Synthesis of all-carbon quaternary stereocentres of 2-oxindole derivatives employing asymmetric bifunctional phase-transfer catalysis and nucleophilic catalysis

Trinity College Dublin

A thesis submitted to the University of Dublin for the degree of Doctor of Philosophy

by

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Under the supervision of Prof. Stephen Connon

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Declaration

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work. Due acknowledgements and references are given to the work of others.

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........................................
Mili Ltvajova
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Abstract

Asymmetric Phase-Transfer Catalysis (PTC) has been efficiently employed in the enantioselective S_N2-type alkylation of highly challenging C,N-bis-acylated 2-oxindole derivatives. The alkylated 2-oxindole-derived products, bearing a newly generated all-carbon quaternary stereocentre, represent highly malleable synthetic targets in organic chemistry. We have shown for the first time that phase-transfer catalysed alkylation can be performed in the absence of a base, providing a water-rich solvent mixture and a chiral phase-transfer catalyst are used. The most efficient phase-transfer catalysts in this study were derived from cinchona alkaloids substituted with a bifunctional urea motif. This novel PTC methodology has been successfully applied in the synthesis of a bioactive spirooxindole target.

Nucleophilic catalysis by anionic species, such as fluoride and acetate ions, has been demonstrated in the O- to C-acyl transfer of 2-oxindole-derived substrates. Such rearrangement leads to direct formation of all-carbon quaternary stereocentres. Tetrabutylammonium fluoride (TBAF) and tetrabutylammonium acetate (TBAOAc) proved to be among the most proficient catalysts in the rearrangement of the acetyl group of 2-oxindole derivatives.

Enantioselective methanolysis of succinic anhydride has been effectively mediated by nucleophilic catalysis. The catalysts employed in this transformation were chiral quaternary ammonium fluorides generated in situ by anion exchange between the cinchona alkaloid-derived quaternary ammonium bromides and KF. Extensive catalyst screening revealed the importance of a bifunctional urea moiety in the catalyst framework and a substitution of the quinuclidine nitrogen atom of quinine with a benzyl unit bearing electron-withdrawing groups.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>aq.</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>BnBr</td>
<td>Benzylbromide</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butoxycarbonyl</td>
</tr>
<tr>
<td>Cat.</td>
<td>Catalyst</td>
</tr>
<tr>
<td>CF₃</td>
<td>Trifluoromethyl</td>
</tr>
<tr>
<td>conc.</td>
<td>Concentrated</td>
</tr>
<tr>
<td>CSP</td>
<td>Chiral stationary phase</td>
</tr>
<tr>
<td>d</td>
<td>Days</td>
</tr>
<tr>
<td>DIAD</td>
<td>Diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(Dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulphoxide</td>
</tr>
<tr>
<td>DPPA</td>
<td>Diphenylphosphoryl azide</td>
</tr>
<tr>
<td>EDG</td>
<td>Electron donating group</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>Ethanol</td>
</tr>
<tr>
<td>ESI</td>
<td>Electrospray ionisation</td>
</tr>
<tr>
<td>equiv.</td>
<td>Equivalent</td>
</tr>
<tr>
<td>EWG</td>
<td>Electron withdrawing group</td>
</tr>
<tr>
<td>FT-IR</td>
<td>Fourier transform–infrared spectroscopy</td>
</tr>
<tr>
<td>HetAr</td>
<td>Heteroaryl</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear multiple bond correlation</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest occupied molecular orbital</td>
</tr>
<tr>
<td>HPLC</td>
<td>High performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectrometry</td>
</tr>
<tr>
<td>HSQC</td>
<td>Heteronuclear single quantum correlation</td>
</tr>
<tr>
<td>IPA</td>
<td>Isopropyl alcohol</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>m-</td>
<td>meta</td>
</tr>
<tr>
<td>M.p.</td>
<td>Melting point</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MeOH</td>
<td>Methanol</td>
</tr>
<tr>
<td>MTBE</td>
<td>Methyl-tert-butyl ether</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>Nuclear Overhauser effect</td>
</tr>
<tr>
<td>o-</td>
<td>ortho</td>
</tr>
<tr>
<td>OMe</td>
<td>Methoxy</td>
</tr>
<tr>
<td>p-</td>
<td>para</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PhMe</td>
<td>Toluene</td>
</tr>
<tr>
<td>pK_s</td>
<td>The negative log of the base dissociation constant</td>
</tr>
<tr>
<td>PTC</td>
<td>Phase-transfer catalyst/catalysis</td>
</tr>
<tr>
<td>ROESY</td>
<td>Rotating-frame Overhauser spectroscopy</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>S_N2</td>
<td>Nucleophilic substitution (bi-molecular)</td>
</tr>
<tr>
<td>tBu</td>
<td>tert-Butyl</td>
</tr>
<tr>
<td>TBAB</td>
<td>Tetrabutylammonium bromide</td>
</tr>
<tr>
<td>temp.</td>
<td>Temperature</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TOCSY</td>
<td>Total correlation spectroscopy</td>
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1 Introduction

1.1 Chirality: general introduction

Chirality can be defined as a geometric property associated with certain molecules and ions. The term ‘chirality’ – derived from the Greek word for hand, χειρ, was first introduced by the physicist Lord Kelvin.\(^1\) Chiral molecules lack the plane of symmetry and they are mirror images of each other that cannot be superimposed. Such species are called enantiomers, or optical isomers.\(^2\) The two enantiomers possess identical chemical and physical properties. One way to distinguish between them is to examine their optical activity behaviour. Two enantiomers rotate plane-polarised light in equal magnitude but in the opposite direction.\(^2\) This astonishing scientific discovery about molecular chirality was made by Louis Pasteur in 1848,\(^3\) when he examined the nature of hemihedral sodium ammonium tartarate crystals and the optical rotation of tartare in solution.\(^4\)

Almost two centuries later, a tremendous number of discoveries has been made in the field of asymmetric synthesis. The fact that two enantiomeric forms of the same molecule behave rather differently when placed in an asymmetric environment,\(^5\) is perhaps one of the most profound. For that reason, the importance of synthesising enantiopure drugs, containing only one specific enantiomeric form, has become of paramount focus. The unfortunate tragedy associated with thalidomide (Figure 1.1), which was prescribed to treat morning sickness but also accidentally contributed to birth defects in newborns in the late 1950s and early 1960s,\(^6\) forced regulatory authorities to redefine policy guidelines for the development and approval of new stereoisomeric drugs. Since then, it has become essential that the pharmacological activity and the pharmacokinetic profile of both enantiomers of a new drug are fully examined and assessed prior to the drug’s approval for manufacturing and its subsequent release to the market.\(^7\)

![Figure 1.1](image_url)  
**Figure 1.1** Enantiomers of thalidomide.
1.1.1 Strategies in asymmetric synthesis: general overview

The growth in the pharmaceutical industry over the past several years has resulted in an increased demand for enantiopure compounds. This surge has inspired remarkable progress in the field of asymmetric synthesis. The three main approaches of asymmetric syntheses include: (a) the resolution (i.e. separation) of two enantiomers from a racemic mixture, employing either a chemical, physical or enzymatic process, (b) the use of chiral auxiliaries or naturally occurring chiral molecules – referred to as the chiral pool synthesis, and (c) asymmetric catalysis. Each of these three strategies has its own inherent advantages and limitations. The preferred method that is normally chosen to pursue the synthesis of an enantiopure molecule, especially in industry, usually depends on several aspects, such as availability of materials, practicality of the process and overall cost-effectiveness.

The resolution of a racemate is perhaps one of the oldest methods that yields an enantiopure compound from a mixture of two enantiomers which are present in equal amounts. The process is based on the conversion of a racemic mixture into a pair of diastereomers by the interaction with an optically pure resolving agent. Since the two diastereomers are physically distinctive, they can be easily separated, e.g. by crystallisation. Although an effective method, there are several drawbacks associated with this technique. The main disadvantage is that the maximum attainable yield of one enantiomer is only 50%, and furthermore, two additional steps are required – the formation and the cleavage of the diastereomeric pair. An alternative approach which can lead up to 100% conversion of a single desired enantiomer, is dynamic kinetic resolution (DKR). As opposed to standard kinetic resolution, where the chiral catalyst reacts faster with one of the enantiomers, still affording the enantioenriched product in only up 50% yield, DKR is based on the concept known as stereoconvergence. This process can be defined as the predominant formation of the same stereoisomer of a reaction product, when there are two different stereoisomers of the reactant employed in the same reaction. Thus, an in situ racemisation that is associated with a DKR process, can lead to a total conversion of the substrate into a single enantiomer, obtaining an overall yield of 100%. 

2
Chiral auxiliaries are enantiopure compounds that can be linked to a substrate and consequently affect the stereochemical outcome of a reaction. A substrate must have a compatible functional group installed in order for the auxiliary to be successful. The auxiliary is usually attached to the substrate prior to the enantioselective step and is removed afterwards. These additional steps associated with the use of auxiliaries, the cost of their stoichiometric amounts, and often imperfect diastereoccontrol, sum up the main reasons why this approach can be rather impractical. Chiral pool synthesis which involves the use of naturally occurring chiral molecules, such as amino acids, carbohydrates and alkaloids, is a very effective method for the synthesis of bioactive natural products. However, the availability of both enantiomers of the required amino acids, carbohydrates etc., can be often limited, rendering this approach relatively deficient.

Asymmetric catalysis generally offers a more efficient approach of synthesising enantiopure compounds by enantioselectively converting an achiral molecule into a chiral one, in the presence of a chiral catalyst. The most attractive features of this strategy that have made it one of the most popular and widely used techniques, especially in industry, are low catalyst loading (typically 0.1-10 mol%) and the prospect of obtaining a single enantiomer in a 100% yield. Among the most widely used catalysts in asymmetric syntheses are enzymes, organometallic catalysts and organocatalysts. Biocatalysis represents a powerful method of using biological compounds, ranging from isolated enzymes to whole microorganisms, to perform asymmetric transformations. Interest in biocatalysis has increased significantly over the past number of years, primarily due to their extremely high chemo-, regio- and enantioselectivity in many chemical reactions, as well as the lack of toxic by-products and mild operating conditions, which make them exceptionally environmentally friendly. The possibility of replacing traditional chemical catalysts with enzymes, especially in the industry, became very intriguing. However, limited substrate scope and high reagent specificity can be a problem.

Organometallic catalysts and organocatalysts are synthetically developed catalysts, incredibly popular due to their tunability and numerous design variations which can be altered specifically for a required reaction, making them extremely versatile and
essentially limitless regarding their catalytic potential. Typi-

24, 25 Typical organometallic catalysts consist of chiral complexes between transition metals (e.g. Rh, Ru, Pd, Ir) and chiral ligands (e.g. phosphines, diamines, amino alcohols). Although a very low catalyst loading is often sufficient for a successful catalysis, often stringent reaction conditions – inert oxygen-free atmosphere and extremely anhydrous environment, are far from optimal. Nonetheless, there have been many remarkable achievements made in this field.

26 Nonethelss, there have been many remarkable achievements made in this field.

27 Over the past two decades, asymmetric organocatalysis has become a highly dynamic research topic, experiencing tremendous development in a comparatively short period of time. The principle of organocatalysis is based on the use of small organic molecules that serve as catalysts. They are generally derived from a wide range of naturally occurring species (e.g. proline, imidazolidinones, cinchona alkaloids) displaying attractive properties such as air/moisture stability, non-toxicity and availability in both enantiomeric forms. There has been a vast number of powerful asymmetric bond-forming reactions, as well as many impressive cascade transformations, that have been described for enantioselective syntheses with exceptional ease from an operational standpoint. As a result, this strategy has shown great potential due to its versatility and it has become a reliable alternative method to conventional asymmetric metal-based catalysis. Although organocatalysis has originally emerged as a complementary strategy to metal-catalysed reactions and biocatalysis, it also, on occasion, offers a new route towards asymmetric catalytic reactions that thus far cannot be achieved by either organometal catalysts or biocatalysts. Research in this exciting area is still on the rise, and novel innovative organocatalysts capable of remarkable asymmetric C-C bond forming processes are emerging constantly. Phase-transfer catalysts represent one example of such a powerful and versatile class of organocatalysts, and they will be discussed in more detail in the following section.

1.2 Phase-transfer catalysis (PTC): general concept

Phase-transfer catalysis enables the reaction between two or more reagents that are placed in at least two immiscible phases, in the presence of a phase-transfer reagent – a species capable of crossing between the immiscible phases and transferring a reactant
from one phase into the other phase which contains the reaction component, thus facilitating the formation of a reaction product, leaving the phase-transfer reagent available for the next cycle.\textsuperscript{37} The most commonly employed phase-transfer catalysts that are normally used in a liquid-liquid or solid-liquid two phase system, include quaternary ammonium salts, quaternary phosphonium salts, crown ethers and cryptands (Figure 1.2).\textsuperscript{38}

![Phase-transfer catalysts](image)

**Figure 1.2** Examples of general structures of phase-transfer catalysts.

Phase-transfer catalysis has been established as a versatile methodology in organic transformations, having many attractive features, such as simple operational procedures, mild reaction conditions, inexpensive and environmentally friendly reagents and solvents, and straightforward large scale preparations suitable for the industry.\textsuperscript{39}

### 1.2.1 Pioneering studies

The foundations of PTC were established by the independent research groups of Starks,\textsuperscript{37} Makosza\textsuperscript{40-43} and Brändström,\textsuperscript{44} in the mid to late 1960s. In 1971, Starks\textsuperscript{37} proposed the term ‘phase-transfer catalysis’ to describe the critical role of tetraalkylammonium or phosphonium salts (Q\textsuperscript{+}X\textsuperscript{-}) in the reaction between two substances placed in different immiscible phases. He noticed that when a primary alkyl halide and an aqueous solution of sodium cyanide were heated together for several weeks, there was no product formed and additionally both reagents completely decomposed. However, in the presence of hexadecyltributylphosphonium bromide (I), the displacement reaction of 1-chlorooctane with an aqueous sodium cyanide was accelerated tremendously and the desired product was obtained in an almost quantitative yield in less than 2 hours (Scheme 1.1).\textsuperscript{37}
Sche 1.1 Cyanide displacement of 1-chlorooctane in the presence of a phase-transfer catalyst 1.

This incredible enhancement in reactivity can be explained by the formation of the quaternary phosphonium cyanide, which makes the cyanide anion soluble in organic solvent and adequately nucleophilic.

1.2.2 Mechanistic models of phase-transfer catalysis

Although there have been significant developments in PTC, the mechanistic insights remain rather ambiguous, primarily due to the difficulty associated with the study of biphasic reaction systems and the complex parameters that have to be considered. Nonetheless, there are two key mechanistic theories that explain a reaction catalysed by a phase-transfer reagent.

1.2.2.1 Extraction mechanism

The extraction mechanism suggested by Starks, describes how a quaternary ammonium or phosphonium halide (Q+X-) dissolved in the organic phase can diffuse back and forth into the aqueous phase (A, Scheme 1.2), facilitating an exchange between the halide and the cyanide ions (B, Scheme 1.2). The highly lipophilic species that forms as a result of this exchange (Q+CN-) is able to migrate into the organic phase (C, Scheme 1.2) where it reacts with the alkyl halide to yield a nitrile adduct. The quaternary onium salt is regenerated for the next catalytic cycle (D, Scheme 1.2).

Scheme 1.2 Extraction mechanism proposed by Starks.
While the extraction mechanism explains the role of the quaternary onium salts in a PTC reaction rather accurately, it has been observed that highly lipophilic catalysts were also very powerful phase-transfer catalysts in the cyanide displacement of alkyl halide. Since these lipophilic species cannot readily diffuse into the aqueous phase, the previous mechanism was modified. It has been suggested that the halide-cyanide exchange must occur at the interface between the two immiscible phases (Scheme 1.3).\textsuperscript{46,47}

\begin{center}
\includegraphics[width=\textwidth]{Scheme1.3.png}
\end{center}

**Scheme 1.3** Modified Starks’ extraction mechanism depicting a halide-cyanide exchange at the interface.

Even though there is a slight difference in these two proposed mechanisms, they both share the same feature – the requirement of a quantitative extraction of the cyanide salt from the aqueous phase into the organic phase or an interface region, for the displacement to occur successfully.

### 1.2.2.2 Interfacial mechanism

The other mechanism that explains the results of reactions where the anionic nucleophile is generated \textit{in situ} by deprotonation with metal hydroxides or carbonates, was suggested by Makosza.\textsuperscript{38,47,48} He proposed that deprotonation of the pronucleophile occurs at the interface by the inorganic base, and consequently this anionic nucleophile, in the absence of a phase-transfer catalyst, is not capable of migrating between either of the two phases (A, Scheme 1.4). However, in the presence of a phase-transfer catalyst, this anionic nucleophile can undergo an interfacial exchange and migrate into the organic phase where it can react with another reagent (B, Scheme 1.4).
Scheme 1.4  Interfacial mechanism proposed by Makosza.

The alternative pathway associated with the interfacial mechanism involves an ion exchange between the phase-transfer catalyst and the metal hydroxide occurring at the interface. This process results in the formation of an alkyl onium hydroxide species (Q⁺−OH) which cannot migrate into the organic phase, as it is not lipophilic enough, and therefore remains in the interfacial region where it can deprotonate the pro-nucleophile. The generated tight ion pair of an anionic nucleophile-alkyl onium (Q⁺R⁻) is able to migrate into the organic phase and undergo a reaction with an electrophile (Scheme 1.5).

Scheme 1.5  Alternative pathway of the interfacial mechanism.

Thus depending on the type of reaction, an appropriate mechanism can be considered. Starks’ extraction mechanism describes the reactions where nuceophiles that are negatively charged and water soluble, *e.g.* −CN, are physically extracted into the organic layer where they can react with the hydrophobic reagent. On the contrary, Makosza’s interfacial mechanism describes the reactions where the anionic species is generated *in situ*, *e.g.* enolate formation.⁴⁶,⁴⁷

NB: Just when this manuscript was completed, Makosza *et al.*⁴⁹ confirmed the existence of the interfacial mechanism of PTC by direct observation of the carbanion formation at the interface region between the two phases; 30 years after his initial theory.
1.2.2.3 Phase-transfer reaction rate matrix

Considering the cyanide displacement reaction outlined previously (Scheme 1.1), it is crucial to note that there are at least two general steps taking place in the catalytic sequence; step 1 – anion transfer and step 2 – the intrinsic reaction.\textsuperscript{50} The anion transfer step is defined as the net rate of the reaction sequences that cause the cyanide to be transferred into the organic phase. In the cyanide displacement, this step is characterised by three equilibria: (1) transfer of the quaternary ammonium chloride from the organic to the aqueous phase, (2) exchange of the chloride for the cyanide anion in the aqueous phase, and (3) transfer of the quaternary ammonium cyanide from the aqueous to the organic phase. The intrinsic reaction, or the organic phase reaction, accounts for the sequence of reactions in the organic phase, from the transferred anion to the formation of the product. In Scheme 1.1, there is only one step; the displacement reaction between quaternary ammonium cyanide and 1-chlorooctane to yield 1-cyanoctane. It is absolutely crucial to distinguish and understand these two steps, mainly to achieve the highest yields possible in the phase-transfer system and to adjust all the necessary variable parameters that affect PTC reactions. These include the type and amount of catalyst, rate of agitation, amount of water in the aqueous phase, temperature, solvent choice and the concentration \textit{etc.}\textsuperscript{50}

In order to understand the kinetics between these two steps and how to design a PTC system in general, Starks has proposed a plot of the intrinsic reaction rate \textit{vs.} the transfer rate, and named it as the PTC reaction rate matrix (Figure 1.3).\textsuperscript{50}

![Figure 1.3 The PTC reaction rate matrix.](image-url)
The PTC matrix is composed of four quadrants. The upper-right quadrant represents the fast region, where both transfer and intrinsic rates are fast. Therefore, almost any catalyst and any set of conditions will result in high rate. The opposite quadrant is the slow region, which would require a careful selection of both catalyst and reaction conditions, as transfer and intrinsic step both proceed very slowly. The lower-right quadrant, is the intrinsic reaction rate limited region, in which the transfer is fast but the intrinsic reaction is slow. And the final quadrant, upper-left, depicts the situation where the transfer step is slow but the the intrinsic rate is high. Hence, in order to achieve the best results, the rate at which an anion is transferred into the organic phase has to be increased.50

Considering this matrix, it is clear that a phase-transfer system is a complicated and kinetically driven process where a phase-transfer catalyst has to be able to promote both the transfer step and also the intrinsic reaction at a reasonable kinetic rate for a reaction to be successful.

1.2.3 Asymmetric phase-transfer catalysis: general remarks

Phase-transfer catalysis has been known to be a versatile methodology employed in asymmetric organic synthesis, both in academia and industry, showcasing simple experimental operations, mild reaction conditions, inexpensive and environmentally benign reagents and facile large-scale preparations of industrial processes. Given these practical attributes, asymmetric phase-transfer catalysis has been recognised as one of the most exciting strategies in asymmetric synthesis and it has become a topic of tremendous scientific interest.51,52

In the recent past, many efforts have been dedicated to the development of effective chiral phase-transfer catalysts and the elucidation of the mechanism for the asymmetric PTC reaction system. Essentially, there are two representative reaction systems that describe the bond formation catalysed by a chiral phase-transfer catalyst. One of them is based on the functionalisation of active methylene or methine groups, which are usually performed under basic conditions. The example in Figure 1.4 depicts an asymmetric alkylation of an active methylene compound with a glycine Schiff base 2 which proceeds via the interfacial mechanism.53
Figure 1.4  The asymmetric alkylation of active methylene compound with a glycine Schiff base 2, via interfacial mechanism.

Initially, the α-proton of the methylene compound 2 is deprotonated at the interface with base (MOH), generating a metal enolate 3 which remains at the interface between the two phases. Following the ion-exchange of the anion with the catalyst (Q*+X⁻), the lipophilic chiral onium enolate 4 is generated, which then migrates deeper into the organic phase and reacts with an alkyl halide, affording the chiral monoalkylated product 5 and regenerated catalyst. The efficacy of the reaction is determined by efficiency in the generation of the highly reactive chiral onium enolate 4 and the ability of the catalyst cation to effectively shield one of the enantiotopic faces of the enolate. This step therefore determines the stereoselectivity of the product.53

The second representative catalytic process involves the nucleophilic addition of an anion lacking a prochiral centre to prochiral electrophiles. In Figure 1.5, the asymmetric epoxidation of α,β-unsaturated ketones using an aqueous solution of sodium hypochlorite is selected as the example. The anion is extracted into the organic phase as a tight chiral ion pair which forms upon the ion-exchange with the catalyst (Q*+X⁻). This highly reactive species (Q*OCl⁻) then attacks the prochiral electrophile 6, affording the product 8 with a newly formed stereocentre. This crucial step determines the stereoselective outcome of the reaction.53
As observed from the mechanisms above, it is critical to select and adjust the optimum reaction conditions and parameters, such as solvent, concentration, temperature, catalyst loading etc., in order to achieve satisfactory reaction rates. Also, it is of paramount importance that the catalyst can discriminate between the enantiotopic faces of the enolate to afford the product of the highest potential stereoselectivity. An additional significant issue that has to be considered, in the liquid-liquid or solid-liquid phase-transfer reaction system is the strongly basic environment which can have an adverse effect on the outcome of the reaction. If not selected carefully, this can result in decomposition of the catalyst, possible hydrolysis of the substrate, racemisation of the product and dialkylation.\(^{53}\)

### 1.2.3.1 Seminal studies on asymmetric phase-transfer catalysis

One of the earliest studies employing asymmetric phase-transfer catalysis was carried out by Wynberg and co-workers in 1976,\(^{54}\) in which they reported the epoxidation of chalcones using quaternary ammonium salts derived from cinchona alkaloids. The optically active epoxides were obtained in excellent yield and with 25\% ee, without any optimisation of the enantioselectivity. Regardless of this early example, it was not until 1984, when a research team in Merck led by Dolling\(^{55}\) described the asymmetric alkylation of indanone derivative 9, employing cinchona-derived quaternary ammonium salts as phase-transfer catalysts (Scheme 1.6). They obtained the alkylated product 11 in excellent yield and high enantiomeric excess (92\% ee).
Scheme 1.6  Asymmetric PTC alkylation of indanone derivative 9\(^{55}\)

The authors studied this reaction in great detail and discovered that high enantioselectivity can be achieved when an electron-withdrawing group is placed on the para position of the benzyl group that is attached to the quinuclidine nitrogen atom. They proved this by employing a catalyst that was lacking an electron-withdrawing substituent, and the enantioselectivity of the product dropped to as low as 20%. Solvent choice was another crucial parameter that had to be optimised. Apolar solvents, such as toluene and benzene, furnished products with a considerably higher ee, while moderately polar solvent, e.g. CH\(_2\)Cl\(_2\) or MTBE, resulted in much lower enantioselectivities. Dolling et al. also proposed a transition state for the asymmetric alkylation of indanone 9 (Scheme 1.6). They reasoned that the enolate 12 forms an ion pair with the cation of the benzyl cinchonium catalyst 10 by means of ionic interactions between the negatively charged enolate and the positively charged nitrogen of the catalyst, and two different \(\pi\)-stacking interactions between the aromatic systems. Additionally, the hydroxyl group on the catalyst 10 acts as a hydrogen bond donor to the oxygen anion of the substrate (Figure 1.6). This provides a spatially better organised transition state, blocking the Si-face of the enolate by the catalyst, leaving the Re-face exposed for the reaction with CH\(_3\)Cl.

Figure 1.6  Transition state for the alkylation of indanone derivative 12 proposed by Dolling et al.\(^{55}\)
This significant publication encouraged the scientific community to explore the possibilities and further opportunities associated with asymmetric phase-transfer catalysis. The first asymmetric synthesis of $\alpha$-amino acids based on the alkylation of tert-butyl ester glycine Schiff base 2, employing a phase-transfer catalyst, was carried out by O’Donnell et al. in 1989 (Scheme 1.7).\textsuperscript{56}

\begin{center}
\includegraphics[width=\textwidth]{scheme17.png}
\end{center}

**Scheme 1.7** The stereoselective synthesis of protected $\alpha$-amino acids 17 by the tert-butyl ester glycine Schiff base 2, promoted by cinchona alkaloid-derived PTCs.\textsuperscript{56}

The important aspect of this reaction is that by simply switching the cinchonine-derived catalyst 14 with its pseudo-enantiomer 15 derived from cinchonidine, the product can be obtained with the opposite absolute configuration but with the similar degree of enantioselectivity. Moreover, upon single recrystallisation and subsequent deprotection of 16, the $\alpha$-amino acid 17 can be obtained in an optically pure form. Because of the major advantage of obtaining both enantiomers of the $\alpha$-amino acid and the relative ease of the synthesis, this reaction has become a benchmark transformation for the evaluation of the efficiency of novel phase-transfer catalysts.
1.2.3.2 Structural diversity of chiral phase-transfer catalysts

Since the pioneering studies of Dolling and O’Donnell, incredible growth has been observed in the development of asymmetric phase-transfer catalysis. An abundance of structurally diverse catalysts have been synthesised and established to promote a vast number of reactions. Phase-transfer catalysts derived from cinchona alkaloids are among the most frequently employed and they will be fully discussed in Section 1.2.4. The focus of this Section is on the development and evaluation of structurally diverse chiral nonracemic phase-transfer catalysts.

In 1999, a novel class of structurally rigid, chiral N-spiro ammonium salts of type 18 derived from (S)- or (R)-1,1’-bi-2-naphthol (BINOL) were developed by Maruoka and Ooi.57 These new C₂-symmetric chiral PTCs were successfully employed in the benchmark enantioselective alkylation of tert-butyl ester glycine Schiff base 2 (Scheme 1.8). The key feature of the mentioned spiro-type catalysts 18 is the 3,3’-bis-(aryl) substituent which has a significant effect on the enantiofacial discrimination. This is evident with catalyst 18a, which gave rise to the alkylated product 19 in 79% ee (Scheme 1.8). However, when the polyfluorinated catalyst 18d was employed, the product was obtained in an enhanced enantioselectivity of 98% ee.58 Another beneficial aspect associated with Maruoka type catalysts such as 18 is the extremely low catalyst loading. The authors observed that by lowering catalyst 18c loading to 0.2 mol%, the yield had slightly diminished to 76%, but the enantioselectivity of the product was retained (98% ee).59 To fully explore the potential catalytic activity of spiro-chiral ammonium salts such as 18e, Maruoka et al. developed a binary phase-transfer system with an appropriate achiral co-catalyst. In the presence of 18e (0.05 mol%), the benzylation proceeded very slowly, giving only 4% yield (92% ee). However, once catalyst 18e was used with [18]crown-6 ether 20 (0.05 mol%), the reaction proceeded smoothly to afford 19 in 90% yield and 98% ee.60 This dramatic rate enhancement can be explained by the ability of the crown ether to extract KOH into the organic phase, subsequently increasing the rate of deprotonation, which would otherwise be a slow process.
Scheme 1.8  Catalytic enantioselective benzylation of tert-butyl ester glycine Schiff base 2 promoted by N-spiro-type chiral PTCs. (For reaction conditions, see ref. 56-63)

Although the conformationally rigid catalysts of type 18, possessing two chiral binaphthyl subunits, proved to be very efficient promoters in the enantioselective benzylation of substrate 2 (Scheme 1.8), structural modifications of the catalyst could only be introduced through the variation of the aryl substituents at the 3,3’-positions. In order to simplify the general structure of the catalyst and allow for the installation of other structural units that would enhance the efficiency and tunability of the promoter, the authors developed a new C$_2$-symmetric chiral ammonium salt 21 bearing an achiral, conformationally flexible biphenyl subunit.$^{61}$ Another discovery related to structural design of the catalyst made by Maruoka et al. was the installation of a flexible straight-chain alkyl group instead of a rigid binaphthyl moiety that resulted in a remarkably active phase-transfer catalyst 22. The reaction of 2 with benzyl bromide proceeded efficiently under mild phase-transfer conditions in the presence of 22 using only 0.01-
0.05 mol% loading, furnishing 19 with excellent enantioselectivity (99% ee). A further modification of catalyst 22, utilising a known, readily available starting chiral source derived from gallic acid, resulted in the synthesis of 23, which also proved to be an effective catalyst. The catalyst 24 bearing dimethylphenylmethyl group at the 4,4’-position of each biphenyl unit was also recognised as an efficient PTC in the above benchmark reaction (Scheme 1.8).

Selected from the vast number of structurally diverse chiral PTCs developed over the years, Scheme 1.9 displays the catalytic activity of a few selected examples used in the enantioselective benzylolation of tert-butyl ester glycine Schiff base 2.

**Scheme 1.9** Catalytic enantioselective benzylation of tert-butyl ester glycine Schiff base 2 promoted by structurally diverse chiral PTCs. (For reaction conditions, see ref. 64-72)
Shibasaki and co-workers\textsuperscript{65,66} adopted the concept of a two-centre asymmetric catalysis and developed a tartarate-derived \textit{bis}(ammonium) catalyst \textbf{25}, which successfully promoted the enantioselective alkylation of \textbf{2} (87\%, 93\% ee). Waser \textit{et al.}\textsuperscript{67} designed tartaric acid derived \textit{N}-spiro catalyst \textbf{26}, which afforded the alkylated product \textbf{19} in good enantioselectivity (87\% ee). A combination of a tartarate derivative and 2,5-dimethylpyrrolidine was incorporated into a catalyst \textbf{27}, which was synthesised by MacFarland and co-workers.\textsuperscript{68} Its ability to act as a chiral phase-transfer catalyst was evaluated in the enantioselective alkylation of \textbf{2}, furnishing the product in moderate yield and low enantioselectivity. Sasai\textsuperscript{69} developed a \textit{bis}(spiroammonium) salt \textbf{28} as a powerful chiral phase-transfer catalyst which afforded \textbf{19} in excellent yield (95\%) and excellent enantioselectivity (95\% ee). Denmark \textit{et al.}\textsuperscript{70} established novel quaternary ammonium salts of type \textbf{29} and examined the catalyst structure-activity/selectivity relationship in the benzylation of \textbf{2}. The systematic approach of this study was carefully designed by incorporating four different groups on the catalyst, leading to a library of more than 160 catalysts. This investigation proved to be very useful in the design of novel PTCs. Lygo and co-workers\textsuperscript{71,72} developed a library of quaternary ammonium salts based on a chiral secondary amine and a conformationally flexible biphenyl unit. They identified a highly effective catalyst \textbf{30}, which exhibited impressive catalytic activity and enantioselectivity (89\%, 97\% ee). Nagasawa \textit{et al.}\textsuperscript{73} investigated the catalytic activity of the \textit{C}_2-symmetric chiral cyclic guanidines of type \textbf{31}. They discovered that the installation of methyl substituents leads to high enantioselectivity in the alkylation product \textbf{19} (90\% ee, Scheme 1.9).

Recently, Tan and Zong\textsuperscript{74} designed a structurally novel pentanidine catalyst \textbf{33}, containing five nitrogen atoms in conjunction to increase the basicity of the catalyst. Although they did not observe any enhanced basicity, the pentanidinium salts proved to be excellent PTCs in the Michael addition of \textbf{2} to \textbf{32} (Scheme 1.10).

\begin{center}
\textbf{Scheme 1.10} The asymmetric Michael addition of \textit{tert}-butyl ester glycine Schiff base \textbf{2} to methyl vinyl ketone \textbf{32}, promoted by pentanidinium catalyst \textbf{33}.\textsuperscript{74}
\end{center}
Various types of chiral quaternary phosphonium salts have been successfully developed for many highly selective phase-transfer reactions. One of the representative examples belonging to this family of catalysts is $P$-spiro chiral tetraaminophosphonium salt 37, designed by Ooi et al. It was found to be an effective phase-transfer catalyst in the asymmetric alkylation of azlactones, such as 35 (Scheme 1.11).

![Scheme 1.11](image)

Scheme 1.11 The asymmetric alkylation of azlactone 35, promoted by $P$-spiro chiral tetraaminophosphonium salt 37.

### 1.2.4 Cinchona alkaloids: brief introduction

Historically, cinchona alkaloids have proven to be popular in science, medicine and chemistry. The genus of cinchona is composed of approximately 40 species of trees and shrubs that belong to the family of Rubiaceae, native to the Andes Mountains of South America. The extracts from the bark of cinchona species have found wide application in the treatment of various diseases. Quinine, one of the main bioactive cinchona alkaloids, was used for treatment of malaria from as early as the 17th century. Over the years, cinchona alkaloids have shown to possess anticancer, analgesic and antibacterial properties, to name but a few. Apart from their use in medicine, cinchona alkaloids have been recognised as efficient chiral reagents, chiral auxiliaries and powerful catalysts in the asymmetric transformations, primarily in the last three decades.

Approximately 30 species have been isolated from the cinchona species, among the best known are quinine (39), cinchonidine (40), quinidine (41) and chinchonine (42) (Figure 1.7).
The structure of cinchona alkaloids is quite complex; the basic framework consisting of two rigid ring moieties; an aromatic quinoline ring and an aliphatic quinuclidine ring (Figure 1.8). They possess five stereocentres; C-3, C-4, N-1, C-8 and C-9, but they occur in pairs that vary in configuration at only N-1, C-8 and C-9, as the absolute configuration at C-3 and C-4 is identical in both pairs. The eight major cinchona alkaloids exist in diastereomeric pairs, often regarded as ‘pseudo-enantiomers’. This can be seen by comparing natural quinine (39) and quinidine (41). The absolute configuration of quinine is 1S,3R,4S,8S,9R and that of quinidine is 1S,3R,4S,8R,9S. Although they are diastereomers, they behave like enantiomers. In asymmetric catalysis, quinine promotes the formation of one enantiomer while quinidine affords the opposite enantiomer with similar selectivity.78

Figure 1.8 The basic structural features and configuration of cinchona alkaloids.

The unique structure of cinchona alkaloids is responsible for the catalytic utility of these species in asymmetric synthesis. The relative positions of the bulky quinoline and quinuclidine ring creates a “chiral pocket” around the substrate which can result in an improved enantioselective discrimination. The basic character of cinchona alkaloids is present in the quinuclidine tertiary amine nitrogen which allows them to act as chiral organic bases while the hydroxyl group present at C-9 acts as a Lewis acid via hydrogen bond donation. The flexible nature of cinchona alkaloids is due to the free rotation about
C-9 – C-4’ and C-8 – C-9 bonds, allowing the quinuclidine ring and the hydroxyl group to cooperate and on occasion exhibit bifunctional behaviour in a defined chiral environment.

Despite the fact that cinchona alkaloids and their derivatives are nowadays among the most frequently employed chiral catalysts in many asymmetric transformations, their first use as organocatalysts in asymmetric synthesis was initially reported by Bredig and Fisk only in 1912.\textsuperscript{80} Although their results were far from encouraging (10% \textit{ee}), it was not until fifty years later when Pracejus investigated the asymmetric addition of methanol to substituted ketenes 43 promoted by the \textit{O}-acylated quinine derivative 44, obtaining the product 45 in moderately good enantioselectivity (Scheme 1.12).\textsuperscript{81}

\begin{equation}
\text{Ph}\text{C}=\text{O} \xrightarrow{44 \ (1 \text{ mol\%}) \ \text{CH}_3\text{OH}} \text{Ph}\text{C}\text{O}\text{OMe}
\end{equation}

\textbf{Scheme 1.12} The asymmetric addition of methanol to substituted ketene 43, promoted by quinine-derived catalyst 44.\textsuperscript{81}

The latter-day scientific interest in cinchona alkaloids as asymmetric organocatalysts was triggered by Wynberg’s research group during 1970s and 1980s, when they successfully applied cinchona alkaloid derivatives as catalysts in numerous enantioselective reactions.\textsuperscript{54,82} Ever since, the cinchona alkaloid scaffold has been extensively modified and adapted to suit many asymmetric transformations. The cinchona alkaloid framework can be readily modified as a number of different functionalities that can be installed with relative ease. Over the years, this has led to several synthetic derivatives that have been prepared to enhance the rate of specific reactions. Some of these structural modifications of cinchona alkaloids are displayed in Figure 1.9.\textsuperscript{83–87} A detailed analysis of all these modifications related to cinchona alkaloids as catalysts is beyond the scope of this thesis; the focus of the following sections will be on cinchona alkaloid-derived phase-transfer catalysts and their application in asymmetric reactions.
1.2.4.1 Cinchona alkaloid-derived phase-transfer catalysts

As outlined in Section 1.2.3.1, Dolling et al.\textsuperscript{55} were the first to successfully demonstrate the application of cinchona alkaloids as efficient phase-transfer catalysts (Scheme 1.6, \textit{vide supra}), followed by the reports published by O’Donnell et al.\textsuperscript{56} (Scheme 1.7, ‘first generation catalysts’). Five years later, O’Donnell’s research group\textsuperscript{88} reported a novel cinchona alkaloid-derived phase-transfer catalyst 47 (‘second generation’), which promoted the asymmetric alkylation of tert-butyl ester glycine Schiff base 2 with enhanced enantioselectivity (up to 81% ee). In addition to improved enantiocontrol, O’Donnell et al. disclosed that the monoalkylated product 19 was formed exclusively, in the absence of any unwanted dialkylated product.\textsuperscript{89} The authors carried out further investigations to evaluate the influence of the alkylation reaction conditions on the unwanted racemisation of 19.\textsuperscript{88} When the optically pure compound (S)-19 was exposed to typical phase-transfer reaction conditions of a phase-transfer catalysed alkylation (50% aqueous NaOH, CH\textsubscript{2}Cl\textsubscript{2}, 25 °C, 10 h), no racemisation of (S)-19 was observed, regardless of the presence or absence of the phase-transfer catalyst Bu\textsubscript{4}NBr (TBAB, Scheme 1.13). However, when a similar product racemisation experiment was performed in the presence of catalyst 15, racemisation of (S)-19 was observed, resulting in the formation of 35% of (R)-19 in two hours, with no further racemisation detected thereafter. In addition, racemisation was not observed when benzyl bromide and catalyst 15 were both present in the reaction mixture. O’Donnell and co-workers proposed that the racemisation of (S)-19 is controlled by the organic soluble ammonium alkoxide 46, which is generated \textit{in situ}, upon deprotonation of the hydroxyl group of catalyst 15. They reasoned that this zwitterionic species could promote the enolisation of (S)-19, which subsequently leads to racemisation of the chiral centre and the formation of (R)-19. Conversely, in the presence of benzyl bromide, the ammonium alkoxide 46 could...
undergo *in situ* benzylaion, resulting in the formation of the *N*-benzyl-*O*-benzyl cinchona salt 47, which is not capable of promoting the racemisation of (S)-19 (Scheme 1.13). These findings prompted O’Donnell *et al.* to re-evaluate the role of the catalytically active species. They suggested that the active catalyst in the asymmetric phase-transfer catalysed alkylation of glycine derivatives is the *N*-alkylated-*O*-alkyl cinchona alkaloid salt 47, which is generated *in situ* during the course of the reaction. This postulate was confirmed when the *N*-benzyl-*O*-benzylcinchonidinium catalyst 47 was synthesised and evaluated in the asymmetric alkylation of tert-butyl ester glycine Schiff base 2, affording similar enantiomeric excess as with catalyst 15.

Scheme 1.13  Racemisation experiments of product (S)-19.

In 1997, two independent research groups developed a new class of cinchona alkaloid-derived phase-transfer catalysts bearing the *N*-anthracenylmethyl substituent on the quinuclidine nitrogen atom (‘third generation catalysts’). Lygo *et al.* developed the *N*-anthracenylmethylammonium salts 48 and 49, and evaluated them in the benchmark asymmetric benzylation of tert-butyl ester glycine Schiff base 2, obtaining excellent enantioselectivity in both (R)-19 and (S)-19 adducts, which could be readily hydrolysed to yield both enantiomers of phenylalanine 50, with high optical purity (Scheme 1.14).
Scheme 1.14 Evaluation of third generation catalysts 48 and 49, developed by Lygo et al.⁹⁰

At the same time, Corey and co-workers⁹¹ independently designed the O-allyl-N-9-anthracenylmethylcinchonidium bromide 51 and evaluated its efficiency in the asymmetric benzylation of tert-butyl ester glycine Schiff base 2. The reaction was carried out in the presence of caesium hydroxide monohydrate, at low temperature. In comparison to the reaction promoted by catalysts developed by Lygo et al.⁹⁰ (Scheme 1.14), the alkylated product 19 was obtained with marginally higher enantioselectivity (94% ee, Scheme 1.15).

Scheme 1.15 Evaluation of third generation catalyst 51, designed by Corey et al.⁹¹

Corey and co-workers⁹¹ investigated the possible causes underpinning the different levels of enantioselective discrimination associated with the N-anthracenylmethyl-substituted catalyst 51 and the N-benzyl-substituted catalyst 47. They suggested that augmented steric hindrance of the anthracenylmethyl group could be accountable for the
improved enantiocontrol obtained with catalyst 51. On the basis of the X-ray crystallographic analysis of catalyst 51, they proposed that if the bridgehead nitrogen atom of the quaternary ammonium salt is visualised at the centre of an imaginary tetrahedron (Figure 1.10, A), three faces of this tetrahedron (F₁ to F₃) are sterically hindered by the quinuclidine ring, quinoline ring and anthracenyl group respectively, therefore blocking the access of the enolate to the quaternary ammonium cation. The fourth face (F₄), which is considerably less shielded, provides the only accessible face for the enolate to interact with the quaternary ammonium cation. The bulky anthracenyl group is able to block one of the faces (e.g. F₃) much more efficiently than the benzyl group, preventing the enolate from interacting with the cation from this face of the imaginary tetrahedron (F₃), which ultimately leads to the formation of product with higher enantioselectivity.⁹¹

**Figure 1.10** Visualisation of N-anthracenylmethyl-substituted catalyst 51 at the centre of an imaginary tetrahedron (A).⁹¹ Proposed transition state between alkyl halide RCH₂X (blue), glycine enolate derivative 4 (black) and catalyst 51 (red) depicting facial approach of the alkylating agent towards nucleophile. The enolate interacts with quaternary ammonium cation via an oxy-anion interaction where the π-face is oriented perpendicular to the face F₄ of the imaginary tetrahedron; the electrophilic attack of the alkylating agent is on the enolate Re face (B), and less favourable transition state resulting from the attack of the enolate Si face (C).⁹²
In an attempt to develop highly powerful and selective phase-transfer catalysts, Jew, Park and co-workers prepared new dimeric and trimeric cinchonidium PTCs such as 52 and 53, connected by an aromatic spacer. The performance of these novel catalytic species was evaluated in the alkylation of tert-butyl ester glycine Schiff base 2. The dimeric catalyst 54, connected via a 2,7-naphthyl unit, was found to promote the formation of (S)-19 with excellent enantioselectivity at a loading of 1 mol% (Scheme 1.16).

![Scheme 1.16](image)

The authors speculated that higher enantioselectivity associated with catalyst 54 was due to the formation of a more favourable conformation, facilitated by the catalyst with a 2,7-naphthalene spacer, which also decreased the steric hindrance between the two cinchona units.

Although it was demonstrated that steric factors can have a major influence on the efficiency and the performance of cinchona alkaloid-derived phase-transfer catalysts in asymmetric synthesis, the electronic factors have not been systematically studied. In 2002, Jew and Park began to investigate the role of the electronic factors in cinchona-derived PTCs (e.g. 55, Scheme 1.17, ‘fourth generation catalysts’). They initiated the study by preparing a series of N-benzyl-cinchonidinium salts bearing various functional
groups at the ortho-, meta- and para-positions. Their catalytic activity was evaluated in the alkylation of tert-butyl ester glycine Schiff base 2 at 0 °C. Among the synthesised catalysts, the ortho-fluoro derivative 57 was found to be superior relative to its unsubstituted analogue 56, albeit having virtually the same steric size. Additionally, their studies revealed that the ortho-fluoro substitution on the benzyl moiety (see catalyst 57), was responsible for the improved enantioselectivity in the alkylated product (S)-19. With the further addition of fluorine atoms (i.e. 2’,3’,4’-trifluoro derivative 63), product (S)-19 was obtained with the highest enantiomeric excess of 96% ee (Scheme 1.17).  

![Scheme 1.17](image)

**Scheme 1.17** The influence of electronic factors in cinchona-derived PTCs, investigated by Jew and Park.  

Jew et al. suggested that a hydrogen-bonding interaction, via a molecule of water, between the oxygen atom at C-9 and the fluorine atom at C-2’ in 57, was contributing to a more rigid conformation of the catalyst structure, resulting in the improved enantioselectivity (Figure 1.11).  

![Figure 1.11](image)

**Figure 1.11** Rigid conformation of catalyst 57 by coordination with H₂O, via hydrogen-bonding.
Further studies from the same research group strongly supported this hypothesis. The catalysts lacking substituents capable of hydrogen-bonding such as 64, 65 and 67, resulted in the formation of products with diminished enantioselectivity, while the N-oxide-substituted catalyst 66 and the cyano-incorporated catalyst 68 promoted the formation of products with excellent enantioselectivities (Scheme 1.18).  

![Scheme 1.18](image)

Scheme 1.18  The influence of hydrogen-bonding in cinchona derived PTCs.  

Upon the establishment of the four generations of cinchona alkaloid-derived phase-transfer catalysts, research groups began to explore the effects of various substituents attached to the cinchona alkaloid scaffold. This led to the development of a diverse group of phase-transfer catalysts, displaying excellent catalytic activity and enantiocontrol in the alkylation of tert-butyl ester glycine Schiff base 2. Some of these efficient promoters are depicted in Scheme 1.19.  

From the selected examples portrayed in Scheme 1.19, Wang et al. 103 developed a novel catalyst of type 72, the structure of which was based on the eight-membered ring system, joining the bridgehead nitrogen atom of quinuclidine with the hydroxyl group at the C-9 position. As these groups block two faces of the imaginary tetrahedron (Figure 1.10), they play a crucial role in the selectivity of the catalyst. Modification of these two groups at the same time, leads to the formation of the ring which can block access of the enolate to three of the faces of the tetrahedron, providing an ideal, sterically controlled chiral environment. Additionally, the eight-membered cyclic structure offers great flexibility, contributing to improved enantioselectivity of the catalyst. Upon evaluation
of 72 in the alkylation of tert-butyl ester glycine Schiff base 2, the desired product (S)-19 was obtained in excellent optical purity (Scheme 1.19).\textsuperscript{103}

**Scheme 1.19** Diverse cinchona alkaloid-derived phase-transfer catalysts evaluated in the alkylation of tert-butyl ester glycine Schiff base 2.\textsuperscript{99-103} (For reaction conditions, see ref. 97-101)

### 1.2.4.2 Bifunctional nature of cinchona alkaloids

Perhaps one of the most fascinating features of cinchona alkaloids is their intrinsic bifunctional nature. In a well-defined chiral environment and in close proximity to each other, a nitrogen atom on the quinuclidine ring is able to act as a Lewis/Brønsted base while a hydroxyl group at the C-9 position can act as a Lewis acid. The bifunctionality of cinchona alkaloids in the asymmetric catalytic transformations was first systematically studied in the 1980s by Wynberg and Hiemstra,\textsuperscript{104} when they examined the influence of cinchona alkaloid-derived catalysts in the Michael addition of aromatic thiols 73 to cyclic enones 74 (Scheme 1.20).
Scheme 1.20 Evaluation of bifunctional catalysis by natural and C-9 modified cinchona alkaloids in the Michael addition of thiol 73 to cyclic enone 74.\textsuperscript{104}

From their studies, the authors observed that natural cinchona alkaloids promoted the formation of product 77 in moderately good enantiomeric excess, while the enantiomeric excess of 77 was almost completely destroyed with the use of catalysts lacking a free hydroxyl group, such as the O-acylated derivative 44 and the deoxy alkaloid 75. Furthermore, the catalyst with inverted absolute configuration at C-9 (i.e. 76) led to the formation of 77 with poor $ee$ (Scheme 1.20).\textsuperscript{104}

These findings encouraged Wynberg and co-workers to hypothesise that both the amine moiety on the quinuclidine ring moiety and the hydroxyl group at the C-9 position operate in a bifunctional manner in a simultaneous activation of both the pronucleophile (i.e. thiol 73) and the electrophile (i.e. enone 74). The nucleophile is activated via deprotonation by the tertiary amine on the quinuclidine, while the electrophile is stabilised by the hydrogen-bond donation via the C-9 hydroxyl group. As a conclusion to his study, Wynberg stated that it might be possible to extend the potential of these hydroxy amines by incorporating a stronger base or a better hydrogen-bond donor into the catalyst structure. He also specified that cinchona alkaloids were not the only species capable of bifunctional catalysis, but combinations of other functional groups could, in principle, exhibit bifunctional behaviour.\textsuperscript{104}
Astonishingly, Wynberg’s statement and studies concerning bifunctionality were overlooked and went unnoticed for decades. It was not until the early 2000s, when the concept of bifunctionality resurfaced again and became extensively investigated by the scientific community.

1.2.4.2.1 Cinchona alkaloid-derived bifunctional organocatalysts

In the pursuit of improving the hydrogen bond-donating properties of cinchona alkaloid derivatives, several modifications have been introduced to the cinchona scaffold. Among the most common is the installation of a dual hydrogen bond-donating moiety such as a (thio)urea or squaramide motif. A general model is depicted in Figure 1.12.

![Figure 1.12 General representation of dual activation of bifunctional (thio)urea catalysts.](image)

Although the first synthesis of C-9 urea-substituted cinchona alkaloid-derived catalyst was reported in 2003, it was not until 2005 when four independent research groups synthesised and employed C-9 (thio)urea-substituted bifunctional cinchona-derived organocatalysts in the asymmetric Michael addition type reactions.

Chen’s research group was the first to synthesise C-9 substituted thiourea organocatalysts. Unfortunately, these species exhibited poor enantioselectivity when employed in the asymmetric Michael addition reaction. The first successful application of the bifunctional cinchona-derived organocatalysts were demonstrated by Soós et al. They reported the enantioselective addition of nitromethane to chalcone 79, promoted by the thiourea-derived catalyst 82, affording the product \((R)-84\) in excellent yield (up to 93%) and 96% ee (Scheme 1.21).
Scheme 1.21 Enantioselective Michael addition of nitromethane to chalcone 79, reported by Soós et al.\textsuperscript{112}

The authors observed that the increased acidity of thiourea moiety at the C-9 position resulted in the enhanced hydrogen-bonding ability of the catalyst, leading to increased catalytic activity. Moreover, they discovered that the absolute configuration at the C-9 position is of paramount importance, as it affects the catalytic activity and enantioselectivity of the catalyst. Indeed, this was demonstrated with catalyst 83, having the naturally occurring absolute configuration (only with a hydroxy group substituted for the urea), which failed to promote the formation of 84, unlike 9-epi derivatives, which proved to be successful catalysts for the reaction (Scheme 1.21).\textsuperscript{112}

Almost at the same time, the research groups led by Connon\textsuperscript{113} and Dixon\textsuperscript{114} reported the Michael-type addition of dimethyl malonate 85 to nitroalkene derivatives (Scheme 1.22). Connon’s research group\textsuperscript{113} prepared a series of thiourea- and urea-substituted bifunctional catalysts, with either natural or inverted (\textit{i.e.} C-9-\textit{epi}) absolute configuration at the C-9 position. Independently to Soós \textit{et al.}, they demonstrated the competence of C-9-\textit{epi} derivatives in the Michael addition of dimethyl malonate 85 to \(\beta\)-nitrostyrene 86, and managed to achieve a high degree of enantioselectivity, even at extremely low catalyst loadings (Scheme 1.22).\textsuperscript{113}
Scheme 1.22 Enantioselective Michael addition of dimethyl malonate 85 to β-nitrostyrene 86, reported by Connon et al. (A) and Dixon et al. (B).

After the publication of these seminal reports, the field of bifunctional organocatalysis experienced remarkable growth in the development of cinchona alkaloid-derived catalysts bearing hydrogen-bonding moieties at the C-9 position.

Rawal et al.\textsuperscript{115} designed novel C-9 squaramide-based cinchona alkaloid-derived catalysts (e.g. 90). The structurally more rigid squaramide group operated as an efficient dual hydrogen bond donor. The squaramide-based catalyst 90 displayed excellent activity and enantioselectivity when evaluated in the Michael-type addition of 1,3-dicarbonyl compounds such as 89 to nitroolefins (Scheme 1.23).\textsuperscript{115}

Scheme 1.23 Evaluation of the squaramide-based cinchona alkaloid-derived catalyst 90, prepared by Rawal et al.\textsuperscript{115}
The success of the squaramide-based catalyst 90 inspired other research groups to explore the design and related structural features of similar squaramide cinchona alkaloid-derived organocatalysts, which have been employed efficiently in numerous asymmetric transformations over recent years.116–121

1.2.4.3 (Thio)urea-based bifunctional cinchona alkaloids as powerful phase-transfer catalysts

As previously outlined in Section 1.2.4.2, the prowess of a chiral bifunctional catalyst lies in its ability to simultaneously activate and coordinate two reaction components. In a similar fashion, a bifunctional phase-transfer catalyst is capable of activating an electrophile via hydrogen bond-donation. It has been suggested that this hydrogen bond-donation allows for the formation of a tight and highly ordered pre-transition assembly, while the nucleophile can be stabilised by the quaternary ammonium cation of the PTC.122

The first detailed investigation regarding the synthesis and application of thiourea-based cinchona alkaloid-derived phase-transfer catalysts was carried out by Lassaletta et al.123 In their report they studied a novel 1,4-addition of cyanide to conjugated nitroalkenes 92, using trimethylsilyl cyanide (TMSCN) as the cyanide source (Scheme 1.24).

**Scheme 1.24** 1,4-Addition of cyanide to conjugated nitroalkenes using trimethylsilyl cyanide (TMSCN), promoted by bifunctional catalyst 94 containing a thiourea moiety and a tertiary amine.
In order to achieve a simultaneous activation of both the electrophile and the nucleophile, Lassaletta and co-workers screened a variety of bifunctional thiourea/tertiary amine incorporated organocatalysts in the cyanosilylation of nitroalkenes. Catalyst 94 was found to be the most efficient, affording 97 in moderate enantiomeric excess (58% ee) albeit with extremely low conversion (Scheme 1.24).123

In an effort to obtain higher activity, Lassaletta et al. evaluated the possibility of conducting the reaction in the presence of an achiral phase-transfer catalyst Bu₄NI (TBAI). They were pleased to observe that TBAI successfully catalysed the reaction, furnishing 97 in full conversion in only 32 h (Scheme 1.25).

![Scheme 1.25 General mechanism for a phase-transfer catalysed 1,4-addition of cyanide to conjugated nitroalkenes using trimethylsilyl cyanide (TMSCN), promoted by TBAI.](image)

Encouraged by the results obtained from an achiral phase-transfer catalysed system (Scheme 1.25), Lassaletta and co-workers decided to explore the potential of chiral PTCs. Their efforts were directed towards the use of cinchona alkaloids, in order to achieve 97 in both high conversion and ee. Upon evaluation of several cinchona-derived PTCs in the model reaction, quinine derivative 100 was found to catalyse the formation of 97 in a high yield and moderate enantioselectivity (40% ee, Scheme 1.26), which was lower than the initially reported result with catalyst 94.
Scheme 1.26 1,4-Addition of cyanide to conjugated nitroalkenes using trimethylsilyl cyanide (TMSCN), promoted by quinine-derived phase-transfer catalyst 100.

Scrutiny of these results led Lassaletta et al. to realise that even though low catalytic activity was observed with thiourea-substituted bifunctional cinchona alkaloid-derived catalyst 94, the addition product 97 was formed with moderate enantioselectivity. On the contrary, the chiral phase-transfer catalyst 100 afforded 97 in high yields but with lower enantiomeric excess. Prompted by these results, the authors combined the concept of bifunctionality with phase-transfer catalysis, leading to the development of a novel catalyst 101, bearing a thiourea motif at the C-6’ position of a cinchona alkaloid-based PTC. Catalyst 101 proved to be successful in the formation of 97, which was obtained in a good yield and with improved enantioselectivity (Scheme 1.27).

Scheme 1.27 1,4-Addition of cyanide to conjugated nitroalkenes promoted by the bifunctional C-6’ thiourea-substituted cinchona alkaloid-derived phase-transfer catalyst 101.

The rationally designed structure of catalyst 101 and its concept were completely unprecedented prior this publication. This novel design and concept offered the opportunity to simultaneously activate the nitroalkene electrophile 92 (via hydrogen
bond-donation) and to stabilise the cyanide ion nucleophile via ionic interactions with the N-alkylated quinuclidine moiety, acting as a phase-transfer motif (Scheme 1.27).

The study accomplished by Lassaletta et al.\textsuperscript{123} is considered a landmark publication for the design and application of novel bifunctional hydrogen bond-donating (thio)urea-substituted PTCs. Despite the encouraging results obtained with the conceptually new bifunctional phase-transfer catalyst \textbf{101}, it is rather surprising that it took a further two years for the emergence of similar bifunctional PTCs.

In 2012, Dixon and co-workers\textsuperscript{124} designed a series of C-9 urea-, amide- and sulphonamide-substituted cinchona alkaloid-derived bifunctional phase-transfer catalysts. The performance of these catalysts was evaluated in the nitro-Mannich reaction of α-amido sulfones \textbf{102} and nitroalkanes such as \textbf{103} (Scheme 1.28).

![Scheme 1.28](image-url)

**Scheme 1.28** Evaluation of C-9 urea-, amide-, sulphonamide-substituted cinchona alkaloid-derived bifunctional PTCs in the nitro-Mannich reaction, reported by Dixon et al.\textsuperscript{124}

Dixon et al. observed that the sulphonamide-based catalyst \textbf{105} failed to promote the formation of \textbf{108}, while urea-based catalysts, such as \textbf{106} and \textbf{107}, readily afforded the
products in high yields and with very good enantiomeric excess. In particular, catalyst 107 was more efficient than its pseudo-enantiomer 106. It was also noted that the dual hydrogen bond-donating ability of the urea group was superior to the single hydrogen bond-donating group on the amide. This was particularly evident with catalyst 104, which promoted the formation of 108 in both lower yield and ee. Additionally, enantioselectivity was further increased by changing the solvent from PhCH₃ to rBuOMe and by lowering the catalyst loading to 5 mol% (Scheme 1.28). Dixon et al.¹²⁴ also reported the formation of 109, possessing two contiguous stereocentres, in excellent enantioselectivity (94% ee) and diastereoselectivity (24:1 dr), the anti-isomer being formed preferentially.

Similar catalysts to those developed by Dixon (e.g. 107) were synthesised and evaluated by two independent groups. In 2013, Smith et al.¹²⁵ reported the enantioselective synthesis of quaternary-substituted indolenine-derivatives promoted by bifunctional cinchona alkaloid-derived PTCs. Massa et al.¹²⁶ evaluated the use of similar catalysts in the asymmetric synthesis of α-amino ester 3-substituted isoindolinones.

A novel class of cinchona alkaloid-derived phase-transfer catalysts such as 112, bearing multiple hydrogen bond-donating moieties, was designed in 2014 by Duan and Lin.¹²⁷ The catalyst design was inspired by the preceeding reports published by Manabe¹²⁸ and Nagasawa¹²⁹ in which PTCs with multiple hydrogen bond-donating functionality were synthesised (Figure 1.13).

![Bifunctional PTCs bearing multiple H-bonding donors](image)

**Figure 1.13** Bifunctional PTCs bearing multiple H-bonding donors, reported by Manabe,¹²⁸ Nagasawa¹²⁹ and the novel design 112 presented by Duan and Li.¹²⁷
Duan et al.\textsuperscript{127} evaluated the efficiency of these novel PTCs (e.g. \textsuperscript{113}) in the nitro-Mannich reaction of \(\alpha\)-amido sulfones with nitroalkanes, achieving the desired product \textbf{108} in excellent yield and enantioselectivity (Scheme 1.29).

![Scheme 1.29 Evaluation of novel multiple H-bond donating PTCs in the nitro-Mannich reaction of \(\alpha\)-amido sulfone \textbf{102} with nitroalkanes.\textsuperscript{127}](image)

The authors discovered that by performing the reaction in a mixture of solvents (PhCH\(_3\)/CHCl\(_3\) 9:1), product \textbf{108} can be obtained in excellent chemical yield and enantioselectivity. When nitroethane was used as the nucleophile, the \textit{anti}-product \textbf{109} was formed in preference to the \textit{syn}-adduct (15:1 \textit{dr}) with excellent enantiomeric excess (96\% \textit{ee}). Duan and co-workers also demonstrated that by using quinidine-based catalyst \textbf{114}, the opposite diastereomer of \textbf{109} could be accessed, in both excellent yield and \textit{ee} (Scheme 1.29).\textsuperscript{127}

In 2017, Duan expanded the scope of the nitro-Mannich reaction to arylnitroalkanes\textsuperscript{130} and \(\beta,\gamma\)-unsaturated nitroalkenes.\textsuperscript{131} The catalyst structure was also slightly modified. The bifunctional quinine-derived PTC \textbf{113}, bearing a benzyl group on the quinuclidine ring was instead substituted with a 3,5-di-\textit{tert}-butyl benzyl moiety, affording the formation of the desired products in excellent yield and with excellent diastereo- and enantioselectivities (up to 99\% yield, > 99:1 \textit{dr} and >99\% \textit{ee}).\textsuperscript{130,131}
1.2.5 Application of phase-transfer catalysts in asymmetric $\text{S}_2\text{N}_2$ $C-C$ bond forming reactions, resulting in the formation of quaternary stereocentres

Phase-transfer catalysis has been recognised as a well established method for promoting many $\text{S}_2\text{N}_2$-type reactions: with those leading to the formation of quaternary stereocentres being among those most exploited.\textsuperscript{132-137} Non-proteinogenic $\alpha,\alpha$-dialkyl amino acids have been an anticipated synthetic target in asymmetric synthesis.\textsuperscript{138-140} The advantage associated with $\alpha,\alpha$-dialkyl amino acids is in the design of peptides, which aid in the elucidation of enzymatic mechanisms. In addition, $\alpha,\alpha$-dialkyl amino acids are often effective enzyme inhibitors and are frequently used in the synthesis of biologically active compounds.\textsuperscript{141} Asymmetric phase-transfer catalysis facilitates a direct enantioselective synthesis of such amino acids,\textsuperscript{62,76,142} employing readily available natural amino acids as starting materials.

One strategy which can be used for the synthesis of $\alpha,\alpha$-dialkyl amino acids is the enantioselective alkylation of protected amino acids under phase-transfer catalysis. Following on the previous studies by Jew, Park \textit{et al.},\textsuperscript{143} Nájera and co-workers\textsuperscript{142} performed the asymmetric alkylation of 2-naphthylaldimine alanine tert-butyl ester \textbf{115} in the presence of cinchona alkaloid-derived PTCs (\textit{i.e.} \textbf{48} and \textbf{49}), accessing both enantiomers of the desired $\alpha,\alpha$-dialkyl amino acid precursor \textbf{116} in excellent optical purity (Scheme 1.30).\textsuperscript{142}

![Scheme 1.30 The asymmetric alkylation of 2-naphthylaldimine alanine tert-butyl ester \textbf{115} by Nájera \textit{et al.}](image)

\textbf{Scheme 1.30} The asymmetric alkylation of 2-naphthylaldimine alanine tert-butyl ester \textbf{115} by Nájera \textit{et al.}\textsuperscript{.142}
In 2012, Maruoka et al.\textsuperscript{144} developed a powerful chiral PTC \textbf{118} with a conformationally fixed 6,6'-bridged ring on the biphenyl unit, which was found to efficiently promote the alkylation of alanine derivative \textbf{117}. The reaction proceeded smoothly under mild reaction conditions and an extremely low catalyst loading of just 0.02 mol\% (Scheme 1.31).\textsuperscript{144}

Scheme 1.31 The asymmetric alkylation of alanine derivative \textbf{117}, employing chiral PTC \textbf{118} with a conformationally fixed biphenyl core, developed by Maruoka et al.\textsuperscript{144}

The performance of the chiral PTC \textbf{121} was evaluated by Maruoka\textsuperscript{145} in the enantioselective methylation of phenyloxazoline tert-butyl ester \textbf{120}. α-Methylserine \textbf{123} was furnished in a moderate yield and with very good enantioselectivity (Scheme 1.32).\textsuperscript{145}

Scheme 1.32 Practical enantioselective methylation of phenyl-oxazoline tert-butyl ester \textbf{120}, reported by Maruoka and co-workers.\textsuperscript{145}

Jew, Park \textit{et al.}\textsuperscript{146} applied a similar synthetic approach in the asymmetric synthesis of α-alkylhomoserine \textbf{129} and α-alkylhomocysteine \textbf{130}. These targets were readily accessed through substrates such as \textbf{124} and \textbf{125}, bearing six-membered ring functionality
(Scheme 1.33). This asymmetric alkylation was promoted by cinchona alkaloid-derived catalyst 126, substituted with a 2,3,4-trifluorobenzyl group.

Scheme 1.33  Phase-transfer catalysed asymmetric synthesis of α-alkylhomoserine 129 and α-alkylhomocysteine 130, reported by Jew, Park et al.\textsuperscript{146}

1.2.5.1  Significance of all-carbon quaternary stereocentres in asymmetric synthesis

An all-carbon quaternary stereocentre – a carbon atom bearing four distinct carbon substituents, is a common structural \textit{motif} present in many biologically active natural products and pharmaceuticals.\textsuperscript{147} The catalytic enantioselective construction of these stereocentres has been studied extensively over recent years and in addition, many efficient methodologies employing the use of either chiral auxiliaires or chiral catalysts exist.\textsuperscript{148–152} However, there is still a high demand for novel chiral organocatalysts, that would efficiently promote asymmetric transformations, leading to the formation of all-carbon quaternary stereocentres.\textsuperscript{153}

Despite the great need for the synthesis of compounds containing all-carbon quaternary stereocentres, their formation poses a formidable challenge in organic synthesis. The construction of all-carbon quaternary stereocentres is impeded mainly due to the steric hindrance imposed by the four attached carbon substituents.\textsuperscript{152} The steric repulsion forces that occur between carbon substituents during the C-C bond formation are even more profound when an all-carbon quaternary stereocentre belongs to an acyclic system.
(more complex due to the number of degrees of freedom associated with these structures) or when contiguous all-carbon quaternary stereocentres are formed, resulting in a steric clash of greater magnitude.\textsuperscript{154}

Although, the formation of these quaternary stereocentres can be often problematic, their advantage is the associated stability due to the strength of the C-C bond. Hence, their absolute configuration is less likely to change, compared to tertiary stereocentres bearing a hydrogen atom which can easily be deprotonated, resulting in an unwanted racemisation of the compound.\textsuperscript{147}

The following Section will detail a number of selected examples resulting in the formation of all-carbon quaternary stereocentres, promoted by asymmetric phase-transfer catalysts \textit{via} S\textsubscript{N}2-type C-C bond forming reactions. The synthesis of 3,3\textsuperscript{-}disubstituted 2-oxindole derivatives bearing all-carbon quaternary stereocentres will be reviewed exclusively in Section 1.3.

\textbf{1.2.5.1.1 Formation of all-carbon quaternary stereocentres \textit{via} S\textsubscript{N}2-type C-C bond forming reactions employing phase-transfer catalysis}

Among various asymmetric approaches for the synthesis of all-carbon quaternary stereocentres, phase-transfer catalysis has been extensively explored since the first successful report by Dolling \textit{et al.} in 1984 (Scheme 1.6, \textit{vide supra}).\textsuperscript{55} In this publication, Dolling outlined the formation of all-carbon quaternary stereocentres by phase-transfer catalysed asymmetric alkylation of indanone derivatives.

Recently, Park \textit{et al.}\textsuperscript{155,156} reported highly enantioselective \(\alpha\)-alkylation of \(\alpha\text{-}\text{tert-}
\text{butoxycarbonyllactam 131}\) catalysed by a phase-transfer catalyst 132, affording the \(\beta\)-quaternary chiral pyrrolidine and piperidine cores in excellent chemical yields and enantioselectivities. These cores were subsequently employed in the total synthesis of (-)-isonitramine (Scheme 1.34).
Scheme 1.34 The asymmetric phase-transfer catalysed alkylation of α-tert-butoxycarbonyl lactam 131, reported by Park et al.\textsuperscript{155,156}

Ooi and co-workers\textsuperscript{157} evaluated the performance of a binaphthyl-modified catalyst 136 – structurally a very similar phase-transfer catalyst to 132 – in the asymmetric alkylation of α-acyl-γ-butyrolactone 135. The resulting α-alkylated keto lactone 137, which serves as a valuable chiral building block used in organic synthesis, was obtained in high yield and excellent ee (Scheme 1.35).

Scheme 1.35 The asymmetric phase-transfer catalysed alkylation of α-acyl-γ-butyrolactone 135, reported by Ooi and co-workers.\textsuperscript{157}

In 2011, two independent research groups\textsuperscript{158,159} succeeded in the highly enantioselective synthesis of α,α-dialkyl malonates under phase-transfer catalysed reaction conditions. The successful enantioselective alkylation of malonic ester 138 catalysed by binaphthyl-derivative catalyst 132, was conducted by Park and co-workers.\textsuperscript{158} They obtained the alkylated product 139 in both excellent yield and enantiomeric excess (Scheme 1.36).
Scheme 1.36  The asymmetric phase-transfer catalysed α-alkylation of diphenylmethyl tert-butyl α-alkylmalonate 138, reported by Park et al.¹⁵⁸

Concurrently, Itoh et al.¹⁵⁹ used a cinchonine-derived phase-transfer catalyst 48 in the alkylation of malonic ester 140, obtaining the desired product 141 in excellent yield and ee (Scheme 1.37).

Scheme 1.37  The asymmetric phase-transfer catalysed alkylation of α-substituted tert-butyl methyl malonate 140, reported by Itoh et al.¹⁵⁹

In 2009, Scheidt¹⁶⁰ developed a novel cinchonidine-derived phase-transfer catalyst 143, which they applied in the enantioselective alkylation of isoflavanone 142 (Scheme 1.38). Isoflavanones are precursors to more complex natural products such as pterocarpans and rotenones, which upon alkylation provide direct access to biologically active homoisoflavanones.

Scheme 1.38  The asymmetric phase-transfer catalysed alkylation of isoflavanone 142, reported by Scheidt et al.¹⁶⁰
A research group in Merck, led by Huffman, reported an efficient asymmetric synthesis of 148, which represents an estrogen receptor β-modulator. They accomplished this by the enantioselective alkylation of an indanone derivative 145, promoted by a cinchona alkaloid-derived phase-transfer catalyst 146. The alkylated product 147 was obtained in excellent yield and good enantiomeric excess (76% ee, Scheme 1.39). Starting from the commercially available 2-fluoroanisole, the overall eight step synthesis was accomplished in 34% yield.

Scheme 1.39 The synthesis of estrogen receptor β-modulator 148 via enantioselective alkylation promoted by a phase-transfer catalyst 146.161

1.3 3,3′-Disubstituted 2-oxindoles

For many years, nature has inspired the synthesis and development of compounds with remarkable biological activity and structural complexity. 3,3′-Disubstituted 2-oxindoles and their cyclised derivatives – spirooxindoles, are privileged structural motifs present in many natural, bioactive and pharmaceutically useful products.162,163 The key structural feature of 3,3′-disubstituted 2-oxindoles, which makes them exceptionally attractive in asymmetric synthesis, is the all-carbon quaternary stereocentre at the C-3 position of the oxindole core, often bearing diverse heterocyclic moieties.164 The simplest members of the spirooxindole family are the naturally occurring coerulescine (149) and horsfiline (150), while more complex natural products include elacomine (151) and rynchophylline (152, Figure 1.14). In addition to natural products possessing a spirooxindole core, many spirocyclic 3,3′-disubstituted 2-oxindole derivatives were
found to be promising candidates in drug discovery (e.g. 153, a lead synthetic drug for the treatment for malaria, and 154, currently in preclinical trials for human cancer).

A further example of an important pharmaceutically active compound, which is not cyclised at the C-3 carbon of the oxindole core, is the anti-cancer agent 155, developed by Hoffmann-La Roche.

Figure 1.14 Representative examples of natural and synthetic 3,3’-disubstituted 2-oxindoles.

Due to the many attractive features associated with 3,3’-disubstituted 2-oxindoles, a plethora of diverse asymmetric C-C bond forming reactions have been reported for their synthesis. As the extent of these transformations leading to the formation of quaternary stereocentres of 2-oxindole derivatives is beyond the scope of this thesis, only the selected examples promoted by phase-transfer catalysis will be described in more detail.

1.3.1 Formation of 3,3’-disubstituted 2-oxindole derivatives possessing an all-carbon quaternary stereocentre via phase-transfer catalysed C-C bond forming reactions

The construction of all-carbon quaternary stereocentres in 3,3’-disubstituted 2-oxindole derivatives has always presented a major synthetic challenge. Nonetheless, a number of organocatalytic approaches have successfully been developed for the synthesis of these
stereogenic centres, with phase-transfer catalysis being among some of the most prominent examples. The following Sections are dedicated to $S_N2$-type alkylations and conjugate additions of oxindoles to electron deficient olefins, promoted by phase-transfer catalysis.

1.3.1.1 $S_N2$ alkylation

One of the earliest examples of $S_N2$-type alkylation, promoted by a phase-transfer catalyst, was reported by Wong and Lee in 1991. This publication has demonstrated an efficient phase-transfer catalysed asymmetric cyanomethylation of oxindole 156, in which a precursor of the alkaloid (-)-esermethole (i.e. 159) was accessed in high yield and good enantioselectivity (Scheme 1.40). The PTC employed in this asymmetric alkylation was derived from a cinchonine alkaloid, possessing a 3,4-dichlorophenylmethyl substituent on the quinuclidine nitrogen atom.

![Scheme 1.40](image)

Scheme 1.40 The asymmetric cyanomethylation of oxindole 156, promoted by the cinchonine-derived PTC 157, in the synthesis of (-)-esermethole.

In 2011, Ooi and co-workers designed a novel class of chiral 1,2,3-triazolium phase-transfer catalysts (e.g. 161, Scheme 1.41). The strategy for the molecular design of this novel catalyst was based on two important synthetic sequences: (1) the construction of the required 1,2,3-triazolium core, employing L-phenylalanine as a starting material, and (2) the introduction of the amide moiety. The single-crystal X-ray diffraction analysis revealed that the triazolium cation is tightly associated with the anion through electrostatic interaction and double hydrogen bonding; one with the triazolium proton on C-5 and the other with the amide proton (Scheme 1.41). Additionally, the amide unit
contributes to enhanced enantiofacial discrimination by the catalyst, by regulating the positions of the substituents at the stereocentre, creating a discrete chiral pocket surrounding the anion. Among the synthesised novel catalysts, 161 was found to be the most effective in the asymmetric alkylation of 3-methyl oxindole 160, furnishing the alkylated product 162 in both excellent chemical yield and ee (Scheme 1.41).\(^{173}\)

Scheme 1.41 The asymmetric alkylation of the 3-substituted oxindole derivative 160, promoted by the novel chiral 1,2,3-triazolium salt 161.\(^{173}\)

In an effort to probe the potential of triazolium catalysis, Ooi et al.\(^ {174}\) expanded the scope of asymmetric alkylation to racemic secondary alkyl halides, which would provide access to contiguous all-carbon quaternary and tertiary stereocentres (Scheme 1.42). Prior to this, the only successful example of this type of asymmetric alkylation, leading to the formation of contiguous two tertiary stereocentres, was reported by Maruoka et al.\(^ {175}\) in the synthesis of \(\beta\)-branched \(\alpha\)-amino acids.

Scheme 1.42 The asymmetric alkylation of the 3-substituted oxindole derivative 163 with racemic (1-bromoethyl)benzene (164), promoted by chiral 1,2,3-triazolium salts.\(^ {174}\)
One of the main challenges Ooi and co-workers had to overcome was the simultaneous double stereocontrol associated with the enantioselective discrimination of prochiral enolate and the kinetic resolution of a chiral non-activated secondary alkyl halide (e.g. 164). Upon evaluating the effect of the amino acid moiety of the catalyst and its ability to discriminate the central chirality of 164, the catalyst derived from \( N \)-ethylglycine (i.e. 165) was found to promote the formation of 168 with excellent enantioselectivity and good diastereoccontrol, although only in moderate chemical yield. Further structural modifications of 165, such as substitution of the geminal aromatic phenyl moiety with a 4-chlorophenyl unit and the introduction of an electron-withdrawing substituent on the phenyl ring attached to the triazolium core, resulted in the design of the optimal catalyst 167. It promoted the formation of 168 complete conversion with excellent diastereo- and almost complete enantiocontrol (Scheme 1.42).\(^{174}\)

Thirty years after their first report on the asymmetric alkylation under phase-transfer catalysis,\(^{55}\) another research group in Merck, this time led by Yasuda,\(^{85}\) designed novel \( N,N' \)-disubstituted cinchona alkaloid-derived PTCs (e.g. 171 and 172). These catalysts successfully promoted the intramolecular spirocyclisation of 3-substituted oxindole derivatives of type 169 in complete conversion and with excellent enantioselectivity (Scheme 1.43).\(^{85}\)

**Scheme 1.43** The asymmetric intramolecular alkylation of 3-substituted oxindole derivative 169, promoted by singly and doubly quaternised cinchona alkaloid-derived PTCs.\(^{85}\)
The discovery of doubly quaternised cinchona alkaloid-derived PTCs began with the evaluation of the first generation catalyst 170 in the asymmetric alkylation of 169, which initially resulted in full conversion of 3,3'-spiro-7-azaoxindole 173 with 92% ee. However, when a new batch of 170 was prepared and tested in the same reaction, the conversion of 173 dropped to 80% and the enantiomeric excess had also significantly diminished to 58% ee. After detailed investigation and extensive ¹H NMR spectroscopic analysis of both batches of catalysts, Yasuda et al. realised that the first batch of catalyst 170 was contaminated with trace amounts of catalyst which was quaternised at both the quinuclidine and quinoline nitrogen atoms (i.e. 171). Upon preparation of catalyst 171 and its subsequent evaluation in the intramolecular alkylation of 169, the desired product 173 was achieved in complete conversion in 1 h, at catalyst loading of just 1 mol%. The enantioselectivity of 173 had also increased to 92% ee, with further enhancement accomplished with a quinidine-derived catalyst 172 (94% ee, Scheme 1.43). ⁸⁵

Maruoka et al. ¹⁷⁶ disclosed an efficient method for the construction of all-carbon quaternary stereocentres from 3-substituted oxindole derivatives (e.g. 174) under mild phase-transfer catalysed reaction conditions. The N-spiro chiral quaternary ammonium bromide 132 promoted the formation of 3,3'-disubstituted oxindole derivative 176 in high yield and optical purity (Scheme 1.44).

Scheme 1.44 The asymmetric alkylation of 3-phenyl oxindole 174, promoted by N-spiro chiral quaternary ammonium bromide 132 as the PTC. ¹⁷⁶

The enantioselective alkylation of N-benzyl-3-phenyl-2-oxindole (177) with activated bromomethanes (e.g. 178) was investigated by Jiang and co-workers. ¹⁷⁷ In their study, they employed a bicyclic guanidium-based phase-transfer catalyst 179, in the presence of a Lewis acid, which acted as a co-catalyst. The alkylation adduct 180, which is a
versatile intermediate for the preparation of pyrroloindolines and furoindolines, was obtained in excellent chemical yield and high enantiomeric excess (Scheme 1.45).

Scheme 1.45 The asymmetric alkylation of protected 3-phenyl-2-oxindole 177 with ethyl bromoacetate (178), catalysed by a bicyclic guanidium 179, in the presence of a Lewis acid.

Very recently, Sorrentino and Connon\textsuperscript{178} reported the first strategy for highly enantioselective alkylation kinetic resolution of chiral enolates derived from 3-substituted oxindoles (e.g. 181), in the presence of a novel squaramide-based cinchona alkaloid-derived phase-transfer catalyst 182 (Scheme 1.46).

Scheme 1.46 The asymmetric alkylation kinetic resolution of 3-substituted oxindole 181, catalysed by squaramide-based phase-transfer catalyst 182.\textsuperscript{178}

The benzylated product 184, incorporating a densely functionalised side chain with an ester at the α-position and a malleable malonate derivative β to the heterocycle moiety was obtained in excellent enantio- and diastereoccontrol, with an extraordinary S factor.
of >200. It was observed that the resolved starting materials can racemise via a retro-Michael/Michael reaction. However, this process can be avoided by introducing a methyl group at the β-carbon of the side chain. Sorrentino and Connon also demonstrated the possibility of extending the scope of the electrophilic component, generating allylated and propargylated 2-oxindole derivatives, in both high enantio- and diastereoc ontrol.\textsuperscript{178}

1.3.1.2 Conjugate addition

Among various approaches for the asymmetric synthesis of 3,3’-disubstituted 2-oxindoles,\textsuperscript{167,179–181} Michael additions or conjugate additions are of particular interest as the addition adducts can be readily converted into important biologically and pharmacologically active compounds. Despite numerous organocatalytic examples of Michael additions of 3-substituted oxindole derivatives,\textsuperscript{182–186} it was in 2009 that Maruoka and co-workers\textsuperscript{187} reported the first successful asymmetric Michael addition of these species under phase-transfer catalysis. In their study, they demonstrated the potential of chiral quaternary tetraalkylphosphonium bromides, \textit{e.g.} 186, as efficient PTCs in the Michael addition of 3-phenyl oxindole 174 to methyl vinyl ketone 185. (Scheme 1.47).

![Scheme 1.47](image)

\textbf{Scheme 1.47}  The asymmetric Michael addition of 3-phenyl oxindole 174, promoted by the quaternary tetraalkylphosphonium salt 186.\textsuperscript{187}

Wu, Cao and Zhao\textsuperscript{188} disclosed a new type of phosphonium PTCs derived from readily available amino acids. They evaluated the efficiency of these novel PTCs in the Michael addition of 174 to 185, achieving excellent yields with moderate to excellent enantioselectivities. The most effective catalyst for the model transformation was derived from isoleucine (\textit{i.e.} 188), affording the Michael adduct 187 in 99% yield and 89% \textit{ee} (Scheme 1.48).
Scheme 1.48 The asymmetric Michael addition catalysed by the amino acid-derived phosphonium salt 188.\textsuperscript{188}

In recent years, Tan \textit{et al.} developed structurally novel pentanidiums as efficient PTCs for several asymmetric transformations.\textsuperscript{189–192} Driven by the desire to further expand the scope of reactions promoted by pentanidiums, the authors examined the potential of pentanidiums in the asymmetric conjugate addition of 3-substituted oxindoles, such as 189, to phenyl vinyl sulfones, obtaining the addition product 192 in good yield and very high optical purity (Scheme 1.49). A broad variety of substrates were evaluated in the asymmetric conjugate addition to 190 promoted by pentanidiums (\textit{e.g.} 191), leading to structurally diverse enantioenriched 3,3''-disubstituted oxindoles.\textsuperscript{193}

Scheme 1.49 The enantioselective phase-transfer catalysed addition of 3-methyl oxindole derivative 189 to phenyl vinyl sulfone 190, promoted pentanidium salt 191.\textsuperscript{193}
A highly Z-selective asymmetric conjugate addition of 3-phenyl oxindole derivatives to β-haloalkene ketones, catalysed by chiral quaternary ammonium salts of type 195 were recently reported by Zhao et al.\textsuperscript{194} Through this efficient transformation, they were able to access a range of 3,3'-disubstituted oxindole derivatives, bearing a usually thermodynamically unstable Z-olefin moiety. The chiral quaternary ammonium bromide 194 successfully promoted the formation of 195 in high yield, very good enantioselectivity and excellent Z/E selectivity (88% ee, >19:1 dr Z/E, Scheme 1.50).

\begin{equation}
\text{Ph} \quad \text{Cl} \quad \text{Ph} \\
\text{O} \quad \text{193} \quad 194 (10 \text{ mol}%) \quad \text{KF, PhCH}_3 \quad \text{rt, 4 h} \quad \text{Ph} \quad \text{O} \\
\text{N} \quad \text{Boc} \quad \text{195} 87\%, 88\% \text{ ee}, >19:1 \text{ dr} \\
\end{equation}

**Scheme 1.50** The asymmetric conjugate addition of 3-substituted oxindoles to β-haloalkene ketones, promoted by the chiral quaternary ammonium salt 194.\textsuperscript{194}

Following up on their previous studies on phase-transfer catalysed conjugate additions of 3-substituted oxindole derivatives (Scheme 1.47, \textit{vide supra}), Maruoka et al.\textsuperscript{195} discovered that they could perform the Michael addition reaction of 3-phenyl oxindole 174 to β-nitrostyrene 86 in the absence of a base, provided the chiral PTC and water-rich solvent were employed in the reaction (Scheme 1.51). Prior to this, the asymmetric phase-transfer catalysis employing base-free neutral reaction conditions had not been reported.

\begin{equation}
\text{Ph} \quad \text{Ph} \quad \text{NO}_2 \\
\text{N} \quad \text{Boc} \quad 196 (1 \text{ mol}%) \quad 0 \text{ °C} \quad \text{Ph} \quad \text{NO}_2 \\
\text{O} \quad \text{174} \quad \text{197} \\
\end{equation}

**Scheme 1.51** Phase-transfer catalysed enantioselective conjugate addition under base-free neutral reaction conditions.\textsuperscript{195}
Initial studies showed that the conjugate addition proceeded smoothly in the presence of a novel chiral quaternary ammonium bromide 196, used as a bifunctional PTC, employing aqueous K$_2$CO$_3$ as a mild base. Shortly afterwards, Maruoka et al. reported: “very surprisingly, we discovered that even without any basic additives, the reaction proceeds smoothly in the presence of a chiral phase-transfer catalyst 196 in 1:2 toluene/water at 0 °C for 2 h to furnish 197 with 90% ee.” It should be noted, that water is absolutely crucial for the promotion of the reaction, as in the absence of water, the product formation is not observed at all (Scheme 1.51).\textsuperscript{195}

As an explanation as to the nature of this phenomenon, Maruoka and co-workers treated 174 with catalyst 196 in a D$_2$O/toluene mixture (2:1) and observed the formation of deuterated\textsuperscript{d}\textsuperscript{-}174 in 88% yield, while recovering 174 in 11% yield (Scheme 1.52).

Regarding these findings, they proposed the formation of an intermediary chiral ion pair 198, between the enolate of the substrate and the quaternary ammonium cation of the catalyst.\textsuperscript{195}

![Scheme 1.52 Deuteration of 3-phenyl oxindole 174.](image)

The application of the base-free neutral reaction system with the use of a chiral phase-transfer catalyst was successfully extended to other asymmetric conjugate additions. In 2013, Maruoka et al.\textsuperscript{196} demonstrated an efficient asymmetric conjugate addition of 174 to acrolein 199, employing novel highly efficient chiral quaternary phosphonium salts (\textit{e.g.} 200), under the base-free neutral reaction conditions (A, Scheme 1.53).

Recently, Shirakawa, Maruoka and Liu\textsuperscript{197} investigated the potential of chiral bifunctional trialkylsulfonium salts of type 203, as phase-transfer catalysts in the asymmetric conjugate addition of 3-substituted oxindoles to maleimides, performed in the base-free neutral reaction system (B, Scheme 1.53). Although the Michael adduct 204 was obtained only in a moderate yield (64%), this was the first example in which the chiral tertiary sulfonium salts were employed as efficient PTCs, furnishing desired product 204 in excellent enantioselectivity.
Scheme 1.53  Highly enantioselective conjugate additions, performed under base-free neutral reaction conditions in the presence of chiral PTCs.\textsuperscript{196,197}

1.4  The role of the fluoride ion in organic synthesis

Over the years, the role of the fluoride ion (F\textsuperscript{−}) in organic synthesis has been established predominantly as a base. A variety of reagents containing fluoride ions have been employed in many chemical transformations, which are discussed in a comprehensive review recently compiled by Iqbal and Langer.\textsuperscript{198} The sources of fluoride ions can be obtained from either alkali metal salts or quaternary ammonium salts (Figure 1.15).

Examples of metal salts: NaF, KF, CsF

\[
\begin{align*}
205 \quad & \text{Tetramethylammonium fluoride (TMAF)} \\
206 \quad & \text{Tetraethylammonium fluoride (TEAF)} \\
207 \quad & \text{Tetraethylammonium fluoride (TBAF)} \\
208 \quad & \text{Tris(dimethylamino)sulphonium difluorotrimethylsilatate (TASF)} \\
209 \quad & \text{Tetrabutyrammonium triphenylfluorosilicate (TBAT)}
\end{align*}
\]

Figure 1.15  Common reagents containing fluoride ions.\textsuperscript{198}

It is well known that reactivity of fluoride ions is dramatically affected by the choice of solvent.\textsuperscript{199} The nucleophilicity of the fluoride ion in aprotic solvents is much higher
than in protic solvents. The reason behind the poor nucleophilicity of F\(^-\) in protic solvents is the formation of strong H-F bonds between the molecules of water and F\(^-\), resulting in the protonation of the fluoride ion. Most of the fluoride salts are also very hygroscopic. The amount of retained water/moisture by the fluoride ion has a significant effect of their reactivity, subsequently affecting the outcome of reaction. Some of organic fluoride salts, e.g. 1-methylhexamethylenetetramine fluoride (MHAf) and tetramethylphosphonium fluoride (TMPF), can be obtained in their anhydrous or ‘naked’ form. This is usually accomplished by heating under dynamic vacuum or azeotropic distillation.\(^{200}\) Often, these procedures are not compatible with other fluoride ion sources. For example, dried tetrabutylammonium fluoride (TBAf, \(^{207}\)) is known to decompose by Hofmann elimination and the isolated dehydrated salt is often contaminated with large amounts of the bifluoride ion (HF\(_2^+\)) and tributylamine (see Scheme 1.68).\(^{201}\) Based on these observations, Fry and Sharma\(^{201}\) stated that “it is very unlikely that pure, anhydrous tetraalkylammonium fluoride salts have ever, in fact, been produced in the case of ammonium ions susceptible to E2 eliminations.” Probably the only effective procedure for the synthesis of anhydrous TBAF was reported by Sun and DiMagno.\(^{200}\) They managed to synthesise TBAF, containing as little as 2% of the bifluoride species, via nucleophilic aromatic substitution of tetrabutylammonium cyanide (TBAC, \(^{210}\)) with hexafluorobenzene (\(^{211}\)). This reaction was performed in a polar aprotic solvent at a low temperature (Scheme 1.54).

Scheme 1.54  Synthesis of anhydrous TBAF, accomplished by Sun and DiMagno.\(^{200}\)

Commercially, TBAF is available in a solid form as a trihydrate or as a solution in anhydrous THF (1.0 M); making these some of the most common sources of TBAF used in organic synthesis.
1.4.1 The fluoride ion as a nucleophilic catalyst: mechanistic insights

Perhaps one of the earliest reports suggesting that fluoride ions can act as nucleophilic catalysts was disclosed in 1967 by Bunton and Fendler. The aim of their investigation was to establish the role of the fluoride anion in the hydrolysis of carboxylic anhydrides. They speculated that the fluoride ion was acting as either a nucleophilic catalyst or a general base. At the time the authors failed to provide sufficient experimental evidence to support the existence of solely one mechanism. Nonetheless, Bunton and Fendler hypothesised that an acyl fluoride was the key intermediate formed during the acyl-transfer step in the hydrolysis of ethanoic and succinic anhydrides. Ueki et al. also suggested formation of the acyl fluoride intermediate during the hydrolysis of esters by TBAF trihydrate in DMF, however he failed to provide satisfactory evidence to demonstrate nucleophilic catalysis of the fluoride anion.

El Seoud and co-workers examined several mechanistic aspects into fluoride ion catalysis in the acylation of cellulose using a TBAF trihydrate/DMSO solvent system. They employed FTIR spectroscopy to detect the formation of the acyl fluoride intermediate, which was suspected to form upon mixing of the anhydride in DMSO with TBAF. Although, they did not use biopolymer in their FTIR experiments, to avoid scattering of IR radiation from the cellulose-TBAF/DMSO solution, they hypothesised that even in protic solvents, F should still be nucleophilic enough to generate the acyl fluoride intermediate.

A more comprehensive study, regarding a TBAF-catalysed deacylation of cellulose esters, was reported by Edgar, Zheng and Gandour, shortly after El Seoud et al. submitted their manuscript describing a fluoride ion-mediated acylation of cellulose. Edgar and Xu had previously observed the highly regioselective deacylation of cellulose esters by TBAF in THF (Scheme 1.55).

![Scheme 1.55](image-url)  
Scheme 1.55 TBAF-catalysed regioselective deacylation of cellulose acetate.
Since the exact course of this reaction was not known and no literature precedent had been previously reported, Edgar et al. investigated the mechanism that would explain the high level of regioselectivity in the deacylated cellulose. It was observed that the deacylation occurred predominantly at the more hindered ester groups, i.e. esters of the secondary alcohols at O-2 and O-3, leading to the formation of cellulose-6-O-esters. Accounting for the exceptional regioselectivity of the deacylation process, the authors speculated that the mechanism for removing the secondary alcohol acetate groups at O-2/3 might differ from the mechanism of the deacylation at O-6. On the basis of kinetic isotope effects (KIE), Edgar et al. were able to compare the reaction rate constants at C-2/3 and C-6. The significant difference between the reaction rate constants supported a hypothesis involving two distinctive mechanisms operating in a TBAF-catalysed deacylation of cellulose esters. Upon KIEs analysis, the authors reasoned that the mechanism of the deacylation at O-2/3 proceeds via E1cB elimination through the ketene intermediate. To explain the observed regioselectivity leading to the deacetylated ester, Edgar et al. proposed a potential attractive interaction between the α-protons of the tetrabutylammonium cation of TBAF and the carbonyl oxygens at O-2/3, facilitated by H-bonding or ion-dipole interactions (Scheme 1.56).

Scheme 1.56  Ketene intermediate mechanism via E1cB elimination at C-2/3 and the proposed chelation of the tetrabutylammonium cation with the vicinal acetate groups at O-2/3.

In terms of the deacylation at O-6, Edgar et al. suggested two possible mechanistic routes. The first mechanism was based on the nucleophilic attack of the fluoride anion on the acyl carbonyl. The subsequent sp³-hybridised tetrahedral intermediate decomposes to generate the C-6 alcohol and acetyl fluoride, which undergoes subsequent hydrolysis to acetic acid (Scheme 1.57).
Scheme 1.57  Mechanism of the nucleophilic attack of a fluoride ion on the carbonyl carbon of cellulose acetate 213, in the deacylation at O-6.205

The other route operates via a general base catalysis mechanism, where a fluoride anion removes a proton concurrently with water attacking the carbonyl carbon. The resulting anionic sp³-hybridised tetrahedral intermediate 225 collapses to give acetate and the C-6 alcohol 223 (Scheme 1.58).

Scheme 1.58  General base mechanism operating at C-6.205

In an attempt to establish which of the two mechanisms was operating in the deacylation at O-6, Edgar et al. examined the effects of adding a base to the reaction mixture. They reasoned that if the general base mechanism was operative then added base should increase the rate of the deacylation at O-6. Conversely, if the deacylation was to proceed via a nucleophilic fluoride attack then added base should have a negligible impact on the reaction rates. When a TBAF-catalysed deacylation of the cellulose ester 213 was carried out in the presence of Na₂CO₃, Edgar and co-workers observed a significant increase in the rate of the deacylation at O-6, supporting the operation of the general base mechanism.

Furthermore, in their initial experiments using TBAF, they noticed that as the reaction progressed, the rate of the deacylation gradually decreased, eventually dropping to zero,
even in the presence of excess TBAF. Edgar et al. assumed that acetic acid, which was generated as a side product during the deacylation, might hinder a base-catalysed reaction, while it should have no effect if the reaction proceeded via nucleophilic catalysis, assuming it does not protonate TBAF under the reaction condition. When they performed a TBAF-catalysed deacylation with an excess of acetic acid added at the start of the reaction, deacylation of the cellulose ester was not observed. The data from this experiment strongly supports a general base mechanism for the fluoride-catalysed deacylation at O-6.

Although, Edgar and co-workers initially hypothesised that the fluoride ion could act as a nucleophilic catalyst in promoting the deacylation of cellulose esters, KIEs and experimental data indicated the occurrence of an E1cb mechanism and general base mechanism of the deacylation at O-2/3 and O-6, respectively. Therefore, the role of the fluoride ion as a nucleophilic catalyst in this scenario was not confirmed.

Further efforts to prove nucleophilic catalysis by the fluoride ion were described by Reboul et al. They claimed that the fluoride ion was acting as a nucleophilic catalyst in the synthesis of 1,4-benzothiazepine from cyclic sulfenamide and the electron-deficient acetylene, reported by Reboul et al.

The first proposed mechanism for the formation of 1,4-benzothiazepine is depicted in Scheme 1.60. The authors hypothesised that F⁻ attacks the electron deficient acetylene, generating an anionic intermediate, which upon protonation leads to the formation of fluoroalkene (Z major). Subsequent reaction of with sulfenamide, followed by an addition-elimination process involving intermediate, results in the formation of the desired product (Scheme 1.60).
Scheme 1.60 Plausible mechanism of the fluoride-catalysed synthesis of 1,4-benzothiazepine 228 suggested by the authors.\cite{207}

Despite the spectroscopic evidence that confirmed the presence of fluoroalkene 230 in the crude product (<5\% by $^1$H NMR spectroscopic analysis), Reboul et al. proposed an alternative mechanism for the synthesis of 228, proposing involvement of F$^-$ as a nucleophilic catalyst once again (Scheme 1.61).

Scheme 1.61 Alternative mechanism for the synthesis of 1,4-benzothiazepine 228, promoted by nucleophilic fluoride ion catalysis.
The first step of the mechanism in Scheme 1.61 involves the fluoride ion attacking the sulfenamide 226, producing sulfenyl fluoride 232. The conjugate addition of 232 to the acetylene 227 results in the formation of the carbanion intermediate 233, which upon cyclisation renders the desired product 228.

As the sulfenyl fluoride intermediate 232 is highly unstable, Reboul et al. were not able to isolate it as proof of the nucleophilic attack of the fluoride ion on sulfenamide 226. However, in an effort to ascertain if the nucleophilic attack of the fluoride ion is indeed taking place, they reacted 226 with CsF in stoichiometric amounts, generating sulfenyl fluoride 232 in situ, which in the presence of water should form disulfide 234. Indeed, upon precipitation from a large amount of water, disulfide 234 was isolated in 20% yield. (Scheme 1.62).

**Scheme 1.62** Synthesis of disulfide 234.

Whether the isolation of disulfide 234 provides plausible evidence to support the existence of sulfenyl fluoride 232 as the key intermediate in the synthesis of 228 is still debatable. Therefore, the role of the fluoride ion as a nucleophilic catalyst in organic synthesis has yet to be conclusively proven.

### 1.4.2 Chiral quaternary ammonium fluorides and their use in asymmetric C-C bond forming reactions

Quaternary ammonium fluorides, especially tetraalkylammonium fluorides, have been established as a convenient source of “naked” fluoride ion in organic synthesis.\(^{198,208,209}\) Over the years, they have been successfully employed in many asymmetric C-C bond forming reactions.\(^{198,210,211}\)

The first example detailing a chiral quaternary ammonium fluoride as a catalyst in asymmetric synthesis was reported in 1978 by Wynberg et al.\(^{212}\) They studied the
asymmetric Michael-type addition of nitromethane (78) to chalcone (79). The chiral ammonium fluorides were generated in situ from the corresponding bromide salt 235 and quinine-derived chloride salt 236 via an anion exchange with excess KF (Scheme 1.63).

Scheme 1.63 The asymmetric Michael addition of nitromethane (78) to chalcone (79), catalysed by chiral ammonium fluoride salts, generated in situ through anion exchange with KF.

Albeit obtaining γ-nitroketone 84 in a low enantiomeric excess, this reaction encouraged further development of the in situ generation of chiral quaternary ammonium fluorides as a catalytic strategy. This was rather advantageous, as many anhydrous ammonium fluoride salts are extremely hygroscopic and therefore often difficult to prepare and purify.

In 2001, Maruoka et al. demonstrated the utility of the in situ generation of chiral quaternary ammonium fluorides in the asymmetric aldol reaction between various aldehydes and trimethylsilyl enol ether 239 (Scheme 1.63). The catalysts employed in this transformation were structurally rigid, $C_2$-symmetric quaternary ammonium hydrogen sulfates 237a and 237b. Upon mixing of these catalysts with KF·2H$_2$O – resulting in the generation of the fluoride analogues 238 – and subsequent treatment with the appropriate aldehyde and 239, the desired β-hydroxy ketone 240 was obtained in excellent yield and with moderate to excellent stereoselectivity. The enantioselectivity of the major erythro isomer was significantly increased with the use of catalyst 237b possessing a trifluoromethyl group on the aryl moiety of the catalyst scaffold. In addition, the use of toluene as a co-solvent resulted in a further improvement of both diastereo- and enantioselectivity of the reaction.
Scheme 1.63 An asymmetric aldol reaction, promoted by the \textit{in situ} generated chiral \( C_2 \)-symmetric quaternary ammonium fluorides 238, developed by Maruoka \textit{et al.}\textsuperscript{213}

The \textit{in situ} generated chiral quaternary ammonium fluoride 238b was efficiently applied to the synthesis of the optically active ester 243 via alkylative kinetic resolution of the secondary alkyl halide 242. A subsequent base-mediated hydrolysis of 242 resulted in the formation of the enantioenriched secondary alcohol 244 (Scheme 1.64).\textsuperscript{214}

Scheme 1.64 The alkylative kinetic resolution of secondary alkyl halide 242, promoted by the \textit{in situ} generated chiral quaternary ammonium fluoride 238b.\textsuperscript{214}

In 1993, Shiori \textit{et al.}\textsuperscript{215} instigated the possibility of preparing chiral quaternary ammonium fluoride salts by methods other than the \textit{in situ} anion exchange with KF or
KF·2H₂O. This led to the development of four different procedures for the generation of fluoride salts, as illustrated in Figure 1.16.

\[
\begin{align*}
\text{Method:} & \\
\text{A} & \text{1. Amberlite IRA-410 } F^- \text{ form; 2. Evaporation} \\
\text{B} & \text{1. Amberlyst A-28 } F^- \text{ form; 2. Evaporation} \\
\text{C} & \text{1. Amberlyst A-26 } \text{OH form; 2. 1 N HF; 3. Evaporation} \\
\text{D} & \text{1. AgF; 2. Filtration; 3. Evaporation}
\end{align*}
\]

**Figure 1.16** Various methods for the preparation of chiral quaternary ammonium fluoride salts, developed by Shiori et al.\(^{215}\)

Anion exchange resins in their \( F^- \) form were used in method A and B, while neutralisation with the ammonium hydroxide and a subsequent fluoridation with HF was involved in method C. A direct anion exchange with silver fluoride was employed in method D. \(^1\)H NMR spectroscopic analysis of \( N \)-benzylcinchonium fluoride (245) indicated no decomposition of the catalyst and the presence of the fluoride counterion was confirmed by \(^{19}\)F NMR spectroscopic analysis, employing CFCI₃ as an internal standard.

The performance of catalyst 245 prepared by four different methods was evaluated in the asymmetric aldol reaction between the enol silyl ether of 2-methyl-1-tetralone 246 with benzaldehyde (Scheme 1.65).\(^{215}\)

\[
\begin{align*}
\text{Scheme 1.65} & \text{ Evaluation of catalyst 245, prepared via four different procedures.}\(^{215}\)
\end{align*}
\]
According to the data presented in Scheme 1.65, the catalytic activity and selectivity of the fluoride catalyst 245 is independent of the preparation method, as the chemical yield and stereoselectivity of 247 were comparable in each case.

Shiori and co-workers\(^{216}\) also examined the effect of 245 and its pseudo-enantiomer 250 on the stereochemical outcome of the asymmetric aldol reaction of the enol silyl ethers derived from acetophenone 248 and pinacolone 249 with benzaldehyde. The pseudo-enantiomer of 245 (i.e. 250) promoted the formation of the opposite enantiomer of the aldol product (Scheme 1.66).

![Scheme 1.66 The influence of 245 and its pseudo-enantiomer 250 on the stereochemical outcome of the asymmetric aldol reaction.\(^{216}\)](image)

In 1999, Corey and Zhang\(^{217}\) developed an effective chiral quaternary ammonium fluoride catalyst 254, bearing a 9-anthracenylmethyl substituent on the quinuclidine ring moiety (Scheme 1.67).

![Scheme 1.67 The enantioselective nitroaldol reaction of protected (S)-phenylalaninal 253 with nitromethane, promoted by a chiral quaternary fluoride 254.\(^{217}\)](image)
Catalyst 254 efficiently promoted the enantioselective nitroaldol reaction of nitromethane with protected (S)-phenylalaninal 253, furnishing 255 in 86% yield and excellent diastereoselectivity (17:1 dr). The nitro alcohol 255 allows for a direct synthesis of amprenavir 256, an important second generation of HIV protease inhibitor (Scheme 1.67).

1.4.3 Chiral quaternary ammonium bifluorides and their use in asymmetric C-C bond forming reactions

Anhydrous tetraalkylammonium fluorides are known to undergo intramolecular self-destruction of the tetraalkylammonium cation via Hoffman elimination, leading to the formation of tetraalkylammonium bifluoride (Scheme 1.68).

Scheme 1.68 Decomposition of tetraalkylammonium fluoride via Hofmann elimination.

The stability of tetraalkylammonium bifluoride is higher compared to the parent fluoride, and therefore it should be easier to handle. Regardless of this advantage, there are only a few examples where bifluoride catalysts have been efficiently employed in asymmetric C-C bond forming reactions.

A cinchonidine-derived bifluoride catalyst 259, developed by Corey and co-workers, has been successfully employed in the Mukaiyama-type aldol reaction of ketene silyl acetal 258 with aldehydes such as 257. The bifluoride catalyst 259 promoted the formation of mostly syn-β-hydroxy-α-amino ester 262 as the major diastereomer in excellent enantiomeric excess (Scheme 1.69).
Scheme 1.69  The Mukaiyama-type aldol reaction promoted by bifluoride salt 259.\textsuperscript{218}

Maruoka \textit{et al}.\textsuperscript{219} investigated the asymmetric nitroaldol reaction of silyl nitronates such as 263 with aldehydes, promoted by chiral bifluorides, \textit{e.g.} 264 and 265. While catalyst 264 promoted the formation of nitroalkanol 266 in only 33\% ee (\textit{anti} isomer), both diastereo- and enantioselectivity of 266 were drastically improved with the use of catalyst 265. The selectivity of catalyst 265 was enhanced with a radially extended 3,3’-aromatic substituent, bearing a 3,5-bistrifluoromethyl group. The desired product 266 was furnished in 95\% ee and excellent diastereoselectivity (92:8 \textit{dr}, Scheme 1.70).\textsuperscript{219}

Scheme 1.70  An asymmetric nitroaldol reaction promoted by chiral \textit{C}_{2}\text{-symmetric quaternary ammonium bifluorides 264} and 265.\textsuperscript{219}

During the course of their studies, Maruoka and co-workers\textsuperscript{220} expanded the scope of the asymmetric nitroaldol reaction to \(\alpha,\beta\)-unsaturated aldehydes, such as \textit{trans-}...
cinnamaldehyde (267). Upon evaluation of various chiral $C_2$-symmetric quaternary ammonium bifluorides, catalyst 269 was found to promote the formation of silyl enol ethers 270 and 271 in excellent yields, with good diastereo- and excellent enantioselectivities (Scheme 1.71).

![Scheme 1.71](image)

**Scheme 1.71** The asymmetric nitroaldol reaction to trans-cinnamaldehydes, catalysed by the chiral bifluoride salt 269.220

The major synthetic advantage of this approach is the generation of highly regio- and stereoselective enol silyl ethers of the optically active $\gamma$-nitroaldehydes (*i.e.* 270 and 271), which represent attractive Mukaiyama donors, often not readily accessible by general asymmetric methods.220

### 1.5 Asymmetric desymmetrisation of meso-anhydrides

#### 1.5.1 Introduction

Asymmetric desymmetrisation is a powerful methodology for the synthesis of multiple stereocentres in one symmetry-breaking process.221 The highly stereoselective products of asymmetric desymmetrisation are often regarded as attractive and versatile building blocks in organic chemistry, frequently employed in the synthesis of complex natural products and bioactive substances.222 Cyclic meso-anhydrides such as 272 are among widespread substrates used in desymmetrisation reactions, resulting in the formation of hemisesters such as 273, which can undergo a variety of useful transformations. The
desymmetrisation of meso-anhydrides occurs by a direct nucleophilic ring opening process (Figure 1.17).

![Figure 1.17](image_url)

**Figure 1.17** The asymmetric desymmetrisation of meso-anhydrides by a direct nucleophilic ring opening.\textsuperscript{223}

Since the seminal review of asymmetric desymmetrisation by Willis\textsuperscript{224} in 1999, a plethora of novel, structurally diverse organocatalysts have been successfully employed in the asymmetric desymmetrisation of meso-anhydrides. Over the years, progress in this field has been efficiently compiled into a number of comprehensive reviews.\textsuperscript{222,223,225–227}

### 1.5.2 Methanolysis: seminal studies

Among a variety of nucleophiles used in the ring opening of cyclic meso-anhydrides, alcohols have been studied extensively.\textsuperscript{226} Initial attempts at the organocatalysed desymmetrisation of cyclic meso-anhydrides, employing methanol as a nucleophile, was carried out by independent groups led by Oda\textsuperscript{228} and Aitken,\textsuperscript{229} in the late 1980s. The nucleophilic ring opening of meso-anhydrides was promoted by cinchona alkaloids; quinine (39) and quinidine (41), furnishing the desired products in low to moderate enantiomeric excess (Scheme 1.72).

![Scheme 1.72](image_url)

**Scheme 1.72** Seminal studies on the asymmetric desymmetrisation of meso-anhydrides by Oda\textsuperscript{228} (A) and Aitken\textsuperscript{229} (B). (For substrate scope, see ref. 228 and 229)

The first major achievement regarding a highly enantioselective desymmetrisation of various meso-anhydrides, was reported by Bolm et al.\textsuperscript{230} in 2000. The nucleophilic attack was promoted by quinine (39) and quinidine (41), affording the hemiester
products in almost quantititative yield and excellent enantiocontrol. A quinidine-promoted desymmetrisation furnished products in slightly higher ee in comparison to a quinine-catalysed methanolysis (Scheme 1.73).

Scheme 1.73 The first highly enantioselective ring opening of meso-anhydrides, mediated by cinchona alkaloids.\textsuperscript{230}

Although Bolm and co-workers\textsuperscript{230} managed to obtain hemiesters in high yields and excellent enantioselectivities, the main drawback associated with their protocol was the necessity for stoichiometric catalyst loadings to achieve efficient desymmetrisation.

\textbf{1.5.2.1 Mechanistic models}

The exact mechanism by which the desymmetrisation reactions occur is, to date, still under debate. However, two possible mechanistic pathways have been considered.\textsuperscript{227} The first mechanism involves general base catalysis, where the catalyst contributes to the attack of the pronucleophile on one of the two prochiral carbonyl groups through a concerted deprotonation (Scheme 1.74, A). The other mechanism proceeds via nucleophilic catalysis, where initially the chiral amine selectively attacks one of the two carbonyl groups, following displacement by the nucleophile (Scheme 1.74, B).
It has been postulated, that if the base used in a desymmetrisation reaction is sterically hindered then it is more likely for the reaction to proceed via general base catalysis. Conversely, less bulky bases, e.g. DMAP, might catalyse the reaction via nucleophilic mechanism. As the nature of the catalyst could influence the course of the reaction, it is difficult to precisely determine the specific mechanistic pathway of the desymmetrisation. In addition, it has been speculated that in certain systems both mechanisms might be operating simultaneously.

### 1.5.2.2 Enantioselective methanolysis of meso-anhydrides by bifunctional cinchona alkaloid-derived organocatalysts

In the past, our group has investigated the use of bifunctional cinchona alkaloid-derived organocatalysts as efficient promoters in various asymmetric transformations. The asymmetric desymmetrisation of meso-anhydrides, mediated by C-9 thio(urea)-substituted cinchona alkaloid-based catalysts, e.g. 81 and 283, have also been studied by our group. It was envisaged that these bifunctional organocatalysts could selectively bind and activate the anhydride electrophile via hydrogen bonding to the thio(urea) moiety, while simultaneously initiating the attack at a single anhydride carbonyl moiety via general base catalysis by a chiral quinuclidine base. Based on these assumptions, it was anticipated that the reaction products would form faster and with improved selectivity.
Upon the initial catalyst evaluation in the asymmetric methanolation of succinic anhydride 274, quinine-derived thiourea-substituted catalyst 81 was found to be the most effective. It promoted the formation of hemiester 285 with the highest enantiomeric excess in literature at that time of 96% ee at very low catalyst loading (1 mol%, Scheme 1.75). The use of ethereal solvent, i.e. MTBE, was absolutely crucial in achieving highly enantioselective methanolation of 274.

![Scheme 1.75](image)

**Scheme 1.75** Catalyst screening in the enantioselective methanolation of succinic anhydride 274 under optimised reaction conditions.\(^ {238}\)

The prowess of the bifunctional catalyst 81 was demonstrated in the methanolation of a myriad of succinic 274-282 and glutaric 286-287 anhydride derivatives, furnishing the corresponding hemiesters in both excellent yield and enantioselectivity (Scheme 1.76).

![Scheme 1.76](image)

**Scheme 1.76** Enantioselective methanolation of succinic and glutaric anhydrides.\(^ {238}\)
Results and discussion
2 Enantioselective S\textsubscript{N}2 alkylation of 2-oxindole derivatives by asymmetric phase-transfer catalysis

2.1 Design rationale of an ester-substituted oxindole substrate

As outlined in Section 1.3.1.1, there are not many examples of the enantioselective S\textsubscript{N}2-type alkylations of 2-oxindole derivatives under phase-transfer catalysed reaction conditions.\textsuperscript{172–176} Most of the previously studied oxindole-based substrates were substituted with either an alkyl or aryl group at the C-3 position (Figure 2.1). The alkylation of such compounds often leads to products with poor synthetic value.

![Figure 2.1 C-3-substituted oxindole-based substrates previously studied by other groups.\textsuperscript{172–176}](image)

In an effort to generate synthetically more malleable alkylated products, we were intrigued by the possibility of utilising the ester-substituted analogues of 2-oxindole derivatives, \textit{i.e.} 288 (Figure 2.2) in the S\textsubscript{N}2-type alkylation reactions.

![Figure 2.2 General structure for the synthetically malleable ester-substituted 2-oxindole derivative.](image)

Although the ester functionality made the substrate synthetically more attractive, it also contributed to certain challenges by increasing the acidity and the potential for base-mediated degradation. To the best of our knowledge, no such substrate has ever been used in the phase-transfer catalysed S\textsubscript{N}2-type alkylation reactions. Therefore, we embarked upon the opportunity to attempt the alkylation of such challenging 2-oxindole derivatives.
2.1.1 Synthetic route towards di-ester-substituted 2-oxindoles

The number of efficient synthetic procedures describing the acylation of 2-oxindoles unsubstituted at the C-3 position are very limited. The preceding synthetic protocols lead to the formation of the diacylated products often in poor yields. In order to develop a more efficient route for the synthesis of the diacylated oxindoles of general type, Simig et al. treated 2-oxindole (289) with triethylamine and chloroformic acid ester 290, generating the N,O-diacylated 2-oxindole analogue 291. Upon rearrangement of 291 in the presence of the stoichiometric amount of DMAP and subsequent acidic work-up, the desired diacylated 2-oxindole derivatives 292 were obtained in very good yield (Scheme 2.1).

![Scheme 2.1](image)

Scheme 2.1 General synthetic route towards the formation of C,N-bis-ester-substituted 2-oxindole derivatives 292, developed by Simig and co-workers.

The C,N-bis-ester-substituted oxindole derivatives normally exist in two tautomeric forms, a keto tautomer 292 and an enol tautomer 292-a, generally occurring in a ratio of 1:1 (Figure 2.3).

![Figure 2.3](image)

Figure 2.3 Two tautomeric forms of C,N-di-ester-substituted oxindole derivatives.

The derivative 294 was selected as the substrate for preliminary investigations into the phase-transfer catalysed alkylation. It was synthesised according to the modified protocol developed by Simig et al., employing ethyl chloroformate (Scheme 2.2). ^1H NMR spectroscopic analysis of substrate 294 in CDCl₃ at 25 °C confirmed the presence of both tautomers in a ratio of 1:1.
**Scheme 2.2** Synthesis of diethyl 2-oxoindoline-1,3-dicarboxylate (294).

### 2.2 Preliminary studies into S$\text{N}_2$ alkylation of 294 under phase-transfer catalysis

Prior to performing the enantioselective S$\text{N}_2$ alkylation, we initially investigated the activity of an achiral phase-transfer catalyst, i.e. Bu$_4$NBr (TBAB), in the alkylation of 294. It was envisaged that TBAB could mimic the catalytic behaviour of cinchona alkaloid-derived PTCs, which we eventually intended to employ in the enantioselective variant of the alkylation reaction.

The preliminary PTC alkylation of oxindole substrate 294 was carried out with benzyl bromide (BnBr) in the presence of an aqueous base K$_2$CO$_3$ and TBAB. Gratifyingly, we observed the formation of the alkylated product 295 in 97% yield after just 4 h (Scheme 2.3).

**Scheme 2.3** Initial alkylation of 294 in the presence of an aqueous base K$_2$CO$_3$, promoted by an achiral TBAB.

Unfortunately, when a similar alkylation reaction was carried out in the absence of a catalyst, the alkylated product 295 was detected with 8% conversion after 6 h. In an effort to find a suitable base that would suppress this background reaction (i.e. the uncatalysed reaction), yet still promote the formation of 295 in a quantitative yield in the presence of a PTC, we evaluated a variety of bases of different strengths in the
model PTC alkylation reaction. K₂HPO₄ in conjunction with TBAB afforded the formation of 295 in full conversion after 4 h (Table 2.1, entry 1), while the background reaction was suppressed until nearly 6 h (2%, entry 2). The reaction in the presence of a weaker base NaHCO₃ and TBAB proceeded rather sluggishly, furnishing almost full conversion of 295 after 6 h (95%, entry 3), while 2% of product was observed in the uncatalysed reaction after 8 h (entry 4). Based on the efficiency of the product formation and the longest suppression of the background reaction, K₂HPO₄ was selected as the base of choice for further optimisation studies.

Table 2.1 Evaluation of weaker bases in the model alkylation reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>TBAB (mol%)</th>
<th>time (h)</th>
<th>conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂HPO₄</td>
<td>5</td>
<td>4</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>K₂HPO₄</td>
<td>0</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>NaHCO₃</td>
<td>5</td>
<td>6</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>NaHCO₃</td>
<td>0</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>

*Determined by ¹H NMR spectroscopic analysis using p-iodoanisole as an internal standard.*

With an optimal base for the alkylation of 294 in hand, we investigated the necessary quantity of base required for an efficient generation of the enolate of 294, in the presence of a PTC, which would effectively lead to the quantitative formation of 295. Upon conducting the equivalency studies using K₂HPO₄, it was observed that 2.0 equivalents of base, in the presence of TBAB, furnished 295 in full conversion (Table 2.2, entry 1), while it took almost 2 h longer to obtain 295 in a quantitative conversion with 1.5 equivalents of K₂HPO₄ under the catalytic conditions (entry 3) as full conversion was not observed after 4 h. Furthermore, it was established that 1.0 equivalents of base, in the presence of TBAB, did not afford satisfactory conversion of 295 (83% after 6 h, entry 5). Therefore, it was concluded that 2.0 equivalents of K₂HPO₄ were required for an efficient alkylation of 294 under TBAB-catalysed reaction conditions.
Further studies were focused on the influence of solvent on the outcome of the reaction. Although CHCl$_3$ enhanced the rate of catalysis (entry 7), the background reaction also accelerated (entry 8). Both EtOAc and MTBE were found to be unsatisfactory solvents for the reaction as extremely low conversions were detected (33% and 15%, respectively, entries 9 and 11). Moreover, the reactants failed to fully dissolve in MTBE, which could potentially be one of the reasons for such a low conversion. Thus, CH$_2$Cl$_2$ remained the preferred solvent for the model PTC alkylation reaction.

**Table 2.2** Further optimisation of the reaction conditions of the model TBAB-catalysed alkylation reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>base equivalence</th>
<th>solvent</th>
<th>TBAB (mol%)</th>
<th>time (h)</th>
<th>conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0</td>
<td>CH$_2$Cl$_2$</td>
<td>5</td>
<td>4</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>CH$_2$Cl$_2$</td>
<td>0</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>CH$_2$Cl$_2$</td>
<td>5</td>
<td>6</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>CH$_2$Cl$_2$</td>
<td>0</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>1.0</td>
<td>CH$_2$Cl$_2$</td>
<td>5</td>
<td>6</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>1.0</td>
<td>CH$_2$Cl$_2$</td>
<td>0</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>2.0</td>
<td>CHCl$_3$</td>
<td>5</td>
<td>3</td>
<td>&gt;99</td>
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<tr>
<td>8</td>
<td>2.0</td>
<td>CHCl$_3$</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>2.0</td>
<td>EtOAC</td>
<td>5</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>10</td>
<td>2.0</td>
<td>EtOAc</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>11</td>
<td>2.0</td>
<td>MTBE</td>
<td>5</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>12</td>
<td>2.0</td>
<td>MTBE</td>
<td>0</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

* Determined by $^1$H NMR spectroscopic analysis using $p$-iodoanisole as an internal standard.
2.2.1 Initial attempts at the enantioselective $S_N2$ alkylation of 294 promoted by chiral phase-transfer catalysts

Encouraged by the results obtained from the preliminary studies on the benzylation of 294 promoted by TBAB, we decided to perform the model alkylation reaction enantioselectively, in the presence of a chiral phase-transfer catalyst. Previously, Dr. Emiliano Sorrentino, a fellow researcher in our group, had investigated the potential of cinchona alkaloid-derived PTCs in the alkylation of oxindole-based substrates such as 181 (Scheme 1.46, *vide supra*). During the course of his PhD studies, Dr. Sorrentino generated a library of C-9 urea-substituted bifunctional cinchona alkaloid-derived PTCs (Figure 2.4), which was available at the outset of our investigation.

![Figure 2.4](image_url)

Figure 2.4 Library of chiral catalysts, generated by Dr. Sorrentino.

Evaluation of these chiral phase-transfer catalysts in the model alkylation of 294, employing the optimised reaction conditions, led to rather disappointing results. It was observed that the catalytic activity of bifunctional cinchona alkaloid-derived PTCs was significantly lower compared to the activity of the achiral TBAB. While full conversion of 295 was obtained with TBAB under optimised PTC conditions (see Table 2.2, entry 1), the highest conversion in the presence of a chiral catalyst was no more than 23%.
(Table 2.3, entry 2), obtained within the restricted time frame of 4 h to avoid the onset of unwanted background reaction.

**Table 2.3** Evaluation of different bifunctional cinchona alkaloid-derived PTCs in the model alkylation reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>conversion (%)(^a)</th>
<th>ee (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>106</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>296</td>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>297</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>299</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>300</td>
<td>7</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>298</td>
<td>12</td>
<td>-9</td>
</tr>
</tbody>
</table>

\(^a\)Determined by \(^1\)H NMR spectroscopic analysis using \(p\)-idoanisole as an internal standard. \(^b\)Determined by CSP-HPLC.

In addition to poor conversion, the enantioselectivity of alkylated 295 was also very low. The highest enantiomeric excess was achieved with \(N\)-benzylated catalyst 106 (24% ee, Table 2.3, entry 1), while the presence of the electron-donating tert-butyl substituents on the benzyl moiety on the quinuclidine resulted in decreased ee (entry 2). The performance of catalyst 297 was comparable to that of catalyst 296, albeit in slightly lower yield (entry 3). An almost racemic product was obtained with \(N\)-anthracenylethyl catalyst 299 (entry 4). Interestingly, the same catalyst bearing a phenyl substituent at the C-2’ position of the quinoline moiety (i.e. 300), afforded product 295 with 22% ee (entry 5). Such a major improvement in the selectivity of the catalyst clearly demonstrates the importance of substitution at the C-2’ position. It is noteworthy to mention a complete inversion of stereochemistry was observed using catalyst 298, possessing a 2,6-dichlorobenzyl group on the quinuclidine nitrogen atom (entry 6). This drastic change could perhaps be attributed to the ortho-substitution on the benzyl moiety, leading to a conformational change in the catalyst by blocking a region of space which is crucial for enantioselective discrimination.
2.3 Alternative strategies for the enolate generation in a phase-transfer catalysed reaction system

As the current optimised reaction conditions employing an aqueous base for the enantioselective alkylation of 294 did not lead to a reasonable conversion within 4 h, we decided to investigate the alternative methods for the generation of the enolate of 294 in the presence of a PTC.

2.3.1 Solid inorganic bases

The solid-liquid PTC system has been known from as early as mid-1970s and since then, a range of solid inorganic bases have been efficiently employed in many organic transformations. Solid base was often employed as an alternative to an aqueous base in reactions where the components were susceptible to hydrolysis. Although, our reagents were unlikely to undergo hydrolysis, we intended to develop a more effective reaction system that would lead to enhanced conversion of products with ideally no background reaction. It was envisaged that solid base, in the presence of a catalyst, would efficiently deprotonate 294, and thus lead to an improved product yield.

We evaluated a range of different solid inorganic bases in the model alkylation reaction and to our disappointment, the conversion of the product was very low. The initial TBAB-catalysed experiment with solid K₂CO₃ at 0 °C afforded 295 in 19% yield (Table 2.4, entry 1), however the background reaction was also observed (7%, entry 2). In order to inhibit the background reaction, the temperature of the reaction was decreased to -30 °C. Unfortunately, this change did not lead to any superior results. The conversion of the catalysed reaction in the presence of solid K₂CO₃ was only 7% (entry 3), while the uncatalysed reaction remained suppressed (entry 4). The use of a weaker K₂HPO₄ afforded 295 in even lower conversion (entry 5), while the reaction carried out in the absence of TBAB was not occurring to any significant degree (entry 6). Furthermore, TBAB-catalysed reactions carried out in the presence of other weak solid bases, such as Na₂CO₃ and Cs₂CO₃, resulted in a barely detectable conversion after 8 days and therefore are not included in Table 2.4.
Table 2.4  Evaluation of solid inorganic bases in the model PTC alkylation reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>TBAB (mol%)</th>
<th>temp. (˚C)</th>
<th>time (h)</th>
<th>conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂CO₃</td>
<td>5</td>
<td>0</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>K₂CO₃</td>
<td>0</td>
<td>0</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>K₂CO₃</td>
<td>5</td>
<td>-30</td>
<td>120</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>K₂CO₃</td>
<td>0</td>
<td>-30</td>
<td>120</td>
<td>1</td>
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<tr>
<td>5</td>
<td>K₂HPO₄</td>
<td>5</td>
<td>-30</td>
<td>120</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>K₂HPO₄</td>
<td>0</td>
<td>-30</td>
<td>120</td>
<td>1</td>
</tr>
</tbody>
</table>

*Determined by ¹H NMR spectroscopic analysis using p-iodoanisole as an internal standard.

2.3.2 Phosphazene bases

In the desire to establish reaction conditions that would allow for an effective alkylation of 294 in a PTC system, we explored the possibility of generating the enolate by the use of a phosphazene base. Phosphazene bases are also known as ‘organic superbases’ due to their high basicity and low nucleophilicity (Figure 2.5). Over the years, they have been efficiently used in many organic transformations.²⁴⁴,³¹

Figure 2.5  Representative examples of phosphazene bases.

In particular, P₁-tBu phosphazene base has been successfully employed in the asymmetric PTC alkylation-type reactions leading to the formation of amino acids.²⁴⁵–²⁴⁷ We anticipated that at low temperature P₁-tBu phosphazene base would lead to the rapid deprotonation of 294, resulting in the formation of the stabilised enolate 305 which might bind to the catalyst in preference to the soft phosphazene cation 306 (Scheme 2.4), hence leading to more efficient product formation.
Scheme 2.4 Hypothesised binding of the enolate 305 to the quaternary ammonium cation of a PTC.

Evaluation of 301 in the uncatalysed alkylation of 294 at -30 °C resulted in the formation of 295 in 30% conversion (Table 2.4, entry 1). Even at a much lower temperature (i.e. -70 °C), the conversion of 295 was already 4% (entry 2). Needless to say, the rate of the uncatalysed reaction was very high, suggesting a rapid deprotonation of 294, even in the absence of TBAB, which led to a subsequent formation of 295.

Table 2.5 Evaluation of phosphazene base P$_{1}$-tBu 301 in the model PTC alkylation.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>temp. (˚C)</th>
<th>time (h)</th>
<th>conv. (%)$^a$</th>
<th>ee (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>---</td>
<td>-30</td>
<td>2</td>
<td>30</td>
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<tr>
<td>2</td>
<td>---</td>
<td>-70</td>
<td>2</td>
<td>4</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>106</td>
<td>-70</td>
<td>1</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

$^a$Determined by $^1$H NMR spectroscopic analysis using p-iodoanisole as an internal standard. $^b$Determined by CSP-HPLC.

Although the use of a phosphazene base did not deliver an efficient system for a TBAB-catalysed alkylation, we pondered whether reasonable conversion could be achieved in the presence of a chiral catalyst. It was observed that in the presence of N-benzyl catalyst 106, the alkylated product 295 was obtained with a very low conversion of only 10% (entry 3). This suggests a rather inefficient binding of the catalyst cation to the enolate, which also had an adverse effect on the enantioselectivity (4% ee, entry 3).
2.3.3 The use of buffers

Since none of the reaction conditions involving base additives led to the development of an efficient PTC system for the model alkylation, we decided to explore other options, which did not involve the direct use of bases. An alternative approach that we assumed might be worthwhile to investigate was based on buffers. A buffer is an aqueous solution of either a weak acid and its conjugate base or a weak base and its conjugate acid. Thus, it is able to maintain a stable pH in a solution by neutralising small quantities of added base or acid.\textsuperscript{248}

We theorised that by utilising a buffer as the aqueous phase of a PTC system at a neutral pH, we could achieve an efficient deprotonation of the substrate by its weakly basic component. Simultaneously a neutral pH of the aqueous phase could be maintained by quenching the acid generated during deprotonation \textit{in situ}, which we thought might have a substantial influence on the effectiveness of the deprotonation. It was postulated that \textit{in situ} generated acid might lead to an unwanted protonation of the enolate anion, forcing the equilibrium towards the enol rather than the enolate.

To test our hypothesis, a phosphate buffer (0.1 M) of pH 7 was prepared by following a method reported in Cold Spring Harbor Protocols.\textsuperscript{249} The preliminary studies indicated that in the presence of a buffer and TBAB, the alkylated product 295 was formed quantitatively (Table 2.6, entry 1).

\textbf{Table 2.6} Evaluation of a phosphate buffer in the model PTC alkylation reaction.

\begin{table}[h]
\centering
\begin{tabular}{cccccc}
\hline
\textbf{entry} & \textbf{buffer conc. (M)} & \textbf{TBAB (mol\%)} & \textbf{time (h)} & \textbf{conversion (\%)} \\
\hline
1 & 0.1 & 5 & 4 & >99 \\
2 & 0.1 & 0 & 4 & 2 \\
3 & 0.01 & 5 & 22 & 67 \\
4 & 0.01 & 0 & 22 & 6 \\
\hline
\end{tabular}
\caption{Evaluation of a phosphate buffer in the model PTC alkylation reaction.}
\end{table}

\textsuperscript{a}Determined by \textsuperscript{1}H NMR spectroscopic analysis using \textit{p}-iodoanisole as an internal standard.
Unfortunately, the uncatalysed reaction was also observed (entry 2). By decreasing the concentration of buffer to 0.01 M, the background reaction remained suppressed for almost 22 h (entry 4), however diminished catalytic activity of TBAB was also observed. It was postulated that the lower buffer concentration was probably insufficient to achieve an effective deprotonation of 294 in the presence of a catalyst, resulting in a moderate conversion (67%, entry 3).

2.3.4 The use of water

As previously mentioned in Section 1.3.1.2, Maruoka et al.\textsuperscript{195} performed the enantioselective conjugate additions of 3-phenyl oxindole derivatives to β-nitrostyrene catalysed by PTCs in the absence of base in a water-rich solvent system (see Scheme 1.51). Taking our cue from their studies, we envisaged that by employing base-free neutral reaction conditions, we might be able to develop an effective PTC system for the benzylation of 294. We already knew that the enolate formation did not require a strong base, in fact, a partial deprotonation of 294 in the catalysed reaction was observed even in the presence of a very dilute buffer (see Table 2.6, entry 3). Thus, we were hopeful that the catalyst would be able to deprotonate 294 and chaperone the resulting enolate anion in the aqueous solution across the interface to the organic phase.

The initial experiments conducted in a base-free CH\textsubscript{2}Cl\textsubscript{2}/H\textsubscript{2}O biphasic PTC reaction system led to several interesting observations. TBAB failed to efficiently catalyse the reaction, affording only 23% conversion after 72 h (Table 2.7, entry 1). However, it was noticed that the uncatalysed reaction remained suppressed even after 72 h (0%, entry 2). In fact, further studies showed that the background reaction was not detected until after three weeks. We were delighted to have finally discovered reaction conditions which prevented the uncatalysed reaction from occurring for such a long period of time.

As mentioned previously, the catalysis mediated by TBAB was not favoured in this reaction system. However, as the goal of the project was to perform this reaction enantioselectively, it was decided to evaluate the catalytic activity of a chiral catalyst. Upon performing the reaction under base-free neutral reaction conditions in the presence of a bifunctional cinchona alkaloid-derived phase-transfer catalyst 296, bearing a 3,5-di-tert-butyl benzyl moiety, the desired alkylated product 295 was obtained in full conversion within 48 h, although with poor enantioselectivity (19% ee,
entry 3). In order to enhance the selectivity of the process, we considered it opportune to modify the catalyst structure of 296. Based on the previous observations made during the enantioselective alkylation attempts of the model reaction in the presence of an aqueous base (see Table 2.3), a phenyl substituent at the C-2’ position of the quinoline ring was introduced. We were pleased to observe that the use of 307 in the alkylation of 294 yielded 295 with enhanced enantioselectivity (36% ee, entry 4).

Table 2.7  Evaluation of a base-free neutral solvent system in the model PTC alkylation reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>cat. loading (mol%)</th>
<th>time (h)</th>
<th>conv. (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBAB</td>
<td>5</td>
<td>72</td>
<td>23</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>---</td>
<td>0</td>
<td>72 → 504</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>296</td>
<td>5</td>
<td>48</td>
<td>&gt;99</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>307&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5</td>
<td>48</td>
<td>&gt;99</td>
<td>36</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using p-iodoanisole as an internal standard. <sup>b</sup>Determined by CSP-HPLC. <sup>c</sup>For synthesis see pages 97-98.

From the preliminary studies involving a base-free neutral reaction system, it was observed that TBAB promoted the formation of 295 very sluggishly (Table 2.7, entry 1). In order to explain why the catalytic activity of TBAB was so poor in a base-free neutral reaction system, we hypothesised that this could be due to insufficient lipophilicity of TBAB. Previously, Maruoka <i>et al.</i> investigated the effect of the alkyl chain length of TBAB in the conjugate addition of 3-phenyloxindole to β-nitrostyrene under base-free neutral phase-transfer conditions (see Section 1.3.1.2). Initially, they also observed very sluggish catalysis with TBAB. However, the use of a catalyst with longer, more lipophilic alkyl chain, such as tetrahexylammonium bromide, resulted in more efficient catalysis. Upon further extension of the alkyl chain, <i>i.e.</i> employing...
tetraoctyl- and tetra(decyl)ammonium bromide as catalysts in the conjugate addition reaction, Maruoka and co-workers obtained the desired adducts in almost quantitative yields. These studies strongly support the hypothesis that high lipophilicity of a phase-transfer catalyst, as in cinchona alkaloid-derived PTCs, is important for the efficient promotion of the reaction under base-free neutral reaction conditions.

### 2.3.4.1 Optimisation of a base-free neutral PTC reaction system

In order to determine the effect of different solvents on the enantioselectivity of the reaction, a solvent screening was carried out in the presence of C-2’ phenyl-substituted catalyst 307. It was observed that polarity had a major impact on the product ee. In non-polar solvents, such as PhCH₃ and xylene, product 295 was obtained in encouraging 62% ee and 58% ee, respectively (Table 2.8, entries 1 and 2).

**Table 2.8** Solvent screening in a base-free neutral PTC reaction system.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>time (h)</th>
<th>conv. (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH₃</td>
<td>45</td>
<td>&gt;99</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>xylene</td>
<td>45</td>
<td>&gt;99</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>PhCl</td>
<td>48</td>
<td>&gt;99</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>48</td>
<td>&gt;99</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>EtOAc</td>
<td>48</td>
<td>&gt;99</td>
<td>31</td>
</tr>
<tr>
<td>6</td>
<td>CHCl₃</td>
<td>45</td>
<td>&gt;99</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>hexane</td>
<td>---</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>PhCH₃/hexane (9:1)</td>
<td>45</td>
<td>&gt;99</td>
<td>54</td>
</tr>
</tbody>
</table>

* Determined by ¹H NMR spectroscopic analysis using p-iodoanisole as an internal standard. * Determined by CSP-HPLC. * Reagents insoluble.

While the use of more polar solvents, *i.e.* CH₂Cl₂, EtOAc and CHCl₃, resulted in diminished enantioselectivity (entries 4, 5 and 6, respectively). It was reasoned that the
reaction performed in hexane, an even less polar solvent than PhCH₃, might lead to higher enantioselectivity of 295, however the reagents did not fully dissolve and therefore the reaction was not monitored (entry 7). In order to reduce the polarity of the reaction medium even further, we decided to mix different solvents to generate a mixed solvent system, *i.e.* PhCH₃/hexane (9:1). Unfortunately, we failed to detect any improvement in enantioselectivity of 295 (entry 8). Upon increasing the amount of hexane in the PhCH₃/hexane mixture (*i.e.* 1:1), poor solubility of reagents was again problematic. Based on these observations, we reasoned that there must be a limit to how non-polar a solvent can be until no further improvement in enantioselectivity is possible, providing the solubility of reagents is not compromised. In addition, we assumed that polarity alone is not the only significant factor affecting enantioselectivity and that other factors, *e.g.* density, might be contributing to enantioselectivity in the neutral PTC reaction system.

Upon selecting PhCH₃ as the optimum solvent for the PTC alkylation of 294 under base-free neutral reaction conditions, we decided to study the effect of water on the course of alkylation in the presence of a phase-transfer catalyst 307.

**Table 2.9**  The effect of water in the model PTC alkylation of 294.

<table>
<thead>
<tr>
<th>entry</th>
<th>PhCH₃/H₂O</th>
<th>time (h)</th>
<th>conv. (%)ᵃ</th>
<th>ee (%)ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:0</td>
<td>504</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>1:1</td>
<td>96</td>
<td>83</td>
<td>61</td>
</tr>
<tr>
<td>3ᵃ</td>
<td>1:10</td>
<td>45</td>
<td>&gt;99</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>1:50</td>
<td>72</td>
<td>95</td>
<td>62</td>
</tr>
</tbody>
</table>

ᵃ Determined by ¹H NMR spectroscopic analysis using p-iodoanisole as an internal standard. ᵇ Determined by CSP-HPLC. ᶜ Reported from Table 2.8.
Interestingly, no discernible catalysis was observed in the absence of H$_2$O for at least three weeks (Table 2.9, entry 1). This is indicative of a crucial importance of the presence of H$_2$O in the reaction system for an efficient phase-transfer catalysed alkylation. Furthermore, catalysis proceeding at a slower rate was observed in the 1:1 and 1:50 PhCH$_3$/H$_2$O systems (entries 2 and 4). The ideal rate of catalysis was achieved with a biphasic solvent mixture of PhCH$_3$/H$_2$O in a ratio of 1:10, furnishing 295 in excellent conversion after 45 h (entry 3). It is worth mentioning that the ee of 295 was not affected by different rates of catalysis, i.e. the same enantiomeric excess was detected in each case.

2.3.4.2 Mechanistic insights into a base-free neutral PTC-promoted S$_\text{N}2$ alkylation

Based on the data presented in Table 2.9, the presence of H$_2$O is absolutely essential for successful alkylation of 294 promoted by a phase-transfer catalyst under base-free neutral reaction conditions. We have already observed from $^1$H NMR spectroscopic analysis of the bis-ester-substituted oxindole analogue 294 that it exists in both keto and enol forms in a ratio of 1:1 in CDCl$_3$. Therefore, we assumed similar behaviour when 294 is placed in the organic phase of a PTC system (Scheme 2.5, A). In the reaction where both H$_2$O and phase-transfer catalyst are present, the enol is ionised to a small extent to generate a highly stabilised enolate 305 (Scheme 2.5, B). It is essential to note that the presence of a phase-transfer catalyst is extremely important as in its absence, the reaction does not occur (see Table 2.7, entry 4). It was postulated that the driving force for enolate formation, presumably at the interface between the two phases, is the desire of the enolate to form a tight ion pair 308 with the quaternary ammonium cation of catalyst 307 (Scheme 2.5, C). During this crucial step, HBr is generated in situ as a by-product. This was confirmed by recording an extremely low pH value of 1.5, indicating a very acidic environment. In the presence of H$_2$O, the hydrophilic HBr can smoothly diffuse into the aqueous phase (Scheme 2.5, D), thus preventing the unwanted protonation of enolate 305. In the absence of H$_2$O, the alkylated product does not form (see Table 2.9, entry 1). This suggests the facile protonation of the enolate by HBr generated in situ, which forms in the organic phase during the equilibrium reaction between enol 294-a and catalyst 307, forcing the equilibrium towards enol.
Scheme 2.5  Proposed mechanism for a base-free neutral enantioselective S_N2-type alkylation of oxindole 294.

If there is an insufficient amount of H_2O present in the aqueous phase, e.g. the biphasic solvent mixture is in a ratio of 1:1 PhCH_3/H_2O (see Table 2.9, entry 2), HBr cannot diffuse into the aqueous phase very efficiently. This leads to a partial protonation of the enolate anion, hindering catalysis and subsequent product formation, thus resulting in a decreased product yield. Conversely, it was reasoned that if the aqueous phase contains too much H_2O, as in a ratio of 1:50 PhCH_3/H_2O (see Table 2.9, entry 4), the organic phase becomes dispersed within the aqueous phase. As catalysis is postulated to take place in the organic phase, this unwanted dispersion has an adverse effect on the course of reaction, resulting in a slower rate of catalysis. Therefore, it is absolutely crucial to determine the optimal quantity of H_2O in the biphasic solvent mixture in advance, as it can considerably influence the rate of catalysis.

Once the more lipophilic species 308 is formed, it migrates deeper into the organic phase, where it undergoes the alkylation reaction with an electrophile (i.e. BnBr), subsequently leading to the formation of the desired alkylated product 295 (Scheme 2.5, E) and regenerating the catalyst for another cycle (Scheme 2.5, F).
2.4 Evaluation of the asymmetric bifunctional phase-transfer catalysts in S_N2 alkylation under base-free neutral PTC conditions

In pursuit of the optimal catalyst that would efficiently promote formation of the alkylated product with high enantioselectivity, we decided to conduct a systematic evaluation of novel, carefully designed and synthesised phase-transfer catalysts, bearing different steric and electronic characteristics.

Prior to initial catalyst screening, 310, the 2-oxindole analogue of 294 was prepared according to the protocol previously reported by Simig et al.,^240 utilising methyl chloroformate to furnish the product in a moderate yield (Scheme 2.6).

![Scheme 2.6 Synthesis of dimethyl 2-oxoindoline-1,3-dicarboxylate (310).](image)

The rationale for using this particular 2-oxindole substrate as well as a thorough evaluation of the substrate scope in the PTC-promoted benzylation will be discussed in Section 2.5.

2.4.1 Selecting the optimal hydrogen bond-donating moiety

Firstly, we decided to evaluate the influence of a hydrogen bond donor of a bifunctional phase-transfer catalyst on the stereochemical outcome of the reaction. Having proposed a potential mechanism for a base-free neutral PTC reaction system (Scheme 2.5, vide supra), it was postulated that hydrogen bonding facilitated by a urea-substituted catalyst might play a significant role in the formation of a chiral ion pair between the enolate anion of substrate and the quaternary ammonium cation of the catalyst (Figure 2.6).
Figure 2.6  Chiral ion pair stabilised by hydrogen-bonding (shown in red) and ionic interactions (shown in blue).

We considered it advantageous to determine the most effective hydrogen bond-donating motif of the bifunctional catalyst scaffold. This was achieved by examining the catalytic competence of both urea- and squaramide-substituted catalysts, such as 296 and 311, respectively (Figure 2.7), both kindly provided by Dr. Emiliano Sorrentino.241

Figure 2.7  Cinchona alkaloid-derived bifunctional phase-transfer catalysts substituted with urea and squaramide moieties, 296 and 311.

Although squaramides are known to act as hydrogen bond donors in a similar way that ureas do, they exhibit very distinctive physiochemical features. Squaramides are planar and structurally more rigid molecules than ureas, which is explained by delocalisation of the lone pair of both nitrogen atoms through the ring system, restricting the two C-N bond rotations.105,251 We were intrigued to determine whether the performance of squaramides would be superior to the catalytic activity of ureas.

Following evaluation of both catalyst types in the benzylation of 310 under optimised base-free neutral reaction conditions, it was revealed that the squaramide catalyst 311 was able to promote the formation of the alkylated product 312 in a moderate conversion of 46%, even after a prolonged reaction time of 7 days (Table 2.10, entry 1).
Table 2.10  Evaluation of the asymmetric bifunctional PTCs in the benzylation of 310 under optimised base-free neutral reaction conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>time (h)</th>
<th>conv. (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>311</td>
<td>161</td>
<td>46</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>296</td>
<td>48</td>
<td>&gt;99</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>307</td>
<td>45</td>
<td>&gt;99</td>
<td>52</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using <i>p</i>-iodoanisole as an internal standard. <sup>b</sup>Determined by CSP-HPLC.

The catalytic ability of the squaramide-based catalyst 311 to promote the reaction enantioselectively was very poor, leading to an almost racemic product (Table 2.10, entry 1). The activity of the urea-based promoter 296 was far superior, affording 312 in a quantitative conversion in 48 h, albeit in only 19% ee (entry 2). These results suggest that the urea moiety is able to stabilise the enolate anion much more efficiently than the rigid squaramide motif (assuming similar lipophilicity), thus resulting in increased catalytic activity. Regarding the enantioselectivity of both catalysts, it was reasoned that the urea-derived catalyst was able to provide a better fit for the enolate anion of 310 within its chiral pocket, leading to enhanced enantiomeric excess of 312. Following these observations, the squaramide hydrogen bond-donating motif was abandoned and the catalyst incorporating a urea moiety was selected as a candidate for further optimisation studies.

As previously highlighted, substitution at C-2’ of the quinoline moiety on the bifunctional PTC was known to afford the alkylated product with higher enantioselectivity, in comparison to its C-2’ unsubstituted equivalent (see Table 2.7, compare entries 3 and 4). Therefore, catalyst 307 was evaluated in the benzylation of 310. We were pleased to observe a significant improvement in the enantiomeric excess, while still obtaining 312 in excellent yield (Table 2.10, entry 3). Prompted by these encouraging results, subsequent optimisation of C-2’ phenyl-substituted catalyst 307
was conducted, leading to the synthesis of novel urea-substituted bifunctional cinchona alkaloid-derived phase-transfer catalysts.

2.4.2 Synthesis and evaluation of novel PTCs: tuning the urea moiety

Having identified a promising candidate, bearing a urea hydrogen bond-donor and a C-2’ phenyl substituent, the next step was to evaluate modifications at the urea moiety of the catalyst scaffold. It was envisaged that by substituting the amide of urea with groups of various steric and electronic bulk, the hydrogen bond donating ability of the catalyst could be tuned to enhance its performance.

Synthesis of the novel PTCs began by following the previously developed procedures in our laboratory.\textsuperscript{252,241} The first step involved phenylation of the quinoline ring at the C-2’ position with an excess of phenyl lithium (PhLi), followed by an \textit{in situ} oxidation of 1,2-dihydroquinuclidine adduct using iodine. The C-2’ alkylated quinine 313 was transformed into a hydrochloride salt 315 \textit{via} a Mitsunobu reaction immediately proceeded by a Staudinger reduction of the \textit{in situ} generated azido intermediate 314. The overall process resulted in the inversion of configuration at C-9 of the quinine salt 315 (Scheme 2.7).

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{Scheme2_7.png}
\end{scheme}

\textbf{Scheme 2.7} The synthesis of hydrochloride salt 315.

The bifunctional urea derivatives of 315, \textit{i.e}. 316 and 317, were synthesised in moderate yields by employing an excess of Et\textsubscript{3}N to liberate the free amine of 315 and subsequent reaction with the relevant isocyanate reagent. Following alkylation of the quinuclidine
nitrogen atom with tert-butyl substituted benzyl bromide under specific reaction conditions – previously optimised by Dr. Emiliano Sorrentino – the novel bifunctional PTCs, i.e. 318 and 319, were obtained in moderate yields (Scheme 2.8).

Scheme 2.8  Synthetic pathway for the assembly of novel bifunctional PTCs.

The bifunctional urea-based catalyst 320 possessing a trityl substituent on the amide moiety was kindly provided by Dr. Claudio Cornaggia. Subsequent alkylation of the quinuclidine ring with 3,5-di-tert-butyl benzyl bromide with a prolonged reaction time (24 h) afforded the desired phase-transfer catalyst 321 in a moderate yield (Scheme 2.9).

Scheme 2.9  Synthesis of phase-transfer catalyst 321, bearing a trityl substituent.

The catalytic performance of the novel bifunctional PTCs was evaluated in the model benzylation of 310, employing base-free neutral reaction conditions (Table 2.11). As previously reported, catalyst 307 bearing electron-withdrawing CF₃ groups on the aromatic ring bound to the urea unit, furnished the benzylated product 312 in excellent yield and good enantioselectivity (52% ee, entry 1). The use of catalyst 318, lacking CF₃ substituents on the aromatic ring, led to a dramatic drop in the enantioselectivity (34% ee, entry 2).
Table 2.11  Evaluation of novel bifunctional PTCs with a modified urea moiety.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>time (h)</th>
<th>conv. (%)\textsuperscript{a}</th>
<th>ee (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{c}</td>
<td>307</td>
<td>45</td>
<td>&gt;99</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>318</td>
<td>48</td>
<td>&gt;99</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>319</td>
<td>114</td>
<td>97</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>321</td>
<td>114</td>
<td>&gt;99</td>
<td>0</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Determined by \textsuperscript{1}H NMR spectroscopic analysis using \(p\)-iodoanisole as an internal standard. \textsuperscript{b} Determined by CSP-HPLC. \textsuperscript{c} Reported from Table 2.10.

A significantly diminished activity was observed with the use of catalyst 319, possessing \textit{iso}-propyl substituents at both \textit{ortho}-positions of the benzyl moiety. Rather disappointingly, the alkylated product 312 was obtained in almost racemic form (entry 3). The catalytic competence of a bulky catalyst 321 incorporating a trityl group on the urea functionality was comparable to that of 319, leading to a completely racemic benzylated product 312 (entry 4). Since none of these novel PTCs were capable of bringing about an enhancement of the product \textit{ee}, catalyst 307 was subjected to further optimisation.

2.4.3 Synthesis and evaluation of novel PTCs: tuning the quinuclidine aryl moiety

As modifications at the urea functionality did not lead to any improvement in the enantioselectivity, the focus of subsequent investigation was at the quinuclidine moiety. The bifunctional urea catalyst 323 was synthesised in a good yield by following the
procedure previously outlined in Scheme 2.7, followed by a similar procedure as in Scheme 2.8, utilising 3,5-bis(trifluoromethyl)phenyl isocyanate (322). Upon subsequent alkylation of the quinuclidine nitrogen atom, employing either procedure A or procedure B (formerly optimised by Dr. Emiliano Sorrentino), the novel PTCs were prepared in moderate to good yields (Scheme 2.10).

The first modification made to catalyst 307 was the incorporation of the unsubstituted benzyl unit attached to the quinuclidine nitrogen atom, as in catalyst 324, accessed through a milder synthetic method carried out at room temperature, i.e. procedure B. On the other hand, installing a methoxy group at the both meta-positions of the aryl moiety of the benzyl unit led to the formation of catalyst 326 with enhanced electron-donating ability. An electron-withdrawing substituent on the benzyl moiety was incorporated in catalyst 325. In an attempt to increase the steric bulk of the motif attached to the quinuclidine unit, catalyst 327 was designed, bearing -OBn groups in the 3,4,5-positions of the aromatic ring (Scheme 2.10).

![Scheme 2.10](file)

**Scheme 2.10** Synthetic route towards novel PTCs, modified at the quinuclidine unit.

Subsequent evaluation of these novel PTCs in the model benzyla

<table>
<thead>
<tr>
<th>procedure</th>
<th>Ar</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>C₆H₅</td>
<td>324</td>
<td>65</td>
</tr>
<tr>
<td>A</td>
<td>3,5-Br₂C₆H₃</td>
<td>325</td>
<td>74</td>
</tr>
<tr>
<td>A</td>
<td>3,5-(OCH₃)₂C₆H₃</td>
<td>326</td>
<td>82</td>
</tr>
<tr>
<td>A</td>
<td>3,4,5-(OBn)₃C₆H₃</td>
<td>327</td>
<td>67</td>
</tr>
</tbody>
</table>

Subsequent evaluation of these novel PTCs in the model benzylation of 310 revealed that the catalysts substituted with electron-donating groups, i.e. catalysts 326 and 327, were slightly superior regarding their ability to provide enantioselective PTC in comparison to 307 conducted at room temperature (Table 2.12, compare entries 2 and 3 with entry 1). Interestingly, the augmented steric bulk associated with catalyst 327 did not lead to any additional improvement in ee. Catalyst 324, bearing an unsubstituted...
aryl moiety promoted the product formation in a slightly diminished ee (entry 4). An almost identical selectivity was observed with the use of catalyst 325, possessing the electron-withdrawing bromine atom, albeit with significantly reduced activity (entry 5). To our disappointment, the bulky catalyst 300 proved to be an inefficient promoter, affording 312 in only a moderate conversion after extended reaction time (168 h) and in practically racemic form (entry 6).

Table 2.12 Evaluation of novel PTCs with a modified quinuclidine moiety.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>cat. loading (mol%)</th>
<th>temp. (˚C)</th>
<th>time (h)</th>
<th>conv. (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>307</td>
<td>5</td>
<td>rt</td>
<td>45</td>
<td>&gt;99</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>326</td>
<td>5</td>
<td>rt</td>
<td>48</td>
<td>&gt;99</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>327</td>
<td>5</td>
<td>rt</td>
<td>48</td>
<td>&gt;99</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>324</td>
<td>5</td>
<td>rt</td>
<td>90</td>
<td>&gt;99</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>325</td>
<td>5</td>
<td>rt</td>
<td>114</td>
<td>90</td>
<td>49</td>
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<td>6</td>
<td>300</td>
<td>5</td>
<td>rt</td>
<td>168</td>
<td>54</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>307</td>
<td>10</td>
<td>3</td>
<td>144</td>
<td>&gt;99</td>
<td>59</td>
</tr>
<tr>
<td>8</td>
<td>326</td>
<td>10</td>
<td>3</td>
<td>144</td>
<td>&gt;99</td>
<td>59</td>
</tr>
<tr>
<td>9</td>
<td>327</td>
<td>5</td>
<td>3</td>
<td>189</td>
<td></td>
<td>69</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using p-iodoanisole as an internal standard. <sup>b</sup>Determined by CSP-HPLC. <sup>c</sup>Reported from Table 2.10.
In an attempt to enhance the selectivity of the process, the model benzylation was conducted at 3 °C, the lowest possible temperature for a base-free neutral reaction system. Any further reduction in temperature resulted in an undesired freezing of the aqueous layer. Unfortunately, even a reduction in the reaction temperature failed to enhance the enantioselectivity of the benzylation. In fact, product 312 was obtained with the identical enantiomeric excess upon catalysis by 307, 326 and 327 (entries 7-9). It is worth mentioning that when the benzylation was conducted at 3 °C, the product conversion was rather low even after a prolonged reaction time (entry 9). This observation prompted us to increase the catalyst loading to 10 mol% in order to improve the reaction yields for the experiments conducted at low temperature.

2.4.4 Further optimisation studies: development of the C-2’ chloro-substituted catalyst 335

During the course of our efforts to optimise the catalyst design, it occurred to us that it might be possible that the nitrogen atom on the quinoline moiety of the catalyst could be protonated by HBr generated in situ. It was hypothesised that this unwanted protonation might be responsible for the catalyst’s inability to efficiently promote the formation of the reaction product with high enantioselectivity.

In order to investigate this matter further, we designed a novel catalyst bearing an electron-withdrawing substituent at the C-2’ position, i.e. chlorine atom. It was anticipated that such a catalyst would reduce the possibility of any – potentially occurring – unwanted protonation by HBr generated in situ during the progression of the reaction. Additionally, it was postulated that the 2-chloro substituent could make the heterocycle less basic, considering the difference in the pKa values of the protonated pyridine (pKa 5.25254) and 2-chloro-pyridine (pKa 0.49255).

Prior to synthesis of the C-2’ chloro-substituted catalyst, it was decided to employ dihydroquinine (DHQ, 328) as an appropriate substitute for quinine – which would be more usually employed – in order to avoid potential hydrohalogenation or oxidation of the alkene unit of the quinine scaffold in the forthcoming reaction sequence. DHQ was efficiently accessed via transfer hydrogenation of quinine using formate and Pd/C (Scheme 2.11), a synthetic protocol recently reported by Hintermann256.
Scheme 2.11  Transfer hydrogenation of quinine.

The first step towards to the synthesis of the C-2’ chloro-substituted catalyst was the oxidation of both nitrogen atoms of DHQ, performed according to a known literature procedure using *meta*-chloroperoxybenzoic acid (*m*-CPBA). The subsequent *bis*-N-oxide DHQ analogue 329 was subjected to a sulfur dioxide solution, also known as sulfurous acid (H₂SO₃), a weak acid and a mild reductant that was used to selectively remove the N-oxide from the nitrogen atom of the quinuclidine moiety. The resulting N-oxide species 330 was converted into the C-2’ chloro-substituted DHQ 331 by reaction with phosphorus(V) oxychloride (POCl₃, Scheme 2.12).

Scheme 2.12  Synthetic route towards the C-2’ chloro-substituted DHQ 331.

The hydrochloride salt 333, bearing a C-2’ chloro substituent, was synthesised according to the Mitsunobu and Staudinger reactions, described in the previous Section (Scheme 2.13).
Scheme 2.13 Synthesis of hydrochloride salt 333 bearing a C-2’ chloro-substituent.

The novel C-2’ chloro-substituted PTC 335 was synthesised as described in Scheme 2.14. Upon liberation of the free amine of hydrochloride salt 333 with an excess of Et₃N and subsequent reaction with the isocyanate reagent 322, the bifunctional catalyst 334 was furnished in a good yield. Finally, the quaternisation of the quinuclidine ring with 3,5-di-tert-butyl benzyl bromide afforded the novel PTC 335 in 71% yield (Scheme 2.14).

Scheme 2.14 Synthetic protocol for the C-2’ chloro-substituted PTC 335.

In order to examine the influence of halides in the C-2’ position other than chlorine, a bromine-version of catalyst 335 was synthesised, i.e. catalyst 340, following the same synthetic pathway as outlined previously, employing phosphorus(V) oxybromide (POBr₃, Scheme 2.15).
Scheme 2.15  Synthetic route towards the C-2’ bromo-substituted PTC 340.

Additionally, we found it advantageous to evaluate the effect of the reduced alkyl unit attached to the quinuclidine moiety. For that reason, we have prepared a synthetic equivalent of the C-2’ chloro-substituted catalyst 335 with a C-2’ phenyl substituent, i.e. catalyst 345. The synthesis of 345 is described in Scheme 2.16.
Scheme 2.16 Synthetic protocol for the C-2’ phenyl-substituted PTC 345.

At a later stage of the catalyst development, it was unexpectedly noticed that the oxidation of quinine (39) by m-CPBA did not affect the alkene functionality, i.e. the alkene unit remained intact throughout the oxidation process (Scheme 2.17).

Scheme 2.17 Oxidation of quinine.
Encouraged by this observation, we decided to synthesise another C-2’ chloro-based PTC, *i.e.* catalyst 352, this time incorporating the quinine scaffold, as a direct comparison to catalyst 307.

Scheme 2.18 Synthetic route towards the C-2’ chloro-substituted PTC 352 derived from quinine.

Upon evaluation of the selectivity of the newly synthesised PTCs in the model reaction, we were frustrated to observe practically unchanged *ee* of the alkylated product 312 (Table 2.13). It was observed that the nature of the halogen atom substituted at the C-2’ position does not any significant effect on the enantioselectivity of the PTC-promoted alkylation (entries 1 and 2). Catalyst 345 bearing a phenyl substituent at the C-2’ position resulted in the formation of 312 with a slightly inferior *ee* (entry 3). The quinine derived analogue of 335, *i.e.* catalyst 352 exhibited almost identical catalytic activity and selectivity (entry 4), while similar behaviour was observed between the
catalysts 345 and 307 (compare entries 3 with 5). This data suggested that the nature of the alkyl substituent of the quinuclidine moiety (ethyl vs. ethylene group) has a negligible effect on the enantioselective discrimination of a PTC.

Table 2.13 Evaluation of the C-2’ chloro-substituted catalyst 335 and its comparable analogues in the model PTC alkylation reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>cat. loading (mol%)</th>
<th>temp. (˚C)</th>
<th>time (h)</th>
<th>conv. (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>335</td>
<td>5</td>
<td>rt</td>
<td>48</td>
<td>&gt;99</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>340</td>
<td>5</td>
<td>rt</td>
<td>60</td>
<td>&gt;99</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>345</td>
<td>5</td>
<td>rt</td>
<td>45</td>
<td>&gt;99</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>352</td>
<td>5</td>
<td>rt</td>
<td>45</td>
<td>&gt;99</td>
<td>54</td>
</tr>
<tr>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>307</td>
<td>5</td>
<td>rt</td>
<td>45</td>
<td>&gt;99</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>335</td>
<td>10</td>
<td>3</td>
<td>144</td>
<td>&gt;99</td>
<td>62</td>
</tr>
<tr>
<td>7</td>
<td>340</td>
<td>10</td>
<td>3</td>
<td>144</td>
<td>&gt;99</td>
<td>58</td>
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<td>8</td>
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<td>9</td>
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<td>10</td>
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<td>&gt;99</td>
<td>59</td>
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<tr>
<td>10&lt;sup&gt;d&lt;/sup&gt;</td>
<td>307</td>
<td>10</td>
<td>3</td>
<td>144</td>
<td>&gt;99</td>
<td>59</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using p-iodoanisole as an internal standard. <sup>b</sup>Determined by CSP-HPLC. <sup>c</sup>Reported from Table 2.10. <sup>d</sup>Reported from Table 2.12.

Upon performing the benzylation of 310 at low temperature, the ee of 312 increased only marginally. The chloro-substituted catalyst 335 was the found to be the most
effective promoter in the model reaction, furnishing the desired product in moderate 62% ee (entry 6). Disappointingly, the evaluation of all the other catalysts in the alkylation of 310 yielded almost identical ee (entries 7-10). Judging by the similarity of the data presented in Table 2.13, it became apparent that protonation of the catalyst by the in situ generated HBr (that we thought might be one of the possible causes for poor selectivity associated with the PTCs) was not a factor.

Even after the extensive optimisation studies we failed to design a catalyst that would promote the formation of product in more than 62% ee, which we obtained with the C-2’ chloro-substituted catalyst 335. Consequently, we decided to stop the catalyst optimisation and direct our efforts towards the substrate scope of the benzylation reaction.

2.5 Synthesis of diverse C,N-bis-acylated 2-oxindole derivatives

Having previously synthesised 2-oxindole-based substrates bearing bis-methoxy and bis-ethoxy esters, i.e. 310 and 294, respectively, we decided to synthesise novel ‘mixed’ substrates, possessing both methoxy and ethoxy ester groups. It was anticipated that upon evaluation of these novel substrates in the benzylation under base-free neutral PTC reaction conditions, we might gain insight into how substrate sterics influence the selectivity of a PTC on the reaction outcome.

The preparation of these ‘mixed’ derivatives was accomplished by following the procedure described in Scheme 2.2, however prior to the final rearrangement process, ammonium carbonate, (NH₄)₂CO₃, was added to the solution of the relevant N,O-bis-acylated derivative (i.e. 309 and 293) in DMF at low temperature. This step resulted in the selective removal of the O-acyl moiety, affording the corresponding N-acylated derivatives 353 and 354 in moderate yields (Scheme 2.19).

![Scheme 2.19](image)

**Scheme 2.19** Synthesis of N-acylated 2-oxindole derivatives.
Upon subsequent acylation with the appropriate chloroformic acid ester, the ‘mixed’ substrates 356 and 358 were synthesised in good yields (Scheme 2.20).

![Scheme 2.20](image)

**Scheme 2.20** Preparation of the ‘mixed’ C,N-bis-acylated 2-oxindoles.

In order to increase the steric bulk of the ester moiety at the C-3 position even further – while keeping the N-acyl unit as sterically small as possible – several synthetic targets were proposed, incorporating the N-acetyl moiety (Figure 2.7).

![Figure 2.7](image)

**Figure 2.7** Synthetic targets – substrates bearing bulky ester groups at the C-3 position of the oxindole scaffold.

The ‘mixed’ N,O-bis-acylated compounds (*i.e.* 359a, 360a and 361a) were efficiently synthesised utilising the relevant chloroformic acid esters (note: the synthesis of 360a was achieved with di-tert-butyl carbonate in the presence of a catalytic DMAP in THF because tert-butyl chloroformate is not commercially available). Unfortunately, the rearrangement of these N,O-bis-acylated derivatives resulted in mixtures of three compounds; N-acetyl analogue 353 and the desired C,N-bis-acylated product in both keto and enol forms (enol tautomer is not shown, Scheme 2.21).
Scheme 2.21 Rearrangement of \(N,O\)-bis-acylated 2-oxindole derivatives, possessing bulky ester groups at the C-3 position.

Due to the tautomeric nature of \(N,O\)-bis-acylated 2-oxindole substrates, it was not possible to separate \(353\) from the keto-enol product by either a flash column chromatography, or a silica plug (degradation of product observed in both cases). Recrystallisation and precipitation techniques were also attempted; employing a variety of solvents. Disappointingly, as \(C,N\)-bis-acylated derivative and \(353\) were formed in almost equal ratio, the desired product was not isolated. To explain the formation of \(353\) which was detected during the rearrangement of bulkier ester groups, we reasoned that a \(\beta\)-decarboxylation-type reaction was occurring, possibly assisted by general acid catalysis (Scheme 2.22).

Scheme 2.22 Proposed \(\beta\)-decarboxylation of \(C,N\)-bis-acylated 2-oxindole substrate and stability of carbocations.

As depicted in Scheme 2.22, it is probable that the driving force for \(\beta\)-decarboxylation is the formation of a stable carbocation. Subsequently, the carbocation undergoes solvolysis to yield the corresponding alcohol, while the enolate anion is protonated by acid leading to the formation of \(353\). It is well known that bulkier carbocations are able to stabilise positive charge much more efficiently than either of their methyl or ethyl counterparts. In order to avoid the unwanted \(\beta\)-decarboxylation during the rearrangement process, we designed a substrate incorporating a bulky 2,2,2-
trichloroethyl substituent. It was postulated that the electron-withdrawing ability of this group would destabilise the carbocation that might form during rearrangement and consequently prevent β-decarboxylation from occurring. If successful, the synthesis of such substrate would facilitate evaluation of a bulky ester moiety at the C-3 position of 2-oxindole on the selectivity of a PTC.

The synthesis of \(N,O\)-bis-acylated derivative 362, bearing a 2,2,2-trichloroethyl substituent, was efficiently synthesised according to the previously described procedure, employing 2,2,2-trichloroethyl chloroformate. To our delight, subsequent rearrangement of 362 resulted in the exclusive formation of 363, albeit in low yield (Scheme 2.23).

![Scheme 2.23 Synthesis of novel substrate 363 possessing a bulky electron-withdrawing 2,2,2-trichloroethyl substituent.](image)

With the aim of evaluating the influence of sterics at the \(N\)-acyl moiety, we synthesised \(N\)-Boc-protected substrates 364 and 365, as well as 2-oxindole derivative 366 incorporating the benzyl acetate moiety at the nitrogen atom (Figure 2.8).

We have also investigated whether the carboxylate functionality at the nitrogen atom of the 2-oxindole scaffold was necessary for an effective stereoselective catalysis. For this purpose, \(N\)-methyl-\(C\)-acetyl 2-oxindole substrate 367 was synthesised (Figure 2.8). The alkylation of the nitrogen atom with methyl group was performed according to a known literature procedure, followed by acylation with methyl chloroformate and the successive rearrangement as outlined in Scheme 2.20.

![Figure 2.8 Diverse \(C,N\)-bis-acylated 2-oxindole substrates.](image)
2.5.1 Evaluation of the substrate scope

Having synthesised a variety of structurally diverse substrates, alkylation with BnBr under previously optimised base-free neutral reaction conditions was next carried out. These substrate evaluation studies were conducted in the presence of the C-2’ phenyl-substituted catalyst 307. As the substrate studies were already well underway with catalyst 307 by the time the C-2’ chloro-substituted catalyst 335 had been identified as the most proficient PTC, and because a significant difference in their catalytic competence had not been observed (see Table 2.13), we decided to continue the substrate screening using catalyst 307.

From the data presented in Table 2.14, substrate 294 bearing two identical acyl groups, seemed to be the most effective substrate for the generation of the benzylated product 295 with the highest enantiomeric excess (62% ee, Table 2.14, entry 1). A comparable level of selectivity was achieved with a ‘mixed’ 2-oxindole derivative 358 (entry 2). The enantiomeric excess of the benzylated product diminished with the use of substrates 356 and 310, both bearing N-acetyl group (entries 3 and 4). The substrates possessing bulky Boc group and benzyl acetate substituent resulted in a major reduction in the ee (entries 5-7), without any substantial effect of the acyl moiety at the C-3 position. It is worth mentioning that the reactivity of substrate 366, incorporating the benzyl acetate group, was somewhat reduced in comparison to the other substrates under scrutiny. The benzylation of substrate 363 resulted in the formation of 373 in extremely low yield and very poor enantioselectivity (entry 8). This is probably due to an adverse effect of electron-withdrawing substituent of the acyl group at C-3. Furthermore, the steric bulk of the C-3-acyl moiety seems to be beneficial for neither reactivity nor enantioselectivity. And finally, it was confirmed that the acyl functionality at the nitrogen atom is absolutely crucial for effective catalysis and greater enantiofacial discrimination by a PTC (compare entries 4 and 9).
Table 2.14 Evaluation of the substrate scope in the benzylation under base-free neutral PTC reaction conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
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<td>295</td>
<td>45</td>
<td>91</td>
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</tr>
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<td>45</td>
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<tr>
<td>3</td>
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<td>369</td>
<td>45</td>
<td>92</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>310</td>
<td>312</td>
<td>45</td>
<td>95</td>
<td>52d</td>
</tr>
</tbody>
</table>
As many natural and bioactive 2-oxindole-based compounds often possess a substituent within their aromatic framework, a number of \( C,N\)-bis-acetyl 2-oxindoles bearing either electron-donating or electron-withdrawing groups within their cores were synthesised. Initially, the Wolff-Kishner reduction of the appropriate isatins was performed, followed by the acylation with methyl chloroformate and subsequent rearrangement furnished the novel substrates in moderate yields (Scheme 2.24).
<table>
<thead>
<tr>
<th>Scheme 2.24</th>
<th>Synthesis of C,N-bis-acetyl 2-oxindole derivatives possessing electronic substituents within their aromatic scaffolds.</th>
</tr>
</thead>
<tbody>
<tr>
<td>These novel substrates substituted on the aromatic ring moiety were evaluated in the PTC benzylation carried out in chlorobenzene instead of the optimal PhCH$_3$. The reason being the extremely poor solubility of these substrates in both PhCH$_3$ or xylene. The acquired results indicated a strong preference for substitution at the C-4 position of the 2-oxindole scaffold, furnishing product 391 in 83% ee, albeit in a lower yield (Table 2.15, entry 2). This can be explained by the increased steric bulk of the bromine substituent (relative to H), which is in close proximity to C-3 where alkylation occurs. Disappointingly, the substrates substituted at the C-5 position with bromine and chlorine, <em>i.e.</em> 388 and 389, respectively, were both inferior to 4-bromo-substituted 2-oxindole derivative 387, furnishing the desired products in only 44% ee and 48% ee, respectively (entries 3 and 4). Even conducting the reaction at a lower temperature, the enantiomeric excess of product 393 was not enhanced (entry 4). The effect of the electron-donating 5-methoxy substituent was more profound than its halogen atom equivalents, affording product 394 in excellent yield and an improved 61% ee (entry 5). However, the use of the optimal PhCH$_3$ as the reaction solvent instead of chlorobenzene could have contributed to this enhanced enantioselectivity.</td>
<td></td>
</tr>
</tbody>
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Table 2.15  Evaluation of substrates substituted on the aromatic oxindole ring.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>time (h)</th>
<th>conv. (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
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<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
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<td><img src="image" alt="312" /></td>
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<td>&gt;99</td>
<td>55</td>
</tr>
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<td><img src="image" alt="391" /></td>
<td>87</td>
<td>80</td>
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<td>5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>390</td>
<td><img src="image" alt="394" /></td>
<td>48</td>
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<td>61</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using <i>p</i>-iodoanisole as an internal standard. <sup>b</sup>Determined by CSP-HPLC. <sup>c</sup>Reported from Table 2.13. <sup>d</sup>Conducted at 3 °C, using 10 mol% cat. loading. <sup>e</sup>Performed in PhCH<sub>3</sub>. 
The promising result obtained with the 4-bromo-substituted oxindole substrate 387 encouraged us to investigate the effect of other similar C-4-substituted 2-oxindoles, e.g. 4-methoxy and 4-phenyl analogues of 387. However, the synthesis of the aforementioned substrates proved to be more challenging than initially anticipated and regrettably, we decided to abandon their synthesis and expend efforts elsewhere.

2.5.1.1 Studies aimed at selecting the optimal substrate

As discussed in the previous Section, the substrate screening studies pointed towards C,N-bis-acylated 2-oxindole derivative 294 as the ideal substrate for the PTC benzylation (see Table 2.14). However, at a later stage of our PTC studies, a rather interesting observation was made. Upon alkylation with substituted benzyl bromides, the enantioselectivity of the resulting product was found to be higher when a substrate bearing smaller acyl substituents was employed.

Based on this finding, a thorough investigation into the effect of substitution at the benzyl bromide electrophile in the alkylation of two structurally different substrates was carried out. The substrates evaluated in this study were C,N-bis-propionyl 2-oxindole derivative 294 and its bis-acetyl analogue 310. The alkylation was promoted by the C-2’ chloro-substituted catalyst 335. According to a solvent screen (Table 2.16, entries 1-3), it was demonstrated that the enantioselectivity of 312 was not affected to any significant degree by either of the solvents tested. Therefore, xylene was selected as the solvent of choice for conducting this particular study.

As initially observed, C,N-bis-propionyl 2-oxindole derivative 294 was marginally superior to its bis-acetyl analogue 310 (compare entries 1 and 4). When alkylation was performed with a substituted benzyl bromide, i.e. 3-nitrobenzyl bromide, the alkylated product 395, possessing C,N-bis-acetyl substituents, was obtained in 73% ee (entry 5). In contrast, product 396, bearing C,N-bis-propionyl substituents, was detected in a slightly diminished 68% ee (entry 6).

Upon analysis of the data presented in Table 2.16, it was established that C,N-bis-acetylated substrate 310 was the optimal substrate, and was to be used for further experiments. Although the previous studies were performed in xylene, due to its high boiling point and tedious removal in vacuo, we decided to replace it with PhCH3 which was considerably easier to handle, yet provided comparable results.
Table 2.16  Evaluation of the effect of substituted vs. unsubstituted BnBr in alkylation of substrates 310 and 294.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>electrophile</th>
<th>solvent</th>
<th>conv. (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td><img src="image1.png" alt="" /></td>
<td>benzyl bromide</td>
<td>xylene</td>
<td>&gt;99</td>
<td>57</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td><img src="image2.png" alt="" /></td>
<td>benzyl bromide</td>
<td>PhCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>&gt;99</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="" /></td>
<td>benzyl bromide</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>&gt;99</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="" /></td>
<td>1-ethyl-3-bromo-2,4-dinitrobenzene</td>
<td>xylene</td>
<td>&gt;99</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="" /></td>
<td>benzyl bromide</td>
<td>xylene</td>
<td>&gt;99</td>
<td>73</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="" /></td>
<td>1-ethyl-3-bromo-2,4-dinitrobenzene</td>
<td>xylene</td>
<td>&gt;99</td>
<td>68</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup><sub>1</sub>H</sup> NMR spectroscopic analysis using <sub>p</sub>-iodoanisole as an internal standard. <sup>b</sup>Determined by CSP-HPLC. <sup>c</sup>Reported from Table 2.13.
2.6 Electrophile screening

2.6.1 Evaluation of the substituted benzyl bromides

The initial electrophile screening was conducted with substituted benzyl bromides possessing different steric and electronic characteristics. To our delight, the preliminary studies with benzyl bromides substituted with electron-withdrawing substituents resulted in the formation of products with exceptionally high ee (Table 2.17).

Table 2.17 Preliminary evaluation of the substituted benzyl bromides in the alkylation of 310, employing base-free neutral PTC reaction conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile</th>
<th>product</th>
<th>time (h)</th>
<th>conversion (%)(^a)</th>
<th>false positive ee (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{Ph-Br})</td>
<td>395</td>
<td>144</td>
<td>&gt;99</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>(\text{Ph-NO}_2)</td>
<td>397</td>
<td>135</td>
<td>&gt;99</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>(\text{Ph-O}_2\text{N})</td>
<td>398</td>
<td>144</td>
<td>&gt;99</td>
<td>96</td>
</tr>
</tbody>
</table>

\(^a\)Determined by \(^1\)H NMR spectroscopic analysis using \(p\)-iodoanisole as an internal standard. \(^b\)Determined by CSP-HPLC.

Unfortunately to our dismay, a precipitate was detected inside HPLC vials that have been subjected to the CSP-HPLC analysis. It has been revealed that the precipitate was essentially the alkylated product in its racemic form, while the remaining homogenous sample was consisting of a single enantiomer of product. Therefore, the CSP-HPLC analysis of such precipitated samples led to a collection of false positive data. In order to prevent precipitation from occurring and to determine the genuine enantiomeric...
excess of the alkylated products, the samples were dissolved in a more polar solvent, such as CH₂Cl₂. Upon re-evaluation of the samples previously analysed by CSP-HPLC, the enantiomeric excess was found to be significantly reduced (Table 2.18).

The unsubstituted benzyl bromide afforded the benzylated product 312 in moderate 62% ee (Table 2.18, entry 1), while the weakly electron-donating 4-methylbenzyl bromide furnished 399 in decreased ee (entry 2). As this experiment was conducted at room temperature, it could have contributed to lower enantioselectivity of the process. The bulky 2-(bromomethyl)naphthalene was an effective electrophile, yielding the desired product in 72% ee (entry 3), effectively shielding one of the enatiotopic faces of the enolate.

The electron-donating ability of the mono-substituted 3-methoxybenzyl bromide furnished 401 in very good ee while 3,5-dimethoxybenzyl bromide was even more superior, resulting in the formation of 402 in both excellent yield and ee (90%. 90% ee, entry 5). Tert-butyl substituents in both of the meta-positions of benzyl bromide also favoured the formation of product in excellent ee (entry 6). The higher enantioselectivity of the alkylation achieved with benzyl bromides substituted with the electron-donating groups can be explained by enhanced stabilisation of the enolate during the PTC process.

The enantiomeric excess of the benzylated product was decreased with the use of benzyl bromides bearing halogen atoms. 3-Chloro- and 4-bromo-substituted benzyl bromide afforded 404 and 405 in moderate ee (entries 7 and 8, respectively), while 3,4-fluorobenzyl bromide furnished 398 in higher enantioselectivity (74% ee, entry 9). Substitution of benzyl bromide with the electron-withdrawing nitro group at the meta-position led to higher ee in comparison to its para-analogue, 4-nitrobenzyl bromide (compare entries 10 and 11). The highly electron-withdrawing effect associated with the trifluoromethyl and cyano groups resulted in good product ee (entries 12 and 13). The electrophiles substituted at the ortho-position with halogen atoms led to products 408 and 409 in moderate enantiomeric excess (entries 14 and 15, respectively), while 2-nitrobenzyl bromide afforded the desired product in very poor 25% ee (entry 16). This can be explained by the undesirable electron-withdrawing effect of the nitro group (destabilising the transition state) as well as its close vicinity to the reaction centre.
Table 2.18  Evaluation of the substituted benzyl bromides in alkylation of 310, employing base-free neutral PTC reaction conditions.

![Chemical structure of 310 and reaction conditions](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile</th>
<th>product</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>苯(1.2equiv.)</td>
<td>312</td>
<td>144</td>
<td>94</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>苯(1.2equiv.)</td>
<td>399</td>
<td>24</td>
<td>&gt;99c</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>苯(1.2equiv.)</td>
<td>400</td>
<td>144</td>
<td>94</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>苯(1.2equiv.)</td>
<td>401</td>
<td>120</td>
<td>89</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>苯(1.2equiv.)</td>
<td>402</td>
<td>144</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>苯(1.2equiv.)</td>
<td>403</td>
<td>120</td>
<td>92</td>
<td>84</td>
</tr>
<tr>
<td>7</td>
<td>苯(1.2equiv.)</td>
<td>404</td>
<td>144</td>
<td>&gt;99c</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>苯(1.2equiv.)</td>
<td>405</td>
<td>144</td>
<td>&gt;99c</td>
<td>64</td>
</tr>
</tbody>
</table>

*No precipitation during analysis*
In pursuit of a synthetically more useful electrophilic component, we decided to investigate the effect of allylic species as electrophiles in the alkylation of 2-oxindole substrate 310. We reasoned that the desired product, bearing an all-carbon quaternary stereocentre and an allyl functionality, could be advantageous in the potential synthesis of various oxindole-based natural and bioactive products.

The preliminary screening of allyl bromide as the electrophile in the alkylation of 310 resulted in the formation of the desired product 411 in both moderate yield and enantioselectivity (50% and 49% ee, Table 2.19, entry 1). However, as the reaction progress was rather sluggish, allyl bromide was substituted for allyl iodide. Gratifyingly, the product formation was observed in quantitative conversion within 2 days. Unfortunately, the use of allyl iodide did not bring any improvement in terms of
selectivity (entry 2). The long reaction times were necessary to obtain reasonable conversions with the substituted allyl bromides promoted by the C-2’ phenyl-based catalyst 307 (entries 3 and 4). The use of 2-methyl-substituted allyl bromide resulted in a slightly more efficient catalysis by 307, furnishing 412 in 86% and enhanced 62% ee (entry 3). The sterically more hindered 2-bromo-substituted allyl bromide led to the formation of product in both lower conversion and ee (entry 4) when compared to 2-methyl allyl bromide.

Table 2.19 Evaluation of allylic electrophiles in the PTC-promoted alkylation of 310 under base-free neutral reaction conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile</th>
<th>product</th>
<th>cat.</th>
<th>time (h)</th>
<th>conv. (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{CH}_3\text{CH=CH}_2 \text{Br})</td>
<td>411</td>
<td>335</td>
<td>118</td>
<td>50</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>( \text{CH}_3\text{CH=CH}_2 \text{I})</td>
<td>411</td>
<td>335</td>
<td>48</td>
<td>&gt;99</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>( \text{CH}_3\text{CH=CH}_2 \text{Br})</td>
<td>412</td>
<td>307</td>
<td>192</td>
<td>85</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>( \text{CH}_3\text{CH=CH}_2 \text{Br})</td>
<td>413</td>
<td>307</td>
<td>288</td>
<td>66</td>
<td>57</td>
</tr>
</tbody>
</table>

\(^a\) Determined by \(^1\)H NMR spectroscopic analysis using \(p\)-idoanisole as an internal standard. \(^b\) Determined by CSP-HPLC.

Since the allyl-substituted species did not prove to be efficient electrophiles in the generation of all-carbon quaternary stereocentres, our research efforts were directed towards other types of electrophiles. We imagined that the use of amides as electrophiles would be extremely beneficial from a synthetic perspective. Such oxindole derivatives incorporating an amide moiety could potentially undergo cyclisation, thus leading to generation of the spirooxindole cores, which are present in plethora natural
and bioactive products. The amides selected as potential electrophilic components for alkylation of 310 are depicted in Figure 2.9.

![Figure 2.9](image)

**Figure 2.9** Selected examples of amides to be evaluated in alkylation of 310.

Disappointingly, all of the amides under scrutiny proved to be almost completely insoluble in PhCH$_3$, which had previously been selected as the optimal reaction solvent. Upon performing the reactions in the more polar CH$_2$Cl$_2$ – which would certainly compromise the enantioselectivity – there was no conversion detected even after a prolonged reaction time of one week. It is well known that reactivity of SN2 alkylating agents increases in the following order: I > Br > Cl. Thus, we were confident that by converting 415 into its iodo-analogue 417 via a Finkelstein reaction (Scheme 2.25), the reactivity of N-phenyl amide would improve. Although iodo-amide 417 was successfully synthesised, it was obtained in a low yield. This can be explained by the poor solubility of the bromo-substituted amide 415 in acetone.

![Scheme 2.25](image)

**Scheme 2.25** Synthesis of the iodo-derived amide 417 via a Finkelstein reaction.

Unfortunately, upon evaluation of 417 in the alkylation of the 2-oxindole substrate 310, the product formation was not observed even after an extremely long reaction time of 14 days (Table 2.20, entry 1). Expanding the amide scope to Weinreb amide analogues, the solubility in PhCH$_3$ was no longer an issue, and thus their performance could be evaluated in the alkylation of 310 under optimised PTC reaction conditions. Although the reactivity of the bromo-substituted Weinreb amide 419 was very poor (entry 2), its iodo-analogue 421 afforded the desired product in excellent conversion, albeit in extremely low ee (entry 3). The use of 2-chloro-1-phenylethan-1-one (422) as the electrophilic component would effectively install a ketone functionality into the alkylated adduct. However, use of this electrophile was completely futile, as the catalysis proceeded sluggishly, affording 423 in completely racemic form (entry 4).
Table 2.20  Evaluation of miscellaneous electrophiles.

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile</th>
<th>product</th>
<th>cat.</th>
<th>time (h)</th>
<th>conv. (%)$^a$</th>
<th>ee (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^c$</td>
<td><img src="image" alt="image of electrophile" /></td>
<td>418</td>
<td>335</td>
<td>336</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="image of electrophile" /></td>
<td>420</td>
<td>335</td>
<td>120</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="image of electrophile" /></td>
<td>420</td>
<td>335</td>
<td>120</td>
<td>$&gt;99$</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="image of electrophile" /></td>
<td>423</td>
<td>307</td>
<td>136</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$ Determined by $^1$H NMR spectroscopic analysis using $p$-idoanisole as an internal standard. $^b$ Determined by CSP-HPLC. $^c$ Conducted in CH$_2$Cl$_2$.

At this stage, we decided to abandon the use of amides as electrophiles in the alkylation of **310** and focus on other possibilities; such as electrophiles incorporating ester functionality.

2.6.3 Evaluation of ester-substituted electrophiles

Among the initial bromo-esters that were considered as prospective electrophiles in the alkylation of **310** were ethyl 2-bromoacetate (424) and tert-butyl 2-bromoacetate (425), both commercially available. However, when these electrophilic species were evaluated
in the alkylation study, a complete lack of reactivity towards 310 was observed (Table 2.21, entries 1 and 2). Having noted improved reactivity of the iodo-substituted derivatives in the previous studies with amides (see Table 2.20), bromo-esters 424 and 425 were converted into their corresponding iodo-analogues 402 and 403, respectively, via a Finkelstein reaction outlined previously in Scheme 2.20 (see Experimental Section for more details).

**Table 2.21**  Evaluation of the ester-substituted electrophiles.

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile</th>
<th>product</th>
<th>cat.</th>
<th>time (h)</th>
<th>conv. (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>424</td>
<td>426</td>
<td>307</td>
<td>336</td>
<td>0</td>
<td>---</td>
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<tr>
<td>2</td>
<td>425</td>
<td>427</td>
<td>307</td>
<td>336</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>428</td>
<td>426</td>
<td>307</td>
<td>168</td>
<td>80</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>429</td>
<td>427</td>
<td>307</td>
<td>192</td>
<td>66</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>430</td>
<td>431</td>
<td>307</td>
<td>144</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>432</td>
<td>431</td>
<td>307</td>
<td>24</td>
<td>&gt;99</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>335</td>
<td>24</td>
<td>&gt;99</td>
<td>54</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis using p-iodoanisole as an internal standard. <sup>b</sup> Determined by CSP-HPLC.
As expected, the reactivity of both 428 and 429 was significantly higher than that of their bromo-equivalents. Although the alkylated products were not obtained in quantitative conversion, the catalysis with iodo-ester 428 afforded the formation of 426 in 80% conversion (entry 3). As expected, the more sterically hindered iodo-ester 429 resulted in a slightly reduced yield (entry 4). In both cases, the enantioselectivity was rather unsatisfactory.

In an attempt to develop more effective ester-derived electrophiles, we decided to introduce an electron-withdrawing group such as -CF₃ on the previously analysed bromo-ester 424 to determine whether it had any influence on the catalysis. 2,2,2-Trifluoroethyl 2-bromoacetate (430) was efficiently synthesised according to a known literature procedure. Upon evaluation of 430, we were delighted to observe a significant improvement in the enantiomeric excess, albeit only in moderate reaction yield (entry 5). Consequently, in order to improve the rate at which the electrophile reacted with 2-oxindole 310, a similar approach of converting 430 into its iodo-analogue 432 via a Finkelstein reaction was adopted (described in Scheme 2.20). Gratifyingly, C-2’ chloro-substituted PTC promoted the alkylation of 310 with the novel 2,2,2-trifluoroethyl 2-iodoacetate (432) to afford product 431 in quantitative conversion after 24 h, although in slightly diminished enantioselectivity (54% ee, entry 7). This result encouraged us to investigate the potential of other esters that could be easily modified to bring about an enhancement in both the reaction rate and the enantioselectivity of the product.

### 2.6.3.1 Optimisation of ester-substituted electrophile structure

Having identified iodo-substituted esters as promising and highly tunable electrophiles in the alkylation of 310 under PTC-promoted base-free neutral reaction conditions, it was decided that further optimisation was required. This systematic investigation began with phenyl 2-iodoacetate (436), which was selected as the starting point for the optimisation studies. As the phenolic group could easily be substituted with analogues of different steric and electronic characteristics, it was envisaged that an efficient iodo-ester electrophile could be designed.

The synthesis of 436 was achieved via a two-step sequence. Initially, phenol (433) was reacted with chloroacetyl chloride (434) in the presence of a catalytic quantity of
DMAP. The resulting phenyl 2-chloroacetate (435) was subjected to a Finkelstein reaction which afforded phenyl 2-iodoacetate (436) in an excellent yield (Scheme 2.26).

\[
\text{Ph} + \text{Cl}_2\text{C}=\text{O} \xrightarrow{\text{DMAP} (10 \text{ mol\%}, \text{Et}_3\text{N} (1.5 \text{ equiv.})} \text{Ph} \text{Cl}_2\text{C}=\text{O} \xrightarrow{\text{rt, 1 h}} \text{Ph} \text{I}\text{C}=\text{O} \text{Cl}_2\text{C}=\text{O} \text{(435) 63\%} \xrightarrow{\text{Nal} (1.2 \text{ equiv.}, \text{acetone} (0.3 \text{ M})} \text{Ph} \text{I}\text{C}=\text{O} \text{(436) 91\%}}
\]

**Scheme 2.26** Synthetic route towards phenyl 2-iodoacetate (436).

Structurally and electronically diverse phenyl-substituted 2-iodoacetate derivatives were prepared according to the synthetic procedure described in Scheme 2.26 (see Experimental Section for more details).

Subsequent evaluation of these 2-iodo esters in the PTC-promoted alkylation of 2-oxindole substrate 310 led to interesting results. The initial screening of phenyl 2-iodoacetate (436) led to the formation of product 448 in excellent yield and moderate ee (Table 2.22, entry 1). Substitution of the phenyl ring with bulky electron-donating tert-butyl groups was responsible for reduced enantioselectivity (entry 2). In contrast, a 4-nitro-substituent enhanced the reaction rate and ee of product 450, albeit still not exceeding the previous result of 52% ee obtained with the unsubstituted analogue 436 (compare entries 1 and 3).

An investigation into the most favoured position for substitution on the aromatic ring was also conducted. An electron-withdrawing bromine atom was employed. It was observed that substitution at both of the ortho- and para-positions rendered iodo-ester 439 completely unreactive, probably due to increased steric hindrance mainly at the ortho-positions (entry 4). Even substitution solely at one of the ortho-positions (i.e. iodo-ester 440) was undesirable, leading to extremely low conversion to product, which was obtained in moderate ee after a prolonged reaction time (entry 5). It was demonstrated that the most favoured positions for substitution of the phenyl unit were at either the meta- or para-position. The experiments conducted with 2-iodo-esters 441 and 442 furnished the desired products in excellent yields and improved enantioselectivity (entries 6 and 7). It was clear that parallel substitution at the meta- and para-positions, as in iodo-ester 445, led to only a slight improvement in the enantioselectivity (compare entries 9 and 10).
Table 2.22  Evaluation of diverse phenyl-substituted 2-iodoacetate derivatives.

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile</th>
<th>product</th>
<th>time (h)</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Structure" /></td>
<td>448</td>
<td>95</td>
<td>94</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Structure" /></td>
<td>449</td>
<td>69</td>
<td>93</td>
<td>41</td>
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<td>452</td>
<td>159</td>
<td>29&lt;sup&gt;c&lt;/sup&gt;</td>
<td>49</td>
</tr>
<tr>
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<td>69</td>
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<td>455</td>
<td>24</td>
<td>92</td>
<td>57</td>
</tr>
</tbody>
</table>
The most effective iodo-esters were those substituted with powerful electron-withdrawing -CF$_3$ groups. Iodo-ester 446, bearing two -CF$_3$ groups at both of the meta-positions, furnished product 458 in 66% ee at room temperature, which was slightly superior to its analogue 447, bearing a -CF$_3$ group solely at the para-position. Interestingly, when the PTC-promoted alkylation reactions were conducted at low temperature (i.e. 3 °C), iodo-ester 447 afforded the product in the highest enantiomeric excess of 76% ee (entry 14).

The misfortune of precipitation (during CSP-HPLC analysis) encountered during the initial investigation into the substituted benzyl bromides as electrophiles (see Section 2.61), proved to be an advantage, as now we were aware of the potential precipitation of the racemic product in non-polar solvents. Therefore, we were able to precipitate the racemic product 459 from hexane, which upon removal in vacuo afforded a single enantiomer of 459 in 99% ee (entry 14). One of the drawbacks associated with this technique is the loss in product yield. Although the catalysis afforded 459 in quantitative yield, upon precipitation the yield of the optically pure 459 was reduced 63%. Hence, the utility of this technique is limited to compounds obtained in reasonably high enantiomeric excess, otherwise such method is not practical due to substantial reduction in the yield of the optically pure product.
With the successful PTC-promoted alkylation protocol that allows for the synthesis of the 3,3’-diester-substituted 2-oxindole derivatives possessing an all-carbon quaternary stereocentre in hand, we decided to evaluate the application of this methodology in target-oriented synthesis.

2.7 Towards the synthesis of the bioactive spirooxindole

In our efforts to find a suitable synthetic target to showcase the utility of the PTC-promoted alkylation of 2-oxindole derivatives under base-free neutral reaction conditions, we encountered a recent report outlining the discovery of a novel class of potent CRTH2 receptor antagonists for the treatment of allergic diseases. In this report, the spirooxindole derivatives of type 460 (Figure 2.10) were found to exhibit extremely small inhibitor constants Ki, when tested in a competitive displacement radioligand binding assay on human CRTH2. In fact, 460 possessed activity in the nanomolar range (Ki of 37±20 nM), which was among the lowest values detected among structurally similar spirooxindole analogues.

![Figure 2.10](image_url) 

**Figure 2.10** The bioactive spirooxindole 460.

Although the authors of the aforementioned report managed to synthesise the desired compound 460, and its analogues, in racemic form in 6 steps, they struggled to prepare the pure enantiomers. After several attempts involving chiral resolution, the authors eventually succeeded in separating the enantiomers by use of preparative HPLC packed with a chiral stationary phase, a process that was not optimal. Thus, we considered it advantageous to synthesise bioactive spirooxindole derivative 460 via the newly developed PTC methodology.
2.7.1 Retrosynthetic analysis of spirooxindole target 460

Having selected a suitable synthetic target, a retrosynthetic analysis of 460 was devised as outlined in Scheme 2.27.

![Scheme 2.27 Retrosynthetic analysis of the bioactive spirooxindole 460.](image)

The proposed retrosynthetic route involved the interconversion of the carboxylic acid moiety to the ester moiety. This could be achieved via hydrolysis of tert-butyl ester of analogue 461, which could be synthesised by N-alkylation of derivative 462, bearing a spirooxindole core with a succinimide unit. It was hypothesised that the spirooxindole derivative 462 could be furnished in one pot from 3,3’-disubstituted 2-oxindole derivative 463 in the presence of a suitable benzylamine, which would deprotect the nitrogen atom and subsequently encourage cyclisation of the amide moiety. The analogue 463 was to be accessed via chlorination of 459 with an appropriate chlorinating agent. Thus, it was envisaged that the target compound 460 could be furnished in 4 steps starting from the previously synthesised 3,3’-disubstituted 2-oxindole derivative 459 in a relatively straightforward fashion.

2.7.1.1 Synthetic approach towards the spirooxindole core

The first step of the synthetic pathway towards bioactive spirooxindole 460 was to install a chlorine atom at the C-5 position of the aromatic ring of the oxindole moiety. The suitable chlorinating agent selected for this task was N-chlorosuccinimide (NCS). Despite several attempts to chlorinate 459, 5-chloro 2-oxindole derivative 463 was not synthesised (Scheme 2.28).
Scheme 2.28  Attempts to chlorinate 3,3’-disubstituted 2-oxindole 459.

An alternative approach where the chlorine atom was installed into the framework of 2-oxindole substrate prior to the PTC alkylation with iodo-ester 447 was also considered. However, upon subsequent evaluation of the 5-chloro-substituted 2-oxindole-derived substrate 389, the desired product 463 was obtained in excellent yield, albeit in low enantioselectivity (43% ee, Scheme 2.29). Thus, it was considered impractical to carry out the necessary precipitation to obtain a pure enantiomer.

Scheme 2.29  Evaluation of 5-chloro-substituted substrate 389 in the enantioselective PTC-promoted alkylation with iodo-ester 447.

Based on these results, it was decided to advance to the following step of the synthetic route. It was anticipated that the chlorination could be successfully performed at a later stage of the synthesis.

The initial efforts to synthesise deprotected spirooxindole derivative 465 incorporating a succinimide unit were rather disappointing. The amidation of 459 with 2-fluorobenzylamine (464) was performed in various solvents over a varied temperature range, and in some cases also in the presence of additives such as Et₃N or DMAP (Scheme 2.30).
 Attempts towards the synthesis of 465.

Most of the reactions outlined in Scheme 2.30 resulted in either decomposition, a miniscule amount of product being formed or there was no change observed at all. However, when the reaction was carried out solely in the presence of 464 and THF, a deprotected analogue of 459, i.e. 466, was detected (Scheme 2.31).

Deprotection of 459 at N-1 by 2-fluorobenzylamine.

Encouraged by this observation, we considered it sensible to perform the reaction in an excess of benzylamine 464, using PhCH$_3$ as the solvent in order to increase the reaction temperature which might favour formation of the amide and potential cyclisation. We were pleased to observe the simultaneous deprotection of 459 and subsequent imide cyclisation in the same step, leading to the formation of desired 467 in excellent yield (Scheme 2.32).

Synthesis of deprotected spirooxindole derivative 467.
However, what we also noticed was a reduction in the product enantiomeric excess. This was a rather frustrating discovery, particularly after the tedious development aimed at the synthesis of spirooxindole derivative 467. Therefore, the synthetic route towards the spirooxindole core had to re-evaluated.

2.7.2 Design of an alternative synthetic pathway towards the spirooxindole target 460

As racemisation of all-carbon quaternary stereocentres via deprotonation is not possible, it was proposed that upon deprotection of the nitrogen atom by 464, a rather unusual rearrangement occurs (Scheme 2.33). This rearrangement leads to destruction of the former stereocentre (intermediate 468), which subsequently results in decreased enantioselectivity observed in spirooxindole 467 (see Scheme 2.32).

Scheme 2.33  Proposed mechanism for destruction of the quaternary stereocentre.

In order to prevent this unwanted rearrangement from occurring and avoid decrease in the ee, we hypothesised that if the nitrogen atom of 3,3'-disubstituted 2-oxindole 459 is initially protected with a substituent that would not be cleaved with benzylamine 464, the only process that could effectively occur would involve the desired amidation and subsequent cyclisation, without loss in ee.

To test our hypothesis, the methyl carbamate at the N-1 position of 3,3'-disubstituted 2-oxindole 459 was initially removed with benzylamine 464 according to the previously described procedure in Scheme 2.31, after an extended reaction time at ambient temperature, where the putative rearrangement is avoided. The deprotected derivative 466 was obtained in good yield and without any reduction in the enantiomeric excess (Scheme 2.34). Subsequent protection of 466 with tert-butyl 2-bromoacetate (471),
which is relevant for the synthesis of 460, resulted in the 3,3’-disubstituted 2-oxindole derivative 472 in a moderate yield and only marginally reduced enantioselectivity.

Scheme 2.34  Synthetic route towards spirooxindole 473, without any substantial loss of enantiomeric excess.

The amidation and subsequent cyclisation was carefully conducted in PhCH$_3$ at a slightly elevated temperature, as room temperature did not favour the formation of 473. To our delight, the desired spirooxindole 473 with the required ester group at the N-1 position was obtained in moderate yield and with almost no loss in ee (Scheme 2.34). This suggests that our hypothesis regarding destruction of the stereocentre via the rearrangement depicted in Scheme 2.33 could be one of the main causes for such a significant reduction in the enantioselectivity.

Since the chlorine atom was yet to be installed at the C-5 position of the oxindole scaffold, chlorination was attempted once again; this time utilising spirooxindole derivative 473 with an excess of NCS, CH$_3$CN as the reaction solvent and an elevated temperature of 85 °C. Gratifyingly, the desired 5-chloro spirooxindole derivative 461 was obtained in good yield in after 16 h. The final step of the synthesis was based on hydrolysis of the tert-butyl ester with trifluoroacetic acid (TFA), furnishing the target compound 460 in both excellent yield and ee (Scheme 2.35).
Overall, the target compound 460 was synthesised in almost optical purity (93% ee) in 73% yield over 8 steps, starting from the commercially available 2-oxindole. In the synthesis of this compound, an effective application of the enantioselective alkylation promoted by a novel phase-transfer catalyst under base-free neutral reaction conditions has been demonstrated.

To assign the absolute stereochemistry of the resulting spirooxindole 460, a crystal structure of its precursor 459 was used. X-ray diffraction analysis revealed that the PTC-promoted alkylation of 310 led to the formation of the (S)-enantiomer (Figure 2.11). By analogy, the absolute stereochemistry of the target compound was assigned as (S)-460.

Disappointingly, it has been demonstrated that the potency of the (R)-enantiomer of 460 was superior to that of its (S)-analogue. However, we believe that the opposite enantiomer could be synthesised via the same synthetic route employing the phase-transfer catalyst prepared from quinidine (41) rather than quinine (39).
2.8 Stereochemical outcome: rationale

The stereochemical outcome of a PTC-promoted alkylation of 2-oxindole derivative 310 under base-free neutral reaction conditions was rationalised. The proposed pathway should be considered speculative, as no computational studies or spectroscopic evidence to support its precise course were collected.

It has been observed that C-2’ chloro-substituted urea-derived cinchona phase-transfer catalyst 335 promoted the alkylation of 2-oxindole substrate 310 with iodo-ester 447 under the optimised conditions (see Table 2.22, entry 14) to afford 3,3’-disubstituted 2-oxindole 459 in high yield and good ee, which upon precipitation of the racemic product resulted in the optically pure enantiomer. The absolute stereochemistry of the product was later demonstrated by X-ray diffraction analysis as (S)-459 (vide supra Figure 2.11).

To explain the stereochemical outcome of the reaction, we proposed a pre-transition state assembly (Figure 2.12). It was postulated that the enolate is stabilised via double hydrogen bonding by the urea moiety and also through the attractive interactions between the ester and the quinuclidinium ion. The carbamate group is facing away from the quinuclidine moiety into solvent: steric bulk here is better tolerated than the ester moiety. As the top face of the enolate is somewhat shielded by the C-2’ chloro quinoline motif, the electrophile approaches the enolate from the bottom, leading to the formation of the desired (S)-product.

![Figure 2.12 Rationale for the stereoselective outcome of the reaction based on catalyst binding to the enolate.](image-url)
2.9 Conclusions

We have successfully developed a protocol for the asymmetric phase-transfer catalysed S_N2 alkylation of 2-oxindole derivatives in the absence of a base, employing water-rich solvent. To the best of our knowledge, these base-free neutral reaction conditions have never been applied to any other PTC-promoted alkylation-type reaction. During our optimisation studies, we have designed and synthesised a large library of novel chiral phase-transfer catalysts based on cinchona alkaloids. It has been demonstrated that the novel C-2’ chloro-substituted bifunctional urea-derived catalyst 335 was the most proficient in promoting the enantioselective alkylation of 2-oxindole-derived substrates. We have proven that C,N-bis-acylated 2-oxindoles of type 292 can be efficiently alkylated under PTC base-free neutral reaction conditions, without any unwanted side products or degradation. This represents a highly effective process for generation of all-carbon quaternary stereocentres. A range of structurally diverse electrophiles have been evaluated in the PTC-promoted alkylation of di-ester-substituted 2-oxindole substrates. Iodo-ester-based electrophiles have led to the formation of synthetically useful products, which were obtained in excellent yield and good enantioselectivity. It was observed that upon precipitation of the racemic product from non-polar solvent, an optically pure enantiomer of 3,3’-disubstituted 2-oxindole derivative can be obtained.

This methodology has been successfully applied in the synthesis of a bioactive spirooxindole target 460, furnishing the desired compound in an overall good yield and almost optical purity (93% ee). The absolute stereochemistry has been assigned by analogy as the (S)-enantiomer, which is in fact the enantiomer that exhibited inferior activity in comparison to its (R)-analogue. However, we believe that it is possible to obtain the target spiroooxindole as the (R)-enantiomer via the same synthetic route employing the phase-transfer catalyst synthesised from quinidine (41) rather than quinine (39).
3 Construction of chiral all-carbon quaternary stereocentres via rearrangement of 2-oxindole derivatives promoted by nucleophilic catalysis

3.1 Steglich rearrangement of 2-oxindole derivatives

The Steglich rearrangement represents a highly efficient method for synthesising quaternary stereocentres, particularly in the case of 2-oxindole derivatives. Generally, the O-to C-acyl transfer is facilitated by the nucleophilic DMAP catalyst. Over the past two decades, many chiral catalysts derived from DMAP or 4-pyrrolidinopyridine (PPY) have been developed and employed in the Steglich rearrangement of azlactones262–266 and benzofuranones/oxindole derivatives.263–265,267–270 Scheme 3.1 depicts the selected examples of the enantioselective Steglich rearrangement of 2-oxindole derivatives.

**Scheme 3.1** Enantioselective Steglich rearrangement of 2-oxindole derivatives promoted by chiral nucleophilic catalysts, e.g. (A) PPY-based catalyst designed by Fu,270 (B) TADMAP derivative developed by Vedejs263 and (C) DMAP-derived 481 prepared by Suga et al.267
The aim of this project was to perform a similar $O$- to $C$-carboxyl transfer of 2-oxindole derivatives but in the presence of a nucleophilic catalyst incorporating a small anionic source such as the fluoride ion. To the best of our knowledge, the fluoride ion has never been employed as a nucleophilic catalyst in such a rearrangement. Furthermore, nucleophilic catalysis by the fluoride ion has never been established beyond doubt in any other transformation. Therefore, we attempted to demonstrate the power of the fluoride anion as an efficient nucleophilic catalyst in the rearrangement of various 2-oxindole derived substrates, leading to the formation of all-carbon quaternary stereocentres. This transformation was chosen, in the main, because effective catalysis can only be of a nucleophilic nature, as there is no external pronucleophile involved.

### 3.2 Synthesis of substrates for preliminary investigations

The substrates chosen for initial studies aimed at the $O$- to $C$-acetyl transfer mediated by nucleophilic catalysis were selected from candidates utilised in reports on the Steglich rearrangement of 2-oxindole derivatives.\textsuperscript{263,264,267} The synthesis of 2-oxindole substrate 480 was accomplished in good yield by following the previously reported protocol,\textsuperscript{271} employing phenyl chloroformate (484, Scheme 3.2).

![Scheme 3.2](image)

**Scheme 3.2** Synthesis of 2-oxindole-based substrate 480.

The substrate 488, incorporating a 2-benzofuranone scaffold, was synthesised in excellent yield as described in Scheme 3.3.

![Scheme 3.3](image)

**Scheme 3.3** Synthetic route towards 2-benzofuranone derivative 488.
Initially, a Wittig reaction\(^{272}\) was employed to convert salicylaldehyde (485) into the corresponding 2-vinylphenol (486) in excellent yield. Subsequent palladium-catalysed regioselective hydroesterification\(^{273}\) of 486 resulted in the formation of 3-methyl-2-benzofuranone (487). The final step of the synthesis towards the \(O\)-acylated benzofuranone substrate 488 was based on a similar procedure to that outlined in Scheme 3.2, utilising phenyl chloroformate (484).

### 3.3 Preliminary rearrangement studies

With two prospective substrates in hand, we attempted the initial \(O\)- to \(C\)-carboxyl transfer in the presence of TBAF as a nucleophilic catalyst (Scheme 3.4).

![Scheme 3.4](image)

**Scheme 3.4** Preliminary studies aimed at the rearrangement of the \(O\)-acylated substrates 480 and 488 promoted by TBAF.

Although, we were pleased to observe a TBAF-promoted rearrangement of 480 leading to the formation of the desired product 482, the yield was extremely low. Furthermore, a deacylated 2-oxindole derivative 489 was also detected, in a substantial yield. The \(O\)-acetyl transfer of 2-benzofuranone-derived substrate 488 was even more disappointing as the formation of the desired product 490 was not observed at all, even after an extended reaction time of 6 days (Scheme 3.4).

In order to investigate the possibility of nucleophilic catalysis by anionic species other than TBAF in the rearrangement of 480, we decided to evaluate tetrabutylammonium acetate, \(\text{Bu}_4\text{NOAc}\) (TBAOAc), as a nucleophilic catalyst in the aforementioned rearrangement. Disappointingly, TBAOAc failed to promote the rearrangement of 480. The only species detected by \(^1\text{H}\) NMR spectroscopy after 3 h were the deacylated by-product 489 and the starting material 480 (Scheme 3.5).
3.4 Alternative substrates and their evaluation in the rearrangement promoted by TBAOAc

In view of the lack of a successful rearrangement catalysed by TBAOAc, we decided to modify the scaffold of the 2-oxindole substrate. Taking our cue from the recent report by Vedejs, a diphenylacetyl moiety was introduced at the nitrogen atom of 2-oxindole. The other modification was based on the alteration of the O-acetyl unit. As mentioned in Section 3.1, Fu has demonstrated an efficient Steglich rearrangement of substrate 474, bearing a 1,1,1-trichloro-2-methylpropan-2-yl carbonate group. We anticipated that by incorporating a similar 2,2,2-trichloroethyl carbonate substituent, the resulting 2-oxindole substrate might undergo a facile TBAOAc-catalysed rearrangement.

The synthesis of substrate 494 began with the protection of 3-methyl 2-oxindole (483) with diphenylacetyl chloride (491), followed by acylation with 2,2,2-trichloroethyl chloroformate (493) to afford the desired substrate 494 in a good yield (Scheme 3.6).

Scheme 3.6 Synthetic pathway towards N-diphenylacetyl-O-2,2,2-trichloroethyl acetyl substrate 494.

Upon subsequent rearrangement of 494 in the presence of TBAOAc, the rearranged product 495 was detected in very low yield, while the formation of the deacylated by-
product 492 was suppressed relative to our first attempt (Scheme 3.7). Regrettably, the remaining starting material was found to undergo decomposition.

This result prompted us to modify the O-acyl moiety. We were concerned that the adventitious water (in the form of retained moisture by a highly hygroscopic TBAOAc) and/or acetic acid (formed as a by-product in catalytic amount during rearrangement) were the potential causes of the unwanted hydrolysis of the acyl electrophile in the catalytic cycle before it could react at the enolate C-atom. Therefore, by incorporating the acetyl substituent, which is smaller and more electrophilic than the previous acyl group in 494, we hypothesised that the rearrangement would proceed more efficiently.

The synthesis of the O-acetylated derivative 497 was accomplished in moderate yield by acylating the N-diphenylacetyl protected 2-oxindole 492 with acetyl chloride (496, Scheme 3.8).

Gratifyingly, the rearrangement of 497 with catalytic TBAOAc led to almost quantitative yield of the desired product 498 (90%) with only 8% of its deacylated analogue 492 (Scheme 3.9).
This transformation represents a major success, in that the acetate anion is acting as a nucleophile in the above rearrangement of 497, furnishing the rearranged product in almost quantitative yield.

### 3.5 Preventing the formation of deacylated by-product during the rearrangement mediated by nucleophilic catalysis

#### 3.5.1 Synthesis of the O-benzoyl-substituted 2-oxindole substrate 500

In an attempt to avoid the formation of the deacetylated product 492, it was postulated that a substrate incorporating a benzoyl group would be more stable than its acetyl analogue 497, and therefore, less prone to hydrolysis. The synthesis of 500 was achieved by following a similar procedure as described in Scheme 3.8, employing benzoyl chloride (499). Regrettably, the reaction resulted in a mixture of four compounds – the starting material 492, the desired O-benzoyl-substituted 2-oxindole 500, its rearranged analogue 501 and benzoic anhydride (502, Scheme 3.10).

**Scheme 3.9** Rearrangement of 498 promoted by TBAOAc.

Although, the target compound 500 was formed during this reaction, its separation from the mixture was not successful by neither column chromatography (the R_f values of 500 and 501 were identical in all of the evaluated solvent systems) nor recrystallisation/precipitation. Even when the same reaction was carried out in the presence of decreased quantities of Et_3N and benzoyl chloride, i.e. 3.0 and 5.0 equiv.,
respectively, the outcome of the reaction was similar, albeit with the increased amount of the unreacted starting material.

An alternative synthetic route employing NaH at low temperature instead of Et₃N for the generation of the enolate of 492 was attempted. However, this reaction furnished the rearranged product 501 almost exclusively in a quantitative yield (Scheme 3.11).

Scheme 3.11  Alternative synthesis of 500 employing NaH as a base.

As we did not succeed in the straightforward synthesis of the O-benzoyl-substituted 2-oxindole substrate 500 – that we assumed might prevent the undesired hydrolysis during rearrangement – we focused on optimisation of the current conditions in the rearrangement of the O-acetyl-substituted 2-oxindole substrate 497.

3.5.2 Optimisation of the reaction parameters in the rearrangement of 497 promoted by TBAOAc

Driven by the desire to either remove or minimise the amount of moisture present in the reaction mixture during rearrangement, we investigated whether the use of additives such as drying agents, e.g. MgSO₄ or molecular sieves would have any effect on the suppression of the putative hydrolysis of substrate 497.

The use of MgSO₄ did not lead to an effective rearrangement. The rearranged product 498 was observed in only 70% yield (Table 3.1, entry 1), while 492 was detected in a comparable amount to that obtained previously in Scheme 3.9, performed in the absence of any additives. This indicated the interference of MgSO₄ with catalysis rather than aiding moisture removal. The use of molecular sieves was also disappointing. Although 3Å molecular sieves assisted in a slight moisture absorption leading to a reduction of the deacetylated by-product 492 (6%), the desired product 498 was obtained in less than optimal yield (52%, entry 2). The rearrangement conducted in the presence of 4Å molecular sieves was found to proceed more efficiently (75%, entry 3) in comparison to the reaction performed with 3Å molecular sieves. However, the effect of moisture
absorption, in terms of the formation of the deacetylated product, was almost identical in the use of both 3Å and 4Å molecular sieves.

**Table 3.1** The effect of additives on the formation of the deacetylated by-product 492 in the rearrangement of 497 promoted by TBAOAc.

<table>
<thead>
<tr>
<th>entry</th>
<th>additive</th>
<th>time (min)</th>
<th>498 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>492 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MgSO&lt;sub&gt;4&lt;/sub&gt;&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30</td>
<td>70</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>Mol. sieves (3Å)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>60</td>
<td>52</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>Mol. sieves (4Å)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>60</td>
<td>75</td>
<td>7</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using p-iodoanisole as an internal standard.  
<sup>b</sup>2.0 equiv. used.  
<sup>c</sup>Mass of molecular sieves equivalent to that of the substrate.

Since the attempts at the moisture removal were not successful, we focused on the potential presence of acetic acid. A series of experiments were conducted where both the starting material 497 and the rearranged product 498 were exposed to acetic acid (Scheme 3.12 (A) and (B), respectively). The aim of this study was to determine whether the added acid would encourage the initial hydrolysis of the starting material 497 or if it would lead to further hydrolysis of product 498.

**Scheme 3.12** Exposure of (A) the starting material 497 and (B) the rearranged product 498 to acetic acid.
According to the data presented in Scheme 3.12, both 497 and 498 were unaffected by the added acetic acid, even when it was added in an excess. Although acetic acid did not seem to be the main cause of hydrolysis, it was hypothesised that a reagent that would neutralise the reaction mixture might lead to the reduced levels of hydrolysis, and consequently decrease the amount of the deacetylated by-product 492. Basic alumina was selected at the reagent of choice for the anticipated neutralisation of the reaction mixture under investigation (Scheme 3.13).

**Scheme 3.13**  Rearrangement of 497 promoted by TBAOAc in the presence of Al\(_2\)O\(_3\).

However, upon performing the rearrangement of 497 in the presence of basic alumina, the formation of 475 was significantly hindered, while the deacetylated by-product 492 was formed in substantial yield (Scheme 3.13).

### 3.5.3 Further optimisation of the reaction conditions

As the presence of additives did not improve the outcome of the rearrangement, another strategy was devised. We envisaged that by lowering the reaction temperature below 0 °C, both H\(_2\)O and acetic acid would freeze, and therefore, the unwanted hydrolysis of 497 would be prevented. However, even at a temperature as low as -30 °C, the deacetylated by-product 492 was formed in 9% yield, while the formation of product was significantly depressed (Scheme 3.14).

**Scheme 3.14**  Rearrangement of 497 promoted by TBAOAc at low temperature.
It was speculated that an increase in catalyst loading might accelerate the rearrangement of 497 to such extent that the full conversion of 498 would be obtained before any of the deacetylated by-product 492 could form. Unfortunately, when 10 mol% of TBAOAc was employed in the rearrangement of 497, 8% of the by-product 492 was already detected after 15 min (Scheme 3.15).

Scheme 3.15 Rearrangement of 497 in the presence of a higher catalyst loading.

Even with all the reagents kept in a dessicator for at least 24 h prior to performing the rearrangement and freshly distilling THF over sodium and benzophenone every time, we did not succeed in reducing the amount of the deacetylated by-product 492 that was always detected throughout the rearrangement. Nonetheless, when distilled THF was treated with molecular sieves (3Å), obtaining an ultra anhydrous solvent, we were pleased to observe reduction of the by-product 492 to 4% (Scheme 3.16).

Scheme 3.16 TBAOAc-promoted rearrangement of 497, utilising anhydrous THF pre-treated with molecular sieves.

In order to establish the optimal solvent for TBAOAc-promoted rearrangement of 497 that might lead to an even more pronounced reduction in the formation of the deacetylated by-product 492, a solvent screen was performed (Table 3.2).
Table 3.2 Evaluation of various solvents in the rearrangement of 497.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>498 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>492 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>497 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>THF</td>
<td>90</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>PhCH₃</td>
<td>48</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>EtOAc</td>
<td>49</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>CH₃CN</td>
<td>36</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂</td>
<td>22</td>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>CHCl₃</td>
<td>2</td>
<td>2</td>
<td>96</td>
</tr>
</tbody>
</table>

<sup>a</sup>Solvents pre-treated with molecular sieves (3Å). <sup>b</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using p-iodoanisole as an internal standard. <sup>c</sup>Reported from Scheme 3.16.

Upon the extensive evaluation of a variety of solvents, THF remained the optimal solvent for the aforementioned rearrangement (entry 1). The use of PhCH₃ and EtOAc led to very similar product yields, with PhCH₃ furnishing the by-product 492 in much higher yield than in EtAOc as solvent (entries 2 and 3, respectively). Media such as CH₃CN and CH₂Cl₂ were found to be unsatisfactory solvents for the acetyl transfer (entries 4 and 5), while CHCl₃ was not compatible with the TBAOAc-catalysed rearrangement at all (entry 6). In addition, solvents such as MTBE and Et₂O poorly solubilised substrate 497, and therefore, were not evaluated as solvents.

3.6 Evaluation of diverse nucleophilic catalysts in the rearrangement of the O-acetylated substrate 497

With the optimised reaction conditions in hand, the catalytic competence of a variety of tetrabutylammonium salts was examined. The most efficient nucleophilic catalysts in the rearrangement of 497 were found to be TBAOAc and TBAF: both furnishing product 498 in excellent yield (Table 3.3, entries 1 and 2). However, the catalytic competence of TBAF was slightly inferior to that of TBAOAc as it encouraged the formation of the deacetylated by-product 492 in higher yield. The use of benzoate-,
azide- and cyanide tetrabutylammonium salts led to the formation of the rearranged product 498 in moderate yields with comparable by-product detection (entries 3-5). Interestingly, TBAB failed to catalyse the rearrangement of 497 even when the reaction time was extended to 2 h (entry 6). To explain the lack of catalysis in the rearrangement, it was postulated that perhaps TBAB is not nucleophilic enough to encourage the acetyl transfer.

Table 3.3 Evaluation of various tetrabutylammonium salts in the rearrangement of 497 using optimised reaction conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>X^-</th>
<th>time (min)</th>
<th>498 (%)^b</th>
<th>492 (%)^b</th>
<th>497 (%)^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td>OAc</td>
<td>30</td>
<td>90</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>30</td>
<td>91</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>OBz</td>
<td>45</td>
<td>75</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>N_3</td>
<td>45</td>
<td>62</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>CN</td>
<td>45</td>
<td>57</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>Br</td>
<td>120</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

^a THF pre-treated with molecular sieves (3Å). ^b Determined by 'H NMR spectroscopic analysis using p-iodoanisole as an internal standard. ^c Reported from Scheme 3.16.

3.7 Synthesis and evaluation of substrates bearing diverse O-acyl moieties

Recognising the potential of nucleophilic catalysis in the rearrangement of the O-acetylated substrate 497, we decided to extend its substrate scope. We intended to demonstrate the rearrangement of substituents other than the acetyl group. For that reason, substrates bearing diverse O-acyl moieties were prepared (Scheme 3.17).
Scheme 3.17  Synthetic route towards substrates possessing diverse O-acyl groups.

As the catalytic performance of TBAF and TBAOAc was comparable in that they both furnished the rearranged product 498 in >90% yield after 30 min (see Table 3.3), it was decided to evaluate the rearrangement of the newly synthesised substrates in the presence of both of these catalysts, respectively. Based on the results, we intended to select the most proficient catalyst that would be employed in further substrate screening.

This study has demonstrated the importance of the acetyl group and its significant impact on the efficiency of rearrangement. While the acetyl group was rearranged readily within 30 min in the presence of TBAF and TBAOAc (Table 3.4, entries 1 and 2), substrate 504 bearing the propionyl group failed to undergo an efficient rearrangement with TBAF (entry 3), while rearrangement barely occurred in the presence of TBAOAc (entry 4). Furthermore, the sterically hindered isobutyryl group was rearranged to only 7% of the desired product 510 after 2 h, while 22% of the deacylated by-product 492 was recorded (entry 5). TBAOAc did not promote the rearrangement of 506 at all (entry 6). The rest of the starting material underwent decomposition. The product 511 possessing the 4-pentenoyl substituent was obtained in moderate yield after 45 min with TBAF (61%, entry 7), while the catalytic activity of TBAOAc was not evaluated due to insufficient availability of 508 in acceptable purity.
Table 3.4  Evaluation of TBAF and TBAOAc in the rearrangement of different O-acylated substrates.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>cat.</th>
<th>time (min)</th>
<th>product (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>492 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>SM (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td><img src="image" alt="Substrate 497" /></td>
<td>498</td>
<td>TBAF</td>
<td>30</td>
<td>91</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td><img src="image" alt="Substrate 498" /></td>
<td>509</td>
<td>TBAOAc</td>
<td>30</td>
<td>90</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
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<td>TBAOAc</td>
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<td>TBAOAc</td>
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<tr>
<td>6</td>
<td><img src="image" alt="Substrate 506" /></td>
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<td>TBAOAc</td>
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<td>TBAF</td>
<td>45</td>
<td>61</td>
<td>10</td>
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</tr>
</tbody>
</table>

<sup>a</sup>THF pre-treated with molecular sieves (3Å).  
<sup>b</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using <sup>p</sup>-iodoanisole as an internal standard.  
<sup>c</sup>Reported from Table 3.3.  
<sup>d</sup>Reported from Scheme 3.16.

Based on the results, TBAF proved to be superior than TBAOAc as a nucleophilic catalyst in the rearrangement of different O-acylated oxindoles. Therefore, TBAF was selected as the catalyst for further substrate screening studies.
3.8 Evaluation of the O-acetylated substrates possessing various substituents at C-3

In order to expand the substrate scope for a TBAF-catalysed rearrangement, a number of O-acetylated substrates bearing various substituents at the C-3 position of the 2-oxindole framework were synthesised. The substrates depicted in Figure 3.1 were prepared by co-workers Mr. Ryan Craig and Ms. Sarah Cronin, according to the previously outlined procedures.

![Various O-acetylated substrates bearing different substituents at C-3.](image)

As demonstrated previously, the O-acetyl substrate 497 was efficiently rearranged in the presence of TBAF (Table 3.5, entry 1). Substrate 515, bearing a benzyl unit at the C-3 position of the oxindole scaffold, also resulted in rapid rearrangement of the acetyl group by TBAF, furnishing the desired product 516 in excellent yield after 30 min. Additionally, we were pleased to observe a complete lack of the formation of the deacetylated by-product (entry 2). The incorporation of the allyl substituent at C-3 encouraged more rapid rearrangement of the acetyl group, yielding 81% of 517 after 15 min (entry 3). Disappointingly, the rearrangement of the acetyl group in substrate 512 was barely discernible, probably due to the close vicinity of the bulky isopropyl group (entry 4). Furthermore, it was assumed that TBAF triggered the decomposition of 512, as a deep brown colouration of the reaction mixture was observed upon the addition of catalyst. Substrate 514, possessing a phenyl substituent at C-3 resulted in even more unsatisfactory results as the rearrangement mediated by TBAF catalysis did not proceed at all (entry 5). It was postulated that the close proximity of the large phenyl group completely inhibited the acetyl transfer.

This study revealed that large or sterically bulky substituents, e.g. the isopropyl or phenyl groups, installed at the C-3 position of the oxindole scaffold can hinder or completely inhibit the rearrangement of the acetyl group promoted by TBAF.
Table 3.5  Evaluation of various *O*-acetylated substrates bearing different substituents at C-3 in the rearrangement promoted by TBAF.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>time (min)</th>
<th>product (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>X (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>SM (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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</thead>
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<td>0</td>
</tr>
<tr>
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<td>45</td>
<td>14</td>
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<td>6</td>
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<sup>a</sup> THF pre-treated with molecular sieves (3Å). <sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis using *p*-iodoanisole as an internal standard. <sup>c</sup> Reported from Table 3.3.
3.9 Mechanistic insights into the rearrangement of the acetyl group promoted by nucleophilic catalysis

To rationalise the role of TBAF as a nucleophilic catalyst in the O- to C-acetyl transfer, we proposed two plausible mechanistic routes. The first mechanism is assumed to proceed via an acetyl fluoride intermediate (i.e. 222, Scheme 3.18), while the alternative mechanism involves the formation of the ketene intermediate 217 (Scheme 3.19).

The first mechanism depicted in Scheme 3.18 involves the nucleophilic attack of the fluoride anion on the acetyl carbonyl group, leading to the formation of the sp3-hybridised tetrahedral intermediate 520. Subsequent decomposition of 520 generates acetyl fluoride (222) and the enolate 521. The attack of 521 on acetyl fluoride generates another sp3-hybridised tetrahedral intermediate 522, which collapses to give the desired product 498.

Scheme 3.18 Proposed mechanism for a TBAF-catalysed acetyl rearrangement proceeding via acetyl fluoride intermediate 222.

The alternative mechanism is based on a proton removal by the fluoride anion to generate the anionic intermediate 523, which leads to the formation of the ketene intermediate 217 and the enolate 521. The following attack of 521 on the ketene intermediate 217 generates the sp2-hybridised anionic intermediate 524, which is subsequently protonated, leading to the formation of the rearranged product 498.

Scheme 3.19 Alternative mechanism for a TBAF-catalysed acetyl rearrangement involving the ketene intermediate 217.
The proposed mechanism for the acetyl rearrangement proceeding via acetyl fluoride intermediate 222 seems to be more plausible than the one involving the ketene intermediate 217. During the course of our studies, it has been demonstrated that the steric bulk of the starting material is very important in order to achieve efficient rearrangement (see Tables 3.4 and 3.5). If deprotonation by fluoride was the key step of the mechanism (as in Scheme 3.19), than the steric bulk of the starting material would not have such a profound effect on the course of rearrangement. Therefore, the nucleophilic catalysis mechanism depicted in Scheme 3.18 is the most probable.

3.10 Attempts directed at enantioselective rearrangement promoted by nucleophilic catalysis

In the desire to construct all-carbon quaternary stereocentres enantioselectively, our research efforts were focused on the development of an enantioselective variant of rearrangement promoted by nucleophilic catalysis. It was hypothesised that by employing the previously synthesised bifunctional quaternary ammonium bromides derived from cinchona alkaloids in conjunction with a fluoride or acetate source, obtained from an inorganic salt such as KF or KOAc, it might be possible to generate the quaternary ammonium fluorides/acetates in situ. It was proposed that such catalysts could promote the rearrangement of the acetyl group enantioselectively.

Initially, a suitable fluoride/acetate source had to be identified. In pursuit of an inorganic salt that would not lead to any background catalysis and would encourage the rearrangement of the acetyl group, a series of control experiments were carried out in the presence of a variety of inorganic salts without other additives.

The use of KF as the source of the fluoride ion catalysed the rearrangement of 497 even in the absence of the bromide catalyst, leading to the formation of 498 in 23% after 24 h (Table 3.6, entry 1). A significant levels of catalysis was observed with CsOAc, affording 498 in 43% yield, while the deacetylated by-product 492 was obtained in 21% (entry 2). KOAc was found to be slightly less active in the rearrangement of 497 (entry 3). When the same reaction was conducted at 0 °C, the unwanted catalysis by the acetate anion was almost completely suppressed (entry 4). Although the use of NaOAc did not lead to any substantial catalysis (entry 5), LiOAc proved to be superior, furnishing product 498 in the lowest yield after 20 h (entry 6) with only a 3% increase after the
additional 20 h (entry 7). Therefore, LiOAc was selected as the optimal source of the acetate anion in the upcoming enantioselective investigations.

Table 3.6  Control experiments employing various inorganic salts in the rearrangement of 497.

<table>
<thead>
<tr>
<th>entry</th>
<th>inorganic salt&lt;sup&gt;b&lt;/sup&gt;</th>
<th>time (h)</th>
<th>498 (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>492 (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>497 (%)&lt;sup&gt;c&lt;/sup&gt;</th>
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</thead>
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<tr>
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<td>23</td>
<td>21</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
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<td>1</td>
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<tr>
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<td>KOAc</td>
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<td>24</td>
<td>12</td>
<td>42</td>
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<tr>
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<td>90</td>
</tr>
<tr>
<td>5</td>
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<td>2</td>
<td>96</td>
</tr>
<tr>
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<td>LiOAc</td>
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<td></td>
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<td>72</td>
</tr>
</tbody>
</table>

<sup>a</sup>THF pre-treated with molecular sieves (3Å).<sup>b</sup> The inorganic salts were dried in the oven at 140 °C for at least 24 h and kept under high vacuum prior to their use. <sup>c</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using p-iodoanisole as an internal standard.<sup>d</sup> Conducted at 0 °C.

Prior to performing the rearrangement enantioselectively, it was necessary to confirm that the quaternary ammonium bromides did not catalyse the acetyl transfer in the absence of the acetate anion. The catalysts selected for this study were based on cinchona alkaloids, specifically the Corey-type catalyst 525, which was synthesised by Ms. Sarah Cronin, quinine-derived quaternary ammonium bromide 526 (synthesis of which is described in Section 4.1.2) and a previously prepared urea-substituted bifunctional quaternary ammonium bromide 345.

The use of quaternary ammonium bromides did not lead to the formation of the rearranged product 498, while the deacetylated by-product 492 was generated only in negligible quantities (Table 3.7). However, what was observed during these studies was
the formation of another product (denoted as $Z$) which will be discussed in more detail in Section 3.10.1.

**Table 3.7**  Control experiments employing various quaternary ammonium bromides in the rearrangement of $497$.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>time (h)</th>
<th>$498$ (%)</th>
<th>$492$ (%)</th>
<th>$Z$ (%)</th>
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<td>40</td>
<td>0</td>
<td>2</td>
<td>41</td>
<td>57</td>
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</table>

*THF pre-treated with molecular sieves (3Å). * Determined by $^1$H NMR spectroscopic analysis using $p$-iodoanisole as an internal standard.

The Corey-type catalyst $525$ promoted the formation of $492$ in only 4%, while 37% of $Z$ product was observed, detecting almost half of the original starting material after 60 h (Table 3.7, entry 1). The quaternised quinine catalyst $526$ furnished $Z$ analogue in a much lower yield, while $497$ was observed in higher quantity (entry 2). The catalytic performance of the bifunctional urea-derived catalyst $354$ was comparable to that of $525$ (entry 3).
Having evaluated the catalytic competence of both the acetate anion source, i.e. LiOAc,
and the quaternary ammonium bromides in the rearrangement of 497 independently, the
potential of generating a quaternary ammonium acetate in situ was assessed. Although,
LiOAc was found to promote the formation of both the rearranged product 497 and the
deacetylated by-product 492 after 40 h, it was envisaged that within this time frame the
acetyl group could be successfully rearranged in the presence of a quaternary
ammonium bromide, providing an efficient anion exchange occurs.

**Table 3.8** Rearrangement of 497 conducted with various quaternary ammonium
bromides and LiOAc.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>time (h)</th>
<th>498 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>492 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>497 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
<td>3</td>
<td>345</td>
<td>40</td>
<td>6</td>
<td>10</td>
<td>77</td>
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</tbody>
</table>

<sup>a</sup>THF pre-treated with molecular sieves (3Å). <sup>b</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis using <sup>p</sup>-
idoanisole as an internal standard.
However, upon evaluation of LiOAc in conjunction with the quaternary ammonium bromides, it was revealed that the rearrangement did not occur to any considerable extent (Table 3.8). The Corey-type catalyst 525 in the presence of LiOAc resulted in the highest product yield of 14%, while a substantial amount of the starting material 497 had been consumed after 60 h (Table 3.8, entry 1). The catalytic performance of either 526 or 345, in conjunction with LiOAc, did not yield any positive results (entries 2 and 3). Furthermore, the reaction time had to be extended beyond 40 h, due to a very low amount of product formation being detected within this time frame. During this additional time, it has been previously demonstrated that the acetate anion catalysed the formation of both 498 and 492 (see Table 3.6, entry 7). Therefore, these results do not necessarily reflect solely the catalytic activity of the quaternary ammonium acetate that we proposed was generated in situ, but also catalysis by LiOAc and probably even the bromide anion itself in the formation of 492.

Despite our efforts to perform the rearrangement enantioselectively by generating the cinchona alkaloid-derived quaternary ammonium fluoride/acetate in situ, we did not succeed in efficient acetyl transfer involving 497.

### 3.10.1 Formation of an alternative product in the rearrangement catalysed by the quaternary ammonium bromides

As mentioned in the previous Section, during the control rearrangement experiments carried out with quaternary ammonium bromides, the starting material was diminished, but the desired product 498 was not detected (see Table 3.7). However, what we did observe was the formation of another product (denoted as Z in Table 3.7). Although this alternative product Z was structurally very similar to the expected 498, it was proposed that the diphenylacetyl group is present at the C-3 position of the oxindole framework, while the acetyl group is at the nitrogen atom as in 527 (Scheme 3.20).

![Scheme 3.20](image-url)  
Scheme 3.20 Rearrangement in the presence of the quaternary ammonium bromide.
The possible structure of 527 was determined by extensive NMR spectroscopic analysis. As shown in Figure 3.2, the product 527 has the same number of protons as 498 (Figure 3.3), yet the position of the methyl substituents is different. While the methyl groups in 498 experience similar environment (1.54 and 1.50 ppm), the environment in 527 is significantly different. It was proposed that the signal at 2.03 ppm denotes the methyl group of the acetyl group attached to the nitrogen atom, while the more upfield signal at 1.41 ppm belongs to the methyl group at C-3.

![Figure 3.2](image1.png)  
**Figure 3.2** $^1$H NMR spectrum of 527.

![Figure 3.3](image2.png)  
**Figure 3.3** $^1$H NMR spectrum of 498.

As we have not managed to obtain a crystal of 527 for X-ray diffraction analysis, its exact structure is yet to be confirmed.
3.11 Conclusions

Rearrangement of the acetyl group in 2-oxindole-derived substrate 497 was efficiently promoted by the fluoride ion, as well as the acetate anion, employing TBAF and TBAOAc catalysts, respectively. To the best of our knowledge, nucleophilic catalysis by these anions has never before been conclusively demonstrated. In the preliminary investigations, it was revealed that the overall substrate structure has a crucial impact on the rearrangement of the O-acyl moiety. It was established that the presence of the diphenylacetyl group at N-1 had a positive effect of the rearrangement. Furthermore, the acetyl group was found to be the ideal choice of the motif to be rearranged in the presence of a nucleophilic catalyst. A strictly anhydrous environment was absolutely essential to prevent the formation of the unwanted deacylated by-product during the rearrangement process. The use of molecular sieves in the reaction solvent proved to be very beneficial in this regard.

The efforts carried out to perform the rearrangement in an enantioselective fashion by combining the quaternary ammonium bromides derived from cinchona alkaloids with inorganic salts, which would provide the source of the fluoride/acetate ion, were not successful.
4 Enantioselective methanolysis of meso-anhydrides mediated by nucleophilic catalysis

4.1 Development of chiral quaternary ammonium fluorides derived from cinchona alkaloids

As previously mentioned in Section 1.5.2.2, our group has succeeded in highly efficient, asymmetric desymmetrisation of meso-anhydrides promoted by bifunctional cinchona alkaloid-derived catalysts. The aim of this project was to demonstrate the ability of the quaternary ammonium fluorides, derived from cinchona alkaloids, to act as efficient nucleophilic catalysts in the enantioselective methanolysis of meso-anhydrides.

A library of chiral quaternary ammonium bromides, formerly employed as enantioselective phase-transfer catalysts, was available at the outset of this investigation. However, since most of these catalysts were substituted with either a urea or a squaramide moiety, we considered it opportune to expand the scope of this library to include other hydrogen-bond donating groups, such as the sulfamide- and sulfonamide-based cinchona alkaloids, derivatives of quinine quaternised at the nitrogen atom and the Corey-type catalysts. It was anticipated that the fluoride analogues of these quaternary ammonium bromides could be readily prepared according to known literature procedures, previously developed by Shiori\textsuperscript{215} (see Section 1.4.2).

This project was a collaboration between two fellow co-workers. Mr. Ryan Craig was investigating the effects of diverse electronic substituents incorporated within the scaffolds of the urea- and squaramide-based catalysts, while Ms. Sarah Cronin was involved in the synthesis of the Corey-type catalysts.

4.1.1 Synthesis of sulfamide- and sulfonamide-based quaternary ammonium bromides

Although the bifunctional sulfamide- and sulfonamide-substituted catalyst precursors were designed and previously prepared by fellow researcher Mr. Romain Claveau, the synthesis of their quaternary ammonium bromide analogues (Figure 4.1) was rather problematic, leading to very poor yields due to difficult purification procedures, requiring several consecutive column chromatography operations.
Figure 4.1 Synthetic targets: the sulfamide-based catalyst 528 and the sulfonamide-substituted cinchona alkaloids 529 and 530.

Unfortunately, after the extensive purification of the aforementioned catalysts, they were found to decompose at room temperature. Their stability was compromised even at low temperatures, at which further degradation was observed. For this reason, we considered the use of such catalysts impractical and abandoned the idea of evaluating the sulfamide and sulfonamide functionality in the forthcoming methanolysis studies.

4.1.2 Synthesis of quinine-based quaternary ammonium bromides

The quinine-derived catalysts were efficiently synthesised according to protocols previously developed by Dr. Emiliano Sorrentino (see Section 2.4.3), employing relevant alkylating agents (Scheme 4.1).

Scheme 4.1 Synthetic route towards quaternised quinine-based catalysts.
4.1.3 Towards the synthesis of quaternary ammonium fluorides

In order to convert the quaternary ammonium bromides into their corresponding fluoride analogues, a number of different approaches were explored. The catalyst selected for these preliminary anion exchange investigations was quinine 531 substituted with a 3,5-(bis)trifluoromethyl benzyl moiety. Due to the presence of a fluorine atom within its scaffold, the requirement for an internal standard, e.g. CFCI3, was eliminated. This was the main reason for selecting 531 as the catalyst of choice for the forthcoming trials.

The initial method for anion exchange involved the use of the fluoride ion supported on a polymer (Amberlyst A-26, 3.0 mmol fluoride ion/g loading). The use of CH2Cl2 as the reaction solvent did not lead to a successful exchange, while THF failed to fully solubilise the catalyst. A more polar solvent, such as MeOH proved to be the most effective solvent, leading to a complete exchange between Br⁻ and F⁻. The efficiency of exchange was determined by ¹⁹F NMR spectroscopic analysis after 30 minutes, sampled directly from the reaction mixture (Scheme 4.2).

![Scheme 4.2](image)

Scheme 4.2   Anion exchange using fluoride ion supported on polymer.

However, upon removal of MeOH in vacuo, the signal corresponding to the fluoride ion in catalyst 534 was no longer observed in the ¹⁹F NMR spectrum. Therefore, another anion exchange method had to be evaluated. This particular method involved the use of Amberlyst OH resin, which was converted into its fluoride form by continuous washing with HF (1.0 N) until the washings were acidic. Subsequent rinsing of the resin with deionised H₂O and Et₂O afforded Amberlyst F⁻ resin, which was thoroughly dried prior to its use.

When the freshly prepared Amberlyst F⁻ resin was employed in the anion exchange involving catalyst 531, we were pleased to observe full conversion of 531 to its fluoride analogue 534 after 30 minutes (Scheme 4.3).
Unfortunately, a similar outcome to the previous attempt with the fluoride on polymer support was observed. Upon removal of the solvent in vacuo, the signal correlating to the fluoride ion in catalyst 534 was not detected by $^{19}$F NMR spectroscopic analysis. Despite the various methods of solvent evaporation, such as using the rotary evaporator without the aid of water bath and removal of MeOH under the flow of argon, the desired fluoride catalyst 534 was not isolated.

An alternative procedure that was attempted also involved Amberlyst −OH resin, however this time, it was added to a solution of catalyst 531 in MeOH until the pH of the mixture was basic (pH 10). Subsequent neutralisation with HF (1.0 N) led to successful anion exchange after 45 min (determined by $^{19}$F NMR spectroscopic analysis, Scheme 4.4).

Scheme 4.3 Anion exchange with Amberlyst F− resin.

Upon filtration of the reaction mixture in order to separate the resin from the catalyst, the $^{19}$F NMR spectrum still indicated the presence of the fluoride anion. However, evaporation of MeOH led to its disappearance once again.

A modified version of the previous method was evaluated next. This procedure employed a column packed with Amberlyst −OH resin, through which the solution of catalyst 531 in MeOH was passed. The resulting solution of the catalyst, now containing hydroxide anions instead of the bromide ions, was neutralised with HF (1.0 N). Regrettably, this method led to an incomplete anion exchange. A systematic study of the
factors that could influence the outcome of anion exchange was conducted. The first study examined the effect of the quantity of Amberlyst OH resin used to pack the column. It was reasoned that if a sufficient quantity of resin was used, then an efficient anion exchange between the bromide and the hydroxide ions could take place. However, when this study was carried out with 5, 10 and 25 equivalents of Amberlyst OH resin relative to the catalyst weight, the results were disappointing (Scheme 4.5).

Scheme 4.5 The effect of Amberlyst OH loading.

Based on 19F NMR spectroscopic analysis of samples taken from the reaction mixtures throughout the study, it was observed that while low levels of anion exchange were achieved with 5 equivalents of Amberlyst resin, 25 equivalents led to over fluoridation, observing 150% fluoride conversion with an extra resonance in the 19F NMR spectrum. However, 10 equivalents of the resin resulted in 50% anion exchange, it was hypothesised that if the solution of catalyst was passed through the column packed with 10 equivalents of Amberlyst OH resin multiple times, then all the bromide anions could be exchanged for the hydroxide ions. Thus, the following neutralisation of the hydroxide anions with HF could lead to a complete conversion to the fluoride species. Regrettably, the outcome of this investigation was disappointing (Scheme 4.6).

Scheme 4.6 Multiple passing of the catalyst solution through Amberlyst OH resin.
Passing the solution of catalyst 531 in MeOH through the column packed with 10 equivalents of Amberlyst resin only once resulted in an extremely low conversion to fluoridated product. However, when the solution was passed through the column three times, considerable overfluoridation was observed, with another fluorine signal being detected in the $^{19}$F NMR spectrum. Even higher levels of fluoridation were obtained when the solution was passed through the column five times.

As neither the fluoride supported on polymer nor the numerous efforts involving the use of Amberlyst ‘OH resin led to successful development of a robust method for an effective anion exchange, our focus was directed towards other possibilities for the synthesis of the quaternary ammonium fluorides.

An alternative technique was achieved based on the generation of the fluoride catalysts in situ. Mr. Ryan Craig succeeded in the establishment of an effective method for the methanolyis of anhydrides catalysed by the in situ generated quaternary ammonium fluorides, formed by anion exchange between the chiral quaternary ammonium bromides and the inorganic salt of KF. Mr. Craig also optimised the reaction conditions, which led to reproducible enantioselectivity data obtained after functionalisation of hemiester 285 with a chiral amine 535 (Scheme 4.7).

![Scheme 4.7 General protocol for the methanolysis of succinic anhydride 274.](image-url)
4.2 Catalyst evaluation in the methanolysis of *meso*-anhydride 274

With an efficient general procedure for the methanolysis of succinic anhydride 274 in hand, and with no background reaction occurring in the control experiments carried out by Mr. Ryan Craig, we embarked upon determining the most proficient catalyst that would afford hemiester 285 in the highest *ee*. The catalyst screening was conducted with fellow co-workers, Mr. Ryan Craig and Ms. Sarah Cronin. The initial study was aimed at evaluation of the quaternised quinine derivatives and Corey-type catalysts.

**Table 4.1** Evaluation of the quaternised quinine bromides and Corey-type catalysts in the methanolysis of 274.

<table>
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<th>cat.</th>
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<th><em>ee</em> (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
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<td>539&lt;sup&gt;d&lt;/sup&gt;</td>
<td>30</td>
<td>-4</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopic analysis. <sup>b</sup>Determined by CSP-HPLC after isolation of the functionalised amide 536 by preparative TLC. <sup>c</sup>Synthesised and evaluated by Mr. Ryan Craig. <sup>d</sup>Synthesised and evaluated by Ms. Sarah Cronin.
Although the quinine-based catalyst 537 afforded hemiester 285 in high conversion after 48 h, it was almost completely racemic (Table 4.1, entry 1). Comparable selectivity was observed using catalysts 526 and 532 (entries 2 and 4), with catalyst 531 possessing electron-withdrawing substituents at the quinuclidine nitrogen atom furnishing the formation of 285 in 10% ee (entry 3). Despite the high conversion of 285 obtained utilising catalyst 525, it was detected with the opposite absolute configuration and only 11% ee (entry 5). It was demonstrated that the Corey-type catalyst 538, incorporating the anthracenylmethyl group, led to a completely racemic formation of hemiester 285 in poor yield (entry 6). A structurally different catalyst, bearing the O-benzyl group attached at the C-9 stereocentre of quinine, i.e. catalyst 539, failed to efficiently catalyse the methanolysis of 274.

Most of the squaramide- and urea-substituted catalysts were found to be superior from the enantioselectivity standpoint compared to the alkylated quinine derivatives and Corey-type catalysts. The squaramide-derived catalysts 540 and 541 encouraged the formation of hemiester 285 in the opposite absolute configuration (Table 4.2, entries 1 and 2). The squaramide-based 541, substituted with fluorine atoms on the benzyl moiety, afforded 285 in comparatively higher ee (entry 2). The urea-derived catalyst 542, bearing a tert-butyl group at the urea motif, resulted in the formation of 285 in almost racemic form (entry 3). A similar catalyst to 542, i.e. catalyst 543, bearing a urea unit substituted with an aromatic ring and electron-withdrawing groups, led to a completely racemic product, albeit in higher conversion (entry 4). Interestingly, the same catalyst bearing a 3,5-dibromo substituent on the quinuclidine moiety – catalyst 544, and a 3,5-(bis) trifluoromethyl group as in catalyst 545, afforded the desired hemiester 285 in 53% ee and 51% ee, respectively (entries 5 and 6). A decreased conversion and ee of 285 was detected in the presence of catalysts 307 and 326, incorporating both electron-donating groups at the aromatic quinuclidine ammonium moiety and a phenyl substituent at C-2’ (entries 7 and 8). The combination of a C-2’ phenyl group with electron-withdrawing fluorine atoms on the aromatic moiety of the quinuclidine nitrogen atom led to the formation of 285 in comparable conversion and selectivity to that obtained with catalyst 545 (entry 6). The most effective promoters in this study were catalysts 547 and 325; bearing electron-withdrawing aryl substituents and a phenyl group at the C-2’ position (entries 10 and 11). The allyl-functionalised catalyst 548 resulted in the formation of 285 with very low ee (entry 12).
Table 4.2  Evaluation of the urea- and squaramide-substituted catalysts.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>conv. (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>1</td>
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<td>11</td>
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<td>60</td>
</tr>
<tr>
<td>12</td>
<td>548&lt;sup&gt;d&lt;/sup&gt;</td>
<td>70</td>
<td>17</td>
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</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis. <sup>b</sup>Determined by CSP-HPLC after isolation of the functionalised amide 536 by preparative TLC. <sup>c</sup>Synthesised and evaluated by Mr. Ryan Craig. <sup>d</sup>Synthesised and evaluated by Ms. Sarah Cronin.
4.2.1 Further catalyst optimisation

From the catalyst evaluation studies, it became clear that the urea-substituted catalysts were the most efficient in facilitating the desymmetrisation of anhydride 274. In particular, urea-based catalysts bearing 3,5-(bis)trifluoromethyl groups on the aromatic ring and electron-withdrawing substituents at the aryl quinuclidine moiety. Driven by the desire to improve the ee of hemiester 285 even further, a novel catalyst design was proposed. It was reasoned that by incorporating a nitro substituent in the para position and a halogen atom in the ortho position of the quinuclidine benzyl moiety, the catalyst would demonstrate superiority over its preceding analogues.

Since 3-bromo-4-nitrobenzyl bromide (550) was not commercially available, it was synthesised in moderate yield from 2-bromo-4-methyl-1-nitrobenzene (549) and NBS promoted by AIBN (Scheme 4.8).

Scheme 4.8 Synthesis of 3-bromo-4-nitrobenzyl bromide (550).

The catalysts 551 and 552 were synthesised in moderate to good yield according to the previously described procedure (Scheme 4.9).

Scheme 4.9 Synthesis of novel catalysts incorporating a halogen atom and a nitro group on the quinuclidine benzyl moiety.
Unexpectedly, evaluation of these novel catalysts in the methanolyis of succinic anhydride 274 led to rather disappointing results. Although the conversion of 285 has slightly improved, the enantioselectivity was essentially the same, 61% ee and 62% ee achieved with catalysts 551 and 552, respectively (Table 4.3, entries 2 and 3).

**Table 4.3** Evaluation of novel optimised catalysts.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>conv. (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>2</td>
<td>551</td>
<td>77</td>
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</tr>
<tr>
<td>3</td>
<td>552</td>
<td>79</td>
<td>62</td>
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</tbody>
</table>

<sup>a</sup>Determined by 1H NMR spectroscopic analysis. <sup>b</sup>Determined by CSP-HPLC after isolation of the functionalised amide 536 by preparative TLC. <sup>c</sup>Reported from Table 4.2.

Since the novel catalysts did not lead to any significant improvement in the enantiomeric excess of hemiester 285, catalyst 552, bearing 3-fluoro and 4-nitro substituents, was selected as the catalyst for further substrate scope, which was conducted by Mr. Ryan Craig and will not be reported in this thesis.
4.3 Conclusions

Catalysis by fluoride ion has been effectively demonstrated in the methanolysis of succinic anhydride 274. After numerous unsuccessful attempts at the synthesis of quaternary ammonium fluorides by anion exchange with either a fluoride ion supported on polymer or Amberlyst ´OH resin, the desired fluoride species were generated \textit{in situ} by anion exchange between the chiral quaternary ammonium bromides and KF. Although the catalyst optimisation studies did not lead to any significant improvements in the enantioselectivity of hemiester 285, it was observed that urea-derived catalysts bearing 3,5-(\textit{bis}) trifluoromethyl groups on the aromatic ring and electron-withdrawing substituents at the aryl quinuclidine moiety were among the most proficient catalysts. The squaramide-based catalyst promoted methanolysis of 274 in the opposite absolute configuration, while the quaternised quinine derivatives and Corey-type catalysts were not suitable promoters at all. It is worth mentioning, that despite the novel mode of catalysis, the overall enantiocontrol was not at the same level as with the previous bifunctional catalyst systems.\textsuperscript{238}

Further studies to expand the scope of desymmetrisation catalysed by the \textit{in situ} generated fluoride ions are being examined in our laboratory. Moreover, investigations aimed at the elucidation of the mechanism of methanolysis mediated by the fluoride ion are also currently underway.
5 Experimental procedures and data

5.1 General

Proton Nuclear Magnetic Resonance (NMR) spectra were recorded on 400 MHz or 600 MHz Bruker Advance spectrometers, using as solvent CDCl$_3$, DMSO-$d_6$, D$_2$O or CD$_3$OD and referenced relative to residual CHCl$_3$ ($\delta = 7.26$ ppm), DMSO ($\delta = 2.50$ ppm), H$_2$O ($\delta = 4.79$ ppm) or CH$_3$OH ($\delta = 3.31$ ppm). Chemical shifts are reported in ppm and coupling constants ($J$) in Hertz. Carbon NMR spectra were recorded on the same instruments (100.6 MHz and 150.9 MHz, respectively) with total proton decoupling. HSQC, HMBC, TOCSY, NOE and ROESY NMR experiments were used to aid assignment of NMR peaks when required. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. ESI mass spectra were acquired using a Waters Micromass LCT-time of flight mass spectrometer (TOF), interfaced to a Waters 2690 HPLC. The instrument was operated was operated in positive or negative mode as required. EI mass spectra were acquired using a GCT Premier Micromass time of flight mass spectrometer (TOF). The instrument was operated in positive mode. Chemical ionisation (CI) mass spectra were determined using a GCT Premier Micromass mass spectrometer in CI mode utilising methane as the ionisation gas. APCI experiments were carried out on a Bruker microTOF-Q III spectrometer interfaced to a Dionex UltiMate 3000 LC or direct insertion probe. The instrument was operated in positive or negative mode as required. Agilent tuning mix APCI-TOF was used to calibrate the system. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated 60F$_{254}$ silica gel plates, and visualised by either UV irradiation or KMnO$_4$ staining. Optical rotation measurements were made on a Rudolph Research Analytical Autopol IV instrument, and are quoted in units of $10^{-1}$ deg cm$^2$ g$^{-1}$. Anhydrous acetonitrile (CH$_3$CN), dichloromethane (CH$_2$Cl$_2$), tetrahydrofuran (THF) and diethyl ether (Et$_2$O) were obtained by using Pure Solv MD-4EN Solvent Purification System. Commercially available anhydrous methanol (MeOH) and $t$-butyl methyl ether (MTBE) were used. Triethylamine and dimethylformamide (DMF) were distilled from calcium hydride and stored under argon. Analytical CSP-HPLC was performed using either Daicel CHIRALPAK AD, AD-H, IA or CHIRALCEL OD, OD-
H (4.6 x 250 mm) columns or Acquity UltraPerformance Convergence Chromatography (UPC²), employing following conditions (steps) in the gradient elution mode.

**STEP 1**  
**Mobile phase:** A = CO₂, B = EtOH/CH₃CN (1:1, v:v)  
**Chiral stationary phase:** Trefoil AMY1 (2.5µm, 3.0 x 150 mm)

**STEP 2**  
**Mobile phase:** A = CO₂, B = MeOH/IPA (1:1, v:v)  
**Chiral stationary phase:** Trefoil CEL1 (2.5µm, 3.0 x 150 mm)

**STEP 3**  
**Mobile phase:** A = CO₂, B = EtOH/CH₃CN (1:1, v:v)  
**Chiral stationary phase:** Trefoil CEL2 (2.5µm, 3.0 x 150 mm)

**STEP 4**  
**Mobile phase:** A = CO₂, B = EtOH/IPA (1:1, v:v)  
**Chiral stationary phase:** Trefoil AMY1 (2.5µm, 3.0 x 150 mm)

<table>
<thead>
<tr>
<th>Gradient Elution Method</th>
<th>time (min)</th>
<th>flow (mL/min)</th>
<th>A (%)</th>
<th>B (%)</th>
<th>curve</th>
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<tr>
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<td>97.0</td>
<td>3.0</td>
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</tr>
<tr>
<td>4.50</td>
<td>1.2</td>
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<td>60.0</td>
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<td>6.10</td>
<td>1.2</td>
<td>97.0</td>
<td>3.0</td>
<td>6</td>
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</tr>
</tbody>
</table>

Prior to CSP-HPLC analysis of the enantioselective product, each alkylated compound was synthesised in its racemic form, which allowed for determination of retention time and ideal separation between two enantiomers.

The X-ray crystallography data for sample TCD929 (C₂₁H₁₆F₃NO₇) were collected on a Bruker APEX DUO using Cu Kα radiation (λ = 1.54178 Å) and a MiTeGen micromount at 100(2) K (Oxford Cobra Cryosystem). Bruker APEX software was used to collect and reduce data, determine the space group, solve and refine the structure. Absorption corrections were applied using SADABS 2014. All final refinements were performed with SHELXL 2014/3. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned to calculated positions using a riding model with appropriately fixed isotropic thermal parameters.

Crystal Data for TCD929 (C₂₁H₁₆F₃NO₇), M = 451.35, triclinic, space group P1 (no. 1), a = 6.0411(3) Å, b = 15.5976(8) Å, c = 22.2056(10) Å, α = 102.604(3)°, β = 90.411(4)°, γ = 97.014(3)°, V = 2025.42(17) Å³, Z = 4, T = 100(2) K, μ(CuKα) = 1.124 mm⁻¹, Dcalc = 1.480 g/cm³, 51848 reflections measured (4.08° ≤ Θ ≤ 137.094°), 14250 unique (Rint = 0.1702, Rsigma = 0.2031) which were used in all calculations. The final R1 was 0.0836 (I > 2σ(I)) and wR2 was 0.2333 (all data), Gof on F² = 1.042.

For clarity the numbering system associated with the assignment of the ¹H NMR peaks did not follow the IUPAC nomenclature system.
5.2 Experimental data for Chapter 2

5.2.1 Preparation of substrates

**General procedure I:** Protocol for the preparation of *N,O*-bis-acylated 2-oxindole derivatives.

An oven dried two-necked round-bottomed flask containing a stirring bar and equipped with a thermometer was charged with the appropriate 2-oxindole (1.0 equiv.), fitted with a septum and placed under an argon atmosphere (balloon). Freshly distilled triethylamine (2.2 equiv.) and anhydrous THF (0.4 M) were added via syringe. The appropriate ester of chloroformic acid (2.2 equiv.) was then added dropwise via syringe, keeping the temperature of the reaction mixture below 30 °C during the addition. After stirring for 30 min at room temperature, the solvent was removed *in vacuo*. Water (0.7 M) was added to the residue and the mixture was stirred for 2 h at 0 °C. The precipitated crude product was then filtered under vacuum and purified either by recrystallisation or column chromatography on silica gel.

**Ethyl 2-((ethoxycarbonyl)oxy)-1H-indole-1-carboxylate (293)**

![Chemical structure](image)

Synthesised according to general procedure I, using 2-oxindole (289, 4.0 g, 30.04 mmol), triethylamine (9.2 mL, 66.09 mmol), THF (75.0 mL) and ethyl chloroformate (6.28 mL, 66.08 mmol). The crude residue was recrystallised from hexanes to yield 293 (7.9 g, 95%) as a pale orange amorphous solid. M.p. 54-56 °C (lit. 274 57-58 °C). The isolated compound exhibited identical spectroscopic data to those reported in the literature.\(^{240}\)

\[\delta_H (400 \text{ MHz, CDCl}_3): 8.08 (d, 1 \text{ H}, J 8.3, \text{ H-7}), 7.50 (d, 1 \text{ H}, J 7.8, \text{ H-4}), 7.32 (\text{app. td}, 1 \text{ H}, J 7.8, 1.1, \text{ H-6}), 7.25 (\text{app. t}, 1 \text{ H}, J 7.8, \text{ H-5}), 6.32 (\text{s}, 1 \text{ H}, \text{ H-3}), 4.48 (\text{q}, 2 \text{ H}, J 7.9, \text{ H-2}), 4.38 (\text{q}, 2 \text{ H}, J 7.9, \text{ H-8}), 1.47-1.40 (\text{m}, 6 \text{ H}, \text{ H-1 and H-9})\]
Methyl 2-((methoxycarbonyl)oxy)-1H-indole-1-carboxylate (309)

Synthesised according to general procedure I, using 2-oxindole (289, 8.0 g, 60.08 mmol), triethylamine (18.4 mL, 132.18 mmol), THF (150.0 mL) and methyl chloroformate (10.2 mL, 132.18 mmol). The crude residue was purified by column chromatography (100% CH₂Cl₂, Rᵣ = 0.6), to afford product 309 (10.4 g, 69%) as a white amorphous solid. M.p. 66-67 °C.

Note: Compound 309 is a known material, however the literature characterisation of this compound is devoid of melting point data. Our ¹H NMR spectroscopy and HRMS data are consistent with those in the literature.²⁷⁵

δ_H (400 MHz, CDCl₃): 8.04 (d, 1 H, J 8.3, H-6), 7.50 (d, 1 H, J 7.4, H-3), 7.32 (app. td, 1 H, J 7.4, 1.3, H-5), 7.25 (td, 1 H, J 7.4, 1.3, H-4), 6.33 (s, 1 H, H-2), 4.03 (s, 1 H, H-1), 3.97 (s, 1 H, H-7)

HRMS (m/z - DIP-APCI): Found: 248.0558 [M–H]⁺ C₁₂H₁₀NO₅ Requires: 248.0564

Benzyl 2-(((benzylxy)carbonyl)oxy)-1H-indole-1-carboxylate (366a)

Synthesised according to general procedure I, using 2-oxindole (289, 5.0 g, 37.55 mmol), triethylamine (11.5 mL, 82.61 mmol), THF (95.0 mL) and benzyl chloroformate (11.8 mL, 82.61 mmol). The crude residue was purified by column chromatography (hexane/EtOAc, 9:1, Rᵣ = 0.3), to afford product 366a (10.1 g, 67%) as a while amorphous solid. M.p. 84-85 °C (lit.²⁷⁶ 86-88 °C). The isolated compound exhibited identical spectroscopic data to those reported in the literature.²⁷⁶
\(\delta_H\) (400 MHz, CDCl\(_3\)): 7.97 (d, 1 H, J 8.0, H-5), 7.38 (app. t, 1 H, J 8.0, H-4), 7.33 (dd, 2 H, J 7.1, 1.4, H-7), 7.30-7.23 (m, 3 H, H-8 and H-9), 7.19-7.11 (m, 2 H, H-3 and H-2), 6.21 (s, 1 H, H-1), 5.21 (s, 2 H, H-6), 4.97 (s, 2 H, H-10)

**General procedure II:** Wolff-Kishner reduction of substituted isatins.

To the appropriate isatin (1.0 equiv.) in a round-bottomed flask containing a stirring bar, hydrazine hydrate (50-60% hydrazine, 0.5 M) was carefully added and the reaction mixture was refluxed at 140 °C for 6 h. The reaction mixture was cooled to rt, poured into ice-water and acidified to pH 2 with HCl (6.0 N, aq.). After standing at room rt for 2 days, the precipitate was collected by vacuum filtration and it was washed with water. The crude product was purified by column chromatography on silica gel.

**4-Bromoindolin-2-one (379)**

![Chemical structure of 4-Bromoindolin-2-one (379)](image)

Synthesised according to general procedure II, using 4-bromoisaatin (375, 5.0 g, 22.12 mmol) and hydrazine hydrate (44 mL). The crude residue was purified by column chromatography (hexane/EtOAc, 1:1, \(R_f = 0.4\)), to afford product 379 (4.5 g, 96%) as a brown amorphous solid. M.p. 210-215 °C (lit.\(^{277}\) 217-220 °C). The isolated compound exhibited identical spectroscopic data to those reported in the literature.\(^{278}\)

\(\delta_H\) (400 MHz, dmso-d\(_6\)): 10.60 (br s, 1 H, H-1), 7.16-7.09 (m, 2 H, H-3 and H-4), 6.81 (dd, 1 H, J 1.7, 6.7, H-5), 3.44 (s, 2 H, H-2)

**5-Bromoindolin-2-one (380)**

![Chemical structure of 5-Bromoindolin-2-one (380)](image)

Synthesised according to general procedure II, using 5-bromoisaatin (376, 0.5 g, 2.212 mmol) and hydrazine hydrate (4.4 mL). The crude residue was purified by column chromatography (CH\(_2\)Cl\(_2\)/MeOH, 95:5, \(R_f = 0.7\)), to afford product 380 (275 mg, 60%) as a brown amorphous solid. M.p. 213-214 °C (lit.\(^{279}\) 216-218 °C). The isolated compound exhibited identical spectroscopic data to those reported in the literature.\(^{279}\)
δH (400 MHz, dmso-d6): 10.47 (br s, 1 H, H-1), 7.37 (app. s, 1 H H-3), 7.33 (dd, 1 H, J 8.2, 2.0, H-4), 6.76 (d, 1 H, J 8.2, H-5), 3.50 (s, 2 H, H-2)

5-Chloroindolin-2-one (381)

Synthesised according to general procedure II, using 5-chloroisatin (377, 5 g, 27.54 mmol) and hydrazine hydrate (55.0 mL). The crude residue was purified by column chromatography (CH₂Cl₂/MeOH, 10:1, Rf = 0.6), to afford product 381 (3.0 g, 65%) as a brown amorphous solid. M.p. 194-197°C (lit. 280-195-196 °C). The isolated compound exhibited identical spectroscopic data to those reported in the literature.

δH (400 MHz, dmso-d6): 10.46 (br s, 1 H, H-1), 7.24 (app. s, 1 H, H-3), 7.20 (dd, 1 H, J 8.3, 2.2, H-4), 6.80 (d, 1 H, J 8.3, H-5), 3.49 (s, 2 H, H-2)

5-Methoxyindolin-2-one (382)

Synthesised according to general procedure II, using 5-methoxyisatin (378, 0.5 g, 2.82 mmol) and hydrazine hydrate (5.6 mL). The crude residue was purified by column chromatography (CH₂Cl₂/MeOH, 95:5, Rf = 0.7), to afford product 382 (190 mg, 41%) as a pale brown amorphous solid. M.p. 130-132°C (lit. 282 132-134 °C). The isolated compound exhibited identical spectroscopic data to those reported in the literature.

δH (400 MHz, dmso-d6): 10.16 (br s, 1 H, H-1), 6.86 (app. s, 1 H, H-3), 6.75-6.69 (m, 2 H, H-6 and H-5), 3.69 (s, 3 H, H-4), 3.43 (s, 2 H, H-2)
Methyl 4-bromo-2-((methoxycarbonyl)oxy)-1H-indole-1-carboxylate (383)

Synthesised according to general procedure I, using 379 (4.0 g, 18.86 mmol), triethylamine (5.78 mL, 41.50 mmol), THF (47.0 mL) and methyl chloroformate (3.20 mL, 41.50 mmol). The crude residue was purified by column chromatography (100% CH₂Cl₂, Rₜ = 0.8), to afford product 383 (3.9 g, 63%) as a white amorphous solid. M.p. 133 °C.

δₕ (600 MHz, CDCl₃): 8.00 (d, 1 H, J 8.0, H-5), 7.42 (d, 1 H, J 8.0, H-3), 7.18 (app. t, 1 H, J 8.0, H-4), 6.43 (s, 1 H, H-2), 4.04 (s, 3 H, H-6), 3.98 (s, 3 H, H-1)

δₒ (100 MHz, CDCl₃): 152.8 (C=O), 150.4 (C=O), 141.8 (q), 132.6 (q), 127.3 (q), 126.4, 125.4, 114.4 (q), 114.4, 97.5, 56.3, 54.2

νₕ (neat)/cm⁻¹: 2959, 1775, 1734, 1613, 1444, 1320, 1247, 1120, 1104, 979, 931, 797, 753, 729, 707

HRMS (m/z - ESI): Found: 349.9634 [M+Na]+ C₁₂H₁₀BrNaN₃O₅ Requires: 349.9635

Methyl 5-bromo-2-((methoxycarbonyl)oxy)-1H-indole-1-carboxylate (384)

Synthesised according to general procedure I, using 380 (0.22 g, 1.038 mmol), triethylamine (0.32 mL, 2.283 mmol), THF (2.6 mL) and methyl chloroformate (0.18 mL, 2.283 mmol). The crude residue was purified by column chromatography (100% CH₂Cl₂, Rₜ = 0.7), to afford product 384 (270 mg, 77%) as a white amorphous solid. M.p. 95-96 °C.
δ_H (600 MHz, CDCl₃): 7.91 (d, 1 H, J 9.0, H-5), 7.63 (d, 1 H, J 1.9, H-3), 7.40 (dd, 1 H, J 9.0, 1.9, H-4), 6.28 (s, 1 H, H-2), 4.03 (s, 3 H, H-6), 3.97 (s, 3 H, H-1)

δ_C (100 MHz, CDCl₃): 152.8 (C=O), 150.3 (C=O), 142.1 (q), 131.0 (q), 128.1 (q), 127.3, 123.3, 116.9, 96.6, 56.3, 54.1

v_max (neat)/cm⁻¹: 2961, 1775, 1734, 1613, 1444, 1321, 1248, 1121, 931, 797, 769, 754, 730

HRMS (m/z - APCI): Found: 267.9608 [M-12H₂O⁺] C₁₀H₇BrNO₃ Requires: 267.9615

**Methyl 5-chloro-2-((methoxycarbonyl)oxy)-1H-indole-1-carboxylate (385)**

![Image of the compound](image)

Synthesised according to general procedure I, using 381 (0.97 g, 5.79 mmol), triethylamine (1.77 mL, 12.73 mmol), THF (14.5 mL) and methyl chloroformate (0.98 mL, 12.73 mmol). The crude residue was purified by column chromatography (100% CH₂Cl₂, R_f = 0.7), to afford 385 (1.32 mg, 81%) as an off-white amorphous solid. M.p. 87-88 °C.

δ_H (400 MHz, CDCl₃): 7.95 (dd, 1 H, J 8.8, 2.1, H-5), 7.48 (d, 1 H, J 2.1, H-3), 7.27 (dd, 1 H, J 8.8, 2.1, H-4), 6.29 (s, 1 H, H-2), 4.03 (s, 3 H, H-6), 3.98 (s, 3 H, H-1)

δ_C (100 MHz, CDCl₃): 152.8 (C=O), 150.3 (C=O), 142.3 (q), 130.7 (q), 129.2 (q), 127.6 (q), 124.7, 120.3, 116.5, 96.7, 56.3, 54.1

v_max (neat)/cm⁻¹: 3129, 2961, 1785, 1745, 1613, 1439, 1320, 1250, 1069, 930, 811, 755

HRMS (m/z - ESI): Found: 306.0129 [M+Na⁺] C₁₂H₁₀ClINaO₅ Requires: 306.0140
Methyl 5-methoxy-2-((methoxycarbonyl)oxy)-1H-indole-1-carboxylate (386)

Synthesised according to general procedure I, using 382 (190 mg, 1.164 mmol), triethylamine (0.36 mL, 2.562 mmol), THF (2.9 mL) and methyl chloroformate (0.20 mL, 2.562 mmol). The crude residue was purified by column chromatography (100% CH₂Cl₂, Rf = 0.8), to afford 386 (140 mg, 43%) as a white amorphous solid. M.p. 91-93 °C.

δH (600 MHz, CDCl₃): 7.91 (d, 1 H, J 9.0, H-6), 6.97 (d, 1 H, J 2.7, H-3), 6.91 (dd, 1 H, J 9.0, 2.7, H-5), 6.26 (s, 1 H, H-2), 4.01 (s, 3 H, H-7), 3.96 (s, 3 H, H-1), 3.83 (s, 3 H, H-4)

δC (100 MHz, CDCl₃): 156.3 (C=O), 153.0 (C=O), 150.5 (q), 141.8 (q), 127.2 (q), 126.8 (q), 116.3, 112.9, 103.7, 97.3, 56.2, 55.6, 53.8

νmax (neat)/cm⁻¹: 2959, 1774, 1734, 1612, 1455, 1378, 1321, 1248, 1209, 1120, 931, 863, 771, 755


An oven dried round-bottomed flask containing a stirring bar was charged with the appropriate N,O-bis-acylated 2-oxindole (1.0 equiv.), fitted with a septum and placed under an argon atmosphere (balloon). Distilled DMF (0.5 M) was added via syringe. Ammonium carbonate (1.2 equiv.) was then added portionwise under the flow of argon at 0 °C. The reaction mixture was stirred for 6 h at rt under an argon atmosphere, and then poured into ice-water. The precipitated crude product was filtered under vacuum, washed with H₂O and purified by column chromatography on silica gel.
Ethyl 2-oxoindoline-1-carboxylate (354)

Synthesised according to general procedure III, using 293 (7.0 g, 25.25 mmol), DMF (50.0 mL) and ammonium carbonate (2.9 g, 30.18 mmol). The crude product was purified by column chromatography (100% CH$_2$Cl$_2$, R$_f$ = 0.3), obtaining product 354 (2.98 g, 58%) as a white amorphous solid. M.p. 77-79 °C (lit. 79-80 °C). The isolated compound exhibited identical spectroscopic data to those reported in the literature.

δ$_H$ (400 MHz, CDCl$_3$): 7.87 (d, 1 H, J 8.3, H-7), 7.32 (app. t, 1 H, J 8.3, 0.9, H-6), 7.25 (app. d, 1 H, J 7.5, H-4), 7.16 (app. td, 1 H, J 7.5, 0.9, H-5), 4.48 (q, 2 H, J 7.4, H-2), 3.69 (s, 2 H, H-3), 1.45 (t, 3 H, J 7.4, H-1)

Methyl 2-oxoindoline-1-carboxylate (353)

Synthesised according to general procedure III, using 309 (8.50 g, 34.11 mmol), DMF (68 mL) and ammonium carbonate (3.93 g, 40.90 mmol). The crude product was purified by column chromatography (hexane/EtOAc, 8:2, R$_f$ = 0.2), obtaining product 353 (4.83 g, 74%) as a white amorphous solid. M.p. 88-89 °C.

**Note:** Compound 353 is a known material, however the literature characterisation of this compound is devoid of melting point data. Our $^1$H NMR spectroscopy and HRMS data are consistent with those in the literature.

δ$_H$ (400 MHz, CDCl$_3$): 7.88 (d, 1 H, J 8.3, H-6), 7.31 (app. td, 1 H, J 8.3, 0.9, H-5), 7.25 (app. d, 1 H, J 7.7, H-3), 7.15 (td, 1 H, J 7.7, 0.9, H-4), 4.00 (s, 3 H, H-1), 3.67 (s, 2 H, H-2)

HRMS (m/z - APCI): Found: 192.0671 [M+H]$^+$ C$_{10}$H$_{10}$NO$_3$ Requires: 192.0655
Benzyl 2-oxindoline-1-carboxylate (366b)

Synthesised according to general procedure III, using 366a (7.50 g, 18.68 mmol), DMF (37 mL) and ammonium carbonate (2.2 g, 22.90 mmol). The crude product was purified by column chromatography (hexane/EtOAc, 6:4, R_f = 0.8), obtaining product 366b (3.2 g, 64%) as a white amorphous solid. M.p. 94-95 °C (lit. 109-110 °C). The isolated compound exhibited identical spectroscopic data to those reported in the literature.

δ_H (400 MHz, CDCl3): 7.87 (d, 1 H, J 8.4, H-5), 7.51 (app. d, 2 H, J 7.1, H-7), 7.41-7.34 (m, 3 H, H-8 and H-9), 7.30 (app. td, 1 H, J 8.4, 3.9, H-4), 7.25 (app. d, 1 H, J 3.5, H-2), 7.15 (app. td, 1 H, J 7.5, 0.9, H-3), 5.45 (s, 2 H, H-6), 3.68 (s, 2 H, H-1)

General procedure IV: Preparation of the mixed N,O-bis-acylated 2-oxindole derivatives.

An oven dried two-necked round-bottomed flask containing a magnetic stirring bar and equipped with a thermometer was charged with the appropriate N-acylated 2-oxindole derivative (1.0 equiv.), fitted with a septum and placed under an argon atmosphere (balloon). Freshly distilled triethylamine (1.1 equiv.) and anhydrous THF (0.4 M) were added via syringe. The appropriate ester of chloroformic acid (1.1 equiv.) was then added dropwise via syringe, keeping the temperature of the reaction mixture below 30 °C during the addition. After stirring for 30 min at rt, the solvent was removed in vacuo. Water (0.7 M) was added to the residue and the mixture was stirred for 2 h at 0 °C. The precipitated crude product was then filtered under vacuum and purified by column chromatography on silica gel.

Ethyl 2-((methoxycarbonyl)oxy)-1H-indole-1-carboxylate (357)
Synthesised according to general procedure IV, using 354 (2.50 g, 12.18 mmol), triethylamine (1.87 mL, 13.40 mmol), THF (30.0 mL) and methyl chloroformate (1.04 mL, 13.40 mmol). The crude residue was purified by column chromatography (hexane/EtOAc, 8:2, R_f = 0.5), to afford product 357 (2.4 g, 75%) as a pale yellow amorphous solid. M.p. 52-53 °C.

δ_H (400 MHz, CDCl₃): 8.09 (d, 1 H, J 8.1, H-6), 7.51 (d, 1 H, J 7.5, H-3), 7.33 (app. td, 1 H, J 7.5, 1.3, H-5), 7.26 (app. td, 1 H, J 8.1, H-4), 6.33 (s, 1 H, H-2), 4.49 (q, 2 H, J 7.1, H-7), 3.97 (s, 3 H, H-1), 1.46 (t, 3 H, J 7.1, H-8)

δ_C (100 MHz, CDCl₃): 153.0 (C=O), 150.1 (C=O), 141.4 (q), 132.6 (q), 126.4 (q), 124.4, 123.4, 120.7, 115.4, 97.2, 63.5, 56.1, 14.1

_ν_max (neat)/cm⁻¹_: 2958, 1776, 1735, 1612, 1455, 1321, 1247, 1207, 1120, 931, 823, 753, 739, 699

HRMS (m/z - ESI): Found: 286.0675 [M+Na]+ _C_{13}H_{13}NNaO_{5} Requires: 286.0686

Methyl 2-((ethoxycarbonyl)oxy)-1H-indole-1-carboxylate (355)

Synthesised according to general procedure IV, using 353 (1.70 g, 8.89 mmol), triethylamine (1.36 mL, 9.78 mmol), THF (22 mL) and ethyl chloroformate (0.93 mL, 9.78 mmol). The crude residue was purified by column chromatography (100% CH₂Cl₂, R_f = 0.6), to afford product 355 (2.3 g, 97%) as a clear oil.

δ_H (400 MHz, CDCl₃): 8.06 (d, 1 H, J 8.3, H-7), 7.50 (dd, 1 H, J 7.7, 1.6, H-4), 7.32 (app. td, 1 H, J 8.3, 1.6, H-6), 7.26 (app. td, 1 H, J 7.7, 1.6, H-5), 6.33 (s, 1 H, H-3), 4.39 (q, 2 H, J 7.1, H-2), 4.03 (s, 3 H, H-8), 1.43 (t, 3 H, J 7.1, H-1)

δ_C (100 MHz, CDCl₃): 152.4 (C=O), 150.6 (C=O), 141.5 (q), 132.5 (q), 126.5 (q), 124.4, 123.5, 120.7, 115.3, 97.3, 65.8, 53.8, 14.1
Methyl 2-(((2,2,2-trichloroethoxy)carbonyl)oxy)-1H-indole-1-carboxylate (362)

Synthesised according to general procedure IV, using 353 (1.0 g, 5.23 mmol), triethylamine (0.80 mL, 5.75 mmol), THF (13 mL) and 2,2,2-trichloroethyl chloroformate (0.80 mL, 5.75 mmol). The crude residue was purified by column chromatography (100% CH$_2$Cl$_2$, R$_f$ = 0.8), to afford product 362 (1.83 g, 96%) as a white amorphous solid. M.p. 72-73 °C.

δ$_H$ (400 MHz, CDCl$_3$): 8.07 (d, 1 H, J 8.4, H-6), 7.53 (d, 1 H, J 7.4, H-3), 7.35 (app. td, 1 H, J 8.4, 1.3, H-5), 7.28 (app. td, 1 H, J 7.4, 1.3, H-4), 6.40 (s, 1 H, H-2), 4.92 (s, 2 H, H-1), 4.04 (s, 3 H, H-7)

δ$_C$ (100 MHz, CDCl$_3$): 151.5 (C=O), 150.6 (C=O), 140.8 (q), 132.5 (q), 126.2 (q), 124.8, 123.7, 120.9, 115.4, 97.7, 93.6 (q), 77.8, 54.0

ν$_{\text{max}}$ (neat)/cm$^{-1}$: 2959, 1777, 1734, 1612, 1579, 1455, 1441, 1397, 1249, 1196, 1044, 931, 762, 753, 738, 698, 679

HRMS (m/z - ESI): Found: 286.0692 [M+Na]$^+$ C$_{13}$H$_{13}$NaO$_5$ Requires: 286.0686

Benzyl 2-((methoxycarbonyl)oxy)-1H-indole-1-carboxylate (366c)

HRMS (m/z - ESI): Found: 363.9557 [M–H]$^+$ C$_{13}$H$_9$NO$_5$Cl$_3$ Requires: 363.9546
Synthesised according to general procedure IV, using 366b (1.50 g, 5.61 mmol), triethylamine (0.86 mL, 6.17 mmol), THF (14 mL) and methyl chloroformate (0.48 mL, 6.17 mmol). The crude residue was purified by column chromatography (hexane/EtOAc, 8:2, Rf = 0.5), to afford product 366c (1.5 g, 83%) as a pale orange amorphous solid. M.p. 59-60 °C.

δH (400 MHz, CDCl3): 8.10 (d, 1 H, J 8.2, H-6), 7.50-7.39 (m, 6 H, H-3, H-8, H-9 and H-10), 7.30 (app. td, 1 H, J 8.2, 1.4, H-5), 7.25 (app. td, 1 H, J 7.4, 1.4, H-4), 6.32 (s, 1 H, H-2), 5.43 (s, 2 H, H-7), 3.68 (s, 3 H, H-1)

δC (100 MHz, CDCl3): 152.9 (C=O), 150.0 (C=O), 141.3 (q), 134.4 (q), 132.7 (q), 128.8, 128.7 (two signals), 126.5 (q), 124.6, 123.6, 120.7, 115.5, 97.4, 69.1, 55.9

νmax (neat)/cm⁻¹: 2958, 1776, 1734, 1612, 1579, 1455, 1441, 1249, 1196, 1119, 931, 823, 753, 737, 679

HRMS (m/z - ESI): Found: 324.0876 [M–H]⁺ C₁₈H₁₄NO₅ Requires: 324.0872

*Tert-butyl 2-oxoindoline-1-carboxylate (364-0)*

![Tert-butyl 2-oxoindoline-1-carboxylate](image)

A 250 mL oven dried round-bottomed flask containing a magnetic stirring bar was charged with 2-oxindole (289, 2.0 g, 15.04 mmol), di-tert-butyl dicarbonate (8.2 g, 37.59 mmol) and sodium carbonate (14.3 g, 135.32 mmol). The flask was fitted with a septum and placed under an argon atmosphere (balloon). Anhydrous THF (60.0 mL, 0.25 M) was then added via syringe and the reaction mixture was heated to 70 °C and stirred at this temperature for 16 h. After cooling the reaction mixture to rt, it was decanted and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (hexane/EtOAc, 9:1, Rf = 0.3) to yield 364-0 (1.47 g, 42%) as a white amorphous solid. M.p. 64-65 °C (lit.285 67 °C). The isolated compound exhibited identical spectroscopic data to those reported in the literature.286

192
δ_\text{H} (600 MHz, CDCl₃): 7.79 (d, 1 H, J 8.3, H-5), 7.29 (app. t, 1 H, J 8.3, H-4), 7.24 (d, 1 H, J 7.2, H-2), 7.13 (app. t, 1 H, J 7.2, H-3), 3.65 (s, 2 H, H-1), 1.64 (s, 9 H, H-6)

_Tert-butyl 2-((methoxycarbonyl)oxy)-1H-indole-1-carboxylate (364a)_

Synthesised according to general procedure IV, using 364-0 (2.70 g, 11.57 mmol), triethylamine (1.77 mL, 12.73 mmol), THF (30 mL) and methyl chloroformate (1.0 mL, 12.73 mmol). The crude residue was purified by column chromatography (hexane/EtOAc, 9:1, R_f = 0.3), to afford product 364-a (2.9 g, 84%) as a white amorphous solid. M.p. 61-63 °C.

δ_\text{H} (400 MHz, CDCl₃): 8.11 (d, 1 H, J 8.4, H-6), 7.51 (d, 1 H, J 7.6, H-3), 7.32 (app. td, 1 H, J 8.4, 1.2, H-5), 7.25 (app. td, 1 H, J 7.6, 1.2, H-4), 6.30 (s, 1 H, H-2), 3.96 (s, 3 H, H-1), 1.67 (s, 9 H, H-7)

δ_\text{C} (100 MHz, CDCl₃): 153.0 (C=O), 148.7 (C=O), 141.5 (q), 132.7 (q), 126.3 (q), 124.2, 123.1, 120.6, 115.4, 96.5, 84.6 (q), 55.9, 28.0

ν_max (neat)/cm⁻¹: 2954, 1735, 1663, 1578, 1488, 1444, 1295, 1193, 1151, 1023, 1000, 744, 721, 707

HRMS (m/z - ESI): Found: 314.0987 [M+Na]⁺ C_{15}H_{17}NNaO₅ Requires: 314.0999

_Tert-butyl 2-((ethoxycarbonyl)oxy)-1H-indole-1-carboxylate (365a)_
Synthesised according to general procedure IV, using 364-0 (2.80 g, 12.00 mmol), triethylamine (1.84 mL, 13.20 mmol), THF (30 mL) and ethyl chloroformate (1.26 mL, 13.20 mmol). The crude residue was purified by column chromatography (hexane/EtOAc, 8:2, R_f = 0.3), to afford product 365a (3.4 g, 93%) as a deep red oil.

δ_H (600 MHz, CDCl_3): 8.09 (d, 1 H, J 8.4, H-7), 7.50 (d, 1 H, J 7.8, H-4), 7.31 (app. td, 1 H, J 8.4, 1.1, H-5), 7.24 (app. td, 1 H, J 7.8, 1.1, H-6), 6.30 (s, 1 H, H-3), 4.37 (q, 2 H, J 7.1, H-2), 1.67 (s, 9 H, H-8), 1.42 (t, 3 H, J 7.1, H-1)

δ_C (151 MHz, CDCl_3): 152.4 (C=O), 148.7 (C=O), 141.7 (q), 132.7 (q), 126.3 (q), 124.1, 123.1, 120.5, 115.3, 96.5, 84.5 (q), 65.6, 28.0, 14.0

ν_max (neat)/cm\(^{-1}\): 1775, 1735, 1229, 1209, 1155, 1118, 993, 742

HRMS (m/z - ESI): Found: 344.0905 [M+K]^+ C_{16}H_{19}NO_{5}K Requires: 344.0900

**General procedure V:** Steglich rearrangement of N,O-bis-acylated 2-oxindole derivatives.

An oven dried round-bottomed flask containing a stirring bar was charged with the appropriate N,O-bis-acylated 2-oxindole derivative (1.0 equiv.), fitted with a septum and placed under an argon atmosphere (balloon). Anhydrous DMF (1.0 M) was added via syringe. A solution of DMAP (1.1 equiv.) in anhydrous DMF (1.1 M) was then added to the reaction mixture at 0 °C. The reaction was stirred for 20 min at rt, then placed into an ice bath and HCl (1.0 equiv.) and ice-water were added. The crude product was filtered under vacuum and recrystallised.

**Diethyl 2-oxindoline-1,3-dicarboxylate (294) and diethyl 2-hydroxy-1H-indole-1,3-dicarboxylate (294-a)**

![Diagram of 294 and 294-a](image-url)
Synthesised according to general procedure V, using 293 (3.72 g, 13.4 mmol) in DMF (13.4 mL), DMAP (1.64 g, 14.7 mmol) in DMF (14.7 mL) and HCl (1.0 M, 13.0 mL). The crude residue was recrystallised from hexane to afford 294 (2.8 g, 75%) as pale orange crystals. M.p. 83-84 °C (lit. 84-85 °C). The isolated compound exhibited identical spectroscopic data to those reported in the literature.

$\delta_H$ (600 MHz, CDCl$_3$), keto form, 294: 7.92 (d, 1 H, J 8.1, H-7), 7.40-7.36 (m, 2 H, H-6 and H-4), 7.20 (app. t, 1 H, J 7.5, H-5), 4.59-4.54 (m, 1 H, H-3), 4.51-4.43 (m, 2 H, H-8), 4.31-4.20 (m, 2 H, H-2), 1.49-1.44 (m, 3 H, H-9), 1.29 (t, 3 H, J 7.2, H-1)

$\delta_H$ (600 MHz, CDCl$_3$), enol form, 294-a: 8.01 (d, 1 H, J 8.1, H-7'), 7.77 (d, 1 H, J 8.1, H-4'), 7.28 (app. td, 1 H, J 7.5, 0.9, H-6'), 7.22 (app. t, 1 H, J 7.5, H-5'), 4.59-4.54 (m, 2 H, H-8'), 4.51-4.43 (m, 2 H, H-2'), 1.51 (t, 3 H, J 7.2, H-9'), 1.49-1.44 (m, 3 H, H-1')

Note: The protic signal (H-3') is not visible in CDCl$_3$.

**Dimethyl 2-oxoindoline-1,3-dicarboxylate (310) and dimethyl 2-hydroxy-1H-indole-1,3-dicarboxylate (310-a)**

![Diagram]

Synthesised according to general procedure V, using 309 (7.10 g, 28.49 mmol) in DMF (28.0 mL), DMAP (3.83 g, 31.34 mmol) in DMF (31.0 mL) and HCl (1.0 M, 28.0 mL). The crude residue was recrystallised from hexane to afford 310 (5.5 g, 77%) as pale orange crystals. M.p. 84-86 °C.
**Note:** Compound 310 is a known material, however the literature characterisation of this compound is devoid of melting point data. Our $^1$H NMR spectroscopy and HRMS data are consistent with those in the literature.²⁷⁵

$\delta_H$ (600 MHz, CDCl$_3$), keto form, 310:

7.94 (d, 1 H, J 8.3, H-6), 7.41-7.37 (m, 2H, H-3 and H-5), 7.21 (app. t, 1 H, J 7.5, H-4), 4.59 (s, 1 H, H-2), 4.03 (s, 3 H, H-7), 3.79 (s, 3 H, H-1)

$\delta_H$ (600 MHz, CDCl$_3$), enol form, 310-a:

8.02 (d, 1 H, J 8.3, H-6’), 7.76 (dd, 1 H, J 7.5,1.0, H-3’), 7.29 (app. td, 1 H, J 8.3, 1.0, H-5’), 7.23 (app. t, 1 H, J 7.5, H-4’), 4.11 (s, 3 H, H-7’), 4.00 (s, 3 H, H-1’)

**Note:** The protic signal (H-2’) is not visible in CDCl$_3$.

HRMS (m/z - APCI): Found: 248.0561 [M–H]$^+$ C$_{12}$H$_{10}$NO$_5$ Requires: 248.0564

1-Ethyl 3-methyl 2-oxoindoline-1,3-dicarboxylate (358) and 1-ethyl 3-methyl 2-hydroxy-1H-indole-1,3-dicarboxylate (358-a)

![Chemical structures](image)

Synthesised according to general procedure V, using 357 (2.20 g, 8.36 mmol) in DMF (8.5 mL), DMAP (1.12 g, 9.19 mmol) in DMF (9.0 mL) and HCl (1.0 M, 8.4 mL). The crude residue was recrystallised from hexane to afford 358 (1.6 g, 73%) as orange crystals. M.p. 78-80 °C.

$\delta_H$ (400 MHz, CDCl$_3$), keto form, 358:

7.92 (d, 1 H, J 8.1, H-6), 7.41-7.36 (m, 2 H, H-3 and H-5), 7.24-7.19 (m, 1 H, H-4), 4.57 (app. s, 1 H, H-2), 4.49 (q, 2 H, J 7.2, H-7), 3.79 (s, 3 H, H-1), 1.46 (t, 3 H, J 7.2, H-8)
δ_H (400 MHz, CDCl_3), enol form, **358-a**: 8.00 (d, 1 H, J 8.1, H-6'), 7.78 (d, 1 H, J 7.7, H-3'), 7.28 (app. t, 1 H, J 8.1, H-5'), 7.24-7.19 (m, 1 H, H-4'), 4.58 (q, 2 H, J 7.2, H-7'), 4.00 (s, 3 H, H-1'), 1.52 (3 H, J 7.2, H-8')

**Note**: The protic signal (H-2') is not visible in CDCl_3.

δ_C (100 MHz, CDCl_3): 168.7 (C=O), 168.2 (C=O), 166.4 (C=O), 159.9 (C=O), 150.7 (C=O), 150.4 (q), 140.2 (q), 129.9 (q), 129.4, 124.8, 124.4, 124.2, 124.1 (q), 123.0, 122.1 (q), 119.3, 115.4, 114.7, 88.1 (q), 64.1, 63.4, 53.1, 52.8, 51.6, 14.1 (two signals)

v_max (neat)/cm⁻¹:
2953, 1736, 1662, 1578, 1488, 1444, 1294, 1192, 1152, 1000, 784, 764, 744, 708, 693

HRMS (m/z - ESI): Found: 262.0709 [M–H]^+ C_{13}H_{12}NO_5 Requires: 262.0721

3-Ethyl 1-methyl 2-oxoindoline-1,3-dicarboxylate (356) and 3-ethyl 1-methyl 2-hydroxy-1H-indole-1,3-dicarboxylate (356-a)

Synthesised according to general procedure V, using **355** (2.27 g, 8.62 mmol) in DMF (8.6 mL), DMAP (1.20 g, 9.49 mmol) in DMF (9.5 mL) and HCl (1.0 M, 8.6 mL). The crude residue was recrystallised from hexane to afford **356** (1.8 g, 79%) as an orange amorphous solid. M.p. 63-64 °C.

δ_H (400 MHz, CDCl_3), keto form, **356**: 7.93 (d, 1 H, J 8.1, H-7), 7.40-7.35 (m, 2 H, H-4 and H-6), 7.23-7.18 (m, 1 H, H-5), 4.55 (s, 1 H, H-3), 4.30-4.18 (m, 2 H, H-2), 4.02 (s, 3 H, H-8), 1.27 (t, 3 H, J 7.1, H-1)
δH (400 MHz, CDCl₃), enol form, 356-a: 8.01 (d, 1 H, J 8.1, H-7’), 7.74 (d, 1 H, J 7.6, H-4’), 7.27 (app. t, 1 H, J 8.1, H-6’), 7.23-7.18 (m, 1 H, H-5’), 4.45 (q, 2 H, J 7.1, H-2’), 4.10 (s, 3 H, H-8’), 1.46 (t, 3 H, J 7.1, H-1’)

Note: The protic signal (H-3’) is not visible in CDCl₃.

δC (100 MHz, CDCl₃): 168.9 (C=O), 168.3 (C=O), 166.0 (C=O), 160.3 (C=O), 151.1 (C=O), 151.0 (q), 140.1 (q), 130.1 (q), 129.4, 128.2 (q), 125.0, 124.5, 124.2, 123.1, 122.3 (q), 119.3, 115.4, 114.7, 88.2 (q), 62.4, 60.8, 54.3, 54.0, 53.0 14.4, 14.0

νmax (neat)/cm⁻¹: 2954, 1735, 1662, 1578, 1444, 1294, 1193, 1114, 1023, 764, 744, 678

HRMS (m/z - ESI): Found: 262.0727 [M–H]+ C₁₃H₁₂NO₅ Requires: 262.0721

1-Methyl 3-(2,2,2-trichloroethyl) 2-oxoindoline-1,3-dicarboxylate (363) and 1-methyl 3-(2,2,2-trichloroethyl) 2-hydroxy-1H-indole-1,3-dicarboxylate (363-a)

Synthesised according to general procedure V, using 362 (1.90 g, 5.18 mmol) in DMF (5.0 mL), DMAP (0.70 g, 5.70 mmol) in DMF (6.0 mL) and HCl (1.0 M, 5.0 mL). The crude residue was recrystallised from hexane to afford 363 (0.8 g, 42%) as a white amorphous solid. M.p. 82-84 °C.

δH (400 MHz, CDCl₃), keto form, 363: 7.96 (d, 1 H, J 8.3, H-6), 7.46-7.39 (m, 2 H, H-5 and H-3), 7.22 (app. t, 1 H, J 7.7, H-4), 4.83 (dd, 2 H, J 15.7, 11.8, H-1), 4.72 (s, 1 H, H-2), 4.04 (s, 3 H, H-7)
δ_H (400 MHz, CDCl₃), enol form, 363-a: 8.00 (d, 1 H, J 8.3, H-6’), 7.93 (d, 1 H, J 7.7, H-3’), 7.33 (app. t, 1 H, J 7.7, H-4’), 7.28 (app. t, 1 H, J 8.3, H-5’), 5.04 (s, 2 H, H-1’), 4.14 (s, 3 H, H-7’)

Note: The protic signal (H-2’) is not visible in CDCl₃.

δ_C (100 MHz, CDCl₃): 172.6 (C=O), 166.1 (C=O), 160.4 (C=O), 151.5 (C=O), 140.6 (C=O), 130.1 (q), 130.0 (q), 128.3, 125.1, 124.6, 124.2, 123.9 (q), 123.2 (q), 119.9, 115.2, 114.8, 99.4 (q), 96.0 (q), 87.8 (q), 76.3, 74.7 (q), 74.0, 54.7, 53.9, 54.2, 36.5

ν_max (neat)/cm⁻¹: 2953, 1736, 1663, 1578, 1488, 1444, 1294, 1167, 1152, 1114, 1022, 999, 889, 783, 721, 708, 678

HRMS (m/z - ESI): Found: 363.9543 [M–H]+  C₁₃H₉NO₃Cl₃ Requires: 363.9546

1-Benzyl 3-methyl 2-oxoindoline-1,3-dicarboxylate (366) and 1-benzyl 3-methyl 2-hydroxy-1H-indole-1,3-dicarboxylate (366-a)

Synthesised according to general procedure V, using 366c (1.4 g, 4.30 mmol) in DMF (4.3 mL), DMAP (0.58 g, 4.73 mmol) in DMF (4.7 mL) and HCl (1.0 M, 4.3 mL). The crude residue was recrystallised from hexane to afford 366 (0.6 g, 43%) as a white amorphous solid. M.p. 65-66 °C.

δ_H (400 MHz, CDCl₃), keto form, 366: 7.92 (d, 1 H, J 8.2, H-6), 7.54-7.51 (m, 2 H, H-8), 7.45-7.33 (m, 5 H, H-3, H-5, H-9 and H-10), 7.22-7.17 (m, 1 H, H-4), 5.46 (dd, 2 H, J 12.4, 5.3, H-7), 4.58 (s, 1 H, H-2), 3.79 (s, 3 H, H-1)
δ_H (400 MHz, CDCl₃), enol form, 366-a: 8.01 (d, 1 H, J 8.2, H-6'), 7.75 (dd, 1 H, J 8.2, 1.1, H-3'), 7.54-7.51 (m, 2 H, H-8'), 7.45-7.33 (m, 3 H, H-9' and H-10'), 7.27 (app. td, 1 H, J 8.2, 1.1, H-5'), 7.22-7.17 (m, 1 H, H-4'), 5.53 (s, 2 H, H-7'), 3.99 (s, 3 H, H-1')

Note: The protic signal (H-2') is not visible in CDCl₃.

δ_C (100 MHz, CDCl₃): 169.0 (C=O), 168.2 (C=O), 166.5 (C=O), 160.2 (C=O), 150.5 (C=O), 150.4 (q), 140.1 (q), 134.7 (q), 134.4 (q), 130.1 (q), 129.6, 128.8 (two signals), 128.7, 128.5, 128.3, 128.1, 125.0, 124.6, 124.4, 124.2 (q), 123.2, 122.1, 119.4, 115.5, 114.9, 88.3 (q), 69.4, 68.9, 53.3, 52.9, 51.8

ν_max (neat)/cm⁻¹: 2953, 1735, 1661, 1584, 1489, 1444, 1295, 1168, 1022, 999, 785, 743, 721, 695

HRMS (m/z - ESI): Found: 324.0876 [M–H]+ C₁₈H₁₄NO₅ Requires: 324.0872

1-(Tert-butyl) 3-methyl 2-oxoindoline-1,3-dicarboxylate (364) and 1-(tert-butyl) 3-methyl 2-hydroxy-1H-indole-1,3-dicarboxylate (364) (364)

Synthesised according to general procedure V, using 364a (2.65 g, 9.10 mmol) in DMF (9.0 mL), DMAP (1.22 g, 10.01 mmol) in DMF (10.0 mL) and HCl (1.0 M, 9.0 mL). The crude residue was recrystallised from hexane to afford 364 (1.6 g, 60%) as yellow crystals. M.p. 80-83 °C.

δ_H (400 MHz, CDCl₃), keto form, 364: 7.85 (d, 1 H, J 8.3, H-6), 7.38-7.34 (m, 2 H, H-5 and H-3), 7.22-7.16 (m, 1 H, H-4),
δ_H (400 MHz, CDCl₃), enol form, 364-a: 7.93 (d, 1 H, J 8.3, H-6’), 7.81 (d, 1 H, J 7.6, H-3’), 7.27 (app. t, 1 H, J 8.3, H-5’), 7.22-7.16 (m, 1 H, H-4’), 3.98 (s, 3 H, H-1’), 1.71 (br s, 9 H, H-7’)

Note: The protic signal (H-2’) is not visible in CDCl₃.

δ_C (100 MHz, CDCl₃): 168.4 (C=O, two signals), 166.7 (C=O), 160.0 (C=O), 149.8 (C=O), 148.8 (q), 140.6 (q), 130.0 (q), 129.4, 127.7, 124.4 (two signals, one of which is quaternary), 124.3, 122.9, 122.1 (q), 119.5, 115.4, 114.7, 88.2 (q), 86.3 (q), 84.8 (q), 53.3, 52.9, 51.6, 28.1, 28.0

ν_max (neat)/cm⁻¹: 2956, 1735, 1679, 1586, 1433, 1339, 1299, 1210, 1151, 1027, 845, 782, 747, 730, 694

HRMS (m/z - ESI): Found: 314.0983 [M+Na]^+ C_{15}H_{27}NNaO_5 Requires: 314.0999

1-(Tert-butyl) 3-ethyl 2-oxoindoline-1,3-dicarboxylate (365) and 1-(tert-butyl) 3-ethyl 2-hydroxy-1H-indole-1,3-dicarboxylate (365-a)

![Keto Enol Equilibrium](image)

Synthesised according to general procedure V, using 365a (1.04 g, 3.41 mmol) in DMF (3.4 mL), DMAP (5.0 g, 4.09 mmol) in DMF (4.0 mL) and HCl (1.0 M, 3.4 mL). The residue was purified by dissolving the crude product in minimum volume of Et₂O and dropping it into vigorously stirred hexane cooled to -78 °C. The solid that crushed out was decanted and washed with cold hexane. Once it was warmed to rt, the solid became a yellow sticky residue, 365 (250 mg, 24%).
δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}), keto form, 365: 7.85 (d, 1 H, J 8.3, H-7), 7.38-7.34 (m, 2 H, H-6 and H-4), 7.22-7.13 (m, 1 H, H-5), 4.53 (s, 1 H, H-3), 4.31-4.20 (m, 2 H, H-2), 1.64 (br s, 9 H, H-8), 1.29 (t, 3 H, J 7.1, H-1)

δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}), enol form, 365-a: 7.94 (d, 1 H, J 8.3, H-7’), 7.79 (d, 1 H, J 7.7, H-4’), 7.24 (app. t, 1 H, J 8.3, H-6’), 7.22-7.13 (m, 1 H, H-5’), 4.45 (q, 2 H, J 7.1, H-2’), 1.70 (br s, 9 H, H-8’), 1.46 (t, 3 H, J 7.1, H-1’)

Note: The protic signal (H-2’) is not visible in CDCl\textsubscript{3}.

δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}): 168.5 (C=O), 168.4 (C=O), 166.3 (C=O), 160.4 (C=O), 149.4 (C=O), 148.9 (q), 140.6 (q), 130.1 (q), 129.3, 124.6, 124.4 (q), 124.3, 124.2, 122.8, 122.3 (q), 119.4, 115.3, 114.7, 88.1 (q), 86.0 (q), 84.8 (q), 62.4, 60.6, 53.1, 28.1, 28.0, 14.4, 14.0

ν\textsubscript{max} (neat)/\text{cm}^{-1}: 2981, 2934, 1740, 1648, 1576, 1487, 1304, 1144, 1024, 790, 745, 677

HRMS (m/z - ESI): Found: 304.1188 [M-H]+ C\textsubscript{16}H\textsubscript{18}NO\textsubscript{5} Requires: 304.1185

Dimethyl 4-bromo-2-oxindoline-1,3-dicarboxylate (387) and dimethyl 4-bromo-2-hydroxy-1H-indole-1,3-dicarboxylate (387-a)

Synthesised according to general procedure V, using 383 (3.70 g, 11.28 mmol) in DMF (11.0 mL), DMAP (1.52 g, 12.40 mmol) in DMF (12.0 mL) and HCl (1.0 M, 11.0 mL). The crude residue was recrystallised from hexane to afford 387 (2.0 g, 54%) as off-white crystals. M.p. 133 °C.
\[ \delta_H \ (400 \text{ MHz, CDCl}_3), \text{keto form, 387:} \ 7.90 \ (d, \ 1 \ H, \ J \ 7.8, \ H-5), \ 7.34 \ (dd, \ 1 \ H, \ J \ 8.2, \ 0.7, \ H-3), \ 7.27 \ (td, \ 1 \ H, \ J \ 8.2, \ 0.7, \ H-4), \ 4.54 \ (s, \ 1 \ H, \ H-2), \ 4.00 \ (s, \ 3 \ H, \ H-1), \ 3.80 \ (s, \ 3 \ H, \ H-6) \]

\[ \delta_C \ (100 \text{ MHz, CDCl}_3): \ 166.8 \ (C=O), \ 164.8 \ (C=O), \ 150.8 \ (C=O), \ 141.5 \ (q), \ 130.9, \ 128.1, \ 123.5 \ (q), \ 119.3 \ (q), \ 114.2, \ 54.8, \ 54.2, \ 53.4 \]

\[ \nu_{\text{max}} \ (\text{neat})/\text{cm}^{-1}: \ 2957, \ 1767, \ 1751, \ 1726, \ 1585, \ 1451, \ 1433, \ 1338, \ 1297, \ 1233, \ 1126, \ 1031, \ 910, \ 762, \ 730, \ 696 \]

HRMS \ ([m/z - ESI]): \ Found: 349.9632 \ [M+Na]^+ \ \text{C}_{12}\text{H}_{10}\text{BrNNaO}_5 \ \text{Requires:} \ 349.9635

**Dimethyl 5-bromo-2-oxoindole-1,3-dicarboxylate (388) and dimethyl 5-bromo-2-hydroxy-1H-indole-1,3-dicarboxylate (388-a)**

\[
\begin{align*}
\text{Br} & \quad \text{O} & \quad \text{O} & \quad ^1 \text{O} \\
3 & \quad 2 & \quad 1 & \quad 1' \\
\text{N} & & & \\
4 & & & \\
5 & & & \\
6 & & & \\
\text{Br} & \quad \text{O} & \quad \text{O} & \quad ^1 \text{O} \\
3' & \quad 2' & \quad 1' & \quad 1'' \\
\text{N} & & & \\
4' & & & \\
5' & & & \\
6' & & & \\
\end{align*}
\]

Synthesised according to general procedure V, using 384 (3.68 g, 11.22 mmol) in DMF (11.0 mL), DMAP (1.51 g, 12.34 mmol) in DMF (12.0 mL) and HCl (1.0 M, 11.0 mL). The crude residue was recrystallised from hexane to afford 388 (1.7 g, 46%) as off-white crystals. M.p. 136-137 °C.

\[ \delta_H \ (600 \text{ MHz, CDCl}_3), \text{keto form, 388:} \ 7.85-7.81 \ (m, \ 1 \ H, \ H-5), \ 7.51-7.49 \ (m, \ 2 \ H, \ H-3 \ \text{and} \ H-4), \ 4.55 \ (s, \ 1 \ H, \ H-2), \ 4.02 \ (s, \ 3 \ H, \ H-6), \ 3.80 \ (s, \ 3 \ H, \ H-1) \]

\[ \delta_H \ (600 \text{ MHz, CDCl}_3), \text{enol form, 388-a:} \ 7.85-7.81 \ (m, \ 2 \ H, \ H-5' \ \text{and} \ H-3''), \ 7.28 \ (dd, \ 1 \ H, \ J \ 8.8, \ 2.1, \ H-4'), \ 4.10 \ (s, \ 3 \ H, \ H-6'), \ 4.00 \ (s, \ 3 \ H, \ H-1') \]

**Note:** The protic signal (H-2’) is not visible in CDCl₃.
\[ \delta \text{C (151 MHz, CDCl}_3): \]
\[ 168.7 \text{ (C=O), 167.3} \text{.0 (C=O), 165.8 (C=O), 160.3 (C=O), 150.7 (C=O), 139.2 (q), 132.5 (q), 131.2, 128.8 (q), 127.5, 125.9, 125.7 (q), 123.9 (q), 122.0, 118.1 (q), 118.0 (q), 117.0, 116.2, 98.5, 87.7 (q), 54.6, 54.2, 53.5, 52.4, 51.9 } \]

\[ \nu_{\text{max (neat)/cm}}: \]
\[ 2959, 1774, 1734, 1439, 1249, 1208, 1120, 1049, 931, 865, 754, 729, 708 \]

HRMS (m/z - ESI):
\[ \text{Found: 325.9660 } [\text{M-}H]^+ \text{ C}_{12}\text{H}_9\text{NO}_5\text{Br Requires: 325.9664} \]

**Dimethyl 5-chloro-2-oxoindoline-1,3-dicarboxylate (389) and dimethyl 5-chloro-2-hydroxy-1\textit{H}-indole-1,3-dicarboxylate (389-a)**

![Diagram of chemical structures](image)

Synthesised according to general procedure V, using 385 (1.25 g, 4.41 mmol) in DMF (4.4 mL), DMAP (0.59 g, 4.85 mmol) in DMF (4.8 mL) and HCl (1.0 M, 4.4 mL). The crude residue was recrystallised from hexane to afford 389 (0.8 g, 64%) as off-white crystals. M.p. 126-127 °C.

\[ \delta \text{H (400 MHz, CDCl}_3), \text{ keto form, 389: } \]
\[ 7.90 \text{ (app. d, 1 H, J 8.7, H-5), 7.38-7.36 (m, 2 H, H-4 and H-3), 4.56 (s, 1 H, H-2), 4.03 (s, 3 H, H-6), 3.81 (s, 3 H, H-1) } \]

\[ \delta \text{H (400 MHz, CDCl}_3), \text{ enol form, 389-a: } \]
\[ 7.95 \text{ (d, 1 H, J 8.7, H-5'), 7.73 (d, 1 H, J 2.0, H-3'), 7.18 (dd, 1 H, J 8.7, 2.0, H-4'), 4.11 (s, 3 H, H-6'), 4.01 (s, 3 H, H-1') } \]

**Note:** The protic signal (H-2') is not visible in CDCl3.

\[ \delta \text{C (100 MHz, CDCl}_3): \]
\[ 168.7 \text{ (C=O), 167.4 (C=O), 165.8 (C=O), 160.5 (C=O), 150.9 (C=O), 150.7 (q), 138.6 (q), 130.5 (q), 130.3 (q), 129.6 (q), 128.3 (q), 125.3 (q), 124.6, 123.6 (q), 123.1, 119.1, 116.7, 115.8, 87.8 (q), 54.6, 54.2, 53.5, 52.5, 51.9 } \]
\( \nu_{\text{max}} \) (neat)/cm\(^{-1}\): 2960, 1741, 1660, 1612, 1572, 1488, 1436, 1318, 1192, 1145, 1033, 861, 788, 761

HRMS (m/z - ESI): Found: 282.0178 [M–H]\(^+\) \( \text{C}_{12}\text{H}_9\text{ClNO}_5 \) Requires: 282.0175

**Dimethyl 5-methoxy-2-oxoindoline-1,3-dicarboxylate (390) and dimethyl 2-hydroxy-5-methoxy-1H-indole-1,3-dicarboxylate (390-a)**

[Diagram of 390 and 390-a]

Synthesised according to general procedure V, using 386 (0.37 g, 1.325 mmol) in DMF (1.3 mL), DMAP (0.18 g, 1.457 mmol) in DMF (1.5 mL) and HCl (1.0 M, 1.3 mL). The crude residue was recrystallised from hexane to afford 390 (180 mg, 49%) as off-white crystals. M.p. 93-95 °C.

\( \delta \)\textsubscript{H} (600 MHz, CDCl\(_3\)), keto form, 390: 7.86 (d, 1 H, \( J \) 8.8, H-6), 6.93-6.89 (m, 2 H, H-5 and H-3), 4.55 (s, 1 H, H-2), 4.02 (s, 3 H, H-7), 3.81 (s, 3 H, H-4), 3.79 (s, 3 H, H-1)

\( \delta \)\textsubscript{H} (600 MHz, CDCl\(_3\)), enol form, 390-a: 7.89 (d, 1 H, \( J \) 8.8, H-6’), 7.29 (d, 1 H, \( J \) 2.6, H-3’), 6.79 (dd, 1 H, \( J \) 8.8, 2.6, H-5’), 4.10 (s, 3 H, H-7’), 4.00 (s, 3 H, H-1’), 3.86 (s, 3 H, H-4’)

**Note:** The protic signal (H-2’) is not visible in CDCl\(_3\).

\( \delta \)\textsubscript{C} (151 MHz, CDCl\(_3\)): 168.8 (C=O), 168.3 (C=O), 166.4 (C=O), 160.2 (C=O), 157.2 (C=O, q), 151.2 (q), 151.1 (q), 133.4 (q), 125.3 (q), 124.2 (q), 123.2 (q), 116.4, 115.6, 114.5, 110.4, 110.3, 103.7, 88.4 (q), 55.6 (two signals), 54.3, 54.0, 53.3, 53.1, 51.7
\[ \nu_{\text{max}} \text{(neat)} / \text{cm}^{-1}: \]

2956, 1736, 1586, 1433, 1328, 1299, 1214, 1127, 846, 782, 748, 714, 694

HRMS (m/z - ESI): Found: 278.0661 \([\text{M} - \text{H}]^+\) C\(_{13}\)H\(_{12}\)NO\(_6\) Requires: 278.0670

**1-Methylindolin-2-one (367a)**

A suspension of sodium hydride (1.62 g, 40.56 mmol, 60% in mineral oil, 1.0 equiv.) and xylene (81.0 mL, 0.5 M) was heated to 130 °C. After 15 min, 2-oxindole (5.40 g, 40.56 mmol, 1.0 equiv.) was added portionwise over 5 min. The resulting light orange suspension was heated under reflux for 1 h. Dimethyl sulfate (4.32 mL, 44.612 mmol, 1.1 equiv.) was added slowly dropwise via syringe. The suspension effervesced during the addition, then quickly became clear and orange. After 2 h, the reaction was cooled and diluted with EtOAc. The organic layer was washed with water and brine, then dried over MgSO\(_4\), and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 3:2, R\(_f\) = 0.2) to yield 367a (4.1g, 69%) as pale yellow crystals. M.p. 76-77 °C (lit.\(^{287}\) 85 °C). The isolated compound exhibited identical spectroscopic data to those reported in the literature.\(^{287}\)

\[ \delta_H (400 \text{ MHz, CDCl}_3): \quad 7.28 \text{ (app. td, 1 H, J 7.6, 0.8, H-5)}, 7.24 \text{ (d, 1 H, J 7.6, H-3)}, 7.04 \text{ (app. td, 1 H, J 7.6, 0.8, H-4)}, 6.82 \text{ (d, 1 H, J 7.6, H-6)}, 3.52 \text{ (s, 2 H, H-2)}, 3.21 \text{ (s, 3 H, H-1)} \]

**Methyl 1-methyl-2-oxoindoline-3-carboxylate (367) and methyl 2-hydroxy-1-methyl-1H-indole-3-carboxylate (367-a)**

To a stirring solution of LDA (4.08 mmol, 1.2 equiv.); prepared by adding BuLi (2.5 M in hexane, 1.36 mL, 3.40 mmol, 1.0 equiv.) to a solution of diisopropylamine (0.6 mL, 4.08 mmol, 1.2 equiv.) in anhydrous THF (4.0 mL, 0.83 M) at -78 °C; 367a (0.5 g, 3.40
(0.40 mL, 5.10 mmol, 1.5 equiv.) was added via syringe. After the addition was complete, the mixture was warmed slowly to -55 °C, and stirred overnight at this temperature. Upon warming the reaction mixture to rt, saturated ammonium chloride solution was added and the mixture was extracted with diethyl ether (3x). The combined organic layers were washed with HCl (1.0 N, aq.) and H₂O, then dried over MgSO₄. The solvent was concentrated in vacuo and the product was purified by recrystallisation from MeOH to afford 367 (320 mg, 46%) as white crystals. M.p. 115-117 °C (lit.²⁸⁸ 117-119 °C).

δ_H (600 MHz, CDCl₃), keto form, 367:
7.34 (app. t, 2 H, J 7.4, H-5 and H-3), 7.08 (app. t, 1 H, J 7.4, H-4), 6.85 (d, 1 H, J 7.4, H-6), 4.44 (s, 1 H, H-2), 3.78 (s, 3 H, H-1), 3.24 (s, 3 H, H-7)

5.2.2 Catalyst synthesis

(R)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methanol
(Dihydroquinine, DHQ, 328)

Dihydroquinine was synthesised by transfer hydrogenation of quinine.²⁸⁹ To a stirred solution of quinine (39, 5.0 g, 15.41 mmol) in MeOH (25.0 mL, 0.62 M) at rt was added formic acid (2.91 mL, 77.06 mmol) dropwise via syringe with vigorous stirring. Ammonium formate (3.89 g, 61.65 mmol) and Pd/C (10 wt. % loading, 330 mg, catalyst/quinine 1:15) were then added consecutively. After 1 h, the reaction mixture was slowly heated to 55 °C and stirred at that temperature for 24 h. The reaction progress was monitored by TLC (CH₂Cl₂/MeOH/Et₃N, 20:1:1). After cooling the reaction mixture, formic acid (0.58 mL, 15.41 mmol) was added dropwise via syringe with vigorous stirring to dissolve the precipitated product. The mixture was filtered through a 1.5 cm layer of Celite in a 125 mL glass sintered funnel and the filter was
washed with MeOH (5 x 30 mL). The filtrate was evaporated to dryness in vacuo and 
H₂O (5 mL) was added to the residue. Aqueous ammonia solution (28-30%, 25 mL) 
was slowly dropped into the vigorously stirred suspension. To complete the 
precipitation of the product, the mixture was slowly heated to about 50 °C. The mixture 
was stirred for 1 h with cooling to attain rt. Filtration and washing of the product with 
H₂O yielded 328 (4.5 g, 89%) as a white amorphous solid. M.p. 169-171 °C (lit. 290 
170-171 °C); [α]D²⁰ = -94.0 (c = 0.6, CHCl₃). The isolated compound exhibited identical 
spectroscopic data to those reported in the literature. 291

δH (400 MHz, CDCl₃): 8.45 (d, 1 H, J 4.5, H-16), 7.87 (d, 1 H, J 8.9, H-15), 7.44 
(d, 1 H, J 4.5, H-17), 7.26 (d, 1 H, J 2.4, H-12), 7.24-7.22 
(m, 1 H, H-14), 5.48 (d, 1 H, J 3.6, H-9), 5.19 (br s, 1 H, 
OH), 3.86 (s, 3 H, H-13), 3.47-3.41 (m, 1 H, H-6a), 3.06- 
2.96 (m, 2 H, H-8 and H-2b), 2.61-2.55 (m, 1 H, H-6b), 
2.34-2.29 (m, 1 H, H-2a), 1.72-1.67 (m, 3 H, H-3, H-7b 
and H-5b), 1.41-1.34 (m, 3 H, H-7a, H-5a and H-4), 1.25- 
1.14 (m, 2 H, H-10), 0.77 (t, 3 H, J 7.3, H-11)

General procedure VI: Oxidation of cinchona alkaloids.

Cinchona alkaloid (1.0 equiv.) was dissolved in CHCl₃ (0.17 M) and the solution was 
cooled to 0 °C. Meta-chloroperoxybenzoic acid (MCPBA, 70-75%, 3.6 equiv.) was 
added in portions under vigorous stirring. The resulting suspension was allowed to 
warm to rt and stirred for 3 h. The reaction was quenched with NaOH (aq., 10% w/v) 
solution until pH 10. The mixture was extracted with a mixed solvent of CHCl₃/MeOH 
(10:1, 5 x 20 mL). The organic extracts were combined and dried over Na₂SO₄. The 
 solvent was removed in vacuo to yield desired doubly N-oxidised product, which was 
used directly in the next step without any further purification.

(1R,2S,4S,5R)-5-ethyl-2-((R)-hydroxy(6-methoxy-1-oxidoquinolin-4-
yl)methyl)quinuclidine 1-oxide (329)
Synthesised according to general procedure VI, using dihydroquinine (328, 9.1 g, 27.88 mmol), CHCl$_3$ (164.0 mL) and MCPBA (17.3 g, 100.36 mmol), affording 329 (9.3 g, 99%) as a pale yellow amorphous solid. M.p. 131-135 °C (lit. 257 123-126 °C); $[\alpha]_D^{20} = -50.7 (c = 0.6, \text{CHCl}_3$). The isolated compound exhibited identical spectroscopic data to those reported in the literature.

$\delta_{H} (400 \text{ MHz, CDCl}_3): 8.59 \text{ (d, 1 H, J 9.5, H-15), 8.30 (d, 1 H, J 6.2, H-16), 7.63 (d, 1 H, J 6.2, H-17), 7.25 (app. d, 1 H, J 2.0, H-12), 7.12 (dd, 1 H, J 9.5, 2.0, H-14), 6.95 (s, 1 H, H-9), 4.56-4.50 (m, 1 H, H-6a), 3.64-3.58 (m, 1 H, H-8), 3.24-3.17 (m, 1 H, H-6b), 3.10-3.05 (m, 4 H, H-13 and H-2b), 2.77-2.72 (m, 1 H, H-2a), 2.42-2.29 (m, 2 H, H-7b and H-5b), 2.01-1.88 (m, 3 H, H-4, H-7a and H-5a), 1.64-1.58 (m, 1 H, H-3), 1.28 (quint, 2 H, J 7.4, H-10), 0.80 (t, 3 H, J 7.4, H-11)

(1R,2S,4S,5R)-2-((R)-hydroxy(6-methoxy-1-oxidoquinolin-4-yl)methyl)-5-vinylquinuclidine 1-oxide (346)

Synthesised according to general procedure VI, using quinine (39, 8.0 g, 24.66 mmol), CHCl$_3$ (145.0 mL) and MCPBA (15.3 g, 88.77 mmol), affording 346 (8.7 g, 99%) as a pale yellow amorphous solid. M.p. 137-139 °C (lit. 292 140-142 °C); $[\alpha]_D^{20} = -69.6 (c = 0.8, \text{CHCl}_3$). The isolated compound exhibited identical spectroscopic data to those reported in the literature.

$\delta_{H} (400 \text{ MHz, CDCl}_3): 8.56 \text{ (d, 1 H, J 9.5, H-15), 8.23 (d, 1 H, J 6.2, H-16), 7.54 (d, 1 H, J 6.2, H-17), 7.29 (d, 1 H, J 2.1, H-12), 7.14 (dd, 1 H, J 9.5, 2.1, H-14), 6.97 (s, 1 H, H-9), 5.67-5.59 (m, 1 H, H-10), 5.02-4.98 (m, 2 H, H-11), 4.49-4.43 (m, 1 H, H-6a), 3.70-3.64 (m, 1 H, H-8), 3.26 (s, 3 H, H-13), 3.26-

To a solution of doubly N-oxidised cinchona alkaloid (1.0 equiv.) in acetone (0.25 M) at 0 °C was added sulfur dioxide solution (H₂SO₃, 6% wt SO₂, 0.63 M) dropwise via syringe. The mixture was warmed to rt and stirred for 12 h. The progress of the reaction was followed by TLC (CH₂Cl₂/MeOH, 10:1). Upon completion of the reaction, acetone was removed in vacuo and the residue was made alkaline with aqueous ammonia solution (pH > 9). CHCl₃ (5 x 20 mL) was used to extract the aqueous layer. The combined organic extracts were dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography on silica gel.

4-((R)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(hydroxy)methyl)-6-methoxyquinoline 1-oxide (330)

Synthesised according to general procedure VII, using 329 (5.5 g, 15.34 mmol), acetone (61.0 mL) and H₂SO₃ (24.4 mL). The crude product was purified by column chromatography on silica gel (CH₂Cl₂/MeOH/Et₃N, 95:5:0.05, Rf = 0.15), obtaining product 330 (3.2 g, 60%) as a pale yellow amorphous solid. M.p. 175-179 °C (lit.²⁵⁸ 185 °C); [α]D²⁰ = -87.7 (c = 0.6, CHCl₃). The isolated compound exhibited identical spectroscopic data to those reported in the literature.²⁵⁸

δH (400 MHz, CDCl₃):

3.23 (m, 1 H, H-2b), 3.11-3.03 (m, 2 H, H-6b and H-2a), 2.86-2.80 (m, 1 H, H-3), 2.41-2.31 (m, 2 H, H-7b and H-5b), 1.99-1.94 (m, 2 H, H-4 and H-5a), 1.67-1.61 (m, 1 H, H-7a)
H-4), 1.53-1.39 (m, 3 H, H-7a, H-5a and H-3), 1.31-1.15 (quint, 2 H, J 7.3, H-10), 0.79 (t, 3 H, J 7.3, H-11)

4-((R)-hydroxy((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)-6-methoxyquinoline 1-oxide (347)

Synthesised according to general procedure VII, using 346 (5.9 g, 16.55 mmol), acetone (66.0 mL) and H$_2$SO$_3$ (26.3 mL). The crude product was purified by column chromatography on silica gel (CH$_2$Cl$_2$/MeOH/Et$_3$N, 95:5:0.05, $R_f$ = 0.2), obtaining product 347 (3.4 g, 60%) as an off-white amorphous solid. M.p. 102-106 °C (lit.$^{293}$ 103-107 °C); $[\alpha]_D^{20}$ = -100.3 (c = 0.3, CHCl$_3$). The isolated compound exhibited identical spectroscopic data to those reported in the literature.$^{293}$

$\delta_H$ (400 MHz, CDCl$_3$):
8.44 (d, 1 H, J 9.5, H-15), 7.89 (d, 1 H, J 6.2, H-16), 7.21-7.18 (m, 2 H, H-17 and H-14), 6.93 (app. d, 1 H, J 2.0, H-12), 6.01 (br s, 1 H, OH), 5.77-5.68 (m, 1 H, H-10), 5.30 (s, 1 H, H-9), 4.98-4.92 (m, 2 H, H-11), 3.88 (s, 3 H, H-13), 3.62-3.54 (m, 1 H, H-6a), 3.13-3.07 (m, 1 H, H-8), 2.97-2.92 (m, 1 H, H-2b), 2.72-2.63 (m, 2 H, H-6b and H-2a), 2.34-2.29 (m, 1 H, H-3), 1.85-1.79 (m, 3 H, H-7b, H-5b and H-4), 1.62-1.53 (m, 2 H, H-5a and H-7a)

**General procedure VIII:** Protocol for the chlorination of cinchona alkaloid-based $N$-oxide derivatives.

To a solution of cinchona alkaloid-based $N$-Oxide derivative (1.0 equiv.) in anhydrous CHCl$_3$ (0.22 M) at 0 °C was added phosphoryl chloride (POCl$_3$, 4.0 equiv.) dropwise via syringe under argon atmosphere. The solution was stirred at 0 °C for 30 min before it was moved into an oil bath at 70 °C. After refluxing for 2 h, the reaction mixture was poured into ice-water and the pH was adjusted with conc. aqueous ammonia solution (35%) until pH 10. The mixture was extracted with CH$_2$Cl$_2$ (4 x 50 mL). The combined
organic extracts were washed with brine and dried over MgSO₄, followed by concentration *in vacuo*. The yellow residue was purified by column chromatography on silica gel.

*(R)-(2-chloro-6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)methanol (331)*

Synthesised according to general procedure VIII, using 330 (1.1 g, 3.21 mmol), CHCl₃ (15 mL) and POCl₃ (1.20 mL, 12.85 mmol). The crude residue was purified by column chromatography (CH₂Cl₂/MeOH, 20:1 + 1% NH₃, Rᵣ = 0.3), obtaining product 331 (0.75 g, 65%) as a white amorphous solid. M.p. 203-207 °C (lit.²⁵⁸ 196-198 °C); [α]_D²⁰ = -5.4 (c = 0.5, CHCl₃). The isolated compound exhibited identical spectroscopic data to those reported in the literature.²⁵⁸

δ_H (400 MHz, CDCl₃):

- 7.79 (d, 1 H, J 9.3, H-15),
- 7.52 (s, 1 H, H-17),
- 7.23 (dd, 1 H, J 9.3, 2.6, H-14),
- 7.06 (d, 1 H, J 2.6, H-12),
- 5.60 (app. s, 1 H, H-9),
- 3.80 (s, 3 H, H-13),
- 3.61-3.54 (m, 1 H, H-6a),
- 3.08-3.00 (m, 2 H, H-8 and H-6b),
- 2.67-2.60 (m, 1 H, H-2b),
- 2.40-2.35 (m, 1 H, H-2a),
- 1.80-1.72 (m, 3 H, H-7b, H-5b and H-4),
- 1.48-1.34 (m, 3 H, H-7a, H-5a and H-3),
- 1.26-1.14 (m, 2 H, H-10),
- 0.78 (t, 3 H, J 7.3, H-11)

*(R)-(2-chloro-6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methanol (348)*
Synthesised according to general procedure VIII, using 347 (3.2 g, 9.40 mmol), CHCl₃ (43 mL) and POCl₃ (3.52 mL, 37.60 mmol). The crude residue was purified by column chromatography (CH₂Cl²/MeOH, 20:1 + 1% NH₃, Rf = 0.3), obtaining product 348 (2.5 g, 74%) as an off-white amorphous solid. M.p. 198-202 °C; [α]D²⁰ = -56.5 (c = 0.4, CHCl₃).

δ_H (400 MHz, CDCl₃): 7.81 (d, 1 H, J 9.1, H-15), 7.52 (s, 1 H, H-17), 7.25 (app. d, 1 H, J 9.1, H-14), 7.09 (s, 1 H, H-12), 5.72-5.62 (m, 2 H, H-10 and H-9), 4.97-4.91 (m, 2 H, H-11), 3.82 (s, 3 H, H-13), 3.63-3.56 (m, 1 H, H-6a), 3.13-3.07 (m, 2 H, H-8 and H-2b), 2.71-2.69 (m, 2 H, H-6b and H-2a), 2.35-2.31 (m, 1 H, H-3), 1.85-1.75 (m, 3 H, H-7b, H-5b and H-4), 1.56-1.45 (m, 2 H, H-5a and H-7a)

δ_C (100 MHz, CDCl₃): 158.0 (q), 150.8 (q), 148.2 (q), 143.7 (q), 141.0, 130.5, 125.1 (q), 122.1, 119.7, 114.9, 101.6, 70.9, 59.9, 56.6, 55.9, 43.3, 39.4, 27.6, 27.0, 21.0

v_max (neat)/cm⁻¹: 2921, 1620, 1508, 1261, 1098, 1044, 905, 822, 653


(R)-(2-bromo-6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-ethylquinuclidin-2-y1)methanol (336)

To a solution of 330 (2.6 g, 7.59 mmol) in anhydrous CHCl₃ (34.5 mL, 0.22 M) at 0 °C was added the solution of phosphoryl bromide (POBr₃, 8.71 g, 30.37 mmol, 4.0 equiv.) in anhydrous CHCl₃ (15.2 mL, 0.5 M) via syringe dropwise under argon atmosphere. The orange solution was allowed to warm to rt and stirred overnight. CHCl₃ (30 mL) was added and the mixture was poured into ice-H₂O (40 mL). The pH was adjusted with aqueous ammonia solution (35%) until pH 10. The mixture was extracted with CH₂Cl₂.
(4 x 50 mL). The combined organic extracts were washed with brine and dried over Na₂SO₄, followed by concentration in vacuo. The crude residue was purified by column chromatography on silica gel, eluting gradient from CH₂Cl₂/MeOH/Et₃N 35:1:0.1 → 15:1:0.1. For better visualisation, TLC was performed using CH₂Cl₂/MeOH/Et₃N, 10:1:0.1, Rf = 0.23. Upon purification, the desired product 336 (1.8 g, 58 %) was obtained as an off-white amorphous solid. M.p. 181-183 °C (lit.258 188-189 °C); [α]D²⁰ = -60.6 (c = 0.6, CHCl₃). The isolated compound exhibited identical spectroscopic data to those reported in the literature.258

δH (400 MHz, CDCl₃): 7.86 (d, 1 H, J 9.1, H-15), 7.65 (s, 1 H, H-17), 7.27 (dd, 1 H, J 9.1, 2.6, H-14), 7.11 (d, 1 H, J 2.6, H-12), 5.52 (s, 1 H, H-9), 3.84 (s, 3 H, H-13), 3.51-3.44 (m, 1 H, H-6a), 3.06-3.00 (m, 2 H, H-8 and H-6b), 2.65-2.58 (m, 1 H, H-2b), 2.39-2.34 (m, 1 H, H-2a), 1.78-1.69 (m, 3 H, H-7b, H-5b and H-4), 1.45-1.39 (m, 3 H, H-7a, H-5a and H-3), 1.27-1.16 (m, 2 H, H-10), 0.79 (t, 3 H, J 7.3, H-11)


An oven dried round-bottomed flask containing a stirring bar was charged with cinchona alkaloid (1.0 equiv.), fitted with a septum and placed under an argon atmosphere (balloon). Anhydrous MTBE (0.17 M) was added via syringe and the suspension was cooled to -10 °C. A solution of phenyl lithium (1.9 M in dibutyl ether, 3.0 equiv.) was added via syringe to the vigorously stirred suspension and the reaction mixture was allowed to stir at -10 °C for 30 min, then warmed to rt and allowed to stir for 2 h. Acetic acid (1.5 M) was added to the reaction at 0 °C, dropwise via syringe, followed by H₂O (40 mL) and EtOAc (40 mL). The reaction was then allowed to warm to rt and iodine was added in several portions to the stirred mixture until the appearance of a persistent deep brown colouration. A solution of sodium thiosulfate (Na₂S₂O₃, 1.0 N, aq.) was added to quench the excess iodine and NH₃ solution (35%, aq.) was added until solution was basic and the mixture was allowed to stir for 10 min. The organic phase was then washed with brine and the aqueous phase was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic extracts were dried over anhydrous MgSO₄ and the
solvent was removed \textit{in vacuo}. The crude oily residue was purified by column chromatography on silica gel.

\((R)-((1S,2S,4S,5R)-5\text{-ethylquinuclidin-2-yl})(6\text{-methoxy-2-phenylquinolin-4-yl})\text{methanol (341)}\)

Synthesised according to general procedure IX, using 328 (3.6 g, 11.03 mmol), MTBE (66.0 mL), PhLi (17.4 mL, 33.1 mmol) and CH$_3$COOH (7.4 mL). The crude residue was purified by column chromatography eluting gradient from CH$_2$Cl$_2$/MeOH/Et$_3$N 9.9:0.1:0.1 to 9.5:0.5:0.1 (TLC is better visualised using CH$_2$Cl$_2$/MeOH/Et$_3$N 9:1:0.1, R$_f$ = 0.3, which allows for a better separation of the product from the starting alkaloid), to afford 341 (2.2 g, 50\%) as a white amorphous solid. M.p. 104-108 °C (lit.$^{294}$ 74.8-78.6 °C); [\(\alpha\)]$_{D}^{20}$ = -6.7 (c = 0.5, CHCl$_3$). The isolated compound exhibited identical spectroscopic data to those reported in the literature.$^{294}$

\[\delta_{H} (400 \text{ MHz, CDCl$_3$}): \]

8.08 (app. d, 2 H, J 7.2, H-18), 8.01 (s, 1 H, H-17), 7.94 (d, 1 H, J 9.2, H-15), 7.47 (app. t, 2 H, J 7.2, H-19), 7.46-7.38 (m, 1 H, H-20), 7.17 (dd, 1 H, J 9.2, 2.6, H-14), 7.05 (d, 1 H, J 2.6, H-12), 5.87 (s, 1 H, H-9), 3.90-3.83 (m, 1 H, H-6a), 3.75 (s, 3 H, H-13), 3.20-3.14 (m, 2 H, H-8 and H-6b), 2.82-2.75 (m, 1 H, H-2b), 2.49-2.45 (m, 1 H, H-2a), 1.94-1.84 (m, 3 H, H-7b, H-5b and H-4), 1.58-1.50 (m, 2 H, H-7a and H-5a), 1.41-1.33 (m, 1 H, H-3), 1.20 (quint, 2 H, J 7.3, H-10), 0.77 (t, 3 H, J 7.3, H-11)
\((R)-(6\text{-methoxy-2-phenylquinolin-4-yl})((1S,2S,4S,5R)-5\text{-vinylquinuclidin-2-yl})\text{methanol}\ (313)\)

![Chemical Structure of 313](image)

Synthesised according to general procedure IX, using quinine \((39,\ 4.0\ g,\ 12.3\ mmol),\) MTBE \((74.0\ mL),\) PhLi \((19.4\ mL,\ 36.9\ mmol)\) and \(\text{CH}_3\text{COOH}\ (8.0\ mL)\). The crude residue was purified by column chromatography (hexane/EtOAc/MeOH/NEt\(_3\), 8:1:0.5:0.5, to achieve better visualisation TLC was carried out in hexane/EtOAc/MeOH/NEt\(_3\), 7:1:1.5:0.5, \(R_f = 0.4\)) to afford 313 \((3.40\ g,\ 69\%)\) as a white amorphous solid. M.p. 142-145 \(^\circ\)C (lit.\(^{\text{295}}\) 151 \(^\circ\)C); \([\alpha]_D^{20} = -25.3\ (c = 0.3,\ \text{CHCl}_3)\). The isolated compound exhibited identical spectroscopic data to those reported in the literature.\(^{\text{296}}\)

\(\delta_H\) (400 MHz, CDCl\(_3\)):

- 8.08 (app. d, 2 H, \(J\ 7.2,\ H-18\)), 8.02 (d, 1 H, \(J\ 9.2,\ H-15\)),
- 7.96 (s, 1 H, H-17), 7.46-7.39 (m, 3 H, H-20 and H-19),
- 7.28 (dd, 1 H, \(J\ 9.2,\ 2.6,\ H-14\)), 7.14 (d, 1 H, \(J\ 2.6,\ H-12\)),
- 5.75-5.66 (m, 2 H, H-10 and H-9), 4.98-4.91 (m, 2 H, H-11), 3.85 (s, 3 H, H-13), 3.66-3.56 (m, 1 H, H-6a), 3.20-3.11 (m, 2 H, H-8 and H-2b), 2.77-2.70 (m, 2 H, H-6b and H-2a), 2.35-2.31 (m, 1 H, H-3), 1.85-1.77 (m, 3 H, H-4, H-7b and H-5b), 1.58-1.49 (m, 2 H, H-7a and H-5a)

**General procedure X:** Protocol for the preparation of 9-\textit{epi}-amine-derivatives (3-HCl salts) of cinchona alkaloid derivatives.

An oven dried round-bottomed flask containing a stirring bar was charged with triphenylphosphine (PPh\(_3\), 1.2 equiv.) and the appropriate cinchona alkaloid derivative (1.0 equiv.), fitted with a septum and placed under an argon atmosphere (balloon). Anhydrous THF (0.15 M) was added \textit{via} syringe and the resulting solution was cooled to 0 \(^\circ\)C. Diisopropyl azodicarboxylate (DIAD, 1.2 equiv.) was added dropwise \textit{via}
syringe into the stirring solution, followed by diphenylphosphoryl azide (DPPA, 1.2 equiv.) and the resulting mixture was allowed to warm to rt. After stirring for 16 h, the solution was heated to 50 °C for 2 h. PPh₃ (1.2 equiv.) was added portionwise and heating was maintained for 2 h. After cooling the solution to ambient temperature, H₂O (0.7 M) was added and the mixture was stirred for 4 h. The reaction was then concentrated in vacuo and the residue dissolved in CH₂Cl₂ and HCl (2 N). The aqueous phase was separated and the organic phase was extracted with HCl (2 N) several times. The combined aqueous extracts were washed with CH₂Cl₂ and concentrated in vacuo. EtOH was repeatedly added to the crude residue and removed in vacuo until the amorphous solid crushed out.

(S)-(2-Chloro-6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)methanamine (3·HCl salt, 333)

Prepared as per general procedure X, using 331 (2.2 g, 6.10 mmol), PPh₃ (1.92 g, 7.32 mmol), DIAD (1.44 mL, 7.32 mmol), DPPA (1.57 mL, 7.32 mmol) and THF (41.0 mL). The Staudinger reduction was carried out using PPh₃ (1.92 g, 7.32 mmol) and H₂O (9.0 mL) to afford 333 (1.9 g, 66%) as a yellow amorphous solid. M.p. 202-220 °C (dec.); [α]D²⁰ = +5.4 (c = 0.6, H₂O).

δH (400 MHz, dmso-d₆): 8.29 (s, 1 H, H-17), 7.96 (d, 1 H, J 9.3, H-15), 7.85 (d, 1 H, J 2.5, H-12), 7.56 (dd, 1 H, J 9.3, 2.5, H-14), 5.85 (d, 1 H, J 10.2, H-9), 4.79-4.72 (m, 1 H, H-8), 4.20-4.13 (m, 1 H, H-6a), 4.02 (s, 3 H, H-13), 3.70-3.64 (m, 1 H, H-2b), 3.34-3.27 (m, 1 H, H-6b), 3.01-2.98 (m, 1 H, H-2a), 1.90-1.76 (m, 5 H, H-3, H-7b, H-5b, H-7a and H-5a), 1.67-1.61 (m, 1 H, H-4), 1.48-1.31 (m, 2 H, H-10), 0.80 (t, 3 H, J 7.3, H-11)
\(\delta_C\) (100 MHz, dmsod6):

158.8 (q), 147.0 (q), 143.6 (q), 141.7 (q), 130.5, 126.8 (q), 123.7, 122.3, 103.0, 58.7, 56.4, 56.1, 54.2, 47.9, 41.6, 34.2, 25.7, 24.0, 23.3, 11.5

\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\):

3380, 2552, 1618, 1509, 1440, 1242, 1022, 915, 837, 775, 681

HRMS (\(m/z\) – APCI):

Found: 360.1836 \([M+H]^+\) \(\text{C}_{20}\text{H}_{27}\text{ClN}_3\text{O}\)

Requires: 360.1843

(S)-(2-Bromo-6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)methanamine (3·HCl salt, 338)

Prepared as per general procedure X, using 336 (2.0 g, 4.93 mmol), PPh\(_3\) (1.55 g, 5.92 mmol), DIAD (1.17 mL, 5.92 mmol), DPPA (1.27 mL, 5.92 mmol) and THF (33.0 mL). The Staudinger reduction was carried out using PPh\(_3\) (1.55 g, 5.92 mmol) and \(\text{H}_2\text{O}\) (7.0 mL) to afford 338 (1.4 g, 56%) as a yellow amorphous solid. M.p. 207-222 °C (dec.); \([\alpha]_D^{20} = +5.2\) (\(c = 2.0, \text{H}_2\text{O}\)).

\(\delta_H\) (400 MHz, dmsod6):

8.05 (s, 1 H, H-17), 7.99 (d, 1 H, J 9.1, H-15), 7.81 (d, 1 H, J 2.4, H-12), 7.60 (dd, 1 H, J 9.1, 2.4, H-14), 5.76 (d, 1 H, J 10.5, H-9), 4.57-4.50 (m, 1 H, H-8), 4.16-4.05 (m, 1 H, H-6a), 4.02 (s, 3 H, H-13), 3.73-3.67 (m, 1 H, H-2b), 3.35-3.28 (m, 1 H, H-6b), 2.95-2.91 (m, 1 H, H-2a), 1.87-1.69 (m, 6 H, H-3, H-7b, H-5b, H-7a, H-5a and H-4), 1.50-1.32 (m, 2 H, H-10), 0.82 (t, 3 H, J 7.3, H-11)

\(\delta_C\) (100 MHz, dmsod6):

158.8 (q), 147.0 (q), 143.6 (q), 141.6 (q), 130.5, 126.7 (q), 123.7, 122.2, 103.2, 58.7, 56.4, 56.0, 54.3, 47.9, 41.5, 34.2, 25.6, 24.0, 23.3, 11.4
$v_{\text{max}}$ (neat)/cm$^{-1}$: 3462, 2566, 1613, 1509, 1357, 1242, 1125, 1018, 831, 682

HRMS ($m/z$ – DIP-APCI): Found: 404.1338 [M+H]$^+$ C$_{29}$H$_{27}$BrN$_3$O Requires: 404.1332

(S)-(6-Methoxy-2-phenylquinolin-4-yl)((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)methanamine (3·HCl salt, 343)

Prepared as per general procedure X, using 341 (2.1 g, 5.22 mmol), PPh$_3$ (1.64 g, 6.26 mmol), DIAD (1.23 mL, 6.26 mmol), DPPA (1.35 mL, 6.26 mmol) and THF (35.0 mL). The Staudinger reduction was carried out using PPh$_3$ (1.64 g, 6.26 mmol) and H$_2$O (8.0 mL), to afford 343 (1.9 g, 71%) as a yellow amorphous solid. M.p. 198-215 °C (dec.); $[\alpha]_D^{20} = +7.5$ (c = 0.3, H$_2$O).

$\delta$$_H$ (400 MHz, dmoso-$d_6$): 8.97 (s, 1 H, H-17), 8.41 (app. d, 2 H, J 7.4, H-18), 8.25 (d, 1 H, J 9.3, H-15), 7.88 (d, 1 H, J 7.4, H-12), 7.61-7.53 (m, 4 H, H-14, H-19 and H-20), 5.94 (d, 1 H, J 9.9, H-9), 4.91-4.84 (m, 1 H, H-8), 4.23-4.21 (m, 1 H, H-6a), 4.04 (s, 3 H, H-13), 3.72-3.66 (m, 1 H, H-2b), 3.36-3.29 (m, 1 H, H-6b), 3.02-2.99 (m, 1 H, H-2a), 1.86-1.81 (m, 4 H, H-3, H-7b, H-5b and H-7a), 1.63-1.57 (m, 1 H, H-5a), 1.47-1.25 (m, 2 H, H-10), 1.89-0.84 (m, 1 H, H-4), 0.77 (t, 3 H, J 7.3, H-11)

$\delta$$_C$ (100 MHz, dmoso-$d_6$): 158.8 (q), 152 (q), 141.9 (q), 141.0 (q), 136.4 (q), 130.4, 129.9, 129.0, 127.8, 127.1 (q), 123.8, 119.6, 102.7, 59.1, 56.5, 56.0, 54.2, 48.3, 41.6, 34.3, 25.7, 24.1, 18.6, 11.5
\[ \text{max (neat)/cm}^{-1}: \quad 3440, 2580, 1619, 1509, 1440, 1280, 1242, 1022, 916, 765, 681 \]

HRMS \( (m/z - \text{APCI}) \):

\[ \text{Found: } 402.2545 [\text{M+H}]^+ \quad \text{C}_{26}\text{H}_{32}\text{N}_3\text{O} \text{ Requires: } 402.2540 \]

\((S)-(6\text{-Methoxyquinolin-4-yl})(2S,2S,4S,5R)-5\text{-vinylquinuclidin-2-yl})\text{methanamine} \quad (3\text{-HCl salt, 296a})

Prepared as per general procedure X, using quinine \((39, 10.0 \text{ g, } 30.82 \text{ mmol}), \text{PPh}_3 (9.7 \text{ g, } 37.0 \text{ mmol}), \text{DIAD} (7.3 \text{ mL, } 36.989 \text{ mmol}), \text{DPPA} (8.0 \text{ mL, } 37.0 \text{ mmol}) \text{ and THF (200 mL)}. \text{The Staudinger reduction was carried out using PPh}_3 (9.7 \text{ g, } 37.0 \text{ mmol}) \text{ and H}_2\text{O (44.0 mL)}, \text{to 296a (11.3 g, 85\%)} \text{ as a yellow amorphous solid. M.p. 185-195 °C, dec. (lit.}^{297} \text{ 220-222 °C, dec.; } [\alpha]_D^{20} = +6.1 \text{ (c = 0.4, H}_2\text{O). The isolated compound exhibited identical spectroscopic data to those reported in the literature.}^{297} \]

\[ \delta_H (400 \text{ MHz, dms}-d_6): \]

\[
\begin{align*}
9.12 & \text{ (d, 1 H, J 5.2, H-16), 8.39 (d, 1 H, J 5.2, H-17), 8.32 (d, 1 H, J 9.4 H-15), 7.99 (d, 1 H, J 2.4, H-12), 7.74 (dd, 1 H, J 9.4, 2.4, H-14), 5.98 (d, 1 H, J 10.3, H-9), 5.93-5.84 (m, 1 H, H-10), 5.29 (d, 1 H, J 17.2, H-11), 5.15 (d, 1 H, J 10.5, H-11), 4.82-4.74 (m, 1 H, H-8), 4.17-4.09 (m, 1 H, H-6a), 4.07 (s, 3 H, H-13), 3.76-3.70 (m, 1 H, H-2b), 3.41-3.33 (m, 2 H, H-6b and H-2a), 2.79-2.74 (m, 1 H, H-3), 1.88-1.84 (m, 3 H, H-4, H-7b and H-5b), 1.54-1.49 (m, 1 H, H-7a), 0.91-0.86 (m, 1 H, H-5a)
\end{align*}
\]
(S)-(6-Methoxy-2-phenylquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methanamine (3·HCl salt, 315)

Prepared as per general procedure X, using 313 (2.2 g, 5.49 mmol), PPh₃ (1.73 g, 6.59 mmol), DIAD (1.30 mL, 6.59 mmol), DPPA (1.42 mL, 6.59 mmol) and THF (37.0 mL).

The Staudinger reduction was carried out using PPh₃ (1.73 g, 6.59 mmol) and H₂O (8.0 mL), to afford 315 (2.5 g, 90%) as a yellow amorphous solid. M.p. 195-205 ºC (dec.); [α]D²⁰ = +25.7 (c = 0.4, H₂O). The isolated compound exhibited identical spectroscopic data to those reported in the literature.¹²⁰

δₜ (400 MHz, dmsö-d₆): 8.77 (s, 1 H, H-17), 8.34 (d, 2 H, J 7.2, H-18), 8.12 (d, 1 H, J 9.2, H-15), 7.82 (d, 1 H, J 2.3, H-12), 7.62-7.51 (m, 4 H, H-20, H-19 and H-4), 5.93-5.84 (m, 2 H, H-9 and H-10), 5.27 (d, 1 H, J 17.3, H-11), 5.12 (d, 1 H, J 10.6, H-11), 4.78-4.71 (m, 1 H, H-8), 4.21-4.14 (m, 1 H, H-6a), 4.03 (s, 3 H, H-13), 3.76-3.72 (m, 1 H, H-2b), 3.39-3.32 (m, 2 H, H-6b and H-2a), 2.79-2.75 (m, 1 H, H-3), 1.88-1.85 (m, 3 H, H-4, H-7b and H-5a), 1.58-1.52 (m, 1 H, H-7a), 0.94-0.89 (m, 1 H, H-5a)

(S)-(2-Chloro-6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methanamine (3·HCl salt, 350)
Prepared as per general procedure X, using 348 (1.6 g, 4.47 mmol), PPh₃ (1.41 g, 5.36 mmol), DIAD (1.06 mL, 5.36 mmol), DPPA (1.15 mL, 5.36 mmol) and THF (30.0 mL). The Staudinger reduction was carried out using PPh₃ (1.41 g, 5.36 mmol) and H₂O (6.0 mL), to afford 350 (1.2 g, 57%) as a yellow amorphous solid. M.p. 195-207 °C (dec.); [α]D²⁰ = +13.0 (c = 0.5, H₂O).

δH (400 MHz, dmso-d₆): 8.30 (s, 1 H, H-17), 7.93 (d, 1 H, J 8.7, H-15), 7.85 (s, 1 H, H-12), 7.54 (d, 1 H, J 8.7, H-14), 5.92-5.85 (m, 2 H, H-9 and H-10), 5.27 (d, 1 H, J 17.3, H-11), 5.13 (d, 1 H, J 10.3, H-11), 4.85-4.75 (m, 1 H, H-8), 4.20-4.11 (m, 1 H, H-6a), 4.01 (s, 3 H, H-13), 3.75-3.70 (m, 1 H, H-2b), 3.36-3.32 (m, 2 H, H-6b and H-2a), 2.79-2.73 (m, 1 H, H-3), 1.91-1.82 (m, 3 H, H-4, H-7b and H-5b), 1.56-1.50 (m, 1 H, H-7a), 0.90-0.84 (m, 1 H, H-5a)

δC (100 MHz, dmso-d₆): 158.8 (q), 146.9 (q), 143.7 (q), 141.9 (q), 138.3, 130.5, 126.8 (q), 123.8, 122.1, 116.7, 103.1, 58.8, 55.6, 52.0, 47.8, 41.8, 35.9, 25.6, 21.8, 18.6

νmax (neat)/cm⁻¹: 3476, 2562, 1617, 1459, 1357, 1241, 1019, 831, 681

HRMS (m/z – APCI): Found: 358.1669 [M+H]+ C₂₀H₂₅ClN₃O Requires: 358.1681

**General procedure XI:** Protocol for the preparation of the urea-substituted epi-amine-cinchona alkaloids.

An oven dried round-bottomed flask containing a stirring bar was charged with the appropriate 9-epi-amine cinchona alkaloid derivative (3-HCl salt, 1.0 equiv.), fitted with a septum and placed under an argon atmosphere (balloon). Anhydrous CH₂Cl₂ (0.08 M) was added *via* syringe, followed by freshly distilled triethylamine (Et₃N, 5.0 equiv.). When the amine had dissolved, the appropriate isocyanate (1.2 equiv.) was added dropwise *via* syringe and the resulting solution was stirred for 12 h at rt. The solvent was removed *in vacuo* and the crude residue was dissolved in EtOAc. The amine salt that crushed out was filtered over cotton wool and the solvent was removed *in vacuo*. The desired crude product was purified by column chromatography on silica gel.
1-(3,5-bis(Trifluoromethyl)phenyl)-3-((S)-(2-chloro-6-methoxyquinolin-4-yl))((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)methyl)urea (334)

Synthesised according to general procedure XI, using 333 (1.9 g, 4.05 mmol), CH₂Cl₂ (51.0 mL), Et₃N (2.8 mL, 20.25 mmol) and 3,5-bis(trifluoromethyl)phenyl isocyanate (0.84 mL, 4.86 mmol). The crude residue was purified by column chromatography eluting in gradient from 30:1 to 10:1 CH₂Cl₂/MeOH (TLC is better visualised using CH₂Cl₂/MeOH 10:1, Rf = 0.3), to afford 334 (1.8 g, 72%) as a white amorphous solid. M.p. 138-140 °C; [α]D 20 = +13.3 (c = 0.6, CHCl₃).

δH (400 MHz, CDCl₃): 8.73 (br s, 1 H, NH¹), 7.93 (d, 1 H, J 9.3, H-15), 7.75-7.72 (m, 3 H, H-18 and H-17), 7.45 (s, 1 H, H-19), 7.40 (dd, 1 H, J 9.3, 2.5, H-14), 7.30 (s, 1 H, H-12), 6.83 (br s, 1 H, NH²), 4.75 (s, 1 H, H-9), 3.98 (s, 3 H, H-13), 3.66-3.54 (m, 2 H, H-8 and H-6a), 3.23-3.17 (m, 1 H, H-2b), 2.84-2.76 (m, 1 H, H-6b), 2.37-2.35 (m, 1 H, H-2a), 1.86-1.67 (m, 4 H, H-7b, H-5a, H-5b and H-3), 1.62-1.54 (m, 1 H, H-4), 1.33-1.21 (m, 2 H, H-10), 1.06-0.96 (m, 1 H, H-7a), 0.77 (t, 3 H, J 7.5, H-11)

δC (100 MHz, CDCl₃): 158.8 (C=O), 156.8 (q), 154.4 (q), 147.8 (q), 146.9 (q), 144.4 (q), 140.6 (q), 140.4, 131.8 (q, J_C-F 33.3) (q), 130.8, 123.3, 123.0 (q, J_C-F 272.3) (q), 117.9, 115.4, 102.2, 59.6, 57.0, 55.8, 50.1, 41.4, 35.8, 26.8, 26.7, 25.7, 24.7, 11.6

δF (376 MHz, CDCl₃): -63.2

ν_max (neat)/cm⁻¹: 3271, 2936, 1690, 1622, 1560, 1473, 1386, 1275, 1172, 1125, 1030, 880, 831
HRMS (m/z – ESI): Found: 613.1805 [M-H] \(-\) C_{29}H_{28}N_{4}O_{2}ClF_{6} Requires: 613.1805

1-(3,5-bis(Trifluoromethyl)phenyl)-3-((S)-(2-bromo-6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)methyl)urea (339)

Synthesised according to general procedure XI, using 338 (1.3 g, 2.53 mmol), CH_{2}Cl_{2} (32.0 mL), Et_{3}N (1.8 mL, 12.66 mmol) and 3,5-bis(trifluoromethyl)phenyl isocyanate (0.50 mL, 3.04 mmol). The crude residue was purified by column chromatography eluting in gradient from 100% CH_{2}Cl_{2} to 95:5 CH_{2}Cl_{2}/MeOH (TLC is better visualised using CH_{2}Cl_{2}/MeOH 10:1, R_{f} = 0.3), to afford 339 (1.1 g, 65%) as a white amorphous solid. M.p. 145-147 °C; [\alpha]_{D}^{20} = +0.4 (c = 0.3, CHCl_{3}).

\(\delta\)H (400 MHz, CDCl_{3}): 8.93 (br s, 1 H, NH\(^1\)), 7.92 (d, 1 H, J 9.3, H-15), 7.75 (s, 2 H, H-18), 7.71 (app. s, 1 H, H-17), 7.46 (s, 1 H, H-19), 7.40 (dd, 1 H, J 9.3, 2.2, H-14), 7.28 (s, 1 H, H-12), 6.97 (br s, 1 H, NH\(^2\)), 5.70 (s, 1 H, H-9), 3.98 (s, 3 H, H-13), 3.74-3.57 (m, 2 H, H-8 and H-6a), 3.22-3.14 (m, 1 H, H-2b), 2.81-2.74 (m, 1 H, H-6b), 2.31-2.29 (m, 1 H, H-2a), 1.86-1.67 (m, 4 H, H-3, H-7b, H-5a and H-5b), 1.62-1.54 (m, 1 H, H-4), 1.30-1.18 (m, 2 H, H-10), 1.04-1.01 (m, 1 H, H-7a), 0.74 (t, 3 H, J 7.3, H-11)

\(\delta\)C (100 MHz, CDCl_{3}): 158.8 (C=O), 154.5 (q), 147.7 (q), 146.7 (q), 144.3 (q), 140.7 (q), 131.6 (q, J_{C-F} 33.2) (q), 130.7, 127.0 (q), 123.3, 123.0 (q, J_{C-F} 273.1) (q), 119.9, 117.8, 115.2, 102.2, 59.4, 56.9, 55.8, 49.9, 41.3, 35.6, 26.6, 26.4, 25.5, 24.6, 11.5

\(\delta\)F (376 MHz, CDCl_{3}): -63.1
$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3271, 2934, 1691, 1622, 1560, 1474, 1386, 1275, 1172, 1126, 1029, 918, 879

HRMS ($m/z$ – ESI): Found: 693.1051 [M+Cl]$^-$ C$_{29}$H$_{29}$BrClF$_6$N$_4$O$_2$ Requires: 693.1072

1-(3,5-bis(Trifluoromethyl)phenyl)-3-((S)-(6-methoxy-2-phenylquinolin-4-yl)((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)methyl)urea (344)

Synthesised according to general procedure XI, using 343 (1.5 g, 2.94 mmol), CH$_2$Cl$_2$ (37.0 mL), Et$_3$N (2.0 mL, 14.69 mmol) and 3,5-bis(trifluoromethyl)phenyl isocyanate (0.61 mL, 3.53 mmol). The crude residue was purified by column chromatography eluting in gradient from 99.5:0.5 to 95:5 CH$_2$Cl$_2$/MeOH (TLC is better visualised using CH$_2$Cl$_2$/MeOH 10:1, $R_f$ = 0.3), to afford 344 (1.72 g, 89%) as a white amorphous solid. M.p. 146-148 °C; $[\alpha]_D^{20} = +14.8$ (c = 0.8, CHCl$_3$).

$\delta$$_H$ (400 MHz, CDCl$_3$): 8.86 (br s, 1 H, NH$^1$), 8.19 (d, 2 H, $J$ 7.2, H-18), 8.13 (d, 1 H, $J$ 9.1, H-15), 7.95 (s, 1 H, H-17), 7.76 (s, 3 H, H-22 and H-21), 7.50-7.41 (m, 4 H, H-19, H-14 and H-12), 7.30 (s, 1 H, H-20), 7.19 (br s, 1 H, NH$^2$), 5.85 (s, 1 H, H-9), 4.03 (s, 3 H, H-13), 3.81-3.71 (m, 2 H, H-8 and H-6a), 3.16-3.10 (m, 1 H, H-2b), 2.81-2.73 (m, 1 H, H-6b), 2.32-2.23 (m, 1 H, H-2a), 1.89-1.82 (m, 1 H, H-3), 1.76-1.65 (m, 3 H, H-7a, H-7b and H-5b), 1.57-1.49 (m, 1 H, H-5a), 1.16-1.07 (m, 3 H, H-10 and H-4), 0.66 (t, 3 H, $J$ 7.1, H-11)

$\delta$$_C$ (100 MHz, CDCl$_3$): 158.5 (C=O), 154.6 (two signals) (q), 145.0 (q), 144.0 (q), 140.8 (q), 139.2 (two signals) (q), 132.1, 131.6 (q, $J_{C\cdot F}$
δF (376 MHz, CDCl3): -63.1
νmax (neat)/cm⁻¹: 3258, 2934, 1692, 1622, 1553, 1474, 1386, 1276, 1173, 1125, 1030, 878, 829
HRMS (m/z – ESI): Found: 691.2263 [M+Cl]⁺ C₃₅H₃₄N₄O₂ClF₆ Requires: 691.2274

1-(3,5-bis(Trifluoromethyl)phenyl)-3-((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)urea (296b)

Synthesised according to general procedure XI, using 296a (2.5 g, 5.78 mmol), CH₂Cl₂ (72.0 mL), Et₃N (4.0 mL, 28.88 mmol) and 3,5-bis(trifluoromethyl)phenyl isocyanate (1.20 mL, 6.93 mmol). The crude residue was purified by column chromatography eluting in gradient from 30:1 to 10:1 CH₂Cl₂/MeOH (TLC is better visualised using CH₂Cl₂/MeOH 10:1, Rf = 0.25), to afford 296b (2.7 g, 82%) as a white amorphous solid. M.p. 138-140 °C (lit.²⁹⁸ 134-135 °C), [α]D²⁰ = +7.9 (c = 0.3, CHCl₃). The isolated compound exhibited identical spectroscopic data to those reported in the literature.²⁹⁸

δH (400 MHz, CDCl₃): 8.97 (br s, 1 H, NH¹), 8.76 (d, 1 H, J 4.5, H-16), 8.02 (d, 1 H, J 9.3, H-15), 7.80 (s, 2 H, H-18), 7.71 (d, 1 H, J 1.7, H-12), 7.40-7.37 (m, 2 H, H-17 and H-14), 7.33 (s, 1 H, H-19), 6.84 (app. s, 1 H, H-9), 5.69-5.60 (m, 1 H, H-10), 5.07-5.03 (m, 2 H, H-11), 4.10 (br s, 1 H, NH²), 3.99 (s, 3 H, H-13), 3.81-3.66 (m, 2 H, H-8 and H-6a), 3.32-3.27 (m, 1 H, H-2b), 2.91-2.78 (m, 2 H, H-6b and H-2a), 2.49-
2.43 (m, 1 H, H-3), 1.91-1.72 (m, 4 H, H-4, H-5a, H-5b and H-7b), 1.07-1.02 (m, 1 H, H-7a)

1-(3,5-\textit{bis}(Trifluoromethyl)phenyl)-3-\textit{(((S)-(6-methoxy-2-phenylquinolin-4-yl))((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)urea} (323)

Synthesised according to general procedure XI, using 315 (1.0 g, 1.97 mmol), CH₂Cl₂ (26.0 mL), Et₃N (1.4 mL, 9.83 mmol) and 3,5-\textit{bis}(trifluoromethyl)phenyl isocyanate (0.40 mL, 2.36 mmol). The crude residue was purified by column chromatography eluting in gradient from 30:1 to 10:1 CH₂Cl₂/MeOH (TLC is better visualised using CH₂Cl₂/MeOH 10:1, \( R_f = 0.27 \)), to afford 323 (1.1 g, 86%) as a white amorphous solid. M.p. 147-148 °C (lit.\textsuperscript{236} 152-153 °C); \([\alpha]_D^{20} = +13.5 \ (c = 0.7, \text{CHCl}_3)\). The isolated compound exhibited identical spectroscopic data to those reported in the literature.\textsuperscript{236}

\( \delta_H \) (400 MHz, CDCl₃):

9.19 (br s, 1 H, NH₁), 8.19 (d, 2 H, J 7.5, H-18), 8.11 (d, 1 H, J 9.2, H-15), 7.97 (s, 1 H, H-17), 7.82 (s, 2 H, H-21), 7.71 (s, 1 H, H-22), 7.48 (t, 2 H, J 7.5, H-19), 7.43-7.39 (m, 2 H, H-14 and H-12), 7.31 (s, 1 H, H-20), 7.23 (br s, 1 H, NH₂), 5.86 (s, 1 H, H-9), 5.67-5.58 (m, 1 H, H-10), 5.07-5.03 (m, 2 H, H-11), 4.01 (s, 3 H, H-13), 3.94-3.91 (m, 2 H, H-8 and H-6a), 3.43-3.37 (m, 1 H, H-2b), 2.99-2.91 (m, 2 H, H-6b and H-2a), 2.55-2.49 (m, 1 H, H-3), 1.97-1.79 (m, 4 H, H-4, H-5a, H-5b and H-7b), 1.18-1.15 (m, 1 H, H-7a)
1-(3,5-\textit{bis}(Trifluoromethyl)phenyl)-3-((S)-(2-chloro-6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)urea (351)

Synthesised according to general procedure XI, using 350 (0.8 g, 1.71 mmol), CH\textsubscript{2}Cl\textsubscript{2} (21.0 mL), Et\textsubscript{3}N (1.2 mL, 8.56 mmol) and 3,5-\textit{bis}(trifluoromethyl)phenyl isocyanate (0.4 mL, 2.054 mmol). The crude residue was purified by column chromatography eluting in gradient from 99.5:0.5 to 95:5 CH\textsubscript{2}Cl\textsubscript{2}/MeOH (TLC is better visualised using CH\textsubscript{2}Cl\textsubscript{2}/MeOH 10:1, R\textsubscript{f} = 0.3), to afford 351 (815 mg, 78%) as a white amorphous solid. M.p. 158-160 °C; [\alpha]\textsubscript{D}\textsubscript{20} = +18.0 (c = 0.6, CHCl\textsubscript{3}).

\(\delta\)\textsubscript{H} (400 MHz, CDCl\textsubscript{3}): 8.18 (br s, 1 H, NH\textsuperscript{1}), 7.94 (d, 1 H, J 9.1, H-15), 7.72-7.70 (m, 3 H, H-18 and H-17), 7.42-7.39 (m, 2 H, H-19 and H-14), 7.34 (s, 1 H, H-12), 6.41 (s, 1 H, H-9), 5.71-5.63 (m, 1 H, H-10), 5.57 (br s, 1 H, H\textsuperscript{2}), 5.02 (d, 1 H, J 10.1, H-11), 4.88 (d, 1 H, J 17.2, H-11), 4.00 (s, 3 H, H-13), 3.51-3.44 (m, 1 H, H-8), 3.22-3.16 (m, 1 H, H-6a), 2.96-2.33 (m, 1 H, H-2b), 2.70-2.63 (m, 1 H, H-6b), 2.35-2.25 (m, 2 H, H-2a and H-3), 1.75-1.60 (m, 4 H, H-5a, H-5b, H-4 and H-7b), 1.03-0.95 (m, 1 H, H-7a)

\(\delta\)\textsubscript{C} (100 MHz, CDCl\textsubscript{3}): 158.6 (C=O), 154.6 (two signals) (q), 147.8 (q), 144.4 (q), 140.4 (q), 140.0, 131.9 (q, \textit{J}_{C-F} 33.4) (q), 130.7, 123.1 (q), 123.0 (q, \textit{J}_{C-F} 272.4) (q), 118.3, 115.6, 115.4, 102.4, 60.0, 55.8, 55.5, 41.3, 38.6, 27.2, 26.9, 26.5, 21.8, 21.5, 14.1

\(\delta\)\textsubscript{F} (376 MHz, CDCl\textsubscript{3}): -63.2

\(\nu\)\textsubscript{max} (neat)/cm\textsuperscript{-1}: 3298, 2942, 1677, 1560, 1173, 1385, 1275, 1171, 1125, 1031, 917, 879

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HRMS (m/z – APCI): Found: 613.1799 [M+H]+ C₂₀H₂₈ClF₆N₄O₂ Requires: 613.1780

1-Phenyl-3-((S)-(6-methoxy-2-phenylquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)urea (316)

Synthesised according to general procedure XI, using 315 (0.5 g, 0.98 mmol), CH₂Cl₂ (12.0 mL), Et₃N (0.7 mL, 4.91 mmol) and phenyl isocyanate (0.13 mL, 1.18 mmol). The crude residue was purified by column chromatography eluting in gradient from 30:1 to 10:1 CH₂Cl₂/MeOH (TLC is better visualised using CH₂Cl₂/MeOH 10:1, Rf = 0.3), to afford 316 (370 mg, 73%) as a white amorphous solid. M.p. 125-128 °C; [α]D²⁰ = +15.7 (c = 0.4, CHCl₃).

δH (400 MHz, CDCl₃): 8.52 (br s, 1 H, NH¹), 8.21 (d, 2 H, J 7.5, H-18), 8.11 (d, 1 H, J 9.3, H-15), 7.96 (s, 1 H, H-17), 7.80 (br s, 1 H, NH²), 7.70 (app. d, 1 H, H-14), 7.53-7.40 (m, 6 H, H-12, H-19, H-20, H-21), 7.20-7.16 (m, 2 H, H-22), 6.93 (app. t, 1 H, J 7.3, H-23), 5.80 (s, 1 H, H-9), 5.54-5.46 (m, 1 H, H-10), 5.09-5.01 (m, 2 H, H-11), 4.00 (s, 3 H, H-13), 3.97-3.82 (m, 2 H, H-8 and H-6a), 3.50-3.44 (m, 1 H, H-2b), 3.10-3.03 (m, 1 H, H-6b), 2.80-2.72 (m, 1 H, H-2a), 2.56-2.50 (m, 1 H, H-3), 2.00-1.85 (m, 3 H, H-5a, H-5b and H-4), 1.74-1.68 (m, 1 H, H-7b), 1.21-1.15 (m, 1 H, H-7a)

δC (100 MHz, CDCl₃): 158.5 (C=O), 155.3 (q), 155.0 (q), 145.0 (q), 142.5 (q), 139.6 (two signals, q), 139.3 (q), 136.8, 132.3, 129.2, 128.9 (two signals), 127.4, 126.8, 122.4, 122.3, 118.9, 117.5, 101.5, 60.7, 56.0, 54.2, 49.7, 41.7, 36.7, 26.8, 24.6, 24.5
\( \nu_{\text{max}} \) (neat)/cm\(^{-1} \):

3012, 1678, 1598, 1498, 1316, 1231, 1029, 833, 747, 694

HRMS (m/z – ESI):

Found: 519.2761 [M+H]+
C\(_{35}\)H\(_{35}\)N\(_4\)O\(_2\) Requires: 519.2760

1-(2,6-di(isopropyl)phenyl)-3-(((S)-(6-methoxy-2-phenylquinolin-4-yl))((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)urea (317)

Synthesised according to general procedure XI, using 315 (0.5 g, 0.982 mmol), CH\(_2\)Cl\(_2\) (12.0 mL), Et\(_3\)N (0.7 mL, 4.910 mmol) and 2,6-di(isopropyl)phenyl isocyanate (0.25 mL, 1.178 mmol). The crude residue was purified by column chromatography eluting in gradient from 70:1 to 20:1 CH\(_2\)Cl\(_2\)/MeOH (TLC is better visualised using CH\(_2\)Cl\(_2\)/MeOH 10:1, R\(_f\) = 0.3), to afford 317 (390 mg, 66%) as a white amorphous solid. M.p. 118-120 °C; \([\alpha]_D^{20}\) = +27.7 (c = 0.3, CHCl\(_3\)).

\( \delta_H \) (400 MHz, dmso-\(d_6\)):

8.29 (app. d, 2 H, J 7.7, H-18), 8.03 (d, 1 H, J 9.2, H-15), 7.85 (d, 1 H, J 2.3, H-12), 7.58-7.54 (m, 3 H, H-19 and H-17), 7.51-7.44 (m, 2 H, H-20 and H-14), 7.14 (app. t, 1 H, J 7.8, H-24), 7.03-7.01 (m, 2 H, H-23), 5.95-5.86 (m, 1 H, H-10), 5.53 (s, 1 H, H-9), 5.11 (app. d, 1 H, J 17.0, H-11), 5.02 (app. d, 1 H, J 10.4, H-11), 3.95 (s, 3 H, H-13), 3.59-3.41 (m, 2 H, H-8 and H-6a), 3.16-2.95 (m, 7 H, H-6b, H-5b, H-2a, H-2b, H-3 and H-22), 1.82-1.70 (m, 3 H, H-7b, H-5a and H-4), 1.61-1.55 (m, 1 H, H-7a), 1.02-0.90 (m, 12 H, H-21)

**Note:** \( ^1H \) NMR spectrum was recorded at 80 °C as the spectrum recorded at 25 °C exposed the presence of rotomers, resulting in significant peak overlap and broadening.
δC (100 MHz, dmsod6): 157.3 (C=O), 156.8, 153.3, 146.7, 146.3, 144.0, 138.9, 132.9, 131.4, 129.2, 128.7, 126.9, 122.6, 121.4, 116.6, 115.3, 114.8, 102.9, 79.2, 58.7, 55.6, 54.5, 50.0, 40.6, 27.7, 26.8, 24.2, 23.5, 23.3, 22.6, 22.1

**Note:** The quaternary carbons were not assigned due to multiple rotomers.

ν<sub>max</sub> (neat)/cm<sup>-1</sup>: 2959, 2866, 1664, 1498, 1347, 1228, 1030, 917, 829

HRMS (m/z – APCI): Found: 603.3698 [M+H]<sup>+</sup> C<sub>39</sub>H<sub>47</sub>N<sub>4</sub>O<sub>2</sub> Requires: 603.3699

**General procedure XII:** Protocol for the alkylation of the bifunctional cinchona alkaloid derivatives.

A round-bottomed flask containing a stirring bar and fitted with a condenser was charged with a bifunctional cinchona alkaloid (1.0 equiv.), the appropriate alkyl bromide (1.2 equiv.) and PhCH<sub>3</sub> (0.1 M). The reaction mixture was stirred for 12-16 h at 75-80 °C. Upon completion of the reaction (TLC), the mixture was cooled to rt and the solvent was removed in vacuo. The crude residue was purified by column chromatography on silica gel. Further purification was achieved by precipitation from Et<sub>2</sub>O.

**General procedure XIII:** Protocol for the alkylation of the bifunctional cinchona alkaloid derivatives.

A round-bottomed flask containing a stirring bar was charged with a bifunctional cinchona alkaloid derivative (1.0 equiv.), the appropriate alkyl bromide (1.2 equiv.) and CH<sub>2</sub>Cl<sub>2</sub> (0.1 M). The reaction mixture was stirred for 2-3 days at rt. Upon completion of the reaction (TLC), the solvent was removed in vacuo and the crude residue was purified by column chromatography on silica gel. Further purification was achieved by precipitation from Et<sub>2</sub>O.
(1S,2S,4S,5R)-2-((S)-(3,5-bis(trifluoromethyl)phenyl)ureido)(2-chloro-6-methoxyquinolin-4-yl)methyl)-1-(3,5-di-tert-butylbenzyl)-5-ethylquinuclidin-1-ium bromide (335)

Synthesised according to general procedure XII, using 334 (1.65 g, 2.68 mmol), 3,5-di-tert-butylbenzyl bromide (0.91 g, 3.22 mmol) and PhCH₃ (27.0 mL). The crude residue was purified by column chromatography (50:1 CH₂Cl₂/MeOH, TLC is better visualised using CH₂Cl₂/MeOH 10:1, Rf = 0.3), to afford 335 (1.7 mg, 71%) as a white amorphous solid. M.p. 177-178 °C; [α]D²⁰ = +5.5 (c = 0.1, CHCl₃).

δH (400 MHz, dmso-d₆): 9.50 (br s, 1 H, NH¹), 8.19 (d, 1 H, J 8.8, H-17), 8.11 (s, 2 H, H-18), 7.98 (d, 1 H, J 9.2, H-15), 7.82 (s, 1 H, H-12), 7.73 (br s, 1 H, NH²), 7.65 (s, 1 H, H-19), 7.57 (app. dd, 1 H, J 9.2, 1.4, H-14), 7.51 (s, 1 H, H-23), 7.31 (s, 2 H, H-21), 6.25-6.21 (m, 1 H, H-9), 5.08 (d, 1 H, J 13.2, H-20b), 4.89-4.86 (m, 1 H, H-8), 4.65 (d, 1 H, J 13.2, H-20a), 4.23-4.19 (m, 1 H, H-6a), 3.98 (s, 3 H, H-13), 3.73-3.69 (m, 1 H, H-2b), 3.17-3.10 (m, 2 H, H-2a and H-6b), 2.19-2.09 (m, 2 H, H-7b and H-5a), 1.95-1.91 (m, 1 H, H-5a), 1.87-1.83 (m, 2 H, H-3 and H-4), 1.46-1.44 (m, 1 H, H-10), 1.39-1.34 (m, 1 H, H-10), 1.25 (app. s, 18 H, H-22), 1.08-1.05 (m, 1 H, H-7a), 0.80 (app. t, 3 H, J 7.3, H-11)

δC (100 MHz, dmso-d₆): 158.5 (C=O), 154.2 (q), 151.1 (q), 147.3 (q), 147.0 (q), 143.7 (q), 141.4 (q), 130.8 (q, JCF 33.1) (q), 130.7, 127.8, 126.9 (q), 126.2 (q), 123.6, 123.2 (q, JCF 274.1) (q), 123.1, 120.6, 118.0, 114.9, 102.7, 65.7, 65.6, 62.4, 55.7, 50.1, 49.0, 34.5 (q), 34.4, 31.0, 26.7, 24.4, 24.2, 24.1, 10.9
δ_F (376 MHz, dmsO-d_6): -61.8

ν_{max} (neat)/cm⁻¹:
2965, 1690, 1560, 1747, 1387, 1276, 1175, 1128, 1028, 880, 681

HRMS (m/z – ESI):
Found: 817.3699 [M]^+  C_{44}H_{52}N_4O_2F_6Cl  Requires: 817.3683

(1S,2S,4S,5R)-2-((S)-(3,5-bis(trifluoromethyl)phenyl)ureido)(2-bromo-6-methoxyquinolin-4-yl)methyl)-1-(3,5-di-tert-butylbenzyl)-5-ethylquinuclidin-1-ium bromide (340)

Synthesised according to general procedure XII, using 339 (0.5 g, 0.76 mmol), 3,5-di-tert-butylbenzyl bromide (0.26 g, 0.91 mmol) and PhCH₃ (7.6 mL). The crude residue was purified by column chromatography (eluting gradient from 90:1 CH₂Cl₂/MeOH to 20:1 CH₂Cl₂/MeOH, TLC is better visualised using CH₂Cl₂/MeOH 10:1, R_f = 0.3), to afford 340 (450 mg, 63%) as a pale yellow amorphous solid. M.p. 173-175 °C; [α]_D²⁰ = +45.3 (c = 0.5, CHCl₃).

δ_H (400 MHz, dmsO-d_6): 9.85 (br s, 1 H, NH¹), 8.39 (br s, 1 H, H-17), 8.10 (s, 2 H, H-18), 7.96 (d, 1 H, J 9.3, H-15), 7.88 (app. s, 1 H, H-12), 7.74 (br s, 1 H, NH²), 7.60-7.50 (m, 3 H, H-14, H-19 and H-23), 7.35 (s, 2 H, H-21), 6.25 (app. s, 1 H, H-9), 5.11-5.00 (m, 2 H, H-20b and H-8), 4.74 (app. d, 1 H, J 2.2, H-20a), 4.26-4.20 (m, 1 H, H-6a), 3.99 (s, 3 H, H-13), 3.71-3.65 (m, 1 H, H-2b), 3.27-3.13 (m, 2 H, H-2a and H-6b), 2.19-2.05 (m, 2 H, H-7b and H-5b), 1.95-1.82 (m, 3 H, H-5a, H-3 and H-4), 1.51-1.33 (m, 2 H, H-10), 1.25 (app. s,
δC (100 MHz, dmsod6): 158.4 (C=O), 154.1 (q), 151.1 (q), 147.3 (q), 147.1 (q), 143.7 (q), 141.5 (q), 130.7 (q, JCF 33.5) (q), 130.6, 127.8, 127.0 (q), 126.2 (q), 123.5, 123.2 (q, JCF 274.5) (q), 123.1, 120.7, 117.7, 114.6, 102.6, 65.7, 65.6, 62.2, 55.7, 50.0, 48.8, 34.5 (two signals, one of which is quaternary), 31.0, 26.7, 24.4, 24.2, 24.1, 10.9

δF (376 MHz, dmsod6): -61.9

νmax (neat) cm⁻¹: 2965, 1689, 1560, 1474, 1387, 1276, 1176, 1130, 1028, 880, 681


(1S,2S,4S,5R)-2-((S)-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)(6-methoxy-2-phenylquinolin-4-yl)methyl)-1-(3,5-di-tert-butylbenzyl)-5-ethylquinuclidin-1-ium bromide (345)

Synthesised according to general procedure XII, using 344 (1.52 g, 2.32 mmol), 3,5-di-tert-butylenyl bromide (0.8 g, 2.78 mmol) and PhCH3 (23.2 mL). The crude residue was purified by column chromatography (eluting gradient from 60:1 CH2Cl2/MeOH to 30:1 CH2Cl2/MeOH, TLC is better visualised using CH2Cl2/MeOH 10:1, Rf = 0.3), to afford 345 (1.59 g, 73%) as a white amorphous solid. M.p. 183-184 °C; [α]D²⁰ = +64.5 (c = 0.3, CHCl3).
δ<sub>H</sub> (400 MHz, dmso-<i>d</i><sub>6</i>):
9.53 (br s, 1 H, NH<sup>1</sup>), 8.36-8.28 (m, 3 H, H-18 and NH<sup>2</sup>), 8.19 (d, 1 H, J 7.8, H-17), 8.11-8.09 (m, 3 H, H-21 and H-15), 7.71 (s, 1 H, H-12), 7.63-7.58 (m, 3 H, H-19 and H-22), 7.55-7.52 (m, 3 H, H-14, H-20 and H-26), 7.34 (s, 2 H, H-24), 6.33-6.27 (m, 1 H, H-9), 5.15-5.07 (m, 2 H, H-23b and H-8), 4.73 (d, 1 H, J 13.3, H-23a), 4.35-4.29 (m, 1 H, H-6a), 4.00 (s, 3 H, H-13), 3.74-3.69 (m, 1 H, H-2b), 3.28-3.16 (m, 2 H, H-2a and H-6b), 2.20-2.10 (m, 2 H, H-7b and H-5b), 2.00-1.84 (m, 3 H, H-5a, H-4 and H-3), 1.48-1.31 (m, 2 H, H-10), 1.25 (app. s, 18 H, H-25), 1.14-1.10 (m, 1 H, H-7a), 0.78 (t, 3 H, J 7.3, H-11)

δ<sub>C</sub> (100 MHz, dmso-<i>d</i><sub>6</sub>):
158.1 (C=O), 154.3 (q), 153.9 (q), 151.2 (q), 144.3 (two signals, q), 141.4 (q), 138.5 (q), 132.0, 130.8 (q, J<sub>C-F</sub> 33.2) (q), 129.6, 128.8, 127.7, 127.2, 127.1 (q), 126.0 (q), 123.7, 123.2 (q, J<sub>C-F</sub> 273.6) (q), 122.3, 117.9, 116.9, 114.8, 101.9, 66.2, 65.7, 62.2, 55.6, 50.1, 49.2, 34.5 (q), 34.4, 31.0, 26.7, 24.6, 24.2, 24.0, 11.0

δ<sub>F</sub> (376 MHz, dmso-<i>d</i><sub>6</sub>):
-61.8

ν<sub>max</sub> (neat)/cm<sup>-1</sup>:
2966, 1686, 1555, 1474, 1386, 1276, 1175, 1129, 880, 681

HRMS (m/z – ESI):
Found: 859.4379 [M]<sup>+</sup> C<sub>50</sub>H<sub>57</sub>N<sub>4</sub>O<sub>2</sub>F<sub>6</sub> Requires: 859.4386

(1S,2S,4S,5R)-2-((S)-(3,5-bis(trifluoromethyl)phenyl)ureido)(6-methoxyquinolin-4-yl)methyl)-1-(3,5-di-tert-butylbenzyl)-5-vinylquinuclidin-1-ium bromide (296)
Synthesised according to general procedure XIII, using 296b (300 mg, 0.52 mmol), 3,5-di-tert-butybenzyl bromide (0.18 g, 0.622 mmol) and CH₂Cl₂ (5.2 mL). The crude residue was purified by column chromatography (30:1 CH₂Cl₂/MeOH, TLC is better visualised using CH₂Cl₂/MeOH 10:1, Rf = 0.3), to afford 296 (240 mg, 62%) as a white amorphous solid. M.p. 178-180 °C (lit.²⁴¹ 178-180 °C); [α]D²⁰ = +16.2 (c = 0.1, CHCl₃).

δH (400 MHz, MeOD): 8.81 (d, 1 H, J 4.4, H-16), 8.12 (s, 2 H, H-18), 8.03 (d, 1 H, J 9.2, H-15), 7.77 (d, 1 H, J 4.4, H-17), 7.75 (s, 1 H, H-12), 7.59 (app. s, 1 H, H-23), 7.56 (s, 1 H, H-19), 7.51 (dd, 1 H, J 9.2, 2.5, H-14), 7.34 (s, 2 H, H-21), 6.46 (d, 1 H, J 10.4, H-9), 5.99-5.90 (m, 1 H, H-10), 5.42 (d, 1 H, J 13.5, H-20b), 5.28-5.22 (m, 2 H, H-11), 5.04-4.98 (m, 1 H, H-8), 4.73 (d, 1 H, J 13.5, H-20a), 4.55-4.49 (m, 1 H, H-6a), 4.04 (s, 3 H, H-13), 3.93-3.87 (m, 1 H, H-2b), 3.65-3.59 (m, 1 H, H-2a), 3.27-3.20 (m, 1 H, H-6b), 2.80-2.73 (m, 1 H, H-3), 2.35-2.21 (m, 2 H, H-5a and H-7b), 2.15-2.06 (m, 1 H, H-5b), 1.97 (app. s, 1 H, H-4), 1.28 (app. s, 19 H, H-7a and H-22)

(1S,2S,4S,5R)-2-((S)-(3,5-bis(trifluoromethyl)phenyl)ureido)(6-methoxy-2-phenylquinolin-4-yl)methyl)-1-(3,5-di-tert-butybenzyl)-5-vinylquinuclidin-1-ium bromide (307)

Synthesised according to general procedure XII, using 323 (400 mg, 0.61 mmol), 3,5-di-tert-butybenzyl bromide (0.21 g, 0.73 mmol) and PhCH₃ (6.1 mL). The crude residue was purified by column chromatography (30:1 CH₂Cl₂/MeOH, TLC is better
visualised using CH$_2$Cl$_2$/MeOH 10:1, R$_f$ = 0.3), to afford 307 (384 mg, 67%) as a white amorphous solid. M.p. 180-181 °C; [α]$_D^{20}$ = +25.4 (c = 0.2, CHCl$_3$).

δ$_H$ (400 MHz, dmso-$d_6$): 9.58 (br s, 1 H, NH$^1$), 8.37-8.26 (m, 4 H, H-17, H-18 and NH$^2$), 8.11-8.08 (m, 3 H, H-21 and H-15), 7.72 (s, 1 H, H-12), 7.63-7.58 (m, 3 H, H-19 and H-22), 7.55-7.52 (m, 3 H, H-26, H-14 and H-20), 7.35 (s, 2 H, H-24), 6.34-6.29 (m, 1 H, H-9), 5.96-5.87 (m, 1 H, H-10), 5.24-5.15 (m, 4 H, H-8, H-23b and H-11), 4.76 (d, 1 H, J 13.2, H-23a), 4.35-4.30 (m, 1 H, H-6a), 4.01 (s, 3 H, H-13), 3.74-3.68 (m, 1 H, H-2b), 3.63-3.59 (m, 1 H, H-2a), 3.26-3.18 (m, 1 H, H-6b), 2.80-2.74 (m, 1 H, H-3), 2.17-2.02 (m, 3 H, H-5a, H-5b and H-7b), 1.90 (app. s, 1 H, H-4), 1.24 (app. s, 19 H, H-7a and H-25)

δ$_C$ (100 MHz, dmso-$d_6$): 158.1 (C=O), 154.3 (q), 153.8 (q), 153.5 (q), 151.2 (q), 144.3 (q), 141.4 (q), 138.5 (q), 137.1, 132.0, 130.8 (q, J$_{C-F}$ 37.5) (q), 129.6, 128.8, 127.7, 127.2, 127.0 (q), 126.0 (q), 123.8, 123.2 (q, J$_{C-F}$ 273.6) (q), 122.3, 117.8, 117.2, 116.9, 114.8, 102.0, 66.4, 65.8, 60.2, 55.6, 50.0, 48.9, 36.5, 34.5 (q), 31.0, 26.9, 26.1, 24.0

δ$_F$ (376 MHz, dmso-$d_6$): -61.8

ν$_{max}$ (neat)/cm$^{-1}$: 2966, 1686, 1623, 1474, 1387, 1276, 1129, 881, 681

HRMS (m/z – ESI): Found: 857.4232 [M]$^+$ C$_{50}$H$_{55}$N$_4$O$_2$F$_6$ Requires: 857.4229
(1S,2S,4S,5R)-1-benzyl-2-((S)-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)(6-methoxy-2-phenylquinolin-4-yl)methyl)-5-vinylquinoclidin-1-ium bromide (324)

Synthesised according to general procedure XIII, using 323 (500 mg, 0.76 mmol), benzyl bromide (0.11 mL, 0.92 mmol) and CH₂Cl₂ (8.0 mL). The crude residue was purified by column chromatography (eluting gradient from 90:1 CH₂Cl₂/MeOH to 30:1 CH₂Cl₂/MeOH, TLC is better visualised using CH₂Cl₂/MeOH 10:1, Rf = 0.3), to afford 324 (410 mg, 65%) as a pale yellow amorphous solid. M.p. 174-175 °C; [α]D²⁰ = +136.5 (c = 0.5, CHCl₃).

δH (400 MHz, CD₃OD-d₄): 8.29 (app. s, 3 H, H-18 and H-17), 8.10 (d, 1 H, J 9.3, H-15), 8.04 (s, 2 H, H-21), 7.76 (s, 1 H, H-12), 7.65-7.61 (m, 2 H, H-19), 7.57-7.48 (m, 8 H, H-26, H-25, H-24, H-22, H-20 and H-14), 6.50 (d, 1 H, J 9.5, H-9), 5.94-5.86 (m, 1 H, H-10), 5.25-5.16 (m, 4 H, H-23b, H-11 and H-8), 5.04 (app. d, 1 H, J 12.3, H-23a), 4.53-4.47 (m, 1 H, H-6a), 4.05 (s, 3 H, H-13), 3.83-3.75 (m, 1 H, H-2b), 3.63-3.49 (m, 2 H, H-2a and H-6b), 2.77-2.71 (m, 1 H, H-3), 2.26-2.09 (m, 3 H, H-7b, H-5a and H-5b), 1.96 (app. s, 1 H, H-4), 1.31-1.27 (m, 1 H, H-7a)

δC (100 MHz, CD₃OD-d₄): 160.5 (C=O), 156.6 (q), 156.2 (q), 146.0 (q), 145.8 (q), 142.4 (q), 140.1 (q), 137.4 (q), 134.6, 133.2 (q, JCF 32.5) (q), 132.7, 131.8, 130.7, 130.5, 129.9, 128.9 (q), 128.8, 127.4, 124.7 (q, JCF 272.6) (q), 124.2, 119.4, 118.7, 118.3, 116.5, 102.4, 68.8, 67.6, 62.0, 56.4, 51.7, 51.0, 38.8, 28.6, 28.2, 25.7
δ_F (376 MHz, CD_3OD-d_4):  -64.7

ν_{max} (neat)/cm^{-1}:

2968, 1686, 1622, 1553, 1474, 1387, 1276, 1175, 1128, 1029, 881, 700, 651

HRMS (m/z – ESI):

Found: 745.2988 [M]+

C_{42}H_{39}N_4O_2F_6

Requires: 745.2972

(1S,2S,4S,5R)-2-((S)-(3,5-bis(trifluoromethyl)phenyl)ureido)(6-methoxy-2-phenylquinolin-4-yl)methyl)-1-(3,5-dibromobenzyl)-5-vinylquinuclidin-1-ium bromide (325)

Synthesised according to general procedure XII, using 323 (500 mg, 0.76 mmol), 3,5-di-bromobenzyl bromide (0.30 g, 0.92 mmol) and PhCH_3 (8.0 mL). The crude residue was purified by column chromatography (30:1 CH_2Cl_2/MeOH, TLC is better visualised using CH_2Cl_2/MeOH 10:1, R_f = 0.4), to afford 325 (556 mg, 74%) as a white amorphous solid. M.p. 179-181 °C; [α]_D^{20} = +158.0 (c = 0.5, CHCl_3).

δ_H (400 MHz, CD_3OD-d_4):

8.32-8.29 (m, 3 H, H-18 and H-17), 8.07 (d, 1 H, J 9.2, H-15), 8.03 (s, 2 H, H-21), 7.85 (app. d, 3 H, J 11.9, H-24 and H-22), 7.74 (s, 1 H, H-25), 7.54-7.45 (m, 5 H, H-20, H-19, H-14 and H-12), 6.47 (d, 1 H, J 10.4, H-9), 5.93-5.85 (m, 1 H, H-10), 5.31-5.08 (m, 5 H, H-23a, H-23b, H-11 and H-8), 4.51-4.45 (m, 1 H, H-6a), 4.03 (s, 3 H, H-13), 3.80-3.66 (m, 2 H, H-2a and H-2b), 3.53-3.45 (m, 1 H, H-6b), 2.79-2.73 (m, 1 H, H-3), 2.25-2.07 (m, 3 H, H-7b, H-5a and H-5b), 1.95 (app. s, 1 H, H-4), 1.29-1.26 (m, 1 H, H-7a)
δC (100 MHz, CD3OD-d₄): 160.5 (C=O), 156.6 (q), 156.2 (q), 150.6 (q), 146.1 (q), 145.5 (q), 142.3 (q), 140.1 (q), 137.3, 136.3, 133.0, 132.9 (q, J_C-F 32.6) (q), 130.6, 129.9, 128.8, 127.4 (q), 124.7 (q), 124.6 (q, J_C-F 273.6) (q), 124.1, 119.4, 118.7, 118.4, 116.6, 116.5, 102.3, 69.0, 65.7, 62.4, 56.4, 51.6, 51.3, 38.8, 28.5, 28.1, 25.7

δF (376 MHz, CD3OD-d₄): -64.6

νmax (neat)/cm⁻¹: 2973, 1686, 1622, 1556, 1474, 1386, 1276, 1175, 1129, 1029, 832, 700, 681

HRMS (m/z – ESI): Found: 901.1195 [M]+ C₄₂H₃₇Br₂NaO₂F₆ Requires: 901.1182

(1S,2S,4S,5R)-2-((S)-(3,5-bis(trifluoromethyl)phenyl)ureido)(6-methoxy-2-phenylquinolin-4-yl)methyl)-1-(3,5-di-methoxybenzyl)-5-vinylquinuclidin-1-ium bromide (326)

Synthesised according to general procedure XII, using 323 (700 mg, 1.07 mmol), 3,5-di-methoxybenzyl bromide (0.30 g, 1.283 mmol) and PhCH₃ (11.0 mL). The crude residue was purified by column chromatography (eluting gradient from 90:1 CH₂Cl₂/MeOH to 30:1 CH₂Cl₂/MeOH, TLC is better visualised using CH₂Cl₂/MeOH 10:1, Rf = 0.3), to afford 326 (776 mg, 82%) as a white amorphous solid. M.p. 185-186 °C; [α]D²⁰ = +75.4 (c = 0.1, CHCl₃).

δH (400 MHz, dmso-d₆): 9.58 (br s, 1 H, NH¹), 8.34-8.23 (m, 4 H, H-18, H-17 and NH²), 8.10-8.07 (m, 3 H, H-21 and H-15), 7.70 (s, 1 H, H-12), 7.62-7.52 (m, 5 H, H-22, H-20, H-19 and H-14), 6.82
(s, 2 H, H-24), 6.70 (app. s, 1 H, H-26), 6.31-6.26 (m, 1 H, H-9), 5.91-5.83 (m, 1 H, H-10), 5.23-4.80 (m, 5 H, H-23a, H-23b, H-11 and H-8), 4.32-4.25 (m, 1 H, H-6a), 4.00 (s, 3 H, H-13), 3.79 (app. s, 7 H, H-25 and H-2b), 3.52-3.40 (m, 2 H, H-2a and H-6b), 2.78-2.73 (m, 1 H, H-3), 2.15-2.03 (m, 3 H, H-5a, H-5b and H-7b), 1.90 (app. s, 1 H, H-4), 1.17-1.12 (m, 1 H, H-7a)

\[ \delta_{\text{C}} (100 \text{ MHz, dms}-d_{6}) : \]

160.7 (C=O), 158.1 (q), 154.4 (q), 154.3 (q), 153.8 (q), 144.3 (q), 141.5 (q), 138.5 (q), 137.0, 132.0, 130.7 (q, \( J_{\text{C}-\text{F}} \) 32.0) (q), 129.6 (q), 129.5, 128.8, 127.1, 125.9 (two signals, one of which is quaternary), 123.2 (q, \( J_{\text{C}-\text{F}} \) 272.4) (q), 122.3, 117.9, 117.3, 116.9, 114.7, 111.6, 102.0, 101.5, 65.7, 65.1, 60.6, 55.6, 55.4, 49.9, 36.8, 26.7, 25.9, 24.2

\[ \delta_{\text{F}} (376 \text{ MHz, dms}-d_{6}) : \]

-61.8

\[ \nu_{\text{max}} \text{ (neat)/cm}^{-1} : \]

2970, 1691, 1598, 1474, 1387, 1277, 1174, 1128, 1028, 943, 830, 681

HRMS (m/z – ESI):

Found: 805.3187 [M]+ C\text{44}H\text{43}N\text{4}O\text{4}F\text{6} Requires: 805.3189

(1S,2S,4S,5R)-2-((S)-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)(6-methoxy-2-phenylquinolin-4-yl)methyl)-1-(3,4,5-tris(benzyloxy)benzyl)-5-vinylquinuclidin-1-ium bromide (327)

Synthesised according to general procedure XII, using \textbf{323} (0.22 g, 0.34 mmol), 3,4,5-tris(benzyloxy)benzyl bromide (0.20 g, 0.403 mmol) and PhCH\textsubscript{3} (3.4 mL). The crude residue was purified by column chromatography (30:1 CH\textsubscript{2}Cl\textsubscript{2}/MeOH, TLC is better
visualised using CH$_2$Cl$_2$/MeOH 10:1, R$_f$ = 0.3), to afford 327 (256 mg, 67%) as an off-white amorphous solid. M.p. 181-182 °C; [α]$_D$$^{20}$ = +1.9 (c = 0.2, CHCl$_3$).

δ$_H$ (400 MHz, dmso-$d_6$): 9.91 (br s, 1 H, NH$_1$), 8.54 (app. d, 1 H, J 7.9, H-17), 8.37-8.34 (m, 3 H, H-18 and H-15), 8.10-8.08 (m, 3 H, H-21 and H-12), 7.66 (br s, 1 H, NH$_2$), 7.57-7.50 (m, 5 H, H-22, H-20, H-19 and H-14), 7.43-7.26 (m, 15 H, H-26, H-27 and H-28), 7.09 (s, 2 H, H-24), 6.32-6.28 (m, 1 H, H-9), 5.93-5.84 (m, 1 H, H-10), 5.30-5.02 (m, 11 H, H-11, H-23a, H-23b, H-8, H-25), 4.96-4.89 (m, 1 H, H-6a), 4.29-4.23 (m, 1 H, H-2b), 4.06 (s, 3 H, H-13), 3.56-3.49 (m, 1 H, H-2a), 3.44-3.34 (m, 1 H, H-6b), 2.74-1.93 (m, 4 H, H-5a, H-5b, H-7b and H-4), 1.28-1.24 (m, 1 H, H-7a)

Note: $^1$H NMR spectrum was recorded at 60 °C as the spectrum recorded at 25 °C exposed the presence of rotomers, resulting in significant peak overlap and broadening.

δ$_C$ (100 MHz, dmso-$d_6$): 158.1 (C=O), 145.5 (q), 153.8 (q), 152.1 (q), 144.3 (q), 141.6 (q), 138.7 (q), 138.5 (q), 137.9, 137.5 (q), 137.1, 136.5 (q), 132.0, 130.7 (q, $J_{C\rightarrow F}$ 32.4) (q), 129.5, 128.8, 128.4, 128.1, 128.0, 127.7, 127.2, 123.4 (q, $J_{C\rightarrow F}$ 274.0) (q), 122.9 (q), 122.3, 117.6, 112.5, 101.9, 74.3, 70.3, 65.1, 60.4, 59.7, 55.6, 50.1, 36.8, 26.8, 26.0, 24.2, 14.1, 13.9

Note: Not all of the aromatic carbons were assigned due to peak overlapping.

δ$_F$ (376 MHz, dmso-$d_6$): -61.8

ν$_{max}$ (neat)/cm$^{-1}$: 2957, 1684, 1578, 1499, 1474, 1387, 1277, 1178, 1128, 1029, 880, 735, 695

HRMS (m/z – ESI): Found: 1063.4224 [M]$^+$ C$_{63}$H$_{57}$N$_4$O$_5$F$_6$ Requires: 1063.4233
(1S,2S,4S,5R)-2-((S)-(3,5-bis(trifluoromethyl)phenyl)ureido)(2-chloro-6-methoxyquinolin-4-yl)methyl)-1-(3,5-di-tert-butylbenzyl)-5-vinylquinuclidin-1-ium bromide (352)

Synthesised according to general procedure XII, using 351 (670 mg, 1.09 mmol), 3,5-di-tert-butylbenzyl bromide (0.37 g, 1.31 mmol) and PhCH₃ (11.0 mL). The crude residue was purified by column chromatography (eluting gradient from 100% CH₂Cl₂ to 90:10 CH₂Cl₂/MeOH, TLC is better visualised using CH₂Cl₂/MeOH 10:1, Rf = 0.3), to afford 352 (0.83 mg, 85%) as an off-white amorphous solid. M.p. 175-176 °C; [α]D<sup>20</sup> = +26.0 (c = 0.1, CHCl₃).

δ<sub>H</sub> (400 MHz, dmoso-d₆): 9.62 (br s, 1 H, NH₁), 8.31 (d, 1 H, J 8.1, H-17), 8.11 (s, 2 H, H-18), 7.97 (d, 1 H, J 9.4, H-15), 7.87 (s, 1 H, H-12), 7.75 (br s, 1 H, NH₂), 7.63-7.51 (m, 3 H, H-14, H-19 and H-23), 7.34 (s, 2 H, H-21), 6.28-6.24 (m, 1 H, H-9), 5.96-5.87 (m, 1 H, H-10), 5.25-5.17 (m, 1 H, H-20b and H-11), 5.07-5.01 (m, 1 H, H-8), 4.70 (d, 1 H, J 13.2, H-20a), 4.26-4.20 (m, 1 H, H-6a), 3.99 (s, 3 H, H-13), 3.72-3.67 (m, 1 H, H-2b), 3.60-3.54 (m, 1 H, H-2a), 3.21-3.13 (m, 1 H, H-6b), 2.79-2.73 (m, 1 H, H-3), 2.17-1.98 (m, 3 H, H-5a, H-5b and H-7b), 1.90 (app. s, 1 H, H-4), 1.24 (app. s, 18 H, H-22), 1.17-1.08 (m, 1 H, H-7a)

δ<sub>C</sub> (100 MHz, dmoso-d₆): 158.4 (C=O), 154.1 (q), 151.1 (q), 147.2 (q), 147.0 (q), 143.7 (q), 141.4 (q), 137.2, 130.7 (q, J<sub>C-F</sub> 33.4) (q), 130.6, 127.8, 126.9 (q), 126.2 (q), 123.7, 123.2 (q, J<sub>C-F</sub> 273.5)
δF (376 MHz, dmso- d6): -61.8

νmax (neat)/cm⁻¹:
2967, 1690, 1560, 1474, 1386, 1276, 1175, 1129, 921, 880, 681

HRMS (m/z – APCI): Found: 815.3502 [M]+ C₄₄H₅₀ClN₄O₂F₆ Requires: 815.3521

(1S,2S,4S,5R)-2-((3-phenyl)ureido(6-methoxy-2-phenylquinolin-4-yl)methyl)-1-(3,5-di-tert-butylbenzyl)-5-vinylquinuclidin-1-ium bromide (318)

Synthesised according to general procedure XII, using 316 (320 mg, 0.62 mmol), 3,5-di-tert-butylbenzyl bromide (0.21 g, 0.74 mmol) and PhCH₃ (6.2 mL). The crude residue was purified by column chromatography (eluting gradient from 90:1 CH₂Cl₂/MeOH to 30:1 CH₂Cl₂/MeOH, TLC is better visualised using CH₂Cl₂/MeOH 10:1, Rf = 0.3), to afford 318 (346 mg, 70%) as a white amorphous solid. M.p. 178-179 °C; [α]D²⁰ = +18.1 (c = 0.3, CHCl₃).

δH (400 MHz, dmso- d6):
8.95 (br s, 1 H, NH¹), 8.40-8.33 (m, 3 H, H-18 and NH²), 8.09 (d, 1 H, J 9.2, H-15), 7.93 (d, 1 H, J 7.6, H-17), 7.67 (s, 1 H, H-12), 7.60-7.52 (m, 5 H, H-21, H-19 and H-14), 7.43-7.40 (m, 4 H, H-27, H-25 and H-20), 7.23-7.19 (m, 2 H, H-22), 6.94-6.91 (m, 1 H, H-23), 6.32-6.27 (m, 1 H, H-9), 5.94-5.85 (m, 1 H, H-10), 5.23-5.14 (m, 4 H, H-24b, H-8 and H-11), 4.84 (d, 1 H, J 13.2, H-24a), 4.49-4.44 (m, 1 H, H-6a), 3.98 (s, 3 H, H-13), 3.74-3.68 (m, 1 H, H-2b),
3.63-3.57 (m, 1 H, H-2a), 3.31-3.25 (m, 1 H, H-6b), 2.79-2.73 (m, 1 H, H-3), 2.19-2.04 (m, 2 H, H-5a and H-7b), 1.90 (app. s, 1 H, H-4), 1.27-1.17 (m, 20 H, H-26, H-7a and H-5b)

δC (100 MHz, dmsod6): 158.6 (C=O), 155.0 (q), 154.4 (q), 151.7 (q), 145.2 (q), 144.8 (q), 139.8 (q), 138.9 (q), 137.5, 132.4, 130.0, 129.4, 129.2, 128.2, 127.7, 127.5 (q), 126.4 (q), 124.1, 122.8, 122.6, 118.4, 117.6, 117.1, 102.4, 66.6, 66.0, 60.5, 56.2, 50.6, 49.7, 37.0, 35.1 (q), 31.6, 27.4, 26.6, 24.5

νmax (neat)/cm⁻¹: 2961, 1685, 1598, 1550, 1498, 1314, 1222, 1079, 1028, 831, 751, 692


(1S,2S,4S,5R)-2-([S]-3-(2,6-diisopropyl)phenyl)ureido)(6-methoxy-2-phenylquinolin-4-yl)methyl)-1-(3,5-di-tert-butylbenzyl)-5-vinylquinuclidin-1-ium bromide (319)

Synthesised according to general procedure XII, using 317 (0.17 mg, 0.28 mmol), 3,5-di-tert-butylbenzyl bromide (96 mg, 0.34 mmol) and PhCH₃ (1.7 mL). The crude residue was purified by column chromatography (30:1 CH₂Cl₂/MeOH, TLC is better visualised using CH₂Cl₂/MeOH 10:1, Rf = 0.3), to afford 319 (182 mg, 73%) as an off-white amorphous solid. M.p. 169-170 °C; [α]D²⁰ = +50.4 (c = 0.2, CHCl₃).

δH (400 MHz, dmsod6): 8.31 (app. d, 2 H, J 7.8, H-18), 8.27 (br s, 1 H, NH₁), 8.11 (d, 1 H, J 9.3, H-15), 7.79 (br s, 1 H, NH₂), 7.66-7.49 (m, 9 H, H-28, H-26, H-20, H-19, H-17, H-14 and H-12), 7.14
(t, 1 H, J 7.7, H-24), 7.00 (app. d, 2 H, J 7.7, H-23), 6.26 (s, 1 H, H-9), 5.97-5.88 (m, 1 H, H-10), 5.29-5.07 (m, 5 H, H-25a, H-25b, H-11 and H-8), 4.51-4.45 (m, 1 H, H-6a), 4.03 (s, 3 H, H-13), 3.58-3.52 (m, 3 H, H-21 and H-2b), 2.84-2.77 (m, 3 H, H-2a, H-6b and H-3), 2.09-1.99 (m, 3 H, H-5a, H-5b and H-7b), 1.92 (app. s, 1 H, H-4), 1.38 (app. s, 18 H, H-27), 1.26-1.22 (m, 1 H, H-7a), 0.81 (app. br s, 12 H, H-22)

**Note:** $^1$H NMR spectrum was recorded at 80 °C as the spectrum recorded at 25 °C exposed the presence of rotomers, resulting in significant peak overlap and broadening.

δ_c (100 MHz, dmsod$_6$):  158.1 (C=O), 156.5, 153.8, 151.1, 144.3, 138.5, 137.5, 132.2, 132.0, 131.9, 131.5, 131.4, 129.5, 128.8 (two signals), 128.7, 127.6, 127.3, 127.1, 127.0, 123.7, 123.5, 122.8, 121.9, 111.7, 116.4, 102.4, 66.4, 66.3, 65.0, 59.9, 55.7, 55.6, 50.6, 50.4, 50.0, 36.7, 34.7, 34.6, 31.2, 27.8, 27.5, 26.0, 24.6, 24.3, 24.0, 23.6, 22.7, 21.3, 19.9

**Note:** The quaternary carbons were not assigned due to multiple rotomers.

ν$_{max}$ (neat)/cm$^{-1}$:  2962, 1671, 1622, 1534, 1459, 1363, 1227, 1028, 853

HRMS (m/z – ESI):  Found: 805.5412 [M]$^+$ C$_{54}$H$_{69}$N$_4$O$_2$ Requires: 805.5421

(1S,2S,4S,5R)-2-((S)-(3-tritylureido)(6-methoxy-2-phenylquinolin-4-yl)methyl)-1-(3,5-di-tert-butylbenzyl)-5-vinylquinuclidin-1-ium bromide (321)
Synthesised according to general procedure XII extending the reaction time to 24 h, using 320 (200 mg, 0.29 mmol), 3,5-di-tert-butylbenzyl bromide (0.10 g, 0.35 mmol) and PhCH₃ (3.0 mL). The crude residue was purified by column chromatography (50:1 CH₂Cl₂/MeOH, TLC is better visualised using CH₂Cl₂/MeOH 10:1, Rf = 0.4), to afford 321 (175 mg, 62%) as an off-white amorphous solid. M.p. 185-187 °C; [α]D²⁰ = +84.3 (c = 0.1, CHCl₃).

δH (400 MHz, dmso-d₆): 8.29 (d, 2 H, J 7.3, H-18), 8.12 (d, 1 H, J 9.2, H-15), 8.09 (app. br s, 1 H, NH₁), 7.62-7.34 (m, 10 H, H-20, H-19, H-17, H-14, H-12 and NH₂), 7.12-7.03 (m, 15 H, H-23, H-22 and H-21), 6.07-6.03 (m, 1 H, H-9), 5.89-5.81 (m, 1 H, H-10), 5.19-5.13 (m, 2 H, H-24b and H-8), 4.94-4.85 (m, 2 H, H-11), 4.63 (app. d, 1 H, J 13.1, H-24a), 4.32-4.24 (m, 1 H, H-6a), 3.84 (br s, 3 H, H-13), 3.59-3.47 (m, 1 H, H-2b), 3.25-3.23 (m, 1 H, H-2a), 2.75-2.67 (m, 2 H, H-6b and H-3), 2.09-1.84 (m, 4 H, H-5a, H-5b, H-4 and H-7b), 1.38 (s, 18 H, H-26), 1.10-1.04 (m, 1 H, H-7a)

Note: ¹H NMR spectrum was recorded at 60 °C as the spectrum recorded at 25 °C exposed the presence of rotomers, resulting in significant peak overlap and broadening.

δC (100 MHz, dmso-d₆): 171.4, 158.2, 156.6, 153.8, 151.1, 145.2, 145.0, 144.4, 138.4, 138.2, 138.0, 137.2, 131.8, 129.5, 128.7, 128.4, 128.1, 127.7, 127.5, 127.3, 127.1, 126.5, 126.2, 125.6, 123.5, 122.4, 117.1, 116.8, 115.8, 102.7, 101.8, 69.1, 64.9, 64.0, 60.2, 55.6, 50.7, 50.1, 36.9, 34.7, 34.4, 31.3, 31.2, 30.4, 29.0, 28.9, 28.7, 28.6, 28.1, 27.3, 26.3, 26.0, 25.3, 24.4, 22.1, 13.9

Note: The quaternary and carbonyl carbons were not assigned due to multiple rotomers.

νmax (neat)/cm⁻¹: 3220, 2956, 1736, 1666, 1622, 1534, 1498, 1349, 1228, 1029, 876, 702, 675

HRMS (m/z – ESI): Found: 887.5263 [M]+ C₆₁H₆₇N₄O₂ Requires: 887.5259
5.2.3 Phase-transfer catalysed alkylation of 2-oxindole derivatives

**General procedure XIV:** Racemic alkylation of C,N-bis-acylated 2-oxindole derivatives under basic conditions.

To a solution of C,N-bis-acylated 2-oxindole-derived substrate (1.0 equiv.), p-iodoanisole (1 equiv., internal standard), electrophile (1.2 equiv.) and TBAB (5 mol%) in CH$_2$Cl$_2$ (0.1 M), was added K$_2$HPO$_4$ (1% w/v aq., 2.0 equiv.). The reaction mixture was left stirring at rt overnight. The biphasic mixture was poured into a separation funnel and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 x 3 mL). The combined organic extracts were washed with brine, dried with MgSO$_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel.

Characterisation of the alkylated 2-oxindole derivatives was carried out with the enantioselective analogues.

**General procedure XV:** Enantioselective alkylation of C,N-bis-acylated 2-oxindole derivatives under base-free neutral conditions.

To a 50 mL round-bottomed flask containing a stirring bar, C,N-bis-acylated 2-oxindole-derived substrate (1.0 equiv.), p-iodoanisole (1.0 equiv., internal standard), electrophile (1.2 equiv.), catalyst (5 mol% or 10 mol% depending on reaction temperature) and organic solvent (making a substrate concentration of 0.1 M) was added millipore water (10:1 v/v relative to the organic solvent). The reaction mixture was stirred at rt or 3 °C for specified time. The biphasic mixture was poured into a separation funnel and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine, dried with MgSO$_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.
Diethyl 3-benzyl-2-oxindoline-1,3-dicarboxylate (295, Table 2.14, entry 1)

Synthesised according to general procedure XV, using substrate 294 (42.7 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), benzyl bromide (22.0 µL, 0.185 mmol), catalyst 307 (7.2 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 45 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, Rf = 0.4), to afford 295 (51.5 mg, 91%, 62% ee) as a white amorphous solid. M.p. 91-92 °C; [α]D20 = +32.2 (c = 0.5, CHCl3).

CSP-HPLC analysis. Acquity UPC² step 2 – Trefoil CEL1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2, B = MeOH/IPA (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 1.907 min (minor enantiomer) and 2.008 min (major enantiomer).

δH (400 MHz, CDCl3):
7.66 (d, 1 H, J 8.2, H-10), 7.35 (dd, 1 H, J 7.6, 1.2, H-7)
7.27 (app. td, 1 H, J 8.2, 1.2, H-9), 7.19 (app. td, 1 H, J 7.6, 1.2, H-8), 7.08-7.00 (m, 3 H, H-6 and H-5), 6.84 (app. d, 2 H, J 6.8, H-4), 4.43-4.32 (m, 2 H, H-11), 4.25-4.13 (m, 2 H, H-2), 3.61 (d, 1 H, J 13.4, H-3), 3.55 (d, 1 H, J 13.4, H-3’), 1.38 (t, 3 H, J 7.2, H-12), 1.18 (t, 3 H, J 7.2, H-1)

δC (100 MHz, CDCl3):
171.8 (C=O), 168.5 (C=O), 150.2 (C=O), 139.9 (q), 133.7 (q), 129.9, 129.3, 127.8, 127.0, 126.3 (q), 124.6, 123.5, 115.1, 63.3, 62.3, 61.4 (q), 40.6, 14.1, 13.8

νmax (neat)/cm⁻¹:
2987, 1765, 1729, 1482, 1340, 1284, 1222, 1152, 772, 700, 674

HRMS (m/z - ESI):
Found: 368.1488 [M+H]+ C21H21NO5 Requires: 368.1492
1-Ethyl 3-methyl 3-benzyl-2-oxoindoline-1,3-dicarboxylate (368, Table 2.14, entry 2)

Synthesised according to general procedure XV, using substrate 358 (40.5 mg, 0.154 mmol), \( p \)-iodoanisole (36.1 mg, 0.154 mmol), benzyl bromide (22.0 µL, 0.185 mmol), catalyst 307 (7.2 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 45 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, \( R_f = 0.4 \)), to afford 368 (50.6 mg, 93%, 61% ee) as a white amorphous solid. M.p. 120-123 °C; \([\alpha]_D^{20} = +37.3 \) (c = 0.5, CHCl₃).

CSP-HPLC analysis. Acquity UPC² step 1 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO₂, B = EtOH/CH₃CN (1:1, v:v); 10 min run time, column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.185 min (major enantiomer) and 2.442 min (minor enantiomer).

\[ \delta_H \ (400 \text{ MHz, CDCl}_3): \]
7.67 (d, 1 H, J 8.1, H-9), 7.35 (dd, 1 H, J 7.5, 1.0, H-6), 7.28 (app. td, 1 H, J 8.1, 1.0, H-8), 7.20 (app. td, 1 H, J 7.5, 1.0, H-7), 7.09-7.01 (m, 3 H, H-5 and H-4), 6.84 (app. d, 2 H, J 7.6, H-2), 4.44-4.32 (m, 2 H, H-10), 3.72 (s, 3 H, H-1), 3.61 (d, 1 H, J 13.4, H-2), 3.57 (d, 1 H, J 13.4, H-2’), 1.39 (t, 3 H, J 7.2, H-11)

\[ \delta_C \ (100 \text{ MHz, CDCl}_3): \]
171.8 (C=O), 169.0 (C=O), 150.2 (C=O), 139.9 (q), 133.6 (q), 130.0, 129.4, 127.9, 127.1, 126.1 (q), 124.6, 123.7, 115.2, 63.4, 61.3 (q), 53.3, 40.1, 14.2

\[ \nu_{\text{max}} \ (\text{neat/cm}^{-1}): \]
2988, 1767, 1730, 1481, 1341, 1285, 1235, 1055, 927, 768, 699

HRMS (\textit{m/z} - ESI): Found: 376.1169 [M+Na]+ \( \text{C}_{20}\text{H}_{19}\text{NNaO}_5 \) Requires: 376.1155

250
3-Ethyl 1-methyl 3-benzyl-2-oxoindoline-1,3-dicarboxylate (369, Table 2.14, entry 3)

Synthesised according to general procedure XV, using substrate 356 (40.5 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), benzyl bromide (22.0 µL, 0.185 mmol), catalyst 307 (7.2 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 45 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, Rf = 0.4), to afford 369 (49.8 mg, 92%, 54% ee) as a white amorphous solid. M.p. 112-116 °C; [α]D20 = 35.1 (c = 0.4, CHCl3).

CSP-HPLC analysis. Acquity UPC² step 1 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2, B = EtOH/CH3CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.107 min (major enantiomer) and 2.530 min (minor enantiomer).

δH (400 MHz, CDCl3): 7.69 (d, 1 H, J 8.0, H-10), 7.37 (dd, 1 H, J 7.4, 0.9, H-7), 7.28 (app. td, 1 H, J 7.4, 0.9, H-8), 7.08-7.00 (m, 3 H, H-6 and H-5), 6.83 (app. d, 2 H, H-4), 4.25-4.12 (m, 2 H, H-2), 3.92 (s, 3 H, H-11), 3.61 (d, 1 H, J 13.4, H-3), 3.56 (d, 1 H, J 13.4, H-3’), 1.17 (t, 3 H, J 7.2, H-1)

δC (100 MHz, CDCl3): 171.7 (C=O), 168.4 (C=O), 150.8 (C=O), 139.7 (q), 133.7 (q), 129.9, 129.3, 127.9, 127.0, 126.3 (q), 124.7, 123.5, 115.2, 62.4, 61.4 (q), 53.9, 40.5, 13.8

νmax (neat)/cm⁻¹: 2962, 1763, 1734, 1440, 1345, 1287, 1221, 1154, 1055, 700, 674

HRMS (m/z - ESI): Found: 376.1164 [M+Na]+ C20H19NNaOs Requires: 376.1155
Dimethyl 3-benzyl-2-oxoindoline-1,3-dicarboxylate (312, Table 2.14, entry 4)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), \( p \)-iodoanisole (36.1 mg, 0.154 mmol), benzyl bromide (22.0 µL, 0.185 mmol), catalyst 307 (7.2 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 45 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, \( R_f \) = 0.4), to afford 312 (49.6 mg, 95%, 52% ee) as a white amorphous solid. M.p. 130-132 °C; \([\alpha]_D^{20} = +51.6\) (c = 0.4, CHCl₃).

CSP-HPLC analysis. Acquity UPC² step 1 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO₂, B = EtOH/CH₃CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 1.994 min (major enantiomer) and 2.414 min (minor enantiomer).

\( \delta_H \) (400 MHz, CDCl₃): 7.70 (d, 1 H, J 8.2, H-9), 7.37 (dd, 1 H, J 7.5, 1.0, H-6), 7.29 (app. td, 1 H, J 8.2, 1.0, H-8), 7.21 (app. td, 1 H, J 7.5, 1.0, H-7), 7.09-7.00 (m, 3 H, H-5 and H-4), 6.84 (app. d, 2 H, J 7.8, H-3), 3.93 (s, 3 H, H-10), 3.71 (s, 3 H, H-1), 3.62 (d, 1 H, J 13.5, H-2), 3.58 (d, 1 H, J 13.5, H-2’)

\( \delta_C \) (100 MHz, CDCl₃): 171.8 (C=O), 169.0 (C=O), 150.9 (C=O), 139.8 (q), 133.6 (q), 130.0, 129.5, 127.9, 127.1, 126.1 (q), 124.8, 123.7, 115.3, 61.3 (q), 53.9, 53.3, 40.5

\( \nu_{\text{max}} \) (neat)/cm⁻¹: 2954, 1794, 1764, 1739, 1480, 1439, 1288, 1223, 1057, 763, 732, 701

HRMS (m/z - ESI): Found: 362.1011 [M+Na]⁺ \( \text{C}_{19}\text{H}_{13}\text{NNaO}_5 \) Requires: 362.0999

252
1-Benzyl 3-methyl 3-benzyl-2-oxoindoline-1,3-dicarboxylate (370, Table 2.14, entry 5)

Synthesised according to general procedure XV, using substrate 366 (50.1 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), benzyl bromide (22.0 µL, 0.185 mmol), catalyst 307 (7.2 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 68 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, Rf = 0.4), to afford 370 (46.1 mg, 72%, 33% ee) as a pale yellow oil; [α]D^20 = +12.8 (c = 0.4, CHCl₃).

CSP-HPLC analysis. Acquity UPC² step 3 – Trefoil CEL2 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO₂, B = EtOH/CH₃CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.542 min (major enantiomer) and 2.692 min (minor enantiomer).

δ_H (400 MHz, CDCl₃): 7.66 (d, 1 H, J 8.0, H-9), 7.45-7.34 (m, 6 H, H-5, H-6, H-11 and H-12), 7.27 (app. td, 1 H, J 8.0, 1.2, H-8), 7.20 (app. td, 1 H, J 7.4, 1.2, H-7), 7.06-7.02 (m, 1 H, H-13), 6.98-6.95 (m, 2 H, H-4), 6.82 (app. d, 2 H, J 7.3, H-3), 5.40 (d, 1 H, J 12.6, H-10'), 5.33 (d, 1 H, J 12.6, H-10), 3.72 (s, 3 H, H-1), 3.62 (d, 1 H, J 13.4, H-2), 3.56 (d, 1 H, J 13.4, H-2')

δ_C (100 MHz, CDCl₃): 171.7 (C=O), 169.0 (C=O), 150.1 (C=O), 139.7 (q), 134.9 (q), 133.5 (q), 129.9, 129.4, 128.6, 128.4, 127.9, 127.8, 127.1, 126.1 (q), 124.7, 123.6, 115.3, 68.5, 61.3 (q), 53.3, 40.8

ν_max (neat)/cm⁻¹: 2955, 1770, 1735, 1480, 1345, 1286, 1154, 1011, 767

HRMS (m/z - ESI): Found: 438.1315 [M+Na]^+ C_{23}H_{21}NNaO_{5} Requires: 438.1312
1-(Tert-butyl) 3-ethyl 3-benzyl-2-oxoindoline-1,3-dicarboxylate (371, Table 2.14, entry 6)

Synthesised according to general procedure XV, using substrate 365 (47.0 mg, 0.154 mmol), \( p \)-iodoanisole (36.1 mg, 0.154 mmol), benzyl bromide (22.0 µL, 0.185 mmol), catalyst 307 (7.2 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 54 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 9:1, \( R_f = 0.3 \)), to afford 371 (57.3 mg, 94%, 34% \( ee \)) as a clear oil; \[ \alpha \]\(_{D}^{20} \) = +12.1 (c = 0.3, CHCl\(_3\)).

CSP-HPLC analysis. Acquity UPC\(^2\) step 3 – Trefoil CEL2 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO\(_2\), B = EtOH/CH\(_3\)CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.131 min (major enantiomer) and 2.257 min (minor enantiomer).

\( \delta_H \) (400 MHz, CDCl\(_3\)): 7.58 (d, 1 H, J 7.9, H-10), 7.32 (dd, 1 H, J 7.5, 1.1, H-7), 7.25 (app. td, 1 H, J 7.9, 1.1, H-9), 7.17 (app. td, 1 H, J 7.5, 1.1, H-8), 7.09-7.00 (m, 3 H, H-6 and H-5), 6.83 (app. d, 2 H, J 7.2, H-4), 4.25-4.13 (m, 2 H, H-2), 3.59 (d, 1 H, J 13.5, H-3), 3.52 (d, 1 H, J 13.5, H-3’), 1.55 (br s, 9 H, H-11), 1.19 (t, 3 H, J 7.2, H-1)

\( \delta_C \) (100 MHz, CDCl\(_3\)): 172.0 (C=O), 168.7 (C=O), 148.5 (C=O), 140.2 (q), 133.8 (q), 130.0, 129.1, 127.7, 127.0, 126.3 (q), 124.3, 123.5, 115.1, 84.2 (q), 62.3, 61.3 (q), 41.0, 28.0, 13.9

\( \nu_{\text{max}} \) (neat)/cm\(^{-1}\): 2982, 1769, 1731, 1346, 1289, 1228, 1146, 1005, 842, 753, 699

HRMS (\( m/z \) - ESI): Found: 418.1646 [M+Na]\(^+\) \( \text{C}_{23}\text{H}_{25}\text{NNaO}_5 \) Requires: 418.1625
1-(Tert-butyl) 3-methyl 3-benzyl-2-oxoindoline-1,3-dicarboxylate (372, Table 2.14, entry 7)

Synthesised according to general procedure XV, using substrate 364 (44.9 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), benzyl bromide (22.0 µL, 0.185 mmol), catalyst 307 (7.2 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 68 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, Rf = 0.5), to afford 372 (52.9 mg, 90%, 31% ee) as a clear oil; [α]D20 = +13.5 (c = 0.3, CHCl3).

CSP-HPLC analysis. Acquity UPC2 step 3 line 2 – Trefoil CEL2 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2, B = MeOH/IPA (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.038 min (major enantiomer) and 2.112 min (minor enantiomer).

δH (400 MHz, CDCl3): 7.58 (d, 1 H, J 8.1, H-9), 7.32 (dd, 1 H, J 7.4, 1.0, H-6), 7.26 (app. td, 1 H, J 8.1, 1.0, H-8), 7.17 (app. td, 1 H, J 7.4, 1.0, H-7), 7.09-7.00 (m, 3 H, H-5 and H-4), 6.83 (app. d, 2 H, J 7.6, H-3), 3.72 (s, 3 H, H-1), 3.59 (d, 1 H, J 13.2, H-2), 3.53 (d, 1 H, J 13.2, H-2′), 1.55 (s, 9 H, H-10)

δC (100 MHz, CDCl3): 171.9 (C=O), 168.2 (C=O), 148.4 (C=O), 140.2 (q), 133.7 (q), 130.0, 129.2, 127.8, 127.0, 126.1 (q), 124.4, 123.6, 115.1, 84.4 (q), 61.2 (q), 53.2, 41.0, 28.0

νmax (neat)/cm⁻¹: 2982, 1768, 1731, 1345, 1247, 1145, 1005, 841, 753, 700

HRMS (m/z - ESI): Found: 404.1477 [M+Na]+ C22H23NNaO5 Requires: 404.1474
1-Methyl 3-(2,2,2-trichloroethyl) 3-benzyl-2-oxoindoline-1,3-dicarboxylate (373, Table 2.14, entry 8)

Synthesised according to general procedure XV, using substrate 363 (56.3 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), benzyl bromide (22.0 µL, 0.185 mmol), catalyst 307 (7.2 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 136 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, Rf = 0.5), to afford 373 (30% conv. by 1H NMR, 18% ee) as a clear oil; [α]D20 = -3.3 (c = 0.5, CHCl3).

CSP-HPLC analysis. Acquity UPC2 step 1 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2, B = EtOH/CH3CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.431 min (major enantiomer) and 2.797 min (minor enantiomer).

δH (400 MHz, CDCl3): 7.72 (d, 1 H, J 8.1, H-9), 7.41 (dd, 1 H, J 7.5, 1.0, H-6), 7.31 (app. td, 1 H, J 8.1, 1.0, H-8), 7.21 (app. td, 1 H, J 7.5, 1.0, H-7), 7.11-7.03 (m, 3 H, H-5 and H-4), 6.88 (app. d, 2 H, J 7.5, H-3), 4.90 (d, 1 H, J 12.0, H-1), 4.64 (d, 1 H, J 12.0, H-1’), 3.94 (s, 3 H, H-10), 3.69 (d, 1 H, J 13.5, H-2), 3.63 (d, 1 H, J 13.5, H-2’)

δC (100 MHz, CDCl3): 170.8 (C=O), 166.8 (C=O), 150.8 (C=O), 140.0 (q), 133.2 (q), 130.1, 129.8, 128.0, 127.3, 125.2 (q), 124.8, 124.1, 115.4, 94.1 (q), 74.4, 61.4 (q), 54.0, 40.0

νmax (neat)/cm⁻¹: 2978, 1775, 1738, 1481, 1437, 1347, 1208, 1154, 1047, 1021, 769, 714

HRMS (m/z - ESI): Found: 477.9989 [M+Na]+ C20H16NNaO5Cl3 Requires: 477.9992
Methyl 3-benzyl-1-methyl-2-oxoindoline-3-carboxylate (374, Table 2.14, entry 9)

![Chemical structure](image)

Synthesised according to general procedure XV, using substrate 367 (31.6 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), benzyl bromide (22.0 µL, 0.185 mmol), catalyst 307 (7.2 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 63 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, R<sub>f</sub> = 0.4), to afford 374 (38.7 mg, 85%, 11% ee) as a white amorphous solid. M.p. 130-135 °C; [α]<sub>D</sub><sup>20</sup> = +6.3 (c = 0.3, CHCl<sub>3</sub>).

CSP-HPLC analysis. Acquity UPC<sup>2</sup> step 1 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO<sub>2</sub>, B = EtOH/CH<sub>3</sub>CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.192 min (major enantiomer) and 2.408 min (minor enantiomer).

δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>):
- 7.33 (d, 1 H, J 7.8, H-6), 7.23 (app. td, 1 H, J 7.8, 1.1, H-8), 7.07 (app. t, 1 H, J 7.8, H-7), 7.05-6.98 (m, 3 H, H-5 and H-4), 6.84 (app. d, 2 H, H-3), 6.58 (d, 1 H, J 7.8, H-9), 3.72 (s, 3 H, H-1), 3.55 (s, 2 H, H-2), 2.95 (s, 3 H, H-10)

δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>):
- 173.4 (C=O), 169.8 (C=O), 144.0 (q), 134.3 (q), 130.0, 129.1, 127.5, 127.3 (q), 126.7, 123.9, 122.5, 108.1, 60.7 (q), 53.1, 40.0, 26.1

ν<sub>max</sub> (neat)/cm<sup>-1</sup>:
- 2950, 1737, 1710, 1608, 1492, 1374, 1353, 1227, 1002, 763, 747, 697

HRMS (m/z - ESI): Found: 318.1115 [M+Na]<sup>+</sup> C<sub>18</sub>H<sub>17</sub>NNaO<sub>3</sub> Requires: 318.1101
Dimethyl 3-benzyl-4-bromo-2-oxoindoline-1,3-dicarboxylate (391, Table 2.15, entry 1)

Synthesised according to general procedure XV, substrate 387 (50.5 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), benzyl bromide (22.0 µL, 0.185 mmol), catalyst 335 (13.8 mg, 0.0154 mmol), chlorobenzene (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 87 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, Rf = 0.4), to afford 391 (80% conv. by 1H NMR, 83% ee) as a pale pink oil; [α]D20 = +10.7 (c = 0.1, CHCl3).

CSP-HPLC analysis. Acquity UPC² step 2 – Trefoil CEL1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2, B = MeOH/IPA (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.115 min (minor enantiomer) and 2.590 min (major enantiomer).

δH (400 MHz, CDCl3): 7.62 (dd, 1 H, J 8.2, 0.7, H-8), 7.35 (dd, 1 H, J 8.2, 0.7, H-6), 7.15 (app. t, 1 H, J 8.2, H-7), 7.08-6.99 (m, 3 H, H-5 and H-4), 6.85 (app. d, 2 H, J 7.5, H-3), 3.96 (d, 1 H, J 13.4, H-2), 3.92 (s, 3 H, H-9), 3.74 (s, 3 H, H-1), 3.66 (d, 1 H, J 13.4, H-2')

δC (100 MHz, CDCl3): 170.7 (C=O), 167.0 (C=O), 150.4 (C=O), 141.5 (q), 133.6 (q), 130.5, 129.4, 128.6, 127.9, 126.2 (q), 118.8 (q), 114.0, 63.1 (q), 54.1, 53.4, 37.7

νmax (neat)/cm⁻¹: 2925, 1774, 1739, 1449, 1340, 1238, 1131, 1051, 930, 775, 708

Dimethyl 3-benzyl-5-bromo-2-oxoindoline-1,3-dicarboxylate (392, Table 2.15, entry 2)

Synthesised according to general procedure XV, using substrate 388 (50.5 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), benzyl bromide (22.0 µL, 0.185 mmol), catalyst 335 (6.9 mg, 0.0077 mmol), chlorobenzene (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 67 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, Rf = 0.4), to afford 392 (91% conv. by ¹H NMR, 44% ee) as a white amorphous solid. M.p. 125-128 °C; [α]D20 = +58.3 (c = 0.5, CHCl3).

CSP-HPLC analysis. Acquity UPC² step 1 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2, B = EtOH/CH3CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.347 min (major enantiomer) and 2.718 min (minor enantiomer).

δH (400 MHz, CDCl3): 7.60 (d, 1 H, J 8.7, H-8), 7.49 (d, 1 H, J 2.0, H-6), 7.41 (dd, 1 H, J 8.7, 2.0, H-7), 7.12-7.04 (m, 3 H, H-5 and H-4), 6.85 (app. d, 2 H, J 7.5, H-3), 3.93 (s, 3 H, H-9), 3.74 (s, 3 H, H-1), 3.61 (d, 1 H, J 13.5, H-2), 3.54 (d, 1 H, J 13.5, H-2’)

δC (100 MHz, CDCl3): 170.9 (C=O), 168.3 (C=O), 150.6 (C=O), 138.7 (q), 133.2 (q), 132.4, 129.9, 128.1 (two signals), 127.3, 126.8, 117.7 (q), 116.9, 61.2 (q), 54.1, 53.5, 40.6

νmax (neat)/cm⁻¹: 2954, 1736, 14871, 1336, 1241, 1154, 836, 740, 702

HRMS (m/z - APCI): Found: 418.0290 [M+H]+ C19H17BrNO5 Requires: 418.0285
Dimethyl 3-benzyl-5-chloro-2-oxoindoline-1,3-dicarboxylate (393, Table 2.15, entry 3)

Synthesised according to general procedure XV, using substrate 389 (43.7 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), benzyl bromide (22.0 µL, 0.185 mmol), catalyst 335 (13.8 mg, 0.0154 mmol), chlorobenzene (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at 3 °C for 144 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, Rf = 0.5), to afford 393 (>99% conv. by 1H NMR, 48% ee) as a white amorphous solid. M.p. 123-125 °C; [α]D20 = +58.4 (c = 0.4, CHCl3).

CSP-HPLC analysis. Acquity UPC2 step 1 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2, B = EtOH/CH3CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.222 min (major enantiomer) and 2.470 min (minor enantiomer).

δH (400 MHz, CDCl3): 7.66 (d, 1 H, J 8.8, H-8), 7.35 (d, 1 H, J 2.1, H-6), 7.26 (dd, 1 H, J 8.8, 2.1, H-7), 7.12-7.04 (m, 3 H, H-5 and H-4), 6.85 (app. d, 2 H, J 7.5, H-3), 3.93 (s, 3 H, H-9), 3.74 (s, 3 H, H-1), 3.61 (d, 1 H, J 13.4, H-2), 3.54 (d, 1 H, J 13.4, H-2’)

δC (100 MHz, CDCl3): 171.0 (C=O), 168.3 (C=O), 150.7 (C=O), 138.2 (q), 133.2 (q), 130.3 (q), 129.9, 129.5, 128.1, 127.8 (q), 127.3, 123.9, 116.5, 61.3 (q), 54.1, 53.5, 40.6

νmax (neat)/cm⁻¹: 2920, 1775, 1735, 1472, 1439, 1336, 1241, 1153, 1055, 943, 837, 702, 676

HRMS (m/z - ESI): Found: 396.0622 [M+Na]+ C19H16ClINaO5 Requires: 396.0609
Dimethyl 3-benzyl-5-methoxy-2-oxoindoline-1,3-dicarboxylate (394, Table 2.15, entry 4)

Synthesised according to general procedure XV, using substrate 390 (43.0 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), benzyl bromide (22.0 µL, 0.185 mmol), catalyst 335 (6.9 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 48 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, Rf = 0.5), to afford 394 (>99% conv. by ¹H NMR, 61% ee) as a white amorphous solid. M.p. 117-120 °C; [α]D<br>20 = +71.4 (c = 0.2, CHCl₃).

CSP-HPLC analysis. Acquity UPC² step 1 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO₂, B = EtOH/CH₃CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.373 min (major enantiomer) and 2.696 min (minor enantiomer).

δH (400 MHz, CDCl₃):
- 7.63 (d, 1 H, J 9.1, H-9), 7.11-7.03 (m, 3 H, H-5 and H-4), 6.90 (d, 1 H, J 2.7, H-6), 6.87 (app. d, 2 H, J 7.5, H-3), 6.81 (dd, 1 H, J 9.1, 2.7, H-8), 5.60 (d, 1 H, J 13.6, H-2), 3.92 (s, 3 H, H-10), 3.82 (s, 3 H, H-7), 3.72 (s, 3 H, H-1), 3.56 (d, 1 H, J 13.6, H-2’)

δC (100 MHz, CDCl₃):
- 171.8 (C=O), 169.0 (C=O), 157.0 (C=O), 150.9 (q), 133.6 (q), 133.1 (q), 129.9, 128.0, 127.3 (q), 127.1, 116.2, 114.3, 109.7, 61.5 (q), 55.7, 53.8, 53.3, 40.5

νmax (neat)/cm⁻¹:
- 2953, 1764, 1734, 1489, 1439, 1282, 1229, 1153, 1050, 928, 828, 768, 702

HRMS (m/z - ESI):
- Found: 392.1120 [M+Na]+ C₂₀H₁₉NNaO₆ Requires: 392.1105
Dimethyl 3-(4-methylbenzyl)-2-oxoindoline-1,3-dicarboxylate (399, Table 2.18, entry 2)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 4-methylbenzyl bromide (34.2 mg, 0.185 mmol), catalyst 355 (6.9 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 24 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, Rf = 0.4), to afford 399 (>99% conv. by ¹H NMR, 52% ee) as a white amorphous solid. M.p. 138-140 °C; [α]D²⁰ = +45.9 (c = 0.3, CHCl₃).

CSP-HPLC analysis. Acquity UPC² step 3 – Trefoil CEL2 (2.5 μm, 3.0 x 150 mm), gradient eluent A = CO₂, B = EtOH/CH₃CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.085 min (major enantiomer) and 2.238 min (minor enantiomer).

δH (400 MHz, CDCl₃): 7.73 (d, 1 H, J 8.2, H-9), 7.37 (dd, 1 H, J 7.5, 1.1, H-6), 7.30 (app. td, 1 H, J 8.2, 1.1, H-8) 7.21 (app. td, 1 H, J 7.5, 1.1, H-7), 6.83 (d, 2 H, J 7.9, H-4), 6.72 (d, 2 H, J 7.9, H-3), 3.95 (s, 3 H, H-10), 3.71 (s, 3 H, H-1), 3.58 (d, 1 H, J 13.6, H-2), 3.54 (d, 1 H, J 13.6, H-2’), 2.18 (s, 3 H, H-5)

δC (100 MHz, CDCl₃): 171.8 (C=O), 169.0 (C=O), 150.9 (C=O), 139.8 (q), 136.6 (q), 130.4 (q), 129.8, 129.4, 128.6, 126.2 (q), 124.7, 123.7, 115.2, 61.4 (q), 53.9, 53.3, 40.0, 20.9

νmax (neat)/cm⁻¹: 2953, 1801, 1736, 1481, 1432, 1316, 1235, 1162, 1055, 1001, 829, 754, 676

HRMS (m/z - APCI): Found: 354.1344 [M+H]+ C₂₀H₂₀NO₅ Requires: 354.1336
Dimethyl 3-(naphthalen-2-ylmethyl)-2-oxoindoline-1,3-dicarboxylate (400, Table 2.18, entry 3)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), \( \text{p-iodoanisole (36.1 mg, 0.154 mmol), 2-(bromomethyl)naphthalene (40.9 mg, 0.185 mmol), catalyst 335 (13.8 mg, 0.0154 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at 3 °C for 144 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, \( R_f \) = 0.4), to afford 400 (56.4 mg, 94%, 72% ee) as a white amorphous solid. M.p. 130-135 °C; \([\alpha]D^{20} = +70.0 \) (c = 0.4, CHCl₃).

CSP-HPLC analysis. Acquity UPC² step 1 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO₂, B = EtOH/CH₃CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.667 min (major enantiomer) and 2.976 min (minor enantiomer).

\[ \delta_H \] (400 MHz, CDCl₃): 7.70 (m, 3 H, H-13, H-7 and H-4), 7.50 (d, 1 H, J 8.4, H-3), 7.44 (dd, 1 H, J 7.4, 1.6, H-10), 7.39-7.35 (m, 3 H, H-8, H-6 and H-5), 7.27 (app. td, 1 H, J 8.2, 1.6, H-12), 7.23 (app. td, 1 H, J 7.4, 1.6, H-11), 6.93 (dd, 1 H, J 8.5, 1.7, H-9), 3.87 (s, 3 H, H-14), 3.79 (d, 1 H, J 13.7, H-2), 3.75 (d, 1 H, J 13.7, H-2'), 3.74 (s, 3 H, H-1)

\[ \delta_C \] (100 MHz, CDCl₃): 171.8 (C=O), 169.0 (C=O), 150.8 (C=O), 139.8 (q), 133.0 (q), 132.3 (q), 131.3 (q), 129.5, 129.1, 127.9, 127.7, 127.5, 127.4, 126.1 (q), 125.8, 125.7, 124.8, 123.7, 115.4, 61.4 (q), 54.9, 53.4, 40.5

\( \nu_{\text{max}} \) (neat)/cm⁻¹: 2954, 1773, 1735, 1481, 1437, 1347, 1290, 1237, 1154, 1020, 860, 751, 676

HRMS (m/z - APCI): Found: 390.1339 \([M+H]^+\) \( \text{C}_{23}\text{H}_{20}\text{NO}_5 \) Requires: 390.1336
Dimethyl 3-(3-methoxybenzyl)-2-oxoindoline-1,3-dicarboxylate (401, Table 2.18, entry 4)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 3-methoxybenzyl bromide (25.9 µL, 0.185 mmol), catalyst 335 (13.8 mg, 0.0154 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at 3 °C for 120 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, Rf = 0.4), to afford 401 (50.6 mg, 89%, 74% ee) as a white amorphous solid. M.p. 96-98 °C; [α]D²⁰ = +49.4 (c = 0.4, CHCl₃).

CSP-HPLC analysis. Acquity UPC² step 1 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO₂, B = EtOH/CH₃CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.088 min (major enantiomer) and 2.545 min (minor enantiomer).

δH (400 MHz, CDCl₃):
- 7.73 (d, 1 H, J 8.1, H-11), 7.37 (dd, 1 H, J 7.5, 1.1, H-8), 7.30 (app. td, 1 H, J 8.1, 1.1, H-10), 7.22 (app. td, 1 H, J 7.5, 1.1, H-9), 6.95 (t, 1 H, J 7.6, H-6), 6.62 (dd, 2 H, J 7.6, 2.5, H-5), 6.47 (app. d, 1 H, J 7.6, H-7), 6.31 (app. t, 1 H, J 2.5, H-3), 3.94 (s, 3 H, H-1, 3.72 (s, 3 H, H-12), 3.60 (d, 1 H, J 13.5, H-2, 3.56 (s, 3 H, H-4), 3.55 (d, 1 H, J 13.5, H-2’)

δC (100 MHz, CDCl₃):
- 171.7 (C=O), 169.0 (C=O), 159.0 (C=O), 150.9 (q), 139.9 (q), 135.0 (q), 129.5, 128.9, 126.2 (q), 124.7, 123.6, 122.4, 115.3, 114.7, 113.4, 61.2 (q), 54.9, 53.9, 53.3, 40.5

νmax (neat)/cm⁻¹:
- 2956, 1769, 1736, 1603, 1466, 1436, 1288, 1231, 1153, 1045, 769, 697

HRMS (m/z - APCI):
- Found: 370.1271 [M+H]+ C₂₀H₂₀NO₆ Requires: 370.1285
Dimethyl 3-(3,5-dimethoxybenzyl)-2-oxoindoline-1,3-dicarboxylate (402, Table 2.18, entry 5)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 3,5-dimethoxybenzyl bromide (42.8 mg, 0.185 mmol), catalyst 335 (13.8 mg, 0.0154 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at 3 °C for 144 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, Rf = 0.5), to afford 402 (55.4 mg, 90%, 90% ee) as a white amorphous solid. M.p. 116-117 °C; [α]D20 = +61.7 (c = 0.4, CHCl3).

CSP-HPLC analysis. Acquity UPC2 step 3 – Trefoil CEL2 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2, B = EtOH/CH3CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.297 min (major enantiomer) and 2.401 min (minor enantiomer).

δH (400 MHz, CDCl3): 7.74 (d, 1 H, J 8.0, H-9), 7.36 (dd, 1 H, J 7.5, 1.0, H-6), 7.31 (app. td, 1 H, J 8.0, 1.0, H-8), 7.22 (app. td, 1 H, J 7.5, 1.0, H-7), 6.18 (t, 1 H, J 2.3, H-5), 5.98 (d, 2 H, J 2.3, H-3), 3.94 (s, 3 H, H-10), 3.72 (s, 3 H, H-1), 3.56 (s, 6 H, H-4), 3.55 (d, 1 H, J 13.4, H-2), 3.52 (d, 1 H, J 13.4, H-2’)

δC (100 MHz, CDCl3): 171.7 (C=O), 168.9 (C=O), 160.1 (C=O), 150.9 (q), 139.9 (q), 135.8 (q), 129.5, 126.3 (q), 124.7, 123.6, 115.3, 107.7, 99.9, 61.2 (q), 55.1, 53.9, 53.3, 40.8

νmax (neat)/cm⁻¹: 2959, 1767, 1738, 1593, 1436, 1343, 1202, 1062, 833, 763, 676

HRMS (m/z – DIP-APCI): Found: 399.1316 [M+H]+ C21H21NO7 Requires: 399.1313
Dimethyl 3-(3,5-di-tert-butylbenzyl)-2-oxoindoline-1,3-dicarboxylate (403, Table 2.18, entry 6)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), \( p \)-iodoanisole (36.1 mg, 0.154 mmol), 3,5-di-tert-butylbenzyl bromide (52.4 mg, 0.185 mmol), catalyst 335 (13.8 mg, 0.0154 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at 3 °C for 120 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, \( R_f = 0.4 \)), to afford 403 (64.0 mg, 92%, 84% ee) as a white amorphous solid. M.p. 102-105 °C; \([\alpha]_D^{20} = +40.6 \) (c = 0.5, CHCl₃).

CSP-HPLC analysis. Acquity UPC² step 1 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO₂, B = EtOH/CH₃CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 1.685 min (minor enantiomer) and 1.833 min (major enantiomer).

\[ \delta_H \text{ (400 MHz, CDCl}_3\text{):} \]
7.65 (d, 1 H, J 8.2, H-9), 7.38 (dd, 1 H, J 6.7, 2.0, H-6), 7.27-7.18 (m, 2 H, H-7 and H-8), 7.07 (t, 1 H, J 1.8, H-5), 6.63 (d, 2 H, J 1.8, H-3), 3.88 (s, 3 H, H-10), 3.73 (s, 3 H, H-1), 3.62 (d, 1 H, J 13.2, H-2), 3.54 (d, 1 H, J 13.2, H-2), 1.10 (s, 18 H, H-4)

\[ \delta_C \text{ (100 MHz, CDCl}_3\text{):} \]
171.8 (C=O), 169.1 (C=O), 150.9 (C=O), 150.1 (q), 139.8 (q), 132.3 (q), 129.2, 126.5 (q), 124.6, 124.3, 123.7, 120.5, 115.1, 61.6 (q), 53.6, 53.2, 41.6, 34.5 (q), 31.1

\[ \nu_{\text{max}} \text{ (neat)/cm}^{-1}: \]
2951, 1769, 1739, 1599, 1434, 1346, 1241, 1156, 1066, 894, 773, 753, 716

HRMS \( m/z \) - APCI: Found: 452.2425 \([M+H]^+\) \( \text{C}_{27}\text{H}_{34}\text{NO}_5 \) Requires: 452.2432
Dimethyl 3-(3-chlorobenzyl)-2-oxoindoline-1,3-dicarboxylate (404, Table 2.18, entry 7)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 3-chlorobenzyl bromide (24.3 µL, 0.185 mmol), catalyst 355 (13.8 mg, 0.0154 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at 3 °C for 144 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, Rf = 0.5), to afford 404 (>99% conv. by 'H NMR, 68% ee) as an off-white amorphous solid. M.p. 113-115 °C; [α]D20 = +60.0 (c = 0.4, CHCl3).

CSP-HPLC analysis. Acquity UPC² step 1 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2, B = EtOH/CH3CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.273 min (major enantiomer) and 2.482 min (minor enantiomer).

δH (400 MHz, CDCl3): 7.73 (d, 1 H, J 8.2, H-10), 7.35 (dd, 1 H, J 7.3,1.0, H-7), 7.32 (app. td, 1 H, J 8.2, 1.0, H-9), 7.23 (app. td, 1 H, J 7.3, 1.0, H-8), 7.06 (app. dt, 1 H, J 7.8, 1.0, H-4), 6.97 (t, 1 H, J 7.8, H-5), 6.83 (app. t, 1 H, J 1.6, H-3), 6.73 (app. d, 1 H, J 7.8, H-6), 3.95 (s, 3 H, H-11), 3.70 (s, 3 H, H-1), 3.58 (d, 1 H, J 13.6, H-2), 3.53 (d, 1 H, J 13.6, H-2’)

δc (100 MHz, CDCl3): 171.5 (C=O), 168.7 (C=O), 150.8 (C=O), 139.7 (q), 135.7 (q), 133.7 (q), 130.0, 129.7, 129.2, 128.2, 127.4, 125.7 (q), 124.9, 123.5, 115.4, 61.0 (q), 54.0, 53.4, 40.0

νmax (neat)/cm⁻¹: 2956, 1771, 1735, 1435, 1346, 1346, 1286, 1234, 1153, 1079, 768, 753, 676

HRMS (m/z - APCI): Found: 374.0798 [M+H]+ C19H17ClNO5 Requires: 374.0790
Dimethyl 3-(4-bromobenzyl)-2-oxoindoline-1,3-dicarboxylate (405, Table 2.18, entry 8)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 4-bromobenzyl bromide (46.2 mg, 0.185 mmol), catalyst 335 (6.9 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at 3 °C for 144 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, Rf = 0.4), to afford 405 (>99% conv. by 1H NMR, 64% ee) as a white amorphous solid. M.p. 130-132 °C; [α]D20 = +53.2 (c = 0.4, CHCl3).

CSP-HPLC analysis. Acquity UPC2 step 1 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2, B = EtOH/CH3CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.449 min (major enantiomer) and 2.565 min (minor enantiomer).

δH (400 MHz, CDCl3): 7.74 (d, 1 H, J 8.2, H-8), 7.36 (dd, 1 H, J 7.5, 1.2, H-5), 7.32 (app. td, 1 H, J 8.2, 1.2, H-7), 7.22 (app. td, 1 H, J 7.5, 1.2, H-6), 7.16 (app. d, 2 H, J 8.3, H-4), 6.72 (app. d, 2 H, J 8.3, H-3), 3.96 (s, 3 H, H-9), 3.71 (s, 3 H, H-1), 3.57 (d, 1 H, J 13.7, H-2), 3.52 (d, 1 H, J 13.7, H-2’)

δC (100 MHz, CDCl3): 171.6 (C=O), 168.8 (C=O), 150.8 (C=O), 139.8 (q), 132.7 (q), 131.7, 131.1, 129.7, 125.7 (q), 124.9, 123.5, 121.3 (q), 115.5, 61.1 (q), 54.0, 53.4, 39.6

νmax (neat)/cm⁻¹: 2955, 1775, 1733, 1479, 1438, 1347, 1287, 1234, 1152, 1020, 943, 752, 675

HRMS (m/z - APCI): Found: 418.0305 [M+H]+ C19H17BrNO5 Requires: 418.0285
Dimethyl 3-(3,5-difluorobenzyl)-2-oxoindoline-1,3-dicarboxylate (398, Table 2.18, entry 9)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 3,5-difluorobenzyl bromide (23.9 µL, 0.185 mmol), catalyst 355 (13.8 mg, 0.0154 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at 3 °C for 144 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, Rf = 0.3), to afford 398 (55.5 mg, 96%, 74% ee) as a white amorphous solid. M.p. 144-145 °C; [α]D20 = +55.5 (c = 0.3, CHCl3).

CSP-HPLC analysis. Acquity UPC2 step 2 – Trefoil CEL1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2, B = MeOH/IPA (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 1.136 min (minor enantiomer) and 1.438 min (major enantiomer).

δH (400 MHz, CDCl3): 7.78 (d, 1 H, J 9.0, H-8), 7.36-7.32 (m, 2 H, H-7 and H-5), 7.24 (app. t, 1 H, J 7.9, H-6), 6.54 (tt, 1 H, J 8.8, 2.4, H-4), 6.42-6.37 (m, 2 H, H-3), 3.98 (s, 3 H, H-9), 3.71 (s, 3 H, H-1), 3.59 (d, 1 H, J 13.7, H-2), 3.54 (d, 1 H, J 13.7, H-2')

δC (100 MHz, CDCl3): 171.4 (C=O), 168.4 (C=O), 162.4 (dd, JCF 235.9, 248.5) (q), 150.8 (C=O), 139.8 (q), 137.6 (t, JCF 9.2) (q), 129.9, 125.5 (q), 125.1, 123.4, 115.5, 112.9 (dd, JCF 11.6, 18.4), 102.8 (t, JCF 25.2), 60.8 (q), 54.1, 53.5, 39.8

δF (376 MHz, CDCl3): -110.1

νmax (neat)/cm⁻¹: 2959, 1770, 1736, 1596, 1437, 1230, 1155, 1014, 858

HRMS (m/z - APCI): Found: 376.0982 [M+H]+ C19H16F2NO5 Requires: 376.0991
Dimethyl 3-(3-nitrobenzyl)-2-oxoindoline-1,3-dicarboxylate (395, Table 2.18, entry 10)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 3-nitrobenzyl bromide (40.0 mg, 0.185 mmol), catalyst 335 (13.8 mg, 0.0154 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at 3 °C for 144 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, Rf = 0.3), to afford 396 (57.4 mg, 97%, 79% ee) as a white amorphous solid. M.p. 190-191 °C; [α]D^20 = +24.6 (c = 0.4, CHCl3).

CSP-HPLC analysis. Acquity UPC^2 step 2 – Trefoil CEL1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2, B = MeOH/IPA (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.196 min (minor enantiomer) and 2.593 min (major enantiomer).

δH (400 MHz, CDCl3): 7.98-7.95 (m, 1 H, H-5), 7.72 (d, 1 H, J 8.0, H-10), 7.66 (app. s, 1 H, H-3), 7.40 (dd, 1 H, J 7.5, 1.0, H-7), 7.33 (app. td, 1 H, J 8.0, 1.0, H-9), 7.29-7.24 (m, 3 H, H-8, H-6 and H-4), 3.95 (s, 3 H, H-11), 3.74 (s, 3 H, H-1), 3.72 (d, 1 H, J 13.6, H-2), 3.66 (d, 1 H, J 13.6, H-2”)

δC (100 MHz, CDCl3): 171.3 (C=O), 168.5 (C=O), 150.7 (C=O), 147.7 (q), 139.6 (q), 136.2, 135.8 (q), 130.0, 129.0, 125.2 (two signals, one of which is quaternary), 124.8, 123.5, 122.3, 115.5, 60.8 (q), 54.1, 53.3, 39.8

ν_{max} (neat)/cm^{-1}: 2957, 1767, 1736, 1528, 1436, 1236, 1155, 1079, 818, 729, 675

HRMS (m/z - APCI): Found: 385.1034 [M+H]^+ C_{19}H_{17}N_{2}O_{7} Requires: 385.1030

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Dimethyl 3-(4-nitrobenzyl)-2-oxoindoline-1,3-dicarboxylate (397, Table 2.18, entry 11)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 4-nitrobenzyl bromide (40.0 mg, 0.185 mmol), catalyst 335 (13.8 mg, 0.0154 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at 3 °C for 144 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, Rf = 0.5), to afford 397 (56.8 mg, 96%, 66% ee) as an off-white amorphous solid. M.p. 128-132 °C; [α]D20 = +71.9 (c = 0.3, CHCl3).

CSP-HPLC analysis. Acquity UPC² step 2 – Trefoil CEL1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO₂, B = MeOH/IPA (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.344 min (minor enantiomer) and 2.544 min (major enantiomer).

δH (400 MHz, CDCl3): 7.91 (app. d, 2 H, J 8.7, H-4), 7.74 (d, 1 H, J 8.2, H-8), 7.39 (dd, 1 H, J 7.4, 1.1, H-5), 7.34 (app. td, 1 H, J 8.2, 1.1, H-7), 7.25 (app. td, 1 H, J 7.4, 1.1, H-6), 7.04 (app. d, 2 H, J 8.7, H-3), 3.96 (s, 3 H, H-9), 3.73 (s, 3 H, H-1), 3.72 (d, 1 H, J 13.4, H-2), 3.66 (d, 1 H, J 13.4, H-2’)

δC (100 MHz, CDCl3): 171.3 (C=O), 168.5 (C=O), 150.6 (C=O), 147.1 (q), 141.5 (q), 139.7 (q), 130.9, 130.0, 125.2 (q), 125.1, 123.4, 123.1, 115.6, 60.9 (q), 54.2, 53.6, 39.8

νmax (neat)/cm⁻¹: 2957, 1770, 1735, 1603, 1519, 1438, 1345, 1287, 1233, 1155, 1020, 857, 752, 675

HRMS (m/z - APCI): Found: 385.1024 [M+H]+ C19H17N2O7 Requires: 385.1030
Dimethyl 3-(4-cyanobenzyl)-2-oxoindoline-1,3-dicarboxylate (406, Table 2.18, entry 12)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), \( p \)-iodoanisole (36.1 mg, 0.154 mmol), 4-(bromomethyl)benzonitrile (36.3 mg, 0.185 mmol), catalyst 335 (13.8 mg, 0.0154 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at 3 °C for 192 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, \( R_f = 0.5 \)), to afford 406 (>99% conv. by \(^1\)H NMR, 62% ee) as a white amorphous solid. M.p. 147-150 °C; \([\alpha]_D^{20} = +60.8 \) (c = 0.4, CHCl₃).

CSP-HPLC analysis. Acquity UPC² step 2 – Trefoil CEL1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO₂, B = MeOH/IPA (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.075 min (minor enantiomer) and 2.235 min (major enantiomer).

\[ \delta_H \text{ (400 MHz, CDCl}_3\text{):} \]
7.73 (d, 1 H, \( J = 8.2 \), H-8), 7.38-7.31 (m, 4 H, H-7, H-5 and H-4), 7.23 (app. td, 1 H, \( J = 7.4 \), 1.1, H-6), 6.97 (app. d, 2 H, \( J = 8.3 \), H-3), 3.96 (s, 3 H, H-9), 3.71 (s, 3 H, H-1), 3.67 (d, 1 H, \( J = 13.4 \), H-2), 3.61 (d, 1 H, \( J = 13.4 \), H-2’)

\[ \delta_C \text{ (100 MHz, CDCl}_3\text{):} \]
171.3 (C=O), 168.5 (C=O), 150.6 (C=O), 139.7 (q), 139.3 (q), 131.7, 130.8, 130.0, 125.3 (q), 125.1, 123.4, 118.5 (q), 115.5, 111.2 (q), 60.9 (q), 54.15, 53.5, 40.1

\[ \nu_{\text{max}} \text{ (neat)/cm}^{-1}: \]
2960, 1765, 1736, 1479, 1437, 1346, 1288, 1231, 1154, 1080, 935, 852, 764, 675

HRMS (\(m/z \) - APCI):
Found: 365.1147 [M+H]+ \( C_{20}H_{17}N_2O_5 \) Requires: 365.1132
Dimethyl 2-oxo-3-(4-(trifluoromethyl)benzyl)indoline-1,3-dicarboxylate (407, Table 2.18, entry 13)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 4-(trifluoromethyl)benzyl bromide (28.6 µL, 0.185 mmol), catalyst 355 (6.9 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 24 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, Rf = 0.4), to afford 407 (59.0 mg, 94%, 68% ee) as a white amorphous solid. M.p. 155-156 °C; [α]D^20 = +50.6 (c = 0.2, CHCl3).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.5 mL min⁻¹, rt, UV detection at 254 nm, retention times: 21.187 min (minor enantiomer) and 25.320 min (major enantiomer).

δH (400 MHz, CDCl3): 7.74 (d, 1 H, J 7.7, H-8), 7.38 (dd, 1 H, J 7.7, 1.0, H-5), 7.33 (app. td, 1 H, J 7.7, 1.0, H-7), 7.30 (d, 2 H, J 7.4, H-4), 7.24 (app. td, 1 H, J 7.7, 1.0, H-6), 6.97 (d, 2 H, J 7.4, H-3), 3.95 (s, 3 H, H-9), 3.72 (s, 3 H, H-1), 3.67 (d, 1 H, J 13.6, H-2), 3.62 (d, 1 H, J 13.6, H-2')

δC (100 MHz, CDCl3): 171.4 (C=O), 168.7 (C=O), 150.7 (C=O), 139.7 (q), 137.9 (q), 130.4, 129.8, 129.4 (q, J_C-F 33.1) (q), 125.6 (q), 125.0, 124.9 (q, J_C-F 3.8), 124.0 (q, J_C-F 272.4) (q), 123.5, 115.5, 61.0 (q), 54.0, 53.5, 39.9

δF (376 MHz, CDCl3): -62.7

ν_max (neat)/cm⁻¹: 2957, 1775, 1735, 1480, 1440, 1348, 1323, 1287, 1242, 1153, 1066, 1019, 851, 752, 675

HRMS (m/z - APCI): Found: 408.1063 [M+H]^+  C_{20}H_{17}F_{3}NO_{5} Requires: 408.1053
Dimethyl 3-(2-fluorobenzyl)-2-oxoindoline-1,3-dicarboxylate (408, Table 2.18, entry 14)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 2-fluorobenzyl bromide (22.3 µL, 0.185 mmol), catalyst 335 (6.9 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 48 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, Rf = 0.3), to afford 408 (>99% conv. by 1H NMR, 59% ee) as a white amorphous solid. M.p. 139-140 °C; [α]D20 = +39.5 (c = 0.4, CHCl3).

CSP-HPLC analysis. Acquity UPC2 step 1 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2, B = Ethanol/CH3CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 1.691 min (major enantiomer) and 2.004 min (minor enantiomer).

δH (400 MHz, CDCl3): 7.72 (d, 1 H, J 8.1, H-10), 7.35 (app. dt, 1 H, J 7.7, 1.4, H-7), 7.28 (app. td, 1 H, J 7.7, 1.4, H-9), 7.16 (app. td, 1 H, J 8.1, 1.4, H-8), 7.09-7.03 (m, 2 H, H-4 and H-3), 6.88 (td, 1 H, J 7.2, 0.9, H-5), 6.77 (app. td, 1 H, J 7.2, 0.9, H-6), 3.98 (s, 3 H, H-11), 3.71 (s, 3 H, H-1), 3.86 (d, 1 H, J 13.9, H-2), 3.54 (d, 1 H, J 13.9, H-2’)

δC (100 MHz, CDCl3): 171.9 (C=O), 168.8 (C=O), 160.8 (d, J_{C-F} 247.1) (q), 151.0 (C=O), 139.5 (q), 131.5 (d, J_{C-F} 3.8), 129.5, 129.1 (d, J_{C-F} 8.5), 125.6 (q), 124.7, 124.2 (d, J_{C-F} 2.9), 123.8, 121.3 (d, J_{C-F} 15.4) (q), 115.1 (d, J_{C-F} 23.1), 114.9, 60.8 (q), 54.0, 53.4, 32.5

δF (376 MHz, CDCl3): -114.8
Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 2-iodobenzyl bromide (54.9 mg, 0.185 mmol), catalyst 335 (13.8 mg, 0.0154 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at 3 °C for 264 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, Rf = 0.4), to afford 409 (>99% conv. by 1H NMR, 53% ee) as a white amorphous solid. M.p. 121-122 °C; [α]D20 = -15.2 (c = 0.3, CHCl3).

CSP-HPLC analysis. Acquity UPC² step 1 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2, B = EtOH/CH3CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.501 min (major enantiomer) and 2.729 min (minor enantiomer).

δH (400 MHz, CDCl3): 7.81 (d, 1 H, J 8.1, H-10), 7.67 (dd, 1 H, J 8.1, 1.2, H-7), 7.31 (td, 1 H, J 8.0, 1.6, H-5) 7.22 (dd, 1 H, J 7.6, 1.6, H-9), 7.17-7.12 (m, 2 H, H-8 and H-6), 7.09 (td, 1 H, J 8.0, 1.6, H-4), 6.81 (app. td, 1 H, J 8.0, 1.6, H-8), 4.02 (s, 3 H, H-11), 3.98 (d, 1 H, J 14.4, H-2), 3.73 (d, 1 H, J 14.4, H-2'), 3.71 (s, 3 H, H-1)

δC (100 MHz, CDCl3): 171.8 (C=O), 168.8 (C=O), 151.1 (C=O), 139.7, 139.6 (q), 137.7 (q), 129.8, 129.5, 128.9, 128.1, 125.5 (q), 124.9, 124.6, 115.0, 103.5 (q), 60.6 (q), 54.1, 53.4, 43.6
$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 2959, 1764, 1736, 1479, 1436, 1346, 1287, 1229, 1155, 1078, 934, 852, 760, 675

HRMS (m/z - APCI): Found: 466.0154 [M+H]+ C$_{19}$H$_{17}$NO$_5$ Requires: 466.0146

Dimethyl 3-(2-nitrobenzyl)-2-oxoindoline-1,3-dicarboxylate (410, Table 2.18, entry 16)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 2-nitrobenzyl bromide (40.0 mg, 0.185 mmol), catalyst 335 (6.9 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 48 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, R$_f$ = 0.4), to afford 410 (>99% conv. by $^1$H NMR, 25% ee) as a pale yellow amorphous solid. M.p. 98-100 °C; $[\alpha]_D^{20}$ = -24.3 (c = 0.4, CHCl$_3$).

CSP-HPLC analysis. Acquity UPC$^2$ step 1 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO$_2$, B = EtOH/CH$_3$CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.268 min (major enantiomer) and 2.582 min (minor enantiomer).

$\delta$H (400 MHz, CDCl$_3$): 7.79 (d, 1 H, J 8.2, H-3), 7.75 (d, 1 H, J 8.0, H-10), 7.48-7.43 (m, 2 H, H-7 and H-5) 7.35-7.30 (m, 2 H, H-9 and H-4), 7.17-7.13 (m, 2 H, H-8 and H-6), 4.31 (d, 1 H, J 14.0, H-2), 3.89 (d, 1 H, J 14.0, H-2'), 3.97 (s, 3 H, H-11), 3.69 (s, 3 H, H-1)

$\delta$C (100 MHz, CDCl$_3$): 171.4 (C=O), 168.7 (C=O), 150.8 (C=O), 149.7 (q), 139.4 (q), 133.2, 132.7, 129.7, 129.5 (q), 128.4, 125.6 (q), 125.3, 124.9, 123.5, 115.2, 60.5 (q), 54.0, 53.5, 36.0

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v<sub>max</sub> (neat)/cm<sup>-1</sup>: 2958, 1770, 1737, 1525, 1436, 1287, 1234, 1157, 1048, 850, 769, 728, 675

HRMS (<i>m</i>/<i>z</i> - APCI): Found: 385.1018 [M+H]<sup>+</sup> C<sub>19</sub>H<sub>17</sub>N<sub>2</sub>O<sub>7</sub> Requires: 385.1030

**Dimethyl 3-allyl-2-oxoindoline-1,3-dicarboxylate (411, Table 2.19, entry 1)**

![Chemical Structure](image)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), <i>p</i>-iodoanisole (36.1 mg, 0.154 mmol), allyl bromide (16.0 µL, 0.185 mmol), catalyst 355 (6.9 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 118 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, <i>R</i><sub>f</sub> = 0.4), to afford 411 (50% conv. by <sup>1</sup>H NMR, 49% ee) as a white amorphous solid. M.p. 88-89 °C; [α]<sub>D</sub><sup>20</sup> = +35.7 (c = 0.5, CHCl<sub>3</sub>).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.5 mL min<sup>-1</sup>, rt, UV detection at 254 nm, retention times: 12.887 min (minor enantiomer) and 16.460 min (major enantiomer).

δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>): 7.94 (d, 1 H, J 8.4, H-8), 7.37 (td, 1 H, J 7.6, 1.2, H-5), 7.28 (app. td, 1 H, J 8.4, 1.2, H-7), 7.21 (app. td, 1 H, J 7.6, 1.2, H-6), 5.40-5.30 (m, 1 H, H-3), 5.09-4.95 (m, 2 H, H-4), 4.02 (s, 3 H, H-9), 3.67 (s, 3 H, H-1), 3.07-2.98 (m, 2 H, H-2)

δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>): 171.8 (C=O), 168.7 (C=O), 151.2 (C=O), 139.7 (q), 130.1, 129.5, 126.3 (q), 125.1, 123.3, 120.7, 115.4, 59.8 (q), 54.1, 53.3, 38.9

ν<sub>max</sub> (neat)/cm<sup>-1</sup>: 3087, 1766, 1734, 1479, 1437, 1346, 1290, 1219, 1137, 1020, 932, 766
HRMS (m/z – ESI): Found: 312.0851 [M+Na]^+ C_{15}H_{15}NNaO_{5} Requires: 312.0842

**Dimethyl 3-allyl-2-oxoindoline-1,3-dicarboxylate (411, Table 2.19, entry 2)**

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), allyl iodide (16.9 μL, 0.185 mmol), catalyst 335 (6.9 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 48 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, R_f = 0.4), to afford 411 (>99% conv. by ^1H NMR, 51% ee) as a white amorphous solid. M.p. 88-89 °C; [α]_D^{20} = +48.1 (c = 0.4, CHCl_3).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.5 mL min^{-1}, rt, UV detection at 254 nm, retention times: 12.793 min (minor enantiomer) and 16.240 min (major enantiomer).

δ_H (400 MHz, CDCl_3): 7.94 (d, 1 H, J 8.4, H-8), 7.37 (td, 1 H, J 7.6, 1.2, H-5), 7.28 (app. td, 1 H, J 8.4, 1.2, H-7), 7.21 (app. td, 1 H, J 7.6, 1.2, H-6), 5.40-5.30 (m, 1 H, H-3), 5.09-4.95 (m, 2 H, H-4), 4.02 (s, 3 H, H-9), 3.67 (s, 3 H, H-1), 3.07-2.98 (m, 2 H, H-2)

δ_C (100 MHz, CDCl_3): 171.8 (C=O), 168.7 (C=O), 151.2 (C=O), 139.7 (q), 130.1, 129.5, 126.3 (q), 125.1, 123.3, 120.7, 115.4, 59.8 (q), 54.1, 53.3, 38.9

ν_max (neat)/cm^{-1}: 3087, 1734, 1479, 1437, 1346, 1218, 1164, 1020, 932, 751

HRMS (m/z – ESI): Found: 312.0849 [M+Na]^+ C_{15}H_{15}NNaO_{5} Requires: 312.0842
Dimethyl 3-(2-methylallyl)-2-oxoindoline-1,3-dicarboxylate (412, Table 2.19, entry 3)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 3-bromo-2-methylprop-1-ene (18.7 µL, 0.185 mmol), catalyst 307 (7.2 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 192 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, Rf = 0.3), to afford 412 (85% conv. by 1H NMR, 62% ee) as a white amorphous solid. M.p. 70-71 °C; [α]D²⁰ = +25.6 (c = 0.5, CHCl₃).

CSP-HPLC analysis. Acquity UPC² step 2 – Trefoil CEL1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO₂, B = MeOH/IPA (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 1.177 min (minor enantiomer) and 1.440 min (major enantiomer).

δH (400 MHz, CDCl₃):
7.93 (d, 1 H, J 8.3, H-8), 7.37 (td, 1 H, J 7.6, 1.4, H-5), 7.28 (app. td, 1 H, J 8.3, 1.4, H-7), 7.19 (app. td, 1 H, J 7.6, 1.4, H-6), 4.67-4.66 (m, 1 H, H-4), 4.65 (app. t, 1 H, J 1.4, H-4), 4.59 (app. s, 1 H, H-4’), 4.02 (s, 3 H, H-9), 3.66 (s, 3 H, H-1), 3.11 (d, 1 H, J 13.9, H-2), 3.04 (d, 1 H, J 13.9, H-2’), 1.34 (s, 3 H, H-3)

δC (100 MHz, CDCl₃):
172.0 (C=O), 169.0 (C=O), 151.3 (C=O), 139.8 (q), 138.9 (q), 129.5, 126.6 (q), 124.9, 123.7, 116.3, 115.4, 60.0 (q), 54.1, 53.3, 41.7, 23.7

νmax (neat)/cm⁻¹:
3084, 1794, 1773, 1733, 1480, 1438, 1344, 1209, 992, 905, 768

HRMS (m/z – ESI):
Found: 326.0992 [M+Na]+ C₁₆H₁₇NNaO₅ Requires: 326.0999
Dimethyl 3-(2-bromo-3-methylbut-2-en-1-yl)-2-oxoindoline-1,3-dicarboxylate (413, Table 2.19, entry 4)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 2,3-dibromoprop-1-ene (22.6 µL, 0.185 mmol), catalyst 307 (7.2 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 12 days. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, Rf = 0.4), to afford 413 (66% conv. by 1H NMR, 57% ee) as a white amorphous solid. M.p. 79-81 °C; [α]D^20 = +13.8 (c = 0.2, CHCl3).

CSP-HPLC analysis. Acquity UPC^2 step 2 – Trefoil CEL1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2, B = MeOH/IPA (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 1.561 min (minor enantiomer) and 1.937 min (major enantiomer).

δH (400 MHz, CDCl3):
- 7.96 (d, 1 H, J 8.2, H-7), 7.40 (td, 1 H, J 7.7, 1.4, H-4), 7.26 (app. dd, 1 H, J 8.2, 1.4, H-6), 7.20 (app. td, 1 H, J 7.7, 1.4, H-5), 5.57 (app. s, 1 H, H-3a), 5.36 (d, 1 H, J 1.8, H-3b), 4.04 (s, 3 H, H-8), 3.67 (s, 3 H, H-1), 3.59 (d, 1 H, J 14.8, H-2), 3.52 (d, 1 H, J 14.8, H-2’)

δC (100 MHz, CDCl3):
- 171.5 (C=O), 168.4 (C=O), 151.2 (C=O), 140.2 (q), 129.8, 125.3 (q), 124.9 (two signals, one of which is quaternary), 124.2, 122.6, 115.6, 59.6 (q), 54.2, 53.6, 44.6

νmax (neat)/cm^-1:
- 3058, 1766, 1728, 1482, 1432, 1345, 1291, 1224, 1148, 1005, 901, 752

HRMS (m/z – ESI):
- Found: 389.9952 [M+Na]^+ C_{15}H_{14}BrNNaO_{5} Requires: 389.9948
**General procedure XVI:** Protocol for the synthesis of the iodo-substituted electrophiles *via* a Finkelstein reaction.

To a solution of sodium iodide (1.2 equiv.) in acetone (0.3 M) was added a solution of the appropriate chloro- or bromo-derivative (1.0 equiv.) dissolved in acetone (5 mL). The mixture was stirred overnight in the dark. Upon completion of the reaction (TLC), the solvent was removed *in vacuo* and the residue was dissolved in H$_2$O. The aqueous layer was extracted with CH$_2$Cl$_2$ (3x). The combined organic layers were washed with Na$_2$S$_2$O$_3$ solution (sat. aq.), brine and dried over MgSO$_4$. The solvent was removed *in vacuo* and the crude residue was purified by column chromatography on silica gel.

**2-Iodo-N-phenylacetamide (417)**

![Chemical Structure](image)

Synthesised according to a modified general procedure XVI, using 2-bromophenylacetamide (415, 0.5 g, 2.336 mmol) dissolved in CH$_3$CN (2.0 mL), NaI (0.42 g, 2.803 mmol) and acetone (7.8 mL). The crude product was washed with Et$_2$O to yield 417 (230 mg, 38%) as a white amorphous solid. M.p. 146-148 °C (lit.$^{299}$ 144-146 °C). The isolated compound exhibited identical spectroscopic data to those reported in the literature.$^{299}$

$\delta_H$ (400 MHz, CDCl$_3$): 7.65 (br s, 1 H, NH, H-2), 7.50 (d, 2 H, J 8.0, H-3), 7.35 (t, 2 H, J 8.0, H-4), 7.15 (t, 1 H, J 8.0, H-5), 3.86 (s, 2 H, H-1)

**2-Bromo-N-methoxy-N-methylacetamide (419)**

![Chemical Structure](image)

To a stirred suspension of $N,O$-dimethyl hydroxylamine hydrochloride (4.0 g, 41.0 mmol, 1.0 equiv.) and K$_2$CO$_3$ (28.3 g, 205.0 mmol, 5.0 equiv.) in anhydrous CH$_3$CN (41.0 mL, 1.0 M) at rt was added bromoacetyl bromide (8.2 mL, 94.3 mmol, 2.3 equiv.) dropwise *via* syringe. After 1 h, the reaction mixture was concentrated *in vacuo* and the residue was dissolved in H$_2$O (50 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (50 mL x 3). The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$.
and concentrated in vacuo to afford crude product which was purified by column chromatography on silica gel (hexane/EtOAc, 6:4, R_f = 0.3). The desired product 419 (6.2 g, 83%) was obtained as a clear oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.

δ_H (400 MHz, CDCl3): 4.00 (s, 2 H, H-1), 3.78 (s, 3 H, H-3), 3.22 (s, 3 H, H-2)

LRMS (m/z – DIP-APCI): Found: 181.98 [M+H]^+ C_4H_9BrNO_2 Requires: 180.97

2-Iodo-N-methoxy-N-methylacetamide (421)

Synthesised according to general procedure XVI, using 2-bromo-N-methoxy-N-methylacetamide (419, 3.76 g, 20.66 mmol), NaI (3.72 g, 24.79 mmol) and acetone (69.0 mL). The crude product was purified by column chromatography (100% CH_2Cl_2, R_f = 0.7), to afford 421 (4.4 g, 93%) as a yellow oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.

δ_H (400 MHz, CDCl3): 3.87 (s, 2 H, H-1), 3.80 (s, 3 H, H-3), 3.20 (s, 3 H, H-2)

HRMS (m/z – APCI): Found: 229.9666 [M+H]^+ C_4H_9INO_2 Requires: 229.9673

Dimethyl 3-(2-(methoxy(methyl)amino)-2-oxoethyl)-2-oxoindoline-1,3-dicarboxylate (420, Table 2.20, entry 3)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 2-iodo-N-methoxy-N-methylacetamide (421, 16.0 µL, 0.185 mmol), catalyst 335 (6.9 mg, 0.0077 mmol), PhMe (1.5 mL) and...
millipore water (15.0 mL). The reaction mixture was stirred at rt for 5 days. The crude product was purified by column chromatography on silica gel (100% EtOAc, Rf = 0.7), to afford 420 (>99% conv. by 1H NMR, 8% ee) as a yellow amorphous solid. M.p. 128-130 °C; [α]D 20 = +35.2 (c = 0.4, CHCl3).

CSP-HPLC analysis. Acquity UPC2 step 2 – Trefoil CEL1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2, B = MeOH/IPA (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 1.806 min (minor enantiomer) and 2.108 min (major enantiomer).

δH (400 MHz, CDCl3): 7.98 (d, 1 H, J 8.2, H-8), 7.35 (td, 1 H, J 7.6, 1.5, H-5), 7.22 (app. dd, 1 H, J 8.2, 1.5, H-7), 7.14 (app. td, 1 H, J 7.6, 1.5, H-6), 4.02 (s, 3 H, H-9), 3.75 (d, 1 H, J 17.8, H-2), 3.70 (s, 3 H, H-4), 3.64 (s, 3 H, H-1), 3.52 (d, 1 H, J 17.8, H-2'), 2.99 (s, 3 H, H-3)

δC (100 MHz, CDCl3): 172.6 (C=O), 169.1 (C=O), 168.7 (C=O), 151.4 (C=O), 140.8 (q), 129.5, 126.9 (q), 124.7, 122.2, 115.5, 61.3, 56.9 (q), 53.9, 53.5, 37.4, 31.9

νmax (neat)/cm⁻¹: 2923, 1793, 1746, 1659, 1392, 1322, 1209, 1168, 988, 818, 725

HRMS (m/z – APCI): Found: 351.1196 [M+H]⁺ C16H19N2O7 Requires: 351.1187

Dimethyl 2-oxo-3-(2-oxo-2-phenylethyl)indoline-1,3-dicarboxylate (423, Table 2.20, entry 4)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 2-chloro-1-phenylethan-1-one (422, 28.6 mg, 0.185 mmol), catalyst 307 (7.2 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore
water (15.0 mL). The reaction mixture was stirred at rt for 136 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, \( R_f = 0.5 \)), to afford 423 (14% conv. by \( ^1\)H NMR, 0% ee) as a white amorphous solid. M.p. 147-148 °C; [\( \alpha \)]\(_{D}^{20} \) = +12.5 (c = 0.1, CHCl\(_3\)).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min\(^{-1} \), rt, UV detection at 254 nm, retention times: 22.973 min and 29.900 min.

\[ \delta_H (400 MHz, CDCl_3): \]

8.05 (d, 1 H, J 8.2, H-9), 7.89 (d, 2 H, J 7.3, H-3), 7.56 (t, 1 H, J 7.3, H-5), 7.43 (app. t, 2 H, J 7.3, H-4), 7.37 (td, 1 H, J 7.5, 1.3, H-6), 7.20 (app. dd, 1 H, J 8.2, 1.3, H-8), 7.12 (app. td, 1 H, J 7.5, 1.3, H-7), 4.34 (d, 1 H, J 18.7, H-2), 4.08 (d, 1 H, J 18.7, H-2'), 4.07 (s, 3 H, H-10), 3.69 (s, 3 H, H-1)

\[ \delta_C (100 MHz, CDCl_3): \]

194.8 (C=O), 172.5 (C=O), 168.7 (C=O), 151.5 (C=O), 140.8 (q), 135.6 (q), 133.7, 129.5, 128.7, 128.2, 126.7 (q), 124.8, 122.1, 115.6, 56.9 (q), 54.0, 53.6, 43.8

\[ \nu_{\text{max}} \] (neat)/cm\(^{-1} \):

2960, 1793, 1740, 1684, 1438, 1347, 1245, 1159, 976, 727

HRMS (\( m/z \) – ESI):

Found: 390.0970 [M+Na]\(^+\) C\(_{20}\)H\(_{17}\)NO\(_6\)Na Requires: 390.0954

**Ethyl 2-iodoacetate (428)**

![Ethyl 2-iodoacetate](image)

Synthesised according to general procedure XVI, using ethyl bromoacetate (424, 5.0 mL, 45.21 mmol), NaI (8.13 g, 54.25 mmol) and acetone (151.0 mL). The crude product was purified by column chromatography (100% CH\(_2\)Cl\(_2\), \( R_f = 0.8 \)), to afford 428 (8.7 g, 90%) as a yellow oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.\(^{302}\)

\[ \delta_H (400 MHz, CDCl_3): \]

4.20 (q, 2 H, J 7.2, H-2), 3.68 (s, 2 H, H-1), 1.28 (t, 3 H, J 7.2, H-3)

LRMS (\( m/z \) – DIP-APCI):

Found: 214.95 [M+H]\(^+\) C\(_4\)H\(_8\)I\(_2\)O Requires: 213.95
*Tert*-butyl 2-iodoacetate (429)

Synthesised according to general procedure XVI, using *tert*-butyl bromoacetate (425, 5.0 mL, 33.86 mmol), NaI (6.10 g, 40.64 mmol) and acetone (113.0 mL). The crude product was purified by column chromatography (100% CH$_2$Cl$_2$, $R_f$ = 0.8), to afford 429 (7.8 g, 95%) as a yellow oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.$^{303}$

$\delta$$_H$ (400 MHz, CDCl$_3$): 3.60 (s, 2 H, H-1), 1.46 (s, 9 H, H-2)

$\delta$$_C$ (100 MHz, CDCl$_3$): 167.9 (C=O), 82.3 (q), 27.6, -2.6

2,2,2-Trifluoroethyl 2-bromoacetate (430)

A 25 mL round-bottomed flask containing a stirring bar and 2,2,2-trifluoroethanol (TFE, 2.26 mL, 30.08 mmol, 2.0 equiv.) was cooled to -10 °C using an ice-bath saturated with NaCl. Bromoacetyl bromide (1.31 mL, 15.04 mmol, 1.0 equiv.) was added to TFE dropwise via syringe. The mixture was allowed to warm to rt overnight. The excess TFE was removed *in vacuo* and the residue was dissolved in Et$_2$O (20 mL). The organic residue was washed with sat. aq. NaCl solution (20 mL x 3), dried over MgSO$_4$ and filtered through a short pad of basic alumina, packed with Et$_2$O. The alumina was flushed with Et$_2$O and the solvent was removed *in vacuo* to afford 430 (2.9 g, 87%) as a clear oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.$^{260}$

$\delta$$_H$ (400 MHz, CDCl$_3$): 4.55 (q, 2 H, J 8.3, H-2), 3.93 (s, 2 H, H-1)

LRMS ($m/z$ – APCI): Found: 218.9281 [M-H]$^-$ C$_4$H$_5$BrF$_3$O$_2$ Requires: 218.9274
2,2,2-Trifluoroethyl 2-iodoacetate (432)

![Structural formula]

Synthesised according to general procedure XVI, using 2,2,2-trifluoroethyl 2-bromoacetate (430, 1.49 g, 6.74 mmol), NaI (1.21 g, 8.09 mmol) and acetone (22.5 mL). The crude product was purified by column chromatography (100% CH₂Cl₂, Rᵣ = 0.8), to afford 432 (1.7 g, 94%) as a yellow oil.

δₜ (400 MHz, CDCl₃): 4.52 (q, 2 H, J 8.3, H-2), 3.79 (s, 2 H, H-1)

δₙ (100 MHz, CDCl₃): 167.4 (C=O), 122.7 (q, J_C-F 278.4) (q), 61.4, -8.0

δ₁₉ (376 MHz, CDCl₃): -73.7

νₘₐₓ (neat)/cm⁻¹: 2977, 1749, 1420, 1285, 1162, 1097, 976, 841

**Note:** The mass of the compound was not detected by HRMS.
Dimethyl 3-(2-ethoxy-2-oxoethyl)-2-oxoindoline-1,3-dicarboxylate (426, Table 2.21, entry 3)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), ethyl 2-iodoacetate (428, 22.0 mg, 0.185 mmol), catalyst 307 (7.2 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 7 days. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, Rf = 0.5), to afford 426 (80% conv. by 1H NMR, 36% ee) as an off-white amorphous solid. M.p. 78-79 °C; [α]D20 = +36.2 (c = 0.2, CHCl3).

CSP-HPLC analysis. Acquity UPC2 step 2 – Trefoil CEL1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2, B = MeOH/IPA (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 1.292 min (major enantiomer) and 1.585 min (minor enantiomer).

δH (400 MHz, CDCl3): 7.97 (d, 1 H, J 8.2, H-8), 7.37 (td, 1 H, J 7.6, 1.4, H-5), 7.24 (app. dd, 1 H, J 8.2, 1.4, H-7), 7.17 (app. td, 1 H, J 7.6, 1.4, H-6), 4.03 (s, 3 H, H-9), 3.98-3.83 (m, 2 H, H-3), 3.65 (s, 3 H, H-1), 3.45 (d, 1 H, J 17.2, H-2), 3.40 (d, 1 H, J 17.2, H-2’), 1.02 (t, 3 H, J 7.2, H-4)

δC (100 MHz, CDCl3): 172.0 (C=O), 168.7 (C=O), 168.0 (C=O), 151.3 (C=O), 140.5 (q), 129.8, 126.1 (q), 125.0, 122.6, 115.5, 61.1, 56.9 (q), 54.1, 53.6, 38.7, 13.7

νmax (neat)/cm⁻¹: 2959, 1774, 1726, 1436, 1346, 1290, 1235, 1154, 1020, 859, 754

HRMS (m/z – APCI): Found: 336.1086 [M+H]+ C16H18NO7 Requires: 336.1078
Dimethyl 3-(2-(tert-butoxy)-2-oxoethyl)-2-oxoindoline-1,3-dicarboxylate (427, Table 2.21, entry 4)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), tert-butyl 2-iodoacetate (429, 28.0 µL, 0.185 mmol), catalyst 307 (7.2 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 8 days. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, $R_f = 0.4$), to afford 427 (66% conv. by $^1$H NMR, 38% ee) as a white amorphous solid. M.p. 100-102 °C; $[\alpha]_D^{20} = +23.1$ ($c = 0.2$ CHCl$_3$).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 1.0 mL min$^{-1}$, rt, UV detection at 254 nm, retention times: 14.020 min (major enantiomer) and 17.187 min (minor enantiomer).

$\delta$H (400 MHz, CDCl$_3$): 7.99 (d, 1 H, J 8.2, H-7), 7.38 (td, 1 H, J 7.6, 1.4, H-4), 7.25 (app. dd, 1 H, J 8.2, 1.4, H-6), 7.17 (app. td, 1 H, J 7.6, 1.4, H-5), 4.03 (s, 3 H, H-8), 3.64 (s, 3 H, H-1), 3.78 (d, 1 H, J 16.5, H-2), 3.32 (d, 1 H, J 16.5, H-2’), 1.10 (s, 9 H, H-3)

$\delta$C (100 MHz, CDCl$_3$): 171.9 (C=O), 168.0 (C=O), 167.4 (C=O), 151.4 (C=O), 140.5 (q), 129.7, 126.3 (q), 125.0, 122.8, 115.5, 81.9 (q), 57.1 (q), 54.0, 53.6, 39.9, 27.4

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 3003, 1794, 1745, 1478, 1437, 1361, 1238, 1152, 1043, 982, 847, 777

HRMS (m/z – DIP-APCI): Found: 363.1316 [M]$^+$ C$_{18}$H$_{21}$NO$_7$ Requires: 363.1313
Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), \( p \)-iodoanisole (36.1 mg, 0.154 mmol), 2,2,2-trifluoroethyl 2-bromoacetate (430, 40.9 mg, 0.185 mmol), catalyst 307 (7.2 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 6 days. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, \( R_f = 0.5 \)), to afford 431 (66% conv. by \( ^1H \) NMR, 60% ee) as a white amorphous solid. M.p. 95-97 °C; [\( \alpha \)]\(_D^{20} = +52.4 \) (c = 0.4, CHCl\(_3\)).

CSP-HPLC analysis. Acquity UPC\(^2\) step 3 line 2 – Trefoil CEL2 (2.5 \( \mu \)m, 3.0 x 150 mm), gradient eluent A = CO\(_2\) (95%), B = Methanol/IPA (1:1, \( v:v \)); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 1.185 min (major enantiomer) and 1.435 min (minor enantiomer).

\( \delta_H \) (400 MHz, CDCl\(_3\)): 8.00 (d, 1 H, \( J \) 8.2, H-7), 7.40 (td, 1 H, \( J \) 7.6, 1.5, H-4), 7.25 (app. dd, 1 H, \( J \) 8.2, 1.5, H-6), 7.19 (app. td, 1 H, \( J \) 7.6, 1.5, H-5), 4.30-4.22 (m, 2 H, H-3), 4.04 (s, 3 H, H-8), 3.67 (s, 3 H, H-1), 3.57 (d, 1 H, \( J \) 17.6, H-2), 3.52 (d, 1 H, \( J \) 17.6, H-2’)

\( \delta_C \) (100 MHz, CDCl\(_3\)): 171.5 (C=O), 167.7 (C=O), 167.4 (C=O), 151.1 (C=O), 140.4 (q), 130.1, 125.4 (q), 125.2, 122.5, 122.4 (q, \( J_{C-F} \) 277.4) (q), 115.7, 60.7 (q, \( J_{C-F} \) 37.7), 56.7 (q), 54.1, 53.7, 38.0

\( \delta_F \) (376 MHz, CDCl\(_3\)): -74.0

\( \nu_{\text{max}} \) (neat)/cm\(^{-1}\): 2940, 1794, 1745, 1438, 1361, 1243, 1156, 1050, 981

HRMS (\( m/z \) – APCI): Found: 390.0788 [M+H]\(^+\) \( C_{16}H_{15}F_3NO_7 \) Requires: 390.0795

289
Dimethyl 2-oxo-3-(2-oxo-2-(2,2,2-trifluoroethoxy)ethyl)indoline-1,3-dicarboxylate (431, Table 2.21, entry 7)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 2,2,2-trifluoroethyl 2-iodoacetate (432, 49.6 mg, 0.185 mmol), catalyst 307 (7.2 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 24 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, Rf = 0.5), to afford 431 (>99% conv. by 1H NMR, 54% ee) as a white amorphous solid. M.p. 95-97 °C; [α]D20 = +35.1 (c = 0.5, CHCl3).

CSP-HPLC analysis. Acquity UPC² step 3 line 2 – Trefoil CEL2 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2 (95%), B = Methanol/IPA (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 1.226 min (major enantiomer) and 1.497 min (minor enantiomer).

δH (400 MHz, CDCl3): 8.00 (d, 1 H, J 8.2, H-7), 7.40 (td, 1 H, J 7.6, 1.5, H-4), 7.25 (app. dd, 1 H, J 8.2, 1.5, H-6), 7.19 (app. td, 1 H, J 7.6, 1.5, H-5), 4.30-4.22 (m, 2 H, H-3), 4.04 (s, 3 H, H-8), 3.67 (s, 3 H, H-1), 3.57 (d, 1 H, J 17.6, H-2), 3.52 (d, 1 H, J 17.6, H-2’)

δC (100 MHz, CDCl3): 171.5 (C=O), 167.7 (C=O), 167.4 (C=O), 151.1 (C=O), 140.4 (q), 130.1, 125.4 (q), 125.2, 122.5, 122.4 (q, JCF 277.4) (q), 115.7, 60.7 (q, JCF 37.7), 56.7 (q), 54.1, 53.7, 38.0

δF (376 MHz, CDCl3): -74.0

νmax (neat)/cm⁻¹: 2940, 1777, 1734, 1406, 1344, 1243, 1156, 976, 751

HRMS (m/z – APCI): Found: 390.0799 [M+H]+ C16H13F3NO7 Requires: 390.0795

290
**General procedure XVII:** Preparation of the substituted phenyl 2-chloroacetates.

To a solution of the appropriate phenol (1.0 equiv.) in anhydrous Et₂O (1.0 M) was added freshly distilled Et₃N (1.5 equiv.) and DMAP (10 mol%). Chloroacetyl chloride (1.1 equiv.) was then added via syringe and the resulting suspension was stirred at rt. After 1h, H₂O was added and the layers were separated. The aqueous layer was extracted with EtOAc (3x). The combined organic extracts were washed with NH₄Cl solution (sat., aq.), brine and dried over MgSO₄. The solvent was removed *in vacuo* and the crude residue was purified by column chromatography on silica gel.

**Phenyl 2-chloroacetate (435)**

\[
\begin{array}{c}
\text{Phenyl 2-chloroacetate (435)}
\end{array}
\]

Synthesised according to general procedure XVII, using phenol (433, 3.0 g, 31.88 mmol), Et₂O (32.0 mL), Et₃N (6.7 mL, 47.82 mmol), DMAP (0.39 g, 3.19 mmol) and chloroacetyl chloride (434, 2.8 mL, 35.07 mmol). The crude product was purified by column chromatography (100% CH₂Cl₂, Rf = 0.8), affording 435 (3.4 g, 63%) as a yellow oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³⁰⁴

\[
\delta_H (400 \text{ MHz, CDCl}_3): \begin{align*}
7.41 & \text{(app. t, 2 H, J 7.9, H-3),} \\
7.27 & \text{(app. t, 1 H, J 7.9, H-4),} \\
7.14 & \text{(app. d, 2 H, J 7.9, H-2),} \\
4.31 & \text{(s, 2 H, H-1)}
\end{align*}
\]

HRMS (m/z – EI): Found: 171.0213 [M+H]+ CsH₈ClO₂ Requires: 171.0207

**3,5-Di-tert-butylphenyl 2-chloroacetate (437a)**

\[
\begin{array}{c}
\text{3,5-Di-tert-butylphenyl 2-chloroacetate (437a)}
\end{array}
\]

Synthesised according to general procedure XVII, using 3,5-di-tert-butyl phenol (2.2 g, 10.66 mmol), Et₂O (11.0 mL), Et₃N (2.2 mL, 16.0 mmol), DMAP (0.13 g, 1.07 mmol) and chloroacetyl chloride (0.93 mL, 11.73 mmol). The crude product was purified by column chromatography (hexane/EtOAc, 9:1, Rf = 0.4), affording 437a (2.3 g, 78%) as a clear oil.
δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}): 7.32 (app. s, 1 H, H-4), 6.95 (d, 2 H, J 1.4, H-2), 4.31 (s, 2 H, H-1), 1.33 (s, 18 H, H-3)

δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}): 166.0 (C=O), 152.5 (q), 150.1 (q), 120.3, 115.2, 41.1, 35.0 (q), 31.3

ν\textsubscript{max} (neat)/cm\textsuperscript{-1}: 2959, 2906, 1779, 1589, 1419, 1245, 1136, 965, 862, 704

HRMS (m/z – DIP-APCI): Found: 282.1380 [M]+ C\textsubscript{16}H\textsubscript{23}ClO\textsubscript{2} Requires: 282.1381

4-Nitrophenyl 2-chloroacetate (438a)

Synthesised according to general procedure XVII, using 4-nitrophenol (4.0 g, 28.75 mmol), Et\textsubscript{2}O (28.8 mL), Et\textsubscript{3}N (6.0 mL, 43.13 mmol), DMAP (0.35 g, 2.88 mmol) and chloroacetyl chloride (2.5 mL, 31.63 mmol). The crude product was purified by column chromatography (100% CH\textsubscript{2}Cl\textsubscript{2}, R\textsubscript{f} = 0.8), affording 438a (3.0 g, 48%) as yellow crystals. M.p. 97-99 °C (lit.\textsuperscript{305} 95-98 °C). The isolated compound exhibited identical spectroscopic data to those reported in the literature.\textsuperscript{306}

δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}): 8.30 (d, 2 H, J 9.1, H-3), 7.35 (d, 1 H, J 9.1, H-2), 4.35 (s, 2 H, H-1)

2,4,6-Tribromophenyl 2-chloroacetate (439a)

Synthesised according to general procedure XVII, using 2,4,6-tribromophenol (5.0 g, 15.12 mmol), Et\textsubscript{2}O (15.0 mL), Et\textsubscript{3}N (3.2 mL, 22.67 mmol), DMAP (0.18 g, 1.51 mmol) and chloroacetyl chloride (1.3 mL, 16.63 mmol). The crude product was purified by column chromatography (hexane/EtOAc, 9:1, R\textsubscript{f} = 0.5), affording 439a (4.5 g, 73%) as a white amorphous solid. M.p. 121-123 °C (lit.\textsuperscript{306} 118.5-119.5 °C).

δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}): 7.73 (s, 2 H, H-2), 4.40 (s, 2 H, H-1)

δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}): 163.5 (C=O), 145.0 (q), 135.0, 120.5 (q), 118.0 (q), 40.3
2-Bromophenyl 2-chloroacetate (440a)

Synthesised according to general procedure XVII, using 2-bromophenol (2.0 mL, 17.34 mmol), Et₂O (17.3 mL), Et₃N (3.6 mL, 26.01 mmol), DMAP (0.21 g, 1.73 mmol) and chloroacetyl chloride (1.5 mL, 19.07 mmol). The crude product was purified by column chromatography (100% CH₂Cl₂, Rf = 0.8), affording 440a (3.7 g, 86%) as a pale yellow oil.

δ_H (400 MHz, CDCl₃): 7.63 (d, 1 H, J 7.6, H-5), 7.36 (app. td, 1 H, J 7.6, 1.5, H-3), 7.19-7.15 (m, 2 H, H-4 and H-2), 4.37 (s, 2 H, H-1)

δ_C (100 MHz, CDCl₃): 165.0 (C=O), 147.6 (q), 113.4, 128.6, 127.8, 123.3, 115.7 (q), 40.6

ν_max (neat)/cm⁻¹: 2953, 1779, 1581, 1470, 1307, 1207, 1129, 1044, 928, 862, 756, 655


3-Bromophenyl 2-chloroacetate (441a)

Synthesised according to general procedure XVII, using 3-bromophenol (3.0 g, 17.34 mmol), Et₂O (17.3 mL), Et₃N (3.6 mL, 26.01 mmol), DMAP (0.21 g, 1.73 mmol) and chloroacetyl chloride (1.5 mL, 19.07 mmol). The crude product was purified by column chromatography (hexane/EtOAc, 9:1, Rf = 0.3), affording 441a (2.7 g, 63%) as a pale yellow oil.

δ_H (400 MHz, CDCl₃): 7.41 (d, 1 H, J 8.6, H-4), 7.33 (t, 1 H, J 2.1, H-5), 7.27 (t, 1 H, J 8.6, H-3), 7.10 (dd, 1 H, J 8.6, 2.1, H-2), 4.29 (s, 2 H, H-1)
δ_C (100 MHz, CDCl₃): 165.5 (C=O), 150.7 (q), 130.7, 129.6, 124.7, 122.5 (q), 120.0, 40.7

_ν_max (neat)/cm⁻¹:_ 2957, 1777, 1583, 1470, 1238, 1192, 1133, 937, 778, 673

**Note:** The mass of the compound was not detected by HRMS.

### 4-Bromophenyl 2-chloroacetate (442a)

![Structure of 4-Bromophenyl 2-chloroacetate](image)

Synthesised according to general procedure XVII, using 4-bromophenol (3.0 mL, 17.34 mmol), Et₂O (17.3 mL), Et₃N (3.6 mL, 26.01 mmol), DMAP (0.21 g, 1.73 mmol) and chloroacetyl chloride (1.5 mL, 19.07 mmol). The crude product was purified by column chromatography (100% CH₂Cl₂, R_f = 0.8), affording 442a (3.4 g, 79%) as a white amorphous solid. M. p. 45-46 °C (lit. 307 38-39 °C).

δ_H (400 MHz, CDCl₃): 7.52 (d, 2 H, J 8.9, H-3), 7.03 (d, 2 H, J 8.9, H-2), 4.29 (s, 2 H, H-1)

δ_C (100 MHz, CDCl₃): 165.6 (C=O), 149.3 (q), 132.7, 122.9, 119.5 (q), 40.7

### 4-Cyanophenyl 2-chloroacetate (443a)

![Structure of 4-Cyanophenyl 2-chloroacetate](image)

Synthesised according to general procedure XVII, using 4-cyanophenol (4.0 g, 33.58 mmol), Et₂O (34.0 mL), Et₃N (7.0 mL, 50.37 mmol), DMAP (0.41 g, 3.36 mmol) and chloroacetyl chloride (2.9 mL, 36.94 mmol). The crude product was purified by column chromatography (100% CH₂Cl₂, R_f = 0.8), affording 443a (3.2 g, 49%) as white needle-like crystals. M. p. 81-82 °C (lit. 308 73-75 °C).

δ_H (400 MHz, CDCl₃): 7.72 (d, 2 H, J 8.7, H-3), 7.30 (d, 2 H, J 8.7, H-2), 4.32 (s, 2 H, H-1)

δ_C (100 MHz, CDCl₃): 165.1 (C=O), 153.3 (q), 133.9, 122.3, 116.3 (q), 110.5 (q), 40.6
4-Chlorophenyl 2-chloroacetate (444a)

![Chemical structure of 4-Chlorophenyl 2-chloroacetate](image)

Synthesised according to general procedure XVII, using 4-chlorophenol (4.0 g, 31.11 mmol), Et₂O (31.0 mL), Et₃N (6.5 mL, 46.67 mmol), DMAP (0.38 g, 3.11 mmol) and chloroacetyl chloride (2.7 mL, 34.23 mmol). The crude product was purified by column chromatography (hexane/EtOAc, 8:2, R_f = 0.6), affording 444a (4.0 g, 63%) as a pale yellow oil.

δ_H (400 MHz, CDCl₃): 7.37 (d, 2 H, J 8.8, H-3), 7.08 (d, 2 H, J 8.8, H-2), 4.29 (s, 2 H, H-1)

δ_C (100 MHz, CDCl₃): 165.6 (C=O), 148.6 (q), 131.7 (q), 129.6, 122.4, 40.2

3,4-Dichlorophenyl 2-chloroacetate (445a)

![Chemical structure of 3,4-Dichlorophenyl 2-chloroacetate](image)

Synthesised according to general procedure XVII, using 3,4-dichlorophenol (4.0 g, 24.54 mmol), Et₂O (25.0 mL), Et₃N (5.1 mL, 36.81 mmol), DMAP (0.30 g, 2.45 mmol) and chloroacetyl chloride (2.1 mL, 26.99 mmol). The crude product was purified by column chromatography (100% CH₂Cl₂, R_f = 0.8), affording 445a (3.2 g, 54%) as a yellow oil.

δ_H (400 MHz, CDCl₃): 7.47 (d, 1 H, J 8.7, H-3), 7.30 (d, 1 H, J 2.7, H-2), 7.03 (dd, 1 H, J 8.7, 2.7, H-4), 4.29 (s, 2 H, H-1)

δ_C (100 MHz, CDCl₃): 165.3 (C=O), 148.8 (q), 133.2 (q), 130.9, 130.5 (q), 123.5, 120.8, 40.6

3,5-bis(Trifluoromethyl)phenyl 2-chloroacetate (446a)

![Chemical structure of 3,5-bis(Trifluoromethyl)phenyl 2-chloroacetate](image)

Synthesised according to general procedure XVII, using 3,5-bis(trifluoromethyl) phenol (5.0 mL, 32.83 mmol), Et₂O (33.0 mL), Et₃N (6.9 mL, 49.25 mmol), DMAP (0.4 g,
3.28 mmol) and chloroacetyl chloride (2.9 mL, 36.12 mmol). The crude product was purified by column chromatography (hexane/EtOAc, 8:2, R_f = 0.6), affording 446a (4.6 g, 46%) as an off-white amorphous solid. M.p. 70-72 °C.

δ_H (400 MHz, CDCl3): 7.81 (s, 1 H, H-3), 7.66 (s, 2 H, H-2), 4.35 (s, 2 H, H-1)
δ_C (100 MHz, CDCl3): 165.1 (C=O), 150.6 (q), 133.3 (q, J_C-F 34.4) (q), 122.5 (q, J_C-F 272.6) (q), 122.1, 120.3 (quint, J_C-F 3.8), 40.4
δ_F (376 MHz, CDCl3): -63.0
ν_max (neat)/cm⁻¹: 3099, 1778, 1462, 1366, 1275, 1121, 955, 802, 699, 683

Note: The mass of the compound was not detected by HRMS.

4-(Trifluoromethyl)phenyl 2-chloroacetate (447a)

![Chemical structure]

Synthesised according to general procedure XVII, using 4-trifluoromethyl phenol (3.0 g, 18.51 mmol), Et₂O (19.0 mL), Et₃N (3.9 mL, 27.76 mmol), DMAP (0.14 g, 1.85 mmol) and chloroacetyl chloride (1.6 mL, 20.36 mmol). The crude product was purified by column chromatography (100% CH₂Cl₂, R_f = 0.8), affording 447a (2.8 g, 64%) as a pale yellow oil.

δ_H (400 MHz, CDCl3): 7.69 (d, 2 H, J 8.6, H-3), 7.28 (d, 2 H, J 8.6, H-2), 4.33 (s, 2 H, H-1)
δ_C (100 MHz, CDCl3): 165.4 (C=O), 152.6 (q), 128.7 (q, J_C-F 33.2) (q), 126.9 (q, J_C-F 3.8), 123.6 (q, J_C-F 276.6) (q), 121.7, 40.7
ν_max (neat)/cm⁻¹: 2961, 1780, 1614, 1513, 1414, 1322, 1205, 1168, 1120, 1063, 1017, 928, 829, 791, 696

Note: The mass of the compound was not detected by HRMS.

Phenyl 2-iodoacetate (436)

![Chemical structure]
Synthesised according to general procedure XVI, using phenyl 2-chloroacetate (435, 1.5 g, 8.792 mmol), NaI (1.6 g, 10.550 mmol) and acetone (29.3 mL). The crude product was purified by column chromatography (100% CH₂Cl₂, Rₖ = 0.8), affording 436 (2.1 g, 91%) as a white amorphous solid. M.p. 77-79 °C (lit. 309 75-77 °C). The isolated compound exhibited identical spectroscopic data to those reported in the literature.³¹⁰

δ_H (400 MHz, CDCl₃): 7.40 (t, 2 H, J 7.9, H-3), 7.26 (t, 1 H, J 7.9, H-4), 7.12 (d, 2 H, J 7.9, H-2), 3.91 (s, 2 H, H-1)


3,5-Di-tert-butylphenyl 2-iodoacetate (437)

![Diagram of 3,5-Di-tert-butylphenyl 2-iodoacetate (437)]

Synthesised according to general procedure XVI, using 3,5-di-tert-butylphenyl 2-chloroacetate (437a, 2.2 g, 7.67 mmol), NaI (4 g, 9.21 mmol) and acetone (25.6 mL). The crude product was purified by column chromatography (100% CH₂Cl₂, Rₖ = 0.8), affording 437 (2.5 g, 87%) as an off-white amorphous solid. M.p. 49-52 °C

δ_H (400 MHz, CDCl₃): 7.30 (app. t, 1 H, J 1.4, H-4), 6.95 (d, 2 H, J 1.4, H-2), 3.92 (s, 2 H, H-1), 1.32 (s, 18 H, H-3)

δ_C (100 MHz, CDCl₃): 167.5 (C=O), 152.4 (q), 150.3 (q), 120.2, 115.0, 35.0 (q), 31.3, -5.6

ν_max (neat)/cm⁻¹: 3055, 2956, 1746, 1415, 1241, 1076, 969, 918, 707

HRMS (m/z – DIP-APCI): Found: 375.0815 [M+H]⁺ C₁₆H₂₄IO₂ Requires: 375.0816

4-Nitrophenyl 2-iodoacetate (438)

![Diagram of 4-Nitrophenyl 2-iodoacetate (438)]

Synthesised according to general procedure SI, using 4-nitrophenyl 2-chloroacetate (438a, 2.8 g, 12.99 mmol), NaI (2.3 g, 15.59 mmol) and acetone (43.3 mL). The crude product was purified by column chromatography (100% CH₂Cl₂, Rₖ = 0.8), affording
438 (3.53 g, 88%) as a yellow amorphous solid. M.p. 79-82 °C (lit.311 80 °C). The isolated compound exhibited identical spectroscopic data to those reported in the literature.312

δ_H (400 MHz, CDCl₃): 8.30 (d, 2 H, J 9.0, H-3), 7.32 (d, 1 H, J 9.0, H-2), 3.94 (s, 2 H, H-1)

d_4,6-Tribromophenyl 2-iodoacetate (439)

Synthesised according to general procedure XVI, using 2,4,6-tribromophenyl 2-chloroacetate (439a, 0.7 g, 1.719 mmol), NaI (0.3 g, 2.062 mmol) and acetone (5.7 mL). The crude product was purified by column chromatography (100% CH₂Cl₂, R_f = 0.8), affording 439 (0.7 g, 81%) as an off-white crystalline solid. M.p. 67-68 °C.

δ_H (400 MHz, CDCl₃): 7.71 (s, 2 H, H-3 and H-2), 4.00 (s, 2 H, H-1)
δ_C (100 MHz, CDCl₃): 164.7 (C=O), 145.0 (q), 135.0, 120.3 (q), 118.4 (q), -8.4
ν max (neat)/cm⁻¹: 3080, 1764, 1552, 1437, 1204, 1065, 915, 853

Note: The mass of the compound was not detected by HRMS.

2-Bromophenyl 2-iodoacetate (440)

Synthesised according to general procedure XVI, using 2-bromophenyl 2-chloroacetate (440a, 3.5 g, 14.03 mmol), NaI (2.5 g, 16.83 mmol) and acetone (46.8 mL). The crude product was purified by column chromatography (100% CH₂Cl₂, R_f = 0.8), affording 440 (4.2 g, 88%) as an orange crystalline solid. M.p. 37-39 °C.

δ_H (400 MHz, CDCl₃): 7.61 (d, 1 H, J 8.1, H-5), 7.34 (td, 1 H, J 8.1, 0.9, H-3), 7.17-7.13 (m, 2 H, H-4 and H-2), 3.97 (s, 2 H, H-1)
δ_C (100 MHz, CDCl₃): 166.3 (C=O), 147.7 (q), 133.5, 128.5, 127.7, 123.1, 116.0 (q), -7.0
ν max (neat)/cm⁻¹: 3038, 1731, 1469, 1413, 1236, 1198, 1079, 924, 743

Note: The mass of the compound was not detected by HRMS.
3-Bromophenyl 2-iodoacetate (441)

Synthesised according to general procedure XVI, using 3-bromophenyl 2-chloroacetate (441a, 2.5 g, 10.02 mmol), NaI (1.8 g, 12.03 mmol) and acetone (33.4 mL). The crude product was purified by column chromatography (100% CH$_2$Cl$_2$, $R_f = 0.8$), affording 441 (2.8 g, 82%) as a yellow oil.

$\delta$H (400 MHz, CDCl$_3$): 7.39 (app. dt, 1 H, $J$ 8.2, 2.1, H-4), 7.32 (t, 1 H, $J$ 2.1, H-5), 7.25 (t, 1 H, $J$ 8.2, H-3), 7.07 (ddd, 1 H, $J$ 8.2, 2.1, 1.3, H-2), 3.88 (s, 2 H, H-1)

$\delta$C (100 MHz, CDCl$_3$): 165.8 (C=O), 150.7 (q), 130.4, 129.2, 124.3, 122.2 (q), 119.7, -6.3

$\nu$max (neat)/cm$^{-1}$: 3064, 1745, 1582, 1469, 1230, 1189, 1075, 934, 775


4-Bromophenyl 2-iodoacetate (442)

Synthesised according to general procedure XVI, using 4-bromophenyl 2-chloroacetate (442a, 3.4 g, 13.63 mmol), NaI (2.5 g, 16.35 mmol) and acetone (45.4 mL). The crude product was purified by column chromatography (100% CH$_2$Cl$_2$, $R_f = 0.8$), affording 442 (4.1 g, 83%) as an orange oil.

$\delta$H (400 MHz, CDCl$_3$): 7.51 (d, 2 H, $J$ 8.9, H-3), 7.01 (d, 2 H, $J$ 8.9, H-2), 3.90 (s, 2 H, H-1)

$\delta$C (100 MHz, CDCl$_3$): 167.0 (C=O), 149.3 (q), 132.4, 122.7 (q), 119.2, -6.2

$\nu$max (neat)/cm$^{-1}$: 3052, 1745, 1482, 1193, 1064, 919, 832

4-Cyanophenyl 2-iodoacetate (443)

\[
\begin{align*}
\text{Synthesised according to general procedure XVI, using 4-cyanophenyl 2-chloroacetate} \\
\text{(443a, 0.7 g, 3.32 mmol), NaI (0.6 g, 3.99 mmol) and acetone (11.1 mL). The crude} \\
\text{product was purified by column chromatography (100% CH}_2\text{Cl}_2, R_f = 0.8), \\
\text{affording 443 (0.8 g, 84%) as a yellow amorphous solid. M.p. 61-62 °C.} \\
\delta_H (400 MHz, CDCl}_3): & \quad 7.72 (d, 2 H, J 8.7, H-3), 7.27 (d, 2 H, J 8.7, H-2), 3.92 (s, 2 H, H-1) \\
\delta_C (100 MHz, CDCl}_3): & \quad 166.7 (C=O), 153.6 (q), 133.8, 122.2, 118.0 (q), 110.3 (q), -6.8 \\
\nu_{max} (neat)/cm^{-1}: & \quad 3094, 2228, 1758, 1556, 1410, 1210, 1066, 916, 854 \\
\text{HRMS (m/z – DIP-APCI):} & \quad \text{Found: 287.9528 [M+H]+ C}_9\text{H}_7\text{INO}_2 \text{Requires: 287.9516} \\
\end{align*}
\]

4-Chlorophenyl 2-iodoacetate (444)

\[
\begin{align*}
\text{Synthesised according to general procedure XVI, using 4-chlorophenyl 2-chloroacetate} \\
\text{(444a, 3.4 g, 16.58 mmol), NaI (3.0 g, 19.90 mmol) and acetone (55.3 mL). The crude} \\
\text{product was purified by column chromatography (100% CH}_2\text{Cl}_2, R_f = 0.8), \\
\text{affording 444 (4.3 g, 87%) as a pale yellow oil.} \\
\delta_H (400 MHz, CDCl}_3): & \quad 7.36 (d, 2 H, J 8.8, H-3), 7.07 (d, 2 H, J 8.8, H-2), 3.90 (s, 2 H, H-1) \\
\delta_C (100 MHz, CDCl}_3): & \quad 167.1 (C=O), 148.8 (q), 131.5 (q), 129.4, 122.3, -6.3 \\
\nu_{max} (neat)/cm^{-1}: & \quad 3052, 1745, 1484, 1236, 1196, 1075, 1013, 920, 834 \\
\text{Note:} & \quad \text{The mass of the compound was not detected by HRMS.} \\
\end{align*}
\]
3,4-Dichlorophenyl 2-iodoacetate (445)

Synthesised according to general procedure XVI, using 3,4-dichlorophenyl 2-chloroacetate (445a, 3.1 g, 12.95 mmol), NaI (2.3 g, 15.53 mmol) and acetone (43.2 mL). The crude product was purified by column chromatography (100% CH₂Cl₂, Rᵣ = 0.8), affording 445 (4.1 g, 94%) as a yellow oil.

δ_H (400 MHz, CDCl₃): 7.47 (d, 1 H, J 8.7, H-3), 7.27 (d, 1 H, J 2.7, H-2), 7.01 (dd, 1 H, J 8.7, 2.7, H-4), 3.89 (s, 2 H, H-1)

δ_C (100 MHz, CDCl₃): 166.8 (C=O), 148.9 (q), 132.9 (q), 130.7, 130.1 (q), 123.2, 120.6, -6.7

ν_max (neat)/cm⁻¹: 3094, 1750, 1590, 1465, 1228, 1199, 1117, 1076, 935, 811


3,5-Bis(trifluoromethyl)phenyl 2-iodoacetate (446)

Synthesised according to general procedure XVI, using 3,5-bis(trifluoromethyl)phenyl 2-chloroacetate (446a, 4.3 g, 14.03 mmol), NaI (2.5 g, 16.83 mmol) and acetone (46.8 mL). The crude product was purified by column chromatography (100% CH₂Cl₂, Rᵣ = 0.8), affording 446 (5.3 g, 94%) as an off-white amorphous solid. M.p. 78-81 °C.

δ_H (400 MHz, CDCl₃): 7.79 (s, 1 H, H-3), 7.62 (s, 2 H, H-2), 3.95 (s, 2 H, H-1)

δ_C (100 MHz, CDCl₃): 166.7 (C=O), 150.9 (q), 133.1 (q, J_C-F 33.9) (q), 122.6 (q, J_C-F 273.7) (q), 122.0 (dq, J_C-F 3.7, 0.9), 120.1 (sep, J_C-F 3.9), -7.5

δ_F (376 MHz, CDCl₃): -63.0

ν_max (neat)/cm⁻¹: 3071, 1757, 1461, 1369, 1276, 1128, 1074, 957, 901, 651

Note: The mass of the compound was not detected by HRMS.
4-(Trifluoromethyl)phenyl 2-iodoacetate (447)

Synthesised according to general procedure XVI, using 4-(trifluoromethyl)phenyl 2-chloroacetate (447a, 2.3 g, 9.64 mmol), NaI (1.7 g, 11.57 mmol) and acetone (32.0 mL). The crude product was purified by column chromatography (100% CH₂Cl₂, Rf = 0.8), affording 447 (3.0 g, 93%) as a yellow oil.

δ_H (400 MHz, CDCl₃): 7.68 (d, 2 H, J 8.6, H-3), 7.25 (d, 2 H, J 8.6, H-2), 3.93 (s, 2 H, H-1)

δ_C (100 MHz, CDCl₃): 167.0 (C=O), 152.9 (q, J_C-F 1.6) (q), 128.6 (q, J_C-F 32.8) (q), 126.9 (q, J_C-F 3.7), 123.7 (q, J_C-F 272.9) (q), 121.5, -6.7

δ_F (376 MHz, CDCl₃): -62.3

ν_max (neat)/cm⁻¹: 3057, 1752, 1612, 1512, 1321, 1235, 1120, 1061, 924, 845, 682

Dimethyl 2-oxo-3-(2-oxo-2-phenoxyethyl)indoline-1,3-dicarboxylate (448, Table 2.22, entry 1)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), phenyl 2-iodoacetate (436, 48.5 mg, 0.185 mmol), catalyst 335 (6.9 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 95 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, Rf = 0.3), affording 448 (55.5 mg, 94%, 52% ee) as a white amorphous solid. M.p. 147-148 °C; [α]D²⁰ = +40.2 (c = 0.4, CHCl₃).

CSP-HPLC analysis. Acquity UPC² step 3 – Trefoil CEL2 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO₂, B = EtOH/CH₃CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.278 min (major enantiomer) and 2.370 min (minor enantiomer).

δH (400 MHz, CDCl₃): 7.99 (d, 1 H, J 8.3, H-9), 7.41 (t, 1 H, J 7.9, H-5), 7.35 (d, 1 H, J 7.5, H-6), 7.28-7.21 (m, 3 H, H-8 and H-4), 7.15 (app. t, 1 H, J 7.5, H-7), 6.77 (d, 2 H, J 7.9, H-3), 4.00 (s, 3 H, H-10), 3.74-3.65 (app. s, 5 H, H-1, H-2 and H-2’)

δC (100 MHz, CDCl₃): 171.7 (C=O), 167.9 (C=O), 167.6 (C=O), 151.2 (C=O), 150.0 (q), 140.6 (q), 130.0, 129.4, 126.1, 125.8 (q), 125.1, 122.7, 121.2, 115.8, 56.9 (q), 54.1, 53.7, 38.8

νmax (neat)/cm⁻¹: 2957, 1776, 1730, 1481, 1347, 1292, 1243, 1152, 1054, 1011, 769, 749

HRMS (m/z – DIP-APCI): Found: 384.1070 [M+H]+ C₂₀H₁₈NO₇ Requires: 384.1078
Dimethyl 3-(2-(3,5-di-tert-butylphenoxy)-2-oxoethyl)-2-oxoindoline-1,3-dicarboxylate (449, Table 2.22, entry 2)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 3,5-di-tert-butylphenyl 2-iodoacetate (437, 69.2 mg, 0.185 mmol), catalyst 335 (6.9 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 69 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, R\text{f} = 0.3), affording 449 (71.0 mg, 93%, 41% ee) as a white amorphous solid. M.p. 110-112 °C; [\alpha]_D^{20} = +27.1 (c = 0.2, CHCl₃).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.5 mL min⁻¹, rt, UV detection at 254 nm, retention times: 13.260 min (minor enantiomer) and 15.273 min (major enantiomer).

δ\textsubscript{H} (400 MHz, CDCl₃): 8.01 (d, 1 H, J 8.2, H-9), 7.44-7.37 (m, 2 H, H-8 and H-6), 7.24 (app. t, 1 H, J 7.6, H-7), 7.18 (app. t, 1 H, J 1.4, H-5), 6.45 (d, 2 H, J 1.4, H-3), 4.00 (s, 3 H, H-10), 3.72 (d, 1 H, J 16.7, H-2), 3.70 (s, 3 H, H-1), 3.67 (d, 1 H, J 16.7, H-2'), 1.21 (s, 18 H, H-4)

δ\textsubscript{C} (100 MHz, CDCl₃): 171.7 (C=O), 167.9 (C=O), 167.4 (C=O), 152.2 (C=O), 151.2 (q), 149.6 (q), 140.7 (q), 130.0, 125.8 (q), 125.1, 122.9, 120.1, 115.8, 115.3, 57.1 (q), 54.1, 53.7, 38.9, 34.9 (q), 31.2

ν\textsubscript{max} (neat)/cm⁻¹: 2956, 1803, 1739, 1608, 1481, 1345, 1242, 1151, 1004, 966, 771

HRMS (m/z – DIP-APCI): Found: 496.2328 [M+H]+ C\textsubscript{28}H\textsubscript{34}NO\textsubscript{7} Requires: 496.2330
Dimethyl 3-(2-(4-nitrophenoxy)-2-oxoethyl)-2-oxoindoline-1,3-dicarboxylate (450, Table 2.22, entry 3)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 4-nitrophenyl 2-iodoacetate (438, 56.8 mg, 0.185 mmol), catalyst 335 (6.9 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 48 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, Rf = 0.2), affording 450 (59.4 mg, 90%, 47% ee) as a white amorphous solid. M.p. 114-116 °C; [α]D20 = +41.8 (c = 0.3, CHCl3).

CSP-HPLC analysis. Acquity UPC2 step 4 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2, B = EtOH/IPA (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 3.375 min (minor enantiomer) and 3.515 min (major enantiomer).

δH (400 MHz, CDCl3): 8.16 (d, 2 H, J 9.1, H-4), 7.99 (d, 1 H, J 8.1, H-8), 7.43 (app. t, 1 H, J 8.1, H-7), 7.35 (d, 1 H, J 7.6, H-5), 7.24 (app. t, 1 H, J 7.6, H-6), 7.00 (d, 2 H, J 9.1, H-3), 4.02 (s, 3 H, H-9), 3.75 (d, 1 H, J 17.3, H-2), 3.71 (s, 3 H, H-1), 3.68 (d, 1 H, J 17.3, H-2’)

δC (100 MHz, CDCl3): 171.5 (C=O), 167.7 (C=O), 166.8 (C=O), 154.5 (C=O), 151.0 (q), 145.5 (q), 140.4 (q), 130.3, 125.5 (q), 125.3, 125.1, 122.8, 122.2, 115.8, 56.8 (q), 54.2, 53.8, 38.7

νmax (neat)/cm⁻¹: 3118, 2955, 1763, 1737, 1528, 1481, 1342, 1241, 1139, 1055, 962, 753

HRMS (m/z – DIP-APCI): Found: 429.0919 [M+H]+ C20H17N2O9 Requires: 429.0929
Dimethyl 3-(2-(2-bromophenoxy)-2-oxoethyl)-2-oxoindoline-1,3-dicarboxylate
(452, Table 2.22, entry 5)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 2-bromophenyl 2-iodoacetate (440, 63.1 mg, 0.185 mmol), catalyst 335 (6.9 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 159 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, Rf = 0.3), affording 452 (29% conv. by 1H NMR, 49% ee) as a white amorphous solid. M.p. 111-113 °C; [α]D20 = +17.4 (c = 0.2, CHCl3).

CSP-HPLC analysis. Acquity UPC2 step 2 – Trefoil CEL1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO2, B = MeOH/IPA (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.424 min (major enantiomer) and 2.505 min (minor enantiomer).

δH (400 MHz, CDCl3): 7.98 (d, 1 H, J 8.2, H-10), 7.49 (d, 1 H, J 8.1, H-6), 7.42-7.35 (m, 2 H, H-7 and H-4), 7.24-7.19 (m, 2 H, H-9 and H-5), 7.05 (app. t, 1 H, J 7.6, H-8), 6.86 (d, 1 H, J 8.1, H-3), 4.00 (s, 3 H, H-11), 3.80 (d, 1 H, J 18.1, H-2'), 3.75 (d, 1 H, J 18.1, H-2), 3.70 (s, 3 H, H-1)

δC (100 MHz, CDCl3): 171.5 (C=O), 167.9 (C=O), 166.9 (C=O), 151.2 (C=O), 147.6 (q), 140.7 (q), 133.3, 130.0, 128.4, 127.6, 125.7 (q), 125.1, 123.4, 122.8, 115.9 (q), 115.8, 56.8 (q), 54.0, 53.7, 38.4

νmax (neat)/cm⁻¹: 2959, 1766, 1739, 1600, 1527, 1479, 1344, 1249, 1140, 1053, 905, 765, 753

HRMS (m/z – DIP-APCI): Found: 462.0166 [M+H]+ C20H17BrNO7 Requires: 462.0183
**Dimethyl 3-(2-(3-bromophenoxy)-2-oxoethyl)-2-oxoindoline-1,3-dicarboxylate**  
(453, Table 2.22, entry 6)

Synthesised according to general procedure XV, using substrate **310** (38.4 mg, 0.154 mmol), *p*-iodoanisole (36.1 mg, 0.154 mmol), 3-bromophenyl 2-iodoacetate (**441**, 63.1 mg, 0.185 mmol), catalyst **335** (6.9 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 69 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, *R*<sub>f</sub> = 0.3), affording **453** (59.1 mg, 90%, 58% ee) as a white amorphous solid. M.p. 141-142 °C; [α]<sub>D</sub><sup>20</sup> = +42.8 (c = 0.6, CHCl₃).

CSP-HPLC analysis. Acquity UPC² step 4 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO₂, B = EtOH/IPA (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 3.000 min (minor enantiomer) and 3.272 min (major enantiomer).

δ<sub>H</sub> (400 MHz, CDCl₃):  
7.99 (d, 1 H, J 8.2, H-10), 7.42 (app. t, 1 H, J 7.7, H-4), 7.34 (d, 1 H, J 7.5, H-7), 7.29 (d, 1 H, J 8.1, J 7.7, H-5), 7.23 (app. t, 1 H, J 8.2, H-9), 7.13 (t, 1 H, J 7.5, H-8), 6.96 (app. t, 1 H, J 7.7, H-6), 6.75 (dd, 1 H, J 7.7, 1.5, H-3), 4.01 (s, 3 H, H-11), 3.69 (s, 3 H, H-1), 3.70 (d, 1 H, J 17.2, H-2), 3.65 (d, 1 H, J 17.2, H-2′)

δ<sub>C</sub> (100 MHz, CDCl₃):  
171.5 (C=O), 167.8 (C=O), 167.1 (C=O), 151.1 (C=O), 150.3 (q), 140.5 (q), 130.4, 130.1, 129.3, 125.6 (q), 125.2, 124.7, 122.7, 122.3 (q), 120.0, 115.7, 56.8 (q), 54.1, 53.7, 38.6

ν<sub>max</sub> (neat)/cm⁻¹:  
2955, 1762, 1607, 1470, 1440, 1347, 1292, 1150, 878

HRMS (m/z − DIP-APCI): Found: 462.0195 [M+H]<sup>+</sup> C<sub>20</sub>H<sub>17</sub>BrNO<sub>7</sub> Requires: 462.0183
Dimethyl 3-(2-(4-bromophenoxy)-2-oxoethyl)-2-oxoindoline-1,3-dicarboxylate
(454, Table 2.22, entry 7)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), \( p \)-iodoanisole (36.1 mg, 0.154 mmol), 4-bromophenyl 2-iodoacetate (442, 63.1 mg, 0.185 mmol), catalyst 335 (6.9 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 63 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, \( R_f = 0.3 \)), affording 454 (67.6 mg, 95%, 60% ee) as a white amorphous solid. M.p. 138-139 °C; \([\alpha]_D^{20} = +47.2\) (c = 0.2, CHCl₃).

CSP-HPLC analysis. Acquity UPC² step 4 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO₂, B = EtOH/IPA (1:1, \( v:v \)); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 3.452 min (minor enantiomer) and 3.610 min (major enantiomer).

\[ \delta_{\text{H}} \] (400 MHz, CDCl₃):

7.99 (d, 1 H, J 8.2, H-8), 7.44-7.33 (m, 4 H, H-7, H-5 and H-4), 7.22 (app. t, 1 H, J 7.6, H-6), 6.67 (d, 2 H, J 8.9, H-3), 4.01 (s, 3 H, H-9), 3.70 (s, 3 H, H-1), 3.70 (d, 1 H, J 17.4, H-2), 3.65 (d, 1 H, J 17.4, H-2')

\[ \delta_{\text{C}} \] (100 MHz, CDCl₃):

171.6 (C=O), 167.8 (C=O), 167.3 (C=O), 151.1 (C=O), 148.9 (q), 140.5 (q), 132.4, 130.1, 125.7 (q), 125.2, 123.0, 122.7, 119.3 (q), 115.8, 56.9 (q), 54.1, 53.8, 38.7

\( \nu_{\text{max (neat/cm}}} \):

3072, 2955, 1771, 1736, 1582, 1470, 1437, 1345, 1291, 1221, 1147, 1054, 989, 771, 746, 671

HRMS (\( m/z \) – DIP-APCI):

Found: 462.0163 [M+H]⁺ \( \text{C}_{20}\text{H}_{17}\text{BrNO}_7 \) Requires: 462.0183
**Dimethyl 3-(2-(4-cyanophenoxy)-2-oxoethyl)-2-oxoindoline-1,3-dicarboxylate (455, Table 2.22, entry 8)**

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

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 4-cyanophenyl 2-iodoacetate (443, 53.1 mg, 0.185 mmol), catalyst 335 (6.9 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 24 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, Rf = 0.2), affording 455 (57.9 mg, 92%, 57% ee) as a white amorphous solid. M.p. 147-148 °C; [α]D^20 = +48.6 (c = 0.4, CHCl3).

CSP-HPLC analysis. Acquity UPC² step 3 – Trefoil CEL2 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO₂, B = EtOH/CH₃CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.889 min (major enantiomer) and 2.974 min (minor enantiomer).

δH (400 MHz, CDCl₃):  7.99 (d, 1 H, J 8.3, H-8), 7.58 (d, 2 H, J 8.6, H-4) 7.43 (app. t, 1 H, J 8.3, H-7), 7.34 (d, 1 H, J 7.5, H-5), 7.23 (app. t, 1 H, J 7.5, H-6), 6.95 (d, 2 H, J 8.6, H-3), 4.02 (s, 3 H, H-9), 3.70 (s, 3 H, H-1), 3.73 (d, 1 H, J 17.4, H-2), 3.66 (d, 1 H, J 17.4, H-2')

δC (100 MHz, CDCl₃): 171.5 (C=O), 167.7 (C=O), 166.8 (C=O), 153.1 (C=O), 151.0 (q), 140.4 (q), 133.6, 130.2, 125.5 (q), 125.2, 122.7, 122.4, 117.9 (q), 115.7, 110.1 (q), 56.8 (q), 54.2, 53.8, 38.7

v_max (neat)/cm⁻¹: 2956, 1769, 1730, 1583, 1469, 1437, 1346, 1242, 1146, 1054, 1020, 959, 770, 745

**Note:** The mass of the compound was not detected by HRMS.
Dimethyl 3-(2-(4-chlorophenoxy)-2-oxoethyl)-2-oxoindoline-1,3-dicarboxylate (456, Table 2.22, entry 9)

![Chemical Structure]

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 4-chlorophenyl 2-iodoacetate (444, 54.9 mg, 0.185 mmol), catalyst 335 (6.9 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 24 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, Rf = 0.5), affording 456 (61.8 mg, 96%, 59% ee) as a white amorphous solid. M.p. 157-158 °C; [α]D<sup>20</sup> = +44.8 (c = 0.4, CHCl₃).

CSP-HPLC analysis. Acquity UPC<sup>2</sup> step 3 – Trefoil CEL2 (2.5 µm, 3.0 x 150 mm), gradient eluent A= CO₂, B = EtOH/CH₃CN (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 2.650 min (major enantiomer) and 2.762 min (minor enantiomer).

δ<sub>H</sub> (400 MHz, CDCl₃): 7.99 (d, 1 H, J 8.2, H-8), 7.42 (app. t, 1 H, J 8.2, H-7) 7.34 (d, 1 H, J 7.5, H-5), 7.24-7.20 (m, 3 H, H-6 and H-4), 6.72 (d, 2 H, J 8.8, H-3), 4.01 (s, 3 H, H-9), 3.69 (s, 3 H, H-1), 3.70 (d, 1 H, J 17.3, H-2), 3.65 (d, 1 H, J 17.3, H-2’)

δ<sub>C</sub> (100 MHz, CDCl₃): 171.6 (C=O), 167.8 (C=O), 167.3 (C=O), 151.1 (C=O), 148.4 (q), 140.5 (q), 131.5 (q), 130.1, 129.4, 125.7 (q), 125.2, 122.7, 122.6, 115.8, 56.9 (q), 54.1, 53.7, 38.7

ν<sub>max</sub> (neat)/cm<sup>-1</sup>: 2955, 1771, 1735, 1582, 1469, 1437, 1346, 1240, 1146, 1054, 959, 770, 745, 672

HRMS (m/z – DIP-APCI): Found: 418.0683 [M+H]<sup>+</sup> C₂₀H₁₉ClNO₇ Requires: 418.0688
Dimethyl 3-(2-(3,4-dichlorophenoxy)-2-oxoethyl)-2-oxoindoline-1,3-dicarboxylate  
(457, Table 2.22, entry 10)  

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 3,4-dichlorophenyl 2-iodoacetate (445, 61.2 mg, 0.185 mmol), catalyst 335 (6.9 mg, 0.0077 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 24 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, \( R_f = 0.4 \)), affording 457 (65.5 mg, 94%, 62% ee) as a white amorphous solid. M.p. 145-146 °C; \( [\alpha]_D^{20} = +49.6 \) (c = 0.5, CHCl₃).

CSP-HPLC analysis. Acquity UPC² step 4 – Trefoil AMY1 (2.5 µm, 3.0 x 150 mm), gradient eluent A = CO₂, B = EtOH/IPA (1:1, v:v); column temperature 30 °C, UV detection at 254 nm with PDA detector, retention times: 3.234 min (minor enantiomer) and 3.629 min (major enantiomer).

\[ \delta_H (400 \text{ MHz, CDCl}_3): \]
7.99 (d, 1 H, J 8.2, H-9), 7.43 (app. t, 1 H, J 8.2, H-8)  
7.34-7.32 (m, 2 H, H-6 and H-4), 7.23 (app. t, 1 H, J 7.8, H-7), 6.93 (d, 1 H, J 2.6, H-3), 6.68 (dd, 1 H, J 8.8, 2.6, H-5), 4.02 (s, 3 H, H-10), 3.70 (s, 3 H, H-1), 3.70 (d, 1 H, J 17.3, H-2), 3.64 (d, 1 H, J 17.3, H-2’)

\[ \delta_C (100 \text{ MHz, CDCl}_3): \]
171.5 (C=O), 167.7 (C=O), 167.0 (C=O), 151.0 (C=O), 148.5 (q), 140.5 (q), 132.9 (q), 130.6, 130.2, 130.1 (q), 125.5 (q), 125.2, 123.5, 122.7, 120.9, 115.8, 56.8 (q), 54.2, 53.8, 38.6

\[ \nu_{\text{max}} (\text{neat})/\text{cm}^{-1}: \]
2960, 1767, 1731, 1589, 1469, 1437, 1346, 1246, 1147, 1021, 892, 770, 752, 677

HRMS (\( m/z \) – DIP-APCI): Found: 452.0283 [M+H]+  
\( C_{20}H_{16}Cl_2NO_7 \) Requires: 452.0298

311
Dimethyl 3-(2-(3,5-bis(trifluoromethyl)phenoxy)-2-oxoethyl)-2-oxoindoline-1,3-dicarboxylate (458, Table 2.22, entry 12)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 3,5-bis(trifluoromethyl)phenyl 2-iodoacetate (446, 73.6 mg, 0.185 mmol), catalyst 335 (13.8 mg, 0.0154 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at 3 °C for 96 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, Rf = 0.6), affording 458 (72.0 mg, 90%, 70% ee) as a white amorphous solid. M.p. 132-134 °C; [α]D20 = +45.5 (c = 0.6, CHCl3).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.5 mL min⁻¹, rt, UV detection at 254 nm, retention times: 16.740 min (minor enantiomer) and 24.180 min (major enantiomer).

δH (400 MHz, CDCl3): 8.00 (d, 1 H, J 8.2, H-8), 7.68 (s, 1 H, H-4) 7.45 (app. t, 1 H, J 8.2, H-7), 7.36 (d, 1 H, J 7.5, H-5), 7.27-7.23 (m, 3 H, H-6 and H-3), 4.03 (s, 3 H, H-9), 3.75 (d, 1 H, J 17.1, H-2), 3.71 (s, 3 H, H-1), 3.69 (d, 1 H, J 17.1, H-2’)

δC (100 MHz, CDCl3): 171.4 (C=O), 167.6 (C=O), 166.8 (C=O), 151.0 (C=O), 150.3 (q), 140.5 (q), 132.9 (q, JCF 35.2) (q), 130.3, 125.4 (q), 125.3, 122.8, 122.6 (q, JCF 272.8) (q), 122.2 (m), 120.0 (quint, JCF 3.8), 115.8, 56.8 (q), 54.2, 53.9, 38.6

δF (376 MHz, CDCl3): -63.0

νmax (neat)/cm⁻¹: 3062, 2960, 1773, 1739, 1608, 1483, 1440, 1346, 1276, 1239, 1130, 1055, 929, 748, 679

HRMS (m/z – DIP-APCI): Found: 520.0807 [M+H]+ C22H16F6NO7 Requires: 520.0825

312
Dimethyl 2-oxo-3-(2-oxo-2-(4-(trifluoromethyl)phenoxy)ethyl)indoline-1,3-dicarboxylate (459, Table 2.22, entry 14)

Synthesised according to general procedure XV, using substrate 310 (38.4 mg, 0.154 mmol), p-iodoanisole (36.1 mg, 0.154 mmol), 4-(trifluoromethyl)phenyl 2-iodoacetate (447, 61.1 mg, 0.185 mmol), catalyst 335 (13.8 mg, 0.0154 mmol), PhMe (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at 3 °C for 96 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, \( R_f = 0.4 \)), affording 459 (68.1 mg, 98%, 76% ee) as a white amorphous solid. M.p. 145-147 °C; [\( \alpha \)]\(_{D}^{20} \) = +50.0 (c = 0.2, CHCl\(_3\)).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min\(^{-1}\), rt, UV detection at 254 nm, retention times: 14.713 min (minor enantiomer) and 18.533 min (major enantiomer).

Upon large scale synthesis of 459, followed by a precipitation of the racemic product from hexane, 459 was obtained as (S)-enantiomer (780 mg, 63%, >99% ee); [\( \alpha \)]\(_{D}^{20} \) = +95.5 (c = 0.1, CHCl\(_3\)).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min\(^{-1}\), rt, UV detection at 254 nm, retention times: 19.633 min.

\[ \delta_H (400 \text{ MHz, CDCl}_3): \]

7.99 (d, 1 H, J 8.2, H-8), 7.54 (d, 2 H, J 8.6, H-4) 7.43 (app. t, 1 H, J 8.2, H-7), 7.35 (d, 1 H, J 7.3, H-5), 7.23 (app. t, 1 H, J 7.3, H-6), 6.92 (d, 2 H, J 8.6, H-3), 4.02 (s, 3 H, H-9), 3.74 (d, 1 H, J 17.1, H-2), 3.71 (s, 3 H, H-1), 3.68 (d, 1 H, J 17.1, H-2')

\[ \delta_C (100 \text{ MHz, CDCl}_3): \]

171.5 (C=O), 167.8 (C=O), 167.1 (C=O), 152.3 (C=O), 151.1 (q), 140.5 (q), 130.2, 128.5 (q, \( J_{C-F} \) 32.8) (q), 126.8
(q, $J_{CF}$ 3.9), 125.6 (q), 125.2, 123.7 (q, $J_{CF}$ 272.7) (q), 122.7, 121.8, 115.8, 56.9 (q), 54.1, 53.8, 38.7

$\delta_F$ (376 MHz, CDCl$_3$): -62.4

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 2959, 1766, 1735, 1607, 1467, 1441, 1347, 1291, 1245, 1149, 1122, 1054, 934, 771, 751

HRMS ($m/z$ – DIP-APCI): Found: 452.0944 [M+H]$^+$ C$_{21}$H$_{17}$F$_3$NO$_7$ Requires: 452.0952

**Dimethyl 5-chloro-2-oxo-3-(2-oxo-2-(4-(trifluoromethyl)phenoxy)ethyl)indoline-1,3-dicarboxylate (463)**

![Chemical structure of Dimethyl 5-chloro-2-oxo-3-(2-oxo-2-(4-(trifluoromethyl)phenoxy)ethyl)indoline-1,3-dicarboxylate (463)](image)

Synthesised according to general procedure XV, using substrate 389 (43.7 mg, 0.154 mmol), p-idoanisole (36.1 mg, 0.154 mmol), 4-(trifluoromethyl)phenyl 2-iodoacetate (447, 61.1 mg, 0.185 mmol), catalyst 335 (6.9 mg, 0.0077 mmol), chlorobenzene (1.5 mL) and millipore water (15.0 mL). The reaction mixture was stirred at rt for 96 h. The crude product was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, $R_f$ = 0.4), affording 463 (>99% conv. by $^1$H NMR, 43% ee) as an off-white amorphous solid. M.p. 182-183 °C; [$\alpha$]$_D^{20}$ = +46.9 (c = 0.4, CHCl$_3$).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min$^{-1}$, rt, UV detection at 254 nm, retention times: 16.813 min (major enantiomer) and 20.347 min (minor enantiomer).

$\delta_H$ (400 MHz, CDCl$_3$): 7.95 (d, 1 H, J 8.6, H-7), 7.57 (d, 2 H, J 8.1, H-4) 7.39 (dd, 1 H, J 8.6, 1.9, H-6), 7.34 (d, 1 H, J 1.9, H-5), 7.03 (d, 2 H, J 8.1, H-3), 4.01 (s, 3 H, H-8), 3.72 (s, 3 H, H-1), 3.74 (d, 1 H, J 17.7, H-2), 3.66 (d, 1 H, J 17.7, H-2′)

314
δC (100 MHz, CDCl₃): 170.8 (C=O), 167.2 (C=O), 167.1 (C=O), 152.3 (C=O), 150.9 (q), 139.1 (q), 130.7 (q), 130.2, 128.6 (q, J_C-F 33.2) (q), 127.3 (q), 126.8 (q, J_C-F 3.8), 123.5 (q, J_C-F 272.6) (q), 123.0, 121.8, 117.0, 56.7 (q), 54.3, 54.0, 38.6

δF (376 MHz, CDCl₃): -62.4

ν_max (neat)/cm⁻¹: 2957, 1765, 1735, 1613, 1480, 1445, 1335, 1248, 1211, 1152, 1052, 905, 821, 770, 679

HRMS (m/z – DIP-APCI): Found: 486.0539 [M+H]^+ C_{21}H_{16}ClF_{3}NO_{7} Requires: 486.0562

5.2.4 Synthesis of the bioactive spirooxindole target

Methyl 2-oxo-3-(2-oxo-2-(4-(trifluoromethyl)phenoxy)ethyl)indoline-3-carboxylate (466)

A 25 mL round-bottomed flask containing a stirring bar was charged with 459 (750 mg, 1.662 mmol, >99% ee, 1.0 equiv.) and placed under an argon atmosphere. Anhydrous THF (16.0 mL, 0.1 M) was added via syringe, followed by the addition of 2-fluorobenzylamine (464, 0.23 mL, 1.994 mmol, 1.2 equiv.) via syringe. The reaction mixture was allowed to stir for 24 h at rt. The progress of the reaction was monitored by TLC (CH₂Cl₂/EtOAc, 10:1). Upon completion of the reaction, the solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (CH₂Cl₂/EtOAc, 10:1, R_f = 0.5), affording 466 (480 mg, 74%, >99% ee) as a clear oil. [α]_D^{20} = +52.5 (c = 0.4, CHCl₃).

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 95/5, 1.0 mL min⁻¹, rt, UV detection at 254 nm, retention times: 48.067 min (major enantiomer).
δ_H (400 MHz, CDCl₃): 8.79 (s, 1 H, H-9), 7.53 (d, 2 H, J 8.5, H-4), 7.36 (d, 1 H, J 7.4, H-5), 7.27 (app. td, 1 H, J 7.4, H-7), 7.07 (app. td, 1 H, J 7.4, 1.2, H-6), 6.94 (d, 2 H, J 8.5, H-3), 6.88 (d, 1 H, J 7.4, H-8), 3.72 (s, 3 H, H-1), 3.64 (d, 1 H, J 16.8, H-2), 3.55 (d, 1 H, J 16.8, H-2’)

δ_C (100 MHz, CDCl₃): 175.3 (C=O), 168.4 (C=O), 167.7 (C=O), 152.5 (q), 141.9 (q), 129.8, 128.3 (q, J_C-F 33.1) (q), 127.3 (q), 126.7 (q, J_C-F 3.8), 123.9, 123.7 (q, J_C-F 272.5) (q), 123.0, 121.9, 110.5, 56.8 (q), 53.6, 38.3

δ_F (376 MHz, CDCl₃): -62.4

ν_max (neat)/cm⁻¹: 3265, 1719, 1615, 1473, 1322, 1122, 1064, 853, 750

HRMS (m/z – APCI): Found: 394.0896 [M+H]^+ C₁₉H₁₅F₃NO₅ Requires: 394.0897

1’-(2-Fluorobenzyl)spiro[indoline-3,3’-pyrrolidine]-2,2’,5’-trione (467)

![Diagram of 1’-(2-Fluorobenzyl)spiro[indoline-3,3’-pyrrolidine]-2,2’,5’-trione](image)

A 25 mL round-bottomed flask containing a stirring bar was charged with racemic 459 (0.34 g, 0.753 mmol, 1.0 equiv.), 2-fluorobenzylamine (464, 0.26 mL, 2.260 mmol, 3.0 equiv.) and PhMe (7.5 mL, 0.1 M). The flask was attached to a condenser and the reaction mixture was refluxed at 115 °C for 16 h. Upon consumption of the starting material, the solvent was removed in vacuo and the crude residue was purified by column chromatography on silica gel (CH₂Cl₂/EtOAc, 10:1, Rᵣ = 0.4), affording 467 (220 mg, 92%) as a white amorphous solid. M.p. 171-173 °C.

δ_H (400 MHz, CDCl₃): 7.72 (br s, 1 H, NH, H-11), 7.34-7.27 (m, 3 H, H-7, H-4 and H-1), 7.14-7.04 (m, 4 H, H-10, H-9, H-3 and H-2), 6.95 (app. d, 1 H, J 7.9, H-8), 4.87 (d, 1 H, J 15.7, H-5), 4.83 (d, 1 H, J 15.7, H-5’), 3.38 (d, 1 H, J 18.2, H-6), 3.02 (d, 1 H, J 18.2, H-6’)

316
δC (100 MHz, CDCl3): 174.6 (C=O), 174.1 (C=O), 172.7 (C=O), 160.6 (d, JCeF 248.9) (q), 141.5 (q), 130.1, 129.8 (d, JCeF 7.9), 129.6 (d, JCeF 3.7), 127.7 (q), 124.4 (d, JCeF 3.6), 123.7, 122.9, 121.8 (d, JCeF 14.4) (q), 115.6 (d, JCeF 21.2), 110.8, 56.9 (q), 38.5, 37.4 (d, JCeF 4.6)

δF (376 MHz, CDCl3): -117.6

νmax (neat)/cm⁻¹: 3250, 1732, 1686, 1618, 1488, 1393, 1168, 1123, 951


Methyl 1-(2-(tert-butoxy)-2-oxoethyl)-2-oxo-3-(2-oxo-2-(4-(trifluoromethyl)phenoxy)ethyl)indoline-3-carboxylate (472)

A 25 mL round-bottomed flask containing a stirring bar was charged with NaH (60% in mineral oil, 63 mg, 1.564 mmol, 1.5 equiv.) and placed under an argon atmosphere. Anhydrous THF (11.5 mL, 0.09 M) was added via syringe, followed by the addition of the solution of 466 (410 mg, 1.042 mmol, >99% ee, 1.0 equiv.) in anhydrous THF (2 mL). After being stirred at rt for 30 min, tert-butylbromoacetate (471, 0.22 mL, 1.459 mmol, 1.4 equiv.) was added to the suspension dropwise via syringe. The reaction mixture was allowed to stir for 16 h at rt. The progress of the reaction was monitored by TLC (hexane/EtOAc, 6:4). Upon completion of the reaction, H2O (20 mL) and EtOAc (20 mL) were added to the mixture. The organic layer was separated and the aqueous layer was extracted with EtOAc (20 mL). The combined organic extracts were washed with brine and dried over MgSO4. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 6:4, Rf = 0.5), affording 472 (233 mg, 44%, 97% ee) as a clear oil. [α]D20 = +12.0 (c = 0.3, CHCl3).
CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.5 mL min\(^{-1}\), rt, UV detection at 254 nm, retention times: 25.300 min (minor enantiomer) and 36.320 min (major enantiomer).

\(\delta_H\) (400 MHz, CDCl\(_3\)): 7.57 (d, 2 H, \(J\,8.6,\,H-4\)), 7.44 (d, 1 H, \(J\,7.7,\,H-5\)), 7.35 (app. td, 1 H, \(J\,7.7,\,1.2,\,H-7\)), 7.11 (app. td, 1 H, \(J\,7.7,\,1.2,\,H-6\)), 7.01 (d, 2 H, \(J\,8.6,\,H-3\)), 6.77 (d, 1 H, \(J\,7.7,\,H-8\)), 4.49 (d, 1 H, \(J\,17.4,\,H-9\)), 4.29 (d, 1 H, \(J\,17.4,\,H-9'\)), 3.72 (s, 3 H, H-1), 3.63 (d, 1 H, \(J\,16.8,\,H-2\)), 3.50 (d, 1 H, \(J\,16.8,\,H-2'\)), 1.43 (s, 9 H, H-10)

\(\delta_C\) (100 MHz, CDCl\(_3\)): 172.8 (C=O), 168.4 (C=O), 167.5 (C=O), 166.0 (C=O), 152.6 (q), 143.4 (q), 129.7, 126.7, 126.5 (q), 124.1, 123.7 (q, \(J_{C-F}\) 274.2) (q), 123.3, 122.0, 108.8, 82.8 (q), 67.9 (q), 56.1, 53.6 (q), 42.6, 38.7, 27.9

\(\delta_F\) (376 MHz, CDCl\(_3\)): -62.4

\(\nu_{\text{max}}\) (neat)/cm\(^{-1}\): 3061, 1722, 1612, 1492, 1323, 1207, 1125, 1017, 854, 751

HRMS (m/z – APCI): Found: 506.1425 [M-H]\(^{-}\) \(C_{25}H_{23}F_{3}NO_{7}\) Requires: 506.1432

*Tert*-butyl 2-(1’-(2-fluorobenzyl)-2,2',5'-trioxospiro[indoline-3,3'-pyrrolidin]-1-yl)acetate (473)

A 10 mL round-bottomed flask containing a stirring bar was charged with 472 (211 mg, 0.416 mmol, 97% ee, 1.0 equiv.) and PhMe (4.2 mL, 0.1 M). 2-Fluorobenzylamine (464, 58.0 \(\mu\)L, 0.499 mmol, 1.2 equiv.) was added via syringe and the flask was attached to a condenser. The reaction mixture was stirred at 75 °C for 20h. The progress of the reaction was monitored by TLC (hexane/EtOAc, 7:3). Upon completion of the
reaction, the solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, R_f = 0.4), affording 473 (65.0 mg, 36%, 94% ee) as a white amorphous solid. M.p. 65-67 °C; [α]_D^20 = +4.3 (c = 0.9, CHCl_3).

CSP-HPLC analysis. Chiralcel OD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min⁻¹, rt, UV detection at 254 nm, retention times: 31.280 min (minor enantiomer) and 49.920 min (major enantiomer).

δ_H (400 MHz, CDCl_3):  7.36-7.28 (m, 3H, H-7, H-4 and H-1), 7.12-7.02 (m, 4 H, H-9, H-8, H-3 and H-2), 6.79 (d, 1 H, J 7.8, H-10), 4.85 (d, 1H, J 15.6, H-5), 4.81 (d, 1 H, J 15.6, H-5'), 4.53 (d, 1 H, J 17.5, H-11), 4.22 (d, 1 H, J 17.5, H-11'), 3.37 (d, 1 H, J 18.4, H-6), 3.02 (d, 1 H, J 18.4, H-6'), 1.43 (s, 9 H, H-12)

δ_C (100 MHz, CDCl_3): 173.9 (C=O), 173.2 (C=O), 172.4 (C=O), 165.7 (C=O), 160.5 (d, J_C-F 247.1) (q), 143.4 (q), 129.9, 129.6 (d, J_C-F 8.3), 129.4 (d, J_C-F 3.5), 126.9 (q), 124.3 (d, J_C-F 3.5), 123.8, 122.7, 121.7 (d, J_C-F 14.5) (q), 115.5 (d, J_C-F 21.0), 109.1, 83.0 (q), 56.3 (q), 42.6, 38.7, 37.2 (d, J_C-F 4.9), 27.8

δ_F (376 MHz, CDCl_3): -117.6

ν_max (neat)/cm⁻¹: 3180, 1745, 1707, 1613, 1491, 1364, 1227, 1146, 928, 756

HRMS (m/z – APCI): Found: 437.1504 [M-H]⁻ C_{24}H_{22}F_{2}N_{2}O_{5} Requires: 437.1518

*Tert*-butyl 2-(5-chloro-1'-(2-fluorobenzyl)-2,2',5'-trioxospiro[indoline-3,3'-pyrrolidin]-1-yl)acetate (461)

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![Chemical structure](image-url)
A 10 mL round-bottomed flask containing a stirring bar and equipped with a condenser was charged with 473 (36.0 mg, 0.082 mmol, 94% ee, 1.0 equiv.) and N-chlorosuccinimide (54.8 mg, 0.411 mmol, 5.0 equiv.). The flask was placed under an argon atmosphere and anhydrous CH$_3$CN (0.4 mL, 0.2 M) was added to the flask via syringe. The reaction mixture was stirred at 85 °C for 16 h. The progress of the reaction was monitored by TLC (hexane/EtOAc, 7:3). Upon completion of the reaction, the solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 7:3, R$_f$ = 0.5), affording 461 (34 mg, 88%, 93% ee) as a white amorphous solid. M.p. 183-184 °C; [α]$_D^{20}$ = +11.0 (c = 0.1, CHCl$_3$).

The isolated compound exhibited identical spectroscopic data to those reported in the literature.$^{26}$

CSP-HPLC analysis. Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1.0 mL min$^{-1}$, rt, UV detection at 254 nm, retention times: 20.507 min (major enantiomer) and 24.127 min (minor enantiomer).

δ$_H$ (400 MHz, CDCl$_3$): 7.34-7.27 (m, 3 H, H-7, H-2 and H-1), 7.14-7.04 (m, 3 H, H-8, H-4 and H-3), 6.72 (d, 1 H, J 8.4, H-9), 4.87 (d, 1 H, J 15.1, H-5), 4.83 (d, 1 H, J 15.1, H-5'), 4.53 (d, 1 H, J 17.3, H-10), 4.20 (d, 1 H, J 17.3, H-10'), 3.38 (d, 1 H, J 18.4, H-6), 3.02 (d, 1 H, J 18.4, H-6'), 1.44 (s, 9 H, H-11)

δ$_C$ (100 MHz, CDCl$_3$): 173.5 (C=O), 172.8 (C=O), 171.8 (C=O), 165.5 (C=O), 160.5 (d, J$_{C\text{-F}}$ 249.1) (q), 142.1 (q), 130.0, 129.9 (d, J$_{C\text{-F}}$ 8.0), 129.6 (d, J$_{C\text{-F}}$ 3.7), 129.2 (q), 128.4 (q), 124.4 (d, J$_{C\text{-F}}$ 3.8), 123.5, 121.6 (d, J$_{C\text{-F}}$ 14.3) (q), 115.6 (d, J$_{C\text{-F}}$ 21.3), 110.1, 83.4 (q), 56.3 (q), 42.7, 38.6, 37.5 (d, J$_{C\text{-F}}$ 4.7) (q), 27.9

δ$_F$ (376 MHz, CDCl$_3$): -117.5

HRMS (m/z – ESI): Found: 495.1095 [M+Na]$^+$ C$_{26}$H$_{22}$ClF$_2$NaO$_5$ Requires: 495.1093
2-(5-chloro-1’-(2-fluorobenzyl)-2,2',5'-trioxospiro[indoline-3,3'-pyrrolidin]-1-yl)acetic acid (460)

A 5 mL round-bottomed flask containing a stirring bar was charged with 461 (24.0 mg, 0.051 mmol, 93% ee, 1.0 equiv.) was placed under argon atmosphere. Anhydrous CH₂Cl₂ (0.6 mL, 0.09 M) was added to the flask via syringe and the mixture was cooled to 0 °C. Trifluoroacetic acid (TFA, 58.0 mL, 0.88 M) was added dropwise via syringe and the reaction mixture was allowed to stir at 0 °C for 30 min. The reaction was stirred at rt for further 72 h. Upon completion of the reaction, the solvent was removed in vacuo and the crude product was precipitated from hexane/Et₂O, affording 460 (20.0 mg, 94%, 93% ee) as a white amorphous solid. M.p. 167-170 °C; [α]D²⁰ = -92.8 (c = 0.1, CH₃CN).

The isolated compound exhibited identical spectroscopic data to those reported in the literature.²⁶¹

δH (400 MHz, dmso-d₆): 13.21 (br s, 1 H, OH, H-11), 7.79 (d, 1 H, J 2.0, H-7), 7.47 (dd, 1 H, J 8.4, 2.0, H-8), 7.38-7.29 (m, 2 H, H-2 and H-1), 7.24-7.16 (m, 3 H, H-9 and H-4), 4.76 (d, 1 H, J 15.6, H-5), 4.69 (d, 1 H, J 15.6, H-5’), 4.56 (d, 1 H, J 17.7, H-10), 4.49 (d, 1 H, J 17.7, H-10’), 3.42 (d, 1 H, J 18.1, H-6), 3.12 (d, 1 H, J 18.1, H-6’)

δC (100 MHz, dmso-d₆): 174.3 (C=O), 173.2 (C=O), 172.3 (C=O), 168.5 (C=O), 159.9 (d, JCF 248.7) (q), 142.8 (q), 129.8 (d, JCF 8.1), 129.5, 128.9 (d, JCF 3.9), 128.2 (q), 127.3 (q), 124.9, 124.5 (d, JCF 3.6), 122.1 (d, JCF 14.6) (q), 115.4 (d, JCF 21.0), 111.2, 56.3 (q), 41.8, 38.6, 36.4 (d, JCF 5.5) (q)

δF (376 MHz, dmso-d₆): -117.9


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5.3 Experimental data for Chapter 3

Phenyl 3-methyl-2-((phenoxy carbonyl)oxy)-1H-indole-1-carboxylate (480)

To a solution of 3-methyl oxindole (483, 1.3 g, 8.83 mmol, 1.0 equiv.) in anhydrous THF (26.0 mL, 0.34 M) at 0 °C, freshly distilled Et$_3$N (2.7 mL, 19.43 mmol, 2.2 equiv.) was added via syringe. Phenyl chloroformate (484, 2.4 mL, 19.43 mmol, 2.2 equiv.) was added to the reaction mixture dropwise via syringe, forming a precipitate. The resulting slurry was stirred at 0 °C to rt overnight. Upon completion of the reaction (TLC hexane/EtOAc, 8:2, R$_f$ = 0.5), it was poured into water. The organic layer was separated and the aqueous layer was extracted with EtOAc (30 mL x 3). The combined organic extracts were washed with HCl (1.0 M, aq.), NaHCO$_3$ (sat., aq.) and brine, dried over MgSO$_4$ and finally concentrated in vacuo. Upon column chromatography (hexane/EtOAc, 8:2, R$_f$ = 0.5), the desired product 480 (2.4 g, 71%) was obtained as a white amorphous solid. M.p. 91-93 °C (lit.$^{271}$ 93-96 °C). The isolated compound exhibited identical spectroscopic data to those reported in the literature.$^{271}$

$\delta_H$ (400 MHz, CDCl$_3$):

| $\delta_H$ | H-1, J 7.9, H-5 | 7.53 (app. dd, 1 H, J 7.2, 1.5, H-2) | 7.48-7.45 (m, 2 H, H-6) | 7.40-7.30 (m, 7 H, H-4, H-7, H-8, H-9 and H-11) | 7.24 (app. t, 1 H, J 7.2, H-3) | 7.12 (dd, 2 H, J 8.2, 1.3, H-10) | 2.28 (s, 3 H, H-1) |

2-Vinylphenol (486)

To a solution of methyltriphenylphosphonium bromide (8.6 g, 24.08 mmol, 2.3 equiv.) and potassium tert-butoxide (2.7 g, 24.08 mmol, 2.3 equiv.) in anhydrous THF (65.0 mL, 0.16 M) under an argon atmosphere was added salicylaldehyde (485, 1.12 mL,
10.47 mmol, 1.0 equiv.). The reaction was heated to 30 °C and stirred for 12 h. Upon cooling the reaction to rt, the solvent was removed *in vacuo* and the residue was extracted with Et₂O. The combined organic extracts were washed with brine and dried over anhydrous Na₂SO₄. The solvent was removed *in vacuo* and the crude product was purified by column chromatography on silica gel (100% CH₂Cl₂, Rₜ = 0.5), affording 486 (1.23 g, 98%) as a pale yellow oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³¹³

δ_H (400 MHz, CDCl₃): 7.39 (dd, 1 H, J 7.8, 1.3, H-6), 7.15 (td, 1 H, J 7.8, 1.3, H-5), 6.98-6.90 (m, 2 H, H-4 and H-2), 6.79 (dd, 1 H, J 8.0, 0.9, H-3), 5.74 (dd, 1 H, J 17.7, 1.2, H-1a), 5.37 (dd, 1 H, J 11.2, 1.2, H-1b)

HRMS (m/z – DIP-APCI): Found: 121.0669 [M+H]⁺ C₈H₉O Requires: 121.0648

3-Methylbenzofuran-2(3H)-one (487)

A palladium-catalysed regioselective hydroesterification²⁷³ was utilised in the synthesis of 487 as follows: to a stirred mixture of Pd(OAc)₂ (47 mg, 0.208 mmol, 5 mol%) and PPh₃ (0.2 g, 0.83 mmol, 0.2 equiv.) in distilled and degassed mesitylene (4.0 mL, 1.0 M) were added phenol derivative 486 (0.5 g, 4.16 mmol, 1.0 equiv.), formic acid (0.16 mL, 4.16 mmol, 1.0 equiv.) and phenyl formate (0.54 mL, 4.99 mmol, 1.2 equiv.) successively *via* syringe. The reaction mixture was stirred under argon atmosphere at 90 °C for 24 h. Upon completion of the reaction (TLC), the crude mixture was purified by column chromatography (hexane/EtOAc, 30:1, TLC hexane/EtOAc 9:1, Rₜ = 0.4), affording 487 as a clear oil. The isolated compound exhibited identical spectroscopic data to those reported in the literature.³¹⁴

δ_H (400 MHz, CDCl₃): 7.32-7.25 (m, 2 H, H-6 and H-3), 7.17-7.09 (m, 2 H, H-4 and H-5), 3.73 (q, 1 H, J 7.7, H-2), 1.58 (d, 3 H, J 7.7, H-1)

HRMS (m/z – DIP-APCI): Found: 147.0447 [M-H]⁻ C₉H₇O₂ Requires: 147.0452
3-Methylbenzofuran-2-yl phenyl carbonate (488)

To a solution of benzofuranone (487, 0.28 g, 1.89 mmol, 1.0 equiv.) in anhydrous THF (7.0 mL, 0.28 M) at 0 °C, freshly distilled Et$_3$N (0.40 mL, 2.84 mmol, 1.5 equiv.) was added via syringe. Phenyl chloroformate (484, 0.36 mL, 2.835 mmol, 1.5 equiv.) was added to the reaction mixture dropwise via syringe, forming a precipitate. The resulting slurry was stirred at 0 °C for 30 min and then it was poured into water. The organic layer was separated and the aqueous layer was extracted with Et$_2$O (20 mL x 3). The combined organic extracts were washed with HCl (1.0 M, aq.), NaHCO$_3$ (sat., aq.) and brine, dried over MgSO$_4$ and finally concentrated in vacuo. Upon column chromatography (hexane/Et$_2$O, 10:1, R$_f$ = 0.4), the desired product 488 (480 mg, 95%) was obtained as a white amorphous solid. M.p. 68-69 °C. The isolated compound exhibited identical spectroscopic data to those reported in the literature.$^{315}$

$\delta$H (400 MHz, CDCl$_3$): 7.51-7.41 (m, 4 H, H-2, H-5 and H-6), 7.32-7.25 (m, 5 H, H-3, H-4, H-7 and H-8), 2.21 (s, 3 H, H-1)

1-(2,2-Diphenylacetyl)-3-methylindolin-2-one (492)

A round-bottomed flask containing a stirring bar, 3-methyl 2-oxindole derivative (483, 2.0 g, 13.59 mmol) and diphenyl acetyl chloride (3.8 g, 16.31 mmol) was heated to 150 °C for 4 h with stirring. Upon consumption of the starting material (TLC hexane/EtOAc, 8:2), the reaction was quenched with H$_2$O (2 mL). After cooling for 5 min, EtOH (30 mL) was added and the solution was allowed to cool to rt. The resulting precipitate was filtered under vacuum and washed with EtOH (20 mL) and H$_2$O (20 mL) to yield 492
(3.8 g, 83 %) as a white amorphous solid. M.p. 92-94 °C. The isolated compound exhibited identical spectroscopic data to those reported in the literature.\(^{269}\)

**Note:** If the product failed to precipitate from EtOH, the crude residue was dry-loaded onto a silica column (hexane/EtOAc, 8:2) and further purification was achieved by subsequent precipitation from Et\(_2\)O.

\[\delta_H (400 \text{ MHz, CDCl}_3): 8.27 \text{ (d, 1 H, } J 8.2, \text{ H-6), 7.36-7.18 (m, 13 H, H-3, H-4, H-5, H-7, H-8, H-9, H-10, H-11 and H-12), 6.62 (s, 1 H, H-7), 3.56 (q, 1 H, } J 7.6, \text{ H-2), 1.45 (d, 3 H, } J 7.6, \text{ H-1)}\]

HRMS (\(m/z\) – APCI): Found: 342.1488 [M+H]\(^+\) C\(_{23}\)H\(_{20}\)NO\(_2\) Requires: 342.1489

1-(2,2-Diphenylacetyl)-3-methyl-1\(H\)-indol-2-yl (2,2,2-trichloroethyl) carbonate (494)

![Chemical structure](image)

To a solution of 492 (1.1 g, 3.22 mmol, 1.0 equiv.) in anhydrous THF (32.0 mL, 0.1 M) at 0 °C was added freshly distilled Et\(_3\)N (0.5 mL, 3.54 mmol, 1.1 equiv.) \*via\* syringe. 2,2,2-Trichloroethyl chloroformate (493, 0.6 mL, 4.189 mmol, 1.3 equiv.) was added to the reaction mixture \*dropwise\* \*via\* syringe. The resulting slurry was stirred at 0 °C to rt for 1 h. Upon completion of the reaction (TLC hexane/EtOAc, 8:2), it was poured into water (30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (30 mL x 3). The combined organic extracts were washed with brine, dried over MgSO\(_4\) and finally concentrated \*in vacuo\*. Upon recrystallisation from hexane, the desired product 494 (1.1 g, 65%) was obtained as a yellow crystalline solid. M.p. 112-115 °C.

\[\delta_H (400 \text{ MHz, CDCl}_3): 8.48 \text{ (d, 1 H, } J 7.7, \text{ H-5), 7.51 (app. dd, 1 H, } J 7.7, 1.8, \text{ H-2), 7.41-7.29 (m, 12 H, H-3, H-4, H-7, H-8, H-9, H-10, H-11 and H-12), 6.03 (s, 1 H, H-6), 4.58 (s, 2 H, H-13), 2.13 (s, 3 H, H-1)}\]

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\(\delta C\) (100 MHz, CDCl\(_3\)): 170.3 (C=O), 150.3 (C=O), 138.7 (q), 136.4 (q), 132.9 (q), 129.3, 128.7, 128.1 (q), 127.5, 125.7, 124.1, 118.8, 116.8, 106.3 (q), 93.7 (q), 77.5, 58.6, 7.4

\(v_{\text{max}}\) (neat)/cm\(^{-1}\): 2949, 1779, 1690, 1645, 1453, 1308, 1202, 1043, 831, 699

HRMS (m/z – DIP-APCI): Found: 516.0536 [M+H]\(^+\) \(C_{26}H_{21}Cl_3NO_4\) Requires: 516.0531

**General procedure XVIII:** Protocol for the synthesis of O-acetylated 3-methyl oxindole derivatives

An oven-dried round-bottomed flask containing a stirring bar was charged with a relevant diphenyl acetyl 2-oxindole derivative (1.0 equiv.), anhydrous THF (0.2 M) and freshly distilled \(\text{Et}_3\text{N}\) (10.0 equiv.), which was added to the reaction mixture via syringe. Upon placing the flask into a water bath, the appropriate acid chloride (5.0 equiv.) was added dropwise via syringe over 5 min (caution: exotherm.). After approx. 1 h, the mixture was poured over water (100 mL) and it was extracted with \(\text{CH}_2\text{Cl}_2\) (3 x). The combined organic extracts were washed with NaHCO\(_3\) (sat., aq.), brine and dried over \(\text{MgSO}_4\). The solvent was removed in vacuo and the crude product was purified by recrystallisation and/or precipitation.

**1-(2,2-Diphenylacetyl)-3-methyl-1H-indol-2-yl methyl carbonate (497)**

![Structure of 1-(2,2-Diphenylacetyl)-3-methyl-1H-indol-2-yl methyl carbonate (497)](image)

Synthesised according to general procedure XVIII, using 492 (3.6 g, 10.55 mmol), THF (53 mL), \(\text{Et}_3\text{N}\) (14.0 mL, 100.55 mmol) and acetyl chloride (496, 3.7 mL, 52.72 mmol). The crude residue was recrystallised from EtOAc to afford 497 (2.9 g, 73%) as a white amorphous solid. M.p. 140-141 °C.

The isolated compound exhibited identical spectroscopic data to those reported in the literature.\(^{269}\)
δ_H (400 MHz, CDCl_3): 8.33-8.30 (m, 1 H, H-5), 7.46-7.43 (m, 1 H, H-2), 7.35-7.23 (m, 12 H, H-3, H-4, H-7, H-8, H-9, H-10, H-11 and H-12), 5.92 (s, 1 H, H-6), 2.02 (s, 3 H, H-1), 1.96 (s, 3 H, H-13)

1-(2,2-Diphenylacetyl)-3-methyl-1H-indol-2-yl ethyl carbonate (504)

Synthesised according to general procedure XVIII, using 492 (0.9 g, 2.64 mmol), THF (13.2 mL), Et_3N (3.7 mL, 26.36 mmol) and propionyl chloride (503, 1.2 mL, 13.18 mmol). The crude residue was precipitated from hexane and subsequently washed with Et_2O to afford 504 (630 mg, 60%) as a white amorphous solid. M.p. 101-103 °C.

δ_H (400 MHz, CDCl_3): 8.34-8.32 (m, 1 H, H-5), 7.44-7.43 (m, 1 H, H-2), 7.34-7.22 (m, 12 H, H-3, H-4, H-7, H-8, H-9, H-10, H-11 and H-12), 5.92 (s, 1 H, H-6), 2.28 (q, 2 H, J 7.5, H-13), 2.00 (s, 3 H, H-1), 1.05 (t, 3 H, J 7.5, H-14)

δ_C (100 MHz, CDCl_3): 170.6 (C=O, two signals), 139.2 (q), 136.8 (q), 133.1 (q), 129.1, 128.7, 128.5 (q), 127.4, 124.9, 123.8, 118.4, 116.3, 105.9 (q), 58.4, 27.0, 8.7, 7.6

ν_max (neat)/cm⁻¹: 2943, 1784, 1695, 1450, 1363, 1089, 1065, 841, 741

HRMS (m/z – ESI): Found: 420.1573 [M+Na]⁺ C_{26}H_{23}NNaO_{3} Requires: 420.1570
1-(2,2-Diphenylacetyl)-3-methyl-1H-indol-2-yl isopropyl carbonate (506)

Synthesised according to general procedure XVIII, using 492 (0.9 g, 2.64 mmol), THF (13.2 mL), Et₃N (3.7 mL, 26.36 mmol) and isobutyryl chloride (505, 1.4 mL, 13.18 mmol). The crude residue was recrystallised from EtOAc and subsequently washed with Et₂O to afford 506 (560 mg, 52%) as white needle-like crystals. M.p. 112-115 °C.

δH (400 MHz, CDCl₃): 8.33-8.31 (m, 1 H, H-5), 7.45-7.43 (m, 1 H, H-2), 7.33-7.22 (m, 12 H, H-3, H-4, H-7, H-8, H-9, H-10, H-11 and H-12), 5.94 (s, 1 H, H-6), 2.52 (sept, 1 H, J 7.0, H-13), 1.99 (s, 3 H, H-1), 1.18 (d, 6 H, J 7.0, H-14)

δC (100 MHz, CDCl₃): 173.4 (C=O), 170.7 (C=O), 139.2 (q), 137.0 (q), 133.1 (q), 129.1, 128.7, 128.5 (q), 127.4, 124.9, 123.7, 118.3, 116.3, 105.6 (q), 58.2, 33.9, 18.8, 7.5

νmax (neat)/cm⁻¹: 2973, 1780, 1698, 1495, 1450, 1356, 1287, 1176, 1052, 834, 741, 696

HRMS (m/z – ESI): Found: 434.1729 [M+Na]⁺ C₂₇H₂₃NNaO₃ Requires: 434.1727

Allyl (1-(2,2-diphenylacetyl)-3-methyl-1H-indol-2-yl) carbonate (508)

Synthesised according to general procedure XVIII, using 492 (0.9 g, 2.64 mmol), THF (13.2 mL), Et₃N (3.7 mL, 26.36 mmol) and 4-pentenoyl chloride (507, 1.5 mL, 13.18 mmol).
mmol). The crude residue was precipitated from hexane and subsequently washed with Et₂O to afford 508 (540 mg, 48%) as a white amorphous solid. M.p. 114-116 °C.

δ_H (400 MHz, CDCl₃): 8.32-8.30 (m, 1 H, H-5), 7.46-7.43 (m, 1 H, H-2), 7.34-7.22 (m, 12 H, H-3, H-4, H-7, H-8, H-9, H-10, H-11 and H-12), 5.91 (s, 1 H, H-6), 5.81-5.71 (m, 1 H, H-14), 5.07 (app. d, 1 H, J 13.9, H-15), 5.04 (app. d, 1 H, J 8.1, H-15), 2.33-2.23 (m, 4 H, H-13 and H-14), 2.00 (s, 3 H, H-1)

δ_C (100 MHz, CDCl₃): 170.5 (C=O), 169.3 (C=O), 165.6 (q), 139.3 (q), 135.7 (q), 133.1, 129.1, 128.7, 128.5 (q), 127.4, 125.0, 123.8, 118.4, 116.3, 116.2, 106.1 (q), 58.5, 32.7, 28.3, 7.7

ν_max (neat)/cm⁻¹: 2977, 1780, 1696, 1638, 1495, 1450, 1362, 1288, 1092, 1054, 817, 741

HRMS (m/z – ESI): Found: 446.1724 [M+Na]^+ C_{28}H_{25}N_{3}NaO_{3} Requires: 446.1727

**General procedure XIX:** Rearrangement of the O-acyl group via nucleophilic catalysis.

An oven-dried 5 mL RBF containing a stirring bar was charged with the appropriate O-acylated substrate (1.0 equiv.) and p-iodoanisole (1.0 equiv.). The flask was fitted with a septum, evacuated under high vacuum and placed under an argon atmosphere (balloon). Anhydrous THF pre-treated with molecular sieves (3 Å, overall concentration 0.1 M) was added via syringe, followed by the solution of catalyst (5 mol%) in anhydrous THF, which was added to the reaction mixture via syringe. The reaction was stirred at rt for specified time. The solvent was removed in vacuo and the crude residue was purified by column chromatography on silica gel to afford the desired rearranged product.

**Note:** When TBAF (1.0 M in THF, 5 mol%) was used as the catalyst, it was added directly to the reaction mixture via syringe, once the appropriate substrate and p-iodoanisole have fully dissolved.
Diphenyl 3-methyl-2-oxoindoline-1,3-dicarboxylate (482)

Synthesised according to general procedure XIX, using 480 (109 mg, 0.281 mmol), p-iodoanisole (65.8 mg, 0.281 mmol), THF (2.8 mL) and TBAF (14.0 µL, 0.014 mmol). The reaction was allowed to stir at rt for 15 min. The crude residue was purified by column chromatography under gravity (100% CH$_2$Cl$_2$, $R_f = 0.7$) to afford 482 (33% conv. by $^1$H NMR) as a white amorphous solid. M.p. 93-95 °C. The isolated compound exhibited identical spectroscopic data to those reported in the literature.²⁷¹

Note: Anhydrous THF was not pre-treated with molecular sieves.

δ$_H$ (400 MHz, CDCl$_3$): 8.06 (d, 1 H, $J$ 8.1, H-5), 7.48-7.43 (m, 4 H, H-6, H-4 and H-2), 7.36-7.29 (m, 6 H, H-3, H-7, H-8 and H-9), 7.24-7.21 (m, 1 H, H-11), 6.98 (app. dd, 2 H, $J$ 8.4, 1.3, H-10), 1.91 (s, 3 H, H-1)

2,2,2-Trichloroethyl 1-(2,2-diphenylacetyl)-3-methyl-2-oxoindoline-3-carboxylate (495)

Synthesised according to general procedure XIX, using 494 (50 mg, 0.097 mmol), p-iodoanisole (22.6 mg, 0.097 mmol), THF (1.0 mL) and TBAOAc (1.5 mg, 0.005 mmol). The reaction was allowed to stir at rt for 30 min. The crude residue was purified by column chromatography under gravity (100% CH$_2$Cl$_2$, $R_f = 0.8$) to afford 495 (17% conv. by $^1$H NMR) as an off-white amorphous solid. M.p. 92-93 °C.

Note: Anhydrous THF was not pre-treated with molecular sieves.
δ_H (400 MHz, CDCl₃): 8.33 (d, 1 H, J 8.3, H-6), 7.41-7.20 (m, 13 H, H-3, H-4, H-5, H-8, H-9, H-10, H-11, H-12 and H-13), 6.60 (s, 1 H, H-7), 4.73 (d, 1 H, J 11.7, H-1), 4.46 (d, 1 H, H-11.7, H-1’), 1.71 (s, 3 H, H-2)

δ_C (100 MHz, CDCl₃): 174.2 (C=O), 172.9 (C=O), 167.1 (C=O), 140.4 (q), 138.2 (q), 138.1, 129.8, 129.3 (two signals), 128.6 (two signals, one is q), 128.1 (q), 127.4, 127.3, 125.7, 123.0, 117.1, 94.1 (q), 74.2, 57.5, 55.9 (q), 20.1

ν_max (neat)/cm⁻¹: 2922, 1780, 1707, 1600, 1477, 1450, 1337, 1254, 1115, 1063, 857, 749

HRMS (m/z – ESI): Found: 538.0328 [M+Na]^+ C_{26}H_{20}Cl_{3}NNaO_{4} Requires: 538.0350

3-Acetyl-1-(2,2-diphenylacetyl)-3-methylindolin-2-one (498, Table 3.4, entry 1)

Synthesised according to general procedure XIX, using 497 (50 mg, 0.130 mmol), p-iodoanisole (30.5 mg, 0.130 mmol), THF (1.3 mL) and TBAF (6.5 µL, 0.0065 mmol).

The reaction was allowed to stir at rt for 30 min. The crude residue was purified by column chromatography under gravity (100% CH₂Cl₂, R_f = 0.8) to afford 498 (91% conv. by ^1H NMR, 84%, 42.0 mg) as a white amorphous solid. M.p. 105-107 °C.

The isolated compound exhibited identical spectroscopic data to those reported in the literature.²⁶⁹

δ_H (400 MHz, CDCl₃): 8.31 (d, 1 H, J 8.2, H-6), 7.41-7.20 (m, 12 H, H-3, H-5, H-8, H-9, H-10, H-11, H-12 and H-13), 7.11 (app. dd, 1 H, J 7.6, 1.2, H-4), 6.60 (s, 1 H, H-7), 1.54 (s, 3 H, H-2), 1.50 (s, 3 H, H-1)
1-(2,2-Diphenylacetyl)-3-methyl-3-propionylindolin-2-one (509, Table 3.4, entry 3)

![Chemical Structure](image)

Synthesised according to general procedure XIX, using 504 (50 mg, 0.126 mmol), p-iodoanisole (29.4 mg, 0.126 mmol), THF (1.3 mL) and TBAF (6.3 µL, 0.0063 mmol). The reaction was allowed to stir at rt for 45 min. The crude residue was purified by column chromatography under gravity (100% CH$_2$Cl$_2$, R$_f$ = 0.8) to afford 509 (55% conv. by $^1$H NMR) as a white amorphous solid. M.p. 96-98 °C.

$\delta$H (400 MHz, CDCl$_3$): 8.30 (d, 1 H, J 8.2, H-7), 7.40-7.25 (m, 11 H, H-4, H-9, H-10, H-11, H-12, H-13 and H-14), 7.20 (app. td, 1 H, J 8.2, 1.2, H-6), 7.11 (app. dd, 1 H, J 7.6, 1.2, H-5), 6.60 (s, 1 H, H-8), 1.72-1.58 (m, 2 H, H-2), 1.55 (s, 3 H, H-3), 0.68 (t, 3 H, J 7.1, H-1)

$\delta$C (100 MHz, CDCl$_3$): 202.2 (C=O), 176.2 (C=O), 173.1 (C=O), 140.4 (q), 137.8 (q), 137.6 (q), 129.4 (two signals), 128.8 (two signals, one is q), 128.5 (two signals), 127.5, 127.4, 125.8, 123.0, 116.7, 62.2 (q), 58.1, 31.5, 19.8, 7.4

$\nu_{max}$ (neat)/cm$^{-1}$: 3029, 1747, 1715, 1478, 1451, 1354, 1255, 1180, 1129, 1063, 812, 741

HRMS (m/z – ESI): Found: 420.1562 $[\text{M+Na}]^+$ C$_{26}$H$_{23}$NNaO$_3$ Requires: 420.1570

1-(2,2-Diphenylacetyl)-3-isobutyryl-3-methylindolin-2-one (510, Table 3.4, entry 5)

![Chemical Structure](image)
Synthesised according to general procedure XIX, using 506 (50 mg, 0.122 mmol), \( p \)-iodoanisole (28.4 mg, 0.122 mmol), THF (1.2 mL) and TBAF (6.1 µL, 0.0061 mmol). The reaction was allowed to stir at rt for 120 min. The crude residue was purified by column chromatography under gravity (100\% CH\(_2\)Cl\(_2\), \( R_f = 0.8 \)) to afford 510 (7\% conv. by \(^1\)H NMR) as a white amorphous solid. M.p. 128-129 °C.

\[ \delta_H (400 \text{ MHz, CDCl}_3): \]
8.32 (d, 1 H, \( J \) 8.4, H-7), 7.41-7.26 (m, 11 H, H-4, H-9, H-10, H-11, H-12, H-13 and H-14), 7.21 (app. td, 1 H, H-6), 7.09 (app. dd, 1 H, H-5), 6.60 (s, 1 H, H-8), 1.96 (sept, 1 H, H-2), 1.54 (s, 3 H, H-3), 0.62 (d, 3 H, \( J \) 6.8, H-1), 0.56 (d, 3 H, \( J \) 6.8, H-1’)

\[ \delta_C (100 \text{ MHz, CDCl}_3): \]
205.9 (C=O), 175.7 (C=O), 173.1 (C=O), 140.5 (q), 138.0 (q), 137.6 (q), 129.5, 129.4, 129.2, 128.8, 128.5 (two signals, one is q), 127.5, 127.4, 125.7, 123.2, 116.9, 62.7 (q), 58.1, 38.3, 20.2 (two signals), 19.3

\[ \nu_{\text{max}} (\text{neat})/\text{cm}^{-1}: \]
2968, 1749, 1710, 1600, 1452, 1350, 1275, 1254, 1181, 1128, 1008, 877, 751, 738

HRMS (m/z – APCI):
Found: 412.1909 [M+H]\(^+\) \( C_{27}H_{26}NO_3 \) Requires: 412.1907

1-(2,2-Diphenylacetyl)-3-methyl-3-(pent-4-enoyl)indolin-2-one (511, Table 3.4, entry 7)

[Diagram of the molecule]

Synthesised according to general procedure XIX, using 508 (50 mg, 0.118 mmol), \( p \)-iodoanisole (27.6 mg, 0.118 mmol), THF (1.2 mL) and TBAF (5.9 µL, 0.0059 mmol). The reaction was allowed to stir at rt for 45 min. The crude residue was purified by column chromatography under gravity (100\% CH\(_2\)Cl\(_2\), \( R_f = 0.8 \)) to afford 511 (61\% conv. by \(^1\)H NMR) as a clear oil.
δ_H (400 MHz, CDCl₃): 8.31 (d, 1 H, J 8.2, H-9), 7.41-7.26 (m, 11 H, H-6, H-11, H-12, H-13, H-14, H-15 and H-16), 7.21 (app. td, 1 H, J 8.2, 1.1, H-8), 7.10 (app. dd, 1 H, J 7.6, 1.1, H-7), 6.60 (s, 1 H, H-10), 5.46-5.36 (m, 1 H, H-2), 4.83 (dd, 1 H, J 1.3, 10.1, H-1 cis), 4.76 (dd, 1 H, J 1.3, 17.2, H-1 trans), 2.01-1.96 (m, 2 H, H-4), 1.87-1.69 (m, 2 H, H-3), 1.55 (s, 3 H, H-5)

δ_C (100 MHz, CDCl₃): 200.6 (C=O), 176.0 (C=O), 173.1 (C=O), 140.4 (q), 137.9 (q), 137.6 (q), 136.2, 129.5, 129.4, 129.3, 128.8, 128.5 (two signals, one of which is q), 127.6, 127.4, 125.8, 123.1, 116.8, 115.4, 62.3 (q), 58.1, 37.2, 27.0, 19.9

ν_max (neat)/cm⁻¹: 3030, 1750, 1714, 1600, 1451, 1336, 1254, 1125, 995, 911, 733, 697

HRMS (m/z – ESI): Found: 446.1727 [M+Na]^+  C_{28}H_{25}N_{1}NaO_3 Requires: 446.1727

3-Acetyl-3-benzyl-1-(2,2-diphenylacetetyl)indolin-2-one (516, Table 3.5, entry 2)

Synthesised according to general procedure XIX, using 515 (50 mg, 0.109 mmol), p-iodoanisole (25.5 mg, 0.109 mmol), THF (1.1 mL) and TBAF (5.5 µL, 0.0055 mmol). The reaction was allowed to stir at rt for 30 min. The crude residue was purified by column chromatography under gravity (100% CH₂Cl₂, R_f = 0.8) to afford 516 (92% conv. by ¹H NMR) as a white amorphous solid. M.p. 97-99 °C. The isolated compound exhibited identical spectroscopic data to those reported in the literature.²⁶⁹

δ_H (400 MHz, CDCl₃): 8.10 (d, 1 H, J 8.1, H-9), 7.35-7.24 (m, 11 H, H-6, H-11, H-12, H-13, H-14, H-15 and H-16), 7.18-7.16 (m, 2 H, H-4), 7.03 (app. td, 1 H, J 8.1, 1.2, H-8), 6.95-6.91 (m, 2 H, 334
H-5 and H-7), 6.68 (app. d, 2 H, J 7.5, H-3), 6.49 (s, 1 H, H-10), 3.45 (s, 2 H, H-2), 1.68 (s, 3 H, H-1)

3-Acetyl-3-allyl-1-(2,2-diphenylacetyl)indolin-2-one (517, Table 3.5, entry 3)

![Chemical Structure](image)

Synthesised according to general procedure XIX, using 513 (50 mg, 0.122 mmol), p-iodoanisole (28.4 mg, 0.122 mmol), THF (1.2 mL) and TBAF (6.1 µL, 0.0061 mmol). The reaction was allowed to stir at rt for 15 min. The crude residue was purified by column chromatography under gravity (100% CH₂Cl₂, Rf = 0.8) to afford 517 (81% conv. by ¹H NMR, 72%, 36.0 mg) as a white solid. M.p. 89-92 °C. The isolated compound exhibited identical spectroscopic data to those reported in the literature.²⁶⁹

δH (400 MHz, CDCl₃):  8.30 (d, 1 H, J 8.3, H-8), 7.39 (app. td, 1 H, J 8.3, 1.2, H-7), 7.36-7.22 (m, 11 H, H-5, H-10, H-11, H-12, H-13, H-14 and H-15), 7.14 (app. td, 1 H, J 7.6, 1.2, H-6), 6.59 (s, 1 H, H-9), 5.10-5.00 (m, 1 H, H-3), 4.86 (dd, 1 H, J 16.8, 1.3, H-4 trans), 4.76 (dd, 1 H, J 9.8, 1.3, H-4 cis), 2.90-2.79 (m, 2 H, H-2), 1.62 (s, 3 H, H-1)

3-Acetyl-1-(2,2-diphenylacetyl)-3-isopropylindolin-2-one (518, Table 3.5, entry 4)

![Chemical Structure](image)

Synthesised according to general procedure XIX, using 512 (50 mg, 0.122 mmol), p-iodoanisole (28.4 mg, 0.122 mmol), THF (1.2 mL) and TBAF (6.1 µL, 0.0061 mmol). The reaction was allowed to stir at rt for 45 min. The crude residue was purified by column chromatography under gravity (100% CH₂Cl₂, Rf = 0.7) to afford 518 (14%
conv. by $^1$H NMR) as a white amorphous solid. M.p. 91-93 °C. The isolated compound exhibited identical spectroscopic data to those reported in the literature.$^{269}$

$\delta_H$ (400 MHz, CDCl$_3$): 8.27 (d, 1 H, J 8.3, H-7), 7.39-7.21 (m, 13 H, H-4, H-5, H-6, H-9, H-10, H-11, H-12, H-13 and H-14), 6.61 (s, 1 H, H-8), 2.73 (sept, 1 H, J 6.8, H-2), 1.81 (s, 3 H, H-1), 0.81 (d, 3 H, J 6.8, H-3), 0.58 (d, 3 H, J 6.8, H-3')
5.4 Experimental data for Chapter 4

(R)-(1S,2S,4S,5R)-1-(3,5-di-tert-butylbenzyl)-5-vinylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methanol (526)

Synthesised according to general procedure XII, using 39 (1.0 g, 3.08 mmol), 3,5-di-tert-butylbenzyl bromide (1.05 g, 3.70 mmol) and PhCH₃ (31.0 mL). The crude residue was purified by column chromatography (eluting gradient from 100% CH₂Cl₂ to 95:5 CH₂Cl₂/MeOH, TLC is better visualised using CH₂Cl₂/MeOH 10:1, Rᵣ = 0.3), to afford 526 (1.3 g, 70%) as a white amorphous solid. M.p. 190-194 °C (lit.¹¹⁶ 197-198 °C); [α]D²⁰ = -166.3 (c = 0.6, MeOH). The isolated compound exhibited identical spectroscopic data to those reported in the literature.¹¹⁶

δ_H (400 MHz, dmso-d₆):

8.78 (d, 1 H, J 4.5, H-16), 8.01 (d, 1 H, J 9.2, H-15), 7.70 (d, 1 H, J 4.5, H-17), 7.52 (app. s, 1 H, H-21), 7.49 (dd, 1 H, J 9.2, 2.2, H-14), 7.46 (app. d, 2 H, J 1.5, H-19), 7.43 (d, 1 H, J 2.2, H-12), 6.68 (d, 1 H, J 4.8, OH), 6.55 (d, 1 H, J 4.8, H-9), 5.81-5.72 (m, 1 H, H-10), 5.32 (d, 1 H, J 12.4, H-18b), 5.09 (d, 1 H, J 17.2, H-11a), 5.00 (d, 1 H, J 10.4, H-11b), 4.76 (d, 1 H, J 12.4, H-18a), 4.33-4.28 (m, 1 H, H-6a), 4.02 (s, 3 H, H-13), 3.83-3.78 (m, 1 H, H-8), 3.67-3.63 (m, 1 H, H-2b), 3.37-3.31 (m, 1 H, H-6b), 3.24-3.17 (m, 1 H, H-2a), 2.75-2.70 (m, 1 H, H-3), 2.26-2.21 (m, 1 H, H-7b), 2.17-2.10 (m, 1 H, H-5b), 2.00-1.98 (m, 1 H, H-4), 1.89-1.84 (m, 1 H, H-7a), 1.56-1.51 (m, 1 H, H-5a), 1.28 (app. s, 18 H, H-20)
(R)-((1S,2S,4S,5R)-1-(3,5-bis(trifluoromethyl)benzyl)-5-vinylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methanol (531)

Synthesised according to general procedure XIII, using 39 (1.0 g, 3.08 mmol), 3,5-bis(trifluoromethyl)benzyl bromide (0.7 mL, 3.70 mmol) and PhCH₃ (31.0 mL). The crude residue was purified by column chromatography (eluting gradient from 100% CH₂Cl₂ to 95:5 CH₂Cl₂/MeOH, TLC is better visualised using CH₂Cl₂/MeOH 10:1, Rf = 0.3), to afford 531 (1.4 g, 72%) as a white amorphous solid. M.p. 179-182 °C (lit.317 192 °C); [α]D₂₀ = -182.9 (c = 0.4, MeOH). The isolated compound exhibited identical spectroscopic data to those reported in the literature.317

δH (400 MHz, dmso-d₆): 8.81 (d, 1 H, J 4.5, H-16), 8.48 (s, 2H, H-19), 8.36 (s, 1 H, H-20), 8.03 (d, 1 H, J 9.3, H-15), 7.75 (d, 1 H, J 4.5, H-17), 7.51 (dd, 1 H, J 9.3, 2.2, H-14), 7.39 (d, 1 H, J 2.2, H-12), 6.69 (d, 1 H, J 4.0, OH), 6.54 (d, 1 H, J 4.0, H-9), 5.80-5.72 (m, 1 H, H-10), 5.61 (d, 1 H, J 12.4, H-18b), 5.13 (d, 1 H, J 17.2, H-11a), 5.02 (d, 1 H, J 10.6, H-11b), 4.97 (d, 1 H, J 12.4, H-18a), 4.40-4.34 (m, 1 H, H-6a), 4.02 (s, 3 H, H-13), 3.84-3.75 (m, 2 H, H-8 and H-2b), 3.48-3.42 (m, 1 H, H-6b), 3.29-3.22 (m, 1 H, H-2a), 2.68-2.62 (m, 1 H, H-3), 2.28-2.23 (m, 1 H, H-7b), 2.18-2.11 (m, 1 H, H-5b), 2.03-2.01 (m, 1 H, H-4), 1.83-1.78 (m, 1 H, H-7a), 1.51-1.45 (m, 1 H, H-5a)

9-(Bromomethyl)anthracene (532a)
An oven-dried 100 mL round-bottomed flask containing a stirring bar was charged with 9-hydroxymethylanthracene (1.2 g, 5.762 mmol, 1.0 equiv.) and placed under argon atmosphere. Anhydrous PhMe (32.0 mL, 0.18 M) was added to the flask via syringe, and the reaction mixture was cooled to 0 °C. Next, phosphorus tribromide (0.65 mL, 6.914 mmol, 1.2 equiv.) was added to the mixture via syringe and the reaction was allowed to warm up to rt over 1 h. Upon completion of the reaction, the solvent was removed in vacuo and the crude residue was recrystallised from hexane/EtOAc solvent mixture to afford 532a (1.0 g, 65%) as yellow needle-like crystals. M.p. 141-143 °C (lit. 178 140-142 °C). The isolated compound exhibited identical spectroscopic data to those reported in the literature. ¹⁷⁸

δ_H (400 MHz, CDCl₃): 8.51 (s, 1 H, H-6), 8.31 (d, 2 H, J 9.0, H-2), 8.05 (d, 2 H, J 9.0, H-5), 7.65 (app. td, 2 H, J 7.7, 1.0, H-4), 7.51 (app. td, 2 H, J 7.7, 1.0, H-3), 5.56 (s, 2 H, H-1)

(R)-((1S,2S,4S,5R)-1-(anthracenyl)-5-vinylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methanol (532)

Synthesised according to general procedure XIII, using 39 (1.0 g, 3.082 mmol), 9-(bromomethyl)anthracene (532a, 1.0 g, 3.70 mmol) and PhCH₃ (31.0 mL). The crude residue was purified by column chromatography (eluting gradient from 100% CH₂Cl₂ to 95:5 CH₂Cl₂/MeOH, TLC is better visualised using CH₂Cl₂/MeOH 10:1, R_f = 0.3) and precipitated from Et₂O, to afford 532 (1.2 g, 63%) as a brown amorphous solid. M.p. 191-193 °C (lit. 318 189-193 °C); [α]_D ²⁰ = -384.9 (c = 0.8, MeOH). The isolated compound exhibited identical spectroscopic data to those reported in the literature. ³¹⁸

δ_H (400 MHz, dmsO-d₆): 8.98 (s, 1 H, H-23), 8.87 (d, 1 H, J 4.5, H-16), 8.81 (dd, 2 H, J 23.1, 9.0, H-19), 8.27 (d, 2 H, J 8.3, H-22), 8.06, (d, 1 H, J 9.2, H-15), 7.88 (d, 1 H, J 4.5, H-7), 7.81-7.73 (m,
2 H, H-21), 7.70-7.63 (m, 3 H, H-20 and H-12), 7.53 (dd, 1 H, J 9.2, 2.5, H-14), 7.16 (d, 1 H, J 3.0, OH), 7.07 (s, 1 H, H-9), 6.65 (d, 1 H, J 14.0, H-18b), 5.76-5.64 (m, 2 H, H-10 and H-18a), 4.97-4.91 (m, 2 H, H-11), 4.60-4.56 (m, 1 H, H-6a), 4.53-4.48 (m, 1 H, H-8), 4.05 (s, 3 H, H-3), 3.88-3.83 (m, 1 H, H-2b), 3.05-3.00 (m, 1 H, H-6b), 2.87-2.80 (m, 1 H, H-2a), 2.41-2.37 (m, 1 H, H-3), 2.29-2.25 (m, 1 H, H-7b), 2.17-2.11 (m, 1 H, H-5b), 1.90-1.87 (m, 1 H, H-4), 1.62-1.57 (m, 1 H, H-7a), 1.50-1.44 (m, 1 H, H-5a)

(1S,2S,4S,5R)-2-((S)-(3,5-bis(trifluoromethyl)phenyl)ureido)(6-methoxy-2-phenylquinolin-4-yl)methyl)-1-(4-nitrobenzyl)-5-vinquinuclidin-1-ium bromide (547)

Synthesised according to general procedure XIII, using 323 (128 mg, 0.20 mmol), 4-nitrobenzyl bromide (51.0 mg, 0.24 mmol) and CH₂Cl₂ (2.0 mL). The crude residue was purified by column chromatography (eluting gradient from 98:2 to 95:5 CH₂Cl₂/MeOH, TLC is better visualised using CH₂Cl₂/MeOH 10:1, Rᵣ = 0.3), to afford 547 (140 mg, 82%) as a white amorphous solid. M.p. 179-182 °C; [α]D²⁰ = +98.9 (c = 0.1, CHCl₃).

δH (400 MHz, dmso-d₆): 9.65 (s, 1 H, NH⁺), 8.37-8.26 (m, 6 H, H-17, H-18, H-15, H-21), 8.10-8.04 (m, 5 H, H-25, H-12, H-19), 7.67 (s, 1 H, NH²), 7.61-7.52 (m, 5 H, H-24, H-22, H-20, H-14), 6.36-6.31 (m, 1 H, H-9), 5.92-5.84 (m, 1 H, H-10), 5.29-5.08 (m, 5 H, H-8, H-23a, H-23b and H-11), 4.41-4.37 (m, 1 H, H-6a), 4.06 (s, 3 H, H-13), 3.70-3.68 (m, 1 H, H-
2b), 3.62-3.55 (m, 2 H, H-6b and H-2a), 2.79-2.74 (m, 1 H, H-3), 2.10-1.94 (m, 4 H, H-5a, H-5b, H-7b and H-4), 1.27-1.22 (m, 1 H, H-7a)

**Note:** $^1$H NMR spectrum was recorded at 80 °C for more defined resonance signals.

$\delta_C$ (100 MHz, dmoso-$d_6$): 158.6 (C=O), 154.8 (q), 154.3 (q), 149.0 (q), 144.9 (q), 144.7 (q), 142.0 (q), 139.0 (q), 137.5, 135.7, 135.6 (q), 132.4, 131.1 (q, $J_{C-F} 32.6$) (q), 130.0, 129.3, 127.6, 126.5 (q), 124.3, 123.7 (q, $J_{C-F} 272.6$) (q), 122.7, 118.3, 117.8, 117.7, 115.0, 102.5, 66.6, 64.2, 60.8, 56.1, 50.5, 50.2, 37.3, 27.3, 26.3, 24.7

$\delta_F$ (376 MHz, dmoso-$d_6$): -61.8

$\nu_{\text{max}}$ (neat)/cm$^{-1}$: 2950, 1798, 1689, 1528, 1385, 1350, 1277, 1176, 1129, 1023, 832, 740, 699

HRMS ($m/z$ – APCI): Found: 790.2793 [M]$^+$ C$_{42}$H$_{38}$N$_5$O$_4$F$_6$ Requires: 790.2823

### 2-bromo-4-(bromomethyl)-1-nitrobenzene (550)

A 100 mL round-bottomed flask containing a stirring bar was charged with 3-bromo-4-nitrotoluene (549, 2 g, 9.26 mmol, 1.0 equiv.), NBS (1.98 g, 11.11 mmol, 1.2 equiv.), AIBN (152.0 mg, 0.926 mmol, 10 mol%) and CCl$_4$ (34.0 mL, 0.27 M). The reaction mixture was heated to 95 °C and allowed to stir at this temperature for 24 h. Upon cooling the reaction to rt, the solvent was removed *in vacuo* and the crude residue was purified by column chromatography (petroleum ether/EtOAc 8:2, $R_f = 0.4$) to afford 550 (1.7 g, 63%) as a yellow amorphous solid. M.p. 73 °C. The isolated compound exhibited identical spectroscopic data to those reported in the literature.$^{319}$

$\delta_H$ (400 MHz, CDCl$_3$): 7.84 (d, 1 H, $J$ 8.4, H-3), 7.77 (d, 1 H, $J$ 1.8, H-2), 7.47 (dd, 1 H, $J$ 8.4, 1.8, H-4), 4.44 (s, 2 H, H-1)
Synthesised according to general procedure XIII, using 323 (0.3 g, 0.458 mmol), 550 (162.0 mg, 0.550 mmol) and CH$_2$Cl$_2$ (4.6 mL). The crude residue was purified by column chromatography (eluting gradient from 100% CH$_2$Cl$_2$ to 98:2 CH$_2$Cl$_2$/MeOH, TLC is better visualised using CH$_2$Cl$_2$/MeOH 10:1, R$_f$ = 0.3), affording 551 (313 mg, 72%) as a white amorphous solid. M.p. 181-184 °C; [α]$_D$ = +84.7 (c = 0.6, CHCl$_3$).

δ$_H$ (400 MHz, dmso-$d_6$): 9.49 (s, 1 H, NH$_1$), 8.31-8.24 (m, 4 H, H-17, H-18, H-25), 8.20-8.15 (m, 2 H, H-15 and H-24), 8.10 (d, 1 H, J = 9.0, H-26), 8.03 (app. s, 2 H, H-21), 8.00-7.98 (m, 1 H, H-14), 7.66 (br s, 1 H, NH$_2$), 7.61-7.58 (m, 2 H, H-19), 7.54-7.51 (m, 3 H, H-22, H-20 and H-12), 6.32-6.27 (m, 1 H, H-9), 5.92-5.83 (m, 1 H, H-10), 5.27-5.17 (m, 2 H, H-23a and H-23b), 5.12-4.98 (m, 3 H, H-11 and H-8), 4.38-4.33 (m, 1 H, H-6a), 4.05 (s, 3 H, H-13), 3.81-3.76 (m, 1 H, H-2b), 3.58-3.55 (m, 2 H, H-2a and H-6b), 2.81-2.74 (m, 1 H, H-3), 2.12-1.95 (m, 4 H, H-5a, H-5b, H-7b and H-4), 1.26-1.22 (m, 1 H, H-7a)

Note: $^1$H NMR spectrum was recorded at 80 °C for more defined resonance signals.

δ$_C$ (100 MHz, dmso-$d_6$): 158.2 (C=O), 154.4 (q), 153.9 (q), 150.8 (q), 144.3 (q), 144.2 (q), 141.5 (q), 139.2, 138.6 (q), 137.0, 134.5, 133.8 (q), 132.0, 130.7 (q, J$_{C-F}$ 32.6) (q), 129.6, 128.9, 127.2, 126.1 (q), 125.5, 123.3 (q, J$_{C-F}$ 272.4) (q), 122.3, 118.3,
δ_F (376 MHz, dmso-d_6): -61.7

ν_max (neat)/cm^{-1}:
3003, 1710, 1566, 1535, 1389, 1278, 1180, 1128, 1031, 882, 826, 651

HRMS (m/z – APCI):
Found: 868.1907 [M]^+  C_{42}H_{37}BrN_{5}O_{4}F_{6}  Requires: 868.1928

(1S,2S,4S,5R)-2-((S)-(3,5-bis(trifluoromethyl)phenyl)ureido)(6-methoxy-2-phenylquinolin-4-yl)methyl)-1-(3-fluoro-4-nitrobenzyl)-5-vinylquinuclidin-1-ium bromide (552)

Synthesised according to general procedure XIII, using 323 (0.3 g, 0.458 mmol), 3-fluoro-4-nitrobenzyl bromide (129.0 mg, 0.550 mmol) and CH_2Cl_2 (4.6 mL). The crude residue was purified by column chromatography (eluting gradient from 100% CH_2Cl_2 to 97:3 CH_2Cl_2/MeOH, TLC is better visualised using CH_2Cl_2/MeOH 10:1, R_f = 0.4), affording 552 (228 mg, 56%) as an off-white amorphous solid. M.p. 179-182 °C; [α]_D^{20} = +121.7 (c = 0.2, CHCl_3).

δ_H (400 MHz, dmso-d_6):
9.60 (br s, 1 H, NH^1), 8.33-8.25 (m, 5 H, H-18, H-17, H-25 and H-24), 8.10 (d, 1 H, J 9.2, H-15), 8.04-8.02 (m, 3 H, H-21 and H-26), 7.83 (app. dd, 1 H, J 9.2, 1.3, H-14), 7.65-7.52 (m, 6 H, H-19, H-20, H-12, H-22 and NH^2), 6.32-6.27 (m, 1 H, H-9), 5.91-5.82 (m, 1 H, H-10), 5.28-5.01 (m, 5 H, H-23a, H-23b, H-11 and H-8), 4.38-4.33 (m, 1 H, H-6a), 4.05 (s, 3 H, H-13), 3.79-3.74 (m, 1 H, H-
2b), 3.62-3.55 (m, 2 H, H-2a and H-6b), 2.79-2.73 (m, 1 H, H-3), 2.15-1.95 (m, 4 H, H-5a, H-5b, H-7b and H-4), 1.25-1.21 (m, 1 H, H-7a)

**Note:** ^1H NMR spectrum was recorded at 60 °C for more defined resonance signals.

\[ \delta_C \ (100 \text{ MHz, dms}-d_6): \]

158.6 (C=O), 155.5 (q), 154.9 (q), 154.3 (q), 153.8 (q), 144.9 (q), 144.7 (q), 142.0 (q), 139.0, 138.4 (d, \( J_{C-F} \) 7.8) (q), 137.4, 136.9 (d, \( J_{C-F} \) 8.4) (q), 132.4, 131.2 (d, \( J_{C-F} \) 2.3) (q), 131.1 (q, \( J_{C-F} \) 32.4) (q), 130.0, 129.3, 127.6, 127.0, 126.5, 124.1 (d, \( J_{C-F} \) 21.1), 123.6 (q, \( J_{C-F} \) 27.2) (q), 122.8, 118.3, 117.8 (d, \( J_{C-F} \) 14.4), 115.0, 102.5, 66.5, 63.7, 61.1, 56.1, 50.7, 50.2, 37.3, 27.2, 26.2, 24.7

\[ \delta_F \ (376 \text{ MHz, dms}-d_6): \]

-61.8 (CF3), -118.7 (F)

\[ \nu_{\text{max}} \ (\text{neat})/\text{cm}^{-1}: \]

3003, 1707, 1621, 1534, 1278, 1179, 1128, 1030, 882, 828, 651

**HRMS (m/z – APCI):**

Found: 808.2734 [M]^+ \( \text{C}_{42}\text{H}_{37}\text{N}_5\text{O}_4\text{F}_7 \) Requires: 808.2728

(1S,2R,3S,4R)-3-(Methoxycarbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (285)

*Cis*-5-norbornene-endo-2,3-dicarboxylic anhydride (284, 50 mg, 0.304 mmol), the appropriate catalyst (5 mol%) and KF (15 mol%, 2.7 mg, 0.046 mmol) were placed in an oven-dried 5 mL RBF containing a stirring bar. The flask was fitted with a septum, evacuated under high vacuum and placed under an argon atmosphere (balloon). Anhydrous THF (3.0 mL, 0.1 M), and anhydrous MeOH (61.5 µL, 1.52 mmol, 5.0 equiv.) were added to the flask via syringe. The septum was replaced with a glass stopper under the flow of argon and the reaction was left stirring at rt for 48 h. Pyrrolidine (25.4 µL, 0.304 mmol, 1.0 equiv.) was added via syringe to quench any remaining starting material and the mixture was allowed to stir for 1 h. The solvent was removed *in vacuo* and the crude residue was purified *via* column chromatography.
(CH₂Cl₂/MeOH 20:1) to afford 285 as a white solid. M.p. 75-78 °C. The isolated compound exhibited identical spectroscopic data to those reported in the literature.²³⁸

δ_H (400 MHz, CDCl₃): 6.36 (dd, 1 H, J 5.5, 3.0, H-4), 6.24 (dd, 1 H, J 5.5, 3.0, H-5), 3.62 (s, 3 H, H-1), 3.37 (dd, 1 H, J 10.0, 3.0, H-7), 3.31 (dd, 1 H, J 10.0, 3.0, H-2), 3.28-3.15 (m, 2 H, H-3 and H-6), 1.52 (app. dt, 1 H, J 9.2, 2.2, H-8b), 1.36 (app. d, 1 H, J 9.2, H-8a)

**General procedure XX:** Derivatisation of hemiester 285 for CSP-HPLC analysis.

An oven-dried 5 mL RBF flask containing a stirring bar was charged with hemiester 285 (1.0 equiv.), DCC (1.1 equiv.) and DMAP (10 mol%). The flask was fitted with a septum, evacuated under high vacuum and placed under an argon atmosphere (balloon). Anhydrous CH₂Cl₂ (0.1 M) was added via syringe, followed by (R)-1-(naphthalen-1-yl)ethan-1-amine (535, 1.0 equiv.) also added via syringe. The reaction mixture was allowed to stir at rt for 16 h, then diluted with CH₂Cl₂ (3 mL), filtered under gravity and purified via preparative TLC (CH₂Cl₂/EtOAc 5:1). The resulting derivative 536 was analysed by CSP-HPLC.

CSP-HPLC analysis. Chiralcel AD-H (4.6 mm x 25 cm), hexane/IPA: 90/10, 0.75 mL min⁻¹, rt, UV detection at 254 nm, retention times: 11.8 min (minor enantiomer) and 18.5 min (major enantiomer).
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Appendix

X-ray crystallography data for (S)-459

Small Molecule X-ray Facility
School of Chemistry
Structure Report

Filename: TCD929

Submitted by: Mili Litvajova
Reference: ML-1153

Figure 1. Four independent molecules in the asymmetric unit of TCD929 with atomic displacement shown at 50% probability. Only heteroatoms labelled for clarity.

15/11/17

Author: Brendan Twamley
**Figure 2.** Packing diagram of TCD923 viewed normal to the a-axis. Dashed lines indicate weak non-conventional CH…O intra and intermolecular hydrogen bonding.

**Figure 3.** Overlay image of all four independent molecules in TCD929 highlighting the differences. Hydrogen atoms omitted for clarity.
Crystal Structure Report for TCD929

A specimen of C_{21}H_{16}F_{3}NO_{7}, approximate dimensions 0.030 mm x 0.030 mm x 0.430 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 100(2)K on a Bruker APEX Kappa Duo with an Oxford Cobra low temperature device using a MiTeGen micromount. See Table 1 for collection parameters and exposure time. Bruker APEX software was used to correct for Lorentz and polarization effects.

A total of 3894 frames were collected. The total exposure time was 42.05 hours. The integration of the data using a triclinic unit cell yielded a total of 51848 reflections to a maximum θ angle of 68.55° (0.83 Å resolution), of which 14250 were independent (average redundancy 3.638, completeness = 99.7%, R_{int} = 17.02%, R_{sig} = 20.31%) and 8055 (56.53%) were greater than 2σ(F^2). The final cell constants of a = 6.0411(3) Å, b = 15.5976(8) Å, c = 22.2056(10) Å, α = 102.604(3)°, β = 90.411(4)°, γ = 97.014(3)°, volume = 2025.42(17) Å^3, are based upon the refinement of the XYZ-centroids of reflections above 20 σ(I). Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.784. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.5906 and 0.7531.

The structure was solved with the XT structure solution program using Intrinsic Phasing and refined with the XL refinement package using Least Squares minimisation with Olex2, using the space group P1, with Z = 4 for the formula unit, C_{21}H_{16}F_{3}NO_{7}. The final anisotropic full-matrix least-squares refinement on F^2 with 1161 variables converged at R1 = 8.36%, for the observed data and wR2 = 23.33% for all data. The goodness-of-fit was 1.042. The largest peak in the final difference electron density synthesis was 0.372 e/Å^3 and the largest hole was -0.370 e/Å^3 with an RMS deviation of 0.083 e/Å^3. On the basis of the final model, the calculated density was 1.480 g/cm^3 and F(000), 928 e^-.

**Refinement Note:** small weakly diffracting chiral sample with 4 independent molecules in the asymmetric unit. Model has Chirality at C12A, S;C12B, S;C12C, S;C12D, S.

**References:**


The complete crystallography report is available upon request.