OPEN ACCESS

University of BRISTOL

This electronic thesis or dissertation has been downloaded from Explore Bristol Research, http://research-information.bristol.ac.uk

Author:
Okoh, Mary A

Title:
Asymmetric Synthesis of -Aryl Quaternary Amino Acids Exploiting Unusual Urea Reactivity

General rights
Access to the thesis is subject to the Creative Commons Attribution - NonCommercial-No Derivatives 4.0 International Public License. A copy of this may be found at https://creativecommons.org/licenses/by-nc-nd/4.0/legalcode This license sets out your rights and the restrictions that apply to your access to the thesis so it is important you read this before proceeding.

Take down policy
Some pages of this thesis may have been removed for copyright restrictions prior to having it been deposited in Explore Bristol Research. However, if you have discovered material within the thesis that you consider to be unlawful e.g. breaches of copyright (either yours or that of a third party) or any other law, including but not limited to those relating to patent, trademark, confidentiality, data protection, obscenity, defamation, libel, then please contact collections-metadata@bristol.ac.uk and include the following information in your message:

• Your contact details
• Bibliographic details for the item, including a URL
• An outline nature of the complaint

Your claim will be investigated and, where appropriate, the item in question will be removed from public view as soon as possible.

Asymmetric Synthesis of α-Aryl Quaternary Amino Acids Exploiting Unusual Urea Reactivity

Mary Abosede Okoh

A dissertation submitted to the University of Bristol in accordance with the requirements for award of the degree of Doctor of Philosophy in the Faculty of Science

School of Chemistry

July 2020

Total Word Count: 69279

Abstract

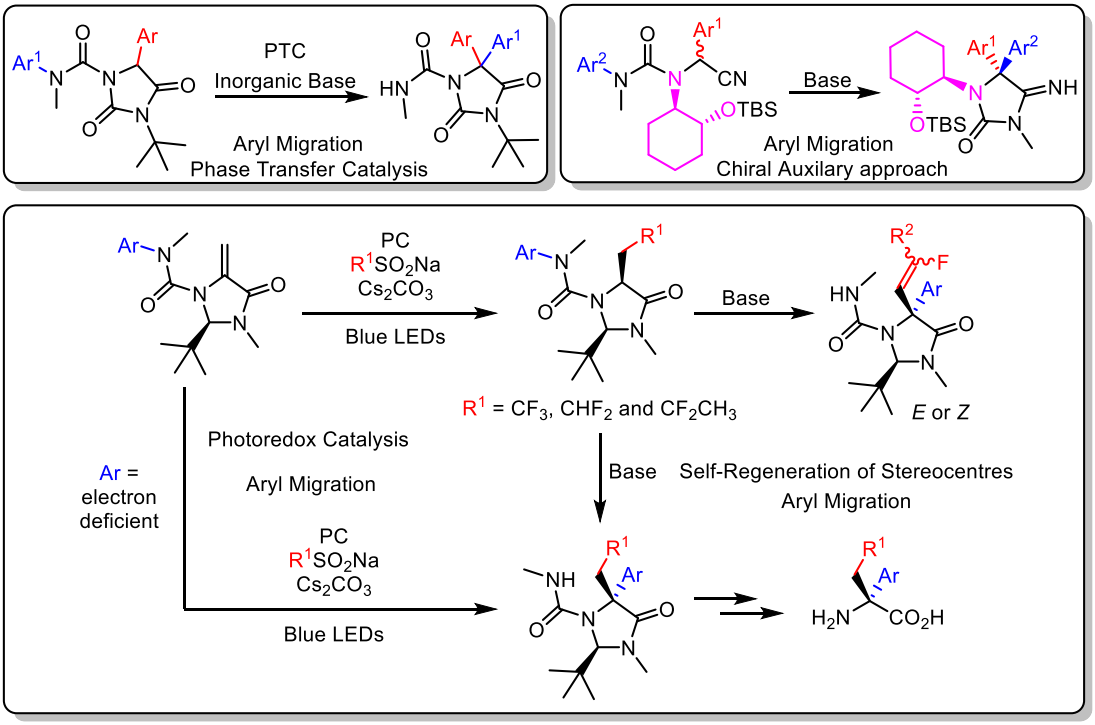
Asymmetric Synthesis of α-Aryl Quaternary Amino Acids Exploiting Unusual Urea Reactivity

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

Mary Abosede Okoh

2020

Amino acids containing quaternary centres can be accessed by the *alkylation* or *arylation* of tertiary amino acid enolates. The *arylation* of tertiary amino acid enolates, however, has proved problematic due to the challenging Csp^3–Csp^2 coupling. Many of the methods available for the arylation of tertiary amino acid enolates are not general and many of them give racemic products or rely on heavy metal catalysis. α-Aryl quaternary amino acids form components of several bioactive compounds; hence the need for a general, metal free route towards their enantioselective synthesis.



In this work, the intramolecular arylation of amino acid enolates employing either phase transfer catalysis (PTC), self-regeneration of stereocentres (SRS) or a chiral auxiliary approach in inducing enantioselectivity has been developed. All the methods take advantage of the unusual ability of metallated *N*'-aryl,*N*-benzyl ureas to undergo aryl migration from the urea distal nitrogen to the benzylic methylene. For the first time, *N* to *C* aryl migration in tertiary amino acid-derived *N*'-aryl ureas was facilitated by the use of mild inorganic bases, and this led to the formation of new quaternary amino acid derivatives arylated at the α-carbon. In addition, the mild conditions of photoredox catalysis was used to initiate radical conjugate addition to *N*'-aryl urea derivatives of dehydroalanine (Dha) and subsequent intramolecular arylation of the enolate formed. To the best of the author's knowledge, illustrated in this thesis, is the first example of the synthesis of α-aryl quaternary amino acids through conjugate addition to *N*'-aryl urea derivatives of Dha.

Dedication and Acknowledgements

Firstly, I want to thank my supervisor, Professor Jonathan Clayden for the opportunity given me to do my PhD in his group and for his continual guidance and support right from Manchester to Bristol. I really appreciate how you always made yourself available for catch-ups especially during the Covid-19 period.

The Clayden group has changed a lot from when I started my PhD in 2016 till now. Many people have come and gone but there are some specific people that I felt the absence of when they left the group. One of such persons is Dr Daniel Leonard – Dan you have been there right from the start of my research journey in Manchester, cannot forget how you taught me to do my first column. I was glad to find out you were joining us again in Bristol and honestly (though selfish of me), I did not want you to leave until after I finished my PhD. Thanks for answering my phone calls and replying my WhatsApp messages even after you left the group. Another of such persons is Dr Hossay Abas, my seatmate. I remember all our discussions on smoothie making and how we tasted each other's smoothie in the office. You were such a good friend Hossay and I pray you continue to shine wherever you go. Dr David Morris (that sounded strange in my head, so I will just say Dabs). Oh Dabs! Where do I even start from? Is it your readiness to answer my chemistry questions, the free guitar lessons, and your ever cheerful self? Seems like nothing ever gets you down. I hope you get an academic position someday; you will make a good teacher/supervisor. Mostafa Mahmoud Amer – There is a portion of the bible that says: "There is a friend that sticks closer than a brother". I am happy to say that you were one of such friends. Though you recently left the group, knowing you were not close any more was saddening. You were ever willing when I needed someone to stay with me in the laboratory on a weekend. I remember all the interesting talks we had about Nigeria and Egypt. I am hopeful Mo that you will one day become the Minister of Education in Egypt….I hope I will not have to book an appointment to see you then.

I want to say gràcies to Dr Josep Mas Roselló for initially supervising me when I joined the group. You were such a pleasure to work with and I am glad you are making great strides in the scientific community. Keep shining Josep!! To my Indian family, Dr & Mrs Rakesh and Manjeet Saunthwal – thank you for receiving me into your home and teaching me how to make those tasty Indian delicacies. I will really miss you both! Rakesh, you were one of those that made me enjoy my stay in the Clayden group. I am sure you will become a popular professor of chemistry in India someday. I want to thank Dr David Tilly for all the laughs, even during a stressful day in the lab. I pray you achieve all your professional pursuits David. A big thank you to Roman Abrams for teaching me all I know about photoredox chemistry. You are such a talented chemist and I am sure I will hear of you making waves in the scientific community. It was nice working across from Branca Catharina Van Veen, staying late in the lab together, discussing "Man issues" and listening to her

Nigerian like Dutch music. I will miss you Branca! Dr Steven Wales – you were such a cool fume hood buddy. Thank you for answering my chemistry questions and giving me great suggestions on my research work. Though I have known you for just a while, I will miss you. I want to thank specially Jonathan, Dabs, Rakesh, Dan, Steve and Roman for taking time out of their busy schedule to proof-read this thesis. I also want to say a big thank you to Frank, Louise, Makenzie, Matthew, Ellie, Dr Ward, Dr Matlock, Dr Hill, Dr Lefebvre, Dr Costil, Dr Cattell, and Dr Tomsett. You all contributed in one way or the other to an enjoyable stay in the Clayden group. I will definitely miss those of you still in the group.

I want to say thank you to the Schlumberger Foundation Faculty for the Future for providing sponsorship for this PhD and also to my home university referee Professor David Ogbeifun for his constant support and guidance.

The story of my stay in Bristol would not be complete without some very special people – my church. You guys are just the best, thank you for all the laughs and tears we shared together. Knowing that I would see you guys on Sunday saw me through the work week. I could not have asked for a better church family. I also want to say a big thank you to my parents and siblings both in Nigeria and the UK. Thanks for your encouragement and prayers. Mum, you are such an amazing woman. You never cease to hold me up in prayers, may you live long to enjoy the fruit of your prayers in Jesus' name.

To my dear husband, Bartholomew Atsado – you are God's special gift to me. Thank you for supporting, covering, protecting, and defending me. I could not have done this PhD without your patience and selflessness. I pray that as we go to the next stage of our lives, God will grant us divine speed and favour in all our endeavours in Jesus' name.

Finally, I dedicate this thesis to God Almighty – You are the one that gives wisdom to the wise and knowledge to the scholars (Daniel 2:21). Words would not be enough to express my deep gratitude to you for seeing me through this journey. All I can do is offer my life to you over and over again to use for your glory. Oh, how I wish the whole world will get to know you and experience the peace and joy you give. To you be all the glory. Amen

Author's Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED: …… DATE: ……

Table of Contents

Abbreviations

4CzIPN – 1,2,3,5-tetrakis-(carbazol-yl)-4,6-dicyanobenzene
A – Acceptor
Ac – Acetyl
AIDA –1-Aminoindan-1,5-dicarboxylic acid
Ala – Alanine
APCI – Atmospheric-pressure chemical ionisation
APICA – 1-Amino-5-phosphonoindan-1-carboxylic acid
aq. – Aqueous
Ar – Aryl
ATR – Attenuated total reflectance
Bn – Benzyl
Boc – *tert*-Butyloxycarbonyl
Bu – Butyl
Bz – Benzoyl
Cbz – benzyloxycarbonyl
δ – Chemical shift
d – day
D – Donor
dba – Dibenzylideneacetone
DBU – 1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC – Dicyclohexylcarbodiimide
DCM – Dichloromethane
DDQ – 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de – Diastereomeric excess
Dha – Dehydroalanine
DMAP – 4-(Dimethylamino)pyridine
DMF – *N*,*N*-Dimethylformamide
DMPU – *N*,*N*'-Dimethylpropyleneurea
DMSO – Dimethyl sulfoxide
dr – Diastereomeric ratio
DTBP – Di-*tert*-butyl peroxide
E^+ – Electrophile
EDG – Electron donating group
ee – Enantiomeric excess
EI – Electron ionisation
eq. – Equivalent(s)
er – Enantiomeric ratio
ESI – Electrospray ionisation
Et – Ethyl
EtOAc – Ethyl acetate
Gly – Glycine
HMPA – Hexamethylphosphoramide
HPLC – High performance liquid chromatography
HRMS – High resolution mass spectrometry
*i*Pr – isopropyl
IR – Infrared
J – Coupling constant
KHMDS – Potassium hexamethyldisilazane
LA – Lewis acid
LDA – Lithium diisopropylamide
LDEA – Lithium diethylamide
LED – Light-emitting diode

Leu – Leucine
LiHMDS – Lithium hexamethyldisilazane
LiTMP – Lithium tetramethylpiperidide
Lys – Lysine
M – Multiplet
M – Molar
m-CPBA – *meta*-chloroperoxybenzoic acid
M4CPG – Methyl-4-carboxyphenylglycine
Me – Methyl
Met – Methionine
MHz – Mega hertz
MOC – Memory of chirality
MOM – Methoxymethyl
mp – Melting point
MPPG – Methyl-4-phosphonophenylglycine
MS – Mass spectrometry
MW – Microwave
NaHMDS – Sodium hexamethyldisilazane
Naph – Naphthyl
Nd – Not determined
NMR – Nuclear magnetic resonance
NOE – Nuclear overhauser effect
o/n – overnight
PC – Photocatalyst
Pet.Ether – Petroleum ether
Ph – Phenyl
Phe – Phenylalanine
Phg – Phenylglycine
ppm – Parts per million
Pr – Propyl
Prg – Propylglycine
Pro – Proline
Psi – Pound-force per square inch
PTC – Phase transfer catalyst/Phase transfer catalysis/Phase transfer catalysed
R_f – Retardation factor
RP – Radical precursor
rt – Room temperature
sat. – Saturated
*s*Bu – *sec*-Butyl
SCE – Saturated calomel electrode
S_NAr – Nucleophilic aromatic substitution
SRS – Self-regeneration of stereocentres
TBAF – Tetra-n-butylammonium fluoride
TBDPS – *tert*-Butyldiphenylsilyl
*t*Bu – *tert*-Butyl
T – Temperature
TBDMS – *tert*-Butyldimethylsilyl
TFA – Trifluoroacetic acid
THF – Tetrahydrofuran
TLC – Thin-layer chromatography
TMS – Trimethylsilyl
Trp – Tryptophan
Tyr – Tyrosine
UV – Ultraviolet
Val – Valine

W – Watt

1 Introduction

1.1 Amino Acids

Amino acids, as the name implies, are compounds containing an amine (NH_2) group and a carboxylic acid (CO_2H) group; other functional groups might be present in them as well.[1] There exists 21 naturally occurring α-amino acids that form components of protein in living organisms,[2] these amino acids have as a general formula: NH_2CHRCO_2H (Figure 1). The side chain, which is the substituent R bonded to the α-carbon, varies from one amino acid to the other. When R is a substituent other than H, a stereogenic carbon centre is formed. α-Amino acids exist in nature as the single L-enantiomers.[3,4]

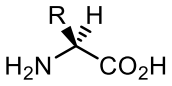


Figure 1: General structure of an α-amino acid

The conformational properties of amino acids allow them to finely modulate the precise chemical architectures required for biological functions.[5,6] Amino acids are synthesised for use as drugs, supplements, flavour enhancers and preservatives. The most common methods for making them are the Strecker synthesis, alkylation of an acetamidomalonate and the nucleophilic substitution reaction of ammonia with a α-haloacid.[7,8]

1.2 Quaternary Amino Acids

A quaternary amino acid manifests when the α-carbon of an amino acid has four substituents bonded to it (Figure 2).[9] When $R^1 \neq R^2$, the quaternary amino acid has potential for optical purity.

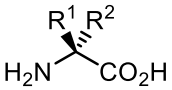


Figure 2: General structure of a quaternary amino acid

In the past few decades, the synthesis of quaternary amino acids has enjoyed significant interest; this is because they have different properties from their tertiary amino acid homologues.[5] Incorporation of these quaternary amino acids into peptides induces a more robust helical secondary structure due to greater steric constraints and results in higher protein stability.[10] An example are the α-alkyl quaternary amino acids which have played an important role in the construction of peptides with more stable conformations.[11–14] Quaternary amino acids have been shown to be efficient enzyme inhibitors due to their conformational restrictions.[15] One class of quaternary amino

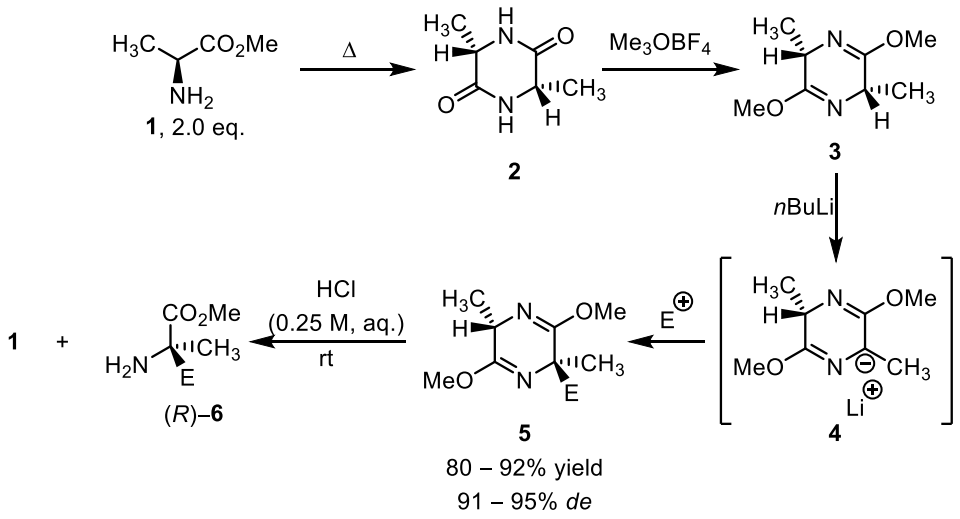
acids, the cyclic quaternary amino acids, incorporate greater conformational restrictions into the structure of proteins because the amino acid is contained within a ring.[16]

1.3 Synthesis of Quaternary Amino Acids

Extensive research has been carried out on the synthesis of quaternary amino acids; as a result, several synthetic routes, both asymmetric (stereoselective) and non-asymmetric (non-stereoselective), now exist towards these useful compounds.[10,15,16] It is noteworthy that several methods exist for the stereoselective *alkylation* of amino acids; the stereoselective *arylation* of amino acids, on the other hand, remains challenging, due to the unreactivity of aromatic coupling partners as electrophiles towards enolates (Csp^3–Csp^2 bond formation). The most representative synthetic routes towards quaternary amino acids are reviewed in this report.

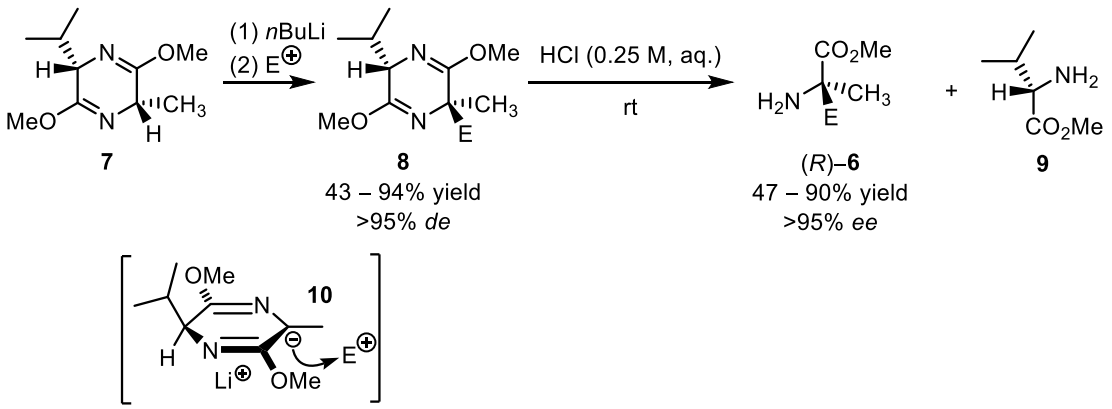
1.3.1 The Chiral Auxiliary Approach

Chiral auxiliary methodology has been particularly useful in the synthesis of α-alkyl quaternary amino acids. It involves the alkylation of an amino acid enolate derivative. A chiral auxiliary is first incorporated into the amino acid derivative and a diastereoselective enolate alkylation is carried out.[10] A disadvantage of this method is that two additional steps are required – the step required to insert the chiral auxiliary and the step required to remove it after the reaction. One significant example of the chiral auxiliary approach is Schöllkopf's bis lactim ether methodology.[17–19] The methodology involves the condensation of a racemic amino acid and enantiopure amino acid to form a heterocyclic intermediate. The enantiopure amino acid component in the heterocycle serves as the chiral auxiliary and induces diastereoselective α-alkylation of the other amino acid component. On hydrolysis of the alkylated product, the chiral auxiliary is recovered along with the newly formed enantiopure quaternary amino acid.



Scheme 1: Enantioselective alkylation of lactim ethers of cyclo-(L-Ala-L-Ala)

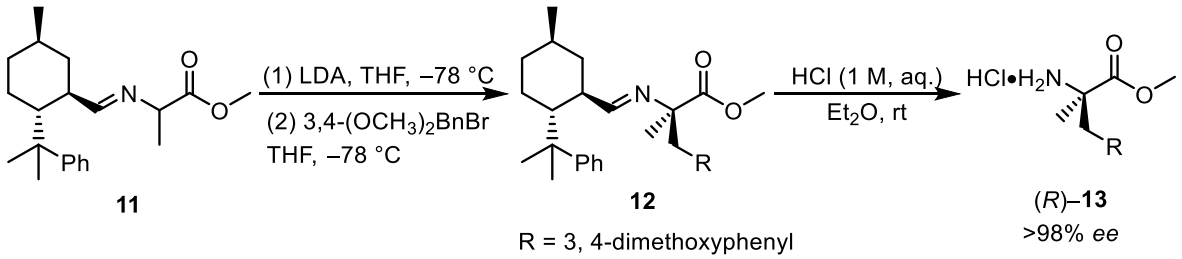
In 1979, Schöllkopf *et al*. reported the enantioselective alkylation of lactim ethers of cyclo-(L-Ala-L-Ala) (Scheme 1).[20] The heterocycle **2** was built up from condensation of 2 molecules of methyl L-alaninate **1**. Methyl L-alaninate served as both the chiral auxiliary component and the body of the new quaternary amino acid that would be formed. Heterocycle **2** was converted to the bis-methoxy lactim ether **3** by treatment with trimethyloxonium tetrafluoroborate. Treatment of **3** with *n*butyl lithium gave the lithiated intermediate **4**, which reacted with a variety of electrophiles to give the adducts **5**. Hydrolysis of **5** liberated the new quaternary amino methyl ester **6** and the chiral auxiliary **1**. The chiral auxiliary **1** and the quaternary amino methyl ester **6** could be separated by distillation if they differ sufficiently in boiling point. They could also be hydrolysed to their respective amino acids, and the amino acids then separated by chromatography. One disadvantage of using a single amino acid in the construction of the bis lactim ether is that only half of the chiral auxiliary **1** is recovered, because the remaining is incorporated in the quaternary amino acid formed. To avoid this, Schöllkopf *et al*. carried out the alkylation of a bis lactim ether built up from two different amino acids (Scheme 2).[21]



Scheme 2: Schöllkopf mixed bis lactim ether chiral auxiliary approach

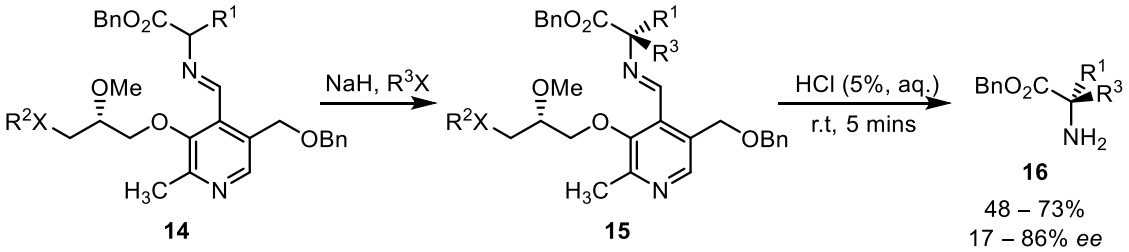
The bis lactim ether **7** was made from methyl D,L-alaninate and methyl L-valinate **9**, of which methyl L-valinate served as the chiral auxiliary. Deprotonation and subsequent alkylation of **7** occurred regioselectively, at the alanine residue. Hydrolysis of **8** led to full recovery of the chiral auxiliary **9** and the formation of **6**. Higher levels of stereoselectivity were obtained with methyl L-valinate as chiral auxiliary than with methyl L-alaninate. This was due to the steric hindrance created by the bulkier isopropyl group in valine. The electrophile enters **10** *trans* to the isopropyl group at C-6. With the bulkier isopropyl group, the facial differentiation is more pronounced than with a methyl group because the isopropyl group offers more shielding of one of the diastereotopic faces. The use of methyl D-valinate as chiral auxiliary led to the formation of the (*S*)-enantiomer. The bis lactim ether methodology has also been exploited to access optically active α-methyl serine,[22] α-alkenyl alanines,[23] α-methylphenylalanine, α-methyldopa, α-methyl-α-allylglycines[21] and α-methyltryptophan.[24]

Meyer *et al*. reported the diastereoselective alkylation of imino methyl alaninate **11** (Scheme 3).[25] The alaninate **11** was formed from condensation of an aldehyde chiral auxiliary and a racemic methyl alaninate. Deprotonation of **11** with LDA followed by alkylation using 3,4-dimethoxybenzyl bromide afforded the alkylated imino methyl alaninate **12** as a single diastereoisomer. On hydrolysis of **12**, quaternary amino methyl ester hydrochloride salt **13**, an enantiomerically pure derivative of (*R*)-α-methyldopa was obtained with excellent enantioselectivity.



Scheme 3: Diastereoselective alkylation of alanine methyl ester using an aldehyde chiral auxiliary

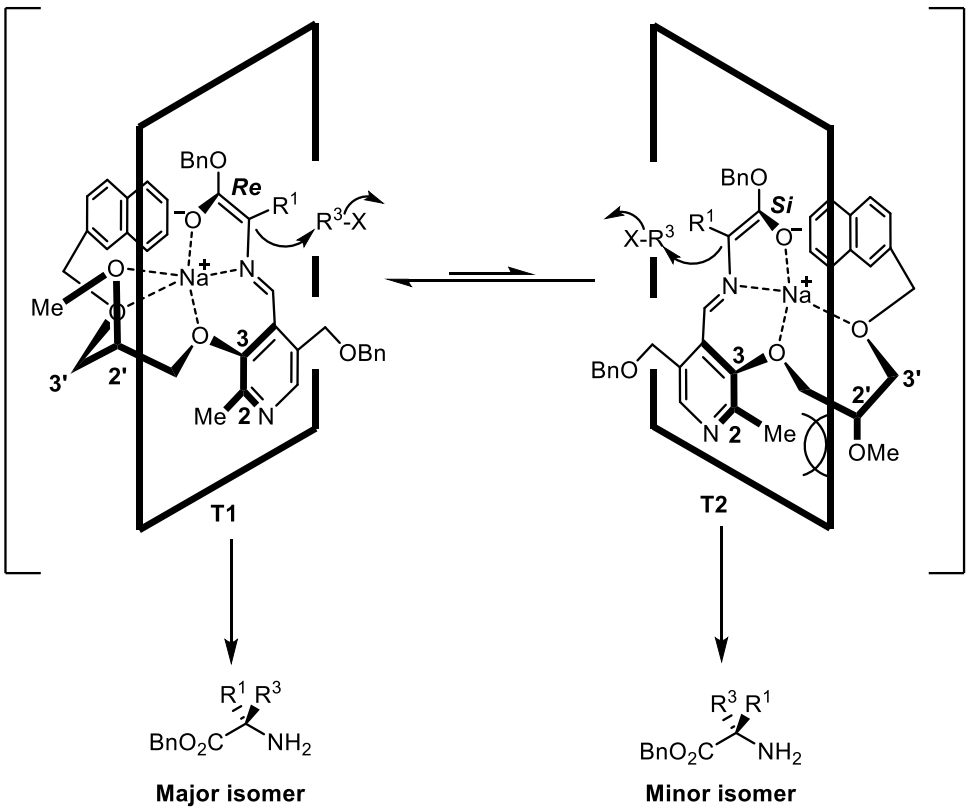
In a similar study, aldimines **14** obtained from amino esters and chiral aldehydes of a pyridoxal model were stereoselectively alkylated (Scheme 4).[26] A range of aldimine substrates and bases were used in this study. Even though the chiral auxiliary component was located on the side chain of the aldimines, the reaction still proceeded with good stereoselectivity. The stereoselectivity of the reaction depended on the metal ion in the base and the side chain of the aldimines. Best yields and stereoselectivity were generally obtained when R^2X in **14** was a 2-naphthylmethoxy group. NaH and NaHMDS were found to be the optimal bases for best stereoselectivities.



R^1 = Me, Bn
R^2X = BnO, BnS, MeO, 1–NaphCH$_2$O, 2–NaphCH$_2$O
R^3 = 4–NO$_2$C$_6$H$_4$CH$_2$, Bn, CH$_2$CO$_2$Et, CH$_2$=CHCH$_2$, Me

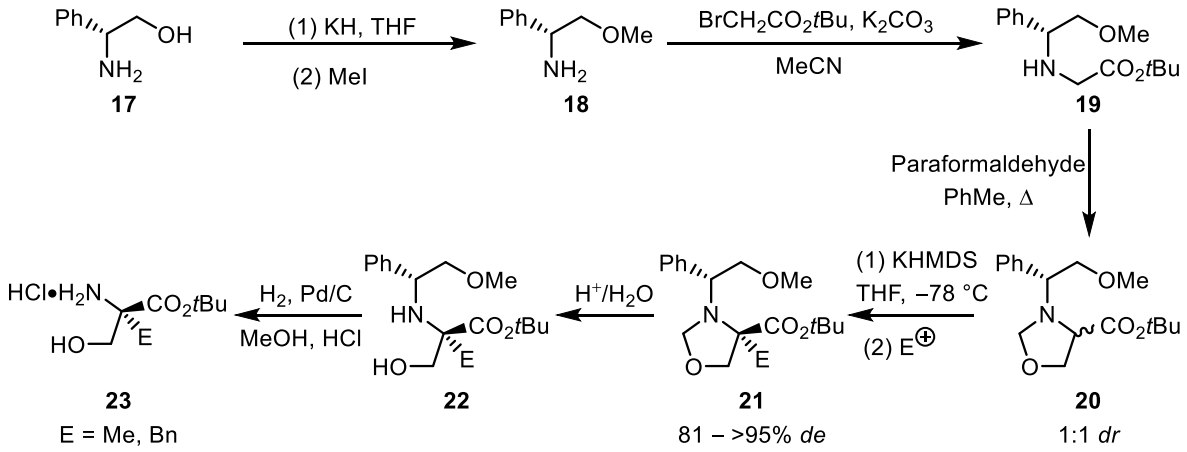
Scheme 4: Diastereoselective alkylation of amino esters using a pyridoxal type chiral auxiliary

It was suggested that the Na^+ counter ion of the base played an important role in stereoselectivity. Perhaps, it coordinates to the oxygen atoms of the chiral auxiliary, bringing them closer to the reactive centre (Scheme 5). Coordination of the sodium ion to the enolate of substrate **14** (R^2X = 2-naphCH$_2$O) provides two possible transition states **T1** and **T2**, in which the 2-naphthyl group shields one of the diastereomeric faces of the enolate. The transition state **T1** offers more stability than **T2** due to an extra coordination by the sodium ion to the oxygen of the 2'-methoxy moiety. In addition, steric repulsion between the 2'-methoxy moiety and the pyridine 2-methyl substituent in **T2** causes instability of that transition state. Approach of the electrophile at the *Re* face in **T1** and subsequent hydrolysis affords the major isomer.



Scheme 5: Possible transition states for the alkylation of **15** (R^2X = 2-naphCH$_2$O)

In the use of a chiral auxiliary, the amino acid synthesis is not always achieved by alkylation of amino acid derivatives. A requirement of the amino acid precursor is that it possesses functionality that can be converted to an amino acid after quaternisation. An example is the functionalisation of oxazolidine ester enolate **20** to produce **21** (Scheme 6).[27] The chiral auxiliary is the amino alcohol **17** which was converted to **20** by a sequence of reactions illustrated in Scheme 6. Direct hydrolysis of **21** revealed the serine side chain in **22**. X-ray analysis of **22** (E = Me) showed that the alkylation occurred at the *Si* face of the enolate. Subsequent hydrogenolysis of **22** produced enantiopure α-substituted serine *tert*-butyl esters **23**.



Scheme 6: Asymmetric functionalisation of an oxazolidine ester enolate

Many other examples exist in the literature on the synthesis of enantiopure quaternary amino acids through the diastereoselective alkylation of amino acid derivatives (Figure 3). Some of these examples include the use of an oxazolidinone chiral auxiliary as seen in **24**,[28] glycine derived chiral auxiliaries such as **25** and **27**,[29–32] a phenylethyl chiral auxiliary as seen in morpholinone **26**[33,34] and chiral auxiliaries built up into oxazinones as seen in **28** and **29**.[35–40] In all of these cases, alkylation is always followed by hydrolysis to produce enantiopure α,α-disubstituted amino acids and recover the chiral auxiliary.

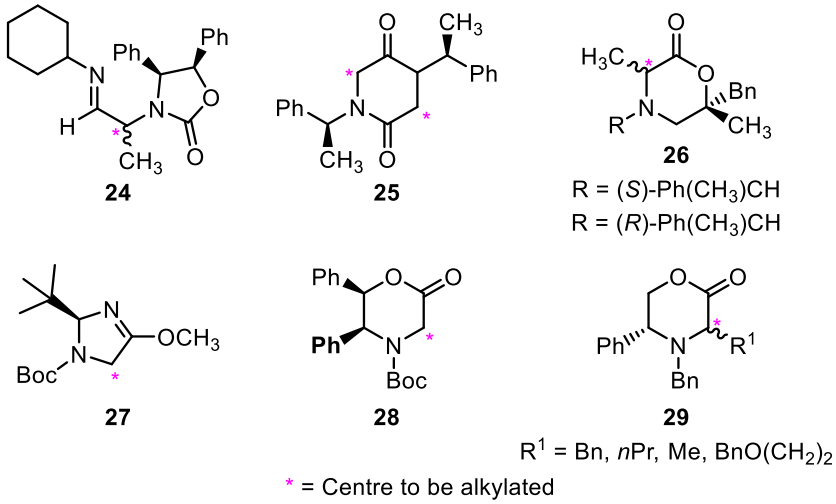
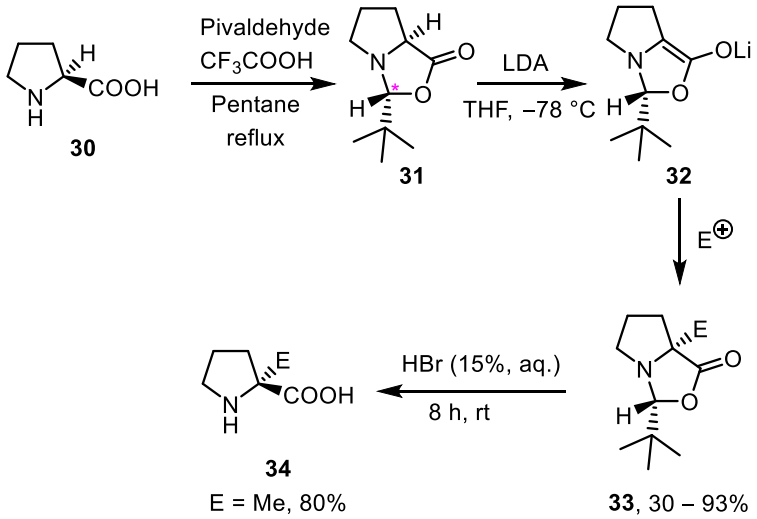


Figure 3: Examples of amino acid derivatives diastereoselectively functionalised in the literature

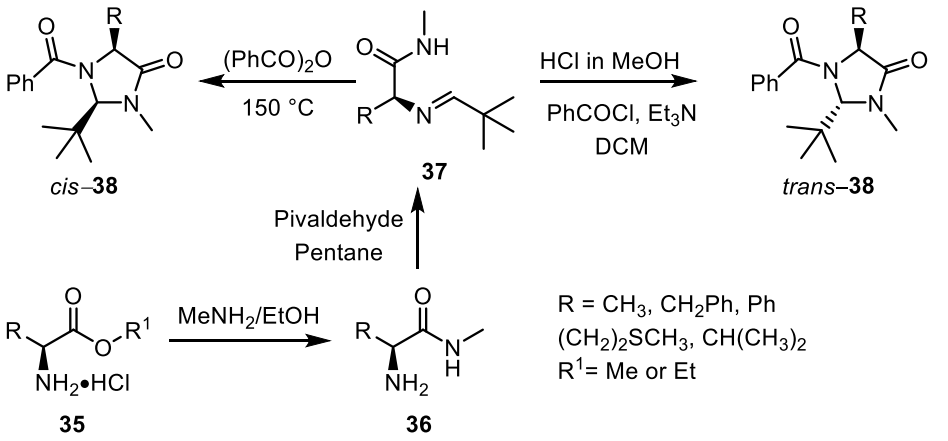
1.3.2 Self-Regeneration of Stereocentres

The term 'Self–Regeneration of Stereocentres' (SRS)[41] is used to describe the destruction and subsequent re-generation of a chiral centre present within an enantiopure molecule. Before the destruction of the chiral centre, a temporary chiral centre is diastereoselectively generated. The original chiral centre is then destroyed by the removal of a substituent. The temporary chiral centre then directs a diastereoselective introduction of another substituent at the previously destroyed chiral centre, hence reproducing chirality at that centre. The temporary chiral centre is then destroyed by hydrolysis, leaving behind the reproduced chiral centre without racemisation. The SRS protocol was developed by Dieter Seebach and has been applied to the synthesis of a variety of enantiopure compounds.[42–44] For the asymmetric synthesis of quaternary amino acids, a chiral cyclic intermediate is usually formed from an enantiopure amino acid. On deprotonation of this intermediate, a chiral enolate having diastereomeric faces is formed; this can then be diastereoselectively alkylated and the temporary chiral centre removed.



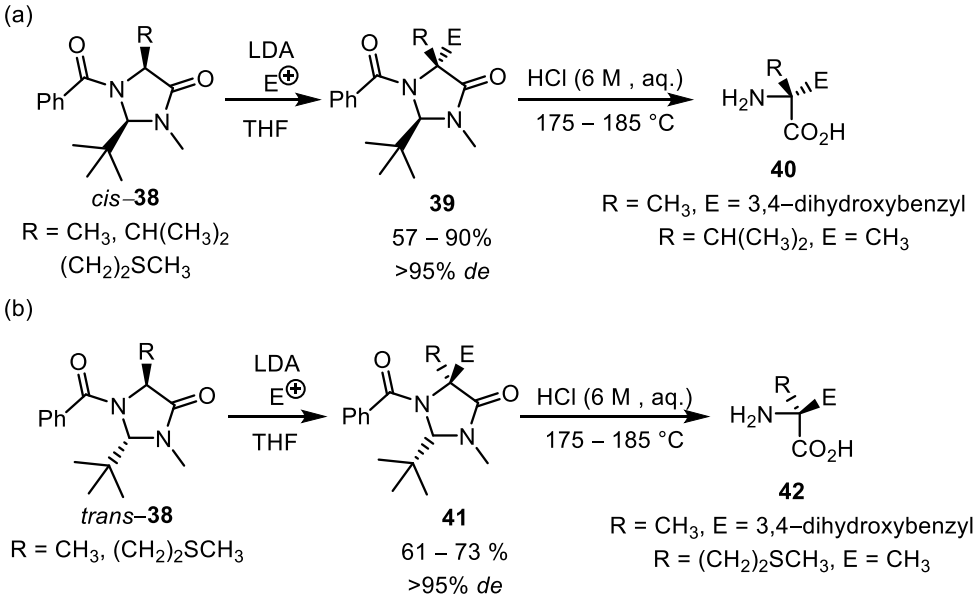
Scheme 7: Alkylation of oxazolidinones via SRS

One of the earliest examples of the "SRS" principle in the synthesis of enantiopure quaternary amino acids is the functionalisation of the α-carbon of proline **30** (Scheme 7).[45,46] Direct introduction of a substituent to the α-carbon of proline would ordinarily lead to a racemic **34**. To prevent this, **30** was condensed with pivaldehyde to give a new chiral centre labelled with a pink asterisk in **31**. The configuration of this new chiral centre was induced by the single chiral centre in **30**. After crystallisation, the product **31** was obtained as a single diastereoisomer, in which the *tert*-butyl group was in the exo position having a *cis* relationship with the α-proton in the proline residue. Treatment of **31** with LDA led to trigonalisation of the original chiral centre to produce the enolate **32**. The enolate was able to react with a variety of electrophiles to produce **33** as essentially single diastereoisomers and with retention of configuration. The direction of entry of the electrophilic substituent was induced by the single chiral centre in the enolate **32** and occurs from the *Re* face of the enolate. This placed both the *tert*-butyl and the new substituent *cis* to each other and on the exo side of the bicycle. Hydrolysis of **33** (E = Me) led to the enantiopure α-methyl proline **34** with retention of configuration.



Scheme 8: Synthesis of *cis*- or *trans*-imidazolidinones

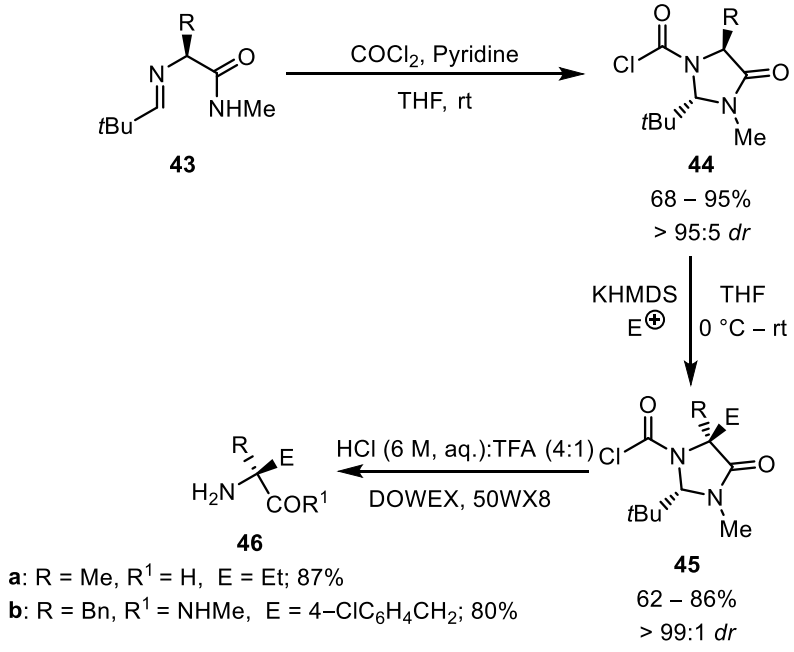
The original SRS protocol illustrated with proline in Scheme 7 could not be achieved with acyclic amino acids, as they did not readily form acetals under the conditions used. As a result of this shortcoming, another route was developed towards achieving chiral cyclic α-amino acid derivatives that could be diastereoselectively α-functionalised to attain enantiopure quaternary amino acids (Scheme 8).[47] This route involves the conversion of an amino acid methyl or ethyl ester hydrochloride **35** to the methylamide **36**. The methylamide is then condensed with pivaldehyde to afford the imine **37**. Depending on the conditions used, **37** could be transformed to give predominantly the *cis*- or *trans*-imidazolidinones **38**. These products could however be crystallised to obtain the single *cis*- or *trans*-isomers. This imidazolidinone route was later exploited for the synthesis of enantiopure quaternary amino acids (Scheme 9).[48]



Scheme 9: Alkylation of: (a) *cis*-imidazolidinones (b) *trans*-imidazolidinones

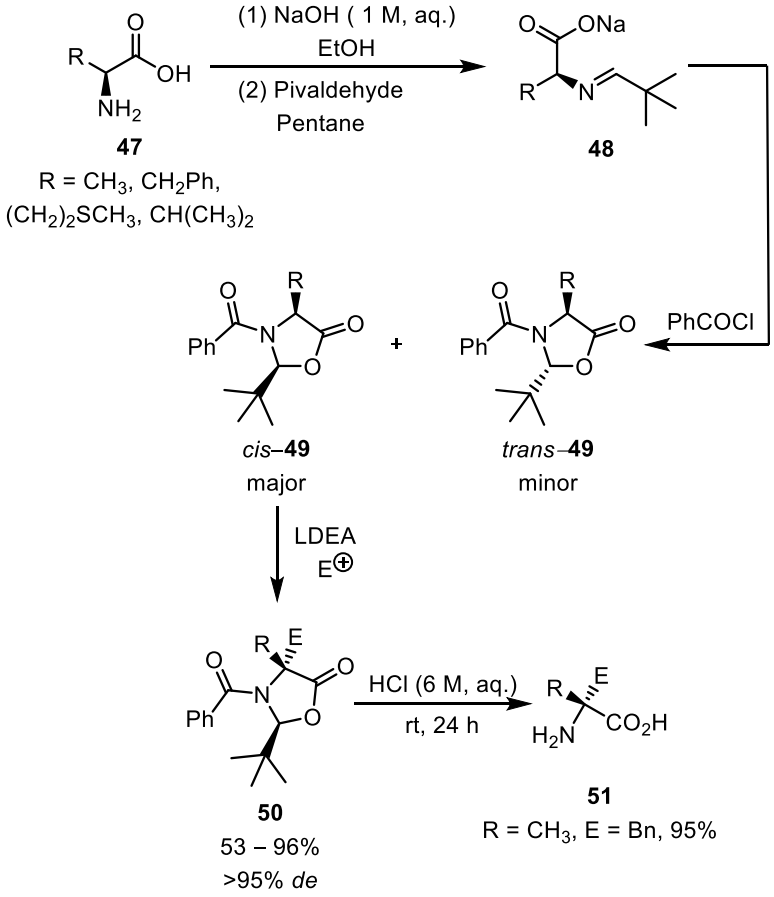
The *cis*- and *trans*-imidazolidinone derivatives of alanine, valine and methionine were converted to their respective quaternary amino acid derivatives **39** and **41**, by deprotonation and subsequent alkylation. In all cases, ≥ 95% diastereoselectivity of **39** and **41** were observed by ^{1}H NMR of the crude mixture. Relative and absolute configurations of selected examples of **39** and **41** were assigned by NOE analysis. Hydrolysis using several harsh acidic conditions led to the production of α-alkylated α-amino acids **40** and **42**. The *cis*-imidazolidinone (*cis*-**38**) led to amino acids **40**, in which the configuration of the tertiary amino acid precursor was retained while the *trans*-imidazolidinone (*trans*-**38**) led to inversion of configuration in the amino acids **42**. This strategy is valuable because opposite enantiomers of a quaternary amino acid are accessible by starting from a single enantiomer of the precursor tertiary amino acid. For example, (*S*)-α-methyldopa which shows antihypertensive activity,[49,50] was exclusively accessed, without contamination by its biologically inactive (*R*)-enantiomer.

Recently, Clayden *et al*. reported a completely diastereoselective method for making *trans*-imidazolidinones (Scheme 10).[51] The imines **43** were made from the corresponding tertiary amino acids through Seebach's methyl amide protocol illustrated in Scheme 8. On treatment with phosgene and pyridine, the imines **43** underwent cyclisation and concomitant acylation, offering the *trans*-*N*-chloroformylimidazolidinones **44** with >99:1 *dr* in most cases. The acylated imidazolidinones **44** were considerably stable under basic conditions, hence they were α-alkylated with several electrophiles to afford the quaternary amino acid derivatives **45**. Hydrolysis to the quaternary amino acid was exemplified by treating selected examples of **45** with HCl/TFA to afford the quaternary amino acid **46a** or the *N*-methyl amide **46b**.



Scheme 10: Alkylation of *trans*-*N*-chloroformylimidazolidinones

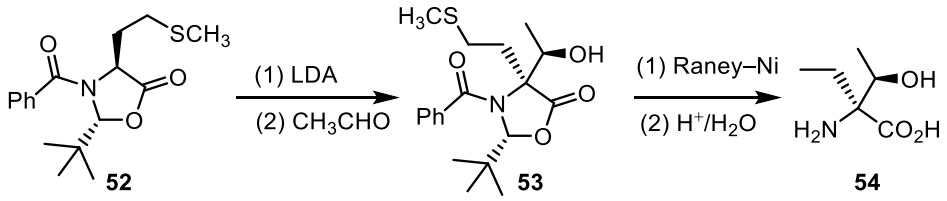
Seebach's imidazolidinone strategy was useful in the synthesis of a variety of important compounds such as derivatives of aspartic and glutamic acids[52] and BIRT 377 **63**, a hydantoin used in the treatment of various inflammatory and immune disorders.[42,43] However, the imidazolidinones usually require harsh conditions to be hydrolysed to the amino acids, hence limiting the incoming electrophiles to acid stable substituents.



Scheme 11: Alkylation of acyclic amino acid derived oxazolidinones

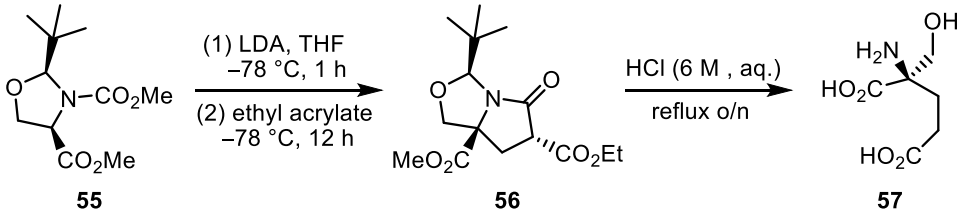
While investigating alternative scaffolds for the diastereoselective functionalisations, Seebach *et al*. found out that it was indeed possible to achieve the acetalisation of acyclic amino acids.[53–55] Going back to the original oxazolidinone route, the sodium salts of **47** were condensed with pivaldehyde to furnish the imines **48** (Scheme 11). Treatment of **48** with PhCOCl at or below room temperature led to diastereoisomers **49**, in which the *cis* was the major diastereoisomer. Surprisingly, treating *cis*-**49** with LDA and subsequent reaction with electrophiles led to low yields of **50**. Using the less sterically hindered lithium diethylamide LDEA, **50** was obtained with good yields and diastereoselectivity of >90% before crystallisation. The hydrolysis of oxazolidinone **50** (R = CH_3, E = Bn) occurred under milder conditions than the corresponding imidazolidinone derivative.[55] Seebach also extended the oxazolidinone strategy to reactions with aldehyde and ketone electrophiles. In an example illustrated in Scheme 12, the lithium enolate of **52** reacted with

acetaldehyde diastereoselectively to produce the hydroxyamide **53**. Desulfurisation and hydrolysis of **53** produced α-ethylthreonine **54**. The (2*S*),(3*R*)-configuration of **54** was obtained by comparison with the ^{1}H NMR of its known diastereoisomer.[56]



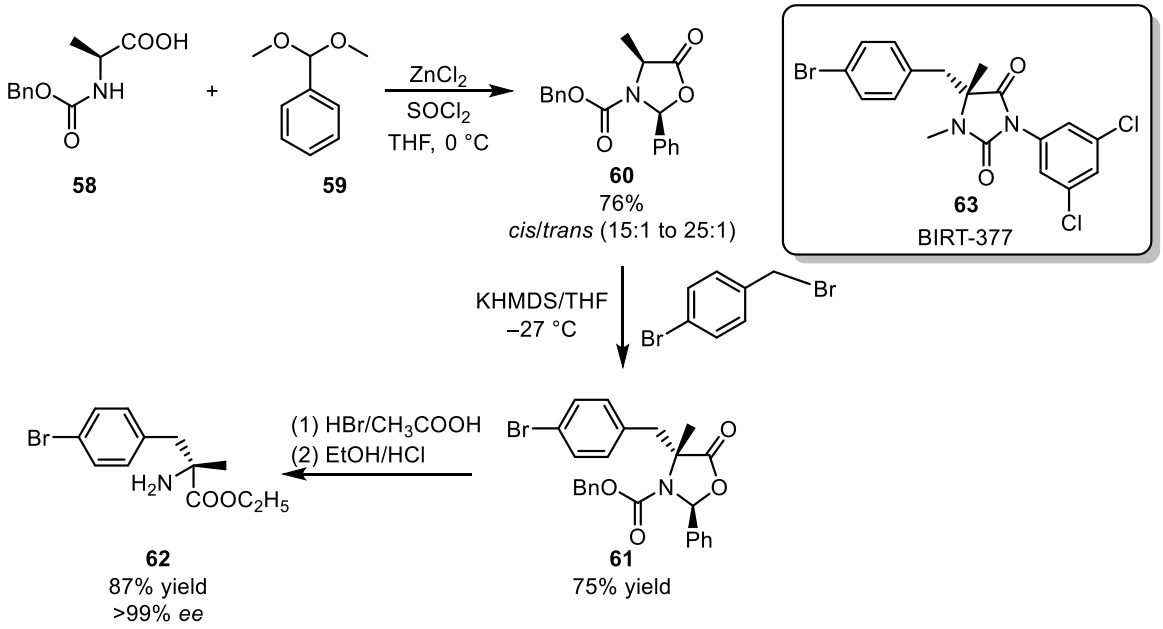
Scheme 12: Functionalisation of an oxazolidinone with an aldehyde

In 2001, Zhang *et al*.[57] reported the synthesis of (2*S*)-α-(hydroxymethyl) glutamate (HMG) **57** (Scheme 13). HMG exhibits metabotropic glutamate receptor agonist activity. After several disappointing results with formyl and Boc *N*-protecting groups, they decided to try serine-derived oxazolidine with a methoxy carbonyl *N*-protecting group **55**. Using LDA as base, oxazolidine **55** was subjected to a Michael addition with ethyl acrylate to afford the bicycle **56** as a single diastereoisomer. The bicycle was then hydrolysed to afford HMG **57** in high yield.



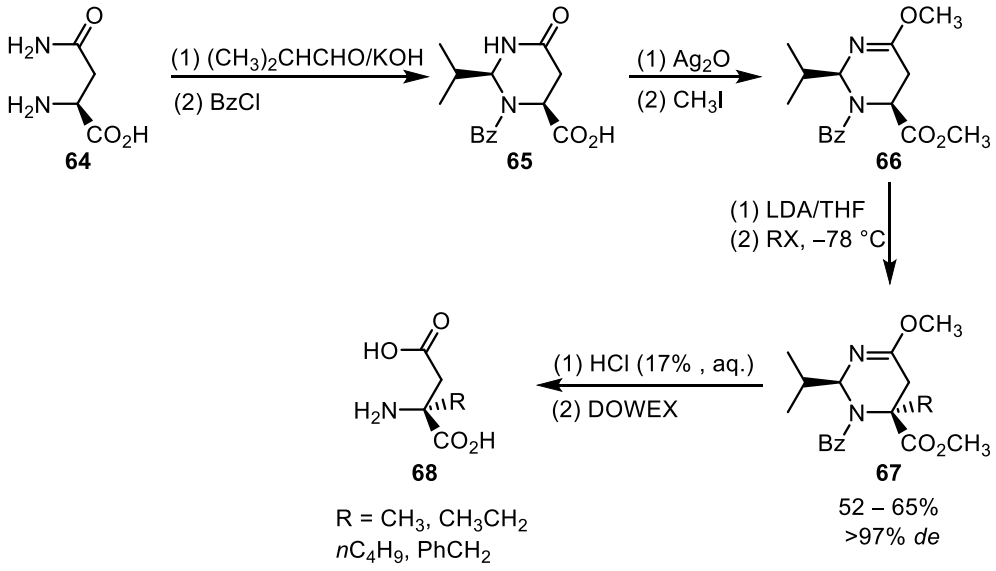
Scheme 13: Synthesis Of (2S)-α-(hydroxymethyl) glutamate (HMG) through SRS

Pivaldehyde has been widely used as auxiliary in "SRS" reactions. This is because the *tert*-butyl group induces good diastereoselectivity due to its bulkiness, it is easily hydrolysed, it is unreactive and quite easy to identify by ^{1}H NMR, as it gives just a singlet in a clearly defined area of the spectrum.[41] Notwithstanding the use of other auxiliaries have been reported. Kapadia *et al*. adopted the SRS principle in the enantioselective synthesis of α-(4-bromo benzyl) alanine ethyl ester **62** through an oxazolidinone (Scheme 14). [58] The oxazolidinone **60** was synthesised predominantly as the *cis*-diastereoisomer by the reaction of the acylated alanine **58** with benzaldehyde dimethyl acetal **59**. Both zinc chloride and thionyl chloride were necessary for the reaction to occur, as reduced equivalents of either of them led to incomplete reaction. Addition of a mixture of **60** and 4-bromobenzyl bromide in THF to KHMDS afforded the alkylated product **61**. The alkylation was stereoselective and occurred *trans* to the phenyl ring. Hydrolysis of **61** was then carried out using hydrogen bromide in acetic acid to give the amino acid hydrobromide which was stirred in ethanol at 70 °C in the presence of HCl gas to afford the amino ester **62** with greater than 99% *ee*. The amino acid derivative **62** was later used for the synthesis of BIRT-377 **63**.



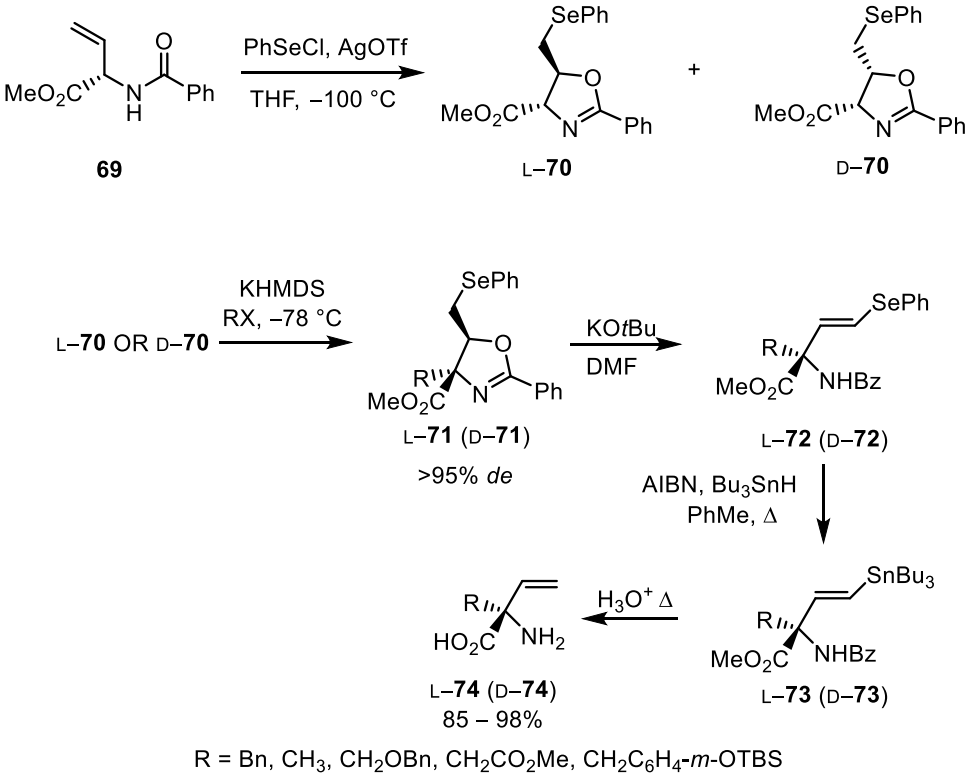
Scheme 14: Alkylation of an oxazolidinone through SRS

Another class of heterocyclic system through which quaternary amino acids could be accessed using the SRS principle is the tetrahydropyrimidinones (Scheme 15). Tetrahydropyrimidinone **65** was obtained from (*S*)-asparagine **64**, isobutyraldehyde and benzoyl chloride. It was then converted to the enantiopure pyrimidinone imino ester **66**. The lithium enolate of **66** was then alkylated by various electrophiles to afford the *trans* alkylated product **67** with >97% *de*. The authors suggested that the high stereoselectivity in the reaction of the lithium enolate of **66** with the electrophiles might be due to the steric hindrance produced by the isopropyl group. Hence, the electrophiles were directed to the face of the enolate opposite the isopropyl group. Hydrolysis of **67** afforded enantiopure α-alkyl aspartic acids **68**.[59]



Scheme 15: Alkylation of a tetrahydropyrimidinone through the SRS principle

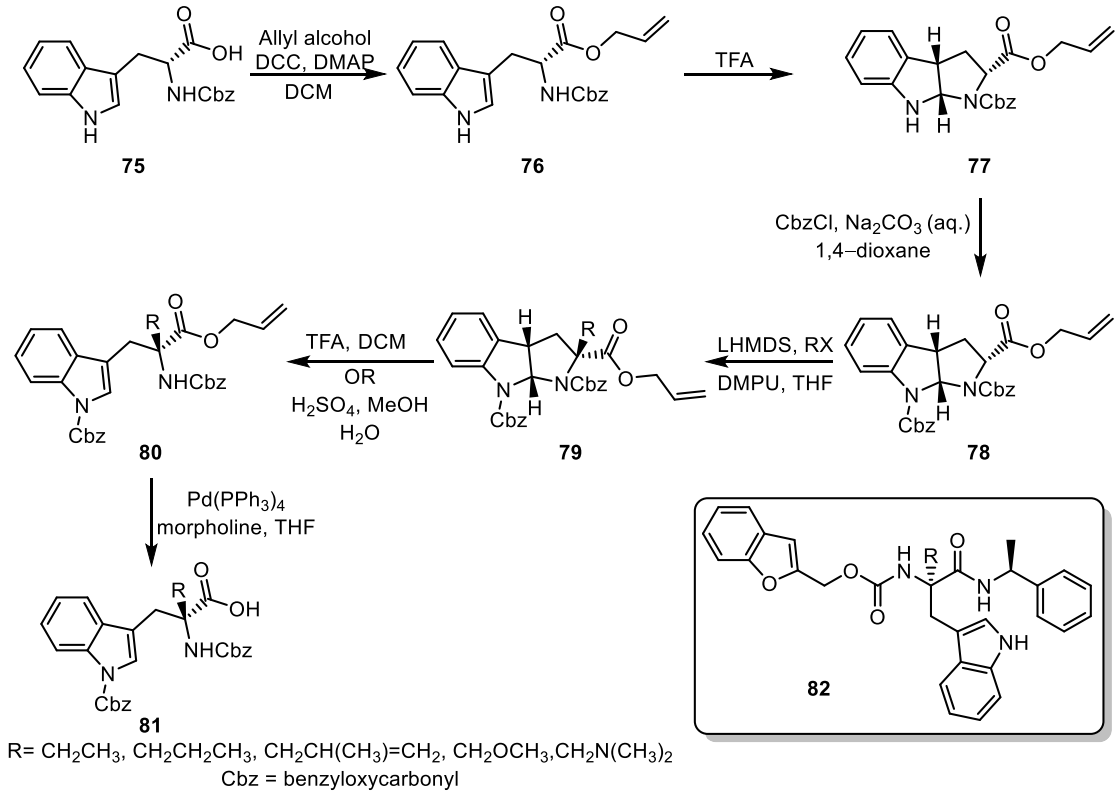
In a case similar to the SRS strategy, quaternary (*R*)-(2-trialkylstannyl)vinyl amino acids were synthesised through cyclic oxazoline intermediates (Scheme 16).[60] A temporary chiral centre was first introduced into the *N*-benzoyl-protected L-vinyl glycine **69** through an episelenonium ion-mediated 5-exo-trig cyclisation. The L and D isomers of **70** produced were easily separated by SiO_2 chromatography. Both isomers were separately subjected to alkylation to produce the new quaternary centre in **71** with >95% *de*. The temporary chiral centre was destroyed, and the original vinyl moiety unmasked by basic hydrolysis to yield **72**. The ring opening reaction was stereoselective, producing only the *E*-isomer of **72**. Substitution reaction of **72** with Bu_3SnH followed by protodestannylation afforded the α-alkyl vinyl amino acids **74**.



Scheme 16: Synthesis of α-alkyl,α-vinyl amino acids through the SRS principle

To investigate the effect of substituents on the α-position of the neurokinin-1 receptor antagonist CI 1021 (**82**), Ashwood *et al.*[61] carried out the alkylation of tryptophan through a tetrahydropyrroloindole intermediate (Scheme 17). Allyl esterification of **75** afforded **76** with slight racemisation when DMAP was used as catalyst. There was no racemisation in the absence of DMAP, but the reaction was slower. **76** was subjected to a cyclisation reaction catalysed by TFA to afford **77**, which was isolated as a single diastereoisomer. The indolinyl nitrogen of **77** was protected with a benzyloxycarbonyl (Cbz) group to afford **78** in excellent yield. Alkylation of **78** proceeded in good yield and was diastereoselective at the α-carbon. Ring opening reaction of **79** to afford **80** was carried out with either TFA in DCM or H_2SO_4 in methanol. **80** was hydrolysed to

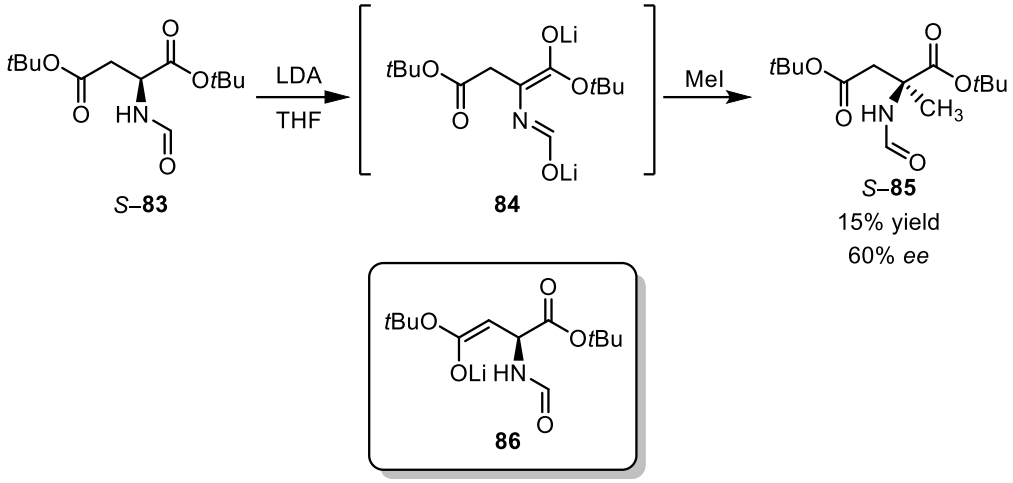
yield the free quaternary amino acids **81**. The amino acid **81** was finally used to make several α-substituted derivatives of the neurokinin-1 receptor antagonist CI 1021 (**82**).



Scheme 17: Alkylation of tetrahydropyrroloindoles through the SRS principle

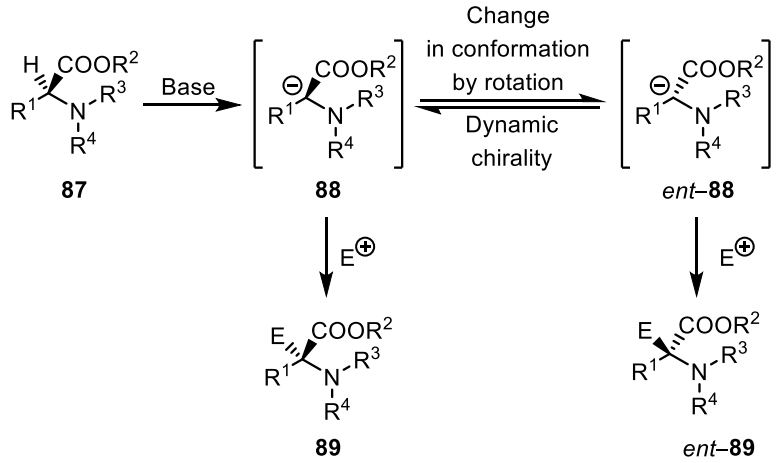
1.3.3 Memory of Chirality

The term "Memory of Chirality" (MOC) is used to describe reactions in which the stereochemistry of a reactant having one chiral centre is retained temporarily in an intermediate formed from destruction of the single chiral centre, and as a result, products formed from reaction with this intermediate retain the stereochemistry of the reactant. It is noteworthy that this process occurs without the influence of an external source of chirality.[62] In the synthesis of quaternary amino acids, the intermediate formed is an enolate and reaction of this enolate with non-chiral electrophiles proceeds enantiospecifically without any other chiral influence.[62,63] This is remarkable because deprotonation of the α-carbon of the only chiral centre in a carbonyl compound should in principle lead to the loss of stereochemical information in the enolate intermediate, hence leading to the formation of racemic products, if there is no external chiral influence.



Scheme 18: Alkylation of the only chiral centre present in a molecule without complete loss of optical purity

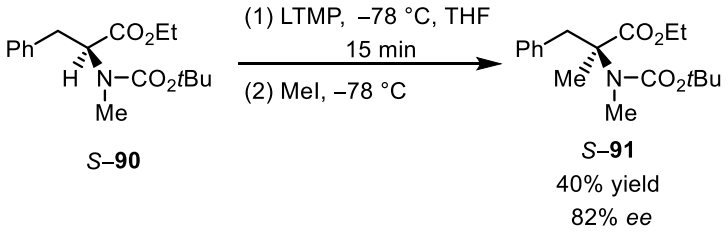
In 1981, while investigating the β-alkylation of the enantiopure aspartic acid derivative **83**, Seebach *et al*. observed that α-alkylated product **85** was formed with a 60% enantiomeric excess (Scheme 18). Surprised at the result, they attributed the enantioretention to either complexes of achiral enolate **84** to the chiral enolate **86**[41,64] or the enolate **84** itself existing in a sufficiently stable conformation that possesses axial chirality.[65–67] Kawabata *et al*. explained that it was possible for an enolate to exist in a conformationally chiral form, whose lifetime is dependent on the temperature of reaction (Scheme 19). The enolate conformations **88** and *ent*-**88** interconvert rapidly and may not be differentiated at elevated temperatures. At lower temperatures, the enolate could persist sufficiently in one conformation for it to get quenched by the electrophile in that conformation.[68]



Scheme 19: Interconversion between two conformational forms of an enolate

To demonstrate the explanation above, Kawabata carried out some variable-temperature alkylations of **90**. Enolate formation at −78 °C produced an enantiomeric excess of 82% in **91** (Scheme 20).[68] Enolate formation at −78 °C and subsequent warming to −40 °C led to a significant reduction in the enantiomeric excess of **91** to 10%. Finally, enolate formation at −78 °C to room temperature

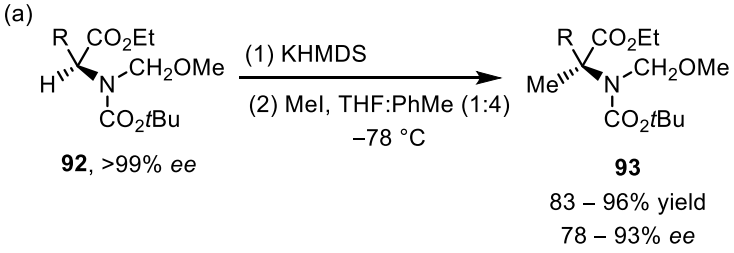
produced racemic **91**. These experiments indicate that racemisation of the enolate intermediate occurs with increase in temperature.



S–**90** *S*–**91**
40% yield
82% *ee*

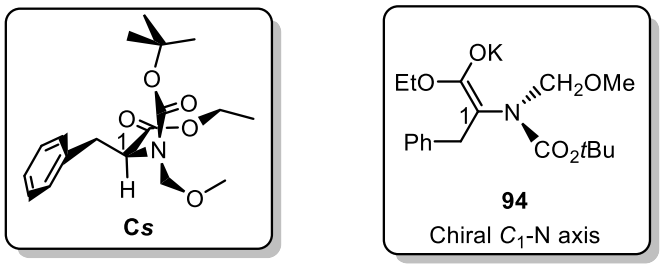
Scheme 20: Enantiospecific alkylation of an L-phenylalanine derivative through memory of chirality

To demonstrate the generality of the MOC strategy in enantioselective quaternary amino acid synthesis, Kawabata *et al*. investigated the methylation of derivatives of amino acids such as phenyl alanine, histidine, valine, leucine, tryptophan, tyrosine and dopa (Scheme 21).[69] Prior investigations showed that having a MOM group as substituent on the nitrogen as seen in **92** produced better results than a methyl group.[68] The methylation of **92** occurred stereoselectively and with comparable enantioretention for all the amino acids used.



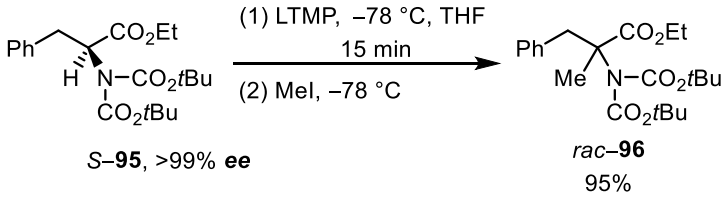
92, >99% *ee* **93**
83 – 96% yield
78 – 93% *ee*

(b)



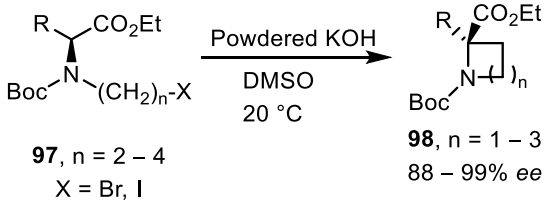
Scheme 21: (a) Direct enantiospecific α-methylation of α-amino acid derivatives (b) A chiral C_1-N axis

Further investigations into the source of enantioretention revealed that there is hindered rotation about the C_1-N bond which produces axial chirality in the enolate. The stereochemical outcome of the reaction was explained using **92** (R = Bn). The substrate **92** (R = Bn) can exist as two conformers. Deprotonation of the more stable conformer (**Cs**) leads to formation of the *N*-chiral enolate **94**. The half-life of racemisation of **94** at −78 °C was calculated to be 22 h, which is enough time for the enolate to attack the electrophile. The methyl electrophile approaches **94** at the direction opposite the sterically demanding Boc group.



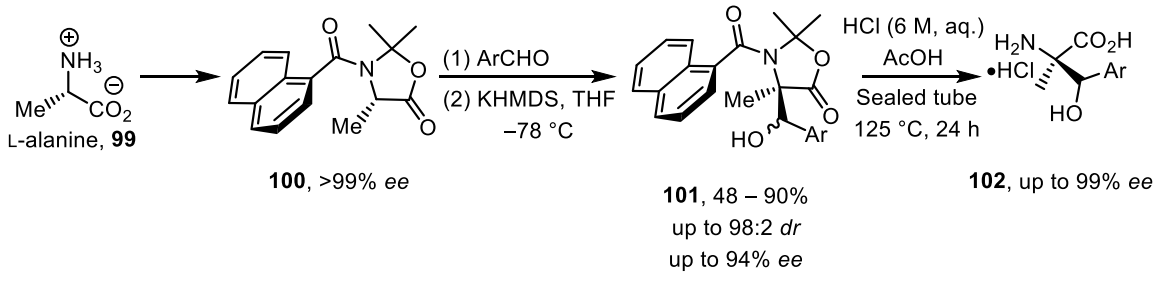
Scheme 22: Proof of the presence of an axially chiral enolate intermediate

Since axial chirality will not exist with two identical groups on the nitrogen, the methylation of **95** occurring with complete racemisation (Scheme 22) was proof that the alkylation of amino acids through the MOC strategy takes place through an axially chiral enolate intermediate.[69]



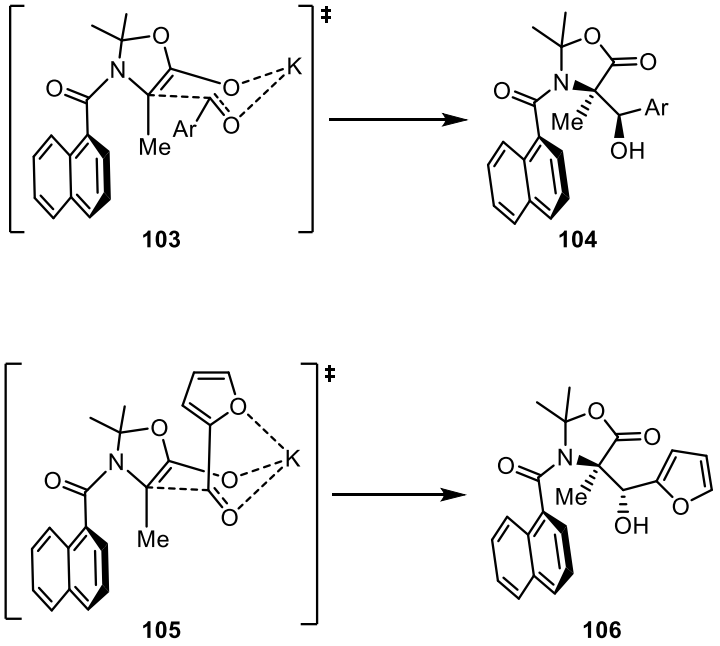
Scheme 23: Intramolecular alkylation of amino acid derivatives through a MOC strategy

Kawabata *et al*. later developed an enantioselective intramolecular alkylation of amino acid derivatives **97** at ambient temperature (Scheme 23).[70] From the outcome of previous investigations, it was assumed that a MOC strategy at ambient temperature would result in diminished enantioselectivities. However, excellent enantioselectivity was observed. It was proposed that this was due to the intramolecular nature of the reaction. Because both alkylating agent and enolate were within the same molecule, the rate of alkylation was able to outcompete the rate of racemisation of the chiral enolate. The enolate formation step was found to be the rate-determining step and it was calculated that after formation of this enolate, it would have to undergo cyclisation within approximately 10 ms at 20 °C to produce an *ee* of ≥88%. The excellent enantioselectivities implied cyclisation occurred as soon as the enolate was formed. The smaller the ring, the faster the rate of cyclisation; hence four-membered cyclic amino acids were obtained faster and with better enantioselectivities than the corresponding 6-membered ring amino acids.



Scheme 24: Quaternary amino acids via aldol condensation and MOC

Synthesis of quaternary amino acids by aldol reactions using the MOC strategy has been reported. Oxazolidinone **100** obtained from L-alanine[71] underwent condensation with aldehydes, with retention of configuration to produce β-hydroxy quaternary α-amino acid derivatives **101** (Scheme 24). Hydrolysis of some examples of **101** led to β-hydroxy quaternary α-amino acids **102** in up to 99% *ee*.[72] The retention of configuration in **101** was due to the dynamic axial chirality in the tertiary aromatic amide of **100**.[71,73] The derivative **101** was obtained as a mixture of two separable diastereoisomers. The temperature, rate, and order of addition of **100**, the aldehyde and KHMDS was relevant to obtaining good diastereoselectivity. The *ee* of the major diastereoisomer of **101** was 80 – 94%, but upon crystallisation, an *ee* of 99% was obtained.



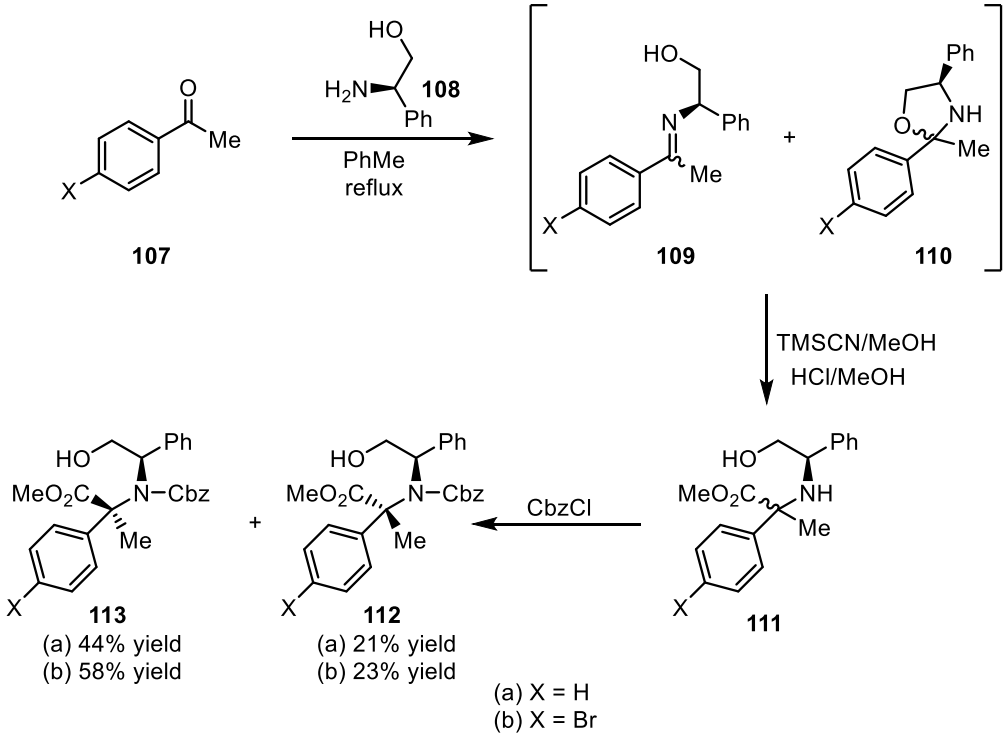
Scheme 25: Observed stereoselectivity in the synthesis of **101**

The major diastereoisomer formed in each reaction was dependent on the structural component of the aldehyde used (Scheme 25).[72] Sterically hindered aldehydes such as *ortho*-substituted benzaldehydes were selective towards the transition state **103**, hence producing **104**. Aldehydes containing electron donor atoms such as furaldehyde favoured the transition state **105**. This is probably because donor atoms in the pseudo axial position will stabilise the transition state **105** more by coordinating with the metal.

1.3.4 Addition of Nucleophiles to C=N Bond

The Strecker synthesis, which involves the reaction of an aldehyde with ammonia and a cyanide, with subsequent cyanide hydrolysis, has been an attractive tool for the synthesis of tertiary amino acids.[74,75] In the enantioselective synthesis of quaternary amino acids through the Strecker route, an enantiopure amine is usually used instead of ammonia and a ketone instead of an aldehyde.[15] The

two groups attached to the carbonyl of the ketone become the two side chains of the quaternary amino acid. An example is the construction of α-methyl phenylglycine derivatives from α-aryl ketones, phenyl glycinol and TMSCN (Scheme 26).[76]



Scheme 26: Asymmetric Strecker-type synthesis of alkylated phenylglycine amino esters

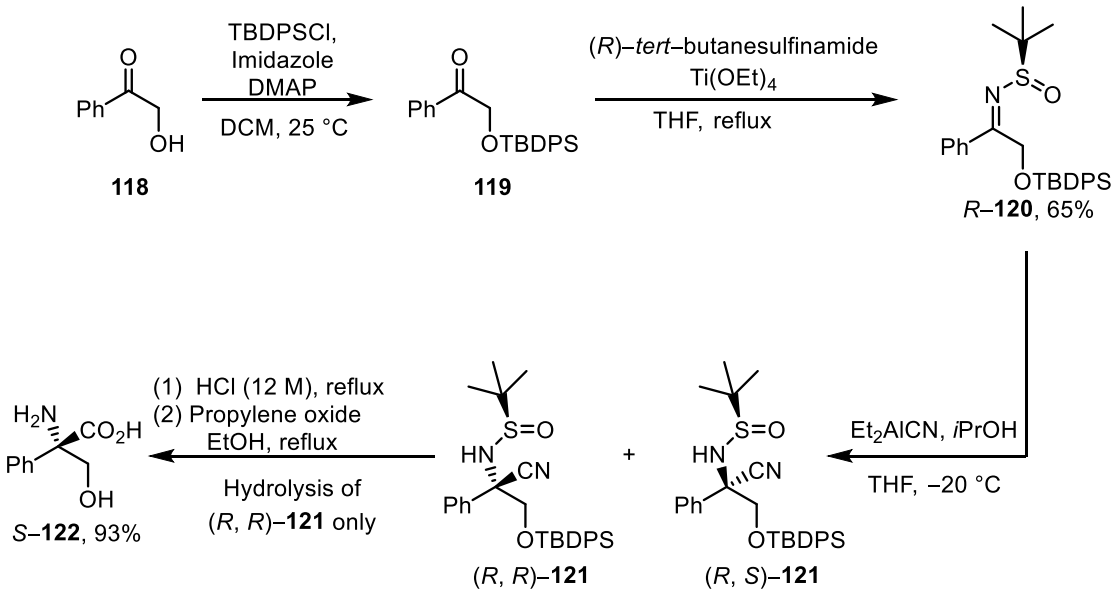
α-Aryl ketone **107** was heated with the amine (*R*)-phenylglycinol **108** in toluene to obtain a mixture of imine **109** and oxazolidine **110**. The mixture of **109** and **110** might exist as an equilibrium. The mixture was subjected to treatment with trimethylsilyl cyanide in methanol to obtain the amino nitrile which was then treated with saturated methanolic HCl to obtain the amino ester **111** as a mixture of two diastereoisomers. The diastereoisomers, which were obtained as a 2:1 mixture for amino ester **111a** and a 2.5:1 mixture for amino ester **111b**, were not easily separable by column chromatography. Protection with a benzyloxycarbonyl group made it possible to separate the diastereoisomers by column chromatography. The major diastereoisomer **113b** was isolated and used in the synthesis of (*S*)-α-M4CPG **114**[77–79] and (*S*)-MPPG **115** (Figure 4).[80] The synthesis of **114** and **115** confirmed that the stereochemistry of the major diastereoisomer of **111** was (*R*,*S*). The method was also extended to the synthesis of (*S*)-AIDA **116**[81] and (*S*)-APICA **117** (Figure 4)[82] which are selective antagonists of metabotropic glutamate receptors.

X = CO_2H, (*S*)–αM4CPG; **114**
X = $P(O)(OH)_2$, (*S*)–MPPG; **115**

X = CO_2H, (*S*)–AIDA; **116**
X = $P(O)(OH)_2$, (*S*)–APICA; **117**

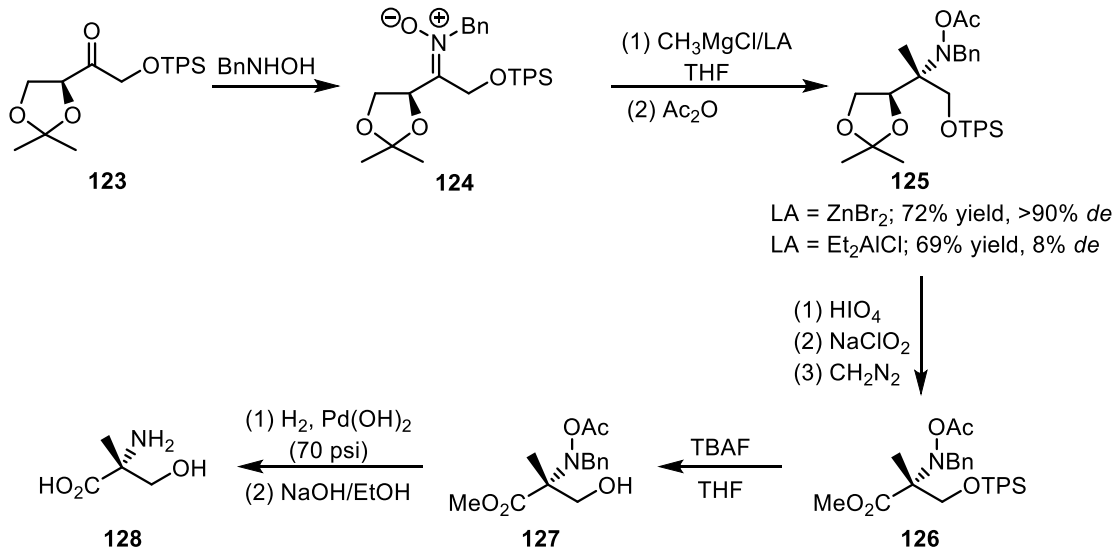
Figure 4: Antagonists of metabotropic glutamate receptor

Sulfinimines are good chiral directing groups for the diastereoselective synthesis of quaternary amino acids and can be cleaved under acidic conditions.[83–85] The stereoselective addition of a cyanide to enantiopure *N*-sulfinyl ketimine was carried out (Scheme 27).[86]



Scheme 27: Synthesis of (*R*)-α-phenylserine through an asymmetric Strecker reaction

N-Sulfinyl ketimine (*R*)-**120**, obtained from condensation of silyl protected 2-hydroxy acetophenone **119** with the amine (*R*)-*tert*-butanesulfinamide, was subjected to an addition reaction with ethyl aluminium cyanoisopropoxide to afford **121** in an 81:19 mixture of the two diastereoisomers. The major diastereoisomer (*R*,*R*)-**121** was isolated through column chromatography. Hydrolysis of (*R*,*R*)-**121** with 12 M HCl, followed by reflux with propylene oxide in ethanol liberated the free amino acid (*S*)-**122** in 93% yield. (*R*)-α-Phenylserine (*R*)-**122** was obtained using the same method but with the substrate (*S*)-**120**.



Scheme 28: Synthesis of (*R*)-(-)-2-methylserine through stereoselective addition of Grignard reagent to a chiral nitrone; LA = Lewis acid

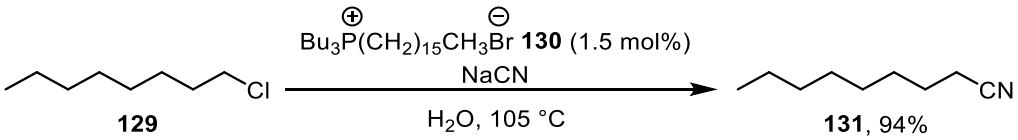
In the Strecker method discussed, the carboxylic acid group was introduced through a cyanide. Alternatively, the side chain of the amino acid could be introduced by the addition of organometallic reagents to an imine. An example was that reported by Portolés *et al*. (Scheme 28).[87] A Grignard reagent was used to introduce the side chain of the amino acid. Nitrone **124**, obtained from the reaction of silylated L-erythrulose acetonide **123** with *N*-benzyl hydroxyl amine was initially reacted with several Grignard reagents to afford *N*-acetoxyamine derivatives such as **125** as a mixture of two diastereoisomers. The results showed that the diastereomeric ratio depended on the Grignard reagent used. Allyl and phenyl Grignard reagents were particularly stereoselective. It was observed that the presence of a Lewis acid in the Grignard reaction favoured one diastereoisomer over the other. $ZnBr_2$, for example, favoured the diastereoisomer with an (*R*)-configuration at the new stereocentre while Et_2AlCl showed poor diastereoselectivity or in some cases, complete reversal in diastereoselectivity in favour of the diastereoisomer having a (*S*)-configuration at the new stereocentre. In the synthesis of (*R*)-(-)-2-methyl serine **128**, sequential treatment of **125** with periodic acid, sodium chlorite and diazomethane afforded the *N*-acetoxy-α-amino esters **126**. Deprotection of **126** with TBAF/THF afforded **127**, which on hydrogenolysis followed by hydrolysis furnished (*R*)-(-)-2-methyl serine **128**.

1.3.5 Phase Transfer Catalysis

The term "phase transfer catalysis" (PTC)[1] was introduced by Stark in 1971 to describe the role of tetra-alkylammonium or phosphonium salts in the reaction between substances at the interface between immiscible phases.[88] A reaction is inhibited when the reactants are separated by solvation

[1] In this thesis, any reference to PTC could mean Phase Transfer Catalysis, Phase Transfer catalysed or Phase Transfer Catalyst

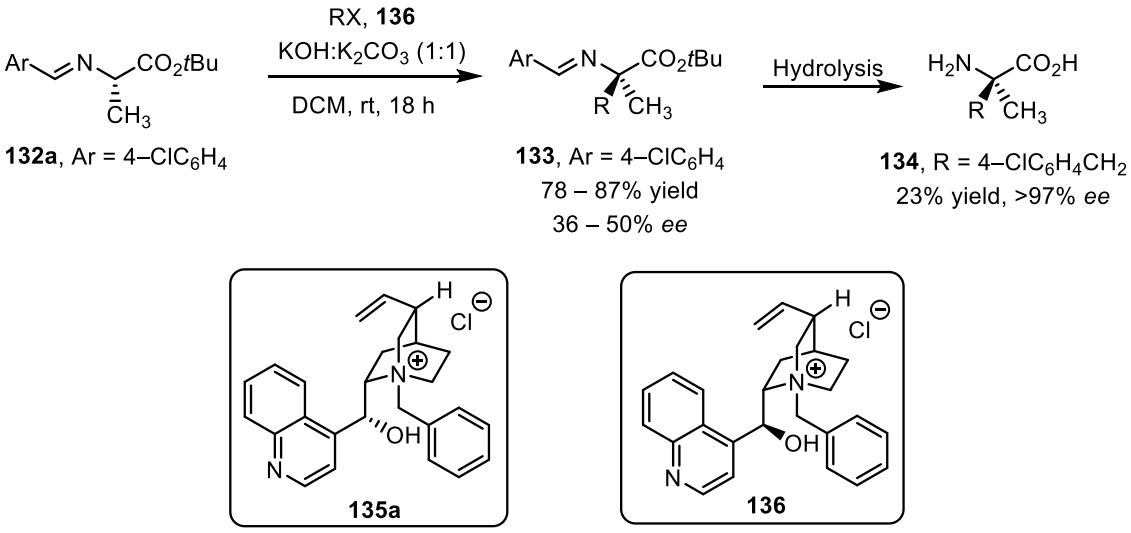
in two different immiscible phases. The reaction, however, can be made possible using a phase transfer catalyst, due to the ability of the catalyst to transfer a reactant from one phase to another. Organic-soluble quaternary ammonium or phosphonium cations are effective in transferring anions from aqueous phases to organic phases.[89] An example is the phosphonium salt-catalysed S_N2 reaction of 1-chlorooctane **129** and aqueous sodium cyanide (Scheme 29).



Scheme 29: S_N2 reaction of 1-chlorooctane with aqueous sodium cyanide under phase transfer catalysis

There was no reaction without the phosphonium catalyst **130**; however, when **130** was introduced, the reaction proceeded with 94% yield. The generation of quaternary phosphonium cyanide makes the cyanide anion organic soluble, facilitating the reaction.[88]

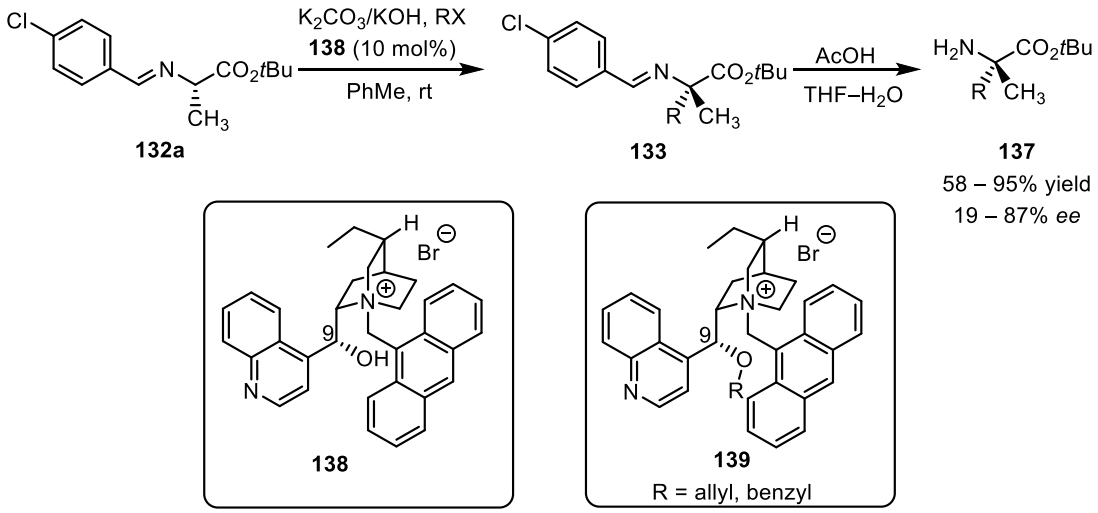
PTC has enjoyed significant attention in both industrial and academic research, this is because of the simplicity of the process. The process eliminates the use of expensive and environmentally unfriendly reactants/solvents, it employs the use of mild reaction conditions and has the possibility of being performed on a large scale. Asymmetric phase transfer catalysis involves the use of a chiral catalyst for the transfer of a reactant from one phase to the other where reaction can occur. The chirality of the catalyst interacts with a reactive intermediate, hence inducing enantioselectivity in the product formed from the intermediate. PTC has been applied to a variety of reactions such as the asymmetric alkylation of amino acid derived imines, Michael addition, aldol reaction and Mannich reaction.[90] The most widely used catalysts in the synthesis of quaternary amino acids under PTC are the cinchona-derived ammonium salts.[91]



Scheme 30: α-Alkylation of alanine using *N*-benzyl cinchoninium chloride (**136**)

In 1992, O'Donnel *et al*. carried out the solid-liquid phase catalytic alkylation of alanine-derived imines **132** (Scheme 30).[92] Of all the bases examined, best enantioselectivities and yields were obtained with a ground mixture of potassium hydroxide and potassium carbonate. Investigation of several aryl groups in **132**, revealed **132a** (Ar = 4-ClC_6H_4) as the optimal in achieving good yields and enantioselectivities of **133**. Other aryl groups made **132** significantly inactive under the KOH:K_2CO_3 system. By using epimers **135a** or **136**, either enantiomer of **133** could be accessed as the major product. However, **136** induced better enantioselectivity than **135a** in the alkylation of **132a**. The use of catalyst **136** in the alkylation afforded the alkylated products **133** in up to 50% *ee* in favour of the (*R*)-enantiomer. As expected, alkylation of enantiopure **132** derived from L-alanine with an achiral catalyst afforded racemic product while alkylation of racemic **132** derived from D,L-alanine with the chiral catalyst **136** afforded enantioenriched product. Though the alkylated products **133** were obtained in moderate to good enantioselectivities, a pure enantiomer could be obtained by crystallisation of the racemate.[93] For example, the amino acid **134** was obtained in greater than 97% *ee* by hydrolysis of enantiopure **133** (R = 4-$ClC_6H_4CH_2$), which was obtained by two recrystallisations to remove racemic product from the corresponding racemate.

N-9-anthracenyl-bearing cinchona salts such as **138** were independently designed by the groups of Lygo[94] and Corey.[95] Corey explained that the quinuclidinyl nitrogen of cinchona-derived salts could be likened to the centre of a tetrahedron and effective shielding of three faces of the tetrahedron could be relevant to obtaining excellent enantioselectivities. The quinuclidine ring already offers effective shielding of one of the three tetrahedral faces. The introduction of a bulky substituent such as a 9-anthracenyl on the nitrogen of the quinuclidine serves as a shield for a second face and provides an additional advantage of positional rigidity. The third face may be shielded by the introduction of an allyl or benzyl on the hydroxyl group as seen in **139**. Hence, substrate interaction with the cinchona salt at those 3 faces becomes difficult, thus leaving the fourth face of the tetrahedron open for interaction of the ammonium ion with the enolate.[95,96]



Scheme 31: α-Alkylation of alanine using a 9-anthracenyl-bearing cinchona salt

Application of *N*-9-anthracenylmethyl dihydrocinchonidinium bromide **138** as catalyst in the alkylation of the alanine-derived imine **132a** was performed (Scheme 31).[97] The chloride analogue of **138** was reportedly used as catalyst in the alkylation of a glycine derived imine under phase transfer catalytic conditions, inducing an enantioselectivity of 94%.[94] It should be noted that the active catalyst in the alkylation of amino acids using cinchona salts bearing a free hydroxyl group at the C-9 position is the *O*-alkylated form which is generated *in situ*; Hence, a new active catalyst is formed with each change in the R-group of RX.[94,98] Research showed that the nature of the alkylating group has an influence on the enantioselectivity. A 22% increase in *ee* was observed when a pre-formed C9-*O*-benzyl cinchona salt was used in place of a pre-formed C9-*O*-methoxymethyl cinchona salt in the benzylation of glycine derived imines. Nevertheless, the pre-formed C9-*O*-benzyl cinchona salt gave the same *er* as the *in situ* formed equivalent.[99] Similar conditions to that used by O'Donnel in Scheme 30 were used in the alkylation of **132a**. The potassium carbonate/hydroxide mixture had to be freshly ground because the use of a moisture absorbed base led to decrease in rate and enantioselectivity. The *tert*-butyl ester **132a** gave best enantioselectivities than other esters. Alkylation of **132a** with alkyl halides, followed by subsequent hydrolysis afforded **137** in moderate to good enantioselectivities. The best *ee*s were obtained with benzylhalides such as benzyl bromide. Investigations into the reaction revealed that there were some background uncatalysed alkylations occurring, rationalising low *ee*s observed in some cases. Optimisation of the reaction to minimise the background alkylations could improve the enantioselectivities. The amino acids **137** could be obtained in enantiopure form by recrystallisation.

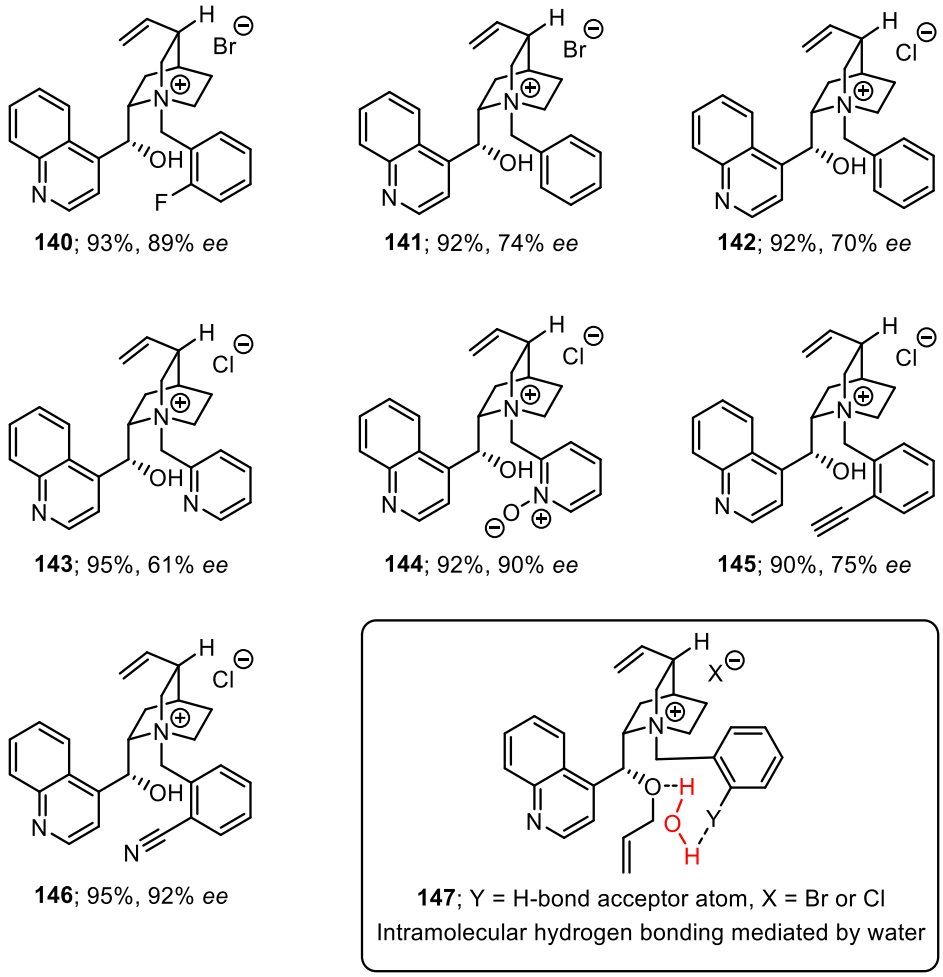
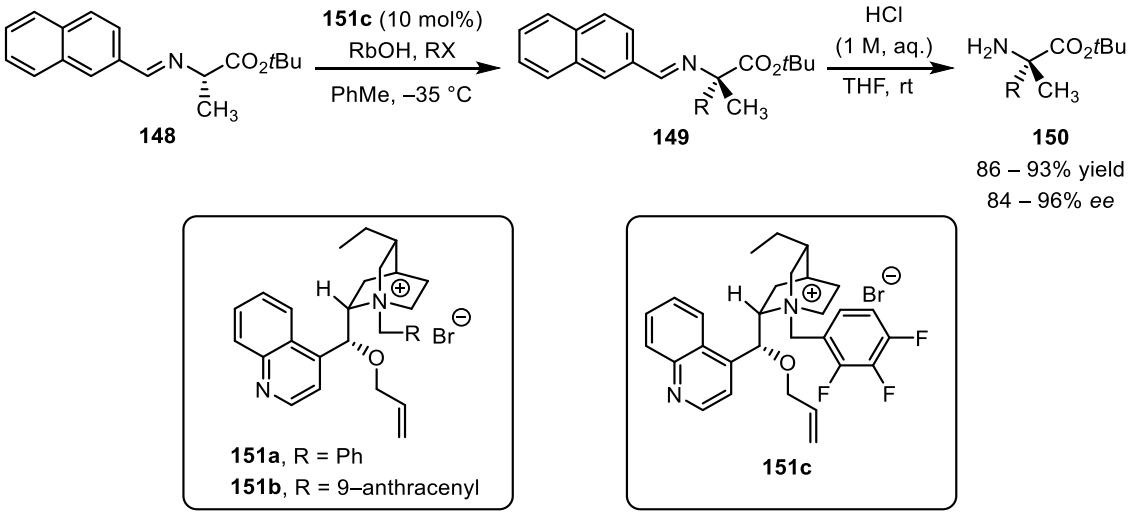


Figure 5: Influence of electronics of the catalyst on enantioselectivity; Conditions: alkylation of a glycine derived imine in PhMe:$CHCl_3$ (7:3) with 50% KOH at 0 °C, 10 mol% of catalyst used in each case

Jew *et al*. studied the electronic influence of the quinuclidine *N*-substituents on the enantioselectivity in the alkylation of a glycine derived imine.[91,100] Since enantioinduction is facilitated by coordination of the chiral ammonium cation of the catalyst with the enolate formed on deprotonation of the amino acid, it is expected that the electronic effects of the *N*-substituents might have an influence on enantioselectivity. *Ortho*-substituted benzylic *N*-substituents generally produced better enantioselectivities than the *para* and *meta* substituted. Additionally, bulky *ortho* substituents on the benzyl gave reduced *ee*s relative to the less bulky ones. Particularly, the *ortho*-fluorobenzyl derivative **140** gave a significantly better *ee* than the unsubstituted benzyl derivative **141** (Figure 5). Further investigations with cinchona-based catalysts having differential fluorine substitutions on the *N*-benzyl revealed that a single fluorine atom at the *ortho* position of the *N*-benzyl substituent was significant in obtaining enhanced enantioselectivities in the alkylation. This could be due to the ability of the fluorine atom to hydrogen bond with the hydroxyl group through water present in the solvent (see **147**). This intramolecular hydrogen bonding produces a more rigid catalyst conformation. Catalysts **144** and **146**, which have hydrogen-bond acceptor atoms on the benzyl, induced significantly better *ee*s than **143** and **145** which have no available hydrogen-bond

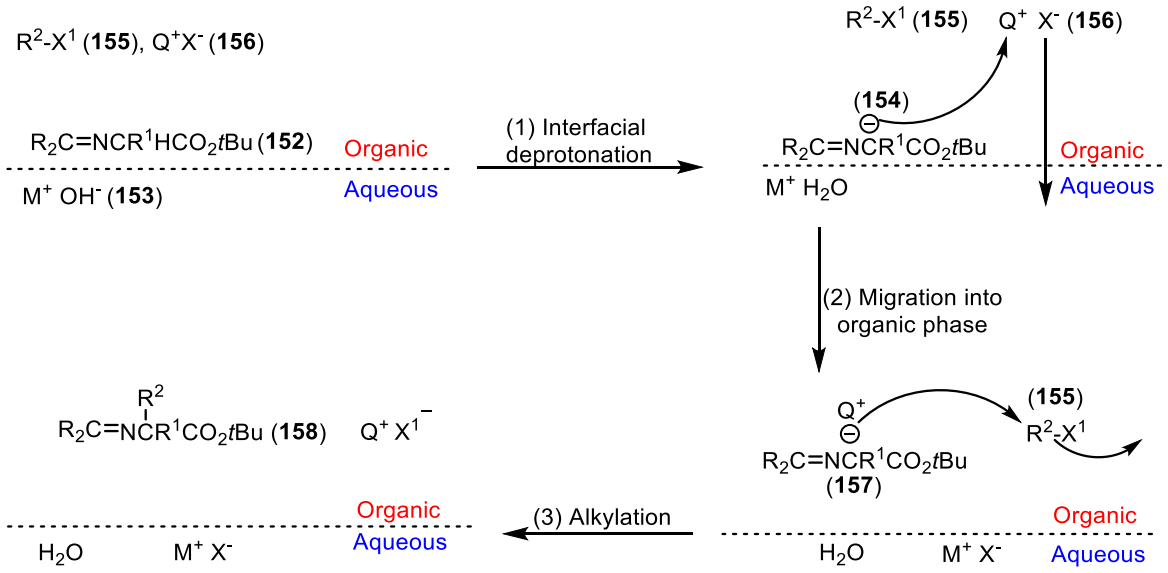
acceptor atoms. This further supported the hypothesis that the potential for intramolecular hydrogen bonding within the catalyst could be the source of enhanced *ee*s in the alkylation.



Scheme 32: α-Alkylation of alanine using a 2,3,4-trifluorobenzyl-bearing cinchona salt

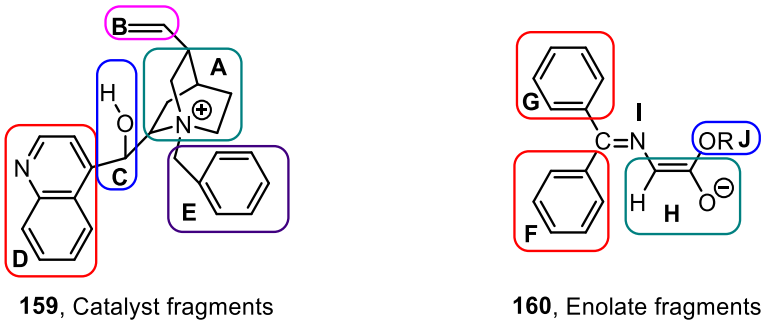
The use of catalyst **151c**, having a 2,3,4-trifluorobenzyl *N*-substituent, induced excellent enantioselectivities in the alkylation of the alanine derived imine **148** in favour of the (*S*)-enantiomer (Scheme 32).[101] The unsubstituted *N*-benzyl derivative **151a** gave a significantly reduced *ee* relative to **151c**. The 9-anthracenyl derivative **151b** also gave a reduced *ee* relative to **151c** but an improved *ee* relative to **151a**. These reactions further show the influence of the sterics and electronics of the catalyst on the enantioselectivity of the alkylation. It was also observed that improved enantioselectivities were obtained at cryogenic temperatures.

The general mechanism for arylation or alkylation of amino acids under liquid-liquid phase transfer catalysis involves the deprotonation of the amino acid derivative **152** at the solvent-solvent interface by the base **153** to give the enolate **154** (Scheme 33).[102] The enolate is transported into the organic layer by coordinating with quaternary ammonium ion (Q^+) from the catalyst **156**. The chiral ammonium enolate complex **157** then reacts with the alkyl halide **155** to produce the alkylated species **158**.



Scheme 33: Mechanism of alkylation of α-amino acids under PTC conditions

In the mechanism, the step involving the coordination of the enolate to the chiral quaternary ammonium ion of the catalyst is the step necessary to induce asymmetry. Computational studies of the quaternary ammonium ion **159** and the glycine-derived enolate **160** revealed that the catalyst fragments, in order of relevance, for binding to the enolate are the quinuclidine (**A**) > the benzyl (**E**) > the hydroxyl (**C**) fragment (Figure 6).[102] The positive charge on the quinuclidine nitrogen is dispersed over fragment **A** and **E**, hence **A** and **E** interact with the enolate through coulomb attractions while fragment **C** interacts with the enolate through hydrogen bonding. Hence, to improve enantioselectivity in the alkylation reactions, the fragments **A**, **C** and **E** might be the fragments to consider for synthetic modification. The vinyl (**B**) and quinoline (**D**) fragments do not bind to the enolate, rather they tend to repel the enolate as it interacts with fragments **A** and **E**. The vinyl fragment plays no role in enantioselectivity; However, the quinoline fragment, even though it does not bind to the enolate, plays an important role by acting as a platform for the enolate to bind to the relevant fragments. The catalyst interacts with all labelled fragments of the enolate, but it is mostly attracted to fragments **H** and **I**.

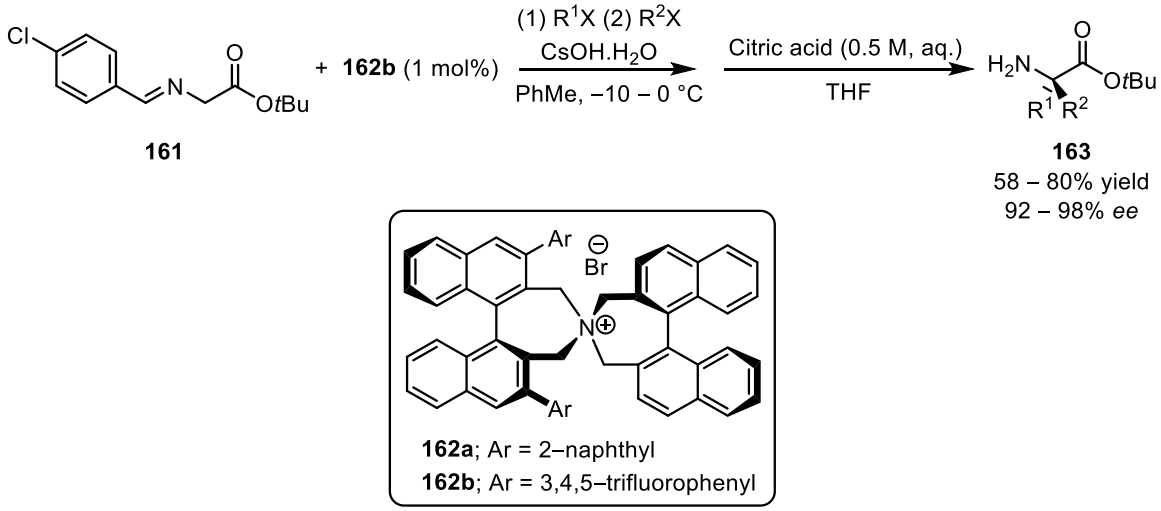


159, Catalyst fragments

160, Enolate fragments

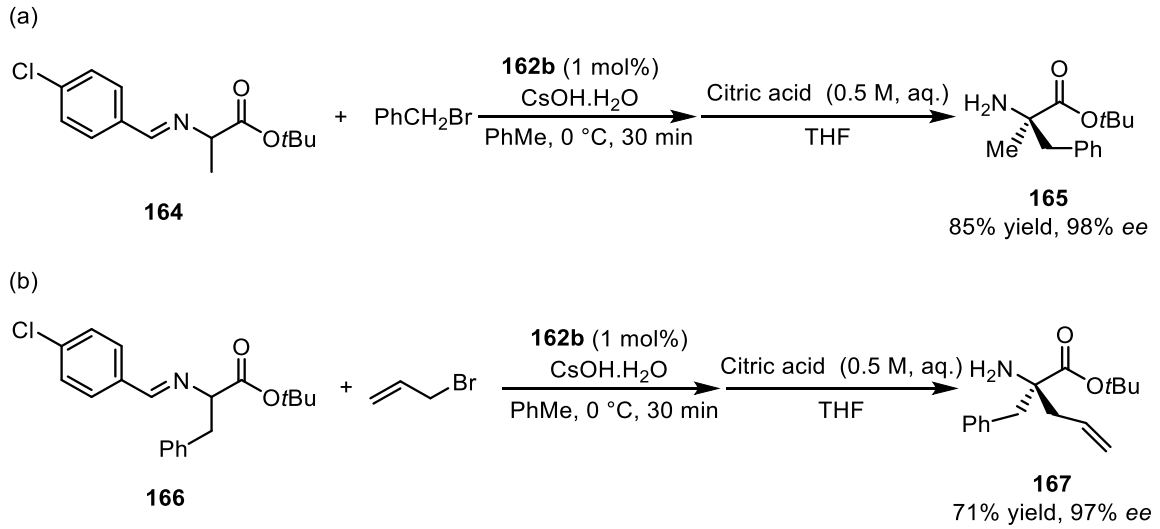
Figure 6: Fragments of the catalyst and enolate components of a phase transfer-catalysed enolate alkylation reaction

Apart from the cinchona alkaloids, another class of catalysts that has been used in the asymmetric alkylation of α-amino acids are the C_2-symmetric chiral ammonium salts designed by Maruoka.[103–105] The one pot double alkylation of the *tert*-butyl ester of glycine-derived imine **161** using the C_2-symmetric catalysts **162a** and **162b** was investigated.[106] The enantioselectivity induced by **162b**, bearing fluorine substituents on the aryl group, was significantly higher than that induced by **162a**, bearing a naphthyl group. These results suggest that in the design of new catalysts for asymmetric alkylation, modification of the electronic nature of the catalyst might be more important than steric factors. Catalyst **162b** was later used in the double alkylation with several alkyl halides (Scheme 34).



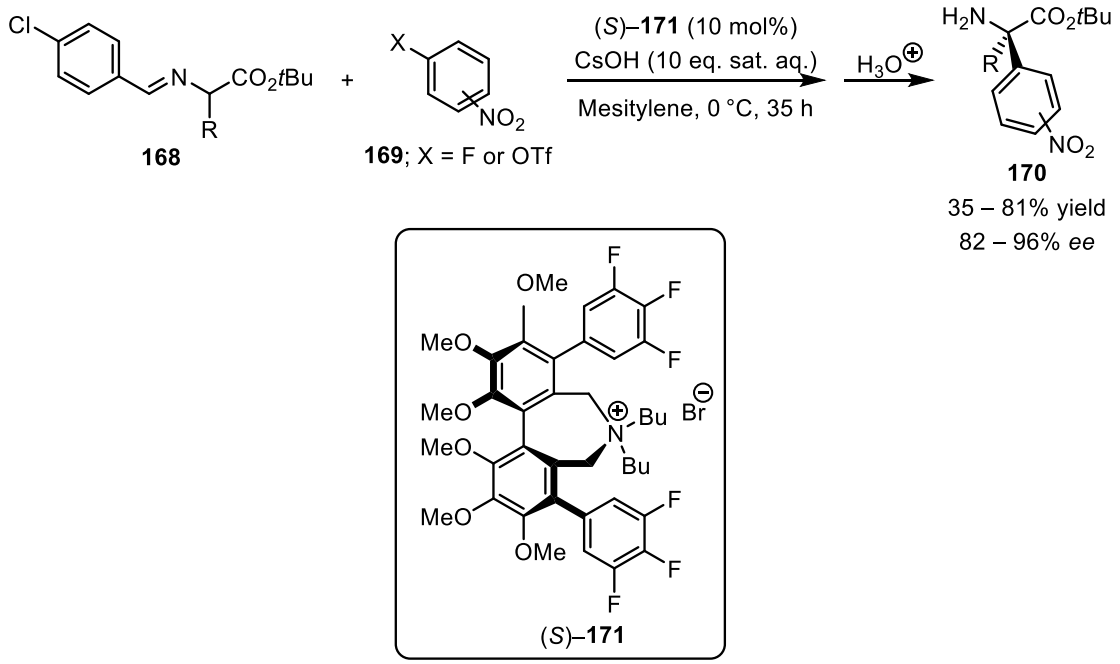
Scheme 34: Double alkylation of glycine-derived imine using a C_2-symmetric chiral catalyst

The first alkyl halide was added at −10 °C, and left for 2 to 3.5 hours before adding the second alkyl halide at 0 °C. The quaternary amino acids **163** were obtained in up to 98% *ee*. The generality in the use of **162b** was demonstrated in the alkylation of alanine and phenylalanine-derived aldimines **164** and **166** (Scheme 35). Excellent yields and enantioselectivities of the alkylated amino acids were obtained in both cases.



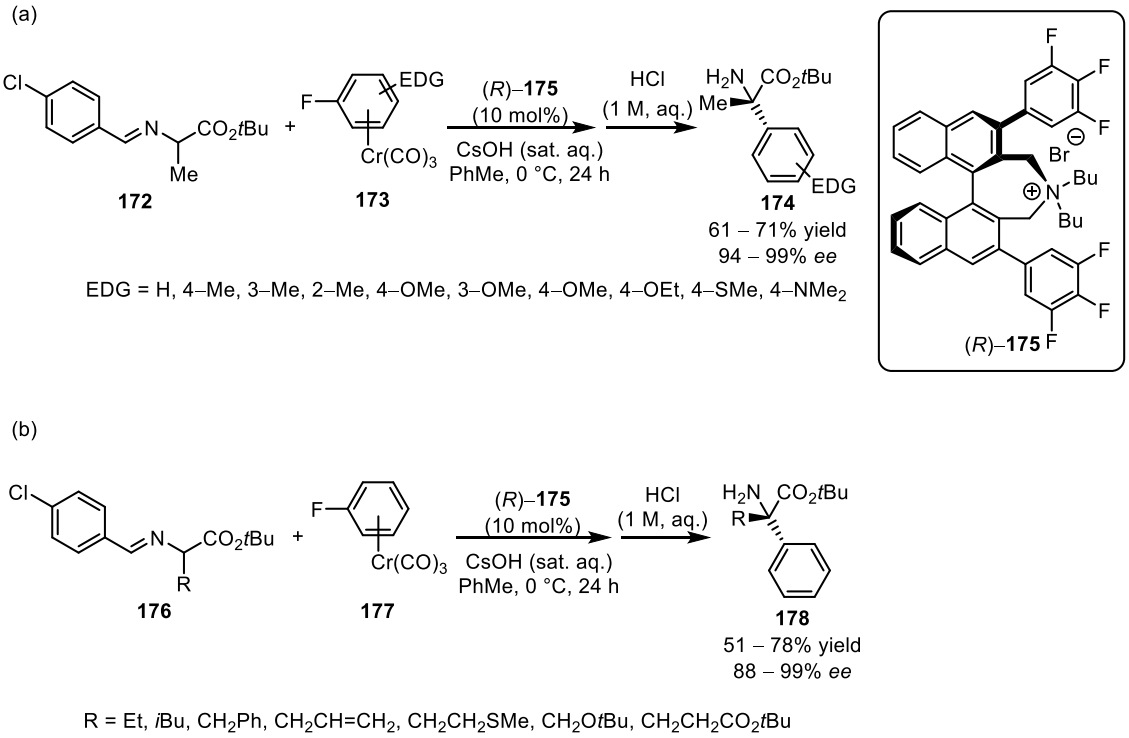
Scheme 35: (a.) Alkylation of an alanine-derived imine using **162b** (b.) Alkylation of a phenylalanine-derived imine using **162b**

In 2014, Maruoka *et al*. reported the highly enantioselective catalysed α-arylation of amino acid derivatives **168** using nitrofluoroarenes **169** as electrophiles (Scheme 36).[107] The arylation was however limited to electron-deficient arenes. A chloride on **169** was not effective enough a leaving group, hence the best leaving groups were found to be a fluoride or triflate. The catalyst (*S*)-**171** induced better enantioselectivities than **162b**, hence it was used in the arylation scope. The arylation was tolerant of various amino acids such as alanine, ethylglycine, methionine and phenylalanine. When an electron-donating group such as a methyl was introduced as a substituent on **169**, the rate and yield of the reaction reduced drastically.



Scheme 36: α-Arylation of α-amino acid derivatives under PTC conditions

To overcome the challenge of the arylation being limited to electron-deficient arenes and consequently expanding the scope of the reaction, the arylation of α-amino acids with fluoroarene chromium complexes as the electrophilic source was investigated (Scheme 37).[108] It was hoped that the arene, no matter how electron-rich, would be activated towards a nucleophilic aromatic substitution through coordination to $Cr(CO)_3$.



Scheme 37: (a) α-arylation of alanine with fluoroarene chromium complexes by phase transfer catalysis (b) α-arylation of other amino acids with fluoroarene chromium complexes by phase transfer catalysis

Optimisation of the arylation reaction with different catalysts revealed catalyst (*R*)-**175** as optimal. Arylation of the alanine derivative **172** with several electron-rich arenes proceeded smoothly with good yields and excellent enantioselectivities (Scheme 37a). The arylation was also tolerant of a variety of amino acids, affording the arylated amino acids **178** in excellent yields and enantioselectivities (Scheme 37b). This arylation strategy is one of the few reported methods for the arylation of α-amino acids. Other existing methods will be discussed in the next section.

1.3.6 α-Arylation of Amino Acid Derivatives

α-Aryl quaternary amino acids and their congeners have been found to exhibit bioactivity, a selection of which are illustrated in Figure 7. The direct arylation of tertiary amino acids using nucleophilic aromatic substitution of haloarenes would seem like the easiest route towards α-aryl quaternary amino acids, but this is synthetically challenging due to the difficulty of coupling an

anionic carbon centre with an electron-rich sp^2 carbon. Nonetheless, a handful of methods have been developed for the racemic and enantioselective α-arylation of α-amino acid derivatives.

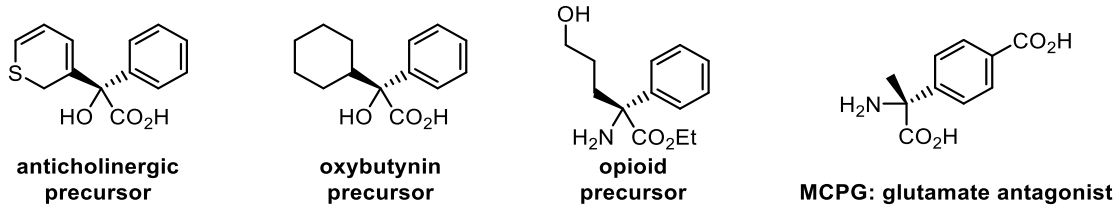
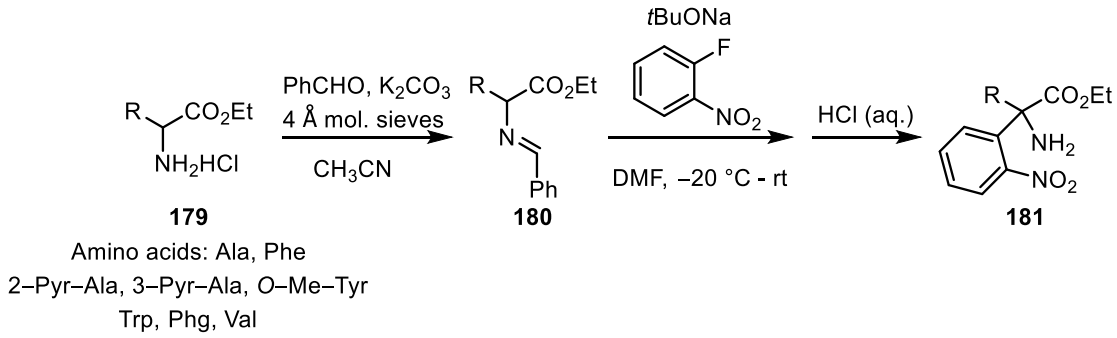


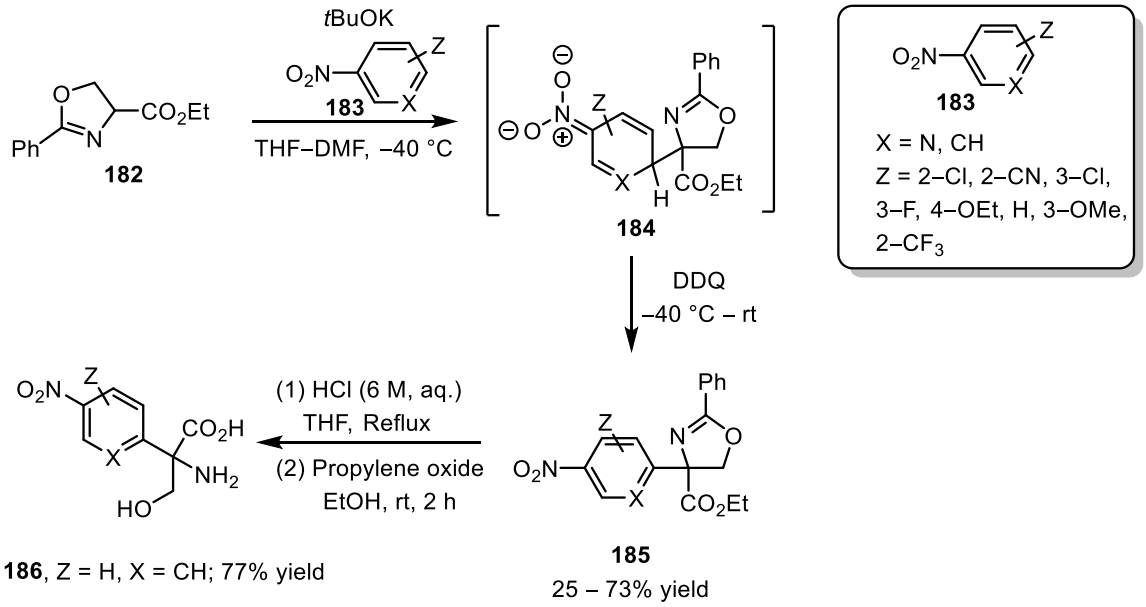
Figure 7: Some biologically active α-aryl quaternary amino acids and their congeners[109–112]

O'Connor and Liu disclosed the direct arylation of racemic amino acid-derived imine **180**.[113] Several amino acid derivatives were arylated using 2-nitrofluorobenzene (Scheme 38). No yields were reported except that of the arylation of the alanine-derived substrate, which gave an overall yield of 41%. The arylated amino acids **181** were actually synthesised for their direct conversion to 3-amino-2-oxindoles, which are important structural motifs found in biologically potent compounds.[114,115]



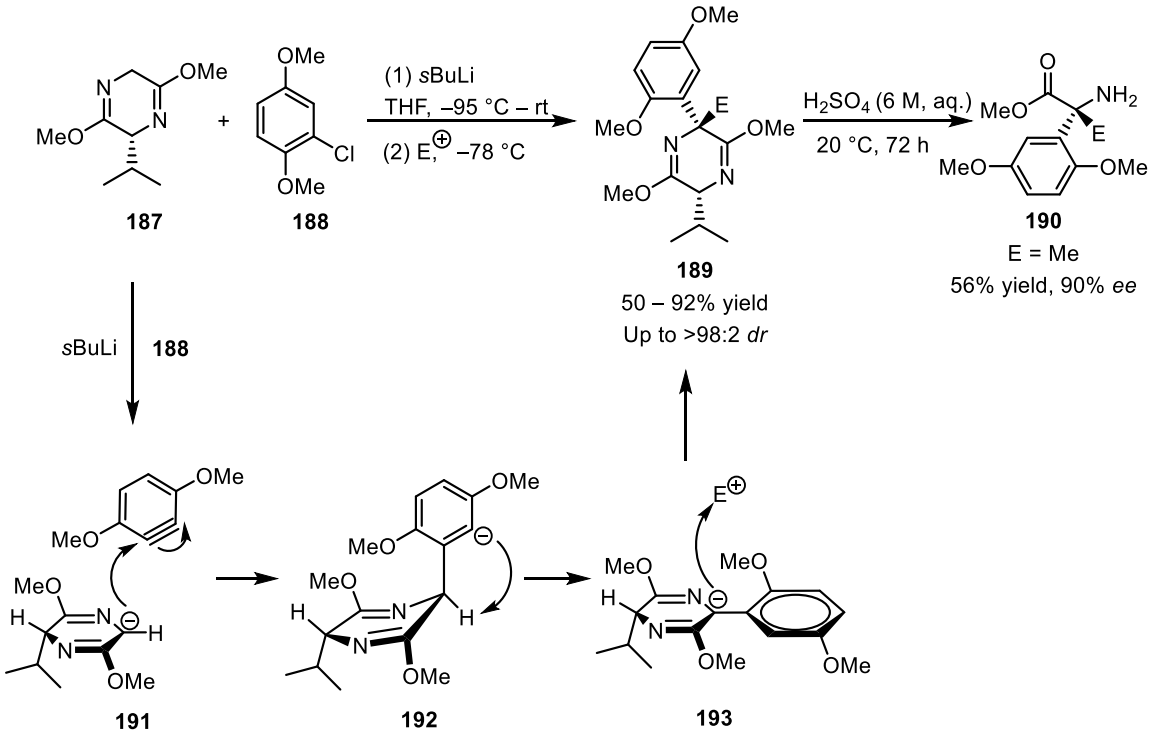
Scheme 38: Arylation of α-amino acids with 2-nitro fluorobenzene

A similar arylation with nitro(hetero)arenes **183** was performed on *O*-protected serine derivative **182**.[116] On treatment of **182** with *t*BuOK, it underwent oxidative nucleophilic addition to the nitroarene to produce the dearomatised adduct **184**, which on treatment with DDQ produced the α-arylated species **185** (Scheme 39). The addition occurred even with an electron-donating or electron-neutral substituent on the nitroarene. Hydrolysis of **185** (Z = H, X = CH) furnished α-4-nitrophenylserine **186** in a good yield. The same authors later disclosed a similar arylation of proline derivatives.[117]



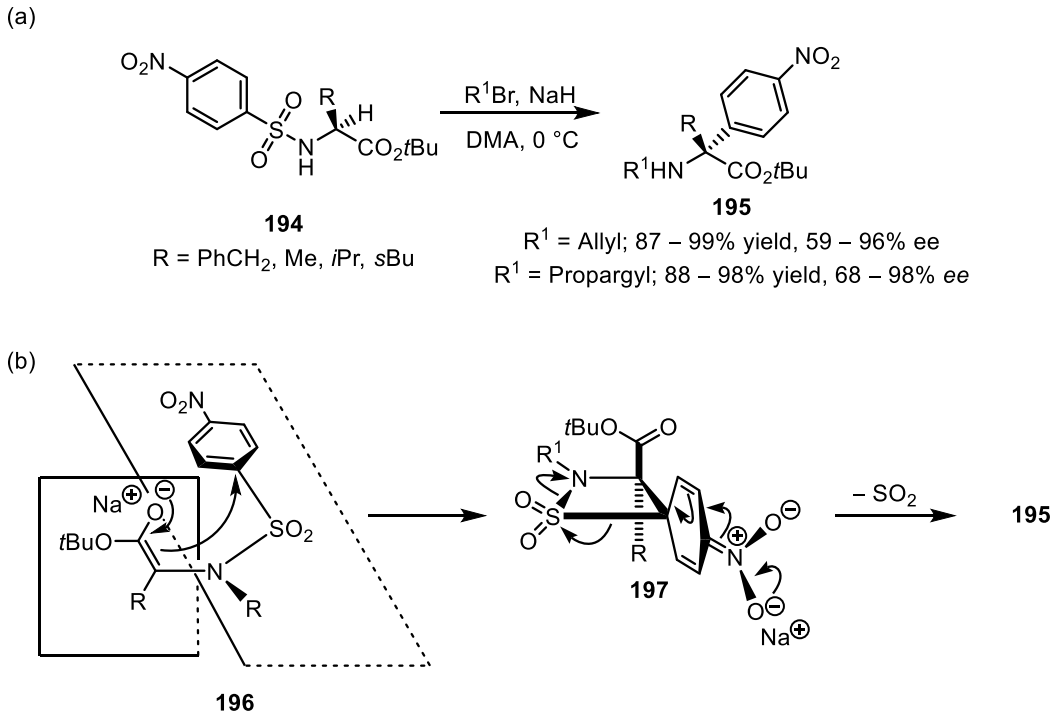
Scheme 39: Arylation of a serine derivative with nitro(hetero)arenes

Arynes are reactive intermediates that undergo electrophilic addition with nucleophiles, resulting in aryl carbanions that are capable of reacting with electrophiles.[118,119] Barett and co-workers employed the reactivity of arynes and Schöllkopf's bis lactim ether chiral auxiliary approach (see section 1.3.1) to a multicomponent coupling reaction with electrophiles (Scheme 40).[120] The aryne was developed *in situ* from **188**. Nucleophilic attack of the secondary anion **191** on the aryne formed the anionic adduct **192**, which underwent a proton exchange to give the tertiary ion **193**. The tertiary ion **193** reacts with several electrophiles to give the new α,α-disubstituted quaternary species **189** with excellent diastereoselectivities. ^{1}H NMR NOESY experiments revealed that the preferentially formed diastereoisomer was the result of electrophile approach from opposite the sterically demanding isopropyl group. The reaction was tolerant of a variety of electrophiles such as alkyl and allyl halides, propargyl bromide, acetyl chloride, esters, and aldehydes.



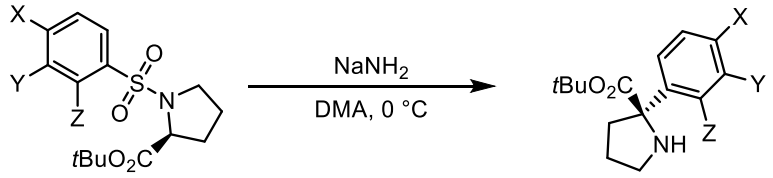
Scheme 40: Electrophilic addition of arynes to bis lactim ethers of chiral amino acids

Penso *et al*. utilised the MOC strategy (see section 1.3.3) for the enantioselective intramolecular arylation of *N*-(4-nitro-benzene)sulfonyl-α-amino acid *tert*-butyl esters **194** (Scheme 41a).[121] A control experiment showed that **194** did not rearrange in the absence of the alkyl bromide indicating that *N*-alkylation of **194** was necessary for the rearrangement to occur. Mechanistic investigations also revealed that the stereochemical retention of the rearrangement was influenced directly by *N*-alkylated **194** through the non-racemic enolate **196**, formed from deprotonation of the most stable conformer of *N*-alkylated **194**. Hence the proposed mechanism for the rearrangement was *N*-alkylation of **194**, followed by deprotonation of the α-carbon to afford the enolate **196**. Attack of the electrophile on the *Re* face of **196** led to the formation of the chiral spirocyclic Meisenheimer intermediate **197**, which collapses to expel sulfur dioxide and produce the α-arylated species **195** with good to excellent enantioretention (Scheme 41b).



Scheme 41: (a) Enantioselective intramolecular arylation of sulfonyl amino acid derivatives via MOC (b) Spirocyclic Meisenheimer intermediate expels sulfur dioxide to give rearranged products

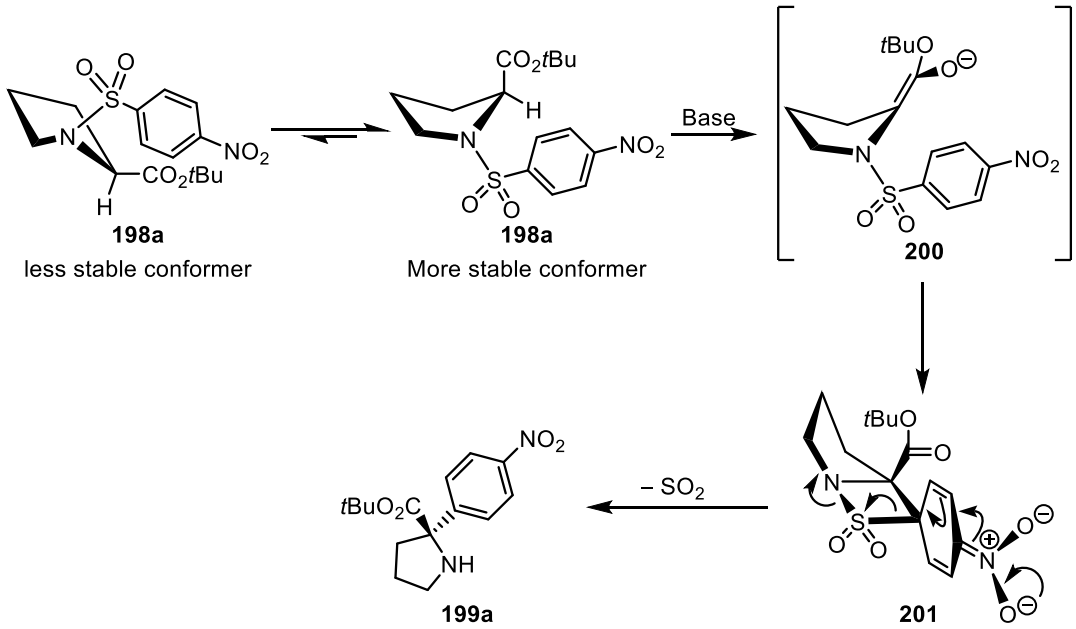
The authors extended the intramolecular arylation strategy to the *N*-sulfonyl proline derivatives **198** (Scheme 42).[122] The use of $NaNH_2$ as base was found to be more effective than NaH. It is thought that the ammonia produced in the use of sodium amide solvates the sodium ion, so that the ion forms a loose ion-pair with the carbanion generated from **198**. This results in a faster reaction rate and better yields relative to when sodium hydride was used. An electron-withdrawing group on either the *para* or *ortho* position of the aryl ring was crucial for efficient stabilisation of the Meisenheimer intermediate. No reaction occurred with electron-donating substituents at the *para* position of the ring.



Scheme 42: Enantioselective intramolecular arylation of sulfonyl proline derivatives via MOC

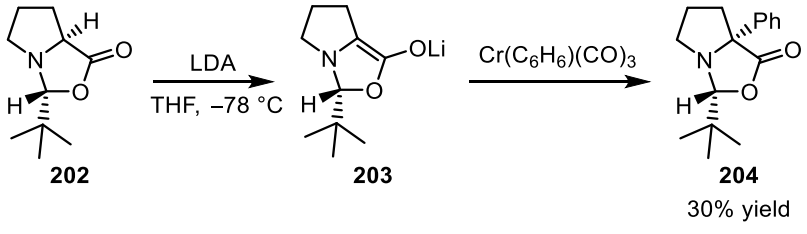
The mechanism of the reaction is like that of the acyclic amino acid derivatives in Scheme 41. The non-racemic enolate **200** is formed from deprotonation of the more stable conformer of the substrate

198a. Intramolecular attack of the enolate on the aryl ring generates the spirocyclic Meisenheimer intermediate **201**, which subsequently undergoes aryl migration to produce **199a** with retention of stereochemistry (Scheme 43).



Scheme 43: Proposed mechanism for arylation of sulfonyl proline derivatives via MOC

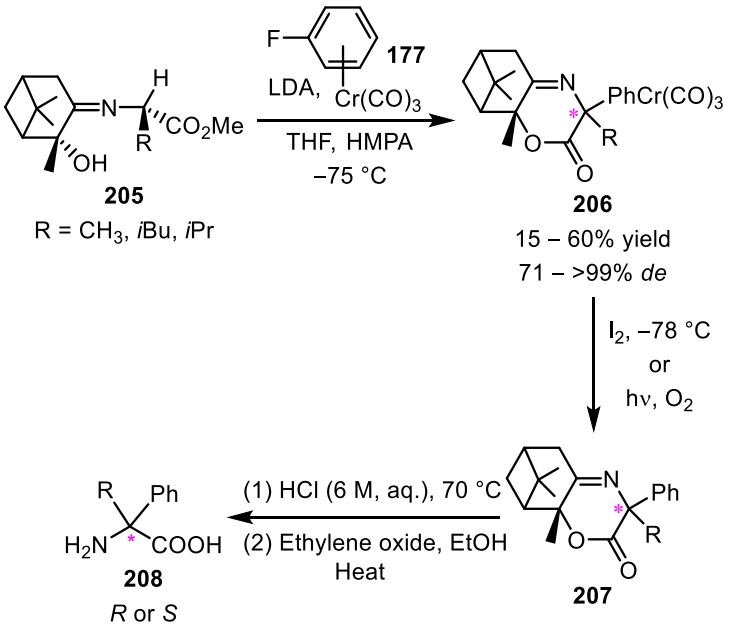
In 1983, Seebach demonstrated a transition metal-catalysed α-phenylation of proline via the self-regeneration of stereocentres (SRS) strategy (Scheme 44).[45] Direct α-alkylation of the proline derivative **202** with several alkyl halides was achievable, but in the case of arylation, phenylation of **202** was achieved with the use of (benzene)(tri-carbonyl)chromium. The electron-withdrawing property of the $Cr(CO)_3$ has been shown to permit nucleophilic attack even on electron-rich aryl rings coordinated to it.[123] The product **204** was obtained as a single diastereoisomer with retention of configuration. Extension of this arylation strategy to other amino acids was later reported by Lavergne (Scheme 45).[124]



Scheme 44: α-Phenylation of a proline derivative via the SRS strategy

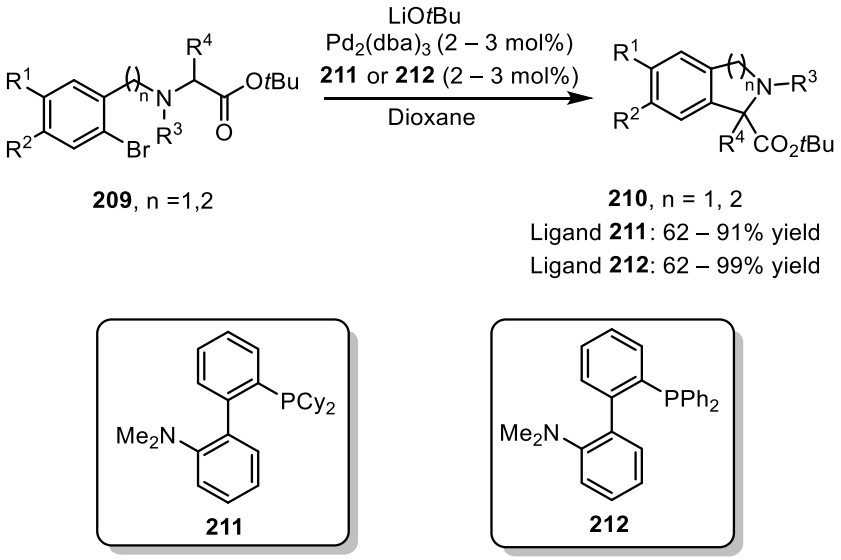
Imine **205** was made from condensation of a chiral auxiliary 2-hydroxypinan-3-one with the desired amino acid methyl ester.[125] Treatment of **205** with the fluorobenzene chromium complex **177** at −75 °C led to α-phenylation and concomitant cyclisation to afford the α-phenylated lactones **206** with good diastereoselectivities. The same reaction at −100 °C was found to offer α-phenylated **205**,

with no cyclisation. The stereochemistry at the new quaternary centre (indicated with a pink asterisk) of the major or only diastereoisomer of **206** and **207** was found to be either *R* or *S*, depending on the steric bulk of the side chain R of the amino acid used. There was evidence of strong interaction between the anion formed on deprotonation of **205** and the electrophile, which is suspected to be the result of coordination of the anion to chromium, by displacement of one CO ligand. Decomplexation, followed by hydrolysis of **206** afforded (*R*)- or (*S*)-**208** depending on the amino acid used.



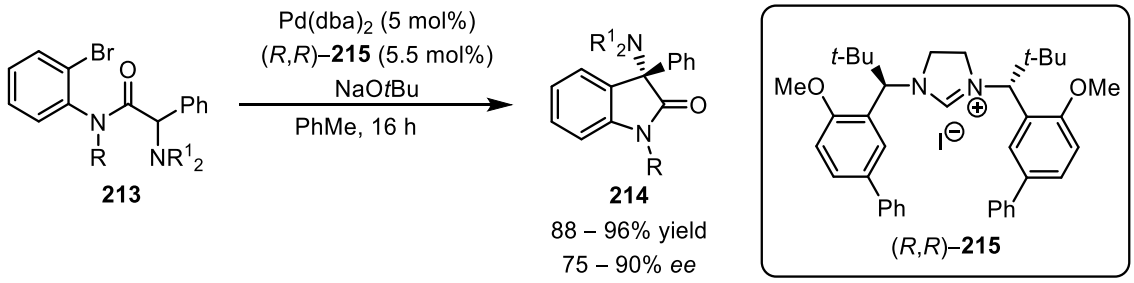
Scheme 45: α-Phenylation of α-amino acid derivatives by a chiral auxiliary approach

The first palladium-catalysed intramolecular arylation of α-amino acid derivatives was reported by Gaertzen and Buchwald (Scheme 46).[126] Treatment of amino acid derivatives **209** with Li*O*t*Bu*, $Pd_2(dba)_3$ and either ligand **211** or **212** afforded isoindoline **210** (n = 1) and tetrahydroisoquinoline **210** (n = 2) in good to excellent yields. Coordination of the aryl bromide in **209** to the palladium complex, formed from coordination of the ligand to $Pd_2(dba)_3$, enables the aryl group to react with the anion formed on deprotonation of the α-proton of **209**. This reaction occurred even when R^1 and R^2 were electron-donating and it was tolerant of a variety of α-amino acids such as phenylglycine, alanine, valine, and proline. In addition, it was tolerant of several different *N*-substituents such as a phenyl, alkyl, and ester groups. The cyclic α-aryl amino acid derivatives **210** were racemic since there was no source of enantioinduction in the reaction.



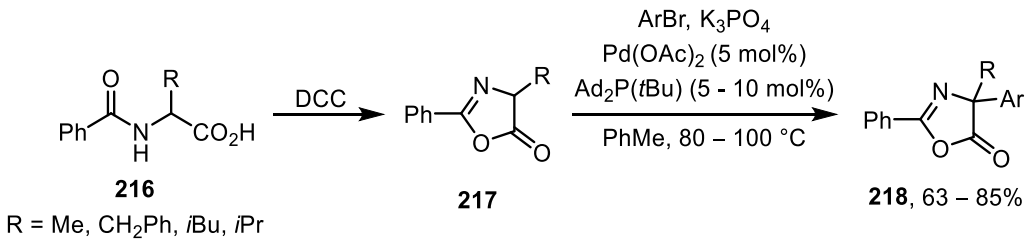
Scheme 46: Palladium-catalysed intramolecular arylation of α-amino acid derivatives

A similar palladium-catalysed intramolecular arylation was reported by Marsden *et.al* (Scheme 47).[127] A racemic version was initially disclosed, employing a combination of $Pd(OAc)_2$ and $HPCy_3.BF_4$ as catalyst and affording 16 examples of the arylated products in 61 – 89% yield.[128] For the asymmetric version, a combination of $Pd(dba)_2$ and the imidazolinium (*R*,*R*)-**215** was used as catalyst, affording the arylated products **214** in up to 90% *ee*. The cyclic α-aryl amino acid derivatives **214** are known as 3-aminooxindoles and constitute a number of biologically active compounds.[129,130]



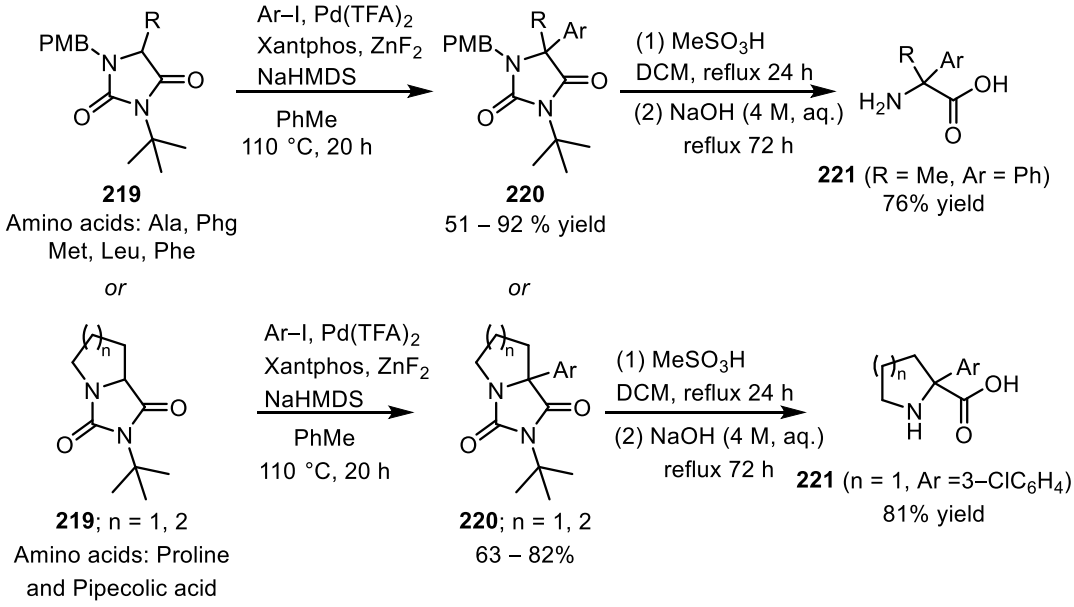
Scheme 47: Palladium catalysed asymmetric intramolecular arylation

Amino acid-derived azlactones **217** were arylated under palladium catalysis to afford the α-aryl amino acid derivatives **218**.[131] Whilst so many combinations of palladium source and ligand gave good yields, arylations carried out with a combination of $Pd(OAc)_2$ and $Ad_2P(tBu)$ as catalyst and K_3PO_4 as base generally gave best yields (Scheme 48). The arylation was tolerant of electron-neutral, electron-donating and electron-withdrawing groups on the aryl bromide. As with many palladium-catalysed reactions, the mechanism of the arylation probably incorporates an oxidative addition,[132] transmetalation and reductive elimination.[133] **218** could be hydrolysed to reveal racemic α-aryl quaternary amino acid derivatives.[134]



Scheme 48: Palladium-catalysed intermolecular arylation of azlactones

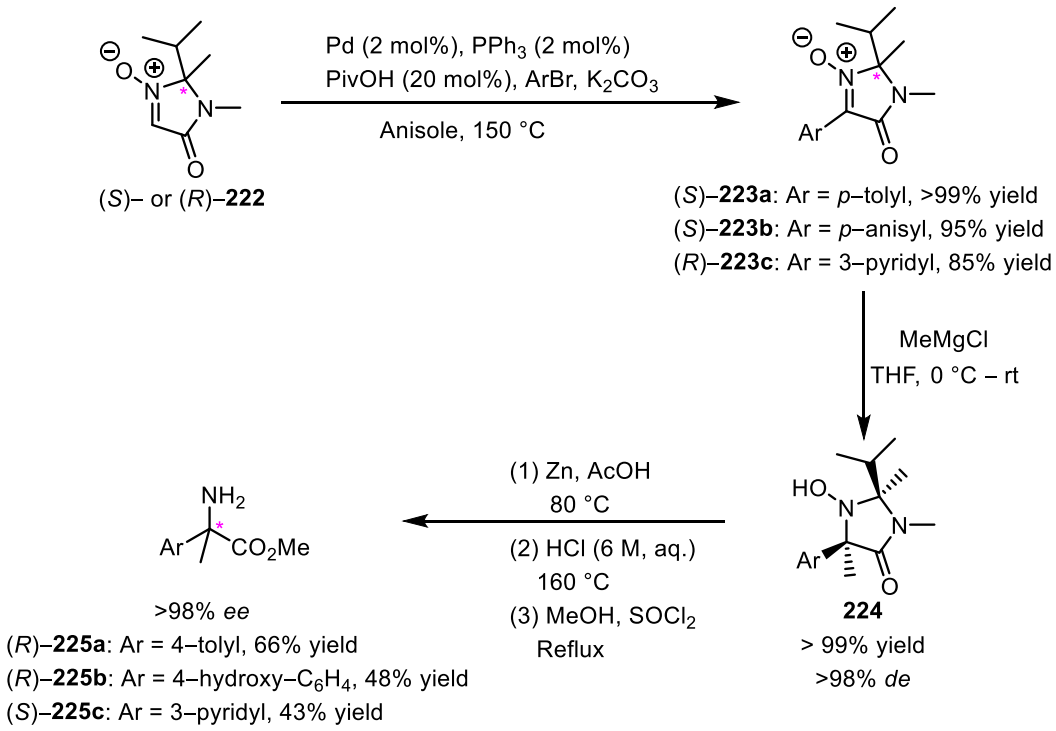
In 2015, Clayden *et al*. reported the palladium-catalysed intermolecular arylation of amino acid-derived hydantoins **219** (Scheme 49).[135] Optimisation of the reaction conditions using alanine-derived hydantoin **219** (R = Me) and iodobenzene revealed a combination of palladium(II)trifluoroacetate and xantphos as the optimal catalyst. Furthermore, the addition of ZnF_2 to the reaction improved the yield, probably due to the formation of a zinc enolate via transmetalation. Using the optimal conditions, several amino acid-derived hydantoins **219** were successfully arylated. The reaction was tolerant of electron-neutral, electron-withdrawing and donating groups on the aryl iodide. Selected examples of the arylated hydantoins **220** were deprotected and subsequently hydrolysed to their corresponding α-aryl quaternary amino acids **221**.



Scheme 49: Palladium catalysed intermolecular arylation of tertiary amino acid-derived hydantoins

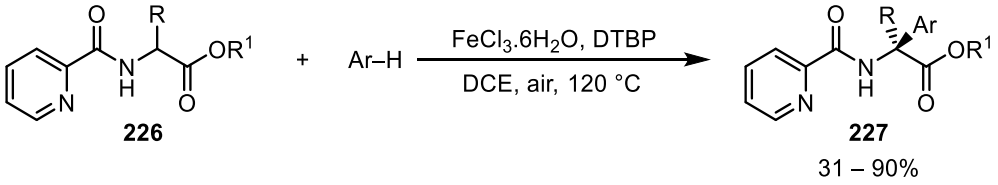
The chiral cyclic nitrone **222** is a derivative of glycine,[136–138] hence α-arylation will lead to a tertiary α-aryl glycine derivative. However, the ability of the nitrone to undergo *ortho* addition to Grignard reagents[137] makes it possible for a second substituent to be introduced to the tertiary centre, thus generating a new quaternary centre. Taking advantage of this, Blandin and co-workers performed the C-α arylation of cyclic nitrones **222** under palladium catalysis (Scheme 50).[139] The active catalyst was a combination of $Pd_2(dba)_3$ and a triphenylphosphine ligand. From kinetic isotope

studies and other experimental investigations, it was presumed that the mechanism for the arylation involved a metalation-deprotonation, which might be a concerted process. Subsequent addition of MeMgCl to **223** afforded **224**, having the new methyl group anti to the bulky isopropyl. Reduction of the N-O bond in **224** with zinc in acetic acid, followed by acid hydrolysis and esterification afforded the α-aryl,α-methyl glycine derivative **225** in greater than 98% *ee*.



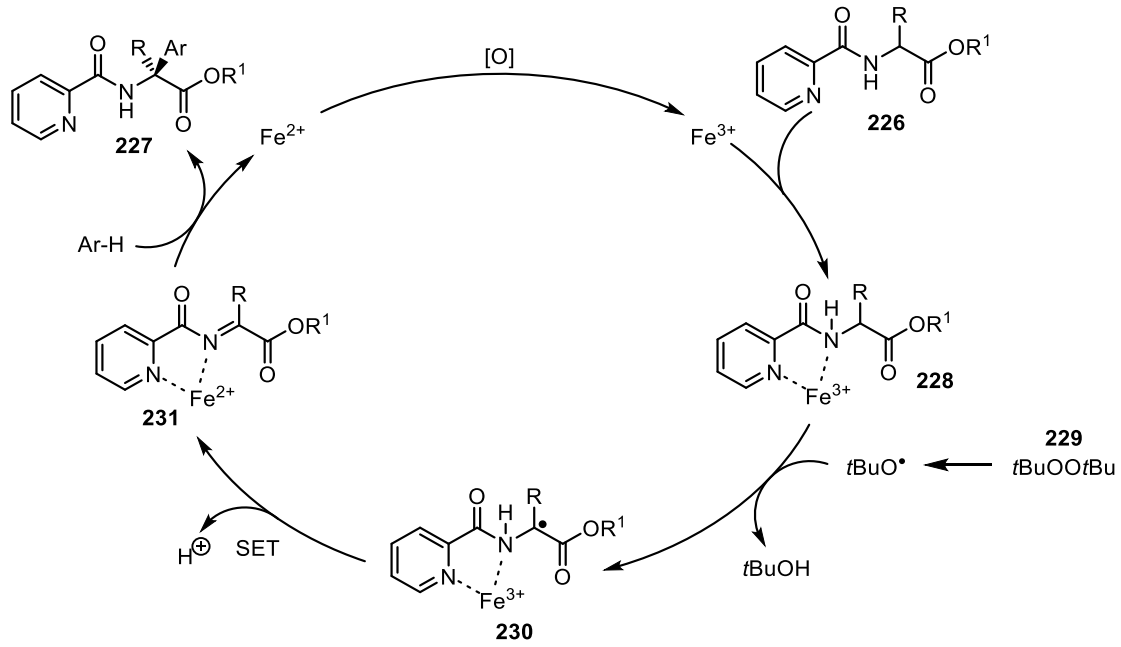
Scheme 50: Palladium catalysed arylation of cyclic nitrones

Iron-catalysed α-C(sp^3)-H functionalisation of amino acid derivatives **226** with nucleophiles was disclosed by You *et al*. (Scheme 51).[140] In this method, the aryl group was not introduced to the tertiary carbon using an aryl halide, but rather through an oxidative C-H/C-H coupling reaction of an aryl nucleophile and the sp^3 tertiary carbon centre of the amino acid derivative. The reaction was found to be general for a range of natural and unnatural tertiary amino acids such as benzyl, allyl, 5-cyano, 4-benzoyl and 4-hydroxylphenylalanine, as well as tyrosine, tryptophan, naphthylalanine and acetyl glycine. The reaction was also tolerant of several nucleophiles such as indoles, electron-rich heteroarenes and 1,2,4,5-tetramethylbenzene.



Scheme 51: Oxidative coupling of aryl nucleophiles to the α-carbon of tertiary amino acid derivatives

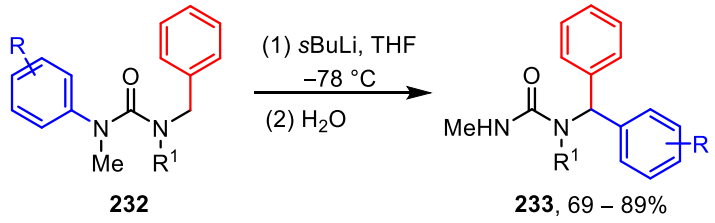
As addition of radical inhibitors to the coupling reaction led to reduced yields, it was proposed that the reaction followed a single electron pathway (Scheme 52). A suggested mechanism for the coupling is coordination of the metal ion to both the nitrogen of the pyridine and the NH in **226** to produce the metal complex **228**. Hydrogen atom abstraction from **228** by a *tert*-butoxy radical, generated from DTBP **229**, produces the metal complex radical **230**. An intramolecular single electron transfer in **230** produces the ketimine **231**, which undergoes addition with a nucleophile to produce the α-arylated-α-amino acid ester **227**.



Scheme 52: Proposed mechanism for the oxidative coupling of aryl nucleophiles to tertiary amino acid derivatives

1.3.7 α-Arylation of Amino Acid Derivatives via Intramolecular *N→C* Migration

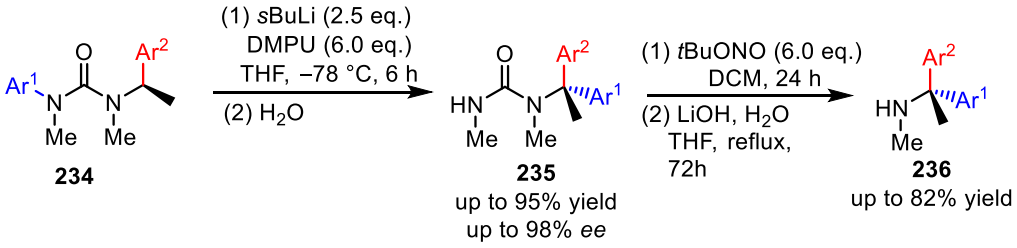
In 2007, Clayden *et al*. reported an intramolecular arylation through the rearrangement of lithiated ureas (Scheme 53).[141] While investigating the regioselective lithiation of *N*-benzyl urea **232** (R = 2,6-dimethyl, R^1 = Ph), it was observed that aryl migration from the distal nitrogen of the urea to the benzylic CH_2 carbon had rapidly taken place after deprotonation, affording the rearranged diaryl methyl urea **233**, after an aqueous quench. The reaction involved a nucleophilic aromatic substitution which is atypical for aromatic compounds, which usually undergo electrophilic aromatic substitution. To test the limit of the rearrangement, it was extended to *N*-benzyl ureas having different migratory aryl rings. Surprisingly, the rearrangement successfully occurred irrespective of the sterics or electronic properties of the migratory aryl ring.



R = Electron neutral, withdrawing or donating group
R^1 = Ph, Me or 4–Tol

Scheme 53: Discovery of *N* to *C* aryl migration in lithiated benzyl ureas

As an enantioselective version of the aryl migration of **232** seemed impractical, the substrates **232** were modified. Enantiomerically pure α-methylbenzylureas **234** were made and subjected to the aryl migration (Scheme 54). The rearrangement occurred more slowly than it did with the lesser substituted substrates **232**; However, addition of DMPU significantly improved the rate and yield of the reaction probably due to activation of the organolithium nucleophile through the generation of a reactive ionic pair.[142,143] The reaction also proceeded with retention of stereochemistry affording the products **235** with minimal loss of optical purity. In addition, the aryl migration yet occurred with both electron-rich and deficient rings.

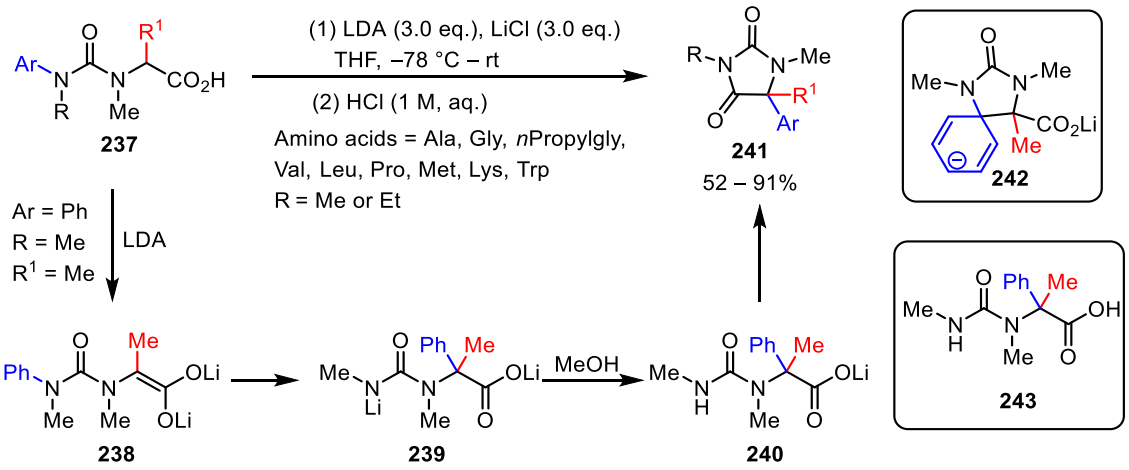


Ar^1 = Ph, 4–ClC_6H_4, 2, 3 or 4–FC_6H_4, 4–$MeOC_6H_4$,
3–$MeOC_6H_4$, 1– or 2–naphthyl
Ar^2 = Ph, 4–$OMeC_6H_4$, 4–ClC_6H_4

Scheme 54: Stereospecific rearrangement via *N* to *C* aryl migration in lithiated α-methyl benzylureas

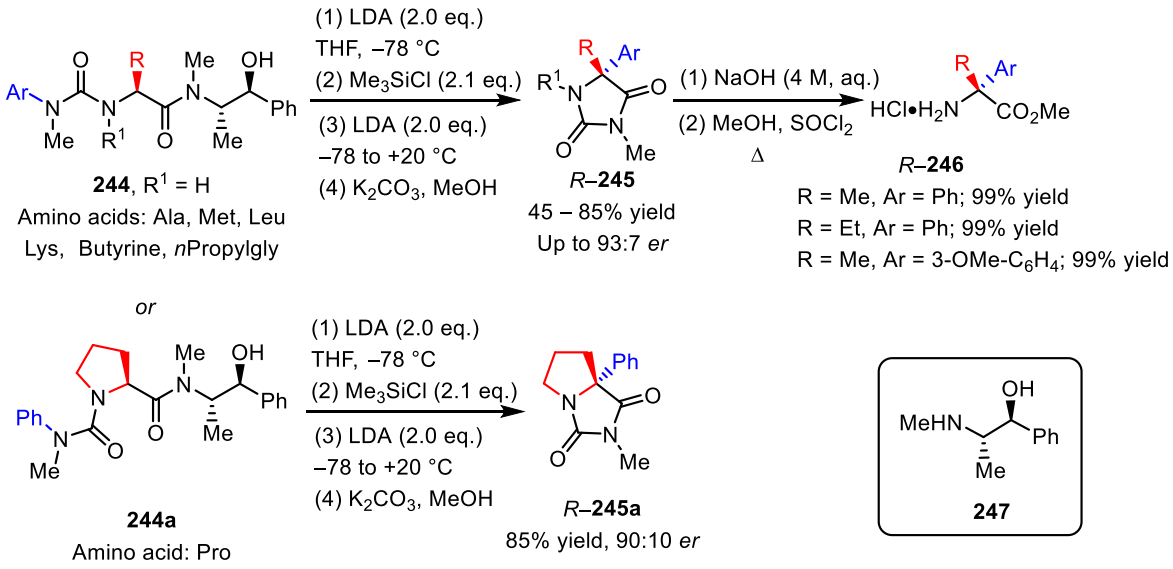
Further studies on the aryl migration unveiled that the reaction was not limited to ureas but could also be employed in the rearrangement of carbamates[142,144–146] and thiocarbamates.[147–149] The migratory groups have also been extended to include both sterically hindered and unhindered alkenyls.[150,151] Of more pertinence is the rearrangement of tertiary amino acid-derived *N*'-arylureas, which has been employed to achieve both racemic and enantioenriched α-aryl quaternary amino acids. For example, Clayden and co-workers carried out the intramolecular arylation of amino acid-derived ureas **237** (Scheme 55).[152] By coupling an aryl group to a tertiary amino acid through a urea linkage as seen in **237**, they were able to achieve quaternary amino acid derivatives **241** through base-mediated translocation of the aryl group to the α-carbon of the amino acid and subsequent cyclisation on quenching with methanol. The aryl migration was tolerant of both electron-withdrawing and donating groups on the migratory aryl ring affording **241** in good to excellent

yields. ReactIR studies of the aryl migration of **237** (Ar = Ph, R = R^1 = Me) revealed the three species **238**, **239** and **240** but showed no evidence of the Meisenheimer intermediate **242**. The hydantoin **241** (Ar = Ph, R = R^1 = Me) was not observed until after the reaction was quenched with MeOH. The cyclisation of **240** to **241** occurred quickly, with no non-cyclised product **243** detected.



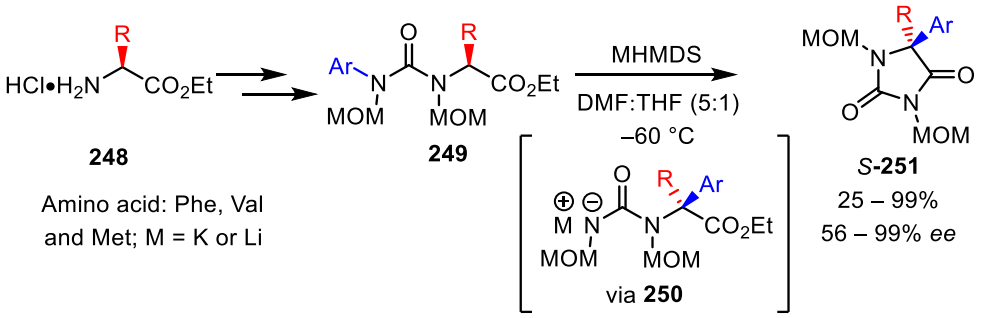
Scheme 55: Rearrangement of amino acid derived *N*'-arylureas via *N* to *C* aryl migration

Employing the chiral auxiliary approach (see section 1.3.1), Clayden *et al*. performed the enantioselective version of the arylation of ureas **237** (Scheme 56).[153] By coupling (*S*,*S*)-pseudoephedrine **247** to analogues of **237**, the ureas **244** were obtained as single diastereoisomers. Intramolecular α-arylation of the derivative **244** (Ar = Ph, R = R^1 = Me) using LDA and LiCl alone afforded the doubly *N*-methylated hydantoin **245** (Ar = Ph, R = R^1 = Me) with good enantioselectivity. However, it was difficult to hydrolyse to the corresponding α-aryl quaternary amino acid derivative. Repeating the reaction with the *N*-unsubstituted analogue **244** (Ar = Ph, R = Me, R^1 = H) led to the formation of racemic **245** (Ar = Ph, R = Me, R^1 = H), indicating that *N*-substitution was conducive to enantioselectivity. Further optimisation revealed that the addition of two equivalents of trimethylsilyl chloride led to *in situ* silylation of the NH, ultimately affording the enantioenriched hydantoin. The reaction was extended to a variety of amino acid-derived ureas **244** (R^1 = H), bearing several migratory aryl groups. A sequence of silylation, enolisation, *N* to *C* aryl migration, cyclisation with expulsion of the chiral auxiliary and proto-desilylation offered the hydantoins (*R*)-**245** in good yields and enantioselectivities. The scope of the migratory aryl group was inclusive of both electron-rich and electron-deficient arenes, with best enantioselectivities obtained with electron-rich migratory aryl rings. The scope of the amino acid was limited to less sterically hindered R-substituents, as no rearrangement was observed with valine and phenylglycine derived ureas, while leucine-derived urea rearranged but with low yield. The hydantoins could easily be hydrolysed to their corresponding α-aryl quaternary amino acids as exemplified in Scheme 56.



Scheme 56: Synthesis of α-aryl quaternary amino acids via a chiral auxiliary directed *N* to *C* aryl migration

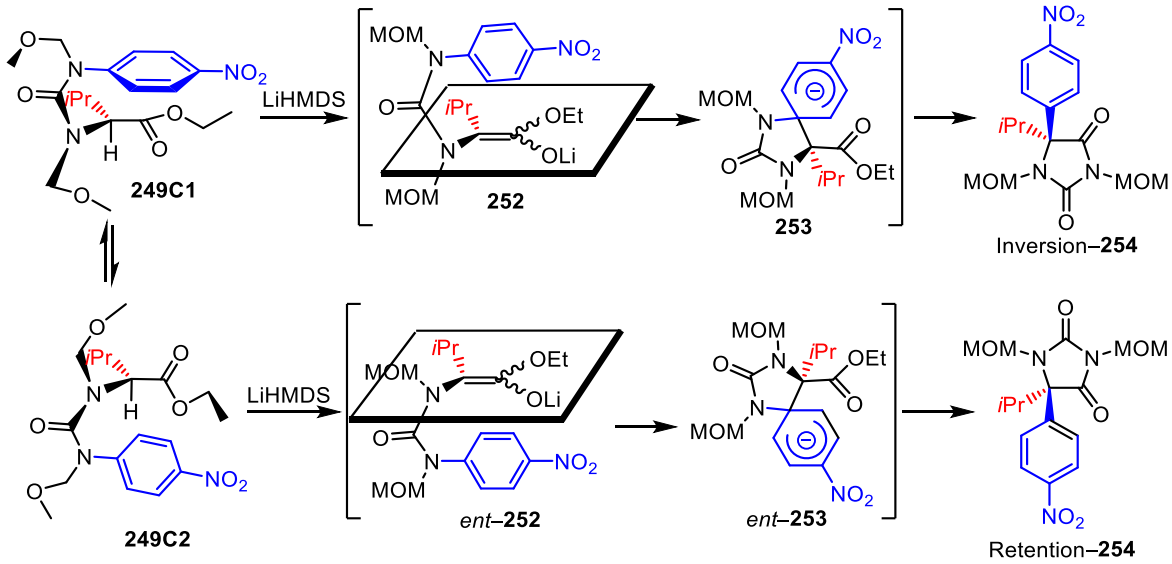
Employing *N* to *C* aryl migration within ureas, Kawabata and co-workers performed the enantioselective intramolecular arylation of amino acid derived ureas **249** (Scheme 57).[154] The MOC strategy was employed for stereocontrol in the arylation. The ureas **249** were synthesised according to the protocol by Clayden *et al.*[141] Treatment of **249** with either LiHMDS or KHMDS led to migration of the aryl group from the distal urea nitrogen to the α-carbon, resulting in a nitrogen-centred anionic urea intermediate **250**, which underwent cyclisation to afford quaternary amino acid derivatives **251**. The migration was limited to only electron-withdrawing and electron-neutral groups on the migrating aryl ring.



Scheme 57: Stereoselective *N* to *C* aryl migration in ureas via MOC

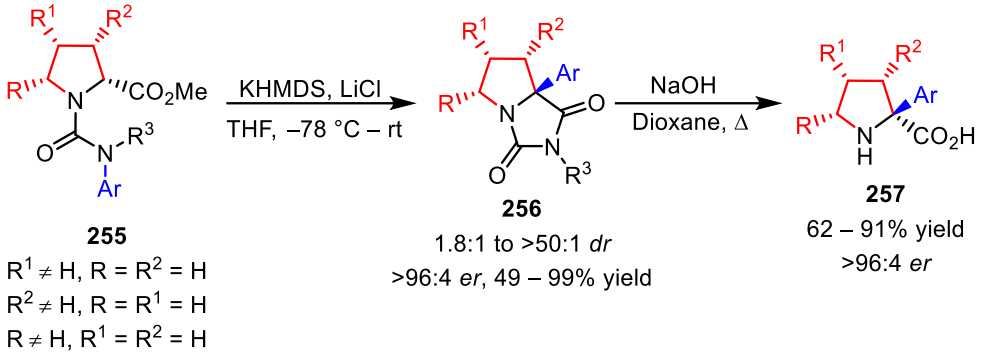
It was found that aryl migration in valine-derived ureas **249** afforded the quaternary products with inversion of configuration. Hence, it was assumed that aryl migration proceeded with inversion of configuration for the phenylglycine and methionine-derived ureas as well. A conformational search for substrate **249** (valine, Ar = 4-nitrophenyl) revealed two stable conformers, **249C1** and **249C2** (Scheme 58). A possible explanation for the inversion of configuration might be that deprotonation of the α-proton in conformer **249C1** was thermodynamically preferred to that of **249C2**,[155–157] resulting in the non-racemic enolate **252**. The half-life of racemisation of the enolate was estimated

to be 5 minutes at −60 °C. Intramolecular attack of the enolate on the aryl ring leads to formation of the Meisenheimer-type complex **253**, which collapses by *N*-acylation to produce **254** with inversion of configuration.



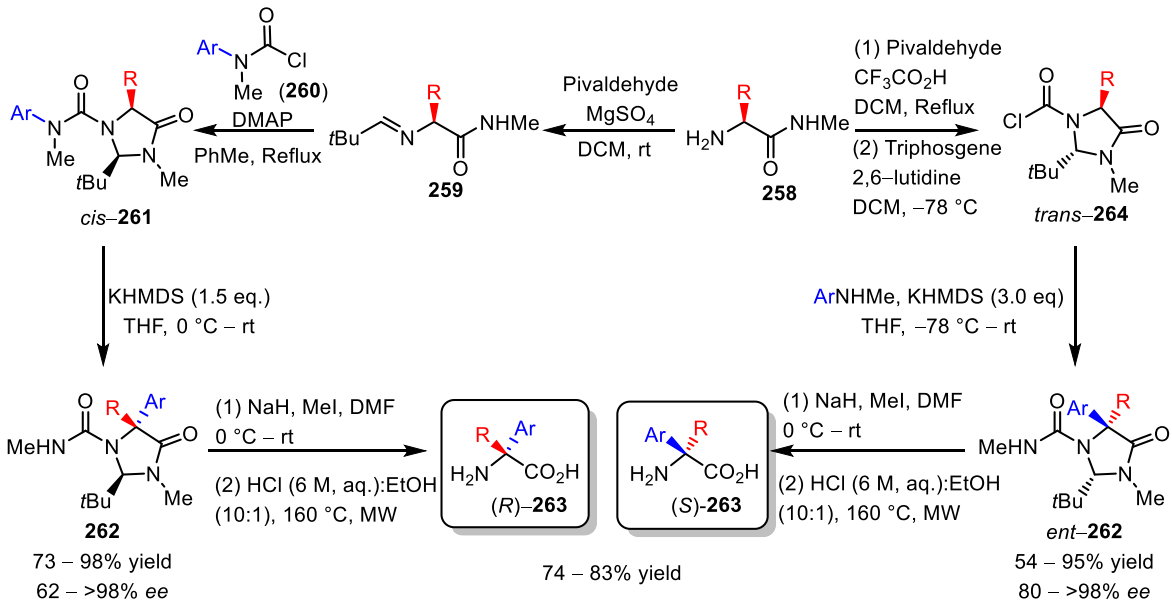
Scheme 58: Stereochemical rationale for inversion of configuration

It was previously demonstrated that intramolecular arylation and subsequent cyclisation of proline derived ureas **255** (R = R^1 = R^2 = H) offered racemic α-arylated hydantoins **256**.[152] Subsequent investigations revealed that introduction of a chiral centre either at the 3, 4 or 5-position of the proline ring in **255** offers enantioenriched hydantoins **256** on aryl migration and ensuing cyclisation (Scheme 59).[158] Most likely, diastereoselectivity in the rearrangement is induced by migration of the aryl group to the less hindered face of the enolate. Hindered, electron-rich and electron-deficient aryl rings migrated successfully. In corroboration with a similar report,[153] lower diastereoselectivities were obtained in the migration of electron-deficient rings. This is presumably due to reversibility in the migration of electron-deficient rings.[159] *N*-methyl hydantoins **256** (R^3 = Me) were resistant to hydrolysis; However, hydrolysis of the *N*-MOM derivatives **256** (R^3 = methoxymethyl) afforded the corresponding α-arylprolines **257** in good yields and enantioselectivities.



Scheme 59: Synthesis of α-aryl prolines via *N* to *C* aryl migration in proline urea derivatives

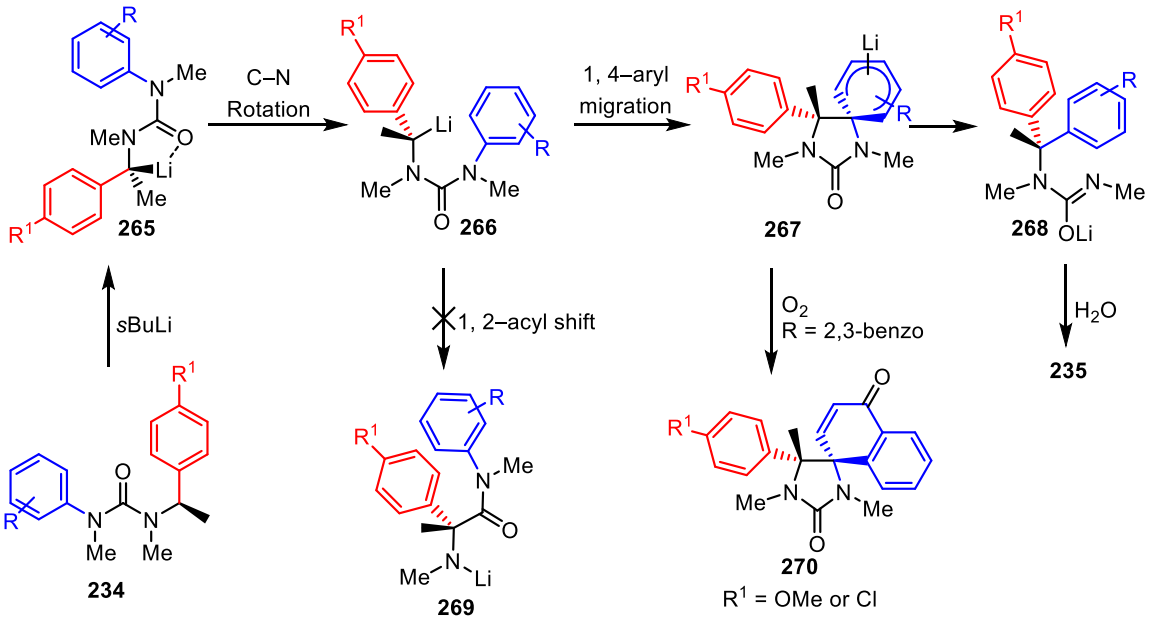
Recently the asymmetric intramolecular arylation of amino acids via SRS was disclosed by Clayden and co-workers (Scheme 60).[160] The method employed the use of Seebach's imidazolidinone strategy in inducing enantioselectivity in the aryl migration of imidazolidinone bearing *N*'-arylureas. This strategy allows the formation of either enantiomer of the α-aryl quaternary amino acid from a single enantiomer of the tertiary amino acid precursor. Condensation of amino acid-derived methyl amide **258** with pivaldehyde and subsequent acylation of **259** with the desired carbamoyl chloride **260** provided the imidazolidinone urea **261** as the *cis*-isomer. Treatment of **261** with KHMDS afforded the rearranged product **262** in up to greater than 98% *ee*. Alternatively, condensation of **258** with pivaldehyde under acidic conditions and subsequent acylation with triphosgene offered the *N*-chloroformylimidazolidinone **264**, predominantly as the *trans*-isomer. Treatment of **264** with an excess of KHMDS and the desired *N*-methylaniline derivative led to one-pot attainment of the rearranged product *ent*-**262**. In the formation of both enantiomers of the α-aryl quaternary amino acids, the stereochemistry at the quaternary centre is directed by the bulky *tert*butyl group. The reaction was general for a variety of tertiary amino acids, both functionalised and unfunctionalised. Rearrangement of phenylglycine derived ureas generally suffered from diminished enantioselectivities. Hydrolysis of the arylated products **262** furnished the enantioenriched α-aryl quaternary amino acids **263** in good yields.



Scheme 60: Stereoselective *N* to *C* aryl migration in Imidazolidinone ureas via SRS. MW = microwave irradiation.

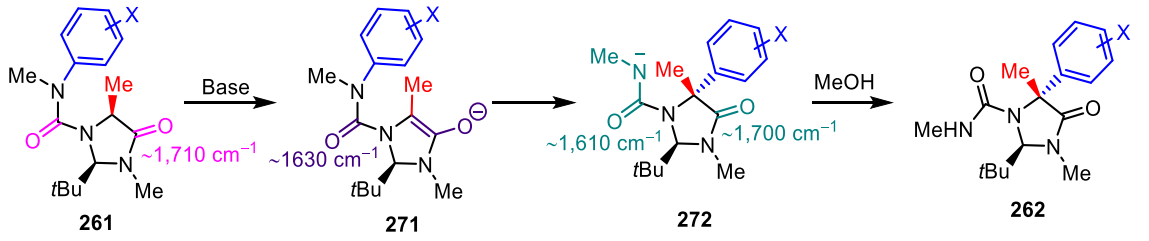
1.4 *N*→*C* Aryl Migration – Mechanistic Discussions

The *N*→*C* aryl migration developed by Clayden and co-workers is similar to the Smiles and Truce-Smiles rearrangements; but unlike these rearrangements, it is not limited to electron-deficient aryl rings, as even electron-rich aryl rings were successfully migrated. The originally proposed mechanism for the aryl migration is exemplified by the urea **234** in Scheme 61 .[161,162] The α-methyl-benzylurea **234** is deprotonated at the benzylic methylene. Coordinated lithium cations and their translocation in the reaction were revealed by DFT calculations to be of importance in the mechanism. Movement of a solvated lithium cation from the organo lithium to the deprotonated benzylic methylene, and ensuing coordination of the lithium ion to the carbonyl oxygen provides **265**. The complex **265** is unreactive, but rotation of the C-N bond in **265** affords the reactive conformation **266**, whose lithiated carbon centre is sufficiently close to the *N*-aryl ring, allowing enantioretentive nucleophilic attack on the ring and resulting in the dearomatised Meisenheimer intermediate **267** in the case of a migrating 1-naphthyl ring. Movement of the lithium cation to the *N*-aryl ring of **267** stabilises the developing negative charge. Ring opening of **267** restores aromaticity and provides the product **268**, which on aqueous quench affords the arylated products **235**. The lithiated species **266** is stable with respect to the addition timescale, hence the stereochemistry of the starting material **234** is retained in the product **235**. The presence of dearomatised intermediate **267** in the case of a migrating 1-naphthyl ring was confirmed by the x-ray structure of enone **270**, which was obtained by exposing the migration of a 1-naphthyl ring to air after the reaction had been stirring for 2 hours.[163] The intramolecular mechanism of the reaction was confirmed by cross over experimental reactions.



Scheme 61: Originally proposed mechanism of *N* to *C* aryl migration in lithiated ureas

Mechanistic investigations using *in situ* ^{1}H NMR spectroscopy further confirmed the presence of the dearomatised intermediate **267** in the migration of a 1-naphthyl ring. There was however no evidence of this intermediate with other aryl migratory groups. Other possible reaction pathways such as migration with inversion of stereochemistry or attack of the lithiated carbon centre in **266** on the carbonyl carbon, resulting in a 1,2-acyl shift were shown from DFT calculations to require higher energy transition states.[161] Though the aryl migration of acyclic α-methylbenzylureas **234** (Scheme 54) was stereospecific, aryl migration of the cyclic analogues produced the racemic rearranged products. It is thought that racemisation of the organolithium intermediate outcompetes aryl migration.[164]



Scheme 62: Recent mechanistic investigations into *N* to *C* aryl migration in lithiated ureas

The question of whether a dearomatised intermediate truly exists for other migratory aryl rings other than the 1-naphthyl was recently investigated by Clayden and co-workers.[160] The use of ReactIR and Hammett plot construction gave new insight into the mechanism of the aryl migration. ReactIR studies of the conversion of **261** (X = H) to **262** (X = H) using the optimised conditions in Scheme 60 revealed no reaction intermediate, suggesting that aryl migration was faster than enolate formation at room temperature. The ReactIR experiment was repeated at −20 °C with LDA as base

and intermediates which were identified to be enolate **271** (X = H) and anion **272** (X = H) were observed. A plot of absorbances against time for the aryl migration of **261** bearing different aryl groups revealed that the formation of the anion **272** from the enolate **271** followed first order kinetics. A Hammett plot of log of rate constants against the aryl substituent constants revealed that the formation of the enolate is the rate-limiting step for the aryl migration of electron-deficient rings. Hence, after formation of the enolate, the rearrangement occurred so fast, it was not possible to identify a dearomatised intermediate between **271** and **272**. This however does not prove the non-existence of a dearomatised intermediate, as electron-withdrawing groups on the aryl migratory ring can stabilise the intermediate. For the electron-rich aryl rings, the value of the Hammett coefficient ρ was +4.5, which indicates that there is a development of negative charge on the arene during the rearrangement. This value was however smaller than that of a typical nucleophilic aromatic substitution,[165,166] probably indicating the absence of a Meisenheimer intermediate.[167–170] It is proposed that the reaction was tolerant of electron-rich aryl migratory groups because the restricted conformation of the urea[171] brings the reactive enolate centre close enough to the aryl ring, so that the electrostatic force of repulsion between the negatively charged enolate and the electron-rich aryl ring is overcome, hence attack of the enolate on the aryl ring occurs.

In summary, *N* to *C* aryl migration within metallated ureas has provided a powerful means for C-arylation through intramolecular nucleophilic attack of an enolate on the *ipso* position of an arene. The reaction has offered access to both racemic and enantioenriched quaternary amino acids. The reaction is indeed unique because it enables nucleophilic attack of enolates on electron-rich arenes without the mediation of a heavy metal. However, the aryl migrations require the use of strong bases such as LiHMDS, KHMDS and LDA (see section 1.3.7). It is therefore important that advances continue to be made, especially in the development of milder conditions for the asymmetric α-arylation of tertiary amino acid enolates via *N* to *C* aryl migration in metallated ureas.

2 Results and Discussion

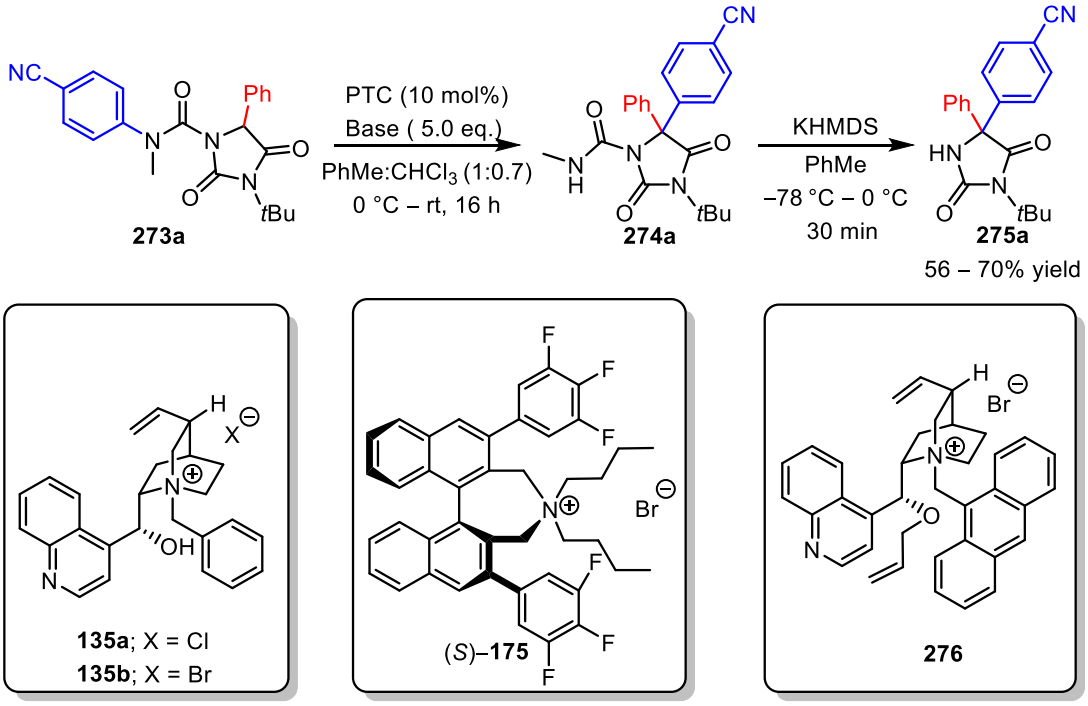
2.1 Aims of the Project

From the review of the various synthetic routes towards quaternary amino acids, it is evident that several methods exist for the synthesis of *α-alkyl* quaternary amino acids. As discussed in section 1.3.6, many biologically active targets or their precursors contain *α-aryl* quaternary amino acids or their congeners,[9,172–175] yet only a few methods are available for their synthesis. Many of these methods are not general and some require the use of heavy metal catalysis, which could be problematic in drug synthesis; furthermore, only a few of them give enantiomerically enriched α-aryl quaternary amino acids.[126,131,135,176] This thesis explores several synthetic routes towards enantiomerically enriched α-aryl quaternary amino acids exploiting the unusual urea reactivity.[141] It provides a detailed description of the work that has been done by the author in developing or improving already existing methods towards these compounds. The first method discussed is the use of chiral phase transfer catalysis (PTC); The aim is to provide the first truly catalytic method for accessing α-aryl quaternary amino acids, as Marouka's PTC method (Scheme 37) required the use of stoichiometric amounts of chromium. To the best of the author's knowledge, there is no phase transfer catalysed intramolecular nucleophilic aromatic substitution yet reported.

2.2 Arylation of Amino Acid Enolates employing Phase Transfer Catalysis

2.2.1 Previous Work

Preliminary work within the Clayden group established that it was possible to carry out urea rearrangements under the mild conditions of PTC (Scheme 63). The hydantoin scaffold (pk_a of hydantoin = 9.16)[177] was chosen for investigation to allow ready formation of the enolate. Phenylglycine-derived hydantoin urea **273a** was treated with simple inorganic bases such as Cs_2CO_3. The rearrangement failed to occur in the absence of a catalyst. However, in the presence of the PTCs **135**, (*S*)-**175** or **276**, the rearrangement occurred. **273a** underwent intramolecular aryl migration to give *N*-methyl hydantoin urea **274a**. The hydantoin **275a** was then obtained by treating **274a** with a strong base such as KHMDS. All the PTCs gave racemic products, except **276** which gave a crude *er* of 80:20 for **274a** when the reaction was performed with Cs_2CO_3 at 0 °C.

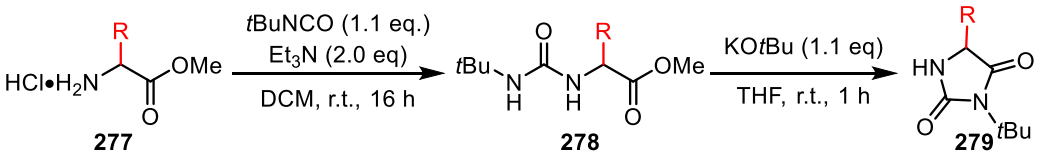


Scheme 63: Urea rearrangement under PTC conditions

2.2.2 Synthesis of Hydantoin Ureas

From preliminary studies discussed in the previous section, it is obvious that the rearrangement of the hydantoin urea employing chiral PTC shows a propensity for achieving stereoselectivity. Nevertheless, the rearrangement needs further optimisation, with the goal being higher enantioselectivity, reactivity and a broad scope of amino acids and arenes. To achieve this, a series of amino acid-derived hydantoin ureas were made.

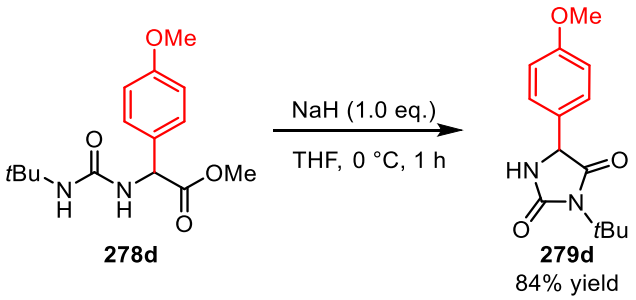
Table 1: Synthesis of hydantoins **279**



Entry	Amino acid	R	Product	Yield (%)	
				278	279
1	Phg	Ph	a	92	75
2	Ala	Me	b	>99	85
3	4-Cl-Phg	4-ClC_6H_4	c	>99	65[a]
4	4-OMe-Phg	4-$OMeC_6H_4$	d	>99	18[a]
5	Gly	H	e	87	57

[a] Reaction performed at 0 °C

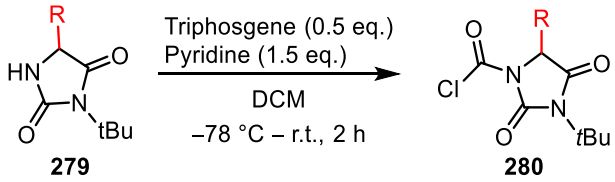
Readily available amino acid methyl ester hydrochlorides **277** were reacted with *tert*-butyl isocyanate to give the amino ester ureas **278**. The ureas **278**, on treatment with potassium *tert*-butoxide, underwent cyclisation to give hydantoins **279** (Table 1). The cyclisation reaction of **278a**, **278c** and **278d** must not be left for more than an hour, as this leads to side reactions, resulting in a lower yield of the cyclisation products. The yield of **279d** was significantly increased when the cyclisation was performed with sodium hydride at 0 °C (Scheme 64).



Scheme 64: Alternative synthesis of **279d**

Hydantoins **279** were treated with triphosgene at −78 °C to room temperature to yield carbamoyl chlorides **280** (Table 2). Earlier work within the Clayden group showed that the carbamoyl chlorides were capable of hydrolysing back to the hydantoins if worked up under basic or acidic conditions.[178] To avoid this, work up of the reaction was performed simply by washing with saturated brine. The acylation of **279d** occurred slowly, with starting material remaining after 16 hours. This is probably because the methoxy substituent is sigma withdrawing due to the electronegativity of the oxygen atom.

Table 2: Synthesis of carbamoyl chlorides **280**

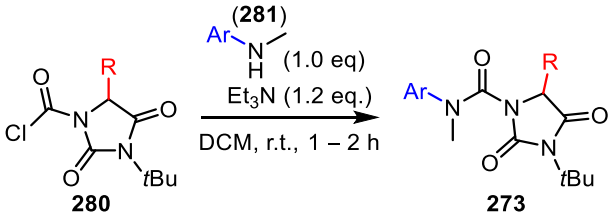


Entry	Product	Amino acid	R	Yield (%)
1	**280a**	Phg	Ph	89
2	**280b**	Ala	Me	>99
3	**280c**	4-Cl-Phg	4-ClC_6H_4	>99
4	**280d**	4-OMe-Phg	4-$OMeC_6H_4$	nd[a]
5	**280e**	Gly	H	93

[a] nd = not determined (recovered as a mixture of **279d** and **280d** even after reaction was left overnight)

To obtain hydantoin ureas **273**, carbamoyl chlorides **280** were coupled with *N*-methylanilines bearing a range of electron-deficient substituents. The crude products were purified by column chromatography to afford **273** in good to excellent yields (Table 3). **273e** was difficult to purify chromatographically because it had the same retention factor as its *N*-methyl-4-nitroaniline precursor. To overcome this issue, 0.9 equivalent of *N*-methyl-4-nitroaniline was used, instead of 1.0, to achieve complete consumption of the aniline in the coupling reaction. Acidic work up was avoided with **273d** to prevent protonation of the pyridyl group.

Table 3: Synthesis of hydantoin ureas **273**

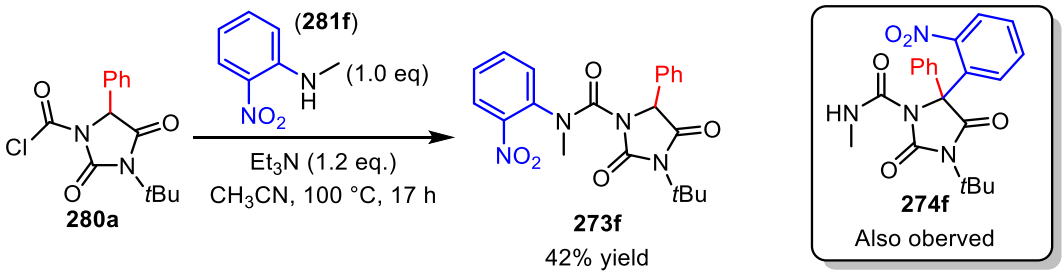


Entry	Product	Amino acid	R	Ar	Yield (%)
1	**273a**	Phg	Ph	4-CNC_6H_4	96
2	**273b**	Phg	Ph	3-CNC_6H_4	79
3[a]	**273c**	Phg	Ph	2-CNC_6H_4	58
4	**273d**	Phg	Ph	4-Pyridyl	70
5[b]	**273e**	Phg	Ph	4-$NO_2C_6H_4$	78
6	**273f**	Phg	Ph	2-$NO_2C_6H_4$	0
7[c]	**273g**	Phg	Ph	3-$NO_2C_6H_4$	95
8	**273h**	Phg	Ph	4-$CF_3C_6H_4$	66
9	**273i**	Phg	Ph	3-CF_3,4-CNC_6H_4	79
10	**273j**	Ala	Me	4-ClC_6H_4	61
11	**273k**	Ala	Me	4-CNC_6H_4	77
12	**273l**	4-Cl-Phg	4-ClC_6H_4	4-CNC_6H_4	60
14	**273m**	Gly	H	Ph	70

[a] Reaction left on overnight; [b] 0.9 eq. of *N*-methyl-4-nitroaniline was used in reaction
[c] Reaction performed in CH_3CN

The coupling of *N*-methyl-2-nitro aniline with **280a** to yield **273f** failed in DCM at room temperature (Table 3, entry 6). This was likely due to the steric hindrance from the 2-NO_2 substituent. On refluxing the coupling reaction overnight in anhydrous acetonitrile (Scheme 65), **273f** was obtained in moderate yield due to resulting intramolecular aryl migration in **273f** to produce **274f**. The same steric hindrance issue was encountered with the coupling reaction to yield **273c**. However, to minimise aryl migration as was encountered in the formation of **273f** (Scheme

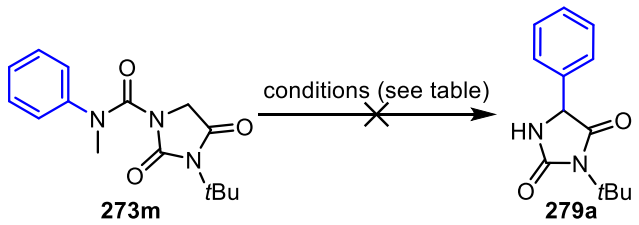
65), the coupling reaction to yield **273c** was not heated, but carried out at room temperature overnight (Table 3, entry 3).



Scheme 65: Synthesis of hydantoin urea **273f**

To investigate if it were possible to obtain **279** from aryl migration of glycine derived hydantoin ureas such as **273m**, rearrangement of **273m** was attempted (Table 4). Under all conditions tried, the hydantoin **279a** was not observed, but instead a cleavage of **273m** to *N*-methyl aniline. This was quite disappointing because the possibility of aryl migration within glycine derived hydantoin ureas would allow facile access to hydantoins **279** bearing different aryl substituents on the α-carbon, saving time and effort needed to source amino acids with the required aryl sidechains.

Table 4: Attempted aryl migration of **273m**



Entry	T (°C)	Base	Solvent	Time (h)
1	rt	KOH	CH_3CN	16
2	−78 – 0	KHMDS	THF	4
3	−78	Cs_2CO_3	THF	6
4	−78 – rt	LDA	THF	16

2.2.3 Optimisation of Aryl Migration

With the amino acid hydantoin ureas successfully made, a route towards achieving enantioselective rearrangements could now be investigated. As discussed in Scheme 63, the chiral ammonium salt **276** (Figure 8) produced a crude *er* of 85:15 in the aryl migration reaction of **273a**. Hence, this PTC was used for further investigations.

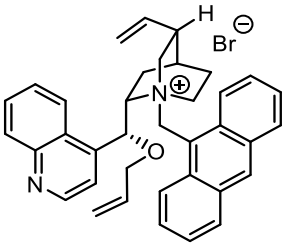
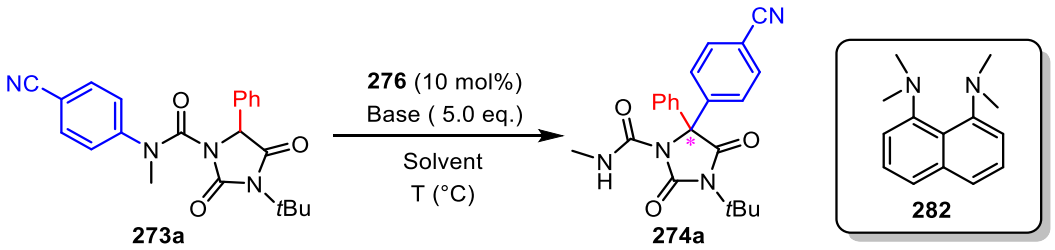


Figure 8: *O*-Allyl-N-(9-anthracenylmethyl) cinchonidinium bromide **276**

Toluene is non-polar so favours ion-pairing; It is also a commonly used solvent for phase transfer catalysed reactions in precedent literature.[104,106] Hence, it was employed in these optimisation studies. Other solvents were also trialled for insight into the influence of solvents on enantioselectivity. For those substrates insoluble in the investigated solvent, $CHCl_3$ was added to aid dissolution. $CHCl_3$ also aids dissolution of the catalysts, which are usually insoluble in non-polar solvents like toluene.[179] Bases were chosen based on control experiments and previous work within the group.[178,180,181] Inorganic bases used in PTC reactions are usually poorly soluble in the organic phase; hence there should be no or minimal reaction occurring in the absence of the PTC.[182] In the presence of the PTC, the cation of the PTC is thought to coordinate with the anion of the base, thus transferring it into the organic phase for substrate deprotonation (see Scheme 75).

Table 5: PTC aryl migration of **273a**

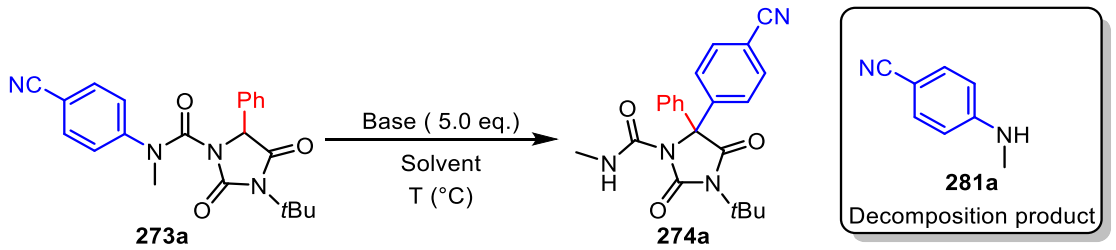


Entry	T (°C)	Solvent	Base	Time	Yield (%)			*er* (274a)
					273a	281a[d]	274a	
1	0	PhMe:$CHCl_3$[a]	Cs_2CO_3	6 d	29	0	9	37:63
2	0	CH_3CN[b]	Cs_2CO_3	<5 h	0	16	46	53:47
3	−20	CH_3CN[b]	Cs_2CO_3	1 d	0	44	11	54:46
4	−20	TBME/$CHCl_3$[a]	KOH	3 d	0	30	13	46:54
5	−20 – 0	TBME/$CHCl_3$[a]	Cs_2CO_3	7 d	14	9	32	40:60
6	0	TBME/$CHCl_3$[a]	K_2CO_3	4 d	53	0	20	45:55
7	0 – rt	PhMe:$CHCl_3$[a]	K_2CO_3	2 d	12	0	62	44:56
8	0 – 70	PhMe:$CHCl_3$[a]	**282**	3 d	>99[c]	0	0	-

[a] 1:0.7 ratio; [b] Anhydrous; [c] Only **273a** observed by ^{1}H NMR; Other yields obtained by ^{1}H NMR and compared with hexamethylbenzene internal standard; [d] 4-(methylamino)benzonitrile

As prior investigations showed that a crude *er* of 80:20 was obtained in the aryl migration reaction of **273a** using Cs_2CO_3 base at 0 °C, it was expedient to repeat the reaction under the same conditions. Hydantoin urea **273a** was subjected to the same conditions (Table 5, entry 1). HPLC analysis of purified **274a** revealed an *er* of 37:63. The yield of **274a** was low and the reaction slow, with starting material remaining after 6 days. A control experiment with **273a** using Cs_2CO_3 in a PhMe:$CHCl_3$ solvent system showed there was no background reaction occurring (Table 6, entry 1). When anhydrous acetonitrile was used as solvent at 0 °C, the reaction was complete in only 5 hours, but the transformation was not enantioselective (Table 5, **e**ntry 2). This was in accordance with various literature reports[183,184] which report a faster phase transfer catalysed reaction in polar solvents in detriment of enantioselectivity, due to polar stabilisation of the enolate by the solvent and not by formation of an ionic pair with the chiral cation of the catalyst. This suggests that non-polar solvents might be required to achieve higher enantioselectivities, perhaps at expense of reactivity. Racemic products were still obtained when the temperature of the reaction was lowered to −20 °C (Table 5, entry 3). There was also an increased decomposition of **273a** to 4-(methylamino)benzonitrile **281a** when the reaction temperature was decreased from 0 to −20 °C (Table 5, entry 2 vs 3). At this point, it was deduced that acetonitrile was not a suitable solvent for achieving enantioselectivity in these reactions.

Table 6: Control experiments for **273a**



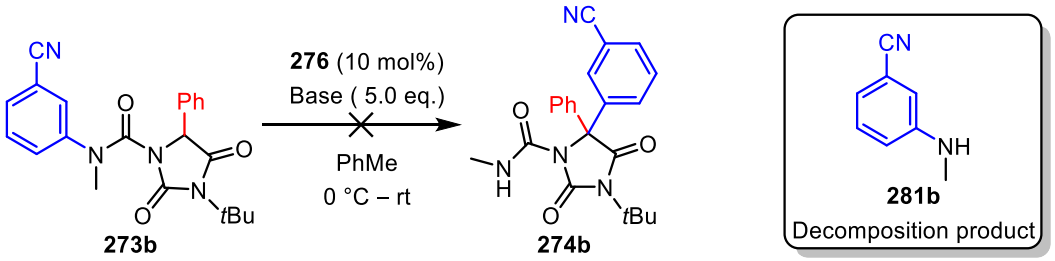
Entry	T (°C)	Solvent	Base	Comments
1	rt	PhMe:$CHCl_3$[a]	Cs_2CO_3	**274a** not observed[181]
2	−20 – 0	TBME/$CHCl_3$[a]	Cs_2CO_3	**274a** not observed at −20 °C; observed at 0 °C
3	−20	TBME/$CHCl_3$[a]	KOH	**274a** observed; **281a** observed
4	0	TBME/$CHCl_3$[a]	K_2CO_3	**274a** not observed

[a] 1:0.7 ratio

Following conditions used by Dixon and co-workers in their enantioselective nitro Mannich reactions,[185] KOH/*tert*-butyl methyl ether (TBME) at −20 °C was used in the aryl migration reaction of substrate **273a** (Table 5, entry 4). The product **274a** obtained was practically racemic, and there was evidence of decomposition. A control reaction showed that there was some background uncatalysed arylation, as well as decomposition of the starting material (Table 6, entry 3). For an effective comparison between toluene and TBME, the aryl migration was repeated with TBME and

Cs_2CO_3 as base. There was no reaction at −20 °C; however, at 0 °C, the product **274a** was formed with an *er* of 40:60 (Table 5, entry 5). A control reaction showed that there was a degree of uncatalysed arylation with Cs_2CO_3/ TBME at 0 °C (Table 6, entry 2). This suggested that if a base that was inactive without the catalyst was used, the *er* could be improved. To probe this, the weaker base K_2CO_3 was trialled (Table 5, entry 6). Surprisingly, the *er* reduced from 40:60 to 45:55. The decrease in *er* was unexpected because a control reaction showed no uncatalysed migration taking place with K_2CO_3 (Table 6, entry 4). Perhaps, racemisation of the chiral ammonium enolate occurred due to the prolonged reaction time. The use of K_2CO_3 was also attempted in toluene (Table 5, entry 7). There was no rearrangement at 0 °C; however, when the temperature was raised to room temperature, 62% rearrangement occurred albeit with poor enantioselectivity. The organic base 1,8-bis(dimethylamino)naphthalene **282** was also trialled. The aryl migration reaction showed no conversion to the product, even when the reaction was heated to 70 °C (Table 5, entry 8). It appears that the decomposition product **281a** is mostly observed at lower temperatures, and with increasing polarity of solvents used. This might be because polar solvents readily absorb water, which is suspected to be the cause of decomposition.

Table 7: PTC aryl migration of **273b**

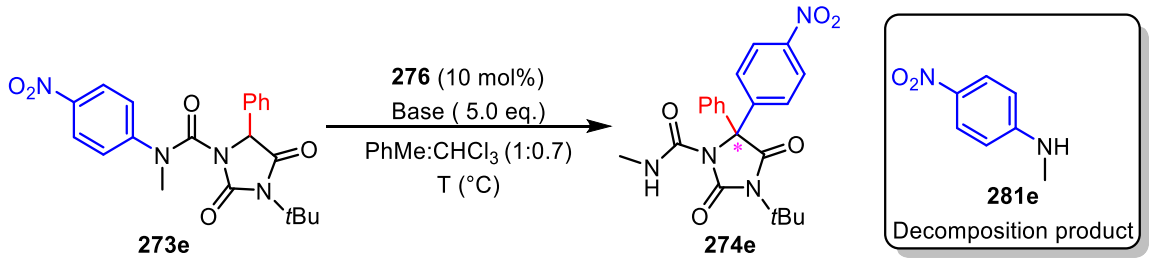


Entry	Base	Time	Yield (%)
1	Cs_2CO_3	6 d	0
2	CsOH	2 h	0

Anhydrous PhMe used

To compare the migration of 3- and 4-cyano substituted rings, the reaction was carried out with **273b** (Table 7). There was no reaction at 0 °C with either Cs_2CO_3 or CsOH in toluene. When the reaction was allowed to warm to room temperature, decomposition of **273b** to the corresponding *N*-methyl aniline **281b** occurred (Table 7, entries 1 and 2). The 3-cyano substituent most likely fails to activate the ring sufficiently towards nucleophilic attack by the enolate.

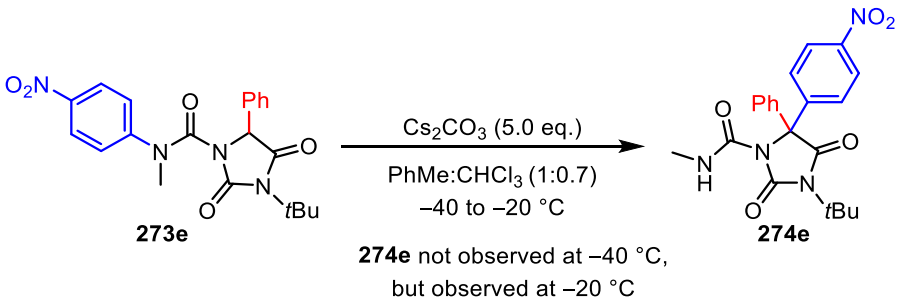
Table 8: PTC aryl migration of **273e**



Entry	T (°C)	Time	Yield (%)			*er* (274e)
			273e	281e	274e	
1	0	<17 h	0	0	48	55:45
2	−40	2 d	75	0	22	58:42

Yields obtained by ^{1}H NMR and compared with hexamethylbenzene internal standard.

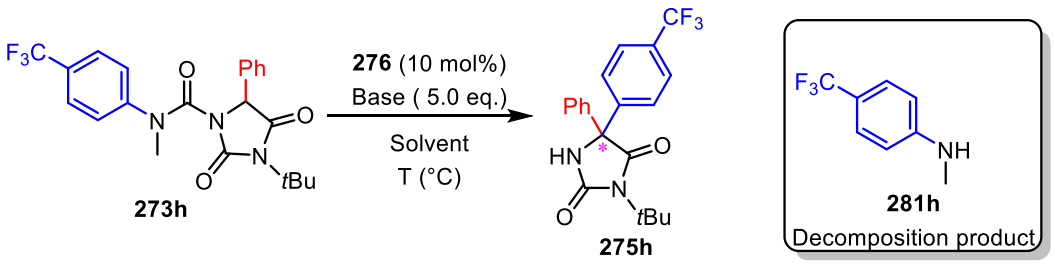
At 0 °C, the aryl migration of **273e** was complete in less than 17 hours, with a slight enantiomeric excess noted (Table 8, entry 1). As enantioselectivity is improved at lower temperatures,[101] the aryl migration was repeated at −40 °C. Unfortunately, at this temperature, the reaction did not go to completion after two days, although the *er* improved slightly (Table 8, entry 2). A control reaction with substrate **273e** showed that background uncatalysed arylation could be observed at −20 °C but not at −40 °C (Scheme 66). This may explain the reason for the slight increase in *er* at −40 °C.



Scheme 66: Control experiment for **273e**

There was no reaction when Cs_2CO_3 was used as base for the aryl migration of **273h** (Table 9, entry 1). However, when a stronger base (CsOH) was used at room temperature (Table 9, entry 2), the reaction proceeded to form the hydantoin **275h**, but with no enantioinduction. It is likely the reaction was not enantioselective because the chiral catalyst played no role in the reaction. When the temperature of the reaction was reduced to 0 °C (Table 9, entry 3), decomposition of the hydantoin urea **273h** to the corresponding *N*-methylaniline **281h** occurred.

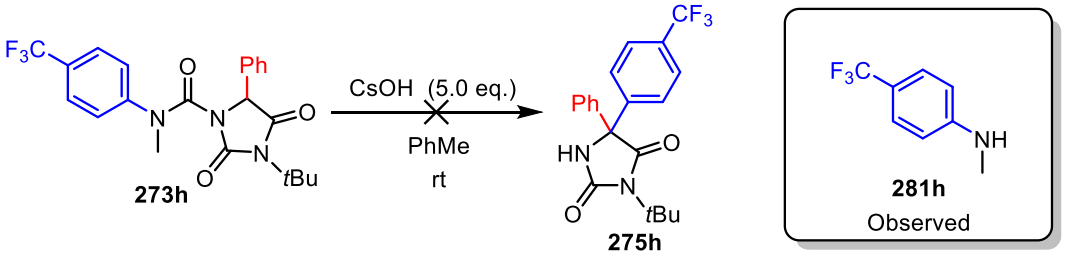
Table 9: PTC aryl migration of **273h**



Entry	T (°C)	Solvent	Base	Time	Yield (%)			*er* (275h)
					273h	281h	275h	
1	0 – rt	PhMe:$CHCl_3$[a]	Cs_2CO_3	7 d	**273h**[c]	**281h**[c]	0	-
2	rt	PhMe[b]	CsOH	1 d	0	20	39	50:50
3	0	PhMe[b]	CsOH	1 d	0	>99[d]	0	-

[a] 1:0.7 ratio; [b] Anhydrous; [c] Mixture of **273h** and **281h** observed by ^{1}H NMR; [d] Only **281h** observed by ^{1}H NMR; Other yields obtained by ^{1}H NMR and compared with hexamethylbenzene internal standard.

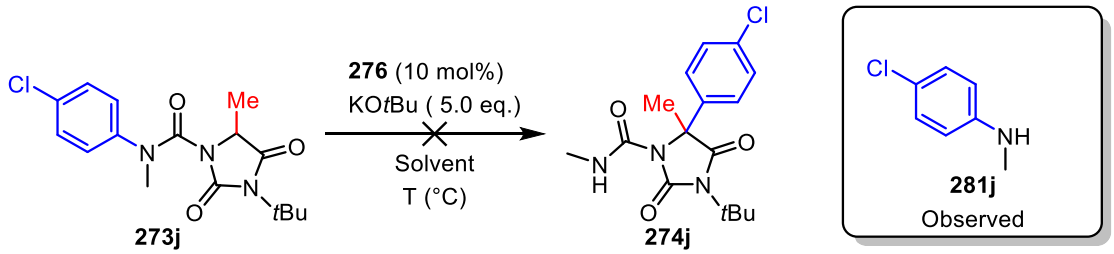
To investigate the participation of the catalyst in the reaction, a control experiment was carried out with substrate **273h** using CsOH in toluene at room temperature (Scheme 67); decomposition of **273h** to **281h** was observed. This suggested that whilst the catalyst must have played a role in the formation of **275h** at room temperature, it did not confer any enantioselectivity.



Scheme 67: Control reaction for **273h**

The aryl migration failed to occur with hydantoin urea **273j** (Table 10). This is likely due to lack of enolate formation due to the less acidic α-proton.

Table 10: PTC aryl migration of **273j**



Entry	T (°C)	Solvent	Time	Yields (%)		
				273j	281j	274j
1	rt – 40	PhMe:$CHCl_3$[a]	3 d	>99[c]	0	0
2	rt	PhMe[b]	1 d	0	>99[c]	0

[a] 1:0.7 ratio; [b] Anhydrous; [c] Only compound observed by ^{1}H NMR.

The PTC aryl migration was investigated further by screening other PTCs (Figure 9). Since the best *er* was obtained for the aryl migration of **273a** (Table 5, entry 1), this substrate was selected for screening of the catalysts. The results of the screening are given in Table 11. The PTCs: **285**, **286**, **287**, **288** and **291** gave the hydroxylated product **297a** (Table 11, entries 3 – 6 and 9). As hydroxylation likely results from oxidation of the enolate by oxygen in the reaction mixture, the reaction with PTC **291** was repeated using degassed solvent. However, the hydroxylated product was still obtained.

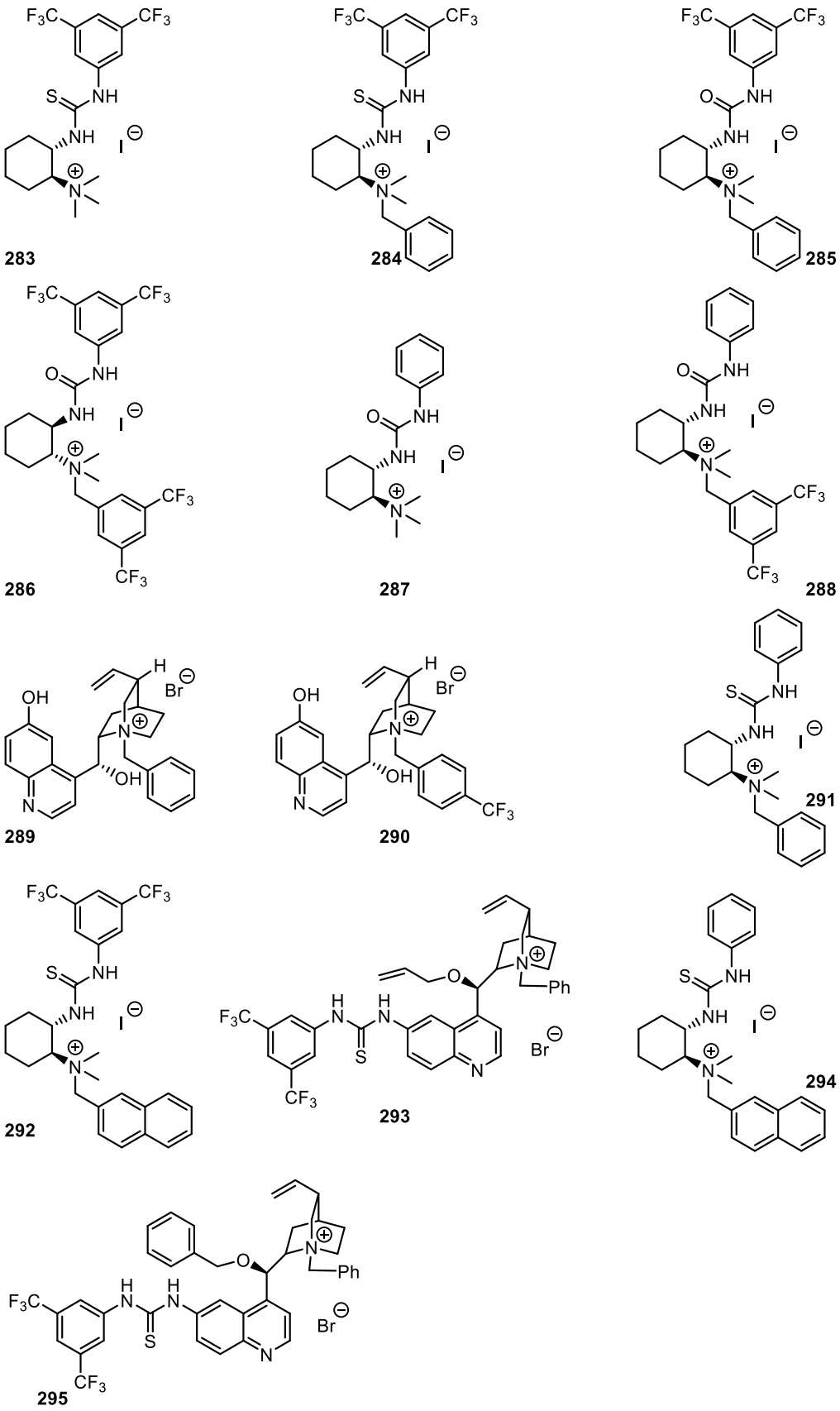
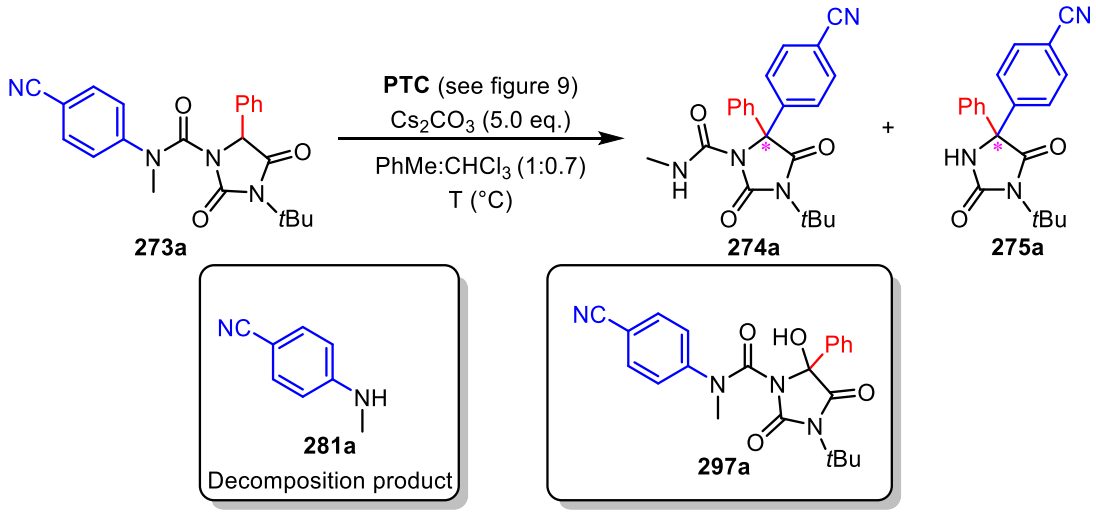


Figure 9: PTCs screened in the aryl migration of **273a**[1]

[1] Thanks to Professor Mario Waser for providing the PTCs

With PTCs **283** and **284**; quinine-derived PTCs **289** and **290**; and PTCs **293 – 295**, there was no reaction at 0 °C after 1 day. When the reactions were warmed to room temperature, the products **274a** and **275a** were formed with practically no enantioselectivity. Decomposition to the *N*-methylaniline **281a** was also observed in many cases. The difference in the results obtained for **284** (Table 11, entry 2) and **285** (Table 11, entry 3) suggests that a thiourea catalyst might be more favourable towards these reactions than a urea. At room temperature, PTC **292** gave the product **274a** along with the corresponding *N*-methylaniline **281a** (Table 11, entry 10). When the reaction was carried out at 0 °C, the *er* improved marginally to 54:46 (Table 11, entry 11).

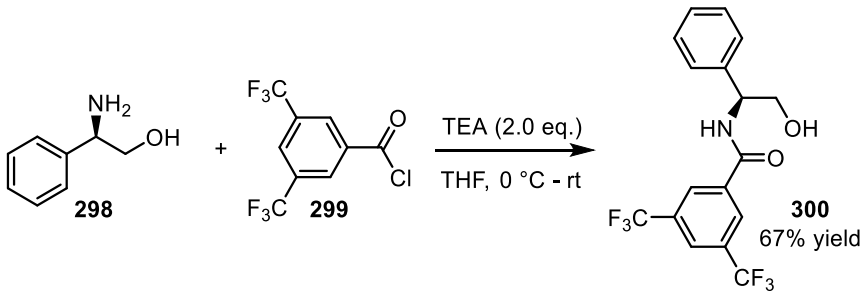
Table 11: Screening of PTCs in the aryl migration of **273a**



Entry	PTC	T (°C)	Time	Yield (%)				*er* (274a)
				273a	281a	274a	275a	
1	**283**	0 – rt	2 d	0	15	5	48	54:46
2	**284**	0 – rt	2 d	0	8	6	18	52:48
3	**285**	0	2 d	0	0	0	0	-
4	**286**	0	3 d	0	0	0	0	-
5	**287**	0	16 h	0	0	0	0	-
6	**288**	0	4 d	0	0	0	0	-
7	**289**	0 – rt	4 d	0	21	9	18	54:46
8	**290**	0 – rt	4 d	0	25	5	8	53:47
9	**291**	0	3 d	0	0	0	0	-
10	**292**	rt	16 h	0	20	11	0	51:49
11	**292**	0	7 d	23	8	8	0	54:46
12	**293**	0 – rt	4 d	0	0	40	21	52:48
13	**294**	0 – rt	2 d	0	18	12	51	50:50
14	**295**	0 – rt	2 d	0	0	44	14	52:48
15	**296**	0 – rt	2 d	0	0	58	trace	45:55

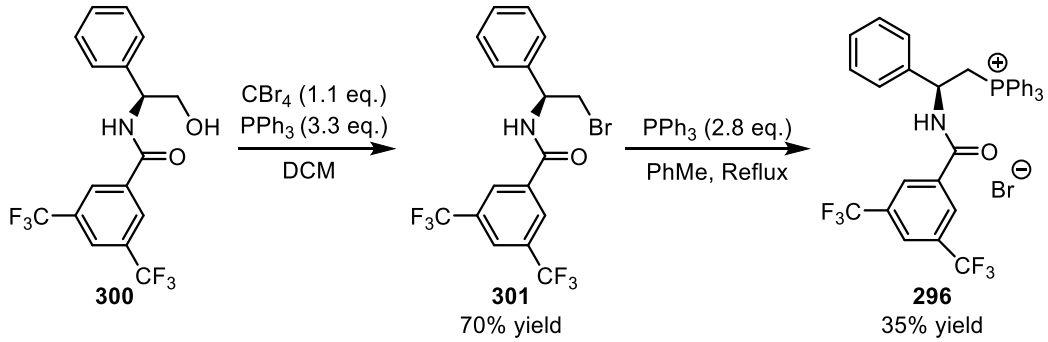
PTC – 10 mol%; Yields obtained by ^{1}H NMR and compared with hexamethylbenzene internal standard.

Wu and co-workers showed that a phosphonium-based catalyst gave good enantioselectivity when used in the phase transfer catalysed addition reaction of oxindoles to vinyl ketones.[186] The excellent enantioselectivities obtained by them and other authors[187,188] who have worked independently on the use of phosphonium based salts for enantioselective phase transfer catalysis prompted the author to synthesise and trial **296**.



Scheme 68: Synthesis of alcohol **300**

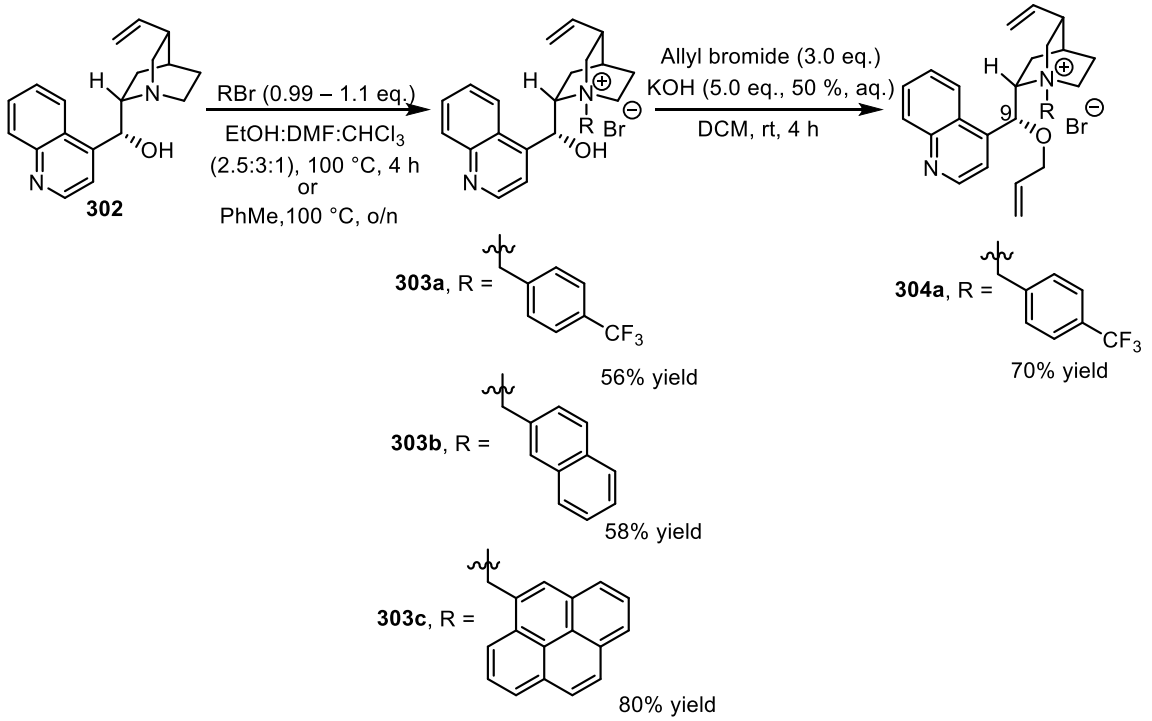
Following the procedure used by Wu and co-workers, the phosphonium catalyst **296** was synthesised in a 3-step procedure. The first step was the nucleophilic addition of the amino alcohol **298** to acyl chloride **299** to afford the addition and concomitant elimination product **300** (Scheme 68). In the second step, **300** was treated with tetrabromomethane and triphenylphosphine to produce halide **301**. Finally, **301** was treated with triphenylphosphine to produce the phosphonium salt **296** (Scheme 69).



Scheme 69: Synthesis of phosphonium salt **296**

The phosphonium salt **296** was applied in the aryl migration of **273a** (Table 11, entry 15). Disappointingly, **296** gave a poor *er* of 45:55.

As all attempts to improve the enantioselectivity using non-cinchona-derived catalysts proved unsuccessful, attention reverted to the cinchona-derived catalysts. Catalysts **303** – **304** were synthesised following literature protocol.[100,189] (-)-Cinchonidine was heated with the desired alkyl halide in either toluene or a mixture of ethanol, DMF and chloroform to obtain the ammonium salts **303**. The ammonium salt **303a** was later converted to its *O*-allylated form **304a** by treating **303a** with potassium hydroxide and allyl bromide (Scheme 70).



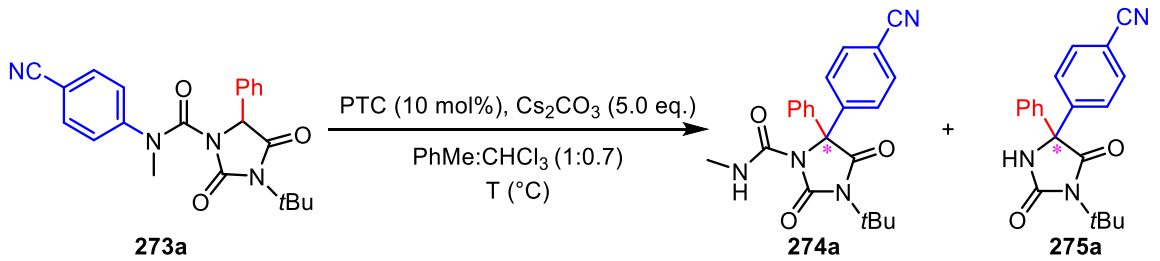
Scheme 70: Synthesis of cinchona-derived catalysts

PTC **303a** was prepared to investigate if having a single hydrogen bonding site as opposed to multiple hydrogen bonding sites (compare PTC **290**) was detrimental or beneficial to the enantioselectivity. Carrying out the aryl migration using PTC **303a** (Table 12, entry 1) indicated that having multiple hydrogen bonding sites on the PTC made no contribution to the enantioselectivity of the aryl migration. This result was not surprising as it was not possible to achieve enantioselectivity with the previously used bifunctional urea and thiourea PTCs (Table 11). Literature reports, however, suggest that enantioselectivity can be significantly increased using PTCs with multiple hydrogen bonding sites.[190,191] Beyond the influence of hydrogen bonding, perhaps the structures of **290** and **303a** exert no stereodiscrimination in the rearrangement.

PTC **304a** showed that the presence of an *O*-allyl group at the C-9 position of the catalyst had no significant influence on the enantioselectivity as a similar *er* (Table 12, entry 2) was obtained to that of **303a** (Table 12, entry 1). Previous studies showed that there was improved enantioselectivity in the α-benzylation of a glycine-derived imine when the cinchona-derived catalyst was C9-*O*-allyl substituted.[91] The benzylation was however intermolecular and not intramolecular. Belyk and Ronchi independently reported a significant reduction in enantioselectivity when a C9-*O*-allylated cinchona-derived PTC was used in place of its unallylated form in certain intramolecular transformations.[192,193] This suggests that a free hydroxyl group at the C-9 position might be crucial to obtaining enantioselective transformations in intramolecular reactions. The reduction in enantioselectivity from 37:63 (Table 5, entry 1) to 43:57 (Table 12, entry 3) corroborates literature findings that having a bulky group at the *N*-position of the quinuclidine ring of the cinchona-based

PTC increases enantioselectivity.[194] Disappointingly, PTC **303c** bearing a pyren-1-yl group at the quaternary nitrogen showed only 15% conversion to **274a** after 2 days, with a *er* of only 44:56 (Table 12, entry 4).

Table 12: PTC optimisation



273a **274a** **275a**

Entry	PTC	T (°C)	Time	Yield (%)				*er* (274a)
				273a	281a[a]	274a	275a	
1	**303a**	0	2 d	31	10	27	0	44:56
2	**304a**	0	3 d	20	8	35	0	45:55
3	**303b**	0	5 d	30	8	15	0	43:57
4	**303c**	0	2 d	48	trace	15	0	44:56
5	**305**	0	3 d	0	8	56	0	60:40
6	**307a**	0	1 d	5	7	76	0	51:49
7	**307b**	0 – rt	2 d	0	3	65	0	50:50
8	**308**	0 – rt	2 d	0	0	5	48	57:43

Yields obtained by ^{1}H NMR and compared with hexamethylbenzene internal standard; [a] 4-(methylamino)benzonitrile

When commercially available bis(hydrocinchonidine)-derived PTC **305** (Figure 10) was used in the aryl migration, an *er* of 60:40 (Table 12, entry 5) was obtained. The reaction was faster and the yield higher relative to previously used single cinchona unit PTCs. Unlike the monomeric cinchona derived catalyst **303b**, there is hindered rotation of the naphthyl in **305**, hence the dimeric cinchona-derived catalyst would offer a more rigid conformation of the ammonium/enolate ion-pair. The use of bicinchona catalysts was explored further.

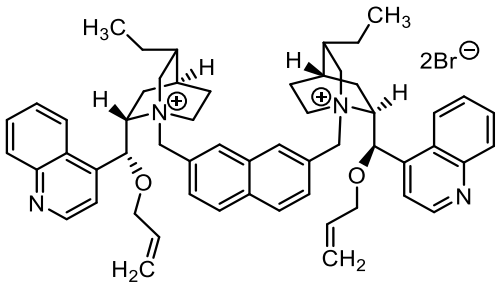
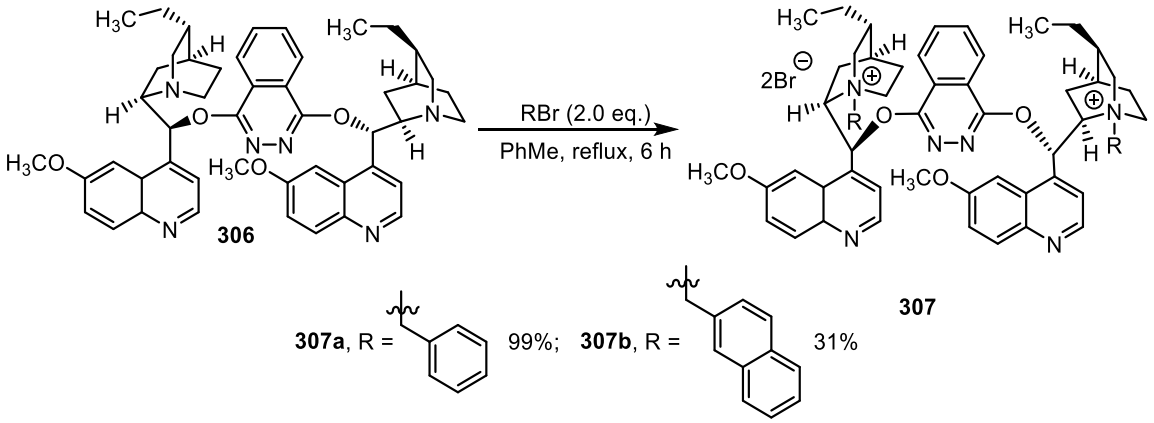


Figure 10: PTC **305**

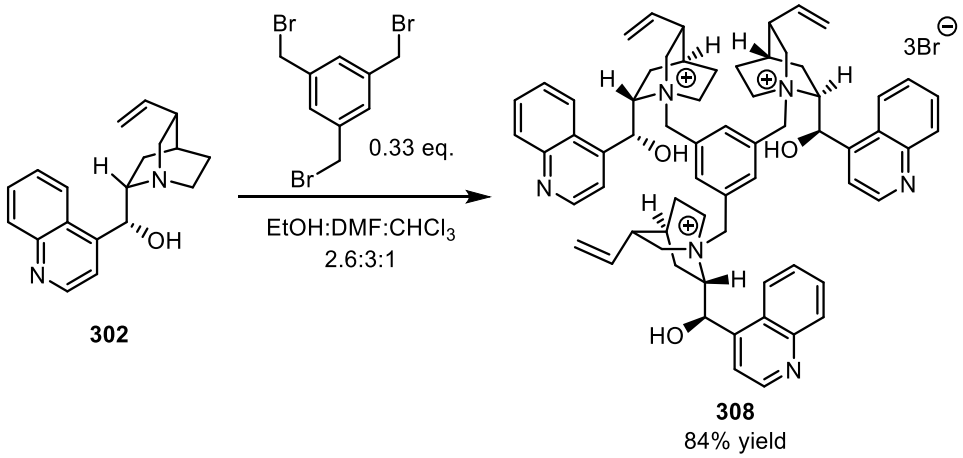
Bicinhona catalysts **307a** and **307b** were synthesised via the 1 step procedure described in Scheme 71.[194] $(DHQD)_2$-PHAL **306** was refluxed with the desired alkyl bromide in toluene to afford **307a** and **307b** in a 99% and 31% yield respectively.



Scheme 71: Synthesis of Bicinchona catalysts

PTC **307a** showed a remarkable increase in the rate and yield of the aryl migration; however, the product **274a** was racemic (Table 12, entry 6). PTC **307b** showed no conversion to the product at 0 °C, hence the reaction was warmed to room temperature. A good yield of 65% was obtained at room temperature but the product **274a** was found to be racemic (Table 12, entry 7). It is uncertain why the catalysts **307a** and **307b** confer no enantioselectivity in the reaction. Jeong and co-workers also reported a 0% *ee* when **307a** was used as PTC in the α-benzylation of a benzophenone glycine derived imine at room temperature.[179] Like **305**, the dimeric cinchona catalyst **307a** significantly improved the rate of the reaction, suggesting that the added cinchona unit provides an additional stabilization of the enolate. Steric clashes between the naphthyl and quinoline ring in **307b** might lead to an unfavourable transition state conformation. This might explain why no reaction occurred at 0 °C.

To get more insight into the influence of polymeric cinchona salts on the rearrangement, tricinchona catalyst **308** was synthesised via the 1 step protocol illustrated in Scheme 72 and used in the aryl migration. No aryl migration occurred at 0 °C; when the reaction was heated to room temperature, **274a** and **275a** were observed in a 5% and 48% yield respectively (Table 12, entry 8). The enantioselectivity of **274a** was disappointingly poor. This result suggests that whilst sterically hindered catalysts are useful in reducing flexibility in the conformation of the ammonium enolate, excessive steric hindrance could lead to high energy transition states and lose ion-pairing of the ammonium enolate complex.



Scheme 72: Synthesis of tricinchona catalyst **308**

Past research showed that cinchona salts having a perfluorinated benzyl group at the quaternary ammonium centre are effective catalysts for inducing excellent enantioselectivities in many transformations.[195–197] It is postulated that an electron-withdrawing group like fluorine results in a more compact ammonium/anion pair, thus improving enantioselectivity.[95,198,199] Furthermore a fluorine atom provides additional stabilisation through stereoelectronic and electrostatic effects; and could also take part in hydrogen bonding.[200,201] Maruoka also observed that the introduction of a 3,4,5-trifluorophenyl substituent on the 3,3' position of his binaphthyl PTCs led to significantly increased enantioselectivities in the double alkylation of glycine-derived imines.[106,202] On the basis of these findings, the cinchona salts **309** – **316** were made by refluxing a mixture of the desired perfluorinated benzyl bromide and cinchona alkaloid in toluene for 24 hours (refer to Scheme 70).[197]

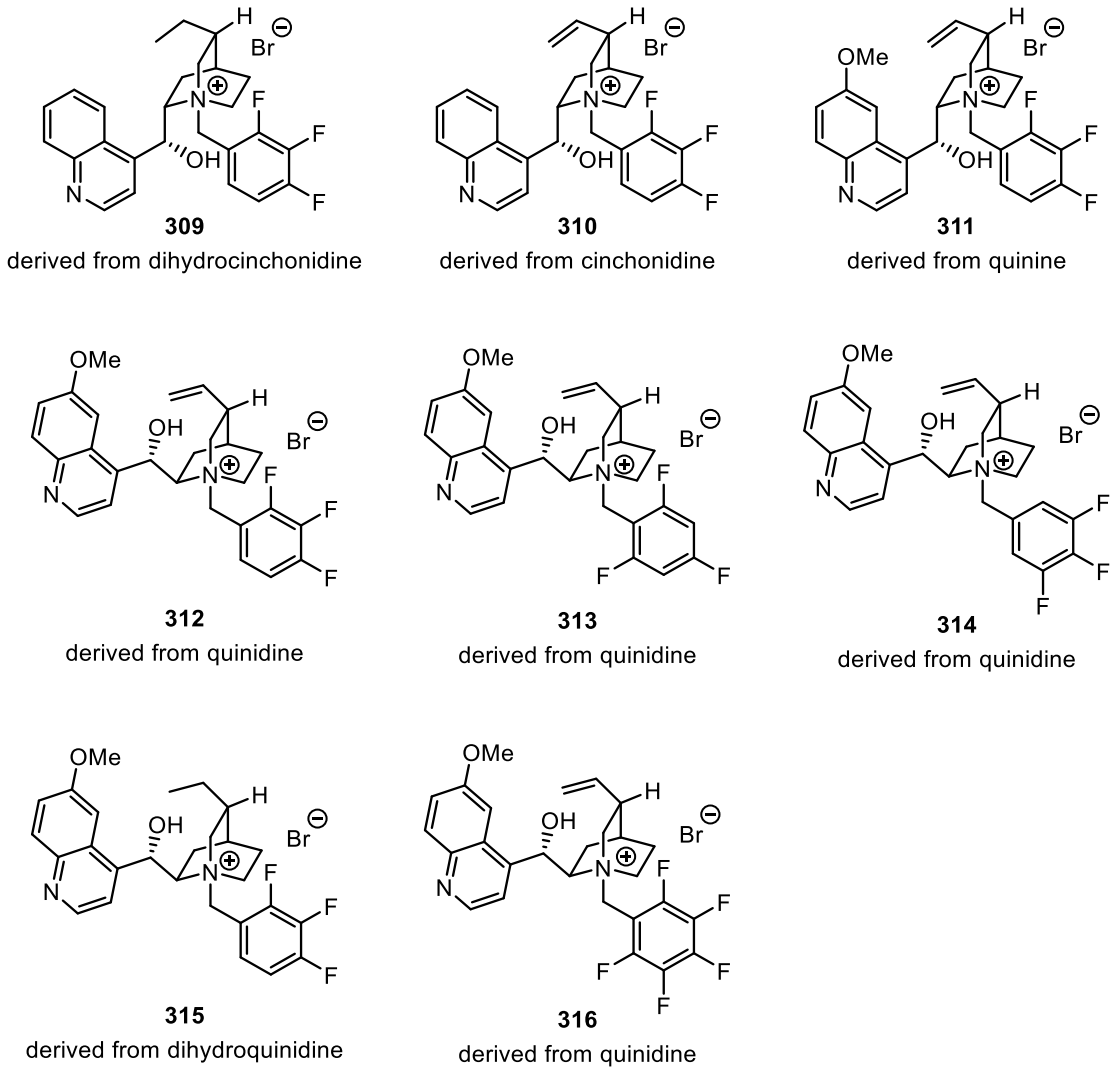
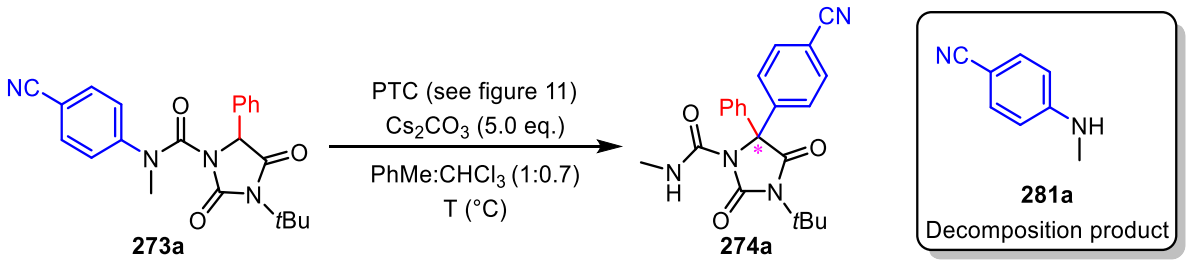


Figure 11: Cinchona-derived PTCs bearing fluorobenzyl groups

PTCs **309** – **316** (Figure 11) bearing different fluorine substitution patterns on the *N*-benzyl group were independently trialled in the aryl migration reaction (Table 13). Delightfully, PTC **314** with 3,4,5-trifluorobenzyl substitution produced an enantiomeric ratio of 78:22 in the aryl migration (Table 13, entry 6). The poor enantioselectivities obtained with all the *ortho*-substituted *N*-benzyl derivatives (Table 13, entries 1 – 5 and 7 – 8) indicated that a H-atom at the ortho position is crucial to obtaining good enantioselectivities, perhaps due to aromatic C-H/π interactions with **273a**.[203] The better enantioselectivity obtained with PTC **315** relative to PTC **309** indicates the importance of the methoxy substituent on the quinoline ring (Table 13, entry 7 vs entry 1). The oxygen atom of the methoxy group likely takes part in hydrogen bonding interactions with **273a**; this implies that an hydroxyl group on the quinoline ring would also take part in hydrogen bonding interactions with **273a**. Proceeding with PTC **314**, the effect of water on the enantioselectivity of the aryl migration was investigated. The use of a mixture of anhydrous toluene and wet (non-anhydrous) chloroform (Table 13, entry 9) decreased the *er* from 78:22 to 69:31, indicating that the presence of water in the reaction contributed to the improved enantioselectivity. PTC **314** is slightly soluble in water;

this might explain the improved enantioselectivity in the presence of water. As expected, the enantioselectivity decreased at higher temperatures, from 69:31 at 0 °C (Table 13, entry 9) to 62:38 at room temperature (Table 13, entry 10).

Table 13: PTC optimisation



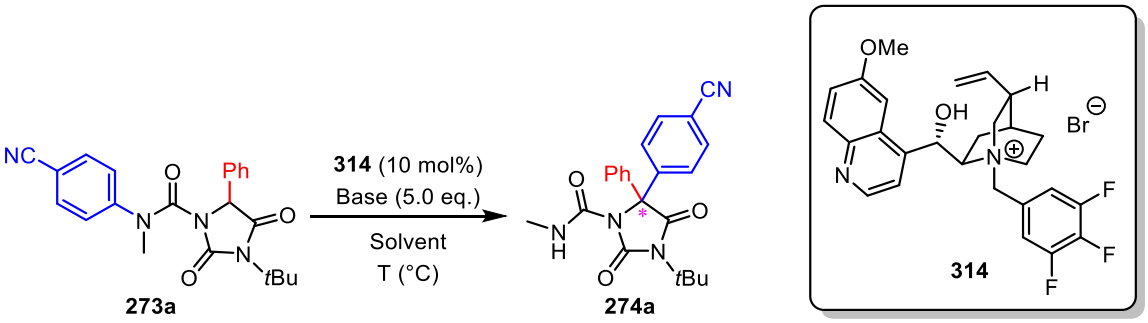
Entry	PTC[1]	T (°C)	Time	Yield (%)			*er* (274a)
				273a	281a	274a	
1	**309**	0	3 d	21	15	19	56:44
2	**310**	0	3 d	10	17	22	54:46
3	**311**	0	3 d	40	13	13	49:51
4	**312**	0	3 d	21	19	18	54:46
5	**313**	0	2 d	10	14	35	53:47
6	**314**	0	2 d	9	15	47	78:22
7	**315**	0	3 d	39	16	11	60:40
8	**316**	0	5 d	> 90	nd	trace	55:45[a]
9[b]	**314**	0	2 d	32	10	19	69:31
10[b]	**314**	rt	16 h	0	0	80[c]	62:38

Except otherwise stated, the reactions were performed in wet solvents; Except otherwise stated, yields were obtained by ^{1}H NMR and compared with hexamethylbenzene internal standard; PTC – 10 mol%; [a] HPLC trace of crude; [b] Reaction carried out in a mixture of anhydrous toluene and wet chloroform; [c] Isolated yield

As solvents have been found to significantly alter enantioselectivity in asymmetric reactions,[196,197] the influence of solvents on the enantioselectivity of the aryl migration was probed (Table 14). When a mixture of THF and toluene was used as solvent at 0 °C, incomplete conversion to **274a** with significantly reduced enantioselectivities were observed after 24 hours (Table 14, entries 2 and 3). The use of THF alone increased the rate of the aryl migration but to the detriment of the enantioselectivity (Table 14, entry 4). With the rationale that a weaker base might produce good enantioselectivity in THF, K_2CO_3 was trialled in the reaction (Table 14, entry 9). Disappointingly, no conversion was observed after 96 h.

[1] Thanks to Professor Martin D. Smith for providing PTCs **309** – **313** and PTC **315**

Table 14: Solvent optimisation[1]



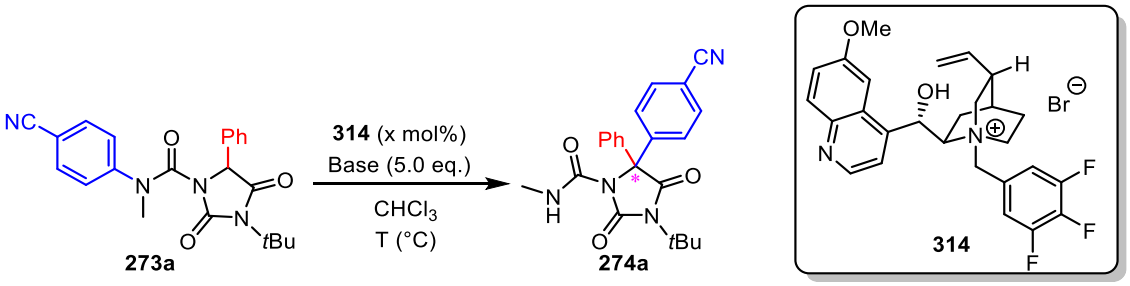
Entry	T (°C)	Solvents (ratio)	Base	Time (h)	Comments	*er*
1	0	PhMe:$CHCl_3$ (0.6:0.4)	Cs_2CO_3	48	47%[b]	78:22[c]
2	0	PhMe:THF (1:1)[a]	Cs_2CO_3	24	Incomplete conversion	54:46
3	0	PhMe:THF (0.9:0.1)[a]	Cs_2CO_3	24	trace conversion	63:37[c]
4	0	THF[a]	Cs_2CO_3	24	100% conversion	52:48[c]
5	0	CF_3Ph[a]	Cs_2CO_3	60	100% conversion	60:40
6	0	PhMe:$CHCl_3$ (0.9:0.1)	Cs_2CO_3	72	No conversion	-
7	rt	PhMe:$CHCl_3$ (0.9:0.1)	Cs_2CO_3	20	Incomplete conversion	60:40
8	0	$CHCl_3$	Cs_2CO_3	72	100% conversion	70:30
9	0	THF	K_2CO_3	96	No conversion	-

Except otherwise stated, the reactions were carried out in wet solvents; [a] Reaction carried out in anhydrous solvent [b] Yield was obtained by ^{1}H NMR and compared with hexamethylbenzene internal standard; [c] HPLC trace of pure product

Complete conversion was observed with trifluoro toluene at 0 °C but the enantioselectivity was reduced (Table 14, entry 5). As expected, no conversion was observed when the amount of PhMe in the PhMe:$CHCl_3$ solvent mixture was increased (compare Table 14, entry 6 to 1); However, when the aryl migration reaction was warmed to room temperature in the same solvent mixture (Table 14, entry 7), some conversion was observed after 20 hours with moderate enantioselectivity. The use of chloroform alone made the reaction faster but the enantioselectivity reduced from 78:22 to 70:30 (Table 14, entry 8 vs 1). Amongst the solvent systems screened, a 0.6:0.4 mixture of PhMe:$CHCl_3$ (Table 14, entry 1) was the optimal solvent system for enantioselectivity, but considering the slower rate of reaction relative to using $CHCl_3$ alone (Table 14, entry 8), the latter was chosen for further optimisations.

[1] Joint work of the author and Dr Rakesh K. Saunthwal

Table 15: Further optimisations[1]



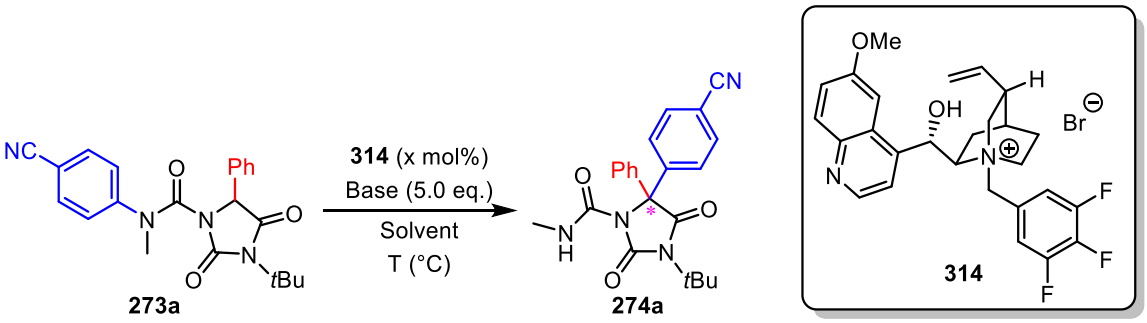
Entry	T (°C)	Base	x	Time	Comments	*er*
1	0	Cs_2CO_3	10	72 h	100% conversion	70:30
2	0	Cs_2CO_3	20	17 h	100% conversion	77:23
3	−10	Cs_2CO_3	20	23 h	100% conversion	82:18
4	−20	Cs_2CO_3	20	36 h	100% conversion	85:15
5	−20 – 0	Rb_2CO_3	20	15 h	Incomplete conversion	73:27
6	−20	Cs_2CO_3	30	24 h	100% conversion	87:13
7	0	Cs_2CO_3	30	22 h	100% conversion	80:20

Wet $CHCl_3$ was used as solvent in all cases

When the catalyst loading was increased from 10 to 20 mol% (Table 15, entry 2), the aryl migration was complete in 17 hours and the *er* improved from 70:30 to 77:23. Reducing the temperature of the aryl migration from 0 to −10 °C slowed down the reaction but improved the *er* from 77:23 to 82:18 (Table 15, entry 3). A further reduction in temperature to −20 °C slowed down the reaction further but improved the *er* to 85:15 (Table 15, entry 4). Using the same conditions as entry 4, a weaker base, Rb_2CO_3 was used instead of Cs_2CO_3 (Table 15, entry 5). There was no conversion at −20 °C, hence the reaction was warmed to 0 °C. The reaction showed slight conversion to **274a** after 15 hours with an *er* of 73:27. Going back to Cs_2CO_3 as base and increasing the catalyst loading from 20 to 30 mol%, the aryl migration occurred with an *er* of 87:13 at −20 °C (Table 15, entry 6). Using this same catalyst loading at 0 °C, the *er* of the aryl migration product **274a** reduced from 87:13 to 80:20 (Table 15, entry 7).

[1] Joint work of the author and Dr Rakesh K. Saunthwal

Table 16: Further solvent optimisations[1]



Entry	T (°C)	Solvents (ratio)	x	Base	Time	Comments	*er*
1	0	PhMe:$CHCl_3$ (0.5:0.5)	20	Cs_2CO_3	24 h	100% conversion	77:23
2	0	PhMe:$CHCl_3$ (0.4:0.6)	20	Cs_2CO_3	18 h	100% conversion	79:21
3	0	PhMe:$CHCl_3$ (0.6:0.4)	30	Cs_2CO_3	18 h	Incomplete conversion	79:21
4	−20	THF[a]	20	Rb_2CO_3	60 h	Incomplete conversion	57:43
5	0	HFIP[a]	20	Cs_2CO_3	48 h	No conversion	-

Except otherwise stated, the reactions were carried out in wet solvents; [a] Anhydrous solvent.

The rate of the aryl migration was faster in chloroform than toluene; However, a non-polar solvent like toluene was needed to promote tighter interactions between the catalyst and the enolate, consequently leading to better enantioselectivity. To obtain an optimal PhMe:$CHCl_3$ solvent system, further investigations were done. A 1:1 ratio of the two solvents (Table 16, entry 1) produced an *er* of 77:23. Decreasing the ratio of toluene to $CHCl_3$ (Table 16, entry 2) produced a comparable *er* of 79:21. Though the rate of the aryl migration reduces with increasing ratio of PhMe:$CHCl_3$, it was thought that increasing the catalyst loading to 30 mol% (Table 16, entry 3) might increase the rate and enantioselectivity of the reaction even when a greater percentage of toluene was used in the solvent mixture. Disappointingly, a comparable rate and enantioselectivity to that obtained in Table 14, entry 1 was noted. From these results, it was inferred that toluene could only solvate a small amount of the catalyst; and this might explain why increasing the catalyst loading to 30 mol% had no significant effect on the enantioselectivity. Chloroform, on the other hand, can solvate the catalyst well even at a low temperature of −20 °C (Table 15, entry 4).

Using 20 mol% catalyst loading, additional optimisations were carried out with the aim of obtaining a better enantioselectivity than 85:15. The use of Rb_2CO_3 in THF at −20 °C gave some conversion to **274a**, but with a low level of enantioenrichment (Table 16, entry 4). No conversion was observed

[1] Joint work of the author and Dr Rakesh K. Saunthwal

in hexafluoro-2-propanol at 0 °C (Table 16, entry 5). At this point, it was concluded that further catalyst optimisations should be carried out with Cs_2CO_3 as base and chloroform as solvent.

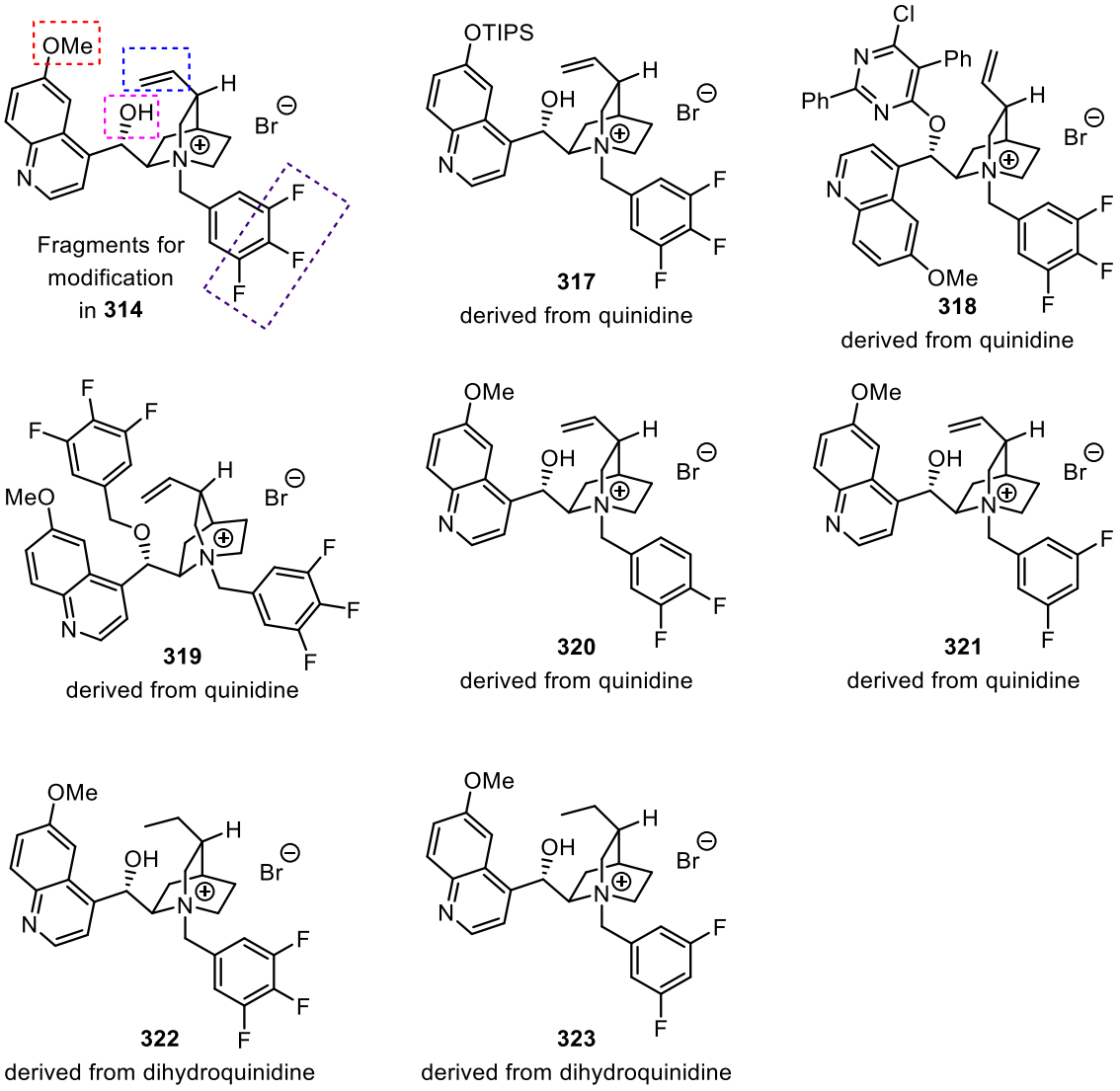
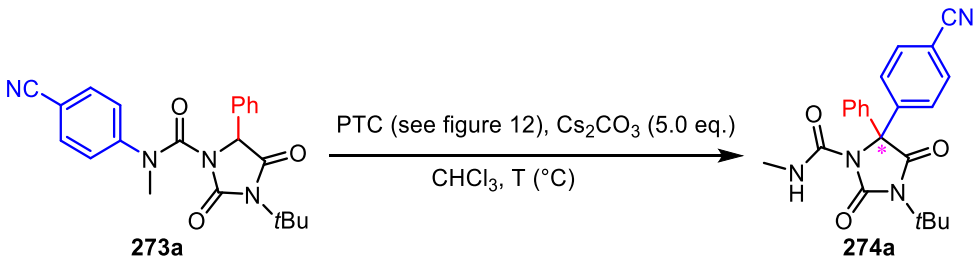


Figure 12: Modification of PTC **314**

To gain further insights into the components of PTC **314** that contribute to enantioselectivity through interaction with the enolate, structural modifications were made to afford PTCs **317** – **323** (Figure 12). It is now known from previous optimisations (Table 13, entry 1 vs 7) that the OMe group on the quinoline is relevant to obtaining improved enantioselectivity. Nonetheless, out of inquisitiveness, **317** bearing an OTIPS instead of an OMe, was tested. No conversion was observed at either −20 or 0 °C, with only starting material observed by ^{1}H NMR after 24 hours (Table 17, entry 2). As noted earlier, a bulky group such as a triisopropylsilyl (TIPS) could lead to the generation of an unfavourable high energy ammonium enolate transition state. The importance of the hydroxyl group in PTC **314** was exemplified by PTC **318** and **319**, both having a substituent on the hydroxyl. They both gave no conversion at −20 °C. Nonetheless, *er*s of 73:27 and 75:25 were

respectively obtained when the reaction was warmed to 0 °C (Table 17, entries 3 and 4). The failure of PTCs **318** and **319** to catalyse the reaction at −20 °C indicates that the hindrance posed by the bulky *O*-substituents is more obvious at lower temperature, but raising the temperature of the reaction to 0 °C, supplies just enough energy for the reaction to occur at a slow rate. With PTC **320**, only starting material was observed by ^{1}H NMR after 18 hours at 0 °C (Table 17, entry 5). This suggests that fluorine substitution at carbon 5 of the benzyl in PTC **314** is pertinent to reactivity. PTC **321** gave a similar *er* to **314** at −10 °C (Table 17, entry 6 vs Table 15, entry 3), indicating that fluorine substitution at carbon 4 of the benzyl in **314** is inconsequential to the enantioselectivity. Fluorine substitution at the *meta* positions (carbon 3 and 5) of the benzyl ring certainly provides a high level of stereodiscrimination that becomes disturbed with further introduction of fluorine to other positions on the ring apart from the *para* position. PTC **322** gave similar enantioselectivity and yield to its dehydrogenated form **314** (Table 17 entry 7 vs entry 1). This corroborates a 1991 literature finding that the vinyl group in a cinchona alkaloid-based catalyst makes no contribution to the enantioselectivity of the reaction in which it is used.[102] PTC **323** having a 3,5-difluoro substitution also gave similar enantioselectivity and yield to both **322** and **314 (**Table 17, entry 8), suggesting again that fluorine substitution at carbon 4 of the benzyl ring was inconsequential to the enantioselectivity.

Table 17: PTC optimisation[1,2]



273a 274a

Entry	PTC	T (°C)	Time	Comments	*er*
1	**314**	−20	36 h	100% conversion	85:15
2	**317**	−20 – 0	24 h	No conversion	-
3	**318**	−20 – 0	22 h	Incomplete conversion	73:27
4	**319**	−20 – 0	18 h	Incomplete conversion	75:25
5	**320**	0	18 h	No conversion	-
6	**321**	−10	23 h	Incomplete conversion	79:21
7	**322**	−20	36 h	100% conversion	85:15
8	**323**	−20	36 h	100% conversion	85:15

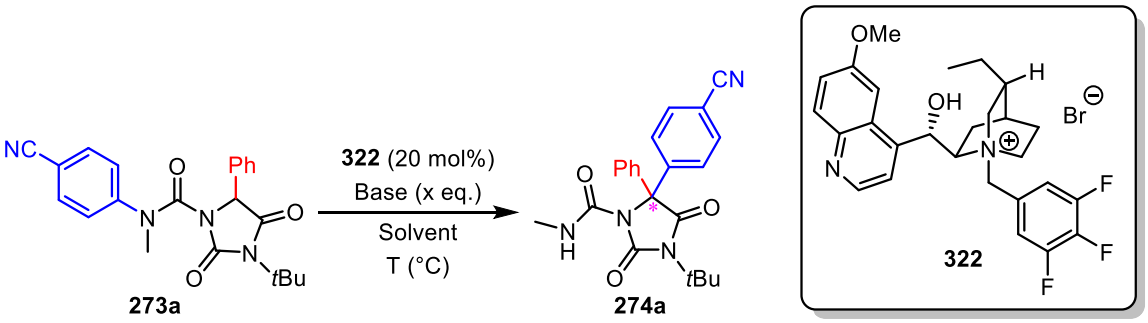
All reactions were carried out in wet chloroform; PTC: 20 mol%.

PTC **322** was used for further optimisation of the reaction conditions (Table 18). The use of the stronger KOH base led to decreased enantioselectivity (Table 18, entry 4 vs 1). Both aqueous and powdered $K_3PO_4.H_2O$ gave no conversion, as observed by ^{1}H NMR (Table 18, entries 5 and 6). Ag_2CO_3 gave no conversion at either −20 or +40 °C (Table 18, entry 7). Changing the solvent to xylene or mesitylene also gave no conversion (Table 18, entries 8 and 9).

It is known from optimisations presented in Table 13, entries 6 and 9 that the use of non-anhydrous solvents enhances enantioselectivity. The influence of water on the reaction was further investigated. Using both anhydrous $CHCl_3$ and Cs_2CO_3 at −20 °C gave no conversion (Table 18, entry 10), indicating that the presence of water was not only relevant to enantioselectivity but also reactivity. Increasing the temperature to −10 °C gave some conversion but with reduced *er* (Table 18, entry 11). Direct addition of water into the reaction (Table 18, entries 12 and 13) made no difference to the enantioselectivity, however, the rate of the reaction was significantly reduced. It appears a minimal amount of water is needed to increase the solubility of the catalyst, hence enhancing the enantioselectivity of the reaction. An excess of water, on the other hand, leads to slow reaction rates due to solvation of the enolate.

[1] Joint work of the author and Dr Rakesh K. Saunthwal
[2] Thanks to Dr Rakesh K. Saunthwal for making PTCs **317** – **319**

Table 18: Further optimisations[1]

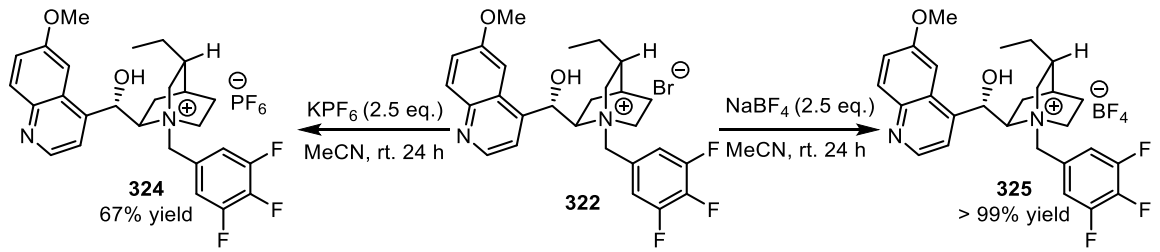


Entry	T (°C)	Solvent	Base	x	Time	Comments	*er*
1	−20	$CHCl_3$	Cs_2CO_3	5	36 h	100% conversion	85:15
2	−10	$CHCl_3$	KOH	3	18 h	Incomplete	70:30
3	−10	$CHCl_3$	KOH	1.2	18 h	100% conversion	77:23
4	−20	$CHCl_3$	KOH	1.2	18 h	100% conversion	77:23
5	−10	$CHCl_3$	$K_3PO_4.H_2O$	3	18 h	No conversion	-
6	−10	$CHCl_3$	$K_3PO_4.H_2O$[a]	2	18 h	No conversion	-
7	−20 – 40	$CHCl_3$	Ag_2CO_3	5	36 h	No conversion	-
8	0	Xylene	Cs_2CO_3	5	22 h	No conversion	-
9	0	Mesitylene	Cs_2CO_3	5	22 h	No conversion	-
10	−20	$CHCl_3$[b]	Cs_2CO_3[b]	5	22 h	No conversion	-
11	−10	$CHCl_3$[b]	Cs_2CO_3[b]	5	23 h	Incomplete	72:28
12	−20	$CHCl_3$[c]	Cs_2CO_3	5	42 h	100% conversion	85:15
13	−20	$CHCl_3$[d]	Cs_2CO_3	5	42 h	100% conversion	85:15

[a] 30% aqueous; [b] Anhydrous; [c] 1µl/10ml($H_2O/CHCl_3$); [d] 3µl/10ml($H_2O/CHCl_3$)

In 2004, Nájera *et al*. reported that the counterion of a cinchona salt could influence the enantioselectivity of a PTC reaction. In their study, the hexafluorophosphate counterion, in particular, gave slightly improved *er* to the bromide counterion.[204] To investigate this effect on the aryl migration, **324** and **325** were made by an anion exchange reaction involving **322** and the respective salts (Scheme 73).

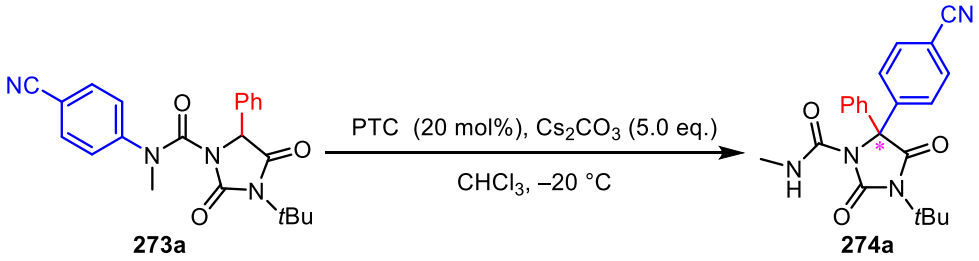
[1] Joint work of the author and Dr Rakesh K. Saunthwal



Scheme 73: Anion exchange synthesis of **324** and **325**[1]

Both **324** and **325** were tested in the aryl migration reaction (Table 19). They both produced the same enantioselectivity as **322**, albeit with a significant reduction in the rate of the reaction. Nájera *et al*. also observed a general reduction in reaction rates with the hexafluorophosphate counterion relative to the bromide counterion. It is imaginable that the ammonium ion is tightly bound to the hexafluorophosphate or tetrafluoroborate counterion, thus leading to slow ion exchange between the PTC and caesium enolate, consequentially leading to slow reaction rates (see PTC mechanism in Scheme 74).

Table 19: Counterion investigation



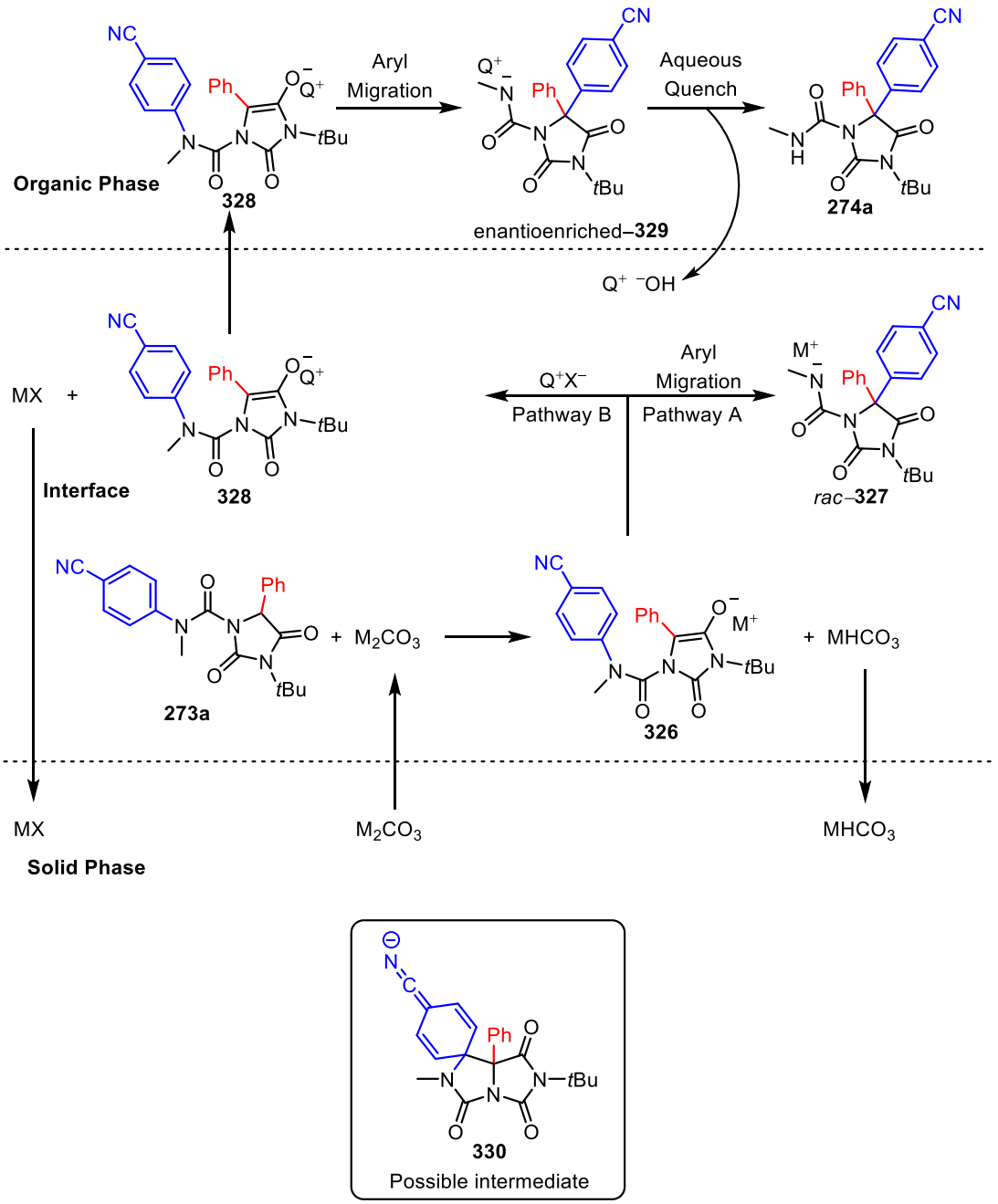
Entry	PTC	Time	Yield (%)	*er*
1	**322**	36 h	(67)	85:15
2	**324**	4 d	33[a]	85:15
3	**325**	2 d	37[a]	85:15

[a] Yields obtained by ^{1}H NMR and compared with hexamethylbenzene internal standard
Wet solvent used; Parenthesis indicate isolated yield

From the optimisation results presented above; and similar reports on PTC rearrangements[205] and solid-liquid PTC,[206] a mechanism is suggested for the PTC rearrangement of hydantoin ureas (Scheme 74). Deprotonation of **273a** by the base (M_2CO_3) occurs at the interface to produce the metal enolate pair **326**. At this stage, there are two possibilities for **326**. The metal enolate **326** could undergo rearrangement directly at the interface, ultimately leading to racemic **274a** (pathway A). Alternatively, **326** could undergo ion exchange with the chiral PTC Q^+X^- to give the chiral ammonium enolate pair **328** (pathway B). The chiral ammonium enolate **328** could undergo

[1] Thanks to Dr Rakesh K. Saunthwal for making PTC **325**

rearrangement directly at the interface or it could migrate to the organic phase, where it rearranges to enantioenriched **329**.



Scheme 74: Proposed mechanism for intramolecular PTC aryl migration; Q^+X^- = quaternary ammonium halide, M = Metal

Finally, an aqueous quench produces the rearranged product **274a** whilst regenerating the catalyst. Rearrangement of **328** in the organic phase would be more favoured than at the interface because the enolate is desolvated on its extraction to the organic phase.[207,208] This probably accounts for the reduction in reaction rate when water was added to the reaction (Table 18, entries 12 and 13). Based on previous studies done in the Clayden group and other nucleophilic aromatic substitution reactions,[160] there is most likely the existence of the dearomatised intermediate **330**, which is

formed from attack of the enolate on the aryl ring in **326** or **328**. Collapse of this intermediate gives **327** or **329**, which gains a proton from the aqueous quench to give **274a**. It is uncertain if the intermediate **330** exists in this reaction. Nonetheless, the presence of this intermediate is feasible as the electron-withdrawing cyano group is able to stabilise **330**.

The mechanism described for this intramolecular PTC arylation is speculative and requires further mechanistic investigations. In intermolecular reactions, where the nucleophile and electrophile are separate molecules (see Scheme 33), the ammonium enolate must migrate to the organic phase to react with the electrophile. As the electrophile is mostly in the organic phase, it is logical that there is minimal or no reaction without the PTC, because the ammonium counterion of the PTC extracts the enolate into the organic phase by formation of an ion-pair with the enolate. In intramolecular reactions, the implication of both electrophile and nucleophile being in the same molecule is that a reaction could happen in the absence of the PTC leading to racemic products even when a chiral PTC is used (Scheme 74, pathway A). This is not the case, as seen in the optimisations presented. In many cases, the rearrangement did not occur or occurred slowly in the absence of the PTC. The formation of enantioenriched products is also evidence that the PTC plays a role in the reaction. Furthermore, reported intramolecular PTC reactions showed that the rates and enantioselectivities of the reactions were influenced by the catalyst.[192,193,209,210] One rationale is that the ammonium enolate **328** exhibits more ionic character than the metal enolate **326**. Hence, rearrangement of the ammonium enolate occurs faster than the metal enolate, thus minimizing uncatalysed rearrangements.[207,211] Another rationale is that the active base carrying out the interfacial deprotonation might not be the metal carbonate **332**, but a chiral ammonium carbonate **333** generated from extraction of the carbonate ion from the metal carbonate **332** (Scheme 75). This rationale was corroborated by studies that showed that quaternary ammonium ions could influence substrate deprotonation by an extraction mechanism.[212–216] In cases where no products were formed in the absence of the PTC, but racemic products were formed in the presence of the PTC, it could be that the PTC aided deprotonation of the substrate but did not have the required structure to induce enantioselectivity in the rearrangements.

Scheme 75: Generation of proposed active base **333**; QX = quaternary ammonium salt, M_2CO_3 = metal carbonate base

In summary, non-polar solvents promoted enantioselectivity but were detrimental to the rate of the rearrangement. Non-anhydrous conditions are required for enhanced enantioselectivities. There was a general reduction in the rate of the reaction, with increasing steric hindrance of catalysts used. The enantioselectivity of the aryl migration is highly sensitive to the structural composition of the cinchona-derived catalyst, as introduction of a fluorine atom to strategic positions of the *N*-benzyl

ring was crucial to enhancing stereodiscrimination. This was probably due to the stereoelectronic effect produced by the fluorine atom at the position. The optimal catalyst was found to be cinchona salts bearing a 3,4,5 or 3,5-perfluorobenzyl substituent, producing an *er* of 85:15 in the migration of a 4-cyanophenyl (Figure 13).

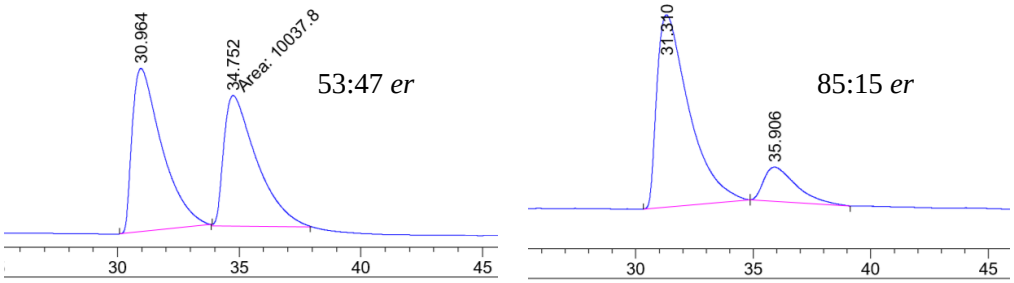
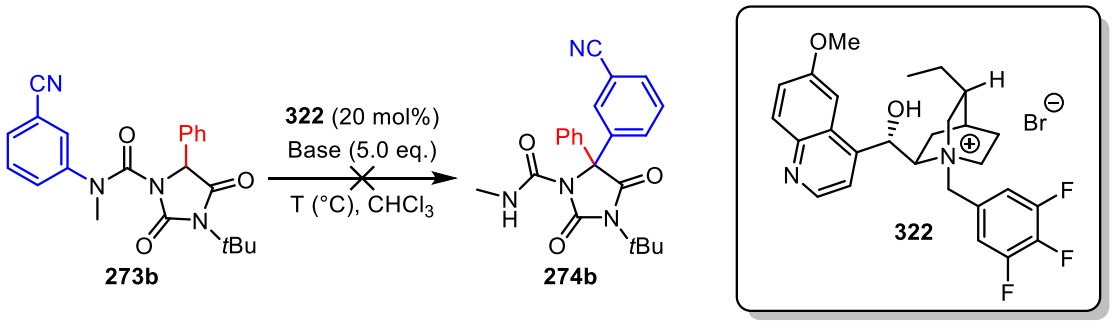


Figure 13: HPLC trace of near-racemic and scalemic **274a**

2.2.4 Attempted Scope for the Aryl migrations

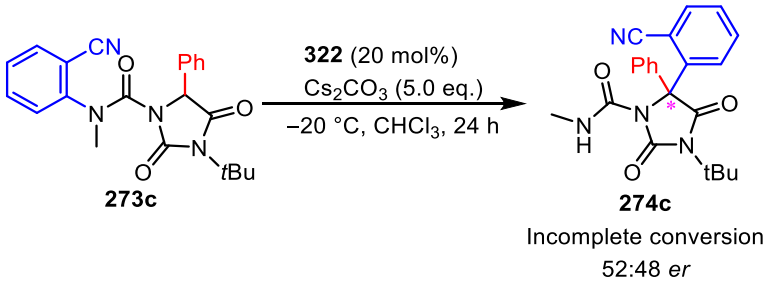
To establish the migratory group tolerance of the phase transfer catalysed aryl migrations, the rearrangement was performed on hydantoin ureas bearing other migratory aryl rings apart from 4-cyanophenyl. The optimal condition: 20 mol% of PTC **322** in non-anhydrous chloroform was used in the reactions.

Table 20: Attempted PTC aryl migration of **273b**



Entry	T (°C)	Solvent	Time	Comments
1	−20	Cs_2CO_3	16 h	No conversion
2	−10	Cs_2CO_3	16 h	No conversion
3	0	Cs_2CO_3	16 h	No conversion
4	rt	Cs_2CO_3	16 h	No conversion
5	40	Cs_2CO_3	16 h	No conversion
6	−20	KOH	16 h	decomposition

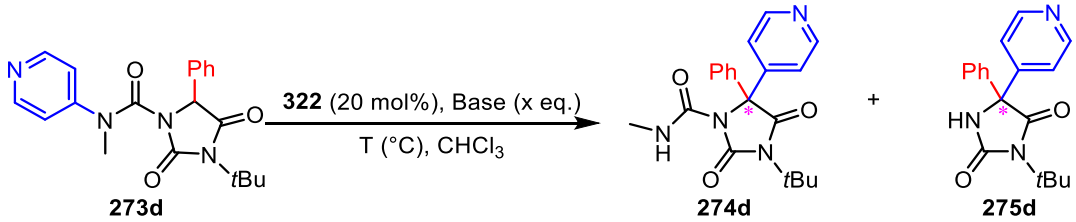
Aryl migration was attempted on hydantoin urea **273b** containing a 3-cyanophenyl migratory ring. Disappointingly, starting material **273b** was observed by ^{1}H NMR when Cs_2CO_3 was used as base at various temperatures (Table 20, entries 1 – 5). The use of KOH at −20 °C only led to decomposition of **273b** to the corresponding *N*-methyl aniline **281b** (Table 20, entry 6). The 3-cyanophenyl ring is probably not electron-deficient enough. A Similar failure to migrate this ring was experienced in earlier optimisations (see Table 7).



Scheme 76: PTC aryl migration of **273c**

Hydantoin urea **273c** bearing a 2-cyanophenyl migratory ring gave incomplete conversion to **274c** after 24 hours (Scheme 76). HPLC analysis of the crude reaction mixture revealed an *er* of 52:48.

Table 21: PTC aryl migration of **273d**

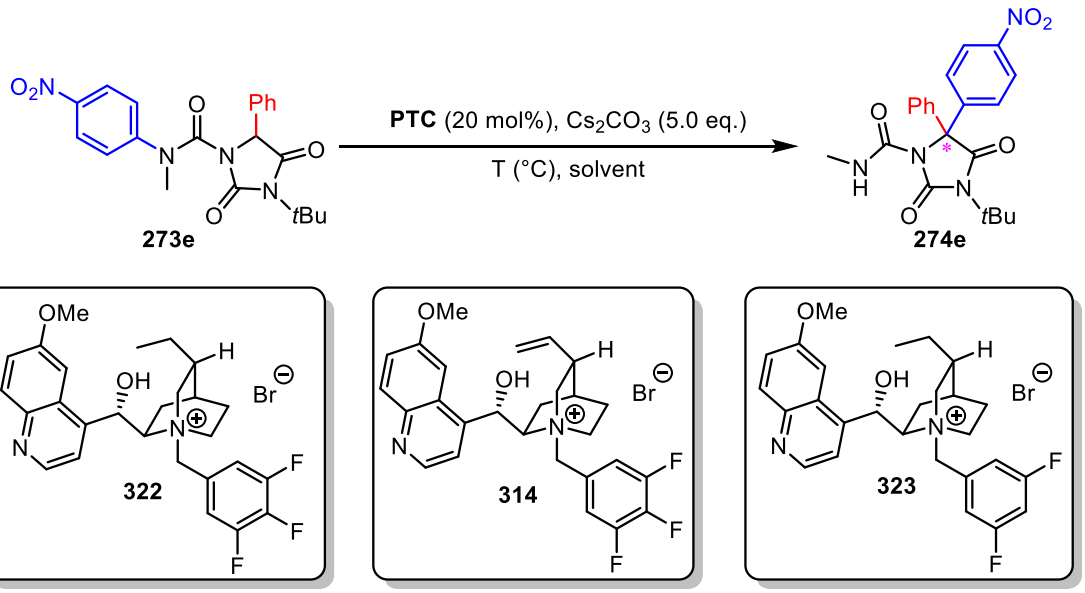


Entry	T (°C)	Base	x	Time	Yield (%)		*er*
					274d	275d	(274d)
1	−20	Cs_2CO_3	5	18 h	0	0	-
2	0	Cs_2CO_3	5	16 h	Incomplete conversion	0	68:32
3	−20	KOH	3	25 h	51	20	70:30

Yields obtained by ^{1}H NMR and compared with hexamethylbenzene internal standard.

Hydantoin urea **273d** bearing an electron-deficient 4-pyridyl group was subjected to the aryl migration reaction (Table 21). No conversion was observed using Cs_2CO_3 as the base at −20 °C (Table 21, entry 1). On warming the reaction to 0 °C (Table 21, entry 2), partial conversion to **274d** was observed by TLC with a crude HPLC analysis revealing an *er* of 68:32. The stronger KOH base gave 51% and 20% conversion to **274d** and **275d** respectively by ^{1}H NMR (Table 21, entry 3); HPLC analysis of **274d** showed a 70:30 enantiomeric ratio.

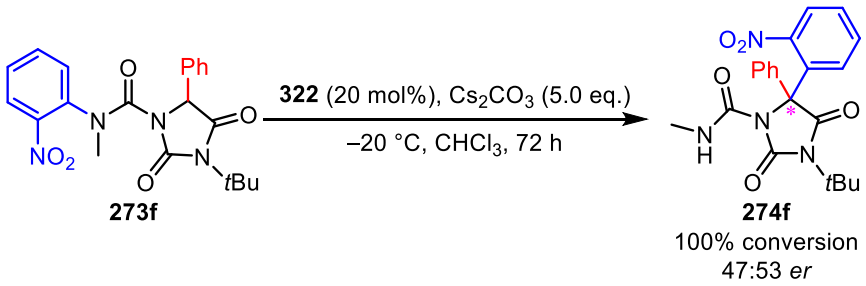
Table 22: PTC aryl migration of **273e**



Entry	T (°C)	Solvent	PTC	Time	Comments	*er*
1	−20	$CHCl_3$	**322**	18 h	100% conversion	55:45
2	−40	$CHCl_3$	**322**	24 h	100% conversion	55:45
3	−40	PhMe:$CHCl_3$[a]	**322**	24h	100% conversion	54:46
4	−40	$CHCl_3$	**314**	23 h	100% conversion	53:47
5	−40	$CHCl_3$	**323**	23 h	100% conversion	53:47

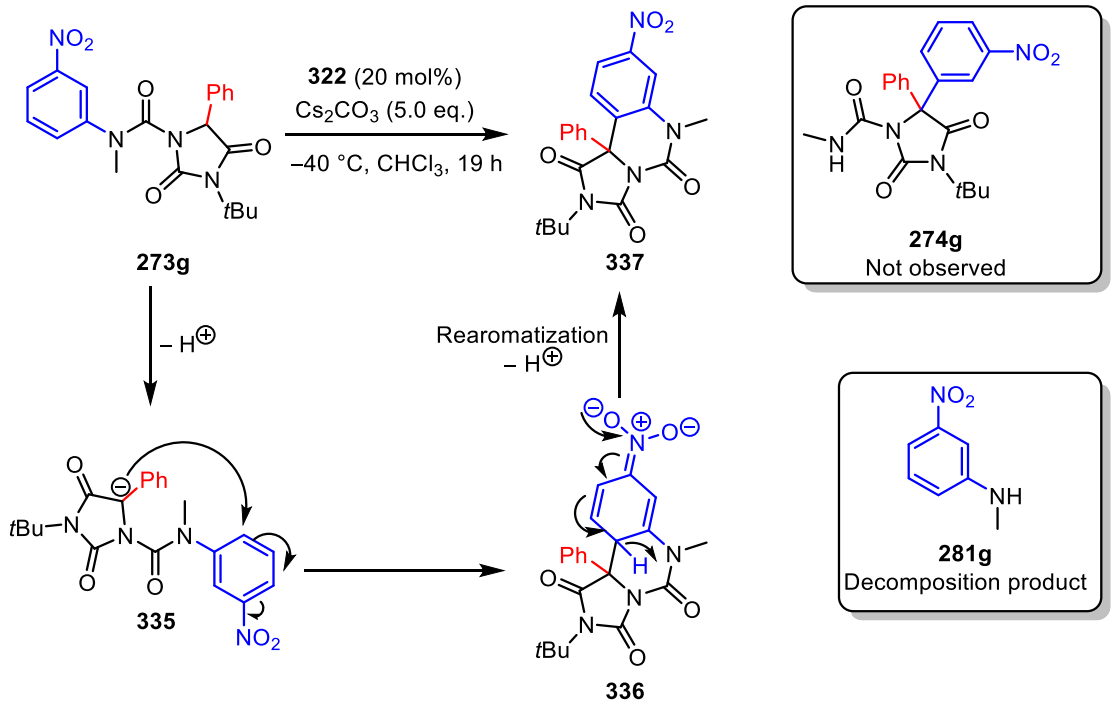
[a] 0.6:0.4 ratio of PhMe:$CHCl_3$

The aryl migration was performed on hydantoin urea **273e** containing a 4-nitrophenyl migratory ring (Table 22). PTC **322** gave 100% conversion to **274e** at both −20 and −40 °C; nevertheless, a poor *er* of 55:45 was obtained in both reactions (Table 22, entries 1 and 2). A change in solvent to a 0.6:0.4 mixture of PhMe:$CHCl_3$ at −40°C made only a minor difference to the reactivity and enantioselectivity (Table 22, entry 2 vs 3). PTC **314** and **323**, which also offered a good *er* of 85:15 in the aryl migration of substrate **273a** in $CHCl_3$ (Table 17, entries 1 and 8), were tested on the aryl migration of **273e** at −40 °C. Both PTCs gave 100% conversion to **274e**; however, a poor *er* of 53:47 was obtained in both cases (Table 22, entries 4 and 5).



Scheme 77: PTC aryl migration of **273f**

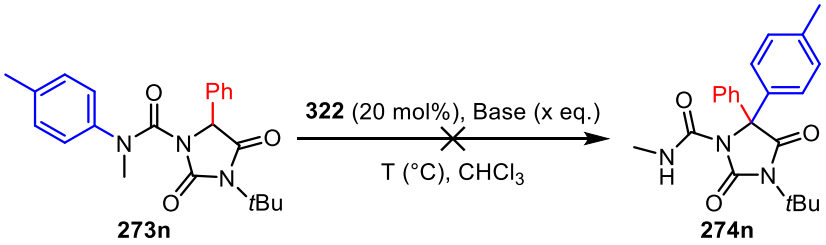
Aryl migration of the 2-nitrophenyl group in hydantoin urea **273f** went on smoothly at −20 °C, with complete conversion to **274f** observed by TLC after 72 hours (Scheme 77). The enantiomeric ratio obtained, however, was poor (47:53). The 4- and 2-nitrophenyl migratory aryl rings are quite electron-deficient. The occurrence of background uncatalysed arylation leading to racemic products is plausible in the migration of these rings.



Scheme 78: Attempted PTC aryl migration of **273g**

Unlike the 4- and 2-nitrophenyl examples, aryl migration was not achieved with the 3-nitrophenyl migrating group (Scheme 78). Instead, attack of the enolate on the *ortho* position of the ring was observed, leading to the dearomatised intermediate **336** that rearomatises to produce the tricycle **337**. It is presumed that this nucleophilic substitution of hydride was likely caused by oxygen in the reaction. Some decomposition of the starting material **273g** to *N*-methyl-3-nitroaniline **281g** was also observed.

Table 23: Attempted PTC aryl migration of **273n**[1]

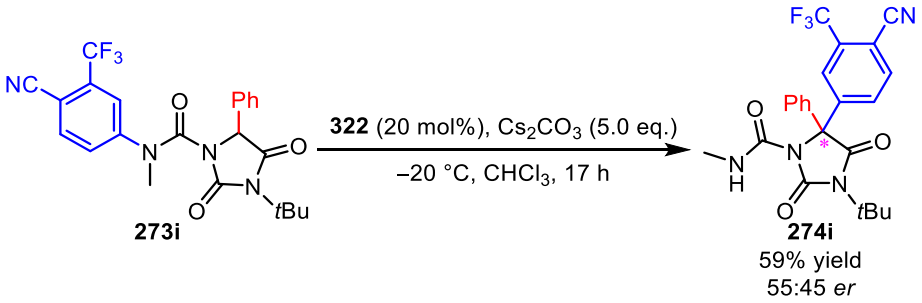


273n **274n**

Entry	T (°C)	Base	x eq.	Time	Comments
1	−20	Cs_2CO_3	5	96 h	No conversion
2	0	Cs_2CO_3	5	24 h	No conversion
3	rt – 40	Cs_2CO_3	5	48 h	No conversion
4	rt	KOH[a]	1.5	20 h	No conversion
5	rt – 40	$CsOH.H_2O$	5	50 h	No conversion

[a] 30% aqueous

The 4-tolyl group of hydantoin urea **273n** failed to migrate under all conditions trialled (Table 23). This is likely due to the 4-tolyl group being electron-rich. Migration of the 4-tolyl group has been reported, but a strong base, KHMDS was used to achieve the transformation.[153]



273i **274i**
59% yield
55:45 *er*

Scheme 79: PTC aryl migration of **273i**

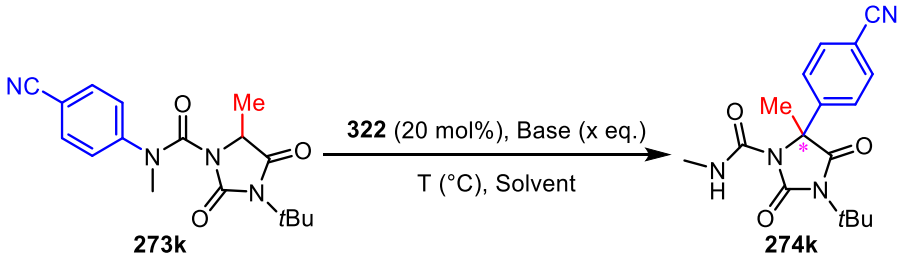
The 3-CF_3,4-CN substituted aryl group in **273i** underwent migration to afford **274i** in a 59% isolated yield; however, the enantioselectivity produced was poor (Scheme 79).

As the PTC **322** seemed to offer good enantioselectivity only in the migration of a 4-cyanophenyl group, alanine-derived hydantoin urea **273k** bearing a 4-cyanophenyl group on the distal urea nitrogen was subjected to the aryl migration conditions (Table 24). As also observed in Table 10, every attempt made to achieve aryl migration of **273k** was not forthcoming. Deprotonation of the less acidic α-proton of **273k** is likely disfavoured because of the instability of the resulting enolate due to the hyperconjugation effect of the methyl group at the α-carbon. Notwithstanding, aryl

[1] Thanks to Dr Rakesh K. Saunthwal for making **273n**

migration within alanine derived ureas have been reported but with the use of strong organic bases for deprotonation of the α-proton.[153,217]

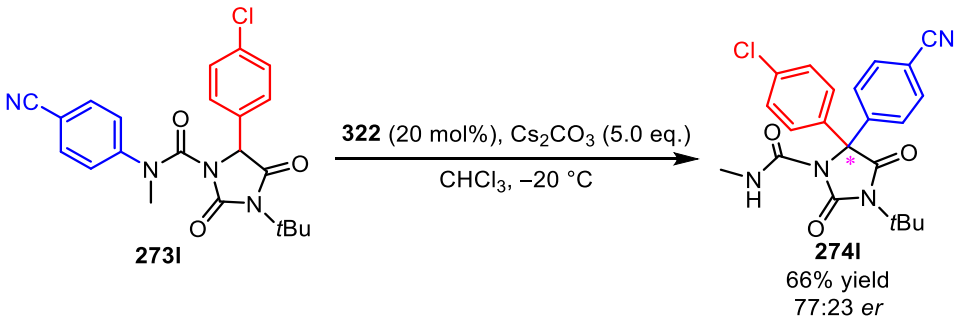
Table 24: Attempted PTC aryl migration of **273k**



Entry	T (°C)	Base	x	Time	Comments	*er*
1	rt	KH	2	18 h	No conversion	-
2	rt – 50	KOH[a]	2	18 h	No conversion	-
3	0 – 50	Cs_2CO_3	5	22 h	trace	-[b]
4	rt	KOH	3	24 h	No conversion	-
5	0	KOH	4	17 h	No conversion	-
6	rt	$CsOH.H_2O$	3	24 h	trace	-[b]

[a] 50% aqueous; [b] Not enough material for an HPLC analysis

To investigate the influence of another enolate stabilising group on the reactivity and enantioselectivity of the aryl migration, hydantoin urea **273l** with a 4-ClC_6H_4 stabilising group on the α-carbon was subjected to the aryl migration reaction (Scheme 80).



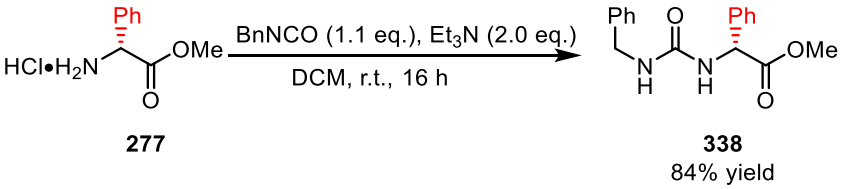
Scheme 80: Aryl migration of **273l**

After 46 h, 66% of **274l** was isolated. Though the yield is similar to that obtained in the aryl migration of **273a**, the rate of reaction for the chlorinated substrate was much faster. TLC analysis of the aryl migration of **273l** after 22 hours showed almost complete consumption of the starting material compared to the aryl migration of **273a** which still showed a significant amount of starting material after 18 hours. As such, this increase in reaction rate can be directly linked to the formation of a more stable enolate. HPLC analysis of **274l** revealed a reduced *er* of 77:23 relative to the *er* of

274a. The reduced enantioselectivity suggests that an electron-withdrawing group on the α-phenyl ring could be detrimental to enantioselectivity. This cannot be ascertained without performing the aryl migration of an hydantoin urea bearing an electron-rich α-aryl substituent.

2.2.5 Alternative Directing Groups

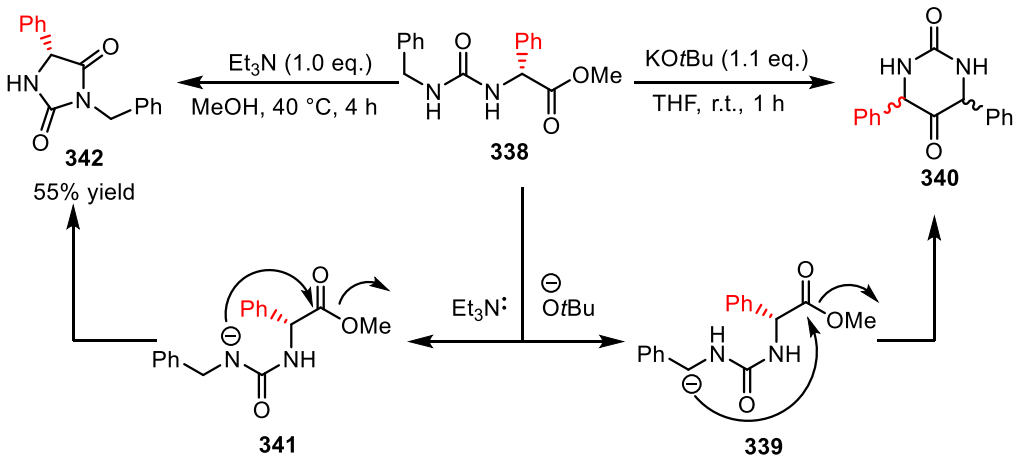
Several hydantoin *N*-protecting groups have been investigated in *N* to *C* aryl migrations within ureas.[152,158] One important factor considered in the choice of protecting groups is the ease of removability. Another factor considered, particularly in asymmetric reactions, is the ability of the protecting group to also act as a directing group to confer selectivity. Amongst many other reasons, the *tert*-butyl is a common protecting group because it is easily removed and is known to enhance stereoselectivity in asymmetric reactions.[41,218]



277 **338** 84% yield

Scheme 81: Synthesis of urea **338**

One alternative to the *tert*-butyl group chosen for investigation is the benzyl group; Methods for removal of the group has been reported.[219–221] Hence it was worth examining if this group would induce a better enantioselectivity than the *tert*-butyl. Following the established procedure, D-phenylglycine methyl ester hydrochloride **277** was treated with benzyl isocyanate to afford the urea **338** in 84% yield (Scheme 81).

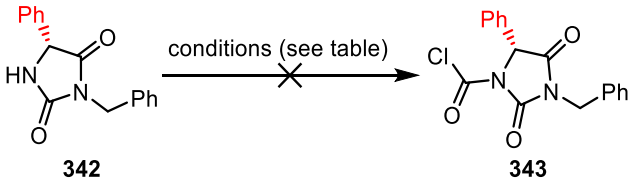


Scheme 82: Synthesis of hydantoin **342**

Treatment of **338** with potassium *tert*-butoxide led to deprotonation of one of the benzylic protons and attack of the ensuing anion **339** at the ester carbonyl, resulting in the six-membered species **340**

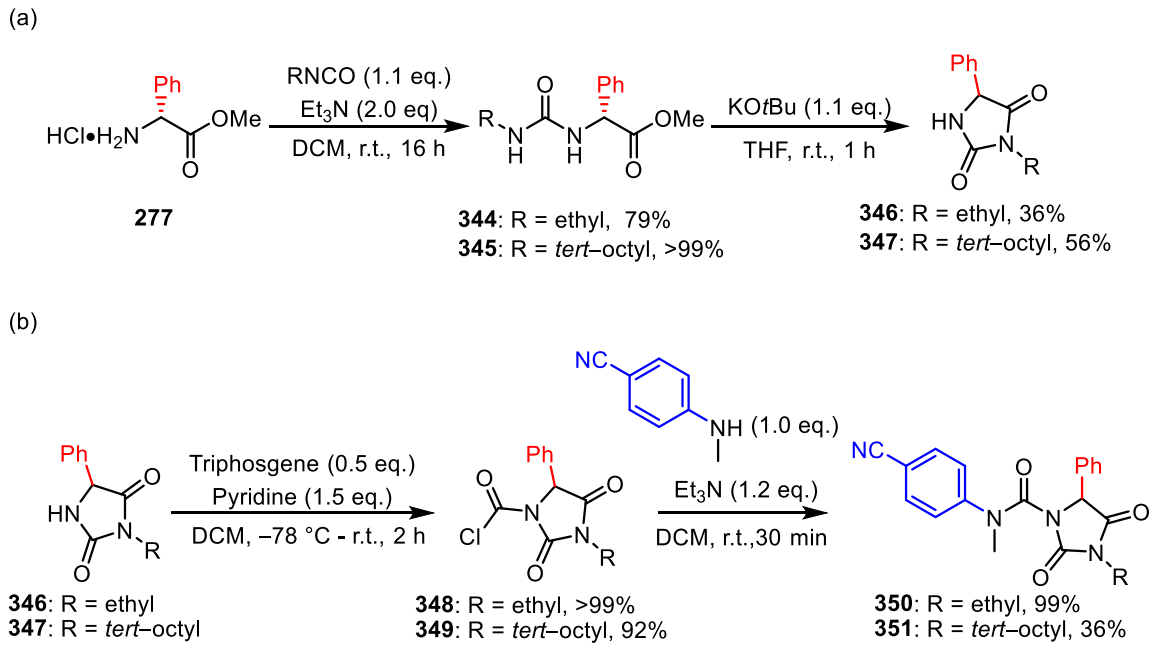
instead of the intended product **342**. Formation of **340** was avoided by treatment of **338** with the milder triethylamine base, affording **342** in a 55% yield (Scheme 82).[222]

Table 25: Attempted acylation of **342**



Entry	T (°C)	Base	Acylating agent	Solvent	Time (h)
1	−78 – rt	Pyridine	Triphosgene	DCM	72
2	0 – rt	Et_3N	Triphosgene	DCM	16
3	0 – 100	Et_3N	Triphosgene	PhMe	16
4	rt	–	Phosgene	THF	3

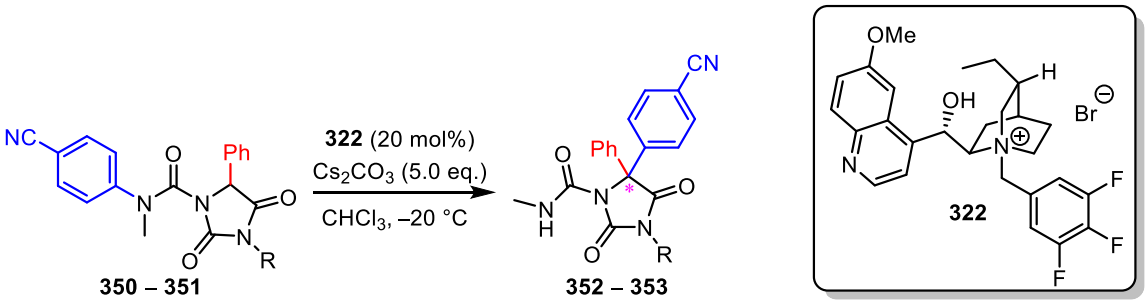
Unfortunately, all attempts to acylate **342** proved unsuccessful. Unreacted **342** was recovered in each case (Table 25). Ethyl and *tert*-octyl are not commonly used directing groups in asymmetric reactions. Nevertheless, they were chosen for further investigation to determine the effect of steric hindrance on the yields and enantioselectivity of the aryl migration. It was anticipated that a bulkier *tert*-octyl group would confer better enantioselectivity than the *tert*-butyl group



Scheme 83: (a) Synthesis of hydantoins bearing an ethyl or *tert*-octyl directing group (b) Synthesis of hydantoin ureas bearing an ethyl or *tert*-octyl directing group

Synthesis of the hydantoin ureas **350** and **351** proceeded smoothly using the established conditions (Scheme 83). The stereochemistry in **346** and **347** is not indicated because racemisation could have occurred in the use of potassium *tert*-butoxide as base. Using the optimal PTC **322**, hydantoin ureas **350** and **351** were subjected to the aryl migration (Table 26). The aryl migration of **350** took place at a comparative rate to substrate **273a**, but the *er* was reduced from 85:15 to 77:23 (Table 26, entry 2). The aryl migration of **351** occurred at a significantly slower rate than **273a**. Incredibly, starting material remained even after the reaction had been left to stir for 144 hours (Table 26, entry 3), owing to the increased steric hindrance of the *tert*-octyl group in **351**. Disappointingly, the *er* induced by the *tert*-octyl group was lower than that induced by the *tert*-butyl group.

Table 26: Aryl migration of **350** and **351**



Entry	Starting material	R	Time (h)	Yield (%)	Product	*er*
1	**273a**	*tert*-Butyl	40	(67)	**274a**	85:15
2	**350**	Ethyl	48	(61)	**352**	77:23
3	**351**	*tert*-Octyl	144	36[a]	**353**	72:28

[a]Yield obtained by ^{1}H NMR and compared with hexamethylbenzene internal standard
Parentheses indicate isolated yields

The optimal PTC **322** seem to be highly substrate-specific producing good stereodiscrimination only for the migration of a 4-cyanophenyl and 4-pyridyl. The fact that **322** is stereoselective only for the migration of these rings implies that one of the sites of interaction of the catalyst with the hydantoin ureas **273** is the fragment E (Figure 14). The implication of this is that a PTC optimisation would be required for each change in the migratory aryl ring. The PTC **322** likely interacts with the fragment E by π-π stacking, C-H/π interactions or by hydrogen bonding between the hydroxyl fragment B and the nitrogen of the cyano substituent. Other plausible interactions between the PTC and **273** are hydrogen bonding between the fragment B and any of the carbonyls (fragment F or G); C-H/π interaction between the *ortho*-H in fragment D and the arene fragment E or H, this would account for why racemic products were obtained with *ortho*-fluoro *N*-benzyl analogues of **322**; An unclassical C–H···O hydrogen bond interaction between the OMe of fragment A and the aromatic hydrogens of **273**,[223] this might account for the slight loss in enantioselectivity when PTC **309** was

used in the aryl migration as opposed to PTC **315** (Table 13, entries 1 vs 7); and electrostatic attraction between the ammonium ion (fragment C) and the enolate (fragment I).

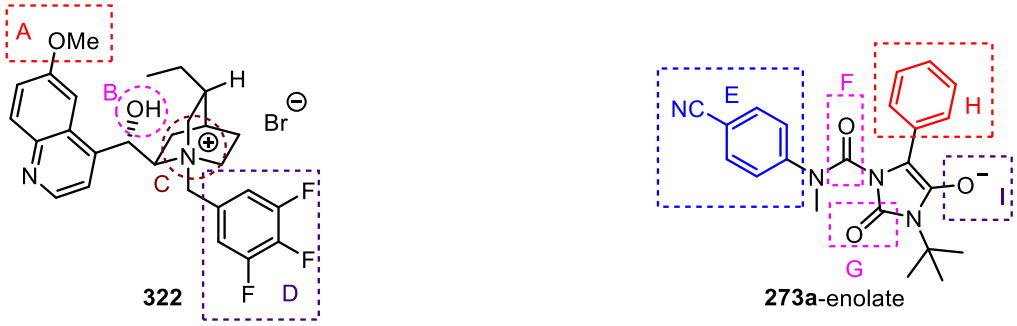


Figure 14: Proposed interaction sites between the PTC and the enolate

It is remarkable how the introduction of fluorine substituents on the *N*-benzyl ring of the cinchona salt led to a dramatic rise in the enantioselectivity. The high electronegativity of the fluorine atom makes the C-F bond highly polarised. As a result of this, the fluorine atom of the C-F bond can engage in dipole-dipole and charge-dipole electrostatic interactions. In addition, the highly polarised C-F bond leads to a hyperconjugation effect due to the low energy $\sigma^*_{C\text{-}F}$ antibonding orbital accepting electron density from adjacent non-bonding electron pairs. The interactions and hyperconjugation effect produced by the presence of fluorine in a molecule can significantly stabilise one transition state or reactive intermediate conformation over another, thus leading to good stereodiscrimination in asymmetric reactions.[200,224] It is uncertain why the fluorine substituents had to be on specific positions of the *N*-benzyl ring for good stereodiscrimination to occur. It could be that the stereoelectronic and electrostatic effects of the fluorine atom is more pronounced at certain positions of the *N*-benzyl ring.

2.2.6 Conclusion and Future Work

The investigations have shown that *N* to *C* aryl migration in ureas under the mild conditions of phase transfer catalysis is achievable. An acidified α-proton, hence the use of α-phenyl substituted hydantoin ureas; and migratory aryl groups bearing electron-withdrawing substituents are important features for these reactions to occur. This is likely due to the mild basic conditions used. The rearrangement also shows potential for enantioselectivity with the migration of a 4-cyano and 4-pyridyl giving an *er* of 85:15 and 70:30, respectively.

Future work should focus on varying the electronics of the cinchona catalyst at the *N*-benzyl position (Figure 15). Previous studies by other authors (see section 1.3.5) showed that H-atom acceptors at the *ortho* position of the *N*-benzyl ring were crucial to obtaining good enantioselectivities in the α-alkylation of amino acids; Cinchona catalysts bearing a 2-fluorophenyl (**140**), *N*-oxy-2-pyridyl (**144**) or 2-cyanophenyl (**146**) gave significantly higher enantioselectivities

than analogues bearing the H-atom acceptor at other positions of the aryl ring.[225] The opposite was observed in the studies presented in this work – cinchona catalysts bearing a 2-fluoro substituent on the *N*-benzyl ring gave poor enantioselectivities while those bearing a fluorine at the *meta* and *para* position i.e. 3,5- or 3,4,5-perfluoro substitution on the *N*-benzyl ring gave good enantioselectivities.

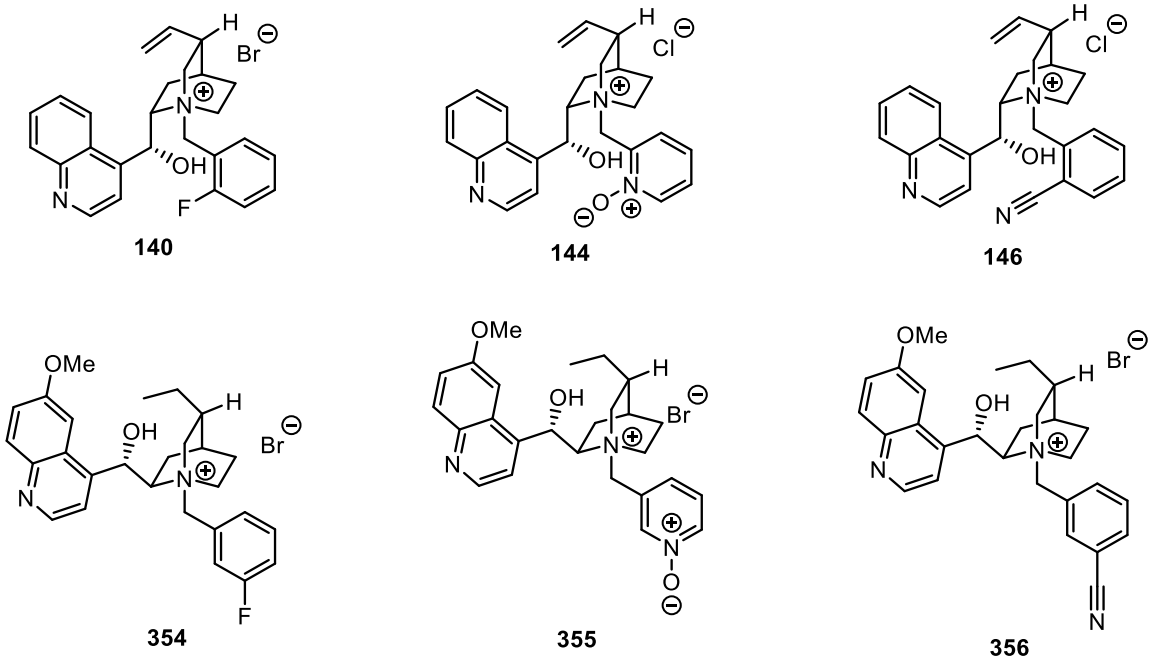


Figure 15: Varying the electronics of cinchona-based PTCs

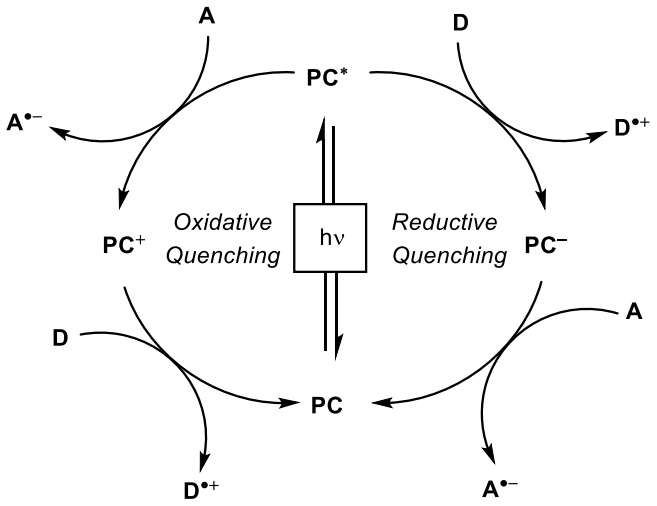
It is worth investigating the effect of the 3-substituted cinchona-derived salts **354**, **355** and **356** on the enantioselectivity of the aryl migrations. The *meta* substituted *N*-benzyl cinchona derivatives **354**, **355** and **356** can easily be made by the reaction of quinidine with the respective arylmethyl halides (see Scheme 70). The *para* substituted analogues of **354**, **355** and **356** could be investigated as well to determine if the enantioselectivity induced by the optimal PTC **322** is a joint contribution of having a fluorine substituent on both the *meta* and *para* position.

The scope of the reaction should also be broadened to include other migratory arenes such as doubly substituted and heterocyclic arenes. Catalyst and base optimisations would likely be required for each reaction substrate. Additionally, conditions for hydrolysis of the aryl migration products **274** or **275** to the respective amino acids would have to be investigated.

2.3 Photoredox-Catalysed Alkylarylation of Dehydroalanine Derivatives for the Preparation of Enantiopure α-Quaternary Amino Acids

2.3.1 Introduction

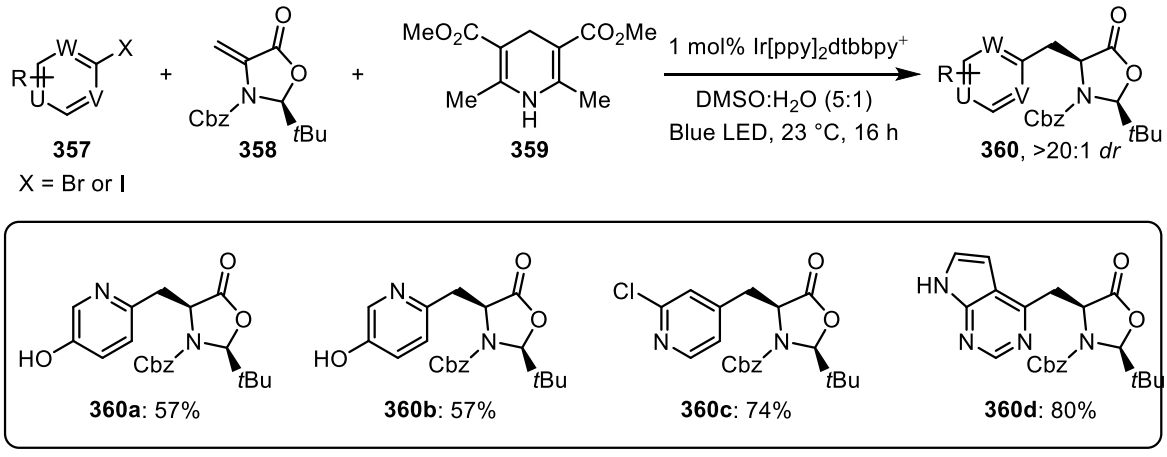
Photoredox Catalysis is a process in which a photocatalyst (PC) gets excited by absorption of photons of light and in this excited state becomes able to facilitate chemical transformations by engaging in single electron transfer with organic or organometallic compounds.[226] Metal polypyridyl complexes and organic dyes have been found to absorb visible light and convert it to chemical energy. These molecules can behave both as an oxidant and a reductant in the excited state, hence they have been widely used as PCs to effect several chemical transformations under mild reaction conditions, which would not have be attainable by alternative two electron transformation pathways.[227–232] A PC induced chemical transformation can follow either an oxidative or reductive quenching cycle, depending on what happens to the excited PC (Scheme 84). The first step in the catalytic cycle is the excitation of the PC by absorption of light. The excited PC is remarkable, in that it is both more oxidizing and reducing than the corresponding ground state PC. In the oxidative quenching cycle, the excited photocatalyst $\mathbf{PC}^{*}$ is oxidised by transferring an electron to an acceptor molecule **A**. This results in the generation of the radical anion $\mathbf{A}^{\bullet-}$ and the oxidised photocatalyst $\mathbf{PC}^{+}$. To complete the catalytic cycle, $\mathbf{PC}^{+}$ is reduced by accepting an electron from a donor molecule **D**. This leads to formation of the radical cation $\mathbf{D}^{\bullet+}$ and regeneration of the ground state **PC**. Alternatively, in the reductive quenching cycle, $\mathbf{PC}^{*}$ is reduced by accepting an electron from a donor molecule **D**. The products of this electron transfer are the radical cation $\mathbf{D}^{\bullet+}$ and the reduced photocatalyst $\mathbf{PC}^{-}$. The catalytic cycle is closed by transfer of an electron from $\mathbf{PC}^{-}$ to an acceptor molecule **A**, thus producing the radical anion $\mathbf{A}^{\bullet-}$ and regenerating the ground state **PC**. The ability of the excited **PC** to be quenched by either oxidation or reduction is defined by the standard reduction potentials. In the oxidative quenching cycle, the excited **PC** must have a lower reduction potential (propensity to be reduced) than the acceptor molecule **A**, while in the reductive quenching cycle, the excited **PC** must have a higher reduction potential than the donor molecule **D**.[233,234]



Scheme 84: Oxidative and reductive pathways of PCs

A photoredox reaction could be net reductive, where the presence of a stoichiometric amount of an electron donor leads to net reduction in the reaction or it could be net oxidative, where the presence of a stoichiometric amount of an electron acceptor leads to net oxidation in the reaction. It could also be redox neutral where both oxidation and reduction occur at various stages of the reaction, resulting in no net change in oxidation state.[234]

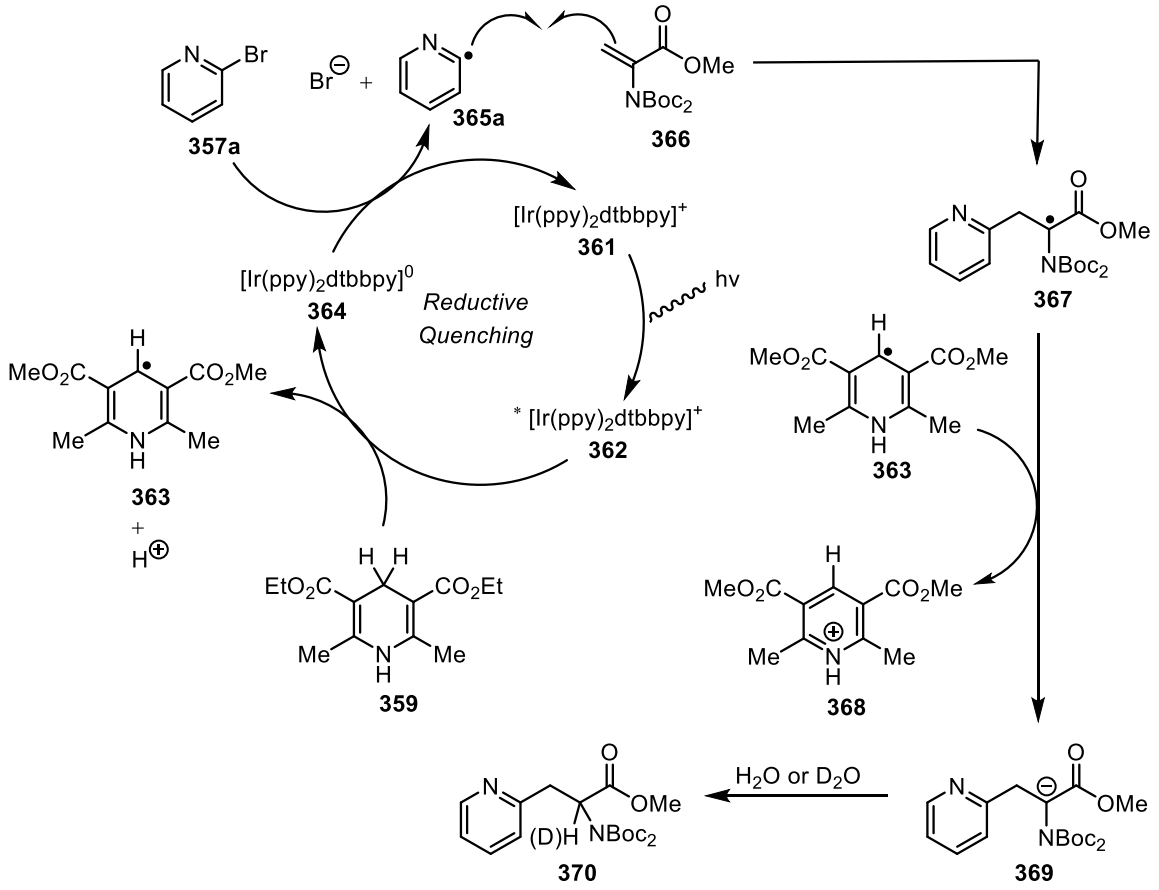
Recent advances in the use of photoredox catalysis in organic chemistry has led to the development of several synthetic transformations,[235–237] one of which is the addition of radicals to olefins.[238–240] Dehydroalanine (Dha) derivatives such as **358** are potent radical acceptors; conjugate addition of radicals to Dha derivatives have been used to access a variety of unnatural amino acids which can potentially be used in the synthesis of new bioactive peptides.[241,242]



Scheme 85: Conjugate addition of heteroaryls to a Dha derivative

In 2017, Jui *et al*. disclosed the first radical approach to heteroaryl amino acids through conjugate addition to a Dha derivative (Scheme 85).[243] The $[Ir(ppy)_2(dtbbpy)PF_6$-mediated addition of heteroaryl radicals, derived from **357**, to the Dha derivative **358** was performed using Hantzsch

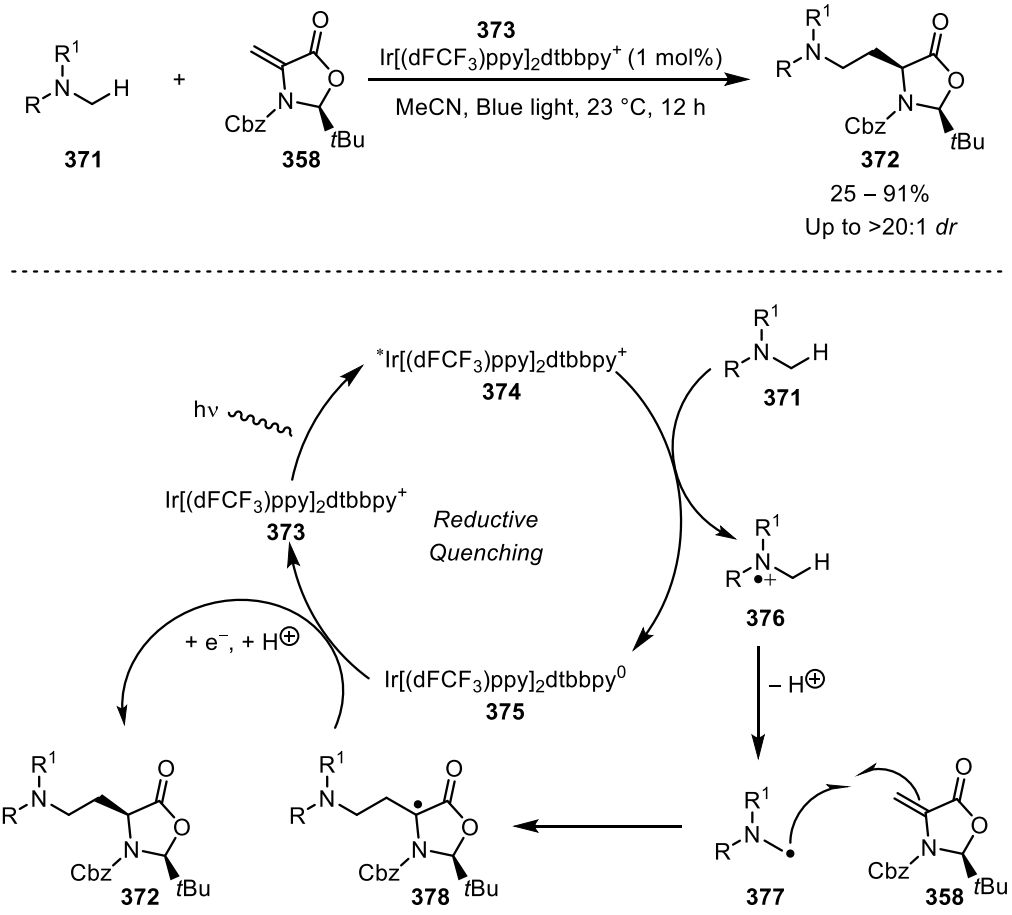
ester **359** as terminal reductant. It was found that 1 mol% of the iridium PC and 1.5 equivalents of the Hantzsch ester in aqueous DMSO was able to promote conjugate addition of heteroaryl radicals to the electron-poor alkene **358** upon irradiation with visible light. The amino acid derivatives **360** were obtained in good yields and diastereoselectivity in favour of the energetically stable *cis*-isomer. Hydrolysis of **360a** afforded the free amino acid in 98% yield and 97% *ee*. The reaction was also applicable to a variety of acyclic Dha derivatives and several electron-deficient and rich halopyridines and pyrimidines, exhibiting good regiospecificity and chemoselectivity. No reaction occurred in the absence of light, the Hantzsch ester or the PC. Stern-Volmer quenching studies revealed that of the components **357**, **358** and **359** present in the reaction, the Hantzsch ester **359** was the most significant excited state quencher, hence it was not surprising that no product was afforded in the absence of the Hantzsch ester. The process is net reductive and a proposed mechanism using the acyclic Dha derivative **366** is detailed in Scheme 86.



Scheme 86: A proposed mechanism for conjugate addition of heteroaryl radicals to a Dha derivative

As with all photoredox reactions, the mechanism starts with absorption of visible light by the PC **361**, resulting in promotion of the PC from the ground state to the excited state **362**. The excited state PC gets quenched by single electron transfer from Hantzsch ester **359**, resulting in the oxidised species **363** and the reduced PC **364**. The reduced PC is a strong reductant ($E_{1/2} = -1.51$ V),[244] hence

it transfers an electron to the bromo-heteroarene **357a** causing mesolytic cleavage to give the bromide ion and the heteroaryl radical **365a**. The ground state PC **361** is regenerated in this step. The heteroaryl radical **365a** behaves as a nucleophile in aqueous DMSO.[245] It undergoes radical conjugate addition to **366**, providing the reactive radical **367**, which on single electron transfer from **363** is reduced to the enolate **369**. Evidence for **369** was shown using D_2O as co-solvent instead of H_2O. The amino acid derivative **370** was revealed with 94% deuterium incorporation in the α-proton.

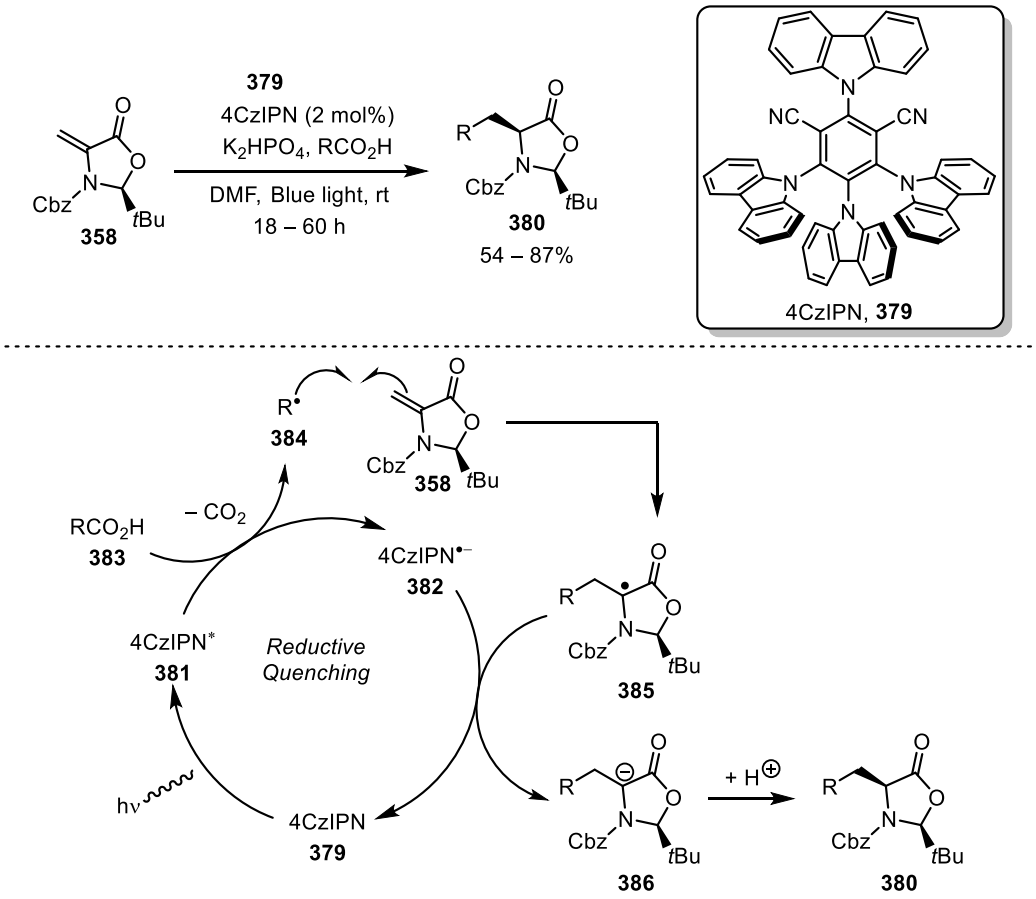


Scheme 87: Addition of α-aminoalkyl radicals to a Dha derivative

The same authors later reported the redox neutral addition of α-aminoalkyl radicals to **358** catalysed by the iridium-based PC Ir[(dFCF$_3$)ppy]$_2$dtbbpy$^+$ **373** (Scheme 87).[242] The amine **371** was capable of directly reducing the excited state PC **374** to obtain the amine radical cation **376** and the reduced PC **375**. The amine radical cation **376** is deprotonated at the α-position to give the α-aminoalkyl radical **377**.[246,247] α-Aminoalkyl radicals are potent nucleophiles,[234] **377** undergoes conjugate addition to **358** to obtain the radical **378**. Reduction of **378** by **375** regenerates the ground state PC **373** and subsequent protonation provides **372**. The adducts **372** were generally obtained in good yields. In most cases the products were formed with complete regio and diastereocontrol. The

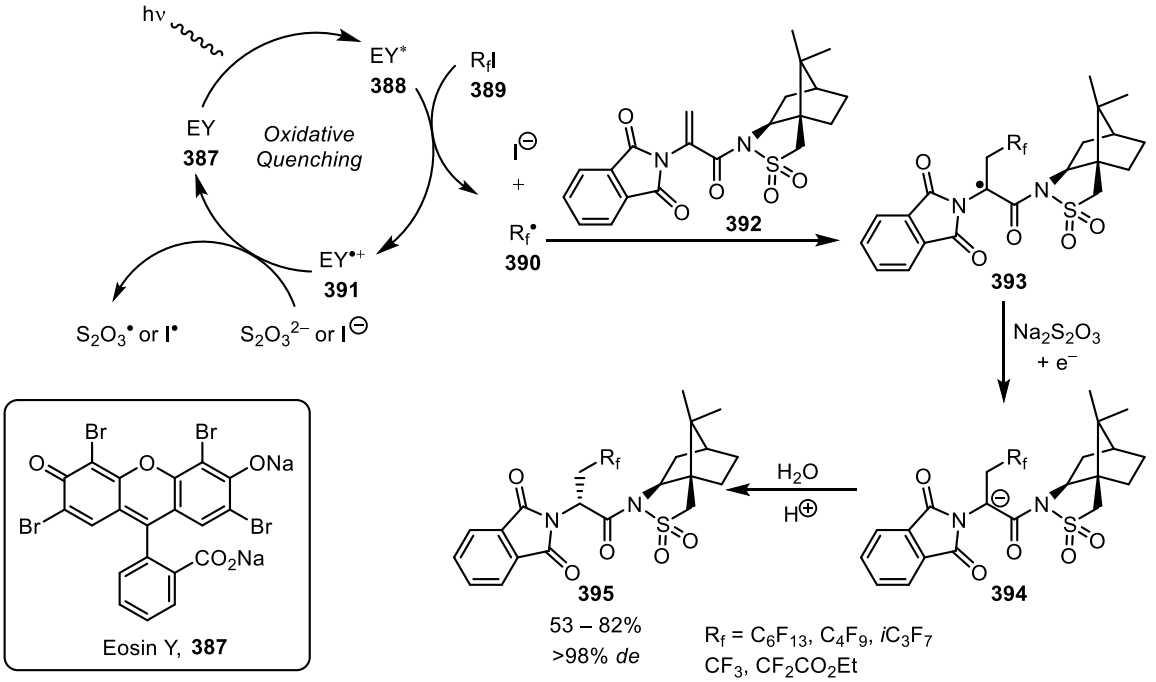
reaction was tolerant of both electron-withdrawing and donating groups as substituents on the amine nitrogen.

More recently, Schubert *et al*. disclosed the visible light-mediated addition of carboxylic acid derived alkyl radicals to **358** using the non-metal based PC 4CzIPN (**379**) (Scheme 88).[248] It was found that 2 mol% of the PC was sufficient, upon irradiation with visible light, to promote efficient addition of alkyl radicals to **358**. The K_2HPO_4 base was needed to promote deprotonation of the carboxylic acid. Control reactions revealed that light, the PC, and the base were necessary for the reaction to occur. As with all the mechanisms discussed above, the reaction follows a reductive quenching pathway. Photoexcitation of **379** generates the oxidizing species **381**, which is subsequently reduced to **382** by a single electron transfer from the carboxylic acid **383**. This single electron transfer causes the acid to expel CO_2 and, in the process, produce the radical **384**. Conjugate addition to **358** by the radical **384** affords the radical adduct **385**, which is reduced by **382** to the enolate **386**. The enolate is finally protonated to afford the products **380**.[249] The products **380** were formed in good yields and as the single *cis*-diastereoisomer. Functional groups like esters, ketones, ethers, amines, and aromatics on the alkyl radical were well tolerated. Sterically hindered alkyl radicals like the adamantyl radical were also well tolerated.



Scheme 88: Decarboxylative radical conjugate addition to a Dha derivative

Yajima and Ikegami described a procedure for the stereoselective addition of perfluoroalkyl radicals to a Dha derivative using Eosin Y **387** as the PC (Scheme 89).[250] By coupling a chiral auxiliary to the Dha derivative (as seen in **392**), the highly diastereoselective hydroperfluoroalkylation of **392** was achieved by using 1 to 5mol% of the PC. 5 equivalents of aqueous sodium thiosulfate was employed as the terminal reductant and acetonitrile as solvent. The mechanism was proposed to go through an oxidative quenching pathway. Single electron oxidation of the photoexcited PC **388** by the perfluoroalkyl iodide **389** generated the perfluoroalkyl radical **390** and the oxidised PC **391**. Addition of **390** to **392** produced the radical **393**, which was reduced to the enolate **394** by sodium thiosulfate. On the basis that quenching with D_2O gave the product **395** with 66% α-deuterium incorporation, it was deduced that protonation of the enolate **394** was achieved by water in the reaction. Meanwhile, single electron reduction of **391** by either sodium thiosulfate or iodide regenerated the ground state PC **387** and closed the catalytic cycle. The authors submitted that iodine radical transfer to **393** was unfavourable because the radical **393** was stable and sterically hindered.

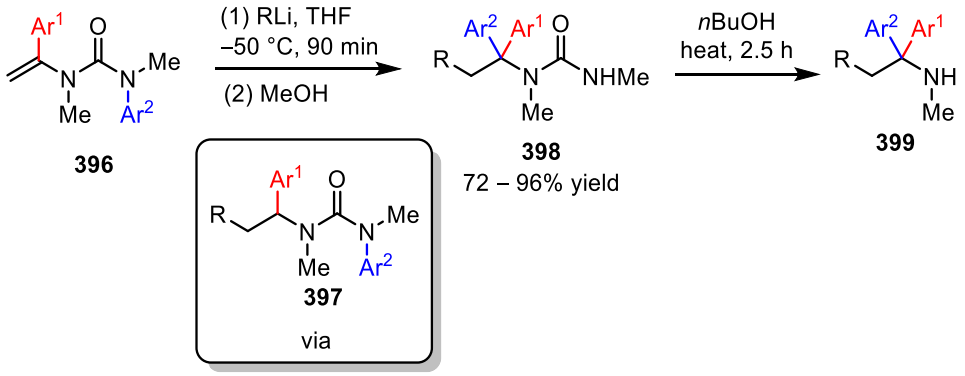


Scheme 89: Hydroperfluoroalkylation of a chiral auxiliary coupled Dha derivative via an oxidative quenching pathway

The above reactions represent examples of tertiary amino acid synthesis through radical conjugate addition to Dha. No example yet exists in the literature for the synthesis of quaternary amino acids through this method. Perhaps the unusual reactivity of metallated ureas could be exploited in bridging this gap through photoredox radical conjugate addition and subsequent aryl migration in *N*'-aryl-urea Dha derivatives.

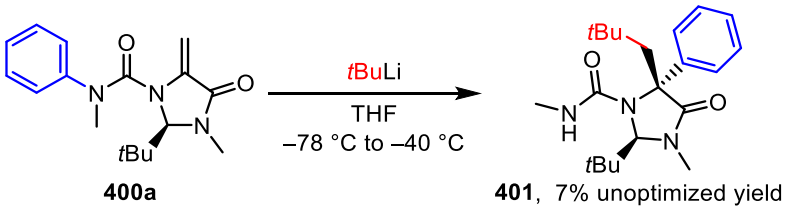
2.3.2 Project Proposal

In 2010, Clayden and co-workers reported the α-arylation of amines by carbolithiation and concomitant rearrangement in vinyl ureas (Scheme 90).[251] The reaction allowed 1,2 alkylarylation of vinyl ureas **396** affording α,α-diaryl quaternary amines **399** on hydrolysis. Both carbolithiation and aryl migration were possible with organolithiums such as *n*BuLi, *s*BuLi, *i*PrLi, PhLi and CH_2=CH_2Li. However, with the bulky *t*BuLi, only carbolithiation was observed.



Scheme 90: Carbolithiation and subsequent aryl migration of vinyl ureas

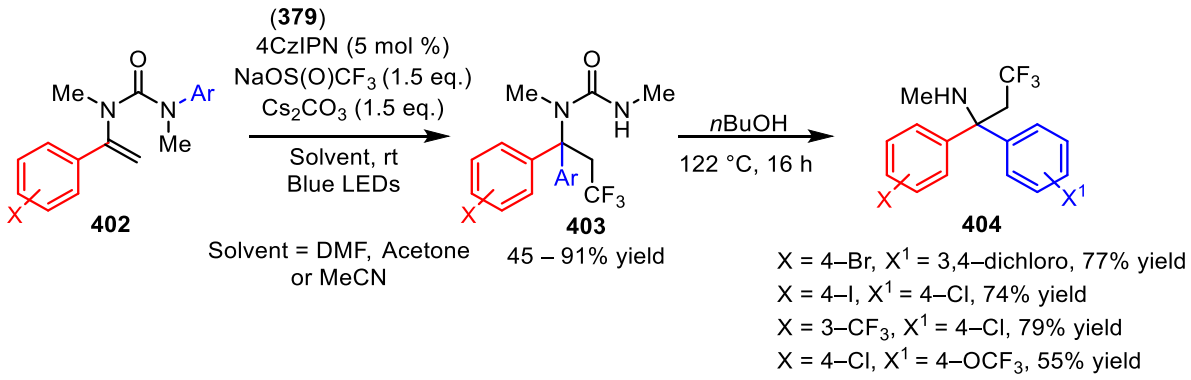
Due to the success of the carbolithiation and ensuing aryl migration in vinyl ureas **396** (Scheme 90), the Clayden group attempted the carbolithiation and aryl migration of tertiary amino acid-derived imidazolidinone vinyl urea **400a** (Scheme 91).[252] The addition of several organometallics to the vinyl urea **400a** was unsuccessful. Surprisingly, with *t*BuLi, addition to the vinyl accompanied by aryl migration occurred affording the arylation product **401** in a yield of 7%.



Scheme 91: Carbolithiation and subsequent aryl migration of imidazolidinone vinyl ureas

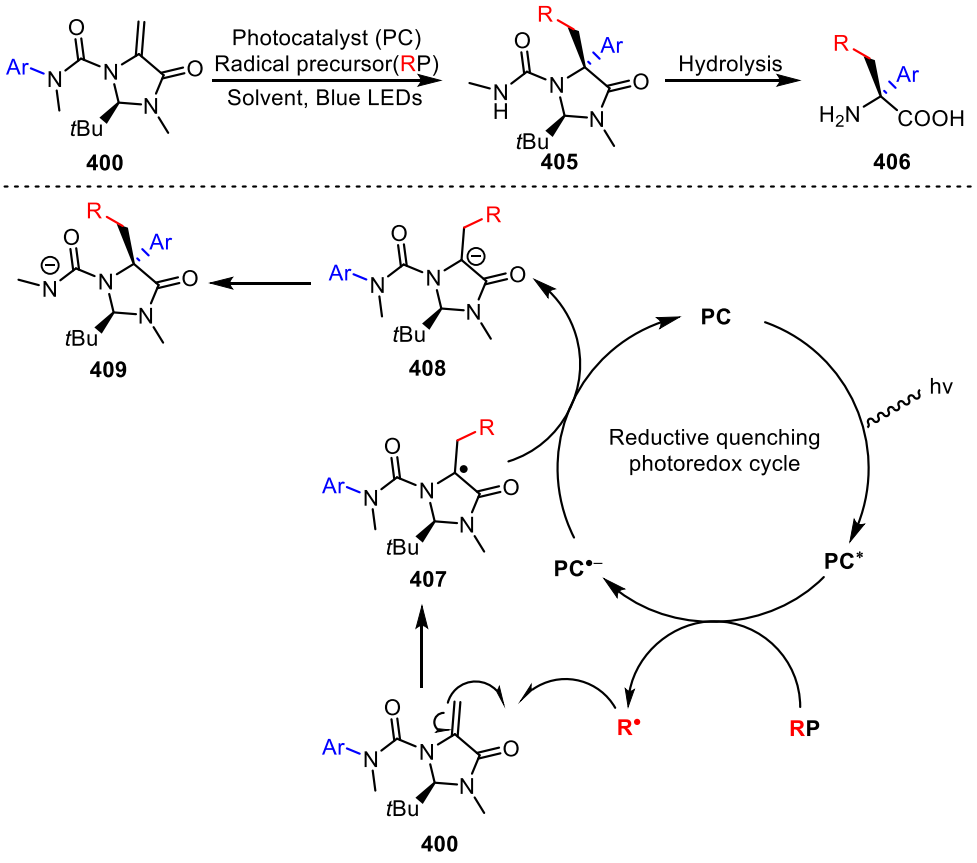
More recently, Clayden and Abrams reported the alkylation with subsequent aryl migration of non-amino acid-derived vinyl ureas, by photoredox catalysis (Scheme 92).[253] Practically, this method uses the organo PC 4CzIPN (**379**) to facilitate the redox cycle and utilises sodium sulfinate radical precursors to yield α-quaternary ureas **403**, which may be simply converted into α-quaternary amines **404** by solvolysis. The proposed mechanism of this photoredox alkylarylation starts with photo excitation of 4CzIPN, which then facilitates the oxidative decomposition of sodium sulfinate salts, generating electrophilic radical that in turn add into the electron-rich olefin of vinyl ureas. After radical addition, a benzylic stabilised radical is formed, which is then reduced to an α-

metallated urea by the radical anion of 4CzIPN formed in sodium sulfinate decomposition, closing the photoredox cycle. The newly formed α-metallated urea then undergoes *N* to *C* aryl migration, delivering an alkylarylation.



Scheme 92: Photoredox catalysed *N* to *C* aryl migration in vinyl ureas

It was envisaged that merging the imidazolidinone SRS protocol (see section 1.3.2) with photoredox catalysis in urea Dha derivatives might provide a useful means of accessing enantiopure α-aryl quaternary amino acids under mild conditions (Scheme 93). In addition, both side chains of the newly formed α-aryl quaternary amino acid would not be limited to the commercially available enantiopure tertiary amino acids.

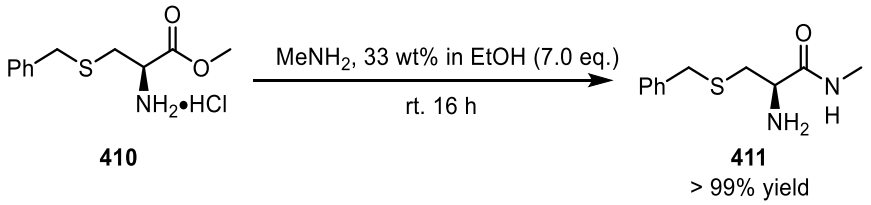


Scheme 93: Project proposal

A suggested mechanism for the proposed addition and ensuing aryl migration in imidazolidinone vinyl urea Dha derivatives is illustrated in Scheme 93. Excitation of the **PC** by visible light occurs to produce the excited photocatalyst **PC***. The excited **PC** is quenched by accepting an electron from the radical precursor **RP**, resulting in formation of the radical **R**$^{\bullet}$ and the reduced photocatalyst **PC**$^{\bullet-}$. The radical **R**$^{\bullet}$ undergoes radical attack on the vinyl urea **400** resulting in the formation of the C-centred radical **407**. In a radical polar cross-over pathway, **407** accepts an electron from the reduced photocatalyst PC$^{\bullet-}$ producing the enolate **408** and recovering the **PC**. The enolate **408** then undergoes intramolecular nucleophilic attack on the *N*-aryl ring leading to transfer of the aryl ring from the nitrogen to the α-carbon resulting in the new quaternary centre in **409**.

2.3.3 Synthesis of Imidazolidinone Vinyl Ureas

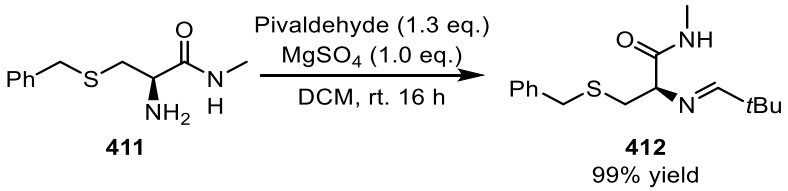
Using a synthetic route established within the Clayden group,[160] the imidazolidinone vinyl ureas were made. (*S*)-benzyl-L-Cysteine methyl ester hydrochloride **410** was reacted with methylamine to afford the methylamide **411** (Scheme 94).



410 **411**
> 99% yield

Scheme 94: Synthesis of methylamide **411**

Condensation of **411** with pivaldehyde produced imine **412** (Scheme 95). The reactions affording the methylamide **411** and imine **412** were quantitative and had no need for further purification.

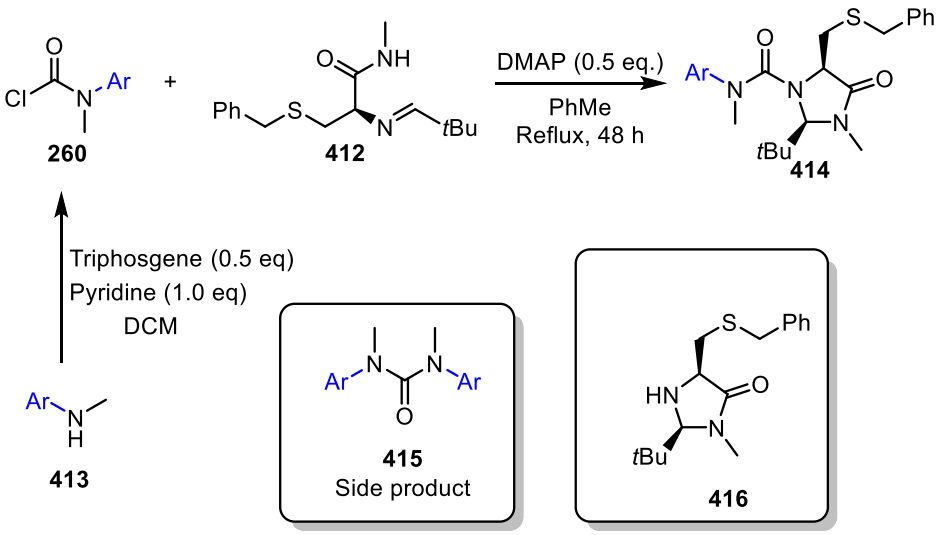


411 **412**
99% yield

Scheme 95: Synthesis of imine **412**

Reaction of **412** with the desired carbamoyl chloride **260**, obtained from phosgenation of the corresponding *N*-methyl aniline **413**, led to the formation of the imidazolidinone urea **414**, in which the *S*-benzyl group of the starting amino acid lies *cis* to the *tert*-butyl group (Table 27).[160]

Table 27: Synthesis of imidazolidinone ureas **414**

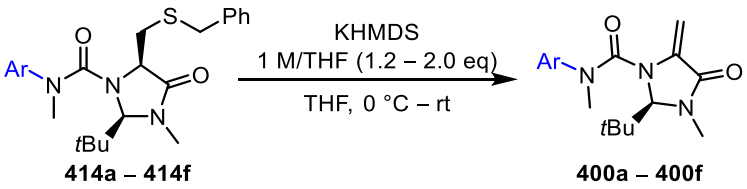


Entry	a-e	Ar	Yield (%)	
			260	414
1	**a**	C_6H_4	n/a[1]	35
2	**b**	4-CNC_6H_4	n/a[2]	40
3	**c**	4-$CF_3C_6H_4$	>99	39
4	**d**	4-ClC_6H_4	>99	53
5	**e**	4-MeC_6H_4	n/a[2]	45
6	**f**	2-pyridyl	n/a[3]	n/a[3]

The reaction producing the imidazolidinone ureas **414** involves a cyclisation and concomitant acylation step, which was low yielding with significant formation of **415**, presumably resulting from nucleophilic attack of the *N*-methylaniline **413**, formed from decomposition of the carbamoyl chloride **260**. Co-elution of **414** with some other product suspected to be non-acylated imidazolidinone **416** was also observed.

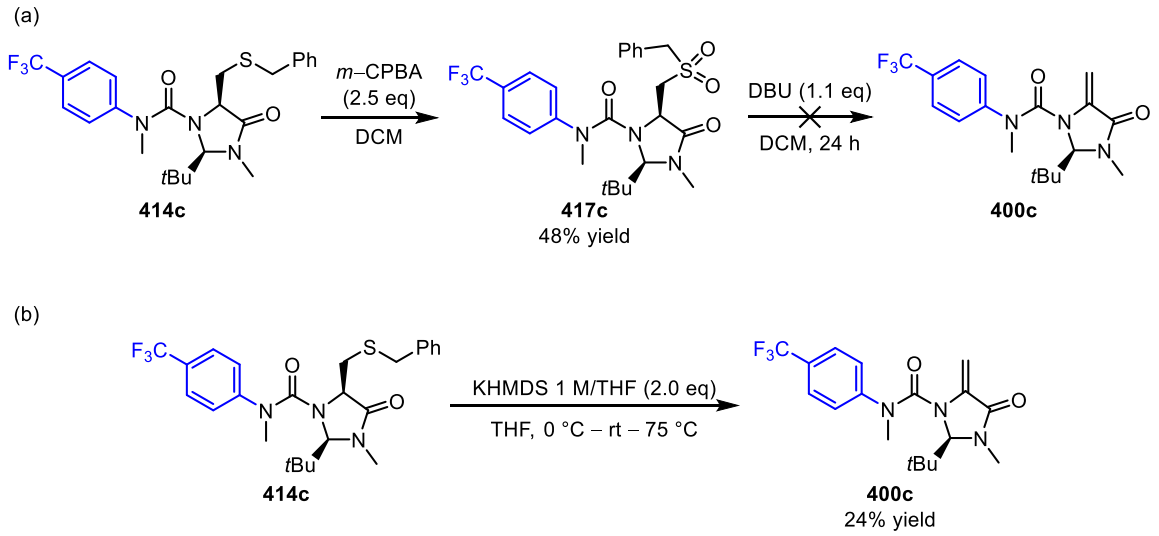
[1] Commercially available
[2] Thanks to Dr Daniel Leonard for making this compound
[3] Thanks to Mehul Jesani for making this compound

Table 28: Elimination to achieve vinyl ureas **400**



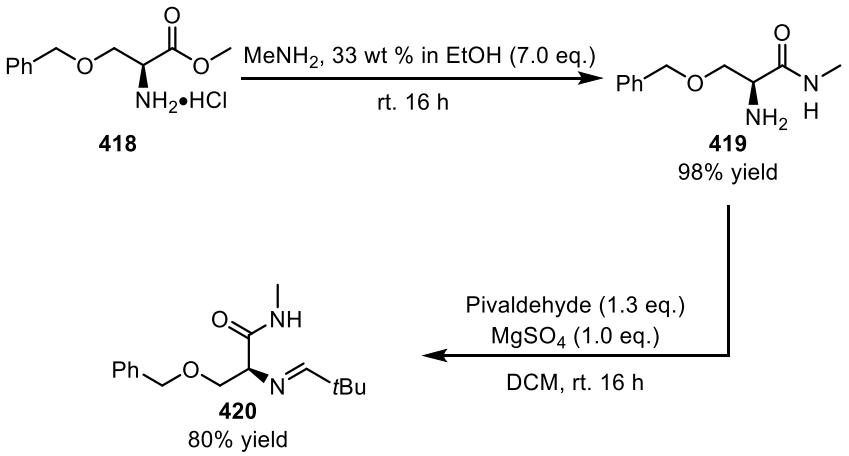
Entry	Ar	Product	Yield (%)
1	C_6H_4	400a	85
2	4-CNC_6H_4	400b	62
3	4-$CF_3C_6H_4$	400c	0
4	4-ClC_6H_4	400d	71
5	4-MeC_6H_4	400e	73
6	2-pyridyl	400f	>99

Treatment of **414** with KHMDS led to elimination of the *S*-benzyl group to afford the desired vinyl ureas **400** in good yields (Table 28). The elimination reaction of **414c** proved challenging (Table 28, entry 3). Complete recovery of **414c** was obtained even after the reaction had been left ongoing for 26 hours. To circumvent this, a similar protocol to that used by Jui *et al*. for the synthesis of vinyl oxazolidines was adopted.[242] The sulfide group in **414c** was successfully oxidised to a sulfone in a moderate yield of 48% (Scheme 96a). Attempted elimination of the sulfone proved difficult with starting material observed by ^{1}H NMR after 24 h. The elimination of **414c** with KHMDS was attempted again; however, the reaction was refluxed at 75 °C for 16 hours to afford **400c** in a moderate yield (Scheme 96b).



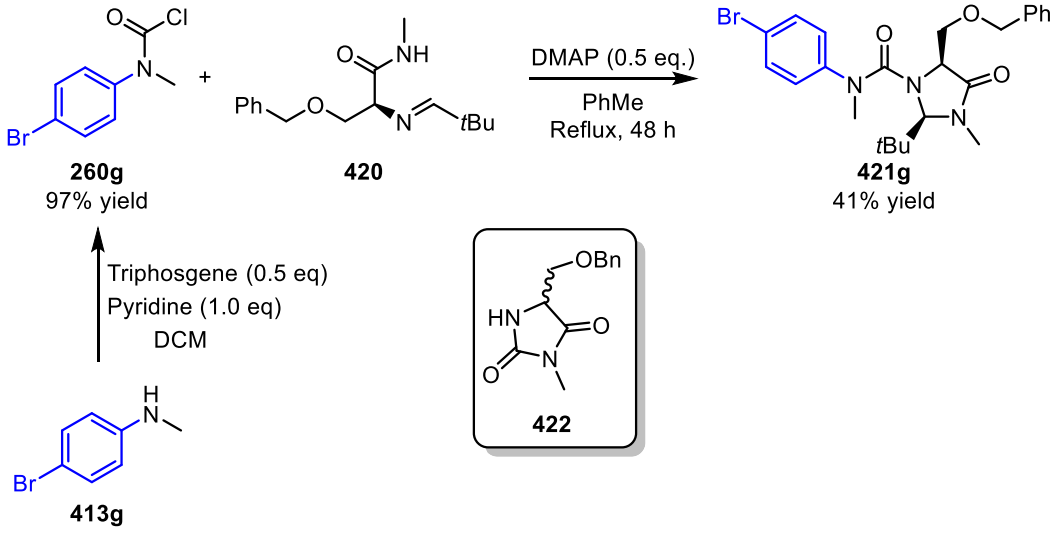
Scheme 96: Attempted routes towards **400c**

As the malodorous benzyl mercaptan is produced as a by-product in the elimination reaction of cysteine, it was decided that serine would be an operationally safer option, since benzyl alcohol would be produced. The synthesis of the vinyl urea bearing a 4-bromophenyl group on the distal nitrogen of the urea was performed using *O*-benzyl-L-serine methyl ester hydrochloride **418**.



Scheme 97: Synthesis of imine **420**

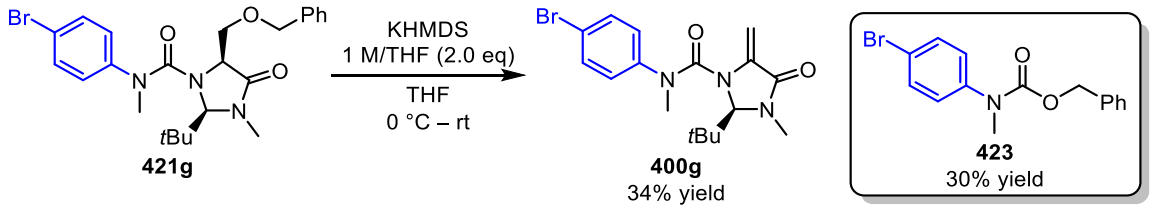
Using already established conditions, the reaction gave excellent yields for the synthesis of the methylamide **419** and imine **420** (Scheme 97). The cyclisation and concomitant acylation of **420** with **260g** gave the product **421g** along with side product **415**, which was also observed when cysteine was used as starting amino acid (see Table 27). Side product **422** resulting from adventitious hydrolysis of the imine was also isolated (Scheme 98).



Scheme 98: Synthesis of imidazolidinone urea **421g**

The elimination reaction of **421g** gave a low yield of **400g** due to competing nucleophilic attack of the eliminated phenyl methoxide ion on the urea carbonyl in **421g**, thereby producing **423** in about

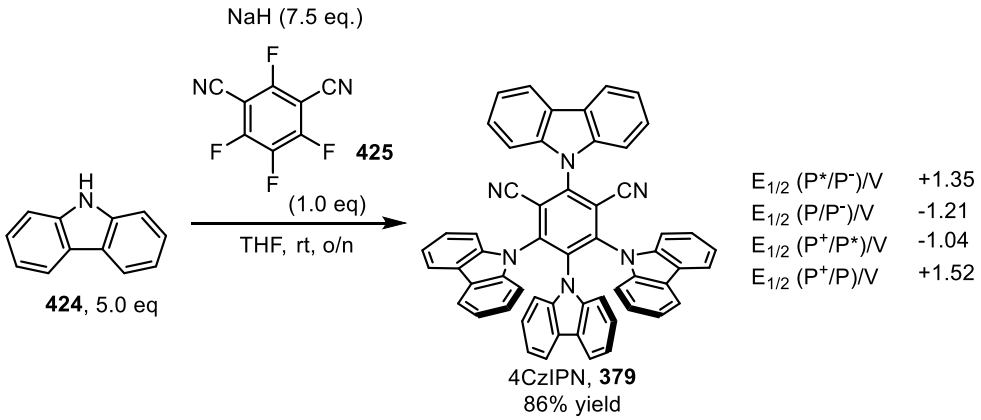
an equal proportion to **400g** (Scheme 99). Though the use of serine is more operationally convenient than cysteine, the latter is necessary to obtain good yields of the elimination product.



Scheme 99: Elimination reaction of serine-derived imidazolidinone urea **421g**

2.3.4 Attempted Aryl Migration employing Photoredox catalysis

With the desired vinyl ureas now accessible, a photoredox mediated radical addition with subsequent intramolecular arylation employing the "SRS" principle could now be investigated with the aim of making enantiopure α-aryl quaternary amino acids. The PC used in this investigation is 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN). As shown in Scheme 92, 4CzIPN (**379**) has already been used as an amenable PC to facilitate the alkylarylation of styryl based vinyl ureas. Furthermore, **379** is a precious metal free catalyst that is preparable in an inexpensive fashion by performing a quadruple S_NAr substitution reaction of tetrafluoroisophthalonitrile **425** by carbazole **424** (Scheme 100).[254]



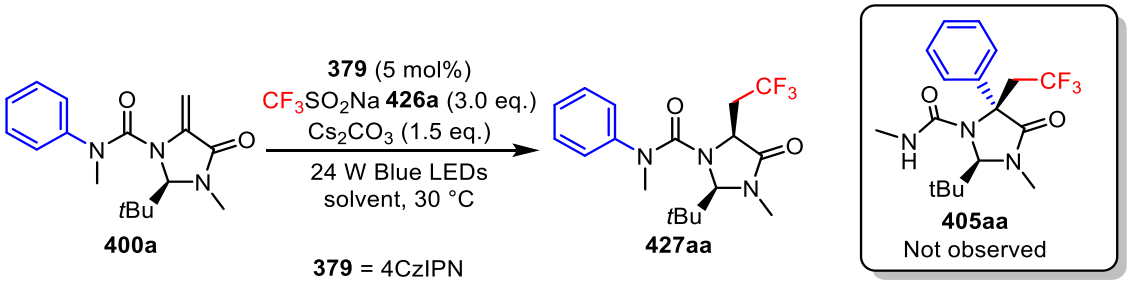
Scheme 100: Synthesis of 4CzIPN **379**. All potentials are given in volts vs the saturated calomel electrode (SCE)

4CzIPN **379** has a high photoluminescence quantum yield and a long-lived excited state (5 μs) – long enough to engage in single electron transfer reactions with organic molecules. It is both a powerful oxidant and reductant in the excited state. In addition, **379** has similar excited state redox potentials to commonly used iridium-centred metal based PCs. This makes **379** an inexpensive alternative to these PCs.[255] Sodium trifluoromethylsulfinate, also known as Langlois reagent **426a** was chosen as radical precursor to the trifluoromethyl radical, because it is commercially available and easy to handle. Langlois reagent possesses an oxidation potential ($CF_3SO_2Na/^{\bullet}CF_3$, $E_{1/2}$ = +1.05

V vs. SCE).[256] Hence, 4CzIPN is capable of single electron oxidation of Langlois reagent[255] to produce trifluoromethyl radical after expulsion of sulfur dioxide. Trifluoromethyl radical has been well established to add to a variety of electron-rich alkenes.[257–259] A potential short coming of the use of Langlois reagent in photoredox manifolds can be that the SO_2 by-product, formed in trifluoromethyl radical formation, demonstrates a reduction potential of –0.7 V.[260] As such, it is possible the radical anion of 4CzIPN can engage in single electron reduction of sulfur dioxide, leading to formation of net-oxidative side product with respect to the vinyl urea. Addition of Cs_2CO_3 has been shown to suppress the occurrence of net-oxidative side products when using Langlois reagent, presumably by adsorption of sulfur dioxide. [253,261,262]

Investigations began with the use of **400a** in optimisation studies towards the alkylarylated product **405aa**. Since the photochemical alkylarylation of styryl based vinyl ureas had already been established in solvents such as CH_3CN, DMF and acetone, it seemed rational to begin optimisation with these solvents (Table 29).

Table 29: Solvent optimisation

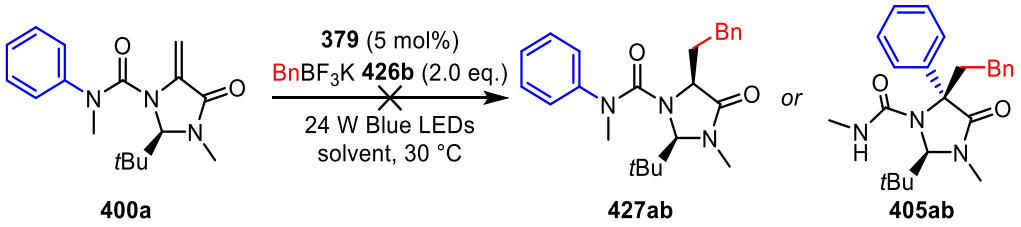


Entry	Solvent	Yield (%)	
		427aa	405aa
1	CH_3CN	66	0
2	Acetone	65	0
3	DMF	65	0

All yields obtained by ^{19}F NMR and compared with α,α,α-trifluoro toluene internal standard
Light source: 24 W blue LED strips

Disappointingly, in the three solvents, the addition product **427aa** was solely obtained and not the desired alkylarylated product **405aa**. The formation of **427aa** was however encouraging because it indicated that radical addition to the vinyl urea occurs.

Table 30: Radical precursor investigation

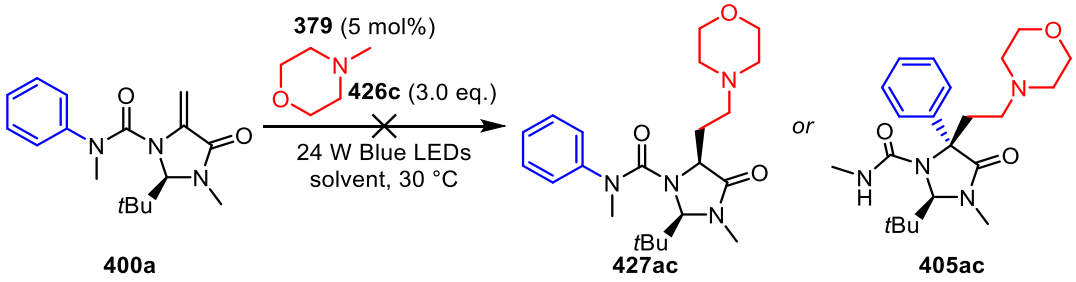


Entry	Solvent	Yield (%)		
		400a	427ab	405ab
1	DMF	100	0	0
2	acetone	100	0	0
3	CH_3CN	100	0	0

Light source: 24 W blue LED strips

Several radical precursors were tested in the alkylarylation of **400a**. The radical precursor $BnBF_3K$ **426b** ($E_{1/2}$ = +1.10 V vs. SCE) is capable of reducing photo excited **379** to produce a benzyl radical.[263,264] α-Amino radicals such as 4-methylmorpholine radical have been formed from single electron oxidation with concurrent deprotonation of their amine precursors using PCs with similar potentials to **379**.[242]

Table 31: Radical precursor investigation



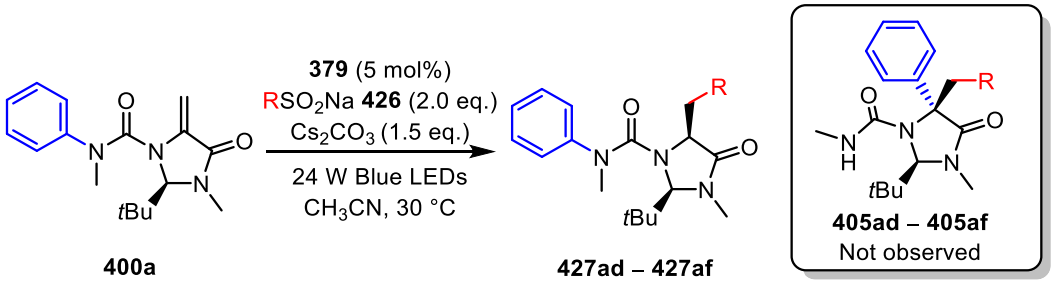
Entry	Solvent	Yield (%)		
		400a	427ac	405ac
1	DMF	100	0	0
2	acetone	100	0	0
3	CH_3CN	100	0	0

Light source: 24 W blue LED strips

These nucleophilic benzyl and α-amino radicals have been reported to add to olefins substituted with electron-withdrawing ester groups.[242,247,264] The olefin of the vinyl urea **400a** is not as electron-deficient as those olefins substituted with ester groups; the proximal nitrogen of the urea in **400a** pushes electron density into the olefin, thereby making it electron-rich. This might be the reason

why starting material was recovered when $BnBF_3K$ **426b** and 4-methylmorpholine **426c** were used as radical precursors in the reaction (Table 30 and Table 31).

Table 32: Radical precursor investigation



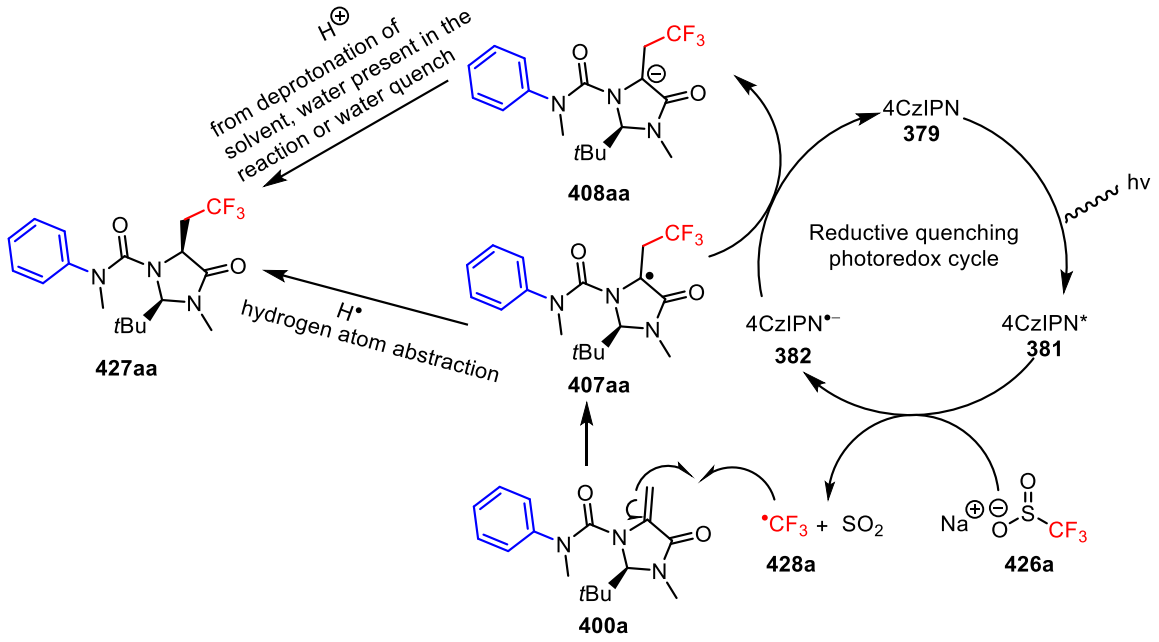
400a 427ad – 427af

Entry	426	R	Product	Yield (%)
1	**426d**	C_4H_9	**427ad**	0
2	**426e**	$C_2H_3F_2$	**427ae**	(64)
3	**426f**	CHF_2	**427af**	(91)

Light source: 24 W blue LED strips; Parenthesis indicate isolated yields

Unlike with Langlois reagent, use of $C_4H_9SO_2Na$ radical precursor **426d** resulted in only starting material being recovered (Table 32, entry 1). The fluorine containing radical precursors, $C_2H_3F_2SO_2Na$ **426e** and CHF_2SO_2Na **426f** were attempted in CH_3CN alone, affording addition product **427ae** and **427af** in a 64% and 91% isolated yield, respectively. No product of aryl migration **405ae** or **405af** was observed in both cases. The configuration of the addition products was determined to be *cis* by 1D NOE experiments (see section 4.4). The screening of the radical precursors gives key information that the vinyl urea used in the reaction is not electron-deficient enough to react with nucleophilic radicals. Therefore, further investigation would be done with electrophilic radicals such as fluorine substituted carbon centred radicals.

With the photochemical alkylation of **400a** by sodium sulfinate radical precursors firmly established, attention was directed towards the question of why the subsequent *N* to *C* aryl transfer was inhibited? One theory may be that the phenyl group is not electrophilic enough for attack by the enolate of **408aa**, resulting in protonation from water impurities in starting materials used or upon work up (Scheme 101). As an alternative hypothesis to why aryl transfer may not occur, the urea radical **407aa** could abstract an H-atom from a H-atom source, such as solvent, before its reduction to **408aa**.



Scheme 101: Proposed reaction pathways for obtaining addition product

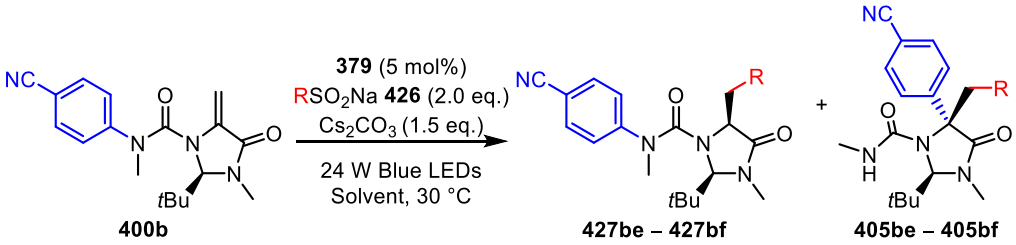
To get some insight into the proton or H-atom source, deuterium experiments were carried out. Though acetone is more acidic than acetonitrile, acetone-D6 was used in the study due to availability. The addition reaction of **400a** with the radical precursor **426e** was repeated under anhydrous conditions using acetone-D6 as solvent (Scheme 102).

Scheme 102: Deuterium experiments with acetone-D6

11% deuterium incorporation was observed by NMR analysis of the α-proton in **427ae**. This gives tentative indication that the enolate formed may be protonated by acetone, but because of the low D incorporation other pathways towards the addition product appear to be more significant. When the reaction was repeated with acetone-D_6 and quenched with D_2O, the deuterium incorporation was increased to 32%, indicating that the α-proton of **427ae** can originate from an aqueous quench. To investigate if a proton source might be the presence of water, the reaction was repeated using non-deuterated DMF as solvent. 5 equivalents of D_2O was added from the start of the reaction and NMR analysis of the α-proton showed 34% deuterium incorporation. This indicated that water present in the reaction could lead to protonation as well. Due to the low D incorporation, there is a possible occurrence to a certain degree of deprotonation of solvent, water present in and water used to quench the reaction; however, hydrogen atom abstraction cannot be ruled out without doing the

reaction in DMF-d_7. Using this information, more electron-deficient aryl migratory rings were investigated in the reaction.

Table 33: Attempted 1,2-alkylarylation of **400b**

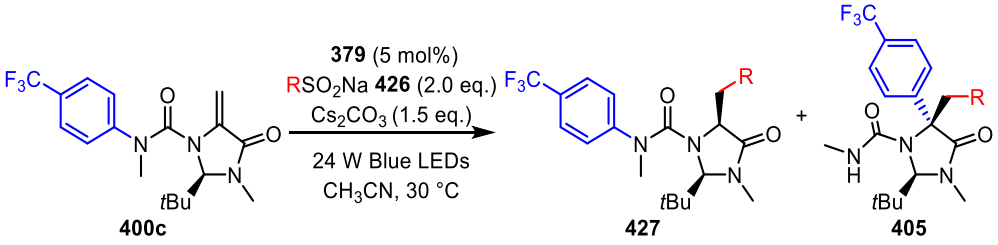


Entry	426	R	Solvent	Product	Yield (%)	
					427	405
1	**426e**	$C_2H_3F_2$	DMF	**be**	4	35
2	**426e**	$C_2H_3F_2$	CH_3CN	**be**	4	44 (32)
3	**426f**	CHF_2	CH_3CN	**bf**	26	45 (42)

Yields obtained by ^{19}F NMR and compared with α,α,α-trifluoro toluene internal standard
Parentheses indicate isolated yields; Light source: 24 W blue LED strips

Using **426e** as radical precursor, the addition and subsequent arylation reaction was attempted on **400b** (Table 33). Delightfully, in DMF, a 35% conversion to the arylation product **405be** was observed by ^1H and ^{19}F NMR (Table 33, entry 1). When the same reaction was repeated in acetonitrile, a 44% conversion to **405be** was observed by ^1H and ^{19}F NMR (Table 33, entry 2). Since comparative yields were obtained in both solvents, acetonitrile was used for further investigations. With the radical precursor **426f**, a 45% conversion of **400b** to **405bf** was observed by ^1H and ^{19}F NMR (Table 33, entry 3).

Table 34: Attempted 1,2-alkylarylation of **400c**

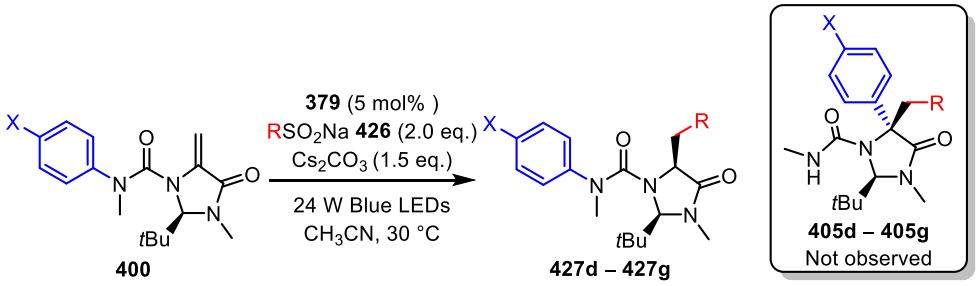


Entry	426	R	Product	Yield (%)	
				427	405
1	**426a**	CF_3	**ca**	54 (39)	2
2	**426e**	$C_2H_3F_2$	**ce**	47	17
3[a]	**426e**	$C_2H_3F_2$	**ce**	60	10
4	**426f**	CHF_2	**cf**	67	8

Yields obtained by ^{19}F NMR and compared with α,α,α-trifluoro toluene internal standard
Parentheses indicate isolated yields; [a] A 40 W kessil blue LED lamp was used

With **426a** as radical precursor, **400c**, having a lesser electron-deficient migratory ring relative to **400b** gave a poor conversion to **405ca** (Table 34, entry 1). With the radical precursor **426e**, a 17% conversion of **400c** to **405ce** was observed (Table 34, entry 2). In a bid to increase the yield of **405ce**, the reaction was repeated using a more powerful LED at 35 °C (Table 34, entry 3), which disappointingly gave a slightly lower yield of the product **405ce**.With **426f** as radical precursor, an 8% conversion of **400c** to **405cf** was observed (Table 34, entry 4).

Table 35: Attempted 1,2-alkylarylation of **400d** and **400g**

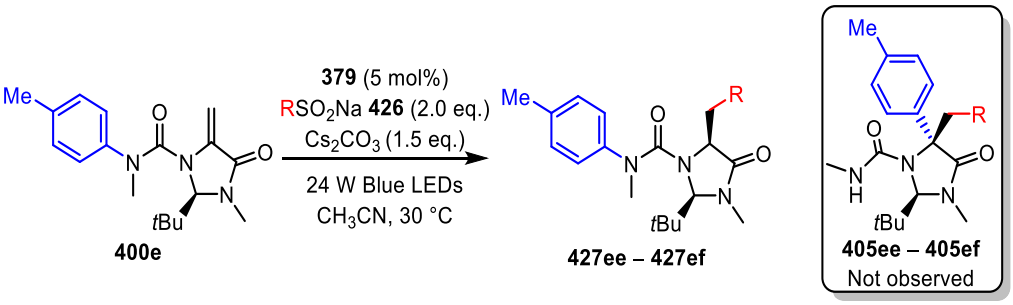


Entry	400	X	426	R	Product	Yield (%)
1	**400d**	Cl	**426a**	CF_3	**427da**	74 (56)
2	**400d**	Cl	**426e**	$C_2H_3F_2$	**427de**	67
3	**400d**	Cl	**426f**	CHF_2	**427df**	(88)
4	**400g**	Br	**426a**	CF_3	**427ga**	(65)

Yields obtained by ^{19}F NMR and compared with α,α,α-trifluoro toluene internal standard
Parentheses indicate isolated yields; Light source: 24 W blue LED strips.

Other electron-deficient migratory rings such as 4-ClC_6H_4 and 4-BrC_6H_4 gave exclusively addition products with all radical precursors used (Table 35). As expected, **400e** having an electron-rich 4-tolyl migratory ring gave only addition product with the two radical precursors used (Table 36).

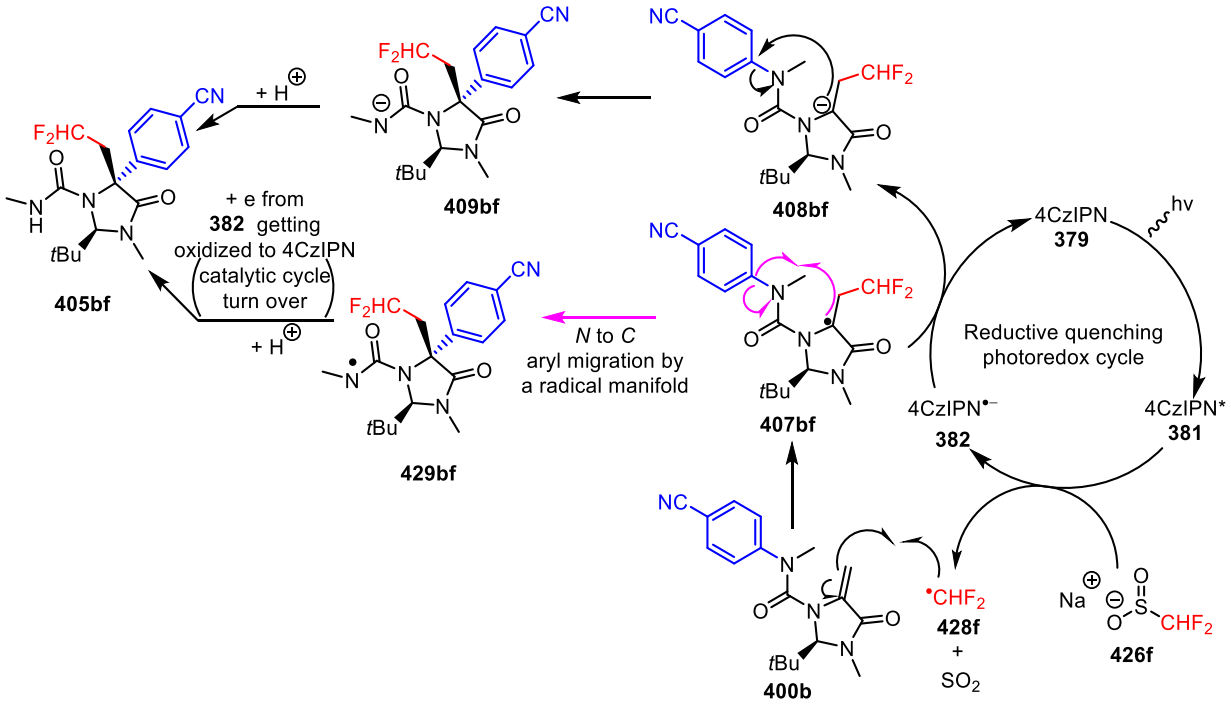
Table 36: Attempted 1,2-alkylarylation of **400e**



Entry	426	R	Product	Yield (%)
1	**426e**	$C_2H_3F_2$	**427ee**	85 (57)
2	**426f**	CHF_2	**427ef**	(75)

Yields obtained by ^{19}F NMR and compared with α,α,α-trifluoro toluene internal standard
Parentheses indicate isolated yields; Light source: 24 W blue LED strips

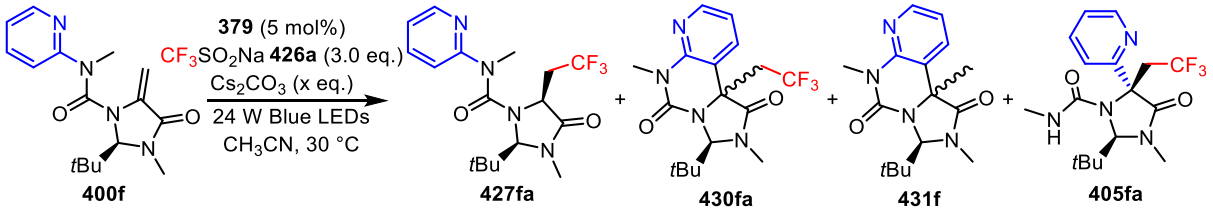
In the formation of the radical addition with subsequent aryl migration product **405**, one of two reaction pathways may be possible (Scheme 103). The difluoromethane radical **428f** is produced by single electron reduction of **381** by CHF_2SO_2Na **426f**. The radical then adds to **400b** to produce the radical addition adduct **407bf**. In a radical polar cross-over pathway, **407bf** can accept an electron from the reduced PC **382**, hence turning over the catalytic cycle. The resulting enolate **408bf** can then undergo an intramolecular nucleophilic attack on the *N*-aryl ring, resulting in migration of the aryl group from *N* to *C* to give the new quaternary centre in **409bf**. On quenching with water, **409bf** accepts a proton to give **405bf**. Alternatively, the C-centred radical **407bf** may facilitate the intramolecular abstraction of the 4-cyanophenyl from the distal urea nitrogen, resulting in the formation of the nitrogen centred radical **429bf**. To turn over the photocatalytic cycle, **429bf** may accept an electron from the reduced PC **382**, followed by protonation to give **405bf**.



Scheme 103: Possible reaction pathways for the formation of aryl migration product **405**

Though no mechanistic investigation has been done to refute the *N* to *C* aryl migration by a radical manifold pathway, the deuterium experiments done previously give evidence of radical polar cross-over, since deuteration of the α-carbon on quenching with D_2O indicates the presence of an anion at the α-carbon.

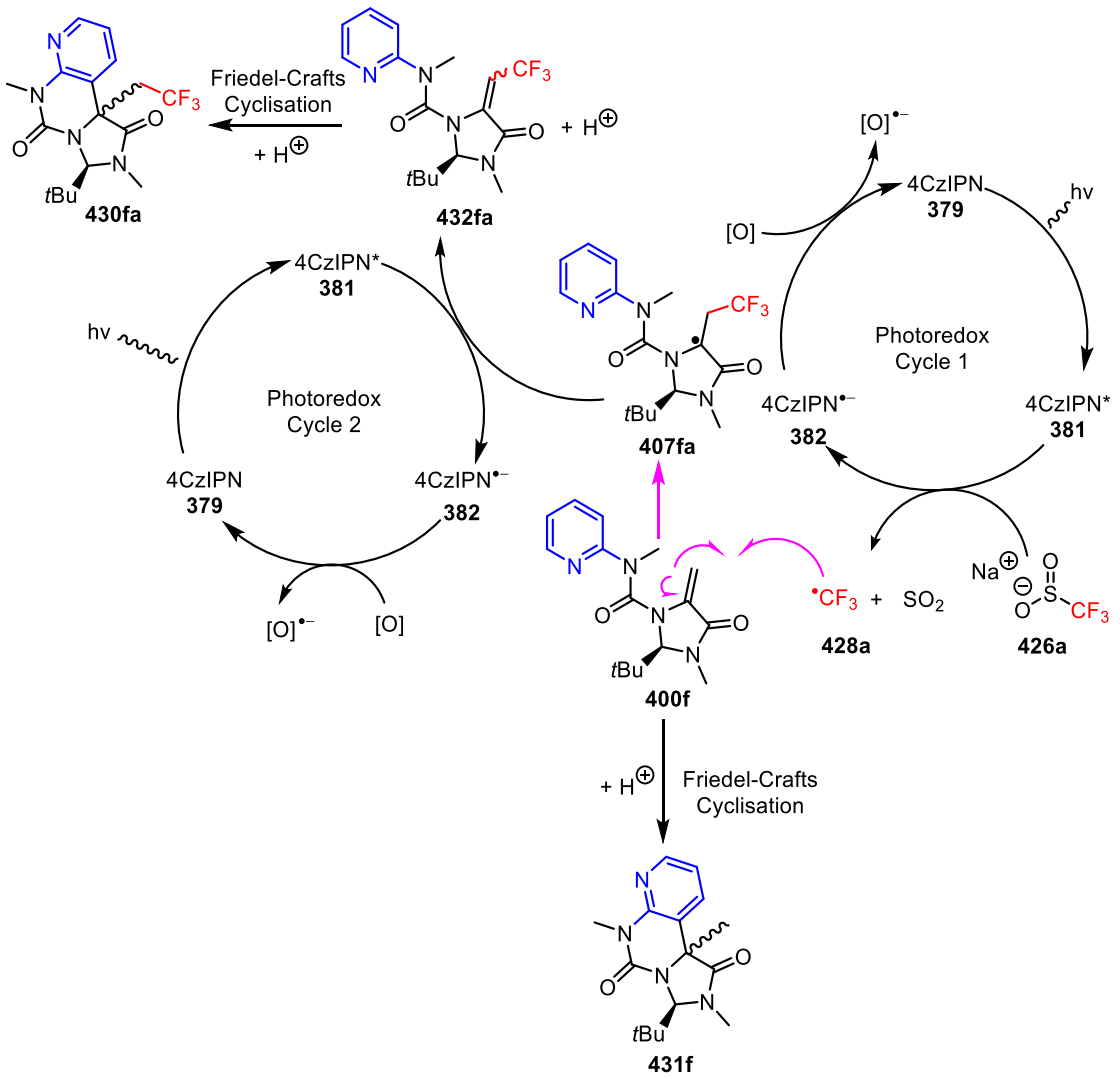
Table 37: Attempted 1,2-alkylarylation of **400f**



Entry	x	Yield (%)			
		427fa	430fa	431f	405fa
1	1.5	28	18	9	0
2	2.5	39	9	1	6

All yields obtained by ^{19}F NMR and compared with α,α,α -trifluoro toluene internal standard
Light source: 24 W blue LED strips. Wavy bond in **430fa** and **431f** represents unknown stereochemistry

In order to investigate the scope of the addition and ensuing arylation further, in terms of electron-deficient aryl migratory rings, the electron-deficient 2-pyridyl substrate **400f** was subjected to the established photoredox conditions (Table 37). Surprisingly, the net oxidation product **430fa** and product of acid catalysed Friedel-Crafts cyclisation of **400f** (**431f**) were observed, alongside the addition product **427fa** (Table 37, entry 1). Presence of net-oxidative side product **430fa** may be due to either the adventitious presence of oxygen in the reaction mixture or insufficient quantities of Cs_2CO_3 to completely sequester SO_2; either or both gases in theory are able to oxidise the radical anion of 4CzIPN **382** resulting in a net oxidative photoredox cycle. To test this supposition, the reaction was repeated with an extra equivalent of Cs_2CO_3 and degassed for 10 – 15 mins. There was a decrease in the yields of **430fa** and **431f** and increase in the yield of the addition product **427fa**. The alkylarylated product **405fa** was also afforded in a 6% ^{19}F NMR yield. The decrease in net oxidation products due to the use of an extra equivalent of Cs_2CO_3 shows the importance of Cs_2CO_3 in the alkylarylation reaction. It is however unclear why both net oxidation and addition products are favoured in this reaction. It is even more unclear why aryl migration is not efficiently occurring, even with such an electron-deficient migratory ring. The fact that **427fa** is formed indicates that addition to the vinyl urea is occurring. The electrophilic radical **407fa** (Scheme 104) is just the same as in previous substrates, the only difference is the electron-deficient 2-pyridyl ring. A proposed mechanism for the formation of **430fa** and **431f** is illustrated in Scheme 104.



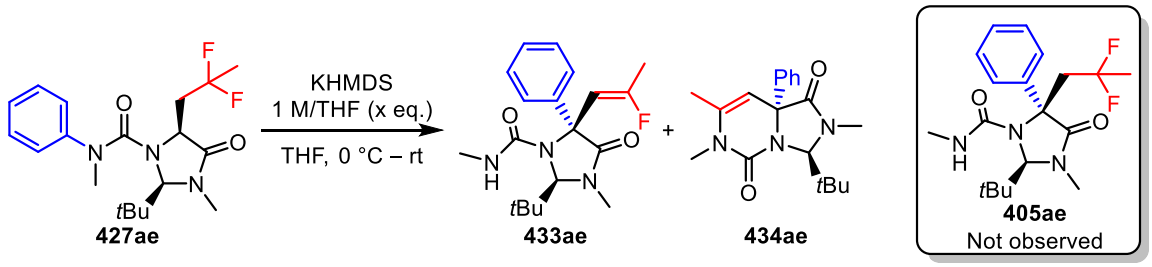
Scheme 104: Proposed mechanism for formation of **430fa** and **431f**

The trifluoromethyl radical **428a** is generated by single electron reduction of the excited PC **381** by Langlois reagent **426a**. The reduced PC **382** could reduce an oxidant present in the reaction, thereby regenerating the PC **379** and closing the first catalytic cycle. Addition of **428a** to vinyl urea **400f** occurs to produce the radical addition adduct **407fa**. The radical **407fa** enters a second photoredox cycle and does a single electron reduction of the excited PC **381** to produce an intermediary cation which loses acid (H^+) to afford **432fa**. The substrates **432fa** and **400f** could then undergo an acid catalysed Friedel-Crafts cyclisation to produce **430fa** and **431f**, respectively. The second catalytic cycle is then closed by reduction of an oxidant present in the reaction by **382** to regenerate **379**. The likely oxidants responsible for the net oxidation photoredox manifold could be either of SO_2 or O_2 still present in the reaction or a CF_3 radical.

2.3.5 Base-mediated Aryl Migration

Next an investigation into whether the addition products **427** can undergo base facilitated intramolecular aryl migration was performed. The addition product **427ae** was treated with 1.5 equivalents of KHMDS (Table 38**,** entry 1). Surprisingly, aryl migration did not only occur but 1,2-elimination of a fluorine to produce the new quaternary centre having an aryl and vinyl fluoride group as seen in **433ae**, and elimination of both fluorines to produce the bicycle **434ae**. However, obtaining just the aryl migration product **405ae** was pertinent. When the number of equivalents of the base was reduced to 1.0 (Table 38, entry 2), only starting material was observed.

Table 38: Attempted base facilitated aryl migration of **427ae**

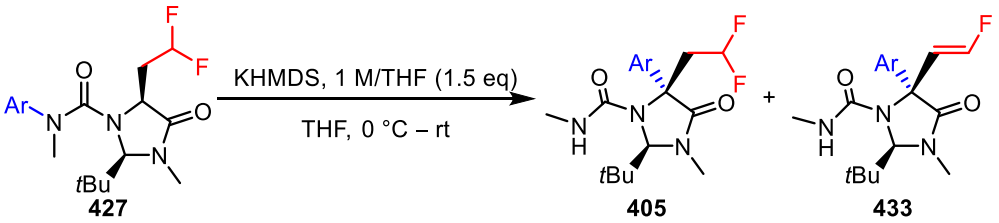


Entry	x	Time	Yield (%)		
			427ae	433ae	434ae
1	1.5	2 h	0	(26)	(18)
2	1.0	2.30 h	100	0	0

Parentheses indicate isolated yields

Addition product **427af** having a difluoromethyl substituent at the β-carbon of the amide carbonyl furnished exclusively the aryl migration and subsequent elimination product **433af** (Table 39, entry 1). Pleasingly, addition product **427df** having a 4-chlorophenyl migratory ring afforded the aryl migration and subsequent elimination product **433df** alongside the desired aryl migration product **405df** after an hour (Table 39, entry 2).

Table 39: Attempted base facilitated aryl migration of **427af** and **427df**



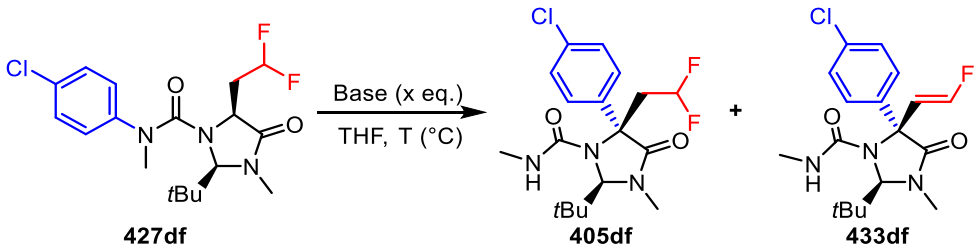
427 **405** **433**

Entry	427	Ar	Time	Yield (%)	
				405	433
1	**427af**	C_6H_5	2.15 h	0	97(54)
2	**427df**	4-ClC_6H_4	1 h	32	31

Yields obtained by ^{19}F NMR and compared with α,α,α-trifluoro toluene internal standard
Parentheses indicate isolated yields

The addition product **427df** seemed promising in furnishing the aryl migration product; hence, it was used for optimisation of the aryl migration and elimination reactions. The reaction was optimised for both the formation of **405df** and **433df** exclusively (Table 40). TLC analysis at various times of the reaction revealed that **405df** was formed before being converted to **433df**. This meant that **433df** might be formed exclusively if the reaction was left for longer than an hour. As anticipated, a minimal amount of **405df** was observed when the reaction was left for 3 hours (Table 40, entry 2). When the number of equivalents of KHMDS was increased to 2.5, the aryl migration and subsequent elimination product **433df** was formed exclusively after approximately 3 hours (Table 40, entry 3). Satisfied with this result, attention was drawn towards optimising the reaction for just the aryl migration product **405df**. It was supposed that performing the reaction with 1.5 equivalents of KHMDS for less than 1 hour would lead to the formation of **405df** exclusively. Nevertheless, some amount of **433df** was observed by ^1H NMR about 20 mins into the reaction. To slow down the rate of the aryl migration and consequently the elimination, the reaction was carried out at −20 °C. After 1 hour, 51% of **405df** was observed along with a trace amount of **433df** (Table 40, entry 4).

Table 40: Optimisation of reaction conditions

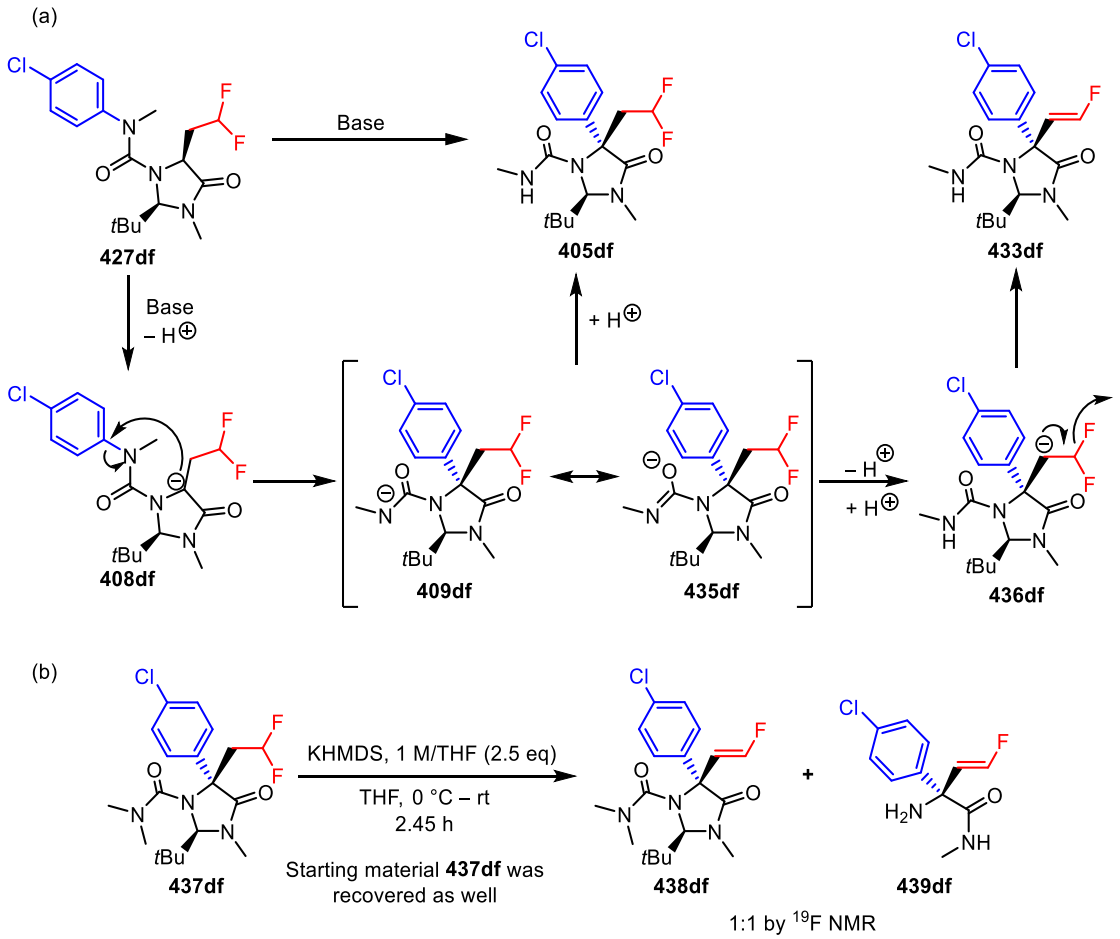


427df 405df 433df

Entry	Base	eq.	T (°C)	Time	Yield (%)		
					427df	405df	433df
1	KHMDS	1.5	0 – rt	1 h	0	32	31
2	KHMDS	1.5	0 – rt	3 h	0	7	61
3	KHMDS	2.5	0 – rt	2.45 h	0	0	(81)
4	KHMDS	1.5	−20	1 h	0	51	trace
5	LDA	2.0	−20	1.75 h	4	28	0
6	LiHMDS	1.5	−20	3.25 h	26	20	0
7	LiHMDS	1.5	0	2 h	0	67	0

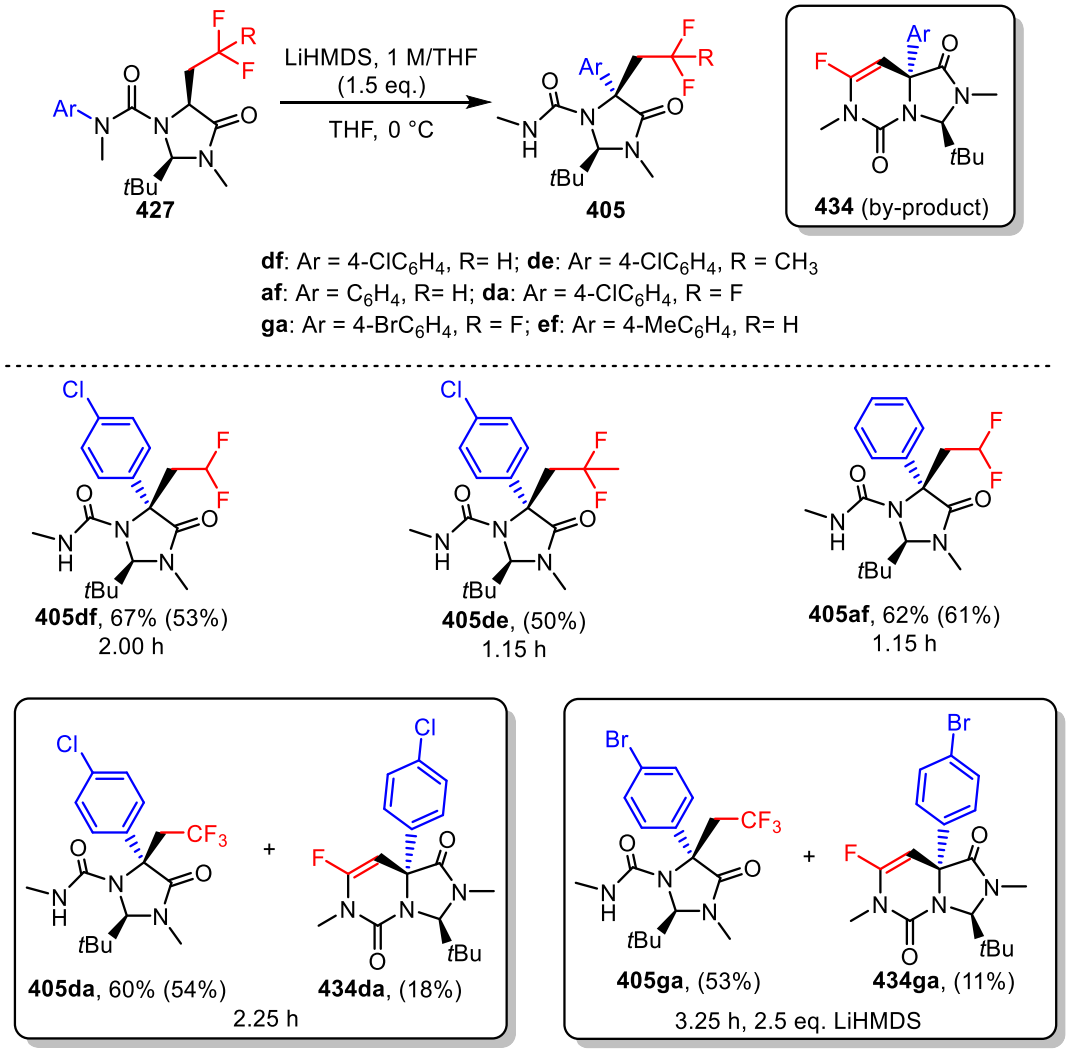
Yields obtained by ^{19}F NMR and compared with α,α,α-trifluoro toluene internal standard
Parentheses indicate isolated yields

Another base, LDA was tested on the aryl migration reaction at −20 °C. There was still starting material left after about 2 hours. Notwithstanding 28% of **405df** was observed by ^{1}H and ^{19}F NMR alongside some unidentified product (Table 40, entry 5). A weaker lithium base, LiHMDS, was utilised at −20 °C. The aryl migration product **405df** was observed exclusively; however, there was still starting material left after approximately 3 hours (Table 40, entry 6). Satisfactorily, when the reaction was repeated with LiHMDS at 0 °C, the aryl migration product **405df** was observed exclusively in 67% ^{19}F NMR yield (Table 40, entry 7).



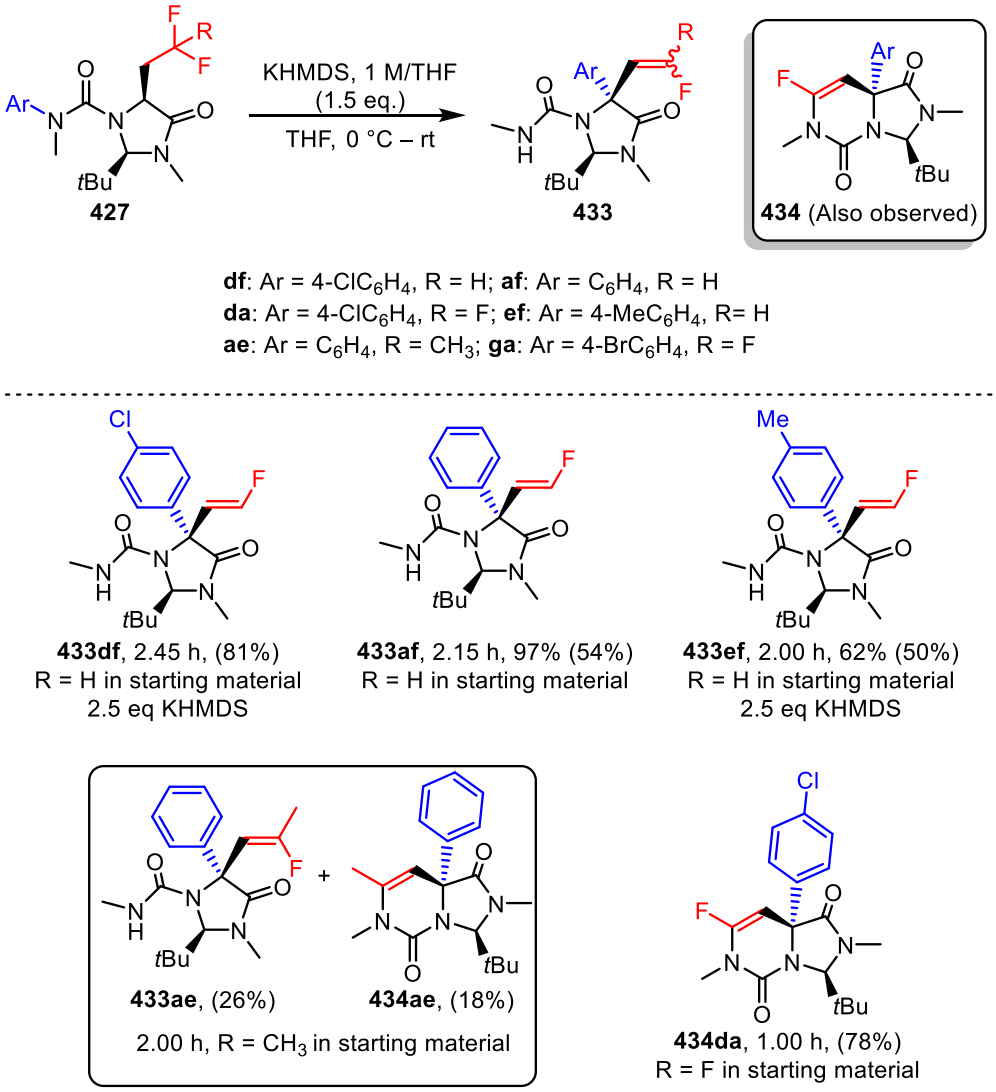
Scheme 105: (a) Proposed mechanism for aryl migration and subsequent elimination reaction (b) Experimental evidence for deprotonation by KHMDS

The formation of **405df** exclusive of **433df** was favoured by lithium bases such as LDA and LiHMDS, while the formation of **433df** exclusive of **405df** was favoured by KHMDS. It was postulated that the lithium cation, due to its smaller size, coordinates more to the oxygen anion in **435df** than the potassium cation does (Scheme 105a). The implication of this, for the use of KHMDS, is that the nitrogen anion in **409df** will be more available to abstract a β-proton, leading to elimination of a fluorine to afford **433df**. This rationale is made, however, on the assumption that the nitrogen anion in **409df** is responsible for the deprotonation of the β-proton and not KHMDS. To prove/disprove this rationale, methylated **405df** (**437df**) was treated with KHMDS (Scheme 105b), the elimination product **438df** was observed by ^{1}H and ^{19}F NMR, as well as some other product of hydrolysis which is suspected to be **439df**. Starting material **437df** was also recovered in the reaction of Scheme 105b. This experiment indicates that KHMDS can carry out deprotonation of the β-proton in **405df** but LiHMDS and LDA cannot. However, it may also be that some deprotonation by the nitrogen ion may be occurring and this might be the reason the reaction was slower with **437df** relative to **427df**



Scheme 106a: Scope of aryl migration reaction; Yields obtained by ^{19}F NMR and compared with α,α,α-trifluoro toluene internal standard; Parenthesis indicate isolated yields

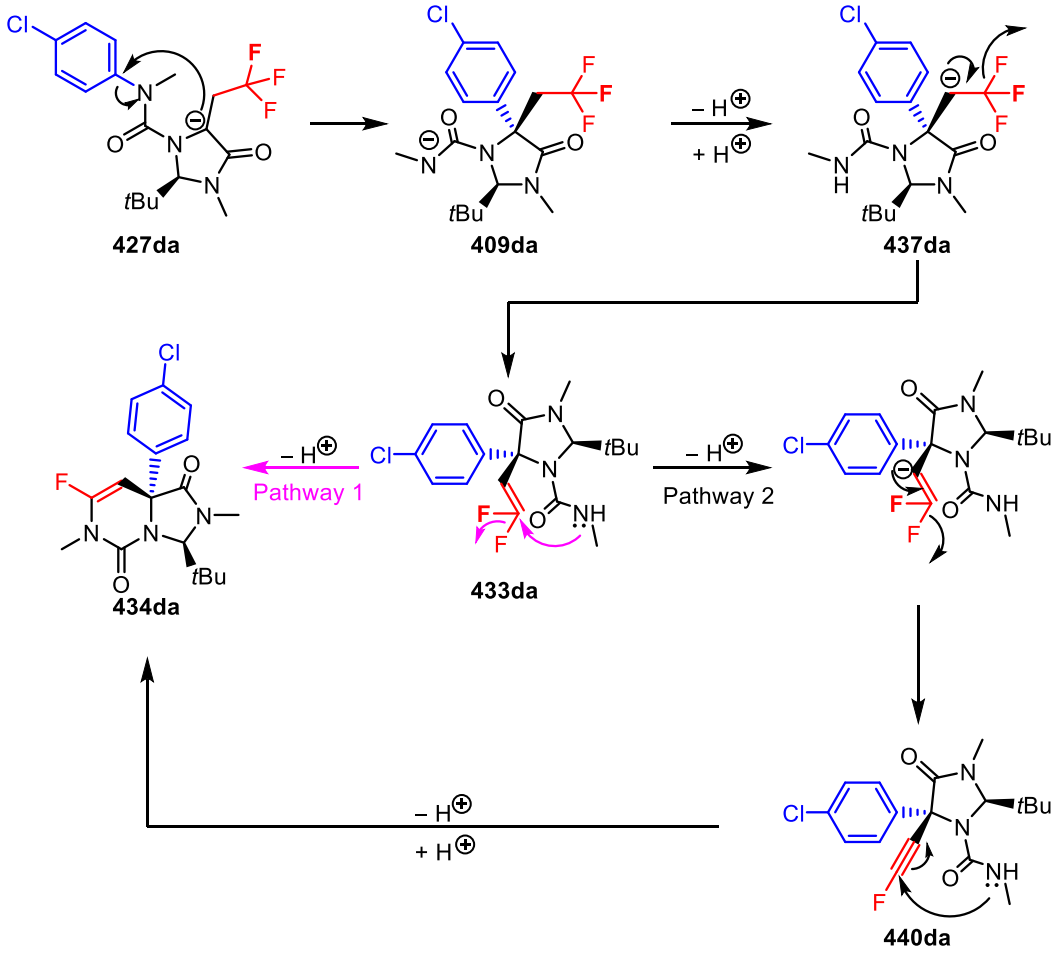
The scope of the aryl migration was explored (Scheme 106a). For the aryl migration, substrates bearing a CHF_2 or CF_2CH_3 on the β-carbon of the amide carbonyl rearranged smoothly furnishing the aryl migration products (**405df**, **405de** and **405af**) exclusively. Substrate **427ef** having an electron-donating 4-methyl group underwent the aryl migration at a slower rate: about an equal proportion of starting material to the arylation product remained, even when the reaction was treated with 3.0 equivalents of LiHMDS and left overnight. To increase the rate of the aryl migration reaction of **427ef**, it was heated up to 40 °C. Unfortunately, total conversion to the elimination product **433ef** was observed (not shown in scheme). The aryl migration of **427da** and **427ga** both having a CF_3 on the β-carbon, led to the formation of the bicyclic product **434da** and **434ga** alongside the respective desired aryl migration products **405da** and **405ga**.



Scheme 106b: Scope of aryl migration and subsequent elimination reaction; Yields obtained by ^{19}F NMR and compared with α,α,α-trifluoro toluene internal standard; Parenthesis indicate isolated yields

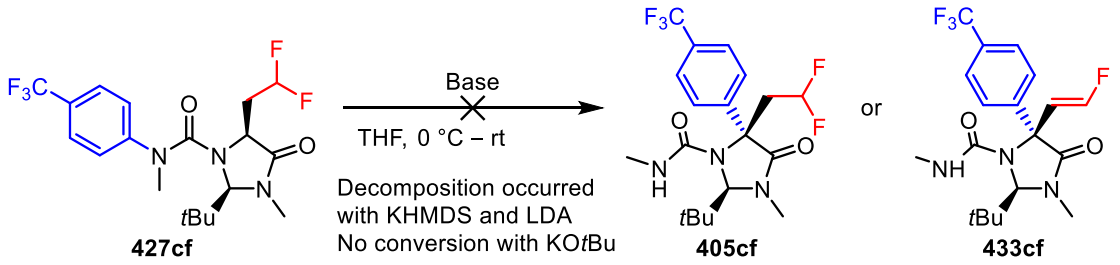
The scope of the aryl migration and subsequent elimination reaction seemed limited to substrates bearing a CHF_2 or CF_2CH_3 on the β-carbon of the amide carbonyl (Scheme 106b). Substrates bearing a CHF_2 group (**427df**, **427af** and **427ef**) smoothly underwent the aryl migration and concomitant elimination to produce the elimination products **433df**, **433af** and **433ef,** respectively. The substrate bearing a CF_2CH_3 group (**427ae**) furnished the elimination product **433ae** alongside the bicyclic side-product **434ae**. For the substrate bearing a CF_3 group (**427da**), the bicyclic product **434da** was furnished exclusively. From the reactions, it is speculated that the presence of the CF_3 group in a substrate promotes the formation of the bicyclic product **434**. While the presence of the CF_2CH_3 group promotes the formation of the bicyclic product only when KHMDS is used as base. In all cases, the aryl migration and elimination products were isolated as single diastereoisomers. The new quaternary centre formed is assumed to be *R* based on previous work done within the Clayden group that showed that aryl migration in similar imidazolidinone ureas occurred at the face opposite the *tert*-butyl group.[160] The *E*/*Z* isomers of the elimination products were assigned based

on their $^{3}J_{H\text{-}F}$ coupling constants ($^{3}J_{H\text{-}F}$ = 20 – 22 Hz for the *E* isomer and 33 – 39 Hz for the *Z* isomer).[265–267]



Scheme 107: Proposed mechanism for formation of bicyclic side-product

It is proposed that the bicyclic product **434** is formed by nucleophilic attack of the urea distal nitrogen in **433** on the vinyl, resulting in substitution of a fluorine to produce **434** (Scheme 107 pathway 1). The substitution reaction in pathway 1 is unusual, and no literature precedent could be found for the reaction. An alternative mechanistic proposal is pathway 2, which has an intermediary fluoroalkyne **440**. Nucleophilic attack of the urea distal nitrogen on the alkyne in **440**, followed by protonation of the resulting anion results in formation of the bicycle **434** (Scheme 107 pathway 2). It is noteworthy that no elimination product **433da** or **433ga** was isolated in the aryl migration reactions of **427da** and **427ga**.

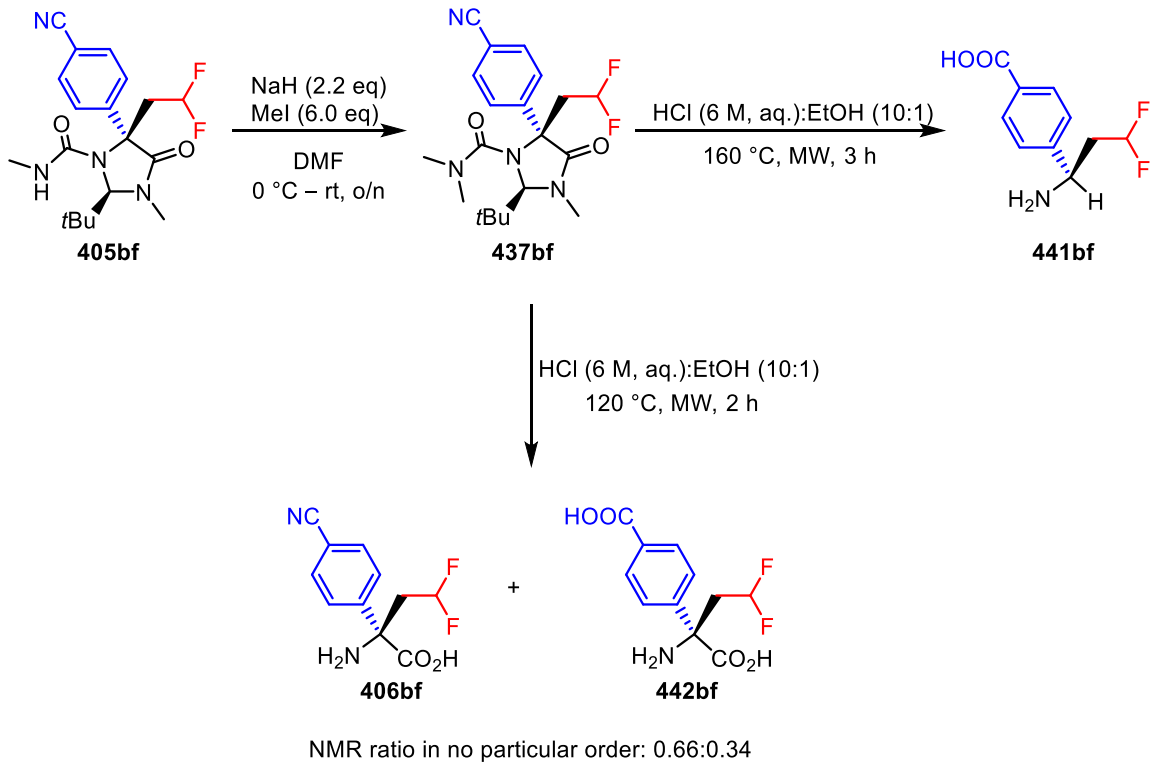


Scheme 108: Failed aryl migration and elimination reaction

Aryl migration failed to occur with substrate **427cf** (Scheme 108). Decomposition was observed with the use of KHMDS and LDA. This was not surprising as previous studies within the group also observed decomposition for the migration of a 4-$CF_3C_6H_4$ using KHMDS.[268] With the weaker KO*t*Bu base, starting material was recovered. Nevertheless, the 4-$CF_3C_6H_4$ ring was migrated under the mild conditions of phase transfer catalysis (see section 2.2.3).

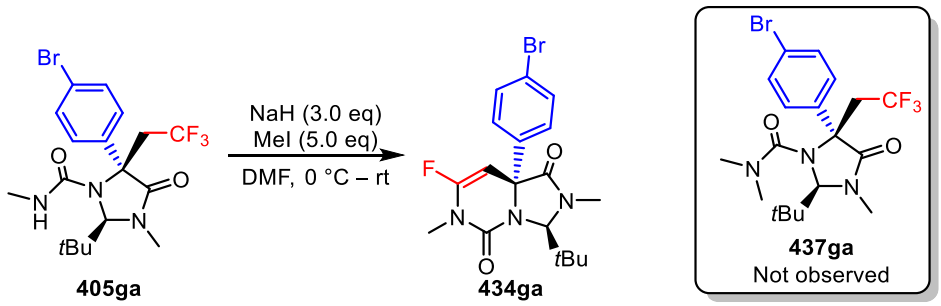
2.3.6 Attempted Hydrolysis to Amino Acids

To show the practicality of the method in affording enantioenriched α-aryl quaternary amino acids containing fluorinated carbon side-chains, the hydrolysis of the aryl migration product **405bf** was attempted. Previous work within the group showed that similar compounds could be cleanly hydrolysed to the respective amino acids using a 10:1 HCl:ethanol solvent system.[160]



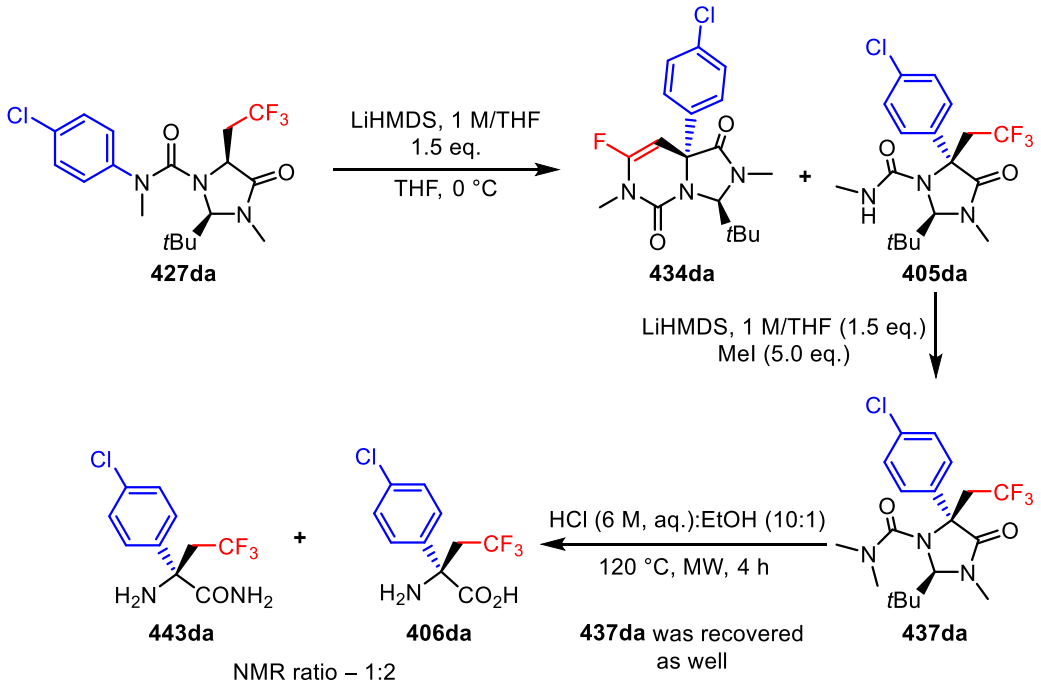
Scheme 109: Attempted hydrolysis of **405bf**

The urea NH in **405bf** was methylated to prevent cyclisation of the urea unto the carboxylic acid that would be revealed on hydrolysis. Treatment of **437bf** with 10:1 6M HCl:ethanol mixture at 160 °C in a microwave reactor afforded the decarboxylated product **441bf** (Scheme 109). Delightfully, when the reaction was repeated at 120 °C, a mixture of hydrolysed products **406bf** and **442bf** was observed by ^{13}C NMR.



Scheme 110: Attempted methylation of **405ga**

Due to unavailability of substrate **405bf** and insufficient time to make more, an attempt was made to carry out the hydrolysis on **405ga** (Scheme 110). Unfortunately, the attempted methylation of **405ga** led to the formation of the bicyclic product **434ga**. To circumvent this, the one pot aryl migration and *N*-methylation of **427da** was performed (Scheme 111). Favourably, the *N*,*N*-dimethylated urea **437da** could be separated from the bicyclic product **434da**. The urea **437da** was finally subjected to the previous hydrolysis conditions for 4 hours in a microwave reactor. A mixture of the amino acid **406da**, amino amide **443da**, and the *N*,*N*-dimethylated urea starting material **437da** was observed by ^{13}C, ^{1}H and ^{19}F NMR.

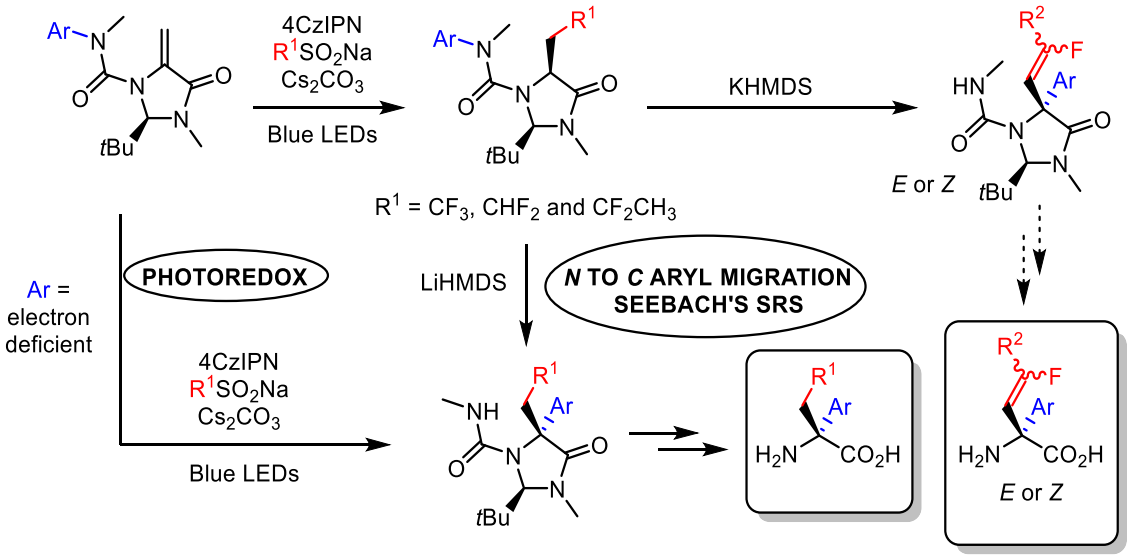


Scheme 111: Attempted hydrolysis of **427da**

Though the optimal hydrolysis conditions have not been achieved yet, these investigations have laid a foundation for further work.

2.3.7 Conclusion and Future Work

The synthesis of α-aryl quaternary amino acids containing fluorinated carbon side-chains has been discussed. The methodology incorporates three important tools: Photoredox catalysis for introducing the fluorocarbon side-chain of the new amino acid; *N* to *C* aryl migration of α-metallated ureas for introducing the aryl side-chain of the new amino acid and Seebach's self-regeneration of stereocentres for inducing diastereoselectivity in the aryl migration (Scheme 112).



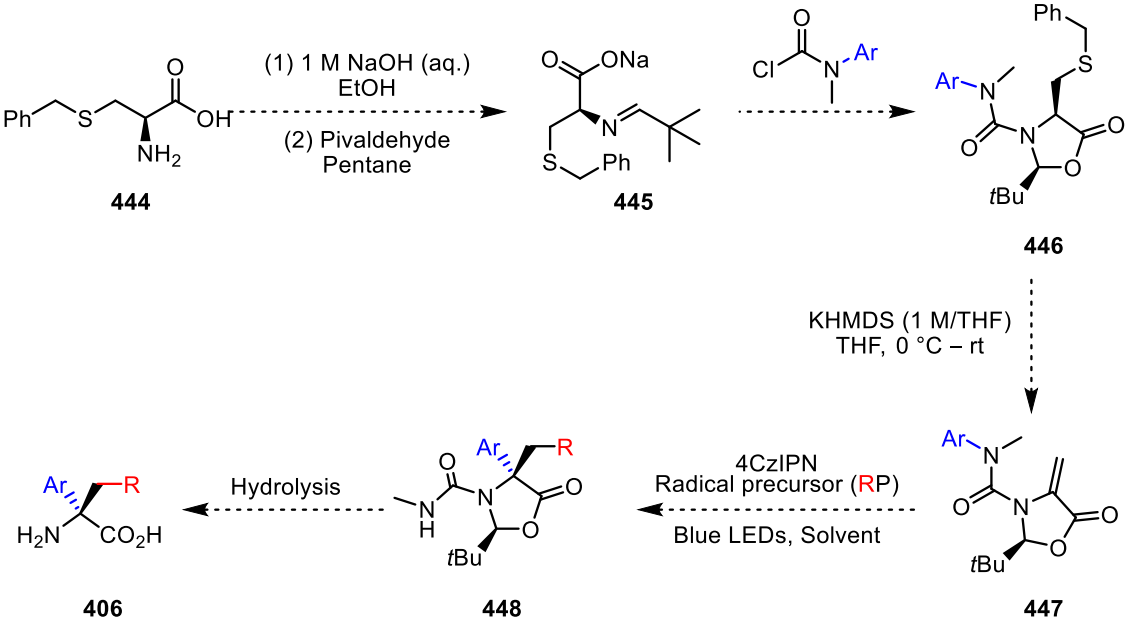
Scheme 112: Summary of work

This method provides a useful route for making fluorinated small molecules. These molecules are important to the field of pharmaceutical industry, as many of them show anti-malarial, anti-ulcer and anti-diabetic activity.[269] In addition, the presence of a C-F bond in peptide-based drugs is known to improve their lipophilicity, metabolic stability and bioavailability.[270,271]

Future work should focus on expanding the scope of the reaction to include additional electron-deficient aryl rings, as well as electron-rich and doubly substituted aryl migratory rings. Further radical precursors should also be considered for the radical conjugate addition step. An example includes phosphinoyl radicals, which have been reported to undergo conjugate addition to styryl based vinyl ureas.[253] Further hydrolysis optimisations to obtain exclusively the amino acid should also be performed.

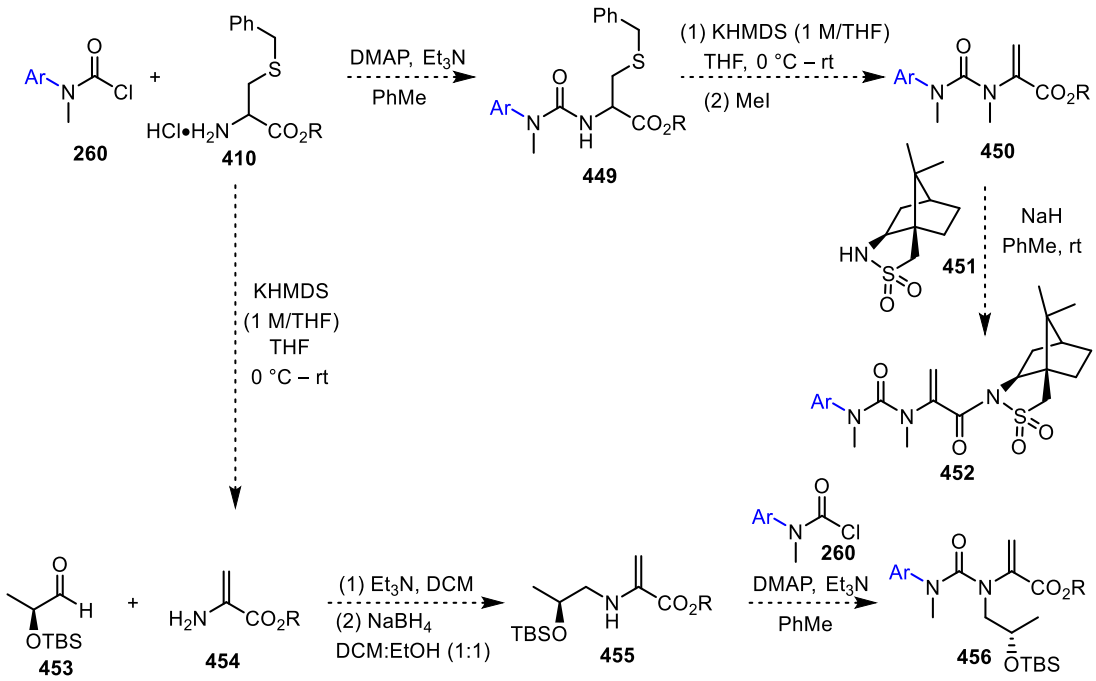
As discussed in section 2.3.1, radical addition to oxazolidinone Dha derivatives is already known. It might be possible to access analogous oxazolidinone vinyl ureas **447** using similar methodology to that used by Seebach for the synthesis of his oxazolidinones (see section 1.3.2). These

oxazolidinone vinyl ureas could then be subjected to radical addition and ensuing *N* to *C* aryl migration under the photoredox conditions to afford **448**, which on hydrolysis should furnish the enantioenriched α-aryl quaternary amino acids **406** (Scheme 113).



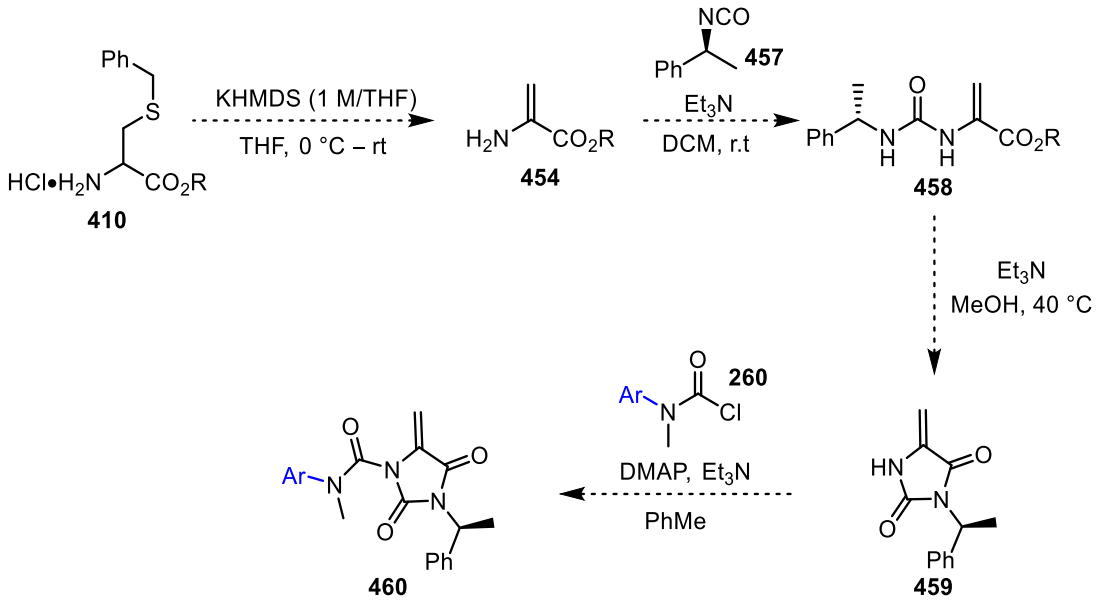
Scheme 113: Oxazolidinone vinyl ureas towards achieving α-aryl quaternary amino acids

A chiral auxiliary approach could also be considered in achieving diastereoselectivity in the radical conjugate addition and ensuing *N* to *C* aryl migrations. The use of chiral auxiliaries would not only induce stereoselectivity but also alter reactivity, hopefully leading to a broader substrate scope. Several pathways could be explored towards attaining the starting chiral vinyl ureas. Coupling of the carbamoyl chloride **260** with amino ester hydrochloride **410** should afford the singly *N*-methylated urea **449**.[152] This urea could then be treated with KHMDS and quenched with methyl iodide to afford the *N*,*N*'-dimethylated vinyl urea **450**. To introduce the chiral auxiliary component, **450** could be reacted with a chiral amine; An example of a chiral amine is the camphorsultam **451**, which was used by Yajima and Ikegami in similar radical conjugate addition reactions.[250] Following similar procedure to that used by Metz and co-workers,[272] the vinyl urea **450** could be reacted with **451** to obtain the final vinyl urea **452**. *Tert*-butanesulfinamide could also be used in place of camphorsultam in the reaction sequence. An alternative pathway is to introduce the chiral auxiliary component directly to the amine residue of the amino acid. Both enantiomers of the aldehyde **453** are easily accessible on a large-scale from the inexpensive (*R*)-Methyl 2-hydroxypropanoate and (*S*)-Ethyl 2-hydroxypropanoate.[273] Reductive amination of **453** with **454**, obtained from treating **410** with KHMDS, should afford the amine **455** as $NaBH_4$ alone is incapable of reducing olefins or esters. Finally, coupling of **455** with carbamoyl chlorides **260** should afford the final vinyl ureas **456** (Scheme 114).



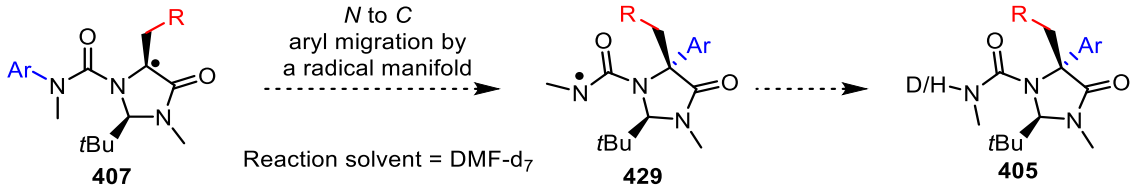
Scheme 114: Synthesis of chiral vinyl ureas employing either camphorsultam or *tert*-butanesulfinamide as chiral auxiliary

Another methodology that could be investigated is introducing the chiral auxiliary component through the commercially available and inexpensive chiral isocyanate **457** (Scheme 115). Treatment of **454** with the isocyanate **457** should afford the urea **458**. To avoid racemisation, cyclisation of **458** to **459** is facilitated by the weak triethylamine base.[222] The cyclised product **459** could then be coupled with carbamoyl chlorides **260** to afford the final vinyl ureas **460**.



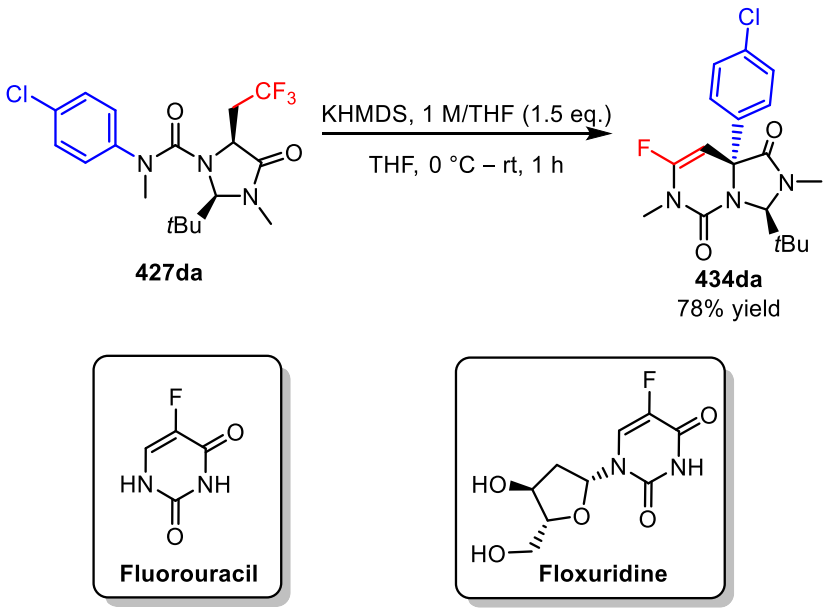
Scheme 115: Synthesis of chiral vinyl ureas employing an isocyanate chiral auxiliary

Ultimately, the mechanism of the aryl migration in all the vinyl urea scaffolds would be probed. As stated earlier, the mechanism for the photoredox catalysed *N* to *C* aryl migration in the imidazolidinone vinyl ureas can either be by a radical manifold or by a radical polar crossover (see Scheme 103). Further deuterium experiments would have to be carried out to ascertain which. Performing the reaction in DMF-d_7 and doing a deuterium analysis of the proton bonded to the urea distal nitrogen in **405** will give some insight into this (Scheme 116). If analysis of the said proton reveals deuterium incorporation, it indicates the occurrence of H-atom abstraction, signifying that the aryl migration could be going through a radical manifold.



Scheme 116: Mechanistic investigation by a deuterium experiment

Similar deuterium experiments could be applied to the other vinyl urea scaffolds suggested above. Additionally, Stern-Volmer studies would have to be done to investigate which substrate in the photoredox reaction is actively quenching the excited PC.



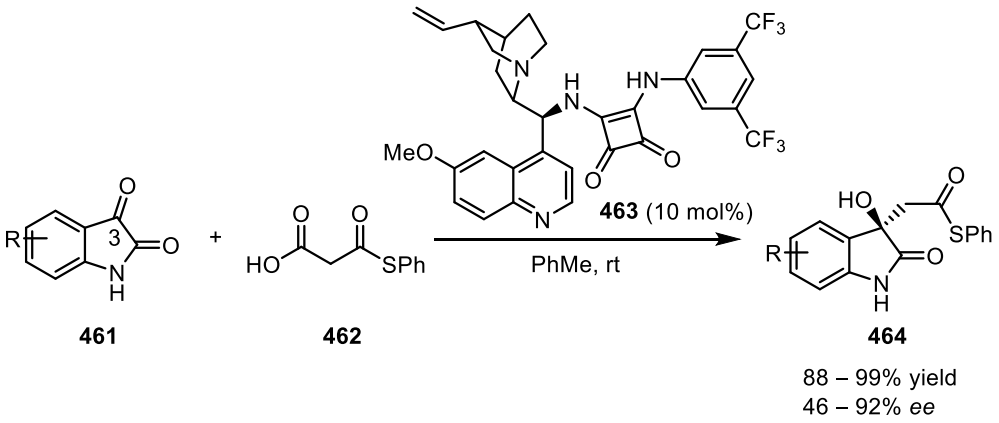
Scheme 117: Attempted aryl migration of **427da**

It was presented in section 2.3.5 that attempted aryl migration of the addition product **427da** gave exclusively the bicyclic product **434da** in a 78% yield (Scheme 117). The product **434da** has the potential of exhibiting bioactivity as similar pyrimidine analogues such as fluorouracil and Floxuridine, are used in the treatment of cancer.[274,275] As **434da** was formed cleanly and easily in only 1 hour, the reaction should be explored further for the synthesis of other analogues.

2.4 Decarboxylative Arylation of Urea Malonic Acid Half Esters

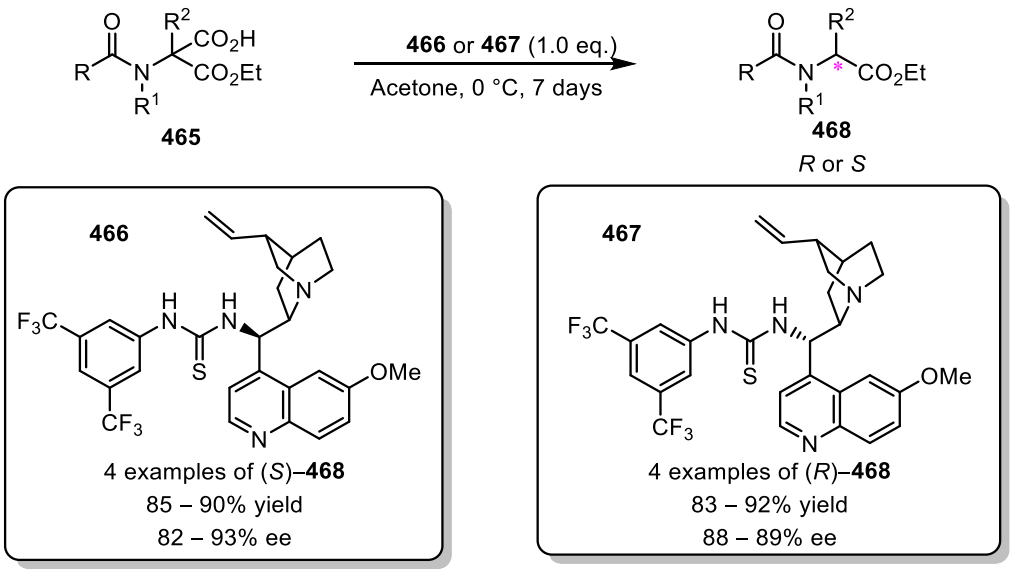
2.4.1 Introduction

Decarboxylative enantioselective C-C or C-H bond formation employing the use of chiral bases is a developing area of modern organic chemistry.[276] The process generally involves the base-mediated extrusion of CO_2 from a carboxylic acid-bearing substrate to produce an anion. The anion can either be quenched by a proton or undergo reaction with electrophiles. An example is the decarboxylative aldol reaction of malonic acid half thioester **462** with isatin **461** (Scheme 118).[277] Decarboxylation of **462** produces an enolate, which undergoes nucleophilic attack on the C-3 carbonyl of **461**, hence producing a new C-C bond between the α-carbon of **462** and carbon 3 of **461**. The reaction was catalysed by the chiral cinchona alkaloid squaramide base **463** and the products **464** were obtained with up to 99% yield and 92% *ee*.



Scheme 118: An example of decarboxylative enantioselective C-C bond formation

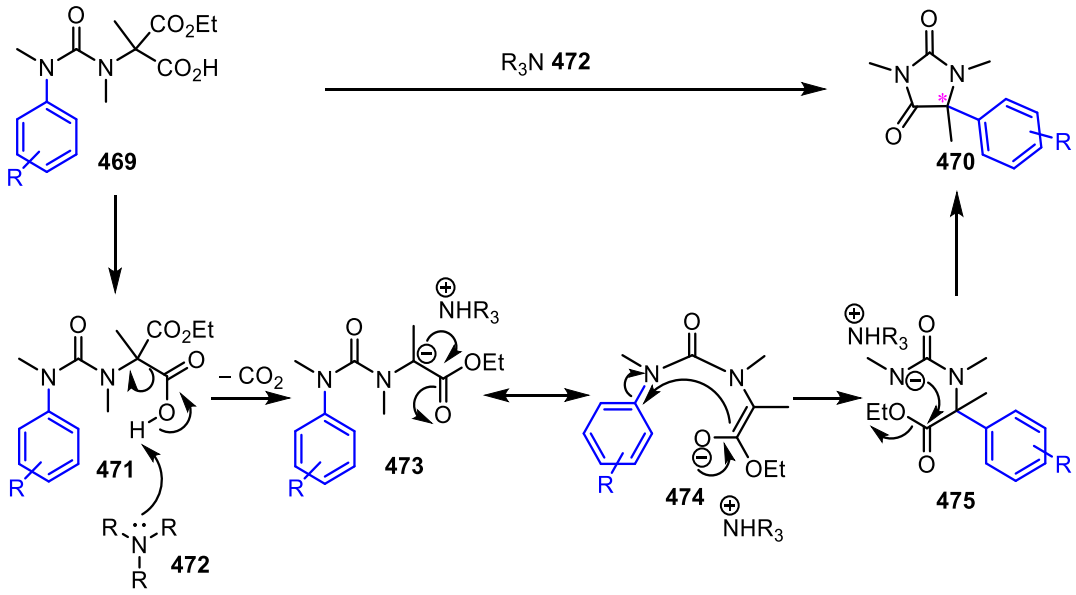
As an example of a C-H bond forming process, Rouden *et al*. disclosed the decarboxylative protonation of amino malonic acid half esters **465** (Scheme 119).[278] Stoichiometric amounts of the cinchona-derived thioureas **466** or **467** were used to facilitate decarboxylation. As there was no available electrophile in the reaction, the enolate formed on decarboxylation was quenched by a proton, affording the (*R*) or (*S*)-tertiary amino acid derivatives **468** in good yields and enantioselectivities. The enantioselectivity of the reaction was reversed simply by inverting the configuration of only one of the four stereocentres in the bases **466** and **467**.



Scheme 119: An example of decarboxylative enantioselective C-H bond formation

2.4.2 Project Proposal

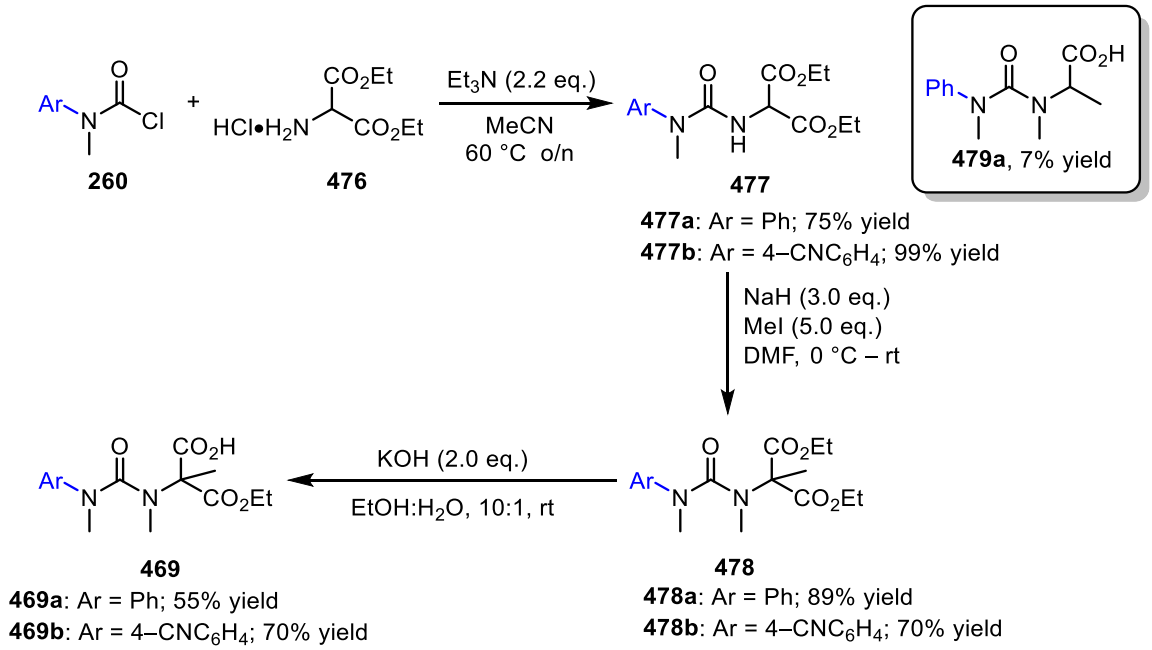
It was envisaged that if a urea bearing an *N*-aryl group were introduced into the α-position of a malonic acid half ester derivative (as in **469**), treatment of this derivative with a chiral amine base **472** would not only lead to decarboxylation, but also attack of the ensuing enolate on the *N*-aryl ring, resulting in aryl migration followed by cyclisation to give an imidazolidinone **470** (Scheme 120). Interaction of the chiral ammonium ion with the enolate should induce enantioselectivity in the formation of the imidazolidinone **470**. The imidazolidinone could then be hydrolysed to give enantiomerically enriched α-aryl quaternary amino acids.



Scheme 120: Proposed mechanism for decarboxylative intramolecular arylation

2.4.3 Synthesis of Urea Malonic Acid Half Esters

To begin the project, the urea malonic acid half esters **469** were synthesised following the 3-step procedure illustrated in Scheme 121. On heating amino malonate ester hydrochloride **476** with carbamoyl chloride **260** and triethylamine in acetonitrile, nucleophilic attack of the amine of **476** on the carbonyl of **260**, followed by a chloride elimination occurred, affording the urea **477** in good to excellent yields. Treatment of **477** with sodium hydride and 5 equivalents of methyl iodide gave the doubly methylated product **478**. It is noteworthy that methylation of **477** with only 2.2 equivalents of methyl iodide in THF resulted in only α-methylation of **477**. Finally, selective basic hydrolysis of one ester group of **478** in ethanol and water afforded the urea malonic acid half ester **469**. No double hydrolysis was observed by ^{1}H NMR, however 7% of decarboxylated product **479a** was isolated when Ar = Ph.



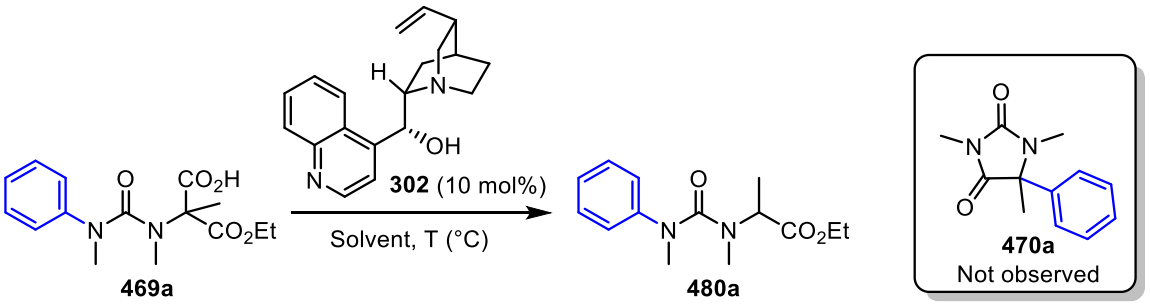
Scheme 121: Synthesis of urea malonic acid half esters

2.4.4 Attempted Aryl Migration of Urea Malonic Half Esters

With a route towards the starting ureas established, the proposed aryl migrations could then be investigated. Urea **469a**, having an electron-neutral phenyl migratory ring was chosen as the model substrate. The chiral cinchonidine base **302** was readily available; hence it was chosen for initial investigations. Several solvents were tested for the aryl migration using a catalytic amount of cinchonidine (Table 41). In THF, decarboxylation and subsequent protonation occurred affording the product **480a**; there was no trace of the desired rearranged product **470a** (Table 41, entry 1). Addition of LiCl to the reaction led to a reduction in the formation of **480a**, but there was still no trace of **470a** by ^{1}H NMR (Table 41, entry 2). The use of less polar solvents like toluene and diethyl

ether led to a significant decrease in the rate of the reaction (Table 41, entries 3 – 5). There was no reaction in chloroform at room temperature, but when the reaction was warmed up to 50 °C, conversion to **480a** was observed (Table 41, entry 6). Unfortunately, in all the reactions, the enolate formed was quenched by a proton before it could undergo nucleophilic attack on the *N*-phenyl ring. It was nevertheless encouraging to know that decarboxylation was occurring.

Table 41: Attempted aryl migration of **469a**

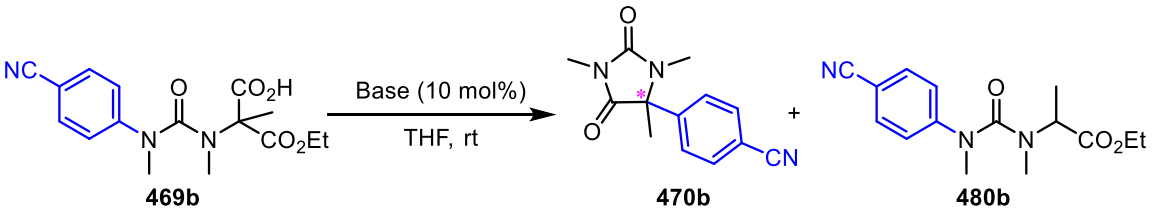


Entry	Solvent	Additive[a]	T (°C)	Time (h)	480a:469a[b]
1	THF	-	rt	20	7:1
2	THF	LiCl	rt	20	2:1
3	PhMe	LiCl	rt	24	1:10
4	PhMe: acetone (5:1)	LiCl	rt	20	1:5
5	Et_2O	LiCl	rt	24	1:10
6	$CHCl_3$	LiCl	rt – 50	48	1:2

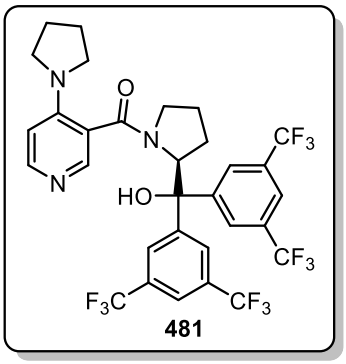
[a] 3.0 eq. of additive [b] Ratio by ^{1}H NMR

With the notion that an electron-deficient aryl ring on the urea might enable aryl migration to outcompete protonation of the enolate, urea **469b**, having an electron-withdrawing 4-cyano group, was subjected to the rearrangement (Table 42). The use of cinchonidine **302** gave only the decarboxylated product **480b** (Table 42, entry 1). Addition of LiCl decreased the rate of the reaction but gave an encouraging 20% of the desired aryl migration product **470b** albeit with poor enantioselectivity (Table 42, entry 2). A control reaction showed that LiCl was not capable of facilitating the aryl migration on its own (Table 42, entry 3). The presence of LiCl in the reaction probably enhances the polarity of the solvent thereby enhancing enolate solubility. Additionally, LiCl has been shown to increase the reactivity of enolate aggregates by formation of mixed aggregates with the enolate.[279]

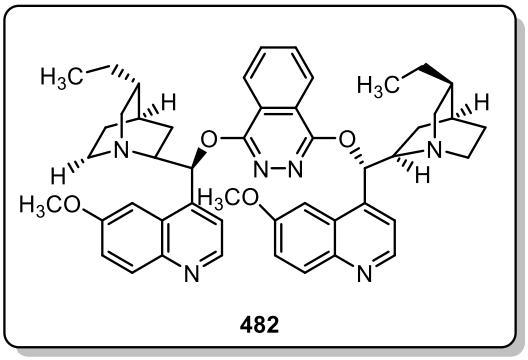
Table 42: Attempted arylation of **469b**



469b **470b** **480b**



481



482

Entry	Base	Additive[a]	Time (h)	Results	*er* (470b)
1	**302**	-	26	**480b**[b]	-
2	**302**	LiCl	29	20[c];32[d]	48:52
3	-	LiCl	44	Trace[c,d]	-
4	**481**	LiCl	48	Trace[c]; 39[d]	-
5	**482**	LiCl	41	16[c];41[d]	50:50
6[e]	**302**	LiCl	48	**470b**:**480b**[f,b]	50:50
7[e]	**302**	-	24	**470b**:**480b**[f,b]	52:48
8[g]	**302**	-	24	**470b**:**480b**[f,b]	51:49

[a] 3 eq. of additive; [b] Complete conversion to; [c] Isolated yield of **470b**, trace: observed by ^{1}H NMR; [d] Isolated yield of **480b**, trace: observed by ^{1}H NMR; [e] 1:4 THF:DMF used as solvent; [f] 1:1 ratio by 1 H NMR; [g] DMF used as solvent

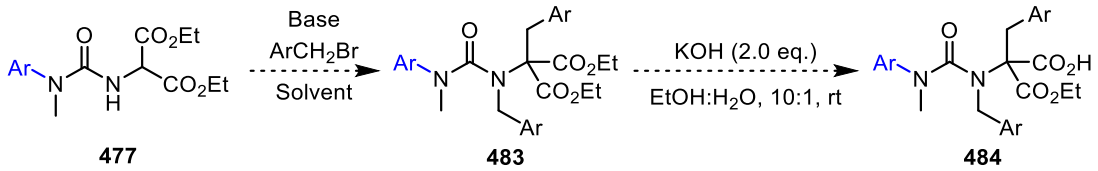
Keeping LiCl as additive, alternative bases were tested for the decarboxylative aryl migration. The use of 4-dimethylaminopyridine derivative **481** gave only trace amounts of the desired product **470b** and about 39% of **480b**, contaminated with starting material (Table 42, entry 4), while $(DHQD)_2$-PHAL **482** gave racemic **470b** in a 16% yield and **480b** in a 41% yield (Table 42, entry 5). It is proposed that the bases **481** and **482** promote the formation of **480b** over **470b** because of their steric bulk. The enolate may be sterically crowded by tight ion-pairing with the ammonium ion of these bases, hence promoting enolate attack on the smaller sized-proton rather than the aryl ring. Additionally, increased steric bulk of the catalyst could disfavour the necessary conformation of the enolate to attack the aryl ring. The less hindered cinchonidine **302** was re-examined using a more polar 1:4 (THF:DMF) solvent system. This led to complete conversion to the products **470b** and **480b** in a 1:1 ^{1}H NMR ratio, both in the presence and absence of lithium chloride (Table 42,

entries 6 and 7). The same result was obtained with the use of DMF alone in the absence of LiCl (Table 42, entry 8). In all cases, poor enantioselectivity was obtained.

2.4.5 Conclusion and Future Work

It is now established that aryl migration and subsequent cyclisation to imidazolidinones is possible in urea malonic acid half esters. The optimisations presented provide key information for future developments – aryl migration is faster and promoted in polar solvents, without the need for an additive. Future work should focus on optimising the reactions further: first by increasing the yield of the aryl migration pathway (imidazolidinone formation) before continuing the development of an enantioselective version. Achiral bases such as triethylamine could be used to achieve a non-enantioselective transformation.[280] Some solvents that have been used effectively in decarboxylative C-H or C-C bond formation include acetone[278] and chloroform.[281,282] Some non-polar solvents that have been used include *tert*-butyl methyl ether and cyclopentyl methyl ether.[283,284] These solvents can be tested in the reaction; however, the non-polar solvents might require an additive. In the development of an enantioselective transformation, several chiral bases could be tested in the reaction; a number of efficient chiral bases for decarboxylative C-C formation have been reported in the literature.[276]

In addition, the urea substrate **469** could be modified by introducing other groups apart from a methyl to the α-carbon of the malonic ester residue and the NH of the urea residue in **477** (Scheme 122). This will not only alter reactivity, but also help to broaden the substrate scope, since the α-carbon and its substituents are preserved in the final amino acid hydrolysis product.

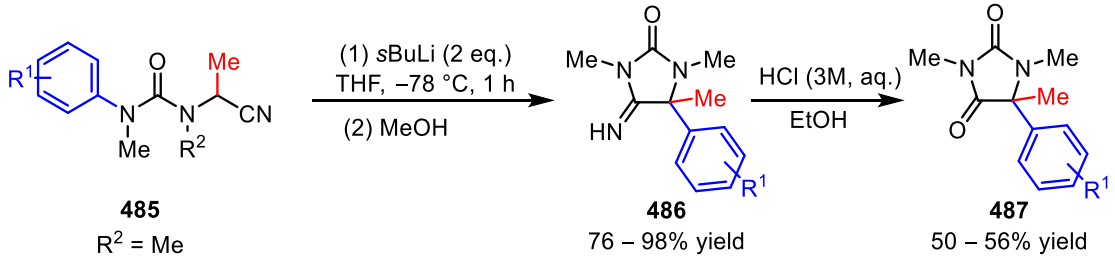


Scheme 122: Proposed modification of the urea malonic acid half ester

2.5 Diastereoselective Arylation of α-Amino Nitriles[1]

2.5.1 Previous work

Earlier work within the Clayden group had developed the base-mediated intramolecular arylation of amino nitriles **485** to afford imino hydantoins **486** (Scheme 123).[152] Migration of the *N′*-aryl substituent of the *N′*-aryl-*N*-1-cyanoethyl ureas **485** to the α-carbon of its amino nitrile had evidently occurred, followed by cyclisation of the urea anion unto the cyano group to reveal **486** in good to excellent yields.



485
R^2 = Me

486
76 – 98% yield

487
50 – 56% yield

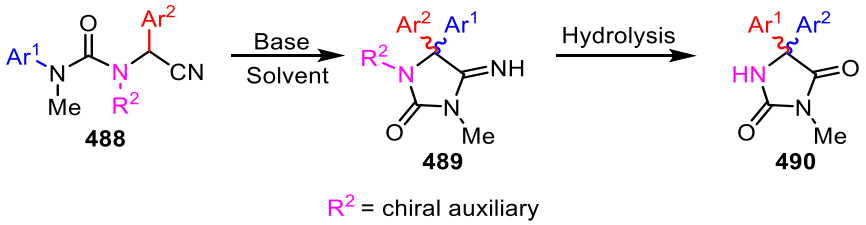
Scheme 123: Aryl migration of amino nitrile ureas

The reaction was tolerant of both electron-neutral and electron-rich migratory rings. A selection of imino hydantoins **486** were subsequently hydrolysed to afford **487** as racemic aryl substituted hydantoin derivatives of alanine.

2.5.2 Overview of Route

The method described in Scheme 123 gives racemic quaternary amino acid derivatives. It has been shown within the Clayden group that enantiopure quaternary amino acids can be accessed by the intramolecular arylation of amino acids through an imidazolidinone intermediate;[160] however, for the synthesis of diarylglycines, lower enantioselectivities were obtained due to racemisation occurring during synthesis of starting materials.[285–287] Hence another method is needed. It was proposed that incorporating a chiral auxiliary as R^2 (refer to **485** in Scheme 123) in an aryl glycine amino nitrile urea **488** (Scheme 124), might cause the intramolecular arylation to take place diastereoselectively, thereby affording enantioenriched α,α-diarylglycine derivatives **490** on hydrolysis. This method would also give access to enantiopure derivatives of phenytoin **490** (Ar^1 = Ar^2 = C_6H_5), an hydantoin used as an anticonvulsant.

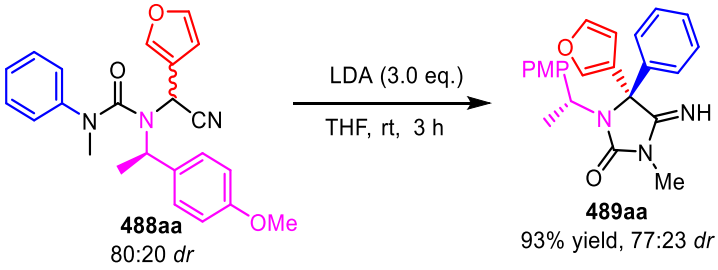
[1] *Published work*: Mas-Roselló, J.; Okoh, M.; Clayden, J. *Chem. Commun.* **2018**, *54*, 10985



Scheme 124: Proposed route towards enantioenriched α,α-diarylglycine derivatives

In addition, this method will have no racemisation issue since the enantioselectivity is determined by the chiral auxiliary and not the amino acid. A wide scope of α,α-diarylglycines could also be accessed since the method will not be limited to only phenylglycine derivatives.

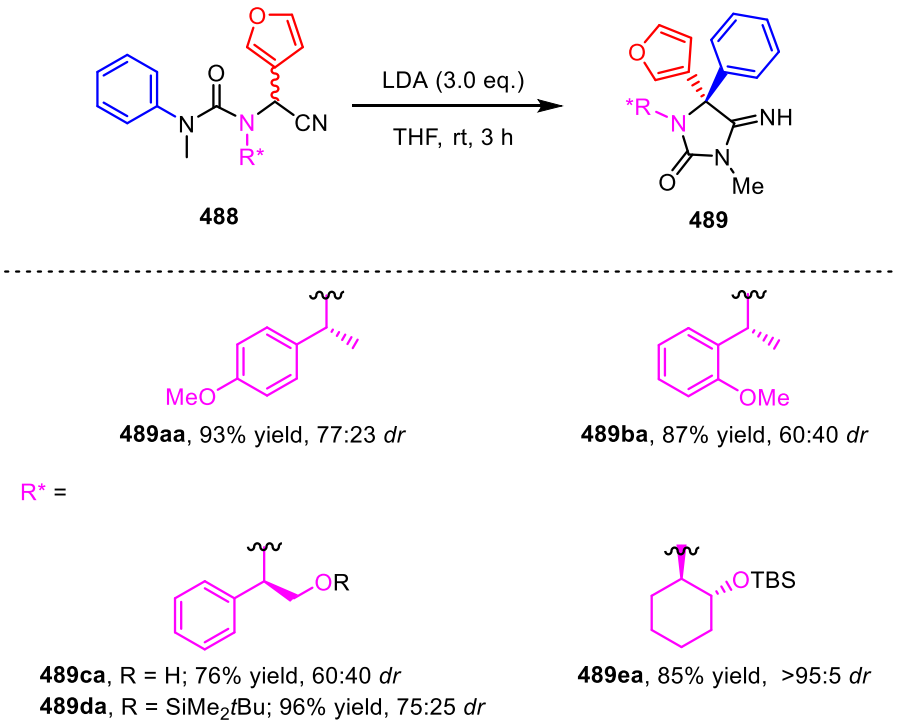
Preliminary investigations using (*R*)-1-(4-methoxyphenyl)ethylamine (indicated in purple) as the chiral auxiliary showed that 3 equivalents of LDA in THF was optimal for the migration of a phenyl group to the α-position of an amino nitrile **488aa** bearing a 3-furyl group at the same position (Scheme 125).



Scheme 125: Optimal condition (Absolute configuration of new stereogenic centre in **489aa** not determined).[1]

Satisfied with a 93% yield of **489aa**, the next endeavour was to improve the diastereoselectivity. A series of amino nitrile ureas **488** was made, as diastereomeric mixtures, from the corresponding enantiopure amines highlighted in purple (refer to Table 43 and Table 44 for synthetic route).

[1] Optimisations done by Dr Josep Mas Roselló



Scheme 126: Optimisation of chiral auxiliary (Absolute configuration of new stereogenic centre in **489** not determined).[1]

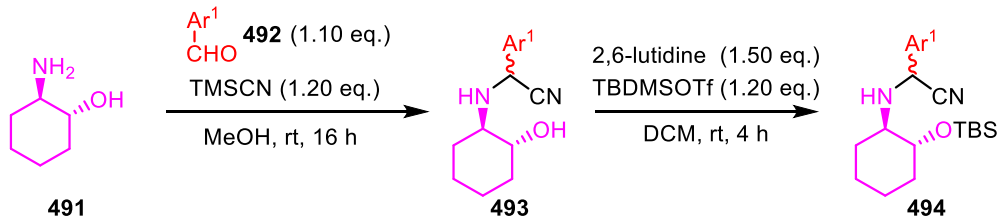
Ureas **488** were subjected to the optimal conditions and *O*-silyl protected (1*R*),(2*R*)-2-amino cyclohexanol (**491**), precursor to **488ea**, was found to be the optimal chiral auxiliary producing a >95:5 *dr* of the aryl migration product **489ea** (Scheme 126). This was convenient because both enantiomers of *trans*-2-amino cyclohexanol **491** are commercially available. Furthermore, they can be easily made by amination of the corresponding meso epoxide.[288,289] The OH group also allows for variation of the steric and electronic properties of the auxiliary.

2.5.3 Synthesis of Amino Nitrile Ureas

With the optimal chiral auxiliary revealed, a selection of amino nitrile ureas **488e** was synthesised by the 4-step synthesis illustrated in Table 43 and Table 44. (1*R*),(2*R*)-2-amino cyclohexanol **491** was reacted with TMSCN and the desired aldehyde **492** to afford the corresponding α-amino nitrile **493**. The amino nitriles were unstable and capable of hydrolysing back to the aldehyde; hence they were used immediately in the next step to afford silyl protected alcohols **494** (Table 43). The diastereoselectivity at the α-carbon is irrelevant as this centre is destroyed in the rearrangement.

[1] Joint work of the author and Dr Josep Mas Roselló

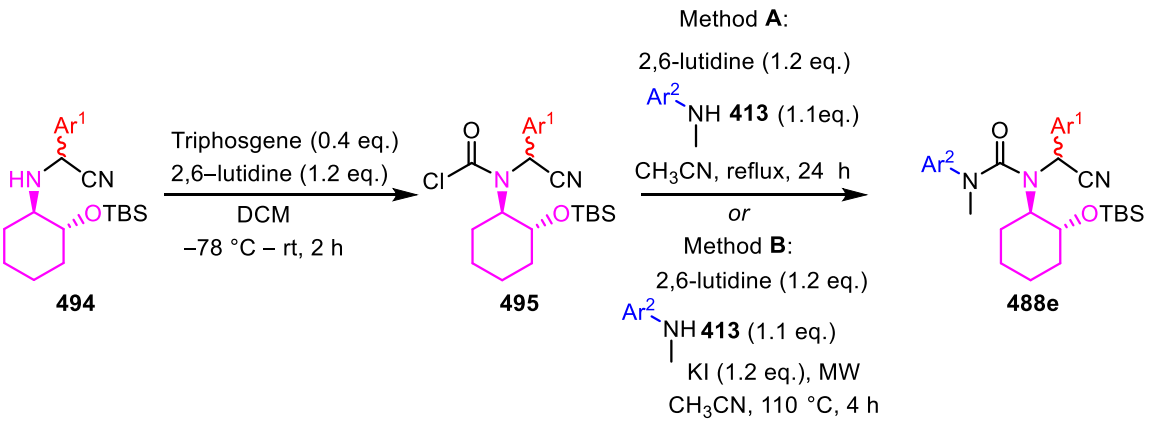
Table 43: Synthesis of α-amino nitriles **494**



Entry	Ar^1	Product	Yield (%)	*dr*
1	3-furyl	**494a**	52	65:35
2	4-FC_6H_4	**494b**	38	75:25
3	Ph	**494c**	49	70:30

Nitriles **494** were subjected to reaction with triphosgene to afford carbamoyl chlorides **495** (Table 44). It was observed that treating **495** with KI, 2,6-lutidine and the corresponding *N*-methylaniline **413** in a microwave reactor at 110 °C (Method **B**) led to the removal of the silyl group and subsequent attack of the exposed hydroxyl group on the carbonyl of **495**, resulting in low yields of **488e**. This issue was resolved by eliminating KI from the reaction and refluxing in acetonitrile for 24 hours (Method **A**).

Table 44: Synthesis of α-amino nitrile ureas **488e**



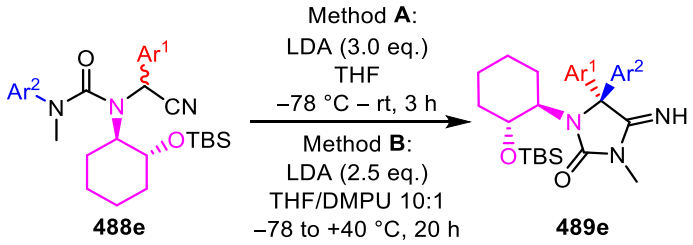
Entry	Ar^1	Ar^2	Product	Yield (%)	*dr*
1	3-furyl	C_6H_5	**488ea**	17[a]	50:50
2	4-FC_6H_4	C_6H_5	**488eb**	11[a]	50:50
3	C_6H_5	4-FC_6H_4	**488ec**	58[b]	50:50
4	C_6H_5	D_5-C_6H_5	**488ed**	51[b]	50:50

[a] Method **B**; [b] Method **A**

2.5.4 Aryl Migration of α-amino nitrile ureas

The aryl migration reactions were carried out on substrates **488e** (Table 45). Using the optimal conditions (method **A**), both diastereoisomers of **488ea** ($\mathbf{D_A}$ and $\mathbf{D_B}$) were independently subjected to the aryl migration reaction (Table 45, entries 1 and 2). In both cases, **489ea** was obtained in good yields and excellent diastereoselectivity. **488eb** and **488ed** showed good conversion to their respective rearranged products **489eb** and **489ed** with excellent diastereoselectivities (Table 45, entries 3 and 5). The substrate **488ed**, however, had to be left for more than 3 hours for complete conversion to occur. The synthesis of **489ed** as a single diastereoisomer shows the usefulness of this method in accessing diarylglycines which might ordinarily be difficult to obtain through normal resolution methods due to the similarity of the two substituents at the chiral centre.[290] Urea **488ec**, which is a positional isomer of **488eb**, surprisingly required more forceful conditions (method **B**) than **488eb** for the aryl migration to occur (Table 45, entry 4). It is remarkable that access to molecules having an opposite configuration at the α-carbon (**489eb** and **489ec**) is possible by alternating the positions of Ar^1 and Ar^2. This would be useful for obtaining opposite enantiomers of the final hydantoin.

Table 45: Aryl migration reactions

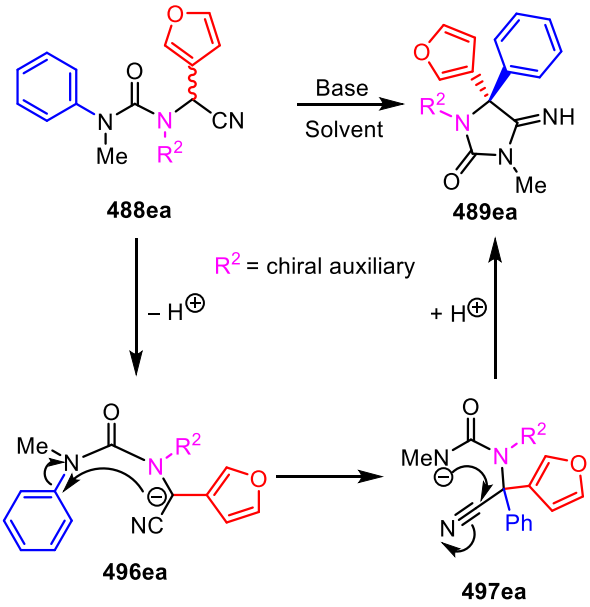


Entry	488	489	Ar^1	Ar^2	Yield (%)	*dr*
1[a]	**488eaD$_A$**	**489ea**	3-furyl	C_6H_5	68	>95:5
2[a]	**488eaD$_B$**	**489ea**	3-furyl	C_6H_5	85	>95:5
3[a]	**488eb**	**489eb**	4-FC_6H_4	C_6H_5	93	98:2
4[b]	**488ec**	**489ec**	C_6H_5	4-FC_6H_4	51	94:6
5[a,c]	**488ed**	**489ed**	C_6H_5	D_5- C_6H_5	75	>95:5

[a] Method A; [b] Method B; [c] Reaction left overnight. The absolute configuration of the new stereogenic centre in **489e** was assigned by analogy to **489ee** (see Scheme 128)

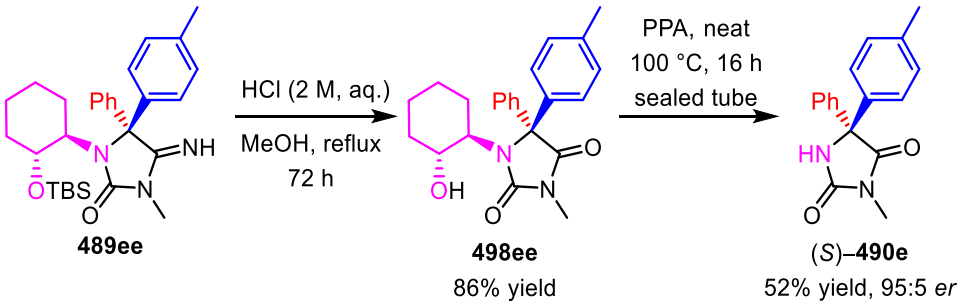
As described in section 1.4, the mechanism of the intramolecular aryl migration is related to a Smiles or Truce-Smiles rearrangement. However, unlike the Smiles rearrangement, the migratory aryl group does not require activation by an electron-withdrawing group.[291] The well-defined conformation[292] of the urea brings the migratory aryl group close enough to the negatively charged

reaction centre in **496ea**, thereby inducing nucleophilic attack on the aryl group even without an electron-withdrawing substituent (Scheme 127).



Scheme 127: Proposed mechanism for intramolecular arylation of α-amino nitrile ureas

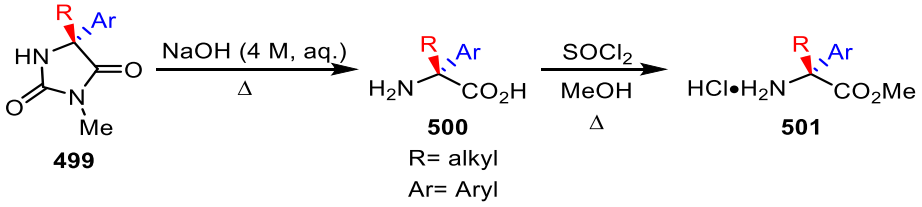
Compounds **489e** could be hydrolysed to the respective hydantoins. Dr Josep Mas Roselló illustrated this with substrate **489ee** (Scheme 128).[293] The aryl migration product **489ee** was firstly refluxed with HCl in methanol to remove the silyl group, resulting in **498ee**. The product **498ee** was then treated with polyphosphoric acid (PPA) to remove the chiral auxiliary, thereby furnishing **490e**. The absolute configuration of **490e** was determined to be *S* based on comparison with the HPLC trace of an authentic sample.[293]



Scheme 128: Hydrolysis of **489ee** into *C*,*C*-diaryl hydantoin **490e**

2.5.5 Conclusion

In summary, a method has been developed for the diastereoselective synthesis of phenytoin derivatives. This method provides access to diarylglycines without the use of a tertiary amino acid having the desired aryl sidechain, which might not be readily available. The method also overcomes the problem of racemisation encountered with the use of phenylglycine in the synthesis of starting materials.



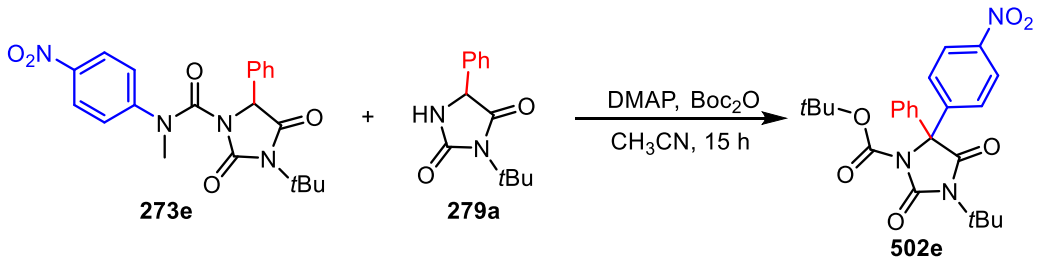
Scheme 129: Hydrolysis of hydantoins to amino acids

The *C*,*C*-diaryl hydantoins **490** can be potentially hydrolysed to α,α-diaryl quaternary amino acids. A literature precedent for this is the hydrolysis of *C*-alkyl,*C*-aryl hydantoins **499** reported in 2015 (Scheme 129).[153] The hydantoins **499** were hydrolysed to the amino acids **500** which due to purification issues were isolated as the amino acid ester hydrochloride salts **501**.

3 Appendix

3.1 Organocatalytic rearrangement using tertiary amines

In the synthesis of the hydantoin urea starting materials for the PTC aryl migrations (section 2.2.2), hydantoin urea **273e** was difficult to purify chromatographically because it had the same retention factor as its *N*-methyl-4-nitroaniline precursor. To obtain a pure fraction of **273e**, a slight excess of the carbamoyl chloride **280a** was added to the reaction mixture to consume the left-over *N*-methyl-4-nitroaniline. This worked well in consuming the *N*-methylaniline, however there was left an excess of carbamoyl chloride **280a** which hydrolysed back to the hydantoin **279a**. Unfortunately, **279a** had the same retention factor as **273e**; hence, they could not be separated by simple chromatography technique. Using a reaction procedure found in Pharm *et al.*,[294] the mixture of **273e** and **279a** was subjected to a reaction with DMAP (catalytic) and Boc anhydride. It was assumed that Boc protecting **279a** would lead to a change in its retention factor; hence making it possible to chromatographically separate **279a** from **273e**. Surprisingly, this was not the case – Boc anhydride, instead reacted with the entire mixture to give the Boc-protected rearranged product **502e** (Scheme 130).

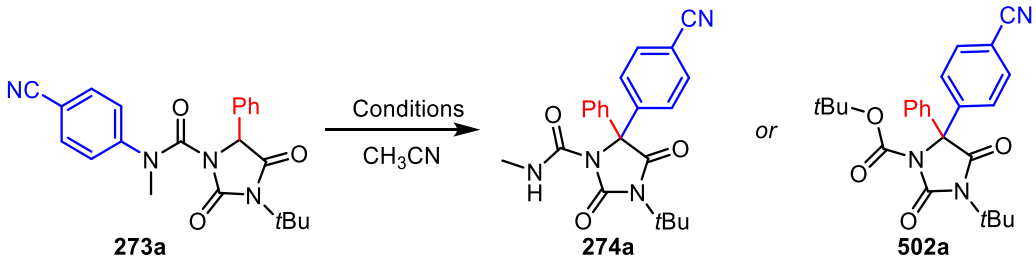


Scheme 130: Attempted protection of **279a** with a Boc group

This was quite remarkable because it was not anticipated that a tertiary amine such as DMAP would be able to deprotonate the α-H of the hydantoin urea **273e**. To investigate the rearrangement, substrate **273a** (having a 4-CNC_6H_4 migratory ring) and **273h** (having a 4-$CF_3C_6H_4$ migratory ring) were independently subjected to the reaction with DMAP and Boc_2O. The substrate **273h** was still unreacted after 15 hours while **273a** gave the product **502a** in 65% yield (Table 46, entry 1). It was assumed that there was no reaction with substrate **273h** because it was less activated towards an S_NAr reaction than **273e** and **273a**. The reaction was further investigated with the use of DMAP alone (without Boc_2O). Hydantoin urea **273a** was used as test substrate. After 15 hours, ^1H NMR showed a 4:1 ratio of starting material **273a** to unprotected product **274a** (Table 46, entry 2). Catalytic amounts of DMAP were continuously added until ^1H NMR showed a constant ratio of 2:1 starting material **273a** to unprotected product **274a** (Table 46, entry 3). When Et_3N + Boc_2O was

used in place of DMAP + Boc_2O, the unprotected rearranged product **274a** was obtained (Table 46, entry 4).

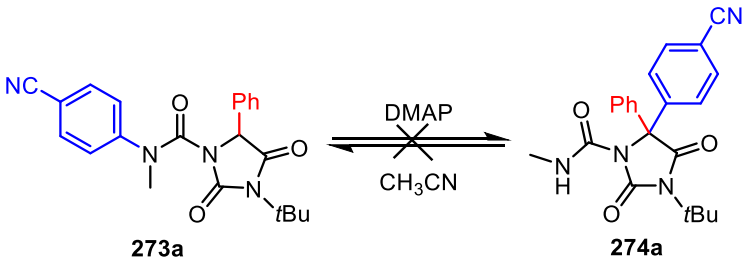
Table 46: Tertiary amine optimisation for rearrangement reaction



Entry	Base	Boc_2O	Comments/Yields
1	DMAP (cat.)	Yes	65% of **502a**[a]
2	DMAP (cat.)	-	4:1 **273a**:**274a**[b]
3	DMAP (non-cat.)	-	2:1 **273a**:**274ab**[b]
4	Et_3N	Yes	**274a**[c]
5	Et_3N	-	**273a**[c]
6	cinchonidine	-	**273a**[c]
7	cinchonidine	Yes	**274a**[c]

[a] Isolated yield; [b] 1H NMR ratio; [c] Observed by 1H NMR

When Et_3N was used in the reaction without Boc anhydride there was still no reaction after 24 hours (Table 46, entry 5), however when Boc anhydride was added to the reaction mixture, the unprotected rearranged product **274a** was formed. This suggests that Boc_2O aids the aryl transfer, probably through a deprotonation by *tert*-butoxide ion; however, a better understanding would be obtained by trying Boc_2O alone to see if it is enough to make the reaction work. Since tertiary amines in the presence of Boc anhydride induced the aryl transfer, it was expedient to check if a chiral tertiary amine in the presence of Boc-anhydride would induce stereoselectivity in the reaction. When the chiral amine cinchonidine was used as base in the reaction, as expected, there was still no reaction after 24 hours (Table 46, entry 6). When Boc anhydride was added to the reaction mixture, the unprotected rearranged product **274a** was formed (Table 46, entry 7). The product **274a** was found to be racemic, suggesting again that Boc anhydride must have aided the aryl transfer and not the chiral base.



273a **274a**

Scheme 131: reaction showing no equilibrium between **273a** and **274a**

To investigate the reversibility or irreversibility of the reaction, a catalytic amount of DMAP was added to an acetonitrile solution of **274a** to see if the reaction would go backwards towards the starting material **273a**. The rearranged product **274a** was still observed by ^{1}H NMR after 15 hours indicating that the rearrangement was not an equilibrium reaction (Scheme 131). As a non-catalytic amount of DMAP was sufficient to carry out the aryl migration without the influence of Boc_2O (Table 46, entry 3), it is worth investigating in the future if chiral tertiary amines would be able to facilitate the aryl migration and also induce enantioselectivity.

4 Experimental

4.1 General Information

Reactions requiring anhydrous conditions and inert atmosphere were carried out under dry nitrogen in flame-dried apparatus. Air- and moisture-sensitive solvents and reagents were transferred via a plastic syringe into the reaction vessels through rubber septa. Reactions carried out in a microwave reactor were completed on a Biotage Initiator+. All reagents were bought from chemical suppliers and used without further purification. The thiourea catalysts were sent to the group from Johannes Kepler University Austria. Some of the fluorinated cinchona-derived catalysts were sent to the group from the University of Oxford, United Kingdom. Anhydrous THF, DCM, PhMe and CH_3CN were dried using an anhydrous Engineering Grubbs-type solvent system. Et_3N was stored over KOH. Blue LEDs used were LED Strip Light MINGER 16.4ft(5m) RGB SMD 5050 LED Rope Lighting Colour Changing Full Kit with 44-Keys IR Remote Controller LED Lighting Strips for Kitchen Christmas Decoration (controller was used to set lights to highest blue intensity). The LEDs required 12 V direct current and were powered by a 2 A power supply resulting in a power output of 24 watts. The LEDs were wrapped around the interior of a glass beaker, with the exterior of the glass beaker wrapped in aluminium foil. During the course of the photo reactions, heat generated from the LED strip resulted in warming of the reaction mixtures to 30 °C.

Thin layer chromatography (TLC) was performed using commercially available aluminium backed silica plates (0.2 mm, 60 F_{254}). Visualisation was done under UV light (254 nm), or by staining with 'Seebach' dip or potassium permanganate.

Flash chromatography was performed on an automated Biotage Isolera™ Spektra Four using gradient elutions on pre-packed silica gel Biotage® SNAP Ultra/ZIP Sphere columns.

Melting points were measured on a Stuart Scientific melting point SMP 10 apparatus and are uncorrected.

FT-IR spectra were recorded on neat compounds using a Perkin Elmer (Spectrum One) FT-IR spectrometer, using a Universal ATR sampling accessory. Only strong and relevant absorptions are reported.

^{1}H NMR spectra were recorded on Jeol ECS or ECZ (400 MHz), Joel ECZ-var (400 MHz), Varian VNMR (400 MHz) or Bruker Ultrashield (400 MHz) spectrometers. Chemical shifts δ_H are quoted in parts per million (ppm) and referenced to the appropriate NMR residual solvent peak(s). For $CDCl_3$ (δ_H: 7.26 ppm), CD_3OD (δ_H: 3.31 ppm) and $(CD_3)_2SO$ (δ_H: 2.50 ppm).

^{13}C NMR spectra were recorded on Jeol ECS or ECZ (101 MHz), Joel ECZ-var (101 MHz), Varian VNMR (101 MHz) or Bruker Ultrashield (101 MHz or 126 MHz) spectrometers. Chemical shifts (δ_C) are quoted in parts per million (ppm) and referenced to the appropriate NMR residual solvent peak(s). For $CDCl_3$ (δ_C: 77.16 ppm), CD_3OD (δ_C: 49.00 ppm) and $(CD_3)_2SO$ (δ_C: 39.52 ppm). 2D-NMR experiments COSY, HSQC and HMBC were used where necessary to assign NMR spectra. Coupling constants (*J*) are quoted in Hertz (Hz).

19F NMR spectra were recorded on Jeol ECS or ECZ (377 MHz), Joel ECZ-var (377 MHz), or Bruker Ultrashield (377 MHz) instruments. Chemical shifts (δ_F) are quoted in parts per million (ppm) and referenced to an external standard. Spin-spin coupling constants (J) are reported in Hertz (Hz).

High resolution mass spectra were recorded on a Bruker Daltronics MicrOTOF 2 mass spectrometer (ESI) with only molecular ions $[M+H]^+$ and $[M+Na]^+$ reported.

4.2 General Procedures

Procedure 1: *Synthesis of cinchona salts*

Method A: To a suspension of the cinchona alkaloid (1.0 eq., 0.52 M) in a mixture of EtOH, DMF and $CHCl_3$ (2.5:3:1) was added the alkyl bromide (1.1 eq.). The reaction was stirred at 100 °C for 4 hours. It was then cooled to room temperature, diluted with methanol, and added to diethyl ether dropwise with stirring. The solid precipitated was filtered and washed with diethyl ether. The crude solid was crystallised from methanol to diethyl ether.

Method B: To a suspension of the cinchona alkaloid (1.0 eq., 0.1 – 0.5 M) in toluene was added the alkyl bromide (1.0 eq.). The reaction was stirred at 100 – 120 °C for 8 – 16 hours. The crude solid was purified by crystallisation.

Procedure 2: *Urea formation from amino methyl ester hydrochloride*

Under a dry, inert atmosphere, Et_3N (2.0 eq.) and the isocyanate (1.1 eq.) was added to a suspension of the amino methyl ester hydrochloride (1.0 eq., 0.5 M) in anhydrous DCM. The reaction was stirred for 16 hours at room temperature. The reaction was quenched with HCl (1.0 M, aq.) and the organic layer washed with $NaHCO_3$ (sat. aq.) and brine, then dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was used without further purification.

Procedure 3: *Hydantoin formation from urea*

Under a dry, inert atmosphere, KO*t*Bu (1.1 eq.) was added to a solution of the urea (1.0 eq., 0.4 M) in anhydrous THF. The reaction was stirred for *not more than* 1 hour at room temperature. The reaction was quenched with HCl (1.0 M, aq.) and the organic solvent removed under reduced pressure. The residue was dissolved in EtOAc and the organic layer separated. The organic layer was washed with $NaHCO_3$ (sat. aq.) and brine. Afterwards, it was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography.

Procedure 4: *Carbamoyl chloride formation from hydantoin*

Under a dry, inert atmosphere, triphosgene (0.5 eq., 0.2 M) in anhydrous DCM was cooled to −78 °C and stirred for 5 minutes. Anhydrous pyridine (1.5 eq.) was added dropwise and the reaction stirred a further 10 minutes. To the reaction, a solution of hydantoin (1.0 eq., 2.0 M) in anhydrous DCM was added dropwise. The solution was allowed to warm to room temperature and stirred for 2 hours. The reaction was cooled to 0 °C and quickly washed with brine. The organic layer was

dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was used without further purification.

Procedure 5: *Hydantoin urea formation from carbamoyl chloride*

Under a dry, inert atmosphere, carbamoyl chloride (1.0 eq., 0.2 M) in anhydrous DCM was stirred at room temperature. Et_3N (1.2 eq.) and the desired *N*-methylaniline (1.0 eq. in a solution of DCM, if solid) were simultaneously added dropwise over 5 minutes. The reaction was stirred for 2 hours before quenching with HCl (1.0 M, aq.). The organic layer was washed with $NaHCO_3$ (sat. aq.) and brine, then dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography.

Procedure 6: *Phase transfer catalysed aryl migration*

Under an inert atmosphere, hydantoin urea (1.0 eq., 0.1 M) in the desired solvent was cooled down to the desired temperature. The PTC (0.1 – 0.2 eq.) and Cs_2CO_3 (5.0 eq.) or KOH (3.0 eq.) were added. The reaction was stirred and left until TLC analysis showed the starting material had been completely consumed. The reaction was quenched with NH_4Cl (sat. aq.). The organic solvent was removed under reduced pressure and the aqueous layer extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography.

Procedure 7: *N-Methylamide formation from amino methyl ester hydrochloride*

$MeNH_2$ (33% *w/w* solution in EtOH, 7.0 eq.) was added to the amino methyl ester hydrochloride (1.0 eq.). The mixture was left to stir at room temperature for 24 hours. The solvent was removed under reduced pressure, the residue dissolved in $NaHCO_3$ (sat. aq.) and extracted 4 times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was used without further purification.

Procedure 8: *Imine formation from amino acid N-methylamide*

Under a dry, inert atmosphere, pivalaldehyde (1.3 eq.) was added to a mixture of $MgSO_4$ (1.0 eq.) and *N*-methylamide (1.0 eq., 2.0 M) in anhydrous DCM. The reaction was left to stir at room temperature for 16 hours. The reaction was filtered, and the organic filtrate washed with water. The washed organic filtrate was collected, and the remaining aqueous layer extracted 3 times with DCM. The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was used without further purification.

Procedure 9: *Carbamoyl chloride formation from N-methylaniline*

Under a dry, inert atmosphere, triphosgene (0.5 eq., 0.4 M) in anhydrous DCM was cooled to −78 °C and stirred for 5 minutes. Anhydrous pyridine (1.0 eq.) was added dropwise, followed by a solution of the desired *N*-methylaniline (1.0 eq., 16.0 M, if solid) in anhydrous DCM. After 10 mins, the reaction was allowed to warm to room temperature and left to stir for 3 hours. The reaction was quenched with HCl (1.0 M, aq.). The organic layer was seperated, and the aqueous layer extracted 3 times with DCM. The combined organic layers were washed with $NaHCO_3$ (sat. aq.), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was used without further purification.

Procedure 10: *Imidazolidinone urea formation from N-methylamide imine*

Under a dry, inert atmosphere, DMAP (0.05 eq.) and *N*-alkyl-*N*-arylcarbamoyl chloride (1.5 eq.) were added to a solution of the *N*-Methylamide imine (1.0 eq., 0.2M) in anhydrous toluene. The reaction mixture was stirred at reflux for 48 hours. The reaction was cooled to room temperature and quenched with HCl (1.0 M, aq.). The organic solvent was removed under reduced pressure and the aqueous layer extracted 3 times with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography.

Procedure 11: *Vinyl urea formation from imidazolidinone urea*

Under a dry, inert atmosphere, KHMDS (1.0 M/THF, 1.2 – 2.0 eq.) was added to a solution of the imidazolidinone urea (1.0 eq., 0.1 M) in anhydrous THF at 0 °C. The reaction was left to stir at 0 °C for 15 minutes and then allowed to warm to room temperature. The reaction was left stirring at room temperature until TLC analysis showed the starting material had been completely consumed. The reaction was quenched with NH_4Cl (sat. aq.) and the organic solvent removed under reduced pressure. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography.

Procedure 12: *Conjugate addition and Aryl migration product via Photoredox catalysis*

The vinyl urea (1.0 eq.), caesium carbonate (1.5 eq.), 4CzIPN (5 mol%) and the radical precursor (2.0 – 3.0 eq.) were added into a dried microwave vial under an inert atmosphere. The mixture was left under vacuum for 10 – 15 mins and then flushed with nitrogen. Anhydrous CH_3CN ([vinyl urea] = 0.1 M) was added and the mixture stirred and degassed for 10 minutes by bubbling nitrogen in through a long needle and oxygen out through a short needle. The reaction mixture was exposed to 12 V blue LED irradiation and allowed to stir for 16 hours at 30 °C. The reaction was quenched

with water and extracted 3 times with EtOAc. The combined organic layers were evaporated under reduced pressure and the crude product purified by flash column chromatography.

Procedure 13: *Aryl migration of conjugate addition product*

Under a dry, inert atmosphere, LiHMDS (1.0 M/THF, 1.5 eq.) was added to a solution of the conjugate addition product (1.0 eq., 0.1 M) in anhydrous THF at 0 °C. The reaction was left to stir at 0 °C until TLC analysis showed the starting material had been completely consumed. The reaction was quenched with NH_4Cl (sat. aq.) and the organic solvent removed under reduced pressure. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography.

Procedure 14: *Aryl migration and subsequent 1,2-elimination of conjugate addition product*

Under a dry, inert atmosphere, KHMDS (1.0 M/THF, 1.5 – 2.5 eq.) was added to a solution of the conjugate addition product (1.0 eq., 0.1 M) in anhydrous THF at 0 °C. The reaction was allowed to warm to room temperature and left to stir until TLC analysis showed the starting material had been completely consumed. The reaction was quenched with NH_4Cl (sat. aq.) and the organic solvent removed under reduced pressure. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography.

Procedure 15: *N-Methylation of aryl migration product*

Under a dry, inert atmosphere, the conjugate addition product (1.0 eq., 0.1 M) in anhydrous THF was cooled to 0 °C. LiHMDS (1 M/THF, 1.5 eq.) was added and the reaction stirred at 0 °C until TLC analysis showed the starting material had been completely consumed. An additional 1.5 eq. of LiHMDS (1 M/THF) was added and the reaction stirred further for 45 minutes at 0 °C, after which MeI (2.0 – 5.0 eq.) was added. The reaction was allowed to warm to room temperature and left to stir for 16 hours. The reaction was quenched with water; and MeI and THF removed under reduced pressure. The residue was partitioned between water and EtOAc, and the organic layer collected. The organic layer was washed with brine, before being dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography.

Procedure 16: *Formation of urea malonic acid ester*

Under a dry, inert atmosphere, diethyl amino malonate hydrochloride salt (1.1 eq.) and Et_3N (2.2 eq.) were added to a solution of *N*-Methyl-*N*-arylcarbamoyl chloride (1.0 eq., 0.1 M) in anhydrous CH_3CN. The mixture was stirred for 16 hours at 60 °C. The solvent was removed under reduced

pressure and the residue partitioned between $NaHCO_3$ (sat. aq.) and DCM. The organic layer was collected, and the aqueous layer extracted 2 times with DCM . The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography.

Procedure 17: *N- and α-alkylation of urea malonic acid ester*

Under a dry, inert atmosphere, a solution of the urea malonic acid ester (1.0 eq., 0.1 M) in anhydrous DMF was cooled to 0 °C, NaH (60% in mineral oil, 3.0 eq.) was added and the reaction left stirring for 15 minutes. MeI (5.0 eq.) was added and the reaction left stirring for a further 1 hour at 0 °C. The reaction mixture was diluted with EtOAc and quenched by addition of ice and NaOH (1.0 M, aq.). The organic layer was collected, and the aqueous layer extracted 2 times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography.

Procedure 18: *Mono hydrolysis of alkylated urea malonic acid ester*

A solution of the alkylated urea malonic acid ester (1.0 eq., 0.7 M) in ethanol:water (10:1) was cooled to 0 °C. KOH (2.0 eq.) was added and the reaction stirred for 15 hours at room temperature. Ethanol was removed under reduced pressure with the temperature of the rotary evaporator set below 20 °C. The residue was then dissolved in $NaHCO_3$ (10%, aq.) and washed 3 times with diethyl ether. The aqueous layer was acidified with HCl (6.0 M, aq.) at 0 °C, and then extracted 3 times with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography.

Procedure 19: *Formation of α-amino nitrile*

Under a dry, inert atmosphere, (1*R*),(2*R*)-2-aminocyclohexanol (1.0 eq. 0.17 M) in MeOH was reacted with the aldehyde (1.1 eq.) and TMSCN (1.2 eq.) for 16 hours at room temperature. The reaction mixture was evaporated under reduced pressure and the crude product used without further purification.

Procedure 20: *Silyl protection of α-amino nitrile*

Under a dry, inert atmosphere, 2,6-lutidine (1.5 eq.) was added to a solution of the α-amino nitrile (1.0 eq., 0.22 M) in anhydrous DCM. Upon cooling to −78 °C, TBDMSOTf (1.2 eq.) was added dropwise to the reaction. After stirring for 5 minutes, the reaction mixture was warmed to room temperature and left to stir for 4 hours. It was then quenched by addition of $NaHCO_3$ (sat. aq.). The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography.

Procedure 21: *Carbamoyl chloride formation from silyl protected α-amino nitrile*

Under a dry, inert atmosphere, triphosgene (0.4 eq., 0.1 M) in anhydrous DCM was cooled to −78 °C. 2,6-Lutidine (1.2 eq.) was added dropwise and the reaction left to stir for 10 minutes. The silyl protected α-amino nitrile (1.0 eq.) was then added dropwise as a solution in DCM. The reaction was warmed to room temperature and left to stir for 2 hours. The reaction was quenched by addition of HCl (1.0 M, aq.). The organic layer was washed with $NaHCO_3$ (sat. aq.) and brine, then dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to obtain the crude carbamoyl chloride, which was used in the next step without further purification.

Procedure 22: *α-Amino nitrile urea formation from carbamoyl chloride and N-methylaniline*

Method A: 2,6-Lutidine (1.2 eq.), the desired *N*-methylaniline (1.1 eq.) and KI (1.2 eq.) were added to a solution of the carbamoyl chloride (1.0 eq., 0.4 M) in anhydrous CH_3CN. The reaction was heated at 110 °C in a microwave reactor for 4 hours. It was then evaporated under reduced pressure and partitioned between EtOAc and HCl (1.0 M, aq.). The aqueous layer was extracted twice with EtOAc and the combined organic layers were washed with $NaHCO_3$ (sat. aq.) and brine, then dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography.

Method B: 2,6-Lutidine (1.2 eq.) and the desired *N*-methylaniline (1.1 eq.) were added to a solution of the carbamoyl chloride (1.0 eq. 0.4 M) in anhydrous CH_3CN. The reaction mixture was refluxed at 100 °C for 24 hours. The solvent was removed under reduced pressure and partitioned between EtOAc and HCl (1.0 M, aq.). The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with $NaHCO_3$ (sat. aq.) and brine, then dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography.

Procedure 23: *Hydantoin formation from aryl migration of α-amino nitrile urea*

Method A: Under a dry, inert atmosphere, LDA (2.0 M in THF/heptane/ethylbenzene, 3.0 eq.) was added dropwise to a solution of the α-amino nitrile urea (1.0 eq., 0.1 M) in anhydrous THF at −78 °C. The reaction was stirred for 10 minutes before warming to room temperature and stirred for another 3 hours. The reaction was quenched by addition of NH_4Cl (sat. aq.) and then partitioned between water and EtOAc. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography.

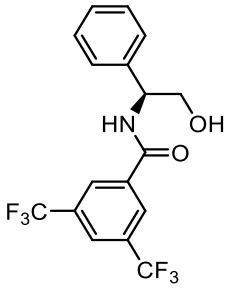
Method B: Under a dry, inert atmosphere, DMPU (DMPU:THF, 1:10) was added to a solution of the α-amino nitrile urea (1.0 eq., 0.11 M) in anhydrous THF. The reaction was cooled to −78 °C and LDA (2.0 M in THF/heptane/ethylbenzene, 2.5 eq.) was added dropwise. The reaction was left to stir for 10 minutes at −78 °C , after which it was warmed to +40 °C and stirred for 20 hours. The reaction was cooled to room temperature and quenched by the addition of NH_4Cl (sat. aq.). It was then partitioned between water and EtOAc and the aqueous layer extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography.

4.3 Characterisation Data

4.3.1 Phase Transfer Catalysed Aryl Migration

4.3.1.1 Synthesis of Phosphonium-based PTC

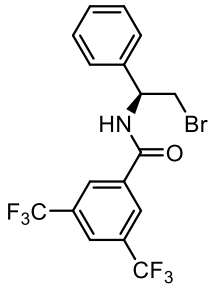
(*S*)-*N*-(2-Hydroxy-1-phenylethyl)-3,5-bis(trifluoromethyl)benzamide (300)



To a solution of (*R*-)-(-)-2-Phenylglycinol (1.00 g, 7.29 mmol, 1.00 eq., 0.20 M) in anhydrous THF (40.0 mL) was added Et_3N (2.00 mL, 14.6 mmol, 2.00 eq.). The reaction was cooled to 0 °C and 3,5-di(trifluoromethyl)benzoyl chloride (1.40 mL, 8.00 mmol, 1.10 eq.) was added slowly through a syringe. Stirring was continued for 2 hours at room temperature. The reaction mixture was then concentrated under reduced pressure. The residue was dissolved in EtOAc (40.0 mL) and the solution was washed successively with $NaHCO_3$ (sat. aq.), HCl (1M, aq.) and brine. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 80:20) to afford the title compound (1.85 g, 67%) as a white solid. **R*f*** (8:2 Pet.Ether:EtOAc) 0.14; **mp**: 155 – 156 °C; **^{1}H NMR** (400 MHz, CD_3OD): δ 8.51 (2H, s, Ar-*H*), 8.17 (1H, s, Ar-*H*), 7.42 (2H, d, *J* = 7.0, Ar-*H*), 7.36 (2H, dd, *J* = 8.5, 6.7, Ar-*H*), 7.28 (1H, t, *J* = 7.2, Ar-*H*), 5.25 (1H, dd, *J* = 7.7, 5.8, C*H*NH), 3.95 – 3.85 (2H, m, CH_AH_BOH); **^{13}C NMR** (126 MHz, CD_3OD**)**: 166.82 (*C*=O), 140.87 (C_{Ar}), 138.26 (C_{Ar}), 133.0 (q, $^2J^{C\text{-}F}$ = 33.6, 2xC_{Ar}), 129.26 (q, $^3J^{C\text{-}F}$ = 3.78, 2xC_{Ar}H), 129.61 (2xC_{Ar}H), 128.62 (C_{Ar}H), 128.07 (2xC_{Ar}H), 125.93 (q, $^3J^{C\text{-}F}$ = 3.78, C_{Ar}H) 124.6 (q, $^1J^{C\text{-}F}$ = 272.2, 2xCF_3), 65.88 (CH_AH_BOH), 58.30 (*C*HNH); **IR (vmax/cm^{-1}) (neat)**: 3302 (OH), 2955, 2884

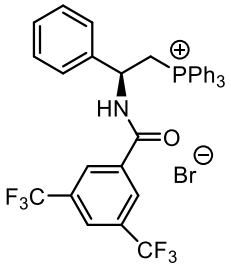
(alkyl C-H), 1639 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{17}H_{13}F_6NO_2Na$ $[M+Na]^+$ 400.074269, found 400.074928.

(*S*)-*N*-(2-Bromo-1-phenylethyl)-3,5-bis(trifluoromethyl)benzamide (301)



Triphenylphosphine (4.22 g, 16.1 mmol, 3.30 eq.) was added to a solution of alcohol **300** (1.80 g, 4.79 mmol, 1.00 eq., 0.30 M) in anhydrous DCM (15.0 mL). The solution was cooled to 0 °C and a solution of tetrabromomethane (1.77 g, 5.32 mmol, 1.10 eq., 1.00 M) in DCM (5.00 mL) was added slowly through a syringe and stirring was continued for 2 hours at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (30.0 mL) and washed with water (15.0 mL). After separation, the aqueous layer was extracted with EtOAc (20.0 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 99.5:0.5) to afford the title compound (1.48 g, 70%) as a white solid. **R*f*** (9.5:0.5 Pet.Ether:EtOAc) 0.12; **^{1}H NMR** (400 MHz, CD_3OD): δ 8.49 (2H, s, Ar-*H*), 8.20 (1H, s, Ar-*H*), 7.46 (2H, d, *J* = 7.7, Ar-*H*), 7.40 (2H, t, *J* = 7.5, Ar-*H*), 7.33 (1H, t, *J* = 7.2, Ar-*H*), 5.44 (1H, q, *J* = 7.5, C*H*NH), 3.90 – 3.82 (2H, m, CH_AH_BBr); **^{13}C NMR** (126 MHz, CD_3OD)**:** 164.70 (*C*=O), 133.4 (q, $^2J^{C\text{-}F}$ = 34.0, 2xC_{Ar}), 129.17 (q, $^3J^{C\text{-}F}$ = 3.78, 2xC_{Ar}H), 130.63 (2xC_{Ar}H), 129.87 (C_{Ar}H), 128.04 (2xC_{Ar}H), 129.25 (C_{Ar}) 128.36 (C_{Ar}) 126.15 (q, $^3J^{C\text{-}F}$ = 3.78, C_{Ar}H), 124.4 (q, $^1J^{C\text{-}F}$ = 273.4, 2xCF$_3$), 65.88 (CH$_A$H$_B$OH), 57.59 (CHNH); **IR (vmax/cm^{-1}) (neat)**: 2935, 2888 (alkyl C-H), 1736 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{25}H_{27}N_3O_4Na$ $[M+Na]^+$ 456.1894, found 456.1900.

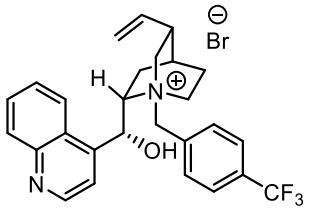
(*S*)-(2-(3,5-Bis(trifluoromethyl)benzamido)-2-phenylethyl)triphenylphosphonium bromide (296)



A mixture of **301** (1.38 g, 3.14 mmol, 1.00 eq.) and triphenylphosphine (2.29 g, 8.70 mmol, 2.80 eq.) was refluxed in toluene (10.0 mL) for 12 hours. The resulting solution was allowed to cool to room temperature and was concentrated under reduced pressure. Diethyl ether (10.0 mL) was added dropwise to the residue while stirring vigorously. The cloudy solution was filtered, and the residue washed with diethyl ether to remove all impurities. It was then concentrated under reduced pressure to afford the title compound (768 mg, 35%) as a white solid. $[\alpha]_D^{24}$ = +8.0 (c = 10 mg/ml, $CHCl_3$); **mp**: 130 – 133 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.37 (1H, br., s, N*H*), 8.39 (2H, s, Ar-*H*), 7.97 – 7.90 (6H, m, Ar-*H*), 7.88 (1H, s, Ar-*H*), 7.76 (2H, d, *J* = 7.1, Ar-*H*), 7.73 – 7.63 (3H, m, Ar-*H*), 7.66 – 7.56 (6H, m, Ar-*H*), 7.36 (2H, t, *J* = 7.5, Ar-*H*), 7.28 (1H, d, *J* = 7.3, Ar-*H*), 6.29 (1H, dt, *J* = 15.9, 11.4, C*H*$_A$H$_B$PPh$_3$), 5.93 – 5.74 (1H, m, C*H*NH), 3.19 (1H, dd, *J* = 15.7, 12.3, CH$_A$*H*$_B$PPh$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): 163.98 (*C*=O), 141.85 (d, $^1J^{C\text{-}P}$ = 13.86, 3xAr), 135.23 (d, $J^{C\text{-}P}$ = 3.78, 3xAr), 134.83 (Ar), 134.25 (d, $J^{C\text{-}P}$ = 10.08, 6xAr), 131.44 (q, $^2J^{C\text{-}F}$ = 34.02, 2xAr), 130.47 (d, $J^{C\text{-}P}$ = 12.6, 6xAr), 129.44 (Ar), 129.15 (2xAr), 129.01 (q, $^3J^{C\text{-}F}$ = 3.78, 2xAr), 128.55 (Ar), 127.37 (2xAr), 124.96 (q, $^3J^{C\text{-}F}$ = 3.78, Ar), 123.21 (q, $^1J^{C\text{-}F}$ = 273.42, 2x*C*F$_3$), 48.97 (d, $^2J^{C\text{-}P}$ = 3.78, *C*HNH), 28.30 (d, $^1J^{C\text{-}P}$ = 47.88, *C*H$_A$H$_B$PPh$_3$); **IR (vmax/cm^{-1}) (neat)**: 2926, 2864 (alkyl C-H), 1661 (C=O); **HRMS** (ESI): *m/z* calcd for $[C_{35}H_{27}F_6NOP]^+$ 622.172897, found 622.173067.

4.3.1.2 Synthesis of Cinchona-based PTCs

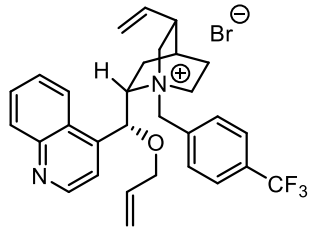
(1*S*,2*S*,4*S*,5*R*)-2-((*R*)-Hydroxy(quinolin-4-yl)methyl)-1-(4-(trifluoromethyl)benzyl)-5-vinylquinuclidin-1-ium bromide (303a)



Following general **procedure 1** (**method A**): (-)-cinchonidine (1.00 g, 3.40 mmol), 4-(trifluoromethyl)benzyl bromide (893 mg, 3.74 mmol) and a mixture of ethanol (2.50 mL), DMF

(3.00 mL) and chloroform (1.00 mL). The title compound (1.00 g, 55%) was afforded as a white solid after crystallisation. $[\alpha]_D^{22}$ = –135 (c = 10 mg/ml, $CHCl_3$); **mp**: 210 – 212 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.79 (1 H, d, *J* = 4.5, Ar-*H*), 8.18 – 8.08 (1H, m, Ar-*H*), 7.87 (2H, d, *J* = 7.8, Ar-*H*), 7.78 (1H, d, *J* = 4.5, Ar-*H*), 7.58 – 7.50 (1H, m, Ar-*H*), 7.41 (2H, d, *J* = 7.7, Ar-*H*), 7.07 – 6.98 (2H, m, Ar-*H*), 6.53 (1H, d, *J* = 5.9, C*H*), 6.48 (1H, br. s, O*H*), 6.31 (1H, d, *J* = 11.9, CH_AH$_B$Ph), 5.58 (1H, d, *J* = 11.9, CH$_A$$H_B$Ph), 5.43 – 5.26 (2H, m, CH_AH$_B$=C*H*), 4.91 (1H, dd, *J* = 9.6, 1.8, CH$_A$$H_B$=CH), 4.65 (1H, q, *J* = 10.4, C*H*), 4.20 (1H, t, *J* = 10.0, C*H*), 3.95 (1H, d, *J* = 12.9, C*H*), 3.07 – 2.86 (2H, m, 2xC*H*), 2.53 – 2.41 (1H, m, C*H*), 2.07 (1H, t, d, *J* = 12.0, C*H*), 1.92 (1H, s, C*H*), 1.88 – 1.79 (1H, m, C*H*), 1.59 (1H, q, *J* = 10.8, C*H*), 1.05 – 0.94 (1H, m, C*H*); **^{13}C NMR** (126 MHz, $CDCl_3$): 149.5 (*C*$_{Ar}$H), 147.2 (*C*$_{Ar}$), 144.2 (*C*$_{Ar}$), 135.7 (CH$_A$H$_B$=*C*H), 134.7 (2x*C*$_{Ar}$H), 132.4 (q, $^2J^{C\text{-}F}$ = 32.5, *C*$_{Ar}$), 131.2 (*C*$_{Ar}$), 129.8 (*C*$_{Ar}$H), 128.4 (*C*$_{Ar}$H), 127.3 (*C*$_{Ar}$H), 125.5 (q, $^3J^{C\text{-}F}$ = 3.8, 2x*C*$_{Ar}$H), 123.5 (q, $^1J^{C\text{-}F}$ = 270.8, *C*F$_3$), 123.4 (*C*$_{Ar}$), 122.7 (*C*$_{Ar}$H), 119.8 (*C*$_{Ar}$H), 118.2 (*C*H$_A$H$_B$=CH), 67.4 (*C*H), 65.4 (*C*H), 61.1 (*C*H$_A$H$_B$Ph), 60.2 (*C*H$_2$), 50.6 (*C*H$_2$), 37.9 (*C*H), 26.4 (*C*H), 25.20 (*C*H$_2$), 22.7 (*C*H$_2$), **IR (vmax/cm^{-1}) (neat)**: 3400 – 3200 (OH, br.) 2953 (alkyl C-H), 1324 (C-F); **MS** (ESI): *m/z* calcd for $[C_{27}H_{28}F_3N_2O]^+$, found 453.21.

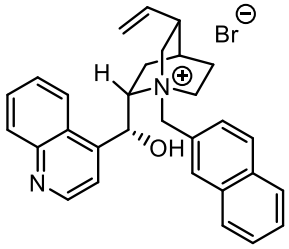
(1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(Allyloxy)(quinolin-4-yl)methyl)-1-(4-(trifluoromethyl)benzyl)-5-vinylquinuclidin-1-ium bromide (304a)



To a suspension of **303a** (687 mg, 1.28 mmol, 1.00 eq., 0.5 M) in DCM (2.70 mL) was added allyl bromide (0.33 mL, 3.86 mmol, 3.00 eq.) and 50% aqueous KOH (0.72 mL, 6.44 mmol, 5.00 eq.). The resulting mixture was stirred vigorously at room temperature for 4 hours. It was then diluted with water (1.70 mL) and extracted with DCM (3x7 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude solid was recrystallised from DCM to Hexane to yield the title compound (517 mg, 70%) as an off-white solid. $[\alpha]_D^{22}$ = –151 (c = 10 mg/ml, $CHCl_3$); **mp**: 138 – 140 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.96 (1H, d, *J* = 4.5, Ar-*H*), 8.87 (1H, d, *J* = 8.5, Ar-*H*), 8.18 – 8.08 (3H, m (*overlapping*), 2xAr-*H*+Ar-*H*), 7.97 – 7.86 (1H, m, Ar-*H*), 7.77 (1H, t, *J* = 8.2, Ar-*H*), 7.73 (2H, d, *J* = 8.0, 2xAr-*H*), 6.85 (1H, d, *J* = 11.8, CH_AH$_B$Ph), 6.16 – 6.02 (1H, m, CH$_A$H$_B$=C*H*CH$_2$), 5.69 (1H, ddd, *J* = 17.0, 10.6, 6.3, CH$_A$H$_B$=C*H*), 5.45 – 5.35 (3H, m (*overlapping*), CH$_A$H$_B$=CHCH_2+CH_AH$_B$=CH), 5.20 – 5.06 (1H, m, C*H*), 5.03 (1H, d, *J* = 10.6, CH$_A$$H_B$=CH), 4.81 – 4.70 (1H, m, C*H*), 4.67 (1H, d, *J* = 11.8, CH$_A$$H_B$Ph), 4.38 (1H, q, *J* = 11.1, C*H*), 4.28 (1H, ddt, *J* = 12.6, 5.3, 1.3, CH_AH$_B$=CHCH$_2$), 4.05

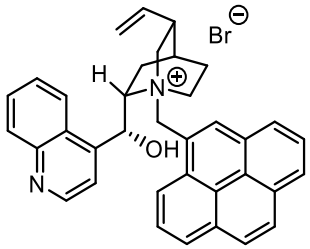
(1H, ddt, *J* = 12.5, 6.7, 1.2, CH_AH_B=CHCH$_2$), 3.33 (1H, td, *J* = 11.1, 10.0, CH), 3.15 (1H, dd, *J* = 12.9, 10.5, C*H*), 2.66 – 2.56 (1H, m, C*H*), 2.23 – 2.03 (3H, m (overlapping), 3xC*H*), 1.86 – 1.77 (1H, m, C*H*), 1.49 – 1.36 (1H, m, C*H*); **^{13}C NMR** (126 MHz, $CDCl_3$): 149.6 (C_{Ar}H), 148.7 (C_{Ar}), 139.7 (C_{Ar}), 135.9 (CH_AH_B=*C*H), 134.8 (2xC_{Ar}H), 132.8 (q, $^2J^{C\text{-}F}$ = 32.9, C_{Ar}), 132.6 (CH_AH_B=*C*HCH$_2$), 131.4 (C_{Ar}), 130.6 (C_{Ar}H), 130.1 (C_{Ar}H), 129.4 (C_{Ar}H), 126.2 (q, $^3J^{C\text{-}F}$ = 3.6, 2xC_{Ar}H), 124.9 (C_{Ar}H), 123.7 (q, $^1J^{C\text{-}F}$ = 270.8, *C*F$_3$), 120.3 (CH_AH_B=CH*C*H$_2$), 119.0 (*C*H_AH_B=CH), 70.5 (*C*H_AH_B=CHCH$_2$), 66.4 (*C*H), 61.2 (*C*H_AH_BPh), 59.9 (*C*H$_2$), 51.7 (*C*H$_2$), 38.0 (*C*H), 27.0 (*C*H), 25.4 (*C*H$_2$), 23.0 (*C*H$_2$); **IR (vmax/cm^{-1}) (neat)**: 2948 (alkyl C-H), 1323 (C-F); **MS** (ESI): *m/z* calcd for $[C_{30}H_{32}F_3N_2O]^+$, found 493.2.

(1*S*,2*S*,4*S*,5*R*)-2-((*R*)-Hydroxy(quinolin-4-yl)methyl)-1-(naphthalen-2-ylmethyl)-5-vinylquinuclidin-1-ium bromide (303b)



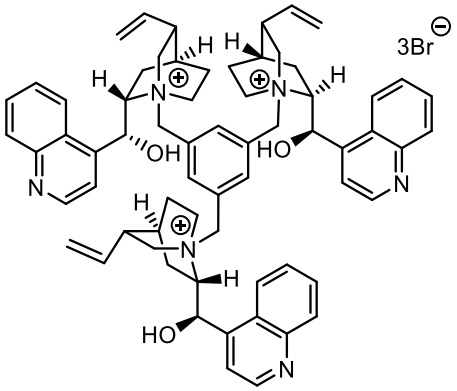
Following general **procedure 1** (**method A**): (-)-cinchonidine (1.00 g, 3.40 mmol), 2-bromo methyl naphthalene (746 mg, 3.37 mmol) and a mixture of ethanol (2.50 mL), DMF (3.00 mL) and chloroform (1.00 mL). The title compound (1.02 g, 58%) was afforded as a white solid after crystallisation. **mp**: 218 – 220 °C (decomposes); **^{1}H NMR** (400 MHz, $(CD_3)_2SO$): δ 9.00 (1H, d, *J* = 4.4, Ar-*H*), 8.38 – 8.30 (2H, m, Ar-*H*), 8.15 – 8.08 (2H, m, Ar-*H*), 8.05 (2H, dt, *J* = 7.2, 2.4, Ar-*H*), 7.89 – 7.81 (3H, m, Ar-*H*), 7.75 (1H, ddd, *J* = 8.3, 6.8, 1.4, Ar-*H*), 7.69 – 7.61 (2H, m, Ar-*H*), 6.79 (1H, br. d, *J* = 4.4, O*H*), 6.62 (1H, br. dd, *J* = 4.4, 2.0, C*H*OH), 5.69 (1H, ddd, *J* = 17.2, 10.5, 6.5, CH$_2$=C*H*), 5.35 (1H, d, *J* = 12.4, CH_AH_B), 5.22 (1H, d, *J* = 12.4, CH_AH_B), 5.17 (1H, dt, *J* = 17.3, 1.3, CH_AH$_B$=CH), 4.96 (1H, dt, *J* = 10.5, 1.3, CH_AH_B=CH), 4.43 – 4.29 (1H, m, C*H*), 4.04 – 3.97 (1H, m, C*H*), 3.89 – 3.80 (1H, m, C*H*), 3.46 – 3.37 (1H, m, C*H*), 3.36 – 3.31 (1H, m, C*H*), 2.65 (1H, br. s, C*H*), 2.20 – 2.02 (2H, m, C*H*+C*H*), 2.00 – 1.98 (1H, br. m, C*H*), 1.86 – 1.71 (1H, m, C*H*), 1.37 – 1.25 (1H, m, C*H*); **^{13}C NMR** (101 MHz, $(CD_3)_2SO$**)**: 150.16 (C_{Ar}H), 147.63 (C_{Ar}), 145.26 (C_{Ar}), 133.27 (C_{Ar}), 132.54 (C_{Ar}), 138.11 (CH$_2$=*C*H), 133.92 (C_{Ar}H), 130.16 (C_{Ar}H), 129.86 (C_{Ar}H), 129.42 (C_{Ar}H), 128.36 (C_{Ar}H), 128.32 (C_{Ar}H), 127.65 (C_{Ar}H), 127.52 (C_{Ar}H), 127.19 (C_{Ar}H), 126.81 (C_{Ar}H), 125.44 (C_{Ar}), 124.31 (C_{Ar}), 123.69 (C_{Ar}H), 120.07 (C_{Ar}H), 116.36 (*C*H_AH_B=CH), 67.56 (*C*H), 64.15 (*C*HOH), 62.84 (*C*H_AH_B), 59.32 (*C*H$_2$), 50.67 (*C*H$_2$), 36.92 (*C*H), 25.88 (*C*H), 24.25 (*C*H$_2$), 20.95 (*C*H$_2$); (**IR (vmax/cm^{-1}) (neat)**: 3421 – 30857 (OH), 3006 (alkene CH), 2954, 2907 (alkyl C-H); **HRMS** (ESI): *m/z* calcd for $[C_{30}H_{31}N_2O]^+$ 435.2431, found 435.2431.

(1*S*,2*S*,4*S*,5*R*)-2-((*R*)-Hydroxy(quinolin-4-yl)methyl)-1-(pyren-4-ylmethyl)-5-vinylquinuclidin-1-ium bromide (303c)



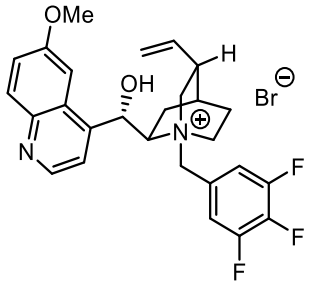
Following general **procedure 1** (**method B**): (-)-cinchonidine (300 mg, 1.02 mmol) and 4-(bromomethyl)pyrene (301 mg, 1.02 mmol) in toluene (12.0 mL). The reaction was stirred at 100 °C for 8 hours. After cooling the reaction mixture to room temperature, it was filtered, and the residue dissolved in MeOH (9.00 mL). The cloudy solution was filtered over celite pad, partly concentrated, and crystallised in diethyl ether to afford the title compound (479 mg, 80%) as an off white solid. $[\alpha]_D^{24}$ = –368 (c = 10 mg/ml, $CHCl_3$); **mp**: 184 – 186 °C (decomposes); **^{1}H NMR** (500 MHz, CD_3OD): δ 9.00 (1H, d, *J* = 4.7, Ar-*H*), 8.63 (1H, d, *J* = 9.4, Ar-*H*), 8.48 – 8.44 (2H, m, Ar-*H*), 8.42 – 8.36 (4H, m, Ar-*H*), 8.28 (1H, d, *J* = 9.0, Ar-*H*), 8.20 (1H, d, *J* = 8.9, Ar-*H*), 8.18 – 8.13 (2H, m, Ar-*H*), 8.07 (1H, d, *J* = 4.5, Ar-*H*), 7.87 (2H, dddd, *J* = 19.1, 8.2, 6.8, 1.4, Ar-*H*), 6.96 (1H, br. d, *J* = 2.5, C*H*OH), 6.19 (1H, d, *J* = 13.1, CH_AH_B), 5.72 (1H, ddd, *J* = 17.3, 10.5, 6.8, CH_2=C*H*), 5.64 (1H, d, *J* = 13.1, CH_AH_B), 5.15 (1H, dt, *J* = 17.2, 1.2, CH_AH_B=CH), 5.01 (1H, dt, *J* = 10.5, 1.2, CH_AH_B=CH), 4.76 (1H, tdt, *J* = 10.8, 5.5, 3.0, C*H*), 4.34 – 4.26 (1H, m, C*H*), 3.95 (1H, ddd, *J* = 12.7, 4.9, 3.1, C*H*), 3.57 (1H, dd, *J* = 12.7, 10.7, C*H*), 3.27 – 3.17 (1H, m, C*H*), 2.61 (1H, d, *J* = 8.9, C*H*), 2.34 (1H, ddt, *J* = 12.6, 8.6, 1.9, C*H*), 2.21 (1H, ddt, *J* = 12.5, 11.0, 4.4, C*H*), 2.07 – 2.00 (1H, m, C*H*), 1.76 – 1.64 (1H, m, C*H*), 1.45 (1H, ddt, *J* = 13.5, 10.1, 3.8, C*H*); **^{13}C NMR** (126 MHz, CD_3OD**)**: 151.09 (*C*$_{Ar}$H), 138.76 (CH_2=*C*H), 133.83 (*C*$_{Ar}$H), 132.59 (*C*$_{Ar}$H), 131.22 (*C*$_{Ar}$H), 130.43 (*C*$_{Ar}$H), 130.39 (*C*$_{Ar}$H), 129.17 (*C*$_{Ar}$H), 128.28 (*C*$_{Ar}$H), 127.89 (*C*$_{Ar}$H), 127.77 (*C*$_{Ar}$H), 127.37 (*C*$_{Ar}$H), 125.98 (*C*$_{Ar}$H), 124.14 (*C*$_{Ar}$H), 123.68 (*C*$_{Ar}$H), 121.40 (*C*$_{Ar}$H), 117.53 (*C*H$_A$H$_B$=CH), 69.66 (*C*H), 66.79 (*C*HOH), 62.60 (CH_2), 61.75 (*C*H$_A$H$_B$), 53.05 (CH_2), 39.34 (*C*H), 27.69 (*C*H), 26.06 (CH_2), 22.78 (CH_2); (**IR (vmax/cm^{-1}) (neat)**: 3608 – 3208 (OH), 2992 (alkyl C-H), 2925 (alkyl C-H); **HRMS** (ESI): *m/z* calcd for $[C_{36}H_{33}N_2O]^+$ 509.2587, found 509.2574.

(2S,4S)-2-((R)-hydroxy(quinolin-4-yl)methyl)-1-(3-(((1R,2S,4S,5S)-2-((R)-hydroxy(quinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium-1-yl)methyl)-5-(((1S,2S,4S,5R)-2-((R)-hydroxy(quinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium-1-yl)methyl)benzyl)-5-vinylquinuclidin-1-ium tribromide (308)



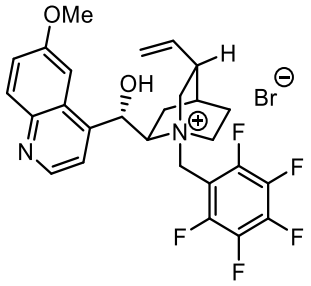
Following a similar procedure to general **procedure 1** (**method A**): (-)-cinchonidine (500 mg, 1.70 mmol, 1.00 eq.), 1,3,5-tris(bromomethyl) benzene (202 mg, 0.57 mmol, 0.33 eq.) and a mixture of ethanol (1.30 mL), DMF (1.50 mL) and chloroform (0.50 mL). The reaction was stirred at 100 °C for 6 hours, after which it was cooled to room temperature, diluted with methanol (5.00 mL) and diethyl ether (15.0 mL) and stirred for 1 hour. The solids were filtered and washed with diethyl ether. The crude solid was recrystallised from methanol to diethyl ether to afford the title compound (591 mg, 84%) as a brown solid. $[\alpha]_D^{24}$ = –236 (c = 10 mg/ml, $CHCl_3$); **mp**: 226 – 227 °C (decomposed);**^{1}H NMR** (400 MHz, $(CD_3)_2SO$): δ 9.02 (3H, d, *J* = 4.5, 3xAr-*H*), 8.38 (3H, d, *J* = 8.5, 3xAr-*H*), 8.28 (3H, br. s, 3xAr-*H*), 8.15 (3H, d, *J* = 8.5, 3xAr-*H*), 7.93 – 7.76 (9H, m (overlap), Ar-*H*), 6.77 (3H, br. d, *J* = 3.6, 3xO*H*), 6.65 (3H, br. s, 3xC*H*OH), 5.73 (3H, ddd, *J* = 17.1, 10.6, 6.5, 3xCH_2=C*H*), 5.25 (6H, br. s, 3xC$H_{2(benzyl)}$), 5.14 (3H, d, *J* = 17.2, 3xCH_AH_B=CH), 4.95 (3H, d, *J* = 10.5, 3xCH_AH_B=CH), 4.29 – 4.13 (6H, m, 6xC*H*), 4.04 – 3.89 (3H, m, 3xC*H*), 3.85 – 3.71 (3H, m, 3xC*H*), 3.68 – 3.55 (3H, m, 3xC*H*), 2.97 – 2.89 (3H, m, 3xC*H*), 2.19 – 2.09 (3H, m, 3xC*H*), 2.04 (3H, br. s, 3xC*H*), 1.97 – 1.87 (6H, br. s, 3xCH_2), 1.42 – 1.28 (3H, m, 3xC*H*); **^{13}C NMR** (126 MHz, $(CD_3)_2SO$)**:** 150.23 (3xC_{Ar}H), 147.68 (3xC_{Ar}), 145.05 (3xC_{Ar}), 140.05 (3xC_{Ar}H), 138.36 (3xCH_2=*C*H), 130.03 (3xC_{Ar}H), 129.51 (3xC_{Ar}H), 129.42 (3xC_{Ar}), 127.24 (3xC_{Ar}H), 124.35 (3xC_{Ar}), 123.52 (3xC_{Ar}H), 120.12 (3xC_{Ar}H), 116.11 (3x*C*H_AH_B=CH), 67.84 (3x*C*H), 64.54 (3x*C*HOH), 62.41 (3x$CH_{2(benzyl)}$), 59.33 (3xCH_2), 50.45 (3xCH_2), 36.72 (3x*C*H), 25.66 (3x*C*H), 24.07 (3xCH_2), 21.24 (3xCH_2); (**IR (vmax/cm^{-1}) (neat)**: 3678 – 3006 (OH), 3072 (alkene CH), 2951, 2881 (alkyl C-H); **HRMS** (ESI): *m/z* calcd for $[C_{66}H_{75}N_6O_3]^{3+}$ 333.1961, found 333.1967.

(1*S*,2*R*,4*S*,5*R*)-2-((*S*)-Hydroxy(6-methoxyquinolin-4-yl)methyl)-1-(3,4,5-trifluorobenzyl)-5-vinylquinuclidin-1-ium bromide (314)



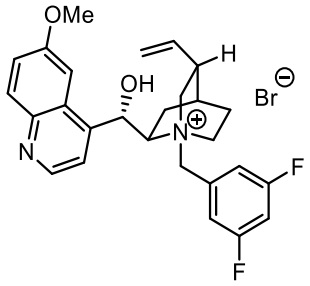
Following general **procedure 1** (**method B**): quinidine (1.00 g, 3.08 mmol) in toluene (6.00 mL); and 3,4,5-trifluoro benzyl bromide (0.45 mL, 3.39 mmol). The reaction mixture was refluxed at 120 °C for 16 h. It was then cooled to room temperature and filtered. The residue was washed with toluene and isolated to afford the title compound (653 mg, 39%) as an off-white solid. $[\alpha]_D^{24}$ = +192 (c = 10 mg/ml, MeOH); **mp**: 208 – 210 °C (decomposed); **^{1}H NMR** (400 MHz, $(CD_3)_2SO$): δ 8.81 (1H, d, *J* = 4.5, Ar-*H*), 8.02 (1H, d, *J* = 9.2, Ar-*H*), 7.93 – 7.84 (2H, m, Ar-*H*), 7.76 (1H, d, *J* = 4.5, Ar-*H*), 7.50 (1H, d, *J* = 9.4, Ar-*H*), 7.43 (1H, br. s, Ar-*H*), 6.77 (1H, br. d, *J* = 3.6, O*H*), 6.47 (1H, br. s, C*H*OH), 6.03 (1H, ddd, *J* = 17.4, 10.4, 6.9, CH_2=C*H*), 5.30 – 5.20 (2H, m, CH_AH_B=CH), 5.07 (1H, d, *J* = 12.7, CH_AH$_B$), 4.81 (1H, d, *J* = 12.6, CH$_A$$H_B$), 4.29 – 4.20 (1H, m, C*H*), 4.07 (3H, s, OCH_3), 4.05 – 3.96 (1H, m, C*H*), 3.83 – 3.73 (1H, m, C*H*), 3.60 – 3.49 (1H, m, C*H*), 3.12 – 2.96 (1H, m, C*H*), 2.68 – 2.57 (1H, m, C*H*), 2.44 – 2.32 (1H, m, C*H*), 1.91 (1H, br. s, C*H*), 1.86 – 1.71 (2H, m, CH_2), 1.19 – 1.07 (1H, m, C*H*); **^{13}C NMR** (126 MHz, $(CD_3)_2SO$**)**: 157.55 (*C*$_{Ar}$), 150.11 (2x*C*$_{Ar}$, ddd, $^1J^{C\text{-}F}$ = 248.6, $^2J^{C\text{-}F}$ = 9.9, $^3J^{C\text{-}F}$ = 3.8), 147.36 (*C*$_{Ar}$H), 143.71 (*C*$_{Ar}$), 143.26 (*C*$_{Ar}$), 140.06 (*C*$_{Ar}$, dt, $^1J^{C\text{-}F}$ = 253.1, $^2J^{C\text{-}F}$ = 15.3), 137.18 (CH_2=*C*H), 131.40 (*C*$_{Ar}$H), 125.47 (*C*$_{Ar}$), 125.05 – 124.67 (*C*$_{Ar}$, m), 121.24 (*C*$_{Ar}$H), 120.36 (*C*$_{Ar}$H), 118.82 (2x*C*$_{Ar}$H, dd, $^2J^{C\text{-}F}$ = 16.8, $^3J^{C\text{-}F}$ = 5.0), 117.01 (*C*H$_A$H$_B$=CH), 102.33 (*C*$_{Ar}$H), 67.72 (*C*H), 64.60 (*C*HOH), 61.44 (*C*H$_A$H$_B$), 55.92 (*C*H$_2$), 55.83 (O*C*H$_3$), 53.96 (*C*H$_2$), 36.89 (*C*H), 26.30 (*C*H), 23.05 (*C*H$_2$), 20.59 (*C*H$_2$); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F –134.46 (2F, d, *J* = 21.8), –159.42 (1F, t, *J* = 21.8); **(IR (vmax/cm^{-1}) (neat)**: 3684 – 3126 (OH), 3013 (alkene CH), 2957, 2907 (alkyl C-H); **MS** (ESI): *m/z* calcd for $[C_{27}H_{28}F_3N_2O_2]^+$, found 469.2039.

(1*S*,2*R*,4*S*,5*R*)-2-((*S*)-Hydroxy(6-methoxyquinolin-4-yl)methyl)-1-((perfluorophenyl)methyl)-5-vinylquinuclidin-1-ium bromide (316)



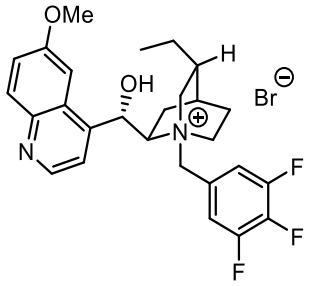
Following general **procedure 1** (**method B**): quinidine (1.00 g, 3.08 mmol) in toluene (6.00 mL); and 2,3,4,5,6-pentafluoro benzyl bromide (0.50 mL, 3.39 mmol). The reaction mixture was refluxed at 120 °C for 16 h. It was then cooled to room temperature and filtered. The residue was washed with toluene and isolated to afford the title compound (1.44 g, 80%) as an off white solid. $[\alpha]_D^{24}$ = +192 (c = 10 mg/ml, MeOH); **mp**: 215 – 218 °C; **^{1}H NMR** (400 MHz, $(CD_3)_2SO$): δ 8.82 (1H, d, *J* = 4.4, Ar-*H*), 8.02 (1H, d, *J* = 9.1, Ar-*H*), 7.77 (1H, d, *J* = 4.6, Ar-*H*), 7.53 – 7.45 (2H, m, Ar-*H*), 6.97 (1H, br. d, *J* = 3.3, O*H*), 6.51 (1H, br. s, C*H*OH), 6.10 – 5.99 (1H, m, CH_2=C*H*), 5.29 – 5.19 (2H, m, CH_AH_B=CH), 5.15 (1H, d, *J* = 13.9, CH_AH_B), 4.91 (1H, d, *J* = 13.9, CH_AH_B), 4.14 – 4.09 (2H, m, 2xC*H*), 4.06 (3H, s, OCH_3), 3.91 – 3.75 (1H, m, C*H*), 3.67 – 3.53 (1H, m, C*H*), 3.49 – 3.35 (1H, m, C*H*), 2.68 – 2.55 (1H, m, C*H*), 2.41 – 2.27 (1H, m, C*H*), 1.93 (1H, br. s, C*H*), 1.90 – 1.74 (2H, m, CH_2), 1.12 – 0.98 (1H, m, C*H*); **^{13}C NMR** (126 MHz, $(CD_3)_2SO$**)**: 157.38 (C_{Ar}), 147.44 (C_{Ar}H), 146.38 (2xC_{Ar}, br. d, $^1J^{C\text{-}F}$ = 250.7), 143.68 (C_{Ar}), 143.00 (C_{Ar}), 142.26 (C_{Ar}, br. d, $^1J^{C\text{-}F}$ = 250.7), 137.59 (2xC_{Ar}, br., dt, $^1J^{C\text{-}F}$ = 248.2, $^2J^{C\text{-}F}$ = 17.0), 137.00 (CH_2=*C*H), 131.32 (C_{Ar}H), 125.31 (C_{Ar}), 121.37 (C_{Ar}H), 120.24 (C_{Ar}H), 103.17 (C_{Ar}, t, $^2J^{C\text{-}F}$ = 16.1), 117.19 (*C*H_AH_B=CH), 102.55 (C_{Ar}H), 67.47 (*C*H), 65.13 (*C*HOH), 55.64 (*C*H_2), 55.53 (O*C*H_3), 54.46 (*C*H_2), 51.37 (*C*H_AH_B), 37.28 (*C*H), 25.74 (*C*H), 23.39 (*C*H_2), 20.67 (*C*H_2); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F –135.25 (2F, d, *J* = 22.0), –150.33 (1F, t, *J* = 22.2), –160.74 (2F, t, *J* = 19.4); (**IR (vmax/cm^{-1}) (neat)**: 3373 – 3080 (OH), 3038 (alkene CH), 2946, 2904 (alkyl C-H); **HRMS** (ESI): *m/z* calcd for $[C_{27}H_{26}F_5N_2O_2]^+$ 505.19.Found 505.1894. Data in agreement with reported values.[195]

(1*S*,2*R*,4*S*,5*R*)-1-(3,5-Difluorobenzyl)-2-((*S*)-hydroxy(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium bromide (321)



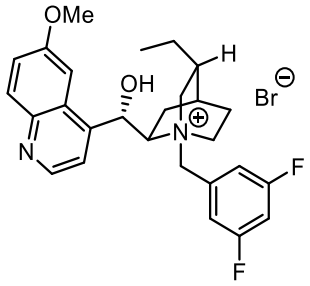
Following general **procedure 1** (**method B**): quinidine (1.00 g, 3.08 mmol) in toluene (6.00 mL); and 3,5-difluoro benzyl bromide (0.44 mL, 3.42 mmol). The reaction mixture was refluxed at 120 °C for 16 h. It was then cooled to room temperature and filtered. The residue was washed with toluene and isolated to afford the title compound (1.40 g, 85%) as an off-white solid.$[\alpha]_D^{24}$ = +188 (c = 10 mg/ml, MeOH); **mp**: 200 – 202 °C; **^{1}H NMR** (400 MHz, $(CD_3)_2SO$): δ 8.81 (1H, d, *J* = 4.5, Ar-*H*), 8.01 (1H, d, *J* = 9.2, Ar-*H*), 7.77 (1H, d, *J* = 4.5, Ar-*H*), 7.63 (2H, br. d, *J* = 5.5, Ar-*H*), 7.55 – 7.48 (2H, m, Ar-*H*), 7.44 (1H, d, *J* = 2.8, Ar-*H*), 6.80 (1H, br. d, *J* = 3.9, O*H*), 6.49 (1H, br. s, C*H*OH), 6.03 (1H, ddd, *J* = 17.3, 10.6, 6.9, CH_2=C*H*), 5.29 – 5.22 (2H, m, CH_AH_B=CH), 5.13 (1H, d, *J* = 12.5, CH_AH$_B$), 4.83 (1H, d, *J* = 12.5, CH$_A$$H_B$), 4.28 (1H, ddd, *J* = 11.7, 8.1, 2.7, C*H*), 4.08 (3H, s, OCH_3), 4.08 – 4.04 (1H, m, C*H*), 3.85 – 3.77 (1H, m, C*H*), 3.55 (1H, ddd, *J* = 12.3, 10.5, 1.6, C*H*), 3.03 (1H, dt, *J* = 11.5, 9.1, C*H*), 2.71 – 2.62 (1H, m, C*H*), 2.43 – 2.35 (1H, m, C*H*), 1.90 (1H, br. s, C*H*), 1.81 – 1.74 (2H, m, CH_2), 1.13 (1H, ddd, *J* = 13.6, 8.7, 5.1, C*H*); **^{13}C NMR** (126 MHz, $(CD_3)_2SO$**)**: 162.26 (2xC_{Ar}, dd, $^1J^{C\text{-}F}$ = 247.0, $^3J^{C\text{-}F}$ = 13.3), 157.54 (C_{Ar}), 147.32 (C_{Ar}H), 143.66 (C_{Ar}), 143.33 (C_{Ar}), 137.20 (CH_2=*C*H), 131.64 (C_{Ar}, t, $^3J^{C\text{-}F}$ = 9.9), 131.34 (C_{Ar}H), 125.47 (C_{Ar}), 121.35 (C_{Ar}H), 120.36 (C_{Ar}H), 117.13 (2xC_{Ar}H, d, $^2J^{C\text{-}F}$ = 26.2), 116.98 (*C*H$_A$H$_B$=CH), 105.89 (C_{Ar}H, t, $^2J^{C\text{-}F}$ = 25.6), 102.28 (C_{Ar}H), 67.77 (*C*H), 64.57 (*C*HOH), 61.71 (*C*H$_A$H$_B$), 56.07 (CH_2), 55.81 (O*C*H$_3$), 54.12 (*C*H$_2$), 36.78 (*C*H), 26.25 (*C*H), 23.07 (*C*H$_2$), 20.62 (*C*H$_2$); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F –108.93 (2F, s); (**IR (vmax/cm^{-1}) (neat)**: 3454 – 3083 (OH), 3028 (alkene CH), 2947, 2888 (alkyl C-H); **MS** (ESI): *m/z* calcd for $[C_{27}H_{29}F_2N_2O_2]^+$, found 451.2264.

(1*S*,2*R*,4*S*,5*R*)-5-Ethyl-2-((*S*)-hydroxy(6-methoxyquinolin-4-yl)methyl)-1-(3,4,5-trifluorobenzyl)quinuclidin-1-ium bromide (322)



Following general **procedure 1** (**method B**): dihydroquinidine (500 mg, 1.53 mmol) in toluene (3.00 mL); and 3,4,5-trifluoro benzyl bromide (0.22 mL, 1.68 mmol). The reaction mixture was refluxed at 120 ℃ for 16 h. It was then cooled to room temperature and filtered. The residue was washed with toluene and isolated to afford the title compound (430 mg, 51%) as an off white solid. $[\alpha]_D^{24}$ = +188 (c = 10 mg/ml, MeOH); **mp**: 224 – 227 ℃ (decomposed); **^{1}H NMR** (500 MHz, $(CD_3)_2SO$): δ 8.81 (1H, d, *J* = 4.5, Ar-*H*), 8.02 (1H, d, *J* = 9.2, Ar-*H*), 7.93 – 7.83 (2H, m, Ar-*H*), 7.79 (1H, d, *J* = 4.6, Ar-*H*), 7.50 (1H, d, *J* = 8.8, Ar-*H*), 7.40 (1H, s, Ar-*H*), 6.73 (1H, br. s, O*H*), 6.45 (1H, br. s, C*H*OH), 5.03 (1H, d, *J* = 12.6, CH_AH_B), 4.76 (1H, d, *J* = 12.6, CH_AH_B), 4.07 (3H, s, OCH_3), 4.02 – 3.92 (2H, m, 2xC*H*), 3.79 – 3.67 (1H, m, C*H*), 3.56 – 3.45 (1H, m, C*H*), 3.07 – 2.93 (1H, m, C*H*), 2.41 – 2.31 (1H, m, C*H*), 1.87 (1H, br. s, C*H*), 1.82 – 1.71 (2H, m, 2xC*H*), 1.71 – 1.61 (1H, m, C*H*), 1.61 – 1.45 (2H, m, CH_2), 1.16 – 1.05 (1H, m, C*H*), 0.88 (3H, t, *J* = 7.4, CH_3); **^{13}C NMR** (126 MHz, $(CD_3)_2SO$**)**: 157.55 (C_{Ar}), 150.10 (2xC_{Ar}, ddd, $^1J^{C\text{-}F}$ = 248.2, $^2J^{C\text{-}F}$ = 9.8, $^3J^{C\text{-}F}$ = 3.2), 147.35 (C_{Ar}H), 143.67 (C_{Ar}), 143.35 (C_{Ar}), 140.04 (C_{Ar}, dt, $^1J^{C\text{-}F}$ = 252.5, $^2J^{C\text{-}F}$ = 15.3), 131.40 (C_{Ar}H), 125.43 (C_{Ar}), 125.08 – 124.76 (C_{Ar}), 121.25 (C_{Ar}H), 120.39 (C_{Ar}H), 118.77 (2xC_{Ar}H, dd, $^2J^{C\text{-}F}$ = 16.7, $^3J^{C\text{-}F}$ = 4.5), 102.26 (C_{Ar}H), 67.83 (*C*H), 64.47 (*C*HOH), 61.41 (*C*H_AH_B), 56.00 (2x*C*H_2), 55.82 (O*C*H_3), 34.87 (*C*H), 24.07 (*C*H), 23.90 (*C*H_2), 23.59 (*C*H_2), 20.33 (*C*H_2), 11.35 (*C*H_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F –134.43 (2F, d, *J* = 21.8), –159.43 (1F, t, *J* = 21.8); (**IR (vmax/cm^{-1}) (neat)**: 3257 – 3123 (OH), 2957, 2900 (alkyl C-H); **HRMS** (ESI): *m/z* calcd for $[C_{27}H_{30}F_3N_2O_2]^+$ 471.225389, found 471.223713.

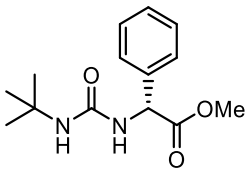
(1*S*,2*R*,4*S*,5*R*)-1-(3,5-Difluorobenzyl)-5-ethyl-2-((*S*)-hydroxy(6-methoxyquinolin-4-yl)methyl)quinuclidin-1-ium bromide (323)



Following general **procedure 1** (**method B**): dihydroquinidine (500 mg, 1.53 mmol) in toluene (3 mL); and 3,5-difluoro benzyl bromide (0.22 mL, 1.68 mmol). The reaction mixture was refluxed at 120 °C for 16 h. It was then cooled to room temperature and filtered. The residue was washed with toluene and isolated to afford the title compound (500 mg, 61%) as an off white solid. $[\alpha]_D^{24}$ = +116 (c = 10 mg/ml, $CHCl_3$); **mp**: 208 – 210 °C (decompose); **^{1}H NMR** (400 MHz, $(CD_3)_2SO$): δ 8.81 (1H, d, *J* = 4.5, Ar-*H*), 8.01 (1H, d, *J* = 9.2, Ar-*H*), 7.80 (1H, d, *J* = 4.5, Ar-*H*), 7.62 (2H, br. d, *J* = 6.1, Ar-*H*), 7.58 – 7.44 (2H, m, Ar-*H*), 7.42 (1H, d, *J* = 2.1, Ar-*H*), 6.76 (1H, br. d, *J* = 3.9, O*H*), 6.48 (1H, br. s, C*H*OH), 5.12 (1H, d, *J* = 12.5, CH_AH_B), 4.80 (1H, d, *J* = 12.5, CH_AH_B), 4.08 (3H, s, OCH_3), 4.10 – 3.95 (2H, m, 2xC*H*), 3.84 – 3.72 (1H, m, C*H*), 3.57 – 3.45 (1H, m, C*H*), 3.05 – 2.91 (1H, m, C*H*), 2.43 – 2.31 (1H, m, C*H*), 1.87 (1H, br. s, C*H*), 1.84 – 1.64 (3H, m, CH_2+C*H*), 1.54 (2H, dq, *J* = 17.6, 6.8, CH_2), 1.10 (1H, ddd, *J* = 13.7, 9.1, 5.0 C*H*), 0.88 (3H, t, *J* = 7.3, CH_3); **^{13}C NMR** (126 MHz, $(CD_3)_2SO$**)**: 162.24 (2xC_{Ar}, dd, $^1J^{C\text{-}F}$ = 247.1, $^3J^{C\text{-}F}$ = 13.3), 157.54 (C_{Ar}), 147.32 (C_{Ar}H), 143.65 (C_{Ar}), 143.40 (C_{Ar}), 131.75 (C_{Ar}, t, $^3J^{C\text{-}F}$ = 9.9), 131.34 (C_{Ar}H), 125.44 (C_{Ar}), 121.37 (C_{Ar}H), 120.40 (C_{Ar}H), 117.10 (2xC_{Ar}H, d, $^2J^{C\text{-}F}$ = 26.1), 105.86 (C_{Ar}H, t, $^2J^{C\text{-}F}$ = 25.7), 102.19 (C_{Ar}H), 67.86 (*C*H), 64.41 (*C*HOH), 61.64 (*C*H_AH_B), 56.15 (*C*H_2), 56.12 (*C*H_2), 55.81 (O*C*H_3), 34.79 (*C*H), 24.00 (*C*H), 23.86 (*C*H_2), 23.61 (*C*H_2), 20.37 (*C*H_2), 11.33 (*C*H_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F –108.91 (2F, s); (**IR (vmax/cm^{-1}) (neat)**: 3333 – 3028 (OH), 2954, 2881 (alkyl C-H); **MS** (ESI): *m/z* calcd for $[C_{27}H_{31}F_2N_2O_2]^+$, found 453.2415.

4.3.1.3 Synthesis of Hydantoin Ureas

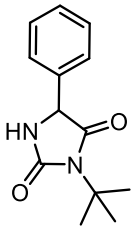
Methyl 2-(3-(*tert*-butyl)ureido)-2-phenylacetate (278a)



Following general **procedure 2**: [*R*]-[-]-2-phenylglycine methyl ester hydrochloride (4.33 g, 21.5 mmol) in anhydrous DCM (40.0 mL), Et_3N (6.00 mL, 43.0 mmol) and *tert*-butyl isocyanate (2.70

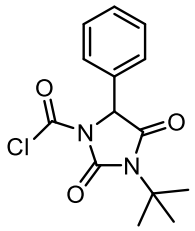
mL, 23.6 mmol). The title compound (5.23 g, 92%) was yielded as a white solid and used without further purification. **R*f*** (1:1 Pet.Ether:EtOAc) 0.61; **mp**: 124 – 125 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38 – 7.28 (5H, m, Ar-*H*), 5.46 (1H, d, *J* =7.2, C*H*Ph), 5.16 (1H, s, N*H*CH), 4.34 (1H, s, $(CH_3)_3CNH$), 3.71 (3H, s, OCH_3), 1.31 (9H, s, $(CH_3)_3CNH$); **^{13}C NMR** (101 MHz, $CDCl_3$): 172.72 $(C{=}O)_{ester}$, 156.10 $(C{=}O)_{urea}$, 137.63 (C_{Ar}), 129.04 ($2xC_{Ar}H$), 128.44 ($C_{Ar}H$), 127.36 ($2xC_{Ar}H$), 57.12 (*C*HPh), 52.82 (OCH_3), 50.83 ($(CH_3)_3C$), 29.56 ($(CH_3)_3C$); **IR (vmax/cm^{-1}) (neat)**: 3345 (NH), 2962, 2925 (alkyl C-H), 1746 (ester C=O), 1633 (urea C=O); **HRMS** (ESI): *m/z* calcd for $C_{14}H_{20}N_2O_3Na$ $[M+Na]^+$ 287.1366, found 287.1359. Data in agreement with reported values.[178]

3-(*tert*-Butyl)-5-phenylimidazolidine-2, 4-dione (279a)



Following general **procedure 3**: KO*t*Bu (1.77 g, 15.8 mmol) and urea **278a** (3.79 g, 14.3 mmol) in anhydrous THF (60.0 mL). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 70:30) to afford the title compound (2.48 g, 75%) as a white solid. **R*f*** (7:3 Pet.Ether:EtOAc) 0.37; **mp**: 125 – 126 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47 – 7.31 (5H, m, Ar-*H*), 5.46 (1H, s, N*H*), 4.87 (1H, d, *J* =1.4, C*H*Ph), 1.61 (9H, s, $NC(CH_3)_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): 173.06 $(C{=}O)_{amide}$, 158.83 $(C{=}O)_{urea}$, 135.29 (C_{Ar}), 129.14 ($2xC_{Ar}H$), 128.96 ($C_{Ar}H$), 126.50 ($2xC_{Ar}H$), 60.06 (*C*HPh), 58.12 ($C(CH_3)_3$), 28.67 ($C(CH_3)_3$); **IR (vmax/cm^{-1}) (neat)**: 3234 (NH), 2973, 2935 (alkyl C-H), 1765, 1698 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{13}H_{16}N_2O_2Na$ $[M+Na]^+$ 255.1104, found 255.1099. Data in agreement with reported values.[178]

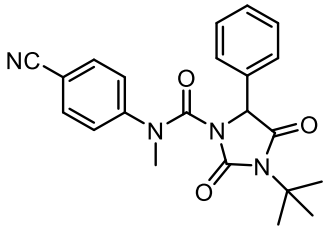
3-(*tert*-Butyl)-2-oxo-5-phenylimidazolidine-1-carbonyl chloride (280a)



Following general **procedure 4**: triphosgene (1.24 g, 4.18 mmol) in anhydrous DCM (21.0 mL), anhydrous pyridine (1.00 mL, 12.2 mmol) and hydantoin **279a** (1.94 g, 8.35 mmol) in anhydrous DCM (4.20 mL). The title compound (2.20 g, 89%) was yielded as a pale yellow oil and used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.48 – 7.39 (3H, m, Ar-*H*), 7.30 (2H,

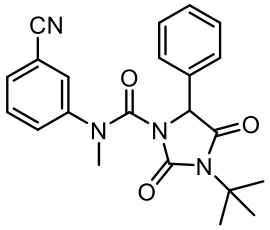
dd, *J* =7.7, 2.0, Ar-*H*), 5.31 (1H, s, C*H*Ph), 1.64 (9H, s, NC(C*H*$_3$)$_3$). Data in agreement with reported values.[180]

3-(*tert*-Butyl)-*N*-(4-cyanophenyl)-*N*-methyl-2,4-dioxo-5-phenylimidazolidine-1-carboxamide (273a)



Following general **procedure 5**: carbamoyl chloride **280a** (800 mg, 2.71 mmol) in anhydrous DCM (13.6 mL), Et_3N (0.44 mL, 3.13 mmol) and 4-(methyl amino) benzonitrile (357 mg, 2.70 mmol). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:Diethyl Ether 100:0 to Pet.Ether:Diethyl ether 60:40) to afford the title compound (1.01 g, 95%) as a white solid. **R*f*** (6:4 Pet.Ether:Diethyl Ether) 0.15; **mp**: 73 – 74 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.58 (2H, d, *J* =8.6, Ar-*H*), 7.45 (3H, dd, *J* =4.9, 1.9, Ar-*H*), 7.27 – 7.22 (2H, m, Ar-*H*), 7.06 (2H, d, *J* = 8.6, Ar-*H*), 5.51 (1H, s, C*H*Ph), 3.35 (3H, s, NC*H*$_3$), 1.50 (9H, s, NC(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): 170.71 (*C*=O)$_{amide}$, 152.43 (*C*=O)$_{urea\ hydantoin}$, 151.87 (*C*=O)$_{urea}$, 147.46 (*C*$_{Ar}$), 133.93 (*C*$_{Ar}$), 132.77 (2x*C*$_{Ar}$H), 129.75 (*C*$_{Ar}$H), 129.34 (2x*C*$_{Ar}$H), 128.44 (2x*C*$_{Ar}$H), 126.51 (2x*C*$_{Ar}$H), 118.37 (*C*N), 110.15 (*C*$_{Ar}$), 62.29 (*C*HPh), 59.27 (N*C*(CH$_3$)$_3$), 38.85 (N*C*H$_3$), 28.46 (NC(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 2978, 2938 (alkyl C-H), 2228 (CN), 1785, 1718, 1683 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{22}H_{22}N_4O_3Na$ $[M+Na]^+$ 413.1584, found 413.1575. Data in agreement with reported values.[178]

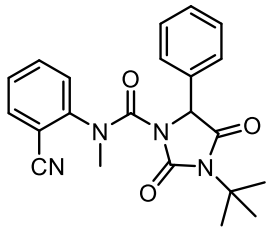
3-(*ter*t-Butyl)-*N*-(3-cyanophenyl)-*N*-methyl-2,4-dioxo-5-phenylimidazolidine-1-carboxamide (273b)



Following general **procedure 5**: carbamoyl chloride **280a** (300 mg, 1.02 mmol) in anhydrous DCM (4.10 mL), Et_3N (0.17 mL, 1.22 mmol) and 3-(methyl amino) benzonitrile (148 mg, 1.12 mmol). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 80:20) to afford the title compound (315 mg, 79%) as a white solid. **R*f*** (8:2 Pet.Ether:EtOAc) 0.19; **mp**: 113 – 115 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.54 – 7.38 (5H, m, Ar-*H*), 7.36 – 7.29 (1H, m, Ar-*H*), 7.23 (2H, dd, *J* = 7.8, 1.7, Ar-*H*), 7.10 (1H, s, Ar-*H*), 5.51 (1H, s,

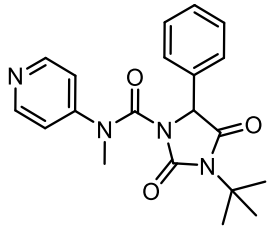
C*H*Ph), 3.33 (3H, s, NC*H*$_3$), 1.49 (9H, s, NC(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): 170.8 (*C*=O)$_{amide,}$ 152.4 (*C*=O)$_{urea\ hydantoin,}$, 152.0 (*C*=O)$_{urea}$, 144.2 (C_{Ar}), 133.9 (C_{Ar}), 131.2 (C_{Ar}), 130.4 (C_{Ar}H), 129.89 (C_{Ar}H), 129.87 (C_{Ar}H), 129.6 (2xC_{Ar}H), 129.8 (C_{Ar}H), 128.5 (2xC_{Ar}H), 117.9 (*C*N), 112.8 (C_{Ar}), 62.3 (*C*HPh), 59.2 (N*C*(CH$_3$)$_3$), 39.1 (N*C*H$_3$), 28.4 (NC(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 2977, 2937 (alkyl C-H), 1783, 1718, 1688 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{22}H_{22}N_4O_3Na$ $[M+Na]^+$ 413.1584, found 413.1583.

3-(*tert*-Butyl)-*N*-(2-cyanophenyl)-*N*-methyl-2,4-dioxo-5-phenylimidazolidine-1-carboxamide (273c)



Following similar procedure to general **procedure 5**: carbamoyl chloride **280a** (138 mg, 0.47 mmol) in anhydrous DCM (2.00 mL), Et_3N (0.08 mL, 0.56 mmol) and 2-(methyl amino) benzonitrile (61.8 mg, 0.47 mmol). *The reaction was stirred for 16 h*. The crude product was purified by flash column chromatography (SiO_2; DCM:MeOH 100:0 to DCM:MeOH 99.5:0.5) to afford the title compound (107 mg, 58%) as a pale yellow oil. **R*f*** (9.95:0.05 DCM:MeOH) 0.49; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.69 (1H, dd, *J* = 7.7, 1.6, Ar-*H*), 7.50 – 7.38 (4H, m, Ar-*H*), 7.38 – 7.33 (1H, m, Ar-*H*), 7.26 – 7.22 (2H, m, Ar-*H*), 6.82 (1H, br. s, Ar-*H*), 5.51 (1H, s, C*H*Ph), 3.40 (3H, s, NC*H*$_3$), 1.49 (9H, s, NC(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.77 (*C*=O)$_{amide,}$ 152.16 (*C*=O)$_{urea\ hydantoin,}$, 146.17 (*C*=O)$_{urea}$, 134.10 (C_{Ar}), 133.66 (C_{Ar}H), 133.03 (C_{Ar}H), 129.58 (C_{Ar}H), 129.26 (2xC_{Ar}H), 128.19 (2xC_{Ar}H), 128.01 (C_{Ar}H), 127.75 (C_{Ar}H), 126.55 (C_{Ar}), 116.47 (*C*N), 112.81 (C_{Ar}), 62.45 (*C*HPh), 59.20 (N*C*(CH$_3$)$_3$), 39.22 (N*C*H$_3$), 28.46 (NC(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 2977, 2938 (alkyl C-H), 2232 (C≡N), 1785, 1721, 1691 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{22}H_{23}N_4O_3$ $[M+H]^+$ 391.1765, found 391.1757.

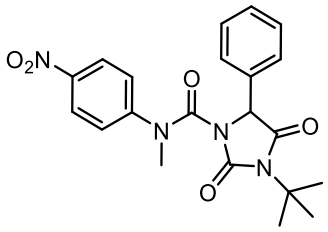
3-(*tert*-Butyl)-*N*-methyl-2,4-dioxo-5-phenyl-*N*-(pyridin-4-yl)imidazolidine-1-carboxamide (273d)



Following similar procedure to general **procedure 5**: Carbamoyl chloride **280a** (300 mg, 1.02 mmol) in anhydrous DCM (4.00 mL), Et_3N (0.17 mL, 1.22 mmol) and 4-(methyl amino)pyridine

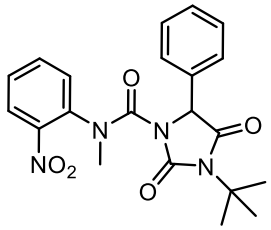
(110 mg, 1.02 mmol). *The reaction mixture was quenched with water and washed with brine*. The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 50:50) to afford the title compound (260 mg, 70%) as a white solid. **R*f*** (5:5 Pet.Ether:EtOAc) 0.14; **mp**: 147 – 149 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.51 (2H, d, *J* =6.4 Ar-*H*), 7.45 (3H, dd, *J* =5.2, 2.1, Ar-*H*), 7.31 – 7.25 (2H, m, Ar-*H*), 6.95 (2H, d, *J* =6.4, Ar-*H*), 5.52 (1H, s, C*H*Ph), 3.36 (3H, s, NCH_3), 1.51 (9H, s, NC(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): 170.71 (*C*=O)$_{amide}$, 152.47 (*C*=O)$_{urea\ hydantoin}$, 151.77 (*C*=O)$_{urea}$, 150.78 (C_{Ar}), 150.65 (2xC_{Ar}H), 133.89 (C_{Ar}), 129.73 (C_{Ar}H), 129.38 (2xC_{Ar}H), 128.40 (2xC_{Ar}H), 119.12 (2xC_{Ar}H), 62.32 (*C*HPh), 59.34 (N*C*(CH$_3$)$_3$), 38.06 (N*C*H$_3$), 28.50 (NC(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 2974, 2936 (alkyl C-H), 1787, 1718, 1683 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{20}H_{22}N_4O_3Na$ $[M+Na]^+$ 389.1584, found 389.1581.

3-(*tert*-Butyl)-*N*-methyl-*N*-(4-nitrophenyl)-2, 4-dioxo-5-phenylimidazolidine-1-carboxamide (273e)



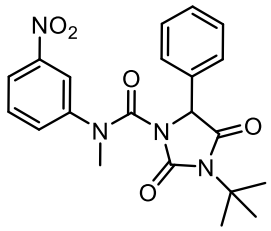
Following general **procedure 5**: carbamoyl chloride **280a** (300 mg, 1.02 mmol) in anhydrous DCM (4.10 mL), Et$_3$N (0.17 mL, 1.22 mmol) and 4-nitro-*N*-methylaniline (139 mg, 0.92 mmol, 0.90 eq.). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 60:40) to afford the title compound (326 mg, 78%) as a pale yellow crystalline solid. **R*f*** (6:4 Pet.Ether:Diethyl ether) 0.17; **mp**: 59 – 61; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.14 (2H, d, *J* =9.1, Ar-*H*), 7.46 (3H, dd, *J* =5.2, 1.9, Ar-*H*), 7.31 – 7.22 (2H, m, Ar-*H*), 7.11 (2H, d, *J* =9.0, Ar-*H*), 5.53 (1H, s, C*H*Ph), 3.38 (3H, s, NCH_3), 1.49 (9H, s, NC(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): 170.6 (*C*=O)$_{amide}$, 152.3 (*C*=O)$_{urea\ hydantoin}$, 151.8 (*C*=O)$_{urea}$, 149.2 (C_{Ar}), 145.4 (C_{Ar}), 133.8 (C_{Ar}), 129.7 (C_{Ar}H), 129.3 (2xC_{Ar}H), 128.3 (2xC_{Ar}H), 126.0 (2xC_{Ar}H), 124.2 (2xC_{Ar}H), 62.2 (*C*HPh), 59.2 (N*C*(CH$_3$)$_3$), 38.8 (N*C*H$_3$), 28.4 (NC(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 2977, 2938 (alkyl C-H), 1786, 1720, 1688 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{21}H_{22}N_4O_5Na$ $[M+Na]^+$ 433.1482, found 433.1486.

3-(*tert*-Butyl)-*N*-methyl-*N*-(2-nitrophenyl)-2,4-dioxo-5-phenylimidazolidine-1-carboxamide (273f)



Following a similar procedure to general **procedure 5**: carbamoyl chloride **280a** (200 mg, 0.68 mmol) in anhydrous CH_3CN (13.0 mL), Et_3N (0.12 mL, 0.78 mmol) and *N*-methyl-2-nitroaniline (103 mg, 0.679 mmol). *The reaction was refluxed for 16 hours at 100 °C.* The crude product was purified by flash column chromatography (SiO_2; DCM:MeOH 100:0 to DCM:MeOH 99.5:0.5) to afford the title compound (116 mg, 42%) as a pale yellow oil. **R*f*** (9.95:0.05 DCM:MeOH) 0.43; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.05 (1H, dd, *J* =8.1, 1.5, Ar-*H*), 7.55 (1H, t, J =7.8, Ar-*H*), 7.49 – 7.38 (5H, m, Ar-*H*), 7.24 – 7.18 (2H, m, Ar-*H*), 5.46 (1H, s, C*H*Ph), 3.39 (3H, s, NCH_3), 1.54 (9H, s, NC(CH_3)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): 170.8 (*C*=O)$_{amide,}$, 153.3 (*C*=O)$_{urea\ hydantoin,}$, 152.3 (*C*=O)$_{urea}$, 137.04 (C_{Ar}), 134.16 (C_{Ar}), 133.81 (C_{Ar}), 129.4 (C_{Ar}H), 129.2 (2xC_{Ar}H), 128.9 (C_{Ar}H), 127.9 (2xC_{Ar}H), 125.7 (C_{Ar}H), 62.6 (*C*HPh), 59.2 (N*C*(CH$_3$)$_3$), 40.1 (N*C*H$_3$), 28.6 (NC(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 2988, 2939 (alkyl C-H), 1785, 1718, 1686 (C=O); **HRMS** (ESI): m/z calcd for $C_{21}H_{22}N_4O_5Na$ $[M+Na]^+$ 433.1482, found 433.1480.

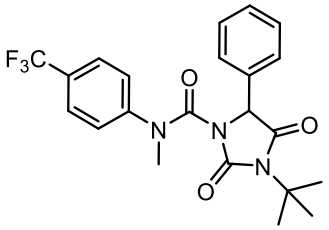
3-(*tert*-Butyl)-*N*-methyl-*N*-(3-nitrophenyl)-2,4-dioxo-5-phenylimidazolidine-1-carboxamide (273g)



Following similar procedure to general **procedure 5**: carbamoyl chloride **280a** (100 mg, 0.34 mmol) in anhydrous CH_3CN (1.70 mL), Et_3N (0.05 mL, 0.39 mmol) and *N*-methyl-3-nitroaniline (52.0 mg, 0.34 mmol). *The reaction was left to stir until TLC analysis showed that the starting material was completely consumed*. The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 70:30) to afford the title compound (132 mg, 95%) as a pale yellow solid. **R*f*** (7:3 Pet.Ether:EtOAc) 0.36; **mp**: 66 – 69 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.10 (1H, ddt, *J* =8.2, 2.1, 1.0, Ar-*H*), 7.86 (1H, d, *J* =2.2, Ar-*H*), 7.47 (5H, m, Ar-*H*), 7.28 (2H, m, Ar-*H*), 5.53 (1H, s, C*H*Ph), 3.39 (3H, s, NCH_3), 1.47 (9H, s, NC(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): 170.7 (*C*=O)$_{amide,}$, 152.5 (*C*=O)$_{urea\ hydantoin,}$, 151.9

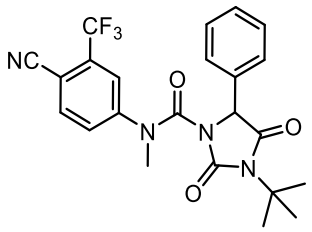
(*C*=O)$_{urea}$, 148.3 (*C*$_{Ar}$), 144.6 (*C*$_{Ar}$), 133.8 (*C*$_{Ar}$), 132.5 (*C*$_{Ar}$H), 129.8 (*C*$_{Ar}$H), 129.7 (*C*$_{Ar}$H), 129.5 (2x*C*$_{Ar}$H), 128.4 (2x*C*$_{Ar}$H), 121.6 (*C*$_{Ar}$H), 121.0 (*C*$_{Ar}$H), 62.5 (*C*HPh), 59.2 (N*C*(CH$_3$)$_3$), 39.2 (N*C*H$_3$), 28.4 (NC(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 2980, 2939 (alkyl C-H), 1784, 1717, 1684 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{21}H_{22}N_4O_5Na$ [M+Na]$^+$ 433.1482, found 433.1477.

3-(*tert*-Butyl)-*N*-methyl-2,4-dioxo-5-phenyl-*N*-(4-(trifluoromethyl)phenyl)imidazolidine-1-carboxamide (273h)



Following general **procedure 5**: carbamoyl chloride **280a** (500 mg, 1.70 mmol) in anhydrous DCM (13.0 mL), Et$_3$N (0.27 mL, 1.96 mmol) and 4-(trifluoromethyl)-*N*-methyl-aniline (0.22 mL, 1.53 mmol). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 80:20) to afford the title compound (487 mg, 66%) as a pale yellow oil. **R*f*** (8:2 Pet.Ether:EtOAc) 0.31; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.55 (2H, d, *J* =7.9, Ar-*H*), 7.45 (3H, dd, *J* = 5.0, 1.9, Ar-*H*), 7.27 – 7.23 (2H, m, Ar-*H*), 7.08 (2H, d, *J* =7.8, Ar-*H*), 5.47 (1H, s, C*H*Ph), 3.35 (3H, s, NC*H*$_3$), 1.49 (9H, s, NC(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): 170.78 (*C*=O)$_{amide}$, 152.53 (*C*=O)$_{urea\ hydantoin}$, 151.99 (*C*=O)$_{urea}$, 146.46 (*C*$_{Ar}$), 133.98 (*C*$_{Ar}$), 129.26 (2x*C*$_{Ar}$H), 128.43 (2x*C*$_{Ar}$H), 126.44 (2x*C*$_{Ar}$H), 128.82 (q, $^2J^{C\text{-}F}$ = 32.7, *C*$_{Ar}$), 125.90 (q, $^3J^{C\text{-}F}$ = 3.7, 2xAr), 123.90 (q, $^1J^{C\text{-}F}$ = 273.4, *C*F$_3$), 62.39 (*C*HPh), 59.10 (N*C*(CH$_3$)$_3$), 39.02 (N*C*H$_3$), 28.40 (NC(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 2976, 2936 (alkyl C-H), 1785, 1719, 1686 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{22}H_{22}F_3N_3O_3Na$ [M+Na]$^+$ 456.1505, found 456.1522.

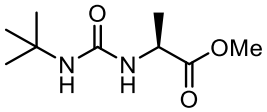
3-(*tert*-Butyl)-*N*-(4-cyano-3-(trifluoromethyl)phenyl)-*N*-methyl-2,4-dioxo-5-phenyl imidazolidine-1-carboxamide (273i)



Following general **procedure 5**: carbamoyl chloride **280a** (200 mg, 0.68 mmol) in anhydrous DCM (2.70 mL), Et$_3$N (0.11 mL, 0.81 mmol) and 2-(trifluoromethyl),4-(methyl amino) benzonitrile (136 mg, 0.68 mmol). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 60:40) to afford the title compound (245

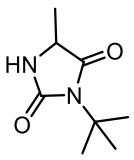
mg, 79%) as a white solid. **R*f*** (6:4 Pet.Ether:Diethyl ether) 0.13; **mp**:156 – 158 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.79 (1H, d, *J* =8.3, Ar-*H*), 7.51 – 7.41 (3H, m, Ar-*H*), 7.43 – 7.35 (2H, m, Ar-*H*), 7.30 – 7.22 (2H, m, Ar-*H*), 5.56 (1H, s, C*H*Ph), 3.41 (3H, s, NCH_3), 1.49 (9H, s, NC(CH_3)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): 170.49 (*C*=O)$_{amide}$, 152.38 (*C*=O)$_{urea\ hydantoin}$, 151.58 (*C*=O)$_{urea}$, 147.92 (C_{Ar}), 133.75 (C_{Ar}), 135.51 (C_{Ar}H), 133.60 (q, $^{2}J^{C\text{-}F}$ = 33.1, C_{Ar}), 129.89 (C_{Ar}H), 129.57 (2xC_{Ar}H), 128.68 (C_{Ar}H), 128.44 (2xC_{Ar}H), 123.29 (q, $^{3}J^{C\text{-}F}$ = 4.6, C_{Ar}), 122.09 (q, $^{1}J^{C\text{-}F}$ = 274.3, *C*F$_3$), 115.15 (*C*N), 107.05 (q, $^{3}J^{C\text{-}F}$ = 2.1, C_{Ar}H), 62.35 (*C*HPh), 59.51 (N*C*(CH$_3$)$_3$), 38.71 (N*C*H$_3$), 28.41 (NC(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 2986, 2941 (alkyl C-H), 2234 (CN), 1788, 1717, 1688 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{23}H_{21}F_3N_4O_3Na$ $[M+Na]^+$ 481.1458, found 481.1467.

Methyl (*tert*-Butyl carbamoyl)-L-alaninate (278b)



Following general **procedure 2**: L-alanine methyl ester hydrochloride (3.00 g, 21.5 mmol) in anhydrous DCM (40.0 mL), Et_3N (6.00 mL, 43 mmol) and *tert*-butyl isocyanate (2.7 mL, 23.6 mmol). The title compound (>99%) was yielded as a white solid and used without further purification. **R*f*** (1:1 Pet.Ether:EtOAc) 0.44; **mp**: 77 – 78 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.97 (1H, d, *J* =7.8, N*H*CH), 4.61 (1H, s, (CH$_3$)$_3$CN*H*), 4.44 (1H, p, *J* =7.3, NHC*H*CH$_3$), 3.72 (3H, s, OCH_3), 1.34 (3H, d, *J* =7.2, CHCH_3), 1.30 (9H, s, (CH_3)$_3$CNH); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 175.3 (*C*=O)$_{ester}$, 156.8 (*C*=O)$_{urea}$, 52.4 (O*C*H$_3$), 50.5 ((CH$_3$)$_3$*C*NH), 48.6 (NH*C*HCH3), 29.6 ((*C*H$_3$)$_3$CNH), 19.2 (CH*C*H$_3$); **IR (vmax/cm^{-1}) (neat)**: 3341 (N-H), 2961, 2924 (alkyl C-H), 1746 (ester C=O), 1633 (urea C=O); **HRMS** (ESI): *m/z* calcd for $C_9H_{18}N_2O_3Na$ $[M+Na]^+$ 225.1210, found 225.1209. Data in agreement with reported values.[178]

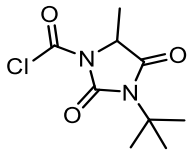
3-(*tert*-Butyl)-5-methyl imidazolidine-2, 4-dione (279b)



Following general **procedure 3**: KO*t*Bu (2.78 g, 24.8 mmol) and urea **278b** (4.54 g, 22.4 mmol) in anhydrous THF (60 mL). The title compound (3.23 g, 85%) was yielded as a white solid and used without further purification. **R*f*** (1:1 Pet.Ether:EtOAc) 0.40; **1H NMR** (400 MHz, $CDCl_3$): δ 6.16 (1H, s, N*H*), 3.89 (1H, qd, *J* =6.9, 1.3, NHC*H*CH$_3$), 1.58 (9H, s, NC(CH_3)$_3$), 1.37 (3H, d, *J* =6.8, C*H*CH$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 175.9 (*C*=O)$_{amide}$, 158.7 (*C*=O)$_{urea}$, 57.7 (N*C*(CH$_3$)$_3$), 52.1 (*C*HCH$_3$), 28.7 (NC(*C*H$_3$)$_3$), 18.0 (CH*C*H$_3$); **IR (vmax/cm^{-1}) (neat)**: 3300 (NH), 2977, 2935 (alkyl

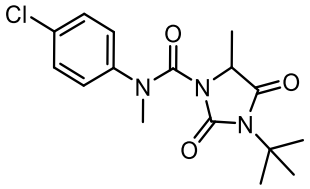
C-H), 1770, 1697 (C=O); **HRMS** (ESI): *m/z* calcd for $C_8H_{14}N_2O_2Na$ $[M+Na]^+$ 193.0947, found 193.0951. Data in agreement with reported values.[178]

3-(*tert*-Butyl)-5-methyl-2, 4-dioxoimidazolidine-1-carbonyl chloride (280b)



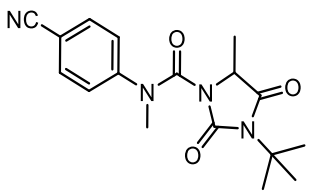
Following general **procedure 4**: triphosgene (3.46 g, 11.7 mmol) in DCM (49.0 mL), anhydrous pyridine (2.68 mL, 33.1 mmol) and hydantoin **279b** (3.86 g, 22.7 mmol) in anhydrous DCM (10 mL). The title compound (2.83 g, 54%) was yielded as a yellow solid and used without further purification. **1H NMR** (400 MHz, $CDCl_3$): δ 4.39 (1H, q, *J* = 6.8, C*H*CH_3), 1.63 (9H, s, NC(C*H*$_3$)$_3$), 1.63 (3H, d, *J* = 6.8, CHC*H*$_3$). Data in agreement with reported values.[180]

3-(*tert*-Butyl)-*N*-(4-chlorophenyl)-*N*, 5-dimethyl-2, 4-dioxoimidazolidine-1-carboxamide (273j)



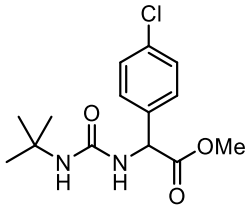
Following general **procedure 5**: carbamoyl chloride **280b** (750 mg, 3.23 mmol) in anhydrous DCM (13.0 mL), Et_3N (0.52 mL, 3.73 mmol) and 4-chloro-*N*-methyl aniline (0.39 mL, 3.22 mmol). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 70:30) to afford the title compound (661 mg, 61%) as a yellow oil. **R*f*** (7:3 Pet. ether: EtOAc) 0.23; **1H NMR** (400 MHz, $CDCl_3$): δ 7.34 – 7.29 (2H, m, Ar-*H*), 7.18 – 7.12 (2H, m, Ar-*H*), 4.48 (1H, q, *J* =6.8, C*H*CH_3), 3.38 (3H, s, NC*H*$_3$), 1.47 (3H, d, *J* =6.9, CHC*H*$_3$), 1.43 (9H, s, NC(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.9 (*C*=O)$_{amide}$, 152.34 (*C*=O)$_{urea\ hydantoin}$, 152.30 (*C*=O)$_{urea}$, 142.2 (*C*$_{Ar}$), 132.49 (*C*$_{Ar}$), 129.15 (2x*C*$_{Ar}$H), 127.38 (2x*C*$_{Ar}$H), 58.66 (N*C*$(CH_3)_3$), 54.72 (*C*HCH_3), 39.32 (N*C*H$_3$), 28.43 (NC(*C*H$_3$)$_3$), 15.74 (CH*C*H$_3$); **IR (vmax/cm^{-1}) (neat):** 1681.90 (C=O), 1715.58 (C=O), 1783.78 (C=O), 2979.84 (C-H); **HRMS** (ESI): *m/z* calcd for $C_{16}H_{20}ClN_3O_3Na$ $[M+Na]^+$ 360.1085, found 360.1098. Data in agreement with reported values.[180]

3-(*tert*-Butyl)-*N*-(4-cyanophenyl)-*N*,5-dimethyl-2,4-dioxoimidazolidine-1-carboxamide (273k)



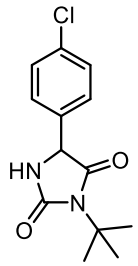
Following general **procedure 5**: carbamoyl chloride **280b** (500 mg, 2.15 mmol) in anhydrous DCM (9.00 mL), Et_3N (0.36 mL, 2.58 mmol) and 4-(methyl amino) benzonitrile (284 mg, 2.15 mmol). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 60:40) to afford the title compound (540 mg, 76%) as a yellow crystal like solid. **R*f*** (6:4 Pet.Ether:Diethyl ether) 0.13; **mp**: 126 – 128 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.63 (2H, d, *J* = 8.2, Ar-*H*), 7.31 (2H, d, *J* = 8.2, Ar-*H*), 4.53 (1H, q, *J* = 6.8 , C*H*CH_3), 3.42 (3H, s, NC*H*$_3$), 1.50 (3H, d, *J* = 6.8, CHC*H*$_3$), 1.40 (9H, s, NC(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): 172.42 (*C*=O)$_{amide}$, 152.01 (*C*=O)$_{urea\ hydantoin}$, 151.82 (*C*=O)$_{urea}$, 147.87 (*C*$_{Ar}$), 132.85 (2x*C*$_{Ar}$H), 125.72 (2x*C*$_{Ar}$H), 118.26 (*C*N), 109.63 (*C*$_{Ar}$), 54.58 (*C*HCH$_3$), 58.68 (N*C*(CH$_3$)$_3$), 38.65 (N*C*H$_3$), 28.26 (NC(*C*H$_3$)$_3$), 15.54 (CH*C*H$_3$); **IR (vmax/cm^{-1}) (neat)**: 2982, 2901 (alkyl C-H), 2231 (C≡N), 1786, 1720, 1683 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{17}H_{20}N_4O_3Na$ $[M+Na]^+$ 351.1428, found 351.1420.

Methyl 2-(3-(*tert*-butyl)ureido)-2-(4-chlorophenyl)acetate (278c)



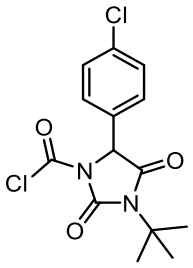
Following general **procedure 2**: methyl 2-amino-2-(4-chlorophenyl)acetate hydrochloride **277c** (1.00 g, 4.24 mmol) in anhydrous DCM (7.70 mL), Et_3N (1.20 mL, 8.47 mmol) and *tert*-butyl isocyanate (0.53 mL, 4.66 mmol). The title compound (1.32 g, >99%) was yielded as a white solid and used without further purification. **mp**: 163 – 165 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33 – 7.28 (4H, br. m, Ar-*H*), 5.44 (1H, d, *J* =6.9, C*H*Ph), 5.27 (1H, d, *J* =6.9, N*H*CH), 4.40 (1H, s, (CH$_3$)$_3$CN*H*), 3.71 (3H, s, OC*H*$_3$), 1.30 (9H, s, (C*H*$_3$)$_3$CNH); **^{13}C NMR** (101 MHz, $CDCl_3$): 172.34 (*C*=O)$_{ester}$, 155.95 (*C*=O)$_{urea}$, 136.40 (*C*$_{Ar}$), 134.28 (*C*$_{Ar}$), 129.16 (2x*C*$_{Ar}$H), 128.69 (2x*C*$_{Ar}$H), 56.43 (*C*HPh), 52.98 (O*C*H$_3$), 50.86 ((CH$_3$)$_3$*C*), 29.53 ((*C*H$_3$)$_3$C); **IR (vmax/cm^{-1}) (neat)**: 3349 (NH), 2968, 2929 (alkyl C-H), 1746 (ester C=O), 1635 (urea C=O); **HRMS** (ESI): *m/z* calcd for $C_{14}H_{19}ClN_2O_3Na$ $[M+Na]^+$ 321.097641, found 321.096406.

3-(*tert*-Butyl)-5-(4-chlorophenyl)imidazolidine-2,4-dione (279c)



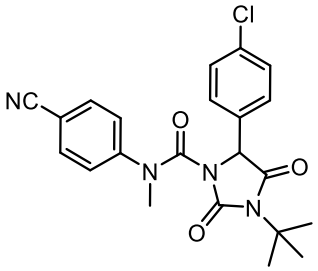
Following similar procedure to general **procedure 3**: KO*t*Bu (539 mg, 4.80 mmol) and urea **278c** (1.30 g, 4.37 mmol) in anhydrous THF (14.0 mL) at 0 °C. *The reaction was quenched with water*. The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 50:50) to afford the title compound (753 mg, 65%) as a white solid. **R*f*** (5:5 Pet.Ether:Diethyl ether) 0.30; **mp**: 135 – 137 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38 (2H, d, *J* =8.6, Ar-*H*), 7.30 (2H, d, *J* =8.6, Ar-*H*), 5.74 (1H, br. s, N*H*), 4.86 (1H, d, *J* =1.6, C*H*Ph), 1.59 (9H, s, NC(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): 172.50 (*C*=O)$_{amide}$, 158.32 (*C*=O)$_{urea}$, 135.13 (C_{Ar}), 133.67 (C_{Ar}), 129.44 (2xC_{Ar}H), 127.85 (2xC_{Ar}H), 59.40 (*C*HPh), 58.39 (N*C*(CH$_3$)$_3$), 28.66 (NC(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 3306 (NH), 2974, 2905 (alkyl C-H), 1773, 1704 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{13}H_{15}ClN_2O_2Na$ $[M+Na]^+$ 289.0714, found 289.0707.

3-(tert-Butyl)-5-(4-chlorophenyl)-2,4-dioxoimidazolidine-1-carbonyl chloride (280c)



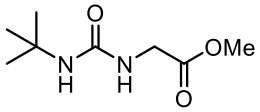
Following general **procedure 4**: triphosgene (111 mg, 0.37 mmol) in anhydrous DCM (1.60 mL), anhydrous pyridine (0.09 mL, 1.12 mmol) and hydantoin **279c** (200 mg, 0.75 mmol). The title compound (282 mg, >99%) was yielded as an orange oil and used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (2H, *J* = 8.5, Ar-*H*), 7.25 (2H, d, *J* =8.5, Ar-*H*), 5.29 (1H, s, C*H*Ph), 1.63 (9H, s, NC(CH_3)$_3$).

3-(*tert*-Butyl)-5-(4-chlorophenyl)-*N*-(4-cyanophenyl)-*N*-methyl-2,4-dioxoimidazolidine-1-carboxamide (273l)



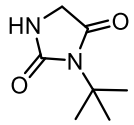
Following general **procedure 5**: carbamoyl chloride **280c** (253 mg, 0.77 mmol) in anhydrous DCM (3.10 mL), Et_3N (0.13 mL, 0.92 mmol) and 4-(methyl amino) benzonitrile (102 mg, 0.77 mmol). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 60:40) to afford the title compound (196 mg, 60%) as a colourless oil. **R*f*** (6:4 Pet.Ether:Diethyl ether) 0.14; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (2H, d, *J* =8.6, Ar-*H*), 7.44 (2H, d, *J* =8.5, Ar-*H*), 7.19 (2H, *J* =8.5, Ar-*H*), 7.11 (2H, d, *J* = 8.6, Ar-*H*), 5.49 (1H, s, C*H*Ph), 3.36 (3H, s, NCH_3), 1.49 (9H, s, NC(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): 170.32 (*C*=O)$_{amide}$, 152.40 (*C*=O)$_{urea\ hydantoin}$, 151.82 (*C*=O)$_{urea}$, 147.40 (C_{Ar}), 135.89 (C_{Ar}), 132.89 (2xC_{Ar}H), 132.39 (C_{Ar}), 129.82 (2xC_{Ar}H), 129.65 (2xC_{Ar}H), 126.52 (2xC_{Ar}H), 118.32 (*C*N), 110.36 (C_{Ar}), 61.67 (*C*HPh), 59.47 (N*C*(CH$_3$)$_3$), 39.00 (N*C*H$_3$), 28.46 (NC(*C*H $_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 2981, 2941 (alkyl C-H), 2229 (CN), 1786, 1721, 1689 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{22}H_{21}ClN_4O_3Na$ $[M+Na]^+$ 447.119439, found 447.120202.

Methyl (*tert*-butyl carbamoyl)glycinate (278e)



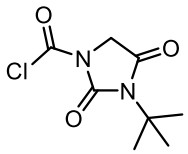
Following general **procedure 2**: glycine methyl ester hydrochloride (3.00 g, 23.9 mmol) in anhydrous DCM (44.0 mL), Et_3N (6.70 mL, 47.8 mmol) and *tert*-butyl isocyanate (3.00 mL, 26.3 mmol). The title compound (3.92 g, 87%) was yielded as an orange oil and used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.20 (1H, t, *J* =5.6, N*H*CH_2), 4.88 (1H, s, (CH$_3$)$_3$CN*H*), 3.94 (2H, d, *J* =5.5, NHCH_2), 3.71 (3H, s, OCH_3), 1.30 (9H, s, (CH_3)$_3$CNH); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.25 (*C*=O)$_{ester}$, 157.39 (*C*=O)$_{urea}$, 52.23 (O*C*H$_3$), 50.48 ((CH$_3$)$_3$*C*NH), 41.90 (NH*C*H$_2$), 29.55 ((*C*H$_3$)$_3$CNH); **IR (vmax/cm^{-1}) (neat)**: 3345 (N-H), 2964, 2931 (alkyl C-H), 1747 (ester C=O), 1641 (urea C=O); **HRMS** (ESI): *m/z* calcd for $C_8H_{16}N_2O_3Na$ $[M+Na]^+$ 211.1053, found 211.1040.

3-(*tert*-Butyl)imidazolidine-2,4-dione (279e)



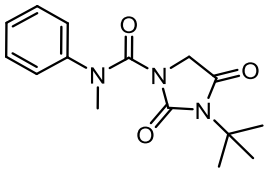
Following general **procedure 3**: KO*t*Bu (2.51 g, 22.4 mmol) and urea **278e** (3.83 g, 20.3 mmol) in anhydrous THF (54.0 mL). The title compound (1.80 g, 57%) was yielded as a white solid and used without further purification. **mp**: 89 – 91 °C; **1HNMR** (400 MHz, $CDCl_3$): δ 6.14 (1H, s, N*H*), 3.82 (2H, s, CH_2), 1.60 (9H, s, NC(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 72.43 (*C*=O)$_{amide}$, 159.70 (*C*=O)$_{urea}$, 57.96 (N*C*(CH$_3$)$_3$), 46.18 (*C*H$_2$), 28.70 (NC(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 3290 (NH), 2972, 2934 (alkyl C-H), 1768, 1696 (C=O); **MS** (ESI): *m/z* calcd for $C_7H_{13}N_2O_2$ $[M+H]^+$, found 157.0984.

3-(*tert*-Butyl)-2,4-dioxoimidazolidine-1-carbonyl chloride (280e)



Following general **procedure 4**: triphosgene (1.69 g, 5.70 mmol) in anhydrous DCM (25.0 mL), anhydrous pyridine (1.40 mL, 17.1 mmol) and hydantoin **279e** (1.78 g, 11.4 mmol). The title compound (2.32 g, 93%) was yielded as a yellow solid and used without further purification. **mp**: 126 – 128 °C (decomposed); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.29 (2H, s, CH_2), 1.62 (9H, s, NC(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.54 (*C*=O), 150.94 (*C*=O), 143.11 (*C*=O), 60.51 (N*C*(CH$_3$)$_3$), 50.23 (*C*H$_2$), 28.45 (NC(*C*H$_3$)$_3$).

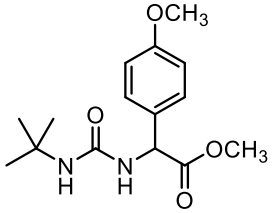
3-(*tert*-Butyl)-*N*-methyl-2,4-dioxo-*N*-phenylimidazolidine-1-carboxamide (273m)



Following general **procedure 5**: carbamoyl chloride **280e** (200 mg, 0.91 mmol) in anhydrous DCM (4.00 mL), Et_3N (0.15 mL, 1.10 mmol) and *N*-methyl aniline (0.10 mL, 0.91 mmol). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 80:20) to afford the title compound (212 mg, 80%) as a white solid. **R*f*** (8:2 Pet.Ether:EtOAc) 0.16; **mp**: 123 – 125 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36 (2H, t, *J* = 7.8, Ar-*H*), 7.25 – 7.15 (3H, m, Ar-*H*), 4.08 (2H, s, CH_2), 3.41 (3H, s, NCH_3), 1.41 (9H, s, NC(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): 169.42 (*C*=O)$_{amide}$, 152.88 (*C*=O)$_{urea\ hydantoin}$, 152.51 (C_{Ar}), 143.75 (*C*=O)$_{urea}$, 129.24 (2xC_{Ar}H), 126.91 (C_{Ar}H), 125.63 (2xC_{Ar}H), 48.66 (*C*H$_2$), 58.76 (N*C*(CH$_3$)$_3$),

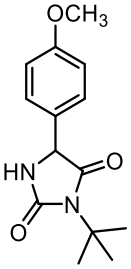
39.33 (N*C*H$_3$), 28.37 (NC(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 2975, 2941 (alkyl C-H), 1788, 1721, 1662 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{15}H_{19}N_3O_3Na$ $[M+Na]^+$ 312.1319, found 312.1314.

Methyl 2-(3-(*tert*-butyl)ureido)-2-(4-methoxyphenyl)acetate (278d)



Following general **procedure 2**: methyl 2-amino-2-(4-methoxyphenyl)acetate hydrochloride **277d** (700 mg, 3.02 mmol) in anhydrous DCM (5.50 mL), Et$_3$N (0.84 mL, 6.04 mmol) and *tert*-butyl isocyanate (0.38 mL, 3.32 mmol). The title compound (857 mg, 96%) was yielded as an off-white solid and used without further purification. **mp**: 134 – 136 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27 (2H, d, *J* =8.7, Ar-*H*), 6.86 (2H, d, *J* =8.7, Ar-*H*), 5.38 (1H, d, *J* =7.1, C*H*Ph), 5.20 (1H, d, *J* =7.1, N*H*CH), 4.41 (1H, s, (CH$_3$)$_3$CN*H*), 3.79 (3H, s, *p*-OC*H*$_3$), 3.70 (3H, s, OC*H*$_3$), 1.30 (9H, s, (C*H*$_3$)$_3$CNH); **^{13}C NMR** (101 MHz, $CDCl_3$): 173.03 (*C*=O)$_{ester}$, 159.67 (*C*=O)$_{urea}$, 156.23 (*C*$_{Ar}$), 129.68 (*C*$_{Ar}$), 128.58 (2x*C*$_{Ar}$H), 114.41 (2x*C*$_{Ar}$H), 56.52 (*C*HPh), 55.43 (*p*-OC*H*$_3$), 52.75 (OC*H*$_3$), 50.73 ((CH$_3$)$_3$*C*), 29.54 ((*C*H$_3$)$_3$C); **IR (vmax/cm^{-1}) (neat)**: 3355 (NH), 2963, 2911 (alkyl C-H), 1744 (ester C=O), 1635 (urea C=O); **HRMS** (ESI): *m/z* calcd for $C_{15}H_{22}N_2O_4Na$ $[M+Na]^+$ 317.147178, found 317.146472.

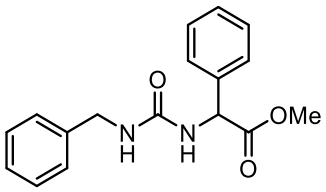
3-(*tert*-Butyl)-5-(4-methoxyphenyl)imidazolidine-2,4-dione (279d)



Following a similar procedure to general **procedure 3**: NaH (6.79 mg, 0.17 mmol, 1.00 eq.) was added to a solution of urea **278d** (50.0 mg, 0.17 mmol, 1.00 eq.) in anhydrous THF (0.60 mL) at 0 °C and the mixture was stirred for 1 hour at 0 °C. The reaction was quenched with water and the solvent removed under reduced pressure. The residue was dissolved in EtOAc and washed with brine. Afterwards, it was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; DCM:MeOH 100:0 to DCM:MeOH 99:1) to afford the title compound (37.5 mg, 84%) as a white solid. **R*f*** (9.9:0.1 DCM:MeOH) 0.24; **mp**: 103 – 105 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (2H, d, *J* =8.8, Ar-*H*), 6.92 (2H, d, *J* =8.8, Ar-*H*), 5.49 (1H, br. s, N*H*), 4.81 (1H, d, *J* =1.4, C*H*Ph), 3.81 (3H, s,

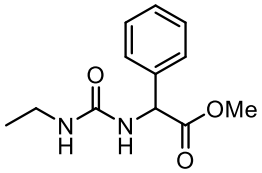
OC*H*$_3$), 1.61 (9H, s, NC(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): 173.41 (*C*=O)$_{amide}$, 160.16 (*C*=O)$_{urea}$, 158.57 (*C*$_{Ar}$), 127.72 (2x*C*$_{Ar}$H), 127.28 (*C*$_{Ar}$), 114.57 (2x*C*$_{Ar}$H), 59.58 (*C*HPh), 58.03 (NC(CH$_3$)$_3$), 55.44 (OCH$_3$), 28.66 (NC(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 3216 (NH), 2963, 2927 (alkyl C-H), 1771, 1704 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{14}H_{19}N_2O_3$ [M+H]$^+$ 263.1390, found 263.1390.

Methyl 2-(3-benzylureido)-2-phenylacetate (338)



Following general **procedure 2**: [*R*]-[-]-2-phenylglycine methyl ester hydrochloride (1.50 g, 7.44 mmol) in anhydrous DCM (14.0 mL), Et_3N (2.10 mL, 14.9 mmol) and benzyl isocyanate (1.00 mL, 8.18 mmol). The title compound (1.87 g, 84%) was yielded as a white solid and used without further purification. **R*f*** (7:3 Pet.Ether:EtOAc) 0.14; **mp**: 132 – 135 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28 – 7.15 (10H, m, Ar-*H*), 5.73 (1H, d, *J* =7.4, N*H*CH), 5.45 (1H, d, *J* =7.3, C*H*Ph), 5.13 (1H, t, *J* =5.6, (CH$_2$N*H*), 4.26 (2H, d, *J* =5.6, C*H*$_2$NH), 3.59 (3H, s, OC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.69 (*C*=O)$_{ester}$, 157.19 (*C*=O)$_{urea}$, 139.10 (*C*$_{Ar}$), 137.41 (*C*$_{Ar}$), 129.02 (2x*C*$_{Ar}$H), 128.72 (2x*C*$_{Ar}$H), 128.46 (*C*$_{Ar}$H), 127.64 (2x*C*$_{Ar}$H), 127.42 (*C*$_{Ar}$H), 127.31 (2x*C*$_{Ar}$H), 57.39 (*C*HPh), 52.79 (OCH$_3$), 44.62 (*C*H$_2$NH); **IR (vmax/cm^{-1}) (neat)**: 3163 (NH), 2954, 2923 (alkyl C-H), 1741 (ester C=O), 1630 (urea C=O); **HRMS** (ESI): *m/z* calcd for $C_{17}H_{18}N_2O_3Na$ [M+Na]$^+$ 321.1210, found 321.1206.

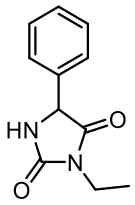
Methyl 2-(3-ethylureido)-2-phenylacetate (344)



Following general **procedure 2**: [*R*]-[-]-2-phenylglycine methyl ester hydrochloride (3.08 g, 15.3 mmol) in anhydrous DCM (28.0 mL), Et_3N (4.30 mL, 30.5 mmol) and ethyl isocyanate (1.3 mL, 16.8 mmol). The title compound (2.85 g, 79%) was yielded as a white solid and used without further purification. **mp**: 106 – 108 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 – 7.27 (5H, m, Ar-*H*), 5.66 (1H, d, *J* =7.4, N*H*CH), 5.50 (1H, d, *J* =7.3, C*H*Ph), 4.79 (1H, t, *J* =5.7, CH$_2$N*H*), 3.17 (2H, qd, *J* =7.2, 5.4, CH$_3$C*H*$_2$NH), 3.70 (3H, s, OC*H*$_3$), 1.08 (3H, t, *J* =7.2, C*H*$_3$CH$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.78 (*C*=O)$_{ester}$, 157.20 (*C*=O)$_{urea}$, 137.51 (*C*$_{Ar}$), 129.02 (2x*C*$_{Ar}$H), 128.45 (*C*$_{Ar}$H), 127.34 (2x*C*$_{Ar}$H), 57.27 (*C*HPh), 52.80 (OCH$_3$), 35.44 (*C*H$_2$NH), 15.43 (*C*H$_3$CH$_2$); **IR (vmax/cm^{-}**

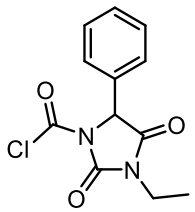
[1]) (neat): 3360 (N-H), 2977 (alkyl C-H), 1738 (ester C=O), 1646 (urea C=O); **HRMS** (ESI): *m/z* calcd for $C_{12}H_{16}N_2O_3Na$ $[M+Na]^+$ 259.1053, found 259.1048.

3-Ethyl-5-phenylimidazolidine-2,4-dione (346)



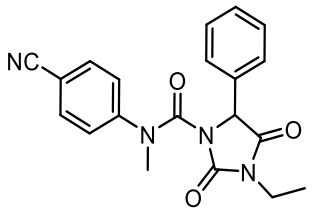
Following general **procedure 3**: KO*t*Bu (1.44 g, 12.9 mmol) and urea **344** (2.76 g, 11.7 mmol) in anhydrous THF (31.0 mL). The crude product was purified by flash column chromatography (SiO_2; DCM:MeOH 100:0 to DCM:MeOH 98:2) to afford the title compound (859 mg, 36%) as a white solid. **R*f*** (9.8:0.2 DCM:MeOH) 0.27; **mp**: 90 – 92 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44 – 7.32 (5H, m, Ar-*H*), 6.43 (1H, s, N*H*), 5.02 (1H, s, C*H*Ph), 3.57 (2H, q, *J* =7.1, C*H*$_2$CH$_3$), 1.21 (3H, t, *J* =7.2 CH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): 172.03 (*C*=O)$_{amide}$, 157.80 (*C*=O)$_{urea}$, 134.47 (C_{Ar}), 129.26 (2xC_{Ar}H), 129.18 (C_{Ar}H), 126.57 (2xC_{Ar}H), 60.82 (*C*HPh), 34.01 (*C*H$_2$), 13.51 (*C*H$_3$); **IR (vmax/cm^{-1}) (neat)**: 3291 (NH), 2980, 2939 (alkyl C-H), 1772, 1701 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{11}H_{13}N_2O_2$ $[M+H]^+$ 205.0972, found 205.0967.

3-Ethyl-2,4-dioxo-5-phenylimidazolidine-1-carbonyl chloride (348)



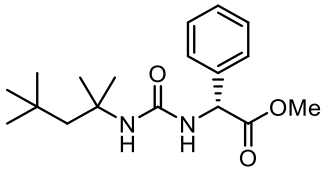
Following general **procedure 4**: triphosgene (624 mg, 2.10 mmol) in anhydrous DCM (9.00 mL), anhydrous pyridine (0.50 mL, 6.31 mmol) and hydantoin **346** (859 mg, 4.21 mmol). The title compound (1.46 g, >99%) was yielded as a cream solid and used without further purification. **mp**: 101 – 103 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47 – 7.40 (3H, m, Ar-*H*), 7.31 (2H, dd, *J* =7.4, 2.2, Ar-*H*), 5.48 (1H, s, C*H*Ph), 3.68 (2H, q, *J* =7.1, C*H*$_2$CH$_3$), 1.27 (3H, t, *J* =7.2, CH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.45 (*C*=O), 150.97 (*C*=O), 143.58 (*C*=O), 132.23 (C_{Ar}), 129.89 (C_{Ar}H), 129.62 (2xC_{Ar}H), 126.46 (2xC_{Ar}H), 64.98 (*C*HPh), 35.22 (*C*H$_2$), 13.07 (*C*H$_3$).

***N*-(4-Cyanophenyl)-3-ethyl-*N*-methyl-2,4-dioxo-5-phenylimidazolidine-1-carboxamide (350)**



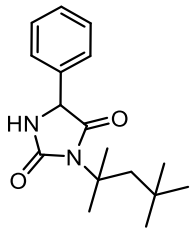
Following general **procedure 5**: carbamoyl chloride **348** (200 mg, 0.75 mmol) in anhydrous DCM (3.00 mL), Et_3N (0.13 mL, 0.90 mmol) and 4-(methyl amino) benzonitrile (99.0 mg, 0.75 mmol). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 70:30) to afford the title compound (271 mg, >99%) as a pale yellow solid. **R*f*** (7:3 Pet.Ether:EtOAc) 0.21; **mp**: 86 – 88 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.57 (2H, d, *J* =8.6, Ar-*H*), 7.49 – 7.44 (3H, dd, m, Ar-*H*), 7.31 – 7.21 (3H, m, Ar-*H*), 7.02 (2H, d, *J* = 8.6, Ar-*H*), 5.69 (1H, s, C*H*Ph), 3.53 (2H, q, *J* =7.0, C*H*$_2$CH$_3$), 3.35 (3H, s, NC*H*$_3$), 1.15 (3H, t, *J* =7.2, CH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): 169.93 (*C*=O)$_{amide}$, 151.83 (*C*=O)$_{urea\ hydantoin}$, 151.58 (*C*=O)$_{urea}$, 147.51 (*C*$_{Ar}$), 133.08 (*C*$_{Ar}$), 132.94 (2x*C*$_{Ar}$H), 129.99 (*C*$_{Ar}$H), 129.42 (2x*C*$_{Ar}$H), 128.70 (2x*C*$_{Ar}$H), 126.50 (2x*C*$_{Ar}$H), 118.32 (*C*N), 110.32 (*C*$_{Ar}$), 63.21 (*C*HPh), 39.09 (N*C*H$_3$), 34.66 (*C*H$_2$), 13.32 (*C*H$_3$); **IR (vmax/cm^{-1}) (neat)**: 2978, 2938 (alkyl C-H), 2228 (CN), 1785, 1718, 1683 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{20}H_{18}N_4O_3Na$ $[M+Na]^+$ 385.1271, found 385.1268.

Methyl (*R*)-2-phenyl-2-(3-(2,4,4-trimethylpentan-2-yl)ureido)acetate (345)



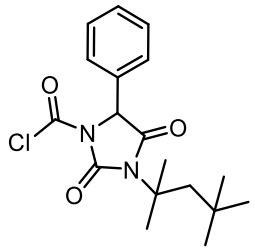
Following general **procedure 2**: [*R*]-[-]-2-phenylglycine methyl ester hydrochloride (3.00 g, 14.9 mmol) in anhydrous DCM (27.0 mL), Et_3N (4.10 mL, 29.8 mmol) and 1,1,3,3-tetramethylbutyl isocyanate (3.00 mL, 16.4 mmol). The title compound (6.37 g, >99%) was yielded as a viscous colourless oil and used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36 – 7.27 (5H, m, Ar-*H*), 5.46 (2H, s, N*H*CH + C*H*Ph overlap), 4.57 (1H, s, (CH$_3$)$_2$CN*H*), 3.69 (3H, s, OC*H*$_3$), 1.69 (2H, d, *J* =7.8, C*H*$_A$H$_B$ + CH$_A$*H*$_B$ overlap), 1.33 (3H, s, (C*H*$_3$)$_A$(CH$_3$)$_B$), 1.33 (3H, s, (CH$_3$)$_A$(C*H*$_3$)$_B$), 0.95 (9H, s, (C*H*$_3$)$_3$C); **^{13}C NMR** (101 MHz, $CDCl_3$): 172.91 (*C*=O)$_{ester}$, 156.08 (*C*=O)$_{urea}$, 137.68 (*C*$_{Ar}$), 128.94 (2x*C*$_{Ar}$H), 128.33 (*C*$_{Ar}$H), 127.34 (2x*C*$_{Ar}$H), 57.08 (*C*HPh), 54.50 ((CH$_3$)$_A$(CH$_3$)$_B$*C*), 52.75 (O*C*H$_3$), 51.75 (*C*H$_2$), 31.66 ((CH$_3$)$_3$*C*), 31.57 ((*C*H$_3$)$_3$C), 30.17 ((*C*H$_3$)$_A$(CH$_3$)$_B$), 30.13 ((CH$_3$)$_A$(*C*H$_3$)$_B$); **IR (vmax/cm^{-1}) (neat)**: 3355 (NH), 2952, 2908 (alkyl C-H), 1744 (ester C=O), 1634 (urea C=O); **HRMS** (ESI): *m/z* calcd for $C_{18}H_{29}N_2O_3$ $[M+H]^+$ 321.2173, found 321.2168.

5-Phenyl-3-(2,4,4-trimethylpentan-2-yl)imidazolidine-2,4-dione (347)



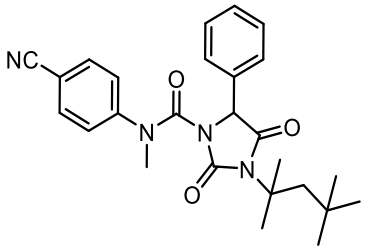
Following a similar procedure to general **procedure 3**: KO*t*Bu (2.20 g, 19.7 mmol) and urea **345** (5.73 g, 17.9 mmol) in anhydrous THF (57.0 mL) at 0 °C. *The reaction was quenched with water*. The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 80:20) to afford the title compound (3.50 g, 68%) as a yellow gum. **R*f*** (8:2 Pet.Ether:EtOAc) 0.39; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 – 7.33 (5H, m, Ar-*H*), 6.44 (1H, s, N*H*), 4.87 (1H, s, C*H*Ph), 1.92 (2H, d, *J* =8.0, CH_AH_B + CH_AH_B overlap), 1.66 (3H, s, $(CH_3)_A(CH_3)_B$), 1.63 (3H, s, $(CH_3)_A(CH_3)_B$), 0.94 (9H, s, $(CH_3)_3C$); **^{13}C NMR** (101 MHz, $CDCl_3$): 173.32 (C=O)$_{amide}$, 159.13 (C=O)$_{urea}$, 134.96 (C_{Ar}), 129.05 (2xC_{Ar}H), 128.90 (C_{Ar}H), 126.54 (2xC_{Ar}H), 61.81 ($(CH_3)_A(CH_3)_BC$), 59.99 (*C*HPh), 50.34 (CH_2), 31.71 ($(CH_3)_3C$), 31.19 ($(CH_3)_3C$), 29.75 ($(CH_3)_A(CH_3)_B$), 29.68 ($(CH_3)_A(CH_3)_B$); **IR (vmax/cm^{-1}) (neat)**: 3298 (NH), 2955, 2904 (alkyl C-H), 1771 (C=O), 1698 (C=O).

2,4-Dioxo-5-phenyl-3-(2,4,4-trimethylpentan-2-yl)imidazolidine-1-carbonyl chloride (349)



Following general **procedure 4**: triphosgene (1.38 g, 4.65 mmol) in anhydrous DCM (20.0 mL), anhydrous pyridine (1.10 mL, 13.9 mmol) and hydantoin **347** (2.68 g, 9.30 mmol). The title compound (3.02 g, 92%) was yielded as a yellow oil and used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 – 7.39 (3H, m, Ar-*H*), 7.32 – 7.28 (2H, m, Ar-*H*), 5.31 (1H, s, C*H*Ph), 1.96 (2H, s, CH_2), 1.72 (3H, s, $(CH_3)_A(CH_3)_B$), 1.67 (3H, s, $(CH_3)_A(CH_3)_B$), 0.96 (9H, s, $(CH_3)_3C$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.63 (C=O), 151.50 (C=O), 143.52 (C=O), 132.75 (C_{Ar}), 129.64 (C_{Ar}H), 129.50 (2xC_{Ar}H), 126.20 (2xC_{Ar}H), 64.48 ($(CH_3)_A(CH_3)_BC$), 64.13 (*C*HPh), 50.18 (CH_2), 31.78 ($(CH_3)_3C$), 31.18 ($(CH_3)_3C$), 29.58 ($(CH_3)_A(CH_3)_B$), 29.38 ($(CH_3)_A(CH_3)_B$).

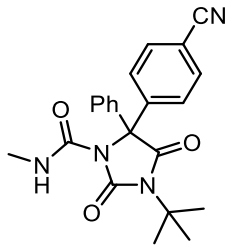
***N*-(4-Cyanophenyl)-*N*-methyl-2,4-dioxo-5-phenyl-3-(2,4,4-trimethylpentan-2-yl) imidazolidine-1-carboxamide (351)**



Following general **procedure 5**: carbamoyl chloride **349** (300 mg, 0.86 mmol) in anhydrous DCM (3.40 mL), Et_3N (0.14 mL, 1.03 mmol) and 4-(methyl amino) benzonitrile (113 mg, 0.86 mmol). The crude product was purified by flash column chromatography (SiO_2; DCM:Acetone 100:0 to DCM:Acetone 99:1) to afford the title compound (280 mg, 73%) as a colourless oil. **R*f*** (9.9:0.1 DCM:Acetone) 0.33; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.58 (2H, d, *J* =8.6, Ar-*H*), 7.47 – 7.43 (3H, m, Ar-*H*), 7.27 – 7.23 (2H, m, Ar-*H*), 7.07 (2H, d, *J* = 8.6, Ar-*H*), 5.49 (1H, s, C*H*Ph), 3.35 (3H, s, NCH_3), 1.97 (1H, d, *J* =15.2, CH_AH$_B$), 1.66 (1H, d, *J* =15.2, CH$_A$$H_B$), 1.57 (3H, s, (C$H_3$)$_A$(CH$_3$)$_B$), 1.56 (3H, s, (CH$_3$)$_A$(C$H_3$)$_B$), 0.85 (9H, s, (C$H_3$)$_3$C); **^{13}C NMR** (101 MHz, $CDCl_3$): 171.28 (*C*=O)$_{amide}$, 152.95 (*C*=O)$_{urea\ hydantoin}$, 151.99 (*C*=O)$_{urea}$, 147.43 (*C*$_{Ar}$), 133.66 (*C*$_{Ar}$), 132.82 (2x*C*$_{Ar}$H), 129.74 (*C*$_{Ar}$H), 129.29 (2x*C*$_{Ar}$H), 128.85 (2x*C*$_{Ar}$H), 127.06 (2x*C*$_{Ar}$H), 118.28 (*C*N), 110.43 (*C*$_{Ar}$), 63.08 ((CH$_3$)$_A$(CH$_3$)$_B$*C*), 62.56 (*C*HPh), 49.96 (*C*H$_2$), 38.90 (N*C*H$_3$), 31.56 ((CH$_3$)$_3$*C*), 31.12 ((*C*H$_3$)$_3$C), 29.92 ((*C*H$_3$)$_A$(CH$_3$)$_B$), 29.27 ((CH$_3$)$_A$(*C*H$_3$)$_B$); **IR (vmax/cm^{-1}) (neat)**: 2953, 2908 (alkyl C-H), 2229 (CN), 1785, 1718, 1690 (C=O).

4.3.1.4 Aryl Migration of Hydantoin Ureas

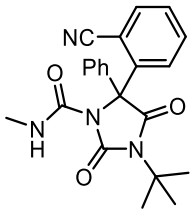
3-(*tert*-Butyl)-5-(4-isocyanophenyl)-*N*-methyl-2,4-dioxo-5-phenylimidazolidine-1-carboxamide (274a)



Following general **procedure 6**: hydantoin urea **273a** (50.0 mg, 0.128 mmol) was stirred in $CHCl_3$ (1.00 mL) at −20 °C. PTC **322** (14.0 mg, 0.026 mmol, 0.20 eq.) and Cs_2CO_3 (211 mg, 0.65 mmol) were added and the reaction stirred for 40 h. The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 60:40) to afford the title compound (33.4 mg, 67%) as a white solid. **R*f*** (6:4 Pet.Ether:Diethyl ether) 0.25; **mp**: 95 – 98 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.14 (1H, d, *J* = 5.0, N*H*), 7.66 (2H, d, *J* =8.5, Ar-*H*), 7.49 (2H,

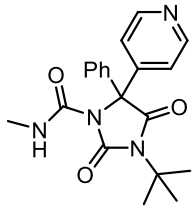
d, *J* =8.5, Ar-*H*), 7.42 – 7.35(5H, m, Ar-*H*), 2.79 (3H, d, *J* =4.7, NHC*H*$_3$), 1.65 (9H, s, NC(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.4 (*C*=O)$_{amide}$, 156.4 (*C*=O)$_{urea\ hydantoin}$, 151.0 (*C*=O)$_{urea}$, 142.2 (*C*$_{Ar}$), 136.0 (*C*$_{Ar}$), 131.9 (2x*C*$_{Ar}$H), 129.5 (2x*C*$_{Ar}$H), 129.1 (*C*$_{Ar}$H), 128.5 (2x*C*$_{Ar}$H), 128.4 (2x*C*$_{Ar}$H), 118.5 (*C*N), 112.5 (*C*$_{Ar}$), 72.4 (N*C*Ph), 60.4 (N*C*(CH$_3$)$_3$), 28.7 (NC(*C*H$_3$)$_3$), 26.7 (NH*C*H$_3$); **HPLC**: *er* = ~85:15, (*R*,*R*) whelk-01, Hexane:EtOAc = 90:10, flow = 1 mL/min, λ = 254 nm, t_R = 31.3 min (major), 35.9 min (minor); **IR (vmax/cm^{-1}) (neat)**: 3362 (NH), 2922 (alkyl C-H), 2229 (C≡N), 1778, 1727, 1701 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{22}H_{22}N_4O_3Na$ $[M+Na]^+$ 413.1585, found 413.1584. Data in agreement with reported values.[181]

3-(*tert*-Butyl)-5-(2-cyanophenyl)-*N*-methyl-2,4-dioxo-5-phenylimidazolidine-1-carboxamide (274c)



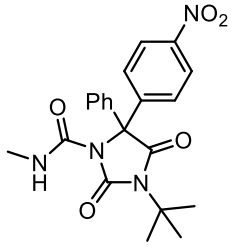
Following general **procedure 6**: hydantoin urea **273c** (46.0 mg, 0.12 mmol) was stirred in $CHCl_3$ (1.00 mL) at −20 °C. PTC **322** (13.0 mg, 0.02 mmol, 0.20 eq.) and Cs_2CO_3 (192 mg, 0.59 mmol) were added and the reaction stirred for 100 hours (monitored by TLC). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 80:20) to afford the title compound (18 mg, 39%) as a white solid. **R*f*** (8:2 Pet.Ether:EtOAc) 0.26; **mp**: 144 – 147 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.25 (1H, br. q, *J* = 4.4, N*H*), 7.70 (1H, dd, *J* =7.5, 1.6, Ar-*H*), 7.58 – 7.48 (2H, m, Ar-*H*), 7.48 (1H, dd, *J* =7.9, 1.5, Ar-*H*), 7.46 – 7.39 (4H, m, Ar-*H*), 7.32 (1H, d, *J* =8.0, Ar-*H*), 2.83 (3H, d, *J* =4.7, NHC*H*$_3$), 1.60 (9H, s, NC(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.77 (*C*=O)$_{amide,}$, 156.42 (*C*=O)$_{urea\ hydantoin,}$, 151.73 (*C*=O)$_{urea}$, 141.78 (*C*$_{Ar}$), 134.63 (*C*$_{Ar}$), 134.59 (*C*$_{Ar}$H), 132.72 (*C*$_{Ar}$H), 132.24 (*C*$_{Ar}$H), 129.23 (*C*$_{Ar}$H), 128.85 (*C*$_{Ar}$H), 128.74 (2x*C*$_{Ar}$H), 127.87 (2x*C*$_{Ar}$H), 117.71 (*C*N), 110.65 (*C*$_{Ar}$), 71.72 (N*C*Ph), 60.31 (N*C*(CH$_3$)$_3$), 28.39 (NC(*C*H$_3$)$_3$), 26.78 (NH*C*H$_3$); **HPLC**: *er* = ~52:48, Chiralpak® IA, Hexane:IPA = 99:1, flow = 1 mL/min, λ = 254 nm, t_R = 15.1 min (major), 17.2 min (minor); **IR (vmax/cm^{-1}) (neat)**: 3358 (NH), 2979, 2904 (alkyl C-H), 2253 (C≡N), 1779, 1725, 1698 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{22}H_{23}N_4O_3$ $[M+H]^+$ 391.1765, found 391.1756.

3-(*tert*-Butyl)-*N*-methyl-2,4-dioxo-5-phenyl-5-(pyridin-4-yl)imidazolidine-1-carboxamide (274d)



Following general **procedure 6**: hydantoin urea **273d** (25.0 mg, 0.07 mmol) was stirred in $CHCl_3$ (0.50 mL) at −20 °C. PTC **322** (7.50 mg, 0.01 mmol, 0.20 eq.) and KOH (11.5 mg, 0.20 mmol) were added and the reaction mixture stirred for 25 h. The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 30:70) to afford the title compound (^{1}H NMR yield: 51%) as a yellow oil. **R*f*** (3:7 Pet.Ether:EtOAc) 0.19; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.63 (2H, d, *J* = 6.3, Ar-*H*), 8.18 – 8.09 (1H, br. m, N*H*), 7.40 – 7.36 (3H, m, Ar-*H*), 7.36 – 7.27 (4H, m, Ar-*H*), 2.80 (3H, d, *J* =4.7, NHCH_3), 1.65 (9H, s, NC(CH_3)$_3$); **Chiral SFC**: *er* = ~30:70, Chiralpak® IB, 10% co-solvent (IPA), flow = 4.0 mL/min, 125 bar, 40 °C, t_R = 2.8 min (major), 3.1 min (minor); **HRMS** (ESI): *m/z* calcd for $C_{20}H_{23}N_4O_3$ $[M+H]^+$ 367.176467, found 367.176847.

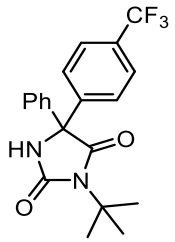
3-(*tert*-Butyl)-*N*-methyl-5-(4-nitrophenyl)-2,4-dioxo-5-phenylimidazolidine-1-carboxamide (274e)



Following general **procedure 6**: hydantoin urea **273e** (87.0 mg, 0.21 mmol) was stirred in a PhMe/$CHCl_3$ system (1.:0.7, 2.00 mL) at 0 °C. PTC **276** (12.8 mg, 0.021 mmol, 0.10 eq.) and Cs_2CO_3 (349 mg, 1.07 mmol) were added and the reaction stirred for 17 h. The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 80:20) to afford the title compound (42 mg, 48%) as a colourless oil. **R*f*** (8:2 Pet.Ether:EtOAc) 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.22 (2H, d, *J* =9.0, Ar-*H*), 7.55 (2H, d, *J* =8.9, Ar-*H*), 7.39 (3H, m, Ar-*H*), 7.35 (2H, m, Ar-*H*), 2.80 (3H, d, *J* =4.7, NHCH_3), 1.66 (9H, s, NC(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): 172.3 (*C*=O)$_{amide}$, 156.3 (*C*=O)$_{urea\ hydantoin,}$, 150.9 (*C*=O)$_{urea}$, 147.8 (C_{Ar}), 144.1 (C_{Ar}), 136.0 (C_{Ar}), 129.8 (2xC_{Ar}H), 129.2 (C_{Ar}H), 128.6 (2xC_{Ar}H), 128.4 (2xC_{Ar}H), 123.3 (2xC_{Ar}H), 72.3 (N*C*Ph), 60.4 (NC(*C*H$_3$)$_3$), (28.7 (NC(*C*H$_3$)$_3$), 26.7 (NH*C*H$_3$); **HPLC**: *er* = ~55:45, (*R*,*R*) whelk-01 Hexane:EtOAc = 90:10, flow = 1 mL/min, λ = 254 nm, t_R = 24 min (major), 27 min (minor); **IR**

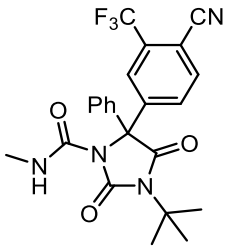
(vmax/cm^{-1}) (neat): 3361 (NH), 2941 (alkyl C-H), 1778, 1722, 1699 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{21}H_{22}N_4O_5Na$ $[M+Na]^+$ 433.1482, found 433.1481.

3-(*tert*-butyl)-*N*-methyl-2,4-dioxo-5-phenyl-5-(4-(trifluoromethyl)phenyl)imidazolidine-1-carboxamide (275h)



Following general **procedure 6**: hydantoin urea **273h** (100 mg, 0.23 mmol), was stirred in PhMe (2.00 mL) at room temperature. PTC **276** (14 mg, 0.023 mmol, 0.1 eq.) and CsOH (196 mg, 1.17 mmol) were added and the reaction stirred for 24 h. The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 90:10) to afford the title compound (34.2 mg, 39%) as a pale oil. **R*f*** (9:1 Pet.Ether:EtOAc) 0.27; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (2H, dt, *J* = 8.3, 0.7, Ar-*H*), 7.53 (2H, dt, *J* = 8.2, 0.7, Ar-*H*), 7.40 – 7.34 (3H, m, Ar-*H*), 7.30 – 7.27 (2H, m, Ar-*H*), 6.60 (1H, br. s, N*H*), 1.63 (9H, s, NC(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): 173.6 (*C*=O)$_{amide}$, 157.4 (*C*=O)$_{urea}$, 143.6 (C_{Ar}), 139.6 (C_{Ar}), 130.8 (q, $^2J^{C-F}$ = 32.8, C_{Ar}), 129.2 (2xC_{Ar}H), 128.9 (C_{Ar}H), 127.6 (2xC_{Ar}H), 126.9 (2xC_{Ar}H), 125.8 (q, $^3J^{C-F}$ = 3.8, 2xC_{Ar}H), 124.0(q, $^1J^{C-F}$ = 272.6, *C*F$_3$), 68.6 (NH*C*Ph), 58.8 (N*C*(CH$_3$)$_3$), 28.7 (NC(*C*H$_3$)$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −62.73 (3F, s); **IR (vmax/cm^{-1}) (neat)**: 3246 (NH), 2925 (alkyl C-H), 1771, 1707 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{20}H_{19}F_3N_2O_2Na$ $[M+Na]^+$ 399.1291, found 399.1292.

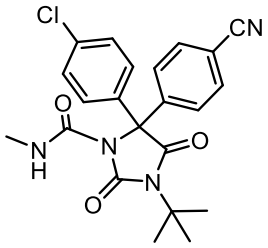
3-(*tert*-Butyl)-5-(4-cyano-3-(trifluoromethyl)phenyl)-N-methyl-2,4-dioxo-5-phenyl imidazolidine-1-carboxamide (274i)



Following general **procedure 6**: hydantoin urea **273i** (25.0 mg, 0.055 mmol) was stirred in $CHCl_3$ (0.50 mL) at −20 °C. PTC **322** (6.00 mg, 0.01 mmol, 0.20 eq.) and Cs_2CO_3 (88.8 mg, 0.27 mmol) were added and the reaction mixture stirred for 22 hours (monitored by TLC). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 60:40) to afford the title compound (15.0 mg, 59%) as a white solid. **R*f*** (6:4 Pet.Ether:Diethyl ether) 0.24; **mp**: 156 – 158 °C **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.12 (1H, br. q, *J*

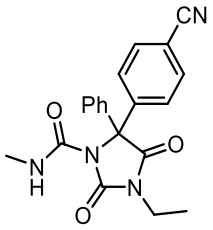
= 4.1, N*H*), 7.84 (1H, d, *J* =8.1, Ar-*H*), 7.76 – 7.68 (2H, m, Ar-*H*), 7.46 – 7.36 (3H, Ar-*H*), 7.30 – 7.27 (2H, m, Ar-*H*), 2.80 (3H, d, *J* =4.8, NHCH_3), 1.66 (9H, s, NC(CH_3)$_3$; **^{13}C NMR** (126 MHz, $CDCl_3$): 171.88 (*C*=O)$_{amide}$, 156.14 (*C*=O)$_{urea\ hydantoin}$, 150.87 (*C*=O)$_{urea}$, 143.13 (C_{Ar}), 135.44 (C_{Ar}), 134.43 (C_{Ar}H), 132.93 (C_{Ar}H), 132.70 (q, $^2J^{C\text{-}F}$ = 32.9, C_{Ar}), 129.41 (C_{Ar}H), 128.81 (2xC_{Ar}H), 128.12 (2xC_{Ar}H), 126.98 (q, $^3J^{C\text{-}F}$ = 4.7, C_{Ar}), 122.30 (q, $^1J^{C\text{-}F}$ = 274.1, *C*F$_3$), 115.27 (*C*N), 110.24 (q, $^3J^{C\text{-}F}$ = 1.9, C_{Ar}H), 72.09 (N*C*Ph), 60.71 (N*C*(CH$_3$)$_3$), 28.64 (NC(*C*H$_3$)$_3$), 26.74 (NH*C*H$_3$); **IR (vmax/cm^{-1}) (neat)**: 3365 (NH), 2988, 2905 (alkyl C-H), 2235 (C≡N), 1781, 1728, 1707 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{23}H_{22}N_4O_3F_3$ $[M+H]^+$ 459.1639, found 459.1630.

3-(*tert*-Butyl)-5-(4-chlorophenyl)-5-(4-cyanophenyl)-N-methyl-2,4-dioxoimidazolidine-1-carboxamide (274l)



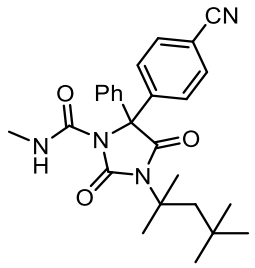
Following general **procedure 6**: hydantoin urea **273l** (50.0 mg, 0.118 mmol) was stirred in $CHCl_3$ (1.00 mL) at −20 °C. PTC **322** (12.9 mg, 0.024 mmol, 0.20 eq.) and Cs_2CO_3 (192 mg, 0.59 mmol) were added and the reaction mixture stirred for 48 hours (monitored by TLC). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 60:40) to afford the title compound (33.2 mg, 66%) as a colourless oil. **R*f*** (6:4 Pet.Ether:Diethyl ether) 0.27; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.12 (1H, br. q, *J* = 4.7, N*H*),7.66 (2H, d, *J* =8.8, Ar-*H*), 7.46 (2H, d, *J* =8.8, Ar-*H*), 7.36 (2H, d, *J* =8.8, Ar-*H*), 7.26 (2H, d, *J* =8.8, Ar-*H*), 2.80 (3H, d, *J* =4.7, NHCH_3), 1.64 (9H, s, NC(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.08 (*C*=O)$_{amide}$, 156.19 (*C*=O)$_{urea\ hydantoin}$, 150.91 (*C*=O)$_{urea}$, 141.81 (C_{Ar}), 135.26 (C_{Ar}), 134.65 (C_{Ar}), 132.09 (2xC_{Ar}H), 129.98 (2xC_{Ar}H), 129.35 (2xC_{Ar}H), 128.76 (2xC_{Ar}H), 118.42 (*C*N), 112.78 (C_{Ar}), 71.98 (N*C*Ph), 60.57 (N*C*(CH$_3$)$_3$), 28.66 (NC(*C*H$_3$)$_3$), 26.71 (NH*C*H$_3$); **HPLC**: *er* = ~77:23, Chiralcel® OD-H, Hexane:IPA = 95:5, flow = 1 mL/min, λ = 254 nm, t_R = 10.8 min (major), 12.4 min (minor).

5-(4-Cyanophenyl)-3-ethyl-*N*-methyl-2,4-dioxo-5-phenylimidazolidine-1-carboxamide (352)



Following general **procedure 6**: hydantoin urea **350** (50.0 mg, 0.138 mmol) was stirred in $CHCl_3$ (1.00 mL) at −20 °C. PTC **322** (15.2 mg, 0.03 mmol, 0.20 eq.) and Cs_2CO_3 (225 mg, 0.69 mmol) were added and the reaction mixture stirred for 48 hours (monitored by TLC). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 60:40) to afford the title compound (30.4 mg, 61%) as a yellow oil. **R*f*** (6:4 Pet.Ether:Diethyl ether) 0.16; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04 (1H, br. q, *J* = 4.7, N*H*),7.67 (2H, d, *J* =8.5, Ar-*H*), 7.50 (2H, d, *J* =8.5, Ar-*H*), 7.44 – 7.34 (3H, m, Ar-*H*), 7.35 – 7.29 (2H, m, Ar-*H*), 3.70 (2H, q, *J* =7.2, C*H*$_2$CH$_3$), 2.82 (3H, d, *J* =4.7, NHC*H*$_3$), 1.30 (3H, t, *J* =7.2, CH$_2$C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.46 (*C*=O)$_{amide}$, 155.57 (*C*=O)$_{urea\ hydantoin,}$, 150.74 (*C*=O)$_{urea}$, 141.51 (*C*$_{Ar}$), 135.39 (*C*$_{Ar}$), 132.04 (2x*C*$_{Ar}$H), 129.55 (2x*C*$_{Ar}$H), 129.29 (*C*$_{Ar}$H), 128.62 (2x*C*$_{Ar}$H), 128.46 (2x*C*$_{Ar}$H), 118.47 (*C*N), 112.75 (*C*$_{Ar}$), 73.73 (N*C*Ph), 35.09 (*C*H$_2$), 26.78 (NH*C*H$_3$), 13.31 (*C*H$_3$); **HPLC**: *er* = ~77:23, (*R*,*R*) whelk-01, Hexane:EtOAc = 85:15, flow = 1 mL/min, λ = 254 nm, t_R = 23.9 min (major), 26.0 min (minor); **IR (vmax/cm^{-1}) (neat)**: 3365 (NH), 2984, 2940 (alkyl C-H), 2229 (C≡N), 1783, 1723, 1699 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{20}H_{19}N_4O_3$ $[M+H]^+$ 363.1452, found 363.1459.

5-(4-Cyanophenyl)-N-methyl-2,4-dioxo-5-phenyl-3-(2,4,4-trimethylpentan-2-yl)imidazolidine-1-carboxamide (353)



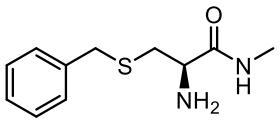
Following general **procedure 6**: hydantoin urea **351** (62.3 mg, 0.14 mmol) was stirred in $CHCl_3$ (1.00 mL) at −20 °C. PTC **322** (15.3 mg, 0.03 mmol, 0.20 eq.) and Cs_2CO_3 (227 mg, 0.70 mmol) were added and the reaction mixture stirred for 144 hours (monitored by TLC). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 70:30) to afford the title compound (^{1}H NMR yield: 36%) as a colourless oil. **R*f*** (7:3 Pet.Ether:EtOAc) 0.27; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.18 (1H, br. q, *J* = 4.7, N*H*), 7.65 (2H, d,

J =8.7, Ar-*H*), 7.48 (2H, d, *J* =8.7, Ar-*H*), 7.39 – 7.35 (3H, m, Ar-*H*), 7.35 – 7.30 (2H, m, Ar-*H*), 2.80 (3H, d, *J* =4.7, NHCH_3), 1.95 (2H, d, *J* =7.5, CH_AH$_B$ + CH$_A$$H_B$ overlap), 1.73 (6H, s, (CH_3)$_2$), 0.83 (9H, s, (CH_3)$_3$C); **HPLC**: *er* = ~72:28, (*R*,*R*) whelk-01 Hexane:EtOAc = 90:10, flow = 1 mL/min, λ = 254 nm, t_R = 21 min (major), 24 min (minor); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.57 (*C*=O)$_{amide}$, 156.74 (*C*=O)$_{urea\ hydantoin}$, 151.04 (*C*=O)$_{urea}$, 142.18 (C_{Ar}), 136.04 (C_{Ar}), 131.83 (2xC_{Ar}H), 129.64 (2xC_{Ar}H), 129.05 (C_{Ar}H), 128.57 (2xC_{Ar}H), 128.42 (2xC_{Ar}H), 118.60 (*C*N), 112.46 (C_{Ar}), 72.42 (N*C*Ph), 64.38 ((CH$_3$)$_A$(CH$_3$)$_B$*C*), 50.29 (*C*H$_2$), 31.63 ((CH$_3$)$_3$*C*), 31.17 ((*C*H$_3$)$_3$C), 29.87 ((*C*H$_3$)$_A$(CH$_3$)$_B$), 29.70 ((CH$_3$)$_A$(*C*H$_3$)$_B$), 26.70 (NH*C*H$_3$); **IR (vmax/cm^{-1}) (neat)**: 3359 (NH), 2954, 2911 (alkyl C-H), 2228 (C≡N), 1778, 1717, 1607 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{26}H_{30}N_4O_3Na$ $[M+Na]^+$ 469.221012, found 469.223058.

4.3.2 Photoredox-Catalysed Alkylarylation of Dehydroalanine Derivatives for the Preparation of Enantiopure α-Quaternary Amino Acids

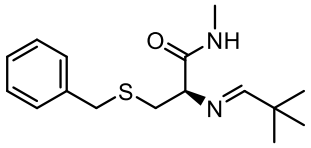
4.3.2.1 Synthesis of Vinyl Ureas

(*R*)-2-amino-3-(benzylthio)-*N*-methylpropanamide (411)



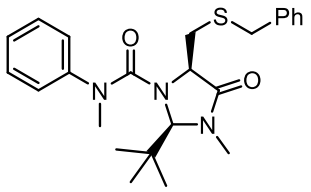
Following general **procedure 7**: $MeNH_2$ (33% *w/w* solution in EtOH, 16.1 mL, 129 mmol) and (*S*)-benzyl-L-cysteine methyl ester hydrochloride **410** (4.82 g, 18.4 mmol). The title compound (>99%) was yielded as a yellow oil and used without further purification. **R*f*** (9.5:0.5 DCM:MeOH) 0.22; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33 – 7.29 (4H, m, Ar-*H*), 7.26 – 7.21 (1H, m, Ar-*H*), 3.71 (2H, s, PhCH_2), 3.42 (1H, dd, *J* =8.6, 3.8, C*H*NH$_2$), 2.99 (1H, dd, *J* =13.7, 3.8, CH_AH$_B$), 2.79 (3H, d, *J* =5.1, NHCH_3), 2.65 (1H, dd, *J* =13.7, 8.6, CH$_A$$H_B$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.94 (*C*=O), 138.28 (C_{Ar}), 129.00 (2xC_{Ar}H), 128.70 (2xC_{Ar}H), 127.28 (C_{Ar}H), 54.06 (*C*HNH$_2$), 37.49 (*C*H$_A$H$_B$), 36.56 (Ph*C*H$_2$), 25.97 (NH*C*H$_3$); **IR (vmax/cm^{-1}) (neat)**: 3360, 3298 (NH), 2915 (alkyl C-H), 1654 (C=O); **MS** (ESI): *m/z* calcd for $C_{11}H_{17}N_2OS$ $[M+H]^+$ Found 225.1064.

(*R*)-3-(benzylthio)-2-((2,2-dimethylpropylidene)amino)-*N*-methylpropanamide (412)



Following general **procedure 8**: *N*-methylamide **411** (2.00 g, 8.92 mmol), $MgSO_4$ (1.07 g, 8.92 mmol) and pivalaldehyde (1.30 mL, 11.6 mmol) in anhydrous DCM (4.50 mL). The title compound (2.59 g, 99%) was yielded as a yellow oil and used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 (1H, s, CN=C*H*), 7.35 – 7.25 (4H, m, Ar-*H*), 7.27 – 7.17 (1H, m, Ar-*H*), 6.81 (1H, br. s, N*H*), 3.68 (2H, d, *J* =4.8, PhCH_AH$_B$ + PhCH$_A$$H_B$ overlap), 3.61 (1H, dd, *J* =9.8, 2.9, CH$_A$H$_B$C*H*), 3.03 (1H, dd, *J* =13.7, 2.9, CH_AH$_B$CH), 2.82 (3H, d, *J* =5.0, NHCH_3), 2.62 (1H, dd, *J* =13.7, 9.8, CH$_A$$H_B$CH), 1.10 (9H, s, C(C$H_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 175.85 (CN=*C*H), 172.53 (*C*=O), 138.39 (*C*$_{Ar}$), 129.09 (2x*C*$_{Ar}$H), 128.64 (2x*C*$_{Ar}$H), 127.16 (*C*$_{Ar}$H), 72.29 (CH$_2$*C*H), 36.93 (Ph*C*H$_2$), 36.84 (*C*(CH$_3$)$_3$), 36.67 (*C*H$_2$CH), 26.94 (C(*C*H$_3$)$_3$), 26.02 (NH*C*H$_3$); **IR (vmax/cm^{-1}) (neat)**: 3326 (NH), 2958, 2932 (alkyl C-H), 1667 (C=O); **MS** (ESI): *m/z* calcd for $C_{16}H_{25}N_2OS$ $[M+H]^+$ Found 293.1675.

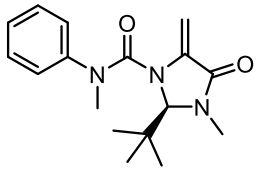
(2*R*)-5-((Benzylthio)methyl)-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxo-*N*-phenylimidazolidine-1-carboxamide (414a)



Following general **procedure 10**: DMAP (52.9 mg, 0.43 mmol), *N*-methyl-*N*-phenylcarbamoyl chloride (2.20 g, 13.0 mmol) and *N*-Methylamide imine **412** (2.53 g, 8.65 mmol) in anhydrous toluene (43.0 mL) were stirred to reflux. The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (1.28 g, 35%) as a yellow oil. **R*f*** (6:4 Pet.Ether:EtOAc) 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44 – 7.38 (2H, m, Ar-*H*), 7.34 – 7.27 (1H, m, Ar-*H*), 7.23 – 7.21 (2H, m, Ar-*H*), 7.20 – 7.16 (5H, m, Ar-*H*), 5.46 (1H, s, C*H*C(CH_3)$_3$), 4.13 (1H, dd, *J* =10.6, 2.4, C*H*CH$_A$H$_B$,), 3.78 (1H, d, *J* =12.6, PhCH_AH$_B$), 3.62 (1H, d, *J* =12.6, PhCH$_A$$H_B$), 3.17 (3H, s, PhNC$H_3$), 2.95 (3H, s, NC$H_3$), 2.15 (1H, dd, *J* =13.6, 10.6, CHCH_AH$_B$), 0.96 (1H, dd, *J* =13.6, 2.4, CHCH$_A$$H_B$), 0.89 (9H, s, C(C$H_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.60 (*C*=O)$_{amide}$, 163.29 (*C*=O)$_{urea}$, 145.63 (*C*$_{Ar}$), 138.52 (*C*$_{Ar}$), 130.50 (2x*C*$_{Ar}$H), 129.33 (2x*C*$_{Ar}$H), 128.39 (2x*C*$_{Ar}$H), 127.34 (2x*C*$_{Ar}$H), 127.19 (*C*$_{Ar}$H), 126.87 (*C*$_{Ar}$H), 82.17 (*C*HC(CH_3)$_3$), 65.36 (*C*HCH$_2$), 41.47 (PhN*C*H$_3$), 37.48 (Ph*C*H$_2$),

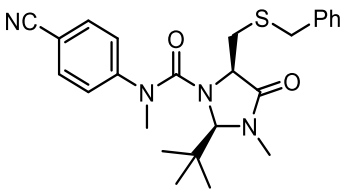
36.66 (*C*(CH_3)$_3$), 33.32 (CH*C*H_2), 31.66 (N*C*H_3), 26.80 (C(*C*H_3)$_3$); **IR (vmax/cm^{-1}) (neat)**: 2973, 2934 (alkyl C-H), 1699, 1658 (C=O); **MS** (ESI): *m/z* calcd for $C_{24}H_{32}N_3O_2S$ $[M+H]^+$, found 426.2212. Data in agreement with reported values.[268]

(*R*)-2-(*tert*-Butyl)-*N*,3-dimethyl-5-methylene-4-oxo-*N*-phenylimidazolidine-1-carboxamide (400a)



Following general **procedure 11**: KHMDS (1.0 M/THF, 3.30 mL, 3.27 mmol, 1.20 eq.) and imidazolidinone urea **414a** (1.16 g, 2.73 mmol) in anhydrous THF (27.3 mL) were stirred for 65 mins (monitored by TLC). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (700 mg, 85%) as a yellow solid. **R*f*** (6:4 Pet.Ether:EtOAc) 0.33; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 – 7.33 (2H, m, Ar-*H*), 7.25 – 7.20 (1H, m, Ar-*H*), 7.11 – 7.06 (2H, m, Ar-*H*), 5.24 (1H, d, *J* =0.9, C=C$H_A$$CH_B$), 5.13 (1H, d, *J* =0.9, C=CH_ACH_B), 4.39 (1H, s, C*H*C(CH_3)$_3$), 3.36 (3H, s, PhNCH_3), 2.80 (3H, s, NCH_3), 0.90 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 164.06 (*C*=O)$_{amide}$, 156.96 (*C*=O)$_{urea}$, 143.95 (C_{Ar}), 137.27 (*C*=CH_2), 129.77 (2xC_{Ar}H), 126.30 (C_{Ar}H), 123.94 (2xC_{Ar}H), 92.70 (C=*C*H_2), 80.96 (*C*HC(CH_3)$_3$), 38.89 (PhN*C*H_3), 39.59 (*C*(CH_3)$_3$), 31.85 (N*C*H_3), 25.58 (C(*C*H_3)$_3$); **IR (vmax/cm^{-1}) (neat)**: 3064 (alkene CH), 2965, 2911 (alkyl C-H), 1704, 1674 (C=O); **MS** (ESI): m/z calcd for $C_{17}H_{24}N_3O_2$ $[M+H]^+$, found 302.1849.

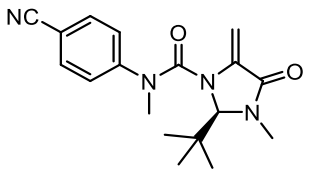
(2*R*,5*R*)-5-((Benzylthio)methyl)-2-(*tert*-butyl)-*N*-(4-cyanophenyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide (414b)



Following general **procedure 10**: DMAP (31.2 mg, 0.26 mmol), *N*-(4-cyanophenyl)-*N*-methylcarbamoyl chloride (1.29 g, 6.64 mmol, 1.30 eq.) and *N*-Methylamide imine **412** (1.49 g, 5.11 mmol) in anhydrous toluene (26.0 mL) were stirred to reflux. The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 10:90) to afford the title compound (930 mg, 40%) as white amorphous solid. **R*f*** (1:9 Pet.Ether:Diethyl ether) 0.16; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.63 (2H, d, *J* =8.6, Ar-*H*), 7.25 –

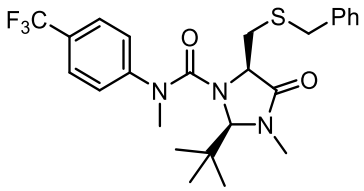
7.21 (2H, m, Ar-*H*), 7.21 – 7.16 (5H, m, Ar-*H*), 5.34 (1H, s, C*H*C(CH_3)$_3$), 4.12 (1H, dd, *J* =9.6, 2.4, C*H*CH$_A$H$_B$), 3.80 (1H, d, *J* =13.0, PhCH_AH$_B$), 3.67 (1H, d, *J* =13.0, PhCH$_A$$H_B$), 3.15 (3H, s, ArNC$H_3$), 2.94 (3H, s, NC$H_3$), 2.31 (1H, dd, *J* =13.9, 9.6, CHCH_AH$_B$), 1.40 (1H, dd, *J* =13.9, 2.4, CHCH$_A$$H_B$), 0.89 (9H, s, C(C$H_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.86 (*C*=O)$_{amide}$, 162.51 (*C*=O)$_{urea}$, 149.56 (*C*$_{Ar}$), 138.06 (*C*$_{Ar}$), 134.14 (2x*C*$_{Ar}$H), 129.22 (2x*C*$_{Ar}$H), 128.50 (2x*C*$_{Ar}$H), 127.06 (*C*$_{Ar}$H), 125.86 (2x*C*$_{Ar}$H), 118.22 (*C*N), 109.61 (*C*$_{Ar}$), 82.42 (*C*HC(CH_3)$_3$), 65.00 (*C*HCH$_2$), 40.56 (PhN*C*H$_3$), 37.23 (Ph*C*H$_2$), 36.80 (*C*(CH$_3$)$_3$), 33.84 (CH*C*H$_2$), 31.68 (N*C*H$_3$), 26.74 (C(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 2967, 2934 (alkyl C-H), 1700 (C=O), 1663 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{25}H_{30}N_4O_2SNa$ [M+Na]$^+$ 473.1982, found 473.1990.

(*R*)-2-(*tert*-Butyl)-*N*-(4-cyanophenyl)-*N*,3-dimethyl-5-methylene-4-oxoimidazolidine-1-carboxamide (400b)



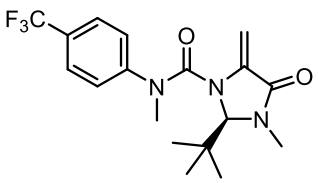
Following general **procedure 11**: KHMDS (1.0 M/THF, 4.10 mL, 4.06 mmol, 2.00 eq.) and imidazolidinone urea **414b** (915 mg, 2.03 mmol) in anhydrous THF (20.0 mL) were stirred for 2.5 hours (monitored by TLC). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 50:50) to afford the title compound (411 mg, 62%) as a yellow solid. **R*f*** (5:5 Pet.Ether:EtOAc) 0.31; **mp**: 180 – 182 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.64 (2H, d, *J* =8.6, Ar-*H*), 7.23 (2H, d, *J* =8.6, Ar-*H*), 5.32 (1H, s, C=CH_ACH$_B$), 4.89 (1H, s, C=CH$_A$CH_B), 4.82 (1H, s, C*H*C(CH_3)$_3$), 3.41 (3H, s, PhNCH_3), 2.99 (3H, s, NCH_3), 0.94 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 163.36 (*C*=O)$_{amide}$, 157.20 (*C*=O)$_{urea}$, 147.39 (*C*$_{Ar}$), 136.45 (*C*=CH$_2$), 133.46 (2x*C*$_{Ar}$H), 122.83 (2x*C*$_{Ar}$H), 118.39 (*C*N), 108.69 (*C*$_{Ar}$), 93.66 (C=*C*H$_2$), 80.93 (*C*HC(CH_3)$_3$), 39.24 (*C*(CH$_3$)$_3$), 38.12 (PhN*C*H$_3$), 32.05 (N*C*H$_3$), 25.67 (C(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 3071 (alkene CH), 2969, 2942 (alkyl C-H), 1701, 1679 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{18}H_{23}N_4O_2$ [M+H]$^+$ 327.1816, found 327.1825.

(2*R*,5*R*)-5-((Benzylthio)methyl)-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxo-*N*-(4-(trifluoromethyl) phenyl)imidazolidine-1-carboxamide (414c)



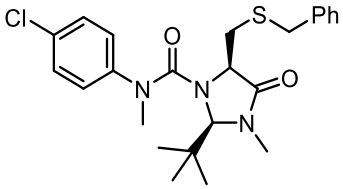
Following general **procedure 9**: triphosgene (1.87 g, 6.31 mmol) in anhydrous DCM (15.8 mL), anhydrous pyridine (1.00 mL, 12.6 mmol) and 4-trifluoromethyl-*N*-methylaniline (1.80 mL, 12.6 mmol). The reaction yielded **260c** (>99%) as a white solid, which was used in the next step without further purification. **260c**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.70 (2H, d, *J* =8.3, Ar-*H*), 7.41 (2H, d, *J* =8.3, Ar-*H*), 3.43 (3H, br. s, NCH_3); **IR (vmax/cm^{-1}) (neat)**: 1728 (C=O); **MS** (ESI): *m/z* calcd for $C_9H_7ClF_3NONa$ $[M+Na]^+$, found 260. Data in agreement with reported values.[295] Following general **procedure 10**: DMAP (57.1 mg, 0.47 mmol), **260c** (3.33 g, 14.0 mmol) and *N*-Methylamide imine **412** (2.73 g, 9.35 mmol) in anhydrous toluene (46.5 mL) were stirred to reflux. The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (1.79 g, 39%) as an orange oil. **R*f*** (6:4 Pet.Ether:EtOAc) 0.36; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.68 (2H, d, *J* =8.1, Ar-*H*), 7.33 – 7.27 (2H, m, Ar-*H*), 7.24 – 7.21 (2H, m, Ar-*H*), 7.21 – 7.15 (3H, m, Ar-*H*), 5.39 (1H, s, C*H*C(CH_3)$_3$), 4.14 (1H, dd, *J* =10.2, 2.4, C*H*CH_AH$_B$), 3.76 (1H, d, *J* =12.8, PhCH_AH$_B$), 3.60 (1H, d, *J* =12.8, PhCH$_A$$H_B$), 3.18 (3H, s, ArNC$H_3$), 2.95 (3H, s, NC$H_3$), 2.27 (1H, dd, *J* =13.5, 10.2, CHCH_AH$_B$), 1.22 (1H, dd, *J* =13.5, 2.4, CHCH$_A$$H_B$), 0.90 (9H, s, C(C$H_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.10 (*C*=O)$_{amide}$, 162.91 (*C*=O)$_{urea}$, 148.86 (br. q, $^{5}J^{C\text{-}F}$ = 1.4, C_{Ar}), 138.13 (C_{Ar}), 129.19 (2xC_{Ar}H), 128.82 (q, $^{2}J^{C\text{-}F}$ = 33.0, Ar), 128.42 (2xC_{Ar}H), 127.50 (q, $^{3}J^{C\text{-}F}$ = 3.6, 2xC_{Ar}H), 126.95 (C_{Ar}H), 126.74 (2xC_{Ar}H), 123.82 (q, $^{1}J^{C\text{-}F}$ = 272.2, *C*F$_3$), 82.34 (*C*HC(CH$_3$)$_3$), 64.91 (*C*HCH$_2$), 41.10 (PhN*C*H$_3$), 37.35 (Ph*C*H$_2$), 36.73 (*C*(CH$_3$)$_3$), 33.79 (CH*C*H$_2$), 31.67 (N*C*H$_3$), 26.75 (C(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 2976, 2874 (alkyl C-H), 1703, 1666 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{25}H_{30}F_3N_3O_2SNa$ $[M+Na]^+$ 516.1903, found 516.1917.

(*R*)-2-(*tert*-Butyl)-*N*,3-dimethyl-5-methylene-4-oxo-*N*-(4-(trifluoromethyl)phenyl) imidazolidine-1-carboxamide (400c)



Following a similar procedure to general **procedure 11**: KHMDS (1.0 M/THF, 5.60 mL, 5.60 mmol, 2.00 eq.) was added to a solution of imidazolidinone urea **414c** (1.37 g, 2.78 mmol) in anhydrous THF (26.6 mL) at 0 °C under nitrogen. The reaction was allowed to warm to room temperature and then heated to 75 °C. The reaction was left stirring until TLC analysis showed the starting material had been completely consumed. The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 70:30) to afford the title compound (246 mg, 24%). **R*f*** (7:3 Pet.Ether:EtOAc) 0.36; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.63 (2H, d, *J* =8.3, Ar-*H*), 7.25 (1H, d, *J* =8.3, Ar-*H*), 5.31 (1H, d, *J* =1.3, C=C*H*$_A$CH$_B$), 4.97 (1H, d, *J* =1.3, C=CH$_A$C*H*$_B$), 4.70 (1H, s, C*H*C(C*H*$_3$)$_3$), 3.42 (3H, s, PhNC*H*$_3$), 2.94 (3H, s, NC*H*$_3$), 0.94 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 163.62 (*C*=O)$_{amide}$, 157.31 (*C*=O)$_{urea}$, 146.72 (q, $^5J^{C\text{-}F}$ = 1.2, *C*$_{Ar}$), 136.80 (*C*=CH$_2$), 127.87 (q, $^2J^{C\text{-}F}$ = 33.0, *C*$_{Ar}$), 126.77 (q, $^3J^{C\text{-}F}$ = 3.8, 2x*C*$_{Ar}$H), 123.91 (q, $^1J^{C\text{-}F}$ = 271.9, *C*F$_3$), 123.33 (2x*C*$_{Ar}$H), 93.16 (C=*C*H$_2$), 80.99 (*C*HC(CH$_3$)$_3$), 39.33 (*C*(CH$_3$)$_3$), 38.50 (PhN*C*H$_3$), 31.98 (N*C*H$_3$), 25.68 (C(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 3082 (alkene CH), 2973, 2924 (alkyl C-H), 1698, 1615 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{18}H_{22}F_3N_3O_2Na$ $[M+Na]^+$ 392.155632, found 392.157425.

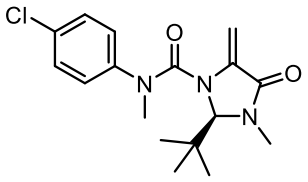
(2*R*,5*R*)-5-((Benzylthio)methyl)-2-(*tert*-butyl)-*N*-(4-chlorophenyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide (414d)



Following general **procedure 9**: triphosgene (1.93 g, 6.50 mmol) in anhydrous DCM (16.3 mL), anhydrous pyridine (1.10 mL, 13.0 mmol) and 4-chloro-*N*-methylaniline (1.60 mL, 13.0 mmol). The reaction yielded **260d** (2.69 g, >99%) as a yellow solid, which was used in the next step without further purification. **260d**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40 (2H, d, *J* =8.1, Ar-*H*), 7.20 (2H, d, *J* =8.1, Ar-*H*), 3.36 (3H, s, NC*H*$_3$); **IR (vmax/cm^{-1}) (neat)**: 1740 (C=O), 2939, 2906 (alkyl C-H). Data in agreement with reported values.[295] Following general **procedure 10**: DMAP (39.7 mg, 0.33

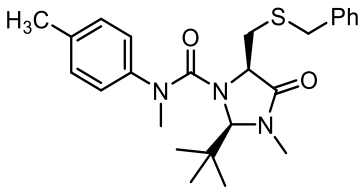
mmol), **260d** (1.99 g, 9.75 mmol) and *N*-Methylamide imine **412** (1.90 g, 6.50 mmol) in anhydrous toluene (32.0 mL) were stirred to reflux. The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (1.57 g, 53%) as a dark orange oil. **R*f*** (6:4 Pet.Ether:EtOAc) 0.28; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 (2H, d, *J* =8.7, Ar-*H*), 7.25 – 7.21 (4H, m, Ar-*H*), 7.21 – 7.17 (1H, m, Ar-*H*), 7.13 (2H, d, *J* =8.7, Ar-*H*), 5.46 (1H, s, C*H*C(C*H*$_3$)$_3$), 4.07 (1H, dd, *J* =10.5, 2.3, C*H*CH$_A$H$_B$,), 3.78 (1H, d, *J* =12.8, PhC*H*$_A$H$_B$), 3.63 (1H, d, *J* =12.8, PhCH$_A$*H*$_B$), 3.14 (3H, s, PhNC*H*$_3$), 2.95 (3H, s, NC*H*$_3$), 2.23 (1H, dd, *J* =13.4, 10.5, CHC*H*$_A$H$_B$), 1.09 (1H, dd, *J* =13.4, 2.3, CHCH$_A$*H*$_B$), 0.89 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.33 (*C*=O)$_{amide}$, 163.13 (*C*=O)$_{urea}$, 144.20 (*C*$_{Ar}$), 138.29 (*C*$_{Ar}$), 132.83 (*C*$_{Ar}$), 130.63 (2x*C*$_{Ar}$H), 129.27 (2x*C*$_{Ar}$H), 128.58 (2x*C*$_{Ar}$H), 128.45 (2x*C*$_{Ar}$H), 126.95 (*C*$_{Ar}$H), 82.26 (*C*HC(C*H*$_3$)$_3$), 65.07 (*C*HCH$_2$), 41.49 (PhN*C*H$_3$), 37.55 (Ph*C*H$_2$), 36.67 (*C*(CH$_3$)$_3$), 33.79 (CH*C*H$_2$), 31.67 (N*C*H$_3$), 26.78 (C(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 2967, 2929 (alkyl C-H), 1698, 1659 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{24}H_{30}ClN_3O_2SNa$ [M+Na]$^+$ 482.1639, found 482.1640.

(*R*)-2-(*tert*-butyl)-*N*-(4-chlorophenyl)-*N*,3-dimethyl-5-methylene-4-oxoimidazolidine-1-carboxamide (400d)



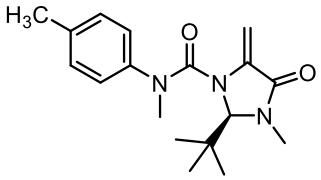
Following general **procedure 11**: KHMDS (1.0 M/THF, 4.10 mL, 4.11 mmol, 1.20 eq.) was added to imidazolidinone urea **414d** (1.57 g, 3.42 mmol) in anhydrous THF (34.0 mL) at 0 °C under nitrogen. The reaction was stirred at room temperature for 2 hours, after which it was cooled to 0 °C and an additional 0.8 equivalents of KHMDS (1.0 M/THF, 2.7 mL, 2.74 mmol) was added. The reaction was then stirred at room temperature for 2.5 hours (monitored by TLC). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (814 mg, 71%) as a yellow solid. **R*f*** (6:4 Pet.Ether:EtOAc) 0.44; **mp**: 150 – 152 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34 (2H, d, *J* =8.8, Ar-*H*), 7.07 (2H, d, *J* =8.8, Ar-*H*), 5.27 (1H, d, *J* =1.2, C=C*H*$_A$CH$_B$), 4.97 (1H, d, *J* =1.2, C=CH$_A$C*H*$_B$), 4.65 (1H, s, C*H*C(C*H*$_3$)$_3$), 3.36 (3H, s, PhNC*H*$_3$), 2.93 (3H, s, NC*H*$_3$), 0.93 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 163.76 (*C*=O)$_{amide}$, 157.20 (*C*=O)$_{urea}$, 142.24 (*C*$_{Ar}$), 137.09 (*C*=CH$_2$), 131.82 (*C*$_{Ar}$), 129.78 (2x*C*$_{Ar}$H), 125.26 (2x*C*$_{Ar}$H), 92.53 (C=*C*H$_2$), 80.97 (*C*HC(C*H*$_3$)$_3$), 39.35 (*C*(CH$_3$)$_3$), 38.99 (PhN*C*H$_3$), 31.96 (N*C*H$_3$), 25.64 (C(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 3050 (alkene CH), 2972, 2925 (alkyl C-H), 1714, 1699 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{17}H_{22}ClN_3O_2Na$ [M+Na]$^+$ 358.129275, found 358.128913.

(2*R*,5*R*)-5-((Benzylthio)methyl)-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxo-*N*-(*p*-tolyl)imidazolidine-1-carboxamide (414e)



Following general **procedure 10**: DMAP (21.4 mg, 0.18 mmol), *N*-(methyl)-*N*-(4-methylphenyl)-carbamoyl chloride (965 mg, 5.23 mmol) and *N*-Methylamide imine **412** (1.02 g, 3.50 mmol) in anhydrous toluene (17.5 mL) were stirred to reflux. The crude product was purified by flash column chromatography (SiO_2; DCM:Acetone 100:0 to DCM:Acetone 95:5) to afford the title compound (695 mg, 45%) as an orange oil. **R*f*** (9.5:0.5 DCM:Acetone) 0.31; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24 – 7.20 (4H, m, Ar-*H*), 7.20 – 7.15 (3H, m, Ar-*H*), 7.10 – 7.05 (2H, m, Ar-*H*), 5.48 (1H, s, C*H*C(C*H*$_3$)$_3$), 4.11 (1H, dd, *J* =10.7, 2.4, C*H*CH$_A$H$_B$,), 3.77 (1H, d, *J* =12.7, PhC*H*$_A$H$_B$), 3.59 (1H, d, *J* =12.7, PhCH$_A$*H*$_B$), 3.14 (3H, s, ArNC*H*$_3$), 2.95 (3H, s, NC*H*$_3$), 2.37 (3H, s, C*H*$_3$), 2.15 (1H, dd, *J* =13.5, 10.7, CHC*H*$_A$H$_B$), 0.96 (1H, dd, *J* =13.5, 2.4, CHCH$_A$*H*$_B$), 0.89 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 171.67 (*C*=O)$_{amide}$, 163.38 (*C*=O)$_{urea}$, 142.97 (*C*$_{Ar}$), 138.57 (*C*$_{Ar}$), 137.16 (*C*$_{Ar}$), 131.09 (2x*C*$_{Ar}$H), 129.27 (2x*C*$_{Ar}$H), 128.39 (2x*C*$_{Ar}$H), 127.23 (2x*C*$_{Ar}$H), 126.85 (*C*$_{Ar}$H), 82.13 (*C*HC(CH$_3$)$_3$), 65.29 (*C*HCH$_2$), 41.55 (PhN*C*H$_3$), 37.51 (Ph*C*H$_2$), 36.63 (*C*(CH$_3$)$_3$), 33.38 (CH*C*H$_2$), 31.65 (N*C*H$_3$), 26.78 (C(*C*H$_3$)$_3$), 21.23 (*C*H$_3$); **IR (vmax/cm^{-1}) (neat)**: 2965, 2926 (alkyl C-H), 1699, 1657 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{25}H_{33}N_3O_2SNa$ $[M+Na]^+$ 462.218569, found 462.221032.

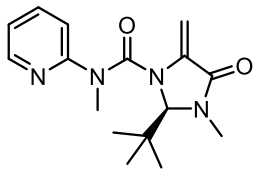
(*R*)-2-(*tert*-Butyl)-*N*,3-dimethyl-5-methylene-4-oxo-*N*-(*p*-tolyl)imidazolidine-1-carboxamide (400e)



Following general **procedure 11**: KHMDS (1.0 M/THF, 4.50 mL, 4.49 mmol, 2.00 eq.) and imidazolidinone urea **414e** (988 mg, 2.26 mmol) in anhydrous THF (23.0 mL) were stirred for 65 mins (monitored by TLC). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 40:60) to afford the title compound (518 mg, 73%) as a yellow solid. **R*f*** (4:6 Pet.Ether:Diethyl ether) 0.22; **mp**: 158 – 159 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.17 (2H, d, *J* =8.5, Ar-*H*), 6.98 (2H, d, *J* =8.5, Ar-*H*), 5.23 (1H, d, *J* =1.0,

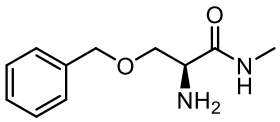
C=CH_ACH$_B$), 5.08 (1H, d, *J* =1.0, C=CH$_A$CH_B), 4.47 (1H, s, C*H*C(CH$_3$)$_3$), 3.34 (3H, s, PhNCH_3), 2.83 (3H, s, NCH_3), 2.34 (CH_3), 0.92 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, CDCl$_3$): δ 164.13 (*C*=O)$_{amide}$, 157.12 (*C*=O)$_{urea}$, 141.36 (*C*$_{Ar}$), 137.40 (*C*=CH$_2$), 136.31 (*C*$_{Ar}$), 130.32 (2x*C*$_{Ar}$H), 124.00 (2x*C*$_{Ar}$H), 92.36 (C=*C*H$_2$), 80.95 (*C*HC(CH$_3$)$_3$), 39.55 (*C*(CH$_3$)$_3$), 39.10 (PhN*C*H$_3$), 31.88 (N*C*H$_3$), 25.63 (C(*C*H$_3$)$_3$), 21.05 (C*H*$_3$); **IR (vmax/cm^{-1}) (neat)**: 3032 (alkene CH), 2969, 2926 (alkyl C-H), 1705, 1674 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{18}H_{26}N_3O_2$ $[M+H]^+$ 316.201954, found 316.201431.

(*R*)-2-(*tert*-butyl)-*N*,3-dimethyl-5-methylene-4-oxo-*N*-(pyridin-2-yl)imidazolidine-1-carboxamide (400f)



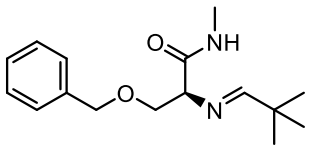
Following general **procedure 11**: KHMDS (1.0 M/THF, 4.20 mL, 4.24 mmol, 1.20 eq.) was added to imidazolidinone urea **414f** (1.51 g, 3.53 mmol) in anhydrous THF (35.0 mL) at 0 °C under nitrogen. The reaction was stirred for 2 hours at room temperature, after which it was cooled down to 0 °C and an additional 0.8 equivalents of KHMDS (1.0 M/THF, 2.8mL, 2.80 mmol) was added. The reaction was then stirred at room temperature for 1 hour (monitored by TLC). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 20:80) to afford the title compound (1.09 g, >99%) as a dark viscous oil. **R*f*** (2:8 Pet.Ether:EtOAc) 0.43; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 8.39 (1H, ddd, *J* =4.9, 2.0, 1.0, Ar-*H*), 7.63 (1H, ddd, *J* =8.4, 7.3, 2.0, Ar-*H*), 7.19 (1H, dt, *J* =8.4, 1.0, Ar-*H*), 7.04 (1H, ddd, *J* =7.3, 4.9, 1.0, Ar-*H*), 5.27 (1H, d, *J* =1.3, C=CH_ACH$_B$), 4.93 (1H, s, C*H*C(CH$_3$)$_3$), 4.85 (1H, d, *J* =1.3, C=CH$_A$CH_B), 3.48 (3H, s, PhNCH_3), 3.02 (3H, s, NCH_3), 0.97 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, CDCl$_3$): δ 163.80 (*C*=O)$_{amide}$, 157.79 (*C*=O)$_{urea}$, 155.49 (*C*$_{Ar}$), 148.37 (*C*$_{Ar}$H), 137.81 (*C*$_{Ar}$H), 136.49 (*C*=CH$_2$), 119.76 (*C*$_{Ar}$H), 116.80 (*C*$_{Ar}$H), 93.83 (C=*C*H$_2$), 81.06 (*C*HC(CH$_3$)$_3$), 39.29 (*C*(CH$_3$)$_3$), 36.31 (PhN*C*H$_3$), 32.08 (N*C*H$_3$), 25.77 (C(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 2967, 2925 (alkyl C-H), 1712 (C=O), 1681 (C=O); **MS** (ESI): *m/z* calcd for $C_{16}H_{23}N_4O_2$ $[M+H]^+$, found 303.2.

(*S*)-2-Amino-3-(benzyloxy)-*N*-methylpropanamide (419)



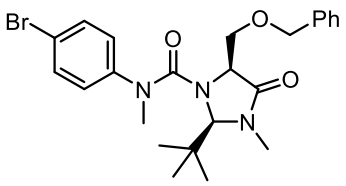
Following general **procedure 7**: $MeNH_2$ (33% *w/w* solution in EtOH, 89.0 mL, 712 mmol) and *O*-benzyl-L-serine methyl ester hydrochloride **418** (25.0 g, 102 mmol). The title compound (20.7 g, 98%) was yielded as a yellow oil and used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37 – 7.26 (5H, m, Ar-*H*), 4.53 (2H, s, PhCH_2), 3.74 (1H, dd, *J* =9.2, 4.0, CH_AH$_B$), 3.64 (1H, dd, *J* =9.2, 6.7, CH$_A$$H_B$)), 3.58 (1H, dd, *J* =6.7, 4.0, C*H*NH_2), 2.81 (3H, d, *J* =5.0, NHCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.31 (*C*=O), 137.98 (C_{Ar}), 128.59 (2xC_{Ar}H), 127.95 (C_{Ar}H), 127.92 (2xC_{Ar}H), 73.39 (Ph*C*H_2), 72.44 (*C*H$_A$H$_B$), 55.19 (*C*HNH_2), 25.95 (NH*C*H_3); **IR (vmax/cm^{-1}) (neat)**: 3371, 3305, 3094 (NH), 2906 (alkyl C-H), 1651 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{11}H_{17}N_2O_2$ $[M+NH]^+$ 209.128454, found 209.128466.

(*S*)-3-(Benzyloxy)-2-((2,2-dimethylpropylidene)amino)-*N*-methylpropanamide (420)



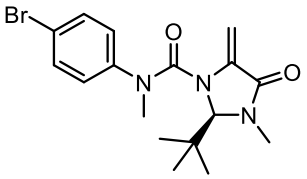
Following general **procedure 8**: *N*-methylamide **420** (2.46 g, 11.8 mmol), $MgSO_4$ (1.42 g, 11.8 mmol) and pivalaldehyde (1.67 mL, 15.3 mmol) in anhydrous DCM (5.90 mL). The title compound (2.62 g, 80%) was yielded as a yellow oil and used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.55 (1H, d, *J* = 0.6, CN=C*H*), 7.33 – 7.28 (2H, m, Ar-*H*), 7.27 – 7.22 (3H, m, Ar-*H*), 7.03 (1H, br. s, N*H*), 4.54 – 4.43 (2H, m, PhCH_AH$_B$ + PhCH$_A$$H_B$ overlap), 3.89 – 3.82 (2H, m, CH$_A$H$_B$C*H* + CH_AH$_B$CH), 3.54 (1H, dd, *J* =10.2, 9.2, CH$_A$$H_B$CH), 2.83 (3H, d, *J* =5.0, NHCH_3), 1.08 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 175.60 (CN=*C*H), 171.43 (*C*=O), 138.22 (C_{Ar}), 129.39 (2xC_{Ar}H), 127.63 (C_{Ar}H), 127.54 (2xC_{Ar}H), 73.02 (Ph*C*H_2), 72.42 (CH_2*C*H), 36.72 (*C*(CH$_3$)$_3$), 71.74 (*C*H_2CH), 26.85 (C(*C*H$_3$)$_3$), 25.97 (NH*C*H_3); **IR (vmax/cm^{-1}) (neat)**: 3395 (NH), 2958, 2901 (alkyl C-H), 1671 (C=O); **MS** (ESI): *m/z* calcd for $C_{16}H_{25}N_2O_2$ $[M+H]^+$ Found 277.1903.

(2*R*,5*S*)-5-((Benzyloxy)methyl)-*N*-(4-bromophenyl)-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide (421g)



Following general **procedure 9**: triphosgene (1.96 g, 6.61 mmol) in anhydrous DCM (16.5 mL), anhydrous pyridine (1.10 mL, 13.2 mmol) and 4-bromo-*N*-methylaniline (1.70 mL, 13.2 mmol). The reaction yielded **260g** (3.19 g, 97%) as a yellow solid, which was used in the next step without further purification. **260g**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.56 (2H, d, *J* =8.6, Ar-*H*), 7.14 (2H, d, *J* =8.6, Ar-*H*), 3.36 (3H, s, NC*H*$_3$). Data in agreement with reported values.[295] Following general **procedure 10**: DMAP (57.3 mg, 0.47 mmol), **260g** (3.49 g, 14.1 mmol) and *N*-Methylamide imine **420** (2.59 g, 9.38 mmol) in anhydrous toluene (47.0 mL) were stirred to reflux. The crude product was purified by flash column chromatography (SiO_2; *n*Hexane:Acetone 100:0 to *n*Hexane:Acetone 60:40) to afford the title compound (1.88 g, 41%) as a yellow oil. **R*f*** (6:4 *n*Hexane:Acetone) 0.42; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47 (2H, d, *J* = 8.7, Ar-*H*), 7.35 – 7.29 (2H, m, Ar-*H*), 7.28 – 7.23 (3H, m, Ar-*H*), 7.07 (2H, d, *J* = 8.7, Ar-*H*), 5.50 (1H, s, C*H*C(C*H*$_3$)$_3$), 4.15 (2H, s, PhC*H*$_2$), 4.05 (1H, dd, *J* =7.0, 2.4, C*H*CH$_A$H$_B$), 3.14 (3H, s, ArNC*H*$_3$), 2.96 (3H, s, NC*H*$_3$), 2.92 (1H, dd, *J* =9.4, 7.0, CHC*H*$_A$H$_B$), 2.38 (1H, dd, *J* =9.4, 2.4, CHCH$_A$*H*$_B$), 0.92 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.89 (*C*=O)$_{amide}$, 163.39 (*C*=O)$_{urea}$, 144.77 (*C*$_{Ar}$), 137.87 (*C*$_{Ar}$), 133.16 (2x*C*$_{Ar}$H), 129.06 (2x*C*$_{Ar}$H), 128.41 (2x*C*$_{Ar}$H), 127.63 (2x*C*$_{Ar}$H), 127.60 (*C*$_{Ar}$H), 120.42 (*C*$_{Ar}$), 82.25 (*C*HC(CH$_3$)$_3$), 73.28 (PhCH$_2$), 70.77 (CHCH$_2$), 63.27 (*C*HCH$_2$), 41.45 (PhNCH$_3$), 36.86 (*C*(CH$_3$)$_3$), 31.56 (NCH$_3$), 26.68 (C(*C*H$_3$)$_3$); **IR (vmax/cm^{-1}) (neat)**: 2973, 2870 (alkyl C-H), 1703, 1658 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{24}H_{30}BrN_3O_3Na$ $[M+Na]^+$ 510.1363, found 510.1357.

(*R*)-*N*-(4-Bromophenyl)-2-(*tert*-butyl)-*N*,3-dimethyl-5-methylene-4-oxoimidazolidine-1-carboxamide (400g)

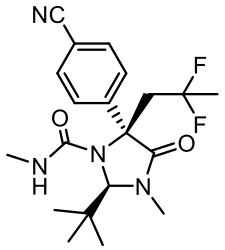


Following general **procedure 11**: KHMDS (1.0 M/THF, 6.00 mL, 5.99 mmol, 1.60 eq.) and imidazolidinone urea **421g** (1.85 g, 3.79 mmol) in anhydrous THF (38.0 mL) were stirred for 2.75 hours (monitored by TLC). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (494 mg, 34%) as

a light brown solid. **R*f*** (6:4 Pet.Ether:EtOAc) 0.40; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.49 (2H, d, *J* =8.8, Ar-*H*), 7.01 (2H, d, *J* =8.8, Ar-*H*), 5.27 (1H, d, *J* =1.2, C=C$H_A$$CH_B$), 4.96 (1H, d, *J* =1.2, C=CH_ACH_B), 4.65 (1H, s, C*H*C$(CH_3)_3$), 3.35 (3H, s, PhNCH_3), 2.93 (3H, s, NCH_3), 0.93 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 163.78 (*C*=O)$_{amide}$, 157.17 (*C*=O)$_{urea}$, 142.77 (C_{Ar}), 137.07 (*C*=CH_2), 132.76 (2xC_{Ar}H), 125.55 (2xC_{Ar}H), 119.53 (C_{Ar}), 92.63 (C=*C*H_2), 80.99 (*C*HC$(CH_3)_3$), 39.36 (*C*$(CH_3)_3$), 38.90 (PhN*C*H_3), 31.98 (N*C*H_3), 25.65 (C(*C*H_3)$_3$); **IR (vmax/cm^{-1}) (neat)**: 2968, 2927 (alkyl C-H), 1714, 1679 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{17}H_{22}BrN_3O_2Na$ $[M+Na]^+$ 402.0788, found 402.0791.

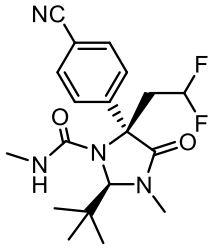
4.3.2.2 Photoredox Radical Conjugate Addition and Aryl Migration

(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-cyanophenyl)-5-(2,2-difluoropropyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide (405be)



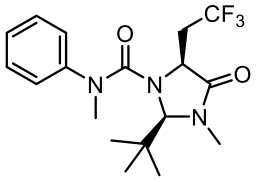
Following general **procedure 12**: vinyl urea **400b** (65.3 mg, 0.20 mmol), caesium carbonate (97.7 mg, 0.30 mmol), 4CzIPN (7.9 mg, 0.01 mmol) and $C_2H_3F_2SO_2Na$ (60.8 mg, 0.40 mmol, 2.00 eq.) in anhydrous CH_3CN (2.00 mL). The crude product was purified by flash column chromatography (SiO_2; DCM:Acetone 100:0 to DCM:Acetone 90:10) to afford the title compound (25.4 mg, 32%) as a white solid. **R*f*** (9:1 DCM:Acetone) 0.48; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (2H, d, *J* =8.7, Ar-*H*), 7.32 – 7.27 (2H, m, Ar-*H*), 5.80 (1H, s, C*H*C(CH_3)$_3$), 4.82 (1H, br. s, N*H*CH_3), 3.27 (1H, ddd, *J* =31.2, 16.6, 2.5, C$H_A$$H_B$), 3.04 (3H, s, NC$H_3$), 2.68 (1H, ddd, *J* =31.2, 16.6, 7.5, $CH_A$$H_B$), 2.37 (3H, d, *J* =4.6, NHCH_3), 1.85 (3H, t, *J* =18.7, CH_3F_2), 1.07 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.08 (*C*=O)$_{amide}$, 158.51 (*C*=O)$_{urea}$, 144.88 (C_{Ar}), 132.46 (2xC_{Ar}H), 126.94 (2xC_{Ar}H), 124.62 (dd, $^{1}J^{C\text{-}F}$ = 242.8, 237.0, *C*F_2), 118.32 (*C*N), 112.23 (C_{Ar}), 81.50 (*C*HC$(CH_3)_3$), 67.93 (N*C*(Ar)), 40.91 (t, $^{2}J^{C\text{-}F}$ = 22.7, NC*C*H_2), 38.19 (*C*$(CH_3)_3$), 32.12 (N*C*H_3), 27.08 (NH*C*H_3), 26.77 (C(*C*H_3)$_3$), 26.05 (t, $^{2}J^{C\text{-}F}$ = 27.2, CH_3F_2); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −84.50 to −85.28 (1F, m), δ_F −89.27 to −90.02 (1F, m); **IR (vmax/cm^{-1}) (neat)**: 3668 (NH), 2969, 2916 (alkyl C-H), 1701 (C=O), 1667 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{20}H_{26}F_2N_4O_2Na$ $[M+Na]^+$ 415.1916, found 415.1938.

(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-cyanophenyl)-5-(2,2-difluoroethyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide (405bf)



Following general **procedure 12**: vinyl urea **400b** (196 mg, 0.60 mmol), caesium carbonate (293 mg, 0.90 mmol), 4CzIPN (23.7 mg, 0.03 mmol) and CHF_2SO_2Na (166 mg, 1.2 mmol, 2.00 eq.) in anhydrous CH_3CN (6.00 mL). The crude product was purified by flash column chromatography (SiO_2; DCM:Acetone 100:0 to DCM:Acetone 90:10) to afford the title compound (94.8 mg, 42%) as a yellow oil; **R*f*** (9:1 DCM:Acetone) 0.46; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.64 (2H, d, *J* =8.6, Ar-*H*), 7.30 (2H, d, *J* =8.6, Ar-*H*), 6.29 (1H, tt, *J* = 55.1, 4.7, C*H*F_2), 5.57 (1H, s, C*H*C(C*H*$_3$)$_3$), 4.43 (1H, br. s, N*H*CH_3), 3.08 (3H, s, NC*H*$_3$), 3.06 – 2.93 (2H, m, NCC*H*$_2$), 2.42 (3H, d, *J* =4.4, NHC*H*$_3$), 1.07 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.15 (*C*=O)$_{amide}$, 158.40 (*C*=O)$_{urea}$, 145.00 (C_{Ar}), 132.79 (2xC_{Ar}H), 126.45 (2xC_{Ar}H), 118.15 (*C*N), 115.33 (t, $^1J^{C\text{-}F}$ = 238.8, *C*HF_2), 112.64 (C_{Ar}), 81.39 (*C*HC(CH$_3$)$_3$), 66.94 (dd, $^3J^{C\text{-}F}$ = 8.9, 3.2, N*C*(Ar)), 40.48 (t, $^2J^{C\text{-}F}$ = 22.5, NC*C*H_2), 38.23 (*C*(CH$_3$)$_3$), 32.21 (N*C*H_3), 27.26 (NH*C*H_3), 26.78 (C(*C*H$_3$)$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −110.14 to −111.26 (1F, m), δ_F −111.34 to −112.46 (1F, m); **IR (vmax/cm^{-1}) (neat)**: 3403 (NH), 2972, 2907 (alkyl C-H), 1703 (C=O), 1668 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{19}H_{24}F_2N_4O_2Na$ $[M+Na]^+$ 401.175953, found 401.175502.

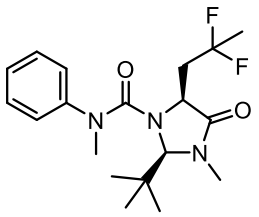
(2*R*,5*S*)-2-(*tert*-Butyl)-*N*,3-dimethyl-4-oxo-*N*-phenyl-5-(2,2,2-trifluoroethyl)imidazolidine-1-carboxamide (moa427aa)



Following general **procedure 12**: vinyl urea **400a** (30.0 mg, 0.10 mmol), caesium carbonate (48.9 mg, 0.15 mmol), 4CzIPN (3.9 mg, 5 x 10^{-3} mmol) and CF_3SO_2Na (46.8 mg, 0.30 mmol, 3.00 eq.) in anhydrous CH_3CN (1.00 mL). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (^{19}F NMR yield: 66%) as a yellow oil. **R*f*** (6:4 Pet.Ether:EtOAc) 0.33; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 – 7.40 (2H, m, Ar-*H*), 7.33 – 7.28 (1H, m, Ar-*H*), 7.18 – 7.14 (2H, m, Ar-*H*), 5.36 (1H, s, C*H*C(C*H*$_3$)$_3$), 4.20 (1H, dd, *J* =11.1, 2.7, C*H*CH_AH_B), 3.19 (3H, s, PhNC*H*$_3$), 2.91 (3H, s, NC*H*$_3$),

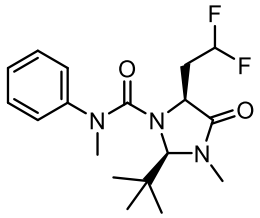
2.14 – 1.98 (1H, m, CHC$H_A$$H_B$), 1.04 – 1.00 (1H, m, CHC$H_A$$H_B$), 0.96 (9H, s, C(C$H_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 169.93 (*C*=O)$_{amide}$, 163.00 (*C*=O)$_{urea}$, 145.34 (C_{Ar}), 130.42 (2xC_{Ar}H), 127.26 (C_{Ar}H), 126.71 (2xC_{Ar}H), 124.77 (q, $^1J^{C\text{-}F}$ = 277.7, *C*F$_3$), 82.45 (*C*HC(CH$_3$)$_3$), 57.24 (q, $^3J^{C\text{-}F}$ = 3.3, *C*HCH$_2$), 41.32 (PhN*C*H$_3$), 37.09 (q, $^2J^{C\text{-}F}$ = 29.1, CH*C*H$_2$), 36.90 (*C*(CH$_3$)$_3$), 31.90 (N*C*H$_3$), 26.86 (C(*C*H$_3$)$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −60.67 (3F, dd, *J* = 11.9, 9.2); **IR (vmax/cm^{-1}) (neat)**: 2976, 2907 (alkyl C-H), 1715, 1661 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{18}H_{24}F_3N_3O_2Na$ $[M+Na]^+$ 394.1713, found 394.1707.

(2*R*,5*S*)-2-(*tert*-Butyl)-5-(2,2-difluoropropyl)-*N*,3-dimethyl-4-oxo-*N*-phenylimidazolidine-1-carboxamide (427ae)



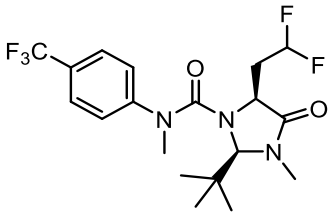
Following general **procedure 12**: vinyl urea **400a** (30.0 mg, 0.10 mmol), caesium carbonate (48.9 mg, 0.15 mmol), 4CzIPN (3.9 mg, 5 x 10^{-3} mmol) and $C_2H_3F_2SO_2Na$ (30.4 mg, 0.20 mmol, 2.00 eq.) in anhydrous CH_3CN (1.00 mL). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (23.6 mg, 64%) as a yellow oil. **R*f*** (6:4 Pet.Ether:EtOAc) 0.33; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40 (2H, t, *J* =7.8, Ar-*H*), 7.29 – 7.22 (1H, m, Ar-*H*), 7.13 (2H, d, *J* =7.5, Ar-*H*), 5.18 (1H, s, C*H*C(C*H*$_3$)$_3$), 4.21 (1H, dd, *J* =10.8, 2.7, C*H*C$H_A$$H_B$), 3.18 (3H, s, PhNC*H*$_3$), 2.86 (3H, s, NC*H*$_3$), 1.93 (1H, tdd, *J* =15.3, 12.3, 10.8, CHC$H_A$$H_B$), 1.57 (3H, t, *J* =18.9, CF$_2$C*H*$_3$), 1.31 – 1.16 (1H, m, CHC$H_A$$H_B$), 0.96 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.08 (*C*=O)$_{amide}$, 163.00 (*C*=O)$_{urea}$, 145.65 (C_{Ar}), 130.15 (2xC_{Ar}H), 126.62 (C_{Ar}H), 126.09 (2xC_{Ar}H), 122.31 (t, $^1J^{C\text{-}F}$ = 240.1, *C*F$_2$), 82.29 (*C*HC(CH$_3$)$_3$), 57.87 (dd, $^3J^{C\text{-}F}$ = 6.6, 4.8, *C*HCH$_2$), 41.15 (PhN*C*H$_3$), 36.91 (*C*(CH$_3$)$_3$), 41.33 (t, $^2J^{C\text{-}F}$ = 26.4, CH*C*H$_2$), 31.78 (N*C*H$_3$), 26.92 (C(*C*H$_3$)$_3$), 24.26 (t, $^1J^{C\text{-}F}$ = 27.1, CH$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −82.86 to −83.74 (1F, m), δ_F −86.13 to −87.01 (1F, m); **IR (vmax/cm^{-1}) (neat)**: 2969, 2874 (alkyl C-H), 1705, 1658 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{19}H_{28}F_2N_3O_2$ $[M+H]^+$ 368.214410, found 368.213678.

(2*R*)-2-(*tert*-Butyl)-5-(2,2-difluoroethyl)-*N*,3-dimethyl-4-oxo-*N*-phenylimidazolidine-1-carboxamide (427af)



Following general **procedure 12**: vinyl urea **400a** (30.0 mg, 0.10 mmol), caesium carbonate (48.9 mg, 0.15 mmol), 4CzIPN (3.9 mg, 5 x 10^{-3} mmol) and CHF_2SO_2Na (27.6 mg, 0.20 mmol, 2.00 eq.) in anhydrous CH_3CN (1.00 mL). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (32.2 mg, 91%) as a colourless oil. **R*f*** (6:4 Pet.Ether:EtOAc) 0.33; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 – 7.40 (2H, m, Ar-*H*), 7.33 – 7.27 (1H, m, Ar-*H*), 7.19 – 7.15 (2H, m, Ar-*H*), 6.08 (1H, tdd, *J* = 56.9, 8.1, 2.7, C*H*F_2), 5.51 (1H, s, C*H*C(CH_3)$_3$), 4.03 (1H, ddd, *J* =11.9, 3.4, 2.1, C*H*C$H_A$$H_B$), 3.19 (3H, s, PhNC$H_3$), 2.92 (3H, s, NC$H_3$), 1.73 – 1.53 (1H, m, CHC$H_A$$H_B$), 0.97 (9H, s, C(C$H_3$)$_3$), 0.59 – 0.46 (1H, m, CHC$H_A$$H_B$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.39 (*C*=O)$_{amide}$, 163.38 (*C*=O)$_{urea}$, 145.29 (C_{Ar}), 130.33 (2xC_{Ar}H), 127.22 (2xC_{Ar}H), 127.19 (C_{Ar}H), 114.67 (dd, $^1J^{C\text{-}F}$ = 240.6, 238.5, *C*HF_2), 82.71 (*C*HC(CH_3)$_3$), 58.40 (dd, $^3J^{C\text{-}F}$ = 11.5, 3.1, *C*HCH_2), 41.47 (PhN*C*H_3), 36.90 (*C*(CH_3)$_3$), 36.81 (t, $^2J^{C\text{-}F}$ = 22.7, CH*C*H_2), 31.68 (N*C*H_3), 26.86 (C(*C*H_3)$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −114.66 to −115.76 (1F, m), δ_F −119.26 (1F, dddd, *J* = 287.8, 57.0, 30.4, 10.4); **IR (vmax/cm^{-1}) (neat)**: 2969, 2933 (alkyl C-H), 1704, 1663 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{18}H_{25}F_2N_3O_2Na$ $[M+Na]^+$ 376.1807, found 376.1808.

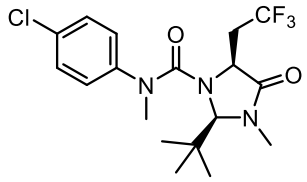
(2*R*,5*S*)-2-(*tert*-Butyl)-5-(2,2-difluoroethyl)-*N*,3-dimethyl-4-oxo-*N*-(4-(trifluoromethyl) phenyl)imidazolidine-1-carboxamide (427cf)



Following general **procedure 12**: vinyl urea **400c** (36.9 mg, 0.10 mmol), caesium carbonate (48.9 mg, 0.15 mmol), 4CzIPN (3.9 mg, 5 x 10^{-3} mmol) and CHF_2SO_2Na (27.6 mg, 0.20 mmol, 2.00 eq.) in anhydrous CH_3CN (1.00 mL). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 70:30) to afford the title compound (^{19}F NMR yield: 67%) as yellow oil. **R*f*** (7:3 Pet.Ether:EtOAc) 0.17; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.70 (2H, d, *J* = 8.0, Ar-*H*), 7.28 (2H, d, *J* = 8.0, Ar-*H*), 6.10 (1H, tdd, *J* = 57.2, 8.2, 2.5, C*H*F_2), 5.46 (1H, s,

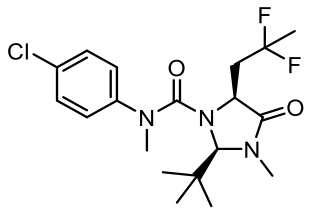
C*H*C(C*H*$_3$)$_3$), 4.05 (1H, dt, *J* =11.5, 2.5, C*H*CH$_A$H$_B$), 3.21 (3H, s, PhNC*H*$_3$), 2.93 (3H, s, NC*H*$_3$), 1.75 (1H, dddt, *J* = 26.4, 13.9, 4.8, 2.5, CHC*H*$_A$H$_B$), 0.98 (9H, s, C(C*H*$_3$)$_3$), 0.72 – 0.58 (1H, m, CHCH$_A$*H*$_B$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.04 (*C*=O)$_{amide}$, 163.00 (*C*=O)$_{urea}$, 148.56 (*C*$_{Ar}$), 129.10 (q, $^2J^{C\text{-}F}$ = 33.2, *C*$_{Ar}$), 127.43 (q, $^3J^{C\text{-}F}$ = 3.7, 2x*C*$_{Ar}$H), 126.86 (2x*C*$_{Ar}$H), 123.75 (q, $^1J^{C\text{-}F}$ = 272.1, *C*F$_3$), 114.41 (t, $^1J^{C\text{-}F}$ = 239.8, *C*HF$_2$), 82.88 (*C*HC(CH$_3$)$_3$), 58.13 (dd, $^3J^{C\text{-}F}$ = 11.6, 3.1, *C*HCH$_2$), 41.14 (PhN*C*H$_3$), 36.98 (*C*(CH$_3$)$_3$), 37.01 (t, $^2J^{C\text{-}F}$ = 22.3, CH*C*H$_2$), 31.70 (NCH$_3$), 26.87 (C(*C*H$_3$)$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ$_F$ −62.56 (3F, s), −114.83 to −115.85 (1F, m), −119.45 (1F, dddd, *J* = 288.5, 57.2, 30.6, 10.5); **IR (vmax/cm^{-1}) (neat)**: 2964, 2933 (alkyl C-H), 1704, 1671 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{19}H_{24}F_5N_3O_2Na$ $[M+Na]^+$ 444.168089, found 444.168662.

(2*R*,5*S*)-2-(*tert*-Butyl)-*N*-(4-chlorophenyl)-*N*,3-dimethyl-4-oxo-5-(2,2,2-trifluoroethyl) imidazolidine-1-carboxamide (moa427da)



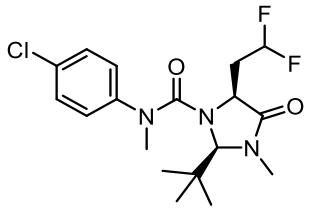
Following general **procedure 12**: vinyl urea **400d** (33.6 mg, 0.10 mmol), caesium carbonate (48.9 mg, 0.15 mmol), 4CzIPN (3.90 mg, 5 x 10^{-3} mmol) and CF_3SO_2Na (31.2 mg, 0.20 mmol, 2.00 eq.) in anhydrous CH_3CN (1.00 mL). The crude product was purified by flash column chromatography (SiO_2; Diethyl ether:Acetone 100:0 to Diethyl ether:Acetone 99:1) to afford the title compound (22.7 mg, 56%) as a yellow oil. **R*f*** (9.9:0.1 Diethyl ether:Acetone) 0.35; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40 (2H, d, *J* = 8.7, Ar-*H*), 7.09 (2H, d, *J* =8.7, Ar-*H*), 5.33 (1H, s, C*H*C(C*H*$_3$)$_3$), 4.19 (1H, dd, *J* =10.9, 2.6, C*H*CH$_A$H$_B$), 3.16 (3H, s, PhNC*H*$_3$), 2.92 (3H, s, NC*H*$_3$), 2.22 – 2.11 (1H, m, CHC*H*$_A$H$_B$), 1.27 – 1.18 (1H, m, CHCH$_A$*H*$_B$), 0.96 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 169.72 (*C*=O)$_{amide}$, 162.76 (*C*=O)$_{urea}$, 143.88 (*C*$_{Ar}$), 132.92 (*C*$_{Ar}$), 130.53 (2x*C*$_{Ar}$H), 127.72 (2x*C*$_{Ar}$H), 124.73 (q, $^1J^{C\text{-}F}$ = 277.8, *C*F$_3$), 82.51 (*C*HC(CH$_3$)$_3$), 57.02 (q, $^3J^{C\text{-}F}$ = 3.3, *C*HCH$_2$), 41.29 (PhN*C*H$_3$), 37.43 (q, $^2J^{C\text{-}F}$ = 29.3, CH*C*H$_2$), 36.93 (*C*(CH$_3$)$_3$), 31.90 (NCH$_3$), 26.85 (C(*C*H$_3$)$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ$_F$ −60.94 (3F, dd, *J* =11.7, 9.2); **IR (vmax/cm^{-1}) (neat)**: 2971, 2929 (alkyl C-H), 1713, 1661 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{18}H_{23}ClF_3N_3O_2Na$ $[M+Na]^+$ 428.1323, found 428.1344.

(2*R*,5*S*)-2-(*tert*-Butyl)-*N*-(4-chlorophenyl)-5-(2,2-difluoropropyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide (427de)



Following general **procedure 12**: vinyl urea **400d** (33.6 mg, 0.10 mmol), caesium carbonate (48.9 mg, 0.15 mmol), 4CzIPN (3.90 mg, 5 x 10^{-3} mmol) and $C_2H_3F_2SO_2Na$ (30.4 mg, 0.20 mmol, 2.00 eq.) in anhydrous CH_3CN (1.00 mL). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (^{19}F NMR yield: 67%) as a yellow oil. **R*f*** (6:4 Pet.Ether:EtOAc) 0.38; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37 (2H, d, *J* =8.7, Ar-*H*), 7.07 (2H, d, *J* =8.7, Ar-*H*), 5.25 (1H, s, C*H*C(C*H*$_3$)$_3$), 4.20 (1H, dd, *J* =10.7, 2.9, C*H*CH$_A$H$_B$), 3.16 (3H, s, PhNC*H*$_3$), 2.90 (3H, s, NC*H*$_3$), 2.06 – 1.90 (1H, m, CHC*H*$_A$H$_B$), 1.59 (3H, t, *J* =18.9, CF$_2$C*H*$_3$), 1.39 – 1.24 (1H, m, CHCH$_A$*H*$_B$), 0.97 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.02 (*C*=O)$_{amide}$, 163.01 (*C*=O)$_{urea}$, 144.14 (*C*$_{Ar}$), 132.21 (*C*$_{Ar}$), 130.23 (2x*C*$_{Ar}$H), 127.37 (2x*C*$_{Ar}$H), 122.21 (t, $^1J^{C\text{-}F}$ = 240.8, *C*F$_2$), 82.37 (*C*HC(CH$_3$)$_3$), 57.76 (dd, $^3J^{C\text{-}F}$ = 7.5, 3.7, *C*HCH$_2$), 41.57 (dd, $^2J^{C\text{-}F}$ = 27.4, 25.3, CH*C*H$_2$), 41.19 (PhN*C*H$_3$), 36.94 (*C*(CH$_3$)$_3$), 31.87 (N*C*H$_3$), 26.94 (C(*C*H$_3$)$_3$), 24.59 (t, $^1J^{C\text{-}F}$ = 27.2, CF$_2$*C*H$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −82.47 to −83.44 (1F, m), δ_F −88.16 (1F, ddq, *J* = 244.6, 35.3, 18.0); **IR (vmax/cm^{-1}) (neat)**: 2976, 2934 (alkyl C-H), 1707, 1662 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{19}H_{26}ClF_2N_3O_2Na$ $[M+Na]^+$ 424.1574, found 424.1578.

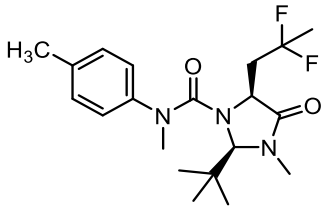
(2*R*,5*S*)-2-(*tert*-Butyl)-*N*-(4-chlorophenyl)-5-(2,2-difluoroethyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide (427df)



Following general **procedure 12**: vinyl urea **400d** (33.6 mg, 0.10 mmol), caesium carbonate (48.9 mg, 0.15 mmol), 4CzIPN (3.90 mg, 5 x 10^{-3} mmol) and CHF_2SO_2Na (27.6 mg, 0.20 mmol, 2.00 eq.) in anhydrous CH_3CN (1.00 mL). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (34.1 mg, 88%) as a yellow solid; **mp**: 87 – 89 °C; **R*f*** (6:4 Pet.Ether:EtOAc) 0.35; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35 (2H, d, *J* =8.7, Ar-*H*), 7.04 (2H, d, *J* =8.7, Ar-*H*), 6.07 (1H, tdd, *J* = 56.9, 8.2, 2.5, C*H*F$_2$), 5.45 (1H, s, C*H*C(C*H*$_3$)$_3$), 3.96 (1H, dt, *J* =11.8, 2.6, C*H*CH$_A$H$_B$), 3.09

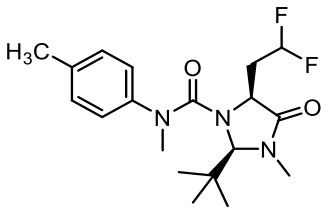
(3H, s, PhNCH_3), 2.87 (3H, s, NCH_3), 1.75 – 1.56 (1H, m, CHCH_AH$_B$), 0.90 (9H, s, C(CH_3)$_3$), 0.68 – 0.54 (1H, m, CHCH$_A$$H_B$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.21 (*C*=O)$_{amide}$, 163.26 (*C*=O)$_{urea}$, 143.87 (C_{Ar}), 132.90 (C_{Ar}), 130.45 (2xC_{Ar}H), 128.43 (2xC_{Ar}H), 114.58 (dd, $^1J^{C\text{-}F}$ = 240.0 *C*HF$_2$), 82.76 (*C*HC(CH$_3$)$_3$), 58.26 (dd, $^3J^{C\text{-}F}$ = 11.7, 2.9, *C*HCH$_2$), 41.49 (PhNCH$_3$), 36.91 (*C*(CH$_3$)$_3$), 37.00 (dd, $^2J^{C\text{-}F}$ = 23.0, 21.4, CH*C*H$_2$), 31.70 (N*C*H$_3$), 26.86 (C(*C*H$_3$)$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −114.57 to −115.63 (1F, m), δ_F −119.44 (1F, dddd, *J* = 288.3, 57.2, 30.9, 10.5); **IR (vmax/cm^{-1}) (neat)**: 2974, 2929 (alkyl C-H), 1702, 1663 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{18}H_{24}ClF_2N_3O_2Na$ $[M+Na]^+$ 410.1417, found 410.1405.

(2*R*,5*S*)-2-(*tert*-Butyl)-5-(2,2-difluoropropyl)-*N*,3-dimethyl-4-oxo-*N*-(*p*-tolyl)imidazolidine-1-carboxamide (427ee)



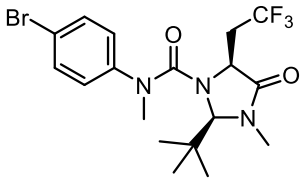
Following general **procedure 12**: vinyl urea **400e** (126 mg, 0.40 mmol), caesium carbonate (195 mg, 0.60 mmol), 4CzIPN (15.8 mg, 0.02 mmol) and $C_2H_3F_2SO_2Na$ (122 mg, 0.80 mmol, 2.00 eq.) in anhydrous CH_3CN (2.00 mL). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 40:60) to afford the title compound (87.0 mg, 57%) as a yellow oil. **R*f*** (4:6:Pet.Ether:Diethyl ether) 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.20 (2H, d, *J* =8.3, Ar-*H*), 7.02 (2H, d, *J* =8.3, Ar-*H*), 5.26 (1H, s, C*H*C(CH_3)$_3$), 4.18 (1H, dd, *J* =10.9, 2.8, C*H*CH$_A$H$_B$), 3.16 (3H, s, PhNCH_3), 2.88 (3H, s, NCH_3), 2.35 (CH_3), 1.98 – 1.81 (1H, m, CHCH_AH$_B$), 1.56 (3H, t, *J* =18.9, CF$_2$CH_3), 1.22 – 1.07 (1H, m, CHCH$_A$$H_B$), 0.96 (9H, s, C(C$H_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.16 (*C*=O)$_{amide}$, 163.21 (*C*=O)$_{urea}$, 142.97 (C_{Ar}), 136.82 (C_{Ar}), 130.73 (2xC_{Ar}H), 126.28 (2xC_{Ar}H), 122.31 (t, $^1J^{C\text{-}F}$ = 240.2, *C*F$_2$), 82.27 (*C*HC(CH$_3$)$_3$), 58.00 (dd, $^3J^{C\text{-}F}$ = 6.4, 4.9, *C*HCH$_2$), 41.31 (PhNCH$_3$), 41.20 (t, $^2J^{C\text{-}F}$ = 26.5, CH*C*H$_2$), 36.87 (*C*(CH$_3$)$_3$), 31.81 (NCH$_3$), 26.97 (C(*C*H$_3$)$_3$), 24.27 (t, $^1J^{C\text{-}F}$ = 27.2, CF$_2$*C*H$_3$), 21.03 (CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −82.50 to −83.55 (1F, m), δ_F −85.94 to −86.99 (1F, m); **IR (vmax/cm^{-1}) (neat)**: 2969, 2931 (alkyl C-H), 1710 (C=O), 1660 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{20}H_{29}F_2N_3O_2Na$ $[M+Na]^+$ 404.212004, found 404.212133.

(2*R*,5*S*)-2-(*tert*-Butyl)-5-(2,2-difluoroethyl)-*N*,3-dimethyl-4-oxo-*N*-(*p*-tolyl)imidazolidine-1-carboxamide (427ef)



Following general **procedure 12**: vinyl urea **400e** (126 mg, 0.40 mmol), caesium carbonate (195 mg, 0.60 mmol), 4CzIPN (15.8 mg, 0.02 mmol) and CHF_2SO_2Na (110 mg, 0.80 mmol, 2.00 eq.) in anhydrous CH_3CN (2.00 mL). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (111 mg, 75%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.22 (2H, d, *J* =8.6, Ar-*H*), 7.04 (2H, d, *J* =8.6, Ar-*H*), 6.06 (1H, tdd, *J* = 56.7, 8.0, 2.7, C*H*F_2), 5.53 (1H, s, C*H*C(C*H*$_3$)$_3$), 4.00 (1H, ddd, *J* =11.9, 3.3, 1.9, C*H*CH_AH_B), 3.15 (3H, s, PhNC*H*$_3$), 2.92 (3H, s, NC*H*$_3$), 2.35 (C*H*$_3$), 1.70 – 1.51 (1H, m, CHC*H*$_A$$H_B$), 0.96 (9H, s, C(C*H*$_3$)$_3$), 0.58 – 0.45 (1H, m, $CHCH_AH_B$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.43 (*C*=O)$_{amide}$, 163.43 (*C*=O)$_{urea}$, 142.57 (*C*$_{Ar}$), 137.32 (*C*$_{Ar}$), 130.84 (2x*C*$_{Ar}$H), 127.09 (2x*C*$_{Ar}$H), 114.70 (dd, $^1J^{C\text{-}F}$ = 240.0 *C*HF_2), 82.64 (*C*HC(CH$_3$)$_3$), 58.42 (dd, $^3J^{C\text{-}F}$ = 11.5, 3.3, *C*HCH_2), 41.48 (PhN*C*H$_3$), 36.86 (*C*(CH$_3$)$_3$), 36.77 (t, $^2J^{C\text{-}F}$ = 22.3, CH*C*H_2), 31.64 (N*C*H$_3$), 26.84 (C(*C*H$_3$)$_3$), 21.02 (*C*H$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −114.43 to −115.70 (1F, m), δ_F −119.08 (1F, dddd, *J* = 288.7, 56.7, 30.2, 10.2); **IR (vmax/cm^{-1}) (neat)**: 2965, 2926 (alkyl C-H), 1699, 1657 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{19}H_{27}F_2N_3O_2Na$ $[M+Na]^+$ 390.196354, found 390.194509.

(2*R*,5*S*)-*N*-(4-Bromophenyl)-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxo-5-(2,2,2-trifluoroethyl) imidazolidine-1-carboxamide (427ga)

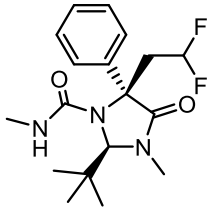


Following general **procedure 12**: vinyl urea **400g** (202 mg, 0.54 mmol), caesium carbonate (259 mg, 0.81 mmol), 4CzIPN (21.3 mg, 0.027 mmol) and CF_3SO_2Na (248 mg, 1.59 mmol, 3.00 eq.) in anhydrous CH_3CN (5.40 mL). The crude product was purified by flash column chromatography (SiO_2; Diethyl ether:Acetone 100:0 to Diethyl ether:Acetone 99:1) to afford the title compound (158 mg, 65%) as a yellow oil. **R*f*** (9.9:0.1 Diethyl ether:Acetone) 0.43; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.56 (2H, d, *J* =8.7, Ar-*H*), 7.03 (2H, d, *J* =8.7, Ar-*H*), 5.34 (1H, s, C*H*C(C*H*$_3$)$_3$), 4.19 (1H, dd, *J* =10.8, 2.6, C*H*CH_AH_B), 3.17 (3H, s, PhNC*H*$_3$), 2.93 (3H, s, NC*H*$_3$), 2.22 – 2.11 (1H, m, CHC*H*$_A$$H_B$), 1.29 – 1.16 (1H, m, $CHCH_AH_B$), 0.96 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$):

δ 169.72 (*C*=O)$_{amide}$, 162.71 (*C*=O)$_{urea}$, 144.41 (*C*$_{Ar}$), 133.54 (2x*C*$_{Ar}$H), 128.02 (2x*C*$_{Ar}$H), 124.74 (q, $^{1}J^{C\text{-}F}$ = 277.6, *C*F$_3$), 120.58 (*C*$_{Ar}$), 82.53 (*C*HC(CH$_3$)$_3$), 57.02 (q, $^{3}J^{C\text{-}F}$ = 3.3, *C*HCH$_2$), 41.22 (PhN*C*H$_3$), 37.44 (q, $^{2}J^{C\text{-}F}$ = 29.2, CH*C*H$_2$), 36.96 (*C*(CH$_3$)$_3$), 31.92 (N*C*H$_3$), 26.87 (C(*C*H$_3$)$_3$); ^{19}F NMR (377 MHz, CDCl$_3$) δ_F −60.74 to −60.91(3F, m); **IR (vmax/cm^{-1}) (neat)**: 2971, 2935 (alkyl C-H), 1715, 1662 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{18}H_{23}BrF_3N_3O_2Na$ [M+Na]$^+$ 472.0818, found 472.0807.

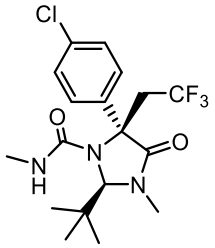
4.3.2.3 Base-mediated Aryl Migration of Conjugate Addition Products

(2*R*,5*R*)-2-(*tert*-Butyl)-5-(2,2-difluoroethyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide (405af)



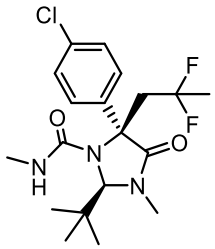
Following general **procedure 13**: LiHMDS (1.0 M/THF, 70 μL, 0.07 mmol) and conjugate addition product **427af** (16.2 mg, 0.046 mmol) in anhydrous THF (0.50 mL). The reaction was complete after 1 hour (monitored by TLC). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (9.9 mg, 61%) as a yellow oil. **R*f*** (6:4 Pet.Ether:EtOAc) 0.35; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 7.39 – 7.33 (2H, m, Ar-*H*), 7.33 – 7.27 (1H, m, Ar-*H*), 7.20 – 7.16 (2H, m, Ar-*H*), 6.31 (1H, tdd, *J* = 55.0, 6.5, 2.5, C*H*F$_2$), 5.64 (1H, s, C*H*C(CH$_3$)$_3$), 4.20 (1H, br. s, N*H*CH$_3$), 3.09 (3H, s, NC*H$_3$*), 3.08 – 2.87 (2H, m, NCC*H$_2$*), 2.35 (3H, d, *J* =4.7, NHC*H$_3$*), 1.08 (9H, s, C(C*H$_3$*)$_3$); **^{13}C NMR** (126 MHz, CDCl$_3$): δ 171.28 (*C*=O)$_{amide}$, 158.87 (*C*=O)$_{urea}$, 139.53 (*C*$_{Ar}$), 129.30 (2x*C*$_{Ar}$H), 128.81 (*C*$_{Ar}$H), 125.56 (2x*C*$_{Ar}$H), 115.67 (t, $^{1}J^{C\text{-}F}$ = 238.7, *C*HF$_2$), 81.31 (*C*HC(CH$_3$)$_3$), 66.72 (dd, $^{3}J^{C\text{-}F}$ = 9.6, 2.4, N*C*(Ar)), 40.60 (t, $^{2}J^{C\text{-}F}$ = 22.4, NC*C*H$_2$), 38.22 (*C*(CH$_3$)$_3$), 32.17 (N*C*H$_3$), 27.23 (NH*C*H$_3$), 26.93 (C(*C*H$_3$)$_3$); ^{19}F NMR (377 MHz, CDCl$_3$) δ_F −109.98 to −111.09 (1F, m), δ_F −111.62 to −112.68 (1F, m); **IR (vmax/cm^{-1}) (neat)**: 3396 (NH), 2971, 2906 (alkyl C-H), 1704, 1666 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{18}H_{25}F_2N_3O_2Na$ [M+Na]$^+$ 376.1807, found 376.1814.

(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-chlorophenyl)-*N*,3-dimethyl-4-oxo-5-(2,2,2-trifluoroethyl) imidazolidine-1-carboxamide (405da)



Following general **procedure 13**: LiHMDS (1.0 M/THF, 160 μL, 0.15 mmol) and conjugate addition product **427da** (42.0 mg, 0.104 mmol) in anhydrous THF (1.00 mL). The reaction was complete after 2 hours (monitored by TLC). The crude product was purified by flash column chromatography (SiO_2; Pentane:Diethyl ether 100:0 to Pentane:Diethyl ether 30:70) to afford the title compound (22.8 mg, 54%) as a yellow oil. **R*f*** (3:7 Pentane:Diethyl ether) 0.28; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33 (2H, d, *J* =8.8, Ar-*H*), 7.10 (2H, d, *J* =8.8, Ar-*H*), 5.68 (1H, s, C*H*C(C*H*$_3$)$_3$), 4.33 (1H, br. s, N*H*CH$_3$), 3.36 – 3.25 (1H, m, C*H*$_A$H$_B$), 3.19 – 3.08 (1H, m, CH$_A$*H*$_B$), 3.07 (3H, s, NC*H*$_3$), 2.45 (3H, d, *J* =4.7, NHC*H*$_3$), 1.07 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.35 (*C*=O)$_{amide}$, 158.85 (*C*=O)$_{urea}$, 137.35 (*C*$_{Ar}$), 134.96 (*C*$_{Ar}$), 129.34 (2x*C*$_{Ar}$H), 127.02 (2x*C*$_{Ar}$H), 125.81 (q, $^1J^{C\text{-}F}$ = 277.7, *C*F$_3$), 81.50 (*C*HC(CH$_3$)$_3$), 66.54 (q, $^3J^{C\text{-}F}$ = 2.4, N*C*(Ar)), 38.30 (q, $^2J^{C\text{-}F}$ = 27.5, NC*C*H$_2$), 38.01 (*C*(CH$_3$)$_3$), 32.11 (N*C*H$_3$), 27.38 (NH*C*H$_3$), 26.82 (C(*C*H$_3$)$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −58.54 (3F, t, *J* = 10.7); **IR (vmax/cm^{-1}) (neat)**: 3423 (NH), 2969, 2907 (alkyl C-H), 1761, 1676 (C=O); **HRMS** (ESI): *m/z* calcd for [$C_{18}H_{23}ClF_3N_3O_2Na$ [M+Na]$^+$ 428.1323, found 428.1332.

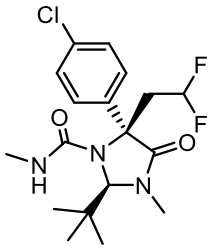
(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-chlorophenyl)-5-(2,2-difluoropropyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide (405de)



Following general **procedure 13**: LiHMDS (1.0 M/THF, 80 μL, 0.08 mmol) and conjugate addition product **427de** (22.6 mg, 0.056 mmol) in anhydrous THF (0.60 mL). The reaction was complete after 1 hour (monitored by TLC). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (11.2 mg, 50%) as a white solid. **R*f*** (6:4 Pet.Ether:EtOAc) 0.25; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29 (2H, d, *J* =8.8, Ar-*H*), 7.11 (2H, d, *J* =8.8, Ar-*H*), 5.78 (1H, s, C*H*C(C*H*$_3$)$_3$), 4.79 (1H, br. s, N*H*CH$_3$), 3.24

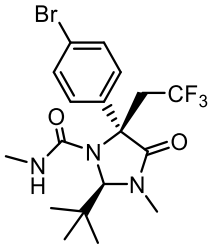
(1H, ddd, *J* =30.1, 16.5, 2.9, CH_AH$_B$), 3.04 (3H, s, NCH_3), 2.65 (1H, , ddd, *J* =30.1, 16.5, 8.3, CH$_A$$H_B$), 2.40 (3H, d, *J* =4.6, NHCH_3), 1.84 (3H, t, *J* =18.9, CH_3F$_2$), 1.07 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.76 (*C*=O)$_{amide}$, 158.79 (*C*=O)$_{urea}$, 138.10 (*C*$_{Ar}$), 134.30 (*C*$_{Ar}$), 128.97 (2x*C*$_{Ar}$H), 127.49 (2x*C*$_{Ar}$H), 124.58 (dd, $^1J^{C\text{-}F}$ = 242.8, 237.2, *C*F$_2$), 81.40 (*C*HC(CH$_3$)$_3$), 67.58 (N*C*(Ar)), 40.94 (t, $^2J^{C\text{-}F}$ = 22.8, NC*C*H$_2$), 38.21 (*C*(CH$_3$)$_3$), 32.08 (N*C*H$_3$), 27.15 (NH*C*H$_3$), 26.83 (C(*C*H$_3$)$_3$), 26.08 (t, $^2J^{C\text{-}F}$ = 27.3, CH_3F$_2$); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −84.42 to −85.15 (1F, m), δ_F −89.58 to −90.20 (1F, m); **IR (vmax/cm^{-1}) (neat)**: 3660 (NH), 2977, 2903 (alkyl C-H), 1701 (C=O), 1662 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{19}H_{26}ClF_2N_3O_2Na$ $[M+Na]^+$ 424.1574, found 424.1569.

(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-chlorophenyl)-5-(2,2-difluoroethyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide (405df)



Following general **procedure 13**: LiHMDS (1.0 M/THF, 120 μL, 0.12 mmol) and conjugate addition product **427df** (30.0 mg, 0.08 mmol) in anhydrous THF (0.80 mL). The reaction was complete after 2 hours (monitored by TLC). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (16.3 mg, 53%) as a yellow oil. **R*f*** (6:4 Pet.Ether:EtOAc) 0.42; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33 (2H, d, *J* =8.8, Ar-*H*), 7.11 (2H, d, *J* =8.8, Ar-*H*), 6.27 (1H, tdd, *J* = 55.0, 6.1, 3.0, C*H*F$_2$), 5.59 (1H, s, C*H*C(CH_3)$_3$), 4.32 (1H, br. s, N*H*CH$_3$), 3.08 (3H, s, NCH_3), 3.03 – 2.86 (2H, m, NCCH_2), 2.42 (3H, d, *J* =4.6, NHCH_3), 1.06 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.83 (*C*=O)$_{amide}$, 158.73 (*C*=O)$_{urea}$, 138.18 (*C*$_{Ar}$), 134.83 (*C*$_{Ar}$), 129.38 (2x*C*$_{Ar}$H), 127.03 (2x*C*$_{Ar}$H), 115.53 (t, $^1J^{C\text{-}F}$ = 239.4, *C*HF$_2$), 81.25 (*C*HC(CH$_3$)$_3$), 66.52 (dd, $^3J^{C\text{-}F}$ = 9.4, 2.6, N*C*(Ar)), 40.58 (t, $^2J^{C\text{-}F}$ = 22.4, NC*C*H$_2$), 38.21 (*C*(CH$_3$)$_3$), 32.18 (N*C*H$_3$), 27.31 (NH*C*H$_3$), 26.85 (C(*C*H$_3$)$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −110.15 to −111.26 (1F, m), δ_F −112.11 (1F, ddt, *J* = 287.7, 55.0, 12.2); **IR (vmax/cm^{-1}) (neat)**: 3396 (NH), 2973, 2906 (alkyl C-H), 1698 (C=O), 1662 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{18}H_{24}ClF_2N_3O_2Na$ $[M+Na]^+$ 410.1417, found 410.1411.

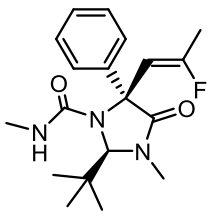
(2*R*,5*R*)-5-(4-Bromophenyl)-2-(*tert*-butyl)-*N*,3-dimethyl-4-oxo-5-(2,2,2-trifluoroethyl) imidazolidine-1-carboxamide (405ga)



Following general **procedure 13**: LiHMDS (1.0 M/THF, 0.82 mL, 0.82 mmol, 2.5 eq.) and conjugate addition product **427ga** (147 mg, 0.33 mmol) in anhydrous THF (3.30 mL). The reaction was complete after 3 hours (monitored by TLC). The crude product was purified by flash column chromatography (SiO_2; Pentane:Diethyl ether 100:0 to Pentane:Diethyl ether 40:60) to afford the title compound (78.4 mg, 53%) as a white foam. **R*f*** (4:6 Pentane:Diethyl ether) 0.35; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.48 (2H, d, *J* =8.7, Ar-*H*), 7.04 (2H, d, *J* =8.7, Ar-*H*), 5.68 (1H, s, C*H*C(C*H*$_3$)$_3$), 4.33 (1H, br. s, N*H*CH$_3$), 3.36 – 3.24 (1H, m, C*H*$_A$H$_B$), 3.19 – 3.08 (1H, m, CH$_A$*H*$_B$), 3.07 (3H, s, NC*H*$_3$), 2.45 (3H, d, *J* =4.6, NHC*H*$_3$), 1.07 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.28 (*C*=O)$_{amide}$, 158.83 (*C*=O)$_{urea}$, 137.90 (*C*$_{Ar}$), 132.31 (2x*C*$_{Ar}$H), 127.30 (2x*C*$_{Ar}$H), 123.16 (*C*$_{Ar}$), 125.66 (q, $^1J^{C\text{-}F}$ = 278.0, *C*F$_3$), 81.52 (*C*HC(CH$_3$)$_3$), 66.63 (q, $^3J^{C\text{-}F}$ = 2.1, N*C*(Ar)), 38.26 (q, $^2J^{C\text{-}F}$ = 27.2, NC*C*H$_2$), 38.02 (*C*(CH$_3$)$_3$), 32.12 (N*C*H$_3$), 27.40 (NH*C*H$_3$), 26.83 (C(*C*H$_3$)$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ$_F$ −58.53 (3F, t, *J* = 10.7); **IR (vmax/cm^{-1}) (neat)**: 3391 (NH), 2964, 2920 (alkyl C-H), 1708 (C=O), 1678 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{18}H_{23}BrF_3N_3O_2Na$ $[M+Na]^+$ 472.0818, found 472.0814.

4.3.2.4 Base-mediated Aryl Migration and Subsequent 1,2-Elimination of Conjugate Addition Products

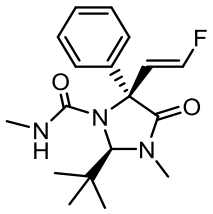
(2*R*,5*R*)-2-(*tert*-Butyl)-5-((*Z*)-2-fluoroprop-1-en-1-yl)-*N*,3-dimethyl-4-oxo-5-phenyl imidazolidine-1-carboxamide (433ae)



Following general **procedure 14**: KHMDS (1.0 M/THF, 100 μL, 0.09 mmol, 1.50 eq.) and conjugate addition product **427ae** (23.6 mg, 0.06 mmol) in anhydrous THF (0.60 mL). The reaction was complete after 2 hours (monitored by TLC). The crude product was purified by flash column

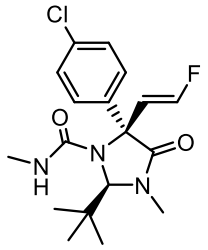
chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (5.4 mg, 26%) as an orange oil. **R*f*** (6:4 Pet.Ether:EtOAc) 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36 – 7.30 (2H, m, Ar-*H*), 7.28 – 7.23 (1H, m, Ar-*H*), 7.20 – 7.15 (2H, m, Ar-*H*), 5.77 (1H, s, C*H*C(C*H*$_3$)$_3$), 5.29 (1H, dq, *J* =39.2, 0.9, C*H*=CFCH$_3$), 4.16 (1H, br. q, *J* = 4.6, N*H*), 3.09 (3H, s, NC*H*$_3$), 2.24 (3H, d, *J* = 4.6, NHC*H*$_3$), 2.12 (3H, dd, *J* =17.1, 0.9, CH=CFC*H*$_3$), 1.02 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.48 (*C*=O)$_{amide}$, 158.44 (*C*=O)$_{urea}$, 158.01 (d, $^1J^{C\text{-}F}$ = 260.4, CH=*C*FCH$_3$), 140.70 (d, $^4J^{C\text{-}F}$ = 2.1, C_{Ar}), 129.09 (2xC_{Ar}H), 128.48 (C_{Ar}H), 125.98 (2xC_{Ar}H), 105.14 (d, $^2J^{C\text{-}F}$ = 6.0, *C*H=CFCH$_3$), 80.69 (*C*HC(CH$_3$)$_3$), 69.20 (N*C*Ph), 38.57 (*C*(CH$_3$)$_3$), 32.13 (N*C*H$_3$), 26.91 (NH*C*H$_3$), 26.27 (C(*C*H$_3$)$_3$), 19.30 (d, $^2J^{C\text{-}F}$ = 29.6, CH=CF*C*H$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −94.42 (1F, dqd, *J* = 34.2, 17.1, 6.1); **IR (vmax/cm^{-1}) (neat)**: 3419 (NH), 3061 (alkene C-H), 2959, 2922 (alkyl C-H), 1704, 1667 (C=O); **MS** (ESI): *m/z* calcd for $C_{19}H_{27}FN_3O_2$ $[M+H]^+$, found 348.21.

(2*R*,5*R*)-2-(*tert*-Butyl)-5-((*E*)-2-fluorovinyl)-*N*,3-dimethyl-4-oxo-5-phenylimidazolidine-1-carboxamide (433af)



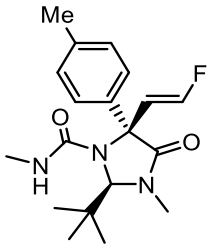
Following general **procedure 14**: KHMDS (1.0 M/THF, 140 μL, 0.14 mmol, 1.50 eq.) and conjugate addition product **427af** (32.2 mg, 0.091 mmol) in anhydrous THF (0.91 mL). The reaction was complete after 2 hours (monitored by TLC). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 40:60) to afford the title compound (16.5 mg, 54%) as a yellow oil. **R*f*** (6:4 Pet.Ether:EtOAc) 0.18; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.40 – 7.33 (2H, m, Ar-*H*), 7.32 – 7.27 (1H, m, Ar-*H*), 7.20 – 7.17 (2H, m, Ar-*H*), 7.05 (1H, dd, *J* = 82.5, 11.2, CH=C*H*F), 6.21 (1H, dd, *J* = 19.3, 11.2, C*H*=CHF), 5.68 (1H, s, C*H*C(C*H*$_3$)$_3$), 3.88 (1H, br. q, *J* = 4.8, N*H*), 3.08 (3H, s, NC*H*$_3$), 2.25 (3H, d, *J* = 4.8, NHC*H*$_3$), 1.06 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.37 (d, $^4J^{C\text{-}F}$ = 2.2, *C*=O)$_{amide}$, 158.01 (*C*=O)$_{urea}$, 153.19 (d, $^1J^{C\text{-}F}$ = 261.7, CH=*C*HF), 140.92 (d, $^4J^{C\text{-}F}$ = 2.4, C_{Ar}), 129.50 (2xC_{Ar}H), 128.88 (C_{Ar}H), 125.66 (2xC_{Ar}H), 112.15 (d, $^2J^{C\text{-}F}$ = 14.9, *C*H=CHF), 80.65 (*C*HC(CH$_3$)$_3$), 67.40 (d, $^3J^{C\text{-}F}$ = 10.1, N*C*Ph), 38.66 (*C*(CH$_3$)$_3$), 32.12 (N*C*H$_3$), 27.02 (NH*C*H$_3$), 26.75 (C(*C*H$_3$)$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −126.04 (1F, dd, *J* = 82.5, 19.3); **IR (vmax/cm^{-1}) (neat)**: 3408 (NH), 3065 (alkene C-H), 2969, 2909 (alkyl C-H), 1698, 1659 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{18}H_{24}FN_3O_2Na$ $[M+Na]^+$ 356.1745, found 356.1742.

(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-chlorophenyl)-5-((*E*)-2-fluorovinyl)-*N*,3-dimethyl-4-oxoimidazolidine-1-carboxamide (433df)



Following general **procedure 14**: KHMDS (1.0 M/THF, 270 μL, 0.27 mmol, 2.50 eq.) and conjugate addition product **427df** (42.1 mg, 0.108 mmol) in anhydrous THF (1.10 mL). The reaction was complete after 2.45 hours (monitored by TLC). The crude product was purified by flash column chromatography (SiO_2; Pentane:Diethyl ether 100:0 to Pentane:Diethyl ether 30:70) to afford the title compound (32.3 mg, 81%) as a yellow oil. **R*f*** (7:3 Pentane:Diethyl ether) 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34 (2H, d, *J* = 8.7, Ar-*H*), 7.13 (2H, *J* = 8.7, Ar-*H*), 7.06 (1H, dd, *J* = 82.1, 11.2, CH=C*H*F), 6.15 (1H, dd, *J* = 19.0, 11.2, C*H*=CHF), 5.66 (1H, s, C*H*C(C*H*$_3$)$_3$), 3.90 (1H, br. s, N*H*), 3.07 (3H, s, NC*H*$_3$), 2.34 (3H, d, *J* = 4.7, NHC*H*$_3$), 1.05 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 169.97 (d, $^4J^{C\text{-}F}$ = 2.1, *C*=O)$_{amide}$, 157.70 (*C*=O)$_{urea}$, 153.44 (d, $^1J^{C\text{-}F}$ = 262.7, CH=*C*HF), 139.50 (d, $^4J^{C\text{-}F}$ = 2.6, C_{Ar}), 134.95 (C_{Ar}), 129.63 (2xC_{Ar}H), 127.12 (2xC_{Ar}H), 111.86 (d, $^2J^{C\text{-}F}$ = 15.1, *C*H=CHF), 80.63 (*C*HC(CH$_3$)$_3$), 67.03 (d, $^3J^{C\text{-}F}$ = 10.2, N*C*Ph), 38.67 (*C*(CH$_3$)$_3$), 32.17 (N*C*H$_3$), 27.12 (NH*C*H$_3$), 26.72 (C(*C*H$_3$)$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −125.16 (1F, dd, *J* = 82.1, 19.0); **IR (vmax/cm^{-1}) (neat)**: 3403 (NH), 3103 (alkene C-H), 2971, 2932 (alkyl C-H), 1703, 1662 (C=O); **HRMS** (ESI): *m/z* calcd for $[C_{18}H_{23}ClFN_3O_2Na$ $[M+Na]^+$ 390.1355, found 390.1349.

(2*R*,5*R*)-2-(*tert*-Butyl)-5-((*E*)-2-fluorovinyl)-*N*,3-dimethyl-4-oxo-5-(*p*-tolyl)imidazolidine-1-carboxamide (433ef)

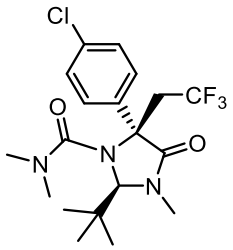


Following general **procedure 14**: KHMDS (1.0 M/THF, 400 μL, 0.37 mmol, 2.50 eq.) and conjugate addition product **427ef** (53.8 mg, 0.146 mmol) in anhydrous THF (1.50 mL). The reaction was complete after 2 hours (monitored by TLC). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (25.4 mg, 50%) as a yellow oil. **R*f*** (6:4 Pet.Ether:EtOAc) 0.24; **^{1}H NMR** (400 MHz,

$CDCl_3$): δ 7.16 (2H, d, *J* = 8.6, Ar-*H*), 7.06 (2H, *J* = 8.6, Ar-*H*), 7.04 (1H, dd, *J* = 82.7, 11.2, CH=C*H*F), 6.18 (1H, dd, *J* = 19.3, 11.2, C*H*=CHF), 5.66 (1H, s, C*H*C(CH_3)$_3$), 3.89 (1H, br. q, *J* = 4.8, N*H*), 3.07 (3H, s, NCH_3), 2.31 (CH_3), 2.28 (3H, d, *J* = 4.8, NHCH_3), 1.05 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.55 (d, $^4J^{C\text{-}F}$ = 2.2, *C*=O)$_{amide}$, 158.10 (*C*=O)$_{urea}$, 153.12 (d, $^1J^{C\text{-}F}$ = 261.4, CH=*C*HF), 138.82 (C_{Ar}), 137.89 (d, $^4J^{C\text{-}F}$ = 2.5, C_{Ar}), 130.20 (2xC_{Ar}H), 125.56 (2xC_{Ar}H), 112.19 (d, $^2J^{C\text{-}F}$ = 14.8, *C*H=CHF), 80.60 (*C*HC(CH_3)$_3$), 67.19 (d, $^3J^{C\text{-}F}$ = 10.2, N*C*Ph), 38.69 (*C*(CH_3)$_3$), 32.14 (N*C*H_3), 27.10 (NH*C*H_3), 26.78 (C(*C*H_3)$_3$), 21.17 (CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −126.26 (1F, dd, *J* = 82.7, 19.3); **IR (vmax/cm^{-1}) (neat)**: 3406 (NH), 3171 (alkene C-H), 2965, 2932 (alkyl C-H), 1703, 1662 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{19}H_{27}FN_3O_2$ $[M+H]^+$ 348.208182, found 348.208386.

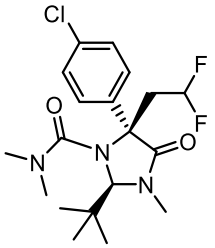
4.3.2.5 N-Methylation of aryl migration products

(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-chlorophenyl)-*N*,*N*,3-trimethyl-4-oxo-5-(2,2,2-trifluoroethyl) imidazolidine-1-carboxamide (437da)



Following general **procedure 15**: conjugate addition product **427da** (137 mg, 0.34 mmol) was dissolved in anhydrous THF (3.40 mL) at 0 °C. LiHMDS (1 M/THF, 0.51 mL, 0.51 mmol, 1.50 eq.) was added and the reaction stirred for 2 hours at 0 °C. An additional 1.50 eq. of LiHMDS (1 M/THF, 0.51 mL, 0.51 mmol) was added and the reaction stirred for 45 mins at 0 °C, after which MeI (110 μL, 1.69 mmol, 5.0 eq.) was added. The reaction was allowed to warm to room temperature and left to stir for 16 hours. The crude product was purified by flash column chromatography (SiO_2; Pentane:Diethyl ether 100:0 to Pentane:Diethyl ether 30:70) to afford the title compound (54.8 mg, 38%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28 (2H, d, *J* =8.3, Ar-*H*), 6.98 (2H, d, *J* =8.3, Ar-*H*), 5.42 (1H, s, C*H*C(CH_3)$_3$), 3.31 (2H, q, J = 10.1, NCCH_2), 3.21 (3H, s, NCH_3), 2.71 (6H, s, br., N(CH_3)$_2$), 1.01 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.42 (*C*=O)$_{amide}$, 163.22 (*C*=O)$_{urea}$, 136.16 (C_{Ar}), 134.83 (C_{Ar}), 128.46 (2xC_{Ar}H), 127.69 (2xC_{Ar}H), 125.17 (t, $^1J^{C\text{-}F}$ = 278.5, *C*F_3), 82.01 (*C*HC(CH_3)$_3$), 68.71 (N*C*(Ar)), 38.76 (q, $^2J^{C\text{-}F}$ = 28.5, NC*C*H_2), 38.23 (N(*C*H_3)$_2$), 36.68 (*C*(CH_3)$_3$), 31.73 (N*C*H_3), 26.49 (C(*C*H_3)$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −57.61 (3F, 10.1); **IR (vmax/cm^{-1}) (neat)**: 2967, 2928 (alkyl C-H), 1713 (C=O), 1667 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{19}H_{25}ClF_3N_3O_2Na$ $[M+Na]^+$ 442.1480, found 442.1485.

(2*R*,5*R*)-2-(*tert*-Butyl)-5-(4-chlorophenyl)-5-(2,2-difluoroethyl)-*N*,*N*,3-trimethyl-4-oxoimidazolidine-1-carboxamide (437df)

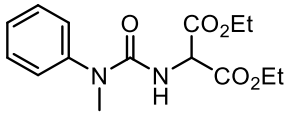


Following general **procedure 15**: conjugate addition product **427df** (160 mg, 0.41 mmol) was dissolved in anhydrous THF (4.10 mL) at 0 °C. LiHMDS (1 M/THF, 0.62 mL, 0.62 mmol, 1.50 eq.) was added and the reaction stirred for 4.5 hours at 0 °C. An additional 1.50 eq. of LiHMDS (1 M/THF, 0.62 mL, 0.62 mmol) was added and the reaction stirred for 45 mins at 0 °C, after which MeI (51 μL, 0.82 mmol, 2.00 eq.) was added. The reaction was allowed to warm to room temperature and left to stir for 16 hours. The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 70:30) to afford the title compound (54.8 mg, 38%) as a white solid. **R*f*** (7:3 Pet.Ether:EtOAc) 0.28; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29 (2H, d, *J* =8.7, Ar-*H*), 7.05 (2H, d, *J* =8.3, Ar-*H*), 6.31 (1H, tt, *J* = 55.6, 4.0, C*H*F_2), 5.40 (1H, s, C*H*C$(CH_3)_3$), 3.36 – 3.20 (1H, m, NCCH_AH_B), 3.18 (3H, s, NCH_3), 2.81 (1H, qd, *J* = 15.4, 14.2, NCCH_AH_B), 2.68 (6H, s, br., N(CH_3)$_2$), 1.00 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.60 (*C*=O)$_{amide}$, 162.65 (*C*=O)$_{urea}$, 135.14 (C_{Ar}), 134.81 (C_{Ar}), 128.44 (2xC_{Ar}H), 128.41 (2xC_{Ar}H), 115.05 (t, $^1J^{C\text{-}F}$ = 239.1, *C*HF_2), 82.07 (*C*HC$(CH_3)_3$), 68.97 (t, $^3J^{C\text{-}F}$ = 6.8, N*C*(Ar)), 41.55 (t, $^2J^{C\text{-}F}$ = 23.2, NC*C*H$_2$), 38.21 (N(*C*H$_3$)$_2$), 36.95 (*C*$(CH_3)_3$), 31.92 (N*C*H$_3$), 26.30 (C(*C*H$_3$)$_3$); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F −109.73 (2F, dtd, *J* = 55.5, 15.8, 10.8); **IR (vmax/cm^{-1}) (neat)**: 2965, 2910 (alkyl C-H), 1700 (C=O), 1659 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{19}H_{26}ClF_2N_3O_2Na$ $[M+Na]^+$ 424.1574, found 424.1583.

4.3.3 Decarboxylative Arylation of Urea Malonic Acid Half Esters

4.3.3.1 Synthesis of Urea Malonic Acid Half Esters

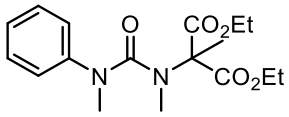
Diethyl 2-(3-methyl-3-phenylureido)malonate (477a)



Following general **procedure 16**: *N*-methyl-*N*-phenylcarbamoyl chloride (73.0 mg, 0.43 mmol) in anhydrous CH_3CN (4.30 mL), diethyl amino malonate hydrochloride salt (100 mg, 0.47 mmol) and Et_3N (0.13 mL, 0.95 mmol). The crude product was purified by flash column chromatography

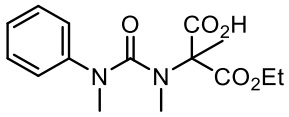
(SiO_2; Pet.Ether:EtOAc 100:0 to Pet: EtOAc 60:40) to afford the title compound (100 mg, 75%) as a colourless oil. **R*f*** (6:4 Pet.Ether:EtOAc) 0.27; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 – 7.40 (2H, m, 2xAr-*H*), 7.34 – 7.28 (3H, m, 3xAr-*H*), 5.37 (1H, br. d, *J* = 7.4, N*H*), 5.11 (1H, d, *J* = 7.4, C*H*), 4.20 (4H, qq, *J* = 10.8, 7.2, 2xOCH_2), 3.27 (3H, s, NCH_3), 1.25 (6H, t, J = 7.1, 2xCH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): 167.21 (2x*C*=O), 155.94 (*C*=O), 142.75 (C_{Ar}), 130.18 (2xC_{Ar}H), 127.71 (C_{Ar}H), 127.17 (2xC_{Ar}H), 62.40 (2xOCH_2), 57.87 (*C*H), 37.36 (NCH_3), 14.07 (2xC$H_2$$CH_3$); (**IR (vmax/cm^{-1}) (neat)**: 3428 (NH), 2982, 2939 (alkyl C-H), 1753, 1737 (C=O_{ester}), 1665(C=O); **HRMS** (ESI): *m/z* calcd for $C_{15}H_{21}N_2O_5$ $[M+H]^+$ 309.144498.Found 309.145197.

Diethyl 2-(1,3-dimethyl-3-phenylureido)-2-methylmalonate (478a)



Following general **procedure 17**: urea malonic acid ester **477a** (772 mg, 2.50 mmol) in anhydrous DMF (25.0 mL), NaH (60% in mineral oil, 300 mg, 7.51 mmol) and MeI (0.78 mL, 12.5 mmol). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (751 mg, 89%) as a colourless oil. **R*f*** (6:4 Pet.Ether:EtOAc) 0.36; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34 (4H, d, *J* = 4.2, 2xAr-*H*), 7.12 (1H, q, J = 4.3, Ar-*H*), 4.25 (4H, qd, *J* = 7.1, 1.4, 2xOCH_2), 3.24 (3H, s, NCH_3), 2.41 (3H, s, NCH_3), 1.70 (3H, s, CCH_3), 1.29 (6H, t, J = 7.1, 2xCH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): 169.12 (2x*C*=O), 161.66 (*C*=O), 146.25 (C_{Ar}), 129.44 (2xC_{Ar}H), 124.77 (C_{Ar}H), 124.50 (2xC_{Ar}H), 69.86 (*C*CH_3), 62.01 (2xOCH_2), 39.25 (NCH_3), 35.02 (NCH_3), 20.25 (CCH_3), 14.18 (2xC$H_2$$CH_3$); (**IR (vmax/cm^{-1}) (neat)**: 2980, 2907 (alkyl C-H), 1746 (C=O_{ester}), 1651 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{17}H_{25}N_2O_5$ $[M+H]^+$ 337.1758, found 337.1768.

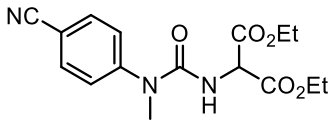
2-(1,3-Dimethyl-3-phenylureido)-3-ethoxy-2-methyl-3-oxopropanoic acid (469a)



Following general **procedure 18**: alkylated urea malonic acid ester **478a** (707 mg, 2.10 mmol) in ethanol:water (10:1, 3.00 mL) and KOH (236 mg, 4.21 mmol). The crude product was purified by flash column chromatography (SiO_2; DCM:MeOH 100:0 to DCM:MeOH 93:7) to afford the title compound **55a** (357 mg, 55%) as a cream solid. **R*f*** (9.3:0.7 DCM:MeOH) 0.30; **mp**: 68 – 70 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.48 – 7.44 (2H, m, 2xAr-*H*), 7.43 – 7.37 (2H, m, 2xAr-*H*), 7.25 – 7.20 (1H, m, Ar-*H*) 4.33 (2H, q, *J* = 7.1, OCH_2), 3.34 (3H, s, NCH_3), 2.38 (3H, s, NCH_3), 1.55 (3H, s, CCH_3), 1.34 (3H, t, J = 7.1, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): 170.62 (*C*=O), 170.24 (*C*=O), 164.68 (*C*=O), 144.43 (C_{Ar}), 129.89 (2xC_{Ar}H), 126.36 (C_{Ar}H), 125.10 (2xC_{Ar}H), 69.15

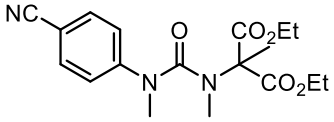
(*C*CH_3), 62.90 (O*C*H_2), 39.65 (N*C*H_3), 34.10 (N*C*H_3), 20.68 (C*C*H_3), 14.12 (CH_2*C*H_3); (**IR (vmax/cm^{-1}) (neat)**: 3300 – 2300 (OH), 2982, 2940 (alkyl C-H), 1788 (C=O), 1739 (C=O) 1646 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{15}H_{21}N_2O_5$ $[M+H]^+$ 309.144498, found 309.143533.

Diethyl 2-(3-(4-cyanophenyl)-3-methylureido)malonate (477b)



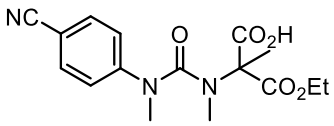
Following general **procedure 16**: *N*-(4-cyanophenyl)-*N*-methylcarbamoyl chloride (575 mg, 2.95 mmol) in anhydrous CH_3CN (29.6 mL), diethyl amino malonate hydrochloride salt (688 mg, 3.25 mmol) and Et_3N (0.91 mL, 6.50 mmol). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet: EtOAc 60:40) to afford the title compound (984 mg, >99%) as a yellow oil. **R*f*** (6:4 Pet.Ether:EtOAc) 0.20; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.73 (2H, d, *J* = 8.7, 2xAr-*H*), 7.49 (2H, d, *J* = 8.8, 2xAr-*H*), 5.59 (1H, br. d, *J* = 7.1, N*H*), 5.13 (1H, d, *J* = 7.1, C*H*), 4.27 (4H, dddd, *J* = 17.8, 10.7, 7.1, 3.6, 2xOC*H*$_2$), 3.35 (3H, s, NC*H*$_3$), 1.31 (6H, t, *J* = 7.1, 2xCH_2C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): 166.95 (2x*C*=O), 155.09 (*C*=O), 147.30 (*C*≡N), 133.85 (2x*C*$_{Ar}$H), 126.64 (2x*C*$_{Ar}$H), 118.31 (*C*$_{Ar}$), 110.22 (*C*$_{Ar}$), 62.76 (2xO*C*H_2), 57.86 (*C*H), 37.07 (N*C*H_3), 14.12 (2xCH_2*C*H_3); (**IR (vmax/cm^{-1}) (neat)**: 3426 (NH), 2965, 2901 (alkyl C-H), 2232 (C≡N), 1753 (C=O$_{ester}$), 1667 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{16}H_{20}N_3O_5$ $[M+H]^+$ 334.1397, found 334.1390.

Diethyl 2-(3-(4-cyanophenyl)-1,3-dimethylureido)malonate (478b)



Following general **procedure 17**: urea malonic acid ester **477b** (899 mg, 2.70 mmol) in anhydrous DMF (27.0 mL), NaH (60% in mineral oil, 324 mg, 8.09 mmol) and MeI (0.84 mL, 13.5 mmol). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (684 mg, 70%) as a colourless oil. **R*f*** (6:4 Pet.Ether:EtOAc) 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (2H, d, *J* = 8.7, 2xAr-*H*), 7.43 (2H, d, *J* = 8.8, 2xAr-*H*), 4.26 (4H, qd, *J* = 7.2, 1.6, 2xOC*H*$_2$), 3.28 (3H, s, NC*H*$_3$), 2.52 (3H, s, NC*H*$_3$), 1.73 (3H, s, C*H*$_3$), 1.30 (6H, t, *J* = 7.1, 2xCH_2C*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$): 168.58 (2x*C*=O), 160.78 (*C*=O), 149.75 (*C*≡N), 133.51 (2x*C*$_{Ar}$H), 122.60 (2x*C*$_{Ar}$H), 118.93 (*C*$_{Ar}$), 106.80 (*C*$_{Ar}$), 69.87 (*C*CH_3), 62.34 (2xO*C*H_2), 37.96 (N*C*H_3), 34.83 (N*C*H_3), 19.99 (*C*H_3), 14.17 (2xCH_2*C*H_3); (**IR (vmax/cm^{-1}) (neat)**: 2982, 2939 (alkyl C-H), 2224 (C≡N), 1742 (C=O), 1660 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{18}H_{24}N_3O_5$ $[M+H]^+$ Found 362.17.

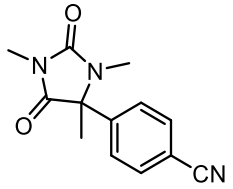
2-(3-(4-Cyanophenyl)-1,3-dimethylureido)-3-ethoxy-2-methyl-3-oxopropanoicacid (469b)



Following general **procedure 18**: alkylated urea malonic acid ester **478a** (653 mg, 1.81 mmol) in ethanol:water (10:1, 2.50 mL) and KOH (203 mg, 3.61 mmol). The title compound (429 mg, 71%) was yielded as a white solid and used without further purification. **R*f*** (9.3:0.7 DCM:MeOH) 0.15; **mp**: 110 – 112 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.69 (2H, d, *J* = 8.7, 2xAr-*H*), 7.58 (2H, d, *J* = 8.8, 2xAr-*H*), 4.34 (2H, q, *J* = 7.1, OC*H*$_2$), 3.36 (3H, s, NC*H*$_3$), 2.51 (3H, s, NC*H*$_3$), 1.61 (3H, s, C*H*$_3$), 1.34 (3H, t, *J* = 7.1, CH_2CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): 171.54 (*C*=O), 169.76 (*C*=O), 163.73 (*C*=O), 148.52 (*C*≡N), 133.89 (2xC_{Ar}H), 124.43 (2xC_{Ar}H), 118.34 (C_{Ar}), 109.10 (C_{Ar}), 68.57 (*C*CH_3), 63.36 (O*C*H_2), 38.94 (N*C*H_3), 34.26 (N*C*H_3), 20.86 (*C*H_3), 14.08 (CH_2CH_3); (**IR (vmax/cm^{-1}) (neat)**: 3378 (OH), 2984, 2936 (alkyl C-H), 2211 (C≡N), 1736 (C=O), 1652 (C=O), 1606 (C=O); **MS** (ESI): *m/z* calcd for $[C_{15}H_{20}N_3O_3]^+$ $[M+H-CO_2]^+$, found 290.15.

4.3.3.2 Aryl Migration of Urea Malonic Acid Half Ester

4-(1,3,4-Trimethyl-2,5-dioxoimidazolidin-4-yl)benzonitrile (470b)

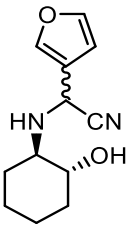


To a solution of **469b** (50.0 mg, 0.15 mmol, 1.00 eq.) and LiCl (19.1 mg, 0.45 mmol, 3.00 eq.) in THF (3 mL), was added cinchonidine (4.42 mg, 0.02 mmol, 0.10 eq.). The reaction was left to stir for 20 hours at room temperature. The reaction was quenched by the drop wise addition of HCl (1.0 M, aq.) to ensure pH was acidic. It was then extracted 3 times with EtOAc, and the combined organic layer dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (7.30 mg, 20%) as a colourless oil. **R*f*** (6:4 Pet.Ether:EtOAc) 0.19; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.71 (2H, d, *J* = 8.6, Ar-*H*), 7.43 (2H, d, *J* = 8.7, Ar-*H*), 3.06 (3H, s, NC*H*$_3$), 2.88 (3H, s, NC*H*$_3$), 1.83 (3H, s, C*H*$_3$), **^{13}C NMR** (101 MHz, $CDCl_3$): 173.88 (*C*=O), 156.28 (*C*=O), 141.92 (C_{Ar}), 133.03 (2xC_{Ar}H), 127.02 (2xC_{Ar}H), 118.20 (*C*≡N), 113.02 (C_{Ar}), 66.72 (*C*CH_3), 25.79 (N*C*H_3), 25.53 (N*C*H_3), 20.67 (*C*H_3); **HPLC**: *er* = ~48:52, Chiralcel® OD-H, Hexane:IPA = 80:20, flow = 1 mL/min, λ = 254 nm, t_R = 18 min (major), 21 min (minor); (**IR (vmax/cm^{-1}) (neat)**: 2929, 2858 (alkyl C-H), 2229 (C≡N), 1772, 1710 (C=O); **HRMS** (APCI): *m/z* calcd for $C_{13}H_{14}N_3O_2$ $[M+H]^+$ 244.1081, found 244.1075.

4.3.4 Diastereoselective Arylation of α-Amino Nitriles

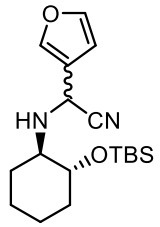
4.3.4.1 Synthesis of α-Amino Nitrile Ureas

2-(Furan-3-yl)-2-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)acetonitrile (493a)



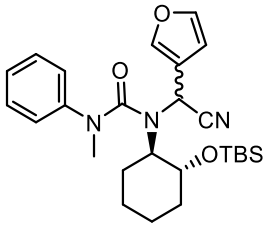
Following general **procedure 19**: (1*R*,2*R*)-2-aminocyclohexanol (1.13 g, 9.79 mmol), 3-furaldehyde (0.93 mL, 10.8 mmol) and TMSCN (1.47 mL, 11.7 mmol) in MeOH (56.0 mL). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 60:40) to afford the title compound (1.3 g, 61%; 65:35 *dr*) as a white solid. **R*f*** (6:4 Pet.Ether:EtOAc) 0.34; **^{1}H NMR** (400 MHz, $CDCl_3$) (mixture of diast A:B in a 0.65:0.35 ratio): δ 7.60 (0.65H, dt, *J* =1.8, 1.0, Ar-*H*, diast. A), 7.58 (0.35H, dt, *J* =1.8, 1.0, Ar-*H*, diast. B), 7.44 (0.65H, t, *J* =1.7, Ar-*H*, diast. A), 7.43 – 7.39 (0.35H, m, Ar-*H*, diast. B), 6.50 (1H, dt, *J* =1.9, 1.0, Ar-*H*, diast. A+B), 4.92 (0.35H, s, NC*H*(Ar)CN, diast. B), 4.79 (0.65H, s, NC*H*(Ar)CN, diast. A), 3.31 (1H, ddt, *J* =13.7, 9.1, 4.1, NHCHC*H*OH, diast. A+B), 2.65 (0.65H, ddd, *J* =11.1, 9.1, 4.1, NHC*H*CHOH, diast. A), 2.55 (0.35H, ddd, *J* =11.2, 9.0, 4.2, NHC*H*CHOH, diast. B), 2.47 – 1.93 (3H, m (*overlapping*), N*H*, diast. A+B, 2xC*H*, diast. A+B), 1.94 – 1.53 (3H, m (*overlapping*), O*H*, diast. A+B, 2xC*H*, diast. A+B), 1.41 – 1.22 (3H, m, 3xC*H*, diast. A+B), 1.21 – 1.02 (1H, m, C*H*, diast. A+B); **^{13}C NMR** (126 MHz, $CDCl_3$): 144.3 (C_{Ar}H, diast. A), 144.2 (C_{Ar}H, diast. B), 140.8 (C_{Ar}H, diast. A), 140.6 (C_{Ar}H, diast. B), 121.8 (C_{Ar}, diast. B), 121.3 (C_{Ar}, diast. A), 120.0 (*C*≡N, diast. B), 118.8 (*C*≡N, diast. A), 109.4 (C_{Ar}H, diast. A), 109.3 (C_{Ar}H, diast. B), 75.5 (NHCH*C*HOH, diast. B), 74.1 (NHCH*C*HOH, diast. A), 62.8 (NH*C*HCHOH, diast. B), 61.3 (NH*C*HCHOH, diast. A), 46.0 (N*C*H(Ar)CN, diast. B), 43.6 (N*C*H(Ar)CN, diast. A), 34.3 (CH_2, diast. A), 33.9 (CH_2, diast. B), 31.6 (CH_2, diast. B), 29.9 (CH_2, diast. A), 25.0 (CH_2, diast. B), 24.5 (CH_2, diast. A), 24.4 (CH_2, diast. A), 24.3 (CH_2, diast. B); **IR (vmax/cm^{-1}) (neat)**: 3600 – 3200 (OH, br.), 3323 (NH), 2932, 2859 (alkyl C-H), 2233 (C≡N); **HRMS** (ESI): *m/z* calcd for $C_{12}H_{17}N_2O_2$ $[M+H]^+$ 221.1284, found 221.1291.

2-(((1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)amino)-2-(furan-3-yl)acetonitrile (494a)



Following general **procedure 20**: 2,6-lutidine (0.08 mL, 0.68 mmol), α-amino nitrile **493a** (100 mg, 0.45 mmol) in anhydrous DCM (2.00 mL) and TBDMSOTf (0.13 mL, 0.55 mmol). The crude product was purified by flash column chromatography (SiO_2; *n*Hexane:EtOAc 100:0 to *n*Hexane:EtOAc 90:10) to afford the title compound (79.7 mg, 52%; 65:35 *dr*) as a yellow oil. **R*f*** (9:1 *n*Hexane:EtOAc) 0.29; **^{1}H NMR** (400 MHz, $CDCl_3$) (mixture of diast A:B in a 0.65:0.35 ratio): δ 7.60 – 7.53 (1H, m (*overlapping*), Ar-*H*, diast. A+B), 7.43 (0.65H, dq, *J* =2.6, 1.6, Ar-*H*, diast. A), 7.40 (0.35H, 1d, *J* =1.7, Ar-*H*, diast. B), 6.58 – 6.39 (1H, m, Ar-*H*, diast. A+B), 4.93 (0.35H, s, NC*H*(Ar)CN, diast. B), 4.72 (0.65H, s, NC*H*(Ar)CN, diast. A), 3.50 – 3.34 (1H, m, NHCHC*H*OTBS, diast. A+B), 2.76 (0.65H, ddd, *J* =11.9, 8.8, 3.9, NHC*H*CHOTBS, diast. A), 2.63 (0.35H, ddd, *J* =9.9, 8.9, 4.0, NHC*H*CHOTBS, diast. B), 2.34 (0.65H, br. d, *J* =11.4, N*H*, diast. A), 2.05 – 1.82 (1.65H, m, 2xC*H*, diast. A; C*H*, diast. B), 1.81 – 1.59 (2.70H, m, 2xC*H*, diast. A; 2xC*H* + CH_2, diast. B), 1.48 – 1.15 (3.35H, 3xC*H*, diast. A; 3xC*H* + N*H*, diast. B), 1.07 (0.65H, qd, *J* =13.2, 12.7, C*H*, diast. A), 0.86 (5.85H, s, SiC(CH_3)$_3$, diast. A), 0.79 (3.15H, s, SiC(CH_3)$_3$, diast. B), 0.07 (1.95H, s, Si($CH_{3,A}$)($CH_{3,B}$), diast. A), 0.05 (1.05H, s, Si($CH_{3,A}$)($CH_{3,B}$), diast. B), 0.03 (1.95H, s, Si($CH_{3,A}$)($CH_{3,B}$), diast. A), 0.01 (1.05H, Si($CH_{3,A}$)($CH_{3,B}$), diast. B); **^{13}C NMR** (101 MHz, $CDCl_3$): 144.15 (C_{Ar}H, diast. A), 143.92 (C_{Ar}H, diast. B), 140.48 (C_{Ar}H, diast. B), 140.40 (C_{Ar}H, diast. A), 121.8 ($C_{Ar,}$ diast. B), 121.6 ($C_{Ar,}$ diast. A), 120.0 (*C*≡N, diast. B), 118.4 (*C*≡N, diast. A), 109.22 (2xC_{Ar}H, diast. A+B), 76.8 (NHCH*C*HOTBS, diast. B), 75.3 (NHCH*C*HOTBS, diast. A), 61.8 (NH*C*HCHOTBS, diast. B), 61.1 (NH*C*HCHOTBS, diast. A), 46.1 (N*C*H(Ar)CN, diast. B), 43.6 (N*C*H(Ar)CN, diast. A), 34.3 (CH_2, diast. A), 32.8 (CH_2, diast. B), 31.4 (CH_2, diast. B), 29.1 (CH_2, diast. A), 25.96 (SiC(CH_3)$_3$ diast. B), 25.91 (SiC(CH_3)$_3$, diast. A), 24.8 (CH_2, diast. B), 24.5 (CH_2, diast. A), 24.3 (CH_2, diast. B), 24.1 (CH_2, diast. A), 18.09 (Si*C*(CH_3)$_3$, diast. A), 18.07 (Si*C*(CH_3)$_3$, diast. B), −3.66 (Si($CH_{3,A}$)($CH_{3,B}$), diast. A), −3.85 (Si($CH_{3,A}$)($CH_{3,B}$), diast. B), −4.43 (Si($CH_{3,A}$)($CH_{3,B}$), diast. B), −4.67 (Si($CH_{3,A}$)($CH_{3,B}$), diast. A); **IR (vmax/cm^{-1}) (neat)**: 3329 (NH), 2929, 2857 (alkyl C-H), 2346 (C≡N); **HRMS** (ESI): *m/z* calcd for $C_{18}H_{31}N_2O_2Si$ $[M+H]^+$ 335.2149, found 335.2137.

1-((1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-1-(cyano(furan-3-yl)methyl)-3-methyl-3-phenylurea (488ea)



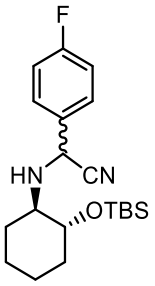
Following general **procedure 21**: triphosgene (347 mg, 1.17 mmol) in anhydrous DCM (13.4 mL), 2,6-lutidine (0.40 mL, 3.51 mmol) and *N*-alkyl-OTBS amino nitrile **494a** (978 mg, 2.92 mmol). The crude carbamoyl chloride **495a** was yielded as a dark brown oil and used without further purification. Following general **procedure 22 method A**: 2,6-lutidine (0.61 mL, 5.23 mmol), *N*-methyl aniline (0.52 mL, 4.79 mmol), KI (868 mg, 5.23 mmol) and carbamoyl chloride **495a** (1.73 g, 4.36 mmol) in anhydrous CH_3CN (11.0 mL). The crude product was purified by flash column chromatography (SiO_2; *n*Hexane:Diethyl ether 100:0 to *n*Hexane:Diethyl ether 70:30) to afford the title compound (228 mg, 17% over 2 steps; 50:50 *dr*, relative stereochemistry undetermined) as the two separated diastereoisomers A:B.

Diast. A: Yellow solid; **R*f*** (7:3 *n*Hexane:Diethyl ether) 0.34; **mp**: 119 – 121 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (1H, dt, *J* =1.8, 0.9, Ar-*H*), 7.37 (1H, t, *J* =1.7, Ar-*H*), 7.36 – 7.31 (2H, m, 2xAr-*H*), 7.17 (1H, ddt, *J* = 7.9, 7.0, 1.2, Ar-*H*), 7.14 – 7.10 (2H, m, Ar-*H*), 6.50 (1H, dd, *J* =1.9, 0.9, Ar-*H*), 5.77 (1H, s, NC*H*(Ar)CN), 4.02 (1H, d, *J* =8.1, NCHC*H*OTBS), 3.22 – 3.15 (1H, m, NC*H*CHOTBS), 3.21 (3H, s, NCH_3), 1.98 – 1.89 (1H, m, C*H*), 1.69 – 1.60 (1H, m, C*H*), 1.60 – 1.50 (2H, m, 2xC*H*), 1.48 – 1.41 (1H, m, C*H*), 1.17 – 1.09 (1H, m, C*H*), 1.05 – 0.92 (1H, m, C*H*), 0.85 (9H, s, SiC(CH_3)$_3$), 0.75 – 0.70 (1H, m, C*H*), 0.06 (3H, s, Si(C$H_{3,A}$)($CH_{3,B}$)), 0.01 (3H, s, Si($CH_{3,A}$)(C$H_{3,B}$)); **^{13}C NMR** (101 MHz, $CDCl_3$): 163.36 (*C*=O), 146.15 (C_{Ar}), 143.36 (C_{Ar}H), 142.14 (C_{Ar}H), 129.78 (2xC_{Ar}H), 125.83 (C_{Ar}H), 124.94 (2xC_{Ar}H), 119.44 (C_{Ar}), 118.14 (*C*≡N), 110.61 (C_{Ar}H), 71.95 (NCH*C*HOTBS), 65.14 (N*C*HCHOTBS), 41.97 (N*C*H(Ar)CN), 40.38 (N*C*H_3), 36.98 (*C*H_2), 29.21 (*C*H_2), 26.14 (SiC(*C*H_3)$_3$), 25.75 (*C*H_2), 24.48 (*C*H_2), 18.23 (Si*C*(CH_3)$_3$), −3.59 (Si($CH_{3,A}$)(*C*$H_{3,B}$)), −3.82 (Si(*C*$H_{3,A}$)($CH_{3,B}$)); (**IR (vmax/cm^{-1}) (neat)**: 2929, 2857 (alkyl C-H), 2243 (C≡N), 1657 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{26}H_{38}N_3O_3Si$ $[M+H]^+$ 468.2677, found 468.2676.

Diast. B: Orange oil; **R*f*** (7:3 *n*Hexane:Diethyl ether) 0.21; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.71 (1H, s, Ar-*H*), 7.42 (1H, t, *J* =1.7, Ar-*H*), 7.34 – 7.28 (2H, m, 2xAr-*H*), 7.19 – 7.14 (1H, m, Ar-*H*), 6.97 – 6.93 (2H, m, Ar-*H*), 6.40 (1H, d, *J* =1.5, Ar-*H*), 4.97 (1H, s, NC*H*(Ar)CN), 3.67 (1H, dt, *J* =10.4, 3.8, NCHC*H*OTBS), 3.28 (1H, ddd, *J* =12.9, 9.3, 4.0, NC*H*CHOTBS), 3.16 (3H, s, NCH_3), 2.10 – 1.97 (1H, m, C*H*), 1.62 – 1.50 (1H, m, C*H*), 1.46 – 1.37 (1H, m, C*H*), 1.20 – 1.10 (1H, m,

C*H*), 1.09 – 0.97 (3H, m, 3xC*H*), 0.95 (9H, s, SiC(CH_3)$_3$), 0.57 (1H, td, *J* = 12.0, 11.6, 5.9, C*H*), 0.23 (3H, s, Si(C$H_{3,A}$)(C$H_{3,B}$)), 0.14 (3H, s, Si(C$H_{3,A}$)(C$H_{3,B}$)); **^{13}C NMR** (126 MHz, $CDCl_3$): 160.5 (*C*=O), 146.4 (C_{Ar}), 143.3 (C_{Ar}H), 142.7 (C_{Ar}H), 129.6 (2xC_{Ar}H), 125.8 (C_{Ar}H), 125.5 (2xC_{Ar}H), 120.0 (C_{Ar}), 118.0 (*C*≡N), 110.1 (C_{Ar}H), 71.6 (NCH*C*HOTBS), 64.9 (N*C*HCHOTBS), 39.8 (N*C*H$_3$ + N*C*H(Ar)CN overlap), 36.7 (*C*H$_2$), 29.2 (*C*H$_2$), 26.3 (SiC(*C*H$_3$)$_3$), 25.2 (*C*H$_2$), 24.4 (*C*H$_2$), 18.3 (Si*C*(CH$_3$)$_3$), −3.3 (Si(CH$_{3,A}$)(*C*H$_{3,B}$)), −3.9 (Si(*C*H$_{3,A}$)(CH$_{3,B}$)); (**IR (vmax/cm^{-1}) (neat)**: 2929 (alkyl C-H), 2857 (alkyl C-H), 2243 (C ≡ N), 1661 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{26}H_{38}N_3O_3Si$ $[M+H]^+$ 468.2677, found 468.2657.

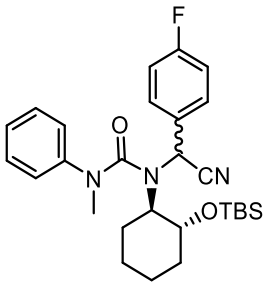
2-(((1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)amino)-2-(4-fluorophenyl)acetonitrile (494b)



Following general **procedure 19**: (1*R*,2*R*)-2-aminocyclohexanol (1.18 g, 10.23 mmol), 4-fluorobenzaldehyde (1.20 mL, 11.3 mmol) and TMSCN (1.50 mL, 12.3 mmol) in MeOH (59.0 mL). The crude α-amino nitrile **493b** (2.70 g, 63:37 *dr*) was yielded as a white solid and used without further purification. Following general **procedure 20**: 2,6-lutidine (1.80 mL, 15.4 mmol), α-amino nitrile **493b** (2.56 g, 10.3 mmol) in anhydrous DCM (47.0 mL) and TBDMSOTf (2.80 mL, 12.4 mmol). The crude product was purified by flash column chromatography (SiO_2; *n*Hexane:Diethyl ether 100:0 to *n*Hexane:Diethyl ether 90:10) to afford the title compound (1.41 g, 38% over 2 steps, 75:25 *dr*) as a pale yellow oil. **R*f*** (7:3 Pet.Ether:EtOAc) 0.23; **^{1}H NMR** (400 MHz, $CDCl_3$) (mixture of diast A:B in a 0.75:0.25 ratio): δ 7.54 – 7.39 (2H, m (Ar-*H*, diast. A+B), 7.08 (2H, ddt, *J* =8.6, 6.7, 2.0 Ar-*H*, diast. A+B), 4.93 (0.25H, s, NC*H*(Ar)CN, diast. B), 4.75 (0.75H, s, NC*H*(Ar)CN, diast. A), 3.43 (1H, dddd, *J* =19.4, 10.8, 8.5, 4.2 NHCHC*H*OTBS, diast. A+B), 2.79 (0.75H, ddd, *J* = 11.1, 8.6, 4.0, NHC*H*CHOTBS, diast. A), 2.62 (0.25H, ddd, *J* =10.4, 8.3, 3.9, NHC*H*CHOTBS, diast. B), 2.33 (0.75H, br. d, *J* = 12.0, N*H*, diast. A), 2.03 (0.75H, ddt, *J* = 12.6, 5.3, 2.6, C*H*, diast. A), 1.98 – 1.82 (1.50H, m, C*H* + N*H*, diast. B; C*H*, diast. A+ B), 1.79 – 1.67 (2H, CH_2, diast. A+B), 1.50 – 1.17 (3.25H, m, C*H* + CH_2, diast. A+B; C*H*, diast. B), 1.18 – 0.97 (0.75H, m, C*H*, diast. A), 0.84 (9H, s (overlapping), SiC(CH_3)$_3$, diast. A+B), 0.06 (3H, s, Si(C$H_{3,A}$)(CH$_{3,B}$), diast. A + B), 0.03 (0.75H, s, Si(CH$_{3,A}$)(C$H_{3,B}$), diast. B), −0.02 (2.25H, s, Si(CH$_{3,A}$)(C$H_{3,B}$), diast. A); **^{13}C NMR** (101 MHz, $CDCl_3$): 164.16 (C_{Ar}, d, *J* =249.9, diast. B), 162.98 (C_{Ar}, d, *J* =248.0, diast. A), 131.96 (C_{Ar}, d, *J* =3.3, diast. B), 131.66 (C_{Ar}, d, *J* =3.3, diast.

A), 129.08 (2xC_{Ar}H, d, J =8.4, diast. A), 129.02 (2xC_{Ar}H, d, J =8.3, diast. B), 120.14 (C≡N, diast. B), 118.57 (C≡N, diast. A), 116.05 (2xC_{Ar}H, d, J = 21.8, diast. A), 115.60 (2xC_{Ar}H, d, J = 21.7, diast. B), 76.29 (NHCH*C*HOTBS, diast. B), 75.27 (NHCH*C*HOTBS, diast. A), 62.15 (NH*C*HCHOTBS, diast. B), 61.36 (NH*C*HCHOTBS, diast. A), 53.04 (N*C*H(Ar)CN, diast. B), 50.83 (N*C*H(Ar)CN, diast. A), 34.47 (CH$_2$, diast. B), 34.32 (CH$_2$, diast. A), 31.17 (CH$_2$, diast. B), 29.20 (CH$_2$, diast. A), 25.91 (SiC(CH$_3$)$_3$ diast. B), 25.88 (SiC(CH$_3$)$_3$, diast. A), 24.49 (CH$_2$, diast. A), 24.32 (CH$_2$, diast. B), 24.24 (CH$_2$, diast. B), 24.04 (CH$_2$, diast. A), 18.07 (SiC(CH$_3$)$_3$, diast. A), 18.04 (SiC(CH$_3$)$_3$, diast. B), −3.65 (Si(CH$_{3,A}$)(CH$_{3,B}$), diast. A), −3.78 (Si(CH$_{3,A}$)(CH$_{3,B}$), diast. B), −4.47 (Si(CH$_{3,A}$)(CH$_{3,B}$), diast. B), −4.75 (Si(CH$_{3,A}$)(CH$_{3,B}$), diast. A); (**IR (vmax/cm^{-1}) (neat)**: 3327 (NH), 2930, 2858 (alkyl C-H); **HRMS** (ESI): *m/z* calcd for $C_{20}H_{32}FN_2OSi$ $[M+H]^+$ 363.2262, found 363.2278.

1-((1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-1-(cyano(4-fluorophenyl)methyl)-3-methyl-3-phenylurea (488eb)



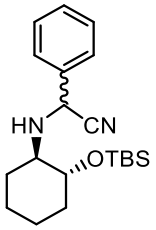
Following general **procedure 21**: triphosgene (428 mg, 1.44 mmol) in anhydrous DCM (16.5 mL), 2,6-lutidine (0.50 mL, 4.32 mmol) and *N*-alkyl-OTBS amino nitrile **494b** (1.31 g, 3.60 mmol). The crude carbamoyl chloride **495b** (1.39 g) was yielded as a yellow oil and used without further purification. Following general **procedure 22 method A**: 2,6-lutidine (0.42 mL, 3.61 mmol), *N*-methyl aniline (0.36 mL, 3.31 mmol), KI (600 mg, 3.61 mmol) and carbamoyl chloride **495b** (1.28 g, 3.01 mmol) in anhydrous CH_3CN (8.00 mL). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 80:20) to afford the title compound (194 mg, 11% over 2 steps; 50:50 *dr*, relative stereochemistry undetermined) as the two separated diastereoisomers A:B.

Diast. A: pale yellow oil. **R*f*** (8:2 Pet.Ether:Diethyl ether) 0.3; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.59 – 7.54 (2H, m, 2xAr-*H*), 7.37 – 7.31 (2H, m, 2xAr-*H*), 7.22 – 7.16 (1H, m, Ar-*H*), 7.11 – 7.02 (4H, m, 4xAr-*H*), 5.76 (1H, s, NC*H*(Ar)CN), 4.09 – 3.97 (1H, m, NCHC*H*OTBS), 3.25 (1H, t, J = 10.4, NC*H*CHOTBS), 3.19 (3H, s, NCH_3), 2.02 – 1.93 (1H, m, C*H*), 1.70 (1H, qd, J = 12.6, 3.5, C*H*), 1.59 – 1.50 (3H, m, 3xC*H*), 1.29 – 1.20 (1H, m, C*H*), 1.18 1.12 (1H, m, C*H*), 0.99 – 0.95 (1H, m, C*H*), 0.85 (9H, s, SiC(CH_3)$_3$), 0.08 (3H, s, Si(C$H_{3,A}$)(CH$_{3,B}$)), 0.01 (3H, s, Si(CH$_{3,A}$)(C$H_{3,B}$)); **^{13}C NMR** (126 MHz, $CDCl_3$): 162.76 (C_{Ar}, d, $^1J^{C-F}$ = 247.5), 161.38 (C=O), 145.75 (C_{Ar}), 130.74 (C_{Ar}),

129.79 (2xC_{Ar}H), 129.67 (2xC_{Ar}H, d, $^{3}J^{C\text{-}F}$ = 8.3), 126.04 (C_{Ar}H), 125.17 (2xC_{Ar}H), 118.58 (C≡N), 115.55 (2xC_{Ar}H, d, $^{2}J^{C\text{-}F}$ = 21.8), 72.09 (NCH*C*HOTBS), 65.37 (N*C*HCHOTBS), 48.57 (N*C*H(Ar)CN), 40.36 (N*C*H$_3$), 36.92 (*C*H$_2$), 29.86 (*C*H$_2$), 26.24 (SiC(*C*H$_3$)$_3$), 25.74 (*C*H$_2$), 24.46 (*C*H$_2$), 18.37 (Si*C*(CH$_3$)$_3$), −3.17 (Si(CH$_{3,A}$)(*C*H$_{3,B}$)), −3.48 (Si(*C*H$_{3,A}$)(CH$_{3,B}$)); **(IR (vmax/cm^{-1}) (neat)**: 2926 (alkyl C-H), 2855 (alkyl C-H), 2242 (C≡N), 1660 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{28}H_{39}FN_3O_2Si$ $[M+H]^+$ 496.2790, found 496.2771.

Diast. B: pale yellow oil. **R*f*** (8:2 Pet.Ether:Diethyl ether) 0.29; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.54 (2H, dd, *J* = 8.5, 5.2, 2xAr-*H*), 7.32 (2H, t, *J* = 7.7, 2xAr-*H*), 7.21 – 7.16 (1H, m, Ar-*H*), 7.10 (2H, t, *J* = 8.5, 2xAr-*H*), 6.87 (2H, d, *J* = 7.9, 2xAr-*H*), 5.05 (1H, s, NC*H*(Ar)CN), 3.81 – 3.65 (1H, m, NCHC*H*OTBS), 3.33 (1H, ddd, *J* = 12.9, 9.3, 4.0, NC*H*CHOTBS), 3.10 (3H, s, NC*H*$_3$), 2.12 – 1.97 (1H, m, C*H*), 1.66 – 1.50 (1H, m, C*H*), 1.50 – 1.43 (1H, m, C*H*), 1.31 – 1.21 (1H, m, C*H*), 1.13 – 1.01 (3H, m, 3xC*H*), 0.96 (9H, s, SiC(C*H*$_3$)$_3$), 0.61 (1H, td, *J* =16.2, 14.5, 11.0, C*H*), 0.26 (3H, s, Si(C*H*$_{3,A}$)(CH$_{3,B}$)), 0.15 (3H, s, Si(CH$_{3,A}$)(C*H*$_{3,B}$)); **^{13}C NMR** (126 MHz, $CDCl_3$): 162.73 (C_{Ar}, d, $^{1}J^{C\text{-}F}$ = 246.9), 160.46 (*C*=O), 146.19 (C_{Ar}), 130.31 (2xC_{Ar}H, d, $^{3}J^{C\text{-}F}$ = 8.3), 130.10 (C_{Ar}, d, $^{4}J^{C\text{-}F}$ = 3.2), 129.56 (2xC_{Ar}H), 125.93 (C_{Ar}H), 125.70 (2xC_{Ar}H), 118.07 (*C*≡N), 115.41 (2xC_{Ar}H, d, $^{2}J^{C\text{-}F}$ = 21.9), 71.63 (NCH*C*HOTBS), 65.06 (N*C*HCHOTBS), 47.11 (N*C*H(Ar)CN), 39.76 (N*C*H$_3$), 36.87 (*C*H$_2$), 29.86 (*C*H$_2$), 26.34 (SiC(*C*H$_3$)$_3$), 25.28 (*C*H$_2$), 24.35 (*C*H$_2$), 18.36 (Si*C*(CH$_3$)$_3$), −3.46 (Si(CH$_{3,A}$)(*C*H$_{3,B}$)), −3.74 (Si(*C*H$_{3,A}$)(CH$_{3,B}$)); **(IR (vmax/cm^{-1}) (neat)**: 2925, 2854 (alkyl C-H), 2242 (C≡N), 1661 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{28}H_{39}FN_3O_2Si$ $[M+H]^+$ 496.2790, found 496.2777.

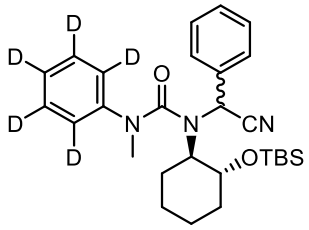
2-(((1*R*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)cyclohexyl)amino)-2-phenylacetonitrile 494c



Following general **procedure 19**: (1*R*,2*R*)-2-aminocyclohexanol (1.17 g, 10.1 mmol), benzaldehyde (1.10 mL, 11.1 mmol) and TMSCN (1.50 mL, 12.2 mmol) in MeOH (58.0 mL). The crude α-amino nitrile **493c** (2.50 g, >99%, 62:38 *dr*) was yielded as a white solid and used without further purification. Following general **procedure 20**: 2,6-lutidine (1.90 mL, 16.3 mmol), α-amino nitrile **493c** (2.50 g, 10.9 mmol) in anhydrous DCM (49.0 mL) and TBDMSOTf (3.00 mL, 13.0 mmol). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 80:20) to afford the title compound (1.72 g, 49% over 2 steps, 70:30 *dr*) as a colourless oil. **R$_f$** (8:2 Pet.Ether:Diethyl ether) 0.26; **^{1}H NMR** (400 MHz, $CDCl_3$) (mixture of diast A:B in a 0.70:0.30 ratio): δ 7.52 – 7.46 (2H, m, 2xC_{Ar}*H*, diast. A+B), 7.43 – 7.33

(3H, m, 3x$C_{Ar}H$, diast. A+B), 4.93 (0.30H, s, NC*H*(Ar)CN, diast. B), 4.77 (0.70H, s, NC*H*(Ar)CN, diast A), 3.52 – 3.36 (1H, m, NCHC*H*OTBS, diast. A+B), 2.81 (0.70H, ddd, *J* = 11.1, 8.6, 4.0 Hz, NC*H*CHOTBS, diast A), 2.66 – 2.57 (0.30H, m, NC*H*CHOTBS, diast. B), 2.38 (0.70 H, br. s, N*H*, diast A), 2.10 – 2.01 (0.70H, m, C*H*, diast A), 2.01 – 1.93 (0.30 H, m, C*H*, diast. B), 1.93 – 1.82 (1H, m, C*H*, diast. A+B), 1.79 – 1.63 (2.30H, m, CH_2, diast. A+B; N*H*, diast. B), 1.49 – 1.22 (3.30H, m, CH_2+C*H*, diast. A+B; C*H*, diast. B), 1.14 – 1.04 (0.70H, m, C*H*, diast. A), 0.85 (6.30 H, s, SiC(CH_3)$_3$, diast A), 0.84 (2.70 H, s, SiC(CH_3)$_3$, diast B), 0.06 (3 H, s, Si($CH_{3,A}$)($CH_{3,B}$), diast A+B), 0.03 (0.90 H, s, Si($CH_{3,A}$)($CH_{3,B}$), diast B), −0.01 (2.10 H, s, Si($CH_{3,A}$)($CH_{3,B}$), diast A); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C = 136.02 (C_{Ar}H, diast B), 135.74 (C_{Ar}H, diast A), 129.12 (2xC_{Ar}H, diast A), 128.97 (2xC_{Ar}H, diast B), 128.53 (C_{Ar}, diast B), 128.31 (C_{Ar}, diast A), 127.25 (2xC_{Ar}H, diast A), 127.22 (2xC_{Ar}H, diast B), 120.36 (*C*≡N, diast B), 118.78 (*C*≡N, diast A), 76.20 (NCH*C*HOTBS, diast B), 75.25 (NCH*C*HOTBS, diast A), 62.18 (N*C*HCHOTBS, diast B), 61.37 (N*C*HCHOTBS, diast A), 53.67 (N*C*H(Ar)CN, diast B), 51.51 (N*C*H(Ar)CN, diast A), 34.45 (CH_2, diast B), 34.35 (CH_2, diast A), 31.07 (CH_2, diast. B), 29.21 (CH_2, diast. A), 25.92 (SiC(CH_3)$_3$, diast B), 25.90 (SiC(CH_3)$_3$, diast A), 24.51 (CH_2, diast A), 24.31 (CH_2, diast B), 24.26 (CH_2, diast B), 24.06 (CH_2, diast A), 18.07 (Si*C*(CH_3)$_3$, diast A), 18.04 (Si*C*(CH_3)$_3$, diast B), −3.64 (Si($CH_{3,A}$)($CH_{3,B}$), diast A), −3.79 (Si($CH_{3,A}$)($CH_{3,B}$), diast B), −4.48 (Si($CH_{3,A}$)($CH_{3,B}$), diast B), −4.74 (Si($CH_{3,A}$)($CH_{3,B}$), diast A); **IR** (neat, cm^{-1}): 3323 (NH), 2929 (alkyl C-H), 2243 (C≡N); **HRMS** (EI^+): *m/z* calcd for $C_{20}H_{33}N_2OSi$ $[M+H]^+$ 345.2357, found 345.2370.

1-((1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-1-(cyano(phenyl)methyl)-3-methyl-3-(phenyl-d5)urea (488ed)

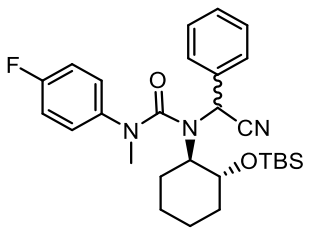


Following general **procedure 21**: triphosgene (187 mg, 0.63 mmol) in anhydrous DCM (7.30 mL), 2,6-lutidine (0.22 mL, 1.90 mmol) and *N*-alkyl-OTBS amino nitrile **494c** (542 mg, 1.57 mmol). The crude carbamoyl chloride **495c** (558 mg) was yielded as a yellow oil and used without further purification. Following general **procedure 22 method B**: 2,6-lutidine (0.18 mL, 1.56 mmol), deuterated-*N*-methyl aniline (160 mg, 1.43 mmol) and carbamoyl chloride **495c** (528 mg, 1.30 mmol) in anhydrous CH_3CN (3.20 mL). The crude product was purified by flash column chromatography (Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 80:20) to afford the title compound (391 mg, 51% over 2 steps; 50:50 *dr*, relative stereochemistry undetermined) as the two separated diastereoisomers A:B

Diast. A: Yellow oil. **R*f*** (8:2 Pet.Ether:Diethyl ether) 0.24; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.57 (2H, d, *J* =7.2, 2xAr-*H*), 7.40 – 7.29 (3H, m, 3xAr-*H*), 5.89 (1H, s, NC*H*(Ar)CN), 4.09 (1H, td, *J* =9.8, 4.2, NCHC*H*OTBS), 3.31 – 3.22 (1H, m, NC*H*CHOTBS), 3.20 (3H, s, NCH_3), 2.01 – 1.91 (1H, m, C*H*), 1.77 – 1.63 (1H, m, C*H*), 1.61 – 1.44 (3H, m, 3xC*H*), 1.19 – 1.12 (1H, m, C*H*), 1.03 – 0.97 (1H, m, C*H*), 0.86 (9H, s, SiC(CH_3)$_3$), 0.79 (1H, d, *J* =12.4, C*H*), 0.09 (3H, s, Si(C$H_{3,A}$)(C$H_{3,B}$)), 0.03 (3H, s, Si(C$H_{3,A}$)(C$H_{3,B}$)); **^{13}C NMR** (126 MHz, $CDCl_3$): 161.49 (*C*=O), 145.74 (C_{Ar}), 134.83 (C_{Ar}), 129.21 (2xC_{Ar}D, t, $^{1}J^{C\text{-}D}$ = 23.94), 125.59 – 124.43 (3xC_{Ar}D, m), 128.59 (2xC_{Ar}H), 128.55 (C_{Ar}H), 127.76 (2xC_{Ar}H), 118.70 (*C* ≡ N), 71.98 (NCH*C*HOTBS), 65.40 (N*C*HCHOTBS), 49.21 (N*C*H(Ar)CN), 40.31 (N*C*H_3), 36.97 (*C*H_2), 29.79 (*C*H_2), 26.25 (SiC(*C*H_3)$_3$), 25.78 (*C*H_2), 24.45 (*C*H_2), 18.34 (Si*C*(CH$_3$)$_3$), −3.25 (Si(CH$_{3,A}$)(*C*H$_{3,B}$)), −3.62 (Si(*C*H$_{3,A}$)(CH$_{3,B}$)); **IR (vmax/cm^{-1}) (neat)**: 2929 (alkyl C-H), 2856 (alkyl C-H), 2250 (C≡N), 1661 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{28}H_{34}D_5N_3O_2SiNa$ $[M+Na]^+$ 505.3018, found 505.3014.

Diast. B: yellow oil. **R*f*** (8:2 Pet.Ether:Diethyl ether) 0.17; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.57 (2H, d, *J* =7.8, 2xAr-*H*), 7.45 – 7.32 (3H, m, 3xAr-*H*), 5.11 (1H, s, NC*H*(Ar)CN), 3.82 – 3.65 (1H, m, NCHC*H*OTBS), 3.34 (1H, ddd, *J* =12.8, 9.2, 4.0, NC*H*CHOTBS), 3.11 (3H, s, NCH_3), 2.11 – 1.97 (1H, m, C*H*), 1.61 – 1.52 (1H, m, C*H*), 1.52 – 1.43 (1H, m, C*H*), 1.39 – 1.20 (1H, m, C*H*), 1.15 – 1.03 (3H, m, C*H*), 0.96 (9H, s, SiC(CH_3)$_3$), 0.67 – 0.55 (1H, m, C*H*), 0.27 (3H, s, Si(C$H_{3,A}$)(CH$_{3,B}$)), 0.16 (3H, s, Si(CH$_{3,A}$)(C$H_{3,B}$)); **^{13}C NMR** (126 MHz, $CDCl_3$): 160.48 (*C*=O), 146.13 (C_{Ar}), 129.01 (2xC_{Ar}D, t, $^{1}J^{C\text{-}D}$=23.94), 125.51 – 125.01 (3xC_{Ar}D), 134.22 (C_{Ar}), 128.53 (C_{Ar}H), 128.45 (2xC_{Ar}H), 128.37 (2xC_{Ar}H), 118.18 (*C* ≡ N) 71.64 (NCH*C*HOTBS), 65.05 (N*C*HCHOTBS), 47.79 (N*C*H(Ar)CN), 39.71 (N*C*H_3), 36.90 (*C*H_2), 29.61 (*C*H_2), 26.36 (SiC(*C*H_3)$_3$), 25.30 (*C*H_2), 24.36 (*C*H_2), 18.37 (Si*C*(CH$_3$)$_3$), −3.51 (Si(CH$_{3,A}$)(*C*H$_{3,B}$)), −3.69 (Si(*C*H$_{3,A}$)(CH$_{3,B}$)); (**IR (vmax/cm^{-1}) (neat)**: 2930, 2856 (alkyl C-H), 2278 (C≡N), 1659 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{28}H_{35}D_5N_3O_2Si$ $[M+H]^+$ 483.319814, found 483.319781.

1-((1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-1-(cyano(phenyl)methyl)-3-(4-fluorophenyl)-3-methylurea (488ec)



Following general **procedure 21**: triphosgene (134 mg, 0.45 mmol) in anhydrous DCM (5.20 mL), 2,6-lutidine (0.16 mL, 1.35 mmol) and *N*-alkyl-OTBS amino nitrile **494c** (389 mg, 1.13 mmol). The crude carbamoyl chloride **495c** (359 mg) was yielded as a yellow oil which was used immediately without further purification. Following general **procedure 22 method B**: 2,6-lutidine (0.12 mL,

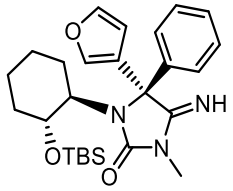
1.06 mmol), 4-fluoro-*N*-methyl aniline (0.12 mL, 0.97 mmol) and carbamoyl chloride **495c** (359 mg, 0.88 mmol) in anhydrous CH_3CN (1.00 mL). The crude product was purified by flash column chromatography (Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 80:20) to afford the title compound (317 mg, 58% over 2 steps; 50:50 *dr*, relative stereochemistry undetermined) as the two separated diastereoisomers A:B.

Diast. A: orange oil. **R*f*** (8:2 Pet.Ether:Diethyl ether) 0.25; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.58 – 7.51 (2H, m, 2xAr-*H*), 7.39 – 7.32 (3H, m, 3xAr-*H*), 7.08 – 6.98 (4H, m, 4xAr-*H*), 5.83 (1H, s, NC*H*(Ar)CN), 4.08 (1H, td, *J* = 9.9, 4.3, NCHC*H*OTBS), 3.28 (1H, td, *J* = 9.9, 3.5, NC*H*CHOTBS), 3.16 (3H, s, NCH_3), 2.04 – 1.95 (1H, m, C*H*), 1.83 – 1.68 (1H, m, C*H*), 1.65 – 1.46 (3H, m, 3xC*H*), 1.33 – 1.11 (2H, m, 2xC*H*), 1.07 – 0.98 (1H, m, C*H*), 0.87 (9H, s, SiC(CH_3)$_3$), 0.09 (3H, s, Si(C$H_{3,A}$)(C$H_{3,B}$)), 0.04 (3H, s, Si(C$H_{3,A}$)(C$H_{3,B}$)); **^{13}C NMR** (126 MHz, $CDCl_3$): 161.57 (*C*=O), 160.57 (*C*$_{Ar}$, d, $^1J^{C\text{-}F}$ = 246.2), 141.84 (*C*$_{Ar}$, d, $^4J^{C\text{-}F}$ = 3.1), 134.71 (*C*$_{Ar}$), 128.62 (3x*C*$_{Ar}$H, overlap), 127.67 (2x*C*$_{Ar}$H), 126.98 (2x*C*$_{Ar}$H, d, $^3J^{C\text{-}F}$ = 8.3), 118.68 (*C*≡N), 116.47 (2x*C*$_{Ar}$H, d, $^2J^{C\text{-}F}$ = 22.6), 71.98 (NCH*C*HOTBS), 65.71 (N*C*HCHOTBS), 49.23 (N*C*H(Ar)CN), 40.57 (N*C*H$_3$), 37.00 (*C*H$_2$), 29.86 (*C*H$_2$), 26.24 (SiC(*C*H$_3$)$_3$), 25.88 (*C*H$_2$), 24.44 (*C*H$_2$), 18.34 (Si*C*(CH$_3$)$_3$), −3.26 (Si(CH$_{3,A}$)(*C*H$_{3,B}$)), −3.53 (Si(*C*H$_{3,A}$)(CH$_{3,B}$)); **(IR (vmax/cm^{-1}) (neat)**: 2926, 2855 (alkyl C-H), 2253 (C≡N), 1661 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{28}H_{38}FN_3O_2SiNa$ $[M+Na]^+$ 518.260953, found 518.259538.

Diast. B: yellow oil. **R*f*** (8:2 Pet.Ether:Diethyl ether) 0.22; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.56 – 7.52 (2H, m, 2xAr-*H*), 7.44 – 7.33 (3H, m, 3xAr-*H*), 7.04 – 6.98 (2H, m, 2xAr-*H*), 6.87 – 6.81 (2H, m, 2xAr-*H*), 5.09 (1H, s, NC*H*(Ar)CN), 3.76 (1H, td, *J* = 9.5, 4.7, NCHC*H*OTBS), 3.34 (1H, ddd, *J* = 12.9, 9.3, 4.0, NC*H*CHOTBS), 3.05 (3H, s, NCH_3), 2.12 – 2.02 (1H, m, C*H*), 1.64 – 1.49 (2H, m, 2xC*H*), 1.32 – 1.18 (1H, m, C*H*), 1.12 – 1.05 (3H, m, 3xC*H*), 0.95 (9H, s, SiC(CH_3)$_3$), 0.74 – 0.66 (1H, m, C*H*), 0.26 (3H, s, Si(C$H_{3,A}$)(CH$_{3,B}$)), 0.16 (3H, s, Si(CH$_{3,A}$)(C$H_{3,B}$)); **^{13}C NMR** (126 MHz, $CDCl_3$): 160.58 (*C*=O), 160.47 (*C*$_{Ar}$, d, $^1J^{C\text{-}F}$ = 246.10), 142.34 (*C*$_{Ar}$, d, $^4J^{C\text{-}F}$ = 3.2), 134.08 (*C*$_{Ar}$), 128.63 (*C*$_{Ar}$H), 128.47 (2x*C*$_{Ar}$H), 128.39 (2x*C*$_{Ar}$H), 127.42 (2x*C*$_{Ar}$H, d, $^3J^{C\text{-}F}$ = 8.2), 118.07 (*C*≡N), 116.31 (2x*C*$_{Ar}$H, d, $^2J^{C\text{-}F}$ = 22.6), 71.63 (NCH*C*HOTBS), 65.23 (N*C*HCHOTBS), 47.71 (N*C*H(Ar)CN), 40.00 (N*C*H$_3$), 36.92 (*C*H$_2$), 29.72 (*C*H$_2$), 26.34 (SiC(*C*H$_3$)$_3$), 25.42 (*C*H$_2$), 24.33 (*C*H$_2$), 18.36 (Si*C*(CH$_3$)$_3$), −3.44 (Si(CH$_{3,A}$)(*C*H$_{3,B}$)), −3.76 (Si(*C*H$_{3,A}$)(CH$_{3,B}$)); **(IR (vmax/cm^{-1}) (neat)**: 2926, 2855 (alkyl C-H), 2240 (C ≡ N), 1662 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{28}H_{39}FN_3O_2Si$ $[M+H]^+$ 496.279009, found 496.277731.

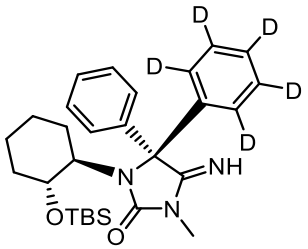
4.3.4.2 Aryl Migration of α-Amino Nitrile Ureas

(*R*)-3-((1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-4-(furan-3-yl)-5-imino-1-methyl-4-phenylimidazolidin-2-one (489ea)



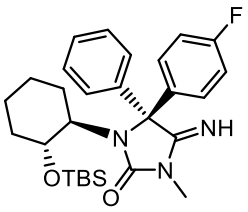
Following general **procedure 23 method A**: LDA (2.0 M in THF/heptane/ethylbenzene, 0.16 mL, 0.32 mmol) and α-amino nitrile urea **488ea** (50.0 mg, 0.107 mmol; diast. A) in anhydrous THF (0.94 mL). The crude product (>95:5 dr by NMR) was purified by flash column chromatography (SiO_2; *n*Hexane:EtOAc 100:0 to *n*Hexane:EtOAc 70:30) to afford the title compound (33.8 mg, 68%; >95:5 *dr*) as a yellow oil. The same diastereoisomer **489ea** was obtained (85%, >95:5 *dr* by ^{1}HNMR) after performing the reaction from **488ea** (diast. B). **R*f*** (7:3 *n*Hexane:EtOAc) 0.19; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.83 – 7.77 (2H, m, 2xAr-*H*), 7.45 (1H, t, =1.7, Ar-*H*), 7.41 – 7.33 (4H, m, 4xAr-*H*), 6.25 (1H, dd, *J* = 2.0, 0.9, Ar-*H*), 4.76 (1H, br. s, NCHC*H*OTBS), 3.11 (3H, s, NCH_3), 3.00 – 2.86 (1H, m, NC*H*CHOTBS), 1.98 – 1.89 (1H, m, C*H*), 1.63 – 1.53 (2H, m, 2xC*H*), 1.50 – 1.40 (1H, m, C*H*), 1.31 – 1.24 (1H, m, C*H*), 1.23 – 1.15 (1H, m, *CH*), 1.06 – 0.95 (1H, m, C*H*), 0.94 (9H, s, SiC(CH_3)$_3$), 0.91 – 0.87 (1H, m, C*H*), 0.19 (3H, s, Si(C$H_{3,A}$)(C$H_{3,B}$)), 0.08 (3H, Si(C$H_{3,A}$)(C$H_{3,B}$)); **^{13}C NMR** (101 MHz, $CDCl_3$): 167.26 (*C*=N), 155.86 (*C*=O), 143.85 (C_{Ar}H), 142.47 (2xC_{Ar}H), 137.84 (C_{Ar}), 128.85 (2xC_{Ar}H), 128.27 (2xC_{Ar}H), 126.20 (C_{Ar}), 110.96 (C_{Ar}H), 69.05 (N*C*(Ar)Ph), 72.48 (NCH*C*HOTBS), 61.16 (N*C*HCHOTBS), 37.48 (*C*H$_2$), 29.87 (*C*H$_2$), 26.23 (SiC(*C*H$_3$)$_3$), 25.7 (N*C*H$_3$), 25.48 (*C*H$_2$), 24.76 (*C*H$_2$), 18.33 (Si*C*(CH$_3$)$_3$), −3.75 (Si(CH$_{3,A}$)(C$H_{3,B}$)), −5.54 (Si(*C*H$_{3,A}$)(CH$_{3,B}$)); (**IR (vmax/cm^{-1}) (neat)**: 3311 (NH), 2929 (alkyl C-H), 2856 (alkyl C-H), 1732 (C=N), 1659 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{26}H_{38}N_3O_3Si$ $[M+H]^+$ 468.267695, found 468.268048.

(*S*)-3-((1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-5-imino-1-methyl-4-phenyl-4-(phenyl-d5)imidazolidin-2-one (489ed)



Following general **procedure 23 method A**: LDA (2.0 M in THF/heptane/ethylbenzene, 0.20 mL, 0.40 mmol) and α-amino nitrile urea **488ed** (65.0 mg, 0.135 mmol) in anhydrous THF (1.20 mL). The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 50:50) to afford the title compound (49.0 mg, 75%; >95:5 *dr* by 2D-NMR) as an orange oil. **R*f*** (5:5 Pet.Ether:Diethyl ether) 0.17; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 – 7.31 (3H, m, 3xAr-*H*), 7.27 – 7.23 (2H, m, 2xAr-*H*), 4.87 – 4.68 (1H, m, NCHC*H*OTBS), 3.14 (3H, s, NCH_3), 2.91 (1H, ddd, J = 11.9, 9.6, 3.0, NC*H*CHOTBS), 1.97 – 1.87 (1H, m, C*H*), 1.57 – 1.46 (1H, m, C*H*), 1.32 – 1.28 (1H, m, C*H*), 1.22 – 1.18 (3H, m, 3xC*H*), 0.97 (9H, s, SiC(CH_3)$_3$), 0.73 – 0.64 (1H, m, C*H*), 0.20 (3H, s, Si(C$H_{3,A}$)($CH_{3,B}$)), 0.09 (3H, Si($CH_{3,A}$)(C$H_{3,B}$)), 0.06 to −0.01 (1H, m, C*H*); **^{13}C NMR** (126 MHz, $CDCl_3$): 167.99 (*C*=N), 155.80 (*C*=O), 128.77 – 127.69 (5xC_{Ar}D, m), 140.99 (C_{Ar}), 138.35 (C_{Ar}), 129.11 (2xC_{Ar}H), 129.07 (C_{Ar}H), 128.83 (2xC_{Ar}H), 75.28 (N*C*(Ar)Ph), 72.52 (NCH*C*HOTBS), 61.11 (N*C*HCHOTBS), 37.59 (*C*H_2), 29.36 (*C*H_2), 26.22 (SiC(*C*H_3)$_3$), 25.61 (N*C*H_3), 25.37 (*C*H_2) 24.72 (*C*H_2), 18.35 (Si*C*(CH_3)$_3$), −3.79 (Si($CH_{3,A}$)(C$H_{3,B}$)), −5.61 (Si(*C*$H_{3,A}$)($CH_{3,B}$)); **(IR (vmax/cm^{-1}) (neat)**: 3314 (NH), 2928 (alkyl C-H), 2855 (alkyl C-H), 1731 (C=N), 1658 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{28}H_{35}D_5N_3O_2Si$ $[M+H]^+$ 483.319814, found 483.319764.

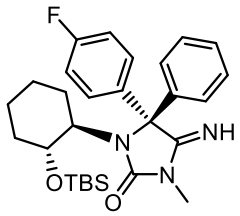
(*S*)-3-((1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-4-(4-fluorophenyl)-5-imino-1-methyl-4-phenylimidazolidin-2-one (489ec)



Following general **procedure 23 method B**: DMPU (0.10 mL), α-amino nitrile urea **488ec** (53.3 mg, 0.107 mmol) in anhydrous THF (1.00 mL) and LDA (2.0 M in THF/heptane/ethylbenzene, 0.13 mL, 0.27 mmol). The crude product (94:6 *dr* by ^{19}F NMR) was purified by flash column chromatography (SiO_2; Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 70:30) to afford the title compound (27.0 mg, 51%; 94:6 *dr*) as a yellow oil. **R*f*** (7:3 Pet.Ether:Diethyl ether) 0.25; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.89 – 7.83 (2H, m, 2xAr-*H*), 7.40 – 7.32 (3H, m, 3xAr-*H*), 7.25 – 7.21 (2H, m, 2xAr-*H*), 7.10 – 7.03 (2H, m, 2xAr-*H*), 4.78 (1H, dt, *J* = 10.2, 5.2, NCHC*H*OTBS), 3.14

(3H, s, NCH_3), 2.87 (1H, ddd, J = 11.9, 9.7, 3.0 NC*H*CHOTBS), 1.97 – 1.88 (1H, m, C*H*), 1.57 – 1.48 (1H, m, C*H*), 1.33 – 1.27 (1H, m, C*H*), 1.24 – 1.17 (3H, m, 3xC*H*), 0.96 (9H, s, SiC(CH_3)$_3$), 0.76 – 0.64 (1H, m, C*H*), 0.20 (3H, s, Si(C$H_{3,A}$)(C$H_{3,B}$)), 0.07 (3H, Si(C$H_{3,A}$)(C$H_{3,B}$)), 0.06 to −0.03 (1H, m, C*H*); **^{13}C NMR** (101 MHz, $CDCl_3$): 167.83 (*C*=N), 162.91 (*C*$_{Ar}$, d, $^1J^{C\text{-}F}$ = 248.0), 155.67 (*C*=O), 140.82 (*C*$_{Ar}$), 134.32 (*C*$_{Ar}$, d, $^4J^{C\text{-}F}$ = 3.1), 130.78 (2x*C*$_{Ar}$H, d, $^3J^{C\text{-}F}$ = 8.0), 129.22 (*C*$_{Ar}$H), 129.00 (2x*C*$_{Ar}$H), 128.95 (2x*C*$_{Ar}$H), 115.58 (2x*C*$_{Ar}$H, d, $^2J^{C\text{-}F}$ = 21.4), 74.81 (N*C*(Ar)Ph), 72.56 (NCH*C*HOTBS), 61.15 (N*C*HCHOTBS), 37.59 (*C*H$_2$), 29.34 (*C*H$_2$), 26.21 (SiC(*C*H$_3$)$_3$), 25.59 (N*C*H$_3$), 25.37 (*C*H$_2$), 24.71 (*C*H$_2$), 18.36 (Si*C*(CH$_3$)$_3$), −3.77 (Si(CH$_{3,A}$)(C*H*$_{3,B}$)), −5.61 (Si(*C*H$_{3,A}$)(CH$_{3,B}$)); **^{19}F NMR** (377 MHz, $CDCl_3$) δ_F −114.09; (**IR (vmax/cm^{-1}) (neat)**: 3321 (NH), 2930 (alkyl C-H), 2856 (alkyl C-H), 1737 (C=N), 1660 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{28}H_{39}FN_3O_2Si$ $[M+H]^+$ 496.279009, found 496.280607.

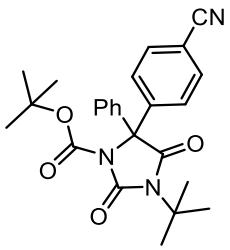
(*R*)-3-((1*R*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)-4-(4-fluorophenyl)-5-imino-1-methyl-4-phenylimidazolidin-2-one (489eb)



Following general **procedure 23 method A**: LDA (2.00 M in THF/heptane/ethylbenzene, 0.14 mL, 0.29 mmol) and α-amino nitrile urea **488eb** (47.5 mg, 0.096 mmol) in anhydrous THF (0.84 mL). The crude product (98:2 *dr* by ^{19}F NMR) was purified by flash column chromatography (SiO_2; Pet.Ether:Diethyl ether 100:0 to Pet.Ether:Diethyl ether 60:40) to afford the title compound (44.1 mg, 93%; 98:2 *dr*) as a colourless oil. **R*f*** (6:4 Pet.Ether:Diethyl ether) 0.17; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.86 – 7.81 (2H, m, 2xAr-*H*), 7.43 – 7.33 (3H, m, 3xAr-*H*), 7.26 – 7.21 (2H, m, 2xAr-*H*), 7.08 – 7.01 (2H, m, 2xAr-*H*), 4.83 – 4.74 (1H, m, NCHC*H*OTBS), 3.13 (3H, s, NCH_3), 2.89 (1H, ddd, *J* = 11.9, 9.6, 3.0 NC*H*CHOTBS), 1.97 – 1.89 (1H, m, C*H*), 1.58 – 1.51 (1H, m, C*H*), 1.39 – 1.21 (2H, m, 2xC*H*), 1.23 – 1.15 (2H, m, 2xC*H*), 0.96 (9H, s, SiC(CH_3)$_3$), 0.78 – 0.66 (1H, m, C*H*), 0.20 (3H, s, Si(C$H_{3,A}$)(CH$_{3,B}$)), 0.12 (1H, br. s, C*H*), 0.08 (3H, Si(CH$_{3,A}$)(C$H_{3,B}$)); **^{13}C NMR** (101 MHz, $CDCl_3$): 167.79 (*C*=N), 162.95 (*C*$_{Ar}$, d, $^1J^{C\text{-}F}$ = 249.8), 155.69 (*C*=O), 138.35 (*C*$_{Ar}$), 137.06 (*C*$_{Ar}$,), 131.05 (2x*C*$_{Ar}$H, d, $^3J^{C\text{-}F}$ = 8.2), 128.80 (2x*C*$_{Ar}$H), 128.70 (2x*C*$_{Ar}$H), 128.53 (*C*$_{Ar}$H), 115.84 (2x*C*$_{Ar}$H, d, $^2J^{C\text{-}F}$ = 21.5), 74.67 (N*C*(Ar)Ph), 72.52 (NCH*C*HOTBS), 61.09 (N*C*HCHOTBS), 37.59 (*C*H$_2$), 29.56 (*C*H$_2$), 26.23 (SiC(*C*H$_3$)$_3$), 25.63 (N*C*H$_3$), 25.40 (*C*H$_2$), 24.70 (*C*H$_2$), 18.35 (Si*C*(CH$_3$)$_3$), −3.78 (Si(CH$_{3,A}$)(C*H*$_{3,B}$)), −5.59 (Si(*C*H$_{3,A}$)(CH$_{3,B}$)); **^{19}F NMR** (377 MHz, $CDCl_3$) δ_F −112.09; (**IR (vmax/cm^{-1}) (neat)**: 3315 (NH), 2929, 2856 (alkyl C-H), 1732 (C=N), 1656 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{28}H_{39}FN_3O_2Si$ $[M+H]^+$ 496.279009, found 496.281124.

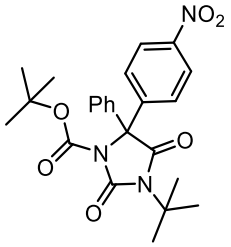
4.3.5 Appendix compounds

***tert*-Butyl 3-(*tert*-butyl)-5-(4-cyanophenyl)-2,4-dioxo-5-phenylimidazolidine-1-carboxylate (502a)**



To a solution of the hydantoin urea **273a** (100 mg, 0.256 mmol, 1.00 eq.), in anhydrous CH_3CN (3.00 mL) was added Boc anhydride (118 mg, 0.54 mmol, 2.08 eq.) and DMAP (6.3 mg, 0.05 mmol, 0.20 eq.). The reaction mixture was stirred at room temperature for 15 hours. The solvent was then removed under reduced pressure and the residue dissolved in ethyl acetate and washed with water. The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 80:20) to afford the title compound (72 mg, 65%) as a cloudy oil. **R*f*** (8:2 Pet.Ether:EtOAc) 0.39; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.73 – 7.66 (2H, m, Ar-*H*), 7.59 – 7.53 (2H, m, Ar-*H*), 7.42 – 7.36 (3H, m, Ar-*H*), 7.32 – 7.28 (2H, m, Ar-*H*), 1.63 (9H, s, NC(CH_3)$_3$), 1.19 (9H, s, OC(CH_3)$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): 172.03 (*C*=O)$_{boc}$, 152.55 (*C*=O), 147.87, (*C*=O), 141.60 (C_{Ar}), 136.03 (C_{Ar}), 131.94 (2xC_{Ar}H), 129.40 (2xC_{Ar}H), 129.23 (C_{Ar}H), 128.56 (2xC_{Ar}H), 128.30 (2xC_{Ar}H), 118.39 (*C*N), 112.75 (C_{Ar}), 84.86 (O*C*(CH_3)$_3$), 72.33 (N*C*Ph), 60.21 (N*C*(CH_3)$_3$), 28.63 (NC(*C*H_3)$_3$), 27.78 (OC(*C*H_3)$_3$)); **IR (vmax/cm^{-1}) (neat)**: 2980, 2931 (alkyl C-H), 2230 (C≡N), 1809, 1748, 1737 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{25}H_{27}N_3O_4Na$ $[M+Na]^+$ 456.1894, found 456.1900.

***tert*-Butyl 3-(*tert*-butyl)-5-(4-nitrophenyl)-2,4-dioxo-5-phenylimidazolidine-1-carboxylate (502e)**



To a solution of the hydantoin urea **273e** (277 mg, 0.68 mmol, 1.00 eq.) in anhydrous CH_3CN was added Boc anhydride (309 mg, 1.41 mmol, 2.08 eq.) and DMAP (17.0 mg, 0.14 mmol, 0.20 eq.). The reaction mixture was stirred at room temperature for 15 hours. The solvent was then removed under reduced pressure and the residue dissolved in ethyl acetate and washed with water. The organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; Pet.Ether:EtOAc 100:0 to Pet.Ether:EtOAc 90:10) to afford the title compound (100 mg, 32%) as a white solid. **R*f*** (9:1 Pet.Ether:EtOAc) 0.29; **mp**: 170 – 173 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.25 (2H, d, *J* = 8.9, Ar-*H*), 7.64 (2H, d, *J* = 8.9, Ar-*H*), 7.40 (3H, dt, *J* = 4.6, 2.9, Ar-*H*), 7.33 – 7.28 (2H, m, Ar-*H*), 1.64 (9H, s, NC(CH_3)$_3$), 1.20 (9H, s, OC(CH_3)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): 171.76 (*C*=O)$_{boc}$, 152.34 (*C*=O)$_{urea}$, 147.82 (*C*=O)$_{amide}$, 147.70 (C_{Ar}), 143.14 (C_{Ar}), 136.01 (C_{Ar}), 129.53 (2xC_{Ar}H) 129.14 (C_{Ar}H), 128.45 (2xC_{Ar}H), 128.13 (2xC_{Ar}H), 123.12 (2xC_{Ar}H), 84.81 (O*C*(CH_3)$_3$), 72.12 (N*C*Ph), 60.11 (N*C*(CH_3)$_3$), 28.47 (NC(*C*H_3)$_3$), 27.63 (OC(*C*H_3)$_3$); **IR (vmax/cm^{-1}) (neat)**: 2980, 2932 (alkyl C-H), 1808, 1747, 1737 (C=O); **HRMS** (ESI): *m/z* calcd for $C_{24}H_{27}N_3O_6Na$ $[M+Na]^+$ 476.1792, found 476.1796.

4.4 1D NOE evidence for *cis* configuration of conjugation addition products

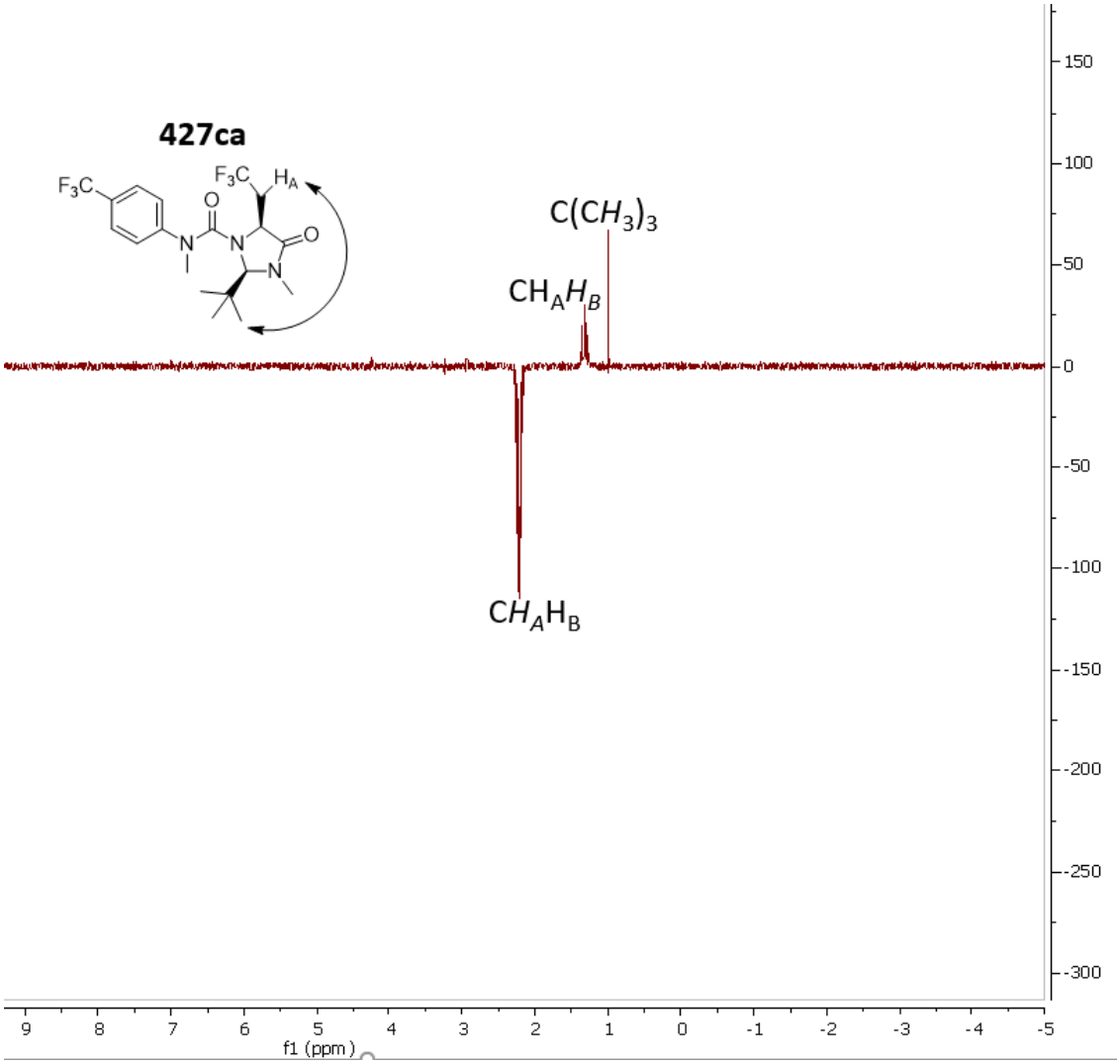


Figure 16: 1D NOE evidence for *cis* configuration of **427ca**

5 References

(1) Clayden, J.; Greeves, N.; Warren, S. Organic Chemistry; Oxford University Press: Oxford, 2012; p 16.

(2) Winter, G.; Todd, C. D.; Trovato, M.; Forlani, G.; Funck, D. *Front. Plant Sci.* **2015**, *6*, 1.

(3) Hornback, J. M. Organic Chemistry; Thomson Brooks/Cole: London, 2006; pp 1146–1147.

(4) Hornback, J. M. Organic Chemistry; Thomson Brooks/Cole: London, 2006; p 1123.

(5) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406.

(6) Dewick, P. M. Essentials of Organic Chemistry; John Wiley & Sons Inc.: New York, 2006; pp 505–513.

(7) Carey, F. A.; Giuliano, R. M. Organic Chemistry; Mc. Graw Hill Companies: New York, 2011; p 1128.

(8) Smith, J. G. Organic Chemistry; Mc. Graw Hill Companies: New York, 2011; pp 1079–1080.

(9) Tanaka, M. *Chem. Pharm. Bull.* **2007**, *55*, 349.

(10) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron Asymmetry* **2007**, *18*, 569.

(11) Formaggio, F.; Crisma, M.; Rossi, P.; Scrimin, P.; Kaptein, B.; Broxterman, Q. B.; Kamphuis, J.; Toniolo, C. *Chem. Eur. J.* **2000**, *6*, 4498.

(12) Pispisa, B.; Stella, L.; Venanzi, M.; Palleschi, A.; Polese, A.; Formaggio, F.; Toniolo, C. *J. Pept. Res.* **2000**, *56*, 298.

(13) Cirilli, M.; Coiro, V. M.; Di Nola, A.; Mazza, F. *Biopolymers* **1998**, *46*, 239.

(14) Tanaka, M.; Imawaka, N.; Kurihara, M.; Suemune, H. *Helv. Chim. Acta* **1999**, *82*, 494.

(15) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron Asymmetry* **1998**, *9*, 3517.

(16) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron Asymmetry* **2000**, *11*, 645.

(17) Schöllkopf, U. *Top. Curr. Chem.* **1983**, *109*, 65.

(18) Schöllkopf, U. *Tetrahedron* **1983**, *39*, 2085.

(19) Schöllkopf, U. *Pure Appl. Chem.* **1983**, *55*, 1799.

(20) Schollkopf, V. U.; Hartwig, W. *Angew. Chemie* **1979**, *91*, 922.

(21) Schöllkopf, U.; Groth, U.; Westphalen, K.-O.; Deng, C. *Synthesis* **1981**, No. 12, 969.

(22) Schöllkopf, U.; Groth, U.; Hartwig, W. *Liebigs Ann. der Chemie* **1981**, No. 12, 2407.

(23) Groth, U.; Schöllkopf, U.; Chiang, Y.-C. *Synthesis* **1982**, No. 10, 864.

(24) Schöllkopf, U.; Lonsky, R.; Lehr, P. *Liebigs Ann. der Chemie* **1985**, No. 2, 413.

(25) Meyer, L.; Poirier, J. M.; Duhamel, P.; Duhamel, L. *J. Org. Chem.* **1998**, *63*, 8094.

(26) Miyashita, K.; Miyabe, H.; Tai, K.; Kurozumi, C.; Iwaki, H.; Imanishi, T. *Tetrahedron* **1999**, *55*, 12109.

(27) Alezra, V.; Bonin, M.; Chiaroni, A.; Micouin, L.; Riche, C.; Husson, H. P. *Tetrahedron Lett.*

2000, *41*, 1737.

(28) Wenglowsky, S. *J. Am. Chem. Soc.* **1998**, *120*, 12468.

(29) Paradisi, F.; Piccinelli, F.; Porzi, G.; Sandri, S. *Tetrahedron-Asymmetry* **2002**, *13*, 497.

(30) Ferioli, F.; Piccinelli, F.; Porzi, G.; Sandri, S. *Tetrahedron Asymmetry* **2002**, *13*, 1181.

(31) Piccinelli, F.; Porzi, G.; Sandri, M.; Sandri, S. *Tetrahedron Asymmetry* **2003**, *14*, 393.

(32) Seebach, D.; Hoffmann, M. *European J. Org. Chem.* **1998**, No. 7, 1337.

(33) Carloni, A.; Porzi, G.; Sandri, S. *Tetrahedron Asymmetry* **1998**, *9*, 2987.

(34) Porzi, G.; Sandri, S. *Tetrahedron Asymmetry* **1998**, *9*, 3411.

(35) Aoyagi, Y.; Williams, R. M. *Synlett* **1998**, No. 10, 1099.

(36) Oishi, S.; Kang, S. U.; Liu, H.; Zhang, M.; Yang, D.; Deschamps, J. R.; Burke, T. R. *Tetrahedron* **2004**, *60*, 2971.

(37) Lee, S. H.; Lee, E. K.; Jeun, S. M. *Bull. Korean Chem. Soc.* **2002**, *23*, 931.

(38) Dixon, D. J.; Harding, C. I.; Ley, V.; Tilbrook, D. M. G. **2003**, 468.

(39) Ding, K.; Ma, D. *Tetrahedron* **2001**, *57*, 6361.

(40) Ma, D.; Ding, K. *Org. Lett.* **2000**, *2*, 2515.

(41) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2708.

(42) Yee, N. K. *Org. Lett.* **2000**, *2*, 2781.

(43) Yee, N. K.; Nummy, L. J.; Frutos, R. P.; Song, J. J.; Napolitano, E.; Byrne, D. P.; Jones, P. J.; Farina, V. *Tetrahedron Asymmetry* **2003**, *14*, 3495.

(44) Knight, B. J.; Stache, E. E.; Ferreira, E. M. *Org. Lett.* **2014**, *16*, 432.

(45) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390.

(46) Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704.

(47) Seebach, D.; Naef, R. **1985**, *68*, 135.

(48) Seebach, D.; Aebi, J. D.; Naef, R.; Weber, T. *Helv. Chim. Acta* **1985**, *68*, 144.

(49) Hess, S. M.; Connamacher, M.; Ozaki, M.; Udenfriend, S. *J. Pharmacol. Exp. Ther.* **1961**, *134*, 129.

(50) Porter, C. C.; Totaro, J. A.; Leiby, C. M. *J. Pharmacol. Exp. Ther.* **1961**, *134*, 139.

(51) Amer, M. M.; Abas, H.; Leonard, D. J.; Ward, J. W.; Clayden, J. *J. Org. Chem.* **2019**, *84*, 7199.

(52) Seebach, D.; Aebi, J. D. **1985**, *68*, 1507.

(53) Karady, S.; Amto, J. S.; Weinstock, L. M. *Tetrahedron Lett.* **1984**, *25*, 4337.

(54) Hiskey, R. G.; Jung, J. M. *J. Am. Chem. Soc.* **1963**, *85*, 578.

(55) Seebach, D.; Fadel, A. *Helv. Chim. Acta* **1985**, *68*, 1243.

(56) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237.

(57) Zhang, J.; Flippen-Anderson, J. L.; Kozikowski, A. P. *J. Org. Chem.* **2001**, *66*, 7555.

(58) Kapadia, S. R.; Spero, D. M.; Eriksson, M. *J. Org. Chem.* **2001**, *66*, 1903.

(59) Juaristi, E.; López-Ruiz, H.; Madrigal, D.; Ramírez-Quirós, Y.; Escalante, J. *J. Org. Chem.* **1998**, *63*, 4706.

(60) Berkowitz, D. B.; McFadden, J. M.; Chisowa, E.; Semerad, C. L. *J. Am. Chem. Soc.* **2000**, *122*, 11031.

(61) Ashwood, V. A.; Field, M. J.; Horwell, D. C.; Julien-Larose, C.; Lewthwaite, R. A.; McCleary, S.; Pritchard, M. C.; Raphy, J.; Singh, L. *J. Med. Chem.* **2001**, *44*, 2276.

(62) Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis* **2005**, No. 1, 1.

(63) Kawabata, T.; Fuji, K. *Top. Stereochem.* **2003**, *23*, 175.

(64) Seebach, D.; Wasmuth, D. *Angew. Chemie* **1981**, *93*, 1007.

(65) Gees, T.; Schweizer, W. B.; Seebach, D. *Helv. Chim. Acta* **1993**, *76*, 2640.

(66) Beagley, B.; Betts, M. J.; Pritchard, Robin, G.; Schofield, A.; Stoodley, R. J.; Vohra, S. *J. Chem. Soc. Chem. Commun.* **1991**, No. 14, 924.

(67) Kawabata, T.; Wirth, T.; Yahiro, K.; Suzuki, H.; Fuji, K. *J. Am. Chem. Soc.* **1994**, *116*, 10809.

(68) Fuji, K.; Kawabata, T. *Chem. - A Eur. J.* **1998**, *4*, 373.

(69) Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. *Angew. Chemie - Int. Ed.* **2000**, *39*, 2155.

(70) Kawabata, T.; Moriyama, K.; Kawakami, S.; Tsubaki, K. *J. Am. Chem. Soc.* **2008**, *130*, 4153.

(71) Branca, M.; Pena, S.; Guillot, R.; Gori, D.; Alezra, V.; Kouklovsky, C. *J. Am. Chem. Soc.* **2009**, *131*, 10711.

(72) Viswambharan, B.; Gori, D.; Guillot, R.; Kouklovsky, C.; Alezra, V. *Org. Lett.* **2014**, *16*, 788.

(73) Bragg, R. A.; Clayden, J.; Morris, G. A.; Pink, J. H. *Chem. - A Eur. J.* **2002**, *8*, 1279.

(74) Williams, R. M. *Synthesis of Optically Active A-Amino Acids*; Pergamon Press: Oxford, 1989.

(75) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.

(76) Ma, D.; Tian, H.; Zou, G. *J. Org. Chem.* **1999**, *64*, 120.

(77) Hayashi, Y.; Sekiyama, N.; Nakanishi, S.; Jane, D. E.; Sunter, D. C.; Birse, E. F.; Udvarhelyi, P. M.; Watkins, J. C. *J. Neurosci.* **1994**, *14*, 3370.

(78) Sekiyama, N.; Hayashi, Y.; Nakanishi, S.; Jane, D. E.; Tse, H. W.; Birse, E. F.; Watkins, J. C. *Br. J. Pharmacol.* **1996**, *117*, 1493.

(79) Ma, D.; Tian, H. *Tetrahedron Asymmetry* **1996**, *7*, 1567.

(80) Jane, D. E.; Pittaway, K.; Sunter, D. C.; Thomas, N. K.; Watkins, J. C. *Neuropharmacology*

1995, *34*, 851.

(81) Pellicciari, R.; Luneia, R.; Costantino, G.; Marinozzi, M.; Natalini, B.; Jakobsen, P.; Kanstrup, A.; Lombardi, G.; Moroni, F.; Thomsen, C. *J. Med. Chem.* **1995**, *38*, 3717.

(82) Ma, D.; Tian, H.; Sun, H.; Kozikowski, A. P.; Pshenichkin, S.; Wroblewski, J. T. *Bioorganic Med. Chem. Lett.* **1997**, *7*, 1195.

(83) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883.

(84) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.

(85) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003.

(86) Avenoza, A.; Busto, J. H.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Synthesis* **2005**, No. 4, 575.

(87) Portolés, R.; Murga, J.; Falomir, E.; Carda, M.; Uriel, S.; Marco, J. A. *Synlett* **2002**, No. 5, 711.

(88) Maruoka, K. Asymmetric Phase-Transfer Catalysis; John Wiley & Sons, 2008; p 1.

(89) Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195.

(90) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656.

(91) Jew, S.-S.; Park, H.-G. *Chem. Commun.* **2009**, No. 46, 7090.

(92) O'Donnell, M. J.; Wu, S. *Tetrahedron: Asymmetry* **1992**, *3*, 591.

(93) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353.

(94) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595.

(95) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.

(96) Corey, E. J.; Noe, M. C.; Ting, A. Y. *Tetrahedron Lett.* **1996**, *37*, 1735.

(97) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671.

(98) O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507.

(99) Lygo, B.; Crosby, J.; Lowdon, T. R.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2391.

(100) Jew, S.-S.; Yoo, M.-S.; Jeong, B.-S.; Park, I. Y.; Park, H.-G. *Org. Lett.* **2002**, *4*, 4245.

(101) Jew, S.-S.; Jeong, B.-S.; Lee, J.-H.; Yoo, M.-S.; Lee, Y.-J.; Park, B.-S.; Kim, M.-G.; Park, H.-G. *J. Org. Chem.* **2003**, *68*, 4514.

(102) Lipkowitz, K. B.; Cavanaugh, M. W.; Baker, B.; O'Donnell, M. J. *J. Org. Chem.* **1991**, *56*, 5181.

(103) Ooi, T.; Uematsu, Y.; Maruoka, K. *Adv. Synth. Catal.* **2002**, *344*, 288.

(104) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519.

(105) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139.

(106) Maruoka, K. *J. Fluor. Chem.* **2001**, *112*, 95.

(107) Shirakawa, S.; Yamamoto, K.; Tokuda, T.; Maruoka, K. *Asian J. Org. Chem.* **2014**, *3*, 433.

(108) Shirakawa, S.; Yamamoto, K.; Maruoka, K. *Angew. Chemie - Int. Ed.* **2015**, *54*, 838.

(109) Wang, B.; Zhang, W.; Zhang, L.; Du, D. M.; Liu, G.; Xu, J. *European J. Org. Chem.* **2008**, No. 2, 350.

(110) Schoepp, D. D.; Jane, D. E.; Monn, J. A. *Neuropharmacology* **1999**, *38*, 1431.

(111) Moune, S.; Niel, G.; Busquet, M.; Eggleston, I.; Jouin, P. *J. Org. Chem.* **1997**, *62*, 3332.

(112) Ohata, K.; Terashima, S. *Chem. Pharm. Bull.* **2009**, *57*, 920.

(113) O'Connor, S. J.; Liu, Z. *Synlett* **2003**, No. 14, 2135.

(114) Gunasekara, N. S.; Spencer, C. M.; Keating, G. M. *Drugs* **2002**, *62*, 1217.

(115) Gallagher, Gregory, J.; Lavanchy, P. G.; Wilson, J. W.; Hieble, J. P.; DeMarinis, R. M. *J. Med. Chem.* **1985**, *28*, 1533.

(116) Mąkosza, M.; Surowiec, M.; Szczepańska, A.; Sulikowski, D.; Maltsev, O. *Synlett* **2007**, No. 3, 470.

(117) Mąkosza, M.; Sulikowski, D.; Maltsev, O. *Synlett* **2008**, No. 11, 1711.

(118) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701.

(119) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 99.

(120) Jones, E. P.; Jones, P.; White, A. J. P.; Barrett, A. G. M. *Beilstein J. Org. Chem.* **2011**, *7*, 1570.

(121) Lupi, V.; Penso, M.; Foschi, F.; Gassa, F.; Mihali, V.; Tagliabue, A. *Chem. Commun.* **2009**, No. 33, 5012.

(122) Foschi, F.; Landini, D.; Lupi, V.; Mihali, V.; Penso, M.; Pilati, T.; Tagliabue, A. *Chem. - A Eur. J.* **2010**, *16*, 10667.

(123) Jaouen, G. *Ann. N. Y. Acad. Sci.* **1977**, *295*, 59.

(124) Chaari, M.; Jenhi, A.; Lavergne, J.-P.; Viallefont, P. *Tetrahedron* **1991**, *47*, 4619.

(125) Oguri, T.; Kawai, N.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull. (Tokyo).* **1978**, *26*, 803.

(126) Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465.

(127) Jia, Y.-X.; Hillgren, J. M.; Watson, E. L.; Marsden, S. P.; Kündig, E. P. *Chem. Commun.* **2008**, No. 34, 4040.

(128) Marsden, S. P.; Watson, E. L.; Raw, S. A. *Org. Lett.* **2008**, *10*, 2905.

(129) Ochi, M.; Kawasaki, K.; Kataoka, H.; Uchio, Y.; Nishi, H. *Biochem. Biophys. Res. Commun.* **2001**, *283*, 1118.

(130) Bernard, K.; Bogliolo, S.; Ehrenfeld, J. *Br. J. Pharmacol.* **2005**, *144*, 1037.

(131) Liu, X.; Hartwig, J. F. *Org. Lett.* **2003**, *5*, 1915.

(132) Stambuli, J. P.; Bühl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9346.

(133) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816.

(134) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727.

(135) Fernández-Nieto, F.; Mas Roselló, J.; Lenoir, S.; Hardy, S.; Clayden, J. *Org. Lett.* **2015**, *17*,

3838.

(136) Thiverny, M.; Demory, E.; Baptiste, B.; Philouze, C.; Chavant, P. Y.; Blandin, V. *Tetrahedron Asymmetry* **2011**, *22*, 1266.

(137) Thiverny, M.; Farran, D.; Philouze, C.; Blandin, V.; Chavant, P. Y. *Tetrahedron Asymmetry* **2011**, *22*, 1274.

(138) Thiverny, M.; Philouze, C.; Chavant, P. Y.; Blandin, V. *Org. Biomol. Chem.* **2010**, *8*, 864.

(139) Demory, E.; Farran, D.; Baptiste, B.; Chavant, P. Y.; Blandin, V. *J. Org. Chem.* **2012**, *77*, 7901.

(140) Li, K.; Tan, G.; Huang, J.; Song, F.; You, J. *Angew. Chemie - Int. Ed.* **2013**, *52*, 12942.

(141) Clayden, J.; Dufour, J.; Grainger, D. M.; Helliwell, M. *J. Am. Chem. Soc.* **2007**, *129*, 7488.

(142) Clayden, J.; Farnaby, W.; Grainger, D. M.; Hennecke, U.; Mancinelli, M.; Tetlow, D. J.; Hillier, I. H.; Vincent, M. A. *J. Am. Chem. Soc.* **2009**, *131*, 3410.

(143) Clayden, J.; Parris, S.; Cabedo, N.; Payne, A. H. *Angew. Chemie - Int. Ed.* **2008**, *47*, 5060.

(144) Fournier, A. M.; Brown, R. A.; Farnaby, W.; Miyatake-Ondozabal, H.; Clayden, J. *Org. Lett.* **2010**, *12*, 2222.

(145) Fournier, A. M.; Clayden, J. *Org. Lett.* **2012**, *14*, 142.

(146) Fournier, A. M.; Nichols, C. J.; Vincent, M. A.; Hillier, I. H.; Clayden, J. *Chem. - A Eur. J.* **2012**, *18*, 16478.

(147) MacLellan, P.; Clayden, J. *Chem. Commun.* **2011**, *47*, 3395.

(148) Mingat, G.; Maclellan, P.; Laars, M.; Clayden, J. *Org. Lett.* **2014**, *16*, 1252.

(149) Mingat, G.; McDouall, J. J. W.; Clayden, J. *Chem. Commun.* **2014**, *50*, 6754.

(150) Mas-Roselló, J.; Hachisu, S.; Clayden, J. *Angew. Chemie - Int. Ed.* **2017**, *56*, 10750.

(151) Abas, H.; Mas-Roselló, J.; Amer, M. M.; Durand, D. J.; Groleau, R. R.; Fey, N.; Clayden, J. *Angew. Chemie - Int. Ed.* **2019**, *58*, 2418.

(152) Atkinson, R. C.; Leonard, D. J.; Maury, J.; Castagnolo, D.; Volz, N.; Clayden, J. *Chem. Commun.* **2013**, *49*, 9734.

(153) Atkinson, R. C.; Fernández-Nieto, F.; Mas Rosellõ, J.; Clayden, J. *Angew. Chemie - Int. Ed.* **2015**, *54*, 8961.

(154) Tomohara, K.; Yoshimura, T.; Hyakutake, R.; Yang, P.; Kawabata, T. *J. Am. Chem. Soc.* **2013**, *135*, 13294.

(155) Yoshimura, T.; Kinoshita, T.; Yoshioka, H.; Kawabata, T. *Org. Lett.* **2013**, *15*, 864.

(156) Watanabe, H.; Yoshimura, T.; Kawakami, S.; Sasamori, T.; Tokitoh, N.; Kawabata, T. *Chem. Commun.* **2012**, *48*, 5346.

(157) Yoshimura, T.; Takuwa, M.; Tomohara, K.; Uyama, M.; Hayashi, K.; Yang, P.; Hyakutake, R.; Sasamori, T.; Tokitoh, N.; Kawabata, T. *Chem. - A Eur. J.* **2012**, *18*, 15330.

(158) Maury, J.; Clayden, J. *J. Org. Chem.* **2015**, *80*, 10757.

(159) Tetlow, D. J.; Vincent, M. A.; Hillier, I. H.; Clayden, J. *Chem. Commun.* **2013**, *49*, 1548.

(160) Leonard, D. J.; Ward, J. W.; Clayden, J. *Nature* **2018**, *562*, 105.

(161) Grainger, D. M.; Campbell Smith, A.; Vincent, M. A.; Hillier, I. H.; Wheatley, A. E. H.; Clayden, J. *European J. Org. Chem.* **2012**, No. 4, 731.

(162) Clayden, J.; Hennecke, U. *Org. Lett.* **2008**, *10*, 3567.

(163) Clayden, J.; Donnard, M.; Lefranc, J.; Tetlow, D. J. *Chem. Commun.* **2011**, *47*, 4624.

(164) Bach, R.; Clayden, J.; Hennecke, U. *Synlett* **2009**, No. 3, 421.

(165) Sung, R. Y.; Choi, H.; Lee, J. P.; Park, J. K.; Yang, K.; Koo, I. S. *Bull. Korean Chem. Soc.* **2009**, *30*, 1579.

(166) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273.

(167) Schimler, S. D.; Cismesia, M. A.; Hanley, P. S.; Froese, R. D. J.; Jansma, M. J.; Bland, D. C.; Sanford, M. S. *J. Am. Chem. Soc.* **2017**, *139*, 1452.

(168) Neumann, C. N.; Ritter, T. *Acc. Chem. Res.* **2017**, *50*, 2822.

(169) Kwan, E. E.; Zeng, Y.; Besser, H. A.; Jacobsen, E. N. *Nat. Chem.* **2018**, *10*, 917.

(170) Rohrbach, S.; Smith, A. J.; Pang, J. H.; Poole, D. L.; Tuttle, T.; Chiba, S.; Murphy, J. A. *Angew. Chemie - Int. Ed.* **2019**, *58*, 16368.

(171) Clayden, J.; Hennecke, U.; Vincent, M. A.; Hillier, I. H.; Helliwell, M. *Phys. Chem. Chem. Phys.* **2010**, *12*, 15056.

(172) Toniolo, C.; Formaggio, F.; Kaptein, B.; Broxterman, Q. B. *Synlett* **2006**, No. 9, 1295.

(173) Gao, Y. *Nat. Prod. Rep.* **2002**, *19*, 100.

(174) Conway, S. J.; Miller, J. C.; Howson, P. A.; Clark, B. P.; Jane, D. E. *Bioorganic Med. Chem. Lett.* **2001**, *11*, 777.

(175) Wang, L.; Xie, J.; Schultz, P. G. *Annu. Rev. Biophys. Biomol. Struct.* **2006**, *35*, 225.

(176) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410.

(177) Verdolino, V.; Cammi, R.; Munk, B. H.; Schlegel, H. B. *J. Phys. Chem. B* **2008**, *112*, 16860.

(178) Davies, J. A.; Clayden, J. *Catalytic Asymmetric Arylation of Amino Acids*; Bristol, 2016.

(179) Lee, J. H.; Yoo, M. S.; Jung, J. H.; Jew, S. sup; Park, H. geun; Jeong, B. S. *Tetrahedron* **2007**, *63*, 7906.

(180) Eagling, L.; Mas-Roselló, J.; Clayden, J. *Catalytic Asymmetric Arylation of Amino Acids*; Bristol, 2016.

(181) Avila, A.; Mas-Roselló, J.; Clayden, J. *Unpublished Work, University of Bristol*; Bristol, 2016.

(182) Brüning, F.; Katayev, D.; Togni, A. *European J. Org. Chem.* **2018**, *2018*, 4256.

(183) Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446.

(184) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, *16*, 4057.

(185) Johnson, K. M.; Rattley, M. S.; Sladojevich, F.; Barber, D. M.; Nuñez, M. G.; Goldys, A. M.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 2492.

(186) Wu, X.; Liu, Q.; Liu, Y.; Wang, Q.; Zhang, Y.; Chen, J.; Cao, W.; Zhao, G. *Adv. Synth. Catal.* **2013**, *355*, 2701.

(187) He, R.; Wang, X.; Hashimoto, T.; Maruoka, K. *Angew. Chemie - Int. Ed.* **2008**, *47*, 9466.

(188) Uraguchi, D.; Asai, Y.; Ooi, T. *Angew. Chemie - Int. Ed.* **2009**, *48*, 733.

(189) Elango, S.; Venugopal, M.; Suresh, P. S.; Eni. *Tetrahedron* **2005**, *61*, 1443.

(190) Berkessel, A.; Guixà, M.; Schmidt, F.; Neudörfl, J. M.; Lex, J. *Chem. - A Eur. J.* **2007**, *13*, 4483.

(191) Lee, H. J.; Cho, C. W. *J. Org. Chem.* **2015**, *80*, 11435.

(192) Belyk, K. M.; Xiang, B.; Bulger, P. G.; Leonard, W. R.; Balsells, J.; Yin, J.; Chen, C. Y. *Org. Process Res. Dev.* **2010**, *14*, 692.

(193) Bandini, M.; Eichholzer, A.; Tragni, M.; Umani-Ronchi, A. *Angew. Chemie - Int. Ed.* **2008**, *47*, 3238.

(194) Capobianco, A.; Di Mola, A.; Intintoli, V.; Massa, A.; Capaccio, V.; Roiser, L.; Waser, M.; Palombi, L. *RSC Adv.* **2016**, *6*, 31861.

(195) Wu, S.; Pan, D.; Cao, C.; Wang, Q.; Chen, F. X. *Adv. Synth. Catal.* **2013**, *355*, 1917.

(196) Qing, H.; Wang, Y.; Zheng, Z.; Chen, S.; Meng, Q. *Tetrahedron Asymmetry* **2016**, *27*, 834.

(197) Jolliffe, J. D.; Armstrong, R. J.; Smith, M. D. *Nat. Chem.* **2017**, *9*, 558.

(198) Corey, E. J.; Zhang, F. Y. *Angew. Chemie - Int. Ed.* **1999**, *38*, 1931.

(199) Brak, K.; Jacobsen, E. N. *Angew. Chemie - Int. Ed.* **2013**, *52*, 534.

(200) Cahard, D.; Bizet, V. *Chem. Soc. Rev.* **2014**, *43*, 135.

(201) Zimmer, L. E.; Sparr, C.; Gilmour, R. *Angew. Chemie - Int. Ed.* **2011**, *50*, 11860.

(202) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228.

(203) Nishio, M. *Phys. Chem. Chem. Phys.* **2011**, *13*, 13873.

(204) Chinchilla, R.; Mazón, P.; Nájera, C.; Ortega, F. J. *Tetrahedron Asymmetry* **2004**, *15*, 2603.

(205) Denmark, S. E.; Cullen, L. R. *J. Org. Chem.* **2015**, *80*, 11818.

(206) Abimannan, P.; Rajendran, V. *Curr. Catal.* **2016**, *05*, 44.

(207) Denmark, S. E.; Weintraub, R. C.; Gould, N. D. *J. Am. Chem. Soc.* **2012**, *134*, 13415.

(208) Jwo, J.-J. Phase Transfer Catalysis: Fundamentals and Selected Systems. In *Interfacial Catalysis*; Volkov, A. G., Ed.; Marcel Dekker: New York, 2003; pp 227–284.

(209) Bandini, M.; Bottoni, A.; Eichholzer, A.; Miscione, G. Pietro; Stenta, M. *Chem. - A Eur. J.* **2010**, *16*, 12462.

(210) Xiang, B.; Belyk, K. M.; Reamer, R. A.; Yasuda, N. *Angew. Chemie - Int. Ed.* **2014**, *53*,

8375.

(211) Kurts, A. L.; Beletskaya, A. M. I. P.; Reutov, O. A. *Tetrahedron* **1971**, *27*, 4759.

(212) Halpern, M.; Sasson, Y.; Willner, I.; Rabinovitz, M. *Tetrahedron Lett.* **1981**, *22*, 1719.

(213) Halpern, M.; Sasson, Y.; Rabinovitz, M. *J. Org. Chem.* **1983**, *48*, 1022.

(214) Halpern, M.; Sasson, Y.; Rabinovitz, M. *J. Org. Chem.* **1984**, *49*, 2011.

(215) Halpern, M.; Zahalka, H. A.; Sasson, Y.; Rabinovitz, M. *J. Org. Chem.* **1985**, *50*, 5088.

(216) Feldman, D.; Halpern, M.; Rabinovitz, M. *J. Org. Chem.* **1985**, *50*, 1746.

(217) Atkinson, R. C.; Leonard, D. J.; Maury, J.; Castagnolo, D.; Volz, N.; Clayden, J. *Chem. Commun* **2013**, *49*, 9734.

(218) Sambri, L.; Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Curr. Org. Synth.* **2012**, *9*, 137.

(219) Yan, L.; Lui, H.; Sun, J.; Gao, L.; Lu, X.; Li, X.; Chen, H. *Carbohydr. Res.* **2019**, *485*, 107807.

(220) Yamamoto, Y.; Shimizu, E.; Ban, K.; Wada, Y.; Mizusaki, T.; Yoshimura, M.; Takagi, Y.; Sawama, Y.; Sajiki, H. *ACS Omega* **2020**, *5*, 2699.

(221) Ji, H.; Jing, Q.; Huang, J.; Silverman, R. B. *Tetrahedron* **2012**, *68*, 1359.

(222) LeTiran, A.; Stables, J. P.; Kohn, H. *Bioorganic Med. Chem.* **2001**, *9*, 2693.

(223) Johnston, C. P.; Kothari, A.; Sergeieva, T.; Okovytyy, S. I.; Jackson, K. E.; Paton, R. S.; Smith, M. D. *Nat. Chem.* **2015**, *7*, 171.

(224) Hunter, L. *Beilstein J. Org. Chem.* **2010**, *6*, 1.

(225) Yoo, M.-S.; Jeong, B.-S.; Lee, J.-H.; Park, H.-G.; Jew, S.-S. *Org. Lett.* **2005**, *7*, 1129.

(226) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898.

(227) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102.

(228) Xuan, J.; Xiao, W.-J. *Angew. Chemie - Int. Ed.* **2012**, *51*, 6828.

(229) Reckenthäler, M.; Griesbeck, A. G. *Adv. Synth. Catal.* **2013**, *355*, 2727.

(230) Schultz, D. M.; Yoon, T. P. *Science (80-.).* **2014**, *343*, 1239176.

(231) Skubi, K. L.; Blum, T. R.; Yoon, T. P. *Chem. Rev.* **2016**, *116*, 10035.

(232) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075.

(233) Matsui, J. K.; Lang, S. B.; Heitz, D. R.; Molander, G. A. *ACS Catal.* **2017**, *7*, 2563.

(234) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.

(235) Yoon, T. P. *Acc. Chem. Res.* **2016**, *49*, 2307.

(236) Hopkinson, M. N.; Tlahuext-Aca, A.; Glorius, F. *Acc. Chem. Res.* **2016**, *49*, 2261.

(237) Arora, A.; Weaver, J. D. *Acc. Chem. Res.* **2016**, *49*, 2273.

(238) Mizuta, S.; Verhoog, S.; Engle, K. M.; Khotavivattana, T.; O'Duill, M.; Wheelhouse, K.; Rassias, G.; Médebielle, M.; Gouverneur, V. *J. Am. Chem. Soc.* **2013**, *135*, 2505.

(239) Wilger, D. J.; Gesmundo, N. J.; Nicewicz, D. A. *Chem. Sci.* **2013**, *4*, 3160.

(240) Tyson, E. L.; Ament, M. S.; Yoon, T. P. *J. Org. Chem.* **2013**, *78*, 2046.

(241) Bruijn, A. D. De; Roelfes, G. *Chem. - A Eur. J.* **2018**, *24*, 11314.

(242) Aycock, R. A.; Pratt, C. J.; Jui, N. T. *ACS Catal.* **2018**, *8*, 9115.

(243) Aycock, R. A.; Vogt, D. B.; Jui, N. T. *Chem. Sci.* **2017**, *8*, 7998.

(244) Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, R. A.; Malliaras, G. G.; Bernhard, S. *Chem. Mater.* **2005**, *17*, 5712.

(245) Aycock, R. A.; Wang, H.; Jui, N. T. *Chem. Sci.* **2017**, *8*, 3121.

(246) Kohls, P.; Jadhav, D.; Pandey, G.; Reiser, O. *Org. Lett.* **2012**, *14*, 672.

(247) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2012**, *134*, 3338.

(248) Zhang, O.; Schubert, J. W. *J. Org. Chem.* **2020**, *85*, 6225.

(249) Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 10886.

(250) Yajima, T.; Ikegami, M. *Fluor. Notes* **2018**, *121*, 1.

(251) Clayden, J.; Donnard, M.; Lefranc, J.; Minassi, A.; Tetlow, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 6624.

(252) Wadsworth, E. Tandem Conjugate Addition-Rearrangement of Amino Acid Derived Enolates, University of Bristol, 2017.

(253) Abrams, R.; Clayden, J. *Angew. Chemie Int. Ed.* **2020**, *59*, 2.

(254) Luo, J.; Zhang, J. *ACS Catal.* **2016**, *6*, 873.

(255) Shang, T. Y.; Lu, L. H.; Cao, Z.; Liu, Y.; He, W. M.; Yu, B. *Chem. Commun.* **2019**, *55*, 5408.

(256) Chandu, P.; Ghosh, K. G.; Das, D.; Sureshkumar, D. *Tetrahedron* **2019**, *75*, 130641.

(257) Wang, P.; Zhu, S.; Lu, D.; Gong, Y. *Org. Lett.* **2020**.

(258) Yang, H. Bin; Selander, N. *Org. Biomol. Chem.* **2017**, *15*, 1771.

(259) Ma, J.; Xie, X.; Meggers, E. *Chem. - A Eur. J.* **2018**, *24*, 259.

(260) Cui, L.; Matusaki, Y.; Tada, N.; Miura, T.; Uno, B.; Itoh, A. *Adv. Synth. Catal.* **2013**, *355*, 2203.

(261) Tullin, C.; Ljungström, E. *Energy and Fuels* **1989**, *3*, 284.

(262) Keener, T. C.; Khang, S. J. *Chem. Eng. Sci.* **1993**, *48*, 2859.

(263) Matsui, J. K.; Primer, D. N.; Molander, G. A. *Chem. Sci.* **2017**, *8*, 3512.

(264) Sim, J.; Campbell, M. W.; Molander, G. A. *ACS Catal.* **2019**, *9*, 1558.

(265) Bargiggia, F.; Dos Santos, S.; Piva, O. *Synthesis* **2002**, No. 3, 427.

(266) Coutrot, P.; Grison, C.; Sauvêtre, R. *J. Organomet. Chem.* **1987**, *332*, 1.

(267) Luo, F.; Lu, D.; Gong, Y. *J. Mol. Catal. B Enzym.* **2011**, *70*, 101.

(268) Leonard, D. J. Intramolecular Arylation of Amino Acid Enolates, University of Manchester, 2016.

(269) Kiss, L.; Ouchakour, L.; Ábrahámi, R. A.; Nonn, M. *Chem. Rec.* **2020**, *20*, 120.

(270) Yerien, D. E.; Bonesi, S.; Postigo, A. *Org. Biomol. Chem.* **2016**, *14*, 8398.

(271) Remete, A. M.; Nonn, M.; Fustero, S.; Fülöp, F.; Kiss, L. *Tetrahedron* **2018**, *74*, 6367.

(272) Bierstedt, A.; Stölting, J.; Fröhlich, R.; Metz, P. *Tetrahedron Asymmetry* **2002**, *12*, 3399.

(273) Gibson, S. M.; Lanigan, R. M.; Benhamou, L.; Aliev, A. E.; Sheppard, T. D. *Org. Biomol. Chem.* **2015**, *13*, 9050.

(274) Çetin, K.; Denizli, A. *Colloids Surfaces B Biointerfaces* **2015**, *126*, 401.

(275) Cappa, V. A.; Rivero, C. W.; Britos, C. N.; Martinez, L. M.; Lozano, M. E.; Trelles, J. A. *Process Biochem.* **2014**, *49*, 1169.

(276) Nakamura, S. *Org. Biomol. Chem.* **2014**, *12*, 394.

(277) Hara, N.; Nakamura, S.; Funahashi, Y.; Shibata, N. *Adv. Synth. Catal.* **2011**, *353*, 2976.

(278) Amere, M.; Lasne, M. C.; Rouden, J. *Org. Lett.* **2007**, *9*, 2621.

(279) Seebach, D.; Bossler, H.; Gründler, H.; Shoda, S.; Wenger, R. *Helv. Chim. Acta* **1991**, *74*, 197.

(280) Blaquiere, N.; Shore, D. G.; Rousseaux, S.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 6190.

(281) Zhong, F.; Yao, W.; Dou, X.; Lu, Y. *Org. Lett.* **2012**, *14*, 4018.

(282) Suh, C. W.; Chang, C. W.; Choi, K. W.; Lim, Y. J.; Kim, D. Y. *Tetrahedron Lett.* **2013**, *54*, 3651.

(283) Bae, H. Y.; Some, S.; Lee, J. H.; Kim, J. Y.; Song, M. J.; Lee, S.; Zhang, Y. J.; Song, C. E. *Adv. Synth. Catal.* **2011**, *353*, 3196.

(284) Hara, N.; Nakamura, S.; Sano, M.; Tamura, R.; Funahashi, Y.; Shibata, N. *Chem. - A Eur. J.* **2012**, *18*, 9276.

(285) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889.

(286) Hirner, S.; Panknin, O.; Edefuhr, M.; Somfai, P. *Angew. Chemie - Int. Ed.* **2008**, *47*, 1907.

(287) Zhang, F.; Sun, H.; Song, Z.; Zhou, S.; Wen, X.; Xu, Q. L.; Sun, H. *J. Org. Chem.* **2015**, *80*, 4459.

(288) De Parrodi, C. A.; Juaristi, E. *Synlett* **2006**, No. 17, 2699.

(289) Overman, L. E.; Sugai, S. *J. Org. Chem.* **1985**, *50*, 4154.

(290) Fritz, S.; Lindner, W.; Roots, I.; Frey, B. M.; Küpfer, A. *J. Pharmacol. Exp. Ther.* **1987**, *241*, 615.

(291) Holden, C. M.; Greaney, M. F. *Chem. - A Eur. J.* **2017**, *23*, 8992.

(292) Bunnett, J. F.; Okamoto, T. *J. Am. Chem. Soc.* **1956**, *78*, 5363.

(293) Mas-Roselló, J.; Okoh, M.; Clayden, J. *Chem. Commun.* **2018**, *54*, 10985.

(294) Pham, T. Q.; Pyne, S. G.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2005**, *70*, 6369.

(295) Iwai, T.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2010**, *132*, 9602.