CH$_2$CH$_2$(O)), 62.0 (4º C), 56.4 (OCH$_3$), 44.3 (NCH$_2$), 37.7 (CHCH$_2$CH$_2$CH$_2$(O)), 33.0 (NCH$_2$CH$_2$), 27.7 (C(CH$_3$)$_3$), 25.6 (CHCH$_2$CH$_2$CH$_2$(O)), 19.6 (CHCH$_2$CH$_2$CH$_2$(O)); IR $\nu_{max}$/cm$^{-1}$ 2973, 1694, 1632, 1512, 1392, 1142; MP 149 – 153 ºC; MS (ES+) m/z (relative intensity %) 801 (2M + Na$^+$, 100%), (2M + K$^+$, 80%), 412 (M + Na$^+$, 75%), 428 (M + K$^+$, 50%); HRMS (ES+): calcd. for C$_{21}$H$_{27}$O$_6$NNa (M + Na$^+$) 412.1731, found 412.1730.

Alternatively treating enol ether 212 with the reagents/conditions shown in Table 7.6 (until no starting material was present by TLC analysis) gave enone 217 and by-products 217b and 217c in the ratios and yields shown. Product ratios were calculated from the crude NMR at 90 ºC; yields are isolated after column chromatography on silica gel under the above conditions.

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<td>12</td>
<td>DIBAL (2.5)</td>
<td>CH₂Cl₂</td>
<td>-20</td>
<td>5.3:1:0</td>
<td>217 58%, 217b 11%</td>
</tr>
<tr>
<td>13</td>
<td>DIBAL (2)</td>
<td>CH₂Cl₂</td>
<td>-78</td>
<td>2:1:0</td>
<td>217 44%, 217b 21%</td>
</tr>
</tbody>
</table>

Table 7.6: Screen of reducing agents/conditions for the reduction of 212.

Alternatively enone 217 was prepared from ethyl-enol ether 218 on a 0.1 mmol scale following the above procedure to give 217 (14 mg, 36%) and 217b (7 mg, 18%).

7.4.3.9 Synthesis and characterisation of tert-butyl-4-hydroxy-3a-(7-methoxy-1,3-benzodioxol-5-yl)octahydro-1H-indole-1-carboxylate 217c (diastereomers A and B)

A solution of 212 (50 mg, 0.12 mmol) in anhydrous THF (3 mL) was prepared and cooled to -78 °C. Super-hydride® (0.26 mL of a 1 M solution, 0.26 mol) and the reaction mixture stirred for 1 h, warmed to -20 °C and stirred for a further 1 h then quenched with 1 M HCl (5 mL). The reaction mixture was extracted with EtOAc (3 x 5 mL) and the combined organics dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel to give 217c as a 1:1 ratio of diastereomers A (12 mg, 26%) as a colourless oil and B (12 mg, 26%) as a colourless oil (separated by column chromatography). 217c diastereomer A: 1H
NMR (500 MHz, d$_6$-DMSO, 90 ºC) $\delta$H 6.76 (1H, d, $J = 1.5$ Hz, ArH), 6.73 (1H, d, $J = 1.5$ Hz, ArH), 5.92 (2H, s, OCH$_2$O), 4.06 (1H, dd, $J = 6.0$, 10.5 Hz, CHN), 3.86 (3H, s, OCH$_3$), 3.66 (1H, dd, $J = 10.5$, 5.0 Hz, CHO), 3.29 – 3.24 (1H, m, NCH$_2$), 3.09 – 3.04 (1H, m, NCH$_2$), 2.25 – 2.22 (2H, m, NCH$_2$CH$_2$), 1.98 – 1.96 (1H, m, CH$_2$CH$_2$), 1.74 – 1.71 (1H, m, CH$_2$CHOH), 1.66 – 1.63 (1H, m, CH$_2$CH$_2$CH$_2$), 1.45 – 1.34 (2H, m, CH$_2$CHOH and CH$_2$CH$_2$CH$_2$), 1.32 (9H, s, C(CH$_3$)$_3$), 1.24 – 1.19 (1H, m, CH$_2$CH$_2$); $^{13}$C NMR (125 MHz, d$_6$-DMSO, 90 ºC) $\delta$C 152.7 (C(O)N), 147.9 (4º ArC), 142.0 (4º ArC), 139.1 (4º ArC), 132.5 (4º ArC), 132.7 (4º ArC), 121.7 (4º ArC), 107.5 (ArCH), 100.8 (OCH$_2$O), 100.2 (ArCH), 77.3 (C(CH$_3$)$_3$), 73.8 (CHOH), 69.0 (CHN), 61.7 (4º C), 56.3 (OCH$_3$), 42.1 (NCH$_2$), 30.5 (NCH$_2$CH$_2$), 27.7 (CH$_2$), 27.6 (C(CH$_3$)$_3$), 25.3 (CH$_2$), 19.8 (CH$_2$CH$_2$CH$_2$); IR $\nu_{\text{max}}$/cm$^{-1}$ 3427, 2935, 1633, 1366; MS (ES-) m/z (relative intensity %) 390 (M – H$^+$, 100%) HRMS (ES+): calcd. for C$_{21}$H$_{29}$O$_6$NNa (M + Na$^+$) 414.1887, found 414.1884.

217c diastereomer B: $^1$H NMR (500 MHz, d$_6$-DMSO, 90 ºC) $\delta$H 6.57 – 6.56 (2H, m, ArH), 5.92 (2H, s, OCH$_2$O), 4.24 (1H, dd, $J = 9.5$, 6.5 Hz, CHO), 4.06 (1H, br. s, CHN), 3.84 (3H, s, OCH$_3$), 3.22 – 3.18 (1H, m, NCH$_2$), 2.84 – 2.78 (1H, m, NCH$_2$), 2.30 (1H, td, $J = 12.5$, 9.5 Hz, NCH$_2$CH$_2$), 2.02 – 1.98 (1H, m, CH$_2$CH$_2$), 1.91 (1H, dd, $J = 12.5$, 7.0 Hz, NCH$_2$CH$_2$), 1.79 – 1.63 (3H, m, CH$_2$CH$_2$CH$_2$ and CH$_2$CHOH), 1.44 – 1.38 (2H, m, CH$_2$CHN and CH$_2$CHOH), 1.41 (9H, s, C(CH$_3$)$_3$); $^{13}$C NMR (125 MHz, d$_6$-DMSO, 90 ºC) $\delta$C 152.7 (C(O)N), 148.0 (4º ArC), 121.7 (4º ArC), 139.1 (4º ArC), 132.5 (4º ArC), 107.3 (ArCH), 100.5 (OCH$_2$O), 100.2 (ArCH), 77.5 (C(CH$_3$)$_3$), 69.0 (CHN), 56.1 (OCH$_3$), 55.9 (CHOH), 52.7 (4º C), 41.9 (NCH$_2$), 32.3 (NCH$_2$CH$_2$), 28.7 (CH$_2$), 27.7 (C(CH$_3$)$_3$), 27.6 (CH$_2$), 16.6 (CH$_2$CH$_2$CH$_2$); IR $\nu_{\text{max}}$/cm$^{-1}$ 3441, 2973, 1686, 1408; MS (ES-) m/z (relative intensity %) 390 (M – H$^+$, 100%) HRMS (ES+): calcd. for C$_{21}$H$_{29}$O$_6$NNa (M + Na$^+$) 414.1887, found 414.1884.

NEOSY NMR confirmed the relative stereochemistry of the 2 diastereomers (Figure 7.3)
Figure 7.3: NOESY interactions observed to confirm relative stereochemistry of the 2 diastereomers of 217c.

7.4.3.10 Synthesis and characterisation of tert-butyl rel-(3aS,6R,7aR)-6-hydroxy-3a-(7-methoxy-1,3-benzodioxol-5-yl)-2,3,3a,6,7,7a-hexahydro-1H-indole-1-carboxylate, 219 and tert-butyl rel-(3aS,6S,7aR)-6-hydroxy-3a-(7-methoxy-1,3-benzodioxol-5-yl)-2,3,3a,6,7,7a-hexahydro-1H-indole-1-carboxylate, 219b

To a stirred solution of enone 217 (365 mg, 0.94 mmol) in THF (15 mL) at -78 °C was added L-Selectride® (1.13 mL of a 1 M solution in THF, 1.13 mmol). The reaction mixture was stirred at -78 °C for 3 h then quenched with sat. aq. NaHCO₃ and extracted with ethyl acetate. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with petroleum ether containing 60 – 70% diethyl ether to give 219 (198 mg, 54%, dr >97:3) as a colourless solid and mixed 219 + 219b (88 mg, 24%, dr 1:1.1) as a colourless solid (combined yield 286 mg, 78%, crude dr 3.5:1). Major diastereomer 219: ¹H NMR (500 MHz, d₆-DMSO, 90 °C) δH 6.69 (1H, d, J = 1.5 Hz, ArH), 6.66 (1H, d, J = 1.5 Hz, ArH), 5.96 (2H, s, OCH₂O), 5.91 (1H, dd, J = 10.0, 2.0 Hz, CH=CHCHOH), 5.53 (1H, d, J = 10.0 Hz, CH=CHCHOH), 4.05 – 4.03 (1H, br. m, CHO), 3.89 – 3.85 (1H, m, CHCH₂CHOH), 3.87 (3H, s, OCH₃), 3.54 (1H, ddd, J = 10.0, 8.0, 3.0 Hz, NCH₂), 3.11 (1H, td, J = 10.0, 6.5 Hz, NCH₂), 2.37 – 2.31 (2H, m, CHCH₂CHOH and NCH₂CH₂), 1.83 (1H, ddd, J = 12.0, 6.5, 3.0 Hz, NCH₂CH₂), 1.56 (1H, ddd, J =
11.5, 8.5, 3.0 Hz, CHCH₂CHOH), 1.43 (9H, s, C(CH₃)₃); ¹³C NMR (125 MHz, d₆-DMSO, 90 ºC) δC 152.9 (N-C(O)O), 148.3 (4° ArC), 142.4 (4° ArC), 138.1 (4° ArC), 133.2 (4° ArC), 132.3 (CH=CHCHOH), 131.0 (CH=CHCHOH), 107.3 (ArCH), 100.6 (OCH₂O), 100.6 (ArCH), 77.9 (C(CH₃)₃), 61.0 (CHOH), 60.7 (CHCH₂CHOH), 56.4 (OCH₃), 49.6 (4° C), 44.8 (NCH₂), 35.0 (NCH₂CH₂), 30.9 (CHCH₂CHOH), 27.7 (C(CH₃)₃); IR νmax/cm⁻¹ 3419, 2976, 1672, 1634, 1511, 1406, 1131; MP 63 – 66 ºC; MS (ES-) m/z (relative intensity %) 388 (M-H⁺, 100%); HRMS (ES+): calcd. for C₂₁H₂₇O₆NNa (M + Na⁺) 412.1731, found 412.1731.

Minor diastereomer 219b: ¹H NMR (500 MHz, d₆-DMSO, 90 ºC) δH 6.56 (1H, d, J = 1.5 Hz, ArH), 6.53 (1H, d, J = 1.5 Hz, ArH), 5.94 (2H, d, J = 2.0 Hz, OCH₂O), 5.72 (1H, d, J = 10 Hz, CH=CHCHOH), 5.65 (1H, dd, J = 10.0, 2.0 Hz, CH=CHCHOH), 5.42 (1H, d, J = 3.5 Hz, OH), 4.23 (1H, br. s, CHOH), 4.04 (1H, dd, J = 10.5, 5.0 Hz, CHCH₂CHOH), 3.84 (3H, s, OCH₃), 3.38 (1H, td, J = 10.0 Hz, CH₂CO₂H), 3.33 – 3.30 (1H, m, NCH₂), 2.37 – 2.31 (1H, m, NCH₂CH₂), 2.20 (1H, td, J = 5.0, 10.0 Hz, CHCH₂CHOH), 2.10 (1H, td, J = 10.0, 13.0 Hz, NCH₂CH₂), 1.60 (1H, q, J = 10.5 Hz, CHCH₂CHOH), 1.40 (9H, s, C(CH₃)₃); ¹³C NMR (125 MHz, d₆-DMSO, 90 ºC) δC 152.8 (N-C(O)O), 148.4 (4° ArC), 142.4 (4° ArC), 139.5 (4° ArC), 133.1 (4° ArC), 131.3 (C=C), 131.1 (C=C), 106.6, (ArCH) 100.5 (OCH₂O), 100.1 (ArCH), 77.8 (C(CH₃)₃), 63.6 (CHOH), 60.6 (CHCH₂CHOH), 56.3 (OCH₃), 49.3 (4° C), 44.0 (NCH₂), 35.2 (NCH₂CH₂), 35.0 (CHCH₂CHOH), 27.7 (C(CH₃)₃); IR νmax/cm⁻¹ 3419, 2360, 1669, 1634, 1450; MP 98 – 100 ºC; MS (ES+) m/z (relative intensity %) 448 (M + NH₄⁺ + MeCN, 100%), 412 (M + Na⁺, 50%), 390 (M + H⁺, 70%); HRMS (ES+): calcd. for C₂₁H₂₇O₆NNa (M + Na⁺) 412.1731, found 412.1730.

The relative stereochemistry of the allylic alcohol was confirmed by NOE analysis (Figure 7.4).
Alternatively reacting enone 217 with the reagents shown in Table 7.7, following the above procedure at the temperature and in the solvents shown, allylic alcohols 219 and 219b were synthesised in the diastereomeric ratio (determined from the crude NMR) and yields shown.

Table 7.7: Screen of reducing conditions for synthesis of allylic alcohol. a calculated from crude NMR at 90 ºC, b overall yield of both diastereomers

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reductant (equiv)</th>
<th>T /ºC</th>
<th>Solvent</th>
<th>dr (^a) (219:219b)</th>
<th>Yield (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Super-hydride(^\circ)</td>
<td>-20</td>
<td>THF</td>
<td>1:2</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>N-Selectride(^\circ)</td>
<td>-20</td>
<td>THF</td>
<td>2:1</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>N-Selectride(^\circ)</td>
<td>-20</td>
<td>CH(_2)Cl(_2)</td>
<td>1:1</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>N-Selectride(^\circ)</td>
<td>-20</td>
<td>toluene</td>
<td>1:1.3</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>N-Selectride(^\circ)</td>
<td>-78</td>
<td>THF</td>
<td>2:1</td>
<td>77%</td>
</tr>
<tr>
<td>6</td>
<td>N-Selectride(^\circ)</td>
<td>rt</td>
<td>THF</td>
<td>2:1</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>K-Selectride(^\circ)</td>
<td>-20</td>
<td>THF</td>
<td>1.7:1</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>L-Selectride(^\circ)</td>
<td>-20</td>
<td>THF</td>
<td>3.5:1</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>L-Selectride(^\circ)</td>
<td>-78</td>
<td>THF</td>
<td>3.5:1</td>
<td>78%</td>
</tr>
</tbody>
</table>

Alternatively, enone 217 (100 mg, 0.26 mmol) was treated with NaBH\(_4\) (23 mg, 0.54 mmol) and CeCl\(_3\).7H\(_2\)O (201 mg, 0.54 mol) in MeOH (7 mL) at 0 ºC for 1 h. The reaction mixture was diluted with sat. aq. NaHCO\(_3\) (10 mL) and extracted with CH\(_2\)Cl\(_2\) (3 x 20 mL). The combined organic portions were dried over Na\(_2\)SO\(_4\), filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with petroleum ether containing 70 -90% diethyl ether to give 219:219b (96 mg, 95%, 1:5.5 dr).
To a stirred solution of 219b (24 mg, 0.06 mmol) in anh THF (1.5 mL) at 0 ºC was added NEt$_3$ (43 μL, 0.31 mmol) and methanesulfonic anhydride (54 mg, 0.31 mmol) as a solution in anh THF (1.5 mL). The reaction mixture was stirred at this temperature for 2 h then evaporated and dissolved in anh DMF (2 mL) and CsOAc (172 mg, 0.9 mmol) was added. The reaction mixture was stirred at room temperature overnight then filtered to remove the solids (washing with EtOAc) and the filtrate concentrated. The residue was dissolved in MeOH (2.5 mL) and K$_2$CO$_3$ (100 mg, 0.72 mmol) was added. The reaction mixture was stirred at room temperature for 3 h then diluted with water (10 mL) and extracted with CH$_2$Cl$_2$ (3 x 5 mL). The combined organics were dried over Na$_2$SO$_4$, filtered and concentrated and the residue purified by column chromatography on silica gel eluting with petroleum ether containing 60 – 70% diethyl ether to give 219 and 219b (18 mg, 75%, 3.1:1 dr), no attempt was made to separate the diastereomers in this case.

7.4.3.11 Synthesis and characterisation of (±)-powelline, 185

Allylic alcohol 219 (21 mg, 0.05 mmol) was dissolved in TFA (1 mL) and stirred at RT for 5 min. The TFA was removed by rotary evaporation and the residue re-dissolved in a second portion of TFA (1 mL). The mixture was stirred at RT for a further 5 min then evaporated and the residue dissolved in CHCl$_3$:isopropyl alcohol (4:1, 5 mL) and sat. aq. NaHCO$_3$ (3 mL) was added. The organic phase was separated and the aqueous extracted with CHCl$_3$:isopropyl alcohol (4:1) (3 x 5 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated to
give crude *rel*-3aR,6S,7aS)-3a-(7-methoxy-1,3-benzodioxol-5-yl)-2,3,3a,6,7,7a-hexahydro-1H-indol-6-ol 220. The residue was used directly in the next step without purification or characterisation, MS (ES+) m/z (relative intensity %) 290 (M + H+, 100%).

Crude 220 was dissolved in MeOH (0.5 mL) and aq. formaldehyde (2 mL, 37% wt.) was added. The reaction mixture was stirred at RT for 15 min then 6 M HCl (5 mL) was added. The reaction mixture was stirred at RT for 10 min then quenched by the addition of solid K₂CO₃ and extracted with CHCl₃/isopropyl alcohol (4:1) (5 x 2 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated, the residue was purified by column chromatography on silica gel, eluting with CH₂Cl₂ containing 1 – 10 % MeOH to give (±)-powelline (±)-185 (7 mg, 49%) as a colourless amorphous solid and a mixture of (±)-powelline (±)-185 and regioisomer (±)-185b (5 mg, 35% 2.5:1 (185:1185b)). (±)-powelline (±)-185:

$^1$H NMR (500 MHz, CDCl₃) δH 6.57 (1H, s, ArH), 6.55 (1H, d, J = 10.0 Hz, CH=CHCHOH), 5.95 (1H, dd, J = 10.0, 5.0 Hz, CH=CHCHOH), 5.87 (1H, d, J = 1.5 Hz, OCH₂O), 5.86 (1H, d, J = 1.5 Hz, OCH₂O), 4.35 (1H, m, C=CHOH), 4.28 (1H, d, J = 17.5 Hz, CH₂N), 3.98 (3H, s, OCH₃), 3.85 (1H, d, J = 17.5 Hz, CH₂N), 3.43 – 3.38 (2H, m, CHN and CH₂CH₂N), 2.93 – 2.88 (1H, m, CH₂CH₂N), 2.21 – 2.16 (1H, m, CH₂CH₂N), 2.08 – 2.05 (1H, br. m, CHCH₂CHOH), 1.95 – 1.89 (1H, m, CH₂CH₂N), 1.75 (1H, td, J = 13.5, 4.0 Hz CHCH₂CHOH); $^{13}$C NMR (125 MHz, CDCl₃) δc 148.2 (4º ArC), 141.0 (4º ArC), 139.0 (4º ArC), 133.4 (4º ArC), 132.2 (CH=CHCHOH), 127.4 (CH=CHCHOH), 116.9 (4º ArC), 100.6 (OCH₂O), 96.8 (ArCH), 64.0 (CHOH), 62.6 (CHCH₂CHOH), 59.2 (ArOCH₃), 58.6 (NCH₂), 53.7 (NCH₂CH₂), 44.2 (NCH₂CH₂), 43.9 (4º C), 32.4 (CH₂CH₂CHOH); MP 95 – 100 °C; IR νmax/cm⁻¹ 3385, 3005, 1617, 1477, 1276, 1261, 1043, 940; MS (ES+) m/z (relative intensity %) 302 (M + H⁺, 100%); HRMS (ES+): calcd. for C₁₇H₂₀O₄N (M + H⁺) 302.1387, found 302.1389.

(±)-185b: $^1$H NMR (500 MHz, CDCl₃) δH 6.60 (1H, d, J = 10 Hz, CH=CHCHOH), 6.50 (1H, s, ArH), 5.97 (1H, dd, J = 10.0, 5.0 Hz, CH=CHCHOH), 5.94 (1H, d, J = 1.0, OCH₂O), 5.92 (1H, d, J = 1.0 Hz, OCH₂O), 4.37 – 4.31 (2H, m, CHOH and CH₂N), 3.90 (3H, s, OCH₃), 3.84 (1H, d, J = 17.0 Hz, CH₂N), 3.45 – 3.38 (2H, m, CHN and CH₂CH₂N), 2.98 – 2.91 (1H, m, CH₂CH₂N), 2.24 – 2.15 (2H, m, CH₂CH₂N, CHCH₂CHOH), 1.99 – 1.93 (1H, m, CH₂CH₂N), 1.79 – 1.73 (1H, td, J
= 9.0, 5.0 Hz, \( \text{CHCH}_2\text{CHOH} \)); \( ^{13}\text{C NMR} \) (125 MHz, \( \text{CDCl}_3 \)) \( \delta \text{C} 146.2 \) (4º \( \text{ArC} \)), 142.0 (4º \( \text{ArC} \)), 139.8 (4º \( \text{ArC} \)), 133.2 (4º \( \text{ArC} \)), 131.6 (CH=CHCHOH), 127.2 (CH=CHCHOH), 107.7 (4º \( \text{ArC} \)), 101.9 (OCH\(_2\)O), 101.6 (ArCH), 64.0 (CHOH), 63.0 (CHCH\(_2\)CHOH), 57.0 (ArOCH\(_3\)), 56.9 (NCH\(_2\)H), 53.7 (NCH\(_2\)CH\(_2\)), 44.5 (NCH\(_2\)CH\(_2\)), 44.0 (4º \( \text{C} \)), 32.6 (CHCH\(_2\)CHOH); \( \text{MS} \) (ES+) \( m/z \) (relative intensity %) 302 (M + H\(^+\), 100%).

The regioselectivity of the Pictet-Spengler reaction and the structures of 185 and 185b were further confirmed by NOE analysis Figure 7.5.

![Figure 7.5: NOE analysis of powelline 185 and regioisomer 185b.](image)

7.4.3.12 Synthesis and characterisation of (±)-C3-epi-powelline, C3-epi-185

Allylic alcohol 219b (15 mg, 0.05 mmol) was dissolved in TFA (1 mL) and stirred at RT for 5 min. The TFA was removed by rotary evaporation and the residue dissolved in a second portion of TFA (1 mL). The mixture was stirred at RT for a further 5 min then evaporated and the residue dissolved in CHCl\(_3\):isopropyl alcohol (4:1, 5 mL) and sat. aq. NaHCO\(_3\) (3 mL) was added. The organic phase was separated and the aqueous extracted with CHCl\(_3\):isopropyl alcohol (4:1) (3 x 5 mL). The combined organic extracts were dried over Na\(_2\)SO\(_4\), filtered and concentrated to give crude C3-epi-220. The residue was used directly in the next step without purification or characterisation, \( \text{MS} \) (ES+) \( m/z \) (relative intensity %) 290 (M + H\(^+\), 100%).
Crude **C3-epi-220** was dissolved in MeOH (0.5 mL) and aq. formaldehyde (2 mL, 37% wt.) was added. The reaction mixture was stirred at RT for 15 min then 6 M HCl (5 mL) was added. The reaction mixture was stirred at RT for 10 min then quenched by the addition of solid K₂CO₃ and extracted with CHCl₃/isopropyl alcohol (4:1) (5 x 2 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated, the residue was purified by column chromatography on silica gel, eluting with CH₂Cl₂ containing 1 – 10 % MeOH to give (±)-C3-epi-powelline **C3-epi-185** (5 mg, 46%) as an off-white solid:

**¹H NMR** (500 MHz, CDCl₃) δH 6.53 (1H, s, ArH), 6.37 (1H, dd, J = 10.0, 2.0 Hz, CH=CHCHOH), 5.87 (1H, d, J = 10.0 Hz, CH=CHCHOH), 4.45 – 4.42 (1H, m, CHOH), 4.29 (1H, d, J = 17.5 Hz, CH₃N), 3.98 (3H, s, OC₃H₃), 3.84 (1H, d, J = 17.5 Hz, CH₂N), 3.53 – 3.48 (1H, m, CH₂CH₂N), 3.25 (1H, dd, J = 13.0, 3.5 Hz, CHCH₂CHOH), 2.94 (1H, ddd, J = 13.5, 9.0, 6.0 Hz, CH₂CH₂N), 2.23 – 2.27 (1H, m, CHCH₂CHOH), 2.20 (1H, ddd, J = 13.5, 9.0, 4.5 Hz, CH₂CH₂N), 2.13 – 2.08 (1H, m, CH₂CH₂N), 1.66 – 1.59 (1H, m, CHCH₂CHOH); NOESY interaction found between NC₃H₂ signal at 3.84 and OCH₃ signal at 3.98; **¹³C NMR** (125 MHz, CDCl₃) δC 148.3 (4º ArC), 140.9 (4º ArC), 139.1 (4º ArC), 133.4 (4º ArC), 131.5 (CH=CHCHOH), 128.5 (CH=CHCHOH), 116.0 (4º ArC), 100.7 (OCH₂O), 96.7 (ArCH), 67.6 (CHOH), 66.3 (CHCH₂CHOH), 59.2 (ArOCH₃), 58.2 (NCH₂), 53.2 (NCH₂CH₂), 44.5 (NCH₂CH₂), 44.4 (4º C), 34.5 (CHCH₂CHOH); **MP** 95 – 100 ºC; **IR** νmax/cm⁻¹ 3406, 3027, 1617, 1477, 1236, 1041; **MS** (ES+) m/z (relative intensity %) 302 (M + H⁺, 100%); **HRMS** (ES+): calcd. for C₁₇H₂₀O₄N (M + H⁺) 302.1387, found 302.1387.

Insufficient quantities of the assumed minor regioisomer **C3-epi-185b** could be obtained for full characterisation. Selected data: **¹H NMR** (500 MHz, CDCl₃) δH 6.45 (1H, s, ArH), 6.43 (1H, dd, J = 10.0, 2.0 Hz, CH=CHCHOH), 5.94 (1H, d, J = 1.5 Hz, OCH₂O), 5.91 (1H, d, J = 1.5 Hz, OCH₂O), 5.78 (1H, d, J = 10.0 Hz, CH=CHCHOH), 4.45 – 4.42 (1H, m, CHOH), 4.30 (1H, d, J = 17.5 Hz, CH₂N), 3.90 (3H, s, OCH₃), 3.79 (1H, d, J = 17.5 Hz, CH₂N), 3.53 – 3.48 (1H, m, CH₂CH₂N), 3.25 – 3.21 (1H, m, CHCH₂CHOH), 2.96 – 2.90 (1H, m, CH₂CH₂N), 2.27 – 2.23 (1H, m, CHCH₂CHOH), 2.21 – 2.17 (1H, m, CH₂CH₂N), 2.13 – 2.06 (1H, m, CH₂CH₂N), 1.66 – 1.59 (1H, m, CHCH₂CHOH); NOESY interaction
found between OCH₃ signal at 3.90 and the aromatic proton signal at 6.45; MS (ES+) m/z (relative intensity %) 302 (M + H⁺, 100%).

7.4.3.13 Synthesis and characterisation of tert-butyl rel-(3aS,6R,7aR)-6-methoxy-3a-(7-methoxy-1,3-benzodioxol-5-yl)-2,3,3a,6,7,7a-hexahydro-1H-indole-1-carboxylate, 221

To a stirred solution of allylic alcohol 219 (36 mg, 0.095 mmol) in THF (2 mL) was added NaH (15 mg of 60% wt. in mineral oil, 0.37 mmol). The reaction mixture was stirred at RT for 5 min then methyl iodide (25 μL, 0.37 mmol) was added. The reaction mixture was stirred at room temperature for 6 h then quenched with saturated aqueous ammonium chloride (5 mL) and extracted with ethyl acetate (3 x 3 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with petroleum ether:diethyl ether (1:1) to give 221 (34 mg, 91%) as a colourless oil: ¹H NMR (500 MHz, d₆-DMSO, 90 ºC) δH 6.63 (1H, d, J = 1.5 Hz, ArH), 6.62 (1H, d, J = 1.5 Hz, ArH), 5.99 (1H, dd, J = 10.0, 3.0 Hz, CH=CHCHOCH₃), 5.95 (2H, s, OCH₂O), 5.68 (1H, d, J = 10.0 Hz, CH=CHCHOCH₃), 3.94 (1H, dd, J = 7.0, 3.0 Hz, CHCH₂CHOCH₃), 3.85 (3H, s, OCH₃), 3.77 – 3.74 (1H, m, CHOCH₃), 3.50 (1H, ddd, J = 11.0, 7.5, 4.5 Hz, NCH₂), 3.30 (3H, s, OCH₃), 3.16 (1H, td, J = 11.0, 7.5 Hz, NCH₂), 2.36 (1H, td, J = 12.5, 7.5 Hz, NCH₂CH₂), 2.32 – 2.28 (1H, m, CHCH₂CHOH), 1.91 – 1.86 (1H, m, NCH₂CH₂), 1.71 (1H, ddd, J = 13.0, 7.0, 3.0 Hz, CHCH₂CHOH), 1.42 (9H, s, C(CH₃)₃); ¹³C NMR (125 MHz, d₆-DMSO, 90 ºC) δc 152.9 (NC(O)O), 148.4 (4º ArC), 142.5 (4º ArC), 137.9 (4º ArC), 133.2 (4º ArC + CH=CHCHOH), 127.6 (CH=CHCHOH), 107.3 (ArCH), 100.6 (OCH₂O), 100.4 (ArCH), 78.0 (C(CH₃)₃), 70.8 (CHOH), 60.1 (CHCH₂CHOCH₃), 56.4 (ArOCH₃), 54.7 (OCH₃), 49.8 (4º C), 44.7 (NCH₂), 34.6 (NCH₂CH₂), 27.7 (C(CH₃)₃), 27.6 (CHCH₂CHOH); IR νmax/cm⁻¹ 2855, 1692, 1633, 1511, 1391, 1172, 1093; MS (ES+) m/z (relative intensity %)
462 (M + NH$_4^+$ + MeCN, 100%); **HRMS (ES+):** calcd. for C$_{22}$H$_{29}$O$_6$NNa (M + H$^+$) 426.1887, found 426.1883

7.4.3.14 Synthesis and characterisation of (±)-buphanidrine, 184

Allylic ether 221 (20 mg, 0.05 mmol) was dissolved in TFA (1 mL) and stirred at RT for 5 min. The TFA was removed by rotary evaporation and the residue redissolved in a second portion of TFA (1 mL). The mixture was stirred at RT for a further 5 min then evaporated and the residue dissolved in CHCl$_3$:isopropyl alcohol (4:1, 5 mL) and sat. aq. NaHCO$_3$ (3 mL) was added. The organic phase was separated and the aqueous extracted with CHCl$_3$:isopropyl alcohol (4:1) (3 x 5 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated to give crude 221b. The residue was used directly in the next step without purification or characterisation, **MS (ES+) m/z (relative intensity %) 304** (M + H$^+$, 100%).

Crude 221b was dissolved in MeOH (1 mL) and aq. formaldehyde (2.5 mL, 37% wt.) was added. The reaction mixture was stirred at RT for 15 min then 6 M HCl (5 mL) was added. The reaction mixture was stirred at RT for 10 min then quenched by the addition of solid K$_2$CO$_3$ and extracted with CHCl$_3$:isopropyl alcohol (4:1) (5 x 2 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated, the residue was purified by column chromatography on silica gel, eluting with CH$_2$Cl$_2$ containing 1 – 10 % MeOH to give (±)-buphanidrine (±)-184 (8 mg, 51%) as a colourless oil and a mixture of (±)-buphanidrine and regioisomer (±)-184b (5 mg, 32% 2.8:1 (184:184b)). (±)-Buphanidrine (±)-184: $^1$H NMR (500 MHz, CDCl$_3$) δH 6.58 (1H, d, J = 10 Hz, CH=CHCHOH), 6.56 (1H, s, ArH), 5.96 (1H, ddd, J = 10.0, 5.0, 1.0, CH=CHCHOCH$_3$), 5.86 (1H, d, J = 1.5 Hz, OCH$_2$O), 5.84 (1H, d, J = 1.5 Hz, OCH$_2$O), 4.25 (1H, d, J = 17.5 Hz, NCH$_2$), 3.96 (3H, s, ArOCH$_3$), 3.81 (1H, d, J = 17.5 Hz, NCH$_2$), 3.83 – 3.81 (1H, m, CHOCH$_3$), 3.35 (3H, s, OCH$_3$), 3.39 – 3.34 (1H, m, NCH$_2$CH$_2$), 3.31 (1H, dd, J = 13.5, 4.0 Hz,
CHCH₂CHOH), 2.88 (1H, ddd, J = 13.5, 9.0, 6.0 Hz, NCH₂CH₂), 2.15 (1H, ddd, J = 13.5, 9.0, 6.0 Hz, NCH₂CH₂), 2.10 (1H, br. d, J = 13.5 Hz, CHCH₂CHOH), 1.91 (1H, ddd, J = 12.0, 10.5, 6.0 Hz, NCH₂CH₂), 2.15 (1H, ddd, J = 13.5, 9.0, 6.0 Hz, NCH₂CH₂), 2.10 (1H, br. d, J = 13.5 Hz, CHCH₂CHOH), 1.91 (1H, ddd, J = 12.0, 10.5, 6.0 Hz, NCH₂CH₂), 1.60 (1H, td, J = 13.5, 4.0 Hz, CHCH₂CHOH); \(^{13}\text{C NMR}\) (125 MHz, CDCl₃) \(\delta_{\text{C}}\) 148.0 (4º Ar C), 140.9 (4º Ar C), 139.4 (4º Ar C), 133.4 (4º Ar C), 133.0 (CH=CHCHOCH₃), 125.3 (CH=CHCHOCH₃), 117.3 (4º Ar C), 100.5 (OCH₂O), 96.9 (Ar CH), 72.6 (CHOCH₃), 62.7 (CHCH₂CHOCH₃), 59.1 (ArOCH₃), 58.6 (NCH₂), 56.4 (OCH₃), 53.7 (NCH₂CH₂), 44.3 (NCH₂CH₂), 44.1 (4º C), 28.7 (CHCH₂CHOH); \(\text{IR} \ \nu_{\text{max}}/\text{cm}^{-1}\) 2925, 1615, 1478, 1314, 1281, 1083, 1045, 936; \(\text{MS}\) (ES+) m/z (relative intensity %) 316 (M + H⁺, 100%); \(\text{HRMS}\) (ES+): calcd. for C₁₈H₂₂O₄N (M + H⁺) 316.1543, found 316.1542.

\((\pm)-184\) : \(^{1}\text{H NMR}\) (500 MHz, CDCl₃) \(\delta_{\text{H}}\) 6.63 (1H, d, J = 10.0 Hz, CH=CHCHOH), 6.49 (1H, s, ArH), 5.97 (1H, dd, J = 11.5, 6.0, CH=CHCHOCH₃), 5.93 (1H, d, J = 1.0 Hz, OCH₂O), 5.90 (1H, d, J = 1.0 Hz, OCH₂O), 4.31 (1H, d, J = 17.0 Hz, CH₂N), 3.89 (3H, s, OCH₃), 3.84 – 3.78 (2H, m, CHOCH₃ and CH₂N), 3.42 – 3.31 (2H, m, CHCH₂CHOCH₃ and CH₂CH₂N), 3.36 (3H, s, OCH₃), 2.94 – 2.87 (1H, m, CH₂CH₂N), 2.20 – 2.10 (2H, m, CHCH₂CHOCH₃ and CH₂CH₂N), 1.97 – 1.89 (1H, m, CH₂CH₂N), 1.63 – 1.57 (1H, m, CHCH₂CHOCH₃); \(^{13}\text{C NMR}\) (125 MHz, CDCl₃) \(\delta_{\text{C}}\) 146.0 (4º Ar C), 141.9 (4º Ar C), 140.2 (4º Ar C), 133.1 (4º Ar C), 132.8 (CH=CHCHOCH₃), 125.2 (CH=CHCHOCH₃), 108.0 (4º Ar C), 101.8 (OCH₂O), 101.5 (Ar CH), 72.5 (CHOCH₃), 63.2 (CHCH₂CHOCH₃), 57.1 (CH₂N), 56.9 (ArOCH₃), 56.5 (OCH₃), 53.7 (NCH₂CH₂), 44.5 (NCH₂CH₂), 44.2 (4º C), 28.8 (CHCH₂CHOCH₃); \(\text{MS}\) (ES+) m/z (relative intensity %) 316 (M + H⁺, 100%).

The regioselectivity of the Pictet-Spengler reaction and the structures of \((\pm)-184\) and \((\pm)-184\) were further confirmed by NOE analysis (Figure 7.6).

Figure 7.6: NOE analysis to confirm structure of 184 and 184b.
7.5 Chapter 5 Experimental

7.5.1 Reagents

Catalysts 135, QD-147, 137, 227-229 and 231-233 are commercially available and were used as received from suppliers. Catalysts 70, QD-71, QD-148, QD-170, QD-225, 152, 68, QD-171, 230, and 270 were prepared according to literature procedures.\textsuperscript{111} For the preparation of catalysts QD-172 - QD-174 see section 7.3.8. Phase transfer catalyst 72 was prepared according to literature procedures.\textsuperscript{51}

7.5.2 Synthesis of enantioenriched oxidative coupling adducts \((+)/(\text{-})-208\) and \((+)/(\text{-})-223\)

Enantioenriched oxidative coupling adducts \((+)-208\) and \((+)-223\) were synthesised according to general procedure C, replacing ps-BEMP with the appropriate organocatalyst. Since the unprotected catechol was found to be unsuitable for HPLC analysis (streaking on silica was observed), initially enantiomeric excesses were measured following methylene acetal protection (compound 208). Since acetate protection is practically easier than methylene acetal protection, later screening was conducted following formation of the diacetate (223).

7.5.2.1 Synthesis and characterisation of 1-tert-Butyl 3-methyl 3-(7-methoxy-1,3-benzodioxol-5-yl)-2-oxopyrrolidine-1,3-dicarboxylate 1-tert-butyl 3-methyl 3-(7-methoxy-1,3-benzodioxol-5-yl)-2-oxo-pyrrolidine-1,3-dicarboxylate, \((+)-208\)

![Chemical structure of (+)-208]

To a stirred solution of 3-methoxycatechol 163 (1.40 g, 10.0 mmol) and 207 (2.43 g, 10.0 mmol) in CH\(_2\)Cl\(_2\) (400 mL) at -20 °C was added cat. QD-265 (936 mg, 2.00 mmol) followed by ps-IO\(_4^–\) (3.22 g 20.0 mmol). The reaction mixture was stirred at this temperature for 7 h then filtered and the resin on the filter washed with CH\(_2\)Cl\(_2\) (3 x 100 mL). The filtrate was stirred with saturated aqueous Na\(_2\)S\(_2\)O\(_4\) (200 mL), the organic phase separated and the aqueous extracted with CH\(_2\)Cl\(_2\) (2 x 50 mL). The combined organic portions were dried over Na\(_2\)SO\(_4\), filtered and concentrated.
The residue was dissolved in DMF and divided equally between 5 sealable vials. To each vial was added CH₂ClBr (0.19 mL, 3 mmol) and Cs₂CO₃ (977 mg, 3 mmol). The vials were sealed and heated at 85 °C for 1 h then cooled to room temperature. The resulting purple-brown solution was concentrated and purified by column chromatography on silica gel, eluting with petroleum ether containing 30 – 60% diethyl ether to give the arylated product (+)-208 (2.24 g, 57% yield) as a pale yellow oil in 70% ee, determined by HPLC analysis [Chiralpak AD, hexane/iso-propanol 85:15, 1.0 mL min⁻¹, λ = 215 nm, t (minor) = 11.95 min, t (major) = 18.30 min] by comparison to a racemic sample prepared according to the general oxidative coupling procedure. [α]D²⁴ = + 38.1 (c 0.52, CHCl₃). Other data identical to racemic compound.

7.5.2.2 Synthesis and characterisation of enantioenriched adduct 1-tert-butyl 3-methyl 3-(3,4-diacetoxy-5-methoxy-phenyl)-2-oxo-pyrrolidine-1,3-dicarboxylate, (+)-223

According to the general oxidative coupling procedure, replacing ps-BEMP with catalyst QD-265, 3-methoxycatechol 163 (14 mg, 0.10 mmol) was reacted with 207 (24 mg, 0.10 mmol) and the crude reaction products dissolved in pyridine (0.5 mL) and Ac₂O (0.25 mL) and stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (5 mL) and washed with saturated aqueous CuSO₄ (3 x 5 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with 70:30 diethyl ether:petroleum ether, to give the arylated product (+)-223 (26 mg, 56%) as a colourless oil in 64% ee, determined by HPLC analysis [Chiralpak AD, hexane/iso-propanol 85:15, 1.0 mL min⁻¹, λ = 215 nm, t (major) = 11.382 min, t (minor) = 22.29 min] by comparison to a racemic sample prepared in 30% yield on a 0.5 mmol scale according to general procedure C. [α]D²⁴ = + 34.4 (c 0.90, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δH 7.17 (1H, d, J = 2.0 Hz, ArH), 6.87 (1H, d, J = 2.0 Hz, ArH), 3.83 (3H, s, ArOCH₃), 3.75 – 3.67 (2H, m, CH₂N), 3.74 (3H, s, OCH₃),
2.95 (1H, ddd, J = 12.5, 7.0 Hz, 5.0 Hz, CH₂CH₂N), 2.42 (1H, td, J = 13.0, 7.5 Hz, CH₂CH₂N), 2.28 (3H, s, OC(O)CH₃), 2.26 (3H, s, OC(O)CH₃), 1.52 (9H, s, C(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃) δC 169.4 (NC(O)), 168.9 (C(O)OCH₃), 168.0 (OC(O)CH₃), 167.6 (OC(O)CH₃), 152.2 (4º ArC), 149.8 (NC(O)O), 143.1 (4º ArC), 134.1 (4º ArC), 131.8 (4º ArC), 113.8 (ArCH), 109.4 (ArCH), 83.6 (C(CH₃)₃), 60.8 (4º C), 56.3 (ArOCH₃), 53.6 (OCH₃), 43.2 (NCH₂), 30.0 (NCH₂CH₂), 27.9 (C(CH₃)₃), 20.5 (OC(O)CH₃), 20.3 (OC(O)CH₃); IR υmax/cm⁻¹ 2981, 1777, 1730, 1611, 1370, 1306, 1206, 1096; MS (ES⁺) m/z (relative intensity %) 524 (M + MeCN + NH₄⁺, 100%), HRMS (ES⁺): calcd. for C₂₂H₂₇O₁₀NNa (M + Na⁺) 488.1527, found 488.1536.

### 7.5.3 Initial Organocatalyst Screen

An initial screen of organocatalysts was conducted according to general procedure C (section 7.3.6), replacing ps-BEMP with the organocatalysts detailed in Table 7.8. For catalyst structures see Chart 5.1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Scale /mmol</th>
<th>Product</th>
<th>t(minor)/min</th>
<th>t(major)/min</th>
<th>% ee</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 b</td>
<td>135</td>
<td>0.1</td>
<td>(-)-223</td>
<td>11.64</td>
<td>23.49</td>
<td>15</td>
<td>41</td>
</tr>
<tr>
<td>2 b</td>
<td>QD-147</td>
<td>0.2</td>
<td>(+)-223</td>
<td>24.52</td>
<td>12.08</td>
<td>11</td>
<td>38</td>
</tr>
<tr>
<td>3 b</td>
<td>137</td>
<td>0.1</td>
<td>(-)-223</td>
<td>11.43</td>
<td>23.26</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td>4 a</td>
<td>70</td>
<td>0.1</td>
<td>(+)-208</td>
<td>7.81</td>
<td>9.65</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
<td>5 a</td>
<td>QD-71</td>
<td>0.1</td>
<td>(+)-208</td>
<td>7.87</td>
<td>9.70</td>
<td>50</td>
<td>35</td>
</tr>
<tr>
<td>5b b</td>
<td>QD-71</td>
<td>0.5</td>
<td>(+)-223</td>
<td>19.61</td>
<td>10.26</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>6 a</td>
<td>QD-148</td>
<td>0.1</td>
<td>(+)-208</td>
<td>7.82</td>
<td>9.62</td>
<td>49</td>
<td>20</td>
</tr>
<tr>
<td>7 a</td>
<td>QD-172</td>
<td>0.1</td>
<td>(+)-208</td>
<td>7.86</td>
<td>9.60</td>
<td>42</td>
<td>28</td>
</tr>
<tr>
<td>8 a</td>
<td>QD-173</td>
<td>0.1</td>
<td>(+)-208</td>
<td>7.88</td>
<td>9.64</td>
<td>31</td>
<td>13</td>
</tr>
<tr>
<td>9 a</td>
<td>QD-174</td>
<td>0.1</td>
<td>(+)-208</td>
<td>7.83</td>
<td>9.65</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>10 a</td>
<td>QD-170</td>
<td>0.1</td>
<td>(+)-208</td>
<td>7.87</td>
<td>9.61</td>
<td>55</td>
<td>25</td>
</tr>
<tr>
<td>11 b</td>
<td>QD-225</td>
<td>0.1</td>
<td>(+)-223</td>
<td>21.16</td>
<td>10.81</td>
<td>6</td>
<td>35</td>
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<tr>
<td>12 b</td>
<td>151</td>
<td>0.1</td>
<td>(+)-223</td>
<td>20.35</td>
<td>10.68</td>
<td>15</td>
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Table 7.8: Initial organocatalyst screen. a HPLC conditions Chiralcel OD-H, heptane/ethanol 85:15, 1.0 mL/min⁻¹, λ = 215 nm. b HPLC conditions Chiralpak AD, hexane/isopropanol 85:15, 1.0 mL/min⁻¹, λ = 215 nm.

7.5.4 Phase transfer catalysis

7.5.4.1 General procedure D for the phase transfer catalysed oxidative coupling

To a stirred solution of 3-methoxycatechol 163 (14 mg, 0.10 mmol) and 207 (24 mg, 0.10 mmol) in CHCl₃/toluene (1 mL, 1:9) at -20 °C was added base (typically 1.5 equiv), catalyst 72 (typically 20 mol %) and ps-IO₄⁻ (35 mg, 0.20 mmol). The reaction mixture was stirred at this temperature for 24 h, then filtered and the filtrate stirred with saturated Na₂S₂O₄(aq) (5 mL). The organic phase was separated and the aqueous extracted with CH₂Cl₂ (2 x 2 mL). The combined organic phase was dried over Na₂SO₄, filtered and concentrated by rotary evaporation. The residue was dissolved in pyridine (0.5 mL) and acetic anhydride (0.25 mL) was added. The reaction mixture was stirred at room temperature overnight then diluted with EtOAc (5 mL) and washed with saturated CuSO₄(aq) (4 x 5 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with 70:30 diethyl ether:petroleum ether to give (-)-223 in the yields and enantiomeric excess shown in Table 7.9.
Spectroscopic data was identical to that for 223, prepared according to general procedure C.

<table>
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<tr>
<th>Entry</th>
<th>Cat. (mol %)</th>
<th>Base (equiv)</th>
<th>t(minor)/min</th>
<th>t(major)/min</th>
<th>Yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72 (20 mol %)</td>
<td>KOH (1.5)</td>
<td>11.51</td>
<td>22.55</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>72 (20 mol %)</td>
<td>H2O (1.5)</td>
<td>11.45</td>
<td>22.55</td>
<td>13</td>
<td>-16</td>
</tr>
<tr>
<td>3</td>
<td>72 (20 mol %)</td>
<td>K2PO4 (1.5)</td>
<td>-</td>
<td>-</td>
<td>a</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>72 (20 mol %)</td>
<td>K2CO3 (1.5)</td>
<td>11.22</td>
<td>21.98</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>KOH (1.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>K2PO4 (1.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>7</td>
<td>-</td>
<td>K2CO3 (1.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>72 (20 mol%)</td>
<td>KOH (0.2)</td>
<td>11.39</td>
<td>22.25</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>72 (1 equiv)</td>
<td>KOH (1.0)</td>
<td>11.25</td>
<td>22.02</td>
<td>11</td>
<td>22</td>
</tr>
</tbody>
</table>

Table 7.9: Screen of bases and conditions in the phase transfer catalysed oxidative coupling. a no conversion to arylated product after 3 days.

7.5.4.2 *Synthesis and characterisation of* (−)-1-tert-butyl 3-ethyl 3-(3,4-diacetoxy-5-methoxyphenyl)-2-oxopyrrolidine-1,3-dicarboxylate 237

According to general phase transfer catalysed oxidative coupling procedure D, 3-methoxycatechol 163 (14 mg, 0.10 mmol) was reacted with 236 (26 mg, 0.10 mmol), KOH (20 mol %) and catalyst 72 (20 mol %) to give, following column chromatography on silica gel eluting with 30:70 petroleum ether:diethyl ether, (−)-237 (5 mg, 13%) in 4% ee, determined by HPLC analysis [Chiralpak AD, hexane/iso-propanol 85:15, 1.0 mL.min⁻¹, λ = 215 nm, t (minor) = 10.87 min, t (major) = 20.10 min] by comparison to a racemic sample prepared in 30% yield on
a 0.5 mmol scale according to general procedure C. $^1$H NMR (500 MHz, CDCl$_3$)

$\delta$H 7.18 (1H, d, $J = 2.0$ Hz, ArH), 6.88 (1H, d, $J = 2.0$ Hz, ArH), 4.24 – 4.19 (2H, m, OCH$_2$CH$_3$), 3.84 (3H, s, OCH$_3$), 3.76 – 3.89 (2H, m, NCH$_2$), 2.94 (1H, ddd, $J = 13.0, 7.0, 5.0$ Hz, NCH$_2$CH$_2$), 2.43 (1H, td, $J = 13.0, 7.5$ Hz, NCH$_2$CH$_2$), 2.29 (3H, s, C(O)CH$_3$), 2.26 (3H, s, C(O)CH$_3$), 1.53 (9H, s, C(CH$_3$)$_3$), 1.23 (3H, t, $J = 7.0$ Hz, OCH$_2$CH$_3$);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 168.9 (C(O)), 168.8 (C(O)), 168.0 (C(O)), 167.6 (C(O)), 152.2 (4º ArC), 149.8 (NC(O)O), 143.0 (4º ArC), 134.1 (4º ArC), 131.7 (4º ArC), 113.9 (ArCH), 109.5 (ArCH), 83.5 (C(CH$_3$)$_3$), 62.6 (OCH$_2$CH$_3$), 60.8 (4º C), 56.3 (OCH$_3$), 43.2 (NCH$_2$), 29.8 (NCH$_2$CH$_2$), 27.9 (C(CH$_3$)$_3$), 20.5 (C(O)CH$_3$), 20.2 (C(O)CH$_3$), 13.8 (OCH$_2$CH$_3$);

IR $\nu_{max}$/cm$^{-1}$ 2980, 2918, 1776, 1724, 1369, 1307, 1153; MS (ES$^+$) m/z (relative intensity %) 981 (2M$^+$ Na$^+$, 100%), 502 (M$^+$ Na$^+$, 50%); HRMS (ES$^+$): calcd. for C$_{23}$H$_{29}$O$_{10}$NNa (M$^+$ Na$^+$) 502.1684, found 502.1677.

Alternatively (+)-237 was prepared in 30% yield following general procedure C replacing ps-BEMP with cat. 265; and in 49% ee determined by HPLC analysis [Chiralpak AD, hexane/isopropanol 85:15, 1.0 mL.min$^{-1}$, $\lambda = 215$ nm, t (major) = 10.57 min, t (minor) = 19.54 min] by comparison to a racemic sample. [$\alpha$]$_D^{25} = +11.4$ (c 1.2, CHCl$_3$); other data matches sample prepared from phase transfer catalysis.

### 7.5.5 Synthesis of alternative pro-nucleophiles

#### 7.5.5.1 General procedure E, for the synthesis of alternative pro-nucleophiles

![General procedure E](image)

A solution of protected lactam (500 mg, 2.70 mmol) in anh THF (2 mL) was added to a solution of LHMDS (5.7 mL of a 1 M solution in THF, 5.70 mmol) in anh THF (2 mL) at -78 °C. The reaction mixture was stirred at this temperature for 5 min then the appropriate electrophile (1 equiv) was added as a solution in anh THF (2 mL). The reaction mixture was stirred for 15 min then quenched with 1 M HCl (10 mL) and warmed to room temperature. The mixture was extracted with EtOAc (3 x
10 mL) and the combined organic extracts dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel to afford the desired pro-nucleophile.

7.5.5.2 Synthesis and characterisation of 1-tert-butyl 3-phenyl 2-oxopyrrolidine-1,3-dicarboxylate 238

According to general procedure E, tert-butyl-2-oxopyrrolidine-1-carboxylate 206 (500 mg, 2.70 mmol) was reacted with phenyl chloroformate (0.34 mL, 2.70 mmol) to give 238 (450 mg, 55%) as a colourless solid. ¹H NMR (500 MHz, CDCl₃) δH 7.31 (2H, t, J = 7.5 Hz, ArH), 7.17 (1H, t, J = 7.5 Hz, ArH), 7.13 (2H, d, J = 7.5 Hz, ArH), 3.87 (1H, ddd, J = 10.5, 9.0, 4.5 Hz, CH₂N), 3.72 (1H, t, J = 9.0 Hz CH), 3.68 (1H, td., J = 10.5, 7.5 Hz, CH₂N), 2.48 – 2.40 (1H, m, CH₂CH₂N), 2.31 – 2.24 (1H, m, CH₂CH₂N), 1.47 (9H, s, C(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃) δC 168.2 (C(O)), 167.4 (C(O)), 150.3 (OC(O)N), 149.7 (4º ArC), 129.4 (ArCH), 126.1 (ArCH), 121.3 (ArCH), 83.5 (C(CH₃)₃), 50.2 (CH), 44.7 (CH₂), 27.9 (C(CH₃)₃), 21.4 (CH₂); MP: 72 – 74 ºC; IR νmax/cm⁻¹ 2980, 2934, 1788, 1756, 1721, 1492, 1370, 1295, 1192, 1143, 1020, 936; MS (ES+) m/z (relative intensity %) 328 (M + Na⁺, 100%), 360 (M + Na⁺ + MeOH, 10%); HRMS (ES+): calcd. for C₁₆H₁₉O₅N₁Na (M + Na⁺) 328.1155, found 328.1151.

7.5.5.3 Synthesis and characterisation of di-tert-butyl 2-oxopyrrolidine-1,3-dicarboxylate 239

According to general procedure E, tert-butyl-2-oxopyrrolidine-1-carboxylate 206 (500 mg, 2.70 mmol) was reacted with tert-butyl chloroformate (0.34 mL, 2.70 mmol) to give 239 (370 mg, 48%) as a colourless solid. ¹H NMR (500 MHz, CDCl₃) δH 3.82 (1H, ddd, J = 10.5, 8.5, 5.5 Hz, NCH₂), 3.64 (1H, td, J = 10.5, 7.5 Hz, NCH₂), 3.39 (1H, t, J = 8.0 Hz, CH), 2.28 (1H, td, J = 15.0, 8.0 Hz, NCH₂CH₂), 2.20 – 2.13 (1H, m, NCH₂CH₂), 1.49 (9H, s, C(CH₃)₃), 1.45 (9H, s, C(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃) δC 169.1 (C(O)), 167.8 (C(O)), 149.9
(C(O)), 83.1 (C(CH₃)₃), 82.3 (C(CH₃)₃), 51.1 (CH), 44.7 (NCH₂), 27.9 (C(CH₃)₃), 27.9 (C(CH₃)₃), 21.5 (NCH₂CH₂); IR ν<sub>max</sub>/cm<sup>-1</sup> 2981, 1789, 1757, 1723, 1369, 1296, 1258, 1147; MP 42 – 44 ºC; MS (ES+) m/z (relative intensity %) 308 (M + Na⁺, 100%); HRMS (ES+): calcd. for C₁₄H₂₄O₅N (M + H⁺) 286.1649, found 286.1647.

7.5.5.4 Synthesis and characterisation of tert-butyl 3-acetyl-2-oxopyrrolidine-1-carboxylate 240

According to general procedure E, tert-butyl-2-oxopyrrolidine-1-carboxylate 206 (500 mg, 2.70 mmol) was reacted with acetyl chloride (0.34 mL, 2.70 mmol) to give 240 (427 mg, 70%) as a pale yellow solid. ¹H NMR (500 MHz, CDCl₃) δ<sub>H</sub> 3.77 – 3.71 (1H, m, NCH₂), 3.70 – 3.63 (2H, m, CH and NCH₂), 2.50 – 2.43 (1H, m, NCH₂CH₂), 2.40 (3H, s, CH₃), 2.00 (1H, dtd, J = 15.0, 9.0, 6.0 Hz, NCH₂C₃H₂), 1.49 (9H, s, C(CH₃)₃); ¹³C NMR (125 MHz, CDCl₃) δ<sub>C</sub> 201.7 (C(O)), 169.1 (NC(O)), 149.7 (NC(O)O), 83.3 (C(CH₃)₃), 57.2 (CH), 44.7 (NCH₂), 29.7 (CH₃), 27.8 (C(CH₃)₃), 18.8 (NCH₂CH₂); IR ν<sub>max</sub>/cm<sup>-1</sup> 2981, 1780, 1718, 1641, 1369, 1311, 1254, 1154; MP 60 – 66 ºC; MS (ES-) m/z (relative intensity %) 226 (M – H⁻, 100%); HRMS (ES+): calcd. for C₁₁H₁₇O₄NNa (M + Na⁺) 250.1050, found 250.1059.

7.5.5.5 Synthesis and characterisation of 1-methyl 3-phenyl 2-oxopyrrolidine-1,3-dicarboxylate 242

According to general procedure E, methyl 2-oxopyrrolidine-1-carboxylate 241 (429 mg, 3.00 mmol) was reacted with phenyl chloroformate (0.38 mL, 3.00 mmol) to give 242 (320 mg, 41%) as a colourless solid after column chromatography on silica gel, eluting with cyclohexane containing 20 – 60% EtOAc. ¹H NMR (400 MHz, CDCl₃) δ<sub>H</sub> 7.39 – 7.34 (2H, m, ArH), 7.25 – 7.21 (1H, m, ArH), 7.14 – 7.10 (2H, m, ArH), 3.97 (1H, ddd, J = 11.0, 8.5, 5.0 Hz, CH₂N), 3.86 (3H, s, OCH₃), 3.82 – 3.75 (2H, m, CH and CH₂N), 2.52 (1H, dtd, J = 13.0, 8.5, 7.5 Hz,
CHCH$_2$CH$_2$N), 2.37 (1H, m, CHCH$_2$CH$_2$N); $^{13}$C NMR (100 MHz, CDCl$_3$) δ$_C$
168.2 (C(O)), 167.2 (C(O)), 151.7 (OC(O)N), 150.3 (4º ArC), 129.4 (ArCH), 126.2
(ArCH), 121.2 (ArCH), 53.7 (OCH$_3$), 49.9 (CH), 44.7 (NCH$_2$), 21.5 (NCH$_2$CH$_2$);

MP: 88 – 90 ºC; IR $\nu_{\text{max}}$/cm$^{-1}$ 1794, 1755, 1731, 1439, 1375, 1293, 1194, 1162,
1142; MS (ES+) m/z (relative intensity %) 286 (M + Na$^+$, 100%); HRMS (ES+):
calcd. for C$_{13}$H$_{13}$O$_5$NNa (M + Na$^+$) 286.0686, found 286.0684.

7.5.5.6 Synthesis and characterisation of 1-benzyl 3-methyl 2-oxopyrrolidine-1,3-dicarboxylate 246

According to general procedure E, benzyl 2-oxopyrrolidine-1-carboxylate 243 (440
mg, 2.00 mmol) was reacted with methyl chloroformate (0.15 mL, 2.00 mmol) to
give 246 (400 mg, 72%) as a colourless solid following column chromatography on
silica gel, eluting with petroleum ether containing 70% diethyl ether. $^1$H NMR (500
MHz, CDCl$_3$) δ$_H$ 7.42 – 7.41 (2H, m, ArH), 7.37 – 7.30 (3H, m, ArH), 5.29 (1H, d,
J = 12.5 Hz, OCH$_2$Ph), 5.26 (1H, d, J = 12.5 Hz, OCH$_2$Ph), 3.93 (1H, ddd, J =
10.5, 8.5, 5.5 Hz, CH$_2$N), 3.78 – 3.73 (1H, m, CH$_2$N), 3.77 (3H, s, OCH$_3$), 3.56
(1H, dd, J = 9.0, 7.5 Hz, CH), 2.44 – 2.37 (1H, m, CH$_2$CH$_2$N), 2.29 – 2.22 (1H, m,
CH$_2$CH$_2$N); $^{13}$C NMR (75 MHz, CDCl$_3$) δ$_C$ 168.8 (C(O)), 168.5 (C(O)), 151.1
(NC(O)O), 134.9 (4º ArC), 128.5 (ArCH), 128.4 (ArCH), 128.1 (ArCH), 68.3
(OCH$_2$Ph), 52.8 (OCH$_3$), 49.8 (CH), 44.8 (CH$_2$N), 21.5 (CH$_2$CH$_2$N); IR $\nu_{\text{max}}$/cm$^{-1}$
2956, 1792, 1730, 1638, 1375, 1289, 1164; MP 39 – 41 ºC; MS (ES-) m/z (relative
intensity %) 276 (M – H$^-$, 100%); HRMS (ES-): calcd. for C$_{14}$H$_{13}$O$_5$NNa (M +
Na$^-$) 300.0842, found 300.0838.

7.5.5.7 Synthesis and characterisation of methyl 1-[(4-
methylphenyl)sulfonyl]-2-oxopyrrolidine-3-carboxylate 247

According to general procedure E, 1-[(4-methylphenyl)sulfonyl]pyrrolidin-2-one
244 (239 mg, 1.00 mmol) was reacted with methyl chloroformate (77 μL, 1.00
mmol) to give 247 (173 mg, 59%) as a colourless solid following column
chromatography on silica gel, eluting with petroleum ether containing 50 – 70% diethyl ether. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta_H \) 7.90 (2H, d, \(J = 8.0 \text{ Hz, ArH}\)), 7.33 (2H, d, \(J = 8.0 \text{ Hz, ArH}\)), 3.99 (1H, ddd, \(J = 9.5, 8.5, 5.5 \text{ Hz, NCH}_2\)), 3.84 (1H, ddd, \(J = 9.5, 8.0, 7.0 \text{ Hz, NCH}_2\)), 3.67 (3H, s, OCH\(_3\)), 3.45 (1H, dd, \(J = 9.0, 7.5 \text{ Hz, CH}\)), 2.46 – 2.39 (1H, m, CH\(_2\)CH\(_2\)N), 2.43 (3H, s, CH\(_3\)), 2.33 – 2.26 (1H, m, CH\(_2\)CH\(_2\)N); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta_C\) 168.2 (C(O)), 168.1 (C(O)), 145.5 (4º ArC), 134.5 (4º ArC), 129.7 (ArCH), 128.1 (ArCH), 52.8 (OCH\(_3\)), 49.2 (CH), 45.6 (NCH\(_2\)), 22.2 (NCH\(_2\)CH\(_2\)), 21.6 (CH\(_3\)); IR \(\nu_{\text{max}}/\text{cm}^{-1}\) 2956, 1750, 130, 1596, 1437, 1361, 1170, 1123; MP 70 – 71 °C; MS (ES+) m/z (relative intensity %) 320 (M + Na\(^+\), 100%); HRMS (ES+): calcd. for C\(_{13}\)H\(_{15}\)O\(_5\)NSNa (M + Na\(^+\)) 320.0563, found 320.0559.

**7.5.5.8 Synthesis and characterisation of methyl 1-benzyl-2-oxopyrrolidine-3-carboxylate 248**

![Image of 248]

According to general procedure E, 1-benzylpyrrolidin-2-one 245 (1.00 g, 5.70 mmol) was reacted with methyl chloroformate (0.44 mL, 5.70 mmol) to give 248 (900 mg, 73%) as a pale yellow oil following column chromatography on silica gel, eluting with cyclo-hexane containing 20 – 60% EtOAc. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta_H\) 7.34 – 7.31 (2H, m, ArH), 7.28 (1H, d, \(J = 7.0 \text{ Hz, ArH}\)), 7.24 (2H, d, \(J = 7.0 \text{ Hz, ArH}\)), 4.47 (2H, s, NCH\(_2\)Ph), 3.78 (3H, s, OCH\(_3\)), 3.50 (1H, dd, \(J = 9.5, 7.0 \text{ Hz, CH}\)), 3.38 (1H, dt, \(J = 9.0, 5.0 \text{ Hz, NCH}_2\)), 3.25 – 3.20 (1H, m, NCH\(_2\)), 2.40 – 2.33 (1H, m, NCH\(_2\)CH\(_2\)), 2.27 – 2.19 (1H, m, NCH\(_2\)CH\(_2\)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta_C\) 170.5 (C(O)), 169.5 (C(O)), 135.6 (4º ArC), 128.4 (ArCH), 127.7 (ArCH), 127.4 (ArCH), 52.3 (OCH\(_3\)), 48.1 (CH), 46.6 (NCH\(_2\)), 44.8 (NCH\(_2\)), 21.9 (NCH\(_2\)CH\(_2\)); IR \(\nu_{\text{max}}/\text{cm}^{-1}\) 2953, 1740, 1691, 1496, 1433, 1356, 1266, 1167, 1079, 993, 702; MS (ES+) m/z (relative intensity %) 256 (M + Na\(^+\), 100%); HRMS (ES+): calcd. for C\(_{13}\)H\(_{16}\)O\(_3\)N (M + H\(^+\)) 234.1125, found 234.1126.
7.5.5.9 Synthesis and characterisation of methyl 2-oxopyrrolidine-3-carboxylate

To a stirred solution of 1-tert-butyl 3-methyl 2-oxopyrrolidine-1,3-dicarboxylate 207 (243 mg, 1.00 mmol) in CH₂Cl₂ (5 mL) was added HCl (1 mL of a 4 M solution in dioxane). The reaction mixture was stirred at room temperature for 18 h then loaded directly onto an isolute strong cation exchange (SCX) cartridge. The cartridge was flushed with methanol (1 column volume) followed by 7 M methanol ammonia (1 column volume). The ammonia eluent was concentrated by rotary evaporation to give 249 (100 mg, 70%) as a colourless solid. ¹H NMR (500 MHz, CDCl₃) δ H 6.80 (1H, br. s, NH), 3.78 (3H, s, OCH₃), 3.53 – 3.48 (1H, m, NCH₂), 3.42 – 3.35 (2H, m, CH and NCH₂), 2.53 (1H, dddd, J = 13.5, 8.5, 7.5, 6.5 Hz, NCH₂CH₂), 2.40 – 2.31 (1H, m, NCH₂CH₂); ¹³C NMR (125 MHz, CDCl₃) δ C 173.6 (C(O)), 170.4 (C(O)), 52.7 (OCH₃), 47.4 (CH), 40.7 (NCH₂), 24.9 (NCH₂CH₂); IR νmax/cm⁻¹ 3434, 2959, 1720, 1676, 1438, 1353, 1282, 1222, 1172; MP 127 – 128 ºC; MS (ES+) m/z (relative intensity %) 166 (M + Na⁺, 100%); HRMS (ES+): calcd. for C₆H₉O₃NNa (M + Na⁺) 166.0475, found 166.0473.

7.5.6 Screen of alternative pro-nucleophiles

7.5.6.1 Synthesis and characterisation of 1-tert-butyl 3-phenyl 3-(3,4-dihydroxy-5-methoxyphenyl)-2-oxopyrrolidine-1,3-dicarboxylate, (+)-250

According to general procedure C, replacing ps-BEMP with catalyst QD-71, 3-methoxycatechol 163 (28 mg, 0.20 mmol) was reacted with 238 (73 mg, 0.20 mol) to give after 12 hours reaction time (+)-250 (26 mg, 29%) as a peach coloured solid in 40% ee determined by HPLC analysis [Chiralpak AD, heptane/ethanol 55:45, 1.0 mL.min⁻¹, λ = 215 nm, t (minor) = 10.78 min, t (major) = 14.85 min] by comparison
to a racemic sample prepared according to the general oxidative coupling procedure. $[\alpha]_D^{24} = +34.2$ (c 0.7, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta_H$ 7.36 – 7.32 (2H, m, ArH), 7.21 (1H, t, $J = 7.5$ Hz, ArH), 7.06 – 7.04 (2H, m, ArH), 6.84 (1H, d, $J = 2.0$ Hz, ArH), 6.74 (1H, d, $J = 2.0$ Hz, ArH), 5.47 (2H, br. s, OH), 3.88 – 3.82 (1H, m, CH$_2$N), 3.87 (3H, s, OCH$_3$), 3.69 (1H, t, $J = 7.5$ Hz, ArH), 3.04 (1H, td, $J = 13.0$, 7.0 Hz, CH$_2$CH$_2$N), 2.57 (1H, ddd, $J = 13.0$, 7.0, 5.5 Hz, CH$_2$CH$_2$N), 1.54 (9H, s, C(CH$_3$)$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta_C$ 169.4 (C(O)), 168.6 (C(O)), 150.6 (OC(O)N), 150.0 (4º ArC), 147.0 (4º ArC), 143.8 (4º ArC), 132.5 (4º ArC), 129.4 (ArCH), 126.8 (4º ArC), 126.1 (ArCH), 121.2 (ArCH), 107.6 (ArCH), 103.0 (ArCH), 83.7 (C(CH$_3$)$_3$), 61.3 (4º C), 43.3 (CH$_2$), 29.9 (CH$_2$), 28.0 (C(CH$_3$)$_3$); MP 137 – 139 ºC (140 – 141 ºC for racemate); IR $\nu_{\text{max}}$/cm$^{-1}$ 3400, 2980, 2934, 1778, 1745, 1723, 1521, 1370, 1308, 1188, 1150; MS (ES+) m/z (relative intensity %) 466 (M + Na$^+$, 100%); HRMS (ES+) calcd. for C$_{23}$H$_{25}$O$_8$NNa (M + Na$^+$) 466.1472, found 466.1473.

7.5.6.2 Synthesis and characterisation of di-tert-butyl 3-(7-methoxy-1,3-benzodioxol-5-yl)-2-oxopyrrolidine-1,3-dicarboxylate, 252

According to general procedure C, replacing ps-BEMP with catalyst QD-71, 3-methoxycatechol 163 (28 mg, 0.20 mmol) was reacted with 239 (57 mg, 0.20 mmol) (6 h reaction time) and the crude residue treated with CH$_2$ClBr/Cs$_2$CO$_3$ to give 252 (21 mg, 25 %) in 0% ee as a colourless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta_H$ 6.76 (1H, d, $J = 1.5$ Hz, ArH), 6.67 (1H, d, $J = 1.5$ Hz, ArH), 5.96 (2H, s, OCH$_2$O), 3.90 (3H, s, OCH$_3$), 3.73 – 3.64 (2H, m, NCH$_2$), 2.82 (1H, ddd, $J = 12.5$, 7.0, 5.0 Hz, NCH$_2$CH$_2$), 2.40 (1H, td, $J = 12.5$, 7.5 Hz, NCH$_2$CH$_2$), 1.53 (9H, s, C(CH$_3$)$_3$), 1.43 (9H, s, C(CH$_3$)$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta_C$ 169.8 (C(O)), 168.6 (C(O)), 150.2 (C(O)), 148.8 (4º ArC), 143.3 (4º ArC), 134.9 (4º ArC), 130.5 (4º ArC), 107.5 (ArCH), 101.8 (ArCH), 101.6 (OCH$_2$O), 83.3 (C(CH$_3$)$_3$), 83.1 (C(CH$_3$)$_3$), 61.9 (4º C), 56.7 (OCH$_3$), 43.2 (NCH$_2$), 31.9 (NCH$_2$CH$_2$), 28.0

173
(C(CH$_3$)$_3$), 27.8 (C(CH$_3$)$_3$); IR $\nu_{\text{max}}$/cm$^{-1}$ 2923, 1719, 1636 (br.), 1511, 1459, 1368, 1312, 1149; MS (ES+) m/z (relative intensity %) 458 (M + Na$^+$, 100%); HRMS (ES+): calcd. for C$_{22}$H$_{29}$O$_8$NNa (M + Na$^+$) 458.1785, found 458.1786.

### 7.5.6.3 Synthesis and characterisation of tert-butyl 3-acetyl-3-(3,4-diacetoxy-5-methoxyphenyl)-2-oxopyrrolidine-1-carboxylate, (+)-255

![Chemical structure]

According to general procedure C, replacing ps-BEMP with catalyst QD-71, 3-methoxycatechol 163 (42 mg, 0.30 mmol) was reacted with 240 (68 mg, 0.30 mmol) (8 h reaction time) and the crude residue treated with Ac$_2$O (0.75 mL) in pyridine (1.5 mL) (see preparation of 223) to give (+)-255 (27 mg, 20%) as a colourless oil in 6% ee determined by HPLC analysis [Chiralpak AD, hexane/isopropanol 85:15, 1.0 mL.min$^{-1}$, $\lambda = 215$ nm, t (major) = 7.07 min, t (minor) = 14.65 min] by comparison to a racemic sample. $[\alpha]_{D}^{25} = +8.00$ (c 0.4, CHCl$_3$); $^{1}$H NMR (500 MHz, CDCl$_3$) $\delta$H 6.97 (1H, d, $J = 2.0$ Hz, ArH), 6.81 (1H, d, $J = 2.0$ Hz, ArH), 3.82 (3H, s, OCH$_3$), 3.65 – 3.62 (2H, m, NCH$_2$), 3.05 – 3.01 (1H, m, NCH$_2$CH$_2$), 2.28 (3H, s, CH$_3$), 2.26 (3H, s, CH$_3$), 2.14 – 2.07 (1H, m, NCH$_2$CH$_2$), 1.53 (C(CH$_3$)$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$C 201.5 (CC(O)CH$_3$), 169.7 (C(O)), 167.9 (C(O)), 167.5 (C(O)), 152.8 (4º ArC), 149.6 (NC(O)O), 143.6 (4º ArC), 135.9 (4º ArC), 131.7 (4º ArC), 113.8 (ArCH), 108.2 (ArCH), 83.6 (C(CH$_3$)$_3$), 67.9 (4º C), 56.4 (OCH$_3$), 43.2 (NCH$_2$), 28.7 (NCH$_2$CH$_2$), 27.9 (C(CH$_3$)$_3$), 26.6 (CH$_3$), 20.5 (CH$_3$), 20.2 (CH$_3$); IR $\nu_{\text{max}}$/cm$^{-1}$ 2981, 1777 (br.), 1718 (br.) 1610, 1370, 1208, 1104; MS (ES+) m/z (relative intensity %) 551 (M + HNEt$_3$$^+$, 100%), 472 (M + Na$^+$, 90%); HRMS (ES+): calcd. for C$_{22}$H$_{27}$O$_9$NNa (M + Na$^+$) 472.1578, found 472.1581.
7.5.6.4 Synthesis and characterization of 1-Methyl-3-phenyl-3-(3,4-dihydroxy-5-methoxyphenyl)-2-oxopyrrolidine-1,3-dicarboxylate, (+)-251

![Chemical Structure](image)

According to general procedure C, replacing ps-BEMP with catalyst QD-71, 3-methoxycatechol 163 (28 mg, 0.20 mmol) was reacted with pro-nucleophile 242 (53 mg, 0.20 mmol) to give, (+)-251 (27 mg, 34 %) in 9% ee, determined by HPLC analysis [Chiralpak AD, heptane/ethanol 70:30, 1.0 mL.min⁻¹, λ = 215 nm, t (minor) = 6.74 min, t (major) = 12.37 min] by comparison to a racemic sample prepared according to the general oxidative coupling procedure (racemate MP 74 – 75 ºC); [a]D²⁴ = + 12.3 (c 0.65, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δH 7.36 – 7.32 (2H, m, ArH), 7.23 – 7.19 (1H, m, ArH), 7.05 – 7.02 (2H, m, ArH), 6.84 (1H, d, J = 2 Hz, ArH), 6.74 (1H, d, J = 2 Hz, ArH), 3.94 – 3.90 (1H, m, C₂H₂N), 3.90 (3H, s, OCH₃), 3.88 (3H, s, OCH₃), 3.75 (1H, td, J = 10.5, 7.0 Hz, CH₂N), 3.08 (1H, ddd, J = 13.0, 7.5, 7.0 Hz, CH₂CH₂N), 2.61 (1H, ddd, J = 13.0, 7.0, 5.5 Hz, CH₂CH₂N);

¹³C NMR (100 MHz, CDCl₃) δC 169.3 (C(O)), 168.3 (C(O)), 152.1 (OC(O)N), 150.6 (4° ArC), 147.1 (4° ArC), 143.9 (4° ArC), 132.6 (4° ArC), 130.1 (4° ArC), 129.4 (ArCH), 126.2 (ArCH), 121.1 (ArCH), 107.7 (ArCH), 102.9 (ArCH), 61.2 (4° C), 56.3 (OCH₃), 53.9 (OCH₃), 43.3 (CH₂), 30.1 (CH₂); MP 74 - 75 ºC; IR vortex/cm⁻¹ 3417, 1783, 1738, 1615, 1439, 1372, 1305, 1223, 1188, 1091; MS (ES⁺) m/z (relative intensity %) 424 (M + Na⁺, 100%); HRMS (ES⁺): calcd. for C₂₀H₁₉O₈NNa (M + Na⁺) 424.1003, found 424.1001.

7.5.6.5 Synthesis and characterization of 1-benzyl 3-methyl 3-(3,4-diacetoxy-5-methoxyphenyl)-2-oxopyrrolidine-1,3-dicarboxylate, (+)-253

![Chemical Structure](image)
According to general procedure C, replacing ps-BEMP with catalyst **QD-71**, 3-methoxycatechol **163** (28 mg, 0.20 mmol) was reacted with **246** (55 mg, 0.20 mmol) and the crude reaction mixture treated with Ac$_2$O (0.75 mL) in pyridine (1.5 mL) (see preparation of **223** to give (+)-**253** (30 mg, 30%) as a pale yellow oil, in 30% ee, determined by HPLC analysis [Chiralpak AS, hexane/iso-propanol 70:30, 1.0 mL.min$^{-1}$, $\lambda = 220$ nm, $t$ (minor) = 15.14 min, $t$ (major) = 18.71 min] by comparison to a racemic sample prepared according to the general oxidative coupling procedure; $[\alpha]_D^{25} = + 7.1$ (c 2.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.43 – 7.42 (2H, m, ArH), 7.38 – 7.32 (3H, m, ArH), 7.17 (1H, d, $J = 2.0$ Hz, ArH), 6.87 (1H, d, $J = 2.0$ Hz, ArH), 5.32 – 5.27 (2H, m, OCH$_2$Ph), 3.83 (3H, s, OCH$_3$), 3.81 – 3.77 (2H, m, CH$_2$N), 3.75 (3H, s, OCH$_3$), 3.01 – 2.96 (1H, m, CH$_2$CH$_2$N), 2.45 (1H, td, $J = 13.0$, 7.5 Hz, CH$_2$CH$_2$N), 2.28 (3H, s, OC(O)CH$_3$), 2.26 (3H, s, OC(O)CH$_3$), $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 169.1 (C(O)), 168.8 (C(O)), 167.5 (C(O)), 152.3 (4º ArC), 151.2 (NC(O)O), 143.1 (4º ArC), 134.9 (4º ArC), 133.9 (4º ArC), 131.9 (4º ArC), 128.6 (ArCH), 128.5 (ArCH), 128.2 (ArCH), 113.8 (ArCH), 109.3 (ArCH), 68.4 (OCH$_2$Ph), 60.6 (4º C), 56.4 (OCH$_3$), 53.7 (OCH$_3$), 43.2 (CH$_2$N), 30.2 (CH$_2$CH$_2$N), 20.5 (OC(O)CH$_3$), 20.3 (OC(O)CH$_3$); IR $\nu_{max}$/cm$^{-1}$ 1781, 1774, 1731, 1371, 1296, 1207, 1098; MS (ES$^+$) m/z (relative intensity %) 522 (M + Na, 100%); HRMS (ES$^+$): calcd. for C$_{25}$H$_{25}$O$_{10}$NNa (M + Na$^+$) 522.1371, found 522.1366.

**7.5.6.6 Synthesis and characterization of methyl 3-(3,4-diacetoxy-5-methoxyphenyl)-1-[(4-methylphenyl)sulfonyl]-2-oxopyrrolidine-3-carboxylate, (+)-**254

![Chemical Structure](image)

According to general procedure C, replacing ps-BEMP with catalyst **QD-71**, 3-methoxycatechol **163** (28 mg, 0.20 mmol) was reacted with **247** (59 mg, 0.20 mmol) and the crude reaction mixture treated with Ac$_2$O (0.75 mL) in pyridine (1.5 mL) (see preparation of **223** to give (+)-**254** (25 mg, 24%) as a pale yellow oil, in 1% ee, determined by HPLC analysis [Chiralpak AD, hexane/iso-propanol 85:15,
1.0 mL.min\(^{-1}\), \(\lambda = 215\) nm, t (major) = 22.39 min, t (minor) = 28.95 min] by comparison to a racemic sample prepared according to the general oxidative coupling procedure; \([\alpha]\)\(_D\)\(^{25}\) = + 5.1 (c 1.0, CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\)H 7.89 (2H, d, \(J = 8.0\) Hz, Ar\(\text{H}\)), 7.33 (2H, d, \(J = 8.0\) Hz, Ar\(\text{H}\)), 6.95 (1H, d, \(J = 2.0\) Hz, Ar\(\text{H}\)), 6.72 (1H, d, \(J = 2.0\) Hz, Ar\(\text{H}\)), 3.87 – 3.84 (2H, m, C\(\text{H}_2\text{N}\)), 3.72 (3H, s, OCH\(_3\)), 3.58 (3H, s, OCH\(_3\)), 3.01 – 2.96 (1H, m, CH\(_2\text{CH}_2\text{N}\)), 2.50 – 2.43 (1H, m, CH\(_2\text{CH}_2\text{N}\)), 2.43 (3H, s, CH\(_3\)), 2.27 (3H, s, OC(O)CH\(_3\)), 2.25 (3H, s, OC(O)CH\(_3\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\)C 168.6 (C(O)), 168.6 (C(O)), 167.9 (C(O)), 167.5 (C(O)), 152.2 (4º ArC), 145.5 (4º ArC), 143.2 (4º ArC), 134.3 (4º ArC), 133.2 (4º ArC), 131.9 (4º ArC), 129.7 (ArCH), 128.2 (ArCH), 113.7 (ArCH), 109.0 (ArCH), 60.1 (4º C), 56.2 (OCH\(_3\)), 53.6 (OCH\(_3\)), 44.0 (CH\(_2\)N), 30.9 (CH\(_2\text{CH}_2\text{N}\)), 21.6 (CH\(_3\)), 20.5 (OC(O)CH\(_3\)), 20.3 (OC(O)CH\(_3\)); IR \(\nu_{\text{max}}/\text{cm}^{-1}\) 1774, 1751, 1734, 1422, 1207, 1173, 1093; MS (ES+) m/z (relative intensity %) 542 (M + Na\(^+\), 100%); HRMS (ES+): calcd. for C\(_{24}\)H\(_{25}\)O\(_{10}\)NSNa (M + Na\(^+\)) 542.1091, found 542.1091.

**7.5.7 Conditions Screen**

**7.5.7.1 Solvent screen**

According to general procedure C (section 7.3.6), replacing ps-BEMP with cat. QD-71 (10 mol %), 3-methoxycatechol 163 was reacted with 207 (1 equiv) in the solvents shown in Table 7.10 (0.1 M solutions), on a 0.1 mmol scale to give 208 or 223 (following methylene acetal or acetate protection) in the yields and enantioselectivities shown. In cases where the yield was not determined, enantiomeric excesses were determined from a sample of product obtained from preparative TLC of a sample of reaction mixture.

<table>
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<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Product</th>
<th>t(minor)/min</th>
<th>t(major)/min</th>
<th>% ee</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH(_2)Cl(_2)</td>
<td>(+)-208</td>
<td>7.87</td>
<td>9.70</td>
<td>50</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>CHCl(_3)</td>
<td>(+)-208</td>
<td>7.96</td>
<td>9.77</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>TBME</td>
<td>(+)-208</td>
<td>7.96</td>
<td>9.78</td>
<td>20</td>
<td>33</td>
</tr>
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</table>
7.5.7.2 Concentration, catalyst loading and temperature screen

According to general procedure C, replacing ps-BEMP with cat. QD-71, 3-methoxycatechol 163 was reacted with 207 in CH₂Cl₂ on a 0.1 mmol scale under the conditions detailed in Table 7.11 to give 208 or 223 (following methylene acetal or acetate protection) in the yields and enantioselectivities shown. In cases where the yield was not determined, enantiomeric excesses were determined from a sample of product obtained from preparative TLC of a sample of reaction mixture.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mol %</th>
<th>T/ºC</th>
<th>Conc./M</th>
<th>t(minor)/min</th>
<th>t(major)/min</th>
<th>% ee</th>
<th>% Yield</th>
</tr>
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<td>19.18</td>
<td>10.16</td>
<td>52</td>
<td>-</td>
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<tr>
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<td>2</td>
<td>-20</td>
<td>0.1</td>
<td>19.63</td>
<td>10.32</td>
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<td>-20</td>
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<td>10.27</td>
<td>56</td>
<td>-</td>
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<tr>
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<td>30</td>
<td>-20</td>
<td>0.01</td>
<td>21.02</td>
<td>10.80</td>
<td>62</td>
<td>-</td>
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<tr>
<td>5</td>
<td>10</td>
<td>0</td>
<td>0.1</td>
<td>22.77</td>
<td>11.41</td>
<td>20</td>
<td>49</td>
</tr>
</tbody>
</table>
Table 7.11: conditions screen of enantioselective oxidative coupling of 3-methoxycatechol 163 and 207.

### 7.5.8 Preparation of catalysts

#### 7.5.8.1 Attempted synthesis of a range of benzyl quinidine derivatives

The synthesis of a range of benzyl-substituted quinidine derived organocatalysts was attempted following procedures reported by Deng and co-workers. De-methylation was attempted following the reported procedure with BBr$_3$, however this resulted in cleavage of the benzyl group in most cases. Additional example were synthesised with thiolate demethylation to prevent cleavage of the benzyl group. 1-dodecanethiol was found to be a suitable alternative for NaSEt that is not malodorous.

#### 7.5.8.2 Synthesis and characterization of (9S)-9-[(4-(1H-pyrazol-1-yl)benzyl)oxy]cinchonan-6'-ol, QD-260

To a stirred solution of quinidine (162 mg, 0.50 mmol) in DMF (5 mL) was added NaH (40 mg of a 60% dispersion in mineral oil, 2.00 mmol) and the reaction mixture stirred at room temperature for 30 min before adding 1-[4-(bromomethyl)phenyl]-1H-pyrazole (119 mg, 0.50 mmol). The reaction mixture was stirred for 4 h then quenched with saturated NaHCO$_3$(aq) (10 mL), diluted with EtOAc (20 mL) and washed with water (3 x 10 mL) and brine (10 mL). The organic phase was dried over Na$_2$SO$_4$, filtered and concentrated. The residue was dissolved in CH$_2$Cl$_2$ (5 mL) and cooled to 0 °C. BBr$_3$ (1 mL of a 1 M solution in CH$_2$Cl$_2$, 1 mmol) and the reaction mixture allowed to warm to room temperature. The reaction mixture was stirred at room temperature for 24 h then quenched with sat. NaHCO$_3$(aq). The organic phase was separated and the aqueous extracted with...
CH₂Cl₂. The combined organic portions were dried over Na₂SO₄, filtered and concentrated. The residue was purified by mass guided HPLC to give QD-260 (44 mg, 19%) as a yellow solid. [α]D²⁵ = +88.7 (c 1.10, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δH 6.64 (1H, d, J = 4.5 Hz, ArH), 8.22 (1H, d, J = 2.5 Hz, ArH), 7.94 (1H, d, J = 9.0 Hz, ArH), 7.74 – 7.72 (3H, m, ArH), 7.58 (1H, br. s, ArH), 7.48 (2H, br. d, J = 8.0 Hz, ArH), 7.36 (1H, dd, J = 9.0, 2.5 Hz, ArH), 7.33 (1H, br. s, ArH), 6.53 (1H, t, J = 2.0 Hz, ArH), 5.99 (1H, ddd, J = 17.5, 10.0, 7.5 Hz, CH=CH₂), 5.32 (1H, br. s, CHOCH₂Ar), 5.03 – 4.97 (2H, m, CH=CH₂), 4.53 (1H, d, J = 11.5 Hz, OCH₂Ar), 4.44 (1H, d, J = 11.5 Hz, OCH₂Ar), 4.31 (1H, br. s, aliphatic CH), 3.09 (1H, br. s, aliphatic CH), 2.92 – 2.85 (2H, br. m, aliphatic CH), 2.79 – 2.73 (1H, br. m, aliphatic CH), 2.29 (1H, dd, J = 17.0, 8.0 Hz, aliphatic CH), 2.18 (1H, br. m, aliphatic CH), 1.73 (1H, br. s, aliphatic CH), 1.60 – 1.50 (2H, br. m, aliphatic CH), 1.24 (1H, br. s, aliphatic CH); ¹³C NMR (75 MHz, CDCl₃) δC 158.0 (4º ArC), 147.5 (ArCH), 145.8 (4º ArC), 144.4 (4º ArC), 142.3 (ArCH), 141.5 (CH=CH₂), 141.1 (4º ArC), 137.6 (4º ArC), 131.7 (ArCH), 130.7 (ArCH), 129.2 (4º ArC), 129.0 (ArCH), 123.5 (ArCH), 120.5 (ArCH), 120.3 (ArCH), 115.3 (CH=CH₂), 108.8 (ArCH), 105.2 (ArCH), 81.0 (COCH₂Ar), 72.0 (OCH₂Ar), 60.7 (NCH), 50.9 (NCH₂), 50.4 (NCH₂), 41.1 (CH), 29.5 (CH), 27.1 (CH₂), 22.2 (CH₂); IR νmax/cm⁻¹ 3070, 2940, 1614, 1526, 1467, 1394, 1030, 830; MP 139 – 144 ºC; MS (ES⁺) m/z (relative intensity %) 467 (M + H⁺, 100%); HRMS (ES⁺): calcd. for C₂₉H₃₁O₂N₄ (M + H⁺) 467.2442, found 467.2439.

7.5.8.3 Synthesis and characterization of (9S)-9-[(3-nitrobenzyl)oxy]cinchonan-6'-ol, QD-261

According to the above procedure for the synthesis of catalyst QD-260, catalyst QD-261 was prepared in 9% yield on a 0.50 mmol scale. [α]D²⁵ = +75.4 (c 0.76, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δH 8.63 (1H, d, J = 4.5 Hz, ArH), 8.30 (1H, s, ArH), 8.17 (1H, dd, J = 8.0, 1.0 Hz, ArH), 7.93 (1H, d, J = 9.0 Hz, ArH), 7.73 (1H, d, J = 8.0 Hz, ArH), 7.59 (1H, t, J = 8.0 Hz, ArH), 7.56 (1H, br. d, J = 4.5 Hz,
ArH), 7.36 (1H, dd, J = 9.0, 2.5 Hz, ArH), 7.33 (1H, br. s, ArH), 6.04 (1H, ddd, J = 17.5, 10.0, 7.5 Hz, CH=CH2), 5.36 (1H, br. s, CHOCH2Ar), 5.05 – 5.00 (2H, m, CH=CH2), 4.61 (1H, d, J = 12.0 Hz, OCH2Ar), 4.58 (1H, d, J = 12.0 Hz, OCH2Ar), 3.37 (1H, br. s, aliphatic CH), 3.14 (1H, br. s, aliphatic CH), 2.95 – 2.86 (2H, m, aliphatic CH), 2.82 – 2.76 (1H, m, aliphatic CH), 2.32 (1H, q, J = 8.5 Hz, aliphatic CH), 2.21 (1H, br. t, J = 10.0 Hz, aliphatic CH), 1.77 (1H, br. s, aliphatic CH), 1.63 – 1.53 (2H, m, aliphatic CH), 1.29 (1H, br. s, aliphatic CH); 13C NMR (75 MHz, CDCl3) δC 158.0 (4º ArC), 149.8 (4º ArC), 147.6 (ArCH), 145.4 (4º ArC), 144.4 (4º ArC), 141.6 (4º ArC), 141.4 (CH=CH2), 135.1 (ArCH), 131.7 (ArCH), 130.8 (ArCH), 129.1 (4º ArC), 123.7 (ArCH), 123.6 (ArCH), 123.5 (ArCH), 120.4 (ArCH), 115.3 (CH=CH2), 105.2 (ArCH), 81.8 (COCH2Ar), 71.4 (OCH2Ar), 60.7 (NCH), 50.9 (NCH2), 50.5 (NCH2), 40.9 (CH), 29.4 (CH), 27.0 (CH2), 22.4 (CH2); IR νmax/cm⁻¹: 3386, 2941, 1617, 1529, 1350, 1270, 809; MP 118 – 122 ºC; MS (ES+) m/z (relative intensity %) 446 (M + H, 100%); HRMS (ES+): calcd. for C26H28O4N3 (M + H⁺) 446.2074, found 446.2071.

7.5.8.4 Synthesis and characterization of (9S)-9-{[3,5bis(trifluoromethyl)benzyl]oxy}cinchonan-6′-ol, QD-267

To a stirred solution of quinidine 135 (324 mg, 1.00 mmol) in DMF (5 mL) was added NaH (80 mg of a 60% dispersion in mineral oil, 2.00 mmol) and the reaction mixture stirred at room temperature for 30 min before adding 1-(bromomethyl)-3,5-bis(trifluoromethyl)benzene (0.18 mL, 1.00 mmol). The reaction mixture was stirred for 4 h then quenched with saturated NaHCO3(aq) (10 mL), diluted with EtOAc (20 mL) and washed with water (3 x 10 mL) and brine (10 mL). The organic phase was dried over Na2SO4, filtered and concentrated. The residue was dissolved in DMF (10 mL). To the DMF solution was added 1-dodecanethiol (1.2 mL, 5 mmol) followed by portion wise addition of NaH (200 mg of a 60% dispersion in mineral oil, 5 mmol). CAUTION: significant foaming of the reaction
mixture occurred upon addition of NaH. The reaction mixture was heated to 110 °C overnight, cooled to room temperature and quenched with saturated NH₄Cl (30 mL). The mixture was diluted with EtOAc (50 mL) and washed with water (3 x 20 mL) and brine (20 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel to give QD-267 (300 mg, 56%) as an off-white solid. [α]D²⁵ = +76.3 (c 0.82, CHCl₃);

**[1H NMR](500 MHz, CD₃OD) δ H 8.62 (1H, d, J = 4.5 Hz, ArH), 7.98 (2H, br. s, ArH), 7.93 (1H, d, J = 9.0 Hz, ArH), 7.89 (1H, br. s, ArH), 7.55 (1H, br. d, J = 4.0 Hz, ArH), 7.37 – 7.35 (2H, br. m, ArH), 6.01 (1H, ddd, J = 17.5, 10.5, 7.5 Hz, CH=CH₂), 5.46 (1H, br. s, CHOCH₂Ar), 5.05 – 5.01 (2H, m, CH=CH₂), 4.69 – 4.64 (2H, br. m, OCH₂Ar), 3.41 (1H, br. s, aliphatic CH), 3.21 (1H, br. s, aliphatic CH), 3.02 – 2.96 (2H, m, aliphatic CH), 2.88 – 2.82 (1H, m, aliphatic CH), 2.37 (1H, q, J = 8.0 Hz, aliphatic CH), 2.24 (1H, br. t, J = 10.0 Hz, aliphatic CH), 1.80 (1H, br. s, aliphatic CH), 1.65 – 1.55 (2H, m, aliphatic CH), 1.29 (1H, br. s, aliphatic CH);**

**[^13C NMR](125 MHz, CD₃OD) δ C 158.1 (4º ArC), 147.6 (ArCH), 144.7 (4º ArC), 144.4 (4º ArC), 142.5 (4º ArC), 140.8 (CH=CH₂), 132.82 (q, J = 33.5 Hz, CF₃) 131.8 (ArCH), 129.2 (ArCH), 129.0 (4º ArC), 123.7 (ArCH), 123.5 (ArCH), 122.5 (m, ArCCF₃), 120.1 (ArCH), 115.6 (CH=CH₂), 105.1 (ArCH), 81.6 (COCH₂Ar), 71.2 (OCH₂Ar), 60.7 (NCH), 50.9 (NCH₂), 50.5 (NCH₂), 40.5 (CH), 29.2 (CH), 26.6 (CH₂), 22.1 (CH₂);**

**[IR] υmax/cm⁻¹ 3077, 2941, 2877, 1620, 1469, 1280, 1177, 1134; MP 97 – 101 °C MS (ES+) m/z (relative intensity %); 537 (M + H⁺, 100%);**

**[HRMS] (ES+): calcd. for C₂₈H₂₇F₆O₂N₂ (M + H⁺) 537.1971, found 537.1957.**

7.5.8.5 Synthesis and characterization of (9S)-9-[(2-(trifluoromethyl)benzyl]oxy]cinchonan-6'-ol, QD-265

According to the above procedure for the preparation of catalyst QD-267, quinidine 135 (3.24 g, 10.0 mmol) was benzylated with 1-(bromomethyl)-2-(trifluoromethyl)benzene (1.52 mL, 10.0 mmol) and demethylated with 1-
dodecanethiol (12.0 mL, 50.0 mmol) to give cat. **QD-265** (3.81 g, 82%) as a pale yellow solid. $[\alpha]_D^{25} = +104.4$ (c 1.78, CHCl$_3$); **$^1$H NMR** (500 MHz, CD$_3$OD) $\delta_H$ 8.63 (1H, d, $J = 4.5$ Hz, ArH), 7.95 (1H, d, $J = 9.5$ Hz, ArH), 7.81 (1H, br. d, $J = 7.5$ Hz, ArH), 7.68 – 7.63 (2H, m, ArH), 7.56 (1H, br. d, $J = 4.0$ Hz, ArH), 7.48 (1H, t, $J = 7.5$ Hz, ArH), 7.38 – 7.36 (2H, m, ArH), 5.95 (1H, ddd, $J = 17.5, 10.0, 7.5$ Hz, CH=CH$_2$), 4.64 (1H, d, $J = 12.0$ Hz, OCH$_2$Ar), 4.60 (1H, d, $J = 12.0$ Hz, OCH$_2$Ar), 3.39 (1H, br. s, aliphatic CH), 3.14 (1H, br. s, aliphatic CH), 2.95 – 2.90 (2H, m, aliphatic CH), 2.31 (1H, q, $J = 8.0$ Hz, aliphatic CH), 2.19 (1H, br. m, aliphatic CH), 1.74 (1H, br. s, aliphatic CH), 1.61 – 1.50 (2H, m, aliphatic CH), 1.25 (1H, br. s, aliphatic CH); **$^{13}$C NMR** (125 MHz, CD$_3$OD) $\delta_C$ 158.0 (4º ArC), 147.5 (ArCH), 145.0 (4º ArC), 144.4 (4º ArC), 141.0 (CH=CH$_2$), 137.3 (4º ArC), 133.5 (ArCH), 131.8 (ArCH), 131.78 (ArCH), 129.4 (4º ArC), 129.0 (ArCH), 128.9 (q, $J = 30.5$Hz, CF$_3$), 126.9 (q, $J = 5.5$ Hz, ArCCF$_3$) 126.9 (ArCH), 123.6 (ArCH), 120.1 (ArCH), 115.4 (CH=CH$_2$), 105.1 (ArCH), 81.7 (CHOCH$_2$Ar), 68.8 (CHOCH$_2$Ar), 60.8 (NCH), 50.8 (NCH$_2$), 50.3 (NCH$_2$), 40.7 (CH), 29.3 (CH), 26.8 (CH$_2$), 22.1 (CH$_2$); **IR** $\nu_{max}$/cm$^{-1}$ 3074, 2941, 2877, 1670, 1619, 1469, 1316, 1167, 1119; **MP** 98 – 101 ºC **MS** (ES+) m/z (relative intensity %); 469 (M + H$^+$, 100%); **HRMS** (ES+): calcd. for C$_{27}$H$_{28}$F$_3$O$_2$N$_2$ (M + H$^+$) 469.2097, found 469.2088.

### 7.5.8.6 Synthesis and characterization of (9R)-9-[(2-(trifluoromethyl)benzyl)oxy]cinchonan-6'-ol Q-265

According to the above procedure for the synthesis of catalyst **Q-265**, quinine **136** (1.62 g, 5.00 mmol) was benzylated with 1-(bromomethyl)-2-(trifluoromethyl)benzene (0.76 mL, 5.00 mmol) and demethylated with 1-dodecanethiol (6.0 mL, 25.0 mmol) to give cat. **Q-265** (1.61 g, 69%) as a cream colored solid, $[\alpha]_D^{25} = -18.5$ (c 1.00, CHCl$_3$); **$^1$H NMR** (500 MHz, CD$_3$OD) $\delta_H$...
8.61 (1H, d, J = 4.5 Hz, ArH), 7.95 (1H, d, J = 9.0 Hz, ArH), 7.78 (1H, br. s, ArH),
7.67 – 7.63 (2H, m, ArH), 7.56 (1H, d, J = 4.0 Hz, ArH), 7.48 – 7.36 (1H, br. s,
ArH), 7.47 (1H, t, J = 7.5 Hz, ArH), 7.37 (1H, d, J = 9.0 Hz, ArH), 5.74 (1H, br.
m, CH=CH2), 5.35 (1H, br. s, CHOCH2Ar), 4.97 – 4.88 (2H, m, CH=C
H2), 4.65
(1H, d, J = 12.0 Hz, OCH2Ar), 4.58 (1H, d, J = 12.0 Hz, OCH2Ar), 3.45 (1H, br. s,
aliphatic CH), 3.17 (1H, br. s, aliphatic CH), 3.07 (1H, t, J = 7.5 Hz, aliphatic
CH), 2.71 – 2.60 (2H, m, aliphatic CH), 2.33 (1H, br. s, aliphatic CH), 1.90 (1H,
br. s, aliphatic CH), 1.79 – 1.75 (2H, br. m, aliphatic CH), 1.64 (1H, br. s, aliphatic
CH), 1.59 – 1.54 (1H, br. m, aliphatic CH); 13C NMR (75 MHz, CD3OD) δC
158.0
(4º ArC), 147.5 (ArCH), 145.3 (4º ArC), 144.5 (4º ArC), 142.5 (CH=CH2), 137.5
(4º ArC), 133.5 (ArCH), 131.8 (ArCH), 131.3 (ArCH), 129.3 (4º ArC), 129.0
(ArCH), 128.7 (q, J = 30.5 Hz, CF3), 126.9 (q, J = 5.5 Hz, ArCCF3), 126.9
(ArCH), 123.5 (ArCH), 120.0 (ArCH), 115.2 (CH=CH2), 105.0 (ArCH), 81.0
(CHOCCH2Ar), 68.7 (OCH2Ar), 61.1 (NCH), 57.5 (NCH2), 44.1 (NCH2), 40.8
(CH), 29.1 (CH), 28.2 (CH2), 22.4 (CH2); IR υmax/cm⁻¹ 3424, 2943, 1637, 1620,
1315, 1167, 1118; MP 207 – 212 ºC; MS (ES+) m/z (relative intensity %) 469 (M+
H⁺, 100%); HRMS (ES+): calcd. for C27H28F3O2N2 (M + H⁺) 469.2097, found
469.2094.

7.5.8.7 Attempted synthesis of halogenated benzyl derivatives

To a solution of quinidine 135 (300 mg, 0.93 mmol) in anh DMF (5 mL) was added
NaH (93 mg of a 60% wt dispersion in mineral oil, 2.33 mmol). The reaction
mixture was stirred at room temperature for 30 min before adding 2-bromobenzyl
bromide (255 mg, 1.02 mmol). The reaction mixture was stirred at room
temperature for 18 h then quenched with brine (30 mL) and extracted with EtOAc
(3 x 10 mL). The combined organic extracts were washed with brine (2 x 10 mL),
dried over Na2SO4, filtered and concentrated. The residue was purified by column
chromatography on silica gel, eluting with CH2Cl2 containing 5 – 10% MeOH to
give 268 (358 mg, 73%). [α]D25 = +98.4 (c 1.75, CHCl3); 1H NMR (500 MHz,
CDCl₃) δH 8.69 (1H, d, J = 4.5 Hz, ArH), 7.98 (1H, d, J = 9.0 Hz, ArH), 7.66 (1H, d, J = 4.5 Hz, ArH), 7.57 – 7.54 (2H, m, ArH), 7.45 – 7.43 (2H, m, ArH), 7.36 (1H, t, J = 7.5 Hz, ArH), 7.22 (1H, dt, J = 7.5, 1.5 Hz, ArH), 5.98 (1H, ddd, J = 17.5, 10.5, 7.5 Hz, CH=CH₂), 5.49 (1H, br. s, CHOCH₂Ar), 5.02 – 4.97 (2H, m, CH=CH₂), 4.58 (1H, d, J = 12.0 Hz, OCH₂Ar), 4.54 (1H, d, J = 12.0 Hz, OCH₂Ar), 3.96 (3H, s, OCH₃), 3.47 – 3.44 (1H, br. m, NCH₂), 3.14 (1H, br. m, CH), 2.96 – 2.96 – 2.88 (2H, m, NCH₂), 2.83 – 2.77 (1H, m, NCH₂), 2.34 – 2.30 (1H, m, CH), 2.25 (1H, br. t, J = 11.0 Hz, CH₂), 1.75 (1H, br. s, CH), 1.61 – 1.51 (2H, m, CH₂), 1.26 (1H, br. m, CH); ¹³C NMR (125 MHz, CDCl₃) δC 159.9 (4º ArC), 148.1 (ArCH), 146.0 (4º ArC), 145.1 (4º ArC), 141.2 (CH=CH₂), 138.2 (4º ArC), 133.9 (ArCH), 131.7 (ArCH), 131.6 (ArCH), 130.9 (ArCH), 128.7 (4º ArC), 128.7 (ArCH), 124.5 (4º ArC), 123.7 (ArCH), 120.5 (ArCH), 115.3 (CH=CH₂), 102.4 (ArCH), 81.5 (CHOCH₂Ar), 72.1 (OCH₂Ar), 61.0 (CH), 56.4 (OCH₃), 50.8 (CH₂), 50.3 (CH₂), 40.7 (CH), 29.3 (CH), 26.8 (CH₂), 22.2 (CH₂); IR νmax/cm⁻¹ 2937, 2873, 1620, 1591, 1508, 1472, 1433, 1241, 1229, 1028, 830, 753; MP 38 – 39 ºC; MS (ES+) m/z (relative intensity %) 493 (M + H⁺, 50%), 495 (M + H⁺, 50%); HRMS (ES+): calcd. for C₂₇H₃₀O₂N₂Br (M + H⁺) 493.1485, found 493.1480.

Attempted de-methylation of 268 with 1-dodecanethiol as described above did not give the desired benzylated catalyst. Therefore an alternative route via TIPS-protected quinidine derivative 270 was attempted.

### 7.5.8.8 Synthesis and characterisation of (9S)-6’-[(2-bromobenzyl)oxy]cinchonan-9-ol, QD-271 and (9S)-6’,9-bis[(2-bromobenzyl)oxy]cinchonan, QD-272

Following the above procedure for the benzylation of quinidine, 270 (100 mg, 0.21 mmol) was reacted with 2-bromobenzy bromide (21 mg, 0.54 mmol) and the crude reaction mixture dissolved in THF (10 mL) and treated with TBAF (55 mg, 0.21
mmol). The reaction mixture was concentrated by rotary evaporation and the residue purified by column chromatography on silica gel, eluting with CH₂Cl₂ containing 1–10% MeOH. The desired organocatalyst was not isolated from the reaction mixture; instead benzylated derivatives QD-271 (21 mg, 15%) as a pale yellow solid and QD-272 (30 mg, 30%) also as a pale yellow solid were obtained.

**QD-271**: [α]₀²⁵ = +109.8 (c 0.47, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δH 8.69 (1H, d, J = 4.5 Hz, ArH), 8.00 (1H, d, J = 9.0 Hz, ArH), 7.70 (1H, d, J = 4.5 Hz, ArH), 7.66 (1H, d, J = 7.5 Hz, ArH), 7.61 (1H, d, J = 7.5 Hz, ArH), 7.57 (1H, d, J = 2.5 Hz, ArH), 7.52 (1H, dd, J = 9.0, 2.5 Hz, ArH), 7.39 (1H, t, J = 7.5 Hz, ArH), 7.27 (1H, dt, J = 7.5, 1.5 Hz, ArH), 6.12 (1H, ddd, J = 17.5, 10.5, 7.5 Hz, CH=CH₂), 5.70 (1H, br. d, J = 3.5 Hz, CHOH), 5.36 (1H, d, J = 12.5 Hz, OCH₂Ar), 5.33 (1H, d, J = 12.5 Hz, OCH₂Ar), 5.16 – 5.10 (2H, m, CH=C₂H₂), 5.16 – 5.10 (2H, m, CH=C₂H₂), 3.63 – 3.59 (1H, br. m, NC₂H₂), 3.22 – 3.19 (1H, br. m, CH), 3.02 – 2.84 (3H, m, NC₂H₂), 2.40 (1H, q, J = 8.5 Hz, C₂H), 2.23 (1H, br. m, C₂H₂), 1.80 (1H, br. s, C₂H), 1.68 – 1.57 (2H, m, C₂H₂), 1.22 – 1.16 (1H, m, C₂H₂); ¹³C NMR (125 MHz, CDCl₃) δC 158.4 (4º ArC), 149.8 (4º ArC), 148.5 (ArCH), 145.0 (4º ArC), 140.8 (CH=CH₂), 137.2 (4º ArC), 134.0 (ArCH), 131.7 (ArCH), 131.1 (ArCH), 131.0 (ArCH), 128.9 (ArCH), 128.0 (4º ArC), 124.3 (4º ArC), 123.5 (ArCH), 120.4 (ArCH), 115.8 (CH=CH₂), 104.2 (ArCH), 71.8 (CHOH), 71.3 (OCH₂Ar), 61.2 (CH), 50.7 (NCH₂), 50.1 (NCH₂), 40.6 (CH), 29.4 (CH), 26.4 (CH₂), 21.5 (CH₂); IR νmax/cm⁻¹ 3211, 2937, 2872, 1620, 1591, 1509, 1457, 1440, 1240, 1224, 1025; MS (ES+) m/z (relative intensity %) 479 (M + H⁺, 50%), 481 (M + H⁺, 50%); HRMS (ES+): calcd. for C₂₆H₂₈O₂N₂Br (M + H⁺) 479.1329, found 479.1329.

**QD-272**: [α]₀²⁵ = +61.7 (c 0.44, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δH 7.57 – 7.53 (3H, m, ArH), 7.50 (1H, br. d, J = 7.5 Hz, ArH), 7.37 – 7.33 (2H, m, ArH), 7.26 – 7.20 (2H, m, ArH), 7.26 – 7.20 (2H, m, ArH), 5.92 (1H, ddd, J = 17.5, 10.5, 7.0 Hz, CH=CH₂), 5.62 (1H, br. s, CHOH₂Ar), 5.36 (1H, d, J = 12.5 Hz, OCH₂Ar), 5.32 (1H, d, J = 12.5 Hz, OCH₂Ar), 5.03 – 4.99 (2H, m, CH=CH₂), 4.58 (1H, d, J = 11.5 Hz, OCH₂Ar), 4.51 (1H, d, J = 11.5 Hz, OCH₂Ar), 3.52 (1H, br. s, NCH₂), 3.31 (1H, br. s, CH), 3.05 (1H, br. m, NCH₂), 2.91 (2H, br. s, NCH₂), 2.44 (1H, br. m, CH), 2.23 (1H, br. m, CH₂), 1.82 (1H, br. s, CH), 1.70 – 1.59 (2H, m, CH₂), 1.40 (1H, br. m, CH₂); ¹³C NMR (125 MHz, CDCl₃) δC 158.5 (4º ArC), 148.5 (ArCH), 145.4
(4º ArC), 144.8 (4º ArC), 139.9 (CH=CH₃), 137.8 (4º ArC), 137.1 (4º ArC), 134.0 (ArCH), 133.9 (ArCH), 133.1 (4º ArC), 132.0 (ArCH), 131.9 (ArCH), 131.1 (ArCH), 131.0 (ArCH), 130.9 (ArCH), 128.8 (ArCH), 128.5 (4º ArC), 124.8 (4º ArC), 124.2 (ArCH), 124.0 (ArCH), 121.4 (ArCH), 116.2 (CH=CH₂), 104.3 (ArCH), 80.5 (CHOCH₂Ar), 72.3 (OCH₂Ar), 71.4 (OCH₂Ar), 61.3 (NCH), 50.6 (NCH₂), 49.8 (NCH₂), 39.7 (CH), 28.9 (CH), 25.7 (CH₂), 22.4 (CH₂); IR νₑₓₑₓ/cm⁻¹ 2936, 2870, 1619, 1590, 1508, 1440, 1226, 1026; MP 58 – 62 °C; MS (ES⁺) m/z (relative intensity %) 647 (M + H⁺, 50%) 649 (M + H⁺, 100%), 651 (M + H⁺, 50%); HRMS (ES⁺): calcd. for C₃₃H₃₃O₂N₂Br₂ (M + H⁺) 649.0886, found 649.0882.

7.5.9 Screen of novel benzyl-functionalised organocatalysts

According to general procedure C (section 7.3.6), replacing ps-BEMP with cat. QD-260, QD-261, QD-265, QD-267 and QD265 (10 mol %), 3-methoxycatechol 163 was reacted with 207 (1 equiv) on a 0.1 mmol scale to give 208 or 223 (following methylene acetal or acetate protection) in the yields and enantioselectivities shown.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (loading)</th>
<th>Product</th>
<th>Conc./M</th>
<th>t(minor)/min</th>
<th>t(major)/min</th>
<th>% ee</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>QD-260 (10 mol %)</td>
<td>(+)-223</td>
<td>0.1</td>
<td>22.32</td>
<td>11.66</td>
<td>43</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>QD-261 (10 mol %)</td>
<td>(+)-223</td>
<td>0.1</td>
<td>22.20</td>
<td>11.65</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>QD-267 (10 mol %)</td>
<td>(+)-223</td>
<td>0.1</td>
<td>22.52</td>
<td>11.32</td>
<td>43</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>Cat QD-265 (10 mol %)</td>
<td>(+)-223</td>
<td>0.1</td>
<td>22.01</td>
<td>11.24</td>
<td>64</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>QD-271 (10 mol %)</td>
<td>(-)-223</td>
<td>0.1</td>
<td>11.905</td>
<td>24.42</td>
<td>44</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>QD-272 (10 mol %)</td>
<td>(+)-223</td>
<td>0.1</td>
<td>24.52</td>
<td>11.78</td>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td>QD-265 (20 mol %)</td>
<td>(+)-223</td>
<td>0.0125</td>
<td>21.71</td>
<td>11.27</td>
<td>73</td>
<td>54</td>
</tr>
</tbody>
</table>
According to the procedure for racemate synthesis (section 7.4.3.3), (+)-208 (2.06 g, 5.25 mmol) was reacted with Super-hydride® (6.3 mL of a 1 M solution in THF, 6.30 mmol) to give (+)-209 (1.87 g, 90%) as a colourless solid, the 4 stereoisomers could not be completely separated by chiral HPLC analysis, $\alpha_D^{24} = +22.6$ (c 0.95, CHCl₃); MP 40 – 44 ºC. Other data identical to racemic compound.

According to the procedure for racemate synthesis (section 7.4.3.5), (+)-209 (1.87 g, 4.73 mmol) was treated with acetic anhydride (2 mL) in pyridine (10 mL) and the crude acetylated product reacted with (isopropenyl)trimethylsilane (7.9 mL, 47.3 mmol) to give (-)-210 (1.89 g, 92%) as a colourless oil in 3:1 dr and 69% ee determined by HPLC analysis [Chiralpak AD, hexane/iso-propanol 95:5, 1.0 mL.min⁻¹, $\lambda = 215$ nm, minor diastereomer: t (major) = 16.12 min, t (minor) = 19.90
min], major diastereomer: t (minor) = 24.41 min, t (major) = 32.41 min] by comparison to a racemic sample. $[\alpha]_D^{24} = -15.4$ (c 0.46, CHCl$_3$). Other data identical to racemic compound.

7.5.10.3 Synthesis and characterisation of (-)-tert-butyl-6-methoxy-3a-(7-methoxy-1,3-benzodioxol-5-yl)-4-oxo-2,3,3a,4,7,7a-hexahydro-1H-indole-1-carboxylate, (-)-212

According to the procedure for racemate synthesis (section 7.4.3.6), (-)-210 (1.83 g, 4.20 mmol) was treated with KO$_t$Bu (8.83 mL of a 1 M solution in THF, 8.83 mmol) and the crude diketone treated with TiCl$_4$ (0.19 mL of a 1M solution in CH$_2$Cl$_2$, 0.19 mmol) in MeOH (20 mL) to give (-)-212 (950 mg, 54%) as a colourless solid in 24% ee determined by HPLC analysis [Chiralpak AD, hexane/isopropanol 95:5, 1.0 mL.min$^{-1}$, $\lambda = 215$ nm, t (major) = 27.73 min, t (minor) = 31.62 min], by comparison to a racemic sample. $[\alpha]_D^{24} = -18.9$ (c 1.82, CHCl$_3$); MP 48 - 52 ºC. Other data identical to racemic compound.

7.5.10.4 Studies into racemisation of (-)-tert-butyl-6-methoxy-3a-(7-methoxy-1,3-benzodioxol-5-yl)-4-oxo-2,3,3a,4,7,7a-hexahydro-1H-indole-1-carboxylate, (-)-212

Any change in enantiomeric excess of enol ether (-)-212 during the reaction was investigated by removing aliquots from the Dieckmann cyclisation at varying time intervals:

To a solution of keto-ester (-)-210 (200 mg, 0.46 mmol) in anh THF (9 mL) at 40 ºC was added KO$^+$Bu (0.97 mL of a 1 M solution in THF, 0.97 mmol). A 2.5 mL
aliquot was removed from the reaction mixture after 1, 5, 10 and 20 min and quenched immediately with 1 M HCl (5 mL). Each mixture was extracted with ethyl acetate (2 x 5 mL) and the crude organic residues treated with TiCl₄ in MeOH according to the procedure for racemate production to give, following column chromatography on silica gel, (−)-212 in the yields and enantioselectivities shown in Table 7.12.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time/min</th>
<th>t(major)/min</th>
<th>t(minor)/min</th>
<th>% Yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>5</td>
<td>26.06</td>
<td>29.73</td>
<td>27</td>
<td>26</td>
</tr>
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<td>3</td>
<td>10</td>
<td>27.48</td>
<td>31.32</td>
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<td>27</td>
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<tr>
<td>4</td>
<td>20</td>
<td>28.05</td>
<td>31.96</td>
<td>17</td>
<td>25</td>
</tr>
</tbody>
</table>

Table 7.12: Measurement of enantiomeric excess of (−)-212 with time, insufficient product could be obtained from the aliquot removed after 1 min, this mainly contained starting material.

Racemisation of the starting material was investigated by quenching the reaction after 1 min and measuring the enantiomeric excess of the recovered starting material:

To a solution of keto-ester (−)-210 (44 mg, 0.1 mmol) in anh THF (2 mL) at 40 °C was added KO'Bu (0.21 mL of a 1 M solution in THF, 0.21 mmol). The reaction mixture was stirred for 1 min then quenched at 40 °C with 1 M HCl (5 mL). The reaction mixture was extracted with ethyl acetate (2 x 5 mL) and the combined organic portions dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel to recover the starting material (−)-210 (20 mg, 45%), in 1.7:1 dr and 26/21% ee for the major/minor diastereomers respectively [Chiralpak AD, hexane/iso-propanol 95:5, 1.0 mL.min⁻¹, λ = 215 nm, minor diastereomer: t (major) = 17.32 min, t (minor) = 20.14 min], major diastereomer: t (minor) = 26.12 min, t (major) = 35.33 min] by comparison to a racemic sample.
8 References


18. For a review on metal catalysed asymmetric conjugate additions see: Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. Synthesis 2007, 9, 1279.


54. For a review on nucleophilic additions to quinones see: Kutyrev, A. A. Tetrahedron 1991, 47, 8043.


75. Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* 2005, 4, 603.


88. The (R)-stereochemical configuration of the major enantiomer of (-)-169r and (+)-169s was assigned by analogy to the work of Deng and co-workers, see references 81(a) and (b).


98. See reference 95(c) for a biomimetic synthesis of crinine.


Appendix I: Crystallographic Data for 217
Crystal data

C_{21}H_{25}NO_{6}  

\( F(000) = 824 \)

\( M_r = 387.43 \)

Monoclinic, \( P2_1/c \)

Hall symbol: \(-P 2ybc\)

Melting point: not measured K

\( a = 5.8975 \) (1) Å

\( b = 12.5457 \) (2) Å

\( c = 25.9990 \) (4) Å

\( \beta = 92.6152 \) (6)°

\( V = 1921.62 \) (5) Å³

\( Z = 4 \)

Cell parameters from 4452 reflections

\( \mu = 0.10 \) mm⁻¹

\( T = 150 \) K

\( \theta = 5–27° \)

\( \theta_{\text{max}} = 27.5°, \theta_{\text{min}} = 5.1° \)

Plate, colourless

0.26 × 0.24 × 0.08 mm

Data collection

Area diffractometer

3384 reflections with \( I > 2.0\sigma(I) \)

graphite

\( R_{\text{int}} = 0.042 \)

\( \omega \) scans

\( \theta_{\text{max}} = 27.5°, \theta_{\text{min}} = 5.1° \)

Absorption correction: multi-scan

DENZO/SCALEPACK

\( h = -7 \rightarrow 7 \)

\( T_{\text{min}} = 0.93, T_{\text{max}} = 0.99 \)

\( k = -16 \rightarrow 13 \)

22970 measured reflections

\( l = -33 \rightarrow 33 \)

4365 independent reflections

Refinement

Refinement on \( F^2 \)

Primary atom site location: structure-invariant direct methods

Least-squares matrix: full

Hydrogen site location: inferred from neighbouring sites

\( R[F^2 > 2\sigma(F^2)] = 0.041 \)

\( wR(F^2) = 0.098 \)

H-atom parameters constrained

Method = Modified Sheldrick \( w = 1/\sigma^2(F^2) + (0.04P)^2 + 0.82P, \) where \( P = \max(F_o^2,0) + 2F_c^2)/3 \)

\( S = 0.94 \)

\( \Delta/\sigma)_{\text{max}} = 0.0004 \)
4365 reflections\hfill $\Delta \rho_{\text{max}} = 0.38 \text{ e Å}^{-3}$
253 parameters\hfill $\Delta \rho_{\text{min}} = -0.36 \text{ e Å}^{-3}$
0 restraints

**Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)**

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<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
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Geometric parameters (Å, °)

O1—C2 1.2167(16)  H71—C7—H73 108.8
C2—O3 1.3477(16)  C4—C7—H72 110.3
C2—N8 1.3603(16)  H71—C7—H72 108.1
O3—C4 1.4794(15)  H73—C7—H72 109
C4—C5 1.512(2)  C2—N8—C9 123.59(10)
C4—C6 1.524(2)  C2—N8—C28 119.48(10)
C4—C7 1.518(2)  C9—N8—C28 112.12(9)
C5—H51 0.971  N8—C9—C10 103.43(9)
C5—H53 0.97  N8—C9—C25 112.89(10)
C5—H52 0.989  C10—C9—C25 112.47(10)
C6—H61 0.99  N8—C9—H91 109.3
C6—H63 0.989  C10—C9—H91 109.1
C6—H62 0.976  C25—C9—H91 109.4
C7—H71 0.998  C9—C10—C11 110.11(10)
C7—H72 0.971  C9—C10—C22 110.97(10)
C7—H73 0.998  C11—C10—C22 111.18(10)
N8—C9 1.4777(15)  C9—C10—C27 102.42(10)
N8—C28 1.4713(16)  C11—C10—C27 115.07(10)
C9—C10 1.5575(16)  C22—C10—C27 106.75(10)
C9—C25 1.5238(18)  C10—C11—C12 120.60(11)
C9—H91 0.981  C10—C11—C19 119.32(11)
C10—C11 1.5351(17)  C12—C11—C19 119.90(12)
C10—C22 1.5121(18)  C11—C12—C13 116.68(12)
C10—C27 1.5413(18)  C11—C12—H121 122.3
C11—C12 1.4048(18)  C13—C12—H121 121.1
C11—C19 1.3969(18)  C12—C13—C17 123.32(12)
C12—C13 1.3770(18)  C12—C13—O14 127.48(12)
C12—H121 0.949  O14—C13—C17 109.21(11)
C13—O14 1.3838(16)  O14—C13—H151 109.3
C13—C17 1.3726(19)  O16—C15—H151 110
O14—C15 1.4382(17)  O16—C15—H152 109.2
C15—O16 1.4359(17)  O16—C15—H152 111.8
C15—H151 0.995  C15—O16—C17 103.55(10)
C15—H152 1.007  C15—O16—C17 103.55(10)
C18—C19  1.4030(18)  O16—C17—C13  110.59(12)
C18—O20  1.3590(16)  O16—C17—C18  127.99(12)
C19—H191  0.953  C13—C17—C18  121.42(12)
O20—C21  1.4356(16)  C17—C18—C19  116.27(12)
C21—H211  0.974  C17—C18—O20  118.73(11)
C21—H212  0.986  C19—C18—O20  125.90(12)
C21—H213  0.974  C18—C19—C11  122.40(12)
C22—C23  1.3330(19)  C18—C19—H191  118.8
C22—H221  0.969  C11—C19—H191  118.8
C23—C24  1.4730(19)  C18—O20—C21  116.63(10)
C23—H231  0.96  O20—C21—H211  105.7
C24—C25  1.4998(18)  O20—C21—H212  110.2
C24—O26  1.2235(16)  H211—C21—H212  110.2
C25—H252  0.988  C21—C22—C23  125.68(12)
C25—H251  0.973  C22—C23—C24  115.6
C27—C28  1.5198(18)  C22—C23—H231  118.6
C27—H271  0.969  C23—C24—C25  120.8
C27—H272  0.976  C23—C24—O26  122.91(12)
C28—H281  0.977  C9—C25—C24  111.57(11)
C28—H282  0.993  C9—C25—H252  107.5
O1—C2—O3  125.74(12)  C24—C25—C24  111.73(11)
O1—C2—N8  123.94(12)  C24—C25—H252  110.5
O3—C2—N8  110.32(11)  C9—C25—H251  110.7
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O3—C4—C7  102.01(11)  C24—C25—H251  109.5
C5—C4—C7  110.72(12)  C24—C25—H251  109.5
C6—C4—C7  111.23(13)  C24—C25—H251  109.5
C4—C5—H51  108.8  H252—C25—H251  109.2
C4—C5—H53  109.9  C10—C27—C28  103.59(10)
H51—C5—H53  107.9  C10—C27—H271  110.3
C4—C5—H52  110.5  C28—C27—H271  108.4
H51—C5—H52  110.3  C10—C27—H272  112.4
H53—C5—H52  109.4  C28—C27—H272  112.5
C4—C6—H61  107.9  H271—C27—H272  109.5
C4—C6—H63  111.8  C27—C28—N8  103.27(10)
H61—C6—H63  110  C27—C28—H281  113.2
C4—C6—H62  109.4  N8—C28—H282  109.7
H61—C6—H62  108  C27—C28—H282  111.8
H63—C6—H62  109.6  N8—C28—H282  109.5
C4—C7—H71  109.2  H281—C28—H282  109.2
C4—C7—H73  111.4
Hydrogen-bond geometry (Å, °)

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<th>H···A</th>
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Symmetry codes: (i) x+1, y, z; (ii) −x+2, −y+2, −z+1; (iii) −x+1, y−1/2, −z+1/2.