

Practical and enantioselective amino acid synthesis *via* novel catalytic ring opening processes



Trinity College Dublin

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

by

Sarah Cronin

Under the supervision of

Prof. Stephen Connon

January 2019

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.

I agree to deposit this thesis in the University's open access institutional repository or allow the library to do so on my behalf, subject to Irish Copyright Legislation and Trinity College Library conditions of use and acknowledgement.

Sarah Cronin

S. A. Cronin, A. Gutiérrez Collar, S. Gundala, C. Cornaggia, E. Torrente, F. Manoni, A. Botte, B. Twamley and S. J. Connon, *Org. Biomol. Chem.*, 2016, **14**, 6955-6959.

R. Craig, M. Litvajova, S. A. Cronin and S. J. Connon, *Chem. Commun.*, 2018, **54**, 10108-10111.

.

Table of contents

1	Introduction.....	1
1.1	Catalysis: An introduction	1
1.2	Chirality: General remarks.....	2
1.3	Asymmetric synthesis	2
1.3.1	Chiral pool-based methodologies.....	3
1.3.2	The use of chiral auxiliaries	3
1.3.3	Kinetic Resolution.....	4
1.3.4	Dynamic Kinetic Resolution.....	5
1.3.5	Asymmetric catalysis	5
1.4	Organocatalysis.....	6
1.4.1	Asymmetric aminocatalysis	7
1.4.2	Hydrogen bond catalysis.....	9
1.5	Chiral bifunctional catalysis.....	11
1.6	Phase-transfer catalysis (PTC)	18
1.7	The Dynamic Kinetic Resolution of Azlactones.....	22
1.7.1	Ti-TADDOLate catalysed DKR of azlactones	22
1.7.2	DKR of azlactones using acyl transfer catalysts	22
1.7.3	DKR of azlactones using bifunctional organocatalysis.....	23
1.7.4	DKR of azlactones using Brønsted acid catalysts.....	25
1.8	Kinetic resolution of oxazinones <i>via</i> alcoholysis.....	26
1.8.1	The importance of β -amino acids.....	27
1.8.2	Kinetic resolution of oxazinones: A historical perspective.....	27
1.8.3	Challenges associated with current methods for the KR of oxazinones	31
1.8.4	Objectives	32
1.9	Cyclic anhydrides in formal cycloaddition reactions.....	33
1.9.1	The formal cycloaddition reaction between enolisable anhydrides and aldehydes.....	34
1.9.2	The asymmetric cycloaddition between enolisable anhydrides and other electrophiles 38	
1.9.3	The formal cycloaddition between enolisable anhydrides and imines.....	40
1.9.4	A historical perspective of the reaction between enolisable anhydrides and imines	41
1.9.5	Multicomponent coupling reactions.....	43
1.9.6	This work	44
1.9.7	Recent developments	44
1.10	Asymmetric organocatalysis with chiral ammonium fluorides.....	46

1.10.1	Fluoride as a nucleophilic catalyst	46
1.10.2	Chiral ammonium fluorides: a historical perspective	49
1.11	Asymmetric desymmetrisation of <i>meso</i> -anhydrides	54
1.11.1	The desymmetrisation of <i>meso</i> -anhydrides by alcoholysis.....	55
1.11.2	Asymmetric desymmetrisation of anhydrides <i>via</i> organocatalysis	55
1.11.3	Acyl-transfer catalysis by fluoride ion.....	57
1.12	Steglich rearrangement of 2-oxindole derivatives	58
1.12.1	O-acylated rearrangements by fluoride ion.....	59
1.13	The KR of acyl centres <i>via</i> aminolysis	59
1.13.1	Purpose.....	61
2	The KR of TCIC-Oxazinones to yield enantioenriched and orthogonally protected β-amino acids.....	63
2.1	The rationale behind the design of the TCIC-subunit.....	63
2.2	The substrate development of TCIC-oxazinones.....	65
2.3	An alternative synthesis of oxazinone 144a.....	70
2.4	Evaluation of the racemic process	72
2.5	Preliminary evaluation of organocatalysts in the KR of oxazinones <i>via</i> alcoholysis	72
2.6	Varying the nucleophilic component	76
2.7	Further catalyst development and evaluation.....	77
2.8	A new class of catalyst.....	81
2.9	Amine-catalysed ring closure to form phthalimide protected products <i>in situ</i>	88
2.10	Synthesis of phthalimide protected amino-ester racemates	90
2.11	Final optimisation of the reaction conditions for the kinetic resolution	91
2.12	KR of 4-oxazinones to yield enantioenriched and orthogonally protected β_3 amino acids... 94	
2.13	Stereochemical rationale	96
2.14	KR of 5-oxazinones to access enantioenriched β^2 -amino acids.....	97
2.15	The design and synthesis of the TCIC-substituted 5-oxazinones	98
2.16	Preliminary evaluation of oxazinone 383 for KR by alcoholysis	100
2.17	Controlling KR vs DKR.....	106
2.18	Conclusion	108
3	The KR of 7-membered rings <i>via</i> alcoholysis to furnish γ-amino acids products	109
3.1	Premise.....	109
3.2	The importance of γ -amino acids.....	109
3.3	The design of the novel TCIC-7-membered rings	110
3.4	Evaluation of 410 for ring opening alcoholysis	113
3.5	Conclusion	114
4	Formal cycloaddition reactions of cyclic anhydrides with imines	115
4.1	Preamble	115

4.2	Preliminary experiments	119
4.3	Optimisation of the esterification protocol	120
4.4	Epimerisation mechanism	122
4.5	Catalyst screen	123
4.6	Evaluation of substrate scope.....	125
4.7	Stereochemical rationale	128
4.8	Conclusion	131
5	Fluoride catalysed desymmetrisations	132
5.1	Generation of the chiral quaternary ammonium fluoride catalysts	132
5.2	Design of a reproducible reaction	133
5.3	Catalyst synthesis and screening.....	134
5.4	Optimisation of the reaction conditions	139
5.5	Mechanistic insight	141
5.6	Recent developments	142
5.7	Conclusion	144
6	Steglich rearrangement of 2-oxindoles catalysed by Fluoride ion.....	145
6.1	Preliminary studies.....	145
6.2	Mechanistic insights.....	146
6.3	Substrate synthesis	147
6.4	TBAF-catalysed Steglich esterification of 2-oxindoles	150
6.5	Efforts towards an enantioselective reaction.....	152
6.6	Conclusion	153
7	The fluoride catalysed aminolysis of oxazinones.....	154
7.1	Preliminary experiments	154
7.2	Design of the amide pronucleophile	156
7.3	Development of the fluoride -catalysed aminolysis of oxazinones.....	157
7.4	Attempted KR of oxazinone 617 via aminolysis	164
7.5	Conclusion	166
8	Fluorinolysis of azlactones	167
8.1	Premise.....	167
8.2	Preliminary experiments	169
8.3	An alternative approach	172
8.4	Conclusion	176
9	Conclusion	177
10	Experimental	179
10.1	General experimental data	179
10.2	Gradient tables for HPLC conditions.....	180

10.3	Experimental data for section 2	181
10.4	Experimental data for section 3	241
10.5	Experimental data for section 4	245
10.6	Experimental data for Section 5.....	260
10.7	Experimental data for Section 6.....	268
10.8	Experimental data for Section 6.....	277
10.9	Experimental data for Section 8.....	288
11	References.....	291
12	Appendix.....	300
12.1	X-ray crystallography data for	300

Acknowledgements

First and foremost I would like to thank my family: my parents, Kitty and John, for sacrificing so much for my education and my brother Neil Cronin B.A., for keeping me fed for those months when money ran short. Also, for providing healthy competition as to who is the favourite child in the family. Looking forward to your next move.

A special thank you to my supervisor Professor Stephen Connon for his endless support and encouragement. For excellent advice both academic and otherwise. Also for all the coffee and cake, it was much appreciated.

I would like to thank my proof-readers and friends: Avene, Lauren, Amy, Michelle, Ciara and Ryan, all of whom were happy to help with plentiful suggestions. Importantly, I would like to thank Amy and Ciara for their ability to make me laugh at any situation. You are exceptional friends.

I would like to thank the past and present members of the Connon group for making the lab a unique and enjoyable place to work. Viva Las Vegas.

I am grateful to the academic staff at Trinity College Dublin who have helped me all along the way: Dr. John O' Brien, Dr. Manuel Ruether, Dr. Martin Feeney and Dr. Gary Hessman. Thank you.

Lastly, I would like to thank Anna and the rest of the beautiful Lunachicks. Thank you to Kate, Alex, Hugh, Wes, Macon and all others who have supported me and reminded me that there is life outside the lab.

A special thank you to Keith for all the last-minute technical help. <3

Abstract

A novel methodology for the kinetic resolution (KR) of tetrachloroisopropoxycarbonyl (TCIC) substituted oxazinones *via* alcoholysis to afford enantioenriched and orthogonally protected β -amino acids has been developed. Upon catalytic ring opening of the oxazinone, the TCIC-subunit can be converted to an *N*-phthalimido-protected amino acid ester in one pot, rendering the synthetically useful *bis*-protected amino acid products; all other available methodologies furnish the benzoyl amide product which lacks synthetic utility. The methodology uses a novel bifunctional *cinchona* alkaloid-based organocatalyst to promote the reaction with outstanding levels of enantiocontrol, obtaining *S* factors of up to 101 for the process. The first organocatalytic protocol for the dynamic kinetic resolution (DKR) of TCIC-substituted oxazinones has also been developed; enabling access to chiral, orthogonally protected β -amino acid with modest levels of enantiocontrol.

The first catalytic, enantioselective protocol for the cycloaddition between imines and enolisable anhydrides has been developed. By carefully tuning the electronics of the imine *via* the placement of electron withdrawing substituents on the nitrogen atom, we have been able to employ bifunctional *cinchona* alkaloid-based organocatalysts to promote the reaction and furnish chiral lactam products bearing two chiral stereocentres. The methodology furnishes diastereomeric mixtures of the *trans* and *cis* products in up to 80% and 79% *ee* respectively.

A novel methodology using fluoride ion as a chiral nucleophilic catalyst has been developed. The methodology uses quinine-derived quaternary ammonium bromides in conjunction with KF to generate a 'chiral' fluoride ion *in situ* to carry out the enantioselective desymmetrisation of *meso*-anhydrides *via* alcoholysis. The methodology afforded the corresponding hemiester products with reasonable levels of enantiocontrol.

Nucleophilic catalysis by fluoride ion has been demonstrated in the *O*- to *C*-acyl transfer of 2-oxindole-derived substrates. The methodology employs Tetra-*n*-butylammonium fluoride (TBAF) as a racemic catalyst to promote the rearrangement leading to the direct formation of an all-carbon quaternary stereocentre in the product. Efforts towards the development of the KR of oxazinones and the DKR of azlactones have also been described.

Abbreviations

Å	Ångström
Ac	Acetyl
AChE	Acetylcholinesterase
AcOH	Acetic acid
AD	Asymmetric dihydroxylation
Alk	Alkyl
Ar	Aryl
APTC	Asymmetric phase-transfer catalysis
Aq.	Aqueous
B	Base
Boc	<i>tert</i> -Butoxycarbonyl
(Boc) ₂ O	Di- <i>tert</i> -butyl dicarbonate
BTM	Benzotetramisole
cat.	Catalyst
CALB	<i>Candida antarctica</i> lipase B
Cbz	Carboxybenzyl
CI	Chemical Ionisation
CNS	Central nervous system
conc.	Concentrated
C or conv.	Conversion
CSP	Chiral Stationary Phase
d	Day
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCC	N, N'-Dicyclohexylcarbodiimide
DFT	Density functional theory
DIAD	Diisopropyl azodicarboxylate
DIPEA	<i>N,N</i> -Diisopropylethylamine
DKR	Dynamic kinetic resolution
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMP	Des-Martin Periodane
DMSO	Dimethyl sulfoxide

DoE	Design of experiment
DPPA	Diphenylphosphoryl azide
dr	Diastereomeric ratio
E	Electrophile
EDG	Electron donating group
<i>ee</i>	Enantiomeric excess
<i>e.g.</i>	For example
EI	Electron ionisation
equiv.	Equivalent
ESI	Electrospray ionization
EWG	Electron withdrawing group
FDA	Food and Drug Administration
GABA	Gamma-Aminobutyric acid
h	Hour
HB	Hydrogen bonding
HBTU	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HIV	Human immunodeficiency virus
HMBC	Heteronuclear Multiple Bond Correlation
HPLC	High performance liquid chromatography
HSQC	Heteronuclear Single Quantum Coherence Spectroscopy
IBX	<i>o</i> -Iodoxybenzoic acid
I ₂	Iodine
IUPAC	International Union of Pure and Applied Chemistry
<i>J</i>	Coupling constant
KIE	Kinetic isotope effect
KR	Kinetic resolution
LA	Lewis Acid
MCR	Multi-component coupling reaction
MeCN	Acetonitrile
MOH	Metal hydroxide
MS	Mass spectrometry
MTBE	Methyl- <i>tert</i> -butyl ether
NHC	<i>N</i> -Heterocyclic Carbene

NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
Nu	Nucleophile
n.d.	Not determined
Pd/C	Palladium on activated charcoal
PTC	Phase-transfer catalysis
(q)	Quaternary
<i>rac</i>	Racemic
ROSEY	Rotating-frame Overhauser Spectroscopy
rt	Room Temperature
SM	Starting material
S	Selectivity factor
T	Temperature
t	Time
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TCIC	Tetrachloroisopropoxycarbonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TMSCHN ₂	Trimethylsilyl diazomethane
TOCSY	Total correlated spectroscopy
TOF	Time of flight
Troc	2,2,2-Trichloroethoxycarbonyl

1 Introduction

1.1 Catalysis: An introduction

Catalysis refers to the phenomenon by which a substance (the catalyst) modifies the rate of a reaction without being consumed by the reaction itself.¹ A catalyst increases the rate of a reaction by lowering the activation energy barrier for the transformation (Figure 1.1). Once the product has formed, it dissociates from the catalyst, thereby leaving the catalyst free to carry out another transformation. This is the catalytic cycle.¹ Usually only sub-stoichiometric amounts of a catalyst are required for a given reaction and thus catalysis is considered to be both an energetically and economically favourable process.

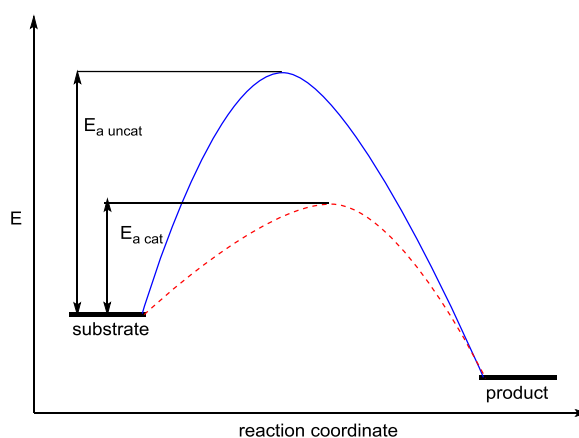


Figure 1.1 Potential energy diagram for the difference in a catalysed and uncatalysed reaction

The Arrhenius equation (Equation 1.1) states that the rate constant (k) is inversely proportional to the activation energy (E_a).² The activation energy (which is directly related to the transition state energy) is lower for a catalysed reaction and consequently, the catalysed reaction will have a faster rate of reaction compared to the uncatalysed pathway.

$$k = Ae^{-E_a/RT}$$

Equation 1.1 Arrhenius equation

Catalysts can be classed as either homogeneous or heterogeneous, depending on whether a catalyst exists in the same phase as the substrate or not. Heterogeneous catalysts operate in a separate phase to the reactants and thus can be easily separated from the product. This is extremely advantageous for industrial manufacturing processes.² When a catalyst occupies the same phase as the reactants it is referred to as homogenous catalysis. Generally, homogeneous catalysis offers faster reaction rates due to greater contact between the catalyst and its substrates, though separation of the product and catalyst can be problematic.²

1.2 Chirality: General remarks

The word chiral is derived from the Ancient Greek word $\chi\epsilon\tilde{\iota\rho}$ (*cheir*) for hand. A chiral molecule is one which is not superimposable on its mirror image. The mirror images of a chiral molecule are referred to as enantiomers - often designated as right handed or left handed. In an achiral environment, two enantiomers have indistinguishable chemical and physical properties, with their main distinction lying in their ability to rotate the plane of polarised light.³ Each stereocenter in a molecule is designated the stereochemical description of *R* or *S* (Rectus or Sinister) to describe the 'handedness' of the molecule.¹

In nature, most chiral molecules exist as a single enantiomer, a characteristic of paramount importance with regards to molecular recognition and replication processes. The development of methodologies which allow for the selective synthesis of enantiopure molecules is a significant challenge at the forefront of chemical research due to the salient medicinal and economic benefits.⁴ Unlike in nature, a chemical reaction performed in the absence of a chiral directing template affords racemic mixtures of products.

Thalidomide (**1**) is an example of a drug whose enantiomers possess vastly different pharmacological profiles (Figure 1.2). It was sold as an over the counter drug for the treatment of morning sickness in pregnant women in the late 1950s, however, it resulted in phocomelia, or a malformation of the limbs, in the new-born infants. The drug was originally sold as a mixture of *R* and *S* enantiomers, though racemisation of the drug was also found to occur *in vivo*.⁵ Whilst the *R* enantiomer was an effective sedative, the *S* enantiomer was teratogenic, giving rise to the birth defects in new-born babies. This disaster prompted many countries including both the EU and the US to introduce stricter regulations for the testing and licensing of drugs.⁶ Thalidomide is still used today, under strict control, for the treatment of certain cancers and leprosy.^{7,8}

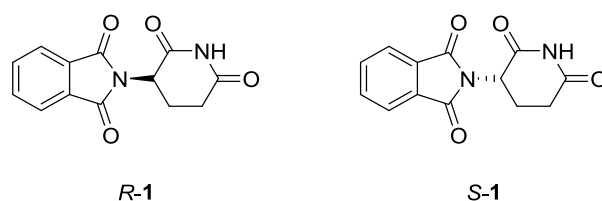


Figure 1.2 *R* and *S* Thalidomide (**1**)

1.3 Asymmetric synthesis

As already highlighted by the thalidomide example, the development of enantioselective transformations which allow for the synthesis of enantiopure compounds is of critical importance to the chemical industry.⁹ As such, a surge of intense research has occurred in this area over the last few decades. Several different approaches to asymmetric synthesis have developed as a result

including: (1) chiral pool-based methodologies; (2) the use of chiral auxiliaries; (3) kinetic resolution; (4) asymmetric catalysis.

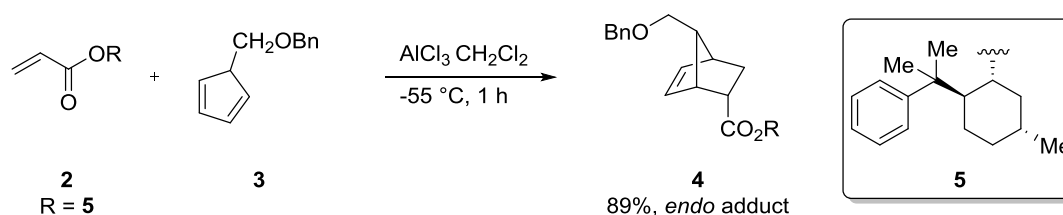
1.3.1 Chiral pool-based methodologies

The ‘chiral pool’ refers to enantiopure building blocks which are available in nature. Chiral pool-based methodologies use the enantiomeric scaffolding of these molecules as a core structure upon which the target molecule is built using the appropriate chemical transformations. Common examples of the chiral pool include monosaccharides and amino acids.¹⁰ In cases where the target molecule bears considerable resemblance to the initial natural product, this can be the cheapest and easiest approach for the synthesis; otherwise laborious protecting group chemistry and functional group conversion may be required. Additionally, if the target molecule requires the opposite configuration to the available natural product, synthesis of the molecule using chiral pool-based methodologies presents an onerous task. In general, commercially available starting materials possessing unnatural stereochemistry (*e.g.* D-amino acids) tend to be much more expensive than those possessing the natural configuration.

1.3.2 The use of chiral auxiliaries

Chiral auxiliaries are stereogenic groups which are temporarily incorporated into organic molecules in order to influence the stereochemical outcome of a reaction.¹¹ The chirality introduced by the auxiliary groups acts as a bias for the stereoselectivity of subsequent reactions; this is referred to as asymmetric induction. The products of these transformations are diastereomers which often enables facile separation *via* chromatography or recrystallisation. The auxiliary group is then removed under non-racemising conditions to yield the enantiopure product.

Chiral auxiliaries were first introduced by E. J. Corey in 1975 in the synthesis of prostaglandins in the form of 8-phenylmenthol (**5**). The molecule was attached to acrylic acid to form **2**, which was used for the asymmetric induction of a Diels-Alder reaction to synthesise the *endo* adduct **4** in 89% yield (Scheme 1.1).¹² To this day, many transformations rely on chiral auxiliary strategies as the only stereoselective methodology available. While successful, there are several limitations to this approach, namely, the requirement for stoichiometric reagent as well as a necessary point of attachment to the prochiral functionality in the starting material.¹³



Scheme 1.1 First use of 8-phenylmethanol (**5**) as a chiral auxiliary

1.3.3 Kinetic Resolution

Kinetic resolution (KR) is a method through which enantiopure compounds can be obtained from a racemic mixture.¹⁴ As mentioned previously, in an achiral environment, two enantiomers of the same compound exhibit identical chemical properties. Introduction of a chiral catalyst into a chemical reaction can result in a change in reactivity between the two enantiomers through the formation of two diastereomeric transition states. The free energies associated with these transition states must be sufficiently different in order to achieve high enantioselectivity (Figure 1.3). As the reaction proceeds and the concentration of the less reactive enantiomer increases relative to that of the more reactive partner, at a certain point the rate of reaction associated with the less reactive enantiomer will become competitive. As such, the enantiomeric composition of the product is a function of the conversion of the starting material and is directly related to $\Delta\Delta G^{\text{TS}}$. Under ideal conditions, the maximum theoretical yield for each enantiomer in a KR is only 50%;¹⁵ this is considered to be a major drawback of KR however, in most situations, the enantioenriched starting material can be recovered. Furthermore, in cases where the enantioselectivity associated with the process is not perfect it has been demonstrated that at conversions exceeding 50% it is possible to obtain the unreacted enantiomer in even higher enantiomeric excess.

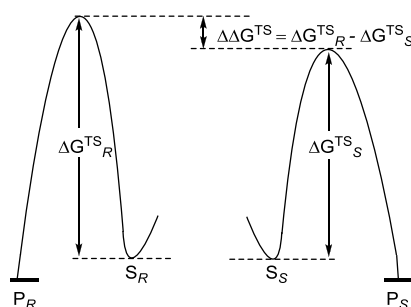


Figure 1.3 Energy diagram for kinetic resolution

Selectivity factor (S) is a convenient way to calculate the efficiency of a resolution process and can be calculated from either the rate constants associated with the reaction of each enantiomer (Equation 1.2A) or more simply from the conversion and enantiomeric excess recorded at any given point in the reaction (Equation 1.2B).¹⁵ In general, an S value of higher than 10 can be deemed synthetically useful; however in cases where it is necessary to drive conversion past 50%, the recovered starting material is highly enriched at the expense of the ee of the product. In these cases, S values of greater than 50 allow isolation of both the starting material and the product in high optical purity.¹⁶

$$S = k_{\text{rel}} = k_{\text{fast}}/k_{\text{slow}} = e^{\Delta\Delta G/RT} \quad (\text{A})$$

$$S = \frac{\ln[1-C(1+ee)]}{\ln[1-C(1-ee)]} = \frac{\ln[1-C(1+ee)]}{\ln[1-C(1-ee)]} \quad (\text{B})$$

C = conversion ($0 < C < 1$)

ee = enantiomeric excess of the starting material ($0 < ee < 1$)

ee' = enantiomeric excess of the product ($0 < ee' < 1$)

Equation 1.2 S factor calculation

1.3.4 Dynamic Kinetic Resolution

A more efficient extension of KR is dynamic kinetic resolution (DKR), which allows a theoretical yield of 100% for the enantiopure product and thus overcomes the waste of material associated with KR. This process involves the resolution step of KR accompanied by the *in situ* racemisation of the stereochemically-labile substrate *i.e.* as the fast reacting enantiomer is consumed, it is also generated by racemisation of the slow reacting enantiomer, ideally resulting in 100% yield of a single enantiomer as the product (Figure 1.4).¹⁷ For highly selective DKR to occur the substrate must be racemised quicker than the slower reacting substrate is converted to the product *i.e.* $k_{\text{rac}} > k_R > k_S$.¹⁸ Racemisation of the substrate is chemically induced and conditions must be chosen carefully to ensure that only the substrate is subject to racemisation and not the product.¹⁵

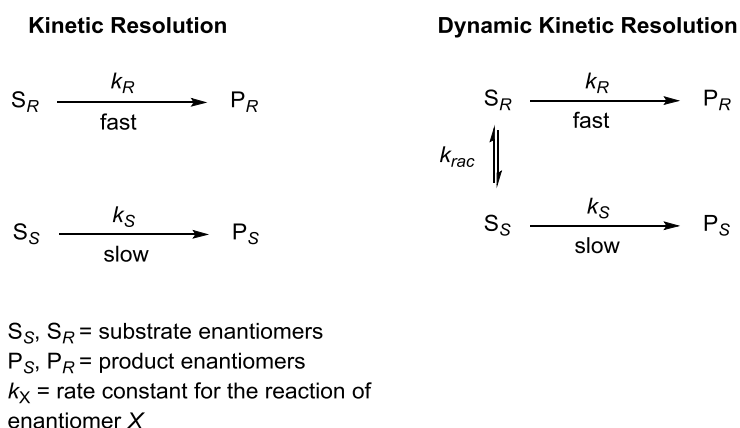


Figure 1.4 Dynamic kinetic resolution

1.3.5 Asymmetric catalysis

Asymmetric catalysis employs a chiral catalyst to impart chiral information to a substrate. This approach offers the greatest potential for asymmetric synthesis as there are virtually no constraints in terms of molecular design or in the multitude of reactions which they can influence.¹⁹ Perhaps the first example of asymmetric catalysis involved the use of *cinchona* alkaloid catalysts in the formation of cyanohydrins in 1912; specifically, the study synthesised maldonitrile from benzaldehyde and HCN in approximately 8% ee using quinine as a catalyst.^{20, 21} Since, the field has seen enormous

growth resulting in the emergence of several subdivisions including enzyme-based catalysis, metal-based catalysis and organocatalysis.

1.3.5.1 Enzyme-based catalysis

Enzymes are macromolecular biocatalysts which possess the unique ability to produce a product with complete enantioselectivity. The active site of an enzyme is the region which binds and carries out catalysis on the enzyme-substrate, organising the transition state in a highly specific manner.²² Enzyme catalysis uses the active site of naturally occurring enzymes as catalysts and thus the approach tends to produce high product enantioselectivity under mild conditions with very low environmental impact.²³ However, being enzymes, they are extremely specific and generally exhibit poor substrate scope. In general, a large number of enzymes need to be screened before an effective catalyst is found for the transformation. As the cost associated with many enzyme catalysts tends to be high, the chemical industries are the main proponents of this form of catalysis.²⁴

1.3.5.2 Metal-based catalysis

Over the years, metal-based catalysis has largely dominated the field of asymmetric catalysis. The area of transition metal catalysis has been awarded three Nobel prizes: first in 2001 for pioneering work in asymmetric rhodium and ruthenium catalysed hydrogenation and osmium catalysed oxidation reactions,²⁵ next in 2005 for the development of ruthenium and molybdenum promoted olefin metathesis,²⁶ and most recently in 2010 for exceptional advances in palladium-catalysed cross couplings in organic synthesis.²⁷ These contributions irreversibly changed the landscape of organic synthesis from both an academic and industrial perspective.

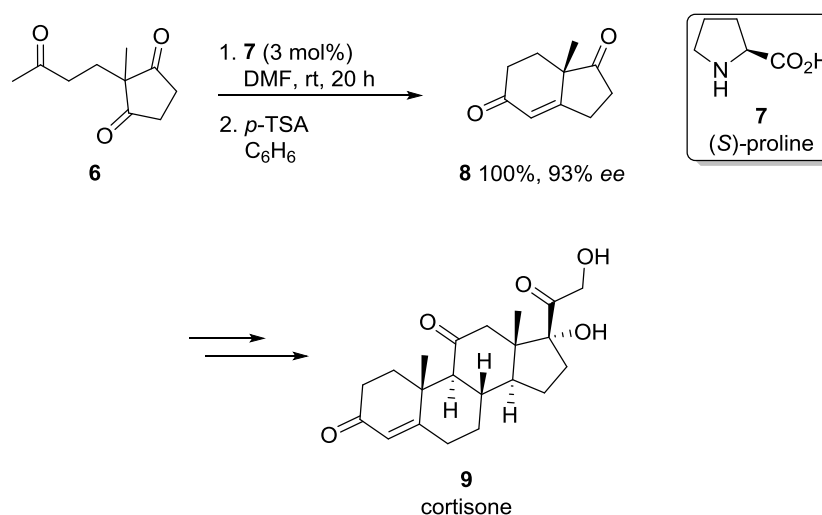
Though the scope for metal-based catalysis is wide, there are several drawbacks associated with these methodologies. Toxicity and sensitivity concerns can often present a major issue for large scale pharmaceutical processes with both metal threshold values in the products and the requirement of strict anhydrous conditions limiting their potential.²⁸ Furthermore, due to the finite supply of metals in the Earth's crust, the availability of certain metals is becoming extremely limited; the 'platinum group' metals are amongst those at the highest risk.²⁵ From an environmental perspective, the long term use of certain metal based catalysts is not viable. The use of organocatalysed transformations is one of several more sustainable alternatives.

1.4 Organocatalysis

Organocatalysis refers to the use of small organic molecules as catalysts for organic transformations. Although the use of organocatalysts has been documented sporadically over the last century, it was not until the late 1990s that interest in the field exploded. Prior to this, catalytic enantioselective synthesis was almost exclusively dominated by metal-based chiral catalysts which, as already mentioned, can be expensive, toxic and air/moisture sensitive.²⁸ Organocatalysts are generally considered to be less toxic and more environmentally friendly. In most cases they are insensitive to

moisture and oxygen, reducing concerns over handling, storage and disposal and thus offer a huge potential benefit to the pharmaceutical industry in comparison to transition metal catalysts. Additionally, they can be synthesised *via* a wide range of naturally occurring compounds and as such, simple organocatalysts are often easily accessible at a low cost.²⁹

In the early 1970s Eder, Sauer and Wiechert,³⁰ and Hajos and Parrish³¹ both independently reported the use of (S)-proline (**7**) to promote the intramolecular aldol cyclisation of triketones to furnish compounds such as **8** in high yield and with excellent enantioselectivity (Scheme 1.2). Arguably, this is considered to be the first significant organocatalytic transformation; it provided access to key chiral intermediates for the total synthesis of cortisone (**9**) and other such steroids with high optical purity without resorting to resolution of a racemic mixture.^{32, 33}



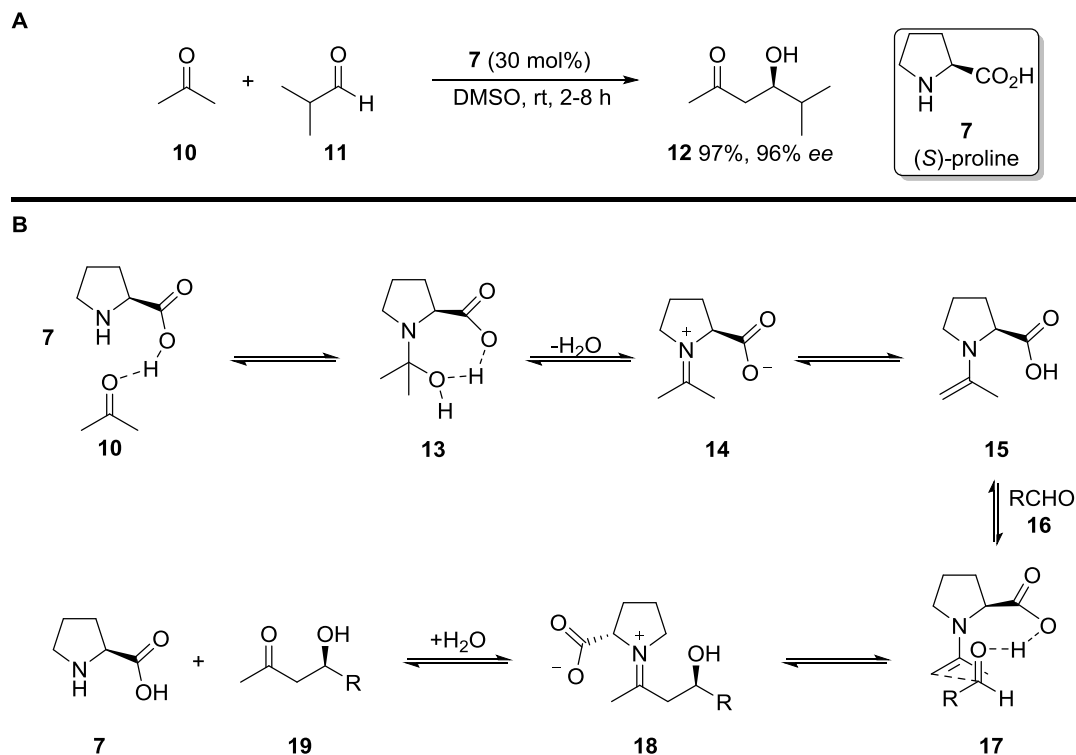
Scheme 1.2 The Hajos-Parrish reaction in the total synthesis of cortisone.

After these publications more examples which utilised small organic molecules as asymmetric catalysts began to appear in the literature. In the year 2000 two key studies were published which defined the beginning of organocatalysis as an independent field of research in asymmetric catalysis, *vide infra*.^{34, 35}

1.4.1 Asymmetric aminocatalysis

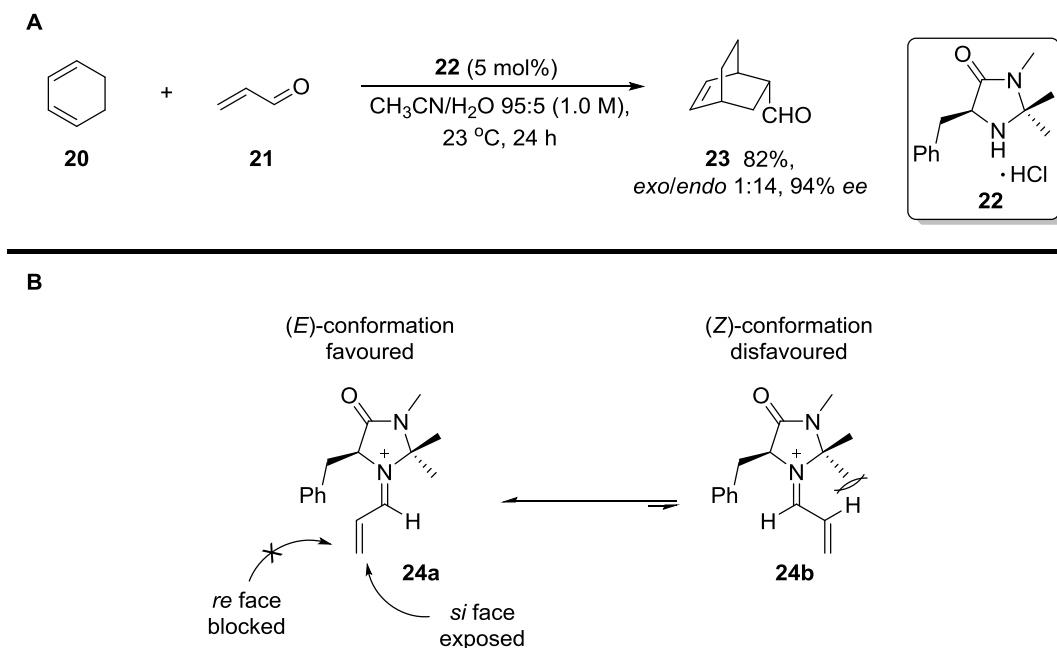
In 2000, List *et al.*³⁵ reported the first example of a direct intermolecular asymmetric aldol reaction catalysed by a non-metallic molecule, further extending the scope of the reaction reported by Hajos and Parrish in 1974.³¹ The study utilised (S)-proline (**7**) to catalyse the asymmetric addition of acetone (**10**) to aldehydes such as **11** to furnish **12** in excellent yield and *ee* (Scheme 1.3 A). The authors proposed that (S)-proline mimicked the activity of enzymes such as class I aldolases, pushing the reaction *via* an enamine intermediate; the carbonyl moiety of **10** is activated by the acid functionality of (S)-proline, which in turn facilitates nucleophilic attack of the amino group on the

ketone (Scheme 1.3 B). Subsequent loss of water from the molecule generates the iminium intermediate **13** which tautomerises to form enamine **14**. Enamine **15** forms the new carbon-carbon bond with aldehyde **16** (via highly organised transition state **17**) which upon hydrolysis of **18** generates the aldol product **19** and concurrently regenerates the catalyst.



Scheme 1.3 (A) Direct intermolecular asymmetric aldol reaction catalysed by (S)-proline (**7**) by List *et al.* (B) Proposed mechanism for the reaction

Later that same year MacMillan and co-workers described the use of synthetic enantiopure amines, such as imidazolidinone **22**, to carry out the first enantioselective organocatalytic Diels-Alder reaction between dienes such as **20** and α,β -unsaturated aldehydes such as **21** (Scheme 1.4).³⁴ They postulated that the reaction proceeded through an iminium ion intermediate, with the preferential adoption of the (*E*)-conformation **24a** over the disfavoured (*Z*)-conformation **24b** to furnish the *endo*-product in 94% *ee*. Computational studies showed that the (*E*) intermediate avoided unfavourable steric interaction between the geminal dimethyl group on the catalyst and the α -vinylic proton of the alkene unit in the substrate. Furthermore, the presence of the catalyst benzyl group ensures facial selectivity, causing the cycloaddition to occur on the *si* face of the alkene.²⁹ These two studies present two of the most common modes of activation in organocatalysis: enamine and iminium catalysis. Hydrogen bond donation constitutes the third most common mode of activation.

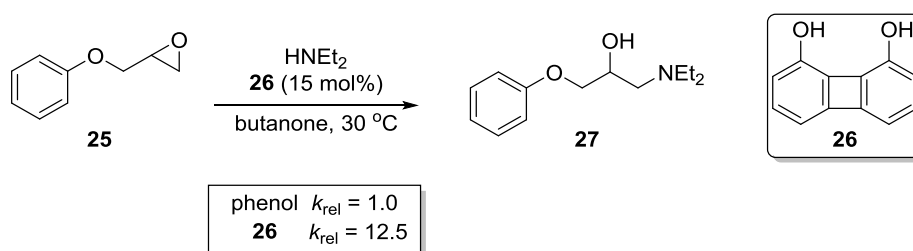


Scheme 1.4 (A) The first asymmetric organocatalysed Diels-Alder reaction reported by MacMillan. (B) The proposed reaction intermediates **24a** and **24b**.

1.4.2 Hydrogen bond catalysis

Hydrogen bond (HB) catalysis is a form of organocatalysis which uses molecules containing hydrogen bond donors as catalysts. Through general acid catalysis these molecules are able to stabilise the developing negative charge in the transition state of a reaction, thus enhancing the reactivity of the electrophile towards nucleophilic attack in the same way as Lewis acids.³⁶ In nature, enzymes have the ability to exploit H-bonding interactions in order to promote a large number of chemical transformations.³⁷ Despite this, it was not until the 1980s that hydrogen bond donation began to grow as a mode of catalysis.

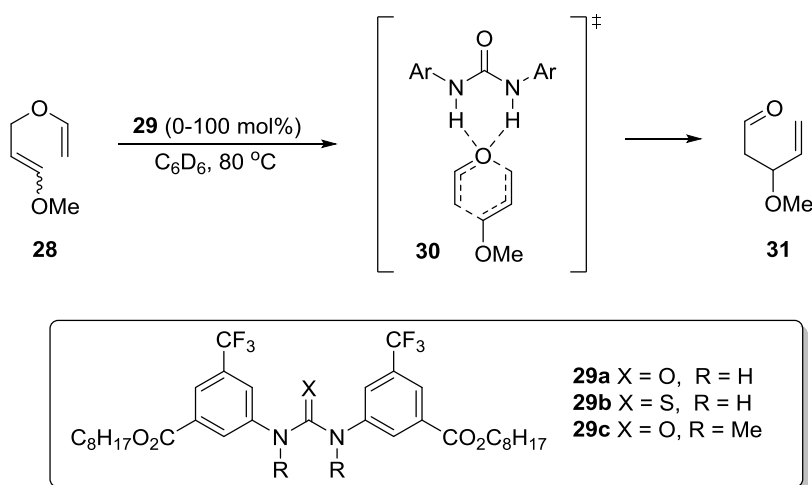
Pioneering investigations conducted by Hine *et al.* described the use of phenol derivatives as catalysts for the addition of diethylamine to phenyl glycidyl ether (**25**, Scheme 1.5). The studies revealed the superior catalytic activity of 1,8-biphenylenediol (**26**) compared to that of phenol itself in the formation of **27**, rationalised by the ability of **26** to function as a dual hydrogen bond donor.³⁸⁻⁴⁰



Scheme 1.5 Epoxide ring opening catalysed by dual hydrogen bond donor **26**

Later, a substituted biphenylenediol was used to promote rate acceleration in Diels-Alder reactions.⁴¹ Computational studies by Jørgensen and co-workers confirmed double hydrogen bond donation to be responsible for this enhanced activity.^{42, 43} It became evident that the use of species capable of the simultaneous donation of two H-bonds was a valid strategy for electrophile activation in synthetic chemistry.³⁷

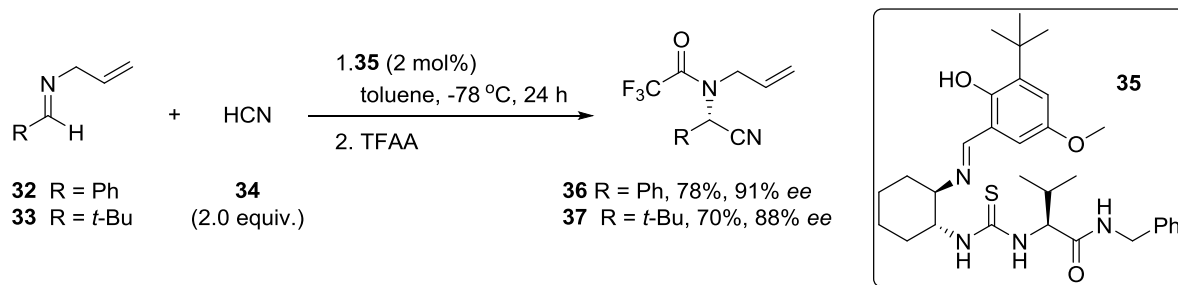
Curran and co-workers reported the first example of general acid catalysis using urea derivatives.^{44, 45} They showed that diarylurea **29a** could be used to promote the allylation of cyclic α -sulfinyl radicals with improved yield and diastereoselectivity relative to the uncatalysed process.⁴⁴ Later, they demonstrated that the same catalyst could be efficiently used in the conversion of **28** to **31** via the Claisen rearrangement (Scheme 1.6).⁴⁵ Whilst the study showed thiourea **29b** was also effective in catalysing the transformation, dialkyl-urea **29c** failed to promote the transformation thus supporting the proposed transition state **30**. These publications inspired the development of numerous ideas and the field of urea catalysis began to grow; soon it was found that the solubility profile and hydrogen bond capability of the catalyst could be tuned by using a thiourea variant or by substitution on the aryl rings.^{45, 46} These diaryl(thio)urea catalysts were shown to be effective in promoting numerous transformations including: the Diels-alder reaction,^{46, 47} the Baylis Hillman reaction,⁴⁸ Friedel-Crafts alkylation⁴⁹ and the Corey-Chaykovsky reaction⁵⁰ to name but a few.



Scheme 1.6 (Thio)urea promoted Claisen rearrangement

The first use of chiral (thio)ureas for asymmetric catalysis was published by Jacobsen *et al.* in 1998 (Scheme 1.7).⁵¹ Whilst studying and evaluating new ligands for the metal ion-promoted asymmetric hydrocyanation of imines (Strecker reaction), they observed that their control reaction, using one specific ligand in the absence of the metal, furnished enhanced enantioselectivity compared to the metal catalysed reaction. Immediately, they embarked upon optimisation of the catalyst structure in order to obtain the highest level of stereocontrol. Catalyst **35** was found to be the most efficient for the Strecker reaction involving aromatic and aliphatic imine derivatives such as **32** and **33**

respectively, using HCN (**34**) as the cyanide source. The Strecker products were obtained in good yield and high enantioselectivity. Computational and mechanistic studies found that the catalyst favourably bound the (*Z*)-isomer of the imine *via* dual hydrogen bond donation to the imine lone pair, in order to reduce steric hindrance with the bulky imine substituents.⁵²

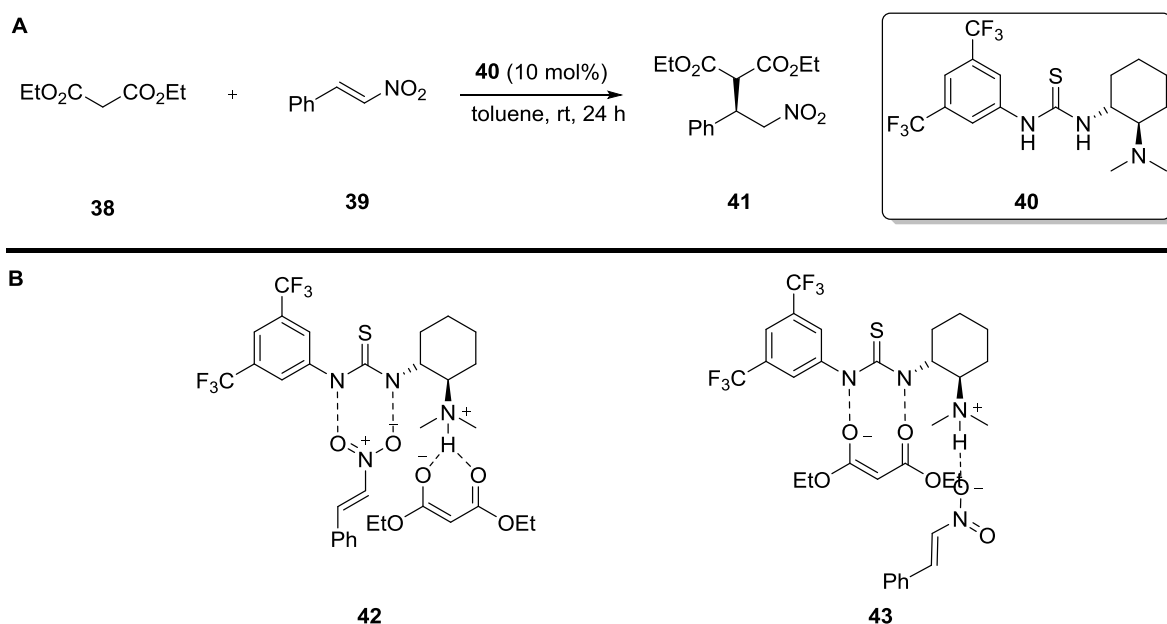


Scheme 1.7 Strecker reaction promoted by chiral thiourea **35**

1.5 Chiral bifunctional catalysis

Soon after the discovery of the potential of the chiral (thio)ureas as catalysts, the exploration of bifunctional catalysis began. Bifunctional catalysis describes the use of catalysts containing both Lewis acidic and Lewis basic components which cooperate to simultaneously activate the electrophilic and nucleophilic components of a reaction often *via* hydrogen bonding.⁵³ These systems can create a well-defined chiral environment resulting in improved catalytic activity and enhanced stereocontrol. Bifunctional organocatalysts have been described to mimic the action of enzymes, though in most cases to a much lower degree in terms of selectivity.

Takemoto *et al.* introduced the first example of asymmetric bifunctional organocatalysis in 2003 (Scheme 1.8 A).⁵⁴ They showed that catalytic amounts of **40** could promote the Michael addition of malonates such as **38** to nitroolefins **39** to furnish the Michael products in high *ee*. It was demonstrated that both the thiourea moiety and the tertiary amino group had to be present on the same chiral scaffold to ensure high yields and selectivity. In a later study, they proposed the pre-transition state **42** to rationalise the stereochemical outcome (Scheme 1.8 B); the nitroalkene **39** is bound and activated by the catalyst *via* hydrogen bond donation by the thiourea moiety, whilst the malonate **38** is deprotonated by the tertiary amine and the resulting amine salt binds the malonate anion *via* hydrogen bond donation (Scheme 1.8 B). Thus, the nucleophile and electrophile are simultaneously activated and organised by the catalyst in a well-defined chiral pocket.⁵⁵ Some years later, Soós and Pápai reported a DFT study which concluded that mechanism proposed by Takemoto was kinetically favourable, but that a second pathway *via* pre-transition state **43** (Scheme 1.8 B) was equally likely.⁵⁶



Scheme 1.8 The first bifunctional thiourea catalysed reaction (A) and two proposed pre-transition states for the reaction (B)

1.5.1.1 *Cinchona* alkaloids in bifunctional organocatalysis

Cinchona alkaloids provide an efficient bifunctional scaffold for organocatalytic applications. They contain five stereogenic centres (*N*-1, *C*-3, *C*-4, *C*-8, and *C*-9) as well as a basic quinuclidine nitrogen atom and a mildly acidic hydroxyl group which are positioned in close proximity to give a well-defined chiral environment (Figure 1.5).⁵⁷ Though relatively rigid in structure, in solution *cinchona* alkaloids can rotate along the *C*-9-*C*-4' and *C*-8-*C*-9 axes to adopt several conformations.⁵⁸ *Cinchona* alkaloids, which include the compounds quinine (**44**) and quinidine (**45**), are natural products extracted from the bark of the *cinchona* species of plants. Both *pseudo*-enantiomers are readily available and can be used to generate either enantiomer of a chiral product of interest.

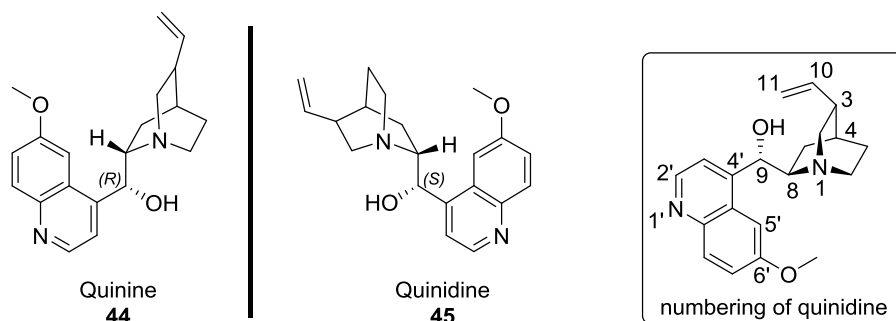
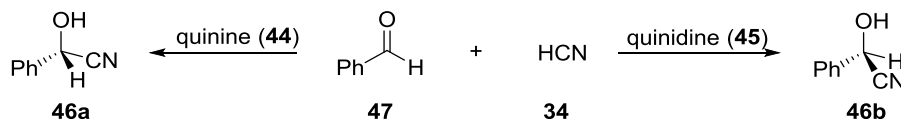


Figure 1.5 Structure of *cinchona* alkaloids quinine (**44**) and quinidine (**45**)

In 1853, Pasteur reported the use of *cinchona* alkaloids as resolving agents for the separation of a racemic mixture of tartaric acid. As previously mentioned, their first use as asymmetric catalysts was

reported in 1912 for the rate acceleration of the addition of HCN to benzaldehyde (Scheme 1.9).⁵⁹ Although this work reported low *ee* for the product measured by optical rotation, it was the first piece of evidence demonstrating that *pseudoenantiomers* such as quinine (**44**) and quinidine (**45**) could be used to obtain enantioenriched products of opposing chirality.



Scheme 1.9 First use of *cinchona* alkaloids as asymmetric catalysts

Despite these earlier studies, it was not until the early 1980s that chemists began to realise the potential in using *cinchona* alkaloids as bifunctional catalysts. Inspired by the seminal studies of Pracejus,⁶⁰ Wynberg and co-workers described the use of cinchonidine **52** (Figure 1.6) and other *cinchona* alkaloids in the enantioselective addition of aromatic thiols such as **49** to cyclic α,β -unsaturated ketones, furnishing thioether products **51** with modest enantioselectivity.⁶¹ They attributed the selectivity obtained to bifunctional catalysis *via* transition state **50**, making this a landmark paper, with activation of the electrophile occurring as a result of H-bond donation from the hydroxy group, whilst nucleophile-activation occurs *via* deprotonation of the thiol by the chiral, tertiary amine. This study marked the beginnings of an expansive career of *cinchona* alkaloids as bifunctional, enantioselective organocatalysts with many examples of these molecules and their derivatives being used for organocatalytic transformations appearing from late 1990s onwards.^{62, 63} Their utility in metal-catalysed processes was already apparent:⁶⁴ in 2001 the Nobel prize in chemistry was awarded to Sharpless and co-workers for the osmium-catalysed asymmetric dihydroxylation (AD) of alkenes which utilises *cinchona* alkaloids as metal ligands.⁶⁵

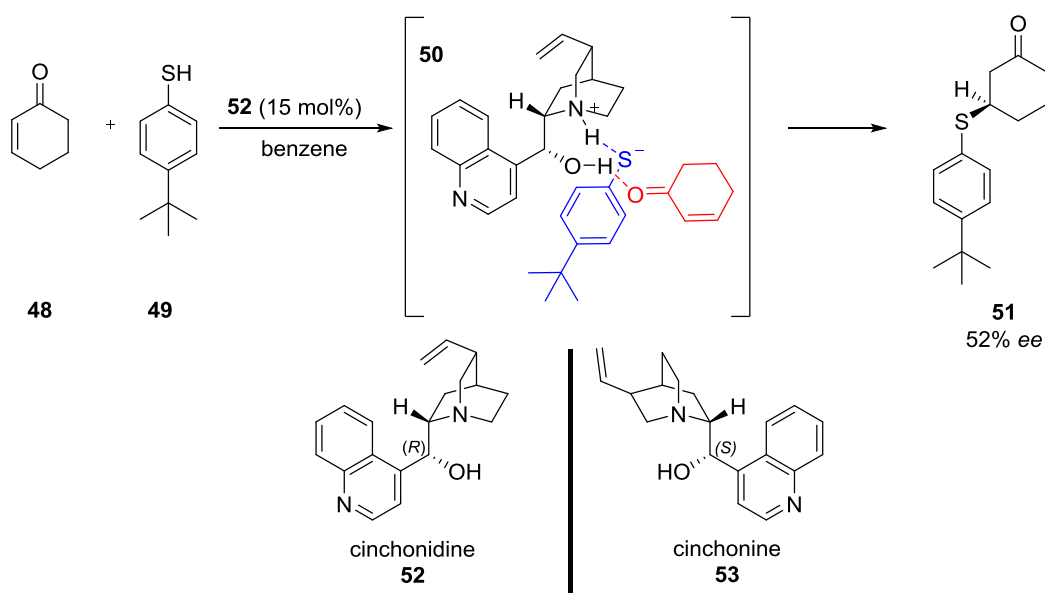
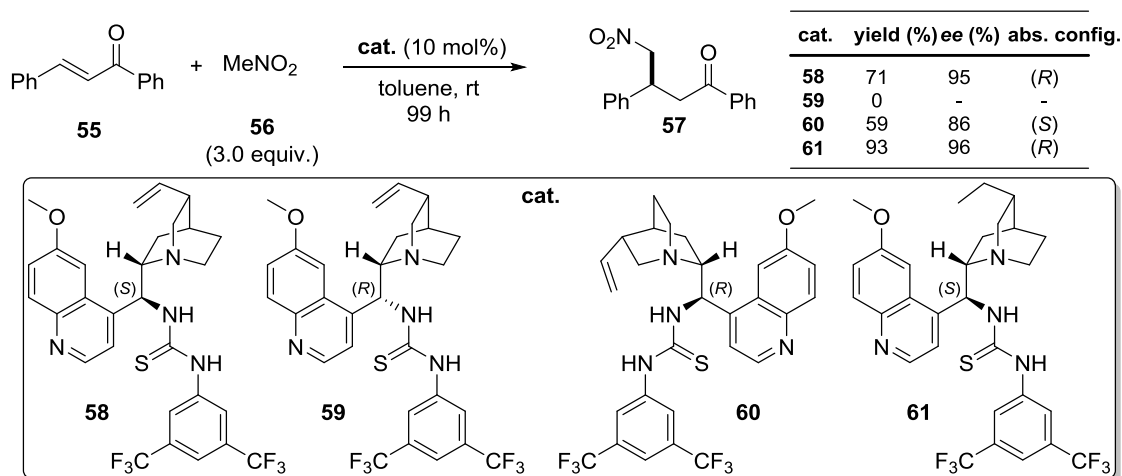


Figure 1.6 Cinchonidine and cinchonine, from the *cinchona* alkaloid family

Two years after Takemoto's initial report introducing bifunctional chiral thioureas as organocatalysts,⁵⁴ the research groups of Chen, Soós, Connon and Dixon each independently reported the use of quinine-derived thioureas as bifunctional organocatalysts in similar transformations. Soós *et al.* developed a range of thiourea-substituted quinine/quinidine derived catalysts **58-61** for the asymmetric Michael-type addition of nitro-methane to chalcone (Scheme 1.10).⁶⁶ The chosen library was developed to investigate the relative optimal stereochemistry at C-8 and C-9.

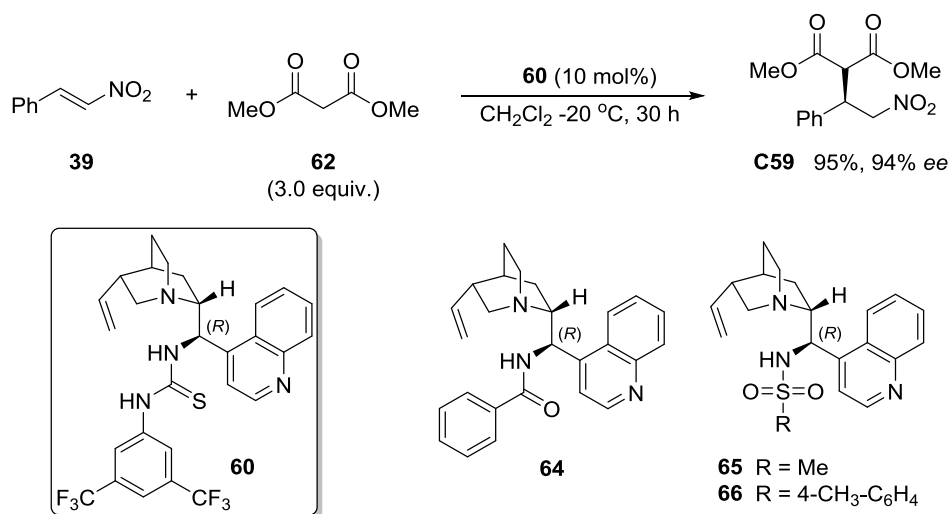


Scheme 1.10 Addition of nitromethanes to chalcones catalysed by thiourea-derived *cinchona* alkaloids

Interestingly, catalysts **59**, derived from quinine with natural stereochemistry, completely failed to promote the reaction whilst its epimer **58** furnished the product **57** in good yields and high

enantioselectivity. Catalysts **60** and **61**, derived from quinidine and dihydroquinine respectively, both containing a C-9 inversion of configuration promoted the reaction with good yields and high *ee*. The results demonstrated the importance of the orientation of the Lewis acidic and Lewis basic sites for effective bifunctional catalysis.⁶⁶

Concurrent studies by Cannon *et al.* and Dixon *et al.* corroborated the requirement for substitution of the C-9 hydroxyl group with a (thio)urea moiety and an inversion of stereochemistry in order to achieve high levels of stereocontrol and reaction rate in the asymmetric addition of dimethylmalonate (**62**) to nitrostyrene (**39**).^{67, 68} Dixon also illustrated the superiority of dual hydrogen bond activation in the reaction. Thiourea **60** promoted the reaction with enhanced rate and enantiocontrol when compared to the reactions using *cinchona* alkaloid catalysts such as **64-66**, each possessing only a single H-bond donor (Scheme 1.11).



Scheme 1.11 Michael addition of dimethylmalonate to nitroolefins using thiourea derived *cinchona* alkaloids by Dixon *et al.*

1.5.1.2 Introduction of the squaramide moiety

As previously stated, hydrogen bonding is a crucial mode of activation in organocatalysis; for many years, chiral structures based on (thio)urea derivatives dominated the field of H-bond donating asymmetric catalysis. Their success was attributed to their ability to donate two hydrogen bonds to a substrate with a well-defined geometry and directionality.

In 2008, Rawal *et al.* introduced the squaramide moiety as a hydrogen bond donating motif (Figure 1.7).⁶⁹ Squaramides (**67**) are structurally more rigid than their (thio)urea counterparts; the lone pair associated with both nitrogen atoms can be delocalised through the ring system, restricting the two C-N bond rotations and imparting a planar structure to the molecule.^{70, 71} Possessing both anion and cation recognition sites, they can form up to four hydrogen bonds (**68**). According to the Hückel rule ($4n + 2$; $n = 0$), higher aromaticity is obtained upon H-bond formation, leading to superior hydrogen

bond donating ability of squaramides in comparison to (thio)ureas. Distances between the hydrogen atoms of each moiety (**67** and **69**) are significantly different along with bond angles, which influences the strength and directionality of hydrogen bonding and thus have a direct impact on asymmetric catalysis.^{70, 71}

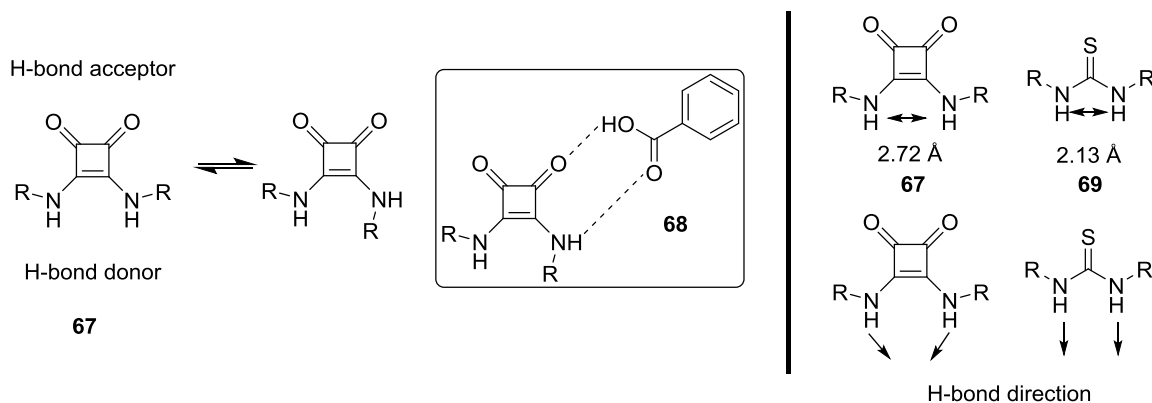
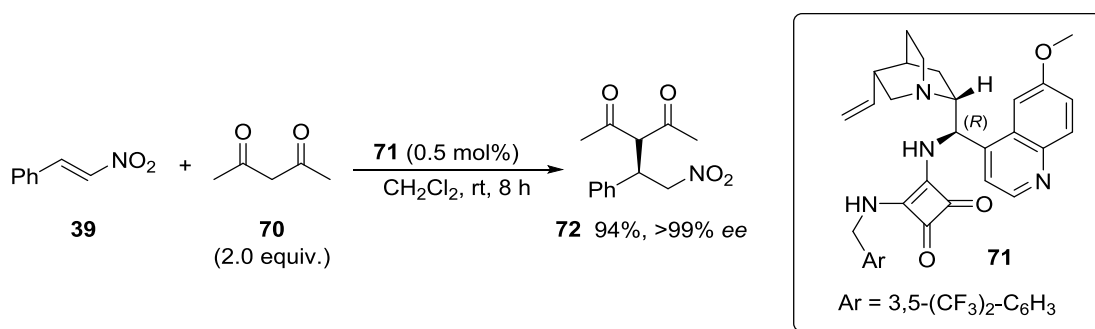


Figure 1.7 The structural proprieties of the squaramides.

In this influential study, Rawal and co-workers designed and utilised catalyst **71**, a squaramide *C*-9 substituted *cinchona* alkaloid, for the extremely efficient addition of 1,3-dicarbonyl compounds to nitroolefins to furnish products such as **72** in high yield and enantioselectivity (Scheme 1.12).⁶⁹



Scheme 1.12 Rawal and co-workers squaramide-based *cinchona* alkaloid organocatalyst for a Michael-type reaction.

1.5.1.3 Other common modifications to the *cinchona* alkaloid scaffold

It is not just manipulations of the hydrogen bond donating unit at *C*-9 that can enhance catalytic activity; several important modifications in the *cinchona* alkaloid backbone are also known. Adjustments at the *C*-6' position to introduce hydrogen bond donating units have proven advantageous in certain reactions. For example, catalyst **73**, which possess a different spatial relationship between the two bifunctional components of the reaction, proved effective in the catalysis of the Baylis-Hillman reaction (Figure 1.8).⁷² The observed increase in reactivity was attributed to the reduced steric hindrance around the quinuclidine moiety, resulting in the

augmentation of nucleophilicity of the amine, in conjunction with the strong H-bond donating potential associated with the C-6' phenolic hydroxy group.

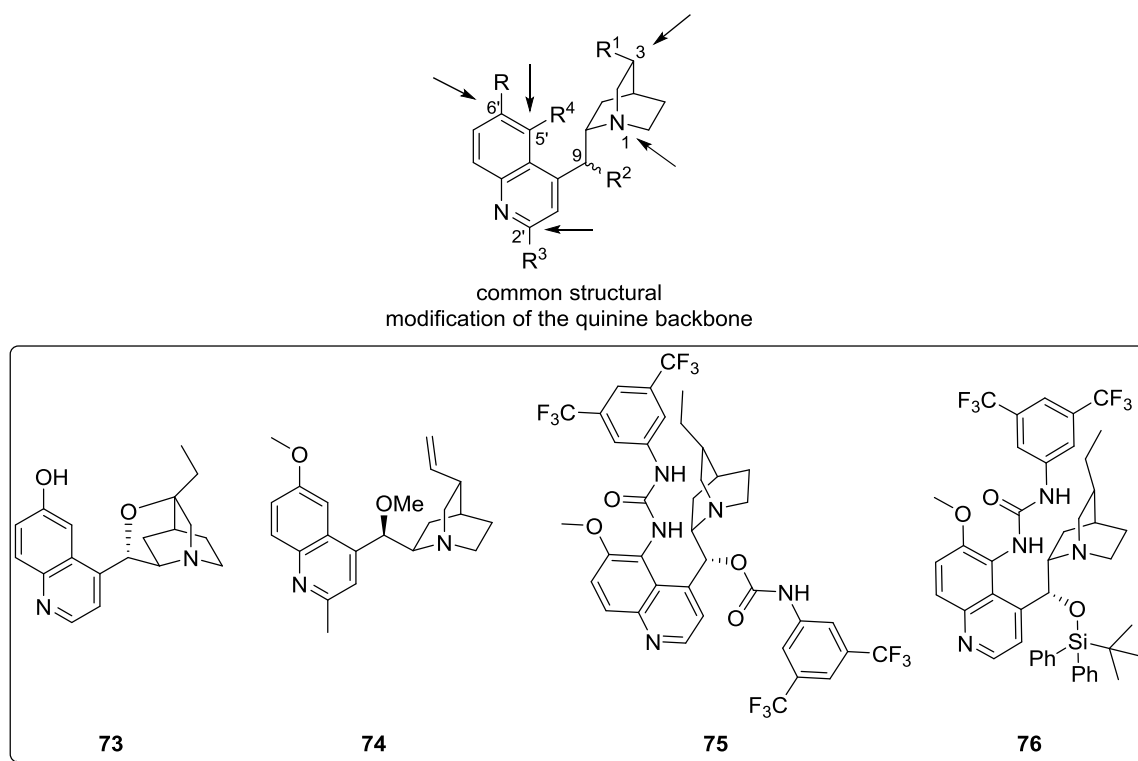


Figure 1.8 Common structural modifications to the *cinchona* alkaloid scaffold

Modifications at the quinine C-2' position are also common. Gaunt *et al.* were the first to introduce a methyl group at this position to synthesise catalyst **74** (Figure 1.8) in order to sterically hinder the quinoline nitrogen atom (N-1') from providing alternative catalytic pathways for the intramolecular cyclopropanation reaction of halogenated ketones.⁷³ Introduction of the methyl group effectively suppressed the nucleophilicity of the quinoline nitrogen atom, allowing the reaction to proceed solely through a quinuclidine-ammonium ylide intermediate. As a result, the reaction proceeded smoothly, furnishing the desired products in high yield and excellent enantioselectivity.

Substitution at the C-5' position is also known. Connon *et al.* synthesised catalyst **75** and **76** (Figure 1.8), once again altering the spatial relationship between the two catalytic functionalities. Catalyst **75** was effective in promoting the enantioselective addition of nitromethane to trifluoromethylketones (the Henry reaction),⁷⁴ whilst catalyst **76** was used for the enantioselective addition of thiols to aromatic alkenes.⁷⁵ Both catalysts performed excellently in relation to yield and enantiocontrol (up to 96% ee) for their respective reactions.

There are two more fundamental types of *cinchona* alkaloid derivatives which are used in asymmetric bifunctional catalysis. The first involves immobilisation of the catalyst on a heterogeneous support, such as polymers⁷⁶ or magnetic nanoparticles,⁷⁷ to simplify recovery of the catalyst at the end of the

reaction. It is usually achieved by chemical transformation of the terminal olefinic double bond on the quinuclidine ring.⁷⁸ This vast domain constitutes its own specific field called solid-supported catalysis⁷⁹ and will not be further detailed in this thesis. The final modification to the *cinchona* alkaloid structure, which will be discussed in the following section, involves alkylation of the quinuclidine nitrogen to form a tetraalkylammonium salt. Molecules possessing such substitutions belong to a subset of organocatalysis referred to as phase transfer catalysis.

1.6 Phase-transfer catalysis (PTC)

Phase transfer catalysis uses tetraalkylammonium or phosphonium salts to catalyse reactions between substances in two immiscible phases.⁸⁰ PTC is an extremely attractive synthetic methodology to the chemical industry due to its operational simplicity; in general PTC requires mild reaction conditions using inexpensive and environmentally benign reagents and solvents which enable large-scale preparations in process chemistry. PTC is currently used in the manufacture of chemicals worth over €10 billion per year in industries such as pharmaceuticals, explosives, agri-chemicals and surfactants to name but a few.⁸¹

In recent years, asymmetric phase transfer catalysis (APTC) has become a topic of tremendous scientific interest. Currently, there are two systems which are generally accepted to explain the mechanistic aspects of asymmetric PTC. The first example follows the Makozsa interfacial mechanism and describes the functionalisation of active methylene groups under basic conditions (Figure 1.9).⁸² The initial step in this mechanism involves the interfacial deprotonation of the α -proton of **77** using metal hydroxide (MOH) to furnish the metal enolate **78**, which is stationary at the interface. Subsequent ion-exchange with catalyst Q^+X^- mobilises the newly formed lipophilic chiral onium enolate **79**, which enters the organic phase for the successive reaction with the alkyl halide (RX) to furnish the product **80** with the concomitant regeneration of the catalyst.⁸² The success of this reaction lies in the propensity of the metal-enolate to undergo ion exchange with the catalyst Q^+X^- and form the chiral onium enolate **79**. The ability of catalyst cation to block one of the two enantiotropic faces of the enolate anion determines the stereoselectivity obtained in the product.

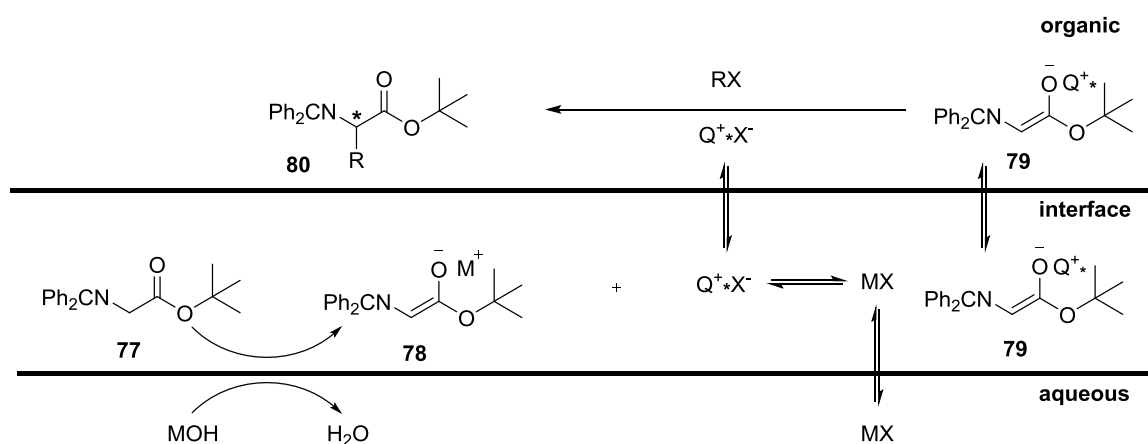


Figure 1.9 Representative APTC mechanism for the alkylation of methylene compounds

The second system explains the nucleophilic addition of an organic or inorganic anion to prochiral electrophiles. The starks extraction mechanism is operative in this process.⁸⁰ Figure 1.10 depicts the asymmetric epoxidation of α,β -unsaturated ketones with NaOCl(aq.) *via* APTC. In this example, the inorganic salt NaOCl undergoes ion-exchange with the phase transfer catalyst at the interface, enabling the nucleophilic ion to enter the organic phase. The newly formed chiral ion pair can now react with the electrophile **55** to furnish the epoxide product (**82**), bearing a new stereogenic centre.⁸³

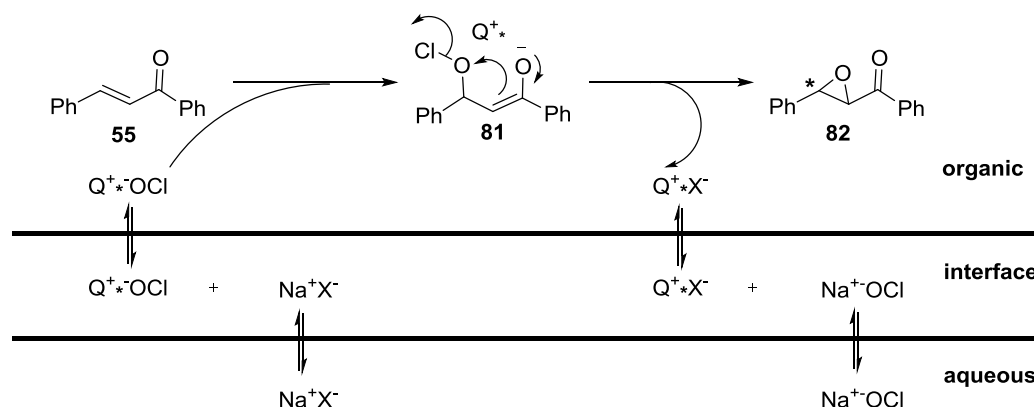
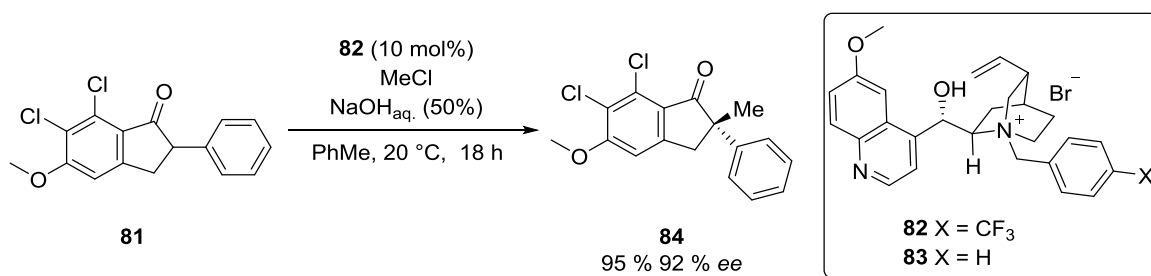


Figure 1.10 Representative APTC mechanism for the epoxidation of α,β -unsaturated ketones

The first example of a *cinchona* alkaloid derived phase-transfer catalyst facilitating a reaction with high levels of enantiocontrol was reported by Dolling *et al.* in 1984 (Scheme 1.13).⁸⁴ They utilised the quaternary ammonium salt **82** to catalyse the enantioselective alkylation of active methylene compounds with reaction yields of 95% and enantioselectivities of up to 92% for the products. The importance of an electron-withdrawing moiety at the *para* position of the *N*-benzyl salt became apparent when catalyst **83** (lacking the aforementioned functionality) was employed, furnishing the product in 25% *ee*.



Scheme 1.13 Alkylation of indanone derivative **81** using phase-transfer catalysis

The rationale proposed by the authors suggested association of the enolate of the substrate with the quinuclidine salt *via* ionic interactions (Figure 1.11). π -Stacking interactions between the aromatic systems as well as hydrogen bonding donation of the catalyst OH group to the enolate oxyanion were also postulated to influence the organisation of the pre-transition state such that the *si*-face of the enolate is blocked by the catalyst. As such, nucleophilic attack on MeCl would occur exclusively from the *re*-face of the enolate to furnish the enantioenriched product.⁸⁴

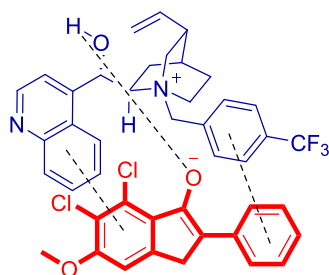
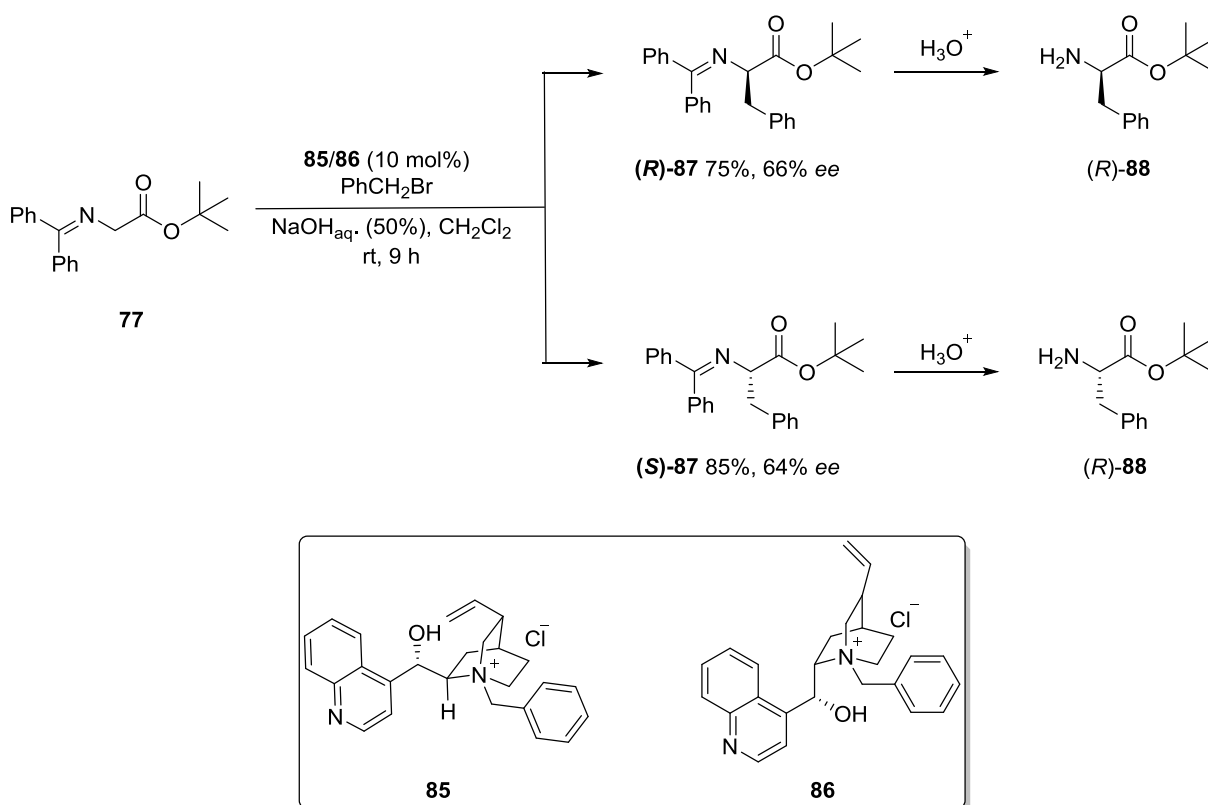


Figure 1.11 Pre-transition state proposed by Dolling *et al.* for the APTC alkylation of **81**

Five years later, O'Donnell and co-workers published a benchmark paper for asymmetric phase-transfer catalysis; illustrating that either enantiomer of a product could be obtained by using the correct *pseudoenantiomer* of the *cinchona* alkaloid derived phase transfer catalyst (Scheme 1.14).⁸⁵ The study employed catalyst **85** and its pseudoenantiomer **86** in two separate reactions to obtain the *R* and *S* phenylalanine derivatives through the alkylation of the Schiff base **77**.



Scheme 1.14 Protected amino acid synthesis *via* Schiff base alkylation using APTC

These initial studies carried out by Dolling⁸⁴ and O'Donnell⁸⁵ inspired the development of a myriad of new phase transfer catalysts and their application in a range of enantioselective reactions. It should be noted that chiral phase-transfer catalysts are not limited to the *cinchona* alkaloid backbone; other known examples include BINOL-derived quaternary ammonium salts such as **89**,⁸⁶ bifunctional quaternary phosphonium salts such as **90**⁸⁷ and urea-amide-guanidinium phase transfer catalysts such as **91**⁸⁸ to name but a few (Figure 1.12).

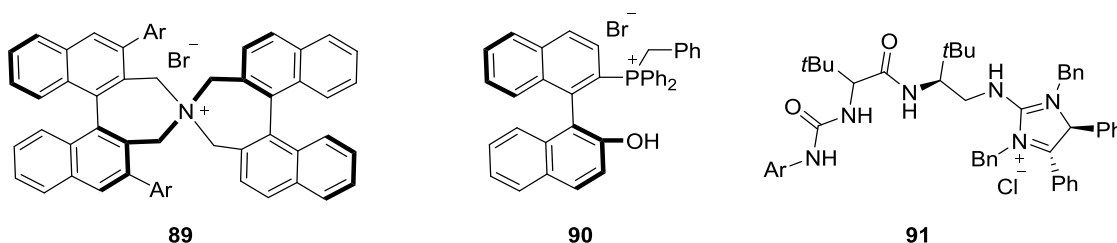


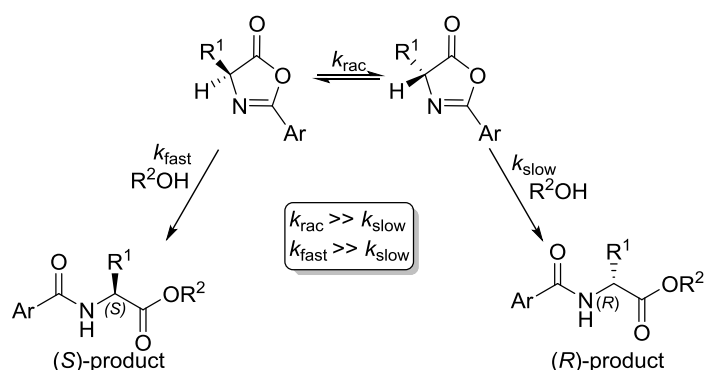
Figure 1.12 Examples of different types of phase transfer catalysts

The development of novel enantioselective methodologies using asymmetric phase transfer catalysts will be discussed in the latter half of this thesis. Prior to that, our use of *cinchona* alkaloid derived bifunctional organocatalysts will be described: first in relation to the kinetic resolution of oxazinones

via ring opening alcoholysis followed by the catalytic asymmetric cycloaddition of imines and enolisable anhydrides.

1.7 The Dynamic Kinetic Resolution of Azlactones

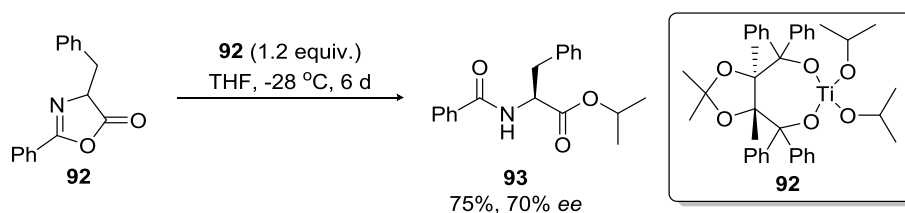
The DKR of α -substituted azlactones by alcoholysis is a well-established route providing access to both natural and unnatural, enantioenriched α -amino acids (Scheme 1.15). The presence of a labile α -hydrogen allows for facile enol formation, making azlactones ideal substrates for DKR. Though enzymatic variants for azlactone DKR had proved successful,⁸⁹ limited scope and lack of pseudo-chirality made the development of non-enzymatic approaches of practical interest.



Scheme 1.15 Azlactone DKR by alcoholysis

1.7.1 Ti-TADDOLate catalysed DKR of azlactones

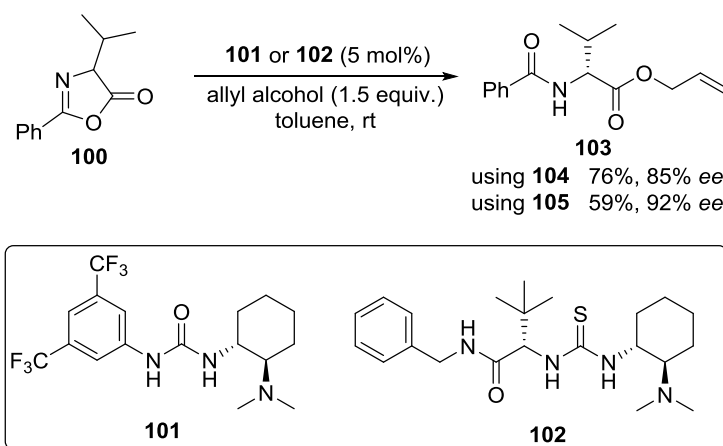
In 1997, Seebach *et al.* reported the first non-enzymatic example of azlactone DKR *via* alcoholysis using a Lewis acid catalyst, Ti(V)TADDOLate **93**, to produce moderate *ee* (up to 68%); however, long reaction times and high catalyst loadings made the methodology inferior to the enzymatic protocols already available (Scheme 1.16).^{90, 91}



Scheme 1.16 Ti-TADDOLate catalysed DKR of azlactones by Seebach and co-workers

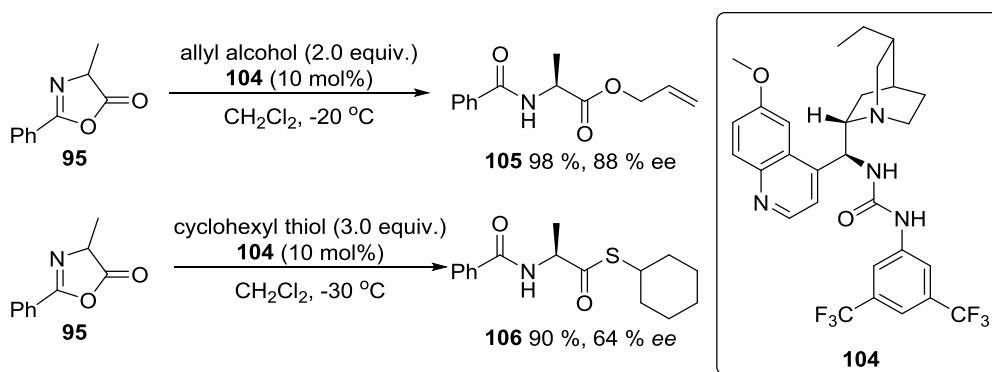
1.7.2 DKR of azlactones using acyl transfer catalysts

The following year, Fu *et al.* published a more promising methodology for this transformation.⁹² The study utilised chiral acyl transfer DMAP-derived catalyst **96** to promote the reaction, furnishing the ring opened products in high yield and moderate enantioselectivity (Scheme 1.17). Benzoic acid was found to be a critical additive in terms of rate and selectivity, without which the reaction proceeded slowly to furnish almost racemic products. Presumably, the acid is required to activate the azlactone



Scheme 1.19 Bifunctional (thio)urea catalyzed DKR of azlactones by Berkessel and co-workers

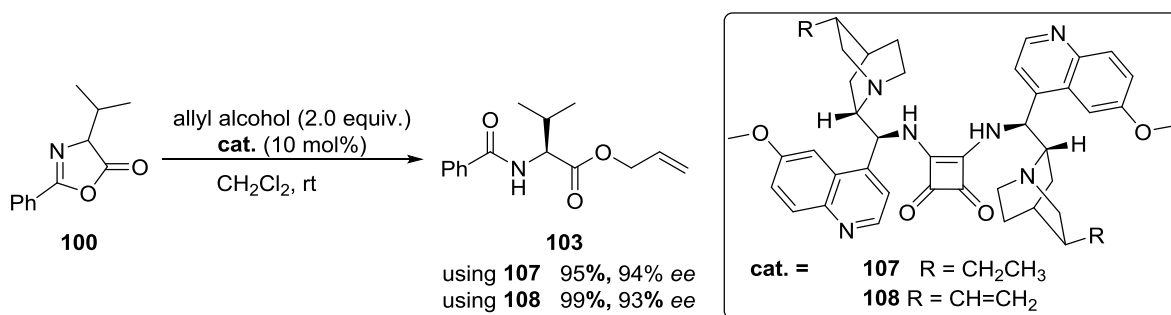
Connon and co-workers demonstrated the use of *cinchona* alkaloid derived catalyst **104** to promote the alcoholysis and thiolysis of azlactones (Scheme 1.20).⁹⁸ The results obtained for the alcoholysis reaction were comparable with those in Berkessels' aforementioned studies (Scheme 1.19),^{95, 96} producing the ester products in high yields and enantioselectivities (up to 88% ee). The importance of this study however, lay in the DKR of the azlactones by thiolysis; this was the first such transformation which yielded the valuable thioester products (important substrates for native chemical ligation)⁹⁹ in excellent yield and moderate selectivity (up to 64% ee). They later improved upon these results, obtaining ees of up to 91% for the thioester products, though the reaction yields were low.¹⁰⁰



Scheme 1.20 Azlactone DKR using bifunctional catalyst **104**

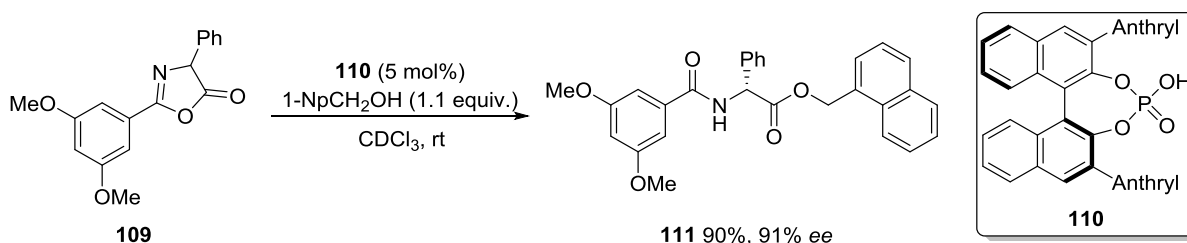
Song *et al.* demonstrated that self-association was a common problem with traditional (thio)urea *cinchona* alkaloid derived catalysts, thus diminishing the availability of reactive catalyst in the reaction in a concentration-dependant manner.¹⁰¹ Accordingly, he designed a series of C_2 -symmetric alkaloid-based catalysts which exhibited an appreciable decrease in self-association (demonstrated by nuclear magnetic resonance (NMR) spectroscopic and crystallographic methods); presumably the two *cinchona* alkaloid units are sufficiently bulky to inhibit hydrogen bonding. Catalysts **107** and

108 both exhibited excellent activity in the alcoholysis of **100** and their efficiency was linked to the avoidance of self-aggregation of the catalyst.¹⁰² A wide range of natural and unnatural amino acid derived azlactones were tolerated by the catalysts' affording the respective products in high yield and enantioselectivity, with a further enhancement in results upon cooling the reaction (**103** was obtained in 98% yield and 97% *ee* when the reaction was carried out at -20 °C). The opposite enantiomer could also be obtained by using the quinidine derived catalysts, albeit higher catalyst loadings were required.



1.7.4 DKR of azlactones using Brønsted acid catalysts

In 2011, Birman and co-workers reported the use of Brønsted acid catalyst **110** for the DKR of aryl azlactones, affording the protected amino acid products in excellent yields and enantiomeric excess (Scheme 1.21).¹⁰³ Soon after, Gong *et al.* reported an almost identical methodology obtaining comparable yields and enantiomeric excess for the DKR of azlactones.¹⁰⁴ Although the Brønsted acid catalysed DKR of azlactones presents a new approach, it fails to compare with current bifunctional organocatalytic methodologies: more sterically encumbered reagents (**109** and 1-Np CH_2OH) are required in order to obtain the protected amino acid products in high yield and enantioselectivity. The protocol requires a more sterically encumbered aryl-substituent on the azlactone (*e.g.* **109**) than previous approaches, furnishing a more complex *N*-benzoyl protecting group in the product (**111**). Furthermore, the transformation requires the use of a more sterically demanding alcohol to enhance results.

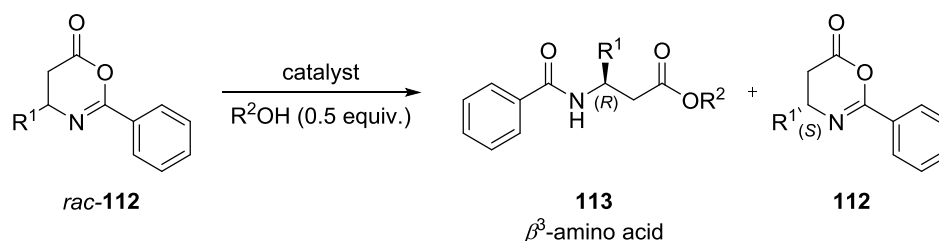


Scheme 1.21 DKR of azlactones using Brønsted acid catalyst **110**

These studies represent the main advances in the dynamic kinetic resolution of traditional azlactones over the last 20 years. The resolution methodologies have mainly been centred on the alcoholysis of these structures to yield protected amino acid-esters as products. Though a few literature examples detail azlactone DKR *via* thiolysis,¹⁰⁵ no methodology exists which yields the valuable thioester products in both high yield and enantioselectivity. Further still, there is currently no literature precedent for the catalytic DKR of azlactones by aminolysis to yield enantioenriched peptide products – thereby carrying out the resolution and peptide coupling in one step. The development of such a protocol would possess enormous value. Chapter 8 of this thesis details our progress in the design of this methodology.

1.8 Kinetic resolution of oxazinones *via* alcoholysis

Compared to their azlactone counterparts, the KR of oxazinones (their ring expanded homoanalogues) has remained vastly underexplored. Insertion of a methylene group between the carbonyl and the α -C of the azlactone moves the nitrogen atom to the β -position to form oxazinones (**112**, Scheme 1.22). Epimerisation of the chiral centre is no longer facile and as such, DKR of these molecules cannot easily occur. Instead, the *R* and *S* enantiomers can be separated by kinetic resolution to yield enantioenriched β -amino acid-ester products (**113**).



Scheme 1.22 KR of oxazinones by alcoholysis

β -Amino acids can be sub-categorised into β^3 - and β^2 -amino acids (Figure 1.13). β^3 -amino acids (**114**) refer to those containing an single side chain at the β - position of the molecule whilst β^2 -amino acids (**115**) possess a single side chain at the α -position.¹⁰⁶ β^2 -amino acids tend to be much harder to prepare as, unlike their β^3 -counterparts, they cannot be synthesised asymmetrically by standard methodologies from the corresponding natural α -amino acid; instead, a sequence of transformations is generally required. This work will discuss the kinetic resolution of oxazinones to afford enantioenriched protected β^3 - and β^2 -amino acids.

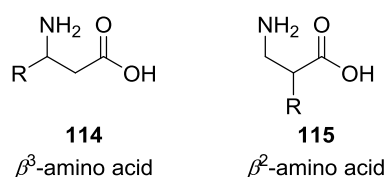
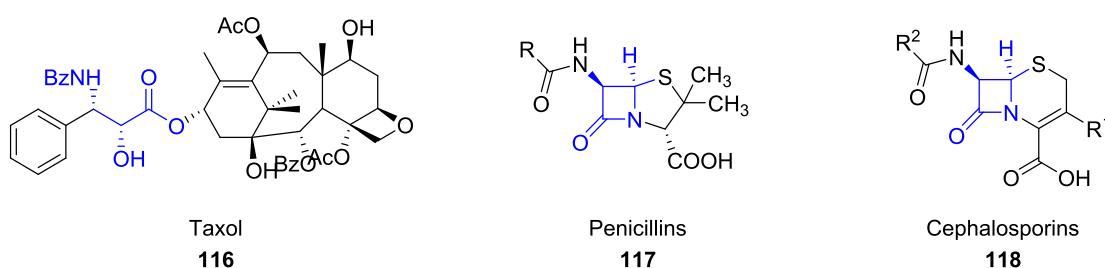


Figure 1.13 The general structure of β^3 - and β^2 -amino acids

1.8.1 The importance of β -amino acids

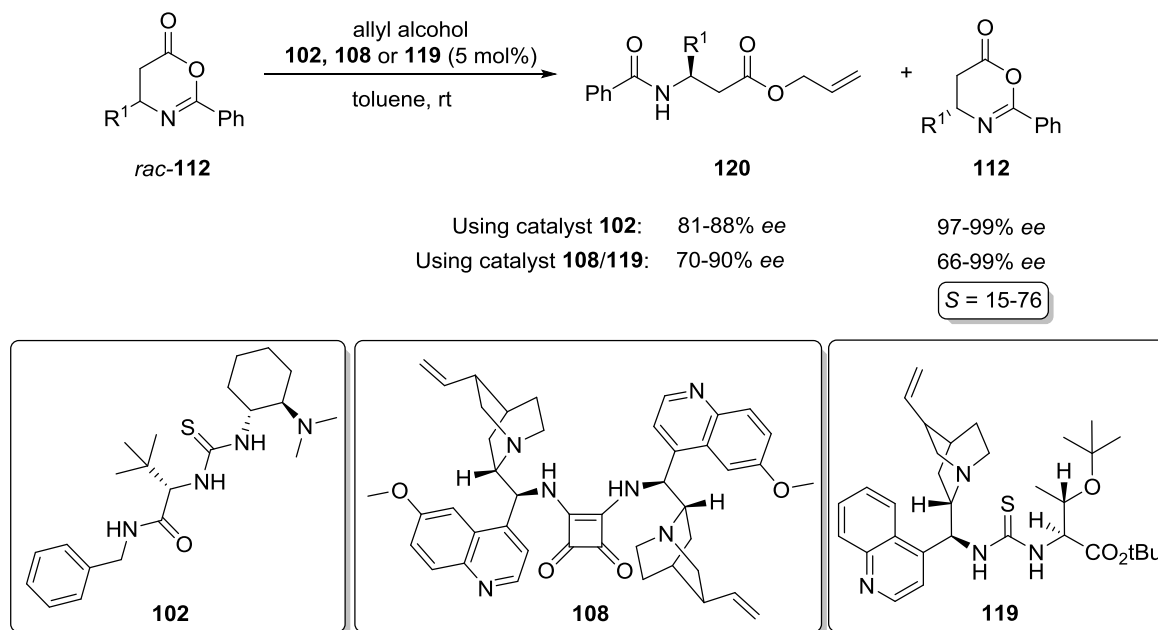
β -Amino acids and their derivatives have received a great deal of attention in recent years due to their unique biological properties, their abundance in natural products, and as precursors for the formation of β -lactams.^{107, 108} In their free form, β -amino acids have demonstrated exciting antifungal and anti-ketogenic properties. They also form the key structural components for many naturally occurring compounds including Taxol (**116**, Scheme 1.23), one of the most active and widely used antitumor agents. When self-lactonised they make up the biologically active core of β -lactam antibiotics, a broad class of antibiotics which include penicillin, n (**117**) and cephalosporin derivatives (**118**). These unique and diverse biological properties have created a high demand for enantiopure β -amino acids. Popular approaches to the synthesis of these enantiomerically pure compounds include the use of chiral auxiliaries, catalytic asymmetric synthesis and kinetic resolution.¹⁰⁹



Scheme 1.23 β -Amino components of representative pharmaceuticals

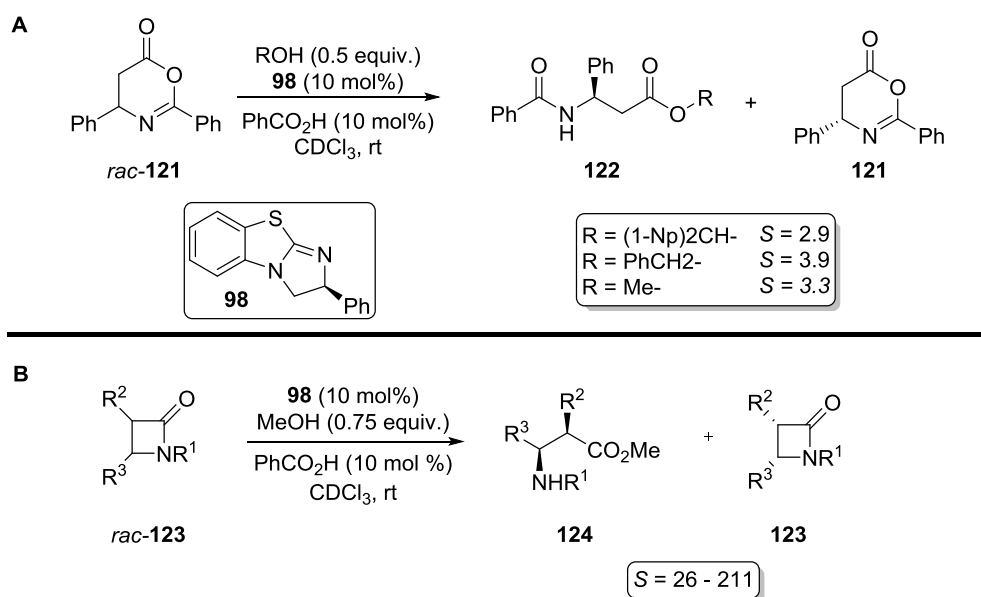
1.8.2 Kinetic resolution of oxazinones: A historical perspective

The KR of 4-substituted oxazinones by alcoholysis was first reported using bifunctional organocatalysis in 2005 (Scheme 1.24).¹¹⁰ Berkessel *et al.* utilised thiourea catalyst **102** (which had also proved successful in azlactone DKR) in the transformation to obtain the unreacted starting material in 97-99% *ee*, though conversions were pushed as far as 64% to obtain high *ee*. Perhaps unsurprisingly, the study failed to report *S* factors describing the overall efficiency of the protocol. In a later publication, Berkessel improved upon these results using the Design of Experiments (DoE) approach.¹¹¹ The study switches between dimeric squaramide catalyst **108** and bifunctional thiourea catalyst **119** to obtain *S* factors of 15-76 for the transformation.



Scheme 1.24 The first catalytic ring openings of oxazinones

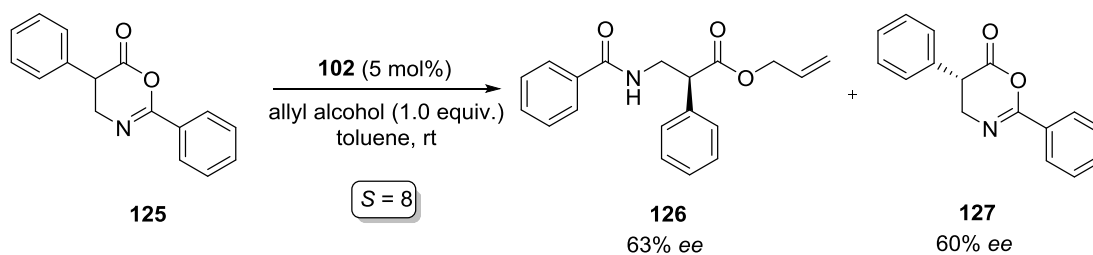
Following their success in azlactone DKR, Birman and co-workers published a paper in which they discussed their attempts to carry out KR on oxazinones using the same BTM catalyst **98** (Scheme 1.25A).¹¹² However, in contrast to their work on the DKR of azlactones, where the enantioselectivity depended critically on the size of the alcohol used, they obtained poor selectivity with similar *S* factors for both hindered and less hindered alcohols; they suggested that despite structural similarities between the two substrates, the origins of stereochemistry may be different. They abandoned their attempts to resolve the oxazinones and instead turned their attention to the KR of *N*-acyl- β -lactams to furnish the β -amino ester products in excellent yields and selectivity (*S* = up to 211, Scheme 1.25B).



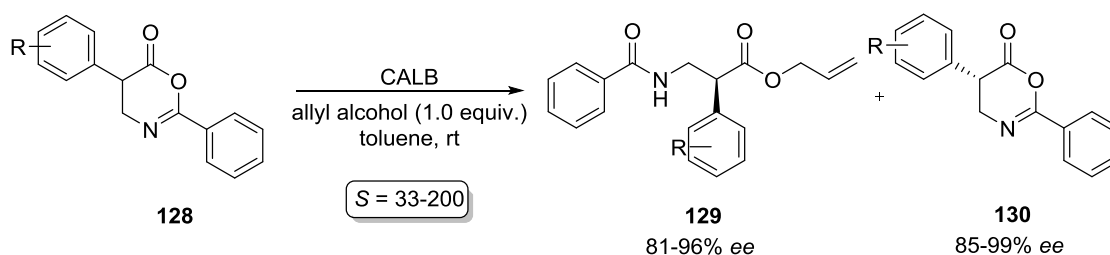
Scheme 1.25 BTM catalysed KR of oxazinones and *N*-acyl- β -lactams

In 2011, Bekessel and co-workers explored the KR of oxazinones as a method of resolving β^2 -amino acids (**129**).¹⁰⁶ In preliminary experiments they investigated the effect of bifunctional catalyst **102**, which had proved highly effective in both the alcoholic DKR of azlactones (Scheme 1.19) and the KR of 4-substituted oxazinones (Scheme 1.24).^{96, 110} Conversely, in the case of these 5-substituted oxazinones (**128**) the methodology did not afford satisfactory results, resulting in a corresponding *S* factor of 8 (Scheme 1.26A). Instead, they attempted enzymatic KR of 5-substituted oxazinones due to similarities in the calculated transition state of the alcoholic ring opening of oxazinones using bifunctional organocatalysts such as **102** and the mechanism of serine hydrolases in the body.¹⁰⁶ The lipase enzyme *Candida antarctica* lipase B (CALB) was found to be extremely efficient in the alcoholic KR of aromatic substituted oxazinones, giving calculated *S* values of up to 200 (Scheme 1.26B). However, as is the case with most enzymes, the substrate scope was limited, with the enzyme providing poor control using oxazinones with either aliphatic side chains or *ortho*-substituted phenyl rings. The study also examined the use of NEt₃ as a base additive to promote efficient DKR of aromatic oxazinones in the presence of CALB (up to 96% *ee*, Scheme 1.26C).¹⁰⁶

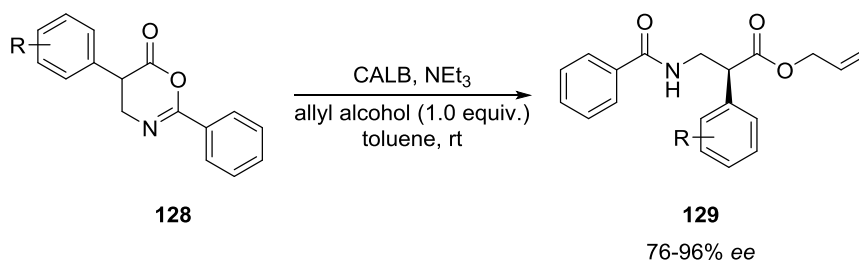
A : Organocatalytic KR



B : Enzymatic KR

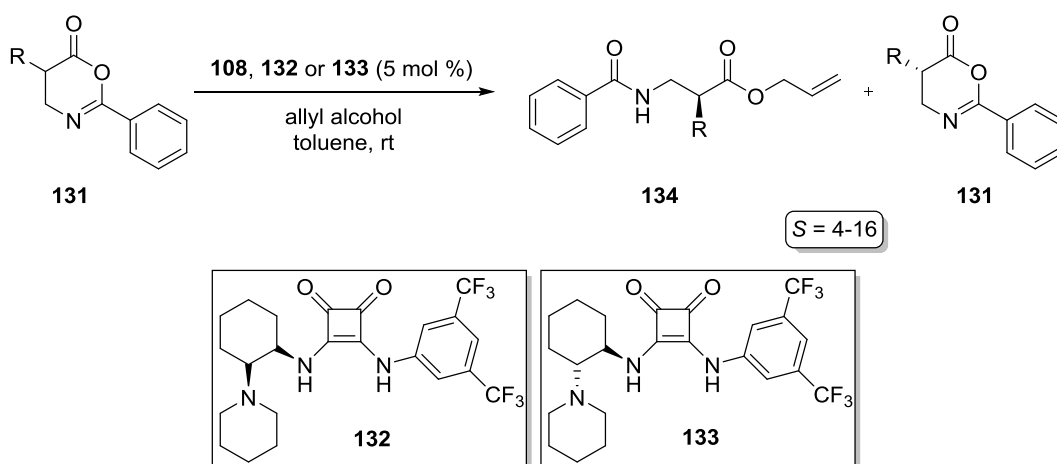


C : Enzymatic DKR



Scheme 1.26 Enzymatic KR and DKR of aromatic 5-substituted oxazinones

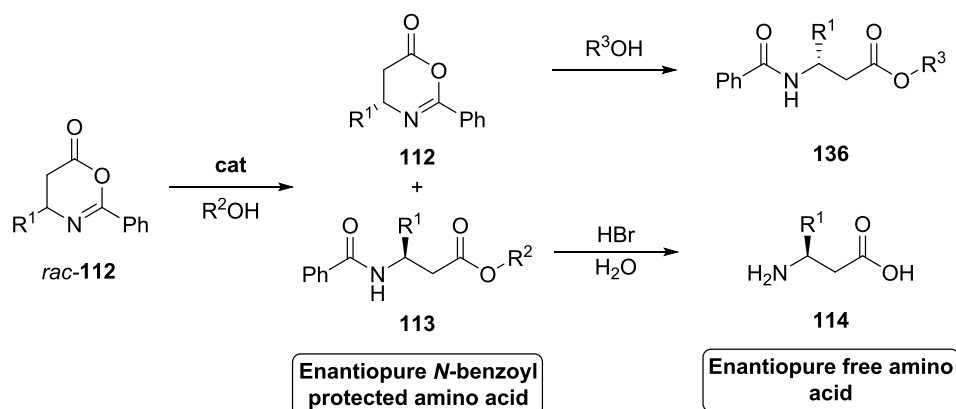
In 2017, Berkessel *et al.* published further efforts to develop an organocatalytic approach for the KR of 5-substituted oxazinones.¹¹³ They hoped that this would enable access to a much wider range of β^2 amino acids, including oxazinones which the enzyme CALB failed to control namely, those bearing alkyl substituents and *ortho*-substituted phenyl rings.¹⁰⁶ Their efforts however, were unsuccessful; the study employed three different bifunctional catalysts (**108**, **132**, and **133**) to resolve a range of aromatic and aliphatic 5-substituted oxazinones (**131**). Variable results were obtained for the transformations, with S factors ranging from 4-16 (Scheme 1.27). No obvious trends were observed in the study and, for the most part, the selectivity obtained was low; no further optimisation of the reaction was carried out.¹¹³ Currently, there is still no literature protocol for the efficient organocatalytic resolution of 5-substituted oxazinones.



Scheme 1.27 Organocatalytic KR of 5-substituted oxazinones

1.8.3 Challenges associated with current methods for the KR of oxazinones

There are several apparent challenges associated with current approaches to the KR of oxazinones *via* alcoholysis. Firstly, all current methods require aryl-oxazinone substrates such as **112** which, upon ring opening, afford the corresponding *N*-benzoyl protected amino acids **113** and **136**. Hydrolysis of the benzoyl amide functionality requires harsh reaction conditions, which results in the simultaneous cleavage of the ester protecting group, rendering the free amino acid **114** (Scheme 1.28). In cases where the product is required for further development, the amino acid would need to be selectively re-protected for subsequent coupling. This lack of orthogonality is considered a severe limitation of this methodology.

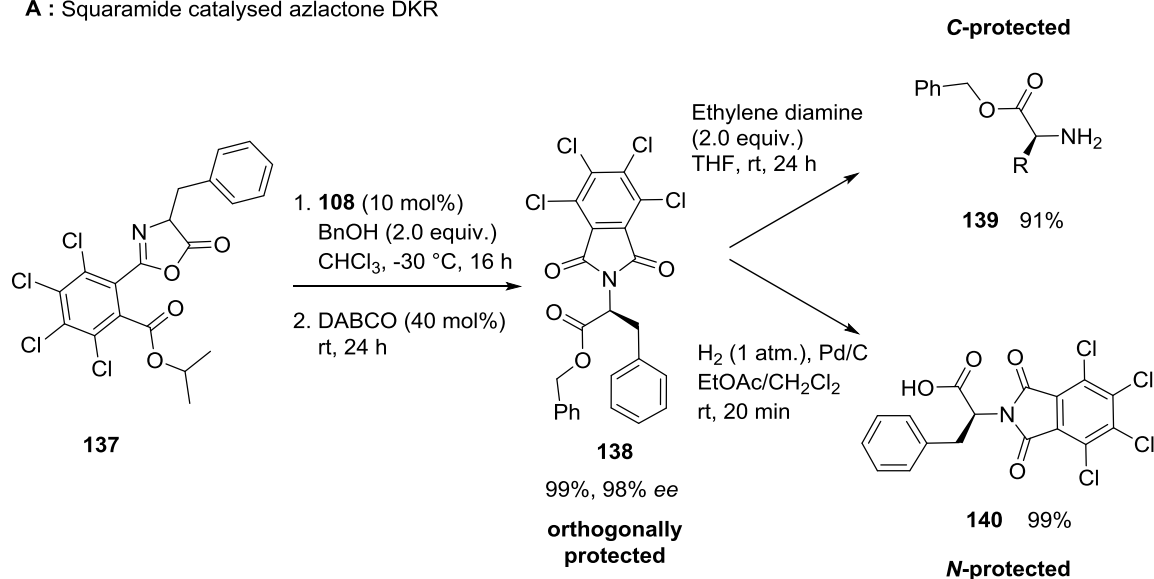


Scheme 1.28 Traditional oxazinone KR *via* alcoholysis and subsequent deprotection

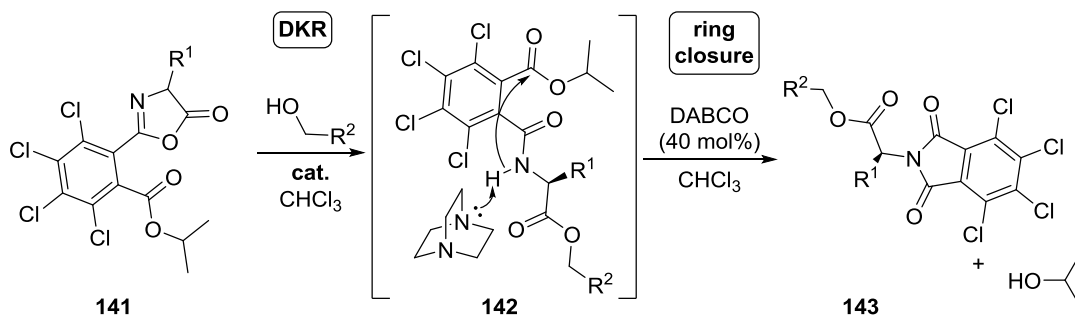
In 2014, the Connon group tackled a similar problem in relation to azlactone DKR.¹¹⁴ The study utilised tetrachloroisopropoxycarbonyl (TCIC) substituted azlactones such as **137** which, upon catalytic ring opening, can be treated with amine base to generate the appropriate *N*-phthalimido-protected amino acid ester in one pot (Scheme 1.29). Subsequent removal of either the phthalimide or ester protecting groups can be carried out cleanly to give the free amine (**139**) or acid (**140**) under

mild conditions. Using catalyst **108**, the DKR of these TCIC-azlactones to furnish enantioenriched and orthogonally protected amino acids was achieved with outstanding enantioselectivity.

A : Squaramide catalysed azlactone DKR



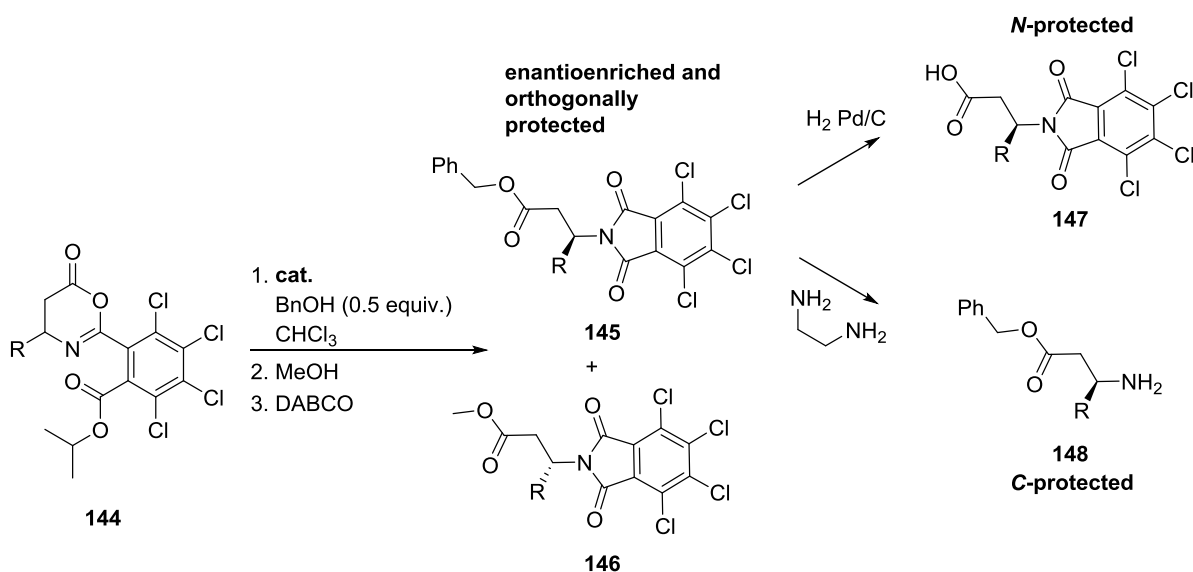
B : Mechanism for phthalimide formation



Scheme 1.29 A practical aryl substituent for the DKR of azlactones

1.8.4 Objectives

In this work, we hoped to incorporate the TCIC-substituent into the oxazinone structure, as a practical aryl unit, which could be used to generate enantioenriched and orthogonally protected β -amino acids upon ring opening alcoholysis (Scheme 1.30). We postulated that the increased steric bulk of the TCIC-subunit could potentially offer enhanced diastereocontrol, allowing us to extend the scope of the reaction far beyond the literature benchmarks, including, but not limited to non-branched alkyl amino acid derivatives. Whilst previous methodologies by Berkessel *et al.* were effective in the resolution of aryl substituted oxazinones, the only aliphatic substrates examined incorporated sterically demanding substituents such as *i*Pr and *t*Bu.^{110, 115}



Scheme 1.30 Incorporation of a practical aryl substituent for the KR of oxazinones

As highlighted in the previous section, there is currently no efficient organocatalytic methodology for the KR of 5-substituted oxazinones. Reported enzymatic variants for the transformation have limited reach, failing to effectively resolve those with alkyl- or *ortho*-phenyl substituents at the 5-position.^{106, 113} Furthermore, in many cases biocatalysis is not considered to be a practical approach due to the high cost and specificity of enzymes. Thus, the development of an effective organocatalytic method is of great synthetic interest.

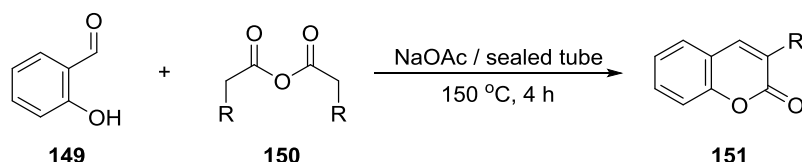
Finally, all current catalytic systems for oxazinone KR are substrate dependant, with small alterations in the amino acid side chain requiring large changes in catalyst structure for effective resolution. This lack of consistency amongst existing methodologies presents a major drawback. Our aim was to find one highly practical, effective approach for the KR of both 4- and 5- substituted TCIC-oxazinones allowing access to a wide range of enantioenriched and orthogonally protected β^3 and β^2 -amino acids.

1.9 Cyclic anhydrides in formal cycloaddition reactions

Carboxylic acid anhydrides are of enormous synthetic significance, particularly as electrophilic acyl transfer agents.¹¹⁶ Reactivity wise, they occupy the territory between the highly electrophilic acyl halides and the more stable but less reactive carboxylic acid esters. Whilst anhydride chemistry is almost completely dominated by their electrophilicity, enolisable anhydrides have also been reported to act as carbon based nucleophiles in formal cycloaddition reactions in an aldol-like coupling process.¹¹⁷ These reactions provide an efficient one step synthesis of polysubstituted heterocyclic molecules – important structural motifs in many natural products.

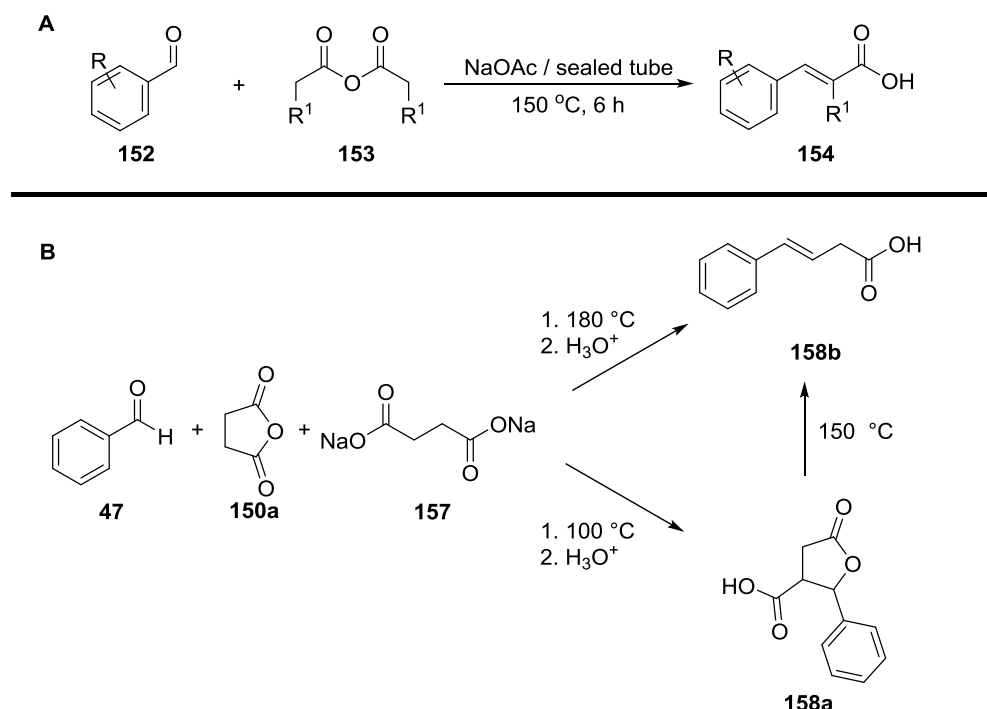
1.9.1 The formal cycloaddition reaction between enolisable anhydrides and aldehydes

The Perkin reaction was the first example in which enolisable anhydrides were used as carbon-based nucleophiles. In 1968, while investigating the action of acetic anhydride on aromatic aldehydes, William H. Perkin observed that at elevated temperatures, enolisable aliphatic anhydrides could in fact behave as carbon-based nucleophiles in the presence of weak carboxylate bases. This work led to the first synthesis of coumarins **151** (using salicylaldehyde (**149**)) *via* ‘the Perkin reaction’ (Scheme 1.31).¹¹⁸



Scheme 1.31 Synthesis of coumarins *via* the Perkin reaction

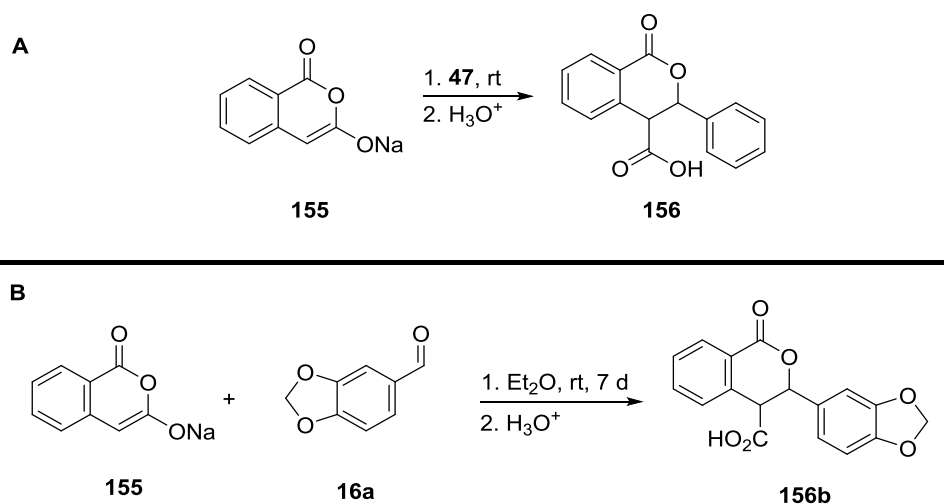
Perkin later extended the scope of this work using different aromatic aldehydes with aliphatic enolisable anhydrides to yield α,β -unsaturated carboxylic acids (**154**) as products (Scheme 1.32A).¹¹⁹ In the same report he also explored the use of cyclic enolisable anhydrides which, when reacted with benzaldehyde (**47**) at 180 °C in the presence of sodium succinate (**157**) afforded the product **158b** (Scheme 1.32B).



Scheme 1.32 Reactivity of anhydrides as carbon-based nucleophiles as reported by Perkin and Fittig

Some years later, Fittig and co-workers proposed a mechanism for the process. They carried out the same reactions at lower temperatures and concluded that the reaction is an addition process, much like the aldol condensation, in which the enolate of the anhydride adds to the aldehyde forming the β -hydroxy intermediate followed by dehydration to yield the α,β -unsaturated acid product.¹²⁰ Proof of the β -hydroxy intermediate came from the reaction between succinic anhydride and benzaldehyde at 100 °C where the major product formed was γ -phenylparaconic acid (**158a**) which occurs as a result of lactonisation of the intermediate hydroxyl acid (Scheme 1.32).¹²¹ Heating molecule **158a** to temperatures above 150 °C causes decarboxylation to furnish product **158b**, observed by Perkin in his original study. Erdmann *et al.* also observed γ -lactone formation when succinic anhydride and aromatic aldehydes were heated in the presence of sodium acetate.¹²²

In 1931, Müller reported the first use of homophthalic anhydride in the Perkin reaction which led to the formation of bicyclic dihydroisocoumarins such as **156**. This corroborated the concept that the cycloaddition reaction occurs between the enolate of the cyclic anhydride and the aldehyde to give the lactone product (Scheme 1.33A).¹²³ Much later, Pinder *et al.* confirmed this reactivity when they reacted the sodium enolate of homophthalic anhydride (**155**) with piperonal (**16a**) at room temperature to obtain the dihydroisocoumarin derivative **156b** (Scheme 1.33B).¹²⁴



Scheme 1.33 Dihydroisocoumarin synthesis by Müller *et al.* (A) and Pinder *et al.* (B)

1.9.1.1 Mechanistic insights

These aforementioned reports by Fittig,¹²¹ Erdmann,¹²² Muller¹²³ and Pinder¹²⁴ were all in agreement that the reaction mechanism is likely to proceed *via* nucleophilic attack of the anhydride enolate (**160**) on the aldehyde (**47**) to generate the intermediate **161** which undergoes intramolecular cyclisation followed by proton transfer to yield the dihydroisocoumarin **156**. Formation of the initial anhydride enolate is promoted by either a Lewis acid or a carboxylate base as shown in Figure 1.14.

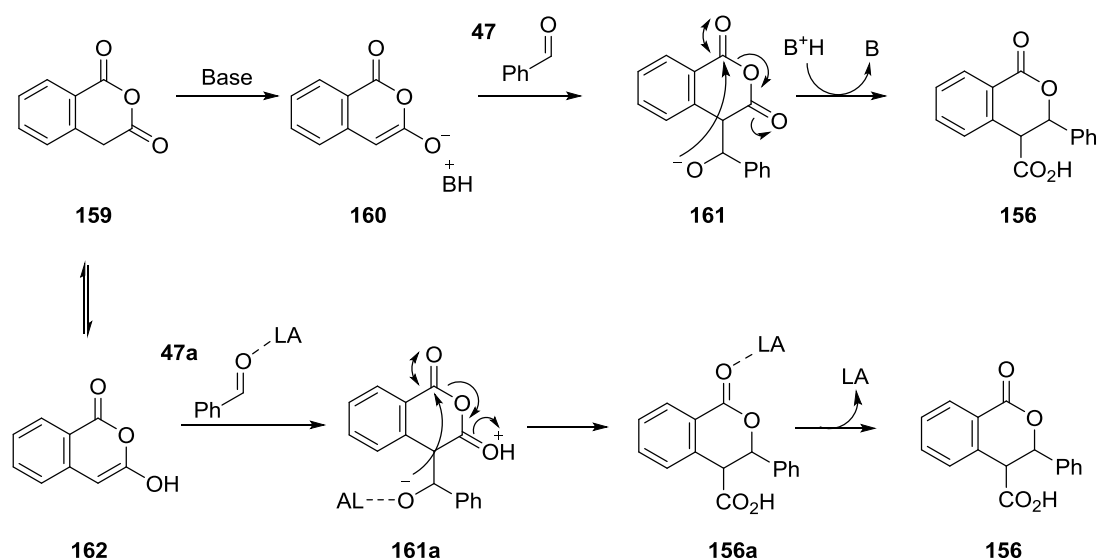
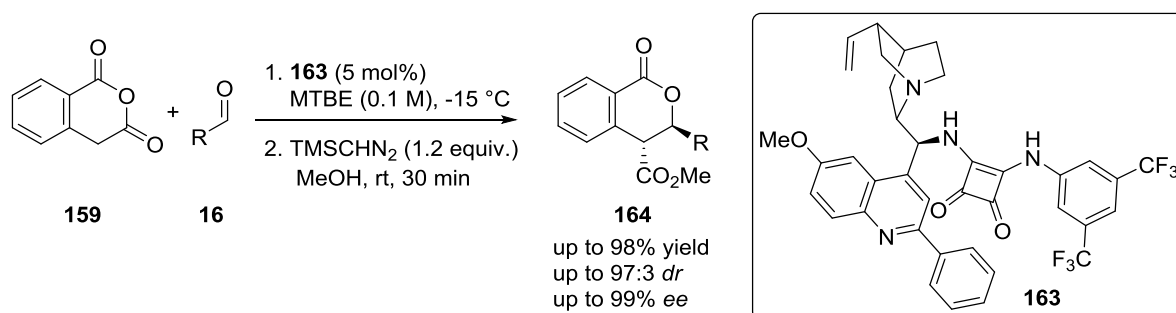


Figure 1.14 Mechanism of action for the formal cycloaddition between homophthalic anhydride (**159**) and benzaldehyde (**47**)

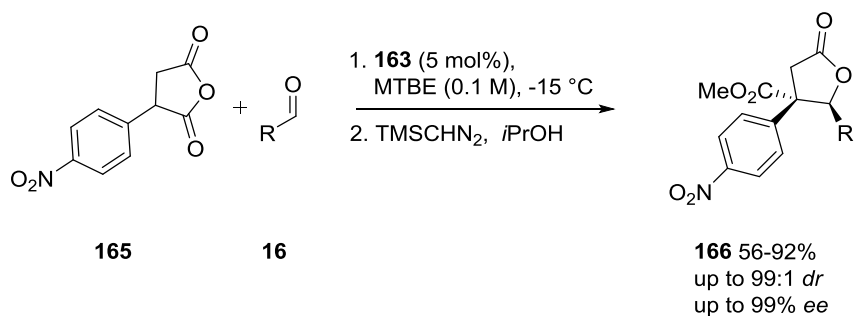
1.9.1.2 The asymmetric reaction

It was Cannon *et al.* who developed the first asymmetric protocol for this cycloaddition process (Scheme 1.34).¹²⁵ They envisaged that in the absence of a strong pronucleophile, chiral bifunctional organocatalysts could be used to activate both the enolisable anhydride nucleophile (*via* keto-enol tautomeric equilibrium) and the aldehyde electrophile (*via* hydrogen bond donation), introducing enantio- and diastereo- control to the reaction. Using catalyst **163**, homophthalic anhydride (**159**) and a range of aldehydes under optimised conditions, they obtained numerous dihydroisocoumarin derivatives with excellent diastereo- and enantioselectivity (up to 99% *ee*). The scope of the reaction was found to be robust in relation to the aldehyde component; electron rich, electron deficient and hindered aldehydes all gave excellent enantioselectivity with good to excellent diastereoselectivity. Substitution on the anhydride component was also well tolerated.



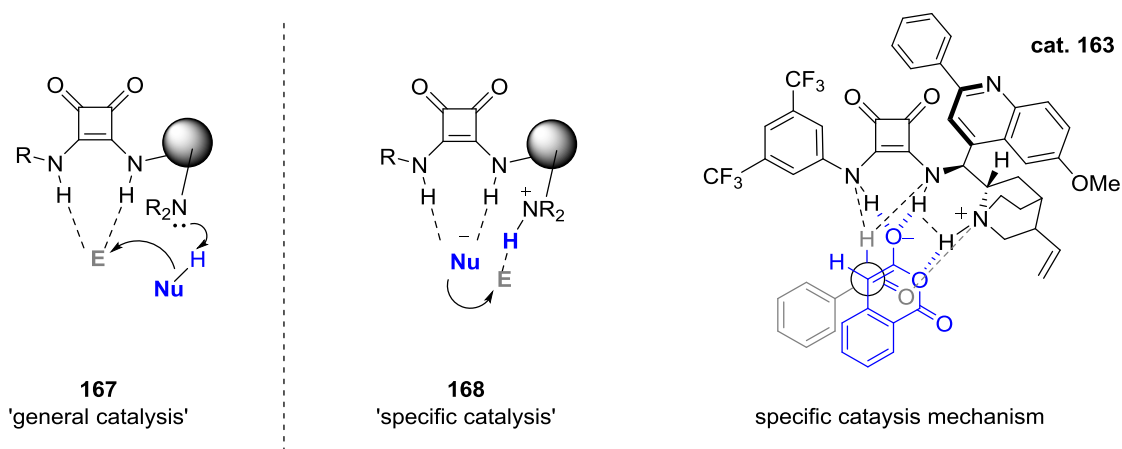
Scheme 1.34 The first asymmetric protocol for the cycloaddition of enolisable anhydrides and aldehydes

In 2012, they further extended the scope of the cycloaddition to substituted succinic anhydrides such as **165** which, when reacted with aldehydes in the presence of **163**, provided access to highly enantio- and diastereo-enriched paraconic acid (γ -butyrolactone) derivatives **166** (up to 99% *ee*, Scheme 1.35)¹²⁶



Scheme 1.35 Asymmetric cycloaddition of succinic anhydrides and aldehydes

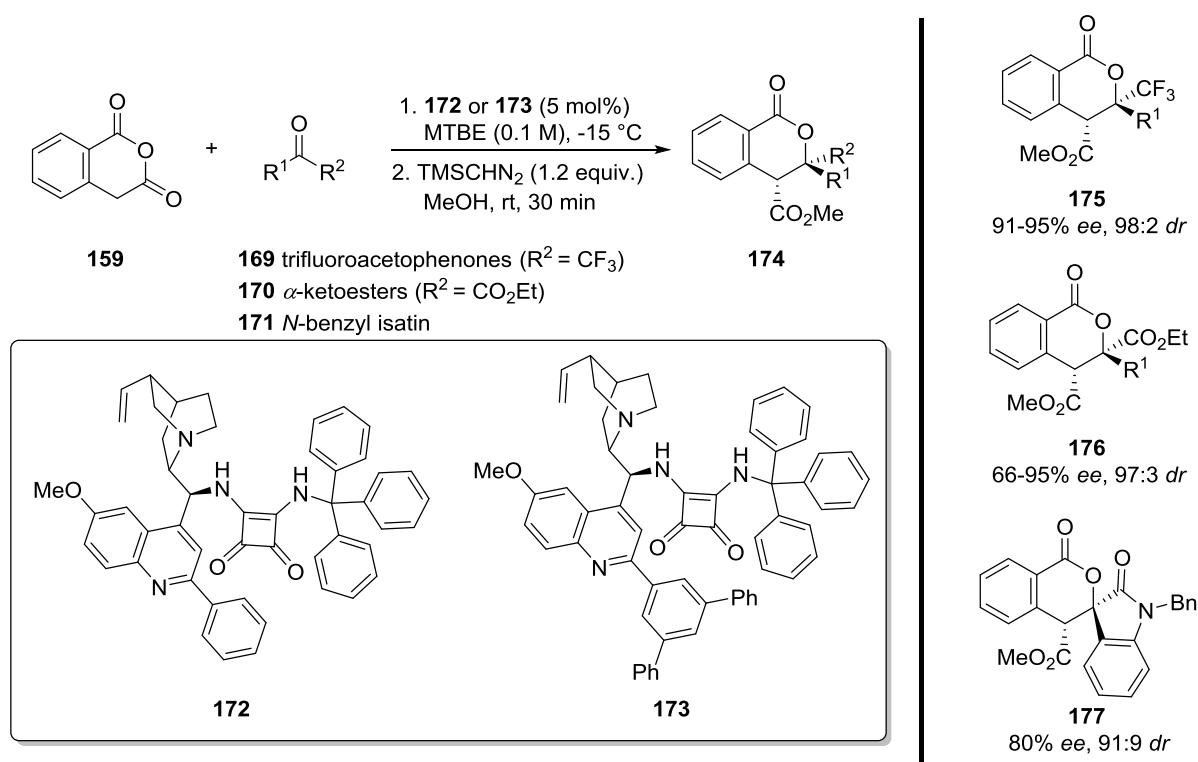
In 2017, Cannon and co-workers also carried out the first DFT study on the mechanism of the cycloaddition of benzaldehyde with homophthalic anhydride using bifunctional organocatalyst **163**.¹²⁷ The study explored two likely pathways for the mechanism of action: general catalysis vs. specific catalysis. The calculations showed an unambiguous preference for the pre-transition state **167** (Scheme 1.36), a specific catalysis pathway, leading to the major product enantiomer. In this mechanism, the anhydride pronucleophile is deprotonated by the basic functionality of the catalyst to afford the enolate nucleophile which is held in place *via* H-bond donation from the squaramide moiety. Meanwhile the aldehyde is activated towards nucleophilic attack by the now protonated ammonium ion. The alternative pathway in the study which explored a ‘general catalysis’ like mechanism was discounted as pre-transition state **168** was found to be considerably higher in energy (Scheme 1.36).



Scheme 1.36 Specific catalysis vs general catalysis: a DFT study.

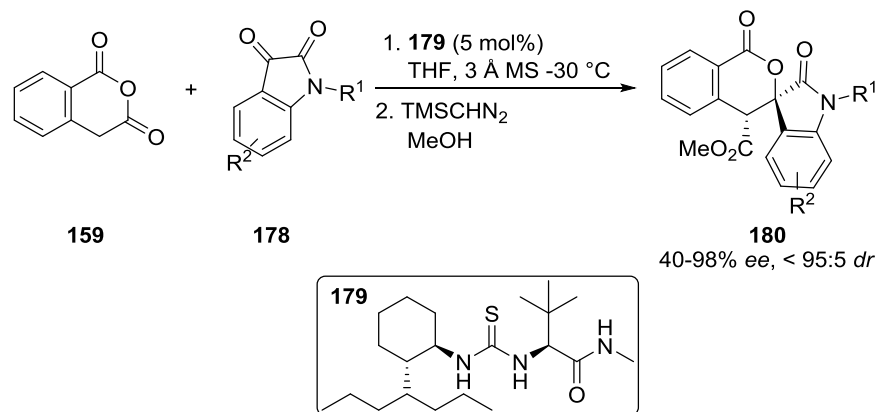
1.9.2 The asymmetric cycloaddition between enolisable anhydrides and other electrophiles

In 2016, Connon and co-workers published the first use of activated ketones in asymmetric cycloaddition reactions with enolisable anhydrides (Scheme 1.37). They demonstrated the use of catalysts **172** and **173** to promote the cycloaddition of homophthalic anhydride (**159**) to trifluoroacetophenone derivatives, α -ketoesters and *N*-benzyl isatin to generate densely functionalised products in excellent diastereo- and enantioselectivity.¹²⁸ Variation of the anhydride component of the reaction was well tolerated; with homophthalic anhydride, α -aryl succinic anhydride and glutaconic anhydrides all reacting with high levels of diastereo- and enantiocontrol.



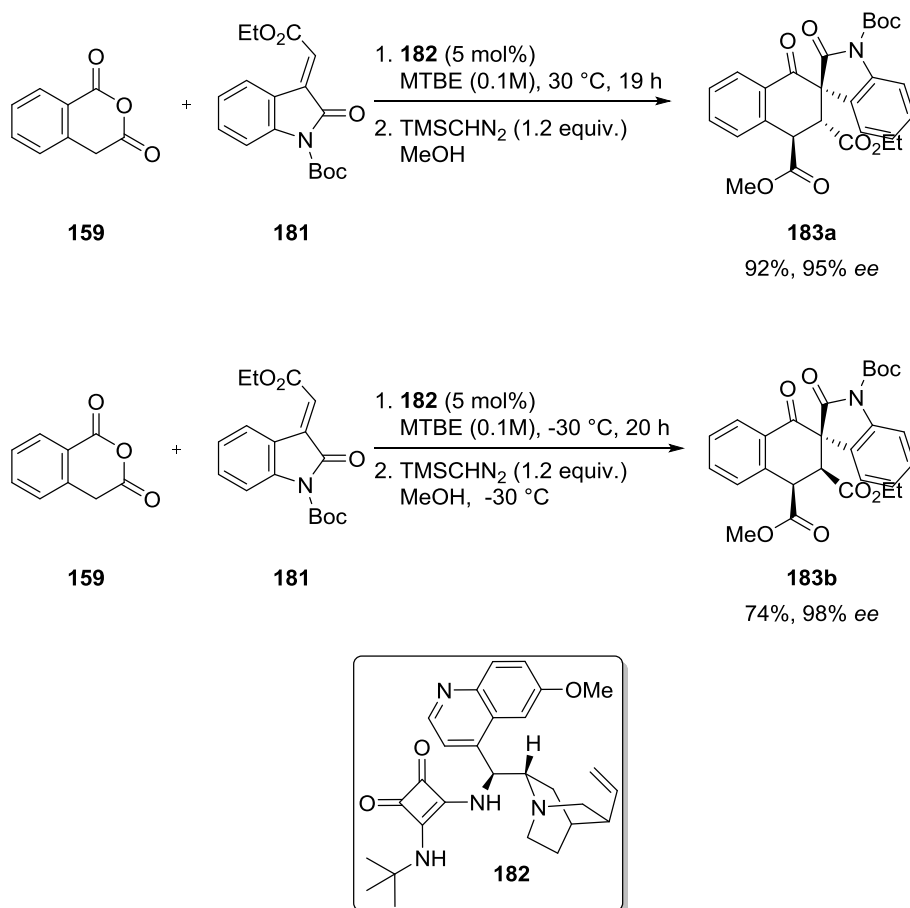
Scheme 1.37 Asymmetric cycloadditions of anhydrides and ketones by Connon *et al.*

In the same year Shi *et. al.* reported the use of chiral organocatalyst **179** in the cycloaddition reaction of enolisable anhydrides and isatins (**178**) to yield highly enantioenriched dihydroisocoumarin spirooxindole scaffolds (**180**, Scheme 1.38).¹²⁹



Scheme 1.38 Asymmetric cycloadditions of anhydrides and isatins by Shi *et al.*

In 2014, Connon *et al.* reported the first catalytic asymmetric variant of the Tamura cycloaddition.¹³⁰ The study used catalyst **182** to promote the reaction between various enolisable anhydrides and doubly activated alkylidene oxindoles (**181**) to form densely functionalised, 3,3-spirooxindole products such as **183** with the formation of three new carbogenic stereocentres in excellent diastereo- and enantiocontrol (Scheme 1.39). They also showed that the identity of the major diastereomeric product could be selected by tuning the reaction temperature.¹³⁰ At room temperature, product **183a** was obtained in 92% yield and 95% ee (Scheme 1.39). At -30 °C, **183b** was furnished as the major diastereomer in 74% yield and 98% ee demonstrating the utility of this process in target-orientated synthesis. Later, Connon *et al.*, further expanded the scope of this work to include singly activated nitroalkenes.¹³¹



Scheme 1.39 The first catalytic, asymmetric Tamura cycloaddition

1.9.3 The formal cycloaddition between enolisable anhydrides and imines

Substituted δ -lactam ring systems are the structural motifs in a wide range of natural products that exhibit biological activity. Amaryllidaceae alkaloids (**184**), which contain a chiral δ -lactam core, have exhibited anti-tumour¹³² and antiviral activity¹³³ (Figure 1.15). Kopsihainanine A (**185**), isolated from *Kopsia hainanensis*, is a known AChE inhibitor.¹³⁴ Small molecules containing this structural motif have also shown important biological activity; compounds such as (+)-SJ733 (**186**) been investigated as an antimalarial agent.¹³⁵ The formal cycloaddition between enolisable anhydrides and imines has been known to generate lactam products for almost 50 years. Despite the obvious utility in generating these products chirally, no catalytic, enantioselective variant of this reaction has existed in the literature until this study, *vide infra*.¹³⁶

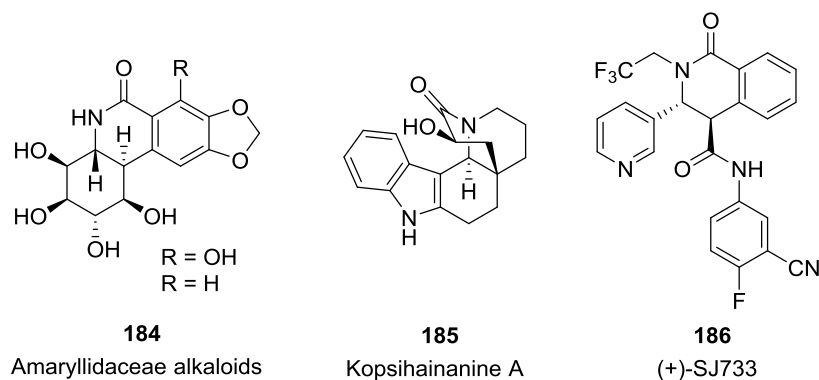
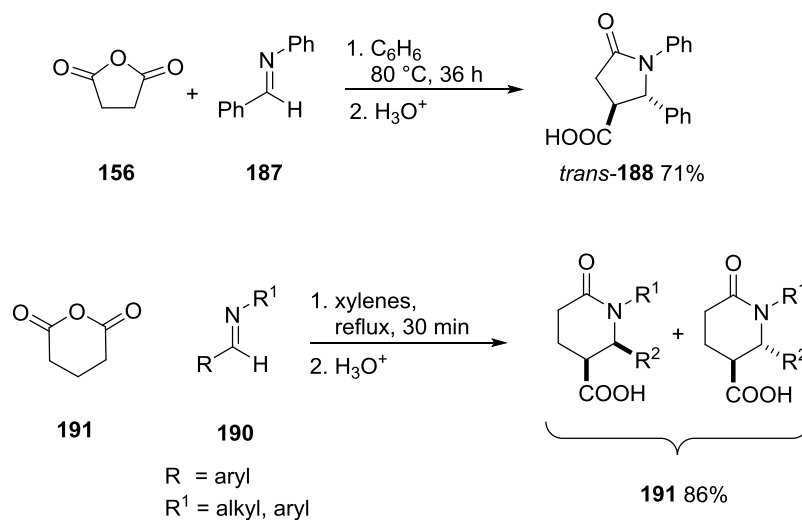


Figure 1.15 Important biological molecules containing a δ -lactam core

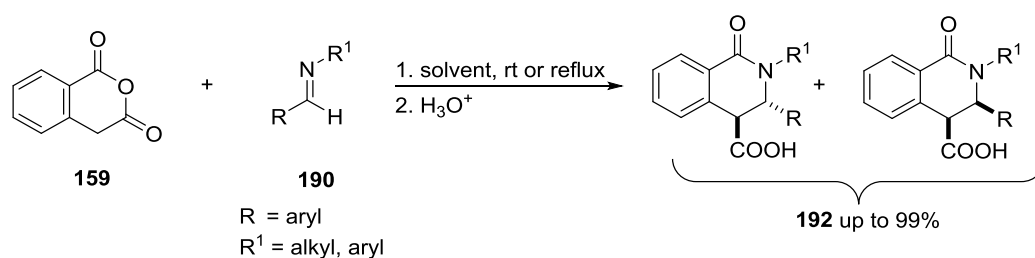
1.9.4 A historical perspective of the reaction between enolisable anhydrides and imines

In 1968, Castagnoli reported the first examples of formal cycloaddition reactions between cyclic anhydrides and imines (Scheme 1.40).¹³⁷ He synthesised γ -lactam **188** in 71% yield by reacting succinic anhydride (**156**) with *N*-aryl imine **187** under thermal conditions. He later extended the scope of this reaction by using glutaric anhydride (**191**) to obtain diastereomeric mixtures of δ -lactams.^{138, 139}



Scheme 1.40 Formal cycloaddition of anhydrides and imines reported by Castagnoli

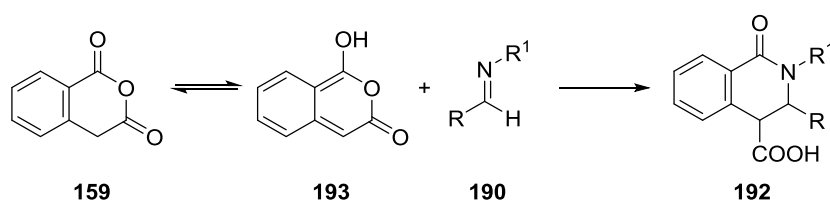
In 1977, both Cushman¹⁴⁰ and Haimova¹⁴¹ independently demonstrated the cycloaddition of homophthalic anhydride (**159**) and imines to furnish a diastereomeric mixture of dihydroisoquinolonic acids **192** (Scheme 1.41).



Scheme 1.41 Formal cycloaddition of homophthalic anhydride and imines reported by Cushman¹⁴⁰ and Haimova¹⁴¹

Cushman extensively explored the reaction between homophthalic anhydride and imines and proposed three plausible pathways for the mechanism: (I) a concerted [4+2] aza-Diels Alder reaction (II) a stepwise process in which the enol of the anhydride attacks the imine and (III) the asynchronous iminolysis of the anhydride.¹⁴² Two of these three pathways have been proven unlikely, *vide infra*. The third, which describes the iminolysis of the anhydride, is currently considered to be the most likely mechanism.

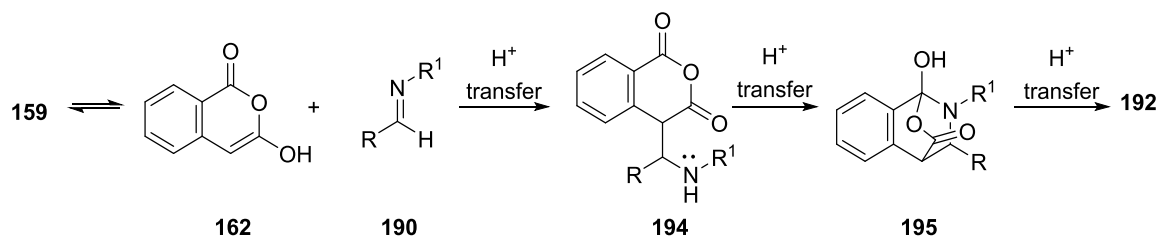
The Diels-Alder mechanism, which is the widely accepted mechanism for the Tamura cycloaddition, has been deemed implausible for the reaction between enolisable anhydrides and imines.¹⁴² In this case, the dienol tautomer (**193**) of homophthalic anhydride (**159**) would react with the imine dienophile (**190**) under neutral reaction conditions to furnish the lactam product **192** (Scheme 1.42). In reality, imines are poor dienophiles and would likely require much more forcing conditions for the reaction to occur in this manner.¹⁴³ Tamura *et al.* reported the necessity of either high temperatures and long reaction times or the presence of a strong base to facilitate the reaction, even in the presence of very reactive dienophiles.¹⁴³⁻¹⁴⁵ These findings were incompatible with the experimental data for the reaction between homophthalic anhydride and imines which furnish the lactam product at room temperature under neutral conditions.



Scheme 1.42 Concerted [4+2] aza-Diels Alder mechanism proposed by Cushman *et al.*

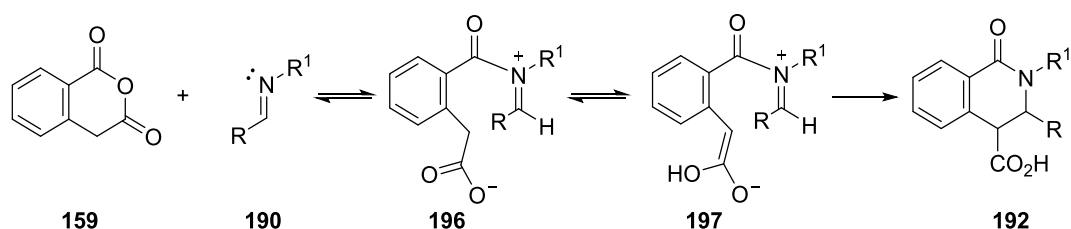
The second pathway explores nucleophilic attack of enol **162** on the electrophilic carbon of imine (**190**) followed by intramolecular cyclisation to furnish the lactam product (**192**, Scheme 1.43). However, this pathway was concluded to be unlikely after a competition reaction between an aldehyde and an imine with homophthalic anhydride (**159**). If both reactions are to proceed through this mechanism, as aldehydes are more electrophilic than imines the lactone should form as the

predominant product; instead the lactam was observed as the major product and thus, a Perkin type mechanism was ruled out.¹⁴²



Scheme 1.43 Perkin mechanism proposed by Cushman

Cushman favoured a third iminolysis mechanism in which the imine nitrogen carries out nucleophilic attack on the anhydride to form Zwitterion **196** followed by an intramolecular Mannich reaction of the enolate **197** onto the iminium ion to form the lactam product **192** (Scheme 1.44).¹⁴²

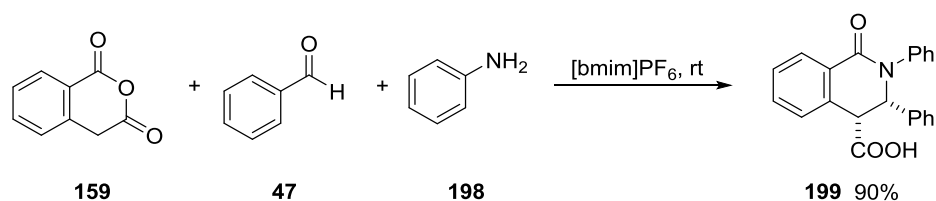


Scheme 1.44 Iminolysis mechanism proposed by Cushman *et al.*

1.9.5 Multicomponent coupling reactions

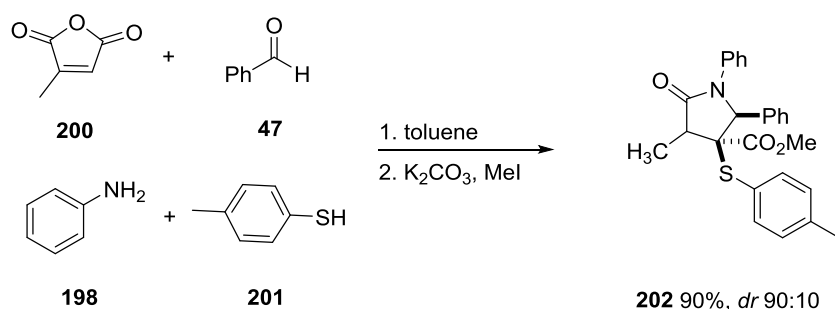
Multicomponent coupling reactions (MCRs) are reactions between three or more reagents in a single vessel which have been added at the same time. The order of addition does not influence the outcome of the reaction. In recent years, MCRs have grown in popularity particularly in the areas of combinatorial chemistry, diversity-oriented synthesis and high throughput screening.¹⁴⁶

Yadav and co-workers first observed that lactam product **199** formed from the condensation reaction of homophthalic anhydride (**159**), aniline (**198**) and benzaldehyde (**47**) at room temperature in the presence of an imidazolium based ionic liquid (Scheme 1.45).¹⁴⁷ Lactam **199** was formed in high yields exclusively as the *cis* isomer. The authors proposed no mechanistic reasoning for the formation of the product in his report.



Scheme 1.45 Formation of **199** via a multicomponent coupling reaction

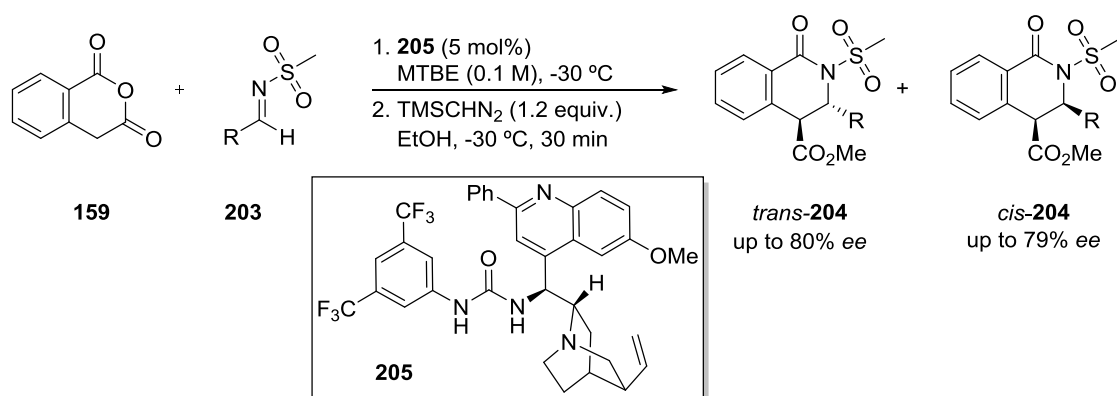
Shaw *et al.* reported the thermal reaction of maleic anhydrides, aldehydes, a primary amine and a thiol followed by *in situ* esterification of the carboxylic acid products to form tetra- and penta-substituted γ -lactams possessing two or three adjacent stereocentres (Scheme 1.46).¹⁴⁸ Only aromatic aldehydes were well tolerated though the amine component could contain either aromatic or aliphatic substituents. Sterically hindered, aromatic thiols such as **201** provide the best diastereoselectivity, with the predominant formation of *cis*-isomers.



Scheme 1.46 Multicomponent coupling reactions by Shaw *et al.*

1.9.6 This work

Despite the obvious value in the preparation of chiral lactam products from simple imine and anhydride precursors, no catalytic, asymmetric variants of the reaction existed in the literature until this work (Scheme 1.47). Herein, we describe the development of the first catalytic, enantioselective cycloaddition of imines with enolisable anhydrides using bifunctional *cinchona* alkaloid based catalysts to furnish diastereomeric mixtures of the *trans* and *cis* products in up to 80% and 79% *ee* respectively.¹³⁶

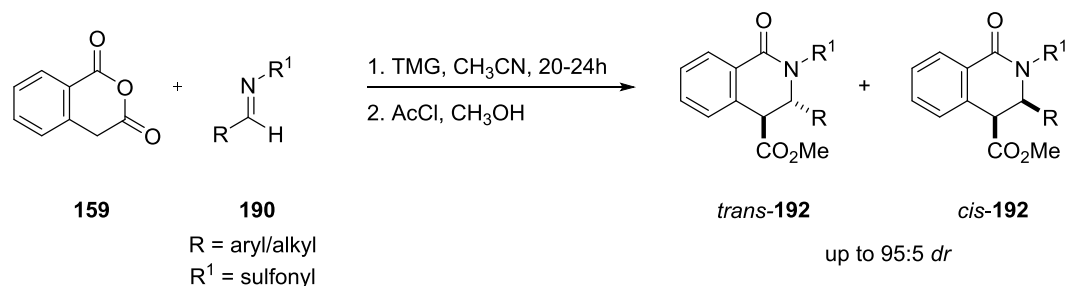


Scheme 1.47 The first catalytic, asymmetric cycloaddition of imines and enolisable anhydrides

1.9.7 Recent developments

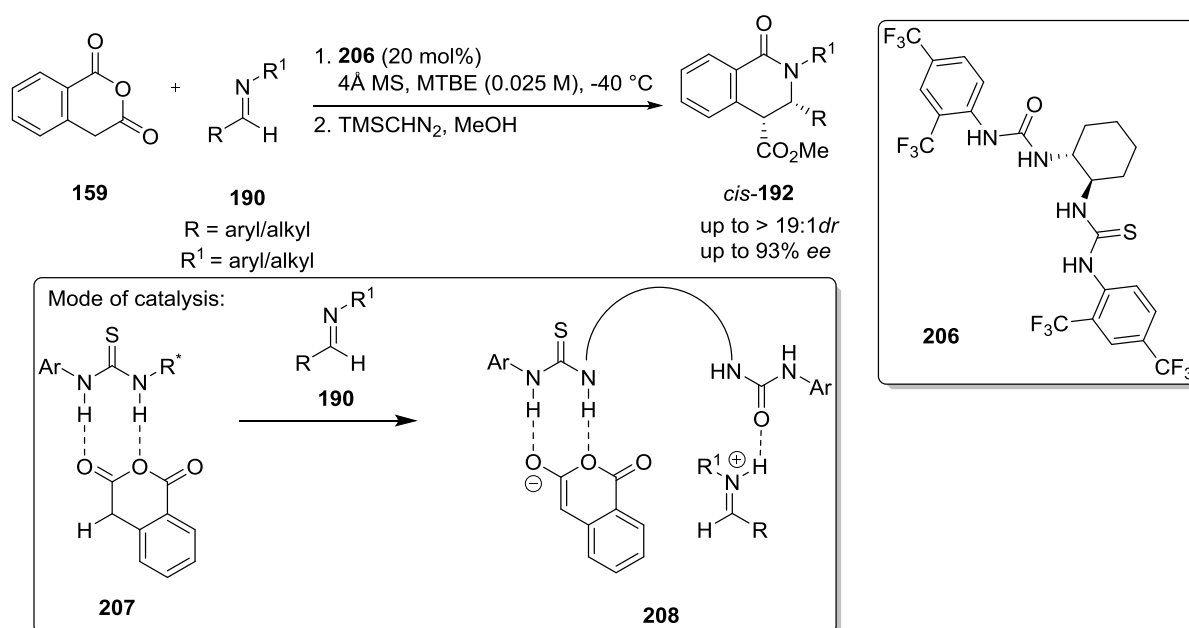
Since the publication of our research,¹³⁶ the field has continued to grow. In 2017, Shaw *et al.* reported a racemic, diastereoselective base-catalysed methodology for the Mannich reaction of enolisable anhydrides and *N*-sulfonyl imines to furnish the lactam products in up to 95:5 *dr* in favour of the *trans*

isomer.¹⁴⁹ In the same study they also reported and optimised a base-mediated epimerisation of the *syn*-lactam allowing isolation of the single, thermodynamically stable *anti*-diastereomer.



Scheme 1.48 Diastereoselective, base-catalysed Mannich reaction of cyclic anhydrides and *N*-sulfonyl imines reported by Shaw *et al.*

That same year, Seidel *et al.* reported the cycloaddition of homophthalic anhydride (**159**) with a range of *N*-aryl and alkyl substituted imines using hydrogen bonding organocatalysts **206** with good *dr* and *ee*'s ranging from 37-93 % for the major diastereomer (Scheme 1.49).¹⁵⁰ It should be noted that, in contrast to our work using bifunctional catalyst **205**, the *cis* lactam was obtained as the major product. DFT calculations for the catalyst substrate intermediate found that unlike classic modes of substrate activation, interaction of the chiral thiourea catalyst with homophthalic anhydride results in the enhanced the acidity of the **159** α -carbon, enabling the formation of chiral ion pair **208** which interacts with the catalyst **206** *via* hydrogen bonding interactions such that the enantioselective Mannich addition occurs.



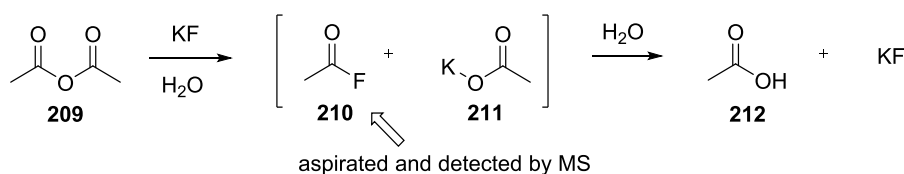
Scheme 1.49 Enantioselective cycloaddition of homophthalic anhydride to imines using hydrogen bonding catalyst **208**

1.10 Asymmetric organocatalysis with chiral ammonium fluorides

Quaternary ammonium fluorides hold a reputable position in organic synthesis, providing access to organic-soluble fluoride ions. Due to the hard nature of fluoride, these reagents are almost invariably used as either catalytic or stoichiometric base,^{151, 152} or as a desilylating agent.¹⁵³ The fluoride ion also possesses nucleophilic properties which, under the right conditions, can be used in an array of selective bond forming reactions.¹⁵¹ The use of chiral ammonium fluorides in asymmetric synthesis is known, though few examples are available throughout the literature.¹⁵⁴

1.10.1 Fluoride as a nucleophilic catalyst

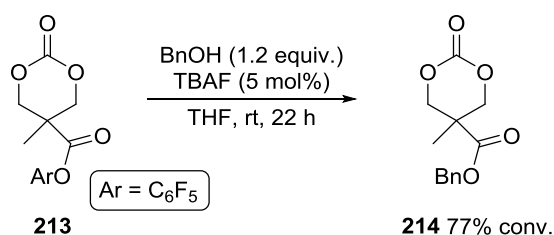
In 1967, Bunton and Fendler reported the use of fluoride ions in the hydrolysis of acetic anhydride (Scheme 1.50).¹⁵⁵ They speculated that the fluoride ion was acting as either a nucleophilic catalyst or a general base. The study used fluoride in the form of KF in both water and aqueous media. Reaction kinetics showed that the rate of consumption of anhydride starting material outstripped the rate of product formation, indicating the build-up of a stable reaction intermediate, which was identified as acetyl fluoride using aspiration experiments. As such, it was concluded that the reaction predominantly proceeded through nucleophilic catalysis, though the authors failed to provide sufficient evidence to support the existence of solely one mechanism. Ueki and co-workers also suggested the formation of a fluoride intermediate for the hydrolysis of esters using TBAF-trihydrate, though mechanistic evidence for nucleophilic catalysis by fluoride was lacking.¹⁵⁶



Scheme 1.50 Accumulation of acetyl fluoride in the fluoride-catalysed hydrolysis of Ac_2O proposed by Bunton and Fendler

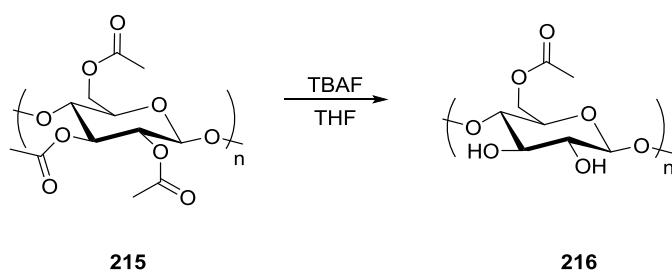
Despite the synthetic potential of the concept, the use of fluoride as an acyl-transfer catalyst has gained little attention since. The use of super-stoichiometric amounts of fluoride is known to catalyse the hydrolysis of phosphodiester, ¹⁵⁷ and for the cleavage of activated amino acid esters ^{158, 159} and carbamates (with nucleophilic catalysis being implicated in the mechanism for cleavage of Boc-protected amines). ¹⁶⁰

Recently, Chan and Hedrick *et al.* used TBAF to catalyse the transesterification of **213** into compounds such as **214** using a range of alcohols (Scheme 1.51). ¹⁶¹ Once again, the authors rationalised the reaction to proceed through nucleophilic catalysis, though no mechanistic evidence was provided; the fluoride ion also has potential to act *via* general base catalysis in such scenarios.



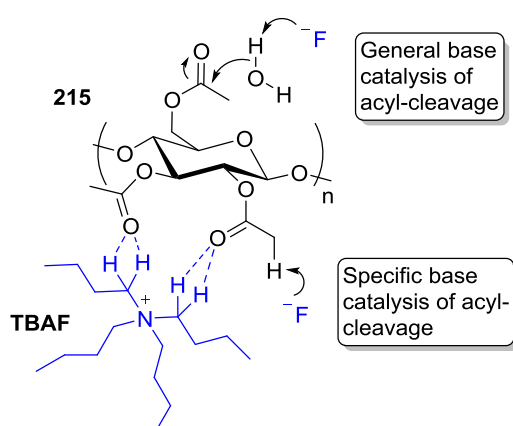
Scheme 1.51 TBAF-mediated transesterification by Chan and Hedrick *et al.*

It was Edgar *et al.* who provided the first comprehensive study into the mechanism behind TBAF-catalysed deacylation; in this investigation the result suggested catalytic activity to be strongly dominated by basic catalysis. ¹⁶² It was found that, when using TBAF in THF, highly regioselective deacylation of cellulose occurred predominantly at the more hindered ester groups (*O*-2 and *O*-3) leading to the formation of **216** (Scheme 1.52). ¹⁶³ The exceptional selectivity obtained indicated that the mechanism of deacylation at the more hindered secondary alcohol acetates at *O*-2/*O*-3 may differ from deacylation at the primary alcohol acetate at *O*-6.



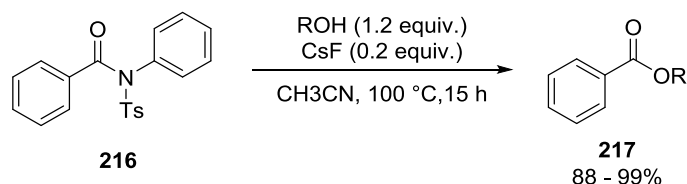
Scheme 1.52 Regioselective deacetylation of cellulose using TBAF as a catalyst

The authors noted a significant difference on comparing the rate constants at *C*-2/*C*-3 and *C*-6, which supported the hypothesis that the reaction proceeded *via* two different mechanisms.¹⁶² Using kinetic isotope effect (KIE) analysis, they proposed that deacetylation occurs at *O*-2/*O*-3 *via* E1_cB elimination. They explained the observed regioselectivity to be facilitated by H-bond activation of the *O*-2/*O*-3 carbonyls with the α -protons of the TBAF cation (Scheme 1.53). In the case of *O*-6 deacetylation, they suggested two possible mechanistic routes: nucleophilic fluoride catalysis vs general base catalysis by the fluoride ion, with mechanistic evidence largely in support of the latter case. They reasoned that, if the reaction were to proceed through general base catalysis, the addition of a base additive should enhance the rate of deacetylation at *O*-6. On the addition of Na₂CO₃ they observed a significant increase in the rate of deacetylation at *O*-6, supporting the operation of the general base mechanism. Furthermore, they noticed that, as the initial TBAF-mediated reaction proceeded, the rate of deacetylation gradually decreased, even in the presence of excess TBAF. They reasoned that as the reaction proceeded the acetic acid side product would hinder the base-catalysed mechanism with no concurrent effect on nucleophilic catalysis. To test this, they carried out the reaction in the presence of excess acetic acid and deacetylation of the *O*-6 ester was not observed, providing further support for general base catalysis.



Scheme 1.53 Proposed mechanisms for TBAF mediated deacetylation the *C*-2/*C*-3 and *C*-6 of cellulose

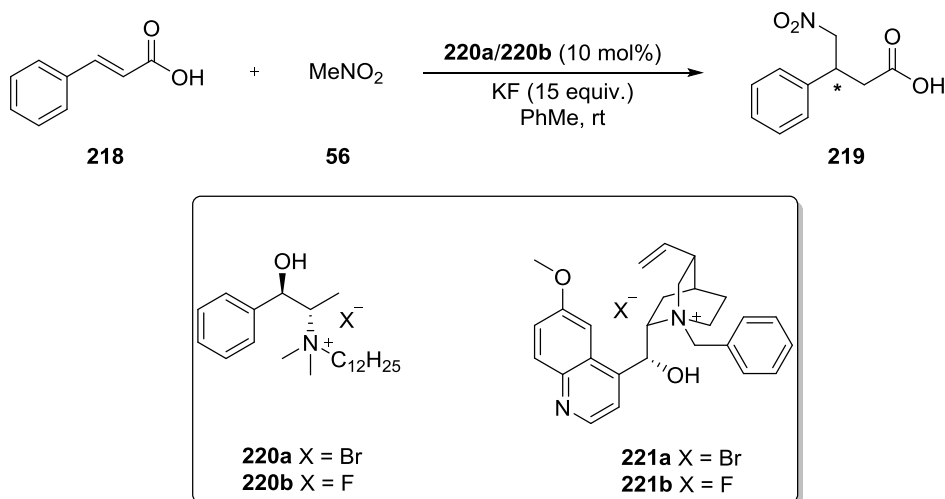
In early 2018, Wu and co-workers reported the ability of CsF to catalyse the esterification of amides **216** at a temperature of 100 °C (Scheme 1.54). A broad scope was demonstrated for the methodology, furnishing a range of ester products in high yield (89–99%). The study also provided ^{19}F NMR spectroscopic data detecting the presence of the benzoyl fluoride intermediate, thus providing unequivocal evidence that the fluoride ion is operating *via* nucleophilic catalysis.¹⁶⁴



Scheme 1.54 Esterification of amide **216** catalysed by CsF

1.10.2 Chiral ammonium fluorides: a historical perspective

The first example showcasing chiral ammonium fluorides as organocatalysts was published in 1978 by Wynberg *et al* where they were used to catalyse the Michael addition of nitromethane to chalcone (Scheme 1.55).¹⁶⁵ Initial experiments using chiral amines **220a** and **221a** in aprotic media resulted in no product formation, presumably due to reduced basicity of the amine salt. Switching the solvent to methanol however, furnished the racemic product in good yield. In this case, the reactivity observed was attributed to enhanced hydrogen bond activation of chalcone by MeOH.



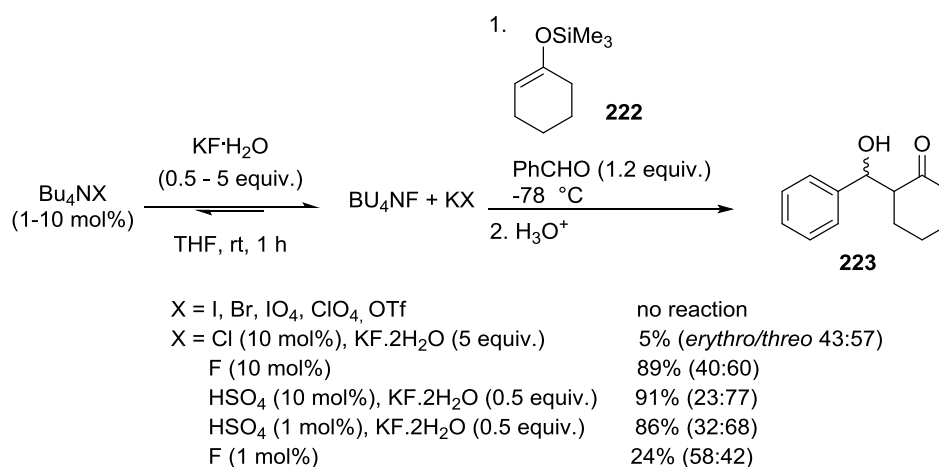
Scheme 1.55 The first use of chiral ammonium fluorides as asymmetric catalysts

Wynberg postulated that chiral ammonium fluorides could potentially be basic enough to catalyse the transformation.¹⁶⁵ He added a large excess of KF to the reactions to initiate ion exchange with the quaternary ammonium bromide and chloride salts to generate the fluoride salt *in situ*. Indeed, the addition of KF furnished yields of 50% when using catalysts **220a** and quantitative yields when using **221a** (Scheme 1.55). Though the enantioselectivities obtained were low (10–23%), Wynberg stated

that these preliminary results “may lead to an important extension in the field of catalytic asymmetric synthesis.”

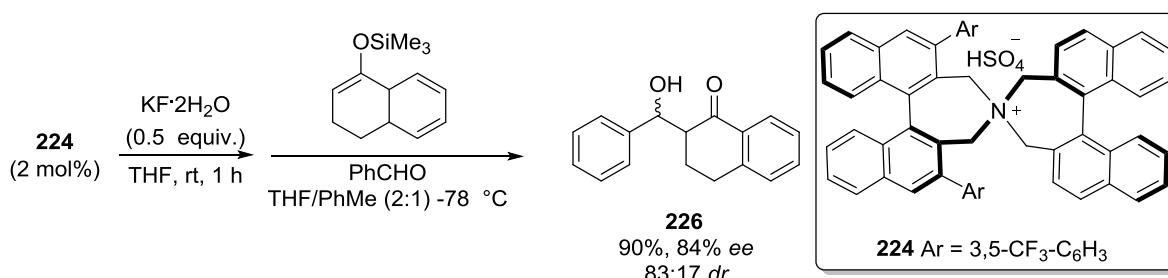
It was not until 2001 that the *in situ* generation of chiral ammonium fluorides was further developed. Maruoka *et al.* synthesised a series of structurally ridged, C₂-symmetric quaternary ammonium hydrogen sulfates, from which the corresponding ammonium fluorides were generated using potassium fluoride dihydrate in THF. These novel catalysts could be used as a source of chiral fluoride ion to liberate carbon nucleophiles from organosilicon compounds. Their utility was demonstrated in the enantoselective Mukaiyama-type aldol reaction (Scheme 1.56).¹⁶⁶

The publication describes a study in which Maruoka employed various tetralkylammonium salts (TBAX) to examine how the identity of X affects the anion exchange with excess KF·2H₂O under solid-liquid phase-transfer conditions (Scheme 1.56). The *in situ* generation of TBAF was evaluated by its subsequent performance in aldol reactions of enol trimethylsilyl ethers (**222**) with benzaldehyde in one pot. Results showed that the identity of the anion moiety (X) played a crucial role in the *in situ* generation of TBAF. Optimised reaction conditions using 0.5 equivalents of KF·2H₂O with HSO₄⁻ were established to be the most efficient for ion exchange. These were subsequently applied in the reaction using C₂-symmetric quaternary ammonium fluoride in the place of TBAX.¹⁶⁶



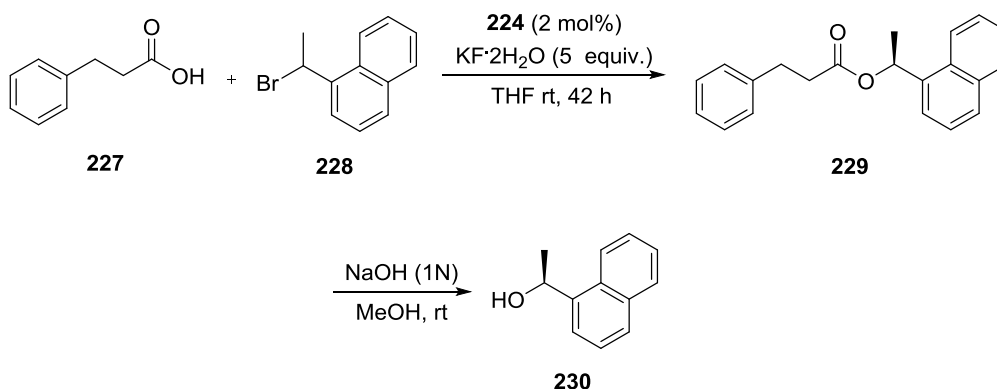
Scheme 1.56 Evaluation of the *in situ* anion exchange of TBAX and KF·H₂O

Catalyst **224**, bearing 3,5-*bis*-(trifluoromethyl)phenyl substituents, was found to be optimum for activity, presumably by increasing the Lewis acidity of the nitrogen atom resulting in a tighter ion pairing of the ammonium enolate. Under the optimised reaction conditions, the catalyst furnished the product **226** in excellent yield with high enantio- and diastereocontrol (Scheme 1.57).¹⁶⁶



Scheme 1.57 Asymmetric aldol reaction catalysed using *in situ* generated C₂-symmetric quaternary ammonium fluorides

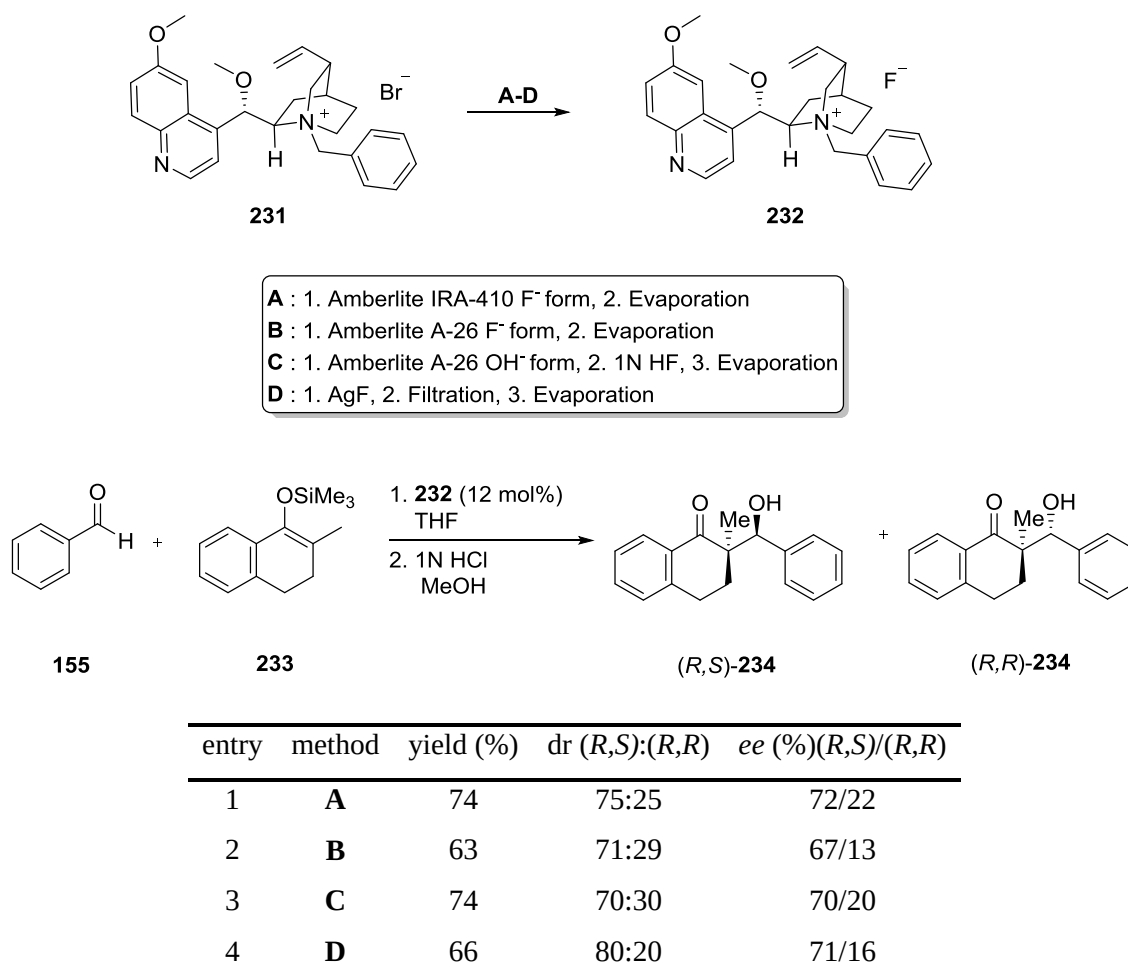
A similar methodology, involving the *in situ* generation of chiral ammonium fluorides from their hydrogen sulfate precursors, has been used in the kinetic resolution of secondary alkyl halides to furnish enantioenriched esters (Scheme 1.58).¹⁶⁷ Catalyst **224** was employed with 5 equivalents of KF·2H₂O to facilitate the reaction between 3-phenyl-propionic acid (**227**) and 1-(1-bromoethyl)naphthalene (**228**). The desired ester **229** was obtained in 98% yield and 58% *ee*. Subsequent hydrolysis of **229** released the optically active secondary alcohol **230**.



Scheme 1.58 KR of secondary alkyl halides using *in situ* generated C₂-symmetric quaternary ammonium fluorides

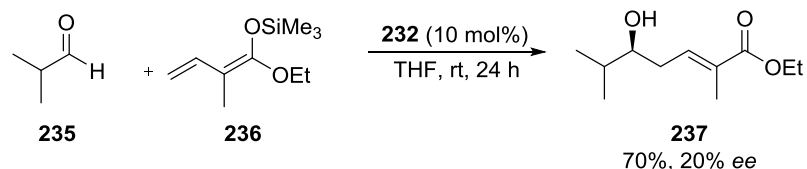
It was Shioiri *et al.* who first explored the *ex situ* generation of chiral ammonium fluorides.¹⁶⁸ They synthesised the chiral catalyst **232** from **231** using the four different methods outlined in Scheme 1.59. Methods **A** and **B** used F⁻ resins for ion exchange followed by evaporation. Method **C** converted the Bromide catalyst into the corresponding OH⁻ catalyst, followed by neutralisation using an aqueous solution of HF and evaporation. AgF was used for direct anion transfer in method **D**. In each case, catalyst **232** was dried overnight in a desiccator under vacuum before use to ensure the ammonium fluoride was as dry as possible. The efficiency of the catalyst was then evaluated in the Mukaiyama-aldol reaction between benzaldehyde (**155**) and silyl enol ether **233**. The results of the experiment showed that the yield and enantioselectivity of the reaction was highly dependent on

the method of preparation for the catalyst. Though no insights into the varied activity of the catalyst was provided at the time, more recent studies carried out on non-chiral quaternary ammonium fluorides have shown that the activity of the fluoride ion is reduced in the presence of water.¹⁶⁹⁻¹⁷³ It is likely that due to the hygroscopic nature of quaternary ammonium fluorides, that the catalysts **232** synthesised using methods **A-D** were not fully dry, thus accounting for inconsistencies in the results of the Aldol reaction.



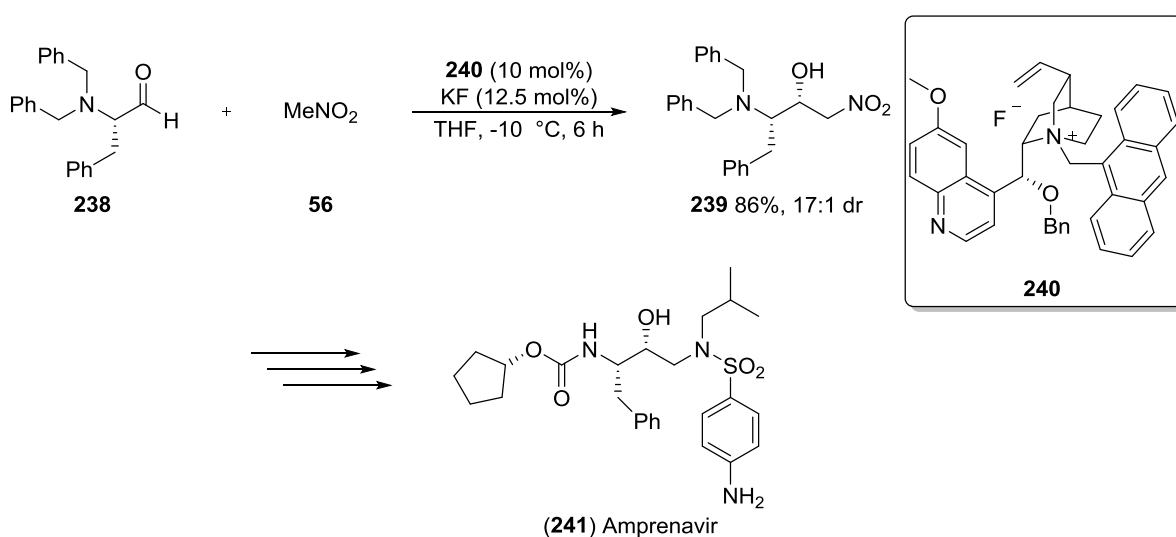
Scheme 1.59 Various preparations of **232** with subsequent use in the Aldol reaction

Campagne and Bluet utilised catalyst **232** in the Mukaiyama-aldol reaction between aldehyde **235** and silyl enol ether **236** to furnish the product **237** with low levels of enantiocontrol.¹⁷⁴ The authors made a series of modifications to the catalyst structure in an effort to improve catalyst selectivity; the addition of electron withdrawing and electron-donating moieties as well as steric augmentations to the *N*-benzyl subunit of **232** proved fruitless. However, a slight improvement in *ee* (30%) was observed on reducing the reaction temperature to 0 °C.



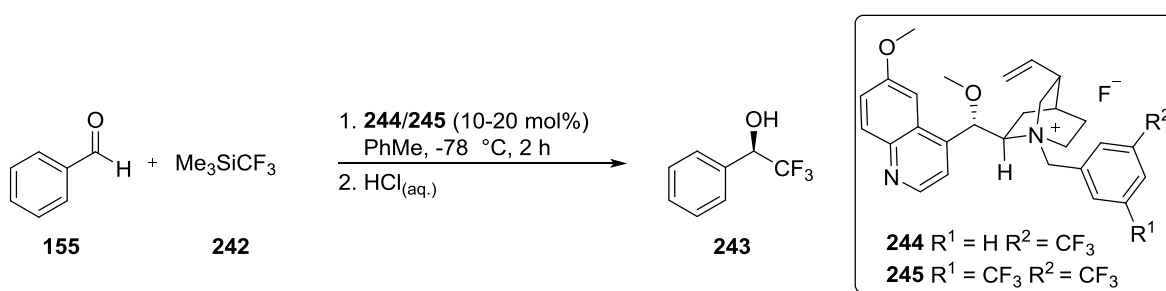
Scheme 1.60 The use of **232** in the Mukaiyama- aldol reaction

Corey and Zhang developed the novel chiral ammonium fluoride **240** bearing a 9-anthracenylmethyl substituent on the quinuclidine ring moiety to promote the addition of nitromethane to protected (*S*)-phenylalaninal **238** to furnish product **239** in 86% yield with a *dr* of 17:1 (Scheme 1.61).¹⁷⁵ **239** was subsequently transformed into Amprenavir (**241**), a second generation of HIV protease inhibitor.



Scheme 1.61 Nitroaldol reaction promoted by **240** and subsequent transformation into Amprenavir

Inspired by the work of Olah *et al.* which described TBAF catalysed nucleophilic trifluoromethylations of carbonyl compounds,¹⁷⁶ Kobayashi *et al.* demonstrated that the catalytic activity of chiral ammonium fluorides was not limited to the Aldol reaction. They synthesised chiral ammonium fluorides **244** and **245** to promote the asymmetric trifluoromethylation of aldehydes while simultaneously exploring the effect of various *N*-benzyl substitutions of the cinchonium salt (Scheme 1.62).¹⁷⁷ Though the products of the reaction were furnished in quantitative yields, they demonstrated poor selectivity. Almost a decade later Caron *et al.* improved upon this work, using chiral ammonium fluoride catalysts for the nucleophilic trifluoromethylation of a ketone in up to 92% *ee*.¹⁷⁸



Scheme 1.62 Nucleophilic trifluoromethylation of aldehydes by chiral quaternary ammonium fluoride catalysts

Quaternary ammonium fluorides are extremely hygroscopic in nature, which poses a fundamental issue in relation to their use as catalysts; several studies have shown that the activity of the fluoride ion is diminished in the presence of water. This hygroscopicity presents difficulties regarding their preparation and storage. The *in situ* generation of the chiral quaternary ammonium fluoride appears to be the most practical approach to obtain the ‘naked fluoride’ ion for catalysis, with ion-exchange of a phase transfer catalyst using excess metal fluoride being the most common method for *in situ* generation. Truly anhydrous tetraalkylammonium fluorides have the potential to undergo Hoffman elimination, resulting in the formation of tetraalkylammonium bifluorides.¹⁷⁹ These bifluorides possess enhanced stability compared to the parent fluoride and have been efficiently employed asymmetric C-C bond forming reactions,¹⁸⁰ though they are not the focal point of this study. Careful consideration during catalyst design should prevent degradation to the bifluoride.

Although the use of chiral quaternary ammonium fluorides in asymmetric synthesis has been known for 40 years, the field remains largely underdeveloped. A dearth of reactions exhibiting high levels of enantiocontrol exist; meaning the reaction scope still remains quite narrow. Extension of this methodology to a broad range of reactions has yet to be achieved. Subsequent chapters of this thesis will discuss our efforts in expanding the use of quaternary ammonium fluoride catalysts to achieve various synthetic transformations. We have employed both known and novel tetraalkylammonium fluoride compounds as catalysts in several transformations, namely: the desymmetrisation of *meso*-anhydrides, the Steglich rearrangement of 2-oxindoles and, the aminolysis of azlactones and oxazinones.

1.11 Asymmetric desymmetrisation of *meso*-anhydrides

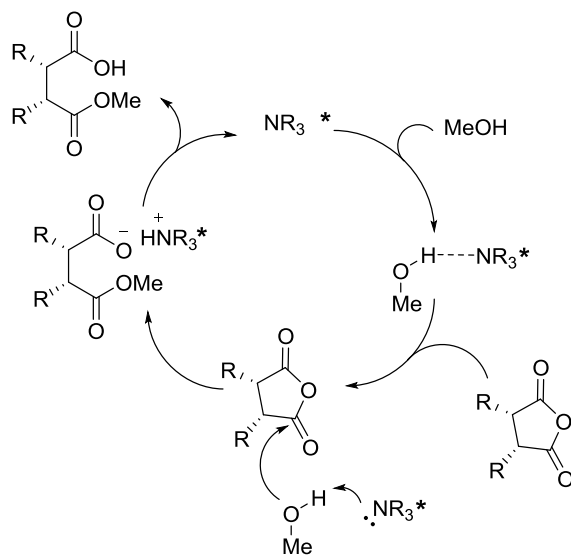
The asymmetric desymmetrisation of *meso*-anhydrides is an important methodology for accessing numerous stereocentres in one symmetry-breaking process.¹⁸¹ The products of these reactions are often desirable building blocks for the synthesis of complex natural products and bioactive substances.¹⁸² Research in this area has received considerable attention with a variety of enzymatic,^{181, 183} metal-based¹⁸⁴ and organocatalytic approaches¹⁸⁵ available in the literature; the

topic has been expertly reviewed on several occasions.^{182, 184-186} Common desymmetrisation strategies include oxidative and reductive processes, nucleophilic ring opening additions and deprotonation reactions.¹⁸⁴

1.11.1 The desymmetrisation of *meso*-anhydrides by alcoholysis

The asymmetric desymmetrisation of *meso*-anhydrides *via* alcoholysis is a simple, elegant method for accessing synthetically useful hemiesters with the formation of two distinct carbonyl functionalities along with the generation of single or multiple stereocentres. The mechanism for the desymmetrisation reaction is subject to debate; both general base catalysis and nucleophilic catalysis have been implicated in the process (Figure 1.16) with certain reactions requiring a combination of the two in order to achieve product formation.^{185, 186}

A : General base catalysis



B : Nucleophilic catalysis

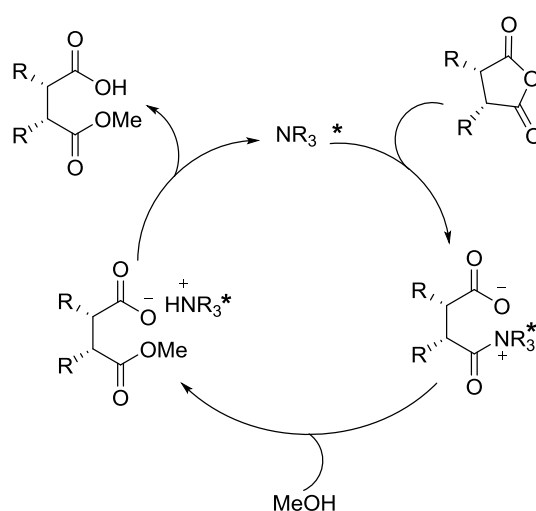


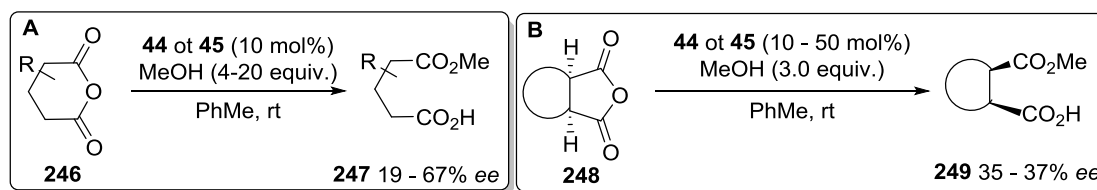
Figure 1.16 Methods for desymmetrisation *via* alcoholysis

For general base catalysis, attack of the pronucleophile on either carbonyl moiety is assisted by a concerted deprotonation event, rendering a more nucleophilic species (Figure 1.16A). In the case of nucleophilic catalysis, the chiral amine attacks the carbonyl moiety to form a leaving group which is liberated by subsequent attack of methanol on the carbonyl centre (Figure 1.16B). In general, sterically hindered bases operate *via* general base catalysis whilst less bulky bases tend to follow the nucleophilic pathway, though in some cases both pathways can occur concurrently.¹⁸⁵

1.11.2 Asymmetric desymmetrisation of anhydrides *via* organocatalysis

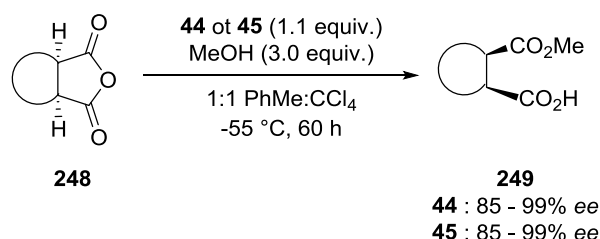
The first organocatalysed ring opening of *meso*-anhydrides was reported in 1985 by Oda *et al.* (Scheme 1.63A).¹⁸⁷ They used quinine (**44**) and quinidine (**45**) for the methanolysis of glutaric and succinic anhydrides to furnish products with moderate levels of enantioselectivity. Later, Atkin

extended the scope of this reaction to norborane-type anhydrides, obtaining the products with modest enantiocontrol (Scheme 1.63B).^{188, 189}



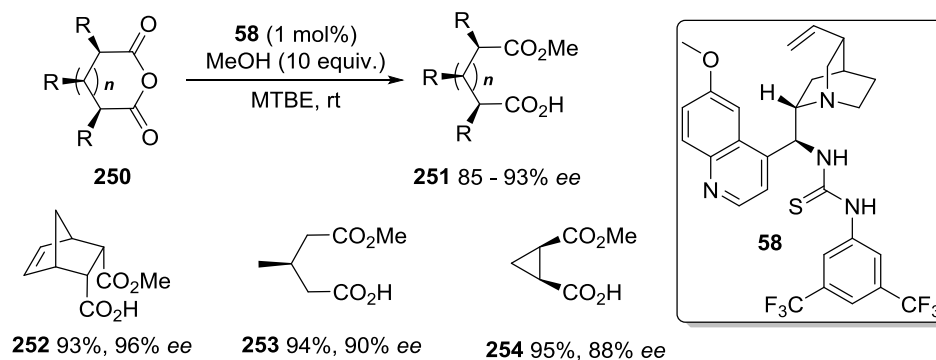
Scheme 1.63 Seminal studies by Oda (**A**) and Aitken (**B**) on the asymmetric desymmetrisation of *meso*-anhydrides

Bolm and co-workers made the first major breakthrough in this reaction from an enantioselective standpoint (Scheme 1.64).¹⁸⁹ They successfully desymmetrised a broad range of substrates in nearly quantitative yields and enantiopurity, though stoichiometric catalyst was required at low temperatures. Both antipodes of the hemiester product could be accessed using the *pseudoenantiomeric* ability of the quinine (**44**) and quinidine (**45**) reagents. Although this synthesis offered a major improvement on previous attempts, there was still room for improvement: ideally, stoichiometric catalyst should not be required.



Scheme 1.64 Highly enantioselective desymmetrisation reported by Bolm and co-workers

The first use of bifunctional organocatalysis in this reaction was published independently by both Cannon *et al.*⁶² and Song *et al.*¹⁹⁰ in 2008. Both groups reported the use of catalyst **58** in the desymmetrisation of *meso*-glutaric and succinic anhydrides affording the corresponding methyl hemiester products with excellent yield and enantiocontrol (Scheme 1.65). The protocol was clearly superior to previous methods requiring a catalyst loading of only 1 mol%. Both research groups deduced that enantiocontrol was highly dependent on concentration, temperature and solvent due to aggregation of the catalyst through the thiourea functionality, making it less available in solution. This issue was later addressed by Song *et al.* by replacing the thiourea functionality with a sulfonamide;¹⁹¹ in this case, catalyst loadings of only 0.5 mol% were required to promote the reaction with similar levels of enantiocontrol.



Scheme 1.65 Desymmetrisation of *meso*-anhydrides using bifunctional catalyst **58**

Bifunctional catalysis offered a clear advantage over previous methodologies for desymmetrisation reactions. Simultaneous activation of the pro-nucleophile and the anhydride (Figure 1.17) in a well-defined chiral pocket resulted in enhanced kinetics and superior enantiocontrol.¹⁸⁶

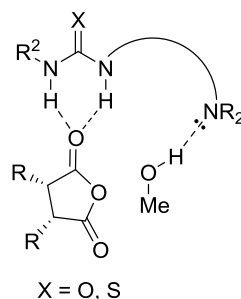


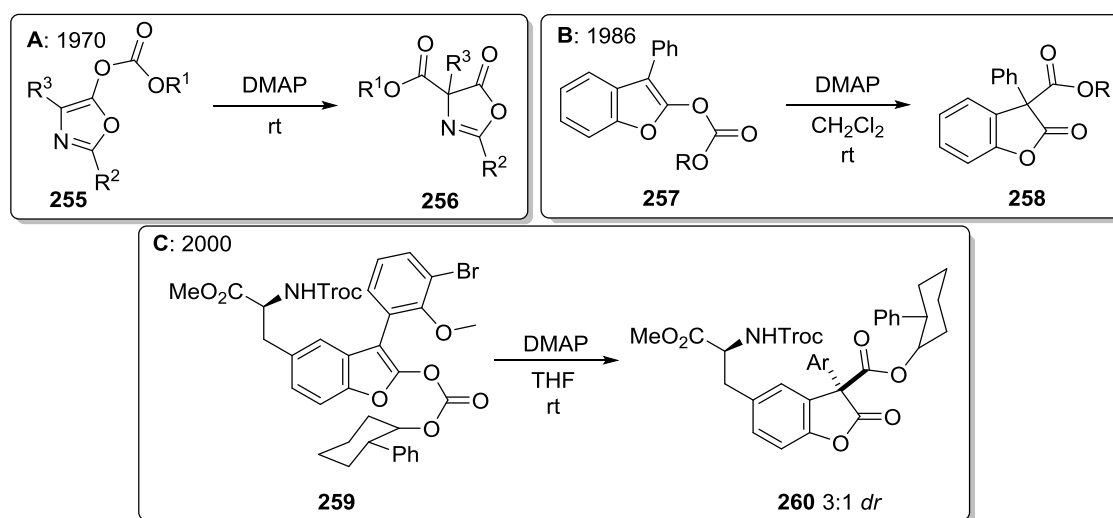
Figure 1.17 Desymmetrisation of *meso*-anhydrides using bifunctional catalysis

1.11.3 Acyl-transfer catalysis by fluoride ion

Inspired by the early works of Bunton and Fendler, which demonstrated that a fluoride ion could catalyse the hydrolysis of succinic anhydride,¹⁵⁵ we postulated that a *cinchona* alkaloid derived bifunctional phase transfer catalyst bearing a fluoride ion could effectively promote the desymmetrisation of *meso*-anhydrides asymmetrically. With examples of TBAF-catalysed transesterification available in the literature,¹⁶¹ we focused our research efforts on the generation and application of chiral quaternary ammonium fluorides in the outlined transformation. As already discussed, the results of the early studies carried out by Bunton and Fendler largely supported nucleophilic catalysis over general base catalysis due to calculations of activation entropies and energies.¹⁵⁵ Soon after, Gold and co-workers strengthened this hypothesis when they showed that nucleophilic attack by an anion on an acyl centre was more entropically favourable than a general base catalysed attack of water on the same acyl centre.¹⁹² We hoped to effectively demonstrate that the fluoride ion operates *via* nucleophilic catalysis for this reaction *via* an acyl fluoride intermediate.

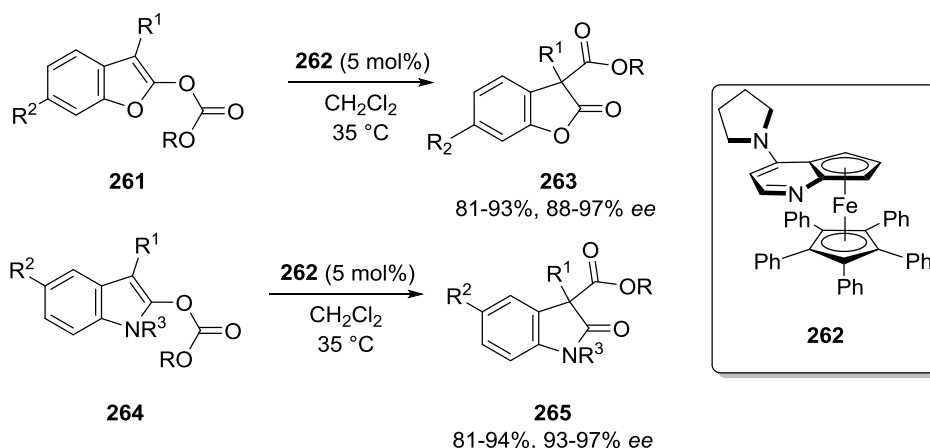
1.12 Steglich rearrangement of 2-oxindole derivatives

The Steglich rearrangement represents a highly efficient method for synthesising all-carbon quaternary stereocentres. The reaction was first reported in the 1970s and detailed the use of DMAP as a nucleophilic catalyst in the *O*- to *C*- acyl transfer of 5 carboxyl oxazole derivatives **255** (Scheme 1.66A).¹⁹³ In 1986, Back *et al.* extended the scope of this reaction to *O*-acylated benzofuranones **257** (Scheme 1.66B).¹⁹⁴ Vedejs and Wang described a diastereoselective variant of this reaction when trying to synthesise an incorrectly assigned structure of diazonamide A (Scheme 1.66C).¹⁹⁵ The correct structure was later shown to contain an oxindole moiety rather than a benzofuranone.



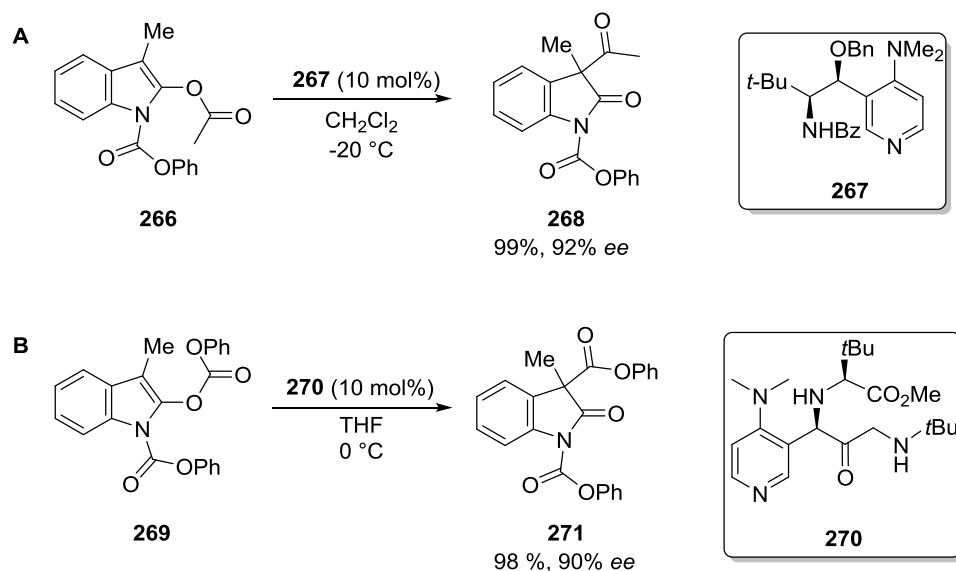
Scheme 1.66 A brief history of the Steglich rearrangement

In 2003, Fu and co-workers published the first method for the catalytic enantioselective rearrangement of *O*-acylated benzofuranones and oxindoles (Scheme 1.67).¹⁹⁶ The study used a DMAP-derived catalyst **262** to furnish the reaction products, bearing a new quaternary stereocentre, in high yield with excellent enantiocontrol.



Scheme 1.67 Asymmetric Steglich esterification of benzofuranones and 2-oxindoles

Later, Vedejs *et al.* utilised chiral DMAP-derived catalyst **267** in the rearrangement of *O*-acylated oxindoles to furnish products such as **268** in excellent yield and enantioselectivity (99%, 92% *ee*) (Scheme 1.68A).¹⁹⁷ More recently, Suga and co-workers demonstrated the rearrangement of **269** and other derivatives using catalyst **270** (Scheme 1.68B). The product **271** was obtained in 98% yield with high levels of enantiocontrol (90% *ee*).¹⁹⁸



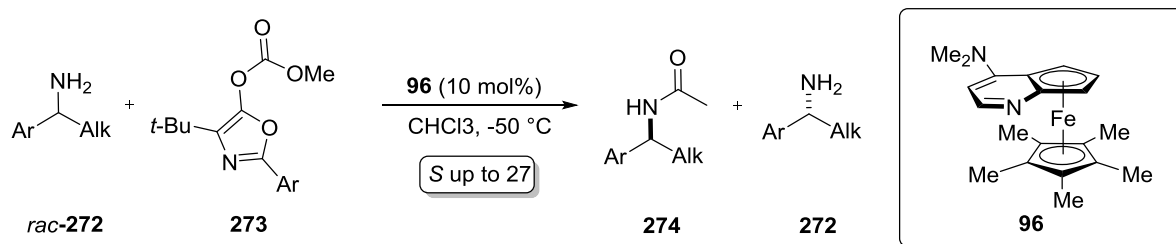
Scheme 1.68 Rearrangements of *O*-acylated oxindoles using chiral DMAP derived catalysts

1.12.1 *O*-acylated rearrangements by fluoride ion

The Steglich rearrangement of *O*-acylated 2-oxindoles is well documented throughout the literature using DMAP derived nucleophilic catalysts. We postulated that a fluoride ion could potentially act as a nucleophilic catalyst for the transformation. In a previous study we have shown that fluoride can act as a nucleophilic catalyst at acyl centres.¹⁹⁹ Later in this thesis, we describe the development of a novel methodology using fluoride ion as a nucleophilic catalyst in the Steglich rearrangement of *O*-acylated 2-oxindoles.

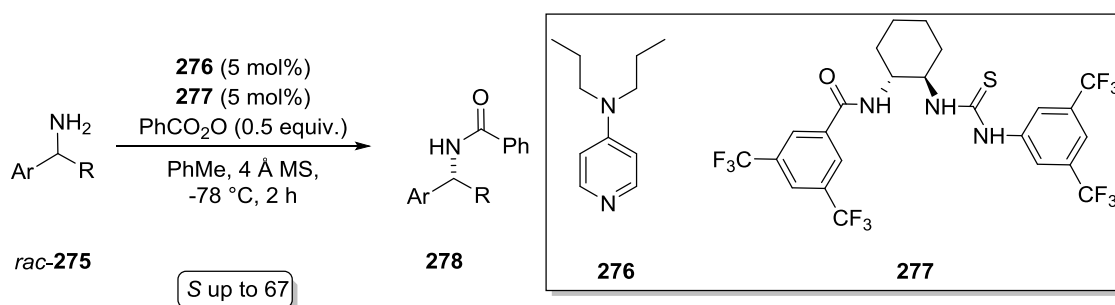
1.13 The KR of acyl centres *via* aminolysis

Over the years, the asymmetric aminolysis of acyl centres has remained elusive goal due to the enhanced reactivity of amines (relative to alcohols) towards acyl centres; most examples of such transformations involve enzymatic methods.²⁰⁰ In 2001, Fu and co-workers reported the first non-enzymatic example involving the KR of amines *via* catalytic acylation (Scheme 1.69).²⁰¹ The study used the structurally complex acyl donor **273** which reacted much more rapidly with the DMAP-derived catalyst **96** than the primary amine **272**; in this manner background aminolysis was avoided and the amine nucleophile reacted solely with the catalyst-acyl intermediate affording *S* factors of up to 27 for the KR of the primary amine.



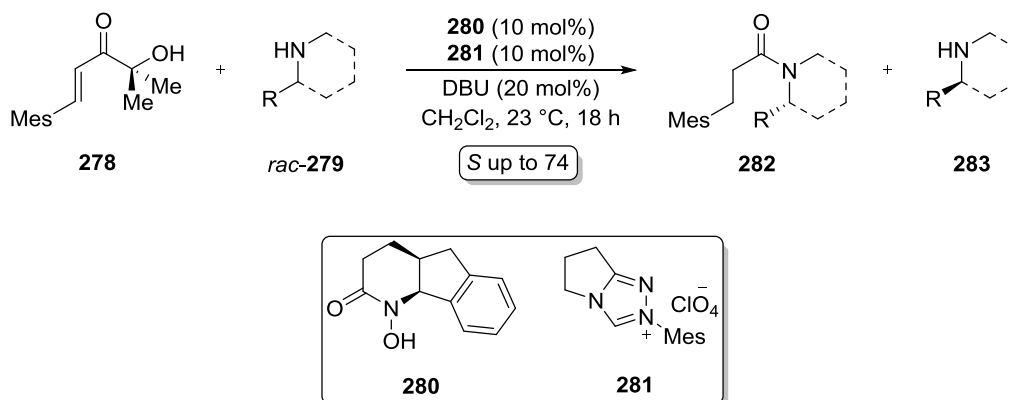
Scheme 1.69 KR of primary amines by Fu and co-workers using DMAP derived catalyst **96**

More recently, the research group of Seidel have achieved the acylative KR of primary amines using a much simpler benzoic anhydride as the acyl donor.^{202, 203} The methodology uses a dual catalysis anion binding approach which generates the chiral acylating agent *in situ* followed by addition of the amine nucleophile **275** which reacts selectively to produce the benzoyl amide **278** with *S* factors reaching as high as 67.



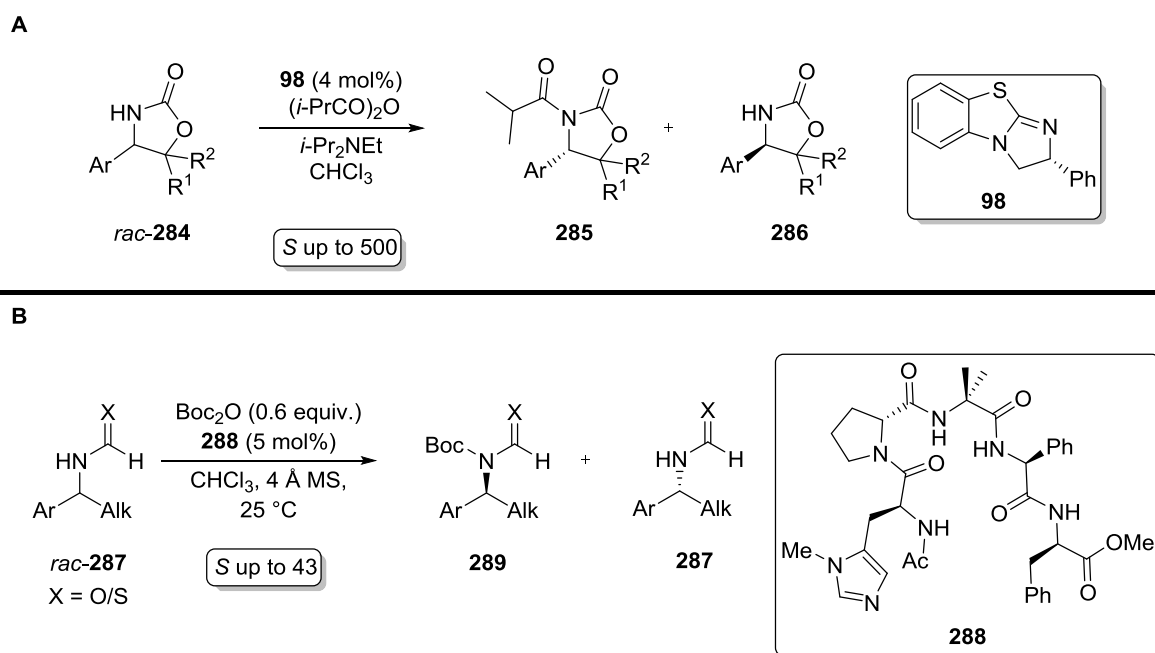
Scheme 1.70 KR of primary amines via a dual catalysis anion approach by Seidel and co-workers

In 2011, Bode *et al.* reported the use of a nucleophilic carbene (**281**) in conjunction with a chiral *N*-hydroxyl additive (**280**) to resolve secondary amines (**279**) demonstrating *S* factors of up to 74 for the transformation (Scheme 1.71).²⁰⁴ In a later study they explored the reaction mechanism using computational analysis. The results of the DFT study suggest that the reaction is likely to proceed via a concerted 7-membered transition state which requires a hydroxamic acid proton transfer.



Scheme 1.71 Catalytic KR of cyclic amines reported by Bode and co-workers

The enantioselective acylation of secondary amides has also been reported. In 2006, Birman *et al.* achieved the KR of oxazolidin-2-ones using the amidine based catalyst **98** (Scheme 1.72A).²⁰⁵ Outstanding selectivity factors of up to 500 were achieved at room temperature. Several years later, Miller *et al.* developed a strategy reporting the KR of acyclic formamides and thioformamides using and boc_2O as the acylating agent (Scheme 1.72B).²⁰⁶ *S* factors of up to 43 were obtained for the protocol using the peptide-based catalyst **288**.



Scheme 1.72 KR of oxazolidinones by Birman *et al.* (**A**) and KR of (thio)formamides by Miller and co-workers (**B**)

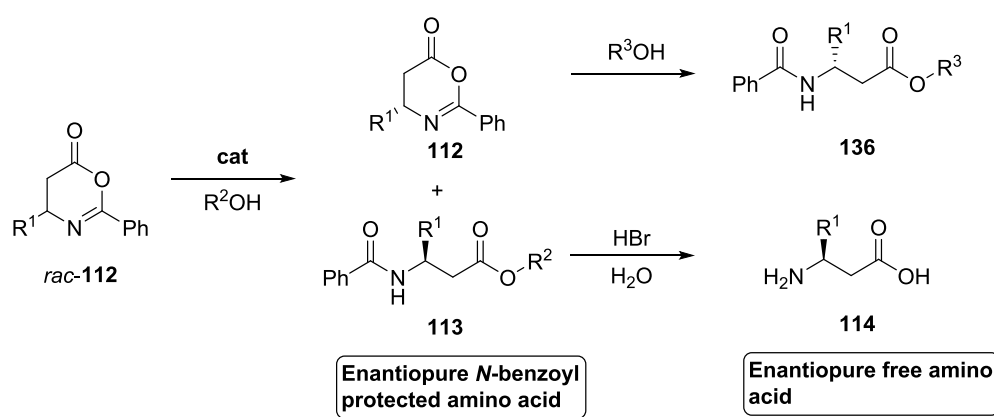
1.13.1 Purpose

As discussed in sections 1.7 and 1.8; the resolution of azlactones (DKR) and oxaziones (KR) *via* alcoholysis are well researched and extensively utilised routes to access natural and unnatural, enantioenriched amino acids. Usually, the amino ester products obtained from these reactions are required for subsequent transformations such as peptide couplings, and thus cleavage of the newly formed ester is necessary to proceed. In this way a three step process (consisting of a resolution, a deprotection and an amide coupling) is required in order to achieve the desired enantioenriched peptide product. Starting with oxazinones, we envisioned the development of a KR protocol *via* aminolysis thereby enabling access to the enantioenriched peptide product in one step. To the best of our knowledge no such methodology exists in the literature. The development of such a protocol would possess enormous value.

We have recently shown that a chiral fluoride ion (generated *in situ*) can catalyse the asymmetric desymmetrisation of *meso*-anhydrides *via* nucleophilic catalysis with moderate levels of enantiocontrol.¹⁹⁹ Later in this thesis, we discuss our separate efforts to resolve oxazinones and azlactones *via* aminolysis using a fluoride ion.

2 The KR of TCIC-Oxazinones to yield enantioenriched and orthogonally protected β -amino acids

As discussed in the introduction, all current methodologies for the KR of oxazinones require aryl-oxazinone substrates such as *rac*-**112**, which furnish the corresponding *N*-benzoyl protected amino acid products **113** and **136** (Scheme 2.1). The selective cleavage of the resulting *N*-benzoyl protecting group is impossible should the molecule require further transformation; extremely harsh reaction conditions are required for the deprotection which would result in the simultaneous cleavage of the ester protecting group, rendering the free amino acid **114**. Selective re-protection of the molecule would be required for subsequent transformations.



Scheme 2.1 Traditional oxazinone KR *via* alcoholysis and subsequent deprotection

2.1 The rationale behind the design of the TCIC-subunit

Connon and co-workers addressed a similar problem in relation to the DKR of azlactones through the design of the TCIC-substituted azlactone **141** (Figure 2.1).¹¹⁴ The rationale behind this design was three-fold:

- It demonstrated enhanced electron deficiency over the traditional phenyl substitution, further activating the azlactone towards nucleophilic attack when compared to azlactones **290** (Figure 2.1).
- It augmented the steric hindrance of the substrate, which could potentially encourage diastereocontrol in the presence of the catalyst.
- It could be transformed into a stable *N*-protecting group *in situ*, after azlactone DKR, which could be selectively cleaved under mild conditions.

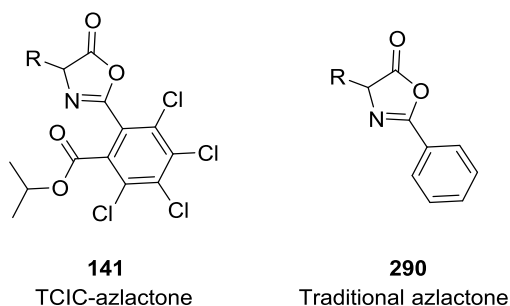
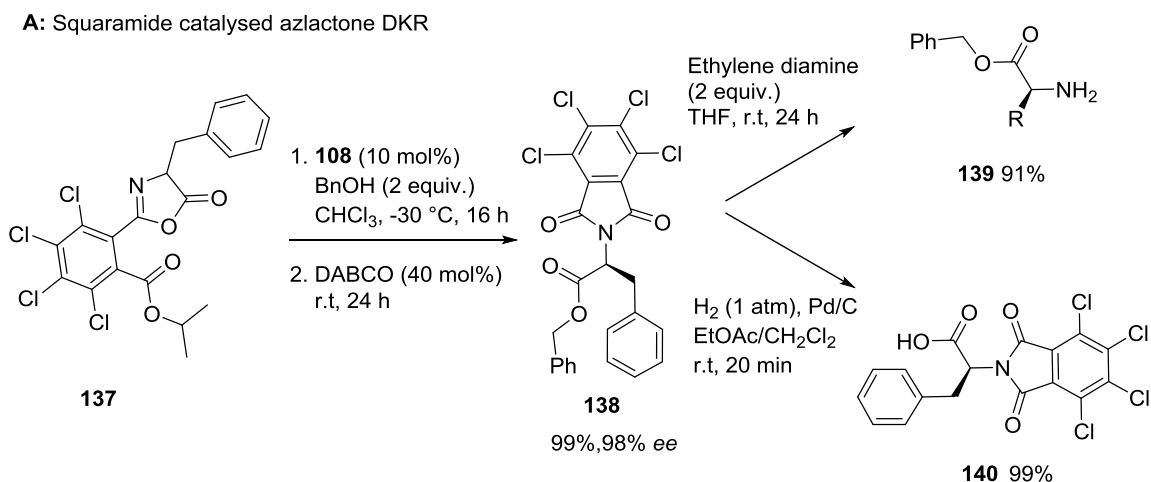
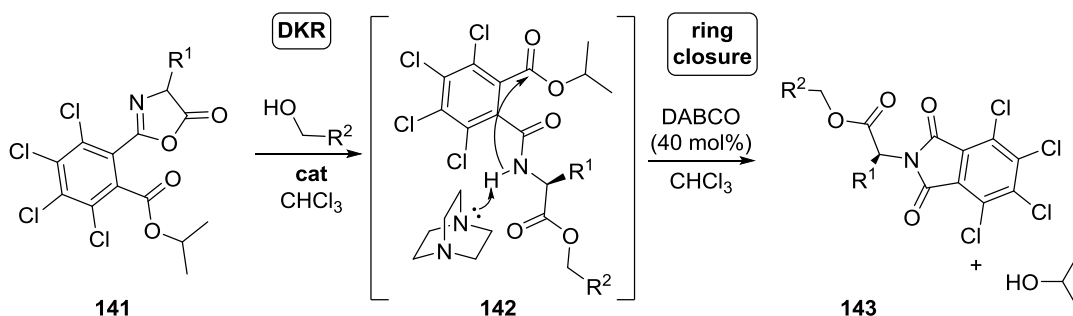


Figure 2.1 General azlactone and oxazinone structures

The use of an isopropyl ester moiety is critical. It was found that upon catalytic ring opening of azlactone **141** to **142**, some ring closure to **143** (presumably catalysed by **108**) occurs even in the absence of the addition of a second amine catalyst (Scheme 2.1B).¹¹⁴ This ring closure results in the liberation of the alcohol leaving group which then is available to compete for the catalytic ring opening. When the simpler methyl and ethyl ester analogues of **141** were used, the methanol and ethanol (respectively) liberated during phthalimide formation competed effectively for the azlactone. Use of the isopropyl ester resulted in the liberation of isopropyl alcohol which was too hindered to participate in azlactone alcoholysis.



B: Mechanism for phthalimide formation



Scheme 2.2 A practical aryl unit

It was hoped that the aforementioned characteristics of TCIC-azlactones would be reflected in the ring expanded homoanalogues **144** enabling us to attain high levels of selectivity for the KR process (Figure 2.2). This chapter discusses the design of these novel TCIC-oxazinones (**144**) and the development of a completely novel catalytic system which effectively resolves oxazinones of type **144** with excellent selectivity to yield enantioenriched and orthogonally protected β -amino acids.

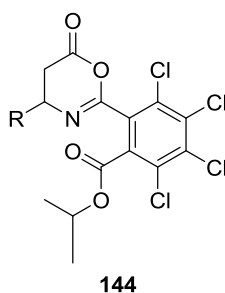
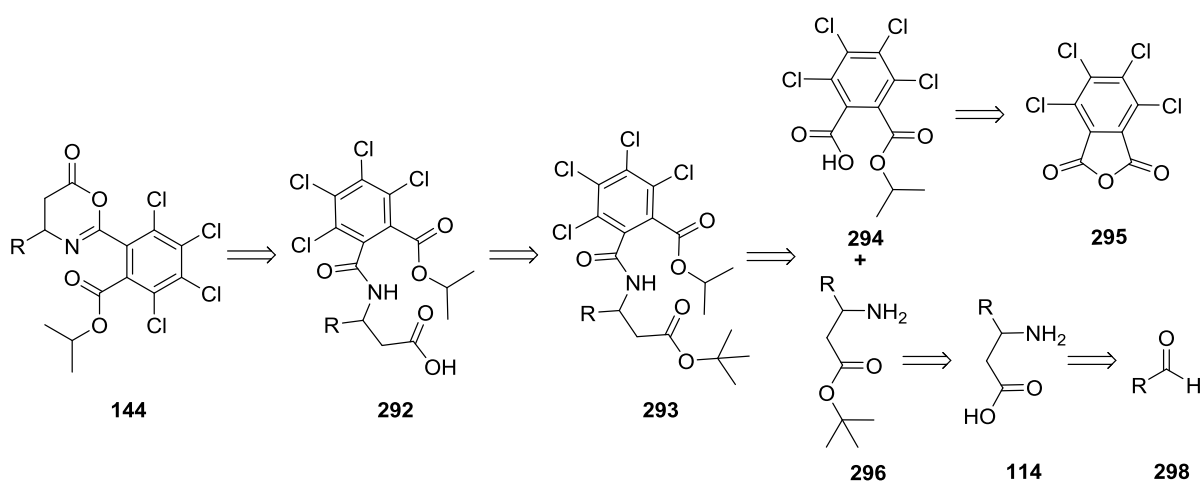


Figure 2.2 General structure for target TCIC-oxazinones (**144**)

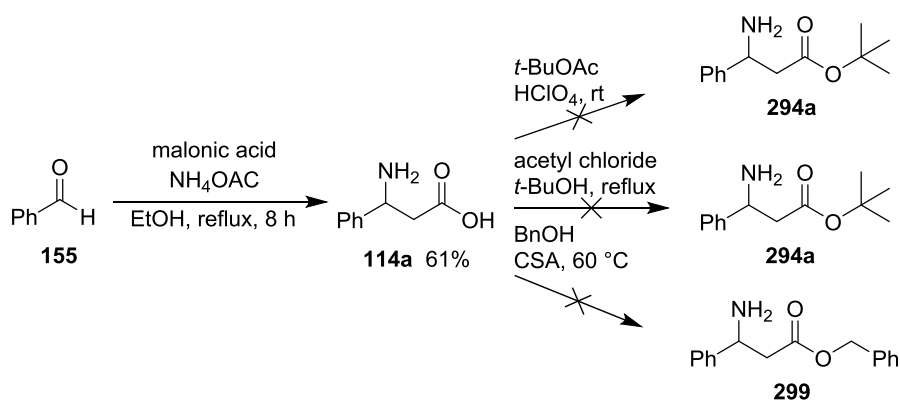
2.2 The substrate development of TCIC-oxazinones

The synthesis of TCIC-substituted oxazinones such as **144** was devised using a retrosynthetic approach, based on the route to TCIC-substituted azlactones previously published by our group.¹¹⁴ In contrast to azlactones, oxazinones are considered to be configurationally stable.¹¹⁰ As such, we anticipated that our new class of oxazinones would be more robust and offer easier handling than their azlactone counterparts (which required strict anhydrous conditions and temperatures of <40 °C during their purification to avoid decomposition). Retrosynthetic analysis of **144** proposed a convergent strategy which would allow access to a wide range of derivatives starting from the appropriate aldehyde **298** (Scheme 2.3). It was envisaged that the oxazinone of type **144** could be synthesised from carboxylic acid **292** via intramolecular ring closure. **292** could be accessed by and amide coupling between carboxylic acid **294** and the appropriate protected β -amino acid **296**.



Scheme 2.3 Retrosynthetic analysis of TCIC-substituted oxazinones

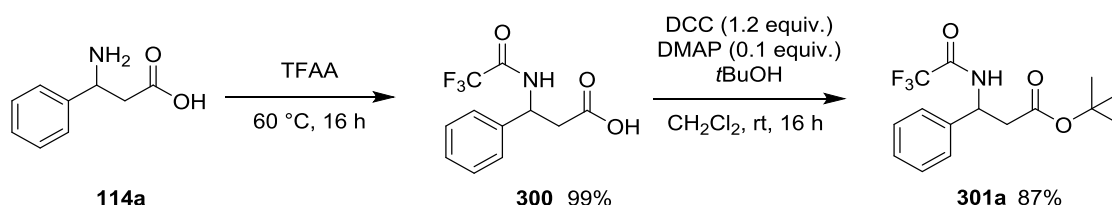
Starting from benzaldehyde (**155**), β -amino acid **114a** was synthesised using a three-component coupling reaction in which malonic acid reacts with the Schiff base (formed *in situ*) via a Knoevenagel-type condensation followed by decarboxylation to furnish the desired β -amino acid (Scheme 2.4). The product **114a** is insoluble in ethanol and so it was easily isolated *via* Büchner filtration with a yield of 61%.



Scheme 2.4 Synthesis of **299**

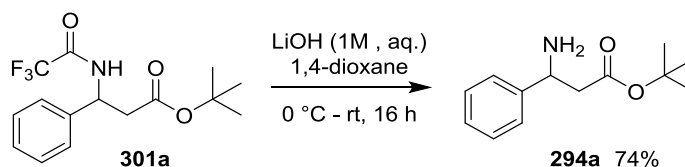
It was envisaged that the amino group could be coupled to **295** (Scheme 2.3) using *N,N'*-dicyclohexylcarbodiimide (DCC) but first protection of the carboxylic acid functionality was required (Scheme 2.4). Protection as the *tert*-butyl ester **294a** was selected as this should be easily removed later in the synthesis whilst maintaining the isopropyl ester moiety in TCIC-subunit. Elimination of the *tert*-butyl ester occurs cleanly under acidic conditions rendering the free carboxylic acid, liberating *iso*-butene gas as a by-product. However, initial attempts at the protection of **114a** using *tert*-butyl acetate and perchloric acid or *via* an anhydride were unsuccessful, with <10% conversion in both cases. Further efforts to form a benzyl ester, another traceless protecting

group, were also unsuccessful and these results were attributed to the poor solubility of amino acid **114a**. To overcome this, the amine was protected with trifluoroacetic anhydride (TFAA); forming trifluoroacetamide **300a** in >99% yield. A Steglich esterification was subsequently employed to install the *tert*-butyl ester moiety in 87% yield (Scheme 2.5).



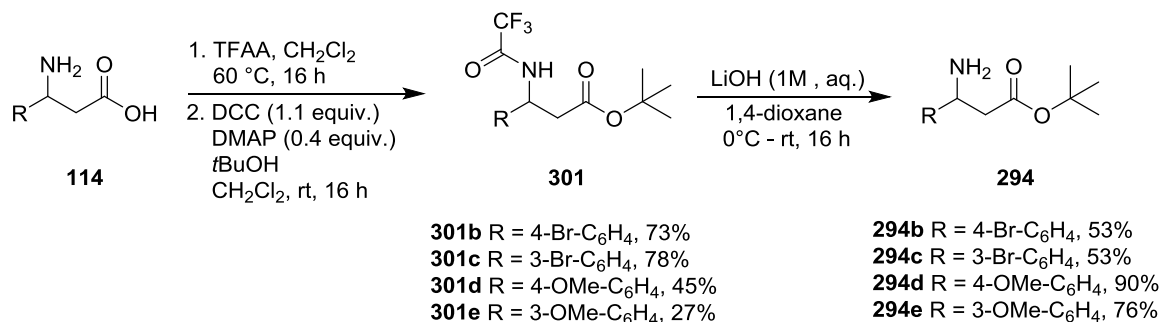
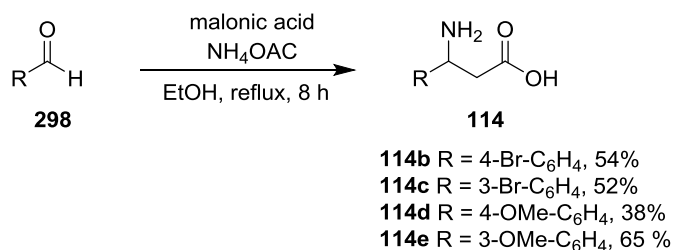
Scheme 2.5 Synthesis of *tert*-butyl ester **301a**

Removal of the trifluoroacetyl group with NaOMe/MeOH or heating under reflux with aqueous K_2CO_3 resulted in low conversion to **294a**. Ultimately, successful deprotection of the amine was achieved using LiOH (1M, aq.), affording **294a** in 74% yield (Scheme 2.6). An overall yield of 63% was obtained for the conversion of **114a** to **294a**. This is comparable to literature values of 40-70% for the initially intended transesterification using *tert*-butyl acetate (Scheme 2.4).²⁰⁷



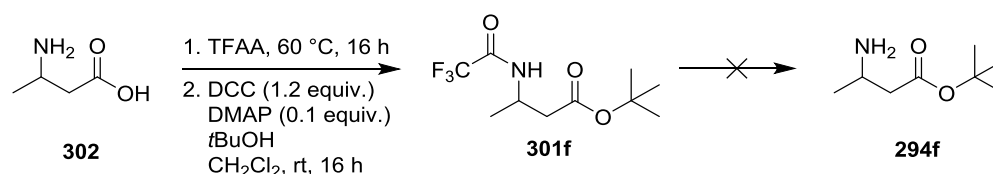
Scheme 2.6 Trifluoroacetamide deprotection

β -Amino acid esters **294b-294e** were synthesised using this methodology starting from the corresponding aldehyde (Scheme 2.7). Lower yields can be attributed to difficulties associated with the isolation of the initial β -amino acids. Protection as the trifluoroacetamide was achieved in near quantitative yields in all cases. Subsequent *tert*-butyl ester synthesis *via* Steglich esterification exhibited high yields in the case of **301b** and **301c**, whereas lower yields were obtained for the electron rich aryl methoxy-substituted **301d** and **301e**. Conversely, amine deprotections were achieved in high yields in the case of electron-rich **294d** and **294e** with lower yields electron poor **294b** and **294c**. Whilst this protection strategy was successful for the synthesis of aromatic β -amino acid esters, a different strategy had to be employed for those containing an aliphatic side chain.



Scheme 2.7 *tert*-Butyl ester synthesis

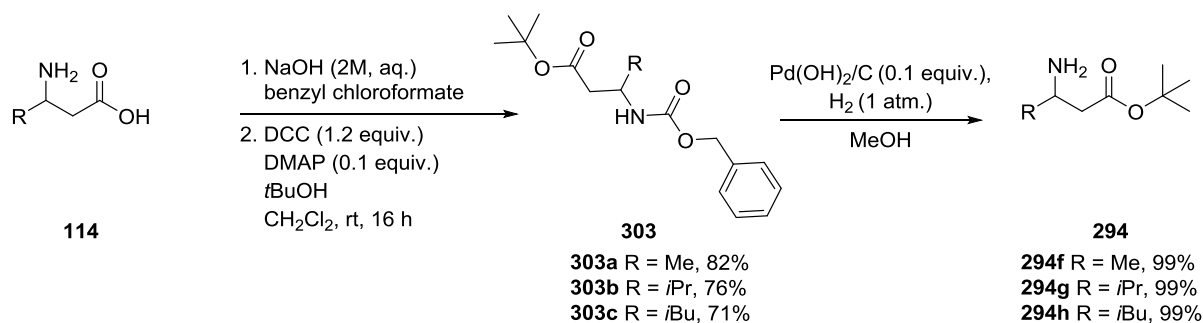
Following the previously developed protection strategy, which had proven to be robust thus far, commercially available **302** was protected as the trifluoroacetamide *tert*-butyl ester **301f** in good yield (Scheme 2.8). However, subsequent cleavage of the trifluoroacetamide protecting group proved problematic. The previously employed conditions of LiOH (1M, aq.) in 1,4-dioxane resulted in the simultaneous cleavage of the *tert*-butyl ester as well as the amide group, rendering the free amino acid **302** as the major product. Further efforts to cleave the trifluoroacetamide using NaOMe/MeOH, NH₄OH and heating under reflux with aqueous K₂CO₃ were also unsuccessful.



Scheme 2.8 Trifluoroacetamide protection strategy

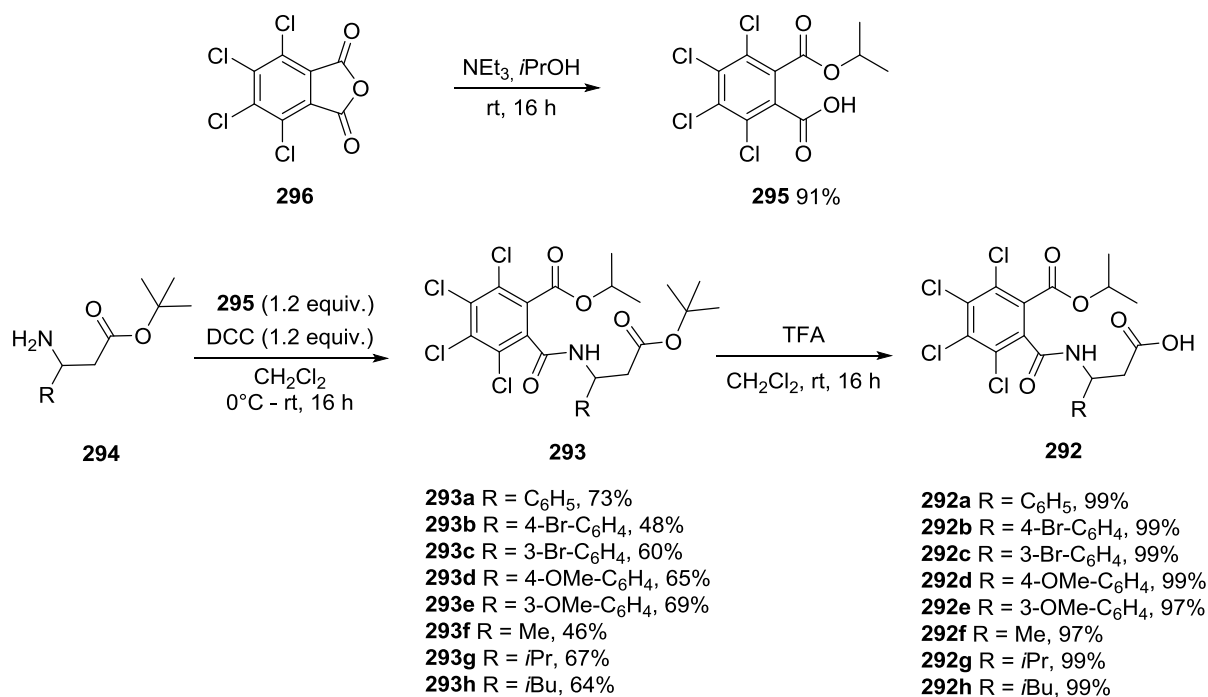
It was clear that a new approach was required. Cbz-protection of the amine was selected as the protection group could be cleanly removed *via* hydrogenolysis whilst maintaining the *tert*-butyl ester moiety. Protection of amino acid **302** was readily achieved using benzyl chloroformate in NaOH (2M, aq.), followed by Steglich esterification to yield the orthogonally protected amino acid **303a** (Scheme 2.9). Gratifyingly, deprotection of the amine was easily achieved in quantitative yield *via* hydrogenolysis using Pearlman's catalyst. This protection strategy was used to synthesise *tert*-butyl amino acid esters **294f-294h** starting from the corresponding, commercially available amino acids

(Scheme 2.9). It is interesting to note that protection of the aromatic amino acid **114a** (Scheme 2.5) as the Cbz -amine was unsuccessful.



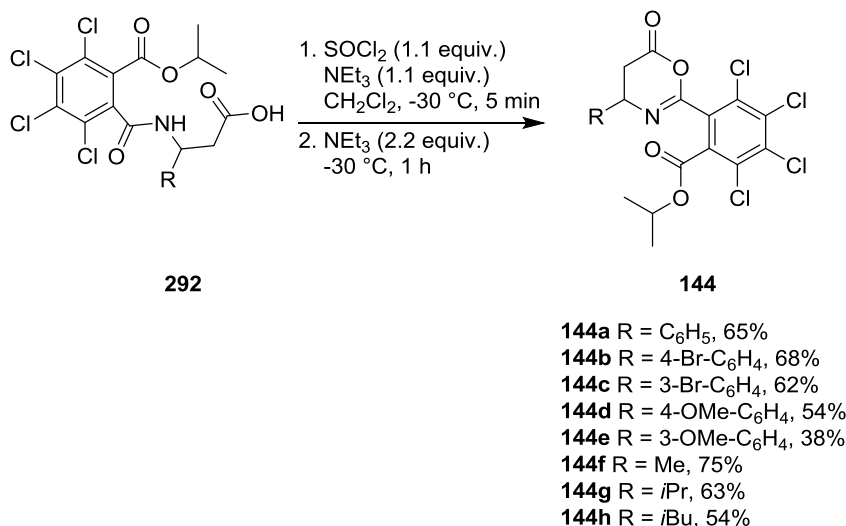
Scheme 2.9 Cbz-protection strategy for aliphatic β -amino acids **294f-294h**

Protection of the carboxylic acid moiety of the amino acid allowed amide coupling of **294a** and **295** using DCC, affording **293a** in 73% yield (Scheme 2.10). Compound **295** was accessed from anhydride **296** in excellent yield (91%) using *i*PrOH and NEt_3 . Amidoester **293a** was treated with trifluoroacetic acid (TFA) to cleave the *tert*-butyl ester group and the product **292a** was used without further purification (Scheme 2.10). This methodology was carried out on all amino acid esters **294** to form a range of carboxylic acids **292**.



Scheme 2.10 Amide coupling and *tert*-butyl ester cleavage to synthesis compounds of general structure **292**

The initial, unsuccessful synthesis of oxazinone **144a** was attempted by the intramolecular ring closure of **292a** via the anhydride; employing conditions disclosed by Berkessel *et al.* using *iso*-butyl chloroformate and NEt₃.¹¹⁰ Further exploration of the literature indicated that a similar transformation had been achieved for more reactive oxazinones via the acid chloride using SOCl₂ and Et₃N at -30 °C.¹¹¹ Under these conditions, full conversion of **292a** to **144a** was observed after one hour (Scheme 2.11). However, the product decomposed during concentration on the rotary evaporator. Removal of the solvent and residual HCl gas at -30 °C circumvented the decomposition of the resulting product, and the residue was subsequently passed through a short silica plug to remove Et₃NHCl. The resulting orange gum was further purified by trituration with ether followed by recrystallisation from diisopropyl ether and ethyl acetate to afford spectroscopically-pure **144a** as colourless crystals in 65% yield. **144a** was prepared in 8 steps starting from benzaldehyde to give an over yield of 19% for the synthesis. Compounds **144b-144h** were synthesised in a similar fashion with small modifications to the purification procedure (Scheme 2.11).

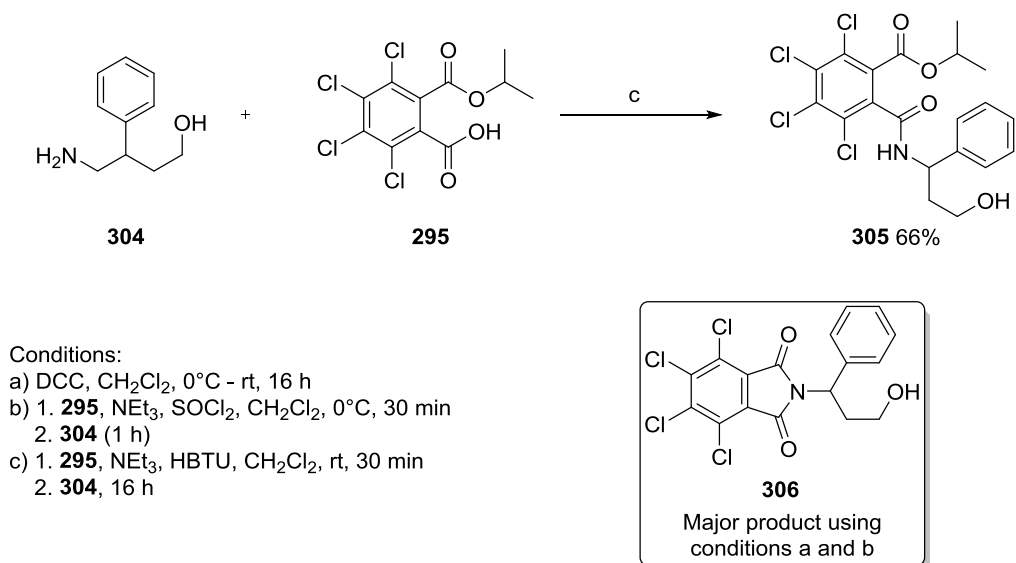


Scheme 2.11 Synthesis of oxazinone **144a** and its derivatives

2.3 An alternative synthesis of oxazinone **144a**

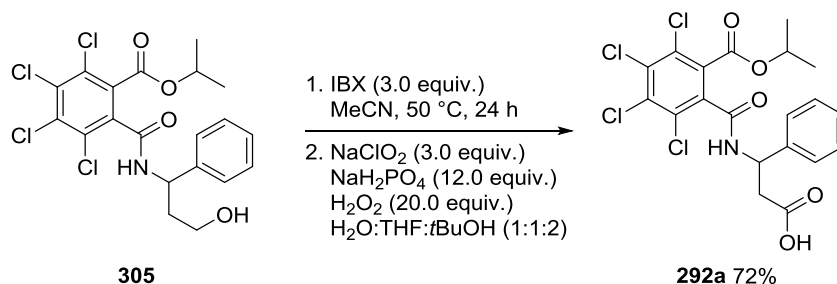
Earlier in the project, an alternative, shorter route to access oxazinones of type **144a** had been explored. This approach started from the appropriate β -amino alcohol, thus eliminating the requirement for a protecting group strategy (provided that the alcohol moiety proved to be sufficiently less reactive than the amino functionality under the chosen reaction conditions). The initial coupling of β -amino alcohol **304** to **295** was attempted using standard DCC coupling. However **306** was obtained as the major product, with intramolecular ring closure of the desired product **305** to the phthalimide product **306**, presumably being catalysed by the urea by-product (Scheme 2.12). Further efforts to carry out the amide coupling via the acid chloride afforded the same result. Gratifyingly, a further attempt which employed HBTU as a coupling agent furnished the desired

product in a 50% yield. Decreasing the concentration of the reaction from 0.65 M to 0.4 M increased the yield to 66% (Scheme 2.12). Product **305** is poorly soluble in the reaction solvent, CH₂Cl₂ and thus purification of the reaction mixture was easily carried out *via* filtration.



Scheme 2.12 Synthesis of amide **305**

With β -amino alcohol **305** in hand, oxidation of the terminal alcohol to carboxylic acid **292a** was envisaged, followed by ring closure to the corresponding oxazinone as carried out in Scheme 2.11. Careful consideration was required for oxidation of the primary alcohol to the carboxylic acid in order to maintain the isopropyl ester moiety in the product. As such, most chromium- and DMSO-based methodologies were ruled out. Instead, a milder two-step approach *via* the aldehyde was selected. Transformation of the alcohol to the aldehyde was initially carried out using Dess-Martin periodinane (DMP) in CH₂Cl₂, though only a 5% yield was obtained; this was attributed to poor solubility of the substrate **305** in CH₂Cl₂. Changing the reaction solvent to a 1:1 mixture of THF:MeCN offered an improvement in yield to 40% which, although encouraging, was still not of practical use. Instead, iodoxybenzoic acid (IBX) a precursor to DMP, was employed the oxidant. Gently heating the reaction to 50 °C in MeCN for 24 h resulted in complete conversion of the alcohol to the aldehyde intermediate. IBX was removed by filtration and the aldehyde was immediately converted to a carboxylic acid **292a** *via* the Pinnick oxidation, which was achieved in 72% yield (Scheme 2.13). Though these results were initially promising, scaling up the reaction for practical purposes resulted in a reduction of the reaction yield to 27%.

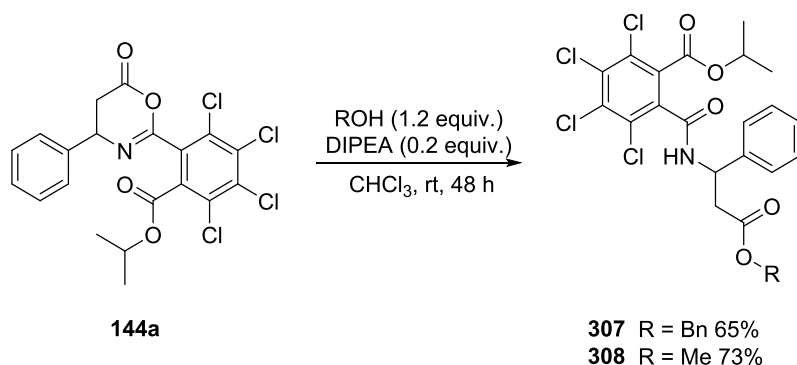


Scheme 2.13 Pinnick oxidation of **305**

Due to the aforementioned scale up difficulties in the synthesis of carboxylic acid **292a**, it was decided that the original synthesis discussed in Section 2.2 would be used to synthesise the oxazinone derivatives. Furthermore, only a small number of the starting β -amino alcohols were commercially available and as such, most would have to be synthesised thereby increasing the number of steps required in overall synthesis. In light of this, oxazinones **144b-144h** were synthesised using the methodology discussed in Section 2.2.

2.4 Evaluation of the racemic process

The first step in the development of a KR process for **144a** via alcoholysis was the development of a racemic reaction. Based on similar transformations in the literature,^{100, 114} DIPEA was selected as a catalyst for the racemic alcoholysis of **144a** using either benzyl alcohol or MeOH as nucleophiles. The transformation was slow in each case and thus both reactions were quenched before full conversion (though this was expected as the literature precedent suggests that H-bond activation of **144a** is important to ensure reactivity).⁹⁷ **307** and **308** were isolated in good yield for the purpose of analysis by CSP-HPLC (Scheme 2.14).

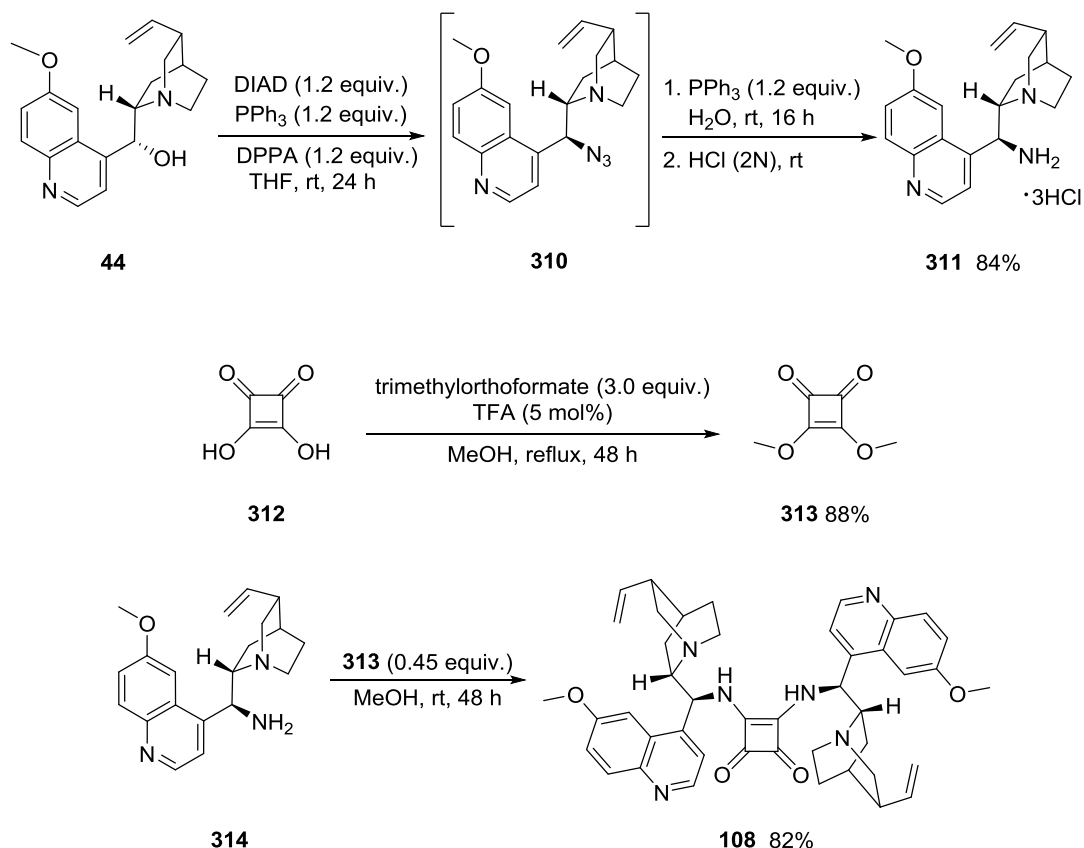


Scheme 2.14 Racemic alcoholysis of **144a** promoted by DIPEA

2.5 Preliminary evaluation of organocatalysts in the KR of oxazinones via alcoholysis

Inspired by the success of bifunctional quinine based organocatalysts in similar transformations both throughout the literature and within the group,^{110, 111, 114} we decided to utilise a *cinchona* alkaloid based core into our catalyst design. Song's C₂-symmetric squaramide catalyst **108** held the current

literature benchmark for both the KR of the traditional phenyl-oxazinones and the DKR of TCIC-azlactones,^{111, 114} exhibiting good to excellent selectivity respectively. As such, the synthesis and evaluation of **108** seemed appropriate for the initial evaluation (Scheme 2.15).

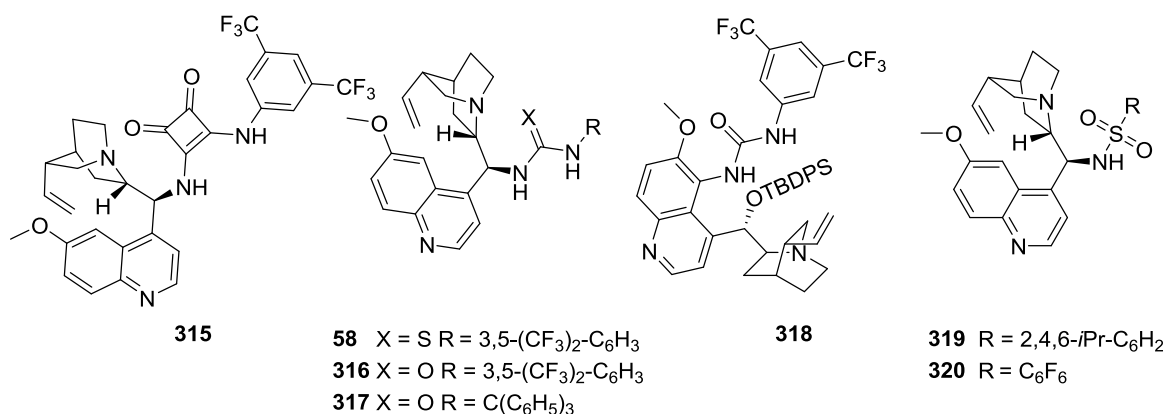


Scheme 2.15 Synthesis of Song's C₂-symmetric squaramide catalyst **108**

Starting from quinine (**44**), the alcohol was converted to the azide (**310**) *via* the Mitsunobu reaction using diphenylphosphoryl azide (DPPA) as the nucleophile. The azide was subsequently reduced *in situ* under Staudinger conditions to afford the amine which was acidified using aqueous HCl and stored as the hydrochloride salt (**311**). The squaric ester **313** was synthesised from squaric acid (**312**) using trimethylorthoformate in high yield. Treatment of **313** with two equivalents of 9-*epi*-quinine amine **314** resulted in di-substitution to furnish the squaramide dimer **108** which precipitated out of solution and was collected by filtration in high yield (Scheme 2.15).

The remaining catalysts employed in the primary screen were readily available within our research group (Scheme 2.16). Squaramide **315**, thiourea **58** and urea **316** are used as standard bifunctional catalysts within the group to compare differences in strength and directionality of hydrogen bond donation with regards to activity. As such, they were selected for the preliminary catalyst screen. Urea **317** was chosen to investigate the effects of variation in R¹ substitution whilst urea **318** explored changes in spatial relationship between the two bifunctional components of the catalyst and its effect

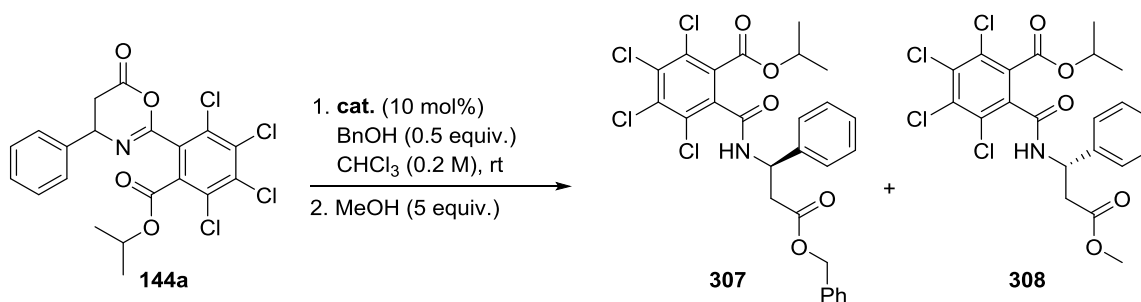
on selectivity. Lastly, sulfonamides **319** and **320** were included to investigate whether mono-hydrogen bond donation would be advantageous from a catalytic standpoint.



Scheme 2.16 Catalysts chosen for the preliminary catalyst screen

For the preliminary evaluation of the aforementioned organocatalysts, a set of standard reaction conditions were chosen based on those employed in the DKR of azlactones.¹¹⁴ Oxazinone **144a** was chosen as the electrophile for the initial study while 0.5 equivalents of benzyl alcohol were used as the nucleophile for the catalytic transformation (Table 2.1). Conversion of the substrate was determined *via* ¹H NMR spectroscopic analysis with 4-iodoanisole as an internal standard. The remaining starting material present after the resolution step was opened *via* methanolysis for analysis by CSP-HPLC.

Table 2.1 Preliminary catalyst screen

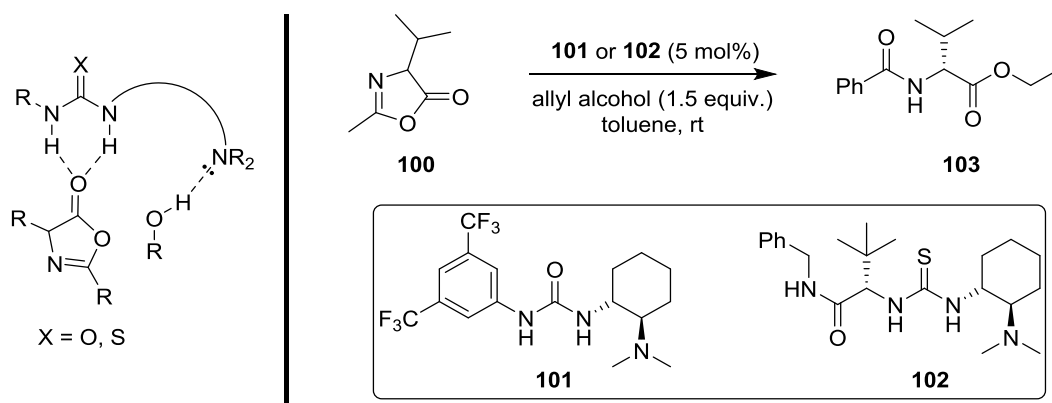


Entry	cat.	t (h)	conv. (%) ^[a]	308 ee (%) ^[b]	S
1	108	4	57	82	10
2	315	16	48	57	6.1
3	58	70	47	58	8.3
4	316	108	38	44	9.6
5	317	108	43	54	10
6	318	168	24	n.d	-
7	319	38	48	46	4.7
8	320	24	49	40	3.5

^a Conversion of the substrate was measured *via* ¹H NMR spectroscopic analysis with 4-iodoanisole (0.5 equiv.) as an internal standard. ^b Determined by CSP-HPLC

As expected from the literature precedent, catalyst **108** afforded promising results producing the best selectivity factor for the reaction ($S = 10$, Table 2.1, entry 1) amongst the chosen library, with an accompanying reaction time of 4 hours at room temperature. Squaramide **315**, whilst still affording an impressive reaction time, promoted the reaction with diminished selectivity (entry 2). Switching the HB-donor from a squaramide to the less acidic thiourea quadrupled the reaction time to 70 hours, though a slight increase in selectivity was observed when compared to its squaramide counterpart **315** (entry 3). Following this trend, ureas **316** and **317**, which are less acidic HB donors still, showed further improvement in selectivity to the detriment of the rate of the reaction (entries 4 and 5). Catalyst **318** (entry 6) was employed to evaluate the effect of changing the orientation of the Lewis basic site. Movement of the basic moiety relative to the hydrogen bond donating substituent proved to be detrimental to reactivity with a conversion of 24% after 7 days. Lastly, sulfonamides **319** and **320**, which possess a single, strongly acidic HB-donating moiety, afforded poor results; furnishing S factors of 5 and 4 for their respective reactions (entries 7 and 8), though they catalysed faster reactions than the urea and thiourea catalysts.

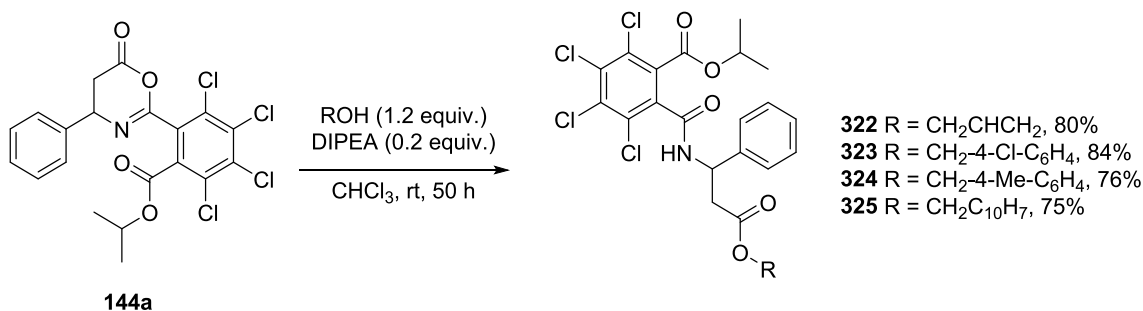
Berkessel *et al.* postulated that bifunctional catalysts **101** and **102** carried out efficient DKR of azlactones through the activation of the azlactone towards alcoholysis *via* hydrogen bonding, whilst the amine functionality enhanced the nucleophilicity of the attacking alcohol (Scheme 2.17).⁹⁷ The results outlined above suggest a similar mode of activation involving **144a**. The strength of HB donation by the catalyst along with orientation of the amine functionality appear to be important factors for the activation of **144a** towards alcoholysis.



Scheme 2.17 Berkessel's postulated mechanism of action of bifunctional organocatalysts in azlactone DKR

2.6 Varying the nucleophilic component

Given the results of the preliminary experiments, a comprehensive study of the activity of squaramide catalysts seemed prudent. At this point, the nucleophilic reaction component was changed due to complications in the analysis of the benzyl ester product **307** by CSP-HPLC. A small screen of 5 different alcohols was carried out using catalyst **108** to find a suitable substitute for benzyl alcohol; a more comprehensive screen would be carried out at a later stage once a suitable catalyst had been selected for optimisation. DIPEA was employed as a basic catalyst to obtain the racemic products for the purpose of analysis of the enantioselective reactions by CSP-HPLC (Scheme 2.18).

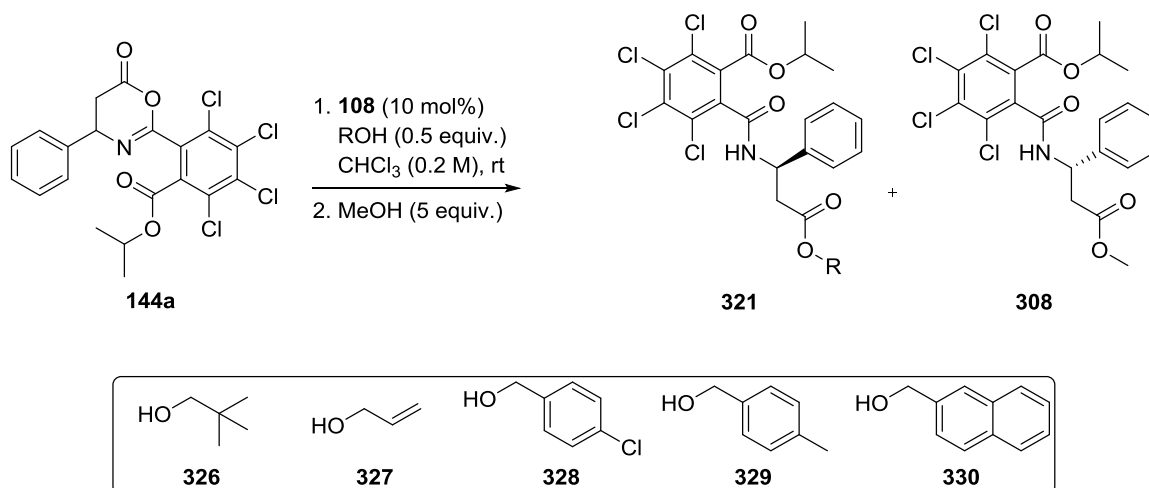


Scheme 2.18 Racemic alcohol screen with **144a**

The results obtained using catalyst **108** (Table 2.2) suggest that selectivity increases with the steric demand of the alcohol, with the exception of **326** (Table 2.2, entry 1) which is assumed to be too hindered to access the substrate. An *S* factor of 6 was obtained when allyl alcohol (**327**) was employed as the nucleophile (entry 2). Implementation of benzylic alcohol **328**, bearing the electron withdrawing *para*-Cl substituent, proved advantageous; affording an *S* factor of 11.3 for the transformation whilst an *S* factor of 7.6 was obtained when the electron rich benzylic alcohol derivative **329** was used as the nucleophile (entries 3 and 4). The largest of the benzylic alcohols, **330**, was found to participate in the most enantiodiscriminative alcoholysis in the presence of **108** furnishing

an *S* factor of 11.7 for the transformation (entry 5). Now that enantiomeric excess of both products of the reaction could be obtained by CSP-HPLC analysis, the conversion could be accurately calculated using Equation 2.1.

Table 2.2 KR of **144a** catalysed **108**



Entry	ROH	t (h)	C (%) ^[a]	321 ee (%) ^[b]	308 ee (%) ^[b]	<i>S</i>
1	326	36	7	n.d	n.d	-
2	327	75	52	54	59	6
3	328	16	56	63	81	11.3
4	329	16	63	49	85	7.6
5	330	16	56	62	82	11.7

^a The conversion was calculated using Equation 2.1. ^b Determined by CSP-HPLC analysis

$$C (\%) = 100 \times [ee / (ee + ee')]]$$

C = conversion (0 < C < 1)

ee = enantiomeric excess of the starting material (0 < ee < 1)

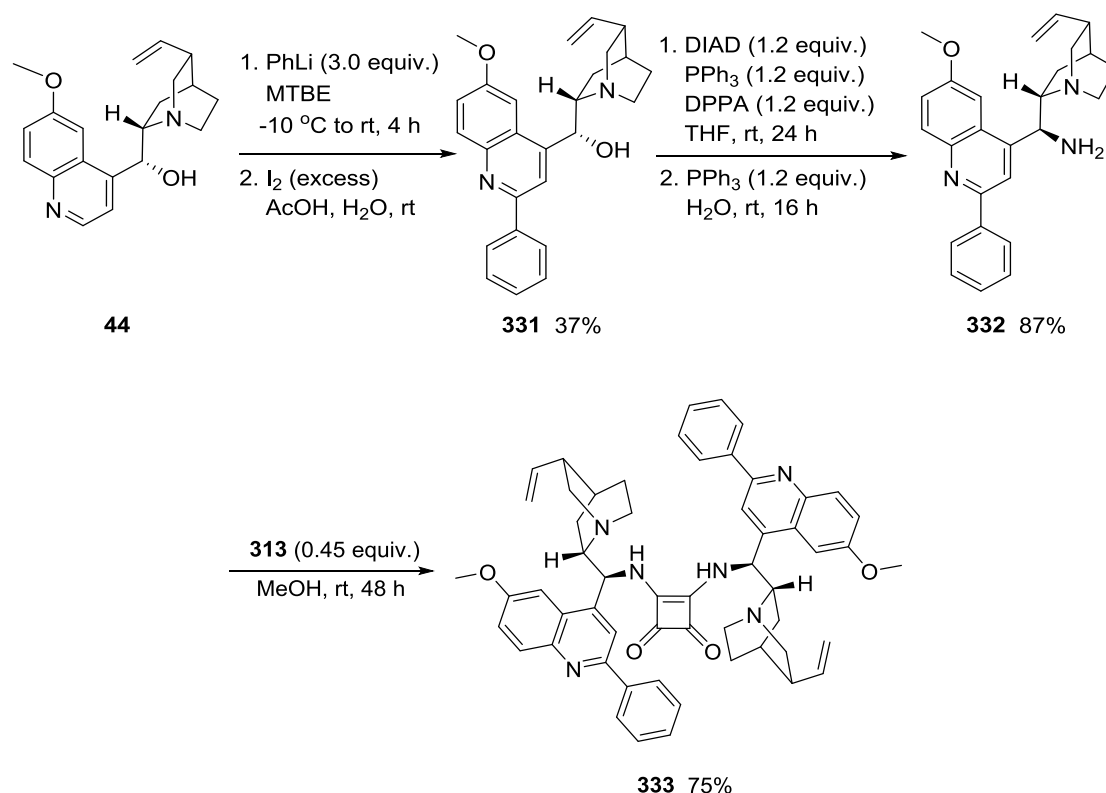
ee' = enantiomeric excess of the product (0 < ee' < 1)

Equation 2.1 Formula to calculate the conversion of KR from the *ee* of the products

2.7 Further catalyst development and evaluation

Encouraged by the promising preliminary results obtained using catalyst **108**, we decided to probe the steric environment surrounding the reactive sites of the catalyst. Previous research carried out in the group had found that enhancing the steric bulk at the quinine C-2' position could offer an improvement in the performance of the catalyst from a selectivity perspective without having a

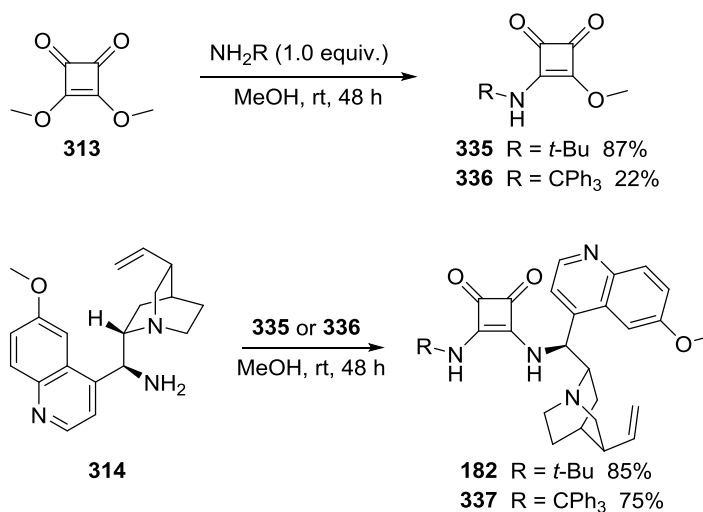
negative effect on the reaction yield.^{128, 136} The distance between the added substituent and the hydrogen bonding moiety is believed to be sufficiently large to not inhibit the formation of hydrogen bonds, whilst still being capable of a steric involvement in the catalysis, potentially improving the performance of the catalyst from a stereoselective standpoint. With this in mind, we decided to install a phenyl substituent at the quinine *C*-2' position of catalyst **108**. This was achieved using a procedure initially reported by Hintermann *et al.* in which PhLi is added to quinine followed by *in situ* oxidation to furnish compound **331**.²⁰⁸ A low yield was obtained for the reaction mainly due to difficulties in separating the product from remaining unreacted starting material. Following this, the alcohol was transformed into an azide *via* a Mitsunobu reaction with a subsequent Staudinger reduction furnishing the free amine **332**. The amine **332** was reacted with the squaric ester **313** using methanol as a solvent to afford the catalyst **333** (Scheme 2.19).



Scheme 2.19 Synthesis of catalyst **333**

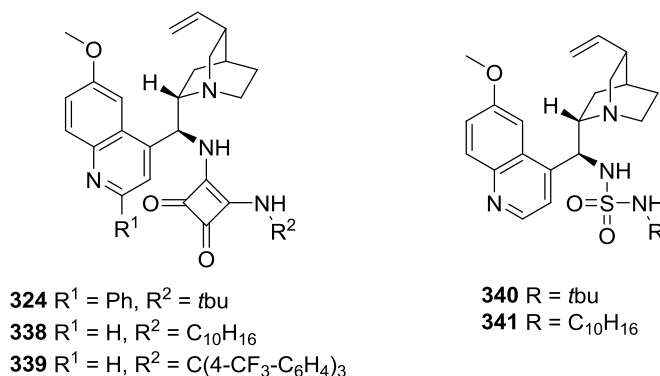
Catalyst **324** (Scheme 2.21), with a *C*-2' phenyl substituent, was already available in the lab and so it seemed prudent to synthesise catalyst **182**, lacking the *C*-2' substituent, as it would allow us to make a direct correlation of the effects of the substitution on catalytic activity. The selectivity obtained for the reaction could also be directly compared with that obtained using catalyst **315** (Scheme 2.16), illustrating the effects of switching from a planar 3,5-(CF₃)₂-C₆H₃ squaramide substituent to a bulky, non-planar substituent. The synthesis of **182** was achieved by coupling squaric ester **313** with *tert*-BuNH₂, followed by a coupling to the free amine **314** to render catalyst **182** in

high yield (Scheme 2.20). Catalyst **337**, which is even bulkier still, was synthesised in a similar fashion though the initial coupling of the squaric ester **313** to trityl amine was low yielding as the amine is extremely sterically hindered (Scheme 2.20).



Scheme 2.20 Synthesis of catalysts **336** and **337**

These catalysts, along with several others available in the laboratory (Scheme 2.21) were evaluated to assess their performance in the KR of oxazinone **144a** using 2-naphthalenemethanol (**330**) as the nucleophile. The results of the catalyst screen are summarised in Table 2.3.

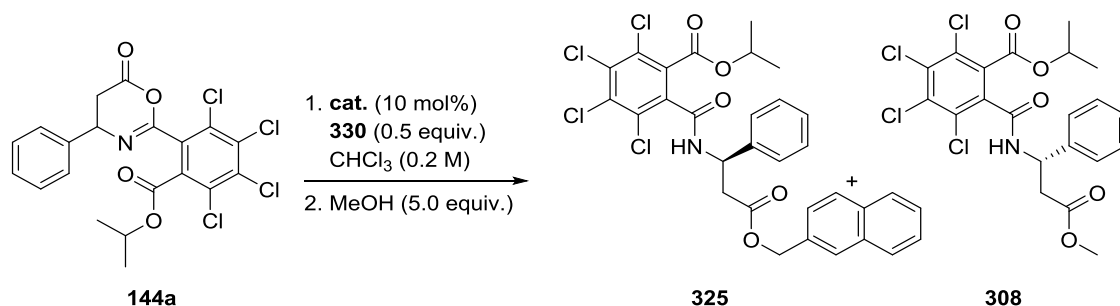


Scheme 2.21 Catalysts **324**, **338**, **339**, **340**, **341**

In the case of catalyst **333**, it was found that installation of a phenyl substituent at the C-2' position resulted in both a drastic decrease in reaction rate and a reduction in selectivity when compared to the use of catalyst **108** (Table 2.3, entries 1 and 2). A similar observation was made using catalysts **182** and **324**; decreased reaction rates and enantiocontrol were observed when the catalyst containing the C-2' phenyl substituent (**324**) was employed (entries 3 and 4). Catalyst **315** (Scheme 2.16) was evaluated under the new conditions (the previous screen utilised benzyl alcohol as the nucleophile) to obtain an *S* factor of 6 for the reaction which, when compared to the results obtained using catalyst **182** (*S* = 11.7), suggests that a bulkier squaramide substituent is beneficial in terms of selectivity

(entry 5). Further augmentation of steric demand at this position were explored in the evaluation of both the trityl (**337**) and adamantyl (**339**) analogues (entries 6 and 7). Similar levels of selectivity were obtained in each case, suggesting that further manipulations of this sort would not be advantageous.

Table 2.3 Squaramide and sulfamide catalyst screen



Entry	cat.	T (°C)	t (h)	C (%) ^[a]	325 ee (%) ^[b]	308 ee (%) ^[b]	S
1	108	rt	4	56	62	82	11.7
2	333	rt	52	42	58	43	6.0
3	182	rt	16	55	65	79	11.1
4	324	rt	24	51	62	63	8.0
5	315	rt	16	48	57	53	6.1
6	337	rt	16	53	67	75	11.2
7	338	rt	16	51	71	68	11.0
8	108	-30	24	52	77	86	23.3
9	182	-30	24	51	83	87	31.0
10	337	-30	24	49	87	83	34.8
11	339	rt	16	51	70	70	10.7
12	339	-30	22	53	73	83	17.1
13	340	rt	36	53	42	48	3.9
14	341	rt	36	53	43	49	4.0

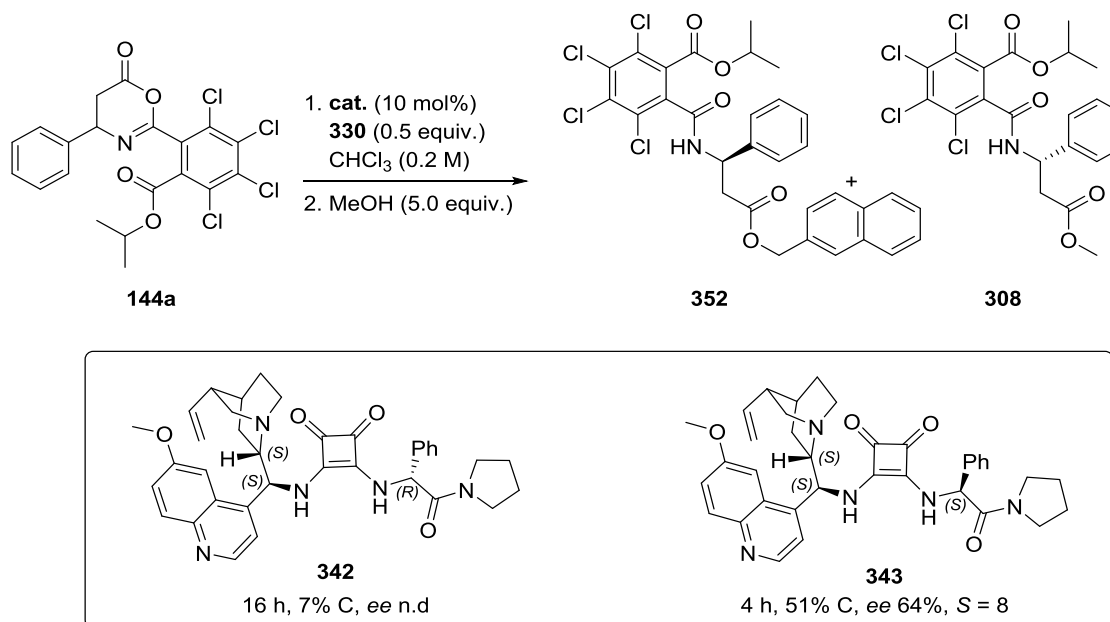
^a The conversion was calculated using Equation 2.1. ^b Determined by CSP-HPLC analysis

Next, we examined the effects of lowering the reaction temperature (-30 °C) for the transformations involving catalysts **108**, **182**, and **337**; S factors of 23.3, 31 and 34.8 were obtained for the respective reactions (Table 2.3, entries 8, 9 and 10). The lower selectivity obtained in the case of **108** was attributed to the poor solubility of the catalyst in CHCl₃ at -30 °C. Changing the solvent to THF resulted in precipitation of the substrate and the reaction was stopped after 24 hours at 7% conversion. Catalyst **339** was synthesised by Dr. Romain Claveau with the idea that addition of CF₃ groups to

the trityl substituent would result in enhanced solubility of the catalyst at low temperatures, compared to **337**, and in turn would increase catalytic activity in this reaction. However, this was not the case (entries 11 and 12). The novel sulfamide catalysts **340** and **341**, developed by Dr. Romain Claveau, were also evaluated, however, they exhibited levels of enantiocontrol obtaining an *S* factor of 3.9 and 4, respectively (entries 13 and 14). As previously discussed, the strength and direction of hydrogen bond donation is believed to be critical in the control of this reaction.⁹⁷ The sulfamide core of these novel catalysts is extremely flexible, and thus the poor results are attributed to lack of rigidity in the transition state.

2.8 A new class of catalyst

Although the results obtained using catalyst **182** and **337** were promising, further investigations into catalyst design were necessary before optimisation of the reaction conditions. A new class of amino acid based squaramide catalysts was under development in the group; Catalysts **342** and **343**, derived from D- and L-phenylglycine respectively, were screened under the standard conditions (Scheme 2.22). The use of catalyst **343** resulted in moderate selectivity at room temperature (*S* = 8) with an impressive reaction time of less than 4 hour to completion. Catalyst **342**, on the other hand, afforded only 7% conversion after 16 hours illustrating the influence of the conformation of the amino acid derived stereocentre on the reaction. In light of these findings, it was postulated that further manipulation of the L-amino acid structure, rather than its D-counterpart, could yield promising results.



Scheme 2.22 Novel amino acid based squaramide catalysts **342** and **343**

Together with Dr. Umar Farid, a library of these novel *cinchona* alkaloid, amino acid derived squaramide catalysts was created. This new class of catalysts contained two separate side chains (R^1 and R^2 , Figure 2.3) which could be easily modified to probe for optimal enantiodiscrimination in the reaction.

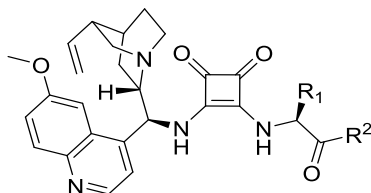
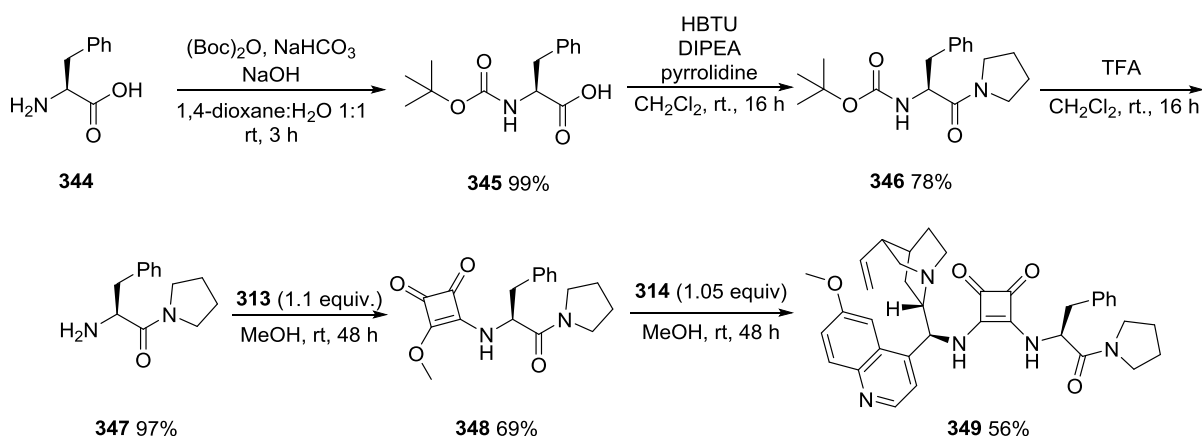


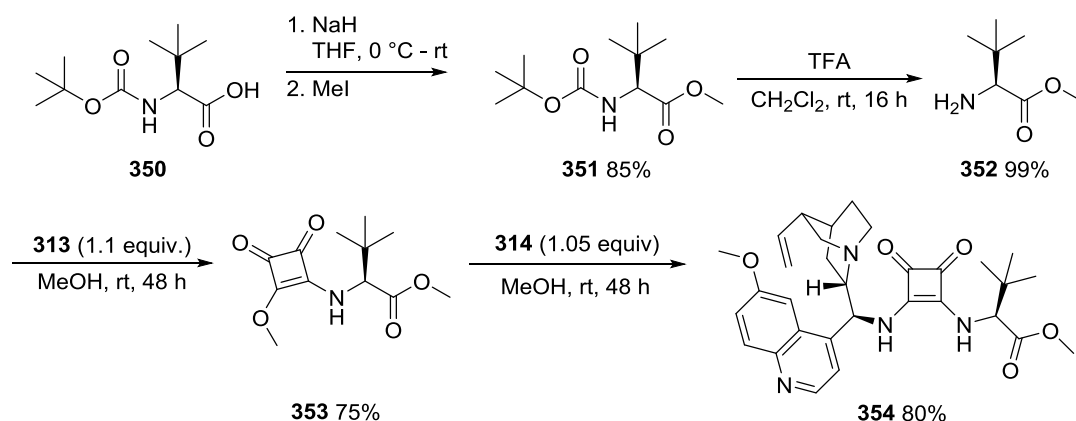
Figure 2.3 Quinine derived amino acid squaramide catalyst structure

The synthesis of catalyst **349** was initiated with *N*-Boc protection of L-phenylalanine, enabling coupling of the carboxylic acid moiety and pyrrolidine using HBTU. This was followed by *N*-Boc deprotection and coupling of the amine moiety to squaric ester **313**. Lastly, coupling of the free amine of the quinine derivative **314** to squaric ester **348** furnished catalyst **349** in moderate yield (Scheme 2.23).



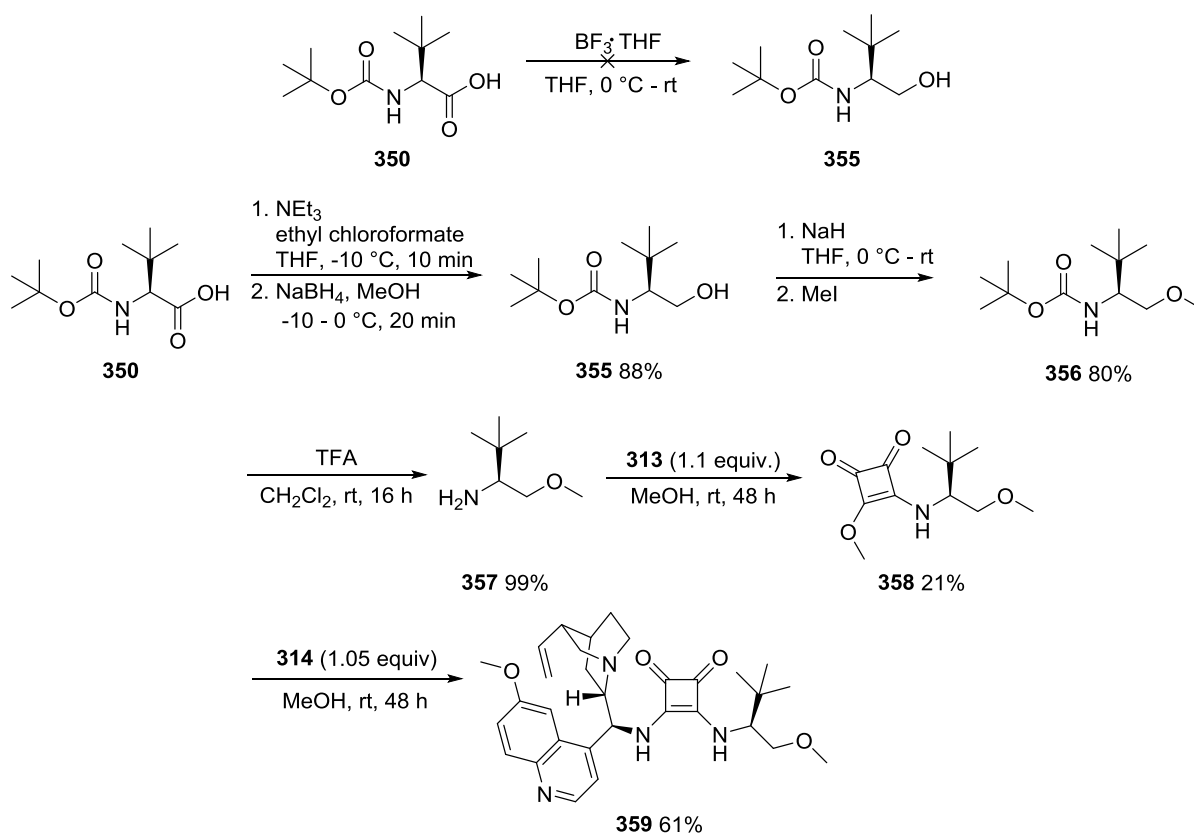
Scheme 2.23 Synthesis of catalyst **349**

Catalyst **354** was synthesised starting from commercially available *N*-Boc-*tert*-leucine (**350**) which was esterified in high yield using NaH and MeI (Scheme 2.24). Subsequent *N*-Boc deprotection allowed for coupling of the free amine **352** to squaric ester **313** in the usual fashion followed by installation of the quinine-based derivative **314** to furnish catalyst **354** in high yield.



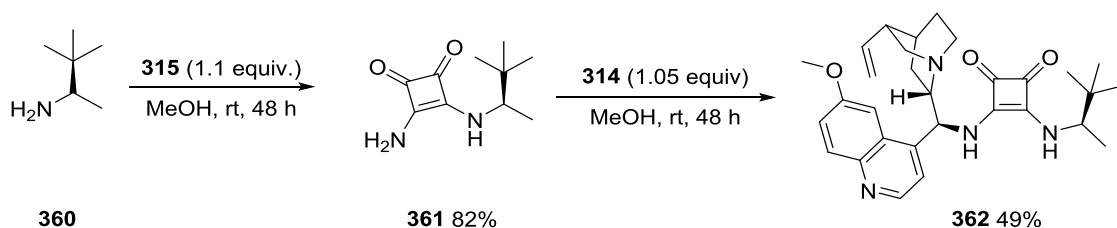
Scheme 2.24 Synthesis of catalyst **354**

Synthesis of catalyst **359** was also carried out starting from **350** (Scheme 2.25). Initial attempts at reducing the carboxylic acid moiety to primary alcohol **355** using BH_3 were unsuccessful, presumably due to the steric hindrance caused by the neighbouring *tert*-butyl substituent. Gratifyingly, the reduction was achieved in 88% yield *via* a mixed anhydride using NaBH_4 and MeOH. Subsequent methylation and *N*-Boc-deprotection yielded free amine **357**, which was coupled to squaric ester **313** and amine **314** to afford catalyst **359**.



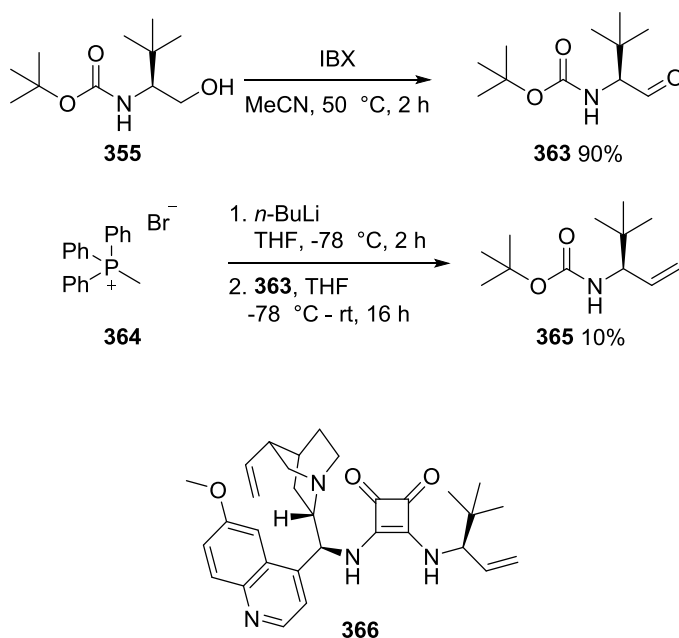
Scheme 2.25 Synthesis of catalyst **359**

Catalyst **362** was synthesised to explore the removal of any heteroatom-induced electronic effects from the amino acid side-chain. Commercially available **360** was coupled to squaric ester **313** at high concentration, followed by coupling to **314** to yield catalyst **362** (Scheme 2.26).



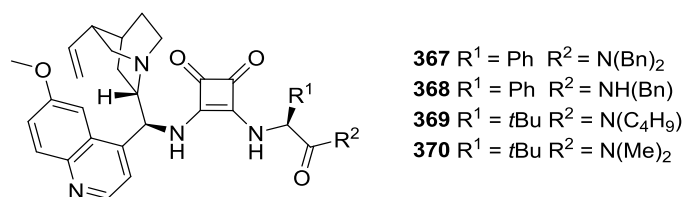
Scheme 2.26 Synthesis of catalyst **362**

Catalyst **366** was designed to examine the effect of further modification to the steric discrepancy between the groups comprising this chiral centre on the catalysts' performance; however, the synthesis of this catalyst was soon abandoned. It was hoped that synthesis of the terminal alkene could be achieved *via* a Wittig reaction. Alcohol **355** was oxidised to the aldehyde using IBX, for subsequent transformation into the desired alkene on reaction with the methyltriphenyl phosphonium bromide (Scheme 2.27). Alkene **365** was obtained in extremely low yield, presumably due to the hindered environment surrounding the aldehyde. Although ultimately, this approach was abandoned due to concerns of potential racemisation at the α -carbon of **366** as a result of trace amounts of *n*-BuLi left over from ylide formation.



Scheme 2.27 Attempted synthesis of catalyst **366**

Catalysts **349**, **354**, **359** and **362** were screened to evaluate their performance in the KR of oxazinone **144a** via alcoholysis, along with catalysts **367-370** (synthesised by Dr. Umar Farid, Scheme 2.28). The results of the screen are shown in Table 2.4.

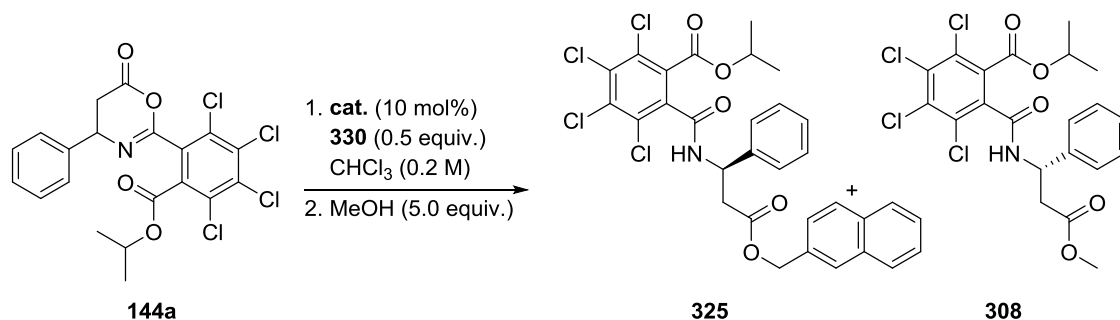


Scheme 2.28 Additional *cinchona* alkaloid, amino acid derived squaramide catalysts

A previously mentioned, the use of catalyst **343**, derived from L-phenylglycine, obtained an *S* factor of 8 for the transformation, with an impressive reaction time of less than 4 hour to completion. Catalyst **342**, derived from D-phenylglycine, afforded an extremely slow reaction, highlighting the requirement of the L-configuration in the catalyst's side-chain for activity (Table 2.4, entries 1 and 2). Following this, analogues **367** and **368** were designed (starting from L-phenylglycine) with the aim of investigating how modifications of the amide substituent would compare with the rigid pyrrolidine unit in **343** (entry 2). The use of larger dibenzyl amide resulted in reduced selectivity (entry 3), while the mono-benzyl amide, possessing both HB-donating and π -stacking capabilities,³⁵ afforded a more selective reaction obtaining an *S* factor of 10.2 for the reaction (entry 4). The use of catalysts **369** and **349** explored variation at the R^1 position of the amino acid side chain via installation of *tert*-butyl and benzyl substituents, resulting in *S* factors of 8.6 and 4.5 respectively (entries 5 and 6). When compared with the results obtained using the original catalyst **343** (*S* = 8), it was deduced that the bulky *tert*-butyl R^1 substituent afforded enhanced enantiodiscrimination. With this in mind, further manipulations of the R^2 group were examined while maintaining the advantageous R^1 *tert*-butyl substitution. A decrease in size to $R^2 = \text{N}(\text{C}_4\text{H}_9)$ saw an increase in selectivity, the same reaction was carried out at reduced temperatures -30 °C and -60 °C which further enhanced enantioselective catalysis obtaining an *S* factor of 29.5 in the latter case (entries 8 and 9). Employment of catalyst **354**, which is smaller still ($R^2 = \text{OMe}$), promoted an even more selective reaction, though the change in electronic properties of the amino-acid side chain may be responsible for enhanced levels of enantiocontrol. Decreasing the reaction temperature to -30 °C, furnished our most promising result of *S* = 36.6 (entries 10 and 11) with no observed precipitation of the catalyst. Encouraged by this result, catalysts **361** and **362** were synthesised to examine how a further decrease in size and modification of the electronic properties of the side chain would affect selectivity. Catalyst **361** demonstrated the highest selectivity of any catalyst at room temperature (*S* = 16, entry 12), but to our disappointment, this enhanced enantiocontrol was not observed at lower temperatures (*S* = 26.4, entry 13). Conversely, catalyst **362** offering slightly lower selectivity at room temperature (*S* = 13.8, entry 14) outperformed at low temperatures with a selectivity factor of *S* = 34.2 (entry 15). Though this

result was slightly lower than that obtained using catalyst **354**, slight precipitation of catalyst **362** was observed at -30 °C. We concluded that if more of catalyst **362** was in solution, it was likely that levels of enantiocontrol could be significantly enhanced.

Table 2.4 Cinchona alkaloid, amino acid derived squaramide catalyst screen



Entry	Cat.	T (°C)	t (h)	C (%) ^[a]	325 ee (%) ^[b]	308 ee (%) ^[b]	S
1	342	rt	16	7	n.d	n.d	-
2	343	rt	4	51	63	64	8.1
3	367	rt	4	53	59	66	7.4
4	368	rt	4	52	65	72	10.2
5	369	rt	4	53	62	70	8.6
6	349	rt	4	53	47	53	4.5
7	370	rt	4	55	63	76	9.5
8	370	-30	24	52	78	86	23.3
9	370	-60	120	51	82	86	29.5
10	354	rt	5	50	71	71	12.3
11	354	-30	24	53	82	93	36.6
12	354	rt	12	51	75	76	16.0
13	354	-30	16	49	83	79	26.4
14	362	rt	4	54	82	69	13.8
15	362	-30	16	53	83	92	34.2

^a The conversion was calculated using Equation 2.1. ^b Determined by CSP-HPLC analysis

Efforts to improve the solubility of **362** began with increasing the reaction temperature from -30 °C (Table 2.5, entry 1) to -15 °C (entry 2). Though precipitation in the reaction was no longer apparent, there was a reduction in selectivity. Our next attempt involved changing the reaction solvent whilst maintaining a temperature of -30 °C. Switching from CHCl_3 to the less polar solvent CH_2Cl_2 afforded diminished levels of selectivity (entry 3). Polar solvents THF, MeCN and EtOAc completely shut down reactivity resulting in 0% conversion after 16 hours (Table 2.5, entries 4, 5 and 6). In the case

of THF, substrate **144a** was completely insoluble at low temperatures. These results suggested that chlorinated solvents are vital to ensure reactivity, with catalyst **362** exhibiting superior levels of enantiocontrol in CHCl_3 . Accordingly, a 1:1 solvent mixture of $\text{MeCN}:\text{CHCl}_3$ was employed, affording 22% conversion after 13 hours. The *ee* of the products of this reaction were not determined due to the comparatively slow reaction rate (entry 7). A mixture of $\text{THF}:\text{CHCl}_3$ (1:1) resulted in 0% conversion of the substrate after 13 hours, which is most likely due to the decreased solubility of the substrate in THF (entry 8). In a final attempt to improve the solubility of catalyst **362** we studied the effects of decreasing the reaction concentration. To our delight, employing CHCl_3 at a reduced concentration of 0.1 M afforded a large increase in the selectivity of the reaction; with *S* factors increasing from *S* = 34.2 to *S* = 60.1 (entry 9). Further decreases in concentration beyond 0.1 M resulted in diminished levels of selectivity (Table 2.5, entries 10 and 11). Moving forward, catalyst **362** would be employed in the transformation using 0.1 M CHCl_3 for optimum activity.

Table 2.5 Optimisation of solvent conditions for the KR of **144a** by catalyst **362**

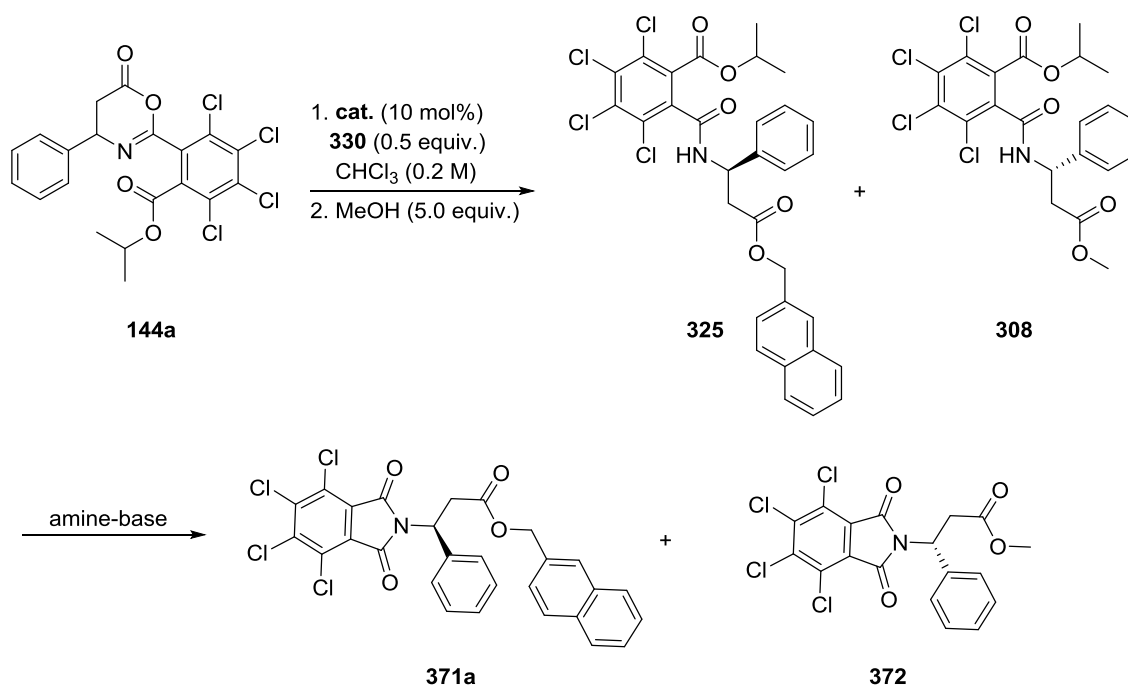
144a **325** **308**

Entry	Solvent	T (°C)	t (h)	C (%) ^[a]	<i>ee</i> 325 (%) ^[b]	<i>ee</i> 308 (%) ^[b]	<i>S</i>
1	CHCl_3 (0.2 M)	-30	16	53	83	92	34.2
2	CHCl_3 (0.2 M)	-15	16	52	79	87	24.0
3	CH_2Cl_2 (0.2M)	-30	20	48	82	75	23.2
4	THF (0.2 M)	-30	16	0	-	-	-
5	MeCN (0.2 M)	-30	16	0	-	-	-
6	EtOAc (0.2 M)	-30	16	0	-	-	-
7	$\text{MeCN}:\text{CHCl}_3$ 1:1 (0.2 M)	-30	13	22	n.d.	n.d.	-
8	$\text{THF}:\text{CHCl}_3$ 1:1 (0.2 M)	-30	13	0	-	-	-
9	CHCl_3 (0.1 M)	-30	16	49	91	89	60.1
10	CHCl_3 (0.07 M)	-30	16	49	86	91	56.0
11	CHCl_3 (0.04 M)	-30	20	49	85	88	46.4
12	CHCl_3 (0.03 M)	-30	20	49	84	82	30.0

^aThe conversion was calculated using Equation 2.1. ^bDetermined by CSP-HPLC analysis

2.9 Amine-catalysed ring closure to form phthalimide protected products *in situ*

Now satisfied with the catalyst design for the KR protocol, we turned our attention to the subsequent, *in situ* generation of the phthalimide product to render the orthogonally protected amino acid products **371a** and **372** (Scheme 2.29); this was extremely important to the underlying concept of this work, *i.e* the generation of genuinely synthetically useful products.



Scheme 2.29 KR of oxazinone **144a** followed by amine catalysed ring closure

The aforementioned studies carried out by the group on the DKR of TCIC-azlactones such as **137** (Scheme 2.2) found that, after the resolution step, the one-pot addition of catalytic DABCO ensured clean and efficient phthalimide formation, thus yielding the enantioenriched and orthogonally protected amino acid products.¹¹⁴ As depicted in Scheme 2.2B, Section 2.1, the use of the amine base additive catalyses deprotonation of the amide (most likely *via* general-base catalysis) followed by intramolecular cyclisation onto the isopropyl ester, to yield the phthalimide product and isopropanol.¹¹⁴ It is noteworthy that, in the absence of DABCO, some ring closure still occurs, presumably catalysed by **108**. As such, addition of the second amine catalyst was necessary only to ensure complete ring closure to phthalimide **138**.

In contrast, our initial experiments on the KR of oxazinone **144a** showed no evidence of intramolecular ring closure to phthalimides **371a** and **372** in the absence of a second amine base additive (Table 2.6, entry 1). This was attributed to increased steric hindrance around the amide moiety of the resolution products **325** and **308** (Scheme 2.29). As intramolecular reactions tend to be favoured at higher solvent concentrations, the reaction concentration was increased from 0.1 M to 0.2 M; however, only trace amounts of phthalimide formation was observed under these conditions

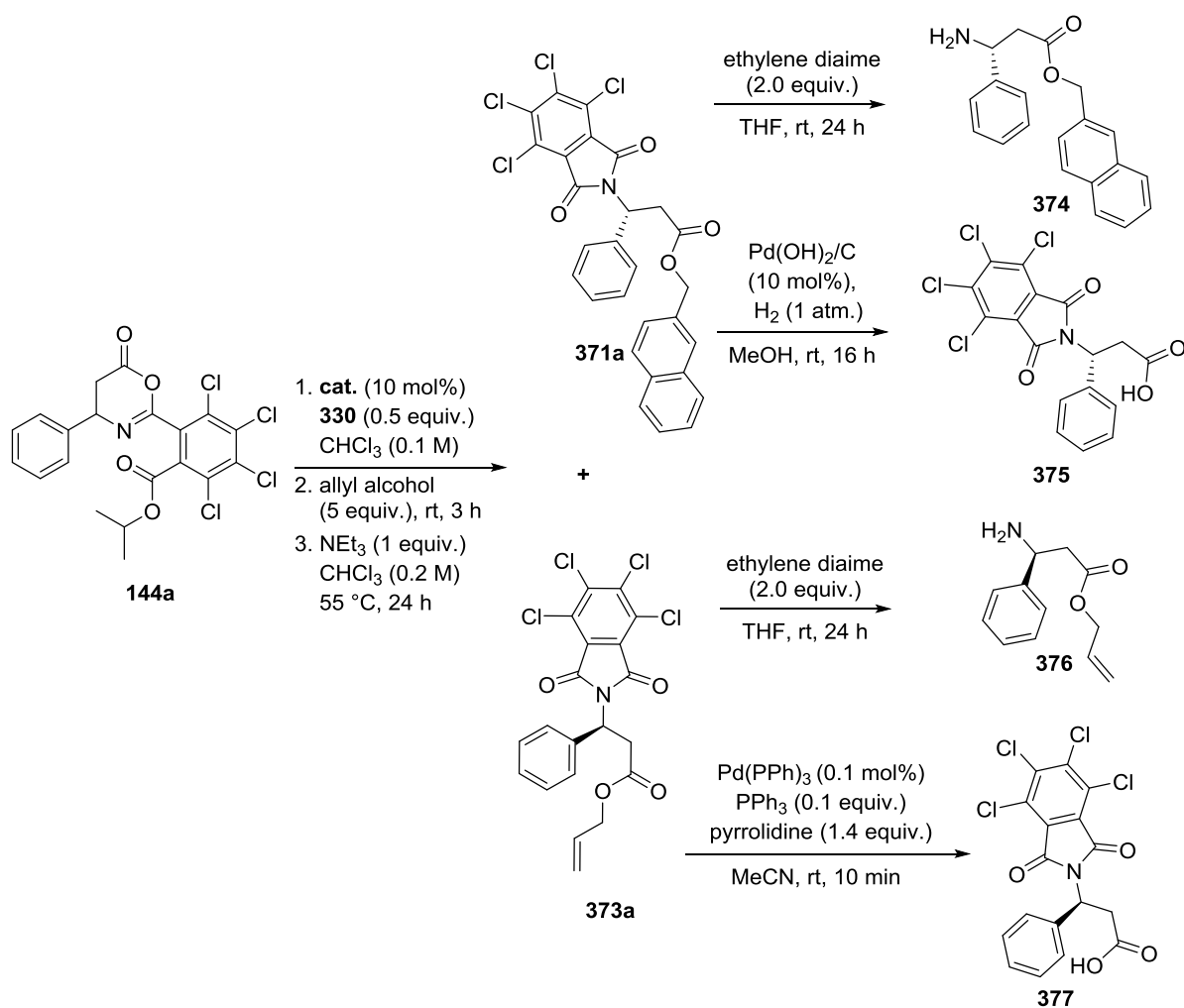
(entry 2). Next, DABCO (40 mol%) was employed as a base additive upon complete consumption of oxazinone **144a**, in order to encourage intramolecular ring closure. Disappointingly, only 20% conversion to the phthalimide products was observed after 48 hours (entry 3). The use of stoichiometric DABCO at room temperature and at 50 °C also furnished low levels of intramolecular ring closure (entries 4 and 5). It was decided that a more basic amine was required for the transformation. One equivalent of NEt₃ (pK_aH = 10.8)²⁰⁹ was next utilised, resulting in 60% conversion to the phthalimide products after 36 hours (entry 6). Gratifyingly, heating the reaction to 55 °C furnished **371a** and **362** in 99.9% yield (determined by ¹H NMR spectroscopic analysis) after 36 hours without compromising *ee* (entry 7). Increasing the concentration of the reaction to 0.2 M prompted a shorter reaction time of 24 hours whilst maintaining the *ee* of the products (entry 8). When the same reaction was repeated under reflux (62 °C), the reaction times were shorter but small deviations in *ee* of the products were observed, presumably due to base-catalysed transesterification by any remaining MeOH from the previous step.

Table 2.6 Optimisation of the amine catalysed ring closure

Entry	Base additive	Equivalents	T(°C)	Conc. (M)	t (h)	C (%) ^[a]
1	-	-	rt	0.1	16	0
2	-	-	rt	0.2	16	3
3	DABCO	0.4	rt	0.2	48	20
4	DABCO	1	rt	0.1	36	44
5	DABCO	1	50	0.1	24	50
6	NEt ₃	1	rt	0.1	36	60
7	NEt ₃	1	50	0.1	36	100
8	NEt ₃	1	55	0.2	24	100

^a Conversion of the substrate was measured via ¹H NMR spectroscopic analysis

Difficulties arose in the separation of the products **371a** and **372** via flash chromatography and thus we were prompted to change the identity of the second alcohol added to the reaction; as the purpose of this step is to react with the left over starting material from the kinetic resolution, the problem was solved without complication. Switching from MeOH to allyl alcohol formed **371a** and **373a** as the reaction products, which were easily separated using flash chromatography (Scheme 2.31). Phthalimide **371a** can be cleaved using ethylene diamine to furnish **374**, while the ester can be hydrogenated to reveal the free acid **375** (Scheme 2.31).^{114, 210} Free amine **376** can be obtained in the same fashion from **373a**, whilst the allyl ester protecting group can be removed using Pd(PPh₃)₄ and a nucleophile to yield **377**.²¹¹ In this way, all amino acid products of the reaction are orthogonally protected.

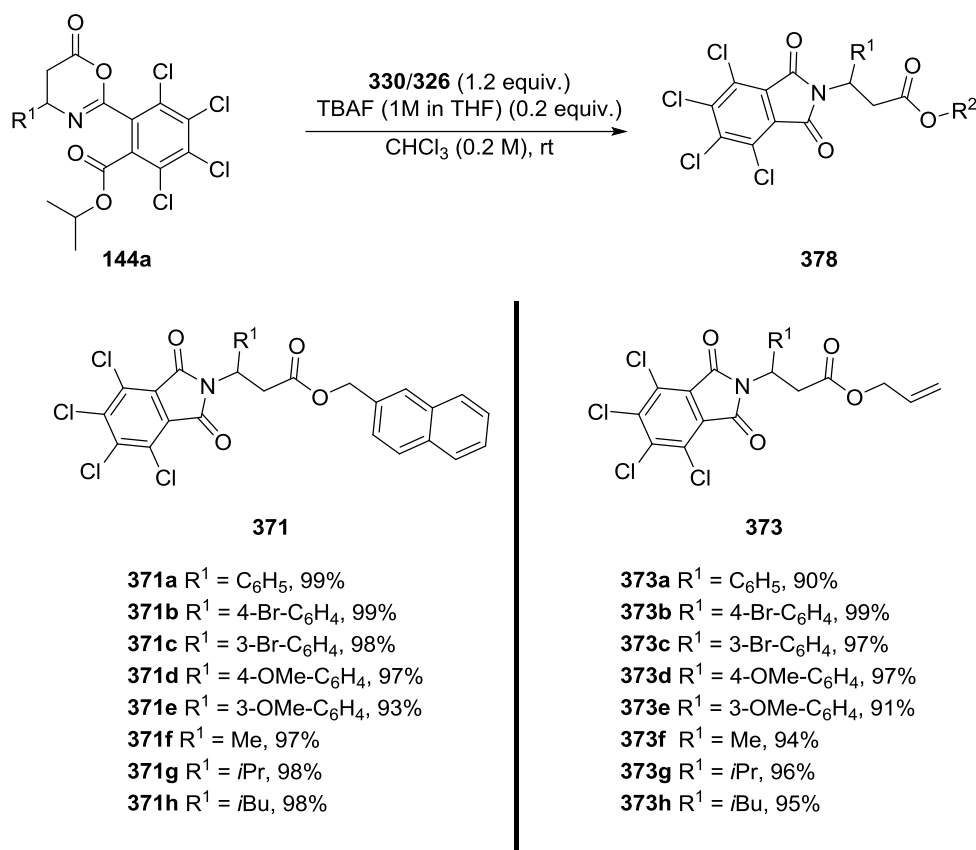


Scheme 2.30 Cleavage of orthogonal protecting groups

2.10 Synthesis of phthalimide protected amino-ester racemates

With a range of oxazinones synthesised to investigate the scope of our KR protocol, we began synthesising the phthalimide amino-ester racemates of type **371** and **373** as product references for both spectroscopic analysis and analysis by CSP-HPLC. As discussed in Section 2.4, previous experiments which employed DIPEA as a racemic catalyst for the addition of alcohol **330** to oxazinone **144a** were slow, requiring 72 hours for complete conversion to the ring-opened product **325**. Following this, elevated temperatures and additional, stoichiometric base were required to convert the resolution products **325** and **308** into the desired phthalimide protected products (**371a** and **372**). In order to improve the efficiency of this process, the use of DIPEA as a catalyst was exchanged for tetra-*n*-butylammonium fluoride (TBAF); which catalysed both the alcoholysis of oxazinone **144a** and the subsequent intramolecular ring closure to the phthalimide product quantitatively in only 20 hours (Scheme 2.31). The enhanced efficiency of TBAF in the transformation could be attributed to either the augmented basicity of the naked fluoride ion (vs the bulky amine DIPEA), or its potential to act as a nucleophilic catalyst, or an amalgam of both properties. Despite the lack of clarity regarding the mechanism of action, the superiority of TBAF as

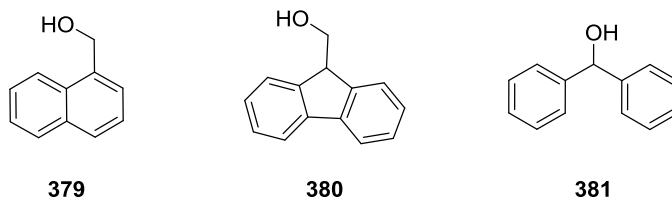
a racemic catalyst for the transformation was apparent. As such, TBAF was employed in the synthesis of all racemates of type **371** and **373** (Scheme 2.31). The fluoride catalysed ring opening of oxazinones and other such structures will be further examined in Sections 7 and 8 of this thesis and therefore will not be elaborated on at this time.



Scheme 2.31 Synthesis of the phthalimide protected amino-ester racemates of type **371** and **373**

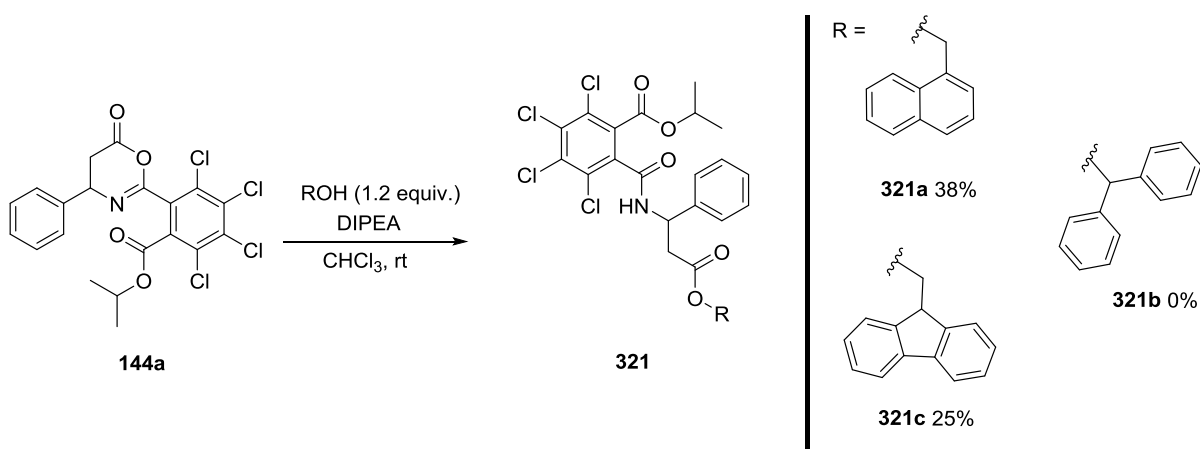
2.11 Final optimisation of the reaction conditions for the kinetic resolution

With catalyst design complete, and the reaction conditions for the *in situ* formation of the phthalimide protected amine fully optimised, we began to make final adjustments to the reaction conditions for the kinetic resolution protocol. In terms of enantiocontrol, the optimum solvent and reaction concentration to use in conjunction with catalyst **362** had already been determined. We decided it was prudent to expand on our initial alcohol screen; the results of the previous study had found that (in general) more sterically encumbered alcohols furnished reactions with enhanced enantiodiscrimination. Alcohols **379**, **380** and **381** were selected for evaluation in the KR protocol to further explore this hypothesis (Scheme 2.32). Each of these reactions would yield amino acid-ester products which could easily be deprotected in the presence of the phthalimide protecting group and *vice versa*.



Scheme 2.32 Alcohols for expanded alcohol screen

Employing DIPEA (20 mol%) as a catalyst to promote the racemic reaction between alcohol **379** (a structural isomer of the benchmark alcohol **330**) and oxazinone **144a** furnished only 20% conversion to the product after 48 hours. An additional equivalent of DIPEA catalyst was added to the reaction mixture and, after a further 48 hours, the reaction was quenched at 53% conversion to afford **321a** 38% yield; 9% of the phthalimide product was also isolated from the reaction mixture. The more sterically encumbered alcohol **380**, which would yield the Fmoc protected product **321b**, afforded only 11% conversion after 48 hours. An additional 2 equivalents of DIPEA catalyst were added, allowing racemic product **321b** to be isolated with a 25% yield after a further 48 hours of stirring. In the case of alcohol **381**, 0% conversion was observed after 48 hours, most likely because the alcohol was too sterically hindered to react with **144a**. Despite this, alcohol **381** was still employed in the reaction catalysed by **362** to see if bifunctional activation could promote reactivity.

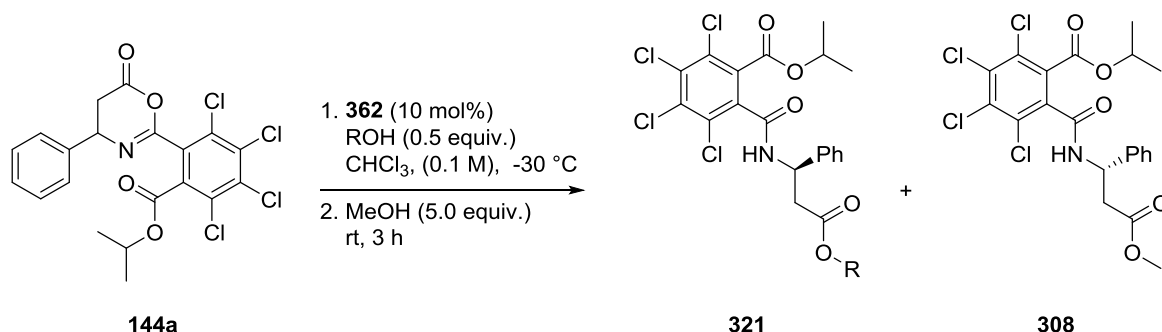


Scheme 2.33 Racemic reactions for expanded alcohol screen

Alcohols **379-381** were next employed in the optimised transformation involving catalyst **362**. The original alcohol **330** remained the optimal for selectivity with $S = 60.1$ (Table 2.7, entry 1). **379** reacted at a slightly slower rate than its structural isomer **330**, whilst also furnishing reduced levels of selectivity ($S = 40.2$, entry 2). Alcohol **380**, which is significantly larger in size, reacted slower still, furnishing only 38% conversion after 60 hours; a large reduction in enantiodiscrimination ($S = 17.2$) was also detected (entry 3). Alcohol **381** failed to react with **144a** in the presence of bifunctional catalyst **362** (entry 4). It was evident that, in the presence of catalyst

362, alcohol **330** offered enhanced levels of enantiocontrol for the KR of **144a**. Moving forward, it would remain our alcohol of choice for the transformation.

Table 2.7 Expanded alcohol screen



Entry	ROH	t (h)	C (%) ^[a]	321 ee (%) ^[b]	308 ee (%) ^[b]	S
1	330	16	49	91	89	60.1
2	379	20	48	88	82	40.2
3	380	60	38	83	50	17.2
4	381	16	0	-	-	-

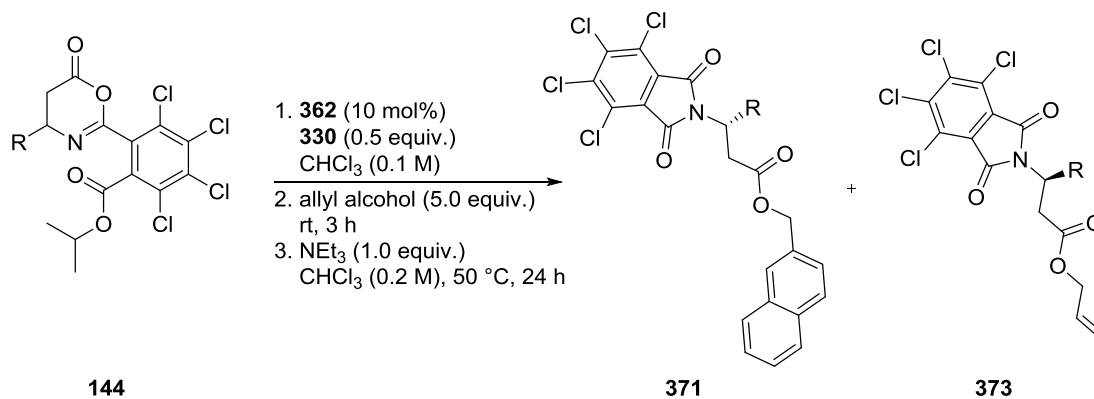
^a The conversion was calculated using Equation 2.1. ^b Determined by CSP-HPLC analysis

In a final effort to improve the selectivity of the reaction, we explored the effects of decreasing the reaction temperature. Previously we had observed that reducing the reaction temperature from room temperature to – 30 °C resulted in a significant enhancement in enantiocontrol. We postulated that a further reduction in temperature could be favourable. It should be noted that temperatures below – 50 °C were not explored in this study as the freezing point of CHCl₃ is – 63.3 °C.²¹²

We began our study with the standard phenyl substituted oxazinone **144a** using reaction temperatures of – 30 °C, – 40 °C and – 50 °C. Gratifyingly, each decrease in temperature afforded a respective increase in the stereospecificity of the catalyst for the substrate, obtaining an impressive result of S = 72.3 at – 50 °C (Table 2.8, entries 1-3). To examine whether this trend was applicable to all oxazinone derivatives, selected examples were chosen from our synthesised library for further evaluation. In the case of substrate **144b** (bearing a *para*-Br substituent on the phenyl ring) each decrease in temperature was associated with an increase in S factor (entries 4-6), thus following the same trend. In contrast, while methyl-substituted **144f** afforded an S factor of 16.2 at – 30 °C it failed to react at temperatures of – 40 °C and – 50 °C (entries 7-9). Furthermore, the isopropyl-substituted **144g** was poorly soluble in CHCl₃ and would only react at room temperature, with reduced selectivity (entries 10-12). Based on these results we concluded that aromatic derivatives of **144** were likely to

react favourably at – 50 °C while the reactivity of aliphatic substituents at lower temperatures was variable.

Table 2.8 **Optimisation of the reaction temperature**



Entry	R	Substrate	T (°C)	T (h)	C (%) ^[a]	371 ee (%) ^[b]	373 ee (%) ^[b]	S
1	C ₆ H ₅	144a	-30	16	49	91	89	60.1
2	C ₆ H ₅	144a	-40	36	51	89	93	69.0
3	C ₆ H ₅	144a	-50	60	51	92	90	72.3
4	4-Br-C ₆ H ₄	144b	-30	16	53	88	99	76.3
5	4-Br-C ₆ H ₄	144b	-40	36	51	91	94	82.5
6	4-Br-C ₆ H ₄	144b	-50	60	52	91	97	93.0
7	Me	144f	-30	70	45	79	64	16.2
8	Me	144f	-40	24	0	-	-	-
9	Me	144f	-50	24	0	-	-	-
10	iPr	144g	-30	24	0	-	-	-
11	iPr	144g	-15	24	0	-	-	-
12	iPr	144g	rt	60	45	65	53	8.2

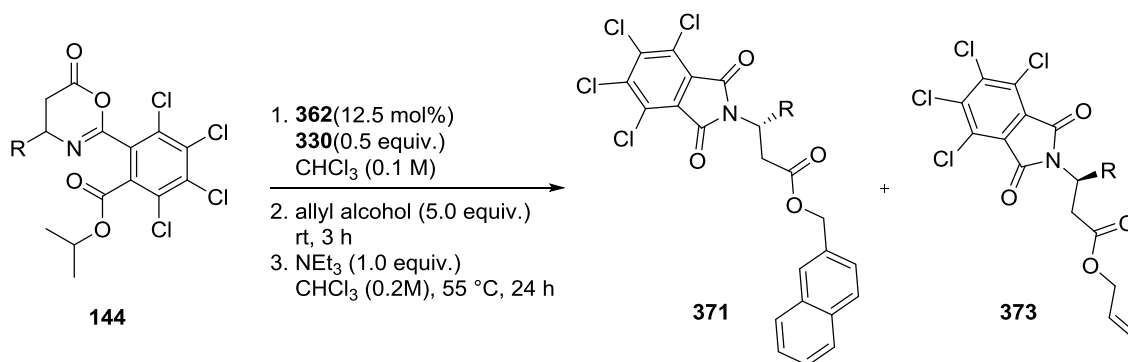
^a The conversion was calculated using Equation 2.1. ^b Determined by CSP-HPLC analysis

2.12 KR of 4-oxazinones to yield enantioenriched and orthogonally protected β_3 amino acids

To the best of our knowledge we had thoroughly explored all reasonable avenues for the optimisation of the reaction conditions to ascertain optimal results for the kinetic resolution of oxazinones of type **144** via alcoholysis. These conditions were employed to the library of TCIC-oxazinones using 12.5 mol % of catalyst **362**. Outstanding selectivity was achieved in reactions employing aryl-oxazinones **144a-e**. An S factor of 84.9 was obtained for the transformation involving phenyl-oxazinone **144a** (Table 2.9, entry 1). Even higher levels of enantiocontrol were observed for KR of substrates bearing *para*- (**144b**) and *meta*- (**144c**) electron withdrawing bromine substituents on the aryl ring. S factors of 94.2 and 100.7 were afforded for the respective reactions (entries 2 and 3). Though the catalyst

brought about slightly reduced levels of enantiodiscrimination for the reactions involving substrates **144d** and **144e**, bearing electron donating *para*-methoxy and *meta*-methoxy aryl substituents, excellent control was still exhibited in each case (entries 4 and 5). Reactions involving oxazinones **144f** and **144h** (containing aliphatic side chains) were carried out at an optimised temperature of –30 °C to afford the corresponding products **371** and **373** in high yields, obtaining *S* factors of 23.4 and 23.7 for the respective transformations (entries 6 and 7). Although these results are significantly lower than those obtained for their aryl oxazinone counterparts, it is necessary to point out that kinetic resolutions with *S* values of higher than 10 are considered to be synthetically useful whilst those above 50 are deemed outstanding.¹⁶ As previously highlighted, oxazinone **144g** demonstrated poor solubility in CHCl₃, and as a result the kinetic resolution was carried out at room temperature to afford a value of *S* = 8.9 for the process (entry 8).

Table 2.9 The KR of oxazinones of type **144** via alcoholysis using catalyst **362**



Entry	R	Substrate	T (°C)	t (h)	C (%) ^[a]	371 ee (%) ^[b]	373 ee (%) ^[b]	<i>S</i>
1	C ₆ H ₅	144a	-50	60	48	94	86	84.9
2	4-Br-C ₆ H ₄	144b	-50	60	49	94	91	94.2
3	3-Br-C ₆ H ₄	144c	-50	60	51	92	97	100.7
4	4-OMe-C ₆ H ₄	144d	-50	60	51	90	94	64.7
5	3-OMe-C ₆ H ₄	144e	-50	60	51	88	89	45.7
6	Me	144f	-30	63	49	82	77	23.4
7	<i>i</i> Bu	144h	-30	63	43	85	63	23.7
8	<i>i</i> Pr	144g	r.t	60	44	68	54	8.9

^a The conversion was calculated using Equation 2.1. ^b Determined by CSP-HPLC analysis.

2.13 Stereochemical rationale

X-ray diffraction analysis of a recrystallised sample of enantioenriched **371b** was carried out by Dr. Brendan Twamley and the absolute stereochemistry of the compound was assigned as (*R*) (Figure 2.4, See Appendix).

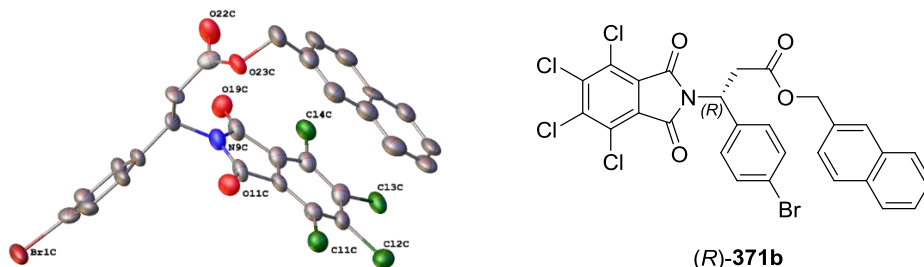


Figure 2.4 Absolute configuration of **371b**

A DFT computational study was carried out by Dr. Cristina Trujillo in order to provide mechanistic insights into the reaction. Based on observations made in the literature in relation to azlactone DKR by alcoholysis, it was assumed that the reaction proceeds *via* a ‘general-catalysis’ type mechanism in which the oxazinone substrate is bound and anchored by the catalyst *via* bifurcated hydrogen bond donation of the squaramide N-H units to the carbonyl oxygen. Meanwhile, the alcohol pronucleophile is activated towards nucleophilic attack by quinuclidine moiety of the catalyst *via* hydrogen bond donation of the hydroxyl group.

The study found that the catalyst was likely to bind the oxazinone such that the bulky TCIC-subunit (R^2) is orientated towards the quinuclidine unit of the catalyst as depicted in Figure 2.5. The opposite arrangement (where the TCIC subunit is pointed away from the catalyst) was also explored however the corresponding energy profile was found to be much higher energy.

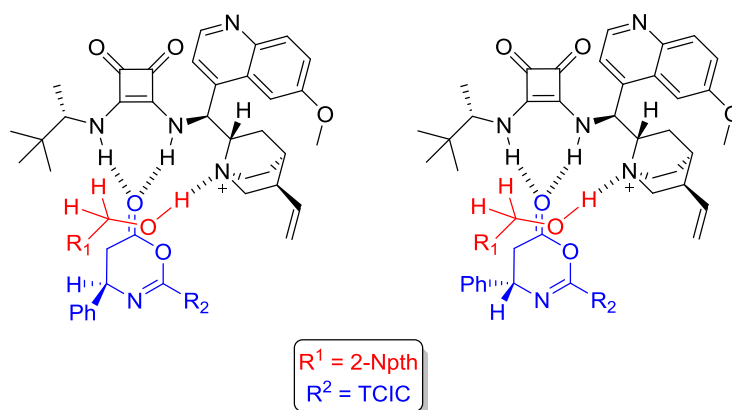


Figure 2.5 Pre-TS assembly complex leading to the *R* and *S* enantiomers

The calculations for the KR process revealed that, in the presence of catalyst **362**, nucleophilic attack of the alcohol on the oxazinone was likely to occur such that the *R* enantiomer would be obtained as

the major product. From an energetic perspective, the transition state leading to the *R* enantiomer (*R*-TS) is 19.0 kJ mol⁻¹ lower in energy than the corresponding *S*-TS. The overall energy profile for the *R* product is more favourable, thereby agreeing with the absolute stereochemistry obtained for the crystal structure (Figure 2.6).

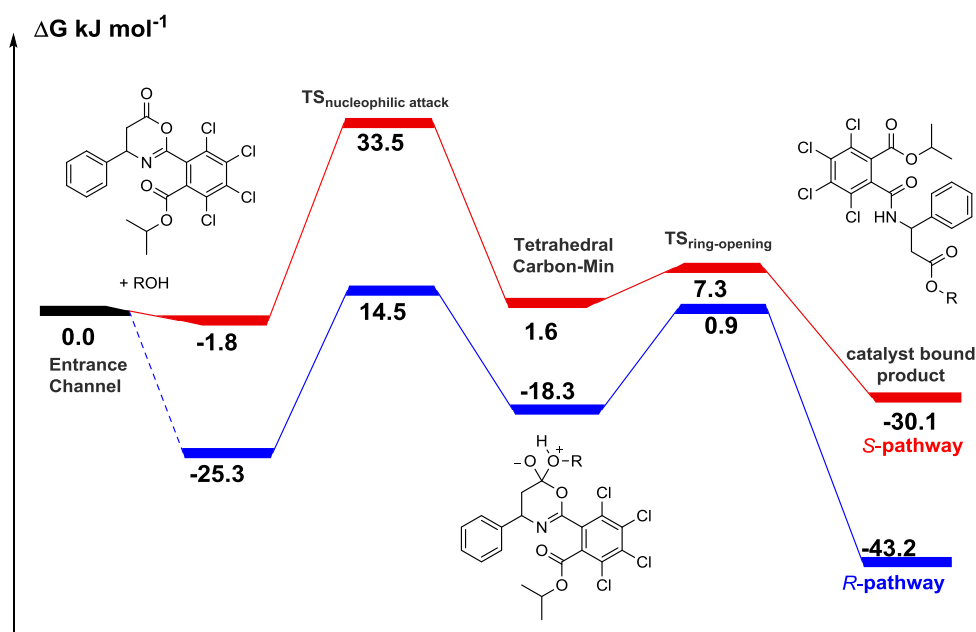


Figure 2.6 Energy profile for the two enantiomers *R* and *S*

2.14 KR of 5-oxazinones to access enantioenriched β^2 -amino acids

In order to access β^2 -amino acids using this methodology, the synthesis of 5-substituted amino acids such as **382** was required (Figure 2.7). As the literature precedent for the development of an organocatalytic protocol for the KR of traditional 5-substituted oxazinones was unsuccessful,¹¹³ we postulated that the introduction of the bulky TCIC-subunit could possibly enhance enantiocontrol as well as providing access to the orthogonally protected amino acid product. Following our success in the development of a procedure for the KR of 4-substituted TCIC oxazinones *via* alcoholysis (by which *S* > 100 was obtained), we envisaged using a similar methodology in the case of molecules such as **382** (Figure 2.7).

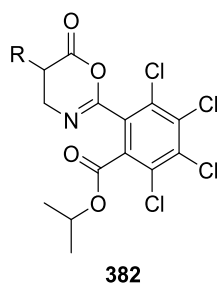
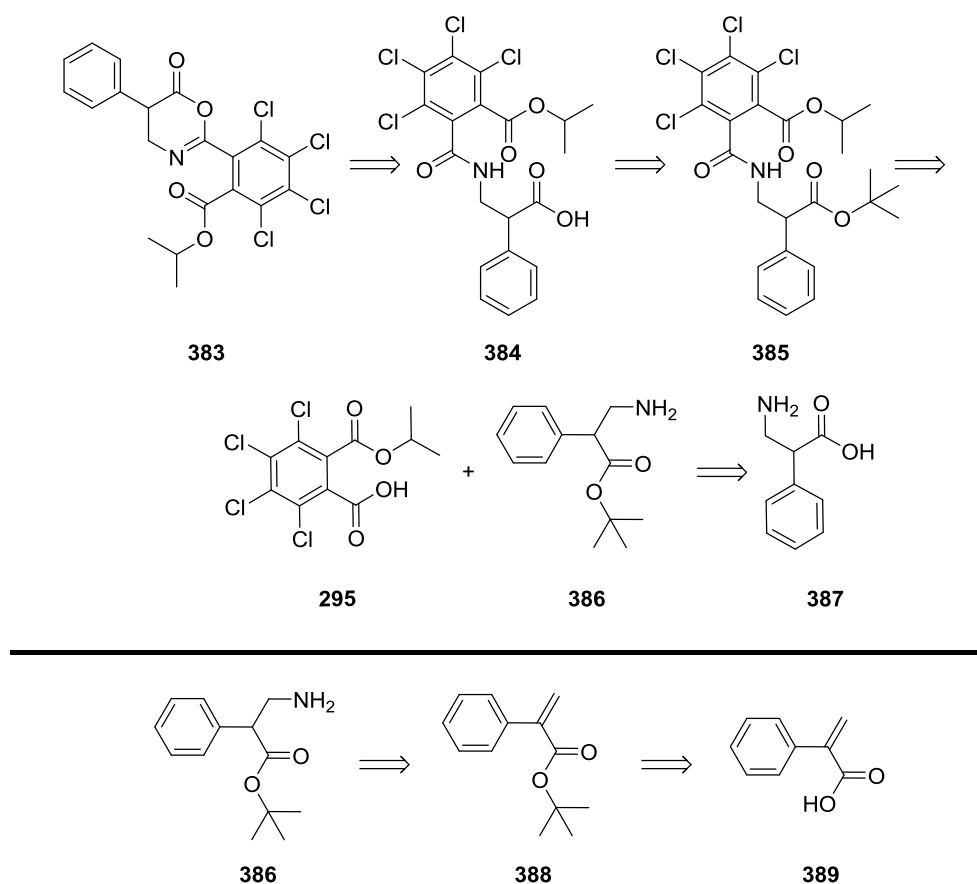


Figure 2.7 General structure of 5-substituted TCIC oxazinones

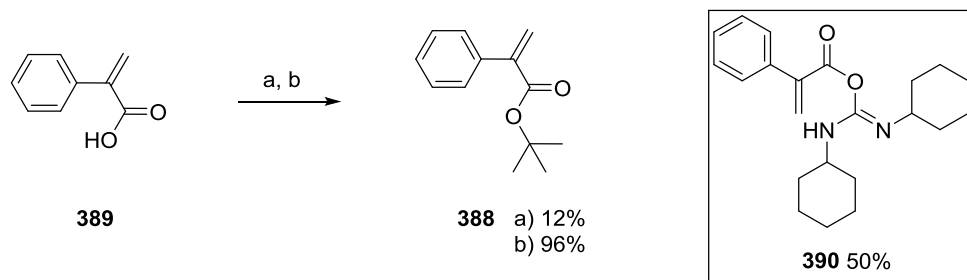
2.15 The design and synthesis of the TCIC-substituted 5-oxazinones

It was forecast that the synthesis of TCIC-substituted 5-oxazinones such as **383** could be carried out similarly to the route established for 4-oxazinones of type **144**. Retrosynthetic analysis of target compound **383** showed that the main challenge arose in accessing the initial β^2 -amino acid **386**. It was envisaged that **386** could be obtained *via* a Michael-type Addition to the corresponding acrylate **388**. The acrylic acid precursor **389** was inexpensive and commercially available (Scheme 2.34).



Scheme 2.34 Retrosynthetic analysis of **383**

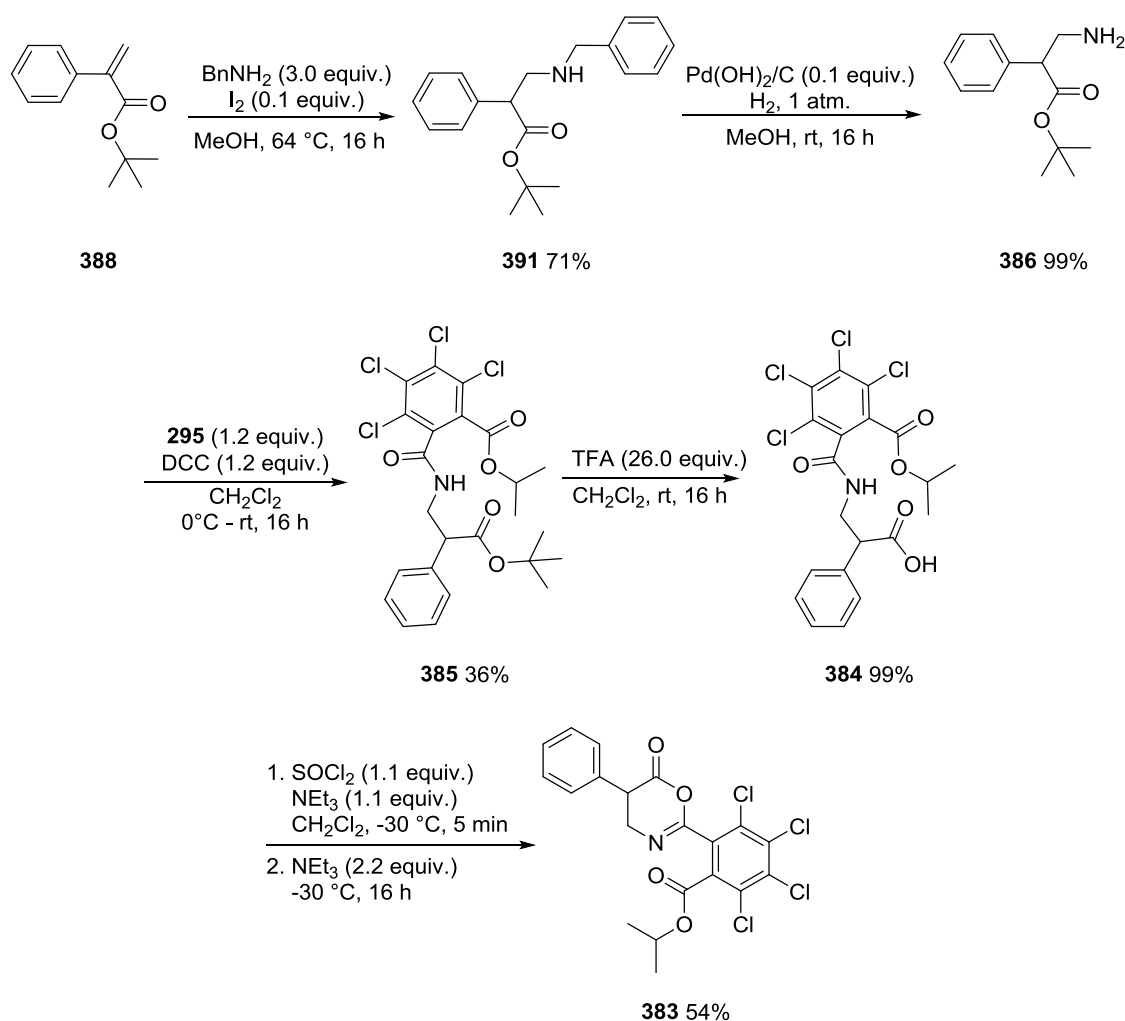
An initial attempt at protecting **389** as the *tert*-butyl ester **388** via Steglich esterification was unsuccessful, affording only a 12% yield for **388** (Scheme 2.35). The major product of the reaction was the intermediate **390**, which was reasoned to be too sterically encumbered for efficient nucleophilic attack of the DMAP catalyst on the acyl centre, an essential step in the esterification mechanism. Gratifyingly, synthesis of **388** was achieved *via* the anhydride using DMAP as a transesterification catalyst with (Boc)₂O to furnish the *tert*-butyl ester in high yield.



a) DCC (1.1 equiv.), DMAP (0.4 equiv.), *t*-BuOH (4.0 equiv.), CH₂Cl₂ (0.5 M).
 b) (Boc)₂O (1.5 equiv.), NEt₃ (1.0 equiv.), DMAP (0.4 equiv.), CH₂Cl₂ (0.5 M).

Scheme 2.35 Synthesis of **388**

388 was transformed into **386** in a two-step procedure involving the Michael addition of benzyl amine to afford **391**. Following this, **391** was subjected to hydrogenolysis conditions in order to selectively cleave the benzyl protecting group in quantitative yield to render desired product **386**. (Scheme 2.36).



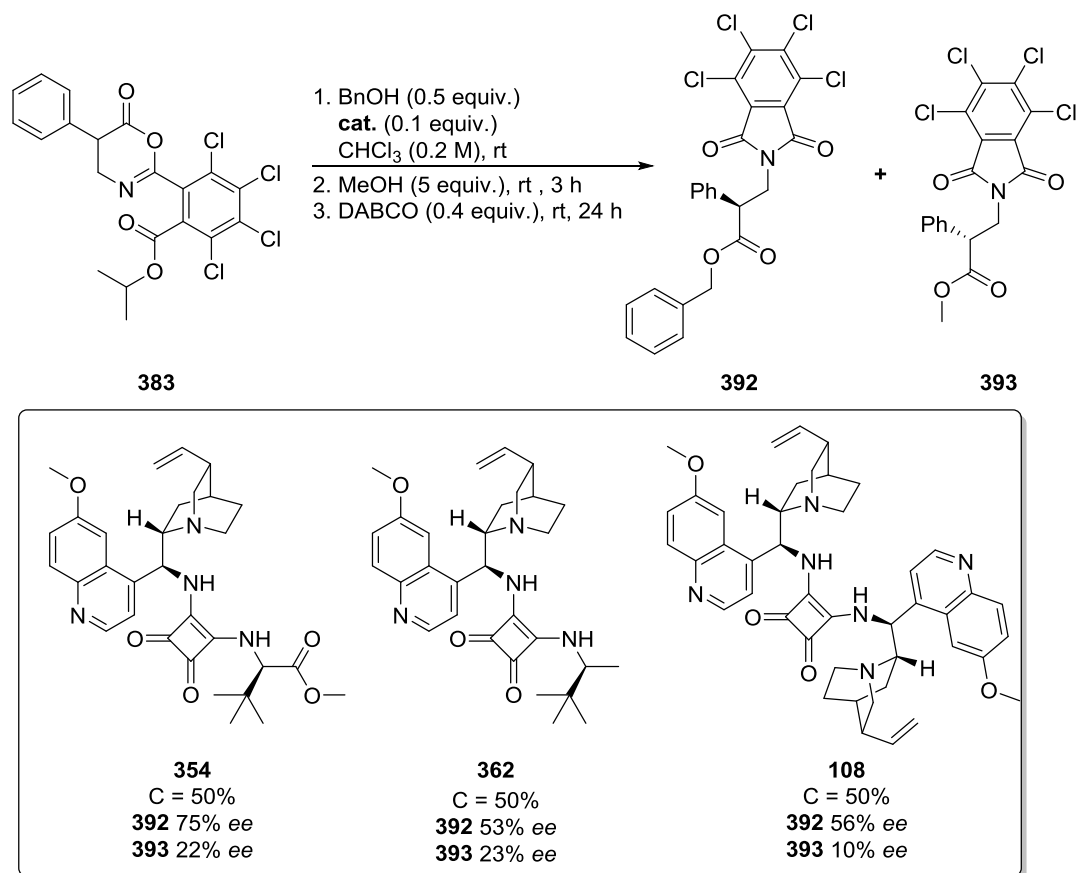
Scheme 2.36 Synthesis of **386**

Now that *tert*-butyl amino acid ester **386** was in hand, we envisaged its transformation into oxazinone **383** would follow the same methodology employed for the synthesis of TCIC-substituted 4-oxazinones (Scheme 2.36). Free amine **386** was coupled to **295** to using DCC. *tert*-Butyl ester cleavage of the resulting compound **385** rendered carboxylic acid **384** in quantitative yield. Intramolecular ring closure of **384** *via* the acid chloride was carried out in the usual manner, though extended reaction times were required to obtain full conversion. **383** was obtained with an overall yield of 13.5 % for the synthesis.

2.16 Preliminary evaluation of oxazinone **383** for KR by alcoholysis

With the TCIC-substituted 5-oxazinone **383** in hand, we commenced with investigations into its performance in the organocatalysed kinetic resolution *via* alcoholysis. Three of the best performing catalysts (**354**, **362** and **108**) from our previous study involving TCIC-substituted 4-oxazinones (**144**) were selected and employed in the initial evaluation of the process (Scheme 2.37). The results obtained for these reactions were surprising. In theory, at 50% conversion the enantiomeric composition of the product and the starting material of a kinetic resolution should mirror each other.

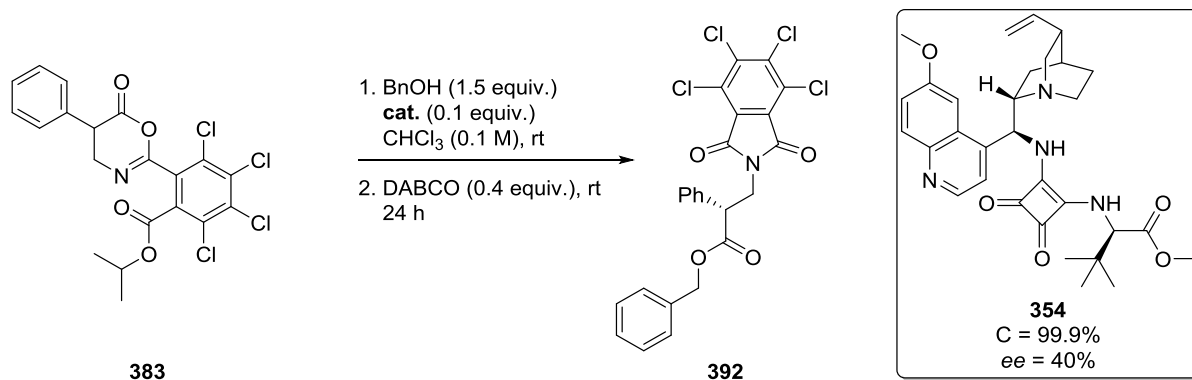
In these reactions however, the *ee* obtained for the products **392** and **393** were not in agreement. Catalyst **354** afforded the benzyl ester product in 75% *ee* at 50% conversion while the methyl ester was obtained in 22% *ee*. Similarly, catalyst **362** furnished the respective products in 53% and 23 % *ee*. The same discrepancy in results was observed using catalyst **108** (56% and 10% *ee* respectively).



Scheme 2.37 Initial KR experiments using **383** as a substrate

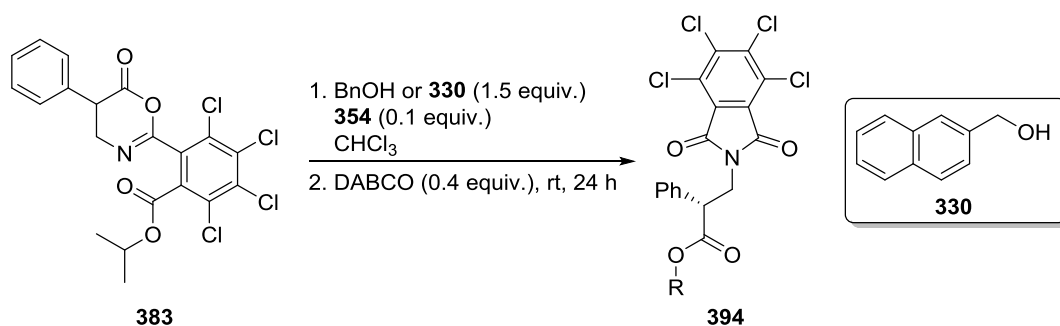
We postulated that DKR was occurring concurrently. It was plausible that the α -proton of substrate **383** was sufficiently acidic to undergo racemisation in the presence of a base; this would certainly explain the mismatched results of the KR experiments. To test our hypothesis, substrate **383** was subjected to DKR conditions using catalyst **354** and excess BnOH (Scheme 2.38). The product **392** was obtained in 40% *ee* thus confirming that **383** is a candidate for DKR; if the substrate was not susceptible to DKR, an *ee* of 0% would have been obtained for the reaction. We were surprised by the apparent reactivity of **383** as a substrate for DKR; previous work by Berkessel *et al.* in the

organocatalytic KR of 5-substituted oxazinones did not report the same observation however, in some cases the *ee* obtained for the second product of the KR reaction were omitted.¹¹³



Scheme 2.38 Preliminary evaluation of **383** for DKR *via* alcoholysis

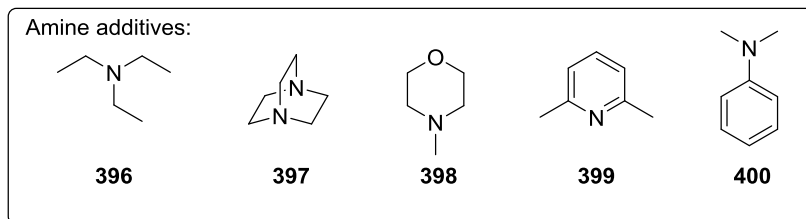
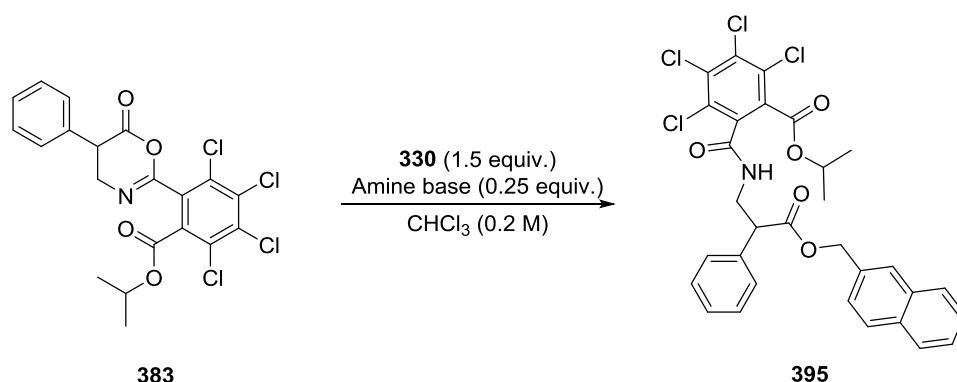
We decided to further explore the DKR of **383** *via* alcoholysis. We commenced the study by decreasing the concentration of the reaction from 0.2 M to 0.1 M. This afforded an increase in the *ee* of the product from 40% to 55%. We hypothesised that the associated increase in reaction time for nucleophilic attack of the alcohol on the oxazinone provided enhanced opportunity for racemisation of the oxazinone substrate (Table 2.10, entries 1 and 2). A concentration of 0.1 M was found to be optimum for DKR; further decreases in concentration offered negligible improvements in enantiocontrol (entry 3). Next we explored the effects of varying the temperature of the reaction on DKR. **383** was insoluble in CHCl₃ at – 30 °C and failed to react under the reaction conditions (entry 4). Increasing the temperature to 0 °C furnished the product with decreased enantiocontrol and longer reaction times (entry 5). The exchange of benzyl alcohol as the nucleophile for 2-naphthylmethanol (**330**) was favourable for DKR furnishing the product with an *ee* of 59% (entry 6). The same reaction was carried out at 0 °C with a concomitant decrease in enantioselectivity thus confirming that low temperatures have a negative impact on DKR (entry 7). Gently warming the reaction to 40 °C was also unfavourable for enantiocontrol (entry 8). We concluded that room temperature reactions at 0.1 M concentration using **330** as the nucleophile were favourable conditions for DKR affording the product in near quantitative yield and moderate enantioselectivity.

Table 2.10 Probing the reaction condition to encourage DKR

Entry	Alcohol	T (°C)	t (h)	Conc. (M)	Conv. (%) ^[a]	ee (%) ^[b]
1	BnOH	rt	48	0.2	99.9	40
2	BnOH	rt	60	0.1	99.9	55
3	BnOH	rt	75	0.7	99.9	56
4	BnOH	-30	48	0.1	0	-
5	BnOH	0	96	0.1	99.9	39
6	330	rt	60	0.1	99.9	59
7	330	0	96	0.1	99.9	22
8	330	40	30	0.1	99.9	44

^aConversion of the substrate was measured via ^1H NMR spectroscopic analysis with 4-iodoanisole (0.5 equiv.) as an internal standard. ^bDetermined by CSP-HPLC analysis.

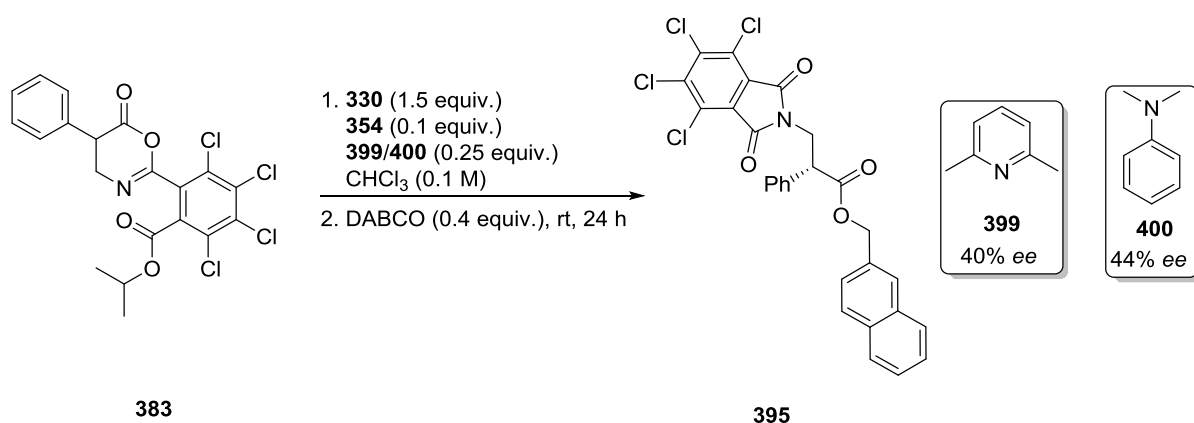
Prompted by the work of Berkessel *et al.*,¹¹⁵ we considered the use of a base additive in the reaction to encourage racemisation of the starting material and improve DKR. However it was important that the base additive did not also catalyse the racemic alcoholysis of **383**, thereby resulting in an overall decrease in the *ee* obtained for the product. A series of control reactions were carried out using a range of amine bases of varying pK_a to test for background alcoholysis. As expected, in the absence of any amine catalyst no conversion to the product **395** was observed after 18 hours (Table 2.11, entry 1). The introduction of NEt_3 (0.25 equiv.) to the reaction furnished the product in quantitative yield after only 18 hours (entry 2). The same result was observed using DABCO (**397**) as a catalyst (entry 3). Encouragingly, catalyst **398** ($\text{pK}_\text{a}\text{H} = 7.38$) afforded only a 10% conversion of the starting material after 18 h (entry 4). Amines **399** ($\text{pK}_\text{a}\text{H} = 6.75$) and **400** ($\text{pK}_\text{a}\text{H} = 5.20$) were next employed;²⁰⁹ to our delight, no conversion of **383** was observed in these reactions (entries 5 and 6).

Table 2.11 Testing for background alcoholysis of **383** with various amine bases

Entry	Base	pK _a H ²⁰⁹	t (h)	Conv. (%) ^[a]
1	-	-	18	0
2	369	10.75	18	100
3	397	8.82	18	100
4	398	7.38	18	10
5	399	6.75	18	0
6	400	5.20	18	0

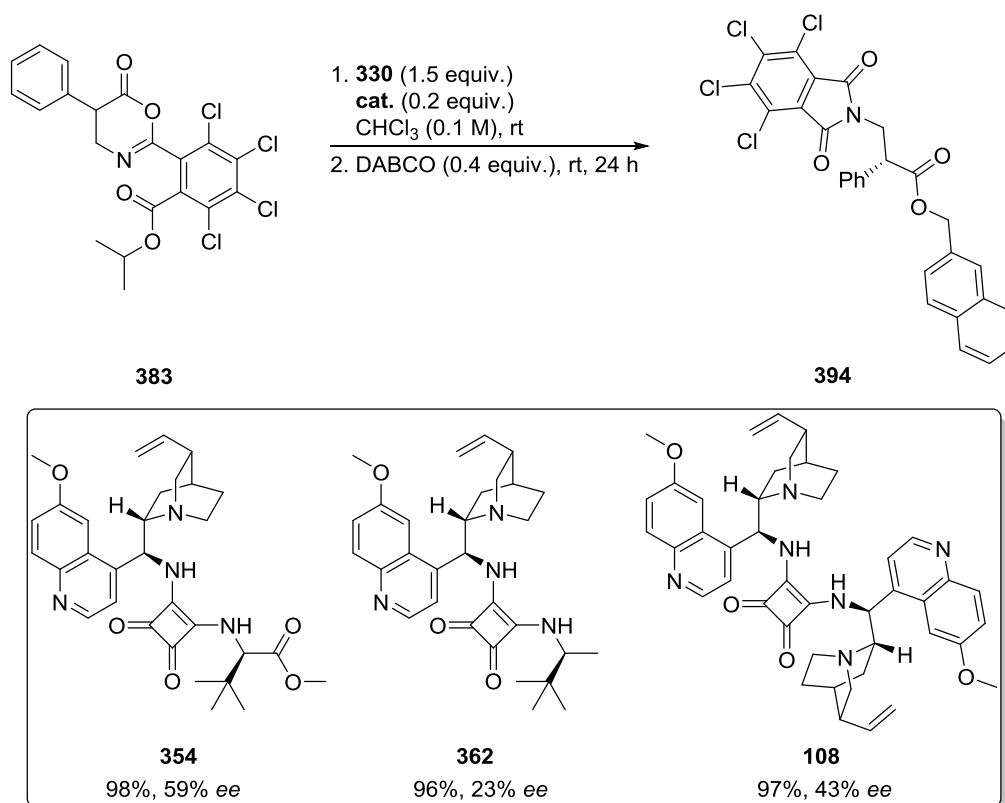
^aConversion of the substrate was measured *via* ¹H NMR spectroscopic analysis with 4-iodoanisole (0.5 equiv.) as an internal standard.

Following this, amines **399** and **400** were employed as base additives in the optimised DKR reaction. (Scheme 2.39). To our disappointment not only did the additives fail to sufficiently encourage racemisation of **383** for enhanced DKR, they also demonstrated a negative impact on enantiocontrol; furnishing the product with reduced *ee* of 40% and 44% for their respective reactions; perhaps in the presence of bifunctional catalyst **354**, bases **399** and **400** are sufficiently basic to catalyse the background alcoholysis of **383**. Thus, it was concluded that the use of an amine base additive was unsuitable for the organocatalytic DKR process.



Scheme 2.39 Use of base additives **399** and **400** in the DKR of **383** via alcoholysis

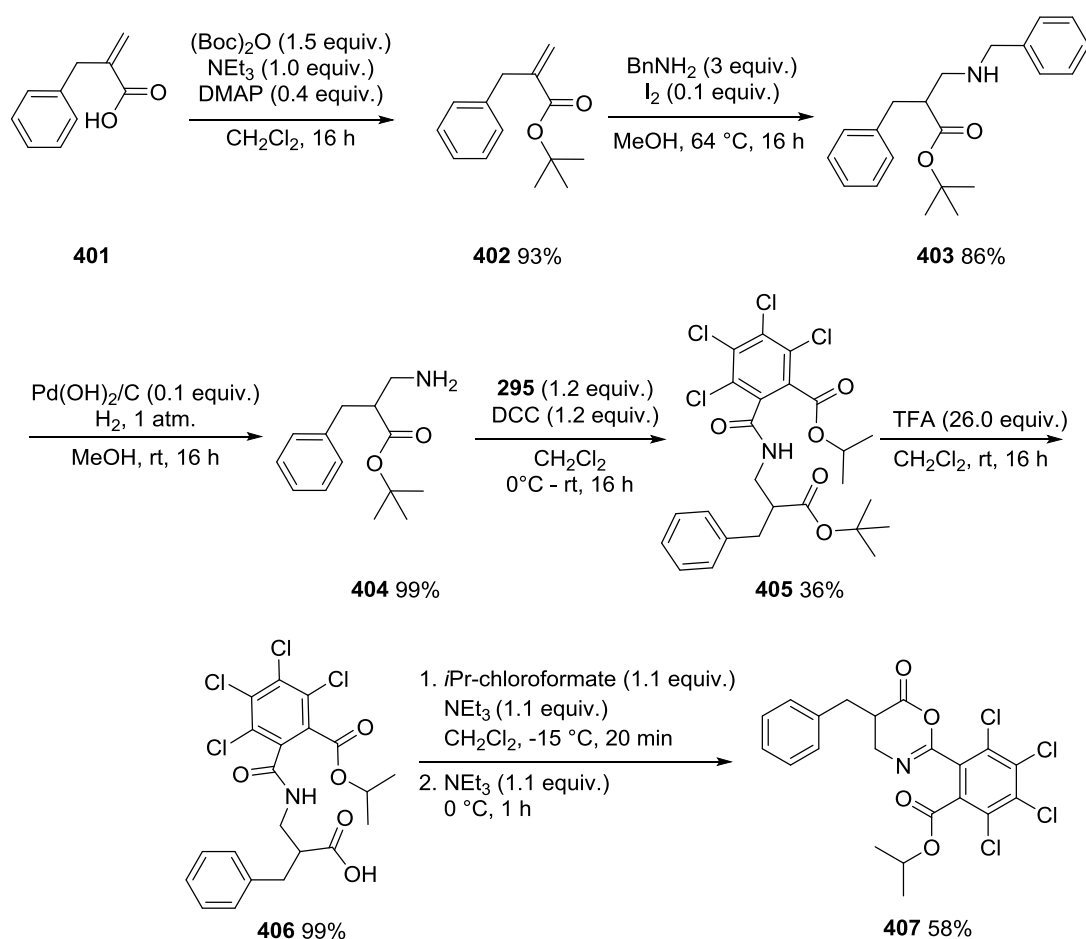
After a thorough investigation, we had determined the optimum reaction conditions for the DKR of **383** via alcoholysis. Using catalyst **354** under these conditions, the product **394** was obtained in 59% ee (Scheme 2.40). Catalysts **362** and **108** were re-evaluated under the optimised DKR reaction conditions to furnish product ee of 23% and 43% for the respective reactions. As such, it was concluded that **354** promoted the most enantioselective reaction.



Scheme 2.40 Re-evaluation of **354**, **362** and **108** in the optimised DKR of **383**

2.17 Controlling KR vs DKR

Having pushed the boundaries of the DKR of TCIC-substituted 5-oxazinones, we wanted to gain control over the KR of these molecules. We proposed that a reduction in the acidity of the α -proton of oxazinone **383** should prevent racemisation of the chiral centre as the alcoholysis reaction proceeds, in the presence of a bifunctional catalyst. We hypothesised that switching the aryl substituent at the 5-position of **383** for an alkyl substituent should sufficiently decrease the acidity of the neighbouring α -proton, to facilitate KR rather than DKR. Aliphatic derivative **407** was synthesised in 16% overall yield starting from benzyl acrylic acid (**401**). The intramolecular ring closure of carboxylic acid **406** to oxazinone **407** was achieved *via* an acid anhydride intermediate as **407** could not be sufficiently purified using the usual methodology (*via* the acid chloride intermediate).

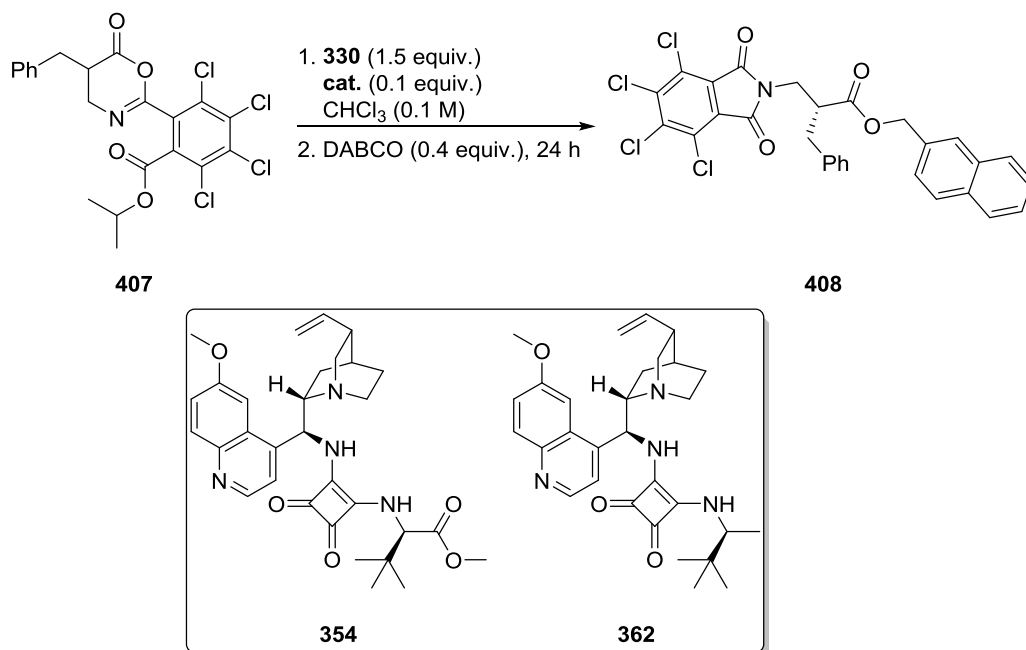


Scheme 2.41 Synthesis of **407**

Substrate **407** was tested for DKR *via* alcoholysis at room temperature in the presence of catalysts **354** and **362**. Contrary to our predictions, DKR was observed in both cases furnishing the product **408** in 17% and 9% *ee*, respectively (Table 2.12, entries 1 and 2). During our exploration into the DKR of **383** *via* alcoholysis, we noted that DKR was reduced at lower temperatures. We decided to

repeat the same reactions at $-50\text{ }^{\circ}\text{C}$ to try and eradicate background DKR. In the case of the reaction catalysed by **354**, the reduction in temperature still furnished the product in 13% *ee* (entry 3). At $-50\text{ }^{\circ}\text{C}$ in the presence of catalyst **362**, the reaction exhibited low levels of DKR, obtaining an *ee* of 3% for the product **408** (entry 4).

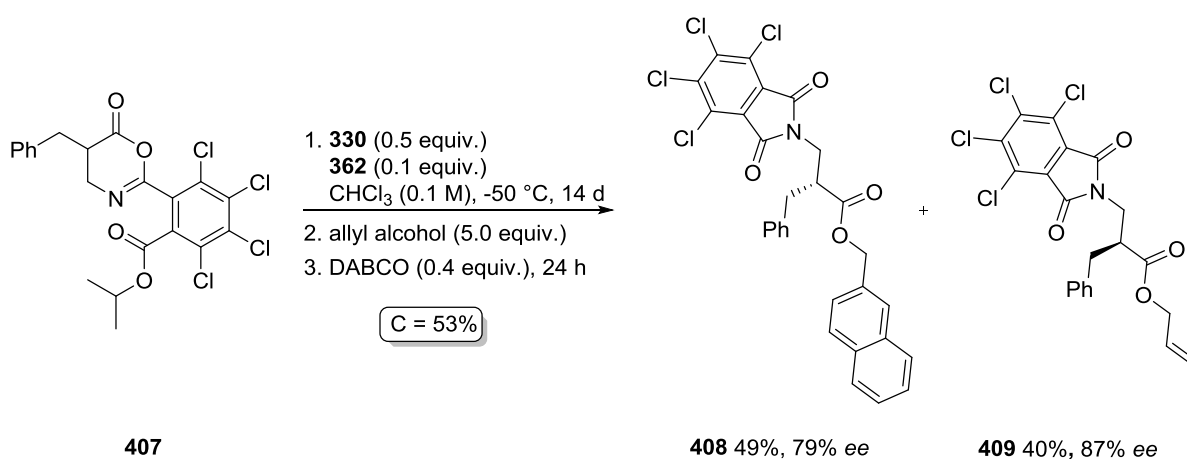
Table 2.12 Testing for DKR in substrate **407**



Entry	Cat.	T (°C)	t (d)	Conv. (%) ^[a]	ee (%) ^[b]
1	354	rt	3	99.9	17
2	354	rt	3	99.9	9
3	362	-50	14	99.9	13
4	362	-50	14	99.9	3

^aConversion of the substrate was measured via ¹H NMR spectroscopic analysis with 4-iodoanisole (0.5 equiv.) as an internal standard. ^bDetermined by CSP-HPLC analysis.

Encouraged by the reduced levels of DKR observed at low temperatures, we employed catalyst **362** in the KR of **407** *via* alcoholysis using optimised reaction conditions which included a temperature of $-50\text{ }^{\circ}\text{C}$ (Scheme 2.42). The reaction was slow, taking 14 days to reach 50% conversion at which point excess allyl alcohol was used to quench the remaining starting material at room temperature. Product **408** was obtained in 79% *ee* while **409** was afforded 87% *ee*.



Scheme 2.42 The KR of **407** using catalyst **362** under optimised conditions

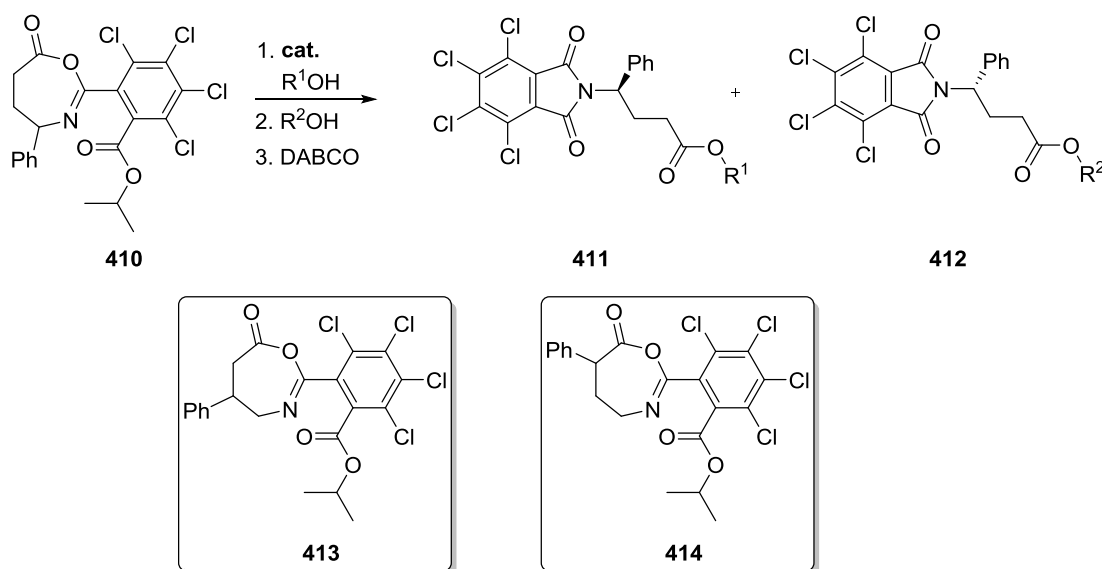
2.18 Conclusion

We have successfully developed a novel methodology for the KR of TCIC-substituted 4-oxazinones *via* alcoholysis, to yield enantioenriched and orthogonally protected β^3 -amino acids; obtaining outstanding *S* factors of up to 101 for this process. Not only does this approach offer significantly enhanced selectivity over the literature precedent, it also represents the first strategy involving the KR of oxazinones which renders synthetically useful *bis*-protected amino acid products; all other methodologies furnish the benzoyl amide product which lack synthetic utility. We have also developed the first organocatalytic protocol for the DKR of TCIC-substituted 5-oxazinones enabling access to chiral, orthogonally protected β^2 -amino acids such as **395** (which was obtained in 59% *ee* demonstrating modest levels of enantiocontrol). Lastly, we have shown that we can promote the KR of TCIC-substituted 5-oxazinones over DKR with careful tuning of the reaction conditions. In this manner product **408** was obtained in 79% *ee* at 53% conversion. The *S* factor for this process was not calculated as the study showed that 3% DKR occurs in the background.

3 The KR of 7-membered rings via alcoholysis to furnish γ -amino acids products

3.1 Premise

Prompted by our work on the KR of TCIC-oxazinones, we decided to investigate if we could apply the same principles to access enantioenriched γ -amino acids. This would require the synthesis of 7-membered rings such as **410** (Scheme 3.1) which would be resolved by ring opening alcoholysis using a chiral organocatalyst, followed by *in situ* phthalimide formation to furnish enantioenriched and orthogonally protected γ -amino acid products (**411** and **412**). No such methodology currently exists in the literature, despite numerous examples of enantioselective ring opening alcoholysis for accessing both α - and β - amino acids.^{110, 213} Furthermore, we recognised the potential to extend the methodology to substrates such as **413** and **414** (in which the position of the chiral centre is moved around the ring), thus enabling access to a wide range of γ -amino acid products.



Scheme 3.1 Premise for γ -amino acid resolution

3.2 The importance of γ -amino acids

γ -Amino acids represent an extremely important group of biologically active compounds in the mammalian central nervous system (CNS).²¹⁴ γ -Amino butyric acid (GABA, **415**, Figure 3.1) is a major inhibitory neurotransmitter and its deficiency in the mammalian CNS has been linked with several neurological disorders including Parkinson's disease, Huntington's disease and epilepsy to name but a few.^{215, 216} The synthesis of GABA derivatives possessing enhanced lipophilicity to facilitate crossing the blood brain barrier is the focal point for the research into the treatment of many neurological disorders.²¹⁷⁻²¹⁹ Pregabalin (**416**) is a potent anticonvulsant which acts as a GABAergic agonist *via* the (*S*)-enantiomer (Figure 3.1).^{220, 221}

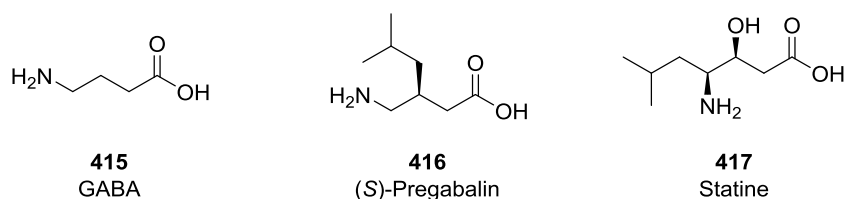


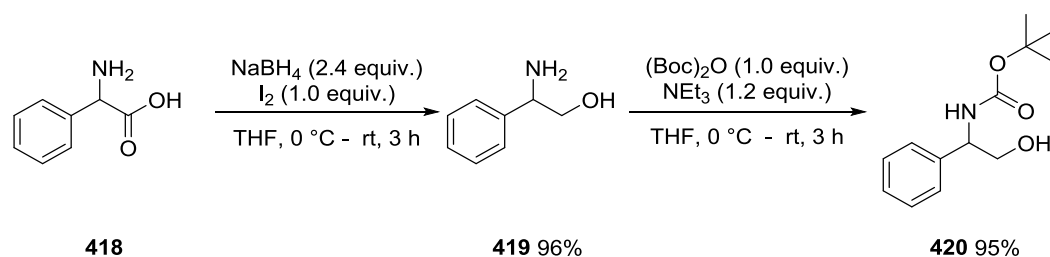
Figure 3.1 Important γ -amino acids GABA (**415**) (S)-Pregabalin (**416**) and Statine (**417**)

Statine (**417**) (Figure 3.1) is an essential component of the natural hexapeptide antibiotic pepstatine which inhibits aspartic acid protease, an enzyme crucial to the onset and proliferation of many disease including AIDS, malaria and Alzheimer's disease.²²²⁻²²⁵

Enantiomerically pure γ -amino acids can also provide access to γ -lactams, δ -amino alcohols and α -substituted pyrrolidines – important building blocks for a wide variety of natural products.^{226, 227} Despite the huge value in the generation γ -amino acids for the synthesis of natural products and pharmaceutical agents, the stereoselective synthesis of these compounds still presents a major challenge.

3.3 The design of the novel TCIC-7-membered rings

Retrosynthetic analysis of **410** proposed a similar synthetic route to that used for the synthesis of TCIC-oxazinones in Section 2.2. The main challenge was predicted to lie with the synthesis of the initial racemic γ -amino acid; those which were commercially available were too expensive for practical purposes. Thus, the development of a reliable route to access the γ -amino acid core was the first port of call. Previously, Gopi *et al.* synthesised γ -amino acid esters from the corresponding α -amino acids,²²⁸ though the target phenylglycine equivalent was not offered as an example. Nonetheless, the chemistry appeared to be robust and we began with the reduction of DL-phenylglycine (**418**) to the corresponding amino alcohol **419** using NaBH₄ and I₂ (Scheme 3.2). Boc-protection of the free amine was carried out to furnish **420** in high yield.

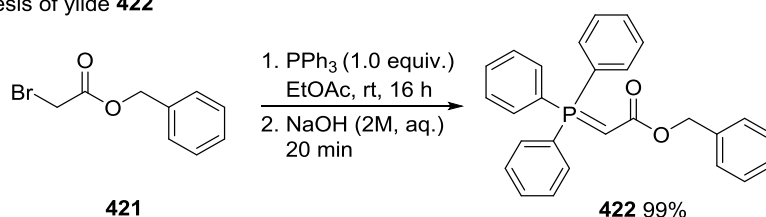


Scheme 3.2 Synthesis of **420**

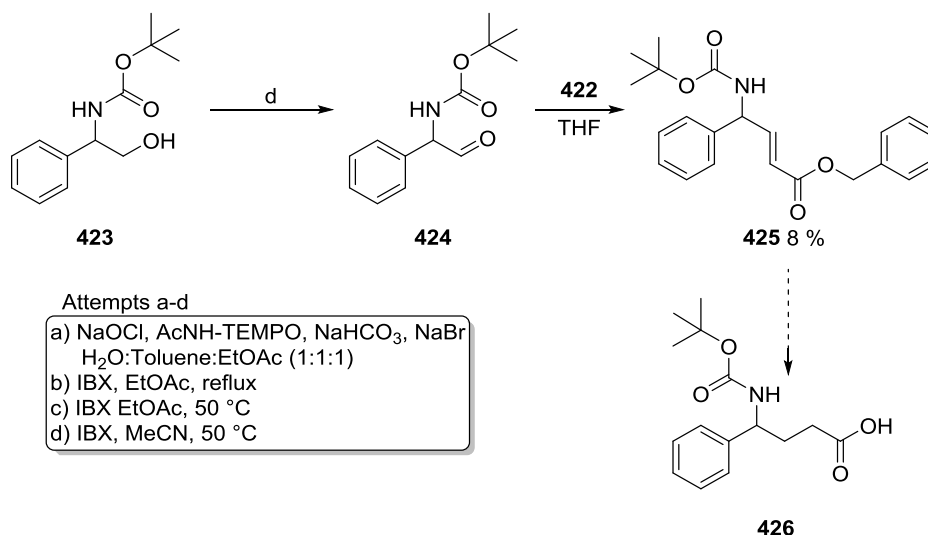
It was envisaged that the alcohol (**420**) could be oxidised to the aldehyde (**424**) followed by Wittig reaction with **422**. Hydrogenation of the Wittig product **425** would furnish the desired *N*-Boc protected γ -amino acid **426**. While the ylide **422** was synthesised easily from benzyl bromoacetate (**421**), issues arose in the synthesis of aldehyde **424**. Initial attempts at using Anelli's oxidation

afforded only 50% conversion to the desired product **424**. As Anelli's oxidation (using AcNH-TEMPO) is carried out in a biphasic system, we postulated that the hydrophilic character of **420** was likely to have hindered the reaction: as oxidation occurs in the organic phase, the substrate must present in high concentrations for efficient oxidation to occur. Instead, an oxidation using IBX was attempted as an alternative. It was found that heating the amino alcohol to reflux in dry EtOAc with IBX for 1 hour furnished the aldehyde product **424**, but also resulted in partial oxidation to the carboxylic acid which catalysed the undesired cleavage of the *N*-Boc protecting group under the given reaction conditions. It was clear that milder conditions were required. The oxidation was repeated at a lower temperature of 50 °C but the reaction proceeded slowly, presumably due to the poorly solubility of IBX in EtOAc at this temperature.²²⁹ Changing the reaction solvent to MeCN resulted in the clean and complete conversion to aldehyde **424** at 50 °C in 4 hours. **420** was immediately employed in a Wittig reaction with **422**, however a reaction yield of only 8% was obtained for the product, isolated from a very complex crude mixture (Scheme 3.3). It was reasoned that aldehyde **424** was too hindered for efficient olefination with the already congested ylide **422**. An alternative route to access the γ -amino acid core was required.

A: synthesis of ylide **422**

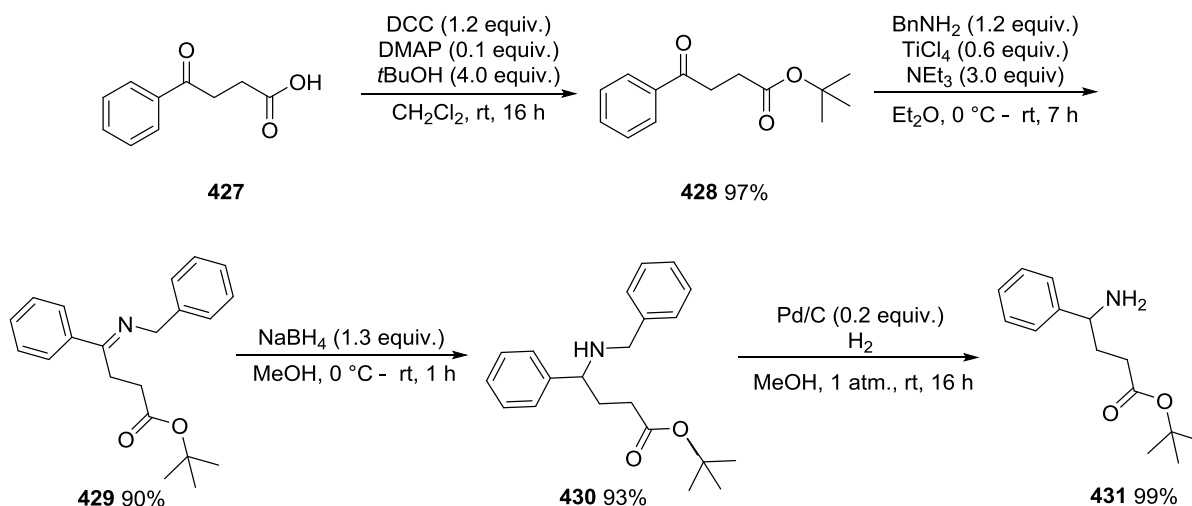


B: synthesis of **425**



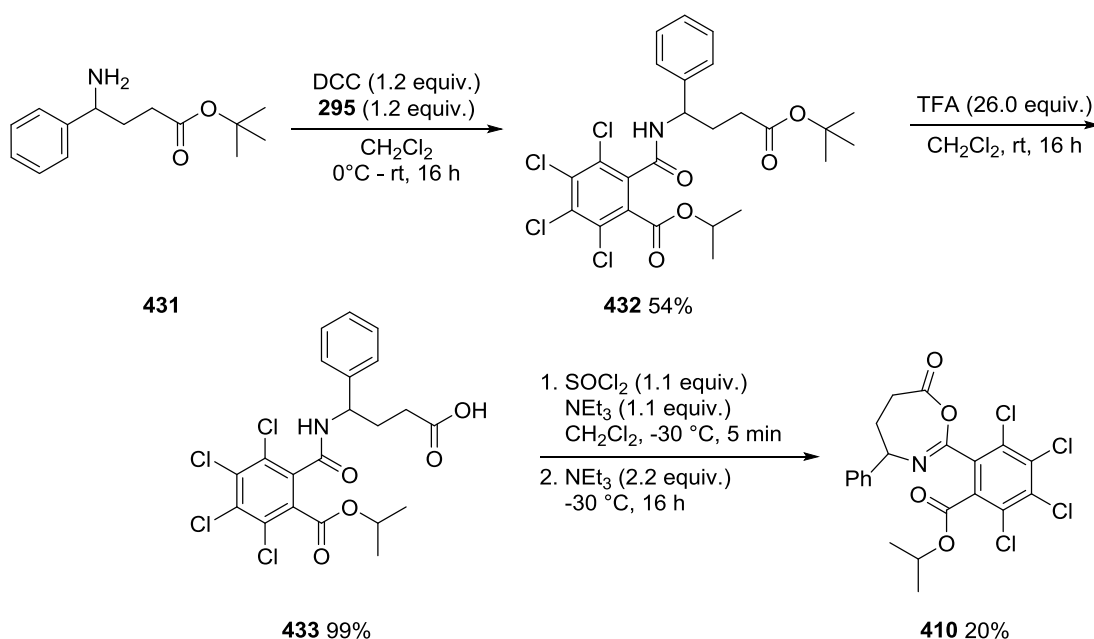
Scheme 3.3 Synthesis of ylide **422** (A) and subsequent Wittig reaction to form **425**

We devised a new route starting from carboxylic acid **427**. The first step involved protection of the carboxylic acid moiety as the *tert*-butyl ester via a Steglich esterification, which was achieved in 97% yield (Scheme 3.4). The resulting compound was reacted with benzyl amine in the presence of TiCl₄ under basic conditions to furnish imine **429**; both the *cis* and *trans* imine **429** were obtained. The selective reduction of the imine component of **429** to the amine **430** (while maintaining the *tert*-butyl ester moiety) was achieved using NaBH₄. Subsequent cleavage of the benzyl protecting group via hydrogenolysis rendered the free amine **431** in quantitative yield (Scheme 3.4).



Scheme 3.4 Synthesis of **431** from **427**

With γ -amino acid ester **431** in hand, we envisioned its transformation into **410** to follow a similar route to that which was developed for the TCIC-oxazinones (Section 2.2). A DCC coupling of amine **431** to **295** furnished compound **432** in moderate yield (54%, Scheme 3.5). Treatment of **432** with TFA rendered carboxylic acid **433** quantitatively. A subsequent intramolecular ring closure of **433** to form **410** was achieved in the usual manner via the acid chloride furnishing the isolated product in 20% yield.

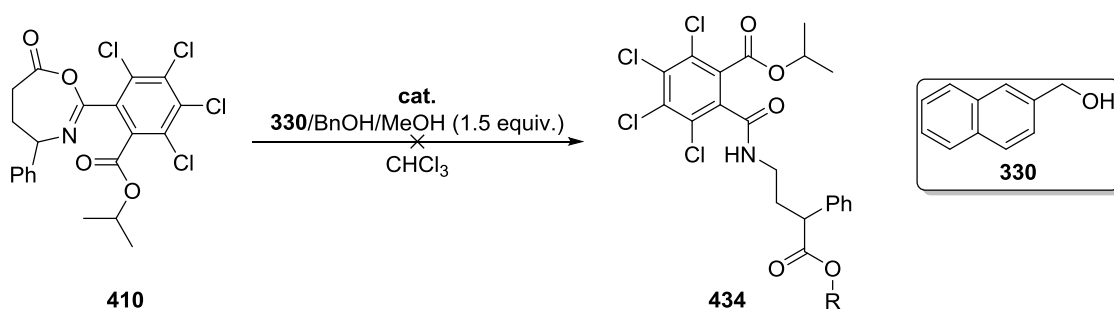


Scheme 3.5 Synthesis of **410**

3.4 Evaluation of **410** for ring opening alcoholysis

In order to investigate the reactivity of **410** towards ring opening alcoholysis, a number of racemic reactions were carried out under varying conditions. The initial evaluation employed DIPEA (20 mol%) to catalyse the addition of alcohol **330** to **410**; however, no conversion to the product **434** was observed (Table 3.1, entry 1). The use of stoichiometric base afforded the same result, as did refluxing conditions with catalytic DIPEA (entries 2 and 3). It was hypothesised that the steric bulk of the alcohol nucleophile may be hindering activity. BnOH and MeOH were subsequently employed as nucleophiles in the reaction, however, **410** remained inert to the reaction conditions in both cases (entries 3 and 4). A final attempt employing bifunctional catalyst **354** was carried out to investigate whether bifunctional activation was required for reactivity. To our disappointment, 0% conversion of **410** was observed (entry 5).

Table 3.1 Evaluation of ring opening alcoholysis of **410**



Entry	cat.	ROH	T (°C)	Conv. (%) ^[a]
1	DIPEA (0.2 equiv.)	330	rt	0
2	DIPEA (1.0 equiv.)	330	rt	0
3	DIPEA (0.2 equiv.)	330	reflux	0
4	DIPEA (0.2 equiv.)	BnOH	rt	0
5	DIPEA (0.2 equiv.)	MeOH	rt	0
6	354 (0.2 equiv.)	330	rt	0

^aConversion of the substrate was measured *via* ¹H NMR spectroscopic analysis using 4-iodoanisole as an internal standard.

3.5 Conclusion

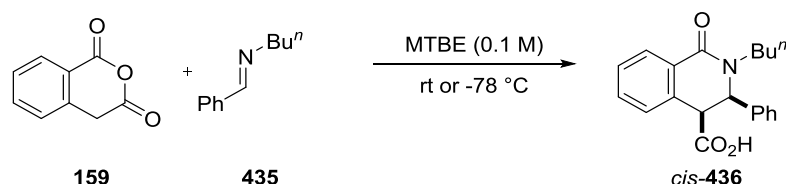
A route to access molecules such as **410** (the ring expanded homoanalogues of TCIC-oxazinones **144**) has been established. However, the organocatalytic alcoholysis of these novel structures has yet to be achieved. Several attempts were made to promote the catalytic ring opening of **410** using DIPEA and bifunctional catalyst **354**, yet, **410** remained inert to alcoholysis. It is evident that **410** possess' enhanced stability compared to its TCIC-oxazinone and TCIC-azlactone counterparts. Future investigations could potentially explore the use of catalysts such as TBAF which we have found to be extremely efficient in the of ring opening of TCIC-oxazinones.

4 Formal cycloaddition reactions of cyclic anhydrides with imines

4.1 Preamble

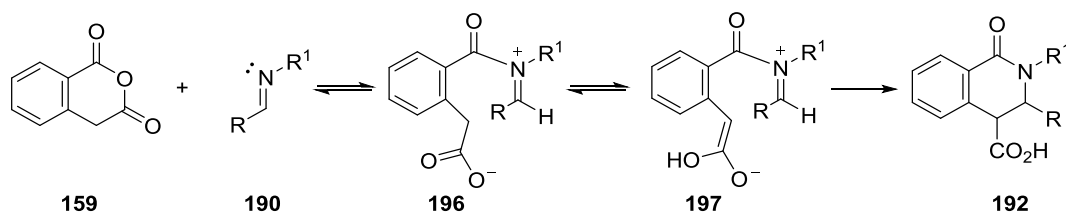
Carbon-carbon bond forming reactions with anhydrides can provide access to a wide range of structures. In 1969, Castagnoli reported that lactams, important structural motifs found in many natural and biologically important compounds, could be formed by heating a mixture of an anhydride and an imine.¹³⁷ In recent years, both Shaw *et al.* and Nair *et al.* have independently worked on multi-component coupling reactions involving anhydrides, carbonyl compounds and amines for the synthesis of γ - and δ - lactams.^{117, 230} Despite the obvious advantages in generating these valuable lactam products asymmetrically, until recently no catalytic, enantioselective variant of this reaction was available in the literature.

Following previous success in our research group in the development of catalytic, asymmetric cycloadditions of enolisable anhydrides with both aldehydes and ketones,^{125, 128} we proposed the use of bifunctional *cinchona* alkaloid-based organocatalysts to promote the reaction between anhydrides and imines to generate chiral lactams. However, initial experimentation by my colleague Dr. C. Cornaggia revealed that a background reaction between homophthalic anhydride **159** and imine **435** proceeded at both room temperature and -78 °C in the absence of catalyst (Scheme 4.1). As such, before we could develop an asymmetric variant of the reaction, it was necessary to devise a method to control this background reaction.



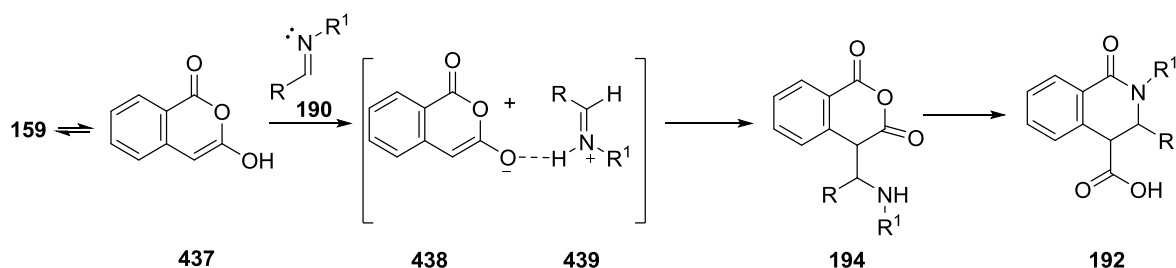
Scheme 4.1 Formal cycloaddition between homophthalic anhydride (**159**) and imine **435**

As discussed in the introduction, the mechanism of the cycloaddition between enolisable anhydrides and imines has been under dispute. Initially, the reaction was believed to proceed *via* an iminolysis mechanism, proposed by Cushman,^{140, 142} in which the nitrogen atom of imine **190** carries out nucleophilic attack on anhydride **159** to yield the Zwitterion intermediate **196** (Scheme 4.2). Subsequent tautomerisation to **197** prepares the molecule for an intramolecular Mannich reaction to furnish lactam **192**.



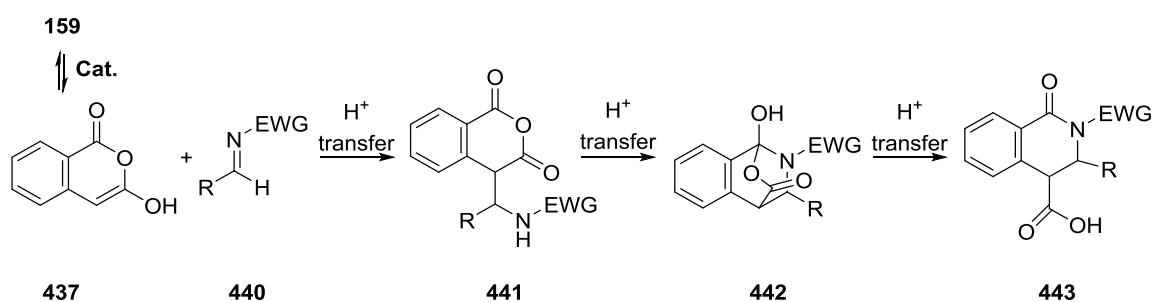
Scheme 4.2 Iminolysis mechanism for the cycloaddition of **159** and **190** proposed by Cushman

However, recent computational studies carried out by Shaw *et al.* have shown that the reaction is likely to proceed *via* a stepwise mechanism in which iminium ion **439** is formed as a result of proton transfer between enol **437** and imine **190** (Scheme 4.3).²³¹ Intermolecular Mannich reaction between **438** and **439** generates **194** which undergoes intramolecular cyclisation of the amine to the anhydride to afford lactam product **192**. It should be noted that only highly acidic anhydrides were compatible with this study.



Scheme 4.3 Mannich-acylation pathway between **159** and **190** proposed by Shaw

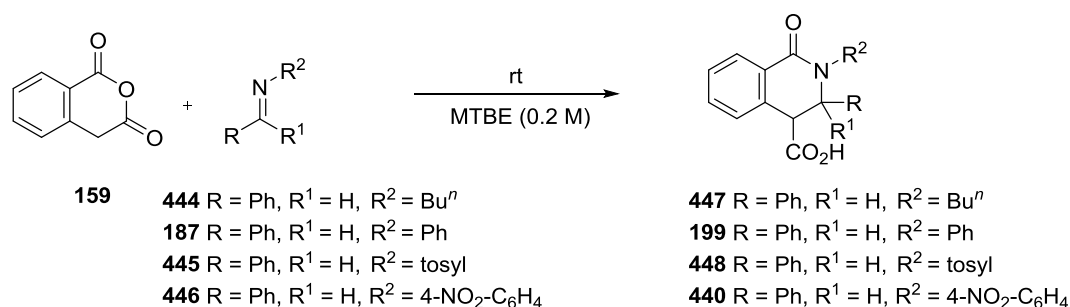
We reasoned that reducing the basic/nucleophilic character of imine **190** would help us to control the aforementioned, uncatalysed pathways. The placement of an electron withdrawing substituents on the imine nitrogen atom should render the imine less nucleophilic, while amplifying the electrophilicity of the carbon centre. In doing this, we believed that it would force the reaction to proceed *via* a third mechanism which, though reported by Cushman, was deemed improbable in the same report using standard imines **190**.¹⁴² Provided the imine was rendered sufficiently electrophilic, we hypothesised that enol **162** would carry out nucleophilic attack on imine **440** to form amine **441** (Scheme 4.4). Intramolecular cyclisation of amine **441** would then occur to generate the desired lactam product **443** *via* **442**. We envisaged that bifunctional *cinchona* alkaloid-based catalysts would promote the keto-enol tautomerisation of the anhydride *via* general-base catalysis, while the reaction between the enol and imine could potentially be assisted by general acid catalysis to form the amine intermediate **441** in a controlled chiral environment. Subsequent cyclisation and tautomerisations would furnish the chiral lactam product.



Scheme 4.4 Proposed mechanism for the cycloaddition between **159** and electrophilic imine **440**

Our colleagues, Dr. E. Torrente De Haro and Dr. C. Cornaggia worked on the identification of a suitable imine substituent which would sufficiently dampen the basicity of the imine nitrogen such that no background reaction would occur with homophthalic anhydride **159** in the absence of a catalyst. A range of imines were synthesised and assessed for uncatalysed reaction with **159** (Table 4.1).

Table 4.1 Background activity between homophthalic anhydride and various imines



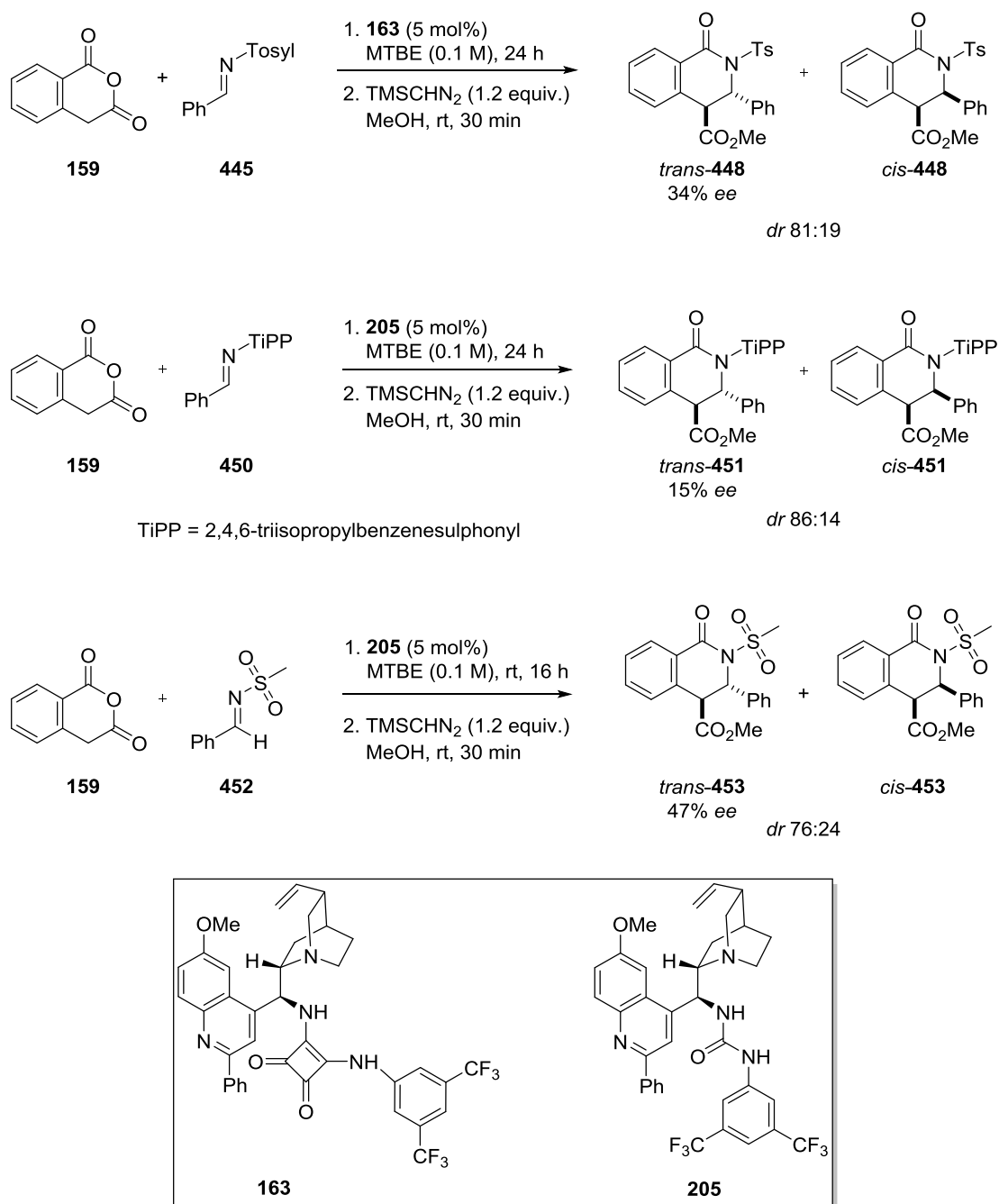
tosyl = *p*-toluene sulphonyl

Entry	Imine	t (h)	Lactam	Yield (%) ^[a]
1	444	2	447	62
2	187	4	199	39
3	445	24	448	0
4	446	24	440	0

^aDetermined via ¹H NMR spectroscopic analysis.

As expected, the electrophilic component of the imine was the determinant as to whether a reaction would occur in the absence of a catalyst. Simple *n*-butylimine (**444**) afforded a 62% background reaction after only two hours (Table 4.1, entry 1). Introduction of an electron-withdrawing phenyl substituent slowed down the formation of the lactam product, though a significant background reaction was still evident (entry 2). Further decreasing the basicity/nucleophilicity of the amine

through use of electron withdrawing sulfonyl groups completely dampened the basicity/nucleophilicity of imines **445** and **446** and hence, no lactam formation was observed (entries 3 and 4) in the absence of catalyst.



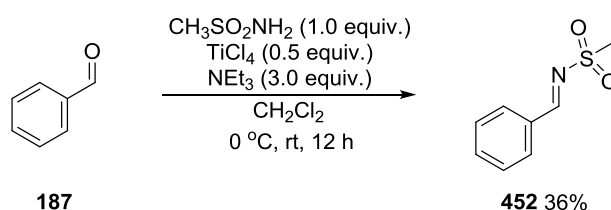
Scheme 4.5 Representative examples from the work carried out by colleagues Dr. E. Torrente De Haro, Dr. C. Cornaggia and Dr. S. Gundala

Our colleagues Dr. E. Torrente De Haro, Dr. C. Cornaggia and Dr. S. Gundala carried out the initial experiments which showed that reactions between homophthalic anhydride and electrophilic imines (e.g. **445**) could in fact be promoted by bifunctional *cinchona* alkaloid based catalysts (Scheme 4.5).

Although good yields and diastereomeric ratios were obtained for the products, the reactions exhibited low levels of enantiocontrol. The reaction between *N*-tosyl imine and homophthalic anhydride in the presence of **163** procured an encouraging dr of 81:19 (*trans*:*cis*) while furnishing the *trans*-lactam **448** in 34% *ee*. This work also found that augmentation of the steric bulk on the imine *N*-substituent had a deleterious effect on enantiocontrol. The reaction between imine **450**, which possessed the largest *N*-sulfonyl group, and homophthalic anhydride in the presence of **205** afforded the *trans*-lactam **451** in 15% *ee* with a diastereomeric ratio of 86:14 *trans*:*cis*. In the case of the smallest, non-acidic *N*-sulfonyl imine **452** a higher *ee* of 47% was obtained using catalyst **205** for the *trans*-lactam product **453** though a lower diastereomeric ratio was observed (76:24 *trans*:*cis*). Moving forward, *N*-sulfonyl imine **452** would be used for reaction optimisation as the reactions involving this imine obtained the lactam product with the highest *ee*.

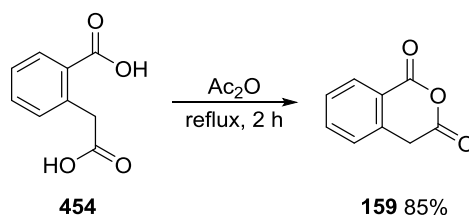
4.2 Preliminary experiments

We began our investigation with the synthesis of the chosen *N*-sulfonyl imine **452**. This was easily synthesised from benzaldehyde (**155**) and methanesulfonamide in the presence of TiCl₄. The resulting imine was purified by recrystallisation to furnish imine **452** in a 36% yield (Scheme 4.6).



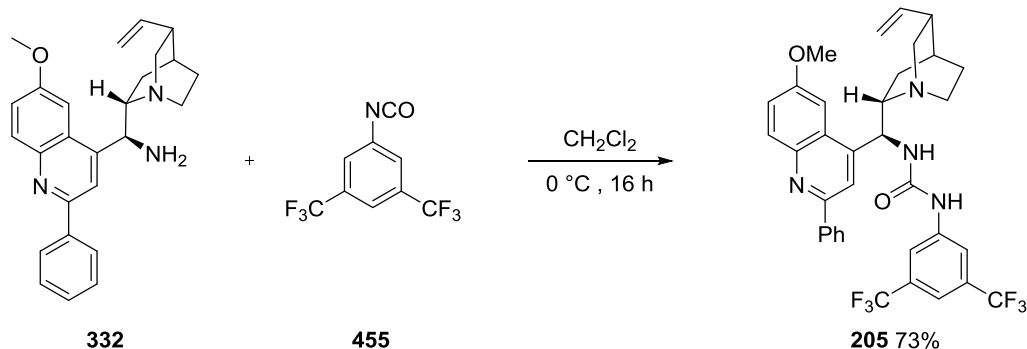
Scheme 4.6 Synthesis of imine **452**

Homophthalic anhydride (**159**) was prepared by heating commercially available homophthalic acid under reflux in acetic anhydride followed by trituration in Et₂O to furnish the product in 85% yield (Scheme 4.7).



Scheme 4.7 Synthesis of homophthalic anhydride (**159**)

Based on the previous work outlined in Section 4.1, we decided that it was prudent to synthesis a large stock of catalyst **205**, to further study the catalysis reaction. Quinine derivative **332** was prepared using the procedure reported in Scheme 2.19, and was stirred with **455** for 16 hours to furnish catalyst **205** with an isolated yield of 73% (Scheme 4.8).

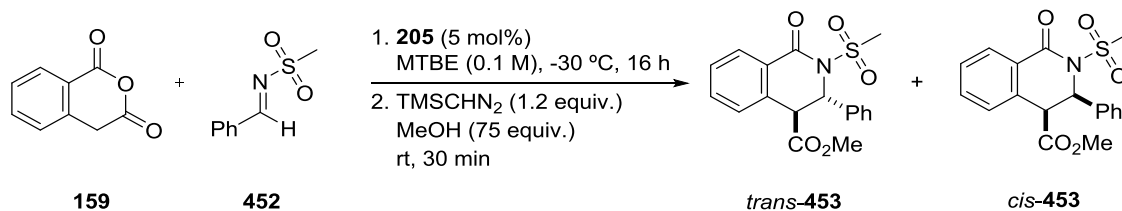


Scheme 4.8 Synthesis of catalyst **205**

4.3 Optimisation of the esterification protocol

A set of standard reaction conditions had already been developed for the bifunctional *cinchona* alkaloid catalysed cycloaddition reactions between enolisable anhydrides and aldehydes and ketones.^{125, 128} The conditions involve low temperature reactions in 0.1 M MTBE, followed by *in situ* esterification of the products at room temperature using trimethylsilyldiazomethane (TMSCHN₂) and methanol. Functionalisation of the carboxylic acid product as the methyl ester enables efficient purification of the reaction mixture *via* silica chromatography and analysis of the product using CSP-HPLC.

The reaction promoted by catalyst **205** between homophthalic anhydride and imine **452** was carried out at -30 °C using the standard reaction conditions for both the catalytic and esterification process (Scheme 4.9). However, reproducibility issues with regards to both yield and *ee* became apparent. The diastereomeric ratio, which was determined using ¹H NMR spectroscopy prior to the esterification step, was consistent across several initial reactions. The yields which determined by ¹H NMR spectroscopic analysis after the esterification reaction, however, were not reflective of this dr, and significantly varied between the reactions; as did the enantiomeric excess. It was evident that epimerisation in favour of *trans*-**453** was occurring under the esterification conditions.

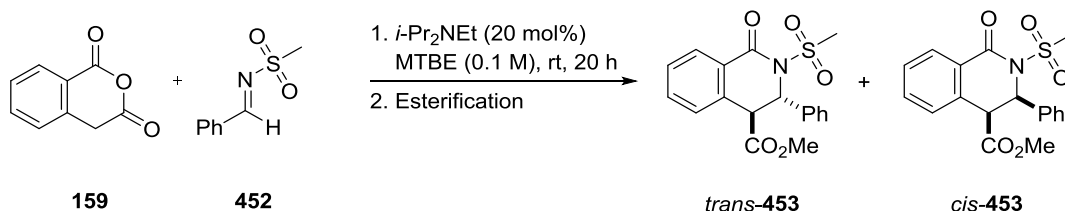


Scheme 4.9 Cycloaddition reaction between **159** and **452** catalysed by **205** followed by derivatisation using TMSCHN₂ and MeOH.

The racemic reaction was also evaluated using DIPEA (20 mol%) as a catalyst. The dr of the products was recorded both before and after methylation using ¹H NMR spectroscopic analysis. Once again, the results were inconsistent and in favour of the *trans* isomer. A number of different esterification

conditions (Table 4.2) were employed to try and eradicate the issue. As before, epimerisation was monitored by comparing the diastereomeric ratios obtained by ^1H NMR spectroscopy both before and after the esterification.

Table 4.2 Epimerisation study



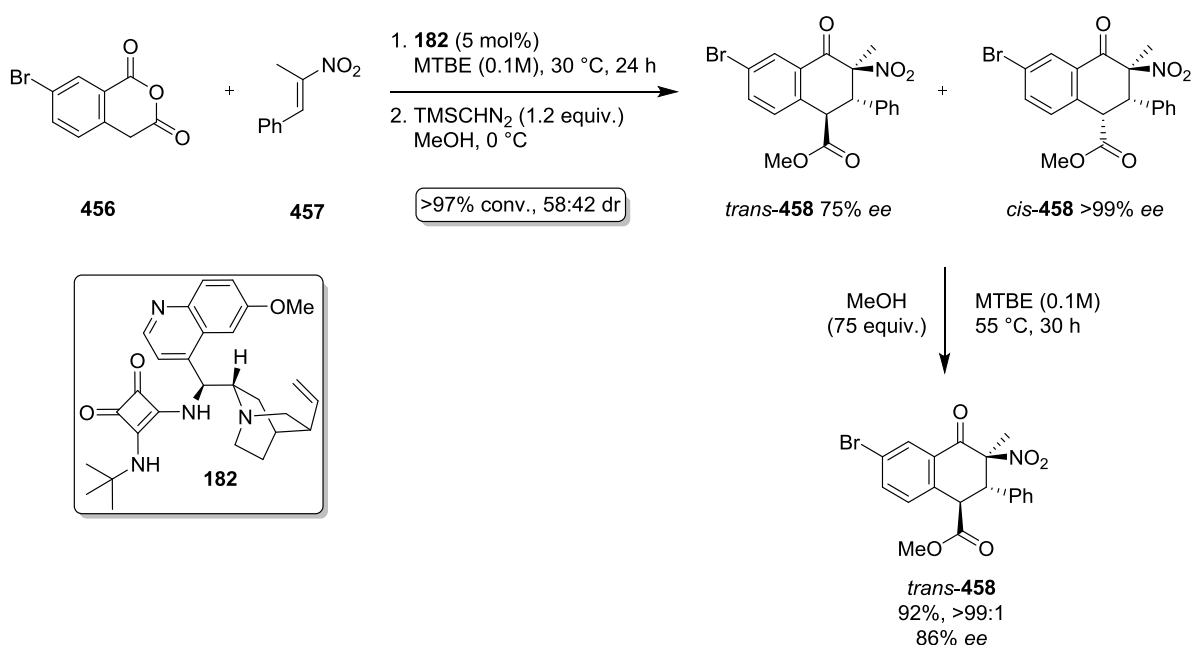
Entry	Esterification reagents	T (°C)	Epimerisation ^[a]
1 ^b	TMSCHN ₂ (1.2 equiv.), MeOH (75 equiv.)	rt	yes
2 ^b	TMSCHN ₂ (1.2 equiv.), MeOH (30 equiv.)	0	yes
3 ^b	TMSCHN ₂ (1.2 equiv.), MeOH (15 equiv.)	0	yes
4 ^b	TMSCHN ₂ (1.2 equiv.), MeOH (30 equiv.)	-30	yes
5 ^b	TMSCHN ₂ (1.2 equiv.), MeOH (15 equiv.)	-30	yes
6	TMSCHN ₂ (1.2 equiv.), IPA (15 equiv.)	0	yes
7	TMSCHN ₂ (1.2 equiv.), IPA (15 equiv.)	-30	yes
8	DCC (1.1 equiv.), DMAP (0.1 equiv.), MeOH (4 equiv.)	0	yes
9	K ₂ CO ₃ (4 equiv.), MeI (4 equiv.)	0	yes
10	TMSCHN ₂ (1.2 equiv.), EtOH (15 equiv.)	-30	no

^aDetermined via ^1H NMR spectroscopic analysis. ^bReaction carried out by Mr. A. Gutierrez Collar

We began the investigation by making modifications to the original esterification protocol using diazomethane. The reaction was carried out at both 0 and -30 °C with varied equivalents of MeOH, though in all cases epimerisation in favour of the *trans*-lactam was still apparent (Table 4.2, entries 1-5), as was the case when IPA was employed as an alternative proton source for the liberation of diazomethane (entries 6 and 7). To our disappointment, alternative approaches *via* Steglich esterification with MeOH and methylation using K₂CO₃ and MeI afforded epimerisation of the product in both cases (entries 8 and 9). We decided to revert to our method of esterification using diazomethane, but this time EtOH was employed as a proton source. Gratifyingly, no epimerisation of the lactam products was observed under these conditions. Moving forward, these would be the esterification conditions of choice.

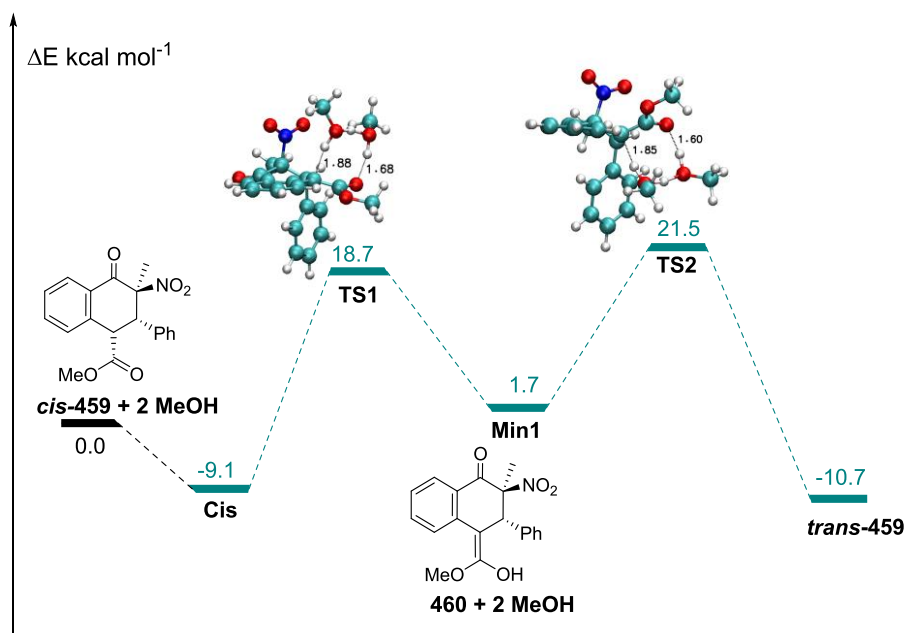
4.4 Epimerisation mechanism

Though the epimerisation problem for these cycloaddition products was first discovered in relation to this reaction, an in-depth study of the process was not explored until later when similar observations were made in the products of catalytic asymmetric Tamura cycloadditions between homophthalic anhydrides and nitroalkenes.¹³¹ The study, conducted by Dr. F. Manioni, found that cycloaddition of **456** to nitroalkene **457** in the presence of **182** afforded the product **458** in 58:42 (*trans*:*cis*) dr with an *ee* of 75% obtained for the major *trans* product (Scheme 4.10). However, exposure of the diastereomeric mixture to 75 equivalents of MeOH for 30 min produced *trans*-**458** in >99:1 dr and 86% *ee*. It was clear that epimerisation was occurring, and in the absence of a basic catalyst.



Scheme 4.10 Tamura cycloaddition between homophthalic anhydride and nitroalkene **457**

A theoretical study (DFT) of the epimerisation mechanism showed that the most likely process was *via* solvent-assisted (methanol) proton transfer.¹³¹ In the first step (**459** to **460**), a concerted deprotonation occurs involving two MeOH molecules which are bound to each other and to the substrate (Scheme 4.11). The energy barrier for *trans*-**459** to form **460** *via* TS2 is slightly higher than for *cis*-**459** *via* TS1, which is in agreement with the data obtained by the deuterium experiments proving the *trans* isomer to be the more stable of the two. The study also suggested that the replacement of MeOH with EtOH should remove the possibility of epimerisation occurring *via* this mechanism as the enhanced steric bulk should inhibit association of the solvent-substrate complex.



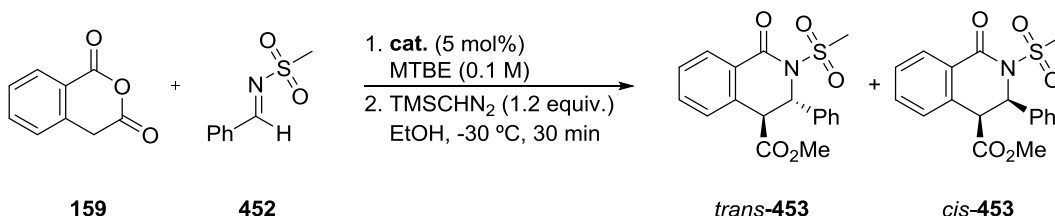
Scheme 4.11 Potential energy surface for MeOH assisted proton transfer with **459**

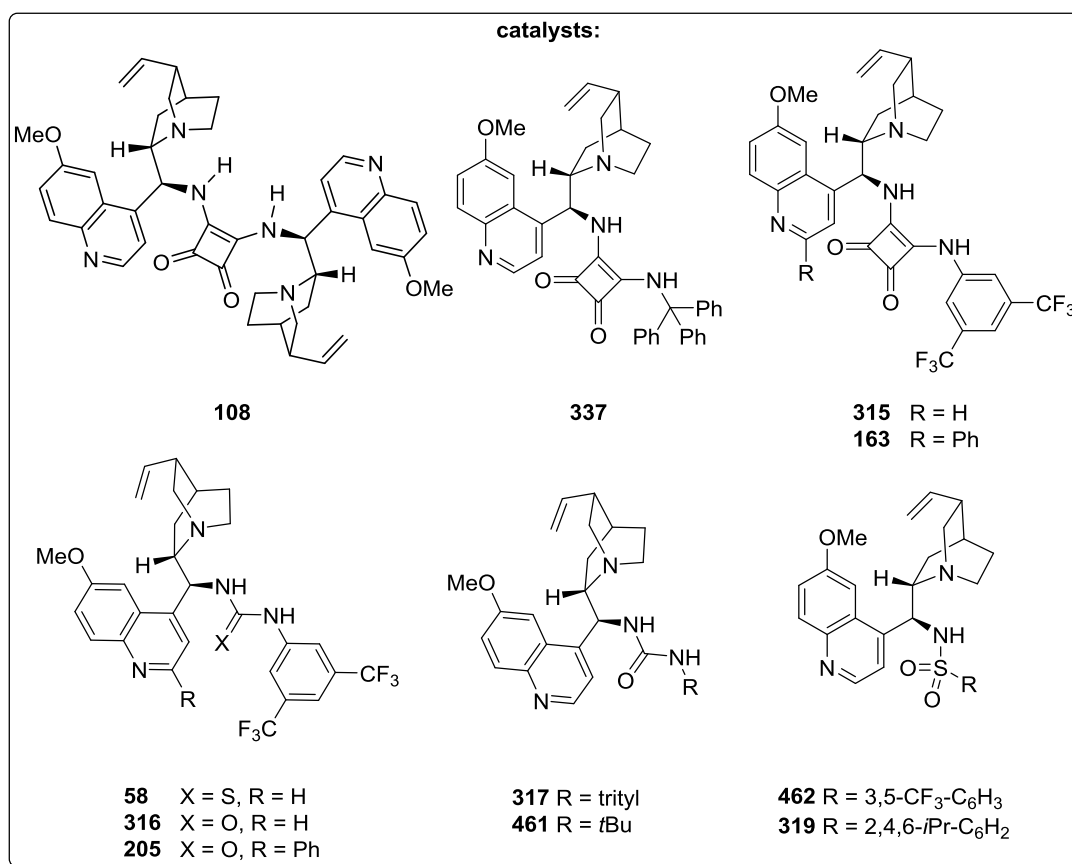
We postulated that the epimerisation observed in the esterification of the lactam products is likely to occur *via* the same mechanism. As was the case with **458**, epimerisation increases the diastereomeric ratio of the product in favour of the more stable *trans*-product. Also, replacement of MeOH with EtOH in the diazomethane esterification inhibits the epimerisation process. Presumably, the association of EtOH with the lactam and subsequent proton transfer is prevented due to the enhanced steric environment of the alcohol.

4.5 Catalyst screen

Now that the epimerisation issue was resolved, a comprehensive catalyst screen ensued, evaluating a range of bifunctional urea, squaramide and sulfonamide *cinchona*-alkaloid based catalysts. The newly optimised esterification conditions were employed for the functionalisation of the carboxylic acid product. This work was a collaborative effort with my colleague Mr. A. Gutierrez Collar.

Table 4.3 Catalyst screen of the formal cycloaddition of **159** and **452**





Entry	Cat	T (°C)	t (h)	Conv. ^[a] (%)	dr ^[a] (<i>trans</i> : <i>cis</i>)	<i>ee</i> _{<i>trans</i>} ^[b] (%)	<i>ee</i> _{<i>cis</i>} ^[b] (%)
1	108	rt	24	>98	61:39	10	12
2	337	rt	24	>98	69:31	15	59
3	315	rt	16	>98	55:45	33	29
4	163	rt	5	>98	74:26	31	0
5	58^c	rt	16	>98	74:26	61	43
6	316	rt	16	>98	77:23	53	16
7	205	rt	16	>98	74:26	61	43
8	317	rt	16	>98	69:31	46	15
9	461^c	rt	16	>98	69:31	56	6
10	462^c	rt	24	>98	66:34	31	21
11	319^c	rt	24	>98	62:38	47	13
12	205	40	5	>98	77:23	53	6
13	205	-30	49	95	64:36	70	27
14	205	-50	72	90	64:36	51	18
15	58	-30	66	>98	63:37	65	42

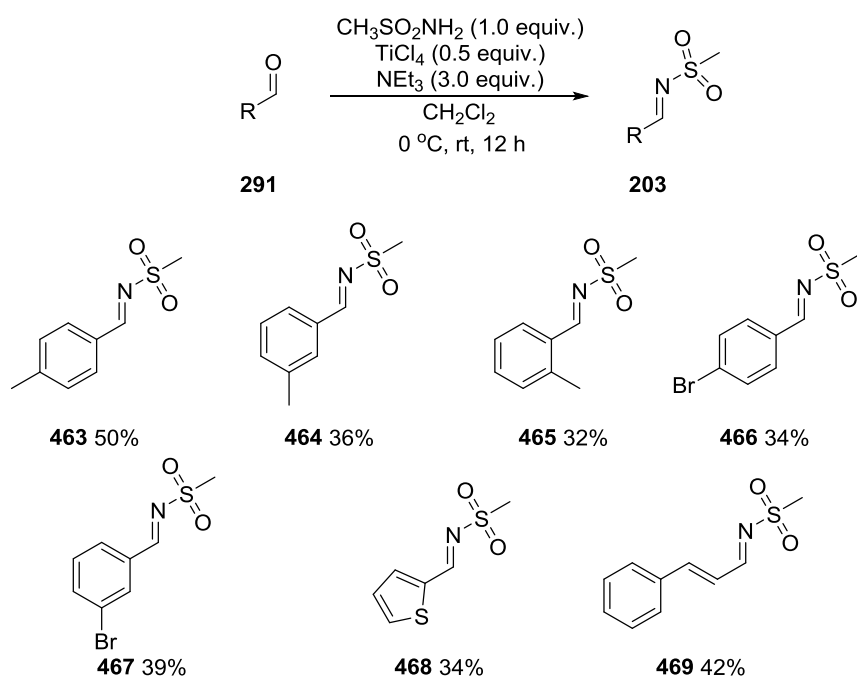
^aDetermined using ¹H NMR spectroscopy. ^bDetermined using CSP-HPLC. ^cReactions carried out by Mr. A. Gutierrez Collar.

Squaramide catalysts **108** and **337** were synthesised as shown in Scheme 2.15 and Scheme 2.20. The C₂-symmetric squaramide **108** promoted the reaction with poor levels of enantiocontrol affording the *trans* and *cis* products in 10% and 12% *ee* (Table 4.3, entry 1). The use of catalyst **337**, containing a bulky trityl substituent, offered a considerable enhancement in *ee* (59%) for the minor *cis* product, though the *ee* obtained for the *trans* lactam remained low (entry 2). Switching the trityl substituent for the less bulky, electron deficient aryl substituent in catalyst **315** furnished a slight improvement in *ee* for the major *trans* product, though still with low levels of enantiocontrol (entry 3). Interestingly, the introduction of a C-2' phenyl substituent in the catalyst structure (**163**) furnished the racemic product for the minor *cis* diastereomer, whilst *ee* remained low for the *trans* product (entry 4).

Disappointed with the performance of the squaramide catalysts, we returned to (thio)urea-based bifunctional catalysts, which changed both the strength and directionality of HB donation. Thiourea **58** introduced an immediate enhancement in the *ee* obtained for the reaction products when compared with the results obtained using its squaramide equivalent **315**: the products *trans*-**453** and *cis*-**453** were furnished in 61% and 43% *ee*, respectively (entry 5). Switching to its less acidic urea counterpart, **316**, resulted in a slight reduction in enantioselectivity while improving diastereocontrol (77:23 *trans*:*cis*, entry 6). The use of urea **205** showed that installation of a C-2' phenyl substituent to the catalyst structure led to slightly improved enantioselectivity for both product isomers, but with a small reduction in diastereocontrol (entry 7); the *trans* product was obtained in 61% *ee* while the *cis* was obtained in 43% *ee*. Increasing the steric bulk of the urea catalyst through the introduction of trityl and *tert*-butyl amine substituents did not lead to any stereochemical improvements (catalyst **317** and **341** respectively, entries 8 and 9), while changing the hydrogen bond donor to a sulfonamide core provided disappointing levels of enantiocontrol (entries 10 and 11). Catalyst **205**, one of the best performing catalysts, was evaluated at a range of temperatures; at 40 °C enhanced diastereocontrol was observed with a concomitant reduction in enantioselectivity (entry 12). A temperature of -30 °C proved to be optimum for the reaction affording the major *trans* product in 70% *ee* with a dr of 64:36 (entry 13). Further decreasing the temperatures resulted in reduced levels of enantiocontrol (entry 14). Thiourea **58** was also evaluated at -30 °C, though it was outperformed by catalyst **205** at low temperatures (entry 15). Thus the urea-based catalyst **205** was chosen for further studies.

4.6 Evaluation of substrate scope

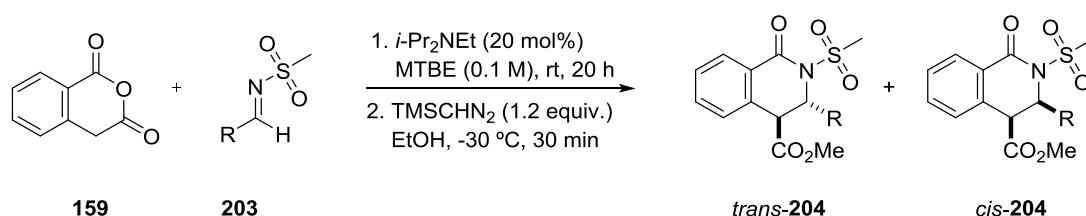
Now that optimum reaction conditions had been established using catalyst **205**, we began to vary the substrate component. A range of *N*-mesyl imines **463** were synthesised from the appropriate aromatic aldehydes and methanesulfonamide (Scheme 4.12). All imines **463-469** were purified by recrystallisation, to afford the isolated products in low yields.



Scheme 4.12 Synthesis of imines **203**

Racemic reactions catalysed by *i*-Pr₂NEt were carried out for each imine to obtain the racemic products for *cis* and *trans* lactams **204** (Table 4.4). In all cases the *cis* diastereomer was furnished as the major product. Racemates **204** were required as a reference for the evaluation of lactams of the asymmetric reaction by CSP-HPLC.

Table 4.4 Synthesis of *rac*-**204**

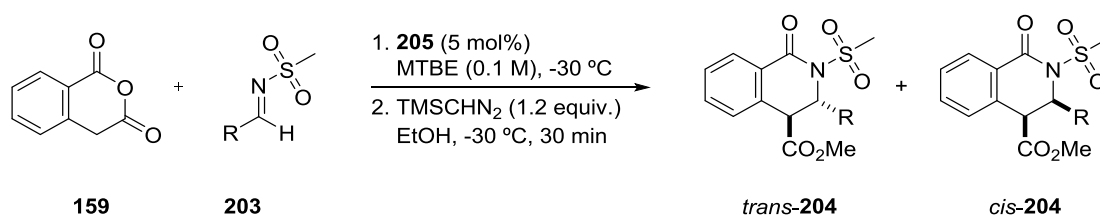


Entry	Imine	Product	Dr ^[a]
(<i>trans</i> : <i>cis</i>)			
1	452	453	30:70
2	464	470	26:74
3	465	471	7:93
4	468	474	35:65
5	470	476	24:76

^a Determined using ¹H NMR spectroscopy

Imines of type **203** were employed in the cycloaddition reaction catalysed by **205** demonstrating the scope of the reaction; the results of this study are shown in Table 4.5. All of the imines employed were within orbit of the process, furnishing enantioenriched lactams **204** as a mixture of diastereomers. In the case of the reactions with imines containing aromatic substituents, the *ee* of the major *trans*-diastereomer was higher than its *cis*-counterpart (Table 4.5, entries 1-7). Imines bearing electron rich aryl-substituents (entries 2,3 and 4) were much slower to react than those bearing electron-withdrawing Br-substituents (entries 5 and 6). Imine **468**, possessing an electron-rich furan substitution, was the least reactive of all the imine substrates; the *trans* and *cis* products were afforded with modest levels of enantiocontrol (entry 7). In contrast to these results, lactam **476** derived from α,β -unsaturated imine **469**, afforded the opposite diastereoselectivity with *cis*-**476** forming as the major product; yet, the *ee* of the major *cis* product remained lower than its *trans* counterpart. In general, the catalytic asymmetric process appears to be insensitive to the electronic characteristic of the substrate.

Table 4.5 Exploring the scope of the imine component

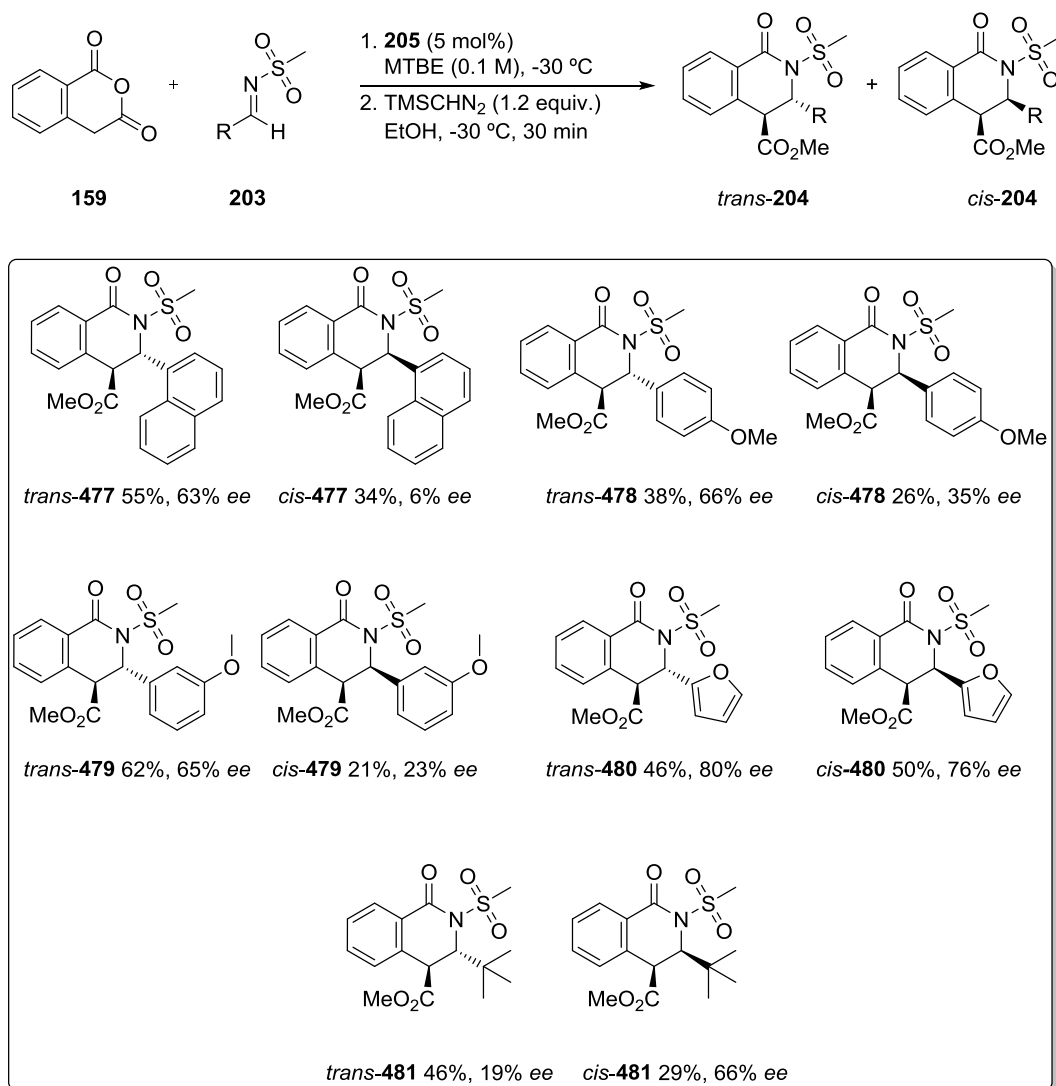


Entry	Imine	Prod.	t (h)	dr ^[a] (<i>trans</i> : <i>cis</i>)	<i>ee</i> _{<i>trans</i>} ^[b] (%)	Yield _{<i>trans</i>} (%)	<i>ee</i> _{<i>cis</i>} ^[b] (%)	Yield _{<i>cis</i>} (%)
1	452	453	48	64:36	70	47	27	27
2	463	470	108	53:47	74	47	43	40
3	464	471	144	59:41	70	48	36	31
4	465	472	180	53:47	33	42	25	36
5	466	473	17	66:34	61	55	4	30
6	467	474	17	61:39	69	51	3	26
7	468	475	264	63:35	51	40	50	23
8	469	476	72	17:81	79	12	35	65

^aDetermined using ¹H NMR spectroscopy. ^bDetermined using CSP-HPLC

The imine scope was simultaneously explored by my colleague Mr. A. Gutierrez Collar. The results of his work are shown in Scheme 4.13. These reactions followed a similar trend; all imines with aromatic substituents furnished the *trans*-isomer as the major product in higher *ee* compared to its *cis*-counterpart. In the case of **481**, containing an aliphatic substituent, while the *trans* lactam was obtained as the major diastereomer, the corresponding *cis* product was afforded in much higher *ee*.

This work, combined with that discussed in Table 4.5 demonstrates the utility of this methodology. The optimised process allows for the enantioselective cycloaddition of homophthalic anhydride with a wide range of *N*-mesyl imines containing electron neutral, electron deficient, electron withdrawing, hindered- and heterocyclic aromatic substituents. We have also shown that it can be expanded to α,β -unsaturated and aliphatic imines allowing access to a wide range of enantioenriched lactam products.



Scheme 4.13 Further exploration of substrate scope carried out by Mr. A. Gutierrez Collar

4.7 Stereochemical rationale

X-ray diffraction analysis of a recrystallised sample of *trans*-**473** was carried out and the absolute stereochemistry of the compound was assigned as (3*S*,4*S*) (Figure 4.1).

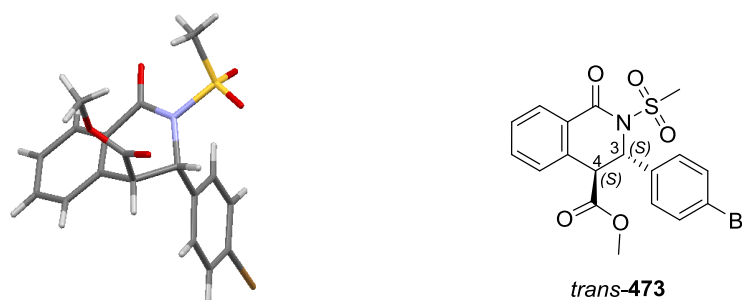


Figure 4.1 Absolute configuration of *trans*-**473** determined by X-ray diffraction analysis

Recently, Connon *et al.* published the first DFT study of the mechanism for the cycloaddition of homophthalic anhydride and benzaldehyde in the presence of catalyst **163**.¹²⁷ The major product of the reaction *trans*-**163** was furnished in 93% *ee* with a dr of 91:9 (*trans*:*cis*) and was assigned the absolute stereochemistry (3*R*,4*R*) (Figure 4.2).

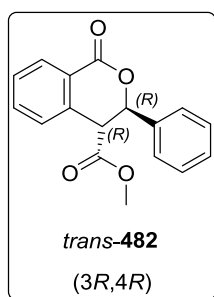


Figure 4.2 Absolute configuration of *trans*-**482**

The study showed that the reaction is likely to follow a ‘specific catalysis’ type mechanism where the anhydride is deprotonated by the quinuclidine portion of the catalyst and the resulting enolate is bound *via* two hydrogen bond interactions with the squaramide moiety (Figure 4.3). Meanwhile the aldehyde is activated by the quaternary ammonium salt through HB donation; it arranges itself such that the bulky phenyl unit is directed away from the squaramide ring. Additionally, there is an attractive interaction between the aldehyde proton and the squaramide *N*-atoms. The face selectivity of the enolate is assisted by attractive interactions with the protonated quinuclidine organising the pre-transition state assembly such that the *si*-face of the enolate will attack the *re*-face of the aldehyde, which would result in the 3*R*,4*R* stereochemistry obtained for *trans*-**482**.

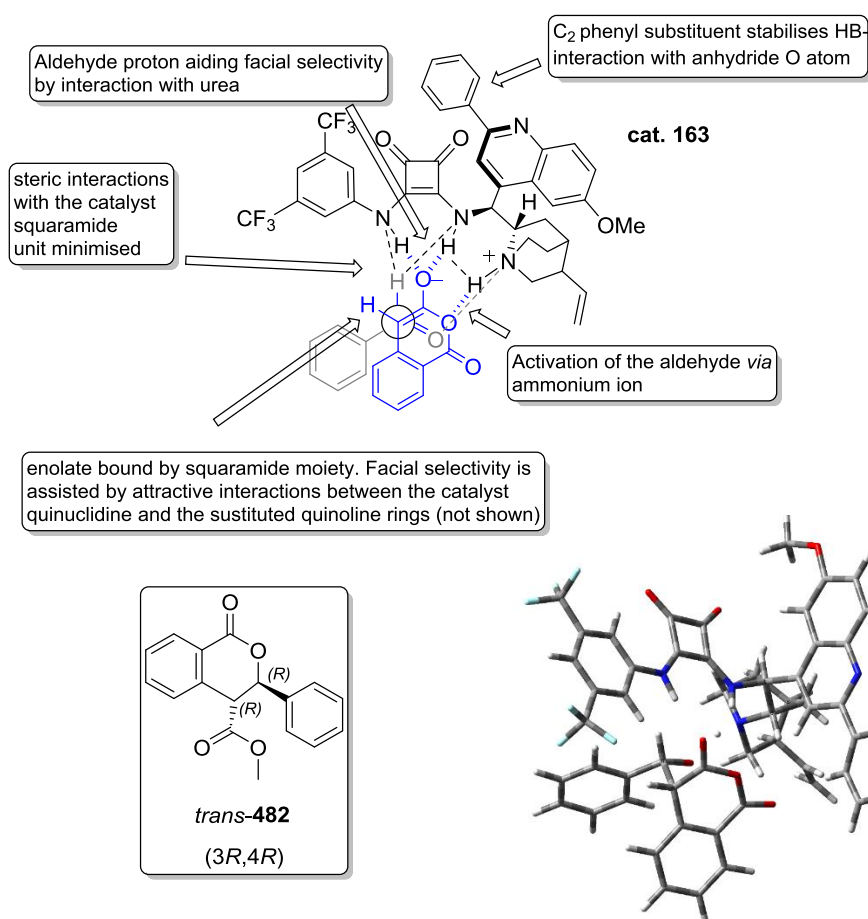
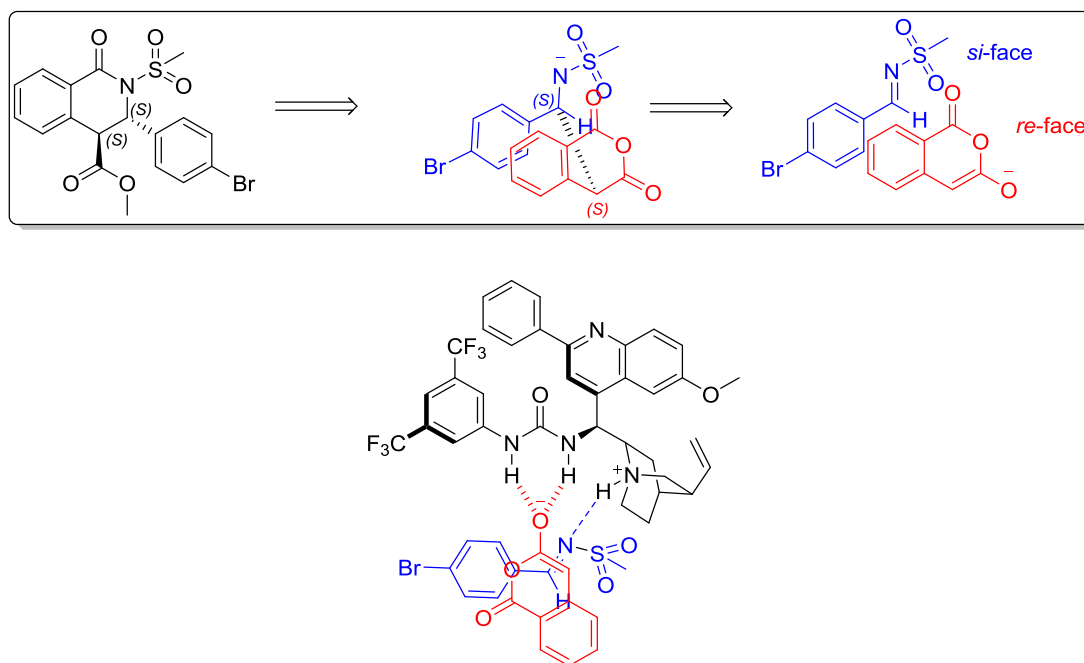


Figure 4.3 Stereochemical rationale for the formation of lactone *trans*-482 in the presence of 163

As already mentioned, our study which involved the cycloaddition between homophthalic anhydride and imines in the presence of catalyst **205** obtained the opposite stereochemistry (3*S*,4*S*) for the major product (e.g. *trans*-lactam **473**). We have proposed a possible explanation for this stereochemical outcome based on the model for the formation of lactone **482** (Scheme 4.14). We suspect that this reaction will also occur *via* a ‘specific catalysis’ pathway, in which case the anhydride is likely to be deprotonated by the quinuclidine of the catalyst and the resulting enolate held by dual hydrogen bond donation from both of the urea N-H units. Following this, we speculate that differences in the mechanism will lie with the binding of the imine electrophile. We propose that protonated quinuclidine will hydrogen bond to the imine, which will be orientated such that the bulky phenyl substituent points away from the catalyst into solvent. In this way, the *re*-face of the enolate (the binding of which has the opposite face selectivity to that seen with the aldehyde to avoid clash between the anhydride carbonyls and the imines mesyl group) will attack the *si*-face of the imine to furnish the 3*S*,4*S* product (Scheme 4.14). Although the proposed model can effectively explain the stereochemical outcome of the cycloaddition reaction between anhydrides and imines, computational

studies have not been carried out to support this binding mode. The model described can only be considered speculative until the reaction is re-examined and more experimental data is available.



Scheme 4.14 Proposed pre-transition state and stereochemical rationale for the formation of lactam *trans*-473 in the presence of catalyst **205**

4.8 Conclusion

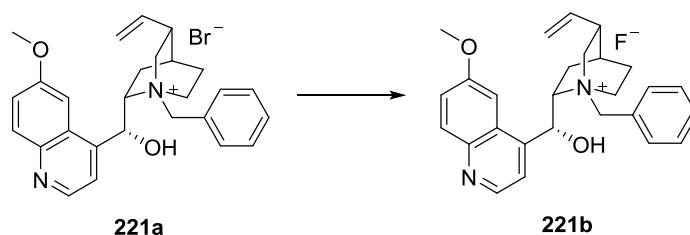
In summary, the first catalytic asymmetric protocol for the cycloaddition between enolisable anhydrides and imines has been developed. By carefully tuning the electrophilicity of the imine through the placement of electron withdrawing substituents on the nitrogen, we have been able to employ bifunctional *cinchona* alkaloid-based organocatalysts to promote the reaction and furnish the lactam products with moderate dr and good to moderate *ee* for the major *trans* diastereomer. Investigation into the mechanism of action should be considered in the future to shed some light on the mode of catalysis, thus potentially enabling us to improve enantioselectivity. Additionally, the evaluation of different enolisable anhydrides would increase the scope and further demonstrate the synthetic utility of this reaction.

5 Fluoride catalysed desymmetrisations

As discussed in Section 1.11, our group has previously employed bifunctional *cinchona* alkaloid catalysts in the highly efficient asymmetric desymmetrisation of *meso*-anhydrides. The aim of this project was to demonstrate the use of *cinchona* alkaloid-derived quaternary ammonium fluorides as efficient nucleophilic catalysts in the enantioselective methanolysis of *meso*-anhydrides. This project was a collaboration with two fellow co-workers: Dr. R. Craig and Dr. M. Litvajova.

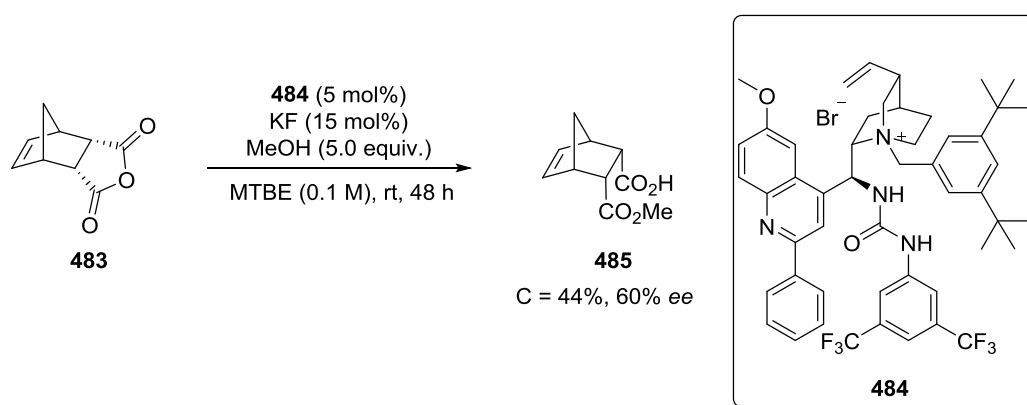
5.1 Generation of the chiral quaternary ammonium fluoride catalysts

We originally envisaged the *ex situ* generation and purification of the chiral quaternary ammonium fluoride catalysts. In this way we could store and use them directly as required throughout the ensuing investigation. Numerous attempts at the synthesis catalysts such as **221b** were carried out using anion exchange conditions on the corresponding bromide salt (such as **221a**).^{177, 178, 232} However, despite the intensive efforts on the part of my colleague Dr. R. Craig, full conversion to the fluoride salt was never achieved.



Scheme 5.1 Anion exchange reactions to form **221b**

Instead, we turned our attention to the *in-situ* generation of the desired catalysts. The literature precedent for such transformations reported the use of up to 5 equivalents of KF or $\text{KF}\cdot\text{H}_2\text{O}$ to generate the required ammonium fluoride.^{166, 167} We reasoned that, as attack of the nucleophile on the acyl fluoride intermediate would likely regenerate the ammonium fluoride catalyst, only catalytic fluoride should be required in order to carry out the transformation. Dr. Ryan Craig carried out a series of experiment using phase transfer catalyst **484** and KF to control the desymmetrisation of **483** *via* methanolysis. A catalyst loading of 5 mol% in conjunction with a 15 mol% of KF was deemed to be optimal conditions -furnishing the product **485** in 60% *ee* with a conversion of 44% after 48 hours (Scheme 5.2). A background of 3% conversion was observed in the absence of catalyst **484** after 48 hours.

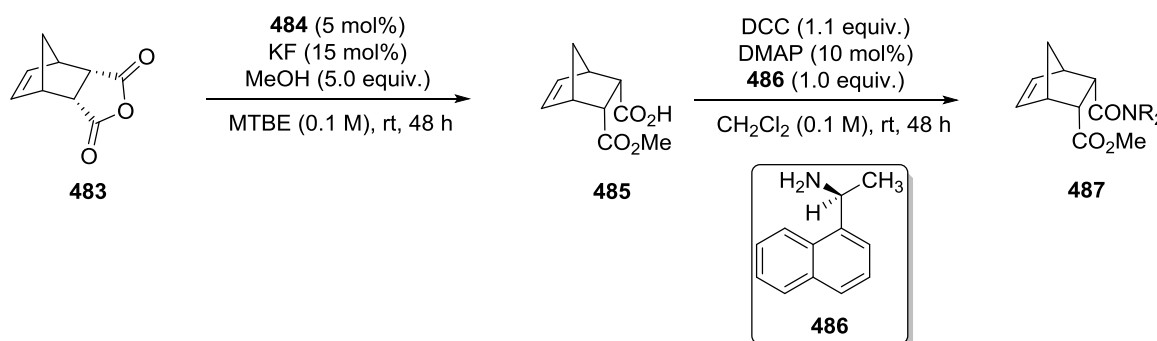


Scheme 5.2 The *in situ* formation of chiral ammonium fluorides to catalyse the methanolysis of **483**

5.2 Design of a reproducible reaction

After some further development, we noticed that the result illustrated in Scheme 5.2 could not be reproduced. Along with two colleagues (Dr. R. Craig and Dr. M. Litvajova), we set up a series of identical experiments using the same source of KF, identical stirring bars, identical stirring speeds and identical 5 mL round-bottomed flasks. The results were conclusive: reproducibility was a major issue. It should be noted that the *ee* of the hemi-ester products **485** were determined *via* CSP-HPLC upon derivitisation of the carboxylic acid functionality as carbonyl **487**.

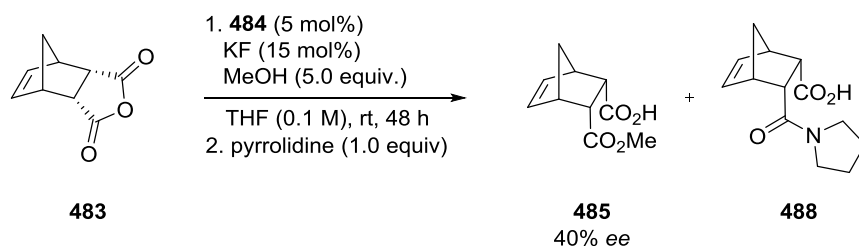
Table 5.1 Investigations into the reproducibility of the reaction



Entry	Conv. (%) ^[a]	<i>ee</i> (%) ^[b]
1	51	51
2	49	49
3 ^c	47	43
4 ^c	41	8
5 ^c	41	2

^a Conversion of the substrate was measured using ¹H NMR spectroscopy. ^b*ee* was determined by CSP-HPLC analysis after isolation of functionalised amide **487**. ^c Reactions were performed using a new batch of catalyst **484**.

We hypothesised that contamination of the catalyst could be responsible for the variation in results; as such, two separate batches of **484** were employed in the investigation. In each case, subsequent reactions resulted in a depletion of product *ee* indicating that the catalyst was not the problem. Next, we postulated that our purification method may potentially be causing the product to racemise. Hemiester **485** was purified from the reaction mixture *via* an acidic work up with aqueous HCl followed by column chromatography using mixture of CH₂Cl₂ and MeOH (20:1) as an eluent. This potentially provided an opportunity for the uncatalysed addition of MeOH to any remaining starting material **483** on the column, thus forming racemic quantities of hemiester **485** which would lower the overall enantiomeric excess obtained for the purified product. Initially, we tried to test this theory by changing the solvent system used for purification *via* column chromatography, though efficient separation of the catalyst and product could not be achieved using other eluents. Instead, we decided to quench any unreacted starting material in the reaction after 48 hours with pyrrolidine – the resulting amide would not be subject to methanolysis on silica, and thus the enantiomeric excess of the reaction should not be compromised. Four consecutive reactions were performed using 1 equivalent of pyrrolidine to quench any remaining starting material after 48 h. An *ee* of 40% was obtained for the product **485** in each case (Scheme 5.3). The reproducibility of the reaction was no longer a problem.



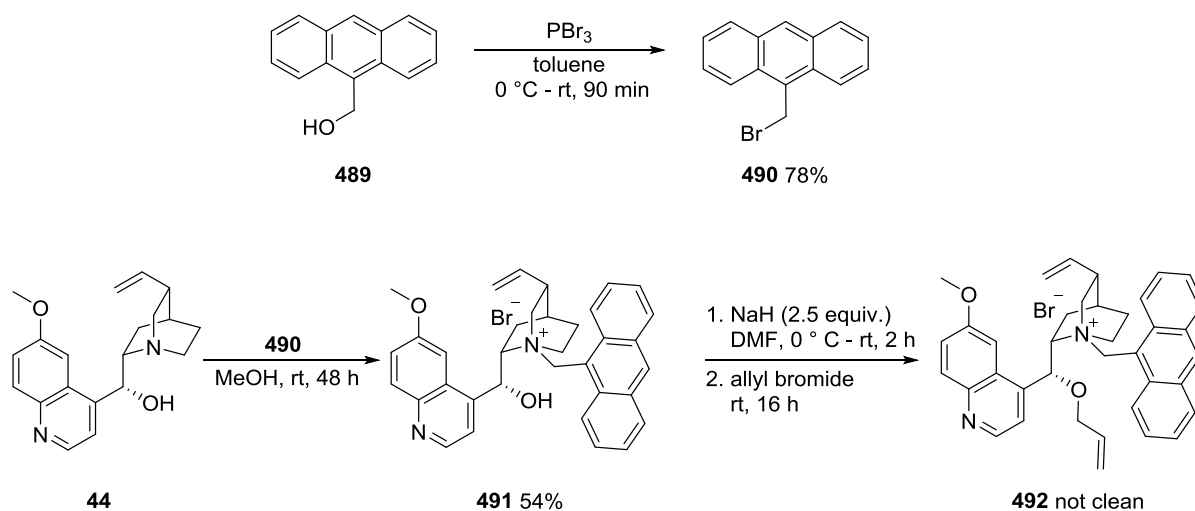
Scheme 5.3 Designing a reproducible reaction

5.3 Catalyst synthesis and screening

With a robust synthetic procedure now in place, we embarked upon optimisation of the catalyst structure. Some *cinchona* alkaloid-based phase-transfer catalysts, such as **484** (synthesised by Dr. Emiliano Sorrentino), were already available for use in our lab. As most of these catalysts possessed either a squaramide or urea moiety we decided to expand the scope of the library through the modification of the hydrogen bond donating substituent. Our initial study involved the evaluation of Corey-type catalysts and quaternised quinine derivatives.

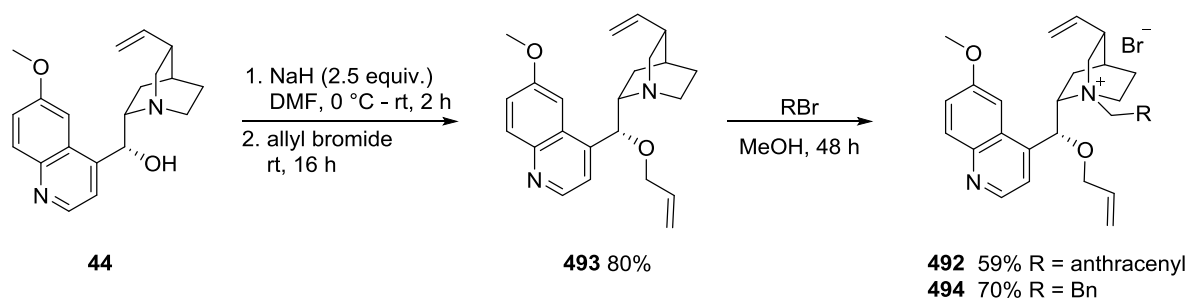
We envisioned the synthesis of a range of Corey-type catalysts, which lack a hydrogen bond-donating substituent, for their evaluation in the fluoride catalysed desymmetrisation reaction. Novel catalysts **492**, **494** and **496** were selected for synthesis. Anthracenyl bromide (**490**) was prepared in good yield from the corresponding alcohol using PBr₃. Initially, the synthesis of **492** was attempted following a procedure devised by Corey *et al.*²³³ for the synthesis of the cinchonidine equivalent. Quinine (**44**)

was reacted with **490** to form the bromide salt **491** followed by alkylation of the C-9 hydroxy group to form **492** (Scheme 5.4). However, several attempts at the purification of **492** via both column chromatography and recrystallisation failed.



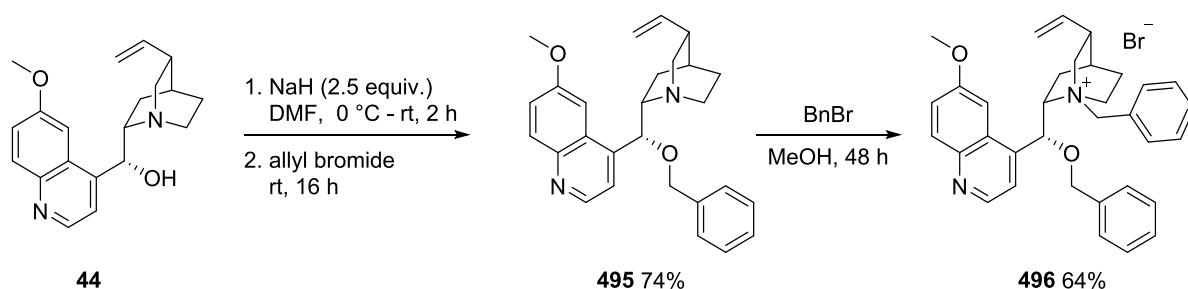
Scheme 5.4 Initial attempt at the synthesis of **492**

It was decided that the order of synthesis should be reversed. We postulated that carrying out the C-9 alkylation first, followed by synthesis of the bromide salt should give cleaner reactions and thus easier purification. Quinine was transformed into **493** using NaH and allyl bromide, followed by synthesis of the tertiary amine to furnish the purified product (**492**) in 59% yield. Catalyst **494** was synthesised in 70% yield from **493** using benzyl bromide as the alkylating agent (Scheme 5.5).



Scheme 5.5 Synthesis of **492** and **494**

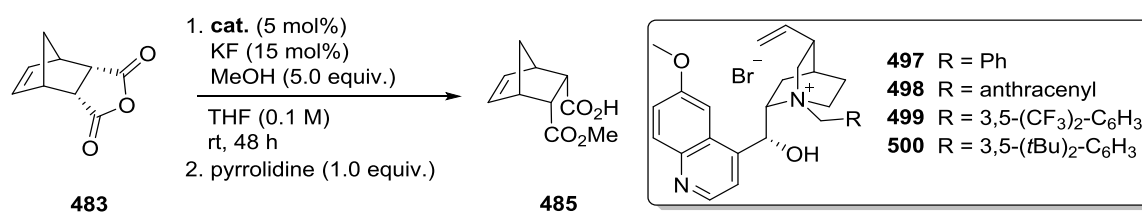
Catalyst **496** was synthesised to explore the impact of varying the steric characteristics of the catalysts by systematically introducing larger C-9 hydroxyl substituents. Quinine (**44**) was converted into the benzyl ether (**495**) followed by alkylation of the quinuclidine nitrogen atom with benzyl bromide to furnish **496** in 70% yield (Scheme 5.6).



Scheme 5.6 Synthesis of **496**

These catalysts (**492**, **494**, and **496**), along with a number of quaternised quinine derived catalysts (**497-500**) were evaluated for their activity in the fluoride-catalysed desymmetrisation of anhydride **483** (Table 5.2).

Table 5.2 Evaluation of Corey-type catalysts and quaternised quinine bromides in the fluoride catalysed methanolysis of **483**



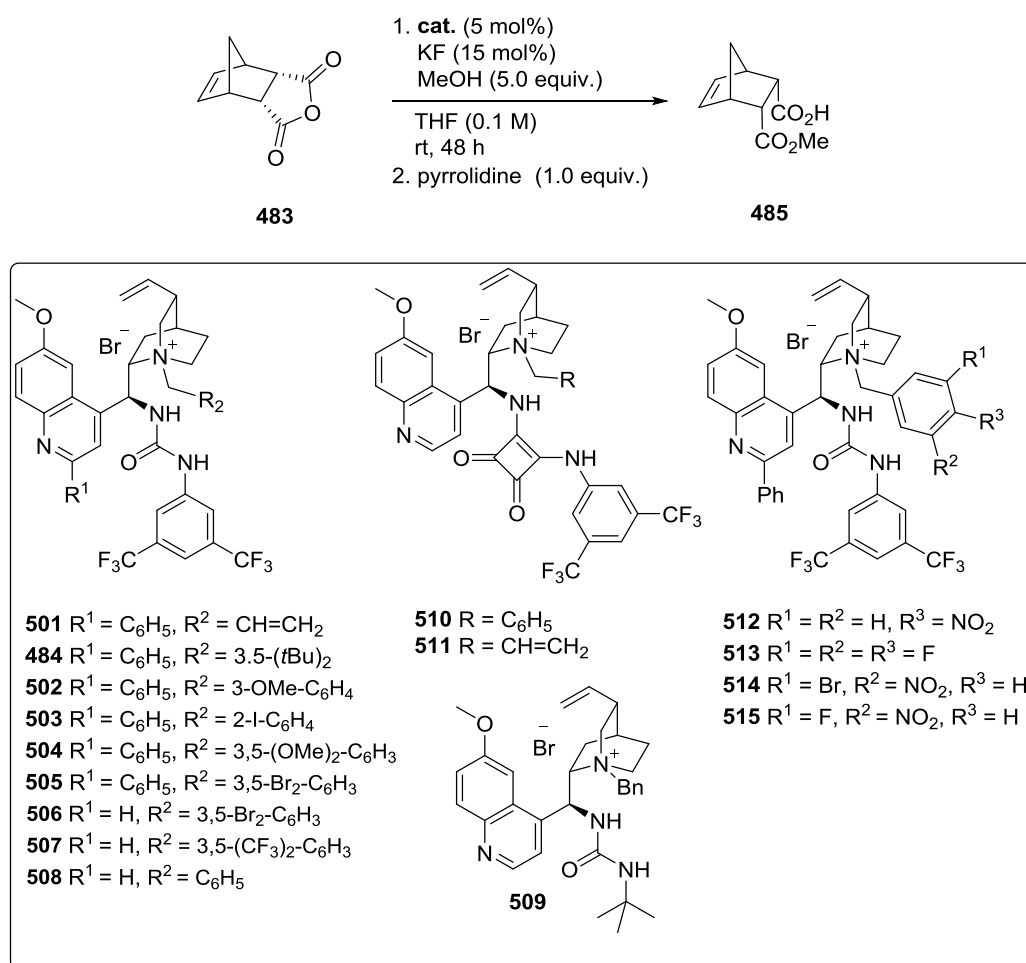
Entry	Cat.	Conv. (%) ^[a]	ee (%) ^[b]
1	492	17	0
2	494	80	-11
3	496	30	-4
4	497^c	58	-3
5	498^d	49	-2
6	499^d	34	10
7	500^d	38	3

^aConversion of the substrate was measured using ¹H NMR spectroscopy. ^bee was determined by CSP-HPLC analysis after isolation of functionalised amide **487**. ^cEvaluated by Dr. R. Craig. ^dEvaluated by Dr. M. Litvajova.

The Corey-type catalysts promoted the methanolysis with varied conversion, furnishing the product **485** as near racemates. The use of catalyst **492**, incorporating a bulky anthracenyl *N*-alkyl substituent, resulted in a slow reaction and failed to provide sufficient levels of enantiocontrol (Table 5.2, entry 1). Decreasing the size of the *N*-alkyl substituent vastly improved the reaction rate, though the enantiomeric excess of the product remained low (entry 2). Changing the *C*-9 alkoxy substituent from allyl to benzyl was detrimental to the reaction rate, with no observed improvement in

enantioselectivity (entry 3). Re-installation of the hydrogen bond capabilities of these molecules through deletion of the C-9 hydroxyl substituent (catalysts **497-500**) failed to improve selectivity over the reaction (entries 4-7). It was clear that the structure of our initial catalyst **484** was better from reactivity and selectivity standpoints (40% *ee*). The fundamental differences in structure lay in the identity of the hydrogen bond donor at C-9, with a concomitant inversion of stereochemistry. As such, the next logical step involved optimisation of this structure: a series of catalysts bearing structural similarities to **484** were evaluated.

Table 5.3 Evaluation of urea and squaramide phase transfer catalysts in the fluoride catalysed methanolysis of **483**



Entry	cat.	Conv. (%) ^[a]	ee (%) ^[b]
1	501	70	17
2	483	44	40
3	502	70	43
4	503	55	23
5	504^d	57	46
6	505	80	53
7	506	79	53
8	507	66	51
9	508^c	70	0
10	509^c	45	-6
11	510^c	47	-23
12	511^c	43	-17
13	512^d	66	60
14	513^d	72	61
15	514^d	77	61
16	515^d	79	62

^aConversion of the substrate was measured using ¹H NMR spectroscopy. ^bee was determined by CSP-HPLC analysis after isolation of functionalised amide **487**. ^cEvaluated by Dr. R. Craig. ^dEvaluated by Dr. M. Litvajova.

The evaluation of **501** in the fluoride catalysed methanolysis of **483** offered an improvement in results (17% ee, Table 5.3, entry 1) when compared with those obtained using the Corey-type catalysts and quaternised quinine bromides, though the benchmark was still held by catalyst **484** (40% ee, entry 2). It was clear that quaternised *N*-benzyl bromides were superior to the corresponding *N*-allyl bromides, and thus further modification to the *N*-benzyl substituent were explored. Introduction of a *para*-methoxybenzyl substituent to the catalyst structure (**502**, entry 3) afforded a small increase in the ee (43 %) and a much faster reaction rate. *Ortho*-substitution of the *N*-benzyl moiety proved to be detrimental to enantioselectivity (entry 4) while a 3,5-substitution was favourable (entries 5 and 6), with 3,5 di-bromo benzyl variant (**505**) furnishing the product in 80% yield and 53% ee. A small library of catalysts without the *cinchona* alkaloid *C*-2' phenyl substituent was also evaluated (entries 7-9). In most cases the ee obtained for **485** was comparable to those obtained using catalyst **505**, except in the case of catalyst **508** (with a simple *N*-benzyl functionalisation) which furnished the racemic product. Switching the planar aryl urea for the bulky *tert*-butyl urea **509** was also disadvantageous; forming **485** in near racemic fashion (entry 10). We next evaluated the performance

of squaramide-substituted phase-transfer catalysts in the reaction; though changing the hydrogen bond donor did not offer enhanced levels of enantiocontrol. Interestingly, these squaramide-based catalysts afforded the opposite enantiomer of the product. The *N*-benzyl derivative **510** catalysed the formation of the product in 23% *ee* while the corresponding *N*-allyl bromide (**511**) led to further loss in enantiocontrol (entries 11 and 12).

It was evident that the use of aryl-urea derived *cinchona* alkaloids bearing a *C*-2' phenyl substitution provided the best results of the catalysts screened with regards to both reaction rate and enantiocontrol, though there was still room for improvement. As such, further optimisation of the ammonium moiety of these catalysts ensued. The aforementioned studies had shown that while *ortho*-substitution of the *N*-benzyl salt was detrimental to activity with regards to rate and enantioselectivity, the insertion of bromo- substituents at the 3,5-positions was advantageous. Catalyst **512** was synthesised to investigate the effects of inserting an electron withdrawing group at the *para* position which, gratifyingly, resulted in an increase in selectivity, furnishing the product in 66% yield and 60% *ee* (entry 13). Catalyst **513** further explored the effect of *para*- substitution and the results remained consistent (entry 14). Seemingly, the introduction of both *meta*- and *para*-electron-withdrawing substituents to the *N*-benzyl unit invoked the largest increases in *ee*; thus it was decided to combine these functionalities. Catalyst **514** and **515** were synthesised to evaluate this combined 3,4-substitution (entries 15 and 16). Disappointingly, the enantioselectivity obtained using these catalysts remained stagnant at 62%, though a notable increase in the rate of reaction was observed.

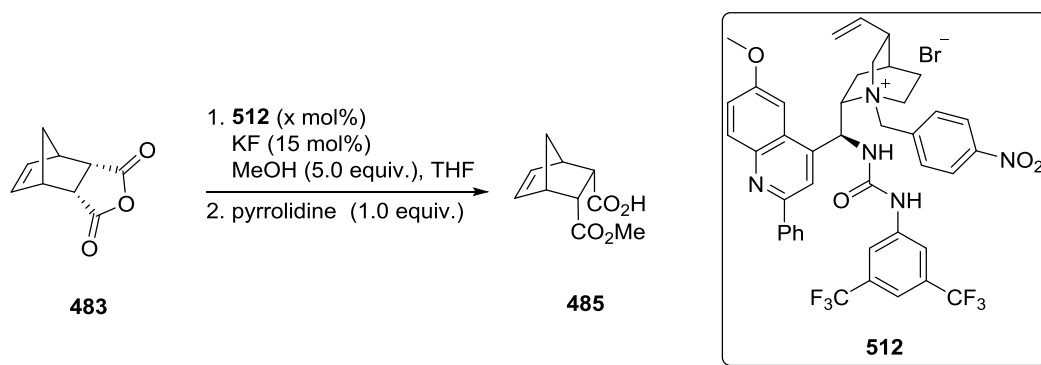
To the best of our knowledge, we had thoroughly manipulated the catalyst's structure in an effort to improve its enantiocontrol over the reaction. Of all those screened, catalyst **515** exhibited the best results in terms of both rate and selectivity. Moving forward, we hoped that optimisation of the reaction conditions could provide enhanced enantioselectivity.

5.4 Optimisation of the reaction conditions

Though catalyst **515** was selected as the best performing catalyst in the reaction, the optimisation of the reaction conditions were carried out using catalyst **512**, which exhibited similar activity to **515** and was in plentiful supply in our research laboratory. We began the study by varying the concentration of the reaction. As standard practice, a control reaction in the absence of catalyst **512** was carried out to confirm that background alcoholysis would occur at increased reaction concentrations (Table 5.4, entry 1). Interestingly, when catalyst **512** was employed, neither increasing the reaction concentration (0.2 M) nor decreasing the reaction concentration (0.05 M) had any effect on enantiocontrol: furnishing the product **485** with an *ee* of 62% in both cases (entries 2 and 3). In general, decreasing the temperature of a catalytic, enantioselective reaction tends to enhance levels of enantiocontrol. In this scenario, however, carrying out the reaction at a reduced

temperature of 0 °C resulted in a slight reduction in the *ee* obtained with a concurrent decrease in reaction rate (entry 4). At -15 °C the reaction was too slow for practical purposes; with a conversion of only 11% after 48 hours, while a further decrease in temperature to -30 °C afforded no reaction at all (entries 5 and 6). Surprisingly, levels of enantiocontrol remained comparatively high when the reaction was heated to 50 °C; **485** was synthesised in 93% yield and 44% *ee* after 48 hours (entry 7). Finally, we tried increasing the catalyst loading whilst keeping the amount of KF constant; though this resulted in an increase in the rate of the reaction, it had no effect on stereocontrol (entry 8). The results of these optimisation studies were unexpected but conclusive: the concentration of the reaction had no effect on levels of enantiocontrol while room temperature remained the optimum temperature for selectivity.

Table 5.4 Optimisation of reaction conditions for the synthesis of **485**



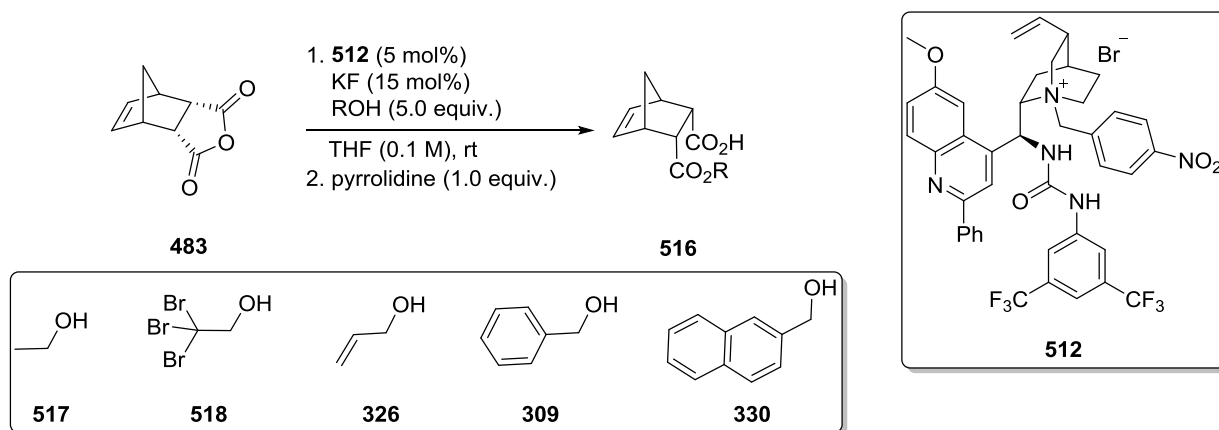
Entry	Conc. (M)	T (°C)	x	t (h)	Conv. (%) ^[a]	<i>ee</i> (%) ^[b]
1	0.2	rt	0	40	0	-
2	0.2	rt	5	50	70	62
3	0.05	rt	5	82	60	62
4	0.1	0	5	96	67	58
5	0.1	-15	5	48	11	n.d
6	0.1	-30	5	96	0	-
7	0.1	50	5	48	93	44
8	0.1	rt	10	48	80	60

^aConversion of the substrate was measured using ¹H NMR spectroscopy. ^b*ee* was determined by CSP-HPLC analysis after isolation of functionalised amide **487**.

In a final effort to enhance the stereocontrol of the reaction, we decided to investigate the effects of changing the alcohol nucleophile. Ethanol (**517**), tribromoethanol (**618**), allyl alcohol (**326**), benzyl alcohol (**309**) and 2-naphthylmethanol (**330**) were selected for screening purposes (Table 5.5). Unfortunately, the corresponding alcoholysis products were formed in much lower *ee* in all but one case; employment of tribromoethanol as the nucleophile resulted in a very slow reaction rate and

thus the *ee* of this product was not determined. Methanol remained the alcohol of choice for future substrate optimisation studies which were conducted by Dr. R. Craig and therefore will not be reported in this thesis.

Table 5.5 Alcohol screen for the fluoride catalysed desymmetrisation of **483**



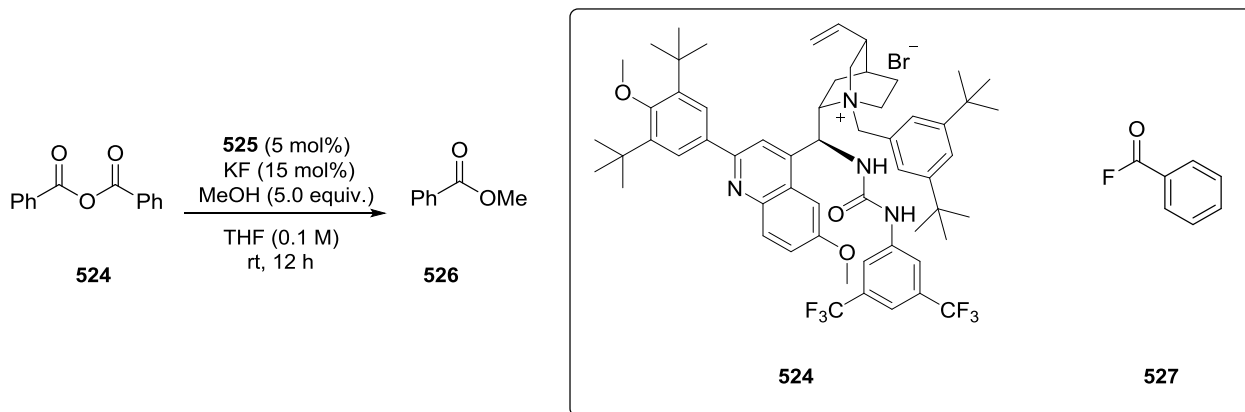
Entry	Alcohol	Product	t (d)	Conv. (%) ^[a]	<i>ee</i> (%) ^[b]
1	517	519	10	54	26
2	518	520	4.5	6	n.d
3	326	521	5	53	7.8
4	309	522	5	52	5.7
5	330	523	6	45	3.2

^a Conversion of the substrate was measured using ¹H NMR spectroscopy. ^b*ee* was determined by CSP-HPLC analysis after isolation of functionalised amide **487**.

5.5 Mechanistic insight

As discussed in the introduction, the fluoride catalysed methanolysis of anhydrides could occur *via* general base catalysis or nucleophilic catalysis. Though some studies in the literature have supported nucleophilic catalysis as the likely mechanism in similar fluoride catalysed transformations,^{155, 161} few have provided solid evidence to support their hypothesis (see Section 1.10.1).¹⁶⁴ We deemed it unlikely that we could trap and isolate the acyl fluoride intermediate in our chosen reaction. Instead, we took a representative transformation in which the acyl fluoride intermediate was known. Dr. R. Craig carried out the methanolysis of benzoic anhydride (**524**) in the presence of a phase-transfer catalyst **525** using conditions identical to those used in the desymmetrisation reaction (Scheme 5.7). Clean formation of the product **526** was observed, and the acyl fluoride intermediate (**527**) could be detected by ¹⁹F NMR spectroscopy and compared with the literature data.²³⁴ Enhanced levels of **527** were detected when the alcohol nucleophile was omitted from the reaction; full conversion of KF was achieved after 5 h. The formation of **527** was not observed in the absence of the phase transfer

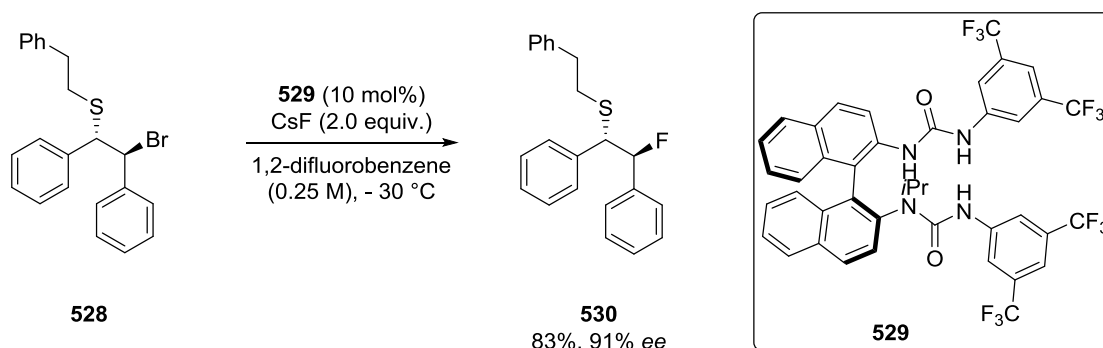
catalyst **525**. These experiments provide conclusive evidence that fluoride does operate *via* nucleophilic catalysis at acyl centres. It is therefore highly likely that nucleophilic catalysis is responsible for much of the observed catalytic activity in our system, though a competing general base catalysed pathway cannot be excluded.



Scheme 5.7 Observation of an acyl fluoride intermediate

5.6 Recent developments

Since the completion of this work, Gouverneur *et al.* have published a paper detailing the asymmetric nucleophilic fluorination of β -bromosulfides such as **528**, using hydrogen bond donating catalyst **529** and stoichiometric CsF (Scheme 5.8).²³⁵



Scheme 5.8 Asymmetric nucleophilic fluorinations by Gouverneur *et al.*

The study contains a detailed computational analysis which proposes that the catalyst acts as a solid-liquid phase transfer catalyst, binding the fluoride ion of the insoluble metal fluoride *via* hydrogen bond donation from the urea moiety, thus forming a chiral fluoride containing reagent.²³⁵ The resulting chiral reagent is soluble in organic media and reacts with the electrophile *via* S_N2 chemistry, to furnish the fluorinated product with concomitant regeneration of the urea catalyst (Figure 5.1).

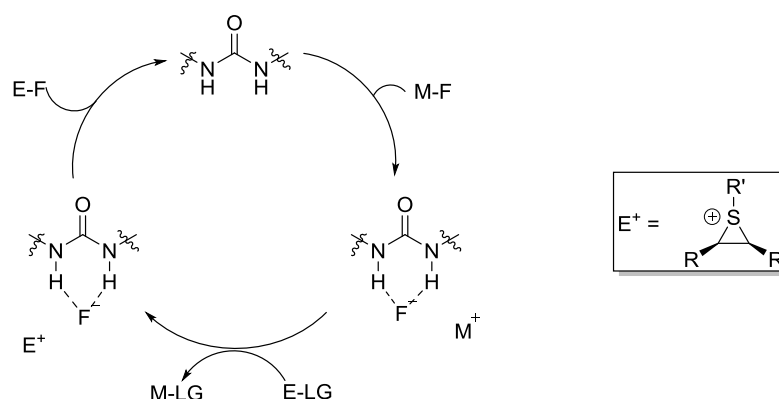
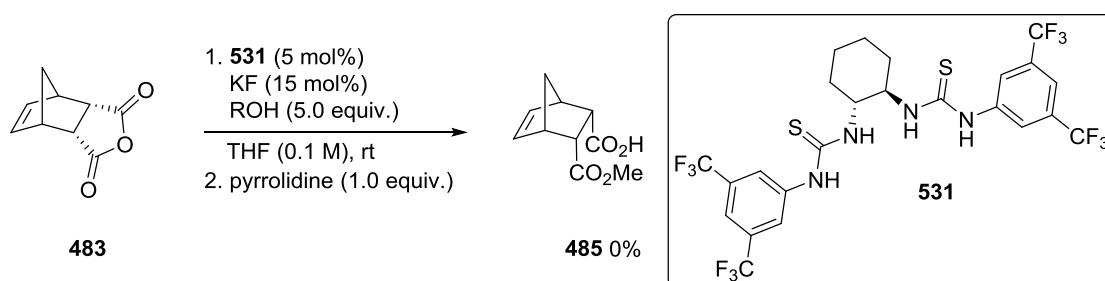


Figure 5.1 The proposed method of fluoride delivery by Gouverneur *et al.*

Prompted by this work, we have considered the possibility that in the fluoride-catalysed desymmetrisation of *meso*-anhydrides, nucleophilic fluoride catalysis could in fact be occurring as a result of chiral urea bound fluoride, rather than the *in situ* generation of a quaternary ammonium fluoride salt. Indeed, all literature precedents for Br⁻/F⁻ anion exchange to form the quaternary ammonium fluoride salt require a large excess of the metal fluoride.^{166, 167} The 1:3 catalyst:KF ratio used in our optimised transformation is comparatively low relative to these aforementioned studies.¹⁹⁹

We decided it was prudent evaluate the performance of a mono-functional hydrogen bond donating catalyst in our reaction. *Bis*-thiourea **531** was employed instead of the usual phase-transfer catalyst under the optimised reaction conditions (Scheme 5.9). No conversion of the anhydride starting material was observed after 3 days. Though no further investigations were carried out at the time, we later found that in certain cases hydrogen bond donating catalysts can reduce the nucleophilic properties of fluoride. This study does not discount the possibility that chiral hydrogen bound fluoride is responsible for reactivity, rather it demonstrates the requirement for phase transfer catalysts such as **515** in the transformation. Computational investigations into the mechanism behind the catalysis have yet to be carried out.



Scheme 5.9 Attempted fluoride-catalysed desymmetrisation using **531**

5.7 Conclusion

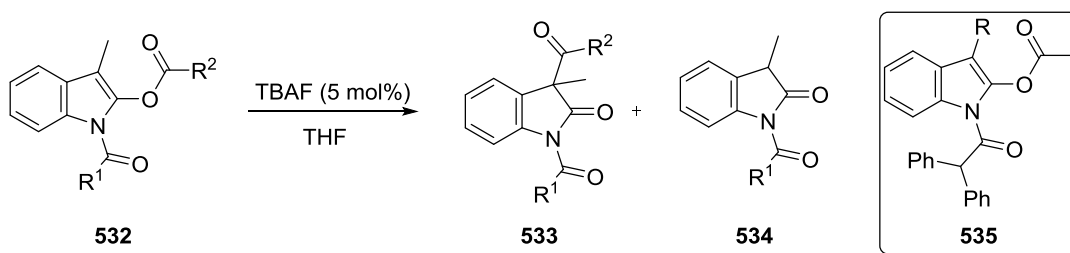
To the best of our knowledge we have developed the first asymmetric reaction involving nucleophilic catalysis by a fluoride ion.¹⁹⁹ We have synthesised a library of quinine-derived quaternary ammonium bromides, from which the corresponding fluoride ion is generated *in situ* to carry out the enantioselective desymmetrisation of anhydrides such as **483** *via* alcoholysis. Novel catalyst **515**, the best performing catalyst, was employed in the reaction to furnishing the hemiester product **485** in 72% yield and 62% *ee* after 48 hours. Interestingly, the optimisation of reaction conditions concluded that varying the concentration of the reaction had no effect on stereocontrol, whilst both increasing and decreasing the reaction temperatures diminished the enantiomeric excess of the product.

6 Steglich rearrangement of 2-oxindoles catalysed by Fluoride ion

The synthesis of quaternary stereocentres *via* the Steglich rearrangement of 2-oxindoles is well documented in the literature.^{196, 236, 237} In general, the *O*- to *C*- acyl transfer is facilitated by a nucleophilic DMAP catalyst or other chiral variants. To the best of our knowledge, the fluoride ion has never been employed as a nucleophilic catalyst in any such rearrangement. We hoped to demonstrate the use of fluoride ion as a nucleophilic catalyst in the Steglich rearrangement of 2-oxindoles resulting in the construction of all carbon quaternary stereocentres. This transformation was chosen as effective catalysis can only be nucleophilic in nature due to the absence of no external pronucleophile. If successful, the study would establish beyond doubt the potential of fluoride ion as a nucleophilic catalyst; until now the basic properties of the fluoride ion have made for considerable debate. This project was a collaboration with Dr. M. Litvajova.

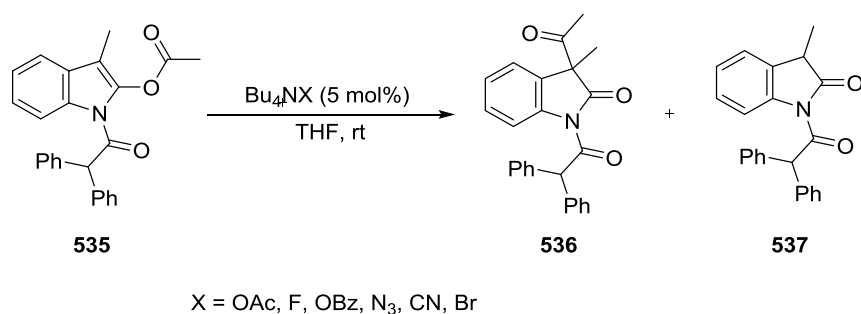
6.1 Preliminary studies

Preliminary studies carried out by Dr. M. Litvajova explored variation in the R^1 and R^2 substituents in 2-oxindole **532** (Scheme 6.1), and how this effected the TBAF-catalysed rearrangement of the oxindole substrate. The efficiency of the reaction was assessed based on the conversion to product **533** along with the minimum formation of the hydrolysed product **534**. Taking our cue from Vedejs *et al.*,²³⁸ a diphenyl acetyl moiety was introduced at the nitrogen atom, while a simple *O*-acetyl group proved optimum for the formation of **533**; bulkier *O*-acyl substituents resulted in the formation of significantly reduced levels of **533**. Moving forward, substrates of general structure **535** were selected to demonstrate catalysis.



Scheme 6.1 Substrate optimisation for the TBAF-catalysed rearrangement

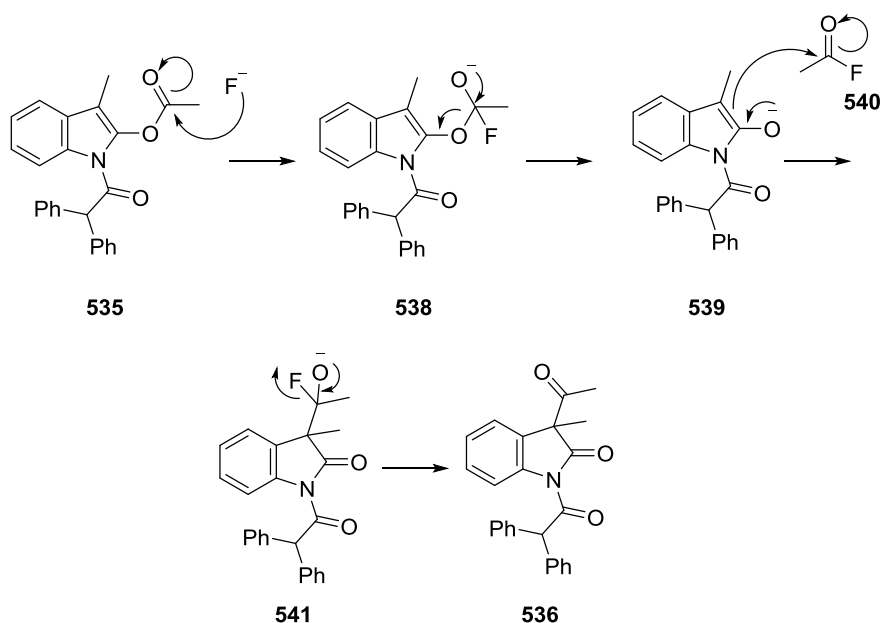
The preliminary studies also evaluated several other tetrabutylammonium salts in the rearrangement of **535** (Scheme 6.2). The results obtained using TBAOAc were comparable but slightly inferior to those employing TBAF, whilst the use of TBAOBz, $TBAN_3$ and TBACN as nucleophilic catalysts depreciated the rate of formation of **536** with comparable by-product formation. The implementation of TBAB as a catalyst resulted in no reaction at all, presumably due to reduced nucleophilicity of the bromide ion. The fluoride salt was thus determined to be the most efficient catalyst for the transformation.



Scheme 6.2 Variation of the tetra-alkylammonium salt

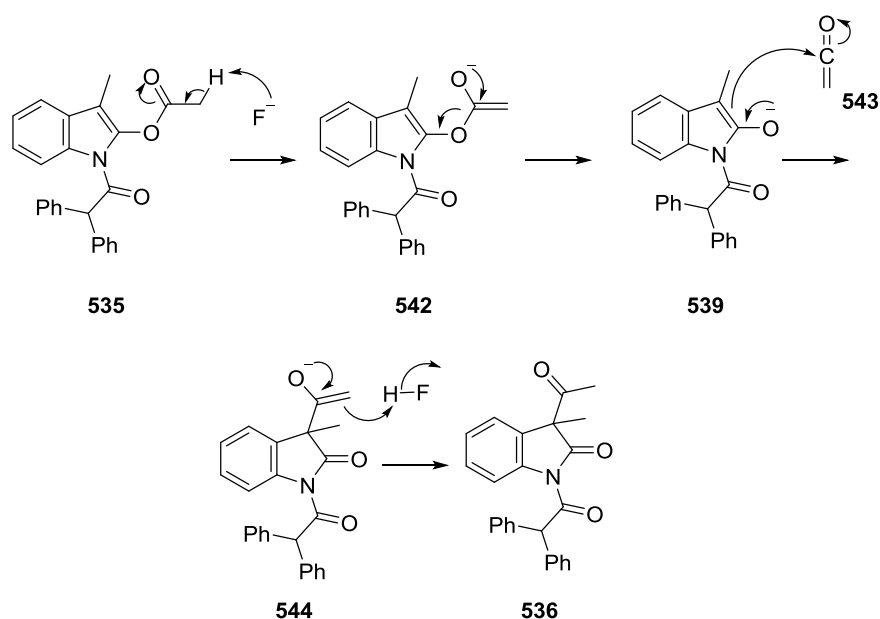
6.2 Mechanistic insights

We have proposed two possible mechanistic routes in order to rationalise the role of TBAF as a catalyst in this *O*- to *C*-acetyl transfer reaction (Scheme 6.3). The first mechanism proceeds *via* an acyl fluoride intermediate. Nucleophilic attack of the fluoride anion on the acetyl group generates **539** and acetyl fluoride **540**. Subsequent attack of **539** on **540** furnished the sp^3 -hybridised tetrahedral intermediate **541**, which collapses to form the product **536**. We believe this to be the most plausible mechanism of action. We will provide evidence to support our hypothesis in the following Section.



Scheme 6.3 Proposed mechanism for the TBAF-catalysed acetyl rearrangement *via* acyl fluoride intermediate **540**.

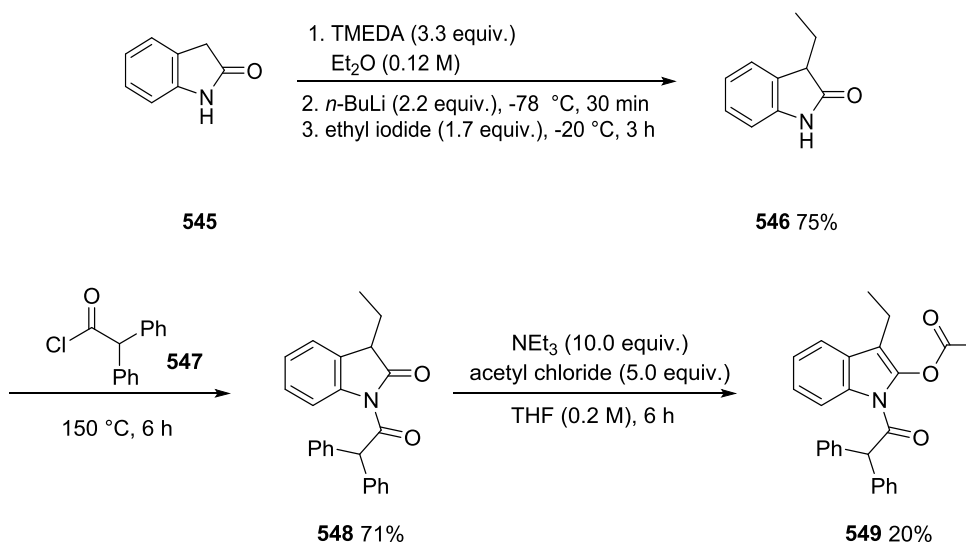
The alternative pathway, which is possible though less likely, occurs *via* basic catalysis. Deprotonation of the acetyl group by fluoride ion generates the anionic intermediate **542** which collapses to form **539** and ketene **543**. Subsequent attack of the enolate on to **543** generates **544** which is protonated to furnish the product **536** (Scheme 6.4).



Scheme 6.4 Alternative mechanism for the TBAF-catalysed acetyl rearrangement in which TBAF acts as a basic catalyst.

6.3 Substrate synthesis

Having established the potential for fluoride to act as an effective nucleophilic catalyst in the rearrangement of **535**, we decided to explore the scope of the reaction based on this optimised structure. A small library, mainly differing in substitution at the 3-position of the oxindole, was envisaged starting with **549**, bearing a 3-ethyl substituent (Scheme 6.5).

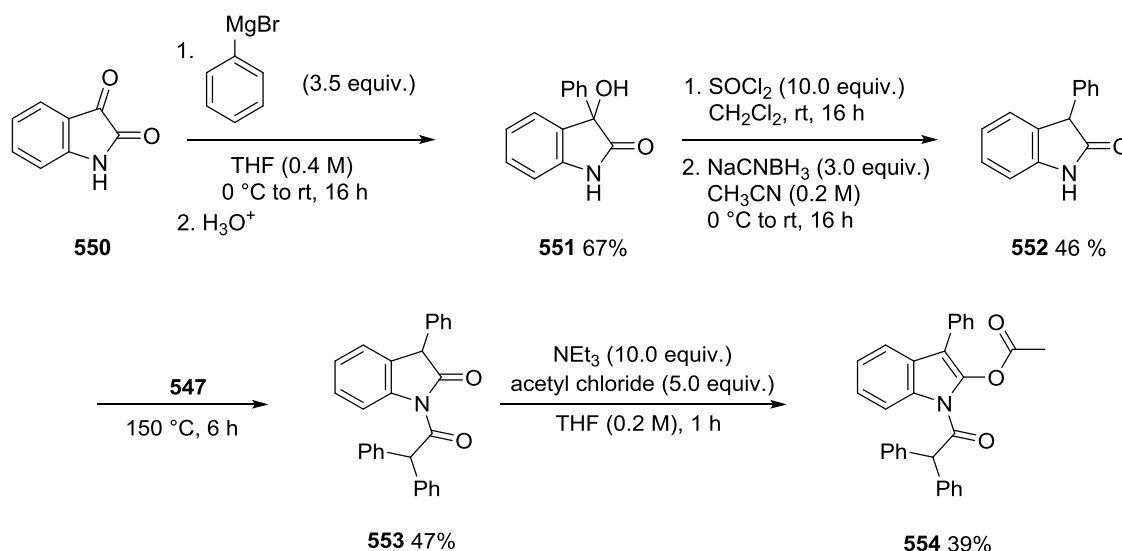


Scheme 6.5 Synthesis of **549**

545 was alkylated at low temperature using *n*-BuLi and ethyl iodide to furnish **546** in 75% yield (Scheme 6.5). Protection of the amide functionality was achieved by heating under reflux **546** in diphenylacetyl chloride for 6 hours. The *O*-acyl unit was installed using excess NEt₃ and acetyl

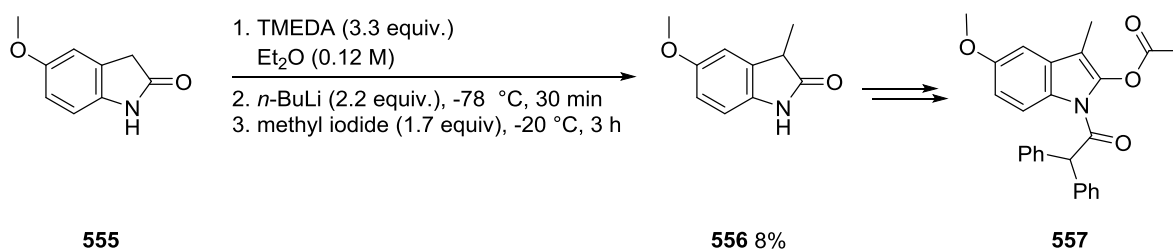
chloride, though conversion to the acetylated product was poor. The product **549** was almost inseparable from the starting material on silica, with concurrent hydrolysis to form **548**. As such, **549** was obtained in low yield.

A different approach was required for the synthesis of **554**. Starting from isatin (**550**) we envisaged installation of the phenyl substituent using a Grignard reagent (Scheme 6.6). Phenyl magnesium bromide was formed *in situ* followed by reaction with isatin to form **551**. Thionyl chloride was employed to form the 3-*O*-acyl chloride with a subsequent reduction using NaCNBH₄ to furnish **552** in moderate yield (46%). Once again, protection of the amide was achieved by refluxing **552** with diphenyl acetyl chloride followed by 2-*O*-acylation with excess NEt₃ and acetyl chloride. In this case, conversion to the product was much improved requiring a reaction time of only one hour. Purification was also much easier; **554** was collected in 39% yield by passing the crude material through a short silica plug, eluting with 20% EtOAc in petroleum ether followed by precipitation with Et₂O.



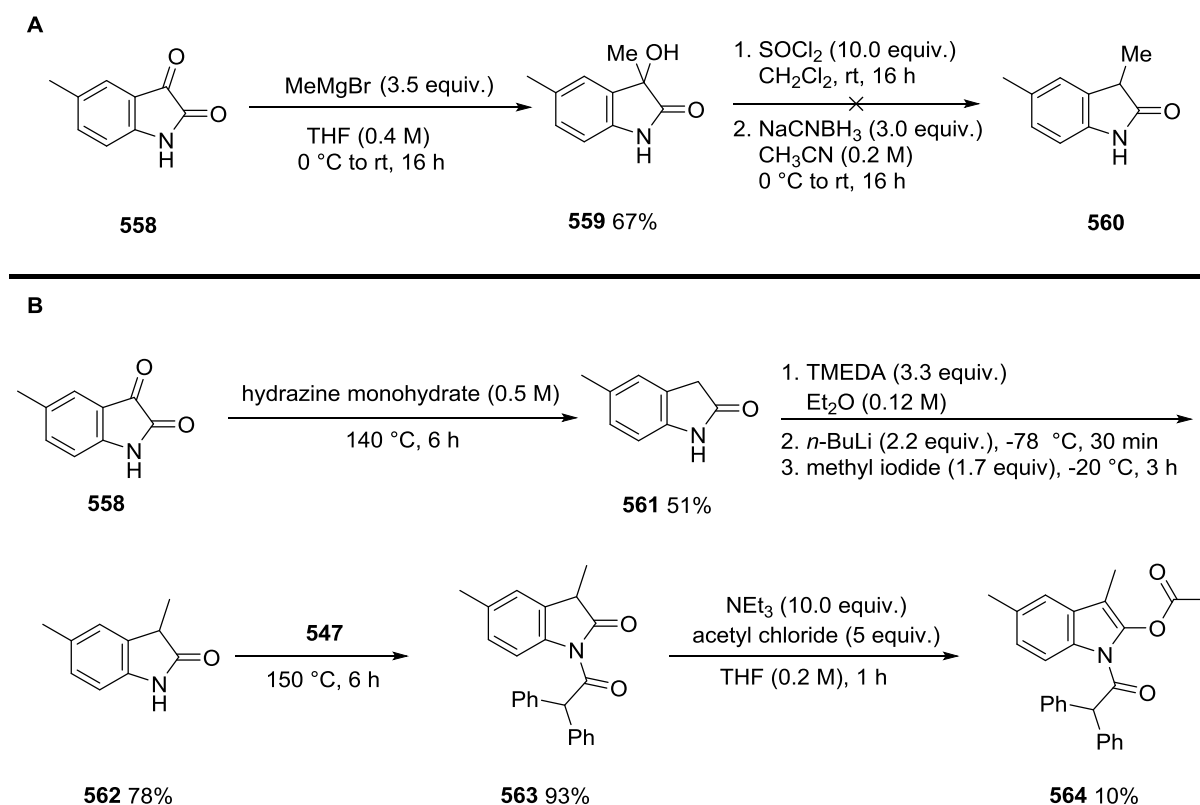
Scheme 6.6 Synthesis of **554**

557 was originally selected for the library in order to demonstrate the effects of introducing an electron donating substituent at 5-position on the phenyl ring (Scheme 6.7). However, the initial step involving the alkylation of **555** proved problematic; the product **556** exhibited enhanced solubility when compared to the starting material at low temperatures, resulting in over-alkylation. Oxindole **556** was obtained in only 8% yield, which was too low for practical purposes. The synthesis of **557** was abandoned. Instead we synthesised **562**, bearing a methyl group at 5-position on the phenyl ring.



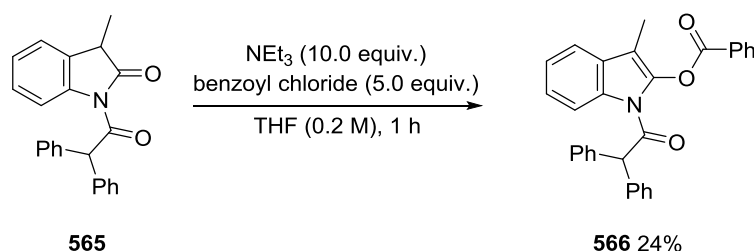
Scheme 6.7 Attempted synthesis of **557**

Based on previous our synthesis **554**, we hoped to access intermediate **560** from the isatin derivative **558** using a Grignard reagent followed by reduction of the hydroxyl group (Scheme 6.8). Though the alkylated product **559** was achieved in moderate yield, the reductive step did not yield any product. As such, we tried an alternative approach. Instead, **558** was reduced to **561** using hydrazine monohydrate. Subsequent alkylation of **561** with *n*-BuLi and methyl iodide, followed by installation of the *N*-protecting group and the sequential *O*-acylation *via* the usual methods furnished the product **564**. Once again a low yield was obtained due to poor separation of **564** and **563** on silica, coupled with the tendency of **564** to hydrolyse back to **563** on silica.



Scheme 6.8 Synthesis of **564**

The final compound **566** was selected in order to demonstrate whether the *O*-acyl rearrangement was occurring *via* nucleophilic or basic catalysis. *O*-Acylation of **565** was achieved using excess NEt₃ and benzoyl chloride to produce **566** in 24% yield (Scheme 6.9).



Scheme 6.9 Synthesis of **566**

6.4 TBAF-catalysed Steglich esterification of 2-oxindoles

With a range of 2-oxindole derivatives in hand, we began to explore the reach of the TBAF-catalysed *O*- to *C*-acetyl transfer (Table 6.1). The optimised reaction was carried out using **535** as the benchmark substrate (entry 1). Complete conversion of the starting material was obtained after only 30 minutes, resulting in 91% formation of the desired product **536** along with 7% hydrolysis to **537**. Ethyl-substituted **549** was slower to react (entry 2); the diminished reaction rate was attributed to the increased steric demand surrounding the reaction centre. The 3-phenyl-substituted oxindole **554** failed to react under the outlined conditions (entry 3); once again, the augmented steric hindrance at the 3-position was the rationale for the lack of activity. Introduction of an electron donating group at 5-position of the oxindole (**564**) was advantageous for reactivity, resulting in 88% formation of the product after only 15 minutes (entry 4).

Oxindole derivative **566** was synthesised in order to help elucidate the mechanism of the rearrangement (Table 6.1, entry 5). As discussed in Section 6.2, two plausible mechanistic pathways for were proposed for the reaction: nucleophilic catalysis *via* acyl fluoride intermediate **540** vs. basic catalysis involving ketene **543**. We postulated that the synthesis of a substrate lacking a labile α -proton on the *O*-acyl group (*i.e.* **566**) would remove any potential for TBAF to act as a basic catalyst, thus the reaction should only proceed through the nucleophilic mechanism outlined in Scheme 6.3. Substrate **566** was subjected to the optimised reaction conditions resulting in excellent conversion after 45 minutes. Product **573** was formed in good yield with small but significant levels of concomitant hydrolysis. The activity of **566** in the reaction provides unequivocal proof that nucleophilic catalysis plays a critical role in the TBAF-catalysed Steglich rearrangement of 2-oxindoles of general structure **567**, though the possibility of coinciding basic catalysis remains for oxindoles substrates containing a labile α -proton (*e.g.* **535**).

Table 6.1 TBAF catalysed Steglich esterification of 2-oxindoles

Reaction scheme showing the TBAF-catalyzed Steglich esterification of 2-oxindole **567** to form products **568** and **569** in THF at room temperature.

Entry	Substrate (567)	Product (568)	t (min)	568 (%) ^[a]	569 (%) ^[a]	SM (%) ^[a]
1 ^b	535	536	30	91	7	0
2	549	570	100	87	11	2
3	554	571	120	0	0	100
4	564	572	15	88	8	2
5	566	573	45	77	16	7

^a Conversion of the substrate was measured using ¹H NMR spectroscopy. ^b Reactions were carried out by Dr. M. Litvajova.

The substrates **576**, **577**, and **578** were also employed in this study (by Dr. M. Litvajova); while the substrates bearing allyl and benzyl substituents at the 3-position performed well, the activity of **578** possessing a bulky *i*Pr substituent was diminished (Table 6.2, entries 1-3).

Table 6.2 TBAF-catalysed Steglich esterification of 2-oxindoles carried out by Dr. M. Litvajova

Reaction scheme showing the TBAF-catalyzed Steglich esterification of 2-oxindole **567a** to form products **568a** and **569a** in THF at room temperature.

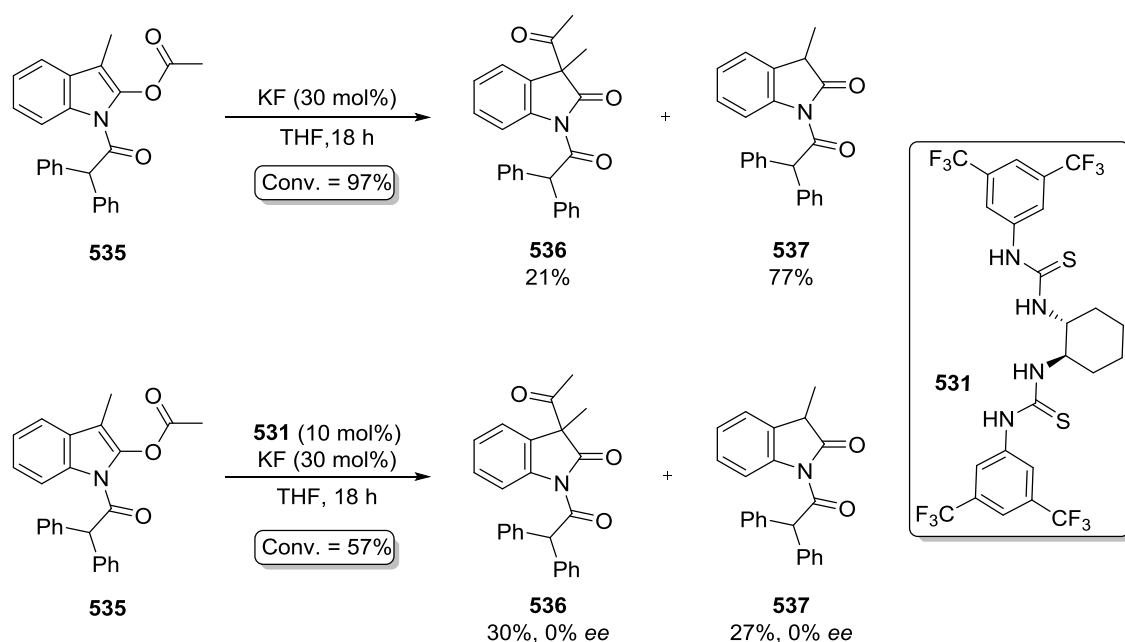
Entry	Substrate (567a)	R	Product (568a)	t (min)	568a (%) ^[a]	569a (%) ^[a]	SM (%) ^[a]
1	576	All	579	15	81	8	0
2	577	Bn	580	30	92	0	0
3	578	<i>i</i> Pr	581	45	14	19	6

^a Conversion of the substrate was measured using ¹H NMR spectroscopy.

In summary, the TBAF-catalysed Steglich rearrangement of 2-oxindoles was achieved in high yield in the case of substrate **535**. The introduction of bulkier alkyl substituents at the 3-position (*e.g.* ethyl and *i*Pr) afforded diminished levels of reactivity, while the installation of electron-donating groups at the 5-position appears to be beneficial. Substrates bearing allyl and benzyl functionalities at the 3-position performed well, in contrast to those bearing bulky phenyl substitutions which resulted in no activity whatsoever.

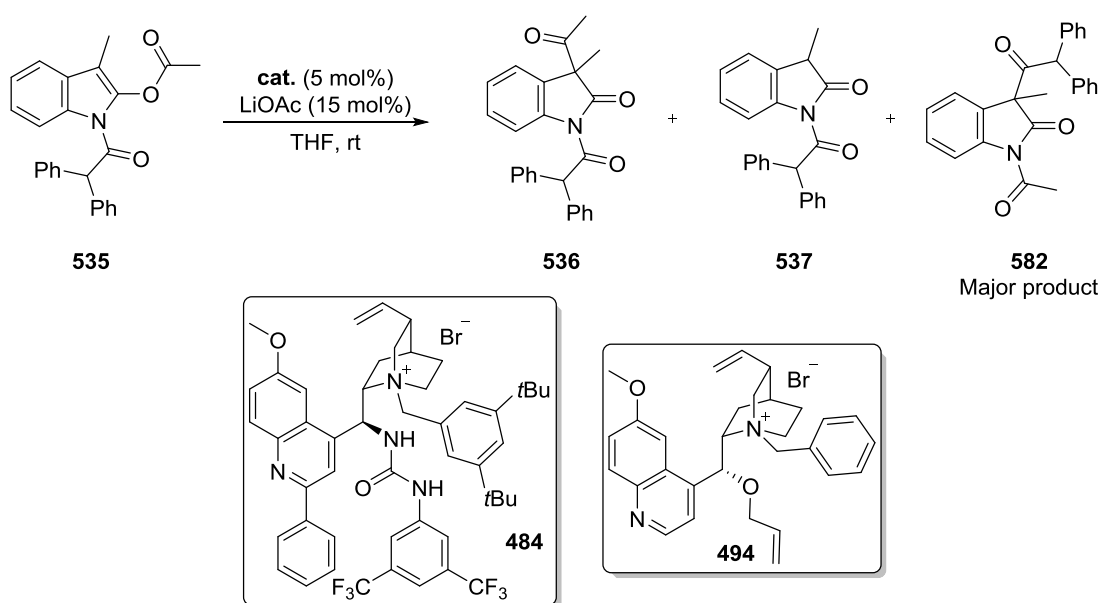
6.5 Efforts towards an enantioselective reaction

Confident that we had effectively demonstrated the use of fluoride ion in catalysing the Steglich rearrangement of 2-oxindoles such as **535**, we directed our efforts towards the development of an enantioselective variant of the reaction. Taking a cue from Gouverneur *et al.*²³⁵ we decided to employ KF along with hydrogen bonding catalyst **531** to act as a solid-liquid phase transfer catalyst to yield a chiral urea-bound fluoride ion as our nucleophilic catalyst. However, a background reaction carried out in the absence of catalyst **531** (*i.e.* using 30 mol% KF alone) resulted in 97% conversion of the starting material after 18 hours (Scheme 6.10). In contrast, when 10 mol% catalyst was employed 57% conversion of the starting material was observed in the same time-frame (Scheme 6.10), suggesting the hydrogen bonding catalyst retards the activity of the fluoride ion (further evidence of these antagonising properties will be explored in Section 8). The ability of fluoride ion to deprotonate (thio)urea N-H atoms under certain reaction conditions is also known. Both the rearranged product **536** and the hydrolysed product **537** were isolated from the reaction mixture and were determined to be racemic by CSP-HPLC. It is likely that the excess KF was responsible for all observed catalytic activity whilst the urea bound fluoride remained inert to the reaction conditions.



Scheme 6.10 Oxindole rearrangement catalysed by KF and **531**

Concurrently, my colleague Dr. Mili Litvajova explored the use of *cinchona* alkaloid-derived quaternary ammonium bromides as phase transfer catalysts in conjunction with LiOAc in the transformation with no success (Scheme 6.11). Interestingly, in these transformations compound **582** was observed as the major product with **536** and **537** being formed in significantly lower amounts. Surprisingly, experiments carried out using TBAB as a catalyst showed that the formation of product **582** was likely to be catalysed by the quaternary ammonium bromide alone rather than the *in situ* reaction with the inorganic metal salt. Despite our best efforts to develop an enantioselective variant of the fluoride catalysed reaction we did not succeed in the asymmetric acetyl transfer involving **535**.



Scheme 6.11 Oxindole rearrangement catalysed by quaternary ammonium bromides and metal salts

6.6 Conclusion

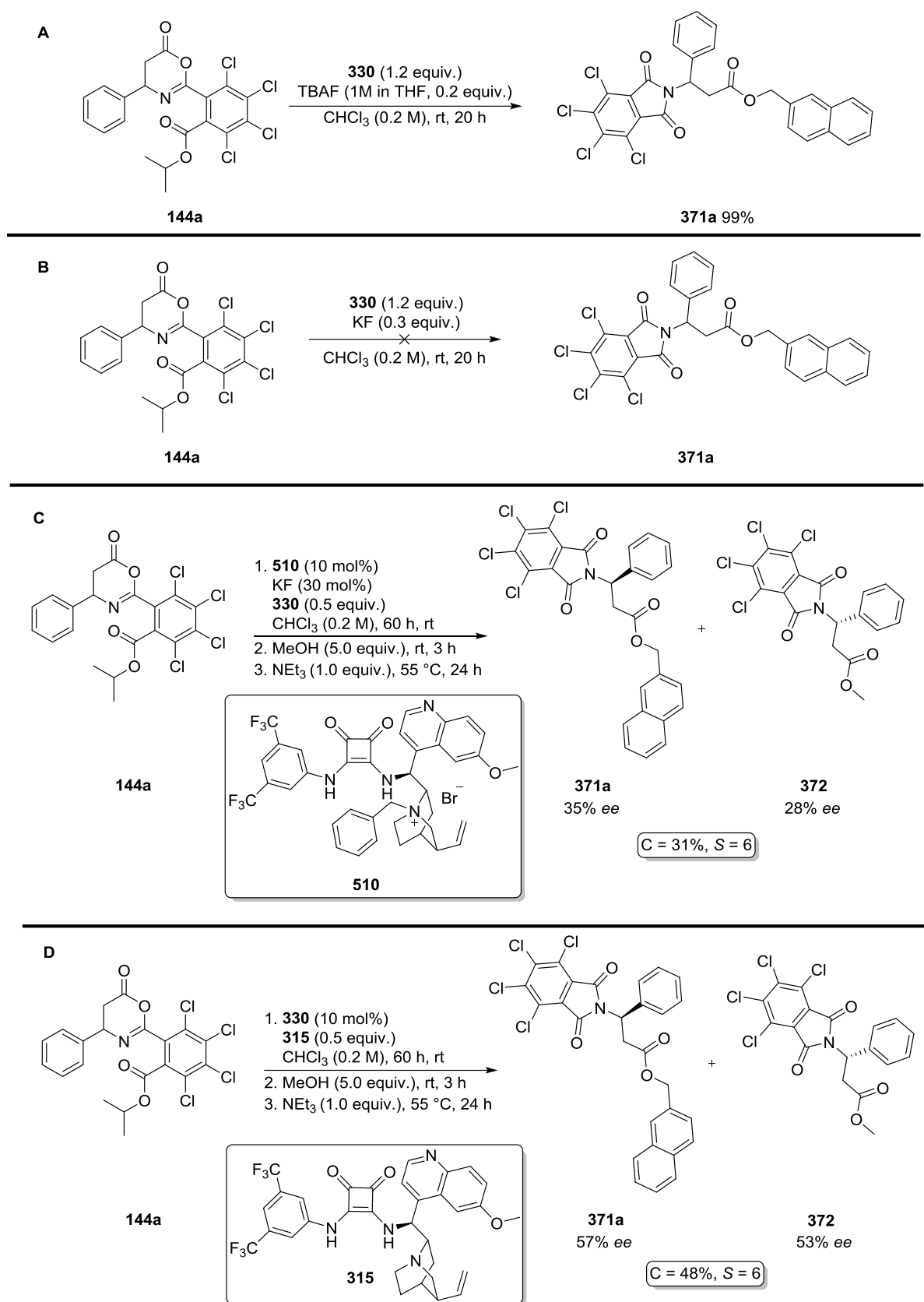
In conclusion, we have demonstrated the first use of a fluoride ion as a nucleophilic catalyst in the Steglich esterification of *O*-acetylated oxindoles. The scope of the reaction was demonstrated on a range of 3-substituted *O*-acetylated oxindoles employing TBAF as a nucleophilic catalyst; to obtain the rearranged products in good yield. We have also provided evidence in support of nucleophilic catalysis as the *modus operandum*. Our efforts to perform the rearrangement in an enantioselective fashion were unsuccessful.

7 The fluoride catalysed aminolysis of oxazinones

Having successfully demonstrated the use of fluoride ion as a nucleophilic catalyst in the asymmetric desymmetrisation of *meso*-anhydrides and in the Steglich esterification of *O*-acetylated oxindoles, we decided to try and use this novel methodology to tackle one of the key challenges in synthetic chemistry: namely, the enantioselective aminolysis of acyl centres. Over the years this has remained an elusive topic. Amine nucleophiles are highly reactive towards acyl centres and thus their addition is extremely hard to control; the background addition of the amine tends to predominate. We envisioned that through careful tuning of the electronic character of the amine, we could potentially control its addition to an oxazinone substrate using a fluoride ion catalyst. In this manner, we hoped to develop a protocol for the KR of oxazinones *via* aminolysis, the invention of which would possess immense synthetic value. To the best of our knowledge no such transformation currently exists in the literature.

7.1 Preliminary experiments

In a previous study exploring the KR of TCIC-oxazinones *via* alcoholysis using bifunctional organocatalysts, we observed that TBAF exhibited enhanced activity in catalysing the racemic reaction relative to the amine catalyst DIPEA (see Section 2.10 and Scheme 7.1A). We postulated that the superior activity of TBAF as a catalyst in this transformation could be due to either the augmented basicity of the naked fluoride ion (*vs* the neutral amine DIPEA) or its potential to act as an unhindered nucleophilic catalyst, or a combination both properties. Having recently developed a methodology for the asymmetric desymmetrisation of *meso*-anhydrides *via* alcoholysis using a chiral ammonium fluoride generated *in situ* using a phase transfer catalyst and catalytic KF, {Craig, 2018 #207} we decided it was prudent to see if a similar system could catalyse the KR of TCIC-oxazinones *via* alcoholysis. First, a control reaction was carried to determine whether alcohol **330** would add to **144a** in the presence of KF alone. No conversion of **144a** was observed after 18 h, thus confirming that no background alcoholysis of **144a** should occur (Scheme 7.1B). Next, phase transfer catalyst **510** was employed in conjunction with catalytic KF. To our delight, the reaction system furnished the desired products **371a** and **372** in 35% *ee* and 28% *ee* respectively; a corresponding *S* factor of 6 was calculated for the overall process (Scheme 7.1C). We were encouraged by this result as this was the first, unoptimised attempt at the resolution of oxazinones using this novel methodology, and the results were comparable with those previously obtained using the equivalent bifunctional catalyst **315** at room temperature (*S* = 6, Scheme 7.1D). As was the case with the TBAF-catalysed reaction, we believed that the transformation could be operating *via* either nucleophilic or general base catalysis, or as an amalgam of the two.

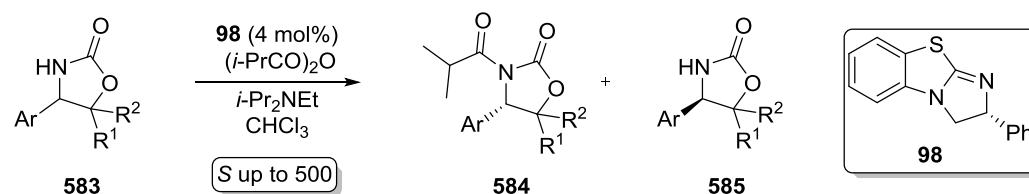


Scheme 7.1 Alcoholysis of **144a**

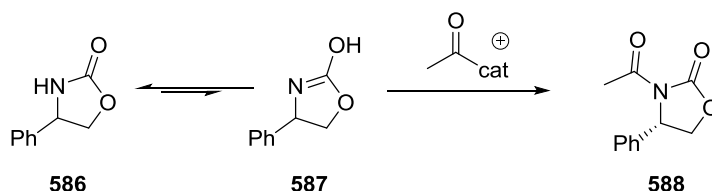
7.2 Design of the amide pronucleophile

Having achieved an enantiodiscriminative reaction for the KR of **144a** *via* alcoholysis using a quaternary ammonium fluoride catalyst, we turned our attention towards the development KR protocol *via* aminolysis using a similar system. As previously mentioned, controlling the addition of amines to acyl centres is problematic due to their enhanced nucleophilicity, relative to alcohols. We envisioned tuning the nucleophilicity of the amine nucleophile through the addition of various electron withdrawing substituents to the nitrogen atom. Indeed, Birman *et al.* had achieved the enantioselective *N*-acylation of secondary amides (oxazolidin-2-ones (**583**)/ β -lactams/thiolactams) with simple anhydrides using BTM catalyst **98**, obtaining *S* factors of up to 500 for the process (Scheme 7.2A).^{239, 240} Interestingly, they noted that the experimentally observed reactivity of the amide component in the acylation reaction was in direct correlation with the corresponding DFT calculated proton acidity of the amide: amides of enhanced acidity exhibited higher reactivity with a threshold proton affinity of 4.29 kcal/mol. Computational modelling verified that the reaction mechanism was most likely to occur as a result of tautomerisation of the oxazolidinone **586** followed by *N*-acylation of the catalyst-activated acyl centre (Scheme 7.2B).²³⁹

A : *N*-acylation of oxazolidin-2-ones

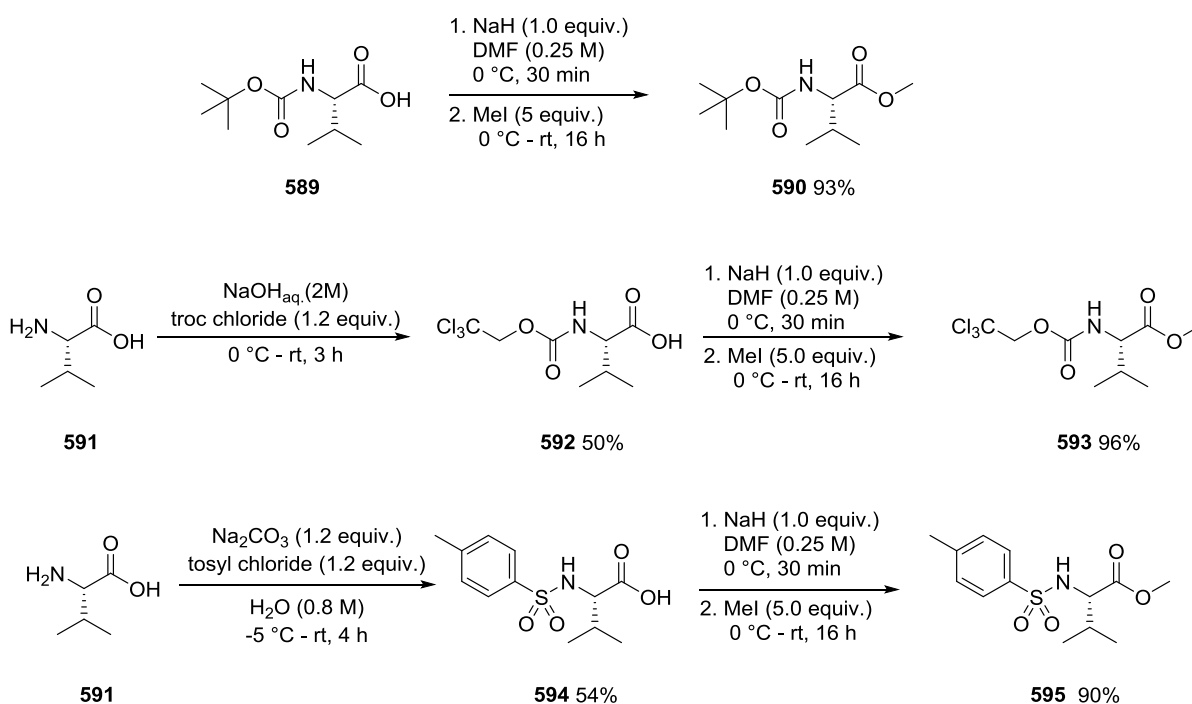


B : proposed mechanism for the *N*-acylation reaction



Scheme 7.2 KR of oxazolidin-2-ones using **98** by Birman *et al.*

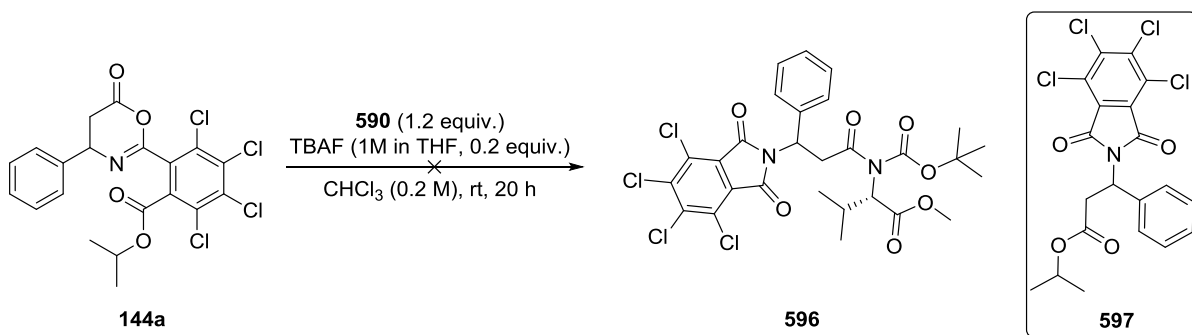
The overall objective of our study was to ultimately achieve KR of oxazinones *via* aminolysis using an *N*-protected amino acid nucleophile, thereby carrying out the resolution and peptide coupling in one step. We began by synthesising a series of *N*-protected methyl valinates of varying pK_a values (Scheme 7.3). Amide **590**, which was synthesised in 93% yield from *N*-*boc* valine and was given an approximate pK_a value of 12 in H_2O .²⁰⁹ Amide **593** was synthesised as it was predicted to be even more acidic due to the electron withdrawing trichloroethanol substituent. Tosyl sulfonamide **595** with an approximate pK_a of 10 was also synthesised for the initial study.²⁰⁹



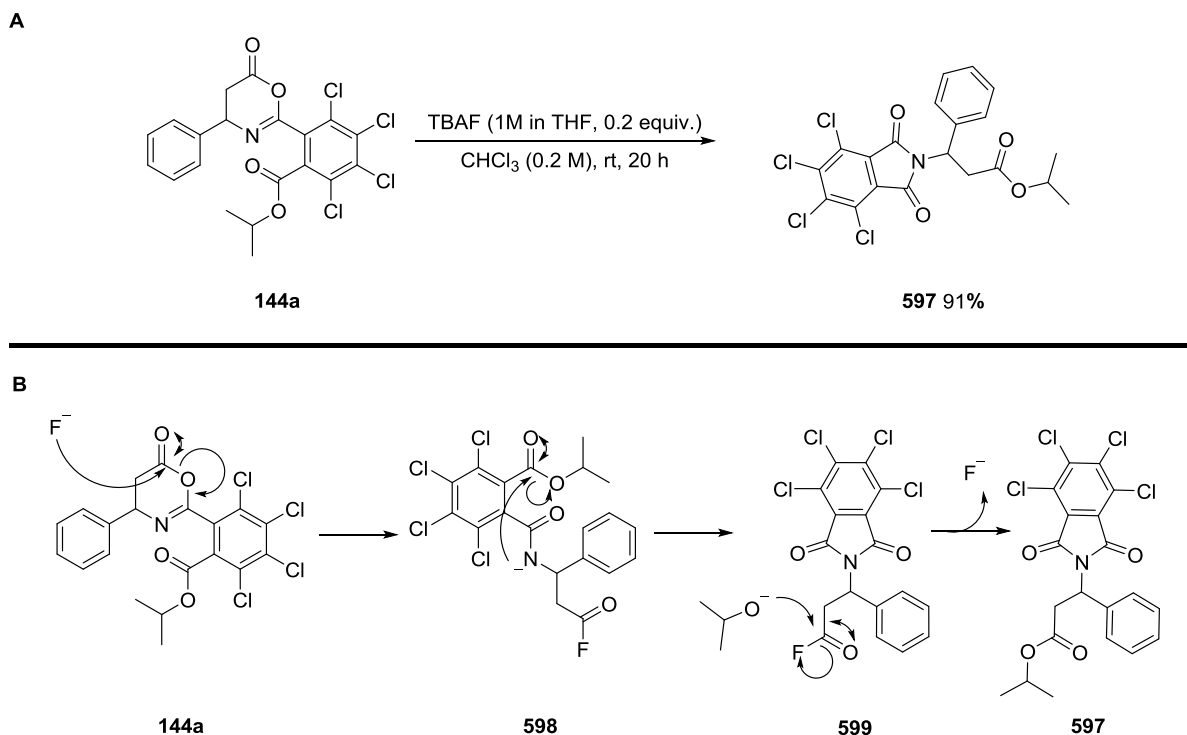
Scheme 7.3 Synthesis of secondary amides **590**, **593** and **595**

7.3 Development of the fluoride -catalysed aminolysis of oxazinones

The use of such acidic sulfonamides as nucleophiles in traditional quinuclidine-catalysed reactions would likely result in the protonation of the catalyst, rendering it inactive. We predicted that this would not be a concern in the case of quaternary ammonium fluoride catalysts. Alkylation of the quinuclidine nitrogen atom to form the quaternary ammonium salt in conjunction with an external source of KF should (in theory) be more tolerant towards pronucleophiles of enhanced acidity. Secondary amide **590** was employed in the aminolysis of **144a** using TBAF as a racemic catalyst however, desired product **596** was not obtained. Instead, the clean conversion of **144a** to **597** was observed (Scheme 7.4).

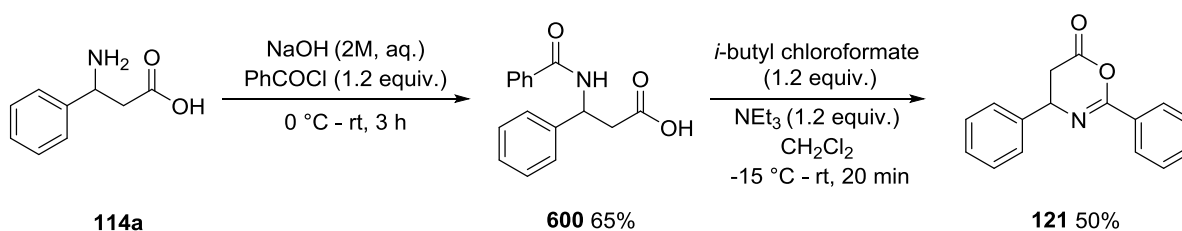


Scheme 7.4 TBAF catalysed ring opening of **144a**



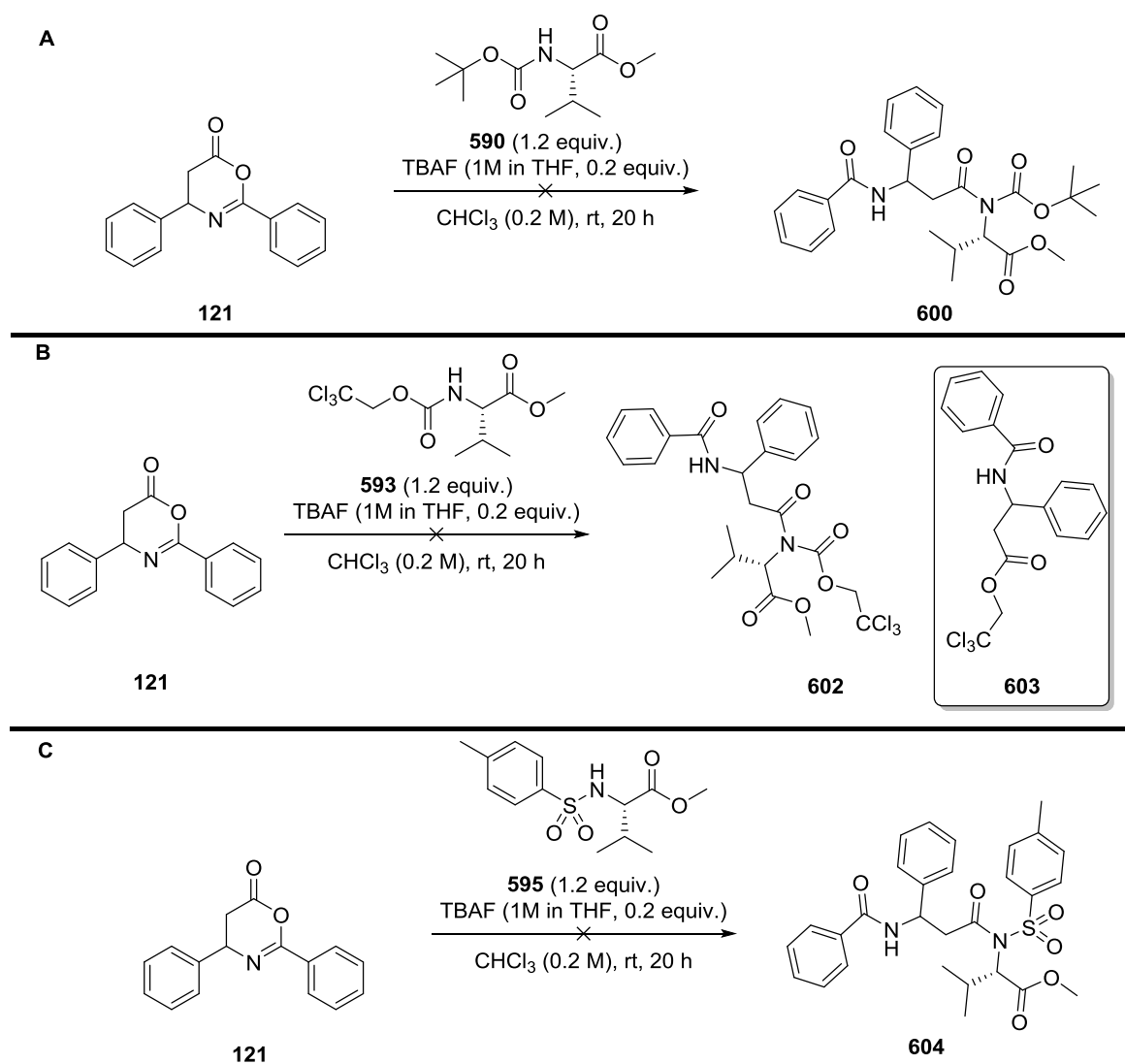
Scheme 7.5 TBAF-catalysed ring opening of **144a** in the absence of a reactive pronucleophile

A control reaction to investigate reactivity between **144a** and TBAF in the absence of a nucleophile was subsequently carried out. Full conversion to the product **597** was observed (Scheme 7.5A). Mechanistically, several plausible routes were suggested for the formation of **597**, one of which includes the ring opening fluorinolysis of **144a** by the TBAF fluoride to form acid fluoride **598**. Intramolecular ring closure of the amide anion onto the isopropyl ester would form phthalimide **599** followed by nucleophilic attack of the liberated isopropoxide anion on the acid fluoride to furnish **597** (Scheme 7.5B). It was concluded that in the absence of a reactive pronucleophile (such as an alcohol) the formation of **597** as a product will predominate. We reasoned that removal of the isopropyl ester moiety should circumvent the issue as there would be no competing pronucleophile for the aminolysis reaction. As such, oxazinone **121** was synthesised from β -amino acid **114a** (Scheme 7.6).



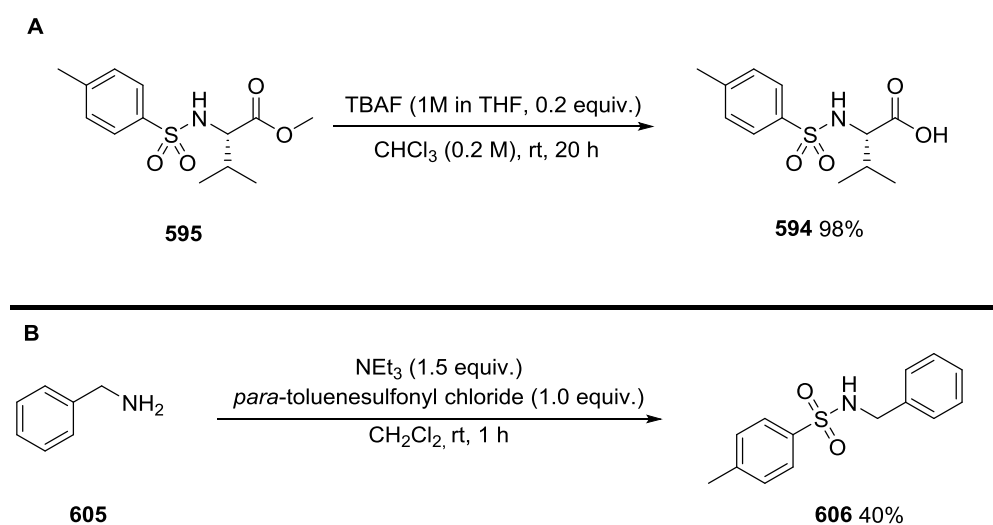
Scheme 7.6 Synthesis of oxazinone **121**

Amide **590** was trialled in the racemic aminolysis of **121** using TBAF as a catalyst. Once again the Boc protected amine failed to ring open the oxazinone and eventually the TBAF catalysed hydrolysis of substrate **121** occurred instead (Scheme 7.7A). The troc-protected amine **593** was next employed in the reaction but the desired product **602** was not observed. Rather, **603** was isolated as the reaction product (Scheme 7.7 B). TBAF is known in the literature to cleave troc-protecting groups, liberating 2,2,2-trichloroethanol as a by-product (though usually an excess of TBAF is required).²⁴¹ In this instance, 20 mol% of TBAF appears to have catalytically cleaved the troc-ester and as such, the accompanying 2,2,2-trichloroethanol took part in the ring opening alcoholysis of **121** to furnish the **603**. Lastly in the case of TBAF catalysed aminolysis of **121** using sulfonamide **595**, no conversion of oxazinone was observed (Scheme 7.7C).



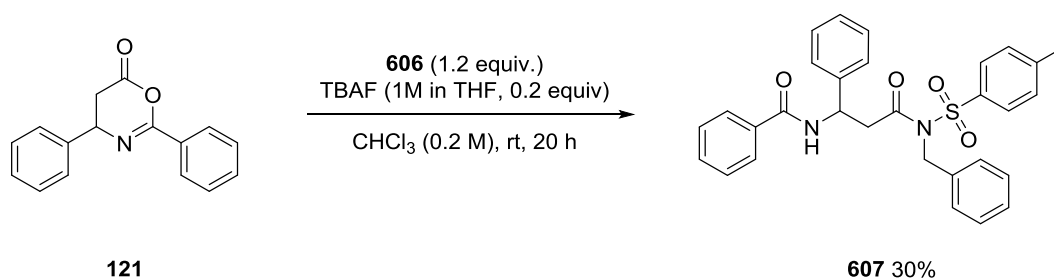
Scheme 7.7 Attempted TBAF catalysed aminolysis of **121** using **590** (A), **593** (B) and **595** (C).

Having noticed that catalytic TBAF resulted in the unexpected cleavage of troc amine **593**, we were curious as to the stability of the methyl ester protecting group present in all three pronucleophiles **590**, **593**, and **595**. To investigate, catalytic TBAF was added to a solution of **595** in CHCl_3 , resulting in 98% cleavage of the methyl ester after 20 h (observed *via* ^1H NMR spectroscopy using *para*-iodoanisole as an internal standard, Scheme 7.8A). We concluded that the other protected amino acid nucleophiles were also likely to be compromised by the reaction conditions. We predicted that the much simpler benzylsulfonamide **606** should not be degraded by TBAF and thus **606** was synthesised in 40% yield from benzyl amine and *para*-toluenesulfonyl chloride (Scheme 7.8 B).



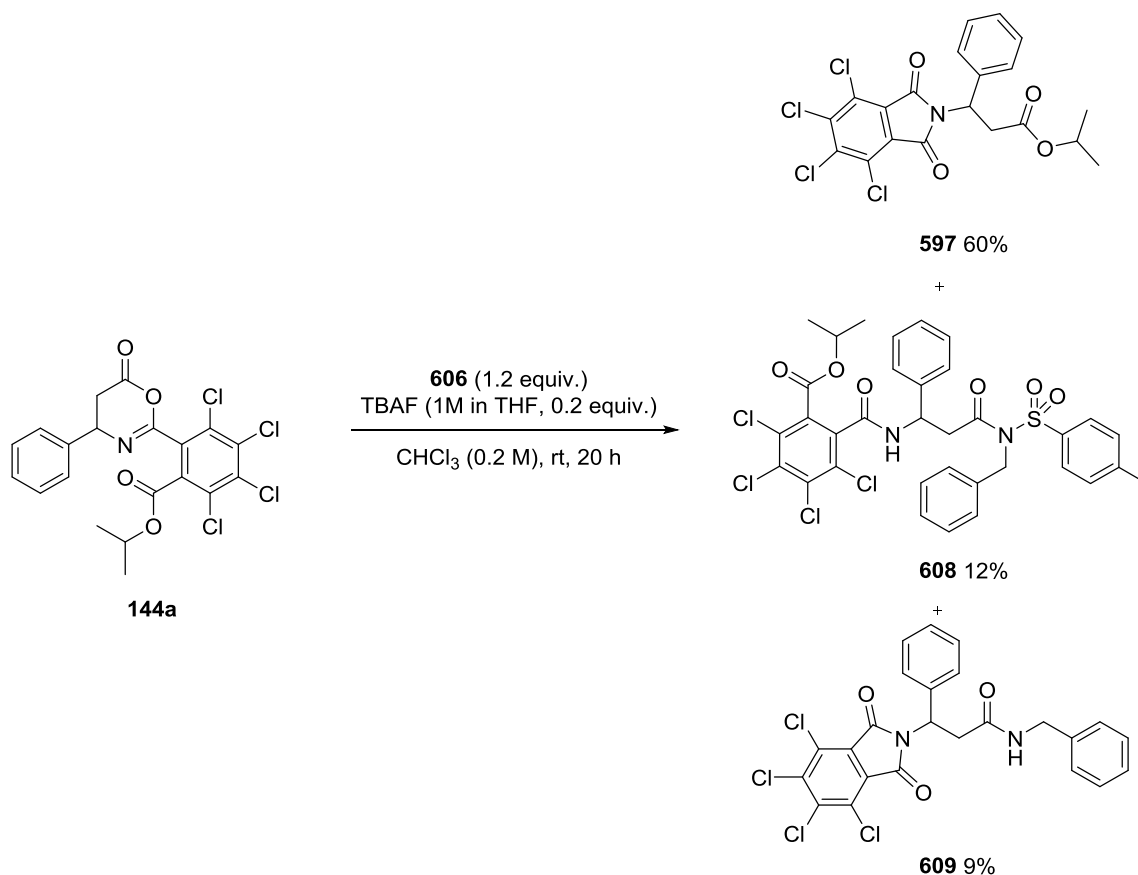
Scheme 7.8 Unexpected TBAF-catalysed deprotection of **595** and synthesis of **606**

Sulfonamide **606** was added to **121** in the presence of catalytic TBAF. To our delight, the product **607** was obtained in 30% yield, with the other 70% comprising the hydrolysed product (Scheme 7.9). A control reaction was simultaneously carried out, confirming that no aminolysis occurred in the absence of TBAF. The results were conclusive: catalytic TBAF could indeed control the addition of sulfonamide **606** to **121**, though addition was slow and the TBAF-catalysed hydrolysis of **121** is competitive.



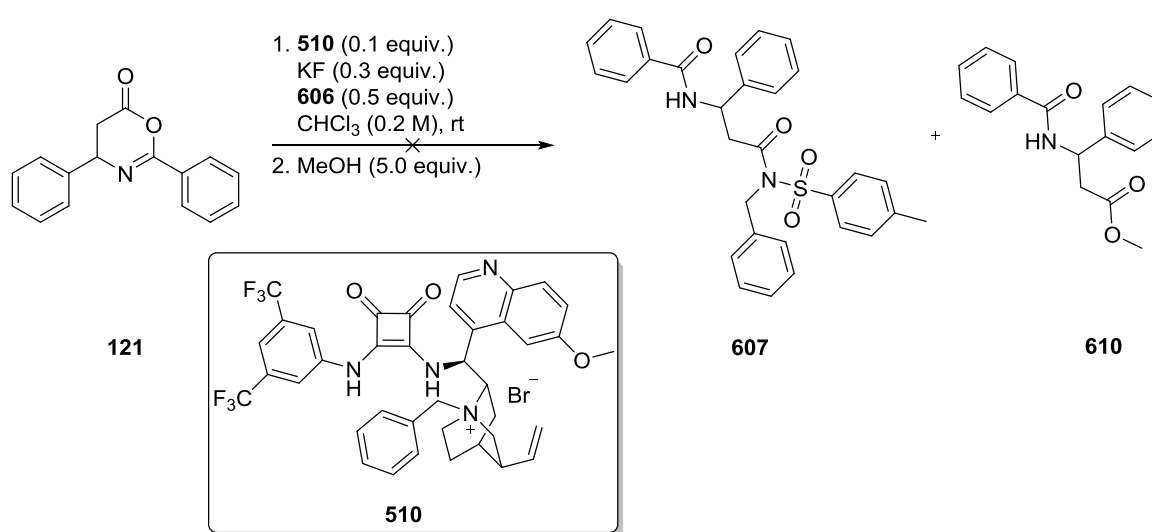
Scheme 7.9 TBAF catalysed aminolysis of **121** with **606**

Sulfonamide **606** was also evaluated for reactivity in the presence of oxazinone **144a**. In the absence of TBAF no conversion of **144a** was observed. When catalytic TBAF was employed, **597** was once again obtained as the predominant product however, **608** and **609** were also isolated in 12% and 9% yield, respectively (Scheme 7.10). Compound **608** is the direct product formed from the aminolysis of **144a** by **606**. Subsequent ring closure of the amide **608** onto the isopropyl ester affords the phthalimide, with an unexpected but concomitant cleavage of the sulfonamide protecting group to furnish **609**. We were encouraged yet perplexed by this finding: ultimately, the synthesis of **609** was the desired outcome of this methodology (as the purpose of the sulfonamide protecting group was to temporarily bias the reactivity of the amine nucleophile in order to control its addition to the oxazinone substrates). Upon aminolysis, the removal of the sulfonamide protecting group from the molecule was envisioned as a subsequent step in the reaction sequence. On further analysis, we noted that cleavage of the sulfonamide protecting group was not observed in the TBAF catalysed aminolysis of **121** which lacked the ability to form the phthalimide product *in situ*. We also observed that, in the case of the aminolysis of **144a**, cleavage of the sulfonamide did not occur until phthalimide formation occurred, as none of the ring-opened desulfonylated product was obtained. In this way, desulfonylation was linked to the liberation of the isopropoxide ion during phthalimide formation, though we can only speculate as to how this exactly occurs.



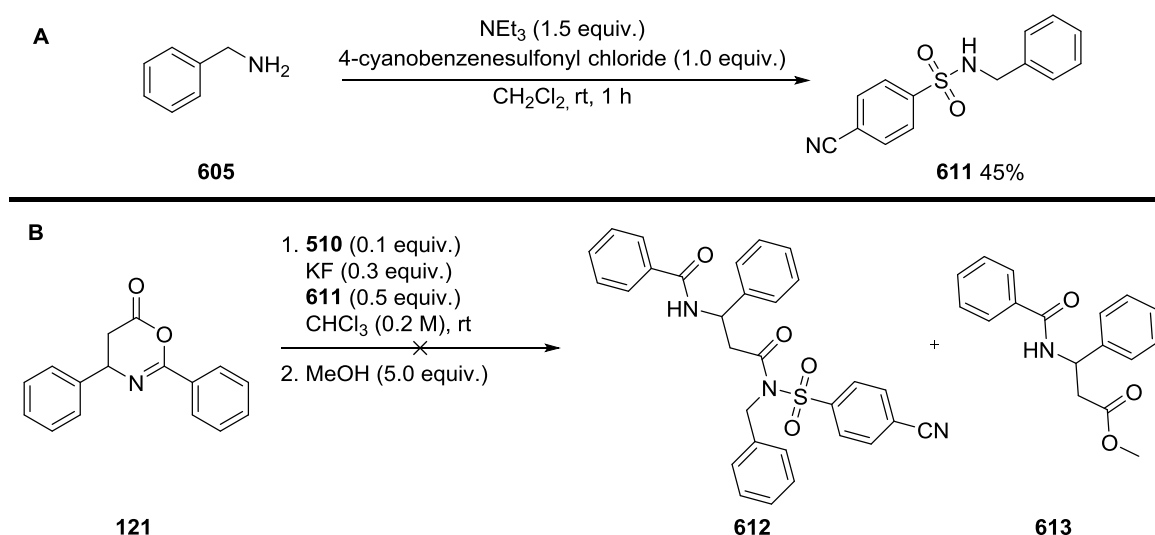
Scheme 7.10 TBAF-catalysed aminolysis of **144a** with **606**

Having successfully and cleanly achieved aminolysis of **121** using TBAF as catalyst we decided to turn our attention towards the development of a KR protocol *via* aminolysis. In a previous study we had employed the use of a phase-transfer catalyst and KF to generate a quaternary ammonium fluoride ion *in situ* (see Section 5).¹⁹⁹ Mimicking this system, phase-transfer catalyst **510** and catalytic KF were employed in the reaction between **121** and **606**, however no conversion of **121** was observed (Scheme 7.11). We postulated that this lack of reactivity is a result of inefficient phase transfer catalysis, giving rise to mass transfer problems. We reasoned that, in this phase transfer system, more reactive reagents may be required to encourage reactivity.



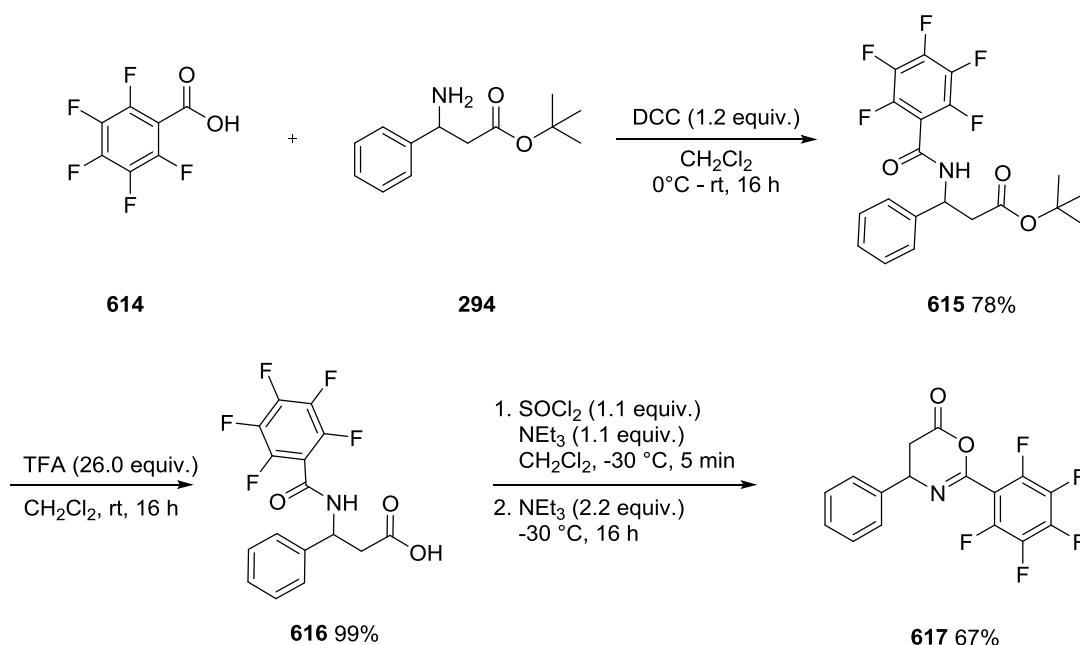
Scheme 7.11 Attempted KR of **121** *via* aminolysis using **510** and KF

Cyanobenzenesulfonamide **611** was synthesised as the N-H moiety was predicted to possess enhanced acidity when compared with toluenesulfonamide counterpart **606** (Scheme 7.12A). However, **121** remained inert to the reaction conditions when **611** was implemented as the pronucleophile in the same phase-transfer reaction (Scheme 7.12B). Rather than further manipulating the amine nucleophile, we turned our attention towards the oxazinone electrophile. We had already achieved the KR of **144a** *via* alcoholysis using the same phase-transfer conditions. As such we reasoned that **121** was not reactive enough for the phase-transfer system and a more reactive oxazinone was required.



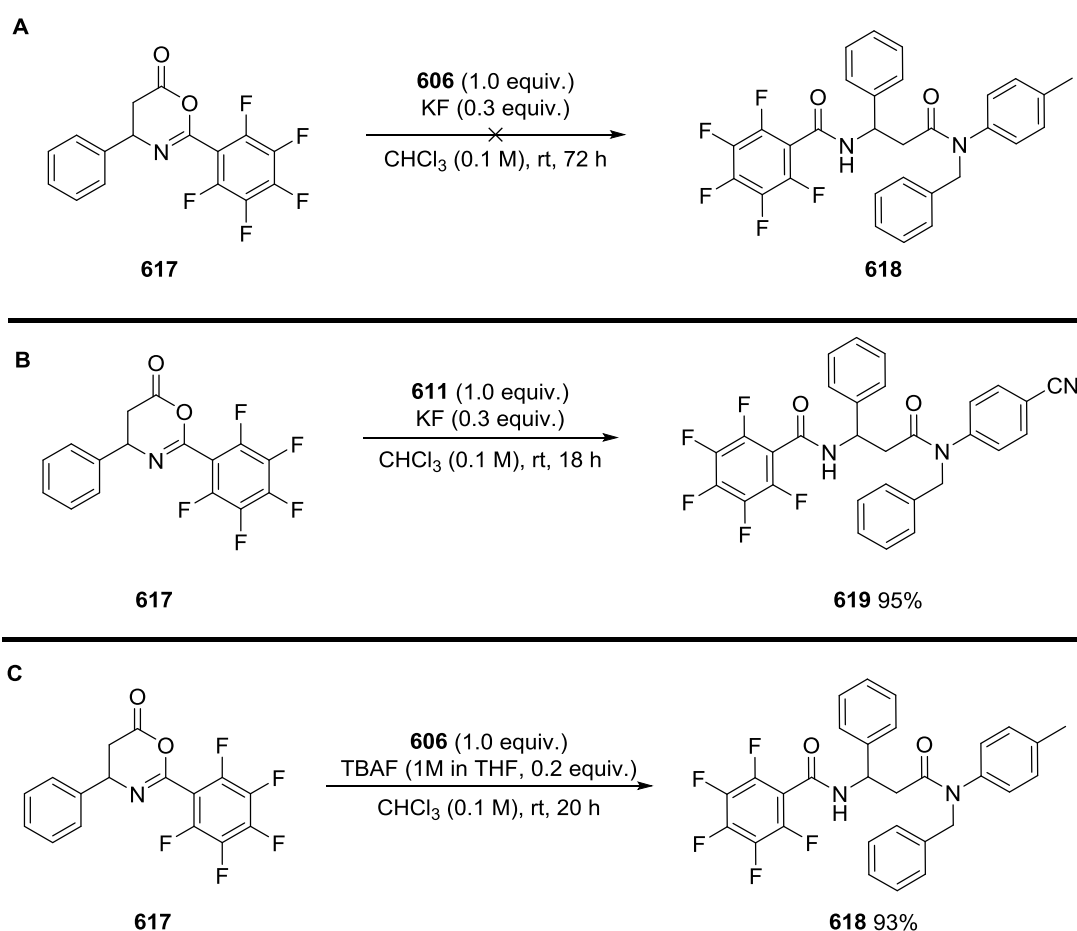
Scheme 7.12 Attempted KR of **121** via aminolysis using amine **611**

Following this, we began the synthesis of oxazinone **617** which we predicted would be more susceptible to fluoride-catalysed ring opening using KF and a phase-transfer catalyst. A DCC-mediated coupling of **614** and **294** afforded **615** in 78% yield (Scheme 7.13). Subsequent deprotection of the *tert*-butyl ester under acidic conditions furnished **616**, which was subjected to SOCl₂ and NEt₃ at low temperatures to promote intramolecular ring closure to **617** which was obtained in 67% yield.



Scheme 7.13 Synthesis of **617**

Initially, we tested for background reactions between **617** and our sulfonamide pronucleophiles **606** and **611** in the presence of KF alone. Encouragingly, no reaction was observed in the case of **606** (Scheme 7.14A). When **611** was employed as a pronucleophile under the same reaction conditions, 95% conversion to **619** occurred after 18 hours (Scheme 7.14 B). In this circumstance it is likely that KF was acting as a base and the enhanced acidity of **611** (due to electron withdrawing *para*-cyano substitution on the aryl-sulfonyl ring), enabled the KF catalysed addition of **611** to **617**. Sulfonamide **611** would not be employed in the asymmetric variant of the reaction due to the uncontrollable background reaction catalysed by KF; rather, our initial, less acidic **606** variant would be utilised. The racemic product **618** was obtained as a reference in 93% yield on reacting **606** and **617** in the presence of TBAF (Scheme 7.14C).



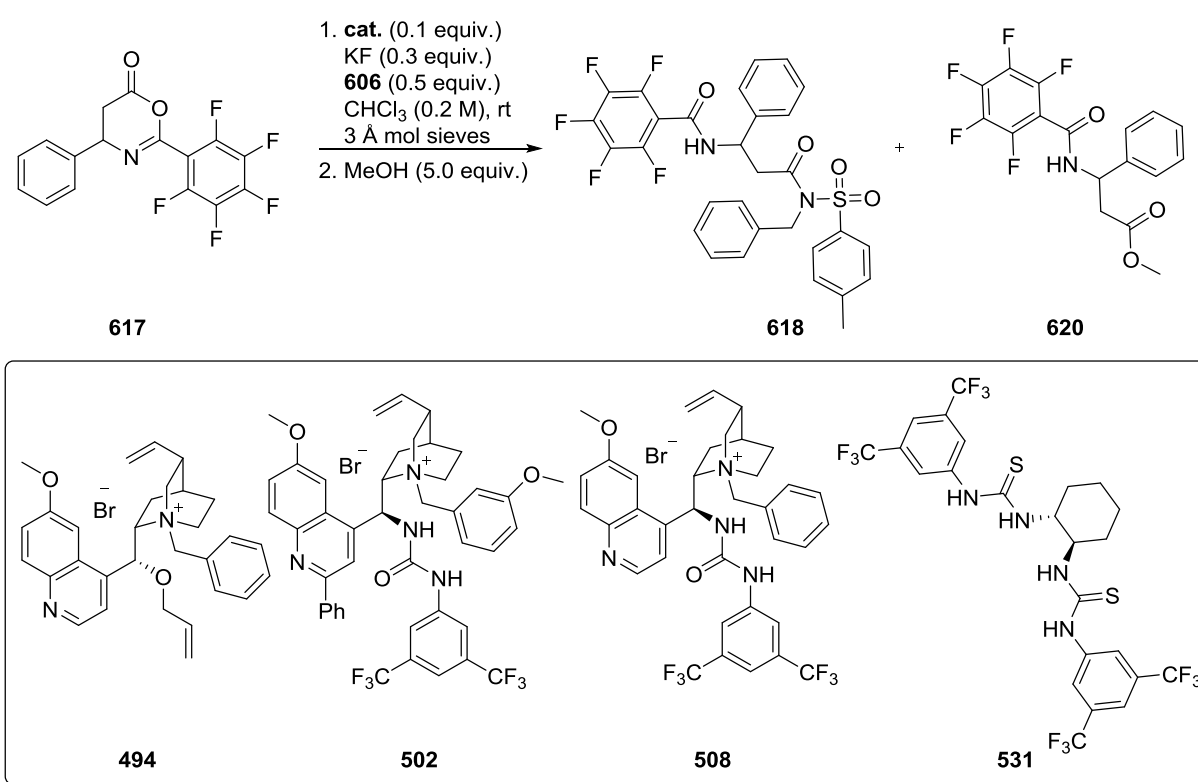
Scheme 7.14 KF and TBAF-catalysed aminolysis of **617**

7.4 Attempted KR of oxazinone **617** via aminolysis

We chose four structurally different catalysts to use in conjunction with KF to investigate whether the enantioselective aminolysis of **617** could be achieved. Strictly anhydrous conditions were employed to minimise the competing hydrolysis reaction. ¹H NMR spectroscopic analysis of the reaction involving the Corey-type catalyst **494** showed 80% conversion of the starting material after

only 36 hours (Scheme 7.1, entry 1); 38% of this belonged to the desired product **618**, while the remaining 42% constituted the hydrolysed product. As the hydrolysis reaction was proving difficult to control, we decided the most accurate assessment of the KR process would lie in the analysis of the remaining starting material at the recorded conversion. Indeed, the *S* factor which measures the efficiency of the overall KR process can be obtained from the *ee* of the starting material at a known conversion using Equation 1.2B (Section 1.3.3) Thus, the remaining starting material (20%) was quenched with methanol and the methyl ester **620** was isolated. To our disappointment, CSP-HPLC analysis of **620** indicated the product to be racemic.

Table 7.1 Aminolysis of **617** with sulfonamide **606** using chiral catalysts **494**, **502**, **508** and **531**



Entry	cat.	t (h)	Conv. (%) ^[a]	618 Yield (%) ^[a]	618 <i>ee</i> (%) ^[b]	620 Yield (%) ^[a]	620 <i>ee</i> (%) ^[b]
1	494	36	80	38	0	20	0
2	502	140	69	15	0	24	0
3	508	84	50	6	0	50	0
4	531	67	69	30	0	31	0

^aDetermined via ¹H NMR spectroscopic analysis. ^bDetermined using CSP-HPLC.

We hoped that the introduction of the hydrogen bonding functionality in catalyst **502** with an accompanying inversion of stereochemistry at C-9 of the quinine backbone would introduce some level of enantiocontrol over the reaction. The use of this catalyst, in partnership with KF, facilitates a much slower reaction; after 140 hours the remaining starting material was quenched using a methanol nucleophile to furnish the racemic product **620** (entry 2). Phase-transfer catalyst **508**, lacking a C-2' phenyl substitution on the quinoline ring, was also used in conjunction with KF to promote 50% conversion of the oxazinone after 84 h, consisting of only 6% of the aminolysis product **618** (entry 3). Discouragingly, the remaining oxazinone starting material was reacted with methanol to afford the racemic product. It was clear that, although the combination of KF and the phase transfer could indeed promote aminolysis of **617**, no enantiodiscrimination was observed. In a final effort to promote the KR of **617** *via* aminolysis, hydrogen bonding catalyst **513** was employed. As was the case with the phase-transfer systems, addition of the sulfonamide to **617** was promoted in racemic fashion (entry 4). The *ee* of the aminolysis products (**618**) of these reactions were also obtained affording the racemic product in each case.

7.5 Conclusion

Although we had successfully managed to promote the addition of sulfonamides such as **606** to oxazinone **617** disappointingly, we failed to achieve enantiocontrol over the reaction. Several structurally distinct catalyst were employed to activate the fluoride ion for catalysis, though in each case, racemic starting material was obtained from the KR process. We postulated that the aminolysis could operate *via* either nucleophilic catalysis, in which the catalyst-facilitated fluoride ion ring-opens the oxazinone to form the acid fluoride followed by nucleophilic attack of the sulfonamide, or general base catalysis where catalyst bound fluoride ion deprotonates the sulfonamide pronucleophile which subsequently adds to the oxazinone. A mixture of the two processes is also possible. Despite our best efforts, we could not promote the reaction asymmetrically; further investigation would have been required to determine the mechanism of aminolysis in order to continue with this work. In view of the racemic products obtained, we decided it was prudent to explore this at a later stage and focus our research efforts in another direction.

8 Fluorinolysis of azlactones

Although our initial strategy towards the development of a KR protocol for the ring-opening aminolysis of oxazinones using PTC and metal fluoride was unsuccessful, we did not abandon hope. The value of the development of such a methodology made further investigation worthwhile. We decided to tackle the problem using an alternative approach. We remained optimistic that fluoride ion could behave as a nucleophilic catalyst in such a transformation. Indeed, our previous studies showed that both TBAF and the PTC/metal fluoride system could successfully catalyse the ring-opening alcoholysis/aminolysis of oxazinones, albeit racemically. We proposed that if we could truly generate a chiral fluoride ion, we could potentially gain enantiocontrol over the fluoride-catalysed ring-opening.

8.1 Premise

We were largely inspired by the work of Seidel *et al.*, who have developed a dual-catalysis anion binding approach for asymmetric acyl transfer reactions (Figure 8.1).²⁴² The concept generates the chiral acylating agent *in situ* with an interplay of three components. Mixtures of DMAP and various acylating agents are known to exist in equilibrium with their acyl pyridinium salts (**622**). Subsequent interaction with a chiral anion receptor forms chiral ion pair **623** which exhibits enhanced electrophilicity/ solubility relative to **622**, and acts as a chiral acyl transfer reagent. Furthermore, addition of the hydrogen bonding catalyst is thought to push the equilibrium of the reaction in favour of the formation of **622**, with which it can react to form **623**.

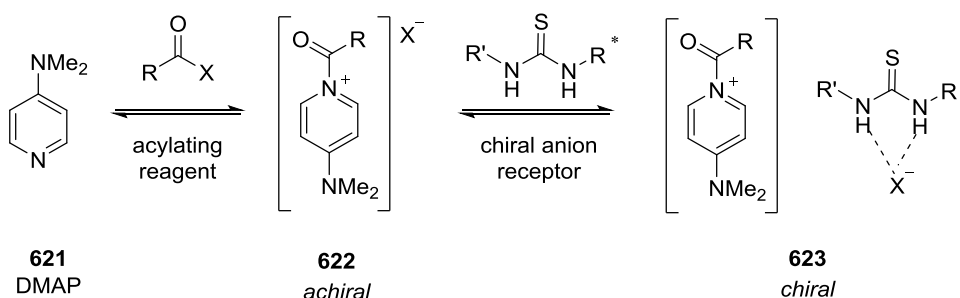
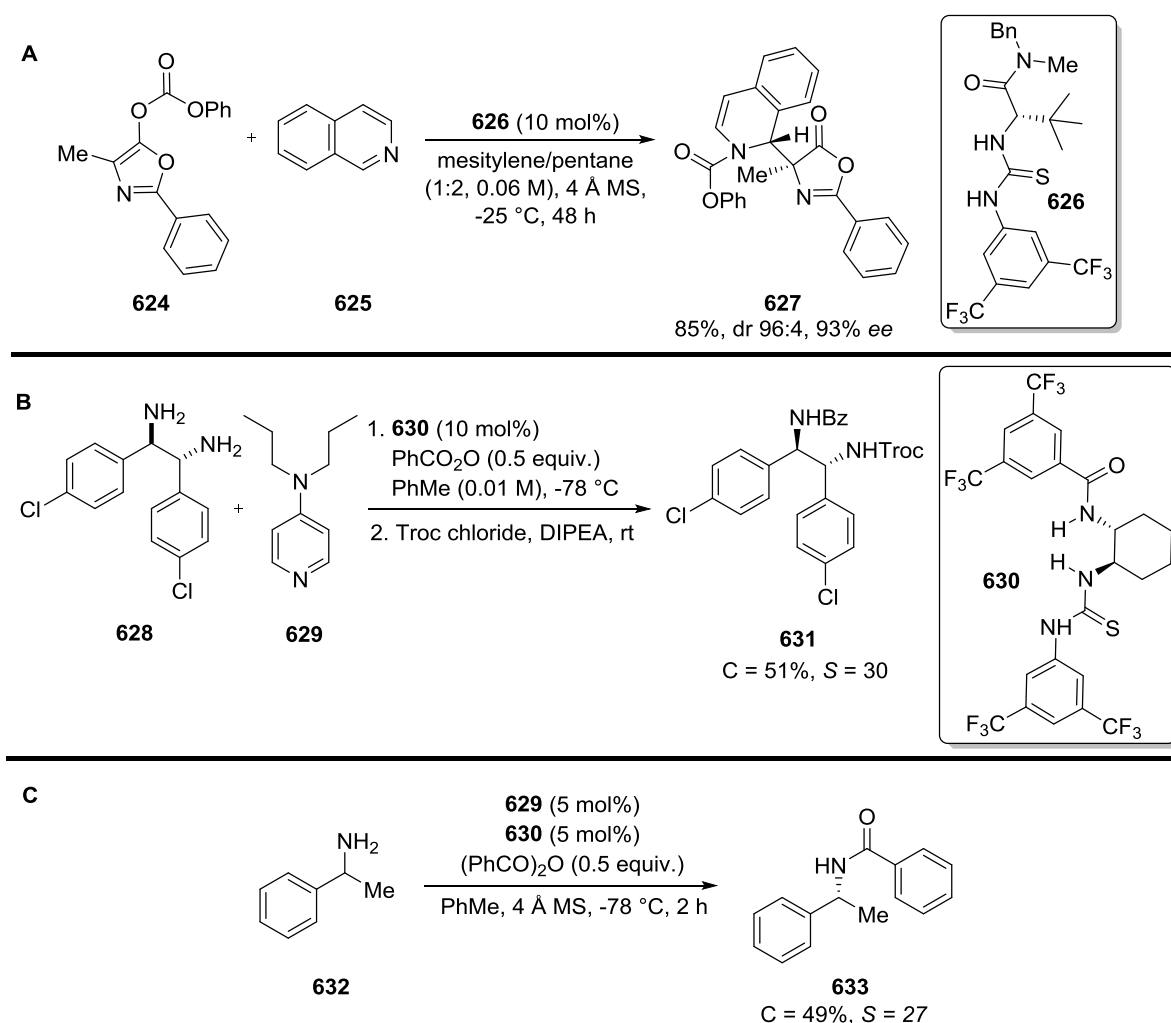


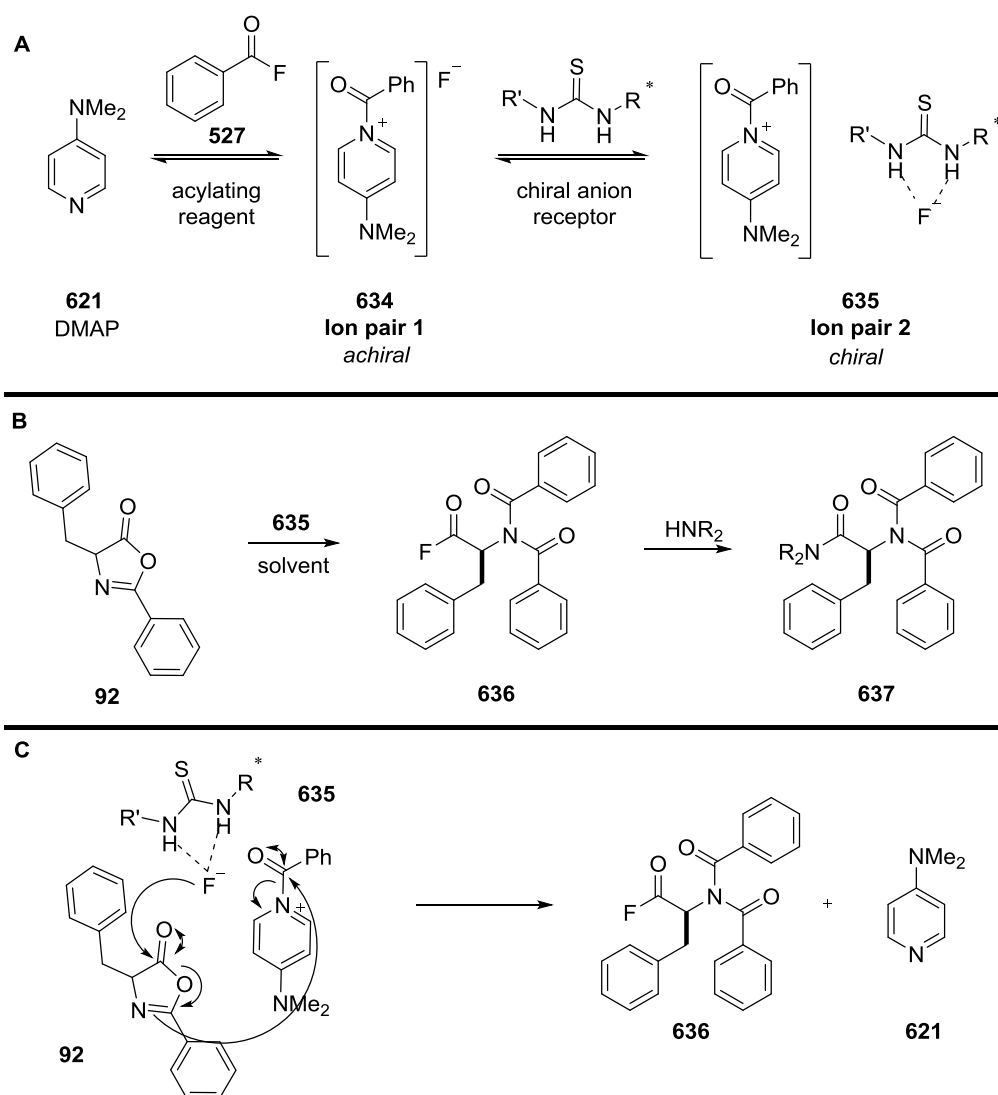
Figure 8.1 Anion-binding concept for asymmetric acyl transfer reactions

Seidel and co-workers have demonstrated the applicability of this novel form of catalysis in a range of acyl transfer reactions including the Steglich rearrangement of *O*-acylated azalactones (Scheme 8.1A), the desymmetrisation of *meso*-diamines (Scheme 8.1B) and the kinetic resolution of various amines (Scheme 8.1C);²⁴² mechanistic insights using both computational and experimental studies have been provided in the latter case.²⁴³ In each of these examples, Seidel uses the chiral ion pair (**623**) as an electrophilic catalyst. In our study, we propose the use of a similar chiral ion pair as a nucleophilic catalyst.



Scheme 8.1 Selected applications of anion-binding catalysis by Seidel and co-workers

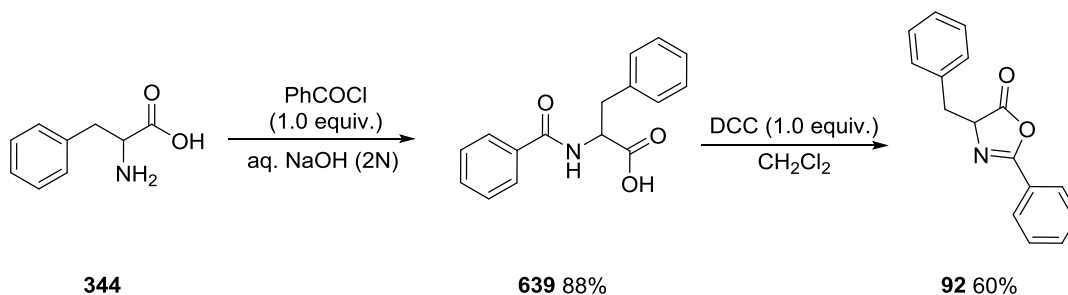
We envisioned using benzoyl fluoride (**527**) as the electrophilic agent, in conjunction with DMAP to generate the chiral ion pair **635** (Scheme 8.2A). Upon addition of azlactone **92**, we hypothesised that the newly generated fluoride ion would act as a nucleophilic catalyst, resulting in the ring-opening of azlactone **92** (Scheme 8.2B). Ideally, this should generate the acid fluoride product **636**, which, upon addition of a protected amino acid nucleophile, would result in the formation of a peptide (**637**, Scheme 8.2B). In theory, any given nucleophile could be used to react with the acid fluoride intermediate, thereby enabling access an endless range of amino acid products. We proposed that enantiomeric excess of the acyl fluoride product (**636**) could be influenced by means of dynamic kinetic resolution using a chiral fluoride ion (Scheme 8.2C) with concomitant regeneration of the DMAP catalyst. DMAP can then react with more benzoyl fluoride (**527**) and ultimately form more of the chiral ion pair **635** for catalysis. Upon full conversion to the acid fluoride product, we envisioned adding the amine nucleophile to generate **637**. In this way, we aimed to achieve the DKR of azlactone **92** with a subsequent peptide coupling in one pot.



Scheme 8.2 Our proposed strategy

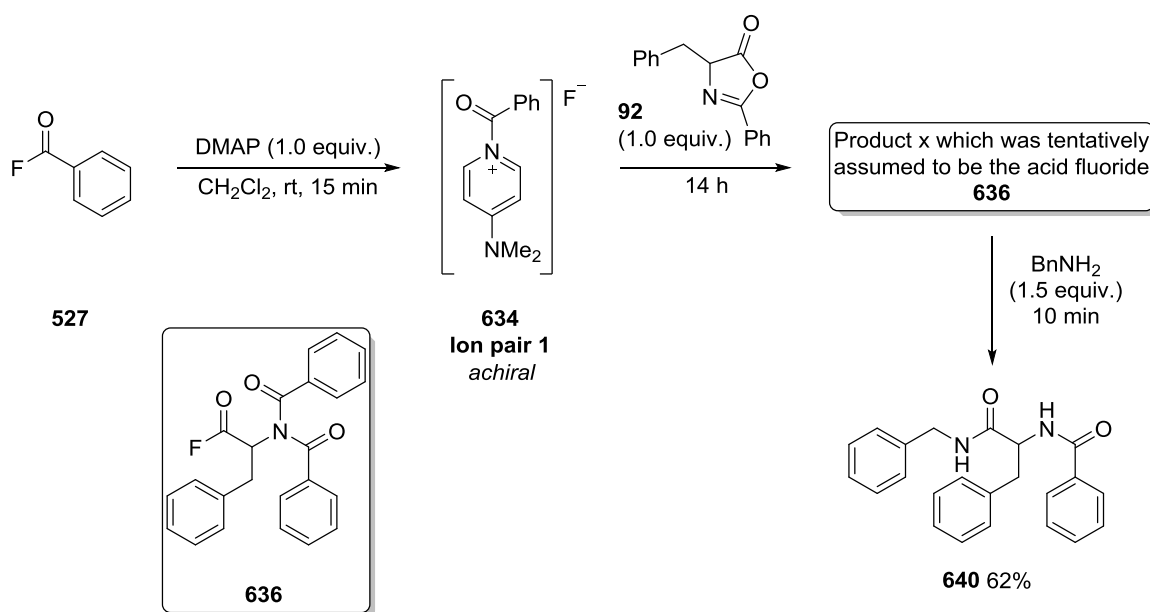
8.2 Preliminary experiments

Azlactone **92** was prepared in a two-step procedure (Scheme 8.3). DL-phenylalanine converted to the *N*-benzoyl amide **639** using benzoyl chloride under basic conditions. Intramolecular ring-closure of **639** was achieved using DCC to furnish **92** in 60% yield.



Scheme 8.3 Synthesis of azlactone **92**

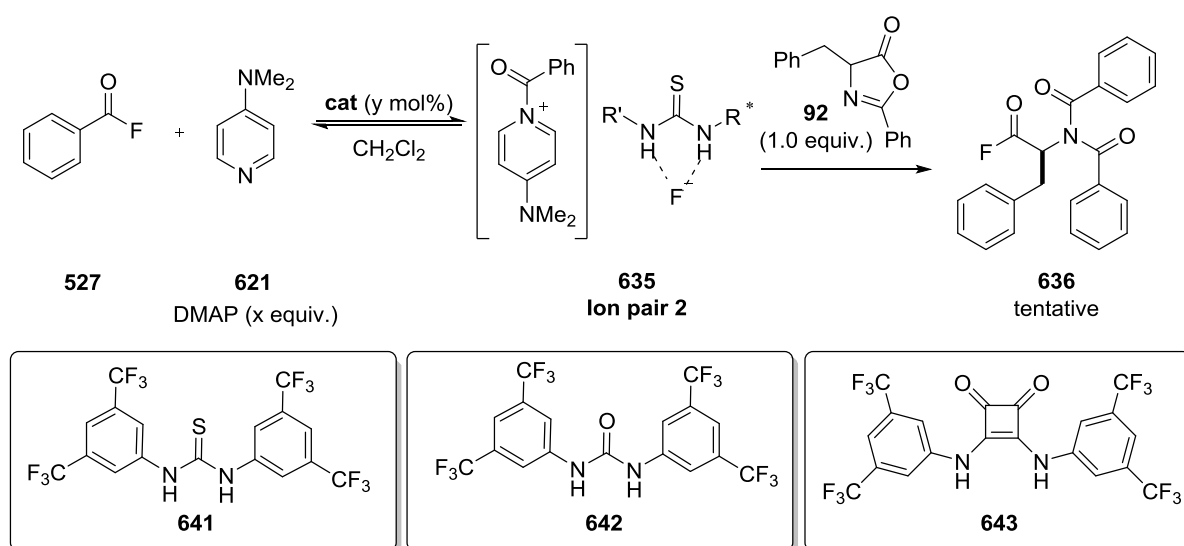
As there is no literature precedent for the envisioned transformation, we began our study with some simple control reactions in order to gauge reactivity. Strictly anhydrous conditions were employed in all cases. Initially, a 1:1 mixture of benzoyl fluoride (**527**) and azlactone **92** were stirred in CH₂Cl₂ overnight, resulting in no reactivity, as was the case when azlactone **92** was exposed to DMAP (1.0 equiv.). Next stoichiometric benzoyl fluoride (**527**) and DMAP were reacted together (Scheme 8.4). After 15 minutes, ¹H NMR spectroscopic analysis of the reaction mixture indicated full conversion to the acyl pyridinium salt **634**. At this point azlactone **92** was added to the reaction mixture. After 14 hours, ¹H NMR spectroscopic analysis of the reaction mixture showed complete disappearance of the azlactone starting material and 84% formation of a new major product. The proton resonances for this novel product were shifted downfield to those of the azlactone starting material, and resembled what we expected of the desired acid fluoride intermediate **636**. ¹⁹F NMR analysis of a sample of the reaction mixture did not indicate the presence of the acid fluoride in the crude product, though we postulated that this could be a result of low concentration samples and a possible reaction of fluoride with the glass of the NMR tube. Benzyl amine was added to the reaction flask and after 10 minutes complete consumption of the reaction intermediate was observed. Interestingly, purification of the crude material obtained the product **640** in 62% yield, rather than the predicted di-benzoyl product **637** (Scheme 8.2B). We postulated that cleavage of the di-benzoyl amide functionality could be catalysed by HF (liberated in the acid fluoride quench) to afford the acquired product **640**. Nonetheless, these initial experiments suggested that the reaction could indeed be operating *via* an acid fluoride intermediate, although catalytic control using a hydrogen-bonding catalyst (*via* ion pair **635**, Scheme 8.2A) was yet to be achieved.



Scheme 8.4 The synthesis of **640** from azlactone **92** and achiral ion pair **634**

We repeated the reaction at a reduced temperature of 0 °C resulting in 64% conversion of the azlactone after 14 hours (Table 8.1, entry 1). Subsequently, hydrogen bonding catalysts **641**, **642** and **643** were employed in three separate reactions under the same conditions. Interestingly, the activity of the fluoride ion was reduced in each case (entries 2, 3 and 4). In previous studies, we had suggested that thiourea-based catalysts possessed the ability to reduce the nucleophilicity of the fluoride ion. Once again, we postulated that perhaps the (thio)urea/squaramide HB donors bound the fluoride ion, rendering it inactive; and that the observed reactivity was due to the excess of ion pair **634** present in solution. Accordingly, we employed a 1:1 catalytic loading of DMAP:**641** in the reaction; in this way only ion pair **635** would be present in the reaction mixture. No conversion of the starting material was observed after 5 days, thus supporting our hypothesis that the employment of a dual hydrogen bond donor such as **641** renders the nucleophilic fluoride ion **635** inactive (entry 5). The same reaction was repeated in the absence of the hydrogen bond donor to furnish 8% conversion after 5 days, further proving our hypothesis (entry 6). The reaction concentration was increased from 0.06 M to 0.2 M to encourage reactivity. Once again a similar trend was observed. In the reaction lacking a hydrogen bonding catalyst, 4% conversion to the presumed intermediate **636** occurred after 21 hours, while the system using 1:1 DMAP:**641** afforded no reaction (entries 7 and 8). We proposed that perhaps an additional equivalent of hydrogen bonding catalyst would be required in order to simultaneously activate the azlactone towards nucleophilic attack by chiral ion pair **635**, through hydrogen bond activation of the carbonyl moiety of **92**. A 1:2 ratio of DMAP:**641** was employed. Disappointingly, no reaction was observed (entry 9).

Table 8.1 Efforts to control fluoride ring opening of **92** using hydrogen bonding catalysts

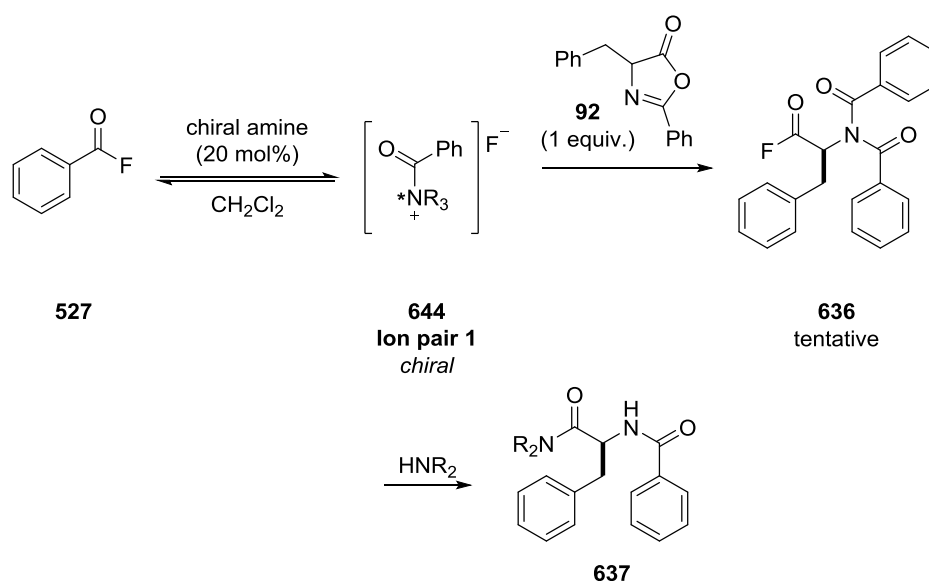


Entry	Conc. (M)	T (°C)	x	cat.	y	t (h)	Conv. (%) ^[a]
1	0.06	0	1.0	-	-	14	64
2	0.06	0	1.0	641	20	14	43
3	0.06	0	1.0	642	20	14	29
4	0.06	0	1.0	643	20	14	17
5	0.06	21	0.2	641	20	120	0
6	0.06	21	0.2	-	-	120	8
7	0.2	21	0.2	-	-	21	4
8	0.2	21	0.2	641	20	21	0
9	0.2	21	0.2	641	40	21	0

^aDetermined *via* ¹H NMR spectroscopic analysis using *para*-iodoanisole as an internal standard

8.3 An alternative approach

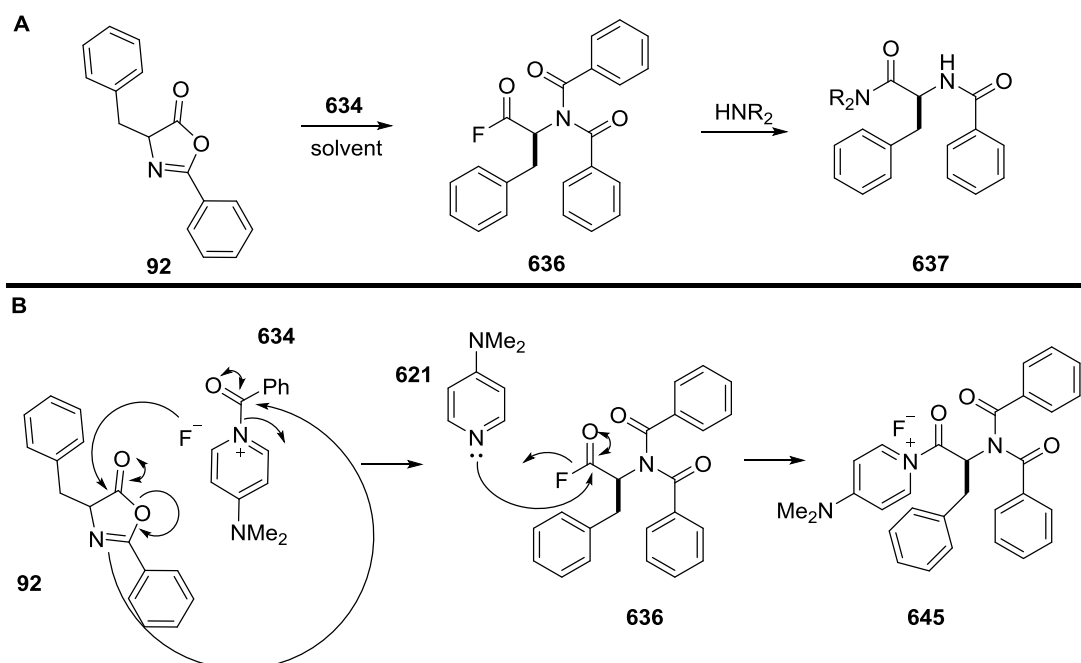
It was clear from the preliminary experiments that the presence of a hydrogen bonding catalyst attenuated reactivity of ion pair 2 (**635**, Scheme 8.2A) and that any observed reactivity was as a result of ion pair 1 (**634**, Scheme 8.4). Instead, we postulated that if we could achieve catalytic turnover *via* ion pair 1 (**634**), the introduction of a chiral amine as a co-catalyst, rather than DMAP, could promote an enantiodiscriminative reaction *via* chiral ion pair **644** (Scheme 8.5).



Scheme 8.5 Postulated ring-opening of **92** by ion pair **644**

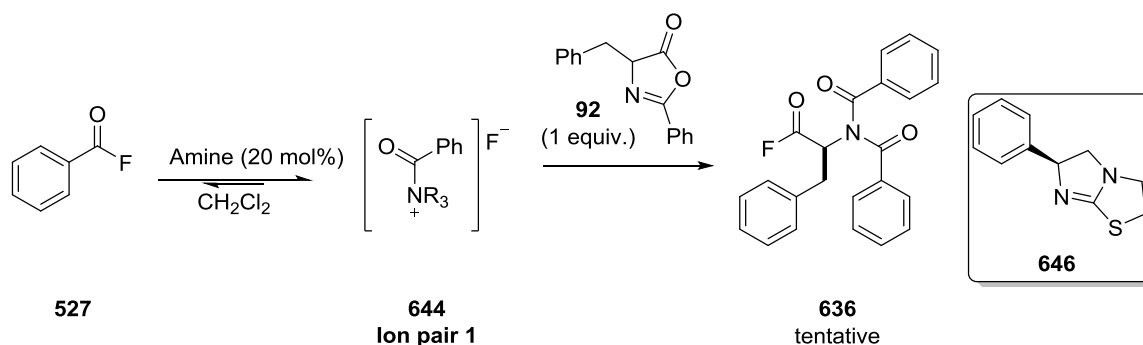
In our previous experiments, reactivity was slow and we struggled to drive conversion when sub-stoichiometric DMAP was employed. We questioned whether a catalytic cycle was occurring; initially we had postulated that ion pair 1 (**634**) reacts with **92** *via* nucleophilic attack of the fluoride ion to form **636** with the concomitant regeneration of the DMAP catalyst. For catalytic turn over to occur, this regenerated DMAP should re-enter the catalytic cycle by attacking another molecule of benzoyl

fluoride (**527**), thus allowing the reaction to proceed to full conversion (Scheme 8.6A). However, should the regenerated DMAP react with **636** instead of benzoyl fluoride (**527**) to form **645** (Scheme 8.6B), re-generation of the reactive ion pair **634** is prevented and achieving catalytic turnover becomes difficult.



Scheme 8.6 Postulated mechanism for the ring opening of azlactone **92** by ion pair **634**

We began our efforts to drive conversion by altering the reaction conditions. The reaction concentration chosen for our initial experiments was based on that used in anion binding chemistry carried out by Seidel and co-workers, which required very dilute reactions. We postulated that, in our case, increased reaction concentration may be necessary to drive conversion. We had already exhibited that using 0.2 M CH_2Cl_2 , only 4% conversion to **636** occurred after 21 hours (Table 8.2, entry 1). Gratifyingly, doubling of the reaction concentration (0.4 M, entry 2) resulted in complete consumption of azlactone **92** and the formation of what we assumed to be the acyl fluoride intermediate **636** as the major reaction product (55%). Catalytic turnover had been achieved, though the reactions were not clean. Switching the reaction solvent to THF also afforded a similar result after 48 hours (entry 3). The use of MeCN as a reaction solvent produced an extremely complex crude reaction mixture with incomplete conversion of the azlactone after 48 hours (entry 4). Variation of the nucleophilic amine catalyst was also explored. Employing DABCO as a nucleophilic catalyst significantly reduced the reaction rate (full conversion of the azlactone was achieved after 6 days), though the reactions were considerably cleaner by ^1H NMR spectroscopic analysis (entry 5). Chiral amine **646** was also employed as a nucleophilic catalyst, though reactivity was slow with only 15% conversion occurring after 6 days (entry 6).

Table 8.2 Alteration of the reaction conditions

Entry	Amine	Solvent	Conc. (M)	t (h)	Conv. (%) ^[a]	636 (%) ^[a]
1	DMAP	CH ₂ Cl ₂	0.2	21	4	4
2	DMAP	CH ₂ Cl ₂	0.4	48	99	55
3	DMAP	THF	0.4	48	99	57
4	DMAP	MeCN	0.4	48	n.d.	n.d.
5	DABCO	CH ₂ Cl ₂	0.4	144	99	62
6	646	CH ₂ Cl ₂	0.4	144	20	15

^a Determined via ¹H NMR spectroscopic analysis using *para*-iodoanisole as an internal standard

Before we proceeded any further, we decided that it was necessary to confirm the identity of the reaction intermediate. If the reaction intermediate was in fact the acid fluoride **636**, we anticipated its isolation from the crude reaction mixture to be extremely problematic. Indeed, analysis of the crude reaction mixture by thin layer chromatography (TLC) alluded to the presence of several different products; this did not align with the NMR spectra of the crude material which indicated one major product. Despite the predicted difficulties, the crude material was quickly but carefully purified using flash chromatography. To our delight, the desired product was obtained from the reaction mixture, albeit contaminated and in extremely poor yield. The major reaction intermediate was tentatively assigned as ketene **647** rather than **636** using mass spectrometry and ¹H, ¹³C and ¹⁹F NMR spectroscopic analysis (Figure 8.2). However, it must be noted that the IR spectra obtained for the compound did not display the characteristic band associated with ketene functional groups which occur from 2000-2100 cm⁻¹; it is possible that degradation of the ketene occurred prior to IR analysis. The formation of product **640** upon addition of benzyl amine to the reaction intermediate (see Scheme 8.4) would also support the proposed structure ketene **647** as the intermediate.

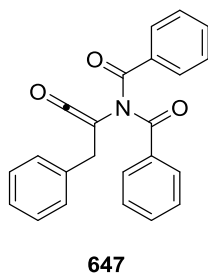
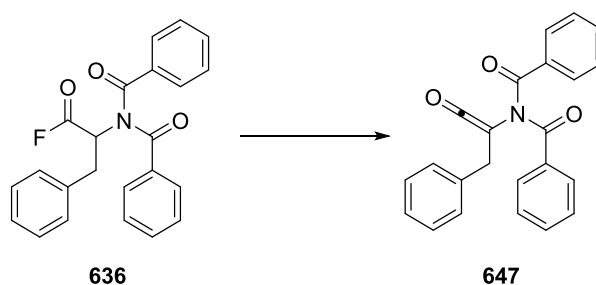


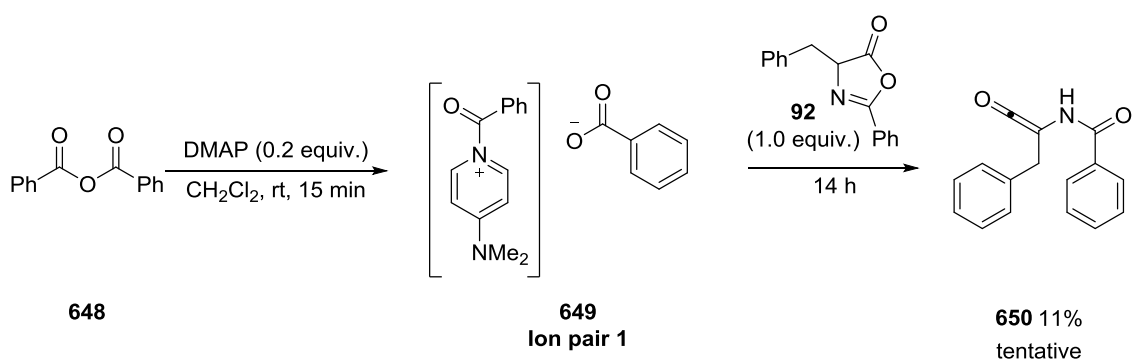
Figure 8.2 Ketene **647**

The presence of **647** in the reaction mixture would suggest that the reaction proceeds *via* nucleophilic attack of the fluoride ion on the azlactone to form **636**. However, **636** must immediately collapse (*via* the elimination of HF across the acyl centre) to form ketene **647**, and thus **636** is not detectable *via* ^1H NMR spectroscopy (Scheme 8.7). The premise of this work was to resolve the azlactone by means of DKR *via* fluorinolysis using a chiral fluoride ion. However, the elimination of the acid fluoride **636** to ketene **647** would destroy any stereochemical information in the acid fluoride product.



Scheme 8.7 Elimination of acid fluoride **636** to form ketene **647**

We postulated that the generation of a less acidic acyl-intermediate could prevent ketene formation, thus maintaining any potential stereochemistry introduced at the α -carbon. Benzoic anhydride was employed as the electrophilic agent instead of benzoyl fluoride to afford an extremely messy crude reaction mixture (Scheme 8.8). Interestingly, a compound was isolated and tentatively assigned to be ketene **648** (possessing a single *N*-benzoyl substitution) using mass spectrometry and ^1H and ^{13}C NMR spectroscopy. Once again, the IR spectra obtained for the compound did not display the characteristic band associated with ketene functional groups. Further investigations in to this reaction are currently underway in the group.



Scheme 8.8 Ring opening of azlactone **92** by ion pair **649**.

8.4 Conclusion

The evidence obtained from the above study would suggest that the achiral ion pair **634**, generated from benzoyl fluoride and catalytic DMAP, can effectively open azlactone **92** to afford the desired acid fluoride product. However, we suspect that immediate elimination of HF occurs across the acyl centre to form ketene **647**, thus destroying any potential stereochemical information in the reaction intermediate. We predict that the formation of a less reactive acyl-intermediate could prevent elimination to ketene **647**, thus maintaining any stereochemistry introduced when a chiral amine is employed. Further investigations into this reaction are currently underway in the group.

9 Conclusion

In this work, we studied a range of differing organocatalytic systems and used them to control a variety of important chemical transformations. These systems explored various methods of activation in the area of organocatalysis including bifunctional, nucleophilic, basic and phase-transfer catalysis.

In chapter 2, the custom design of a novel *cinchona* alkaloid derived organocatalyst and its use in the KR of TCIC-oxazinones is described. The kinetic resolution of oxazinones *via* alcoholysis presents one highly under-utilised method for accessing enantioenriched β -amino acids, extremely important chemical precursors in both the pharmaceutical and agrochemical industries. In chapter 2 of this thesis, the custom design of a novel *cinchona* alkaloid derived organocatalyst and its use in the KR of the completely novel TCIC-oxazinones is described. The introduction of the TCIC-subunit to the oxazinone structure presents highly practical solution to a longstanding problem in the resolution of the molecules: namely, the generation of stubborn *N*-benzoyl protected amino acid products which cannot be selectively cleaved and are therefore considered impractical for multi-step synthesis. Upon the KR of the TCIC-oxazinones *via* alcoholysis, the new subunit can be converted into stable *N*-phthalimide protecting group *in situ* to afford the enantioenriched and orthogonally protected amino acid product; the phthalimide can be selectively cleaved in the presence of the ester functionality and *vice versa*. In this way, the products of the KR are ready for further chemical manipulation. Using our specially designed bifunctional catalyst, we achieved outstanding levels of enantiocontrol for the KR of a range TCIC-oxazinones obtaining *S*-factors of >100 for the process. Additionally, through the careful manipulation of the substrate structure, the first organocatalytic DKR of oxazinones by alcoholysis was achieved with moderate levels of enantiocontrol.

In chapter 4, the development of the first catalytic, enantioselective cycloaddition between enolisable anhydrides and imines is described to afford chiral lactam products bearing two stereocentres. Through the placement of electron-withdrawing substituents on the imine nitrogen, the nucleophilic/basic properties of the imine were sufficiently dampened such that it can only behave as an electrophile in the presence of homophthalic anhydride and a bifunctional organocatalyst. In this way, the *cinchona* alkaloid derived catalyst **205** was used to control the cycloaddition reaction between homophthalic anhydride and a wide range of *N*-sulfonyl imines with modest levels of diastereo- and enantiocontrol.

The latter half of this thesis details the utilisation of fluoride ion as a nucleophilic catalyst at acyl centres. The development of this concept was based on literature precedent detailing the use of both KF and TBAF to catalyse transesterification reactions. However, conclusive evidence as to the mechanism of action remained elusive; both the basic and nucleophilic properties of fluoride ion had been implicated in these processes. The aim of this work was to shed some light on the mechanism

of action of fluoride at acyl centres and to use this knowledge to develop a chiral nucleophilic fluoride catalyst.

Chapter 5 describes the *in situ* generation of *cinchona* alkaloid derived quaternary ammonium fluorides from the corresponding bromide salts using catalytic KF. The catalytic activity of these molecules was showcased in the alcoholysis *meso*-anhydrides, a well-established reaction in the area of organocatalysis, obtaining moderate levels of enantiocontrol for the process. Importantly, this work provided conclusive evidence that fluoride ion could behave as a nucleophilic catalyst at acyl centres through the detection of the benzoyl fluoride intermediate in the methanolysis of benzoic anhydride using ^1H and ^{19}F NMR spectroscopic analysis.

Chapter 6 provides further evidence towards the nucleophilic activity of fluoride ion at acyl centres through the development of the TBAF catalysed Steiglich rearrangement of 2-oxindoles. This reaction was chosen due to the lack of an external pronucleophile; as such only nucleophilic catalysis could be implicated in this process. A wide range of 2-oxindoles with varying substitutions were tolerant to this methodology.

Chapters 7 discusses efforts towards the development of a KR protocol for the aminolysis of oxazinones using the newly developed system of *cinchona* alkaloid derived quaternary ammonium bromides and catalytic KF. Through careful substrate design, the controlled ring opening aminolysis of oxazinones using sulfonamide nucleophiles was achieved using the *in situ* generated quaternary ammonium fluorides (previously described in chapter 5). However, much to our disappointment the system offered no level of enantiocontrol over the reaction, furnishing the racemic products in all cases. In light of this, we decided it was prudent to focus our research efforts in another direction.

The final chapter of this thesis explores the DKR of azlactones *via* fluorinolysis. In this work, the nucleophilic fluoride ion was formed on the reaction of benzoyl fluoride with catalytic DMAP. The use of a chiral DMAP derivative was envisioned in order to generate a source of chiral fluoride ion, which would resolve the azlactone by means of DKR *via* fluorinolysis to afford the enantioenriched amino acid-fluoride product. The subsequent addition of a protected amino acid nucleophile would quench the acid fluoride intermediate resulting in the formation of a new peptide bond; in this way, the DKR of the azlactone and subsequent peptide coupling would be achieved in one pot. However, when the aforementioned catalytic system was employed, the reaction was found to proceed through the ketene intermediate rather than the acid fluoride. The elimination of HF across the acyl centre to form the ketene would destroy any potential stereocentre set up in the DKR process. As such, only racemic products would be obtained. Efforts to inhibit ketene formation and therefore maintain the resolved stereocentre are currently underway within the Connon research group.

10 Experimental

10.1 General experimental data

Proton Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker DPX 400 MHz and Bruker Avance II 600MHz spectrometers, using as solvent CDCl_3 , DMSO-d_6 or D_2O and referenced relative to residual CHCl_3 ($\delta = 7.26$ ppm) DMSO ($\delta = 2.50$ ppm) or H_2O ($\delta = 4.79$ 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 proton decoupling. Fluorine NMR spectra were recorded on the Bruker DPX400 machine (376.5 MHz). HSQC, HMBC, TOCSY NOE and ROESY NMR experiments were used to aid assignment of NMR peaks when required. All melting points are uncorrected. 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 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 Ionization (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 60F₂₅₄ slides, and visualized by UV irradiation and KMnO_4 staining. Optical rotation measurements are quoted in units of $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. CHCl_3 was pre-treated with K_2CO_3 , distilled over P_2O_5 and was stored under argon. Toluene was dried over activated 3 Å molecular sieves. Anhydrous acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), tetrahydrofuran (THF) and diethyl ether (Et_2O) were obtained by using Pure Solv MD-4EN Solvent Purification System. Commercially available anhydrous *t*-butyl methyl ether (MTBE), MeOH, EtOH and allyl alcohol was used. Analytical CSP-HPLC was performed on Daicel Chiralpak, AD, AD-H, IA, or Chiralcel OD, OD-H, OJ-H (4.6 mm x 25 cm) columns or ACQUITY UPC2 on chiral Trefoil AMY1, CEL1, CEL2 (2,5 μm , 3.0 x 150mm) columns.

10.2 Gradient tables for HPLC conditions

Table 10.1 A: CO₂ B: EtOH/ACN (1:1)

Time (min)	FR (mL/min)	% A	% B	Curve
Initial	1.200	97.0	3.0	Initial
4.50	1.200	40.0	60.0	6
12.00	1.200	40.0	60.0	6
12.10	1.200	97.0	3.0	6

Table 10.2 A: CO₂ B: EtOH/IPA

Time (min)	FR (mL/min)	% A	% B	Curve
Initial	1.200	97.0	3.0	Initial
6.00	1.200	40.0	60.0	6
8.00	1.200	40.0	60.0	6
8.10	1.200	97.0	3.0	6

Table 10.3 A: CO₂ B: MeOH/IPA

Time (min)	FR (mL/min)	% A	% B	Curve
Initial	1.200	97.0	3.0	Initial
4.50	1.200	40.0	60.0	6
10.00	1.200	40.0	60.0	6
10.10	1.200	97.0	3.0	6

Table 10.4 A: CO₂ B: EtOH/ACN

Time (min)	FR (mL/min)	% A	% B	Curve
Initial	1.200	97.0	3.0	Initial
4.50	1.200	90.0	60.0	6
13.00	1.200	40.0	60.0	6
18.00	1.200	40.0	3.0	6

Table 10.5 A: CO₂ B: EtOH/ACN

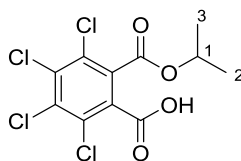
Time (min)	FR (mL/min)	% A	% B	Curve
Initial	1.200	97.0	3.0	Initial
5.00	1.200	8.00	60.0	6
12.00	1.200	40.0	60.0	6
13.00	1.200	40.0	3.0	6

Table 10.6 A: CO₂ B: EtOH/ACN

Time (min)	FR (mL/min)	% A	% B	Curve
Initial	1.200	97.0	3.0	Initial
4.50	1.200	90.0	60.0	6
15.00	1.200	40.0	60.0	6
20.00	1.200	40.0	3.0	6

10.3 Experimental data for section 2

10.3.1 2,3,4,5-Tetrachloro-6-(isopropoxycarbonyl)benzoic acid (**296**)



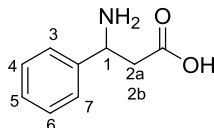
A suspension of 3,4,5,6-tetrachlorophthalic anhydride (10.0 g, 35.0 mmol), IPA (60.0 mL) and NEt₃ (4.9 mL, 35.0 mmol) were stirred under argon for 16 h. Aqueous HCl (2N, 30 mL) was added and the reaction mixture was extracted with Et₂O (3 x 30 mL). The combined organic extracts were dried over MgSO₄ and the solvent was removed *in vacuo* to furnish **296** as a white solid (9.5 g, 94%). M.p. 141-143 °C (lit.¹¹⁴ 143-145 °C). The isolated product exhibited identical spectroscopic data to those in the literature.¹¹⁴

δ_{H} (400 MHz, CDCl₃): 10.34 (1H, s, OH), 5.31 (1H, sept., *J* 6.3, H-1), 1.39 (6H, d, *J* 6.3, H-2, H-3).

10.3.2 General procedure A: β -amino acid synthesis

A suspension of malonic acid (1.0 equiv.), the appropriate aldehyde (1.1 equiv.) and ammonium acetate (1.3 equiv.), in EtOH (1.0 M) was heated under at 87 °C for 16 h. The resulting precipitate was cooled, filtered and washed with ice cold EtOH to yield the corresponding β -amino acid.

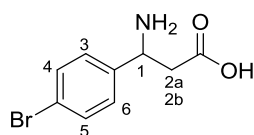
10.3.2.1 3-Amino-3-phenylpropanic acid (**114a**)



Prepared according to **General Procedure A** using malonic acid (10.0 g, 96.0 mmol), benzaldehyde (10.9 mL, 105.7 mmol) and ammonium acetate (9.6 g, 124.9 mmol) in EtOH (100.0 mL) to yield compound **114a** (9.7 g, 61%) as a white solid. M.p. 218-220 °C (lit.²⁴⁴ 222-223 °C). The isolated product exhibited identical spectroscopic data to those in the literature.¹¹⁰

δ_{H} (400 MHz, D₂O): 7.31-7.35 (5H, m, H-3 H-4, H-5, H-6, H-7), 4.51 (1H, dd, *J* 7.9, 6.6, H-1), 2.65-2.80 (2H, m, H-2a, H-2b).

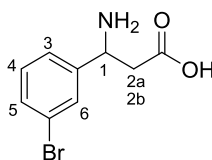
10.3.2.2 3-Amino-3-(4-bromophenyl)propanoic acid (**114b**)



Prepared according to **General Procedure A** using malonic acid (4.5 g, 43.2 mmol), 4-bromobenzaldehyde (8.0 g, 43.2 mmol) and ammonium acetate (4.3 g, 56.1 mmol) in EtOH (50.0 mL) to yield compound **114b** (5.6 g, 54%) as a white solid. M.p. 227-228 °C, (lit.²⁴⁵ 228-229 °C). The isolated product exhibited identical spectroscopic data to those in the literature.²⁴⁵

δ_{H} (400 MHz, D₂O): 7.44-7.39 (2H, m, H-4, H-5), 7.19-7.15 (2H, m, H-3, H-6), 4.09 (1H, m, H-1), 2.50-2.36 (2H, m, H-2a, H-2b).

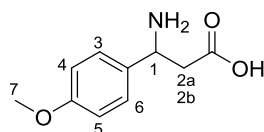
10.3.2.3 3-Amino-3-(3-bromophenyl)propanoic acid (**114c**)



Prepared according to **General Procedure A** using malonic acid (3.6 g, 34.1 mmol), 4-bromobenzaldehyde (6.3 g, 34.1 mmol) and ammonium acetate (3.4 g, 44.3 mmol) in EtOH (40.0 mL) to yield compound **114c** (4.7 g, 52%) as a white solid. M.p. 225-227 °C, (lit.²⁴⁵ 225-226 °C). The isolated product exhibited identical spectroscopic data to those in the literature.²⁴⁵

δ_{H} (400 MHz, D₂O): 7.45 (1H, s, H-6), 7.35 (1H, d, *J* 7.5, H-5), 7.26-7.14 (2H, m, H-4, H-3), 4.09 (1H, m, H-1), 2.48-2.38 (2H, m, H-2a, H-2b).

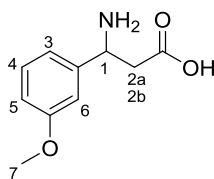
10.3.2.4 3-Amino-3-(4-methoxyphenyl)propanoic acid (**114d**)



Prepared according to **General Procedure A** using malonic acid (3.6 g, 34.6 mmol), 4-anisaldehyde (4.2 mL, 34.6 mmol) and ammonium acetate (3.5 g, 45.0 mmol) in EtOH (40.0 mL) to yield compound **114d** (2.7 g, 38%) as a white solid. M.p. 233-234 °C (lit.²⁴⁶ 238-239 °C). The isolated product exhibited identical spectroscopic data to those in the literature.²⁴⁶

δ_{H} (400 MHz, D₂O): 7.31-7.26 (2H, m, H-3, H-6), 6.95-6.91 (2H, m, H-4, H-5), 4.49 (1H, m, H-1), 3.73 (3H, s, H-7), 2.82-2.64 (2H, m, H-2a, H-2b).

10.3.2.5 3-Amino-3-(3-methoxyphenyl)propanoic acid (**114e**)



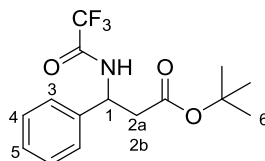
Prepared according to **General Procedure A** using malonic acid (7.6 g, 73.4 mmol), 3-anisaldehyde (9.0 mL, 73.4 mmol) and ammonium acetate (3.5 g, 45.0 mmol) in EtOH (40.0 mL) to yield compound **114e** (9.3 g, 65%) as a white solid. M.p. 209-210 °C (lit.¹¹⁰ 213-214 °C). The isolated product exhibited identical spectroscopic data to those in the literature.¹¹⁰

δ_{H} (400 MHz, D₂O): 7.25 (1H, m, H-5), 7.00-6.82 (3H, m, H-3, H-4, H-6) 4.19 (1H, m, H-1), 3.73 (3H, s, H-7), 2.35-2.28 (2H, m, H-2a, H-2b).

10.3.3 General procedure B: Two-step protection as the trifluoroacetamide *t*-Butyl ester

Trifluoroacetic anhydride (1.3 equiv.) was added to a suspension of the appropriate β -amino acid (1.0 equiv.) at 0 °C under argon. The resulting solution was heated under reflux for 16 h. The mixture was concentrated *in vacuo* to give the trifluoroacetamide. To this was added DMAP (0.4 equiv.) and DCC (1.0 equiv.) and the flask was purged with argon and a septum with a balloon of argon was fitted. Anhydrous CH₂Cl₂ (0.5 M) was added and the mixture was cooled to 0 °C. *tert*-Butanol (4.0 equiv.) was added *via* syringe and the mixture was warmed to rt and was stirred for 16 h. The resulting suspension was filtered and washed with CH₂Cl₂. The filtrate was purified *via* silica chromatography to yield the di-protected product.

10.3.3.1 *tert*-Butyl 3-phenyl-3-(2,2,2-trifluoroacetamido)propanoate (**301a**)



Prepared according to **General Procedure B**. The trifluoroacetamide was synthesised using **114a** (14.2 g, 44.7 mmol) and TFAA (18.9 mL, 134.1 mmol) and was brought forward to the next step. To this was added DMAP (545.0 mg, 4.5 mmol), DCC (10.1 g, 49.1 mmol), CH₂Cl₂ (88.0 mL) and *tert*-Butanol (13.2 mL³, 178.6 mmol). The product was purified *via* silica chromatography, eluting with 10 % EtOAc in hexane to yield **301a** as a white solid (13.0 g, 91%). M.p. 57-60 °C.

δ_{H} (400 MHz, CDCl₃): 7.85 (1H, br-s, NH), 7.86-7.29 (5H, m, H-3, H-4, H-5), 5.43-5.39 (1H, m, H-1), 2.93-2.82 (2H, m, H-2a, H-2b), 1.38 (9H, s, H-6).

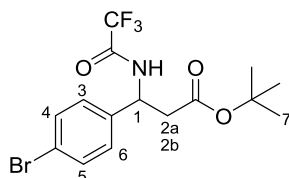
δ_{C} (100 MHz, CDCl₃): 170.2 (C=O), 156.4 (C=O, $J_{\text{C-F}}$ = 37.1) 138.6, 128.9, 128.1, 126.1, 111.6-120.2 (q, $J_{\text{C-F}}$ = 289.4), 82.3, 50.1, 40.3, 27.9.

δ_F (376 MHz, $CDCl_3$) -76.41.

ν_{max} (neat)/ cm^{-1} : 3277, 1728, 1696.

HRMS (m/z - ESI): Found: 316.1166 (M-H)⁻ $C_{15}H_{17}F_3NO_3$ Requires: 316.1611.

10.3.3.2 *tert*-Butyl 3-(4-bromophenyl)-3-(2,2,2-trifluoroacetamido)propanoate (**301b**)



Prepared according to **General Procedure B**. The trifluoroacetamide was synthesised using **114b** (5.1, g, 17.3 mmol) and TFAA (7.3 mL, 51.8 mmol) and was brought forward to the next step. To this was added DMAP (0.8 g, 6.9 mmol), DCC (4.1 g, 19.7 mmol), CH_2Cl_2 (34.0 mL) and *tert*-Butanol (6.5 mL, 69.0 mmol). The product was purified *via* silica chromatography, eluting with 10% EtOAc in hexane to yield **301b** as a white solid (5.0 g, 73%). M.p. 83-85 °C.

δ_H (400 MHz, $CDCl_3$): 7.97 (1H, d, J 7.5, NH), 7.47 (2H, d, J 8.3, H-4, H-5), 7.16 (2H, d, J 8.3, H-3, H-6), 5.33-5.27 (1H, m, H-1) 2.81 (2H, m, H-2a, H-2b), 1.37 (9H, s, H-7).

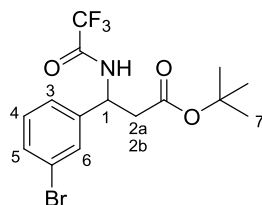
δ_C (100 MHz, $CDCl_3$): 170.1 (C=O), 156.5 (C=O, J_{C-F} = 37.5) 137.9 (q), 132.0, 127.9, 115.8 (q, J_{C-F} = 287.8), 82.6 (q), 49.7, 40.0, 27.9.

δ_F (376 MHz, $CDCl_3$) -75.9.

ν_{max} (neat)/ cm^{-1} : 3276, 1727, 1698.

HRMS (m/z - ESI): Found: 418.0237 (M+Na)⁺ $C_{15}H_{17}BrF_3NNaO_3$ Requires: 418.0236.

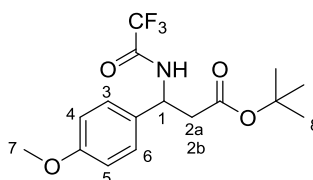
10.3.3.3 *tert*-Butyl 3-(3-bromophenyl)-3-(2,2,2-trifluoroacetamido)propanoate (**301c**)



Prepared according to **General Procedure B**. The trifluoroacetamide was synthesised using **114c** (4.0 g, 13.7 mmol) and TFAA (5.8 mL, 41.0 mmol) and was brought forward to the next step. To this DMAP was added (0.7 g, 5.5 mmol), DCC (3.1 g, 15.0 mmol), CH_2Cl_2 (28.0 mL) and *tert*-Butanol (5.2 mL, 54.7 mmol). The product was purified *via* silica chromatography, eluting with 10% EtOAc in hexane to yield **301c** as a white solid (4.2 g, 78%). M.p. 99-101°C.

δ_{H} (400 MHz, CDCl_3):	8.01-7.90 (1H, br-s, NH), 7.47-7.40 (2H, m, H-5, H-6), 7.25-7.29 (2H, m, H-3, H-4), 5.36-5.29 (1H, m, H-1), 2.81 (2H, app. d, H-2a, H-2b), 1.38 (9H, s, H-7).
δ_{C} (100 MHz, CDCl_3):	170.1 (C=O), 156.4 (C=O, $J_{\text{C-F}} = 37.0$) 141.1 (q), 131.3, 130.4, 129.3, 124.9, 122.9, 115.7 (q, $J_{\text{C-F}} = 290.5$), 82.7 (q), 49.7, 40.1, 27.9.
δ_{F} (376 MHz, CDCl_3)	-75.90.
ν_{max} (neat)/ cm^{-1} :	3277, 1727, 1697.
HRMS (m/z - ESI):	Found: 394.0264 (M-H) ⁻ $\text{C}_{15}\text{H}_{16}\text{BrF}_3\text{NO}_3$ Requires: 394.0271.

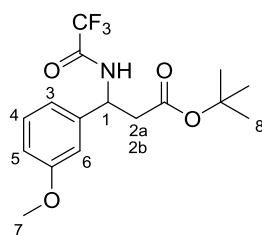
10.3.3.4 *tert*-Butyl 3-(4-methoxyphenyl)-3-(2,2,2-trifluoroacetamido)propanoate (**301d**)



Prepared according to **General Procedure B**. The trifluoroacetamide was synthesised using **114d** (9.8 g, 49.9 mmol) and TFAA (21.2 mL, 149.8 mmol) and was brought forward to the next step. To this was added DMAP (2.4 g, 19.9 mmol), DCC (11.4 g, 59.9 mmol) CH_2Cl_2 (100.0 mL) and *tert*-Butanol (19.0 mL, 199.7 mmol) were added. The product was purified *via* silica chromatography, eluting with 10% EtOAc in hexane to yield **301d** as a white solid (7.9 g, 45%). M.p. 61-64 °C.

δ_{H} (400 MHz, CDCl_3):	7.76-7.66 (1H, m, NH), 7.20 (2H, d J 8.6, H-3, H-6), 6.89 (2H, d, J 8.9, H-4, H-5), 5.36-5.30 (1H, m, H-1), 3.80 (3H, s, H-7), 2.89-2.76 (2H, m, H-2a, H-2b), 1.37 (9H, s, H-8).
δ_{C} (400 MHz, CDCl_3):	170.2 (C=O), 159.3 (q), 156.3 (C=O, $J_{\text{C-F}} = 37.3$) 130.8 (q), 127.4, 115.6 (q, $J_{\text{C-F}} = 288.1$), 114.2, 81.2 (q), 55.3, 49.8 40.4, 27.9.
δ_{F} (376 MHz, CDCl_3)	-75.96.
ν_{max} (neat)/ cm^{-1} :	3256, 1721, 1698.
HRMS (m/z - ESI):	Found: 370.1236 (M+Na) ⁺ $\text{C}_{16}\text{H}_{20}\text{F}_3\text{NNaO}_3$ Requires: 370.1236.

10.3.3.5 *tert*-Butyl 3-(3-methoxyphenyl)-3-(2,2,2-trifluoroacetamido)propanoate (**301e**)



Prepared according to **General Procedure B**. The trifluoroacetamide was synthesised using **114e** (5.3 g, 27.4 mmol) and TFAA (11.6 mL, 81.8 mmol) and was brought forward to the next step. To this was added DMAP (1.3 g, 10.9 mmol), DCC (6.2 g, 30.0 mmol), CH₂Cl₂ (55.0 mL) and *tert*-Butanol (10.4 mL, 109.1 mmol). The product was purified *via* silica chromatography eluting with 10% EtOAc in hexane to yield **301e** as a white solid (2.6 g, 27%). M.p. 66-68 °C.

δ_{H} (400 MHz, CDCl₃): 7.85-7.79 (1H, m, NH), 7.29-7.24 (1H, m, H-4), 6.89-76.79 (3H, m, H-3, H-5, H-6), 5.39-5.31 (1H, m, H-1), 3.80 (3H, s, H-7), 2.89-2.76 (2H, m, H-2a, H-2b), 1.37 (9H, s, H-8).

δ_{C} (400 MHz, CDCl₃): 165.5 (C=O), 155.2 (q), 151.6 (C=O, $J_{\text{C-F}} = 38.1$), 135.5 (q), 125.2, 113.5, 111.4 (q, $J_{\text{C-F}} = 286.2$), 108.6, 107.4, 77.6 (q), 50.5, 45.4 35.5, 23.1.

δ_{F} (376 MHz, CDCl₃) -80.7.

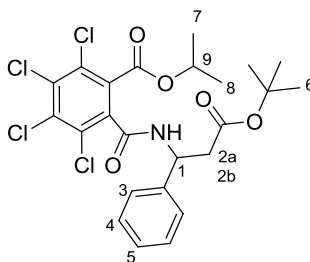
ν_{max} (neat)/cm⁻¹: 3277, 1724, 1700.

HRMS (m/z - ESI): Found: 370.1226 (M+Na)⁺ C₁₆H₂₀F₃NNaO₃ Requires: 370.1237.

10.3.4 General procedure C: Trifluoroacetamide removal and subsequent amide coupling

A solution of LiOH (1M, aq., 2 mL/mmol) was added to an RBF containing a magnetic stirring bar and the appropriate protected amino acid (1.0 equiv.) in 1,4-dioxane (2.5 mL/mmol) at 0 °C. The mixture was warmed to rt and was stirred for 16 h. The solution was concentrated *in vacuo* and the resulting residue was re-dissolved in H₂O and extracted with EtOAc (x3). The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo* to give the free amine. To this **295** (1.1 equiv.) and DCC (1.1 equiv.) were added. The flask was purged with argon and a septum with a balloon of argon was fitted. Anhydrous CH₂Cl₂ (0.5M) was added *via* syringe at 0 °C. The mixture was warmed to rt and was stirred for 16 h. The resulting suspension was filtered *via* suction filtration and the filtrate was purified *via* silica chromatography.

10.3.4.1 isoPropyl-2-((3-(*tert*-butoxy)-3-oxo-1-phenylpropyl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (293a)



Prepared according to **General Procedure C** using compound **301a** (5.4 g, 17.0 mmol), LiOH (1M, aq. 34.0 mL), and 1,4- dioxane (50.0 mL) to yield the free amine (4.0 g, 12.6 mmol). To this was added **296** (4.3 g, 12.7 mmol) and DCC (2.6 g, 12.7 mmol) and anhydrous CH₂Cl₂ (25.0 mL). The crude product was purified *via* silica chromatography eluting with a gradient of 5-30% EtOAc in hexane to yield **293a** as a white solid (4.0 g, 54%), M.p. 67-70 °C.

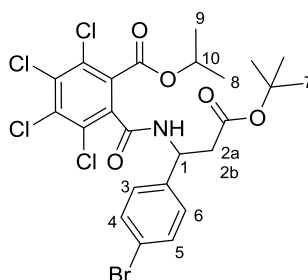
δ_{H} (400 MHz, CDCl₃): 7.35-7.15 (5H, m, H-3, H-4, H-5), 5.52-5.47 (1H, m, H-1), 5.08 (1H, sept., *J* 6.3, H-9), 2.94 (1H, dd, *J* 4.8, 15.8, H-2a), 2.80 (1H, dd, *J* 6.2, 15.8, H-2b), 1.28 (9H, s, H-6), 1.22-1.18 (6H, m, H-7, H-8).

δ_{C} (100 MHz, CDCl₃): 170.3 (C=O), 163.4 (C=O), 162.3 (C=O), 139.4 (q), 135.0 (q), 134.8 (q), 134.4 (q), 132.9 (q), 130.0 (q), 129.8 (q), 128.5, 127.7, 126.6, 81.6 (q), 71.2, 50.4, 40.3, 27.9, 21.3, 21.3.

ν_{max} (neat)/cm⁻¹: 3275, 1729, 1645, 1541.

HRMS (*m/z* - ESI): Found: 570.0366 (M+Na)⁺ C₂₄H₂₅Cl₄NO₅Na Requires: 570.0385.

10.3.4.2 isoPropyl 2-((1-(4-bromophenyl)-3-(*tert*-butoxy)-3-oxopropyl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (293b)



Prepared according to **General Procedure C** using **301b** (4.7 g, 12.5 mmol), LiOH (1M, aq., 25.0 mL), and 1,4- dioxane (32.0 mL) to yield the free amine (2.1 g, 6.9 mmol, 53%). To this was added **296** (2.4 g, 6.9 mmol) and DCC (1.4 g, 6.9 mmol) and anhydrous CH₂Cl₂ (14.0 mL). The crude product was purified *via* silica chromatography eluting with a gradient of 5-30% EtOAc in hexane to yield **293b** as a white solid (2.1 g, 48%), M.p. 153-155 °C.

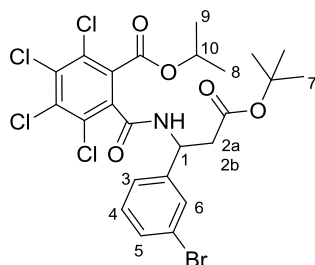
δ_{H} (400 MHz, CDCl_3): 7.51-7.45 (2H, m, H-4, H-5), 7.28-7.23 (2H, m, H-3, H-6), 5.50-5.42 (1H, m, H-1), 5.12 (1H, sept., J 6.3, H-10), 2.90 (1H, dd, J 4.8, 16.1 H-2a), 2.80 (1H, dd, J 5.8, 16.2, H-2b), 1.33 (9H, s, H-7), 1.28-1.20 (6H, m, H-8, H-9).

δ_{C} (100 MHz, CDCl_3): 165.4 (C=O), 158.7 (C=O), 157.7 (C=O), 133.9 (q), 130.30 (q), 130.2 (q), 129.5 (q), 128.1(q), 126.8, 125.3 (q), 125.0 (q), 123.7, 116.9, 77.2 (q), 66.5, 45.1, 35.2, 23.2, 23.2, 23.1, 16.7, 16.6.

ν_{max} (neat)/ cm^{-1} : 3247, 1727, 1655, 1545.

HRMS (m/z - ESI): Found: 647.9475 ($\text{M}+\text{Na}$) $^+$ $\text{C}_{24}\text{H}_{24}\text{BrCl}_4\text{NNaO}_5\text{Na}$ Requires: 647.9484.

10.3.4.3 *iso*Propyl 2-((1-(3-bromophenyl)-3-(*tert*-butoxy)-3-oxopropyl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (**293c**)



Prepared according to **General Procedure C** using **301c** (4.2 g, 10.6 mmol), LiOH (1M, aq., 22.0 mL), and 1,4-dioxane (27.0 mL) to yield the free amine (1.7 g, 5.7 mmol, 53%). To this was added **296** (2.0 g, 5.7 mmol) and DCC (1.2 g, 5.7 mmol) and anhydrous CH_2Cl_2 (12.0 mL). The crude product was purified *via* silica chromatography eluting with a gradient of 5-30% EtOAc in hexane to yield **293c** as a white solid (2.1 g, 60%). M.p. 157-159 $^{\circ}\text{C}$.

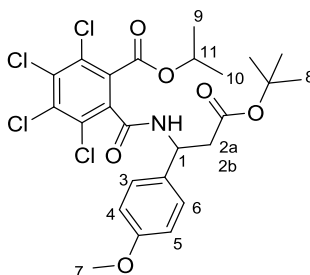
δ_{H} (400 MHz, CDCl_3): 7.51-7.45 (2H, m, H-4, H-5), 7.28-7.23 (2H, m, H-3, H-6), 5.50-5.42 (1H, m, H-1), 5.12 (1H, sept., J 6.3, H-10), 2.90 (1H, dd, J 4.9, 15.9 H-2a), 2.80 (1H, dd, J 5.9, 15.9, H-2b), 1.33 (9H, s, H-7), 1.28-1.20 (6H, m, H-8, H-9).

δ_{C} (100 MHz, CDCl_3): 170.1 (C=O), 163.4 (C=O), 162.5 (C=O), 142.0 (q), 135.0 (q), 135.0 (q), 134.3 (q), 132.9 (q), 130.8, 130.1 (q), 130.1, 129.8, 129.7 (q), 125.4, 122.6 (q), 82.1 (q), 71.3, 71.2, 49.9, 49.9, 40.1, 27.9, 21.3.

ν_{max} (neat)/ cm^{-1} : 3274, 1728, 1648, 1538.

HRMS (m/z - ESI): Found: 647.9471 ($\text{M}+\text{Na}$) $^+$ $\text{C}_{24}\text{H}_{24}\text{BrCl}_4\text{NNaO}_5\text{Na}$ Requires: 647.9484.

10.3.4.4 isoPropyl 2-((3-(*tert*-butoxy)-1-(4-methoxyphenyl)-3-oxopropyl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (293d)



Prepared according to **General Procedure C** using **301d** (7.8 g, 22.7 mmol), LiOH (1M, aq., 44.0 mL), and 1,4-dioxane (56.0 mL) to yield the free amine (5.2 g, 20.6 mmol, 90%). To this was added **296** (7.2 g, 20.6 mmol) and DCC (4.3 g, 20.6 mmol) and anhydrous CH₂Cl₂ (40.0 mL). The crude product was purified *via* silica chromatography eluting with a gradient of 5-30% EtOAc in hexane to yield **293d** as a colourless oil (7.7 g, 65%).

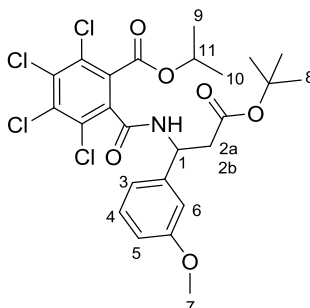
δ_{H} (400 MHz, CDCl₃): 7.34-7.27 (2H, m, H-3, H-6), 7.13 (1H, d, *J* 8.3, NH), 6.91-6.86 (2H, m, H-4, H-5), 5.50-5.42 (1H, m, H-1), 5.12 (1H, sept., *J* 6.3, H-11), 3.81 (3H, s, H-7), 2.97 (1H, dd, *J* 4.8, 15.8, H-2a), 2.80 (1H, dd, *J* 6.5, 15.8, H-2b), 1.34 (9H, s, H-8), 1.29-1.23 (6H, m, H-9, H-10).

δ_{C} (100 MHz, CDCl₃): 170.4 (C=O), 163.5 (C=O), 162.2 (C=O), 159.1 (q), 135.0 (q), 134.8 (q), 134.5 (q), 132.9 (q), 131.6 (q), 130.0 (q), 129.8 (q), 127.9, 113.9, 81.6 (q), 71.2, 55.3, 50.0, 40.4, 27.9, 21.4.

ν_{max} (neat)/cm⁻¹: 2981, 1775, 1735, 1717.

HRMS (*m/z* - ESI): Found: 600.0496 (M+Na)⁺ C₂₅H₂₇Cl₄NNaO₆ Requires: 600.0485.

10.3.4.5 isoPropyl 2-((3-(*tert*-butoxy)-1-(3-methoxyphenyl)-3-oxopropyl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (293e)



Prepared according to **General Procedure C** using compound **301e** (2.6 g, 7.4 mmol), LiOH (1M, aq., 14.0 mL), and 1,4-dioxane (21.0 mL) to yield the free amine (2.2 g, 5.6 mmol, 76%). To this was added **296** (1.9 g, 5.6 mmol) and DCC (1.2 g, 5.6 mmol) and dry CH₂Cl₂ (12.0 mL). The crude

product was purified *via* silica chromatography eluting with a gradient of 5-30% EtOAc in hexane to yield **293e** as a colourless oil (2.2 g, 69%).

δ_{H} (400 MHz, CDCl_3): 7.29-7.17 (2H, m, H-5, H-6), 6.96-6.78 (3H, m, NH, H-3, H-4), 5.53-5.45 (1H, m, H-1), 5.11 (1H, sept., J 6.3, H-11), 3.81 (3H, s, H-7), 2.94 (1H, dd, J 4.8, 15.9, H-2a), 2.82 (1H, dd, J 6.1, 15.9, H-2b), 1.32 (9H, s, H-8), 1.26-1.19 (6H, m, H-9, H-10).

δ_{C} (100 MHz, CDCl_3): 170.4 (C=O), 170.2 (C=O), 163.4 (C=O), 159.8 (q), 141.1 (q), 140.3 (q), 134.9 (q), 134.5 (q), 132.9 (q), 130.1 (q), 129.9 (q), 129.6, 118.7, 118.3, 113.5, 113.3, 112.2, 81.7 (q), 71.2, 55.3, 50.3, 50.1, 40.2, 27.9, 27.8, 21.35.

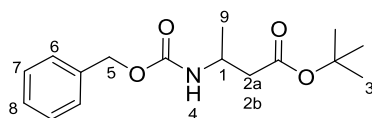
ν_{max} (neat)/ cm^{-1} : 3279, 1728, 1649, 1538.

HRMS (m/z - ESI): Found: 600.0482 ($\text{M}+\text{Na}$) $^+$ $\text{C}_{25}\text{H}_{27}\text{Cl}_4\text{NNaO}_6$ Requires: 600.0485.

10.3.5 General procedure D: Two step protection as the Cbz-amino- *t*-Butyl ester

The appropriate β -amino acid (1.0 equiv.) was dissolved in 2M NaOH_{aq} solution (1 mL /mmol) and was cooled to 0 °C. Benzyl chloroformate (1.2 equiv.) was added and the mixture was stirred at 0 °C for 30 min, followed by rt for another 2 h. The mixture was acidified to pH 2 using conc. HCl and was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over MgSO_4 and concentrated *in vacuo* to yield the Cbz-protected amine. To this was added DMAP (0.4 equiv.) and DCC (1.0 equiv.) and the flask was purged with argon and a septum with a balloon of argon was fitted. Anhydrous CH_2Cl_2 (0.5 M) was added and the mixture was cooled to 0 °C. *tert*-Butanol (4.0 equiv.) was added *via* syringe and the mixture was allowed to warm to rt and was stirred for 16 h. The resulting suspension was filtered and washed with CH_2Cl_2 . The filtrate was purified *via* silica chromatography to yield the di-protected product.

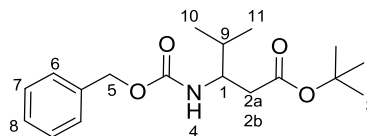
10.3.5.1 *tert*-Butyl 3-(((benzyloxy)carbonyl)amino)butanoate (**303a**)



Prepared according to **General Procedure D**. The amine was protected as the Cbz-amide using DL-3-aminobutanoic acid (2.0 g, 19.4 mmol), NaOH (2M, aq., 20.0 mL), and benzyl chloroformate (3.3 mL, 23.3 mmol). To this DMAP (0.9 g, 7.8 mmol), DCC (4.4 g, 21.3 mmol), CH_2Cl_2 (40.0 mL) and *tert*-Butanol (7.3 mL, 77.6 mmol) were added. The product was purified *via* silica chromatography eluting with a gradient of 0-10% EtOAc in hexane to yield the **303a** as a colourless oil (4.70 g, 82%). The isolated product exhibited identical spectroscopic data to those in the literature.²⁴⁷

δ_{H} (400 MHz, CDCl_3): 7.36-7.27 (5H, m, H-6, H-7, H-8), 5.30-5.00 (3H, m, NH, H-5), 4.14-4.0 (1H, m, H-1), 2.44-2.36 (2H, m, H-2a, H-2b), 1.42 (9H, s, H-8), 1.21 (3H, d, J 6.7, H-9).

10.3.5.2 *tert*-Butyl 3-(((benzyloxy)carbonyl)amino)-4-methylpentanoate (**303b**)

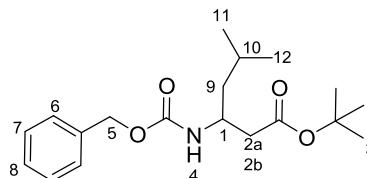


Prepared according to **General Procedure D**. The amine was protected as the Cbz-amide using DL- β -leucine (2.0 g, 15.5 mmol), NaOH (2M, aq., 16.0 mL), and benzyl chloroformate (2.7 mL, 18.5 mmol). To this DMAP (0.8 g, 6.2 mmol), DCC (3.5 g, 17.0 mmol), CH_2Cl_2 (25.0 mL) and *tert*-Butanol (5.8 mL, 62.0 mmol) were added. The product was purified *via* silica chromatography eluting with a gradient of 0-10% EtOAc in hexane to yield the **303b** as a colourless oil (3.5 g, 76%). The isolated product exhibited identical spectroscopic data to those in the literature.²⁴⁸

δ_{H} (400 MHz, CDCl_3): 7.33-7.28 (5H, m, H-6, H-7, H-8), 5.17-5.04 (3H, m, NH, H-5), 3.84-3.72 (1H, m, H-1), 2.47-2.30 (2H, m, H-2a, H-2b), 1.88-1.73 (1H, m, H-9), 1.40 (9H, s, H-8), 1.26-1.19 (6H, m, H-10, H-11).

HRMS (m/z - ESI): Found: 322.1936 ($\text{M}+\text{H}$)⁺ $\text{C}_{19}\text{H}_{29}\text{NO}_5$ Requires: 322.1940.

10.3.5.3 *tert*-Butyl 3-(((benzyloxy)carbonyl)amino)-5-methylhexanoate (**303c**)



Synthesised according to **General Procedure D**. The amine was protected as the Cbz-amide using DL- β -homoleucine (1.7 g, 12.0 mmol), NaOH (2M, aq., 12.0 mL), and benzyl chloroformate (2.1 mL, 14.4 mmol). To this DMAP (0.6 g, 4.8 mmol), DCC (2.7 g, 13.2 mmol), CH_2Cl_2 (10.0 mL) and *tert*-Butanol (4.5 mL, 47.9 mmol) were added. The product was purified *via* silica chromatography eluting with a gradient of 0-10% EtOAc in hexane to yield the **303c** as an oil (3.0 g, 71%). The isolated product exhibited identical spectroscopic data to those in the literature.²⁴⁹

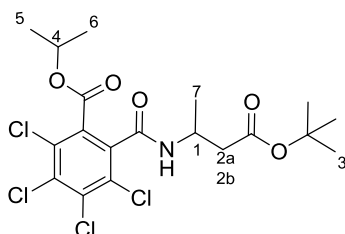
δ_{H} (400 MHz, CDCl_3): 7.39-7.26 (5H, m, H-6, H-7, H-8), 5.19-5.02 (3H, m, NH, H-5), 4.07-3.95 (1H, m, H-1), 2.50-2.31 (2H, m, H-2a, H-2b), 1.72-1.57 (1H, m, H-9a), 1.51-1.36 (10H, m, H-3, H-9b), 1.35-1.24 (1H, m, H-10), 0.98-0.79 (6H, m, H-11, H-12).

HRMS (m/z - APCI): Found: 336.2169 ($\text{M}+\text{H}$)⁺ $\text{C}_{19}\text{H}_{30}\text{NO}_4$ Requires: 336.2169.

10.3.6 General procedure E: Removal of Cbz protecting group and subsequent amide coupling

MeOH (0.5 M) was added to an RBF containing a magnetic stirring bar and the appropriate protected amino acid (1.0 equiv.) and the flask was flushed with argon. Pd(OH)₂/C (20 wt. %, 0.1 equiv.) was added, the flask was evacuated and purged with argon (x 3). On the final evacuation of the flask a septum and hydrogen balloon were fitted. The reaction mixture was stirred vigorously for 16 h. This mixture was filtered *via* suction filtration and the filtrate was concentrated *in vacuo* to yield the free amine. To this **296** (1.1 equiv.) and DCC (1.1 equiv.) were added. The flask was purged with argon and a septum with a balloon of argon was fitted. Anhydrous CH₂Cl₂ (0.5M) was added *via* syringe at 0 °C. The mixture was warmed to rt and was stirred for 16 h. The resulting suspension was filtered *via* suction filtration and the filtrate was purified *via* silica chromatography.

10.3.6.1 *iso*Propyl 2-((4-(*tert*-butoxy)-4-oxobutan-2-yl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (**293f**)



The Cbz deprotection of **303a** (1.7 g, 7.1 mmol) was achieved using Pd(OH)₂/C (20 wt. %, 0.4 g, 0.7 mmol) and MeOH (14.0 mL). **296** (2.7 g, 7.8 mmol), DCC (1.6 g, 7.8 mmol) and anhydrous CH₂Cl₂ (14.0 mL) were added to the resulting amine (1.3 g, 7.1 mmol). The product of the reaction was purified by silica chromatography eluting with a 0-20% EtOAc in hexane gradient to yield **293f** colourless oil (1.6 g, 46%).

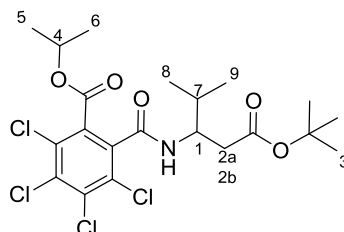
δ_H (400 MHz, CDCl₃): 6.68 (1H, d, *J* 8.3, NH), 5.24 (1H, sept., *J* 6.3, H-4), 4.44 (1H, m, H-1), 2.52 (2H, m, H-2a, H-2b), 1.45 (9H, s, H-3), 1.40-1.29 (9H, m, H-5, H-6, H-7).

δ_C (100 MHz, CDCl₃): 170.9 (C=O), 163.5 (C=O), 162.2 (C=O), 135.0 (q), 134.7 (q), 134.7 (q), 132.7 (q), 130.0 (q), 129.7 (q), 81.5 (q), 71.1, 43.0, 40.2, 28.1, 21.5, 19.3.

ν_{max} (neat)/cm⁻¹: 2955, 1777, 1735, 1713.

HRMS (*m/z* - ESI): Found: 508.0222 (M+Na)⁺ C₁₉H₂₃Cl₄NNaO₅ Requires: 508.0222.

10.3.6.2 isoPropyl 2-((1-(*tert*-butoxy)-4-methyl-1-oxopentan-3-yl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (**293g**)



The Cbz deprotection of **303b** (3.5 g, 9.1 mmol) was achieved using Pd(OH)₂/C (20 wt. %, 0.9 g, 0.9 mmol), and MeOH (18.0 mL). **296** (3.2 g, 9.2 mmol), DCC (1.9 g, 9.2 mmol) and anhydrous CH₂Cl₂ (18.0 mL) were added to the resulting amine (1.7 g, 9.1 mmol). The product of the reaction was purified by silica chromatography, eluting with a 0-20% EtOAc in hexane gradient to yield **293g** as a colourless oil (3.12 g, 67%).

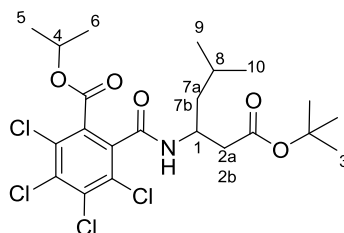
δ_{H} (400 MHz, CDCl₃): 6.72 (1H, d, *J* 9.3, NH), 5.27-5.26 (1H, m, H-4), 4.13-4.02 (1H, m, H-1), 2.63-2.46 (2H, m, H-2a, H-2b), 2.02-1.89 (1H, m, H-7) 1.43 (9H, s, H-3), 1.37-1.32 (6H, m, H-5, H-6), 1.02-0.90 (6H, m, H-8, H-9).

δ_{C} (100 MHz, CDCl₃): 169.3 (C=O), 161.7 (C=O), 160.7 (C=O), 133.0 (q), 132.9 (q), 132.7 (q), 131.1 (q), 128.0 (q), 127.7 (q), 79.4 (q), 69.2, 50.9, 34.7, 29.0, 26.1, 19.6, 19.6, 17.5, 17.4.

ν_{max} (neat)/cm⁻¹: 3282, 1728, 1646, 1551.

HRMS (*m/z* - ESI): Found: 536.0547 (M+Na)⁺ C₂₁H₂₇Cl₄NO₅ Requires: 536.0536.

10.3.6.3 isoPropyl 2-((1-(*tert*-butoxy)-5-methyl-1-oxohexan-3-yl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (**293h**)



The Cbz deprotection of **303c** (2.6 g, 7.8 mmol) was achieved using Pd(OH)₂/C (20 wt. %, 0.5 g, 0.8 mmol) and MeOH (16.0 mL). **296** (2.7 g, 7.9 mmol), DCC (1.6 g, 7.9 mmol) and dry CH₂Cl₂ (16.0 mL) were added to the resulting amine (1.6 g, 7.8 mmol). The product of the reaction was purified by silica chromatography, eluting with a 0-20% EtOAc in hexane gradient to yield **293h** as a colourless oil (2.7, 64%).

δ_{H} (400 MHz, CDCl_3): 6.58 (1H, d J 9.1, NH), 5.30-5.16 (1H, m, H-4), 4.45-4.33 (1H, m, H-1), 2.54-2.50 (2H, m, H-2a, H-2b), 1.79-1.52 (3H, m, H-7a, H-7b, H-8) 1.43 (9H, s, H-3), 1.37-1.32 (6H, m, H-5, H-6), 0.98-0.89 (6H, m, H-9, H-10).

δ_{C} (100 MHz, CDCl_3): 170.1 (C=O), 163.6 (C=O), 162.4 (C=O), 134.9 (q), 134.8 (q), 134.7 (q), 133.0 (q), 130.0 (q), 129.7 (q), 81.4 (q), 71.2, 45.3, 42.5, 39.0, 28.1, 24.9, 22.9, 22.1, 21.6, 21.5.

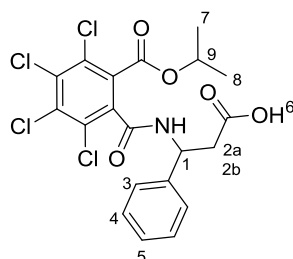
ν_{max} (neat)/ cm^{-1} : 3281, 1728, 1654, 1551.

HRMS (m/z - ESI): Found: 550.0695 ($\text{M}+\text{Na}$) $^+$ $\text{C}_{22}\text{H}_{29}\text{Cl}_4\text{NNaO}_5$ Requires: 550.0692.

10.3.7 General procedure F: *t*-Butyl ester deprotection

An RBF containing a magnetic stirring bar was charged with the appropriate *tert*-butyl ester (1.0 equiv.). The flask was purged with argon and a septum with a balloon of argon was fitted. Anhydrous CH_2Cl_2 (2.0 ml/mmol) and trifluoroacetic acid (TFA) (2.0 ml/mmol) were added *via* syringe and the mixture was stirred for 16 h. The resulting solution was concentrated *in vacuo* to yield the free acid.

10.3.7.1 3-Phenyl-3-(2,3,4,5-tetrachloro-6-(isopropoxycarbonyl)benzamido)propanoic acid (292a)



Prepared according to **General Procedure D** using **293a** (4.0 g, 7.7 mmol), TFA (20.0 mL) and anhydrous CH_2Cl_2 (20.0 mL) to yield **292a** (3.8 g, 99 %) as a white solid. M.p 195-197 °C.

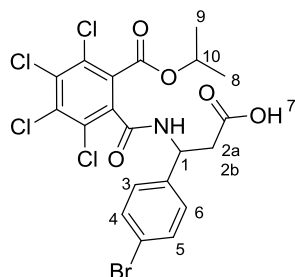
δ_{H} (400 MHz, $\text{DMSO}-d_6$): 9.65 (1H, d, J 8.0, NH), 7.52-7.38 (5H m, H-3, H-4, H-5), 5.30 (1H, m, H-1), 5.92 (1H, sept. J 6.3, H-9), 2.66-2.79 (2H, m, H-2a, H-2b), 1.09-1.06 (6H, m, H-7, H-8).

δ_{C} (100 MHz, $\text{DMSO}-d_6$): 176.4 (C=O), 167.5 (C=O), 166.4 (C=O), 146.2 (q), 140.6 (q), 138.9 (q), 138.1 (q), 137.3 (q), 134.9 (q), 133.8 (q), 133.4, 132.5, 132.1, 75.9, 55.6, 45.9, 26.1, 26.0.

ν_{max} (neat)/ cm^{-1} : 3273, 2981, 1735, 1697, 1647.

HRMS (m/z - ESI): Found: 591.8857 ($\text{M}+\text{Na}$) $^+$ $\text{C}_{20}\text{H}_{16}\text{BrCl}_4\text{NNaO}_5$ Requires: 591.8858.

10.3.7.2 3-(4-Bromophenyl)-3-(2,3,4,5-tetrachloro-6-(isopropoxycarbonyl)benzamido)propanoic acid (292b)



Prepared according to **General Procedure D** using **293b** (2.1 g, 3.3 mmol), TFA (7.0 mL) and anhydrous CH₂Cl₂ (7.0 mL) to yield **292b** (1.7 g, 99%) as a white solid. M.p. 208-209 °C.

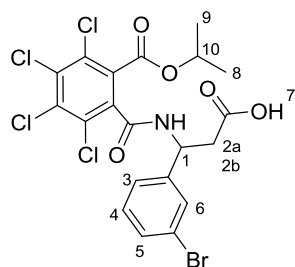
δ_{H} (400 MHz, CDCl₃): 7.54 (1H, s, H-6), 7.44 (1H, m, H-5), 7.32-7.20 (2H, m, H-3, H-4), 7.0 (1H, d *J* 8.9, NH), 5.59-5.51 (1H, m, H-1), 5.14 (1H, sept. *J* 6.3, H-11), 3.11-2.94 (2H, m, H-2a, H-2b), 1.85 (1H, bs, H-7), 1.27-1.21 (6H, m, H-9, H-10).

δ_{C} (100 MHz, MeOD): 170.4 (C=O), 161.6 (C=O), 161.4 (C=O), 138.3 (q), 133.3 (q), 132.6 (q), 132.4 (q), 131.1 (q), 129.8, 127.3, 119.6 (q), 69.6, 50.0, 38.2 18.7.

ν_{max} (neat)/cm⁻¹: 3297, 2981, 1733, 1698, 1640.

HRMS (*m/z* - ESI): Found: 591.8857 (M+Na)⁺ C₂₀H₁₆BrCl₄NNaO₅ Requires: 591.8858.

10.3.7.3 3-(3-Bromophenyl)-3-(2,3,4,5-tetrachloro-6-(isopropoxycarbonyl)benzamido)propanoic acid (292c)



Prepared according to **General Procedure D** using **293c** (2.1 g, 3.4 mmol), TFA (7.0 mL) and anhydrous CH₂Cl₂ (7.0 mL) to yield **292c** (1.9 g, 99%) as a white solid. M.p. 172-174 °C.

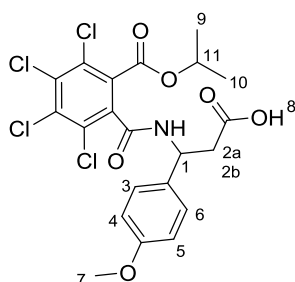
δ_{H} (400 MHz, CDCl₃): 7.54 (1H, s, H-6), 7.44 (1H, m, H-5), 7.32-7.20 (2H, m, H-3, H-4), 7.0 (1H, d *J* 8.9, NH), 5.59-5.51 (1H, m, H-1), 5.14 (1H, sept. *J* 6.3, H-11), 3.11-2.94 (2H, m, H-2a, H-2b), 1.85 (1H, bs, H-7), 1.27-1.21 (6H, m, H-9, H-10).

δ_{C} (100 MHz, MeOD): 172.3 (C=O), 163.6 (C=O), 163.2 (C=O), 143.6 (q), 135.2 (q), 134.7 (q), 134.4 (q), 133.0 (q), 131.0 (q), 130.9 (q), 130.6, 130.4 (q), 130.3, 126.0, 71.5, 51.0, 40.3, 39.4, 20.6, 20.6.

ν_{max} (neat)/ cm^{-1} : 3292, 2925, 1738, 1720, 1636.

HRMS (m/z - ESI): Found: 591.8859 ($\text{M}+\text{Na}$) $^{+}$ $\text{C}_{20}\text{H}_{16}\text{BrCl}_4\text{NNaO}_5$ Requires: 591.8858.

10.3.7.4 3-(4-Methoxyphenyl)-3-(2,3,4,5-tetrachloro-6-(isopropoxycarbonyl)benzamido)propanoic acid (292d)



Prepared according to **General Procedure D** using compound **293d** (7.7 g, 13.2 mmol), TFA (26.0 mL) and anhydrous CH_2Cl_2 (26.0 mL) to yield **292d** (6.9 g, 99%) as a white solid. M.p. 149-151 $^{\circ}\text{C}$.

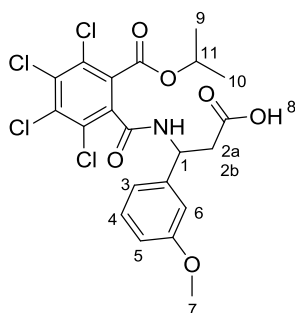
δ_{H} (400 MHz, CDCl_3): 7.32-7.21 (2H, m, H-4, H-5), 6.93-6.80 (2H, m, H-3, H-6), 5.58-5.44 (1H, m, H-11), 5.18-5.03 (1H, m, H-1), 3.79 (3H, s, H-7), 3.16-2.85 (2H, m, H-2a, H-2b), 1.34-1.15 (6H, m, H-9, H-10).

δ_{C} (100 MHz, CDCl_3): 174.6 (C=O), 163.8 (C=O), 162.4 (C=O), 159.3 (q), 135.1 (q), 135.0 (q), 134.3 (q), 132.7 (q), 131.1 (q), 130.0 (q), 129.8 (q), 127.8, 114.2, 71.5, 55.3, 49.6, 38.9, 21.4, 21.4.

ν_{max} (neat)/ cm^{-1} : 3275, 2971, 1735, 1720, 1636.

HRMS (m/z - ESI): Found: 543.9842 ($\text{M}+\text{Na}$) $^{+}$ $\text{C}_{21}\text{H}_{19}\text{Cl}_4\text{NNaO}_6$ Requires: 543.9859.

10.3.7.5 3-(4-Methoxyphenyl)-3-(2,3,4,5-tetrachloro-6-(isopropoxycarbonyl)benzamido)propanoic acid (292e)



Prepared according to **General Procedure D** using compound **293e** (2.2 g, 3.8 mmol), TFA (8.0 mL) and anhydrous CH₂Cl₂ (8.0 mL) to yield **292e** (1.9 g, 97%) as a white solid. M.p. 170-172 °C.

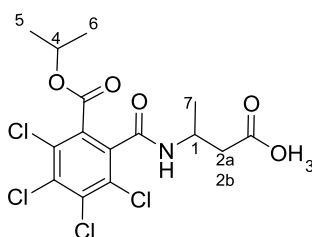
δ_{H} (400 MHz, CHCl₃): 7.32-7.27 (1H, m, H-4), 6.95-6.83 (3H, m, H-3, H-5, H-6), 5.16 (1H, sept., *J* 6.2, H-11), 5.00-4.94 (1H, m, H-1), 3.82 (3H, s, H-7), 3.06 (1H, dd, *J* 5.14, 16.3, H-2a), 2.75 (1H, dd, *J* 11.5, 16.3, H-2b), 1.32-1.23 (6H, m, H-9, H-10).

δ_{C} (100 MHz, CHCl₃): 172.7 (C=O), 163.7 (C=O), 162.6 (C=O), 160.0 (q), 140.6 (q), 135.1 (q), 135.1 (q), 134.3 (q), 132.8 (q), 130.1 (q), 129.9, 120.0 (q), 118.5, 113.6, 113.6, 112.3, 71.5, 55.3, 50.0, 38.5, 21.4, 21.4.

ν_{max} (neat)/cm⁻¹: 3306, 2977, 1736, 1691, 1640.

HRMS (*m/z* - ESI): Found: 543.9835 (M+Na)⁺ C₂₁H₁₉Cl₄NNaO₆ Requires: 543.9859.

10.3.7.6 3-(2,3,4,5-tetrachloro-6-(isopropoxycarbonyl)benzamido)butanoic acid (292f)



Prepared according to **General Procedure D** using **293f** (1.6 g, 3.2 mmol), TFA (6.0 mL) and anhydrous CH₂Cl₂ (6.0 mL) to yield **292f** (1.3 g, 97%) as a white solid. M.p 162-164 °C.

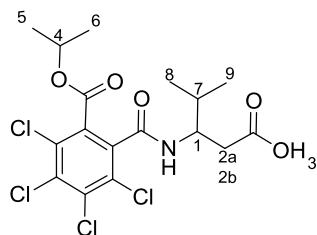
δ_{H} (400 MHz, CHCl₃): 6.49 (1H, d *J* 8.4, NH), 5.22 (1H, sept., *J* 6.3, H-4), 4.55-4.42 (1H, m, H1) 2.70-2.64 (2H, m, H-2a, H-2b), 1.37-1.30 (9H, m, H-5, H-6, H-7).

δ_{C} (100 MHz, CHCl₃): 175.3 (C=O), 163.8 (C=O), 162.5 (C=O), 135.1 (q), 134.9 (q), 134.4 (q), 132.6 (q), 130.0 (q), 129.7 (q), 71.4, 42.7, 38.9, 21.5, 19.4.

ν_{max} (neat)/cm⁻¹: 3278, 2981, 1736, 1697, 1642.

HRMS (*m/z* - ESI): Found: 451.9594 (M+Na)⁺ C₁₅H₁₅Cl₄NNaO₅ Requires: 451.9597.

10.3.7.7 4-Methyl-3-(2,3,4,5-tetrachloro-6-(isopropoxycarbonyl)benzamido)pentanoic acid (292g)



Prepared according to **General Procedure D** using **293g** (3.1 g, 6.1 mmol), TFA (12.0 mL) and anhydrous CH₂Cl₂ (12.0 mL) to yield **292g** (2.8 g, 99%) as a white solid. M.p 109-111 °C.

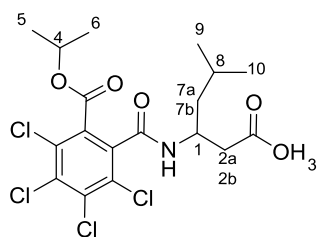
δ_H (400 MHz, CHCl₃): 6.68 (1H, d *J* 9.2, NH), 5.24 (1H, sept., *J* 6.3, H-4), 4.22-4.13 (1H, m, H-1), 2.77-2.63 (2H, m, H-2a, H-2b), 2.02-1.89 (1H, m, H-7), 1.40-1.35 (6H, m, H-5, H-6), 1.05-0.96 (6H, m, H-8, H-9).

δ_C (100 MHz, CHCl₃): 175.7 (C=O), 164.2 (C=O), 163.2 (C=O), 135.1 (q), 134.9 (q), 134.5 (q), 132.6 (q), 130.0 (q), 129.7 (q), 71.8, 52.7, 35.4, 30.8, 21.5, 21.5, 19.3, 19.1.

ν_{max} (neat)/cm⁻¹: 3336, 2980, 1718, 1699, 1620.

HRMS (*m/z* - ESI): Found: 479.990 (M+Na)⁺ C₁₇H₁₉Cl₄NNaO₅ Requires: 479.9910.

10.3.7.8 5-Methyl-3-(2,3,4,5-tetrachloro-6-(isopropoxycarbonyl)benzamido)hexanoic acid (292h)



Prepared according to **General Procedure D** using **293h** (2.7 g, 5.0 mmol), TFA (10.0 mL) and dry CH₂Cl₂ (10.0 mL) to yield **292h** (2.4 g, 99%) as a white solid. M.p 116-118 °C.

δ_H (400 MHz, CHCl₃): 6.46 (1H, d *J* 9.1, NH), 5.25 (1H, sept., *J* 6.3, H-4), 4.54-4.43 (1H, m, H1) 2.78 (1H, dd, *J* 5.6, 17.0, H-2a) 2.68 (1H, dd, *J* 4.3, 17.0, H-2b), 1.82-1.62 (2H, m, H-7a, H-7b), 1.46-1.35 (7H, m, H-5, H-6, H-8), 1.02-0.94 (6H, m, H-9, H-10).

δ_C (100 MHz, CHCl_3): 175.2 (C=O), 163.9 (C=O), 162.7 (C=O), 135.0 (q), 134.8 (q), 134.6 (q), 132.8 (q), 130.0 (q), 129.7 (q), 71.5, 45.0, 42.5, 37.8, 24.9, 23.0, 21.9, 21.6, 21.5.

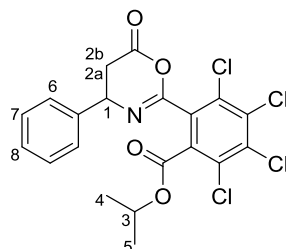
ν_{max} (neat)/ cm^{-1} : 3263, 2980, 1719, 1644, 1554.

HRMS (m/z - APCI): Found: 472.0242 ($\text{M}+\text{H}$) $^+$ $\text{C}_{18}\text{H}_{22}\text{Cl}_4\text{NO}_5$ Requires: 472.0247.

10.3.8 General procedure G: Preparation of TCIC-oxazinones

An RBF containing a magnetic stirrer bar was charged with the appropriate carboxylic acid (1.0 equiv.). The flask was purged with argon and a septum with a balloon of argon was fitted. Anhydrous CH_2Cl_2 (2M) and freshly distilled NEt_3 (1.1 equiv.) were added *via* syringe and the solution was cooled to $-30\text{ }^\circ\text{C}$. Freshly distilled SOCl_2 (1.1 equiv.) was added *via* syringe and the mixture was stirred for 5 min followed by a further dropwise addition of freshly distilled NEt_3 (2.2 equiv.) *via* syringe. The mixture was stirred for 1 h at $-30\text{ }^\circ\text{C}$ followed by evaporation of the solvent *in vacuo* at $-30\text{ }^\circ\text{C}$. The remaining solid was re-dissolved in dry toluene and was filtered under argon to remove the insoluble solid (Et_3NHCl). The filtrate was concentrated *in vacuo* and was purified as instructed to yield the appropriate TCIC-oxazinone.

10.3.8.1 *iso*Propyl-2,3,4,5-tetrachloro-6-(6-oxo-4-phenyl-5,6-dihydro-4H-1,3-oxazin-2-yl)benzoate (144a)



Prepared according to **General Procedure G** using **292a** (5.5 g, 11.1 mmol), CH_2Cl_2 (5.0 mL), NEt_3 (1.7 mL, 12.3 mmol), SOCl_2 (0.9 mL, 12.3 mmol) and a second aliquot of NEt_3 (3.4 mL, 24.6 mmol). The crude product was passed through a silica plug, eluting with 30% EtOAc in hexane followed by recrystallisation from a mixture of diisopropyl ether (*i*Pr₂O) and EtOAc to furnish **144a** as pale yellow crystals (3.4 g, 65%). M.p $103\text{--}106\text{ }^\circ\text{C}$.

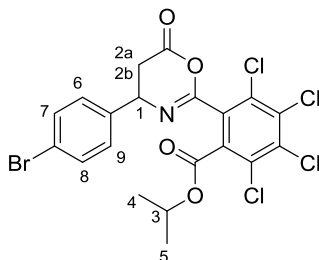
δ_H (400 MHz, CDCl_3): 7.42–7.38 (5H, m, H-6, H-7, H-8), 5.18 (1H, app. sept., H-3), 5.02 (1H, dd, J 5.1, 11.7, H-1), 3.09 (1H, dd, J 5.1, 16.3, H-2a), 2.77 (1H, dd, J 11.7, 16.3, H-2b), 1.32–1.30 (6H, m, H-4, H-5).

δ_C (100 MHz, CDCl_3): 164.1 (C=O), 163.6 (C=O), 151.0 (q), 139.3 (q), 136.0 (q), 135.5 (q), 134.0 (q), 131.9 (q), 130.4 (q), 129.0, 128.1, 126.2, 71.4, 57.4, 35.4, 21.6, 21.5.

$\nu_{\max}$ (neat)/ cm^{-1} : 1793, 1722, 1708.

HRMS (m/z - ESI): Found: 469.9886 (M-H) $\text{C}_{21}\text{H}_{16}\text{Cl}_4\text{NO}_3$ Requires: 469.9884.

10.3.8.2 isoPropyl-2-(4-(4-bromophenyl)-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)-3,4,5,6-tetrachlorobenzoate (144b)



Prepared according to **General Procedure G** using **292b** (1.6 g, 2.7 mmol), CH_2Cl_2 (3.0 mL), NEt_3 (0.4 mL, 3.0 mmol), SOCl_2 (0.2 mL, 3.0 mmol) and a second aliquot of NEt_3 (0.8 mL, 6.0 mmol). The crude product was passed through as silica plug, eluting with 30% EtOAc in hexane followed by recrystallisation using a mixture of $i\text{Pr}_2\text{O}$ and EtOAc to furnish **144b** as pale yellow crystals (1.0 g, 68%). M.p. 100-103 $^\circ\text{C}$.

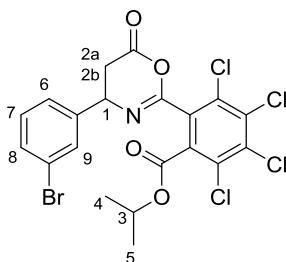
δ_{H} (400 MHz, CHCl_3): 7.55-7.48 (2H, m, H-7, H-8), 7.30-7.21 (2H, m, H-6, H-9), 7.24-7.22 (1H, m, H-3), 5.02-4.92 (1H, m, H-1), 3.06 (1H, dd, J 4.1, 16.0, H-2a), 2.69 (1H, dd, J 12.3, 16.0, H-2b), 1.34-1.24 (6H, m, H-4, H-5).

δ_{C} (100 MHz, CHCl_3): 163.7 (C=O), 163.7 (C=O), 151.3 (C=N), 138.4 (q), 136.1 (q), 135.6 (q), 133.9 (q), 132.1, 131.8 (q), 130.4 (q), 130.2 (q), 127.9, 122.1 (q), 71.4, 56.8, 35.3, 21.6, 21.5.

$\nu_{\max}$ (neat)/ cm^{-1} : 1783, 1717, 1693.

HRMS (m/z - APCI): Found: 551.8941 (M+H) $^+$ $\text{C}_{20}\text{H}_{15}\text{BrCl}_4\text{NO}_4$ Requires: 551.8933.

10.3.8.3 isoPropyl-2-(4-(3-bromophenyl)-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)-3,4,5,6-tetrachlorobenzoate (144c)



Prepared according to **General Procedure G** using **292c** (1.8 g, 3.1 mmol), CH_2Cl_2 (3.5 mL), NEt_3 (0.5 mL, 3.5 mmol), SOCl_2 (0.3 mL, 3.5 mmol) and a second aliquot of NEt_3 (1.0 mL, 6.9 mmol).

The crude product was passed through as silica plug, eluting with 30% EtOAc in hexane followed by recrystallisation using a mixture of *i*Pr₂O and EtOAc to furnish **144c** as pale yellow crystals (1.0 g, 62%). M.p. 109-110 °C.

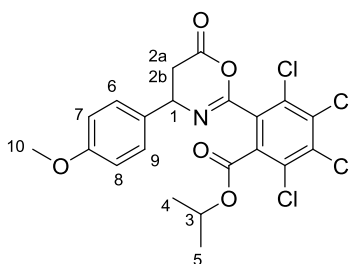
δ_{H} (400 MHz, CHCl₃): 7.57-7.53 (1H, m, H-9), 7.49-7.44 (1H, m, H-8), 7.31-7.22 (2H, m, H-6, H-7), 5.18 (1H, sept., *J* 6.2, H-3), 5.00-4.93 (1H, m, H-1), 3.07 (1H, dd, *J* 4.9, 16.3, H-2a), 2.71 (1H, dd, *J* 12.3, 16.3, H-2b), 1.34-1.27 (6H, m, H-4, H-5).

δ_{C} (100 MHz, CHCl₃): 163.7 (C=O), 151.5 (C=O), 141.6 (C=N), 136.1 (q), 135.6 (q), 133.8 (q), 131.9 (q), 131.3, 130.5, 130.5 (q), 130.2 (q), 129.4, 124.9, 123.0 (q), 71.5, 56.7, 35.2, 21.6, 21.5

ν_{max} (neat)/cm⁻¹: 1799, 1720, 1696.

HRMS (*m/z* - APCI): Found: 551.8938 (M+H)⁺ C₂₀H₁₅BrCl₄NO₄ Requires: 551.8933.

10.3.8.4 *iso*Propyl-2,3,4,5-tetrachloro-6-(4-(4-methoxyphenyl)-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)benzoate (**144c**)



Prepared according to **General Procedure G** using **292c** (4.9 g, 9.3 mmol), CH₂Cl₂ (9.5 mL), NEt₃ (1.4 mL, 10.3 mmol), SOCl₂ (0.7 mL, 10.3 mmol) and a second aliquot of NEt₃ (2.9 mL, 20.5 mmol). The product was purified *via* silica chromatography, eluting with a gradient of 5-20% EtOAc in hexane to furnish **144c** as pale yellow solid (2.6 g, 54%). M.p. 50-52 °C.

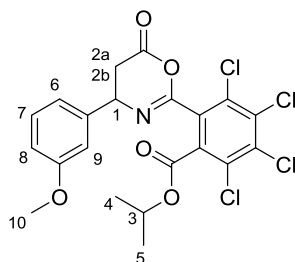
δ_{H} (400 MHz, CHCl₃): 7.27 (2H, d, *J* 8.7, H-6, H-9), 6.89 (2H, d, *J* 8.7, H-7, H-8), 5.16 (1H, sept., *J* 6.2, H-3), 5.02-4.91 (1H, m, H-1), 3.79 (3H, s, H-10), 3.05 (1H, dd, *J* 5.1, 16.2, H-2a), 2.73 (1H, dd, *J* 11.5, 16.2, H-2b), 1.35-1.24 (6H, m, H-4, H-5).

δ_{C} (100 MHz, CHCl₃): 164.3 (C=O), 163.6 (C=O), 159.4 (q), 150.7 (C=N), 135.9 (q), 135.4 (q), 134.0 (q), 131.9 (q), 131.4 (q), 130.3 (q), 127.8 (q), 127.4, 114.3, 71.4, 56.9, 55.3, 35.5, 21.6, 21.5.

ν_{max} (neat)/cm⁻¹: 1799, 1719, 1696.

HRMS (*m/z* - APCI): Found: 503.9945 (M+H)⁺ C₂₁H₁₈Cl₄NO₅ Requires: 503.9934.

10.3.8.5 isoPropyl 2,3,4,5-tetrachloro-6-(4-(3-methoxyphenyl)-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)benzoate (144e)



Prepared according to **General Procedure G** using **292e** (3.4 g, 6.6 mmol), CH₂Cl₂ (6.5 mL), NEt₃ (1.0 mL, 7.2 mmol), SOCl₂ (0.5 mL, 7.2 mmol) and a second aliquot of NEt₃ (2.0 mL, 14.9 mmol). The product was purified *via* silica chromatography, eluting with a gradient of 5-20% EtOAc in hexane to furnish **144e** as pale yellow solid (1.3 g, 38%). M.p. 48-50 °C.

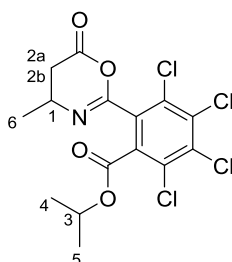
δ_H (400 MHz, CHCl₃): 7.30 (1H, t, *J* 8.1, H-7), 6.96-6.81 (3H, m, H-6, H-8, H-9), 5.17 (1H, sept., *J* 6.2, H-3), 5.02-4.95 (1H, m, H-1), 3.80 (3H, s, H-10), 3.07 (1H, dd, *J* 5.1, 16.5, H-2a), 2.74 (1H, dd, *J*, 11.8, 16.5, H-2b), 1.33-1.25 (6H, m, H-4, H-5).

δ_C (100 MHz, CHCl₃): 164.1 (C=O), 163.6 (C=O), 160.1 (q) 150.9 (C=N), 140.8 (q), 135.9 (q), 135.4 (q), 134.0 (q), 131.9 (q), 130.3 (q), 130.3 (q), 130.0, 118.4, 113.5, 112.1, 71.4, 57.3, 55.3, 35.4, 21.6, 21.4.

ν_{max} (neat)/cm⁻¹: 1800, 1720, 1695.

HRMS (*m/z* - APCI): Found: 503.9943 (M+H)⁺ C₂₁H₁₈Cl₄NO₅ Requires: 503.9934.

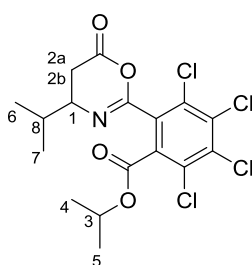
10.3.8.6 isoPropyl-2,3,4,5-tetrachloro-6-(4-methyl-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)benzoate (144f)



Prepared according to **General Procedure G** using **292f** (1.2 g, 2.7 mmol), CH₂Cl₂ (3.0 mL), NEt₃ (0.4 mL, 3.0 mmol), SOCl₂ (0.2 mL, 3.0 mmol) and a second aliquot of NEt₃ (0.8 mL, 6.0 mmol). The crude product was passed through as silica plug, eluting with 30% EtOAc in hexane and the resulting product was triturated in hexane to furnish **144f** as white solid (845 mg, 75%). M.p. 64-66 °C.

δ_{H} (400 MHz, CHCl_3):	5.23 (1H, sept., J 6.3, H-3), 4.04-3.91 (1H, m, H-1), 2.80 (1H, dd, J 5.2, 16.1, H-2a), 2.50 (1H, dd, J 9.3, 16.1, H-2b), 1.40-1.34 (9H, m, H-4, m H-5, H-6).
δ_{C} (100 MHz, CHCl_3):	164.5 (C=O), 163.5 (C=O), 149.9 (C=N), 135.7 (q), 135.3 (q), 133.9 (q), 131.8 (q), 130.2 (q), 130.2 (q), 71.2, 49.9, 34.8, 21.6, 21.6, 20.7.
ν_{max} (neat)/ cm^{-1} :	1804, 1728, 1708.
HRMS (m/z - APCI):	Found: 411.9683 ($\text{M}+\text{H}$) $^+$ $\text{C}_{15}\text{H}_{14}\text{Cl}_4\text{NO}_4$ Requires: 411.9671.

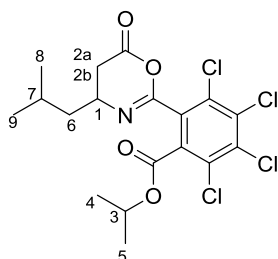
10.3.8.7 isoPropyl 2,3,4,5-tetrachloro-6-(4-isopropyl-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)benzoate (144g)



Prepared according to **General Procedure G** using **292g** (2.8 g, 6.1 mmol), CH_2Cl_2 (6.0 mL), NEt_3 (0.9 mL, 6.7 mmol), SOCl_2 (0.5 mL, 6.7 mmol) and a second aliquot of NEt_3 (1.9 mL, 13.4 mmol). The crude product was passed through as silica plug, eluting with 30% EtOAc in hexane followed by trituration in Et_2O to furnish **144g** a white solid (1.69 g, 63%). M.p. 55-57 °C.

δ_{H} (400 MHz, CHCl_3):	5.22 (1H, sept., J 6.5, H-3), 3.63-3.58 (1H, m, H-8), 2.76 (1H, dd, J 4.8, 16.1, H-2a), 2.51 (1H, dd, J 11.9, 16.1, H-2b), 1.96-1.88 (1H, m, H-8), 1.40-1.36 (6H, m, H-4, H-5), 1.06-1.02 (6H, m, H-6, H-7).
δ_{C} (100 MHz, CHCl_3):	165.5, 163.6, 149.8, 135.7, 135.4, 133.8, 131.9, 130.5, 130.3, 71.3, 59.6, 32.5, 30.6, 21.7, 18.5, 18.3.
ν_{max} (neat)/ cm^{-1} :	1799, 1728, 1693.
HRMS (m/z - APCI):	Found: 439.9972 ($\text{M}+\text{H}$) $^+$ $\text{C}_{17}\text{H}_{18}\text{Cl}_4\text{NO}_4$ Requires: 439.9984.

10.3.8.8 isoPropyl-2,3,4,5-tetrachloro-6-(4-isobutyl-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)benzoate (144h)



Prepared according to **General Procedure G** using **292h** (1.3 g, 2.7 mmol), CH₂Cl₂ (3.0 mL), NEt₃ (0.4 mL, 2.9 mmol), SOCl₂ (0.2 mL, 2.9 mmol) and a second aliquot of NEt₃ (0.6 mL, 5.9 mmol). The crude product was passed through as silica plug, eluting with 30% EtOAc in hexane followed by trituration in Et₂O to furnish **144h** as pale yellow solid (630 mg, 52%). M.p. 90-92 °C.

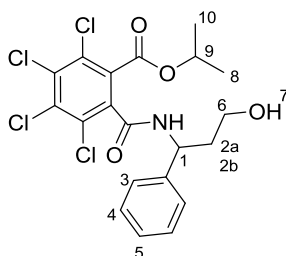
δ_H (400 MHz, CHCl₃): 5.29-5.18 (1H, m, H-3), 3.96-3.85 (1H, m, H-1), 2.80 (1H, dd, *J* 4.8, 16.1, H-2a), 2.56-2.40 (1H, dd, *J* 9.7, 16.1, H-2b), 1.93-1.83 (1H, m, H-7), 1.70-1.55 (2H, m, H-6), 1.46-1.32 (6H, m, H-4, H-5), 1.04-0.91 (6H, m, H-8, H-9).

δ_C (100 MHz, CHCl₃): 164.9, 163.6, 149.7, 135.7, 135.4, 133.8, 131.9, 130.4, 130.3, 71.3, 52.3, 44.3, 33.7, 24.4, 22.7, 22.1, 21.7, 21.6.

ν_{max} (neat)/cm⁻¹: 1804, 1728, 1687.

HRMS (*m/z* - APCI): Found: 454.0151 (M+H)⁺ C₁₈H₂₀Cl₄NO₄ Requires: 454.0141.

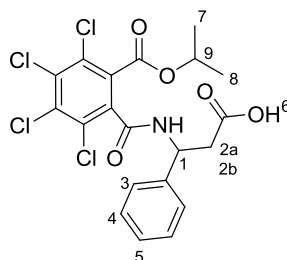
10.3.9 isoPropyl 2,3,4,5-tetrachloro-6-((3-hydroxy-1-phenylpropyl)carbamoyl)benzoate (305)



296 (5.0 g, 14.1 mmol), and HBTU (5.3 g, 14.1 mmol) were dissolved in anhydrous CH₂Cl₂ (35.0 mL) under argon and freshly distilled NEt₃ (2.0 mL, 14.1 mmol) was added. The reaction mixture was stirred for 16 h and the resulting precipitate was filtered and washed with cold CH₂Cl₂ to yield **305** as white solid (4.5 g, 66%). M.p 158-160 °C.

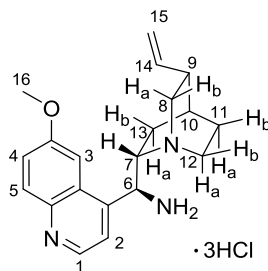
δ_{H} (400 MHz, CHCl_3):	7.37-7.25 (5H, m, H-3, H-4, H-5), 6.63 (1H, d, J 8.0, NH), 5.39-5.30 (1H, m, H-1), 5.12 (1H, sept., J 6.3, H-9), 3.83-3.70 (2H, m, H6), 2.22-2.10 (1H, m, H-2a), 2.04-1.91 (1H, m, H-2b), 1.29-1.22 (6H, m, H-8, H-10).
δ_{C} (100 MHz, CHCl_3):	168.1 (C=O), 163.9 (C=O), 140.3 (q), 135.1 (q), 135.0 (q), 134.3 (q), 132.9 (q), 130.0 (q), 129.8 (q), 128.8, 127.8, 126.7, 71.6, 59.1, 52.3, 38.2, 21.4, 21.4.
ν_{max} (neat)/ cm^{-1} :	3528, 3251, 1707, 1664, 1587.
HRMS (m/z - ESI):	Found: 511.9770 ($\text{M}+\text{H}$) $^+$ $\text{C}_{20}\text{H}_{19}\text{Cl}_5\text{NO}_4$ Requires: 511.9762.

10.3.9.1 3-Phenyl-3-(2,3,4,5-tetrachloro-6-(isopropoxycarbonyl)benzamido)propanoic acid (292a)



305 (215 mg, 0.4 mmol) and IBX (378 mg, 1.4 mmol) were placed in and RBF under argon atmosphere and anhydrous MeCN (0.9 mL) was added. The reaction mixture was stirred for 48 h at 50 °C. The mixture was cooled and filtered through a bed of celite and the filtrate was concentrated *in vacuo*. To this NaClO_4 (123 mg, 1.4 mmol) and NaH_2PO_4 (648 mg, 5.4 mmol) were added followed by a 1:1:2 H_2O :THF:*t*-BuOH mixture (2.0 mL). The mixture was cooled to 0 °C and H_2O_2 (0.3 mL, 9.0 mmol) was added. The reaction was stored for 16 h. Sat. NH_4Cl (aq., 3.0 mL) was added and the product was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo* to yield **292a** as a white solid (160 mg, 72%). M.p. 158-159 °C. The spectral data was identical to that obtained when **292a** was synthesised according to **General Procedure D**.

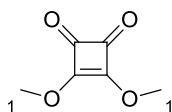
10.3.10 (S)-(6-Methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methanamine·3HCl (311)



Quinine (**44**, 10.0 g, 30.8 mmol) and triphenylphosphine (9.7 g, 37.0 mmol) were dissolved in anhydrous THF (140 mL) at 0 °C under argon atmosphere. Diisopropyl azodicarboxylate (DIAD) (7.3 mL, 37.0 mmol) was added and the mixture was stirred for 30 min followed by the dropwise addition of a solution of diphenylphosphoryl azide (DPPA, 8.0 mL, 37.0 mmol) in anhydrous THF (64 mL). The reaction mixture warmed to rt and stirred followed by heating at 50 °C for 2 h. The reaction was cooled to rt and triphenylphosphine (10.5 g, 40.1 mmol) was added portion-wise followed by further heating at 50 °C until the gas evolution had ceased (2 h). After cooling to rt, water (10 mL) was added and the mixture was stirred for an additional 4 h. The THF was removed *in vacuo* and the residue was dissolved in aqueous HCl (2N, 80 mL). The aqueous layer washed with CHCl₂ (3 x 40 mL) and concentrated under reduced pressure to yield **311** as a yellow solid (11.5 g, 84%). M.p. 218 °C (decomp.) (lit.²⁵⁰ m.p. 220-222 °C); $[\alpha]_D^{20} = +22.1$ ($c = 0.75$, MeOH). Spectral data for this compound were consistent with those in the literature.²⁵⁰

δ_H (400 MHz, D₂O): 9.04 (1 H, d, J 5.8, H-1), 8.29 (1 H, d, J 9.4, H-5), 8.15 (1 H, d, J 5.8, H-2), 7.94 (1 H, dd, J 2.4, 9.4 H-4), 7.84 (1 H, bs, H-3), 5.90 (1 H, ddd, J 6.8, 10.5, 17.2, H-14), 5.56 (1 H, d, J 10.6, H-6), 5.32-5.18 (2 H, m, H-15), 4.35-4.23 (1 H, m, H-7), 4.13 (3 H, s, H-16), 4.04-3.92 (1 H, m, H-12a), 3.85 (1 H, dd, J 10.6, 13.3, H-8b), 3.59-3.45 (2 H, m, H-8a, H-12b), 3.00-2.90 (1 H, m, H-9), 2.17-2.00 (3 H, m, H-10, H-11a, H-11b), 1.96-1.84 (1 H, m, H-13b), 1.18 (1 H, dd, J 7.2, 14.2, H-13a).

10.3.11 3,4-Dimethoxycyclobut-3-ene-1,2-dione (313)

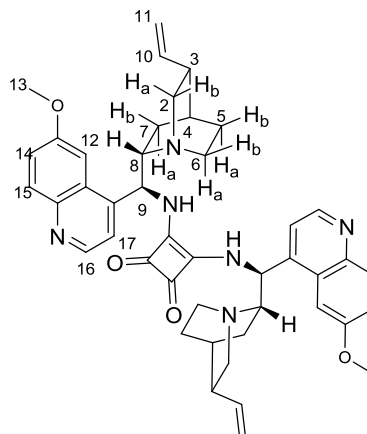


Squaric acid (**312**, 2.0 g, 17.5 mmol) was dissolved in anhydrous MeOH (20 mL) under argon followed by the addition of trimethyl orthoformate (5.8 mL, 52.6 mmol) and TFA (0.3 mL, 3.5 mmol). The flask was fitted with a condenser and the reaction mixture was heated at reflux

temperature for 48 h and then cooled to rt. The reaction mixture was concentrated *in vacuo* and was purified by silica column chromatography, eluting with 30% EtOAc in hexane to furnish **313** as a white solid (2.9 g, 88%). M.p. 51-53 °C (lit.²⁵¹ m.p. 52-54 °C). Spectral data for this compound were consistent with those in the literature.²⁵¹

δ_{H} (400 MHz, CDCl_3): 4.38 (6 H, s, H-1).

10.3.12 3,4-bis((1S)-(6-Methoxyquinolin-4-yl)((2S)-8-vinylquinuclidin-2-yl)methylamino)-cyclobut-3-ene-1,2-dione (108)

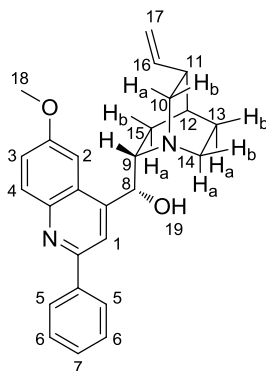


308 (3.0 g, 7.0 mmol) was dissolved in CH_2Cl_2 (20 mL) followed by treatment with NEt_3 (3.9 mL, 28.0 mmol) and the resultant mixture stirred at room temperature for 1 h. Water (20 mL) was added and the organic phase separated, washed with NaOH (1 N, aq., 10 mL) and dried over MgSO_4 . The solvent was concentrated. *in vacuo* and the residue was dissolved in MeOH (10 mL). To this **313** (0.5 g, 3.2 mmol) was added in one portion and the reaction mixture was stirred under an atmosphere of argon. After 48 h, the reaction mixture was filtered to yield **108** as a white solid (1.9 g, 82%). M.p. 204 °C (decomp.) (Lit.¹⁰² m.p. 284 °C) $[\alpha]_{\text{D}}^{20} = -94.5$ (c 0.2, CHCl_3). Spectral data for this compound were consistent with those in the literature.¹⁰²

δ_{H} (400 MHz, $\text{DMSO}-d_6$): 8.79 (1H, d, J 4.5, H-16), 7.99 (1H, d, J 9.2, H-15), 7.81 (1H, d, J 2.6, H-12), 7.69 (1H, br s, NH), 7.50 (1H, d, J 4.5, H-17), 7.45 (1H, dd, J 9.2, 2.6, H-14), 5.93-5.88 (2H, m, H-9, H-10), 5.02-4.95 (2H, m, H-11), 3.97 (3H, s, H-13), 3.32-3.21 (3H, m, H-8, H-6a, H-2b), 2.63-2.52 (2H, m, H-6b, H-2a), 2.23 (1H, m, H-3), 1.56-1.43 (4H, m, H-4, H-5a, H-5b, H-7b), 0.63-0.57 (1H, m, H-7a).

HRMS (m/z -ES) : Found: 723.3652 ($\text{M} - \text{H}^-$) $\text{C}_{44}\text{H}_{47}\text{N}_6\text{O}_4$ Requires : 723.3659.

10.3.13 (R)-(6-Methoxy-2-phenylquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methanol (331)

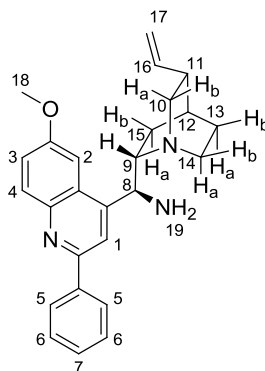


Quinine (**44**, 6.5 g, 20.0 mmol) was dissolved in anhydrous MTBE (120 mL) under an atmosphere of argon and the suspension was cooled to -10 °C. A solution of phenyl lithium (1.8 M in THF, 33. mL, 59.9 mmol) was added *via* syringe in two equal portions to the vigorously stirred suspension and the mixture was stirred at this temperature for 30 min, followed by a further 2 h of stirring at rt. Acetic acid (15 mL) was added dropwise to the reaction at 0 °C, followed by water (50 mL) and EtOAc (50 mL). After warming the mixture to rt, iodine was added in several portions with continuous stirring until the appearance of a persistent deep brown colouration. A solution of sodium thiosulfate (Na₂S₂O₃, 3.0 g) in water (50 mL), followed by a concentrated solution of aqueous ammonia (35%, 30 mL) were added and the mixture was stirred for 10 min. The organic phase was then washed with brine and the aqueous phase extracted with dichloromethane (3 x 40 mL), the combined organic extracts were dried over anhydrous MgSO₄, filtered and the solvent removed *in vacuo*. The crude material was purified *via* silica chromatography, eluting in gradient from 0-5% MeOH in EtOAc:NEt₃ (19:1) to furnish **331** (2.7 g, 37%) as a white solid. M.p. 160-162 °C (lit.²⁰⁸ 161-163 °C) ; $[\alpha]_D^{20} = -168.2$ (c 1.0, CHCl₃). Spectral data for this compound were consistent with those in the literature.²⁰⁸

δ_H (400 MHz, CDCl₃):* 8.11-8.01 (3 H, m, H-4, H-5), 7.90 (1 H, s, H-1), 7.51-7.37 (3 H, m, H-6, H-7), 7.34 (1 H, dd, *J* 2.6, 9.2, H-3), 7.15 (1 H, d, *J* 2.5, H-2), 5.73 (1 H, ddd, *J* 7.7, 10.3, 17.3, H-16), 5.50 (1 H, d, *J* 3.7, H-8), 5.01-4.85 (2 H, m, H-17), 3.89 (3 H, s, H-18), 3.52-3.37 (1 H, m, H-10b), 3.18-3.03 (2 H, m, H-9 and H-14a), 2.73-2.59 (2 H, m, H-14b, H-10a), 2.32-2.19 (1 H, m, H-11), 1.84-1.65 (3 H, m, H-13b, H-15b, H-12), 1.61-1.41 (2 H, m, H-13a, H-15a).

* The protic signal (H-19) is not visible in CDCl₃.

10.3.14 (S)-(6-Methoxy-2-phenylquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methanamine (332)

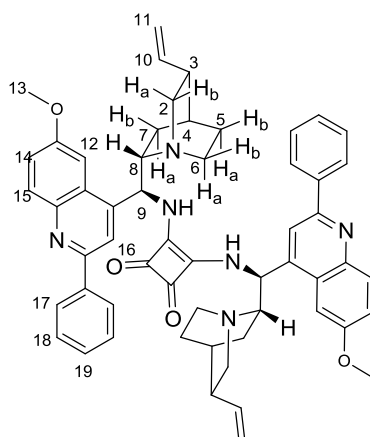


Diisopropyl azodicarboxylate (DIAD, 1.7 mL, 8.4 mmol) was added to a stirred solution of **331** (2.8 g, 7.0 mmol) and triphenylphosphine (2.2 g, 8.4 mmol) in anhydrous THF (50 mL) at 0 °C under argon atmosphere. After 30 min diphenylphosphoryl azide (DPPA, 1.8 mL, 8.4 mmol) was added dropwise and the reaction mixture was warmed to rt and stirred for 16 h followed by heating at 50 °C for 2 h. Triphenylphosphine (2.2 g, 8.4 mmol) was added portionwise and heating was maintained for 2 h. After cooling the reaction mixture to rt, water (10 mL) was added and the mixture stirred for 4 h. The mixture was concentrated *in vacuo* and the residue was dissolved in aqueous HCl (2N, 20 mL) and washed with CH₂Cl₂ (3 x 20 mL). The aqueous layer was treated with aqueous NaOH (2N) and extracted with CH₂Cl₂ (4 x 10 mL), the combined organic extracts were dried over anhydrous MgSO₄ and the solvent removed *in vacuo* to yield **332** as a yellow oil (2.1 g, 87%). [α]_D²⁰ = +28.6 (c 0.5, CHCl₃). Spectral data for this compound were consistent with those in the literature.²⁵²

δ_{H} (400 MHz, CDCl₃): 8.15 (2H, d, *J* 7.3, H-5), 8.11 (1H, d, *J* 9.2, H-4), 7.99 (1H, bs, H-1), 7.80-7.61 (1H, m, H-2), 7.52 (2H, m, H-6), 7.48-7.36 (2H, m, H-3, H-7), 5.79 (1 H, ddd, *J* 7.8, 10.1, 17.5, H-16), 5.05-4.91 (2H, m, H-17), 4.78-4.57 (1 H, m, H-8), 3.98 (3H, s, H-18), 3.36-3.05 (3H, m, H-9, H-10b, H-14a), 2.90-2.75 (2H, m, H-10a, H-14b), 2.35-2.23 (1H, m, H-11), 2.13-1.77 (2H, m, H-19), 1.67-1.51 (3H, m, H-12, H-13a, H-13b), 1.50-1.36 (1H, m, H-15b), 0.92-0.78 (1H, m, H-15a).

HRMS (*m/z* - ESI): Found: 400.2382 (M+H)⁺ C₂₆H₃₀N₃O Requires: 400.2389.

10.3.15 3,4-bis((1S)-(2-Phenyl-6-methoxyquinolin-4-yl)((2S)-8-vinylquinuclidin-2-yl)methylamino)-cyclobut-3-ene-1,2-dione (333)



332 (800 mg 2.0 mmol) and **313** (128 mg, 0.9 mmol) in MeOH (8.0 mL) under an atmosphere of argon and the mixture was stirred for 48 h. The resulting precipitate was collected *via* filtration to furnish **333** (601 mg, 75%) as a white solid. M.p. 240 °C (decomp.). $[\alpha]_D^{20} = +81.4$ (c 0.5, MeOH).

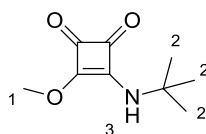
δ_H (400 MHz, DMSO- d_6): 8.27 (2H, d, J 7.5, H-17), 8.19 (1H, br s, H-16), 8.05 (1H, d, J 9.1, H-15), 7.84 (1H, br s, H-12), 7.57-7.47 (4H, m, H-19, H-18, H-14), 6.12 (1H, m, H-9), 5.88 (1H, m, H-10), 4.95-4.85 (2H, m, H-11), 3.97 (3H, s, H-13), 3.62 (1H, m, H-8), 3.27 (1H, m, H-2b), 3.01 (1H, m, H-6a), 2.54-2.48 (2H, m, H-6b, H-2a), 2.15 (1H, m, H-3), 1.47-1.43 (4H, H-7b, H-5a, H-5b, H-4), 0.53 (1H, m, H-7a).

δ_C (100 MHz, DMSO- d_6): 182.1 (q), 166.7 (q), 158.4 (q), 154.1 (q), 145.6 (q), 144.6 (q), 142.6, 139.1 (q), 132.3, 129.8, 129.3, 127.4, 126.9 (q), 122.9, 116.9, 114.6, 101.8, 58.9, 56.1, 55.8, 53.2, 39.2, 38.9, 27.4 (2C), 26.5.

ν_{max} (neat)/cm⁻¹: 2941, 1791, 1592, 1495, 1441, 1348, 1226, 1027, 828, 772, 693

HRMS (m/z -ESI) : Found: 877.4402 ($M + H$)⁺ C₅₆H₅₇N₆O₄ Requires: 877.4441

10.3.16 3-(*tert*-Butylamino)-4-methoxycyclobut-3-ene-1,2-dione (335)



313 (570 mg, 4.0 mmol) was dissolved in MeOH (15.0 mL) under an argon atmosphere and *t*-butylamine (423 μ L, 4.0 mmol) was added. The resultant mixture stirred at rt for 48 h followed by

purification *via* silica chromatography, eluting with 30% EtOAc in hexane to furnish **335** as a white solid (610 mg, 87%). M.p. 99-100 °C.

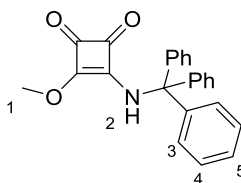
δ_{H} (400 MHz, CDCl_3): 6.09 (1 H, bs, H-3), 4.44 (3 H, s, H-1), 1.39 (9 H, s, H-2).

δ_{C} (100 MHz, CDCl_3): 190.1 (C=O), 183.5 (C=O), 176.2 (q), 170.8 (q), 60.3, 53.3 (q), 30.0.

ν_{max} (neat)/ cm^{-1} : 3276, 1802, 1693, 1621, 1526.

HRMS (m/z - ESI): Found: 206.0784 ($\text{M}+\text{Na}$) $^+$ $\text{C}_9\text{H}_{13}\text{NO}_3\text{Na}$ Requires: 206.0793.

10.3.17 3-Methoxy-4-(tritylamino)cyclobut-3-ene-1,2-dione (**336**)



313 (207 mg, 1.5 mmol) was dissolved in anhydrous THF (1.0 mL) under argon atmosphere and tritylamine (378 mg 1.5 mmol) was added. The mixture was stirred at rt for 96 h followed by cooling to 0 °C in an icebath. The resulting precipitate was filtered to furnish **336** as a white solid (128 mg, 22%).

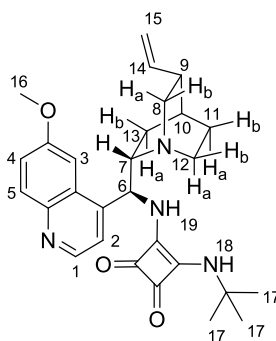
δ_{H} (400 MHz, CDCl_3): 7.37-7.30 (9 H, m, H-4, H-5), 7.14-7.06 (6 H, m, H-3), 6.78 (1 H, bs, H-2), 3.78 (3 H, bs, H-1).

δ_{C} (100 MHz, CDCl_3): 189.2 (q), 184.5 (C=O), 178.1 (C=O), 172.4 (q) 143.7 (q), 128.7, 128.3, 127.9, 73.0 (q), 59.8.

ν_{max} (neat)/ cm^{-1} : 3380, 3023, 2961, 1701, 1593.

HRMS (m/z - ESI): Found: 392.1267 ($\text{M}+\text{Na}$) $^+$ $\text{C}_{24}\text{H}_{19}\text{NO}_3\text{Na}$ Requires: 392.1263.

10.3.18 3-(*tert*-Butylamino)-4-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (**182**)



314 (1.3 g, 3.9 mmol) and **335** (650 mg, 3.6 mmol) were dissolved in MeOH (10.0 mL) under an atmosphere of argon and the resultant mixture was stirred at rt for 48 h. The crude mixture was purified *via* flash chromatography, eluting with 0-10% MeOH in EtOAc to furnish **182** as a white solid (1.6 g, 85%). M.p. 250 °C (decomp.) $[\alpha]_D^{20} = +233.0$ (c 0.20, CHCl₃).

δ_H (400 MHz, CDCl₃): * 8.70 (1H, d, *J* 4.0, H-1), 8.02 (1H, d, *J* 9.2, H-5), 7.78 (1H bs, H-3), 7.56 (1H, d, *J* 4.0, H-2), 7.40 (1H, d, *J* 9.2, H-4), 6.29-5.84 (1H, m, H-6), 5.82-5.65 (1H, m, H-14), 5.05-4.88 (2H, m, H-15), 3.96 (3H, s, H-16), 3.67-3.27 (2H, m, H-7, H-12a), 3.15 (1H, m, H-8b), 2.82-2.62 (2H, m, H-8a, H-12b), 2.36-2.19 (1H, m, H-9), 1.75-1.52 (3H, m, H-10, H-11a, H-11b), 1.51-1.38 (1H, m, H-13b), 1.17 (9H, s, H-17), 0.91-0.72 (1H, m, H-13a).

δ_C (100 MHz, CDCl₃):* 182.6 (C=O), 181.5 (C=O), 168.3 (q), 168.1 (q), 158.9 (q), 147.9, 145.0 (q), 144.1 (q), 141.1, 132.0, 128.0 (q), 122.5, 120.0, 115.1, 101.5, 60.8, 56.2, 56.0, 53.4 (q), 41.0, 39.5, 30.5, 27.7, 27.6, 26.0.

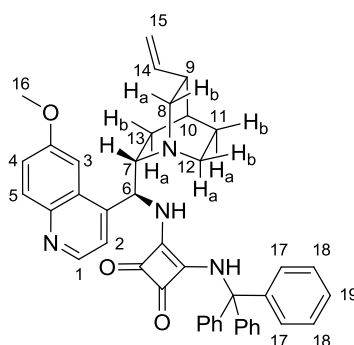
ν_{max} (neat)/cm⁻¹: 3307, 3224, 2974, 2943, 2861, 1792, 1654, 1562.

HRMS (*m/z* - ESI): Found: 475.2712 (M+H)⁺ C₂₈H₃₅N₄O₃ Requires: 475.2709.

* The protic signals (H-18 and H-19) are not visible in CDCl₃.

* The resonance of one carbon could not be identified in the spectrum.

10.3.19 3-(((S)-(6-Methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-4-(tritylamino)cyclobut-3-ene-1,2-dione (**337**)

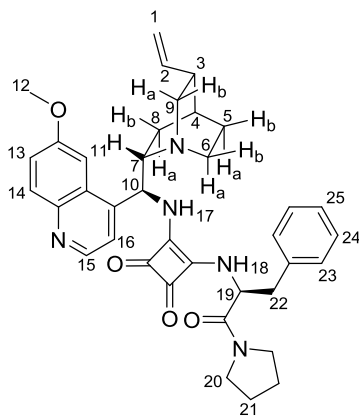


314 (150 mg, 0.5 mmol) and **336** (156 mg, 0.5 mmol) were dissolved in MeOH (5.0 mL) and the resultant mixture was stirred at rt for 48 h. The crude mixture was purified *via* flash chromatography, eluting with 0-10% MeOH in EtOAc to furnish **337** as a white solid white solid (200 mg, 75%). M.p. 160-162 °C; $[\alpha]_D^{20} = +41.8$ (c = 0.10, CHCl₃).

δ_{H} (400 MHz, CDCl_3):	8.62 (1H, d, J 4.5, H-1), 8.01 (1H, d, J 9.2, H-5), 7.57-7.49 (1H, bs, H-3), 7.39 (1H, dd, J 2.6, 9.2, H-4), 7.20-7.12 (9H, m, H-18, H-19), 7.03-6.98 (6H, m, H-17), 6.56 (1H, bs, H-2), 6.49 (1H, bs, N-H), 5.88-5.75 (2 H, m, H-6, H-14), 5.06-4.98 (2H, m, H-15), 3.91 (3H, s, H-16), 3.74 (1 H, bs, N-H), 3.31-3.17 (2H, m, H-8b, H-12a), 2.65-2.57 (3H, m, H-7, H-8a, H-12b), 2.28 (1H, m, H-9), 1.67-1.61 (1H, m, H-10), 1.56-1.42 (3H, m, H-11a, H-11b, H-13b), 0.68-0.63 (1H, m, H-13a).
δ_{C} (151 MHz, CDCl_3):*	183.5 (C=O), 183.0 (C=O), 167.0 (q), 158.5 (q), 146.8, 144.8 (q), 144.1 (q), 142.8 (q), 141.8, 131.4, 128.6, 128.5, 128.2, 122.7, 117.9, 114.4, 101.2, 72.1 (q), 60.1, 56.5, 56.1, 52.5, 40.8, 39.7, 27.7, 27.5, 26.5.
ν_{max} (neat)/ cm^{-1} :	3281, 3090, 3021, 2953, 1798, 1764, 1671, 1578.
HRMS (m/z - APCI):	Found: 661.3173 ($\text{M}+\text{H}$) $^+$ $\text{C}_{43}\text{H}_{41}\text{N}_4\text{O}_3$ Requires: 661.3143.

* The resonance of one carbon could not be identified in the spectrum

10.3.20 3-(((S)-(6-methoxyquinolin-4-yl)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-4-(((S)-1-oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)amino)cyclobut-3-ene-1,2-dione (349)



Phenylalanine (**344**, 1.0 g, 6.1 mmol), was dissolved in a mixture of 1,4 dioxane: H_2O (30.0 mL, 2:1) and a solution of NaOH (1N, aq., 6.0 mL) was added. The reaction mixture was cooled to 0 °C and Boc_2O (2.0 g, 9.1 mmol) and NaHCO_3 (539 mg, 6.1 mmol). The reaction mixture was warmed to rt and was stirred for 16 h. The resulting mixture was acidified to pH 2 using conc. HCl and the product was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over MgSO_4 and concentrated *in vacuo* to furnish **345** (1.6 g, 6.0 mmol, 99%) as a white solid. **345** (1.6 g, 6.0 mmol) was redissolved in anhydrous CH_2Cl_2 (12.0 mL) under argon and HBTU (2.5 g, 6.6 mmol), DIPEA

(1.2 mL, 6.6 mmol) and pyrrolidine (0.6 mL) were added. The reaction mixture was stirred for 16 h and a solution of HCl (1.5N, aq., 15 mL) was added and the organic layer was separated and washed with sat. NaHCO₃ (aq.), dried over MgSO₄ and was concentrated *in vacuo* to furnish **346** (1.5 g, 4.7 mmol, 68%). **346** (1.5 g, 4.7 mmol) was re-dissolved in anhydrous CH₂Cl₂ (10.0 mL) under an atmosphere of argon and TFA (10.0 mL) was added *via* syringe. The resulting solution was stirred for 16 h and was concentrated *in vacuo* to afford **347** (990 mg, 4.5 mmol, 97%). Amine **347** (990 mg, 4.5 mmol) and squaric ester **313** (638 mg, 4.5 mmol) were dissolved in MeOH (6.0 mL) under an atmosphere of argon at rt and were stirred for 48 h. The resulting mixture was purified *via* silica chromatography, eluting with 30% EtOAc in hexane to furnish **357** (1.0 mg, 3.1 mmol, 69%) which was redissolved in MeOH (6.0 mL) under argon. To this **314** (1.0 g, 3.1 mmol) was added and the reaction was stirred at rt for 48 h. The resulting mixture was purified *via* silica chromatography, eluting with a gradient of 0-5% MeOH in CH₂Cl₂ to furnish **349** (1.1 g, 56%) as a white solid. M.p. 165–167 °C. $[\alpha]_D^{20} = -89.7$ (*c* 0.15 CHCl₃).

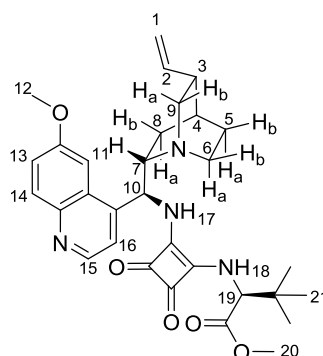
δ_H (400 MHz, DMSO-D₆): 8.80 (1H, d, *J* 4.5, H-15), 8.09 (1H, bs, NH), 7.97 (1H, d, *J* 9.1, H-14), 7.76 (2H, m, H-11, NH), 7.57 (1H, d, *J* 4.5, H-16), 7.44 (1H, dd, *J* 2.4, 9.1, H-13), 7.32-7.14 (5H, m, H-23, H-24, H-25), 6.01-5.87 (2H, m, H-2, H-10), 5.09-5.95 (3H, m, H-1, H-19), 3.93 (3H, s, H-12), 3.47-3.11 (6H, m, H-5b, H-7, H-6b, H-8b, H-9a, H-9b), 3.02-2.94 (2H, m, H-22a, H-22b), 2.76-2.57 (3H, m, H-5a, H-6a, H-8a), 2.33-2.24 (1H, m, H-3), 1.74-1.40 (9H, m, H-4, H-20, H-21).

δ_C (151 MHz, DMSO-D₆): 183.0 (C=O), 182.2 (C=O), 168.8 (C=O), 167.1 (q), 166.9 (q), 158.3 (q), 148.2, 144.8 (q), 144.2 (q), 142.7, 136.6 (q), 132.0, 129.8, 128.7, 127.8 (q), 127.3, 122.3, 120.2, 114.7, 102.1, 79.6, 59.2, 56.2, 56.2, 46.1, 45.9, 40.8, 40.5, 40.2, 39.6, 27.8, 26.7, 25.7, 24.0.

ν_{max} (neat)/cm⁻¹: 3235, 2923, 1795, 1672, 1621.

HRMS (*m/z* - ESI): Found: 620.3240 (M+H)⁺ C₃₇H₄₂N₅O₄ Requires: 620.3240.

10.3.21 Methyl-(S)-2-((2-(((S)-6-methoxyquinolin-4-yl)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethylbutanoate (354)



Boc-*t*-Leu (**350**, 679 mg, 2.9 mmol) was dissolved in anhydrous DMF (3.0 mL) under argon and NaHCO₃ (587 mg, 5.9 mmol) was added. After 30 mins, MeI (0.3 mL, 4.7 mmol) was added and the reaction mixture was stirred for 16 h. Brine (10.0 mL) was added and the product was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed sat. Na₂SO₃ (aq., 1 x 15 mL), brine (1 x 15 mL) and the organic extract was dried over MgSO₄ and concentrated *in vacuo* to afford **351** (610 mg, 2.5 mmol, 85%). **351** (610 mg, 2.5 mmol) was redissolved in anhydrous CH₂Cl₂ (5.0 mL) under an atmosphere of argon and TFA (5.0 mL) was added *via* syringe. The resulting solution was stirred for 16 h and was concentrated *in vacuo* to afford **352** (358 mg, 2.5 mmol, 99%). Amine **352** (358 mg, 2.5 mmol) and squaric ester **313** (350 mg, 2.5 mmol) were dissolved in MeOH (5.0 mL) under an atmosphere of argon at rt and were stirred for 48 h. The resulting mixture was purified *via* silica chromatography, eluting with 30% EtOAc in hexane to furnish **353** (443 mg, 1.8 mmol, 75%) which was redissolved in MeOH (6.0 mL) under argon. To this **314** (633 mg, 1.9 mmol) was added and the reaction was stirred at rt for 48 h. The resulting mixture was purified *via* silica chromatography, eluting with a gradient of 0-5% MeOH in CH₂Cl₂ to furnish **354** (805 mg, 56%) as a white solid. M.p. 200 °C (decomp.). [α]_D²⁰ = -134.8 (c 0.05, CHCl₃).

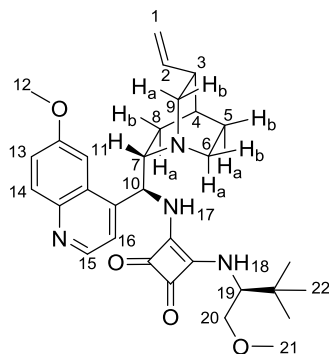
δ_H (400 MHz, CDCl₃): 8.84 (1H, d, *J* 4.3, H-15), 8.09 (1H, d, *J* 9.2, H-14), 7.65-7.58 (1H, m, H-11), 7.58-7.51 (1H, m, H-16), 7.46 (1H, dd, *J* 2.5, 9.2, H-13), 5.78-5.63 (1H, m, H-2), 5.08-4.92 (2H, m, H-1), 4.73-4.63 (1H, m, H-10), 4.22-3.80 (4H, m, H-12, H-19), 3.67 (3H, s, H-20), 3.47-2.96 (3H, H-6a, H-7, H-9a), 2.95-2.68 (2H, m, H-6b, H-9b), 2.47-2.29 (1H, m, H-3), 1.85-1.57 (3H, m, H-4, H-5b, H-8b), 1.54-1.33 (1H, m, H-8a), 1.13-0.96 (1H, m, H-5a), 0.78-0.13 (9H, bs, H-21).

δ_C (151 MHz, CDCl₃): 184.2 (C=O), 182.6 (C=O), 171.6 (C=O), 171.2 (q), 167.6 (q), 166.5, 159.2, 147.8, 145.1 (q), 143.9 (q), 140.5, 127.7 (q), 127.3, 122.9, 119.7 (q), 115.2, 63.7, 55.9, 55.6, 51.9, 40.8, 39.1, 35.0, 30.2, 29.7, 27.6, 27.2, 25.6.

$\nu_{\max}$ (neat)/cm⁻¹: 3347, 3099, 1737, 1676, 1602.

HRMS (*m/z* - ESI): Found: 547.2931 (*M*+H)⁺ C₃₁H₃₉N₄O₅ Requires: 547.2915.

10.3.22 3-(((*S*)-1-Methoxy-3,3-dimethylbutan-2-yl)amino)-4-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (359)



Boc-*t*-leu (**350**, 1.5 g, 6.5 mmol) and NEt₃ (0.9 mL, 6.5 mmol) were dissolved in THF (30.0 mL) and the solution was cooled to -10 °C. Ethyl chloroformate (0.6 mL, 6.5 mmol) was added and stirred for 10 mins. NaBH₄ (735 mg, 19.4 mmol) was added, followed by the slow addition of MeOH (60.0 mL) over 10 mins. The reaction was stirred for a further 10 mins and HCl (1N, aq. 15.0 mL) was added. The product was extracted with EtOAc (x2) and the combined organic layers were washed with a solution of NaHCO₃ (5%, aq.) followed by H₂O, dried over MgSO₄ and concentrated *in vacuo* to furnish the reduced product **355** (1.3 g, 5.7 mmol, 88%). **355** (1.3 g, 5.7 mmol) was dissolved in anhydrous DMF (8.0 mL) under argon and was cooled to 0 °C. NaH (60 % dispersion in mineral oil, 205 mg, 5.7 mmol) was added and the mixture was stirred at 0 °C for 5 mins. MeI (1.4 mL, 28.4 mmol) was added and the reaction mixture was warmed to rt and stirred for 16 h. H₂O (20.0 mL) was added and the product was extracted with EtOAc (x2). The combined organic layers were dried over MgSO₄ and were concentrated *in vacuo* to afford **356** (1.1 g, 4.5 mmol, 80%). **356** (1.1 g, 4.5 mmol) was dissolved in anhydrous CH₂Cl₂ (10.0 mL) under argon and TFA (10.0 mL) was added. The mixture was stirred for 16 h and was concentrated *in vacuo* to furnish the free amine **357** (589 mg, 4.5 mmol, 99%). Amine **357** (589 mg, 4.5 mmol) and squaric ester **313** (638 mg, 4.5 mmol) were dissolved in MeOH (6.0 mL) under an atmosphere of argon at rt and were stirred for 48 h. The resulting mixture was purified *via* silica chromatography, eluting with 30% EtOAc in hexane to furnish **358** (227 mg, 0.9 mmol, 21%) which was redissolved in MeOH (6.0 mL) under argon. To this **314** (365 mg, 1.3 mmol) was added and the reaction was stirred at rt for 48 h. The resulting mixture was purified *via* silica chromatography, eluting with 0-3% MeOH in CH₂Cl₂ to furnish **359** (305 mg, 61%) as a white solid. M.p. 180 °C (decomp.). [α]_D²⁰ = -91.7 (*c* 0.14, CHCl₃).

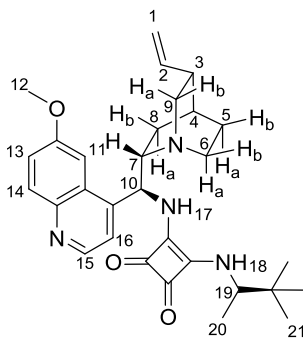
δ_{H} (400 MHz, CDCl_3): 8.81 (1H, d, J 4.5, H-15), 8.07 (1H, d, J 9.2, H-14), 7.78-7.61 (2H, m, H-11, H-16), 7.45 (1H, dd, J 2.6, 9.2, H-13), 5.86-5.67 (1H, m, H-2), 5.28-5.04 (2H, m, H-1), 4.54-2.69 (15H, m, H-6a, H-6b, H-7, H-9a, H-9b), H-10, H-12, H-19, H-20, H-21), 2.69-2.50 (1H, m, H-3), 2.01-1.82 (2H, m, H-5b, H-8b), 1.78-1.56 (1H, m, H-4), 1.32-1.23 (1H, m, H-8b), 1.12-1.00 (1H, m, H-5b), 0.80 (9H, bs, H-22).

δ_{C} (151 MHz, CDCl_3): 183.5 (C=O), 169.0 (q), 158.8, 152.2 (q), 147.7, 145.1 (q), 143.9 (q), 140.5, 140.2 (q), 132.3, 127.6 (q), 122.6, 115.2, 100.6, 72.0, 61.6, 58.6, 56.0, 55.67, 53.1, 46.0, 40.9, 39.1, 33.8, 27.4, 27.3, 26.3, 25.5 (q).

ν_{max} (neat)/ cm^{-1} : 3245, 2940, 1668, 1621, 1585.

HRMS (m/z - ESI): Found: 533.3108 ($\text{M}+\text{H}^+$) $\text{C}_{31}\text{H}_{41}\text{N}_4\text{O}_4$ Requires: 533.3122.

10.3.23 methyl-(2S)-2-((2-(((1S)-(6-methoxyquinolin-4-yl)((2R)-5-vinylquinuclidin-2-yl)methyl)amino)-3,4-dioxocyclobut-1-en-1-yl)amino)-3,3-dimethylbutanoate (362)



Amine **360** (0.3 mL, 1.9 mmol) and squaric ester **313** (295 mg, 2.1 mmol) were dissolved in MeOH (4.0 mL) under an atmosphere of argon at rt and were stirred for 48 h. The resulting mixture was purified *via* silica chromatography, eluting with 30% EtOAc in hexane to furnish **361** (327 mg, 1.6 mmol, 82%) which was redissolved in MeOH under argon. To this **314** (552 mg, 1.7 mmol) was added and the reaction was stirred at rt for 48 h. The resulting mixture was purified *via* silica chromatography, eluting with a gradient of 0-5% MeOH in CH_2Cl_2 to furnish **362** (382 mg, 49%) as a white solid. M.p. 180 °C (decomp.). $[\alpha]_{\text{D}}^{20} = -94.1$ (c 0.12, CHCl_3).

δ_{H} (400 MHz, MeOD): 8.75 (1H, d, J 4.7, H-15), 8.00 (1H, d, J 9.3, H-14), 7.91-7.88 (1H, bs, H-11), 7.58 (1H, d, J 4.7, H-16), 7.48 (1H, dd, J 2.6, 9.3, H-13) 6.29-6.20 (1H, m, H-10), 6.00-5.93 (1H, m, H-2), 5.15-5.05 (2H, m, H-1), 4.05-3.98 (4H, m, H-12, H-19), 3.67-3.47 (2H, m, H-6a, H-7), 3.40-3.30 (1H, m, H-9b), 2.90-2.76 (2H, m, H-6b, H-9a), 2.50-2.39 (1H,

m, H-3), 1.76-1.63 (4H, m, H-4, H-5b, H-8a, H-8b), 1.22 (3H, d, *J* 6.8, H-20), 0.88 (9H, s, H-21), 0.78-0.68 (1H, m, H-5a).

δ_c (151 MHz, MeOD): 181.8 (C=O), 181.7 (C=O), 167.9 (q), 166.6 (q), 159.1(q), 147.0, 144.5 (q), 144.1, 130.2, 128.2 (q), 123.1, 118.6, 113.8, 100.7, 78.1, 77.9, 77.7, 59.7, 58.7, 55.8, 55.4, 40.3, 39.3, 34.1 (q), 27.5, 27.0, 26.2, 24.7, 15.8.

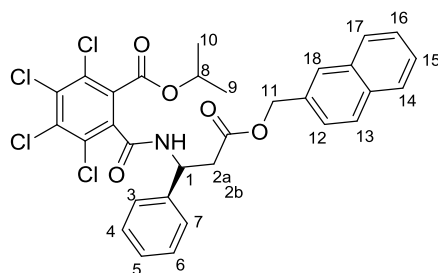
$\nu_{\max}$ (neat)/cm⁻¹: 3536, 3258, 2985, 1646, 1566, 1528, 1428, 1268.

HRMS (*m/z* - ESI): Found: 503.3021 (M+H)⁺ C₃₀H₃₉N₄O₃ Requires: 503.3017.

10.3.24 General procedure G: Racemic ring opening alcoholysis of **144** using DIPEA

Oxazinone of general structure **144** (1 equiv.) and the appropriate alcohol (1.2 equiv.) were placed in an RBF equipped with a stirrer bar and nitrogen balloon. Anhydrous CHCl₃ (0.2 M) was added followed by DIPEA (0.2 equiv.) and the resulting mixture was stirred at rt for 48 h. The mixture was purified by silica chromatography, eluting with 20% EtOAc in hexane to yield the required product.

10.3.24.1 *iso*-Propyl-2,3,4,5-tetrachloro-6-((3-(naphthalen-2-ylmethoxy)-3-oxo-1-phenylpropyl)carbamoyl)benzoate (**325**)



144a (50.0 mg, 0.11 mmol), **362** (5.3 mg, 0.06 mmol) and 2-naphthylmethanol (8.3 mg, 0.06 mmol) were cooled to -30 °C and anhydrous CHCl₃ (0.1M) was added. The reaction was stirred at -30 °C for 16 h followed the addition of MeOH (15.0 μ l, 0.30 mmol). The mixture was warmed to rt and was stirred for a further 3 h. The resulting mixture was purified *via* silica chromatography, eluting with 20% EtOAc in hexane to furnish **325** (31.9 mg, 48%) as a colourless oil. $[\alpha]_D^{20} = 14.5$ (c 0.17, CHCl₃).

CSP-HPLC conditions: Chiralpak IA column (4.6 mm x 250mmL), hexane/IPA: 90/10, 1 mL min⁻¹, rt, UV detection at 220 nm, retention times 19.20 min and 23.83 min.

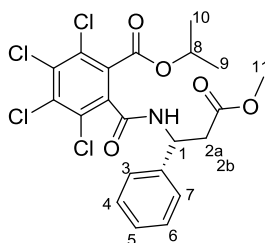
δ_H (400 MHz, CDCl₃): 7.87-7.27(12H, m, H-3, H-4, H-5, H-6, H-7, H-12, H-13, H-14, H-15, H-16, H-17, H-18), 7.04 (1H, d, *J* 8.5, NH), 5.66-5.61 (1H, m, H-1), 5.24 (2H, m, H-11), 5.13 (1H, sept., *J* 6.3, H-8), 3.20-3.02 (2H, m, H-2a, H-2b), 1.26-1.22 (6H, m, H-9, H-10).

δ_C (100 MHz, $CDCl_3$): 170.7 (C=O), 163.4 (C=O), 162.4 (C=O), 139.1 (q), 135.0 (q), 134.9 (q), 134.2 (q), 133.1 (q), 133.0 (q), 132.9 (q), 132.6 (q), 130.1 (q), 129.7 (q), 128.7, 128.3, 127.9, 127.9, 127.6, 127.5, 126.4, 126.4, 126.3, 125.7, 71.3, 66.9, 50.3, 39.4, 21.3, 21.3.

ν_{max} (neat)/ cm^{-1} : 3331, 1727, 1654, 1509.

HRMS (m/z - ESI): Found: 654.0385 ($M+Na$)⁺ $C_{31}H_{25}Cl_4NO_5Na$ Requires: 654.0487.

10.3.24.2 iso-Propyl-2,3,5-tetrachloro-6-((3-methoxy-3-oxo-1-phenylpropyl)carbamoyl)benzoate (308)



144a (50.0 mg, 0.11 mmol), **362** (5.3 mg, 0.06 mmol) and 2-naphthylmethanol (8.3 mg, 0.06 mmol) were cooled to -30 °C and anhydrous $CHCl_3$ (0.1M) was added. The reaction was stirred at -30 °C for 16 h followed the addition of MeOH (15.0 μ l, 0.30 mmol). The mixture was warmed to rt and was stirred for a further 3 h. The resulting mixture was purified *via* silica chromatography, eluting with 20% EtOAc in hexane to furnish **308** (26.1 mg, 49%) as a colourless oil. $[\alpha]_D^{20} = -9.7$ (c 0.35, $CHCl_3$).

CSP-HPLC conditions: Chiralpak IA column (4.6 mm x 250mmL), hexane/IPA: 90/10, 1 mL min^{-1} , rt, UV detection at 220 nm, retention times 9.98 min and 11.53 min.

δ_H (400 MHz, $CDCl_3$): 7.34-7.26 (5H, m, H-3, H-4, H-5, H-6, H-7), 6.98 (1H, d, J 8.4, NH), 5.58-5.53 (1H, m, H-1), 5.08 (1H, sept., J 6.1, H-8), 3.61 (1H, s, H-11), 3.06-2.90 (2H, m, H-2a, H-2b), 1.23-1.19 (6H, m, H-9, H-10).

δ_C (100 MHz, $CDCl_3$): 171.4 (C=O), 163.5 (C=O), 162.4 (C=O), 139.4 (q), 135.1 (q), 135.0 (q), 134.3 (q), 132.9 (q), 130.1 (q), 129.8 (q), 128.8, 127.9, 126.5, 71.3, 52.0, 50.3, 39.2, 21.4, 21.4.

ν_{max} (neat)/ cm^{-1} : 3290, 1750, 1731, 1644.

HRMS (m/z - ESI): Found: 527.9923 ($M+Na$)⁺ $C_{21}H_{19}Cl_4NO_5Na$ Requires: 527.9915.

10.3.25 General procedure I: Synthesis of the amino acid naphthalen-2-ylmethyl ester racemates

The appropriate oxazinone (1.0 equiv.) and 2-naphthylmethanol (1.2 equiv.) were dissolved in anhydrous CHCl_3 under argon at rt. TBAF (1M in THF, 0.2 equiv.) was added and the reaction was stirred for 48 h. The resulting mixture was purified *via* silica chromatography, eluting with 10% EtOAc in hexane to furnish the racemic product

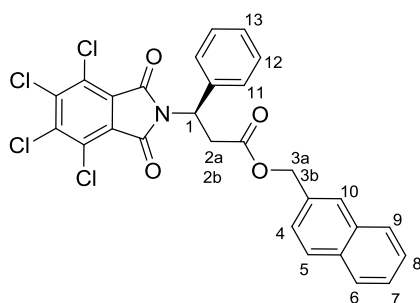
10.3.26 General procedure J: Synthesis of the amino acid allyl ester racemates

The appropriate oxazinone (1.0 equiv.) was dissolved in anhydrous CHCl_3 under argon at rt and allyl alcohol (1.2 equiv.) was added *via* syringe. To this TBAF (1M in THF, 0.2 equiv.) was added and the reaction was stirred for 48 h. The resulting mixture was purified *via* silica chromatography, eluting with 15% EtOAc in hexane to furnish the racemic product.

10.3.27 General procedure K: Optimised protocol for the KR of oxazinones

The appropriate oxazinone (1.0 equiv.), 2-naphthylmethanol (0.5 equiv.) and catalyst **362** (0.1 equiv.) were cooled to the required temperature under argon and anhydrous CHCl_3 (0.1 M) was added. The reaction was stirred until full consumption of 2-naphthylmethanol was observed (using ^1H NMR spectroscopy). Allyl alcohol (5.0 equiv.) was added and the mixture was stirred at rt for 3 h. The reaction mixture was concentrated *in vacuo* and redissolved in anhydrous CHCl_3 . Freshly distilled NEt_3 (1.0 equiv.) was added and the mixture was heated to 55 °C for 24 h. The resulting mixture was purified *via* chromatography, eluting with a gradient of 3-15% EtOAc in hexane to furnish the naphthalen-2-ylmethyl ester and allyl ester products.

10.3.28 Naphthalen-2-ylmethyl-3-(R)-phenyl-3-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)propanoate (**371a**)



Prepared according to **General Procedure K** using **144a** (50.00 mg, 0.11 mmol), 2-naphthylmethanol (8.30 mg, 0.05 mmol), **362** (7.91 mg, 0.01 mmol), CHCl_3 (1.0 mL) at -50 °C. After 60 h allyl alcohol (35.0 μL , 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 μL , 0.11 mmol) in CHCl_3 (0.50 mL). The crude material was purified as instructed to furnish **371a** (29.0 mg, 46%) as a white solid. M.p. 135-138 °C. $[\alpha]_{\text{D}}^{20} = -27.3$ (c 0.11, CHCl_3).

HPLC analysis. ACQUITY UPC² Trefoil CELI, 2.5 μm (3.0 x 150 mm). ABPR 1500 (psi). A = CO₂ / B = EtOH:MeCN (1:1, v:v) gradient as shown in **Table 10.1**, column temperature : 30 °C, UV detection at 254 nm, retention times: 5.47 min and 6.03 min.

δ_{H} (400 MHz, CHCl₃): 7.71-7.23 (12H, m, H-4, H-5, H-6, H-7, H-8, H-9, H-10, H-11, H-12, H-13), 5.77 (1H, dd, *J* 4.5, 12.1, H-1), 5.26 (1H, d, *J* 11.7, H-3a), 5.20 (1H, d, *J* 11.7, H-3b), 4.04 (1H, dd, *J* 12.3, 15.9, H-2a), 3.08 (1H, dd, *J* 4.5, 15.9, H-2b).

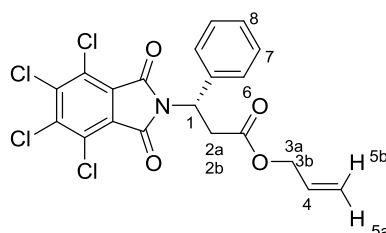
δ_{C} (100 MHz, CHCl₃): 169.9 (C=O), 163.0 (C=O), 139.6 (q), 137.5 (q), 132.8 (q), 132.7 (q), 132.6 (q), 129.2 (q), 128.9, 128.6, 128.2, 128.1, 127.7, 127.7, 127.4, 126.7, 126.6 (q), 126.5, 126.3, 66.7, 52.0, 35.8.

ν_{max} (neat)/cm⁻¹: 1776, 1738, 1716.

HRMS (*m/z* – DIP-APCI):* Found: 570.9782 (M+H)⁺ C₂₈H₁₃BrCl₄NO₄ Requires: 570.9906.

***Note:** Error for HRMS is 21.7 ppm

10.3.29 Allyl 3-(*S*)-phenyl-3-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)propanoate (**373a**)



Prepared according to **General Procedure K** using **144a** (50.00 mg, 0.11 mmol), 2-naphthylmethanol (8.30 mg, 0.05 mmol), **362** (7.91 mg, 0.01 mmol), CHCl₃ (1.0 mL) at -50 °C. After 60 h allyl alcohol (35.0 μL , 0.52 mmol) was added as instructed. This was followed by treatment with NEt₃ (14.6 μL , 0.11 mmol) in CHCl₃ (0.5 mL). The crude material was purified as instructed to furnish **373a** (27.0 mg, 51%) as a white solid. M.p. 60-63 °C. [α]_D²⁰ = -10.5 (*c* 0.19, CHCl₃).

CSP-HPLC conditions: Chiralpak IA column (4.6 mm x 250mmL), hexane/IPA: 90/10, 1 mL min⁻¹, rt, UV detection at 220 nm, retention times 18.70 min and 20.97 min.

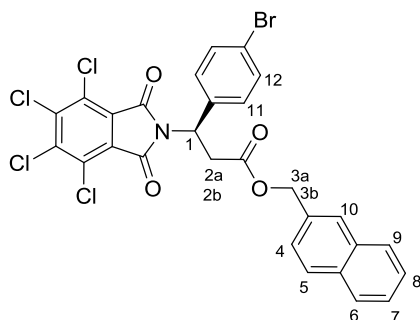
δ_{H} (400 MHz, CHCl₃): 7.54-7.28 (5H, m, H-6, H-7, H-8), 5.88-5.76 (2H, m, H-1, H-4), 5.28-5.14 (2H, m, H-5a, H-5b), 4.56-4.50 (2H, m, H-3a, H-3b), 3.87 (1H, dd, *J* 10.7, 16.8, H-2a), 3.21 (1H, dd, *J* 5.1, 16.8, H-2b).

δ_{C} (100 MHz, CHCl₃): 170.1 (C=O), 163.3 (C=O), 140.2 (q), 137.5 (q), 131.6, 129.8 (q), 128.9, 128.6, 127.9, 127.3 (q), 118.7, 65.6, 51.6, 35.1.

$\nu_{\max}$ (neat)/cm⁻¹: 1776, 1738, 1711.

HRMS (*m/z* - APCI): Found: 471.9678 (M+H)⁺ C₂₀H₁₄Cl₄NO₄ Requires: 471.9671.

10.3.30 Naphthalen-2-ylmethyl 3-(R)-(4-bromophenyl)-3-(4,5,6,7-tetrachloro-1,3-dioxisoindolin-2-yl)propanoate (371b)



Prepared according to **General Procedure K** using **144b** (58.20 mg, 0.11 mmol), 2-naphthylmethanol (8.30 mg, 0.05 mmol), **362** (7.91 mg, 0.01 mmol), CHCl₃ (1.00 mL) at -50 °C. After 63 h allyl alcohol (35.00 μ l, 0.52 mmol) was added as instructed. This was followed by treatment with NEt₃ (14.60 μ l, 0.11 mmol) in CHCl₃ (0.50 mL). The crude material was purified as instructed to furnish **371b** (33.70 mg, 47%) as a white solid. M.p. 168-170 °C. [α]_D²⁰ = 19.4 (*c* 0.16, CHCl₃).

HPLC analysis. ACQUITY UPC² Trefoil CELI, 2.5 μ m (3.0 x 150 mm). ABPR 1500 (psi). A = CO₂ / B = EtOH:MeCN (1:1, v:v) gradient as shown in **Table 10.1**, column temperature : 30 °C, UV detection at 254 nm, retention times: 5.11 min and 5.32 min.

δ_{H} (400 MHz, CHCl₃): 7.72-7.28 (11H, m, H-4, H-5, H-6, H-7, H-8, H-9, H-10, H-11, H-12), 5.71 (1H, dd, *J* 4.9, 11.8, H-1), 5.25 (1H, d, *J* 11.7, H-3a), 5.19 (1H, d, *J* 11.7, H-3b), 3.95 (1H, dd, *J* 4.0, 15.9, H-2a), 3.07 (1H, dd, *J* 4.9, 15.9, H-2b).

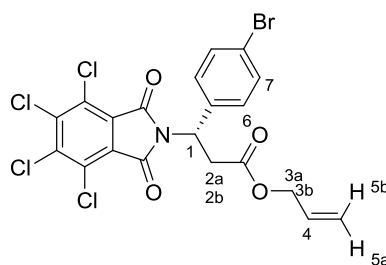
δ_{C} (100 MHz, CHCl₃): 169.6 (C=O), 162.9 (C=O), 139.8 (q), 136.4 (q), 132.7 (q), 132.6 (q), 132.6 (q), 132.1, 129.5, 129.3 (q), 128.2, 128.1, 127.7, 127.4, 126.7, 126.5 (q), 126.5, 126.3, 122.7 (q), 66.8, 51.3, 35.7.

$\nu_{\max}$ (neat)/cm⁻¹: 1744, 1741, 1713.

HRMS (*m/z* - DIP): * Found: 648.8817 (M+H)⁺ C₂₈H₁₆BrCl₄NO₄ Requires: 648.9011.

***Note:** Error for HRMS is -30.0 ppm

10.3.31 Allyl 3-(4-bromophenyl)-3-(S)-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)propanoate (373b)



Prepared according to **General Procedure K** using **373b** (58.20 mg, 0.11 mmol), 2-naphthylmethanol (8.30 mg, 0.05 mmol), **362** (7.91 mg, 0.01 mmol), CHCl_3 (1.00 mL) at $-50\text{ }^\circ\text{C}$. After 63 h allyl alcohol (35.00 μL , 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 μL , 0.11 mmol) in CHCl_3 (0.50 mL). The crude material was purified as instructed to furnish **373b** (30.40 mg, 50%) as a white solid. M.p. $106\text{--}108\text{ }^\circ\text{C}$. $[\alpha]_{\text{D}}^{20} = -8.7$ (c 0.16, CHCl_3).

HPLC analysis. ACQUITY UPC² Trefoil CELI, 2.5 μm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = EtOH:IPA (1:1, v:v) gradient as shown in **Table 10.2**, column temperature : $30\text{ }^\circ\text{C}$, UV detection at 254 nm, retention times: 6.71 min and 8.05 min.

δ_{H} (400 MHz, CHCl_3): 7.55–7.45 (2H, m, H-7) 7.42–7.37 (2H, m, H-6), 5.88–5.71 (2H, m, H-1, H-4), 5.31–5.13 (2H, m, H-5a, H-5b), 4.55–4.51 (2H, m, H-3a, H-3b), 3.77 (1H, dd, J 10.4, 16.8, H-2a), 3.21 (1H, dd, J 5.6, 16.8, H-2b).

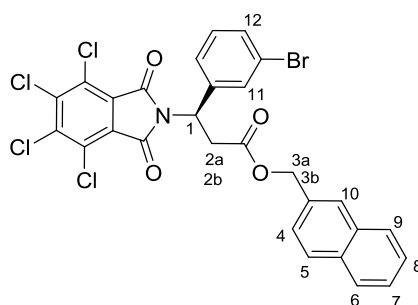
δ_{C} (100 MHz, CHCl_3): 169.7 (C=O), 163.2 (C=O), 140.4 (q), 136.3 (q), 132.0, 131.5 (q), 129.9 (q), 129.7, 129.5 (q), 127.2, 122.8 (q), 118.8, 65.7, 50.9, 35.0.

ν_{max} (neat)/ cm^{-1} : 1777, 1734, 1708.

HRMS (m/z - DIP): Found: 549.8661 ($\text{M}-\text{C}_2\text{H}_3$)⁺ $\text{C}_{20}\text{H}_{13}\text{BrCl}_4\text{NO}_4$ Requires: 549.8777.

***Note:** Error for HRMS is -21.0 ppm

10.3.32 Naphthalen-2-ylmethyl-3-(R)-(3-bromophenyl)-3-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)propanoate (371c)



Prepared according to **General Procedure K** using **144c** (58.20 mg, 0.11 mmol), 2-naphthylmethanol (8.30 mg, 0.05 mmol), **362** (7.91 mg, 0.01 mmol), CHCl₃ (1.00 mL) at -50 °C. After 60 h and allyl alcohol (35.00 µl, 0.52 mmol) was added as instructed. This was followed by treatment with NEt₃ (14.60 µl, 0.11 mmol) in CHCl₃ (0.50 mL). The crude material was purified as instructed to furnish **371c** as a white solid (33.70 mg, 47%). M.p. 230 °C (decomp.). [α]_D²⁰ = 17.7 (*c* 0.13, CHCl₃).

HPLC analysis. ACQUITY UPC² Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO₂ / B = EtOH:MeCN (1:1, v:v) gradient as shown in **Table 10.1**, column temperature : 30 °C, UV detection at 230 nm, retention times: 5.14 min and 5.58 min.

δ_H (400 MHz, CHCl₃): 7.75-7.16 (11H, m, H-4, H-5, H-6, H-7, H-8, H-9, H-10, H-11, H-12), 5.73 (1H, dd, *J* 4.7, 11.9, H-1), 5.30 (1H, d, *J* 11.7, H-3a) 5.22 (1H, d, *J* 11.7, H-3b), 4.00 (1H, dd, *J* 11.9, 16.0, H-2a), 3.10 (1H, dd, *J* 4.7, 16.0, H-2b).

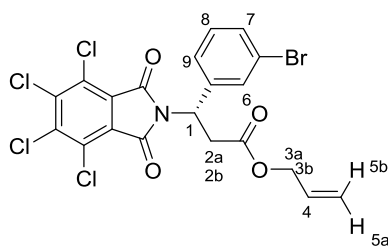
δ_C (100 MHz, CHCl₃): 169.6 (C=O), 162.9 (C=O), 139.8 (q), 139.5 (q), 132.7 (q), 132.7 (q), 132.6 (q), 131.8, 130.8, 130.5, 129.3 (q), 128.2, 128.1, 127.7, 127.4, 126.7, 126.5 (q), 126.5, 126.3, 126.3, 122.9, 66.8, 51.3, 35.6.

ν_{max} (neat)/cm⁻¹: 1774, 1734, 1713.

HRMS (*m/z* - DIP):* Found: 648.8773 (M+H)⁺ C₂₈H₁₆BrCl₄NO₄ Requires: 648.9011.

***Note:** Error for HRMS is -36.7 ppm.

10.3.33 Allyl 3-(3-bromophenyl)-3-(S)-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)propanoate (**373c**)



Prepared according to **General Procedure K** using **144c** (58.20 mg, 0.11 mmol), 2-naphthylmethanol (8.30 mg, 0.05 mmol), **362** (7.91 mg, 0.01 mmol), CHCl₃ (1.00 mL) at -50 °C. After 60 h and allyl alcohol (35.00 µl, 0.52 mmol) was added as instructed. This was followed by treatment with NEt₃ (14.60 µl, 0.11 mmol) in CHCl₃ (0.50 mL). The crude material was purified as instructed to furnish **373c** (29.10 mg, 28%) as a white solid. M.p. 70-72 °C. [α]_D²⁰ = -17.5 (*c* 0.12, CHCl₃).

HPLC analysis. ACQUITY UPC² Trefoil CELI, 2.5 μ m (3.0 x 150 mm). ABPR 1500 (psi). A = CO₂ / B = MeOH:IPA (1:1, v:v) gradient as shown in **Table 10.3**, column temperature : 30 °C, UV detection at 254 nm, retention times: 5.03 min and 6.53 min.

δ_H (400 MHz, CHCl₃): 6.69-7.64 (1H, m, H-6) 7.51-7.44 (2H, m, H-7, H-9), 7.28-7.22 (1H, m, H-8), 5.92-5.74 (2H, m, H-1, H-4), 5.28-5.18 (2H, m, H-5a, H-5b), 4.56-4.51 (2H, m, H-3a, H-3b), 3.86 (1H, dd, *J* 10.7, 16.8, H-2a), 3.21 (1H, dd, *J* 5.2, 16.8, H-2b).

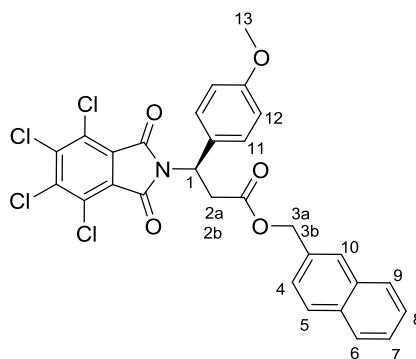
δ_C (100 MHz, CHCl₃): 169.7 (C=O), 163.1 (C=O), 140.3 (q), 139.5 (q), 131.8, 131.5(q), 131.0 (q), 130.5, 129.9 (q), 127.2, 126.5, 118.8, 65.7, 50.6, 35.0.

$\nu_{\max}$ (neat)/cm⁻¹: 1776, 1735, 1715.

HRMS (*m/z* – DIP-APCI):* Found: 549.8652 (M-C₂H₃)⁺ C₂₀H₁₃BrCl₄NO₄ Requires: 549.8777.

***Note:** Error for HRMS is 27.6 ppm.

10.3.34 Naphthalen-2-ylmethyl-3-(*R*)-(4-methoxyphenyl)-3-(4,5,6,7-tetrachloro-1,3-dioxisoindolin-2-yl)propanoate (**371d**)



Prepared according to **General Procedure K** using **144d** (53.0 mg, 0.11 mmol), 2-naphthylmethanol (8.30 mg, 0.05 mmol), **362** (7.91 mg, 0.01 mmol), CHCl₃ (1.00 mL) at -50 °C. After 60 h allyl alcohol (0.35 μ l, 0.52 mmol) was added as instructed. This was followed by treatment with NEt₃ (14.60 μ l, 0.11 mmol) in CHCl₃ (0.50 mL). The crude material was purified as instructed to furnish **371d** (32.50 mg, 49%) as a white solid. M.p. 182-184 °C. [α]_D²⁰ = 15.0 (c 0.12, CHCl₃).

HPLC analysis. ACQUITY UPC² Trefoil CELI, 2.5 μ m (3.0 x 150 mm). ABPR 1500 (psi). A = CO₂ / B = MeCN:EtOH:IPA (1:1, v:v) gradient as shown in Table 10.4, column temperature : 30 °C, UV detection at 254 nm, retention times: 14.87 min and 16.10 min.

δ_H (400 MHz, CHCl₃): 7.56-7.31 (4H, m, H-11, H-12), 7.46-7.20 (5H, m, H-4, H-5, H-6, H-9, H-10), 6.87-6.81 (2H, m, H-7, H-8), 5.73 (1H, dd, *J* 4.7, 11.3, H-1), 5.27 (1H, d, *J* 11.8, H-3a), 5.22 (1H, d, *J* 11.8, H-3b), 4.02 (1H,

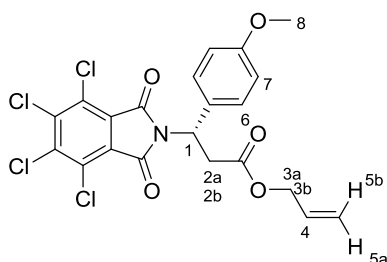
dd, *J* 12.0, 15.8, H-2a), 3.77 (3H, s, H-13), 3.09 (1H, dd, *J* 4.7, 15.8, H-2a).

δ_C (100 MHz, CHCl_3): 170.0 (C=O), 163.0 (C=O), 159.7 (q), 139.6 (q), 132.8 (q), 132.6 (q), 132.6 (q), 129.6 (q), 129.1, 129.1 (q), 128.1, 128.0, 127.7, 127.4, 126.6, 126.6 (q), 126.5, 126.3, 114.1, 66.6, 55.2, 51.5, 36.0.

ν_{max} (neat)/ cm^{-1} : 1774, 1734, 1714.

HRMS (*m/z* - ESI): Found: 623.9915 ($\text{M}+\text{Na}$)⁺ $\text{C}_{29}\text{H}_{19}\text{Cl}_4\text{NNaO}_5$ Requires: 623.9905.

10.3.35 Allyl-3-(4-methoxyphenyl)-3-(*S*)-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)propanoate (373d)



Prepared according to **General Procedure K** using **144d** (53.00 mg, 0.11 mmol), 2-naphthylmethanol (8.30 mg, 0.05 mmol), **362** (7.91 mg, 0.01 mmol), CHCl_3 (1.00 mL) at -50°C . After 60 h allyl alcohol (35.00 μL , 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 μL , 0.11 mmol) in CHCl_3 (0.50 mL). The crude material was purified as instructed to furnish **373d** (26.0 mg, 47%) as a white solid. M.p. $102\text{--}104^\circ\text{C}$. $[\alpha]_{\text{D}}^{20} = -26.3$ (*c* 0.11, CHCl_3).

HPLC analysis. ACQUITY UPC² Trefoil CELI, 2.5 μm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeOH:IPA (1:1, v:v) gradient as shown in Table 10.3, column temperature : 30°C , UV detection at 212 nm, retention times: 4.64 min and 4.93 min.

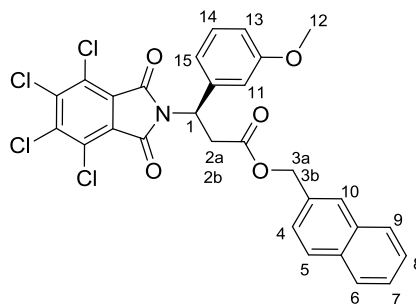
δ_H (400 MHz, CHCl_3): 7.48 (2H, d, *J* 8.6, H-6), 6.88 (2H, d, *J* 8.6, H-7) 5.90-5.76 (2H, m, H-1, H-4), 5.31-5.18 (2H, m, H-5a, H-5b), 4.58-4.53 (2H, m, H-3a, H-3b), 3.90-3.78 (4H, m, H-2a, H-8), 3.22 (1H, dd, *J* 5.4, 16.8, H-2b).

δ_C (100 MHz, CHCl_3): 170.1 (C=O), 163.3 (C=O), 159.6 (q), 140.1 (q), 131.6 (q), 129.7 (q), 129.6 (q), 129.3, 127.3, 118.7, 114.1, 65.5, 55.3, 51.0, 35.3.

ν_{max} (neat)/ cm^{-1} : 1780, 1734, 1710.

HRMS (*m/z* - ESI): Found: 501.9766 ($\text{M}+\text{Na}$)⁺ $\text{C}_{21}\text{H}_{15}\text{Cl}_4\text{NO}_5$ Requires: 501.978.

10.3.36 Naphthalen-2-ylmethyl-3-(*R*)-(3-methoxyphenyl)-3-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)propanoate (371e)



Prepared according to **General Procedure K** using **144e** (53.00 mg, 0.11 mmol), 2-naphthylmethanol (8.30 mg, 0.05 mmol), **G50** (7.91 mg, 0.01 mmol), CHCl₃ (1.00 mL) at -50 °C. After 60 h allyl alcohol (35.00 µl, 0.52 mmol) was added as instructed. This was followed by treatment with NEt₃ (14.60 µl, 0.11 mmol) in CHCl₃ (0.50 mL). The crude material was purified as instructed to furnish **371e** (32.40 mg, 49%) as a white solid. M.p. 102-104 °C. [α]_D²⁰ = 23.3 (c 0.15, CHCl₃).

CSP-HPLC analysis: Chiralpak IA column (4.6 mm x 250mmL), hexane/IPA: 90/10, 1 mL min⁻¹, r.t, UV detection at 220 nm, retention times 25.50 min and 31.05 min

δ_H (400 MHz, CHCl₃): 7.73-6.75 (11H, m H-4, H-5, H-6, H-7, H-8, H-9, H-10, H-11, H-13, H-14, H-15), 5.71 (1H, dd, *J* 4.6, 12.0, H-1), 5.25 (1H, d, *J* 11.7, H-3a), 5.20 (1H, d, *J* 11.7, H-3b), 4.01(1H, dd, *J* 12.0, 16.8, H-2a) 3.76 (3H, s, H-12), 3.07 (1H, dd, *J* 3.1, 16.8, H-2b).

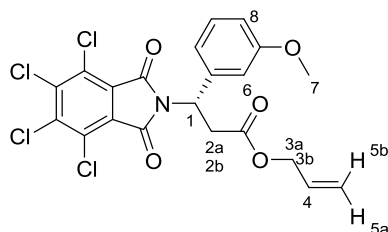
δ_C (100 MHz, CHCl₃): 169.9 (C=O), 163.0 (C=O), 159.8 (q), 136.0 (q), 138.9 (q), 132.8 (q), 132.6 (q), 132.6 (q), 130.0, 129.1 (q), 128.2, 128.0, 127.7, 127.4, 126.7, 126.6 (q), 126.5, 126.3, 119.1, 114.0, 113.4, 66.7, 55.2, 51.9, 35.8.

ν_{max} (neat)/cm⁻¹: 1774, 1734, 1714.

HRMS (*m/z* – DIP-APCI):* Found: 601.9925 (M-H)⁻ C₂₉H₂₀BrCl₄NO₅ Requires: 602.0090.

***Note:** Error for HRMS is -27.3 ppm.

10.3.37 Allyl-3-(3-methoxyphenyl)-3-(S)-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)propanoate (373e)



Prepared according to **General Procedure K** using **144e** (53.00 mg, 0.11 mmol), 2-naphthylmethanol (8.30 mg, 0.05 mmol), **362** (7.91 mg, 0.01 mmol), CHCl₃ (1.00 mL) at -50 °C. After 60 h allyl alcohol (35.00 µl, 0.52 mmol) was added as instructed. This was followed by treatment with NEt₃ (14.60 µl, 0.11 mmol) in CHCl₃ (0.50 mL). The crude material was purified as instructed to furnish **373e** as a white solid (26.60 mg, 48%). M.p. 139-141 °C. [α]_D²⁰ = -20.0 (c 0.01, CHCl₃).

CSP-HPLC analysis: Chiralpak IA column (4.6 mm x 250mmL), hexane/IPA: 90/10, 1 mL min⁻¹, r.t, UV detection at 220 nm, retention times 18.70 min and 20.97 min

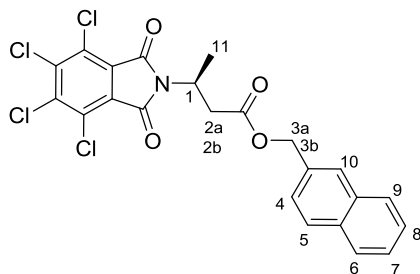
δ_H (400 MHz, CHCl₃): 7.28-6.79 (4H, m H-6, H-8, H-9, H-10), 5.91-5.69 (2H, m, H-1, H-4), 5.32-5.11 (2H, m, H-5a, H-5b), 4.58-4.47 (2H, m, H-3a, H-3b), 3.91-3.73 (4H, m, H-2a, H-7), 3.19 (1H, dd, *J* 5.1, 16.8, H-2b).

δ_C (100 MHz, CHCl₃): 170.0 (C=O), 163.2 (C=O), 159.8 (q), 140.1 (q), 138.9 (q), 131.6 (q), 129.9, 129.7 (q), 127.3, 120.0 (q), 118.7, 65.5, 55.3, 51.5, 35.1.

ν_{max} (neat)/cm⁻¹: 1777, 1709, 1599.

HRMS (*m/z* –APCI): Found: 501.9704 (M+H)⁺ C₂₁H₂₆Cl₄NO₅ Requires: 501.9704.

10.3.38 Naphthalen-2-ylmethyl-3-(R)-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)butanoate (371f)



Prepared according to **General Procedure K** using **144f** (45.60 mg, 0.11 mmol), 2-naphthylmethanol (8.30 mg, 0.05 mmol), **362** (7.91 mg, 0.01 mmol), CHCl₃ (1.00 mL) at -30 °C. After 63 h allyl alcohol (35.00 µl, 0.52 mmol) was added as instructed. This was followed by treatment with NEt₃ (14.60 µl,

0.11 mmol) in CHCl₃ (0.50 mL). The crude material was purified as instructed to furnish **371f** (26.40 mg, 47%) as a white solid. M.p. 170-173 °C. [α]_D²⁰ = 2.5 (c 0.12, CHCl₃).

HPLC analysis. ACQUITY UPC² Trefoil CELI, 2.5 μ m (3.0 x 150 mm). ABPR 1500 (psi). A = CO₂ / B = EtOH:MeCN (1:1, v:v) gradient as shown in **Table 10.1**, column temperature : 30 °C, UV detection at 254 nm, retention times: 4.58 min and 4.79 min.

δ_H (400 MHz, CHCl₃): 7.75-7.26 (7H, m, H-4, H-5, H-6, H-7, H-8, H-9, H-10), 5.17 (2H, s, H-3a, H-3b), 4.82-4.71 (1H, m, H-1), 3.39 (1H, dd, *J* 11.1, 15.4, H-2a), 2.71 (1H, dd, *J* 4.7, 15.4, H-2b), 1.44 (3H, d, *J* 6.7, H-11).

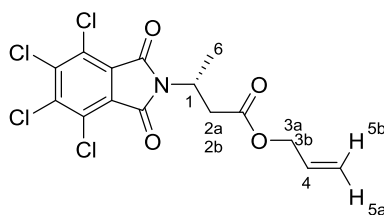
δ_C (100 MHz, CHCl₃): 170.2 (C=O), 163.1 (C=O), 139.6 (q), 132.8 (q), 132.7 (q), 132.7 (q), 129.1 (q), 128.1, 127.8, 127.7, 127.5, 126.8 (q), 126.6, 126.5, 126.2, 66.7, 44.7, 37.8, 18.8.

ν_{max} (neat)/cm⁻¹: 1772, 1716, 1702.

HRMS (*m/z* – DIP-APCI):* Found: 508.9608 (M+H)⁺ C₂₃H₁₅Cl₄NO₄ Requires: 508.9750.

*Note: Error for HRMS is 27.9 ppm.

10.3.39 Allyl 3-(S)-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)butanoate (373f)



Prepared according to **General Procedure K** using **144f** (45.60 mg, 0.11 mmol), 2-naphthylmethanol (8.30 mg, 0.05 mmol), **362** (7.91 mg, 0.01 mmol), CHCl₃ (1.00 mL) at -30 °C. After 63 h allyl alcohol (35.00 μ l, 0.52 mmol) was added as instructed. This was followed by treatment with NEt₃ (14.60 μ l, 0.11 mmol) in CHCl₃ (0.50 mL). The crude material was purified as instructed to furnish **373f** (21.30 mg, 47%) as a white solid. M.p. 147-150 °C. [α]_D²⁰ = -10.0 (c 0.12, CHCl₃).

HPLC analysis. ACQUITY UPC² Trefoil CELI, 2.5 μ m (3.0 x 150 mm). ABPR 1500 (psi). A = CO₂ / B = EtOH:MeCN (1:1, v:v) gradient as shown in Table 10.5, column temperature : 30 °C, UV detection at 254 nm, retention times: 6.48 min and 6.79 min.

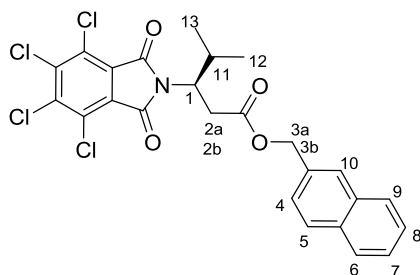
δ_H (400 MHz, CHCl₃): 5.90-5.76 (1H, m, H-4), 5.29-5.13 (2H, m, H-5a, H-5b), 4.86-4.75 (1H, m, H-1), 4.53-4.49 (2H, m, H-3a, H-3b), 3.22 (1H, dd, *J* 9.8, 16.6, H-2a), 2.78 (1H, dd, *J* 5.4, 16.6, H-2b), 1.51 (3H, d, *J* 6.9, H-6).

δ_{C} (100 MHz, CHCl_3): 170.2 (C=O), 163.3 (C=O), 140.1 (q), 131.7, 129.7 (q), 127.4 (q), 118.7, 65.4, 44.4, 37.3, 18.6.

ν_{max} (neat)/ cm^{-1} : 1733, 1713, 1702.

HRMS (m/z - APCI): Found: 409.9520 ($\text{M}+\text{H}$) $^+$ $\text{C}_{21}\text{H}_{15}\text{Cl}_4\text{NNaO}_5$ Requires: 409.9515.

10.3.40 Naphthalen-2-ylmethyl-4-methyl-3-(*R*)-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)pentanoate (371g)



Prepared according to **General Procedure K** using **144g** (46.30 mg, 0.11 mmol), 2-naphthylmethanol (8.30 mg, 0.05 mmol), **362** (7.91 mg, 0.01 mmol), CHCl_3 (1.00 mL) at rt. After 60 h, allyl alcohol (35.00 μL , 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 μL , 0.11 mmol) in CHCl_3 (0.50 mL). The crude material was purified as instructed to furnish **371g** (25.50 mg, 43%) as a white solid. M.p. 102-104 $^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{20} = 5.0$ (c 0.04, CHCl_3).

HPLC analysis. ACQUITY UPC² Trefoil CELI, 2.5 μm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeOH:IPA (1:1, v:v) gradient as shown in **Table 10.3**, column temperature : 30 $^{\circ}\text{C}$, UV detection at 230 nm, retention times: 4.08 min and 4.43 min.

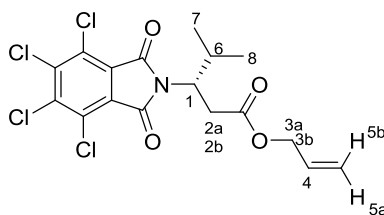
δ_{H} (400 MHz, CHCl_3): 7.73-7.26 (7H, m, H-4, H-5, H-6, H-7, H-8, H-9, H-10), 5.16 (1H, d, J 11.7, H-3a), 5.11 (1H, d, J 11.7, H-3b), 4.92-4.20 (1H, m, H-1), 3.36 (1H, dd, J 12.2, 15.2, H-2a), 2.83 (1H, dd, J 4.0, 15.2), 2.30-2.19 (1H, m, H-11), 1.01 (3H, d, J 6.5, H-12), 0.78 (3H, d, J 6.8, H-13).

δ_{C} (100 MHz, CHCl_3): 170.7 (C=O), 163.4 (C=O), 139.6 (q), 132.8 (q), 132.6 (q), 132.6 (q), 129.1 (q), 128.1, 128.0, 127.7, 127.5, 126.7, 126.5, 126.5 (q), 126.3, 66.5, 55.3, 34.5, 30.6, 20.0, 19.7.

ν_{max} (neat)/ cm^{-1} : 1774, 1731, 1715.

HRMS (m/z - APCI): Found: 538.0126 ($\text{M}+\text{H}$) $^+$ $\text{C}_{25}\text{H}_{20}\text{Cl}_4\text{NO}_4$ Requires: 538.0141.

10.3.41 Allyl 4-methyl-3-(S)-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)pentanoate (373g)



Prepared according to **General Procedure K** using **144g** (46.30 mg, 0.11 mmol), 2-naphthylmethanol (8.30 mg, 0.05 mmol), **362** (7.91 mg, 0.01 mmol), CHCl₃ (1.00 mL) at rt. After 60 h, allyl alcohol (35.00 µl, 0.52 mmol) was added as instructed. This was followed by treatment with NEt₃ (14.60 µl, 0.11 mmol) in CHCl₃ (0.50 mL). The crude material was purified as instructed to furnish **373g** as a white solid (21.70 mg, 45%). M.p. 55-57 °C. [α]_D²⁰ = -16.7 (c 0.03, CHCl₃).

HPLC analysis. ACQUITY UPC² Trefoil CELI, 2.5 µm (3.0 x 150 mm). ABPR 1500 (psi). A = CO₂ / B = MeOH:IPA (1:1, v:v) gradient as shown in **Table 10.3**, column temperature : 30 °C, UV detection at 230 nm, retention times: 2.76 min and 3.73 min.

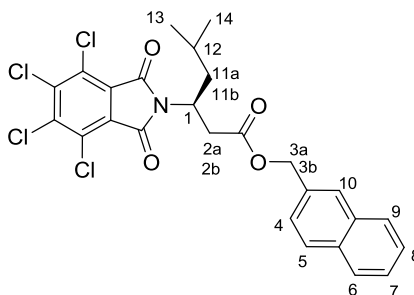
δ_H (400 MHz, CHCl₃): 5.88-5.74 (1H, m, H-4), 5.28-5.13 (2H, m, H-5a, H-5b), 4.78-4.69 (1H, m, H-1), 4.51-4.47 (2H, m, H-3a, H-3b), 3.19 (1H, dd, *J* 10.1, 16.1, H-2a), 2.71 (1H, dd, *J* 4.8, 16.1, H-2b), 2.15-2.02 (1H, m, H-6), 0.75-0.88 (6H, m, H-7, H-8).

δ_C (100 MHz, CHCl₃): 170.7 (C=O), 163.7 (C=O), 140.1 (q), 131.6 (q), 129.7 (q), 127.2, 118.8, 65.4, 55.0, 33.8, 30.4, 20.0, 19.7.

$\nu_{\max}$ (neat)/cm⁻¹: 1732, 1728, 1717.

HRMS (*m/z* - ESI): Found: 437.9755 (M+H)⁺ C₁₇H₁₅Cl₄NO₄ Requires: 437.9755.

10.3.42 Naphthalen-2-ylmethyl-5-methyl-3-(R)-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)hexanoate (371h)



Prepared according to **General Procedure K** using **144h** (47.80 mg, 0.11 mmol), 2-naphthylmethanol (8.30 mg, 0.05 mmol), **362** (7.91 mg, 0.01 mmol), CHCl₃ (1.00 mL) at -30 °C. After 63 h, allyl alcohol (35.00 µl, 0.52 mmol) was added as instructed. This was followed by treatment with NEt₃

(14.60 μ l, 0.11 mmol) in CHCl_3 (0.50 mL). The crude material was purified as instructed to furnish **371h** (24.30 mg, 40%) as a white solid. M.p. 110-112 $^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{20} = 12.0$ (c 0.05, CHCl_3).

HPLC analysis. ACQUITY UPC² Trefoil CELI, 2.5 μm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = $\text{MeCN}:\text{EtOH}:\text{IPA}$ (1:1:1, v:v) gradient as shown in Table 10.4, column temperature : 30 $^{\circ}\text{C}$, UV detection at 254 nm, retention times: 8.36 min and 8.80 min.

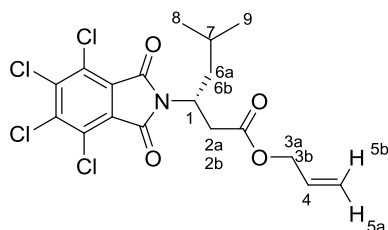
δ_{H} (400 MHz, CHCl_3): 7.75-7.26 (7H, m, H-4, H-5, H-6, H-7, H-8, H-9, H-10), 5.18-5.10 (2H, m, H-3a, H-3b), 4.75-4.65 (1H, m, H-1), 3.35 (1H, dd, J 11.6, 15.4, H-2a), 2.68 (1H, dd, J 4.3, 15.4, H-2b), 2.04-1.93 (1H, m, H-12), 1.49-1.30 (2H, m, H-11a, H-11b), 0.92-0.84 (6H, m, H-13, H-14).

δ_{C} (100 MHz, CHCl_3): 170.3 (C=O), 163.3 (C=O), 139.6 (q), 132.7 (q), 132.7(q), 132.7(q), 129.1 (q), 128.1, 127.8, 127.7, 127.5, 126.7, 126.6 (q), 126.6, 126.5, 126.1, 66.6, 47.4, 41.3, 36.9, 25.0, 22.8, 21.7.

ν_{max} (neat)/ cm^{-1} : 1773, 1731, 1712.

HRMS (m/z - ESI): Found: 574.0105 ($\text{M}+\text{Na}$)⁺ $\text{C}_{26}\text{H}_{21}\text{Cl}_4\text{NNaO}_4$ Requires: 574.0117.

10.3.43 Allyl 5-methyl-3-(S)-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)hexanoate (**373h**)



Prepared according to **General Procedure K** using **144h** (47.80 mg, 0.11 mmol), 2-naphthylmethanol (8.30 mg, 0.05 mmol), **362** (7.91 mg, 0.01 mmol), CHCl_3 (1.00 mL) at -30 $^{\circ}\text{C}$. After 63 h, allyl alcohol (35.00 μ l, 0.52 mmol) was added as instructed. This was followed by treatment with NEt_3 (14.60 μ l, 0.11 mmol) in CHCl_3 (0.50 mL). The crude material was purified as instructed to furnish **373h** (27.90 mg, 56%) as a white solid. M.p. 85-87 $^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{20} = -40.0$ (c 0.01, CHCl_3).

HPLC analysis. ACQUITY UPC² Trefoil CELI, 2.5 μm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = $\text{EtOH}:\text{MeCN}$ (1:1, v:v) gradient as shown in **Table 10.1**, column temperature : 30 $^{\circ}\text{C}$, UV detection at 230 nm, retention times: 2.52 min and 2.86 min.

δ_{H} (400 MHz, CHCl_3): 5.89-5.78 (1H, m, H-4), 5.32-5.16 (2H, m, H-5a, H-5b), 4.80-4.72 (1H, m, H-1), 4.51 (2H, app. d, J 5.9, H-3a, H-3b), 3.21 (1H, dd, J

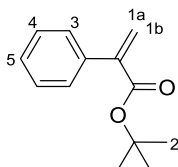
10.3, 16.4, H-2a), 2.74 (1H, dd, *J* 4.9, 16.4, H-2b), 2.16-2.08 (1H, m, H-7), 1.53-1.42 (2H, m, H-6a, H-6b), 1.01-0.91 (6H, m, H-8, H-9).

δ_C (100 MHz, CHCl_3): 170.3 (C=O), 163.6 (C=O), 140.1 (q), 131.7, 129.7 (q), 127.3 (q), 118.7, 65.5, 47.2, 41.1, 36.5, 25.1, 23.0, 21.7.

ν_{max} (neat)/ cm^{-1} : 1731, 1720, 1715.

HRMS (*m/z* - ESI): Found: 451.9980. $(\text{M}+\text{H})^+$ $\text{C}_{18}\text{H}_{18}\text{Cl}_4\text{NO}_4$ Requires: 451.9984.

10.3.44 *tert*-Butyl 2-phenylacrylate (**386**)

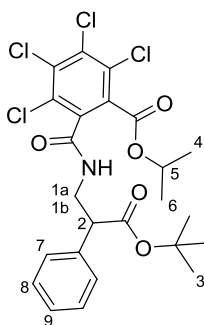


Phenyl acrylic acid (1.6 g, 10.7 mmol), $(\text{Boc})_2\text{O}$ (3.5 g, 16.1 mmol) and DMAP (524 mg, 4.3 mmol) were dissolved in anhydrous CH_2Cl_2 (21.5 mL) at 0 °C under argon and NEt_3 (1.5 mL, 10.7 mmol) was added *via* syringe. The reaction mixture was stirred for 16 h followed by concentration *in vacuo*. The crude material was purified *via* silica chromatography, eluting with 10% EtOAc in hexane to furnish **386** as a colourless oil (2.1 g, 97%). The spectroscopic data obtained for **386** was identical to those found in the literature.²⁵³

δ_H (400 MHz, CHCl_3): 7.44-7.29 (5H, m, H-3, H-4, H-5), 6.24 (1H, d, *J* 1.32, H-1a), 5.81 (1H, d, *J* 1.32, H-1b), 1.53 (9H, s, H-2).

HRMS (*m/z* - ESI): Found: 205.1148. $(\text{M}+\text{H})^+$ $\text{C}_{13}\text{H}_{16}\text{O}_2$ Requires: 205.1149.

10.3.45 *iso*Propyl-2-((3-(*tert*-butoxy)-3-oxo-2-phenylpropyl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (**385**)



386 (6.1 g, 30.0 mmol) and BnNH_2 (9.8 mL, 90.0 mmol) were dissolved in MeOH (30.0 mL) and I_2 (0.4 g, 3.0 mmol) was added. The mixture was refluxed for 48 h and was concentrated *in vacuo*. The crude material was purified *via* silica chromatography, eluting with a mixture of 9:1:0.5 hexane:EtOAc: NEt_3 to yield the hydroaminated product (7.8 g, 80%). To this $\text{Pd}(\text{OH})_2/\text{C}$ (20 wt. %,

1.7 g, 2.4 mmol) and MeOH (4.8 mL) were added under an atmosphere of argon. The flask was subsequently evacuated and purged with argon (x 3). On the final evacuation of the flask a septum and hydrogen balloon were fitted. The reaction mixture was stirred vigorously for 16 h. This mixture was filtered *via* suction filtration and the filtrate was evaporated to yield the free amine (5.3 g, 99%). To this **296** (9.5 g, 24.0 mmol) and DCC (5.0 g, 24.0 mmol) were added. The flask was purged with argon and a septum with a balloon of argon was fitted. Anhydrous CH₂Cl₂ (48.0 mL) was added *via* syringe at 0 °C. The mixture was warmed to room temperature and was stirred for 16 h. The resulting suspension was filtered *via* suction filtration and the filtrate was purified *via* silica chromatography to yield **385** as a white solid (4.7 g, 8.6 mmol). M.p 110-112 °C.

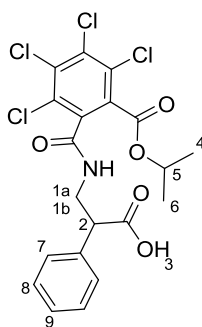
δ_{H} (400 MHz, CHCl₃): 7.35-7.25 (5H, m, H-7, H-8, H-9), 6.43 (1H, t, *J* 6.0, NH), 5.22 (1H, sept., *J* 6.3, H-5), 3.96-3.66 (3H, m, H1-a, H-1b, H-2), 1.37 (9H, s, H-3), 1.33 (6H, d, *J* 6.3, H-4, H-6).

δ_{C} (100 MHz, CHCl₃): 172.0 (C=O), 163.3 (C=O), 163.2 (C=O), 136.6 (q), 135.0 (q), 134.9 (q), 134.6 (q), 132.7 (q), 130.1 (q), 129.6 (q), 128.9, 127.8, 127.6, 81.7 (q), 71.1, 51.6, 42.6, 27.9, 21.5, 21.5.

ν_{max} (neat)/cm⁻¹: 1725, 1650, 1539.

HRMS (*m/z* - ESI): Found: 570.0375 (M+Na)⁺ C₂₄H₂₅Cl₄NNaO₅ Requires: 570.0379.

10.3.46 2-Phenyl-3-(2,3,4,5-tetrachloro-6-(isopropoxycarbonyl)benzamido)propanoic acid (**384**)



Prepared according to **General Procedure F** using **385** (4.7 g 8.6 mmol), TFA (17.0 mL) and CH₂Cl₂ (17.0 mL) to yield **384** as a product (4.2 g, 99%) as a white solid. M.p 166-167 °C.

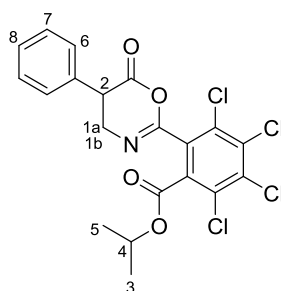
δ_{H} (400 MHz, CHCl₃): 7.40-7.24 (5H, m, H-7, H-8, H-9), 6.86 (1H, t, *J* 6.0), 5.24 (1H, sept., *J* 6.2), 4.02-3.65 (3H, m, H-1a, H-1b, H-2), 3.01 (1H, bs, H-3), 1.38-1.31 (6H, m, H-4, H-5).

δ_{C} (100 MHz, CHCl_3): 176.2 (C=O), 164.2 (C=O), 163.4 (C=O), 135.8 (q), 135.1 (q), 134.8 (q), 134.5 (q), 132.3 (q), 129.9 (q), 129.8 (q), 129.0, 128.0, 127.9, 71.8, 51.0, 42.6, 21.6.

ν_{max} (neat)/ cm^{-1} : 1736, 1718, 1646.

HRMS (m/z - ESI): Found: 513.9764 ($\text{M}+\text{Na}$) $^+$ $\text{C}_{20}\text{H}_{27}\text{Cl}_4\text{NNaO}_5$ Requires: 513.9753.

10.3.47 isoPropyl 2,3,4,5-tetrachloro-6-(6-oxo-5-phenyl-5,6-dihydro-4H-1,3-oxazin-2-yl)benzoate (383)



Prepared according to **General Procedure G** using **384** (2.1 g, 4.1 mmol), NEt_3 (628.0 μl , 4.5 mmol), SOCl_2 (324.0 μl , 4.5 mmol) and NEt_3 (1.2 mL, 8.9 mmol). The crude material was purified according as instructed, followed by recrystallisation from hexane/EtOAc to furnish **383** as a white solid (1.1 g, 2.2 mmol). M.p. 147-150 $^{\circ}\text{C}$.

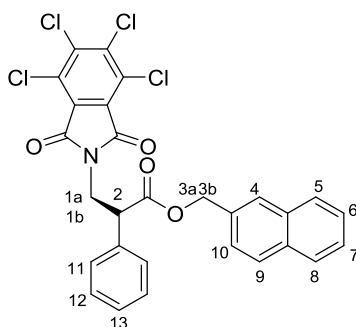
δ_{H} (400 MHz, CHCl_3): 7.45-7.29 (5H, m, H-6, H-7, H-8), 5.26 (1H, sept., J 6.3, H-4), 4.12-3.88 (3H, m, H-1a, H-1b, H-2), 1.41-1.35 (6H, m, H-3, H-5).

δ_{C} (100 MHz, CHCl_3): 165.9 (C=O), 163.6 (C=O), 151.4 (C=N), 147.9 (q), 135.9 (q), 135.4 (q), 134.1 (q), 133.1 (q), 131.9 (q), 130.2 (q), 130.0 (q), 129.1, 128.4, 128.3, 71.2, 49.9, 44.5, 21.7, 21.6.

ν_{max} (neat)/ cm^{-1} : 1791, 1788, 1709.

HRMS (m/z - APCI): Found: 473.9827 ($\text{M}+\text{H}$) $^+$ $\text{C}_{20}\text{H}_{16}\text{Cl}_4\text{NO}_4$ Requires: 473.9828.

10.3.48 Naphthalen-2-ylmethyl-(*R*)-2-phenyl-3-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)propanoate (**395**)



383 (50.00 mg, 0.11 mmol) catalyst **354** (5.74 mg, 0.01 mmol) and 2-naphthylmethanol (24.90 mg, 0.16 mmol) were dissolved in anhydrous CHCl_3 (1.00 mL) under argon and were stirred at rt for 60 h. DABCO (4.71 mg, 0.04 mmol) was added and the reaction mixture was stirred for a further 24 h. The crude mixture was purified *via* silica chromatography, eluting with a gradient of 5-20% EtOAc in hexane to furnish **I30b** (58.4 mg, 97%) as a white solid. M.p. 163-164 °C. $[\alpha]_{\text{D}}^{20} = 25.3$ (*c* 0.15, CHCl_3).

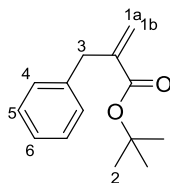
δ_{H} (400 MHz, CHCl_3): 7.76-7.16 (13H, m, H-4, H-5, H-6, H-7, H-8, H-9, H-10, H-11, H-12, H-13), 5.27 (1H, d, *J* 12.3, H-3a), 5.14 (1H, d, *J* 12.3, H-3b), 4.48-4.26 (2H, m, H-1a, H-2) 3.92 (1H, dd, *J* 6.7 13.5, H-1b).

δ_{C} (100 MHz, CHCl_3): 171.2 (C=O), 163.0 (C=O), 139.9 (q), 134.9 (q), 132.9 (q), 132.7 (q), 132.7 (q), 129.3 (q), 128.9, 128.4, 128.0, 127.7, 127.5, 127.2, 126.9, 126.4, 126.4 125.7, 66.9, 48.6, 41.1.

ν_{max} (neat)/ cm^{-1} : 3034, 1778, 1711.

HRMS (*m/z* - APCI): Found: 571.9911 ($\text{M}+\text{H}^+$) $\text{C}_{28}\text{H}_{18}\text{Cl}_4\text{NO}_4$ Requires: 570.0012.

10.3.49 *tert*-Butyl 2-benzylacrylate (**402**)

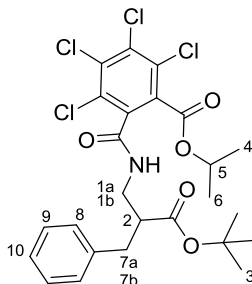


Benzyl acrylic acid (12.1 g, 74.9 mmol), $(\text{Boc})_2\text{O}$ (24.5 g, 112.3 mmol) and DMAP (3.7 mg, 29.9 mmol) were dissolved in anhydrous CH_2Cl_2 (150.0 mL) at 0 °C. The reaction mixture was warmed to rt and was stirred for 16 h. The crude material was purified *via* silica chromatography, eluting with 10% EtOAc in hexane to furnish **402** as a colourless oil (15.3 g, 93%). The spectroscopic data obtained for **402** was identical to those found in the literature.²⁵⁴

δ_{H} (400 MHz, CHCl_3): 7.29-7.18 (5H, m, H-4, H-5, H-6), 6.13-6.11 (1H, m, H-1a), 5.36-5.33 (1H, m, H-1b), 3.57 (2H, s, H-3), 1.41 (9H, s, H-2).

HRMS (m/z - ESI): Found: 219.13307 ($\text{M}+\text{H}$)⁺ $\text{C}_{14}\text{H}_{19}\text{O}_2$ Requires: 219.1307.

10.3.50 isoPropyl-2-((2-benzyl-3-(tert-butoxy)-3-oxopropyl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (405)



402 (4.3 g, 19.5 mmol) and BnNH_2 (6.4 mL, 58.5 mmol) were dissolved in MeOH (20.0 mL) and I_2 (247 mg, 2.0 mmol) was added. The mixture was refluxed for 48 h and was concentrated *in vacuo*. The crude material was purified *via* silica chromatography eluting with a mixture of 9:1:0.5 hexane:EtOAc: NEt_3 to yield the hydroaminated product (5.5 g, 16.8 mmol). To this, $\text{Pd}(\text{OH})_2/\text{C}$ (20 wt. %, 1.2 g, 1.7 mmol) and MeOH (17 mL) were added under an atmosphere of argon. The flask was subsequently evacuated and purged with argon (x 3). On the final evacuation of the flask a septum and hydrogen balloon were fitted. The reaction mixture was stirred vigorously for 16 h. This mixture was filtered *via* suction filtration and the filtrate was evaporated to yield the free amine (4.0 g, 99%). To this **296** (7.3 g, 18.5 mmol) and HBTU (7.0 g, 18.5 mmol) NEt_3 (2.6 mL, 18.5 mmol) were added. The flask was purged with argon and a septum with a balloon of argon was fitted. Anhydrous CH_2Cl_2 (34.0 mL) was added *via* syringe and the mixture was stirred for 16 h. HCl (1.5M, aq., 20 mL) and the product was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified *via* silica chromatography eluting with a gradient of 5-10% EtOAc in hexane to yield **405** as a white solid (3.4 g, 36%). M.p 105-107 °C.

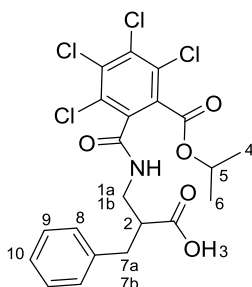
δ_{H} (400 MHz, CHCl_3): 7.33-7.17 (5H, m, H-8, H-9, H-10), 6.52 (1H, t, J 5.5, N-H), 5.23 (1H, sept., J 6.3, H-5), 3.69-3.58 (1H, m, H-1a), 3.54-3.42 (1H, m, H-1b), 3.01-2.86 (2H, m, H-7a, H-7b), 1.34 (9H, s, H-3).

δ_{C} (100 MHz, CHCl_3): 173.5 (C=O), 163.4 (C=O), 163.2 (C=O), 138.0 (q), 135.0 (q), 134.8 (q), 132.8 (q), 134.7 (q), 132.8 (q), 130.1 (q), 129.6 (q), 129.1, 128.4, 126.6, 81.6, 71.1, 71.1, 46.8, 40.6, 36.2, 27.9, 21.5, 21.5.

ν_{max} (neat)/ cm^{-1} : 1721, 1641, 1572.

HRMS (m/z - APCI): Found: 584.0537 ($M+Na$)⁺ C₂₅H₂₇Cl₄NNaO₅ Requires: 584.0536.

10.3.51 2-Benzyl-3-(2,3,4,5-tetrachloro-6-(isopropoxycarbonyl)benzamido)propanoic acid (406)



Prepared according to **General Procedure F** using **405** (3.1 g, 5.5 mmol), TFA (11.0 mL) and CH₂Cl₂ (11.0 mL) to yield **406** as a product (3.1 g, 99%) as a white solid. M.p 57-60 °C.

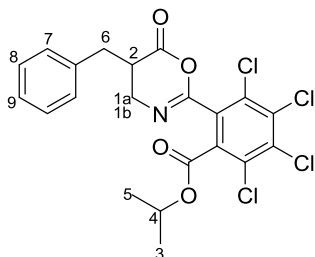
δ_H (400 MHz, CHCl₃): 7.37-7.17 (5H, m, H-8, H-9, H-10), 6.81-6.68 (1H, m, NH), 5.30-5.21 (1H, m, H-5), 3.78-3.67 (1H, m, H-1a), 3.53-3.41 (1H, m, H-1b), 3.12-2.87 (2H, m, H-7a, H-7b), 1.39-1.33 (6H, m, H-4, H-6).

δ_C (100 MHz, CHCl₃): 164.2 (C=O), 164.1 (C=O), 163.4 (C=O), 137.5 (q), 135 (q), 134.8 (q), 134.5 (q), 129.0, 128.8, 128.7 (q), 128.3 (q), 126.9, 71.7, 46.2, 40.4, 35.8, 21.5.

ν_{max} (neat)/cm⁻¹: 1778, 1725, 1715.

HRMS (m/z - ESI): Found: 527.9901 ($M+Na$)⁺ C₂₁H₁₉Cl₄NNaO₅ Requires: 527.9909.

10.3.52 isoPropyl 2-(5-benzyl-6-oxo-5,6-dihydro-4H-1,3-oxazin-2-yl)-3,4,5,6-tetrachlorobenzoate (407)



406 (2.6 g, 4.5 mmol) and NEt₃ (758 μ l, 5.5 mmol) were dissolved in anhydrous CH₂Cl₂ (20.0 mL) under an atmosphere of argon. The mixture was cooled to -15 °C and *iso*-propylchloroformate (1M in toluene, 5.5 mmol, 5.5 mL) was added dropwise. The mixture was stirred for 20 mins and a second aliquot of NEt₃ (758 μ l, 5.5 mmol) was added. The mixture was warmed to 0 °C and was stirred for 1 h followed by evaporation of the solvent *in vacuo* at 0 °C. The remaining solid was re-dissolved in dry toluene and was filtered under argon to remove the insoluble solid (Et₃NHCl). The filtrate was

concentrated *in vacuo* and was purified *via* silica chromatography using a gradient of 0-10% EtOAc in hexane to yield the product **407** as a colourless oil (1.3 g, 58%).

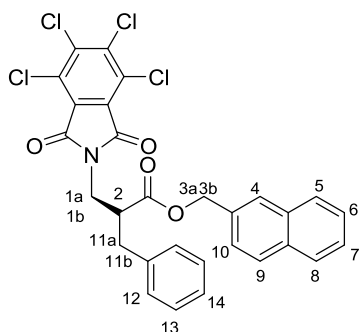
δ_{H} (400 MHz, CHCl_3): 7.40-7.23 (5H, m, H-7, H-8, H-9), 5.24 (1H, sept., J 6.3, H-4), 3.78 (1H, dd, J 6.2, 16.2, H-1a), 3.51 (1H, dd, J 10.5, 16.2, H-1b), 3.30-3.34 (1H, m, H-2), 3.01-2.85 (2H, m, H-6a, H-6b), 1.38-1.32 (6H, m, H-3, H-5).

δ_{C} (100 MHz, CHCl_3): 166.9 (C=O), 163.6 (C=O), 151.0 (C=N), 136.8 (q), 135.9 (q), 135.3 (q), 134.1 (q), 131.8 (q), 130.2 (q), 130.0 (q), 129.1, 128.8, 127.2, 71.2, 47.1, 39.4, 33.4, 21.6, 21.6.

ν_{max} (neat)/ cm^{-1} : 1729, 1721, 1709.

HRMS (m/z - APCI): Found: 487.9982 ($\text{M}+\text{H}$) $^+$ $\text{C}_{21}\text{H}_{18}\text{Cl}_4\text{NO}_5$ Requires: 487.9984.

10.3.53 Naphthalen-2-ylmethyl-(*R*)-2-benzyl-3-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)propanoate (**408**)



407 (35.70 mg, 0.07 mmol), 2 naphthylmethanol (5.80 mg, 0.04 mmol) and catalyst **362** (3.70 mg, 0.01 mmol) were dissolved in anhydrous CHCl_3 under argon at $-50\text{ }^\circ\text{C}$ and the mixture was stirred for 14 days until the alcohol was completely consumed by the reaction (monitored by ^1H NMR spectroscopy). Allyl alcohol (24.80 μL , 0.37 mmol) was added and the mixture was warmed to rt and was stirred for a further 3 h. DABCO (3.30 mg, 0.29 mmol) was added and the mixture was stirred for 24 h. The resulting mixture was purified *via* silica chromatography to afford **408** (20.14 mg, 49%) as a white solid. M.p. $128\text{--}130\text{ }^\circ\text{C}$. $[\alpha]_{\text{D}}^{20} = 23.3$ (c 0.12, CHCl_3).

HPLC analysis. ACQUITY UPC² Trefoil CELI, 2.5 μm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeCN:EtOH:IPA (1:1:1, v:v) gradient as shown in Table 10.6, column temperature : $30\text{ }^\circ\text{C}$, UV detection at 254 nm, retention times: 14.07 min and 16.87 min.

δ_{H} (400 MHz, CHCl_3): 7.75-7.40 (7H, m, H-4, H-5, H-6, H-7, H-8, H-9, H-10), 7.26-7.20 (5H, H-12, H-13, H-14), 5.20 (1H, d, J 12.0, H-3a), 5.02 (1H, d, J 12.0, H-3b), 3.99 (1H, dd, J 9.7, 13.9, H-1a), 3.70 (1H, dd, J 5.8, 13.9,

H-1b), 3.47 (1H, m, H-2), 3.18 (1H, dd, J 7.7, 14.3, H-11a), 2.83 (1H, dd, J 7.5, 14.3, H-11b).

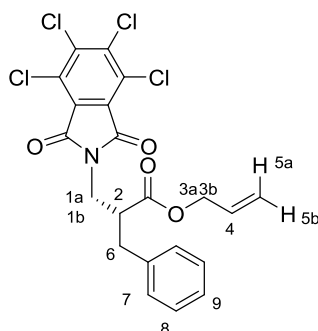
δ_C (100 MHz, CHCl_3): 172.3 (C=O), 163.1 (C=O), 139.7 (q), 137.7 (q), 132.7 (q), 132.7 (q), 132.6 (q), 129.2 (q), 128.7 128.6, 128.0, 127.7, 127.6, 127.1, 126.9 (q), 126.6, 126.5, 126.4, 125.7, 66.8, 44.3, 40.2, 35.7, 29.7.

ν_{max} (neat)/ cm^{-1} : 2981, 2929, 1791, 1721.

HRMS (m/z – DIP-APCI):* Found: 584.9875 (M-H) $^+$ $\text{C}_{29}\text{H}_{19}\text{Cl}_4\text{NO}_4$ Requires: 585.0063.

*Note: Error for HRMS is -32.0 ppm.

10.3.54 Allyl (S)-2-benzyl-3-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)propanoate (409)



407 (35.7 mg, 0.07 mmol), 2 naphthylmethanol (5.8 mg, 0.04 mmol) and catalyst **362** (3.70 mg, 0.01 mmol) were dissolved in anhydrous CHCl_3 under argon at $-50\text{ }^\circ\text{C}$ and the mixture was stirred for 14 days until the alcohol was completely consumed by the reaction (monitored by ^1H NMR spectroscopy). Allyl alcohol (24.80 μl , 0.37 mmol) was added and the mixture was warmed to rt and was stirred for a further 3 h. DABCO (3.30 mg, 0.29 mmol) was added and the mixture was stirred for 24 h. The resulting mixture was purified *via* silica chromatography to afford **409** as a colourless oil (14.42 mg, 40%). $[\alpha]_{\text{D}}^{20} = -26.7$ (c 0.15, CHCl_3).

HPLC analysis. ACQUITY UPC² Trefoil CELI, 2.5 μm (3.0 x 150 mm). ABPR 1500 (psi). A = CO_2 / B = MeCN:EtOH:IPA (1:1:1, v:v) gradient as shown in **Table 10.3**, column temperature : $30\text{ }^\circ\text{C}$, UV detection at 254 nm, retention times: 4.46 min and 4.84 min.

δ_H (400 MHz, CHCl_3): 7.24-7.07 (5H, m, H-7, H-8, H-9), 5.84-5.69 (1H, m, H-4), 5.22-5.10 (2H, m, H5a, H-5b), 4.49 (2H, app. d, J 5.8, H-3a, H-3b), 3.98 (1H, dd, J 8.1, 13.9, H-1a), 3.86 (1H, dd, J 6.6, 13.8, H-1b), 3.39-2.86 (1H, m, H-2), 3.13 (1H, dd, J 7.2, 14.5, H-6a), 2.80 (1H, dd, J 8.3, 14.7, H-6b).

δ_C (100 MHz, CHCl_3): 172.2 (C=O), 163.2 (C=O), 140.0 (q), 137.7 (q), 131.7, 129.6 (q), 128.6 128.5, 127.3 (q), 126.4, 118.8, 65.9, 44.6, 40.0, 36.0.

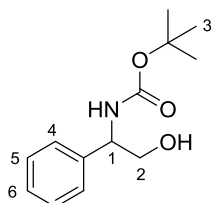
$\nu_{\max}$ (neat)/ cm^{-1} : 2922, 1723, 1673.

HRMS (m/z - DIP):* Found: 485.9972 ($\text{M}-\text{C}_2\text{H}_3$)⁺ $\text{C}_{21}\text{H}_{16}\text{Cl}_4\text{NO}_4$ Requires: 485.9828.

*Note: Error for HRMS is -11.6 ppm

10.4 Experimental data for section 3

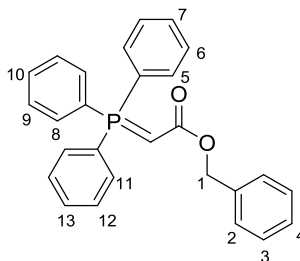
10.4.1 *tert*-Butyl (2-hydroxy-1-phenylethyl)carbamate (**420**)



Phenylglycine (5.0 g, 33.1 mmol) and NaBH_4 (3.0 g, 79.4 mmol) were dissolved in anhydrous THF (80 mL) under argon and was cooled to 0 °C. I_2 (8.4 g, 33.1 mmol) in THF (50 mL) was added slowly *via* dropping funnel. When the brown colour disappeared, the mixture was refluxed at 67 °C for 19 h followed by cooling to rt. MeOH was added dropwise with stirring until all precipitate had dissolved. The solution was concentrated *in vacuo* and was re-dissolved in a solution of KOH (20%, aq.) and was stirred for 6 h. The product was extracted with CH_2Cl_2 (x 3) and the combined organic extracts were washed with brine (x 2), dried over MgSO_4 , filtered and were concentrated *in vacuo* to furnish amino alcohol **419** (4.4 g, 31.8 mmol, 96%). **419** (4.4 g, 31.8 mmol) was re-dissolved in anhydrous THF (50 mL) under argon and NEt_3 (5.3 mL, 38.1 mmol) was added. The solution was cooled to 0 °C and $(\text{Boc})_2\text{O}$ (6.9 g, 31.8 mmol) was added. The mixture was stirred for 3 h followed by concentration *in vacuo*. The crude product was re-dissolved in CH_2Cl_2 (50 mL) and was washed with HCl (1M, aq., x2). The resulting organic layer was dried over MgSO_4 , filtered and the filtrate concentrated *in vacuo* to furnish the *N*-Boc amino alcohol **420** (7.2 g, 30.2 mmol) as white solid. M.p. 128-132 °C (lit²⁵⁵ 133-135 °C). Spectral data for this compound were consistent with those in the literature.²⁵⁶

δ_{H} (400 MHz, CHCl_3): 7.41-7.23 (5H, m, H-4, H-5, H-6), 5.26-5.07 (1H, m, NH), 4.83-4.69 (1H, m, H-1), 3.90-3.77 (2H, m, H-2), 1.41 (9H, s, H-3).

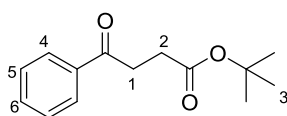
10.4.2 1-(Benzyloxy)-3-(triphenyl-*l*-5-phosphanyliden)propan-2-one (**422**)



PPh₃ (3.0 g, 19.1 mmol) was dissolved in EtOAc (30 mL) and solution of bromobenzyl acetate (3.0 mL, 19.0 mmol) in EtOAc (10 mL) was added slowly *via* dropping funnel. The reaction mixture was stirred for 16 h. The precipitate was filtered and dissolved in NaOH (1N, aq., 30 mL) and the solution was stirred for 20 min. The product was extracted with CH₂Cl₂ (x3) and the combined organic extracts were dried over MgSO₄, filtered and the filtrate was concentrated *in vacuo* to furnish **422** as a white solid (7.5 g, 96%). M.p. 117-119 °C (lit.²⁵⁷ 115-120 °C). Spectral data for this compound were consistent with those in the literature.²⁵⁷

δ_{H} (400 MHz, DMSO-D₆): 7.69-7.45 (20H, m, H-2, H-3, H-4, H-5, H-6, H-7, H-8, H-9, H-10, H-11, H-12, H-13), 7.72 (2H, s, H-1).

10.4.3 *tert*-Butyl 5-oxo-5-phenylpentanoate (**428**)

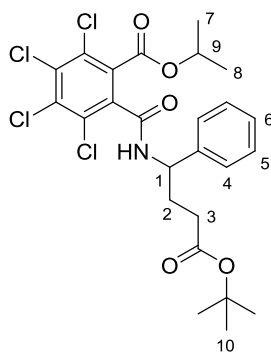


427 (2.5 g, 14.0 mmol), DMAP (513 mg, 4.2 mmol), and DCC (3.42 g, 16.8 mmol) were dissolved in anhydrous CH₂Cl₂ (33 mL) and were cooled to 0 °C. *tert*-Butanol (5.3 mL, 56.0 mmol) was added *via* syringe. The mixture was warmed to rt and was stirred for 16 h. The resulting suspension was filtered and washed with CH₂Cl₂. The filtrate was purified *via* silica chromatography, eluting with 7% EtOAc in hexane to furnish **428** (3.2 g, 97%) as a colourless oil. Spectral data for this compound were consistent with those in the literature.²⁵⁸

δ_{H} (400 MHz, CHCl₃): 7.99-7.94 (2H, m, H-4), 7.59-7.52 (1H, m, H-6), 7.48-7.41 (2H, m, H-5), 3.24 (2H, t, *J* 6.7, H-1), 2.67 (2H, t, *J* 6.7, H-2), 1.43 (9H, s, H-3).

HRMS (*m/z* - ESI): Found: 235.1335 (M+H)⁺ C₁₄H₁₈O₃ Requires: 235.1334.

10.4.4 *iso*Propyl-2-((4-(*tert*-butoxy)-4-oxo-1-phenylbutyl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (**432**)



428 (3.8 g, 16.2 mmol) was dissolved in Et₂O (30 mL) and was cooled to 0 °C. NEt₃ (6.8 mL, 48.5 mmol) was added followed by benzyl amine (2.1 mL, 19.4 mmol) and TiCl₄ (1.0 mL, 9.7 mmol).

The reaction was allowed to warm to rt and was stirred for 16 h. The resulting precipitate was filtered and the filtrate was concentrated *in vacuo* to furnish the imine product **429** (4.7 g, 90%) as a colourless oil. **429** (4.7 g, 14.6 mmol) was re-dissolved in MeOH (30 mL) and was cooled to 0 °C. NaBH₄ (718 mg, 19.0 mmol) was added portion-wise and the reaction mixture was stirred for 1 h. H₂O (15 mL) was added and the product was extracted with CH₂Cl₂ (x3). The combined organic extracts were dried over MgSO₄ and were concentrated *in vacuo* to furnish the secondary amine **430** (4.4 g, 93%). **430** (4.4 g, 13.6 mmol) was dissolved in MeOH (28 mL) under argon atmosphere. Pd/C (10 wt.%, 2.8 g, 2.7 mmol) was added and the flask was evacuated and purged with argon (x 3) and on the final evacuation of the flask a septum and hydrogen balloon were fitted. The reaction mixture was stirred vigorously for 16 h. This mixture was filtered *via* suction filtration and the filtrate was concentrated *in vacuo* to furnish **431** (3.2 g, 13.4 mmol, 99%) as a white solid. To this **296** (5.6 g, 16.1 mmol) and DCC (3.3 g, 16.1 mmol) were added. The flask was purged with argon and a septum with a balloon of argon was fitted. Anhydrous CH₂Cl₂ (32 mL) was added *via* syringe at 0 °C. The mixture was warmed to rt and was stirred for 16 h. The resulting suspension was filtered *via* suction filtration and the filtrate was purified *via* silica chromatography, eluting with a gradient of 5-10% EtOAc in hexane to furnish **432** (4.3 g, 54%) as a colourless oil.

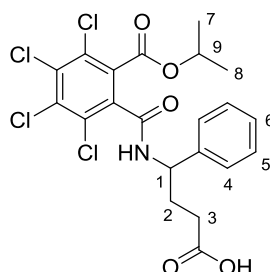
δ_{H} (400 MHz, CHCl₃): 7.37-7.25 (5H, m, H-4, H-5, H-6), 6.54 (1H, d, *J* 7.7, NH), 5.12-4.94 (2H, m, H-1, H-9), 2.41-2.03 (4H, m, H-2, H-3), 1.39 (9H, s, H-10), 1.21 (3H, d, *J* 6.1, H-7), 1.13 (3H, d, *J* 6.1, H-8).

δ_{C} (100 MHz, CHCl₃): 172.7 (C=O), 163.4 (C=O), 162.3 (C=O), 140.7 (q), 134.8 (q), 134.6 (q), 134.5 (q), 132.6 (q), 129.9 (q), 129.7 (q), 128.7, 127.7, 126.7, 80.8 (q), 71.3, 54.3, 32.2, 30.9, 27.9, 21.4, 21.2.

ν_{max} (neat)/cm⁻¹: 3263, 2980, 2901, 1726, 1644.

HRMS (*m/z* - APCI): Found: 562.0705 (M + H)⁺ C₂₁H₁₉Cl₅NO₅ Requires: 562.0716

10.4.5 4-Phenyl-4-(2,3,4,5-tetrachloro-6-(isopropoxycarbonyl)benzamido)butanoic acid (**433**)



Prepared according to **General procedure D** using **432** (834 mg, 1.4 mmol), TFA (2.5 mL) and anhydrous CH₂Cl₂ (2.5 mL) to yield **433** (820 mg, 99%) as a white solid. M.p. 157-160 °C.

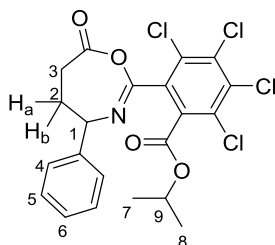
δ_{H} (400 MHz, DMSO- D_6): 12.09 (1H, bs, OH), 9.18 (1H, d, J 8.12, NH), 7.37-7.18 (5H, m, H-4, H-5, H-6), 4.95-4.84 (2H, m, H-1, H-9), 2.33-1.82 (4H, m, H-2, H-3), 1.12-1.03 (6H, m, H-7, H-8).

δ_{C} (100 MHz, DMSO- D_6): 177.0 (C=O), 163.7 (C=O), 162.5 (C=O), 140.0 (q), 135.0 (q), 134.9 (q), 134.2 (q), 132.7 (q), 129.9 (q), 129.9 (q), 128.9, 128.0, 126.7, 71.5, 54.0, 30.6, 30.5, 21.4, 21.3.

ν_{max} (neat)/ cm^{-1} : 3243, 2987, 1726, 1702, 1646.

HRMS (m/z - APCI): Found: 539.9111 ($\text{M}+\text{Cl}$) $^-$ $\text{C}_{21}\text{H}_{19}\text{Cl}_5\text{NO}_5$ Requires: 539.9711.

10.4.6 *iso*Propyl-2,3,4,5-tetrachloro-6-(7-oxo-4-phenyl-4,5,6,7-tetrahydro-1,3-oxazepin-2-yl)benzoate (410)



Prepared according to **General Procedure F** using **433** (630 mg, 1.3 mmol), CH_2Cl_2 (3.0 mL), NEt_3 (191 μL , 1.4 mmol), SOCl_2 (99 μL , 1.4 mmol) and a second aliquot of NEt_3 (380 μL , 2.7 mmol). The reaction mixture was stirred for 24 h. The crude product was passed through as silica plug, eluting with 30% EtOAc in hexane to furnish **410** (126 mg, 20%) as an orange oil.

δ_{H} (400 MHz, CHCl_3): 7.48-7.21 (5H, m, H-4, H-5, H-6), 5.49-5.43 (1H, m, H-1), 2.24 (1H, sept., J 6.4, H-9), 2.88-2.52 (3H, m, H-2a, H-3), 2.17-2.08 (1H, m, H-2b), 1.40 (3H, d, J 6.4, H-7), 1.36 (2H, d, J 6.4, H-8).

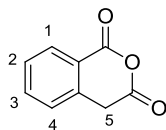
δ_{C} (100 MHz, CHCl_3): 174.7 (C=O), 163.7 (C=O), 140.7 (C=N), 140.3 (q), 135.4 (q), 135.2 (q), 134.4 (q), 130.1 (q), 129.4 (q), 128.8, 128.0, 125.8, 71.2, 60.5, 31.2, 27.6, 21.7, 21.5.

ν_{max} (neat)/ cm^{-1} : 1755, 1729, 1685, 1258.

HRMS (m/z - APCI): Found: 487.9995 ($\text{M}+\text{H}$) $^+$ $\text{C}_{21}\text{H}_{18}\text{Cl}_4\text{NO}_5$ Requires: 487.9944.

10.5 Experimental data for section 4

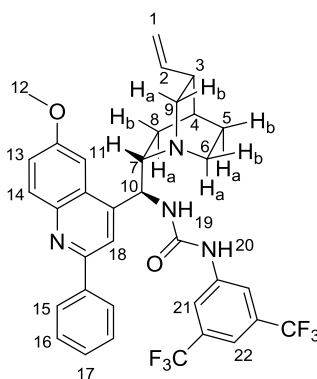
10.5.1 Homophthalic anhydride (159)



Homophthalic acid (4.0 g, 22.2 mmol) was dissolved in acetic anhydride (30.0 mL) and was heated 80 °C for 2 h. The reaction mixture was concentrated *in vacuo* and the resulting solid was triturated with Et₂O (15.0 mL), filtered and dried to obtain homophthalic anhydride as a white solid (3.2 g, 85%). M.p. 140-144 °C.¹³⁶

δ_{H} (400 MHz, DMSO-*d*₆): 8.05 (1H, d, *J* 8.2, H-1), 7.75 (1H, m, H-3), 7.52 (1H, m, H-2), 7.44 (1H, d, *J* 7.8, H-4), 4.27 (1H, s, H-5).

10.5.2 1-(3,5-bis(trifluoromethyl)phenyl)-3-((S)-(6-methoxy-2-phenylquinolin-4-yl))((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)urea (205)



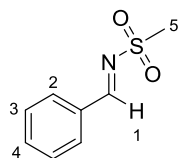
332 (1.0 g, 2.5 mmol) was dissolved in anhydrous CH₂Cl₂ (20.0 mL) under argon and was cooled to 0 °C. Trifluoromethylphenyl isocyanate (**455**, 520 μ L, 3.0 mmol) and the reaction was stirred at 0 °C to room temperature for 16 h. The solvent was removed *in vacuo* and the crude residue was purified by silica chromatography, eluting with 5% MeOH in CH₂Cl₂ to yield **205** as a white solid (1.2 g, 73%).¹³⁶ M.p. 152-153 °C. [α]_D²⁰ = +14.8 (*c* 0.6 CHCl₃).

δ_{H} (400 MHz, CDCl₃): 8.37 (1H, bs, H-20), 8.19-8.15 (3H, m, H-14, H-15), 7.90-7.75 (4H, m, H-18, H-22, H-21), 7.56-7.36 (4H, m, H-13, H-16, H-17), 7.02 (s, H-11), 6.75 (1H, m, H-10), 5.78 (1H, bs, H-19), 5.60-5.51 (1H, m, H-2), 4.93-4.88 (2H, m, H-1), 4.05 (3H, s, H-12), 3.68-3.54 (2H, m, H-6a, H-7), 3.08 (1H, m, H-9a), 2.75-2.73 (1H, m, H-6a), 2.52-2.50 (1H, m, H-6b, H-9b), 2.33 (1H, m, H-3), 1.79-1.70 (4H, m, H-4, H-5a, H-5b, H-8a), 1.09-1.06 (1H, m, H-8b).

10.5.3 General procedure L: Sulfonyl imine synthesis

The appropriate aldehyde (1.0 equiv.) was dissolved in anhydrous CH_2Cl_2 under argon and was cooled to 0 °C. NEt_3 (3.0 equiv.) and methyl sulfonamide (1.0 equiv.) were added followed by TiCl_4 (0.5 equiv.). The reaction mixture was stirred for 1 h followed by filtration through celite. The filtrate was concentrated *in vacuo* and the resulting material was re-dissolved in toluene and was filtered. The filtrate was concentrated *in vacuo* and the product was recrystallised using a mixture of hexane and CH_2Cl_2 .

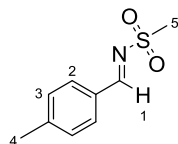
10.5.3.1 (E)-N-Benzylidenemethanesulfonamide (452)



Prepared according to **General Procedure L** using methanesulfonamide (1.0 g, 10.0 mmol), NEt_3 (4.2 mL, 30.0 mmol), benzaldehyde (1.2 mL, 10.0 mmol) in anhydrous CH_2Cl_2 (25 mL) and TiCl_4 (0.6 mL, 5.0 mmol). The product was purified by recrystallization from CH_2Cl_2 :hexane to afford **452** as an off-white solid (695 mg, 36%).¹³⁶ M.p. 92-93 °C.

δ_{H} (400 MHz, CDCl_3): 9.04 (1H, s, H-1), 7.96 (2H, d, *J* 7.4, H-2), 7.64-7.68 (2H, m, H-3), 7.55 (1H, t, *J* 7.4, H-4), 3.14 (3H, s, H-5).

10.5.3.2 (E)-N-(4-Methylbenzylidene) methanesulfonamide (463)

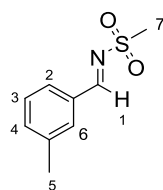


Prepared according to **General Procedure L** using methanesulfonamide (807 mg, 8.5 mmol), NEt_3 (3.5 mL, 25.4 mmol), 4-methyl-benzaldehyde (1.0 mL, 8.5 mmol) and TiCl_4 (0.5 mL, 4.3 mmol) in anhydrous CH_2Cl_2 (25 mL). The product was purified by recrystallisation from CH_2Cl_2 :hexane to afford **463** as a pale yellow solid (850 mg, 50%).¹³⁶

δ_{H} (400 MHz, CDCl_3): 9.02 (1H, s, H-1), 7.86 (2H, d, *J* 7.9, H-2), 7.35 (2H d, *J* 7.9, H-3), 3.15 (3H, s, H-5), 2.48 (3H, s, H-4).

HRMS (m/z-ESI): Found: 198.0580 ($\text{M}+\text{H}$)⁺ $\text{C}_9\text{H}_{12}\text{NO}_2\text{S}$ requires 198.0589.

10.5.3.3 (*E*)-*N*-(3-Methylbenzylidene) methanesulfonamide (**464**)

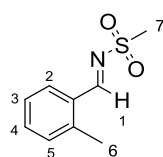


Prepared according to **General Procedure L** using methanesulfonamide (0.8 g, 8.5 mmol), NEt₃ (3.5 mL, 25.4 mmol), 3-methyl-benzaldehyde (1.0 mL, 8.5 mmol) and TiCl₄ (0.5 μ L, 4.3 mmol) in anhydrous CH₂Cl₂ (25 mL). The product was purified by vacuum distillation to afford **464** as a pale yellow oil (600 mg, 36%).¹³⁶

δ_{H} (400 MHz, CDCl₃): 9.03 (1H, s, H-1), 7.787.71 (2H, m, H-2, H-6), 7.50-7.38 (2H, m, H-3, H-4), 3.16 (3H, s, H-7), 2.46 (3H, s, H-5).

HRMS (m/z-ESI): Found 198.0595 (M+H)⁺ C₉H₁₂NO₂S requires 198.0589.

10.5.3.4 (*E*)-*N*-(2-Methylbenzylidene) methanesulfonamide (**465**)

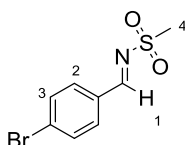


Prepared according to **General Procedure L** using methanesulfonamide (1.0 g, 10.0 mmol), NEt₃ (4.20 mL, 30.0 mmol), 2-methyl-benzaldehyde (1.1 mL, 10.0 mmol) and TiCl₄ (0.6 mL, 5.0 mmol) in anhydrous CH₂Cl₂ (25 mL). The product was purified by recrystallisation from CH₂Cl₂:hexane to afford **465** as a pale yellow solid (746 mg, 32%).¹³⁶

δ_{H} (400 MHz, CDCl₃): 8.82 (1H, s, H-1), 7.78-7.80 (1H, m, H-2), 7.46-7.27 (3H, m, H-3, H-4, H-5), 3.14 (3H, s, H-7), 2.62 (3H, s, H-6).

HRMS (m/z-ESI): Found 198.0594. (M+H)⁺ C₉H₁₂NO₂S requires 198.0589.

10.5.3.5 (*E*)-*N*-(4-Bromobenzylidene) methanesulfonamide (**466**)



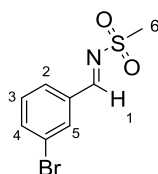
Prepared according to **General Procedure L** using methanesulfonamide (1.0 g, 10.0 mmol), NEt₃ (4.2 mL, 30.0 mmol), 4-bromobenzaldehyde (1.9 g, 10.0 mmol) and TiCl₄ (0.6 mL, 5.0 mmol) in

anhydrous CH₂Cl₂ (25 mL). The product was purified by recrystallisation from CH₂Cl₂:hexane to afford **466** as a pale yellow solid (940 mg, 34%).¹³⁶

δ_{H} (400 MHz, CDCl₃): 8.97 (1H, s, H-1), 7.82 (2H, d, *J* 7.4, H-3), 7.66 (2H, d, *J* 7.4, H-2), 3.16 (3H, s, H-4).

HRMS (m/z-ESI): Found 261.9530. (M+H)⁺ C₈H₉BrNO₂S. Requires 261.9532.

10.5.3.6 (E)-N-(3-Bromobenzylidene) methanesulfonamide (**467**)

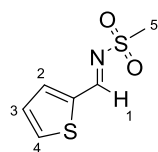


Prepared according to **General Procedure L** using methanesulfonamide (0.8 g, 8.6 mmol), NEt₃ (3.9 mL, 25.7 mmol), 3-bromo-benzaldehyde (1.0 mL, 8.6 mmol) and TiCl₄ (0.5 mL, 4.3 mmol) in anhydrous CH₂Cl₂ (25 mL). The product was purified by recrystallisation from CH₂Cl₂:hexane to afford **467** as a white solid (625 mg, 39%).¹³⁶

δ_{H} (400 MHz, CDCl₃): 9.01 (1H, s, H-1), 8.18 (1H, s, H-5), 7.89 (1H, d, *J* 7.9, H-4), 7.81 (1H, d, *J* 7.9, H-2), 7.46 (1H, t, *J* 7.9, H-3), 3.18 (3H, s, H-6).

HRMS (m/z-ESI): Found 261.9540. (M+H)⁺ C₈H₉NO₂SBr requires 261.9537.

10.5.3.7 (E)-N-(Thiophen-2-ylmethylene) methanesulfonamide (**468**)

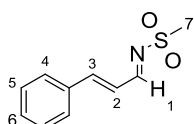


Prepared according to **General Procedure L** using methanesulfonamide (0.9 g, 10.0 mmol), NEt₃ (4.2 mL, 30.0 mmol), 2-thiophenecarbaldehyde (0.9 mL, 10.0 mmol) and TiCl₄ (0.6 mL, 5.0 mmol) in anhydrous CH₂Cl₂ (25 mL). The product was purified by recrystallisation from CH₂Cl₂:hexane to afford **468** as a pale yellow solid (643 mg, 34%).¹³⁶

δ_{H} (400 MHz, CDCl₃): 9.08 (1H, s, H-1), 7.79-7.83 (2H, m, H-2, H-4), 7.23-7.25 (1H, m, H-3), 3.11 (3H, s, H-5).

HRMS (m/z-ESI): Found 189.9998. (M+H)⁺ C₆H₈NO₂S₂ requires 189.9996.

10.5.3.8 *N*-((1*E*,2*E*)-3-Phenylallylidene) methanesulfonamide (**469**)



Prepared according to **General Procedure L** using methanesulfonamide (0.8 g, 7.9 mmol), NEt₃ (3.3 mL, 23.7 mmol), cinammaldehyde (1.0 mL, 7.9 mmol) and TiCl₄ (0.4 mL, 4.0 mmol) in anhydrous CH₂Cl₂ (25.0 mL). The product was purified by recrystallisation from CH₂Cl₂:hexane to afford **469** as a pale yellow solid (0.7 g, 42%).¹³⁶

δ_{H} (400 MHz, CDCl₃): 8.79 (1H, d, *J* 9.5, H-1), 7.63-7.46 (6H, m, H-3, H-4, H-5, H-6), 7.03 (1H, dd, *J* 9.5, 15.8, H-2), 3.11 (3H, s, H-7).

HRMS (*m/z*-ESI): Found 210.0582. (M+H)⁺ C₁₀H₁₂NO₂S requires 210.0589.

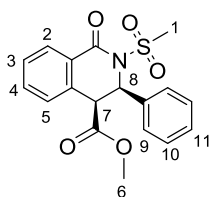
10.5.4 General procedure M: protocol for the preparation of racemic lactams via annulation reactions between K1 and imines.

The appropriate imine (0.25 mmol) was dissolved in anhydrous MTBE (2.50 mL, 0.1 M) under an atmosphere of argon. Anhydride **159** (39.90 mg, 0.25 mmol) was added to the reaction followed by *N,N*-diisopropylethylamine (4.30 μ L, 0.02 mmol, 10 mol%) and the resulting mixture was stirred for 24 h at room temperature. The reaction mixture containing the corresponding carboxylic acids was placed at -30 °C and anhydrous EtOH (220 μ L), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150 μ L, 0.30 mmol) were added *via* syringe and the reaction was allowed to stir for exactly 30 min at -30 °C. The solvent was then concentrated *in vacuo* at room temperature and the crude mixture of diastereomeric esters was purified immediately by flash chromatography to isolate the racemic diastereomers.

10.5.5 General procedure N: Asymmetric cycloaddition reaction of imines with homophthalic anhydride (**159**)

Anhydride **159** (39.90 mg, 0.25 mmol) was dissolved in anhydrous MTBE (2.5 mL) under an atmosphere of argon and the reaction mixture was then cooled to -30 °C. The appropriate imine (0.25 mmol) was added followed by catalyst **205** (8.20 mg, 0.01 mmol, 5 mol%) and the reaction was stirred at -30 °C until completion. The conversion of the reaction was determined by ¹H NMR spectroscopic analysis using *p*-iodoanisole (28.80 mg, 0.12 mmol) as an internal standard. To the reaction mixture containing the diastereomeric mixture of carboxylic acid lactam products, anhydrous EtOH (220 μ L), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 150 μ L, 0.30 mmol) were added *via* syringe and the reaction was allowed to stir for exactly 30 min at -30 °C. The solvent was then removed *in vacuo* at room temperature and the crude mixture of diastereomeric esters was purified immediately by column chromatography.

10.5.5.1 *syn*-Methyl-2-(methylsulfonyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*syn*-453)



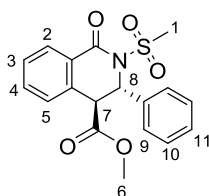
Prepared according to **General Procedure N** using anhydride **159** (39.90 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **452** (48.50 mg, 0.25 mmol) and catalyst **205** (8.20 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 48 h to give a diastereomeric mixture of carboxylic acids in a 64:36 ratio (*anti:syn*). After esterification, the diastereomer **syn-453** was purified by column chromatography, eluting with 30% EtOAc in hexane. The product was isolated as a white solid (24 mg, 27%, 27% ee).¹³⁶ M.p. 156-158 °C. $[\alpha]_D^{20} = -34.0$ (c 0.05, acetone).

CSP-HPLC analysis, Chiralcel AD (4.6 mm x 25 cm), hexane/IPA: 70/30, 1 mL min⁻¹, RT, UV detection at 254 nm, retention times: 8.9 min and 10.1 min.

δ_H (400 MHz, CDCl₃): 8.30 (1H, d, *J* 7.9, H-2), 7.62-7.49 (3H, m, H-3, H-4, H-5), 7.27-7.17 (3H, m, H-10, H-11), 7.01 (2H, d, *J* 7.2, H-9), 6.07 (1H, d, *J* 6.2, H-8), 4.88 (1H, d, *J* 6.2, H-7), 3.07 (3H, s, H-1), 3.67 (3H, s, H-6).

HRMS (m/z-ESI): Found: 360.0904 (M+H)⁺ C₁₈H₁₈NO₅S Requires: 360.0906.

10.5.5.2 *anti*-Methyl-2-(methylsulfonyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*anti*-453)



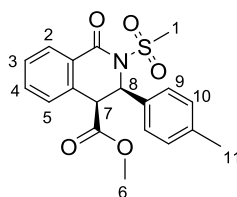
Prepared according to **General Procedure N** using anhydride **159** (39.90 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **452** (48.50 mg, 0.25 mmol) and catalyst **205** (8.20 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 48 h to give a diastereomeric mixture of carboxylic acids in a 64:36 ratio (*anti:syn*). After esterification, the diastereomer **anti-453** was purified by column chromatography, eluting with 30% EtOAc in hexane. The product was isolated as a white solid (42 mg, 47%, 70% ee).¹³⁶ M.p. 130-135 °C. $[\alpha]_D^{20} = 15.3$ (c 0.15, acetone).

CSP-HPLC analysis, Chiralcel AD (4.6 mm x 25 cm), hexane/IPA: 70/30, 1 mL min⁻¹, RT, UV detection at 254 nm, retention times: 18.2 min and 30.1 min.

δ_{H} (400 MHz, CDCl₃): 8.18 (1H, d, *J* 7.9, H-2), 7.51-7.45 (2H, m, H-3, H-4), 7.25-7.14 (6H, m, H-5, H-9, H-10, H11), 6.22 (1H, app. s, H-8), 4.12 (1H, app. s, H-7), 3.74 (3H, s, H-1), 3.45 (3H, s, H-6).

HRMS (m/z-ESI): Found: 360.0904 (M+H)⁺ C₁₈H₁₈NO₅S Requires: 360.0906.

10.5.5.3 *syn*-Methyl-2-(methanysulfonyl)-1-oxo-3-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*syn*-470)



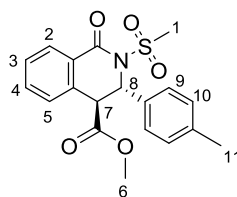
Prepared according to **General Procedure N** using anhydride **159** (39.90 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **463** (48.50 mg, 0.25 mmol) and catalyst **205** (8.20 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 180 h to give a diastereomeric mixture of carboxylic acids in a 53:47 ratio (*anti:syn*). After esterification, the diastereomer **syn**-470 was purified by column chromatography, eluting with 30% EtOAc in hexane. The product was isolated as a white solid (37 mg, 40%, 34% *ee*).¹³⁶ M.p. 140-142°C. [α]_D²⁰ = 50 (*c* 0.07, acetone).

CSP-HPLC analysis, Chiralcel ODH (4.6 mm x 25 cm), hexane/IPA: 90/10, 1 mL min⁻¹, RT, UV detection at 254 nm, retention times: 23.0 min and 33.7 min.

δ_{H} (400 MHz, CDCl₃): 8.29 (1H, dd, *J* 1.1, 7.8, H-2), 7.63-7.48 (3H, m, H-4, H-5, H-6), 6.99-6.87 (4H, m, H-9, H-10), 6.03, (1H, d, *J* 6.3, H-8), 4.85 (1H, d, *J* 6.3, H-7), 3.68 (3H, s, H-1), 3.07 (3H, s, H-6), 2.23 (3H, s, H-11).

HRMS (m/z-ESI): Found: 372.0917. (M+H)⁺ C₁₉H₁₈NO₅S Requires: 372.0906.

10.5.5.4 *anti*-Methyl-2-(methanesulfonyl)-1-oxo-3-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*anti*-470)



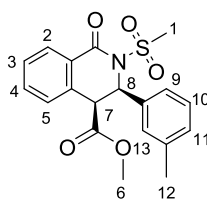
Prepared according to **General Procedure N** using anhydride **159** (39.90 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **463** (48.50 mg, 0.25 mmol) and catalyst **205** (8.20 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 180 h to give a diastereomeric mixture of carboxylic acids in a 53:47 ratio (*anti*:*syn*). After esterification, the diastereomer **anti-470** was purified by column chromatography, eluting with 30% EtOAc in hexane. The product was isolated as a white solid (43 mg, 47%, 74% *ee*).¹³⁶ M.p. 170-173°C. $[\alpha]^{20}_D = 36.0$ (c 0.20, acetone).

CSP-HPLC analysis, Chiralcel ODH (4.6 mm x 25 cm), hexane/IPA: 90/10, 1 mL min⁻¹, RT, UV detection at 254 nm, retention times: 29.9 min and 33.6 min.

δ_H (400 MHz, CDCl₃): 8.15 (1H, dd, *J* 1.5, 7.6, H-2), 7.50-7.41 (2H, m, H-3, H-4), 7.21-7.20 (1H, m, H-5), 7.02 (4H, app. s, H-9, H-10), 6.17, (1H, d, *J* 1.5, H-8), 4.09 (1H, d, *J* 1.5, H-7), 3.73 (3H, s, H-1), 3.42 (3H, s, H-6), 2.22 (3H, s, H-11).

HRMS (m/z-ESI): Found: 372.0917. (M+H)⁺ C₁₉H₁₈NO₅S Requires: 372.0906.

10.5.5.5 *syn*-Methyl-2-(methanesulfonyl)-1-oxo-3-(*m*-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*syn*-471)



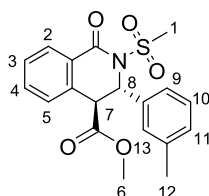
Prepared according to **General Procedure N** using anhydride **159** (39.90 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **464** (48.50 mg, 0.25 mmol) and catalyst **205** (8.20 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 144 h to give a diastereomeric mixture of carboxylic acids in a 59:41 ratio (*anti*:*syn*). After esterification, the diastereomer **syn-471** was purified by column chromatography, eluting with 30 % EtOAc in hexane. The product was isolated as a white solid (28 mg, 31%, 36% *ee*).¹³⁶ M.p. 117-120°C. $[\alpha]^{20}_D = 2.3$ (c 0.15, acetone).

CSP-HPLC analysis, Chiralcel ODH (4.6 mm x 25 cm), hexane/IPA: 90/10, 1 mL min⁻¹, RT, UV detection at 254 nm, retention times: 24.6 min and 33.7 min.

δ_H (400 MHz, CDCl₃): 8.29 (1H, dd, *J* 1.0, 7.7, H-2), 7.63-7.47 (3H, m, H-3, H-4, H-5), 7.04-7.05 (2H, m, H-9, H-10), 6.81-6.75 (2H, m, H-11, H-13), 6.02, (1H, d, *J* 6.3, H-8), 4.86 (1H, d, *J* 6.3, H-7), 3.68 (3H, s, H-1), 3.08 (3H, s, H-6), 2.20 (3H, s, H-12).

HRMS (m/z-ESI): Found: 372.0910. (M+H)⁺ C₁₉H₁₈NO₅S Requires: 372.0906.

10.5.5.6 *anti*-Methyl-2-(methylsulfonyl)-1-oxo-3-(*m*-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*anti*-471)



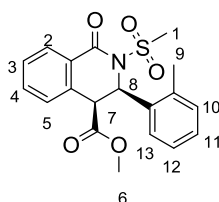
Prepared according to **General Procedure N** using anhydride **159** (39.90 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **464** (48.50 mg, 0.25 mmol) and catalyst **205** (8.20 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 144 h to give a diastereomeric mixture of carboxylic acids in a 59:41 ratio (*syn:anti*). After esterification, the diastereomer ***anti*-471** was purified by column chromatography, eluting with 30% EtOAc in hexane. The product was isolated as a white solid (44 mg, 48%, 70% *ee*).¹³⁶ M.p. 157-160°C. [α]_D²⁰ = 14.1 (c 0.27, acetone).

CSP-HPLC analysis, Chiralcel ODH (4.6 mm x 25 cm), hexane/IPA: 90/10, 1 mL min⁻¹, RT, UV detection at 254 nm, retention times: 28.2 min and 31.3 min.

δ_H (400 MHz, CDCl₃): 8.15 (1H, dd, *J* 1.2, 7.5, H-2), 7.51-7.42 (2H, m, H-3, H-4), 7.22-7.20 (1H, m, H-5), 7.10-6.88 (4H, m, H-9, H-10, H-11, H-13), 6.16, (1H, d, *J* 1.4, H-8), 4.11 (1H, d, *J* 1.4, H-7), 3.73 (3H, s, H-1), 3.44 (3H, s, H-6), 2.23 (3H, s, H-12).

HRMS (m/z-ESI): Found: 372.0910. (M-H)⁻ C₁₉H₁₈NO₅S requires 372.0906.

10.5.5.7 *syn*-Methyl-2-(methylsulfonyl)-1-oxo-3-(*o*-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*syn*-472)



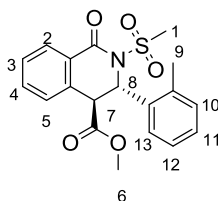
Prepared according to **General Procedure N** using anhydride **159** (39.90 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **465** (48.50 mg, 0.25 mmol) and catalyst **205** (8.20 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 180 h to give a diastereomeric mixture of carboxylic acids in a 53:47 ratio (*anti:syn*). After esterification, the diastereomer **syn-472** was purified by column chromatography, eluting with 30% EtOAc in hexane. The product was isolated as a white solid (33 mg, 36%, 25% *ee*).¹³⁶ M.p. 175-178 °C. $[\alpha]_D^{20} = 9.3$ (c 0.14, acetone).

CSP-HPLC analysis, Chiralcel ODH (4.6 mm x 25 cm), hexane/IPA: 90/10, 1 mL min⁻¹, RT, UV detection at 254 nm, retention times: 26.6 min and 42.0 min.

δ_H (400 MHz, CDCl₃): 8.33 (1H, d, *J* 7.7, H-2), 7.59-7.48 (2H, m, H-3, H-4), 7.28-7.12 (3H, m, H-5, H-10, H-12), 6.91-6.83 (2H, m, H-11, H-13), 6.36 (1H, d, *J* 6.8, H-8), 4.93 (1H, d, *J* 6.8, H-7), 3.63 (3H, s, H-1), 2.99 (3H, s, H-6), 2.40 (3H, s, H-9).

HRMS (m/z-ESI): Found: 373.1067. (M+H)⁺ C₁₉H₁₉NO₅S Requires: 373.1062.

10.5.5.8 *anti*-Methyl-2-(methanesulfonyl)-1-oxo-3-(*o*-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*anti*-472)



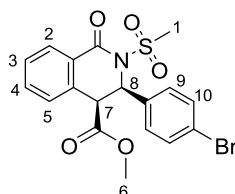
Prepared according to **General Procedure N** using anhydride **159** (39.90 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **465** (48.50 mg, 0.25 mmol) and catalyst **205** (8.20 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 180 h to give a diastereomeric mixture of carboxylic acids in a 53:47 ratio (*anti:syn*). After esterification, the diastereomer **anti-472** was purified by column chromatography, eluting with 30% EtOAc in hexane. The product was isolated as a colourless oil (39 mg, 42%, 33% *ee*).¹³⁶ $[\alpha]_D^{20} = -3.2$ (c 0.05, acetone).

CSP-HPLC analysis, Chiralcel ODH (4.6 mm x 25 cm), hexane/IPA: 90/10, 1 mL min⁻¹, RT, UV detection at 254 nm, retention times: 21.30 min and 30.9 min.

δ_H (400 MHz, CDCl₃): 8.15 (1H, d, *J* 7.8, H-2), 7.51-7.41 (2H, m, H-3, H-4), 7.22-7.20 (1H, m, 5-H), 7.00-6.99 (4H, m, H-10, H-11, H-12, H-13), 6.18 (1H, app. s, H-8), 4.11 (1H, app. s, H-7), 3.72 (3H, s, H-1), 3.42 (3H, s, H-6), 2.22 (3H, s, H-9).

HRMS (m/z-ESI): Found: 373.1067. (M+H)⁺ C₁₉H₁₉NO₅S Requires: 373.1062.

10.5.5.9 *syn*-Methyl 3-(4-bromophenyl)-2-(methylsulfonyl)1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*syn*-473)



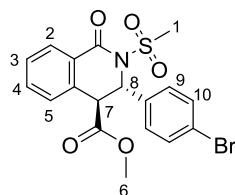
Prepared according to **General Procedure N** using anhydride **159** (39.90 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **466** (64.50 mg, 0.25 mmol) and catalyst **205** (8.20 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 17 h to give a diastereomeric mixture of carboxylic acids in a 66:34 ratio (*anti*:*syn*). After esterification, the diastereomer ***syn*-473** was purified by column chromatography eluting with 30% EtOAc in hexane. The product was isolated as a colourless oil (28 mg, 30%, 4% *ee*).¹³⁶ $[\alpha]_{\text{D}}^{20} = 14.3$ (*c* 0.14, acetone).

CSP-HPLC analysis, Chiralcel AD (4.6 mm x 25 cm), hexane/IPA: 70/30, 1 mL min⁻¹, RT, UV detection at 254 nm, retention times: 10.4 min and 13.1 min.

δ_{H} (400 MHz, CDCl₃): 8.28 (1H, d, *J* 7.4, H-2), 7.65-7.50 (3H, m, H-3, H-10), 7.33-7.31 (2H, m, H-3, H-4), 6.90-6.87 (2H, m, H-9), 6.03 (1H, d, *J* 6.2, H-8), 4.86 (1H, d, *J* 6.2, H-7), 3.70 (3H, s, H-6), 3.14 (3H, s, H-1).

HRMS (*m/z*-ESI): Found: 438.0014. $[\text{M}+\text{H}]^+ \text{C}_{18}\text{H}_{17}\text{NO}_5\text{SBr}$ Requires: 438.0011.

10.5.5.10 *anti*-Methyl-3-(4-bromophenyl)-2-(methylsulfonyl)1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*anti*-473)



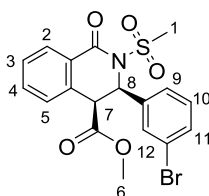
Prepared according to **General Procedure N** using anhydride **159** (39.90 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **466** (64.50 mg, 0.25 mmol) and catalyst **205** (8.20 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 17 h to give a diastereomeric mixture of carboxylic acids in a 66:34 ratio (*anti*:*syn*). After esterification, the diastereomer ***anti*-473** was purified by column chromatography, eluting with 30% EtOAc in hexane. The product was isolated as a white solid (60 mg, 55%, 61% *ee*).¹³⁶ M.p. 178-181 °C. $[\alpha]_{\text{D}}^{20} = 29.4$ (*c* 0.35, acetone).

CSP-HPLC analysis, Chiralcel AD (4.6 mm x 25 cm), hexane/IPA: 70/30, 1 mL min⁻¹, RT, UV detection at 254 nm, retention times: 32.7 min and 37.4 min.

δ_{H} (400 MHz, CDCl₃): 8.15 (1H, d, *J* 7.7, H-2), 7.53-7.42 (2H, m, H10), 7.36 (2H, d, *J* 8.2, H-3, H-4), 7.22 (1H, d, *J* 7.2, H-5), 7.03 (2H, d, *J* 8.2, H-9), 6.15 (1H, app. s, H-8), 4.07 (1H, app. s, H-7), 3.73 (3H, s, H-1), 3.46 (3H, s, H-6).

HRMS (m/z-ESI): Found: 438.0014. (M+H)⁺ C₁₈H₁₇NO₅SBr Requires: 438.0011.

10.5.5.11 *syn*-Methyl 3-(3-bromophenyl)-2-(methanesulfonyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*syn*-474)



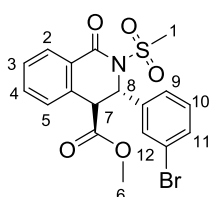
Prepared according to **General Procedure N** using anhydride **159** (39.90 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **467** (64.50 mg, 0.25 mmol) and catalyst **205** (8.20 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 17 h to give a diastereomeric mixture of carboxylic acids in a 61:39 ratio (*anti*:*syn*). After esterification, the diastereomer **syn-474** was purified by column chromatography, eluting with 30% EtOAc in hexane. The product was isolated as a white solid (28 mg, 26%, 3% *ee*).¹³⁶ M.p. 157-160°C. [α]_D²⁰ = 78.0 (c 0.10, acetone).

CSP-HPLC analysis, Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1 mL min⁻¹, RT, UV detection at 254 nm, retention times: 20.2 min and 23.4 min.

δ_{H} (400 MHz, CDCl₃): 8.28 (1H, m, H-2), 7.65-7.37 (4H, m, H-4, H-5, H-11, H-12), 7.18 (1H, m, H-9), 7.05 (1H, t, *J* 7.9, H-10), 6.91-6.89 (1H, m, H-3), 6.02 (1H, d, *J* 6.2, H-8), 6.02, (1H, d, *J* 6.2, H-7), 3.71 (3H, s, H-1), 3.16 (3H, s, H-6).

HRMS (m/z-ESI): Found: 438.0005. (M+H)⁺ C₁₈H₁₇NO₅SBr Requires: 438.0011.

10.5.5.12 *anti*-Methyl-3-(3-bromophenyl)-2-(methanesulfonyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*anti*-474)



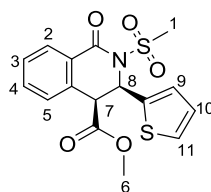
Prepared according to **General Procedure N** using anhydride **159** (39.90 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **467** (64.50 mg, 0.25 mmol) and catalyst **205** (8.20 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 17 h to give a diastereomeric mixture of carboxylic acids in a 61:39 ratio (*anti:syn*). After esterification, the diastereomer **anti-474** was purified by column chromatography, eluting with 30% EtOAc in hexane. The product was isolated as a white solid (55 mg, 51%, 69% *ee*).¹³⁶ M.p. 180-182°C. $[\alpha]^{20}_D = 18.5$ (c 0.13, acetone).

CSP-HPLC analysis, Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1 mL min⁻¹, RT, UV detection at 254 nm, retention times: 43.7 min and 53.3 min.

δ_H (400 MHz, CDCl₃): 8.15 (1H, dd, *J* 1.3, 7.6, H-2), 7.54-7.44 (2H, m, H-11, H-12), 7.34-7.32 (2H, m, H-4, H-5), 7.24-7.22 (2H, m, H-9, H-10), 7.10-7.04 (1H, m, H-3), 6.16, (1H, d, *J* 1.4, H-8), 4.08 (1H, d, *J* 1.4, H-7), 3.73 (3H, s, H-1), 3.47 (3H, s, H-6).

HRMS (m/z-ESI): Found: 438.0005 (M+H)⁺ C₁₈H₁₇NO₅SBr Requires: 438.0011.

10.5.5.13 *syn*-Methyl-2-(methylsulfonyl)-1-oxo-3-(thiophen-2-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*syn*-475)



Prepared according to **General Procedure N** using anhydride **159** (39.90 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **468** (48.50 mg, 0.25 mmol) and catalyst **205** (8.20 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 264 h to give a diastereomeric mixture of carboxylic acids in a 63:35 ratio (*anti:syn*). After esterification, the diastereomer **syn-475** was purified by column chromatography, eluting with 30% EtOAc in hexane. The product was isolated as a colourless oil (21 mg, 23%, 50% *ee*).¹³⁶ $[\alpha]^{20}_D = 34.0$ (c 0.10, acetone).

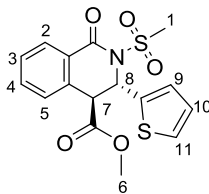
CSP-HPLC analysis, Chiralcel AD (4.6 mm x 25 cm), hexane/IPA: 95/5, 1 mL min⁻¹, RT, UV detection at 254 nm, retention times: 6.4 min and 12.0 min.

δ_H (400 MHz, CDCl₃): 8.26 (1H, d, *J* 8.0, H-2), 7.74-7.72 (1H, m, H-4), 7.68-7.65 (1H, m, H-3), 7.53 (1H, m, H-11), 7.09-7.08 (1H, m, H-5), 6.92-6.91 (1H, m, H-10), 6.84-6.81 (1H, m, H-11), 6.40 (1H, d, *J* 5.6, H-8), 4.83 (1H, d, *J* 5.6, H-7), 3.74 (3H, s, H-1), 3.07 (3H, s, H-6).

HRMS (m/z-ESI):

Found: 388.0293. (M+H)⁺ C₁₆H₁₅NO₅S₂Na Requires: 388.0289.

10.5.5.14 *anti*-Methyl-2-(methylsulfonyl)-1-oxo-3-(thiophen-2-yl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*anti*-475)



Prepared according to **General Procedure N** using anhydride **159** (39.90 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **468** (48.50 mg, 0.25 mmol) and catalyst **205** (8.20 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 264 h to give a diastereomeric mixture of carboxylic acids in a 63:35 ratio (*anti*:*syn*). After esterification, the diastereomer ***anti*-475** was purified by column chromatography, eluting with 30% EtOAc in hexane. The product was isolated as a white solid (40 mg, 40%, 51% *ee*).¹³⁶ M.p. 106-109 °C. [α]_D²⁰ = 70.0 (*c* 0.24, acetone).

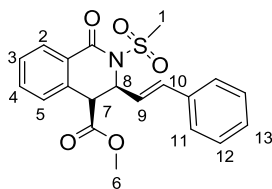
CSP-HPLC analysis, Chiralcel AD (4.6 mm x 25 cm), hexane/IPA: 95/5, 1 mL min⁻¹, RT, UV detection at 254 nm, retention times: 42.3 min and 48.1 min.

δ_H (400 MHz, CDCl₃): 8.15 (1H, d, *J* 8.1, H-2), 7.62-7.58 (1H, m, H-4), 7.53-7.49 (1H, m, H-3), 7.39 (1H, d, *J* 7.6, H-5), 7.08 (1H, dd, *J* 0.8, 5.2, H-11), 6.98 (1H, d, *J* 3.6, H-9), 6.84-6.80 (1H, m, H-10), 6.49 (1H, app. s, H-8), 4.21 (1H, app. s, H-7), 3.74 (3H, s, H-1), 3.36 (3H, s, H-6).

HRMS (m/z-ESI):

Found: 388.0293. (M+H)⁺ C₁₆H₁₅NO₅S₂Na requires 388.0289.

10.5.5.15 *syn*-Methyl-2-(methylsulfonyl)-1-oxo-3-((*E*)-styryl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*syn*-476)



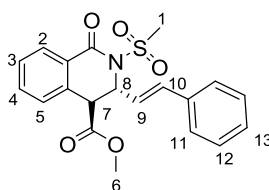
Prepared according to **General Procedure N** using anhydride **159** (39.9 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **469** (51.5 mg, 0.25 mmol) and catalyst **205** (8.2 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 72 h to give a diastereomeric mixture of carboxylic acids in a 17:81 ratio (*anti*:*syn*). After esterification, the diastereomer ***syn*-476** was purified by column chromatography, eluting with 30% EtOAc in hexane. The product was isolated as a white solid (62 mg, 65%, 35% *ee*).¹³⁶ M.p. 140-143 °C. [α]_D²⁰ = 44.4 (*c* 0.27, acetone).

CSP-HPLC analysis, Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1 mL min⁻¹, RT, UV detection at 254 nm, retention times: 19.2 min and 23.8 min.

δ_{H} (400 MHz, CDCl₃): 8.21 (1H, dd, *J* 1.1, 7.8, H-2), 7.65-7.46 (3H, m, H-3, H-4, H-5), 7.24-7.23 (5H, m, H-11, H-12, H-13), 6.70 (1H, d, *J* 15.7, H-9), 6.04, (1H, dd, *J* 9.0, 15.7, H-10), 5.63 (1H, dd, *J* 5.0, 9.0, H-8), 4.65 (1H, d, *J* 5.0, H-7), 3.80 (3H, s, H-1), 3.36 (3H, s, H-6).

HRMS (m/z-ESI): Found: 408.0883. (M+Na)⁺ C₂₀H₁₉NO₅SNa requires 408.0882.

10.5.5.16 *anti*-Methyl-2-(methylsulfonyl)-1-oxo-3-((*E*)-styryl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (*anti*-476)



Prepared according to **General Procedure N** using anhydride **159** (39.90 mg, 0.25 mmol), anhydrous MTBE (0.1 M, 2.5 mL), imine **469** (51.50 mg, 0.25 mmol) and catalyst **205** (8.20 mg, 0.01 mmol, 5 mol%). The reaction was stirred at -30 °C for 72 h to give a diastereomeric mixture of carboxylic acids in a 17:81 ratio (*anti:syn*). After esterification, the diastereomer ***anti*-476** was purified by column chromatography, eluting with 30% EtOAc in hexane. The product was isolated as a colourless oil (11 mg, 12%, 79% *ee*).¹³⁶ [α]_D²⁰ = -9.8 (c 0.05, acetone).

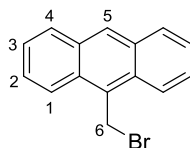
CSP-HPLC analysis, Chiralcel IA (4.6 mm x 25 cm), hexane/IPA: 90/10, 1 mL min⁻¹, RT, UV detection at 254 nm, retention times: 57.2 min and 75.7 min.

δ_{H} (400 MHz, CDCl₃): 8.14 (1H, dd, *J* 1.1, 7.7, H-2), 7.58-7.45 (2H, m, H-4, H-5), 7.36 (1H, app. d, H-3), 7.24-7.22 (5H, m, H-11, H-12, H-13), 6.71 (1H, dd, *J* 1.8, 15.7, H-9), 5.99 (1H, dd, *J* 7.0, 15.7, H-10), 5.76 (1H, m, H-8), 3.97 (1H, d, *J* 1.8, H-7), 3.71 (3H, s, H-1), 3.44 (3H, s, H-6).

HRMS (m/z-ESI): Found 408.0883. (M+Na)⁺ C₂₀H₁₉NO₅SNa Requires: 408.0882.

10.6 Experimental data for Section 5

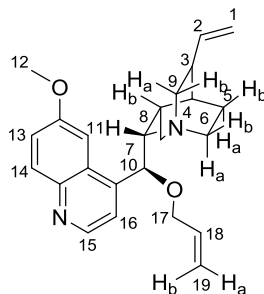
10.6.1 9-(Bromomethyl)anthracene (490)



9-Anthracenylmethanol (4.0 g, 19.2 mmol) was dissolved in anhydrous THF (45 mL) under argon and was cooled to 0 °C and PBr₃ (1.6 mL, 22.3 mmol) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C followed by 30 min at rt until the mixture becomes homogenous. The mixture was re-cooled to 0 °C and H₂O (25 mL) was added slowly with continuous stirring. The product was extracted with ether (x3) and the combined organic extracts were washed with brine, dried over MgSO₄, filtered and the filtrate was concentrated *in vacuo* to furnish **490** (4.1g, 78%) as a yellow solid. M.p. 140-142 °C. (lit²⁵⁹ 140-142 °C). Spectral data for this compound were consistent with those in the literature.²⁵⁹

δ_{H} (400 MHz, CHCl₃): 8.54 (1H, s, H-5), 8.30 (2H, d, *J* 9.0, H-1), 8.03 (2H, d, *J* 8.5, H-4), 7.66-7.60 (2H, m, H-2), 7.51-7.47 (2H, m, H-3), 5.54 (2H, s, H-6).

10.6.2 (1S,2R,4S,5R)-2-((R)-(Allyloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (493)



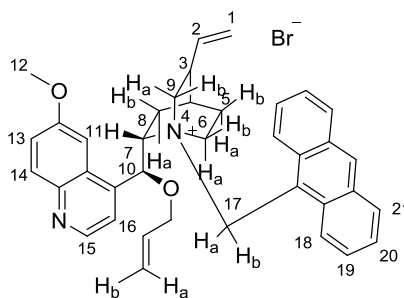
Quinine (4.1 g, 12.8 mmol) was dissolved in anhydrous DMF (40 mL) under an atmosphere of argon and was cooled to 0 °C. NaH (60% in mineral oil, 1.3 g, 31.9 mmol) was added at this temperature. The mixture was allowed to warm to rt and was stirred for 2 h. Allyl bromide (1.1 mL, 12.8 mmol) was added dropwise and the resulting mixture was stirred for 16 h. The solvent was evaporated at reduced pressure. The product was re-dissolved in EtOAc (30 mL) and washed with brine (2 x 30 mL). The organic layer was dried over MgSO₄ and was evaporated at reduced pressure followed by purification *via* silica chromatography eluting with 3% MeOH in EtOAc to give **493** as a yellow oil (3.6 g, 80%). [α]_D²⁰ = -27.5 (*c* 0.14 CHCl₃). Spectral data for this compound were consistent with those in the literature.²⁶⁰

δ_{H} (400 MHz, CHCl₃): 8.71 (1H, d, *J* 4.5, H-15), 8.00 (1H, d, *J* 9.2, H-14), 7.54 (1H, d, *J* 2.8, H-11), 7.36 (1H, dd, *J* 2.8, 9.2, H-13), 7.38 (1H, d, *J* 4.5, H-16), 6.24-

6.12 (1H, m, H-18), 5.93-5.80 (2H, m, H-2, H-10), 5.21-5.07 (4H, m, H-1, H-19), 4.00-8.85 (5H, m, H-12, H-17), 3.08-2.70 (3H, m, H-6a, H-7, H-9a), 2.50-2.04 (4H, m, H-2, H-3, H-6b, H-9b), 1.78-1.60 (4H, m, H-5a, H-5b, H-8a, H-8b).

HRMS (m/z - ESI): Found: 618.0380 ($M+Na$)⁺ C₂₈H₂₅Cl₄NO₅Na Requires: 618.0385.

10.6.2.1 (1S,2S,4S)-2-((S)-(Allyloxy)(6-methoxyquinolin-4-yl)methyl)-1-anthracenyl-5-vinylquinuclidin-1-ium bromide (492)



493 (737 mg, 2.0 mmol) was dissolved in anhydrous CH₂Cl₂ (10 mL) under an atmosphere of argon at rt. 9-(bromomethyl)anthracene (575 mg, 2.1 mmol) was added and the reaction was stirred for 48 h. The solvent was evaporated and the mixture was purified *via* silica chromatography eluting with a gradient of 1-3% MeOH in CH₂Cl₂ to give **492** as a brown solid (730 mg, 59%). M.p. 130 °C (decomp.). [α]_D²⁰ = -274.2 (*c* 0.16 CHCl₃).

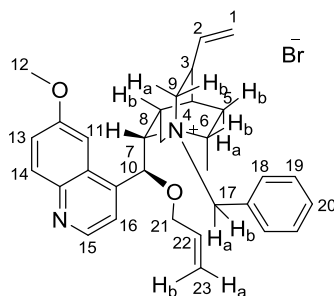
δ_H (400 MHz, MeOD): 8.93 (1H, s, H-22), 8.89 (1H, d, *J* 4.5, H-15), 8.61-8.50 (2H, m, H-18), 8.28 (2H, d, *J* 8.5, H-21), 8.13 (1H, d, *J* 9.2, H-14), 7.9 (1H, d, *J* 4.5, H-16), 7.85-7.60 (5H, m, H-11, H-13, H-16, H-19, H-20), 6.93 (1H, app. s, H-10), 6.57-6.37 (2H, m, H-1a, H-23), 5.80-5.67 (m, 3H, H-1b, H-2, H-25a), 5.55 (1H, dd, *J* 10.5, 1.1, H-25b), 5.01-4.97 (2H, m, H-17), 4.59-4.42 (3H, m, H-23a, H-23b, H-9b, H-7), 4.10 (3H, s, H-12), 3.75-3.70 (1H, m, H-6a), 3.27-3.18 (1H, m, H-6b), 3.06-2.96 (1H, m, H-9b), 2.58-2.53 (1H, m, H-8b), 2.49-2.40 (1H, m, H-3), 2.33-2.22 (1H, m, H-5b), 2.04-1.98 (1H, m, H-4), 1.77-1.65 (2H, m, H-5a, H-8a).

δ_C (100 MHz, MeOD): 159.3 (q), 147.3, 144.4 (q), 140.5 (q), 137.4, 133.8, 133.7 (q), 133.5 (q), 133.1, 132.1 (q), 132.1 (q), 131.2, 130.4, 130.3, 128.7 (q), 128.3, 125.7, 123.9, 123.7, 122.8, 120.9, 118.0, 117.6 (q), 116.8, 101.6, 70.6, 69.8, 62.0, 56.9, 55.4, 53.2, 38.6, 26.4, 25.3, 21.9.

ν_{max} (neat)/cm⁻¹: 2329, 2319, 1619, 1507, 1449.

HRMS (m/z - ESI): Found: 618.0380 ($M+Na$)⁺ C₂₈H₂₅Cl₄NO₅Na Requires: 618.0385.

10.6.3 (1S,2S,4S)-2-((S)-(Allyloxy)(6-methoxyquinolin-4-yl)methyl)-1-benzyl-5-vinylquinuclidin-1-ium bromide (494)



493 (725 mg, 2.0 mmol) was dissolved in anhydrous CH₂Cl₂ (10 mL) under an atmosphere of argon at rt. Benzyl bromide (248 μ L, 2.1 mmol) was added and the reaction was stirred for 48 h. The solvent was evaporated and the mixture was purified *via* silica chromatography eluting with a gradient of 1-3% MeOH in CH₂Cl₂ to give as a brown **494** solid (500 mg, 70%). M.p. 152-154 °C. [α]_D²⁰ = -119.4 (*c* 0.1 CHCl₃).

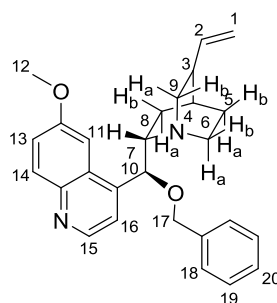
δ_H (400 MHz, MeOD): 8.82 (1H, d, J 4.6, H-15), 8.08 (1H, d, J 9.33, H-14), 7.82 (1H, d, J 4.6, H-16), 7.82-7.44 (7H, m, H-11, H-13, H-18, H-19, H-20), 6.46 (1H, app. s, H-10), 6.29-6.19 (1H, m, H-22), 5.80-5.70 (1H, m, H-2), 5.55-5.48 (2H, m, H-23a), 5.42-5.32 (2H, m, H-17a, H-23b), 5.18-5.04 (H2, m, H-1), 4.75 (1H, d, J 12.22, H-17b), 4.40-4.10 (3H, m, H-6a, H-21a, H-21b), 4.07 (3H, s, H-12), 3.98-3.90 (1H, m, H-10), 3.55 (H2, d, J 8.7, H-9), 3.51-3.39 (1H, m, H-6b), 2.75-2.70 (1H, m, H-3), 2.58-2.48, (1H, m, H-8b), 2.40-2.29 (1H, m, H-5b), 2.16-2.09 (1H, m, H-7), 2.00-1.90 (1H, m, H-5a), 1.74-1.62 (1H, m, H-8a).

δ_C (100 MHz, MeOD): 159.3 (q), 147.3, 144.2 (q), 140.8 (q), 137.4, 133.8, 133.8, 131.1, 131.0, 129.6, 127.4, 127.1, 122.6, 120.6, 118.0, 116.8, 101.4, 72.9, 70.3, 69.4, 65.3, 60.7, 55.4, 51.9, 38.1, 27.2, 24.9, 21.3.

ν_{max} (neat)/cm⁻¹: 3382, 2924, 1620, 1508, 1456.

HRMS (m/z - ESI): Found: 618.0380 ($M+Na$)⁺ C₂₈H₂₅Cl₄NO₅Na Requires: 618.0385.

10.6.4 (1*S*,2*R*,4*S*,5*R*)-2-((*R*)-(Benzyloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (495)

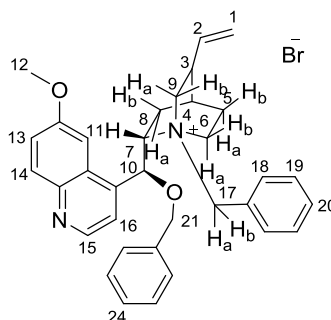


Quinine (3.0 g, 9.3 mmol.) was dissolved in anhydrous DMF (30 mL) under an atmosphere of argon and was cooled to 0 °C. NaH (60% in mineral oil, 929 mg, 23.3 mmol.) was added at this temperature. The mixture was allowed to warm to rt and was stirred for 2 h. Benzyl bromide (1.1 mL, 9.3 mmol) was added dropwise and the resulting mixture was stirred for 16 h. The solvent was evaporated at reduced pressure. The product was re-dissolved in EtOAc (30 mL) and washed with brine (2 x 30 mL). The organic layer was evaporated at reduced pressure and purified *via* silica chromatography eluting with gradient of 1-6% MeOH in CH₂Cl₂ to give **495** as a yellow oil. (2.8 g, 74%). [α]_D²⁰ = 43.7 (c 0.21 CHCl₃). Spectral data for this compound were consistent with those in the literature.²⁶¹

δ_{H} (400 MHz, CHCl₃): 8.77 (1H, d, *J* 4.5, H-15), 8.07 (1H, d, *J* 9.2, H-14), 7.50 (1H, d, *J* 4.5, H-16), 7.48-7.28 (7H, m, H-11, H-13, H-18, H-19, H-20), 5.78-5.69 (1H, m, H-2), 5.43 (1H, bs, H-10), 5.00-4.93 (2H, m, H-1a, H-1b), 4.51-4.44 (2H, m, H-17), 3.97 (3H, s, H-12), 3.60-3.45 (1H, m, H-7), 3.21-3.12 (2H, m, H-6b, H-9b), 2.79-2.68 (2H, m, H-6a, H-9a), 2.40-2.29 (1H, m, H-3), 1.98-1.50 (5H, m, H-4, H-5a, H-5b, H-8a, H-8b).

HRMS (*m/z* - ESI): Found: 415.2377 (M+H) C₂₇H₃₁N₂O₂ Requires: 414.2307.

10.6.5 (1*S*,2*S*,4*S*)-2-((*S*)-(Allyloxy)(6-methoxyquinolin-4-yl)methyl)-1-benzyl-5-vinylquinuclidin-1-ium bromide (496)



495 (680 mg, 1.6 mmol) was dissolved in anhydrous CH₂Cl₂ (5 mL) under an atmosphere of argon at rt. Benzyl bromide (205 μ L, 1.7 mmol) was added and the reaction was stirred for 48 h. The solvent was evaporated and the mixture was purified *via* silica chromatography eluting with a gradient of 1-3% MeOH in CH₂Cl₂ to give **496** as a brown solid (428 mg, 64%). M.p. 142-145 °C. $[\alpha]_D^{20} = -99.1$ (*c* 0.21 CHCl₃).

δ_H (400 MHz, MeOD): 8.86 (1H, d, *J* 4.4, H-15), 8.11 (1H, d, *J* 8.9, H-14), 7.91 (1H, d, *J* 4.4, H-16), 7.61-7.42 (12H, m, H-11, H-13, H-18, H-19, H-20, H-22, H-23, H-24), 6.47 (1H, s, H-10), 5.77-5.68 (1H, m, H-2), 5.14-5.00 (3H, m, H-1, H-17a), 4.78 (2H, dd, *J* 10.9, 35.7, H-21), 4.6 (1H, d, *J* 11.8, H-17b) 4.13-4.02 (4H, m, H-6a, H-12), 3.95-3.91 (1H, m, H-7), 3.51-3.41 (2H, m, H-9a, H-9b), 3.33-3.32 (1H, m, H-6b), 2.72-2.69 (1H, m, H-3), 2.57-2.52 (1H, m, H-8b), 2.27-2.17 (1H, m, H-5b), 2.11-2.09 (1H, m, H-4), 1.90-1.84 (1H, m, H-5a), 1.72-1.66 (1H, m, H-8b).

δ_C (100 MHz, MeOD): 159.3 (q), 147.3, 144.3 (q), 140.5 (q), 137.4, 136.8 (q), 133.7, 131.2, 131.0, 129.5, 129.2, 129.1, 128.9 (q), 127.2 (q), 122.6, 121.0, 116.8, 101.4, 97.7, 71.4, 69.3, 64.9, 60.7, 55.4, 51.7, 38.0, 27.1, 24.8, 21.4.

ν_{max} (neat)/cm⁻¹: 2923, 2365, 1619, 1507, 1454.

HRMS (*m/z* - ESI): Found: 618.0380 (M+Na)⁺ C₂₈H₂₅Cl₄NO₅Na Requires: 618.0385.

10.6.6 General Procedure O: Racemic alcoholysis of *meso*-anhydrides

Anhydride **483** (1.0 equiv.), TBAF (1M in THF, 0.2 equiv.) and the appropriate alcohol (2.2 equiv.) were dissolved in anhydrous THF (0.1 M) under argon. A glass stopper was fitted and the reaction was stirred for 48 h. Pyrrolidine (1.0 equiv.) was added and the reaction mixture was stirred for a further hour. The resulting mixture was concentrated *in vacuo* and was purified *via* silica chromatography, eluting with 5% MeOH in CH₂Cl₂ to furnish the desired hemi-ester product which was functionalised according to **General Procedure Q** to obtain the racemic product as a reference for analysis by CSP-HPLC.

10.6.7 General Procedure P: Desymmetrisation of *meso*-anhydrides

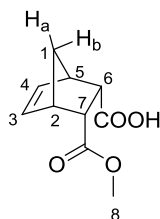
The anhydride **483** (50.00 mg, 0.30 mmol), catalyst **512** (0.02 mmol) and KF (2.65 mg, 0.05 mmol) were placed in an oven dried RBF. The flask was evacuated and placed under an atmosphere of argon. Anhydrous THF (3.00 mL, 0.1M) was added followed by the appropriate alcohol (1.52 mmol). A glass stopper was fitted and the reaction was stirred at rt for the allotted time. Conversion was monitored *via* ¹H NMR spectroscopy. Pyrrolidine (1.0 equiv.) was added and the reaction mixture was stirred for 1 h. The resulting mixture was concentrated *in vacuo* and was purified *via* silica

chromatography, eluting with 5% MeOH in CH₂Cl₂ to furnish the desired hemi-ester product which was functionalised according to **General Procedure Q** to ascertain the product *ee*.

10.6.8 General Procedure Q: Derivatisation of hemi-ester products.

The hemi-ester product (1.0 equiv.), DCC (1.1 equiv.) and DMAP (10 mol%) were dissolved in anhydrous CH₂Cl₂ (0.1M) under an atmosphere of argon. Chiral amine **486** (1.0 equiv.) was added and the reaction was stirred for 16 h followed by filtration. The filtrate was concentrated *in vacuo* and purified *via* preparative TLC, eluting with 15% EtOAc in CH₂Cl₂.

10.6.8.1 (1*S*,2*R*,4*R*)-3-(methoxycarbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**485**)



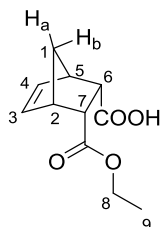
Prepared according to **General Procedure P** using MeOH (61.50 μ L, 1.52 mmol). The reaction was stirred for 48 h to give 66% conversion at which point it was quenched and purified to furnish **485** as a white solid. (37.0 mg, 62 %).¹⁹⁹ M.p. 76-78 °C, $[\alpha]_D^{20} = -7.4$ (c 0.13, CHCl₃).

δ_H (400 MHz, CDCl₃): 66.63 (1H, dd, *J* 3.0, 5.5, H-4), 6.24 (1H, dd, *J* 3.0, 5.5, H-3), 3.62 (3H, s, H-8), 3.37 (1H, dd, *J* 3.0, 10.0, H-7), 3.31 (1H, dd, *J* 3.0, 10.0, H-6), 3.15-3.28 (2H, m, H-2, H-5), 1.52 (1H, m, H-1a), 1H, m, H-1b).

Hemi-ester **485** was derivatised according to **General Procedure Q** for analysis by CSP-HPLC.

CSP-HPLC conditions: Chiralpak AD-H column (4.6 mm x 250mmL), hexane/IPA: 90/10, 0.5 mL/min⁻¹, rt, UV detection at 220 nm, retention times: 10.25 min and 16.98 min.

10.6.8.2 (1*S*,2*R*,4*R*)-3-(Ethoxycarbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**519**)



Prepared according to **General Procedure P** using ethanol (88.8 μ L, 1.52 mmol). The reaction was stirred for 10 d to give 54% conversion at which point it was quenched and purified to furnish **519** as a white solid. (33.0 mg, 52 %). M.p. 54-56 °C. $[\alpha]_D^{20} = +8.0$ (c 0.1 CHCl₃).

δ_H (400 MHz, $CDCl_3$): 6.31-6.22 (2H, m, H-3, H-4), 4.10-4.01 (2H, m, H-8), 3.34-3.26 (2H, m, H-6, H-7), 3.19-3.17 (2H, m, H-2, H-5), 1.50-1.32 (2H, m, H-1a, H-1b) 1.20 (3H, t, J 7.1, 14.2, H-9).

δ_C (100 MHz, $CDCl_3$): 176.4 (C=O), 172.4 (C=O), 135.4, 134.5, 60.5, 48.7, 48.4, 47.7, 46.6, 46.2, 14.0.

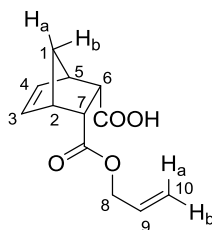
ν_{max} (neat)/ cm^{-1} : 2974, 1733, 1700, 1424.

HRMS (m/z - ESI): Found: 618.0380 ($M+Na$)⁺ $C_{28}H_{25}Cl_4NO_5Na$ Requires: 618.0385.

Hemi-ester **519** was derivatised according to **General Procedure Q** for analysis by CSP-HPLC.

CSP-HPLC conditions: Chiralpak AD-H column (4.6 mm x 250mmL), hexane/IPA: 90/10, 0.75 mL/min⁻¹, rt, UV detection at 220 nm, retention times: 9.61 min and 15.05 min.

10.6.8.3 (1S,2R,4R)-3-((Allyloxy)carbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**520**)



Prepared according to **General Procedure P** using allyl alcohol (103.40 μ L, 1.52 mmol). The reaction was stirred for 5 d to give 53% conversion at which point it was quenched and purified to furnish **520** as a white solid. (34.5 mg, 50 %). M.p. 63-64 °C. $[\alpha]_D^{20} = +0.01$ (c 0.1 $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 6.32-6.22 (2H, m, H-3, H-4), 5.91-5.83 (1H, m, H-9), 5.31-5.19 (2H, m, H-10a, H-10b), 4.57-4.43 (2H, m, H-8a, H-8b), 3.36-3.29 (2H, m, H-6, H-7), 3.20-3.19 (2H, m, H-2, H-5), 1.50-1.33 (2H, m, H-1a, H-1b).

δ_C (100 MHz, $CDCl_3$): 176.4 (C=O), 172.4 (C=O), 135.4, 134.5, 118.2, 65.3, 53.4, 48.7, 48.3, 47.8, 46.6, 46.2.

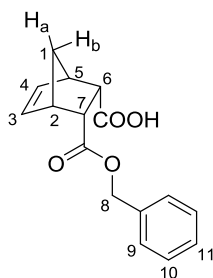
ν_{max} (neat)/ cm^{-1} : 2923, 1733, 1701, 1423, 1340.

HRMS (m/z - ESI): Found: 618.0380 ($M+Na$)⁺ $C_{28}H_{25}Cl_4NO_5Na$ Requires: 618.0385.

Hemi-ester **520** was derivatised according to **General Procedure Q** for analysis by CSP-HPLC.

CSP-HPLC conditions: Chiralpak AD-H column (4.6 mm x 250mmL), hexane/IPA: 90/10, 0.75 mL/min⁻¹, rt, UV detection at 220 nm, retention times: 9.91 min and 13.60 min.

10.6.8.4 (1*S*,2*R*,4*R*)-3-((Benzyloxy)carbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (522)



Prepared according to **General Procedure P** using benzyl alcohol (0.16 mL, 1.52 mmol). The reaction was stirred for 5 d to give 52% conversion at which point it was quenched and purified to furnish **522** as a white solid. (40.3 mg, 49 %). M.p. 106-108 °C. $[\alpha]_D^{20} = +0.1$ (c 0.1 CHCl₃).

δ_H (400 MHz, CDCl₃): 7.37-7.30 (5H, m, H-9, H-10, H-11), H6.30-6.23 (2H, m, H-3, H-4), 5.10 (1H, d, *J* 11.8, H-8a), 4.95 (1H, d, *J* 11.8, H-8a), 3.34-3.33 (2H, m, H-6, H-7), 3.20-3.19 (2H, m, H-2, H-5), 1.50-1.32 (2H, m, H-1a, H-1b)

δ_C (100 MHz, CDCl₃): 175.8 (C=O), 172.2 (C=O), 135.9 (q), 135.4, 134.5, 128.5, 128.3, 128.1, 66.4, 48.7, 48.3, 47.7, 46.6, 46.2.

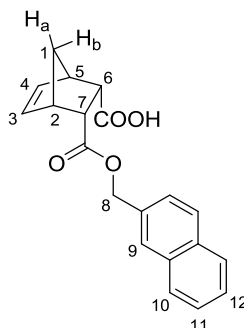
ν_{max} (neat)/cm⁻¹: 2923, 2853, 1742, 1698, 1484.

HRMS (*m/z* - ESI): Found: 295.0948 (M+Na)⁺ C₁₆H₁₆ NaO₄ Requires: 272.1049.

Hemi-ester **522** was derivatised according to **General Procedure Q** for analysis by CSP-HPLC.

CSP-HPLC conditions: Chiralpak AD-H column (4.6 mm x 250mmL), hexane/IPA: 90/10, 0.75 mL/min⁻¹, rt, UV detection at 220 nm, retention times: 16.18 min and 20.25 min.

10.6.8.5 (1*S*,2*R*,4*R*)-3-((Naphthalen-2-ylmethoxy)carbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (523)



Prepared according to **General Procedure P** using 2-naphthylmethanol (0.24 g, 1.52 mmol). The reaction was stirred for 6 d to give 45% conversion at which point it was quenched and purified to furnish **523** as a white solid. (40.9 mg, 42 %). M.p. 188-120 °C. $[\alpha]_D^{20} = +32.5$ (c 0.01 CHCl₃).

δ_{H} (400 MHz, CDCl_3): 7.87-7.75 (4H, m, H-10, H-11, H-12, H-13), 7.52-7.40 (3H, m, H-9, H-14, H-15), 6.32-6.22 (2H, m, H-3, H-4), 5.26 (1H, d, J 12.6, H-8a), 5.12 (1H, d, J 12.6, H-8b), 3.40-3.27 (2H, m, H-6, H-7) 3.20-3.15 (2H, m, H-2, H-5), 1.50 (1H, J 8.7, H-1b), 1.35 (1H, d, J 8.7, H-1a).

δ_{C} (100 MHz, CDCl_3): 177.2 (C=O), 172.3 (C=O), 135.5, 134.6, 133.4 (q), 133.2 (q), 133.1 (q), 128.3, 128.0, 127.7, 127.4, 126.2, 126.2, 126.0, 66.6, 48.8, 48.4, 48.0, 46.6, 46.3.

ν_{max} (neat)/ cm^{-1} : 2922, 2855, 1723, 1680, 1450.

HRMS (m/z - ESI): Found: 295.0948 ($\text{M}+\text{Na}$) $^+$ $\text{C}_{16}\text{H}_{16}\text{NaO}_4$ Requires: 272.1049.

Hemi-ester **523** was derivatised according to **General Procedure Q** for analysis by CSP-HPLC.

CSP-HPLC conditions: Chiralpak AD-H column (4.6 mm x 250mmL), hexane/IPA: 90/10, 0.75 mL/min $^{-1}$, rt, UV detection at 220 nm, retention times 10.53 min and 14.74 min.

10.7 Experimental data for Section 6

10.7.1 General Procedure R: The alkylation of 2-oxindoles

The appropriate oxindole (1.0 equiv.) was dissolved in anhydrous THF (0.2 M) under an argon atmosphere. TMEDA (3.3 equiv.) was added and the solution was cooled to $-78\text{ }^{\circ}\text{C}$. To this $n\text{-BuLi}$ (2.5M in hexane, 2.2 equiv.) was added and the solution was stirred for 30 min. The appropriate alkyl halide (1.7 equiv.) was added and the solution was warmed to $-20\text{ }^{\circ}\text{C}$ and was stirred for 3 h. The mixture was quenched with sat. NH_4Cl (aq.) and was extracted with EtOAc (x3). The resulting mixture was purified by silica chromatography to yield the alkylated product.

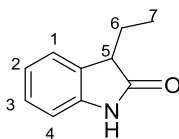
10.7.2 General Procedure S: Amide protection as the diphenylacetamide

The appropriate oxindole (1.0 equiv.) and diphenylacetyl chloride (1.2 equiv.) were refluxed at $150\text{ }^{\circ}\text{C}$ for 6 h. The mixture was cooled to rt and was passed through a short silica plug eluting with 20% CH_2Cl_2 in hexane. EtOH was added to the resulting product and the precipitate was collect by filtration to yield the protected oxindole product.

10.7.3 General Procedure T: Synthesis of substrates for rearrangement

The appropriate compound was dissolved in anhydrous THF (0.1M) under an atmosphere of argon and freshly distilled NEt_3 (10.0 equiv.) was added. The appropriate acyl chloride (5.0 equiv.) was added dropwise and the mixture was stirred for 1 h. Water was added to the reaction mixture which was extracted with CH_2Cl_2 (x3) and washed with brine. The resulting mixture was purified as dictated to yield the acetylated product.

10.7.3.1 3-Ethylindolin-2-one (546)

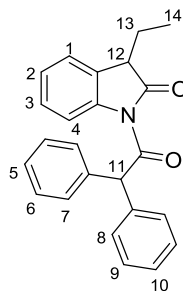


Prepared according to **General Procedure R** using oxindoles (**545**, 1.5 g, 11.7 mmol), TMEDA (5.6 mL, 37.2 mmol), *n*-BuLi (2.5M, 9.9 mL, 24.7 mmol), and ethyl iodide (1.5 mL, 19.1 mmol). The crude mixture was purified *via* silica chromatography, eluting with 30% EtOAc in petroleum ether to yield **546** as a white solid (1.2 g, 75%). Spectral data for this compound were consistent with those in the literature.²⁶²

δ_{H} (400 MHz, CDCl_3): 8.20 (1H, bs, NH), 7.26-7.19 (2H, m, H-2, H-4), 7.05-7.01 (1H, m, H-3), 6.88 (1H, d, *J* 7.7, H-2), 3.45 (1H, m, H-5), 2.07- 2.00 (2H, m, H-6), 0.92 (3H, t, *J* 7.5, H-7).

HRMS (*m/z* - ESI): Found: 162.0909 ($\text{M}+\text{H}$)⁺ $\text{C}_{10}\text{H}_{11}\text{NO}$ Requires 161.0841.

10.7.3.2 1-(2,2-Diphenylacetyl)-3-ethylindolin-2-one (548)

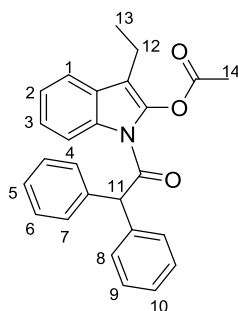


Prepared according to **General Procedure S** using **546** (1.2 g, 8.4 mmol) and diphenylacetyl chloride (2.3 g, 10.1 mmol) to yield **548** (2.1 g, 71%) as white solid. Spectral data for this compound were consistent with those in the literature.¹⁹⁷

δ_{H} (400 MHz, CDCl_3): 8.27 (1H, d, *J* 8.3, H-4), 7.33-7.16 (13H, m, H-1, H-2, H-3, H-5, H-6, H-7, H-8, H-9, H-10), 6.63 (1H, s, H-11), 3.54 (1H, t, *J* 5.4, H-12), 2.08-1.85 (2H, m, H-13), 0.65 (3H, t, *J* 7.4, H-14).

HRMS (*m/z* - ESI): Found: 356.1645 ($\text{M}+\text{H}$)⁺ $\text{C}_{24}\text{H}_{21}\text{NO}_2$ Requires 355.1572.

10.7.3.3 1-(2,2-Diphenylacetyl)-3-ethyl-1H-indol-2-yl acetate (**549**)

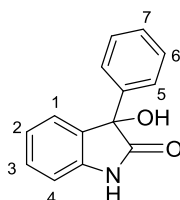


Prepared according to **General Procedure T** using **548** (1.5 g, 4.3 mmol), freshly distilled NEt₃ (6.0 mL, 40.3 mmol), and acetyl chloride (1.5 mL, 21.5 mmol), in anhydrous THF (21.5 mL). The crude product was purified by silica chromatography eluting with a gradient of 0-10% EtOAc in petroleum ether to give **549** as a white solid (0.4 g, 20%). Spectral data for this compound were consistent with those in the literature.¹⁹⁷

δ_{H} (400 MHz, CDCl₃): 8.32-8.23 (1H, m, H-4), 7.54-7.42 (1H, m, H-1), 7.38-7.17 (12H, m, H-2, H-3, H-5, H-6, H-7, H-8, H-9, H-10), 5.90 (1H, s, H-11), 2.49 (2H, q, *J* 7.7, H-12), 1.94 (3H, s, H-14) 1.20 (3H, t, *J* 7.6, 15.1, H-13).

HRMS (*m/z* - ESI): Found: 398.1747 [M+H]⁺ C₂₆H₂₃NO₃ Requires 398.1751.

10.7.4 3-Hydroxy-3-phenylindolin-2-one (**551**)

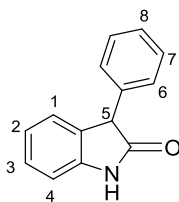


Mg turnings (1.7 g, 71.4 mmol) were placed in an RBF equipped with a reflux condenser under an atmosphere of argon. Freshly distilled bromobenzene (7.5 mL, 71.4 mmol) in anhydrous THF (17.0 mL) was added in two equal portions, waiting for the reaction to commence in between. Once added, the reaction mixture was refluxed for 1 h. The mixture was cooled to 0 °C and a solution of isatin (**550**) (3.0 g, 20.4 mmol) in anhydrous THF (50 mL) was added dropwise. The mixture was allowed to warm to rt and was stirred for 16 h. The reaction mixture was quenched with sat. NH₄Cl (aq.) and was extracted with EtOAc (x3). The combined organic layers were subsequently washed with NaHCO₃ followed by brine, dried over MgSO₄ and were concentrated *in vacuo* to yield **551** as orange solid (3.0 g, 67%). Spectral data for this compound were consistent with those in the literature.²⁶³

δ_{H} (400 MHz, CDCl₃): 10.37 (1H, s, NH), 7.32-7.17 (6H, m, H-1, H-5, H-6, H-7), 7.07 (1H, d, *J* 7.5, H-4), 6.94 (1H, m, H-3), 6.87 (1H, m, H-2), 6.59 (1H, s, OH).

HRMS (*m/z* - ESI): Found: 208.0756 (M+H)⁺ C₁₄H₁₁NO₂ Requires 225.0790.

10.7.5 3-Phenylindolin-2-one (552)

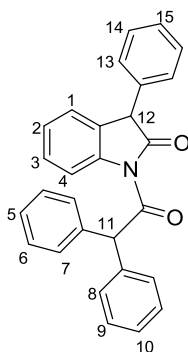


551 (1.8g, 8.0 mmol) was dissolved in anhydrous CH_2Cl_2 (10.0 mL) under argon atmosphere and freshly distilled SOCl_2 (7.0 mL, 79.9 mmol) was added. The mixture was stirred for 16 h followed by concentration *in vacuo*. The resulting compound was redissolved in anhydrous MeCN (4.0 mL) under argon atmosphere and NaCNBH_3 (1.5 g, 24.0 mmol) was added. The mixture was stirred for 16 h, quenched with sat. NaHCO_3 (aq.) and extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over MgSO_4 and were concentrated *in vacuo*. The crude product was purified *via* silica chromatography eluting with 25% petroleum ether in EtOAc to yield **552** as a white solid (904 mg, 54%). Spectral data for this compound were consistent with those in the literature.²⁶³

δ_{H} (400 MHz, CDCl_3): 7.61 (1H, bs, NH), 7.38-7.10 (6H, m, H-1, H-6, H-7, H-8), 7.14 (1H, m, H-4), 7.04 (1H, m, H-3), 6.93 (1H, m, H-2), 4.63 (1H, s, H-5).

HRMS (m/z - ESI): Found: 210.0916 ($\text{M}+\text{H}$)⁺ $\text{C}_{14}\text{H}_{11}\text{NO}$ Requires 209.0841.

10.7.5.1 1-(2,2-Diphenylacetyl)-3-phenylindolin-2-one (553)

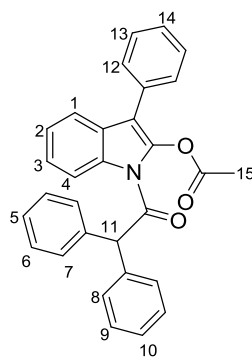


Prepared according to **General Procedure S** using **552** (0.9 g, 4.3 mmol) and diphenylacetyl chloride (1.2 g, 5.2 mmol) to yield **553** (0.8 g, 46%) as white solid. Spectral data for this compound were consistent with those in the literature.¹⁹⁷

δ_{H} (400 MHz, CDCl_3): 8.33 (1H, d, J 7.9, H-1), 7.38-6.97 (16H, m, H-2, H-3, H-4, H-5, H-6, H-7, H-8, H-9, H-10, H-13, H-14, H-15), 6.57 (1H, s, H-11), 4.70 (1H, s, H-12).

HRMS (m/z - ESI): Found: 404.1574 ($\text{M}+\text{H}$)⁺ $\text{C}_{28}\text{H}_{21}\text{NO}_2$ Requires 403.1572.

10.7.5.2 1-(2,2-Diphenylacetyl)-3-phenyl-1H-indol-2-yl acetate (554)

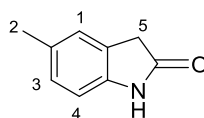


Prepared according to **General Procedure T** using **553** (0.8 g, 1.8 mmol), freshly distilled NEt₃ (2.5 mL, 18.6 mmol), and acetyl chloride (0.7 mL, 9.3 mmol), in anhydrous THF (9.3 mL). The crude product was passed through a short silica plug eluting with 20% EtOAc in petroleum ether. The product was precipitated using Et₂O and was collected *via* suction filtration to yield **554** as a white solid (0.3 g, 39%). Spectral data for this compound were consistent with those in the literature.¹⁹⁷

δ_{H} (400 MHz, CDCl₃): 8.33 (1H, d *J* 7.7, H-1), 7.66-7.60 (1H, m, H-4), 7.55-7.41 (4H, m, H-12, H-13), 7.39-7.22 (13H, m, H-2, H-3 H-5, H-6, H-7, H-8, H-9, H-10, H-14), 5.98 (1H, s, H-11), 1.77 (3H, s, H-15).

HRMS (*m/z* - APCI): Found: 446.1756 (M+H)⁺ C₃₀H₂₃NO₃ Requires: 445.1751.

10.7.6 5-Methylindolin-2-one (561)

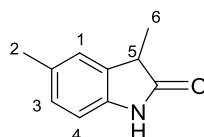


5-Methylindoline-2,3-dione (**558**, 2.5 g, 15.5 mmol) and hydrazine monohydrate (0.5 M, 31.3 ml) were heated to 140 °C for 6 h. The mixture was cooled to rt and was acidified to pH 2 using HCl (2M, aq.). The resulting mixture was allowed to stand for 48 h and **561** was collected *via* suction filtration as a purple solid (1.3 g, 51%). Spectral data for this compound were consistent with those in the literature.²⁶⁴

δ_{H} (400 MHz, DMSO-*d*₆): 10.22 (1H, s, NH), 7.01-6.89 (2H, m, H-1, H-4), 6.66 (1H, d, *J* 7.7, H-3), 3.38 (2H, s, H-5), 2.21 (3H, s, H-2).

HRMS (*m/z* - APCI): Found: 148.0764 (M+H)⁺ C₉H₉NO Requires: 147.0684.

10.7.6.1 3,5-Dimethylindolin-2-one (562)

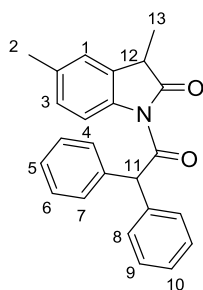


Prepared according to **General Procedure R** using **561** (1.3 g, 7.9 mmol), TMEDA (3.9 mL, 26.1 mmol), *n*-BuLi (2.5M, 6.9 mL, 17.4 mmol), MeI (0.8 mL, 13.4 mmol) and THF (7.5 mL). The crude mixture was purified *via* silica chromatography eluting with 40% EtOAc in petroleum ether to yield **562** as a white solid (1.0 g, 78%). Spectral data for this compound were consistent with those in the literature.²⁶⁵

δ_{H} (400 MHz, CDCl_3): 7.40 (1H, bs, NH), 7.03-7.00 (2H, m, H-1, H-4), 6.74 (1H, d J 7.7, H-3), 3.42 (1H, q, J 7.7, 15.4, H-5), 2.33 (3H, s, H-2), 1.48 (3H, d, J 7.6, H-6).

HRMS (m/z - ESI): Found: 162.0912 ($\text{M}+\text{H}$)⁺ $\text{C}_{10}\text{H}_{11}\text{NO}$ Requires 161.0841.

10.7.6.2 1-(2,2-Diphenylacetyl)-3,5-dimethylindolin-2-one (**563**)



Prepared according to **General Procedure S** using **562** (1.3 g, 8.1 mmol) and diphenylacetyl chloride (2.2 g, 9.8 mmol) to yield **563** (2.7 g, 92%) as white solid. M.p. 41-43 °C.

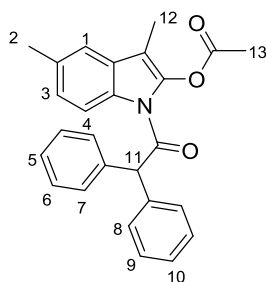
δ_{H} (400 MHz, CDCl_3): 8.14 (1H, d, J 8.4, H-4), 7.36-7.20 (10H, m, H-5, H-6, H-7, H-8, H-9, H-10), 7.10 (1H, d, J 8.4, H-3), 7.03 (1H, bs, H-1) 6.60 (1H, s, H-11) 3.54-3.48 (1H, m, H-12), 2.30 (3H, s, H-2) 1.43 (3H, d, J 7.6, H-13).

δ_{C} (100 MHz, CDCl_3): 178.6 (C=O), 172.9 (C=O), 138.6 (q), 138.5 (q), 138.0 (q), 135.0 (q), 129.6 (q), 129.3, 129.2, 128.7, 128.6, 128.5, 127.2, 127.1, 123.8, 116.4, 57.4, 41.3, 21.1, 15.9.

ν_{max} (neat)/ cm^{-1} : 3028, 2919, 1753, 1701, 1483.

HRMS (m/z - ESI): Found: 356.1652 ($\text{M}+\text{H}$)⁺ $\text{C}_{24}\text{H}_{21}\text{NO}_2$ Requires 355.1572.

10.7.6.3 1-(2,2-Diphenylacetyl)-3,5-dimethyl-1H-indol-2-yl acetate (564)



Prepared according to **General Procedure T** using **563** (2.7 g, 7.6 mmol), freshly distilled NEt₃ (10.6 mL, 75.9 mmol), and acetyl chloride (1.5 mL, 37.9 mmol), in anhydrous THF (37.9 mL). The crude product was purified by silica chromatography eluting with a gradient of 0-10% EtOAc in petroleum ether to give **564** as a white solid (0.3 g, 10%). M.p. 130-131 °C.

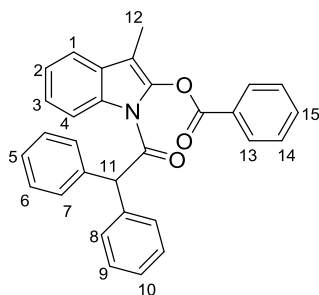
δ_{H} (400 MHz, CDCl₃): 8.21 (1H, d, *J* 8.5, H-4), 7.36-7.22 (13H, m, H-1, H-3, H-5, H-6, H-7, H-8, H-9, H-10), 5.92 (1H, s, H-11), 2.44 (3H, s, H-2), 2.00 (3H, s, H-12), 1.97 (3H, s, H-13).

δ_{C} (100 MHz, CDCl₃): 170.3 (C=O), 170.0 (C=O), 139.3 (q), 136.8 (q), 133.5 (q), 131.2 (q), 129.2, 128.7, 128.6 (q), 127.4, 126.2, 118.5, 116.1, 106.0 (q), 58.5, 21.4, 20.1, 7.6.

ν_{max} (neat)/cm⁻¹: 1798, 1659, 1463, 1361.

HRMS (*m/z* - ESI): Found: 398.1756 (M+H)⁺ C₂₆H₂₃NO₃ Requires 397.1678.

10.7.6.4 1-(2,2-Diphenylacetyl)-3-methyl-1H-indol-2-yl benzoate (566)



Prepared according to **General Procedure T** using **565** (0.5 g, 1.4 mmol), freshly distilled NEt₃ (1.9 mL, 13.9 mmol), and freshly distilled benzoyl chloride (0.5 mL, 7.0 mmol), in anhydrous THF (14.0 mL). The crude product was purified by silica chromatography eluting with a gradient of 50% CH₂Cl₂ in petroleum ether to give **566** as a white solid (0.2 g, 24%). M.p. 105-106 °C.

δ_{H} (400 MHz, CDCl₃): 8.46 (1H, d, *J* 8.0, H-4), 8.02 (2H, d, *J* 8.0, H-13), 7.68 (1H, t, *J* 7.3, H-15), 7.54-7.44 (3H, m, H-1, H-14), 7.37-7.03 (22H, m, H-2, H-3,

H-5, H-6, H-7, H-8, H-9, H-10), 5.92 (1H, s, H-11), 2.04 (3H, s, H-12).

δ_C (100 MHz, $CDCl_3$): 170.5 (C=O), 162.8 (C=O), 138.7, 136.9 (q), 134.4, 133.4 (q), 130.5, 129.1, 128.7 (q), 128.6 (q), 128.5, 127.7 (q), 127.2 125.1, 123.9, 118.4, 116.7, 106.0 (q), 58.3, 7.6.

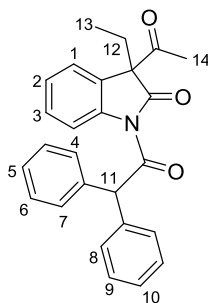
ν_{max} (neat)/ cm^{-1} : 3016, 1761, 1686, 1449.

HRMS (m/z - APCI): Found: 446.1758 ($M+H$)⁺ $C_{30}H_{23}NO_3$ Requires 445.1678.

10.7.7 General Procedure U: TBAF catalysed rearrangement of 2 oxindoles.

The appropriate 2-oxindole (1.0 equiv.) was dissolved in anhydrous THF (0.2 M) under argon. TBAF (1M in THF, 5 mol%) was added and the reaction mixture was stirred for the designated time. The reaction mixture was concentrated *in vacuo* and was purified *via* silica chromatography to furnish the rearranged product.

10.7.7.1 3-Acetyl-1-(2,2-diphenylacetyl)-3-ethylindolin-2-one (570)

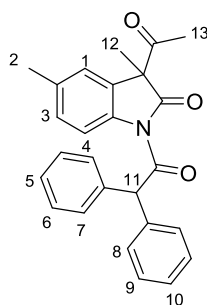


Prepared according to **General Procedure U** using **549** (42.80 mg, 0.20 mmol), TBAF (5.00 μ L, 0.01 mmol) and THF (1.10 mL). The reaction mixture was stirred for 100 min followed by purification *via* silica chromatography, eluting with 100% CH_2Cl_2 to furnish **570** as a white solid (37.60 mg, 87%).¹⁹⁷

δ_H (400 MHz, $CDCl_3$): 8.30 (1H, d, J 8.2, H-4), 8.12 (2H, d, J 8.2, H-1) 7.42-7.07 (12H, m, H-2, H-3, H-5, H-6, H-7, H-8, H-9, H-10), 6.60 (1H, s, H-11), 2.23-2.02 (2H, m, H-12), 1.61 (3H, s, H-14), 0.41 (3H, t, J 7.5, H-13).

HRMS (m/z - APCI): Found: 398.1760 ($M+H$)⁺ $C_{26}H_{23}NO_3$ Requires 397.1678.

10.7.7.2 3-Acetyl-1-(2,2-diphenylacetyl)-3,5-dimethylindolin-2-one (572)



Prepared according to **General Procedure U** using **564** (25.30 mg, 0.06 mmol), TBAF (3.20 μ L, 0.01 mmol) and THF (0.70 mL). The reaction mixture was stirred for 15 min followed by purification *via* silica chromatography, eluting with 100% CH_2Cl_2 to furnish **572** as a white solid (21.20 mg, 83%). M.p. 158-159 $^\circ\text{C}$.

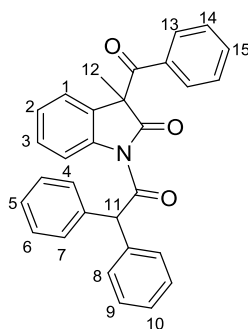
δ_{H} (400 MHz, CDCl_3): 8.17 (1H, d J 8.3, H-4), 7.38-7.15 (12H, m, H-1, H-3, H-5, H-6, H-7, H-8, H-9, H-10), 6.90 (1H, s, H-11), 6.57 (1H, s), 2.32 (3H, s, H-2), 1.51 (3H, s, H-13), 1.48 (3H, s, H-12).

δ_{C} (100 MHz, CDCl_3): 199.3 (C=O), 176.1 (C=O), 173.0 (C=O), 138.0 (q), 137.9 (q), 137.7 (q), 135.8 (q), 130.1, 129.4, 129.3, 128.8, 128.5, 128.4 (q), 127.5, 127.4, 123.6, 116.6, 62.6 (q), 58.0, 25.5, 21.1, 19.7.

ν_{max} (neat)/ cm^{-1} : 2981, 1749, 1713, 1484

HRMS (m/z - APCI): Found: 398.1756 ($\text{M}+\text{H}$) $^+$ $\text{C}_{26}\text{H}_{23}\text{NO}_3$ Requires 397.1678.

10.7.7.3 3-Benzoyl-1-(2,2-diphenylacetyl)-3-methylindolin-2-one (573)

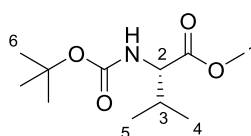


Prepared according to **General Procedure U** using **566** (30.50 mg, 0.07 mmol), TBAF (3.30 μ L, 0.03 mmol) and THF (0.70 mL). The reaction mixture was stirred for 45 mins followed by purification *via* silica chromatography, eluting with 50% petroleum ether in CH_2Cl_2 to furnish **573** as a white solid (14.90 mg, 76%) M.p. 136-137 $^\circ\text{C}$.

δ_{H} (400 MHz, CDCl_3):	8.39 (1H, d, J 8.2, H-4), 7.46-7.05 (18H, m, H-1, H-2, H-3, H-5, H-6, H-7, H-8, H-9, H-10, H-13, H-14, H-15), 6.57 (1H, s, H-11), 1.62 (3H, s, H-12).
δ_{C} (100 MHz, CDCl_3):	193.4 (C=O), 176.2 (C=O), 173.3 (C=O), 139.6 (q), 138.0 (q), 137.6 (q), 135.5 (q), 132.8, 130.4 (q), 129.5, 129.3, 129.2, 128.7, 128.6, 127.8, 127.5, 127.4, 127.4, 126.1, 122.9, 117.3, 60.8 (q), 57.6, 23.8.
ν_{max} (neat)/ cm^{-1} :	2923, 2853, 1750, 1710, 1683
HRMS (m/z - APCI):	Found: 446.1732 ($\text{M}+\text{H}$) $^+$ $\text{C}_{30}\text{H}_{23}\text{NO}_3$ Requires: 445.1678.

10.8 Experimental data for Section 6

10.8.1 Methyl (tert-butoxycarbonyl)-L-valinate (590)

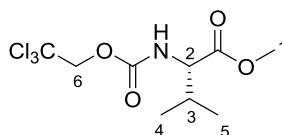


N-Boc-L-valine (0.5 g, 2.4 mmol) was dissolved in anhydrous DMF (0.5 mL) under argon and was cooled to 0 °C. NaH (60% in mineral oil, 0.1 g, 2.3 mmol) was added and was stirred for 30 min followed by the addition of MeI (0.6 mL, 11.8 mmol). The reaction mixture was warmed to rt and was stirred for 16 h. NaOH (1N, aq., 5 mL) was added and the product was extracted with EtOAc (x3) and dried over MgSO_4 and concentrated *in vacuo*. The material obtained was purified *via* silica chromatography eluting with 10% EtOAc in hexane to furnish **590** (543 mg, 93%) as a colourless oil. Spectral data for this compound were consistent with those in the literature.²⁶⁶

δ_{H} (400 MHz, CDCl_3):	5.08-4.90 (1H, m, NH), 4.23-4.13 (1H, m, H-2), 3.71 (3H, s, H-1), 2.19-2.03 (1H, m, H-3), 1.42 (9H, s, H-6), 0.94 (3H, d, J 6.8, H-4), 0.87 (3H, d, J 6.8, H-5).

HRMS (m/z - ESI):	Found: 2681528. ($\text{M} + \text{Na}$) $^+$ $\text{C}_{12}\text{H}_{23}\text{O}_4\text{NNa}$ Requires: 268.1519.

10.8.2 Methyl ((2,2,2-trichloroethoxy)carbonyl)-L-valinate (593)



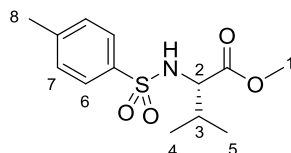
L-valine (1.20 g, 6.90 mmol) was dissolved in a solution of NaOH (2N, aq., 6 mL), and cooled to 0 °C. Troc-chloride (1.1 mL, 8.3 mmol) was added and the reaction was warmed to rt. After 2 h of stirring H_2O was added and the aqueous layer was washed with ether followed by acidification to pH 3 using conc. HCl. The product was extracted with EtOAc (x3) and the combined organic extracts

were dried over MgSO_4 and were concentrated *in vacuo* to furnish the Troc-protected amino acid **592** (1.1 g, 3.5 mmol, 50%) which was dissolved in anhydrous DMF (13.2 mL) under argon and was cooled to 0 °C. NaH (60% in mineral oil, 130.0 mg, 2.5 mmol) was added and was stirred for 30 min followed by the addition of MeI (0.8 mL, 16.5 mmol). The reaction mixture was warmed to rt and was stirred for 16 h. NaOH (1N, aq., 15 mL) was added and the product was extracted with EtOAc (x3) and dried over MgSO_4 and concentrated *in vacuo*. The material obtained was purified *via* silica chromatography eluting with 10% EtOAc in hexane to furnish **593** (1.1 g, 96%) as a colourless oil. Spectral data for this compound were consistent with those in the literature.

δ_{H} (400 MHz, CDCl_3): 5.47 (1H, d, J 8.6, NH), 4.78 (1H, d, J 12.3, H-6a), 4.66 (1H, d, J 12.3, H-6b), 4.30 (1H, dd, J 4.8, 9.2, H-2), 3.74 (3H, s, H-1), 2.25-2.12 (1H, m, H-3), 0.97 (3H, d, J 6.9, H-4), 0.91 (3H, d, J 6.9, H-5).

HRMS (m/z - ESI): Found: 305.9987 ($\text{M}+\text{H}$)⁺ $\text{C}_9\text{H}_{14}\text{Cl}_4\text{NO}_4$ Requires: 513.1846

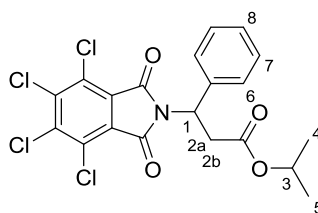
10.8.3 Methyl tosyl-L-valinate (**595**)



L-valine (1.1 g, 9.4 mmol) and NaCO_3 (1.2 g, 11.3 mmol) were dissolved in H_2O (15.0 mL) and were cooled to -5 °C. Tosyl chloride (2.2 g, 11.3 mmol) was added in four portions over 1 h and the resulting mixture was warmed to rt and was stirred for a further 4 h. The reaction mixture was acidified to pH 2 using conc. HCl and the resulting crystals were filtered and washed with H_2O to furnish the tosyl-protected product **594** (1.4 g, 5.1 mmol, 54%) which was dissolved in anhydrous DMF (26.0 mL) under argon and was cooled to 0 °C. NaH (60% in mineral oil, 200.0 mg, 5.1 mmol) was added and was stirred for 30 min followed by the addition of MeI (1.6 mL, 32.5 mmol). The reaction mixture was warmed to rt and was stirred for 16 h. NaOH (1N, aq., 30 mL) was added and the product was extracted with EtOAc (x3) and dried over MgSO_4 and concentrated *in vacuo*. The material obtained was purified *via* silica chromatography eluting with 10% EtOAc in hexane to furnish **595** (1.1 g, 96%) as an off white solid. M.p 58-60 °C. Spectral data for this compound were consistent with those in the literature.²⁶⁷

δ_{H} (400 MHz, CDCl_3): 7.70 (1H, d, J 8.1, H-6), 7.28 (1H, d, J 8.1, H-7), 5.02 (1H, d, J 5.0, NH), 3.73 (1H, dd, J 5.0, 10.1, H-1), 3.44 (3H, s, H-1), 2.08-1.94 (1H, m, H-3), 0.94 (3H, d, J 6.9, H-5), 0.86 (3H, d, J 6.9, H-4).

10.8.4 *iso*Propyl 3-phenyl-3-(4,5,6,7-tetrachloro-1,3-dioxisoindolin-2-yl)propanoate (597)



Oxazinone **144a** (17.00 mg, 0.04 mmol) was dissolved in anhydrous CHCl_3 (0.35 mL) under argon. TBAF (1M in THF, 0.07 mL) was added and the reaction mixture was stirred for 20 h. The resulting mixture was purified *via* silica chromatography, eluting with 10% EtOAc in hexane to furnish **597** (15.40 mg, 91%) as a white solid. M.p 189-191 °C.

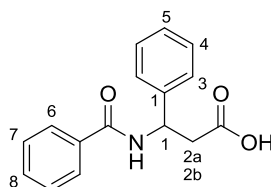
δ_{H} (400 MHz, CHCl_3): 7.53-7.34 (5H, m, H-6, H-7, H-8), 5.35 (1H, dd, J 6.2, 12.5, H-1), 3.92 (1H, sept., J 6.3, H-3), 3.54 (1H, dd, J 12.5, 15.6, H-2a), 3.17 (1H, dd, J 3.12, 15.6, H-2b), 1.00 (3H, d, J 6.0, H-4), 0.91 (3H, d, J 6.0, H-4).

δ_{C} (100 MHz, CHCl_3): 171.5 (C=O), 166.3 (C=O), 145.1 (q), 140.4 (q), 136.2 (q), 131.6, 127.7, 127.7 (q), 127.0, 126.1, 50.3, 49.1, 41.2, 21.6.

ν_{max} (neat)/ cm^{-1} : 2983, 1775, 1731.

HRMS (m/z - ESI): Found: 473.9755 ($\text{M}+\text{H}$) $^+$ $\text{C}_{20}\text{H}_{16}\text{Cl}_4\text{NO}_4$ Requires: 473.9755.

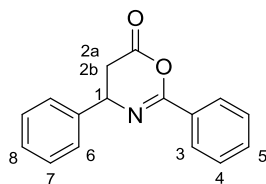
10.8.5 3-Benzamido-3-phenylpropanoic acid (600)



114a (6.6 g, 39.7 mmol) was dissolved in NaOH (2N, aq., 40 mL) was cooled to 0 °C. Benzoyl chloride (5.1 mL, 43.6 mmol) was added followed by the slow addition of a second aliquot of NaOH (2N, aq., 40 mL). The mixture was stirred for 30 min followed acidification with conc. HCl to pH 2. The precipitate was filtered and recrystallised from EtOH/ H_2O to furnish **600** (7.0 g, 65%). M.p 191-193 °C. (lit.¹¹⁰ 192-194) Spectral data for this compound were consistent with those in the literature.¹¹⁰

δ_{H} (400 MHz, $\text{DMSO}-d_6$): 12.29 (1H, s, OH), 8.89 (1H, d, J 8.3, NH), 7.84-7.87 (2H, m, H-6), 7.20-7.56 (8H, m, H-3, H-4, H-5, H-7, H-8), 5.41-5.49 (1H, m, H-1), 2.91 (1H, dd, J 8.9, 15.7, H-2a), 2.78 (1H, dd, J 6.2, 15.7, H-2b).

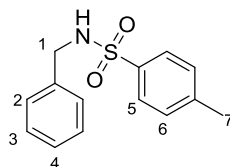
10.8.6 2,4-Diphenyl-4,5-dihydro-6H-1,3-oxazin-6-one (121)



600 (5.0 g, 18.6 mmol) was dissolved in anhydrous CH_2Cl_2 under argon and freshly distilled NEt_3 (3.2 mL, 22.4 mmol) was added. The solution was cooled to $-15\text{ }^\circ\text{C}$ and isobutyl chloroformate (2.9 mL, 22.3 mmol) was added slowly. The mixture was stirred at $-15\text{ }^\circ\text{C}$ for 15 min followed by 10 min at $0\text{ }^\circ\text{C}$ and a further 15 min at rt. The reaction mixture was concentrated *in vacuo* and was purified *via* silica chromatography, eluting with 20% EtOAc in hexane to furnish **121** as a white solid. (2.3 g, 50%). M.p $102\text{--}103\text{ }^\circ\text{C}$ (lit.¹¹⁰ $100\text{--}102\text{ }^\circ\text{C}$). Spectral data for this compound were consistent with those in the literature.¹¹⁰

δ_{H} (400 MHz, CDCl_3): 8.12–8.14 (2H, m, H-3), 7.31–7.57 (8H, m, H-4, H-5, H-6, H-7, H-8), 5.06 (1H, m, H-1), 3.08 (1H, dd, J 5.2, 16.1, H-2a), 2.67 (1H, dd, J 11.0, 16.1, H-2b).

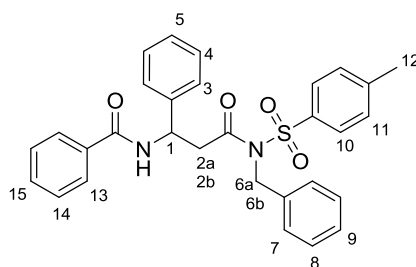
10.8.7 *N*-Benzyl-4-methylbenzenesulfonamide (606)



Benzylamine (2.5 mL, 45.8 mmol) and NEt_3 (3.5 mL, 68.7 mmol) were dissolved in CH_2Cl_2 (80.0 mL) and 4-methylbenzenesulfonyl chloride (4.4 g, 45.8 mmol) was added in small portions. The reaction mixture was stirred for 1 h and was quenched with H_2O (30.0 mL). The product was extracted with CH_2Cl_2 (x3), dried over MgSO_4 and was concentrated *in vacuo*. The resulting material was recrystallised using hexane and CH_2Cl_2 to furnish **606** as colourless crystals (1.2g, 10%). M.p $104\text{--}106\text{ }^\circ\text{C}$ (lit.²⁶⁸ $109\text{--}111\text{ }^\circ\text{C}$). Spectral data for this compound were consistent with those in the literature.²⁶⁹

δ_{H} (400 MHz, CDCl_3): 7.76 (2H, m, H-5), 7.33–7.16 (7H, m, H-2, H-3, H-4, H-5, H-6), 4.65–4.55 (1H, m, NH), 4.12 (2H, d, J 6.2), 2.44 (3H, s, H-7).

10.8.8 N-(3-((N-Benzyl-4-methylphenyl)sulfonamido)-3-oxo-1-phenylpropyl)benzamide (607)



121 (20.9 mg, 0.1 mmol) and **606** (21.7 mg, 0.1 mmol) were dissolved in anhydrous CH₃Cl under argon and a solution of TBAF (1M in THF, 16.0 μ L) was added. The reaction was stirred for 20 h followed by purification *via* silica chromatography, eluting with a gradient of 10-40% EtOAc in hexane to furnish **607** (12.3 mg, 30%) as a white solid. M.p 166-168 °C.

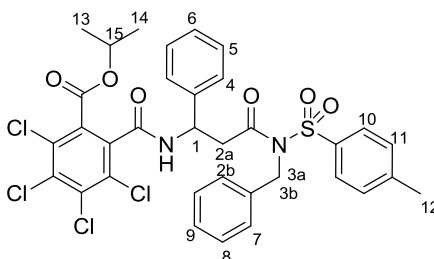
δ_H (400 MHz, CHCl₃): 7.77-7.73 (2H, m, H-13), 7.59-7.08 (17H, m, H-3, H-4, H-5, H-7, H-8, H-9, H-10, H-11, H-14, H-15), 5.63-5.55 (1H, m, H-1), 5.05 (1H, d, *J* 16.0, H-6a), 4.98 (1H, d, *J* 16.0, H-6b), 3.53 (1H, dd, *J* 6.0, 16.4, H-2a), 3.06 (1H, dd, *J* 5.1, 16.4), 2.41 (3H, s, H-12).

δ_C (100 MHz, CHCl₃): 171.6 (C=O), 166.4 (C=O), 145.2 (q), 140.5 (q), 136.4 (q), 136.2 (q), 134.1 (q), 131.6 (q), 129.9, 128.6, 128.6, 128.6, 127.8, 127.7 (q), 127.6, 127.4 (q), 127.1, 126.1, 50.4, 49.3, 21.6.

ν_{max} (neat)/cm⁻¹: 1706, 1630, 1360.

HRMS (*m/z* - ESI): Found: 523.1841 (M+H)⁺ C₃₀H₂₈N₂O₄S Requires: 513.1846

10.8.9 isoPropyl-2-((3-((N-benzyl-4-methylphenyl)sulfonamido)-3-oxo-1-phenylpropyl)carbamoyl)-3,4,5,6-tetrachlorobenzoate (608)



Oxazinone **144a** (34.40 mg, 0.07 mmol) and **606** (18.92 mg, 0.07 mmol) were dissolved in anhydrous CHCl₃ under argon and a solution of TBAF (1M in THF, 14 μ L) was added. The reaction was stirred for 20 h followed by purification *via* silica chromatography, eluting with a gradient of 10-40% EtOAc in hexane to furnish **608** (6.18 mg, 12%) as a white solid. M.p 120-122 °C (decomp.).

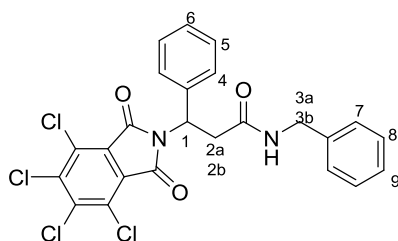
δ_{H} (400 MHz, CHCl_3): 7.79 (1H, d, J 8.3, NH), 7.50 (2H, d, J 8.3, H-10), 7.37-7.03 (12H, m, H-4, H-5, H-6, H-7, H-8, H-9, H-11), 5.57-5.53 (1H, m, H-1), 5.11 (1H, sept., J 6.2, H-15), 5.07-5.00 (2H, m, H-3a, H-3b), 3.55 (1H, dd, J 4.8, 17.1, H-2a), 3.18 (1H, dd, J 5.7, 17.2, H-2b), 2.45 (3H, s, H-12), 1.25-1.20 (6H, m, H-13, H-14).

δ_{C} (100 MHz, CHCl_3): 170.9 (C=O), 162.4 (C=O), 145.2 (q), 139.1 (q), 136.3 (q), 136.2 (q), 134.4 (q), 132.9 (q), 129.9, 129.8, 128.7, 128.6, 128.0, 127.9, 127.2, 126.4, 71.2, 50.3, 49.1, 40.7, 21.6, 21.4, 21.4.

ν_{max} (neat)/ cm^{-1} : 3250, 1780, 1726, 1630, 1365.

HRMS (m/z - APCI): Found: 734.0648 ($\text{M}+\text{H}$) $^+$ $\text{C}_{33}\text{H}_{31}\text{Cl}_4\text{N}_2\text{O}_6\text{S}$ Requires: 735.0642

10.8.10 4-(3-(Benzylamino)-3-oxo-1-(4,5,6,7-tetrachloro-1,3-dioxoisindolin-2-yl)propyl)benzene-1-ylum (609)



Oxazinone **144a** (34.40 mg, 0.07 mmol) and **606** (18.92 mg, 0.07 mmol) were dissolved in anhydrous CHCl_3 under argon and a solution of TBAF (1M in THF, 14.00 μL) was added. The reaction was stirred for 20 h followed by purification *via* silica chromatography, eluting with a gradient of 10-40% EtOAc in hexane to furnish **N24** (3.28 mg, 9%) as a white solid.

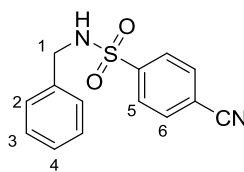
δ_{H} (400 MHz, CHCl_3): 7.53-7.50 (2H, m, H-4), 7.37-7.29 (3H, m, H-5, H-6), 7.17-7.04 (5H, m, H-7, H-8, H-9), 5.99-5.93 (1H, m, NH), 5.90 (1H, dd, J 5.2, 11.6, H-1), 4.60 (1H, dd, J 7.2, 14.4, H-3a), 4.12 (1H, dd, J 5.0, 14.4, H-3b), 3.75 (1H, dd, J 11.5, 14.5, H-2a), 2.98 (1H, dd, J 5.2, 14.4, H-2b).

δ_{C} (100 MHz, CHCl_3): 170.0 (C=O), 163.6 (C=O), 140.1 (q), 138.3 (q), 138.0 (q), 129.7 (q), 129.0, 128.6, 128.4, 127.8, 127.8, 127.2, 127.1 (q), 53.1, 43.5, 38.2.

ν_{max} (neat)/ cm^{-1} : 3675, 1706, 1638.

HRMS (m/z - APCI): Found: 554.9599 ($\text{M}+\text{Cl}^-$) $\text{C}_{24}\text{H}_{16}\text{Cl}_5\text{N}_2\text{O}_3$ Requires: 554.9609.

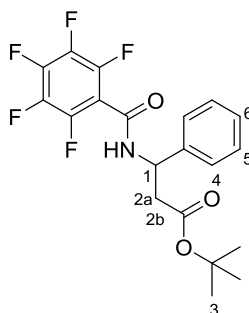
10.8.11 *N*-Benzyl-4-cyanobenzenesulfonamide (**611**)



Benzylamine (0.3 mL, 2.5 mmol) and NEt_3 (0.5 mL, 3.7 mmol) were dissolved in CH_2Cl_2 (5 mL) and 4-cyanobenzenesulfonyl chloride (0.5 g, 2.5 mmol) was added in small portions. The reaction mixture was stirred for 3 h and was quenched with H_2O (30 mL). The product was extracted with CH_2Cl_2 (x3), dried over MgSO_4 and was concentrated *in vacuo*. The resulting material was recrystallised using hexane and CH_2Cl_2 to furnish **611** as colourless crystals (0.3 g, 45%). M.p 127-129 °C (lit.²⁷⁰ 141-142 °C). Spectral data for this compound were consistent with those in the literature.²⁷¹

δ_{H} (400 MHz, CHCl_3): 7.92 (2H, d, J 8.4, H-6), 7.76 (2H, d, J 8.4, H-5), 7.29-7.13 (5H, m, H-2, H-3, H-4), 4.91-4.81 (1H, m, NH), 4.21 (2H, d, J 6, H-1).

10.8.12 *tert*-Butyl 3-(perfluorobenzamido)-3-phenylpropanoate (**615**)



595 (3.2 g, 9.2 mmol), DCC (1.9 g, 9.2 mmol) and anhydrous CH_2Cl_2 (18.0 mL) were added to **114a** (1.7 g, 9.1 mmol) and were stirred for 16 h. The resulting precipitate was filtered and the filtrate was concentrated *in vacuo* followed by purification *via* silica chromatography, eluting with a 0-20% EtOAc in hexane gradient to yield **615** as a white solid (3.0 g, 78%). M.p 109-111 °C.

δ_{H} (400 MHz, CHCl_3): 7.51-7.25 (5H, m, H-4, H-5, H-6), 5.60-5.50 (1H, m, H-1), 2.94-2.81 (2H, m, H-2a, H-2b), 1.33 (9H, s, H-3).

δ_{C} (100 MHz, CHCl_3): 170.5 (C=O), 156.6 (C=O), 144.0 (*o*-C-F, J 250.2), 142.1 (*p*-C-F, J 257.6), 139.5 (q), 137.4 (*m*-C-F, J 257.2), 128.7, 127.8, 126.1, 111.7 (q), 81.9 (q), 50.5, 40.7, 27.8.

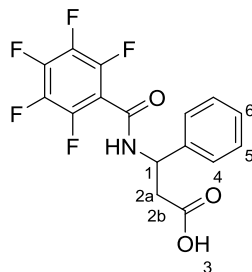
δ_{F} (376 MHz, CDCl_3): -138.9 (2F, d, J 18.2), 149.12 (1F, t, J 21.1), -160.14 (2F, t, J 20.1).

ν_{max} (neat)/ cm^{-1} : 3310, 1723, 1656.

HRMS (m/z – DIP-APCI):* Found: 416.1201 ($M+H$)⁺ C₂₀H₁₃F₅NO₃ Requires: 416.1280.

*Note: Error for HRMS is -18.8 ppm.

10.8.13 3-(*per*Fluorobenzamido)-3-phenylpropanoic acid (**616**)



Prepared according to **General procedure D** using **615** (4.0 g, 7.7 mmol), TFA (20.0 mL) and anhydrous CH₂Cl₂ (20.0 mL) to yield **616** (2.7 g, 99 %) as a white solid. M.p 195-197 °C.

δ_H (400 MHz, CHCl₃): 7.43-7.14 (6H, m, H-4, H-5, H-6, NH), 5.72-5.61 (1H, m, H-1), 3.12 (1H, dd, J 5.5, 16.7, H-2a). 3.03 (1H, dd, J 5.8, 16.7, H-2b).

δ_C (100 MHz, CHCl₃): 163.5 (C=O), 145.3 (C=O), 145.2 (*o*-C-F, J 251.0), 142.7 (*p*-C-F, J 248.2), 139.1 (q), 137.7 (*m*-C-F, J 253.9), 129.1, 128.2, 126.0, 108.2 (q), 57.6, 35.8.

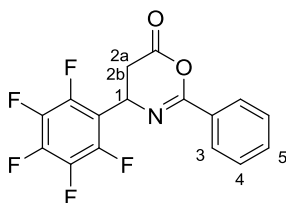
δ_F (376 MHz, CDCl₃): -140.3 (d, J 15.8), -150.3 (t, J 19.3), -160.8 (t, J 21.2).

ν_{max} (neat)/cm⁻¹: 3273, 1806, 1705, 1662.

HRMS (m/z - DIP-APCI): Found: 360.0618 ($M+H$)⁺ C₁₆H₁₁F₅NO₃ Requires: 360.0654.

*Note: Error for HRMS is -9. ppm

10.8.14 4-(*per*Fluorophenyl)-2-phenyl-4,5-dihydro-6H-1,3-oxazin-6-one (**617**)

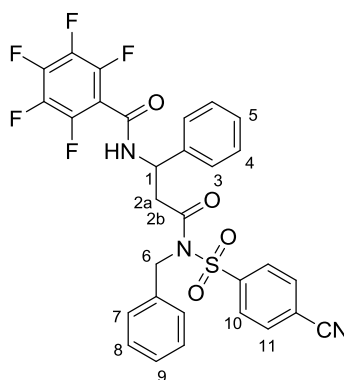


Prepared according to **General Procedure F** using **616** (5.5 g, 11.1 mmol), CH₂Cl₂ (5.0 mL), NEt₃ (1.7 mL, 12.3 mmol), SOCl₂ (0.9 mL, 12.3 mmol) and a second aliquot of NEt₃ (3.4 mL, 24.6 mmol). The product was recrystallised from a mixture of diisopropyl ether (*i*Pr₂O) and EtOAc to furnish **617** as yellow crystals (2.7 g, 67 %). M.p 113-115 °C.

δ_H (400 MHz, CHCl₃): 7.45-7.30 (5H, m, H-3, H-4, H-5), 5.15 (1H, dd, J 5.3, 11.1, H-1), 3.13 (1H, dd, J 5.4, 16.3, H-2a), 2.78 (1H, dd, J 11.1, 16.3, H-2b).

δ_{C} (100 MHz, CHCl_3):	163.5 (C=O), 145.2 (<i>o</i> -C-F, <i>J</i> 237.8), 143.9 (<i>p</i> -C-F, <i>J</i> 263.0), 139.0 (q), 137.7 (<i>m</i> -C-F, <i>J</i> 251.9), 129.2, 128.6, 126.1, 118.9 (q), 57.7, 36.0.
δ_{F} (376 MHz, CDCl_3):	-138.9 (d, <i>J</i> 18.2), -149.12 (t, <i>J</i> 21.1), -160.14 (t, <i>J</i> 20.1).
ν_{max} (neat)/ cm^{-1} :	1806, 1684, 1656, 1503.
HRMS (<i>m/z</i> - APCI):	Found: 342.0546 ($\text{M}+\text{H}$) ⁺ $\text{C}_{16}\text{H}_9\text{F}_5\text{N}_2\text{O}_2$ Requires: 342.0547.

10.8.15 *N*-(3-((*N*-Benzyl-4-cyanophenyl)sulfonamido)-3-oxo-1-phenylpropyl)-2,3,4,5,6-pentafluorobenzamide (619)

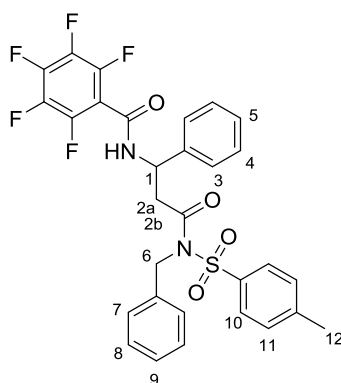


617 (19.30 mg, 0.06 mmol), **611** (15.25 mg, 0.06 mmol) and KF (0.98 mg, 0.02 mmol) were dissolved in anhydrous CH_3Cl (0.86 mL) under argon and were stirred for 18 h. The resulting mixture was purified *via* silica chromatography, eluting with a gradient of 10-40% EtOAc in hexane to furnish **619** (35.0 mg, 95%) as a colourless oil.

δ_{H} (400 MHz, CHCl_3):	7.35-7.08 (14H, m, H-3, H-4, H-5, H-7, H-8, H-9, H-10, H-11), 5.58-5.48 (1H, m, H-1), 5.03 (2H, s, H-6), 3.41 (1H, dd, <i>J</i> 4.9, 17.0, H-2a), 3.10 (1H, dd, <i>J</i> 5.7, 17.0, H-2b).
δ_{C} (100 MHz, CHCl_3):*	171.1 (C=O), 156.7 (C=O), 142.8 (C=N), 138.7 (q), 135.2 (q), 132.6, 128.9, 128.9, 128.5, 128.3, 128.0, 127.5, 126.1, 117.5 (q), 116.8 (q), 50.7, 49.4, 41.0.
δ_{F} (376 MHz, CDCl_3):	-140.4 (d, <i>J</i> 15.8), -150.1 (t, <i>J</i> 20.0), -159.7 (t, <i>J</i> 15.8).
ν_{max} (neat)/ cm^{-1} :	3675, 1777, 2298, 1655, 1497, 1362, 1154.
HRMS (<i>m/z</i> - APCI):	648.0746 ($\text{M}+\text{Cl}$) ⁻ $\text{C}_{30}\text{H}_{20}\text{ClF}_5\text{N}_3\text{O}_4\text{S}$ Requires: 648.0789.

* *pentafluorobenzene* cannot be seen in ^{13}C NMR spectra.

10.8.16 *N*-(3-((*N*-Benzyl-4-methylphenyl)sulfonamido)-3-oxo-1-phenylpropyl)-2,3,4,5,6-pentafluorobenzamide (618)



617 (39.50 mg, 0.10 mmol), **606** (13.64 mg, 0.05 mmol) catalyst **494** (5.56 mg, 0.01 mmol), anhydrous KF (1.81 mg, 0.03 mmol) and *para*-iodoanisole (12.21 mg, 0.05 mmol) were placed in an RBF and the flask was evacuated and flushed with argon using schlenk technique and a rubber stopper and argon balloon were fitted. Anhydrous CHCl₃ (1.0 mL) was added and the reaction mixture was stirred for 36 h. MeOH (0.23 mL, 0.58 mmol) was added and the mixture was stirred for a further 3 h. The resulting mixture was purified *via* silica chromatography, eluting with a gradient of 10-40% EtOAc in hexane to furnish **618** as a white solid (22.89 mg, 38%).

CSP-HPLC conditions: Chiralpak IA column (4.6 mm x 250mmL), hexane/IPA: 90/10, 1 mL min⁻¹, rt, UV detection at 220 nm, retention times: 26.83 min and 41.46 min.

δ_H (400 MHz, CHCl₃): 7.52-6.99 (14H, m, H-3, H-4, H-5, H-7, H-8, H-9, H-10, H-11), 5.59-5.51 (1H, m, H-1), 4.99 (2H, s, H-6), 3.51 (1H, dd, *J* 5.7, 16.9, H-2a), 3.09 (1H, dd, *J* 5.2, 16.9, H-2b).

δ_C (100 MHz, CHCl₃):* 171.3 (C=O), 156.6 (C=O), 145.2 (q), 143.5 (q), 136.2 (q), 136.0 (q), 129.9, 129.7, 128.7, 128.6, 127.9, 127.8, 127.8, 127.2, 126.0, 50.6, 49.1, 40.9, 21.5.

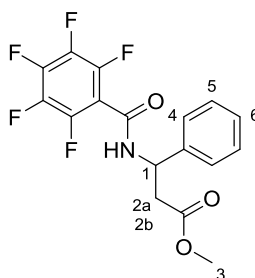
δ_F (376 MHz, CDCl₃): -140.3 (d, *J* 14.9), -150.7 (t, *J* 20.1), -160.5 (t, *J* 18.3).

ν_{max} (neat)/cm⁻¹: 3675, 1709, 1656, 1517, 1495, 1362, 1153.

HRMS (*m/z* - ESI): Found: 601.1239 (M-H)⁻ C₃₀H₂₂F₅N₂O₄S Requires: 601.1226.

* *pentafluorobenzene* cannot be seen in ¹³C NMR spectra.

10.8.17 Methyl 3-(perfluorobenzamido)-3-phenylpropanoate (**620**)



617 (39.50 mg, 0.10 mmol), **606** (13.64 mg, 0.05 mmol) catalyst **494** (5.56 mg, 0.01 mmol), anhydrous KF (1.81 mg, 0.03 mmol) and *para*-iodoanisole (12.21 mg, 0.05 mmol) were placed in an RBF and the flask was evacuated and flushed with argon using schlenk technique and a rubber stopper and argon balloon were fitted. Anhydrous CHCl_3 (1.0 mL) was added and the reaction mixture was stirred for 36 h. MeOH (0.23 mL, 0.58 mmol) was added and the mixture was stirred for a further 3 h. The resulting mixture was purified *via* silica chromatography, eluting with a gradient of 10-40% EtOAc in hexane to furnish **620** as a white solid (7.47 mg, 20%). M.p. 90-92 °C.

CSP-HPLC conditions: Chiralpak IA column (4.6 mm x 250mmL), hexane/IPA: 90/10, 1 mL min⁻¹, rt, UV detection at 220 nm, retention times 17.22 min and 41.05 min.

δ_{H} (400 MHz, CHCl_3): 7.45-7.22 (5H, m, H-4, H-5, H-6), 5.67-5.58 (1H, m, H-1), 3.64 (3H, s, H-3), 3.07-2.93 (2H, m, H-2a, H-2b).

δ_{C} (100 MHz, CHCl_3):* 171.7 (C=O), 156.7 (C=O), 144.3 (*o*-C-F, *J* 256.8), 142.4 (*p*-C-F, *J* 291.8) 139.3 (q), 137.5 (*m*-C-F, *J* 251.9) 128.9, 128.0, 126.1, 111.6 (q), 52.1, 50.3, 39.4.

δ_{F} (376 MHz, CDCl_3): -140.3 (d, *J* 17.8), -150.5 (t, *J* 20.3), -159.9 (t, *J* 17.6).

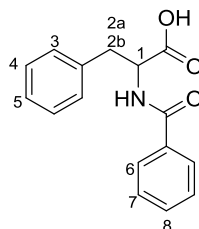
ν_{max} (neat)/cm⁻¹: 3236, 1731, 1662.

HRMS (*m/z* - APCI): Found: 374.0817 (M+H)⁺ C₁₇H₁₃F₅NO₃ Requires: 374.0810.

* *pentafluorobenzene* cannot be seen in ¹³C NMR spectra.

10.9 Experimental data for Section 8

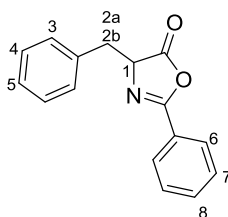
10.9.1 Benzoylphenylalanine (**639**)



DL-phenylalanine (**344**, 4.1 g, 165.2 mmol) was dissolved in NaOH (2N, aq., 25 mL) and was cooled to 0 °C. Benzoyl chloride was added dropwise and the resulting mixture was stirred for 16 h. The mixture was acidified to pH 2 using HCl (2N, aq.) and the resulting precipitate was collected by filtration to furnish **639** as a white solid (3.9 g, 88%). M.p. 185-187 °C (Lit.²⁷² m.p. 183-184 °C). Spectral data for this compound were consistent with those in the literature.²⁷³

δ_{H} (400 MHz, CHCl_3): 8.14-8.06 (1H, m, H-6), 7.73-7.57 (1H, m, H-8), 7.53-7.39 (2H, m, H-7), 7.35-7.19 (5H, m, H-3, H-4, H-5), 6.54 (1H, d, J 8.4, NH), 5.16-5.04 (1H, m, H-1), 3.34 (2H, m, H-2a, H-2b).

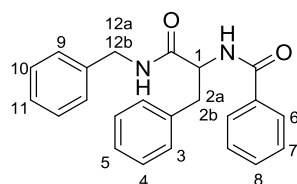
10.9.2 4-Benzyl-2-phenyloxazol-5(4H)-one (**92**)



639 (3.1 g, 11.4 mmol) was dissolved in anhydrous CH_2Cl_2 (90 mL) under argon and cooled to 0 °C. To this DCC (2.4g, 11.4 mmol) was added and the reaction mixture was stirred for 1 h at rt. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* and was purified *via* silica chromatography eluting with CH_2Cl_2 to afford **92** (1.7 g, 60%) as a white solid. M.p. 69-70 °C (Lit.²⁷³ m.p. 169-70 °C). Spectral data for this compound were consistent with those in the literature.²⁷³

δ_{H} (400 MHz, CHCl_3): 7.98-7.88 (2H, m, H-6), 7.59-7.39 (3H, m, H-7, H-8), 7.32-7.28 (5H, m, H-3, H-4, H-5), 4.69 (1H, m, H-1), 3.38 (1H, dd, J 5.0, 14.0, H-2a), 3.19 (1H, dd, J 6.7, 14.0, H-2b).

10.9.3 N-Benzoyl-N-(1-(benzylamino)-1-oxo-3-phenylpropan-2-yl)benzamide (640)



Benzoyl fluoride (10.8 μ L, 0.1 mmol) and DMAP (11.2 mg, 0.1 mmol) were dissolved in anhydrous CH_2Cl_2 (1.7 mL) under argon in the presence of 3 Å MS and no stirrer bar. The mixture left to stand for 15 min followed by the addition of **92** (25.1 mg, 0.1 mmol). The resulting mixture was allowed to react for 14 h until complete consumption of **92** was observed *via* ^1H NMR spectroscopic analysis. Benzylamine (16.4 μ L, 0.2 mmol) was added and the reaction mixture was stirred for 10 mins followed by purification of the crude mixture *via* silica chromatography eluting with a gradient of 10-50% EtOAc in hexane to afford **640** (22.2 mg, 62%) as a white solid. M.p. 193-195 °C.

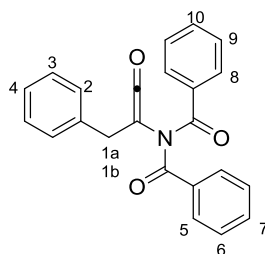
δ_{H} (400 MHz, CHCl_3): 7.75 (2H, d J 7.8, H-6), 7.53 (1H, t, J 7.8, H-11), 7.45 (2H, t, J 7.8, 14.9, H-10), 7.32-7.23 (8H, m, H-3, H-5, H-9, H-10, H-11), 7.11-7.07 (2H, m, H-4), 6.95 (1H, d, J 7.5, NH), 6.17-6.11 (1H, m, NH), 4.90-4.84 (1H, m, H-1), 4.41 (1H, dd, J 6.0, 14.8, H-12a), 4.33 (1H, dd, J 5.5, 14.8, H-12b), 3.28 (1H, dd, J 5.8, 13.7, H-2a), 3.13 (1H, dd, J 8.3, 13.7, H-2b).

δ_{C} (100 MHz, CHCl_3): 170.6 (C=O), 167.1 (C=O), 137.4 (q), 136.6 (q), 133.7 (q), 131.9, 129.4, 128.8, 128.7, 128.7, 127.7, 127.5, 127.1, 127.0, 55.0, 43.6, 38.8.

ν_{max} (neat)/ cm^{-1} : 3327, 2980, 1718, 1627.

HRMS (m/z - APCI): Found: 359.1760 ($\text{M}+\text{H}^+$) $\text{C}_{23}\text{H}_{23}\text{N}_2\text{O}_2$ Requires: 359.1754

10.9.4 N-Benzoyl-N-(1-oxo-3-phenyl-1H-prop-1-en-2-yl)benzamide (639)



Benzoyl fluoride (10.8 μ L, 0.1 mmol) and DMAP (2.2 mg, 0.2 mmol) were dissolved in anhydrous CH_2Cl_2 (250 μ L) under argon in the presence of 3 Å MS with not stirrer bar. The mixture left to stand for 15 min followed by the addition of **92** (25.1 mg, 0.1 mmol). The resulting mixture was allowed to react for 48 h until complete consumption of **92** was observed *via* ^1H NMR spectroscopic analysis.

The crude mixture *via* silica chromatography eluting with a gradient of 0-30% EtOAc in hexane to afford **693** (22.2 mg, 62%) as a colourless oil.

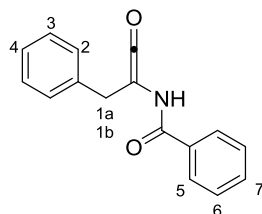
δ_{H} (400 MHz, CHCl_3): 8.26-8.22 (2H, m, H-5), 7.93-7.89 (2H, m, H-8), 7.65-7.38 (6H, m, H-6, H-7, H-9, H-10), 7.35-7.11 (5H, m, H-2, H-3, H-4), 3.79 (1H, d, J 13.6, H-1a), 3.55 (1H, d, J 13.6, H-1b).

δ_{C} (100 MHz, CHCl_3): 191.7 (C=O), 173.4 (C=O), 162.1 (C=O), 135.1 (q), 134.5 (q), 133.5, 133.1, 132.8 (q), 130.6, 129.9, 128.7, 128.6, 128.3, 128.1, 127.6, 42.2, 22.6 (q).

ν_{max} (neat)/ cm^{-1} : 2926, 1830, 1765, 1682, 1220.

HRMS (m/z - APCI): Found: 356.1279 ($\text{M}+\text{H}$) $^+$ $\text{C}_{23}\text{H}_{18}\text{NO}_3$ Requires: 356.1281

10.9.5 *N*-(1-Oxo-3-phenyl-1 β -prop-1-en-2-yl)benzamide (**648**)



Benzoic anhydride (22.6 g, 0.1 mmol) and DMAP (2.2 mg, 0.2 mmol) were dissolved in anhydrous CH_2Cl_2 (250 μL) under argon in the presence of 3 Å MS with not stirrer bar. The mixture left to stand for 15 min followed by the addition of **92** (25.1 mg, 0.1 mmol). The resulting mixture was allowed to react for 48 h until complete consumption of **92** was observed *via* ^1H NMR spectroscopic analysis. The crude mixture *via* silica chromatography eluting with a gradient of 0-50% EtOAc in hexane to afford **648** (2.8 mg, 11%) as a colourless oil.

δ_{H} (400 MHz, CHCl_3): 7.85-7.80 (2H, m, H-5), 7.59-7.52 (1H, m, H-7), 7.41 (2H, app. t, J 8.0, H-6), 7.23-7.13 (5H, m, H-2, H-3, H-4), 3.81 (1H, d, J 13.1, H-1a), 3.71 (1H, d, J 13.1, H-1b).

δ_{C} (100 MHz, CHCl_3): 176.4 (C=O), 161.9 (C=O), 133.1 (q), 132.9, 132.8 (q), 130.6, 130.4 (q) 128.6, 128.2, 128.2, 127.5, 37.5, 29.7(q).

ν_{max} (neat)/ cm^{-1} : 2924, 1819, 1716, 1625.

HRMS (m/z - APCI): Found: 251.0938 ($\text{M}+\text{H}$) $^+$ $\text{C}_{16}\text{H}_{13}\text{NO}_2$ Requires: 251.0941.

11 References

1. A. D. McNaught and A. D. McNaught, *Compendium of chemical terminology*, Blackwell Science Oxford, 1997.
2. J. H. A. Burrows, A. Parsons, G. Pilling, G. Price, *Chemistry cubed*, 1st edn., 2009.
3. R. D. McKelvey, *J. Chem. Educ.*, 1996, **73**, A174.
4. J. McConathy and M. J. Owens, *Primary Care Companion to The Journal of Clinical Psychiatry*, 2003, **5**, 70-73.
5. S. K. Teo, W. A. Colburn, W. G. Tracewell, K. A. Kook, D. I. Stirling, M. S. Jaworsky, M. A. Scheffler, S. D. Thomas and O. L. Laskin, *Clinical Pharmacokinetics*, 2004, **43**, 311-327.
6. S. Conroy, J. McIntyre and I. Choonara, *Archives of Disease in Childhood - Fetal and Neonatal Edition*, 1999, **80**, F142-F145.
7. W. A. Silverman, *Pediatrics*, 2002, **110**, 404-406.
8. D. R. Bielenberg and P. A. D'Amore, *Lymphatic Research and Biology*, 2008, **6**, 203-207.
9. W. H. Brooks, W. C. Guida and K. G. Daniel, *Curr. Top. Med. Chem.*, 2011, **11**, 760-770.
10. M. P. Koskinen Ari, *Journal*, 2011, **83**, 435.
11. G. Roos, *Key Chiral Auxiliary Applications*, Academic Press, 2014.
12. E. J. Corey and H. E. Ensley, *J. Am. Chem. Soc.*, 1975, **97**, 6908-6909.
13. Y. Gnas and F. Glorius, *Synthesis*, 2006, **2006**, 1899-1930.
14. F. Kurt, *Chem. Eur. J.*, 2001, **7**, 5004-5010.
15. M. A. Filatov, S. Karuthedath, P. M. Polestshuk, S. Callaghan, K. J. Flanagan, T. Wiesner, F. Laquai and M. O. Senge, *ChemPhotoChem*, 2018, **2**, 606-615.
16. M. C. E. and S. P. R., *Angew. Chem. Int. Ed.*, 2011, **50**, 6012-6042.
17. H. Pellissier, *Tetrahedron*, 2003, **59**, 8291-8327.
18. M. Kitamura, M. Tokunaga and R. Noyori, *Tetrahedron*, 1993, **49**, 1853-1860.
19. B. M. Trost, *Proc. Natl. Acad. Sci. U.S.A.*, 2004, **101**, 5348-5355.
20. G. Bredig and P. Fiske, *Biochem. Z.*, 1913, **46**, 7-23.
21. H. B. Kagan and K. Gopalaiah, *New J. Chem.*, 2011, **35**, 1933-1937.
22. G. M. Cooper, Sinauer Associates, 2000.
23. O. Kirk, T. V. Borchert and C. C. Fuglsang, *Curr. Opin. Biotechnol.*, 2002, **13**, 345-351.
24. A. Schmid, J. S. Dordick, B. Hauer, A. Kiener, M. Wubbolts and B. Witholt, *Nature*, 2001, **409**, 258.
25. J. R. Ludwig and C. S. Schindler, *Chem*, 2017, **2**, 313-316.
26. C. P. Casey, *J. Chem. Educ.*, 2006, **83**, 192.
27. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chem. Int. Ed.*, 2012, **51**, 5062-5085.
28. H. G. Albrecht Berkessel, *Asymmetric Organocatalysis: from biomimetic concepts to applications in asymmetric synthesis*, Wiley-VHC, 2005.
29. D. W. C. MacMillan, *Nature*, 2008, **455**, 304.
30. E. Ulrich, S. Gerhard and W. Rudolf, *Angew. Chem. Int. Ed.*, 1971, **10**, 496-497.
31. Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, 1974, **39**, 1615-1621.
32. Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, 1973, **38**, 3244-3249.
33. Z. G. Hajos, D. R. Parrish and E. P. Oliveto, *Tetrahedron*, 1968, **24**, 2039-2046.
34. K. A. Ahrendt, C. J. Borths and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2000, **122**, 4243-4244.
35. B. List, R. A. Lerner and C. F. Barbas, *J. Am. Chem. Soc.*, 2000, **122**, 2395-2396.

36. C. S. J., *Chem. Eur. J.*, 2006, **12**, 5418-5427.
37. T. M. S. and J. E. N., *Angew. Chem. Int. Ed.*, 2006, **45**, 1520-1543.
38. J. Hine, S. M. Linden and V. M. Kanagasabapathy, *J. Am. Chem. Soc.*, 1985, **107**, 1082-1083.
39. J. Hine, S. M. Linden and V. M. Kanagasabapathy, *J. Org. Chem.*, 1985, **50**, 5096-5099.
40. J. Hine, K. Ahn, J. C. Gallucci and S. M. Linden, *J. Am. Chem. Soc.*, 1984, **106**, 7980-7981.
41. T. R. Kelly, P. Meghani and V. S. Ekkundi, *Tetrahedron Lett.*, 1990, **31**, 3381-3384.
42. J. F. Blake and W. L. Jorgensen, *J. Am. Chem. Soc.*, 1991, **113**, 7430-7432.
43. D. L. Severance and W. L. Jorgensen, *J. Am. Chem. Soc.*, 1992, **114**, 10966-10968.
44. D. P. Curran and L. H. Kuo, *J. Org. Chem.*, 1994, **59**, 3259-3261.
45. D. P. Curran and L. H. Kuo, *Tetrahedron Lett.*, 1995, **36**, 6647-6650.
46. A. Wittkopp and P. R. Schreiner, *Chem. Eur. J.*, 2003, **9**, 407-414.
47. P. R. Schreiner and A. Wittkopp, *Org. Lett.*, 2002, **4**, 217-220.
48. D. J. Maher and S. J. Connon, *Tetrahedron Lett.*, 2004, **45**, 1301-1305.
49. G. Dessole, R. P. Herrera and A. Ricci, *Synlett*, 2004, **2004**, 2374-2378.
50. S. A. Kavanagh, A. Piccinini, E. M. Fleming and S. J. Connon, *Org. Biomol. Chem.*, 2008, **6**, 1339-1343.
51. M. S. Sigman and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1998, **120**, 4901-4902.
52. P. Vachal and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 10012-10014.
53. D. H. Paull, C. J. Abraham, M. T. Scerba, E. Alden-Danforth and T. Lectka, *Acc. Chem. Res.*, 2008, **41**, 655-663.
54. T. Okino, Y. Hoashi and Y. Takemoto, *J. Am. Chem. Soc.*, 2003, **125**, 12672-12673.
55. T. Okino, Y. Hoashi, T. Furukawa, X. Xu and Y. Takemoto, *J. Am. Chem. Soc.*, 2005, **127**, 119-125.
56. A. Hamza, G. Schubert, T. Soós and I. Pápai, *J. Am. Chem. Soc.*, 2006, **128**, 13151-13160.
57. S.-K. Tian, Y. Chen, J. Hang, L. Tang, P. McDaid and L. Deng, *Acc. Chem. Res.*, 2004, **37**, 621-631.
58. L. Mink, Z. Ma, R. A. Olsen, J. N. James, D. S. Sholl, L. J. Mueller and F. Zaera, *Top. Catal.*, 2008, **48**, 120-127.
59. G. Bredig and P. Fiske, *Biochem. Z.*, 1912, **46**, 7-23.
60. H. Pracejus and H. Mätje, *J. Prakt. Chem.*, 1964, **24**, 195-205.
61. H. Hiemstra and H. Wynberg, *J. Am. Chem. Soc.*, 1981, **103**, 417-430.
62. S. J. Connon, *Chem. Commun.*, 2008, 2499-2510.
63. A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713-5743.
64. T. P. Yoon and E. N. Jacobsen, *Science*, 2003, **299**, 1691-1693.
65. H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483-2547.
66. B. Vakulya, S. Varga, A. Csámpai and T. Soós, *Org. Lett.*, 2005, **7**, 1967-1969.
67. J. Ye, D. J. Dixon and P. S. Hynes, *Chem. Commun.*, 2005, 4481-4483.
68. S. H. McCooey and S. J. Connon, *Angew. Chem. Int. Ed.*, 2005, **44**, 6367-6370.
69. J. P. Malerich, K. Hagihara and V. H. Rawal, *J. Am. Chem. Soc.*, 2008, **130**, 14416-14417.
70. J. Alemán, A. Parra, H. Jiang and K. A. Jørgensen, *Chem. Eur. J.*, 2011, **17**, 6890-6899.
71. R. I. Storer, C. Aciro and L. H. Jones, *Chem. Soc. Rev.*, 2011, **40**, 2330-2346.
72. Y. Iwabuchi, M. Nakatani, N. Yokoyama and S. Hatakeyama, *J. Am. Chem. Soc.*, 1999, **121**, 10219-10220.

73. C. C. Johansson, N. Bremeyer, S. V. Ley, D. R. Owen, S. C. Smith and M. J. Gaunt, *Angew. Chem. Int. Ed.*, 2006, **45**, 6024-6028.
74. C. Palacio and S. J. Connon, *Org. Lett.*, 2011, **13**, 1298-1301.
75. C. Palacio and S. J. Connon, *Chem. Commun.*, 2012, **48**, 2849-2851.
76. M. Benaglia, A. Puglisi and F. Cozzi, *Chem. Rev.*, 2003, **103**, 3401-3430.
77. S. Shylesh, V. Schünemann and W. R. Thiel, *Angew. Chem. Int. Ed.*, 2010, **49**, 3428-3459.
78. O. Gleeson, G.-L. Davies, A. Peschiulli, R. Tekoriute, Y. K. Gun'ko and S. J. Connon, *Org. Biomol. Chem.*, 2011, **9**, 7929-7940.
79. F. Cozzi, *Adv. Synth. Catal.*, 2006, **348**, 1367-1390.
80. C. M. Starks, *J. Am. Chem. Soc.*, 1971, **93**, 195-199.
81. C. M. Starks, C. L. Liotta and M. E. Halpern, in *Phase-Transfer Catalysis: Fundamentals, Applications, and Industrial Perspectives*, Springer Netherlands, Dordrecht, 1994, DOI: 10.1007/978-94-011-0687-0_2, pp. 23-47.
82. M. Makosza, *Pure Appl. Chem.*, 1975, **43**, 439-462.
83. B. Lygo and P. G. Wainwright, *Tetrahedron Lett.*, 1997, **38**, 8595-8598.
84. U. H. Dolling, P. Davis and E. J. Grabowski, *J. Am. Chem. Soc.*, 1984, **106**, 446-447.
85. M. J. O'Donnell, W. D. Bennett and S. Wu, *J. Am. Chem. Soc.*, 1989, **111**, 2353-2355.
86. T. Ooi, M. Kameda and K. Maruoka, *J. Am. Chem. Soc.*, 1999, **121**, 6519-6520.
87. S. Shirakawa, T. Tokuda, A. Kasai and K. Maruoka, *Org. Lett.*, 2013, **15**, 3350-3353.
88. B. Zhu, R. Lee, Y. Yin, F. Li, M. L. Coote and Z. Jiang, *Org. Lett.*, 2018, **20**, 429-432.
89. J. Z. Crich, R. Brieva, P. Marquart, R. L. Gu, S. Flemming and C. J. Sih, *J. Org. Chem.*, 1993, **58**, 3252-3258.
90. K. Gottwald and D. Seebach, *Tetrahedron*, 1999, **55**, 723-738.
91. D. Seebach, G. Jaeschke, K. Gottwald, K. Matsuda, R. Formisano, D. A. Chaplin, M. Breuning and G. Bringmann, *Tetrahedron*, 1997, **53**, 7539-7556.
92. J. Liang, J. C. Ruble and G. C. Fu, *J. Org. Chem.*, 1998, **63**, 3154-3155.
93. X. Yang, G. Lu and V. B. Birman, *Org. Lett.*, 2010, **12**, 892-895.
94. P. Liu, X. Yang, V. B. Birman and K. N. Houk, *Org. Lett.*, 2012, **14**, 3288-3291.
95. A. Berkessel, F. Cleemann, S. Mukherjee, T. N. Müller and J. Lex, *Angew. Chem. Int. Ed.*, 2005, **44**, 807-811.
96. A. Berkessel, S. Mukherjee, F. Cleemann, T. N. Müller and J. Lex, *Chem. Commun.*, 2005, 1898-1900.
97. A. Berkessel, S. Mukherjee, T. N. Müller, F. Cleemann, K. Roland, M. Brandenburg, J.-M. Neudorfl and J. Lex, *Org. Biomol. Chem.*, 2006, **4**, 4319-4330.
98. A. Peschiulli, C. Quigley, S. Tallon, Y. K. Gun'ko and S. J. Connon, *J. Org. Chem.*, 2008, **73**, 6409-6412.
99. E. C. B. Johnson and S. B. H. Kent, *J. Am. Chem. Soc.*, 2006, **128**, 6640-6646.
100. C. Palacio and S. J. Connon, *Eur. J. Org. Chem.*, 2013, **2013**, 5398-5413.
101. J.-S. Oh, J.-W. Lee, T. H. Ryu, J. H. Lee and C. E. Song, *Org. Biomol. Chem.*, 2012, **10**, 1052-1055.
102. J. W. Lee, T. H. Ryu, J. S. Oh, H. Y. Bae, H. B. Jang and C. E. Song, *Chem. Commun.*, 2009, 7224-7226.
103. G. Lu and V. B. Birman, *Org. Lett.*, 2011, **13**, 356-358.
104. C. Wang, H.-W. Luo and L.-Z. Gong, *Synlett*, 2011, **2011**, 992-994.
105. A. Berkessel, I. Jurkiewicz and R. Mohan, *ChemCatChem*, 2011, **3**, 319-330.
106. A. Kuhl, M. G. Hahn, M. Dumić and J. Mittendorf, *Amino Acids*, 2005, **29**, 89-100.
107. M. Liu and M. P. Sibi, *Tetrahedron*, 2002, **58**, 7991-8035.

108. E. Juaristi and V. A. Soloshonok, *Enantioselective synthesis of beta-amino acids*, John Wiley & Sons, 2005.
109. A. Berkessel, F. Cleemann and S. Mukherjee, *Angew. Chem. Int. Ed.*, 2005, **44**, 7466-7469.
110. P. Renzi, C. Kronig, A. Calrone, S. Eroksuz, A. Berkessel and M. Bella, *Chem. Eur. J.*, 2014, **20**, 11768-11775.
111. X. Yang, V. D. Bumbu and V. B. Birman, *Org. Lett.*, 2011, **13**, 4755-4757.
112. S. Eröksüz, J. M. Neudörfl and A. Berkessel, *Synlett*, 2017, **28**, 1278-1281.
113. S. Tallon, F. Manoni and S. J. Connon, *Angew. Chem. Int. Ed.*, 2014, **54**, 813-817.
114. E. Gianolio, R. Mohan and A. Berkessel, *Adv. Synth. Catal*, 2016, **358**, 30-33.
115. J. March, *Advanced organic chemistry: reactions, mechanisms, and structure*, John Wiley & Sons, 1992.
116. M. González-López and J. T. Shaw, *Chem. Rev.*, 2009, **109**, 164-189.
117. W. H. Perkin, *J. Chem. Soc.*, 1868, **21**, 181-186.
118. W. H. Perkin, *J. Chem. Soc.*, 1877, **31**, 388-427.
119. J. R. Johnson, in *Organic Reactions*, John Wiley & Sons, Inc., 2004, DOI: 10.1002/0471264180.or001.08.
120. R. Fittig and H. W. Jayne, *Liebigs Ann.*, 1883, **216**, 97-114.
121. E. Hugo, *Liebigs Ann.*, 1888, **247**, 306-366.
122. E. Müller, *Liebigs Ann.*, 1931, **491**, 251-265.
123. J. B. Jones and A. R. Pinder, *J. Chem. Soc.*, 1958, DOI: 10.1039/JR9580002612, 2612-2618.
124. C. Cornaggia, F. Manoni, E. Torrente, S. Tallon and S. J. Connon, *Org. Lett.*, 2012, **14**, 1850-1853.
125. F. Manoni, C. Cornaggia, J. Murray, S. Tallon and S. J. Connon, *Chem. Commun.*, 2012, **48**, 6502-6504.
126. C. Trujillo, I. Rozas, A. Botte and S. J. Connon, *Chem. Commun.*, 2017, **53**, 8874-8877.
127. C. Cornaggia, S. Gundala, F. Manoni, N. Gopalasetty and S. J. Connon, *Org. Biomol. Chem.*, 2016, **14**, 3040-3046.
128. W. Jia-Le, D. Bai-Xiang, Z. Yu-Chen, H. Ying-Ying, W. Jing-Yi, W. Ping and S. Feng, *Adv. Synth. Catal.*, 2016, **358**, 2777-2790.
129. F. Manoni and S. J. Connon, *Angew. Chem. Int. Ed.*, 2014, **53**, 2628-2632.
130. F. Manoni, U. Farid, C. Trujillo and S. J. Connon, *Org. Biomol. Chem.*, 2017, **15**, 1463-1474.
131. R. Havelek, D. Muthna, P. Tomsik, K. Kralovec, M. Seifrtova, L. Cahlikova, A. Hostalkova, M. Safratova, M. Perwein, E. Cermakova and M. Rezacova, *Chem. Biol. Interact.*, 2017, **275**, 121-132.
132. J. He, W. B. Qi, L. Wang, J. Tian, P. R. Jiao, G. Q. Liu, W. C. Ye and M. Liao, *Influenza and Other Respiratory Viruses*, 2013, **7**, 922-931.
133. S. H. Tan, M. G. Banwell and A. C. Willis, *J. Org. Chem.*, 2016, **81**, 8022-8028.
134. M. B. Jiménez-Díaz, D. Ebert, Y. Salinas, A. Pradhan, A. M. Lehane, M.-E. Myrand-Lapierre, K. G. O'Loughlin, D. M. Shackleford, M. Justino de Almeida, A. K. Carrillo, J. A. Clark, A. S. M. Dennis, J. Diep, X. Deng, S. Duffy, A. N. Endsley, G. Fedewa, W. A. Guiguemde, M. G. Gómez, G. Holbrook, J. Horst, C. C. Kim, J. Liu, M. C. S. Lee, A. Matheny, M. S. Martínez, G. Miller, A. Rodríguez-Alejandre, L. Sanz, M. Sigal, N. J. Spillman, P. D. Stein, Z. Wang, F. Zhu, D. Waterson, S. Knapp, A. Shelat, V. M. Avery, D. A. Fidock, F.-J. Gamo, S. A. Charman, J. C. Mirsalis, H. Ma, S. Ferrer, K. Kirk, I. Angulo-Barturen, D. E. Kyle, J. L. DeRisi, D. M. Floyd and R. K. Guy, *Proc. Natl. Acad. Sci. U.S.A.*, 2014, **111**, E5455-E5462.

135. S. A. Cronin, A. Gutiérrez Collar, S. Gundala, C. Cornaggia, E. Torrente, F. Manoni, A. Botte, B. Twamley and S. J. Connon, *Org. Biomol. Chem.*, 2016, **14**, 6955-6959.
136. N. Castagnoli, *J. Org. Chem.*, 1969, **34**, 3187-3189.
137. M. Cushman and N. Castagnoli, *J. Org. Chem.*, 1973, **38**, 440-448.
138. M. Cushman and N. Castagnoli, *J. Org. Chem.*, 1974, **39**, 1546-1550.
139. M. Cushman, J. Gentry and F. W. Dekow, *J. Org. Chem.*, 1977, **42**, 1111-1116.
140. M. A. Haimova, N. M. Mollov, S. C. Ivanova, A. I. Dimitrova and V. I. Ognyanov, *Tetrahedron*, 1977, **33**, 331-336.
141. M. Cushman and E. J. Madaj, *J. Org. Chem.*, 1987, **52**, 907-915.
142. Y. Tamura, A. Wada, M. Sasho and Y. Kita, *Tetrahedron Lett.*, 1981, **22**, 4283-4286.
143. Y. Tamura, M. Sasho, K. Nakagawa, T. Tsugoshi and Y. Kita, *J. Org. Chem.*, 1984, **49**, 473-478.
144. Y. Tamura, A. Wada, M. Sasho, K. Fukunaga, H. Maeda and Y. Kita, *J. Org. Chem.*, 1982, **47**, 4376-4378.
145. J. Zhu, Q. Wang and M. Wang, *Multicomponent reactions in organic synthesis*, John Wiley & Sons, 2014.
146. J. S. Yadav, B. V. S. Reddy, K. Saritha Raj and A. R. Prasad, *Tetrahedron*, 2003, **59**, 1805-1809.
147. P. Y. Ng, C. E. Masse and J. T. Shaw, *Org. Lett.*, 2006, **8**, 3999-4002.
148. S. W. Laws, L. C. Moore, M. J. Di Maso, Q. N. N. Nguyen, D. J. Tantillo and J. T. Shaw, *Org. Lett.*, 2017, **19**, 2466-2469.
149. C. L. Jarvis, J. S. Hirschi, M. J. Veticatt and D. Seidel, *Angew. Chem. Int. Ed.*, 2017, **56**, 2670-2674.
150. J. H. Clark, *Chem. Rev.*, 1980, **80**, 429-452.
151. A. Hameed, R. D. Alharthy, J. Iqbal and P. Langer, *Tetrahedron*, 2016, **22**, 2763-2812.
152. I. Kuwajima and E. Nakamura, *Acc. Chem. Res.*, 1985, **18**, 181-187.
153. F. Legros, S. Oudeyer and V. Levacher, *Chem. Rec.*, 2017, **17**, 429-440.
154. C. A. Bunton and J. H. Fendler, *J. Org. Chem.*, 1967, **32**, 1547-1551.
155. M. Ueki, K. Kai, M. Amemiya, H. Horino and H. Oyamada, *J. Chem. Soc., Chem. Commun.*, 1988, 414-415.
156. K. K. Ogilvie and S. L. Beaucage, *J. Chem. Soc., Chem. Commun.*, 1976, DOI: 10.1039/C3976000443B, 443b-444.
157. M. Namikoshi, B. Kundu and K. L. Rinehart, *J. Org. Chem.*, 1991, **56**, 5464-5466.
158. C. J. Salomon, E. G. Mata and O. A. Mascaretti, *Tetrahedron*, 1993, **49**, 3691-3734.
159. U. Jacquemard, V. Bénéteau, M. Lefoix, S. Routier, J.-Y. Mérour and G. Coudert, *Tetrahedron*, 2004, **60**, 10039-10047.
160. J. M. Chan, H. Sardon, A. C. Engler, J. M. García and J. L. Hedrick, *ACS Macro Letters*, 2013, **2**, 860-864.
161. X. Zheng, R. D. Gandour and K. J. Edgar, *Biomacromolecules*, 2013, **14**, 1388-1394.
162. D. Xu and K. J. Edgar, *Biomacromolecules*, 2012, **13**, 299-303.
163. H. Wu, W. Guo, S. Daniel, Y. Li, C. Liu and Z. Zeng, *Chem. Eur. J.*, 2018, **24**, 3444-3447.
164. S. Colonna, H. Hiemstra and H. Wynberg, *J. Chem. Soc., Chem. Commun.*, 1978, 238-239.
165. T. Ooi, K. Doda and K. Maruoka, *Org. Lett.*, 2001, **3**, 1273-1276.
166. T. Ooi, H. Sugimoto, K. Doda and K. Maruoka, *Tetrahedron Lett.*, 2001, **42**, 9245-9248.
167. A. Ando, T. Miura, T. Tatematsu and T. Shioiri, *Tetrahedron Lett.*, 1993, **34**, 1507-1510.

168. K. O. Christe, W. W. Wilson, R. D. Wilson, R. Bau and J. A. Feng, *J. Am. Chem. Soc.*, 1990, **112**, 7619-7625.
169. R. Z. Gnann, R. I. Wagner, K. O. Christe, R. Bau, G. A. Olah and W. W. Wilson, *J. Am. Chem. Soc.*, 1997, **119**, 112-115.
170. H. Sun and S. G. DiMagno, *J. Am. Chem. Soc.*, 2005, **127**, 2050-2051.
171. S. J. Ryan, S. D. Schimmler, D. C. Bland and M. S. Sanford, *Org. Lett.*, 2015, **17**, 1866-1869.
172. S. Elias, N. Karton-Lifshin, L. Yehezkel, N. Ashkenazi, I. Columbus and Y. Zafrani, *Org. Lett.*, 2017, **19**, 3039-3042.
173. G. Bluet and J.-M. Campagne, *J. Org. Chem.*, 2001, **66**, 4293-4298.
174. E. J. Corey and F.-Y. Zhang, *Angew. Chem. Int. Ed.*, 1999, **38**, 1931-1934.
175. G. K. S. Prakash, R. Krishnamurti and G. A. Olah, *J. Am. Chem. Soc.*, 1989, **111**, 393-395.
176. K. Iseki, T. Nagai and Y. Kobayashi, *Tetrahedron Lett.*, 1994, **35**, 3137-3138.
177. S. Caron, N. M. Do, P. Arpin and A. Larivee, *Synthesis*, 2003, **2003**, 1693-1698.
178. R. K. Sharma and J. L. Fry, *J. Org. Chem.*, 1983, **48**, 2112-2114.
179. T. Ooi and K. Maruoka, *Acc. Chem. Res.*, 2004, **37**, 526-533.
180. E. García-Urdiales, I. Alfonso and V. Gotor, *Chem. Rev.*, 2005, **105**, 313-354.
181. I. Atodiresei, I. Schiffers and C. Bolm, *Chem. Rev.*, 2007, **107**, 5683-5712.
182. E. Schoffers, A. Golebiowski and C. R. Johnson, *Tetrahedron*, 1996, **52**, 3769-3826.
183. M. C. Willis, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1765-1784.
184. A. Borissov, T. Q. Davies, S. R. Ellis, T. A. Fleming, M. S. W. Richardson and D. J. Dixon, *Chem. Soc. Rev.*, 2016, **45**, 5474-5540.
185. Z. Rodriguez-Docampo and S. J. Connon, *Journal*, 2012, **4**, 151-168.
186. J. Hiratake, Y. Yamamoto and J. i. Oda, *J. Chem. Soc., Chem. Commun.*, 1985, 1717-1719.
187. R. A. Aitken and J. Gopal, *Tetrahedron: Asymmetry*, 1990, **1**, 517-520.
188. C. Bolm, I. Schiffers, C. L. Dinter and A. Gerlach, *J. Org. Chem.*, 2000, **65**, 6984-6991.
189. H. S. Rho, S. H. Oh, J. W. Lee, J. Y. Lee, J. Chin and C. E. Song, *Chem. Commun.*, 2008, DOI: 10.1039/B719811F, 1208-1210.
190. S. H. Oh, H. S. Rho, J. W. Lee, J. E. Lee, S. H. Youk, J. Chin and C. E. Song, *Angew. Chem. Int. Ed.*, 2008, **47**, 7872-7875.
191. V. Gold, D. G. Oakenfull and T. Riley, *J. Chem. Soc. B*, 1968, DOI: 10.1039/J29680000515, 515-519.
192. W. Steglich and G. Hofle, *Tetrahedron Lett.*, 1970, 4727-&.
193. T. H. Black, S. M. Arrivo, J. S. Schumm and J. M. Knobloch, *J. Chem. Soc., Chem. Commun.*, 1986, 1524-1525.
194. E. Vedejs and J. Wang, *Org. Lett.*, 2000, **2**, 1031-1032.
195. I. D. Hills and G. C. Fu, *Angew. Chem.*, 2003, **115**, 4051-4054.
196. T. A. Duffey, S. A. Shaw and E. Vedejs, *J. Am. Chem. Soc.*, 2009, **131**, 14-15.
197. H. Mandai, T. Fujiwara, K. Noda, K. Fujii, K. Mitsudo, T. Korenaga and S. Suga, *Org. Lett.*, 2015, **17**, 4436-4439.
198. R. Craig, M. Litvajova, S. A. Cronin and S. J. Connon, *Chem. Commun.*, 2018, **54**, 10108-10111.
199. F. van Rantwijk and R. A. Sheldon, *Tetrahedron*, 2004, **60**, 501-519.
200. S. Arai, S. Bellemin-Laponnaz and G. C. Fu, *Angew. Chem. Int. Ed.*, 2001, **40**, 234-236.
201. C. K. De, E. G. Klauber and D. Seidel, *J. Am. Chem. Soc.*, 2009, **131**, 17060-17061.

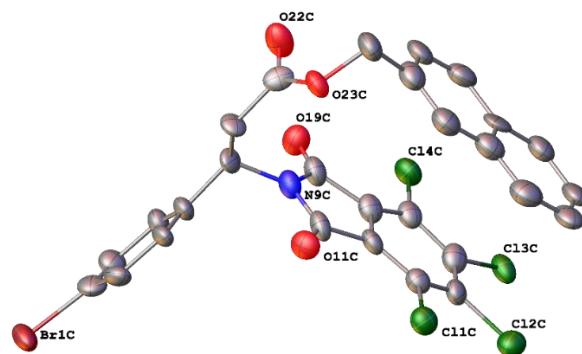
202. E. G. Klauber, C. K. De, T. K. Shah and D. Seidel, *J. Am. Chem. Soc.*, 2010, **132**, 13624-13626.
203. M. Binanzer, S.-Y. Hsieh and J. W. Bode, *J. Am. Chem. Soc.*, 2011, **133**, 19698-19701.
204. V. B. Birman, H. Jiang, X. Li, L. Guo and E. W. Uffman, *J. Am. Chem. Soc.*, 2006, **128**, 6536-6537.
205. B. S. Fowler, P. J. Mikochik and S. J. Miller, *J. Am. Chem. Soc.*, 2010, **132**, 2870-2871.
206. M. Bodanzky, *The practice of peptide synthesis*, Springer-Verlag, 1984.
207. H. Lukas, S. Marco and E. Ulli, *Angew. Chem. Int. Ed.*, 2007, **46**, 5164-5167.
208. D. Evans and D. Ripin, *Web Resource*, 2005, 1-6.
209. L. Lázár, L. Jánossy, M. Csávás, M. Herczeg, A. Borbás and S. Antus, *Selective removal of the (2-naphthyl)methyl protecting group in the presence of p-methoxybenzyl group by catalytic hydrogenation*, 2012.
210. D. R. Vutukuri, P. Bharathi, Z. Yu, K. Rajasekaran, M.-H. Tran and S. Thayumanavan, *J. Org. Chem.*, 2003, **68**, 1146-1149.
211. L. W. McCay and W. Foster, *J. Am. Chem. Soc.*, 1904, **26**, 306-308.
212. P. P. de Castro, A. G. Carpanez and G. W. Amarante, *Chem. Eur. J.*, 2016, **22**, 10294-10318.
213. G. G. Lunt, *J. Neurochem.*, 1995, **64**, 1424-1424.
214. A. Schousboe, *Journal*, 1978.
215. G. M. Wall and J. K. Baker, *J. Med. Chem.*, 1989, **32**, 1340-1348.
216. W. M. Pardridge, *Annual Rep Med Chem*, 1985, **20**, 305-315.
217. N. Greig, in *Physiology and pharmacology of the blood-brain barrier*, Springer, 1992, pp. 487-523.
218. C. F. Baxter and E. Roberts, *J. Biol. Chem.*, 1958, **233**, 1135-1139.
219. M. S. Hoekstra, D. M. Sobieray, M. A. Schwindt, T. A. Mulhern, T. M. Grote, B. K. Huckabee, V. S. Hendrickson, L. C. Franklin, E. J. Granger and G. L. Karrick, *Org. Process Res. Dev.*, 1997, **1**, 26-38.
220. G. J. Sills, *Curr. Opin. Pharmacol.*, 2006, **6**, 108-113.
221. D. H. Rich, *J. Med. Chem.*, 1985, **28**, 263-273.
222. M. L. Moore, W. M. Bryan, S. A. Fakhoury, V. W. Magaard, W. F. Huffman, B. D. Dayton, T. D. Meek, L. Hyland, G. B. Dreyer and B. W. Metcalf, *Biochem. Biophys. Res. Commun.*, 1989, **159**, 420-425.
223. R. K. Hom, L. Y. Fang, S. Mamo, J. S. Tung, A. C. Guinn, D. E. Walker, D. L. Davis, A. F. Gailunas, E. D. Thorsett and S. Sinha, *J. Med. Chem.*, 2003, **46**, 1799-1802.
224. H. Umezawa, T. Aoyagi, H. Morishima, M. Matsuzaki, M. Hamada and T. Takeuchi, *J. Antibiot.*, 1970, **23**, 259-262.
225. L. Rajender Reddy, K. Prasad and M. Prashad, *J. Org. Chem.*, 2012, **77**, 6296-6301.
226. D. Seebach, A. K. Beck and D. J. Bierbaum, *Chem. Biodivers.*, 2004, **1**, 1111-1239.
227. M. Ganesh Kumar, S. M. Mali and H. N. Gopi, *Org. Biomol. Chem.*, 2013, **11**, 803-813.
228. J. D. More and N. S. Finney, *Org. Lett.*, 2002, **4**, 3001-3003.
229. V. Nair, S. Vellalath and B. P. Babu, *Chem. Soc. Rev.*, 2008, **37**, 2691-2698.
230. O. Pattawong, D. Q. Tan, J. C. Fettingner, J. T. Shaw and P. H.-Y. Cheong, *Org. Lett.*, 2013, **15**, 5130-5133.
231. S. Colonna, A. Re, G. Gelbard and E. Cesarotti, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2248-2252.
232. E. J. Corey, F. Xu and M. C. Noe, *J. Am. Chem. Soc.*, 1997, **119**, 12414-12415.
233. J. Zakzeski, I. S. Fan and A. T. Bell, *Appl. Catal., A.*, 2009, **360**, 33-37.

234. G. Pupo, F. Ibba, D. M. H. Ascough, A. C. Vicini, P. Ricci, K. E. Christensen, L. Pfeifer, J. R. Morphy, J. M. Brown, R. S. Paton and V. Gouverneur, *Science*, 2018, **360**, 638-642.
235. S. A. Shaw, P. Aleman, J. Christy, J. W. Kampf, P. Va and E. Vedejs, *J. Am. Chem. Soc.*, 2006, **128**, 925-934.
236. H. Mandai, T. Fujiwara, K. Noda, K. Fujii, K. Mitsudo, T. Korenaga and S. Suga, *Org. Lett.*, 2015, **17**, 4436-4439.
237. T. A. Duffey, S. A. Shaw and E. Vedejs, *J. Am. Chem. Soc.*, 2008, **131**, 14-15.
238. X. Yang, V. D. Bumbu, P. Liu, X. Li, H. Jiang, E. W. Uffman, L. Guo, W. Zhang, X. Jiang, K. N. Houk and V. B. Birman, *J. Am. Chem. Soc.*, 2012, **134**, 17605-17612.
239. V. B. Birman and X. Li, *Org. Lett.*, 2006, **8**, 1351-1354.
240. M. Namikoshi, B. Kundu and K. L. Rinehart, *J. Org. Chem.*, 1991, **56**, 5464-5466.
241. D. Seidel, *Synlett*, 2014, **25**, 783-794.
242. N. Mittal, K. M. Lippert, C. K. De, E. G. Klauber, T. J. Emge, P. R. Schreiner and D. Seidel, *J. Am. Chem. Soc.*, 2015, **137**, 5748-5758.
243. H. Mäenpää, L. T. Kanerva and A. Liljeblad, *ChemCatChem*, 2016, **8**, 1226-1232.
244. W. Szymanski, B. Wu, B. Weiner, S. de Wildeman, B. L. Feringa and D. B. Janssen, *J. Org. Chem.*, 2009, **74**, 9152-9157.
245. C. Y. K. Tan and D. F. Weaver, *Tetrahedron*, 2002, **58**, 7449-7461.
246. H. Doi, T. Sakai, K.-i. Yamada and K. Tomioka, *Chem. Commun.*, 2004, 1850-1851.
247. D. A. Evans, L. D. Wu, J. J. M. Wiener, J. S. Johnson, D. H. B. Ripin and J. S. Tedrow, *J. Org. Chem.*, 1999, **64**, 6411-6417.
248. A. El Marini, M. L. Roumestant, P. Viallefont, D. Razafindramboa, M. Bonato and M. Follet, *Synthesis*, 1992, **1992**, 1104-1108.
249. A. Peschiulli, Ph. D, Trinity College Dublin.
250. N. Fu, A. D. Allen, S. Kobayashi, T. T. Tidwell, S. Vukovic, T. Matsuoka and M. Mishima, *J. Org. Chem.*, 2008, **73**, 1768-1773.
251. A. Lee, A. Michrowska, S. Sulzer-Mosse and B. List, *Angew. Chem. Int. Ed.*, 2011, **50**, 1707-1710.
252. S. Kawashima, K. Aikawa and K. Mikami, *Eur. J. Org. Chem.*, 2016, **2016**, 3166-3170.
253. D. B. Ramachary, C. Venkaiah and Y. V. Reddy, *Org. Biomol. Chem.*, 2014, **12**, 5400-5406.
254. H.-Y. Wang, K. Huang, M. De Jesús, S. Espinosa, L. E. Piñero-Santiago, C. L. Barnes and M. Ortiz-Marciales, *Tetrahedron: Asymmetry*, 2016, **27**, 91-100.
255. A. Del Vecchio, F. Caillé, A. Chevalier, O. Loreau, K. Horkka, C. Halldin, M. Schou, N. Camus, P. Kessler, B. Kuhnast, F. Taran and D. Audisio, *Angew. Chem. Int. Ed.*, 2018, **57**, 9744-9748.
256. R. Alan Aitken, J. M. Armstrong, M. J. Drysdale, F. C. Ross and B. M. Ryan, *J. Chem. Soc., Perkin Trans. 1*, 1999, 593-604.
257. G.-Z. Wang, R. Shang, W.-M. Cheng and Y. Fu, *Org. Lett.*, 2015, **17**, 4830-4833.
258. E. Sorrentino and S. J. Connon, *Org. Lett.*, 2016, **18**, 5204-5207.
259. Y. Ishii, R. Fujimoto, M. Mikami, S. Murakami, Y. Miki and Y. Furukawa, *Org. Process Res. Dev.*, 2007, **11**, 609-615.
260. H. Li, Y. Wang, L. Tang and L. Deng, *J. Am. Chem. Soc.*, 2004, **126**, 9906-9907.
261. A. Rossetti, A. Sacchetti, M. Bonfanti, G. Roda, G. Rainoldi and A. Silvani, *Tetrahedron*, 2017, **73**, 4584-4590.
262. B. M. Trost, J. Xie and J. D. Sieber, *J. Am. Chem. Soc.*, 2011, **133**, 20611-20622.
263. J. Wang, J. Zhao and H. Gong, *Chem. Commun.*, 2017, **53**, 10180-10183.
264. B. Li, Y. Park and S. Chang, *J. Am. Chem. Soc.*, 2014, **136**, 1125-1131.

265. E. Speckmeier, M. Klimkait and K. Zeitler, *J. Org. Chem.*, 2018, **83**, 3738-3745.
266. Č. Malavašič, B. Stanovnik, J. Waggener and J. Svete, *Tetrahedron: Asymmetry*, 2011, **22**, 1364-1371.
267. Y.-y. Jiang, Q.-Q. Wang, S. Liang, L.-M. Hu, R. D. Little and C.-C. Zeng, *J. Org. Chem.*, 2016, **81**, 4713-4719.
268. X. Tang, L. Huang, C. Qi, X. Wu, W. Wu and H. Jiang, *Chem. Commun.*, 2013, **49**, 6102-6104.
269. S. Dosa, M. Stirnberg, V. Lülldorff, D. Häußler, E. Maurer and M. Gütschow, *Biorg. Med. Chem.*, 2012, **20**, 6489-6505.
270. S. Dosa, J. Daniels and M. Gütschow, *J. Heterocycl. Chem.*, 2011, **48**, 407-413.
271. A. P. Krapcho and E. A. Dundulis, *Tetrahedron Lett.*, 1976, **17**, 2205-2208.
272. E. Badiola, B. Fiser, E. Gómez-Bengoa, A. Mielgo, I. Olaizola, I. Urruzuno, J. M. García, J. M. Odriozola, J. Razkin, M. Oiarbide and C. Palomo, *J. Am. Chem. Soc.*, 2014, **136**, 17869-17881.

12 Appendix

12.1 X-ray crystallography data for



A specimen of $C_{28}H_{16}BrCl_4NO_4$, approximate dimensions 0.020 mm x 0.050 mm x 0.400 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 Cryosystem 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 3280 frames were collected. The total exposure time was 43.50 hours. The integration of the data using a monoclinic unit cell yielded a total of 19087 reflections to a maximum θ angle of 68.60° (0.83 Å resolution), of which 19087 were independent (average redundancy 1.000, completeness = 98.2%, $R_{\text{int}} = 20.75\%$, $R_{\text{sig}} = 17.59\%$) and 12446 (65.21%) were greater than $2\sigma(F^2)$. The final cell constants of $a = 13.692(3)$ Å, $b = 23.378(5)$ Å, $c = 16.716(3)$ Å, $\beta = 108.41(3)^\circ$, volume = $5076.8(19)$ Å³, are based upon the refinement of the XYZ-centroids of reflections above $20\sigma(I)$. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.552. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.1840 and 0.8820.

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 $P2_1$, with $Z = 8$ for the formula unit, $C_{28}H_{16}BrCl_4NO_4$. The final anisotropic full-matrix least-squares refinement on F^2 with 1398 variables converged at $R1 = 10.23\%$, for the observed data and $wR2 = 29.31\%$ for all data. The goodness-of-fit was 1.053. The largest peak in the final difference electron density synthesis was $0.986 \text{ e}^-/\text{\AA}^3$ and the largest hole was $-0.931 \text{ e}^-/\text{\AA}^3$ with an RMS deviation of $0.177 \text{ e}^-/\text{\AA}^3$. On the basis of the final model, the calculated density was 1.706 g/cm^3 and $F(000)$, 2608 e^- .

Refinement Note: Weakly diffracting crystal and refined as a rotational twin. Rotated from first domain by 179.9° about reciprocal axis 1.000 -0.001 -0.385 and real axis 1.000 -0.001 0.001. Twin law to convert hkl from first to this domain (SHELXL TWIN matrix): 1.000 -0.002 0.000 -0.009 -

1.000 -0.014 -0.771 0.007 -1.000. Refined BASF ratio 0.445(3). 4 independent molecules in the asymmetric unit. One naphthalene moiety modelled as disordered over two positions with 52:48% occupancy. Restraints (SIMU) and a rigid model used to refine this disorder. Restraints (SIMU, ISOR) used throughout the model, mainly for the remaining naphthalene fragments and associated linking atoms.

References:

- Bruker (2013). SAINT v8.37A, Bruker AXS Inc., Madison, WI, USA.
- Bruker (2017). APEX3 v2017.3-0, Bruker AXS Inc., Madison, WI, USA.
- Bruker (2016/2). SADABS, Bruker AXS Inc., Madison, Wisconsin, USA.
- Dolomanov, O.V., Bourhis, L.J., Gildea, R.J., Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
- Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.
- Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8